Synthesis of Five-Membered Heterocycles:

Novel Allosteric Modulators for Nicotinic Receptors and New Gold-Catalysed Reactions

A dissertation presented by

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degree of

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Declaration

I, Jarryl D'Oyley, confirm that the work presented in this thesis is my own. Where information is derived from other sources, I confirm that it has been indicated and acknowledged.

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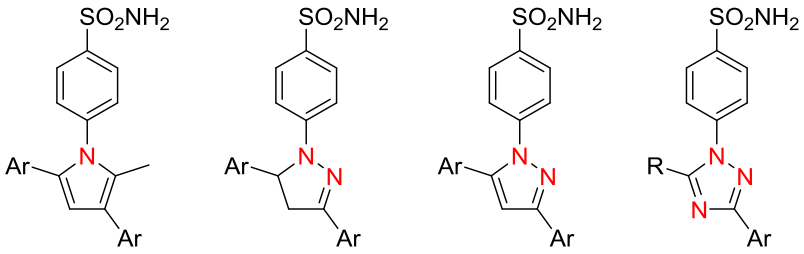
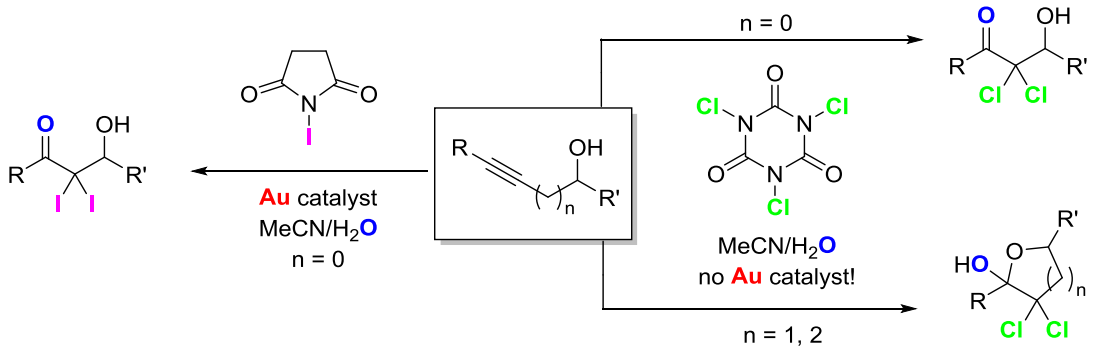
Abstract

The Drug Discovery project is centred on the design, synthesis and characterisation of novel positive allosteric modulators (PAMs) for α7 nicotinic receptors (nAChR). These receptors are widely found in the central and peripheral nervous systems and are involved in a range of physiological processes. They are active targets for the treatment of pain as well as psychiatric and neurodegenerative disorders. Nicotinic receptors are ion channels which open and allow ions to flow in or out of the neuron upon binding of an agonist. Positive allosteric modulators (PAM) enhance the receptor's response to the binding of the endogenous agonist, giving greater ion flow than the effect for binding of the agonist alone. A number of novel heterocycles were designed and synthesised and their effect on the α7 nAChR evaluated. The nitrogen heterocycles gave varied pharmacological effects on the receptor and small changes in structure led to large changes in pharmacological activity.



During the course of this project we have discovered Au-catalysed and non-catalysed processes for the dihalohydration of alkynols to form diiodoketoalcohols, dichloroketoalcohols and dichlorolactols.



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- P. Starkov, F. Rota, J. M. D'Oyley, T. D. Sheppard, *Adv. Synth. Catal*. **2012**, *354*, 3217
- S. Ishikawa, T. D. Sheppard, J. M. D'Oyley, A. Kamimura, W. B. Motherwell, *Angew. Chem.* **2013**, *125*, 10244
- J. M. D'Oyley, A. E. Aliev, T. D. Sheppard, *Angew. Chem* **2014**, *126*, 10923
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- A. Chatzidaki, J. M. D'Oyley, T. D. Sheppard, N. S. Millar, *Manuscript in Preparation*

Contents

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I thank my family because without them I would not have had the education and support to complete my PhD. Thanks to my parents for being proud of me even though they have no clue about what I do.

I remember walking past UCL Chemistry with my wife (then girlfriend) talking about whether I should apply to do a PhD. She gave me the encouragement and faith to pursue my PhD and with her love and support I have completed it, I will be eternally grateful to her.

Abbreviations

AcOH	Acetic acid
MeCN	Acetonitrile
Ac	Acetyl
Bn	Benzyl
Bp	Boiling point
Cat.	Catalytic
X	Counter ion
Cy	Cyclohexyl
DBA	Dibromoisocyanuric acid
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	*N*,*N*-Diisopropylethylamine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
EI	Electron Impact
EWG	Electron withdrawing group
E	Electrophile
EI	Electrospray ionisation
er	Enantiomeric ratio
Et_2O	Diethyl ether
EtOH	Ethanol
Et	Ethyl
EtOAc	Ethyl acetate
Eq.	Equivalents
g	Grams
HEPES	4-(2-Hydroxyethyl)-1-piperazineethanesulfonic acid
HRMS	High resolution mass spectrometry
h	Hour(s)
n	Integer number
i	Iso
IPr	2,6-bis(disopropylphenyl)imidazol-2-ylidene
LA	Lewis acid
L	Ligand
LiHMDS	Lithium hexamethyldisilazide

Mp	Melting point
m-	meta
MeOH	Methanol
Me	Methyl
Mg	Milligram
mL	Millilitre
mmol	Millimole
µW	microwave
nAChR	nicotinic acetylcholine receptor
NAM	Negative Allosteric Modulator
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
nm	Nanometre
NHC	*N*-Heterocyclic carbene
NMR	Nuclear magnetic resonance spectroscopy
Nu	Nucleophile
o-	Ortho
p-	Para
PAM	Positive Allosteric Modulator
ppm	Parts per million
Ph	Phenyl
PMP	Paramethoxyphenyl
Pr	Propyl
Ref.	Reference
RT	Room temperature
Temp	Temperature
t or *tert*	*T*ertiary
TBS	tert-Butyl dimethylsilyl
TCA	Trichloroisocyanuric acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMADCl	Tetromethylammonium dichloroiodide
PhMe	Toluene

TEA or NEt_3	Triethylamine
UCL	University College London
ν	Wavenumber

Chapter 1 Introduction

1.1 The Nervous System

The nervous system is an organ system which conducts signals to and from different parts of the body. The way that animals act and react depends on this complex, organised and discrete neuronal processing.

The nervous system can be split into two main systems: the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS includes the brain and the spinal cord whilst the PNS has nerves which connect the CNS to the extremities of the body. Both nervous systems are mainly comprised of neurons and their supporting cells. Neurons are specialised cells which are able to conduct electrical signals to other neurons (up to 15,000). The three functional classes of neuron are: interneurons, efferent neurons and afferent neurons. Around 99% of the neurons in the nervous system are interneurons and lie entirely within the CNS. It is believed that humans have $> 1\times10^{11}$ interneurons.

Neurons have a cell body (soma) which contains the nucleus and have dendrites to connect to other cells. Neurons also have an axon which is insulated in a myelin sheath which leads to other neurons. Dendrites can receive a signal which travels through the axon to the terminal where there is a synapse with the next neuron, the signal causes vesicles containing neurotransmitters in the cells to be released into the synaptic cleft. The neurotransmitters diffuse to receptor sites on the post-synaptic membrane; initiating electrical signal in this neuron, relaying the original signal. This process is known as neurotransmission.

1.2 Neuron receptors

1.2.1 Cys-loop ion channel receptors

The neurotransmitters interact with the receptors on the surface of post-synaptic membranes. The receptors on the phospholipid bilayer are membrane-bound proteins that have a neurotransmitter receptor site and a central pore that allows ions to flow through once activated. These receptors on neurons are known as Cys-loop receptors. The name is derived from the characteristic loop formed by a disulfide bond between two cysteine residues in the *N*-terminal extracellular domain. Cys-loop receptors are ligand-gated ion

channels which include $GABA_A$, $GABA_A$-ρ ($GABA_C$), serotonin (5-HT_3), glycine and acetylcholine (ACh) receptors. 5-HT_3 is structurally the most similar to nicotinic receptors.

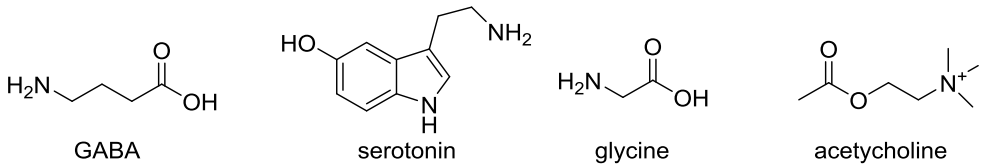


Figure 1.1: Endogenous neurotransmitters for Cys-Loop receptors

$GABA_A$ and $GABA_C$ receptors are inhibitory and upon activation become permeable to Cl^-. The $GABA_A$-ρ receptors contain only rho-subunits and are highly expressed in the retina. 5-HT_3 receptors upon activation become permeable to Na^+, K^+ and Ca^{2+}. Glycine receptors are also inhibitory and upon activation become permeable to Cl^-. They can be activated by β-alanine and taurine. Nicotinic acetylcholine receptors, upon activation by acetylcholine (ACh) allow the flow of Na^+, K^+ and Ca^{2+} ions and this receptor will be explained further in this section.

The function of the Cys-loop receptors is the direct conversion of a chemical (neurotransmitter) signal from the pre-synaptic neuron to an action potential in the post-synaptic neuron. This group are characterised by the presence of two domains: the intracellular domain including the ion pore and the extracellular domain which includes the binding site for ligands. Upon neurotransmitter binding, there is a conformational change in the protein allowing ions to flow.

1.2.2 Nicotinic acetylcholine receptors (nAChR) in vertebrates

Nicotinic receptors are the most intensively studied type of neurotransmitter-gated ion channel. The α7 nicotinic acetylcholine receptor (nAChR), with 5 identical α7 subunits was the first ligand-gated ion channel to be discovered and is part of the superfamily of Cys-loop receptors.[2] In mammals nicotinic receptors are found on the post-synaptic membrane of neuronal cells, as well as non-neuronal cells such as lymphocytes, macrophages, epithelial and endothelial cells.[3]

The nAChR is comprised of 5 homomeric or heteromeric protein subunits, symmetrically arranged around a central pore to form a receptor subtype. Each subunit comprises a large extracellular amino-terminal domain, 4 transmembrane helices (TM1-TM4) and a long cytoplasmic loop between TM3 and TM4 and the *C*-termini located extracellularly.[4] Each subunit comprises of: amino-terminal extracellular domain, transmembrane domain and a variable cytoplasmic domain.

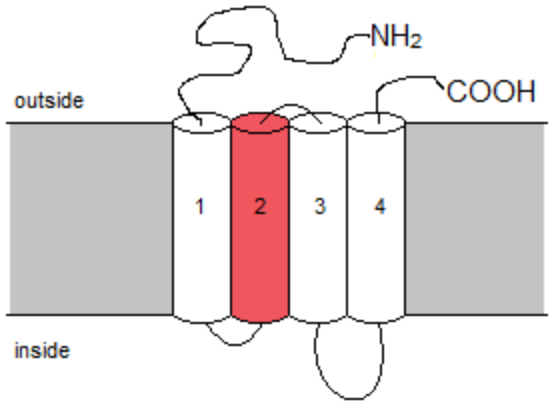


Figure 1.2: Topology of a single receptor subunit showing the 4 transmembrane domains (TM)

The subunits may all be identical such as in the α7 nAChR or be different such as in the case of α4β2 subtype (3 × β2 units and 2 × α4 subunits). Neuronal nAChR subtypes expressed in mammalian brain and ganglia are assembled in combinations of α2-9 and β2-4 and are pharmacologically classified into two branches based on their sensitivity to α-Bungarotoxin (α-BGT). α-BGT is a component of the venom of the Taiwanese snake *Bungarus multicinctus*. The peptide consists of 74 amino acids and weighs 8 kD. There are many entropically viable forms of this peptide which retains its structure after boiling or addition of strong acid.

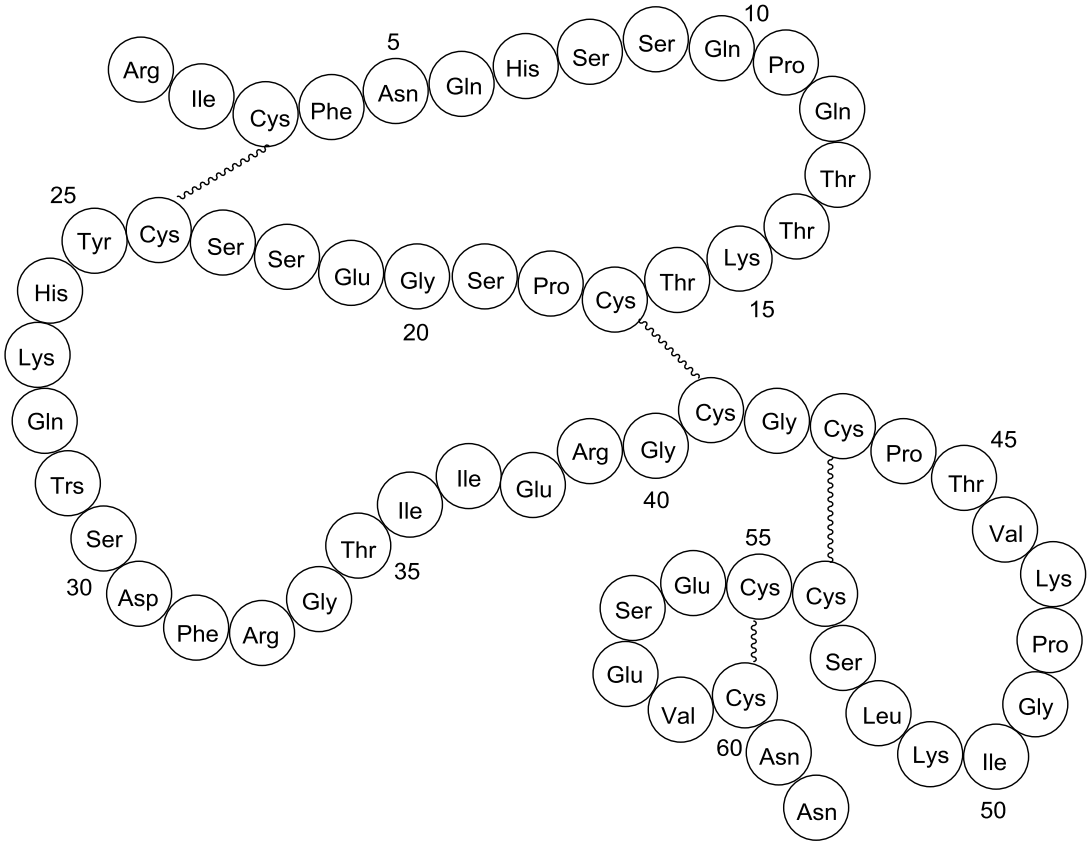


Figure 1.3: α-Bungarotoxin

It is a neurotoxin that is known to bind irreversibly and competitively to the nAChR. The α-BGT insensitive branch is made up of subtypes with combinations of α2-6 and β2-4 subunits. The α7-9 subunits are involved in the α-BGT sensitive subtypes in brain and ganglia, and the amount of α7-containing receptor is comparable to that of the α4β2 subtype in brain.[5]

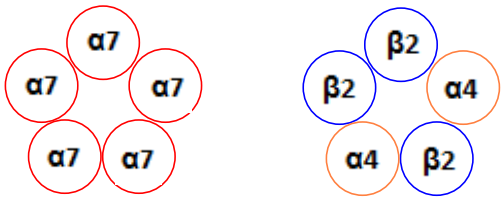


Figure 1.4: Topology of α4β2 and α7 nicotinic receptors

The α7 and α4β2 nAChR subtypes are the prominent subtypes expressed in the mammalian brain.[6] The α7 nAChR was discovered in the early 1990s and since then has received considerable attention.[7,8]

The different subunits vary in their primary amino acid structure which allows changes in the interaction between the subunits, providing structural variation in the protein giving

the proteins their unique characteristics. The many different subtypes are distributed throughout the nervous system dependent on their function. The α7 nAChR is also highly expressed in the hippocampus, a region that is known to be involved in memory formation. Gene knockout studies have also shown that α7 nAChRs have a role in learning, attention and memory. Genetic and pharmacological studies have shown that the nAChRs are implicated in a number of neurodegenerative diseases leading to decreased cognitive function, learning and memory, motor control and immune function.[9] Due to their fundamental role in the CNS, targeting α7 nAChRs is a viable strategy for the treatment of a variety of disorders, particularly those involving attention deficits and cognition. It is proposed that enhancing nAChR function by activation makes the receptor an attractive drug target due to the potential to ameliorate pathophysiological deficits in certain disease states.[9] These receptors are currently active targets for the treatment of pain, psychiatric and neurodegenerative disorders.[10]

1.2.3 Nicotinic acetylcholine receptors (nAChR) in insects

The introduction thus far has focused on vertebrate nAChRs, however, the invertebrates also have a nervous system. It was found that invertebrate nAChRs are the site of action for neuroactive pesticides known as neonicotinoids. Once nicotine itself was characterised as an agonist of nAChRs, researchers found that it could act as an insecticide by activating and blocking insect nAChRs causing convulsions, then paralysis and eventually death. Nicotine is still in use as an insecticide today, however, the use of neonicotinoids is much more prevalent. Their advantage over nicotine is their selectivity for insect nAChRs and low vertebrate toxicity.

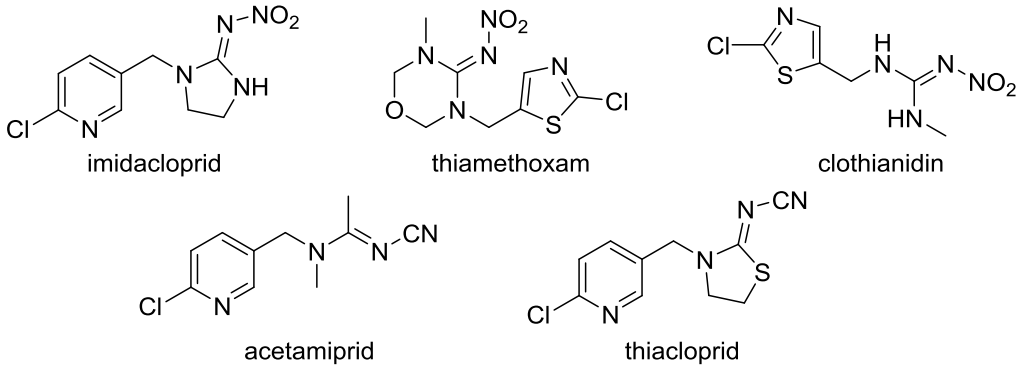


Figure 1.5: Top-selling neonicotinoid pesticides

The best-selling neonicotinoids are shown in **Figure 1.5** and note that these molecules have either nitramide or cyanamide moieties. Imidacloprid is the best-selling insecticide in the world and was developed by Bayer Cropscience in 1986. Neonicotinoids act as irreversible agonists of the nicotinic receptor, this leads to blocking of receptors and accumulation of acetylcholine. Insect nAChRs are poorly understood compared to vertebrate nAChRs in terms of diversity and functional architecture. The pharmacological characterisation of many insect nAChRs has been hindered due to the difficulty of achieving recombinant nAChR expression to give functional receptors.[11] Researchers have created functional *hybrid* receptors by co-expession of *Drosophila* α-subunits and vertebrate β-subunits in *Xenopus* oocytes. These receptors are more sensitive to imidacloprid than the equivalent vertebrate receptors. The rationale for the selectivity of imidacloprid (and the other neonicotinoids) for insect receptors is that they are not ionised at physiological pH and do not interact strongly with vertebrate nAChR receptor sites. In insect nAChRs at physiological pH, one of the amines on the pesticides is charged and can interact with amino-acid sidechains of the receptor. It is believed by many that the reason of decline of bee population may be due to neonicotinoids causing colony collapse disorder.[12]

1.3 Alzheimer's Disease (AD) and other neurodegenerative disorders

Alzheimer's Disease (AD) is the most common form of dementia and is the most common neurodegenerative disorder. It was first described by Alois Alzheimer, a German neurologist. Currently the condition can only be confirmed by autopsy by finding the characteristic brain lesions associated with the disease. These brain lesions are neuritic plaques and neurofibrilliary tangles that are dispersed in the cerebral cortex and the hippocampus. The neuritic plaques have a central core of extracellular, waxy, fibrous protein known as β-amyloid surrounded by degenerating dendritic and axonal nerve endings. The neurofibrilliary tangles are closed bundles of abnormal filaments that accumulate in the cell bodies of affected neurons. The formation of these lesions damage the acetylcholine (ACh), releasing axons, leading to the loss of these neurons and results in the reduced ACh in these areas. AD is characterised by cognitive decline, a loss of neurons and synapses, as well as a reduction in nAChR expression. One of the key stages of AD proliferation in terms of memory loss is the decrease in the production of ACh.[13,14] AD affects millions of people worldwide and with only limited treatments currently available, much effort is devoted towards new therapies. The current approved drugs for AD are

acetylcholine esterase (AChE) inhibitors.[15] Donezepil hydrochloride, rivastigmine and galantamine are recommended for patients with mild to moderate symptoms of AD in the UK.

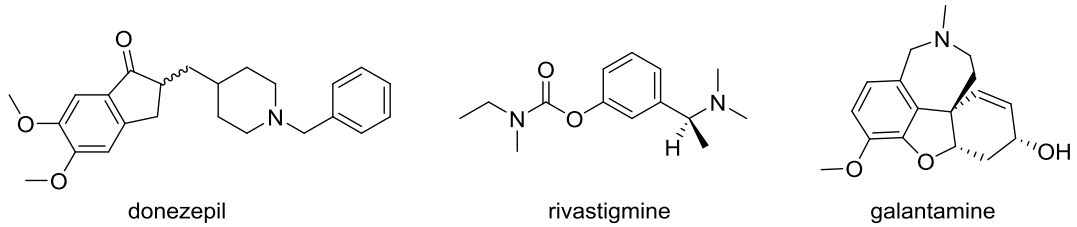


Figure 1.6: Acetylcholine esterase inhibitors

These molecules block the breakdown of ACh by inhibition of the enzyme that degrades ACh in the synaptic cleft which help to maintain the existing supplies of ACh. Another cause of the proliferation of AD is the excess of the neurotransmitter glutamate, causing excitotoxicity leading to cell death.

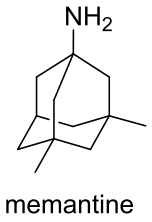
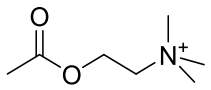


Figure 1.7: An antagonist of NMDA receptors

Memantine is an uncompetitive antagonist of glutamatergic *N*-methyl-D-aspartate (NMDA) receptors, which limits the overstimulation by glutamate. In the cerebral cortex, neurodegeneration is mainly associated with the α4β2 subtype, whereas in the hippocampus the decline is predominately in the α7 subtype (with strong correlation with loss of cognitive function). Molecules that selectively affect the α7 nAChR result in improvement in the cognitive deficits associated with AD.[13]

1.4 Activation of nicotinic receptors

Acetylcholine (ACh) is the endogenous ligand for nAChRs and is found as a neurotransmitter in both the peripheral and central nervous systems. [2] ACh is the ester of acetic acid and choline and was the first neurotransmitter to be discovered. ACh is biosynthesised by the enzyme choline acetyl transferase with choline and acetyl-CoA.

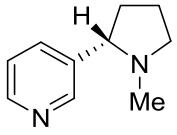


ACh

Figure 1.8: Acetylcholine (ACh)

Upon binding of ACh, the nAChR ion channel is stabilised in the open conformation for several milliseconds. The channel then closes to a resting state or a desensitised state that is unresponsive to ACh or other agonists. Whilst open, nAChRs conduct cations, which can cause a local depolarisation of the membrane and produce an intracellular ionic signal.[16]

Activation of nAChRs in the brain results in increased release of other key neurotransmitters, many of them activate Cys-loop receptors and include dopamine, γ-aminobutyric acid (GABA), glutamate and serotonin. Nicotine is a plant alkaloid from the nightshade family (*Solanaceae*) which is synthesised in the roots and accumulates in the leaves of the plants.



nicotine

Figure 1.9: Nicotine

Nicotine has strong affinity for nAChRs and gives a strong agonist effect.[16,17] Long term effects of nicotine exposure are the desensitisation and upregulation of the receptors. ACh and nicotine have varying potency dependent on the receptor subtype. Research has shown that chronic exposure to ACh or nicotinic drugs causes a decrease in the rate of the ionic response causing desensitisation of the receptor. Long term exposure to nicotinic drugs can cause significant changes in receptor properties and numbers. The α7 nAChR has been implicated in the memory-enhancing potential of nicotine. The number of binding

sites, as well as the affinities for agonists and antagonists is highly dependent on the receptor subtypes, creating challenges for drug design.

1.4.1 Agonists of α7 nAChRs

In this section we will focus on subtype-selective agonists for nicotinic receptors. In the absences of an agonist, the receptor is predominantly in the closed state, with the integral ion channel closed. This 'resting' state is responsive to the application of an agonist allowing flux across the membrane. Agonists either stabilise the open channel conformation or destabilise the closed channel conformation, allowing the conduction of cations, which cause a local depolarisation of the membrane and produce an intracellular ionic signal. The 'active' state can be short-lived, such that the receptor undergoes a series of transitions to a 'desensitised state' with the agonist bound in high affinity while the channel is closed. Loss of the agonist would lead to the receptor returning to the resting state.

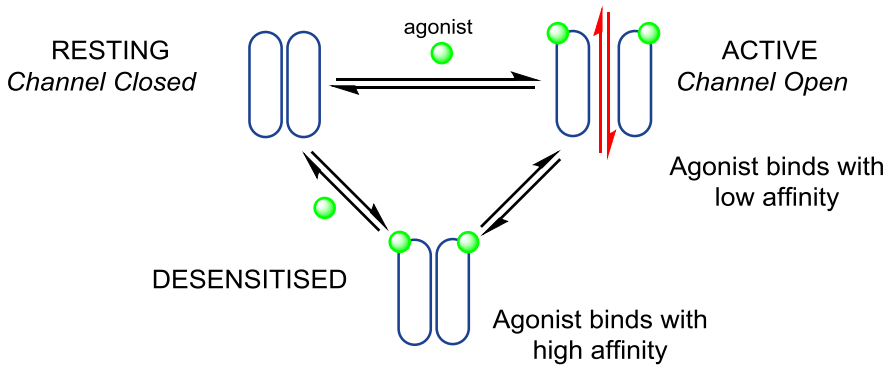


Figure 1.10: Representation of Receptor opening and closing

The speed of activation, the intensity of membrane depolarisation, the size of ionic signal and the types of cation conducted will all depend on the nAChR subunit composition.[16] Below are some examples of agonists that are selective for α7 nicotinic receptors.

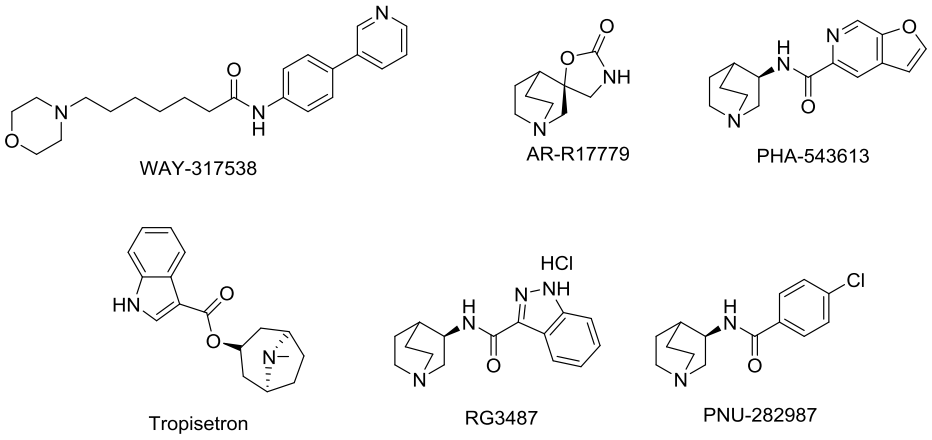


Figure 1.11: Agonists of α7 nicotinic receptors

WAY-317538 is a potent small molecule agonist of α7 nAChRs with excellent *in vitro* and *in vivo* profiles, excellent brain penetration and oral bioavailability.[18] AR-R17779 is a small molecule which was, at the time (2004), the first potent subtype-selective α7 nAChR agonist.[19] PHA-543613 has been identified as a potential treatment of cognitive deficits in schizophrenia.[20] Tropisetron is a 5-HT_3 antagonist which was found to display a potent and selective partial agonism of the α7 nAChR.[21] This drug has been used in clinical trials as an antiemetic, but since the discovery of this dual effect on ion channels, it is not understood whether this effect is due to the nicotinic receptor agonism or serotonin receptor antagonism.[22] RG3487 like tropistron acts a partial agonist on the α7 nAChR and an antagonist of the 5-HT_3R. In a rat model, this molecule leads to the exhibition of improved spatial learning and object recognition memory.[23] PNU-282987 is the most potent of a set of benzamides discovered through a high-throughput assay. This molecule is a potential treatment for some of the symptoms of schizophrenia.[24] Four of these molecules contain a quinuclidine moiety, as well as amides, carbamates or esters. There is a clear structure-activity (SAR) that provides selectivity and potency for the α7 nicotinic receptor. Nicotinic receptor agonists are currently in clinical trials for Alzheimers Disease, schizophrenia and cognitive dysfunctions.[25–27]

The benefits of subtype selective agonists of nAChRs are limited due to the uncertainty in whether chronic treatment with agonists might provide suboptimal benefit due to sustained activation and desensitisation of the nAChR.[8] One of the disadvantages of using small molecules for stimulation of receptors is that there can be poor selectivity for a specific receptor subtype.

1.4.2 Antagonists of α7 nAChRs

Antagonists act as inhibitors and decrease (or completely block) the peak response in the presence of an agonist. This effect can occur by competitive inhibition or by blocking of the ion channel. Nicotinic receptor antagonists have been used in the clinic for the blocking of the receptors for treatment of illnesses such as drug addiction. Below are some examples of antagonists of nicotinic receptors (**Figure 1.12**).

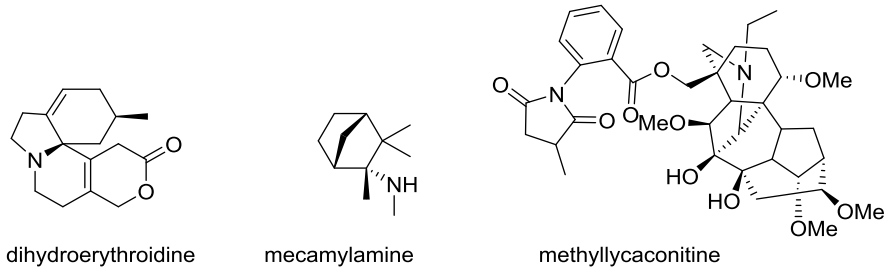


Figure 1.12: Antagonists of α7 nicotinic receptors

Dihydro-β-erythroidine is one of 70+ alkaloids isolated from the *Erythrina* genus.[28] The family of compounds are known for their hypotensive, sedative and CNS activity. The hydrobromide salt of this compound is an α4 selective antagonist. Mecamylamine is a synthetic antihypertensive which is a non-competitive antagonist of nAChRs and used as a treatment for nicotine addiction.[29] Methyllycaconitine is a plant alkaloid which is a potent selective antagonist of α7 containing nAChRs, often used in studies as a selective blocker of α7 homomeric nicotinic receptors.[30]

1.4.3 Allosteric Modulation of Ion Channels

Allosteric modulation is the change in peak response with an agonist due to binding of a molecule at an allosteric site. An allosteric site is any site on the receptor where the endogenous ligand does not bind (there is no competition between allosteric or orthosteric ligands). An increase of the peak response relative to the agonist alone is termed positive allosteric modulation (PAM) and a decrease of the response relative to the agonist alone is termed negative allosteric modulation (NAM). A therapeutic example of allosteric binding is the benzodiazepine drugs. Benzodiazepines are positive allosteric modulators or potentiators of the $GABA_A$ receptor by facilitating opening of the receptor integral Cl^- channel.[31] This effect is the underlying principle of anxioltic (reduction of anxiety) action of benzodiazepines.[32]

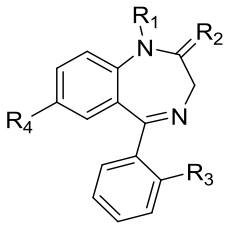


Figure 1.13: General structure of Benzodiazepines

The advantage of using positive allosteric modulators (PAM) over agonists is that modulation is only revealed in the presence of the endogenous ligand and the modulator has no action alone. They exhibit their function upon binding of the protein at an allosteric site, affecting the conformational stability of the protein to give an inhibiting or activating effect. There are many advantages for targeting allosteric sites, the most significant is that the drugs have a decreased potential for toxic effects by preservation of temporal and spatial stability of the receptor. Due to their co-operativity they have little or no effect alone irrespective of the dose.

Enhancing the effects of the endogenous transmitter acetylcholine via positive allosteric modulation and utilising the existing cholinergic neurotransmission for activation of the receptor provides an excellent opportunity for drug discovery for many CNS centred illnesses.[8]

In some cases, the *in vitro* properties and physiochemical properties remain to be further optimised but the molecules currently available are limited by low potency, low solubility, low metabolic stability and poor CNS penetration. For these reasons, identification of selective, potent and pharmacologically suitable PAMs for nAChRs is an active area of research. A key part of achieving this goal will be the identification of allosteric sites and assessing clarification of *in vitro* functional profiles.[8]

Relying on the endogenous transmitter is a potential disadvantage of the PAM approach, with reduced neurotransmitter efficacy, such as in the advanced stages of neurodegeneration.[8] However, this strategy can give an improvement to current available therapies. Modulation of nAChRs can be potentially used to treat brain disorders, such as Alzheimer's disease, attention deficit hyperactivity disorder (ADHD), depression, schizophrenia and many addictions.

1.5 Positive Allosteric modulation of α7 nAChRs

Positive allosteric modulators (PAMs) give an enhanced response when binding of ACh takes place and negative allosteric modulators (NAMs) give an inhibitory effect upon binding of ACh (compared to binding of ACh alone). There has been evidence that allosteric ligands bind in the transmembrane domain and cytoplasmic domains of nAChRs. Allosteric modulators often have no or little intrinsic activity, allowing greater physiological selectivity than agonists that act on receptors selectively, but indiscriminately with regard to ongoing physiological activity. This area of neuropharmacology has been extensively reviewed in the literature and the receptor subtype most investigated is the α7 nicotinic receptor. [9,33,34] Some early examples of allosteric modulators of the nicotinic receptor are outlined in **Figure 1.14**.

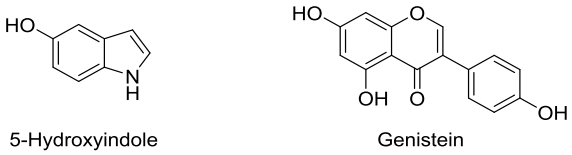


Figure 1.14: 5-Hydroxyindole and Genistein

5-Hydroxyindole causes a significant increase in subsequent ACh-evoked current. The receptor interaction with 5-hydroxyindole is weak and non-selective, requiring high concentrations for potentiation of the receptor. Genistein is a tyrosine kinase inhibitor which was found to act as a PAM in a very similar way to 5-hydroxyindole. These molecules are not selective and act on the other Cys-loop receptors. After these molecules were characterised, research was conducted to discover molecules that give selective Type 1 or Type 2 positive allosteric modulation for α7 nicotinic receptors.

1.5.1 Type 1 positive allosteric modulators (PAMs)

Type 1 PAMs facilitate the transition from 'resting' to 'open' channel state upon binding of ACh, increasing the agonist response amplitude without significant effect on the response decay rate (no effect on desensitisation).[8] Type 1 PAMs affect the apparent peak current, agonist sensitivity and Hill coefficient. The Hill coefficient quantifies the cooperative binding effect, where the binding of the PAM facilitates the binding of ACh, with higher cooperative binding the higher the Hill coefficient. PAMs that increase peak current response in the presence of an agonist are designated as Type 1 PAMs (**Figure 1.15**).

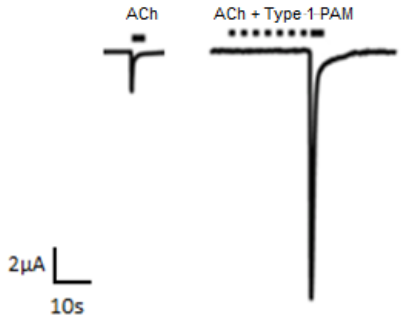


Figure 1.15: Profile of Type 1 PAMs[9]

In the presence of ACh alone there is a relatively small peak current response, but with ACh in the presence of a Type 1 PAM the peak response is much greater. This potentiation is attained by decreasing the energy between the 'closed' and 'open' states upon binding of an allosteric ligand. Below are examples of recent molecules that show Type 1 PAM activity and are selective for the α7 nAChR.

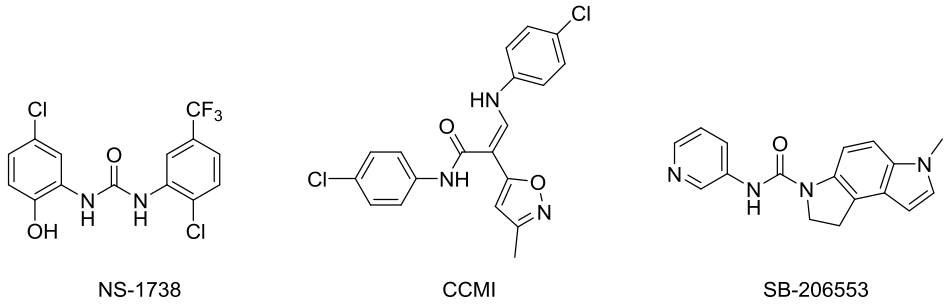


Figure 1.16: Type 1 PAMs: NS-1738, CCMI, SB-206553

NS-1738 was first reported in 2007 as a Type 1 PAM. It also improved performance in the rat social recognition test to the same extent as nicotine, demonstrating that NS-1738 is capable of producing cognitive enhancement *in vivo*.[35] CCMI evokes robust positive modulation of agonist-induced currents at α7 nAChRs. CCMI was discovered from a library of $GABA_A$ receptor agonists but has little to no efficacy at other ligand-gated ion channels.[36] SB-206553 was discovered as a mixed antagonist of serotonin receptors, but was later found to be a PAM for the α7 nicotinic receptor.[37]

1.5.2 Type 2 positive allosteric modulators (PAMs)

PAMs that upon ligand binding stabilise the open channel state to an extent that there is not only an increase in amplitude, but also a reduction of the receptor desensitisation are described as Type 2 PAMs.[8]

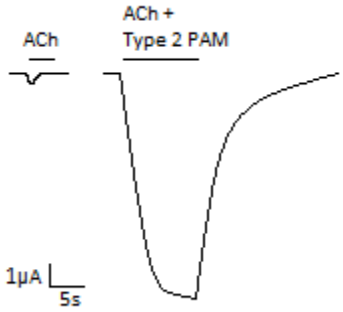


Figure 1.17: Profile of Type 2 PAMs[9]

As before, Type 2 positive allosteric modulators increase the peak current response compared to the agonist alone. The transition from the 'open' state to the 'desensitised' state can occur quickly (Type 1 PAM) or slowly (Type 2 PAM). Type 2 positive allosteric modulators slow the desensitisation kinetics, by binding the receptor in such a way that stabilises the open conformation with respect to the desensitised state, causing slower receptor closing. Some examples of Type 2 PAMs of α7 nAChRs are below (**Figure 1.18**).

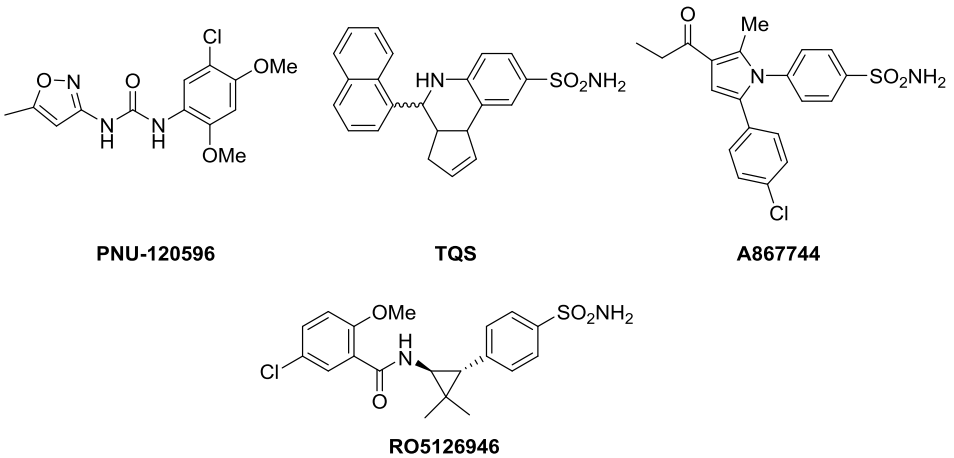


Figure 1.18: Type 2 PAMs: PNU-120596, TQS, A867744 and RO512946

PNU-120596 is one of the better characterised PAMs and is structurally similar to NS-1738. One interesting characteristic of this compound is its ability to restore activity to the agonist-desensitised channel.[38] TQS was discovered to be a Type 2 allosteric modulator by

our collaborators, this molecule will be discussed further later in this section.[39] A867744 is also a well characterised Type 2 PAM reported by Abbott in 2009 with good potency and selectivity.[34] RO5126946 is an aminocyclopropane which is a potent Type 2 PAM selective for the α7 nAChR which was found to have cognitive enhancing properties.[40]

1.6 Recent Research in the Sheppard Group

As shown in the previous section, the Millar group has previously identified a Type 2 positive allosteric modulator selective for α7 nAChRs through a high throughput screen. These molecules were discovered after TQS, which was found to be an early example of an allosteric agonist for nicotinic receptors.[39]

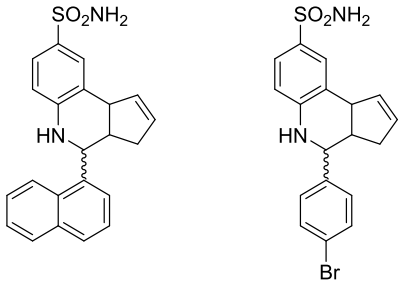
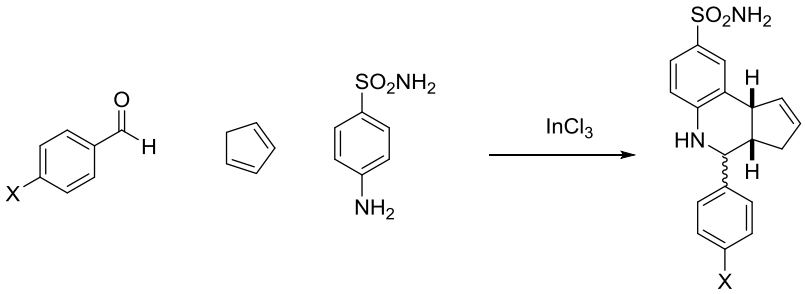


Figure 1.19: Tetrahydroquinoline based molecules that affect nAChRs

4BPTQS was found to be a very potent allosteric agonist (does not bind in the orthosteric site, where ACh binds, but binds elsewhere on the receptor and gives an agonist response). With this interesting result, analogues of these molecules were synthesised in the Sheppard Group. A plethora of tetrahydroquinoline-based products were synthesised and characterised. These compounds were synthesised through a 3-component reaction with $InCl_3$ catalyst.[41]



Scheme 1.1: An Indium chloride catalysed multicomponent reaction

This multicomponent reaction with an aldehyde, cyclopentadiene and sulfanilamide has a wide substrate scope and provided compounds that were analysed by our collaborators at UCL Pharmacology. The compounds above exhibit an allosteric agonism and PAM effects on the receptor. A selection of compounds is shown in **Figures 1.20** and **1.21**.

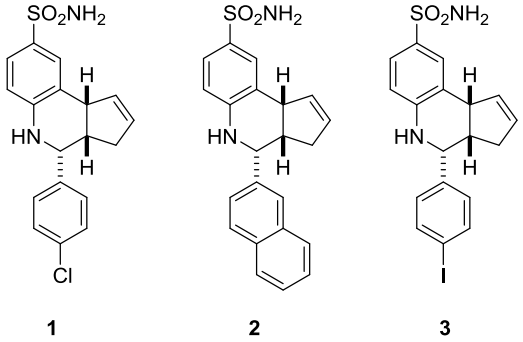


Figure 1.20: TQS-based allosteric agonists

Compounds **1**, **2** and **3** have a strong allosteric agonist effect on the receptor. Many other TQS compounds exhibit positive allosteric modulation on the receptor.

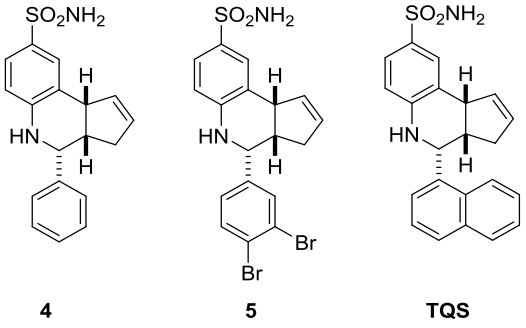


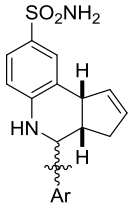
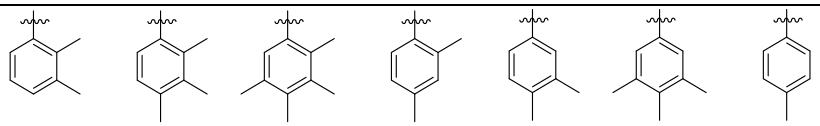
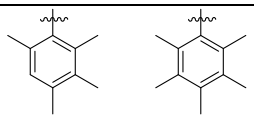
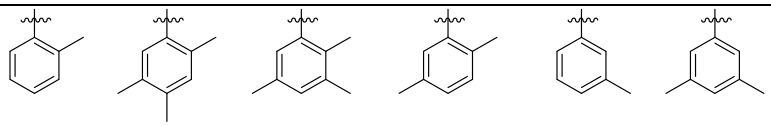
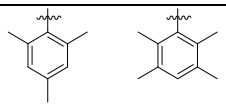
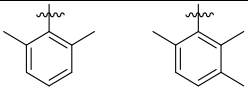
Figure 1.21: TQS-based positive allosteric moduators

Compounds **4**, **5** and TQS were found to be PAMs for the α7 nAChR. A clear result from this study is that small structural changes of the molecule can give different pharmacology.

The understanding that small changes in the chemistry can lead to distinct changes in pharmacology led to further work in this area. The synthesis of a number of new tetrahydroquinoline compounds with different methyl groups on one of the aromatic rings was completed.

As predicted the different molecules gave different effects on the receptor. Changes in the methyl-substitution of one of the phenyl rings were characterised as eliciting 5 different pharmacological responses.

Table 1.1: Pharmacological effect of structurally related TQS compounds

Pharmacological Effect	
allosteric agonism	
Type1 PAM	
Type2 PAM	
Silent allosteric modulation (SAM)	
negative allosteric modulation (NAM)	

Allosteric agonisms and positive allosteric modulation have been discussed previously in this section. Silent allosteric modulators (SAMs) are molecules which do not affect the peak response with ACh, however, they must bind in the allosteric site as they block the effect of other allosteric agonists and PAMs. Negative allosteric modulators (NAMs), also known as

non-competitive antagonists bind in such a way that reduces the peak response compared to ACh alone. Although these molecules give a diverse array of pharmacological effects their chemical properties are lacking for further drug development.

There are limitations for the use of TQS-based molecules for the exploration of these receptors. The molecules are synthesised as a mixture of diasteromers with potentially only one active isomer. The molecules are quite lipophilic with poor aqueous solubility and potentially low bioavailability. These molecules are covered by patents, therefore there is no privilege in pursuing molecules covered by another organisations intellectual property. The molecules are also not particularly drug-like,[42] following the Lipinski's Rules of five: <5 H-bond donors, <10 H bond acceptors, molecular mass <500 and octanol/water partition coefficient, log *P* <5. Several criteria were felt to be important for any potential modulators to meet based on the current limitations of TQS-based allosteric modulators:

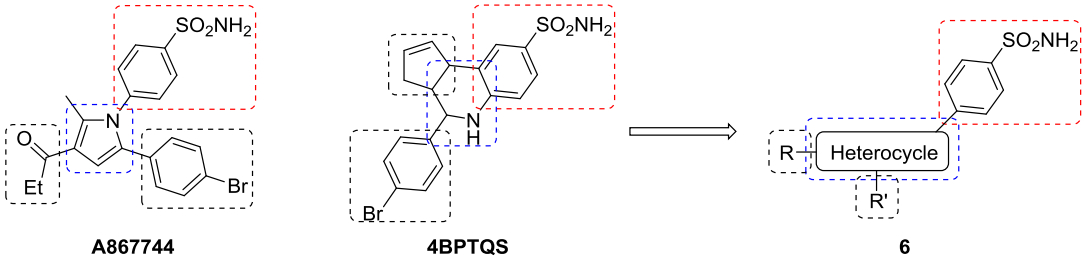
- Select for α7 nAChRs (over any other heteromeric nAChRs)
- Good aqueous solubility
- Structurally novel

The aim of this drug discovery project is to synthesise novel allosteric modulators of the α7 nicotinic acetylcholine receptor. We believe that there is potential for the synthesis of new molecules with a new molecular framework. These molecules will help to expand the understanding of the receptor, its allosteric site, its mechanism of receptor opening and its desensitisation.

Chapter 2 Novel Allosteric Modulators for Nicotinic Receptors

2.1 Aim

The aim of this Drug Discovery project is the synthesis of novel allosteric modulators for α7 nicotinic receptors. This work would expand the success in the Sheppard group in the synthesis of a series of novel tetrahydroquinoline based allosteric agonists and positive allosteric modulators (PAMs).[41] We approached this project by using the basic structures of 4BPTQS (an allosteric agonist) and a literature molecule which displays Type 1 positive allosteric modulation on the same receptor A867744.[34]



Scheme 2.1: A867744 and 4BPTQS and a representation of the proposed effectors of the receptor

By the union of these two frameworks, we have the potential to synthesise molecules with pharmacological activity on the α7 nAChR. A pharmacophore approach was enlisted to describe the molecular 'features' that give pharmacological effects with the receptor. The primary aryl sulfonamide (red), a heterocyclic core (blue) and groups attached to the core (black) were the features selected.

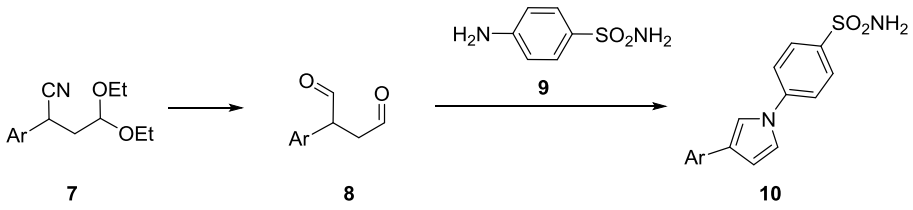
We want to overcome the limitations of TQS by the synthesis of novel molecules that are not covered by patents and that are drug-like (adhering to the Lipinski Rules) with good aqueous solubility.

2.2 Pyrroles

2.2.1 Synthesis of Pyrroles (First Generation molecules)

We started the project with the synthesis of a biaryl pyrrole. This would have the primary aryl sulfonamide and a heterocycle with only one aromatic group attached to it. This was proposed to ascertain whether the two other groups attached to the heterocycle are actually required for pharmacological activity.

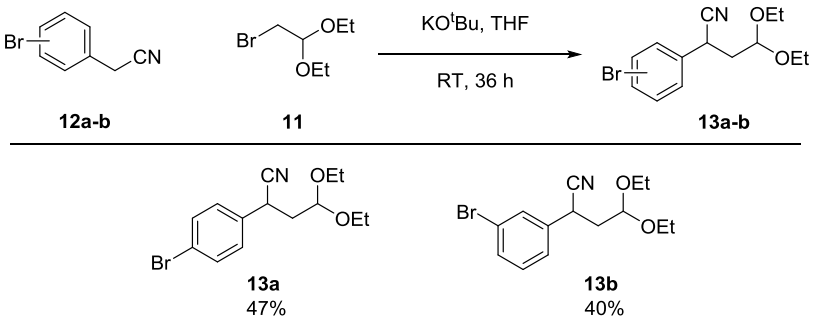
We began the project with the synthesis of a set of pyrroles **10**. The approach used well established chemistry and a relatively short route that would allow us to isolate sufficient material for pharmacological testing. The forward synthesis is outlined in **Scheme 2.2**.



Scheme 2.2: Synthetic plan for pyrroles

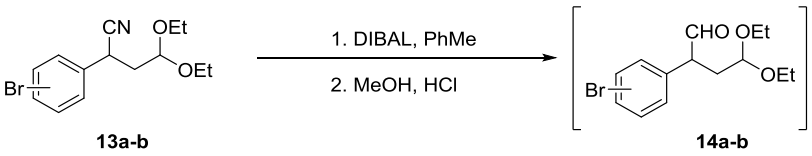
The synthesis begins with a reduction and hydrolysis of **7** to give dicarbonyl **8**. After the Paal-Knorr reaction with sulfanilamide **9** and intermediate **8** gives the pyrrole **10**.

The first step was a nucleophilic displacement of a bromide **11** with nitriles **12a-b** to set up cyanoacetals **13a-b** in acceptable yields. The cyanoacetals acts as 'masked' 1,4-dicarbonyls which, after reduction of the nitrile and hydrolysis give the desired Paal-Knorr precursor.



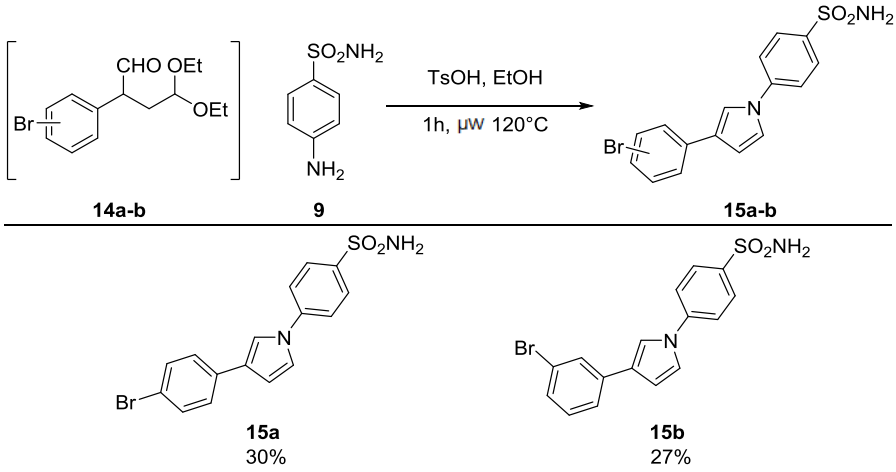
Scheme 2.3: Nucleophilic substitution of a bromide **11**

The next step was to reduce the nitriles to imines with diisobutylaluminum hydride (DIBAL) in toluene. The crude imines were treated with 2M HCl to form the aldehyde-acetals **14a-b**.



Scheme 2.4: Reduction and hydrolysis to give cyclisation precursors

This step was designed to hydrolyse the acetal as well as the imine, however, after a number of hours the acetal was still present. It was thought that the acetal would be hydrolysed in the subsequent step, cleaved during the temperature and acidic conditions of the Paal-Knorr reaction.[43,44]



Scheme 2.5: Paal-Knorr pyrrole synthesis

The Paal-Knorr reaction between the aldehyde **14a-b** and sulfanilamide **9** under microwave heating gave the disubstituted pyrroles **15a-b** in poor yield. This poor yield was later attributed to the self-condensation of the aldehyde under the conditions to the furan, as well as other impurities in the reaction mixture. Once the desired products were isolated, they were both characterised. This was the first opportunity to assess molecules that could affect the nAChR and they were submitted for testing.

2.2.2 Pyrroles (First Generation molecules) – Pharmacological results by AC at UCL Pharmacology

The pharmacological activity of the compounds synthesised were tested by our collaborators in the Millar group at UCL Pharmacology.

Their properties were examined on α7 nAChRs expressed from Xenopus oocytes.[45] Oocytes were placed in a recording chamber and continuously perfused with a saline solution (115 mM NaCl, 2.5 mM KCl, 1.8 mM $CaCl_2$, and 10 mM HEPES, pH 7.3) with a flow rate of approximately 15 ml/min. Two electrode voltage-clamp recordings were performed (with the oocyte membrane potential held at -60 mV).[41] There is a change in membrane resistance due to the effect of various stimuli, which is measured in the change in the membrane potential which is constantly measured.

It was found that the molecules **15a** and **15b** did not give an agonist response when applied to the α7 nAChR alone, this result indicates that these molecules are not agonists. It was also found that when the compounds were co-applied with acetylcholine there was no potentiation of the response. This result shows us that the molecules were not acting as a positive allosteric modulators (PAM). When the compound was co-applied with 4BrTQS (allosteric agonist) the compounds were showing a small amount of inhibition of the response. This result gives us evidence that the molecules bind at the same site but have no pharmacological response, these are silent allosteric modulators (SAMs).

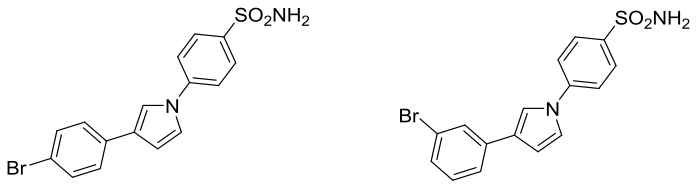


Figure 2.1: 1st generation pyrroles with no effect on the receptor

The lack of response was attributed to a weak interaction between the receptor and the compound, leading to binding but no pharmacological effect. It was proposed that 2 groups connected to the pyrrole in addition to the aryl sulfonamide would give a greater interaction with the receptor and potential allosteric agonism/modulation. We then synthesised a number of larger more substituted pyrroles.

2.2.3 Synthesis of Pyrroles (Second Generation molecules)

From the pharmacological testing, it was found that the molecules did bind. Therefore, we understand that our first target (with 2 groups on the pyrrole ring) would be more likely to give satisfactory effects.

