One-pot, multicomponent reactions *via* indolium ion intermediates: synthesis of spiropyrans and pyrroloindolines

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I certify that all material in this thesis which is not my own work has been identified and that any material that has previously been submitted and approved for the award of a degree by this or any other University has been acknowledged.

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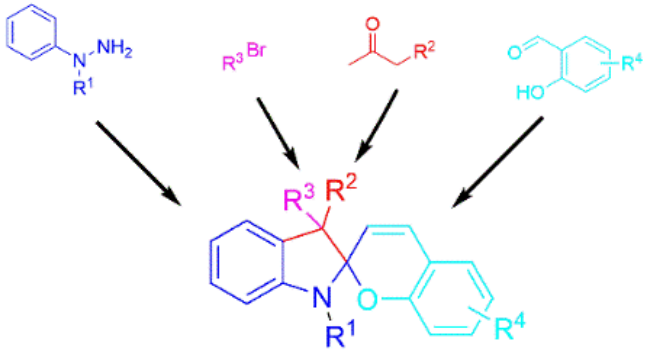
The Author

[Christopher Hughes-Whiffing]

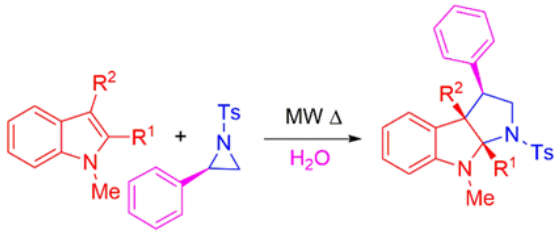
Abstract

Nitrogen-containing heterocylces such as indoles, pyrroloindolines and spiropyrans are a common motif in a variety of diverse, natural products, which exhibit interesting physical and biological properties. Accessing these structures has inspired numerous synthetic procedures.

Herein, we have developed a one-pot, 4-component synthesis of spiropyrans based on a Fischer Indolisation, tandem, alkylation-condensation cascade promoted by *para*-toluene sulfonic acid, starting from hydrazine, ketone, alkyl-bromide and salicylaldehyde starting materials, under mild conditions in environmentally benign solvents, ethanol and water. Our procedure produced 23 diverse spiropyran compounds with unique and useful functional groups for further elaboration, and steric control of the spiropyran-merocyanine isomerism.



Furthermore, we have developed a microwave assisted, one-pot, 2-step, solvent free, [3+2] dearomative cycloaddition cascade in the synthesis of pyrolloindolines from 1,2,3-trimethylindole and *N*-tosylaziridines. This procedure consistently produced simple methyl substituted pyrolloindoline scaffolds in a solvent and catalyst free manner. We then expanded the scope of this process to encompass alternative aziridines, thereby generating phenyl stablised pyrolloindolines.



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1.

Chapter 1 Harnessing indoles from, and exploiting their reactivity in, one-pot, multicomponent reactions.

1.1. Introduction

The aim of this thesis is to demonstrate how we can exploit reactivity of the indolium ion to develop methods for spiropyran and pyrroloindoline synthesis. This chapter will provide an overview on what multicomponent reactions are, how we can use them to access indoles, and conclude with the use of indoles as substrates in multicomponent reactions.

1.2. Multicomponent reactions

Multicomponent reactions (MCR's) are, broadly, a process in which 3 or more starting materials are combined to produce a desired product from a single synthesis. Combining 3 or more reactants, with reactive functional groups, can lead to the generation of side reactions and unwanted by-products, hence, MCR's must be carefully designed, and the substrates well considered [1]. By incorporating structural complexity in a single step, most MCR's can proceed under mild conditions with most of the integrated components appearing in the final product [2] this in turn gives these processes a greater atom economy. Due to the mild conditions, high atom economy and the ability to incorporate several building blocks simultaneously, MCR's have seen an increase in interest and application to combinatorial chemistry, drug discovery, and natural product synthesis [3].

When a MCR process has been developed, and the role of each reactant in product formation has been determined, it is often practical to assess the scope of the procedure using single reactant replacement (SRR) studies [4]. The modular nature of MCR's allow for this iterative approach which enables; i) The assessment of the scope and tolerance of the conditions for different

substrates, of which leads to, ii) rapid generation of vast, diverse libraries of functional and structural isomers.

The most robust MCR methodologies can be performed in a one-pot process, which, as the name implies, is a synthetic strategy using a single reactor, subjecting reactants to multiple transformations. Sequential addition of components to a one-pot process which does not require the isolation of intermediates, are commonly referred to as a telescoped process. Telescoped processes are beneficial from an economic and environmental perspective as the isolation, purification, and subsequent reaction of intermediates is avoided, which can often be costly and, in some cases, hazardous, depending on the solvent requirements.

One-pot procedures allow for the use of microwave assisted (MWA) MCR's which have recently seen a surge in use for the synthesis of biologically relevant heterocycles, such as, acridines [5], pyrimidines [6], purines [7], quinazolinones [8] and indoles [9].

1.3. Multicomponent indole synthesis

Indoles, (Figure 1 -1.) are bicyclic fused aromatic benzene-pyrrole ring systems, a motif observed in many biomolecules such as tryptophan amino acids (Figure 1 - 2.), natural products with pharmaceutical application, such as the pyrroloindoline derivative Physostigmine (Figure 1 – 3.) and natural products that are pharmaceutically ambiguous, such as vincamine (Figure 1 – 4.).

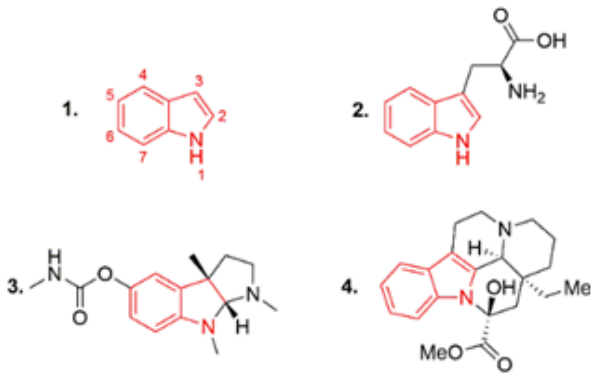

*Figure 1- 1.*Indoles and the occurrence of the ring structure in 2. Tryptophan, 3. Physostigmine, 4. Vincamine

The Fischer Indole synthesis is one of the oldest and most useful reactions in organic chemistry and the primary method for accessing indoles. Broadly, the indolisation procedure starts with, phenylhydrazine, reacting with a carbonyl to form the phenylhydrazone, which, isomerises to the ene-hydrazine. Catalysed by acid, the transfer of protons results in the [3-3]-sigmatropic rearrangement of the ene-hydrazine to the imine, which cyclises to the aminal, eliminating ammonia in the formation of the pyrrole ring.

The reaction itself is simple, which, with the importance of the indole ring has led to the development of many MCR's which modify the indolisation process, making it greener, with benign solvents or solvent free, more efficient, by accruing greater yields, or better substrate incorporation, and to introduce functional substituents, generating indoles with functional groups and interesting substituent patterns, such as, the synthesis of 2,3-disubstituted indoles by a rhodium catalysed, hydroformylation- Fischer indole synthesis. This is an example of a tandem-cascade procedure which dovetails the original process, here, the imine/ketone reactive species is formed *in situ* by hydroformylation of nitrile/carboxylic acid starting material, which proceeds with hydrazone formation by reaction with the arylhydrazine hydrochloride [10]. Cascade reactions perform well in MCR as a particular transformation must occur before the reaction can continue.

Other MCR methods for indole synthesis branch away from the hydrazine-ketone condensation entirely. Using *o*-iodonitrophenol, allylamine, isocyanides and aldehydes in an Ugi-Smiles reaction forms a functionalised aniline intermediate, which can undergo Heck cyclization in the formation of indole [11]. Furthermore, this process allows for functionalization of the phenol, which could impart substituent variation to the 4,5 +7 carbons of the indole -benzene ring.

± We recently reported a One-Pot, three-component, microwave assisted, Fischer indolisation-*N*-alkylation for the rapid synthesis of 1,2,3-trisubstituted indoles [12], This procedure uses microwave irradiation to accelerate the traditional indolisation between arylhydrazine hydrochloride salts and ketones whilst implementing *N*-alkylation as a method to generate indoles bearing diverse, functional, and useful substituents, as substrates for further elaboration in this work and other pursuits.

1.4. Reactions of indoles in multicomponent cascades

Aside from being synthesised by MCR's, Indoles are also useful substrates when participating in MCR's, this is due to it having discrete reactivities at several locations of the pyrrole ring. The four 4 main points of reactivity of the indole (Figure 1, 1) are carbon 3 (C3) the nitrogen (N1) the C2-C3 π bond, and the C2-N1 σ bond. With undecorated indoles i) C3 is the most reactive to electrophilic addition reactions, however when substituted at C3, ii) N1, with its lone electron pair becomes the best nucleophile, iii) when N and C3 are both substituted (*Figure 2*), the "enamine" reactivity affords di-substitution at C3, generating quaternary stereocentres, iv) the formation of the stereocentre also results in the indolium ion, which displays "iminium" like reactivity (*Figure 2*), v) the indolium ions can be quenched by nucleophiles dearomatizing the indole.

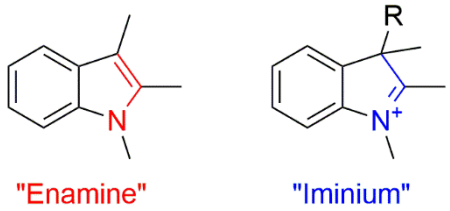

Figure 2 Structural representation of the "enamine" and "iminium" type reactivity of substituted indoles.

This selectable, stepwise, reactivity affords elaboration of the simple core to structurally diverse, biologically active and medically important motifs [13]. Crucially the core indole structure is retained throughout, whilst tolerating a number of MCR's such as: Figure 3 (a) 1,3-dipolar cycloadditions to 3-azidoindoles cascading into dipolar cyclization and lactam ring formations, in the synthesis of annelated indolo-[2,3-e][1,2,3]-triazolo[1,5-a]-pyrimidines [14]. (b) Functionalizations of C3 taking advantage of the initial affinity of dimedone for condensation with 2-hydroxybenzaldehyde followed by Michael-type addition to the indole [15], this has also been shown to work when catalysed by L-Proline in sodiumdodecyl sulfate (SDS) and H_2O and results in fused 4*H*-Chromenes and indolyl xanethones, respectivley [16]. (c) The amino acid tryptamine, an indole, has shown to be successful in 3-component, acid

catalysed reactions with dimedone and 3-phenacylideneoxindoles in the synthesis of 3-{1-[2-(1H-Indol-3-yl)ethyl]-4,5,6,7-tetrahydro-1H-indol-3-yl}indolin-2-ones [17] an interesting structure linking indoles and oxindoles, by an *in situ* "pyrrole" ring. (d) Away from C-3 functionlisations, access to [2,3]-fused ring indoline derivatives through intermolecular cascade dearomatizations of indoles with carbenium ions as an approach to pyrroloindoilines and furoindolines [18]. (e) *C*-Alkylation of an already substitued indole enables the formation of inequivalent 3-3-disubstitued indolium ions, which allows access to the "imminum type" reactivity, promoting subsequent condensation with sailcyladehyde, in EtOH, in the synthesis of diverse, inequivalent, and sterically constrained SP's [19].

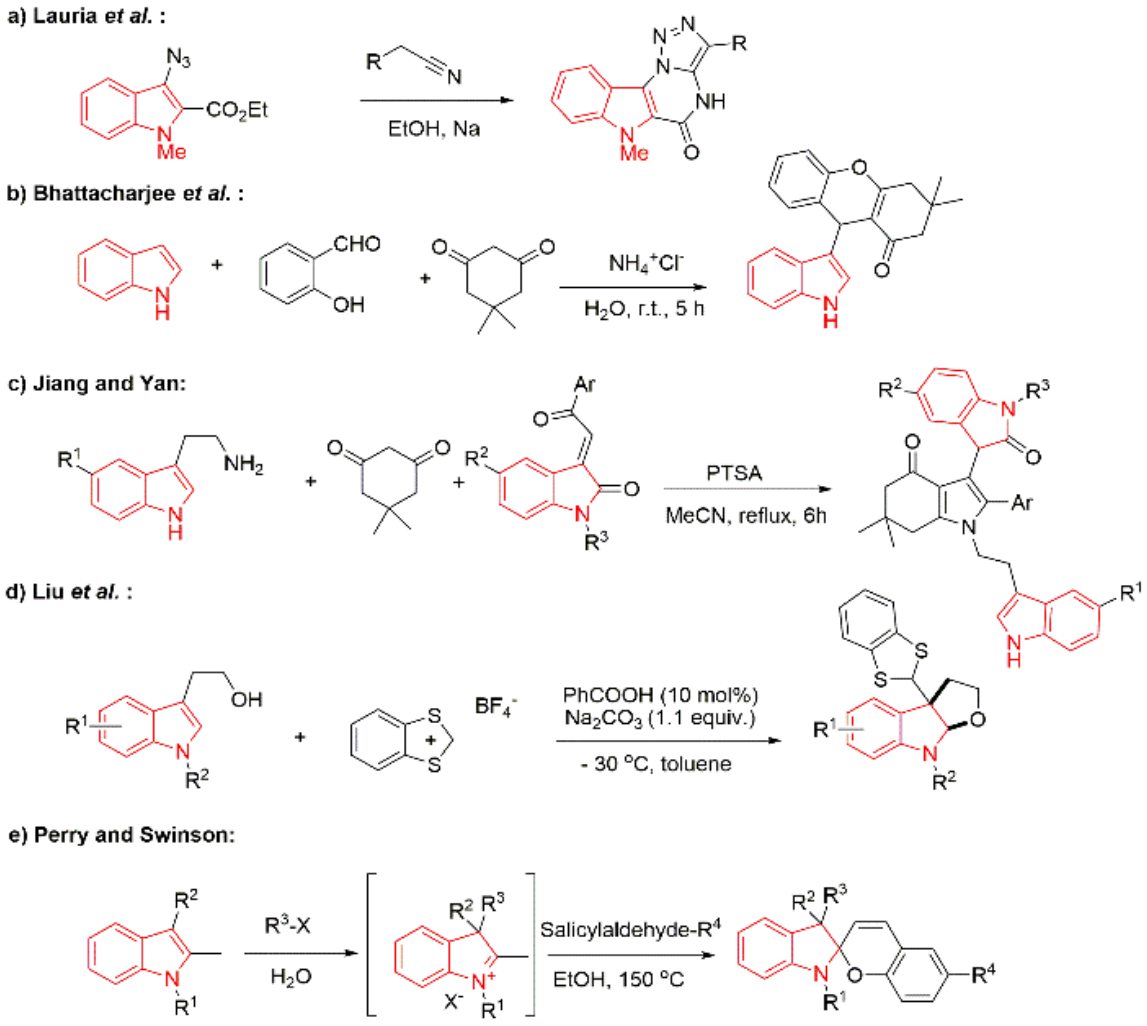

Figure 3-Precedence for the multicomponent reactions of indoles in the synthesis of expanded indole-centred products (a-e; references [8]-[13])

1.5. Concluding Remarks

Indoles are a privileged scaffolds which exhibit remarkable and selectable reactivity affording the elaboration of the simple core structure into biologically and physically interesting compounds, such as spiropyrans and pyrroloindolines. This chapter outlines modern strategies which have been used for the synthesis of, and reactions with indoles and indolium ions, taking advantage of robust MCR methodologies. Whilst the research fields of indole synthesis, and reactions involving indoles is saturated, we believe that there is precedence for the development of complementary methodologies which enable rapid, facile, environmentally friendly, and diverse methodologies, using easily accessible building blocks in the synthesis of spiropyrans and pyrroloindolines.

2.

Chapter 2 - One-pot, 4-component, reaction cascades for the synthesis of spiropyrans

2.1. Introduction

Spiropyrans (SP) are dynamic functional materials which are capable of isomerising between the spiropyran, merocyanine (MC) forms, the resulting shift sees changes in molecular length, planarity, and polarity. This isomerism and can be mediated by temperature [20], solvent [21] and light [22] (Figure 4). In this capacity, they have been applied as organic materials, and have been attached to biological compounds such as DNA [23] and proteins [24], equipping these molecules with photochromic switches, enabling properties such as photoinducible binding. The photochromic behaviour and characteristic shift in coloration centres around the electrocyclic cleavage of the C_{spiro}-O bond, this behaviour and susceptibility to cleavage in indoline spiropyrans results from the elongated and weakened C_{-spiro}-O bond due to interactions between the indolenine nitrogen lone pair, and the antibonding orbital, resulting in

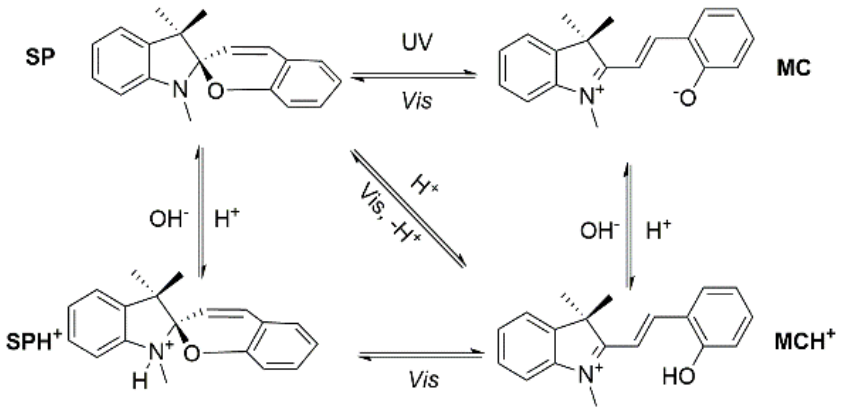

Figure 4 Scheme showing the reversible photo and acidochromism of spiropyrans. SP = Spiropyran MC = Merocyanine MCH+ = protonated merocyanine and SPH+ = protonated spiropyran. Derived from *[51]*

zwitterionic, merocyanine. This activity of SP can be further affected by its substituents, mesomeric and inductive effects influence the degree of C_{spiro}-O cleavage, for example, 6'- NO_2 being *para* to the pyran ring, stabilizes the MC. Furthermore, isomeric control can be established by incorporation of substituents at the indole 3-position, influencing isomerism, through steric and

inductive effects. Also inequivalent substituents at C-3 have been shown to impact SP stereochemistry allowing facial control of the pyran ring closure [25].

This chapter will provide an overview of current SP synthesis, addressing topical issues in the synthetic procedure, substituent variation and will conclude with our work on the development of a facile, acid catalysed one-pot, 4-component Fischer indolisation (FI), tandem, alkylation-condensation (A-C) cascade inthe synthesis of functionalised spiropyrans, starting from hydrazines, ketones, salicylaldehydes and alkylating agents, incorporating interesting and novel N, C-3,and 6'- substitutions for the elaboration and functionalization of SP's.

2.2. Strategies for the Synthesis of spiropyrans

Broadly, spiropyrans are accessed from methylene bases/heterocyclic cations with active methylene groups, undergoing condensation reactions with *o*-hydroxy aldehydes. Due to this discrete reactivity, and the necessity for the indoline nitrogen and phenolate oxygen interactions to enable the photochromic behaviour of the SP, there are few alternative routes in accessing these compounds, as such, new methodologies tend to be developed to address the economy and diversity of these reactions. More recently, focus has been on i) reducing the environmental impact of procedures and ii) incorporating a variety of diverse substituents.

