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Electrophilic Cyclisations of 3-Arylpenta-1,4-diyn-3-ols for the Synthesis of Heterocycles

A Thesis Submitted to the University of Huddersfield in Partial Fulfilment of the Requirements for the Degree of Doctor of Philosophy

Rebecca Wilson

The University of Huddersfield

December 2020
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Abstract

This project was concerned with investigating the electrophilic cyclisation reactions of 3-phenylpenta-1,4-diyn-3-ols possessing either an ortho-N-linked- or an ortho-S-linked- sulfonamide function. Cyclisations of both series of sulfonamides mediated by alkynophilic initiators [e.g. I₂, ICl, AgOAc or In(OTf),] provided access to novel functionalised heterocycles.

Thus, addition of methyl 2-(arenesulfonamido)benzoates to alkynyllithium reagents furnished 3-[(2-arenesulfonamido)phenyl]penta-1,4-diyn-3-ols in which the alkyne termini possess identical substituents. Dialkynols having unsymmetrical alkyne terminal groups have been obtained from the addition of an alkynyllithium reagent or HC≡CMgBr to 3-aryl-1-(2-tosylamidophenyl)prop-2-yn-1-ones. The ortho-S-linked sulfonamides have been accessed directly from N-substituted saccharins that readily add alkynyllithiums to provide 3-(2-sulfamoylphenyl)penta-1,4-diyn-3-ols in good yields.

Desilylation (5M NaOH in MeOH) of 1,5-bis(trimethylsilyl)-3-(2-tosylamidophenyl)penta-1,4-diyn-3-ol also triggered cyclisation via a 5-exo-dig pathway and gave a quantitative yield of 3-ethynyl-2-methylene-1-tosylindolin-3-ol. However, when both silyl functions were replaced with either a propyl- or a phenyl- group, cyclisation to the 1-tosylindolin-3-ol did not occur with base. A quantitative yield of 3-(phenylethynyl)-1-tosyl-1H-indol-2-yl(1-phenyl)methanol was obtained from treatment of 1,5-diphenyl-3-(2-tosylamidophenyl)penta-1,4-diyn-3-ol with AgOAc in MeCN. The analogous reaction with 6-(2-tosylamidophenyl)undeca-4,7-diyn-6-ol, provided 1-[3-(pent-1-yn-1-yl]-1-tosyl-1H-indol-2-yl]butan-1-ol, together with smaller amounts of (E)-2-but-1-en-1-yl-3-pentyn-1-yl-1-tosyl-1H-indole and 4-pentyn-1-yl-2-propylquinoline. It was found that when 3-(2-tosylamidophenyl)penta-1,4-diyn-3-ols possessed bulky groups on the alkyne units, the reaction followed an alternative course giving access to the (Z)-2-benzylidene-, (Z)-2-(2,2-dimethylpropylidene)- and (Z)-2-(trimethylsilylmethylene)- derivatives of 3-alkynyl-1-tosylindolin-3-ols. Mechanisms to account for these outcomes have been proposed. Contrasting behavior was observed from the In(OTf),-mediated cyclisation of 1,5-diphenyl-3-(2-tosylaminophenyl)penta-1,4-diyn-3-ol, which promoted an unexpected and remarkable cascade pathway leading to 2,4-diphenyl-1-tosyl-4,5-dihydrofuro[2,3-c]quinoline, albeit in moderate yield.

Attempted iodocyclisation (ICl in MeCN) of 1,5-diphenyl-3-[2-(N-methylsulfamoyl)phenyl]penta-1,4-diyn-3-ol resulted only in cyclodehydration to give the novel 3,3-bis(phenylethynyl)-2-methyl-1,2-benzisothiazole 1,1-dioxide. However, application of these conditions to 1,5-diphenyl-3-[2-(N-p-tolylsulfamoyl)phenyl]penta-1,4-diyn-3-ol provided a novel derivative of the unusual 1,2-benzisothiazolo[2,3-α]quinoline system that was characterised by X-ray crystallography; the
corresponding 2-aryl-3,3-di(alkynyl)-1,2-benzisothiazole 1,1-dioxide was also formed. The latter also underwent iodocyclisation to give the 1,2-benzisothiazolo[2,3-\(\alpha\)]quinolines. It was established that the 3,3-di(alkynyl)-1,2-benzisothiazole 1,1-dioxides could be generated most efficiently by treatment of the 3-[2-(sulfamoyl)phenyl]penta-1,4-diyn-3-ols with In\((\text{OTf})_3\) in DCM.

Iodocyclisation (ICI in MeCN) of 3-[2-tosylamidophenyl]penta-1,4-diyn-3-ols having symmetrical alkyne substituents afforded novel 4-alkynyl-3-iodoquinolines. However, the unsymmetrically-substituted pentadiynols cyclised less efficiently to give, in some cases, mixtures of regioisomeric 3-iodoquinolines. The cyclisation of 1-[4-methoxyphenyl]-5-phenyl-3-(2-tosylamidophenyl)penta-1,4-diyn-3-ol regiospecifically generated 3-iodo-2-(4-methoxyphenyl)-4-(phenylethynyl)quinoline, as anticipated.

Silver-catalysed cyclisation (AgOAc in MeCN) of 3-[2-(N-arylsulfamoyl)phenyl]penta-1,4-diyn-3-ols proceeds stereoselectively to \((Z)\)-3-alkyllidene-4-alkynyl-2-aryl- and \((Z)\)-4-alkynyl-2-aryl-3-arylidene-1,2-benzothiazin-4-ol 1,1-dioxides \textit{via} a 6-endo-\textit{dig} pathway in good to excellent yields, constituting a new approach to this ring system. Two of the pentadiynols also furnished 1,2-benzothiazepine 1,1-dioxides \textit{via} a 7-endo-\textit{dig} ring closure. Mechanisms for the formation of these novel compounds are proposed.

With a range of heterocycles to hand some were subjected to functionalisation or annulation reactions. Of note is the Pd-mediated domino-amination-hydroamination of 4-alkynyl-3-iodoquinolines with a range of primary amines. This approach was exploited to access novel 2,3,4-trisubstituted pyrrolo[2,3-c]quinolines, analogues of the biologically active Marinoquinolines. However, in some instances the hydroamination step was suppressed and the major or exclusive product was a 4-alkynyl-3-amino-2-arylquinoline. Suzuki-Miyaura couplings to 4-alkynyl-2-iodo-3-arylquinolines and efforts to effect iodocyclisations of the products are also described.
Guide to the Referencing System

The referencing system employed in this thesis is that devised by Katritzky and utilised in Advances in Heterocyclic Chemistry, and the annual reviews Progress in Heterocyclic Chemistry and also for the major reference works Comprehensive Heterocyclic Chemistry Pergamon Press, Oxford 1984 and Comprehensive Heterocyclic Chemistry II and III, Elsevier, Oxford 1996 and 2008 respectively.

This system is used in place of numerical references and allows the reader to extract the reference directly from the text. The references are given in the format [NNLLNN] where the initial numbers denote the year in which the citation was published, the letters indicate the journal, book or patent from which the citation has originated, and the final numbers refer to the page number. For journals which publish more than one volume per year, the volume number is given in parentheses after the journal code. Less common journals, new journals and books are assigned the code MI.
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<td>HMBC</td>
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<td>HMPA</td>
<td>Hexamethylphosphoramidie</td>
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<td>Abbreviation</td>
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<td>High Resolution Mass Spectrometry</td>
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<tr>
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<td>Heteroatom Single Quantum Coherence Spectroscopy</td>
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Chapter 1

Introduction
Chapter 1 Introduction

1.1 Natural Occurrence, Applications and Synthesis of Quinolines

Bark from the Cinchona tree (Cinchona officinalis) has been known to exhibit anti-malarial activity since around 1600. Pure cinchonine and quinine were first isolated from the bark of Cinchona officinalis in 1820 by Pelletier and Caventou. Quinoline was first isolated by Runge (1834) from coal tar, later Gerhardt (1842) isolated quinoline from cinchonine [67MI1].

Within the natural world quinolines are a very important class of heterocycle. The quinoline skeleton is ubiquitous in natural products especially, alkaloids [10MI1], as well as pharmaceuticals [10COB347], electrically conducting materials, dyes and agrochemicals. Some examples of important quinoline-containing compounds are shown in Figure 1.1.

![Figure 1.1 Quinoline derivative examples](image)

Consequently, much attention has been paid to the synthesis of quinoline derivatives. There are a plethora of ways by which the quinoline ring can be constructed. Some classical
examples being; Conrad-Limpach-Knorr, Combes, Friedländer, Gould-Jacobs and Skraup syntheses (Scheme 1.1). All of the important routes rely upon construction of the heterocyclic ring onto a benzene (aniline) derivative [03MI1, 10MI2]. With extensive reviews relating to quinoline synthesis, structure and reactivity available in all the editions of Comprehensive Heterocyclic Chemistry [synthesis: 84CHEC-I(2)395, 96CHEC-II(5)167, 08CHEC-III(7)217; structure: 84CHEC-I(2)99, 96CHEC-II(5)1, 08CHEC-III(7)1; reactivity: 84CHEC-I(2)165, 84CHEC-I(2)315, 96CHEC-II(5)37, 96CHEC-II(5)91, 08CHEC-III(7)41, 08CHEC-III(7)101]. Reviews in the literature are also summarised yearly (1991 – present) in Progress in Heterocyclic Chemistry.

**Scheme 1.1**

**1.2 Natural Occurrence, Applications and Synthesis of Indoles**

Indole and its derivatives are prevalent throughout both the plant and animal kingdom and indoles is therefore classed as a privileged structure [10COB347], some examples include; dyes like indigo, amino acids (tryptophan), hormones (indole-3-acetic acid), and skatole (3-methylindole) which is found in citrus oils and widely used within fragrances. Possibly the most useful application of the Fischer indole synthesis is its use in the synthesis of the neurotransmitter serotonin, and its derivatives which act as agonists of serotonin.
Derivatives of serotonin have been used as pharmaceuticals, for example Sumatriptan is used to treat migraines. A few more examples of important indoles are shown in Figure 1.2 below. Extensive reviews relating to indole synthesis, structure and reactivity have been summarised in *Comprehensive Heterocyclic Chemistry* [synthesis: 84CHEC-I(4)313, 96CHEC-II(2)119, 08CHEC-III(3)269; structure: 84CHEC-I(4)155, 96CHEC-II(2)1, 08CHEC-III(3)1; reactivity: 84CHEC-I(4)39, 84CHEC-I(4)201, 96CHEC-II(2)39, 08CHEC-III(3)45]. Developments in the literature are also summarised yearly (1991 – present) in *Progress in Heterocyclic Chemistry*.

**Figure 1.2** Indole derivative examples

The Fischer indole synthesis has been the most important method for the preparation of substituted indoles since its discovery in 1883. Fischer and Jourdan treated pyruvic acid 1-methylphenylhydrazone with alcoholic hydrogen chloride, which resulted in the formation of 1-methylindole-2-carboxylic acid [1883MI2241]. The general reaction conditions for the
Fischer indole synthesis involve the heating of arylhydrazines with an α-methylene ketone or an aliphatic aldehyde in the presence of an acid (Scheme 1.2) [06CRV2875].

Another widely used application of the Fischer indole synthesis is in the synthesis of the so-called Fischer base (1,3,3-trimethyl-2-methyleneindoline) (1.1, Scheme 1.2), which has been utilised extensively in industry for the synthesis of cyanine dyes and photochromic compounds [16JST426, 17DP481, 17JMC5111]. Fischer base is obtained via the reaction of PhNHNH₂ with 3-methylbutan-2-one followed by alkylation of the resulting 2,3,3-trimethyl-3H-indole. Alternatively indolisation of 3-methylbutan-2-one with PhN(Me)NH₂ affords the product directly.

![Scheme 1.2](image)

There are a plethora of indole syntheses that allow access to variously substituted derivatives, a selection of examples are provided by the Bartoli indole synthesis, the Bischler-Möhlau indole synthesis, Hegedus, Larock, Gassman and the Madelung synthesis (Scheme 1.3) [03MI1, 16MI39].
1.3 Heterocycles via Electrophilic Cyclisations

Both alkenes and alkynes possessing a pendant nucleophilic function can, providing the necessary stereochemical requirements are fulfilled, cyclise upon treatment with an electrophilic initiator. This process has been developed as a means to access a wide range of heterocycles and application to functionalised alkynes has been extensively exploited. The most useful electrophilic initiators are selected from halogen or positive halogen sources. Of these elemental iodine or iodine-containing reagents have been widely employed i.e. I₂, NIS, ICl or, less commonly, bis(pyridine)iodonium tetrafluoroborate (IPy₂BF₄, Barluenga’s reagent). The uses of these reagents in electrophilic cyclisations leading to novel heterocyclic compounds has been reviewed [11CRV2937, 15S1961, 16OBC7639]. Some examples of these iodocyclisation reactions are shown in Scheme 1.4. Electrophilic iodocyclisation reactions have been used for the construction of highly functionalized pyrroles, indoles, furans, thiophenes, selenophenes, pyridines, quinolines, benzo[b] furans and the review literature details many examples [11CRV2937, 15S1961, 16CC853,
Additional examples relating to the construction of indoles [17OL6744], quinolines [17JOC4625] and quinoline annulation to generate thieno[2,3-\textit{b}]quinolines [18OBC245] are noteworthy.

All the reactions depicted in Scheme 1.4 proceed via initial iodination of the triple bond to generate a bridged iodonium ion. Subsequent attack by an adjacent nucleophile facilitates cyclisation, most commonly via a 5-exo-dig or 6-endo-dig pathway. These mechanisms are considered in more detail in the following chapters.

These electrophilic cyclisations often proceed with incorporation of an iodo-substituent into the ring. Thus, heterocycles with an iodine substituent allows for further structural modifications and access to structurally complex compounds. In addition, the halogen atom can sometimes enhance the bioactivity [10T1177].

**Scheme 1.4**

Metal-containing Lewis acid catalysts are developing as powerful reagents to effect the cyclisation of alkynes, as many can be used in tandem reactions to both couple a terminal
alkyne to the starting material *in situ* and then to induce cyclisation (in most cases a domino oxidative cross-coupling electrophilic cyclisation) Scheme 1.5 [08CRV3174, 11CC12855, 11CRV1780, 13CC7549, 13OBC1456]. For example, silver(I) was employed to catalyse the A3 reaction of 4-imidazolocarboxaldehyde, phenylacetylene and a secondary amine to obtain alkyne 1.2, the pyrrole 1.3 and ketone 1.4 (A, Scheme 1.5) [11CC12855]. Another silver-mediated oxidative cross-coupling and cyclisation reaction made use of a β-enamino ester and arylacetylenes affording substituted pyrroles 1.5 (B, Scheme 1.5) in varying yields (37 – 84%) [13CC7549]. Tsuchimoto and co-workers employed In(III) to activate phenylindole derivatives to addition of propargyl ethers, subsequent *in situ* cyclisation afforded 6-methyl-7H-benzo[c]carbazoles 1.6 and 1.6’ (C, Scheme 1.5) [13OBC1456].

Scheme 1.5

A range of alkynol substrates and solvents are tolerated (Scheme 1.6) for the metal-catalysed cyclisation, reviews of catalytic activation have been published [16CC853, 18MI31129]. Metal containing Lewis acid catalysts most relevant to the present project, which have also been reviewed are; Ag(I) [15CSR8124], In(III) [03S633, 07S1, 04T1959] Au(I)
and Au(III) [07CC333]. The mechanisms of the reactions shown in Scheme 1.6 will be discussed in subsequent chapters in the context of results from the present study.

\[ \text{Scheme 1.6} \]

1.4 Electrophilic Cyclisations for the Synthesis of Indoles and Fused-Ring Derivatives

1.4.1 From 1-(2-Aminophenyl)- or 1-[2-(Alk)oxyphenyl]-prop-2-yn-1-ol Derivatives

Chan and co-workers used a gold(I) catalyst to cyclise the propargylic alcohol 1.7 and effect iodination with NIS in acetone to produce 1H-indole-2-carbaldehydes. It was found that by keeping the mixture at a low temperature (-40 °C) the reaction could be halted at the iododeauration step (Scheme 1.7) [11JOC7633].
Subsequent work showed that when $R^1 \neq H$ in 1-(2-anilinyl)prop-2-yn-1-ols 1.8, treatment with molecular iodine affords a mixture of 3-iodoquinolinium salts and 2-acyl-1H-indoles (Scheme 1.8) [06OL243, 11OL2598]. When the alkynols (1.8) were treated with NIS the course of the reaction is controlled by the nature of the R group, and two routes can operate. When NIS was used to trigger the cyclisation of the nitrogen nucleophile to the alkyne, intermediate A was formed. Thus, if $R \neq H$ then A was susceptible to an hydroxyl group shift followed by alkyl migration and oxidation to afford 3-(diiodomethyl)indolin-2-ones. However in A $R = H$ a 1,2-hydride shift and oxidation of the secondary carbinol centre resulted in formation of 2-(iodomethylene)indolin-3-one (Scheme 1.8) [13CEJ1978].
In a further extension of the reactions in Scheme 1.8, it was found that when non-distilled solvents were used the yield of indole-2-carbaldehyde was increased. This led to the optimisation of solvents in which H$_2$O – acetone (6:1 v/v) and 2.15 equiv. of NIS was used, affording the highest yields of **1.9** (Scheme 1.9) [13T7471].

**Scheme 1.9**

A suggested mechanism for the formation of indole-2-carbaldehyde **1.9** involves an initial iodicyclisation to the 2-(iodomethylene)-indolin-3-ol **1.10**. Co-ordination to the alcohol by another molecule of NIS facilitates dehydration, nucleophilic substitution of the activated species by H$_2$O generating **1.11**, the loss of HI then generates **1.9** (Scheme 1.10).
Chan et al. found that Ag(I) salts catalysed the cyclisation of 1-[(2-tosylamido)aryl]but-2-yn-1,4-ols 1.12, affording 2-alkynylindoles 1.13 in fair to excellent yields 38 – 94 % (Scheme 1.11) [12CEJ6133].

A suggested mechanism for the formation 1.13 is via allene 1.14. Silver(I) co-ordination of the alcohol promotes the deprotonation of 1.15, followed by elimination of [Ag]-OH which on protonolysis regenerates the catalyst and a molecule of water (Scheme 1.12) [12CEJ6133].
1-[2-(Tosylamino)phenyl]prop-2-yn-1-ols **1.16** were cyclised (5-exo-dig) upon treatment with AgOAc in acetonitrile, when \( R^1 = H \) a Fischer base-like structure was produced (Scheme 1.2, **1.1**). (Z)-2-Methylene-1-sulfonylindolin-3-ols **1.17** were also obtained from a range of alkyl and/or aryl substituents (Scheme 1.13). However when the nitrogen protecting group was replaced with an acetyl or a Boc function, the cyclisation did not proceed and resulted only in quantitative recovery of starting material [12JOC7166].

\[
\begin{align*}
\text{R} & = \text{aryl, Me} \\
\text{R}^1 & = \text{H, aryl, alkyl} \\
\end{align*}
\]

**Scheme 1.13**

Ramasastr and co-workers used silver(I) acetate along with other Lewis acids and Brønsted acids in a relay system, via **1.18**, to generate cyclopenta[b]indoles **1.19** – when a protic acid was used (CSA, p-TsOH or TfOH). However, in the presence of Bi(OTf)\(_3\) the intermediate 3-vinylindolin-3-ol **1.18** underwent rearrangement with concomitant aromatisation to afford indole **1.20**. Treatment of the latter with Pd(OAc)\(_2\) promoted oxidative cyclisation to the furo[3,4-b]indoles **1.21** (Scheme 1.14) [16OBC5563].

\[
\begin{align*}
\text{R} & = \text{aryl} \\
\text{[16OBC5563]} & \quad \text{[16OBC5563]} \\
\end{align*}
\]

**Scheme 1.14**
Reddy et al. used silver(I) carbonate to cyclise 2-hydroxyphenyl propargyl alcohols to the dihydrobenzofuran-3-ol e.g. 1.22, which was then subjected to treatment with TMSN$_3$ to afford 2-(α-azidobenzyl)benzofuran (A, Scheme 1.15). It was found that this and related reactions also proceeded in a one-pot sequence to give moderate to high yields of products (52 – 92 %) [16OBC4077]. Another example of silver(I) catalysis for the cyclisation of propargylic alcohols is provided by the ynone-terminated example from Chan and co-workers (B, Scheme 1.15). When the substituent on the amine function was a tosyl group, only the allene 1.23 was obtained. However, when the N-allyl-protected propargylamines was employed the reaction proceeded to the spirocycle 1.24 in high yields [14OL4110].

Scheme 1.15

Shi and co-workers treated 1-[2-(tosylamino)phenyl]prop-2-yn-1-ol 1.25 with a gold(I) – iron(II) catalyst system to effect cyclisation to 1.26 and 1.27. However, there was no concern with obtaining good yields of indolines 1.26, as they were intermediates in the synthesis of indole aldehydes 1.27 (Scheme 1.16). When only the gold(I) catalyst was used only a 13% yield of 1.26 was obtained. None of the indole-2-carbaldehyde 1.27 was formed. This observation was attributed to a slow protodeauration step. However, in the presence of both gold(I) and iron(II) catalysts the yield of 1.27 increased to 78% [15JAC8912].
Ramasastry and Dhiman treated 1-\((N\text{-tosylaminophenyl})\text{prop-2-yn-1-ols}\) with a gold(I) catalyst in the presence of base, followed by addition of a 1,3-dicarbonyl and triflic acid in a two-step, one-pot synthesis of cyclopenta[b]indoles. Indoline 1.28 could be isolated when gold(I) and base was used alone. However, TfOH did not facilitate the cyclisation in the absence of AuCl (Scheme 1.17) [15CC557].

Another example of gold catalysis for the cyclisation of aryl propargyl alcohols is provided by Chan and co-workers (Scheme 1.18). They found that either indole or acyclic structures could be obtained by varying the reaction conditions. Thus gold(I) chloride and an AgOTf co-catalyst with 20 mol % HMPA and CaSO₄ in toluene gave tetracycle 1.29, in excellent yield (94%). However, if DMAP was employed instead of HMPA the Meyer-Schuster product 1.30 was obtained in a high yield (87%). It was found that indoline 1.31 could be transformed into 1.29 by using the same catalyst and solvent system but discarding the HMPA. Indole 1.32 could only be obtained in low yields from all the conditions investigated [10AGE4619].
Silver(I) was employed to cyclise the enynol 1.33, via indoline 1.34, to afford the β-carboline 1.35 in good to high yields (67 – 81%). However, with AuCl and K₂CO₃ 1.33 gave the 6-exo-trig product 1.36 exclusively (Scheme 1.19) [16AGE7737].

A copper(I) species promotes the tandem cyclisation-condensation reaction of 3-(2-aminophenyl)prop-2-yn-1-ols with acetylacetone to indole 1.37. The reaction which can also be conducted in a stepwise manner, affords indoline 1.38 in the absence of the diketone. However, access to 1.37 by the stepwise procedure is less efficient than the one-pot reaction (Scheme 1.20) [19OBC2663].
Wang and co-workers showed that alkynols 1.39 in the presence of boron trifluoride etherate, cyclised to the corresponding spiro(indenebenzosultams) 1.40 (Scheme 1.21). Interestingly, it was found that at low temperature, or after a short reaction time, the Meyer-Schuster product 1.41 could be isolated in a 94% yield. It was also found that when 1 equiv. of NiS was added to the reaction mixture, the iodospiro(indenebenzosultams) 1.42 were obtained [15OL242].

1.4.2 From (2-Aminophenyl)acetylene Derivatives

Larock et al. showed that \( N,N \)-disubstituted-2-(\( p \)-tolylethynyl)anilines undergo facile iodocyclisations to indoles, in which a range of substituents on the alkyne are tolerated (Scheme 1.22) [04OL1037].
Thieno[2,3-b]quinolines were synthesised in high yields (61 – 91%) from 3-alkynyl-2-(methylthio)quinolines via a 5-endo-dig cyclisation initiated by a positive iodine source (Scheme 1.23). It was found that the efficiency of the cyclisation was highly dependent on the nature of the iodinating reagent. However, the reaction tolerated a variety of functional groups once the optimised conditions were established [18OBC245].

Muñiz and Fra used a hypervalent iodine reagent to activate the triple bond of an alkynyl sulfonamide to nucleophilic attack from the sulfonamide nitrogen. Subsequent nucleophilic attack of the aromatic ring and re-aromatisation ensued to afford the tetracycle 1.43 (Scheme 1.24) [16CEJ4351].
1.5 Formation of Six-Membered Rings and Benzologues

1.5.1 From 1-(2-Aminophenyl)- or 1-[2-(Alk)oxyphenyl]-prop-2-yn-1-ol Derivatives

Ali et al. found molecular iodine promoted the cyclisation of 1-[2-(tosylamino)phenyl]prop-2-yn-1-ols, to 3-iodoquinolines. If nitromethane was employed as the solvent, yields were poor. However, when replaced with methanol, moderate to excellent yields (40 – 99%) of the 3-iodoquinoline could be obtained \textbf{1.44} (Scheme 1.25) [11OL2598].

![Scheme 1.25](image)

Kumer et al. exploited the iodocyclisation of \textit{N}-unsubstituted 1-(2-aminophenyl)propanylols to prepare quinolines. The amino function was not protected because the enhanced nucleophilicity and diminished bulk of the amino group was envisaged to increase the reaction rates. It was found that cyclisation to the 3-iodoquinoline could be achieved under mild conditions. Furthermore the 2,4-disubstituted quinolines were also easily obtained via a Brønsted acid catalysed cyclisation (Scheme 1.26) [12MI3986].

![Scheme 1.26](image)

When either the secondary or tertiary 1-(2-aminophenyl)alk-2-yn-1-ols \textbf{1.45} were subjected to iodocyclisation conditions, the outcome could be manipulated by choice of solvent (Scheme 1.27). In dichloromethane or acetonitrile, the 6-\textit{endo-dig} product was obtained. Yet when either ethanol or methanol was used a 2-acylindole derived from a 5-\textit{exo-dig} pathway was generated [06OL243]. These results lead to the conclusion that it is the protic nature of the solvent that is the key factor in controlling the outcome of the reaction. This observation is contrary to the results of Ali – that in MeOH the 6-\textit{endo-dig} pathway is favoured (Scheme 1.25) [11OL2598]. However, the substrates used by Hessian and Flynn
possessed a 2-dimethylamino group whereas Ali used 2-tosylamido compounds; clearly the tosyl group will greatly affect the nucleophilicity of the nitrogen.

![Scheme 1.27](image)

The alkylnol formed from the addition of LiC≡COEt to 2-aminobenzaldehyde or 2-aminophenyl ketones could not be isolated, as cyclisation ensued on work up with aq. NH₄Cl to afford 2-ethoxy-4-quinolines in good yields (Scheme 1.28) [12EJO5803].

![Scheme 1.28](image)

Yamamoto and co-workers used a range of Lewis acids and Brønsted acids (e.g. I₂, Br₂, TfOH, TFA and HNTf₂) to cyclise 1-azido-2-(2-propynyl)benzenes (1.46) to afford 3-unsubstituted quinolines E = H and 3-haloquinolines E = Br, I (A, Scheme 1.29). It was also found that with some catalysts a small amount of 3-phenyl-4H-[1,2,3]triazolo[1,5-a]indole 1.47 was also obtained [10JOC1266]. 3-Iodoquinolines were synthesised from 2-aminobenzophenones and an acetylene in a single pot reaction (B, Scheme 1.29). The intermediary of the phenyl alkylnol 1.48 was established by its isolation in quantitative yield [17EJO4600].
3-iodocoumarins can be accessed easily by the cyclisation of ethoxyalkyne diols in moderate to high yields (A, Scheme 1.30) [13JOC5878]. Laing et al. found that iodination occurred twice upon cyclisation of alkynols 1.49 to afford 3,4-diiodochromenes when molecular iodine was used; with either IBr or with ICl both halogens added to the chromene. A range of chromanones could be synthesised when a Brønsted acid was used to catalyse the cyclisation of the same alkynol 1.49 (B, Scheme 1.30) [15CEJ3480].
1.5.2 From N-Arylpropargylamines

Larock reported that iodine was an excellent electrophilic initiator for the cyclisation of N-(2-alkynyl)anilines [05OL763]. Iodine monochloride produced slightly lower yields but at faster reaction rates (Scheme 1.31), which is not surprising as it is a harder electrophile than molecular iodine [07CSR354]. It was found that the iodocyclisation tolerated a variety of substituents. However, the presence of electron withdrawing groups were found to also produce side products, including a 3,6-diiodoquinoline derivative when \( R = 4\text{-MeCOC}_6\text{H}_4 \) [05OL763]. Larock also reported that N-propargyltriflamides could be cyclised to 3-iodoquinolines in moderate yields (Scheme 1.31) [10T1177].

![Scheme 1.31](image)

Zhang et al. achieved good yields (64 – 81%) of 3-iodo-2,4-diarylquinolines (1.50) from N-phenyl propargylamines and NIS in 1,4-dioxane; together with trace amounts of the 3,6-diiodo-2,4-diphenylquinolines (Scheme 1.32). In MeOH the product distribution was reversed, suggesting that the solvent promotes \( p \)-iodination of the aromatic ring prior to cyclisation. Zhang et al. also proposed that the cyclisation proceeds via a radical pathway, however no evidence in support of this assertion was presented [17OBC6901].

![Scheme 1.32](image)
3-Iodochromenes have been synthesised in a one pot reaction, involving *in situ* O-arylation of a propargylic alcohol with diphenyliodonium triflate \([13S183]\) and subsequent iodocyclisation under Lewis acid catalysis (A, Scheme 1.33). Yields could be improved by addition of DCM \([16OL944]\). Togo and co-workers went on to adapt the method to synthesise 3-iodoquinolines from *N*-tosylproparylamines (B, Scheme 1.33). The dihydroquinoline was isolated before removal of the tosyl group (B, step iii, Scheme 1.33). However, removal of the tosyl function (NaOH in MeOH) could also be achieved without isolation of the intermediate \([17JOC11727]\).

![Scheme 1.33](image)

**Scheme 1.33**

1.5.3 From 1-Arylprop-2-ynone Derivatives

Hessian and Flynn reported that regioselectivity from the iodocyclisation of 2-[2-(substituted)phenyl]alkyl-3-yn-2-ones was achievable. Thus, either the 5-*exo-dig* or 6-*endo-dig* cyclisation route could be controlled by the appropriate choice of starting material. When 1-[[2-alkylthio]phenyl]alk-2-yn-1-ones were subjected to iodocyclisation conditions they underwent exclusive 5-*exo-dig* ring closure (A, Scheme 1.34). However, the analogous 1-[2-(dimethylamino)phenyl]prop-2-yn-1-ones were highly selective for the 6-*endo-dig* pathway (B, Scheme 1.34). These pathways were unaffected by variations of the iodine source (I₂, ICl, NIS) and solvent (DCM, EtOH, MeCN) \([03OL4377, 06OL243]\).
Larock and co-workers published a route to access 3-iodo(thio)chromones and 3-iodo-4-quinolones from an ICl-induced electrophilic cyclisation (6-endo-dig) of 1-(aryl)propyn-1-ones. The starting alkynones were synthesised from a Sonogashira coupling of a 2-substituted benzoyl chloride and a terminal acetylene, which allowed access to a variety of compounds with different substituents by utilising this approach. Cyclisations of the alkynones ensue under mild conditions affording fair to excellent yields (45 – 99%) of products (Scheme 1.35) [06JOC1626].

Derivatives of 1-[2-(BocNH)phenyl]prop-2-yn-1-ones cyclise upon heating with acid, over a prolonged time (four days) to give 4-quinolones from which the Boc group has been cleaved (A, Scheme 1.36). When the temperature was increased, several side products were also formed [09TL6494]. Moreover, 4-quinolones have been synthesised from ynones by a gold(I)-mediated cyclisation. Helaja and co-workers obtained a range of 2-substituted quinolones in yields ranging from 19 to 96% (B, Scheme 1.36) [14EJO4044].
The highly alkynophilic gold(I) species [Ph₃PAu]SbF₆ (generated in situ) was used to cyclise ynone 1.51 to indenochromen-4-ones (A, Scheme 1.37), the substrate scope was extended to generate indenoquinoline-4-ones 1.52 (B, Scheme 1.37). It was proposed that activation of the triple bond by the gold(I) species is assisted by hydrogen bonding of the hydroxyl group to the carbonyl function. In the case of the amino substrate, a protecting group was needed to change the electron density of the amino group so allowing better hydrogen bonding with the ynone carbonyl function [16CC11516]. Although not involving direct electrophilic activation of the triple bond, Zhu and co-workers developed a radical process to cyclise 2-azidoaryl propynones 1.53 to obtain 2-aryl-3-tosylquinolin-4(1H)-one derivatives (C, Scheme 1.37). Attack of the ynone by the electrophilic radical TolSO₂• has been invoked to explain the outcome of this reaction [16JOC12181].
1.5.4 From ortho-Substituted Phenylacetylenes

Larock demonstrated that the substituents played an essential role in determining the nature of the final product when 2-(1-alkynyl)benzylic alcohols were iodocyclised with molecular iodine and an inorganic base (NaHCO₃, K₂CO₃, KHCO₃ or NaH) in acetonitrile (Scheme 1.38) [10JOC897]. When the triple bond was substituted with a 3-thienyl-, a 1-cyclohexenyl- or an n-butyl-group the 6-endo-dig product was generated. Furthermore, when the starting material possessed either electron withdrawing or electron donating groups meta to the hydroxyalkyl group, the 6-endo-dig product was formed. However, with increasing steric hindrance in the substrate, complex reaction mixtures were produced. If the substrate was configured as a tertiary alcohol function, the 5-exo-dig product was obtained.

Pal et al. took advantage of the alkyne moiety in 2-sulfamoylphenylacetylenes 1.54 to form 2H-1,2-benzothiazine 1,1-dioxides 1.55, using a silver(I) catalyst such as AgSbF₆ [07JOC8547] or AgNO₃ [12TL6577] (Scheme 1.39). The reaction tolerated both alkyl and aryl substituents on the alkyne moiety [07JOC8547, 12TL6577]. However, the choice of solvent for each silver(I) catalyst was different, when AgSbF₆ was employed with DMF the yield of 2H-1,2-benzothiazine 1,1-dioxide was still high (82%) but EtOH increased the yield to 89% [07JOC8547].
1,2-Benzothiazine 1,1-dioxides could be obtained from the Lewis acid-catalysed cyclisation of 1.56 with phenyltrifluoromethanesulfanylamide (A, Scheme 1.40). It was found that when R¹ was an alkyl group the 5-exo-dig product 1.57 was obtained; the cyclisation pathway could be controlled by the nature of the R group, if electron-withdrawing groups (Cl and CF₃) were used then the 6-endo-dig product was obtained selectively [13CC8647]. 2-Bromobenzenesulfonamides can be coupled with a range of acetylenes via a Sonogashira reaction to synthesise 1,2-benzothiazine 1,1-dioxides (B, Scheme 1.40). Intermediate 1.58 was isolated to establish how the reaction proceeds. Alkynes 1.58 could be activated by complexation with copper(I) in a separate step demonstrating that Cu(I) promotes the 6-endo-dig cyclisation (Scheme 1.40) [15JOC3940].
1.6 Seven-Membered Rings via Electrophilic Cyclisations

Within the literature there are very few examples of electrophilic cyclisations of substrates leading to seven-membered carbocyclic or heterocyclic rings. However some examples are discussed below.

Chen and co-workers found that the iodocyclisations of alkynone 1.59 could operate via two pathways, to give either the 7-endo-dig 1.60 or the 6-endo-dig 1.61 product (Scheme 1.41). It was found that the substituents on the distal phenyl ring can control the cyclisation pathway. If a strong electron-donating group is present in the para position the 6-endo-dig (1.61) pathway is favoured, if this group is removed then the 7-endo-dig product (1.60) predominates [13CEJ9795, 14JOC3452].

```
\text{R} = \text{H, OMe}
\text{R}^1 = \text{alkyl, aryl}
\text{R}^2 = \text{H, OMe, Cl, OPh, F, SMe, Me}
[13CEJ9795, 14JOC3452]
```

Scheme 1.41

Palladium(0) generated in situ has been utilised in the synthesis of polycyclic sultams by a novel tandem reaction. The ArPdBr species generated from 1-bromo-2-(cyclopropylidenemethyl)benzenes 1.62 undergoes carbopalladation with 2-alkynylbenzenesulfonamides 1.63 and rearrangement to a cyclopropyl-PdBr species (Scheme 1.42). The latter is intercepted by the sulfonamide function from which the product results with reductive elimination of Pd(0). However, it was expected that the cyclopropane ring would open under these conditions, but this pathway was not observed [17OCF14].
Scheme 1.42

Alkylation of the sulfonamide 1.64 in the presence of potassium carbonate in MeCN was found to facilitate the cyclisation to isothiazole 1.65 albeit in low yields (9%, Scheme 1.42). Use of the base without allyl bromide provided the isothiazole in high yields (78%) [09T3180]. Cobalt(0) was used to cyclise 1.66 in a Pauson-Khand reaction, affording the tricyclic sultam 1.67 (Scheme 1.43) [09T3180].

Scheme 1.43

1,2-Benzothiazepine 1,1-dioxide derivatives 1.68 were afforded in good to excellent yields (56 – 99%) from a Pd(II) catalysed reaction of 1-(2-alkynyl)benzenesulfonamide and 2-alkynylvinyl bromide (Scheme 1.44). Wu and co-workers suggest that the reaction proceeds via intermediate A, which after intramolecular insertion of a triple bond affords intermediate B. The latter then undergoes a C-N coupling to afford the 1,2-benzothiazepine 1,1-dioxide 1.68 (Scheme 1.44) [13JCD4410].
1.7 Aims of the Project

There is a remarkable gap in the literature in that no systematic study of the electrophilic cyclisation of dialkynols, specifically derivatives of 3-arylpenta-1,4-diyn-3-ols possessing a nucleophilic ortho substituent have been reported.

The objective of the present study was to redress this deficiency and to:

(i) Synthesise a range of 3-phenylpenta-1,4-diyn-3-ols having an ortho-N-linked sulfonamide function via addition of alkynyllithiums to methyl 2-(arenesulfonamido)benzoates. The compounds so obtained will have symmetrical terminating groups on the alkyne moieties.

(ii) Synthesise a range of 3-[2-(arenesulfonamido)phenyl]penta-1,4-diyn-3-ols having electronically and sterically dissimilar alkyne terminal groups via addition of alkynyllithiums or alkynyl-Grignard reagents to 1-[(2-arenesulfonamido)phenyl]prop-2-yn-1-ones.

(iii) Investigate the reactivity of N-substituted saccharins towards alkynyllithium reagents to access novel 3-(2-sulfamoylphenyl)penta-1,4-diyn-3-ols. These S-linked sulfonamides, isomeric to those prepared initially in (i) have effectively a chain-extension to the nucleophilic centre.

The compounds obtained from (i) – (iii) above will then be treated with a variety of electrophilic/alkynophilic activators [e.g. TsOH, I₂, ICl, Ag(I) and In(III) salts] as the subsequent cyclisations are anticipated to generate novel alkyne-linked heterocyclic rings, which would not be accessible by other means. The scope of these cyclisations will be investigated.
Chapter 2

Synthesis of

3-Arylpenta-1,4-diyn-3-ols
Chapter 2 Synthesis of 3-Arylpenta-1,4-diyn-3-ols

2.1 3-[2-(Arenesulfonamido)phenyl]-penta-1,4-diyn-3-ols

Many routes already exist to synthesise propargylic alcohols, such as 1-aryl- and 1,1-diarlyl-prop-2-yn-1-ols. Generally these involve the reaction of aryl aldehydes or aryl ketones (possessing either an aryl or alkyl substituent) with an alkynyl lithium or alkynyl magnesium halide. Various groups on the phenyl ring are tolerated in this reaction, including alkyl, amino, hydroxy, halogens and methoxy groups (Scheme 2.1) [13OL5222, 14OL5246, 14SC1924, 15AGE13711, 15OL5796, 17JOC11659, 18OL3202, 19AGE8898].

Other alkynyl organometallic reagents have been employed to generate secondary and tertiary propargylic alcohols [15MI201], for example alkynylzincs generated in situ from a dialkylzinc reagent (Me₂Zn or Et₂Zn). These reactions have been developed to provide enantioselective routes to alkynols, in the presence of a chiral auxiliary. Niwa and Soai varied the chiral auxiliary to optimise the ee and yields achieved, the β-amino alcohol ligand Y (A, Scheme 2.2) was found to be the most efficient with 99% yield and 34% ee (where R =
R$^1 = \text{Ph}$ [90J(P1)937]. Cozzi described additions of zinc alkynides to various ketones with the use of a modified salen ligand (L) affording enantioselectively tertiary alcohols (B, Scheme 2.2) [03AGE2895].

Scheme 2.2

There are also numerous examples of dialkynols, some of which have been known for decades, of particular interest are 3-phenylpenta-1,4-diyn-3-ols 2.1. Routes to these include the reaction of alkynyllithiums or alkynylmagnesium halides with aryl benzoates or aroyl chlorides (Scheme 2.3) [1921CB2520, 71JOC749, 13OL5222, 18MI78].

Scheme 2.3

However, to date there is only one example of a fully characterised 3-(2-pto-sylamidophenyl)penta-1,4-diyn-3-ol derivative 2.2 that was reported by Chan and co-workers (Scheme 2.4) [12CEJ6133]. No experimental details of how they obtained the 1-[(2-
tosylamido)aryl]but-2-yn-1,4-diol 2.3 from X were provided. We envisage that alcohol X was oxidised to the ynone, followed by addition of ethynylmagnesium bromide to afford 2.3.

![Scheme 2.4](image)

As described in Section 1.3, alkynes and to a lesser extent alkynols have been used extensively in electrophilic cyclisations to access a diverse array of heterocycles with a range of substituents. The use of alkynes and propargylamines to synthesise heterocycles has been reviewed [14COSII(4)412, 15SL1305, 16MI49730, 19AHC(127)1]. Therefore it is surprising that only one example of a 3-(2-p-tosylamidophenyl)penta-1,4-diyn-3-ol derivative has been described so far (2.2, Scheme 2.4). The latter was cyclised with a silver(I) salt to a 2,3-alkynylindole (Scheme 1.11) [12CEJ6133]. Previous work carried out by the group [16UP1] has shown that the synthesis of 3-(2-p-tosylamidophenyl)penta-1,4-diyn-3-ols can be carried out with ease.

Initially, the requisite 2-sulfonamido-benzoates were prepared by sulfonylation of methyl 2-aminobenzoate. Thus, a solution of the ester in DCM or CHCl₃ containing pyridine, was treated with the relevant sulfonyl chloride, and the mixture was stirred at room temperature overnight (Scheme 2.5). After an aqueous work up the products 2.4a – 2.4d (Table 2.1) were obtained in good to excellent yields, following recrystallisation from methanol. All compounds synthesised in this way were characterised by their IR, ¹H NMR spectra, and where appropriate, literature melting points.
Varying the nature of the R group on the phenylsulfonyl function will change the nucleophilicity of the sulfonamide nitrogen in 2.4. The nitro group being electron withdrawing will render the sulfonamide less nucleophilic, and therefore cyclisations with this substrate were predicted to be slower than the others. In contrast the methoxy group, which is electron donating, should enhance the nucleophilicity of the nitrogen centre thus promoting a more efficient cyclisation when the alkyne is exposed to an electrophile.

With the sulfonamides 2.4 to hand, their reactivity towards alkynyllithiums to afford dialkynols was explored, to date only the phenyl and n-butyl substituted 4-methylphenyl sulfonamido compounds 2.5a and 2.5c (R\(^1\) = Ph or C\(_4\)H\(_9\)) have been synthesised by the author [16UP1]. n-Butyllithium (3.5 equiv.) was added dropwise to a cold (-78 °C) solution of the appropriate acetylene (3.5 equiv.), to ensure complete reaction, in anhydrous THF. Excess alkynyllithium is needed to compensate for the deprotonation of the sulfonamide. A solution of the methyl 2-(arylsulfonamido)benzoate (1.0 equiv.) in anhydrous THF was added dropwise to the warm (-5 °C to 5 °C) solution of the alkynyllithium compound. After stirring for 1 h or until complete by TLC, the mixture was quenched with aqueous NH\(_4\)Cl and diluted with ethyl acetate (Scheme 2.6). Purification of crude products either by recrystallisation or by flash column chromatography afforded the corresponding dialkynols 2.5 – 2.8 in varying, generally high yields (Table 2.2).
Scheme 2.6

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Table 2.2 Yields of dialkynols 2.5 – 2.8. a = From 1-bromopropene and excess LDA, b = reaction with ethynylmagnesium bromide in warm (40 °C) THF
All of the dialkynol compounds 2.5 – 2.8 showed two characteristic signals in their $^{13}$C NMR spectra ($\beta$, $\gamma$, Table 2.2) corresponding to the acetylenic carbons. These are similar to the shifts reported by Komatsu et al. for the dialkynol 1,3,5-triphenylpenta-1,4-diyne-3-ol 2.9, in which the acetylenic carbons resonate at $\delta_C$ 89.1 ($\beta$) and 84.9 ($\gamma$) ppm and the quaternary benzylic C-OH carbon ($\alpha$) resonated at $\delta_C$ 65.7 ppm [88TL5157]. The disappearance of the ester methyl protons in the $^1$H NMR spectra further confirmed the formation of the dialkynols, as did the appearance of a singlet for the OH proton between $\delta_H$ 2.90 and 4.11 ppm.

The nitrophenylsulfonamides (entries 15 and 16, Table 2.2) provided the poorest yields of products presumably due to side reactions of the nitro group with the organolithium reagent. Nitro arenes are known to undergo ortho lithiation, [82ACR300] other side reactions can occur also with Grignard reagents and nitro groups [12OL5618].

Attempts to synthesise the terminal alkyne analogue 2.5I $R^1$ = H (entry 12, Table 2.2) involved addition of ethynylmagnesium bromide to 2.4a in warm (40 °C) anhydrous THF followed by heating under reflux. Unfortunately, the crude material obtained following aqueous work-up was a complex mixture which afforded no identifiable products.

Compound 2.8b (entry 18, Table 2.2) was shown by $^1$H NMR to be approximately 50% pure, unfortunately attempts at purification were thwarted, as it co-eluted with unreacted starting material. Methyl 2-(p-tosylamido)benzoate 2.4a was reacted with LiC≡CCH$_2$OMe, derived from methyl propargyl ether or with the dianion LiC≡CCH$_2$OLi derived from propargyl alcohol (entries 6 and 9 respectively, Table 2.2). Unfortunately, both acetylides failed to react and in each case only starting material was recovered. Evidently double addition of these acetylides to the ester function was not favoured. Formation of the 2-hydroxy-2-(3-methoxyprop-1-yn-1-yl)-cyclohexane-1-carboxylate 2.10 (A, Scheme 2.7) by preferential addition of the (3-methoxyprop-1-yn-1-yl)magnesium chloride to the ketone
moiety has been reported [17OL4980]. In a similar manner the dianion LiC≡CCH₂OLi reacted smoothly with the steroidal ketone 2.11 (B, Scheme 2.7) [08BAC1987].

Prop-1-yn-1-yllithium was generated in situ from treatment of 1-bromopropene with excess LDA in THF [92SC2997], as shown in Scheme 2.8. Addition of the ester 2.4a to the propynyllithium solution afforded dialkynol 2.5g in only 16% yield (entry 7, Table 2.2), this is the lowest yield achieved from acetylide addition to ester 2.4a (Table 2.2).

Ethoxyethynyllithium generated in situ from chloroacetaldehyde diethyl acetal and LDA (Scheme 2.9) [87JOC2332, 05MI254], also failed to provide the corresponding ethoxyalkynol 2.5h (entry 8, Table 2.2). Only a complex black mixture was obtained from the reaction, this could have been due to the unfavourable double addition to an ester moiety or the degradation of the acetylene.
Regrettably, lithiation of commercially available ethoxyacetylene (solution in hexanes) was also unsuccessful in affording the desired alkynol 2.5h. Many reactions have been reported with effective addition of ethoxyacetylene to ketones and aldehydes [06JA15106, 07JOC9736, 08JA13528, 12EJO5803, 12SL1675, 14AGE10747, 14OL1176].

Acyl chlorides are more reactive than esters towards nucleophiles due to the electron withdrawing chlorine, which in-turn makes the sp² carbon of the carbonyl group more electrophilic. Therefore a suitable acyl chloride may provide an alternative starting material for the dialkynols which could not be accessed from 2.4a. 2-(Tosylamido)benzoyl chloride 2.13 was synthesised from N-tosylantranilic acid as shown in Scheme 2.10 [11T5564].
2-(Tosylamido)benzoyl chloride was used in the reactions that had either failed or had provided some of the lower yielding products from ester 2.4a. Thus, reaction of the benzoyl chloride 2.13 with excess lithium (trimethylsilyl)acetylide provided dialkynol 2.5e in a substantially better yield (65%, Scheme 2.11) than from methyl N-tosylantranilate 2.4a (39%, entry 5, Table 2.2). It was thought that the acid chloride would react smoothly with the dianion LiC≡CCH₂OLi, derived from propargyl alcohol at the terminal carbon anion to afford the desired dialkynol 2.5i. However, the only product obtained from the reaction was readily identified as propynyl N-tosylantranilate 2.14 (Scheme 2.11), which is a novel compound.

Scheme 2.11

The $^{13}$C NMR signals of 2.14 showed the presence of an ester carbonyl rather than the quaternary sp$^3$ centre from a tertiary alcohol. Hradil previously reported the propargyl ester 2.15 (Figure 2.1), prepared from isatoic anhydride and HC≡CHCH₂ONa, for which the NMR ($^1$H and $^{13}$C) resonances are similar to these observed for 2.14 [13JHC528].
Yrones exemplified by structure 2.16 provide an interesting set of compounds, as they have been shown to cyclise in the presence of an iodine electrophile. Larock demonstrated that 1-(2-methoxyphenyl)prop-2-yn-1-ones having either a 3-alkyl- or a 3-aryl- substituent cyclised easily to 3-iodochromones with ICl to give mostly high yields (44 – 99%) (Scheme 2.12). They also reported the synthesis of 3-iodothiochromones and 3-iodoquinolin-4-ones via this procedure, again in high yields (Scheme 2.12) [06JOC1626].

Scheme 2.12

There are a plethora of routes to synthesise yrones and some of the more useful pathways are shown in Scheme 2.13 [19CRV11110]. A large number of examples provided are by the C-H bond insertion of a metal to a terminal alkyne and the subsequent coupling reaction with an acyl chloride (A, Scheme 2.13) [56JA1675, 82JOC2549, 75JOC131, 11AGE10448]. Other examples include; organometallic (alkynylmetal) addition to a Weinreb amide (B,
Scheme 2.13 [81TL3815], alkylnyl Grignard reagent addition to an acid anhydride (C, Scheme 2.13) [36JA1861], oxidation of a secondary propargyl alcohol (D, Scheme 2.13) [15MI107] or the Pd-mediated carbonylative coupling of a terminal acetylene and an aryl halide (E, Scheme 2.13) [03OL3057].

**Scheme 2.13**

Cyclisations of 1-[2-tosylamidophenyl]propynones 2.17 could offer a simple route to synthesise 3-iodo-1-tosyl-4-quinolones 2.18 of which there are currently no examples. Furthermore, it was envisaged that addition of a lithium acetylide would provide an entry to access unsymmetrical dialkynols 2.19, Scheme 2.14.

**Scheme 2.14**
Initially access to the ynones 2.17 utilised the Weinreb amide 2.20 (2-amino-N-methoxy-N-methylbenzamide) that was synthesised by acylation of $N,O$-dimethylhydroxylamine with isatoic anhydride in aqueous EtOH under basic conditions. Following work-up, flash column chromatography provided the Weinreb amide 2.20 in 50% yield (Scheme 2.15) [14CC12293].

The $^1$H NMR spectrum of 2.20 showed the appearance of two singlets corresponding to the methyl protons, indicating that isatoic anhydride unit was no longer intact. Subsequent $N$-sulfonylation of the Weinreb amide (2.20) was accomplished by treatment with TsCl in refluxing pyridine (Scheme 2.15). Following an acidic aqueous workup, the crude material was purified by flash column chromatography and trituration of the resulting oil with ether to afford the tosylated amide 2.21 in 81% yield [16JOC2930].

Scheme 2.15

The 1-arylpropynones 2.17 were synthesised simply by treatment of Weinreb amide 2.21 with an excess of alkynyllithium in THF at -78 °C to 0 °C for 1 h (Scheme 2.16). After this time the mixture was quenched with aqueous NH$_4$Cl. Isolation via EtOAc gave an orange oil which crystallised on trituration with ether. This crude product was washed with cold ether to afford the compounds in Table 2.3.
The $^1$H NMR spectra of ynones 2.17 matched those reported by Ramasastry et al. [16AGE7737]. The ynone $R^1 = C_3H_7$ (2.17B) is a novel compound and so was further confirmed by HRMS, that exhibited a molecular ion [M+H]$^+$ at m/z 342.1148 corresponding to C$_{19}$H$_{19}$NO$_3$S.

1-(2-Tosylamidophenyl)propynones 2.17 were the primary starting materials for the unsymmetrical dialkynols (2.19). The latter were obtained by two methods with the majority being synthesised by simple treatment with an excess of an alkynyllithium in THF for 1 h (Method A, Scheme 2.17). After this time the mixture was quenched with aqueous NH$_4$Cl. Isolation $via$ EtOAc gave the crude product which was purified either by recrystallisation or by flash column chromatography, to afford the novel compounds in Table 2.4 in generally high yields. Excess ethynylmagnesium bromide (0.5 M in THF) was added to a warm solution of 2.19 in anhydrous THF and refluxed until complete by TLC (Method B, Scheme 2.17). After this time the mixture was allowed to cool and quenched with aqueous NH$_4$Cl, isolation $via$ EtOAc gave the crude product, which was purified by flash column chromatography, to afford the novel compounds in Table 2.4
Scheme 2.17

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ynone</th>
<th>R¹</th>
<th>R²</th>
<th>Method</th>
<th>Unsymmetrical dialkynol</th>
<th>Yield (%)</th>
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<td>86</td>
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<td>86</td>
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<td>t-Bu</td>
<td>A</td>
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<td>Ph</td>
<td>H</td>
<td>B</td>
<td>2.19Ai</td>
<td>65</td>
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<td>C₃H₇</td>
<td>H</td>
<td>B</td>
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<td>C₃H₇</td>
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<td>2.19Cb</td>
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<td>2.19Cf</td>
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<td>4-MeOC₆H₄</td>
<td>H</td>
<td>B</td>
<td>2.19Ci</td>
<td>64</td>
</tr>
</tbody>
</table>

Table 2.4 Yields of unsymmetrical dialkynols 2.19. a = From 2-bromopropene and excess LDA

All the compounds 2.19 (Table 2.4) exhibited four carbon signals in the range δC 60 – 89 ppm corresponding to the acetylenic carbons and the quaternary C-OH signal between δC 65 – 66 ppm. Of particular note was that some of the acetylides which did not react with the ester 2.4a added smoothly to the ynones 2.17 (entry 3, 7, 8, 10 and 11, Table 2.4); (3-
methoxyprop-1-yn-1-yl)lithium (entry 3 and 10 Table 2.4) and ethynylmagnesium bromide (entry 7, 8, and 11 Table 2.4) provided good yields of products. No doubt smooth addition of the acetylide and Grignard reagent was facilitated by the less conjugated, less hindered carbonyl group in the ynone 2.17 compared to that in the ester 2.4a. The ready formation of 2.19 indicated that double addition and/or addition to an ester, of these acetylides, was unfavourable.

2.2 3-[2-(Sulfamoyl)phenyl]penta-1,4-diyn-3-ols

To date there are few aryl (di)alkynols in which the aryl ring is substituted with a primary, secondary or tertiary sulfamoyl group i.e. -SO₂NH₂, -SO₂NHR or -SO₂NR₂ respectively. The majority of known compounds have the alkyne moiety bonded to the same aromatic ring as the sulfonamide function e.g. 2.22 (via Cₛᵖ – Cₛᵖ² bond), rather than as a tertiary propargylic alcohol function (via Cₛᵖ – Cₛᵖ³ – Cₛᵖ² linkages) e.g. 2.23.

\[
\text{SO}_2\text{NHR}
\]

\[2.22\]

Compounds of the general structure 2.5 – 2.8 represent N-linked sulfonamides as described previously (Section 2.1). Isomeric to these are the S-linked sulfonamides 2.23 (2-sulfamoylphenyl dialkynols) which will be referred to as reversed sulfonamides (in some cases) throughout.

\[
\begin{align*}
\text{HO} & \text{NH} & \text{O}_2\text{S} \\
\text{R} & \text{R} & \text{R}
\end{align*}
\]

\[2.5 - 2.8\]

\[
\begin{align*}
\text{HO} & \text{HN} & \text{R}
\end{align*}
\]

\[2.23\]

\text{N-linked sulfonamides referred to as sulfonamides}

\text{S-linked sulfonamides referred to herein as reversed sulfonamides}
Pal et al. employed a Sonogashira cross-coupling to 2-iodo-N-methylbenzenesulfonamides, to give a range of 2-alkynyl benzenesulfonamides in high yields A, Scheme 2.18 [07JOC8547]. Wang and co-workers also utilised a Sonogashira coupling to synthesise a range of propargylic alcohols B, Scheme 2.18 [15OL242].

Scheme 2.18

2-Sulfamoylphenyl dialkynols could be potentially synthesised by the ring opening of o-sulfobenzoic anhydride with MeOH and subsequent halogenation with PCl5 [06JA11693] to obtain methyl 2-(chlorosulfonyl) benzoate. Subsequent reaction with an aromatic amine and DMAP would afford ester 2.24 [WO9912916]. Nucleophilic addition to the ester moiety would afford the target dialkynol 2.23 (Scheme 2.19).

Scheme 2.19
A drawback to this approach is the number of steps to provide dialkynol 2.23, as well as the cost of o-sulfobenzoic anhydride (£10.00 per g, Fluorochem). The anhydride can also be synthesised from saccharin, via hydrolysis-dehydration with H₂SO₄ [11SC1101]. However this process will add an extra step in the sequence. A more direct route to the corresponding 1,5-disubstituted-3-[2-(N-arylsulfamoyl)phenyl]penta-1,4-diyne-3-ols 2.23 would involve addition of an alkynyllithium to an N-substituted saccharin derivative 2.25 (Scheme 2.20).

![Scheme 2.20](image)

Surprisingly the reaction of organometallic reagents to saccharin derivatives has received almost no attention [03T7445, 10CM65]. The only report for many decades related to the reaction of N-phenylsaccharin with Grignard reagents (MeMgI, EtMgBr and PhMgBr) to afford the tertiary alcohol, from an addition, ring cleavage addition sequence as shown in Scheme 2.21 [52JCS1339].

![Scheme 2.21](image)

However, more recently, the reaction of saccharin with excess PhMgBr has been reported. The crude reaction mixture was subjected to treatment with acid (TsOH) to afford the cyclodehydration product, 3-phenyl-1,2-benzoisothiazole 1,1-dioxide (Scheme 2.22) [19ASC4495].
Earlier work by Oppolzer described the preparation of 3-alkyl-1,2-benzisothiazole 1,1-dioxides from reaction of saccharin with either methyllithium [90TL4117] or with t-BuLi [91TL4893] in THF at low temperature. No tertiary alcohols were observed from these reactions.

Initially a series of substituted saccharins were synthesised by either N-alkylation or N-arylation. For example, iodomethane was added dropwise to a solution of sodium saccharin in DMF, the mixture was stirred at 100 °C overnight (Method A, Scheme 2.23). After this time the reaction mixture was allowed to cool, quenched with water and the resultant precipitate was collected to afford 2.25A in a 63% yield [15CEJ5532].

For N-aryl saccharins a Chan-Lam-(Evans) coupling of saccharin with arylboronic acids in the presence of Cu(OAc)_2 and pyridine (Method B, Scheme 2.23) was employed to afford 2.25B – 2.25H (Table 2.5) in variable yields.
A proposed catalytic pathway for the Chan-Lam-(Evans) coupling reaction of saccharin and arylboronic acids is shown in Scheme 2.24 [17JA4769, 17OBC801]. First saccharin is deprotonated by pyridine, followed by complexation with the Cu(II) to give species X. Subsequent transmetallation with the arylboronic acid leads to the transfer of the aryl group from the boronic acid to the Cu(II) species and concomitant oxidation generated the copper(III) intermediate (Y). Reductive elimination of the N-substituted saccharin and sequential oxidation and ligand exchange regenerates the Cu(OAc)$_2$.

The pathway depicted in Scheme 2.24 is based upon the stabilities of intermediates in related Chan-Lam reactions as predicted by DFT calculations [17OBC801].
The constitution of all of the \( \text{N-} \)substituted saccharins \( \text{2.25} \) were confirmed by comparison of their m.p., \( \text{^1H} \) and \( \text{\textsuperscript{13}C} \) NMR spectra to those in the literature [15CEJ5532, 17SL2000]. The \( \text{N-} \)substituted saccharins \( \text{2.25} \) are all known compounds, with \( \text{2.25A, B and E – H} \) (entries 1, 2, 5, 7 and 8, Table 2.5) being synthesised \textit{via} a Chan-Lam coupling of the relevant aryl boronic acid and saccharin [15CEJ5532]. However, compounds \( \text{2.25C – D} \) (entries 3 and 4, Table 2.5) were prepared previously by a Pd-catalysed carbonylative cyclisation of \( \text{N-} \)aryl-2-iodobenzenesulfonamides [17SL2000]. Use of the Chan-Lam coupling therefore represents a new route to these \( \text{N-} \)aryl saccharins.

Attempted \( \text{N-} \)arylation of saccharin with thiophene-2-boronic acid gave none of the desired product \( \text{2.25F} \) (entry 6, Table 2.5). No doubt this failure stems from the propensity of thiophene-2-boronic acid to undergo protodeboronation under a variety of conditions [10JA14073]. On the other hand, coupling of thiophene-3-boronic acid to saccharin afforded \( \text{2.25G} \) in 65% yield with a m.p. 170 – 172 °C (literature m.p. 173 – 175 °C) [15CEJ5332]. 2-(2-Thienyl)saccharin \( \text{2.25F} \) is a known compound but was prepared \textit{via} an oxidative (Selectfluor) copper-catalysed (CuCl) amination reaction of thiophene with saccharin Scheme 2.25 [15MI1354].
Scheme 2.2

With a series of N-substituted saccharins (2.25) now available, their reactivity towards a variety of alkynyllithiums was investigated. Thus, n-butyllithium (2.3 equiv.) was added slowly to a cold (-78 °C) solution of the appropriate acetylene (2.3 equiv.) in anhydrous THF. A solution of the saccharin derivative 2.25 (1.0 equiv.) in anhydrous THF was added slowly to the cold (-5 °C to 5 °C) lithium acetylide solution. After stirring for 1 h, the mixture was then quenched with aqueous NH₄Cl and diluted with EtOAc (Scheme 2.26). Purification of crude products either by recrystallisation or by flash column chromatography afforded the novel compounds 2.23Aa – Hb (Table 2.6) in varying yields.
Scheme 2.26

Table 2.6 Yields of reversed sulfonamide dialkynols 2.23
The formation of the reversed sulfonamides **2.23Aa – Hb** can be rationalised as shown in Scheme 2.27. Initial nucleophilic addition of a lithium acetylide unit to the amide carbonyl group results in ring opening to afford ynone **2.26**, which possess a sulfonamide-stabilised anion. Facile addition of the second lithium acetylide species will then take place. Finally, an aqueous acidic work up will lead to the formation of the corresponding dialkynol (**2.23Aa – Hb**).

**Scheme 2.27**

All reversed sulfonamides **2.23Aa – Hb** showed two characteristic signals in their $^{13}$C NMR spectra (β, γ, Table 2.6) corresponding to the acetylenic carbons, which are similar to that seen for the dialkynols **2.5 – 2.8** (Table 2.2). Of note is the downfield shift of the β carbon in the TMS substituted compounds **2.23Ae, 2.23Be** and **2.23De** (entries 3, 7 and 15, Table 2.6). Trimethyl(phenylethynyl)silane has been reported to have similar $^{13}$C shifts (Scheme 2.28) to those seen in the TMS substituted reversed sulfonamides **2.23Ae, 2.23Be** and **2.23De**, this deshielding of the β-carbon has been attributed to the resonance form shown in Scheme 2.28 [89MRC1112].

**Scheme 2.28**
Interestingly these sulfamoyl-substituted dialkynols or reversed sulfonamides (2.23Aa – Hb) have very different $^1$H NMR spectra to those of the 2-tosylamido dialkynols $\text{2.5} – \text{2.8}$ derived from the $N$-tosyl anthranilate. The $^1$H NMR spectra in Figure 2.2 (2.5a and 2.23Ba) are illustrative of the striking difference between the two species. The most deshielded proton in 2.5a gives rise to the apparent doublet at $\delta_H$ 7.91 ppm (black star, red spectrum, Figure 2.2) whereas in the reversed sulfonamide 2.23Ba the same signal is substantially deshielded and absorbs at $\delta_H$ 8.44 ppm (black star, blue spectrum, Figure 2.2). In both cases the low field signal originates from the 2-$H$ proton i.e. ortho to the dialkynylmethanol moiety. The assignments of both these (black stars) signals was established from consideration of the 2D NMR spectra ($^1$H – $^1$H COSY, HSQC and HMBC) of both compounds.

![Figure 2.2 400 MHz $^1$H NMR spectral comparison of 2.5a and 2.23Ba in CDCl$_3$](image)

The HMBC spectrum of 2.5a provided definitive confirmation that the apparent doublet at $\delta_H$ 7.91 ppm (black star, red spectrum, Figure 2.2) corresponds to 2-$H$ because of a correlation ($^3J$ coupling) with the quaternary sp$^3$ C-OH at $\delta_C$ 66.27 ppm (Figure 2.3). The $^1$H – $^1$H COSY spectrum (Figure 2.3) of 2.5a enabled identification of the tosyl group protons. Thus, the two-proton doublet at $\delta_H$ 7.79 ppm (red spectrum, pink star, Figure 2.2) can be assigned to the protons ortho to the sulfone function. The COSY exhibits a cross peak between the doublet ($\delta_H$ 7.79 ppm) and the partially overlapped doublet at $\delta_H$ 7.01 ppm. The latter signal is coupled to the methyl protons ($\delta_H$ 2.28 ppm) and consequently corresponds to the meta Ar-$H$ protons (Figure 2.3).
Figure 2.3 2D NMR spectra (HMBC and COSY) of 2.5a
In the $^1$H NMR spectrum of the reversed sulfonamide 2-(N-tolylsulfamoyl)dialkynol 2.23Ba, the doublet at $\delta_H$ 6.90 ppm (blue spectrum, pink star, Figure 2.2) corresponds to the two tolyl ring protons ortho to the NH function. The $^1$H – $^1$H COSY spectrum (Figure 2.4) revealed the Ar-H protons ortho to the Ar-Me group absorb at $\delta_H$ 6.97 ppm, confirming the assignment of the pink starred signal (blue spectrum, Figure 2.2).

Most striking in the $^1$H NMR spectrum of 2.23Ba (blue spectrum, Figure 2.2) is the low field doublet of doublets at $\delta_H$ 8.45 ppm (black star, blue spectrum, Figure 2.2). At first it was thought the signal corresponded to the 5-H proton (ortho to the electron withdrawing sulfamoyl group, -SO$_2$NHTolyl). However this was dismissed by examination of the HMBC spectrum (Figure 2.4) which revealed an interaction ($^{(3)}J$) between the 2-H proton and the quaternary sp$^3$ carbon C-OH ($\delta_C$ 67.05 ppm). The pronounced downfield shift of the 2-H in 2.23Ba (black star, blue spectrum, Figure 2.2) is most unusual and is observed throughout the reversed sulfonamide series 2.23Aa – Hb. Presumably this deshielding originated from the proximity of the 2-H to one of the anisotropic alkyne units. Protons situated above alkene or alkyne moieties are known to experience deshielding and the origins of this have been reviewed [14MI308].
Figure 2.4 2D NMR spectra (COSY and HMBC) of 2.23Ba
Interestingly the X-ray crystal structure of 2.23Bb (Figure 2.5) revealed that the 2-\(H\) proton is located (in the crystal) near one of the alkyne functions. Of course, it must be recognised that the conformation may differ in solution.

![2.23Bb](image)

**Figure 2.5** X-Ray crystal structure of 2-(6-hydroxyundeca-4,7-diyn-6-yl)-\(N\)-(p-tolyl)benzenesulfonamide 2.23Bb

Lithium ethoxyacetylide and the dianion LiC≡CCH\(_2\)OLi, from propargyl alcohol both failed to react with \(N\)-(p-tolyl)saccharin (entry 9 and 10, Table 2.6). In the case of the ethoxyacetylide entry 10 (Table 2.6) a very complex mixture was obtained, whereas with the dianion (entry 10, Table 2.6) only starting material was recovered. These observations support the previous findings that the double addition of these lithium acetylides (LiC≡CCH\(_2\)OLi and LiC≡COEt) is not favourable (cf. Section 2.1, page 51).
2.3 Base-Mediated 5-Exo-Dig Cyclisation of 3-[2-(Tosylamido)phenyl]penta-1,4-diyn-3-ols

As the addition of ethynylmagnesium bromide to ester 2.4a, did not yield any tractable products (entry 12, Table 2.2), attempts to access the parent dialkynol 2.5l ($R^1 = H$) then focused on removal of the TMS groups from dialkynol 2.5e, which was envisaged to proceed straightforwardly (Scheme 2.29).

Thus, 1,5-bis(trimethylsilyl)-3-[2-(tosylamido)phenyl]penta-1,4-diyn-3-ol was stirred in cold MeOH with the slow addition of aqueous 5M NaOH (2 equiv.). After dilution with water and isolation via EtOAc, attempts to purify the mixture by column chromatography produced numerous decomposition products and only one identifiable fraction was isolated in a very low yield (2%). The $^1$H NMR spectrum (Figure 2.6) of this material showed the presence of an alkene moiety, due to the appearance of two doublets ($^2J = 2.0$ Hz) each integrating for one proton at $\delta_H$ 5.90 and 5.47 ppm (Figure 2.6).

After careful examination of both 1D and 2D NMR spectra ($^1$H – $^1$H COSY, HSQC and HMBC) the unknown product was characterised as 3-ethynyl-2-methylene-1-tosyl-2,3-dihydroindol-3-ol 2.27 a hitherto unknown compound.
The doublets at $\delta_H$ 5.92 and 5.48 ppm have similar shifts to those reported by Chan and co-workers, for a related indoline (2.28, Scheme 2.30), prepared by Ag(I)-mediated cyclisation of an o-(tosylamido)phenylpropynol, with singlets at $\delta_H$ 5.78 and 5.14 ppm [12JOC7166].

Initially it was thought that the formation of 2.27 could be due to the acidity of the silica used in flash column chromatography, and can be rationalised by protonation of one of the alkyne units to give the vinylic carbocation 2.29, which is susceptible to attack from the sulfonamido group, with cyclisation to afford 3-ethynyl-2-methylene-1-tosyl-2,3-dihydroindol-3-ol 2.27 (Scheme 2.31). No improvement in yield was observed if the reaction mixture (crude desilylation) was acidified (AcOH) or heated with AcOH. Unfortunately attempts to further purify the material from acidic reactions was unsuccessful, producing a complex mixture of products. Due to the difficulty in purification, no other acid catalysts were explored.
As acid did not promote cyclisation of the expected terminal dialkynol 2.5l to 2.27 as anticipated, it was thought that the cyclisation must occur during removal of the TMS groups. Removal of the TMS groups from 2.5e was again attempted, but a large excess of aqueous 5M NaOH (28.3 equiv.) was used. After an aqueous workup the $^1$H NMR spectrum showed that crude material was indeed the desired 1-tosylindoline 2.27, moreover the conversion was quantitative. Consequently, the cyclisation is base catalysed.