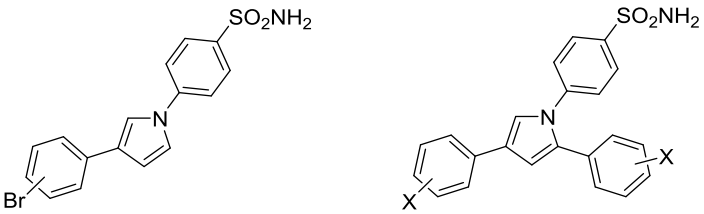
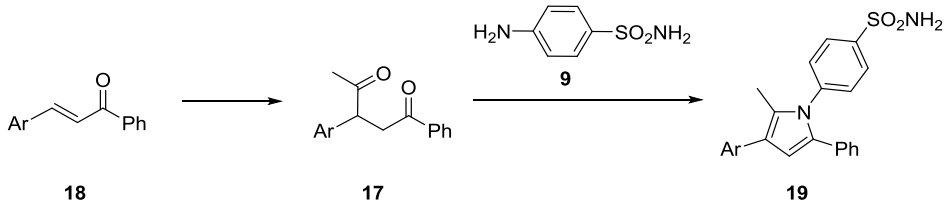


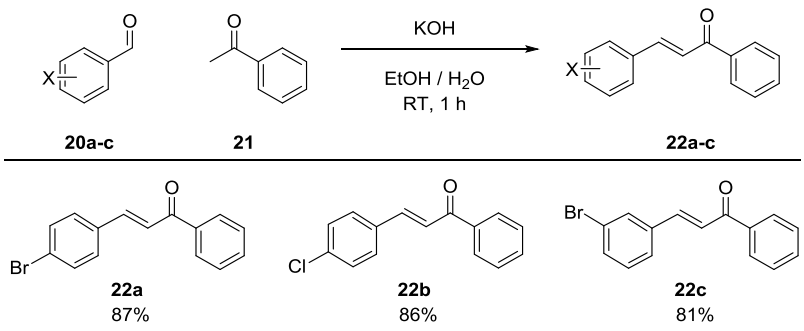
Figure 2.2: A new target – triaryl pyrroles

Although there was a small change in structure, the change requires new disconnections for the 1,4-dicarbonyl compound for heterocycle formation. The 1,4 dicarbonyl **17** is the precursor for the Paal-Knorr synthesis, which was derived from a Stetter reaction between acetaldehyde and chalcone **18**. The chalcones were produced through a Claisen-Schmidt condensation.



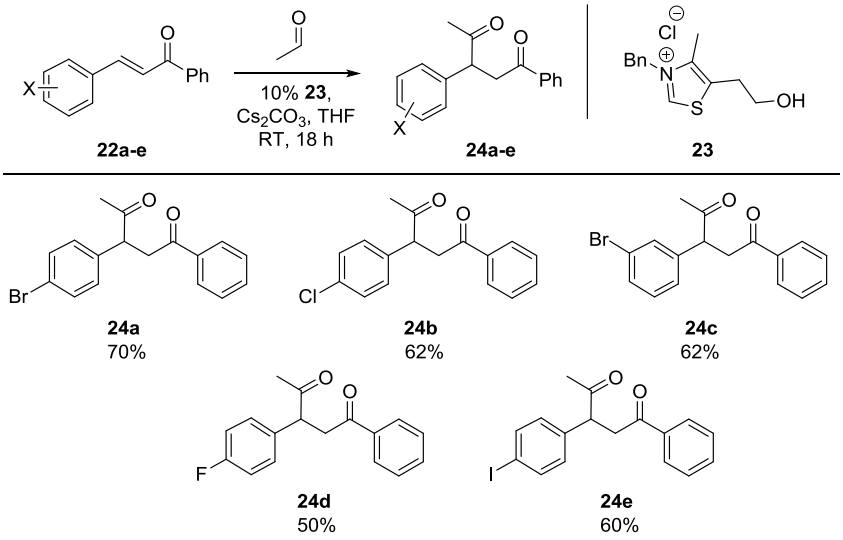
Scheme 2.6: Synthetic plan for triaryl pyrroles

A straightforward aldol condensation between halo-substituted benzaldehydes **20a-c** and benzophenone **21** cleanly formed α,β-unsaturated ketones **22**. These were purified by flash chromatography to give the (*E*)-enones.



Scheme 2.7: Claisen-Schmidt condensation to give chalcones

With these products in hand we subjected these substrates to an intermolecular Stetter reaction with a *N*-heterocyclic carbene catalyst **23**. This would set up a 1,4-dicarbonyl suitable for Paal-Knorr pyrrole synthesis.

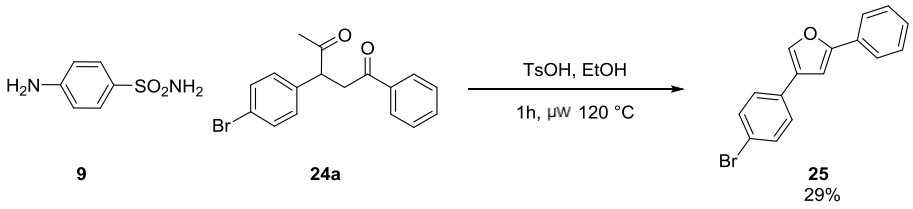


Scheme 2.8: Intermolecular Stetter reaction

We followed a procedure by Kim co-workers[46] (using a different *N*-heterocyclic carbene (NHC) catalyst). From repetition of this reaction it was found that it was important that the acetaldehyde was freshly distilled and added in great excess. The reaction appears to halt after 24 h and the reaction was not reinitiated by addition of base, thiazole salt or acetaldehyde. Fortunately, it was possible to separate the products from the starting materials to give diketones **24a-e** in good yields.

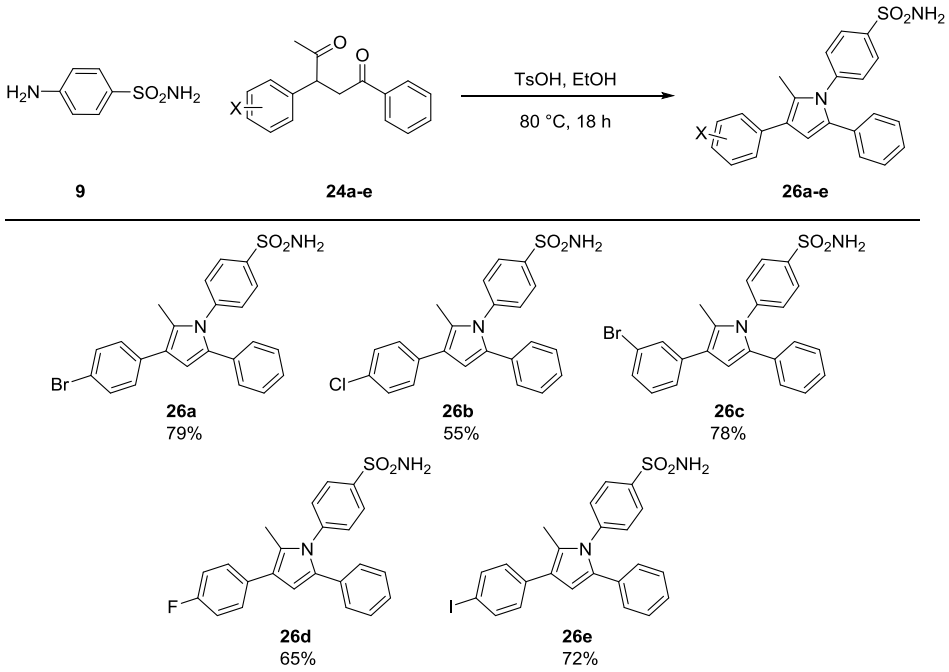
The last step was the Paal-Knorr pyrrole synthesis. When this reaction was attempted in the microwave with AcOH only the furan **25** was formed (See **Scheme 2.9**). Slow initial

imine formation allowed the acid-catalysed intramolecular cyclisation and dehydration to give the furan.



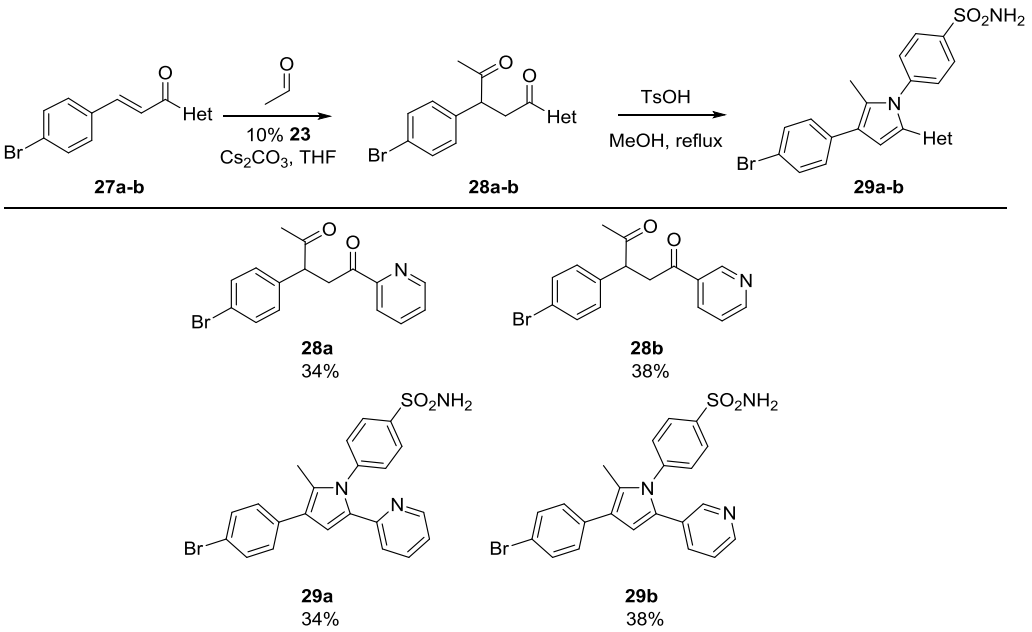
Scheme 2.9: Formation of furan **25**

The reaction was then performed thermally at 100 °C, this reaction did exhibit some formation of the pyrrole alongside the furan. However, after a number of days the starting material remained. The reaction conditions were changed, using MeOH as the solvent and an excess of the sulfanilamide **9** in the microwave at 120 °C. After 15 min, the starting material remained but after 1 h all the starting material had been consumed. The reaction went cleanly to the desired product with trace amounts of the furan as a side product. It was found that using an excess of sulfanilamide **9** was the most important factor. In addition, microwave heating was not required and the reaction could be heated thermally at reflux overnight. With these conditions we synthesised a number of pyrroles with different halogens on one of the aromatic rings.



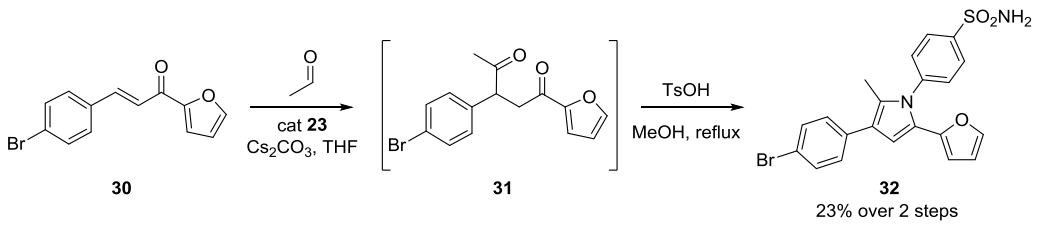
Scheme 2.10: Paal-Knorr pyrrole synthesis of triaryl pyrroles

The pyrrole synthesis gave the desired products in generally good yields. After the completion of the halogen series of the pyrroles **26a-e**, we found that the molecules had quite low solubility in DMSO, which led to problems in the assay with compounds precipitating out of solution under high concentrations. Therefore we decided to synthesise new analogues, replacing the phenyl ring with heteroaromatic rings in view to increase the solubility in DMSO.



Scheme 2.11: Synthesis of pyridine containing pyrroles

The Stetter reactions were challenging for these heteroaromatic substrates and gave the diketones **28a-b** in poor yield. The crude products contained many different substances that made purification by flash chromatography challenging. The poor conversion was attributed to electron donation into the chalcone from the heteroatoms, causing the chalcone to be electron rich and less accepting of the electron density from the nucleophile. We also synthesised a furan derivative (**32**) using the same method.



Scheme 2.12: Synthesis of pyridine containing pyrroles

As with the 2-pyridyl example **31**, the crude product was a complex mixture. This 1,4 diketone **31** could not be isolated cleanly and the semi-purified product was used in the next step to obtain the pyrrole **32**. None of the products gave a significant increase in solubility in DMSO for the assay. However, we were keen to assess the effect of these molecules on the α7 nicotinic receptor.

2.2.4 Pyrroles (Second Generation molecules) – Pharmacological results by AC at UCL Pharmacology

We synthesised a number of substituted pyrroles and these were, as before, tested at UCL Pharmacology. The products were co-applied with ACh and the measurement of the change of the peak response relative to ACh alone was made.

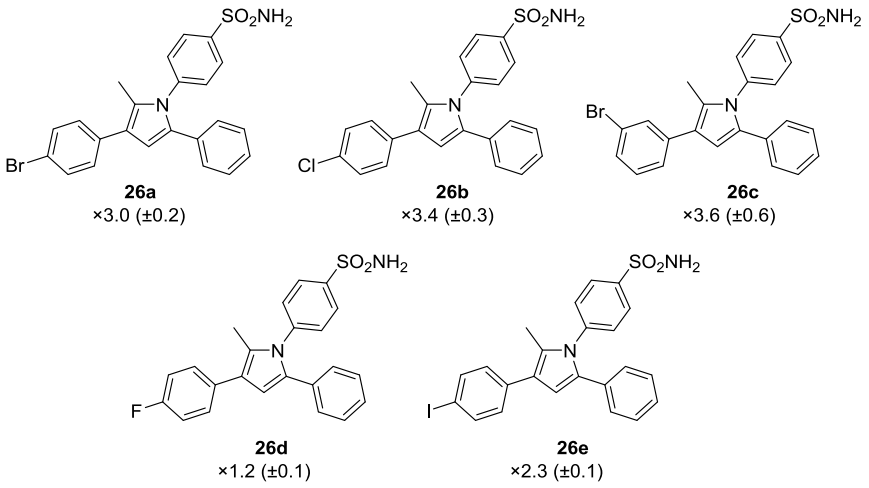


Figure 2.3: Novel pyrrole Type 1 positive allosteric modulators of the α7 nAChR

The values under the molecules represent the n-fold peak potential increase compared to acetylcholine alone. Therefore a value of 1.0 would show no improvement over acetylcholine alone and a value of 2.0 would be twice as effective as acetylcholine alone.

We were very pleased to find that these molecules gave some positive allosteric modulation of the α7 nAChr. From the halogen series we found that the **26c** derivative had the greatest allosteric modulation effect of × 3.6, which is only slightly higher than derivative **26b** with a value of × 3.4. Its was found that compound **26a** only had a tiny effect and derivative **26e** only increased the peak response by 2.

With these positive results we looked to examine the range of molecules of a similar structure that would give a pharmacological response. This was done for 2 reasons:

- These molecules are sparingly soluble in DMSO (the solvent used in the assay) and therefore dose-response curves at higher concentrations can not be constructed and the poor solubility of the products may limit their efficacy
- There is possible overlap between the structures and the Abbott patent structures, which could cause possible patent protection problems in the future

Note that the rings at the 1 and 3 positions are in the same plane and the phenyl ring lies orthogonal to this plane. This conformation minimises the steric clash between the aromatic rings of the 1 and 2 positions.

We believe that the planar nature of this molecule leads to the poor solubility but also leads to the good pharmacological action. Therefore it was hoped that by incorporating heteroaromatics in the molecule it would allow more hydrogen bonding and keep the molecule in solution during the assay. These more polar products have the same geometry as previous products analysed. A new set of pyrroles were synthesised using the same methodology used previously to form furan and pyridine derivatives.

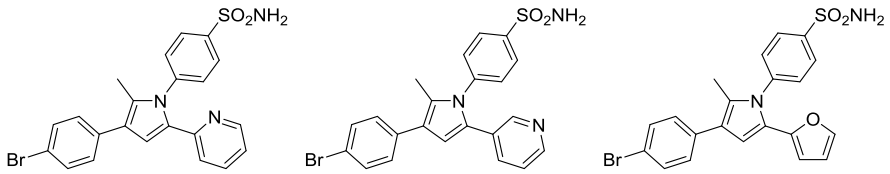


Figure 2.4: Novel pyrrole Type 1 positive allosteric modulators of the α7 nAChR

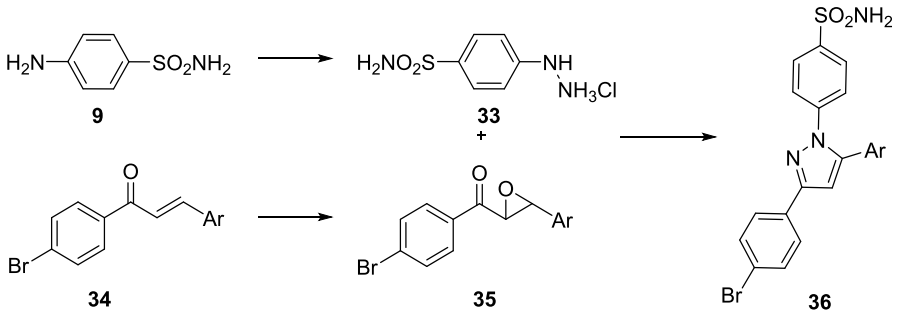
There was significant improvement in the activity with the furan derivative **32** with × 8.2 on the pyrrole and little change with using the pyridyl ring compared the phenyl ring. This small change must affect the way the molecule **32** interacts with the receptor to reduce the energy between the 'open' and 'closed' state compared to molecule **26a**.

With these encouraging results we decided to expand our set of molecules to pyrazoles. Pyrazole derivatives of these molecules contain 2 nitrogen atoms as the heteraromatic core. It was hoped that these molecules would give similar effects on the receptor but with greater aqueous solubility.

2.3 Pyrazolines and Pyrazoles

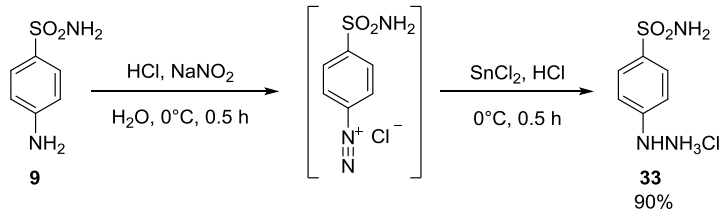
2.3.1 Synthesis of Pyrazolines and Pyrazoles

After the success of the finding that pyrroles **26a-e**, **29a-b**, **32** are novel Type 1 PAMs for nicotinic receptors, it was proposed that structurally related pyrazoles would behave in a similar fashion, with increased pharmacokinetics in new patent space. The initial plan was similar to the pyrrole formation. We began the synthesis with enone formation, this enone would be oxidised to the epoxide, followed by reaction with sulfanilhydrazine to form the desired pyrazole.



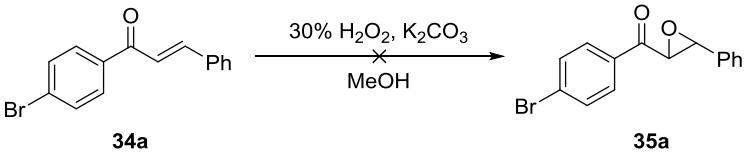
Scheme 2.13: Route towards novel pyrazoles

The first reaction completed was the large scale synthesis of the hydrazine reagent, as this was a key intermediate for the synthesis of pyrazoles with the N-N bond of the ring obtained from a preformed hydrazine derivative. Sulfanilamide **9** was converted to the diazo salt with conc. HCl and $NaNO_2$ followed by reduction with $SnCl_2$ to give the hydrazide salt **33** in excellent yield.



Scheme 2.14: Synthesis of hydrazine salt **33**

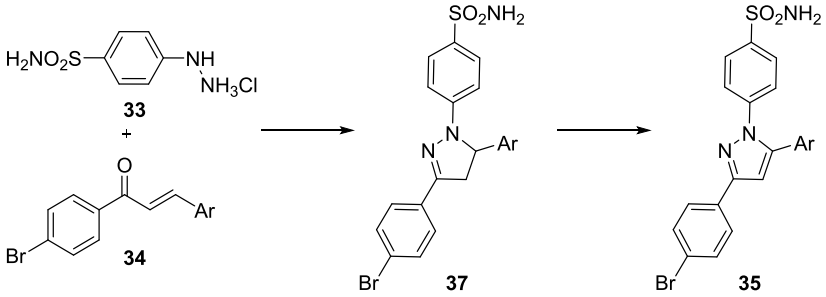
The next step was the synthesis of the chalcone **34a**, which as before, was simple and gave good yields for most of the reactions. The next step was the oxidation of the enone.



Scheme 2.15: Attempted of oxidation of an enone

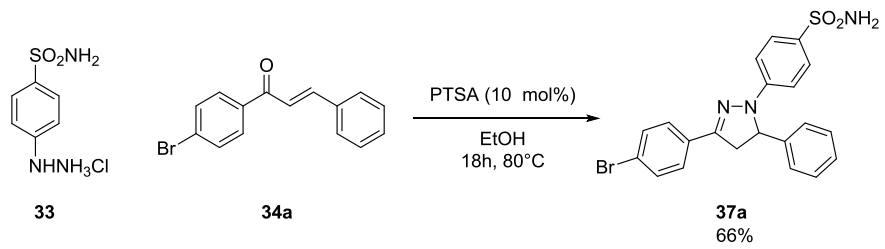
The oxidation reaction was complete after 2 h, however, no epoxide was seen in the crude product mixture. The crude product contained mostly unidentifiable degradation products and therefore we decided to explore alternative routes for formation of pyrazoles.

The new route employed used the chalcone **34** directly with the hydrazine salt **33** to form a pyrazoline **37**. This pyrazoline is an interesting intermediate itself which would oxidise under the reaction conditions to the desired pyrazole **35**.



Scheme 2.16: Revised route towards novel pyrazoles

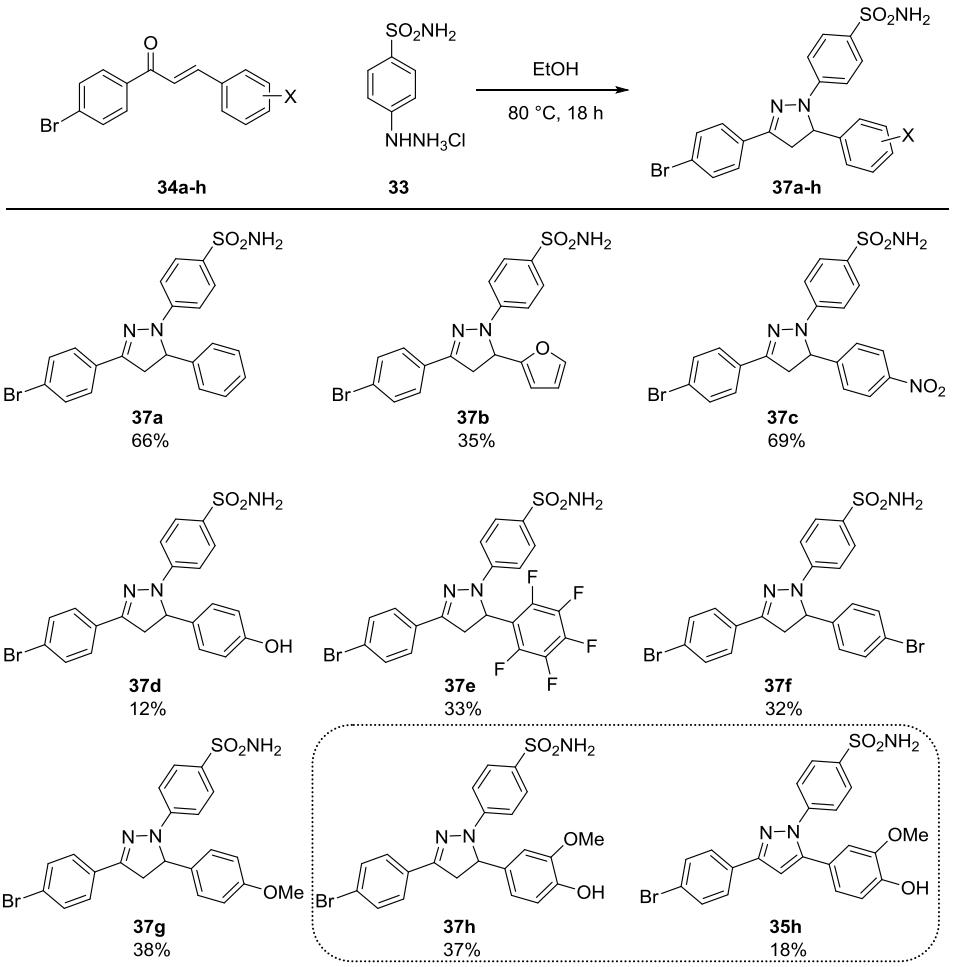
The enone **34a** was reacted directly overnight with the hydrazine in AcOH and NaOAc to form the desired pyrazoline **37a**. In the crude product there were some degradation products, which could be attributed to the long reaction times and relatively acidic conditions. This reaction was optimised first by using sub-stoichiometic quantities of *p*-tolulenesulfonic acid (PTSA) in EtOH, which led to less by-products. It was also found that the reaction completed within 4 h and that the reaction works without the presence of PTSA to form the pyrazoline **37a** in good yield.



Scheme 2.17: Pyrazoline formation

The pyrazoline **37a** is of a similar structure to the pyrrole **26a** previously seen. The pyrazoline is chiral and the orientation of the phenyl ring can be either in or outside the plane of the remainder of the molecule giving it an unique interaction with the receptor.

The pyrazoline **37a**, although not a target molecule, was believed to have slightly different interactions with the receptor. Therefore a number of pyrazolines were synthesised using the conditions outlined previously from the enones.

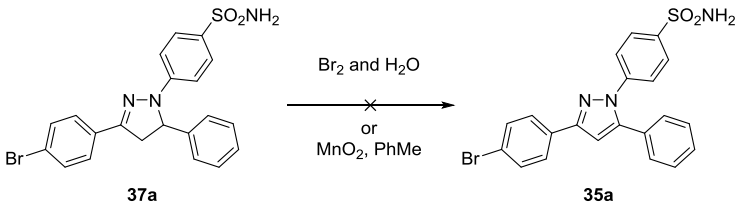


Scheme 2.18: Synthesis of pyrazolines **37a-h**

The reactions gave pyrazolines **37a-h** in varied yields from poor to good. The phenol derivative **37d** formed in very poor yields, this was attributed to the delocalisation of the phenol lone pair leading to deactivation of the enone to nucleophilic attack of the hydrazine. The pyrazoline **37h** was produced along with a small quantity of the pyrazole **35h** (produced through auto-oxidation). After the successful isolation and characterisation

of these novel pyrazolines, they were oxidised to the pyrazoles as they did not oxidise spontaneously as predicted.

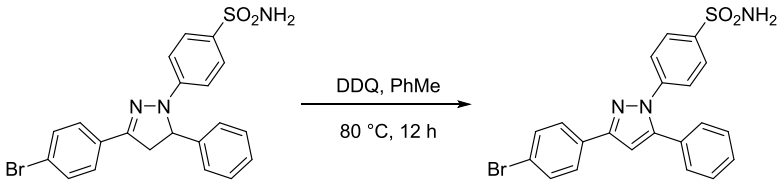
A method using bromine water was attempted which led to unidentified brominated products and a method using MnO_2 was also attempted with no success.



37a 35a

Scheme 2.19: Attempted oxidation of pyrazoline **37a**

Pyrazole formation was accomplished with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) in toluene over 2 h, after a quick purification step the pyrazole was isolated in good yield.

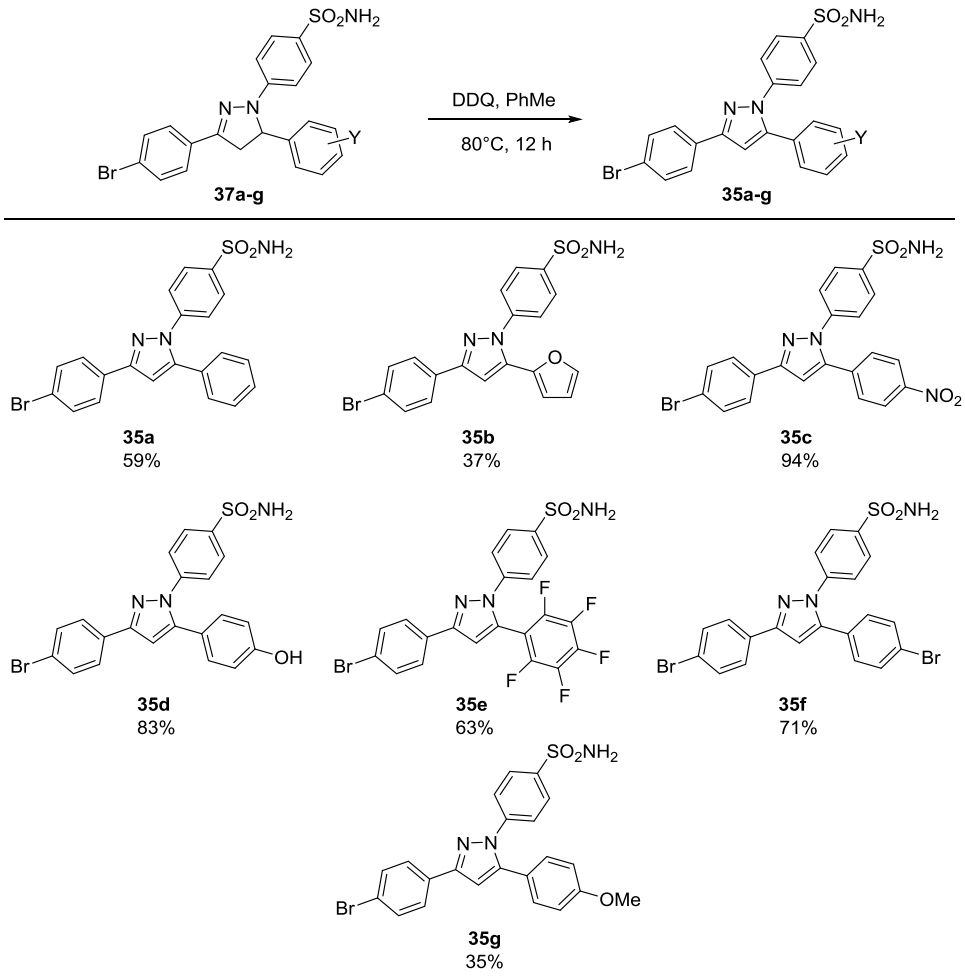


37a 35a 59%

Scheme 2.20: Successful oxidation of pyrazoline **37a** to pyrazole **35a**

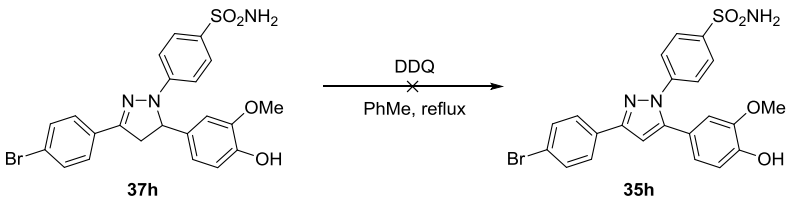
Using this protocol we oxidised the remainder of the pyrazolines **37b-h** also in good yields (in most cases).

The oxidation is successful with most substrates, however, the highly electron-rich aromatics cause problems with the DDQ oxidation of **35h**.



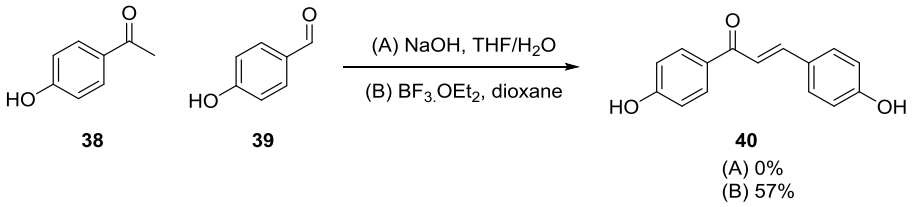
Scheme 2.21: Oxidation of pyrazolines to pyrazoles **35a-g**

Fortunately, there was some oxidation in the previous pyrazoline formation step which was conducted on a large enough scale to give enough of the pyrazole **35h** for pharmacological testing.



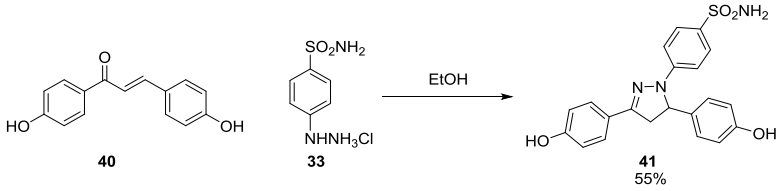
Scheme 2.22: Unsuccessful oxidation of pyrazoline **37h** to pyrazole **35h**

We decided to synthesise a pyrazole with 2 phenol rings, therefore we started with the aldol condensation, which proved unsuccessful and so we tried an alternative approach.[47] The use of a Lewis acid in dioxane allowed the formation of the desired chalcone in good yield.



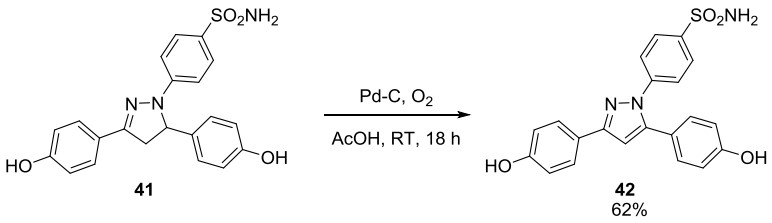
Scheme 2.23: Successful phenolic chalcone formation

The conditions for pyrazoline formation were satisfactory for this substrate and gave the pyrazoline **41** in good yield.



Scheme 2.24: Successful pyrazoline formation

With the product in hand and the difficulty in oxidation with DDQ, we used an alternative approach to the DDQ oxidation. We used palladium on carbon under an oxygen atmosphere, which successfully oxidised the pyrazoline **41** to pyrazole **42**.



Scheme 2.25: Successful oxidation of pyrazoline **41** to a bis-phenol pyrazole **42**

The reaction went cleanly to give the pyrazole in good yield. With a wide set of pyrazolines and pyrazoles, the compounds were evaluated by our collaborators at UCL Pharmacology.

These compounds have been synthesised from the α,β-unsaturated ketones or enones. We wanted to synthesise more molecules, however, the synthesis is only suitable for biaryl enones. To explore the pharmacology of potentially new molecules, a new synthesis of pyrazoles in one-pot from the enones derived from propargylic alcohols was initiated. This research is outlined and discussed in Chapter 3.

2.3.2 Pyrazolines – Pharmacological results by AC at UCL Pharmacology

We synthesised a number of pyrazoles and their intermediate pyrazolines and these were assessed at UCL Pharmacology.

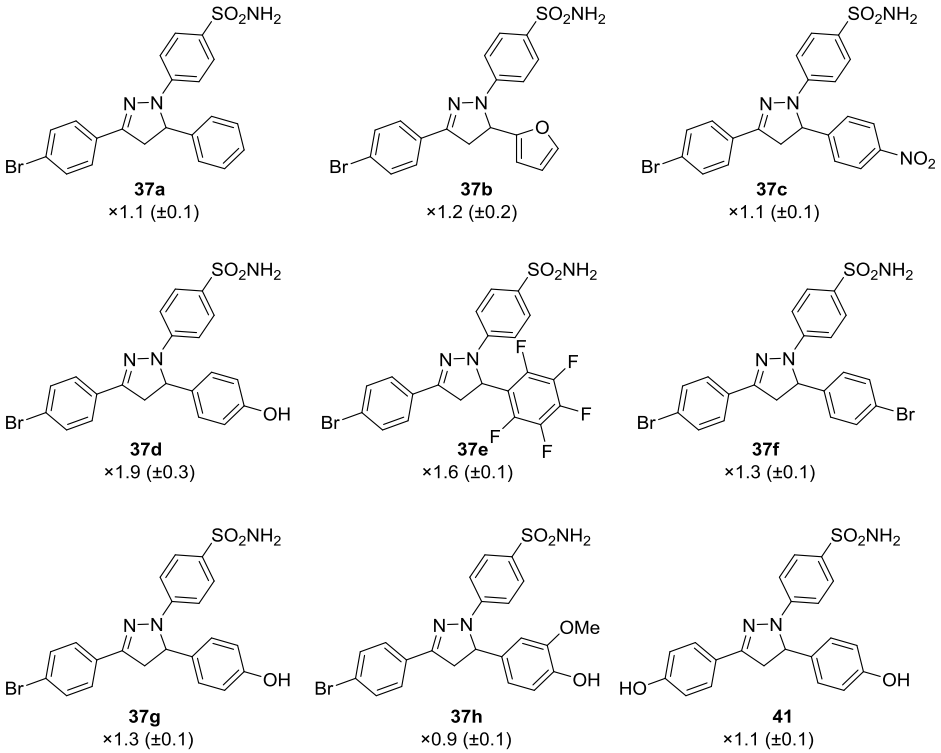


Figure 2.5: Pyrazolines with little or no PAM activity

We found that many of the derivatives do not display any PAM activity on the receptor. The molecules that do elicit a response seem to show only very small effects. It is surprising that there is little difference between pharmacology of these dissimilar structures. The furan derivative (**37b**) had no effect, which is interesting because these compounds gave the greatest fold potentiation effects as the pyrrole derivatives.

The orientation of the aromatic rings of the 1 and 3 positions of pyrazolines are in the same plane and this is different to the pyrrole. The aromatic ring at the 5 position of the pyrazoline is positioned out of the plane and backwards. These differences may account for the reduced pharmacological effect.

One positive result from this set of compounds was that they were markedly more soluble in DMSO than the pyrrole derivatives. Although disappointed with the poor pharmacological effect, these molecules were merely intermediates to the pyrazoles.

2.3.3. Pyrazoles – Pharmacological results by AC at UCL Pharmacology

We synthesised a number of pyrazoles and these were assessed at UCL Pharmacology.

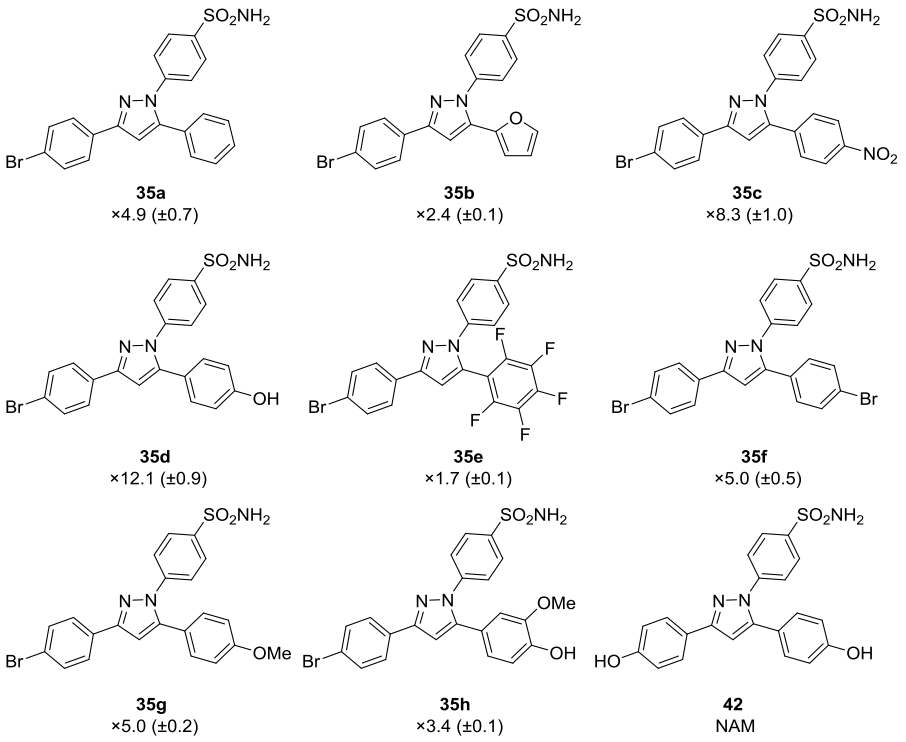


Figure 2.6: Pyrazoles with Type 1 PAM activity

All the synthesised pyrazoles **35a-h** exhibited PAM activity with all giving enhanced response compared to the corresponding pyrazoline. The most effective PAM was found to be the *para*-OH analogue **35d** with 12 times more depolarisation than ACh alone. The bis-phenol derivative **42** quenched the effect of ACh and acted as a negative allosteric modulator (NAM). This change could be attributed to the free OH interacting strongly in the allosteric site. Interestingly, replacement of Br in this molecule for an OH, causes a change from PAM activity to NAM activity, which is surprising for such a small change. The difference in pharmacology must be due to the difference on how the OH interacts with the receptor.

The bis-phenol **42** must increase the energy barrier between the 'open' and 'closed' state; by stabilising the 'closed' state or by destabilising the 'open' state. Pyrazole **35a** must decrease the energy barrier between the 'open' and 'closed' states so that when ACh is introduced there is an enhanced effect.

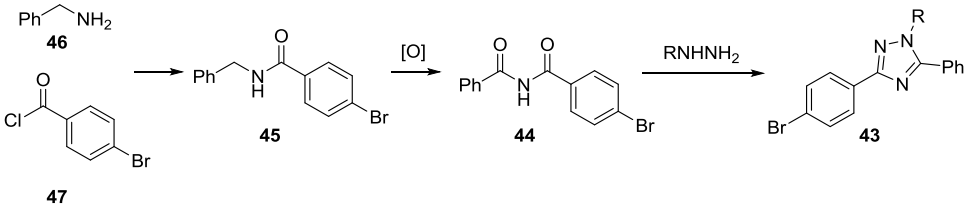
The furan derivative **35d** only gave a mild improvement relative to the analogous pyrrole **26a**. Surprisingly, the *para*-NO_2 analogue **35c** had very good activity whereas the pyrazoline **37c** gave none. In comparison to the pyrroles, the shape of these molecules are shaped differently with the aromatic rings at the 1 and 3 positions of the pyrazole almost in the same plane (orthogonal in the pyrrole) and the aromatic in the 5-position orthogonal to the heteroaromatic ring (same as the pyrrole).

Following the success of forming the pyrazoles (2 nitrogen atoms in the core), we envisaged that triazoles (3 nitrogen atoms in the core) would allow synthesis of molecules with similar molecular shape with increased solubility. The next section will discuss the synthesis of 1,2,4-triazoles and their effect on the receptor.

2.4 Triazoles

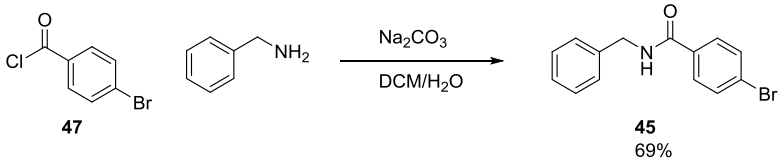
2.4.1 Synthesis of 1,2,4-Triazoles

From the research conducted on the pyrroles and pyrazoles, it was natural to progress to triazoles. The proposed plan involves a significantly different approach to what has been explored thus far. The triazole **43** is derived from a condensation reaction between the imide **44** and a hydrazine. The imide is obtained through an oxidation of amide **45**, formed through an amidation reaction.



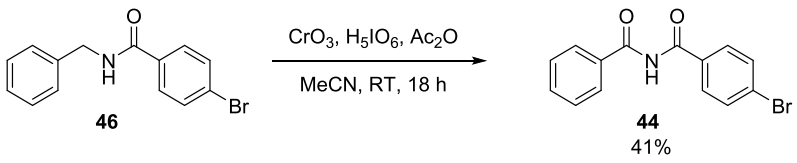
Scheme 2.26: Proposed synthetic route to triazoles

The first step, an amidation reaction, was completed with benzylamine, the acid chloride and base to give the product **47** in good yield. The next step, oxidation with a catalytic quantity of CrO_3 was a more challenging reaction.[48]



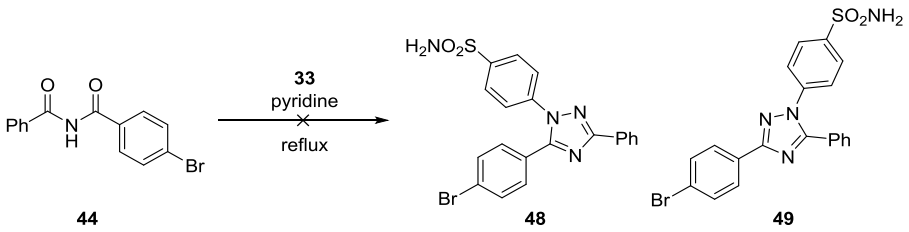
Scheme 2.27: Successful amidation reaction

The reaction was slower than the literature procedure leading to the addition of more of the catalyst and longer reaction times. The crude product was purified by flash chromatography to give the imide as a colourless oil for the triazole formation.



Scheme 2.28: Successful oxidation to form imide

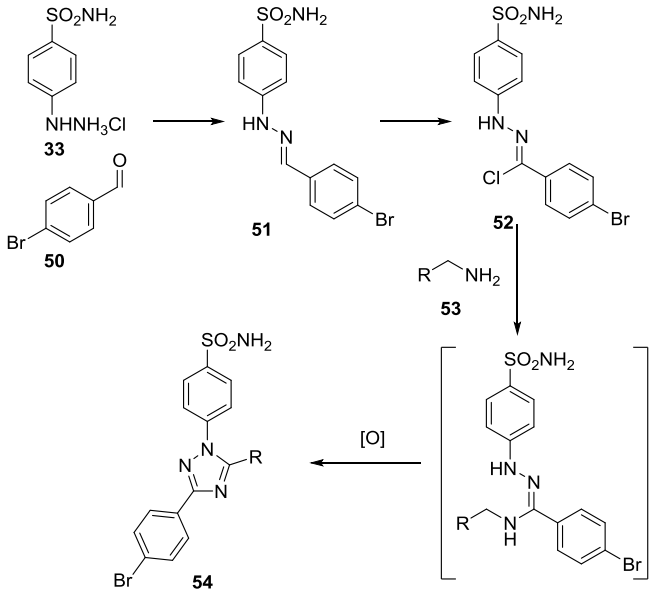
Unfortunately, the condensation-cyclisation step did not occur with any of the conditions attempted. The hydrazine remained, but the imide seemed to degrade. We expected that 1,3,5-triaryl substituted triazole **49** to be the sole product from this reaction, but found that there was the possibility that triazole **48** could also be a product of this reaction.



Scheme 2.29: Unsuccessful triazole formation

Although there was the potential to form two products in this reaction, no products were seen. Therefore, we decide to pursue an alternative route for a regioselective triazole formation.

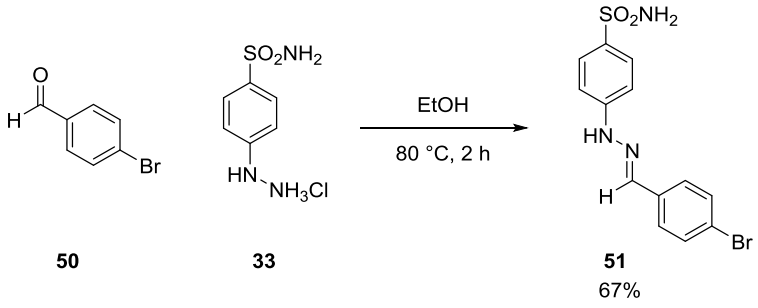
This new route to the triazole involved the formation of an intermediate hydrazonamide **51**. The forward synthesis begins with a hydrazone formation from hydrazine **33** and aldehyde **50**. The hydrazone **51** is then chlorinated to the hydrazonyl chloride **52** which is then reacted with a primary amine to give the 1,2,4-triazole **54** after oxidation.



Scheme 2.30: Revised synthetic route to triazoles

This route has the advantage that it will not form regioisomeric products and also that the substituent at position 5 of the triazole is added in the final reaction. This meant that with a stock of hydrazonyl chloride **52**, it would be possible to synthesise a number of analogues with different R groups on **54**. This route provides greater diversity than the syntheses for the pyrroles and pyrazoles.

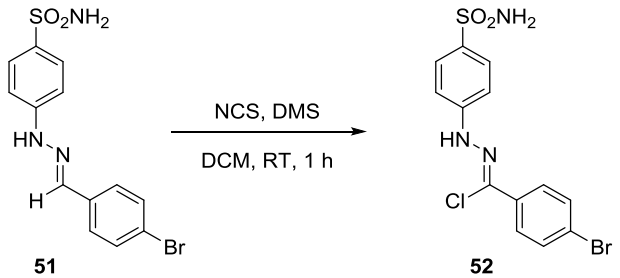
We started with the large scale synthesis of the hydrazone from a condensation of sulfanilhydrazine **33** and 4-bromobenzaldehyde **50**. The reaction to form the hydrazone went cleanly in good yield.



50 **33** **51**
67%

Scheme 2.31: Hydrazone formation

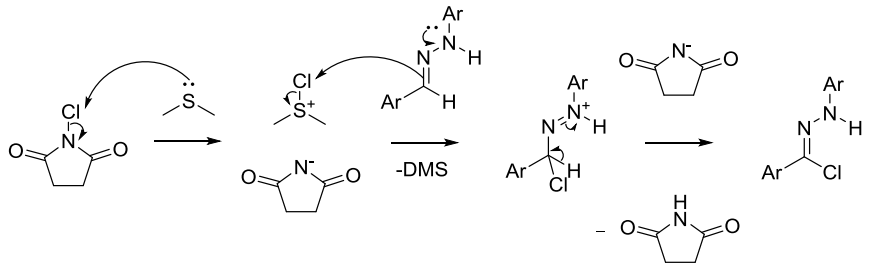
The formation of the hydrazonyl chloride was a more challenging reaction. In this reaction there was no starting material after 4 h and after workup and flash chromatography, the desired product was isolated in only 20% yield.



51 **52**
20%

Scheme 2.32: Hydrazonyl chloride formation

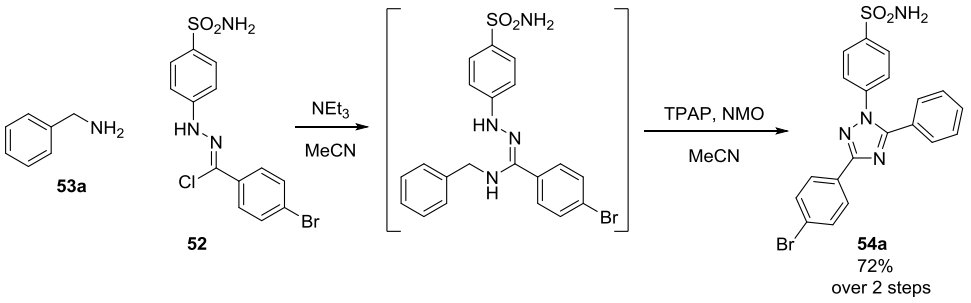
There were difficulties in this reaction from the start, the hydrazone only sparingly dissolves in the reaction solvent at room temperature. Also, the hydrazonyl chloride is likely to be unstable to the acidic nature of silica, thus flash chromatography is not a desirable purification technique. The proposed mechanism for the reaction is outlined below.



Scheme 2.33: Hydrazonyl chloride formation mechnanism

In our attempts to find a solution we used other solvents and mixtures of solvents that would allow the formation of the dimethylsulfonium chloride with good dissolution. Unfortunately, none of these changes led to an improvement in the yield of the reaction. Because the yield for this step was low and with the possibility of alternative routes it was decided to abandon this route.

A small amount of hydrazonyl chloride was obtained and a reaction to form the triazole was attempted. The hydrazonamide intermediate was not isolated; the crude product from the first reaction was used in the next step with the addition of tetrapropylammonium perruthenate (TPAP) and *N*-methyl morpholine oxide (NMO). After removing the solvent from the reaction and purification by flash chromatography, the triazole was isolated in very good yield.

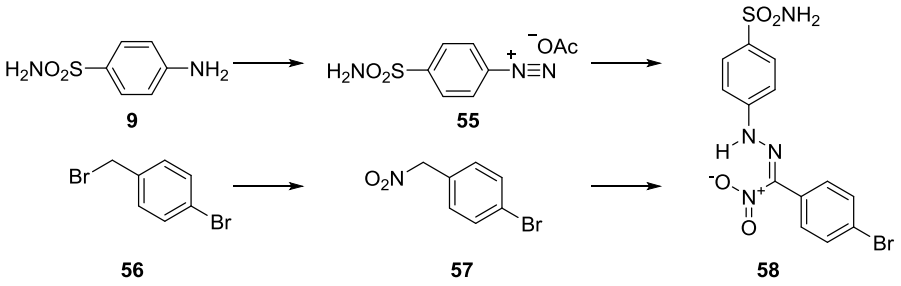


Scheme 2.34: Triazole formation from a hydrazonyl chloride

With this success, we found that this synthetic route was viable for the synthesis of triazoles. The problem was the formation of the hydrazone with a leaving group. After exploration of the literature we found a potential solution by using a nitrohydrazone (NO_2 as leaving group).

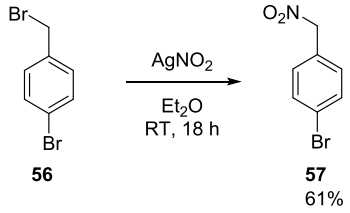
A new route was proposed with a similar reterosynthetic path, this route has the hydrazonamide intermediate derived from a nitrohydrazone **58**. This nitrohydrazone **58**

was synthesised from the diazo salt of sulfanilamide **55** and an appropriate nitro compound **57**. The nitro compound was formed from the nucleophilic displacement.



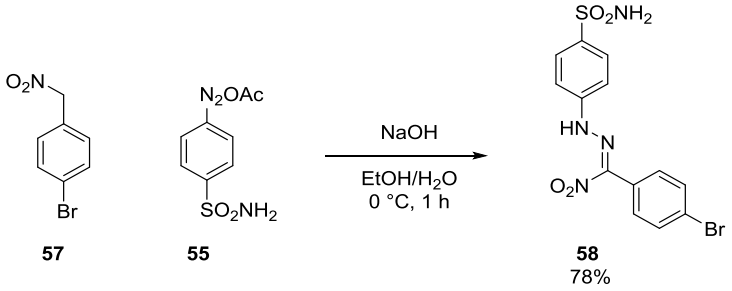
Scheme 2.35: Proposed route to nitrohydrazone **58**

The synthesis began with the nucleophilic displacement of bromobenzyl bromide **56** with $AgNO_2$ to give the nitromethyl benzene product **57**. The formation of the nitro compound occurred in good yield, following a literature procedure.[49]



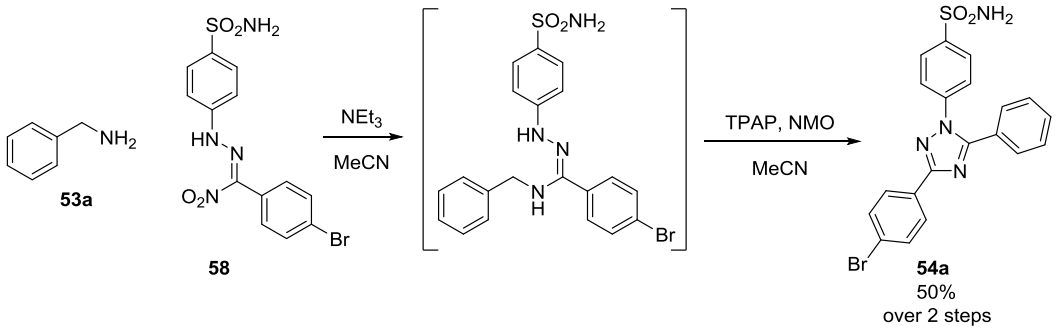
Scheme 2.36: Nitromethylbenzene formation

The formation of the nitrohydrazone was achieved by adding the diazo salt **55** to an ice-cold solution of deprotonated nitro compound **57**, which quickly precipitates the nitrohydrazone product **58**.



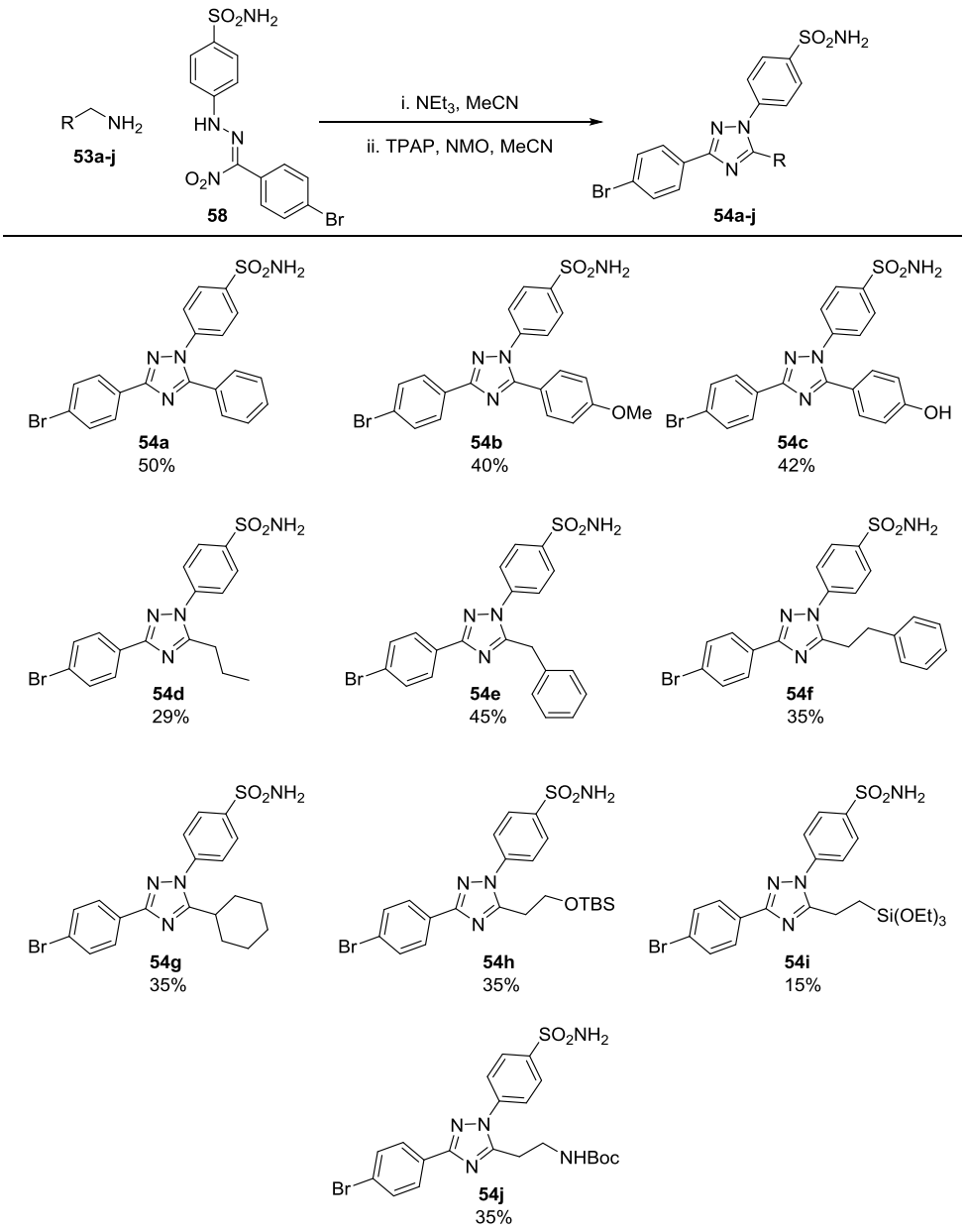
Scheme 2.37: Nitrohydrazone formation

With this product in hand, we repeated the triazole formation reaction replacing the hydrazonyl chloride **52** with the nitrohydrazone **58**. The reaction provides the 1,2,4-triazole product in good yield.