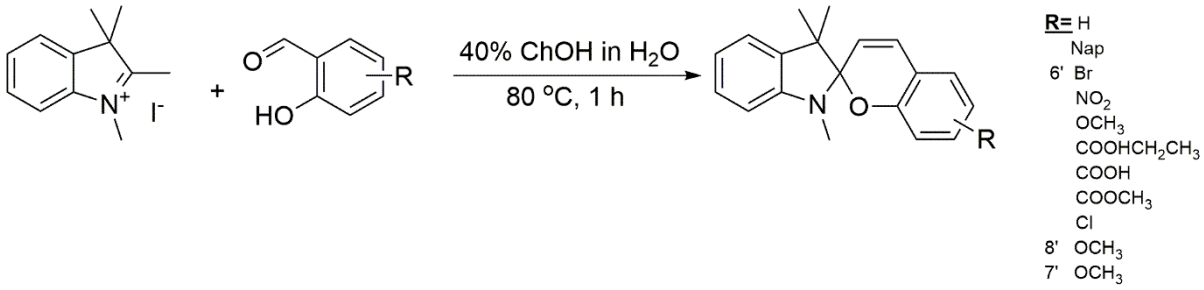

Figure 5 Paragonkar et al.'s choline hydroxide promoted synthesis of Spiropyrans

Starting from tetramethyl-indolium iodide salts, Paragonkar [26] and others, devised conditions addressing the use of organic and inorganic bases in SP preparations. Common bases such as pyridine, piperidine and NaOH, among others are frequently used. These bases are considered hazardous, often requiring the use of solvents such as triethylamine (Et_3N), methanol,

(MeOH) and *N*,*N*-Dimethylformamide (DMF). They identified choline hydroxide (ChOH), a member of the vitamin B family, as a potential substitute, due to the catalytic performance displayed in aldol and transesterification reactions in biodiesel synthesis. Comparing yields, as a measure of the efficacy of the reaction they found that conventional methods generated isolable SP products in the regions of 40-61 %, whereas their optimised conditions with 40 % ChOH in H_2O yielded 81 %. They asserted that the improved efficiency of the reaction was due to their catalyst being homogenous in aqueous media, accelerating the reaction by increasing the solubility of substrates through hydrogen bonding. The process developed also showed broad tolerance for substituent variation in salicylaldehyde reagent, incorporating EWG's and EDG's at the terminus of the SP molecule (Figure 5). The novelty in these conditions stems from the "green" approach using H_2O as a solvent, under mild conditions, with a catalytic base, furthermore they discovered that if filtered off during the isolation of the SP product, that the ChOH catalyst could be reused up to 5 times before showing a significant reduction in yield. Development of green synthetic approaches is at the forefront of modern chemical synthesis.

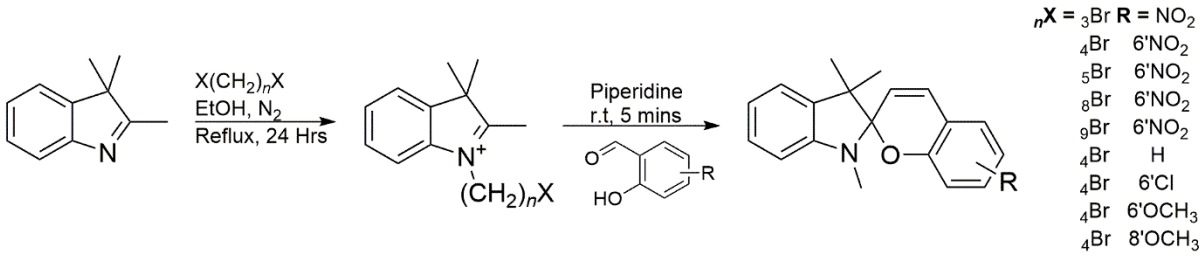

Figure 6 Zhang et al. 's One-Pot Synthesis of Spiropyrans

Looking to condense traditional 3 step synthetic routes to synthesise common SP motifs, Zhang *Et al.* developed a method addressing the requirements of successive N-alkylation and deprotonation of 2,3,3-trimethyl-*3H*-indole to generate the indoline intermediates followed by condensation with salicylaldehyde. Stating that the common practice of 3-step approaches is neither environmentally nor economically friendly, especially on a commercial scale. To this end a "One-Pot" process in which successive addition of reagents was devised [27] they identified that the deprotonation-condensation step could be condensed to a single step under N_2. Furthermore, they found that the addition of piperidine at room temperature, facilitated the condensation reaction

between the indolium ion and salicylaldehyde immediately, avoiding the reflux over time requirement, which was previously stipulated. They further confirmed that the reaction was successful in several common solvents such as toluene, acetonitrile (CH_3CN) and EtOH, preferring that latter due to its “green” credentials. This process showed broad substrate scope regarding N-Alkyl and terminal substitution of the salicylaldehyde, tolerating a range of alkyl chain lengths and EWG/EDG’s (Figure 6). By condensing the three steps to a one pot process there is further environmental benefit, by not having to purify or isolate intermediates by flash chromatography (or others) reducing the impact of this process.

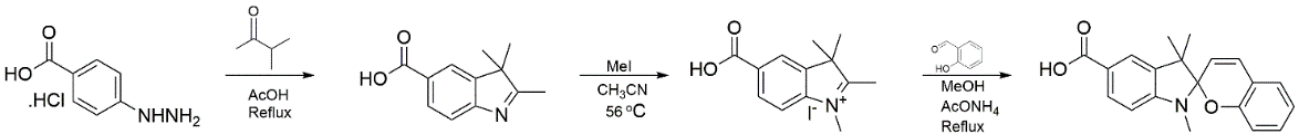

Figure 7 Synthetic route to spiropyrans from Hydrazine’s used by da Costa Duarte et al. when investigating the Electrochemical and Photophysical properties of this SP and how it interacts with BSA

Starting from the hydrazine hydrochloride salt, da Costa Duarte and others [28] were able to select aryl substituents in the generation of 5-carboxy indoles, which would later be elaborated to spiropyrans via a method from Lee *et al.* [29]. By starting from the hydrazine, they demonstrate the novelty of being able to define characteristics of the SP product, in this case an electron withdrawing carboxylic acid on the indolenine side of the chromene ring, with no substituents on the salicylaldehyde, this pattern prevented the SP from showing the photoinducible isomerism for which they are famed. This proved useful when sensing proteins (BSA) in solution as the MC form is stabilised through binding at the phenolate oxygen, resulting in a location to capture metal ions and bind with proteins. The other reason for incorporating the carboxylic acid *para* to the indoline nitrogen was in a bid to prevent dimerization of the SP radical cations generated by the oxidation of the indoline nitrogen.

Functionality aside, the importance of selecting substituents for SP shows importance in both the SP characteristics and their use as sensors in biological systems. The procedure for their synthesis is a 3-step reaction, with acetic acid (AcOH) catalysed indolisation occurring between carboxy-hydrazine

hydrochloride and 3-methylbutan-2-one, formation of the indolium salt by alkylation in CH_3CN under nitrogen, followed by condensation under Knoevenagel conditions.

Summarising the above conditions (Figures 5 – 7) we can deduce that there is need for SP synthesis and each of these address different aspects, (i) selectable substituents at the terminal ends of the SP and the indoline nitrogen, (ii) one-pot or telescoped reactions. A recurring theme with all these SP products, is the lack of diversity at the indolenine C-3, these all show *gem*-dimethyl substituent patterns. Furthermore, the above paper investigating SP behaviour used a method dated from 2014 in accessing SPs from hydrazine starting materials, which required the isolation and purification of indoline and indolium intermediates. This lack of diversity in SP C-3 substituents was addressed through the development of 3-component alkylation-condensation cascades.

2.3. The 3-component alkylation-condensation cascade

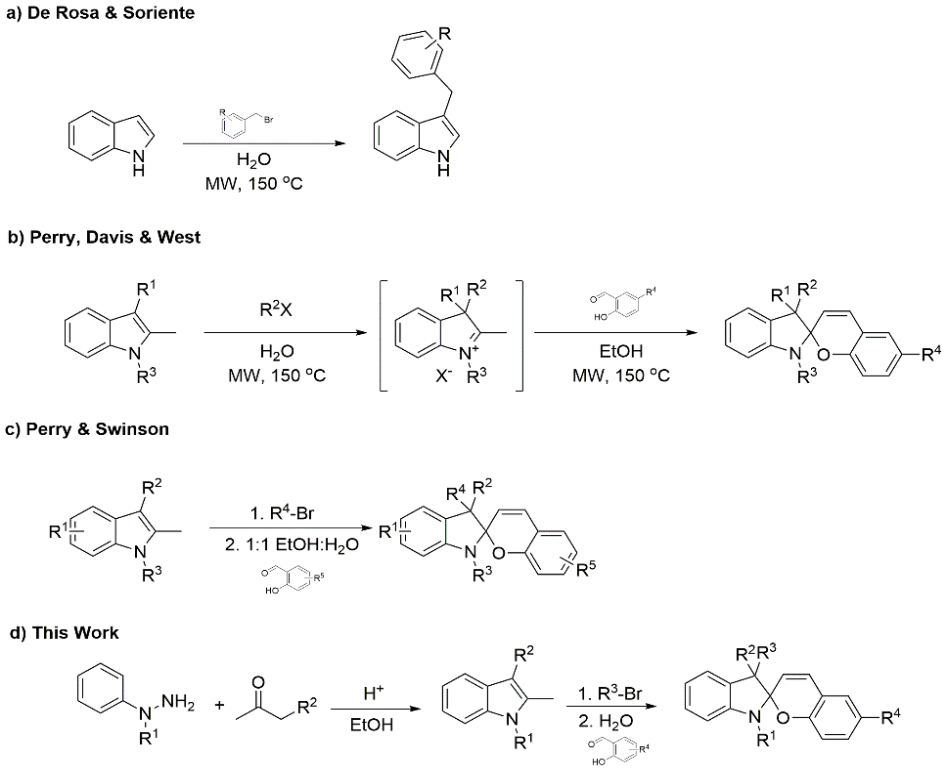

Figure 8 Schemes representing the development of the 3-component tandem alkylation-condensation cascade.

Incorporating the work of DeRosa, who demonstrated microwave assisted indole alkylation in H_2O [30],(Figure 8a) a microwave assisted two-step, one-pot synthesis of spiropyrans was devised. in a bid to address the underdeveloped C-3 substitution of spiropyrans, wherein they were able to synthesise a variety of sterically congested SPs with non-equivalent C-3 substituents which can influence the stereoselectivity of the SP ring closure [25] (Figure 8b). This was further refined from a telescoped reaction to a 3-component, tandem alkylation-condensation sequence, generating 25 structurally diverse SP products from indoles, alkyl bromides and salicylaldehydes, including substituents which alter SP:MC isomerism, absorbance, facial selectivity as well as incorporating functional groups appropriate for elaboration of the SP structure [19] (Figure 8c).

The aim of our work was to build upon this tandem indole alkylation-condensation cascade, expanding this 3-component sequence to 4 -component processes by in-situ generation of 1,2,3-trisubstituted indoles from *N*-aryl hydrazines and ketones as the first step of a one-pot multicomponent reaction cascade. To this end we needed to consider the conditions required for the FI reaction in the context of the latter A-C sequence. The A-C sequence requires addition of Alkyl-X, to the indole to form the indolium ion intermediate , which reacts with salicylaldehyde to give the SP product, this tandem sequence occurs in 1:1 EtOH-H_2O at 70 ^oC (Figure 8d).

2.4. The devlopment of a one-pot, 4-component, 2-step, indolisation, alkylation-condensation cascade, to synthesise spiropyrans.

2.4.1. Rationale for incorporating the Fischer indolisation

Overall FI forms ammonium as a byproduct, which, although weakly acidic, is unlikley to interfere with subsequent reactions in the formation of spiropyran compounds. For the following alkylation step the addition of alkyl bromide results in the indolium ion being stablised by X^- as the indolium salt. FI commonly uses ketones in stoichiometric quantity [31] , and is not a concern regarding further, or side reactions.

Indolisation reactions are achievable without the addition of acid catalyst by using the HCl salts of aryl-hydrazines as a starting material [28] [32], resulting in *in* situ formation of hydrochloric acid, however, as these are often anhydrous in ether they are inconvenient for our cascade in aqueous EtOH. Furthermore, aryl-hydrazine hydrochlorides have limited commercial availability, which subsequently narrows the range of substituents we could incorporate. By using an acid catalysed approach we would have greater opportunity to elaborate on the *N*-Substituent in our indole/SP synthesis.

Fischer indolisations are often catalysed by readily available acids, such as acetic acid [33] sulfuric acid [34] p-toluene sulfonic (PTSA) acid [35] and trifluoroacetic acid (TFA) [36]. Precedence exists for acid catalysed Fischer indolisations in EtOH as well, using perchloric acid [31], and PTSA [37]. Viability of the reaction in EtOH is preferable to maintaining our one pot approach with the subsequent condensation steps proceeding in aqueous EtOH.

With indolisation being practical in EtOH, generating quiescent ammonium salts, the next consideration is the effect of the acid catalysts later in our cascade, for example TFA and PTSA. The acid catalysts would likley be “neutralised “ in the formation of ammonium trifluroacetate and ammonium toluenesulfonate salts respectivley, and should not interfere with subsequent reactions. However, regard must be taken for the pH tolerance of SP formation. For the purposes of this research the resulting isomer is arbritrary, however,

there doesn’t appear to be any supporting literature regarding the pH tolerace of the condensation procedure in forming SP’s, however, the mechanism relies on proton availability from solvents such as EtOH.

In summary, based on the requirements of the FI and subsequent A-C reactions, incorporating FI into the cascade should be relativley simple due to the affinity of indoles and resulting SP’s for the solvent requirements and the neutralization of catalysts. By incorporating FI into this cascade we hoped to design a process by which a desired SP, with a number of functionalised substituents could be identified, the corresponding hydrazine, ketone, alkylating agent and salicylaldehyde can be selected, subjected to a mild procedure, in benign solvents, and isolated, in an effective and efficient manner.

2.4.2. Identification and selection of a suitable acid catalyst

We began by assessing the feasibility of this FI/A/C cascade using N-benzylphenyl hydrazine hydrochloride, methyl ethyl ketone (MEK), benzyl bromide (BnBr) and 5-nitro salicylaldehyde. FI was carried out at 60 ^{o}C and stirred overnight. Removing a 200 µL aliqout , ^{1}H-NMR confirmed formation of 1-benzyl-2,3-dimethyl-1H-indole, we then employed tandem alkylation condensation conditions (1:1 Ald: BnBr/ in 1 mL 1:1 H_2O: EtOH) successfully yielding the spiropyran product (**6**) (**Table 1 Entry 1**). With this key result in hand, we then investigated using methyl phenyl hydrazine with a Brønsted acid catalyst, *para*-toluene sulfonic acid (PTSA), (checking for indole formation before proceeding with the tandem alkylation condensation step, by removing an aliqout and characterising by ^{1}H-NMR) we observed the desired spiropyran product.

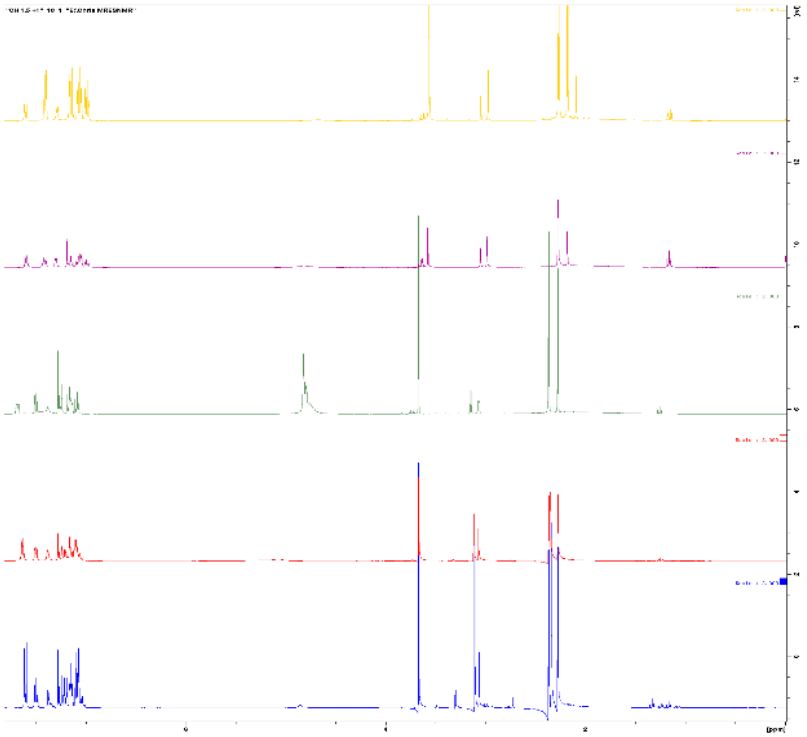

Figure 9 Hourly ^{1}H-NMR spectra of PTSA catalysed reaction, progressing (bottom to top).

16 hour indolisations (**Entries 1 + 2**) are unwieldy for the sort of reactions we were hoping to achieve. Our next step was to compare the duration of the indolisation step for the HCl salt, and PTSA catalysed, reactions respecitvley, (**Entries 3 + 4**), this was achieved by ^{1}H-NMR analysis of aliqouts from reaction mixture on an hourly basis (Figure 9). The HCl salt required 3 hours, and PTSA catalysis required 5 hours.

Having demonstrated that acid-catalysed indolisation is tolerated by the subsequent A-C reactions we proceeded to assess to other organic acids (**Entries 6 + 7**). Acetic acid was ineffective after 6 hours, however TFA catalysed indolisation completed after 3 hours.

2.4.3. Optimisation of reaction conditions

With two potential catalysts in hand we continued to optimise the conditions for both. We opted not to adjust the temperature for the indolisation because 70 ^{o}C struck a balance between speed and mildness of reaction conditions. The optimised, published conditions, for the A-C step was 110 minutes at 50 ^{o}C [19], and so first we used these conditions for each acid **(Entries 8 + 9**).

Optimisation in terms of reaction medium had a severe effect on yield. A-C proceeds optimally in 1:1 ratio of aqueous EtOH, however, adding 1 mL of 1:1 EtOH: H_2O required by the A-C step to 1 mL of EtOH for the indolisation resulted in a 3:1 ratio of EtOH : H_2O overall (**Entries 8 – 10**). Increased quantitites of EtOH have previously been shown to reduce yields. We addressed this by using EtOH, 1 mL, for the indolisation and adding H_2O, 1 mL, for the A-C step only, moving forward.

We then compared the acid catalysts (**Entries 11 +12**) allowing a whole day for indolisation and overnight for the A-C step, and this identified a 10 % disparity in yield between the two acids. Through further investigation we deduced that the greatest yields were achieved with 3 hour indolisation for TFA and 5 hours for PTSA (**Entries 11-16**), alongside 4 hours for the A-C steps. To try and simplify the process, we tested the effect of simulataneous addition of H_2O and EtOH on the reaction, however, results showed that spiropyran did not form. (**Entries 22-23**) .

Previously, microwave irradiation has been shown to accelerate the rates of reaction for both indole alkylation [30] and SP synthesis [25], as such we explored this here. We tested both TFA and PTSA using this method, which has shown success in the advancement of multicomponent reaction cascadesof heterocylic compounds [2]. Considering that our approach was using

environmentally benign solvents, it was worth exploring, if we could reduce the energy consumption and reaction duration using this method. In all cases (**Entry 17, 20 + 21**), the crude reaction mixture was a poorly soluble tar. Furthermore, the yields were inferior when compared to the open flask method (**Entries 20+21**) and in the case of TFA, the the hydrazone was isolated indicating the indole did not form.

Overall, PTSA is our preferred acid catalyst for reasons of yield and handling. Being crystalline as the mono-hydrate, non-volatile and soluble in EtOH , PTSA was simple to handle and the ammonium salt of PTSA was easily removed from the product by washing with water.

