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DOMINO REACTIONS OF *N*-(PROPARGYL)INDOLE-2-CARBONITRILES WITH *O*-, *C*- AND *N*-NUCLEOPHILES

1.4.3. Organic chemistry

THESIS

for a PhD degree in chemistry

Research supervisor:
Doctor of Chemical Science
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ФЕДЕРАЛЬНОЕ ГОСУДАРСТВЕННОЕ АВТОНОМНОЕ ОБРАЗОВАТЕЛЬНОЕ УЧРЕЖДЕНИЕ ВЫСШЕГО ОБРАЗОВАНИЯ «УНИВЕРСИТЕТ ДРУЖБЫ НАРОДОВ ИМЕНИ ПАТРИСА ЛУМУМБЫ»

На правах рукописи

Залте Раджеш Рохидас

ДОМИНО-РЕАКЦИИ *N*-(ПРОПАРГИЛ)ИНДОЛ-2-КАРБОНИТРИЛОВ с *O*-, *C*- И *N*-НУКЛЕОФИЛАМИ

1.4.3. Органическая химия

Диссертация

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Table of contests

1. Introduction

1.1. Domino reactions – the concept for the efficient synthesis of annulated indole scaffolds

Domino reactions are described as reaction processes of two or more bond-generation under uniform reaction conditions, where subsequent transformation proceeds at the functionalities obtained in the former transformation. Domino transformation gave access to the most efficient synthesis of complex molecules from simple substrates in economically and ecologically favourable pathways.

The quality of the domino reaction is correlated to the number of chemical bonds formed considering the complexity and diversity achieved in the process, e.g. the bond-forming efficiency index reported by Tietze [1]. The multicomponent reaction concept wherein three or more starting materials are combined into one compound in a single chemical operation is usually considered an innate domino process allowing access to biologically active compounds. The scaffold diversity of multicomponent reactions has been recognised by the scientific community in industry and academia as the preferred method to both design and discover biologically active compounds. The classical Ugi-type multicomponent reactions [2], Ugi four-component tetrazole, Ugi lactam, Ugi four-component hydantoin, Ugi five-centre four-component, and Ugi three-component reactions are examples that demonstrate the advances of multicomponent reactions which are a key set of domino transformations in organic synthesis. The diverse library of biologically active organic compounds consists mainly of heterocycles and indole-containing scaffolds widely used in the pharmaceutical, agrochemical, and dye industries, as well as in the variety of natural products such as indole derivatives of biological significance, i.e., Vinblastine (anti-cancer) [3], Reserpine (hypertension) [4] etc in fig 1.

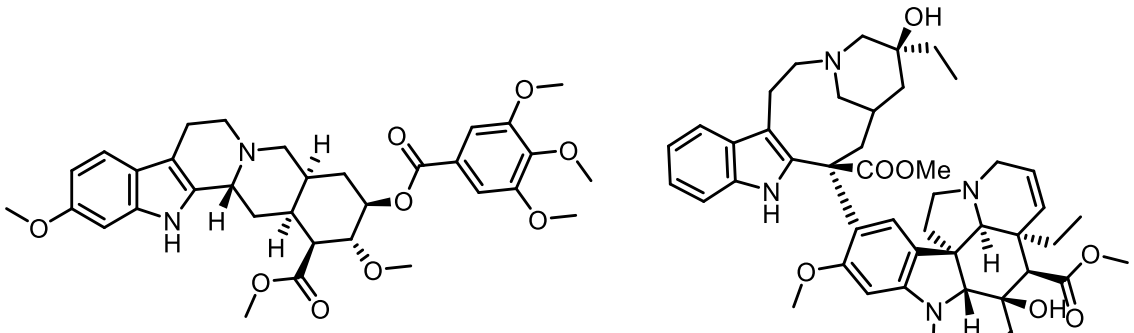


Figure 1. Natural origin of annulated indole derivatives

The inherent biological activity of natural products is driven by specific and selective interactions with macromolecules in living organisms, making them potential bioactive and drug candidates. The wide-scale diversity of indole-containing heterocycles, such as indole diterpenoids

natural products, comprise a larger class of natural products with diverse structure topology, as well as a broad range of biological activities [6].