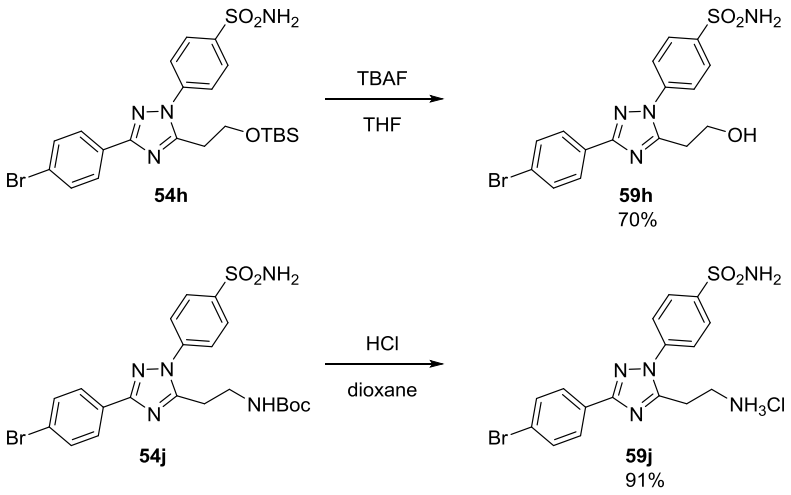
Scheme 2.38: Triazole formation from a nitrohydrazone

There was a similar reaction profile between both the hydrazones **52** and **58**, with the hydrazonyl chloride giving a higher yield over the last steps. Due to the difficulties in the formation of the hydrazonyl chloride, the overall efficiency of using the nitrohydrazone route is much greater. With the ease of formation of this novel triazole we explored a number of different primary amines as potential substrates for triazole formation.



Scheme 2.39: Formation of a number of triazoles

A range of triazoles **54a-j** were synthesised in relatively low yields over the two steps, but this method allowed the formation of triazoles with non-aromatic R-groups in the 5-position. The next step was the deprotection of the alcohol **54h** and amine **54j**, this was completed using TBAF and HCl respectively, to give the alcohol and the free amine salt.

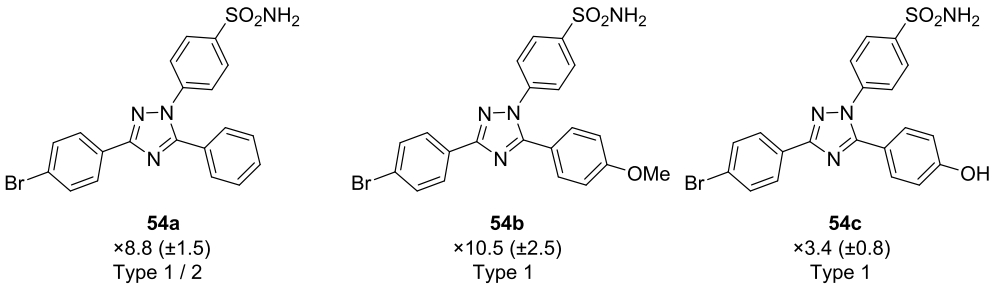


Scheme 2.40: Deprotections of **54h** and **54j**

These reactions were successful and gave the products in good to excellent yields. We felt that we produced a wide range of triazole molecules that would have diverse pharmacological effects on the nicotinic receptor. The triazoles were tested at UCL Pharmacology.

2.4.2 Triazoles – Pharmacological results by AC at UCL Pharmacology

We synthesised a number of triazoles and these were assessed at UCL Pharmacology. The first set synthesised were 3 nitrogen analogues of some previously active pyrazoles.



54a
×8.8 (±1.5)
Type 1 / 2

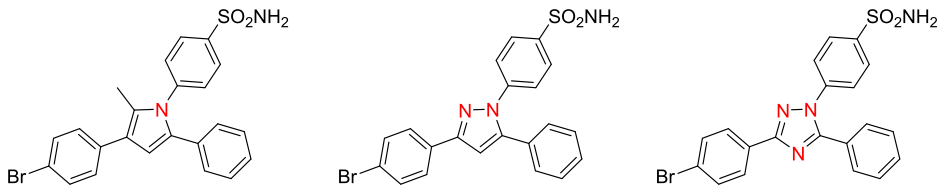
54b
×10.5 (±2.5)
Type 1

54c
×3.4 (±0.8)
Type 1

Figure 2.7: Triazoles

Interestingly, triazole **54a** shows a small amount of Type 2 PAM activity whilst the other triazoles **54b** and **54c** are just Type 1 PAMs. Type 2 PAMs not only facilitate the opening of the receptor upon the addition of ACh but also slow the desensitisation kinetics. The justification for intermediate PAM activity is due to the broad classification of PAM types, they are based on functional profiles and not on molecular mechanisms or binding sites. Therefore, more complex and intermediate effects can be observed with PAMs. All of the pyrroles, pyrazolines and pyrazoles synthesised exhibit only Type 1 PAM, NAM or no activity at all. The differences between the triazole **54a** and the pyrazole **35a** are only small in terms of molecular shape. The triazole **54a** does show a small amount of Type 2 PAM activity whilst the pyrazole **35a** shows solely Type 1 PAM activity.

We now have the opportunity to compare pyrrole **26a**, pyrazole **35a** and triazole **54a**; these molecules only vary in their heteroaromatic core.



26a
×3.0 (±0.2)
Type 1

35a
×4.9 (±0.7)
Type 1

54a
×8.8 (±1.5)
Type 1 / 2

Figure 2.8: Comparison of pyrrole **26a**, pyrazole **35a** and triazole **54a**

A general trend for the heterocycles is that they show greater n-fold peak potentials with the increase of nitrogens in the heterocyclic core.

The triazole synthesis that we have developed allowed the formation of a number of different R groups other than aromatic groups at the 5 position of the triazole. This allows us to synthesise more flexible and 3D triazoles that could not be done with the pyrazole synthesis. We were happy to find that the triazoles synthesised exhibited positive allosteric modulation and negative allosteric modulation, generally with good solubility.

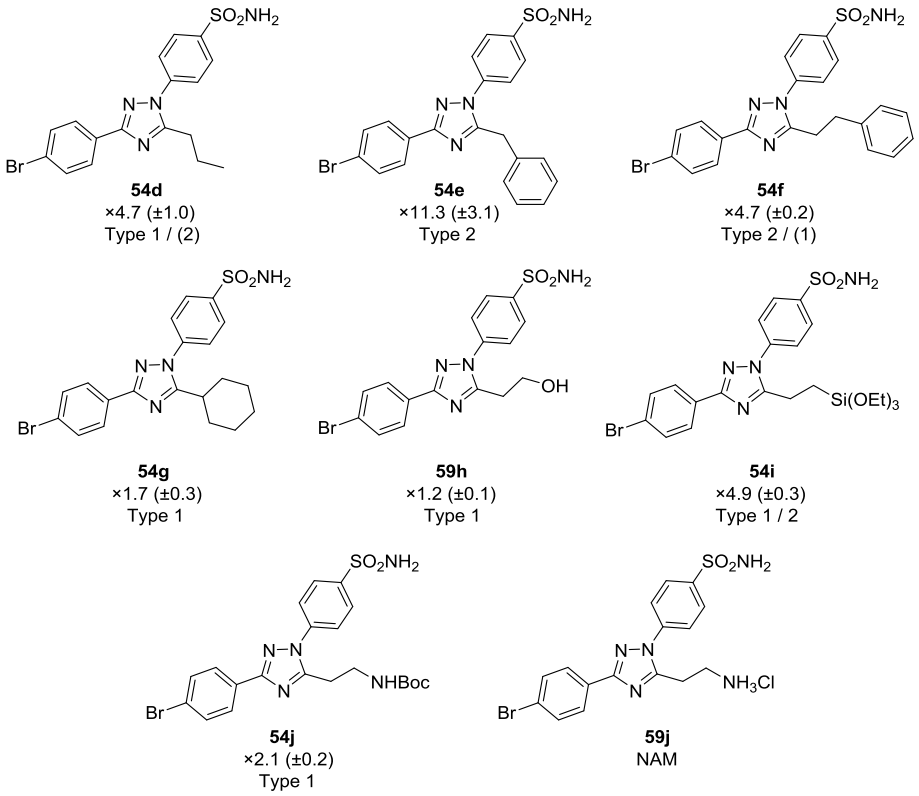


Figure 2.9: Triazoles with varied pharmacological activity

Changes at the 5 position of the triazoles gave changes in the pharmacological response. Hydrophobic groups at this 5 position (**54a-b**, **54d-g** and **54i**) gave good PAM activity. In addition to the enhancement in the peak response when co-applied with ACh, there is a degree of desensitisation of the receptor. The example where the group at the 5-position of the triazole is benzyl (**54e**) was found to have very interesting receptor kinetics. The benzyl derivative **54e** has fast initial response to the same magnitude to the ACh alone, followed by the increase in the n-fold peak potential along with increased desensitisation kinetics, that makes it a Type 2 PAM. There is little difference in terms of molecular shape between **54e** and **54b** which displays solely Type 1 activity.

The difference may be due (in part) to the fact the methylene unit between the phenyl ring and the heteroaromatic core conveys greater flexibility. This molecule must reduce the

energy between receptor opening **A** and closing. This effect can be attributed to the molecule stabilising the 'active' state and also binds in such a way that slows the transition **B** from the 'active' state to the 'desensitised state' by destabilising the 'desensitised' state (See **Figure 2.10**).

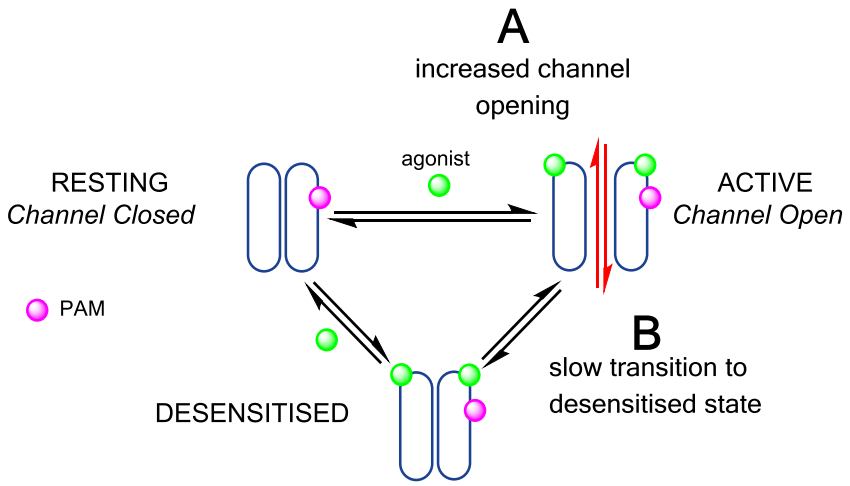


Figure 2.10: Representation of receptor opening and closing with a PAM

More polar groups (**54c**, **54h** and **59h**) give only slight PAM activity and as the polarity is increased to the amine salt **59j**, PAM activity is lost and this molecule acts as a NAM. The amine salt acting as a NAM may be due to the polar group causing electrostatic repulsion of the ions in the channel. This restriction of channel opening would stabilise the 'resting' state which will cause a reduced response to the addition of the agonist.

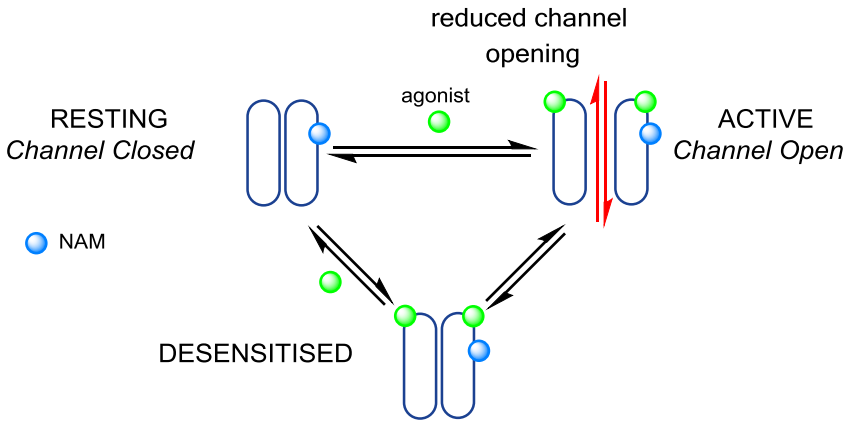


Figure 2.11: Representation of receptor opening and closing with a NAM

For some of the triazoles (**54a-b**, **54d-f**), our collaborators conducted a more in-depth study of the effect of the molecules on native α7 nAChRs and mutant receptors. This is because

the molecules display Type 1 and Type 2 positive allosteric modulation, as well as intermediates of these effects. Type 1 PAMs show little to no desensitisation of the receptor upon activation whereas Type 2 PAMs show dramatic slowing of the desensitisation.

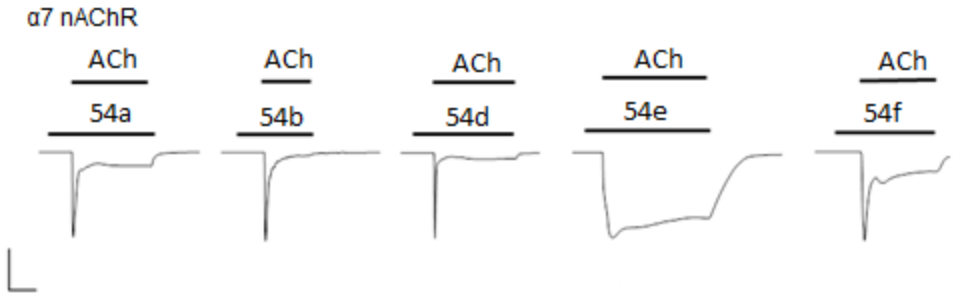


Figure 2.12: α7 receptors with a selection of molecules (co-applied with ACh)

They found that these triazoles were selective for human and rat α7 nicotinic receptors over α4β2 nAChRs, Mouse 5-HT_{3A} (serotonin receptor), and rat α7/5-HT_{3A} (Chimeric receptor), see **Table 2.1**.

Table 2.1

Receptor Subtype	Compound **54a** % inhibition / Fold potentiation	Compound **54b** % inhibition / Fold potentiation	Compound **54d** % inhibition / Fold potentiation	Compound **54e** % inhibition / Fold potentiation	Compound **54f** % inhibition / Fold potentiation
Human α7	8.8 ± 1.5	10.5 ± 2.5	4.7 ± 1.0	11.3 ±3.1	4.7 ± 0.2
Human α4β2	20.1 ± 19.0	23.1 ± 5.7	20.5 ± 5.9	1.7 ± 0.4	3.2 ± 0.9
Human α3β4	53.7 ± 18.3	68.4 ± 3.0	9.0 ± 3.5	31.1 ± 0.6	15.6 ± 12.7
Rat α7	10.9 ± 0.73	8.7 ± 5.3	1.9 ± 0.2	3.6 ± 1.0	4.3 ± 0.6
Mouse 5-HT_{3A}	18.3 ± 13.3	30.8 ± 15.5	15.2 ± 4.3	10.4 ± 7.5	10.4 ± 1.9
Rat α7/5-$HT3_A$	47.3 ± 10.1	13.4 ± 7.7	26.4 ± 16.0	9.2 ± 12.8	1.0 ± 1.0

There are potential individual point mutations in nAChRs that can have significant effects on the pharmacological response of receptors, increasing or decreasing their selectivity and pharmacological responses to ligands. There is growing evidence that indicates that Type 1, Type 2 PAMs and allosteric agonists can act via a transmembrane site in α7 nAChRs. Therefore, point mutations provide a valuable insight into receptor binding of these molecules, receptor opening and the allosteric binding site. The mutation L247T is a replacement of a leucine residue as the 247th amino acid in the α7 subunit is replaced by a threonine residue. This mutation lies towards the middle of the second transmembrane domain (TM2) of the subunit, this change can cause a dramatic slowing of receptor desensitisation.

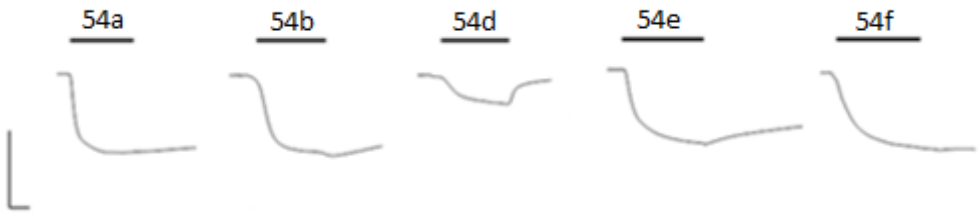


Figure 2.13: L247T mutated α7 receptors with a selection of molecules

In the α7 nAChRs displaying the L247T mutation all five compounds showed agonist activity, regardless of whether they were Type 1 or Type 2 PAMs on human α7 nAChRs. This is different to other PAMs, for example, they showed NS-1738 does not exhibit any activity on this receptor. These molecules stabilise the 'open' state upon binding of the agonist in the native receptor. With this mutation, these molecules are able to stabilise the 'open' state to allow the ions to flow. The mutation must in some way lower the energy between the 'resting' and 'open' states.

In contrast to the L247T mutation, the M260L mutation (replacement of methionine for leucine), located higher in TM2 usually shows little to no effect on the rate of receptor desensitisation.

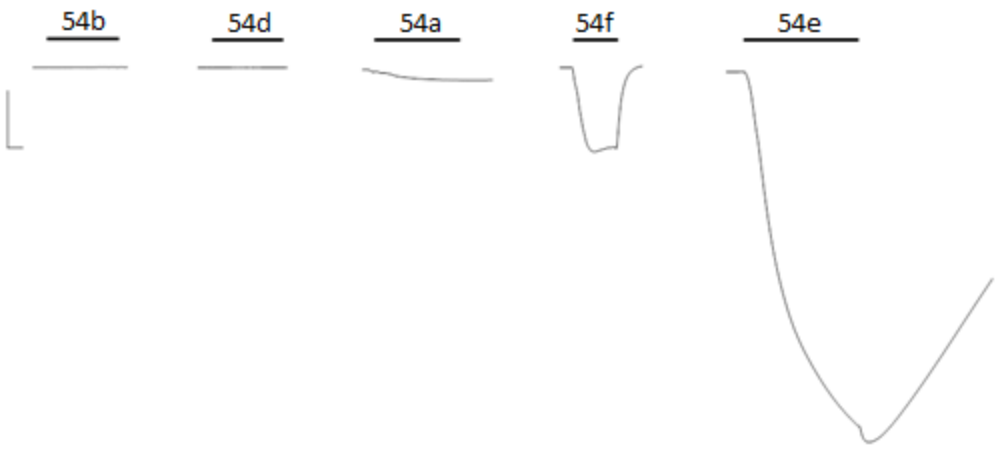
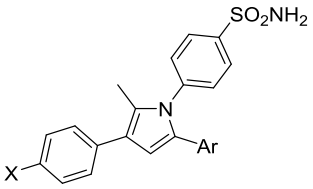


Figure 2.14: M260L mutated α7 receptors with a selection of molecules

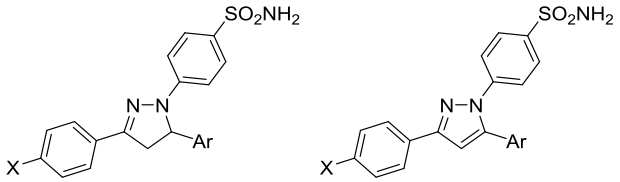
For the α7 nAChRs containing the M260L mutation, strong agonist activity was only seen with 2 molecules (**54e** and **54f**) the other molecules had little to no effect on the receptor. Coincidentally, these molecules exhibited the greatest reduction in desensitisation in the wild-type α7 receptors. These molecules must interact with the receptor in such a way that stabilise the 'open' or destabilise the 'resting' states of the receptor. The molecules **54e** and **54f** are Type 2 PAMs on the native α7 nAChR and act as agonists on the M260L mutated receptors. This is interesting because the intermediate and Type 1 PAMs on the native α7 nAChR do not have any effect on the mutated M260L receptor.

2.5 Conclusion

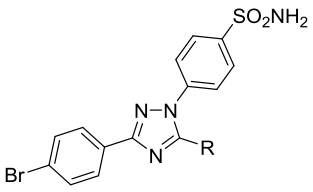
We have designed and developed routes for the synthesis of novel substituted heterocycles that exhibit allosteric modulation effects on the α7 nicotinic acetylcholine receptor. We began the project with the synthesis of novel pyrroles that were found to act as Type 1 positive allosteric modulators for the receptors, before the synthesis of more complex molecules.



Pyrazolines were produced as intermediates, which were discovered to be also novel (but weak) allosteric modulators for nicotinic receptor. Pyrazoles showed strong Types 1 PAM effects on the receptor.



After the exploration of the core containing 2 N-atoms (pyrazoles) we then explored the 3 N-atoms (triazoles) derivatives and found a mixture of pharmacological effects.



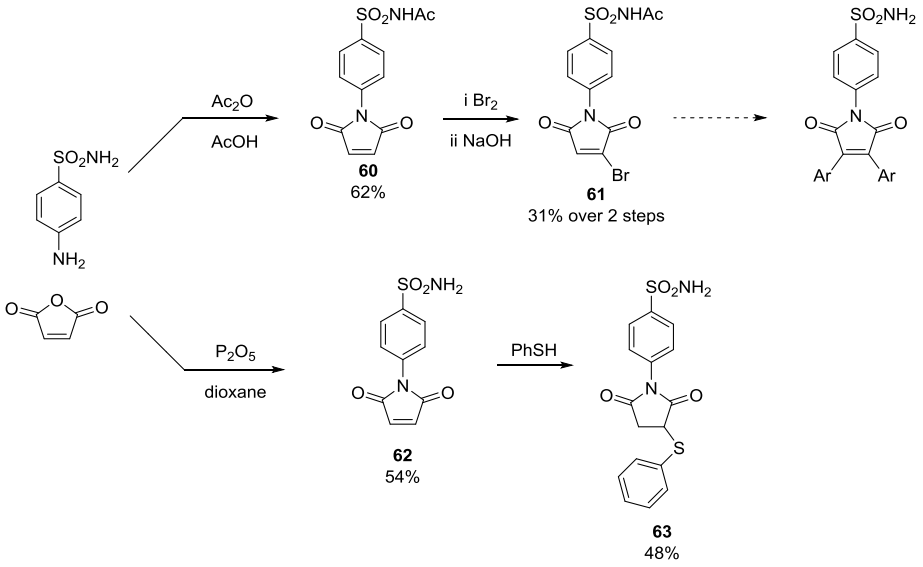
Dependent on the R group the molecules exhibit effects including: Type 1 PAM, Type 2 PAM and negative allosteric modulation. We also found that with site-selective mutagenesis we can see changes in pharmacological response with small differences in the molecular structure.

2.6 Future Work

Future work in this project would be to explore more molecules that will display a pharmacological response on nicotinic receptors.

Maleimides

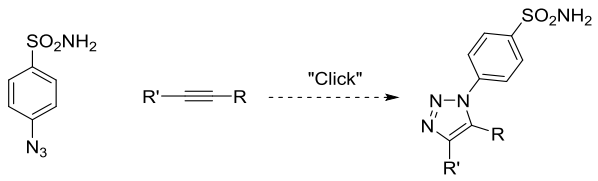
One promising area of progress is with maleimide reagents. As these molecules contain a Micheal acceptor, it could be possible for reaction with the amino acid residues on the protein which would give further evidence for the location of the allosteric binding site.



The dehydration reaction between maleic anhydride and sulfanilamide in AcOH with acetic acid led to a maleimide product, however, some monoacylation of the amine also occurred during this reaction. An alternative route, using P_2O_5 as the dehydrating agent, led to the desired maleimide product. The maleimide **62** was reacted with thiophenol to give succinimide **63**. This molecule was tested and was found to have no effect on nicotinic receptors. No further work was completed.

1,2,3-Triazoles

With the diverse structures that gave activity on the receptor, it is possible that novel 1,2,3-triazoles would acts as modulators on the receptor. The benefits of this approach would be a very facile synthesis of a number of analogues through a well understood and established method with readily available starting materials.

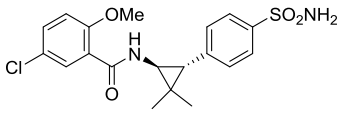


Molecules that act on non-α7 nAChRs

In this project we have focused on synthesis of molecules that act as modulators of the α7 nicotinic receptor. Many of the molecules synthesised have been subtype selective, however, synthesis of α4β2 or other subtypes of receptors would be very interesting in the project moving forward. Another possible extension would be the synthesis of agonist or modulators that are selective for insect nAChRs.

Synthesis of aminocyclopropane that affect nicotinic receptors

During my PhD I have been able to work on the synthesis of aminocyclopropanes.[50] Selective α7 nAChR Type 2 PAM RO5126946 is an aminocyclopropane and we believe that we could potentially synthesise analogues through this route.



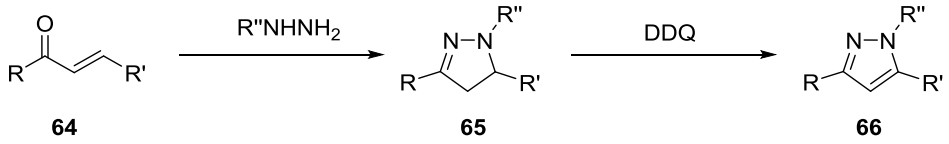
RO5126946

Chapter 3 Gold-catalysed reactions

3.1 Pyrazole formation using gold-catalysis

3.1.1. Introduction

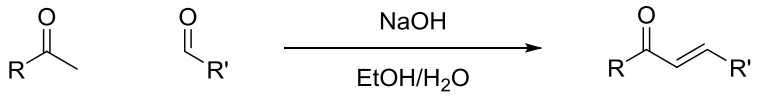
In Chapter 2, the conversion of enones into pyrazoles was discussed (**Scheme 3.1**). The reaction is a two-step process, first the hydrazine addition to form the pyrazoline **65** followed by oxidation to give the pyrazole **66**.



64 **65** **66**

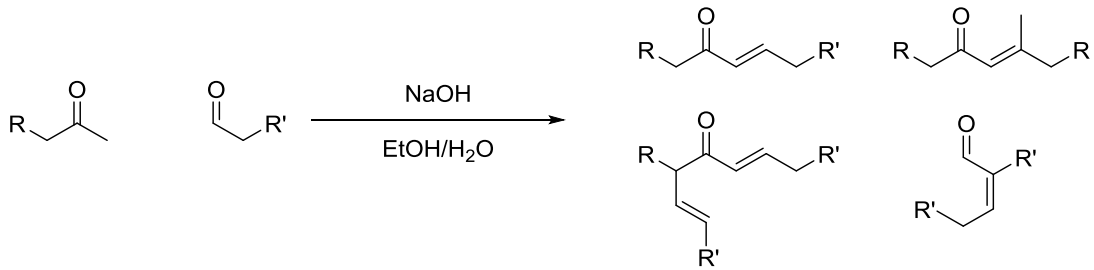
Scheme 3.1: Two-step pyrazole formation from the enone **64**

The limitation of this reaction is derived from the formation of the enone **64**. The enones used primarily in the nicotinic project are produced by a Claisen-Schmit condensation from an aldehyde and a ketone.



Scheme 3.2: Claisen-Schmidt condensation

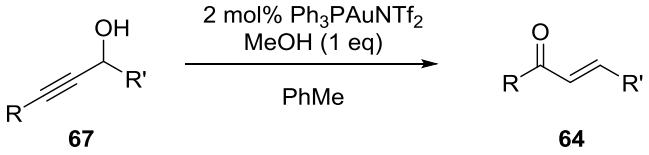
These reactions are very efficient when R and R’ are aromatic rings, however, where R and R’ are alkyl groups there are more α-protons giving unselective deprotonation, which lead to by-product forming reactions and polymerisation pathways.



Scheme 3.3: Potential products from Claisen-Schmit formation

There are many reviews on the gold activation of alkynes.[51–55] In particular, the Meyer-Schuster rearrangement[56] would be a more controlled approach to this class of enones

starting from readily synthesised propargylic alcohols. Our plan was to synthesise pyrazoles from propargylic alcohols through enone intermediates. Previous work in the Sheppard group has shown the utility of propargylic alcohols by their clean transformation into enones with the use of a gold catalyst and a protic additive. This protocol for the Meyer-Schuster rearrangement is mild and convenient (**Scheme 3.4**). [57,58] Alternative conditions can also be used for Meyer-Schuster rearrangement.[59,60]

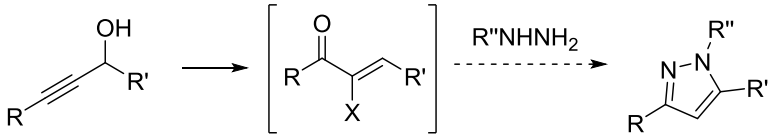


67 **64**

Scheme 3.4: Gold-catalysed Meyer-Schuster rearrangement

Gagosz's catalyst, [Bis(trifluoromethanesulfonyl)imidate] (triphenylphosphine)Au(I) (2:1) toluene adduct is commercially available and is a highly effective catalyst for this transformation. The reaction is tolerant of a variety of functional groups and enones that are inaccessible using the Claisen-Schmidt procedure can now be produced.

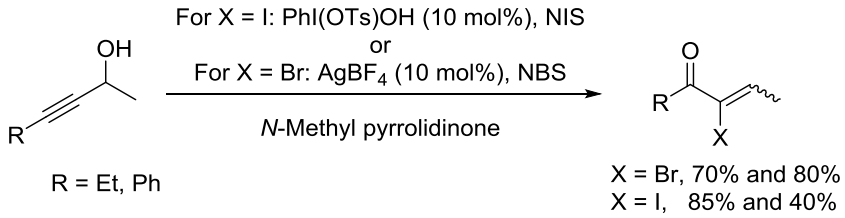
Another limitation of the pyrazole formation discussed in Chapter 2 is that the reaction is broken into two steps, first the pyrazoline formation, then the oxidation to the pyrazole. An intuitive approach to the pyrazole would be the formation of an oxidised enone in the form of a α-haloenone (**Scheme 3.5**).



67 **68** **66**

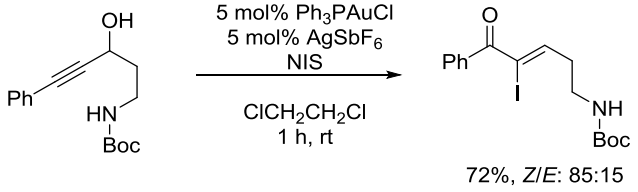
Scheme 3.5: Haloenones to Pyrazoles

The advantage of this approach is that there will be no requirement for a separate oxidation step. In 1991, McNelis and co-workers first reported the formation of a α-haloenones from propargylic alcohols. [61] Both protocols use *N*-halosuccinimides (NXS) as the electrophilic halogen source. The reactions give good yield but a limitation is the poor substrate scope.



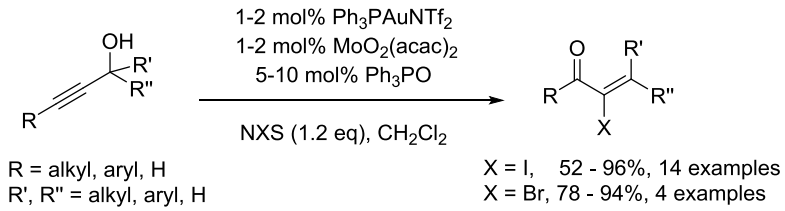
Scheme 3.6: Meyer-Schuster rearrangement halogenation[61]

In 2013, Gault and co-workers reported an α-iodoenone from a propargylic alcohol as a unwanted product. [62] The reaction requires gold-catalysis in the presence of NIS and gives the enone with good yield and *E*/*Z* selectivity.



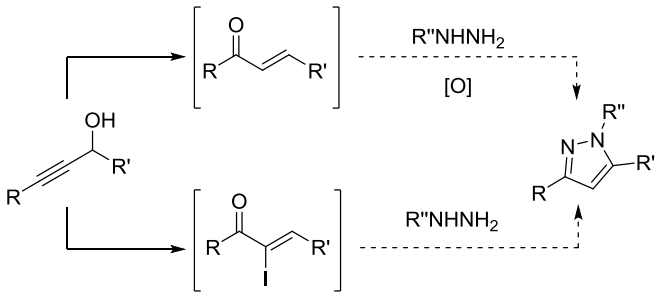
Scheme 3.7: Gold-catalysed Meyer-Schuster rearrangement iodination[62]

The most prominent work in this field has been competed by Zhang and co-workers in 2009.[63] The reaction has a wide substrate scope to give iodoenones and bromoenones in generally good to excellent yields.



Scheme 3.8: Gold-catalysed Meyer-Schuster rearrangement halogenation[63]

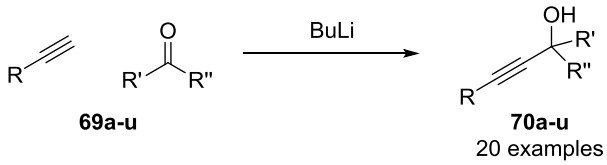
The aim of this project is the synthesis of pyrazoles either from enones (with an oxidant) or iodoenones, both of which are derived from propargylic alcohols.



Scheme 3.9: Aim of Chapter 3- Pyrazole synthesis

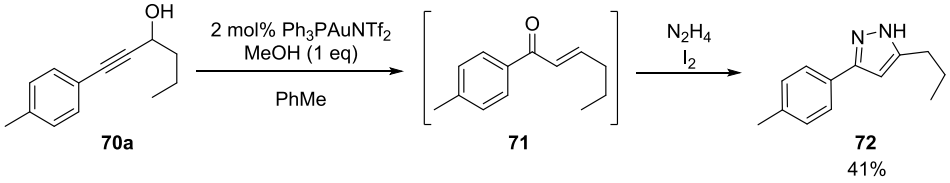
3.1.2. Synthesis of a pyrazole from a propargylic alcohol

The propargylic alcohols in this project were produced using a preparation previously used in the group with *n*-BuLi, a carbonyl compound and a terminal alkyne.



Scheme 3.10: Propargylic alcohol formation

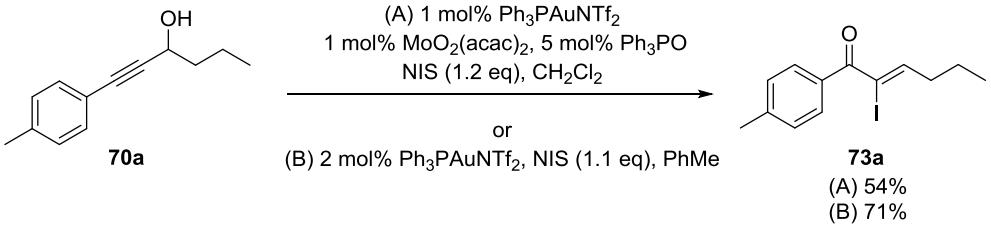
The reactions to synthesise propargylic alcohols are generally efficient with isolated yields of 45 – 96%. These substrates are suitable for the Meyer-Schuster rearrangement. As the product from the Meyer-Schuster rearrangement is clean, we envisaged that the product could be telescoped in the subsequent reaction to form pyrazoles directly from the reaction mixture in one-pot. The first reaction attempted was enone formation with Gagosz's Au catalyst and MeOH in toluene.



Scheme 3.11: Pyrazole formation from the enone

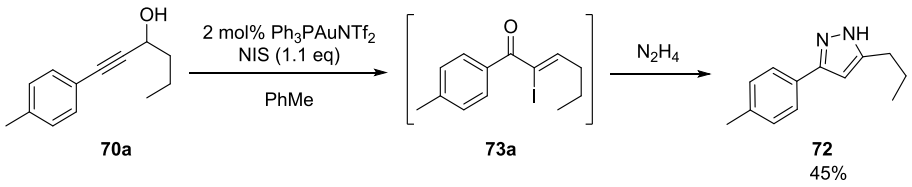
Propargylic alcohol **70a** was converted to the pyrazole **72** via the enone **71**, however, the efficiency of the overall reaction was rather low. The presence of hydrazine and iodine, we

believe, led to diazene and ultimately nitrogen formation. At the same time there is degradation of I_2 giving a fairly low conversion to the pyrazole. The hydrazine addition and oxidation in separate steps may decrease the amount of side-product formation. Therefore, we used a preparation from the literature to synthesise the iodoenone **73a**.[64]



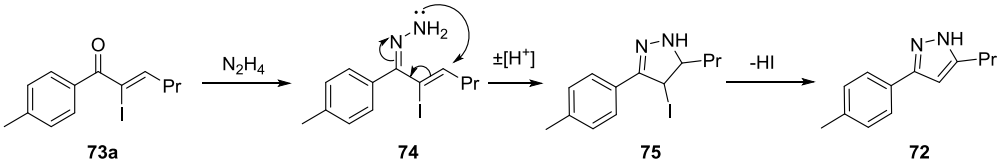
Scheme 3.12: Iodoenone formation

In our hands the yield was 54% for the iodoenone **73a**. We believed the preparation did not require the co-catalysts ($MoO_2(acac)_2$ and Ph_3PO) and thus we attempted a synthesis closely related to the Meyer-Schuster rearrangement conditions used previously in our group. Addition of NIS to the reaction mixture allowed the successful isolation of the iodoenone **73a** in 71% yield. This result is particularly impressive as the reaction conditions were not optimised. We then submitted the propargylic alcohol to the iodoenone formation until complete conversion of SM. This was then followed by the addition of hydrazine.



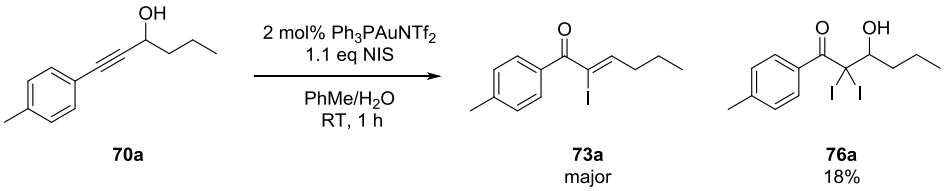
Scheme 3.13: Pyrazole formation from the iodoenone

The first attempt for the synthesis of a pyrazole via the iodoenone was successful but provided pyrazole **72** in disappointing 45% yield. We predict that upon hydrazine addition we would expect hydrazone formation, followed by attack of the pendant amine to give a iodopyrazoline **75**, with loss of HI gives the pyrazole. The poor yield may be attributed to the instability of the hydrazone **74**.



Scheme 3.14: Proposed mechanism for pyrazole formation from an iodoenone

With the repetition of the iodoenone synthesis we see the formation of a new by-product. This product appeared to be derived from the addition of 2 atoms of iodine and water to the propargylic alcohol to give an α,α-diiodo-β-hydroxyketone **76a**. The structure was confirmed by isolation of this product by adding water to the reaction mixture.

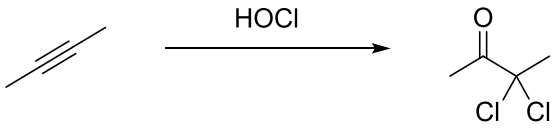


Scheme 3.15: First isolation of a diiodoketoalcohol **76a**

This unprecedented reaction is the diiodohydration of a propargylic alcohol which has not been previously reported. In addition, this is the first example of a gold-catalysed diiodohydration reaction.

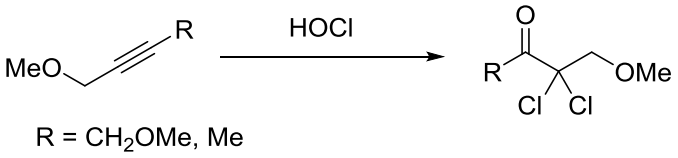
3.2 Literature Review of Dihalohydration Reactions

The addition of water and halogens to an alkyne to give a dihaloketone was first discovered in the 19th century. The addition of water and halogens across a carbon-carbon triple bond is termed dihalohydration. Dihalohydration of alkynes has existed for a long time with the earliest report in 1895 with the dichlorohydration of 2-butyne to give 3,3-dichlorobutan-2-one by Faworksi.[65] The details of this transformation are not available other than hypochlorous acid as the reagent.



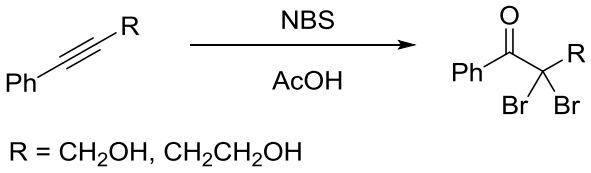
Scheme 3.16: First report of a dihalohydration of an alkyne[65]

Later in 1910, a report of dichlorohydration of alkynylethers was completed also using hypochlorous acid by Jozitsch.[66] The procedure was the same used by Faworski, but with a slightly wider substrate scope.



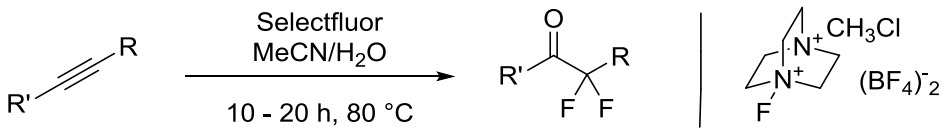
Scheme 3.17: Another early report of dihalohydration[66]

The next significant report was in 1967, with the first report of dibromohydration of alkynes by Jovtscheff and co-workers.[67] The electrophilic bromine source is *N*-bromosuccinimide (NBS).



Scheme 3.18: First report of dibromohydration of alkynes[67]

In 1995, the first procedure of difluorohydration of an alkyne was reported by Stavber and co-workers.[68] The procedure involves Selectfluor as an electrophilic fluorine source, the yields of this transformation are only moderate.

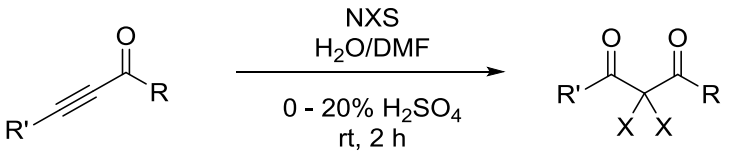


R = Ph, H, Me, *t*-Bu
R' = Ph

36 - 51%, 4 examples

Scheme 3.19: First report of difluorohydration of alkynes[68]

In 1998, the dibromohydration and diiodohydration of conjugated alkynes was reported by Eden.[69] There are only 4 examples of the reaction, therefore the reaction scope has not been fully explored. The diiodides can be produced in excellent yields from an operationally simple procedure.

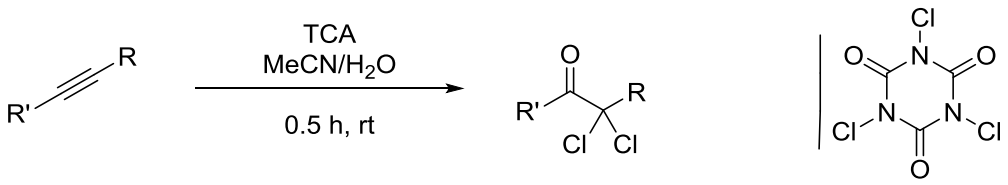


R = Me, OMe
R' = Et, Ph

X = Br, 43 - 80%, 4 examples
X = I, 95%, 4 examples

Scheme 3.20: Dihalohydration of conjugated alkynes [69]

In 2003, a report was published of a operationally facile approach for the synthesis of dichloroketones from alkynes.[70] The substrate scope of this transformation is not particularly wide. The general efficiency of the transformation is good.



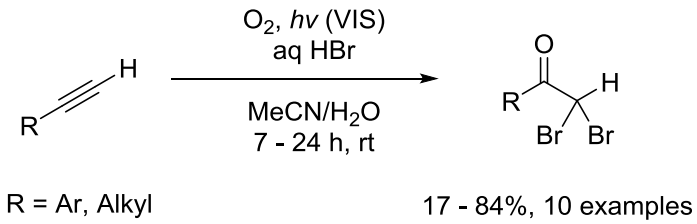
R = Ph, Pr, Bu, Hex
R' = H, Et, Pr, Bu

59 - 79%, 6 examples

TCA

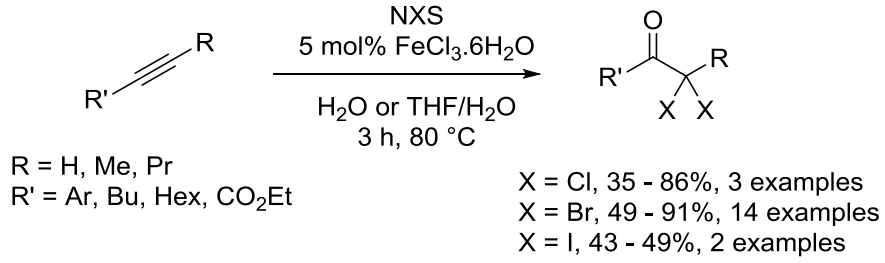
Scheme 3.21: Dichlorohydration of alkynes[70]

The facile aerobic photo-oxidative dibromohydration of terminal alkynes to dibromoacetophenones was reported in 2010 by Itoh and co-workers. The reaction works excellently where R is aromatic, whereas where R is alkyl the yield is only 17%.[71]



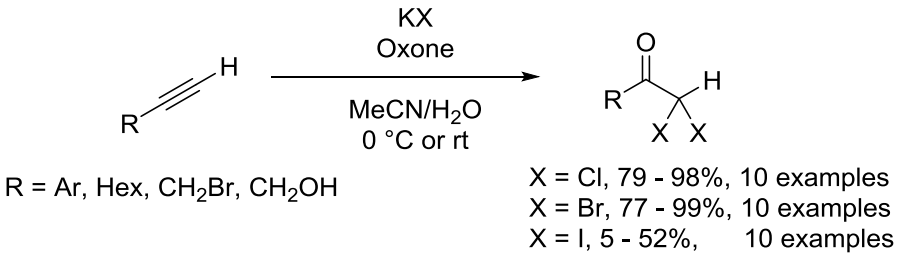
Scheme 3.22: Light-activated dibromohydration of terminal alkynes[71]

The dihalohydration of a number of alkynes with wide reaction scope was reported by Li[72] and co-workers in 2010. The reaction requires a readily available iron catalyst and *N*-halosuccinimides. Terminal aromatic alkynes could be converted to dihaloacetophenones in water alone in good to excellent yields.



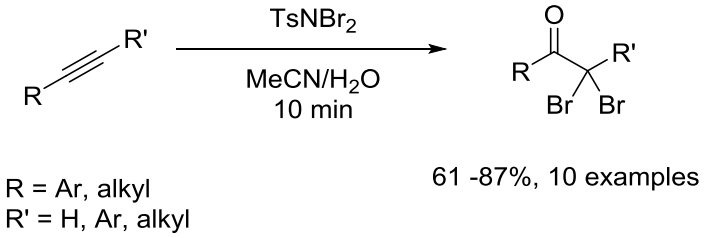
Scheme 3.23: Dihalohydration using a iron catalyst[72]

Vangipuram and co-workers reported the synthesis of dihaloacetophenones in 2013.[73] The dichlorides and dibromides are produced in generally good to excellent yields. However, the diiodides are can only be isolated in poor to moderate yields.



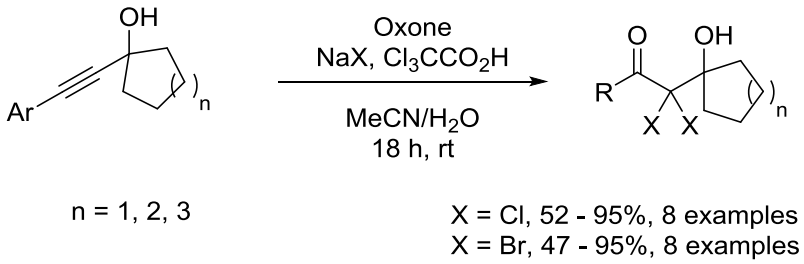
Scheme 3.24:Dihalohydration of terminal alkynes[73]

Also in 2013, there was a report of dibromohydration of alkynes using *N*,*N*-dibromo-toluenesulfonamide ($TsNBr_2$). This route to dibromoketones is rapid with good yields with no catalysts required.[74]



Scheme 3.25:Dibromohydration using $TsNBr_2$[74]

In 2014, Moran and co-workers reported the conversion of propargylic alcohols to dibromoketoalcohols and dichloroketoalcohols.[75] The reaction conditions are similar to the conditions used by Vangipuram, however, this propargylic alcohol system is more complicated than the terminal alkyne system. The researchers were unsuccessful in their attempts to synthesise diiodoketoalcohols using NaI as the salt.



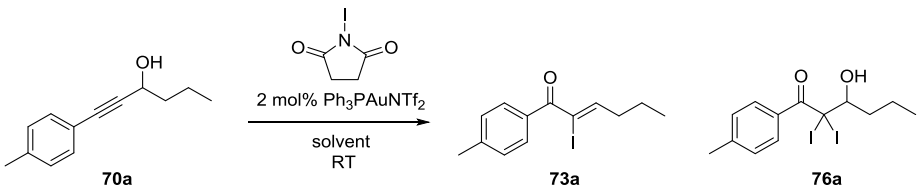
Scheme 3.26: Dihalohydration using oxone and sodium salts [75]

In the literature there are many examples of dihalohydrations of alkynes. In the past five years there has been resurgence in this area of research. The limitations of the diiodohydration reactions in the literature are that they suffer from poor yields and poor substrate scope. The use of a gold-catalyst and NIS for the conversion of propargylic alcohols to give diiodoketoalcohols would be a valuable and significant addition to the dihalohydrations in the literature.

3.3 Synthesis of Diiodoketoalcohols

During the investigation of a gold-catalysed iodoenone synthesis from propargylic alcohols we found that in addition to the iodoenone, a new ketone product was being formed in very small quantities (which we could not isolate). This product was found to be an α,α-diiodo-β-hydroxyketone. This class of compounds, to the best of our knowledge, has not been reported previously. This transformation would be a useful addition to previously developed Au-catalysed reactions in the Sheppard group.[76] This diiodoketoalcohol product also has the benefit of geminal iodine atoms which will allow potential exploration of new reactions based on the ketone, alcohol and the diiodide all placed in close proximity. At this time, we sought to optimise the reaction conditions in favour of the diiodoketoalcohol over the iodoenone.

Table 3.1: Optimisation of the diiodohydration reaction



70a **73a** **76a**

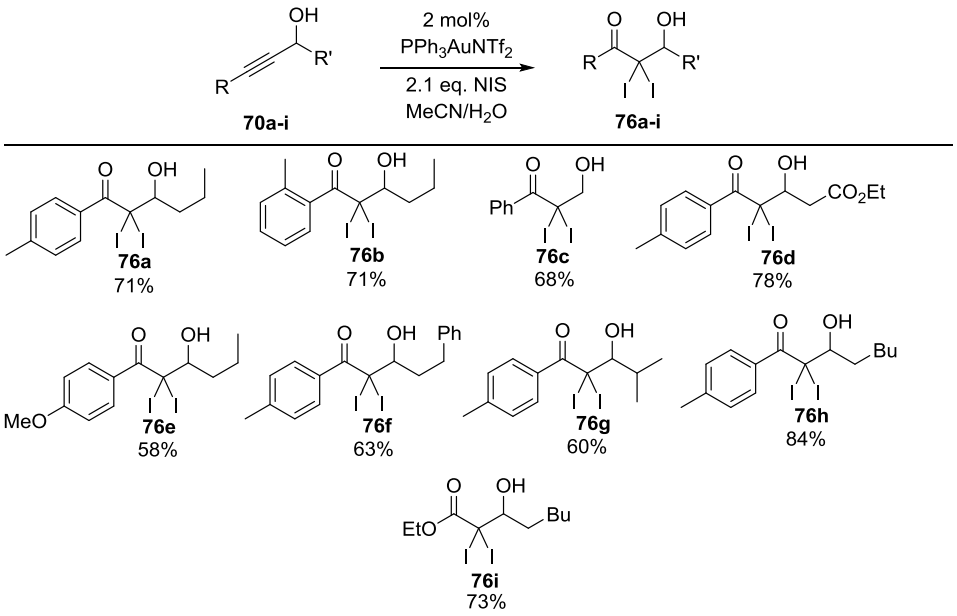
Entry	Solvent	NIS (eq.)	Time	Yield **73a**	Yield **76a**
1	PhMe	1.2	2 h	71%	trace
2	PhMe:H_2O 20:1	1.2	18 h	major	18%
3	PhMe:H_2O 20:1	2.4	5 h	n.d.[a]	49%
4	Et_2O:H_2O 20:1	2.2	45 min	n.d.	50%
5	THF:H_2O 20:1	2.2	45 min	n.d.	38%
6	MeCN:H_2O 20:1	2.2	30 min	n.d.	64%
7	MeCN:H_2O 10:1	2.1	1 h	n.d.	71%
8	MeCN:H_2O 10:1	2.1	18 h	0%[b]	0%[b]

[a] n.d. = not detected. [b] The gold catalyst was omitted.

Water was required for the hydration of the alkyne, therefore, we added water to the reaction mixture enabling diiodide **76a** to be isolated. The ketoalcohol **76** was the major product of this reaction but the isolated yield was low (Entry 2, 18%). Two atoms of iodine

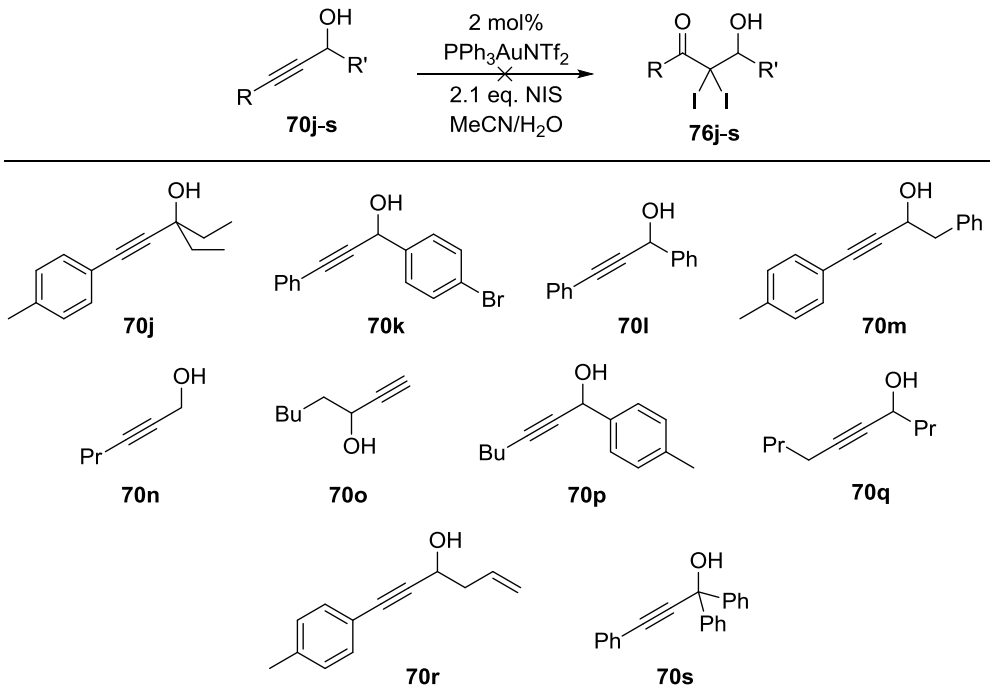
are incorporated into the molecule and so an experiment with excess NIS was conducted to give the product **76a** in acceptable yield (Entry 3, 49%). The lower yield was attributed to the poor solubility of water in PhMe, therefore, we conducted the experiment with some alternative solvents: Et_2O, THF and MeCN (Entries 4-6). Et_2O and THF gave no significant improvement, but acetonitrile gave a slight improvement in yield (Entry 6). A further increase in yield was achieved through the scale up of the reaction (more accurate measurement of the quantities), a greater quantity of water in the solvent mixture and a reduction in the excess of NIS (Entry 7). These changes in the conditions also led to none of the undesired iodoenone **73a** being detected.

We next set out to determine the scope of this diiodohydration reaction by applying these optimised conditions to various propargylic alcohols.



Scheme 3.27: Successful diiodoketoalcohol formation

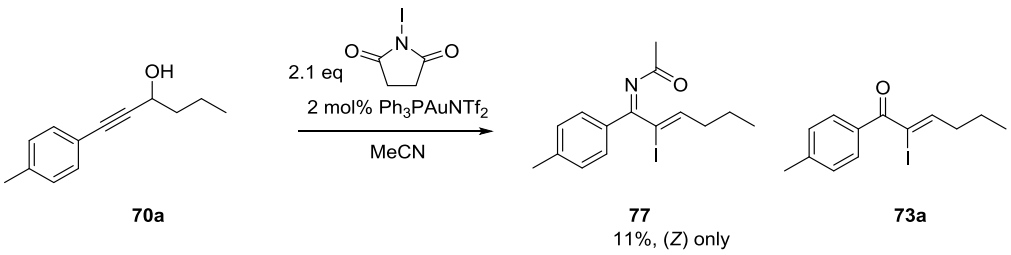
Pleasingly, a selection of α,α-diiodo-β-hydroxyketones **76a–h** could be obtained and isolated in acceptable to excellent yield. Secondary alcohols **76a**, **76b**, **76d–i** can be produced as well as primary alcohol **76c** derived from commercially available propargylic alcohol **76c**. Diiodohydroxyester (**76i**) could be produced in excellent yield from the corresponding alkynyl ether. The reaction generally requires an electron-releasing substituent (tolyl, PMP and OEt) on the alkyne and other groups do not give the desired products.



Scheme 3.28: Unsuccessful diiodoketoalcohol formation

Tertiary propargylic alcohols (**70j** and **70s**) led to a mixture of unidentified products as did propargylic alcohols with aryl groups on the alcohol (**70k**, **70l**, **70p** and **70s**). This could be attributed to the electron-releasing nature of the aromatic group along with the steric strain on forming the geminal diiodide. Failure of propargylic alcohol **70m** was surprising, however, this could also be attributed to steric clash in the formation of the diiodide. Aliphatic propargylic alcohols **70n**, **70p** and **70q** led to side-reactions and the desired diiodides could not be detected. Terminal propargylic alcohol (**70o**) was not a suitable substrate as little reaction occurred, and after 24 h only SM and unidentified products were seen. In the reaction with the pendant alkene (**70r**) there is potential for reaction on the alkene, as well as the alkyne. However, the reaction appeared clean but after column chromatography the major fraction was a mixture of two unidentified products produced in a low yield.

We have explored the substrate scope and the limitations of this diiodohydration reaction. To justify and understand the reasons for these limitations we conducted experiments to gain an understanding of the potential mechanism(s) of this transformation. Firstly, we carried out the reaction under 'water-free' conditions.



Scheme 3.29: Diiodohydration reaction under water-free conditions

The reaction yields mostly the iodoenone **73a** as seen previously, but also present was a new product **77**, which was apparently being hydrolysed to this iodoenone **73a**. This product was assigned to be iodoacetamide **77** which was formed as a single geometrical isomer. The finding that the product was formed as a single geometrical isomer was completed in collaboration with Dr Abil Aliev, who conducted nuclear Overhauser effect spectroscopy (nOesy) experiments.