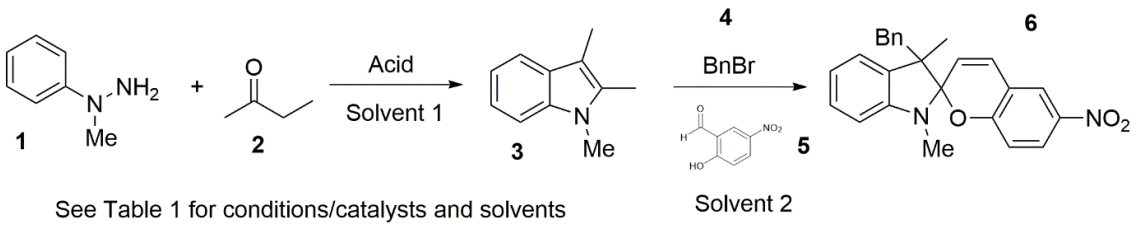

Figure 10 Scheme for our one-pot,2-step, 4-component, indolisation, *C*-alkylation-condensation cascade

Entry	R[1]	Acid Catalyst	Time FI + A/C (Hrs)[2]	Method [1]	Solvent 1	Solvent 2	Volume S1|S2 (mL)	Total Ratio (EtOH:H_2O)	Heat Source[2]	Isolated Yield (%)[3]
1	Benzyl	HCl	16 + 2	Stepwise	EtOH	EtOH:H_2O (1:1)	1|1	3:1	Oil Bath	N/A
2	Methyl	PTSA	16 + 2	Stepwise	EtOH	EtOH:H_2O (1:1)	1|1	3:1	Oil Bath	N/A
3	Benzyl	HCl	2 + 0	Indole	EtOH	N/A	1	1:0	Oil Bath	N/A
4	Methyl	PTSA	5 + 0	Indole	EtOH	N/A	1	1:0	Oil Bath	N/A
5	Methyl	PTSA	24	Tandem	EtOH:H_2O (1:1)	N/A	1	1:1	Oil Bath	0
6	Methyl	HOAc	6 + 0	Indole	EtOH	N/A	1	1:0	Oil Bath	N/A
7	Methyl	TFA	3 + 0	Indole	EtOH	N/A	1	1:0	Oil Bath	N/A
8	Methyl	PTSA	5 + 2	Stepwise	EtOH	EtOH:H_2O (1:1)	1|1	3:1	Oil Bath	N/A
9	Methyl	TFA	3 + 2	Stepwise	EtOH	EtOH:H_2O (1:1)	1|1	3:1	Oil Bath	14
10	Methyl	TFA	1 + 2	Stepwise	EtOH	EtOH:H_2O (1:1)	1|1	3:1	Oil Bath	N/A
11	Methyl	PTSA	5 + 17	Stepwise	EtOH	H_2O	0.5|0.5	1:1	Oil Bath	58
12	Methyl	TFA	5 + 17	Stepwise	EtOH	H_2O	0.5|0.5	1:1	Oil Bath	47
13	Methyl	PTSA	1 + 2	Stepwise	EtOH	H_2O	0.5|0.5	1:1	Oil Bath	0
14	Methyl	TFA	1 + 2	Stepwise	EtOH	H_2O	0.5|0.5	1:1	Oil Bath	23
15	Methyl	PTSA	5 + 2	Stepwise	EtOH	H_2O	0.5|0.5	1:1	Oil Bath	33
16	Methyl	TFA	3 + 2	Stepwise	EtOH	H_2O	0.5|0.5	1:1	Oil Bath	31
17	Methyl	TFA	0.25 + 0.25	Stepwise	EtOH	H_2O	0.5|0.5	1:1	MW	N/A
18	Methyl	PTSA	5 + 4	Stepwise	EtOH	H_2O	0.5|0.5	1:1	Oil Bath	67
19	Methyl	TFA	3 + 4	Stepwise	EtOH	H_2O	0.50.5	1:1	Oil Bath	28
20	Methyl	PTSA	0.25 + 0.25	Stepwise	EtOH:H_2O (1:1)	N/A	0.5|0.5	1:1	MW	10
21	Methyl	PTSA	0.5 + 0.5	Stepwise	EtOH:H_2O (1:1)	N/A	0.5|0.5	1:1	MW	14
22	Methyl	PTSA	6 + 17	Stepwise	EtOH	H_2O	0.5|0.5	1:1	Oil Bath	67
23	Methyl	PTSA	6 + 17	Stepwise	EtOH:H_2O (1:1)	N/A	0.5|0.5	1:1	Oil Bath	0
24	Benzyl	HCl	6 + 17	Stepwise	EtOH	H_2O	0.5|0.5	1:1	Oil Bath	33
25	Phenyl	HCl	6 + 17	Stepwise	EtOH	H_2O	0.5|0.5	1:1	Oil Bath	0

[1-] All reagents used in equimolar quantities, (0.622 mmol). Stepwise, refers to heating **1,2** in acid catalyst and solvent 1, for the allotted time, and subsequently adding **4,5** and solvent 2. Tandem refers to the addition of **1,2,4,5**, acid, and Solvents 1 and 2 and a single period of heating. Instances where N/A is shown are due to only indole formation being monitored

[2-] For the oil bath, all reactions were conducted at 70^{o} C in a round bottomed flask, MW denotes microwave irradiation at 150 ^{o}C/ 300 W/ 250 psi.

[3-] *% Yield of isolated **6***

Table 1 Details of the optimization of our one-pot,2-step, 4-component, indolisation, *C*-alkylation-condensation cascade

2.4.4. Optimisation of Purification techniques

During the optimisation of our reaction conditions, we also had to develop a suitable way of purifying our SP products. Previous work showed that many SP's are purifiable by precipitation from acetone [19] and filtration, where possible, we adopted this process for our procedure, but included a water wash to remove ammonium trifluoroacetate and ammonium toluenesulfonate salts generated by indolisation with acid catalysis. We were keen to retain the precipitation method of purification as it is far less laborious and requires less solvent than flash chromatography. The concerns faced with the water wash were the potential loss in yield due to MC being slightly soluble in water, and it was likely that even if the SP isomer predominated, a proportion would be MC. Through trial and error, we determined that considerable yield loss occurred when both acetone and H_2O where both present, hence, ample time should be allocated for the acetone to be removed post precipitation, otherwise everything dissolves upon the addition of water (**Entries 8 – 10**).

In cases where the SP would not precipitate from acetone then we had to purify by flash chromatography eluting with methanol (MeOH) and ethyl acetate (EtOAc). Purifying spiropyrans in protic solvents on silica presents a challenge, due to their photochromic behaviour isomerising between the SP and MC. We know that spiropyran photochromism can be pH gated, often resulting in the protonation of SP, stabilising the Z-Merocyanine (Z-MCH$^+$) isomer [38], this isomer can interact with silica surface *via* hydrogen bonding between the silica (Si-OH) and MC (C-O$^-$), preventing elution [39]. Due to the reduced yields observed the SP's which required chromatography we felt it necessary to determine the extent to which this would affect our yields. To this end we ran 100 mg pure of 1-H-3,3-dimethyl-1,3-dihydrospiro[chromene-2,2'-indole], a functionally simple spiropyran, through a silica gel column, eluting in MeOH: EtOAc and retrieved only 69 mg from solution. In a bid to try and subvert the onset of "negative photochromism", we repeated the above whilst irradiating the column with a strong source of visible light, to try and promote the SP. Irradiation with visible light enabled the retrieval of 81 mg, an improvement but

we found it difficult to wholly irradiate the entire column, we therefore defined a 20% loss in yield to be an appropriate benchmark for this process.

Having determined the optimal conditions (**Entry 18**) for our facile 1-pot, 4-component indolisation, tandem alkylation-condensation sequence, in the synthesis of spiropyrans, we then explored the scope and substituent tolerance of our conditions.

2.4.5. Scope of the 4 Component reaction

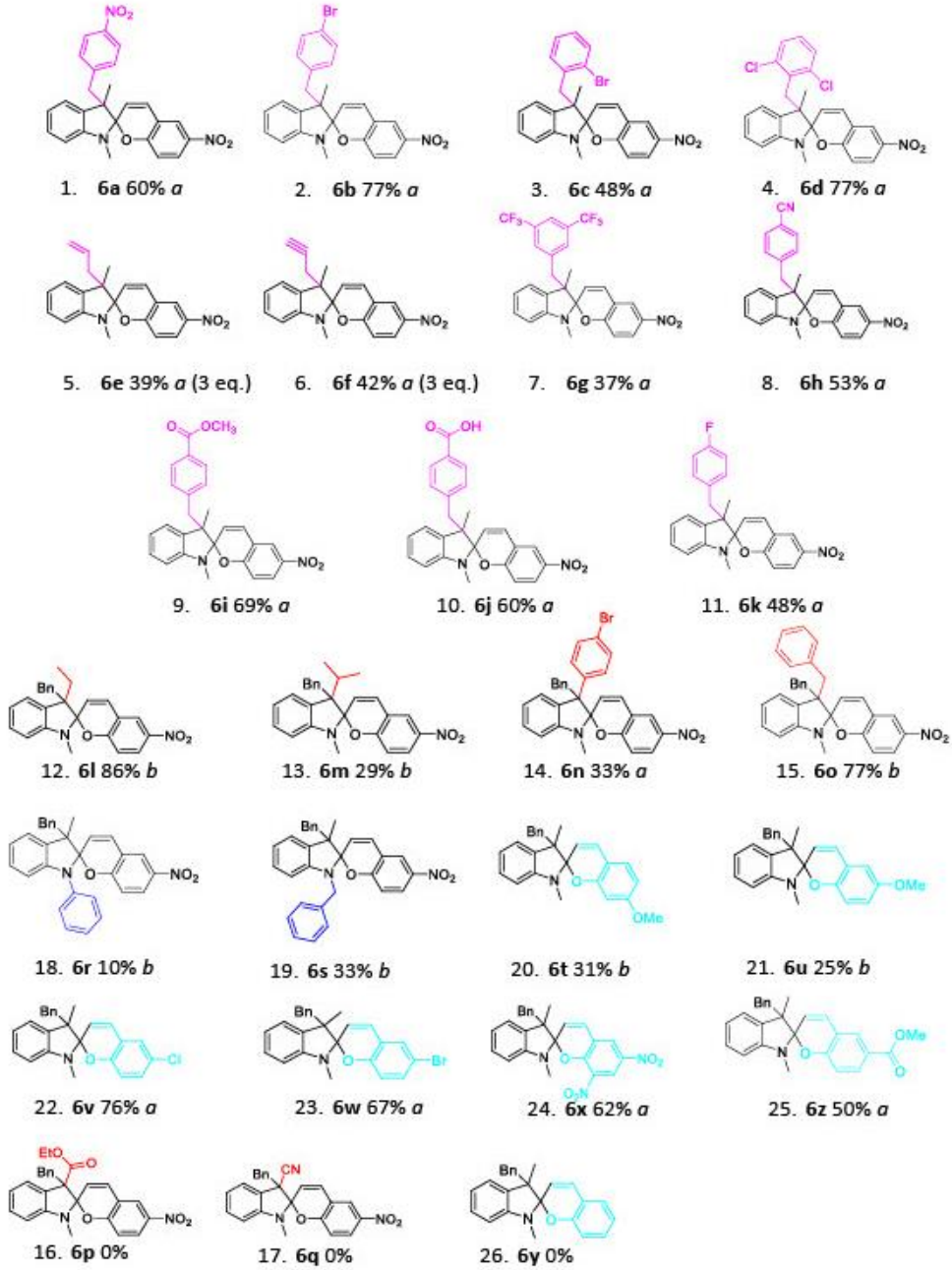

Table 2 The scope of our one-pot,2-step, 4-component, indolisation, *C*-alkylation-condensation cascade.

With optimized conditions in hand, we then explored the scope of our one-pot 4-component SP synthesis, across varied hydrazine, ketone, alkyl halide and salicylaldehyde components. Broadly we saw successful incorporation of functional substituents across the spiropyran structure, the combination of FI, with the robust, well tolerated, tandem A-C reaction cascades (**6a-6z**) enabled us to generate many structurally diverse, sterically congested, spiropyrans, bearing interesting and useful functionality.

Expanding the hydrazine from *N*-Methyl (R^1) saw mixed results, incorporation of an *N*-phenyl substituent was low yielding, perhaps due to sterics (**Entry 18)**. *N*-benzyl substituents were tolerated from both the HCl salt (**Table 1-Entry 1**) and PTSA catalysis (**Entry 19**). We could not access **6r** from the HCl salt with this method (**Table 1-Entry 25**) however, the corresponding indole has been reported from the HCl salt of **1a** and **2** in acetic acid [40]. *N*-substituted SP's **6r + 6s** allude to the incorporation of further *N*-substituted hydrazine, whilst there are few examples in this work, it enables precedence for incorporation of *N*-diaryl hydrazine into SP products. Furthermore, this could dovetail into a 5-component reaction via hydrazine allylation, Kun Xu *et al.* [41] recently published a method for the synthesis of *N*-Allylic indoles via the allylation of monosubstituted aryl hydrazine, this was achieved by coupling phenylhydrazine with cyclohexylallene (1.5 eq.) using $[Rh(COD)Cl]_2$ (1.25 mmol%) and DPEphos (5.0 mmol%) in 1,2-dichloroethane at 80 °C, to generate the *N*-allylic phenylhydrazine, followed by an FI reaction with substituted ketone in acetic acid at 70 ^oC, a process under similar conditions to those we have explored.

Further expanding the substrates for the FI step of our cascade, we varied the ketone (R^2), there seemed to be 2 factors to effecting SP synthesis. (i) Electron withdrawing groups adjacent to the ketone prevent indolisation, or stabilise the indolium ion, preventing subsequent A-C steps from occurring (**Entries 16 + 17**), (ii) sterically hindered ketones, or those which yield a hindered indole, will proceed with A-C, at a comparatively low yield (**Entries 13 + 14**). However, with an appropriate unhindered, EDG, (**Entries 12 + 15**) 86

and 77 % yield were achieved respectively. Variation in the ketone (**6l-6o**) along with an alkylating agent allowed us to choose both substituents on the C-3 of the SP product resulting in inequivalent, sterically constrained, SP's (**6l – 6n**) and a C3, equivalent *gem*-dibenzyl SP (**6o**). Steric hindrance seems to be relative to the freedom of the substituent to rotate in space, rather than general bulk, e.g., substituents two carbons removed from C3 such as **6l** and **6o** gave a substantially greater yield than those which are removed from C3 by a single carbon (**6m, 6n**). For **6p** indolisation was effective, we isolated the indole intermediate from the reaction mixture, however the A-C reaction was ineffective, and no SP was formed. This could be due to the ethyl ester on C3 being enolisable. Conjugation of the "enol" tautomer with the indolium ion would stabilise this transition state. A similar explanation would work for **6q,** however, in this case it failed to proceed beyond the hydrazone intermediate, which could have been stabilised by the nitrile substituent. Both SP's **6p** and **6q** have been previously reported in the 3-component, tandem A-C cascade [19].In terms of functional groups, **6n** has an aryl halide at C3, a substrate for Pd cross couplings, of particular interest might be the use of Buchwald-Hartwig Amination, allowing access to aryl C-N bonds, at the C3 of the SP [42], with scope to couple switchable SP's to nitrogenous natural products such as amino acids and peptides.

For (R^3), alkylating agents, we had no issue implementing *C*-alkylation, provided the indole had formed, all SP products incorporated benzyl bromide (BnBr) well, as shown by De Rosa *et al.* [30]. Furthermore, were able to show success with electron withdrawing (EW) and electron donating (ED) substituents, and for the functionalised benzyl alkylating agents we saw broad tolerance for *ortho*, *para* and *meta* substituents (**Table 2 Entries 1 -11**). By *in situ* alkylation of 1,2,3-trimethylindole we have generated several SP's bearing inequivalent C3 substituents, the size mismatch has been shown to impact facial discrimination of the SP ring closure [25]. **6a** has a *p*-nitro benzyl substituent which can be easily reduced to an amine and used in C-C bond forming S_NAr processes [43]. As previously mentioned, aryl halides such as **6b**,**6c** and **6d**, are all substrates for Pd cross coupling reactions, having halide targets at *ortho* and *para* positions of the benzyl substituent. **6e** and **6f** were alkylated by less reactive electrophiles, allyl and propargyl bromide respectively,

resulting in low yields, however, moderate yields were achieved with 3 eq. Terminal alkenes (**6e**) are targets for olefin metathesis and thiol-ene click reactions. Hydrothiolation of spiropyranes has been used in the production of "smart" photochromic fabrics [44] furthermore being able to form C-S bonds would enable coupling of SPs to amino acids such as Cysteine. Alkyne substituents (**6f**) allow copper-catalysed alkyne-azide click chemistry reactions to occur enabling the use of SP in biorthogonal reactions [45] [46]. F and CF_3 substituents are bioisosteres for H and CH_3 respectively, which are utilised in medicinal chemistry, synthetic methods that incorporate these are actively pursued. Here we have isolated 2 fluorinated SPs (**6g + 6k**). Fluorinated compounds have also been used for positron emission tomography (PET) via ^{18}F radiolabelling, which has shown utility with *in vivo* imaging and central nervous system, drug discovery efforts [47]. **6h** features a benzonitrile substituent offering a versatile target for hydrolysis to carboxylic acids or reductions to 1^o amines. **6i** incorporates an aryl ester, esters attached to SP materials could be used in the synthesis of photo-controllable polymers and copolymers [48]. **6j** an aryl carboxylic acid which can undergo Fischer and Steglich esterification, generate amides, thioesters, anhydrides, and many more classical carboxylic acid reactions. More recently decarboxylative C-N bond formation [49] has been of particular interest due to the application of C(aryl)-X bonds to pharmaceutical, materials and agro-chemical research. Furthermore, benzoic acid substituents can direct C-H functionalisation allowing for transformations such as *ortho* - arylations [50].

For the Salicylaldehyde (R^4) component we found success with electron withdrawing groups (EWG's) (**Entries 22-24**) and electron donating groups (EDG's) (**Entries 20, 21, 25**), though, lower yields were observed with EDG's (**Entries 20 and 21**) . It has been well documented that C-6' substituent variation has a direct impact on SP-MC isomerism, wherein EWG's in the 6' position stabilise the MC isomer [51] through conjugation to the phenolate oxygen. EDG in the 6'-positions destabilize the phenolate, whilst increasing the overall basicity of the Zwitterionic MC, tending toward the protonated MCH^+ form. Here we report a variety of 6'-substituents (**6t – 6z**) which might allow for fine tuning of SP-MC isomerism. Exploiting SP:MC isomerism has shown several uses within mechanochemistry [52] due in part to the increase in

molecular length through isomerisation. Salicylaldehyde was unreactive under these conditions (**Entry 26**), and this is in accordance with previous reports [19]. Beyond the impact on isomerism, **6v** and **6w** are again aryl halide targets for C-C and C-N bond forming through Pd cross couplings, in solvent and solid states [53]. Methyl ethers (**6t, 6u**) could be demethylated to the corresponding alcohols and used in the C-O cross coupling [54] affording another method and location for the ligation of SP products.

2.5. Concluding remarks

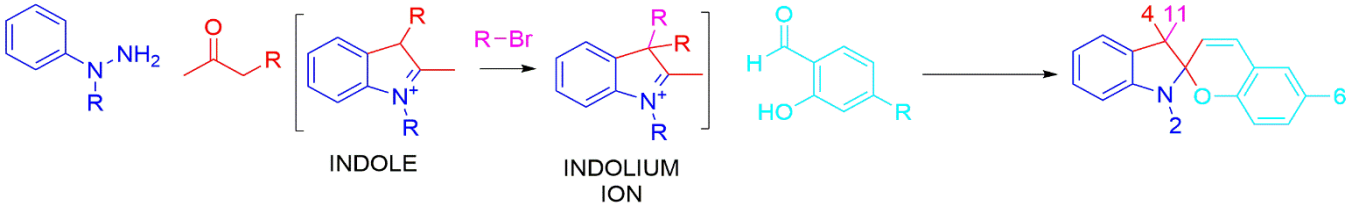

Figure 11 Schematic of the SP synthesis showing the number of single reagent substituents we incorporated with our MCR conditions.

To conclude, we have developed and optimised an acid catalysed, 4-component indolisation, C-alkylation-condensation cascade to synthesise spiropyrans from hydrazine, ketone, salicylaldehyde and alkyl bromide starting materials. Our procedure is operationally simple and able to proceed without isolating indole, or indolium intermediates, uses environmentally benign solve nts and is catalysed by a crystalline, soluble acid, which is simple to handle, extract and is not listed on RCRA. Our process also does not require or rely on protecting groups or metal-catalysis. Our procedure shows broad tolerance and generality allowing us to incorporate a range of functional groups, from each of the four components (Figure 11), including, alkenes, alkynes, carboxylic acids/esters, aryl halides and nitro groups, which provide synthetic handles for further derivatization and control of the spiropyrans properties

3.

Chapter 3- Microwave promoted aziridine ring opening reactions in the synthesis of hexahydropyrollo[2,3-b] indole from indoles.

3.1. Introduction

Hexahydropyrollo[2,3-*b*] indole (HPI) commonly referred to as pyrroloindolines, are an expansion on the indole ring system we have been investigating, they are based on a [6,5,5] fused indole, pyrrole ring system (Figure 12), a core motif present in many natural products which exhibit remarkable biological and pharmaceutical activities [55] (Figure 13).

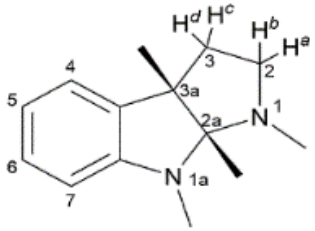

Figure 12 The pyrroloindoline core and its nomenclature.

Of particular interest, and synthetic challenge are the C3a all carbon quaternary centres, also referred to as the bridgehead, of HPI, as they are a common point of structural elaboration often impacting biological activity. Figure 13- B) Flustramine B, and C) Gliocladin C are marine alkaloids of synthetic interest due to on-going drug discovery efforts, these HPI have diverse bridgeheads such as 3-methylbut-2-enyl [56] and 1*H*-indole.