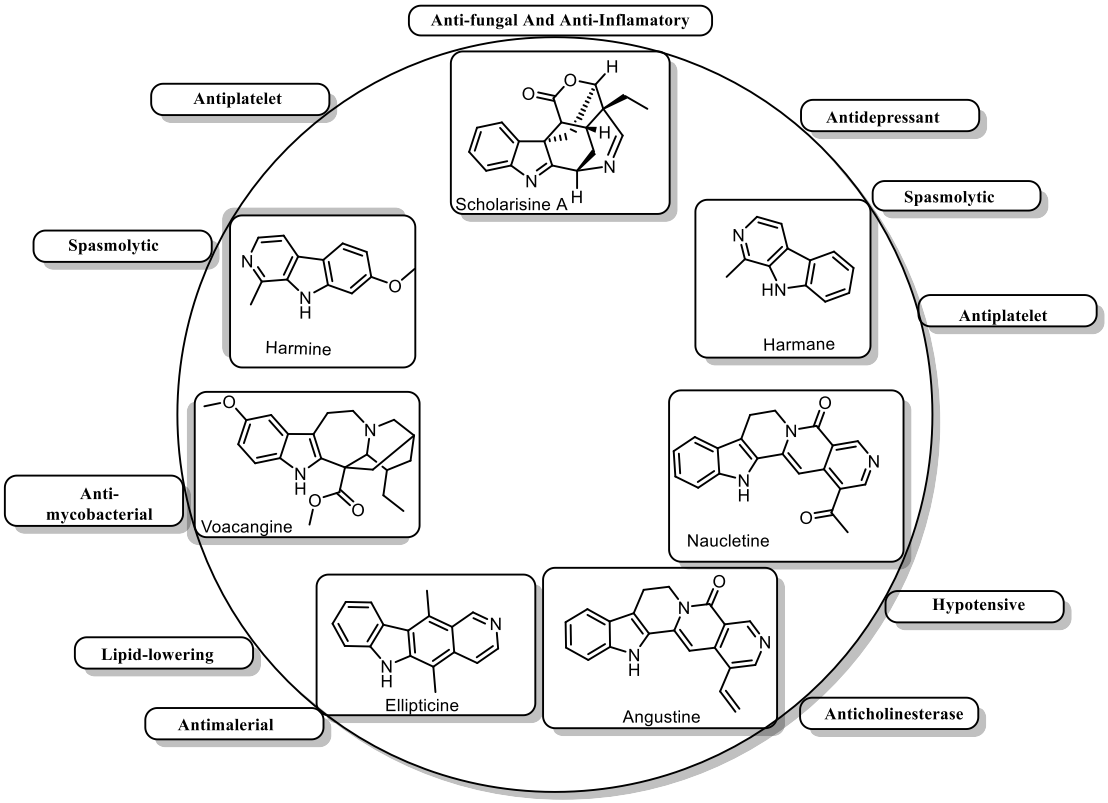


Figure 2. Pharmacological activity of the major class of annulated indoles

Therefore, the investigation of promising building blocks of indole derivatives has attracted the attention of chemists to pyrazinoindoles and pyridoindoles. The increased interest in these fragments is due to the three-fused heterocyclic ring structure subsuming an indole. The fused polycyclic indole core structure is necessary to synthesise potential drugs, which is evident by indole (an example of a fused five and six-membered ring structure) being an exemplary and established privileged scaffold in medicinal chemistry. Pyrazine-fused indoles have been documented regarding their biological activities and therapeutic uses, particularly as antifungal, antibacterial, serotonergic receptor inhibitors, central nervous system depressants, anticonvulsants, antihistaminic, protein kinase C inhibitors, and anti-depressants [7]. In turn, pyrido[1,2-*a*]indoles are valuable heterocyclic motifs present in numerous natural products, e.g., canthin-6-ones [8], homofascaplysins [9], and dibenzopyrrocoline alkaloids [10]. Synthetic compounds possess optical properties, and thus are used in organic electronics, bioimaging [11], and sensing technologies [12]. Although various synthesis strategies are available, the medical relevance of the pyrazinoindoles and pyridoindoles demands the development of versatile and simple novel methodologies.