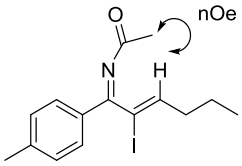
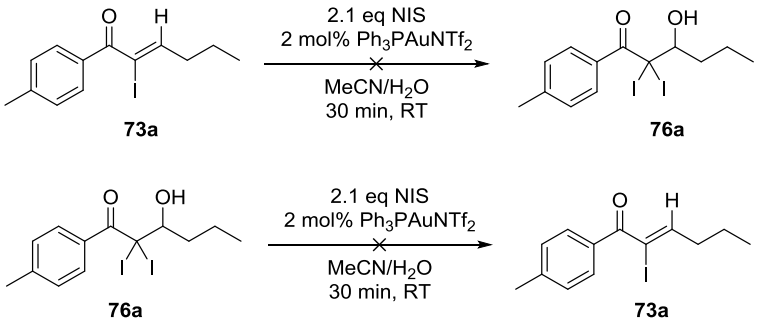


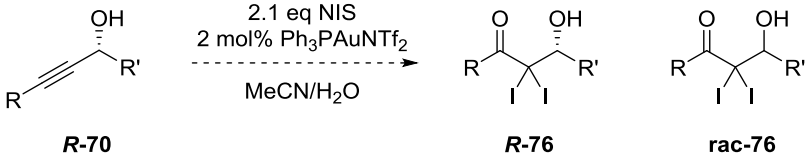
Figure 3.1: nOesy experiments confirming (*E*)-geometry of **77**

There is nOe between the acetamide methyl group and the enone CH. This result suggests that the acetonitrile solvent is incorporated into the molecule to form **77** which is then hydrolysed to give the iodoenone **73a**. We conducted experiments to determine whether the iodoenone **73a** is an intermediate towards diiodide formation or that the diiodide **76a** is an intermediate towards the iodoenone **73a** formation.



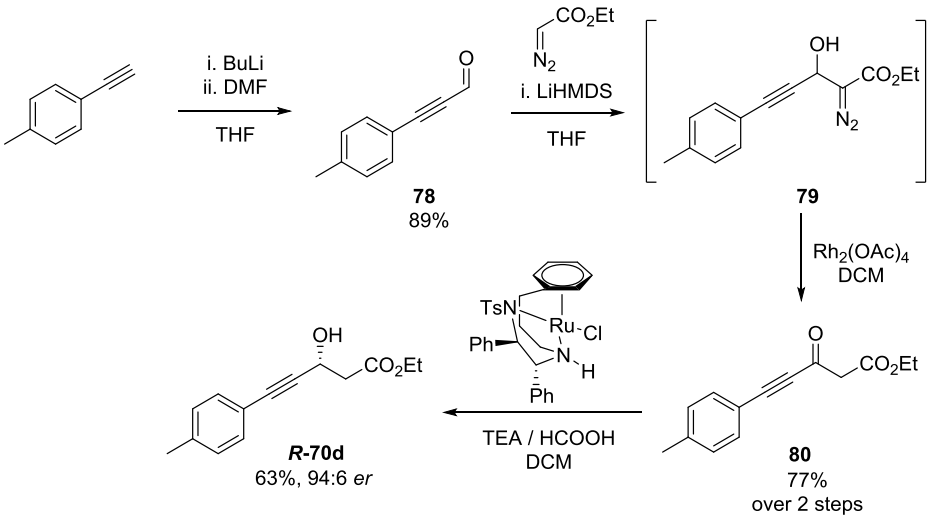
Scheme 3.30: Re-exposure to reaction conditions

These experiments suggest that the two products are produced by divergent mechanisms. Another method to discover whether the iodoenone is an intermediate for the diiodohydration is to synthesise an enantioenriched propargylic alcohol.



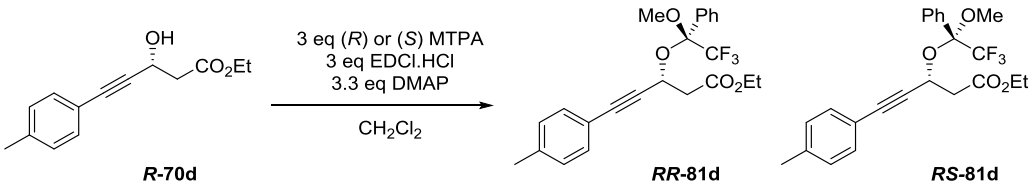
Scheme 3.31: Diiodohydration of enantioenriched propargylic alcohol

If there is no racemisation of the alcohol (***R*-76**) in the diiodohydration reaction, this would suggest that an intermediate iodoenone is unlikely. If the product is racemic (**rac-76**) this would suggest that there would be an achiral intermediate. The synthesis of enantioenriched propargylic alcohol ***R*-70d** is outlined in **Scheme 3.32**.



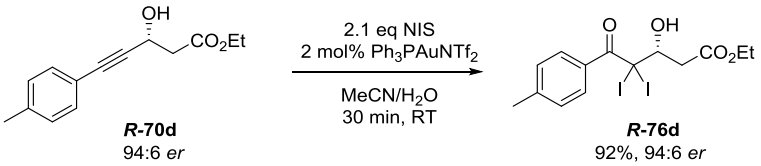
Scheme 3.32: Synthesis of an enantioenriched propargylic alcohol

The reaction of tolylacetylene with DMF led to the formation of propargylic aldehyde **78** in good yield. Ethyl diazoacetate was added to the aldehyde in a nucleophilic addition reaction to give the diazocompound **79**, which was treated with $Rh_2(OAc)_4$ for 1 h to give the ketone **80** in good yield over the 2 steps. The transfer hydrogenation of the ketone[77] **80** with (*R*,*R*)-Teth-TsDPEN-RuCl catalyst gave clean conversion to the enantioenriched propargylic alcohol ***R*-70d**. The enantiopurity was determined by Moshers esters analysis.



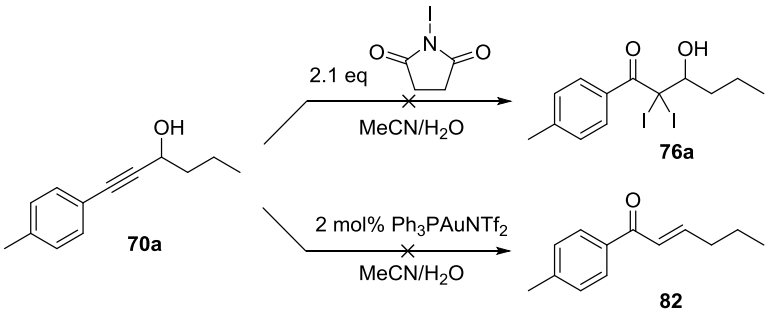
Scheme 3.33: Moshers Ester determination of enantiopurity

The NMR analysis of the crude reaction mixture gives a measure of enantiopurity of the alcohol from the diastereomers. This enantioenriched propargylic alcohol was then subjected to the diiodohydration conditions.



Scheme 3.34: Diiodohydration with an enantioenriched propargylic alcohol

No racemisation of the alcohol had occurred. This demonstrates that the mechanism of the reaction does not involve an achiral iodoenone intermediate. It is likely that the iodoenone and diiodoketoalcohol are being formed through a divergent mechanism. The omission of the Au-catalyst from the optimised reaction conditions led to no reaction being seen with SM remaining after a number of hours. With the omission of NIS, we could expect the Meyer-Schuster rearrangement products, however, we do not see any reaction after a number of hours.

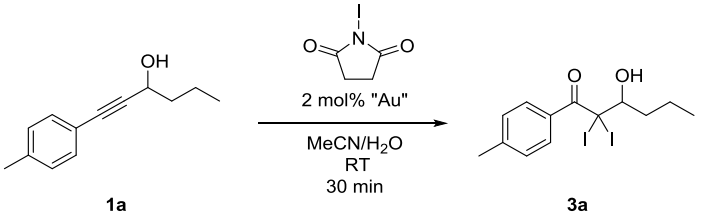


Scheme 3.35: Unsuccessful transformation of propargylic alcohols

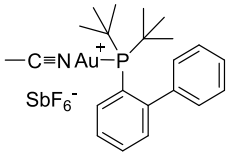
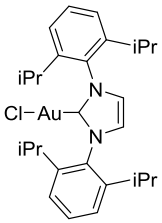
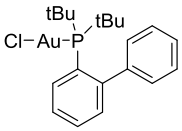
These results show us that without gold, there is no activation for any reaction to occur and that without NIS there is no electrophile to give the hydration. These results gives us a

valuable insight into the reaction mechanism, the reaction requires both gold catalyst and NIS. NIS is not only an iodine source but also a strong oxidant. It is possible that the Au^{I} catalyst is oxidised by the NIS to form Au^{III} as a reactive species which catalyses the hydration.[78–80] To test this hypothesis we conducted a catalyst screen NMR study (**Table 3.2**).

Table 3.2: Diiodohydration reaction with different gold catalysts



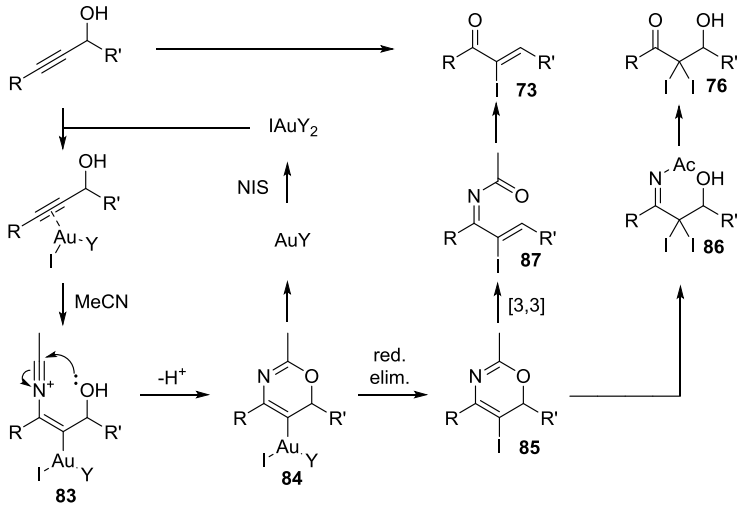
1a **3a**

Entry	Catalyst	Yield **3a**[a]
1		72%
2		86%
3	$Cl{-}Au{-}SMe_2$	86%
4		74%
5	$Cl{-}Au{-}PPh_3$	86%
6	$Tf_2N{-}Au{-}PPh_3$	99% (75%[b])
7	$AuCl_3$	60% (**76a**) 16% (**73a**)
8	$AuBr_3$	99%

[a]Yield calculated by crude NMR with trimethoxybenzene as an internal standard. [b]1 eq of 2,6-di-tert-butylpyridine was added; yield measured after 24 h.

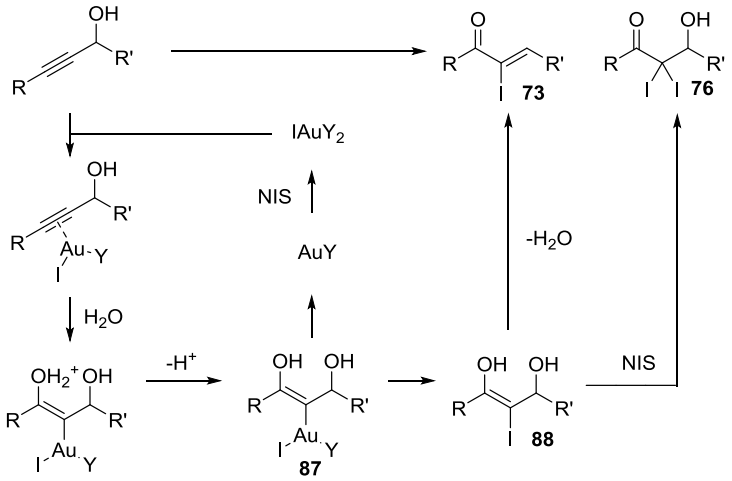
We found that a number of gold catalysts were competent for the conversion to the diiodoketoalcohol including both Au^{I} and Au^{III} catalysts. This included catalysts with

phosphine ligands (Entries 1 (Echavarren's catalyst), 4 - 6), *N*-heterocyclic carbene ligand (Entry 2), thiol ligand (Entry 3) and Au^{III} catalysts (Entries 7 an 8). It can be predicted that the ligand is not important because the majority of the catalysts give the desired product regardless of the counter ion or the ligand. A gold(I) – gold(III) catalytic cycle is possible where the gold is oxidised by NIS.[78–80] Another possibility is that gold catalyst could be acting as a Lewis acid, activating the NIS for the addition to the alkyne. With these observations, we have proposed a mechanism for this diiodohydration reaction. The reaction begins with the activation of the alkyne by $IAuY_2$ (where Y = NTf_2, I, PPh_3 or a mixture thereof) which induces nucleophilic attack by acetonitrile to give an intermediate **83**, which undergoes cyclisation to give oxazine **84**. Reductive elimination gives us iodo-oxazine **85** and Au^{I} which is oxidised by NIS to the active Au^{III} species and completes the catalytic cycle. With the addition of another equivalent of NIS, it iodinates the oxazine and H_2O opens the oxazine and gives us *N*-acylimine **86**. After hydrolysis, we can observe the diiodoketoalcohol **76**. From iodo-oxazine **85**, a [3,3]-sigmatropic rearrangement (potentially Au catalysed) gives the iodoacetamide **87**, which accounts for the product **77** as a single geometrical isomer. This iodoacetamide **87** intermediate is hydrolysed to give the iodoenone **73**, this product is only seen when no water is present in the reaction mixture.



Scheme 3.37: Plausible Au^{I} - Au^{III} mechanism with MeCN as solvent for diiodohydration

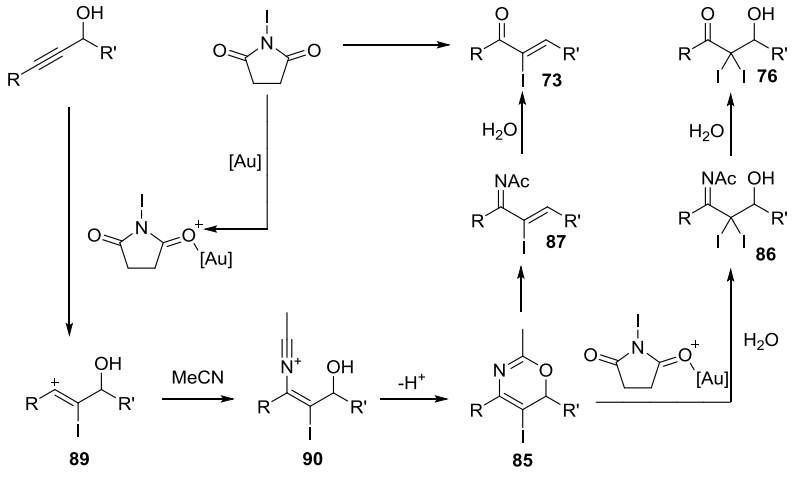
It is worth noting that MeCN is not required for diiodohydration reaction. Therefore this is not the only possible mechanism, it must be possible for H_2O to attack the activated alkyne directly, but this must be a less efficient process (giving lower yields for the reaction)



Scheme 3.38: Plausible Au^{I} – Au^{III} mechanism with a non-nitrile solvent for diiodohydration

The gold catalyst activates the alkyne as in the acetonitrile solvent, however, water must attack and form the vinyl-gold intermediate **87**. Reductive elimination of the Au-intermediate **87** gives the iodoenol **88**. Loss of water from **88** gives the iodoenone **73**. The iodoenol **88** can also react with another equivalent of NIS to give the diiodoketoalcohol **76**.

Another plausible mechanism involves the gold catalyst behaving as a Lewis acid (**Scheme 3.39**)



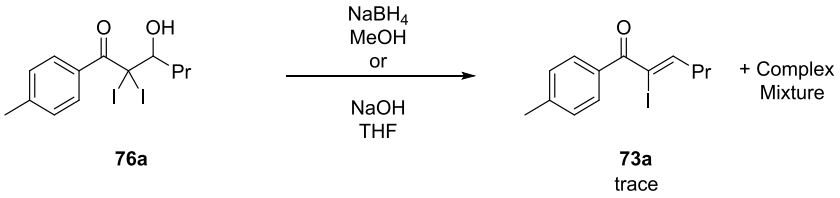
Scheme 3.39: Plausible Lewis acid mechanism with MeCN as solvent for diiodohydration

The gold is able to activate the NIS for nucleophilic attack from the alkyne, which forms a vinyl cation intermediate **89**. This intermediate can undergo nucleophilic attack from the MeCN followed by formation of an iodo-oxazine **85**. This intermediate **85** can perform the same pathways seen in the gold(I)-gold(III) mechanism to give the iodoenone and the

diiodoketoalcohol. We proceeded to explore what transformations were possible with these usual products containing a ketone, an alcohol and a diiodide.

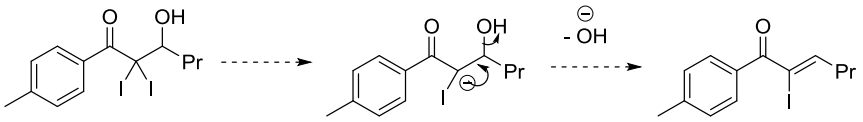
3.3.1 The reactions of the Diiodoketoalcohol Products

We explored the reactivity of these novel products by completing some test reactions. A sodium borohydride reduction of the ketone **76a** was attempted. The reaction gave a complex mixture of products including the iodoenone **73a**. There was a similar result upon the addition of base (NaOH) to give the iodoenone as the only identified product.



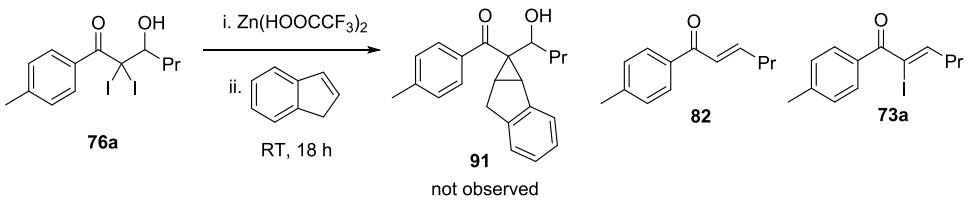
Scheme 3.40: Unsuccessful reactions of diiodohydration products

It is possible that reactions of these molecules with nucleophiles and bases are governed by the ability for the formation of a stabilised anion/enolate which can eliminate $^{-}$OH to give the enone (**Scheme 3.41**).



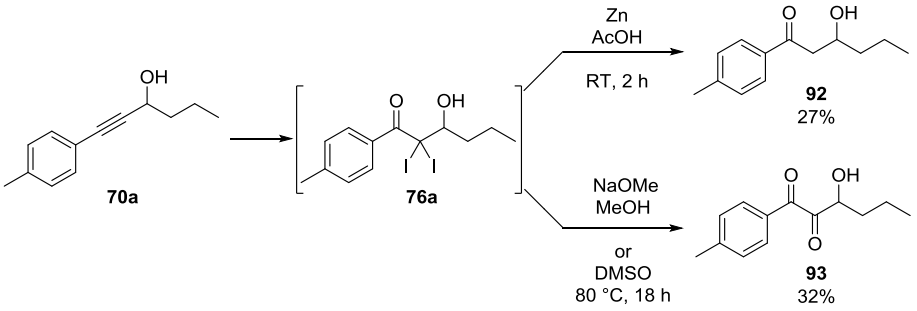
Scheme 3.41: Proposed mechanism of the iodoenone formation

In the literature, a common use of *gem*-diiodides in the form of diiodomethane is the Simmons-Smith reaction.[81,82] This reaction coverts the diiodide into an active organozinc carbenoid, which can react with an appropriate alkene to form a cyclopropane. We attempted to synthesise a cyclopropane using this methodology.



Scheme 3.42: Unsuccessful Simmons-Smith reaction

After 18 h, none of the starting material remained and after purification by chromatography it was unclear what the main product of the reaction was. One fraction was found to contain a mixture of the iodoenone **73a**, what appears to be enone **82** and another unidentified product. Success was achieved in terms of breaking C-I bonds, however there was no evidence of new C-C bond formation. This system is much more complex than diiodomethane (substrate used in most Simmons-Smith reactions) and may lead to breakdown of the carbenoid prior to any reaction with the alkene. Some successful experiments are shown below (**Scheme 3.43**) for the conversion of the diiodide to a β-hydroxyketone **92** and diketone **93**.

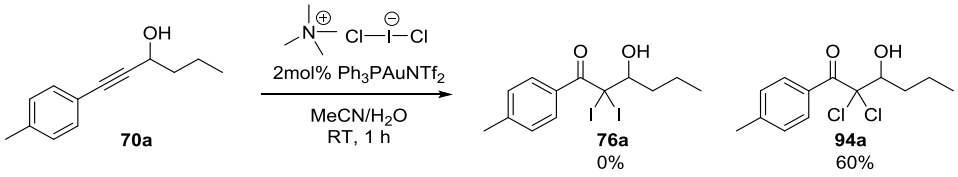


Scheme 3.43: Successful reactions of diiodoketoalcohol **76a**

The oxidation of the diiodide with sodium methoxide gave only poor conversions to the diketone **93**. An alternate method using DMSO at 80 °C also gave to diketone **93**, however the reaction could not be repeated and just gave degradation products. Although both of these transformations are not particularly high yielding, it was important to explore the potential reactions of these products.

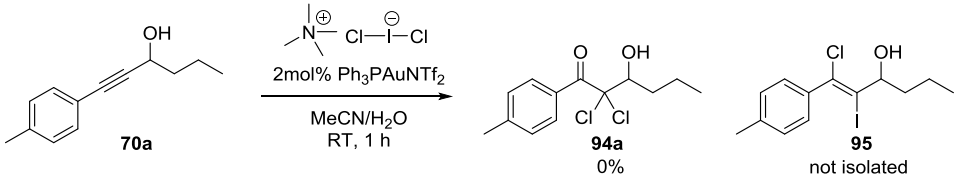
3.3.2 Alternative electrophilic iodine sources for diiodoketoalcohols

In the exploration of alternative electrophilic iodine sources that would allow diiodohydration of propargylic alcohols, we found TMADCI (tetramethylammonium dichloroiodide). This reagent dissociates into tetramethylammonium chloride and iodine monochloride. It was believed that this reagent would be a more stable, easy to handle form of iodine monochloride. The expectation was that this reagent in the diiodohydration reaction replacing NIS would give the diiodide **76a**. However, the diiodide **76a** was not detected and the major product was dichloroketoalcohol **94a**, isolated in good yield.



Scheme 3.44: Unsuccessful diiodoketoalcohol formation

We were excited to find that we could synthesise this product and we intended to determine the substrate scope to produce this interesting product. However, it was quickly discovered that the reaction was sometimes irreproducible or unreliable when repeated with a mixture of products produced, none of which was the dichloroketoalcohol **94a**. One product appeared to show signals consistent with chloroiodoalkene **95**.[83,84]



Scheme 3.45: Unsuccessful dichloroketoalcohol formation

This result led to a change in the focus of the research from diiodohydration towards dichlorohydration.

3.4 Synthesis of Dichloroketoalcohols

With the successful synthesis of a number of diiodohydration products from a number of substrates, a natural expansion of this work would be other dihalohydrations. These products would be of interest due to the synthesis of chlorolipid natural products isolated from Mediterranean mussels *Mytilus galloprovincialis*, such as mytilipin B.[85]

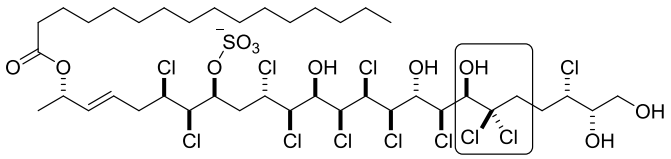
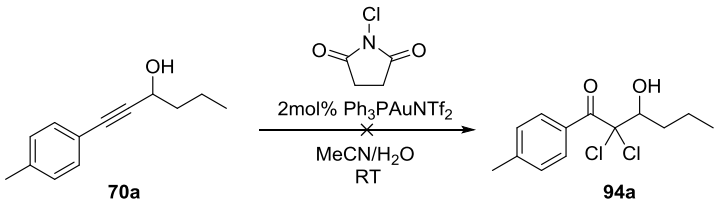


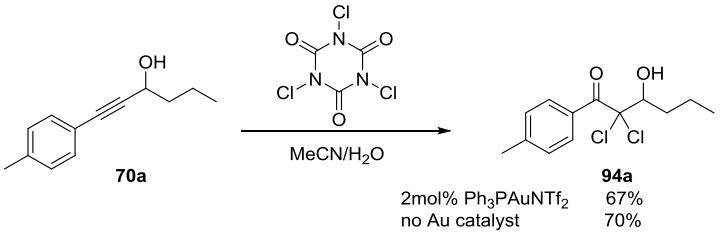
Fig 3.2: Sulfochlorolipid natural product

We took the opportunity to explore whether we could synthesise α,α-dichloro-β-hydroxyketones using the same method as the diiodohydration. This was due to the interest in the geminal dichlorides in natural products and the dichlorohydration reactions in the literature. To this end, we examined a number of electrophilic Cl^+ sources in order to synthesise novel dichloroketoalcohols. We used **70a** as our substrate and initially *N*-chlorosuccinimide (NCS) as electrophilic chlorine source.



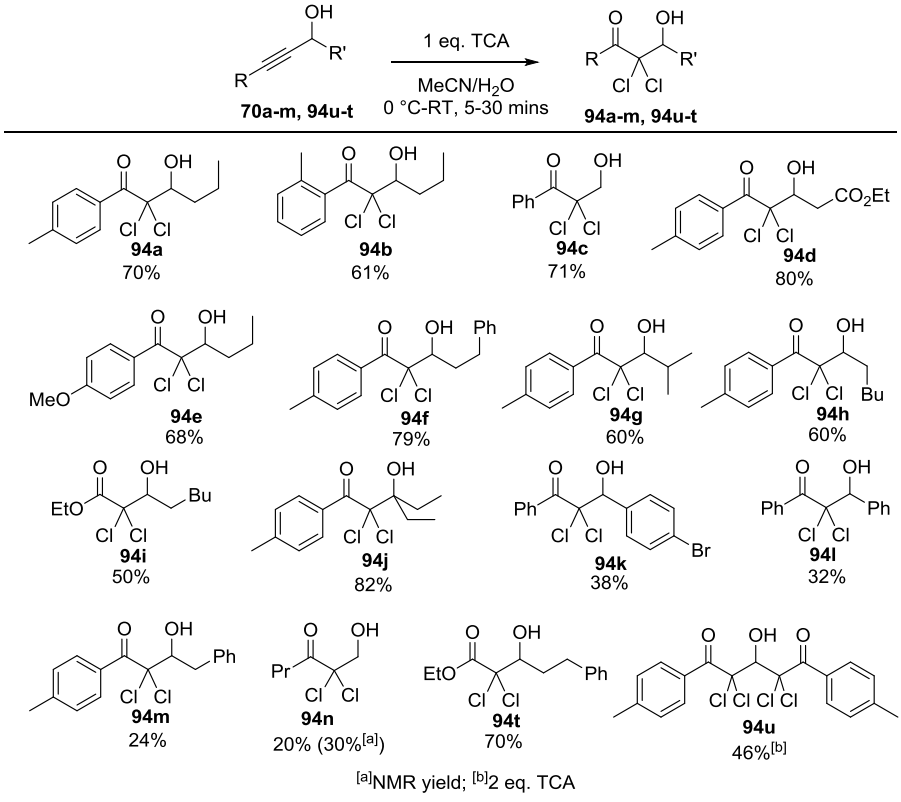
Scheme 3.46: Unsuccessful dichloroketoalcohol formation

Unfortunately, there was no reaction with NCS after long reaction times, this may be attributed to the relatively weak oxidising power compared to NIS. We then examined an alternative chlorinating agent, trichloroisocyanuric acid (TCA) under the gold-catalysed dihalohydration conditions.



Scheme 3.47: Successful dichloroketoalcohol formation

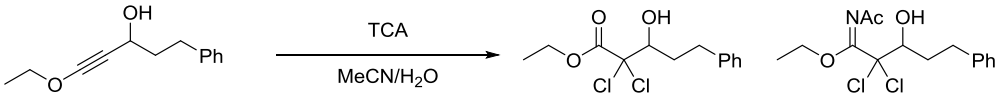
The reaction with TCA and propargylic alcohol was surprisingly fast (<5 min) and very clean by TLC to give the desired dichlorohydration product **94a**. The reaction mixture gets very warm from this quick exothermic reaction, therefore we decided to cool the reaction mixture before the addition of TCA to reduce the formation of by-products. The rate of reaction was so quick that we questioned whether gold was actually catalysing the reaction. We repeated the reaction without the Au-catalyst and found similar yield and reaction time was achieved. This indicates that the gold catalyst is not required and thus this reaction must have a different mechanism to the diiodohydration previously seen. Pleasingly, the reaction was higher yielding and more reproducible than the TMADCI protocol. We then explored the scope of this TCA induced dichlorohydration reaction.



Scheme 3.48: Successful dichloroketoalcohol formation reactions

Pleasingly, a variety of dichloroketoalcohols (**94a–h**, **4j**, **94n**, and **94u**) and dichloroesters (**94i** and **94t**) could be produced from the corresponding propargylic alcohols in good to excellent yields. The reaction was applicable for primary (**94c** and **94n**), secondary (**94a–b**, **94d–i**, **94k–m** and **94t**) and tertiary alcohols (**94j**) (not suitable for diiodohydration) in generally good yield. The synthesis of dichloroketoalcohols **94k–m** is generally poor, but these substrates do not give the respective diiodohydration products at all. Low molecular weight alcohol (**94n**) could be synthesised but isolated in poor yield. The symmetric dialkynol **70u** was an acceptable substrate for the synthesis of a tetrachlorodiketoalcohol **94u**.

In this dichlorohydration reaction the propargylic alcohols give the dichloroketoalcohol as the only isolable product. However, in the reaction with the alkynylether **70t** we observed two distinct products forming: the major dihalohydration product **94t** and a minor product **96**.



70t **94t** 70% **96** 27%

Scheme 3.49: Successful dichloroketoalcohol formation

The minor product is *N*-acyl imidate ester **96**, which gives a combined isolated yield of 97%. The imidate ester **96** is formed as a single (*E*) geometrical isomer and hydrolyses slowly to the ester **94t**. The finding that the product was formed as a single geometrical isomer was completed in collaboration with Dr Abil Aliev, who conducted nuclear Overhauser effect spectroscopy (nOesy) experiments.

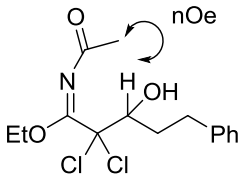
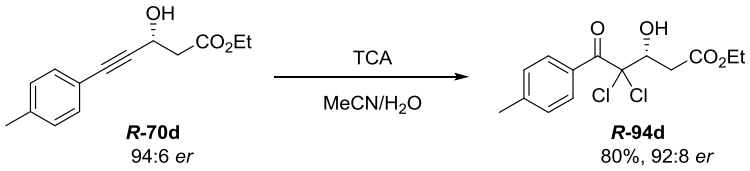


Figure 3.3: nOesy experiments confirming (*E*)-geometry

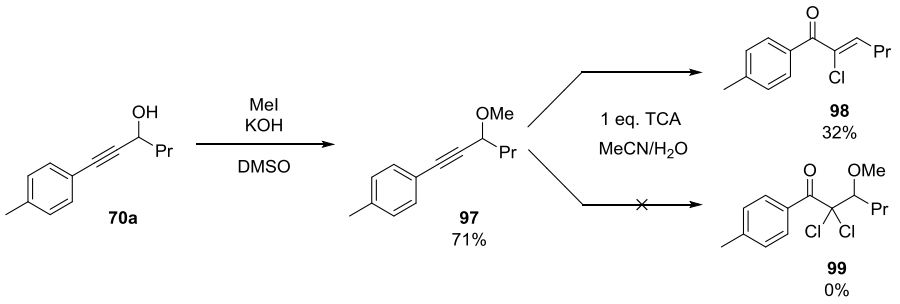
We found a weak nOe between the methyl group of the acetamide and the proton next to the dichloride. In order to ascertain whether this dichlorohydration reaction follows a similar mechanism to the diiodohydration reaction we conducted further experiments. We

used our dichlorohydration conditions with our enantioenriched propargylic alcohol ***R*-70d** as a substrate.



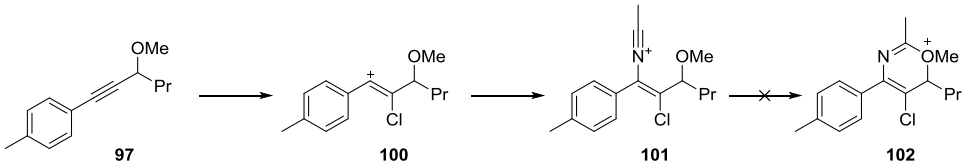
Scheme 3.50: Dichlorohydration with an enantioenriched propargylic alcohol

This reaction produced the desired product in the same yield as the racemic variant. There was a small reduction in the enantiopurity of the product but this could be possibly attributed to inaccuracies in the measurement of the enantiopurity. This result suggests that the reaction mechanism does not go through an enone intermediate. We then decided to investigate whether the alcohol was required for the reaction to occur. We synthesised propargylic ether **97** and subjected it to our dichlorohydration procedure (**Scheme 3.51**).



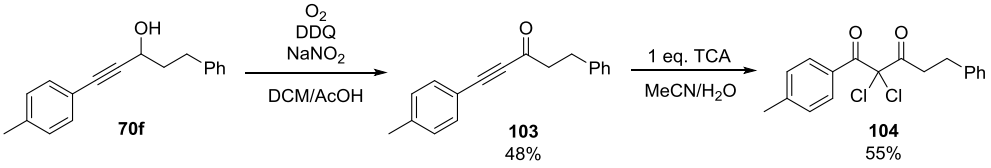
Scheme 3.51: Propargylic ether formation

The methylation of the alcohol worked well giving good yield of ether **97**. The dichlorohydration procedure led not to our desired product, but chloroenone **98** in poor yield. This reaction gives further evidence that the free alcohol is involved in the mechanism of this reaction. With this substrate the chloro-oxazine **102** intermediate is not able to be formed.



Scheme 3.52: Possible mechanism for dichlorohydration of ether **97**

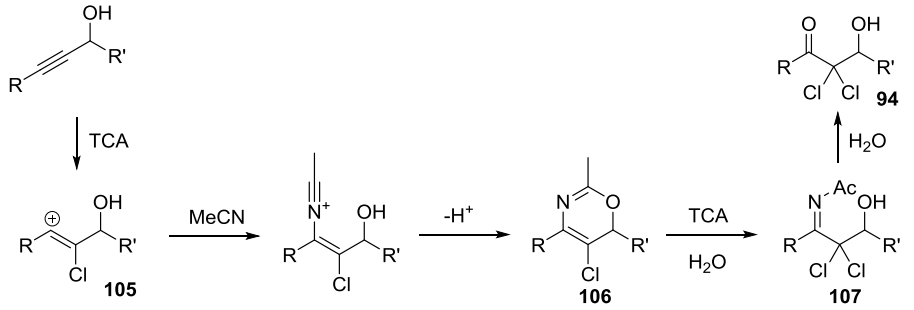
Synthesis of propargyl ketone **103** was completed by oxidation of the respective alcohol **70f**. We then exposed this ketone **103** to our dichlorohydration conditions, the reaction was slow (2 h) but successful to the dichlorodiketone **104** in good yield.



Scheme 3.53: Propargylic alcohol oxidation

This reaction shows that the alcohol does not need to be present for the dichlorohydration reaction to occur and ketone **103** can still participate to form the dichlorodiketone **104**. This product is novel and further work could be done to explore the scope and limitations of this reaction.

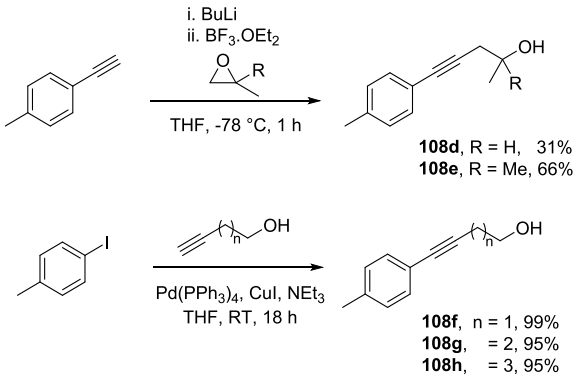
We propose a mechanism for the dichlorohydration reaction in **Scheme 3.54**. Nucleophilic attack of the alkyne to TCA gives the vinyl cation **105**. Nucleophilic attack of the nitrogen atom of MeCN to the cation **105** and cyclisation gives the chloro-oxazine **106**. The chloro-oxazine can be chlorinated again and water added to open the oxazine into the imine **107**, which is hydrolysed to the product **94**.



Scheme 3.54: Proposed mechanism for the dichlorohydration of propargylic alcohols

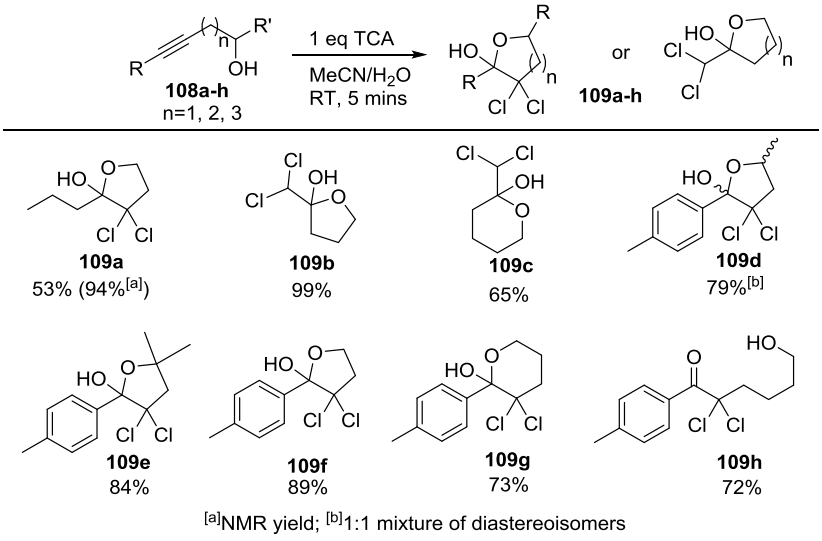
3.4.1 Dichlorohydration of Alkynols

Encouraged by the simplicity and utility of this protocol with the wider range of substrates we decided to investigate whether alkynols could be acceptable substrates for the dichlorohydration reaction. Some homopropargylic alcohols and alkynols are commercially available (**108a-c**), however some require synthesis (**108d-h**).



Scheme 3.55: Homopropargylic alcohol and alkynol formation

Homopropargylic alcohols **108d-e** were synthesised by a ring opening of an epoxide. Alkynols **108f-h** were synthesised by a Sonogashira coupling of the commercially available alkynols and tolyliodide to give the products in excellent yields. These homopropargylic alcohols and alkynols were suitable substrates for the dichlorohydration procedure.

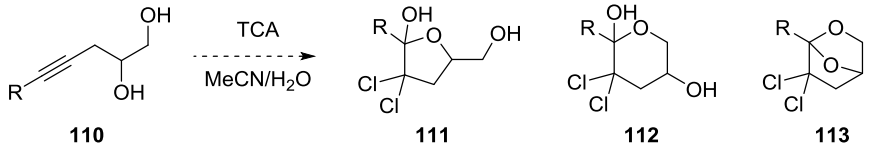


Scheme 3.56: Dichlorohydration of alkynols

We were delighted to find that a number of dichlorolactols were produced in generally good to excellent yields. We can produce both five-membered (**109a**–**b**, **109d**–**f**) and six-

membered (**109c** and **109g**) lactols via both *endo* (**109a**, **109d–g**) and *exo* (**109b–c**) cyclisation reactions. The 5-membered ring formation is generally more efficient than the 6-membered ring formation. Looking at the dichlorohydration mechanism, the most stabilised vinyl carbocation is formed making the product regioselectively. With alkynol **109h** as the substrate there is no cyclisation to the seven-membered ring, but this example shows that a free OH is tolerated in the reaction.

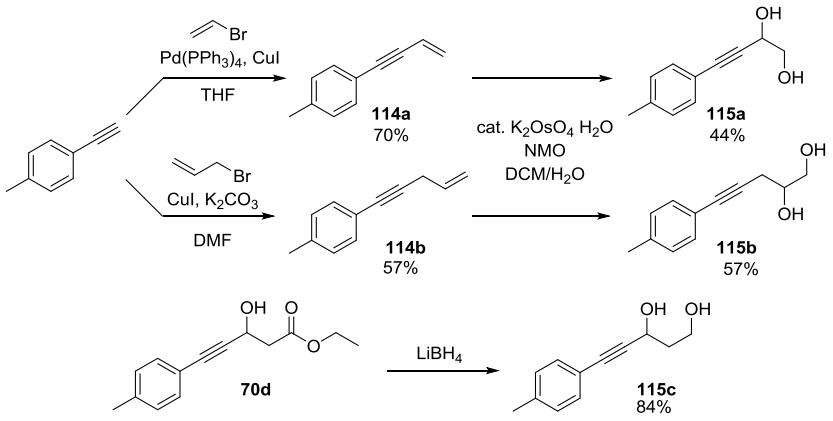
We wanted to assess the effect of having more than one free alcohol to determine whether the 5-membered ring was faster forming or more stable than the 6-membered ring.



110 **111** **112** **113**

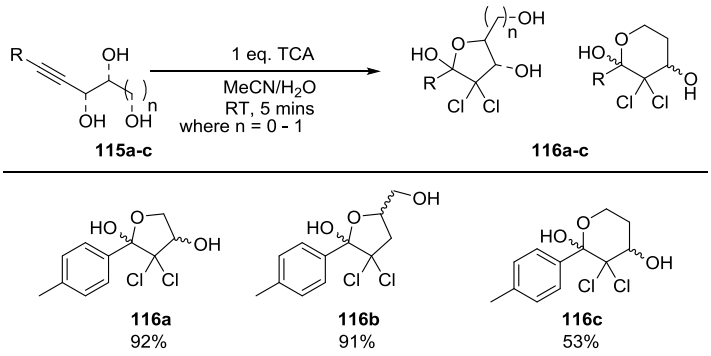
Scheme 3.57: Potential synthesis of dichlorobicycle **113**

To test whether the formation of these cyclic-complexes were possible we needed to synthesise some alkynyldiols **115a-c**. The eneyne **114a** was produced from the Sonogashira coupling of tolylacetylene with vinyl bromide in good yield. The same reaction was attempted with allyl bromide to give the enyne **114b**, however no reaction occurred, therefore we used a procedure using a Cu^{I} source in an aprotic polar solvent (DMF) to give the enyne in moderate yield. The alkenes **114a**-**b** were dihydroxylated with K_2OsO_4 to give the diols **115a**-**b** in adequate yields.



Scheme 3.58: Synthesis of alkynyldiols

The alkynediol **115c** was produced from the reduction of **70d** in excellent yield. We subjected these alkyndiols to our dichlorohydration conditions.



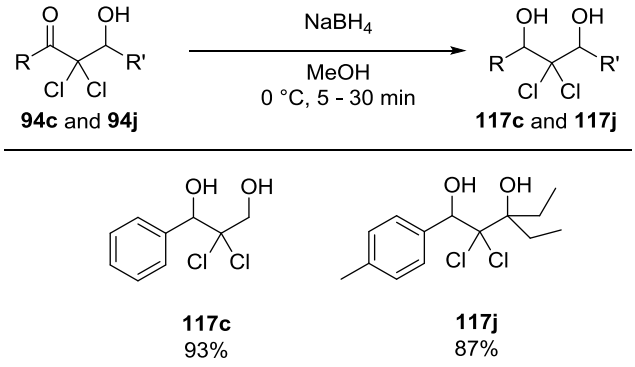
Scheme 3.59: Dichlorohydration of alkynyldiols

We were happy to synthesise these complex lactols in moderate to excellent yields albeit as mixtures of the diastereoisomers.

We then turned our attention to the possible reactions of the dichlorinated products (**94** and **109**) as they appear more stable than the corresponding diiodohydration products.

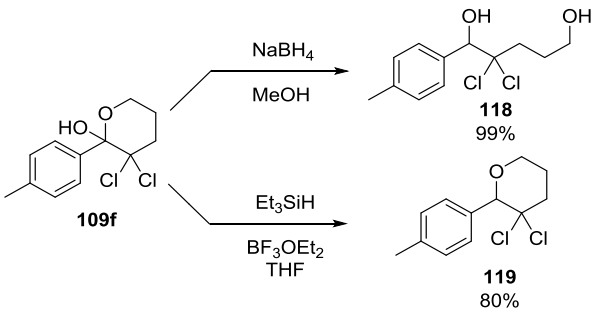
3.4.2 Reactions of the Dichlorohydration Products

The dichlorohydration products appear more stable than the related diiodohydration products and it was hoped that we could manipulate/derivatise them in a useful way.



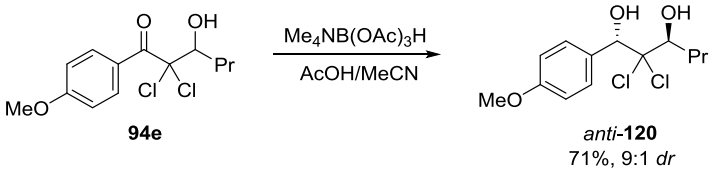
Scheme 3.60: Reduction of some of the dichlorohydration products

Happily, we were able to isolate the diols **117c** and **117j** from these reductions in excellent yields. The dichlorolactol **109f** could also be reduced with $NaBH_4$ to the linear diol **118** in excellent yield and with triethylsilane (Et_3SiH) and $BF_3.OEt_2$ we can isolate the dichlorotetrahydropyran **119** in very good yield.



Scheme 3.61: Reduction of dichlorohydration product **109f**

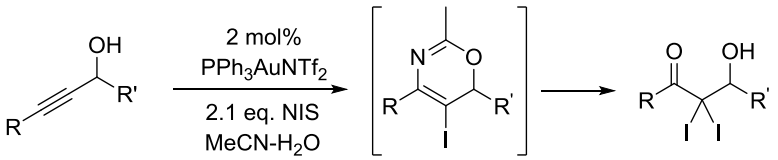
In addition, a diastereoselective reduction of alcohol **94e** with tetramethylammonium triacetoxyborohydride gives diol *anti*-**120**.



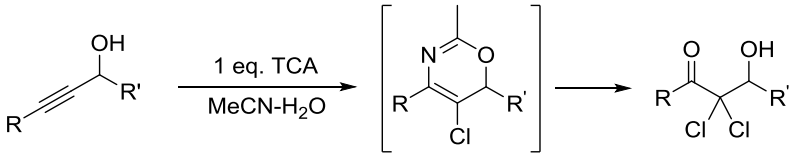
Scheme 3.62: Diasteroselective reduction of dichloride **94e**

3.5 Conclusion

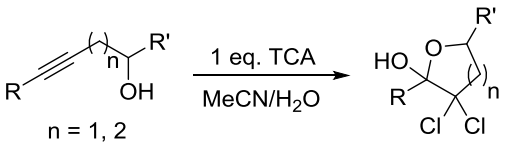
We have developed an unprecedented, mild, gold-catalysed reaction for the diiodohydration of propargylic alcohols to α,α-diiodo-β-hydroxyketones. This reaction gives good to excellent yields on a range of substrates and we have found that enantioenriched alcohols retain their enantiopurity. We have proposed plausible mechanisms based on the observations seen and intermediates that we have identified and believe the solvent is involved in the mechanism via formation of a halo-oxazine intermediate.



We have also developed a non-catalysed dichlorohydration reaction of propargylic alcohols to α,α-dichloro-β-hydroxyketones. This reaction occurs without the use of a gold catalyst and this is because a more electrophilic halogen source was employed.



This reaction has a wider substrate scope than the diiodohydration reaction and includes homoproparglyic alcohols and other alkynols for the synthesis of 5 and 6-membered ring dichlorolactols.

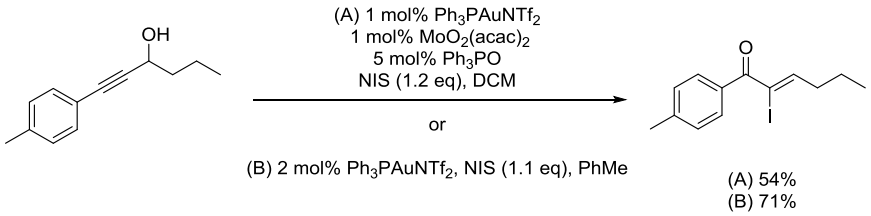


We believe that these reactions are of interest to the scientific community due to wide substrate scope, facile reaction conditions, and relatively cheap readily available or easy synthesised starting materials. The products could be building blocks for pharmaceuticals and agrochemicals.

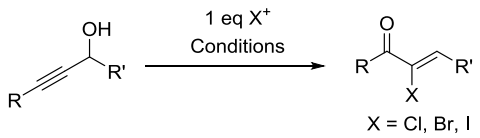
3.6 Future Work

Haloenone formation

The synthesis of haloenones from propargylic alcohols has been explored in the literature, however the use of this protocol only gave adequate yields in our hands (54%). With modified Meyer-Schuster conditions with no optimisation we were able to achieve a good yield of 71%.



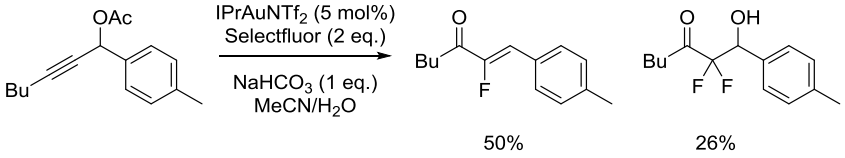
We believe that the Mo-catalyst and Ph_3PO are not required for the synthesis of iodoenones and it would be interesting to investigate further and optimise the conditions to produce other α-haloenones. These products could be useful for Pd cross coupling reactions.



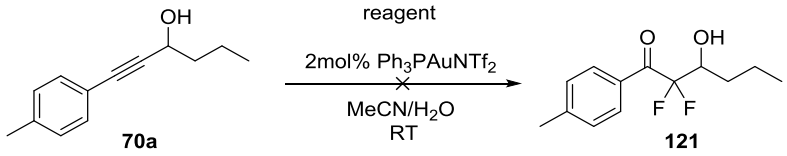
Difluorohydration

After the exploration of the diiodohydrations and dichlorohydrations a natural progression was to examine difluorohydrations and dibromohydrations.

A mild Au-catalysed method to induce a difluorohydration of a propargylic alcohol would be of particular importance to the scientific community. This is because late-stage fluorination in pharmaceuticals can confer some stability to metabolism and give tunable interaction kinetics with proteins. There is one example from the literature with a propargylic acetate as the starting material and an IPr ligand (N-heterocyclic carbene) on the Au catalyst with excess Selectfluor.[86]



This reaction would be particularly useful in our manipulation of propargylic alcohols. The literature reaction conditions were mimicked with the difference being the starting material propargylic alcohol **70a** was used and the omission of $NaHCO_3$. Unfortunately, no reaction was seen under these conditions. Test reactions showed that using the electrophilic halogen source Selectfluor or many other F^+ sources in place of NIS in our diiodohydration conditions does not lead to the formation of the desired difluorohydration product.

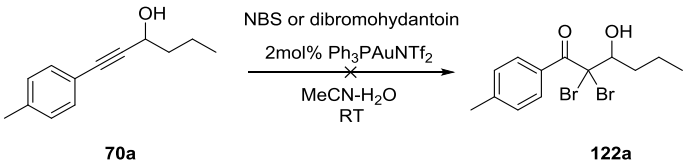


Entry	Reagent (2.1 eq)	Result after 24 h
1	Selectfluor	No reaction
2	$(PhSO_2)NF$	No reaction
3	XeF_2	No reaction
4	*N*-Fluoropyridinium triflate	No reaction
5	*N*-Fluoro-2,4,6-trimethylpyridinium triflate	No reaction

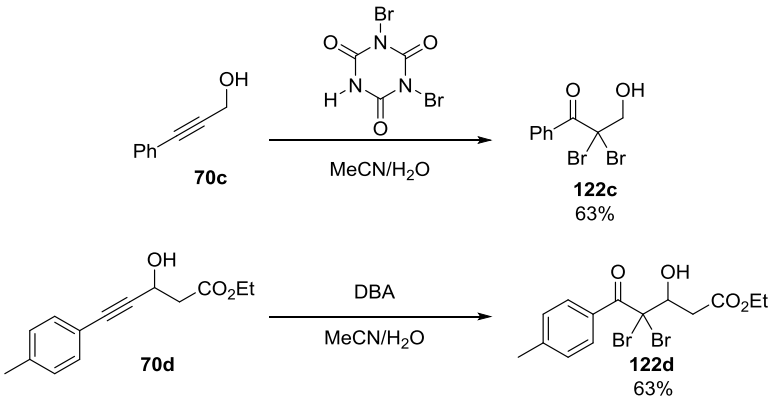
In these reactions, no products were seen with just the SM remaining. The reaction is potentially possible, however it may require more forcing conditions and optimisation.

Dibromohydration

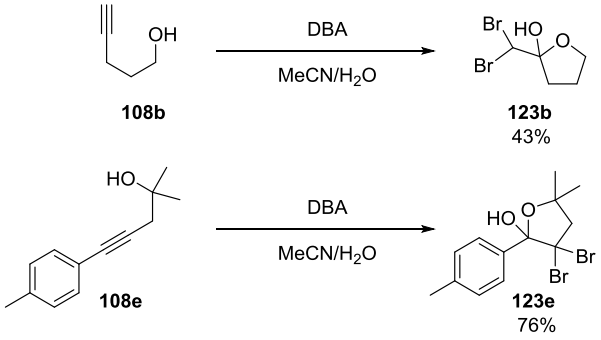
For a procedure for dibromohydration we began with NBS as an electrophilic bromine source in the place of NIS in our gold catalysed diiodohydration procedure. We found that we saw no reaction under these conditions (as with NCS).



Using a more potent electrophilic bromine source allows the dibromohydration reaction to occur. We found that dibromoisocyanuric acid (DBA) is commercially available and explored whether this reagent could induce reaction.



Early results suggest that this protocol can be used for the dibromohydration of propargylic alcohols to form α,α-dibromo-β-hydroxyketones. Further results show that alkynols can be used to form dibromolactols.



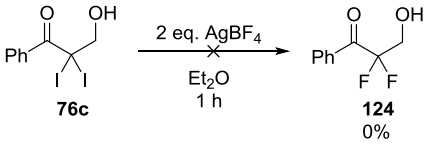
These products give similar NMR spectra to the -chloro and -iodo analogues but the yield for these transformations is lower than the other analogues. These reduced yields may be

due to reduced reactivity of the halogen source or due to the steric requirements for the installation of a *gem*-dibromide. Further work on the mechanism and limitations of this reaction would be useful.

Diiodides into difluorides

We are still interested in the potential reactions of these unusual α,α-diiodo-β-hydroxyketones. With our lack of success in the difluorohydration products, it may be possible to convert the diiodides to difluorides using $AgBF_4$. Simple diiodides have been coverted into difluorides reported by Mitchell and co-workers in 1987.[87]

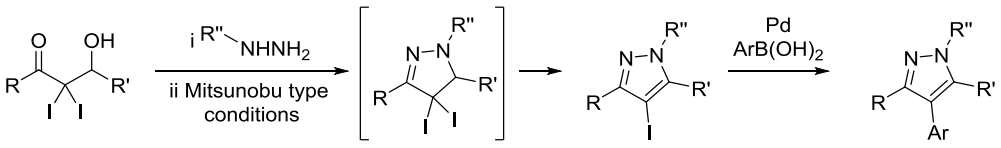
We used these conditions on our diiodide **76c** to ascertain whether this more complex substrate could be converted into the difluoride **123**. This reaction was unsuccessful.



There was an immediate colour change upon the addition of the $AgBF_4$ to the solution containing the diiodide from brown to yellow and a yellow precipitate was formed (indicating AgI formation). Although the crude reaction mixture did not contain the starting material after 1 h, there were no identifiable products seen.

Iodopyrazoles

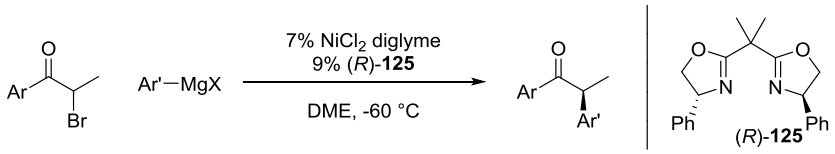
In previous work, we wanted to achieve the synthesis of pyrazoles from propargylic alcohols. It could be possible to synthesise iodopyrazoles and these could be interesting products in their own right.



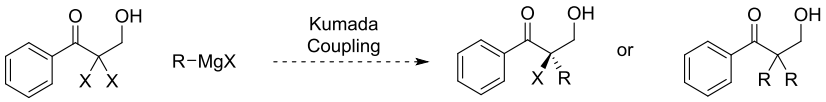
The iodopyrazoles could be used in Pd cross-coupling for the synthesis of tetra-substituted pyrazoles.

Use of dihaloketoalcohols in C-C bond formations

Forming new C-C bonds is an increasingly important challenge in modern synthetic organic chemistry. Fu has reported Kumada-type coupling of a Grignard reagent and a α-bromoketone in the presence of a transition metal catalyst.[88,89] The particular utility of this process is that the addition of a ligand can covert a racemic bromide to create a new C-C bond regioselectively.

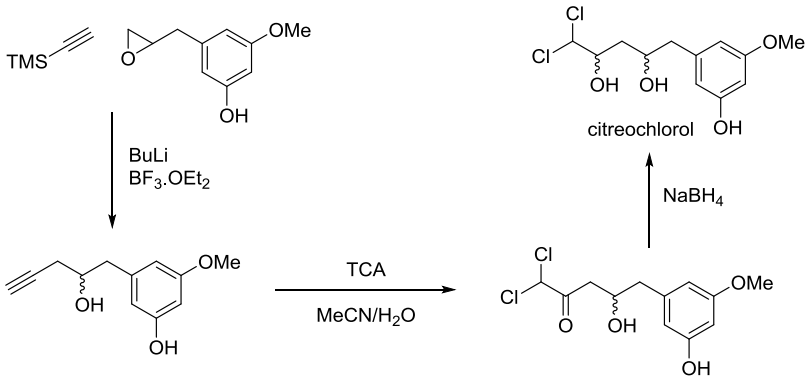


It could be envisaged that the dihalohydration products can be used for the synthesis of new products.



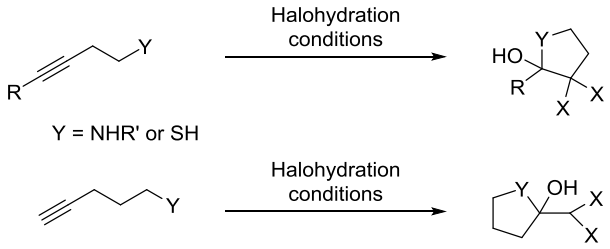
Synthesis of geminal dihalide natural products

A potential use of dihalohydrations is to synthesise natural products: Citreochlorol is a metabolite isolated from the mycelia of the *Penicillium* species.[90]



Synthesis of aminals and thiolactols

In this project we have found that alkynols can be used to form dichlorolactols. A natural progression would be to examine whether alkynthiols or alkynamines could form dichlorinated thiolactols and aminals respectively.