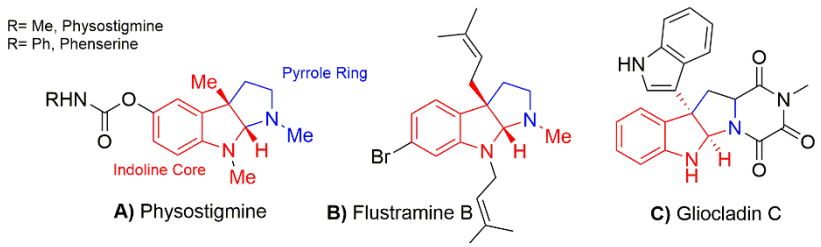

Figure 13 C3a functionalised HPI natural products

Conversely simple CH_3 substituents are also desirable, these have received interest and dedication of resources due to their apparent medicinal properties. Physostigmine, a functionalised HPI, and its analogues (Figure 13A)), operate

as acetylcholine esterase (AChE) inhibitors, used for the treatment of glaucoma and myasthenia gravis. The indoline carbamate is crucial to the reversible inhibition of AChE [57], however, other components of the core pyrroloindoline motif contribute to its inhibitory activity. Tertiary amines (N1) of the pyrrolidine ring are easily ionised at blood pH and can pass through the blood brain barrier, as well as the benzene ring of the indole, which may be involved with hydrophilic binding at the enzymes active site [58], illustrating the importance of the whole structure.

This chapter will provide an overview of the methods in accessing HPI's from indoles and aziridines and will include the presentation of our work developing a solvent free, one-pot microwave assisted aziridine ring opening/cyclization cascade for the synthesis of pyrroloindolines.

3.2. Strategies to synthesise Pyrroloindolines from Indoles.

Due to there being a short step from indoles to HPI's there is considerable precedence for use of indoles as starting materials. Broadly, they can be accessed by several methods, shown in Figure 14: (**1a,1b**) Tandem C3 functionalisation of the indole, starting from tryptophan/tryptamine derivatives [59], often referred to as the "biomimetic" approach due to the commonality with its proposed biosynthesis. Wherein, s-adenosyl methionine (SAM) co-substrates methylate tryptamine by an unknown enzyme (**1c**) a formal [3+2] cycloaddition of substrates with inducible dipoles to a C3 substituted indole [60]. Furthermore, they can be accessed from suitably disubstituted oxindoles (Figure 14, **2a**) undergoing a similar process to tryptophan cyclization, at a different oxidation state. This can be cascaded with a Pd (II) catalysed intramolecular Heck reaction, to form the oxindole *in situ* (Figure 14, **2b** [61]). However, the focus of this thesis is reactivity of indolium ions and the exploitation of discrete indole-indolium reactivity in synthesis and oxindole-based approaches will not be further addressed here: (substantial reviews exist for the synthesis of HPI from oxindoles in the literature [62]).

C3 functionalisation -cyclisation cascades encompass "biomimetic" cyclisation of tryptophan derivatives, wherein the reactivity of a substituted

indole is exploited through electrophilic functionalisation, generating an indolium ion, to which a terminal nucleophile on the tryptophan derivative will cyclise. This method allows for a diversification of the bridgehead (C3a) which can be achieved by selection of an appropriate electrophile (Figure 15).

[3+2] cycloaddition strategies exploit similar indolium chemistry as the tandem C3- functionalisation, except the electrophile and cyclising nucleophile are a single substrate, these cascades can proceed from simple, undecorated, indoles and proceed by C-C-N 1,3-dipoles, this strategy allows for functionalisation of the bridgehead and C2/C3 by selecting substituents on the indole starting material, and the dipolar substrate (Figure 14).

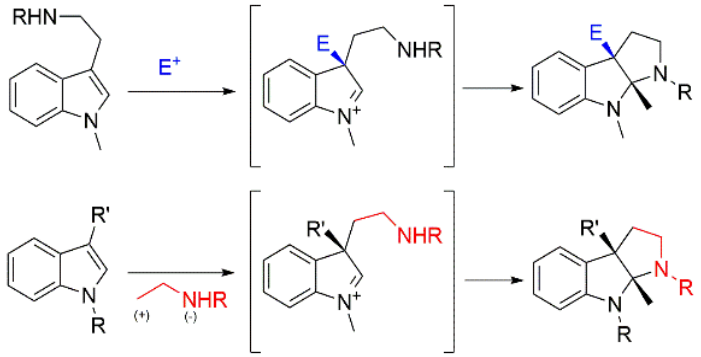

Figure 14 Schemes for the C3 functionalisation and [3+2] cycloadditions.

3.2.1. Tandem C3 functionalization and cyclization.

Typically, electrophilic functionalization at the C3 exploits the nucleophilicity of the C3 position of the indole and electrophilic addition yields 1,3,3 trisubstituted indolium ions containing a quaternary stereogenic centres. Tethered nucleophiles on C3 substituent attack the iminium ion, cyclizing to a tetrahydropyrrole ring (Figure 15). This is an efficient method for stereoselective synthesis of HPI products.

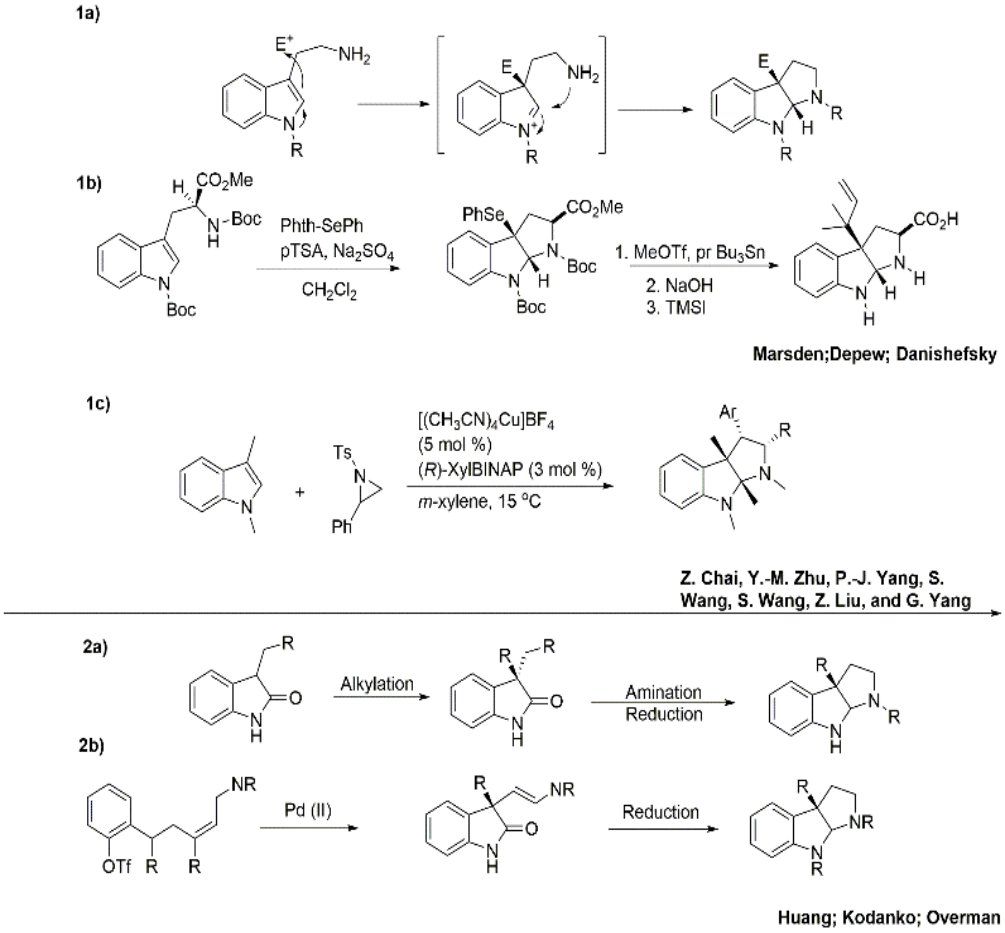

Figure 15 1a) general scheme for C3 functionalization-cyclisation, 1b) A step in the synthesis of amauromine *[59]* 1c) Synthesis of HPI from 1,3-disubstituted indoles and N-Sulfonyl Aziridines *[85]*

This method was used by Dashinefsky *et al*. (Figure 15 (**1b)**) in the synthesis of amauromine, a hypotensive vasodilator, furnishing the bridgehead of the HPI with phenyl selenide, that is used for a subsequent prenylation reaction. A C2 carboxylic acid is incorporated by cyclisation of the C3 pendant, a target for later esterification by Bis(2-oxo-3oxazolidinyl) phosphonic chloride (BOP-Cl). Use of a *N*-BOC protected indole is an example of a protected

tryptamine leading the cyclisation reaction, however, oxygen-based nucleophiles sych as tryptophol, can also be used in the synthesis of furoindolines [63]. Dashinefsky *et al.* incorporated selenation-cyclization as a point for further reactions, and this functionalisation-cyclization cascade also tolerates, alkylation [64], arylation [65], halogenation (F and Br) [66], oxidation [60] and allylation [67], all using metal or organo-catalysis, leading to a diverse range of bridgehead substituents, attesting to the versatility and scope of this process. However, these processes require well-furnished indole starting materials, with nucleophilic ethyl substituents, which limits elaboration of the pyrollidine ring with desirable functional groups. [3+2] cycloadditions address this, where the indole C3 substituent becomes the bridgehead, and the pendant is incorporated from a 1-3 dipole, enabling alternative diversification of the HPI core (Figure 15).

3.2.2. Dearomative cycloaddition reactions.

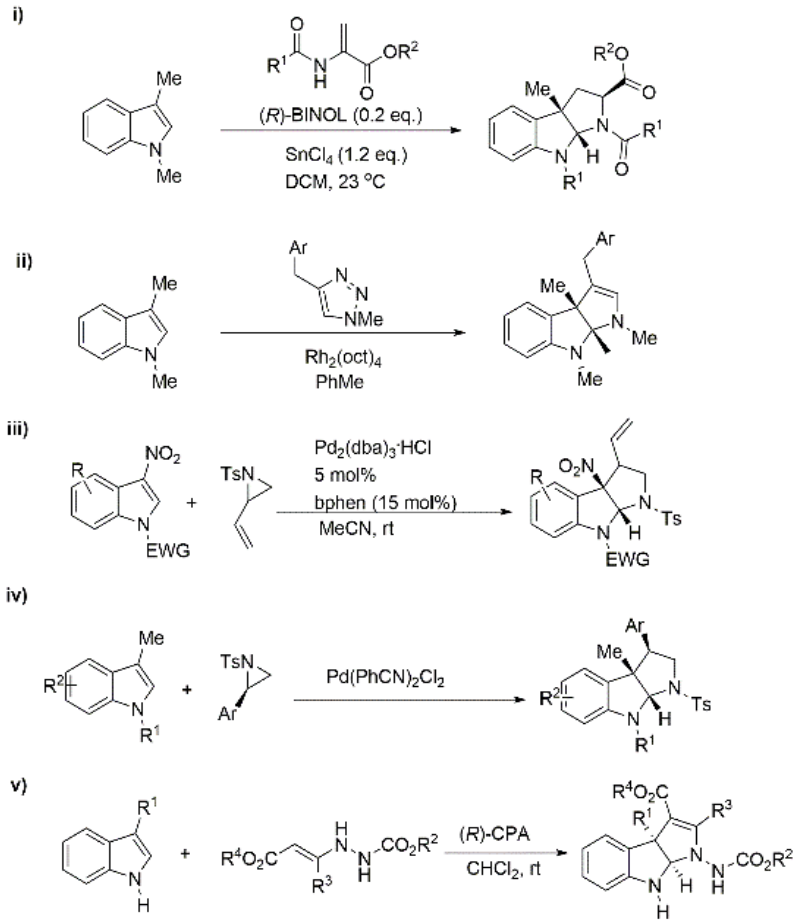

Figure 16 A diverse selection of recent [3+2] cycloaddition reactions in the synthesis of HPI. (i-v, correspond to references [65]-[70]).

Catalytic asymmetric dearomative [3+2] cycloadditions are another method of accessing valuable HPIs from indole starting materials. The design of these procedures is not trivial, due to them requiring suitable catalytic systems and carefully designed substrates. In the last decade, several metal catalysed, asymmetric dearomatisations using 1-3 dipoles have been reported, accessing the HPI core from simple indole starting materials. These are illustrated in Figure 16; i) 1,3-dimethylindole and 2-amidoacrylates in conjunction with (*R*)-BINOL· $SnCl_4$ [68], ii) 4-aryl-1-sulfonyl-1,2,3-triazoles with rhodium (II)-tetracarboxylate [69], iii) 3-nitroindoles dearomatized by 1-tosyl-2-vinylaziridine and $Pd_2(dba)_3{\cdot}CHCl_3$ yielding C3a= NO_2 functionalised HPI's [70] iv) (2R-1-(4-Methylbenzene sulfonyl)-2-phenyl aziridine, among other chiral aziridines by a ligand free, $Pd(PhCN)_2Cl_2$ catalysis with C3= CH_3 indoles [71] v) Implemented a different approach, using a variety of chiral phosphoric acid (CPA) organocatalysts to provide asymmetric control of the addition of azoalkenes, which are traditionally used as electron deficient heterodienes for [4+2] cyclization [72]. Mei *et al.* however, postulated that the hydrazone-enamine tautomerism could be exploited and subsequently operate as 1,3-dipoles [73]. Consequently, this provides a rare example which does not use metal catalysis and takes advantage of the reactivity of the substrate to facilitate the reaction.

3.2.3. Aziridines in reaction cascades.

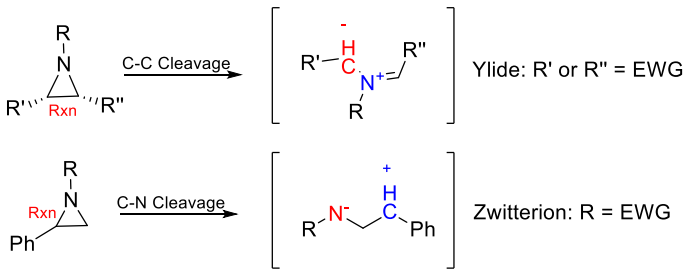

Figure 17 Scheme showing the effect of EWG's on aziridine ring opening.

Aziridines are strained ring systems, which can undergo ring opening (RO) reactions to form zwitterions or ylides, depending on the location of the electron withdrawing group (Figure 17). Non-activated aziridines ring open via C-C cleavage where an EWG is situated on either of the carbons of the 3 membered ring or, an EDG is situated at N, generating an ylide which undergoes S_N1/S_N2 reactions, depending on substituents electrophiles and nucleophiles. Activated aziridines, where an EWG is situated on the nitrogen, undergo C-N cleavage participating in formal S_N2 reactions at the least hindered carbon.

The RO reaction is useful in accessing synthetically and medicinally useful enantiomeric compounds such as oseltamivir an antiviral medication [74] and oxaliplatin on of a triad of chemotherapeutic medications used in cancer treatments [75]. As mentioned, the RO aziridines can act as [C,C,N] dipoles in [3+2] cycloaddition reactions with C3 substituted indoles in the synthesis of HPI [71]. The RO reaction can be achieved with nucleophiles under mild conditions in several different media, including, H_2O [76] silica gel [77] and even in a solvent free manner [78], [79].

3.3. Development of the "One-Pot" Microwave assisted [3+2] synthesis of pyrroloindolines from indoles via aziridine ring opening reactions.

3.3.1. Optimising Microwave assisted conditions with TMI and N-Tosylaziridine.

Building further into the utility of indolium ions as reactive intermediates we wanted to explore their use for the purpose of ring opening reactions exploiting the nucleophilicity of C3 its ability to receive electrophiles in the in the formation of the indolium ions. To this end we hypothesised that subjecting trisubstituted indoles, to thermally unstable N-tosylaziridines (TsAzr) the application of heat, and a nucleophilic site, could force the TsAzr to ring-open, resulting in the *in-situ* formation of a 1-3 dipole, effectively alkylating C3, forming the quaternary stereocentre, with a nucleophilic nitrogen pendant which would then cyclize to the HPI product.

Our initial attempt reaction with 1,2,3-trimethylindole (TMI) and TsAzr in H_2O at 100 ^oC. The TsAzr had ring-opened (RO) without reacting with the indole (**Entry 1**), and the hydrolysis product had formed (Figure 18).

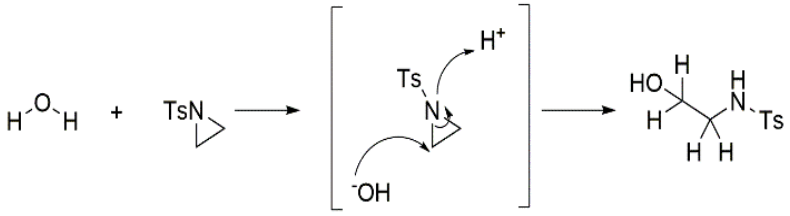

Figure 18 Proposed hydrolysis product of *N*-tosylaziridine

To avoid hydrolysis, we looked to pursue a solvent-free method, using microwave assisted reactions (MAR's) which had previously been effective toward indole alkylation [30]. Furthermore, MARs are well suited to solvent-free protocols [80]. **Entry 2** showed that the HPI product would form under these conditions, albeit in low yield. **Entry 1** started at the boiling point of H_2O, this was a contingent, due to the thermal stability of TsAzr, we had hoped to ensure that the aziridine ring remained intact, rather than opening prematurely, however, we observed the counter. Out of solution, the reaction could be initiated at 200 ^oC. Considering this, we repeated in water over a substantial period to see if our assertion of the role of was H_2O correct (**Entry 3**). Characterisation data was consistent with the solvolysis product, implying that hydrolysis had a greater effect on RO rate than temperature alone.

Due to the convenience of MAR's, the isolation of HPI from this method, and the knowledge that solvolysis would initiate RO, we proceeded to optimise conditions, monitoring reaction progress by tracking the consumption of TsAzr using ^{1}H-NMR (Figure 19).

Entry 4 shows that adequate yields were obtained after 4 x 10-minute cycles,

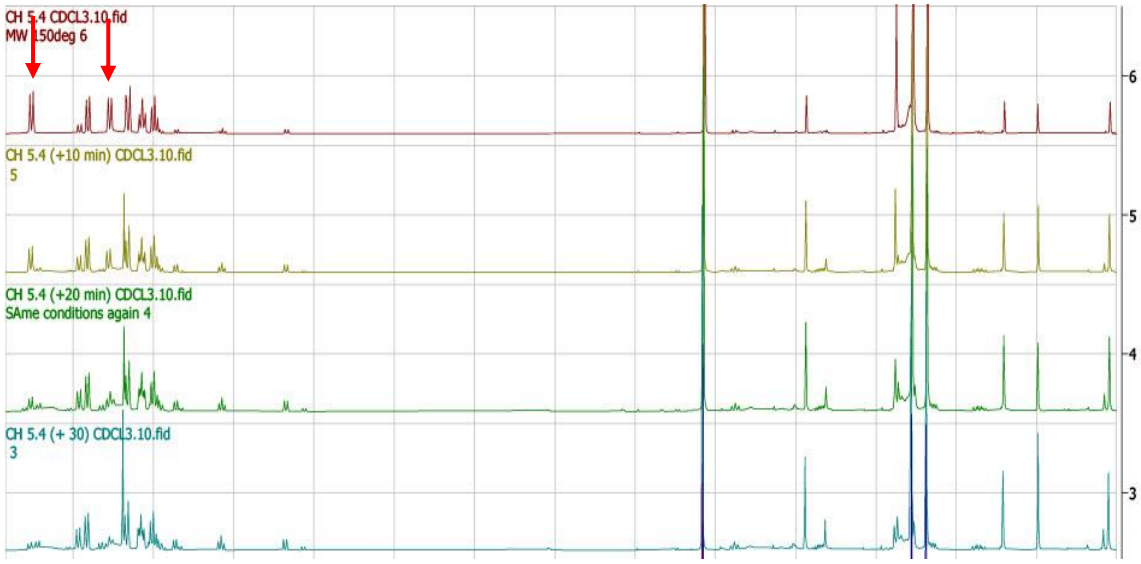

Figure 19 ^{1}H-NMR showing the consumption of aziridine over time, the red arrows denoting p-disubstituted protons of free N-Tosyl aziridine, which decrease in integration over time, showing consumption via ring opening reactions.

with TsAzr consumption being recorded every 10 minutes. This in turn, raised another question, how was intermittent heating effecting the reaction? That aside, we observed that the TsAzr was largely consumed after 2 x 10-minute heating cycles and proceeded to define optimum temperatures (**Entries 5 – 9**).