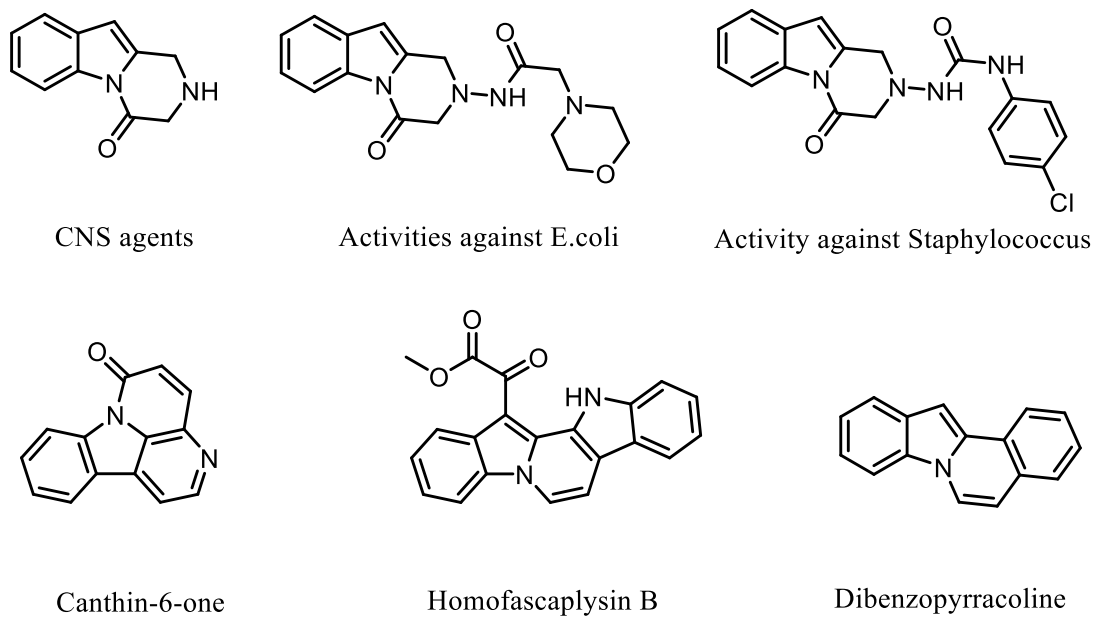


Figure 3. Importance of pyrazinoindoles and pyridoindoles

A variety of synthetic ventures have been developed to synthesise pyrazinoindoles and pyridoindoles as they constitute the backbone of many therapeutic drugs. However, microorganisms causing harmful diseases continually mutate and evolve, often developing drug resistance, so modifications to the structure and synthetic methods are necessary. A group of recently developed derivatives of pyrazinoindoles and pyridoindoles has huge scope in organic synthesis. In the field of synthetic heterocyclic chemistry and drug discovery, the development of more efficient and sustainable methods that are eco-friendly and have high yield potential. This work involves the study of effective domino transformations of *N*-(propargyl)indole-2-carbonitriles towards annulated indole derivatives.

2. Review

"Recent advances in the development of domino reactions towards annulated indoles"

2.1. Introduction

The synthesis of annulated indole derivatives has received remarkable attention due to its importance in the modern chemistry of heterocyclic compounds. Annulated indole structures fused with 5-membered, 6-membered and medium-sized rings were efficiently synthesised through various domino reactions characterised according to the nomenclature of likely transformations e.g. anionic, cationic, transition-metal-catalysed and free radical.

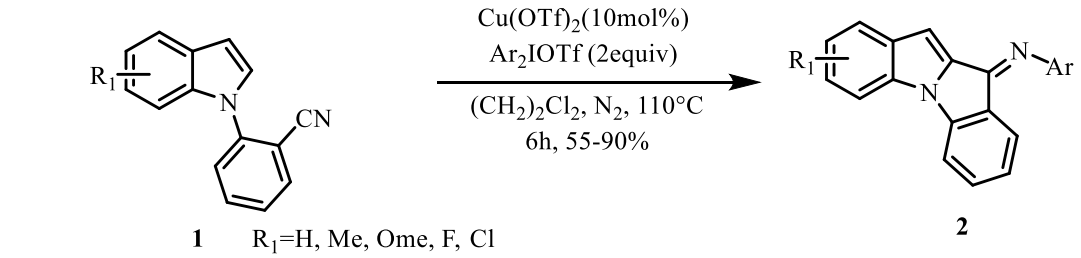
2.2. Classification of domino reactions for annulation