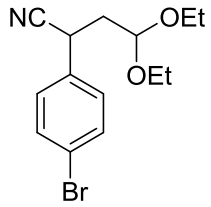


The synthesis of substituted pyrrolidines and tetrahydrothiophenes from linear, easily synthesised starting materials would be a new route to these structures.[91] The benefit of this chemistry is the tetrafunctionalisation of an alkyne in one step to give synthetically useful products and building blocks.

Chapter 4: Experimental

All reactions were carried out in oven-dried glassware under a nitrogen atmosphere unless otherwise indicated. Diethyl ether (Et_2O), tetrahydrofuran (THF), toluene (PhMe) and dichloromethane (DCM) were used following purification from an anhydrous engineering zeolite drying apparatus. All other chemicals were used as supplied unless otherwise indicated. Column chromatography was carried out using BDH (40-60 μm) silica gel and analytical thin layer chromatography was carried out using Merck Kieselgel aluminium-backed plates coated with silica gel. Components were visualised using combinations of ultra-violet lights and potassium permanganate. Melting points were determined using a Reichert hot-stage apparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer 241 or Perkin-Elmer 343 polarimeter (sodium D-line, 529 nm) and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}, concentration (*c*) in g per 100 mL. Infrared (IR) spectra were recorded on a Perkin-Elmer 1605 Fourier transform spectrometer or a Perkin-Elmer spectrum 100 FT-IR spectrometer as thin films. ^1H NMR spectra were recorded at 500 MHz on a Bruker Avance 500 spectrometer or at 600 MHz on a Bruker Avance 600 spectrometer in the stated solvent using residual protic solvent $CHCl_3$ (δ = 7.26 ppm, s), as the internal standard. Chemical shifts are quoted in ppm using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; sx, sextet; m, multiplet; br, broad or a combination of these. The coupling constants (*J*) are measured in Hertz. ^{13}C NMR spectra were recorded at 125 MHz on a Bruker Avance 500 spectrometer or at 150 MHz on a Bruker Avance 600 spectrometer in the stated solvent using the central reference of $CHCl_3$ (δ = 77.0 ppm, t) as the internal standard. Chemical shifts are reported to the nearest 0.1 ppm and 0.01 ppm for ^{13}C and ^1H respectively. Mass spectra were obtained using either a VG70-SE or MAT 900XP spectrometer at the Department of Chemistry, University College London.

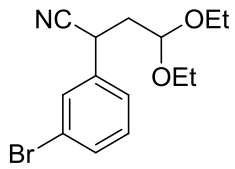
2-(4-Bromophenyl)-4,4-diethoxybutanenitrile (13a)



Potassium *t*-butoxide (0.63 g, 5.11 mmol) was added to a stirring solution of 4-bromophenylacetonitrile (1.00 g, 5.10 mmol) and bromoacetaldehyde diethyl acetal (0.77 mL, 5.10 mmol) in THF (20 mL) at RT. After 48 h, the solution was cooled to 0 °C and ice-water (15 mL) added. The product was extracted with ether (2 x 15 mL), the solution was dried ($MgSO_4$) and filtered before the solution was concentrated under reduced pressure. The crude product was purified by flash chromatography (7% EtOAc/petrol) to give the acetal **13a**.

Yellow oil, 754 mg, 2.42 mmol, 47%; ν_{max} (film/cm^{-1}) 3058 (C-H), 2880 (C-H), 2220 (C≡N), 1683 (C=C), 1583 (C=C), 1488 (C=C), 1394 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (2H, d, *J* = 8.4, 2 × ArH), 7.19 (2H, d, *J* = 8.4, 2 × ArH), 4.54 (1H, dd, *J* = 6.7, 4.9, OCHO), 3.90 (1H, dd, *J* = 9.3, 6.6, CHCN), 3.58 – 3.71 (2H, m, OCH_2), 3.41 – 3.58 (2H, m, OCH_2), 2.18 (1H, ddd, *J* = 13.8, 9.3, 4.9, CH*H*CHO_2), 2.04 (1H, dt, *J* = 13.8, 6.6, C*H*$HCHO_2$), 1.20 (3H, dt, *J* = 6.9, CH_3), 1.17 (3H, t, *J* = 7.1, CH_3); ^{13}C NMR (125MHz, $CDCl_3$) δ 134.6, 132.4, 129.1, 122.3, 120.1, 100.0, 62.7, 62.0, 39.5, 32.8, 15.33, 15.28; LRMS: (CI): 312 ($[M+H]^+$, 10), 267 (90), 238 (50), 196 (55), 103 (100); HRMS: Found (CI): $[M+H]^+$ 312.06045, $C_{14}H_{19}O_2NBr$ requires 312.05991

2-(3-Bromophenyl)-4,4-diethoxybutanenitrile (13b)

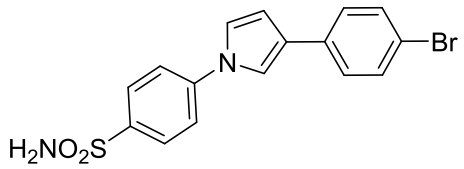


Potassium *t*-butoxide (0.63 g, 5.11 mmol) was added to a stirring solution of 3-bromophenylacetonitrile (1.00 g, 5.10 mmol) and bromoacetaldehyde diethyl acetal (0.77 mL, 5.10 mmol) in THF (20 mL) at RT. After 48 h, the solution was cooled to 0 °C and ice-water (15 mL) added. The product was extracted with ether (2 x 15 mL), the solution was dried ($MgSO_4$) and filtered before the solution was concentrated under reduced pressure.

The crude product was purified by flash chromatography (7% EtOAc/petrol) to give acetal **13b**.

Yellow oil, 639 mg, 2.05 mmol, 40%; ν_{max} (film/cm^{-1}) 2976 (C-H), 2881 (C-H), 2244 (C≡N), 1596 (C=C), 1571 (C=C), 1475 (C=C), 1429 (C=C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (1H, t, *J* = 1.7, ArH), 7.46 (1H, br. d, *J* = 7.9, ArH), 7.29 (1H, br. d, *J* = 7.9, ArH) 7.25 (1H, m, ArH), 4.58 (1H, dd, *J* = 6.9, 4.7, OCHO), 3.93 (1H, dd, *J* = 9.4, 6.4, CHCN), 3.63 – 3.74 (2H, m, OCH_2), 3.47 – 3.63 (2H, m, OCH_2), 2.22 (1H, ddd, *J* = 13.8, 9.4, 4.7, $CH\mathit{H}_2CHO_2$), 2.09 (1H, dt, *J* = 13.8, 6.8, $C\mathit{H}H_2CHO_2$), 1.24 (3H, dt, *J* = 7.2, CH_3), 1.20 (3H, t, *J* = 7.2, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.7, 131.5, 130.8, 130.6, 126.2, 123.2, 120.1, 100.1, 62.8, 62.2, 39.6, 33.0, 15.39, 15.33; LRMS: (CI): 312 ([M+H]$^+$, 20), 268 (65), 103 (100); HRMS: Found (CI): [M+H]$^+$ 312.06045, $C_{14}H_{19}O_2NBr$ requires 312.06018

4-(3-(4-Bromophenyl)-1*H*-pyrrol-1-yl)benzenesulfonamide (15a)

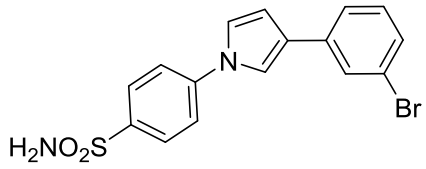


A solution of 1M diisobutylaluminium hydride in THF (0.86 mL, 0.86 mmol) was added dropwise to a solution of **13a** (180 mg, 0.57 mmol) in toluene (10 mL) at -78 °C. The solution was then allowed to stir for 2 h. MeOH (1 mL) was added and the solution was allowed to warm to RT and 2M HCl (10 mL) was added and the solution was stirred for 1 h. The product was extracted with ether (3 x 25 mL), organic layers combined and washed with brine before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was dissolved in EtOH (5 mL) and TsOH (11 mg, 0.06 mmol) and sulfanilamide (98 mg, 0.57 mmol) were added and reacted in the mW at 100 °C for 15 min. The residue was purified by flash chromatography (40% EtOAc/petrol) to give pyrrole **15a**.

Pale yellow solid, 65 mg, 0.24 mmol, 30%; Mp 245 – 247 °C; ν_{max} (film/cm^{-1}) 3378 (N-H), 3362 (N-H), 2922 (C-H), 1599 (C=C), 1320 (S=O), 1153 (S=O); ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.11 (1H, t, *J* = 1.9, NCHC), 7.91 (2H, d, *J* = 9.0, 2 × ArH), 7.88 (2H, d, *J* = 9.0, 2 × ArH), 7.64 (2H, d, *J* = 8.8, 2 × ArH), 7.59 (1H, d, *J* = 2.7, NC*H*CH), 7.54 (2H, d, *J* = 8.8, 2 × ArH), 7.42 (2H, s, NH_2), 6.80 (1H, dd, *J* = 2.7, 1.9, NCHC*H*); ^{13}C NMR (150 MHz, DMSO-d_6) δ 141.8, 140.6,

134.0, 131.6, 127.4, 126.8, 125.5, 120.6, 118.8, 118.6, 116.4, 109.5; LRMS: (ES): 375 ([M-H]$^+$, 100); HRMS: Found (ES): [M-H]$^+$ 374.9812, $C_{16}H_{12}N_2O_2SBr$ requires 374.9803

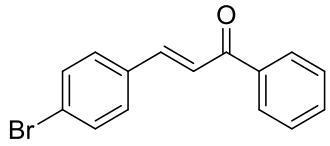
4-(3-(3-Bromophenyl)-1*H*-pyrrol-1-yl)benzenesulfonamide (15b)



A solution of 1M diisobutylaluminium hydride in THF (0.86 mL, 0.86 mmol) was added dropwise to a solution of **13b** (180 mg, 0.57 mmol) in toluene (10 mL) at -78 °C. The solution was then allowed to stir for 2 h. MeOH (1 mL) was added and the solution was allowed to warm to RT and 2M HCl (10 mL) was added and solution was stirred for 1 h. The product was extracted with ether (3 x 25 mL), organic layers combined and washed with brine before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was dissolved in EtOH (5 mL) and TsOH (11 mg, 0.06 mmol) and sulfanilamide (98 mg, 0.57 mmol) were added and reacted in the mW at 100 °C for 15 min. The residue was purified by flash chromatography (40% EtOAc/petrol) to give pyrrole **15b**.

Pale yellow solid, 56 mg, 0.15 mmol, 26%; Mp 173 – 175 °C; ν_{max} (film/cm^{-1}) 3370 (N-H), 3360 (N-H), 2925 (C-H), 1594 (C=C), 1511 (C=C), 1321 (C=C), 1157 (S=O); ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.18 (1H, t, *J* 1.8, NCHC), 7.91 (1H, s, ArH), 7.90 (4H, m, 4 × ArH), 7.68 (1H, d, *J* = 7.9, ArH), 7.60 (1H, d, *J* = 2.7, NC*H*CH), 7.41 (2H, s, NH_2), 7.37 (1H, d, *J* = 8.7, ArH), 7.32 (1H, t, *J* = 7.5, ArH), 6.84 (1H, dd, *J* = 2.7, 1.8, NCHC*H*); ^{13}C NMR (150 MHz, DMSO-d_6) δ 141.7, 140.6, 137.2, 130.8, 128.5, 127.4, 127.2, 125.2, 123.7, 122.4, 120.6, 118.8, 116.9, 109.5; LRMS: (ES): 377 ([M+H]$^+$, 100); HRMS: Found (ES): [M+H]$^+$ 376.9948, $C_{16}H_{14}N_2O_2SBr$ requires 376.9959

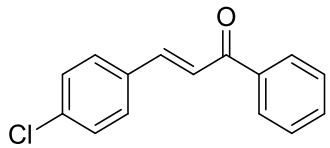
(*E*)-3-(4-Bromophenyl)-1-phenylprop-2-en-1-one (22a)



KOH (505 mg, 9.00 mmol) in water (10 mL) was added to a stirring mixture of 4-Bromobenzaldehyde (555 mg, 3.00 mmol) and acetophenone (360 mg, 3.00 mmol) in EtOH (10 mL) at 0 °C and the reaction stirred for 1 h at RT. A precipitate formed and this was filtered and washed with water (2 x 10 mL) and dried under reduced pressure to give alkene **22a**.

Yellow powder, 749 mg, 2.61 mmol, 87%; Mp 115-118 °C [126-129 °C][92]; ν_{max} (film/cm^{-1}) 1657 (C=O), 1607 (C=C), 1485 (Ar); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (2H, dd, *J* = 8.3, 1.2, 2 × ArH), 7.74 (1H, d, *J* = 15.8, COCH), 7.57 - 7.62 (1H, m, ArH), 7.48 - 7.57 (7H, m,7 × ArH); ^{13}C NMR (125MHz, $CDCl_3$) δ 190.3, 143.4, 138.1, 133.9, 133.0, 132.3, 129.9, 128.8, 128.6, 124.9, 122.7

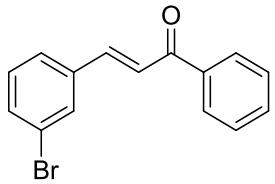
(*E*)-3-(4-Chlorophenyl)-1-phenylprop-2-en-1-one (22b)[92]



KOH (505 mg, 9.00 mmol) in water (10 mL) was added to a stirring mixture of 4-Chlorobenzaldehyde (420 mg, 3.00 mmol) and acetophenone (360 mg, 3.00 mmol) in EtOH (10 mL) at 0 °C and the reaction stirred for 1 h at RT. A precipitate formed and this was filtered and washed with water (2 x 10 mL) and dried under reduced pressure to give the alkene **22b**.

Yellow powder, 627 mg, 2.58 mmol, 86%; Mp 104-106 °C [114-117 °C][92]; ν_{max} (film/cm^{-1}) 1658 (C=O), 1603 (C=C), 1489 (Ar); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 – 8.05 (2H, m, 2 × ArH), 7.75 (1H, d, *J* = 15.8, COCH), 7.54 - 7.62 (3H, m, 3 × ArH), 7.54 - 7.47 (3H, m, 3 × ArH), 7.39 (2H, d, *J* = 8.5, 2 × ArH); ^{13}C NMR (125MHz, $CDCl_3$) δ 190.3, 143.4, 138.1, 136.5, 133.5, 133.0, 129.7, 129.3, 128.8, 128.6, 122.5

(*E*)-3-(3-Bromophenyl)-1-phenylprop-2-en-1-one (22c)[93]



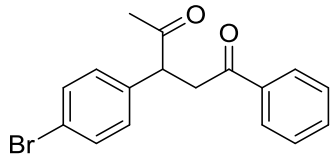
KOH (505 mg, 9.00 mmol) in water (10 mL) was added to a stirring mixture of 3-Bromobenzaldehyde (555 mg, 3.00 mmol) and acetophenone (360 mg, 3.00 mmol) in EtOH (10 mL) at 0 °C and the reaction stirred for 1 h at RT. A precipitate formed and this was filtered and washed with water (2 x 10 mL) and dried under reduced pressure to give alkene **22c**.

Yellow powder, 695 mg, 2.42 mmol, 81%; Mp 75-78 °C [83-85 °C][93]; ν_{max} (film/cm^{-1}) 1665 (C=O), 1607 (C=C), 1314 (Ar); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 - 8.05 (2H, m, 2 × ArH), 7.78 (1H, t, *J* = 1.7, ArH), 7.71 (1H, d, *J* = 15.8, COCH), 7.57 - 7.62 (1H, m, ArH), 7.48 - 7.55 (5H, m, 5 × ArH), 7.28 (1H, t, *J* = 7.9, ArH); ^{13}C NMR (125MHz, $CDCl_3$) δ 190.1, 143.0, 138.0, 137.1, 133.3, 133.1, 130.9, 130.6, 128.8, 128.6, 127.3, 123.3, 123.2

General Procedure A: acetophenone to 1,4-diketone

A solution of KOH (3 eq.) in water (1M) was added to a stirring mixture of aldehyde (1 eq.) and acetophenone (1 eq.) in EtOH (1M) at 0 °C and the reaction stirred for 1 h at RT. A precipitate formed and this was filtered and washed with water (2 x 10 mL) and dried to give the mixture of *E* and *Z* **alkenes**. $CsCO_3$ (0.10 eq.) was added to a stirring solution of **alkenes** (1 eq.), 3-Benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (0.10 eq.) and freshly distilled acetaldehyde (10 eq.) in anhydrous THF (1M) at RT. After 24 h, the reaction was quenched with water (1 mL) before the product extracted with EtOAc (2 x 2 mL), the combined organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/petrol) to give the diketone.

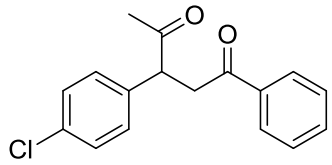
3-(4-Bromophenyl)-1-phenylpentane-1,4-dione (24a)[46]



General Procedure A: acetophenone to 1,4-diketone

Colourless oil, 115 mg, 0.35 mmol, 70%; ν_{max} (film/cm^{-1}) 1715 (C=O), 1683 (C=O), 1596 (C=C), 1485 (C=C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 - 7.96 (2H, m, 2 × ArH), 7.54 - 7.58 (1H, m, ArH), 7.47 - 7.50 (2H, m, 2 × ArH), 7.43 - 7.46 (2H, m, 2 × ArH), 7.16 - 7.19 (2H, m, 2 × ArH), 4.40 (1H, dd, *J* = 9.8, 4.0, COCH), 3.97 (1H, dd, *J* = 18.1, 9.8, COC*H*H), 3.13 (1H, dd, *J* = 18.1, 4.0, COCH*H*), 2.22 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.9, 197.9, 137.0, 136.4, 133.5, 132.4, 130.4, 128.8, 128.2, 121.8, 53.3, 42.3, 29.4

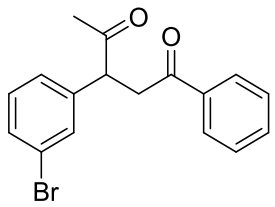
3-(4-Chlorophenyl)-1-phenylpentane-1,4-dione (24b)



General Procedure A: acetophenone to 1,4-diketone

Colourless oil, 30 mg, 0.31 mmol, 62%; ν_{max} (film/cm^{-1}) 1716 (C=O), 1683 (C=O), 1596 (C=C), 1489 (C=C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (2H, dd, *J* = 8.3, 1.1, 2 × ArH), 7.54 - 7.58 (1H, m, ArH), 7.43 - 7.47 (2H, m, 2 × ArH), 7.31 - 7.35 (2H, m, 2 × ArH) 7.22 - 7.25 (2H, m, 2 × ArH), 4.41 (1H, dd, *J* = 9.9, 3.9, COCH), 3.97 (1H, dd, *J* = 18.1, 9.9, COC*H*H), 3.13 (1H, dd, *J* = 18.1, 3.9, COCH*H*), 2.22 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.0, 198.0, 136.5, 136.4, 133.7, 133.5, 129.8, 129.4, 128.7, 128.2, 53.3, 42.3, 29.4; LRMS: (ES): 287 ([M+H]$^{+}$, 100), 278 (50); HRMS: Found (ES): [M+H]$^{+}$ 287.0832, $C_{17}H_{16}O_2Cl$ requires 287.0839

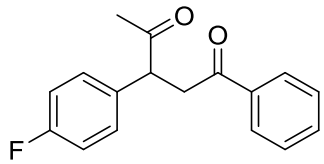
3-(3-Bromophenyl)-1-phenylpentane-1,4-dione (24c)



General Procedure A: acetophenone to 1,4-diketone

Colourless oil, 103 mg, 62%; ν_{max} (film/cm^{-1}) 1715 (C=O), 1682 (C=O), 1596 (C=C), 1449 (C=C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 - 7.96 (2H, m, 2 × ArH), 7.53 - 7.58 (1H, m, ArH), 7.41 - 7.46 (4H, m, 4 × ArH), 7.20 - 7.24 (2H, m, 2 × ArH), 4.39 (1H, dd, *J* = 10.1, 3.7, COCH), 3.98 (1H, dd, *J* = 18.1, 10.1, COC*H*H), 3.13 (1H, dd, *J* = 18.1, 3.7, COCH*H*), 2.23 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.7, 197.8, 140.3, 136.3, 133.5, 131.4, 131.0, 130.8, 128.8, 128.2, 127.2, 123.3, 53.5, 42.4, 29.5; LRMS: (ES): 331 ([M+H]$^+$, 100); HRMS: Found (ES): [M+H]$^+$ 331.0318, $C_{17}H_{16}O_2Br$ requires 331.0334

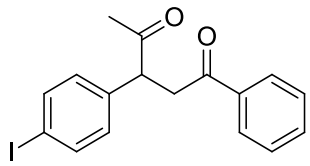
3-(4-Fluorophenyl)-1-phenylpentane-1,4-dione (24d)



General Procedure A: acetophenone to 1,4-diketone

Colourless oil, 185 mg, 50%; ν_{max} (film/cm^{-1}) 3067 (C-H), 1716 (C=O), 1683 (C=O), 1508 (C=C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (2H, d, *J* = 8.3, 2 × ArH), 7.56 (1H, t, *J* = 7.4, ArH), 7.45 (2H, t, *J* = 7.4, 2 × ArH), 7.24 - 7.28 (2H, m, 2 × ArH), 7.05 (2H, m, 2 × ArH), 4.42 (1H, dd, *J* = 9.9, 4.1, COCH), 3.97 (1H, dd, *J* = 18.1, 9.9, COC*H*H), 3.13 (1H, dd, *J* = 18.1, 4.1, COCH*H*), 2.22 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.3, 198.1, 162.4 (d, *J* =246.2), 136.4, 133.8 (d, *J* = 3.6), 133.7, 130.0 (d, *J* = 7.8), 128.7, 128.2, 116.2 (d, *J* = 21.5), 53.1, 42.5, 29.3; LRMS: (EI): 270 ([M]$^+$, 50), 228 (90), 105 (100); HRMS: Found (EI): [M]$^+$ 270.10550, $C_{17}H_{15}O_2F$ requires 270.10506

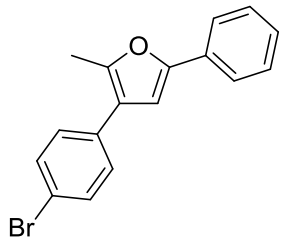
3-(4-Iodophenyl)-1-phenylpentane-1,4-dione (24e)



General Procedure A: acetophenone to 1,4-diketone

Colourless oil, 148 mg, 60%; ν_{max} (film/cm^{-1}) 3059 (C-H), 1714 (C=O), 1681 (C=O), 1482 (C=C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (2H, d, *J* = 7.5, 2 × ArH), 7.68 (2H, d, *J* = 8.3, 2 × ArH), 7.56 (1H, t, *J* = 7.5, ArH), 7.45 (2H, t, *J* = 7.5, 2 × ArH), 7.05 (2H, d, *J* = 8.3, 2 × ArH), 4.37 (1H, dd, *J* = 9.8, 3.9, COCH), 3.96 (1H, dd, *J* = 18.0, 9.8, COC*H*H), 3.12 (1H, dd, *J* = 18.0, 3.9, COCH*H*), 2.22 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.9, 197.9, 138.4, 137.7, 136.4, 133.5, 130.4, 128.8, 128.8, 93.3, 53.5, 42.3, 29.4; LRMS: (EI): 378 ([M]$^+$, 40), 336 (30), 105 (100); HRMS: Found (EI): [M]$^+$ 378.01119, $C_{17}H_{15}O_2I$ requires 378.01112

3-(4-Bromophenyl)-2-methyl-5-phenylfuran (25)



TsOH (5 mg, 0.03 mmol) was added to ketone **24a** (91 mg, 0.28 mmol) and sulfanilamide **9** (48 mg, 0.28 mmol) in MeOH (5 mL) and reacted in the μW at 120 °C for 1 h. EtOAc (10 mL) and saturated $NaHCO_3$ (5 mL) were added and the product was extracted with EtOAc (3 x 10 mL) before the solution was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude product. The residue was purified by flash chromatography (EtOAc/petrol) to give furan **25**.

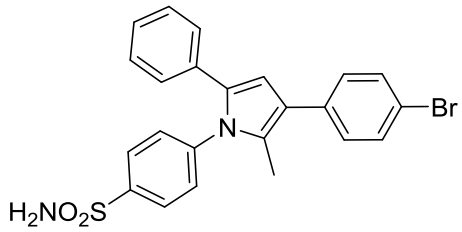
Yellow oil, 25 mg, 29%; ν_{max} (film/cm^{-1}) 2985 (C-H), 1479 (C=C), 1465 (C=C), 1373 (C=C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (2H, d, *J* = 7.5, 2 × ArH), 7.53 (2H, d, *J* = 8.3, 2 × ArH), 7.39 (2H, t, *J* = 7.5, 2 × ArH), 7.30 (2H, d, *J* = 8.3, 2 × ArH), 7.25 (1H, t, *J* = 7.5, ArH), 6.74 (1H, s, OCCHC), 1.56 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.0, 147.9, 133.1, 131.8, 130.7, 129.2, 128.8, 127.3, 123.6, 122.2, 120.4, 106.2, 13.3; LRMS: (CI): 313 ([M+H]$^+$, 70), 277

(30), 234 (20), 89 (100); HRMS: Found (CI): $[M+H]^+$ 313.02350, $C_{17}H_{14}OBr$ requires 313.02280

General Procedure B: Pyrrole Formation

TsOH (0.1 eq.) was added to ketone (1 eq.) and sulfanilamide (3 eq.) in MeOH (5M) and reacted in the mW at 100 °C for 1 h. EtOAc (10 mL) and saturated $NaHCO_3$ (5 mL) were added and the product was extracted with EtOAc (3 x 10 mL) before the solution was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude product. The residue was purified by flash chromatography (EtOAc/petrol) to give the pyrrole.

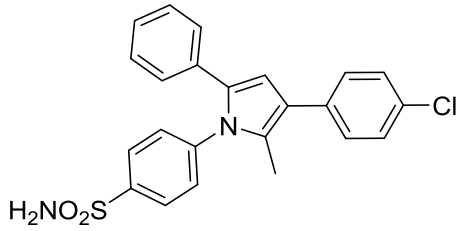
4-(3-(4-Bromophenyl)-2-methyl-5-phenyl-1*H*-pyrrol-1-yl)benzenesulfonamide (26a)



General Procedure B: pyrrole formation

Yellow solid, 11 mg, 0.02 mmol, 79%; Mp 214 – 218 °C; ν_{max} (film/cm^{-1}) 3410 (N-H), 1656 (C=C), 1218 (S=O); ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.87 (2H, d, J = 8.7, 2 × ArH), 7.60 (2H, d, J = 7.9, 2 × ArH), 7.51 (2H, s, NH_2), 7.47 (2H, d, J = 8.1, 2 × ArH), 7.45 (2H, d, J = 8.7, 2 × ArH), 7.22 (2H, t, J = 8.1, 2 × ArH), 7.15 (1H, t, J = 8.1, ArH), 7.09 (2H, d, J = 7.9, 2 × ArH), 6.64 (1H, s, CH on pyrrole), 2.17 (3H, s, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ 143.3, 141.2, 135.4, 133.5, 132.4, 131.5, 129.6, 129.1, 128.4, 128.0, 127.7, 126.8, 126.4, 121.3, 118.6, 109.7, 12.3; LRMS: (ES): 465 ($[M-H]^+$, 100); HRMS: Found (ES) $[M-H]^+$ 465.0255, $C_{23}H_{18}O_2N_2SBr$ requires 465.0272

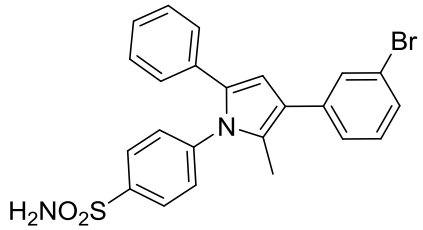
4-(3-(4-Chlorophenyl)-2-methyl-5-phenyl-1*H*-pyrrol-1-yl)benzenesulfonamide (26b)



General Procedure B: pyrrole formation

Yellow solid, 10 mg, 78%; Mp 236 – 240 °C; ν_{max} (film/cm^{-1}) 3627 (N-H), 1421 (C=C), 1359 (S=O), 1220 (S=O); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 7.87 (2H, d, *J* = 8.5, 2 × ArH)), 7.42 - 7.53 (8H, m, NH_2, 6 × ArH), 7.21 (2H, t, *J* = 7.4, 2 × ArH), 7.14 (1H, m, ArH), 7.08 (2H, d, *J* = 8.5, 2 × ArH), 6.62 (1H, s, CH on pyrrole), 2.16 (3H, s, CH_3); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ143.3, 141.2, 135.0, 133.4, 132.4, 130.1, 129.2, 129.0, 128.5, 128.3, 127.9, 127.6, 126.7, 126.4, 121.3, 109.7, 12.2; LRMS: (ES): 423 ([M+H]$^+$, 100); HRMS: Found (ES): [M+H]$^+$ 423.0944, $C_{23}H_{20}O_2N_2SCl$ requires 423.0934

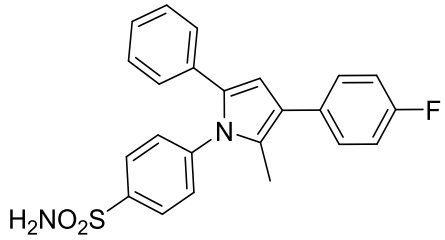
4-(3-(3-Bromophenyl)-2-methyl-5-phenyl-1*H*-pyrrol-1-yl)benzenesulfonamide (26c)



General Procedure B: pyrrole formation

Yellow solid, 15 mg, 76%; Mp 202 – 204 °C; ν_{max} (film/cm^{-1}) 3567 (N-H), 1420 (C=C), 1359 (S=O), 1220 (S=O); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 7.87 (2H, d, *J* = 8.5, 2 × ArH), 7.65 (1H, t, *J* = 1.7, ArH), 7.44 – 7.50 (5H, m, NH_2, 3 × ArH), 7.41 – 7.44 (1H, m, ArH), 7.37 (1H, t, *J* = 7.7, ArH), 7.21 (2H, t, *J* = 7.2, 2 × ArH), 7.12 – 7.16 (1H, m, ArH), 7.09 (2H, d, *J* = 8.5, 2 × ArH), 6.66 (1H, s, CH on pyrrole), 2.17 (3H, s, CH_3); ^{13}C NMR (125MHz, DMSO-d$_6$) δ 143.3, 141.1, 138.7, 133.5, 132.3, 130.6, 129.9, 129.0, 128.3, 128.2, 127.6, 126.7, 126.5, 126.4, 122.0, 121.0, 109.8, 12.2; LRMS: (ES): 465 ([M-H]$^+$, 100); HRMS: Found (ES): [M-H]$^+$ 465.0273, $C_{23}H_{18}O_2N_2SBr$ requires 465.0255

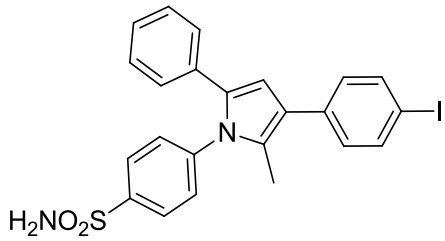
4-(3-(4-Fluorophenyl)-2-methyl-5-phenyl-1*H*-pyrrol-1-yl)benzenesulfonamide (26d)



General Procedure B: pyrrole formation

Yellow oil, 18 mg, 65%; ν_{max} (film/cm^{-1}) 3277 (N-H), 3059 (C-H), 1596 (C=C), 1498 (C=C), 1297 (S=O), 1167 (S=O); ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 7.87 (2H, d, *J* = 8.7, 2 × ArH), 7.49 - 7.52 (2H, m, 2 × ArH), 7.51 (2H, s, NH_2) , 7.47 (2H, d, *J* = 8.7, 2 × ArH), 7.25 (2H, t, *J* = 8.8, 2 × ArH), 7.22 (2H, t, *J* = 7.5, 2 × ArH), 7.15 (1H, t, *J* = 6.8, ArH), 7.09 (2H, d, *J* = 8.7, 2 × ArH), 6.61 (1H, s, CH on pyrrole), 2.16 (3H, s, CH_3); ^{13} C NMR (150 MHz, DMSO-d$_6$) δ 160.6 (d, *J* = 242.0), 143.2, 141.3, 133.2, 132.6 (d, *J* = 3.0), 132.4, 129.4 (d, *J* = 7.7), 129.1, 128.4, 127.6, 126.7, 126.3, 121.61, 121.58, 115.4 (d, *J* = 21.5), 109.9, 12.2; LRMS: (ES): 405 ([M-H]$^+$, 100); HRMS: Found (ES): [M-H]$^+$ 405.1080, $C_{23}H_{18}N_2O_2SF$ requires 405.1073

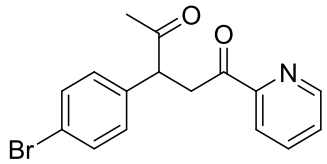
4-(3-(4-Iodophenyl)-2-methyl-5-phenyl-1*H*-pyrrol-1-yl)benzenesulfonamide (26e)



General Procedure B: pyrrole formation

Yellow oil, 21 mg, 72%; ν_{max} (film/cm^{-1}) 3245 (N-H), 2922 (C-H), 2593 (C=C), 1326 (S=O), 1155 (S=O); ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 7.87 (2H, d, *J* = 8.7, 2 × ArH), 7.76 (2H, d, *J* = 8.3, 2 × ArH), 7.51 (2H, s, NH_2), 7.47 (2H, d, *J* = 8.7, 2 × ArH), 7.31 (2H, d, *J* = 8.3, 2 × ArH), 7.22 (2H, t, *J* = 7.2, 2 × ArH), 7.15 (1H, t, *J* = 7.2, ArH), 7.08 (2H, d, *J* = 7.2, 2 × ArH), 6.63 (1H, s, CH on pyrrole), 2.17 (3H, s, CH_3); ^{13} C NMR (150 MHz, DMSO-d$_6$) δ 143.3, 141.2, 137.3, 135.7, 133.5, 132.4, 129.8, 129.1, 128.4, 128.0, 127.7, 126.8, 126.4, 121.4, 109.6, 91.1, 12.3; LRMS: (ES): 513 ([M-H]$^+$, 100); HRMS: Found (ES): [M-H]$^+$ 513.0145, $C_{23}H_{18}N_2O_2SI$ requires 513.0134

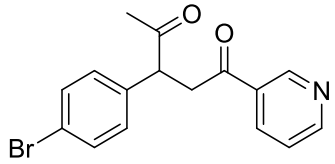
3-(4-Bromophenyl)-1-(pyridin-2-yl)pentane-1,4-dione (28a)



General Procedure A: acetophenone to 1,4-diketone

Colourless oil, 48 mg, 22%; ν_{max} (film/cm^{-1}) 2924 (C-H), 1715 (C=O), 1696 (C=O), 1486 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (1H, dq, *J* = 4.7, 1.2, ArH), 7.98 (1H, dt, *J* = 7.8, 1.2, ArH), 7.82 (1H, td, *J* = 7.8, 1.2, ArH), 7.44 - 7.48 (3H, m, 3 × ArH), 7.18 (2H, d, *J* = 8.4, 2 × ArH), 4.35 (1H, dd, *J* = 10.2, 3.9, COCH), 4.19 (1H, dd, *J* = 18.9, 10.2, COC*H*H), 3.40 (1H, dd, *J* = 18.9, 3.9, COCH*H*), 2.20 (3H, s, CH_3); ^{13}C NMR (125MHz, $CDCl_3$) δ 206.8, 199.6, 152.9, 149.1, 137.1, 137.0, 132.2, 130.2, 127.4, 121.9, 121.7, 53.5, 41.4, 29.2; LRMS: (ES): 332 ([M+H]$^+$, 100), 273 (80%); HRMS: Found (ES): [M+H]$^+$ 332.0287, $C_{16}H_{15}NO_2Br$ requires 332.0286

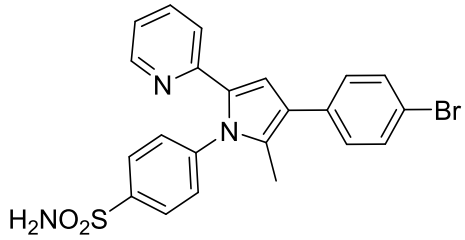
3-(4-Bromophenyl)-1-(pyridin-3-yl)pentane-1,4-dione (28b)



General Procedure A: Acetophenone to 1,4-diketone

Colourless oil, 88 mg, 42%; ν_{max} (film/cm^{-1}) 2911 (C-H), 1707 (C=O), 1685 (C=O), 1584 (C=C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.11 (1H, s, ArH), 8.71 (1H, d, *J* = 2.3, ArH), 8.15 (1H, dt, *J* = 7.9, 2.3, ArH), 7.43 (2H, d, *J* = 8.5, 2 × ArH), 7.35 (1H, dd, *J* = 7.9, 4.9, ArH), 7.12 (2H, d, *J* = 8.5, 2 × ArH), 4.35 (1H, dd, *J* = 10.2, 3.8, COCH), 3.91 (1H, dd, *J* = 18.1, 10.2, COC*H*H), 3.05 (1H, dd, *J* = 18.1, 3.8, COCH*H*), 2.14 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.5, 196.8, 153.8, 149.6, 136.6, 135.5, 132.5, 131.7, 130.1, 123.8, 122.0, 53.2, 42.2, 29.2; LRMS: (ES): 332 ([M+H]$^+$, 100), 289 (50); HRMS: Found (ES): [M+H]$^+$ 332.0272, $C_{16}H_{15}NO_2Br$ requires 332.0286

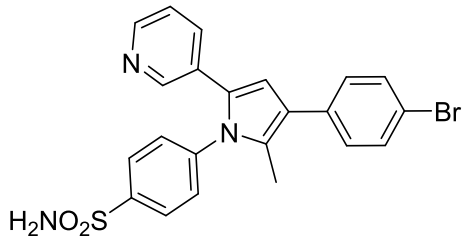
4-(3-(4-Bromophenyl)-2-methyl-5-(pyridin-2-yl)-1*H*-pyrrol-1-yl)benzenesulfonamide (29a)



General Procedure B: pyrrole formation

Yellow oil, 15 mg, 34%; ν_{max} (film/cm^{-1}) 3265 (N-H), 3068 (C-H), 1592 (C=C), 1484 (C=C), 1334 (S=O), 1163 (S=O); ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 8.22 (1H, td, *J* = 2.4, 0.9, ArH), 7.87 (2H, d, *J* = 8.7, 2 × ArH), 7.66 (1H, td, *J* = 7.6, 1.7, ArH), 7.61 (2H, d, *J* = 8.3, 2 × ArH), 7.50 (2H, s, NH_2), 7.45 (2H, d, *J* = 8.7, 2 × ArH), 7.46 (2H, d, *J* = 8.3, 2 × ArH), 7.35 (1H, d, *J* = 7.6, ArH), 7.07 (1H, ddd, *J* = 7.6, 4.8, 0.9, ArH), 6.97 (1H, s, CH on pyrrole), 2.15 (3H, s, CH_3); ^{13} C NMR (150 MHz, DMSO-d$_6$) δ 150.7, 148.7, 143.0, 142.1, 136.5, 135.2, 132.8, 131.5, 129.6, 128.7, 126.5, 121.5, 121.4, 120.9, 118.8, 111.7, 12.3; LRMS: (ES): 468 ([M+H]$^+$, 100); HRMS: Found (ES): [M+H]$^+$ 468.0399, $C_{22}H_{19}N_3O_2SBr$ requires 468.0381

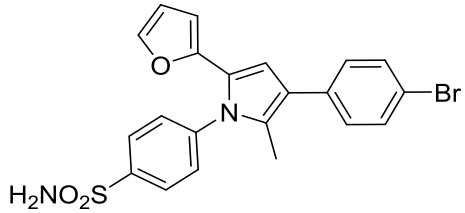
4-(3-(4-Bromophenyl)-2-methyl-5-(pyridin-3-yl)-1*H*-pyrrol-1-yl)benzenesulfonamide (29b)



General Procedure B: pyrrole formation

Yellow oil, 18 mg, 38%; ν_{max} (film/cm^{-1}) 3333 (N-H), 2965 (C-H), 1593 (C=C), 1485 (C=C), 1345 (S=O), 1164 (S=O); ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 8.34 (1H, dd, *J* = 4.5, 1.5, ArH), 8.33 (1H, d, *J* = 1.5, ArH), 7.90 (2H, d, *J* = 8.3, 2 × ArH), 7.62 (2H, d, *J* = 8.7, 2 × ArH), 7.53 (2H, s, NH_2), 7.52 (1H, d, *J* = 8.7, 2 × ArH), 7.46 (1H, d, *J* = 8.3, 2 × ArH), 7.42 (1H, dt, *J* = 8.0, 1.9, ArH), 7.25 (1H, dd, *J* = 8.0, 4.5, ArH), 6.80 (1H, s, CH on pyrrole), 2.19 (3H, s, CH_3); ^{13} C NMR (150 MHz, DMSO-d$_6$) δ 148.1, 147.2, 143.6, 140.7, 135.2, 134.6, 131.5, 130.1, 129.6, 129.2, 129.0, 128.3, 126.9, 123.4, 121.6, 118.8, 110.7, 12.3; LRMS: (ES): 468 ([M+H]$^+$, 100), 389 (20); HRMS: Found (ES): [M+H]$^+$ 468.0381, $C_{22}H_{19}N_3O_2SBr$ requires 468.0381

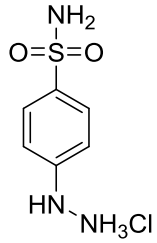
4-(3-(4-Bromophenyl)-5-(furan-2-yl)-2-methyl-1*H*-pyrrol-1-yl)benzenesulfonamide (32)



General Procedure B: pyrrole formation

Yellow oil, 16 mg, 23% over 2 steps; ν_{max} (film/cm^{-1}) 2921 (C-H), 2590 (C=C), 1329 (S=O), 1157 (S=O); ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.98 (2H, d, *J* = 8.3, 2 × ArH), 7.60 (4H, d, *J* = 8.3, 4 × ArH), 7.57 (2H, s, NH_2), 7.53 (1H, s, OCH), 7.43 (2H, d, *J* = 8.3, 2 × ArH), 6.73 (1H, s, CH on pyrrole), 6.35 (1H, m, ArH), 5.46 (1H, d, *J* = 3.4, ArH), 2.12 (3H, s, CH_3); ^{13} C NMR (150 MHz, DMSO-d_6) δ 146.4, 144.2, 141.7, 140.9, 135.1, 131.5, 129.5, 129.2, 128.2, 127.0, 124.5, 121.0, 118.7, 111.2, 108.1, 105.1, 11.9; LRMS: (ES): 457 $(M+H)^+$, 100), 370 (40), 332 (40), 279 (40); HRMS: Found (ES): $[M+H]^+$ 457.0196, $C_{21}H_{18}N_2O_3SBr$ requires 457.0222

2-(4-Sulfamoylphenyl)hydrazin-1-ium chloride (33)



Sulfanilamide (1.16 g, 6.7 mmol) was added to a stirring conc. HCl (5 mL) at RT then cooled to -5 °C. A solution of $NaNO_2$ (489 mg, 7.1 mmol) in water (3 mL) was added to the reaction mixture dropwise over 5 min, then allowed to stir for 1 h. The solution was then cooled to -20 °C before the addition of $SnCl_2$ (2.9 g, 12.1 mmol) in conc. HCl (3 mL) dropwise over 5 mins. The solution was stirred at RT for 1 h before the precipitate was filtered and washed with water to give hydrazine **33**.

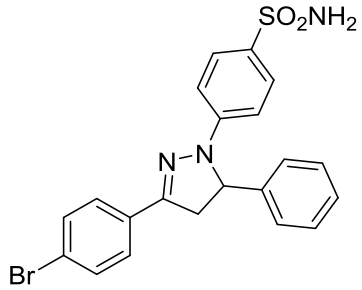
Orange powder, 1.06 g, 85%; Mp 210 – 212 °C; ν_{max} (film/cm^{-1}) 3257 (N-H), 3000 (C-H), 1594 (C=C), 1513 (C=C), 1315 (S=O), 1159 (S=O); ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.41 (2H, br. s, NHNH_2), 8.84 (1H, br. s, N$H$$NH_2$), 7.69 (2H, d, *J* = 8.7, 2 × ArH), 7.19 (2H, br. s, SO_2NH_2), 7.01 (2H, d, *J* = 8.7, 2 × ArH); ^{13}C NMR (150 MHz, DMSO-d_6) δ 148.3, 136.2, 126.9, 113.3; LRMS:

(CI): 187 ([M-Hl]$^+$, 70), 172 ([M-NH_3]$^+$, 70), 156 (100); HRMS: Found (CI): [M-Hl]$^+$ 187.040892, $C_6H_9N_3O_2S$ requires 187.04100

General Procedure C: Acetophenone to Pyrazoline

KOH (3 eq.) in water (1M) was added to a stirring mixture of aldehyde (1 eq.) and acetophenone (1 eq.) in EtOH (1M) at 0 °C and the reaction stirred for 1 h at RT. A precipitate formed and this was filtered and washed with water (2 x 10 mL) and dried to give the mixture of *E* and *Z* alkenes. 2-(4-Sulfamoylphenyl)hydrazin-1-ium chloride **33** (1.5 eq.) and alkenes (1 eq.) in EtOH (2 mmolmL^{-1}) were heated to 100 °C for 12 h. After which the solvent was removed under reduced pressure and the residue was purified by flash chromatography (EtOAc /petrol) to give the pyrazoline.

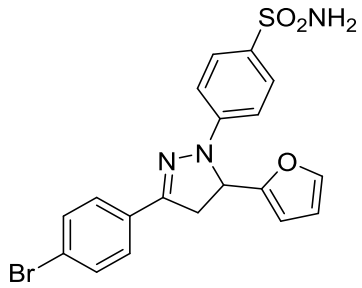
4-(3-(4-Bromophenyl)-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)benzenesulfonamide (37a)



General Procedure C: Acetophenone to pyrazoline

Yellow oil, 68mg, 87%; ν_{max} (film/cm^{-1}) 3249 (N-H), 2924 (C-H), 1592 (C=C), 1506 (C=C), 1329 (S=O), 1154 (S=O); ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.73 (2H, d, *J* = 8.7, 2 × ArH), 7.65 (2H, d, *J* = 8.7, 2 × ArH,), 7.58 (2H, d, *J* = 9.0, 2 × ArH), 7.34 (1H, t, *J* = 7.5, ArH), 7.23 - 7.28 (2H, m, 2 × ArH), 7.08 (2H, d, *J* = 9.0, 2 × ArH), 7.03 - 7.05 (2H, m, 2 × ArH), 5.67 (1H, dd, *J* = 12.3, 5.3, CH), 3.97 (1H, dd, *J* = 17.6, 12.3, C*H*H), 3.19 (1H, dd, *J* = 17.6, 5.3, CH*H*); ^{13} C NMR (150 MHz, DMSO-d_6) δ = 157.1, 148.7, 145.7, 141.5, 133.3, 131.7, 129.2, 128.0, 127.7, 127.2, 125.8, 122.5, 112.1, 62.5, 42.8; LRMS: (EI): 455 ([M]$^+$, 100), 403 (30); HRMS: Found (EI): [M]$^+$ 455.03041, $C_{21}H_{18}O_2N_3SBr$ requires 455.02976

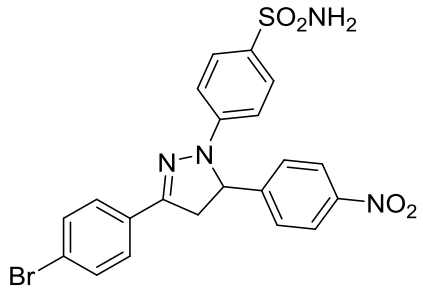
4-(3-(4-Bromophenyl)-5-(furan-2-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)benzenesulfonamide (37b)



General Procedure C: Acetophenone to pyrazoline

Orange oil, 30 mg, 37%; ν_{max} (film/cm^{-1}) 3256 (N-H), 2935 (C-H), 1593 (C=C), 1506 (C=C), 1326 (S=O), 1155 (S=O); ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 7.75 (2H, d, *J* = 8.5, 2 × ArH), 7.66 (2H, d, *J* = 8.5, 2 × ArH), 7.62 (2H, d, *J* = 9.0, 2 × ArH), 7.56 (1H, d, *J* = 1.9, OCH), 7.23 (2H, d, *J* = 9.0, 2 × ArH), 7.08 (2H, s, NH_2), 6.51 (1H, d, *J* = 3.0, OCCH), 6.38 (1H, dd, *J* = 3.0, 1.9, OCHC*H*), 5.80 (1H, dd, *J* = 12.1, 4.9, CH), 3.82 (1H, dd, *J* = 17.4, 12.1, C*H*H), 3.43 (1H, dd, *J* = 17.4, 4.9, CH*H*); ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 152.1, 149.0, 145.7, 143.2, 133.6, 131.8, 131.0, 128.0, 127.1, 122.5, 112.3, 110.4, 108.4, 56.1, 38.1; LRMS: (EI): 445 ([M]$^+$, 20), 379 (30), 84 (100); HRMS: Found (EI): [M]$^+$ 445.00948, $C_{19}H_{16}O_3N_3SBr$ requires 445.00903

4-(3-(4-Bromophenyl)-5-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)benzenesulfonamide (37c)

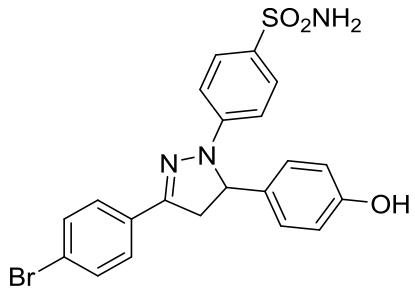


General Procedure C: Acetophenone to pyrazoline

Orange solid, 64 mg, 69%; Mp 89 – 94 °C; ν_{max} (film/cm^{-1}) 3360 (N-H), 2971 (C-H), 1593 (C=C), 1366 (N-O), 1349 (S=O); ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 8.22 (2H, d, *J* = 9.0, 2 × ArH), 7.73 (2H, d, *J* = 8.7, 2 × ArH), 7.65 (2H, d, *J* = 8.7, 2 × ArH), 7.60 (2H, d, *J* = 9.0, 2 × ArH), 7.53 (2H, d, *J* = 8.7, 2 × ArH), 7.09 (2H, d, *J* = 8.7, 2 × ArH), 7.08 (2H, s, NH_2), 5.86 (1H, dd, *J* =

12.1, 5.1, CH), 4.02 (1H, dd, *J* = 18.0, 12.1, C*H*H), 3.25 (1H, dd, *J* = 18.0, 5.1 CH*H*); ^{13}C NMR (150 MHz, DMSO-d_6) δ 148.92, 148.90, 147.0, 145.4, 133.7, 131.8, 130.8, 128.1, 127.4, 127.3, 124.5, 122.7, 112.2, 61.9, 42.4; LRMS: (ES): 499 ([M-H]$^+$, 100), 318 (40); HRMS: Found (ES): [M-H]$^+$ 499.0097, $C_{21}H_{16}O_4N_4SBr$ requires 499.0076

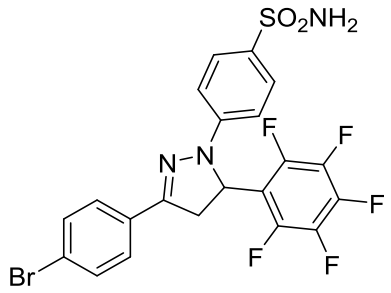
4-(3-(4-Bromophenyl)-5-(4-hydroxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)benzenesulfonamide (37d)



General Procedure C: Acetophenone to pyrazoline

Orange solid, 133 mg, 13%, Mp 129 – 132 °C; ν_{max} (film/cm^{-1}) 3330 (O-H), 2962 (C-H), 1592 (C=C), 1510 (C=C), 1328 (S=O), 1151 (S=O); ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.44 (1H, s, OH), 7.72 (2H, d, *J* = 8.7, 2 × ArH), 7.64 (2H, d, *J* = 8.3, 2 × ArH), 7.58 (2H, d, *J* = 8.7, 2 × ArH), 7.08 (2H, d, *J* = 8.7, 2 × ArH), 7.05 (2H, d, *J* = 8.3, 2 × ArH), 7.03 (2H, s, NH_2), 6.70 (2H, d, *J* = 8.7, 2 × ArH), 5.53 (1H, dd, *J* = 12.1, 5.2, CH), 3.90 (1H, dd, *J* = 17.7, 12.1 C*H*H), 3.14 (1H, dd, *J* = 17.7, 5.2 CH*H*); ^{13} C NMR (150 MHz, DMSO-d_6) δ 156.8, 148.6, 145.8, 133.2, 131.69, 131.71, 131.2, 128.0, 127.1, 127.0, 122.4, 115.8, 112.2, 62.3, 42.8; LRMS: (ES): 470 ([M-H]$^+$, 100), 301 (20), 276 (20); HRMS: Found (ES): [M-H]$^+$ 470.0182, $C_{21}H_{17}O_2N_3SBr$ requires 470.0174

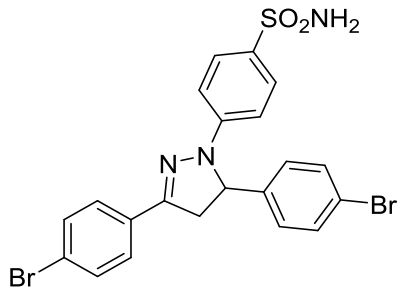
4-(3-(4-Bromophenyl)-5-(perfluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)benzenesulfonamide (37e)



General Procedure C: Acetophenone to pyrazoline

Yellow powder, 29 mg, 33%, Mp 219 – 222 °C; ν_{max} (film/cm^{-1}) 3350 (N-H), 2970 (C-H), 1645 (C=C), 1368 (S=O), 991 (C-F); ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 7.73 (2H, d, *J* = 8.7, 2 × ArH), 7.68 (2H, d, *J* = 8.7, 2 × ArH), 7.65 (2H, d, *J* = 9.0, 2 × ArH), 7.12 (2H, s, NH_2), 7.06 (2H, d, *J* = 9.0, 2 × ArH), 6.02 (1H, dd, *J* = 13.1, 5.3, CH), 4.01 (1H, dd, *J* = 17.8, 13.1 C*H*H), 3.52 (1H, dd, *J* = 17.8, 5.3, CH*H*); ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 149.2, 145.1, 134.1, 131.8, 130.6, 128.0, 127.5, 122.8, 111.8, 52.7, 40.1 - peaks missing due to multiple couplings with ^{19}F; LRMS: (ES): 554 ([M-H]$^+$, 100); HRMS: Found (ES): [M-H]$^+$ 543.9784, $C_{21}H_{12}O_2F_5N_3SBr$ requires 543.9754

4-(3,5-Bis(4-bromophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)benzenesulfonamide (37f)

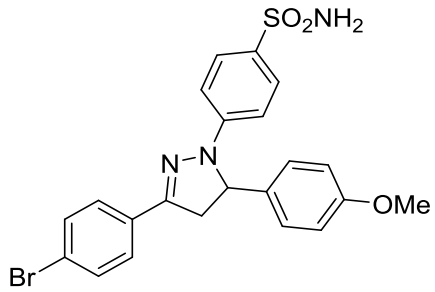


General Procedure C: Acetophenone to pyrazoline

Orange solid, 158 mg, 32%; Mp 125 – 128 °C; ν_{max} (film/cm^{-1}) 3253 (N-H), 2971 (C-H), 1590 (C=C), 1488 (C=C), 1383 (S=O), 1151 (S=O); ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 7.72 (2H, d, *J* = 8.7, 2 × ArH), 7.65 (2H, d, *J* = 8.7, 2 × ArH), 7.60 (2H, d, *J* = 8.9, 2 × ArH), 7.55 (2H, d, *J* = 8.5, 2 × ArH), 7.21 (2H, d, *J* = 8.5, 2 × ArH), 7.08 (2H, d, *J* = 8.9, 2 × ArH), 7.05 (2H, s, NH_2), 5.68 (1H, dd, *J* = 12.1, 5.1, CH), 3.96 (1H, dd, *J* = 17.6, 12.1, C*H*H), 3.20 (1H, dd, *J* = 17.6, 5.1,

CH*H*), ^{13}C NMR (150 MHz, DMSO-d_6) δ 148.8, 145.5, 140.9, 133.5, 132.1, 131.7, 131.0, 128.2, 128.1, 127.2, 122.6, 120.8, 112.2, 61.9, 42.5; LRMS: (EI): 533 ([M]$^+$, 100); HRMS: Found (EI): [M]$^+$ 532.93685, $C_{21}H_{17}O_2N_3SBr_2$requires 532.94027

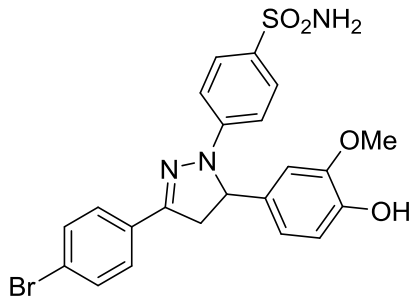
4-(3-(4-Bromophenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)benzenesulfonamide (37g)



General Procedure C: Acetophenone to pyrazoline

Orange oil, 30 mg, 38%; ν_{max} (film/cm^{-1}) 3265 (N-H), 2970 (C-H), 1595 (C=C), 1492 (C=C), 1353 (S=O), 1164 (S=O); ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.73 (2H, d, *J* = 8.5, 2 × ArH), 7.65 (2H, d, *J* = 8.5, 2 × ArH), 7.58 (2H, d, *J* = 9.0, 2 × ArH), 7.17 (2H, d, *J* = 8.8, 2 × ArH), 7.09 (2H, d, *J* = 9.0, 2 × ArH), 7.04 (2H, s, NH_2), 6.90 (2H, d, *J* = 8.8, 2 × ArH), 5.61 (1H, dd, *J* = 12.3, 5.1, CH), 3.93 (1H, dd, *J* = 17.8, 12.3, C*H*H), 3.70 (3H, s, OCH_3), 3.16 (1H, dd, *J* = 17.8, 5.1, CH*H*); ^{13}C NMR (150 MHz, DMSO-d_6) δ 158.6, 153.8, 145.7, 140.8, 131.7, 131.1, 127.9, 127.1, 127.0, 126.9, 122.4, 114.4, 112.2, 62.1, 55.0, 30.4; LRMS: (ES): 484 ([M-H]$^+$, 100), 460 (25); HRMS: Found (ES): [M-H]$^+$ 484.0330, $C_{22}H_{19}O_3N_3SBr$ requires 484.0313

4-(3-(4-Bromophenyl)-5-(4-hydroxy-3-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)benzenesulfonamide (37h)



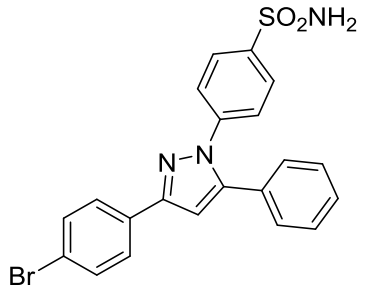
General Procedure D: Oxidation with DDQ

Orange oil, 185 mg, 37%; ν_{max} (film/cm^{-1}) 3489 (O-H), 3247 (N-H), 1593 (C=C), 1518 (C=C), 1301 (S=O), 1146 (S=O); ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 9.02 (1H, s, OH), 7.73 (2H, d, *J* = 8.5, 2 × ArH), 7.65 (2H, d, *J* = 8.5, 2 × ArH), 7.59 (2H, d, *J* = 8.9, 2 × ArH), 7.10 (2H, d, *J* = 8.9, 2 × ArH), 7.03 (2H, s, NH_2), 6.88 (1H, s, ArH), 6.69 (1H, d, *J* = 7.9, ArH), 6.57 (1H, d, *J* = 7.9, ArH), 5.50 (1H, dd, *J* = 12.1, 5.6, CH), 3.91 (1H, dd, *J* = 17.5, 12.1, C*H*H), 3.72 (3H, s, OCH_3), 3.18 (1H, dd, *J* = 17.5, 5.6, CH*H*); ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 148.7, 147.9, 145.99, 145.97, 133.2, 132.4, 131.7, 131.2, 128.0, 127.1, 122.4, 117.9, 115.9, 112.2, 110.1, 62.7, 55.6, 42.9; LRMS: (ES): 500 ([M-H]$^+$, 40), 283 (60), 255 (100), 212 (60); HRMS: Found (ES): [M-H]$^+$ 500.0280, $C_{22}H_{19}O_4N_3SBr$ requires 500.0293

General Procedure D: Oxidation with DDQ

Pyrazoline (1 eq.) and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (1.5 eq.) in PhMe (1M) were heated to 90 °C and stirred for 12 h. The solution was then concentrated under reduced pressure before purification by flash chromatography (EtOAc/petrol) to give the pyrazole.