It is not known whether the cyclisation proceeds with initial desilylation (pathway A, Scheme 2.32) or if this step follows formation of the indoline ring (pathway B, Scheme 2.32). Therefore, the proposed mechanisms for both the TMS protected dialkynol and the deprotected dialkynol are shown in Scheme 2.32. In both cases the sulfonamide nitrogen will be deprotonated under basic conditions and can then undergo nucleophilic attack on the triple bond to cyclise via a 5-exo-dig pathway affording 2.27.
This novel base-mediated indoline ring synthesis was investigated further. Replacement of the alkyne terminal groups was explored (Scheme 2.33). Thus, 2.5a and 2.5b were subjected to basic conditions to investigate whether internal alkynes would also cyclise. Unfortunately only starting material was recovered from these reactions, suggesting that either the presence of a silyl moiety or a terminal alkyne group is a necessary prerequisite.

**Scheme 2.33**

Literature examples of purely base-mediated cyclisations onto pendant alkynes are scarce, and of relevance is the 5-exo-dig cyclisation of 2-alkynylanilines to afford mostly indoles (Scheme 2.34). Knochel and co-workers synthesised a variety of indoles and related ring-fused derivatives, it was found the reaction worked with a range of bases but KH or KOTBu were used in varying ratios (A, Scheme 2.34) [00AGE2488]. Sodium hydroxide was used to promote the base-mediated cyclisation of 2-alkynylanilines affording a range of indoles in
high yields (74 – 91%) (B, Scheme 2.34). However the conditions used were rather harsh [08SL3006, 11JOC3416]. Sanz et al. also observed the deprotection of the silyl groups when o-trimethylsilylethynylanilides were used (C, Scheme 2.34), affording 2-unsubstituted 4-halo-1H-indoles (R = H). They did not allude to the point of the desilylation step in the cyclisation [11JOC3416].

Scheme 2.34
With this novel pathway to indoline 2.27 it was envisioned that previously synthesised unsymmetrical dialkynols 2.19Ai, 2.19Bi and 2.19Ci may also undergo this base mediated 5-exo-dig cyclisation, Scheme 2.35.

![Scheme 2.35](image)

In order to verify this proposal, a range of other TMS-substituted unsymmetrical dialkynols 2.19Ae, 2.19Be and 2.19Ce (Scheme 2.33) were synthesised by addition of Li-C≡C-TMS to the appropriate ynone 2.17A – C. The TMS-dialkynols were obtained in excellent yields as oils; examination of the crude products’ $^1$H NMR spectra revealed trace amounts of the indolin-3-ols. Consequently, the dialkynols 2.19Ae, 2.19Be and 2.19Ce were not purified further and carried forward directly for the base-catalysed cyclisations. The desilyldialkynols (Scheme 2.17, Table 2.4, page 59) were prepared by addition of ethynylmagnesium bromide (0.5 M in THF) to the appropriate ynone 2.17A – C (Scheme 2.36).

![Scheme 2.36](image)

(i) THF, 40 °C to Δ; (ii) n-BuLi (2.1 equiv.), THF, -78 °C to r.t.
Base-mediated cyclisations of the unsymmetrical dialkynols \(2.19\text{Ai} – 2.19\text{Ci}\) and \(2.19\text{Ae} – 2.19\text{Ce}\) was explored (Scheme 2.37). The outcomes from these cyclisations are collated in Table 2.7.

![Scheme 2.37](image)

**Table 2.7** Yields of the base mediated cyclisation to \(2.27\) and \(2.30\). *By \(^1\text{H} \text{NMR})*

<table>
<thead>
<tr>
<th>Entry</th>
<th>(R^1)</th>
<th>Dialkynol</th>
<th>Time (h)</th>
<th>Base equiv.</th>
<th>Product</th>
<th>Yield (%)</th>
<th>(\delta_c = \text{CH}_2) (ppm)</th>
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<td>28.3</td>
<td>2.27</td>
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<td>11.2</td>
<td>2.30A</td>
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<tr>
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<td>Ph</td>
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<td>59.5</td>
<td>2.30A</td>
<td>70*</td>
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<tr>
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<td>(C_3H_7)</td>
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<td>2.30B</td>
<td>62</td>
<td>101.77</td>
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<tr>
<td>5</td>
<td>(C_3H_7)</td>
<td>2.19Bi</td>
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<td>5.0</td>
<td>2.30B</td>
<td>91</td>
<td>102.07</td>
</tr>
<tr>
<td>6</td>
<td>4-MeOC_6H_4</td>
<td>2.19Ce</td>
<td>24</td>
<td>22.9</td>
<td>2.30C</td>
<td>40</td>
<td>102.07</td>
</tr>
<tr>
<td>7</td>
<td>4-MeOC_6H_4</td>
<td>2.19Ci</td>
<td>24</td>
<td>60.4</td>
<td>2.30C</td>
<td>77</td>
<td></td>
</tr>
</tbody>
</table>

Table 2.7 indicates that in some cases a large excess of base was used to effect the ring closure. Generally, sufficient aqueous 5M NaOH was added to a methanolic solution of the dialkynol until TLC indicated that formation of the product had commenced or was complete.

The quantitative yield achieved from entry 1 (Table 2.7) in comparison to the other entries may indicate that the TMS group exerts a stabilising influence upon the cyclisation intermediate (anion), by the \(\alpha\)-effect of the silyl group [93JOC1778, 94JA8304]. However this was not the case with the other silyl dialkynols and in general the terminal alkyne
derivatives produced better yields, with exception of 2.19Ai (entry 3, Table 2.7). This difference is probably due to the difficulties in purification of the indoline 2.30A from this substrate compared with the reaction of its TMS analogue 2.19Ae (entry 2, Table 2.7).

All 2-methyleneindolines 2.27 and 2.30A – C showed two characteristic doublets in the region of $\delta_H 5.80 - 5.90$ ppm and $5.41 - 5.47$ ppm with a geminal coupling of $^2J = 2.0 - 1.7$ Hz, corresponding to the alkene protons.

It is noteworthy that the 3-alkynyl-2-methylene-1-tosylindolin-3-ols 2.27 and 2.30A – C are all novel compounds and thus represent the ‘missing’ examples in the series below (Scheme 2.38). Chan et al. synthesised the 3-phenyl- and 3-methyl- substituted indolin-3-ols from alkynols with the use of Ag(I) catalysis [12JOC7166]; the phenyl analogue (R = Ph) was also obtained in a poor yield with a Au(I) catalyst (A, Scheme 2.38) [15JA8912]. Ramasastry and co-workers could not access the 3-allylindoline 2.31 (R = H) but the benzylidene indolinol (R = Ph) was generated from a Ag(I) mediated cyclisation (B, Scheme 2.38) [16AGE7737].

\[ \text{Scheme 2.38} \]
2.4 Silver(I) Catalysed 5-Exo-Dig Cyclisation of 3-[2-(Tosylamido)phenyl]penta-1,4-diyn-3-ols

Many cyclisations of alkynes reported in the literature use silver(I) salts due to their affinity for triple bonds, the exploitation of this affinity has been reviewed numerous times [08CRV3174, 15CSR8124, 19AHC(127)1, 19MI1]. Silver has the electronic configuration [Kr]4d^{10}5s^{1}. The alkynophilicity of Ag(I) can be explained by invoking σ-overlap of a vacant orbital on the metal with the C≡C π-system (M ← L) with simultaneous, but weaker, back-donation from a silver 4d orbital to an alkyne π* orbital (M → L). Overall, the decrease in the electron density in the triple bond (with a decrease in bond order) renders it susceptible to nucleophilic attack. Detailed discussion of the nature of alkyne-metal π-complexation for silver and related metals is available. The Dewar-Chatt-Duncanson (DCD) and Metallacyclopropene models have been used to rationalise Ag(I)-alkyne interactions with an alkyne (Scheme 2.39) [14MI134, 15CSR8124, 19MI1]. Alkynophilicity has also been attributed to electrostatic forces between the metal salt and the triple bond [07AGE3140, 04JCP3134].

![Scheme 2.39](image)

Some examples in which silver(I) salts have been used to catalyse the cyclisation of alkynes to various heterocycles are shown in Scheme 2.40. 4-Hydroxyquinoline2(1H)-ones can be synthesised by the Ag(I) catalysed intramolecular rearrangement of 4-alkylidene-3,1-benzoazin-2-ones generated in situ form 2-alkynylanilines in the presence of CO₂ (A, Scheme 2.40) [13OL3710]. Hao et al. accessed pyrrolo[1,2-a]indoles from the silver(I) catalysed reaction of a variety of propargyl alcohols and 3,5-disubstituted indoles in varying yields (32 – 96%). It was found that the reaction pathway proceeded via two different routes, for secondary alcohols C2-propargylation followed by 5-endo-dig cyclisation, whilst with tertiary alcohols a C2-allenlylation was followed by a 5-endo-trig cyclisation (B, Scheme 2.40) [10ASC3215]. 3-Substituted-1,2-benzothiazines were obtained from the Ag(I)
mediated cyclisations of \( o \)-\((1\text{-alkynyl})\)benzenesulfonamides in high yields 75 – 80\% (C, Scheme 2.40) [12TL6577].

A selection of conditions were evaluated with dialkynol 2.5a to investigate its reactivity towards silver(I) and its potential for cyclisation, by activating the alkyne unit towards intramolecular nucleophilic attack from the sulfonamide nitrogen Scheme 2.41.

(i) AgOTf (5 mol \%), PhMe, 90 °C, 2 h
(ii) AgOTf (10 mol \%), DCM, r.t., 2.5 h
(iii) AgOAc (5 mol \%), MeCN, \( \Delta \), 21 h
(iv) AgNO\(_3\) on silica (5 mol \%, 10 \% w/w), MeCN, \( \Delta \), 18 h

Scheme 2.41
Reactions of the dialkynol 2.5a with either AgOTf 5 mol % in PhMe (i), or with AgOTf 10 mol % in DCM (ii), provided only a complex mixture of products (i, Scheme 2.41) or recovery of starting material (ii, Scheme 2.41) respectively. On the other hand, AgOAc (5 mol %) in MeCN (iii, Scheme 2.41) resulted in a more successful outcome and provided a quantitative yield of the novel indole 2.32a as a brown oil. The structure of 2.32a was established from its NMR spectra, which is discussed on page 90 (Figure 2.10). Treatment of 2.5a with AgNO₃ on silica (5 mol %) in MeCN (vi, Scheme 2.41) followed a different course to give (Z)-2-benzylidene-3-(phenylethynyl)-1-tosylindolin-3-ol 2.33a in a quantitative yield. The constitution of the indol-3-ol 2.33a was established principally from its ¹H spectrum which exhibited broadened doublets at δH 7.86 and 7.54 ppm corresponding to the 4-H and 7-H protons respectively (Figure 2.7). The signals for these protons were assigned from the HMBC spectrum. The 7-H proton exhibits an interaction with the 7a carbon. The benzylidene proton (blue star, Figure 2.7) absorbs at δH 6.99 ppm, however it overlaps with the tolyl ring protons.

![Figure 2.7 400 MHz ¹H NMR spectrum of (Z)-2-benzylidene-3-(phenylethynyl)-1-tosylindolin-3-ol 2.33a in CDCl₃](image)

Confirmation of the stereochemistry of (Z)-2-benzylidene-3-(phenylethynyl)-1-tosylindolin-3-ol 2.33a was established by the NOESY spectrum. Figure 2.8 shows the energy minimised Chem3D structure of 2.33a and its likely conformation. This structure reveals that the p-tolyl group is by virtue of attachment to the tetrahedral sulfone unit, inclined towards the C-3 phenylethynyl group. There is a through-space interaction of the phenylethynyl group ortho-
protons and the methine proton (**blue star**, interaction Z, Figure 2.8). Another means by which the NOESY spectrum confirmed the (Z)-stereochemistry was the absence of a through-space interaction of the phenyl groups from the benzylidene moiety and the PhC≡C- unit, which would be consistent with (E)-stereochemistry.
Figure 2.8 Chem 3D structure, NOESY and COSY spectra of 2.33a
Chan and co-workers also found that when 1-[2-(tosylamino)phenyl]prop-2-yn-1-ol was treated with AgOAc in MeCN, 2-benzylidene-3-phenyl-1-tosylindolin-3-ol was obtained as the (Z)-stereoisomer exclusively (Scheme 2.42) [12JOC7166].

It was of interest to investigate the course of the Ag-mediated dialkynol cyclisation when the terminal phenyl group in 2.5a was replaced by alkyl groups. Thus, 6-(2-p-tosylamidophenyl)undeca-4,7-diyn-6-ol 2.5b was subjected to the treatment with AgNO$_3$ on silica (Scheme 2.43).

Unfortunately these conditions provided only a small amount of 4-(pent-1-yn-1-yl)-2-propylquinoline 2.35b (6%). Formation of the latter is likely promoted by the Brønsted acidity of the silica rather than the Ag(I) salt (Scheme 2.44). The cyclisation of unsubstituted 1-(2-aminophenyl)propynols with PPTS to afford 2,4-disubstituted quinolines was also found to occur by Kumar et al. (page 33, Scheme 1.26). Consequently, AgNO$_3$ was not used for any further cyclisations.
The $^1$H NMR spectrum of 2.35b (Figure 2.9) exhibits a one proton singlet at $\delta_H$ 7.36 ppm corresponding to the C-3 position. Other features of 4-alkynylquinoline spectra are discussed in more detail in Section 3.1.

![Figure 2.9 400 MHz $^1$H NMR spectrum of 2.35b in CDCl$_3$](image)

The formation of 2.35b from 2.5b and AgNO$_3$-silica is outlined in the proposed mechanism below (Scheme 2.44). In a Meyer-Schuster type reaction, initial loss of water generates the propargylic/allenic carbocation 2.36 that is susceptible to attack from water to afford an enone. Cyclisation by attack of the sulfonamide nitrogen ensues. Aromatisation by elimination of water and subsequently TsOH affords quinoline 2.35b.

![Scheme 2.44](image)

Due to the failure of AgNO$_3$-silica to promote efficient cyclisations of the dialkynols 2.5a – b, attention shifted to the use of AgOAc in refluxing MeCN, which proved effective for cyclisation of 2.5a to the benzylic alcohol 2.32a (iii, Scheme 2.41). Thus dialkynols 2.5a – k
were subjected to AgOAc in refluxing MeCN (Scheme 2.45). The results of these reactions are collated in Table 2.8.

![Scheme 2.45](image)

Table 2.8 Yields from the AgOAc cyclisations of 2.5a – k to 2.32a – k. a, b and c other products were isolated.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>Dialkynol</th>
<th>Time (h)</th>
<th>Indole</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>2.5a</td>
<td>19</td>
<td>2.32a</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>C₃H₇</td>
<td>2.5b</td>
<td>1.5</td>
<td>2.32bₐ</td>
<td>62ₐ</td>
</tr>
<tr>
<td>3</td>
<td>4-MeOC₆H₄</td>
<td>2.5c</td>
<td>21</td>
<td>2.32c</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>TMS</td>
<td>2.5e</td>
<td>19</td>
<td>2.32eₗ</td>
<td>0ₗ</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>2.5g</td>
<td>21</td>
<td>2.32g</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>t-Bu</td>
<td>2.5j</td>
<td>21</td>
<td>2.32jₗ</td>
<td>0ₗ</td>
</tr>
<tr>
<td>7</td>
<td>(CH₃)C=CH₂</td>
<td>2.5k</td>
<td>21</td>
<td>2.32k</td>
<td>0</td>
</tr>
</tbody>
</table>

Whilst the dialkynol 2.5a provided the indole 2.32a quantitatively and 2.5b also gave the corresponding indole (62%) other products were isolated from this and some of the other substrates (entries 4 and 6) and these are discussed subsequently.

The ^1H spectrum of 2.32a (Figure 2.10) exhibited a doublet at δ_H 6.95 ppm integrating for one proton with a geminal coupling constant of 2_J = 7.1 Hz, corresponding to the benzylic proton. The ^3H – ^1H COSY showed an interaction of the benzylic proton and the OH proton at δ_H 5.19 ppm.
Figure 2.10 400 MHz $^1$H NMR spectrum of phenyl[3-(phenylethynyl)-1-tosyl-1H-indol-2-yl]methanol 2.32a in acetone-$d_6$
Resonances for the benzylic and OH protons ($\delta_H$ 6.95 and 5.19 ppm, $^2J = 7.1$ Hz) in 2.32a are different to those reported ($\delta_H$ 6.30 and 4.72 ppm, $^2J = 11.84$ Hz) by Chan et al. for 2.37 (Scheme 2.46) [12JOC7166]. On the other hand, the benzylic CH(OH) carbon resonance ($^{13}$C NMR) is nearly identical; $\delta_C$ 68.4 ppm for 2.32a and $\delta_C$ 68.6 ppm for 2.37. The downfield shift of the CH proton (benzylic) in the $^1$H spectrum of 2.32a is probably due to the anisotropic deshielding effect of the adjacent triple bond.

Scheme 2.46

A reasonable mechanism for the formation of indoles 2.32a–b is shown in Scheme 2.47. Coordination of silver(I) to the triple bond will form the $\pi$-complex (metallacycloprenenium ion) which is susceptible to attack by the nucleophilic sulfonamide function and will cyclise accordingly, via a 5-exo-dig pathway. Following protodeargenation (loss of silver by attack of a proton) and protonation of the alcohol, dehydration (E1) will lead to the carbocation 2.38. Subsequent hydration of the alkene moiety and aromatisation will afford the corresponding 1-tosylindole 2.32a–b.
Flash column chromatography of the crude material from the reaction of 6-(2-p-tosylamidophenyl)undeca-4,7-diyne-6-ol 2.5b with AgOAc afforded three products (fractions A, B and C in order of increasing polarity). The lowest yielding being 8% (fraction B), which was readily identified as 4-(pent-1-yn-1-yl)-2-propylquinoline 2.35b. The $^1$H NMR spectra of the fastest running fraction A (red spectrum, Figure 2.11) and slowest eluting fraction C from the column were similar (blue spectrum, Figure 2.11).

The $^1$H and $^{13}$C NMR spectra of fraction A confirmed the presence of a pentynyl substituent and a 1-tosylindole system. Fraction A, exhibited a doublet (signal a) at $\delta_H$ 6.99 ppm ($J = 15.8$ Hz) and a doublet of triplets (signal b) at $\delta_H$ 6.79 ppm ($J = 15.8$ and 6.5 Hz). Both chemical shifts and signal multiplicities were indicative of trans-alkene protons, in the case of signal b, additional coupling to an adjacent methylene group. When taken in conjunction with the integrations and multiplicities of the aliphatic proton signals these data indicated the presence of a but-1-enyl group i.e. $\text{CH} = \text{CHCH}_2\text{CH}_3$ unit. The absence of exchangeable protons was confirmed by addition of D$_2$O (red spectrum, Figure 2.12). Therefore the constitution of fraction A was established as $(E)$-2-(but-1-en-1-yl)-3-(pent-1-yn-1-yl)-1-tosyl-1H-indole 2.39.

Fraction C provided the major product from the reaction and the presence of a 1-tosylindole core together with a pentynyl substituent was readily confirmed from the $^1$H and $^{13}$C NMR spectra. However, the side chain in fraction C was different to that of fraction A and gave
rise to a series of complex signals and splitting patterns. Discounting the aromatic signals the most downfield signal absorbed at $\delta_H 5.51$ ($J = 10.8, 7.2 \text{ Hz}$) as a doublet of triplets (x) corresponding to one proton. A higher field signal absorbed at at $\delta_H 3.72 \text{ ppm}$ as a doublet ($J = 10.8 \text{ Hz}$) (signal y) integrating for one proton.

Although no signals disappeared upon addition of D$_2$O to fraction A (red spectrum, Figure 2.12) confirming the structure of 2.39. In fraction C however, the doublet of triplets (signal x) collapsed to a triplet and the doublet (signal y) disappeared completely (blue spectrum, Figure 2.12), so indicating that the side chain contained a -CH(OH)CH$_2$- moiety. These data and the remaining aliphatic proton signals established the presence of a -CH(OH)CH$_2$CH$_2$CH$_3$ unit, so confirming that fraction C was 1-[3-(pent-1-yn-1-yl)-1-tosyl-1H-indol-2-yl]butan-1-ol 2.32b.
The cyclisation products from treatment of 2.5b with AgOAc were thus the novel 3-alkynylindoles 2.32b and 2.39 and the 4-alkynylquinoline 2.35b (Scheme 2.48).

As with the formation of the 2-(α-hydroxyalkyl)indoles 2.32 (Scheme 2.47) a possible mechanism for the generation of the 2-buten-1-ylindole 2.39 (Scheme 2.49) involves initial coordination of silver(I) to the triple bond, forming the π-complex 2.40 which is then attacked by the nucleophilic sulfonamide function and intramolecular cyclisation via a 5-exo-dig pathway. Subsequent protodeargenation and protonation of the alcohol, followed by dehydration will lead to the highly delocalised carbocation 2.41. Deprotonation of the aromatic species 2.42 will afford alkene 2.39. Elimination from 2.42 occurs stereospecifically to afford the least sterically hindered (E)-alkene. In the case of the quinoline 2.35b its formation proceeds by a 6-endo-dig cyclisation of the π-complex 2.40 and loss of water to
form the quinolinium salt 2.43, which will facilitate displacement of tosyl the group to afford 2.35b (Scheme 2.49).

Scheme 2.49

The reaction of the dilalkynol 2.5j with AgOAc in MeCN (entry 6, Table 2.8) did not afford the expected indole 2.32j Scheme 2.50. After careful consideration of the 1D (1H and 13C) and 2D (HSQC, HMBC, NOESY) NMR spectral data of the product, its structure was found to be the (Z)-3-(3,3-dimethylbut-1-yn-1-yl)-2-(2,2-dimethylpropylidene)-1-tosylinolin-3-ol 2.33j (Scheme 2.50).

Scheme 2.50

The signals of interest in the 1H spectrum of 2.33j are the 4-H aromatic proton and methine proton. The 4-H proton for 2.33j absorbs at δH 7.67 ppm as a doublet, whereas in the fully aromatic indole 2.32a 4-H is deshielded and absorbs at δH 8.20 ppm. The methine proton in
tosylindolin-3-ol 2.33j absorbs at δH 6.08 ppm as a singlet. However, it would be expected that the latter signal would be a doublet if the product from 2.5j were the indole derivative 2.32j, due to coupling of the methine proton with the OH moiety. Another indication that the product was the 2-(2,2-dimethylpropylidene)indoline 2.33j accrued from comparison with the 13C spectra of indole alcohols 2.32a and 2.32b. These latter compounds exhibited signals for the benzylic side-chain [ArCH(OH)R] carbons at δC 68.38 and 68.74 ppm respectively. No similar resonance was observed for 2.33j. The alkylidene carbon signal absorbed at δC 138.58 ppm as confirmed by a correlation in the HMBC spectrum (Figure 2.13) with the alkene proton signal at δH 6.08 ppm. These data confirmed that the C-2 side chain is sp² rather than sp³ hybridised.
Figure 2.13 400 MHz $^1$H NMR and HMBC spectra of 2.33 in CDCl$_3$
Another example from this series of cyclisation reactions of 3-[2(tosylamido)phenyl]penta-1,4-diyn-3-ols 2.5a – k with AgOAc which also provided different products to the expected indole was the dialkynol derivative 2.5a (entry 4, Table 2.8) Scheme 2.51.

![Scheme 2.51](image)

However, treatment of 2.5e with AgOAc in MeCN did not provide any of the α-(trimethylsilyl)arylmethanol 2.32e. Despite their apparent simplicity, such compounds are generally only accessible via a Wittig-type rearrangement. For example, PhCH(OH)SiMe₃ has only been prepared via deprotonation of PhCH₂OSiMe₃ with s-BuLi in THF at r.t. [82JOC5051].

The reaction of N-{2-[3-hydroxy-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl]phenyl}-4-methylbenzenesulfonamide 2.5e with AgOAc, gave several products that could be separated by flash column chromatography on silica (10% EtOAc – petroleum ether) and obtained in varying yields (Scheme 2.52). The order in which the products eluted (left to right) is that as arranged in Scheme 2.52. Of note is that the major product was the vinylsilane 2.33e'.

The formation of 2.33e and 2.33e' is of interest because it represents an unusual synthesis of an exocyclic vinylsilane. Few examples of an analogous structural motif exist. An example is provided by the iodolactamisation of 2-[2-(trimethylsilyl)vinyl]-N-benzylbenzamide which proceeds with spontaneous elimination of HI to afford a phthalimide derivative (Scheme 2.52) [09S257].
The structure of indolines 2.33e and 2.33e’ were confirmed by their 1D (\(^1\)H and \(^{13}\)C) and 2D NMR spectra (HSQC and HMBC) spectra. The \(^1\)H and \(^{13}\)C NMR data of significant signals in 2.33e and 2.33e’ are shown in Table 2.9. The methine proton resonances are shielded in comparison to that in the indoline 2.33a (\(\delta_H\) 6.99 ppm) but similar to that of 2.33j (\(\delta_H\) 6.08 ppm). However the methine carbon resonances of 2.33e and 2.33e’ are shielded compared with that of 2.33j (\(\delta_C\) 138.58 ppm) but similar to 2.33a (\(\delta_C\) 124.34 ppm). The shielding of the \(^1\)H and \(^{13}\)C signals seen in 2.33 and 2.33’ is probably due to the electron donating effect (+I) of the TMS group.

<table>
<thead>
<tr>
<th>Indoline</th>
<th>4-(H) (\delta_H) (ppm)</th>
<th>Methine Proton (\delta_H) (ppm)</th>
<th>Methine Carbon (\delta_C) (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.33e</td>
<td>7.79</td>
<td>6.14</td>
<td>124.48</td>
</tr>
<tr>
<td>2.33e’</td>
<td>7.75</td>
<td>6.05</td>
<td>122.97</td>
</tr>
</tbody>
</table>

Table 2.9 \(^1\)H and \(^{13}\)C NMR data for 2.33e and 2.33e’

Comparative spectra for the four indolines generated from cyclisation of 2.5e with AgOAc are presented in Figure 2.14.
Figure 2.14 400 MHz $^1$H NMR spectra comparison of 2.27, 2.27', 2.33e and 2.33e' in CDCl$_3$.
To understand the nature of the cyclisation of 2.5e further – both with base (Scheme 2.32) and Ag(I) catalysis – indolines 2.33e and 2.33e’ were treated with 5M NaOH (2 equiv.) in MeOH for 24 h (Scheme 2.53). In the case of 2.33e (A, Scheme 2.53) a quantitative yield of (Z)-3-ethynyl-1-tosyl-2-[(trimethylsilyl)methylene]indolin-3-ol 2.33e’ was obtained. However, use of excess base with 2.33e’ provided only unreacted starting material.

![Scheme 2.53](image)

The findings above provided an insight into the formation of indolines 2.27 and 2.27’. Consequently, it can be envisaged that the reaction proceeds with removal of one of the TMS groups followed by cyclisation onto the ethynyl function. The remaining alkynylsilyl group will be deprotected. This sequence of events will also be applicable for the base-mediated 5-exo-dig cyclisation to 2.27 (Section 2.3, Scheme 2.32), Scheme 2.54 depicts the steps in the sequence.
The formation of the indolines 2.33e, 2.33e' and 2.33j from the reaction of 2.5e – j with AgOAc in MeCN can be postulated to proceed by the mechanism in Scheme 2.55. Coordination of silver(I) to the triple bond will form the π-complex (metallacyclopropenium ion) 2.44, which is susceptible to attack by the nucleophilic nitrogen of the sulfonamide function and will cyclise accordingly via a 5-exo-dig pathway. Subsequent protodeargenation (loss of silver by attack of a proton) will afford the corresponding indoline 2.33e and 2.33j. In the case where R₁ = TMS the deprotection of the trimethylsilylethynyl group leads to 2.33e' (Scheme 2.55).

The minor by-products from reaction of 2.5e with AgOAc in MeCN (2.27 and 2.27', Scheme 2.52) will proceed by coordination of silver(I) to the triple bond will form the
metallacyclopropenium ion 2.45 which is susceptible to attack by the nucleophilic sulfonamide function and cyclisation via a 5-exo-dig pathway. However the vinylsilane will be protonated to form the carbocation 2.46 which can be stabilised by a combination of the β-silicon effect and electron release from the ring nitrogen. The carbocation is then susceptible to hydrolytic desilylation which in turn affords 2.27', further desilylation then affords 2.27 (Scheme 2.56).

Thus, these findings parallel the report by Chan et al. [12JOC7166] that treatment 3-(2-p-tosylamidophenyl)penta-1,4-diyn-3-ols with AgOAc in MeCN, effects cyclisation via a 5-exo-dig pathway to indolines (Scheme 2.46) and not to indoles. Formation of indolines 2.33e and 2.33j in preference to the indoles 2.32e and 2.32j is possibly due to the presence of bulky groups (R1 = t-Bu and TMS) hindering attack at the cationic centre. In the case of the TMS derivative, protonation of the indolin-3-ol and dehydration (E1), will lead to a carbocation which cannot be stabilised by the β-silicon effect. Therefore, hydration of the alkene moiety (attack of H2O) and aromatisation is very unlikely.

The reaction of dialkynols 2.5c, g and k with AgOAc in MeCN failed to provide any tractable products (entries 3, 5 and 7 respectively, Table 2.8), only complex mixtures were obtained. The reactions complied in Table 2.8 demonstrate that the product obtained from the AgOAc-mediated cyclisations of 3-[2(tosylamido)phenyl]penta-1,4-diyn-3-ols can be manipulated by the nature of the alkyne substituents.
2.5 Indium(III) Promoted Cascade Cyclisation to a Furo[2,3-c]quinoline

In common with other group 13 elements In(III) exhibits Lewis acidity, albeit softer than other metal trihalides [63JA3533], such as AlCl$_3$ and BCl$_3$, due to its larger ionic radius. This Lewis acidity has been exploited for a variety of applications and In(III) use in synthesis to access a range of products has been reviewed a number of times [00EJO2347, 03S633, 07S1, 18OBC5733]. There are examples of In(III) reactivity towards alkynes in Scheme 2.57 and subsequent cyclisations to a variety of heterocycles [00EJO2347, 03S633, 07S1, 18OBC5733]. Indium-catalysed hydroarylation of aryl propargyl ethers proceeds efficiently to afford a range of 4-substituted 2H-chromenes (A, Scheme 2.57), including 4-halogenated chromenes (R$^1$ = Br, I) [15OBC379]. Nakamura and co-workers found that 2-alkynyl-6-methoxysulfonanilides (2.47) upon treatment with InBr$_3$, cyclised to indoles via a 5-endo-dig pathway (B, Scheme 2.57). Indium(III) also facilitated the migration of the arylsulfonyl group (1,3 and 1,7-migration) [07AGE2284]. Intramolecular hydroarylation of (2.48), afforded azaepinoindoles in high yields (60 – 89%) and could be initiated in the presence of In(OTf)$_3$ (C, Scheme 2.57) [13CC6803]. Surprisingly, there are no examples in the literature that describe the use of In(III) to cyclise propargylic alcohols, specifically analogues of 1-arylprop-2-yn-1-ols. It was therefore of interest to explore the behaviour towards the 3-arylpenta-1,4-diyn-3-ols.

Scheme 2.57
Initially 2.5a was treated with indium(III) chloride in toluene at 90 °C for 20 h. TLC examination of the reaction mixture showed this to contain mostly unreacted starting material. Efforts to purify the mixture proved unsuccessful and only the starting material could be isolated. With this result, the reactivity of 2.5a towards an alternative indium(III) salt – In(OTf)₃ – was investigated. Dialkynol 2.5a was treated with In(OTf)₃ in DCM at room temperature for 2.5 h (Scheme 2.58). TLC examination again revealed the presence of mostly starting material, although a new faster running (non-polar) compound was also present. Purification of the reaction mixture by flash chromatography provided the faster running component, following recrystallisation from hexane – EtOAc, as a beige powder. The ¹H NMR spectrum of this unknown compound ‘X’ showed an upfield shift of the aromatic protons compared to those of the indole systems but were similar to indoline 2.33a as shown in Figure 2.15.
Figure 2.15 400 MHz $^1$H NMR spectra comparison of 2.32a, 2.33a and ‘X’ in acetone-d$_6$
Most surprising was the $^{13}$C NMR spectrum (Figure 2.16), which revealed the absence of acetylenic carbon signals, evidently, both alkyne moieties had participated in this indium(III) catalysed reaction.

![Figure 2.16 150 MHz $^{13}$C NMR spectrum of unknown compound ‘X’ in acetone-d$_6$](image)

Two possible structures can be postulated from the NMR data, the furo[3,4-$b$]indole 2.49 or the pyrano[3,4-$c$]indole 2.50 which could have been derived from 2.32a via a 5-exo-dig or 6-endo-dig cyclisation respectively (Scheme 2.59).
However, treatment of the alcohol **2.32a** with In(OTf)_3 in DCM failed to effect cyclisation to ‘X’. TLC examination showed only starting material was present (Scheme 2.60).

This finding established that neither **2.49** nor **2.50** was the product isolated from the reaction of **2.5a** with In(OTf)_3. Moreover, NMR data from similar fragments as the furo[3,4-b]indole **2.49** and pyrano[3,4-c]indole **2.50** – (Z)-2-benzylidene-5-phenyl-2,5-dihydrofuran **2.51** [09T1839] and 1,3-diphenyl-1H-isochromene **2.52** [17AGE5116] respectively – did not match the 'H data of ‘X’. The chemical shift of the 3-‘H proton from 1,3-diphenyl-1H-isochromene (**2.52**), highlighted in red, is the only similar (δ_H 6.67 ppm, δ_C 100.4 ppm) aromatic resonance (Figure 2.17) [17AGE5116]. This data provided further confirmation that neither **2.49** nor **2.50** were the correct structure of ‘X’.
After careful consideration, another possibility for the structure of ‘**X**’ is the tricyclic 4,5-dihydrofuro[2,3-c]quinoline **2.53**, NMR data for this structure is a better fit with that of several model compounds and structural fragments shown below (Figure 2.18) [11JOC2379, 14CC8324, 17MI42168, 15AGE3116]. *N*-Furan-2-yl(phenyl)methyl]-4-methylbenzenesulfonamide (structure **B**) is particularly informative due to the similar furan **1**H and **1**3C shifts as well as the non-aromatic carbon **1**3C (C-H) shift, with structure **C** also confirming that 2-C is saturated as the **1**3C shift is identical. The shift of the methine proton in **D** is similar to that in ‘**X**’ i.e. structure **2.53**.

The mechanism for the formation of this novel structure **2.53** is shown in Scheme 2.61. It can be postulated that dehydration of **2.5a** leads to the formation of a stabilised cation.
Hydroxide (or water) attack on one of the alkyne motifs, followed by tautomerization of this intermediate \((2.54)\) produces an \(\alpha,\beta\)-unsaturated ketone in a Meyer-Schuster rearrangement [00EJO2347, 03S633, 07S1, 16CC12147, 18OBC5733]. Indium activates the remaining alkyne function to attack from the carbonyl oxygen to form a conjugated oxonium cation \(2.55\), nucleophilic attack of the sulfonamide nitrogen on this alkylidene intermediate will effect cyclisation to \(2.53\).

![Scheme 2.61]

Reaction of indium(III) triflate with \(2.5a\) has therefore afforded a novel furoquinoline by an unprecedented cascade sequence. However the yield of \(2.53\) from the reaction was only 23%. In attempts to optimise the yield different solvents, catalysts and loadings were investigated (Table 2.10).
<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Loading (mol %)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield of 2.53 (%) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>In(OTf)\textsubscript{3}</td>
<td>5</td>
<td>DCM</td>
<td>r.t.</td>
<td>2.5</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>In(OTf)\textsubscript{3}</td>
<td>10</td>
<td>DCM</td>
<td>r.t.</td>
<td>2.5</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>In(OTf)\textsubscript{3}</td>
<td>15</td>
<td>DCM</td>
<td>r.t.</td>
<td>2.5</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>In(OTf)\textsubscript{3}</td>
<td>2.5</td>
<td>DCM</td>
<td>r.t.</td>
<td>2.5</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>In(OTf)\textsubscript{3}</td>
<td>5</td>
<td>MeOH</td>
<td>60</td>
<td>2.5</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>In(OTf)\textsubscript{3}</td>
<td>5</td>
<td>MeCN</td>
<td>60</td>
<td>2.5</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>In(OTf)\textsubscript{3}</td>
<td>5</td>
<td>EtOAc</td>
<td>60</td>
<td>2.5</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>In(OTf)\textsubscript{3}</td>
<td>5</td>
<td>CHCl\textsubscript{3}</td>
<td>60</td>
<td>2.5</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>In(OTf)\textsubscript{3}</td>
<td>5</td>
<td>DCE</td>
<td>90</td>
<td>2.5</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>In(OTf)\textsubscript{3}</td>
<td>5</td>
<td>70% EtOH aq.</td>
<td>90</td>
<td>2.5</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>In(OTf)\textsubscript{3}</td>
<td>5</td>
<td>THF</td>
<td>60</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>12\textsuperscript{a}</td>
<td>In(OTf)\textsubscript{3}</td>
<td>5</td>
<td>DCM</td>
<td>r.t.</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>13\textsuperscript{b}</td>
<td>In(OTf)\textsubscript{3}</td>
<td>5</td>
<td>DCM</td>
<td>r.t.</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>Ga(OTf)\textsubscript{3}</td>
<td>5</td>
<td>DCM</td>
<td>r.t.</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>Sc(OTf)\textsubscript{3}</td>
<td>10</td>
<td>DCM</td>
<td>r.t.</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>AgOTf : Sc(OTf)\textsubscript{3}</td>
<td>2 : 10</td>
<td>DCE</td>
<td>85</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>17\textsuperscript{cd}</td>
<td>AuPPh\textsubscript{3}NTf\textsubscript{2}</td>
<td>2</td>
<td>Dry PhMe</td>
<td>110</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>18\textsuperscript{d}</td>
<td>Au(PPh)\textsubscript{3}Cl : AgOTf</td>
<td>5 : 2</td>
<td>Dry PhMe</td>
<td>110</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>19</td>
<td>Cu(OTf)\textsubscript{2}</td>
<td>5</td>
<td>DCM</td>
<td>r.t.</td>
<td>24</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 2.10** Optimising conditions to 2.53, \(^{1}\text{H} \text{NMR yields. a = 50% w/wmontmorillonite K-10 added, b = 10 equiv. of water added, c = 1 equiv. dry MeOH added, d = reaction carried out in the dark}**

All the yields in Table 2.10 (excluding entry 1) were derived from \(^{1}\text{H} \text{NMR data only, by the appearance and integration of two distinct signals present in the spectrum of 2.53 (δ \text{H} 6.67 and 6.51 ppm, Figure 2.15). Scale may be a factor in the yields achieved, as the majority of the entries did not produce anything other than unreacted starting material.}

The increased catalyst loading of In(III) (entry 3, Table 2.10) was scaled up to see if 2.53 could be isolated in a higher yield than the initial result with DCM. However at increased scale only 15% of 4,5-dihydro-furo[2,3-c]quinoline 2.53 could be isolated.
Changing the polarity of the solvent (DCM) to a more polar system (higher dielectric constant), could help stabilise the charged species formed (Scheme 2.61) and therefore increase the yield. However this modification did not enhance the reaction as envisaged. Other Lewis acids known for their alkynophilicity were investigated; Ga(III), Sc(III), Au(I) and Cu(II), [02JOC1414, 04T1959, 07AGE3140, 14AGE13532, 19OBC2663] unfortunately these reactions (entry 14 – 19, Table 2.10) only afforded unreacted starting material. Hence the conditions used initially (5 mol % In(OTf)₃ in DCM) were optimal. It is possible that purification of the crude reaction product plays a role in the yield obtained of 2.53, thus the acidity of the silica used in flash column chromatography may cause degradation of the furoquinoline 2.53.

Other dialkynols 2.5b and 2.5c were subjected to the conditions discussed above – In(OTf)₃ 5 mol % in DCM – but in each case only starting material was obtained (Scheme 2.62). The reasons for this outcome are unknown and it is proposed that the phenyl dialkynol analogue is a ‘goldilocks’ compound, because if the phenyl rings provide a stabilising effect then the 4-MeOC₆H₄ analogue 2.5c should also have afforded the corresponding furo[2,3-c]quinoline.

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^1 \\
\text{C}_3H_7 & \quad \text{C}_3H_7 \\
\text{4-MeOC}_6H_4 & \quad \text{4-MeOC}_6H_4
\end{align*}
\]

Scheme 2.62

The synthesis of the furoquinoline 2.53 is a remarkable result and warrants further investigation. Within the literature there is little work in relation to the synthesis of furo[2,3-c]quinolines, existing examples are shown in Scheme 2.63. Yang reported the coupling of 2-formyl-3-furanboronic acid with 2-bromonitrobenzene followed by reduction and deoxygenation with PBr₃ which yielded furo[2,3-c]quinoline in 92% yield together with 4-bromofuro[2,3-c]quinoline in 4% yield (A, Scheme 2.63) [89SC1001]. A one-pot reaction to 1,2,4-trisubstituted furo[2,3-c]quinolines involved the domino reaction of ortho-
alkynylanilines, aldehydes and an isocyanatoacetamide (B, Scheme 2.63). The reactions provided the relevant furo[2,3-c]quinolines in fair to good yields (42 – 75%), and aryl, alkyl as well as electron withdrawing substituents can be introduced into the 4-position by this approach (derived from the aldehyde) [02AGE3633]. Scheme 2.63 C illustrates a similar method to afford 2-alkoxyfuro[2,3-c]quinolines 2.56 [12EJO475].

3-Hydroxyquinoline was utilised as a starting material for the synthesis of furo[2,3-c]quinolines by an initial iodination followed by a Sonogashira coupling, in which the Cu(I) also facilitates the 5-endo-dig cyclisation to 2.57 [13JME6871]. The coupling of a 3-furanylbornic acid with 2-iodoaniline affords 2.58. Subsequent condensation with an aryl aldehyde in the presence of a catalyst results in the formation of the tricyclic system in a variant of the Pictet-Spengler reaction (E, Scheme 2.63). Both Lewis and Bønsted acids were employed, with iron(III) chloride found to be the most efficient (37 – 94% yield). By this method only 4-arylfuro[2,3-c]quinolines were synthesised, no other position of the ring system was substituted [16MI46073].
With the novel furo[2,3-c]quinoline 2.53 being the only product obtained from the mild Lewis acid promoted dehydration of the sulfonamides 2.5a – 2.5c, attention now focussed on investigating the reactivity of 1,5-disubstituted-3-[2-(N-substituted sulfamoyl)phenyl]penta-1,4-dyn-3-ols (reversed sulfonamides 2.23Aa – Hb) towards In(OTf)_3, using the conditions found to be optimum for the cyclisation of the dialkynol 2.5a (entry 1, Table 2.10).
2.6 Indium(III) Mediated Synthesis of 3,3-Di(alkynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxides

Initially a solution of the sulfonamide 2.23Aa in DCM and 5 mol % In(OTf)₃ was stirred at room temperature (Scheme 2.64). TLC examination after 4 h showed no change, so the reaction mixture was left overnight. After this time the ¹H NMR spectrum of the crude reaction product revealed quantitative conversion to the novel 1,2-benzisothiazole 1,1-dioxide 2.59Aa. Surprisingly both 2.23Aa and 2.59Aa have identical Rf values in a range of solvent systems, so the reaction may proceed to completion in less than 24 h.

Scheme 2.64

The success of this novel cyclodehydration reaction prompted examination of the cyclisation of a range of the other reversed sulfonamides 2.23Aa – Hb to these new 3,3-di(alkynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxides 2.59Aa – Hb, Scheme 2.65. The results are collated in Table 2.11.
Scheme 2.65

![Diagram](image)

Table 2.11 Yields of In(OTf)$_3$ promoted cyclisation of 2.23Aa – Hb to 2.59Aa – Hb

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dialkynol</th>
<th>R</th>
<th>R$^1$</th>
<th>1,2-Benzisothiazole 1,1-dioxide</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.23Aa</td>
<td>Me</td>
<td>Ph</td>
<td>2.59Aa</td>
<td>24</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>2.23Ab</td>
<td>Me</td>
<td>C$_3$H$_7$</td>
<td>2.59Ab</td>
<td>5</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>2.23Ba</td>
<td>Tolyl</td>
<td>Ph</td>
<td>2.59Ba</td>
<td>24</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>2.23Bb</td>
<td>Tolyl</td>
<td>C$_3$H$_7$</td>
<td>2.59Bb</td>
<td>24</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>2.23Bc</td>
<td>Tolyl</td>
<td>4-MeOC$_6$H$_4$</td>
<td>2.59Bc</td>
<td>23</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td>2.23Be</td>
<td>Tolyl</td>
<td>TMS</td>
<td>2.59Be</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td>7</td>
<td>2.23Bf</td>
<td>Tolyl</td>
<td>CH$_2$OMe</td>
<td>2.59Bf</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>2.23Ca</td>
<td>3-MeC$_6$H$_4$</td>
<td>Ph</td>
<td>2.59Ca</td>
<td>24</td>
<td>53</td>
</tr>
<tr>
<td>9</td>
<td>2.23Cb</td>
<td>3-MeC$_6$H$_4$</td>
<td>C$_3$H$_7$</td>
<td>2.59Cb</td>
<td>24</td>
<td>82</td>
</tr>
<tr>
<td>10</td>
<td>2.23Da</td>
<td>2-MeOC$_6$H$_4$</td>
<td>Ph</td>
<td>2.59Da</td>
<td>22</td>
<td>37</td>
</tr>
<tr>
<td>11</td>
<td>2.23Db</td>
<td>2-MeOC$_6$H$_4$</td>
<td>C$_3$H$_7$</td>
<td>2.59Db</td>
<td>3</td>
<td>63</td>
</tr>
<tr>
<td>12</td>
<td>2.23Ea</td>
<td>3-MeOC$_6$H$_4$</td>
<td>Ph</td>
<td>2.59Ea</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>2.23Eb</td>
<td>3-MeOC$_6$H$_4$</td>
<td>C$_3$H$_7$</td>
<td>2.59Eb</td>
<td>24</td>
<td>100</td>
</tr>
<tr>
<td>14</td>
<td>2.23Ga</td>
<td>3-thienyl</td>
<td>Ph</td>
<td>2.59Ga</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>2.23Gb</td>
<td>3-thienyl</td>
<td>C$_3$H$_7$</td>
<td>2.59Gb</td>
<td>24</td>
<td>49</td>
</tr>
<tr>
<td>16</td>
<td>2.23Ha</td>
<td>2-naphthyl</td>
<td>Ph</td>
<td>2.59Ha</td>
<td>24</td>
<td>43</td>
</tr>
<tr>
<td>17</td>
<td>2.23Hb</td>
<td>2-naphthyl</td>
<td>C$_3$H$_7$</td>
<td>2.59Hb</td>
<td>7.3</td>
<td>45</td>
</tr>
</tbody>
</table>
Formation of 2.59Aa – Hb is the result of an E1 type elimination, facilitated by indium(III) coordination to the alcohol, the resulting carbocation will be highly stabilised but will be readily intercepted by the sulfonamide group (Scheme 2.66).

![Scheme 2.66](image)

The foregoing cyclodehydration reaction constitutes a new approach to 2,3-dihydro-1,2-benzisothiazole 1,1-dioxides although numerous routes to these systems exist (Scheme 2.67). For example, reduction of a 3-alkyl- or a 3-aryl-1,2-benzisothiazole 1,1-dioxide with a ruthenium(II) catalyst (A, Scheme 2.67) [96JA2521]. More recently, Tao and Gilbertson reported the Brønsted acid-mediated reductive cyclisation of an ortho-alkynyl sulfonamide to 2.60 (B, Scheme 2.67). It was also found that heating induces reductive cleavage of the sulfonamide N-substituent, resulting in the sultam 2.61 [18CC11292].

![Scheme 2.67](image)

However, less common are routes to 3,3-disubstitued-1,2-benzisothiazole 1,1-dioxides, some examples are shown in Scheme 2.68. The N-ortho dilithiated benzenesulfonamides 2.62 have been intercepted with ketones and subsequent dehydration affords the
corresponding 1,2-benzisothiazole 1,1-dioxides (A, Scheme 2.68) [68JOC900, 79OR1].

Rhodium-promoted arylation of N-sulfonyl ketimines with sodium tetraarylborates in the presence of L18 provided 3,3-diaryl-1,2-benzisothiazole 1,1-dioxides 2.63 with excellent enantioselectivity (94 – 98%) and high yields 72 – 90% (B, Scheme 2.68) [13JA971]. To date there is the only one example of a 3-alkynyl-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide 2.64 (Scheme 2.68) however, Arai and co-workers did not report how it was synthesised [13JOC4366]. Therefore the results described above (Scheme 2.65) represents a novel pathway to the hitherto unknown 3,3-di(alkynyl)-1,2-benzisothiazole 1,1-dioxides 2.59Aa – Hb.

Scheme 2.68

The 3,3-di(alkynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxides 2.59Aa – Hb were characterised from their NMR spectra, which exhibited acetylene carbon resonances within the range of $\delta_C$ 99.79 – 75.58 ppm and the quaternary C-3 carbon absorbed in the range of $\delta_C$ 55.33 – 58.54 ppm (Figure 2.19). The most downfield acetylene carbon resonances (Figure 2.19) are from 2-(p-tolyl)-3,3-bis[(trimethylsilyl)ethynyl]-2,3-dihydro-1,2-benzoisothiazole 1,1-dioxide 2.59Be.

The quaternary C-3 carbon exhibited the largest resonance change, being shifted upfield by up to 10 ppm in comparison to the starting dialkynols 2.23Aa – Hb (Section 2.1, Table 2.6). This shift is not surprising after removal of the OH function. However, it is significantly different to that of C-3 in the 3,3-diaryl-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide 2.65.
Evidently the magnetic anisotropy of the alkyne units in 2.59Aa – Hb are responsible for this shielding.

\[
\begin{array}{c}
91.59 - 75.58 \text{ ppm} \\
2.59Aa - Hb
\end{array}
\]

\[
\begin{array}{c}
99.79 - 82.54 \text{ ppm} \\
58.54 - 55.33 \text{ ppm}
\end{array}
\]

\[
\begin{array}{c}
71.1 \text{ ppm} \\
2.65
\end{array}
\]

\textbf{Figure 2.19} \textsuperscript{13}C NMR data for 2.59Aa – Hb and a derivative 2.65 [13JA971]

The reaction of 1,5-disubstituted-3-[2-(N-aryl)sulfamoyl)phenyl]penta-1,4-diyn-3-ols (2.23Bf, 2.23Ea and 2.23Ga) with In(OTf)\textsubscript{3} in DCM, entries 7, 12 and 14 (Table 2.11) respectively, provided complex mixtures from which no identifiable products could be obtained. All the other reversed sulfonamides gave fair to excellent yields of the 1,2-benzoisothiazole 1,1-dioxides. Where yields were poor the reaction failed to reach completion and unreacted starting material was recovered as the other component.

The aromatic 4-\(H\) protons signal of 3,3-di(arylethynyl)-2,3-dihydro-1,2-benzoisothiazole 1,1-dioxides 2.59Aa – Ga and 2.59Bc are shifted further downfield than that of the 7-\(H\) protons (Table 2.12). However, in the 3,3-di(alkylethynyl)-2,3-dihydro-1,2-benzoisothiazole 1,1-dioxides 2.59Ab – Gb, 2.59Be and 2.59Bf a differing trend in chemical shifts emerge, the 7-\(H\) signals are shifted downfield (Table 2.13). An exception of this trend is provided by the 2-(naphthalen-2-yl)-3,3-di(alkynyl)-2,3-dihydro-1,2-benzoisothiazole 1,1-dioxides 2.59Ha – b where the chemical shifts are opposite to that described above. When \(R^1 = \text{Ph} (2.59Ha)\) 7-\(H\) proton resonance is shifted downfield and when \(R^1 = C_3H_7 (2.59Hb)\) 4-\(H\) proton is at lower field.
Assignments of protons signals in **2.59Aa – Hb** were established by their 2D NMR spectra (HSQC, HMBC and COSY). Figure 2.20 and Figure 2.21 show the HMBC spectra of **2.59Aa** and **2.59Bb** respectively. The HMBC spectrum 2-methyl-3,3-bis(phenylethynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide **2.59Aa** (Figure 2.20) exhibits a through bond correlation between the 4-\(H\) proton at \(\delta_{H} 7.90\) ppm and the quaternary carbon C-3 at \(\delta_{C} 57.01\) ppm. The doublet at \(\delta_{H} 7.84\) ppm corresponding to 7-\(H\) shows a cross peak with the quaternary ring junction C-7a at \(\delta_{C} 137.80\) ppm. However, in 3,3-di(pent-1-yn-1-yl)-2-(p-tolyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide **2.59Bb** the shifts of the 4-\(H\) and 7-\(H\) signals are reversed. Thus, Figure 2.21 exhibits a cross peak between the doublet (7-\(H\) proton) at \(\delta_{H} 7.84\) ppm and the ring junction carbon C-7a at \(\delta_{C} 138.72\) ppm. The 4-\(H\) proton resonates at \(\delta_{H} 7.77\) ppm and displays a through-bond correlation with the quaternary C-3 carbon at \(\delta_{C} 57.93\) ppm. These HMBC correlations allow the distinction between the 4-\(H\) and 7-\(H\) protons of the 3,3-di(alkynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxides **2.59Aa – Hb**.

<table>
<thead>
<tr>
<th></th>
<th>4-(H) (ppm)</th>
<th>5-(H) (ppm)</th>
<th>6-(H) (ppm)</th>
<th>7-(H) (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(H)</td>
<td>8.10 – 7.94</td>
<td>7.90 – 7.76</td>
<td>7.78 – 7.65</td>
<td>7.95 – 7.84</td>
</tr>
</tbody>
</table>

**Table 2.12** \(^1\)H NMR proton resonances of **2.59Aa – Gb** and **2.59Bc**

<table>
<thead>
<tr>
<th></th>
<th>4-(H) (ppm)</th>
<th>5-(H) (ppm)</th>
<th>6-(H) (ppm)</th>
<th>7-(H) (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(H)</td>
<td>7.74 – 7.82</td>
<td>7.75 – 7.50</td>
<td>7.65 – 7.56</td>
<td>7.87 – 7.72</td>
</tr>
</tbody>
</table>

**Table 2.13** \(^1\)H NMR proton resonances of **2.59Ab – Gb, 2.59Be and 2.59Bf**
2.7 Iodine-Mediated Cyclodehydration to 3,3-Di(alkynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxides and 6-Endo-Dig Cyclisation to 1,2-Benzisothiazolo[2,3-a]quinolines

Other extensively used electrophilic activators that promote the cyclisation of alkynes and propargyl alcohols are iodine, iodine monochloride and NIS (Section 1.3) [14COS-II(4)412, 15S1961, 16OBC7639, 16MI49730]. They not only activate alkynes to nucleophilic attack and accompanying cyclisation, but an iodo-group can be incorporated into the structure, allowing further functionalisation of the ring.
With a selection of the reversed sulfonamide dialkynols 2.23Aa – Hb to hand their reactivity towards an iodine electrophile was explored. Initially 2.23Aa was subjected to optimised conditions found for another set of cyclisations (see Section 3.1); and was treated with 2 equiv. of ICl in MeCN. After 3.5 h at reflux the reaction mixture was quenched with aqueous sodium thiosulfate. Flash column chromatography (10% EtOAc – petroleum ether) of the crude material, provided 3,3-di(alkynyl)-1,2-benzisothiazole 1,1-dioxide 2.59Aa in 48% yield as a brown oil (Scheme 2.69), a lower yield than that achieved with In(OTf)₃ in DCM (100%, entry 1, Table 2.11). However, this outcome is not too surprising as iodine monochloride (effectively I⁺) is a softer Lewis acid compared to In(III) [63JA3533].

![Scheme 2.69](image)

In order to investigate the scope of this iodine-promoted cyclisation the behaviour of the N-p-tolyl sulfonamide (2.23Ba) towards ICl was explored. Thus, treatment of 2.23Ba with ICl (2 equiv.) in MeCN under reflux for 24 h gave a crude product that was purified by flash column chromatography (12% EtOAc – Pet ether). The ¹H NMR spectrum of the fast eluting fraction revealed the presence of 17 aromatic protons (Figure 2.22), one less than in the starting dialkynol 2.23Ba, a high field broad singlet integrating for one proton at δH 6.68 ppm was also present. The ¹³C NMR spectrum of this initial fraction showed that there was either only one alkyne unit intact or that both alkyne functions were in the same chemical environment (δC 86.82 and 83.99 ppm). In addition, a quaternary carbon signal at δC 64.97 was present. However these signals did not match those of the acetylenic and the C-3 quaternary carbons in the starting material 2.23Ba (δC 67.05, 86.92 and 88.80 ppm), nor in 3,3-bis(phenylethynyl)-2-(p-tolyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide 2.59Ba (δC 86.19, 84.71 and 58.58 ppm). Another signal at δC 101.43 ppm suggested the presence of an alkenic carbon, perhaps indicating a C-I bond.
Figure 2.22 400 MHz $^1$H NMR spectrum of the unknown iodocyclisation product in CDCl$_3$. 
The HRMS of this unknown compound revealed a molecular ion at \( m/z \) \([M+H]^+ = 586.0328\) corresponding to \( C_{30}H_{20}NO_2S \). In order to definitely establish the constitution of this compound an X-ray crystal structure (Figure 2.23) was obtained and revealed the novel tetracyclic, \( 6aH-1,2\)-benzisothiazolo[2,3-\( a \]quinoline structure \textbf{2.66Ba-3} (19% yield). The later eluting fraction from the column provided the \( 1,2\)-benzoisothiazole \( 1,1\)-dioxide \textbf{2.59Ba} in a 36% yield (Scheme 2.70).

![Figure 2.23 X-Ray crystal structure of 6-iodo-3-methyl-5-phenyl-6a-(phenylethynyl)-6aH-1,2-benzisothiazolo[2,3-\( a \]quinoline 11,11-dioxide \textbf{2.66a-3}](image)

**Scheme 2.70**

A plausible mechanism for the formation of \textbf{2.66a-3} is shown in Scheme 2.71. The initial step involves an \( E_1 \) elimination, from the alkylnol facilitated by co-ordination of \( I^+ \). Following this, nucleophilic attack on the stabilised carbocation by the sulfonamide function will generate \textbf{2.59Ba} as an intermediate. Subsequent coordination of an iodine electrophile to
one of the alkyne moieties results in the formation of an iodonium ion (2.67). The latter is activated towards nucleophilic attack from the electron rich tolyl ring via a 6-endodig pathway, to give following completion of the S_{Ar} sequence, the 1,2-benzisothiazolo[2,3-a]quinoline 2.66a-3.

Scheme 2.71

Ring systems such as 2.66a-3 possessing a 2,3-fused 1,2-benzisothiazole unit are unusual. Indeed, only two examples of the 1,2-benzisothiazolo[2,3-a]quinoline core have been reported (Scheme 2.72). Thus, Kiran et al. recently described the cycloaddition of 3-styryl-1,2-benzisothiazole 1,1-dioxide with benzyne, generated by the Kobayashi protocol, provided 2.68 in a 67% yield (A, Scheme 2.72) [17JOC1823]. A Ni-catalysed Mukaiyama-Mannich reaction between 3-(ethoxycarbonyl)-1,2-benzisothiozole 1,1-dioxide and a silyl enol ether proceeds with a high degree of enantiocontrol and high yield (99% ee, 96% yield), in the presence of the chiral auxiliary L2. A subsequent intramolecular S_{Ar} reaction proceeds with displacement of bromide to provide the tetracycle 2.69 in an excellent yield 95% (B, Scheme 2.72) [17OCF1858].
Scheme 2.72

A tricyclic core closely related to 2.66a-3 was obtained from N-allylsaccharin via a five-step sequence by Modolo and co-workers [09JOC1982]. The starred quaternary carbon in Scheme 2.73 (2.70) resonates at $\delta_C$ 62.70 ppm, comparable to that observed for the teracycle 2.66a-3 which absorbs at $\delta_C$ 64.97 ppm.

Scheme 2.73

Attempts to optimise the yield of 2.66a-3 investigated the use of different solvents and electrophile ratios. The results are summarised in Table 2.14.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>Equiv.</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>2.59Ba Yield (%)</th>
<th>2.66a-3 Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ICl</td>
<td>2</td>
<td>MeCN</td>
<td>24</td>
<td>36</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>ICl</td>
<td>3</td>
<td>MeCN</td>
<td>24</td>
<td>45</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>ICl</td>
<td>5</td>
<td>MeCN</td>
<td>24</td>
<td>36</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>I₂</td>
<td>3</td>
<td>MeOH</td>
<td>24</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2.14 Optimisation of iodocyclisation conditions to 2.66a-3

Use of molecular iodine (entry 4, Table 2.14) provided only the 1,2-benzisothiazole 2.59Ba in quantitative yield, none of the tetracycle 2.66a-3 was observed. Cyclisation to the latter proved to be most efficient with 3 equiv. ICl. Use of 5 equiv. did not increase the yield.

With the optimised iodocyclisation conditions at hand, their application to the propargyl alcohols 2.23Aa – Hb was evaluated (Scheme 2.74 – 2.76). The results are compiled in Table 2.15 – 2.18.
R and R¹ as defined in Table 2.15

\[
\begin{align*}
\text{HO} & \quad \text{HN} \\
\text{R} & \quad \text{R¹} \\
\end{align*}
\]

ICl (3 equiv.), MeCN
r.t. to 82 °C, 1 - 24 h

\[
\begin{align*}
\text{and/or} & \quad \text{and/or} \\
\text{2.59Aa - Eb} & \quad \text{2.66, 2.71} \\
\end{align*}
\]

\[
\begin{align*}
\text{R}^1 & \quad \text{as defined in Table 2.15} \\
\end{align*}
\]

Scheme 2.74

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R¹</th>
<th>Dialkynol</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>1,2-Benzisothiazole</th>
<th>Yield (%)</th>
<th>Tetracycle</th>
<th>R³</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>Me</td>
<td>Ph</td>
<td>2.23Aa</td>
<td>3.5</td>
<td>82</td>
<td>2.59Aa</td>
<td>48</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>C₃H₇</td>
<td>2.23Ab</td>
<td>24</td>
<td>82</td>
<td>2.59Ab</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>3</td>
<td>Tolyl</td>
<td>Ph</td>
<td>2.23Ba</td>
<td>24</td>
<td>82</td>
<td>2.59Ba</td>
<td>45</td>
<td>2.66a-3</td>
<td>Me</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>Tolyl</td>
<td>C₃H₇</td>
<td>2.23Bb</td>
<td>3.5</td>
<td>r.t.</td>
<td>2.59Bb</td>
<td>36</td>
<td>2.66b-3</td>
<td>Me</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>Tolyl</td>
<td>4-MeOC₆H₄</td>
<td>2.23Bc</td>
<td>22</td>
<td>82</td>
<td>2.59Bc</td>
<td>0</td>
<td>266c</td>
<td>Me</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Tolyl</td>
<td>CH₂OMe</td>
<td>2.23Bf</td>
<td>1</td>
<td>82</td>
<td>2.59Bf</td>
<td>40</td>
<td>2.66f</td>
<td>Me</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>3-MeC₆H₄</td>
<td>Ph</td>
<td>2.23Ca</td>
<td>4.5</td>
<td>82</td>
<td>2.59Ca</td>
<td>47</td>
<td>2.66a</td>
<td>Me</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>3-MeC₆H₄</td>
<td>C₃H₇</td>
<td>2.23Cb</td>
<td>1.5</td>
<td>82</td>
<td>2.59Cb</td>
<td>75</td>
<td>2.66b</td>
<td>Me</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>2-MeOC₆H₄</td>
<td>Ph</td>
<td>2.23Da</td>
<td>3</td>
<td>82</td>
<td>2.59Da</td>
<td>0</td>
<td>2.71a</td>
<td>OMe</td>
<td>0</td>
</tr>
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<td>10</td>
<td>2-MeOC₆H₄</td>
<td>C₃H₇</td>
<td>2.23Db</td>
<td>21</td>
<td>82</td>
<td>2.59Db</td>
<td>0</td>
<td>2.71b</td>
<td>OMe</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>3-MeOC₆H₄</td>
<td>Ph</td>
<td>2.23Ea</td>
<td>21</td>
<td>82</td>
<td>2.59Ea</td>
<td>0</td>
<td>2.71a</td>
<td>OMe</td>
<td>0</td>
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<td>3-MeOC₆H₄</td>
<td>C₃H₇</td>
<td>2.23Eb</td>
<td>21</td>
<td>82</td>
<td>2.59Eb</td>
<td>54</td>
<td>2.71b</td>
<td>OMe</td>
<td>0</td>
</tr>
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</table>

Table 2.15 Yields from the iodocyclisation of dialkynols 2.23Aa – Eb with ICl. *2 equiv. of ICl used
Scheme 2.75

Table 2.16 Attempted iodocyclisations of dialkynols 2.23Ga–b with ICl

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R¹</th>
<th>Dialkynol</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>1,2-Benzothiazole</th>
<th>Yield (%)</th>
<th>Tetracycle</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-thienyl</td>
<td>Ph</td>
<td>2.23Ga</td>
<td>2.5</td>
<td>r.t.</td>
<td>2.59Ga</td>
<td>0</td>
<td>2.72a</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>3-thienyl</td>
<td>C₃H₇</td>
<td>2.23Gb</td>
<td>1.5</td>
<td>82</td>
<td>2.59Gb</td>
<td>0</td>
<td>2.72b</td>
<td>0</td>
</tr>
</tbody>
</table>
Scheme 2.76

Table 2.17 Attempted iodocyclisations of dialkynols 2.23Ha – b with ICl
The majority of reactions, summarised in the entries in Table 2.15 – 2.17 gave complex mixtures from which no identifiable products could be isolated. Only N-p-tolyl (R₁ = Ph and C₃H₇ analogues) entries 3 and 4 (Table 2.15) gave the corresponding 1,2-benzisothiazolo[2,3-α]quinoline (2.66a-3 and 2.66b-3). It is surprising that the reversed sulfonamides with N-(3-thienyl) units (2.23Ga – b) entries 13 and 14 (Table 2.16) failed to give tractable products, as both the C-2 and C-5 positions on the 3-thienyl derivatives are activated for electrophilic attack.

Moreover, dialkynols 2.23Ea – b should also be activated to attack from electrophiles in the ortho (to the nitrogen) position on the aromatic ring, due to the methoxy group being ortho/para directing (Scheme 2.77). It would be expected that cyclisation of 2.23Ea – b would afford the 1,2-benzisothiazolo[2,3-α]quinolines 2.71a – b-2 as these would be the least hindered products.

Another interesting result from these ICl cyclisations is the formation of the 3,3-bis(3-methoxyprop-1-yn-1-yl)-2-(p-tolyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide 2.59Bf (entry 6, Table 2.15). When the reversed sulfonamide 2.23Bf was treated with In(OTf)₃; which proved to be highly effective in the dehydration and cyclisation of the dialkynols 2.23Aa – Hb, none of the corresponding 1,2-benzisothiazole (2.59Bf) was isolated (Scheme 2.78). The reasons for this are not known, it could be postulated that the alkynyl unit being terminated with a methoxymethyl group will change the reactivity of the species towards certain Lewis acids, possibly via coordination to a OMe group.
In order to verify the intermediacy of 3,3-di(alkynyl)-1,2-benzothiazole 1,1-dioxides 2.59Ba – Hb in the formation of 1,2-benzothiazolo[2,3-α]quinoline 2.66a – c, e and 2.71a – 2.73b, it was thought that addition of an iodine electrophile to preformed 2.59Ba – Hb in a separate reaction would also give 2.66a – c, e and 2.71a – 2.73b. Accordingly, treatment of 2.59Ba with 3 equiv. of ICl in MeCN at reflux was investigated. After 24 h TLC examination showed that the reaction had gone to completion and work-up provided 2.66a-3 in an excellent yield (91%, entry 1, Table 2.18), thereby reinforcing the suggested mechanism in Scheme 2.71. The reactivity of 2.59Ba – Hb towards the optimised conditions (3 equiv. ICl in MeCN) were investigated as shown in Schemes 2.79 and 2.80, the results are collated in Tables 2.18 and 2.19.
**Scheme 2.79**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R¹</th>
<th>1,2-Benzothiazole</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Tetracycle</th>
<th>R³</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tolyl</td>
<td>Ph</td>
<td>2.59Ba</td>
<td>24</td>
<td>82</td>
<td>2.66a-3</td>
<td>Me</td>
<td>91</td>
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<tr>
<td>2</td>
<td>Tolyl</td>
<td>C₃H₇</td>
<td>2.59Bb</td>
<td>21</td>
<td>82</td>
<td>2.66b-3</td>
<td>Me</td>
<td>40</td>
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<tr>
<td>3</td>
<td>Tolyl</td>
<td>4-MeOC₆H₄</td>
<td>2.59Bc</td>
<td>4</td>
<td>82</td>
<td>2.66f</td>
<td>Me</td>
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<td>4</td>
<td>3-MeC₆H₄</td>
<td>Ph</td>
<td>2.59Ca</td>
<td>22</td>
<td>82</td>
<td>2.66a</td>
<td>Me</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>3-MeC₆H₄</td>
<td>C₃H₇</td>
<td>2.59Cb</td>
<td>22</td>
<td>82</td>
<td>2.66b</td>
<td>Me</td>
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<td>C₃H₇</td>
<td>2.59Db</td>
<td>22</td>
<td>82</td>
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<td>0</td>
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<tr>
<td>7</td>
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<td>5</td>
<td>82</td>
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<tr>
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<td>C₃H₇</td>
<td>2.59Eb</td>
<td>1</td>
<td>82</td>
<td>2.71b-2</td>
<td>OMe</td>
<td>41</td>
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</table>

**Table 2.18** Yields from iodocyclisations of 3,3-di(alkynyl)-1,2-benzothiazole 1,1-dioxides 2.59Ba – Eb
Scheme 2.80

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>1,2-Benzothiazole</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Tetracycle</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-thienyl</td>
<td>C₃H₇</td>
<td>2.59Gb</td>
<td>3</td>
<td>82</td>
<td>2.72b</td>
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</tr>
<tr>
<td>2</td>
<td>2-naphthyl</td>
<td>Ph</td>
<td>2.59Ha</td>
<td>24</td>
<td>82</td>
<td>2.73a</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>2-naphthyl</td>
<td>C₃H₇</td>
<td>2.59Hb</td>
<td>24</td>
<td>82</td>
<td>2.73b</td>
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</tr>
</tbody>
</table>

Table 2.19 Attempted iodocyclisations of 3,3-di(alkynyl)-1,2-benzothiazole 1,1-dioxides 2.59Gb – Hb
Unfortunately the 3,3-di(alkynyl)-1,2-benzothiazole 1,1-dioxides $2.59\text{Ca} - b \ R = 3$-$\text{MeC}_6\text{H}_4, \ R^1 = \text{Ph}$ and $\text{C}_3\text{H}_7$ (entries 4 and 5, Table 2.18) and $2.59\text{Ha} - b \ R = 2$-naphthyl, $R^1 = \text{Ph}$ and $\text{C}_3\text{H}_7$ (entries 2 and 3, Table 2.19) provided only starting material from the reaction with ICl in MeCN. The other substrates failed to yield any identifiable products and afforded only complex mixtures. The 1,2-benzothiazolo[2,3-$a$]quinolines $2.66\text{a-3}$ and $2.66\text{b-3}$ (entries 1 and 2, Table 2.18), furnished higher yields from this stepwise sequence in comparison to the one-pot reaction Scheme 2.74 (entries 3 and 4, Table 2.15).