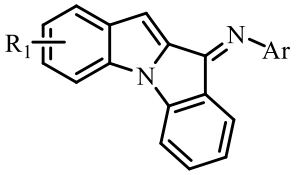
Different classes of domino reactions are involved in indole annulation. Generally, domino reactions play an important role in the synthetic methodology to obtain desired products with minimum effort and high productivity. The classification of domino reaction is based on the mechanism and is classified as cationic, anionic, photochemical, transition-metal catalysed transformations and pericyclic approaches.

2.3 Cationic domino reactions

2.3.1. 5-membered annulated indole

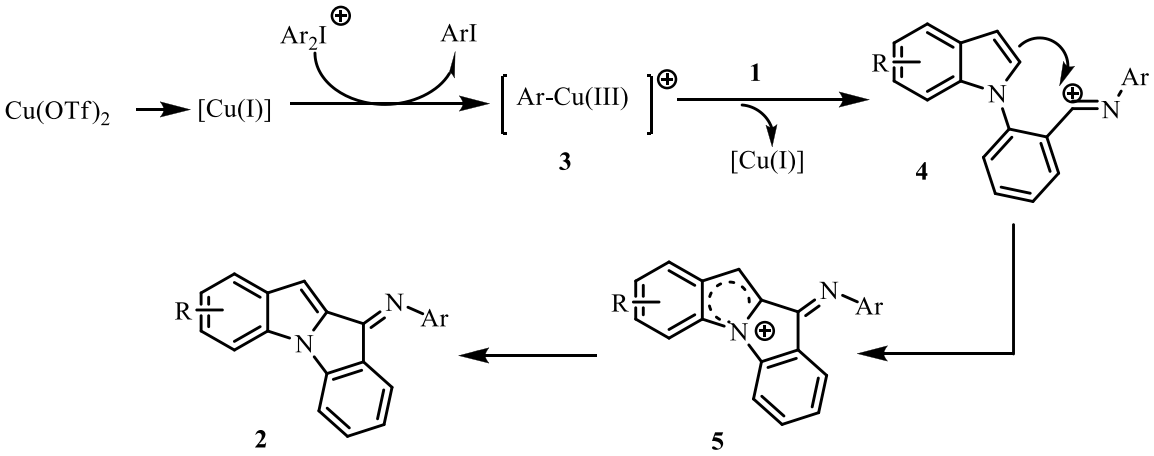
Synthesis of annulated polycyclic indole **2** is achieved by treating *N*-(2-cyanophenyl)indole **1** with diaryliodonium salts (Ar_2IOTf) in DCE under an inert atmosphere in the presence of $Cu(OTf)_2$. The reaction starts with the formation of Ar-Cu(III) **3** species capable of arylating the nitrile group to form intermediate **4**, then sequential intramolecular cyclization in the latter and aromatization form target polycycle **2**. The reaction is tolerant to the substituents in indole moiety with various diaryliodonium salts (Scheme 1). The electronic effect and regioselectivity were investigated by using unsymmetrical diaryliodonium salts, the reaction of **1** treated with unsymmetrical diaryliodonium salts **6** and **7** under optimised reaction conditions. The results (Scheme 2) showed in that unsymmetrical diaryliodonium salts **6** under standard conditions only yielded an electron-rich product **8** (yield 64%) but the treatment of unsymmetrical diaryliodonium salts **7** yielded an electron-deficient product **9** (yield 59%) with no formation of electron-rich product **10**. The steric hindrance strongly influences the product formed [13].