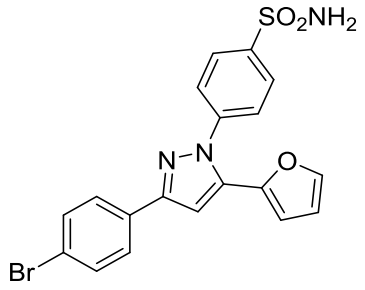
4-(3-(4-Bromophenyl)-5-phenyl-1*H*-pyrazol-1-yl)benzenesulfonamide (35a)



General Procedure D: Oxidation with DDQ

Brown solid, 35 mg, 59%, Mp 100 – 105 °C; ν_{max} (film/cm^{-1}) 3405 (N-H), 2926 (C-H), 1596 (C=C), 1485 (C=C), 1339 (S=O), 1162 (S=O); ^{1}H NMR (600Hz, DMSO-d$_6$) δ 7.90 (2H, d, *J* = 8.9, 2 × ArH), 7.84 (2H, d, *J* = 8.7, 2 × ArH), 7.67 (2H, d, *J* = 8.7, 2 × ArH), 7.52 (2H, d, *J* = 8.9, 2 × ArH), 7.49 (2H, s, NH$_2$), 7.41 - 7.45 (3H, m, 3 × ArH), 7.31 - 7.35 (2H, m, 2 × ArH), 7.26 (1H, s, CH on pyrazole); ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 150.7, 144.7, 142.9, 141.9, 131.8, 131.6, 129.6, 129.0, 128.9, 128.7, 127.5, 126.7, 125.2, 121.5, 106.5; LRMS: (EI): 453 ([M]$^+$,100); HRMS: Found (EI): [M]$^+$ $C_{21}H_{16}O_2N_3SBr$ 453.01461, requires 453.01411

4-(3-(4-Bromophenyl)-5-(furan-2-yl)-1*H*-pyrazol-1-yl)benzenesulfonamide (35b)

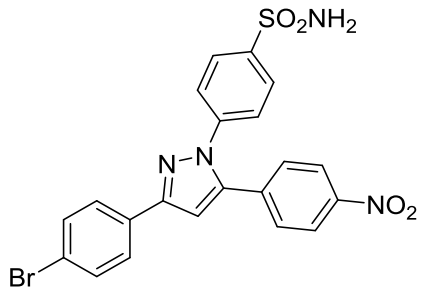


General Procedure D: Oxidation with DDQ

Orange oil, 30 mg, 37%; ν_{max} (film/cm^{-1}) 3040 (C-H), 1595 (C=C), 1499 (C=C), 1342 (S=O), 1162 (S=O); ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 7.94 (2H, d, *J* = 8.7, 2 × ArH), 7.89 (2H, d, *J* = 8.7, 2 × ArH), 7.79 (1H, d, *J* = 1.7, OCCH), 7.67 (2H, d, *J* = 8.3, 2 × ArH), 7.65 (2H, d, *J* = 8.3, 2 × ArH), 7.54 (2H, s, NH$_2$), 7.37 (1H, s, CH on pyrazole), 6.62 (1H, dd, *J* = 3.4, 1.7, OCCH), 6.48 (1H, d, *J* = 3.4, OCHC*H*); ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 150.8, 144.3, 143.6, 142.8, 142.1, 135.4, 131.9, 131.2, 127.6, 126.8, 125.3, 121.7, 111.9, 110.6, 105.3; LRMS: (CI): 444

([M+H]$^+$, 30), 366 (100%); HRMS: Found (CI): [M+H]$^+$ 444.00150, $C_{19}H_{15}O_3N_3SBr$ requires 444.00175

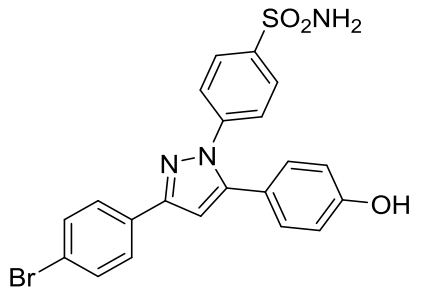
4-(3-(4-Bromophenyl)-5-(4-nitrophenyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (35c)



General Procedure D: Oxidation with DDQ

Brown oil, 15 mg, 94%; ν_{max} (film/cm^{-1}) 3252 (N-H), 2923 (C-H), 1595 (C=C), 1515, 1342 (S=O), 1148 (S=O); ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 8.27 (2H, d, *J* = 8.9, 2 × ArH), 7.90 (2H, d, *J* = 8.7, 2 × ArH), 7.87 (2H, d, *J* = 8.7, 2 × ArH), 7.68 (2H, d, *J* = 8.7, 2 × ArH), 7.60 (2H, d, *J* = 8.9, 2 × ArH), 7.55 (2H, d, *J* = 8.7, 2 × ArH), 7.52 (2H, s, NH_2), 7.44 (1H, s, CH on pyrazole); ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 151.0, 147.3, 143.2, 142.6, 141.5, 135.8, 131.9, 131.2, 129.9, 127.0, 125.4, 124.0, 121.8, 107.7; LRMS: (ES): 497 ([M-H]$^+$, 100); HRMS: Found (ES): [M-H]$^+$ 496.9944, $C_{21}H_{14}O_4N_4SBr$ requires 496.9919

4-(3-(4-Bromophenyl)-5-(4-hydroxyphenyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (35d)

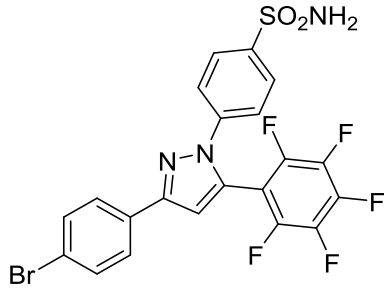


General Procedure D: Oxidation with DDQ

Orange solid, 33 mg, 83%; Mp 224 – 228 °C; ν_{max} (film/cm^{-1}) 3265 (N-H), 2920 (C-H), 1596 (C=C), 1492 (C=C), 1341 (S=O), 1162 (S=O); ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 9.82 (1H, s, OH), 7.89 (2H, d, *J* = 8.7, 2 × ArH), 7.85 (2H, d, *J* = 8.7, 2 × ArH), 7.66 (2H, d, *J* = 8.3, 2 × ArH), 7.52

(2H, d, *J* = 8.3, 2 × ArH), 7.45 (2H, s, NH_2), 7.12 (1H, s, CH on pyrazole), 7.13 (2H, d, *J* = 8.1, 2 × ArH), 6.80 (2H, d, *J* = 8.1, 2 × ArH); ^{13}C NMR (150 MHz, DMSO-d_6) δ 158.0, 150.5, 145.0, 142.6, 142.1, 131.79, 131.75, 130.1, 127.5, 126.6, 125.0, 121.4, 120.2, 115.6, 105.7; LRMS: (ES): 470 ([M+H]$^+$, 100), 454 (30), 180 (60); HRMS: Found (ES): [M+H]$^+$ 470.0157, $C_{21}H_{17}O_2N_3SBr$ requires 470.0174

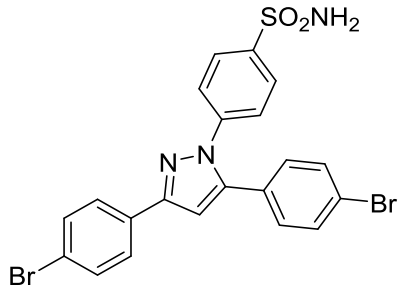
4-(3-(4-Bromophenyl)-5-(perfluorophenyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (35e)



General Procedure D: Oxidation with DDQ

Brown oil, 10 mg, 63%; ν_{max} (film/cm^{-1}) 3046 (C-H), 1596 (C=C), 1492 (C=C), 1162 (S=O), 988; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.91 (2H, d, *J* = 8.7, 2 × ArH), 7.87 (2H, d, *J* = 8.7, 2 × ArH), 7.69 (2H, d, *J* = 8.7, 2 × ArH), 7.65 (2H, d, *J* = 8.7, 2 × ArH), 7.53 (2H, s, NH_2), 7.47 (1H, s, CH on pyrazole); ^{13}C NMR (150 MHz, DMSO-d_6) δ 151.4, 143.2, 141.2, 132.0, 130.8, 128.5, 127.7, 127.2, 123.3, 122.0, 109.9 peaks missing/broad peaks dues to coupling with ^{19}F nuclei; LRMS: (ES): 554 ([M+H]$^+$, 100); HRMS: Found (ES): [M+H]$^+$ 543.9723, $C_{21}H_{12}O_2F_5N_3SBr$ requires 543.9754

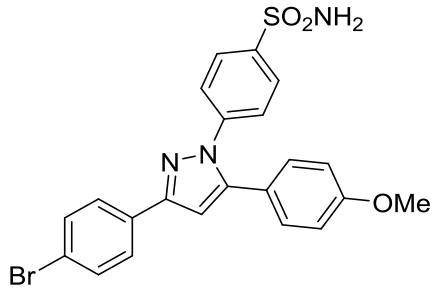
4-(3,5-Bis(4-bromophenyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (35f)



General Procedure D: Oxidation with DDQ

Orange solid, 32 mg, 79%; Mp 238 – 240 °C; ν_{max} (film/cm^{-1}) 3189 (N-H), 3058 (C-H), 1595 (C=C), 1480 (C=C), 1338 (S=O), 1161 (S=O); ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 7.90 (2H, d, *J* = 8.7, 2 × ArH), 7.87 (2H, d, *J* = 8.7, 2 × ArH), 7.68 (2H, d, *J* = 8.7, 2 × ArH), 7.65 (2H, d, *J* = 8.7, 2 × ArH), 7.54 (2H, d, *J* = 8.7, 2 × ArH), 7.49 (2H, s, NH_2), 7.31 (1H, s, CH on pyrazole), 7.28 (2H, d, *J* = 8.7, 2 × ArH); ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 150.8, 143.5, 143.0, 141.7, 131.87, 131.86, 131.5, 130.7, 128.8, 127.5, 126.8, 125.3, 122.5, 121.6, 106.8; LRMS: (ES): 530 ([M-H]$^+$, 30), 495 (50), 481 (100); HRMS: Found (ES): [M-H]$^+$ 529.9173, $C_{21}H_{14}O_2N_3SBr_2$ requires 529.9185

4-(3-(4-Bromophenyl)-5-(4-methoxyphenyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (35g)

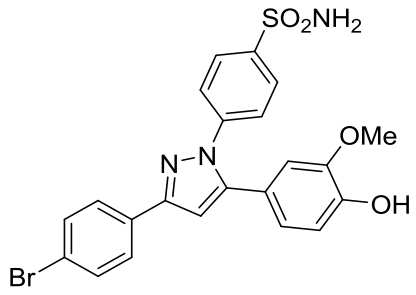


General Procedure D: Oxidation with DDQ

Orange oil, 30 mg, 35%; ν_{max} (film/cm^{-1}) 3424 (N-H), 3045 (C-H), 1591 (C=C), 149 (C=C), 1335 (S=O), 1163 (S=O); ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 7.89 (2H, d, *J* = 8.7, 2 × ArH), 7.85 (2H, d, *J* = 8.7, 2 × ArH), 7.67 (2H, d, *J* = 8.7, 2 × ArH), 7.53 (2H, d, *J* = 8.7, 2 × ArH), 7.47 (2H, s, NH_2), 7.26 (2H, d, *J* = 8.7, 2 × ArH), 7.18 (1H, s, CH on pyrazole), 6.99 (2H, d, *J* = 8.7, 2 × ArH), 3.78 (3H, s, OCH_3); ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 159.6, 150.6, 144.6, 142.7, 142.1, 131.8,

131.7, 130.1, 127.5, 126.7, 125.1, 121.8, 121.4, 114.3, 106.0, 55.3; LRMS: (ES): 482 ($[M-H]^+$, 100), 460 (25); HRMS: Found (ES): $[M-H]^+$ 482.0174, $C_{22}H_{17}O_3N_3SBr$ requires 482.0182

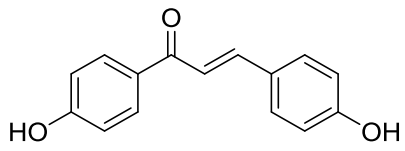
4-(3-(4-Bromophenyl)-5-(4-hydroxy-3-methoxyphenyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (35h)



General Procedure C: Acetophenone to pyrazoline

Orange solid, 15 mg, 18%; Mp 206 – 208 °C; ν_{max} (film/cm^{-1}) 3296 (O-H, broad), 2976 (C-H), 1596 (C=C), 1495 (C=C), 1341 (S=O), 1162 (S=O); ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.43 (1H, s, OH), 7.89 (2H, d, *J* = 8.3, 2 × ArH), 7.86 (2H, d, *J* = 8.3, 2 × ArH), 7.67 (2H, d, *J* = 8.3, 2 × ArH), 7.53 (2H, d, *J* = 8.7, 2 × ArH), 7.48 (2H, s, NH_2), 7.18 (1H, s, CC*H*COMe), 6.85 (1H, s, CH on pyrazole), 6.78 (1H, d, *J* = 8.0, CHC*H*COH), 6.68 (1H, dd, *J* = 8.0, 1.7, C*H*CHCOH), 3.63 (3H, s, OCH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ 150.4, 147.5, 147.3, 145.1, 142.7, 142.2, 131.80, 131.77, 127.5, 126.6, 125.2, 121.6, 121.4, 120.3, 115.7, 112.8, 105.6, 55.5; LRMS: (ES): 498 ($[M-H]^+$, 10), 482 (20), 283 (20), 255 (60), 212 (100); HRMS: Found (ES): $[M-H]^+$ 498.0123, $C_{22}H_{17}O_4N_3SBr$ requires 498.0115

(*E*)-1,3-Bis(4-hydroxyphenyl)prop-2-en-1-one (40)[94]

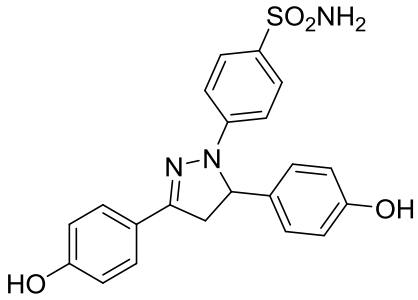


$BF_3.OEt_2$ (0.43 mL, 3.5 mmol) was added over 5 mins to a solution of 4-Hydroxyacteophenone (953 mg, 7.0 mmol) and 4-hydroxybenzaldehyde (855 mg, 7.0 mmol) in dioxane (3 mL) and stirred at RT for 3 h. Et_2O (40 mL) was added before the solution was washed with water (3 × 45 mL), dried ($MgSO_4$) and filtered. The solvent was

removed under reduced pressure and the residue was purified by flash chromatography (EtOAc/Petrol) to give the chalcone **40**.

Orange powder, 960 mg, 57%; Mp 200 – 202 °C [196 – 198 °C][94]; ν_{max} (film/cm^{-1}) 3289 (O-H), 2011 (C-H), 1641 (C=O), 1581 (C=C), 1544 (C=C); ^{1}H NMR (600 MHz, MeOD) δ 7.99 (2H, d, *J* = 8.7, 2 × ArH), 7.70 (1H, d, *J* = 15.4 CH), 7.58 (2H, d, *J* = 8.7, 2 × ArH), 7.55 (1H, d, 15.4, CH), 6.89 (2H, d, *J* = 8.7, 2 × ArH), 6.84 (2H, d, *J* = 8.7, 2 × ArH), 4.95 (2H, br. s, OH); ^{13}C NMR (150 MHz, MeOD) δ 191.1, 163.8, 161.5, 145.8, 132.3, 131.7, 131.2, 127.9, 119.5, 116.9, 116.4; LRMS: (EI): 240 ([M]$^{+}$, 100), 121 (40); HRMS: Found (EI): [M]$^{+}$ 240.077980, $C_{15}H_{12}O_3$ requires 240.07810

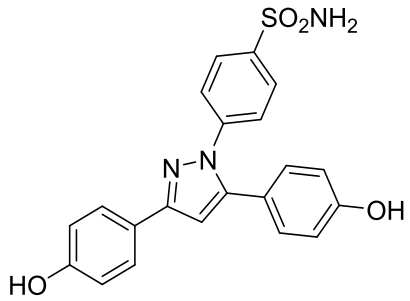
4-(3,5-Bis(4-hydroxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)benzenesulfonamide (41)



General Procedure C: Acetophenone to pyrazoline

Orange solid, 95 mg, 55%; Mp 163 – 167 °C; ν_{max} (film/cm^{-1}) 3316 (O-H, broad), 1590 (Ar), 1503 (Ar), 1151 (S=O); ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 9.88 (1H, s, OH), 9.42 (1H, s, OH), 7.62 (2H, d, *J* = 8.7, 2 × ArH), 7.55 (2H, d, *J* = 9.0, 2 × ArH), 7.04 (2H, d, *J* = 8.7, 2 × ArH), 7.01 (2H, d, *J* = 9.0, 2 × ArH), 6.99 (2H, s, NH_2), 6.83 (2H, d, *J* = 8.7, 2 × ArH), 6.70 (2H, d, *J* = 8.7, 2 × ArH), 5.44 (1H, dd, *J* = 12.0, 5.1, NCH), 3.85 (1H, dd, *J* = 17.4, 12.0, CHC*H*H), 3.07 (1H, dd, *J* = 17.4, 5.1, CHCH*H*); ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 158.8, 156.7, 150.0, 146.2, 132.2, 132.0, 127.8, 127.5, 127.1, 127.0, 115.7, 115.6, 111.7, 61.8, 43.2; LRMS: (CI): 409 ([M]$^{+}$, 100), 172 (sulfanilamide, 25), 156 (35); HRMS: Found (CI): [M]$^{+}$ 409.10944, $C_{21}H_{19}O_4N_3S$, requires 409.10908; anal. cald. For $C_{21}H_{19}O_4N_3S$ C, 61.60; H, 4.68; N, 10.26 Found: C, 59.30; H, 5.09; N, 9.20

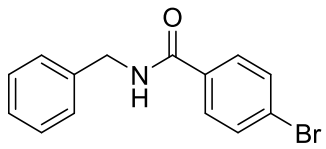
4-(3,5-Bis(4-hydroxyphenyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (42)



(*E*)-1,3-bis(4-hydroxyphenyl)prop-2-en-1-one **40** (100 Mg, 0.42 mmol) in EtOH (2 mL) was added 2-(4-Sulfamoylphenyl)hydrazin-1-ium chloride **33** (79 mg, 0.42 mmol) heated at 80 °C for 24 h. The solution was cooled to RT and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/Petrol 1:1). The pyrazoline was dissolved in AcOH (2 mL) and to this solution was added Pd on Carbon, under an atmosphere of O_2 at 80 °C for 2h. The solution was cooled and filtered through Celite washing with EtOAc and purified by flash chromatography (EtOAc/ petrol) to give pyrazole **42**.

Bright orange oily solid, 58 mg, 34% over 2 steps; ν_{max} (film/cm^{-1}) 3155 (O-H, broad), 1613 (Ar), 1592 (Ar), 1497 (Ar), 1155 (S=O); ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.83 (1H, br. s, OH), 9.65 (1H, br. s, OH), 7.83 (2H, d, *J* = 8.7, 2 × ArH), 7.73 (2H, d, *J* = 8.7, 2 × ArH), 7.48 (2H, d, *J* = 8.7, 2 × ArH), 7.45 (2H, s, NH_2), 7.12 (2 H, d, *J* = 8.3, 2 × ArH), 6.84 (2H, d, *J* = 8.7, 2 × ArH), 6.79 (2H, d, *J* = 8.3, 2 × ArH); ^{13}C NMR (150 MHz, DMSO-d_6) δ 157.9, 157.7, 151.9, 144.5, 142.4, 142.2, 130.1, 126.9, 126.6, 124.7, 123.5, 120.5, 115.6, 115.5, 105.1; LRMS: (CI): 407 ([M]$^+$, 100); HRMS: Found (CI): [M]$^+$ 407.09419, $C_{21}H_{17}O_4N_3S$, requires 407.09343

***N*-Benzyl-4-bromobenzamide (46)**[95]

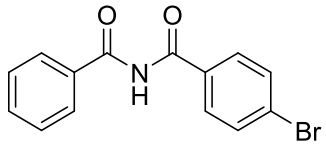


Benzylamine (0.99 mL) was dissolved in water (5 mL) and Na_2CO_3 (0.74 g) and the 4-bromobenzoyl chloride was added portionwise. The solution was stirred for 30 min then the product was extracted with DCM (3 x 10 mL) and dried ($MgSO_4$). This solution was then

put through a silica plug (DCM) and the solvent removed under reduced pressure to give amide **46**.

Fluffy white crystals, 695 mg, 69%; Mp 155-158 °C [160-163 °C][95]; ν_{max} (film/cm^{-1}) 3313 (N-H), 3029 (C-H), 1639 (C=O), 1549 (Ar), 1482 (Ar) 1320 (Ar); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (2H, d, *J* = 8.7, 2 × ArH), 7.57 (2H, d, *J* = 8.7, 2 × ArH), 7.30 - 7.40 (5H, m, 5 × ArH), 6.33 (1H, br. s, NH), 4.64 (2H, d, *J* = 5.7, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 146.7, 137.9, 133.3, 131.9, 129.0, 128.6, 128.1, 127.9, 44.4; LRMS: (EI): 289 ($[M]^+$, 80), 185 ($[BnNH_3]^+$, 100); HRMS: Found (EI): $[M]^+$ 289.009877, $C_{14}H_{12}BrNO$ requires 289.00968

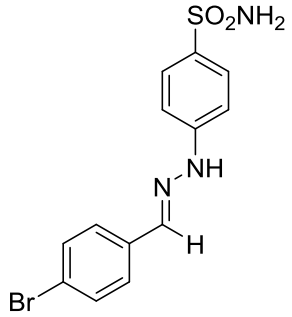
_N_-Benzoyl-4-bromobenzamide (44)[96]



A solution of CrO_3 in MeCN (0.1 mL, 0.05 mmol) was added to a stirring solution of periodic acid (1.1 g, 6.0 mmol) in MeCN (10 mL). After 30 min, acetic anhydride (614 mg, 6.0 mmol) was added dropwise then cooled to 0 °C and the amide **46** (290 mg, 1 mmol) added. After 18 h, water (10 mL) was added, before the product was extracted with EtOAc (2 x 10 mL). The combined organic fractions were washed with sat. $NaHCO_3$ (10 mL), sat $Na_2S_2O_3$ (10 mL) and brine (10 mL) before the solution was dried ($MgSO_4$) and solvent removed under reduced pressure. The residue was purified by flash chromatography (EtOAc/petrol) to give diimide **44**.

Colourless oil, 126 mg, 41%; ν_{max} (film/cm^{-1}) 3275 (N-H), 3065 (C-H), 1716 (C=O), 1676 (C=O), 1588 (Ar), 1466 (Ar); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.03 (1H, br. s., NH), 7.87 (2H, d, *J* = 8.7, 2 × ArH), 7.73 (2H, d, *J* = 8.7, 2 × ArH), 7.63 (3H, m, 3 × ArH), 7.51 (2H, t, *J* = 7.3, 2 × ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.49, 166.45, 133.4, 133.1, 132.3, 132.1, 129.8, 129.0, 128.2, 128.1; LRMS: (EI): 303 ($[M]^+$, 20), 185 ($[BnNH_3]^+$, 30), 105 (30); HRMS: Found (EI): $[M]^+$ 302.989417, $C_{14}H_{10}BrNO_2$ requires 302.98894

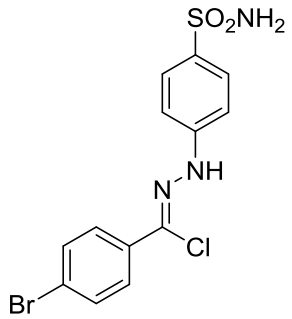
(*E*)-4-(2-(4-Bromobenzylidene)hydrazinyl)benzenesulfonamide (51)



2-(4-Sulfamoylphenyl)hydrazin-1-ium chloride (258 mg, 3.0 mmol) and 4-bromobenzaldehyde (295 mg, 1.5 mmol) in EtOH were heated at reflux for 2 h after which the reaction was cooled and the product crystallised out to give hydrazone **51**.

Orange powder, 515 mg, 98%; Mp 167 – 170 °C; ν_{max} (film/cm^{-1}) 3270 (N-H), 1594 (Ar), 1487 (Ar), 1326 (S=O), 1146 (S=O); ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 10.90 (1H, s, CHN), 7.91 (1H, s, NH), 7.67 (2H, d, *J* = 8.9, 2 × ArH), 7.65 (2H, d, *J* = 8.7, 2 × ArH), 7.60 (2H, d, *J* = 8.9, 2 × ArH), 7.15 (2H, d, *J* = 8.7, 2 × ArH), 7.10 (2H, s, NH$_2$); ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 147.6, 137.7, 134.6, 133.8, 131.7, 127.9, 127.5, 121.5, 111.3; LRMS: (ES): 352 ([M-H]$^+$, 100); HRMS: Found (ES): [M-H]$^+$ 351.9755, $C_{13}H_{11}O_2N_3SBr$ requires 351.9755

(*Z*)-4-Bromo-*N*-(4-sulfamoylphenyl)benzohydrazonoyl chloride (52)

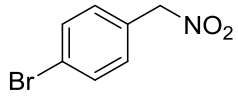


Dimethylsulfide (177 mg, 1.33 mmol) was added dropwise to an ice-cold dry solution of *N*-chlorosuccinimide (165 mg, 2.63 mmol in anhydrous DCM (3 mL). After 30 mins the solution was cooled to -78 °C and a solution of (*E*)-4-(2-(4-Bromobenzylidene)hydrazinyl)benzenesulfonamide (156 mg, 0.44 mmol) in anhydrous DCM (3 mL) was added dropwise over 10 mins. After the addition, the solution was stirred at this temperature for 1 h before warming to RT and allowed to stir for 18 h. The solution

was washed with water and brine before being dried ($MgSO_4$) and purified by flushing through a silica pad (EtOAc/petrol) to give hydrazonyl chloride **52**.

Off white solid, 35 mg, 20%; Mp 195 – 199 °C; ν_{max} (film/cm^{-1}) 3345 (NH), 3322 (NH), 3253 (NH), 2922 (C-H), 1597 (Ar), 1510 (Ar), 1316 (S=O), 1137 (S=O); ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.39 (1H, s, NH), 7.87 (2H, d, J = 8.7, 2 × ArH), 7.72 (2H, d, J = 9.0, 2 × ArH), 7.69 (2H, d, J = 8.7, 2 × ArH), 7.47 (2H, d, J = 9.0, 2 × ArH), 7.18 (2H, s, NH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ 146.6, 135.7, 133.2, 131.8, 128.2, 127.3, 123.5, 123.1, 113.2; LRMS: (ES): 386 ([M-H]$^+$, 100); HRMS: Found (ES): [M-H]$^+$ 385.9368, $C_{13}H_{10}O_2N_3ClSBr$ requires 385.9366

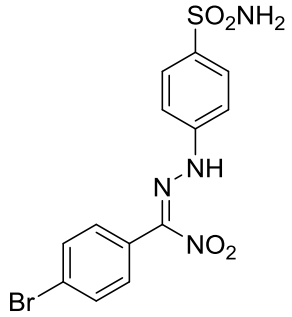
1-Bromo-4-(nitromethyl)benzene (57)[49]



$AgNO_2$ was added to a solution of bromobenzylbromide in Et_2O (20 mL). The solution was stirred in the dark for 18 h before filtering off AgBr and solvent removed from the filtrate under reduced pressure. The residue was purified by flash chromatography (EtOAc/petrol) to give nitro-compound **57**.

White crystals, 720 mg, 55%; Mp 54 – 56 °C, [55 – 56 °C][49]; ν_{max} (film/cm^{-1}) 1552 (Ar), 1588 (Ar), 1370; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (2H, d, J = 8.4, 2 × ArH), 7.34 (2H, d, J = 8.4, 2 × ArH), 5.39 (2H, s, CH_2); ^{13}C NMR (125MHz, $CDCl_3$) δ 132.4, 131.7, 128.6, 124.7, 79.3; LRMS: (CI): 169 ([M-NO_2]$^+$, 100)

(*Z*)-4-(2-((4-Bromophenyl)(nitro)methylene)hydrazinyl)benzenesulfonamide (58)



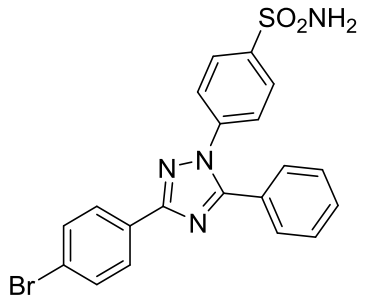
Sulfanilamide (992 mg, 5.8 mmol) was added to a stirring conc. HCl (5 mL) at RT then cooled to -5 °C. A solution of $NaNO_2$ (415 mg, 6.02 mmol) in water (3 mL) was added to the sulfanilamide solution dropwise over 5 min, then allowed to stir for 30 mins. NaOAc (4.7 g, 58 mmol) was then added one portion and stirred vigorously. Then an aliquot of the solution (7.5 mL) was added to a solution of nitrobenzene **57** (300 mg, 1.40 mmol) and NaOH (58 mg, 1.4 mmol) in a solution of EtOH/H_2O (30 mL, 4:1). The solution was allowed to stir for 1 h before the precipitate was filtered and the solid was dried to give nitrohydrazone **58**.

Orange solid; 437 mg, 79%; Mp 165 – 167 °C; ν_{max} (film/cm^{-1}) 3385 (N-H), 3265 (N-H), 1549 (Ar), 1492 (Ar), 1143 (S=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.03 (1H, s, NH) 7.97 (2H, d, *J* = 8.2, 2 × ArH) 7.63 (2H, d, *J* = 8.6, 2 × ArH) 7.57 (2H, d, *J* = 8.6, 2 × ArH) 7.45 (2H, d, *J* = 8.2, 2 × ArH) 4.76 (2H, s, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.7, 143.4, 142.4, 131.9, 130.1, 127.6, 127.3, 124.0, 116.9; LRMS: (ES): 497 ([M-H]$^+$, 10), 369 (100); HRMS: Found (ES): [M-H]$^+$ 396.9619, $C_{13}H_{10}N_4O_4SBr$ requires 396.9606

General Procedure E: Triazole formation

To hydrazonyl chloride/nitrohydrazone in MeCN (1M), was added triethylamine (NEt_3) (1.2 eq.) and primary amine (1.2 eq.) and stirred at RT for 15 h. The solvent was removed under reduced pressure before addition of MeCN (2 mL) followed by tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine oxide (NMO) and stirred for 3 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (EtOAc/petrol).

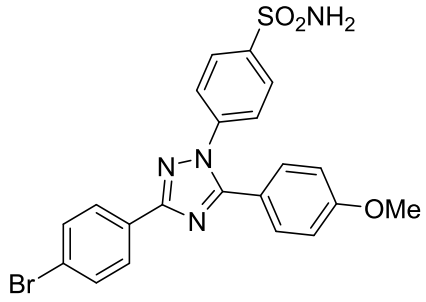
4-(3-(4-Bromophenyl)-5-phenyl-1*H*-1,2,4-triazol-1-yl)benzenesulfonamide (54a)



General Procedure E: Triazole formation

Yellow solid, 23 mg, 50%; Mp 182 – 186 °C; ν_{max} (film/cm^{-1}) 3315 (N-H), 2922 (C-H), 1599 (Ar), 1484 (Ar), 1342 (S=O), 1162 (S=O); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.06 (2H, d, *J* = 8.4, 2 × ArH), 7.92 (2H, d, *J* = 8.5, 2 × ArH), 7.73 (2H, d, *J* = 8.4, 2 × ArH), 7.67 (2H, d, *J* = 8.5, 2 × ArH), 7.53 (2H, s, NH_2), 7.43 - 7.55 (5H, m, 5 × ArH); ^{13}C NMR (125 MHz, DMSO-d$_6$) δ 160.2, 155.1, 144.3, 140.0, 132.0, 130.5, 129.4, 128.9, 128.8, 128.0, 127.3, 127.0, 126.0, 123.1; LRMS: (CI): 454 ([M]$^+$, 100), 353 (25), 170 (35), 106 (100); HRMS: Found (CI): [M]$^+$ 454.010788, $C_{20}H_{15}O_2N_4SBr$ requires 454.00991; anal. cald. For $C_{20}H_{15}O_2N_4SBr$ C, 50.97; H, 3.21; N, 11.89; Found: C, 48.63; H, 3.85; N, 10.69

4-(3-(4-Bromophenyl)-5-(4-methoxyphenyl)-1*H*-1,2,4-triazol-1-yl)benzenesulfonamide (54b)

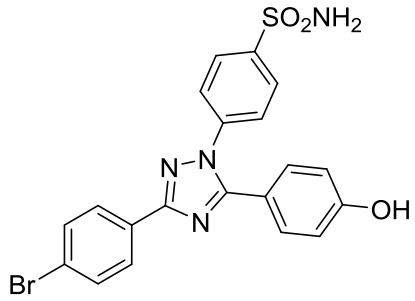


General Procedure E: Triazole formation

Yellow solid, 19 mg, 40%; Mp 290 – 294 °C; ν_{max} (film/cm^{-1}) 3400 (N-H), 1655 (Ar), 1023 (S=O); ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 8.05 (2H, d, *J* = 8.3, 2 × ArH), 7.94 (2H, d, *J* = 8.5, 2 × ArH), 7.73 (2H, d, *J* = 8.3, 2 × ArH), 7.69 (2H, d, *J* = 8.5, 2 × ArH), 7.56 (2H, s, NH_2), 7.47 (2H, d, *J* = 8.7, 2 × ArH), 7.02 (2H, d, *J* = 8.7, 2 × ArH) 3.80 (3H, s, CH_3); ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 160.8, 160.1, 155.0, 144.3, 140.3, 132.0, 130.5, 129.5, 128.1, 127.1, 126.0,

123.1, 119.4, 114.3, 55.4; LRMS: (CI): 485 ([M+H]$^+$, 30), 173 (35), 85 (100); HRMS: Found (CI): [M+H]$^+$ 485.026337, $C_{21}H_{18}O_3N_4SBr$ requires 485.02830

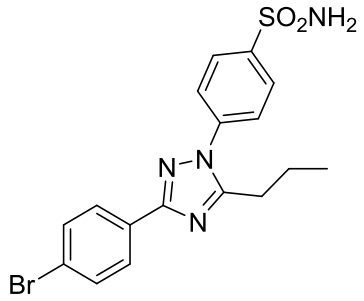
4-(3-(4-Bromophenyl)-5-(4-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl)benzenesulfonamide (54c)



General Procedure E: Triazole formation

Yellow solid, 50 mg, 42%; Mp 250 – 252 °C; ν_{max} (film/cm^{-1}) 3310 (N-H), 2923 (C-H), 1590 (Ar), 1337 (S=O), 1157 (S=O); ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 10.11 (1H, s, OH), 8.04 (2H, d, *J* = 8.3, 2 × ArH), 7.93 (2H, d, *J* = 8.7, 2 × ArH), 7.73 (2H, d, *J* = 8.3, 2 × ArH), 7.67 (2H, d, *J* = 8.7, 2 × ArH), 7.55 (2H, s, NH$_2$), 7.35 (2H, d, *J* = 8.7, 2 × ArH), 6.81 (2H, d, *J* = 8.7, 2 × ArH); ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 160.0, 159.4, 155.4, 144.1, 140.3, 132.0, 130.6, 129.6, 128.1, 127.0, 126.0, 123.0, 117.7, 115.6; LRMS: (CI): 471 ([M+H]$^+$, 100), 219 (20); HRMS: Found (CI): [M+H]$^+$ 471.009846, $C_{20}H_{16}O_3N_4SBr$ requires 471.01210

4-(3-(4-Bromophenyl)-5-propyl-1*H*-1,2,4-triazol-1-yl)benzenesulfonamide (54d)

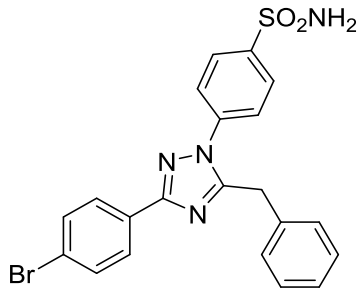


General Procedure E: Triazole formation

Yellow solid, 24 mg, 29%; Mp 204 – 208 °C; ν_{max} (film/cm^{-1}) 3321 (N-H), 3073 (C-H), 1597 (Ar), 1497 (Ar), 1340 (S=O), 1161 (S=O); ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 8.02 (2H, d, *J* = 8.7,

2 × ArH), 7.99 (2H, d, *J* = 8.5, 2 × ArH), 7.87 (2H, d, *J* = 8.7, 2 × ArH), 7.70 (2H, d, *J* = 8.5, 2 × ArH), 7.58 (2H, s, NH_2), 2.87 (2H, t, *J* = 7.5, $C(N)CH_2$), 1.75 (2H, sxt, *J* = 7.5, CH_2CH_3), 0.92 (3H, t, *J* = 7.5, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ 159.7, 157.4, 144.1, 139.4, 131.9, 129.7, 128.0, 127.1, 125.3, 122.9, 28.0, 20.3, 13.6; LRMS: (CI): 421 ($[M+H]^+$, 100), 343 (10); HRMS: Found (CI): $[M+H]^+$ 421.032564, $C_{17}H_{18}O_2N_4SBr$ requires 421.03338

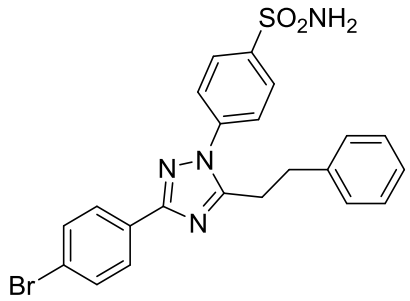
4-(5-Benzyl-3-(4-bromophenyl)-1*H*-1,2,4-triazol-1-yl)benzenesulfonamide (54e)



General Procedure E: Triazole formation

Yellow solid, 38 mg, 45%; Mp 203 – 205 °C; ν_{max} (film/cm^{-1}) 3365 (N-H), 3266 (N-H), 1595 (Ar), 1494 (Ar), 1328 (S=O), 1157 (S=O); ^1H NMR (600 MHz, DMSO-d_6) δ 7.99 (2H, d, *J* = 8.7, 2 × ArH), 7.98 (2H, *J* = 8.3, 2 × ArH), 7.83 (2H, d, *J* = 8.7, 2 × ArH), 7.70 (2H, d, *J* = 8.3, 2 × ArH), 7.57 (2H, s, NH_2), 7.28 (2H, t, *J* = 7.3, 2 × ArH), 7.22 (1H, t, *J* = 7.3, ArH), 7.17 (2H, d, *J* = 7.3, 2 × ArH), 4.34 (2H, s, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ 159.9, 156.1, 144.3, 139.3, 135.8, 132.0, 129.5, 128.7, 128.6, 128.0, 127.1, 126.9, 125.4, 123.0, 32.1; LRMS: (CI): 469 ($[M]^+$, 100); HRMS: Found (CI): $[M]^+$ 469.030795, $C_{21}H_{17}O_2N_4SBr$ requires 469.03338

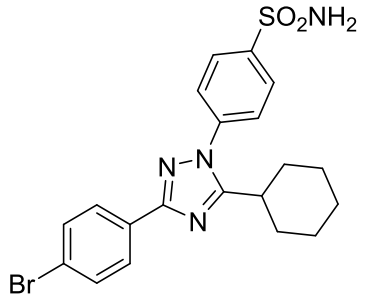
4-(3-(4-Bromophenyl)-5-phenethyl-1*H*-1,2,4-triazol-1-yl)benzenesulfonamide (54f)



General Procedure E: Triazole formation

Orange powder, 32 mg, 33%; Mp 184 – 186 °C; ν_{max} (film/cm^{-1}) 3282 (N-H), 3015 (C-H), 1495 (Ar), 1332 (S=O), 1159 (S=O); ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 8.02 (2H, d, *J* = 8.7, 2 × ArH), 7.98 (2H, d, *J* = 8.7, 2 × ArH), 7.74 (2H, d, *J* = 8.5, 2 × ArH), 7.72 (2H, d, *J* = 8.5, 2 × ArH), 7.56 (2H, s, NH_2), 7.23 - 7.27 (2H, m, 2 × ArH), 7.16 - 7.20 (3H, m, 3 × ArH), 3.19 (2H, t, *J* = 7.8, C(N)CH_2), 3.09 (2H, t, *J* = 7.8, PhCH_2); ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 159.7, 156.8, 144.1, 140.3, 139.3, 132.0, 129.6, 128.44, 128.38, 128.0, 127.1, 126.3, 125.2, 122.9, 32.7, 28.2; LRMS: (CI): 483 ([M+H]$^+$, 100), 111 (55); HRMS: Found (CI): [M+H]$^+$ 483.047112, $C_{22}H_{20}O_2N_4SBr$ requires 483.04903

4-(3-(4-Bromophenyl)-5-cyclohexyl-1*H*-1,2,4-triazol-1-yl)benzenesulfonamide (54g)

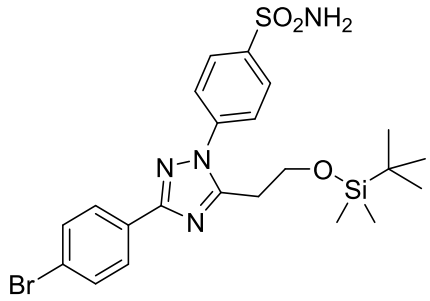


General Procedure E: Triazole formation

Brown solid, 32 mg, 35%,; Mp 209 – 214 °C; ν_{max} (film/cm^{-1}) 3354 (N-H), 2930 (C-H), 1495 (Ar), 1336 (S=O), 1163 (S=O); ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 8.03 (2H, d, *J* = 8.5, 2 × ArH), 7.98 (2H, d, *J* = 8.7, 2 × ArH), 7.84 (2H, d, *J* = 8.5, 2 × ArH), 7.69 (2H, d, *J* = 8.7, 2 × ArH), 7.59 (2H, s, NH_2), 2.87 (2H, tt, *J* = 11.5, 3.5, C*H*(CH_2)$_2$), 1.89 (2H, br. d, *J* = 12.8, 2 × cyclohexylCH), 1.72 - 1.78 (2H, m, 2 × cyclohexylCH), 1.58 - 1.68 (3H, m, 3 × cyclohexylCH), 1.26 (3H, br. s, 3 × cyclohexylCH); ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 161.3, 159.7, 144.4, 139.4, 131.9, 129.7,

128.0, 127.2, 125.9, 122.8, 34.7, 31.2, 25.3, 14.1; LRMS: (CI): 461 ([M]$^+$, 100); HRMS: Found (CI): [M]$^+$ 461.063421, $C_{20}H_{21}O_2N_4SBr$ requires 461.0646

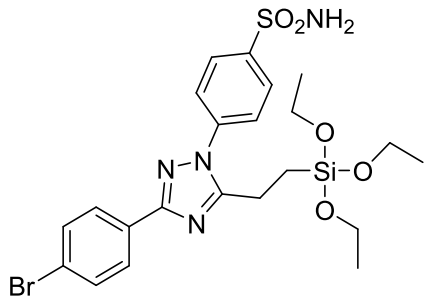
4-(3-(4-Bromophenyl)-5-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1*H*-1,2,4-triazol-1-yl)benzenesulfonamide (54h)



General Procedure E: Triazole formation

Yellow solid, 36 mg, 34%; Mp 175 – 178 °C; ν_{max} (film/cm^{-1}) 3262 (N-H), 2927 (C-H), 1598 (Ar), 1333 (S=O), 1156 (S=O); ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 8.03 (2H, d, *J* = 8.5, 2 × ArH), 7.99 (2H, d, *J* = 8.6, 2 × ArH), 7.90 (2H, d, *J* = 8.5, 2 × ArH), 7.71 (2H, d, *J* = 8.6, 2 × ArH), 7.57 (2H, s, NH_2), 4.04 (2H, t, *J* = 6.1, OCH_2), 3.10 (2H, t, *J* = 6.1, OCH_2CH_2), 0.73 (9H, s, $C(CH_3)_3$), -0.07 (6H, s, 2 × $SiCH_3$); ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 159.9, 155.7, 144.2, 139.4, 132.0, 129.6, 127.9, 127.1, 125.3, 122.9, 61.1, 29.7, 25.6, 17.9, -5.5; LRMS: (CI): 537 ([M+H]$^+$, 100), 481 (65); 414 (25), 219 (25); HRMS: Found (CI): [M+H]$^+$ 537.099346, $C_{22}H_{30}O_3N_4SBrSi$ requires 537.09913

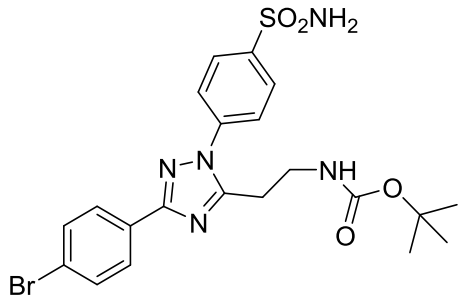
Amino(4-(3-(4-bromophenyl)-5-(2-(triethoxysilyl)ethyl)-1*H*-1,2,4-triazol-1-yl)phenyl)(l1-oxidanyl)-l5-sulfanone (54i)



General Procedure E: Triazole formation

Pink solid, 17 mg, 15%; Mp 118 – 121 °C; ν_{max} (film/cm^{-1}) 3266 (N-H), 2975 (C-H), 1596 (Ar), 1492 (Ar), 1404 (S=O), 1067 (S=O); ^{1}H NMR (600 Hz, DMSO-d$_6$) δ 8.02 (2H, d, *J* = 8.7, 2 × ArH), 7.99 (2H, d, *J* = 8.5, 2 × ArH), 7.86 (2H, d, *J* = 8.7, 2 × ArH), 7.70 (2H, *J* = 8.5, 2 × ArH), 7.58 (2H, s, NH_2), 3.68 (6H, q, *J* = 7.2, 3 × OCH_2), 2.88 - 2.94 (2H, m, $CNCH_2$), 1.05 (2H, m, $SiCH_2$), 1.07 (9H, t, *J* = 7.2, 3 × CH_3); ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 159.6, 158.7, 144.2, 139.4, 131.9, 129.7, 127.9, 127.0, 125.4, 122.8, 57.8, 20.1, 18.1, 8.1; LRMS: (CI): 569 ([M]$^+$, 100), 525 (70); HRMS: Found (CI): [M]$^+$ 569.086787, $C_{22}H_{29}O_5N_4SBrSi$ requires 569.0889

***Tert*-butyl (2-(3-(4-bromophenyl)-1-(4-sulfamoylphenyl)-1*H*-1,2,4-triazol-5-yl)ethyl)carbamate (54j)**

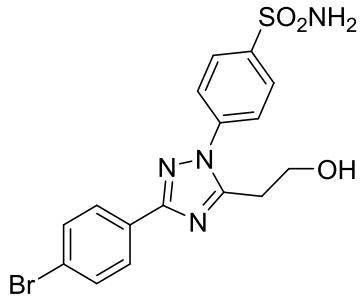


General Procedure E: Triazole formation

Red solid, 131 mg, 35%; Mp 97 – 98 °C; ν_{max} (film/cm^{-1}) 3251 (N-H), 2976 (C-H), 1685 (C=O), 1497 (Ar), 1335 (S=O), 1158 (S=O); ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 8.01 (2H, d, *J* = 9.1, 2 × ArH), 8.00 (2H, d, *J* = 8.9, 2 × ArH), 7.86 (2H, d, *J* = 9.1, 2 × ArH), 7.71 (2 H, d, *J* = 8.9, 2 × ArH), 7.58 (2H, s, NH_2), 6.99 (1H, t, *J* = 5.8, NH), 3.36 (2H, q, *J* = 7.1, NHC*H*$_2$), 3.01 (2H, t, *J* =

7.1, $NHCH_2CH_2$), 1.32 (9H, $C(CH_3)_3$); ^{13}C NMR (150 MHz, DMSO-d_6) δ 159.7, 155.6, 155.4, 144.1, 139.3, 131.9, 129.7, 128.0, 127.1, 125.3, 122.9, 77.8, 38.0, 28.2, 27.1; LRMS: (CI): 522 ($[M]^+$, 20), 468 (100); HRMS: Found (CI): $[M]^+$ 522.081428, $C_{21}H_{24}O_4N_5SBr$ requires 522.08106

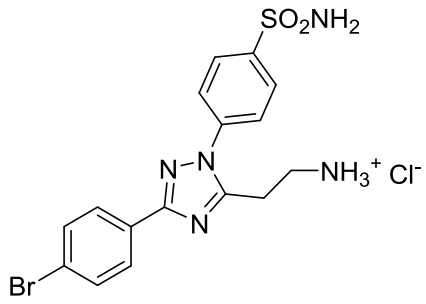
4-(3-(4-bromophenyl)-5-(2-hydroxyethyl)-1*H*-1,2,4-triazol-1-yl)benzenesulfonamide (59h)



TBAF (1M in THF, 0.136 mL, 0.136 mmol) was added to a stirring solution of **54h** (31 mg, 0.068 mmol) in THF (1 mL). After 20 min the solvent was removed under reduced pressure before the residue was purified by flash chromatography (EtOAc) to give alcohol **59h**.

Yellow powder, 20 mg, 70%; Mp 249 – 252 °C; ν_{max} (film/cm^{-1}) 3380 (O-H, broad), 1460 (Ar), 993; ^1H NMR (600 MHz, DMSO-d_6) δ 8.02 (2H, d, J = 8.7, 2 × ArH), 8.00 (2H, d, J = 8.3, 2 × ArH), 7.91 (2H, d, J = 8.7, 2 × ArH), 7.71 (2H, d, J = 8.3, 2 × ArH), 7.58 (2H, s, NH_2), 4.92 (1H, t, J = 5.3, OH), 3.83 (2H, q, J = 6.4, OCH_2), 3.03 (2H, t, J = 6.4, OCH_2CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ 159.8, 155.9, 144.2, 139.4, 131.9, 129.7, 128.0, 127.0, 125.5, 122.9, 59.0, 30.0; LRMS: (CI): 422 ($[M-H]^+$, 100), 257 (25), 389 (25); HRMS: Found (CI): $[M-H]^+$ 423.011994, $C_{16}H_{15}O_3N_4SBr$ requires 423.01265

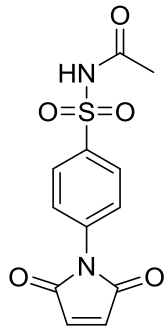
2-(3-(4-Bromophenyl)-1-(4-sulfamoylphenyl)-1*H*-1,2,4-triazol-5-yl)ethan-1-aminium chloride (59j)



HCl (4M in dioxane, 0.8 mL, 3.2 mmol) was added to solution of **59j** (107 mg, 0.2 mmol) in dioxane (2 mL) at 0 °C. After 1h stirring at RT the solvent was removed under reduced pressure to give hydrochloride salt **59j**.

Orange solid, 85 mg, 91%; Mp 109 – 114 °C; ν_{max} (film/cm^{-1}) N-H too broad, 2922 (C-H), 1594 (Ar), 1330 (S=O), 1159 (S=O); ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.24 (3H, br. s, NH_3), 8.05 (2H, d, *J* = 8.3, 2 × ArH), 8.04 (2H, d, *J* = 8.3, 2 × ArH), 7.89 (2H, d, *J* = 8.3, 2 × ArH), 7.72 (2H, d, *J* = 8.3, 2 × ArH), 7.64 (2H, s, NH_2), 3.30 (2H, m, NCH_2), 3.27 (2H, m, NCH_2CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ 159.8, 154.2, 144.3, 139.0, 132.0, 129.4, 128.1, 127.2, 125.2, 123.1, 36.5, 24.4; LRMS: (CI): 422 ([M]$^+$, 55), 394 (100), 219 (50), 121 (35); HRMS: Found (CI): [M]$^+$ 422.02796, $C_{16}H_{17}O_2N_5SBr$ requires 422.02863

***N*-((4-(2,5-Dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)phenyl)sulfonyl)acetamide (60)**

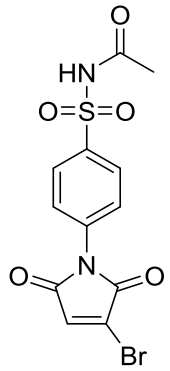


Maleic anhydride (98 mg, 1.0 mmol), sulfanilamide (172 mg, 1.0 mmol) and NaOAc (30 mg, 0.37 mmol) in AcOAc (4 mL) were heated to 100 °C. After 1 h, the solution was poured into ice-water (20 mL) and the product was extracted with EtOAc (3 × 10 mL) and the combined organic fractions were dried ($MgSO_4$) and filtered. The solvent was removed under reduced

pressure and the residue purified was purified by column chromatography (EtOAc/petrol) to give maleimide **60**.

White solid, 62%; Mp 166 – 167 °C; ν_{max} (film/cm^{-1}) 3389 (N-H), 2848 (C-H), 1711 (C=O), 1655 (C=O), 1591 (C=C), 1335 (S=O), 1154 (S=O); ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.20 (1H, s, NH), 8.02 (2H, d, J = 8.7, 2 × ArH), 7.63 (2H, d, J = 8.7, 2 × ArH), 7.26 (2H, s, CH=CH), 1.94 (3H, s, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.4, 169.0, 137.7, 136.1, 135.0, 128.4, 126.5, 23.3; HRMS: Found (CI): $[M+H]^+$ 295.03848, $C_{12}H_{11}N_2O_5S$ requires 295.03832

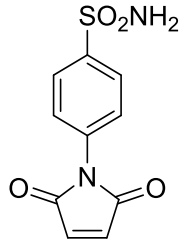
***N*-((4-(3-Bromo-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)phenyl)sulfonyl)acetamide (61)**



Bromine (0.1 mL, 20 mmol) was added to a stirring solution of maleimide **60** (529 mg, 1.8 mmol) in Et_2O (2.5 mL) and heated at reflux for 1 h. The mixture was cooled to 0 °C and NEt_3 (0.28 mL, 20 mmol) was added and stirred for 1 h. The solution was diluted with water (4 mL) and EtOAc (4 mL), before the solution was extracted with EtOAc (3 × 5 mL) and the combined organic fractions were washed with brine (10 mL), dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography (EtOAc/petrol) to give bromide **61**.

Yellow solid, 31% over 2 steps; Mp 209 – 211 °C; ν_{max} (film/cm^{-1}) 3265 (N-H), 1597 (C=C), 1347 (S=O) 1158 (S=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (2H, d, J = 8.8, 2 × ArH), 7.65 (2H, d, J = 8.8, 2 × ArH), 7.08 (1H, s, BrC=CH), 2.09 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.49, 167.47, 166.6, 137.5, 136.3, 132.2, 129.7, 129.6, 125.5, 23.7; HRMS: Found (CI): $[M+H]^+$ 372.94875, $C_{12}H_{10}N_2O_5SBr$ requires 372.94883

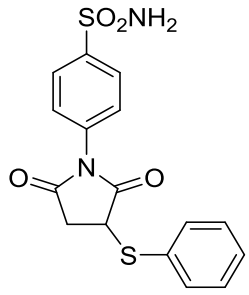
4-(2,5-Dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)benzenesulfonamide (62)



Maleic anhydride (1.40 g, 14 mmol), sulfanilamide (3.9 g, 23 mmol) and P_4O_{10} (3.0 g, 10 mmol) in dioxane (20 mL) were heated to 110 °C. After 18 h, the solution was filtered whilst hot and the filtrate was cooled and ice-water (20 mL) added. The precipitate that formed was collected to give maleimide **62**.

White solid, 54%; Mp 240 - 243 °C; ν_{max} (film/cm^{-1}) 3367 (N-H), 3262 (N-H), 1721 (C=O), 1702 (C=O) 1422 (C=C), 1299 (S=O) 1153 (S=O); ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.92 (2H, d, *J* = 8.7, 2 × ArH), 7.56 (2H, d, *J* = 8.7, 2 × ArH), 7.46 (2H, s, CH=CH), 7.23 (2H, s, NH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.6, 142.9, 134.9, 134.5, 126.8, 126.4; HRMS: Found (CI): $[M+H]^+$ 253.02830, $C_{10}H_9N_2O_4S$ requires 253.02830

4-(2,5-Dioxo-3-(phenylthio)pyrrolidin-1-yl)benzenesulfonamide (63)



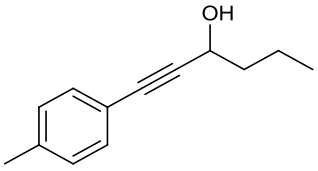
A solution of thiophenol (116 mg, 1.05 mmol) in benzene (1 mL) was added to a stirring solution of maleimide **62** (252 mg, 1.0 mmol) in benzene (1 mL) before NEt_3 (14 mg, 0.14 mmol) was added. After 18 h, the solvent was removed under reduced pressure to give the *succinimide*.