As a result, we saw those temperatures exceeding 140 ^{o}C were most effective, reinforcing the theory that hydrolysis was having a greater effect on TsAzr stability, than temperature in our initial reactions. As such, we identified that a “balancing act” between the rate of reaction and the thermal stability of TsAzr needed to be met, as our HPI synthesis requires the TsAzr to remain cyclic until the indole nucleophile induced RO or remained a linear zwitterion [81], from heat induced RO without reacting with solvents.

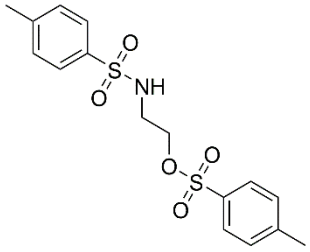

Figure 20 Structure of the bis-tosylate by-product

The upper limit of this was deduced by **Entry 10** where the reaction the formed bis-tosylate (Figure 18) and other unidentified by-products, narrowing our optimal temperature range between 140-180 ^{o}C, with this result in hand, we continued with a selection of temperatures within this range whilst exploring any discrepancies between intermittent and continuous heating cycles.

The optimum yield of 40 % (**Entry 14**) was achieved at 150 ^{o}C after 40 minutes of continuous heating, however, 25 ^{o}C above gave a significantly lower yield for the same duration, (**Entry 20**), inferring a narrow margin between stability and reactivity. Furthermore, intermittent heating under these conditions had a pronounced effect on yield (**Entry 13**) over continuous heating. This was not evident at higher temperatures (**Entries 11 + 12**), where the margin of change was 5 % overall, perhaps due to the increased temperature forcing the ring opening reaction, which would be comparably unaffected by intermittent cycles as a large proportion of the TsAzr substrate would be RO irrespective of the nucleophile. Thus far we determined that continuous heating, for 40 minutes at 150 ^{o}C to be the most favourable condition.

Next, we addressed the stoichiometry of our reagents. Initially we used a 2:1 ratio of TMI:TsAzr (**Entries 2 + 4-15**). Equimolar ratios **Entry 16** had a marked effect on yield, implying that TMI in excess was implicit to the reaction proceeding. We continued to increase the equivalents of TMI (**Entries 17 + 18**),

to assess the effect, with each increase we observed a reduction in yield of isolated HPI.

Due to our reaction being neat, (i.e., without additional solvent) we considered that TMI was behaving as both nucleophile and non-polar solvent. Typically activated aziridines such as TsAzr undergo S_N2 reactions [82], the rate of which, should be affected by the concentration of TMI and TsAzr. Our observations of a reduced yield, considering significant molar excess (2 eq.) of TMI could be explained by excessive TMI concentrations stabilising the zwitterionic, RO state of TsAzr. As such, when equimolar quantities of TMI and TsAzr were reacted under optimum conditions (**Entry 19**), 17 % yield of isolable HPI product formed. To confirm, we repeated the process with TsAzr in excess (**Entry 22**), in equimolar quantity (**Entry 23**) and with TMI in excess (**Entry 24**). From this we determined that 2:1 ratio of TMI:TsAzr to strike the best balance between nucleophilic and solvation effects.

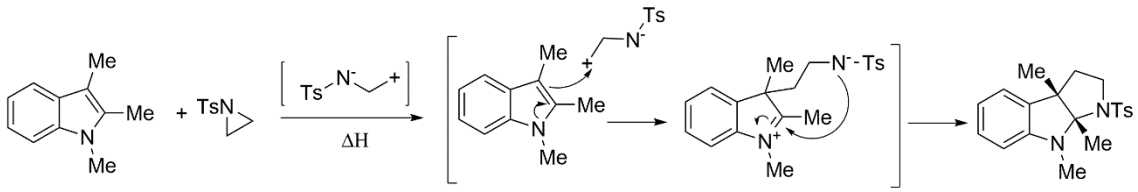

Figure 21 Possible scheme for the *N*-tosylaziridine ring opening reaction in the formation of HPI's

Entry	TMI: TsAzr (eq.)	Solvent	Temp (°C)	Time (Heat/Hold (mins)	Yield (%)
1*	1:1	H_2O	100	240	0
2	2:1	None	200	10/10	17
3	1:1	H_2O	100	1080	0
4	2:1	None	150	4x(10/10)	41
5	2:1	None	100	20/20	0
6	2:1	None	125	20/20	0
7	2:1	None	140	20/20	19
8	2:1	None	150	20	0
9	2:1	None	140	20/20	28
10	2:1	None	180	20/20	0
11	2:1	None	165	6 x 10/10	24
12	2:1	None	165	60/60	29
13	2:1	None	150	4 x 10/10	15
14	2:1	None	150	40/40	40
15	2:1	None	150	60/60	19
16	1:1	None	150	40/40	0
17	3:1	None	150	40/40	10

18	6:1	None	150	40/40	0
19	1:1	None	150	40/40	17
20	2:1	None	165	40/40	3
21	2:1	None	165	10/10	12
22	1:2	None	150	40/40	7
23	1:1	None	150	40/40	17
24	2:1	None	150	40/40	54

Table 3 Optimization of the Microwave assisted [3+2] cycloaddition of N-tosylaziridine to 1,2,3-trimethylindole. *Entry 1 was not a microwave assisted reaction.

With best conditions in hand (i.e., 1,2,3-trimethylindole 157 mg (0.984 mmol) added to *N*-tosylaziridine 97 mg (0.492 mmol) and stirred in the MW at 150 ^{o}C for 40 minutes.

We then explored the scope of this procedure with respect to i) incorporating a one-pot Fischer indolisation, similar to that explored in (Chapter 2) and ii) indoles with varied functional groups.

3.3.2. Incorporating Fischer indolisation

Our initial attempt to incorporate FI into the RO reaction we subjected 1-benzyl-2,3-dimethylindole to our RO conditions (Figure 20) i) 83% of the indole was

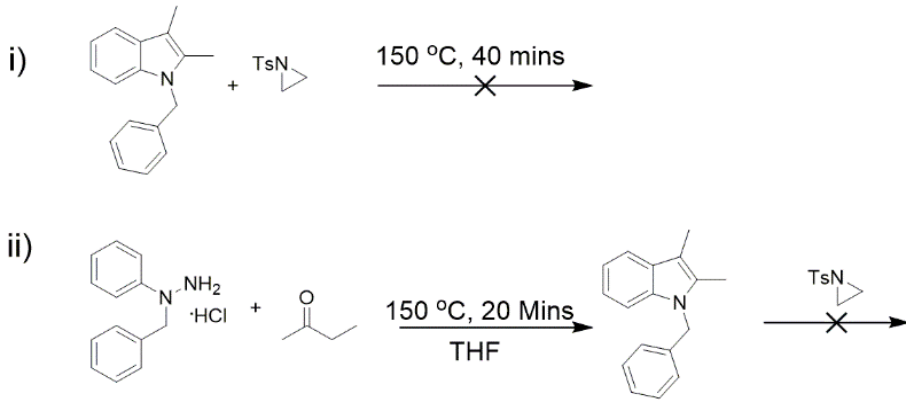

Figure 22 Schemes for implementing N-substituted hydrazines, and indoles into the RO reaction.

recovered from the solvent free procedure. ii) We repeated the procedure incorporating the indolisation step in Tetrahydrofuran (THF), which achieved 90 % yield, we then added TsAzr and subjected the mixture to our MW conditions. 85 % of the indole and 71% of RO TsAzr was retrieved. We determined that Fischer indolisation functions well in THF and that TsAzr likely ring opens in THF. At this point we realised that the indole nitrogen must be CH_3 substituted to progress with RO reactions, thus limiting their scope.

Setting aside the one-pot indolisation reaction we continued to explore scope of our aziridine RO procedure using substituted and functionalised indoles we had prepared [12].

3.3.3. Substrate scope of the *N*-Tosylaziridine ring-opening reaction.

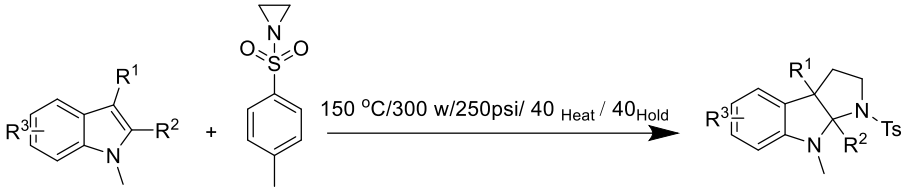

Figure 23 Generalised Scheme for scope exploration Using a 2:1 ratios of Indole:TsAzr

Entry	R^1	R^2	R^3	Solvent	Yield (%)
1	Et	Me	H	None	0
2	CHO	Me	H	None	0
3	Me	Me	5-Me	None	0
4	Me	Me	5-Br	None	0
5	Me	Me	H	None	28
6	Me	Me	H	THF	22
7	Me	Me	5-Br	THF	0
8	Me	Me	H	CPME	0
9	Me	Me	H	Toluene	0
10	Me	Me	H	CH_3CN	0
11	Et	Me	H	None	0
12	Bn	Me	H	None	0
13	Ph-*p*-Br	Me	H	None	0
14	*i*Pr	Me	H	None	0
15	3,2-Cyclopentyl		H	None	22
16	Me	Ethyl	H	None	0
17	Me	Me	5-OMe	None	0
18	Me	Me	7-F	None	0
19	3,2-Cyclohexyl		H	None	0
20	Me	Me	5-Me	None	16
21	Me	Me	5-Br	None	0
22	Me	H	H	None	0
23	Et	Me	H	None	0
24	Me	Et	H	None	0

Table 4 Scope assessment table; Determining the substrates suitable for the RO procedure

With the knowledge that the *N*-Benzyl substituted indole would not participate in the ring opening reaction we retained *N*-Me motif for our scope of substrate tolerance. **Entries 1-4** did not complete the RO reaction, which was striking, when we considered that **Entries 3 + 4** bear identical substituent patterns on

the pyrrole ring that is being dearomatized as TMI. We considered that the lack of reactivity for these could be a result of state/phase incompatibility. Neat TMI is liquid, and behaves as a solvent, whereas 5-Bromo-1,2,3-trimethylindole and 1,2,3,5-tetramethylindole (**Entries 4 + 5**) used in our assessment of scope were crystalline solids. This was the only observable difference between the two. Therefore, we revisited the addition of solvent to mobilise the reagents.

Tetrahydrofuran (THF) had no significant effect on the reaction with TMI (**Entries 5+6**) with a 6% difference in yield, or for the 5-Br functionalised TMI (**Entries 4 + 7**) both yielding 0% HPI, however, the RO reaction with TMI functioned in THF (**Entry 6**), a “borderline” polar aprotic solvent, we decided to try a range of solvents which were greener (CPME), Non-Polar (Toluene) and Polar aprotic (CH_3CN). No isolable HPI product was obtained from using these solvents (**Entries 7 - 10**).

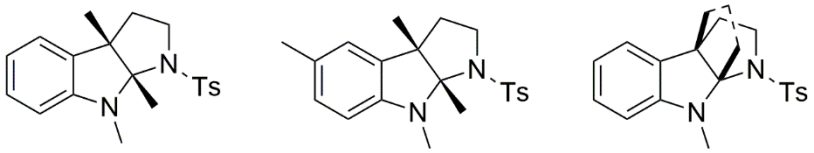

Figure 24 Structures of isolated HPI products from exploration of Scope

We returned to the solvent free approach introducing more substituted indoles to explore scope (**Entries 11 – 24**). Other than TMI we found success in isolating the HPI of 4-Methyl-1,2,3,4-tetrahydrocyclopenta[b]indole (**Entry 15**) and 1,2,3,5-Tetramethylindole **(Entry 20**) (Figure 24). It is interesting and thought provoking that these produced isolable HPI’s when other indoles, which are more closely related structurally and electronically to our TMI starting material did not, e.g., 3-Ethyl-1,2-dimethylindole **Entry 23**.

Whilst this method did not allow us to incorporate a vast array of substituents to the HPI structure, we were able to access consistently, and easily, isolate C3a = Me 1a,2a,3a-trimethyl-1-phenyltosyl-pyrroloindolines and eventually, isolate 1a,2a,3a,5-tetramethyl-1-phenyltosyl-pyrroloindoline and 1a-methyl-([3a-2a]-1,2,3,4- tetrahydrocyclopenta)-1-phenyltosyl-pyrolloindoline (Figure 22). From a synthetic perspective 1a-methyl-([3a-2a]- 1,2,3,4- tetrahydrocyclopenta)-1-phenyltosyl-pyrolloindoline is an interesting, and somewhat unlikely, tetracyclic compound, which could be a useful precursor for the synthesis of HPI alkaloids such as Borreverine [83].

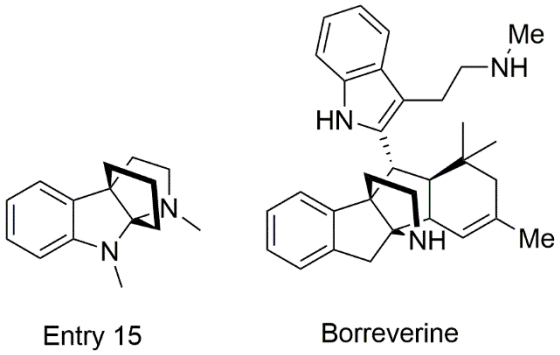

Figure 25 The Structures of 1a-methyl-([3a-2a]- 1,2,3,4-tetrahydrocyclopenta)-1-phenyltosyl-pyrolloindoline and Borreverine, a bis-indole alkaloid.

Our next step was to explore an alternative aziridine for the ring opening reaction: -(2R)-1-(4-Methyl benzene sulfonyl)-2- phenyl aziridine (TsPhAzr) as this was cited as being more stable in water, an improved stability in water may allow us to use water as a solvent, our goal here was to try and further improve the yields observed in the previous aziridine ring opening reactions, whilst accessing different HPI products.

3.3.4. Optimizing the ring opening reaction with a substituted aziridine

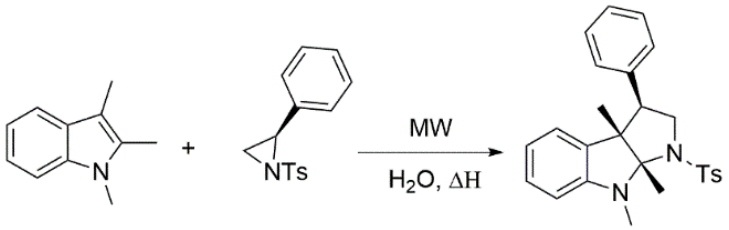

Figure 26 Scheme for the cycloaddition of (2R)-1-(4-Methyl benzene sulfonyl)-2- phenyl aziridine

Entry	H_2O (mL)	Temperature (^oC)	Time (Mins)	Yield (%)
1	0	150	40	0
2	1	100	10	0
3	1	100	20	16
4	1	150	20	8
5	0.5	150	10	20
6	0.5	150	20	37
7	0.25	150	20	13
8	0.5	150	30	11
9	0.5	150	30	20
10	0.5	125	20	16
11	0.5	175	20	0
12	0.5	150	20	27
13*	0.5	150	20	30

Table 5 Optimization of conditions for the MW assisted addition of (2R)-1-(4-Methyl benzene sulfonyl)-2- phenyl aziridine to 1,2,3-trimethylindole. Entry 13 was carried out with TMI in a 3:1 Excess

Using (2R)-1-(4-Methyl benzene sulfonyl)-2- phenyl aziridine (PhTsAzr) provides a more solvent stable aziridine and furnishes the HPI with a C3 enantiomeric phenyl substituent.

We initially tested PhTsAzr as a substrate under our best conditions for the previous TMI:TsAzr reactions, however no isolable HPI formed (**Entry 1**). Our first alteration was to reduce the temperature to the boiling point of H_2O and trial a 10-minute reaction, and this resulted in hydrolysis product (**Entry 2**). Doubling the time for the reaction, we saw our first quantifiable HPI product (**Entry 3**), by increasing the temperature we saw a reduction in yield (**Entry 4**) and an increase in the solvolysis products of the aziridine. Taking into consideration the issues we had with solvent/nucleophile balance with TMI, we applied this to H_2O, (which can obviously RO the aziridine substrate) by reducing the volume of H_2O to 0.5 mL. After 10 minutes in 0.5 mL, 20 % yield of HPI was isolated (**Entry 5**), and doubling the duration almost doubled the yield to 37 % (**Entry 6**). Considering the increased yields from a reduced volume of H_2O, we further reduced the volume to 0.25 mL (**Entry 7**) however, this trend did not continue. We also observed stark differences in yield between **Entres 5 + 6**, returning to 0.5 mL H_2O we gave the reaction 30 minutes and saw another reduction in isolated HPI, 11 %, **Entry 8,** and 20 % **Entry 9**. Due to the good yields observed **Entry 6** we were able to isolate both R/S diastereomers of 1a,2a,3a-trimethyl-1-phenyltosyl-3-phenyl pyrroloindoline by flash chromatography.

To consolidate the optimisation process, we attempted the synthesis at 125 ^oC and 175 ^oC (**Entries 10 + 11**) this identified, again, that there is a fine balancing

act to be observed between reactivity and stability with N-tosylaziridines in catalyst free reactions, with yields of 16% and 0% respectively. **Entry 12** was a repeat of our best conditions to verify the procedure, we summarised our optimisation by increasing the concentration of TMI to 3:1 (**Entry 13**), 30 % yield was isolated, comparable to the 2:1 ratio, leaving more TMI starting material to recover from column chromatography.

3.4. Concluding remarks

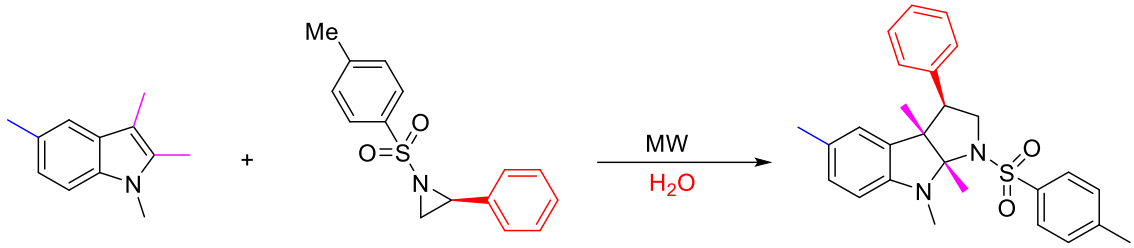

Figure 27 Scheme outlining the explored Aziridine ring-opening reactions.

In summary we have developed and optimised a one-pot procedure to synthesise pyrroloindolines from simple trisubstituted indoles via a microwave promoted aziridine ring opening, [3+2] cycloaddition (Figure 27). Due to the nature of the reagents these conditions have a very narrow tolerance for deviation from the conditions arrived. Regarding scope, as with the conditions, the range of materials suitable for these reactions are narrow with only 3 total substrates forming quantifiable HPI's from this process. However, we have managed to devise a way of accessing simple HPI core structures from unfurnished indole starting materials, which could later be used as scaffolds for further elaboration, by other processes, in the synthesis of HPI-Alkaloid natural products.

Secondly, we also devised a process in which we utilised water to access phenyl substituted pyrroloindolines (Figure 27 RED) from 1,2,3-trimethylindole and (2R)-1-(4-methyl benzene sulfonyl)-2- phenyl aziridine in water. We initially wanted to use this substrate due to its increased stability as a 1-3 dipole in H_2O, to further improve our yields. This was not the case; comparable yields were achieved. It would have been interesting to see the scope of this reagent with other functionally substituted indoles and would perhaps provide insight as to why the TMI, TsAzr, reaction operated over very specific substrate scope, however we did not have the time to do this. Both processes are rapid,

operationally simple, environmentally benign and achieved isolatable HPI without metal or organo-catalysis.

4. Outlook and Future Work:

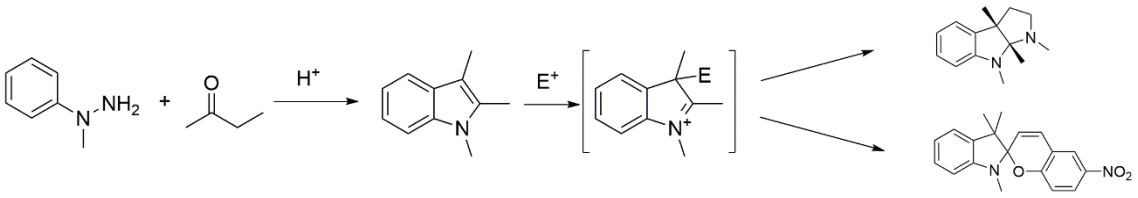

Figure 28 Scheme showing how Indolium ion reactivity has been used in this research.