The 1,2-benzothiazolo[2,3-$a$]quinoline $2.71\text{b-2}$ was isolated in 41% yield (entry 8, Table 2.18); as discussed previously (Scheme 2.77) the 3-$\text{MeO}\text{C}_6\text{H}_4$ group should be significantly more reactive in the ortho positions of the aromatic ring to electrophilic attack from the alkyne derived iodonium ion. The 2-methoxy-1,2-benzothiazolo[2,3-$a$]quinoline $2.71\text{b-2}$ isolated from treatment of $2.59\text{Eb}$ with ICl was found to be the expected regioisomer (Scheme 2.81). Cyclisation having occurred at the least hindered position ortho to nitrogen (i.e. para to OMe). None of the alternative regioisomer (the 1-methoxy derivative) arising from $S\text{E}Ar$ ortho to the methoxy group was observed.

![Scheme 2.81](image)

The structure of $2.71\text{b-2}$ was confirmed by the $^1\text{H}$ NMR spectrum (Figure 2.24), and consideration of the splitting patterns and coupling constants of the aromatic ring protons.
The reaction of reversed sulfonamides 2.23Aa – Hb and/or the 3,3-di(alkynyl)-1,2-benzisothiazole 1,1-dioxides 2.59Aa – Hb with ICl in MeCN provides a pathway to the novel ring system 1,2-benzisothiazolo[2,3-a]quinoline 2.66a – b and 2.71a – 2.73b. Iodocyclisation of a pre-formed 3,3-di(alkynyl)-1,2-benzisothiazole 1,1-dioxides appears to offer the most efficient route to these compounds, the chemistry of which merit further investigation.
Chapter 3

Electrophilic Cyclisations of 3-Arylpenta-1,4-diyn-3-ols via 6-Endo-dig or 6-Exo-dig Pathways
Chapter 3 Electrophilic Cyclisations of 3-Aryl-penta-1,4-diyn-3-ols via 6-Endo-dig or 6-Exo-dig Pathways

3.1 Iodocyclisations of 3-[2-(Arenesulfonamido)phenyl]penta-1,4-diyn-3-ols to 4-Alkynyl-3-iodoquinoline and Derivatives

Iodine-mediated electrophilic cyclisations of alkynes have been exploited to generate a wide variety of different heterocycles (cf. Scheme 1.4). A significant advantage of this approach is that many of the resulting rings will possess an iodo substituent, allowing the further functionalisation or annulation of the ring. A number of reviews covering iodocyclisation reactions are available [14COS-II(4)412, 14MI251, 15S1961, 16OBC7639, 16MI49730].

Molecular iodine has been utilised to promote the cyclisation of 2-(tosylamino)phenylpropynols to afford 3-iodoquinolines. If nitromethane was used as the solvent the yields were poor. However, when replaced with methanol high yields (40 – 99%) of the 3-iodoquinoline were obtained (Scheme 3.1) [11OL2598].

![Scheme 3.1](image)

To date, no example of the iodocyclisations of alkynols in which $R_1$ = alkynyl have been reported. In the present work, initial experiments therefore focused on the behaviour of 1,5-disubstituted-3-[2-(arenesulfonylamido)phenyl]penta-1,4-diyn-3-ols 2.5 – 2.8 towards an electrophilic iodine source (iodenium ion I+). It is pertinent to note that both 5-exo-dig (3.1) and 6-endo-dig (3.2) pathways are possible from the iodonium ion intermediate X affording indoles (3.1) or quinoline derivatives (3.2) respectively (Scheme 3.2).
Preliminary work showed that when \textbf{2.5a} was treated with iodine in refluxing MeOH (Scheme 3.3), a good yield of iodoquinoline \textbf{3.2a} could be obtained (66\%) [16UP1]. The product was characterised by its $^1$H and $^{13}$C NMR spectra (Figure 3.1) as well as by HMRS that exhibited a molecular ion at $m/z$ [M+H]$^+$ = 432.0245 corresponding to C$_{23}$H$_{14}$IN.

Various quinolines with similar structural features to 3-iodo-2-phenyl-4-(phenylethynyl)quinoline \textbf{3.2a} are shown in Scheme 3.4. 3-Iodoquinolines in Scheme 3.4 A and B have different $^1$H NMR aromatic resonances for the benzo ring protons of the quinoline compared with those in \textbf{3.2a} (Figure 3.1). However, $^1$H NMR data for 4-phenylethynylquinoline in C Scheme 3.4 reveals that upon incorporation of an alkyne unit in
the 4-postion of the quinoline, the peri proton (5-H) is deshielded and moves downfield in comparison to 8-H. The \(^1\)H NMR resonance for the 5-H proton on 3-iodo-2-phenyl-4-(phenylethynyl)quinoline 3.2a (\(\delta_H 8.39\) ppm, Figure 3.1) is therefore similar to that of the 4-phenylethynyl quinoline shown in C Scheme 3.3 (\(\delta_H 8.38\) ppm). The quaternary 3-C-I \(^{13}\)C NMR resonance of quinoline 3.2a (\(\delta_C 102.29\) ppm) is comparable to that reported for 2,4-diphenyl-3-iodoquinoline \(\delta_C 98.5\)ppm (B, Scheme 3.4) and for a number of other 2-substituted-3-iodo-4-phenylquinoline derivatives for which 3-C-I carbon resonates in the region of \(\delta_C 100.2 – 101.6\) ppm (D, Scheme 3.4). Addition of substituents to the quinoline ring clearly changes the shift of the \(^{13}\)C NMR 3-C-I carbon resonance, as that in the 3-iodoquinoline (A, Scheme 3.4) is shielded by nearly 10 ppm in comparison to the 2,4-diphenyl-3-iodoquinoline in B Scheme 3.4.
Scheme 3.4

A

$\delta_H$

$\delta_C$

141
Figure 3.1 400 MHz $^1$H and 100 MHz $^{13}$C NMR spectra of 3.2a in CDCl$_3$
On repeating treatment of 2.5a with iodine in refluxing MeOH (Scheme 3.3) was found that unfortunately the yield of 3.2a was not as high nor as reproducible as previously achieved [16UP1]. However, an additional minor product was isolated by flash column chromatography from the reaction mixture. Both 1D and 2D NMR analysis (COSY, HSQC and HMBC) as well as HMRS confirmed the constitution of the product. The latter exhibited a molecular ion at \( m/z \) \([\text{M+H}]^+ = 306.1285\) corresponding to \( \text{C}_{23}\text{H}_{15}\text{N} \). The compound was found to be the 2-phenyl-4-(phenylethynyl)quinoline 2.35a but was only isolated in very low yields (6% - Table 3.1).

Formation of 2.35a, as described in Section 2.4 (Scheme 2.44) is generated via a Meyer-Schuster rearrangement and concomitant cyclisation of the intermediate enone (Scheme 3.5)

To establish whether acidic conditions would effect cyclisation of the dialkynol 2.5a to 2-phenyl-4-(phenylethynyl)quinoline 2.35a, the former was treated with TsOH in toluene at 100 °C for 19 h (Scheme 3.6). The \(^1\text{H}\) NMR spectrum of the crude material indicated that 2.35a had indeed been formed and was 90% pure, however attempts to effect purification by column chromatography resulted in degradation. Nevertheless, this result confirmed that acidic conditions were the reason for the competing formation of the 4-alkynylquinoline 2.35a.
Reddy et al. found that iodocyclisation ($I_2$) of alkynols to 3-iodoquinolines also afforded 2,4-substituted quinolines (3.3) in up to 30% yield (Scheme 3.7). They did not allude to the formation of the latter but it is envisaged to proceed via a Meyer-Schuster rearrangement.

It was found that high yields (70 – 90%) of the quinoline 3.3 could be obtained by treatment of the 1-(2-aminophenyl)propynols with PPTS [12MI3986].

In efforts to optimise the yield of 3-iodo-2-phenyl-4-(phenylethynyl)quinoline 3.2a from dialkynol 2.5a different solvents and positive iodine sources were investigated (Scheme 3.8); as well as the addition of base which should supress the acidic formation of the parent (uniodinated) quinoline 2.35a. The results are collated in Table 3.1.
Scheme 3.8

\[
\begin{align*}
\text{2.5a} & \xrightarrow{\text{I-X, solvent, base}} \text{3.2a} \\
X = \text{I, Cl, } & \text{and/or} \\
\text{2.35a} & 
\end{align*}
\]
<table>
<thead>
<tr>
<th>Entry</th>
<th>I* source</th>
<th>Equiv.</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Base</th>
<th>Equiv.</th>
<th>Yield of 3.2a (%)</th>
<th>Yield of 2.35a (%)</th>
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<td>–</td>
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</tr>
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<td>MeOH</td>
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<td>–</td>
<td>26</td>
<td>1</td>
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<td>–</td>
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<td>–</td>
<td>–</td>
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</tr>
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<td>–</td>
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</tr>
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<tr>
<td>20</td>
<td>ICl</td>
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<td>MeCN</td>
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<td>r.t.</td>
<td>–</td>
<td>–</td>
<td>19</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 3.1 Optimisation of conditions for the iodocyclisation of 2.5a to 3.2a. a = 3,6-dioido-2-phenyl-4-(phenylethynyl)quinoline 3.4a also isolated
With elemental iodine the use of dry solvents did not increase the yield of 3-iodoquinoline \textit{3.2a} substantially, nor decrease the yield of the quinoline \textit{2.35a}. However, increasing molar equivalents of the electrophile did exert a positive benefit (entry 5, Table 3.1). Iodocyclisations in which iodine was used in the absence of base (entries 1 – 6, Table 3.1), generated 2-phenyl-4-(phenylethynyl)quinoline \textit{2.35a} (TLC) but separation from the 3-iodoquinoline \textit{3.2a} was not always achievable, due to very similar Rf values in various solvent systems.

Treatment of \textit{2.5a} with of \textit{I}_{2} and \textit{Na}_{2}HPO_{4} (entries 7 and 8, Table 3.1) produced very complex reaction mixtures, it was thought that the base strength of \textit{Na}_{2}HPO_{4} may have an adverse influence, therefore a weaker base (\textit{NaHCO}_{3}) was employed. A less complex reaction mixture was obtained, however yields of the desired compound \textit{3.2a} were still low. Although, as predicted no 2-phenyl-4-(phenylethynyl)quinoline \textit{2.35a} appeared to be present (TLC).

Interestingly, with \textit{NaHCO}_{3} and \textit{I}_{2} in dry MeOH (entry 9, Table 3.1) in addition to 3-iodo-2-phenyl-4-(phenylethynyl)quinoline \textit{3.2a}, a faster running product was also isolated by flash column chromatography (5% EtOAc – hexane). This unknown material readily crystallised and when washed with cold hexane, produced white needles. The \textit{^1H} NMR spectrum of the compound exhibited a doublet at \(\delta_{H} 8.75 \text{ ppm (}J_{5-7} = 1.9 \text{ Hz})\) and a doublet of doublets at \(\delta_{H} 8.00 \text{ ppm (}J_{7-8} = 8.8 \text{ Hz, }J_{7-5} = 1.9 \text{ Hz})\), which implied that the quinoline benzo moiety was now substituted (Figure 3.2). Indeed, ESI-HRMS confirmed the constitution as a diodinated species (\textit{3.4a}) with a molecular ion at \(m/z \ [\text{M+H}^+] = 557.9207\) corresponding to \textit{C}_{23}\text{H}_{13}\text{I}_{2}\text{N}.

Furthermore, the \textit{^{13}C} NMR spectrum exhibited high field signals in the region characteristic for an aromatic C-I bond, \(\delta_{C} 102.90 \text{ ppm for the 3-C-I and at }\delta_{C} 100.03 \text{ ppm for another sp² C-I.}\) These shifts are similar to those reported by Zhang for 3,6-diodo-2,4-diphenylquinoline (\(\delta_{C} 99.58\) and 93.31 ppm, Scheme 3.10) [170BC6901]. The diodoquinoline was assigned the structure \textit{3.4a} (Figure 3.2, 3,6-disubstituted) due to the electron releasing effect of the sulfonamide nitrogen at the para position in \textit{2.5a} (Scheme 3.9), the yield of \textit{3.4a} was 4% and that of the 3-iodoquinoline \textit{3.2a} was 11%. 
The mechanism for the formation of 3,6-diiodoquinoline 3.4a is envisaged to be electrophilic aromatic substitution (S$_{E}$Ar) of the benzo ring with an iodine electrophile, followed by the activation of the triple bond and subsequent cyclisation to the quinoline 3.4a (Scheme 3.9).

Electrophilic cyclisation of dialkynol 2.5a with NIS was also explored. As this positive iodine source has been reported to be highly effective for the synthesis of several heterocycles via iodo cyclisation including but not limited to quinolines, indoles and dihydrofurans [14MI251, 19S1841]. Zhang et al. achieved good yields of 3-iodo-2,4-diphenylquinoline from an N-phenyl propargylamine with NIS in 1,4-dioxane, together with trace amounts of 3,6-diiodo-2,4-diphenylquinoline; whereas in MeOH the product distribution was reversed (Scheme 3.10) [17OBC6901].
Chan and co-workers found that with NIS in dry MeNO₂ at reflux, 1-(2-tosylamidophenyl)prop-2-yn-1-ol in which \( R^1 \neq H \) would cyclise easily to diodomethyl-indolin-2-ones, but at ambient temperature when \( R^1 = H \) iodomethylene-indolin-3-ones were be obtained. However, when non-distilled solvent was used 3-phenyl-1-tosyl-1\( H \)-indole-2-carbaldehyde was produced (A, Scheme 3.11) [13CEJ1978]. Similar behaviour was observed from treatment of the propynols with NIS in \( H_2O - acetone \), this reaction also tolerated \( R^1 = H \) (B, Scheme 3.11) [13T7471].

Reactions of the dialkynol 2.5a with NIS were not successful in a variety of solvents (entries 11 – 14, Table 3.1), providing little (7%, entry 13, Table 3.1) or no 3-iodoquinoline 3.2a. Interestingly, NIS in dry MeOH (entry 13, Table 3.1) also provided the 3,6-diiodoquinoline 3.4a in 14% yield. This finding is in line with that of Zhang et al. from the cyclisation of \( N \)-phenyl propargylamines with NIS in MeOH (Scheme 3.10) [17OBC6901]. We did not find 4-
alkynyl-3,6-diiodoquinoline 3.4a to be generated in the same high yields as those reported by Zhang et al. for the 2,4-diaryl-3,6-diiodoquinoline (59 – 76% yield). The N-phenyl propargylamines are much more electron rich than the 1,5-disubstituted-3-[2-(benzenesulfonylamido)phenyl]penta-1,4-diyn-3-ol 2.5a used in this work.

Since NIS was not a favourable electrophile for the cyclisation of 2.5a (entries 11 – 14, Table 3.1), the highly electrophilic species ICl was employed. With only a few papers describing its use as an electrophilic initiator to synthesise quinoline derivatives from arylacetylenes, arylpropynones and (most relevant) propynol derivatives (Scheme 3.17) [05OL763, 06JOC1626, 06OL243, 10JOC1266, 10T1177]. Iodine monochloride has found more extensive use for cyclisations leading to chromone and isocoumarins and the use of ICl to initiate electrophilic cyclisation has been reviewed [15S1961].

Thus treatment of dialkynol 2.5a with ICl (2 equiv.) in acetonitrile (entry 15, Table 3.1) resulted in a rapid reaction and TLC indicated that after 1 h only a small amount of starting material remained. The mixture was purified by flash column chromatography. The initial fractions afforded TsCl whilst the main fractions provided a solid that was further purified by recrystallisation from EtOH – EtOAc to give 3-iodo-2-phenyl-4-(phenylethynyl)quinoline 3.2a in 60% yield. With this being the highest yield achieved in the optimisation studies other 1,5-disubstituted-3-[2-(benzenesulfonylamido)phenyl]penta-1,4-diyn-3-ols 2.5 – 2.8 possessing a variety of substituents on the alkyne and benzenesulfonyl moieties, were then subjected to treatment with ICl in acetonitrile (Method A, Scheme 3.13, Table 3.2).

Unfortunately, exposure of the N-[2-(6-hydroxyundeca-4,7-diyn-6-yl)phenyl]-4-methylbenzenesulfonyamide 2.5b to ICl in MeCN provided a complex mixture that could not be purified by flash column chromatography. Consequently, alkylacetylene-derived dialkynols (2.5b, d, g, j, k and 2.6b, 2.7b) were subjected to the ‘next best’ option in the screening procedure (Table 3.1), I2 (3 equiv.) in MeOH at reflux (Method B, Scheme 3.13),
which allowed access to the 2-alkyl-4-alkynyl-3-iodoquinolines in yields ranging from 12 – 63% (Table 3.2).

**Scheme 3.13**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R¹</th>
<th>Dialkynol</th>
<th>Method</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
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<td>Ph</td>
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<td>1.0</td>
<td>3.2a</td>
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<tr>
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<td>NO₂</td>
<td>C₃H₇</td>
<td>2.7b</td>
<td>B</td>
<td>19.0</td>
<td>3.2b</td>
<td>12</td>
</tr>
<tr>
<td>12</td>
<td>H</td>
<td>Ph</td>
<td>2.8a</td>
<td>A</td>
<td>2.0</td>
<td>3.2a</td>
<td>41</td>
</tr>
</tbody>
</table>

**Table 3.2** Yields from the iodocyclisation of dialkynols 2.5 – 2.8. a = Reaction also afforded 3,6-diodo-2-phenyl-4-(phenylethynyl)quinoline 3.4a
N-[2-(3-Hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)phenyl]-4-nitrobenzenesulfonamide 2.7a (entry 10, Table 3.2) reacted with ICl in MeCN to also afford the 3,6-diiodoquinoline 3.4a in 18% yield (Scheme 3.14) and was the only dialkynol to do so under the optimised conditions. This observation can be ascribed to the diminished nucleophilicity of the sulfonamide nitrogen and subsequent slowing of its addition to the iodonium cation, allowing competitive electrophilic iodination of the aromatic ring.

Scheme 3.14

Dialkynols 2.5j and 2.5k (entries 6 and 7, Table 3.2) provided complex mixtures and no identifiable products could be isolated from these reactions. Dialkynols 2.5j and 2.5k were also subjected to Method A conditions (2 equiv. ICl in MeCN, r.t. for 24 h) but again only a complex mixture was obtained. However, with these two exceptions the other dialkynols provided access to a range of 4-alkynyl-3-iodoquinolines (Table 3.2).

Of the novel 4-alkynyl-3-iodoquinolines 3.2, Figure 3.3 shows the ranges of $^1$H and $^{13}$C NMR resonances for 5-$H$ – 8-$H$ protons and for the 3-$C$ carbon. The 3-$C$-I carbon bond is shielded in comparison to the normal range for an aromatic carbon ($\delta_C$ 120 – 160) due to the heavy-atom effect of the iodine substituent [98CEJ118, 16JTC199]. The $^1$H NMR ranges of the benzo ring protons are similar to those reported by Batsyts et al. for 4-(phenylethynyl)quinoline (Scheme 3.3) [19OBC4102].
Iodocylisations of 1,5-disubstituted-3-[2-(benzenesulfonylamido)phenyl]penta-1,4-diyn-3-ols 2.5 – 2.8 followed the expected trend; the benzenesulfonyl group containing the electron donating methoxy group (2.6a – b) provided better yields of 4-alkynyl-3-iodoquinolines in a faster time (entries 8 and 9, Table 3.2), whereas the dialkynols possessing the electron withdrawing 4-nitrobenzenesulfonyl group (2.7a – b) provided lower yields of 4-alkynyl-3-iodoquinolines and required a longer reaction time (entries 10 and 11, Table 3.2).

It is surprising that ICl did not react cleanly with the alkyl-terminated dialkynols 2.5b, d, g, j and k as it is a better electrophile than iodine, due to the permanent dipole that exists and which facilitates electrophilic attack [07JOC977, 14MI251]. The phenyl ring will impart some stability to the intermediate iodonium ion, as in the strain-free ring-opened form, the vinyl carbocation X, there will be conjugation with the aryl group (Scheme 3.15) [93TL8205]. However, when the aryl substituent is replaced with an alkyl group only inductive stabilisation of the cation is possible. Presumably the lower yields of the 2-alkyl-4-alkynyl-3-iodoquinolines 3.2b, d, g, j and k, compared to those of the 2-aryl-4-alkynyl-3-iodoquinoline derivatives 3.2a and 3.2 are a reflection of the diminished stability of the cationic intermediate.

Scheme 3.15
The mechanism for the formation of the 4-alkynyl-3-iodoquinolines 3.2 proceeds via an iodonium intermediate which was initially suggested by Larock and co-workers for the iodocyclisation of 1-(2-methoxyphenyl)prop-2-yn-1-ols to 3-iodochromones [06JOC1626], and subsequently for quinolines from 1-(2-tosylamindophenyl)prop-2-yn-1-ols by Ali and co-workers [11OL2598]. Overall, the reaction sequence can be envisaged as proceeding by anti-attack of the electrophile and the nitrogen on the alkyne moiety via a 6-endo-dig pathway to produce the intermediate quinolinium salt, which then dehydrates to afford the N-tosylquinolinium salt. Subsequent elimination of the arenesulfonyl moiety will be facile, to afford the product 3.2 (Scheme 3.16). When iodine monochloride is used the benzenesulfonyl chloride is isolated, it is expected that in the cases when molecular iodine is used TsOH will be lost.

The 4-alkynyl-3-iodoquinolines (3.2a – g) obtained in this work are all novel compounds and as such represent a missing series of novel functionalised quinolines. Both the alkyne and the iodo functions allow the ring to be further elaborated, giving access to more complex heterocyclic systems via annulation reactions. With only a handful of literature examples of substituted 3-iodoquinolines and, as to date, only three papers accessing them via propargylic alcohols exist (A, B and C, Scheme 3.17) [11OL2598, 12MI3986, 17EJO4600]. In reaction D Scheme 3.17, no external iodine electrophile was utilised to afford the 3-
iodoquinoline. A copper(II) catalysed tandem reaction of diaryliodonium salts, nitriles and 1-haloalkynes afforded 2,4-disubstitued-3-haloquinolines with varying substituents, both aryl and alkyl groups are tolerated (D, Scheme 3.17) [16ASC2332]. Ramanathan and Liu utilised a similar set of starting materials to synthesise 2,4-disubstitued-3-iodoquinolines, from aryldiazonium salts with 1-iodoalkynes (E, Scheme 3.17) [17T4317]. 1-Azido-2-(2-propynyl)benzene cyclised with ICl in nitromethane at r.t. to afford 3-iodo-2-arylquinoline after the loss of N₂, only two examples were reported with this method (F, Scheme 3.17) [10JOC1266]. The majority of the other 3-iodoquinolines reported in the literature have been synthesised from the iodocyclisation of alkynylanilines (G – K, Scheme 3.17), with varying iodine electrophiles and solvents [04JOC8251, 05OL763, 10T1177, 17JOC4625, 17JOC11727, 17OBC6901]. Simple diazotisation of 3-aminoquinoline and substitution with KI afforded the 3-iodo-3-phenylquinoline (L, Scheme 3.17) [12S290]. The N-methylquinolinium salt (M, Scheme 3.17) was also afforded after the iodocyclisation of a dimethylaminoalkynol [06OL243].
Scheme 3.17

(i) H₂O, EtOAc, I₂, r.t.; (ii) I₂, DCM, r.t.; (iii) I₂, MeOH, 60 °C; (vi) Cu(OTf)₂ (10 mol %), DCE, Δ; (v) 80 °C; (vi) I₂, MeNO₂, r.t.; (vii) NIS (1.5 equiv.), BF₃·Et₂O (1.5 equiv.), DCM, 0 °C; (viii) Evaporation, NaOH (10.0 equiv.), MeOH, 60 °C; (ix) I₂, DCM, -78 °C; (x) NaOMe, MeOH, r.t.; (xi) NaHCO₃, MeCN, I₂, r.t.; (xii) NIS, 1,4-dioxane, r.t.; (xiii) NIS, CuI, MeCN, Δ; (xiv) TsOH, NaNO₂, KI, MeCN, 0 °C;

A = R = H, Cl, Br
R¹ = Ph, 2-HalC₆H₄, 4-FC₆H₄
R² = aryl, alkyl
[17EJO4600]

B = R = H, NO₂
R¹ = Ph, Me
R² = aryl, alkyl
[12M13986]

C = R = H, Cl, Br
R¹ = aryl, alkyl
R² = aryl, alkyl
[11OL2598]

D (vi)

E (v)

F

G = R = H
R¹ = aryl, alkyl
R² = H
G = Ts
[17JOC11727]

H = R = H, OMe, Br
R¹ = aryl, alkyl
R² = H
G = Tf
[10T11177]

J = R = H, Me, OMe,
R¹ = Ph, CF₃
R² = Ph, tolyl, 4-FC₆H₄
[17OBC6901]

K = R = H, Me, Cl, Br, F
R¹ = alkyl, aryl
R² = aryl
[17JOC4625]

L (xiv)

M

R = H
R¹ = H, Me
R² = 4-MeOC₆H₄, n-Pr
[06OL243]
The foregoing work demonstrated the successful iodocyclisation of 1,5-disubstituted-3-[2-(benzenesulfonylamido)phenyl]penta-1,4-diyln-3-ols 2.5 – 2.8 to novel 4-alkynyl-3-iodoquinolines 3.2. Subsequent investigations were directed to exploring the regiochemical preferences in the iodocyclisations of the unsymmetrical dialkynols 2.19 with the optimised conditions; iodine monochloride in MeCN (Method A) or with elemental iodine in refluxing MeOH Method B (Scheme 3.18, Table 3.3).

![Scheme 3.18](image)

Method A: ICl (2 equiv.), MeCN, r.t.
Method B: I₂ (3 equiv.), MeOH, Δ

(X) and/or (Y) R¹ and R² as defined in Table 3.3
<table>
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<th>Entry</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>Dialkynol Method</th>
<th>Time (h)</th>
<th>Quinoline</th>
<th>Quinoline-X yield</th>
<th>Quinoline</th>
<th>Quinoline-Y yield</th>
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<td>1</td>
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<td>4.3</td>
<td>3.5Ab-X</td>
<td>14</td>
<td>3.5Ab-Y</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>C$_3$H$_7$</td>
<td>2.19Ab B</td>
<td>1</td>
<td>3.5Ab-X</td>
<td>0</td>
<td>3.5Ab-Y</td>
<td>15</td>
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<td>3</td>
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<td>3.5Ac-X</td>
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<td>19</td>
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<td>0</td>
<td>3.5Ak-Y</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td>H</td>
<td>2.19Ai A</td>
<td>1.5</td>
<td>3.5Ai-X</td>
<td>0</td>
<td>3.5Ai-Y</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>4-MeOC$_6$H$_4$</td>
<td>C$_3$H$_7$</td>
<td>2.19Cb B</td>
<td>1.25</td>
<td>3.5Cb-X</td>
<td>28</td>
<td>3.5Cb-Y</td>
<td>0</td>
</tr>
<tr>
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<td>CH$_2$OMe</td>
<td>2.19Cf B</td>
<td>2.3</td>
<td>3.5Cf-X</td>
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<td>3.5Cf-Y</td>
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<td>H</td>
<td>2.19Ci A</td>
<td>1.5</td>
<td>3.5Ci-X</td>
<td>0</td>
<td>3.5Ci-Y</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3.3 Yields from the iodoscyclisations of unsymmetrical dialkynols 2.19
It was difficult to isolate any pure products from the majority of the reactions because the compounds produced possessed very similar Rf values. In some cases, complex mixtures were produced from which no identifiable products could be isolated.

3-iodo-4-(phenylethynyl)-2-propylquinoline **3.5Ab-Y** (entry 1 and 2, Table 3.3) was characterised by both 1D and 2D NMR (COSY, HSQC, HMBC) spectra, with the $^1$H NMR data of 3-iodo-4-(pent-1-yn-1-yl)-2-propylquinoline **3.2b** providing a useful comparison. The similarity of the CH$_2$ splitting pattern and the chemical shift of the C-2 propyl group in quinoline **3.2b** ($\delta_H$ 3.19 ppm, red spectrum, Figure 3.4), are comparable to that seen in **3.5Ab-Y** ($\delta_H$ 3.25 ppm, blue spectrum, Figure 3.4). Moreover, the HMBC spectrum of 3-iodo-4-(phenylethynyl)-2-propylquinoline **3.5Ab-Y** shows a correlation between the CH$_2$ protons of the 2-propyl group and the resonance corresponding to the 3-C carbon at $\delta_C$ 100.38 ppm (Figure 3.5). Surprisingly, the major isomer from the cyclisation of **2.19Ab** was the 2-propylquinoline **3.5Ab-Y**, using either Method A or Method B (entry 1 and 2, Table 3.3). The iodocyclisation did not provide the 2-phenylquinoline **3.5Ab-X** as the major isomer. The latter would be expected because the phenyl ring should impart a stabilising effect on the intermediate iodonium ion (Scheme 3.15). The difference in the yields obtained maybe due to the difficulties in separating the two isomers (Scheme 3.19).

An indication that the cyclisation proceeds via cyclisation onto the more stabilised iodonium ion intermediate was obtained by consideration of the other entries in the table which gave the expected major isomer **3.5Ac-Y**, **3.5Aj-X** and **3.5Cb-X** (Table 3.3, entries 3, 6, and 9, respectively). Thus, **2.19Ac** provided the 3-iodo-2-(4-methoxyphenyl)quinoline **3.5Ac-Y** exclusively. In a similar manner **2.20Aj** and **2.20Cb** provided the 2-aryl-3-iodoquinoline as the only characterisable products, albeit in low yields.
Scheme 3.19

Method A: ICl (2 equiv.), MeCN, r.t.
Method B: I₂ (3 equiv.), MeOH, 65 °C

Figure 3.4 400 MHz ¹H NMR spectra comparison of 3.2a and 3.5Ab-Y in CDCl₃

Figure 3.5 HMBC spectrum of 3.5Ab-Y
The quinolines \textbf{3.5Ag-X}, \textbf{3.5Ag-Y} and \textbf{3.5Aj-X} (entry 5 and 6, Table 3.3) were also characterised by their 1D and 2D NMR (COSY, HSQC, HMBC) spectra. In the case of 3-iodo-2-phenyl-4-(prop-1-yn-1-yl)quinoline \textbf{3.5Ag-X} (entry 5, Table 3.3) the alkylnl-linked methyl group exhibits a similar \(^{1}\text{H} \) NMR chemical shift (\(\delta_{\text{H}} 2.36 \text{ ppm} \)) to the starting material \textbf{2.19Ag} (\(\delta_{\text{H}} 1.92 \text{ ppm} \), Figure 3.6). Moreover, the \(^{13}\text{C} \) NMR shift of the methyl carbon in \textbf{3.5Ag-X} (\(\delta_{\text{C}} 5.18 \text{ ppm} \)) is strongly shielded due to the anisotropic effect of the alkyne unit, thus confirming the structure as \textbf{3.5Ag-X}.

On the other hand, the next fraction (\textbf{3.5Ag-Y}) obtained from the iodo cyclisation of \textbf{2.19Ag} exhibits a significant downfield shift of the methyl group both in the \(^{1}\text{H} \) NMR (\(\delta_{\text{H}} 3.03 \text{ ppm} \)) and the \(^{13}\text{C} \) NMR resonance (\(\delta_{\text{C}} 31.20 \text{ ppm} \)) as shown in Figure 3.6, in comparison to the starting material \textbf{2.19Ag} (\(\delta_{\text{H}} 1.92 \text{ ppm} \) and \(\delta_{\text{C}} 2.64 \text{ ppm} \)), implying that the methyl group is no longer shielded by the anisotropic effect of the alkyne, therefore supporting to the structure 3-iodo-2-methyl-4-(phenylethynyl)quinoline \textbf{3.5Ag-Y}. Moreover, the HMBC spectrum of \textbf{3.5Ag-Y} exhibits a correlation between the 2-methyl protons (\(\delta_{\text{H}} 3.03 \text{ ppm} \)) and the quaternary 3-C carbon (\(\delta_{\text{C}} 100.90 \text{ ppm} \)). The \(^{1}\text{H} \) and \(^{13}\text{C} \) NMR chemical shifts for the methyl groups in quinolines \textbf{3.5Ag-X} and \textbf{3.5Ag-Y} are nearly identical those that of the isomeric 3-iodo-2-methyl-4-(prop-1-yn-1-yl)quinoline \textbf{3.2g} (Figure 3.6), further confirming each assigned structure of quinolines \textbf{3.5Ag-X} and \textbf{3.5Ag-Y} (Figure 3.6).

The iodo cyclisation reaction of dialkynol \textbf{2.19Ag} and molecular iodine in refluxing MeOH (entry 5, Table 3.3) provided the unexpected major isomer 2-methylquinoline \textbf{3.5Ag-Y} in a higher yield. As discussed previously this could be due to the difficulties in purifying the reaction mixture.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.6.png}
\caption{\(^{1}\text{H} \) and \(^{13}\text{C} \) NMR chemical shift comparison of \textbf{2.19Ag}, \textbf{3.5Ag-X}, \textbf{3.5Ag-Y} and \textbf{3.2g}}
\end{figure}
Of all the iodocyclisation products obtained from the unsymmetrical dialkynols (Table 3.3) the most challenging to characterise was that obtained from \(2.19\text{Ac}\) in which the two alkyne units are terminated by different aryl groups. Clearly the cyclisation could afford either the 2-phenylquinoline \(3.5\text{Ac-X}\) or the 2-(4-methoxyphenyl) derivative \(3.5\text{Ac-Y}\) (Scheme 3.20). It was anticipated that the latter would be generated preferentially because of the greater nucleophilicity of the (4-methoxyphenyl)ethynyl group towards ICl compared to the phenylethylnyl functions. In addition, the enhanced stability of the iodonium cation bearing an electron donating 4-methoxyphenyl group (c.f. Scheme 3.15) should also assist in directing the cyclisation.

Thus exposure of \(2.19\text{Ac}\) to ICl in MeCN afforded a single 3-iodoquinoline derivative in 32% yield (entry 3, Table 3.3). The constitution of this compound was established as the expected product i.e. 3-iodo-2-(4-methoxyphenyl)-4-(phenylethynyl)quinoline \(3.5\text{Ac-Y}\) by comparison of its \(^1\text{H}\) NMR spectrum, firstly with that of the 3-iodo-2-(4-methoxyphenyl)-4-(pent-1-yn-1-yl)quinoline \(3.5\text{Cb-X}\) which revealed that the \(^1\text{H}\) NMR shifts of the 2-(4-methoxyphenyl) protons (red boxes, B, Figure 3.7, \(\delta_H\) 7.57 ppm and 7.01 ppm) are similar to that found in \(3.5\text{Ac-Y}\) (red boxes, A, Figure 3.7, \(\delta_H\) 7.60 ppm and 7.02 ppm). Furthermore the \(^1\text{H}\) NMR resonances for the phenyl unit in 3-iodo-4-(phenylethynyl)-2-propylquinoline \(3.5\text{Ac-Y}\) (green boxes, A, Figure 3.7) have similar chemical shifts to that for quinoline \(3.5\text{Ab-Y}\) (green boxes, C, Figure 3.7), further confirming the assignment of entry 3 (Table 3.3) to quinoline \(3.5\text{Ac-X}\).
Figure 3.7 ¹H NMR spectra comparison of 3-iodoquinolines 3.5Ac-Y with 3.5Cb-X and 3.5Ab-Y in CDCl₃

Ali *et al.* reported the preparation of 3-ido-2-(4-methoxyphenyl)-4-phenylquinoline 3.6 (Scheme 3.21) [11OL2598]. The ¹H NMR absorptions for the 2-(4-methoxyphenyl) unit (δ_H 7.60 ppm and 7.01 ppm) are nearly identical to those of 3.5Ac-Y (δ_H 7.60 ppm and 7.02 ppm). Thus, this data further corroborates the assignment of the quinoline structure as 3.5Ac-Y.

Scheme 3.21

In summary, synthesis of the 3-iodoquinolines 3.5 from the unsymmetrical dialkynols 2.19 proved to be less successful than those from their symmetrical counterparts 2.5 – 2.8 that give the 4-alkynyl-3-iodoquinolines 3.2. Some examples of quinolines 3.5 provided very low
yields or an intractable mixture of products. Clearly future optimisation of the reaction is required.

3.2 Silver(I) Mediated Cyclisations of [3-2-(Sulfamoyl)phenyl]penta-1,4-diyn-3-ols to 1,2-Benzothiazine 1,1-dioxides and Derivatives

Since the 1960s there has been sustained interest in 1,2-benzothiazines and especially their 1,1-dioxides, following the discovery of the non-steroidal anti-inflammatory oxicams, of which three representatives are shown below.

Traditional routes to 1,2-benzothiazine 1,1-dioxides involve the intramolecular Claisen condensation of sulfonamides derived from methyl 2-(chlorosulfonyl)benzoate and α-amino carbonyl compounds. The base-promoted ring expansion of N-(acylmethyl) saccharins provides access to 3-acyl-4-hydroxy-1,2-benzothiazine 1,1-dioxides. These and related approaches have been reviewed [81AH(28)73, 20MRO148]. Developments in the chemistry and synthetic routes to 1,2-benzothiazines have been reviewed more recently [18SC3033]. Some of the recent syntheses of the ring system are outlined in Section 1.5.4 and below. This section describes a novel means to construct the 1,2-benzothiazine 1,1-dioxide nucleus.

As discussed in Section 2.2 there are few aryl (di)alkynols in which the aryl ring is substituted with a primary, secondary or tertiary sulfamoyl group i.e. -SO₂NH₂, -SO₂NHR or -SO₂NR₂ respectively. Indeed, the only examples are arylacetylenes possessing an ortho-sulfamoyl group, whilst compounds containing a 1-(2-sulfamolyphenyl)prop-2-yn-1-ol unit e.g. 3.7 have not been reported previously (cf. Section 2.2). Silver(I)-mediated cyclisations of (2-sulfamoylphenyl)acetylenes (2-alkynylbenzenesulfonamides) have been shown to afford 1,2-benzothiazine 1,1-dioxides 3.8 via a 6-endo-dig pathway (Scheme 3.22) [07JOC8547, 12TL6577].
Other more expensive metal catalysts have been utilised for the formation of 1,2-benzothiazine 1,1-dioxides and complexes of palladium(0) and rhodium(III) have proved particularly useful [18SC3033]. Reddy and co-workers produced a range of sultams (A, Scheme 3.23) utilising a Pd(0) catalyst generated in situ from [PdCl2(PPh3)2], to activate the triple bond of N-(phenylsulfonyl)propargylamines to attack from a range of nucleophiles [16ASC1625]. Pham, Ye and Cramer synthesised a range of 1,2-benzothiazines (B, Scheme 3.23) from a Rh(III)-mediated oxidative C-H activation-alkynylation reaction of N-acetylbenzenesulfonylamides. It was found that low or stoichiometric loadings of copper(I) were unfavourable and that to minimise acetyl group cleavage, molecular oxygen was required as a terminal oxidant [12AGE10610].
The present project has demonstrated that silver(I) salts are effective for the cyclisation of the tosylamidophenyl dialkynols 2.5 to afford indoles 2.32 and indolines 2.33 (Section 2.4) via a 5-*exo*-dig pathway. Clearly the isomeric sulfamoylphenyldialkynols (reversed sulfonamides) 2.23Aa – Hb could not cyclise in the same manner and upon π-complexation with Ag(I) would be activated to ring closure via either 6-*exo*-dig or 7-*endo*-dig pathways (Scheme 3.24). Both pathways are favoured under Baldwin’s rules [76CC734, 16CMS487]. The cyclisations potentially constitute a novel means to construct the 1,2-benzothiazine and/or 1,2-benzothiazepine ring systems.
Initially the dialkynol 2.23Aa was treated with AgOAc (5 mol %) in MeCN at reflux overnight. Purification of the reaction mixture by flash chromatography (10% EtOAc – hexane) provided a complex minor component in the initial fractions. However, the major final fraction exhibited a very different $^1$H NMR spectrum to that of the starting material (blue spectrum, Figure 3.8). The benzo ring signals are shifted upfield (red spectrum, Figure 3.8) compared with that of the starting material, furthermore the N-Me group signal is shifted downfield and appears as a singlet, consistent with formation of a cyclisation product (Figure 3.8). Coupling of the NH proton with the methyl group ($J_{NHMe} = 5.3$ Hz) is a distinctive feature of the $^1$H NMR spectrum of the starting material 2.23Aa (blue spectrum, Figure 3.8).
There are three potential cyclisation products from the cyclisation of dialkynol 2.23Aa (Scheme 3.25). Coordination of Ag(I) to the alkyne activates it to nucleophilic attack from the sulfonamide nitrogen; the cyclisation pathway could then proceed \textit{via} 6-exo or 7-endo-dig pathways to give six membered (3.9Aa) or seven membered (3.10Aa) rings respectively (Scheme 3.25). Furthermore, the benzylic enynol 3.9Aa could also undergo a 1,3-allylic alcohol isomerization (1,3-AAI) [07TL8505] to give the isomeric 1,2-benzothiazine system 3.11Aa (Scheme 3.25).

\textbf{Figure 3.8} 400 MHz $^1$H NMR spectra comparison of 2.23Aa to unknown fraction in CDCl$_3$
If the reaction had furnished **3.11Aa** it would be expected that two doublets with a *geminal* coupling would be present in the $^1$H spectrum (as there was for indole **3.32Aa**), corresponding to the alcohol and the benzylic CH protons. However, the absence of these signals discount structure **3.11Aa**. Moreover, it was considered less likely that the major product was the seven-membered 1,2-benzothiazepine ring **3.10Aa** because of the less favoured conformation the substituents must adopt for the cyclisation to proceed.

Of the possible structures, the 1,2-benzothiazine 1,1-dioxide **3.9Aa**, resulting from a 6-*exo*-dig cyclisation, would appear to be the most probable. It was considered likely that the product will process (Z)-stereochemistry as interactions of the benzylidene moiety and the benzothiazine C-4 substituents in the intermediate silver(I) species **3.12** will be minimised. Furthermore, the 6-*exo*-dig cyclisation will proceed *via* an anti-addition of the sulfonamide function to the metallocyclopropene intermediate as shown below in Scheme 3.26.
The constitution of 1,2-benzothiazine 1,1-dioxide 3.9Aa was established by examination of the NOESY spectrum (Figure 3.9), which revealed a through-space interaction between the benzylidene CH signal (δ_H 7.49 ppm) and the OH signal (δ_H 3.42 ppm). The latter signal also exhibited a correlation with that of the apparent doublet at δ_H 8.10 ppm, thus providing confirmation that the most deshielded signal corresponds to the 5-H proton (cf. Section 2.2, Figure 2.2). Further evidence in support of the (Z)-stereochemistry of 3.9Aa was provided by the cross-peak (Figure 3.9) corresponding to an interaction between the ortho-Ph protons (δ_H 7.47 ppm) of the benzylidene unit and the Me protons (δ_H 3.12 ppm).

Both 1,2-benzothiazine 1,1-dioxide 3.9Aa and 1,2-benzothiazepine 1,1-dioxide 3.10Aa structures are novel, and additional derivatives were required not only to confirm the structure of 3.9Aa but also to investigate the scope and limitations of these cyclisation reactions. Consequently, the reactivity of a range of reversed sulfonamides 2.23Aa – Hb towards AgOAc in MeCN was examined, Scheme 3.27. The results of these cyclisations are collated in Table 3.4.
Scheme 3.27

$$\text{2.23Aa - Hb} \xrightarrow{\text{AgOAc (5 mol %)}} \xrightarrow{\text{MeCN, } \Delta} \text{3.9Aa - Hb} \quad \text{and/or} \quad \text{3.10Aa - Hb}$$

R and R' as defined in Table 3.4
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<th>Entry</th>
<th>R</th>
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<th>Product</th>
<th>Yield (%)</th>
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<th>Yield (%)</th>
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<td>3.9Hb</td>
<td>84</td>
<td>3.10Hb</td>
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Table 3.4 Yields from the AgOAc cyclisation of reversed sulfonamides 2.23Aa – Hb. a = 3-(1-Hydroxybutyl)-2-methyl-4-(pent-1-yn-1-yl)-2H-1,2-benzothiazine 1,1-dioxide 3.11Ab also obtained from this reaction. b = yield from 1H NMR spectrum c = 4-Hydroxy-3-methylene-2-(p-tolyl)-4-[(trimethylsilyl)ethynyl]-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide 3.9Be also obtained from the reaction.
The reaction of 2-(6-hydroxyundeca-4,7-diyn-6-yl)-N-methylbenzenesulfonamide 2.23\textsuperscript{Ab} AgOAc in MeCN (entry 2, Table 3.4) provided a mixture of compounds that could only be separated with difficulty by extensive flash column chromatography. However, it proved possible to identify three novel compounds (Scheme 3.28). The major fraction from flash column chromatography, was identified as an inseparable mixture of 1,2-benzothiazine 1,1-dioxide 3.9\textsuperscript{Ab} and starting material 2.23\textsuperscript{Ab} (in several solvents). The yield quoted (12%, Table 3.4) is from integration ratios in the $^1$H NMR spectrum. (Z)-3-Butenylidene-1,2-benzothiazin-4-ol 3.9\textsuperscript{Ab} (Scheme 3.28) was identified on the basis of its $^1$H NMR spectrum which exhibited a triplet at δ\textsubscript{H} 6.64 ppm ($J$ = 7.3 Hz). The constitution of this material was also confirmed by LC-MS with a molecular ion at $m$/\textit{z} [M+H]$^+$ = 333.1391 corresponding to C\textsubscript{18}H\textsubscript{22}NO\textsubscript{3}S.

A faster running (less polar) component was isolated and identified as the 7-\textit{endo-dig} product the 1,2-benzothiazepine 1,1-dioxide 3.10\textsuperscript{Ab} (7%, Scheme 3.28). The $^1$H NMR spectrum exhibited two singlets at δ\textsubscript{H} 5.77 and 5.34 ppm corresponding to the 4-\textit{H} and OH protons respectively (Figure 3.10). The absence of allylic coupling between the C-3 propyl group and the 4-\textit{H} is noteworthy (Figure 3.10). HRMS also provided additional support for 3.10\textsuperscript{Ab} and displayed [M+H]$^+$ at $m$/\textit{z} 334.1463 corresponding to C\textsubscript{18}H\textsubscript{23}NO\textsubscript{3}S.
Another non-polar orange oil was also obtained from attempted purification of the reaction mixture (entry 2, Table 3.4) and identified as 3-(1-hydroxybutyl)-2-methyl-4-(pent-1-yn-1-yl)-2H-1,2-benzothiazine 1,1-dioxide 3.11Ab (15% yield, Scheme 3.28). This compound is thought to be formed during repeated chromatographic purification during which the 1,2-benzothiazin-4-ol 3.9Ab is protonated by the acidic silica gel. Subsequent dehydration will generate the highly delocalised carbocation 3.13 which is susceptible to nucleophilic attack (S\textsubscript{N}1) from water to afford 3.11Ab (Scheme 3.28). The latter was characterised by its \textsuperscript{1}H NMR spectrum which exhibited a multiplet for the side-chain methine proton centred at \(\delta\textsubscript{H} 5.18\) ppm. The adjacent OH proton appeared as a doublet (\(J_{CH-OH} = 5.2\) Hz) at \(\delta\textsubscript{H} 2.59\) ppm. Characteristic signals for the alkyne carbons were observed at \(\delta\textsubscript{C} 74.18\) and 100.61 ppm.

**Figure 3.10** 400 MHz \textsuperscript{1}H NMR spectrum of 1,2-benzothiazepine 1,1-dioxide 3.10Ab in CDCl\textsubscript{3}
Lei and co-workers synthesised the (1-hydroxyethyl)-1,2-benzothiazine 1,1-dioxides \textbf{3.14} and \textbf{3.15}, by anodic oxidation of an \textit{N}-heteroaryl sulfonamide and but-3-yn-2-ol in an undivided cell (Scheme 3.29). However, NMR data was only reported for the major isomer \textbf{3.14} \cite{20GC1548}. There are no other similar model compounds to 3-hydroxy-1,2-benzothiazine 1,1-dioxide (\textbf{3.11Ab}) in the literature to date.

\textbf{Scheme 3.29}

1,2-Benzothiazepines are relatively uncommon. Synthetic routes to this ring system are highlighted in Scheme 3.26 and often involve numerous steps or employ specialist photochemical equipment \cite{80CJC369, 08SC3662, 11JME716, 13JCD4410, 17OCF14, 17OL6020, 19JOC3871}. Sulfonamide \textbf{3.16} (A, Scheme 3.30) was reductively cyclodehydrated to 1,2-benzothiazepines with high ee (91 – 99\%) \cite{15MI106866574}. 2-Azidothiochromone 1,1-dioxides upon irradiation in acetophenone undergoes a ring
expansion affording 3.17 in an 81% yield (B, Scheme 3.30) [80CJC369]. 1,2-Benzothiazin-3-ones undergo a ring expansion in the presence of a strong base (C, Scheme 3.30) [08SC3662]. Ganguly and co-workers found that the readily available N-allylsulfonamides 3.18 undergo a radical chain cyclisation to saturated 1,2-benzothiazepine-1,1-diones (D, Scheme 3.30) [11JME7176]. The palladium(II)-catalysed reaction of 2-alkynylnitrobenzylsulfonamides and 2-alkynylvinyl bromide were employed to synthesise 6H-benzo[f]cyclopenta[d][1,2]thiazepine 5,5-dioxides (E, Scheme 3.30) in high yields (56 – 99%) [13JCD4410]. Wen used a rhodium(III) complex to catalyse the C-H functionalisation of sulfoximines with enones to afford 1,2-benzothiazepine 1-oxides 3.19 (F, Scheme 3.30) [17OL6020]. Figueroa et al. obtained the 1,2-benzothiazepin-5-one 1,1-dioxide 3.20 from a photochemically induced ring expansion of sodium saccharin with phenylacetylene (G, Scheme 3.30) [19JOC3871].
Scheme 3.30

(i) X, Pd(OCOCF$_3$)$_2$, (R,S)$_p$-Josiphos, TsOH, H$_2$O, H$_2$, TFE, 80 °C

(iii) NaOCl, H$_2$O

(i) Pd(OAc)$_2$ (5 mol %), DPPP (5 mol %), 1,4-dioxane, K$_2$CO$_3$, Δ

(i) [Cp*RhCl$_2$]$_2$ (2.5 mol %), Ag$_2$CO$_3$ (10 mol %), 1-AdCO$_2$H (3 equiv.), PhMe, 100 °C

R = H when HCl used
R = Me when Mel used

[15MI106866574]

[08SC3662]

[11JME7176]

[13JCD4410]

[17OL6020]

[19JOC3871]
Although 7-endo-dig cyclisations are known, they are still relatively scarce. A SciFinder search uncovered 65 references. An example of a 7-endo-dig cyclisation pertinent to the present project is illustrated in Scheme 3.31. The Ag(II)-catalysed cyclisation of the 2-(2-alkynylphenyl)amino-1,4-naphthoquinones 3.21 to benzo[b]naptho[2,3-f]azepine-6,11-diones proceeds in excellent yields (69 – 99%) [18OBC5483].

![Scheme 3.31](image)

The AgOAc-mediated ring closure of the 3-(N-methylsulfamoylphenyl)pentadiynols 2.23Aa – b provided an entry to novel 1,2-benzothiazine 1,1-dioxides albeit in fair yields (entries 1 and 2, Table 3.4). It was of interest to explore the scope of the influence of the alkyne groups upon the outcome of the reaction. To this end, the Ag-mediated cyclisation was extended to the range of 3-[2-(N-tolylsulfamoyl)phenyl]penta-1,4-diyn-3-ol derivatives. Thus, the dialkynols 2.23Ba – f cyclised efficiently to afford the corresponding 2-(4-methylphenyl)-1,2-benzothiazine 1,1-dioxides 3.9Ba – f in yields ranging from 61 – 82% (entries 3 – 7, Table 3.4). All of the products were obtained as yellow or orange oils after flash column chromatography and the cyclisation was successful with alkynes possessing either alkyl or aryl terminal groups.

In the case of the sulfamoyl dialkynol 2.23Be the cyclisation proceeded rapidly (2 h) to afford 3.9Be in 61% yield (entry 6, Table 3.4). In addition, a small amount of a compound identified as the desilylation product as 3.9Be’ (Scheme 3.32) was also obtained in 2% yield. The structure of the latter was confirmed by the $^1$H NMR spectrum, which exhibited two doublets at $\delta_H$ 5.82 and 4.76 ppm ($^2J = 1.8$ Hz) corresponding to the alkenic protons. The constitution of 3.9Be’ was also confirmed by HRMS with which exhibited a molecular ion at $m/z$ [M+H]$^+$ = 398.1251 corresponding to C$_{21}$H$_{23}$NO$_3$S$i$. 

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The N-aryl group in 2.23 was also varied to give three additional compound series of 1,2-benzothiazine 1,1-dioxides 3.9C–E (entries 8–13, Table 3.4) (Scheme 3.33), of which the latter were obtained in generally high yields (59–96%). A near quantitative yield was obtained of 3.9Ea. None of these cyclisations were accompanied by a 1,2-benzothiazepine 1,1-dioxide.

Replacement of the N-aryl substituent in dialkynols 2.23B–E with a 3-thienyl unit provided the N-heteroarylsulfonamide 2.23Gb. In this case, silver-mediated cyclisation proceeded readily to give the 2-(3-thienyl)-1,2-benzothiazine 1,1-dioxide 3.9Gb in 70% yield, together with a small amount of the 7-endo-dig cyclisation product 3.10Gb (Scheme 3.34). The latter was characterised from its $^1$H and $^{13}$C NMR spectra, the former exhibited a singlet at $\delta_H$ 5.91 ppm for the 4-$H$ proton together with an OH signal at $\delta_H$ 5.43 ppm. The presence of alkyne
carbon signals at $\delta_C$ 89.00 and 82.06 ppm confirmed the presence of the pentynyl group, whilst the quaternary 5-C signal resonated at $\delta_C$ 72.89 ppm.

The 2-methyl- and 2-(3-thienyl)-1,2-benzothiazepine 1,1-dioxides 3.10Ab and 3.10Gb isolated from 2.23Ab and 2.23Gb respectively (entries 2 and 14, Table 3.4) contained impurities, further attempts to purify these compounds began to result in degradation ($^1$H NMR). The indication seemed to be that both the 1,2-benzothiazepines were unstable in ambient conditions (air and light). It is noteworthy that 1,2-benzothiazepine formation (i.e. 7-endo-dig cyclisation) was only observed from the undecadiynols 2.23Ab and 2.23Gb, a feature that merits further investigation.

Within the literature there are no 1,2-benzothiazepine 1,1-dioxides analogous to 3.10Ab and 3.10Gb. However, the chemical shift of the 4-H protons in these examples are remarkably close to those in the 2-benzazepin-1-ones 3.22 and 3.23 that contain an electronically similar enamide moiety Scheme 3.35 [12S1410, 18CEJ3584].
Cyclisations of \(N\)-(2-naphthyl)sulfonamide 2.23H (entries 15 and 16, Table 3.4) proceeded straightforwardly to afford the 2-(2-naphthyl)-1,2-benzothiazine 1,1-dioxides 3.9Ha – b in high yields.

Characterisation data for the compounds prepared merit some consideration. The benzylidene (methine) proton (\(CH\)) of benzothiazines 3.9Aa – Ha and 3.9Bc (Table 3.5), are in some cases shifted downfield by as much as 1 ppm in comparison to the 3-alkylidene-1,2-benzothiazines 3.9Ab – Hb and 3.9Be – f (Table 3.6). There does not appear to be any examples of 3-alkylidene-1,2-benzothiazin-4-ols or -4-ones in the literature for comparison with the data in Table 3.6. However, in the series 3.9Ab – 3.9Hb and 3.9Be – f, shielding of the alkenic hydrogen stems from a combination of the inductive effect of the alkyl group and the absence of a geminal anisotropic group.

Whilst the NOESY spectrum for 1,2-benzothiazine 1,1-dioxide 3.9Aa (Figure 3.9) established a (Z)-configuration it is worth noting that the chemical shift of the benzylidene proton (\(\delta_H\) 7.49 ppm, \(\delta_C\) 131.06 ppm) is also in accord with these of the (Z)-3-benzylidene-2-methyl-2H-1,2-benzothiazine-4-(3H)-one 1,1-dioxide derivative 3.24 obtained by Asharaf and co-workers. The latter (3.24) was obtained from a ketone and arylaldehyde in a base-catalysed aldol condensation (Scheme 3.36) [18JME282]. It was observed that electron donating substituents in the benzylidene group resulted in shielding of the methine proton signal, whereas the latter was deshielded when an electron withdrawing substituent was present. However, the chemical shift differences between the derivatives of 3.24 were small (\(\delta_H\) 7.77 – 7.62 ppm, \(\Delta\delta_H\) 0.15 ppm). A similar small difference was observed here between 3.9Ba (\(\delta_H\) 8.24 ppm) and 3.9Bc (\(\delta_H\) 8.22 ppm).

![Scheme 3.36](image-url)
The coupling constants (Table 3.6) of the methine proton and the \( CH_2 \) in the 3-alkylidene series \( 3.9Ab - Hb \) and \( 3.9Be - f \) along with the similarity of the \(^{13}C\) shift of the methylidene carbon in both the 3-arylidene- and 3-alkylidene-1,2-benzothiazines (Tables 3.5 and 3.6 respectively) is noteworthy; on the basis of this data and the probable reaction mechanism (Scheme 3.37) \((Z)\)-stereochemistry is also assigned to the 3-alkylidene-1,2-benzothiazines \( 3.9Ab - Hb \) and \( 3.9Be - f \).

Table 3.5 \(^1H\) and \(^{13}C\) NMR shifts for aryl substituted 1,2-benzothiazine 1,1-dioxides \( 3.9Aa - Ha \) and \( 3.9Bc \). a = overlapping with other signals
Table 3.6 $^1$H and $^{13}$C NMR shifts for alkyl substituted 1,2-benzothiazine 1,1-dioxide 3.9Ab – 3.9Hb and 3.9Be – f

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<th>8-H (ppm)</th>
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<th>$J_{H-CH_2}$ (Hz)</th>
<th>$\delta$C CH= (ppm)</th>
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The 6-exo-dig and 7-endo-dig cyclisation pathways are depicted in Scheme 3.37. At present it is unclear why there was competition from the latter pathway with two of the dialkynol substrates. Further investigation of this aspect is clearly merited. The cyclisation of the sulfamoyl dialkynols 2.23Aa – Hb under Ag(I) catalysis represents a new route to 1,2-benzothiazine 1,1-dioxides.

The proposed mechanism for the synthesis of 1,2-benzothiazine 1,1-dioxides 3.9Aa – Hb and 1,2-benzothiazepine 1,1-dioxides 3.10Ab and 3.10Gb, via path a and path b
respectively. Both routes are envisaged to start from silver coordination to the triple bond by \( \pi \)-complexation [15CSR8124, 19MI1] which activates the triple bond to attack from the nucleophilic sulfonamide nitrogen. Cyclisation can occur via path a (6-exo-dig) or b (7-endo-dig), followed by protodeargentation and proton removal from the quaternary nitrogen (by most likely an acetate anion), affording the relevant products (Scheme 3.37).

![Scheme 3.37](image-url)
Chapter 4

Ring Functionalisations and Annulations
Chapter 4 Ring Functionalisations and Annulations

4.1 Functionalisation of the 3-Alkynylindol-3-ol Ring System

With the aim of exploiting the multifunctional nature of the ring systems prepared during the course of this project (Sections 2.0 and 3.0), the 3-alkynyl-2-methyleneindol-3-ols (2.27, 2.30A-C and 2.33a) and the 4-alkynyl-3-iodoquinoline 3.2a – c were subjected to a selection of reactions which will be discussed in this chapter. Initially chosen because it has multiple motifs which can be easily manipulated, was the 2-methyleneindoline 2.27.

One way in which 2.27 can potentially be elaborated utilises the embedded alkynol function in a cyclocondensation reaction with 2-naphthol as shown below (Scheme 4.1).

Montmorillonite has been utilised to catalyse the formation of naphthopyran derivatives in high yields (66 – 98%) from the cyclocondensation of 1,1-diaryl-2-propyn-1-ols and 2-naphthol (A, Scheme 4.2) [14MI1081]. Montmorillonite K-10 is an inexpensive, green, heterogenous clay catalyst, which over the past 30 years has found numerous uses in the catalysis of many reaction types [19EROS1]. It can also be used as a support for a variety of metal salts [18MI1249]. Yaragorla and Khan found that when alkynols and 2-naphthol were heated with p-TsOH (neat), the naphthopyran 4.1 could be isolated; the reaction could also be driven to the rearrangement product 4.2 in fair to excellent yields (58 – 98%) (B, Scheme 4.2) [18OBC7920]. Naphtho[1,2-b]pyrans have been synthesised from the acid catalysed reaction of propyn-1-ols and 1-naphthols to give 4.3 (C, Scheme 4.2). The (E)-4-[3,3-bis(aryl)allylidene]naphthalen-1(4H)-ones 4.4 were also isolated as intense red dyes, their formation was rationalised by SeAr of 1-naphthol by a propargylic-allenic cation to give a 4-
allenynaphthol derivative, which undergoes a subsequent [1,7]-H shift [03EJO1220]. Kim and co-workers utilised 3-alkynyl-3-hydroxyindoline-2-ones 4.5 as a substrate in the Lewis acid-catalysed condensation with 2-naphthols (D, Scheme 4.2). 3-(Naphthofuranyl)-2-oxindoles were obtained in fair to good yields (45 – 78%) [16TL4280].

Another way in which the novel 3-alkynylindol-3-ol ring system 2.27 could be exploited is via the dehydration and subsequent interception of the cation with a nucleophile (Scheme 4.3). The addition of a 1,3-dicarbonyl nucleophile to a propargylic cation (formed by dehydration), under metal catalysis or acidic (Brønsted and Lewis acid) conditions affords a functionalised alkyne that has been shown to cyclise under either basic or acidic conditions. Some examples are shown in Scheme 4.4 [10S3715, 14EJO4999, 15CC557, 19OBC7920].
Thus, 1,3-diphenylprop-2-yn-1-ol underwent easy nucleophilic addition of a 1,3-dicarbonyl compound in the presence of a Lewis acid. The corresponding intermediate compound 4.6 undergoes base-catalysed cyclisation to substituted furans (A, Scheme 4.4) [1053715]. 2-Propynyl-1,3-dicarbonyl compounds 4.7 undergo cyclisation in the presence of base to yield dihydrofuran derivatives 4.8 (B, Scheme 4.4) in excellent yields (76 – 93%) [14EJO4999].

Dhiman et al. found that 1,2,3-trisubstituted cyclopenta[b]indoles 4.9 could be obtained in a one-pot reaction from propargylic alcohols via an initial formation of indole 4.10 in the presence of a Au(I) catalyst with a basic co-catalyst. Subsequent addition of a 1,3-dicarbonyl compound to 4.10 in the presence of a Brønsted acid generates the indole dicarbonyl compound 4.11. The latter underwent an intramolecular Friedel-Crafts type reaction to give the tricyclic heterocycle 4.9 (C, Scheme 4.4). Both intermediates were isolated to provide evidence for the reaction mechanism [15CC557]. A Cu(I) catalysed tandem cyclisation and addition reaction was observed when 1-(2-amidophenyl)propynol derivatives were treated with a range of 1,3-dicarbonyl nucleophiles (D, Scheme 4.4). The corresponding indoline intermediate 4.12 could also be isolated in the absence of a nucleophile in 92% yield (when PG = Ts, R = Me and R₁ = H). Addition of the nucleophile to the pre-formed indoline, also proceeded smoothly with the Cu(I) catalyst. Nucleophilic addition to indoline 4.12 was also successful when p-TsOH (1 equiv.) was used as the catalyst but gave much lower yields of the indole 4.13 (when PG = Ts, R = Me and R₁ = H). However, p-TsOH alone did not initiate the same tandem cyclisation and addition pathway as the Cu(I) catalyst [19OBC2663].
Initially indoline 2.27 was subjected to a variety of reaction conditions, some of which were adapted, from literature examples (Scheme 4.5) [12JOC7166, 16TL4280, 17TL21, 17TL4094]. These include; dehydration and interception with a nucleophile (i, Scheme 4.5), cyclocondensation with 2-naphthol (iv, v, Scheme 4.5), 1,3-AAI (vi, Scheme 4.5) and oxidative rearrangement (vii, Scheme 4.5). Surprisingly and disappointingly no tractable products could be isolated from any of these reactions, only very complex mixtures were obtained, suggesting that 3-ethynyl-2-methylene-1-tosylindol-3-ol 2.27 is highly reactive and undergoes multiple reactions and/or degradation. The $^1$H NMR spectrum of the crude product from reaction (i) in Scheme 4.5 indicated that no starting material was present, but purification was not possible due to the complexity of the mixture (TLC). Thus, the mixture was carried forward into the next reaction and treated under basic conditions (ii, iii, Scheme 4.5). However, no characterisable products could be isolated from exposure to either $K_2CO_3$ in MeCN or to DBU in MeCN.

All efforts to effect a cyclocondensation with 2-naphthol were unsuccessful (iv and v, Scheme 4.5), as were attempts to induce 1,3-AAI to the isomeric 2-(hydroxymethyl)indole
(vi, Scheme 4.5). Although Chan reported that 3-phenyl-2-methylene-1-tosylindol-3-ol undergoes an iodination rearrangement to 3-(iodomethyl)-3-phenyl-1-tosyloxindole with NIS [12JOC7166] efforts to extend this reaction to 2.27 gave only an intractable mixture (vii, Scheme 4.5).

Due to the complexity of the mixtures obtained from the reactions of 3-ethynyl-2-methylene-1-tosylindol-3-ol 2.27 shown in Scheme 4.5, no other reactions with this substrate were attempted.

In view of these disappointing results investigations were extended to the 2-benzylideneindoline 2.33a with the rationale that the additional phenyl group would stabilise intermediates formed in the reactions. Thus 2.33a and acetylacetone (in DCE) in the presence of an acid catalyst (Montmorillonite K-10) was refluxed for 2h; after filtration
though Celite, the \(^1\)H NMR spectrum of the crude material showed the reaction had gone to completion (100% yield). After consideration of 1D NMR spectra (\(^1\)H and \(^{13}\)C), the isolated product was not the expected indoline but the indole 4.14a (Scheme 4.6).

Scheme 4.6

The \(^1\)H NMR spectrum of 3-\{phenyl[3-(phenylethynyl)-1-tosyl-1H-indol-2-yl]methyl\}pentane-2,4-dione 4.14a is shown in Figure 4.1. Neither this nor the \(^{13}\)C NMR spectrum exhibit any peaks corresponding to the enol tautomer, which is in line with similar compounds reported in the literature [07OL727, 19OBC2663]. Interestingly, the doublets corresponding to the vicinal sp\(^3\) hydrogens absorb over a close range, \(\delta_H 6.10\) and 5.95 ppm (\(^3\)J = 12.06 Hz).

Figure 4.1 400 Mhz \(^1\)H NMR spectrum of 4.14a in CDCl\(_3\)

The proton signals for 4.14a (Figure 4.1) were assigned from examination of the NOESY spectrum (Figure 4.2). The stronger though-space interaction between the doublet at \(\delta_H 6.10\) ppm and the phenyl protons established distinction between the vicinal protons. The doublet at \(\delta_H 5.95\) ppm displayed an interaction with the two methyl groups (\(\delta_H 2.19\) and
1.97 ppm) of the diketone unit. The high field aromatic proton doublet ($\delta_H$ 7.08 ppm), integrating for two protons, shows a correlation with the tosyl methyl group protons ($\delta_H$ 2.28 ppm). Comparison of the $^1$H NMR shifts with those of some model compounds is instructive (Scheme 4.7).

Figure 4.2 NOESY spectrum of 4.14a

Song and co-workers reported the vicinal sp$^3$ hydrogens in indole 4.15 (Scheme 4.7) absorbed at $\delta_H$ 4.64 and 3.44 ppm [19OBC2663]. The 3-(1,3-diphenylprop-2-yn-1-yl)pentane-2,4-dione 4.16a exhibits two doublets at $\delta_H$ 4.67 and 4.23 ppm with a coupling constant of $^3J = 10.9$ Hz. The downfield shift of the methine proton signals seen in 4.14a compared to the model compounds in Scheme 4.7, is presumably due to the combined influence of the adjacent alkyne moiety along with the anisotropic indole and phenyl groups deshielding the protons. The vicinal proton shifts in the 1,3-diketones 4.16a – c exhibit increased deshielding with increased steric crowding (Scheme 4.7).
The indole 4.14a can be envisaged as being generated from the nucleophilic addition of the enolic nucleophile to the benzylic cation derived from the 2-benzylideneindol-3-ol 2.33a (Scheme 4.9). Consequently 4.14a should also be accessible from the indolyl alcohol 2.32a, under identical conditions. In order to verify this proposal, the latter was also treated with acetylacetone in DCE in the presence of K-10. Gratifyingly, under these conditions the 3-alkynylindole 4.14a was also obtained in quantitative yield (Scheme 4.8).
The formation of the indole 4.14a from indoline 2.33a can be rationalised by the initial protonation and elimination of water (E₁) followed by generation of the benzylic cation 4.17 (Scheme 4.9). This cation (4.17) will also be formed from dehydration (E₁) of the indolyl alcohol 2.32a, after protonation, the nucleophilic centre of the 1,3-diketone will then attack the cation leading to 4.14a in which aromaticity is retained (Scheme 4.9).

Scheme 4.9

With 3-{phenyl[3-(phenylethynyl)-1-tosyl-1H-indol-2-yl]methyl}pentane-2,4-dione 4.14a to hand it was subjected to basic conditions (K₂CO₃, DBU and Cs₂CO₃). However, in each case only starting material was recovered from the reaction and none of the cyclisation products were observed (i – iii, Scheme 4.10). Consequently, it was envisaged the triple bond of 4.14a may require additional activation to nucleophilic attack from the enol or enolic OH. Therefore, a variety of electrophilic activators – I⁺, Ag(I) and In(III) – were employed along with K₂CO₃ in MeCN (iv – viii, Scheme 4.10). Again, only starting material was isolated from these reactions. More work is required to define the scope and limitations of this reaction, use of a wider range of solvents may increase the amount of enol tautomer [85JOC1216] and therefore the ability to react with the alkyne moiety.
All of the attempted base-catalysed intramolecular cyclisations of 3-{(phenyl[3-(phenylethynyl)-1-tosyl-1H-indol-2-yl]methyl)pentane-2,4-dione 4.14a were unsuccessful (Scheme 4.10). No further indoles and/or indolines were investigated as substrates for intramolecular alkyne cyclisations.