Pink solid, 54%; Mp 228 – 232 °C; ν_{max} (film/cm^{-1}) 3367 (N-H), 3265 (N-H), 1712 (C=O), 1697 (C=O), 1304 (S=O), 1155 (S=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.90 (2H, d, *J* = 8.8, 2 × ArH), 7.50 - 7.56 (2H, m, 2 × ArH), 7.44 (2H, s, NH_2), 7.38 - 7.42 (3H, m, 3 × ArH), 7.28 (2H, d, *J* = 8.8, 2 × ArH), 4.54 (1H, dd, *J* = 9.4, 4.1, CHSPh), 3.44 (1H, dd, *J* = 18.4, 9.4, C*H*HCHSPh), 2.84

(1 H, dd, *J* = 18.4, 4.1, CH*H*CHSPh); ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.7, 173.7, 143.8, 134.8, 133.1, 131.3, 129.4, 128.7, 127.3, 126.4, 43.8, 36.4; HRMS: Found (CI): $[M]^+$ 362.03794, $C_{16}H_{14}N_2O_4S_2$ requires 362.03950

General Procedure F: Propargylic Alcohol Formation [58]: *n*-Butyllithium (1.6M in hexanes, 1.2 eq.) was added dropwise to a stirred solution of alkyne (1 eq.) in dry THF (1 mLmmol^{-1}) at -78 ˚C under an argon atmosphere. After 1 h aldehyde or ketone (1 eq.) was added and the resulting solution was stirred for 5 min at 0 ˚C and 1h at rt. The reaction was quenched with saturated NH_4Cl solution and the organic phase extracted with Et_2O. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/petrol) to give the propargylic alcohol.

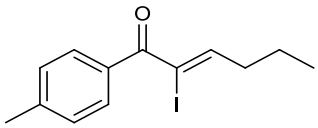
1-(*p*-Tolyl)hex-1-yn-3-ol (70a)



General Procedure F: Propargylic alcohol formation

Yellow oil, 96%; ν_{max} (film/cm^{-1}) 3331 (O-H), 2959 (C-H), 2932 (C-H), 1509 (Ar); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (2H, d, *J* = 7.9, 2 × ArH), 7.10 (2H, d, *J* = 7.9, 2 × ArH), 4.60 (1H, t, *J* = 6.6, C*H*OH), 2.34 (3H, s, $ArCH_3$), 2.28 (1H, br. s, OH), 1.72 - 1.84 (2H, m, CHC*H*$_2$), 1.54 (2H, sx, *J* = 7.4, C*H*$_2$CH$_3$), 0.98 (3H, t, *J* = 7.4, CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 131.7, 129.2, 119.7, 89.7, 85.0, 62.9, 40.1, 21.6, 18.7, 13.9; HRMS: Found (EI): $[M]^+$ 188.119621, $C_{13}H_{16}O$ requires 188.12012;

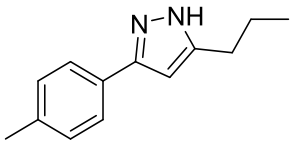
(*Z*)-2-Iodo-1-(p-tolyl)hex-2-en-1-one (73a)



N-Iodosuccinimide (NIS) (124 mg, 0.55 mmol) was added to a stirring solution of propargylic alcohol **70a** (0.5 mmol) and $Ph_3PAuNTf_2$ (2 mol%) in PhMe (2mL). Once the reaction was complete (TLC), the solvent was removed under reduced before the residue was purified by column chromatography (EtOAc/petrol) to give iodoenone **73a**.

Yellow oil, 71%; ν_{max} (film/cm^{-1}) 2960 (C-H), 2198 (C≡C), 1657 (C=O), 1603 (Ar), 1456 (Ar), 1258, 1179; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (2H, d, *J* = 8.1, 2 × ArH), 7.24 (2H, d, *J* = 8.1, 2 × ArH), 6.58 (1H, t, *J* = 7.0, CH), 2.39 - 2.44 (2H, m, CHC*H*$_2$), 2.41 (3H, s, $ArCH_3$), 1.55 (2H, sx, *J* = 7.5, C*H*$_2$$CH_3$), 0.99 (3H, t, *J* = 7.5, CH_2C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.0, 153.4, 143.5, 133.1, 130.1, 129.2, 108.4, 39.6, 21.8, 21.3, 14.1; HRMS: Found (EI): $[M]^+$ 314.015395, $C_{13}H_{15}OI$ requires 314.01676

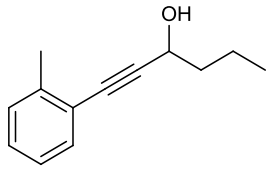
5-Propyl-3-(*p*-tolyl)-1*H*-pyrazole (72)



N-Iodosuccinimide (NIS) (124 mg, 0.55 mmol) was added to a stirring solution of propargylic alcohol **70a** (0.5 mmol) and $Ph_3PAuNTf_2$ (2 mol%) in PhMe (2mL). Once the reaction was complete (TLC), the solvent was removed under reduced to give the crude iodoenone. Hydrazine (3 eq.) and MeOH (1 mL) was added to this crude product and stirred or 3 h at RT before the solvent was removed under reduced pressure to give a residue that was was purified by column chromatography (EtOAc/Petrol) to give the pyrazole **72**.

Yellow oil, 44 mg, 45%; ν_{max} (film/cm^{-1}) 3191 (N-H), 2959 (C-H), 2929 (C-H), 1682 (C=O), 1510 (C=C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (2H, d, *J* = 7.9, 2 × ArH), 7.20 (2 H, d, *J* = 7.9, 2 × ArH), 6.33 (1H, s, CH), 2.64 (2H, t, *J* = 7.4, CCH_2), 2.37 (3H, s, $ArCH_3$), 1.71 (2H, sx, *J* = 7.4, C*H*$_2$$CH_3$), 0.99 (3H, t, *J* = 7.4 CH_2C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) 149.8, 148.1, 137.8, 129.7, 129.5, 125.6, 101.0, 28.7, 22.7, 21.4, 14.0; HRMS: Found (EI): $[M]^+$ 200.131019, $C_{13}H_{16}N_2$ requires 200.13135;

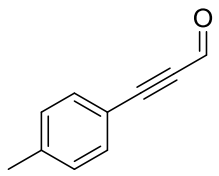
1-(*o*-Tolyl)hex-1-yn-3-ol (70b)



General Procedure F: Propargylic alcohol formation

Yellow oil, 87%; ν_{max} (film/cm^{-1}) 3323 (O-H), 2958 (C-H), 2954 (C-H), 2872 (C-H), 1485 (Ar), 1456 (Ar); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (1H, d, *J* = 7.7, ArH), 7.17 - 7.23 (2H, m, 2 × ArH), 7.12 (1H, td, *J* = 7.7, 1.9, ArH), 4.65 (1H, t, *J* = 6.6, C*H*OH), 2.43 (3H, s, ArCH_3), 2.13 (1H, br. s, OH), 1.80 (2H, m, CHCH_2), 1.57 (2H, sx, *J* = 7.5, CH_2CH$_3$), 0.99 (3H, t, *J* = 7.5, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2, 132.1, 129.5, 128.4, 125.6, 122.5, 94.3, 83.7, 63.0, 40.2, 20.7, 18.6, 13.7; HRMS: Found (CI): $[M+H]^+$ 189.128098, $C_{13}H_{17}O$ requires 189.12794

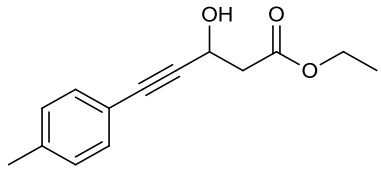
3-(*p*-Tolyl) Propiolaldehyde (78)[97]



General Procedure F: Propargylic alcohol formation

Orange oil, 2.5 g, 89%; ν_{max} (film/cm^{-1}); 2855 (C-H), 2181 (C≡C), 1651 (C=O), 1508 (Ar); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.40 (1H, s, CHO), 7.50 (2H, d, *J* = 8.1, 2 × ArH), 7.20 (2H, d, *J* = 8.1, 2 × ArH), 2.39 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.0, 142.3, 133.5, 129.7, 116.4, 96.1, 88.6, 21.9; LRMS: (EI): 144 ($[M]^+$, 100), 115 (80)

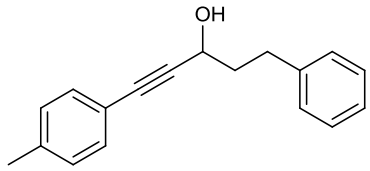
Ethyl 3-hydroxy-5-(*p*-tolyl)pent-4-ynoate (70d)



LiHMDS (1M in THF, 2 eq.) was added dropwise to a stirred solution of EtOAc (1 eq.) in dry THF (1 mLmmol^{-1}) at -78 ˚C under an argon atmosphere. After 1 h 3-(p-tolyl)propiolaldehyde **78** (1 eq.) was added and the resulting solution was stirred for 15 min. The reaction was quenched with saturated NH_4Cl solution and the organic phase extracted with Et_2O. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography to give propargylic alcohol **70d**.

Orange oil, 71%; ν_{max} (film/cm^{-1}) 3438 (O-H), 2982 (C-H), 1734 (C=O), 1510 (Ar), 1213, 1097; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (2H, d, J = 8.3, 2 × ArH), 7.10 (2H, d, J = 8.3, 2 × ArH), 4.98 (1H, br. d, J = 5.6, OCH), 4.21 (2H, m, OCH_2), 2.83 (2H, m, $CHCH_2$), 2.33 (3H, s, $ArCH_3$), 1.28 (3H, t, J = 7.2, CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 138.8, 131.8, 129.2, 119.3, 87.5, 85.3, 61.2, 59.4, 42.2, 21.6, 14.3; HRMS: Found (CI): $[M+H]^+$ 233.11731, $C_{14}H_{17}O_3$ requires 233.11777

5-Phenyl-1-(p-tolyl)pent-1-yn-3-ol (70f)

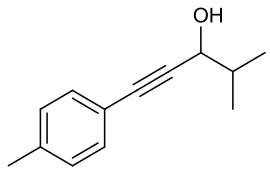


General Procedure F: Propargylic alcohol formation

Yellow solid, 93%; Mp 64 – 65 °C; ν_{max} (film/cm^{-1}) 3383 (O-H), 3061 (C-H), 2923 (C-H), 2227 (C≡C), 1509 (Ar); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 - 7.39 (2H, m, 2 × ArH), 7.30 - 7.34 (2H, m, 2 × ArH), 7.25 - 7.29 (2H, m, 2 × ArH), 7.21 - 7.25 (1H, m, 1 × ArH), 7.14 (2H, d, J = 7.9, 2 × ArH), 4.59 - 4.65 (1H, m, C*H*OH), 2.89 (2H, t, J = 7.5, $PhCH_2$), 2.37 (3H, s, $ArCH_3$), 2.11 - 2.20 (2H, m, $CHCH_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.5, 138.7, 131.8, 129.2, 128.7, 128.6, 126.1,

119.6, 89.3, 85.5, 62.4, 39.5, 31.7, 21.6; HRMS: Found (CI): $[M]^+$ 250.135335, $C_{18}H_{18}O$ requires 250.13577

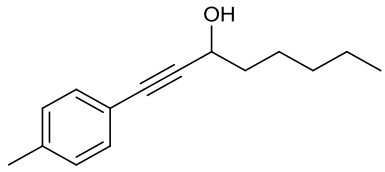
4-Methyl-1-(p-tolyl)pent-1-yn-3-ol (70g)



General Procedure F: Propargylic alcohol formation

Yellow oil, 76%; ν_{max} (film/cm^{-1}) 3351 (O-H), 2961 (C-H), 2872 (C-H), 2225 (C≡C), 1509 (Ar); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (2 H, d, *J* = 7.9, 2 × ArH), 7.11 (2H, d, *J* = 7.9, 2 × ArH), 4.39 (1H, d, *J* = 5.3, C*H*OH), 2.34 (3H, s, $ArCH_3$), 2.17 (1H, br. s, OH), 1.97 (1H, sx, *J* = 6.8), 1.08 (3H, d, *J* = 6.8, $CHCH_3CH_3$), 1.05 (3H, d, *J* = 6.8, $CHCH_3CH_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 131.7, 129.2, 119.8, 88.3, 85.8, 68.5, 34.8, 21.6, 18.4, 17.7; HRMS: Found (EI): $[M-H]^+$ 187.112643, $C_{13}H_{15}O$ requires 187.11229

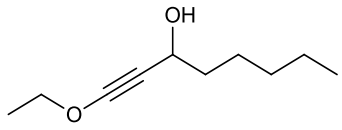
1-(*p*-Tolyl)oct-1-yn-3-ol (70h)



General Procedure F: Propargylic alcohol formation

Yellow oil, 75%; ν_{max} (film/cm^{-1}) 3337 (O-H), 2954 (C-H), 2927 (C-H), 2859 (C-H), 1509 (Ar); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (2H, d, *J* = 8.1, 2 × ArH), 7.11 (2H, d, *J* = 8.1, 2 × ArH), 4.58 (1H, t, J = 6.6, C*H*OH), 2.34 (3H, s, $ArCH_3$), 1.75 - 1.82 (2H, m, $CHCH_2$), 1.48 - 1.56 (2H, m, $CHCH_2CH_2$), 1.31 - 1.38 (4H, m, $CH_2CH_2CH_3$), 0.91 (3H, t, *J* = 7.3, CH_2CH_3); ^{13}C NMR (125MHz, $CDCl_3$) δ 138.5, 131.6, 129.1, 119.7, 89.7, 85.0, 63.1, 38.0, 31.6, 25.0, 22.6, 21.5, 14.1; HRMS: Found (EI): $[M]^+$ 216.151670, $C_{15}H_{20}O$ requires 216.15142

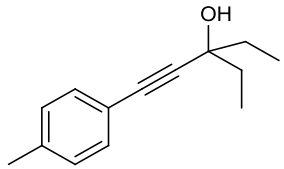
1-Ethoxyoct-1-yn-3-ol (70i)



General Procedure F: Propargylic alcohol formation

Colourless oil, 49%; ν_{max} (film/cm^{-1}) 3379 (O-H), 2955 (C-H), 2930 (C-H), 2859 (C-H), 2262 (C≡C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.38 (1H, m, C*H*OH), 4.08 (2H, q, *J* = 7.2, OC*H*$_2$CH$_3$), 1.74 (1H, br. s, OH), 1.57 - 1.69 (2H, m, CHC*H*$_2$CH$_2$), 1.42 (2H, sx, *J* =7.5, CHCH$_2$C*H*$_2$), 1.36 (3H, t, *J* = 7.2, OCH$_2$C*H*$_3$), 1.26 - 1.34 (4H, m, C*H*$_2$C*H*$_2$CH$_3$), 0.88 (3H, t, *J* = 6.8, CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 93.8, 74.7, 62.6, 39.8, 38.8, 31.6, 25.1, 22.7, 14.5, 14.1; HRMS: Found (CI): $[M+H]^+$ 171.137987, $C_{10}H_{19}O_2$ requires 171.13850

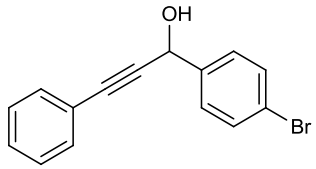
3-Ethyl-1-(p-tolyl)pent-1-yn-3-ol (70j)



General Procedure F: Propargylic alcohol formation

Yellow oil, 92%; ν_{max} (film/cm^{-1}) 3384 (O-H), 2969 (C-H), 2937 (C-H), 2226 (C≡C), 1509 (Ar), 1459 (Ar); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (2H, d, *J* = 7.9, 2 × ArH), 7.10 (2H, d, *J* = 7.9, 2 × ArH), 2.39 (1H, s, OH), 2.34 (3H, s, ArCH$_3$), 1.78 (4H, 2 × dq, *J* = 14.3, 7.5, 2 × CH$_2$), 1.12 (6H, t, *J* = 7.5, 2 × CH$_2$C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.3, 131.7, 129.1, 120.0, 91.2, 84.7, 72.7, 34.6, 21.6, 8.9; HRMS: Found (CI): $[M]^+$ 202.136131, $C_{14}H_{18}O$ requires 202.13577

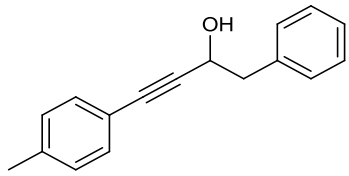
1-(4-Bromophenyl)-3-phenylprop-2-yn-1-ol (70k)



General Procedure F: Propargylic alcohol formation

Yellow solid, 81%; Mp 75 – 77 °C; ν_{max} (film/cm^{-1}) 3452 (O-H), 1590 (Ar), 1487 (Ar), 1370, 1011, 905; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (2H, d, *J* = 8.6, 2 × ArH), 7.49 (2H, d, *J* = 8.6, 2 × ArH), 7.46 (2H, dd, *J* = 7.4, 1.8, 2 × ArH), 7.31 - 7.35 (3H, m, 3 × ArH), 5.65 (1H, s, OCH), 2.34 (1H, br. s, OH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.7, 131.88, 131.87, 128.9, 128.6, 128.5, 122.6, 122.2, 88.2, 87.1, 64.6; HRMS: Found (EI): $[M]^+$ 285.99857, $C_{15}H_{11}OBr$ requires 285.99878

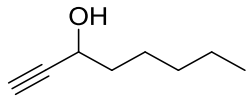
1-Phenyl-4-(p-tolyl)but-3-yn-2-ol (70m)



General Procedure F: Propargylic alcohol formation

Yellow solid, 40%, Mp 40 – 43 °C; ν_{max} (film/cm^{-1}) 3410 (O-H), 2939 (C-H), 2893 (C-H), 2226 (C≡C), 1509 (Ar), 1499 (Ar), 1337; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 - 7.39 (3H, m, 3 × ArH), 7.34 - 7.37 (2H, m, 2 × ArH), 7.30 - 7.34 (1H, m, 1 × ArH), 7.15 (2H, d, *J* = 7.9, 2 × ArH), 4.83 (1H, t, *J* = 6.3, C*H*OH), 3.14 (2H, dd, *J* = 6.3, 1.5, CHCH_2), 2.41 (1H, br. s, OH), 2.39 (3H, s, $ArCH_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.7, 136.9, 131.7, 130.1, 129.2, 128.5, 127.0, 119.7, 89.1, 86.1, 63.9, 44.4, 21.7; HRMS: Found (CI): $[M]^+$ 236.119176, $C_{17}H_{16}O$ requires 236.11957

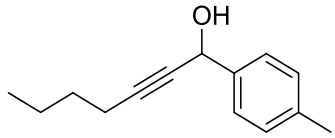
Oct-1-yn-3-ol (70o)



Hexanal (0.96 mL, 7.8 mmol) was added dropwise to stirring 0.5 M ethynyl MgBr (22 mL, 11 mmol) at -20 °C. After 1 h, the solution stirred at RT for a further 1 h before addition of saturated NH_4Cl (25 mL). The product was extracted with Et_2O (3 × 20 mL) and the combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography (EtOAc/petrol) to give the propargylic alcohol.

Orange oil, 37%; ν_{max} (film/cm^{-1}) 3362 (O-H), 2920 (O-H), 2205 (C≡C), 1509 (C=C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.35 (1H, td, *J* = 6.6, 2.0, C*H*OH), 2.44 (1H, d, *J* = 2.0, C≡CH), 1.65 - 1.74 (2H, m, CHCH_2), 1.40 - 1.49 (2H, m, $CHCH_2CH_2$), 1.26 - 1.36 (4H, m, $CH_2CH_2CH_2CH_3$), 0.88 (3H, t, *J* = 6.9, CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 85.2, 72.8, 62.4, 37.7, 31.5, 24.7, 22.6, 14.0; LRMS: (EI): 127 ($[M+H]^+$, 30), 99 (50), 83 (100)

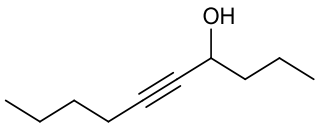
1-(*p*-Tolyl)hept-2-yn-1-ol (70p)



General Procedure F: Propargylic alcohol formation

Yellow oil, 79%; ν_{max} (film/cm^{-1}) 3369 (O-H), 2957 (C-H), 2931 (C-H), 2203 (C≡C), 1604 (Ar), 1512 (Ar), 1269; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (2H, d, *J* = 8.1, 2 × ArH), 7.18 (2H, d, *J* = 8.1, 2 × ArH), 5.41 (1H, s, C*H*OH), 2.36 (3H, s, $ArCH_3$), 2.28 (2H, td, *J* = 7.3, $C{\equiv}CCH_2$), 2.22 (1H, br. s, OH), 1.53 (2H, sx, *J* = 7.3, $CH_2CH_2CH_3$), 1.43 (2H, sx, *J* = 7.3, CH_2CH_3), 0.92 (3H, t, *J* = 7.3, CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 138.1, 129.3, 126.7, 87.6, 80.2, 64.8, 30.8, 22.1, 21.3, 18.7, 13.8; HRMS: Found (EI): $[M]^+$ 202.13514, $C_{14}H_{18}O$ requires 202.13577

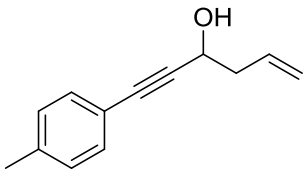
Dec-5-yn-4-ol (70q)



General Procedure F: Propargylic alcohol formation

Colourless oil, 64%; ν_{max} (film/cm^{-1}) 3345 (O-H), 2958 (C-H), 2933 (C-H), 2873 (C-H), 2223 (C≡C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.31 - 4.37 (1H, m, C*H*OH), 2.19 (2H, td, *J* = 7.2, 1.9, C≡CH_2), 1.85 (1H, d, *J* = 4.9, OH), 1.57 - 1.69 (2H, m, C≡CCH_2CH_2), 1.46 (4H, sx, *J* =7.5, 2 × CH_2), 1.39 (2H, sx, *J* = 7.2, CHCH_2CH_2CH_3), 0.93 (3H, t, *J* = 7.5, OHCH(CH_2)$_2$CH_3), 0.89 (3H, *t*, *J* =7.2 CH(CH_2)$_3$CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 85.5, 81.4, 62.6, 40.4, 30.9, 22.0, 18.6, 18.4, 13.9, 13.7; LRMS: (CI): 155 ([M]$^+$, 100)

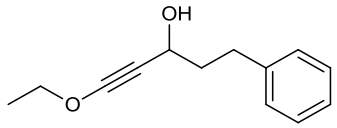
1-(*p*-Tolyl)hex-5-en-1-yn-3-ol (70r)



Propargyl aldehyde **78** (288 mg, 2.0 mmol) was added dropwise to a stirring solution of 1 M allyl MgBr (3 mL, 3 mmol) at 0 °C. After 2 h, water was added (5 mL) and the product was extracted with Et_2O (3 × 5 mL) before the combined organic fractions were dried ($MgSO_4$), and filtered. The solvent was removed under reduced pressure and the residue purified by column chromatography (EtOAc/petrol) to give alkene **70r**.

Orange oil, 37%; ν_{max} (film/cm^{-1}) 3362 (O-H), 2920 (O-H), 2205 (C≡C), 1509 (C=C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (2H, d, *J* = 7.9, 2 × ArH), 7.11 (2H, d, *J* = 7.9, 2 × ArH), 5.96 (1H, ddt, *J* = 17.2, 10.5, 7.1, CH_2C*H*=CHH), 5.24 (1H, d, *J* = 17.2, CH_2CH=CH*H*), 5.21 (1H, d, *J* = 10.5, CH_2CH=C*H*H), 4.65 (1H, t, *J* = 6.0, C*H*OH), 2.55 - 2.59 (2H, m, CH_2) , 2.34 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.7, 133.2, 131.7, 129.2, 119.5, 119.2, 88.8, 85.5, 62.2, 42.4, 21.6; HRMS: Found (EI): [M]$^+$ 186.104226, $C_{13}H_{14}O$ requires 186.10447

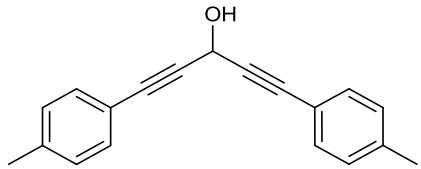
1-Ethoxy-5-phenylpent-1-yn-3-ol (70t)



General Procedure F: Propargylic alcohol formation

Yellow oil, 1.025 g, 59%; ν_{max} (film/cm^{-1}) 3372 (O-H), 2931 (C-H), 2260 (C≡C), 1495 (Ar), 1231; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (2H, t, J = 7.5, 2 × ArH), 7.18 - 7.24 (3H, m, 3 × ArH), 4.42 (1H, t, J = 6.4, C*H*OH), 4.11 (2H, q, J = 7.1, OCH_2), 2.79 (2H, m, $PhCH_2$), 1.93 - 2.05 (2H, m, CH_2CH), 1.39 (3H, t, J = 7.1, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.8, 128.6, 128.5, 126.0, 94.2, 74.8, 61.9, 40.3, 39.5, 31.8, 14.5; HRMS: Found (CI): $[M+H]^+$ 205.122313, $C_{13}H_{17}O_2$ requires 205.12285

1,5-Di-p-tolylpenta-1,4-diyn-3-ol (70u)



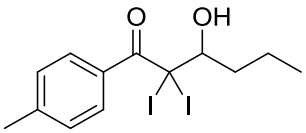
General Procedure F: Propargylic alcohol formation

Brown solid, 45%; Mp 90 – 92 °C, [82 - 84 °C][98]; ν_{max} (film/cm^{-1}) 3326 (O-H), 2973 (C-H), 2881 (C-H), 1379 (Ar), 1087, 1045; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (4H, d, J = 8.1, 4 × ArH), 7.13 (4H, d, J = 8.3, 4 × ArH), 5.55 - 5.58 (1H, m, CH), 2.35 (6H, s, 2 × CH_3); ^{13}C NMR (125MHz, $CDCl_3$) δ 139.2, 131.9, 129.2, 119.0, 85.5, 84.8, 53.5, 21.7; LRMS: (CI): 261 ($[M+H]^+$, 90), 143 ($[M-OH]^+$, 40), 145 (M-tolylacetylene]$^+$,100)

General Procedure G: Diiodohydration

N-Iodosuccinimide (248 mg, 1.1 mmol) was added to a stirring solution of propargylic alcohol (0.5 mmol) and $Ph_3PAuNTf_2$ (2 mol%) in MeCN/H_2O (2 mL, 10:1). Once the reaction was complete (TLC), the solvent was removed under reduced pressure before the residue was purified by column chromatography (EtOAc/Petrol) to give the diiodohydroxyketone.

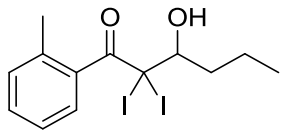
3-Hydroxy-2,2-diiodo-1-(*p*-tolyl)hexan-1-one (76a)



General Procedure G: Diiodohydration

Yellow solid, 71%; Mp 88 – 90 °C; ν_{max} (film/cm^{-1}) 3507 (O-H), 2955 (C-H), 1642 (C=O), 1601 (Ar), 1379, 1230; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.38 (2H, d, *J* = 8.3, 2 × ArH), 7.24 (2H, d, *J* = 8.3, 2 × ArH), 3.68 (1H, br. s, OH), 3.37 (1H, ddd, *J* = 9.4, 4.4, 1.5, CH), 2.45 (3H, s, $ArCH_3$), 2.15 (1H, m, CH(OH)C*H*H), 1.78 (1H, dtd, *J* = 13.9, 9.4, 5.5, CH(OH)CH*H*), 1.68 - 1.75 (1H, m, CH_3C*H*H*)*, 1.51 – 1.59 (1H, m, CH_3CH*H)*, 1.02 (3H, t, *J* = 7.5, CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.9, 144.9, 132.0, 130.4, 128.6, 78.7, 39.0, 25.0, 21.9, 19.6, 14.2; HRMS: Found (CI): $[M+H]^+$ 458.93132, $C_{13}H_{17}O_2I_2$ requires 458.93179; anal. cald. For $C_{13}H_{17}O_2I_2$ C, 34.09; H, 3.52; Found: C, 33.33; H, 3.42

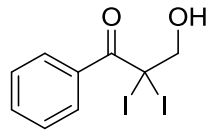
3-Hydroxy-2,2-diiodo-1-(*o*-tolyl)hexan-1-one (76b)



General Procedure G: Diiodohydration

Brown oil, 71%; ν_{max} (film/cm^{-1}) 3470 (O-H), 2958 (C-H), 1662 (C=O), 1598 (Ar), 1230; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (1H, d, *J* = 7.7, ArH), 7.36 (1H, t, *J* = 7.7, ArH), 7.25 (1H, d, *J* = 7.7, ArH), 7.21 (1H, t, *J* = 7.7, ArH), 3.45 – 3.49 (1H, m, CH), 2.92 (1H, br. s, OH), 2.33 (3H, s, $ArCH_3$), 2.11 - 2.21 (1H, m, CH(OH)CH*H*), 1.64 - 1.75 (2H, m, CH(OH)C*H*H and CH_3C*H*H), 1.48 - 1.58 (1H, m, CH_3CH*H*), 1.01 (3H, t, *J* = 7.3, CH_2CH_3); ^{13}C NMR (125MHz, $CDCl_3$) δ 198.1, 137.23, 137.17, 131.1, 130.7, 128.8, 125.1, 78.4, 39.1, 29.3, 20.6, 19.5, 14.0; HRMS: Found (CI): $[M+H]^+$ 458.93219, $C_{13}H_{17}O_2I_2$ requires 458.93179

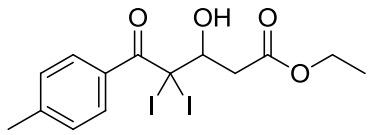
3-Hydroxy-2,2-diiodo-1-phenylpropan-1-one (76c)



General Procedure G: Diiodohydration

Brown oil, 68%; ν_{max} (film/cm^{-1}) 3414 (O-H), 2915 (C-H), 1649 (C=O), 1445 (Ar), 1229; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (2H, d, *J* = 8.5, 2 × ArH), 7.57 (1H, t, *J* = 7.4, ArH), 7.46 (2H, t, *J* = 7.9, 2 × ArH), 4.21 (2H, d, *J* = 7.7, CH_2), 3.42 (1H, t, *J* = 7.7, OH); ^{13}C NMR (125MHz, $CDCl_3$) δ 191.5, 134.0, 131.6, 130.4, 128.0, 76.0, 10.0; HRMS: Found (CI): $[M+H]^+$ 402.8692, $C_9H_9O_2I_2$ requires 486.8684

Ethyl 3-hydroxy-4,4-diiodo-5-oxo-5-(*p*-tolyl)pentanoate (76d)



General Procedure G: Diiodohydration

Brown oil, 78%; ν_{max} (film/cm^{-1}) 3503 (O-H), 2978 (C-H), 1723 (C=O), 1648 (C=O), 1602 (Ar), 1372, 1182; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.37 (2 H, d, *J* = 8.5, 2 × ArH), 7.25 (1H, d, *J* = 8.5, 2 × ArH), 4.22 (2H, q, *J* = 7.2, OCH_2), 4.10 (1H, ddd, *J* = 9.5, 3.7, 1.9, C*H*OH), 3.94 (1H, dd, *J* = 4.1, 1.9, OH), 3.26 (1H, d, *J* = 16.0, CHOHC*H*H), 2.87 (1H, dd, *J* = 16.0, 9.5, CHOHCH*H*), 2.45 (3H, s, $ArCH_3$), 1.31 (3H, t, *J* = 7.2, CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.1, 171.0, 145.1, 131.9, 130.0, 128.7, 75.9, 61.2, 42.7, 21.9, 19.6, 14.3; HRMS: Found (CI): $[M-H]^+$ 502.92162, $C_{14}H_{17}O_4I_2$ requires 502.921095;

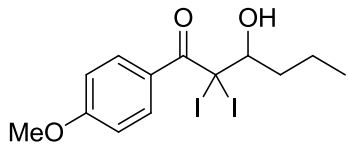
Ethyl 3-hydroxy-4,4-diiodo-5-oxo-5-(*p*-tolyl)pentanoate (*R*-76d)

Determination of the enantiomeric ratios of alcohols obtained with the Mosher's esters analysis: A solution of alcohol (1 eq.) and (*R*) or (*S*)-MTPA (3 eq.) in DCM (0.2M) was stirred at RT. EDCl.HCl (3 eq.) was added, followed by DMAP (3.3 eq.) and the resulting solution was stirred at RT for 24 h. The mixture was partitioned between water and DCM; the

phases were separated and the organic layer was dried ($MgSO_4$), filtered and solvent removed under reduced pressure. The crude product was analysed by ^1H NMR. The enantiomeric ratio was determined from the integration of the peaks of the two diastereoisomers.

92%, $[\alpha]_D^{20}$ − 15.8, (*c* 0.26, $CHCl_3$) 94:6 er, (*R*). The enantiomeric purity was determined by integration of the peaks at 8.24 and 8.21 ppm, indicating a diastereomeric ratio of 94:6

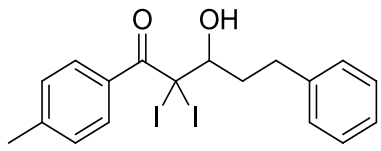
3-Hydroxy-2,2-diiodo-1-(4-methoxyphenyl)hexan-1-one (70e)



General Procedure G: Diiodohydration

Brown oil, 58%; ν_{max} (film/cm^{-1}) 3253 (O-H), 2960 (C-H), 1716 (C=O), 1656, 1595 (Ar), 1259, 1173; ^1H NMR (600 MHz, $CDCl_3$) δ 8.49 (2H, d, *J* = 9.0, 2 × ArH), 6.89 (2H, d, *J* = 9.0, 2 × ArH), 3.88 (3H, s, OCH_3), 3.84 (1H, br. s, OH), 3.34 (1H, d, *J* = 9.4, CH), 2.14 (1H, m, CH(OH)C*H*H), 1.78 (1H, dtd, *J* = 14.3, 9.4, 4.9, CH(OH)CH*H*), 1.67 - 1.75 (1H, m, CH_3CHH), 1.50 – 1.59 (1H, m, CH_3CHH), 1.01 (3H, t, *J* = 7.5, CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.7, 163.8, 134.5, 125.4, 113.1, 78.8, 55.7, 39.0, 25.5, 19.7, 14.2; HRMS: Found (CI): $[M+H]^+$ 474.92581, $C_{13}H_{17}O_3I_2$ requires 474.92671

3-Hydroxy-2,2-diiodo-5-phenyl-1-(*p*-tolyl)pentan-1-one (70f)

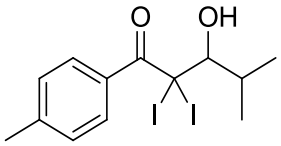


General Procedure G: Diiodohydration

Brown oil, 63%; ν_{max} (film/cm^{-1}) 3504 (O-H), 2959 (C-H), 1637 (C=O), 1601 (Ar), 1228; ^1H NMR (600 MHz, $CDCl_3$) δ 8.37 (2H, d, *J* = 8.7, 2 × ArH), 7.27 - 7.34 (4H, m, 4 × ArH), 7.19 - 7.25 (3H, m, 3 × ArH), 3.79 (1H, br. s, OH), 3.37 (1H, dd, *J* = 9.4, 3.0, CH), 3.04 (1H, ddd, *J* =

13.8, 9.4, 4.8, C(OH)HC*H*H), 2.83 (1H, ddd, *J* = 13.8, 9.4, 7.5, C(OH)HCH*H*), 2.55 (2H, td, *J* = 11.3, 8.7, C(OH)HCH$_2$C*H*H), 2.45 (3H, s, ArCH$_3$), 2.13 (1H, dtd, *J* =13.8, 9.4, 4.8, C(OH)HCH$_2$CH*H*); ^{13}C NMR (150 MHz, CDCl$_3$) δ 191.7, 145.0, 141.7, 132.0, 130.2, 128.8, 128.64, 128.56, 126.1, 78.1, 38.6, 32.4, 24.3, 21.9; HRMS: Found (CI): $[M+H]^+$ 520.94711, $C_{18}H_{19}O_2I_2$ requires 520.94744

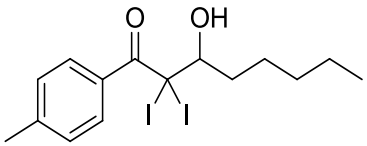
3-Hydroxy-2,2-diiodo-4-methyl-1-(*p*-tolyl)pentan-1-one (70g)



General Procedure G: Diiodohydration

Brown oil, 60%; ν_{max} (film/cm^{-1}) 3527 (O-H), 2961 (C-H), 2925 (C-H), 1646 (C=O), 1603 (Ar), 1229, 1182; ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.29 (2H, d, *J* = 8.3, 2 × ArH), 7.23 (2H, d, *J* = 8.3, 2 × ArH), 3.52 (1H, dd, *J* = 5.8, 3.8, C*H*OH), 3.43 (1H, d, *J* = 5.8, OH), 2.44 (3H, s, ArCH$_3$), 2.26 (1H, sptd, *J* = 6.8, 3.8, C*H*(CH$_3$)$_2$), 1.18 (3H, d, *J* = 6.8, CH(C*H*$_3$)(CH$_3$)), 1.08 (3H, d, *J* = 6.8, CH(CH$_3$)(C*H*$_3$)); ^{13}C NMR (150 MHz, CDCl$_3$) δ 192.2, 144.5, 131.8, 130.7, 128.8, 81.4, 34.8, 25.4, 23.7, 21.8, 18.6; HRMS: Found (APCI): $[M+H]^+$ 458.9300, $C_{13}H_{17}O_2I_2$ requires 458.9312

3-Hydroxy-2,2-diiodo-1-(*p*-tolyl)octan-1-one (70h)

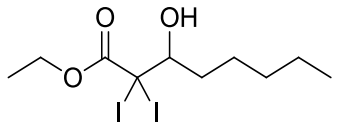


General Procedure G: Diiodohydration

Brown oil, 55%; ν_{max} (film/cm^{-1}) 3534 (O-H), 2953 (C-H), 1645 (C=O), 1603 (Ar), 1230, 1183; ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.38 (2H, d, *J* = 8.5, 2 × ArH), 7.24 (2H, d, *J* = 8.5, 2 × ArH), 3.69 (1H, br. s, OH), 3.35 (1H, d, *J* = 9.4, CH), 2.45 (3H, s, ArCH$_3$), 2.14 - 2.22 (1H, m, C(OH)HC*H*H), 1.78 (1H, dtd, *J* = 13.9, 9.2, 4.9, C(OH)HCH*H*), 1.65 - 1.73 (1H, m, C(OH)HCH$_2$C*H*H), 1.49 - 1.57 (1H, m, C(OH)HCH$_2$H*H*), 1.32 - 1.43 (4H, m, CH$_3$C*H*$_2$C*H*$_2$), 0.92 (3H, t, *J* = 7.0, C*H*$_3$CH$_2$);

^{13}C NMR (150 MHz, $CDCl_3$) δ 191.9, 144.9, 132.0, 130.4, 128.6, 79.0, 36.9, 31.8, 26.1, 25.6, 22.8, 21.9, 14.2; HRMS: Found (CI): $[M+H]^+$ 486.96200, $C_{15}H_{21}O_2I_2$ requires 486.96309

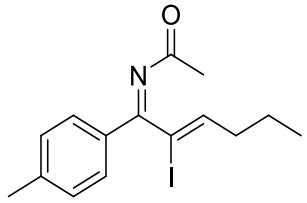
Ethyl 3-hydroxy-2,2-diiodooctanoate (70i)



General Procedure G: Diiodohydration

Brown oil, 73%; ν_{max} (film/cm^{-1}) 3479 (O-H), 2927 (C-H), 1705 (C=O), 1462 (Ar), 1239; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.33 (2H, q, J = 7.2, OCH_2), 3.13 (1H, d, J = 9.0, CH), 1.96 - 2.05 (1H, m, OH), 1.58 - 1.67 (2H, m, C(OH)HCH_2), 1.48 (1H, m, C(OH)HCH$_2$CHH), 1.35 (3H, t, J = 7.2, OCH_2CH_3), 1.29 - 1.40 (5H, m, C(OH)HCH$_2$CHH and $CH_3CH_2CH_2$), 0.91 (3H, dt, J = 6.7, $CH_2CH_2CH_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.2, 78.7, 64.0, 36.4, 31.7, 25.9, 22.7, 14.2, 13.6, 12.9; HRMS: Found (CI): $[M+H]^+$ 440.94238, $C_{10}H_{19}O_3I_2$ requires 440.94236

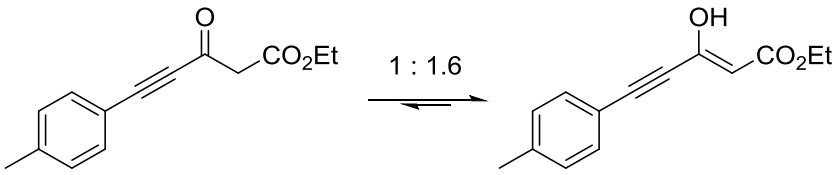
***N*-((1*Z*,2*Z*)-2-Iodo-1-(p-tolyl)hex-2-en-1-ylidene)acetamide (77)**



N-iodosuccinimide (248 mg, 1.1 mmol) was added to a stirring solution of propargylic alcohol (0.5 mmol) in MeCN (2 mL) and $Ph_3PAuNTf_2$ (2 mol%). Once reaction was complete (TLC), the solvent was removed under reduced before the residue was purified by column chromatography (EtOAc/Petrol) to give the imine as a orange oil.

Orange oil, 10%; ν_{max} (film/cm^{-1}) 2960 (C-H), 2931 (C-H), 1701 (C=O), 1619 (C=N), 1605 (C=C), 1458 (Ar), 1206, 1179; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (2H, d, J = 8.1, 2 × ArH), 7.21 (2H, d, J = 8.1, 2 × ArH), 6.12 (1H, t, J = 7.0, CH), 2.40 (3H, s, $ArCH_3$), 2.34 (2H, q, J = 7.0, CHCH_2), 2.09 (3H, s, $COCH_3$), 1.49 - 1.54 (2H, m, CH_2CH$_3$), 0.97 (3H, t, J = 7.3, CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.0, 162.3, 149.5, 141.8, 131.3, 129.3, 128.9, 99.5, 39.1, 25.1, 21.6, 21.4, 13.9; HRMS: Found (CI): $[M+H]^+$ 356.049974, $C_{15}H_{19}INO$ requires 356.05058

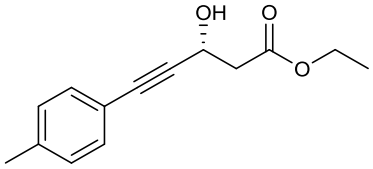
Ethyl 3-oxo-5-(*p*-tolyl)pent-4-ynoate (80)



Ethyl diazoacetate (1.0 mL, 9.6 mmol) in THF (10 mL) was added dropwise to a suspension of NaH (387 mg, 9.6 mmol) in THF (20 mL) at 0 °C. After 15 min the stirring was continued at RT for 1 h before aldehyde **78** (752 mg, 5.2 mmol) in THF (10 mL) was added dropwise over 10 min. After 3 h, the solution was filtered through a sinter, the solvent removed under reduced pressure and the residue purified by flash chromatography (EtOAc/petrol) to give the diazo-compound **79**. This product was stable but mass spectrometry data could not be obtained. The oil **79** dissolved in DCM (5 mL) was added dropwise to a solution of $Rh_2(OAc)_4$ in DCM (10 mL) and stirred for 1 h before the solvent was removed under reduced pressure. The residue was purified by flash chromatography (EtOAc/petrol) to give the product.

Yellow solid, 574 mg, 77% over 2 steps; Mp 77 – 79 °C; ν_{max} (film/cm^{-1}) 2982 (C-H), 2202 (C≡C), 1740 (C=O), 1670 (Ar), 1602 (Ar); ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.97 (1H, =CH, major), 7.48 (2H, d, J = 8.1, 2 × ArH, minor), 7.42 (2H, d, J = 7.9, 2 × ArH, major), 7.20 (2H, d, J = 8.1, minor), 7.17 (2H, d, J = 7.9, major), 5.43 (1H, s, OH, major), 4.21 - 4.27 (4H, m, OCH_2, major and minor), 3.68 (2H, s, $COCH_2CO$, minor), 2.39 (3H, s, $ArCH_3$, minor), 2.37 (3H, s, $ArCH_3$, major), 1.30 (3H, t, J = 7.2, CH_2CH_3, major), 1.31 (3H, t, J = 7.2, CH_2CH_3, minor); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.9, 172.4, 166.4, 155.6, 142.2, 140.5, 133.4, 132.3, 129.6, 129.4, 117.8, 116.4, 97.0, 94.0, 87.4, 83.1, 61.8, 60.7, 51.5, 21.9, 21.9, 21.8, 14.3, 14.2; HRMS: Found (CI): $[M+H]^+$ 231.101994, $C_{14}H_{15}O_3$ requires 231.10212

(*R*)-Ethyl 3-hydroxy-5-(p-tolyl)pent-4-ynoate, ((*R*)-70d)

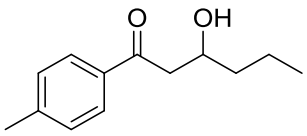


(*R*,*R*)-Teth-TsDPEN-RuCl (0.6 mg, 1.0 × 10^{-3} mmol) and HCO_2H/Et_3N 5/2 azeotropic mixture (168 mg) was added into a flask, and Ethyl 3-oxo-5-(p-tolyl)pent-4-ynoate **80** (0.2 mmol) in

degassed dichloromethane (1 cm^3) was injected under a nitrogen atmosphere. The mixture was stirred at rt until reaction was complete and then the solution was concentrated and the residue purified by column chromatography (EtOAc/petrol) to give the chiral alcohol.

Orange oil, 66%; $[\alpha]_D^{20}$ + 8.1, (*c* 1.0, $CHCl_3$) 94:6 *er*, (*R*) The enantiomeric ratios of the alcohol was determined by Mosher's esters analysis as described above for ***R*-76d**.

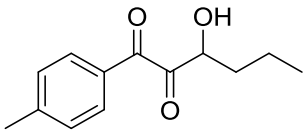
3-Hydroxy-1-(*p*-tolyl)hexan-1-one (92)



N-Iodosuccinimide (113 mg, 0.5 mmol) was added to a stirring solution of propargylic alcohol (47 mg, 0.25 mmol) and $Ph_3PAuNTf_2$ (2 mol%) in $MeCN/H_2O$ (10:1, 2mL). Once the reaction was complete (TLC), $MgSO_4$ (200 mg) was added followed by AcOH (0.5 mL) and zinc powder (60 mg, 1 mmol) and the solution stirred for 2 h before the solvent was removed under reduced pressure. The residue was purified by flash chromatography (EtOAc/petrol) to give the hydroxyketone.

Yellow oil, 14 mg, 27% over 2 steps; ν_{max} (film/cm^{-1}) 3457 (O-H), 2958 (C-H), 1737 (C=O), 1672 (Ar), 1607 (Ar); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.3, 2 × ArH), 7.27 (2H, d, *J* = 8.3, 2 × ArH), 4.19 - 4.25 (1 H, m, OCH), 3.31 (1H, br. s, OH), 3.15 (1H, dd, *J* = 17.5, 2.4, COC*H*H), 3.00 (1H, dd, *J* = 17.5, 9.2, COCH*H*), 2.41 (3H, s, $ArCH_3$), 1.57 - 1.65 (1H, m, CHC*H*H), 1.39 - 1.56 (3H, m, CHCH*H* and CH_2CH_3), 0.93 - 0.98 (3H, t, *J* = 7.2, CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.9, 144.6, 134.4, 129.5, 128.3, 67.6, 44.6, 44.9, 38.7, 21.8, 8.9, 14.2; HRMS: Found (CI): $[M]^+$ 206.129623, $C_{13}H_{18}O_2$ requires 206. 13013

3-Hydroxy-1-(*p*-tolyl)hexane-1,2-dione (93)



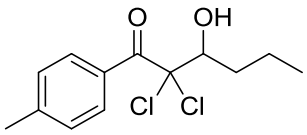
N-Iodosuccinimide (113 mg, 0.5 mmol) was added to a stirring solution of propargylic alcohol (47 mg, 0.25 mmol) and $Ph_3PAuNTf_2$ (2 mol%) in MeCN/H_2O (10:1, 2mL). Once the reaction was complete (TLC), NaOMe (54 mg, 1 mmol) was added and the solution stirred for 1 h before the solvent was removed under reduced pressure. The residue was purified by flash chromatography (EtOAc/petrol) to give the dione.

Yellow oil, 17 mg, 32% over 2 steps; ν_{max} (film/cm^{-1}) 3457 (O-H), 2962 (C-H), 1721 (C=O), 1738 (C=O), 1666 (Ar), 1604 (Ar); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (2H, d, J = 8.3, 2 × ArH), 7.32 (2H, d, J = 8.3, 2 × ArH), 4.93 (1H, dd, J = 8.3, 3.8. OCH), 3.05 (1H, br. s, OH), 2.45 (3H, s, $ArCH_3$), 1.77 (1H, m, CHC*H*H), 1.48 - 1.60 (3H, m, CHCH*H* and C*H*$_2$CH$_3$), 0.91 (3H, t, J = 7.3, CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) 204.3, 192.1, 146.8, 130.3, 129.9, 129.7, 74.2, 34.9, 22.1, 18.7, 13.9; HRMS: Found (CI): $[M]^+$ 220.109258, $C_{13}H_{16}O_3$ requires 220.10940

General Procedure H: Dichlorohydration

Trichloroisocyanuric acid (116 mg, 0.5 mmol) was added to a stirring solution of propargylic alcohol (0.5 mmol) in MeCN/H_2O (2 mL, 10:1). Once the reaction was complete (TLC), the solvent was removed under reduced pressure before the residue was purified by column chromatography (EtOAc/Petrol) to give the dichlorohydroxyketone.

3-Hydroxy-2,2-dichloro-1-(*p*-tolyl)hexan-1-one (94a)

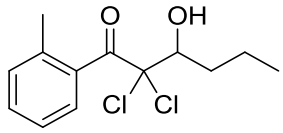


General Procedure H: Dichlorohydration

White solid, 70%; Mp 64 – 65 °C; ν_{max} (film/cm^{-1}) 3357 (O-H), 2962 (C-H), 1676 (C=O), 1606 (Ar), 1257, 1187; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (2H, d, J = 8.1, 2 × ArH), 7.27 (2H, d, J =

8.1, 2 × ArH), 4.39 (1H, d, *J* = 9.4, CH), 3.26 (1H, br. s, OH), 2.43 (3H, s, $ArCH_3$), 1.90 - 2.00 (1H, m, C(OH)HCH*H*), 1.67 - 1.79 (2H, m, C(OH)HC*H*H and C(OH)HCH_2H*H*), 1.44 - 1.55 (1H, m, C(OH)HCH_2*H*H), 1.01 (3H, t, *J* = 7.3, CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 189.9, 145.4, 131.5, 129.1, 129.0, 88.1, 76.7, 32.6, 21.9, 19.4, 14.1; HRMS: Found (APCI): $[M+H]^+$ 275.0598, $C_{13}H_{17}O_2Cl_2$ requires 275.0600.

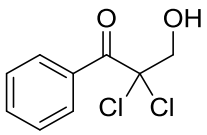
3-Hydroxy-2,2-dichloro-1-(*o*-tolyl)hexan-1-one (94b)



General Procedure H: Dichlorohydration

Colourless oil, 61%; ν_{max} (film/cm^{-1}) 3444 (O-H), 2961 (C-H), 1705 (C=O), 1238; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.89 (1H, d, *J* = 7.7, ArH), 7.39 (1H, t, *J* = 7.7, ArH), 7.25 (2H, m, 2 × ArH), 4.47 (1H, m, CH), 2.63 (1H, d, *J* = 6.4, OH), 2.37 (3H, s, $ArCH_3$), 1.91 – 1.99 (1H, m, CH(OH)CH*H*), 1.64 - 1.75 (2H, m, CH(OH)C*H*H and CH_3C*H*H), 1.44 - 1.54 (1H, m, CH_3CH*H*), 1.00 (3H, t, *J* = 7.5, CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 195.6, 137.9, 135.3, 131.4, 131.2, 127.9, 125.0, 90.3, 76.5, 33.2, 20.5, 19.3, 14.0; HRMS: Found (ES+): $[M+Na]^+$ 297.0475, $C_{13}H_{16}O_2Cl_2Na$ requires 297.0425.

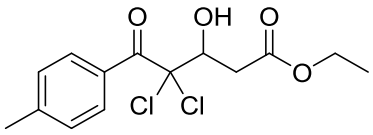
3-Hydroxy-2,2-dichloro-1-phenylpropan-1-one (94c)



General Procedure H: Dichlorohydration

Colourless oil, 71%; ν_{max} (film/cm^{-1}) 3397 (O-H), 1683 (C=O), 1596 (Ar), 1580 (Ar), 1259; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.32 (2H, d, *J* = 8.5, 2 × ArH), 7.62 (1H, t, *J* = 7.4, ArH), 7.49 (2H, t, *J* = 7.7, 2 × ArH), 4.27 (2H, d, *J* = 7.7, CH_2); ^{13}C NMR (125MHz, $CDCl_3$) *δ* 189.3, 134.3, 131.3, 131.2, 128.4, 70.7, 63.7; HRMS: Found (ES+): $[M+H]^+$ 218.9995, $C_9H_9O_2Cl_2$ requires 218.9980

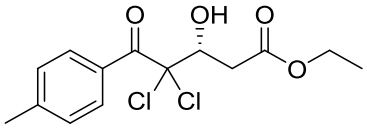
Ethyl 4,4-dichloro-3-hydroxy-5-oxo-5-(*p*-tolyl)pentanoate (94d)



General Procedure H: Dichlorohydration

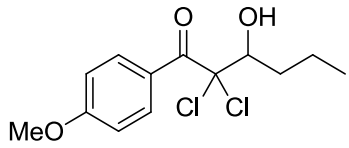
Colourless oil, 80%; ν_{max} (film/cm^{-1}) 3496 (O-H), 2982 (C-H), 1732 (C=O), 1680 (C=O), 1569 (Ar); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (2H, d, *J* = 8.5, 2 × ArH), 7.28 (2H, d, *J* = 8.5, 2 × ArH), 5.02 (1H, dt, *J* = 9.7, 2.5, C*H*OH), 4.22 (2H, q, *J* = 7.2, CH_2CH$_3$), 3.58 (1H, br. s, OH), 3.06 (1H, dd, *J* = 16.0, 2.5, CHOHC*H*H), 2.83 (1H, dd, *J* = 16.0, 9.7, CHOHCH*H*), 2.44 (3H, s, ArCH$_3$), 1.30 (3H, t, *J* = 7.2, CH$_2$C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.0, 171.1, 145.6, 131.5, 129.1, 128.8, 86.5, 73.8, 61.2, 36.8, 21.9, 14.3; HRMS: Found (APCI): $[M+H]^+$ 319.0496, $C_{14}H_{17}Cl_2O_4$ requires 319.0498

Ethyl (*R*)-3-hydroxy-4,4-dichloro-5-oxo-5-(*p*-tolyl)pentanoate ((*R*)-94d)



80%, $[\alpha]_D^{20}$ − 18.5 (*c* 1.0, $CHCl_3$) 92:8 er, (*R*). The enantiomeric ratio was determined by Mosher's esters analysis as described above for **R-76d**. The enantiomeric purity was determined by integration of the peaks at 2.92 and 2.81 ppm, indicating a diastereomeric ratio of 92:8

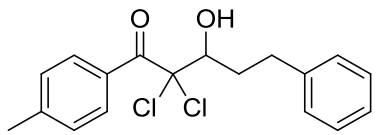
3-Hydroxy-2,2-dichloro-1-(4-methoxyphenyl)hexan-1-one (94e)



General Procedure H: Dichlorohydration

White solid, 68%; Mp 78 – 80 °C; ν_{max} (film/cm^{-1}) 3516 (O-H), 2960 (C-H), 1665 (C=O), 1596 (Ar), 1253, 1179; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.32 (2H, d, *J* = 9.0, 2 × ArH), 6.95 (2H, d, *J* = 9.0, 2 × ArH), 4.37 (1H, d, *J* = 9.4, CH), 3.90 (3H, s, OCH_3), 3.34 (1H, br. s, OH), 1.91 – 2.00 (1H, m, CH(OH)C*H*H), 1.68 - 1.80 (2H, m, C(OH)HC*H*H and C(OH)HCH$_2$CH*H*), 1.44 – 1.54 (1H, m, C(OH)HCH$_2$C*H*H), 1.01 (3H, t, *J* = 7.5, CH$_2$C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 188.9, 164.3, 134.0, 124.2, 113.6, 88.0, 76.7, 55.7, 32.5, 19.4, 14.1; HRMS: Found (ES+): $[M+H]^+$ 291.0579, $C_{13}H_{17}O_3Cl_2$ requires 291.0555.