Indoles and their corresponding indolium ions have a privileged place in synthetic and medicinal chemistry. Throughout the project, our objective was to exploit the reactivity of indolium ions in the synthesis of interesting and potentially useful, indole centred compounds.

To this end we have developed a one-pot four-component synthetic route to generate a diverse library of spiropyrans using environmentally benign solvents. Furthermore, we also developed a solvent free, microwave assisted ring aziridine ring-opening procedure to access pyrroloindolines (Figure 28).

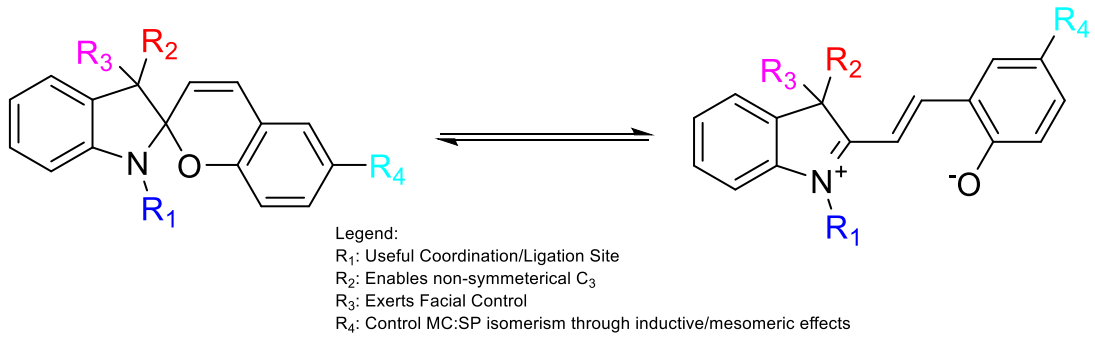

Figure 29 scheme depicting the explored areas for substituent variation and the possible effect on SP:MC isomerism, “R groups” denoting regions for substrate variation.

The next step for our SP synthesis would be to explore multiple functional group substitutions on a single SP compound (Figure 29). Our work showed itolerance for a number of functional groups which would affect the SP:MC isomerism. This ring opening can be mediated by UV excitation, and is often limited to ~365 nm, tuning an SP compound to be photo responsive at higher and lower wavelengths (Vis/NIR) could be important in the use and development of SP’s as inducible medicines and sensors.

When exploring multi-substituent variations, it would be worth selecting groups which impart properties onto the SP that effect the optical durability and solubility, of the compounds by selecting ionizable substituents or carboxylates such as 6j in this work. Furthermore, incorporating multiple functional groups for further chemistries such as alkynes, carboxylic acids/esters for coupling would provide a suitable method of preparing hybrid organic/inorganic substrates and a method of linking them to biomolecules, polymers and inorganic scaffolds.

Precedence for such is shown in our work, given the simplicity of our method we envision that such explorations could also allow for unprecedented and previously unexplored applications for SP compounds.

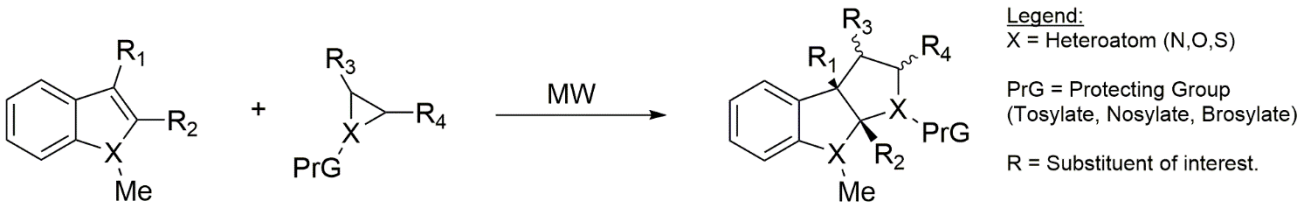

Figure 30 Schematic suggesting future development of our aziridine ring opening procedure

As for the aziridine ring opening procedure, we maintained the simplicity of the core pyrroloindoline structure, focusing on retaining the C3a = CH_3, in our products. Further work could look at removing the protecting group (Ts), possibly using a different protected aziridine, such as Nosyl or Brosyl. Furthermore, exploring different substituents on the indole and aziridine substrates would be worthwhile, allowing for the generation of large compound libraries whilst simultaneously assessing the substrate tolerance of our method (Figure 30). Furthermore, it would be worthwhile to investigate if this synthetic route would tolerate the synthesis of furoindoles, using epoxide substrates in place of aziridines, a feat we had hoped to achieve ourselves, to generate analogues of compounds such as Aspidophylline A (Figure 31).

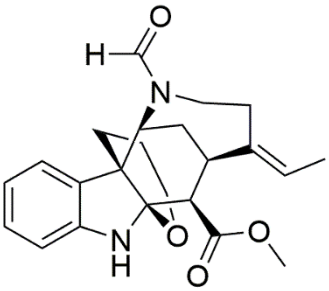

Figure 31 Structure of Aspidophylline A

As for the future of HHPI's, as long as alkaloids of medical interest remain largely difficult to obtain, due to their scarcity or location, synthetic methods to obtain and isolate these compounds in a simple manner will continue to be important and will complement research into the medical and pharmaceutical applications of these compounds. In tandem with computational chemistry, it would even be possible to generate libraries of compounds yielding new, or more effective derivatives of scaffold which targets GABA receptors such as physostigmine.

Experimental

5.1. General Experimental Information

All solvents and reagents used were commercially supplied. Water refers to deionised water. Silica gel used for flash-chromatography was of the 43-63 mm particle size. The microwave assisted reactions were performed in a CEM Discover microwave, using 10 mL microwave tubes fitted with septum caps and magnetically stirred. Mass spectra has yet to be recorded but this thesis will be updated when it has. ^{1}H-NMR was recorded at 400 MHz and ^{13}C-NMR at 100 MHz using a Bruker Avance III HD400 spectrometer. Infrared spectra acquired from novel compounds as thin films using attenuated total reflectance with a Nicolet iS5 FTIR spectrometer. Analytical thin layer chromatography was carried out using Merck Kieselgel 60 F254, coated aluminium plates.

5.2. Procedures and characterization relevant to Chapter 2.

General Procedure illustrated by 1,3-dimethyl-6'-nitro-3-(4-nitrobenzyl)-1,3-dihydrospiro[chromene-2',2-indole] (6a)

PTSA (118 mg, 0.622 mmol) was added to a suspension of 1-Methyl-1-phenyl hydrazine (73 uL, 0.622 mmol) and butanone (58 µL, 0.622 mmol.) in ethanol (0.5 mL) and the resulting mixture heated at 70 ^{o}C for 5 hours. H_2O (0.5 mL), 4-nitrobenzyl bromide (134 mg, 0.622 mmol) and 5-nitrosalicylaldehyde (103 mg, 0.622 mmol) were added and stirred at 70 ^{o}C for 4 hours. The reaction mixture

was concentrated *in vacuo* and the product was precipitated from acetone. If precipitates [a] if not [b].

[a] the precipitate was filtered, washed with acetone then H_2O yielding yellow powder **6**.

[b] Preadsorbed onto silica and purified by flash chromatography eluting with MeOH:EtOAc,

3-Benzyl-1,3-dimethyl-6'-nitro-1,3-dihydrospiro[chromene-2',2-indole] (6)

Procedure as above, yielding 160 mg yellow powder. (HCl)

^{1}H NMR (400 MHz, DMSO) δ 9.12 (s, 1H, 5'-H), 8.62 (d, *J* = 16.4 Hz, 1H, 4'-H), 8.34 (d, *J* = 9.2 Hz, 1H, 7'-H), 8.03 (d, *J* = 16.5 Hz, 1H, 3'-H), 7.93 (d, *J* = 7.5 Hz, 1H, 4-H), 7.74 (d, *J* = 7.9 Hz, 1H, 7-H), 7.66 (t, *J* = 7.5 Hz, 1H, 6-H), 7.59 (t, *J* = 7.9 Hz, 1H, 5-H), 7.24 (d, *J* = 9.2 Hz, 1H, 8'-H), 7.03 (dt, *J* = 15.0, 7.5 Hz, 3H, Bn-3,4,5-H), 6.64 (d, *J* = 7.4 Hz, 2H, Bn-2,6-H), 3.94 (s, 3H, 1-Me), 3.76 (s, 2H, 3-Ethyl-H), 1.94 (s, 3H, 3-Me).

1,3-imethyl-6'-nitro-3-(4-nitrobenzyl)-1,3-dihydrospiro[chromene-2',2-indole] (6a)

Same methods and quantities using 4-nitrobenzyl bromide 134 mg, 1 eq. Yielding 160 mg, 60%, yellow powder.

^{1}H NMR (400 MHz, DMSO) δ 9.12 (d, *J* = 2.9 Hz, 1H, 5'-H), 8.59 (d, *J* = 16.5 Hz, 1H, 4'-H), 8.35 (dt, *J* = 9.3, 2.4 Hz, 1H, 7'-H), 8.03 (d, *J* = 16.5 Hz, 1H, 3'-H), 7.95 (d, *J* = 7.5 Hz, 1H, 4-H), 7.91 (d, *J* = 8.3 Hz, 2H, 3-Nitro, 3,5-H), 7.76 (d, *J* = 7.5 Hz, 1H, 7-H), 7.68 (t, *J* = 7.5 Hz, 1H, 6-H), 7.61 (t, *J* = 7.5 Hz, 1H, 5-H), 7.23 (dd, *J* = 9.3, 3.1 Hz, 1H, 8'-H), 6.95 (d, *J* = 8.5 Hz, 2H, 3-Nitro 2,6-H), 3.97 (s, 3H, 1-Me), 3.91 (s, 2H, 3-Et-H), 2.09 (s, 3H, 2-Me), 1.96 (s, 3H, 3-Me).

3-(4-bromobenzyl)-1,3-dimethyl-6'-nitro-1,3-dihydrospiro[chromene-2',2-indole] (6b)

Same methods and quantities using 4-bromobenzyl bromide 155 mg, 1 eq. Yielding 222 mg, 77% orange powder.

^{1}H NMR (400 MHz, DMSO) δ 9.12 (d, *J* = 2.9 Hz, 1H, 5'-H), 8.59 (d, *J* = 16.5 Hz, 1H, 4'-H), 8.35 (dd, *J* = 9.0, 2.8 Hz, 1H, 7'-H), 8.02 (d, *J* = 16.6 Hz, 1H, 3'-H), 7.94 (d, *J* = 7.5 Hz, 1H, 4-H), 7.78 (d, *J* = 7.5 Hz, 1H, 7-H), 7.64 (dt, *J* = 24.0, 7.5 Hz, 2H, 5,6-H), 7.23 (dd, *J* = 8.7, 5.2 Hz, 3H, 3-BnBr 3,5-H, 8'-H), 6.61 (d, *J* = 8.0 Hz, 2H, 3-BnBr 2,6-H), 3.98 (s, 3H, 1-Me), 3.74 (s, 2H, 3-Et-H), 1.93 (s, 3H, 3-Me).

3-(2-bromobenzyl)-1,3-dimethyl-6'-nitro-1,3-dihydrospiro[chromene-2',2-indole] (6c)

Same methods and quantities using 2-bromobenzyl bromide 155 mg, 1 eq. Yielding 133 mg, 48%, orange powder.

^{1}H NMR (400 MHz, DMSO) δ 9.02 (d, *J* = 2.8 Hz, 1H, 5'-H), 8.39 (d, *J* = 16.6 Hz, 1H, 4'-H), 8.32 (dd, *J* = 9.1, 2.8 Hz, 1H, 7'-H), 8.01 (d, *J* = 16.5 Hz, 1H, 3'-H), 7.90 (d, *J* = 7.5 Hz, 1H, 4-H), 7.63 (t, *J* = 7.5 Hz, 1H, 6-H), 7.54 (t, *J* = 7.5 Hz, 1H, 5-H), 7.45 (dd, *J* = 21.1, 7.5 Hz, 2H, 7, 8'-H), 7.27 (t, *J* = 7.5 Hz, 1H, 3-Bn 4-H), 7.18-7.07 (m, 3H, 3-Bn 3,5,6-H), 4.15 (s, 3H, 1-Me), 3.78 (d, *J* = 14.2 Hz, 1H, 3-Et-Hb), 3.65 (d, *J* = 14.2 Hz, 1H, 3-Et-Ha), 1.94 (s, 3H, 3-Me).

3-(2,6-dichlorobenzyl)-1,3-dimethyl-6'-nitro-1,3-dihydrospiro[chromene-2',2-indole] (6d)

Same methods and quantities using 2,6-dichlorobenzyl bromide 149 mg, 1 eq. Yielding 218 mg, 77%, yellow powder.

^{1}H NMR (400 MHz, DMSO) δ 9.05 (d, *J* = 2.9 Hz, 1H, 5'-H), 8.31 – 8.25 (m, 1H, 4'-H), 8.07 – 7.98 (m, 1H, 7'-H), 7.96 (d, *J* = 7.5 Hz, 1H, 4-H), 7.63 (t, *J* = 7.5 Hz, 1H. 5-H), 7.42 (d, *J* = 7.5 Hz, 3H, 3-Bn 3,4,5-H), 7.27 (t, *J* = 7.5 Hz, 1H, 6-H), 7.19 (d, *J* = 9.2 Hz, 1H, 3'-H), 7.13 (d, *J* = 7.5 Hz, 1H, 7-H), 4.24 (s, 3H, 1-Me), 3.81 (d, *J* = 14.2 Hz, 1H, 3-Et-Ha), 3.62 (d, *J* = 14.3 Hz, 1H, 3 Et-Hb), 1.97 (s, 3H, 3-Me).
IR: ν_{max} /cm^{-1}: 2685, 1603, 1546, 1520, 1490, 1471, 1435, 1392, 1392, 1340, 1289, 1260, 1229, 1161, 1086, 1027, 1006, 970, 858, 836, 788, 760, 745, 680, 655, 636, 567, 454 cm^{-1}
*Awaiting Full Characterization

3-Allyl-1,3-dimethyl-6'-nitro-1,3-dihydrospiro[chromene-2',2-indole] (6e)

Same methods and quantities using allyl bromide 55 µL, 1 eq. Yielding 58 mg yellow powder.

Using allyl bromide ,161 µL, 3 eq. yielding 88 mg, 39%, yellow powder.

^{1}H NMR (400 MHz, DMSO) δ 9.08 (d, *J* = 2.9 Hz, 1H, 5'-H), 8.49 (d, *J* = 16.5 Hz, 1H, 4'-H), 8.32 (dd, *J* = 9.2, 2.9 Hz, 1H, 7'-H), 8.03 (d, *J* = 16.6 Hz, 1H, 3'-H), 7.71 – 7.58 (m, 2H, 5, 6-H), 7.48 (d, *J* = 7.5 Hz, 1H, 4-H), 7.32 – 7.20 (m, 2H), 7.11 (dd, *J* = 29.4, 21.6 Hz, 1H), 5.13 (ddt, *J* = 17.0, 9.9, 7.1 Hz, 1H, 3'-H), 4.93 – 4.80 (m, 2H, Allyl -1,3-H), 4.18 (s, 3H, 1-Me), 3.23 (dd, *J* = 14.2, 7.1 Hz, 1H, Allyl C-Hb), 3.12 (dd, *J* = 14.2, 7.3 Hz, 1H, Allyl C-Ha), 2.28 (s, 1H, Allyl C-H), 1.83 (s, 3H, MC 3-Me).

3-propargyl-1,3-dimethyl-6'-nitro-1,3-dihydrospiro[chromene-2',2-indole] (6f)

Same methods and quantities using propargyl bromide 46 µL, 1 eq. yielding 30 mg yellow powder

Using propargyl bromide, 140 µL, 3 eq. yielding 82 mg, 42%, yellow powder.

^{1}H NMR (400 MHz, DMSO) δ 9.07 (s, 1H, 5'-H), 8.46 (d, *J* = 16.5 Hz, 1H, 4'-H), 8.32 (d, *J* = 9.3 Hz, 1H, 7'-H), 8.09 – 7.94 (m, 3H, 4, 5, 7-H), 7.69 (br, 1H, 6-H), 7.47 (d, *J* = 7.7 Hz, 0H), 7.26 (d, *J* = 9.1 Hz, 1H, 8'-H), 7.11 (dd, *J* = 29.6, 21.9 Hz, 1H), 4.19 (s, 3H, 1-Me), 2.85 (s, 1H, C-H), 1.84 (s, 3H, 3-Me).

3-(3,5-bis(trifluoromethyl)benzyl)-1,3-dimethyl-6'-nitro-1,3-dihydrospiro[chromene-2',2-indole] (6g)

Same methods and quantities using 3,5 bis(trifluoromethyl) benzyl bromide 114 µL, 1 eq. Yielding 139 mg, 37%, orange powder.

^{1}H NMR (400 MHz, DMSO) δ 9.04 (d, *J* = 2.9 Hz, 1H, 5'-H), 8.44 (d, *J* = 16.4 Hz, 1H, 4'-H), 8.34 (dd, *J* = 9.2, 2.9 Hz, 1H, 7'-H), 7.97 (d, *J* = 16.4 Hz, 1H, 3'-H), 7.88 (d, *J* = 5.6 Hz, 2H, Bn 2, 6-H), 7.79 (d, *J* = 7.5 Hz, 1H, 4-H), 7.66 (pent, *J* = 7.3 Hz, 2H, 5, 6-H), 7.36 (s, 2H, 7, 8'-H), 7.31 – 7.20 (m, 3H), 7.01 (s, 2H), 3.94 (s, 3H, 1-Me), 3.89 (s, 2H, C-H2), 1.97 (s, 3H, 3-Me).
δC (100 MHz, DMSO) : 180.9, 164.8, 148.9, 146.1, 142.6, 140.8, 140.6, 138.2, 130.6, 130.2, 130.2, 130.0, 129.9, 129.6, 128.5, 128,1, 124.8, 124.6, 122.1, 121.9, 121.5, 117.9, 115.9, 115.7, 57.9, 43.8, 35.1, 23.6, 21.2.
IR: v_{max} /cm^{-1}: 2986, 1737, 1605, 1521, 1456, 1376, 1342, 1278, 1167, 1123, 1034, 1008, 952, 896, 838, 814, 747, 710, 682, 639, 557, 457.

*Awaiting Full Characterization

4-((1,3-dimethyl-6'-nitro-1,3-dihydrospiro[chromene-2',2-indole]-3-yl)methyl)benzonitrile (6h)

Same methods and quantities using 4-cyanobenzyl bromide 121 mg, 1 eq. Yielding 171 mg, 53%, yellow powder.

^{1}H NMR (400 MHz, DMSO) δ 9.12 (d, *J* = 2.9 Hz, 1H, 5'-H), 8.59 (d, *J* = 16.5 Hz, 1H, 4'-H), 8.34 (dd, *J* = 9.2, 2.9 Hz, 1H, 7'-H), 8.03 (d, *J* = 16.5 Hz, 1H, 3'-H), 7.96 (d, *J* = 7.5 Hz, 1H, 4-H), 7.77 (d, *J* = 7.5 Hz, 1H, 7-H), 7.64 (dt, *J* = 24.6, 7.5 Hz, 2H, 5, 6-H), 7.52 (d, *J* = 7.8 Hz, 2H, Bn 3, 5-H), 7.26 (d, *J* = 9.2 Hz, 1H, 8'-H), 6.86 (d, *J* = 7.9 Hz, 2H, Bn 2, 6-H), 3.98 (s, 3H, 1-Me), 3.87 (br, 2H, Et-H), 1.96 (s, 3H, 3-Me).
δC (100 MHz, DMSO) : 148.2, 140.7, 132.2, 130.4, 129.9, 128.6, 124.4, 121.9, 118.9, 117.8, 116.1, 115.6, 58.0, 44.8, 35.0, 24.7.
IR: v_{max}/cm^{-1}: 2776, 2568, 2226, 1609, 1585, 1554, 1518, 1476, 1442, 1413, 1345, 1306, 1288, 1262, 1228, 1162, 1125, 1083, 1023, 969, 903, 855, 839, 824, 760, 746, 699, 646, 632, 572, 549, 455

*Awaiting Full Characterization

Methyl 4-((1,3-dimethyl-6'-nitro-1,3-dihydrospiro[chromene-2',2-indole]-3-yl)methyl)benzoate (6i)

Same methods and quantities using methyl 4-(bromomethyl) benzoate 143 mg, 1 eq. Yielding 148 mg, 69%, orange powder.