4.2 Annulations of 4-Alkynyl-3-iodoquinolines: Synthesis of Pyrrolo[2,3-c]quinolines

Pyrrolo[2,3-c]quinolines which can be obtained from marine bacteria (Ohtaekwangia kribbensis, Mooreia alkaloidigena, and Catalinimonas alkaloidigena), have attracted interest because of their varied biological activities [11TL3186]. Recently discovered Marinoquinolines A – K (Scheme 4.11) [11JNP603, 18JME5547] have been found to exhibit anti-bacterial and cytotoxic properties and a number also exhibit anti-malarial activity.
Aplidiopsamine A and Trigonoine B are two more pyrrolo[2,3-c]quinoline structures. Aplidiopsamine A has been obtained from the Australian ascidian, *Aplidiopsis confluata* [10JOC8291]. Whilst Trigonoine B has been isolated from four plant species native to China *Trigonostemon thyrsoides*, *Trigonostemon huangmosu*, *Trigonostemon lii*, and *Trigonostemon filipes* [11TL3186]. These compounds also exhibit interesting biological activities (Aplidiopsamine A anti-malarial and Trigonoine B weak anti-HIV activities).

It is therefore surprising that relatively little attention has been paid to the total synthesis of these compounds. Only Aplidiopsamine A and Marinoquinolines (A to F and K) have been synthesised. The approaches are outlined in Scheme 4.12 [12AGE10610, 12OL5804, 12OL5808, 12TL1271, 12TL4836, 13SL461, 15JOC957, 18ACR1784, 18JME5547, 19MI35068, 20OL2215, 20JOC650].

Aplidiopsamine A was synthesised in a five-step sequence, 21% overall yield (A, Scheme 4.12). Halide displacement from the bromoacetamide intermediate 4.18 could also be employed with a variety of other nucleophiles to obtain, following cyclodehydration, other pyrrolo[2,3-c]quinoline derivatives [12OL5808]. Marinoquinoline A was synthesised in a high yield over three steps via Pd-mediated cyclisation of the imine from 2-acetyl-1-phenylsulfonylpyrrole and 2-iodoaniline. The protected pyrrolo[2,3-c]quinoline 4.19 obtained could be further elaborated to Aplidiopsamine A (B, Scheme 4.12) [12OL5804]. Willis *et al.* utilised an Ullman cross-coupling reaction of pyrrole-2-carbaldehyde 4.20 and 2-bromonitrobenzene. Subsequent treatment with MeLi was followed by oxidation of the secondary alcohol and reductive cyclisation with magnesium, afforded Marinoquinoline A in four steps in 85% overall yield (C, Scheme 4.12) [12AJO160]. Yamaoka and co-workers achieved the total syntheses of Marinoquinolines A and C and Aplidiopsamine A [15JOC957] by initially assembling the arene-ynamide 4.21 from a series of coupling reactions.
The latter was then subjected to a Brønsted acid (Tf₂NH) mediated cyclisation affording pyrrolo[2,3-c]quinolines in high yields (73 – 90%). Interestingly, it was found that weaker acids lowered the product yield. For Aplidiopsamine A, arene-yamide \( \text{4.21} \) could be transformed in a one-pot reaction to \( \text{4.22} \) from which halide displacement with adenine afforded Aplidiopsamine A in a final 90% yield (D Scheme 4.12). Yamaoka and co-workers extended this reaction to synthesise different (hetero)areno[2,3-c]quinolines [15JOC957]. Marinoquinolines A – C were synthesised from an initial Knoevenagel condensation, followed by the reduction of the nitro moiety and subsequent acylation of ethyl-2-aminocinnamate (E, Scheme 4.12). The \( \alpha,\beta \)-unsaturated ester was then subjected to cyclocondensation with TosMIC to obtain pyrrole \( \text{4.23} \) which underwent a Morgan-Walls reaction to give Marinoquinolines A – C in excellent yields (85 – 92%) [12TL1271]. Schwalm and Correia synthesised Marinoquinolines A, B, C and E among other 3H-pyrrolo[2,3-c]quinolines, using different aldehydes to vary the substituent in the C-4 position, from the Pictet-Spengler reaction of 2-(1H-pyrrol-3-yl)aniline \( \text{4.24} \) with aldehydes followed by aromatization (F, Scheme 4.12) [12TL4836]. Most recently Banwell and co-workers synthesised the widest range of Marinoquinolines (A – F and K) via 3-tosyl-3H-pyrrolo[2,3-c]quinoline 5-oxide \( \text{4.25} \) using a range of conditions (G, Scheme 4.12). The \( N \)-oxide \( \text{4.25} \) was prepared by a Pd-catalysed Ullmann coupling of 3-iodo-1-tosylpyrrole-2-carbaldehyde with 2-bromonitrobenzene followed by reductive cyclisation [20JOC650].
A = (i) Pd(OAc)$_2$, SPhos, K$_3$PO$_4$, n-BuOH, H$_2$O, 2-iodoaniline; (ii) NaOMe, MeOH; (iii) BrCOCH$_2$Br, Et$_3$N, DCM; (iv) adenine, NaH, DMF; (v) HCl, dioxanes, microwave 130 °C

B = (i) p-TsOH, PhMe, 2-iodoaniline, Δ; (ii) Pd(OAc)$_2$, PPh$_3$, Ag$_2$CO$_3$, 1,4-dioxane, 120 °C; (iii) MeOH, K$_2$CO$_3$, Δ; (iv) NBS, BPO, CCl$_4$; (v) K$_2$CO$_3$, 6-chloropurine, DMF, 50 °C; (vi) MeOH, NH$_3$, 150 °C

C = (i) 2-bromonitrobenzene, Cu(0)/Cu(I), PdCl$_2$(dppf)$_2$, DMSO; (ii) MeLi, THF, -78 °C; (iii) Dess-Martin periodinane, DCM, 0 °C; (iv) Mg, MeOH, r.t.

D = (i) TFOH, DCM, -78 °C, NBS; (ii) CsCO$_3$, MeCN, r.t.; (iii) TFA, DCM, r.t.
\[
\text{Scheme 4.12}
\]

\[
\begin{align*}
E &= (i) \text{CH}_2(\text{COOH})_2, \text{piperidine, pyridine, 85 °C}, (ii) \text{EtBr}, K_2\text{CO}_3, \text{DMF}, \text{r.t. or EtOH c.H}_2\text{SO}_4, \Delta; (iii) \text{Fe/NH}_2\text{Cl, EtOH/THF/H}_2\text{O = 6:2:1, 85 °C}; (iv) \text{ROCl, Et}_3\text{N, DCM, r.t.}; (v) \text{TosMIC, t-BuOK, DMSO, r.t.}; (vi) \text{POCl}_3, \text{MeCN, \Delta}; (vii) \text{c.HCl, \Delta}
\end{align*}
\]

\[
F = (i) = \text{TFA, MgSO}_4, \text{DCM, 60 °C}
\]

\[
G = (i) = \text{Cu(I)/Cu(0), PdCl}_2(\text{dppf}), \text{DMSO, 75 °C}; (ii) \text{H}_2, \text{Raney nickel, THF, r.t.}; (iii) \text{NaOMe, MeOH, r.t.}; (iv) \text{RMgBr, THF, 0 °C to r.t.}; (v) \text{NaOMe, MeOH, \Delta}; (vi) 4-\text{MeOC}_3\text{H}_2\text{CH}_2\text{MgBr, THF, r.t.}; (vii) \text{H}_2, 5\% \text{Pd on C, MeOH, r.t.}; (viii) \text{BBBr}_3, \text{DCM, 0 °C to r.t.}; (ix) \text{Ts}_2\text{O, indole, THF, r.t.}; (x) \text{POBr}_3, \text{DCM, r.t.}; (xi) \text{n-BuLi, Et}_2\text{O, -78 °C}; (xii) \text{MnO}_2, \text{DCM, r.t.}
\]
The earliest reported synthesis of 3H-pyrrolo[2,3-c]quinoline involved the high temperature cyclodehydration of 3-formamido-4-methylquinoline under vacuum in the presence of P₄O₁₀ from which the reaction gave low yields [49MC607]. Later work investigated the indolisation of 3-hydrazino-2-phenylquinoline with butanone in conc. HCl [57JCS3722]. In 1976 Parrick and Wilcox reported the synthesis of 3H-pyrrolo[2,3-c]quinolines via a Fischer indole synthesis by heating 3-hydrazino-2-methylquinoline 4.26 with either cyclohexanone or butanone in the presence of acetic acid. Routes to pyrrolo[2,3-b] and pyrrolo[3,2-c]quinolines were also proposed (A, Scheme 4.13) [76J(P1)2121]. A cascade reaction involving the copper(II)-mediated reductive amination of quinoline-3-boronic acid with di-tert-butyl azodicarboxylate afford 3H-pyrroloquinoline in situ. When conducted in the presence of 2-phenylacetaldehyde the Fischer indolisation product, 1-phenyl-3H-pyrrolo[2,3-c]quinoline was obtained in 61% yield (B, Scheme 4.13) [12TL564].

3-Substituted-3H-pyrrolo[2,3-c]quinolin-4(5H)-ones were obtained in moderate to excellent yields (45 – 99%) from a Pd(II)-catalysed domino amination-hydroamination sequence, starting from 3-bromo-4-trifloxyquinolin-2(1H)-ones 4.27 (C, Scheme 4.13) [14JOC9628]. Interestingly, in the case where R¹ = Me, R² = H, R³ = Ph and R⁴ = c-C₆H₁₁ only the amination product, 3-(cyclohexylamino)-1-methyl-4-(phenylethynyl)quinolin-2(1H)-one, was isolated in 69% yield, the reasons for this were not explained. It was also found that 1-methyl-3-nitro-4-trifloxy-2-quinolone 4.28 readily undergoes Sonogashira coupling with aliphatic alkynes and selective metal-acid reduction provide access to the corresponding 4-alkynyl-3-aminoquinolones. The latter are smoothly hydroaminated upon treatment with PdCl₂ (10 mol %) in DMF to 2-alkyl-3H-pyrrolo[2,3-c]quinoline-4-(5H)-ones. However, access to the 2-aryl derivatives was only possible via initial formation of 4.29 and Sonogashira coupling with an aryl iodide (D, Scheme 4.13) [13OBC7334].

Other routes to pyrrolo[2,3-c]quinoline-4-(5H)-ones include nucleophilic addition of the TosMIC anion to 3-(acylmethylene)oxindoles (E, Scheme 4.13) [02T9179, 13T10836]. None of the routes outlined in C, D or E has been adapted for the synthesis of fully unsaturated pyrrolo[2,3-c]quinolines. In addition to the routes to the aromatic tricycles outlined in A and B Scheme 4.13 which are of limited scope other syntheses include: The Hemetsberger indole synthesis has been adapted to access pyrrolo[2,3-c]quinolines. Thus, condensation of 2-arylquinoline-4-carbaldehydes with ethyl azidoacetate proceeds readily at low temperature,
on warming to 0 °C expulsion of N₂ occurs with concomitant cyclisation to the tricycle (F, Scheme 4.13) [93S225].

The parent 3H-pyrrolo[2,3-c]quinoline system has been generated via a domino Pd-catalysed α-arylation-condensation reaction of 3-amino-4-bromoquinoline with acetaldehyde (G, Scheme 4.13) [09ARK(vi)174]. More recently the bicyclisation of 2-methyleneaminochalcones 4.30 and an imine in the presence of a base and oxidant (H, Scheme 4.13), affords the corresponding pyrrolo[2,3-c]quinolines in varying yields (35 – 84%) [17OL6712].

The Bartoli reaction is applicable to nitroquinolines and treatment of 2-chloro-3-nitroquinoline with 5 equiv. of vinylmagnesium bromide affords the 4-chloropyrroloquinolines in 49% yield (I, Scheme 3.14). Halide displacement by a variety of primary and secondary amines proceeds in high yields [18MI5386]. 2-Isocyanochalcones are 1,5-bielectrophiles and condensation with the anion of nitromethane generates a 3-nitro-1,4-dihydroquinoline. Reductive cyclisation of the latter also proceeds with dehydrogenation to the aromatic tricycle (J, Scheme 4.13) [18ASC1870]. Nucleophilic addition of enaminoesters to 2-azidochalcones under oxidative condations affords an intermediate pyrrole, from which a Staudinger-aza-Wittig reaction effects ring closure to afford a 1,2,3,4-tetrasubstituted-3H-pyrrolo[2,3-c]quinoline (K, Scheme 4.13) [19SL717].
(i) Pd(PPh₃)₄Cl₂ (10 mol %), CuI (20 mol %), Et₃N (3.0 equiv.), DMF, r.t.
(ii) Pd(OAc)₂ (5 mol %), (R)-BINAP (10 mol %), K₂PO₄ (3.0 equiv.), DMA, 130 °C

(iii) R = TMS (i) - (iii)

(i) R-acetylene, Pd(PPh₃)₄/Cul (10 mol %), K₂CO₃, THF, r.t.; (ii) Fe, DCM, HOAc, H₂O; (iii) K₂CO₃ (1.5 equiv.), MeOH, DCM; (iv) RI, Pd(PPh₃)₄/Cul (5 mol %), Et₃N, THF, r.t.; (v) PdCl₂ (10 mol %), DMF, Δ
Scheme 4.13
Buchwald et al. reported a copper-promoted domino amidation-hydroamidation sequence Scheme 4.14, to synthesise a range of pyrroles and pyrazoles. Copper(I) iodide was used as a pre-catalyst in place of a palladium species. Initial copper(I)-mediated amidation of an haloenyne 4.31 was followed by an intramolecular hydroamidation of the alkyne 4.32 affording both pyrroles and indoles in good yields (52 – 91%). Pyrazoles result from the use of tert-butyl carbazate (Boc-NHNNH$_2$) [06AGE7079].

There are many other examples in the literature of this domino amination-hydroamination reaction [05T11311, 09ASC1064, 11CC6936, 12JOC8191, 15TL86, 17TL3407]. The metal-initiated amination of alkenes and alkynes has been reviewed [98CRV675] as well as the metal-mediated hydroamination of alkenes and alkynes [19MI1b]. 4-Alkynyl-3-iodoquinolines 3.2 have the same structural fragment (shown in red, Scheme 4.15) as the examples in Scheme 4.13 and 4.14. Thus, employing a domino amination-hydroamination reaction on these substrates could furnish pyrrolo[2,3-c]quinolines, thereby providing a possible new route to Marinoquinolines (Scheme 4.11) and derivatives. This approach would also provide pyrrolo[2,3-c]quinolines with substituents in both the 2- and the 4-position of the ring system, to date there are only three examples of pyrrolo[2,3-c]quinolines substituted at both these positions (A, F and H, Scheme 4.13).
The isomeric 1H-pyrrolo[3,2-c]quinoline 4.33 (A, Scheme 4.16) has been synthesised in a similar manner to that proposed in Scheme 4.15 (i.e. the amination of a haloquinoline and the intramolecular hydroamination of an adjacent alkyne). The requisite 3-alkynylquinoline was synthesised by initial SNAr displacement of chloride with PhNH₂ followed by a Sonogashira coupling of phenylacetylene with the 4-aniilino-3-iodoquinoline. Under these conditions a domino hydroamination also occurred to afford 4.33. The reaction was undertaken in a reversed manner (B, Scheme 4.16) to confirm the intermediacy of the 3-alkynyl-4-aminoquinoline 4.34 in the reaction [10T6040].

Scheme 4.15

Scheme 4.16

In the light of the foregoing studies, initial experiments to access the pyrrolo[2,3-c]quinolines system utilised conditions reported by Buchwald (Scheme 4.14) and were first applied to 3-ido-2-phenyl-4-(phenylethynyl)quinoline 3.2a. The latter was treated with tert-butyl carbamate in the presence of Cul (5 mol %), DMEDA (20 mol %) and Cs₂CO₃ in THF (Scheme 4.17). The mixture was stirred at 75 °C for 24 h, after this time the solution was evaporated to give a brown solid, that was purified by column chromatography (10% EtOAc – hexane). Unfortunately, the product and starting material co-eluted. Multiple attempts to
purify the mixture were unsuccessful, including the use of preparative TLC; signs of additional products resulting from degradation of the mixture became evident (\(^1\)H NMR).

\[
\begin{align*}
\text{3.2a} & \xrightarrow{(i)} \text{BocNH}_2 (1.2 \text{ equiv.}) \\
\text{2,4-diphenyl-3-(p-tolyl)-3H-pyrrolo[2,3-c]quinoline 4.35Aa} & \xrightarrow{(i)} \text{21\% yield} \\
\text{Scheme 4.17}
\end{align*}
\]

Consequently, an alternative set of conditions to effect the Buchwald-Hartwig amination were employed, a modified method based on that from Wang et al. (Scheme 4.13) [14JOC9628] was adopted. Under these conditions we were delighted to observe that the domino amination-hydroamination of 3.2a afforded 2,4-diphenyl-3-(p-tolyl)-3H-pyrrolo[2,3-c]quinoline 4.35Aa in a fair yield (21%), along with an orange solid subsequently identified as the amination product 4.36Aa; both of these compounds are novel (Scheme 4.18).

\[
\begin{align*}
\text{3.2a} + \text{NH}_2 & \xrightarrow{(i)} \text{Pd(OAc)}_2 (8 \text{ mol \%), Xantphos (10 mol \%), K}_2\text{CO}_3 (3 \text{ equiv.}), \text{DMA (0.04 g/mL), 80 °C} \\
\text{4.35Aa} & \xrightarrow{(i)} 21\% \\
\text{4.36Aa} & \xrightarrow{(i)} 38\% \\
\text{Scheme 4.18}
\end{align*}
\]

A distinct singlet for the pyrrole proton (1-H) is present at \(\delta_H 7.33\) ppm in the \(^1\)H NMR spectrum of 4.35Aa (Figure 4.3) with a corresponding \(^{13}\)C resonance at \(\delta_C 102.23\) ppm. The 2,4-diphenyl-3-(p-tolyl)-3H-pyrrolo[2,3-c]quinoline structure was also confirmed by HRMS which exhibited a molecular ion at \(m/z [M+H]^+ = 411.1859\) corresponding to C\(_{30}\)H\(_{22}\)N\(_2\). The aromatic protons for 4.35Aa (Figure 4.3) were assigned with the aid of 2D NMR spectra (HSQC, HMBC and NOESY). The NOESY spectrum shows a through-space interaction.
between the 1-H and 9-H protons and thus established that the latter resonates at $\delta_H 8.32$ (Figure 4.4). Furthermore, the phenyl rings can be distinguished by the HMBC NMR spectrum, which shows an interaction between the phenyl c-ring ortho protons (4-postion) and the 4-C carbon (Figure 4.4). Moreover, and interaction between 1-H proton and the phenyl a-ring protons (2-position) with the quaternary 2-C carbon HMBC spectrum (Figure 4.4) leads to the assignments shown in Figure 4.3.

**Figure 4.3** 400 MHz $^1$H NMR spectrum of 4.35Aa in CDCl$_3$
Figure 4.4 NOESY and HMBC spectra of 4.35Aa

The structure of the 3-aminoquinoline 4.36Aa was confirmed by its $^1$H NMR and $^{13}$C NMR spectra. The former exhibited the presence of a broad singlet at $\delta_H$ 6.03 ppm for the amine proton (Figure 4.5), additionally two quaternary carbon resonances at $\delta_C$ 106.29 and 83.99 ppm indicated the presence of acetylenic carbons. The assignments of protons in Figure 4.5 were confirmed by 2D NMR experiments (COSY, HSQC, HMBC and NOESY). A through-space interaction (NOESY) is observed (Figure 4.6) between the NH proton and the protons ortho to the NH in the tolyl ring. In addition, there is an interaction between the NH and phenyl c-ring ortho protons which absorb at $\delta_H$ 7.76 ppm (Figure 4.6). From these observations, the NOESY and the COSY spectra can be fully interpreted to assign all of the other phenyl ring protons, as shown in Figure 4.6.
Figure 4.5 400 MHz $^1$H NMR spectrum of 4.36Aa in CDCl$_3$

Figure 4.6 NOESY and COSY spectra of 4.36Aa
The resonances for the 1-\(H\) position are similar to those of Marinoquinoline A (4-methyl-3H-pyrrolo[2,3-c]quinoline) which exhibits resonances at \(\delta_H\) 7.12 ppm and \(\delta_C\) 102.04 ppm (Scheme 4.19) [11JNP603]. A feature observed in \textbf{4.35Aa} is the 7-\(H\) and 8-\(H\) protons absorb over a very small range (\(\delta_H\) 7.65 and 7.59 ppm), which is also a feature in Marinoquinoline A (Scheme 4.19).

The \(^1\)H NMR signals for the benzo ring protons in aminoquinoline \textbf{4.36Aa} differ to those found in 3-anilinoquinoline \textbf{4.37} (Scheme 4.19) [06T6258]. Of importance are the shifts of the 5-\(H\) and 8-\(H\) protons in 2-phenyl-4-(phenylethynyl)-\(N\)-(p-tolyl)quinolin-3-amine \textbf{4.36Aa}, in which the 5-\(H\) proton absorbs at \(\delta_H\) 8.30 ppm and 8-\(H\) at \(\delta_H\) 8.11 ppm. However, as described in Section 3.1, Scheme 3.3 the C-4 alkyne moiety in the quinoline ring imparts a pronounced deshielding effect on the (peri) 5-\(H\) proton. The phenyl ring protons of the amine \textbf{4.37} are deshielded compared with those observed in \textbf{4.36Aa} (\(\delta_H\) 7.01 ppm and 6.80 ppm) for the electron-rich p-toluidine moiety.
With the initial success of the Pd-catalysed amination-(hydroamination) reaction with p-toluidine the reaction of 3-iodo-2-phenyl-4-(phenylethynyl)quinoline 3.2a towards a range of amines or amides was investigated Scheme 4.20. The results of these reactions are documented in Table 4.1. In many cases the 3-aminoquinoline was the major product from the reaction and in every case eluted first on purification by column chromatography (non-polar).

The reaction was also extended to 3-iodo-4-(pent-1-yn-1-yl)-2-propylquinoline 3.2b and to 3-iodo-2-(4-methoxyphenyl)-4-[(4-methoxyphenyl)ethynyl]quinoline 3.2c. In each case the amination-hydroamination reaction was investigated with p-toluidine and with aniline as substrates (Scheme 4.21). The results of these reactions are collated in Table 4.2.
Scheme 4.20

(i) Pd(OAc)$_2$ (8 mol %), Xantphos (10 mol %), K$_2$CO$_3$ (3 equiv.), DMA (0.04 g/mL), 80 °C
<table>
<thead>
<tr>
<th>Entry</th>
<th>Iodoquinoline R¹</th>
<th>Amine or Amide</th>
<th>Pyrrolo[2,3-c]quinolines</th>
<th>Pyrrolo[2,3-c]quinoline Yield (%)</th>
<th>δH 1-H (ppm)</th>
<th>3-Aminoquinoline</th>
<th>3-Aminoquinoline Yield (%)</th>
<th>δH NH (ppm)</th>
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*Table 4.1 Yields of 4.35A and 4.36A from amination-hydroamination reaction of 3-iodo-2-phenyl-4-(phenylethynyl)quinoline 3.2a*
Scheme 4.2

![Chemical Structure]

3.2b, R₁ = C₃H₇
3.2c, R₁ = 4-MeOC₆H₄

<table>
<thead>
<tr>
<th>Entry</th>
<th>Iodoquinoline R¹</th>
<th>Amine or Amide</th>
<th>Pyrrolo[2,3-c]quinolines</th>
<th>Pyrrolo[2,3-c]quinoline Yield (%)</th>
<th>δ_H 1-H (ppm)</th>
<th>3-Aminoquinoline</th>
<th>3-Aminoquinoline Yield (%)</th>
<th>δ_H NH (ppm)</th>
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(i) Pd(OAc)₂ (8 mol %), Xantphos (10 mol %), K₂CO₃ (3 equiv.), DMA (0.04 g/mL), 80 °C

Table 4.2 Yields of 4.35B – C and 4.36B – C from amination-hydroamination reaction of 4-alkynyl-3-idoquinoline 3.2b – c
The Pd-catalysed amination of 3.2a with p-toluidine provided a mixture of the pyrroloquinoline 4.35Aa and the 3-aminoquinoline 4.36Aa in which the latter predominated (entry 1, Table 4.1). Separation of the two compounds was readily accomplished by flash column chromatography on silica with 10% EtOAc – pet ether. Under these conditions the 3-aminoquinoline 4.36Aa eluted first from the column. When aniline was coupled with 3.2a, 2,3,4-triphenyl-3H-pyrrolo[2,3-c]quinoline 4.35Ab was obtained in excellent yield (74%, entry 2, Table 4.1), together with a trace amount of the corresponding 3-aninoquinoline 4.36Ab. However, near equal yields of both products 4.35Ad and 4.36Ad were obtained from the coupling of 3.2a with p-anisidine (entry 4, Table 4.1). Although the electron deficient 4-trifluoromethylaniline coupled to 3.2a to furnish modest yields of both the pyrroloquinoline 4.35Af and the aminoquinoline 4.36Af, the latter was obtained in slightly higher yield (entry 6, Table 4.1).

Amination of 3.2a with benzylamine provided exclusively the 3-(benzylamino)quinoline derivative 4.36Ae; none of the pyrroloquinoline 4.35Ae was observed (entry 5, Table 4.1). It is difficult to rationalise the outcome of this latter hydroamination, that failed to provide any of the pyrroloquinoline, whilst the coupling of 3.2a with aniline (a less nucleophilic amine) furnished the pyrroloquinoline 4.35Ab in excellent yield. Attempts to effect Pd-catalysed amidation of the 3-iodoquinoline 3.2a with either tert-butyl carbamate or with tert-butylsulfinamide were unsuccessful (entries 3 and 7 respectively, Table 4.1), these reactions are considered in more detail on page 224.

Efforts to accomplish the amination-hydroamination reaction with 3-iodo-4-(pent-1-yn-1-yl)-2-propylquinoline 3.2b with either aniline or p-toluidine were unsuccessful and failed to afford tractable products (entry 1 and 2, Table 4.2). In contrast the Pd-mediated coupling of 3-iodo-2-(4-methoxyphenyl)-4-(4-methoxyphenylethynyl)quinoline 3.2c with both amines was successful, p-toluidine provided the pyrroloquinoline 4.35Ca as the only isolable product in 40% yield (entry 3, Table 4.2). Whereas, amination with aniline afforded both the pyrroloquinoline 4.35Cb and a somewhat lower yield of the 3-anilino-quinoline 4.36Cb (entry 4, Table 4.2).

Pyrrolo[2,3-c]quinolines 4.35A – C and N-substituted-4-alkynylquinolin-3-amines 4.36A – C were characterised by all the usual physical techniques. Interestingly the melting points of
the pyrroloquinolines 4.35A – C were on average 50 °C higher than the 3-aminoquinolines 4.36A – C.

The \(^1\)H NMR spectrum of 2,4-diphenyl-3-(p-tolyl)pyrrolo[2,3-c]quinoline 4.35Aa (cf. Figure 4.3) is shown in Figure 4.7 along with those of the analogues 4.35Ab, 4.35Ad and 4.35Af. A notable characteristic of the spectra in that the 1-H signal resonances fall within the range \(\delta_H 7.58 – 7.25 \text{ ppm}\). Although a contribution to these differences can be attributed to solvent effects, particularly noteworthy is the deshielding of the 1-H signal in the trifluoromethyl analogue 4.35Af (\(\delta_H 7.58 \text{ ppm}\)) compared to the 3-(p-anisyl)pyrroloquinoline 4.35Ad (\(\delta_H 7.52 \text{ ppm}\)), presumably a consequence of the electron withdrawing substituent in the former.

An interesting feature of the \(^1\)H spectra of the pyrroloquinolines 4.35Ab, 4.35Ad and 4.35Af is that all display non-first order splitting of the signals for the 6-H and 9-H protons and these together with 7-H and 8-H form part of an AA'XX' system. Clearly this feature cannot be attributed to solvent effects because of the similarity of the spectra of 4.35Ab (in CD\(_2\)Cl\(_2\)) with 4.35Ad and 4.35Af (both in acetone-d\(_6\)). In contrast, the 6-H and 9-H signals in the 3-(p-tolyl)pyrroloquinoline 4.35Aa both have first order-like appearance, giving rise to broadened double doublets (Figure 4.7, see also Figure 4.3). A similarity of all the pyrroloquinoline 4.35 \(^1\)H spectra is the narrow range in which the (superimposed) signals for 7-H and 8-H resonate (ca. \(\delta_H 7.58 – 7.71 \text{ ppm}\)) and this is also the case for the corresponding protons i.e. 6-H and 7-H in the aminoquinolines 4.36A (Figure 4.8). Within this series the quinoline 5-H and 8-H protons appear as a broadened double doublet and are the most deshielded signals (cf. Figures 4.5 and 4.6). Deshielding of the anilino-substituted protons is observed with 2-phenyl-4-(phenylethynyl)-N-[4-(trifluoromethyl)phenyl]quinoline-3-amine 4.36Af in which the ring protons ortho to the CF\(_3\) group are deshielded and resonate at \(\delta_H 7.50 \text{ ppm}\), a shift of ca. 0.5 ppm compared to those in the tolyl derivative 4.36Aa.

The 3-(benzylamino)quinoline 4.36Ae exhibits a broadened signal at \(\delta_H 4.48 \text{ ppm}\) which also displays partial splitting by virtue of coupling with the NH proton and because they are also diastereotopic (Figure 4.8).
Figure 4.7 $^1$H NMR spectra comparison of pyrrolo[2,3-c]quinolines 4.35Aa – f
Figure 4.8 $^1$H NMR spectra comparison of N-substituted-2-phenyl-4-(phenylethynyl)quinolin-3-amines 4.36Aa – f
Formation of both N-substituted-4-(alkynyl)quinolin-3-amines \(4.36A - C\) and the pyrrolo[2,3-c]quinolines \(4.35A - C\) can be postulated to proceed by two competing catalytic cycles. Formation of N-substituted-4-(alkynyl)quinolin-3-amines \(4.36A - C\) is proposed to involve a Buchwald-Hartwig amination as shown in catalytic cycle A (Scheme 4.22). The cycle has been adapted for \(4.36A - C\) from the review by Dorel et al. for Pd-mediated amination with a bidentate ligand (in this case Xantphos) [00JA4618, 19AGE17118]. Aminoquinoline \(4.36A - C\) will then enter the next catalytic cycle B, in which hydroamination takes place. Palladium(II) will coordinate with the \(\pi\)-electrons of the triple bond, activating it to attack from the amino nitrogen to give the palladium complex \(4.38\) [02JA764]. Following protodemetalation, aided by acetic acid, the corresponding pyrrolo[2,3-c]quinolines \(4.35A - C\) will be obtained.

\[ \text{Scheme 4.22} \]

Surprisingly, 4-alkynyl-3-iodoquinolines \(3.2b\) (\(R^1 = C_8H_7\)) did not work with the amination-hydroamination conditions used (Scheme 4.21, entries 3 and 4, Table 4.2), with no identifiable products isolated from the reactions. As with the synthesis of the 3-iodoquinoline \(3.2b\), different conditions are possibly needed for the alkyl substituted derivatives (Section 3.1, Scheme 3.13, page 151). Moreover when \(R^1 = 4\text{-MeOC}_6H_4\) (\(3.2c\)) the
yields of pyrrolo[2,3-c]quinolines 3.35Ca – b were higher than 4-alkynyl-3-aminoquinoline 3.36Ca – b which is different to that seen for the phenyl derivatives (R1 = Ph) 3.35Aa – f. Evidently changing the substituents on the alkyne unit significantly affects the reactivity of the compound.

The use of amines possessing readily cleavable N-protecting groups can be envisaged to allow access to a free NH i.e. an N-3-unsubstuted 3H-pyrrolo[2,3-c]quinoline. Thus, benzylamine was an obvious choice. The reaction proceeded smoothly with 3.2a to afford the aminooquinoline 4.36Ae in a good yield (60%, entry 5, Table 4.1), this was the only Pd-mediated amination reaction in the series to produce an oil. With the N-protected compound to hand the removal of the Bn group and possible domino-hydroamination of the 4-alkynyl-3-aminoquinoline 4.36Ae was attempted (A, Scheme 4.23) [05OL2361, 15OBC11046]. Thus, treatment of the latter with Pd/C and ammonium formate, which acts as a hydrogen source, in MeOH was attempted. Unfortunately, no tractable products could be isolated from the reaction. These conditions were taken from the hydrogenolysis depicted in B Scheme 4.23, in which the benzyl group was removed with ease to afford the indole derivative 4.39 in 71% yield. Another set of conditions attempted for the deprotection of the benzyl group from 4.36Ae, was the use of NIS in DCM reported by Grayson and Davies (C Scheme 4.23) [05OL2361]. In the case of the latter conditions, it was hoped that along with benzyl deprotection the alkynophilicity of NIS would activate the triple bond to hydroamination and possible retention of an iodine substituent in the subsequent 3H-pyrrolo[2,3-c]quinoline structure (1-postion). However the use of NIS also failed to provide the desired 3H-pyrrolo[2,3-c]quinoline, with only starting material being isolated from the reaction.
Due to unsuccessful attempts to deprotect of the benzyl group from aminoquinoline 4.36Ae attention turned to accessing 3-benzyl-2,4-diphenyl-3H-pyrrolo[2,3-c]quinoline 3.35Ae by an alternative means. As discussed in D Scheme 4.13 (v), PdCl$_2$ in DMF has been shown to be effective in the hydroamination of 4-alkynyl-3-amino-2-quinolones to afford 3H-pyrrolo[2,3-c]quinolin-4(5H)-ones [13OBC7334]. Thus, $N$-benzyl-2-phenyl-4-(phenylethynyl)quinolin-3-amine 4.36Ae was treated with PdCl$_2$ (10 mol %) in DMF for 2 h (Scheme 4.24), following purification of the crude mixture by flash column chromatography (10 % EtOAc – pet ether) a fast eluting fraction was isolated as a yellow oil. On inspection of the $^1$H NMR spectrum the fraction was found to be 3-benzyl-2,4-diphenyl-3H-pyrrolo[2,3-c]quinoline 4.35Ae in a 60% yield. It can be postulated that the hydroamination mechanism is similar to that with Pd(OAc)$_2$ (Scheme 4.22, cycle B); palladium(II) will coordinate with the $\pi$-electrons of the triple bond, activating it to attack from the amino nitrogen to give the palladium complex X.
Following protodemetalation, aided by HCl, 3-benzyl-2,4-diphenyl-3H-pyrrolo[2,3-c]quinoline 3.35Ae will be obtained (Scheme 4.25).

(i) PdCl$_2$ (10 mol %), DMF, 100 °C, 2 h

Scheme 4.24

The $^1$H NMR spectrum of 4.35Ae has similar features and chemical shifts to the other pyrrolo[2,3-c]quinolines 4.35Aa – f; for example overlapping of the 7-$H$ and 8-$H$ protons, the 1-$H$ proton resonance at $\delta_H$ 7.33 ppm which is identical to that in 4.35Aa. However, a striking difference is the high field doublet at $\delta_H$ 6.11 ppm, integrating for two protons.
corresponding to the benzyl group ortho protons (blue circle, Figure 4.9). The remarkable upfield shift is a consequence of the proximity of the benzylic ortho protons to the adjacent phenyl substituents at C-2 and C-4. Either, or both of these aryl groups will adopt an orthogonal disposition to the N-benzyl group, so exposing the ortho protons to an anisotropic shielding region. Similar structural fragments to 4.35Ae possessing either C- or N-linked benzyl groups do no exhibit such high field signals for their aromatic protons (Scheme 4.26) [11JNP603, 17JOC4435, 20SL1613]. It is noteworthy that the aromatic proton signals in benzyllamine for 4.36Ae (pink and green circles, Figure 4.9) are in the range of δH 7.20 – 7.39 ppm (CDCl3), those in 4.35Ae are shielded by 1 ppm compared to the amine substrate.

Figure 4.9 400 MHz 1H NMR spectrum of 4.35Ae in CDCl3

[11JNP603] [17JOC4435] [20SL1613]

Scheme 4.26
Donohoe and co-workers showed that β-carboline 4.40 undergoes benzyl deprotection in a high yield (88%) with excess AlCl₃ in PhMe at room temperature (Scheme 4.27) [17JOC4435]. Thus, pyrrolo[2,3-c]quinoline 4.35Ae was dissolved in dry PhMe and added to a suspension of excess AlCl₃ (6 equiv.) in dry PhMe at 0 °C. The mixture was stirred for 30 minutes, after which it was allowed to warm to room temperature and stirred overnight. After quenching with aq. NaHCO₃ and isolation with EtOAc the ¹H NMR spectrum revealed only starting material (4.35Ae) was present (Scheme 4.27). The use of alternative protected amines or ammonia surrogates was therefore sought.

Attempts to couple tert-butyl carbamate (BocNH₂) with 3-iodoquinoline 3.2a (entry 3, Table 4.1) were unsuccessful and only starting material could be isolated from the reaction mixture. BocNH₂ has been utilised extensively in palladium-catalysed C-N coupling reactions, which has been reviewed by Buchwald and Ruiz-Castillo [16CRV12564]. An alternative means to access an N-unsubstituted pyrroloquinoline was to employ tert-butylsulfinamide (t-BuSONH₂) because it has been utilised as an ammonia surrogate in the synthesis of 2-arylindoles (A, Scheme 4.28) [11TL5625]. However, use of tert-butylsulfinamide was also unsuccessful and only starting material was isolated from the reaction mixture (entry 7, Table 4.1), even when the reaction was attempted using the same conditions reported by Sivakumar and co-workers (B, Scheme 4.27). It is possible that the failure of tert-butylsulfinamide to couple with 3.2a is a consequence of the substrate being an iodo-compound. The palladium(0)-catalysed reaction of tert-butylsulfinamide with aryl halides (C,
Scheme 4.28) shows a significant difference in yields by changing the halide. Aryl bromides appear to couple most efficiently [12JOC4454].

![Scheme 4.28](image)

Iodo-compounds are known to not react as successfully in the C-N forming reactions [09JA5766] in comparison to other halide substrates (bromides or chlorides). Buchwald and co-workers suggest the poor yields from aryl iodides in C-N bond formations is due to the iodide salt generation competing with the amine binding to the Pd(II) oxidative addition complex (X, Scheme 4.29) or iodide binding with the amino Pd(II) complex slowing the rate of reductive elimination (Y, Scheme 4.29). Of note is that these studies were carried out using different reactions conditions [09JA5766] to those described here. Therefore the use of an amide instead of an amine and the substrate being an iodo compound may be the reasons for the failure of BocNH₂ and t-BuSONH₂ to afford the corresponding amidation products (entries 3 and 7, Table 4.1); the scope and limitations of this reaction needs to be investigated further.
Another simple way in which the 4-alkynyl-3-iodoquinoline structure could be functionalised or extended is by application in a Suzuki, Heck or Sonogashira coupling. Some examples of iodoquinolines subjected to these coupling reactions are shown in Scheme 4.30 [11JOC1163, 11OL2598, 17EJO4600, 17OBC6901, 18EJO1863]. Interestingly when 2,4-diiodo-3-phenylquinoline was subject to Heck or Sonogashira coupling conditions with excess alkene or acetylene (2.0 – 2.2 equiv.) the coupling would occur regioselectively at the 4-position [11JOC1163].
Heck reaction conditions = (i) Pd(PPh₃)₄ (5 mol %), MeCN, 100 °C; (ii) Pd(OAc)₂ (5 mol %), Bu₄NBr (1 equiv.), K₂CO₃, DMF, 80 °C, 3 equiv. ethyl acrylate

Sonogashira reaction conditions = (i) PdCl₂(PPh₃)₂ (1 mol %), Cul, Et₂N, 60 °C; (ii) PdCl₂(PPh₃)₂ (5 mol %), Cul, Et₂N, r.t., 1.3 equiv. phenylacetylene; (iii) Pd(OAc)₂ (2 mol %), DABCO, MeCN, 2.0 equiv. phenylacetylene, r.t.; (vi) PdCl₂(PPh₃)₂ (10 mol %), Cul, Na₂CO₃, DMF, 120 °C, 1.5 equiv. phenylacetylene

Suzuki reaction conditions = (i) PdCl₂(PPh₃)₂ (5 mol %), K₂CO₃, DMF/H₂O, 100 °C; (ii) Pd(OAc)₂ (5 mol %), Na₂CO₃, 1.3 equiv. PhB(OH)₂, DMF/H₂O, 100 °C; (iii) Pd(PPh₃)₄ (5 mol %), Na₂CO₃, 1.5 equiv. PhB(OH)₂, THF/H₂O, 70 °C

Scheme 4.30
3-Iodo-2-phenyl-4-(phenylethynyl)quinoline 3.2a was coupled with phenylboronic acid in the presence of Pd(PPh$_3$)$_4$ and K$_2$CO$_3$ in a PhMe : EtOH mixture (50:50) and stirred at reflux for 22 h. After an aqueous work-up and purification by flash column chromatography (8% EtOAc – hexane) the 4-alkynyl-2,3-diphenylquinoline 4.41a was obtained as a white powder in 68% yield.

(i) Pd(PPh$_3$)$_4$ (2.5 mol %), K$_2$CO$_3$ (2.4 equiv.), phenylboronic acid (2.3 equiv.), PhMe : EtOH, Δ, 22 h, N$_2$

Scheme 4.31

The 2,3-diphenyl-4-(phenylethynyl)quinoline 4.41a was characterised by its $^1$H and $^{13}$C NMR spectra; the appearance of five extra aromatic protons corresponding to the new phenyl ring ($^1$H) as well as the disappearance of the C-3 quaternary carbon signal i.e. C-I ($\delta_C$ 102.29 ppm) were confirmative. The $^1$H NMR spectrum of 2,3-diphenyl-4-(phenylethynyl)quinoline 4.41a shows an upfield shift of all of the phenyl protons in comparison to those of the starting material 3.2a (Figure 4.10).

![Figure 4.10 400 MHz $^1$H NMR spectra; comparison of 3.2a and 4.41a in CDCl$_3$](image)
It was envisaged that the alkyne moiety may undergo activation from treatment with an iodine electrophile thus rendering it susceptible to subsequent nucleophilic attack from the phenyl ring (Scheme 4.32), as observed for the cyclisation of 3,3-bis(phenylethynyl)-2-(p-tolyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide 2.59Ba to 6-iodo-2-methyl-5-phenyl-6a-(phenylethynyl)-6aH-1,2-benzisothiazolo[2,3-a]quinoline 11,11-dioxide 2.66a-3, Section 2.7, Scheme 2.71.

Consequently, 4.41a was dissolved in MeCN and following addition of 3 equiv. of ICl, the mixture was stirred at reflux overnight. After quenching the mixture with aqueous sodium thiosulfate, the resultant solid was washed with pentane. However the orange solid isolated was found to be neither of the two possible teracycles (Scheme 4.32) but the novel dihalogenated species 4.42a (92% yield, Scheme 4.33). Confirmation of the presence of two halogen functions was established by HMRS that exhibited a molecular ion at \( m/z \) \([M+H]^+ = 544.0314\) corresponding to \( C_{29}H_{19}^{35}\)ClIN.
Further confirmation that iodochlorination had occurred on the triple bond was derived from the upfield shift of the 5-H proton in comparison to the starting material (Figure 4.11). Assignment of the proton shift was determined by consideration of the 2D NMR data (HSQC) Figure 4.12 and with the aid of known $^{13}$C shifts for other quinoline derivatives (see Section 3.1).

![Figure 4.11 $^1$H NMR spectra comparison of 4.41a and 4.42a](image)

![Figure 4.12 HSQC spectrum of 4.42a](image)
The *trans*-dihalo product will be formed in preference to the *cis* isomer due to the intermediacy of an iodonium intermediate 4.43, which only enables attack of chloride on the opposite face (Scheme 4.34) [03JOC10175, 07MI1000]

![Scheme 4.34](image)

Recently Zeng *et al.* reported the regio- and stereoselective synthesis of dihaloalkenes from *in situ* generated ICl and various alkynes (Scheme 4.35) [20MI1018]. In all cases it was found that the *trans* isomer was the major or exclusive isomer obtained. The reason for the regioselectivity of the reaction was ascribed to addition of the chloride nucleophile to the most stabilised carbocation centre (neighbouring group stabilisation).

![Scheme 4.35](image)

In the case of 4.43 the most stable carbocation would be that adjacent to the phenyl ring, in comparison to the carbon adjacent to the quinoline ring which is electron deficient and therefore would exert a lesser stabilising effect. Consequently the structure is assigned as shown i.e. *(E)*-4-(2-chloro-1-iodo-2-phenylvinyl)-2,3-diphenylquinoline (Scheme 4.32). However, to fully ascertain the structure of 4.42a and its regio- and stereochemistry a X-ray crystal structure would be required.
The results above clearly demonstrated the ease with which an iodonium ion can be generated from 4-alkynyl-2,3-diphenylquinoline 4.41a. It was envisioned that the presence of a more electron rich 3-C aryl group may facilitate iodocarbocyclisations shown in Scheme 4.32.

Accordingly, 4-tolylbicenic acid was employed in the Suzuki coupling with 3.2a, to give 4.41b in a 70% yield (Scheme 4.36). The constitution of 2-phenyl-4-(phenylethynyl)-3-(p-tolyl)quinoline 4.41b was confirmed by $^1$H and $^{13}$C NMR spectra and by HRMS that exhibited a molecular ion at $m/z$ [M+H]$^+$ = 396.1739 corresponding to C$_{30}$H$_{21}$N. Addition of the methyl group in the para position of the aromatic ring should increase the overall electron density in the ring and thus facilitate the cyclisation (Scheme 4.32). Unfortunately, subsequent reaction with ICl in refluxing MeCN provided only unreacted starting material (Scheme 4.36). The reasons for this outcome are not clear and further work is required to understand the scope and limitations of this reaction.

![Scheme 4.36](image-url)
Chapter 5
Conclusions
Chapter 5 Conclusions

5.1 Chapter 2 Conclusions

- The synthesis of novel 3-(2-arenesulfonamidophenyl)penta-1,4-diyn-3-ols has been accomplished from addition of alkynyllithium reagents to methyl 2-(arenesulfonamido)benzoates in varying yields (11 – 90%). The electron density and thus nucleophilicity of the sulfonamide group could be attenuated by the nature of the arenesulfonyl function. Both electron rich and electron-deficient sulfonamides were prepared.

- The synthesis of novel 3-(2-tosylamidophenyl)penta-1,4-diyn-3-ols possessing unsymmetrical alkyne-terminal groups was readily accomplished in varying yields (28 – 88%) from the reaction of 3-aryl-1-(2-tosylamidophenyl)prop-2-yn-1-ones with alkynyllithiums or with HC≡CMgBr. The propynes could be accessed directly from the Weinreb amide, N-methoxy-N-methyl-2-(tosylamido)benzamide and an alkynyllithium reagent.

- The synthesis of N-arylsaccharins was achieved from a Chan-Lam-(Evans) coupling of arylboronic acids with saccharin. Subsequent addition of an alkynyllithium reagent resulted in an addition-ring opening-addition sequence giving access to the novel 1,5-disubstituted-3-[2-(N-arylsulfamoyl)phenyl]penta-1,4-diyn-3-ols in varying yields (42 – 98%).

- Attempts to effect a base-mediated double desilylation of 1,5-bis(trimethylsilyl)-3-(2-tosylamidophenyl)penta-1,4-diyn-3-ol afforded, unexpectedly, a novel 3-ethynyl-2-methylene-1-tosylindolin-3-ol. A mechanism has been proposed to account for this transformation (Schemes 2.32 and 2.54)
  - This base-mediated 5-exo-dig ring closure was applicable to a range of 1-alkyl- or 1-aryl- 5-trimethylsilyl-3-(2-tosylamidophenyl)penta-1,4-diyn-3-ols as well as the 5-desilyl-derivatives. Both series of dialkynols provided high yields of 3-alkynyl-2-methylene-1-tosylindolin-3-ols and six examples were prepared.
  - The base-mediated dialkynol cyclisation was not applicable to internal 3-(2-tosylamidophenyl)penta-1,4-diyn-3-ols.
Silver-catalysed cyclisation (AgNO$_3$ on silica) of 1,5-diphenyl-3-(2-tosylamidophenyl)penta-1,4-diyn-3-ol underwent a 5-exo-dig cyclisation to the novel (Z)-2-benzylidene-3-(phenylethynyl)-1-tosylindolin-3-ol in quantitative yield.

- The stereochemistry of (Z)-2-benzylidene-3-(phenylethynyl)-1-tosylindolin-3-ol was established by examination of 2D NMR spectra, primarily the NOESY spectrum.
- A related, stereospecific 5-exo-dig cyclisation of 1,3-diphenyl-1-[2-(tosylamido)phenyl]prop-2-yn-1-ol with AgOAc to 2-benzylidene-3-phenyl-1-tosylindolin-3-ol has been reported by Chan and co-workers (Scheme 2.42) [12CEJ2666].

Attempts to affect the cyclisation of other 3-(2-tosylamidophenyl)penta-1,4-diyn-3-ols with AgNO$_3$ proved unsuccessful.

Treatment of 3-(2-tosylamidophenyl)penta-1,4-diyn-3-ols with silver(I) acetate brought about a 5-exo-dig cyclisation and subsequent isomerisation to afford the novel phenyl[3-(phenylethynyl)-1-tosyl-1H-indol-2-yl]methanol in quantitative yield.

- Exposure of 6-(2-tosylamidophenyl)undeca-4,7-diyn-6-ol to AgOAc initiated multiple reaction pathways. The major product was characterised as 1-[3-(pent-1-yn-1-yl)-1-tosyl-1H-indol-2-yl]butan-1-ol. The minor products were identified as the dehydration product (E)-2-but-1-en-1-yl-3-pentyn-1-yl-1-tosyl-1H-indole together with 4-pentyn-1-yl-2-propylquinoline from a 6-endo-dig pathway. All three products are novel.
- However when the alkyne termini in 3-(2-tosylamidophenyl)penta-1,4-diyn-3-ols were substituted with TMS or tert-Bu groups, cyclisation did not proceed to the expected 2-(α-hydroxyalkyl)indoles. Instead the (Z)-2-(trimethylsilylmethylene)- or (Z)-2,2-dimethylpropylidene)- derivatives of the 3-alkynyl-1-tosylindolin-3-ols were isolated. A plausible mechanism for these conversions has been postulated (Scheme 2.55). It is proposed that the presence of bulky groups hinders attack of water on the vinylic carbocation intermediate.

Indium(III) triflate induced a remarkable and unexpected cascade cyclisation of 1,5-diphenyl-3-(2-tosylamidophenyl)penta-1,4-diyn-3-ol to the novel the 2,4-diphenyl-1-tosyl-4,5-dihydrofuro[2,3-c]quinoline. It is proposed that an initial Meyer-Schuster rearrangement is followed by a 5-exo-dig cyclisation of an enynone from which a 6-
endo-trig ring closure ultimately ensues. Optimisation studies revealed that yields were maximised with 5 mol % In(OTf)$_3$ in DCM at r.t.

- This novel cyclisation pathway was only applicable to 1,5-diphenyl-3-(2-tosylamidophenyl)penta-1,4-diyn-3-ol and none of the other 3-(2-tosylaminophenyl)penta-1,4-diyn-3-ol derivatives provided analogous, isolatable products.

- Treatment of 1,5-disubstituted-3-[2-(N-arylsulfamoyl)phenyl]penta-1,4-diyn-3-ols with indium(III) triflate initiated dehydration (via an E$_1$ pathway) and subsequent cyclisation to afford novel 2-aryl-3,3-d(alkynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxides in fair to high yields (37 – 100%). This cyclodehydration reaction could also be accomplished, but in lower yields, by treatment with iodine monochloride.

- Iodine monochloride also induced cyclisation of 1,5-disubstituted-3-[2-(N-arylsulfamoyl)phenyl]penta-1,4-diyn-3-ols to a novel 1,2-benzisothiazolo[2,3-$a$]quinoline that was characterised by X-ray crystallography. It was found that 2-aryl-3,3-di(alkynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxides were intermediates of the reaction and a plausible mechanism for this unusual iodocyclisation reaction has been described (Scheme 2.71).

- 1,2-Benzisothiazolo[2,3-$a$]quinolines could be generated from both a stepwise manner utilising preformed 2-aryl-3,3-di(alkynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxides and in a one-pot domino reaction from 1,5-disubstituted-3-[2-(N-arylsulfamoyl)phenyl]penta-1,4-diyn-3-ols by treatment with iodine monochloride.
5.2 Chapter 3 Conclusions

- Treatment of 1,5-diphenyl-3-(2-tosylamidophenyl)penta-1,4-diyn-3-ol with molecular iodine in refluxing MeOH initiates cyclisation via a 6-endo-dig pathway to afford the novel 3-iodo-2-phenyl-4-(phenylethynyl)quinoline in 25% yield.
  - Optimisation studies revealed that 2 equiv. ICl in MeCN at r.t. gave the best results providing the 3-iodoquinoline in 60% yield. (Table 3.1).
  - However when 6-(2-p-tosylamidophenyl)undeca-4,7-diyn-6-ol was treated with ICl in MeCN the reaction provided complex mixtures. Therefore, for the alkyl-terminated dialkynol derivatives molecular iodine (3 equiv.) in refluxing MeOH was used.
- Changing the electron density of the sulfonamide nitrogen affected the reaction rate and yields of the 4-alkynyl-3-iodo-2-substituted quinolines.
  - With an electron withdrawing 4-nitrophenylsulfonyl group, lower yields and slower reactions times were observed. In contrast, the more electron donating (4-methoxyphenylsulfonyl group provided higher yields of products and faster reaction rates were achieved.
- 3-(2-Tosylamidophenyl)penta-1,4-diyn-3-ols possessing unsymmetrical alkyne-terminal groups also underwent the 6-endo-dig cyclisation to 4-alkynyl-3-iodoquinolines, however only poor yields were achieved and many reactions failed to give any tractable products.
- 1,5-Disubstituted-3-[2-(N-arylsulfamoyl)phenyl]penta-1,4-diyn-3-ols underwent a silver-catalysed 6-exo-dig cyclisation to (Z)-3-alkylidene-4-alkynyl-2-aryl- and (Z)-4-alkynyl-2-aryl-3-arylidene- derivatives of 1,2-benzothiazin-4-ol 1,1-dioxides. Some sixteen examples were prepared in fair to excellent yields (30 – 96%). This reaction represents a novel means to assemble the 1,2-benzothiazine system.
  - The reaction was stereospecific giving the (Z)-isomer exclusively, the stereochemistry of the products was established from the 1D and 2D NMR (1H and NOESY) spectra.
  - 2-(6-Hydroxyundeca-4,7-diyn-6-yl)-N-methylbenzenesulfonamide and 2-(6-hydroxyundeca-4,7-diyn-6-yl)-N-(thiophen-3-yl)benzenesulfonamide also cyclised
via a 7-endo-dig pathway to yield small amounts of the novel 1,2-benzothiazepine 1,1-dioxides (7% and 11% respectively).
5.3 Chapter 4 Conclusions

- A variety of reactions with 3-ethynyl-2-methylene-1-tosylindolin-3-ol (dehydration and interception with a nucleophile, cyclocondensation with 2-naphthol, 1,3-AAI and oxidation reactions) to extend the functionality of the ring system gave no tractable products (Scheme 4.5).
  - When (Z)-2-benzylidene-3-(phenylethynyl)-1-tosylindolin-3-ol was treated with acetylacetone under acidic conditions facile dehydration and interception with the nucleophilic enolate tautomer was achieved in quantitative yield to afford 3-{phenyl[3-(phenylethynyl)-1-tosyl-1H-indol-2-yl]methyl}pentane-2,4-dione.
  - However when the indole-linked 1,3-dione was subjected to basic conditions, cyclisation did not ensue. External electrophilic π-bond activators – Ag(I), In(III) and sources of I⁺ – also failed to initiate cyclisation. Further work is needed to establish the scope and limitations of the reaction (Scheme 4.10).

- Palladium(0)catalysed coupling of 4-alkynyl-3-iodquinolines with various aniline derivatives and with benzylamine afforded both the amination [4-(alkynyl)quinolin-3-amine] and hydroamination (pyrrolo[2,3-c]quinoline) products. With many of the couplings affording the former, 4-(alkynyl)quinolin-3-amines as the major product. Formation of the pyrrolo[2,4-c]quinolines is of interest as it enables access to novel analogues of the biologically active marinoquinolines.
  - The Pd-mediated amination reaction was also attempted with ammonia surrogates (tert-butyl carbamate and tert-butyl sulfinamide) but only starting material was isolated from these reactions.
  - In a separate reaction N-benzyl-2-phenyl-4-(phenylethynyl)quinolin-3-amine with PdCl₂ in DMF effected the hydroamination cyclisation to 3-benzyl-2,4-diphenyl-3H-pyrrolo[2,3-c]quinoline in 60% yield.
  - Attempts to deprotect the 3-benzyl-2,4-diphenyl-3H-pyrrolo[2,3-c]quinoline to achieve access to the N-unsubstituted 2,4-diphenyl-3H-pyrrolo[2,3-c]quinoline by dealkylation with excess AlCl₃ provided futile and only starting material was isolated.
  - 4-Pentyn-1-yl-2-propylquinoline did not afford any amination-hydroamination products, only starting material was isolated.
Chapter 6

Experimental
Chapter 6 Experimental

6.1 Equipments and Reagents

Unless otherwise stated, reagents were used as supplied. Reagents were purchased from Alfa Aesar, Fluorochem, TCI, Fisher and Sigma Aldrich.

NMR spectra were recorded on a Bruker Avance 400 spectrometer (\(^1\)H 400 MHz and \(^{13}\)C 100 MHz), unless otherwise stated. Coupling constants are given in Hz. Accurate mass measurements were obtained from the IPOS Mass Spectrometry Service at The University of Huddersfield. Single crystal studies were recorded on a Bruker D8 Venture with Dual I\(\mu\)S Microfocus Sources using Mo and/or Cu radiation. The temperature of data collection was 150 K.

Melting points were determined in capillary tubes, using a Stuart SMP10 melting point apparatus, and are uncorrected. FT-IR spectra were recorded on a Nicolet 380 Spectrum Spotlight system, equipped with a diamond probe ATR attachment (neat sample). TLC was performed on Merck TLC Aluminium sheets, silica gel 60 F254 using a range of eluent systems of differing polarity. Flash Chromatographic separations were performed on Aldrich, 35-70 \(\mu\) 60 Å silica gel, according to the literature procedure [78JOC2923]. When stated flash column chromatography separations were performed using Biotage® Isolera 4 Automated Purification System equipped with Biotage® Snap Ultra Biotage® HP-Sphere™ 25 \(\mu\)m cartridges.

6.2 Chapter 2.0 Experimental

6.2.1 Synthesis of 2-Sulfamidobenzoic Acid Derivatives

Synthesis of methyl 2-[(4-methylphenyl)sulfonamido]benzoate (2.4a)
Under an inert (N₂) atmosphere methyl 2-aminobenzoate (9.71 mL, 75.0 mmol, 1.0 equiv.) was dissolved in DCM (75 mL). Pyridine (7.28 mL, 90.0 mmol, 1.2 equiv.) was added dropwise over 10 minutes and the solution stirred for 60 minutes. Toluene-4-sulfonyl chloride (17.2 g, 90.0 mmol, 1.2 equiv.) dissolved in DCM (100 mL) was added dropwise over 10 minutes and the reaction mixture was stirred at r.t. overnight. After this time the mixture was quenched with 2M HCl, diluted with DCM (approx. 100 mL). The organic phase was separated, washed with water and brine, dried (Na₂SO₄) and evaporated to give white crystals. The crude material was recrystallised from MeOH to give the title compound as white crystals (18.6 g, 81%) m.p. 113 – 114 °C (lit. m.p. 113 °C [04H(63)1113]).

δH (CDCl₃) 10.62 (1H, s, NH), 7.91 (1H, dd, J = 8.0, 1.6 Hz, 2-H), 7.74 (2H, d, J = 8.2 Hz, o-Ar-H), 7.68 (1H, dd, J = 8.0, 1.6 Hz, 5-H), 7.47 – 7.42 (1H, m, 4-H), 7.22 (2H, d, J = 8.2 Hz, m-Ar-H), 7.05 – 7.01 (1H, m, 3-H), 3.88 (3H, s, CO₂Me), 2.36 (3H, s, Ar-Me). δc 168.31 (C=O), 143.93 (qC), 140.52 (qC), 136.43 (qC), 134.50 (CH), 131.17 (CH), 129.64 (CH), 127.29 (CH), 122.83 (CH), 118.97 (CH), 115.81 (qC), 52.48 (CH₃), 21.54 (CH₃).

νmax/cm⁻¹: 3131 b (NH), 1687 s (CO₂R), 1587 s (C=C), 1492 s (CH₃), 1316 s (SO₂), 1256 s (CO₂R), 1088 s (SO₂).

**Synthesis of methyl 2-[(4-methoxyphenyl)sulfonamido]benzoate (2.4b)**

Under an inert (N₂) atmosphere methyl 2-aminobenzoate (3.15 mL, 24.2 mmol, 1.0 equiv.) was dissolved in chloroform (20 mL). Pyridine (5.85 mL, 72.6 mmol, 3.0 equiv.) was added dropwise over 10 minutes and the solution stirred for 60 minutes. 4-Methoxybenzenesulfonyl chloride (5.00 g, 24.2 mmol, 1.0 equiv.) dissolved in chloroform (30 mL) was added dropwise over 15 minutes and stirred at r.t. overnight. After this time the mixture was quenched with 2M HCl, diluted with chloroform (approx. 30 mL). The organic phase was separated, washed with water and brine, dried (Na₂SO₄) and evaporated to give a light red oil. On standing the oil crystallised and subsequent recrystallisation from
EtOH to give the title compound as white crystals (4.85 g, 62%) m.p. 80 – 82 °C (lit. m.p. 81 – 85 °C [75USP3920687]).

δ_H (CDCl₃) 10.58 (1H, s, NH), 7.91 (1H, dd, J = 7.9, 1.5 Hz, 2-H), 7.81 (2H, m, o-Ar-H), 7.68 (1H, dd, J = 7.9, 1.5 Hz, 5-H), 7.47 – 7.43 (1H, m, 4-H), 7.05 – 7.01 (1H, m, 3-H), 6.90 – 6.87 (2H, m, m-Ar-H), 3.88 (3H, s, CO₂Me), 3.82 (3H, s, O-Me). δ_c 168.29 (C=O), 163.11 (q_C), 140.62 (q_C), 134.49 (CH), 131.16 (CH), 131.01 (CH), 129.47 (CH), 122.76 (CH), 119.02 (CH), 115.82 (q_C), 114.15 (CH), 55.58 (CH₃), 52.47 (CH₃).

ν_max/cm⁻¹: 3137 b (NH), 1682 s (CO₂R), 1588 s (C=C), 1490 s (CH₃), 1255 s (CO₂R), 1152 s (SO₂), 1087 s (SO₂).

**Synthesis of methyl 2-[(4-nitrophenyl)sulfonamido]benzoate (2.4c)**

![Chemical structure](image)

Under an inert (N₂) atmosphere methyl 2-aminobenzoate (2.70 mL, 21.4 mmol, 1.0 equiv.) was dissolved in DCM (30 mL). Pyridine (1.70 mL, 21.4 mmol, 1.0 equiv.) was added dropwise over 10 minutes and the solution was stirred for 60 minutes. 4-Nitrobenzenesulfonyl chloride (5.00 g, 21.4 mmol, 1.0 equiv.) dissolved in DCM (30 mL) was added dropwise over 20 minutes and stirred at r.t. overnight. After this time the mixture was quenched with 2M HCl, diluted with DCM (approx. 30 mL). The organic phase was separated, washed with water and brine, dried (Na₂SO₄) and evaporated to give a red solid. The crude material was recrystallised from EtOH to give the title compound as yellow needles (4.97 g, 71%) m.p. 152 – 153 °C (lit. m.p. 154.9 – 155.7 °C [13MOL6883]).

δ_H (CDCl₃) 10.82 (1H, s, NH), 8.29 – 8.25 (2H, m, m-Ar-H), 8.05 – 8.01 (2H, m, o-Ar-H), 7.95 (1H, dd, J = 8.0, 1.5 Hz, 2-H), 7.73 (1H, dd, J = 8.0, 1.5 Hz, 5-H), 7.53 – 7.49 (1H, m, 4-H), 7.13 – 7.09 (1H, m, 3-H), 3.88 (3H, s, CO₂Me). δ_c 168.35 (C=O), 150.24 (q_C), 145.03 (q_C), 139.55 (q_C), 134.83 (CH), 131.48 (CH), 128.55 (CH), 124.27 (CH), 123.90 (CH), 119.36 (CH), 116.26 (q_C), 52.73 (CH₃).
$v_{\text{max}}/\text{cm}^{-1}$: 3108 b (NH), 1698 s (CO$_2$R), 1600 s (C=C), 1586 w (NO$_2$), 1526 s (CH$_3$), 1349 s (NO$_2$), 1313 s (SO$_2$), 1265 s (CO$_2$R), 1088 s (SO$_2$).

**Synthesis of methyl 2-(phenylsulfonamido)benzoate (2.4d)**

![Image](image_url)

Under an inert (N$_2$) atmosphere methyl 2-aminobenzoate (9.80 mL, 75.0 mmol, 1.0 equiv.) was dissolved in DCM (75 mL). Pyridine (18.2 mL, 225 mmol, 3.0 equiv.) was added dropwise over 10 minutes and solution stirred for 60 minutes. Benzenesulfonyl chloride (12.5 mL, 97.5 mmol, 1.3 equiv.) dissolved in DCM (40 mL) was added dropwise over 5 minutes and stirred at r.t. overnight. After this time the mixture was quenched with 2M HCl, diluted with DCM (approx. 100 mL). The organic phase was separated, washed with water and brine, dried (Na$_2$SO$_4$) and evaporated to give white crystals. The crude material was recrystallised from MeOH to give the title compound as white crystals (15.3 g, 70%) m.p. 105 – 106 °C (lit. m.p. not quoted [06BMC5562]).

$\delta$ (CDCl$_3$) 10.65 (1H, s, NH), 7.91 (2H, dd, $J = 8.0$, 1.4 Hz, 2-H), 7.86 – 7.84 (2H, m, o-Ar-H) 7.70 (1H, app. d, 5-H), 7.75 – 7.41 (4H, m, Ar-H), 7.06 – 7.02 (1H, m, 3-H), 3.87 (3H, s, CO$_2$Me). $\delta_c$ 168.29 (C=O), 140.36 (qC), 139.36 (qC), 134.53 (CH), 133.03 (CH), 131.17 (CH), 129.01 (CH), 127.25 (CH), 123.03 (CH), 119.22 (CH), 116.00 (qC), 52.51 (CH$_3$).

$\nu_{\text{max}}/\text{cm}^{-1}$: 3157 b (NH), 1681 s (CO$_2$R), 1582 s (C=C), 1489 s (CH$_3$), 1315 s (SO$_2$), 1265 s (CO$_2$R), 1087 s (SO$_2$).

**Synthesis of 2-[(4-methylphenyl)sulfonamide]benzoic acid (2.12)**

![Image](image_url)
Anthranilic acid (5.00 g, 36.46 mmol, 1 equiv.) and toluene-4-sulfonyl chloride (8.32 g, 43.6 mmol, 1.2 equiv.) was suspended in water (400 mL). To this NaOH (1.50 g, 37.5 mmol, 1.0 equiv.) was added portion wise over 10 minutes and the solution was stirred at r.t. overnight. After this time the mixture was filtered and washed with water, the crude material was used without further purification (8.80 g, 83%) m.p. 200 – 202 °C (literature m.p. 112 °C. [07JME1219]).

**Synthesis of 2-[(4-methylphenyl)sulfonamide]benzoyl chloride (2.13)**

![Chemical Structure](image)

Under an inert (N₂) atmosphere 2-[(4-methylphenyl)sulfonamide]benzoic acid (8.72 g, 29.9 mmol, 1.0 equiv) was suspended in anhydrous DCM (100 mL). Oxalyl chloride (3.80 mL, 44.3 mmol, 1.5 equiv) was added dropwise to the cold solution (0 °C), a catalytic amount of DMF was then added to the solution. The solution was stirred at r.t. for 2 h. After this time the mixture was evaporated to give the title compound as an off white solid. The crude material was used without further purification (8.30 g, 90%) m.p. 115 – 117 °C (literature m.p. 117 – 118 °C. [14MI435]).

**6.2.2 Synthesis of N-[2-{3-Hydroxy-penta-1,4-diyn-3-yl}phenyl]benzenesulfonamides**

**General Method for Synthesis of N-[2-{3-Hydroxy-penta-1,4-diyn-3-yl}phenyl]benzenesulfonamides**

Method A: Under an inert (N₂) atmosphere n-BuLi (3.5 equiv.) was added to a cold (-75 °C) solution of the appropriate alkyne (X mmol, 3.5 equiv.) in anhydrous THF (approx. 100 mL). A solution of the appropriate sulfonamide (Y mmol, 1.0 equiv.) in anhydrous THF (approx. 60 mL) was added dropwise to the cold (0 °C) solution and the mixture was allowed to warm to r.t. and stirred for 1 h. After this time the mixture was quenched with aqueous NH₄Cl and diluted with EtOAc. The organic phase was separated, dried (Na₂SO₄) and evaporated to give
the crude material which was purified by recrystallisation or by flash column chromatography. The following compounds were synthesised by this method.

Method B: Under an inert (N₂) atmosphere 1-bromo-1-propene (X mmol, 3.5 equiv.) was added to a cold (-75 °C) solution of LDA 3.5 equiv. (DIPA, 2.1 equiv. and n-BuLi, 3.5 equiv.) in anhydrous THF (approx. 50 mL) and was stirred for 3 h. A solution of the appropriate sulfonamide (Y mmol, 1.0 equiv.) in anhydrous THF (approx. 30 mL) was added dropwise to the cold (0 °C) solution and the mixture was allowed to warm to r.t. and stirred for 1 h. After this time the mixture was quenched with aqueous NH₄Cl and diluted with EtOAc. The organic phase was separated, dried (Na₂SO₄) and evaporated to give the crude material which was purified by recrystallisation or by flash column chromatography. The following compounds were synthesised by this method.

\[ \text{N-[2-(3-Hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)phenyl]-4-methylbenzenesulfonamide (2.5a)} \]

Using Method A from phenylacetylene (69.0 mmol) and methyl 2-[(4-methylphenyl)sulfonyl]benzoate (19.7 mmol) to give a yellow oil. The product crystallised on standing. The crude material was then recrystallised from hexane – EtOAc to give the title compound as an off white powder (7.99 g, 85%) m.p. 137 – 138 °C; HRMS found [M+Na]^+ = 500.1287; C₃₀H₂₃NO₃SNa [M+Na]^+ requires = 500.1291.

\[ \delta (\text{CDCl}_3) \text{ mmH} \]

Using Method A from phenylacetylene (69.0 mmol) and methyl 2-[(4-methylphenyl)sulfonyl]benzoate (19.7 mmol) to give a yellow oil. The product crystallised on standing. The crude material was then recrystallised from hexane – EtOAc to give the title compound as an off white powder (7.99 g, 85%) m.p. 137 – 138 °C; HRMS found [M+Na]^+ = 500.1287; C₃₀H₂₃NO₃SNa [M+Na]^+ requires = 500.1291.

\[ \delta (\text{CDCl}_3) \text{ mmH} \]

Using Method A from phenylacetylene (69.0 mmol) and methyl 2-[(4-methylphenyl)sulfonyl]benzoate (19.7 mmol) to give a yellow oil. The product crystallised on standing. The crude material was then recrystallised from hexane – EtOAc to give the title compound as an off white powder (7.99 g, 85%) m.p. 137 – 138 °C; HRMS found [M+Na]^+ = 500.1287; C₃₀H₂₃NO₃SNa [M+Na]^+ requires = 500.1291.

\[ \delta (\text{CDCl}_3) \text{ mmH} \]
ν_{max}/cm^{-1}: 3409 b (OH), 3282 w (NH), 2981 w (Ar-H), 1583 s (C=C), 1488 s (CH_{3}), 1326 s (SO_{2}), 1087 s (R-OH), 1012 s (SO_{2}).