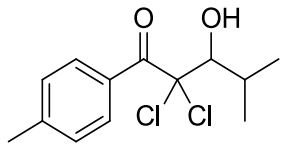
3-Hydroxy-2,2-dichloro-5-phenyl-1-(*p*-tolyl)pentan-1-one (94f)



General Procedure H: Dichlorohydration

Yellow oil, 79%; ν_{max} (film/cm^{-1}) 3433 (O-H), 2969 (C-H), 1675 (C=O), 1604 (ArH), 1256, 1187; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (2H, d, *J* = 8.3, 2 × ArH), 7.19 - 7.36 (7H, m, 7 × ArH), 4.40 (1H, br. d, *J* = 10.2, CH), 3.40 (1H, d, *J* = 1.9, OH), 3.06 (1H, ddd, *J* = 13.7, 9.6, 4.6, C(OH)HC*H*H), 2.79 (1H, ddd, *J* = 13.7, 9.1, 7.7, C(OH)HCH*H*), 2.44 (3H, s, ArCH_3), 2.34 (1H, ddd, *J* = 14.1, 9.1, 7.7, C(OH)HCH$_2$C*H*H), 2.11 (1H, ddd, *J* = 14.1, 9.6, 4.6, C(OH)HCH$_2$CH*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.8, 145.5, 141.6, 131.5, 129.2, 129.0, 128.7, 128.6, 128.2, 87.8, 76.1, 32.16, 32.11, 21.9; HRMS: Found (ES+): $[M+H]^+$ 337.0771, $C_{18}H_{19}O_2Cl_2$ requires 337.0762

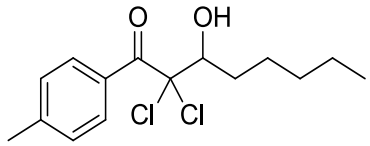
2,2-Dichloro-3-hydroxy-4-methyl-1-(*p*-tolyl)pentan-1-one (94g)



General Procedure H: Dichlorohydration

Colourless oil, 60%; ν_{max} (film/cm^{-1}) 3545 (O-H), 2964 (C-H), 1674 (C=O), 1605 (Ar), 1238, 1186; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (2H, d, *J* = 8.3, 2 × ArH), 7.27 (2H, d, *J* = 8.3, 2 × ArH), 4.30 (1H, d, *J* = 3.4, C*H*OH), 3.10 (1H, br. s, OH), 2.43 (3H, s, $ArCH_3$), 2.38 (1H, sptd, *J* = 6.8, 3.4, C*H*$(CH_3)_2$), 1.14 (3H, d, *J* = 6.8, CH(C*H*$_3$)(CH_3)), 1.12 (3H, d, *J* = 6.8, $CH(CH_3)$(C*H*$_3$)); ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.0, 145.1, 131.3, 129.4, 129.0, 88.8, 79.6, 30.0, 22.8, 21.9, 17.5; HRMS: Found (CI): $[M+H]^+$ 275.06975, $C_{13}H_{17}O_2Cl_2$ requires 275.06056

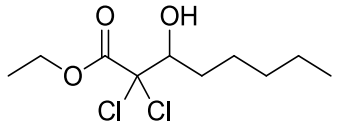
3-Hydroxy-2,2-dichloro-1-(*p*-tolyl)octan-1-one (94h)



General Procedure H: Dichlorohydration

Colourless oil, 60%; ν_{max} (film/cm^{-1}) 3551 (O-H), 2957 (C-H), 2928 (C-H), 1674 (C=O), 1605 (ArH), 1254, 1186; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (2H, d, *J* = 8.2, 2 × ArH), 7.27 (2H, d, *J* = 8.2, 2 × ArH), 4.37 (1H, dd, *J* = 9.7, 1.5, CH), 3.10 - 3.31 (1H, br. s, OH), 2.43 (3H, s, $ArCH_3$), 1.98 (1H, m, C(OH)HC*H*H), 1.65 - 1.78 (2H, m, C(OH)HCH*H* and C(OH)HCH$_2$H*H*), 1.42 - 1.51 (1H, m, C(OH)HCH$_2$*H*H), 1.32 - 1.42 (4H, m, $CH_3CH_2CH_2$), 0.92 (3H, t, *J* = 7.1, C*H*$_3$CH$_2$); ^{13}C NMR (125MHz, $CDCl_3$) δ 189.9, 145.2, 131.4, 129.2, 129.0, 88.3, 76.9, 31.7, 30.5, 25.8, 22.7, 21.8, 14.1; HRMS: Found (ES+): $[M+H]^+$ 303.0894, $C_{15}H_{21}O_2Cl_2$ requires 303.0919

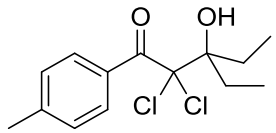
Ethyl 3-hydroxy-2,2-dichloro-octanoate (94i)



General Procedure H: Dichlorohydration

Colourless oil, 50%; ν_{max} (film/cm^{-1}) 3431 (O-H), 2957 (C-H), 2931 (C-H), 1743 (C=O), 1250, 1022; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.35 (2H, q, J = 7.2, OCH_2), 4.17 – 4.23 (1H, m, CH), 2.56 (1H, d, J = 6.0, OH), 1.81 – 1.88 (1H, m, C(OH)HCH*H*), 1.56 - 1.66 (2H, m, C(OH)HC*H*H and C(OH)HCH$_2$C*H*H), 1.89 – 1.46 (1H, m, C(OH)HCH$_2$CH*H*), 1.27 – 1.38 (4H, m, $CH_3CH_2CH_2$), 1.36 (3H, t, J = 7.2, OCH_2CH_3), 0.90 (3H, t, J = 6.7, CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.0, 87.2, 77.4, 64.1, 31.6, 31.1, 25.7, 22.6, 14.1, 13.9; HRMS: Found (ES+): $[M+H]^+$ 257.0708, $C_{10}H_{19}O_3Cl_2$ requires 257.0711

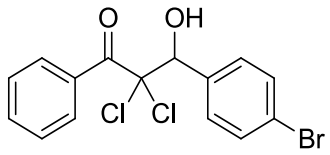
3-Hydroxy-2,2-dichloro-3-ethyl-1-(p-tolyl)pentan-1-one (94j)



General Procedure H: Dichlorohydration

Colourless oil, 85%; ν_{max} (film/cm^{-1}) 3532 (O-H), 2972 (C-H), 1671 (C=O), 1604 (Ar), 1235, 1187; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (2H, d, J = 8.3, 2 × ArH), 7.26 (2H, d, J = 8.3, 2 × ArH), 4.05 (1H, br. s., CH), 2.43 (3H, s, $ArCH_3$), 2.01 (4H, q, J = 7.5, 2 × CH_2CH$_3$), 1.07 (6H, t, J = 7.5, 2 × CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.4, 144.9, 131.3, 130.5, 128.8, 92.0, 81.4, 29.0, 21.9, 9.22; HRMS: Found (CI): $[M+H]^+$ 289.075911, $C_{14}H_{19}Cl_2O_2$ requires 289.075911

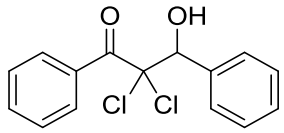
3-(4-Bromophenyl)-2,2-dichloro-3-hydroxy-1-phenylpropan-1-one (94k)



General Procedure H: Dichlorohydration

Yellow solid, 38%; Mp 135 – 139 °C; ν_{max} (film/cm^{-1}) 3567 (O-H), 1669 (C=O), 1592 (Ar), 1283, 1010; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (2H, d, *J* = 7.5, 2 × ArH), 7.63 (1H, t, *J* = 7.2, ArH), 7.52 - 7.55 (2H, m, 2 × ArH), 7.47 - 7.51 (4H, m, 4 × ArH), 5.54 (1H, d, *J* = 3.4, C*H*(OH)), 3.82 (1H, br. s., OH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.7, 134.7, 134.6, 134.4, 131.6, 131.5, 130.8, 128.4, 123.3, 86.2, 77.5; HRMS: Found (CI): $[M+H]^+$ 372.93860, $C_{15}H_{12}O_2Cl_2Br$ requires 372.93977

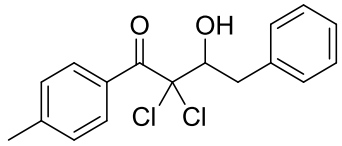
3-Hydroxy-2,2-dichloro-1,3-diphenylpropan-1-one (94l)



General Procedure H: Dichlorohydration

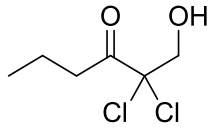
White solid, 32%; Mp 93 – 96 °C; ν_{max} (film/cm^{-1}) 3537 (O-H), 1666 (C=O), 1240, 1059; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (2H, d, *J* = 8.5, 2 × ArH), 7.60 - 7.64 (3H, m, 3 × ArH), 7.49 (2H, t, *J* = 7.8, 2 × ArH), 7.38 - 7.43 (3H, m, 3 × ArH), 5.59 (1H, d, *J* = 4.0, C*H*OH), 3.76 (1H, d, *J* = 4.0, OH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.9, 135.7, 134.1, 132.0, 131.3, 129.9, 129.0, 128.3, 127.6, 86.7, 78.0; HRMS: Found (APCI): $[M+H]^+$ 295.0286, $C_{15}H_{13}Cl_2O_2$ requires 295.0287

3-Hydroxy-2,2-dichloro-4-phenyl-1-(*p*-tolyl)butan-1-one (94m)



White solid, 24%; Mp 85 – 88 °C; ν_{max} (film/cm^{-1}) 3516 (O-H), 2934 (C-H), 1671 (C=O), 1603 (Ar), 1258; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (2H, d, *J* = 8.3, 2 × ArH), 7.32 - 7.38 (4H, m, 4 × ArH), 7.26 - 7.31 (3H, m, 3 × ArH), 4.61 (1H, dd, *J* = 9.8, 2.3, C*H*(OH)), 3.38 (1H, d, *J* = 13.9, CHC*H*H), 3.25 (1H, br. s, OH), 2.97 (1H, dd, *J* = 13.9, 9.8, CHCH*H*), 2.45 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.6, 145.5, 138.3, 131.5, 129.7, 129.1, 129.0, 128.6, 126.8, 87.5, 78.3, 37.2, 21.9; HRMS: Found (CI): $[M+H]^+$ 323.06101, $C_{17}H_{17}O_2Cl_2$ requires 323.06056

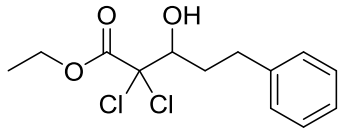
1-Hydroxy-2,2-dichloro-hexan-3-one (94n)



General Procedure H: Dichlorohydration

Colourless oil, 20%; ν_{max} (film/cm^{-1}) 3547 (O-H), 2959 (C-H), 1675 (C=O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.13 (2H, s, OCH_2), 2.87 - 2.94 (2H, t, *J* = 7.3, $COCH_2$), 2.74 (1H, br. s, OH), 1.70 (2H, sx, *J* = 7.3, C*H*$_2$CH$_3$), 0.97 (3H, t, *J* = 7.3, CH$_2$C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.8, 85.9, 69.3, 37.6, 17.8, 13.5; HRMS: Found (CI): $[M+H]^+$ 185.0135412, $C_6H_{11}Cl_2O_2$ requires 185.01361

Ethyl 3-hydroxy-2,2-dichloro-5-phenylpentanoate (94t)

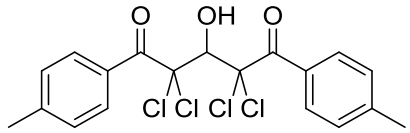


General Procedure H: Dichlorohydration

Colourless oil, 70%; ν_{max} (film/cm^{-1}) 3473 (O-H), 2934 (C-H), 1741 (C=O), 1454 (Ar), 1392, 1235; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 - 7.33 (2H, m, 2 × ArH), 7.20 - 7.25 (3H, m, 3 × ArH),

4.33 (2H, q, *J* = 7.2, OCH_2), 4.22 (1H, m, CH(OH)), 2.98 (1H, ddd, *J* = 14.0, 9.3, 4.8, CH(OH)C*H*H), 2.72 - 2.78 (2H, m, CH(OH)CH*H* and OH), 2.16 - 2.22 (1H, m, ArC*H*H), 1.97 (1H, ddd, *J* = 14.0, 9.3, 4.8, ArCH*H*), 1.34 (3H, t, *J* = 7.2, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 166.0, 141.2, 128.7, 128.65, 128.62, 126.3, 86.7, 76.6, 64.2, 32.8, 32.0, 13.9; HRMS: Found (CI): $[M+H]^+$ 291.05567, $C_{13}H_{17}O_3Cl_2$ requires 291.05547

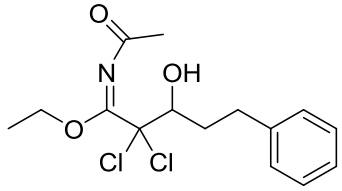
3-Hydroxy-2,2,4,4-tetrachloro-1,5-di-*p*-tolylpentane-1,5-dione (94u)



General Procedure H: Dichlorohydration

White solid, 46%; Mp 145 – 148 °C; ν_{max} (film/cm^{-1}) 3443 (O-H), 1679 (C=O), 1602 (Ar); ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 8.02 (4H, d, *J* = 8.3, 4 × ArH), 7.26 (4H, d, *J* = 8.3, 4 × ArH), 5.99 (1H, d, *J* = 9.4, OH), 4.17 (1H, d, *J* = 9.4, C*H*(OH)), 2.42 (6H, s, 2 × CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 188.9, 144.7, 130.9, 129.6, 129.1, 86.8, 77.7, 21.9; HRMS: Found (APCI): $[M+H]^+$ 432.9920, $C_{19}H_{17}Cl_4O_3$ requires 432.9926

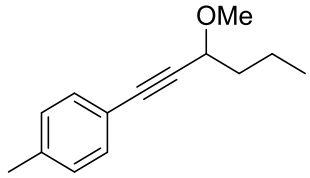
(*E*)-*N*-Acetyl-2,2-dichloro-3-hydroxy-5-phenylpentanimidate (96)



General Procedure H: Dichlorohydration

Colourless oil, 27%; ν_{max} (film/cm^{-1}) 1754 (C=O), 1620 (C=N), 1370, 1215; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.27 - 7.32 (2H, m, 2 × ArH), 7.18 - 7.23 (3H, m, 3 × ArH), 5.76 (1H, dd, *J* = 9.4, 2.4, OCH), 4.65 (2H, m, OCH_2), 2.69 (2H, t, *J* = 8.1, $PhCH_2$), 2.10 - 2.22 (2H, m, OCHCH_2), 2.13 (3H, s, $COCH_3$), 1.45 (3H, t, *J* = 7.1, CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 170.1, 165.3, 140.8, 128.6, 128.5, 126.3, 88.0, 76.3, 72.3, 33.0, 32.1, 20.9, 15.4; HRMS: Found (CI): $[M+H]^+$ 332.082067, $C_{15}H_{20}NO_3Cl_2$ requires 332.08202

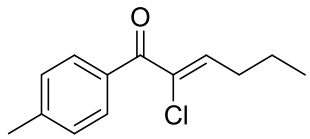
1-(3-Methoxyhex-1-yn-1-yl)-4-methylbenzene (97)



Powdered KOH (225 mg, 4.0 mmol) was added to a stirring solution of methyl iodide (375 µL, 6.0 mmol) and propargylic alcohol **70a** (376 mg, 2.00 mmol) in DMSO (20 mL) under an argon atmosphere. After 2 h, the solution was put through a silica plug (petrol). Water (10 mL) was added to the solution and the product was extracted with Et_2O (3 × 10 mL), the combined organic fractions was dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure and the residue purified by column chromatography (EtOAc/petrol) to give ether **97**.

Yellow oil, 71%; ν_{max} (film/cm^{-1}) 2959 (C-H) 2932 (C-H), 1509 (Ar), 1089; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (2H, d, *J* = 8.1, 2 × ArH), 7.11 (2H, d, *J* = 8.1, 2 × ArH), 4.16 (1H, t, *J* = 6.6, C*H*OCH_3), 3.46 (3H, s, OCH_3), 2.34 (3H, s, $ArCH_3$), 1.71 - 1.83 (2H, m, $CHCH_2$), 1.53 (2H, sx, *J* = 7.4, CH_2CH_3), 0.96 (3H, t, *J* = 7.4, CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.5, 131.7, 129.1, 119.9, 87.5, 86.0, 71.7, 56.6, 37.9, 21.6, 18.7, 14.0; HRMS: Found (EI): $[M]^+$ 202.134827, $C_{14}H_{18}O$ requires 202.13577

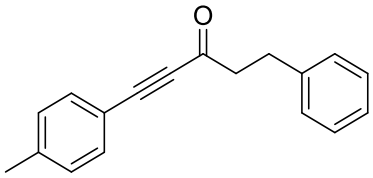
(*Z*)-2-Chloro-1-(*p*-tolyl)hex-2-en-1-one (98)



General Procedure H: Dichlorohydration

Yellow oil, 32%; ν_{max} (film/cm^{-1}) 2961 (C-H) 2930 (C-H), 1663 (C=O), 1607 (Ar), 1269; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (2H, d, *J* = 7.9, 2 × ArH), 7.26 (2H, d, *J* = 7.9, 2 × ArH), 6.64 (1H, t, *J* = 7.4, CH), 2.45 (2H, q, *J* = 7.4, $CHCH_2$), 2.42 (3H, s, $ArCH_3$), 1.54 (2H, sx, *J* = 7.4, CH_2CH_3), 0.98 (3H, t, *J* = 7.4, CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.3, 144.6, 143.4, 134.2, 133.3, 129.8, 129.2, 31.9, 21.8, 21.4, 14.1; HRMS: Found (EI): $[M]^+$ 222.080149, $C_{13}H_{15}ClO$ requires 222.08114

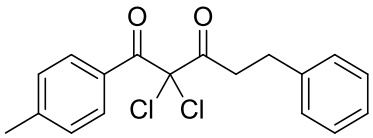
5-Phenyl-1-(*p*-tolyl)pent-1-yn-3-one (103)



Propargylic alcohol **70f** (500 mg, 2.00 mmol) was added to a stirring solution of 2,3-dichloro-1,4-dicyanobenzoquinone (DDQ) (5 mg, 0.02 mmol) and $NaNO_2$ (14 mg, 0.02 mmol) in DCM/AcOH (10:1, 10 mL). This solution was stirred for 48 h under an argon atmosphere before the solvent was removed under reduced pressure and the residue purified by column chromatography (EtOAc/petrol) to give the ketone **103**.

Yellow oil, 48%; ν_{max} (film/cm^{-1}) 3028 (C-H), 2196 (C≡C), 1663 (C=O), 1604 (Ar), 1089; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (2H, d, *J* = 7.9, 2 × ArH), 7.28 - 7.32 (2H, m, 2 × ArH), 7.18 - 7.25 (5H, m, 5 × ArH), 3.04 - 3.08 (2H, m, $COCH_2$), 2.98 - 3.03 (2H, m, $PhCH_2$), 2.39 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 187.1, 141.7, 140.5, 133.3, 129.6, 128.7, 128.5, 126.4, 116.9, 92.0, 87.8, 47.1, 30.2, 21.9; HRMS: Found (EI): $[M]^+$ 248.11920, $C_{18}H_{16}O$ requires 248.12012

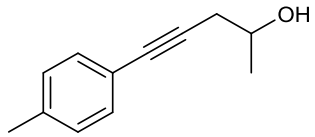
2,2-Dichloro-5-phenyl-1-(*p*-tolyl)pentane-1,3-dione (104)



General Procedure H: Dichlorohydration

Colourless oil, 55%; ν_{max} (film/cm^{-1}) 3029 (C-H), 1747 (C=O), 1674 (C=O), 1604 (Ar), 1186; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (2H, d, *J* = 8.5, 2 × ArH), 7.24 - 7.28 (2H, m, 2 × ArH), 7.23 (2H, d, *J* = 8.5, 2 × ArH), 7.17 - 7.21 (1H, m, ArH), 7.15 (2H, d, *J* = 7.2, 2 × ArH), 3.03 - 3.06 (2H, m, $COCH_2$), 2.97 - 3.01 (2H, m, $PhCH_2$), 2.42 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.3, 185.5, 145.9, 140.0, 130.8, 129.5, 128.7, 128.5, 128.3, 126.5, 86.9, 39.3, 30.6, 22.0; HRMS: Found (EI): $[M]^+$ 334.05177, $C_{18}H_{16}O_2Cl_2$ requires 334.05274

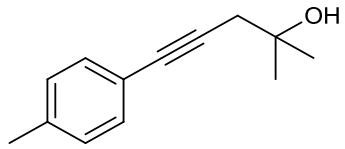
5-(*p*-Tolyl)pent-4-yn-2-ol (108d)



n-Butyllithium (1.6M in hexane, 1.2 eq.) was added dropwise to a stirred solution of alkyne (1 eq.) in dry THF (1 mLmmol^{-1}) at -78 ˚C under an argon atmosphere. After 1 h BF_3OEt_2 (2.5 eq.) was added and stirred for 30 min before epoxide (2.5 eq.) was added and the resulting solution was stirred for 5 min at 0 ˚C and 1h at rt. The reaction was quenched with saturated NH_4Cl solution and the organic phase extracted with Et_2O. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography to give homopropargylic alcohol **108d**.

Yellow oil, 31%; ν_{max} (film/cm^{-1}) 3353 (O-H), 2970 (C-H), 2922 (C-H), 1509 (Ar); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (2H, d, *J* = 8.1, 2 × ArH), 7.10 (2H, d, *J* = 8.1, 2 × ArH), 4.04 (1H, qdd, *J* = 6.4, 6.4, 5.1, C*H*(OH)), 2.62 (1H, dd, *J* = 16.8, 5.2, CH(OH)C*H*H), 2.54 (1H, dd, *J* = 16.8, 6.4, CH(OH)CH*H*), 2.34 (3H, s, $ArCH_3$), 1.32 (3H, d, *J* = 6.4, CHCH_3); ^{13}C NMR (125MHz, $CDCl_3$) δ 138.1, 131.6, 129.1, 120.3, 85.4, 83.3, 66.7, 30.2, 22.5, 21.6; HRMS: Found (CI): $[M+H]^+$ 175.112819, $C_{12}H_{15}O$ requires 175.11229

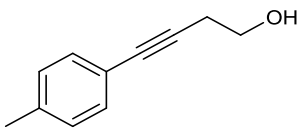
2-Methyl-5-(*p*-tolyl)pent-4-yn-2-ol (108e)



n-Butyllithium (1.6M in hexane, 1.2 eq.) was added dropwise to a stirred solution of alkyne (1 eq.) in dry THF (1 mLmmol^{-1}) at -78 ˚C under an argon atmosphere. After 1 h BF_3OEt_2 (2.5 eq.) was added and stirred for 30 min before epoxide (2.5 eq.) was added and the resulting solution was stirred for 5 min at 0 ˚C and 1 h at rt. The reaction was quenched with saturated NH_4Cl solution and the organic phase extracted with Et_2O. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/petrol) to give homopropargylic alcohol **108e**.

Pale yellow oil, 66%; ν_{max} (film/cm^{-1}) 3393 (O-H), 2973 (C-H), 1509 (Ar), 1376, 1213; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (2H, d, J = 8.0, 2 × ArH), 7.10 (2H, d, J = 8.0, 2 × ArH), 2.59 (2H, s, CH_2), 2.34 (3H, s, $ArCH_3$), 1.37 (6H, s, $CH_2C(CH_3)(CH_3)$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.1, 131.6, 129.1, 120.4, 85.6, 83.7, 70.4, 35.2, 28.8, 21.6; HRMS: Found (EI): $[M]^+$ 188.120324, $C_{13}H_{16}O$ requires 188.12012

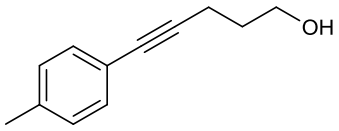
4-(*p*-Tolyl)but-3-yn-1-ol (108f)[99]



$Pd(PPh_3)_4$ (0.01 eq.) and CuI (0.02 eq.) were added to the solution of iodotoluene (2.0 equiv) and alkynol (1.0 eq.) in NEt_3 (10 eq.) and THF (0.5M) under Ar. The reaction mixture was stirred at rt for 12 h. The mixture was filtered and the filtrate was concentrated under reduced pressure. The product was purified by column chromatography (EtOAc/petrol) to give alkynol **108f**.

Yellow oil, 846mg, 99%; ν_{max} (film/cm^{-1}) 3298 (O-H), 2882 (C-H), 1508 (Ar), 1371; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (2H, d, J = 8.1, 2 × ArH), 7.10 (2H, d, J = 8.1, 2 × ArH), 3.81 (2H, t, J = 6.2, OCH_2), 2.68 (2H, t, J = 6.2, CCH_2), 2.34 (3H, s, CH_3), 1.79 (1H, br. s, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 131.6, 129.1, 120.3, 85.5, 82.7, 61.3, 23.9, 21.5; LRMS: (EI): 160 ($[M]^+$, 10), 129 ($[M\text{-}EtOH]^+$, 100)

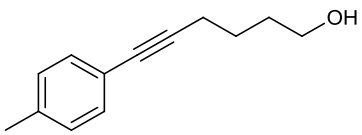
5-(*p*-Tolyl)pent-4-yn-1-ol (108g)[100]



$Pd(PPh_3)_4$ (0.01 eq.) and CuI (0.02 eq.) were added to the solution of iodotoluene (2.0 equiv) and alkynol (1.0 eq.) in triethylamine (10 eq.) and THF (0.5M) under Ar. The reaction mixture was stirred at rt for 12 h. The mixture was filtered and the filtrate was concentrated under reduced pressure. The product was purified by column chromatography (EtOAc/petrol) to give alkynol **108g**.

Orange solid, 880 mg, 95%; Mp 40 – 41 °C; ν_{max} (film/cm^{-1}) 3324 (O-H), 2924 (C-H), 1509 (Ar), 1045; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (2H, d, J = 7.9, 2 × ArH), 7.09 (2H, d, J = 7.9, 2 × ArH), 3.82 (2H, t, J = 6.5, OCH_2), 2.53 (2H, t, J = 6.5, CCH_2), 2.33 (3H, s, $ArCH_3$), 1.85 (2H, qn, J = 6.5, 2 OCH_2CH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.8, 131.5, 129.1, 120.7, 88.6, 81.3, 62.0, 31.5, 21.5, 16.1; LRMS: (CI): 175 ([M+H]$^+$, 90), 131 ([M-EtOH]$^+$, 100)

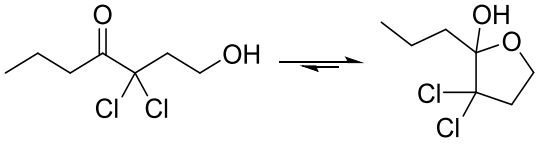
6-(*p*-Tolyl)hex-5-yn-1-ol (108h)[101]



$Pd(PPh_3)_4$ (0.01 eq.) and CuI (0.02 eq.) were added to the solution of iodotoluene (2.0 equiv) and alkynol (1.0 eq.) in triethylamine (10 eq.) and THF (0.5 mLmmol^{-1}) under Ar. The reaction mixture was stirred at rt for 12 h. The mixture was filtered and the filtrate was concentrated under reduced pressure. The product was purified by column chromatography (EtOAc/petrol) to give alkynol **108h**.

Orange oil, 968 mg, 95%; ν_{max} (film/cm^{-1}) 3337 (O-H), 2937 (C-H), 1509 (Ar), 1058; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (2H, d, J = 8.1, 2 × ArH), 7.08 (2H, d, J = 8.1, 2 × ArH), 3.71 (2H, t, J = 6.4, OCH_2), 2.44 (2H, t, J = 6.8, CCH_2), 2.33 (3H, s, CH_3), 1.72 - 1.77 (2H, m, CCH_2CH_2), 1.65 - 1.71 (2H, m, OCH_2CH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.7, 131.5, 129.1, 120.9, 89.2, 81.1, 62.6, 32.0, 25.2, 21.5, 19.3; HRMS: Found (EI): $[M]^+$ 188.120621, $C_{13}H_{16}O$ requires 188.12012

3,3-Dichloro-2-propyltetrahydrofuran-2-ol (109a)

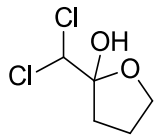


General Procedure H: Dichlorohydration

Colourless oil, 53%; ν_{max} (film/cm^{-1}) 3421 (O-H), 2967 (C-H), 1730 (C=O), 1046; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.09 (1H, td, J = 8.8, 2.9, OCHH), 4.03 (1H, br. q, J = 8.8, OCHH), 3.01 (1H, dt, J = 13.2, 8.8, OCH_2CHH), 2.75 (1 H, ddd, J = 13.2, 7.3, 2.9, $OCH_2CH$$H$), 1.53 - 1.67 (4H, m,

$CH_3CH_2CH_2$), 0.99 (3H, t, *J* = 7.3, CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 106.6, 91.6, 64.4, 43.9, 36.2, 16.6, 14.5; HRMS: Found (CI): $[M-H_2O]^+$ 181.017931, $C_7H_{11}Cl_2O$ requires 181.01870

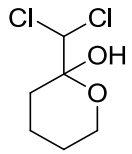
2-(Dichloromethyl)tetrahydrofuran-2-ol (109b)



General Procedure H: Dichlorohydration

White solid, 99%; Mp 66 – 68 °C; ν_{max} (film/cm^{-1}) 3422 (O-H), 3010 (C-H), 1208, 1005; ^1H NMR (600 MHz, $CDCl_3$) δ 5.73 (1H, s, $CHCl_2$), 4.16 - 4.22 (1H, m, OC*H*H), 4.02 (1H, m, OCH*H*), 2.88 - 3.03 (1H, m, OH), 2.14 - 2.25 (3H, m, OCH_2CH_2, OCH_2CH_2CHH), 1.99 - 2.06 (1H, m, OCH_2CH_2CHH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 106.2, 76.3, 70.4, 34.9, 25.2; HRMS: Found (CI): $[M+H]^+$ 170.99651, $C_5H_9Cl_2O_2$ requires 170.99796; anal. cald. For $C_5H_9Cl_2O_2$ C, 35.12; H, 4.72; Found: C, 33.33; H, 4.42

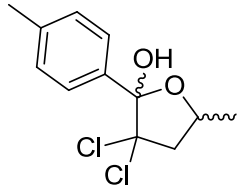
2-(Dichloromethyl)tetrahydro-2*H*-pyran-2-ol (109c)



General Procedure H: Dichlorohydration

Colourless oil, 65%; ν_{max} (film/cm^{-1}) 3432 (O-H), 2847 (C-H), 2881 (C-H), 1727 (C=O); ^1H NMR (600 MHz, $CDCl_3$) δ 5.57 (1H, s, $CHCl_2$), 3.93 – 3.97 (1H, m, OC*H*H), 3.79 – 3.92 (1H, m, OCH*H*), 2.78 (1H, d, *J* = 2.7, OH), 1.95 (1H, dt, *J* = 13.3, 3.3, (C)C*H*H), 1.82 - 1.89 (1H, m, OCH_2CH_2CHH), 1.72 - 1.79 (1H, m, OCH_2CH_2CHH), 1.64 (1 H, ddd, *J* = 13.3, 4.8, 2.6, (C)CH*H*), 1.53 - 1.62 (2H, m, OCH_2CH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ 96.0, 78.2, 62.7, 30.2, 24.7, 19.0; HRMS: Found (ES-): $[M-H]^+$ 182.9928, $C_6H_9O_2Cl_2$ requires 182.9980;

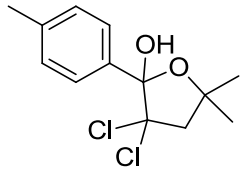
3,3-Dichloro-5-methyl-2-(*p*-tolyl)tetrahydrofuran-2-ol (109d)



General Procedure H: Dichlorohydration

Colourless oil, 79%; ν_{max} (film/cm^{-1}) 3403 (O-H), 2977 (C-H), 1513 (Ar), 1184; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 - 7.66 (2H, m, 2 × ArH), 7.16 - 7.22 (2H, m, 2 × ArH), 4.60 (1H, dqd, *J* = 9.5, 6.2, 5.8 OCH), 3.00 (1H, dd, *J* = 12.9, 5.8, OCHCH*H*), 2.86 (1H, dd, *J* = 12.9, 9.5, OCHC*H*H-major), 2.38 (3H, s, $ArCH_3$), 1.42 - 1.48 (3H, m, CHCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.4, 134.9, 128.5, 127.4, 106.1, 91.8, 74.1, 51.8, 22.6, 21.4; HRMS: Found (CI): $[M+H]^+$ 261.043998, $C_{12}H_{15}Cl_2O_2$ requires 261.04491

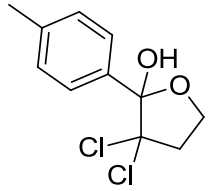
3,3-Dichloro-5,5-dimethyl-2-(*p*-tolyl)tetrahydrofuran-2-ol (109e)



General Procedure H: Dichlorohydration

White solid, 84%; Mp 77 – 79 °C; ν_{max} (film/cm^{-1}) 3420 (O-H), 2988 (C-H), 1440 (Ar); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (2H, d, *J* = 8.3, 2 × ArH), 7.19 (2H, d, *J* = 8.3, 2 × ArH), 3.10 (1H, d, *J* = 13.6, COC*H*H), 3.03 (1H, s, OH), 2.93 (1H, d, *J* = 13.6, COCH*H*), 2.38 (3H, s, $ArCH_3$), 1.56 (3H, s, C(CH_3)(CH_3), 1.54 (3H, s, C(CH_3)(CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.3, 135.2, 128.5, 127.3, 106.8, 92.0, 80.8, 56.4, 32.2, 28.6, 21.4; HRMS: Found (CI): $[M-H]^+$ 275.059913, $C_{13}H_{17}O_2Cl_2$ requires 275.06056

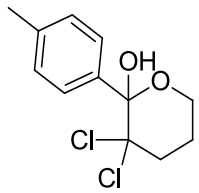
3,3-Dichloro-2-(*p*-tolyl)tetrahydrofuran-2-ol (109f)



General Procedure H: Dichlorohydration

White solid, 89%; Mp 115 – 118 °C; ν_{max} (film/cm^{-1}) 3357 (O-H), 1441 (Ar), 1268; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (2H, d, *J* = 8.3, 2 × ArH), 7.22 (2H, d, *J* = 8.3, 2 × ArH), 4.23 (1H, ddd, *J* = 9.4, 8.3, 7.1, OCH*H*), 4.12 (1H, ddd, *J* = 9.4, 8.3, 2.2, OC*H*H), 3.60 (1H, s, OH), 3.19 (1H, dt, *J* = 13.1, 9.4, OCH_2CHH), 2.90 (1 H, ddd, *J* =13.1, 7.1, 2.2, OCH_2CH*H*), 2.41 (3H, s, $ArCH_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.5, 134.4, 128.6, 127.4, 105.9, 91.2, 64.6, 44.5, 21.4; HRMS: Found (EI): $[M]^+$ 246.021313, $C_{11}H_{12}Cl_2O_2$ requires 246.02143; anal. cald. For $C_{11}H_{12}Cl_2O_2$ C, 53.47; H, 4.89; Found: C, 53.93; H, 4.94

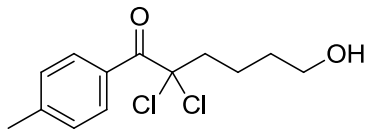
3,3-Dichloro-2-(*p*-tolyl)tetrahydro-2*H*-pyran-2-ol (109g)



General Procedure H: Dichlorohydration

White solid, 57%; Mp 97 – 99 °C; ν_{max} (film/cm^{-1}) 3411 (O-H), 2971 (C-H), 1617 (C=O), 1388, 1074; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (2H, d, *J* = 8.1, 2 × ArH), 7.19 (2H, d, *J* = 8.1, 2 × ArH), 4.23 (1H, ddd, *J* = 13.6, 11.4, 3.0, OC*H*H), 3.86 (1 H, dd, *J* = 11.4, 5.5, OCH*H*), 2.95 (1H, td, *J* = 13.6, 4.3, OCH_2CH*H*), 2.85 (1H, s, OH), 2.55 (1H, d, *J* = 13.6, OCH_2CH*H*), 2.30 - 2.39 (4H, m, $ArCH_3$, OCH_2CH_2CHH), 1.63 - 1.69 (1H, m, OCH_2CH_2CH*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.2, 136.5, 128.6, 128.0, 98.8, 91.0, 60.3, 40.4, 23.9, 21.4; HRMS: Found (CI): $[M+H]^+$ 261.044010, $C_{12}H_{15}Cl_2O_2$ requires 261.04491

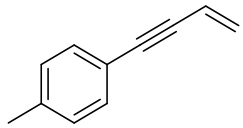
6-Hydroxy-2,2-dichloro-1-(*p*-tolyl)hexan-1-one (109h)



General Procedure H: Dichlorohydration

Colourless oil, 72%; ν_{max} (film/cm^{-1}) 3345 (O-H), 2941 (C-H), 2873 (C-H), 1685 (C=O), 1606, 1253; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (2H, d, *J* =8.3, 2 × ArH), 7.26 (2H, d, *J* = 8.3, 2 × ArH), 3.72 (2H, t, *J* = 6.4, OCH_2), 2.50 - 2.55 (2H, m, Cl_2CCH_2), 2.43 (3H, s, CH_3), 1.76 - 1.83 (2H, m, Cl_2CCH_2), 1.67 – 1.72 (2H, m, C*H*$_2$OCH$_2$C*H*$_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 188.2, 144.7, 131.3, 129.2, 128.9, 87.4, 62.6, 44.2, 32.1, 21.9, 21.4; HRMS: Found (CI): $[M-H]^+$ 275.060120, $C_{13}H_{17}O_2Cl_2$ requires 275.06056

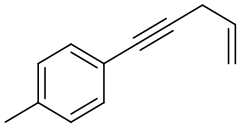
1-(But-3-en-1-yn-1-yl)-4-methylbenzene (114a)[102]



Vinyl bromide (1M in THF, 15 mL, 15mmol) was added in one portion to a stirring solution of tolylacetylene (1.16 g, 10 mmol) and diisopropylamine (5 mL), followed by the addition of $Pd(PPh_3)_4$ (184 mg) and CuI (92 mg). After 18 h, water (40 mL) was added and the product was extracted with Et_2O (3 × 20 mL), the combine organic fractions were dried ($MgSO_4$), filtered and solvent was removed under reduced pressure before purification by flash chromatography (petrol) to give eneyne **114a**.

Colourless oil, 990 mg, 70%; ν_{max} (film/cm^{-1}) 3030 (C-H), 1601 (C=C), 1507 (Ar); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (2H, d, *J* = 8.1, 2 × ArH), 7.13 (2H, d, *J* = 8.1, 2 × ArH), 6.02 (1H, dd, *J* = 17.7, 11.2, C*H*H), 5.72 (1H, dd, *J* = 17.7, 2.1, CH*H*), 5.52 (1H, dd, *J* = 11.2, 2.1, CH), 2.35 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 131.6, 129.2, 126.6, 120.1, 117.4, 90.3, 87.6, 21.6; LRMS: (EI): 142 ($[M-H]^+$, 50), 115 (100), 63 (40)

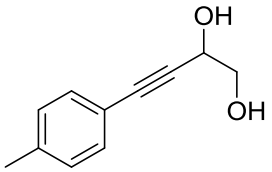
1-Methyl-4-(pent-4-en-1-yn-1-yl)benzene (114b)[103]



Allyl bromide (1.3 mL, 15 mmol) was added to stirring solution of tolylacetylene (1.16 g, 10 mmol), K_2CO_3 (2.4 g, 17 mmol), CuI (190 mg) in anhydrous DMF (10 mL). After 18 h, water (40 mL) was added and the product was extracted with Et_2O (3 × 20 mL), the combined organic fractions were dried ($MgSO_4$), filtered and solvent was removed under reduced pressure before purification by flash chromatography (petrol) to give eneyne **114b**.

Colourless oil, 890 mg, 57%; ν_{max} (film/cm^{-1}) 2981 (C-H), 1641 (C=C), 1509 (Ar); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (2H, d, *J* = 8.0, 2 × ArH), 7.10 (2H, d, *J* = 8.0, 2 × ArH), 5.90 (1H, ddt, *J* = 16.9, 10.0, 5.3, CH), 5.41 (1H, dtd, *J* = 16.9, 1.9, 1.7, =C*H*H), 5.16 (1H, dtd, *J* = 10.0, 1.9, 1.7, =CH*H*), 3.19 (2H, ddd, *J* = 5.3, 1.9, 1.7, CCH_2), 2.34 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.9, 132.7, 131.6, 129.1, 120.7, 116.7, 116.3, 85.8, 83.0, 23.9, 21.6; LRMS: (EI): 156 ($[M]^+$, 50), 141 (70), 128 (70), 115 (100); HRMS: Found (EI): $[M]^+$ 156.09357, $C_{11}H_{12}$ requires 156.09390

4-(*p*-Tolyl)but-3-yne-1,2-diol (115a)

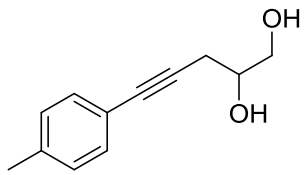


$K_2OsO_4.H_2O$ (94 mg) was added to a stirring solution of alkene **114a** (710 mg, 5.0 mmol), *N*-methylmorpholine oxide (NMO) (892 mg, 7.5 mmol) in DCM/H_2O (40:5, 20 mL). After 18 h, saturated $Na_2S_2O_3$ solution (15 mL) was added and the product was extracted with DCM (3 × 20 mL) before the combined organic fractions were washed with brine and dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure before the residue was purified by flash chromatography (EtOAc/petrol) to give diol **115a**.

White solid, 385 mg, 44%; Mp 90 – 91 °C; ν_{max} (film/cm^{-1}) 3208 (O-H), 2921 (C-H), 1509 (Ar); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (2H, d, *J* = 8.0, 2 × ArH), 7.12 (2H, d, *J* = 8.0, 2 × ArH), 4.68 (1H, dd, *J* = 6.8, 3.8, OCH), 3.83 (1H, dd, *J* = 11.4, 3.8, OC*H*H), 3.78 (1H, dd, *J* = 11.4, 6.8,

CH*H*), 2.35 (3H, s, CH_3), 2.24 (2H, br. s, 2 × OH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.1, 131.8, 129.2, 119.0, 86.6, 85.8, 66.7, 63.9, 21.6; LRMS: (EI): 176 ([M]$^+$, 30), 145 (100), 115 (30); HRMS: Found (EI): [M]$^+$ 176.08311, $C_{11}H_{12}O_2$ requires 176.08373

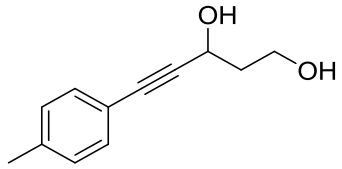
5-(*p*-Tolyl)pent-4-yne-1,2-diol (115b)



$K_2OsO_4.H_2O$ (94 mg) was added to a stirring solution of alkene **114b** (950 mg, 5 mmol), *N*-methylmorpholine oxide (NMO) (892 mg, 7.5 mmol) in DCM/H_2O (40:5, 20 mL). After 18 h, saturated $Na_2S_2O_3$ solution (15 mL) was added and the product was extracted with DCM (3 × 20 mL) before the combined organic fractions were washed with brine and dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure before the residue was purified by flash chromatography (EtOAc/petrol) to give diol **115b**.

White solid, 543 mg, 57%; Mp 59 – 62 °C; ν_{max} (film/cm^{-1}) 3298 (O-H), 2916 (C-H), 1508 (Ar); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (2H, d, *J* = 8.0, 2 × ArH), 7.10 (2H, d, *J* = 8.0, 2 × ArH), 3.96 (1H, dddd, *J* = 6.5, 6.5, 6.1, 3.5, OCH), 3.81 (1H, dd, *J* = 11.3, 3.5, OC*H*H), 3.66 (1H, dd, *J* = 11.3, 6.5, OCH*H*), 2.68 (1H, dd, *J* = 16.8, 6.5, CC*H*H), 2.64 (1H, dd, *J* = 16.8, 6.1, CCH*H*), 2.34 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.3, 131.6, 129.2, 120.1, 84.5, 83.4, 70.5, 65.8, 24.6, 21.6; LRMS: (EI): 176 ([M]$^+$, 40), 129 (100), 115 (60); HRMS: Found (EI): [M]$^+$ 190.098911, $C_{12}H_{14}O_2$ requires 190.09938

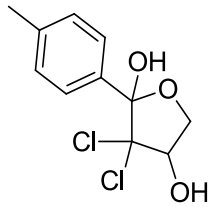
5-(*p*-Tolyl)pent-4-yne-1,3-diol (115c)



$LiBH_4$ (2 eq.) was added to a stirring solution of ester **70d** (150 mg, 0.64 mmol) in Et_2O (2 mL) at 0 °C. After 2 h the solvent was removed under reduced pressure before the residue was purified by column chromatography (EtOAc/petrol) to give diol **115c**.

Yellow oil, 102 mg, 0.54 mmol, 84%; ν_{max} (film/cm^{-1}) 3325 (O-H), 2921 (C-H), 1509 (Ar), 1421; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (2H, d, *J* = 7.9, 2 × ArH), 7.11 (2H, d, *J* = 7.9, 2 × ArH), 4.87 (1H, dd, *J* = 6.8, 4.5, OCH), 4.07 (1H, ddd, *J* = 11.0, 7.4, 4.0, OC*H*H), 3.92 (1H, ddd, *J* = 11.0, 6.8, 4.0, CH*H*), 2.34 (3H, s, CH_3), 2.07 - 2.14 (1H, m, OCH_2CHH), 2.00 - 2.06 (1H, m, OCH_2CHH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.8, 131.7, 129.2, 119.4, 88.7, 85.6, 62.4, 60.7, 39.1, 21.6; HRMS: Found (CI): $[M]^+$ 190.098631, $C_{12}H_{14}O_2$ requires 190.09938

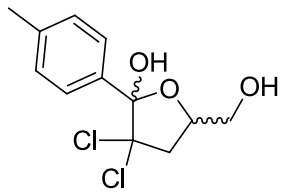
3,3-Dichloro-2-(*p*-tolyl)tetrahydrofuran-2,4-diol (116a)



General Procedure H: Dichlorohydration

White solid, 92%; Mp 126 – 128 °C; ν_{max} (film/cm^{-1}) 3456 (O-H), 3402 (O-H), 3336 (O-H), 3120 (C-H), 1512 (Ar), 1421 (Ar); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (2H, d, *J* = 8.3, 2 × ArH), 7.21 (2H, d, *J* = 8.3, 2 × ArH), 4.62 (1H, dd, *J* = 10.1, 5.1, OC*H*H), 4.54 - 4.57 (1H, m, OCH), 4.26 (1H, dd, *J* = 10.1, 0.9, OCH*H*), 4.06 (1H, s, OH), 3.54 (1H, br. d, *J* = 7.3, OH), 2.38 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.6, 133.4, 128.6, 127.5, 106.1, 92.7, 79.8, 72.5, 21.4; HRMS: Found (CI): $[M+H]^+$ 263.024050, $C_{11}H_{13}Cl_2O_3$ requires 263.02417

3,3-Dichloro-5-(hydroxymethyl)-2-(*p*-tolyl)tetrahydrofuran-2-ol (116b)

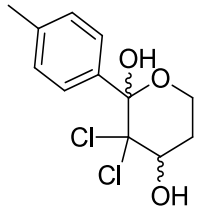


General Procedure H: Dichlorohydration

White solid, 91%; Mp 71 – 75 °C; ν_{max} (film/cm^{-1}) 3030 (O-H), 3008 (C-H), 2920 (C-H), 1602 (C=O), 1508 (Ar), 1410 (C-H); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (2H, d, *J* = 8.1, 2 × ArH), 7.19 (2H, d, *J* = 8.1, 2 × ArH), 4.58 (1H, dddd, *J* = 9.3, 6.4, 3.1, 3.1, OCH), 3.88 (1H, ddd, *J* = 6.0,

6.0, 2.9, OC*H*H), 3.54 (1H, ddd, *J* = 6.0, 6.0, 3.1, OCH*H*), 3.06 - 3.11 (1H, m, CCl_2CHH), 2.84 (1H, ddd, *J* = 6.7, 6.6, 2.2, CCl_2CHH), 2.38 (3H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.3, 133.9, 128.5, 127.3, 105.7, 91.9, 76.3, 62.7, 44.6, 21.4; HRMS: Found (CI): $[M+H]^+$ 258.029542, $C_{12}H_{13}Cl_2O_2$ requires 259.02926

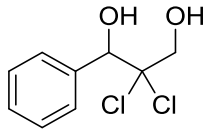
3,3-Dichloro-2-(*p*-tolyl)tetrahydro-2*H*-pyran-2,4-diol (116c)



General Procedure H: Dichlorohydration

White solid, 53%; Mp 122 – 126 °C; ν_{max} (film/cm^{-1}) 3533 (O-H), 3391 (O-H), 3297 (O-H), 2953 (C-H), 1461 (Ar), 1435 (Ar); ^1H NMR (600 MHz, $CDCl_3$) δ 7.67 (2H, d, *J* = 8.3, 2 × ArH), 7.21 (2H, d, *J* = 8.3, 2 × ArH), 4.53 - 4.59 (1H, m, OCH), 4.20 - 4.28 (1H, m, OC*H*H), 3.89 - 3.95 (1H, m, OCH*H*), 2.38 (3H, s, CH_3), 2.13 - 2.22 (1H, m, OCH_2CHH), 1.97 - 2.02 (1H, m, OCH_2CHH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.5, 136.0, 128.5, 128.2, 100.5, 96.2, 73.1, 58.9, 31.6, 21.4; HRMS: Found (APCI): $[M+H]^+$ 277.0393, $C_{12}H_{15}Cl_2O_3$ requires 277.0393

2,2-Dichloro-1-phenylpropane-1,3-diol (117c)

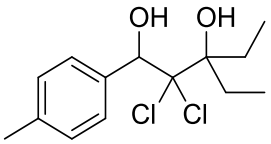


$NaBH_4$ (1.2 eq.) was added to a stirring solution of ketone **94c** in MeOH (0.5 mL) at 0 °C. Once the reaction is complete (TLC), the reaction mixture was quenched with saturated NH_4Cl solution and the organic phase extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography to give diol **117c**.

White solid, 93%; Mp 104 – 105 °C; ν_{max} (film/cm^{-1}) 3326 (O-H), 3203 (O-H), 1452 (Ar), 1110; ^1H NMR (600 MHz, $CDCl_3$) δ 7.52 - 7.57 (2H, m, 2 × ArH), 7.36 - 7.41 (3H, m, 3 × ArH), 5.24

(1H, s, CHPh), 4.11 (1H, d, *J* = 12.4, C*H*H) , 3.89 (1H, d, *J* = 12.4, CH*H*), 3.01 (1H, br. s, OH), 2.57 (1H, br. s, OH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.6, 129.2, 128.6, 128.1, 95.4, 78.6, 70.3; HRMS: Found (APCI): $[M+NH_4]^+$ 238.0392, $C_9H_{14}Cl_2NO_2$ requires 238.0396; anal. cald. For $C_9H_{10}Cl_2O_2$ C, 48.90; H, 4.56; Found: C, 48.82; H, 4.56

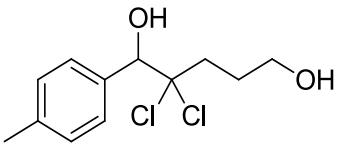
2,2-Dichloro-3-ethyl-1-(*p*-tolyl)pentane-1,3-diol (117j)



$NaBH_4$ (1.2 eq.) was added to a stirring solution of ketone **94j** in MeOH (0.5 mL) at 0 °C. Once the reaction is complete (TLC), the reaction mixture was quenched with saturated NH_4Cl solution and the organic phase extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography to give diol **117j**.

White solid, 87%, Mp 68 – 70 °C; ν_{max} (film/cm^{-1}) 3335 (O-H), 2971 (C-H), 2943 (C-H), 1458 (Ar), 1410 (Ar); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (2H, d, *J* = 8.1, 2 × ArH), 7.17 (2H, d, *J* = 8.1, 2 × ArH), 5.33 (1H, s, C*H*(OH)), 2.37 (3H, s, $ArCH_3$), 2.02 - 2.19 (4H, m, 2 × CH_2CH$_3$), 1.16 (3H, t, *J* = 7.5, CH_2CH_3), 1.03 (3H, t, *J* = 7.5, CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 134.9, 129.9, 128.2, 100.7, 83.4, 79.5, 28.4, 27.2, 21.4, 9.8, 8.6; HRMS: Found (CI): $[M+H]^+$ 291.091218, $C_{14}H_{21}Cl_2O_2$ requires 291.09186

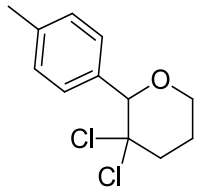
2,2-Dichloro-1-(*p*-tolyl)pentane-1,5-diol (118)



$NaBH_4$ (1.2 eq.) was added to a stirring solution of lactol **109f** in MeOH (0.5 mL) at 0 °C. Once the reaction is complete (TLC), the reaction mixture was quenched with saturated NH_4Cl solution and the organic phase extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography to give diol **118**.

White solid, 99%; Mp 74 – 77 °C; ν_{max} (film/cm^{-1}) 3341 (O-H), 3178 (O-H), 2966 (C-H), 1452 (ArH), 1048; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (2H, d, J = 8.1, 2 × ArH), 7.17 (2H, d, J = 8.1, 2 × ArH), 5.00 (1H, s, CH), 3.68 (2H, t, J = 6.0, CH_2OH), 2.36 (3H, s, CH_3), 2.25 (1H, ddd, J = 15.6, 7.9, 6.2, C(Cl)$_2$CHH), 2.17 (1H, ddd, J = 15.6, 7.9, 6.2, CCl_2CHH), 2.00 (2H, dt, J = 14.3, 6.4, CH_2CH$_2$OH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.9. 133.7, 128.74, 128.73, 98.6, 81.9, 62.2, 39.2, 28.2, 21.4; HRMS: Found (CI): [M]$^+$ 262.051223, $C_{12}H_{16}O_2Cl_2$ requires 262.05274

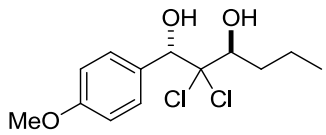
3,3-Dichloro-2-(*p*-tolyl)tetrahydro-2*H*-pyran (119)



BF_3.OEt_2 (3 eq.) was added to stirring solution of $HSiEt_3$ (2 eq.) and lactol **109f** (1 eq.) in DCM (0.5 mL) at -78 °C and then warmed to rt over 15 mins. The solvent was then removed under reduced pressure and the residue was purified by column chromatography to give tetrahydropyran **119**.

White solid, 80%; Mp 78 – 79 °C; ν_{max} (film/cm^{-1}) 2974 (C-H), 1515 (Ar), 1439 (Ar), 1185; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (2H, d, J = 8.3, 2 × ArH), 7.17 (2H, d, J = 8.3, 2 × ArH), 4.54 (1H, s, OCH), 4.21 (1H, dddd, J = 11.8, 4.9, 1.6, 1.5, OCHH), 3.65 (1H, ddd, J = 12.1, 11.8, 2.3, OCHH), 2.82 (1 H, dddd, J = 13.8, 4.2, 2.3, 2.1, OCH_2CHH), 2.49 (1H, td, J = 13.2, 4.2, OCH_2CHH), 2.36 (3H, s, $ArCH_3$), 2.31 - 2.34 (1H, m, CCl_2CHH), 1.67 - 1.71 (1H, m, CCl_2CHH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.5, 132.9, 129.2, 128.2, 89.7, 87.1, 69.0, 45.5, 24.7, 21.4; HRMS: Found (EI): [M]$^+$ 244.042276, $C_{12}H_{14}OCl_2$ requires 244.04217

(1*S*,3*S*)-2,2-Dichloro-1-(4-methoxyphenyl)hexane-1,3-diol (*anti*-**120e**)



A solution of ketone **94e** (1 eq.) in MeCN (0.5mL) was added dropwise to a sFtirring solution of tetramethylammonium triacetoxyborohydride (8 eq.) in anhydrous MeCN (1.5

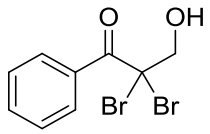
mL) and glacial acetic acid (1.5 mL) at -40 °C. After 2 h, the reaction mixture was diluted with DCM (5 mL) and washed with saturated $NaHCO_3$ then the aqueous phase was extracted with DCM. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography to give a 9:1 mixture of diastereomers of diol *anti*-**120e**.

Colourless oil, 71%; ν_{max} (film/cm^{-1}) 3410 (O-H), 2960 (C-H), 1611, 1513 (Ar), 1247; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (2H, d, J = 8.9, 2 × ArH), 6.91 (2H, d, J = 8.9, 2 × ArH), 5.25 (1H, s, ArC*H*OH), 4.12 (1H, d, J = 9.8, C*H*OHCH$_2$), 3.83 (3H, s, ArOCH$_3$), 2.01 - 2.08 (1H, m, CHOHC*H*H), 1.63 - 1.71 (2H, m, CHOHCH*H* and CH$_3$C*H*H), 1.43 - 1.47 (1H, m, CH$_3$CH*H*), 0.99 (3H, t, J = 7.2, CH$_2$C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.0, 130.3, 129.3, 97.9, 78.5, 77.3, 55.4, 34.3, 19.5, 14.0; HRMS: Found (CI): $[M+H]^+$ 293.071013, $C_{13}H_{19}O_3Cl_2$ requires 293.7112

General Procedure I: Dibromohydration

Dibromoisocyanuric acid (215 mg, 0.75 mmol) was added to a stirring solution of propargylic alcohol (0.5 mmol) in MeCN/H_2O (2 mL, 10:1). Once the reaction was complete (TLC), the solvent was removed under reduced pressure before the residue was purified by column chromatography (EtOAc/Petrol) to give the dibromohydroxyketone.

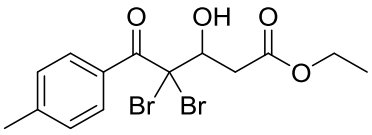
2,2-Dibromo-3-hydroxy-1-phenylpropan-1-one (122c)



General Procedure I: Dibromohydration

Yellow oil, 63%; ν_{max} (film/cm^{-1}) 3422 (O-H), 2918 (C-H), 1667 (C=O), 1446 (C=C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.40 (2H, dd, J = 8.6, 1.2, 2 × ArH), 7.61 (1H, tt, J = 7.4, 1.2, ArH), 7.49 (2H, dd, J = 8.6, 7.4, 2 × ArH), 4.35 (2H, s, CH_2), 3.12 (1H, br. s, OH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.5, 134.3, 131.7, 131.4, 128.3, 72.1, 63.4; HRMS: Found (CI): $[M+H]^+$ 306.89622, $C_9H_9Br_2O_2$ requires 306.89693

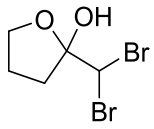
Ethyl 4,4-dibromo-3-hydroxy-5-oxo-5-(*p*-tolyl)pentanoate (122d)



General Procedure I: Dibromohydration

Pale yellow oil, 63%; ν_{max} (film/cm^{-1}) 3514 (O-H), 2980 (C-H), 1732 (C=O), 1666 (C=O) 1568 (Ar); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.28 (2H, d, *J* = 8.2, 2 × ArH), 7.27 (2H, d, *J* = 8.2, 2 × ArH), 4.88 (1H, dd, *J* = 9.6, 2.2, C*H*OH), 4.23 (2H, q, *J* = 7.2, C*H*$_2$CH$_3$), 3.71 (1H, br. s, OH), 3.18 (1H, dd, *J* = 16.0, 2.2, CHOHC*H*H), 2.88 (1H, dd, *J* = 16.0, 9.6, CHOHCH*H*), 2.44 (3H, s, ArCH$_3$), 1.30 (3H, t, *J* = 7.2, CH$_2$C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.2, 171.1, 145.4, 131.7, 129.4, 128.9, 74.4, 68.5, 61.2, 39.0, 21.9, 14.3; HRMS: Found (CI): $[M+H]^+$ 406.94910, $C_{14}H_{17}Br_2O_4$ requires 406.94936

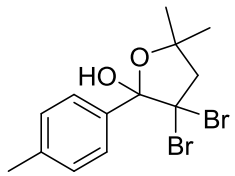
2-(Dibromomethyl)tetrahydrofuran-2-ol (123b)



General Procedure I: Dibromohydration

White crystals, 43%; Mp 70 – 71 °C; ν_{max} (film/cm^{-1}) 3354 (O-H), 3014 (C-H); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.72 (1H, s, CH), 4.17 - 4.23 (1H, m, OC*H*H), 4.00 - 4.07 (1H, m, OCH*H*), 3.05 (1H, br. s, OH), 2.19 - 2.29 (3H, m, OCH$_2$C*H*$_2$C*H*H), 2.01 - 2.10 (1H, m, OCH$_2$C*H*$_2$CH*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 105.6, 70.4, 51.6, 35.2, 25.6; HRMS: Found (ES): $[M-H]^+$ 256.8821, $C_5H_7Br_2O_2$ requires 256.8813

3,3-Dibromo-5,5-dimethyl-2-(*p*-tolyl)tetrahydrofuran-2-ol (123e)



General Procedure I: Dibromohydration

Yellow solid, 76%; Mp 65 – 67 °C; ν_{max} (film/cm^{-1}) 3519 (O-H), 2970 (C-H); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (2H, d, *J* = 8.2, 2 × ArH), 7.20 (2H, d, *J* = 8.2, 2 × ArH), 3.41 (1H, d, *J* = 14.1, CH*H*), 3.18 (1H, d, *J* = 14.1, C*H*H), 2.97 (1H, s, OH), 2.38 (3H, s, $ArCH_3$), 1.62 (3H, s, CCH_3CH_3), 1.52 (3H, s, CCH_3CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.3, 136.3, 128.4, 127.2, 106.8, 81.5, 68.2, 58.8, 32.6, 28.7, 21.4; HRMS: Found (CI): $[M]^+$ 361.95116, $C_{13}H_{16}Br_2O_2$ requires 361.95170

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