^{1}H NMR (400 MHz, DMSO) δ 9.10 (d, *J* = 2.8 Hz, 1H, 5'-H), 8.59 (d, *J* = 16.5 Hz, 1H, 4'-H), 8.34 (dd, *J* = 9.2, 2.8 Hz, 1H, 7'-H), 8.02 (d, *J* = 16.5 Hz, 1H, 3'-H), 7.94 (d, *J* = 7.5 Hz, 1H, 4-H), 7.73 (d, *J* = 7.5 Hz, 1H, 7-H), 7.66 (t, *J* = 7.5 Hz, 1H, 5-H), 7.60 (d, *J* = 8.0 Hz, 3H, Bn 3,5-H, 6-H), 7.23 (d, *J* = 9.2 Hz, 1H, 8'-H), 6.81 (d, *J* = 8.0 Hz, 2H, Bn 2, 6-H), 3.95 (s, 3H, 1-Me), 3.84 (s, 2H, Bn Et-H), 3.75 (s, 3H, Bn-OMe), 1.96 (s, 3H, 3-Me).
δC (100 MHz, DMSO) : 181.2, 166.2, 164.8, 148.1, 146.0, 142.6, 141.3, 140.7, 140.5, 138.2, 130.0, 129.9, 129.8, 129.4, 129.2, 128.8, 128.7, 128.6, 128.2, 125.9, 124.4, 121.9, 117.9, 116.2, 115.6, 58.2, 52.5, 45.1, 35.0, 24.7, 21.2. IR: ν_{max} /cm^{-1}: 2986, 1715, 1604, 1543, 1521, 1492, 1435, 1339, 1285, 1158, 1117, 1032, 1006, 970, 835, 813, 747, 709, 681, 637, 563, 456.

*Awaiting Full Characterization

4-((1,3-dimethyl-6'-nitro-1,3-dihydrospiro[chromene-2',2-indole]-3-yl)methyl)benzoic acid (6j)

Same methods and quantities using methyl 4-(bromomethyl) benzoic acid 134 mg, 1 eq. Yielding 216 mg, 60%, orange powder.

^{1}H NMR (400 MHz, DMSO) δ 9.09 (s, 1H, 5'-H), 8.61 (d, *J* = 16.5 Hz, 1H, 4'-H), 8.31 (d, *J* = 9.2 Hz, 1H, 7'-H), 8.05 (d, *J* = 16.5 Hz, 1H, 3'-H), 7.93 (d, *J* = 7.5 Hz, 1H, 4-H), 7.72 (d, *J* = 7.5 Hz, 1H, 7-H), 7.65 (t, *J* = 7.5 Hz, 1H, 5-H), 7.58 (t, *J* = 7.5 Hz, 3H, Bn 3,5-H, 6-H), 7.14 (dd, *J* = 26.3, 8.5 Hz, 1H, 8'-H), 6.77 (d, *J* = 7.5 Hz, 2H, Bn 2, 6-H), 3.93 (s, 3H, 1-Me), 3.83 (s, 2H, Bn Et-H), 1.95 (s, 3H, 3-Me).
δC (100 MHz, DMSO) : 181.2, 167.4, 164.8, 148.1, 145.9, 142.6, 141.3, 140.6, 140.0, 138.3, 131.9, 130.0, 129.9, 129.6, 129.3, 128.6, 126.0, 124.4, 121.9, 117.9, 116.1, 115.6, 58.2, 45.2, 34.9, 24.8, 21.2.
IR: ν_{max} /cm^{-1}: 2970, 2360, 2340, 1700, 1651, 1607, 1556, 1520, 1474, 1419, 1340, 1287, 1263, 1225, 1176, 1117, 1008, 954, 860, 833, 747, 681, 654, 566, 453.

*Awaiting Full Characterization

3-(4-fluorobenzyl)-1,3-dimethyl-6'-nitro-1,3-dihydrospiro[chromene-2',2-indole] (6k)

Same methods and quantities using 4-fluoro benzyl bromide 76.3 µL, 1 eq..yielding 121 mg, 48% yellow powder.

δC (100 MHz, DMSO) : 159.9, 141.04, 133.4, 133.3, 132.0, 129.2, 128.5, 126.3, 126.0, 124.6, 123.3, 122.0, 118.7, 115.9, 114.7, 114.5, 114.3, 107.8, 107.7, 57.1, 29.3, 16.8.
IR: ν_{max} /cm^{-1}: 2929, 1736, 1651, 1603, 1508, 1476, 1335, 1268, 1218, 1157, 1124, 1085, 1008, 949, 921, 799, 745, 681, 657, 637, 566, 522, 485,.

*Awaiting Full Characterization

3-benzyl-3-ethyl-1-methyl-6'-nitro-1,3-dihydrospiro[chromene-2',2-indole], (6l)

Same methods and quantities using 2-pentanone, 66 µL 1 eq. Yielding 227 mg, 86 %, of yellow powder.

^{1}H NMR (400 MHz, DMSO) δ 8.76 (d, *J* = 3.2 Hz, 1H, 5'-H), 8.59 (d, *J* = 14.9 Hz, 1H, 4'-H), 8.51 (br, 1H, 3'-H), 7.89 – 7.78 (m, 2H, 4, 7'-H), 7.05 – 6.89 (m, 3H, Bn 3, 4, 5-H), 6.59 (d, *J* = 6.8 Hz, 2H, Bn 2, 6-H), 6.30 (d, *J* = 9.8 Hz, 1H, 8'-H), 3.78 (d, *J* = 13.6 Hz, 1H, Et-H), 3.67 (d, *J* = 13.6 Hz, 1H, Et-H), 3.62 (s, 3H, 1-Me), 1.99 (s, 1H, C-H), 1.90 (s, 1H, C-H), 0.39 (t, *J* = 7.3 Hz, 3H, Me).

3-benzyl-3-isopropyl-1-methyl-6'-nitro-1,3-dihydrospiro[chromene-2',2-indole] (6m)

Same methods and quantities using methyl isobutyl ketone, 49 µL 1 eq. yielding 56 mg, 29 %, of yellow powder

^{1}H NMR (400 MHz, DMSO) δ 8.79 (s, 1H, 5'-H), 8.64 (d, *J* = 15.3 Hz, 1H, 4'-H), 8.41 (s, 1H, 3'-H), 7.94 (dt, *J* = 5.8, 3.0 Hz, 1H, 4-H), 7.89 (dd, *J* = 9.7, 3.2 Hz, 1H, 7'-H), 7.60 – 7.52 (m, 3H, 5, 6, 7-H), 6.95 (dt, *J* = 14.7, 7.2 Hz, 3H, Bn 3,4,5-H), 6.54 (d, *J* = 7.5 Hz, 2H, Bn 2,6-H), 4.14 (s, 2H, C-H2), 4.03 (q, *J* = 7.1 Hz, 2H, Bn C-H2), 3.90 (s, 2H), 3.64 (s, 3H, 1-Me), 3.17 (s, 1H, H-CMe2), 1.17 (t, *J* = 6.6 Hz, 3H, C-Me), 0.34 (d, *J* = 6.6 Hz, 3H, C-Me)

3-benzyl-3-(4-bromophenyl)-1-methyl-6'-nitro-1',3'-dihydrospiro[chromene-2',2-indole] (6n)

Same methods and quantities using bromophenyl acetone, 132 uL 1 e.q. yielding 94 mg, 33%, orange powder.

^{1}H NMR (400 MHz, DMSO) δ 8.00 (d, *J* = 2.8 Hz, 1H, 5’-H), 7.70 (dd, *J* = 9.0, 2.9 Hz, 1H, 7’-H), 7.62 (d, *J* = 12 Hz, 2H, pTSA). 7.44 (dd, *J* = 9.4, 4.5 Hz, 2H, Ph 3, 5-H), 7.38 (d, *J* = 12 Hz, 2H, pTSA), 7.28 – 7.19 (m, 4H, Ph 2, 6-H, Bn, 3, 5-H), 7.06 (d, *J* = 7.5 Hz, 1H, 4-H), 7.00 (t, *J* = 7.5 Hz, 2H, 5-H, Bn 4-H), 6.82 (d, *J* = 7.5 Hz, 1H, 7-H), 6.63 (t, *J* = 7.5 Hz, 1H, 6-H), 6.46 (d, *J* = 7.5 Hz, 2H, Bn 2, 6-H), 6.39 (d, *J* = 10.4 Hz, 1H, 3’-H), 6.21 (d, *J* = 9.0 Hz, 1H, 8’-H), 6.02 (d, *J* = 7.5 Hz, 1H, 7-H), 3.85 (d, *J* = 13.4 Hz, 1H, Et-Hb), 3.53 (d, *J* = 13.4 Hz, 1H, Et-Ha), 2.81 (s, 3H, 1-Me).

3,3-dibenzyl-1-methyl-6’-nitro-1,3-dihydrospiro[chromene-2’,2-indole] (6o)

Same methods and quantities using benzyl acetone, 93 µL 1 eq. yielding 119 mg, 77%, purple amorphous film.

^{1}H NMR (400 MHz, DMSO) δ 8.86 (d, *J* = 3.2 Hz, 1H, 5'-H), 8.81 (d, *J* = 15.1 Hz, 1H, 4'-H), 8.51 (d, *J* = 15.2 Hz, 1H, 3'-H), 8.01 (d, *J* = 7.5 Hz, 1H, 4-H), 7.88 (dd, *J* = 9.8, 3.1 Hz, 1H, 7'-H), 7.49 (dd, *J* = 7.5, 4.7 Hz, 1H, 7-H), 7.41 (td, *J* = 7.5, 1.2 Hz, 1H, 6-H), 7.30 (td, *J* = 7.5, 3.6 Hz, 1H, 5-H), 7.23 – 7.05 (m, 2H), 7.00 (qd, *J* = 8.6, 7.7, 3.7 Hz, 6H, Bn 3,4,5-H), 6.65 (dd, *J* = 6.5, 1.3 Hz, 4H, Bn

1,6-H), 6.34 (d, *J* = 9.8 Hz, 1H, 8'-H), 3.99 (d, *J* = 13.8 Hz, 2H, Bn-ethyl-H), 3.87 (d, *J* = 13.8 Hz, 2H, Bn-ethyl-H), 3.17 (s, 3H, 1-Me).

3-benzyl-3-methyl-6'-nitro-1-phenyl-1,3-dihydrospiro[chromene-2',2-indole] (6r)

Same methods and quantities using diphenyl hydrazine. 87.3 mg, 1 eq. yielding nothing.

From diphenyl hydrazine hydrochloride Yielding 29 mg white powder.

^{1}H NMR (400 MHz, DMSO) δ 8.14 (d, *J* = 2.8 Hz, 1H, 5'-H), 8.01 (d d, *J* = 8.9, 2.8 Hz, 1H, 7'-H), 7.34 (t, *J* = 7.5 Hz, 2H, 4', 4-H), 7.29 – 7.03 (m, 8H, 5-, Ph, 2, 3, 4, 5- Bn 3, 4, 5-H), 6.95 (d, *J* = 9.0 Hz, 1H, 8'-H), 6.73 – 6.60 (m, 3H, 5, Bn 2, 6-H), 6.47 (d, *J* = 7.5 Hz, 1H, 7-H), 6.29 (dd, *J* = 7.2, 5.9 Hz, 1H), 6.21 (d, *J* = 10.4 Hz, 1H, 3'-H), 2.83 (ddd, *J* = 12.6, 8.8, 0.0 Hz, 2H, C-H2), 1.23 (s, 3H, 3-Me).

1,3-dibenzyl-3-methyl-6'-nitro-1,3-dihydrospiro[chromene-2',2-indole] (6s)

Same methods and quantities using 1-benzyl-1-phenyl hydrazine 112 µL, 1 eq. yielding 82 mg, 33%, purple amorphous film.

1H NMR (400 MHz, DMSO) δ 8.24 (s, 1H, 5'-H), 8.03 (d, *J* = 2.8 Hz, 1H, 4'-H), 8.01 (dd, *J* = 9.1, 2.9 Hz, 1H, 7'-H), 7.31 – 7.16 (m, 7H, 4, Bn 3, 4,5-H), 7.02 (q, *J* = 8.8, 6.8 Hz, 2H, 5, 6-H), 6.91 (dd, *J* = 22.2, 9.8 Hz, 1H, 8'-H), 6.65 (d, *J* = 7.3 Hz, 2H, 1 Bn 2, 6-H), 6.44 (br, 1H, 7-H), 6.29 (d, *J* = 7.3 Hz, 2H, 3 Bn 2, 6-H), 4.48 (d, *J* = 16.7 Hz, 1H, 1-CH2) 4.29 (d, *J* = 16.7 Hz, 1H, 1-CH2), 2.91 (d, *J* = 12.1 Hz, 2H, 3 CH2), 2.86 (dd, *J* = 12.1 Hz, 2H, 3 CH2), 1.23 (s, 3H, 3 Me)

3-benzyl-7'-methoxy-1,3-dimethyldihydrospiro[chromene-2',2-indole] (6t)

Same methods and quantities using 2-hydroxy-4-methoxybenzaldehyde, 95 mg, 1 eq. yielding 83 mg, 31%, of red powder.

^{1}H NMR (400 MHz, DMSO) δ 7.21 - 7.13 (m, 3H, 4'-H, 5'-H, 4-H), 7.13 - 7.06 (m, 3H, 3'-H), 7.92 (d, *J* = 7.5 Hz, 1H, 4-H), 7.82 (d, *J* = 16.5 Hz, 1H, 3'-H), 7.64 (td, *J* = 22.2, 20.1, 7.9 Hz, 4H, 5,6,7-H, 8'-H), 7.03 (m, 3H, Bn, 3,4,5-H), 6.61 (d, *J* = 7.4 Hz, 2H, Bn 2, 6-H), 3.90 (s, 3H, 1-Me), 3.76 (d, *J* = 13.8 Hz, 1H, C-Ha), 3.65 (d, *J* = 13.8 Hz, 1H, C-Hb), 1.91 (s, 3H, 3-Me).

3-benzyl-6'-methoxy-1,3-dimethyldihydrospiro[chromene-2',2-indole] 6u

Same methods and quantities using 2-hydroxy-5-methoxybenzaldehyde, 95 mg, 1 eq. yielding 59 mg,25% of red powder.

*Awaiting full characterization

3-benzyl-6'-chloro-1,3-dimethyl-1,3-dihydrospiro[chromene-2',2-indole] (6v)

Same methods and quantities with 97 mg, 1 e.q 5-chloro-2-hydroxy benzaldehyde, yielding 189 mg, 76%, of purple amorphous film.

^{1}H NMR (400 MHz, DMSO) δ 8.59 (d, *J* = 16.4 Hz, 1H, 4'-H), 8.32 (d, *J* = 2.8 Hz, 1H, 5'-H), 7.94 (d, *J* = 7.5 Hz, 1H, 4-H), 7.84 (d, *J* = 16.4 Hz, 1H, 3'-H), 7.71 (d, *J* = 7.5 Hz, 1H, 7-H), 7.65 (t, *J* = 7.5 Hz, 1H, 5-H), 7.58 (t, *J*= 7.5 Hz, 6-H), 7.53 (dd, *J*= 8.9, 2.6 Hz, 7'-H), 7.13 (d, *J* = 8.9 Hz, 1H, 8'-H), 7.03 (m, 3H, Bn 3, 4, 5-H), 6.61 (d, *J* = 7.4 Hz, 2H, Bn 2,6-H), 3.92 (s, 3H, 1-Me), 3.78 (d, *J* = 13.7 Hz, 1H, C-Hb), 3.66 (d, *J* = 13.7 Hz, 1H, C-Ha), 1.92 (s, 3H, 3-Me).

3-benzyl-6'-bromo-1,3-dimethyl-1,3-dihydrospiro[chromene-2',2-indole] (6w)

Same methods and quantities with 125 mg, 1 e.q. 5-bromo-2-hydroxy benzaldehyde, yielding 162 mg, 67 %, of amorphous purple film.

^{1}H NMR (400 MHz, DMSO) δ 8.57 (d, *J* = 16.4 Hz, 1H, 4'-H), 8.41 (br, 1H, 5'-H), 7.92 (d, *J* = 7.5 Hz, 1H, 4-H), 7.82 (d, *J* = 16.5 Hz, 1H, 3'-H), 7.64 (td, *J* = 22.2, 20.1, 7.9 Hz, 4H, 5,6,7-H, 8'-H), 7.03 (m, 3H, Bn, 3,4,5-H), 6.61 (d, *J* = 7.4 Hz, 2H, Bn 2, 6-H), 3.90 (s, 3H, 1-Me), 3.76 (d, *J* = 13.8 Hz, 1H, C-Ha), 3.65 (d, *J* = 13.8 Hz, 1H, C-Hb), 1.91 (s, 3H, 3-Me).

3-benzyl-1,3-dimethyl-6',8'-dinitro-1,3-dihydrospiro[chromene-2',2-indole] (6x)

Same methods and quantities with 132 mg, 1 e.q. 3,5-dinitro-2-hydroxy benzaldehyde yielding 156 mg, 62 %, purple amorphous film.

^{1}H NMR (400 MHz, DMSO) δ 8.98 (d, *J* = 3.3 Hz, 1H, 7'-H), 8.61 (d, *J* = 4.3 Hz, 3H, 5'-H), 7.87 (d, *J* = 7.3 Hz, 1H, 4-H), 7.62 (d, *J* = 7.7 Hz, 1H, 7-H), 7.57 (t, *J* = 7.2 Hz, 1H, 5-H), 7.52 (t, *J* = 7.5 Hz, 1H, 6-H), 7.48 (d, *J* = 7.7 Hz, 1H, 4'-H), 7.18 (dt, *J* = 15.0, 7.8 Hz, 1H, 3'-H), 7.02 (dt, *J* = 14.4, 7.0 Hz, 3H, Bn 3, 4, 5-H), 6.61 (d, *J* = 7.3 Hz, 2H, Bn 2, 6-H), 3.82 (d, *J* = 13.4 Hz, 1H, C-Hb), 3.73 (s, 3H, 1-Me), 3.72 (d, *J* = 14.4 Hz, 1H, C-Ha),1.93 (s, 3H, 3-Me). δC (100 MHz, DMSO) : 181.6, 170.2, 153.2, 142.8, 141.6, 141.3, 135.8, 135.3, 129.5, 129.2, 128.9, 128.7, 128.2, 127.5, 126.6, 125.8, 124.2, 114.5, 111.9, 57.6, 55.4, 45.7, 33.8, 31.2, 29.5, 25.5.
IR: ν_{max} /cm^{-1}: 2939, 1610, 1520, 1493, 1435, 1394, 1339, 1275, 1230, 1205, 1159, 1124, 1080, 1017, 966, 925, 856, 787, 745, 700, 639, 570, 487, 465.

*Awaiting full characterization.

Methyl-3-benzyl-1,3-dimethyl-1,3-dihydrospiro[chromene-2',2-indole]-6'-carboxylate (6z)

Same methods and quantities with 112 mg, 1 eq. methyl 3-formyl-4-hydroxy benzoate, yielding 104 mg, 50 %, purple amorphous film.

^{1}H NMR (400 MHz, DMSO) δ 8.74 (d, *J* = 2.2 Hz, 1H, 5'-H), 8.67 (d, *J* = 16.5 Hz, 1H, 4'-H), 8.06 (dd, *J* = 8.7, 2.2 Hz, 1H, 7'-H), 7.95 (d, *J* = 8.5 Hz, 1H, 3'-H), 7.73 (d, *J* = 7.5 Hz, 1H, 4-H), 7.65 (t, *J* = 7.5 Hz, 1H, 5-H), 7.58 (td, *J* = 7.5, 1.3 Hz, 1H, 6-H), 7.21 (d, *J* = 7.5 Hz, 1H, 7-H), 7.12- 6.97 (m, 3H, Bn 3, 4, 5-H), 6.63 (d, *J* = 7.0 Hz, 2H, Bn 2, 6-H), 3.90 (d, *J* = 12.6 Hz, 6H, 1-Me, O-Me), 3.76 (s, 2H, C-H2), 2.28, 1.94 (s, 3H

5.3. Procedures and characterization relevant to Chapter 3

Aziridine ring-opening reactions:

N-Tosylaziridine (98 mg, 0.498 mmol) was added to 1,2,3-Trimethylindole (157 mg, 0.986 mmol) and the resulting mixture heated at 150 ^{o}C for 40 minutes.