*Overlapping with CDCl_{3} signal

**N-[2-(6-Hydroxyundeca-4,7-diyn-6-y1)phenyl]-4-methylbenzenesulfonamide (2.5b)**

Using Method A from 1-pentyne (23.0 mmol) and methyl 2-[(4-

methylphenyl) sulfonamido]benzoate (6.57 mmol) to give a yellow oil. The product crystallised on standing. The crude material was then recrystallised from hexane – EtOAc to give the title compound as a beige powder (2.09 g, 78%) m.p. 88 – 89 °C; HRMS found [M+Na]^+ = 432.1589; C_{24}H_{27}NO_{3}SNa [M+Na]^+ requires = 432.1589.

δ_{H} (CDCl_{3}) 8.51 (1H, s, NH), 7.81 (2H, d, J = 8.3 Hz, o-Ar-H), 7.77 (1H, dd, J = 7.9, 1.5 Hz, 2-H), 7.50 (1H, dd, J = 7.9, 1.5 Hz, 5-H), 7.24 – 7.19 (3H, m, Ar-H), 7.00 (1H, app. t, 3-H), 2.80 (1H, s, OH), 2.37 (3H, s, Ar-Me), 2.26 (4H, t, J = 7.3 Hz, CH_{2}), 1.59 (4H, sxt, J = 7.3 Hz, CH_{2}), 1.00 (6H, t, J = 7.3 Hz, CH_{3}). δ_{C} 143.60 (q C), 137.18 (q C), 135.74 (q C), 129.64 (CH), 129.53 (CH), 128.99 (q C), 127.64 (CH), 127.48 (CH), 123.07 (CH), 119.20 (CH), 87.79 (q C), 79.40 (q C), 65.36 (q C), 21.71 (CH_{2}), 21.55 (CH_{3}), 20.82 (CH_{2}), 13.59 (CH_{3}).

ν_{max}/cm^{-1}: 3400 b (OH), 3285 m (NH), 2963 w (Ar-H), 2932 w (CH_{2}, CH_{3}), 2871 w (CH_{2}, CH_{3}), 1588 s (C=C), 1492 s (CH_{2}), 1456 s (CH_{3}), 1333 s (SO_{2}), 1184 w (R-OH), 1090 s (SO_{2}).

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Using Method A from 1-ethynyl-4-methoxybenzene (34.5 mmol) and methyl 2-[(4-methylphenyl)sulfonamido]benzoate (9.86 mmol) to give the title compound as a golden powder (4.77 g, 90%) m.p. 132 – 134 °C; HRMS found [M+Na]^+ = 560.1491; C_{32}H_{27}NO_{5}SNa [M+Na]^+ requires = 560.1502.

δ_{H} (CDCl_{3}) 8.68 (1H, s, N-H), 7.90 (1H, dd, J = 7.9, 1.4 Hz, 2-H), 7.79 (2H, d, J = 8.3 Hz, Ar-H), 7.56 (1H, dd, J = 7.9, 1.4 Hz, 5-H), 7.46 (4H, d, J = 8.8 Hz, Ar-H), 7.28 – 7.24* (1H, m, 4-H), 7.07 – 7.03 (3H, m, Ar-H, 3-H), 6.87 (4H, d, J = 8.8 Hz, Ar-H), 3.83 (6H, s, O-Me), 2.30 (3H, s, Ar-Me). δ_{C} 160.28 (qC), 143.58 (qC), 136.94 (qC), 133.59 (CH), 133.57 [2 X C (qC)(CH)], 129.88 (CH), 129.53 (CH), 127.85 (qC), 127.55 (CH), 123.17 (CH), 119.14 (CH), 114.02 (CH), 113.50 (qC), 86.85 (qC), 86.00 (qC), 66.27 (qC), 55.36 (CH_{3}), 21.54 (CH_{3}).

ν_{max}/cm^{-1}: 3383 b (OH), 3273 w (NH), 2228 s (C≡C), 1604 s (C=C), 1399 w (CH_{3}), 1307 w (SO_{2}), 1174 s (R-OH), 1154 s (SO_{2}).

*Overlapping with CDCl_{3} signal

\(N\)-[2-\{3-Hydroxytrideca-5,8-diyn-7-yl\}phenyl]-4-methylbenzenesulfonamide (2.5d)

Using Method A from 1-hexyne (69.0 mmol) and methyl 2-[(4-methylphenyl)sulfonamido]benzoate (19.7 mmol) to give the title compound as off white...
crystals (7.71 g, 89%) m.p. 80 – 82 °C; HRMS found [M+Na]⁺ = 460.1926; C₂₆H₃₁NO₃SNa [M+Na]⁺ requires = 460.1917.

δH (CDCl₃) 8.54 (1H, s, NH), 7.81 (2H, d, J = 8.3 Hz, o-Ar-H), 7.77 (1H, dd, J = 7.9, 1.5 Hz, 2-H), 7.50 (1H, dd, J = 7.9, 1.5 Hz, 5-H), 7.24 – 7.19 (3H, m, Ar-H), 7.00 (1H, app. t, 3-H), 2.80 (1H, s, OH), 2.37 (3H, s, Ar-Me), 2.26 (4H, t, J = 7.3 Hz, CH₂), 1.59 (4H, sx, J = 7.3 Hz, CH₂), 1.00 (6H, t, J = 7.3 Hz, CH₃). δc 143.60 (qC), 137.18 (qC), 135.74 (qC), 129.64 (CH), 129.53 (CH), 128.99 (qC), 127.64 (CH), 127.48 (CH), 123.07 (CH), 119.20 (CH), 87.79 (qC), 79.40 (qC), 65.36 (qC), 21.71 (CH₂), 21.55 (CH₃), 20.82 (CH₂), 13.59 (CH₃).

νmax/cm⁻¹: 2956 m (Ar-H), 2930 m (CH₂, CH₃), 2871 m (CH₂, CH₃), 1599 s (C=C), 1494 w (CH₂), 1456 w (CH₃), 1379 w (SO₂), 1158 s (R-OH), 1008 s (SO₂).

**N-[2-[3-Hydroxy-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl]phenyl]-4-methylbenzenesulfonamide (2.5e)**

Using Method A from (trimethylsilyl)acetylene (34.6 mmol) and methyl 2-[(4-methylphenyl)sulfonamido]benzoate (9.89 mmol) to give a red oil. The product crystallised on standing. The crude material was purified by flash column chromatography (30% EtOAc – hexane) to give the title compound as an off white powder (1.80 g, 39%) m.p. 138 – 140 °C decomp; HRMS found [M+Na]⁺ = 463.1304; C₂₄H₂₇NO₃SNa [M+Na]⁺ requires = 463.1298.

δH (CDCl₃) 8.34 (1H, s, NH), 7.82 (2H, d, J = 8.3 Hz, o-Ar-H), 7.80 (1H, dd, J = 8.0, 1.3 Hz, 2-H), 7.41 (1H, app. d, 5-H), 7.25 – 7.20* (3H, m, Ar-H), 7.02 (1H, app. t, 3-H), 2.38 (3H, s, Ar-Me), 0.24 (18H, s, Si-Me₃). δc 143.71 (qC), 137.17 (qC), 135.81 (qC), 129.97 (CH), 129.63 (CH), 127.86 (CH), 127.68 (qC), 127.51 (CH), 123.23 (CH), 119.53 (CH), 102.21 (qC), 92.62 (qC), 65.33 (qC), 21.57 (CH₃), -0.44 (Si-Me₃).

νmax/cm⁻¹: 3373 b (OH), 3285 m (NH), 2962 w (CH₃), 1586 s (C=C), 1494 s (CH₃), 1325 s (SO₂), 1149 s (R-OH), 1090 s (SO₂).
*Overlapping with CDCl₃ signal

**N-[2-(4-Hydroxyhepta-2,5-diyn-4-yl)phenyl]-4-methylbenzenesulfonamide (2.5g)**

\[ \text{Using Method B from 1-bromo-1-propene (22.9 mmol) and methyl 2-[(4-methylphenyl)sulfonamido]benzoate (6.55 mmol) to give the title compound as a white powder (0.36 g, 16%) m.p. 140 °C decomp; HRMS found [M+Na]⁺ = 376.0973; C₂₀H₁₉NO₃SNa [M+Na]⁺ requires = 376.0978.} \]

\[ \delta_{\text{H}} (\text{CDCl₃}) \text{ 8.51 (1H, s, N₃H)}, \text{ 7.81 (2H, d, J = 8.3 Hz, o-Ar-H)}, \text{ 7.75 (1H, dd, J = 7.9, 1.4 Hz, 2-H)}, \text{ 7.52 (1H, app. d, 5-H)}, \text{ 7.24 – 7.20 (3H, m, m-Ar-H, 4-H)}, \text{ 7.01 (1H, app. t, 3-H)}, \text{ 2.37 (3H, s, Ar-Me)}, \text{ 1.92 (6H, s, Me)}. \]

\[ \delta_{\text{c}} \text{ 143.64 (αC)}, \text{ 137.20 (αC)}, \text{ 135.73 (αC)}, \text{ 129.69 (CH)}, \text{ 129.53 (CH)}, \text{ 128.96 (αC)}, \text{ 127.65 (CH)}, \text{ 127.48 (CH)}, \text{ 123.16 (CH)}, \text{ 119.31 (CH)}, \text{ 83.56 (αC)}, \text{ 78.31 (αC)}, \text{ 65.40 (αC)}, \text{ 21.55 (CH₃)}, \text{ 3.91 (CH₃)}. \]

\[ \nu_{\text{max}}/\text{cm}^{-1}: \text{ 3392 b (OH)}, \text{ 3244 m (NH)}, \text{ 2921 w (CH₃)}, \text{ 1597 s (C=C)}, \text{ 1406 w (CH₃)}, \text{ 1319 s (SO₂)}, \text{ 1191 s (R-OH)}, \text{ 1152 s (SO₂)}. \]

**N-[2-(5-Hydroxy-2,2,8,8-tetramethylnona-3,6-diyn-5-yl)phenyl]-4-methylbenzenesulfonamide (2.5j)**

\[ \text{Using Method A from 3,3-dimethyl-1-butyne (5.74 mmol) and methyl 2-[(4-methylphenyl)sulfonamido]benzoate (1.64 mmol) to give the title compound as a white} \]
solid (0.56 g, 79%) m.p. 138 – 140 °C decomp; HRMS found [M+Na]+ = 460.1915; C_{26}H_{31}NO_3SNa [M+Na]+ requires = 460.1917.

δ_H (CDCl_3) 8.50 (1H, s, NH), 7.82 (2H, d, J = 8.2 Hz, o-Ar-H), 7.75 (1H, dd, J = 7.9, 1.5 Hz, 2-H), 7.40 (1H, dd, J = 7.9, 1.5 Hz, 5-H), 7.24 – 7.17 (3H, m, m-Ar-H, 4-H), 7.00 (1H, td, J = 7.9, 1.5 Hz, 3-H), 2.82 (1H, s, O-H), 2.37 (3H, s, Ar-Me), 1.28 (18H, s, Me_3). δ_c 143.61 (q_C), 137.33 (q_C), 135.78 (q_C), 129.61 (CH), 129.55 (CH), 129.21 (q_C), 127.60 (CH), 127.45 (CH), 123.01 (CH), 119.22 (CH), 95.54 (q_C), 78.00 (q_C), 64.98 (q_C), 30.50 (CH_3), 27.60 (q_C), 21.56 (CH_3).

ν_max/cm\(^{-1}\): 3409 b (OH), 3263 m (NH), 2964 m (CH_3), 2866 w (Ar-H), 2240 w (C≡C), 1599 s (C=C), 1400 w (CH_3), 1335 s (SO_2), 1158 s (R-OH), 1121 s (SO_2).

N-[2-(5-Hydroxy-2,8-dimethylnona-1,8-dien-3,6-diyn-5-yl)phenyl]-4-methylbenzenesulfonamide (2.5k)

Using Method A from 2-methyl-1-butene-3-yne (11.5 mmol) and methyl 2-[(4-methylphenyl)sulfonamido]benzoate (3.27 mmol) to give the title compound as a yellow solid (0.86 g, 65%) m.p. 138 – 139 °C; HRMS found [M+K]^+ = 444.1368; C_{24}H_{23}NO_3SK [M+K]^+ requires = 444.1030.

δ_H (CDCl_3) 8.49 (1H, s, NH), 7.85 (2H, d, J = 8.3 Hz, o-Ar-H), 7.77 (1H, dd, J = 7.9, 1.5 Hz, 2-H), 7.49 (1H, app. d, 5-H), 7.27 – 7.23 (3H, m, m-Ar-H, 4-H), 7.04 (1H, app. t, 3-H), 5.47 (2H, s, CH_2), 5.39 (2H, s, CH_2), 2.39 (3H, s, Ar-Me), 1.96 (6H, s, Me). δ_c 143.70 (q_C), 137.04 (q_C), 135.84 (q_C), 129.92 (CH), 129.62 (CH), 128.04 (q_C), 127.73 (CH), 127.54 (CH), 127.30 (CH), 125.47 (q_C), 124.18 (CH_2), 123.12 (CH), 119.13 (CH), 87.88 (q_C), 85.92 (q_C), 65.89 (q_C), 22.99 (CH_3), 21.56 (CH_3).

ν_max/cm\(^{-1}\): 3370 b (OH), 3288 m (NH), 2917 w (CH_3), 1602 s (C=C), 1493 s (CH_3), 1335 s (SO_2), 1175 s (SO_2), 1089 s (R-OH), 987 s (C=CH_2), 905 s (C=CH_2).
\textit{N-[2-(3-Hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)phenyl]-4-methoxybenzenesulfonamide (2.6a)}

\begin{center}
\includegraphics[width=0.2\textwidth]{image}
\end{center}

Using Method \textit{A} from phenylacetylene (21.8 mmol) and methyl 2-[(4-methoxyphenyl)sulfonamido]benzoate (6.22 mmol) to give an orange oil. The product crystallised on standing, which was then recrystallised from hexane – EtOAc to give the title compound as an off white powder (2.16 g, 70\%) m.p. 126 °C decomp; HRMS found [M+Na]$^+$ = 516.1230; C$_{30}$H$_{23}$NO$_4$SNa [M+Na]$^+$ requires = 516.1240.

$\delta$\textsubscript{H} (CDCl$_3$) 8.64 (1H, s, NH), 7.91 (1H, dd, $J = 7.8, 1.2$ Hz, 2-H), 7.85 – 7.82 (2H, m, o-Ar-H), 7.61 (1H, dd, $J = 7.8, 1.2$ Hz, 5-H), 7.53 – 7.51 (4H, m, Ph-H), 7.41 – 7.33 (6H, m, Ph-H), 7.29 – 7.28 (1H, m, 4-H), 7.06 (1H, td, $J = 7.8, 1.2$ Hz, 3-H), 6.69 – 6.66 (2H, m, m-Ar-H), 3.73 (3H, s, O-Me), 3.31 (1H, s, OH). $\delta$\textsubscript{c} 162.93 (q C), 135.96 (q C), 132.01 (CH), 131.30 (q C), 130.04 (CH), 129.75 (CH), 129.27 (CH), 128.43 (CH), 128.04 (q C), 127.89 (CH), 123.18 (CH), 121.44 (q C), 119.13 (CH), 114.00 (CH), 87.09 (q C), 86.82 (q C), 66.27 (q C), 55.44 (CH$_3$).

$\nu$\textsubscript{max}/cm$^{-1}$: 3413 b (OH), 3305 w (NH), 1596 s (C=C), 1489 s (CH$_3$), 1329 w (SO$_2$), 1148 s (SO$_2$), 1093 s (R-OH), 748 s (Ph-H), 689 s (Ph-H).

\textit{N-[2-(6-Hydroxyundeca-4,7-diyn-6-yl)phenyl]-4-methoxybenzenesulfonamide (2.6b)}

\begin{center}
\includegraphics[width=0.2\textwidth]{image}
\end{center}

Using Method \textit{A} from 1-pentyne (21.8 mmol) and methyl 2-[(4-methoxyphenyl)sulfonamido]benzoate (6.22 mmol) to give a yellow oil. The product
crystallised on standing, the resultant solid was washed with hexane to give the title compound an orange solid (1.87 g, 73%) m.p. 84 – 85 °C; HRMS found [M+Na]^+ = 448.1541; C_{24}H_{27}NO_{3}SNa [M+Na]^+ requires = 448.1553.

δ_{H} (CDCl_{3}) 8.49 (1H, s, NH), 7.87 – 7.83 (2H, m, o-Ar-H), 7.77 (1H, dd, J = 7.9, 1.5 Hz, 2-H), 7.51 (1H, dd, J = 7.9, 1.5 Hz, 5-H), 7.24 – 7.19 (1H, m, 4-H), 7.00 (1H, app. t, 3-H), 6.91 – 6.87 (2H, m, m-Ar-H), 3.82 (3H, s, O-Me), 2.87 (1H, s, OH), 2.27 (4H, t, J = 7.2 Hz, CH_{2}), 1.59 (4H, sxt, J = 7.2 Hz, CH_{2}), 1.00 (6H, t, J = 7.2 Hz, CH_{3}). δ_{C} 162.94 (q-C), 135.77 (q-C), 131.66 (q-C), 129.65 (CH), 129.62 (CH) 127.65 (CH), 123.05 (CH), 119.22 (CH), 114.03 (CH), 87.77 (q-C), 79.44 (q-C), 55.54 (CH_{3}), 21.72 (CH_{2}), 20.82 (CH_{2}), 13.59 (CH_{3}).

ν_{max}/cm^{-1}: 3407 b (OH), 3287 m (NH), 2963 w (Ar-H), 2932 w (CH_{2}, CH_{3}), 2840 w (CH_{2}, CH_{3}), 1597 s (C=C), 1493 s (CH), 1458 w (CH_{3}), 1331 w (SO_{2}), 1186 s (R-OH), 1091 s (SO_{2}).

\(N\)-[2-(3-Hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)phenyl]-4-nitrobenzenesulfonamide (2.7a)

Using Method A from phenylacetylene (20.9 mmol) and methyl 2-[(4-nitrophenyl)sulfonamido]benzoate (5.98 mmol) to give an orange oil. The product crystallised on trituration with hexane – EtOAc, which was then recrystallised from hexane – EtOAc to give the title compound as a fine orange powder (0.31 g, 10%) m.p. 180 °C decomp; HRMS found [M+Na]^+ = 531.0967; C_{29}H_{20}N_{2}O_{5}SNa [M+Na]^+ requires = 531.0985.

δ_{H} ([CD_{3}]_{2}CO) 10.16 (1H, s, NH), 8.12 – 8.10 (2H, m, m-Ar-H), 7.92 – 7.90 (2H, m, o-Ar-H), 7.70 (1H, dd, J = 7.6, 1.5 Hz, 2-H), 7.55 (1H, app. d, 5-H), 7.48 – 7.45 (4H, m, Ph-H), 7.39 – 7.36 (6H, m, Ph-H), 6.97 (1H, m, 4-H), 6.62 (1H, app. t, 3-H). δ_{C} 153.57 (q-C), 148.08 (q-C), 147.17 (q-C), 131.45 (CH), 131.23 (q-C), 128.41 (CH), 128.25 (CH), 127.95 (CH), 127.82 (CH), 125.39 (CH), 124.99 (CH), 124.47 (CH), 123.05 (CH), 119.99 (CH), 119.22 (CH), 114.03 (CH), 109.22 (CH), 79.44 (q-C), 55.54 (CH_{3}), 21.72 (CH_{2}), 20.82 (CH_{2}), 13.59 (CH_{3}).
126.30 (CH), 123.28 (qC), 122.94 (CH), 118.93 (CH), 117.17 (CH), 92.19 (qC), 82.23 (qC), 67.53 (qC).

ν\text{max}/\text{cm}^{-1}: 1593 \text{ m} (C=C), 1532 \text{ s} (NO_2), 1439 \text{ s} (CH_3), 1362 \text{ s} (NO_2), 1287 \text{ s} (SO_2), 1234 \text{ s} (R-OH), 1099 \text{ m} (SO_2).

**N-[2-(6-Hydroxyundeca-4,7-diyn-6-yl)phenyl]-4-nitrobenzenesulfonamide (2.7b)**

Using Method A from 1-pentyne (20.8 mmol) and methyl 2-[(4-nitrophenyl)sulfonamidobenzoate (5.95 mmol) to give an orange oil. The product crystallised on standing and the crude material was recrystallised from hexane – EtOAc to give a brick red powder. From the liquor subsequent recrystallised from EtOH\text{aq} to give the title compound as straw crystals (total = 0.29 g, 11%) m.p. 100 – 101 °C; HRMS found [M+Na]^+ = 463.1304; C_{24}H_{27}NO_3SNa [M+Na]^+ requires = 463.1298.

δH [(CD\textsubscript{3})_2CO] 9.38 (1H, s, NH), 8.43 – 8.39 (2H, m, m-Ar-H), 8.23 – 8.19 (2H, m, o-Ar-H), 7.81 (1H, dd, J = 7.9, 1.5 Hz, 2-H), 7.58 (1H, app. d, 5-H), 7.29 (1H, app. t, 4-H), 7.08 (1H, td, J = 7.9, 1.5 Hz, 3-H), 6.78 (1H, s, OH), 2.24 – 2.20 (4H, m, CH\textsubscript{2}), 1.53 (4H, sxt, J = 7.2 Hz, CH\textsubscript{2}), 0.98 (6H, t, J = 7.2 Hz, CH\textsubscript{3}). δ\textsubscript{c} 145.71 (qC), 135.44 (qC), 130.55 (qC), 129.31 (CH), 128.82 (CH), 127.81 (CH), 124.35 (CH), 123.51 (CH), 118.64 (CH), 86.19 (qC), 80.18 (qC), 64.96 (qC), 21.61 (CH\textsubscript{2}), 20.12 (CH\textsubscript{2}), 12.79 (CH\textsubscript{3}).

ν\text{max}/\text{cm}^{-1}: 2961 w (CH\textsubscript{2}, CH\textsubscript{3}), 2871 w (CH\textsubscript{2}, CH\textsubscript{3}), 1594 m (C=C), 1528 s (NO\textsubscript{2}), 1477 s (CH\textsubscript{2}), 1360 s (NO\textsubscript{2}), 1292 s (SO\textsubscript{2}), 1132 s (R-OH), 1096 m (SO\textsubscript{2}).
\[N\text{-}[2\text{-}(3\text{-Hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)}\text{phenyl}]\text{benzenesulfonamide (2.8a)}\]

Using Method A from phenylacetylene (69.0 mmol) and methyl 2-(phenylsulfonamido)benzoate (19.7 mmol) to give an orange oil. The product crystallised on standing, which was then recrystallised from hexane – EtOAc to give the title compound as a white powder (6.19 g, 65\%) m.p. 127 – 128 °C; HRMS found [M+Na]\(^+\) = 486.1134; 
C\(_{29}\)H\(_{21}\)NO\(_3\)SNa [M+Na]\(^+\) requires = 486.1134.

\[\delta\text{H (CDCl\(_3\)) 8.69 (1H, s, NH), 7.93 – 7.90 (3H, m, Ar-H), 7.58 (1H, dd, J = 8.0, 1.0 Hz, 5-H), 7.55 – 7.52 (4H, m, Ph-H), 7.43 – 7.33 (7H, m, Ar-H), 7.30 – 7.24 (4H, m, Ar-H), 7.07 (1H, td, J = 8.0, 1.0 Hz, 3-H). \delta\text{C 139.96 (qC), 135.82 (qC), 132.85 (CH), 132.02 (CH), 130.08 (CH), 129.31 (CH), 128.89 (CH), 128.42 (CH), 128.14 (qC), 127.92 (CH), 127.47 (CH), 123.37 (CH), 121.37 (qC), 119.27 (CH), 86.96 (qC), 86.94 (qC), 66.28 (qC).}\]

\[\nu_{\text{max/cm}^{-1}}: 3344 \text{ b (OH), 3224 m (NH), 2230 w (C≡C), 1583 s (C=C), 1324 s (SO}_2\text{), 1148 s (R-OH), 1107 s (SO}_2\text{).}\]

\[\text{Prop-2-yn-1-yl 2-[[(4-methylphenyl)sulfonamide]benzoate (2.14)}\]

Under and inert N\(_2\) atmosphere \(n\)-BuLi (3.5 equiv.) was added to a cold (-75 °C) solution of propargyl alcohol (0.96 mL, 11.3 mmol, 3.5 equiv.) in anhydrous THF (approx. 50 mL). A solution of 2-[[4-methylphenyl)sulfonamide]benzoyl chloride (1.00 g, 3.23 mmol, 1.0 equiv.) in anhydrous THF (approx. 20 mL) was added dropwise to the cold (0 °C) solution and the
mixture was allowed to warm to r.t. and stirred for 1 h. After this time the mixture was quenched with aqueous NH$_4$Cl and diluted with EtOAc. The organic phase was separated, dried (Na$_2$SO$_4$) and evaporated to give the title compound as a cream powder (0.75 g, 70%) m.p. 150 – 151 °C; HRMS found [M+Na]$^+$ = 352.0613; C$_{17}$H$_{15}$NO$_4$SNa [M+Na]$^+$ requires = 352.0613.

δ$_H$ (CDCl$_3$) 10.43 (1H, s, NH), 7.96 (1H, dd, $J$ = 8.0, 1.5 Hz, 2-H), 7.74 (2H, d, $J$ = 8.2 Hz, o-Ar-H), 7.69 (1H, app. d, 5-H), 7.49 – 7.45 (1H, m, 4-H), 7.22 (2H, d, $J$ = 8.2 Hz, m-Ar-H), 7.07 – 7.03 (1H, m, 3-H), 4.86 (2H, d, $J$ = 2.5 Hz, CH$_2$), 2.55 (1H, d, $J$ = 2.5 Hz, CH), 2.37 (3H, s, Ar-Me), 1.59 (1H, s, OH). δ$_C$ 167.03 (qC), 143.99 (qC), 140.75 (qC), 136.37 (qC), 134.95 (CH), 131.38 (CH), 129.68 (CH), 127.32 (CH), 122.89 (CH), 119.08 (CH), 115.16 (qC), 77.23 (qC), 75.62 (CH), 52.90 (CH$_2$), 21.56 (CH$_3$).

ν$_{max}$/cm$^{-1}$: 3273 s (C≡C-H), 3171 w (CH$_2$), 1683 s (RCO$_2$R), 1597 s (C=C), 1490 s (CH$_3$), 1326 s (SO$_2$), 1153 s (SO$_2$), 1084 s (R-OH).

6.2.3 Synthesis of Ynones

2-Amino-N-methoxy-N-methylbenzamide (2.20)

$N,O$-Dimethylhydroxylamine hydrochloride (7.29 g, 74.5 mmol, 1.5 equiv.) was dissolved in 90% EtOH$_{(aq)}$ (60 mL). Triethylamine (10.4 mL, 74.5 mmol, 1.5 equiv.) was added dropwise over 10 minutes and the solution stirred for 10 minutes at r.t., a solution of isatoic anhydride (8.13 g, 49.8 mmol, 1.0 equiv.) in 90% EtOH$_{(aq)}$ (50 mL) was added portion-wise over 20 minutes. The mixture was then refluxed for 2 h. After this time the mixture was poured onto equal volumes of ice and saturated aqueous Na$_2$CO$_3$ and the EtOH was removed under reduced pressure. The aqueous solution was diluted with EtOAc (approx. 100 mL). The organic phase was separated, washed with brine, dried (Na$_2$SO$_4$) and evaporated to give dark orange oil. The crude material was purified by flash column chromatography (10% EtOAc – hexane) to give the title compound as an orange oil (5.74 g, 64%) [14CC12293].
δ_{H} (CDCl$_3$) 7.36 (1H, app. d, Ar-$H$), 7.21 – 7.16 (1H, m, Ar-$H$), 6.71 – 6.67 (2H, m, Ar-$H$), 4.64 (2H, s, NH$_2$), 3.60 (3H, s, O-Me), 3.35 (3H, s, N-Me). δ$_c$ 170.03 (q C), 146.78 (q C), 131.43 (CH), 129.21 (CH), 117.25 (q C), 116.87 (CH), 116.68 (CH), 61.12 (CH$_3$), 34.35 (CH$_3$).

$N$-Methoxy-$N$-methyl-2-[(4-methylphenyl)sulfonamide]benzamide (2.21)

Under an inert (N$_2$) atmosphere, 2-amino-$N$-methoxy-$N$-methylbenzamide (5.74 g, 31.9 mmol, 1.0 equiv.) was dissolved in pyridine (40 mL) and to this toluene-4-sulfonyl chloride (7.59 g, 39.6 mmol, 1.3 equiv.) was added in one portion. The mixture was refluxed overnight. Then cooled and diluted with EtOAc and washed with 2M HCl. The organic phase was separated, washed with water and brine, dried (Na$_2$SO$_4$) and evaporated to give dark orange oil. The crude material was purified by flash column chromatography (10% EtOAc – hexane) to give an orange oil which crystallised on trituration with ether to afford the title compound as an off-white solid (7.50 g, 70%) m.p. 109 – 110 °C (lit m.p. not quoted [16JOC2930]).

δ$_H$ (CDCl$_3$) 8.96 (1H, s, N$_H$), 7.70 – 7.65 (3H, m, 2-$H$, o-Ar-$H$), 7.48 (1H, app. d, 5-$H$), 7.40 – 7.36 (1H, m, 4-$H$), 7.22 (2H, d, $J$ = 8.1 Hz, m-Ar-$H$), 7.10 – 7.06 (1H, m, 3-$H$), 3.19 (6H, s, O-Me, N-Me), 2.35 (3H, s, Ar-Me). δ$_c$ 167.85 (q C), 143.65 (q C), 136.87 (q C), 136.73 (q C), 131.72 (CH), 129.58 (CH), 129.21 (CH), 127.31 (CH), 123.75 (CH), 123.23 (q C), 122.87 (CH), 60.94 (CH$_3$), 33.69 (CH$_3$), 21.48 (CH$_3$).

ν$_{max}$/cm$^{-1}$: 3166 b (NH), 2937 w (CH$_3$), 1616 s (C=O), 1594 s (C=C), 1450 w (CH$_3$), 1334 s (SO$_2$), 1157 s (SO$_2$).

General Method for Synthesis of Ynones

Under and inert (N$_2$) atmosphere $n$-BuLi (2.2 equiv.) was added to a cold (-75 °C) solution of an acetylene derivative (X mmol, 2.2 equiv.) in anhydrous THF (50 – 100 mL). The solution was warmed to 0 °C and $N$-methoxy-$N$-methyl-2-[(4-methylphenyl)sulfonamide]benzamide
(Y mmol, 1.0 equiv.) in anhydrous THF (15 – 30 mL) was added dropwise to the solution. When addition was complete the mixture was allowed to warm to r.t. and stirred for 1 h. After this time the mixture was quenched with aqueous NH₄Cl and diluted with EtOAc. The organic phase was separated, dried (Na₂SO₄) and evaporated. The following were synthesised by this method.

**1-[2-(4-Toluenesulfonamido)phenyl]-3-phenylprop-2-yn-1-one (2.17A)**

![Chemical structure of 1-[2-(4-Toluenesulfonamido)phenyl]-3-phenylprop-2-yn-1-one](image)

From phenylacetylene (39.5 mmol) and N-methoxy-N-methyl-2-[(4-methylphenyl)sulfonamide]benzamide (17.9 mmol) to give an orange oil which on trituration with ether gave the title compound as a bright yellow solid (3.76 g, 56%) m.p. 138 – 140 °C (lit m.p. 149 – 152 °C [16AGE7737]).

δₕ (CDCl₃) 11.25 (1H, s, NH), 8.28 (1H, app. d, 2-H), 7.78 (2H, d, J = 8.2 Hz, o-Ar-H), 7.73 (1H, app. d, 5-H), 7.67 (2H, d, J = 8.2 Hz, m-Ar-H), 7.53 – 7.49 (2H, m, Ar-H), 7.45 – 7.42 (2H, m, Ar-H), 7.24 (2H, d, J = 8.0 Hz, Ar-H), 7.13 (1H, app. t, 3-H), 2.36 (3H, s, Ar-Me). δₛ 180.51 (C=O), 144.08 (₉C), 140.94 (₉C), 136.46 (₉C), 135.73 (CH), 134.77 (CH), 133.11 (CH), 131.22 (CH), 129.76 (CH), 128.80 (CH), 127.33 (CH), 122.62 (CH), 122.49 (₉C), 118.42 (CH), 95.27 (₉C), 86.61 (₉C), 21.56 (CH₃).

νₑₙ/cm⁻¹: 3056 w (NH), 2202 m (C≡C), 1706 s (C=O), 1591 s (C=C), 1449 s (CH₃), 1363 s (SO₂), 1167 s (SO₂).

**N-[2-(Hex-2-ynoyl)phenyl]-4-methylbenzenesulfonamide (2.17B)**

![Chemical structure of N-[2-(Hex-2-ynoyl)phenyl]-4-methylbenzenesulfonamide](image)
From 1-pentyne (15.8 mmol) and N-methoxy-N-methyl-2-[(4-methylphenyl)sulfonamide]benzamide (7.18 mmol) to give an orange oil which on trituration with ether gave the title compound as a baby pink solid (1.62 g, 66%) m.p. 93–94 °C; HRMS found [M+H]+ = 341.1072; C_{19}H_{20}NO_{3}S [M+H]+ requires = 342.1158.

δ_{H} (CDCl_{3}) 11.25 (1H, s, NH), 8.18 (1H, dd, J = 7.9, 1.5 Hz, 2-H), 7.76 (2H, d, J = 8.2 Hz, o-Ar-H), 7.68 (1H, app. d, 5-H), 7.49 – 7.45 (1H, m, 4-H), 7.23 (2H, d, J = 8.2 Hz, m-Ar-H), 7.08 (1H, app. t, 3-H), 2.48 (2H, t, J = 7.2 Hz, CH_{2}), 2.37 (3H, s, Ar-Me), 1.69 (2H, sxt, J = 7.2 Hz, CH_{2}), 1.07 (3H, t, J = 7.2 Hz, CH_{3}). δ_{c} 180.80 (C=O), 144.01 (qC), 140.85 (qC), 136.48 (qC), 135.50 (CH), 134.93 (CH), 129.72 (CH), 127.31 (CH), 122.47 (CH), 122.38 (qC), 118.21 (CH), 99.08 (qC), 79.55 (qC), 21.56 (CH_{3}), 21.26 (CH_{2}), 21.24 (CH_{2}), 13.64 (CH_{3}).

ν_{max}/cm^{-1}: 3272 w (NH), 2980 w (CH_{2}, CH_{3}), 2214 m (C≡C), 1604 s (C=C), 1175 s (SO_{2}).

**N-2-[3-(4-Methoxyphenyl)propioloyl]phenyl]-4-methylbenzenesulfonamide (2.17C)**

![Structure of N-2-[3-(4-Methoxyphenyl)propioloyl]phenyl]-4-methylbenzenesulfonamide](image)

From 1-ethynyl-4-methoxybenzene (39.5 mmol) and N-methoxy-N-methyl-2-[(4-methylphenyl)sulfonamide]benzamide (17.9 mmol) to give an orange oil which on trituration with ether gave the title compound as a bright yellow solid (4.83 g, 66%) m.p. 163 – 165 °C (lit m.p. 134 – 136 °C [16AGE7737]).

δ_{H} (CDCl_{3}) 11.31 (1H, s, NH), 8.26 (1H, dd, J = 8.0, 1.5 Hz, 2-H), 7.77 (2H, d, J = 8.1 Hz, o-Ar-H), 7.71 (1H, app. d, 5-H), 7.64 – 7.60 (2H, m, o-Ar-H), 7.52 – 7.47 (1H, m, 4-H), 7.23 (2H, d, J = 8.1 Hz, m-Ar-H), 7.15 – 7.11 (1H, m, 3-H), 6.96 – 6.92 (2H, m, m-Ar-H), 3.87 (3H, s, O-Me), 2.35 (3H, s, Ar-Me). δ_{c} 180.52 (C=O), 162.10 (qC), 144.03 (qC), 140.82 (qC), 136.46 (qC), 135.47 (CH), 135.27 (qC), 135.28 (CH), 134.64 (CH), 129.74 (CH), 127.31 (CH), 122.62 (qC), 122.60 (CH), 118.47 (CH), 114.55 (CH), 111.33 (qC), 96.70 (qC), 86.78 (qC), 55.52 (CH_{3}), 21.56 (CH_{3}).

ν_{max}/cm^{-1}: 3033 w (NH), 2184 m (C≡C), 1602 s (C=C), 1328 w (SO_{2}), 1126 s (SO_{2}).
6.2.4 Synthesis of Unsymmetrical $N$-[2-{3-Hydroxy-penta-1,4-diyn-3-yl}phenyl]benzenesulfonamides

**General Method for the Synthesis of Unsymmetrical $N$-[2-{3-Hydroxy-penta-1,4-diyn-3-yl}phenyl]benzenesulfonamides**

Method A: Under an inert (N$_2$) atmosphere $n$-BuLi (2.1 equiv.) was added to a cold (-75 °C) solution of the appropriate alkyne (X mmol, 2.1 equiv.) in anhydrous THF (50 – 100 mL). The solution was warmed to 0 °C and 1-[2-{4-toluenesulfonamido}phenyl]-3-phenylprop-2-yn-1-one derivative (Y mmol, 1 equiv.) in anhydrous THF (30 – 60 mL) was added dropwise to the solution. When the addition was complete the mixture was allowed to warm to r.t., then stirred for 1 h. After this time the mixture was quenched with aqueous NH$_4$Cl and diluted with EtOAc. The organic phase was separated, dried (Na$_2$SO$_4$) and evaporated to give crude material which was purified by recrystallisation or washing with cold hexane. The following were synthesised by this method.

Method B: Under an inert (N$_2$) atmosphere ethynylmagnesium bromide (2.1 equiv., 0.5M in THF) was added to a warm (40 °C) solution of 1-[2-{4-toluenesulfonamido}phenyl]-3-phenylprop-2-yn-1-one derivative (X mmol, 1 equiv.) in anhydrous THF (30 mL). The solution was refluxed until the reaction was complete by TLC. After this time the mixture was allowed to cool and was quenched with aqueous NH$_4$Cl and diluted with EtOAc. The organic phase was separated, dried (Na$_2$SO$_4$) and evaporated to give crude material which was purified by flash column chromatography (10% EtOAc – pet ether, unless otherwise stated). The following were synthesised by this method.

Method C: Under an inert (N$_2$) atmosphere 1-bromo-1-propene (X mmol, 2.5 equiv.) was added to a cold (-75 °C) solution of LDA 2.5 equiv. (DIPA, 1.1 equiv. and $n$-BuLi, 2.5 equiv.) in anhydrous THF (approx. 50 mL) and was stirred for 3 h. The solution was warmed to 0 °C and 1-[2-{4-toluenesulfonamido}phenyl]-3-phenylprop-2-yn-1-one derivative (Y mmol, 1 equiv.) in anhydrous THF (30 mL) was added dropwise to the solution. When the addition was complete the mixture was allowed to warm to r.t. and then stirred for 1 h. After this time the mixture was quenched with aqueous NH$_4$Cl and diluted with EtOAc. The organic phase was separated, dried (Na$_2$SO$_4$) and evaporated to give crude material which was
purified by recrystallisation or washing with cold hexane. The following were synthesised by this method.

**N-[2-(3-Hydroxy-1-phenylocta-1,4-diyn-3-yl)phenyl]-4-methylbenzenesulfonamide (2.19Ab)**

Using Method A from 1-pentyne (8.40 mmol) and 1-[2-(4-toluenesulfonamido)phenyl]-3-phenylprop-2-yn-1-one (4.00 mmol) to give the title compound as an orange solid (1.52 g, 86%) m.p. 127 – 129 °C; HRMS found [M+Na]+ = 466.1452; C₂₇H₂₅NO₃SNa [M+Na]+ requires = 466.1447.

δ<sub>H</sub> (CDCl<sub>3</sub>) 8.59 (1H, s, NH), 7.84 (1H, dd, J = 7.9, 1.5 Hz, 2-H), 7.79 (2H, d, J = 8.2 Hz, o-Ar-H), 7.55 (1H, dd, J = 7.9, 1.5 Hz, 5-H), 7.50 – 7.47 (2H, m, Ph-H), 7.37 – 7.31 (3H, m, Ph-H), 7.26 – 7.22* (1H, m, 4-H), 7.10 (1H, d, J = 7.9 Hz, m-Ar-H), 7.03 (1H, td, J = 7.9, 1.5 Hz, 3-H), 3.13 (1H, s, OH), 2.32 – 2.28 (5H, m, Ar-Me, CH₂), 1.62 (2H, sxt, J = 7.3 Hz, CH₂), 1.03 (3H, t, J = 7.3 Hz, CH₃). δ<sub>c</sub> 143.61 (qC), 137.00 (qC), 135.84 (qC), 131.96 (CH), 129.83 (CH), 129.52 (CH), 129.11 (CH), 128.53 (qC), 128.35 (CH), 127.78 (CH), 127.50 (CH), 123.14 (CH), 121.59 (qC), 119.17 (CH), 88.74 (qC), 87.64 (qC), 85.91 (qC), 78.91 (qC), 65.80 (qC), 21.70 (CH₂), 21.53 (CH₃), 20.88 (CH₂), 13.63 (CH₃).

ν<sub>max</sub>/cm<sup>-1</sup>: 3348 b (OH), 3254 m (NH), 2968 w (Ar-H), 2931 w (CH₂, CH₃), 2871 w (CH₂, CH₃), 2359 w (C≡C), 1597 s (C=C), 1490 s (CH₂), 1324 s (SO₂), 1150 s (SO₂), 1087 s (R-OH).

*Overlapping with CDCl₃ signal
**N-{2-[3-Hydroxy-1-(4-methoxyphenyl)-5-phenylpenta-1,4-diyn-3-yl]phenyl}-4-methylbenzenesulfonamide (2.19Ac)**

Using Method A from 1-ethynyl-4-methoxybenzene (8.40 mmol) and 1-[2-(4-toluenesulfonamido)phenyl]-3-phenylprop-2-yn-1-one (4.00 mmol) to give the title compound as an off white powder (1.75 g, 86%) m.p. 139 – 140 °C decomp; HRMS found [M+Na]^+ = 530.1395; C_{31}H_{25}NO_{4}SNa [M+Na]^+ requires = 530.1397.

δ_H (CDCl₃) 8.65 (1H, s, NH), 7.90 (1H, dd, J = 7.8, 1.4 Hz, 2-H), 7.79 (2H, d, J = 8.3 Hz, o-Ar-H), 7.58 (1H, app. d, 5-H), 7.54 – 7.51 (2H, m, Ph-H), 7.49 – 7.45 (2H, m, o-Ar-H), 7.41 – 7.34 (3H, m, Ph-H), 7.29 – 7.25* (1H, m, 4-H), 7.08 – 7.04 (3H, m, m-Ar-H, 3-H), 6.89 – 6.86 (2H, m, m-Ar-H), 3.83 (3H, s, O-Me), 3.20 (1H, s, OH), 2.29 (3H, s, Ar-Me). δ_c 160.33 (q_C), 143.60 (q_C), 136.91 (q_C), 135.91 (q_C), 133.58 (CH), 132.00 (CH), 129.97 (CH), 129.52 (CH), 129.22 (CH), 128.40 (CH), 128.22 (q_C), 127.86 (CH), 127.53 (CH), 123.20 (CH), 121.50 (q_C), 119.17 (CH), 114.03 (CH), 113.40 (q_C), 87.19 (q_C), 86.65 (q_C), 85.74 (q_C), 78.91 (q_C), 66.23 (q_C), 55.37 (CH₃), 21.53 (CH₃).

ν_max/cm⁻¹: 3402 b (OH), 3274 s (NH), 2224 s (C≡C), 1604 s (C=C), 1324 s (SO₂), 1153 s (SO₂), 1089 s (R-OH).

*Overlapping with CDCl₃ signal*
Using Method A from methyl propargylic ether (2.79 mmol) and 1-[2-[(4-toluenesulfonylamido)phenyl]-3-phenylprop-2-yn-1-one (1.33 mmol) to give the title compound as a golden powder (0.45 g, 73%) m.p. 141 °C decomp; HRMS found [M+Na]^+ = 468.1238; C_{26}H_{23}NO_4SNa [M+Na]^+ requires = 468.1240.

δ_H ([CD_3]_2CO) 9.19 (1H, s, NH), 7.87 – 7.83 (3H, m, 2-H, α-Ar-H), 7.56 (1H, app. d, 5-H), 7.50 – 7.48 (2H, m, Ph-H), 7.45 – 7.42 (3H, m, Ph-H), 7.31 – 7.24 (3H, m, 4-H, m-Ar-H), 7.06 (1H, app. t, 3-H), 4.21 (2H, AB, J = 16.1 Hz, CH_2CH_3), 3.35 (3H, s, O-Me), 2.22 (3H, s, Ar-Me). δ_C 143.86 (α-C), 137.36 (α-C), 136.43 (α-C), 131.64 (CH), 129.60 (CH), 129.56 (CH), 129.23 (CH), 128.64 (CH), 128.47 (α-C), 127.66 (CH), 127.43 (CH), 122.77 (CH), 121.72 (α-C), 118.05 (CH), 88.04 (α-C), 85.19 (α-C), 84.85 (α-C), 82.54 (α-C), 65.39 (α-C), 59.20 (CH_2), 56.89 (CH_3), 20.49 (CH_3).

ν_{max}/cm^{-1}: 3255 b (OH), 2361 m (C≡C), 2342 m (C≡C), 1597 s (C=C), 1490 s (CH_2), 1335 s (SO_2), 1183 s (SO_2), 1088 s (R-OH).

N-[2-(3-Hydroxy-1-phenylhexa-1,4-diyn-3-yl)phenyl]-4-methylbenzenesulfonamide (2.19Ag)
Using Method C from 1-bromo-1-propene (12.3 mmol) and 1-[2-(4-toluenesulfonamido)phenyl]-3-phenylprop-2-yn-1-one (5.86 mmol) to give an orange oil which on trituration with hexane – EtOAc gave the title compound as an a pale pink solid (0.31 g, 28%) m.p. 127 °C decomp; HRMS found [M+Na]⁺ = 438.1128; C_{25}H_{21}NO_{3}SNa [M+Na]⁺ requires = 438.1134.

δH [(CD)₂CO] 9.24 (1H, s, NH), 7.85 – 7.81 (3H, m, 2-H, o-Ar-H), 7.77 (1H, dd, J = 8.2, 1.1 Hz, 5-H), 7.49 – 7.46 (2H, m, Ph-H), 7.44 – 7.40 (3H, m, Ph-H), 7.29 – 7.23 (3H, m, m-Ar-H, 4-H), 7.03 (1H, td, J = 8.2, 1.1 Hz, 3-H), 2.32 (3H, s, Ar-Me), 1.92 (3H, s, Me). δC 143.82 (qC), 137.45 (qC), 136.35 (qC), 131.60 (CH), 129.57 (CH), 129.33 (CH), 129.09 (CH), 128.62 (CH), 127.69 (CH), 127.42 (CH), 122.69 (CH), 121.91 (qC), 117.90 (CH), 88.67 (qC), 84.55 (qC), 82.83 (qC), 78.42 (qC), 65.40 (qC), 20.49 (CH₃), 2.64 (CH₃).

νmax/cm⁻¹: 3392 b (OH), 3255 m (NH), 2980 w (CH₃), 2336 w (C≡C), 1597 s (C=C), 1489 s (CH₃), 1330 s (SO₂), 1153 s (SO₂).

**N-[2-(3-Hydroxy-6,6-dimethyl-1-phenylhepta-1,4-diyn-3-yl)phenyl]-4-methylbenzenesulfonamide (2.19Aj)**

Using Method A from 3,3-dimethyl-1-butylene (2.79 mmol) and 1-[2-{4-toluenesulfonamido)phenyl]-3-phenylprop-2-yn-1-one (1.33 mmol) to give the title compound as a yellow oil (0.54 g, 88%); HRMS found [M+K]⁺ = 496.1339; C_{28}H_{27}NO_{3}SK [M+K]⁺ requires = 496.1343.

δH (CDCl₃) 8.60 (1H, s, NH), 7.84 – 7.79 (3H, m, 2-H, o-Ar-H), 7.53 – 7.47 (3H, m, 5-H, Ph-H), 7.39 – 7.31 (3H, m, Ph-H), 7.26 – 7.22* (1H, m, 4-H), 7.10 (2H, d, J = 7.9 Hz, m-Ar-H), 7.01 (1H, td, J = 7.8, 1.2 Hz, 3-H), 3.09 (1H, s, OH), 2.31 (3H, s, Ar-Me), 1.32 (9H, s, Me₃). δC 143.60 (qC), 137.05 (qC), 135.85 (qC), 131.95 (CH), 129.80 (CH), 129.55 (CH), 129.06 (CH), 128.62
(qC), 128.35 (CH), 127.72 (CH), 127.49 (CH), 123.11 (qC), 119.15 (CH), 96.65 (qC), 87.75 (qC), 85.71 (qC), 65.60 (qC), 30.54 (CH$_3$), 27.71 (qC), 21.53 (CH$_3$).

$\nu_{\text{max}}$/cm$^{-1}$: 3392 b (OH), 3269 m (NH), 2968 w (CH$_3$), 2235 w (C≡C), 2205 w (C≡C), 1598 s (C=C), 1492 s (CH$_3$), 1332 s (SO$_2$), 1153 s (SO$_2$), 1092 s (R-OH).

*Overlapping with CDCl$_3$ signal

$N$-[2-(3-Hydroxy-6-methyl-1-phenylhepta-6,1,4-diyn-3-yl)phenyl]-4-methylbenzenesulfonamide (2.19Ak)

Using Method A from 2-methyl-1-buten-3-yne (12.3 mmol) and 1-[2-(4-toluenesulfonylamido)phenyl]-3-phenylprop-2-yn-1-one (5.85 mmol) to give the title compound as a straw solid (0.90 g, 76%) m.p. 120 – 123 °C; HRMS found [M+K]$^+ = 480.1038$; C$_{27}$H$_{23}$NO$_3$S$^+ [M+K]$^+$ requires = 480.1030.

$\delta$ ([(CD)$_3$]CO) 7.85 – 7.83 (3H, m, o-Ar-H, 2-H), 7.54 (1H, app. d, 5-H), 7.51 – 7.48 (2H, m, Ph-H), 7.45 – 7.40 (3H, m, Ph-H), 7.27 (1H, app. t, 4-H), 7.22 (2H, d, $J = 8.1$ Hz, m-Ar-H), 7.04 (1H, app. t, 3-H), 5.41 – 5.39 (2H, m, CH$_2$), 2.87 (1H, s, OH) 3.31 (3H, s, Ar-Me), 1.92 (3H, s, CH$_3$).

$\delta$$_c$ 143.76 (qC), 137.52 (qC), 136.66 (qC), 131.65 (CH), 129.59 (CH), 129.49 (CH), 129.19 (CH), 128.63 (CH), 127.60 (CH), 127.38 (CH), 125.92 (qC), 123.18 (CH$_2$), 122.68 (CH), 121.80 (qC), 118.04 (CH), 88.17 (qC), 87.09 (qC), 86.65 (qC), 85.14 (qC), 65.67 (qC), 22.48 (qC), 22.27 (CH$_3$), 20.51 (CH$_3$).

$\nu_{\text{max}}$/cm$^{-1}$: 3655 m (OH), 3388 m (NH), 3256 w (Ar-H), 2980 s (C=C-H), 2889 s (CH$_3$), 2202 w (C≡C), 1594 s (C=C), 1491 s (CH$_3$), 1327 s (SO$_2$), 1153 s (SO$_2$), 1090 s (R-OH), 997 s (C=CH$_2$), 940 s (C=CH$_2$).
**N-[2-(3-Hydroxy-1-phenylpenta-1,4-diyn-3-yl)phenyl]-4-methylbenzenesulfonamide (2.19Ai)**

Using Method B ethynylmagnesium bromide (5.61 mmol) and N-[2-(hex-2-ynoyl)phenyl]-4-methylbenzenesulfonamide (2.67 mmol) to give the title compound as an orange oil (0.69 g, 65%); HRMS found [M+Na]⁺ = 424.0990; \( \text{C}_{26}\text{H}_{19}\text{NO}_3\text{SNa} \) [M+Na]⁺ requires = 424.0978.

\[ \delta_{\text{H}} (\text{CDCl}_3) 8.78 (1\text{H}, \text{s}, \text{N}-\text{H}), 7.85 (1\text{H}, \text{dd}, J = 1.4, 7.9 \text{ Hz}, 2-\text{H}), 7.80 (2\text{H}, \text{d}, J = 8.0 \text{ Hz}, \text{o}-\text{Ar-H}), 7.61 (1\text{H}, \text{dd}, J = 1.4, 7.9 \text{ Hz}, 5-\text{H}), 7.48 - 7.45 (2\text{H}, \text{m}, \text{Ph-H}), 7.35 - 7.26^* (4\text{H}, \text{m}, \text{Ph-H}, 4-\text{H}), 7.09 - 7.02 (3\text{H}, \text{m}, \text{m}-\text{Ar-H}, 3-\text{H}), 4.48 (1\text{H}, \text{s}, \text{OH}), 2.78 (1\text{H}, \text{s}, \text{CH}), 2.27 (3\text{H}, \text{s}, \text{Ar-Me}). \delta_{\text{C}} 143.80 (\text{qC}), 136.85 (\text{qC}), 135.87 (\text{qC}), 131.99 (\text{CH}), 130.05 (\text{CH}), 129.57 (\text{CH}), 129.26 (\text{CH}), 128.39 (\text{CH}), 128.02 (\text{qC}), 127.89 (\text{CH}), 127.53 (\text{CH}), 123.40 (\text{CH}), 121.36 (\text{qC}), 119.42 (\text{CH}), 86.87 (\text{qC}), 86.65 (\text{qC}), 82.03 (\text{qC}), 75.25 (\text{CH}), 65.55 (\text{qC}), 21.52 (\text{CH}_3). \]

\[ \nu_{\text{max}}/\text{cm}^{-1}: 3279 \text{ b (OH)}, 2227 \text{ w (C≡C)}, 1598 \text{ s (C=C)}, 1490 \text{ s (CH}_3), 1328 \text{ s (SO}_2), 1153 \text{ s (SO}_2), 1089 \text{ s (R-OH)}, 753 \text{ s (Ph-H)}, 689 \text{ s (Ph-H)}. \]

*Overlapping with CDCl₃ signal

**N-[2-(3-Hydroxyocta-1,4-diyn-3-yl)phenyl]-4-methylbenzenesulfonamide (2.19Bi)**

Using Method B ethynylmagnesium bromide (6.15 mmol) and N-[2-(hex-2-ynoyl)phenyl]-4-methylbenzenesulfonamide (2.93 mmol) to give a brown oil. The crude material was
purified by flash column chromatography to give the title compound as yellow oil (0.57 g, 64%); HRMS found [M+Na]⁺ = 390.1133; C₂₄H₁₉NO₃SNa [M+Na]⁺ requires = 390.1134.

δ_H (CDCl₃) 8.64 (1H, s, NH), 7.80 – 7.76 (3H, m, o-Ar-H, 2-H), 7.56 (1H, dd, J = 7.7, 1.1 Hz, 5-H), 7.25 – 7.18 (3H, m, 4-H, m-Ar-H), 7.00 (1H, td, J = 7.7, 1.1 Hz, 3-H), 3.92 (1H, s, OH), 2.66 (1H, s, CH), 2.32 (3H, s, Ar-Me), 2.23 (2H, t, J = 7.2 Hz, CH₂), 1.56 (2H, sxt, J = 7.2 Hz, CH₂), 0.97 (3H, t, J = 7.2 Hz, CH₃). δ_c 143.78 (qC), 137.00 (qC), 135.75 (qC), 129.86 (CH), 129.57 (CH), 128.45 (qC), 127.78 (CH), 127.51 (CH), 123.32 (CH), 119.43 (CH), 88.68 (qC), 82.56 (qC), 78.60 (qC), 74.29 (CH), 65.11 (qC), 21.64 (CH₂), 21.53 (CH₃), 20.77 (CH₂), 13.60 (CH₃).

ν_max/cm⁻¹: 3278 b (OH), 2970 s (CH₂, CH₃), 2236 s (C≡C), 1599 s (C=C), 1493 s (CH₂), 1331 s (SO₂), 1155 s (SO₂), 1090 s (R-OH).

_N-[2-[3-Hydroxy-1-[4-methoxyphenyl]octa-1,4-diyn-3-yl]phenyl]-4-methylbenzenesulphonamide (2.19Cb)_

Using Method A from 1-pentyne (5.19 mmol) and 1-[2-[4-toluenesulphonamido]phenyl]-3-phenylprop-2-yn-1-one (2.47 mmol) to give the title compound as an white solid (0.87 g, 74%) m.p. 122 – 123 °C; HRMS found [M+K]⁺ = 512.1310; C₂₈H₂₇NO₄SK [M+K]⁺ requires = 512.1292.

δ_H (CDCl₃) 8.57 (1H, s, NH), 7.85 – 7.89 (3H, m, 2-H, Ar-H), 7.53 (1H, dd, J = 8.2, 1.0 Hz, 5-H), 7.45 – 7.41 (2H, m, Ar-H), 7.24* (1H, td, J = 8.2, 1.0 Hz, 4-H), 7.13 (2H, d, J = 8.1 Hz, Ar-H), 7.03 (1H, td, J = 8.2, 1.0 Hz, 3-H), 6.88 – 6.84 (2H, m, Ar-H), 3.83 (3H, s, O-Me), 2.98 (1H, s, OH), 2.33 – 2.29 (5H, m, Ar-Me, CH₂), 1.62 (2H, sxt, J = 7.3 Hz, CH₂), 1.03 (3H, t, J = 7.3 Hz, CH₃). δ_c 160.21 (qC), 143.59 (qC), 137.04 (qC), 135.81 (qC), 133.52 (CH), 129.76 (CH), 129.53 (CH), 128.68 (qC), 127.75 (CH), 127.52 (CH), 123.12 (CH), 119.15 (CH), 113.98 (CH), 113.57
(qC), 88.56 (qC), 86.36 (qC), 86.15 (qC), 79.04 (qC), 65.81 (qC), 55.35 (CH3), 21.71 (CH2), 21.55 (CH3), 20.88 (CH2), 13.63 (CH3).

νmax/cm⁻¹: 3386 b (OH), 3230 m (NH), 2960 w (Ar-H), 2935 w (CH2, CH3), 2872 w (CH2, CH3), 2229 w (C≡C), 1605 s (C=C), 1440 s (CH2), 1325 s (SO2), 1153 s (SO2), 1089 s (R-OH).

*Overlapping with CDCl3 signal

N-[2-[3-Hydroxy-6-methoxy-1-(4-methoxyphenyl)hexa-1,4-diyn-3-yl]phenyl]-4-methylbenzenesulphonamide (2.19Cf)

Using Method A from methyl propargylic ether (2.79 mmol) and 1-[2-(4-toluenesulphonamido)phenyl]-3-phenylprop-2-yn-1-one (1.33 mmol) to give the title compound as a golden powder (0.45 g, 73%) m.p. 141 °C decomp; HRMS found [M+Na]+ = 468.1238; C26H23NO4SNa [M+Na]+ requires = 468.1240.

δH [(CD3)2CO] 9.19 (1H, s, NH), 7.87 – 7.83 (3H, m, 2-H, o-Ar-H), 7.56 (1H, app. d, 5-H), 7.50 – 7.48 (2H, m, Ph-H), 7.45 – 7.42 (3H, m, Ph-H), 7.31 – 7.24 (3H, m, 4-H, m-Ar-H), 7.06 (1H, app. t, 3-H), 4.23 (2H, ABq, J = 15.8 Hz, CH2H2O), 3.35 (3H, s, O-Me), 2.22 (3H, s, O-Me). δc 143.86 (qC), 137.36 (qC), 136.43 (qC), 131.64 (CH), 129.60 (CH), 129.56 (CH), 129.23 (CH), 128.64 (CH), 128.47 (qC), 127.66 (CH), 127.43 (CH), 122.77 (CH), 121.72 (qC), 118.05 (CH), 88.04 (qC), 85.19 (qC), 84.85 (qC), 82.54 (qC), 65.39 (qC), 59.20 (CH2), 56.89 (CH3), 20.49 (CH3).

νmax/cm⁻¹: 3255 b (OH), 2980 m (CH2, CH3), 2233 m (C≡C), 1606 s (C≡C), 1340 s (SO2), 1184 s (SO2), 1091 s (R-OH).
Using Method B ethynylmagnesium bromide (5.19 mmol) and \(N\)-{2-[3-\{4-methoxyphenyl\}propioloyl]phenyl}-4-methylbenzenesulfonamide (2.47 mmol) to give a brown oil. The crude material was purified by flash column chromatography (15% acetone – pet ether) and recrystallisation from hexane – EtOAc to give the title compound as white needles (0.68 g, 64%) m.p. 108 – 110 °C; HRMS found [M+Na]+ = 454.1083; \(\text{C}_{25}\text{H}_{21}\text{NO}_4\text{SNa}\) [M+Na]+ requires = 454.1083.

\[\delta^H (\text{CDCl}_3)\]

8.58 (1H, s, NH), 7.83 (1H, dd, \(J = 7.9, 1.5\) Hz, 2-H), 7.79 (2H, d, \(J = 8.3\) Hz, o-Ar-H), 7.60 (1H, dd, \(J = 7.9, 1.5\) Hz, 5-H), 7.42 (2H, d, \(J = 8.3\) Hz, o-Ar-H), 7.30 – 7.24* (1H, m, 4-H), 7.14 (2H, d, \(J = 8.3\) Hz, m-Ar-H), 7.04 (1H, td, \(J = 7.9, 1.5\) Hz, 3-H), 6.85 (2H, d, \(J = 8.3\) Hz, m-Ar-H), 3.81 (3H, s, Ar-Me), 3.53 (1H, s, OH), 2.76 (1H, s, CH), 2.32 (3H, s, O-Me). \(\delta^c\) 160.35 (\(\text{q}\)C), 143.71 (\(\text{q}\)C), 136.99 (\(\text{q}\)C), 135.83 (\(\text{q}\)C), 133.57 (CH), 130.08 (CH), 129.54 (CH), 127.95 (\(\text{q}\)C), 127.82 (CH), 127.53 (CH), 123.37 (CH), 119.56 (CH), 114.04 (CH), 113.19 (\(\text{q}\)C), 87.14 (\(\text{q}\)C), 85.38 (\(\text{q}\)C), 82.05 (\(\text{q}\)C), 75.08 (CH), 65.62 (\(\text{q}\)C), 55.37 (CH\(_3\)), 21.54 (CH\(_3\)).

\(\nu_{\max}/\text{cm}^{-1}\): 3295 b (OH), 3287 s (C=\(\equiv\)C-H), 2226 s (C=\(\equiv\)C), 1604 s (C=C), 1322 s (SO\(_2\)), 1153 s (SO\(_2\)), 1087 (R-OH).

*Overlapping with CDCl\(_3\) signal

**6.2.5 Synthesis of N-Substituted Saccharins**

**2-Methylbenzo[\(d\)]isothiazol-3(2\(H\))-one 1,1-dioxide (2.25A)**
Sodium saccharin (4.00 g, 19.5 mmol, 1.0 equiv.) was dissolved in DMF (100 mL). Iodomethane (4.50 mL, 68.3 mmol, 3.5 equiv.) was added dropwise and the solution was stirred at 100 °C overnight. After this time the mixture was quenched with water and filtered [17CC901] to give the title compound as a white solid (2.73 g, 63%) m.p. 134 – 135 °C (literature m.p. 130 – 131 °C [51JOC1582]).

δ_H (CDCl_3) 8.09 – 8.07 (1H, m, 4-H), 7.96 – 7.94 (1H, m, 7-H), 7.90 – 7.82 (2H, m, 5-H, 6-H), 3.28 (3H, s, Me). δ_C 158.74 (C=O), 137.63 (qC), 134.69 (CH), 134.36 (CH), 127.62 (qC), 125.16 (CH), 121.02 (CH), 23.27 (CH_3).

ν_max/cm⁻¹: 3095 w (Ar-H), 2980 w (CH_3), 1735 s (C=O), 1594 s (C=C), 1468 s (CH_3), 1311 s (SO_2), 1055 s (SO_2).

**General Method for the Synthesis of N-Aryl Substituted Saccharins**

Saccharin (X mmol, 1.0 equiv.) and an appropriate boronic acid (Y mmol, 2.0 equiv.) was suspended in DCM (10 – 15 mL/g). To this pyridine (Y mmol, 2.0 equiv.) and then Cu(OAc)_2 (Y mmol, 2.0 equiv.) were added, the reaction mixture was stirred at r.t. for 48 h. After this time the mixture was quenched with water and diluted with DCM (approx. 100 mL). The mixture was acidified with HCl and filtered. The organic phase was separated, dried (Na_2SO_4) and evaporated to give the title compound. The following were synthesised by this method [98TL2933].

**2-(p-Tolyl)benzo[d]isothiazol-3(2H)-one,1,1-dioxide (2.25B)**

From p-tolyloboronic acid (0.22 mol) to give the title compound as a white solid (28.4 g, 95%) m.p. 200 °C (literature m.p. 210 – 212 °C [15CEJ5332]).

δ_H (CDCl_3) 8.16 (1H, app. d, 4-H), 8.00 (1H, app. d, 7-H), 7.90 – 7.82 (2H, m, 5-H, 6-H), 7.41 (2H, d, J = 8.3 Hz, o-Ar-H), 7.36 (2H, d, J = 8.3 Hz, m-Ar-H), 3.28 (3H, s, Ar-Me). δ_C 158.52 (C=O), 140.53 (qC), 137.67 (qC), 135.01 (CH), 134.41 (CH), 130.63 (CH), 128.64 (CH), 127.31 (qC), 125.78 (qC), 125.62 (CH), 121.26 (CH), 21.36 (CH_3).
\( \nu_{\text{max}}/\text{cm}^{-1} \): 1730 s (C=O), 1613 w (C=C), 1402 s (CH\textsubscript{3}), 1310 s (SO\textsubscript{2}), 1159 s (SO\textsubscript{2}).

2-(m-Tolyl)benzo[d]isothiazol-3(2\textit{H})-one 1,1-dioxide (2.25C)

\begin{center}
\includegraphics[width=0.2\textwidth]{225C.png}
\end{center}

From \textit{m}-tolylboronic acid (65.5 mmol) to give the title compound as a beige solid which was recrystallised from EtOH – EtOAc to give a white powder (4.35 g, 59%) m.p. 149 – 150 °C (literature m.p. not quoted [14CEJ14321]).

\( \delta_{\text{H}} (\text{CDCl}_3) \) 8.16 (1H, app. d, 4-H), 8.00 (1H, app. d, 7-H), 7.95 – 7.86 (2H, m, 5-H, 6-H), 7.46 – 7.42 (1H, m, Ar-H), 7.34 – 7.33 (3H, m, Ar-H), 2.43 (3H, s, Ar-Me). \( \delta_{\text{c}} \) 158.46 (C=O), 140.14 (q-C), 137.66 (q-C), 135.05 (CH), 134.44 (CH), 131.04 (CH), 129.71 (CH), 129.29 (CH), 128.47 (q-C), 127.26 (q-C), 125.79 (CH), 125.63 (CH), 121.26 (CH), 21.35 (CH\textsubscript{3}).

\( \nu_{\text{max}}/\text{cm}^{-1} \): 1721 s (C=O), 1602 s (C=C), 1455 w (CH\textsubscript{3}), 1333 s (SO\textsubscript{2}), 1179 s (SO\textsubscript{2}).

2-(2-Methoxyphenyl)benzo[d]isothiazol-3(2\textit{H})-one 1,1-dioxide (2.25D)

\begin{center}
\includegraphics[width=0.2\textwidth]{225D.png}
\end{center}

From 2-methoxyphenylboronic acid (0.11 mol) to give the title compound as a beige solid (7.56 g, 48%) m.p. 184 – 185 °C (literature m.p. not quoted [17SYN2000]).

\( \delta_{\text{H}} (\text{CDCl}_3) \) 8.17 – 8.14 (1H, m, 4-H), 8.04 – 7.99 (1H, m, 7-H), 7.94 – 7.87 (2H, m, 5-H, Ar-H), 7.55 – 7.48 (2H, m, 6-H, Ar-H), 7.13 – 7.08 (2H, m, Ar-H), 3.84 (3H, s, O-Me). \( \delta_{\text{c}} \) 158.52 (C=O), 140.53 (q-C), 137.67 (q-C), 135.01 (CH), 134.41 (CH), 130.63 (CH), 128.64 (CH), 127.31 (q-C), 125.78 (q-C), 125.62 (CH), 121.26 (CH), 21.36 (CH\textsubscript{3}).

\( \nu_{\text{max}}/\text{cm}^{-1} \): 3094 w (Ar-H), 2945 w (CH\textsubscript{3}), 1734 s (C=O), 1593 m (C=C), 1499 s (CH\textsubscript{3}), 1323 s (SO\textsubscript{2}), 1182 s (SO\textsubscript{2}).
2-(3-Methoxyphenyl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (2.25E)

From 3-methoxyphenylboronic acid (32.8 mmol) to give the title compound as a golden powder (3.90 g, 82%) m.p. 170 – 172 °C (literature m.p. 207 – 209 °C [15CEJ5332]).

δH (CDCl3) 8.16 (1H, app. d, 4-H), 8.00 (1H, app. d, 7-H), 7.95 – 7.87 (2H, m, 5-H, 6-H), 7.47 – 7.43 (1H, m, Ar-H) 7.13 (1H, app. d, Ar-H), 7.07 – 7.06 (2H, m, Ar-H), 3.35 (3H, s, O-Me). δc

160.61 (C=O), 158.34 (qC), 137.32 (qC), 135.10 (CH), 134.47 (CH), 130.55 (CH), 129.61 (qC), 127.18 (qC), 125.67 (CH), 121.25 (CH), 120.74 (CH), 116.31 (CH), 113.96 (CH), 55.34 (CH3).

νmax/cm⁻¹: 1721 s (C=O), 1602 m (C=C), 1509 s (CH3), 1333 s (SO2), 1179 s (SO2).

2-(Thiophen-3-yl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (2.25G)

From 3-thienylboronic acid (10.9 mmol) to give the title compound as a red solid (0.94 g, 65%) m.p. 170 – 172 °C (literature m.p. 173 – 175 °C [15CEJ5332]).

δH (CDCl3) 8.16 (1H, app. d, 4-H), 8.01 (1H, app. d, 7-H), 7.96 – 7.86 (2H, m, 5-H, 6-H), 7.72 (1H, m, Ar-H), 7.50 (1H, dd, J = 3.2, 5.2 Hz, Ar-H), 7.35 (1H, dd, J = 1.2, 5.2 Hz, Ar-H). δc

157.80 (C=O), 137.32 (qC), 135.15 (qC), 134.61 (CH), 127.06 (qC), 126.44 (CH), 125.62 (CH), 124.73 (CH), 122.27 (CH), 121.31 (CH).

νmax/cm⁻¹: 3093 w (Ar-H), 1716 s (C=O), 1593 m (C=C), 1332 s (SO2), 1175 s (SO2).

2-(Naphthalen-2-yl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (2.25H)
From 2-naphthylene boronic acid (65.5 mmol) to give the title compound as a beige solid which was recrystallised from EtOH – EtOAc to give a beige powder (8.77 g, 87%) m.p. 184 – 185 °C (literature m.p. 219 – 221 °C [15CEJ5332]).