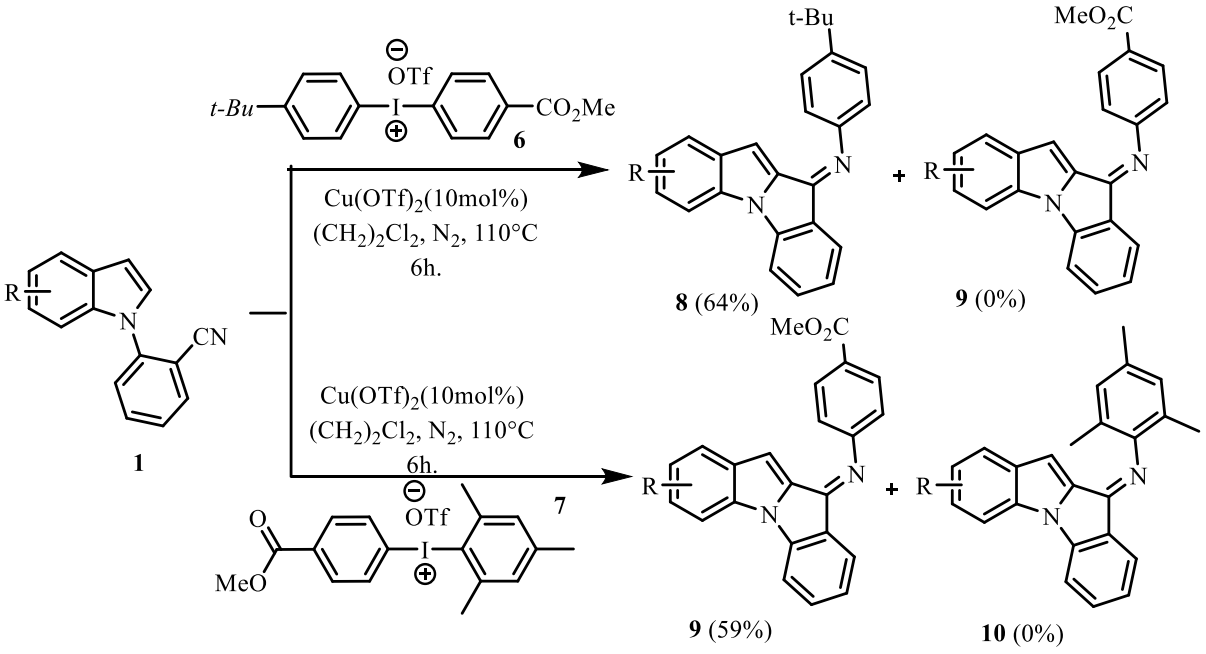


2(a-d)