(2R)-1-(4-Methyl benzene sulfonyl)-2- phenyl aziridine (77 mg, 0.285 mmol) was added to a suspension of 1,2,3-Trimethylindole (91 mg, 0.57 mmol) in H_2O (0.5 mL) and heated at 150 ^{o}C for 20 minutes.

Purification by flash chromatography eluting with 20 % EtOAc:Hexane, concentrated *in vacuo* to produce a coloured oil.

1a,2a,3a-trimethyl-1-phenyltosyl-pyrolloindoline

Conditions: 150 ^{o}C/ 250 psi/ 300 w/ 60 mins (T)/ 60 mins (H)

Reagents: 2:1, 157 mg (0.984 mmol) 1,2,3-Trimethyl Indole, 97 mg (0.498 mmol) N-Tosyl Aziridine

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.3 Hz, 2H, Tos 2, 6-H), 7.1 (d, *J* = 8.3 Hz, 2H, Tos 3, 5-H), 7.04 (td, *J* = 7.5, 1.2 Hz, 1H, 6-H), 6.93 (dd, *J* = 7.5, 1.2 Hz, 1H, 4-H), 6.64 (td, *J* = 7.5, 1.2 Hz, 1H, 5-H), 6.25 (d, *J* = 7.5 Hz, 1H, 7-H), 3.45 (ddd, *J* = 9.2, 7.7, 1.5 Hz, 1H, Hb), 3.01 (s, 3H, 1a-Me), 2.91 (ddd, *J* = 11.2, 9.2, 5.9 Hz, 1H, Ha), 2.35 (s, 3H, Tos-Me), 2.22 (ddd, *J* = 12.5, 5.9, 1.5 Hz, 1H, Hc), 1.93 (ddd, *J* = 11.3, 3.7, 1.0 Hz, 1H, Hd), 1.78 (s, 3H, 2a-Me), 1.12 (s, 3H. 3a-Me). δC (100 MHz, $CDCl_3$) : 149.1, 142.5, 137.9, 133.1, 129.2, 128.3, 126.9, 121.5, 117.9, 106.5, 94.5, 56.8, 47.8, 35.2, 30.3, 23.1, 21.4, 19.7
IR: ν_{max} /cm^{-1}: 3854, 3734, 3374, 3764, 3648, 3628, 2961, 2360, 2340, 1736, 1713, 1651, 1606, 1558, 1491, 1454, 1370, 1330, 1219, 1155, 1111, 1080, 1021, 997, 903, 862, 815, 745, 706, 672, 651, 603, 580, 547.

*Awaiting Full Characterization

1a,2a,3a,5-Tetramethyl-1-phenyltosyl-pyrolloindoline

Reagents: 2:1, 157 mg (0.984 mmol) 1,2,3,5-Tetramethyl Indole, 97 mg (0.498 mmol) N-Tosyl Aziridine

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.3 Hz, 2H, Tos 2, 6-H), 7.08 (d, *J* = 8.3 Hz, 2H, Tos 3, 5-H), 6.76 (d, *J* = 7.5 Hz, 1H, 6-H), 6.67 (s, 1H, 4-H), 6.09 (d, *J* = 7.5 Hz, 1H, 7-H), 3.36 (ddd, *J* = 9.2, 7.7, 1.5 Hz, 1H, Hb), 2.90 (s, 3H, 2a-Me), 2.83 (ddd, *J* = 11.2, 9.2, 5.9 Hz, 1H, Ha), 2.29 (s, 3H, Tos-Me), 2.15 (s, 3H, 5-Me) 2.11 (ddd, *J* = 12.5, 5.9, 1.5 Hz, 1H, Hc), 1.85 (ddd, *J* = 11.3, 3.7, 1.0 Hz, 1H, Hd), 1.68 (s, 3H, 2a-Me), 1.05 (s, 3H. 3a-Me). δC (100 MHz, $CDCl_3$) :147.1, 142.5, 137.9, 133.4, 129.2, 128.6, 127.1, 126.9, 123.9, 122.4, 118.8, 108.7, 106.4, 94.8, 56.8, 54.6, 47.8, 35.4, 30.6, 21.4, 21.4, 20.8, 19.7 IR: ν_{max} /cm^{-1}: 3734, 3674, 3648, 3275, 2630, 2340, 1735, 1716, 1699, 1650, 1558, 1540, 1500, 1457, 1363, 1331, 1217, 1155, 1078, 995, 904, 804, 670, 660, 647.

*****Awaiting Full Characterization

1a-methyl-([3a-2a]- 1,2,3,4- tetrahydrocyclopenta)-1-phenyltosyl-pyrolloindoline

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.3 Hz, 2H, Tos 2, 6-H), 7.18 (d, *J* = 8.3 Hz, 2H, Tos 3, 5-H), 7.02 (t, *J* = 7.5 Hz, 1H, 6-H), 6.90 (d, 1H, 4-H), 6.54 (t, *J* = 7.5 Hz, 1H, 5-H), 6.23 (d, 7.5 Hz, 1H, 7-H), 3.44 (ddd, *J* = 9.2, 7.7, 1.5 Hz, 1H, Hb), 3.01 (ddd, 9.2, 7.7, 1.5 Hz, 1H, Ha), 2.96 (s, 3H, Tos-Me), 2.56 (ddd, *J* = 9.2, 7.7, 1.5 Hz, Hc), 2.35, (s, 3H, 1a-Me), 2.05 (m, 2H, Cyp-HH), 1.87 (m, 2H, Cyp-HH), 1.70 (m, 3H, Hd, Cyp-3a-HH) δC (100 MHz, $CDCl_3$) : 151.9, 143.0, 137.9, 129.5, 128.4, 127.1, 122.7 117.5, 105.6, 102.5, 67.4, 49.9, 40.8, 38.4, 36.4, 30.9, 26.9, 21.5 IR: ν_{max} /cm^{-1}: 3853, 3838, 3801, 3674, 3648, 3628, 3566, 2946, 2866, 2360, 2340, 1735, 1713, 1683, 1651, 1604, 1558, 1541, 1490, 1459, 1364, 1311, 1241, 1203, 1152, 1111, 1089, 999, 942, 917, 892, 860, 814, 742, 705, 672, 655, 580, 543, 403

1a,2a,3a-trimethyl-(3-phenyl)-1-phenyltosyl-pyrolloindoline

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.3 Hz, 2H, Tos 2, 6-H), 7.23 (dd, *J* = 11.3, 3.7 Hz, 3H) 7.15 (d, *J* = 8.3 Hz, 2H, Tos 3, 5-H), 6.09 (dd, *J* = 7.5, 1.2 Hz, 1H, 4-H), 6.93 (t, *J* = 7.5, 1.2 Hz, 1H, 5-H), 6.26 (t, *J* = 7.5 Hz, 1H, 7-H), 6.22 (t, *J* = 7.5 Hz, 1H, 6-H), 5.73 (d, *J*= 7.5 Hz, 1H), 3.52 (ddd, *J* = 9.2, 7.7, 1.5 Hz, 1H, Hb), 3.32 (ddd, *J* = 9.2, 7.7, 1.5 Hz, 1H, Ha), 3.15 (ddd, *J* = 9.2, 7.7, 1.5 Hz, 1H, Hc), 2.98 (s, 3H, 1a-Me), 2.91 (ddd, *J* = 11.2, 9.2, 5.9 Hz, 1H, Ha), 2.32 (s, 3H, Tos-Me), 1.83 (s, 3H, 2a-Me), 1.13 (s, 3H, 3a-Me).

*Awaiting Further Characterization.

5.4. Synthesis of aziridine substrates

N-Tosyaziridine [84]

Procedure:

Tosyl chloride (TsCl) (2.38 g/ 12.5 mmol) was added portion wise at room temperature to a rapidly stirring mixture of ethanolamine (302 uL/ 5 mmol), KOH (10 g), CH_2Cl_2 (10 mL) and H_2O (10 mL). After 3 hours Ice and H_2O were added, the organic layer extracted and washed with further water and dried over $MgSO_4$, excess solvent was removed *in vacuo* yielding a white crystalline product.

*We could not isolate the *N*-tosylaziridine product from this method.

(2R)-1-(4-Methyl benzene sulfonyl)-2- phenyl aziridine [84] ,

Procedure:

Tosyl chloride (3.06 g/ 16 mmol) was added portion wise to a stirring mixture of (*R*)-(-)-2-Phenylglycinol (1.00 g/ 7.29 mmol), K_2CO_3 (4.03 g/ 29 mmol) in CH_3CN (70 mL) and left to stir over night. The white precipitate was washed with toluene and filtered through paper. The filtrate was collected and condensed under vacuum yielding a yellow oil. This oil was purified by flash chromatography in 60:40 Hexane:EtOAc which upon further solvent removal formed a crystalline white solid (2R)-1-(4-Methyl benzene sulfonyl)-2- phenyl aziridine (89 %).

Characterization:

(2R)-1-(4-Methyl benzene sulfonyl)-2- phenyl aziridine

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.5 Hz, 2H, Tos 2, 6-H), 7.35 (d, *J* = 8.5 Hz, 2H, Tos 3, 5-H), 7.30 (m, 3-H, Ph-H), 7.23 (m, 2H, Ph-H), 3.79, (dd, *J* = 16.2, 8.5 Hz, 1H), 3.00, (d, 7.2 Hz, 1H), 2.45 (s, 3H, Tos-Me), 2.41 (d, *J* = 7.2 Hz, 1H), 1.59 (s, 1H).

5.5. Synthesis of indole precursors

One-pot, three-component Fischer indolisation–N-alkylation for rapid synthesis of 1,2,3-trisubstituted indoles DOI: 10.1039/D0OB02185G [12]

Drawing from our requirements to have access to diverse indole starting materials for our studies into spiropyran and pyrroloindoline synthesis, a one-pot, three-component protocol for the synthesis of 1,2,3-trisubstituted indoles was developed. The author of this thesis contributed to this publication by assisting in the scope determination of this procedure by generating the indoles listed below.

Entry	R1	R2	R3	Yield (%)
1	H	Et	Me	97
2	H	Bn	Me	91
3	H	4-BrPh	Me	67
4	H	iPr	Me	95
5	H	2,3-Cyclopentyl		74
6	H	Me	Et	92
7	5-OMe	Me	Me	72
8	7-F	Me	Me	80
9	5-NO_2	Me	Me	0
10	H	2,3-Cyclohexyl		85
11	H	2,3-Cycloheptyl		80
12	H	Pyridonyl		0
13	5-Br	Me	Me	75
14	5-Me	Me	Me	98

Method:

Pentan-2-one 76 µL was added to a stirring suspension of benzylphenylhydrazine hydrochloride 98.9 mg in Tetrahydrofuran (300 uL) in a 1 cm diameter walled microwave tube. The tube was capped and placed into the microwave chamber wherein it was subjected to Microwave irradiation at 150 ^{o}C/300 W/ 250 psi for 10 minutes. Upon cooling, the cap was removed and sodium hydride (60% dispersion in mineral oil) (110 mg/ 4 eq.) was added carefully, in small amounts to a stirring reaction mixture, followed by the injection of N'-N'-Dimethyl formamide (500 µL) the chamber was then capped and placed into an oil bath at 80 ^{o}C. After 5 minutes had elapsed Benzyl bromide was added and the vessel resubmerged in the oil bath for 30 minutes. The reaction was quenched by the dropwise addition of methanol and excess

solvent removed *in vacuo*. The crude indole was purified by flash chromatography using ethyl acetate in petrol, eluting at 3% to give 3-ethyl-1,2-dimethylindole (155 mg/ 97 %) as an orange/yellow oil.

3-benzyl-1,2-dimethyl indole

Reagents: Phenyl hydrazine Hydrochloride, 98.9 mg (0.684 mmol), Pentan-2-one, 76 µL (0.719 mmol), NaH, 110 mg (2.74 mmol), Iodomethane, 106 uL (1.71 mmol), yielding 144.2 mg of orange oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 (d, *J* = 7.5 Hz, 1H, 7-H), 7.28 (m, 5H, Bn-H), 7.15 (t. *J* = 7.5 Hz, 5-H), 7.01 (d, *J* = 7.5 Hz, 1H, 6-H), 5.31 (s, 2H, BnEt-HH-N), 2.32, (d, 12.5 Hz, 6H, 2,3-Me)

3-(4-bromophenyl)-1,2-dimethyl-indole

Reagents: Phenyl hydrazine Hydrochloride, 98.9 mg (0.684 mmol), 4-bromophenyl acetone, 108 µL (0.719 mmol), NaH, 110 mg (2.74 mmol), Iodomethane, 106 uL (1.71 mmol) Yielding 145 mg of yellow powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.53 (d, *J* – 7.5 Hz, 1H, 7-H), 7.50 (d, *J* = 7.0 Hz, 2H, Ph-3,5-H), 7.28 (d, *J* = 7.0 Hz, 2H, Ph-2,6-H), 7.25 (d, *J* – 7.5 Hz, 1H, 4-H), 7.14 (t, *J* = 7.5 Hz, 1H, 6-H) 7.04 (t, *J* = 7.5 Hz, 1H, 5-H), 3.67 (s, 3H, 1-Me), 2.40 (s, 3H, 2-Me),

3-isopropyl-1,2-dimethyl- indole

Reagents: Phenylhydrazine Hydrochloride, 98.9 mg (0.684 mmol), 4-Methyl-pentan-2-one, 90 µL (0.719 mmol), NaH, 110 mg (2.74 mmol), Iodomethane, 106 uL (1.71 mmol). Yielding 121 mg of a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (d, *J* – 7.5 Hz, 1H, 7-H), 7.18 (d, *J* = 7.5 Hz, 1H, 4-H), 7.05 (t, *J* = 7.5 Hz, 1H, 6-H), 6.96 (t, *J* = 7.5 Hz, 1H, 5-H), 3.57 (s, 3H, 1-Me), 2.30 (s, 3H, 2-Me), 1.35 (d, *J* = 2.8 Hz, 6H, CH_3-C-CH_3)

4-Methyl-1,2,3,4-tetrahydrocyclopenta[b]indole

Reagents: Phenyl hydrazine Hydrochloride, 98.9 mg (0.684 mmol), Cyclopentanone, 64 µL (0.719 mmol), NaH, 110 mg (2.74 mmol), Iodomethane, 106 uL (1.71 mmol). Yielding 87 mg of brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (d, *J* – 7.5 Hz, 1H, 7-H), 7.15 (d, *J* = 7.5 Hz, 1H, 4-H), 7.05 (t, *J* = 7.5 Hz, 1H, 6-H), 6.98(t, *J* = 7.5 Hz, 1H, 5-H), 3.57 (s, 3H, 1-Me), 2.76 (t, *J* = 8.2 Hz, 4H, tetra 1a, 3a-CH_2), 2.46 (p, *J* = 8.2 Hz, 2H, tetra 2a-CH_2)

2-Ethyl-1,3-dimethyl indole

Reagents: Phenyl hydrazine Hydrochloride, 98.9 mg (0.684 mmol), 3-pentanone, 76 µL (0.719 mmol), NaH, 110 mg (2.74 mmol), Iodomethane, 106 µL (1.71 mmol). Yielding 109 mg yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (d, *J* – 7.5 Hz, 1H, 7-H), 7.16 (d, *J* = 7.5 Hz, 1H, 4-H), 7.07 (t, *J* = 7.5 Hz, 1H, 6-H), 7.08 (t, *J* = 7.5 Hz, 1H, 5-H), 3.61 (s, 3H,

1-Me), 2.69 (dd, *J* = 7.5, 3.5 Hz, 2H, -CH_2-), 2.19 (s, 3H, 2-Me), 1.19 (t, *J* = 12.2 Hz, 3H, 3Et-Me)

5-Methoxy-1,2,3-trimethyl Indole

Reagents: 4-methoxyphenylhydrazine hydrochloride, 120 mg (0.684 mmol), methyl ethyl ketone, 65 µL (0.719 mmol), NaH, 110 mg (2.74 mmol), Iodomethane, 106 µL (1.71 mmol). Yielding 94 mg of blue solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.02 (d, *J* = 7.5 Hz, 1H, 7-H), 6.83 (s, 1H, 4-H), 6.17 (d, *J* = 7.5 Hz, 1H, 6-H), 3.77 (s, 3H, O-Me), 3.51 (s, 3H, 1-Me), 2.29 (s, 3H, 3-Me), 2.14 (s, 3H, 2-Me)

7-Fluoro-1,2,3-trimethyl indole

Reagents: 6-fluro-phenylhydrazine Hydrochloride, 111.2 mg (0.684 mmol), methyl ethyl ketone, 65 µL (0.719 mmol), NaH, 110 mg (2.74 mmol), Iodomethane, 106 µL (1.71 mmol). Yielding 97 mg yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.13 (d, *J* – 7.5 Hz, 1H, 6-H), 6.84 (dt, *J* = 7.5 Hz, 1H, 5-H), 6.71 (dd, *J* = 12.2, 7.5 Hz, 1H, 4-H), 3.78 (s, 3H, 1-Me), 2.24 (s, 3H, 3-Me), 2.15 (s, 3H, 2-Me)

9-Methyl-2,3,4,9-tetrahydrocarbazole

Reagents: Phenyl hydrazine Hydrochloride, 98.9 mg (0.684 mmol), cyclohexanone, 74 µL (0.719 mmol), NaH, 110 mg (2.74 mmol), Iodomethane, 106 µL (1.71 mmol). Yielding 107 mg brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (d, *J* – 7.5 Hz, 1H, 7-H), 7.15 (d, *J* = 7.5 Hz, 1H, 4-H), 7.13 (s, 0.5 H, Imp) 7.06 (t, *J* = 7.5 Hz, 1H, 6-H), 6.98 (t, *J* = 7.5 Hz, 1H, 5-H), 3.51 (s, 3H, 1-Me), 2.63 (dd, *J* = 8.8, 7.6 Hz, 4H, Cyc- 2,3-H_2), 1.86 (m, 2H, Cyc- 9-H_2), 1.78 (m, 2H, Cyc-4-H_2)

5-Methyl-5,6,7,8,9,10-hexahydrocyclohepta[b]indole

Reagents: Phenyl Hydrazine Hydrochloride, 98.9 mg (0.684 mmol), cycloheptanone, 85 µL (0.719 mmol), NaH, 110 mg (2.74 mmol), Iodomethane, 106 µL (1.71 mmol). Yielding 109 mg brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41 (d, *J* – 7.5 Hz, 1H, 7-H), 7.15 (d, *J* = 7.5 Hz, 1H, 4-H), 7.05 (t, *J* = 7.5 Hz, 1H, 6-H), 6.98 (t, *J* = 7.5 Hz, 1H, 5-H), 3.59 (s, 3H, 1-Me), 2.72 (ddd, *J* = 8.2, 7.6, 1.2 Hz, 4H), 1.80 (m, 2H), 1.70 (m, 4H)

5-bromo-1,2,3-trimethyl indole

Reagents: 5-bromo-phenyl hydrazine hydrochloride, 152 mg (0.684 mmol), methylethylketone, 74 µL (0.719 mmol), NaH, 110 mg (2.74 mmol), Iodomethane, 106 µL (1.71 mmol) Yielding 110 mg of orange solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51 (d, *J* – 7.5 Hz, 1H, 7-H), 7.16 (d, *J* = 7.5 Hz, 1H, 4-H), 7.00 (d, *J* = 8.2 Hz, 1H, 6-H), 3.53 (s, 3H, 1-Me), 2.62 (s, 3H, 3-Me), 2.14 (s, 3H, 2-Me).

1,2,3,5-Tetramethyl indole

Reagents: *p*-Tolylhydrazine hydrochloride, 109 mg (0.684 mmol), methylethylketone, 65 µL (0.719 mmol), NaH, 110 mg (2.74 mmol), Iodomethane, 106 µL (1.71 mmol). Yielding 116 mg as a red oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.18 (br, 1H, 7-H), 7.02 (d (br), *J* = 8.2 Hz, 1H, 4-H), 6.87 (d (br), *J* = 8.2 Hz, 1H, 6-H), 3.51 (s, 3H, 1-Me), 2.37 (s, 3H, 5-Me), 2.22 (s, 3H, 3-Me), 2.14 (s, 3H, 2-Me).

Appendices

^{1}H and ^{13}C spectra corresponding to the tabulated data are available as supplementary file.

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