$\delta_H$ (CDCl$_3$) 8.18 (1H, app. d, 4-H), 8.09 (1H, app. s, Ar-H), 8.01 (2H, d, $J = 8.3$ Hz, Ar-H), 7.95 – 7.86 (4H, m, Ar-H), 7.61 – 7.54 (3H, m, Ar-H). $\delta_C$ 158.60 (C=O), 137.71 (qC), 135.15 (CH), 134.52 (CH), 133.62 (qC), 133.49 (qC), 130.05 (CH), 128.43 (CH), 128.23 (CH), 127.89 (CH), 127.55 (CH), 127.26 (qC), 126.98 (CH), 126.09 (qC), 125.68 (CH), 125.40 (CH), 121.31 (CH).

$\nu_{max}$/cm$^{-1}$: 1739 s (C=O), 1504 w (C=C), 1329 s (SO$_2$), 1182 s (SO$_2$).

6.2.6 Synthesis of 3-[2-(Aminosulfamoyl)phenyl]penta-1,4-diyn-3-ols

General Method for the Synthesis of 3-[2-(Aminosulfamoyl)phenyl]penta-1,4-diyn-3-ols

Under an inert (N$_2$) atmosphere n-BuLi (2.5 M, 2.5 equiv.) was added to a cold (-75 °C) solution of the appropriate alkyne (X mmol, 2.5 equiv.) in anhydrous THF (approx. 100 mL). A solution of the appropriate N-substituted saccharin (Y mmol, 1.0 equiv.) in anhydrous THF (approx. 60 mL) was added dropwise to the cold (0 °C) solution and the mixture was allowed to warm to r.t. and stirred for 1 h. After this time the mixture was quenched with aqueous NH$_4$Cl and diluted with EtOAc. The organic phase was separated, dried (Na$_2$SO$_4$) and evaporated to give the crude material which was purified by recrystallisation or by washing with cold hexane. The following compounds were synthesised by this method.

2-(3-Hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-N-methylbenzenesulphonamide (2.23Aa)

From phenylacetylene (12.9 mmol) and 2-methylbenzo[d]isothiazol-3(2H)-one 1,1-dioxide (5.07 mmol) to give the title compound as an off white solid (1.99 g, 98%) m.p. 145 – 146 °C; HRMS found [M+Na]$^+$ = 424.0981; $C_{24}H_{19}NO_3SNa$ [M+Na]$^+$ requires = 424.0978.
δ_H (CDCl₃) 8.44 (1H, dd, J = 7.9, 1.1 Hz, 2-H), 8.16 (1H, dd, J = 7.9, 1.1 Hz, 5-H), 7.67 (1H, td, J = 7.9, 1.1 Hz, 3-H), 7.58 – 7.52 (5H, m, 4-H, Ph-H), 7.40 – 7.32 (6H, m, Ph-H), 5.95 (1H, s, OH), 5.63 (1H, app. s, NH), 2.62 (3H, d, J = 5.3 Hz, Me). δ_c 139.82 (q C), 135.50 (q C), 133.28 (CH), 132.92 (CH), 131.89 (CH), 130.65 (CH), 129.33 (CH), 129.12 (CH), 128.51 (CH), 121.39 (q C), 88.54 (q C), 86.61 (q C), 67.02 (q C), 29.74 (CH₃).

ν_max/cm⁻¹: 3413 b (OH), 3320 m (NH), 2233 w (C≡C), 1489 m (C=C), 1372 w (CH₃), 1325 s (SO₂), 1164 s (R-OH), 1045 s (SO₂), 751 s (Ph-H), 688 s (Ph-H).

2-{6-Hydroxyundeca-4,7-diyn-6-yl)-N-methylbenzenesulfonamide (2.23Ab)

From 1-pentyne (12.7 mmol) and 2-methylbenzo[d]isothiazol-3(2H)-one 1,1-dioxide (5.07 mmol) to give the title compound as an orange oil (1.64 g, 97%); HRMS found [M+Na]^+ = 356.1304; C₁₈H₂₃NO₃SNa [M+Na]^+ requires = 356.1291.

δ_H (CDCl₃) 8.28 (1H, dd, J = 7.9, 1.1 Hz, 2-H), 8.10 (1H, dd, J = 7.9, 1.1 Hz, 5-H), 7.60 (1H, td, J = 7.9, 1.1 Hz, 3-H), 7.49 (1H, td, J = 7.9, 1.1 Hz, 4-H), 5.68 (1H, q, J = 5.2 Hz, NH), 5.51 (1H, s, OH), 2.62 (3H, d, J = 5.2 Hz, Me), 2.29 (4H, t, J = 7.1 Hz, CH₂), 1.59 (4H, sxt, J = 7.1 Hz, CH₂), 1.00 (6H, t, J = 7.1 Hz, CH₃). δ_c 140.70 (q C), 135.00 (q C), 132.98 (CH), 131.92 (CH), 130.71 (CH), 128.59 (CH), 87.23 (q C), 81.04 (q C), 66.29 (q C), 29.69 (CH₃), 21.70 (CH₂), 20.85 (CH₂), 13.55 (CH₃).

ν_max/cm⁻¹: 3413 b (OH), 3315 b (NH), 2965 m (Ar-H), 2934 w (CH₂, CH₃), 2873 w (CH₂, CH₃), 2236 w (C≡C), 1463 s (CH₂), 1393 s (CH₃), 1317 s (SO₂), 1156 s (R-OH), 1034 s (SO₂).
2-[3-Hydroxy-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl]-N-methylbenzenesulfonamide (2.23Ae)

From (trimethylsilyl)acetylene (11.2 mmol) and 2-methylbenzo[d]isothiazol-3(2H)-one 1,1-dioxide (5.07 mmol) to give the title compound as a brown solid (1.36 g, 68%) m.p. 71 – 73 °C; HRMS found [M+Na]$^+$ = 416.1140; C$_{18}$H$_{27}$NO$_3$SSi$_2$Na [M+Na]$^+$ requires = 416.1142.

δ$_{H}$ (CDCl$_3$) 8.18 (1H, dd, J = 7.9, 1.2 Hz, 2-)$_{-}$, 7.91 (1H, dd, J = 7.9, 1.2 Hz, 5-)$_{-}$, 7.45 (1H, td, J = 7.9, 1.2 Hz, 3-)$_{-}$, 7.35 (1H, td, J = 7.9, 1.2 Hz, 4-)$_{-}$, 5.79 (1H, s, OH)$_{-}$, 5.70 (1H, q, J = 5.2 Hz, NH)$_{-}$, 2.42 (3H, d, J = 5.2 Hz, Me) 0.19 (18H, s, Si-Me$_3$). δ$_{c}$ 138.55 (qC), 135.19 (qC), 133.25 (CH), 132.26 (CH), 130.73 (CH), 129.07 (CH), 92.14 (qC), 87.10 (qC), 66.30 (qC), 29.43 (CH$_3$), -0.29 (Si-Me$_3$).

v$_{\text{max}}$/cm$^{-1}$: 3342 b (NH), 2960 m (CH$_3$), 2167 w (C≡C), 1315 m (SO$_2$), 1160 s (R-OH).

2-[3-Hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl]-N-(p-tolyl)benzenesulfonamide (2.23Ba)

From phenylacetylene (9.15 mmol) and 2-(p-tolyl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (3.66 mmol) to give the title compound as a pale orange powder (1.40 g, 80%) m.p. 145 – 147 °C; HRMS found [M+Na]$^+$ = 500.1291; C$_{30}$H$_{23}$NO$_3$SNa [M+Na]$^+$ requires = 500.1291.

δ$_{H}$ (CDCl$_3$) 8.45 (1H, dd, J = 7.9, 1.1 Hz, 2-)$_{-}$, 7.68 (1H, dd, J = 7.9, 1.1 Hz, 5-)$_{-}$, 7.61 - 7.56 (6H, m, 3-)$_{-}$, Ph-H), 7.38 - 7.28 (7H, m, Ph-H, 4-)$_{-}$, NH), 6.97 (2H, d, J = 8.3 Hz, m-Ar-H), 6.90 (2H, d, J = 8.3 Hz, o-Ar-H), 6.10 (1H, s, OH), 2.25 (3H, s, Ar-Me). δ$_{c}$ 139.34 (qC), 136.48 (qC),

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135.46 (qC), 133.36 (CH), 133.19 (qC), 132.37 (CH), 131.91 (CH), 130.33 (CH), 129.78 (CH), 129.39 (CH), 128.55 (CH), 128.30 (CH), 124.15 (CH), 121.29 (qC), 88.80 (qC), 86.92 (qC), 67.05 (qC), 20.93 (CH3).

$\nu_{\text{max}}$/cm$^{-1}$: 3400 b (OH), 3268 w (NH), 2224 w (C≡C), 1508 s (C=C), 1436 w (CH$_3$), 1325 s (SO$_2$), 1159 s (R-OH), 1163 s (SO$_2$).

**2-(6-Hydroxyundeca-4,7-diyn-6-yl)-N-(p-tolyl)benzenesulfonamide (2.23Bb)**

From 1-pentyne (9.15 mmol) and 2-(p-tolyl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (3.66 mmol) to give the title compound as a pale yellow powder (1.13 g, 76%) m.p. 102 – 103 °C; HRMS found [M+Na]$^+$ = 432.1608; C$_{24}$H$_{27}$NO$_3$SNa [M+Na]$^+$ requires = 432.1604.

δ$_H$ (CDCl$_3$) 8.31 (1H, dd, $J = 7.9$, 1.0 Hz, 2-H), 7.71 (1H, s, NH), 7.59 (1H, dd, $J = 7.9$, 1.0 Hz, 5-H), 7.52 (1H, td, $J = 7.9$, 1.0 Hz, 3-H), 7.23 (1H, td, $J = 7.9$, 1.0 Hz, 4-H), 7.99 (2H, d, $J = 8.2$ Hz, m-Ar-H), 6.90 (2H, d, $J = 8.2$ Hz, o-Ar-H), 5.83 (1H, s, OH), 2.33 (4H, t, $J = 7.0$ Hz, CH$_2$), 2.27 (3H, s, Ar-Me), 1.66 – 1.57 (4H, m, CH$_2$), 1.02 (6H, t, $J = 7.0$ Hz, CH$_3$). δ$_C$ 140.07 (qC), 136.56 (qC), 135.06 (qC), 133.34 (qC), 133.10 (CH), 132.01 (CH), 130.39 (CH), 129.75 (CH), 128.45 (CH), 124.38 (CH), 87.62 (qC), 81.44 (qC), 66.28 (qC), 21.71 (CH$_2$), 20.95 (CH$_3$), 20.91 (CH$_2$), 13.60 (CH$_3$).

$\nu_{\text{max}}$/cm$^{-1}$: 3405 b (OH), 3264 m (NH), 2955 m (Ar-H), 2933 m (CH$_2$, CH$_3$), 2870 w (CH$_2$, CH$_3$), 2240 w (C≡C), 1508 s (C=C), 1437 w (CH$_2$), 1389 w (CH$_3$), 1299 s (SO$_2$), 1165 s (R-OH), 1064 s (SO$_2$).
2-[3-Hydroxy-1,5-bis(4-methoxyphenyl)penta-1,4-diyn-3-yl]-N-(p-tolyl)benzenesulfonamide (2.23Bc)

From 1-ethynyl-4-methoxybenzene (27.5 mmol) and 2-(p-tolyl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (11.0 mmol) to give the title compound as a pale orange powder (5.50 g, 93%) m.p. 145 – 146 °C; HRMS found [M+Na]^+ = 560.1505; C_{32}H_{27}NO_5SNa [M+Na]^+ requires = 560.1507.

δ_H (CDCl_3) 8.44 (1H, dd, J = 7.8, 1.1 Hz, 2-H), 7.64 (1H, app. d, 5-H), 7.57 (1H, td, J = 7.9, 1.1, Hz, 3-H), 7.50 (4H, m, Ar-H), 7.28* (1H, td, J = 7.8, 1.1 Hz, 4-H), 6.96 (2H, d, J = 8.2 Hz, m-Ar-H), 6.90 – 6.85 (6H, m, o-Ar-H, Ar-H), 6.10 (1H, s, NH), 3.81 (6H, s, O-Me), 2.24 (3H, s, Ar-Me). δ_C 160.37 (qC), 139.68 (qC), 136.44 (qC), 135.34 (qC), 133.45 (CH), 133.32 (CH), 133.25 (qC), 132.33 (CH), 130.33 (CH), 129.75 (CH), 128.75 (CH), 128.17 (CH), 114.18 (CH), 113.30 (qC), 87.78 (qC), 86.92 (qC), 67.06 (qC), 55.35 (CH3), 20.93 (CH3).

ν_max/cm^{-1}: 3291 b (OH), 2955 w (NH), 2226 w (C≡C), 1605 s (C═C), 1456 w (CH3), 1390 w (SO_2), 1164 s (R-OH), 1029 s (SO_2).

*Overlapping with CDCl_3 signal

2-[3-Hydroxy-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl]-N-(p-tolyl)benzenesulfonamide (2.23Be)
From (trimethylsilyl)acetylene (27.5 mmol) and 2-(p-tolyl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (11.0 mmol) to give the title compound as an orange oil (3.27 g, 63%); HRMS found [M+Na]+ = 492.1464; C24H31NO5SSi2Na [M+Na]+ requires = 492.1455.

δH (CDCl3) 8.38 (1H, app. d, 2-H), 7.92 (1H, s, NH), 7.54 (1H, td, J = 7.7, 1.1 Hz, 3-H), 7.49 (1H, app. d, 5-H), 7.24* (1H, app. t, 4-H), 7.01 (2H, d, J = 8.2 Hz, m-Ar-H), 6.99 (2H, d, J = 8.2 Hz, o-Ar-H), 6.24 (1H, s, OH), 2.27 (3H, s, Ar-Me), 0.25 (18H, s, Si-Me3). δc 138.41 (qC), 137.51 (qC), 135.62 (qC), 133.80 (CH), 133.40 (qC), 132.82 (CH), 130.84 (CH), 130.24 (CH), 129.33 (CH), 125.63 (CH), 105.25 (qC), 93.09 (qC), 66.83 (qC), 21.49 (CH3), 0.00 (Si-Me3).

νmax/cm⁻¹: 3420 w (OH), 3261 w (NH), 2960 m (CH3), 1509 s (C=C), 1334 m (SO2), 1163 s (R-OH), 1053 m (SO2).

*Overlapping with CDCl3 signal

2-(4-Hydroxy-1,7-dimethoxyhepta-2,5-diyne-4-yl)-N-(p-tolyl)benzenesulfonamide (2.23Bf)

From methyl propargyl ether (9.15 mmol) and 2-(p-tolyl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (3.66 mmol) to give the title compound as a beige powder (0.99 g, 66%) m.p. 110 – 111 °C; HRMS found [M+K]+ = 452.0930; C22H23NO5SK [M+K]+ requires = 452.0937.

δH (CDCl3) 8.29 (1H, app. d, 2-H), 7.95 (1H, s, NH), 7.55 – 7.50 (2H, m, 5-H, 3-H), 7.24* (1H, app. t, 4-H), 7.04 – 6.97 (4H, m, Ar-H), 6.28 (1H, s, OH), 4.27 (4H, ABq, J = 15.7 Hz, CH2H6), 3.41 (6H, s, Me), 2.29 (3H, s, Ar-Me). δc 138.62 (qC), 136.46 (qC), 136.06 (qC), 133.15 (qC), 133.10 (CH), 132.59 (CH), 129.74 (CH), 129.62 (CH), 128.87 (CH), 124.60 (CH), 85.84 (qC), 82.84 (qC), 65.72 (qC), 60.15 (CH2), 58.47 (CH3), 20.97 (CH3).

νmax/cm⁻¹: 3386 b (OH), 3281 m (NH), 2939 w (CH2, CH3), 2824 w (CH2, CH3), 1508 s (C=C), 1434 w (CH2), 1394 w (CH3), 1328 m (SO2), 1167 s (R-OH), 1093 s (SO2).

*Overlapping with CDCl3 signal
2-(3-Hydroxy-1,5-diphenylpenta-1,4-diyne-3-yl)-N-(m-tolyl)benzenesulfonamide (2.23Ca)

From phenylacetylene (18.3 mmol) and 2-(m-tolyl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (7.32 mmol) to give the title compound as an orange powder (3.28 g, 94%) m.p. 178 – 180 °C; HRMS found [M+Na]^+ = 500.1291; C_{30}H_{23}NO_{3}SNa [M+Na]^+ requires = 500.1297.

δ_H (CDCl₃) 8.44 (1H, dd, J = 7.9, 1.2 Hz, 2-H), 7.74 (1H, dd, J = 7.9, 1.2 Hz, 5-H), 7.61 – 7.56 (6H, m, 3-H, Ph-H), 7.40 – 7.29 (7H, m, Ph-H, 4-H), 7.05 – 7.02 (1H, m, m-Ar-H), 6.93 – 6.91 (1H, m, o-Ar-H), 6.82 – 6.80 (2H, m, Ar-H), 6.04 (1H, s, NH), 2.19 (3H, s, Ar-Me). δ_c 139.43 (qC), 139.24 (qC), 135.85 (qC), 135.59 (qC), 133.36 (CH), 132.27 (CH), 131.92 [2 X C (CH)], 130.36 (CH), 129.34 (CH), 128.93 (CH), 128.88 (CH), 128.54 [2 X C (CH)], 127.11 (CH), 124.30 (CH), 121.33 (qC), 120.36 (CH), 88.82 (qC), 86.90 (qC), 67.08 (qC), 21.23 (CH₃).

ν_max/cm⁻¹: 3383 b (OH), 3292 m (NH), 2224 s (C≡C), 1608 w (C=C), 1385 s (CH₃), 1326 s (SO₂), 1169 s (SO₂), 1155 s (R-OH), 729 w (Ph-H), 688 s (Ph-H).

2-(6-Hydroxyundeca-4,7-diyne-6-yl)-N-(m-tolyl)benzenesulfonamide (2.23Cb)

From 1-pentyne (18.3 mmol) and 2-(m-tolyl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (7.32 mmol) to give the title compound as a pale pink powder (2.51 g, 84%) m.p. 117 – 118 °C; HRMS found [M+Na]^+ = 432.1607; C_{24}H_{27}NO_{3}SNa [M+Na]^+ requires = 432.1610.
\[ \delta_H \text{ (CDCl}_3\text{)} 8.31 \text{ (1H, dd, } J = 7.9, 1.3 \text{ Hz, 2-H)}, 7.72 \text{ (1H, s, NH)}, 7.64 \text{ (1H, dd, } J = 7.9, 1.3 \text{ Hz, 5-H)}, 7.52 \text{ (1H, td, } J = 7.9, 1.3 \text{ Hz, 3-H)}, 7.24 \text{ (1H, td, } J = 7.9, 1.3 \text{ Hz, 4-H)}, 7.08 \text{ (1H, app. t, m-Ar-H)}, 6.96 – 6.94 \text{ (1H, m, o-Ar-H)}, 6.89 \text{ (1H, app. s, o-Ar-H)}, 6.81 – 6.79 \text{ (1H, m, p-Ar-H)}, 5.76 \text{ (1H, s, OH)}, 2.33 \text{ (4H, t, } J = 7.1 \text{ Hz, CH}_2\text{)}, 2.25 \text{ (3H, s, Ar-Me)}, 1.63 \text{ (4H, sxt, } J = 7.3 \text{ Hz, CH}_2\text{)}, 1.03 \text{ (6H, t, } J = 7.3 \text{ Hz, CH}_3\text{). } \delta_c 140.16 \text{ (q C)}, 139.21 \text{ (q C)}, 136.01 \text{ (q C)}, 135.19 \text{ (q C)}, 133.10 \text{ (CH)}, 131.90 \text{ (CH)}, 130.41 \text{ (CH)}, 128.89 \text{ (CH)}, 128.41 \text{ (CH)}, 127.27 \text{ (CH)}, 124.72 \text{ (CH)}, 120.84 \text{ (CH)}, 87.59 \text{ (q C)}, 81.46 \text{ (q C)}, 66.31 \text{ (q C)}, 21.71 \text{ (CH}_2\text{)}, 21.27 \text{ (CH}_3\text{)}, 20.91 \text{ (CH}_2\text{)}, 13.57 \text{ (CH}_3\text{).}

\nu_{\text{max}}/\text{cm}^{-1}: 3403 \text{ b (OH)}, 3278 \text{ m (NH)}, 2961 \text{ w (Ar-H)}, 2932 \text{ w (CH}_2\text{, CH}_3\text{)}, 2870 \text{ w (CH}_2\text{, CH}_3\text{)}, 1590 \text{ s (C=C)}, 1494 \text{ w (CH}_2\text{, CH}_3\text{)}, 1392 \text{ s (SO}_2\text{)}, 1173 \text{ w (RO-H)}, 1107 \text{ w (SO}_2\text{).}

2-\{3-Hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl\}-N-(2-methoxyphenyl)benzenesulfonamide (2.23Da)

From phenylacetylene (8.65 mmol) and 2-(2-methoxyphenyl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (3.46 mmol) to give the title compound as a golden powder (1.09 g, 59%) m.p. 133 – 135 °C; HRMS found [M+Na]^+ = 516.1248; C\text{_{30}H\text{_{23}NO\text{_{4}}SNa}} [M+Na]^+ requires = 516.1240.

\[ \delta_H \text{ ([CD}_3\text{]_2\text{CO]} 8.45 \text{ (1H, app. d, 2-H)}, 7.91 \text{ (1H, dd, } J = 7.9, 0.9 \text{ Hz, 5-H)}, 7.72 \text{ (1H, td, } J = 7.9, 0.9 \text{ Hz, 3-H)}, 6.91 \text{ (1H, app. t, Ar-H)}, 6.85 \text{ (1H, app. d, Ar-H)}, 7.59 – 7.53 \text{ (5H, m, Ar-H, Ph-H), 7.49 – 7.40 \text{ (7H, m, 4-H, Ph-H), 7.06 \text{ (1H, td, } J = 7.9, 1.4 \text{ Hz, Ar-H), 3.56 \text{ (3H, s, O-Me). } \delta_c 150.74 \text{ (q C)}, 140.17 \text{ (q C)}, 137.51 \text{ (q C)}, 133.08 \text{ (CH)}, 131.61 \text{ (CH)}, 131.43 \text{ (CH)}, 129.73 \text{ (CH)}, 129.05 \text{ (CH)}, 128.58 \text{ (CH)}, 128.57 \text{ (CH)}, 126.56 \text{ (q C)}, 125.55 \text{ (CH)}, 122.43 \text{ (CH)}, 122.16 \text{ (q C)}, 120.65 \text{ (CH)}, 111.22 \text{ (CH)}, 89.63 \text{ (q C)}, 85.31 \text{ (q C)}, 66.41 \text{ (q C)}, 55.21 \text{ (CH}_3\text{).}
\]

\nu_{\text{max}}/\text{cm}^{-1}: 3411 \text{ w (OH)}, 3243 \text{ w (NH)}, 2221 \text{ w (C≡C)}, 1596 \text{ w (C=C)}, 1447 \text{ m (CH}_3\text{)}, 1259 \text{ m (SO}_2\text{)}, 1168 \text{ s (R-OH)}, 1048 \text{ w (SO}_2\text{)}, 750 \text{ s (Ph-H)}, 686 \text{ s (Ph-H).}
2-(6-Hydroxyundeca-4,7-diyn-6-yl)-N-(2-methoxyphenyl)benzenesulfonamide (2.23Db)

From 1-pentyne (8.65 mmol) and 2-(2-methoxyphenyl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (3.46 mmol) to give the title compound as a red oil (1.08 g, 74%); HRMS found [M+Na]+ = 448.1562; C_{24}H_{27}NO_4SNa [M+Na]+ requires = 448.1553.

δ_H (CDCl_3) 8.29 (1H, dd, J = 7.9, 1.0 Hz, 2-H), 7.95 (1H, s, NH), 7.58 (1H, dd, J = 7.9, 1.5 Hz, Ar-H), 7.52 (1H, dd, J = 7.9, 1.0 Hz, 5-H), 7.45 (1H, td, J = 7.9, 1.0 Hz, 3-H), 7.19 (1H, td, J = 7.9, 1.0 Hz, 4-H), 7.11 (1H, td, J = 7.9, 1.5 Hz, Ar-H), 6.95 (1H, td, J = 7.9, 1.5 Hz, Ar-H), 6.65 (1H, app. d, Ar-H), 5.83 (1H, s, OH), 3.36 (3H, s, O-Me), 2.32 (4H, t, J = 7.1 Hz, CH_2), 1.61 (4H, sxt, J = 7.1 Hz, CH_2), 1.03 (6H, t, J = 7.1 Hz, CH_3). δ_c 151.59 (q C), 140.74 (q C), 136.17 (q C), 132.77 (CH), 131.10 (CH), 129.98 (CH), 127.99 (CH), 126.89 (CH), 125.80 (CH), 125.41 (CH), 121.07 (CH), 110.74 (CH), 87.17 (q C), 80.88 (q C), 66.15 (q C), 55.31 (CH), 21.88 (CH_2), 21.74 (CH_2), 20.95 (CH_2), 13.59 (CH_3).

ν_{max}/cm^{-1}: 3435 w (OH), 3253 w (NH), 2963 m (Ar-H), 2934 m (CH_2, CH_3), 2872 w (CH_2, CH_3), 2242 w (C≡C), 1600 m (C=C), 1497 s (CH_2), 1382 m (CH_3), 1333 s (SO_2), 1156 s (R-OH), 1110 s (SO_2).

2-[3-Hydroxy-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl]-N-(2-methoxyphenyl)benzenesulfonamide (2.23De)

From (trimethylsilyl)acetylene (17.3 mmol) and 2-(2-methoxyphenyl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (6.91 mmol) to give the title compound as a brown solid (2.08 g, 62%)
m.p. 138 – 139 °C; HRMS found [M+Na]^+ = 508.1404; C_{24}H_{31}NO_{4}SSi_{2}Na [M+Na]^+ requires = 508.1404.

δ_H (CDCl_3) 8.34 (1H, app. d, 2-H), 8.02 (1H, s, NH), 7.57 – 7.50 (2H, m, 3-H, Ar-H), 7.42 (1H, app. d, 5-H), 7.22 – 7.15 (2H, m, 4-H, Ar-H), 7.01 – 6.97 (1H, m, Ar-H), 6.68 – 6.65 (1H, m, Ar-H), 6.12 (1H, s, O-H), 3.31 (3H, s, O-Me), 0.25 (18H, s, Si-Me_3). \delta_c 152.27 (q-C), 138.92 (q-C), 136.39 (q-C), 131.26 (CH), 129.87 (CH), 128.24 (CH), 127.63 (CH), 127.49 (CH), 124.87 (q-C), 121.03 (CH), 104.00 (q-C), 91.87 (q-C), 66.32 (q-C), 54.99 (q-C), -0.50 (Si-Me_3).

ν_max/cm⁻¹: 3424 w (OH), 3219 b (NH), 2961 m (CH_3), 1598 s (C=C), 1325 m (SO_2), 1157 s (R-OH), 1059 m (SO_2).

2-(3-Hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-N-(3-methoxyphenyl)benzenesulfonamide (2.23Ea)

From phenylacetylene (13.0 mmol) and 2-(3-methoxyphenyl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (5.18 mmol) to give the title compound as a beige powder (2.16 g, 84%) m.p. 150 – 152 °C; HRMS found [M+Na]^+ = 516.1244; C_{30}H_{23}NO_{4}SNa [M+Na]^+ requires = 516.1245.

δ_H (CDCl_3) 8.43 (1H, dd, J = 7.9, 1.0 Hz, 2-H), 7.91 (1H, app. d, 5-H), 7.63 (1H, s, NH), 7.61 – 7.56 (5H, m, 3-H, Ph-H), 7.40 – 7.30 (7H, m, 4-H, Ar-H), 7.04 (1H, app. t, Ar-H), 6.66 – 6.62 (2H, m, Ar-H), 6.56 (1H, dd, J = 8.0, 1.1 Hz, Ar-H), 5.96 (1H, s, OH), 3.67 (3H, s, O-Me). \delta_c 160.16 (q-C), 139.43 (q-C), 137.16 (q-C), 133.44 (CH), 132.27 (CH), 131.92 (CH), 130.40 (CH), 129.84 (CH), 129.40 (CH), 128.94 (CH), 128.58 (CH), 128.29 (CH), 121.80 (q-C), 115.34 (CH), 112.16 (CH), 109.02 (CH), 88.78 (q-C), 86.90 (q-C), 67.08 (q-C), 55.30 (CH_3).

ν_max/cm⁻¹: 3404 b (OH), 3271 w (NH), 2229 w (C≡C), 1606 w (C=C), 1488 m (CH_3), 1392 s (SO_2), 1149 s (R-OH), 1049 w (SO_2), 730 s (Ph-H), 688 s (Ph-H).
2-(6-Hydroxyundeca-4,7-diyn-6-yl)-N-(3-methoxyphenyl)benzenesulfonamide (2.23Eb)

From 1-pentyne (13.0 mmol) and 2-(3-methoxyphenyl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (5.18 mmol) to give the title compound as an orange powder (1.63 g, 74%) m.p. 84–85 °C; HRMS found [M+Na]+ = 448.1555; C_{24}H_{27}NO_4SNa [M+Na]^+ requires = 448.1558.

δ_H (CDCl_3) 8.29 (1H, dd, J = 1.0, 7.9 Hz, 2-H), 7.98 (1H, s, NH), 7.69 (1H, dd, J = 7.9, 1.0 Hz, 5-H), 7.52 (1H, td, J = 7.9, 1.0 Hz, 3-H), 7.26* (1H, td, J = 7.9, 1.0 Hz, 4-H), 7.10 – 7.05 (1H, m, Ar-H), 6.69 – 6.68 (2H, m, Ar-H), 6.56 (1H, app. d, Ar-H), 5.69 (1H, s, OH), 3.73 (3H, s, O-Me), 2.33 (4H, t, J = 7.1 Hz, CH_2), 1.62 (4H, sxt, J = 7.1 Hz, CH_2), 1.03 (6H, t, J = 7.1 Hz, CH_3). δ_C 160.15 (qC), 140.20 (qC), 137.34 (qC), 135.08 (qC), 133.16 (CH), 131.90 (CH), 130.46 (CH), 129.79 (CH), 128.48 (CH), 115.75 (CH), 112.13 (CH), 109.56 (CH), 87.62 (qC), 81.43 (qC), 66.33 (qC), 55.33 (CH), 21.70 (CH_2), 20.90 (CH_2), 13.57 (CH_3).

ν_{max}/cm⁻¹: 3402 b (OH), 3254 m (NH), 2963 m (Ar-H), 2932 m (CH_2, CH_3), 2871 w (CH_2, CH_3), 2235 w (C≡C), 1606 m (C=C), 1491 s (CH_2), 1394 m (CH_3), 1327 s (SO_2), 1169 s (R-OH), 1109 s (SO_2).

*Overlapping with CDCl_3 signal

2-(3-Hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-N-(thiophen-3-yl)benzenesulfonamide (2.23Ga)
From phenylacetylene (18.9 mmol) and 2-(thiophen-3-yl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (7.54 mmol) to give the title compound as a brown solid (1.49 g, 42%) m.p. 107 °C decomp; HRMS found [M+Na]⁺ = 492.0699; C₂₇H₁₉NO₃S₂Na [M+Na]⁺ requires = 492.0698.

δH (CDCl₃) 8.43 (1H, dd, J = 8.0, 1.2 Hz, 2-H), 7.80 (1H, app. d, 5-H), 7.72 (1H, s, NH), 7.61 (1H, td, J = 8.0, 1.2 Hz, 3-H), 7.59 – 7.55 (2H, m, Ph-H), 7.50 – 7.47 (3H, m, Ph-H), 7.41 – 7.30 (6H, m, Ph-H, 4-H), 7.12 – 7.10 (1H, m, Ar-H), 6.83 (1H, dd, J = 3.0, 1.3 Hz, Ar-H), 6.74 (1H, dd, J = 5.0, 1.3 Hz, Ar-H), 5.95 (1H, s, OH). δC 139.42 (qC), 135.33 (qC), 133.87 (qC), 133.53 (CH), 132.35 (CH), 131.90 (CH), 130.42 (qC), 128.98 (CH), 128.73 (CH), 128.58 (CH), 128.30 (CH), 125.56 (CH), 123.94 (CH), 115.74 (CH), 88.66 (qC), 86.87 (qC), 67.05 (qC).

νmax/cm⁻¹: 3415 w (OH), 3275 w (NH), 2235 w (C≡C), 1597 w (C=C), 1488 s (R-OH), 1277 m (SO₂), 1155 w (SO₂), 776 s (Ph-H), 670 s (Ph-H).

2-(6-Hydroxyundeca-4,7-diynyl)-N-(thiophen-3-yl)benzenesulfonamide (2.23Gb)

From 1-pentyne (18.9 mmol) and 2-(thiophen-3-yl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (7.54 mmol) to give the title compound as a light brown solid (2.19 g, 69%) m.p. 87 – 88 °C; HRMS found [M+Na]⁺ = 424.1016; C₂₁H₂₃NO₃S₂Na [M+Na]⁺ requires = 424.1011.

δH (CDCl₃) 8.30 (1H, dd, J = 7.9, 1.1 Hz, 2-H), 7.86 (1H, s, NH), 7.72 (1H, dd, J = 7.9, 1.1 Hz, 5-H), 7.55 (1H, td, J = 8.0, 1.2 Hz, 3-H), 7.29 (1H, td, J = 8.0, 1.2 Hz, 4-H), 7.15 – 7.13 (1H, m, Ar-H), 6.85 (1H, dd, J = 4.0, 1.3 Hz, Ar-H), 6.80 (1H, dd, J = 4.0, 1.3 Hz, Ar-H), 5.65 (1H, s, OH), 2.32 (4H, t, J = 7.3 Hz, CH₂), 1.61 (4H, sxt, J = 7.3 Hz, CH₂), 1.02 (6H, t, J = 7.3 Hz, CH₃). δC 140.21 (qC), 134.94 (qC), 134.10 (qC), 133.25 (CH), 131.97 (CH), 130.49 (CH), 128.51 (CH), 125.50 (CH), 124.22 (CH), 116.19 (CH), 87.57 (qC), 81.30 (qC), 66.31 (qC), 21.71 (CH₂), 20.88 (CH₂), 13.59 (CH₃).

νmax/cm⁻¹: 3393 b (OH), 3234 m (NH), 2963 m (Ar-H), 2904 w (CH₂, CH₃), 2869 w (CH₂, CH₃), 2222 w (C≡C), 1452 w (CH₂), 1362 m (CH₃), 1336 s (SO₂), 1163 s (R-OH), 1107 s (SO₂).
2-(3-Hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-N-(naphthalen-2-yl)benzenesulfonamide (2.23Ha)

From phenylacetylene (24.3 mmol) and 2-(naphthalen-2-yl)benzod[1]isothiazol-3(2H)-one 1,1-dioxide (9.70 mmol) to give a beige powder which was recrystallised (EtOAc – pentane) to give the title compound as a beige powder (4.88 g, 98%) m.p. 166 – 168 °C; HRMS found [M+Na]+ = 536.1301; C_{33}H_{23}NO_{3}SNa [M+Na]+ requires = 536.1300.

δ_{H} (CDCl_{3}) 8.43 (1H, dd, J = 8.0, 1.2 Hz, 2-H), 7.86 (1H, s, NH), 7.74 – 7.72 (2H, m, Ar-\textit{H}, 5-H), 7.65 – 7.53 (7H, m, Ar-\textit{H}, 3-H), 7.47 (1H, d, J = 2.1 Hz, Ar-\textit{H}), 7.44 – 7.33 (8H, m, Ar-\textit{H}), 7.23 (1H, td, J = 8.0, 1.2 Hz, 4-H), 7.17 (1H, dd, J = 8.7, 2.1 Hz, Ar-\textit{H}), 5.99 (1H, s, OH). δ_{C} 139.46 (qC), 135.54 (qC), 133.51 (qC), 133.45 (CH), 133.43 (qC), 132.21 (CH), 131.94 (CH), 131.58 (qC), 130.45 (CH), 129.42 (CH), 129.20 (CH), 129.00 (CH), 128.57 (CH), 127.63 (CH), 127.60 (CH), 126.61 (CH), 125.88 (CH), 122.43 (CH), 121.32 (qC), 121.06 (CH), 88.85 (qC), 86.96 (qC), 67.16 (qC).

ν_{max}/cm^{-1}: 3387 b (OH), 3270 m (NH), 3055 w (Ar-H), 2226 s (C≡C), 1598 w (C=C), 1373 m (SO_{2}), 1162 s (R-OH), 1032 s (SO_{2}), 752 s (Ph-H), 721 s (Ph-H).

2-(6-Hydroxyundeca-4,7-diyn-6-yl)-N-(naphthalen-2-yl)benzenesulfonamide (2.23Hb)
From 1-pentyne (24.3 mmol) and 2-(naphthalen-2-yl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (9.70 mmol) to give the title compound as yellow flakes (3.85 g, 89%) m.p. 127 – 128 °C; HRMS found [M+Na]+ = 468.1601; C_{27}H_{27}NO_3SNa [M+Na]+ requires = 468.1610.

δ_H (CDCl_3) 8.30 (1H, dd, J = 7.9, 1.1 Hz, 2-H), 7.99 (1H, s, NH), 7.77 – 7.75 (1H, m, Ar-H), 7.71 – 7.67 (2H, m, Ar-H), 7.64 (1H, dd, J = 7.9, 1.1 Hz, 5-H), 7.50 – 7.41 (4H, m, Ar-H), 7.21 – 7.14 (2H, m, Ar-H, 4-H), 5.72 (1H, s, OH), 2.35 (4H, t, J = 7.3 Hz, CH_2), 1.64 (4H, sxt, J = 7.3 Hz, CH_2), 1.04 (6H, t, J = 7.3 Hz, CH_3). δ c 140.21 (q C), 135.13 (q C), 133.67 (q C), 133.47 (q C), 133.16 (CH), 131.85 (CH), 131.68 (q C), 130.52 (CH), 129.16 (CH), 128.54 (CH), 127.65 (CH), 127.63 (CH), 126.62 (CH), 125.93 (CH), 122.79 (CH), 121.48 (CH), 87.68 (q C), 81.40 (q C), 66.40 (q C), 21.70 (CH_2), 20.94 (CH_2), 13.59 (CH_3).

ν_max/cm^{-1}: 3405 b (OH), 3261 m (NH), 2961 m (Ar-H), 2933 w (CH_2, CH_3), 2870 w (CH_2, CH_3), 2219 w (C≡C), 1602 w (Ar-H), 1453 w (CH_2), 1353 m (CH_3), 1322 s (SO_2), 1162 s (R-OH), 1110 s (SO_2).

6.2.7 General Method for Synthesis of 3-Alkynyl-2-methylene-1-tosylindolin-3-ols

![Diagram](image)

Scheme 6.1

To a cold (0 °C) solution of N-[2-{3-hydroxy-1,5-disubstituted-1,4-diyln-3-yl}phenyl]-4-benzenesulfonamide derivative (X mmol, 1 equiv.) in MeOH (10 – 80 mL) was added 5M NaOH (Y equiv.) dropwise. The mixture was brought to r.t. and stirred for 0.5 – 24 h (Table 5.1). After this time, the reaction mixture was diluted with water and EtOAc. The organic phase was separated, dried (Na_2SO_4) and evaporated. The following were synthesised by this method.
Table 6.1 Base mediated cyclisation to 2.27 and 2.30. *By $^1$H NMR

3-Ethynyl-2-methylene-1-tosylindolin-3-ol (2.27)

Entry 1 (Table 6.1) to give the title compound as a brown oil; HRMS found [M+Na]$^+$ = 348.0661; C$_{18}$H$_{15}$NO$_3$SNa [M+Na]$^+$ requires = 348.0665.

$\delta$H (CDCl$_3$) 7.84 (1H, app. d, 4-H), 7.57 (2H, d, J = 8.2 Hz, o-Ar-H), 7.45 (1H, app. d, 7-H), 7.42 – 7.37 (1H, m, 5-H), 7.20 – 7.15 (3H, m, 6-H, m-Ar-H), 5.90 (1H, d, J = 2.0 Hz, CH), 5.46 (1H, d, J = 2.0 Hz, CH), 2.55 (1H, s, CH), 2.32 (3H, s, Ar-Me), 2.21 (1H, s, OH). $\delta$C 149.73 (qC), 144.82 (qC), 140.81 (qC), 133.64 (qC), 132.20 (qC), 130.98 (CH), 129.49 (CH), 127.427 (CH), 125.66 (CH), 124.44 (CH), 116.89 (CH), 102.41 (CH$_2$), 82.21 (qC), 74.68 (CH), 72.13 (qC), 21.59 (CH$_3$).

$\nu$max/cm$^{-1}$: 3498 s (OH), 3284 w (C=O-H), 1658 w (C=C), 1597 s (C=C), 1353 s (SO$_2$), 1164 s (R-OH), 1089 w (SO$_2$), 1018 m (C=CH$_2$), 936 m (C=CH$_2$).

2-Methylene-3-(phenylethynyl)-1-tosylindolin-3-ol (2.30A)
From entries 2 or 3 (Table 6.1) to give the title compound as an orange oil; HRMS found [M+Na]^+ = 424.0979; C_{24}H_{19}NO_3SNa [M+Na]^+ requires = 424.0978.

δ_H ([CD_3]_2CO) 7.78 (1H, app. d, 4-H), 7.61 (2H, d, J = 8.3 Hz, o-Ar-H), 7.47 (1H, dd, J = 7.8, 0.9 Hz, 7-H), 7.40 – 7.36 (1H, m, 5-H), 7.32 – 7.29 (3H, m, Ph-H), 7.23 – 7.16 (5H, m, Ph-H, 6-H, m-Ar-H), 5.78 (1H, d, J = 1.7 Hz, CH), 5.65 (1H, s, OH), 5.41 (1H, d, J = 1.7 Hz, CH), 2.17 (3H, s, Ar-Me). δ_c 151.30 (q C), 144.96 (q C), 140.45 (q C), 134.16 (q C), 133.96 (q C), 131.53 (q C), 131.44 (CH), 130.21 (CH), 129.51 (CH), 128.71 (CH), 128.45 (CH), 127.45 (CH), 125.39 (CH), 124.71 (CH), 115.95 (CH), 99.70 (CH_2), 89.36 (q C), 85.24 (CH), 72.16 (q C), 20.47 (CH_3).

ν_max/cm⁻¹: 3387 s (OH), 2222 w (C≡C), 1658 w (C=C), 1597 s (C=C), 1355 s (SO_2), 1167 s (R-OH), 1089 w (SO_2), 1020 m (C=CH_2), 938 m (C=CH_2).

2-Methylene-3-(pent-1-yn-1-yl)-1-tosylindolin-3-ol (2.30B)

From entries 4 or 5 (Table 6.1) to give the title compound as a red oil; HRMS found [M-H_2O+H]^+ = 350.1213; C_{21}H_{20}NO_5S [M-H_2O+H]^+ requires = 350.1205.

δ_H (CDCl_3) 7.84 (1H, app. d, 4-H), 7.58 (2H, d, J = 8.3 Hz, o-Ar-H), 7.44 (1H, dd, J = 7.5, 0.9 Hz, 7-H), 7.37 (1H, app. t, 5-H), 7.19 – 7.14 (3H, m, 6-H, m-Ar-H), 5.86 (1H, d, J = 1.9 Hz, CH), 5.44 (1H, d, J = 1.9 Hz, CH), 2.32 (3H, s, Ar-Me), 2.11 (2H, t, J = 7.2 Hz, CH_2), 1.99 (1H, s, OH), 1.46 (2H, sxt, J = 7.1 Hz, CH_2), 0.91 (3H, t, J = 7.2 Hz, CH_3). δ_c 150.49 (q C), 144.65 (q C), 140.65 (q C), 133.78 (q C), 133.19 (q C), 130.62 (CH), 129.42 (CH), 127.48 (CH), 125.54 (CH), 124.36 (CH), 116.80 (CH), 101.77 (CH_2), 87.56 (q C), 78.99 (q C), 72.49 (q C), 21.76 (CH_2), 21.58 (CH_3), 20.65 (CH_2), 13.41 (CH_3).

ν_max/cm⁻¹: 3481 s (OH), 2961 w (Ar-H), 2929 w (CH_2, CH_3), 2871 w (CH_2, CH_3), 2236 w (C≡C), 1716 w (C≡C), 1598 m (C≡C), 1463 s (CH_2, CH_3), 1355 s (SO_2), 1168 s (R-OH), 1089 s (SO_2), 1025 m (C=CH_2), 942 m (C=CH_2).
3-[(4-Methoxyphenyl)ethynyl]-2-methylene-1-tosylvindolin-3-ol (2.30C)

From entries 6 or 7 (Table 6.1) to give the title compound as an orange oil; HRMS found [M+Na]+ = 454.1081; C25H21NO4SNa [M+Na]+ requires = 454.1089.

δH (CDCl3) 7.87 (1H, app. d, 4-H), 7.59 (2H, d, J = 8.2 Hz, o-Ar-H), 7.51 (1H, app. d, 7-H), 7.40 – 7.40 (1H, app. t, 5-H), 7.24* (2H, d, J = 8.8 Hz, m-Ar-H), 6.80 (2H, d, J = 8.8 Hz, Ar-H), 5.92 (1H, d, J = 1.9 Hz, CH), 3.79 (3H, s, O-Me), 2.22 (3H, s, Ar-Me), 2.13 (1H, s, OH). δc 159.99 (qC), 150.40 (qC), 144.74 (qC), 140.70 (qC), 133.72 (qC), 133.24 (CH), 133.05 (qC), 130.72 (CH), 129.42 (CH), 127.48 (CH), 125.64 (CH), 124.47 (CH), 116.93 (CH), 113.90 (qC), 113.87 (CH), 102.07 (CH2), 86.48 (qC), 86.11 (CH), 72.88 (qC), 55.32 (CH3), 21.48 (CH3).

νmax/cm⁻¹: 2359 w (C≡C), 1604 w (C=C), 1509 m (C=C), 1355 m (SO2), 1168 s (R-OH), 1069 m (SO2), 1031 w (C=CH2), 943 w (C=CH2).

*Overlapping with CDCl3 signal

6.2.8 Silver(I) Catalysed Cyclisations of N-[2-(3-Hydroxy-penta-1,4-diyn-3-yl)phenyl]benzenesulfonamides

(Z)-2-Benzylidene-3-(phenylethynyl)-1-tosylvindolin-3-ol (2.33a)

To a solution of N-[2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)phenyl]-4-methylbenzenesulfonamide (1.00g, 2.09 mmol, 1 equiv.) in MeCN (38.3 mL/mmol) was added AgNO3 on silica (5 mol %, 10 % w/w) and the mixture stirred at reflux overnight. After
this time the reaction mixture was allowed to cool, filtered through Celite and evaporated to give the title compound as a brown oil (1.00 g, 100%); HRMS found [M+Na]^+ = 500.1293; C_{30}H_{23}NO_3SNa [M+Na]^+ requires = 500.1291.

δ_H [(CD_3)_2CO] 7.82 – 7.79 (3H, m, Ph-H, 4-H), 7.52 (1H, dd, J = 7.6, 0.8 Hz, 7-H), 7.48 – 7.44 (3H, m, 5-H, o-Ar-H), 7.39 – 7.34 (7H, m, Ph-H), 7.28 – 7.24 (2H, m, Ph-H, 6-H), 7.00 (2H, d, J = 8.1 Hz, m-Ar-H), 6.94 (1H, s, CH), 5.51 (1H, s, OH), 2.05* (3H, s, Ar-Me). δ_C 144.44 (q_C), 143.13 (q_C), 141.43 (q_C), 136.60 (q_C), 136.13 (q_C), 133.76 (q_C), 131.64 (CH), 129.83 (CH), 129.73 (CH), 128.94 (CH), 128.73 (CH), 128.71 (q_C), 128.48 (CH), 127.75 (CH), 127.47 (CH), 126.44 (CH), 124.46 (CH), 122.49 (q_C), 121.74 (CH), 118.570 (CH), 89.04 (q_C), 85.70 (q_C), 73.41 (q_C), 20.39 (CH_3).

ν_{max}/cm^{-1}: 3526 w (OH), 1595 m (C=C), 1355 s (SO_2), 1162 s (R-OH), 1087 w (SO_2), 770 s (Ph-H), 690 s (Ph-H).

*Overlapping with (CD_3)_2CO signal

**General Method for the AgOAc-Mediated Cyclisation of N-[2-{3-Hydroxy-penta-1,4-diyn-3-yl}phenyl]benzenesulfonamides**

To a solution of N-[2-{3-hydroxy-1,5-disubstituted-1,4-diyn-3-yl}phenyl]-4-benzenesulfonamide derivative (1.0 equiv.) in MeCN (38.3 mL/mmol) was added AgOAc (5 mol %) and the mixture stirred at reflux overnight. After this time the reaction mixture was allowed to cool, filtered through Celite and evaporated. The residue was purified by flash column chromatography. The following were synthesised by this method.

**Phenyl[3-{phenylethynyl}-1-tosyl-1H-indol-2-yl]methanol (2.32a)**
From N-[2-{3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl}phenyl]-4-methylbenzenesulfonylamide (2.09 mmol) to give the title compound as a brown oil (1.00 g, 100%); HRMS found [M+Na]^+ = 500.1298; C_{30}H_{23}NO_3SNa [M+Na]^+ requires = 500.1291.

δ_H ([CD_3]_2CO) 8.20 (1H, app. d, 4-H), 7.73 – 7.71 (3H, m, 7-H, o-Ar-H), 7.57 – 7.55 (2H, m, Ph-H), 7.49 – 7.42 (3H, m, Ph-H, 6-H), 7.39 – 7.33 (6H, m, Ph-H, 5-H), 7.29 – 7.26 (3H, m, m-Ar-H, Ph-H), 6.95 (1H, d, J = 7.1 Hz, CH), 5.19 (1H, d, J = 7.1 Hz, OH), 2.32 (3H, s, Ar-Me). δ_C 145.79 (qC), 145.63 (qC), 142.45 (qC), 135.81 (qC), 135.08 (qC), 131.43 (CH), 130.07 (qC), 129.97 (CH), 128.48 (CH), 128.44 (CH), 128.07 (CH), 127.22 (CH), 126.96 (CH), 126.53 (CH), 126.00 (CH), 124.52 (CH), 123.17 (qC), 120.00 (CH), 115.18 (CH), 106.70 (qC), 97.26 (qC), 80.52 (qC), 68.38 (CH), 20.58 (CH_3).

ν_max/cm\(^{-1}\): 3519 w (OH), 3062 w (Ar-H), 2922 w (CH_3), 1709 s (C=C), 1596 m (C=C), 1362 s (SO_2), 1168 s (R-OH), 1087 s (SO_2), 749 s (Ph-H), 690 s (Ph-H).

1-[3-(Pent-1-yn-1-yl)-1-tosyl-1H-indol-2-yl]butan-1-ol (2.32b)

From N-[2-{6-hydroxyundeca-4,7-diyn-6-yl}phenyl]-4-methylbenzenesulfonylamide (2.44 mmol). From flash column chromatography (5% EtOAc – hexane) to give the title compound as an orange oil (0.62 g, 62%); HRMS found [M+Na]^+ = 500.1298; C_{30}H_{23}NO_3SNa [M+Na]^+ requires = 500.1291.

δ_H (CDCl_3) 8.06 (1H, app. d, 4-H), 7.71 (2H, d, J = 8.4 Hz, o-Ar-H), 7.55 (1H, app. d, 7-H), 7.32 – 7.23* (2H, m, 6-H, 5-H), 7.13 (2H, d, J = 8.4 Hz, m-Ar-H), 5.51 (1H, dt, J = 10.8, 7.1 Hz, CH), 3.72 (1H, d, J = 10.8 Hz, OH), 2.49 (2H, t, J = 7.2 Hz, CH_2), 2.26 (3H, s, Ar-Me), 2.16 – 2.10 (2H, m, CH_2), 1.68 (2H, sxt, J = 7.2 Hz, CH_2), 1.08 (3H, t, J = 7.2 Hz, CH_3), 0.98 – 0.86 (5H, m, CH_3, CH_2). δ_C 145.25 (qC), 145.16 (qC), 136.06 (qC), 135.02 (qC), 130.21 (qC), 129.87 (CH), 126.59 (CH), 125.63 (CH), 124.15 (CH), 120.11 (CH), 114.99 (CH), 107.07 (qC), 99.27 (qC), 71.52 (qC), 68.74 (CH), 39.75 (CH_2), 22.19 (CH_2), 21.76 (CH_2), 21.52 (CH_3), 19.35 (CH_2), 13.85 (CH_3), 13.62 (CH_3).
\( \nu_{\text{max}}/\text{cm}^{-1} \): 3544 w (OH), 2959 w (Ar-H), 2932 w (CH\(_2\), CH\(_3\)), 2871 w (CH\(_2\), CH\(_3\)), 1597 w (C=C), 1451 s (CH\(_2\), CH\(_3\)), 1364 s (SO\(_2\)), 1172 s (R-OH), 1088 s (SO\(_2\)).

*Overlapping with CDCl\(_3\) signal

\((E)-2\)-(But-1-en-1-yl)-3-(pent-1-yn-1-yl)-1-tosyl-1H-indole (2.39)

From \(N\)-(2-{6-hydroxyundeca-4,7-diyn-6-yl}phenyl)-4-methylbenzenesulfonamide (2.44 mmol). From flash column chromatography (5% EtOAc – hexane) to give the title compound as a brown oil (0.16 g, 17%); HRMS found \([\text{M+Na}]^+ = 414.1497\); \(C_{24}H_{25}NO_2SNa\) \([\text{M+Na}]^+\) requires = 414.1498.

\(\delta\) (CDCl\(_3\)) 8.19 (1H, app. d, 4-H), 7.60 (2H, d, \(J = 8.3\) Hz, o-Ar-H), 7.53 (1H, app. d, 7-H), 7.32 – 7.24* (2H, m, 5-H, 6-H), 7.13 (2H, d, \(J = 8.4\) Hz, m-Ar-H), 6.99 (1H, d, \(J = 15.8\) Hz, CH), 6.79 (1H, dt, \(J = 15.8, 6.5\) Hz, CH), 2.47 (2H, t, \(J = 7.2\) Hz, CH\(_2\)), 2.41 – 2.33 (2H, m, CH\(_2\)), 2.30 (3H, s, Ar-Me), 1.65 (2H, sxt, \(J = 7.2\) Hz, CH\(_2\)), 1.18 (3H, t, \(J = 7.4\) Hz, CH\(_3\)), 1.08 (3H, t, \(J = 7.2\) Hz, CH\(_3\)). \(\delta_c\) 144.85 (q-C), 140.69 (CH), 140.03 (q-C), 135.69 (q-C), 135.43 (q-C), 131.27 (q-C), 129.59 (CH), 126.73 (CH), 125.15 (CH), 124.06 (CH), 119.77 (CH), 118.24 (CH), 115.14 (CH), 104.29 (q-C), 97.02 (q-C), 73.35 (q-C), 26.69 (CH\(_2\)), 22.26 (CH\(_2\)), 21.86 (CH\(_2\)), 21.56 (CH\(_3\)), 13.64 (CH\(_3\)), 13.40 (CH\(_3\)).

\(\nu_{\text{max}}/\text{cm}^{-1} \): 2962 w (Ar-H), 2931 w (CH\(_2\), CH\(_3\)), 2872 w (CH\(_2\), CH\(_3\)), 1682 w (C=C), 1597 w (C=C), 1450 s (CH\(_2\), CH\(_3\)), 1370 s (SO\(_2\)), 1171 s (R-OH), 1088 s (SO\(_2\)), 965 w (trans CH=CH).

*Overlapping with CDCl\(_3\) signal
4-{Pent-1-yn-1-yl}-2-propylquinoline (2.35b)

From N-[2-{6-hydroxyundeca-4,7-diyne-6-yl}phenyl]-4-methylbenzenesulfonamide (2.44 mmol). From flash column chromatography (5% EtOAc – hexane) to give the title compound as an orange oil (0.04 g, 8%); HRMS found [M+H]+ = 238.1604; C17H20N [M+H]+ requires = 238.1590.

δH (CDCl3) 8.22 (1H, app. d, 5-H), 8.04 (1H, app. d, 8-H), 7.70 – 7.66 (1H, m, 7-H), 7.54 – 7.50 (1H, m, 6-H), 7.36 (1H, s, CH), 2.93 – 2.89 (2H, m, CH2), 2.56 (2H, t, J = 7.3 Hz, CH2), 1.89 – 1.70 (4H, m, CH2), 1.33 (3H, t, J = 7.3 Hz, CH3), 1.01 (3H, t, J = 7.3 Hz, CH3). δc 162.30 (qC), 147.67 (qC), 130.78 (qC), 129.63 (CH), 129.01 (CH), 126.63 (qC), 126.05 (CH), 125.80 (CH), 123.95 (CH), 99.83 [2 X C (qC)], 41.01 (CH2), 23.24 (CH2), 22.10 (CH2), 21.76 (CH2), 14.01 (CH3), 13.69 (CH3).

νmax/cm⁻¹: 2960 m (Ar-H), 2931 m (CH2, CH3), 2871 m (CH2, CH3), 1597 s (C=C), 1453 m (CH2, CH3).

(Z)-1-Tosyl-3-[(trimethylsilyl)ethynyl]-2-[(trimethylsilyl)methylene]indolin-3-ol (2.33e)

From N-[2-{3-hydroxy-1,5-bis(trimethylsilyl)penta-1,4-diyne-3-yl}phenyl]-4-methylbenzenesulfonamide (4.26 mmol). From flash column chromatography (5% EtOAc – hexane) to give the title compound as a white powder (0.22 g, 11%) m.p. 164 – 165 °C; HRMS found [M+H]+ = 470.1635; C24H32NO3SSi2 [M+H]+ requires = 470.1636.

δH (CDCl3) 7.79 (1H, app. d, 4-H), 7.42 – 7.38 (4H, m, o-Ar-H, 7-H, 5-H), 7.20 (1H, app. t, 6-H), 7.09 (2H, d, J = 8.1 Hz, m-Ar-H), 6.14 (1H, s, CH), 2.29 (3H, s, Ar-Me), 1.08 (1H, s, OH), 0.33 (9H,
s, Si-Me₃), 0.15 (9H, s, Si-Me₃). δ_c 153.22 (qC), 144.67 (qC), 141.71 (qC), 134.25 (qC), 133.37 (qC), 130.55 (CH), 129.27 (CH), 128.12 (CH), 126.43 (CH), 124.61 (CH), 124.43 (CH), 119.14 (CH), 103.48 (qC), 91.76 (qC), 74.15 (qC), 21.57 (CH₃), 0.29 (Si-Me₃).

ν_max/cm⁻¹: 3438 m (OH), 2951 w (Ar-H), 2898 w (CH₃), 1644 s (C=C), 1599 s (C=C), 1340 s (SO₂), 1166 s (R-OH), 1092 s (SO₂).

(Z)-3-Ethynyl-1-tosyl-2-[(trimethylsilyl)methylene]indolin-3-ol (2.33e')

From N-{2-[3-hydroxy-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl]phenyl}-4-methylbenzenesulfonamide (4.26 mmol). From flash column chromatography (5% EtOAc – hexane) to give the title compound as a brown powder (0.88 g, 64%) m.p. 64 – 65 °C; HRMS found [M+H]^+ = 398.1239; C₂₁H₂₄NO₃S₂Si [M+H]^+ requires = 398.1241.

δ_H (CDCl₃) 7.75 (1H, app. d, 4-H), 7.40 – 7.34 (4H, m, o-Ar-H, 7-H, 5-H), 7.16 (1H, app. t, 6-H), 7.05 (2H, d, J = 8.2 Hz, m-Ar-H), 6.05 (1H, s, CH), 2.43 (1H, s, OH), 2.26 (3H, s, Ar-Me), 0.32 (9H, s, Si-Me₃). δ_c 153.69 (qC), 144.56 (qC), 141.38 (qC), 134.44 (qC), 133.49 (qC), 130.46 (CH), 129.24 (CH), 128.31 (CH), 126.47 (CH), 124.40 (CH), 122.95 (CH), 119.04 (CH), 82.45 (qC), 74.57 (CH), 73.40 (qC), 21.56 (CH₃), 0.11 (Si-Me₃).

ν_max/cm⁻¹: 3561 w (OH), 3286 w (C≡C-H), 2951 w (Ar-H), 1640 s (C=C), 1598 s (C=C), 1359 s (SO₂), 1166 s (R-OH), 1068 s (SO₂).

2-Methylene-1-tosyl-3-[(trimethylsilyl)ethynyl]indolin-3-ol (2.27')

From N-{2-[3-hydroxy-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl]phenyl}-4-methylbenzenesulfonamide (4.26 mmol). From flash column chromatography (5% EtOAc –
hexane) to give the title compound as a brown oil (0.01 g, 1%); HRMS found [M+H]+ = 398.1243; C21H23NO3SSi [M+H]+ requires = 398.1241.

δH (CDCl3) 7.84 (1H, app. d, 4-H), 7.58 (2H, d, J = 8.3 Hz, o-Ar-H), 7.45 (1H, app. d, 7-H), 7.41 – 7.37 (1H, m, 5-H), 7.20 – 7.15 (3H, m, 6-H, m-Ar-H), 5.89 (1H, d, J = 2.0 Hz, CH), 5.47 (1H, d, J = 2.0 Hz, CH), 2.32 (3H, s, Ar-Me), 0.13 (9H, s, Si-Me3). δc 149.93 (q C), 144.75 (q C), 140.88 (q C), 133.74 (q C), 132.48 (q C), 130.84 (CH), 129.47 (CH), 127.45 (CH), 125.57 (CH), 124.56 (CH), 116.74 (CH), 103.05 (CH2), 102.29 (q C), 91.56 (q C), 72.54 (q C), 21.61 (CH3), -0.33 (Si-Me3).

(Z)-3-(3,3-Dimethylbut-1-yn-1-yl)-2-(2,2-dimethylpropyldiene)-1-tosylindolin-3-ol (2.33)

From N-[2-(5-hydroxy-2,2,8,8-tetramethylnona-3,6-diyn-5-yl)phenyl]-4-methylbenzenesulfonamide (2.29 mmol). From flash column chromatography (5% EtOAc – hexane) to give the title compound as an off white solid (0.54 g, 54%) m.p. 125 – 126 °C; HRMS found [M+H]+ = 438.2102; C26H32NO3S [M+H]+ requires = 438.2098.

δH (CDCl3) 7.67 (1H, app. d, 4-H), 7.43 – 7.36 (4H, m, o-Ar-H, 7-H, 5-H), 7.20 (1H, app. t, 6-H), 7.09 (2H, d, J = 8.1 Hz, m-Ar-H), 6.08 (1H, s, CH), 2.29 (3H, s, Ar-Me), 1.36 (9H, s, Me3), 1.20 (9H, s, Me3). δc 144.65 (q C), 142.42 (q C), 138.95 (q C), 138.58 (CH), 136.61 (q C), 133.40 (q C), 130.04 (CH), 129.16 (CH), 128.66 (CH), 126.71 (CH), 124.27 (CH), 119.77 (CH), 95.79 (q C), 77.54 (q C), 74.46 (q C), 34.37 (q C), 30.73 (Me3), 29.44 (Me3), 27.43 (q C), 21.57 (CH3).

νmax/cm⁻¹: 3490 w (OH), 2963 m (Ar-H), 2868 w (CH3), 1598 m (C=C), 1461 s (CH3), 1354 s (SO2), 1166 s (R-OH), 1088 s (SO2).
6.2.9 Synthesis of 2,4-Diphenyl-5-tosyl-4,5-dihydrofuro[2,3-c]quinoline (2.53)

To a solution of \( N\)-[2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)phenyl]-4-
methylbenzenesulfonylamine (1.00 g, 2.09 mmol, 1 equiv.) in DCM (38.3 mL/mmol) was
added indium(III) trifluoromethanesulfonate (5 mol%), the mixture stirred at r.t. for 18 h.
After this time the reaction mixture was filtered through Celite. The residue was purified by
flash column chromatography (10% EtOAc – hexane) and recrystallised with EtOAc – hexane
to give the title compound as a beige powder (0.22 g, 22%) m.p. 130 – 131 °C; HRMS found
\([M+H]^+ = 478.1477; C_{30}H_{24}NO_3S [M+H]^+ \) requires = 478.1472.

\( \delta^H ([CD_3]_2CO) \) 7.75 – 7.73 (2H, m, Ph-H), 7.70 (1H, dd, \( J = 7.8, 1.2 \) Hz, 9-H), 7.49 – 7.45 (2H, m,
Ph-H), 7.41 (1H, dd, \( J = 7.8, 1.2 \) Hz, 6-H), 7.38 – 7.22 (10H, m, Ph-H, 8-H, 7-H, o-Ar-H), 7.02
(2H, d, \( J = 8.0 \) Hz, m-Ar-H), 6.95 (1H, s, Ar-H), 6.73 (1H, s, 1-H), 2.15 (3H, s, Ar-Me). \( \delta^C \) 154.72
(\( \delta^C \)), 147.80 (\( \delta^C \)), 143.91 (\( \delta^C \)), 137.73 (\( \delta^C \)), 134.43 (\( \delta^C \)), 131.24 (\( \delta^C \)), 130.28 (\( \delta^C \)), 129.20 (CH),
129.00 (CH), 128.85 (CH), 128.65 (CH), 128.21 (CH), 127.83 (CH), 127.70 (CH), 126.83 (\( \delta^C \)),
126.77 (CH), 126.69 (CH), 126.65 (CH), 123.67 (CH), 123.06 (CH), 118.53 (\( \delta^C \)), 100.91 (CH),
56.49 (CH), 20.36 (CH_3).

\( \nu_{\max }/\text{cm}^{-1} \): 1599 w (C=C), 1450 s (CH_3), 1353 s (SO_2), 1164 s (SO_2), 750 s (Ph-H), 685 s (Ph-H).
6.2.10 General Method for the Synthesis of 3,3-Di(alkynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxides

Method A: To a solution of 3-[2-(sulfamoyl)phenyl]penta-1,4-diyn-3-ols derivative (1.0 equiv.) in MeCN (38.3 mL/mmol) was added ICl (3.0 equiv.), the mixture was stirred at the temperature for the time indicated in Table 5.2. After this time the reaction mixture was quenched with aqueous sodium thiosulfate. The organic phase was separated, dried (Na$_2$SO$_4$) and evaporated. The residue was purified by flash column chromatography or by recrystallisation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R$^1$</th>
<th>Dialkynol</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>1,2-Benzisothiazole 1,1-dioxide</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>Me</td>
<td>Ph</td>
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<tr>
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<td>82</td>
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Table 6.2 Cyclisation of dialkynols 2.23Aa – Eb with ICl to 2.59Aa – Eb results. * 2 equiv. of ICl used
Method B: To a solution of 3-[2-(sulfamoyl)phenyl]penta-1,4-diyn-3-ols derivative (1.0 equiv.) in DCM (38.3 mL/mmol) was added indium(III) trifluoromethanesulfonate (5 mol %), the mixture stirred at r.t. for the time indicated in Table 5.3. After this time the reaction mixture was filtered through Celite and evaporated to give the title compound. The residue was purified by column chromatography or by recrystallisation.

<table>
<thead>
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<th>Entry</th>
<th>Dialkynol</th>
<th>R</th>
<th>R₁</th>
<th>1,2-Benzisothiazole 1,1-dioxide</th>
<th>Time (h)</th>
<th>Yield (%)</th>
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<tbody>
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<td>1</td>
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<td>C₃H₇</td>
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<td>100</td>
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<tr>
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<td>C₃H₇</td>
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<td>27</td>
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<td>Ph</td>
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<td>53</td>
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<td>C₃H₇</td>
<td>2.59Cb</td>
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<td>82</td>
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<td>Ph</td>
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<td>C₃H₇</td>
<td>2.59Db</td>
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<td>C₃H₇</td>
<td>2.59Eb</td>
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</table>

Table 6.3 Yields of In(OTf)₃ promoted cyclisation of 2.23Aa – Hb to 2.59Aa – Hb

2-Methyl-3,3-bis(phenylethynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (2.59Aa)
From 2-(3-hydroxy-1,5-diphenylpenta-1,4-dyn-3-yl)-N-methylbenzenesulfonamide (Method A: 1.74 mmol, Method B: 1.25 mmol). Method A – From column chromatography (10% EtOAc – pet ether) to give the title compound as a brown oil (Method A: 0.32 g, 48%, Method B: 0.48 g, 100%); HRMS found [M+H]^+ = 384.1047; C_{24}H_{18}NO_2S [M+H]^+ requires = 384.1053.

δ_H (CDCl_3) 7.90 (1H, app. d, 4-H), 7.84 (1H, app. d, 7-H), 7.73 (1H, app. t, 6-H), 7.62 (1H, app. t, 5-H), 7.49 – 7.46 (4H, m, Ph-H), 7.38 – 7.28 (6H, m, Ph-H), 3.16 (3H, s, Me). δ_c 137.80 (q C), 133.84 (CH), 133.02 (q C), 132.11 (CH), 130.43 (CH), 129.37 (CH), 128.39 (CH), 124.96 (CH), 121.36 (CH), 121.16 (q C), 85.95 (q C), 83.29 (q C), 57.01 (q C), 25.56 (CH_3).

ν_{max}/cm⁻¹: 3056 w (Ar-H), 2229 w (C≡C), 1597 w (C=C), 1490 s (CH_3), 1309 s (SO_2), 1158 s (SO_2), 752 s (Ph-H), 688 s (Ph-H).

2-Methyl-3,3-di(pent-1-yn-1-yl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (2.59Ab)

From 2-(6-hydroxyundeca-4,7-dyn-6-yl)-N-(p-tolyl)benzenesulfonamide (Method B: 3.00 mmol) to give the title compound as an orange oil (Method B: 0.87 g, 92%); HRMS found [M+H]^+ = 316.1368; C_{18}H_{22}NO_2S [M+H]^+ requires = 316.1375.

δ_H (CDCl_3) 7.77 (1H, app. d, 7-H), 7.73 (1H, app. d, 4-H), 7.68 (1H, app. t, 5-H), 7.56 (1H, app. t, 6-H), 3.00 (3H, s, Me), 2.20 (4H, t, J = 7.0 Hz, CH_2), 1.53 (4H, sxt, J = 7.3 Hz, CH_2), 0.96 (6H, t, J = 7.3 Hz, CH_3). δ_c 138.91 (q C), 133.45 (CH), 132.84 (q C), 129.90 (CH), 124.65 (CH), 121.09 (CH), 86.59 (q C), 75.58 (q C), 56.31 (q C), 25.08 (CH_3), 21.70 (CH_2), 20.63 (CH_2), 13.37 (CH_3).

ν_{max}/cm⁻¹: 2964 m (Ar-H), 2934 m (CH_2, CH_3), 2873 w (CH_2, CH_3), 2241 w (C≡C), 1455 s (CH_2), 1380 w (CH_3), 1306 s (SO_2), 1158 s (SO_2).
3,3-Bis(phenylethynyl)-2-(p-tolyl)-2,3-dihydro-1,2-benzothiazole 1,1-dioxide (2.59Ba)

From 2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-N-(p-tolyl)benzenesulfonamide (Method A: 2.09 mmol, Method B: 1.47 mmol). Method A – From column chromatography (12% EtOAc – pet ether) to give the title compound as a brown powder (Method A: 0.43 g, 45%, Method B: 0.68 g, 100%) m.p. 130 – 131 °C; HRMS found [M+H]$^+$ = 460.1371; $C_{30}H_{28}NO_2S$ [M+H]$^+$ requires = 460.1366.

δ$^H$ (CDCl$_3$) 7.96 – 7.92 (2H, m, 4-H, 7-H), 7.78 (1H, app. t, 5-H), 7.73 (2H, d, $J$ = 8.2 Hz, o-Ar-H), 7.68 (1H, app. t, 6-H), 7.42 – 7.40 (4H, m, Ph-H), 7.35 – 7.28 (6H, m, Ph-H, m-Ar-H), 2.43 (3H, s, Me). δ$_C$ 140.03 ($q$C), 137.53 ($q$C), 133.67 (CH), 133.42 ($q$C), 132.10 (CH), 131.93 (CH), 130.44 (CH), 130.02 (CH), 129.25 (CH), 128.91 ($q$C), 128.34 (CH), 125.18 (CH), 121.50 (CH), 121.32 ($q$C), 86.19 ($q$C), 84.71 ($q$C), 58.58 ($q$C), 21.41 (CH$_3$).

$\nu_{\text{max}}$/cm$^{-1}$: 3056 w (Ar-H), 2229 w (C≡C), 1597 w (C=C), 1490 s (CH$_3$), 1311 s (SO$_2$), 1173 s (SO$_2$), 754 s (Ph-H), 688 s (Ph-H).

3,3-Di(pent-1-yn-1-yl)-2-(p-tolyl)-2,3-dihydro-1,2-benzothiazole 1,1-dioxide (2.59Bb)

From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-N-(p-tolyl)benzenesulfonamide (Method B: 1.71 mmol) to give the title compound as a brown powder (Method B: 0.66 g, 98%) m.p. 131 – 133 °C; HRMS found [M+Na]$^+$ = 414.1518; $C_{24}H_{25}NO_2SNa$ [M+Na]$^+$ requires = 414.1498.
$\delta$ (CDCl$_3$) 7.84 (1H, app. d, 7-H), 7.77 (1H, app. d, 4-H), 7.71 (1H, app. t, 5-H), 7.62 – 7.58 (3H, m, o-Ar-H, 6-H), 7.28 (1H, d, $J = 5.2$ Hz, m-Ar-H), 2.42 (3H, s, Ar-Me), 2.15 (4H, t, $J = 7.3$ Hz, CH$_2$), 1.48 (4H, sxt, $J = 7.3$ Hz, CH$_2$), 0.90 (6H, t, $J = 7.3$ Hz, CH$_3$). $\delta_c$ 139.58 (qC), 138.72 (qC), 133.35 (CH), 133.16 (qC), 131.87 (CH), 129.94 (CH), 129.78 (CH), 129.06 (qC), 124.90 (CH), 121.19 (CH), 87.00 (qC), 76.88 (qC), 57.93 (qC), 21.60 (CH$_2$), 21.38 (CH$_3$), 13.46 (CH$_3$).

$\nu_{\max}$/cm$^{-1}$: 2965 m (Ar-H), 2935 m (CH$_2$, CH$_3$), 2873 w (CH$_2$, CH$_3$), 2235 w (C≡C), 1508 s (C≡C), 1455 s (CH$_2$), 1380 w (CH$_3$), 1299 s (SO$_2$), 1024 s (SO$_2$).

3,3-Bis[(4-methoxyphenyl)ethynyl]-2-(p-tolyl)-2,3-dihydro-1,2-benzothiazole 1,1-dioxide (2.59Bc)

From 2-[3-hydroxy-1,5-bis(4-methoxyphenyl)penta-1,4-diyn-3-yl]-N-(p-tolyl)benzenesulfonamide (Method B: 1.86 mmol) to give the title compound as a brown powder (Method B: 0.95 g, 99%) m.p. 140 – 141 °C; HRMS found [M+Na]$^+$ = 542.1403; $C_{32}H_{25}NO_5SNa$ [M+Na]$^+$ requires = 542.1402.

$\delta$ (CDCl$_3$) 7.96 – 7.90 (2H, m, 4-H, 7-H), 7.78 – 7.64 (4H, m, 5-H, o-Ar-H, 6-H), 7.42 – 7.40 (4H, m, Ph-H), 7.35 – 7.30 (6H, m, Ar-H, m-Ar-H), 6.82 (2H, d, $J = 8.8$ Hz, Ar-H), 3.80 (6H, s, O-Me), 2.42 (3H, s, Ar-Me). $\delta_c$ 160.25 (qC), 139.88 (qC), 137.96 (qC), 133.59 (CH), 133.48 [2 X C (CH)], 133.37 (qC), 132.13 (CH), 130.27 (CH), 129.96 (CH), 129.01 (qC), 125.21 (CH), 121.41 (CH), 113.94 (CH), 113.40 (qC), 86.16 (qC), 83.64 (qC), 55.33 (qC), 21.41 (CH$_3$).

$\nu_{\max}$/cm$^{-1}$: 2952 w (Ar-H), 2840 w (CH$_3$), 2224 w (C≡C), 1605 s (C≡C), 1508 s (C≡C), 1294 s (SO$_2$), 1174 s (SO$_2$).
2-\{(p-Tolyl)-3,3-bis[(trimethylsilyl)ethynyl]-2,3-dihydro-1,2-benzothiazole 1,1-dioxide (2.59Be)

From 2-[3-hydroxy-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl]-N-(p-tolyl)benzenesulfonamide (Method B: 2.13 mmol) to give the title compound as white crystals (Method B: 0.26 g, 27%) m.p. 183 °C; HRMS found [M+H]+ = 452.1335; C24H30NO2SSi2 [M+H]+ requires = 452.1538.

δH (CDCl3) 7.72 (1H, app. d, 7-H), 7.66 (1H, app. d, 4-H), 7.59 (1H, td, J = 1.1, 7.4 Hz, 5-H), 7.51 – 7.44 (4H, m, 6-H, α-Ar-H), 7.15 (2H, d, J = 8.1 Hz, m-Ar-H), 2.30 (3H, s, Ar-Me), 0.00 (18H, s, Si-Me3). δc 140.02 (qC), 137.18 (qC), 133.56 (CH), 133.22 (qC), 132.36 (CH), 130.29 (CH), 129.74 (CH), 128.67 (qC), 125.11 (CH), 121.33 (CH), 99.79 (qC), 91.59 (qC), 58.28 (qC), 21.42 (CH3), -0.54 (Si-Me3).

νmax/cm⁻¹: 2960 m (Ar-H), 1508 m (C=C), 1310 s (SO₂), 1173 s (SO₂).

3,3-Bis(3-methoxyprop-1-yn-1-yl)-2-\{(p-tolyl)-2,3-dihydro-1,2-benzothiazole 1,1-dioxide (2.59Bf)

From 2-(4-hydroxy-1,7-dimethoxyhepta-2,5-diyn-4-yl)-N-(p-tolyl)benzenesulfonamide (Method A: 1.21 mmol). Flash column chromatography (10% EtOAc – hexane) to give the title compound as a brown powder (Method A: 0.19 g, 40%) m.p. 115 °C decomp; HRMS found [M+Na]+ = 418.1092; C22H21NO4SNa [M+Na]+ requires = 418.1083.

δH (CDCl3) 7.87 (1H, app. d, 7-H), 7.82 (1H, app. d, 4-H), 7.74 (1H, td, J = 7.4, 1.1 Hz, 5-H), 7.67 – 7.61 (3H, m, α-Ar-H, 6-H), 7.29 (1H, d, J = 8.1 Hz, m-Ar-H), 4.10 (4H, s, CH2), 3.29 (6H, s, CH3), 2.42 (3H, s, Ar-Me). δc 140.02 (qC), 136.98 (qC), 133.67 (CH), 133.28 (qC), 131.71 (CH), 302
130.54 (CH), 130.03 (CH), 128.69 (qC), 124.95 (CH), 121.44 (CH), 82.54 (qC), 81.83 (qC), 59.66 (CH₂), 57.84 (CH₃), 21.38 (CH₃).

νₘαₓ/cm⁻¹: 2942 m (CH₂, CH₃), 1507 s (C=C), 1453 s (CH₂), 1373 w (CH₃), 1312 s (SO₂), 1178 s (SO₂).

3,3-Bis(phenylethynyl)-2-(m-tolyl)-2,3-dihydro-1,2-benzothiazole 1,1-dioxide (2.59Ca)

From 3,3-Di(pent-1-yn-1-yl)-2-(m-tolyl)-2,3-dihydro-1,2-benzothiazole 1,1-dioxide (2.59Cb)

δH (CDCl₃) 7.97 – 7.91 (2H, m, 4-H, 7-H), 7.78 (1H, td, J = 7.5, 1.1 Hz, 5-H), 7.69 – 7.64 (3H, m, 6-H, Ar-H), 7.42 – 7.38 (5H, m, Ar-H), 7.36 – 7.27 (7H, m, Ar-H), 2.41 (3H, s, Ar-Me) δc 139.15 (qC), 137.50 (qC), 133.67 (CH), 133.46 (qC), 132.67 (CH), 131.89 (CH), 131.71 (qC), 130.57 (CH), 130.44 (CH), 129.25 (CH), 129.05 (CH), 129.00 (CH), 128.33 (CH), 125.17 (CH), 121.48 (CH), 121.33 (qC), 86.34 (qC), 84.75 (qC), 58.54 (qC), 21.42 (CH₃).

νₘαₓ/cm⁻¹: 2233 m (C≡C), 1604 w (C=C), 1488 m (CH₃), 1311 s (SO₂), 1171 s (SO₂), 784 s (Ph-H), 690 s (Ph-H).
From 2-(6-hydroxyundeca-4,7-diyne-6-yl)-N-(m-tolyl)benzenesulfonamide (Method A: 2.44 mmol, Method B: 0.49 mmol). Method A - The residue was recrystallised from EtOH – H2O, the liquor was subject to flash column chromatography (20% Ether – pet ether) to give the title compound as beige crystals (Method A: 0.26 g, 75%, Method B: 0.16 g, 82%) m.p. 100 – 101 °C; HRMS found [M+H]+ = 392.1681; C24H26NO2S [M+H]+ requires = 392.1686.

δH (CDCl3) 7.84 (1H, app. d, 7-H), 7.78 (1H, app. d, 4-H), 7.71 (1H, td, J = 7.4, 1.1 Hz, 5-H), 7.60 (1H, td, J = 7.4, 1.1 Hz, 6-H), 7.56 – 7.53 (2H, m, Ar-H), 7.36 (1H, app. t, Ar-H), 7.29 – 7.27 (1H, m, Ar-H), 2.41 (3H, s, Ar-Me), 2.16 (4H, t, J = 7.2 Hz, CH2), 1.49 (4H, sxt, J = 7.2 Hz, CH2), 0.90 (6H, t, J = 7.2 Hz, CH3). δc 138.56 (qC), 138.71 (qC), 133.35 (CH), 133.19 (qC), 132.32 (CH), 131.85 (qC), 130.15 (CH), 129.94 (CH), 128.77 (CH), 128.75 (CH), 124.89 (CH), 121.17 (CH), 87.06 (qC), 76.93* (qC), 57.86 (qC), 21.59 (CH2), 21.34 (CH3), 20.70 (CH2), 13.41 (CH3).

νmax/cm⁻¹: 2964 m (Ar-H), 2935 m (CH2, CH3), 2872 w (CH2, CH3), 2235 w (C≡C), 1604 w (C=C), 1454 m (CH2), 1296 s (SO2), 1176 s (SO2).

*Overlapping with CDCl3 signal

2-(2-Methoxyphenyl)-3,3-bis(phenylethynyl)-2,3-dihydro-1,2-benzothiazole 1,1-dioxide (2.59Da)

From 2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-N-(2-methoxyphenyl)benzenesulfonamide (Method B: 1.01 mmol). Flash column chromatography (10% EtOAc – hexane) to give the title compound as a white solid (Method B: 0.18 g, 37%) m.p. 165 – 166 °C; HRMS found [M+Na]+ = 498.1135; C30H21NO3SNa [M+Na]+ requires = 498.1132.

δH (CDCl3)(600 MHz) 7.94 (1H, app. d, 4-H), 7.92 – 7.90 (2H, m, 7-H, Ar-H), 7.76 (1H, td, J = 7.8, 1.1 Hz, 5-H), 7.65 (1H, td, J = 7.8, 1.1 Hz, 6-H), 7.49 – 7.46 (1H, m, Ar-H), 7.41 – 7.39 (4H, m, Ph-H), 7.34 – 7.27 (6H, m, Ph-H), 7.09 – 7.05 (1H, m, Ar-H), 3.76 (3H, s, O-Me) δc (150
MHz) 160.05 (qC), 137.93 (qC), 134.99 (CH), 133.52 (CH), 131.89 (CH), 131.70 [2 X C (CH) (qC)], 130.25 (CH), 129.08 (CH), 128.27 (CH), 125.13 (CH), 121.58 (qC), 121.49 (CH), 120.51 (CH), 119.56 (qC), 112.65 (CH), 85.53 (qC), 84.96 (qC), 58.31 (qC), 56.15 (CH3).

νmax/cm⁻¹: 1496 m (C=C), 1443 m (CH3), 1314 s (SO2), 1020 s (SO2).

2-(2-Methoxyphenyl)-3,3-di(pent-1-yn-1-yl)-2,3-dihydro-1,2-benzothiazole 1,1-dioxide (2.59Db)

From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-N-(2-methoxyphenyl)benzenesulfonamide (Method B: 0.94 mmol). Trituration with acetone to give the title compound as a white crystalline solid (Method B: 0.24 g, 63%) m.p. 200 °C; HRMS found [M+Na]+ = 430.1449; C24H25NO3SNa [M+Na]+ requires = 430.1453.

δH (CDCl3) 7.84 – 7.76 (3H, m, 7-H, Ar-H, 4-H), 7.69 (1H, app. t, 5-H), 7.58 (1H, app. t, 6-H), 7.45 (1H, app. t, Ar-H), 7.05 – 7.02 (2H, m, Ar-H), 3.82 (3H, s, O-Me), 2.15 (4H, t, J = 7.2 Hz, CH2), 1.47 (4H, sxt, J = 7.2 Hz, CH2), 0.89 (6H, t, J = 7.2 Hz, CH3). δc 159.98 (qC), 139.20 (qC), 134.92 (CH), 133.36 (qC), 133.17 (CH), 131.39 (CH), 129.74 (CH), 124.84 (CH), 121.23 (qC), 120.34 (CH), 119.75 (qC), 112.53 (CH), 86.33 (qC), 76.80* (qC), 55.94 (CH3), 21.63 (CH2), 20.77 (CH2), 13.44 (CH3).

νmax/cm⁻¹: 2966 m (Ar-H), 2936 m (CH2, CH3), 2874 w (CH2, CH3), 2235 w (C≡C), 1592 m (C=C), 1498 s (CH2), 1298 s (SO2), 1176 s (SO2).

*Overlapping with CDCl3 signal
2-(3-Methoxyphenyl)-3,3-di(pent-1-yn-1-yl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide
(2.59Eb)

From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-N-(3-methoxyphenyl)benzenesulfonamide (Method A and B: 1.17 mmol). Method A – From column chromatography (20% EtOAc – pet ether) to give the title compound as a black solid (Method A: 0.26 g, 54%, Method B: 0.48 g, 100%) m.p. 98 – 100 °C; HRMS found [M+H]^+ = 408.1634; C_{24}H_{26}NO_{3}S [M+H]^+ requires = 408.1635.

δ_H (CDCl_3) 7.84 (1H, app. d, 7-H), 7.78 (1H, app. d, 4-H), 7.72 (1H, td, J = 7.4, 1.1 Hz, 5-H), 7.9 (1H, app. t, 6-H), 7.38 – 7.35 (2H, m, Ar-H), 7.32 – 7.31 (1H, m, Ar-H), 7.04 – 7.00 (1H, m, Ar-H), 3.82 (3H, s, O-Me), 2.16 (4H, t, J = 7.2 Hz, CH_2), 1.48 (4H, sxt, J = 7.2 Hz, CH_2), 0.90 (6H, t, J = 7.2 Hz, CH_3). δ_c: 159.96 (q C), 138.68 (q C), 133.45 (CH), 133.20 (q C), 133.06 (q C), 130.00 (CH), 129.50 (CH), 124.87 (CH), 123.48 (CH), 121.14 (CH), 116.55 (CH), 115.38 (CH), 87.17 (q C), 76.88* (q C), 57.77 (q C), 55.38 (CH_3), 21.59 (CH_2), 20.71 (CH_2), 13.43 (CH_3).

ν_{max}/cm^{-1}: 2965 m (Ar-H), 2934 w (CH_2, CH_3), 2872 w (CH_2, CH_3), 2237 w (C≡C), 1597 s (C≡C), 1486 s (CH_2), 1303 s (SO_2), 1038 s (SO_2).

*Overlapping with the CDCl_3 signal

3,3-Di(pent-1-yn-1-yl)-2-(thiophen-3-yl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide
(2.59Gb)
From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-N-(thiophen-3-yl)benzenesulfonamide (Method B: 2.49 mmol). Flash column chromatography (10% EtOAc – pet ether) to give the title compound as red oil (Method B: 0.47 g, 49%); HRMS found [M+H]+ = 384.1090; C_{21}H_{22}NO_{2}S_{2} [M+H]+ requires = 384.1096.

δH (CDCl3) 7.83 (1H, app. d, 7-H), 7.78 (1H, app. d, 4-H), 7.73 – 7.69 (2H, m, 5-H, Ar-H), 7.60 (1H, td, J = 7.8, 1.1 Hz, 6-H), 7.46 – 7.44 (1H, m, Ar-H), 7.39 – 7.37 (1H, m, Ar-H), 2.16 (4H, t, J = 7.2 Hz, CH_{2}), 1.48 (4H, sxt, J = 7.2 Hz, CH_{2}), 0.90 (6H, t, J = 7.2 Hz, CH_{3}). δc 138.44 (qC), 133.60 (CH), 132.70 (qC), 130.05 (CH), 129.93 (qC), 127.22 (CH), 124.88 (CH), 124.68 (CH), 123.71 (CH), 121.19 (CH), 86.98 (qC), 76.76* (qC), 57.58 (qC), 21.59 (CH_{2}), 20.67 (CH_{2}), 13.41 (CH_{3}).

νmax/cm⁻¹: 2962 w (Ar-H), 2932 w (CH_{2}, CH_{3}), 2872 w (CH_{2}, CH_{3}), 1453 w (CH_{2}), 1306 s (SO_{2}), 1174 s (SO_{2}).

*Overlapping with CDCl₃ signal

2-(Naphthalen-2-yl)-3,3-bis(phenylethynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (2.59Ha)

From 2-(3-hydroxy-1,5-diphenylpenta-1,4-diy-3-yl)-N-(naphthalen-2-yl)benzenesulfonamide (Method B: 1.95 mmol). Flash column chromatography (toluene) to give the title compound as a brown foam (Method B: 0.41 g, 43%) m.p. 82 – 83 °C; HRMS found [M+Na]+ = 518.1178; C_{33}H_{21}NO_{2}SNa [M+Na]+ requires = 518.1191.

δH [(CD_{3})_{2}CO] 8.51 (1H, d, J = 1.9 Hz, Ar-H), 8.22 (1H, app. d, 7-H), 8.16 (1H, app. d, 4-H), 8.11 – 8.09 (2H, m, Ar-H), 8.06 – 7.99 (3H, m, Ar-H, 5-H, 6-H), 7.92 (1H, td, J = 7.6, 1.0 Hz, Ar-H), 7.68 – 7.61 (2H, m, Ar-H), 7.51 – 7.48 (4H, m, Ph-H, Ar-H), 7.47 – 7.38 (6H, m, Ph-H). δc 137.06 (qC), 134.38 (CH), 133.67 (qC), 133.62 (qC), 133.55 (qC), 131.69 (CH), 131.29 (CH), 131.23 (CH), 129.99 (qC), 129.61 (CH), 129.02 (CH), 128.78 (CH), 128.68 (CH), 128.23 (CH),
$127.82 \text{ (CH)}, 127.36 \text{ (CH)}, 126.80 \text{ (CH)}, 125.52 \text{ (CH)}, 121.32 \text{ (qC)}, 120.97 \text{ (qC)}, 86.37 \text{ (qC)}, 84.71 \text{ (qC)}, 58.54 \text{ (qC)}.$

$\nu_{\text{max}}/\text{cm}^{-1}$: 2228 m ($\text{C} \equiv \text{C}$), 1595 w ($\text{C} = \text{C}$), 1309 s ($\text{SO}_2$), 1174 s ($\text{SO}_2$), 752 s ($\text{Ph}-\text{H}$), 688 s ($\text{Ph}-\text{H}$).

2-{(Naphthalen-2-yl)-3,3-di(pent-1-yn-1-yl)-2,3-dihydro-1,2-benzothiazole 1,1-dioxide (2.59Hb)}

From 2-{(6-hydroxyundeca-4,7-diyn-6-yl)-N-(naphthalen-2-yl)benzenesulfonamide (Method B: 2.24 mmol). Flash column chromatography (toluene) to give the title compound as a grey powder (Method B: 0.43 g, 45%) m.p. 93 – 94 °C; HRMS found [M+H]$^+$ = 428.1678; $\text{C}_{27}\text{H}_{26}\text{NO}_2\text{S} [\text{M+H}]^+$ requires = 428.1686.

$\delta_H (\text{CD}_2\text{Cl}_2)$ 8.33 (1H, app. s, Ar-H), 7.98 – 7.92 (3H, m, 4-H, Ar-H), 7.85 – 7.74 (4H, m, Ar-H, 7-H, 5-H), 7.65 (1H, td, $J = 7.7$, 1.0 Hz, 6-H), 7.60 – 7.53 (2H, m, Ar-H), 2.17 (4H, t, $J = 7.2$ Hz, CH$_2$), 1.48 (4H, sxt, $J = 7.2$ Hz, CH$_2$), 0.89 (6H, t, $J = 7.2$ Hz, CH$_3$). $\delta_C$ 138.53 (qC), 133.65 (CH), 133.41 (qC), 133.35 (qC), 133.11 (qC), 130.84 (CH), 130.26 (CH), 129.76 (qC), 128.71 (CH), 128.56 (CH), 128.26 (CH), 127.66 (CH), 127.04 (CH), 126.45 (CH), 125.05 (CH), 120.94 (CH), 87.53 (qC), 76.80 (qC), 58.03 (qC), 21.77 (CH$_2$), 20.54 (CH$_2$), 13.18 (CH$_3$).

$\nu_{\text{max}}/\text{cm}^{-1}$: 2961 w (Ar-H), 2932 w (CH$_2$, CH$_3$), 2871 w (CH$_2$, CH$_3$), 1511 w (Ar-H), 1463 w (CH$_2$), 1311 s (SO$_2$), 1164 s (SO$_2$).
6.2.11 General Method for the Synthesis of 1,2-Benzisothiazolo[2,3-a]quinoline 11,11-dioxides

Method A: To a solution of 3-[2-{aminosulfamoyl}phenyl]penta-1,4-diyn-3-ols derivative (1 equiv.) in MeCN (38.3 mL/mmol) was added ICl (3 equiv.) and the mixture stirred at the temperature and time indicated in Table 6.4. After this time the reaction mixture was quenched with aqueous sodium thiosulfate. The organic phase was separated, dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography.

Method B: To a solution of 3,3-di(alkynyl)-N-(substituted)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (1 equiv.) in MeCN (38.3 mL/mmol) was added ICl (3 equiv.) and the mixture stirred at the temperature and time indicated in Table 6.5. After this time the reaction mixture was quenched with aqueous sodium thiosulfate. The organic phase was separated, dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R¹</th>
<th>Dialkynol</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Tetracycle</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tolyl</td>
<td>Ph</td>
<td>2.23Ba</td>
<td>24</td>
<td>82</td>
<td>2.66a-3</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>Tolyl</td>
<td>C₃H₇</td>
<td>2.23Bb</td>
<td>3.5</td>
<td>r.t.</td>
<td>2.66b-3</td>
<td>33</td>
</tr>
</tbody>
</table>

Table 6.4 Cyclisation of dialkynols 2.23Ba – Bb with ICl
mixture was quenched with aqueous sodium thiosulfate. The organic phase was separated, dried (Na\textsubscript{2}SO\textsubscript{4}) and evaporated. The residue was purified by flash column chromatography.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{3}</th>
<th>1,2-Benzothiazole</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Tetracycle</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>4-Me</td>
<td>2.59Ba</td>
<td>24</td>
<td>82</td>
<td>2.66a-3</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>C\textsubscript{3}H\textsubscript{7}</td>
<td>4-Me</td>
<td>2.59Bb</td>
<td>3.5</td>
<td>r.t.</td>
<td>2.66b-3</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>C\textsubscript{3}H\textsubscript{7}</td>
<td>3-OMe</td>
<td>2.59Eb</td>
<td>1</td>
<td>82</td>
<td>2.71b-2</td>
<td>41</td>
</tr>
</tbody>
</table>

Table 6.5 Results of iodocyclisation of 3,3-di(alkynyl)-1,2-benzothiazole 1,1-dioxide 2.59Ba – Eb

6-iodo-3-methyl-5-phenyl-6a-(phenylethynyl)-6aH-1,2-benzothiazolo[2,3-a]quinoline 11,11-dioxide (2.66a-3)

From 2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-N-(p-tolyl)benzenesulfonamide (Method A: 1.26 mmol, entry 1, Table 5.4) from flash column chromatography (12% EtOAc – pet ether). From 3,3-bis(phenylethynyl)-2-(p-tolyl)-2,3-dihydro-1,2-benzoisothiazole 1,1-dioxide (Method B: 0.44 mmol, entry 1, Table 5.5). To give the title compound as a beige powder m.p. 96 – 98 °C; HRMS found [M+H]\textsuperscript{+} = 586.0328; C\textsubscript{30}H\textsubscript{21}INO\textsubscript{2}S [M+H]\textsuperscript{+} requires = 586.0330.

\(\delta\textsubscript{H}(\text{CDCl}_3)\) 8.23 (1H, app. d, 7-H), 7.90 (1H, app. d, 10-H), 7.77 (1H, app. t, 8-H), 7.68 – 7.61 (2H, m, 9-H, Ar-H), 7.54 – 7.50 (1H, m, Ar-H), 7.45 – 7.24* (9H, m, Ar-H), 7.08 – 7.06 (1H, m, Ar-H), 6.68 (1H, app. s, Ar-H), 2.25 (3H, s, Ar-Me). \(\delta\textsubscript{c}\) 144.92 (qC), 142.13 (qC), 138.06 (qC), 137.86 (qC), 133.94 (qC), 132.12 (CH), 130.50 (CH), 130.37 (CH), 130.14 (CH), 130.05 (qC), 129.57 (CH), 129.24 (CH), 128.99 (CH), 128.80 (CH), 128.77 (CH), 128.37 (CH), 128.32 (CH), 128.17 (CH), 127.06 (qC), 125.35 (CH), 121.48 (qC), 121.20 (CH), 101.43 (qC), 86.82 (qC), 83.99 (qC), 64.97 (qC), 21.35 (CH\textsubscript{3}).

\(\nu\textsubscript{max}/\text{cm}^{-1}\): 2980 s (C-H), 2224 w (C≡C), 1486 s (CH\textsubscript{3}), 1319 s (SO\textsubscript{2}), 1173 s (SO\textsubscript{2}), 755 s (Ph-H), 690 s (Ph-H), 573 s (C-I).
*Overlapping with CDCl₃ signal

6-ido-3-methyl-6a-(pent-1-yn-1-yl)-5-propyl-6aH-1,2-benzothiazolo[2,3-a]quinoline 11,11-dioxide (2.66b-3)

From 2-(6-hydroxyundeca-4,7-diyln-6-y1)-N-(p-tolyl)benzenesulfonamide (Method A: 2.56 mmol, entry 2, Table 5.4) from flash column chromatography (20% ether – pet ether). From 3,3-di(pent-1-yn-1-yl)-2-(p-tolyl)-2,3-dihydro-1,2-benzothiazole 1,1-dioxide (Method B: 1.53 mmol, entry 2, Table 5.5). To give the title compound as an orange oil; HRMS found [M+H]⁺ = 518.0644; C₂₅H₂₅INO₂S [M+H]⁺ requires = 518.0652.

δH (CDCl₃) 8.12 (1H, app. d, 7-H), 7.81 (1H, app. d, 10-H), 7.77 (1H, td, J = 7.7, 1.1 Hz, 8-H), 7.61 (1H, td, J = 7.7, 1.1 Hz, 9-H), 7.54 (1H, d, J = 8.0 Hz, Ar-H), 7.35 (1H, app. s, Ar-H), 7.24 (1H, d, J = 8.0 Hz, Ar-H), 2.79 (2H, t, J = 7.5 Hz, CH₂), 2.44 (3H, s, Ar-Me), 2.09 (2H, t, J = 7.0 Hz, CH₂), 1.67 – 1.49 (2H, m, CH₂), 1.42 (2H, sxt, J = 7.5 Hz, CH₂), 0.99 (3H, t, J = 7.5 Hz, CH₃), 0.85 (3H, t, J = 7.0 Hz, CH₃). δc 140.95 (q C), 138.90 (q C), 137.65 (q C), 133.98 (q C), 131.78 (CH), 130.18 (CH), 130.04 [2 X C (CH)], 127.56 (q C), 128.62 (q C), 125.82 (CH), 125.74 (CH), 120.99 (CH), 101.75 (q C), 87.91 (q C), 75.60 (q C), 64.72 (q C), 40.09 (CH₂), 21.66 (CH₂), 21.64 (CH₃), 21.33 (CH₂), 20.75 (CH₂), 13.84 (CH₃), 13.25 (CH₃).

νmax/cm⁻¹: 2960 m (Ar-H), 2930 m (CH₂, CH₃), 2871 m (CH₂, CH₃), 2260 w (C≡C), 1489 s (C=C), 1453 w (CH₃), 1316 s (SO₂), 1175 s (SO₂), 572 (C-I).

6-ido-2-methoxy-6a-(pent-1-yn-1-yl)-5-propyl-6aH-1,2-benzothiazolo[2,3-a]quinoline 11,11-dioxide (2.71b-2)
From 2-(3-methoxyphenyl)-3,3-di(pent-1-yn-1-yl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (Method B: 0.58 mmol, entry 3, Table 5.5) from flash column chromatography (15% EtOAc – pet ether) to give the title compound as a white powder; HRMS found [M+H]^+ = 534.0595; C_{24}H_{25}INO_3S [M+H]^+ requires = 534.0602.

δ_H (CDCl_3) 8.13 (1H, app. d, 7-H), 7.82 (1H, app. d, 10-H), 7.74 (1H, app. t, 8-H), 7.62 (1H, app. t, 9-H), 7.47 (1H, d, J = 8.8 Hz, Ar-H), 7.20 (1H, d, J = 2.6 Hz, Ar-H), 6.91 (1H, dd, J = 8.8, 2.6 Hz, Ar-H), 3.89 (3H, s, O-Me), 2.76 (2H, t, J = 7.7 Hz, CH_2), 2.10 (2H, t, J = 7.0 Hz, CH_2), 1.64 – 1.39 (4H, m, CH_2), 0.97 (3H, t, J = 7.3 Hz, CH_3), 0.85 (3H, t, J = 7.0 Hz, CH_3). δ_c 160.17 (q-C), 140.71 [2 X C (q-C)], 138.79 (q-C), 133.89 (q-C), 131.83 (CH), 130.18 (CH), 130.04 (CH), 126.54 (CH), 121.90 (q-C), 120.93 (CH), 114.16 (CH), 110.34 (CH), 97.83 (q-C), 87.65 (q-C), 75.83 (q-C), 64.71 (q-C), 55.66 (CH_3), 40.14 (CH_2), 21.66 (CH_2), 21.34 (CH_2), 20.74 (CH_2), 13.78 (CH_3), 13.23 (CH_3).

ν_max/cm⁻¹: 2959 m (Ar-H), 2929 m (CH_2, CH_3), 2870 m (CH_2, CH_3), 1586 s (C=C), 1462 s (CH_2, CH_3), 1316 s (SO_2), 1174 s (SO_2), 557 (C-I).
6.3 Chapter 3 Experimental

6.3.1 General Method for the Synthesis of 4-Alkynyl-3-iodo-quinolines

Method A

\[ \text{R and R'} \]

as defined in Table 6.6

\[
\begin{align*}
\text{HO} & \quad \equiv \quad \equiv \\
& \quad \text{R'}
\end{align*}
\]

2.5 - 2.8a, 2.5c

\[
\begin{align*}
\text{N} & \quad \equiv \\
& \quad \text{O}_\text{S}\text{O}_{\text{S}}
\end{align*}
\]

Method B

\[ \text{R and R'} \]

as defined in Table 6.6

\[
\begin{align*}
\text{HO} & \quad \equiv \quad \equiv \\
& \quad \text{R'}
\end{align*}
\]

2.5 - 2.7b and 2.5d, g, j, k

Scheme 6.4

Method A: To a solution of \( N\)-[2-(3-hydroxy-1,5-disubstituted-1,4-diyn-3-yl)phenyl]-4-benzenesulfonamide derivative (1.0 equiv.) in MeCN (38.3 mL/mmol) was added ICl (2.0 equiv.) in MeCN and the mixture stirred at r.t. for the time indicated in Table 6.6. After this time the reaction mixture was quenched with aqueous sodium thiosulfate. The organic phase was separated, dried (\( \text{Na}_2\text{SO}_4\)) and evaporated. The residue was purified by flash column chromatography or washed with cold hexane.

Method B: To a solution of \( N\)-[2-(3-hydroxy-1,5-disubstituted-1,4-diyn-3-yl)phenyl]-4-benzenesulfonamide derivative (1.0 equiv.) in MeOH (38.3 mL/mmol) was added I\(_2\) (3.0 equiv.) and stirred at 65 °C for the time indicated in Table 5.6. After this time the reaction mixture was concentrated and diluted with EtOAc and quenched with aqueous sodium thiosulfate. The organic phase was separated, dried (\( \text{Na}_2\text{SO}_4\)) and evaporated. The residue was purified by flash column chromatography.
<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R¹</th>
<th>Dialkynol</th>
<th>Method</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Ph</td>
<td>2.5a</td>
<td>A</td>
<td>1.0</td>
<td>3.2a</td>
<td>60</td>
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<tr>
<td>2</td>
<td>Me</td>
<td>C₃H₇</td>
<td>2.5b</td>
<td>B</td>
<td>1.0</td>
<td>3.2b</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>4-OMeC₆H₄</td>
<td>2.5c</td>
<td>A</td>
<td>1.0</td>
<td>3.2c</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>C₄H₉</td>
<td>2.5d</td>
<td>B</td>
<td>1.5</td>
<td>3.2d</td>
<td>63</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>Me</td>
<td>2.5g</td>
<td>B</td>
<td>2.25</td>
<td>3.2g</td>
<td>26</td>
</tr>
<tr>
<td>8</td>
<td>OMe</td>
<td>Ph</td>
<td>2.6a</td>
<td>A</td>
<td>1.0</td>
<td>3.2a</td>
<td>63</td>
</tr>
<tr>
<td>9</td>
<td>OMe</td>
<td>C₃H₇</td>
<td>2.6b</td>
<td>B</td>
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<td>3.2b</td>
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</tr>
<tr>
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<td>Ph</td>
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<td>A</td>
<td>1.0</td>
<td>3.2a</td>
<td>32</td>
</tr>
<tr>
<td>11</td>
<td>NO₂</td>
<td>C₃H₇</td>
<td>2.7b</td>
<td>B</td>
<td>19.0</td>
<td>3.2b</td>
<td>12</td>
</tr>
<tr>
<td>12</td>
<td>H</td>
<td>Ph</td>
<td>2.8a</td>
<td>A</td>
<td>2.0</td>
<td>3.2a</td>
<td>41</td>
</tr>
</tbody>
</table>

**Table 6.6** Iodocyclisations of dialkynols 2.5 – 2.8 results. a = 3,6-diiodo-2-phenyl-4-(phenylethynyl)quinoline 3.4a also isolated.

3-Iodo-2-phenyl-4-(phenylethynyl)quinoline (3.2a)

From entries; 1, 8, 10 and 12 (Table 6.6). From column chromatography (5% ether – hexane) resultant material recrystallised from EtOH – EtOAc to give the title compound as off-white needle-like crystals m.p. 149 – 150 °C; HRMS found [M+H]+ = 432.0245 C₂₃H₁₅I₂N requires [M+H]+ = 432.0244.

δH (CDCl₃) 8.41 (1H, app. d, 5-H), 8.13 (1H, app. d, 8-H), 7.80 – 7.75 (3H, m, Ar-H), 7.66 – 7.62 (3H, m, Ar-H), 7.53 – 7.44 (6H, m, Ph-H). δc 161.77 (qC), 146.60 (qC), 143.27 (qC), 137.60 (qC), 132.04 (CH), 130.52 (CH), 129.82 (CH), 129.74 (CH), 129.21 (CH), 128.76 (CH), 128.66 (CH), 128.05 (CH), 127.96 (CH), 127.56 (qC), 126.30 (CH), 122.17 (qC), 102.29 (qC), 99.21 (qC), 89.70 (qC).

υmax/cm⁻¹: 2217 w (C≡C), 1580 s (C=C), 756 s (Ph), 690 s (Ph), 543 s (C-I).

314
2-Phenyl-4-(phenylethynyl)quinoline (2.35a)

From flash column chromatography (5% ether – hexane) to give the title compound as a pale yellow solid (0.04 g, 6%) m.p. 100 °C; HRMS found [M+H]^+ = 306.1285; C_{23}H_{16}N [M+H]^+ requires = 306.1204.

δH (CDCl3) 8.37 (1H, dd, J = 8.3, 0.9 Hz, 5-H), 8.21 – 8.17 (3H, m, Ar-H), 8.08 (1H, s, 3-H), 7.79 – 7.75 (1H, m, 7-H), 7.72 – 7.69 (2H, m, Ph-H), 7.66 – 7.60 (1H, m, 6-H), 7.57 – 7.43 (6H, m, Ph-H). δc 156.91 (q-C), 148.23 (q-C), 139.20 (q-C), 132.00 (CH), 130.41 (q-C), 130.13 (CH), 130.11 (CH), 129.54 (CH), 129.35 (CH), 128.91 (CH), 128.62 (CH), 127.53 (CH), 126.91 (CH), 126.62 (q-C), 125.76 (CH), 122.34 (q-C), 121.69 (CH), 98.16 (q-C), 85.48 (q-C).

ν_{max}/\text{cm}^{-1}: 3055 w (Ar-H), 2216 m (C≡C), 1597 s (C=C), 756 s (Ph-H), 690 s (Ph-H).

3,6-Diiodo-2-phenyl-4-(phenylethynyl)quinoline (3.4a)

From entry 10 (Table 6.6). From flash column chromatography (5% EtOAc – hexane) to give the title compound as white needles (0.05 g, 18%) m.p. 245 – 246 °C; HRMS found [M+H]^+ = 557.9207; C_{23}H_{14}I_{2}N [M+H]^+ requires = 557.9210.

δH (CDCl3) 8.75 (1H, d, J = 1.9 Hz, 5-H), 8.00 (1H, dd, J = 8.8, 1.9 Hz, 7-H), 7.82 (1H, d, J = 8.8 Hz, 8-H), 7.78 – 7.75 (2H, m, Ph-H), 7.63 – 7.60 (2H, m, Ph-H), 7.53 – 7.45 (6H, m, Ph-H). δc 162.36 (q-C), 145.57 (q-C), 142.93 (q-C), 139.33 (CH), 136.48 (q-C), 135.17 (CH), 132.11 (CH), 125.76 (CH), 122.34 (q-C), 121.69 (CH), 98.16 (q-C), 85.48 (q-C).
131.39 (CH), 129.96 (CH), 129.11 (CH), 128.94 (CH), 128.80 (qC), 128.71 (CH), 128.08 (CH), 121.86 (qC), 102.90 (qC), 100.03 (qC), 94.01 (qC), 89.23 (qC).

ν_{max}/cm^{-1}: 3061 w (Ar-H), 2205 m (C≡C), 1590 w (C=C), 759 s (Ph), 687 s (Ph), 534 m (C-I), 528 m (C-I).

3-Iodo-4-(pent-1-yn-1-yl)-2-propylquinoline (3.2b)

From entries: 2, 9 and 11 (Table 6.6). Flash column chromatography (6% EtOAc – hexane) to give the title compound as a yellow oil; HRMS found [M+H]^+ = 364.0565; C_{17}H_{19}I[N [M+H]^+ requires = 364.0557.

δ_{H} (CDCl3) 8.21 (1H, app. d, 5-H), 7.98 (1H, app. d, 8-H), 7.69 (1H, app. t, 7-H), 7.51 (1H, app. t, 6-H), 3.21 – 3.17 (2H, m, CH2), 2.65 (2H, t, J = 7.3 Hz, CH2), 1.92 – 1.76 (4H, m, CH2), 1.18 (3H, t, J = 7.3 Hz, CH3), 1.08 (3H, t, J = 7.3 Hz, CH3). δ_{C} 162.53 (qC), 146.48 (qC), 137.76 (qC), 129.97 (CH), 128.93 (CH), 127.53 (qC), 126.90 (CH), 126.42 (CH), 104.76 (qC), 100.69 (qC), 81.27 (qC), 44.98 (CH2), 22.51 (CH2), 22.07 (CH2), 21.94 (CH2), 14.09 (CH3), 13.87 (CH3).

ν_{max}/cm^{-1}: 3058 w (Ar-H), 2957 m (CH2, CH3), 2927 m (CH2, CH3), 2869 m (CH2, CH3), 2217 w (C=C), 1582 w (C=C), 602 w (C-I).

3-Iodo-2-(4-methoxyphenyl)-4-[(4-methoxyphenyl)ethynyl]quinoline (3.2c)

δ_{H} (CDCl3) 8.21 (1H, app. d, 5-H), 7.98 (1H, app. d, 8-H), 7.69 (1H, app. t, 7-H), 7.51 (1H, app. t, 6-H), 3.21 – 3.17 (2H, m, CH2), 2.65 (2H, t, J = 7.3 Hz, CH2), 1.92 – 1.76 (4H, m, CH2), 1.18 (3H, t, J = 7.3 Hz, CH3), 1.08 (3H, t, J = 7.3 Hz, CH3). δ_{C} 162.53 (qC), 146.48 (qC), 137.76 (qC), 129.97 (CH), 128.93 (CH), 127.53 (qC), 126.90 (CH), 126.42 (CH), 104.76 (qC), 100.69 (qC), 81.27 (qC), 44.98 (CH2), 22.51 (CH2), 22.07 (CH2), 21.94 (CH2), 14.09 (CH3), 13.87 (CH3).

ν_{max}/cm^{-1}: 3058 w (Ar-H), 2957 m (CH2, CH3), 2927 m (CH2, CH3), 2869 m (CH2, CH3), 2217 w (C=C), 1582 w (C=C), 602 w (C-I).
From entry 3 (Table 6.6). From flash column chromatography (10% EtOAc – pet ether) to give the title compound as yellow needles m.p. 163 – 165 °C; HRMS found [M+H]^+ = 492.0448; C\textsubscript{25}H\textsubscript{19}INO\textsubscript{2} [M+H]^+ requires = 492.0455.

δ\textsubscript{H} (CDCl\textsubscript{3}) 8.38 (1H, dd, J = 7.6, 0.7 Hz, 5-H), 8.10 (1H, app. d, 8-H), 7.78 – 7.34 (1H, m, 7-H), 7.72 – 7.68 (2H, m, o-Ar-H), 7.63 – 7.59 (3H, m, Ar-H, 6-H), 7.04 – 7.01 (2H, m, Ar-H), 6.98 – 6.95 (2H, m, Ar-H), 3.89 (3H, s, O-Me), 3.88 (3H, s, O-Me). δ\textsubscript{c} 160.81 (q C), 159.96 (q C), 146.65 (q C), 137.95 (q C), 135.98 (q C), 133.68 (CH), 130.77 (CH), 130.36 (CH), 129.69 (CH), 127.63 (CH), 127.27 (q C), 126.36 (CH), 114.33 (CH), 113.35 (CH), 102.76 (q C), 99.21 (q C), 89.06 (q C), 55.45 (CH\textsubscript{3}), 55.39 (CH\textsubscript{3}).

v\textsubscript{max}/cm\textsuperscript{-1}: 3058 w (Ar-H), 2833 s (CH\textsubscript{3}), 2209 s (C≡C), 1605 s (C=C), 1339 s (CH\textsubscript{3}).

2-Butyl-4-(hex-1-yn-1-yl)-3-idoquinoline (3.2d)

From entry 4 (Table 6.6). From flash column chromatography (2% ether – hexane) to give the title compound as a brown oil; HRMS found [M+H]^+ = 392.0882; C\textsubscript{19}H\textsubscript{23}IN [M+H]^+ requires = 392.0870.

δ\textsubscript{H} (CDCl\textsubscript{3}) 8.20 (1H, app. d, 5-H), 7.97 (1H, app. d, 8-H), 7.69 (1H, app. t, 7-H), 7.51 (1H, app. t, 6-H), 3.26 – 3.19 (2H, m, CH\textsubscript{2}), 2.67 (2H, t, J = 7.0 Hz, CH\textsubscript{2}), 1.83 – 1.72 (4H, m, CH\textsubscript{2}), 1.66 – 1.45 (6H, m, CH\textsubscript{2}), 1.10 – 0.96 (6H, m, CH\textsubscript{3}). δ\textsubscript{c} 162.75 (q C), 146.56 (q C), 137.74 (q C), 129.93 (CH), 128.95 (CH), 127.51 (q C), 126.85 (CH), 126.41 (CH), 104.84 (q C), 100.65 (q C), 81.13 (q C), 42.89 (CH\textsubscript{2}), 31.24 (CH\textsubscript{2}), 30.44 (CH\textsubscript{2}), 22.76 (CH\textsubscript{2}), 22.20 (CH\textsubscript{2}), 19.76 (CH\textsubscript{2}), 14.02 (CH\textsubscript{3}), 13.67 (CH\textsubscript{3}).

v\textsubscript{max}/cm\textsuperscript{-1}: 2954 m (CH\textsubscript{2}, CH\textsubscript{3}), 2926 m (CH\textsubscript{2}, CH\textsubscript{3}), 2870 w (CH\textsubscript{2}, CH\textsubscript{3}), 1562 w (C=C), 627 m (C-I).
3-Iodo-2-methyl-4-(prop-1-yn-1-yl)quinoline (3.2g)

From entry 5 (Table 6.6). Flash column chromatography (5% EtOAc – hexane) to give the title compound as a yellow solid m.p. 90 °C decomp; HRMS found [M+H]^+ = 307.9938; C_{13}H_{11}IN [M+H]^+ requires = 307.9931.

δ^H (CDCl₃) 8.23 – 8.20 (1H, m, 5-H), 7.96 (1H, app. d, 8-H), 7.72 – 7.67 (1H, m, 7-H), 7.54 – 7.49 (1H, m, 6-H), 2.97 (3H, s, Me), 2.32 (3H, s, Me). δ^C 159.73 (qC), 146.43 (qC), 137.47 (qC), 130.05 (qC), 128.76 (CH), 127.45 (CH), 126.91 (CH), 126.39 (CH), 100.64 (qC), 100.41 (qC), 80.03 (qC), 31.33 (CH₃), 5.14 (CH₃).

ν\text{max}/\text{cm}^{-1}: 2981 s (Ar-H), 2911 m (CH₃), 2217 w (C≡C), 1564 w (C=C), 1484 s (CH₃), 640 s (C-I).

6.3.2 General Method for the Synthesis of 4-Alkynyl-3-iodo-quinolines from Unsymmetrical Dialkynols

Method A: To a solution of N-[2-(3-hydroxy-1,5-disubstituted-1,4-diyln-3-yl)phenyl]-4-benzenesulfonamide derivative (1 equiv.) in MeCN (38.3 mL/mmol) was added ICl (2 equiv.) in MeCN and the mixture stirred at r.t. for the time indicated in Table 6.7. After this time the reaction mixture was quenched with aqueous sodium thiosulfate. The organic phase was separated, dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography or washed with cold hexane.

Method B: To a solution of N-[2-(3-hydroxy-1,5-disubstituted-1,4-diyln-3-yl)phenyl]-4-benzenesulfonamide derivative (1 equiv.) in MeOH (38.3 mL/mmol) was added I₂ (3 equiv.) and stirred at 65 °C for the times indicated in Table 6.7. After this time the reaction mixture was concentrated, diluted with EtOAc and quenched with aqueous sodium thiosulfate. The organic phase was separated, dried (Na₂SO₄) and evaporated. The residue was purified by flash column chromatography.
Scheme 6.5

Table 6.7 Results of iodoncyclisations of unsymmetrical dialkynols 2.20

<table>
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<tr>
<th>Entry</th>
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<th>R²</th>
<th>Dialkynol</th>
<th>Method</th>
<th>Time (h)</th>
<th>Quinoline</th>
<th>Product -X yield</th>
<th>Quinoline</th>
<th>Product -Y yield</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Ph</td>
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</tr>
<tr>
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<td>A</td>
<td>0.75</td>
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<td>3.5Aj-Y</td>
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</tr>
<tr>
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<td>28</td>
<td>3.5Cb-Y</td>
<td>0</td>
</tr>
</tbody>
</table>
3-Iodo-4-(pent-1-yn-1-yl)-2-phenylquinoline (3.5Ab-X)

From entries; 1 and 2 (Table 6.7). From flash column chromatography (5% ether – hexane) to give the title compound as an orange paste; HRMS found [M+H]⁺ = 398.0400; C₂₀H₁₇lN [M+H]⁺ requires = 398.0407.

δH (CDCl₃) 8.30 (1H, dd, J = 8.3, 0.9 Hz, 5-H), 8.09 (1H, app. d, 8-H), 7.76 – 7.72 (1H, m, 6-H), 7.61 – 7.57 (3H, m, Ph-H), 7.51 – 7.45 (3H, m, Ph-H, 7-H), 2.67 (2H, t, J = 7.1 Hz, CH₂), 1.81 (2H, sxt, J = 7.1 Hz CH₂), 1.18 (3H, t, J = 7.1 Hz, CH₃). δC 161.73 (qC), 146.50 (qC), 143.44 (qC), 138.44 (qC), 130.33 (CH), 129.67 (CH), 129.15 (CH), 128.65 (CH), 127.99 (CH), 127.93 (qC), 127.73 (CH), 126.48 (CH), 105.19 (qC), 99.05 (qC), 81.39 (qC), 22.11 (CH₂), 21.92 (CH₂), 13.83 (CH₃).

νmax/cm⁻¹: 3056 w (Ar-H), 2956 m (CH₂, CH₃), 2928 m (CH₂, CH₃), 2869 m (CH₂, CH₃), 2210 m (C≡C), 1596 w (C=C), 756 s (Ph-H), 688 s (Ph-H), 584 w (C-I).

3-Iodo-4-(phenylethynyl)-2-propylquinoline (3.5Ab-Y)

From entries; 1 and 2 (Table 6.7). From flash column chromatography (5% Ether – hexane) to give the title compound as a yellow solid. m.p. 107 – 108 °C; HRMS found [M+H]⁺ = 398.0406; C₂₀H₁₇lN [M+H]⁺ requires = 398.0400.

δH (CDCl₃) 8.33 (1H, app. d, 5-H), 8.04 (1H, app. d, 8-H), 7.78 – 7.73 (3H, m, Ph-H, 6-H), 7.58 (1H, app. t, 7-H), 7.48 – 7.47 (3H, m, Ph-H), 3.27 – 3.23 (2H, m, CH₂), 1.90 (2H, sxt, J = 7.3 Hz
(CH2), 1.12 (3H, t, J = 7.3 Hz, CH3). δc 162.60 (qC), 146.60 (qC), 136.87 (qC), 131.96 (CH), 130.14 (CH), 130.62 (CH), 129.11 (CH), 128.63 (CH), 127.12 (CH), 126.23 (CH), 122.26 (qC), 102.93 (qC), 100.85 (qC), 89.57 (qC), 44.91 (CH2), 22.51 (CH2), 14.09 (CH3).

νmax/cm⁻¹: 2955 m (CH2, CH3), 2869 w (CH2, CH3), 2210 m (C≡C), 1595 w (C=C), 781 s (Ph-H), 688 s (Ph-H), 603 m (C-I).

3-Iodo-2-(4-methoxyphenyl)-4-(phenylethynyl)quinoline (3.5Ac-Y)

From entry 3 (Table 6.7). From washing the precipitate, obtained in the crude product, with cold hexane, to give the title compound as yellow needles (0.29 g, 32%) m.p. 125 – 126 °C; HRMS found [M+H]+ = 462.0356; C25H19INO2 [M+H]+ requires = 462.0349.

δH (CDCl3) 8.38 (1H, app. d, 5-H), 8.10 (1H, app. d, 8-H), 7.77 – 7.75 (3H, m, 7-H, Ph-H), 7.62 – 7.60 (3H, m, o-Ar-H, 6-H), 7.45 – 7.44 (3H, m, Ph-H), 7.02 (2H, d, J = 8.5 Hz, m-Ar-H), 3.89 (3H, s, O-Me). δc 161.31 (qC), 159.99 (qC), 146.65 (qC), 137.56 (qC), 135.77 (qC), 131.98 (CH), 130.75 (CH), 130.39 (CH), 129.72 (CH), 129.66 (CH), 128.61 (CH), 127.73 (CH), 127.32 (qC), 126.24 (CH), 122.19 (qC), 113.34 (CH), 102.10 (qC), 99.56 (qC), 89.78 (qC), 55.36 (CH3).

νmax/cm⁻¹: 3061 w (Ar-H), 2980 w (Ar-H), 2840 w (CH3), 2206 m (C≡C), 1607 s (C=C), 752 s (Ph-H), 708 s (Ph-H), 521 s (C-I).

3-Iodo-2-phenyl-4-(prop-1-yn-1-yl)quinoline (3.5Ag-X)
From entry 4 (Table 5.7). From using Biotage Isolera 4 (SNAP Ultra 10g cartridge, EtOAc – pet ether 10% → 100%) to give the title compound as a beige solid (0.007 g, 8%); HRMS found [M+H]^+ = 370.0098; C_{18}H_{13}IN [M+H]^+ requires = 370.0087.

δ_{H} (CDCl_{3}) 8.33 (1H, dd, J = 8.2, 0.8 Hz, 5-H), 8.11 (1H, app. d, 8-H), 7.79 – 7.75 (1H, m, 7-H), 7.63 – 7.59 (3H, m, Ph-H), 7.53 – 7.46 (3H, m, 6-H, Ph-H), 2.36 (3H, s, Me). δ_{C} 161.72 (qC), 146.51 (qC), 143.41 (qC), 138.39 (qC), 131.99 (qC), 130.35 (CH), 129.88 (qC), 129.67 (CH), 129.14 (CH), 128.66 (CH), 127.99 (CH), 127.73 (CH), 126.48 (CH), 100.70 (qC), 98.97 (qC), 80.43 (qC), 5.18 (CH_{3}).

3-iodo-2-methyl-4-(phenylethynyl)quinoline (3.5Ag-Y)

From entry 4 (Table 6.7). From using Biotage Isolera 4 (SNAP Ultra 10g cartridge, EtOAc – pet ether 10% → 100%) to give the title compound as a beige solid (0.015 g, 17%); HRMS found [M+H]^+ = 370.0095; C_{18}H_{13}IN [M+H]^+ requires = 370.0087.

δ_{H} (CDCl_{3}) 8.33 (1H, dd, J = 8.3, 0.8 Hz, 5-H), 8.02 (1H, app. d, 8-H), 7.78 – 7.74 (3H, m, Ph-H, 7-H), 7.61 – 7.57 (1H, m, 6-H), 7.49 – 7.45 (3H, m, Ph-H), 3.03 (3H, s, Me). δ_{C} 159.83 (qC), 146.46 (qC), 136.72 (qC), 131.99 (CH), 130.24 (CH), 129.68 (CH), 128.87 (CH), 128.64 (CH), 127.17 (CH), 126.99 (qC), 126.22 (CH), 122.19 (qC), 102.13 (qC), 100.90 (qC), 89.29 (qC), 80.43 (qC), 5.18 (CH_{3}).

4-(3,3-Dimethylbut-1-yn-1-yl)-3-iodo-2-phenylquinoline (3.5Aj-X)
From entry 5 (Table 6.7). From flash column chromatography (5% EtOAc – pet ether) to give the title compound as an orange paste (0.12 g, at 60% purity, 19%); HRMS found [M+H]+ = 412.0558; C21H13IN [M+H]+ requires = 412.0564.

δH (CDCl3) 8.26 (1H, dd, δ = 8.3, 0.8 Hz, 5-H), 8.08 (1H, app. d, δ = 6-H), 7.76 – 7.72 (1H, m, 6-H), 7.61 – 7.45 (6H, m, Ph-H, 7-H), 1.49 (9H, s, Me3). δc 161.71 (qC), 146.49 (qC), 143.47 (qC), 138.28 (qC), 130.31 (CH), 129.63 (CH), 129.14 (CH), 128.93 (qC), 128.64 (CH), 127.99 (CH), 127.72 (CH), 127.69 (qC), 126.45 (CH), 112.93 (qC), 99.30 (qC), 80.17 (qC), 30.66 (CH3).

νmax/cm⁻¹: 3057 w (Ar-H), 2923 s (CH3), 2224 m (C≡C), 1361 m (CH3), 771 s (Ph-H), 695 s (Ph-H), 583 m (C-I)

3-iodo-2-(4-methoxyphenyl)-4-(pent-1-yn-1-yl)quinoline (3.5Cb-X)

From entry 6 (Table 6.7). From using Biotage Isolera 4 (SNAP Ultra 25g cartridge, EtOAc – pet ether 1% → 20%) to give the title compound as a brown oil (0.20 g, 28%); HRMS found [M+H]+ = 428.0512; C21H19INO [M+H]+ requires = 428.0506.

δH (CDCl3) 8.28 (1H, dd, δ = 8.4, 1.0 Hz, 5-H), 8.07 (1H, app. d, δ = 6-H), 7.75 – 7.71 (1H, m, 7-H), 7.59 – 7.55 (3H, m, o-Ar-H, 6-H), 7.03 – 6.99 (2H, m, m-Ar-H), 3.88 (3H, s, O-Me) 2.67 (2H, t, J = 7.3 Hz, CH3), 1.81 (2H, sxt, J = 7.3 Hz, CH2), 1.18 (3H, t, J = 7.3 Hz, CH3). δc 161.30, 159.92 (qC), 146.58 (qC), 138.43 (qC), 135.99 (qC), 130.72 (CH), 130.25 (CH), 129.60 (CH), 127.78 (qC), 127.54 (CH), 126.45 (CH), 113.31 (CH), 105.03 (qC), 99.46 (qC), 81.49 (qC), 55.38 (CH3) 22.11 (CH2), 21.92 (CH2), 13.86 (CH3).

νmax/cm⁻¹: 2959 w (Ar-H), 2930 w (CH2, CH3), 2970 w (CH2, CH3), 2833 w (CH2, CH3), 2217 m (C≡C), 1606 s (C=C), 825 s (An-H), 578 m (C-I)
6.3.3 General Method for the Synthesis of 1,2-Benzothiazine 1,1-dioxides and 1,2-Benzothiazepine 1,1-dioxides

Scheme 6.6

To a solution of 2-(3-hydroxypenta-1,4-diyn-3-yl)-N-(substituted)benzenesulfonamide derivative (1 equiv.) in MeCN (38.3 mL/mmol) was added AgOAc (5 mol %) and the mixture stirred at reflux for the time indicated in Table 5.8. After this time the reaction mixture was allowed to cool, filtered through Celite and evaporated. The residue was purified by flash column chromatography unless otherwise stated. The following were synthesised by this method.
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Table 6.8 Yields from the AgOAc cyclisation of reversed sulfonamides 2.23Aa – Hb. a = 3-(1-Hydroxybutyl)-2-methyl-4-(pent-1-ynyl)-2H-1,2-benzothiazine 1,1-dioxide 3.11Ab also obtained from this reaction. b = yield from ¹H NMR spectrum c = 4-Hydroxy-3-methylene-2-(p-tolyl)-4-[(trimethylsilyl)ethynyl]-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide 3.9Be also obtained from the reaction.
(Z)-3-Benzylidene-4-hydroxy-2-methyl-4-(phenylethynyl)-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (3.9Aa)

From 2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-N-methylbenzenesulfonamide (2.02 mmol). From flash column chromatography (10% EtOAc – hexane) to give the title compound as a yellow powder (0.39 g, 48%) m.p. 79 – 80 °C; HRMS found [M+Na]+ = 424.0980; C_{24}H_{19}NO_3SNa [M+Na]^+ requires = 424.0978.

δ H (CDCl₃)(600MHz) 8.10 (1H, dd, J = 8.0, 1.1 Hz, 5-H), 7.87 (1H, dd, J = 8.0, 1.1 Hz, 8-H), 7.82 – 7.81 (2H, m, Ph-H), 7.65 (1H, td, J = 8.0, 1.1 Hz, 6-H), 7.52 (1H, td, J = 8.0, 1.1 Hz, 7-H), 7.49 (1H, s, CH), 7.48 – 7.46 (2H, m, Ph-H), 7.42 – 7.32 (6H, m, Ph-H), 3.42 (1H, s, OH), 3.12 (3H, s, N-Me).

δ c (150 MHz) 139.17 (q C), 138.22 (q C), 133.98 (q C), 133.24 (q C), 133.22 (q C), 131.67 (CH), 131.03 (CH), 129.55 (CH), 129.52 (CH), 129.17 (CH), 129.11 (CH), 129.03 (CH), 128.65 (CH), 128.42 (CH), 124.03 (CH), 121.49 (q C), 89.12 (q C), 87.89 (q C), 68.32 (q C), 38.38 (CH₃).

ν max/cm⁻¹: 3433 b (OH), 1490 w (C=C), 1443 s (CH₃), 1327 s (SO₂), 1165 s (R-OH), 1132 m (SO₂), 755 s (Ph-H), 690 s (Ph-H), 661 w (C=CH).

(Z)-3-Butylidene-4-hydroxy-2-methyl-4-(pent-1-yn-1-yl)-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (3.9Ab)

From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-N-methylbenzenesulfonamide (3.00 mmol). From flash column chromatography (10% EtOAc – hexane) to give the title compound as a yellow
oil (0.31 g, at 40% purity by NMR, 12%); LC-MS found [M+H]+ = 333.1391; C18H23NO3S [M+H]+ requires = 333.1400.

δH (CDCl3) 7.94 (1H, dd, J = 8.0, 1.0 Hz, 5-H), 7.77 (1H, dd, J = 8.0, 1.0 Hz, 8-H), 7.60 – 7.56 (1H, m, 6-H), 7.48 – 7.44 (1H, m, 7-H), 6.64 (1H, t, J = 7.3 Hz, CH), 3.15 (3H, s, Me), 3.03 (1H, s, OMe), 2.34 – 2.32 (2H, m, CH2), 2.26 – 2.23 (2H, m, CH2), 1.58 – 1.47 (4H, m, CH2), 0.99 – 0.94 (6H, m, CH3). δc 138.93 (qC), 138.92 (qC), 136.19 (CH), 135.06 (qC), 134.22 (qC), 132.74 (CH), 131.87 (CH), 130.67 (CH), 129.28 (CH), 129.05 (CH), 123.96 (CH), 88.87 (qC), 81.06 (qC), 67.72 (qC), 39.68 (CH3), 38.91 (CH2), 21.77 (CH2), 20.76 (CH2), 14.00 (CH3), 13.52 (CH3).

5-Hydroxy-2-methyl-5-(pent-1-yn-1-yl)-3-propyl-2,5-dihydrobenzo[f][1,2]thiazepine 1,1-dioxide (3.10Ab)

From 2-(6-hydroxyundeca-4,7-diyln-6-yl)-N-methylbenzenesulfonamide (3.00 mmol). From flash column chromatography (10% EtOAc – pet ether) to give the title compound as an orange oil (0.065 g, 7%); HRMS found [M+H]+ = 334.1463; C18H24NO3S [M+H]+ requires = 334.1479.

δH (CDCl3) 8.41 (1H, app. d, 6-H), 7.96 (1H, dd, J = 7.7, 1.2 Hz, 9-H), 7.67 (1H, td, J = 7.7, 1.2 Hz, 7-H), 7.53 (1H, td, J = 7.7, 1.2 Hz, 8-H), 5.78 (1H, s, 4-H), 5.36 (1H, s, OH), 2.78 (3H, s, Me), 2.37 (2H, t, J = 7.3 Hz, CH2), 1.69 – 1.60 (4H, m, CH2), 1.26 (2H, t, J = 7.3 Hz, CH2), 1.06 (3H, t, J = 7.3 Hz, CH3), 1.01 (3H, t, J = 7.3 Hz, CH3).

νmax/cm⁻¹: 3339 b (OH), 2964 m (Ar-H), 2932 m (CH2, CH3), 2874 w (CH2, CH3), 1463 m (CH2), 1337 s (SO2), 1162 s (R-OH), 1127 m (SO2).

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3-(1-Hydroxybutyl)-2-methyl-4-(pent-1-yn-1-yl)-2H-1,2-benzothiazine 1,1-dioxide (3.11Ab)

From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-N-methylbenzenesulfonamide (3.00 mmol). From flash column chromatography (10% EtOAc – pet ether) to give the title compound as an orange oil (0.15 g, 15%); HRMS found [M+Na]^+ = 356.1294; C_{18}H_{23}NO_{3}SNa [M+Na]^+ requires = 356.1297.

δ_H (CDCl_3) 7.88 (1H, app. d, 5-H), 7.82 (1H, dd, J = 7.6, 1.1 Hz, 8-H), 7.63 (1H, td, J = 7.6, 1.1 Hz, 6-H), 7.51 (1H, td, J = 7.6, 1.1 Hz, 7-H), 5.18 (1H, m, CH), 3.28 (3H, s, Me), 2.69 (1H, d, J = 5.2 Hz, OH), 2.48 (2H, t, J = 7.2 Hz, CH_2), 1.61 – 1.84 (2H, m, CH_2), 1.72 – 1.55 (4H, m, CH_2), 1.07 (3H, t, J = 7.2 Hz, CH_3), 1.00 (3H, t, J = 7.4 Hz, CH_3). δ_c 149.20 (q, C), 132.56 (q, C), 132.07 (CH), 131.39 (q, C), 128.59 (CH), 127.23 (CH), 122.03 (CH), 108.54 (q, C), 100.61 (q, C), 74.18 (q, C), 72.23 (CH), 37.63 (CH_2), 35.53 (CH_3), 22.14 (CH_2), (CH_2), 21.69 (CH_2), 19.22 (CH_2), 13.85 (CH_3), 13.70 (CH_3).

ν_{max}/cm^{-1}: 3442 b (OH), 2960 m (Ar-H), 2933 m (CH_2, CH_3), 2872 w (CH_2, CH_3), 1580 w (C=C), 1470 m (CH_2), 1336 s (SO_2), 1180 s (R-OH), 1127 m (SO_2).

(Z)-3-Benzylidene-4-hydroxy-4-(phenylethynyl)-2-(p-tolyl)-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (3.9Ba)

From 2-(3-hydroxy-1,5-diphenypenta-1,4-diyn-3-yl)-N-(p-tolyl)benzenesulfonamide (2.09 mmol). From flash column chromatography (20% ether – pet ether) to give the title
compound as an orange oil (0.78 g, 78%); HRMS found [M+Na]^+ = 500.1294; C_{30}H_{23}NO_{3}SNa [M+Na]^+ requires = 500.1291.

δ_{H} (CDCl$_3$) 8.24 (1H, app. d, 5-H), 7.79 (1H, app. d, 8-H), 7.68 – 7.64 (3H, m, 6-H, Ph-H), 7.57 (1H, s, CH), 7.50 – 7.43 (3H, m, Ph-H, 7-H), 7.38 – 7.31 (2H, m, Ph-H), 7.28 – 7.18 (3H, m, Ph-H), 7.12 (2H, d, J = 8.5 Hz, o-Ar-H), 6.86 (2H, d, J = 8.5 Hz, m-Ar-H), 4.16 (1H, s, OH), 2.12 (3H, s, Ar-Me). δ$_c$ 141.16 (qC), 138.80 (qC), 137.11 (qC), 136.44 (qC), 134.67 (qC), 133.65 (CH), 133.25 (CH), 131.85 (CH), 129.74 (CH), 129.42 (CH), 129.25 (CH), 129.23 (CH), 129.20 (CH), 128.79 (CH), 128.63 (qC), 128.50 (CH), 128.25 (CH), 125.04 (CH), 124.29 (CH), 121.70 (qC), 89.31 (qC), 88.06 (qC), 69.24 (qC), 20.85 (CH$_3$).

ν$_{\text{max}}$/cm$^{-1}$: 3432 b (OH), 2920 w (Ar-H), 1700 m (C=C), 1597 w (C=C), 1443 s (CH$_3$), 1347 s (SO$_2$), 1172 s (R-OH), 1127 s (SO$_2$), 755 s (Ph-H), 733 s (C=C), 690 s (Ph-H).

(Z)-3-Butylidene-4-hydroxy-4-(pent-1-yn-1-yl)-2-(p-tolyl)-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (3.9Bb)

From 2-(6-hydroxyundeca-4,7-diyln-6-yl)-N-(p-tolyl)benzenesulfonamide (2.44 mmol). From flash column chromatography (10% EtOAc – hexane) to give the title compound as an orange oil (0.82 g, 82%); HRMS found [M+Na]^+ = 432.1612; C$_{24}$H$_{27}$NO$_3$SNa [M+Na]^+ requires = 432.1610.

δ$_H$ (CDCl$_3$) 8.13 (1H, app. d, 5-H), 7.77 (1H, dd, J = 7.8, 1.1 Hz, 8-H), 7.64 (1H, td, J = 7.8, 1.1 Hz, 6-H), 7.46 (1H, td, J = 7.8, 1.1 Hz, 7-H), 7.19 (2H, d, J = 8.4 Hz, o-Ar-H), 7.05 (2H, d, J = 8.4 Hz, m-Ar-H), 6.62 (1H, t, J = 7.3 Hz, CH$_2$), 3.52 (1H, s, OH), 2.35 (2H, t, J = 7.1 Hz, CH$_2$), 2.28 (3H, s, Ar-Me), 2.16 – 1.98 (2H, m, CH$_2$), 1.62 (2H, sxt, J = 7.1 Hz, CH$_2$), 1.28 (2H, sxt, J = 7.3 Hz, CH$_2$), 1.02 (3H, t, J = 7.1 Hz, CH$_3$), 0.79 (3H, t, J = 7.3 Hz, CH$_3$). δ$_c$ 141.29 (qC), 139.24 (qC), 138.16 (qC), 136.29 (qC), 135.17 (qC), 135.00 (CH), 133.17 (CH), 129.48 (CH), 129.11 (CH),

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128.91 (CH), 125.01 (CH), 124.15 (CH), 89.14 (qC), 80.61 (qC), 68.76 (qC), 29.32 (CH\textsubscript{2}), 21.85 (CH\textsubscript{2}), 20.93 (CH\textsubscript{3}), 20.87 (CH\textsubscript{2}), 13.79 (CH\textsubscript{3}), 13.62 (CH\textsubscript{3}).

\(\nu_{\text{max}}/\text{cm}^{-1}: 3466 \text{ b (OH)}, 2960 \text{ w (Ar-H)}, 2931 \text{ m (CH\textsubscript{2}, CH\textsubscript{3})}, 2871 \text{ w (CH\textsubscript{2}, CH\textsubscript{3})}, 1509 \text{ w (C=C)}, 1463 \text{ w (CH\textsubscript{2})}, 1323 \text{ s (SO\textsubscript{2})}, 1164 \text{ s (R-OH)}, 1127 \text{ s (SO\textsubscript{2})}, 734 \text{ s (C=CH)}.

\((Z)-4\text{-Hydroxy-3-(4-methoxybenzylidene)-4-[(4-methoxyphenyl)ethynyl]-2-(p-tolyl)-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (3.9Bc)}\)

\[\begin{align*}
\text{δ}_H (\text{CDCl}_3) & \quad 8.22 (1H, \text{app. d, 5-H}), 7.79 (1H, \text{app. d, 8-H}), 7.68 – 7.63 (3H, \text{m, Ar-H, 6-H}), 7.51 (1H, s, CH), 7.47 – 7.40 (3H, m, 7-H, Ar-H), 7.19 (2H, d, J = 8.4 \text{ Hz, o-Ar-H}), 6.89 (2H, d, J = 8.4 \text{ Hz, m-Ar-H}), 6.85 (2H, d, J = 8.8 \text{ Hz, Ar-H}), 6.79 (2H, d, J = 8.8 \text{ Hz, Ar-H}), 3.79 (3H, s, O-Me), 3.75 (3H, s, O-Me), 2.60 (1H, s, OH), 2.14 (3H, s, Ar-Me). \\
\text{δ}_C & \quad 160.17 (qC), 159.94 (qC), 139.26 (qC), 138.72 (qC), 137.30 (qC), 136.17 (qC), 134.65 (qC), 133.51 (CH), 133.32 (CH), 131.43 [2 \times \text{C (CH)}], 129.25 [2 \times \text{C (CH)}], 129.20 (CH), 125.88 (qC), 124.71 (CH), 124.15 (CH), 114.05 (CH), 113.80 (CH), 113.68 (qC), 88.30 (qC), 87.88 (qC), 69.22 (qC), 55.35 (CH\textsubscript{3}), 55.22 (CH\textsubscript{3}), 20.82 (CH\textsubscript{3}).
\end{align*}\]

\(\nu_{\text{max}}/\text{cm}^{-1}: 3432 \text{ b (OH)}, 2969 \text{ w (Ar-H)}, 2837 \text{ w (CH\textsubscript{3})}, 1700 \text{ m (C=CH)}, 1604 \text{ s (C=CH)}, 1508 \text{ s (CH\textsubscript{3})}, 1350 \text{ s (SO\textsubscript{2})}, 1246 \text{ s (R-OH)}, 1172 \text{ s (SO\textsubscript{2})}, 764 \text{ m (C=CH)}.

From 2-[3-hydroxy-1,5-bis(4-methoxyphenyl)penta-1,4-diyne-3-yl]-N-(p-tolyl)benzenesulphonamide (1.86 mmol). From flash column chromatography (20% EtOAc – pet ether) to give the title compound as an orange oil (0.62 g, 62%); HRMS found [M+Na]\(^{+}\) = 560.1509; \(C_{32}H_{27}NO_{5}S\) Na [M+Na]\(^{+}\) requires = 560.1508.
(Z)-4-Hydroxy-2-(p-tolyl)-4-[(trimethylsilyl)ethynyl]-3-[(trimethylsilyl)methylene]-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (3.9Be)

From 2-[3-hydroxy-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl]-N-(p-tolyl)benzenesulfonamide (2.13 mmol). From flash column chromatography (15% EtOAc – pet ether) to give the title compound as a straw coloured oil (0.61 g, 61%); HRMS found [M+Na]⁺ = 492.1459; C₂₄H₃₁NO₃SSi₂Na [M+Na]⁺ requires = 492.1461.

δH (CDCl₃) 8.16 (1H, dd, J = 7.9, 1.0 Hz, 5-H), 7.73 (1H, dd, J = 7.9, 1.0 Hz, 8-H), 7.65 (1H, td, J = 7.9, 1.0 Hz, 6-H), 7.44 (1H, td, J = 7.9, 1.0 Hz, 7-H), 7.27 – 7.24 (2H, m, o-Ar-H), 7.05 (2H, d, J = 8.1 Hz, m-Ar-H), 6.91 (1H, s, CH), 3.94 (1H, s, OH), 2.28 (3H, s, Ar-Me), 0.29 (9H, s, SiMe₃), 0.00 (9H, s, SiMe₃). δC 154.96 (qC), 138.78 (qC), 138.60 (qC), 136.14 (qC), 134.71 (CH), 133.97 (qC), 133.49 (CH), 129.30 (CH), 129.28 (CH), 129.20 (CH), 124.65 (CH), 124.26 (CH), 105.68 (qC), 93.21 (qC), 69.74 (qC), 20.84 (CH₃), -0.35 (CH₃), -1.35 (CH₃).

νmax/cm⁻¹: 3456 b (OH), 2958 s (CH₃), 1509 s (C=C), 1356 w (SO₂), 1159 m (R-OH), 1116 s (SO₂), 723 w (CH=CH).

4-Hydroxy-3-methylene-2-(p-tolyl)-4-[(trimethylsilyl)ethynyl]-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (3.9Be')

From 2-[3-hydroxy-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl]-N-(p-tolyl)benzenesulfonamide (2.13 mmol). From flash column chromatography (15% EtOAc – pet ether) to give the title compound as a straw coloured oil (0.02 g, 2%); HRMS found [M+H]⁺ = 398.1251; C₂₁H₂₄NO₃SSi [M+H]⁺ requires = 398.1248.
δ\textsubscript{H} (CDCl\textsubscript{3}) 8.14 (1H, dd, J = 8.0, 1.0 Hz, 5-H), 7.90 (1H, dd, J = 8.0, 1.0 Hz, 8-H), 7.70 (1H, td, J = 8.0, 1.0 Hz, 6-H), 7.57 (1H, td, J = 8.0, 1.0 Hz, 7-H), 7.34 – 7.31 (2H, m, o-Ar-H), 7.57 (1H, td, J = 8.1 Hz, m-Ar-H), 5.82 (1H, d, J = 1.8 Hz, CH), 4.76 (1H, d, J = 1.8 Hz, CH), 2.38 (3H, s, Ar-Me), 0.25 (9H, s, Si-Me\textsubscript{3}).

δ\textsubscript{C} 148.96 (qC), 138.87 (qC), 136.87 (qC), 136.82 (qC), 135.86 (qC), 134.42 (qC), 133.36 (CH), 130.44 (CH), 129.56 (CH), 128.50 (CH), 128.41 (CH), 123.30 (CH), 107.86 (CH\textsubscript{2}), 102.94 (qC), 94.10 (qC), 69.54 (qC), 21.21 (CH\textsubscript{3}), -0.36 (CH\textsubscript{3}).

ν\textsubscript{max}/cm\textsuperscript{-1}: 3346 b (OH), 2924 s (CH\textsubscript{3}), 1611 s (C=C), 1508 s (CH\textsubscript{3}), 1347 s (SO\textsubscript{2}), 1168 s (R-OH), 1097 s (SO\textsubscript{2}) 733 s (C=CH).

\((Z)\)-4-Hydroxy-3-(2-methoxyethyldiene)-4-(3-methoxyprop-1-yn-1-yl)-2-(p-tolyl)-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (3.9Bf)

From 2-(4-hydroxy-1,7-dimethoxyhepta-2,5-diyn-4-yl)-N-(p-tolyl)benzenesulfonamide (2.42 mmol) to give the title compound as a brown oil (0.86 g, 86%); HRMS found [M+Na]\textsuperscript{+} = 436.1190; C\textsubscript{22}H\textsubscript{23}NO\textsubscript{5}SNa [M+Na]\textsuperscript{+} requires = 436.1195.

δ\textsubscript{H} (CDCl\textsubscript{3}) 8.14 (1H, dd, J = 7.9, 0.9 Hz, 5-H), 7.79 (1H, dd, J = 7.9, 0.9 Hz, 8-H), 7.66 (1H, td, J = 7.9, 0.9 Hz, 6-H), 7.49 (1H, td, J = 7.9, 0.9 Hz, 7-H), 7.18 (2H, d, J = 8.5 Hz, o-Ar-H), 7.07 (2H, d, J = 8.5 Hz, m-Ar-H), 6.67 (1H, t, J = 5.6 Hz, CH\textsubscript{a}), 4.22 (2H, s, CH\textsubscript{2}), 4.04 (1H, dd, J = 14.1, 5.8 Hz, CH\textsubscript{a}CH\textsubscript{b}), 3.99 (1H, s, OMe), 3.92 (1H, dd, J = 14.1, 5.8 Hz, CH\textsubscript{a}CH\textsubscript{b}), 3.39 (3H, s, O-Me), 3.20 (3H, s, O-Me), 3.28 (3H, s, Ar-Me). δ\textsubscript{C} 141.99 (qC), 138.14 (qC), 137.45 (qC), 136.88 (qC), 135.02 (qC), 133.48 (CH), 131.43 (CH), 129.77 (CH), 129.47 (CH), 128.83 (CH), 125.07 (CH), 124.24 (CH), 86.09 (qC), 84.26 (qC), 68.09 (CH\textsubscript{2}), 68.07 (qC), 59.89 (CH\textsubscript{2}), 58.47 (CH\textsubscript{3}), 58.00 (CH\textsubscript{3}), 20.95 (CH\textsubscript{3}).

ν\textsubscript{max}/cm\textsuperscript{-1}: 3346 b (OH), 2924 s (CH\textsubscript{3}), 1611 s (C=C), 1508 s (CH\textsubscript{3}), 1347 s (SO\textsubscript{2}), 1168 s (R-OH), 1097 s (SO\textsubscript{2}) 733 s (C=CH).
(Z)-3-Benzylidene-4-hydroxy-4-(phenylethynyl)-2-(m-tolyl)-3,4-dihydro-2H-1,2-
benzothiazine 1,1-dioxide (3.9Ca)

From 2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-N-(m-tolyl)benzenesulfonamide (2.09 mmol). From flash column chromatography (20% EtOAc – hexane) and resultant solid recrystallised from ether – hexane to give the title compound as a white powder (0.72 g, 72%) m.p. 160 – 161 °C; HRMS found [M+Na]^+ = 500.1291; C_{30}H_{23}NO_{3}SNa [M+Na]^+ requires = 500.1297. 

δ_H (CDCl₃) 8.26 (1H, dd, J = 7.9, 1.0 Hz, 5-H), 7.84 (1H, dd, J = 7.9, 1.0 Hz, 8-H), 7.71 (1H, td, J = 7.9, 1.0 Hz, 6-H), 7.63 – 7.61 (2H, m, Ar-H), 7.59 (1H, s, CH), 7.56 – 7.50 (3H, m, Ar-H, 7-H), 7.42 – 7.34 (3H, m, Ar-H), 7.28 – 7.19* (2H, m, Ar-H), 7.04 (2H, m, Ar-H), 6.98 (1H, t, J = 7.6 Hz, Ar-H), 6.82 (1H, m, Ar-H), 3.74 (1H, s, OH), 2.13 (3H, s, Ar-Me). δ_c 141.11 (q_C), 139.38 (q_C), 138.65 (q_C), 138.39 (q_C), 134.81 (q_C), 133.62 (CH), 133.19 (q_C), 131.82 [2 X C (CH)], 129.65 (CH), 129.48 (CH), 129.25 (CH), 129.09 (CH), 128.69 (CH), 128.49 (CH), 128.31 (CH), 128.14 (CH), 127.30 (CH), 125.92 (CH), 124.31 (CH), 121.98 (CH), 121.64 (q_C), 89.04 (q_C), 88.25 (q_C), 69.52 (q_C), 21.27 (CH₃).

v_max/cm⁻¹: 3470 b (OH), 1489 m (C=C), 1349 s (SO₂), 1180 s (R-OH), 1137 s (SO₂), 757 s (C=C).

*Overlapping with CDCl₃ signal
(Z)-3-Butylidene-4-hydroxy-4-(pent-1-yn-1-yl)-2-(m-tolyl)-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (3.9Cb)

From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-N-(m-tolyl)benzenesulfonamide (2.44 mmol). From flash column chromatography (15% EtOAc – pet ether) to give the title compound as a yellow glass-like solid (0.59 g, 59%); HRMS found [M+Na]+ = 432.1611; C24H27NO3SNa [M+Na]+ requires = 432.1610.

δH (CDCl3) 8.11 (1H, dd, J = 7.9, 1.2 Hz, 5-H), 7.79 (1H, dd, J = 7.9, 1.2 Hz, 8-H), 7.64 (1H, td, J = 7.8, 1.2 Hz, 6-H), 7.47 (1H, td, J = 7.8, 1.2 Hz, 7-H), 7.21 – 7.21 (1H, m, Ar-H), 7.15 – 7.13 (2H, m, Ar-H), 6.99 – 6.96 (1H, m, Ar-H), 6.62 (1H, t, J = 7.3 Hz, CH), 3.40 (1H, s, OH), 2.35 (2H, t, J = 7.1 Hz, CH2), 2.29 (3H, s, Ar-Me), 2.16 – 1.99 (2H, m, CH2), 1.62 (2H, sxt, J = 7.1 Hz, CH2), 1.32 – 1.22 (2H, m, CH2), 1.02 (3H, t, J = 7.1 Hz, CH3), 0.78 (3H, t, J = 7.3 Hz, CH3). δC 140.72 (qC), 140.59 (qC), 139.18 (qC), 138.77 (qC), 135.39 (qC), 135.02 (CH), 133.12 (CH), 129.16 (CH), 128.79 (CH), 128.59 (CH), 127.05 (CH), 125.50 (CH), 124.05 (CH), 121.75 (CH), 89.22 (qC), 80.58 (qC), 68.87 (qC), 29.27 (CH2), 21.84 (CH2), 21.41 (CH3), 21.27 (CH2), 20.86 (CH2), 13.76 (CH3), 13.69 (CH3).

νmax/cm⁻¹: 3455 b (OH), 2961 m (Ar-H), 2933 w (CH2, CH3), 2871 w (CH2, CH3), 2233 w (C≡C), 1605 m (C=C), 1488 m (CH2), 1319 s (SO2), 1163 s (R-OH), 1126 s (SO2), 734 s (C=CH).

(Z)-3-Benzylidene-4-hydroxy-2-(2-methoxyphenyl)-4-(phenylethynyl)-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (3.9Da)

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From 2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-N-(2-methoxyphenyl)benzenesulfonamide (2.03 mmol). From flash column chromatography (20% ether – hexane) to give the title compound as a golden foam (0.86 g, 86%); HRMS found [M+Na]^+ = 516.1239; C_{30}H_{23}NO_4SNa [M+Na]^+ requires = 516.1246.

δ_H (CDCl_3) 8.30 (1H, dd, J = 8.0, 0.9 Hz, 5-H), 7.84 (1H, dd, J = 8.0, 0.9 Hz, 8-H), 7.70 (1H, td, J = 8.0, 0.9 Hz, 6-H), 7.64 (1H, s, CH), 7.57 – 7.54 (2H, m, Ar-H), 7.52 – 7.48 (3H, m, 7-H, Ar-H), 7.38 – 7.34 (3H, m, Ar-H), 7.28 – 7.19* (3H, m, Ar-H), 7.06 – 7.01 (1H, m, Ar-H), 6.95 (1H, dd, J = 9.0, 1.6 Hz, Ar-H), 6.68 (1H, dd, J = 9.0, 1.6 Hz, Ar-H), 6.59 (1H, td, J = 9.0, 1.6 Hz, Ar-H), 5.04 (1H, s, O-H), 3.46 (3H, s, Ar-Me). δ_c 153.90 (q C), 139.63 (q C), 135.63 (q C), 134.04 (q C), 133.04 (CH), 131.81 (CH), 131.57 (CH), 130.21 (CH), 129.07 (CH), 129.02 (CH), 128.94 [2 X C (CH)], 128.87 [2 X C (CH)], 128.68 (CH), 128.45 (CH), 128.03 (CH), 127.43 (q C), 123.22 (CH), 122.00 (q C), 120.73 (CH), 112.30 (CH), 89.23 (q C), 87.50 (q C), 70.06 (q C), 55.44 (CH_3).

ν_max/cm\(^{-1}\): 3399 b (OH), 1595 m (C=O), 1341 s (SO_2), 1172 s (R-OH), 1131 m (SO_2), 751 s (Ph-H), 691 s (C=CH), 690 s (Ph-H).

*Overlapping with CDCl_3 signal

(Z)-3-Butylidene-4-hydroxy-2-(2-methoxyphenyl)-4-(pent-1-yn-1-yl)-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (3.9Db)

From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-N-(2-methoxyphenyl)benzenesulfonamide (2.56 mmol). From flash column chromatography (20% EtOAc – pet ether) to give the title compound as a pink oil (0.67 g, 61%); HRMS found [M+Na]^+ = 448.1550; C_{24}H_{27}NO_4SNa [M+Na]^+ requires = 448.1559.

δ_H (CDCl_3) 8.15 (1H, dd, J = 8.0, 1.0 Hz, 5-H), 7.77 (1H, dd, J = 8.0, 1.0 Hz, 8-H), 7.63 (1H, td, J = 8.0, 1.0 Hz, 6-H), 7.54 (1H, dd, J = 7.9, 1.6 Hz, Ar-H), 7.43 (1H, td, J = 8.0, 1.0 Hz, 7-H), 7.26 – 7.22* (1H, m, Ar-H), 6.96 (1H, td, J = 7.9, 1.6 Hz, Ar-H), 6.86 (1H, dd, J = 7.9, 1.6 Hz, Ar-H),
6.62 (1H, t, $J = 7.4$ Hz, CH), 4.73 (1H, s, O-H), 3.57 (3H, s, O-Me), 2.34 (2H, t, $J = 7.2$ Hz, CH$_2$), 2.15 – 2.08 (2H, m, CH$_2$), 1.62 (2H, sxt, $J = 7.2$ Hz, CH$_2$), 1.24 – 1.17 (2H, m, CH$_2$), 1.02 (3H, t, $J = 7.2$ Hz, CH$_3$), 0.77 (3H, t, $J = 7.4$ Hz, CH$_3$). δ$_c$ 154.48 (q-C), 140.68 (q-C), 140.08 (q-C), 135.77 (q-C), 133.69 (CH), 132.72 (CH), 130.80 (CH), 129.05 (CH), 128.84 (CH), 128.44 (q-C), 128.41 (CH), 123.11 (CH), 121.19 (CH), 112.63 (CH), 88.40 (q-C), 80.81 (q-C), 60.42 (q-C), 55.54 (CH$_3$), 29.22 (CH$_2$), 21.92 (CH$_2$), 21.57 (CH$_2$), 20.90 (CH$_2$), 13.72 (CH$_3$), 13.65 (CH$_3$).

ν$_{\text{max}}$/cm$^{-1}$: 3444 b (OH), 2960 w (Ar-H), 2932 m (CH$_2$, CH$_3$), 2871 w (CH$_2$, CH$_3$), 1498 s (C=C), 1459 m (CH$_2$), 1334 s (SO$_2$), 1123 s (R-OH), 1097 w (SO$_2$), 742 s (C=CH).

*Overlapping with CDCl$_3$ signal

(Z)-3-Benzylidene-4-hydroxy-2-(3-methoxyphenyl)-4-(phenylethynyl)-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (3.9Ea)

From 2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-N-(3-methoxyphenyl)benzenesulfonamide (2.03 mmol). From flash column chromatography (30% ether – pet ether) to give the title compound as a yellow oil (0.96 g, 96%); HRMS found [M+Na]$^+$ = 516.1239; C$_{30}$H$_{23}$NO$_4$SNa [M+Na]$^+$ requires = 516.1246.

δ$_\text{H}$ (CDCl$_3$) 8.26 (1H, dd, $J = 7.9$, 1.0 Hz, 5-H), 7.84 (1H, dd, $J = 7.9$, 1.0 Hz, 8-H), 7.71 (1H, td, $J = 7.9$, 1.0 Hz, 6-H), 7.66 – 7.63 (2H, m, Ph-H), 7.61 (1H, s, CH), 7.54 – 7.49 (3H, m, Ph-H, 7-H), 7.39 – 7.33 (3H, m, Ph-H), 7.30 – 7.21* (3H, m, Ph-H), 7.00 (1H, t, $J = 8.2$ Hz, Ar-H), 6.87 – 6.85 (1H, m, Ar-H), 6.82 – 6.81 (1H, m, Ar-H), 6.58 – 6.55 (1H, m, Ar-H), 3.87 (1H, s, OH), 3.57 (3H, s, O-Me). δ$_c$ 159.53 (q-C), 140.93 (q-C), 140.61 (q-C), 138.68 (q-C), 134.98 (q-C), 133.68 (CH), 133.20 (q-C), 132.25 (CH), 131.83 (CH), 129.68 (CH), 129.50 (CH), 129.26 (CH), 129.12 (CH), 128.81 (CH), 128.48 (CH), 128.24 (CH), 124.31 (CH), 121.59 (q-C), 117.39 (CH), 112.52 (CH), 110.78 (CH), 89.09 (q-C), 88.17 (q-C), 69.36 (q-C), 55.18 (CH$_3$).
\[ \nu_{\text{max}}/\text{cm}^{-1}: 3459 \text{ b (OH)}, 2960 \text{ m (Ar-H)}, 2932 \text{ w (CH}_3, \text{CH}_2), 2871 \text{ w (CH}_2, \text{CH}_3), 1601 \text{ s (C=C), 1489 s (CH}_3), 1318 \text{ s (SO}_2), 1163 \text{ s (R-OH), 1126 s (SO}_2), 733 \text{ s (C=C).} \]

*Overlapping with CDCl$_3$ signal

(Z)-3-Butyldiene-4-hydroxy-2-(3-methoxyphenyl)-4-(pent-1-yn-1-yl)-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (3.9Eb)

From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-N-(3-methoxyphenyl)benzenesulfonamide (1.39 mmol). From flash column chromatography (20% EtOAc – hexane) to give the title compound as an orange oil (0.47 g, 80%); HRMS found [M+Na]$^+$ = 448.1555; C$_{24}$H$_{27}$NO$_4$SNa [M+Na]$^+$ requires = 448.1559.

\( \delta \) (CDCl$_3$) 8.11 (1H, dd, \( J = 7.9, 1.0 \text{ Hz}, 5-H \)), 7.78 (1H, dd, \( J = 7.9, 1.0 \text{ Hz}, 8-H \)), 7.64 (1H, td, \( J = 7.9, 1.0 \text{ Hz}, 6-H \)), 7.47 (1H, td, \( J = 7.9, 1.0 \text{ Hz}, 7-H \)), 7.15 – 7.13 (1H, m, Ar-H), 6.96 – 7.93 (2H, m, Ar-H), 6.72 – 6.70 (1H, m, Ar-H), 6.64 (1H, t, \( J = 7.3 \text{ Hz}, \text{CH} \)), 3.75 (3H, s, O-Me), 3.44 (1H, s, OH), 2.34 (2H, t, \( J = 7.3 \text{ Hz}, \text{CH}_2 \)), 2.18 – 2.00 (2H, m, \text{CH}_2), 1.62 (2H, sxt, \( J = 7.3 \text{ Hz}, \text{CH}_2 \)), 1.30 (2H, sxt, \( J = 7.3 \text{ Hz}, \text{CH}_2 \)), 1.01 (3H, t, \( J = 7.3 \text{ Hz}, \text{CH}_3 \)), 0.79 (3H, t, \( J = 7.3 \text{ Hz}, \text{CH}_3 \)).

\( \delta_c \) 159.83 (qC), 141.75 (qC), 140.67 (qC), 139.17 (qC), 135.49 (CH), 135.22 (qC), 133.20 (CH), 129.40 (CH), 129.20 (CH), 128.83 (CH), 124.09 (CH), 117.10 (CH), 111.96 (CH), 110.62 (CH), 89.26 (qC), 80.54 (qC), 68.79 (qC), 55.32 (CH$_3$), 29.30 (CH$_2$), 21.84 (CH$_2$), 21.30 (CH$_2$), 20.89 (CH$_2$), 13.82 (CH$_3$), 13.62 (CH$_3$).

\( \nu_{\text{max}}/\text{cm}^{-1}: 3459 \text{ b (OH)}, 2960 \text{ m (Ar-H)}, 2932 \text{ w (CH}_3, \text{CH}_2), 2871 \text{ w (CH}_2, \text{CH}_3), 1601 \text{ s (C=C), 1489 s (CH}_3), 1318 \text{ s (SO}_2), 1163 \text{ s (R-OH), 1126 s (SO}_2), 733 \text{ s (C=C).} \)
(Z)-3-Butyldiene-4-hydroxy-4-(pent-1-yn-1-yl)-2-(thiophen-3-yl)-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (3.9Gb)

From 2-(6-hydroxyundeca-4,7-diyln-6-yl)-N-(thiophen-3-yl)benzenesulfonamide (1.25 mmol). From flash column chromatography (20% EtOAc – hexane) to give the title compound as an orange oil (0.35 g, 70%); HRMS found [M+H]+ = 402.1195; C_{21}H_{24}NO_{3}S_{2} [M+H]+ requires = 402.1199.

δ_{H} (CDCl_{3}) 8.07 (1H, app. d, 5-H), 7.80 (1H, app. d, 8-H), 7.63 (1H, app. t, 6-H), 7.48 (1H, app. t, 7-H), 7.18 – 7.16 (1H, m, Ar-H), 7.13 – 7.11 (1H, m, Ar-H), 7.08 (1H, dd, J = 5.1, 1.4 Hz, Ar-H), 6.67 (1H, t, J = 7.3 Hz, CH), 3.20 (1H, s, OH), 2.31 (2H, t, J = 7.3 Hz, CH_{2}), 2.19 – 2.17 (2H, m, CH_{2}), 2.16 – 1.98 (2H, m, CH_{2}), 1.59 (2H, sxt, J = 7.3 Hz, CH_{2}), 1.35 (2H, sxt, J = 7.3 Hz, CH_{2}), 1.00 (3H, t, J = 7.3 Hz, CH_{3}), 0.85 (3H, t, J = 7.3 Hz, CH_{3}). δ_{c} 139.93 (qC), 139.10 (qC), 138.22 (qC), 135.81 (CH), 135.12 (qC), 133.16 (CH), 129.25 (CH), 128.93 (CH), 124.61 (CH), 124.22 (CH), 123.99 (CH), 115.49 (CH), 89.19 (qC), 80.56 (qC), 68.62 (qC), 29.18 (CH_{2}), 21.81 (CH_{2}), 21.39 (CH_{2}), 20.83 (CH_{2}), 13.83 (CH_{3}), 13.60 (CH_{3}).

v_{\text{max}}/\text{cm}^{-1}: 3407 \text{ b} (OH), 2960 \text{ m} (Ar-H), 2930 \text{ m} (CH_{2}, CH_{3}), 2871 w (CH_{2}, CH_{3}), 1585 m (C=C), 1468 w (CH_{2}), 1390 m (CH_{3}), 1352 s (SO_{2}), 1177 s (R-OH), 1068 w (SO_{2}) 766 (C=CH).

5-Hydroxy-5-(pent-1-yn-1-yl)-3-propyl-2-(thiophen-3-yl)-2,5-dihydrobenzo[\text{f}]1,2-thiazepine 1,1-dioxide (3.10Gb)
From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-N-(thiophen-3-yl)benzenesulfonamide (1.25 mmol). From flash column chromatography (20% EtOAc – hexane) to give the title compound as an orange oil (0.05 g, 11%); HRMS found [M+H]^+ = 402.1199; C_{21}H_{24}NO_{3}S_2 [M+H]^+ requires = 402.1279.

δ_H (CDCl_3) 8.45 (1H, app. d, 6-H), 7.68 – 7.64 (2H, m, 9-H, 7-H), 7.40 (1H, app. t, 8-H), 7.15 – 7.12 (1H, m, Ar-H), 6.83 – 6.82 (1H, m, Ar-H), 6.72 (1H, dd, J = 5.0, 1.1 Hz, Ar-H), 5.91 (1H, s, 4-H), 5.43 (1H, s, OH), 2.41 (2H, t, J = 7.2 Hz, CH_2), 2.09 – 2.02 (1H, m, CH_2), 1.96 – 1.88 (1H, m, CH_2), 1.70 (2H, sxt, J = 7.2 Hz, CH_2), 1.64 – 1.55 (2H, m, CH_2), 1.09 (3H, t, J = 7.2 Hz, CH_2), 0.97 (3H, t, J = 7.2 Hz, CH_3). δ_c 137.47 (q C), 137.03 (q C), 135.10 (q C), 134.86 (q C), 133.93 (CH), 130.87 (CH), 128.80 (CH), 128.38 (CH), 126.24 (CH), 125.15 (CH), 122.19 (CH), 120.87 (CH), 89.00 (q C), 82.06 (q C), 72.89 (q C), 37.68 (CH_2), 21.95 (CH_2), 20.99 (CH_2), 20.62 (CH_2), 13.75 (CH_3), 13.01 (CH_3).

ν_{max}/cm^{-1}: 3129 b (OH), 2962 w (Ar-H), 2927 m (CH_2, CH_3), 2871 w (CH_2, CH_3), 2207 w (C≡C) 1631 s (C=C), 1593 w (C=C), 1465 s (CH_2), 1364 m (CH_2), 1329 s (SO_2), 1157 s (R-OH), 1060 w (SO_2).

(Z)-3-Benzylidene-4-hydroxy-2-(naphthalen-2-yl)-4-(phenylethynyl)-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (3.9Ha)

From 2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-N-(naphthalen-2-yl)benzenesulfonamide (1.95 mmol). From flash column chromatography (20% EtOAc – hexane) and resultant solid recrystalised from ether – hexane to give the title compound as a beige foam (0.75 g, 75%) m.p. 94 – 96 °C; HRMS found [M+Na]^+ = 536.1297; C_{33}H_{23}NO_3SNa [M+Na]^+ requires = 536.1297.
\[ \delta^H ([\text{CD}_3]_2\text{CO})(600 \text{ MHz}) \] 8.23 (1H, dd, \( J = 8.0, 0.9 \text{ Hz, 5-H} \)), 7.89 (1H, app. s, Ar-H), 7.84 (1H, dd, \( J = 8.0, 0.9 \text{ Hz, 8-H} \)), 7.77 – 7.75 (1H, m, 6-H), 7.66 – 7.63 (3H, m, Ar-H), 7.61 – 7.57 (5H, m, Ar-H, 7-H), 7.33 – 7.24 (7H, m, Ar-H), 7.16 – 7.13 (2H, m, Ar-H), 7.07 – 7.04 (1H, m, Ar-H), 6.66 (1H, s, OH). \( \delta^C (150 \text{ MHz}) \) 139.84 (q C), 139.39 (q C), 137.16 (q C), 135.54 (q C), 133.48 (CH), 133.33 (q C), 133.06 (q C), 131.52 (CH), 131.28 (q C), 130.23 (CH), 129.45 (CH), 129.37 (CH), 129.05 (CH), 128.74 (CH), 128.55 (CH), 128.53 (CH), 128.03 (CH), 127.99 (CH), 127.54 (CH), 127.35 (CH), 126.36 (CH), 125.72 (CH), 123.57 (CH), 123.37 (CH), 122.43 (CH), 121.90 (q C), 90.82 (q C), 86.70 (q C), 68.08 (q C).

\( \nu_{\text{max}}/\text{cm}^{-1} \): 3454 w (OH), 1596 w (C=C), 1508 w (C=C), 1490 m (CH\textsubscript{3}), 1342 s (SO\textsubscript{2}), 1170 s (R-OH), 1131 s (SO\textsubscript{2}), 753 s (Ph-H), 690 s (C=CH), 667 m (Ph-H).

(Z)-3-Butylidene-4-hydroxy-2-(naphthalen-2-yl)-4-(pent-1-yn-1-yl)-3,4-dihydro-2\( H \)-1,2-benzothiazine 1,1-dioxide (3.9Hb)

From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-N-(naphthalen-2-yl)benzenesulfonamide (2.24 mmol). From flash column chromatography (toluene) to give the title compound as an orange oil (0.84 g, 84%); HRMS found [M+Na]\(^+\) = 468.1609; \( \text{C}_{27}\text{H}_{27}\text{NO}_3\text{SNa} \) [M+Na]\(^+\) requires = 468.1610.

\( \delta^H (\text{CDCl}_3) \) 8.15 (1H, dd, \( J = 8.0, 0.9 \text{ Hz, 5-H} \)), 7.83 – 7.73 (5H, m, Ar-H), 7.65 (1H, td, \( J = 7.7, 1.3 \text{ Hz, 6-H} \)), 7.52 – 7.40 (4H, m, Ar-H), 6.68 (1H, t, \( J = 7.2 \text{ Hz, CH} \)), 3.44 (1H, s, OH), 2.37 (2H, t, \( J = 7.0 \text{ Hz, CH}_2 \)), 2.15 – 1.98 (2H, m, CH\textsubscript{2}), 1.64 (2H, sxt, \( J = 7.2 \text{ Hz, CH}_2 \)), 1.27 (2H, sxt, \( J = 7.2 \text{ Hz, CH}_2 \)), 1.03 (3H, t, \( J = 7.1 \text{ Hz, CH}_3 \)), 0.74 (3H, t, \( J = 7.2 \text{ Hz, CH}_3 \)). \( \delta^C \) 140.50 (q C), 139.15 (q C), 138.05 (q C), 135.32 (CH), 133.35 (q C), 133.25 (CH), 131.50 (q C), 129.27 (CH), 128.82 (CH), 128.74 (CH), 127.90 (CH), 127.54 (CH), 126.48 (CH), 125.94 (CH), 124.08 (CH), 123.42 (CH), 122.44 (CH), 89.41 (q C), 80.56 (q C), 68.92 (q C), 29.30 (CH\textsubscript{2}), 21.86 (CH\textsubscript{2}), 21.31 (CH\textsubscript{2}), 20.90 (CH\textsubscript{2}), 13.76 (CH\textsubscript{3}), 13.65 (CH\textsubscript{3}).
\[ \nu_{\text{max}}/\text{cm}^{-1}: 3453 \text{ b (OH)}, 2959 \text{ m (Ar-H)}, 2929 \text{ m (CH}_2, \text{ CH}_3), 2870 \text{ m (CH}_2, \text{ CH}_3), 2231 \text{ w (C≡C)}, 1631 \text{ m (C=C)}, 1597 \text{ m (C=C)}, 1508 \text{ m (C=C)}, 1465 \text{ m (CH}_2, \text{ CH}_3), 1317 \text{ s (SO}_2\text{)}, 1162 \text{ s (R-OH)}, 1125 \text{ s (SO}_2\text{)}, 732 \text{ s (C=CH)}. \]

### 6.4 Chapter 4 Experimental

#### 6.4.1 Reactions with (Z)-2-Benzylidene-3-(phenylethynyl)-1-tosylindolin-3-ol

3-[Phenyl[3-(phenylethynyl)-1-tosyl-1H-indol-2-yl]methyl]pentane-2,4-dione (4.14a)

![Chemical Structure](image)

Under an argon atmosphere (Z)-2-benzylidene-3-(phenylethynyl)-1-tosylindolin-3-ol (0.20 g, 0.004 mmol, 1 equiv.) was dissolved in DCE (10 mL) to this 100% w/w montmorillonite K-10 (0.20 g) and acetylacetone (0.13 mL, 0.01 mmol, 3 equiv.) was added, and the mixture stirred at reflux for 2 h. After this time the reaction mixture was allowed to cool, filtered through Celite and evaporated to give the title compound as a brown oil (0.24 g, 100%); HRMS found [M+Na]+ = 582.1711; C\textsubscript{35}H\textsubscript{29}NO\textsubscript{4}S Na [M+Na]+ requires = 582.1709.

\[ \delta (\text{CD}_2\text{Cl}_2) \]

8.04 – 8.00 (1H, m, 4-H), 7.72 – 7.70 (3H, m, Ph-H), 7.63 – 7.62 (4H, m, Ar-H, Ph-H), 7.53 – 7.46 (3H, m, Ph-H), 7.37 – 7.29 (5H, m, Ph-H, 5-H, 6-H, 7-H), 7.15 (2H, d, J = 8.0 Hz, m-Ar-H), 6.08 (1H, d, J = 12.0 Hz, CH), 6.00 (1H, d, J = 12.0 Hz, CH), 2.33 (3H, s, Ar-Me), 2.23 2.22 (3H, s, Me), 2.06 (3H, s, Me). \[ \delta \]

191.30 (C=O), 145.35 (\text{aC}), 144.17 (\text{aC}), 139.13 (\text{qC}), 135.36 (\text{qC}), 135.08 (\text{qC}), 131.18 (CH), 129.55 (CH), 129.40 (CH), 128.95 (CH), 128.78 (CH), 128.76 (CH), 127.45 (CH), 127.19 (CH), 125.51 (CH), 124.00 (CH), 122.78 (\text{qC}), 119.63 (CH), 115.07 (CH), 97.55 (\text{qC}), 82.17 (\text{qC}), 72.74 (CH), 58.38 (\text{qC}), 43.38 (CH), 31.32 (CH\textsubscript{3}), 29.20 (CH\textsubscript{3}), 21.25 (CH\textsubscript{3}).

\[ \nu_{\text{max}}/\text{cm}^{-1}: 1729 \text{ s (C=O)}, 1699 \text{ s (C=O)}, 1597 \text{ m (C=C)}, 1377 \text{ s (CH}_3\text{)}, 1352 \text{ s (SO}_2\text{)}, 1168 \text{ s (R-OH)}, 1120 \text{ s (SO}_2\text{)}, 754 \text{ s (Ph-H)}, 690 \text{ s (Ph-H)}. \]
6.4.2 Reactions of 4-Alkynyl-3-iodo-quinolines

General Method for the Synthesis of Pyrrolo[2,3-c]quinolines and 3-Amino-4-alkynylquinolines

Under an inert (N₂) atmosphere anhydrous DMA (5 mL) was added to a mixture of 4-alkynyl-3-iodoquinoline (1 equiv.), Pd(OAc)₂ (8 mol %), potassium carbonate (1.38 mmol, 3 equiv.) and Xantphos (10 mol %). To this mixture was added the relevant amine (1.2 equiv.), the reaction mixture was heated to 80 °C and stirred for 16 h. After this time the mixture was cooled, diluted with EtOAc, washed with water and brine. The organic phase was separated, dried (Na₂SO₄) and evaporated, and the crude material was purified by flash column chromatography unless otherwise stated. Reactions that provided 3-aminoquinolines gave these as the fastest running compounds (non-polar) from the column. The following were synthesised by this method.

2,4-Diphenyl-3-(p-tolyl)-3H-pyrrolo[2,3-c]quinoline (4.35Aa)

From 3-iodo-2-phenyl-4-(phenylethynyl)quinoline (0.20 g) and p-toluidine (0.063 g). From column chromatography (10% EtOAc – pet ether) to give the title compound as off white crystals (0.04 g, 21%) m.p. 229 °C; HRMS found [M+H]⁺ = 411.1859; C₃₅H₂₅N₂ [M+H]⁺ requires = 411.1863.

δn (CDCl₃) 8.32 – 8.29 (1H, m, 9-H), 8.23 (1H, app. d, 6-H), 7.66 – 7.58 (2H, m, 7-H, 8-H), 7.33 (1H, s, 1-H), 7.25 – 7.22 (5H, m, Ph-H), 7.12 – 7.07 (3H, m, Ph-H), 7.00 – 6.95 (2H, m, Ph-H), 6.70 – 6.65 (4H, m, Ar-H), 2.23 (3H, s, Ar-Me). δc 148.62 (qC), 143.53 (qC), 142.32 (qC), 139.14 (qC), 137.23 (qC), 135.44 (qC), 132.25 (qC), 130.22 (qC), 129.73 [2 X C (CH)], 129.67(qC), 128.98 (CH), 128.68 (CH), 128.66 (CH), 128.10 (CH), 127.88 (CH), 127.28 (CH), 126.80 (CH), 126.50 (CH), 125.89 (CH), 122.68 (CH), 122.65 (qC), 102.21 (CH), 21.02 (CH₃).

νmax/cm⁻¹: 3032 w (Ar-H), 1511 s (C=C), 1380 s (CH₃), 759 s (Ph-H), 695 s (Ph-H).
2-Phenyl-4-(phenylethynyl)-N-(p-tolyl)quinolin-3-amine (4.36Aa)

From 3-iodo-2-phenyl-4-(phenylethynyl)quinoline (0.20 g) and p-toluidine (0.063 g). From column chromatography (10% EtOAc – pet ether) to give the title compound as a bright yellow powder (0.07 g, 38%) m.p. 187 – 188 °C; HRMS found [M+H]^+ = 411.1860; C_{30}H_{23}N_{2} [M+H]^+ requires = 411.1863.

δ_H (CDCl_3) 8.33 – 8.29 (1H, m, 5-H), 8.14 – 8.10 (1H, m, 8-H), 7.74 – 7.71 (2H, m, Ph-H), 7.66 – 7.58 (2H, m, 6-H, 7-H), 7.48 – 7.37 (3H, m, Ph-H), 7.34 – 7.26* (3H, m, Ph-H), 7.13 – 7.10 (2H, m, Ph-H), 7.01 (2H, d, J = 8.1 Hz, m-Ar-H), 6.80 (2H, d, J = 8.1 Hz, o-Ar-H), 6.03 (1H, s, NH), 2.28 (3H, s, Ar-Me). δ_C 154.96 (qC), 144.00 (qC), 140.49 (qC), 138.44 (qC), 135.77 (qC), 131.69 (CH), 130.95 (qC), 129.75 (CH), 129.25 (CH), 129.00 (CH), 128.87 [2 X C (CH)], 128.77 (CH), 128.23 (CH), 128.08 (qC), 127.78 (CH), 127.42 (CH), 125.00 (CH), 122.54 (qC), 118.38 (CH), 117.85 (qC), 106.29 (qC), 83.99 (qC), 20.65 (CH_3).

ν_max/cm⁻¹: 3391 s (NH), 3051 w (Ar-H), 2917 w (CH_3), 1609 w (C=C), 1386 s (CH_3), 772 s (Ph-H), 700 s (Ph-H).

*Overlapping of CDCl_3 signal

2,3,4-Triphenyl-3H-pyrrolo[2,3-c]quinoline (4.35Ab)
From 3-iodo-2-phenyl-4-(phenylethynyl)quinoline (0.20 g) and aniline (50 µL). From column chromatography (toluene) and resulting residue washed with pentane to give the title compound as an orange powder (0.12 g, 74%) m.p. 163 °C; HRMS found [M+H]+ = 397.1695; C29H22N2 [M+H]+ requires = 397.1706.

δH (CD2Cl2) 8.40 – 8.38 (1H, m, 9-H), 8.20 – 8.16 (1H, m, 6-H), 7.71 – 7.64 (2H, m, 7-H, 8-H), 7.41 (1H, s, 1-H), 7.31 – 7.26 (5H, m, Ph-H), 7.16 – 7.03 (6H, m, Ph-H), 7.00 – 6.96 (2H, m, Ph-H), 6.90 – 6.87 (2H, m, Ph-H). δC 148.43 (qC), 143.64 (qC), 142.36 (qC), 139.16 (qC), 138.15 (qC), 132.25 (qC), 130.15 (qC), 129.69 (CH), 129.51 (CH), 129.49 (qC), 129.09 (CH), 128.86 (CH), 128.08 (CH), 128.02 (CH), 127.89 (CH), 127.39 (CH), 127.16 (CH), 127.08 (CH), 126.41 (CH), 125.81 (CH), 122.66 (CH), 122.57 (qC), 102.32 (CH).

νmax/cm⁻¹: 1498 s (C=C), 759 s (Ph-H), 694 s (Ph-H).

N2,2-Diphenyl-4-(phenylethynyl)quinolin-3-amine (4.36Ab)

From 3-iodo-2-phenyl-4-(phenylethynyl)quinoline (0.20 g) and aniline (50 µL). From column chromatography (toluene) to give the title compound as yellow crystals (0.006 g, 3%) m.p. 136 – 137 °C; HRMS found [M+H]+ = 397.1696; C29H21N2 [M+H]+ requires = 397.1706.

δH [(CD3)2CO] 8.26 – 8.23 (1H, m, 5-H), 7.96 – 7.93 (1H, m, 8-H), 7.71 – 7.68 (2H, m, Ph-H), 7.68 – 7.53 (2H, m, 6-H, 7-H), 7.18 (1H, s, NH), 7.15 – 7.12 (2H, m, Ph-H), 7.06 – 7.01 (2H, m, Ph-H), 6.77 – 6.74 (2H, m, Ph-H), 6.70 – 6.66 (2H, m, Ph-H). δC 156.35 (qC), 144.79 (qC), 144.53 (qC), 139.23 (qC), 135.37 (qC), 131.69 (CH), 129.75 (CH), 129.17 (CH), 128.94 (CH), 128.68 (CH), 128.59 (CH), 128.43 (CH), 128.23 (CH), 128.07 (CH), 127.67 (qC), 127.47 (CH), 125.06 (CH), 122.48 (qC), 121.21 (qC), 119.68 (CH), 116.29 (CH), 105.32 (qC), 83.79 (qC).

νmax/cm⁻¹: 3392 s (NH), 3052 w (Ar-H), 2206 m (C≡C), 1597 s (C=C), 745 s (Ph-H), 694 s (Ph-H).
3-(4-Methoxyphenyl)-2,4-diphenyl-3H-pyrrolo[2,3-c]quinoline (4.35Ad)

From 3-ido-2-phenyl-4-(phenylethynyl)quinoline (0.20 g) and p-anisidine (0.069 g). From column chromatography (10% EtOAc – hexane) to give the title compound as red crystals (0.07 g, 35%) m.p. 195 °C; HRMS found [M+H]^+ = 427.1805; C_{30}H_{23}N_{2}O [M+H]^+ requires = 427.1812.

$\delta_H$ [(CD$_3$)$_2$CO] 8.49 – 8.45 (1H, m, 9-H), 8.12 – 8.07 (1H, m, 6-H), 7.66 – 7.63 (2H, m, 7-H, 8-H), 7.52 (1H, s, 1-H), 7.35 – 7.29 (5H, m, Ph-H), 7.18 – 7.14 (3H, m, Ph-H), 7.08 – 7.04 (2H, m, Ph-H), 6.89 – 6.85 (2H, m, Ar-H), 6.56 – 6.52 (2H, m, Ar-H), 3.73 (3H, s, O-Me). $\delta_C$ 158.98 (qC), 148.46 (qC), 143.62 (qC), 142.42 (qC), 139.55 (qC), 132.43 (qC), 130.97 (qC), 130.18 (qC), 129.90 (qC), 129.78 (CH), 129.66 (CH), 129.55 (CH), 129.10 (CH), 128.07 (CH), 127.88 (CH), 126.89 (CH), 126.71 (CH), 126.17 (CH), 125.72 (CH), 122.82 (CH), 122.76 (qC), 113.38 (CH), 102.03 (CH), 54.88 (CH$_3$).

$\nu_{\text{max}}$/cm$^{-1}$: 3031 w (Ar-H), 2925w (CH$_3$), 1508 s (C=C), 1383 s (CH$_3$), 766 s (Ph-H), 696 s (Ph-H).

$N$-(4-Methoxyphenyl)-2-phenyl-4-(phenylethynyl)quinolin-3-amine (4.36Ad)

From 3-ido-2-phenyl-4-(phenylethynyl)quinoline (0.20 g) and p-anisidine (0.069 g). From column chromatography (10% EtOAc – hexane) to give the title compound as bright orange crystals (0.08 g, 40%) m.p. 131 – 132 °C; HRMS found [M+H]^+ = 427.1800; C_{30}H_{23}N_{2}O [M+H]^+ requires = 427.1812.
δH [(CD3)2CO] 8.21 – 8.17 (1H, m, 5-H), 7.90 – 7.86 (1H, m, 8-H), 7.67 – 7.64 (2H, m, Ph-H), 7.53 – 7.47 (2H, m, 7-H, 8-H), 7.27 – 7.19 (6H, m, Ph-H), 7.18 – 7.14 (2H, m, Ph-H), 6.92 (1H, s, NH), 5.76 – 5.72 (2H, m, α-Ar-H), 6.64 – 6.60 (2H, m, m-Ar-H). 3.55 (3H, s, O-Me). δc 155.34 (q C), 154.65 (q C), 144.01 (q C), 139.23 (q C), 137.72 (q C), 136.65 (CH), 129.70 (CH), 129.93 (CH), 127.93 (CH), 127.52 (CH), 127.44 (CH), 127.75 (CH), 122.64 (q C), 119.27 (CH), 117.70 (q C), 114.05 (CH), 105.29 (q C), 83.87 (q C), 54.94 (CH3).

νmax/cm⁻¹: 3393 m (NH), 3056 w (Ar-H), 2926 w (CH3), 2200 m (C≡C), 1506 s (C=C), 1388 m (CH3), 753 s (Ph-H), 687 s (Ph-H).

N-Benzyl-2-phenyl-4-(phenylethynyl)quinolin-3-amine (4.36Ae)

From 3-iodo-2-phenyl-4-(phenylethynyl)quinoline (0.20 g) and benzylamine (60 µL). From column chromatography (toluene) to give the title compound as a dark orange oil (0.11 g, 60%); HRMS found [M+H]^+ = 411.1850; C30H23N2 [M+H]^+ requires = 411.1863.

δH (CDCl3) 8.24 – 8.22 (1H, m, 5-H), 8.04 – 8.02 (1H, m, 8-H), 7.75 – 7.72 (2H, m, Ph-H), 7.57 – 7.43 (8H, m, 6-H, 7-H, Ph-H), 7.38 – 7.35 (3H, m, Ph-H), 7.28 – 7.20* (4H, m, Ph-H), 4.72 (1H, app. s, NH), 4.48 (2H, d, J = 4.0 Hz, CH2). δc 153.04 (q C), 142.51 (q C), 141.82 (q C), 139.73 (q C), 139.18 (q C), 131.47 (CH), 129.64 (CH), 128.98 (CH), 128.95 (CH), 128.92 (CH), 128.69 (CH), 128.62 (CH), 128.55 (CH), 128.21 (q C), 127.65 (CH), 127.40 (CH), 127.36 (CH), 126.59 (CH), 124.49 (CH), 122.76 (q C), 111.89 (q C), 102.73 (q C), 84.08 (q C), 51.54 (CH2).

νmax/cm⁻¹: 3057 w (Ar-H), 1509 w (C=C), 14911 w (CH2), 753 s (Ph-H), 687 s (Ph-H).

*Overlapping with CDCl3 signal
2,4-Diphenyl-3-[4-(trifluoromethyl)phenyl]-3H-pyrrolo[2,3-c]quinoline (4.35Af)

From 3-iodo-2-phenyl-4-(phenylethynyl)quinoline (0.20 g) and trifluoromethylaniline (70 µL). From column chromatography (20% toluene – hexane) to give the title compound as white needles (0.04 g, 20%) m.p. 250 °C; HRMS found [M+H]^+ = 465.1570; C$_{30}$H$_{20}$F$_3$N$_2$ [M+H]^+ requires = 465.1580

δ$_H$ [(CD$_3$)$_2$CO](600 MHz) 8.51 – 8.47 (1H, m, 9-H), 8.15 – 8.11 (1H, m, 6-H), 7.71 – 7.66 (2H, m, 7-H, 8-H), 7.58 (1H, s, 1-H), 7.34 – 7.30 (7H, m, Ph-H), 7.17 – 7.11 (5H, m, Ph-H, Ar-H), 7.05 – 7.01 (2H, m, Ar-H). δ$_C$ (150 MHz) 148.00 (q C), 143.40 (q C), 142.62 (q C), 141.75 – 141.74 (d, J = 1.4 Hz, q C), 139.26 (q C), 131.89 (q C), 130.41 (q C), 129.95 (CH), 129.80 (CH), 129.61 (CH), 129.46 (q C) 129.04 (CH), 128.24 [2 X C (CH)], 127.12 [2 X C (CH)], 127.09 (CH), 126.71 – 121.32 (q, J = 271.78 Hz, q C), 126.52 (CH), 126.00 (CH), 125.13 – 125.05 (q, J = 3.8 Hz, CH), 122.92 (CH), 122.66 (q C), 102.99 (CH). 19F [(CD$_3$)$_2$CO](376 MHz) δ$_F$ -63.14.

ν$_{max}$/cm$^{-1}$: 3057 w (Ar-H), 1597 w (C=C), 753 s (Ph-H), 687 s (Ph-H).

2-Phenyl-4-(phenylethynyl)-N-[4-(trifluoromethyl)phenyl]quinolin-3-amine (4.36Af)

From 3-iodo-2-phenyl-4-(phenylethynyl)quinoline (0.20 g) and trifluoromethylaniline (70 µL). From column chromatography (20% toluene – hexane) to give the title compound as a bright yellow solid (0.08 g, 35%) m.p. 184 – 185 °C; HRMS found [M+H]^+ = 465.1567; C$_{30}$H$_{20}$F$_3$N$_2$ [M+H]^+ requires = 465.1580
δ_H [(CD_3)_2CO] (600 MHz) 8.41 (1H, dd, J = 8.2, 0.7 Hz, 5-H), 8.11 (1H, app. d, 8-H), 7.92 (1H, s, NH), 7.83 – 7.81 (2H, m, Ph-H), 7.80 – 7.77 (1H, m, 7-H), 7.73 – 7.71 (1H, m, 6-H), 7.50 (2H, d, J = 8.6 Hz, m-Ar-H), 7.43 – 7.40 (4H, m, Ph-H), 7.37 – 7.35 (2H, m, Ph-H), 7.24 – 7.23 (2H, m, Ph-H), 7.01 (2H, d, J = 8.6 Hz, o-Ar-H). δ_c (150 MHz) 157.00 (q C), 148.31 – 148.29 (q, J = 1.0 Hz, q C), 145.54 (q C), 133.78 (q C), 131.63 (CH), 129.83 (CH), 129.48 (CH), 129.06 [2 X C (CH)], 129.05 (q C), 128.73 (CH), 128.51 (CH), 128.11 (CH), 127.88 – 122.52 (q, J = 269.72 Hz, q C), 127.66 (CH), 127.45 (q C), 126.16 – 126.08 (q, J = 3.8 Hz, CH), 125.36 (CH), 123.87 (q C), 122.17 (q C), 120.22 – 119.58 (q, J = 3.2 Hz, q C), 114.99 (CH), 105.70 (q C), 83.64 (q C).

ν_max/cm⁻¹: 3393 m (NH), 3052 w (Ar-H), 2207 m (C≡C), 1611 s (C=C), 1099 s (C-F), 755 s (Ph-H), 688 s (Ph-H).

2,4-Bis(4-methoxyphenyl)-3-(p-tolyl)-3H-pyrrolo[2,3-c]quinoline (4.35Ca)

From 3-iodo-2-(4-methoxyphenyl)-4-[(4-methoxyphenyl)ethynyl]quinoline (0.25 g) and p-toluidine (0.09 g). From column chromatography (10% EtOAc – pet ether) to give the title compound as off white powder (0.09 g, 40%) m.p. 238 – 239 °C; HRMS found [M+H]^+ = 471.2061; C_{32}H_{27}N_2O_2 [M+H]^+ requires = 471.2074.

δ_H (CDCl_3) 8.29 – 8.27 (1H, m, 9-H), 8.23 – 8.21 (1H, m, 6-H), 7.63 – 7.55 (2H, m, 7-H, 8-H), 7.25* (1H, s, 1-H), 7.13 – 7.10 (2H, m, Ar-H), 7.03 – 6.99 (2H, m, Ar-H), 6.75 – 6.72 (4H, m, Ar-H), 6.64 (2H, d, J = 8.3 Hz, Ar-H), 6.52 – 6.48 (2H, m, Ar-H), 3.75 (3H, s, O-Me), 3.72 (3H, s, O-Me), 2.23 (3H, s, Ar-Me). δ_c 159.27 (q C), 158.95 (q C), 148.22 (q C), 143.48 (q C), 142.32 (q C), 136.97 (q C), 135.68 (q C), 131.65 (q C), 130.91 (CH), 130.27 (q C), 130.16 (CH), 129.54 [2 X C (q C) (CH)], 128.77 (CH), 128.65 (CH), 126.40 (CH), 125.64 (CH), 124.62 (q C), 122.65 (CH), 122.57 (q C), 113.59 (CH), 112.80 (CH), 101.62 (CH), 55.33 (CH_3), 55.21 (CH_3), 21.02 (CH_3).
ν\textsubscript{max}/cm\textsuperscript{-1}: 1607 s (C=C), 1485 s (CH\textsubscript{3}).

*Overlapping with CDCl\textsubscript{3} signal

2,4-Bis(4-methoxyphenyl)-3-phenyl-3H-pyrrolo[2,3-c]quinoline (4.35Cb)

\[
\begin{array}{c}
\text{OMe} \\
\text{N} \\
\text{OMe} \\
\end{array}
\]

From 3-iodo-2-(4-methoxyphenyl)-4-[(4-methoxyphenyl)ethynyl]quinoline (0.16 g) and aniline (33 µL). From column chromatography (10% EtOAc – pet ether) to give the title compound as a yellow solid (0.06 g, 37%) m.p. 186 – 187 °C; HRMS found [M+H]\textsuperscript{+} = 457.1906; C\textsubscript{31}H\textsubscript{25}N\textsubscript{2}O\textsubscript{2} [M+H]\textsuperscript{+} requires = 457.1918.

δ\textsubscript{H} (CDCl\textsubscript{3}) 8.30 – 8.28 (1H, m, 9-H), 8.25 – 8.23 (1H, app. d, 6-H), 7.65 – 7.56 (2H, m, 7-H, 8-H), 7.27 (1H, s, 1-H), 7.11 – 7.03 (5H, m, Ar-H), 6.98 – 6.94 (2H, m, Ph-H), 6.78 (2H, app. d, Ph-H), 6.76 – 6.73 (2H, m, Ar-H), 6.53 – 6.49 (2H, m, Ar-H), 3.76 (3H, s, O-Me), 3.72 (3H, s, O-Me). δ\textsubscript{C} 159.32 (qC), 158.91 (qC), 148.09 (qC), 143.62 (qC), 142.30 (qC), 138.27 (qC), 131.43 (qC), 130.93 (CH), 130.45 (qC), 130.16 (CH), 129.47 (CH), 129.29 (qC), 129.08 (CH), 128.10 (CH), 127.19 (CH), 126.52 (CH), 125.72 (CH), 124.52 (qC), 122.65 (CH), 122.51 (qC), 113.59 (CH), 112.94 (CH), 101.87 (CH), 55.36 (CH\textsubscript{3}), 55.22 (CH\textsubscript{3}).

ν\textsubscript{max}/cm\textsuperscript{-1}: 2933 w (Ar-H), 2834 w (CH\textsubscript{3}), 1607 s (C=C), 1500 s (C=C), 1371 s (CH\textsubscript{3}), 756 s (Ph-H), 699 s (Ph-H).
2-(4-Methoxyphenyl)-4-[[4-methoxyphenyl]ethynyl]-N-phenylquinolin-3-amine (4.36Cb)

From 3-iodo-2-(4-methoxyphenyl)-4-[[4-methoxyphenyl]ethynyl]quinoline (0.16 g) and aniline (33 µL). From column chromatography (10% EtOAc – pet ether) to give the title compound as a brown solid (0.03 g, 20%) m.p. 135 – 136 °C; HRMS found [M+H]+ = 457.1904; C_{31}H_{25}N_{2}O_{2} [M+H]+ requires = 457.1918.

δ_{H} (CDCl_{3}) 8.29 (1H, dd, J = 8.0, 1.0 Hz, 5-H), 8.11 (1H, dd, J = 8.0, 1.0 Hz, 8-H), 7.71 – 7.68 (2H, m, Ar-H), 7.66 – 7.56 (2H, m, 6-H, 7-H), 7.23 – 7.19 (2H, m, Ph-H), 7.06 – 7.03 (2H, m, Ar-H), 6.97 – 6.90 (3H, m, Ar-H, Ph-H), 6.86 (2H, app. d, Ph-H), 6.82 – 6.78 (2H, m, Ar-H), 6.04 (1H, s, NH), 3.83 (3H, s, O-Me), 3.81 (3H, s, O-Me). δ_{C} 160.26 (qC), 160.21 (qC), 155.03 (qC), 144.45 (qC), 143.26 (qC), 134.69 (qC), 133.32 (CH), 130.85 (qC), 130.28 (CH), 129.58 (CH), 128.81 (CH), 128.05 (CH), 127.70 (qC), 127.08 (CH), 125.20 (CH), 120.85 (CH), 120.12 (qC), 117.37 (CH), 114.53 (qC), 114.22 (CH), 113.95 (CH), 106.66 (qC), 84.00 (qC), 55.37 (CH_{3}), 55.33 (CH_{3}).

ν_{max}/cm\(^{-1}\): 3390 s (NH), 2927 w (Ar-H), 2837 w (CH_{3}), 2200 s (C≡C), 1601 s (C=C), 1510 s (C=C), 751 m (Ph-H), 693 m (Ph-H).

Synthesis of 3-Benzyl-2,4-diphenyl-3H-pyrrolo[2,3-c]quinoline (4.35Ae)
Under an inert (N₂) atmosphere N-benzyl-2-phenyl-4-(phenylethynyl)quinolin-3-amine (0.10 g, 0.002 mmol, 1.0 equiv.) and PdCl₂ (10 mol %) in 5 mL of anhydrous DMF was stirred at 160 °C for 2 h. After this time the mixture was allowed to cool to r.t. and the solvent removed, the residue was purified by flash column chromatography (10% – pet ether) to give the title compound as a yellow oil (0.06 g, 60%); HRMS found [M+H]⁺ = 411.1854; C₃₀H₂₃N₂ [M+H]⁺ requires = 411.1863.

δH (CDCl₃) 8.29 – 8.27 (1H, m, 9-H), 8.23 – 8.21 (1H, m, 6-H), 7.64 – 7.57 (2H, m, 7-H, 8-H), 7.51 – 7.48 (2H, m, Ph-H), 7.43 – 7.37 (4H, m, Ph-H), 7.34 – 7.28 (4H, m, Ph-H), 7.26 (1H, s, 1-H), 7.04 – 7.00 (1H, m, Ar-H), 6.96 – 6.92 (2H, m, Ar-H), 6.11 (2H, app. d, Ar-H), 5.15 (2H, s, CH₂). δC 148.65 (qC), 145.75 (qC), 142.23 (qC), 139.62 (qC), 138.35 (qC), 132.14 (qC), 131.05 (qC), 129.75 (CH), 129.51 (CH), 129.11 (CH), 128.91 (qC), 128.78 (CH), 128.68 (CH), 128.38 (CH), 128.12 (CH), 127.96 (CH), 126.85 (CH), 126.60 (CH), 125.91 (CH), 125.13 (CH), 122.71 (qC), 122.65 (CH), 102.45 (CH), 49.46 (CH₂).

νmax/cm⁻¹: 3055 w (Ar-H), 2924 w (CH₂), 1566 w (C=C), 1478 s (CH₂), 769 s (Ph-H), 696 s (Ph-H).

**General Method for the Suzuki-Miyaura Couplings of 3-Iodo-2-phenyl-4-(phenylethynyl)quinoline**

To a mixture of degassed EtOH : PhMe (50 : 50) was added 3-iodo-2-phenyl-4-(phenylethynyl)quinoline (0.50 g, 1.16 mmol, 1.0 equiv.), the appropriate boronic acid (2.3 equiv.), potassium carbonate (0.38 g, 2.78 mmol, 2.4 equiv.) and Pd(PPh₃)₄ (2.5 mol %). The solution was stirred under N₂ at reflux for 22 h. After this time the mixture was cooled, diluted with EtOAc, washed with water and brine. The organic phase was separated, dried (Na₂SO₄) and evaporated. The crude material was purified by flash column chromatography (8% EtOAc – hexane) the following were synthesised by this method.
2,3-Diphenyl-4-(phenylethynyl)quinoline (4.41a)

From phenylboronic acid (0.32 g, 2.67 mmol) to give the title compound as a yellow powder (0.30 g, 68%) m.p. 148 – 149 °C; HRMS found [M+H]^+ = 382.1590; C_{29}H_{17}N [M+H]^+ requires = 382.1597.

δH (CDCl₃) 8.44 (1H, dd, J = 8.3, 0.8 Hz, 5-H), 8.22 (1H, app. d, 8-H), 7.76 – 7.72 (1H, m, 7-H), 7.65 – 7.61 (1H, m, 6-H), 7.43 – 7.39 (2H, m, Ph-H), 7.34 – 7.29* (10H, m, Ph-H), 7.24 – 7.20 (3H, m, Ph-H). δc 158.59 (qC), 147.09 (qC), 140.62 (qC), 138.63 (qC), 136.21 (qC), 131.86 (CH), 131.08 (CH), 130.03 [2 X C (CH)], 129.96 (CH), 129.67 (qC), 129.17 (CH), 128.46 (CH), 127.95 (CH), 127.84 (CH), 127.77 (CH), 127.45 (CH), 127.36 (CH), 126.62 (qC), 126.31 (CH), 122.57 (qC), 101.99 (qC), 85.61 (qC).

νmax/cm⁻¹: 3055 w (Ar-H), 2208 w (C≡C), 1596 s (C=C), 755 s (Ph-H), 689 s (Ph-H).

*Overlapping with CDCl₃ signal

2-Phenyl-4-(phenylethynyl)-3-(p-tolyl)quinoline (4.41b)

From p-tolylboronic acid (0.36 g, 2.67 mmol) to give the title compound as a white powder (0.32 g, 70%) m.p. 174 – 175 °C; HRMS found [M+H]^+ = 382.1590; C_{29}H_{17}N [M+H]^+ requires = 382.1597.
δ\textsubscript{H} [(CD\textsubscript{3})\textsubscript{2}CO] 8.51 (1H, dd, J = 8.3, 0.9 Hz, 5-H), 8.14 (1H, app. d, 8-H), 7.87 – 7.83 (1H, m, 7-H), 7.77 – 7.73 (1H, m, 6-H), 7.47 – 7.39 (7H, m, Ar-H), 7.31 – 7.20 (7H, m, Ar-H), 2.36 (3H, s, Ar-Me). δ\textsubscript{c} 158.43 (qC), 147.00 (qC), 140.96 (qC), 137.09 (qC), 136.17 (qC), 135.75 (qC), 131.67 (CH), 130.87 (CH), 130.04 (CH), 129.92 (CH), 129.85 (CH), 129.40 (CH), 129.06 (qC), 128.66 (CH), 128.39 (CH), 127.72 (CH), 127.56 (CH), 127.44 (CH), 126.28 (qC), 126.07 (CH), 122.36 (qC), 101.57 (qC), 85.24 (qC), 20.42 (CH\textsubscript{3}).

ν\textsubscript{max}/cm\textsuperscript{-1}: 3055 w (Ar-H), 2980 w (CH\textsubscript{3}), 2208 m (C≡C), 761 s (Ph-H), 695 s (Ph-H).

**{(E)}-4-{1-Chloro-2-iodo-2-phenylvinyl}-2,3-diphenylquinoline (4.42a)**

To a solution of 2,3-diphenyl-4-(phenylethynyl)quinoline (0.20 g, 0.55 mmol, 1 equiv.) in MeCN (15 mL) was added iodine monochloride (78 μL, 1.65 mmol, 3 equiv.) and the mixture stirred at reflux for 16 h. After this time the reaction mixture was quenched with aqueous sodium thiosulfate and diluted with EtOAc. The organic phase was separated, dried (Na\textsubscript{2}SO\textsubscript{4}) and evaporated to give a powder which was washed with pentane to give the title compound as an orange powder (0.26 g, 92%) m.p. 180 °C decomp; HRMS found [M+H]\textsuperscript{+} = 544.0314; C\textsubscript{29}H\textsubscript{17}\textsubscript{35}ClIN [M+H]\textsuperscript{+} requires =544.0331.

δ\textsubscript{H} (CD\textsubscript{2}Cl\textsubscript{2}) (600 MHz) 8.29 (1H, app. d, 8-H), 8.13 (1H, app. d, 5-H), 7.87 (1H, app. t, 7-H), 7.78 (1H, app. t, 6-H), 7.63 (2H, d, J = 7.2 Hz, Ph-H), 7.49 – 7.39 (7H, m, Ph-H), 7.35 – 7.26 (7H, m, Ph-H). δ\textsubscript{c} (150 MHz) 159.33 (qC), 147.75 (qC), 146.08 (qC), 140.55 (qC), 140.27 (qC), 137.76 (qC), 133.95 (qC), 131.43 (qC), 130.30 (CH), 130.08 (CH), 130.02 (CH), 129.74 (CH), 129.51 (CH), 128.74 (CH), 128.50 (CH), 127.86 (CH), 127.83 (CH), 127.75 (CH), 127.72 (CH), 127.54 (CH), 127.36 (CH), 125.01 (CH), 122.55 (qC), 88.91 (qC).

ν\textsubscript{max}/cm\textsuperscript{-1}: 1483 w (C=C), 756 s (Ph-H), 693 s (Ph-H).
Chapter 7

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Chapter 8

Appendices
Chapter 8 Appendices

8.1 Appendices 1.0

Crystal structure information for: 6-iodo-2-methyl-5-phenyl-6α-(phenylethynyl)-6αH-1,2-benzisothiazolo[2,3-α]quinoline 11,11-dioxide
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Table 8.1 Crystal data for 6-iodo-2-methyl-5-phenyl-6α-(phenylethynyl)-6αH-1,2-benzisothiazolo[2,3-a]quinoline 11,11-dioxide 2.66-3
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**Table 8.2** Bond lengths and angles for 6-ido-2-methyl-5-phenyl-6α-(phenylethynyl)-6αH-1,2-benzisothiazolo[2,3-α]quinoline 11,11-dioxide 2.66-3
Crystal structure information for: 2-(6-Hydroxyundeca-4,7-diyn-6-yl)-N-(p-tolyl)benzenesulfonamide
Table 8.3 Crystal data for 2-(6-Hydroxyundeca-4,7-diyn-6-yl)-N-(p-tolyl)benzenesulfonamide 2.23Bb

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O1         S1        O2        108.33
O1         S1        C8        106.49
O2         S1        C8        109.44
S1         N1        H1        120.13
S1         N1        C1        119.75
H1         N1        C1        120.13
H3         O3        C14       109.47
N1         C1        C2        121.17
N1         C1        C6        119.41
C2         C1        C6        119.41
C1         C2        H2        120.39
C1         C2        C3        119.21
H2         C2        C3        120.40
C2         C3        H3a       118.99
C2         C3        C4        122.04
H3a        C3        C4        118.97
C3         C4        C5        117.97
C3         C4        C7        120.84
C5         C4        C7        121.19
C4         C5        H5        119.51
C4         C5        C6        120.96
H5         C5        C6        119.52
C1         C6        C5        120.41
C1         C6        H6        119.79
C5         C6        H6        119.81
C4         C7        H7a       109.48
C4         C7        H7b       109.48
C4         C7        H7c       109.47
H7a        C7        H7b       109.47
H7a        C7        H7c       109.46

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C8          C13      C14      124.53
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O3          C14      C13      106.58
O3          C14      C15      113.25
O3          C14      C20      108.98
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C15        C16      C17      174.53
C14        C20      C21      172.90
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H22a        C22      C21      58.660
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H22b        C22      C23      109.22
H22b        C22      C21      51.270
H22b        C22      C21      109.20
C23        C22      H22c      111.34
C23        C22      C21      111.98
H22c        C22      C21      136.50
C22        C23      H23a      108.86
C22        C23      H23b      108.86
H23a        C23      H23b      107.72
H24a        C24      H24b      109.47
H24a        C24      H24c      109.47
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**Table 8.4** Bond lengths and angles for 2-(6-Hydroxyundeca-4,7-diyln-6-yl)-N-(p-tolyl)benzenesulfonamide 2.23Bb