R_1= OMe (2a) = 89%
Me (2b) = 82%
F (2c) = 67%
Cl (2d) = 75%



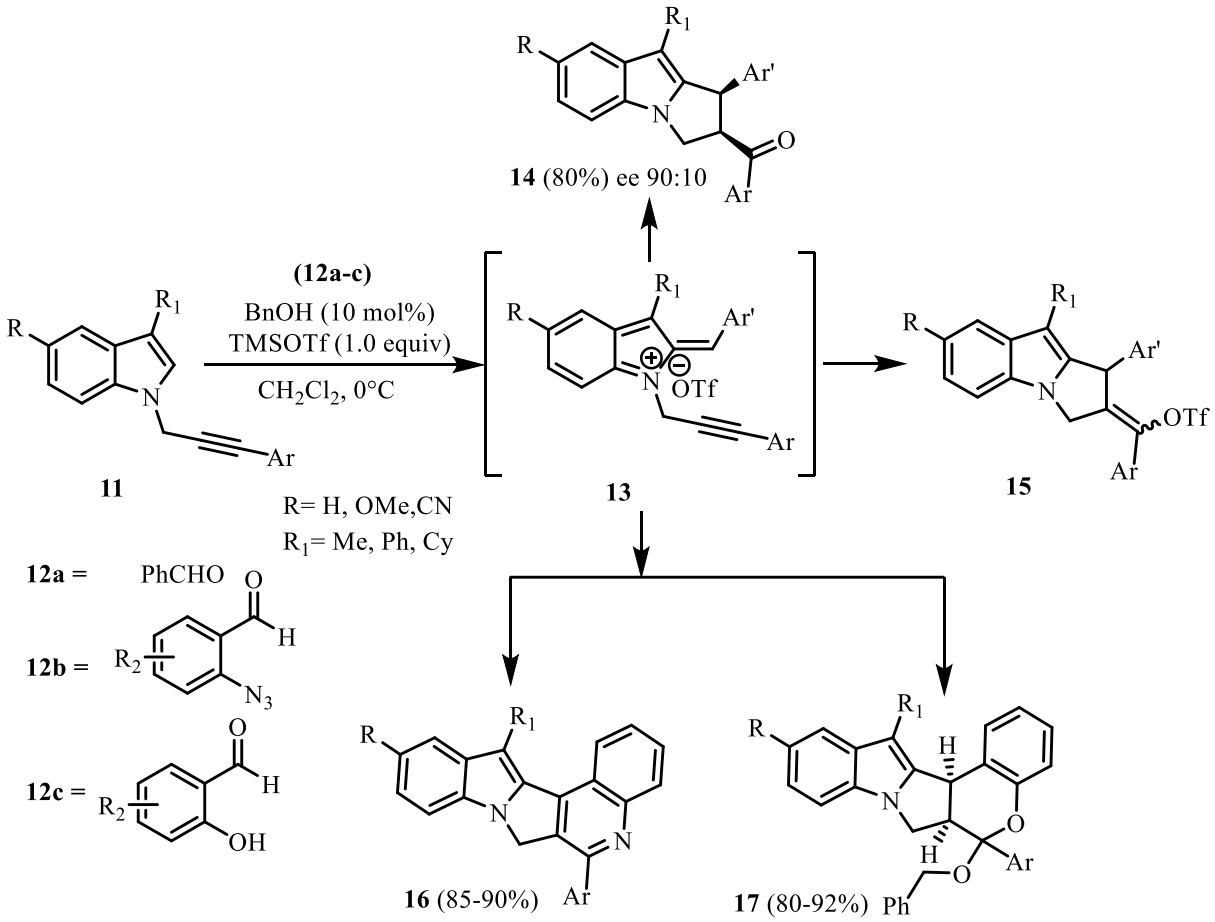
Scheme 1



Scheme 2

Lewis acid catalysed domino synthesis of pyrrolo[1,2-a]indole derivatives (Scheme 3) via the Friedel-Crafts/alkyne indol-2-yl cation promoted cyclisation. The study represents *N*-Propargyl indoles **11** and various aryl aldehydes **12a** that generate indol-2-yl cations **13** in the presence of BnOH and TMSOTf at 0°C. The intramolecular reaction with a tethered alkyne, a π-nucleophile, followed by trapping of vinyl cation by a tethered nucleophile or counter anion of the Lewis acid yields the annulated indole derivative **14** in good yield and diastereoselectivity (*ee* 90:10). Product **14** is obtained by hydrolysis of the unstable triflate **15** moiety converted to ketone functionality. Various types of aryl aldehyde which carry the nucleophile group were evaluated so that the nucleophile would trap the generated vinyl cation **13.** Indole derivative **11** reacts with salicylaldehyde **12c** during optimised reaction conditions via Friedel-Craft/alkyne indol-2-yl cation/vinyl cation **13** trapping the phenolic group and reacting with BnOH to generate oxonium ion under acidic conditions to produce an excellent yield of product **17.**

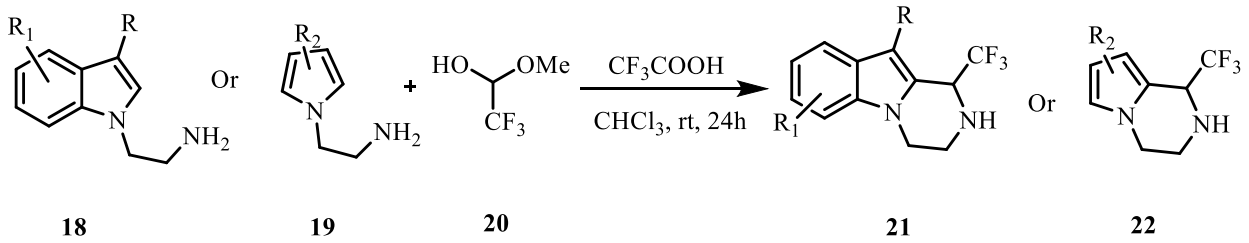
2-Azidobenzaldehyde **12b** was further transformed to obtain an excellent yield of pyrrolizino-quinoline **16** under optimised reaction conditions. Furthermore, the study was expanded for mild electronic deficient and electronic-rich alkyne reactions with electron-rich and electronic deficient aldehyde resulting in the corresponding pyrrolizino quinolines [14].



Scheme 3

2.3.2. 6-membered annulated indoles

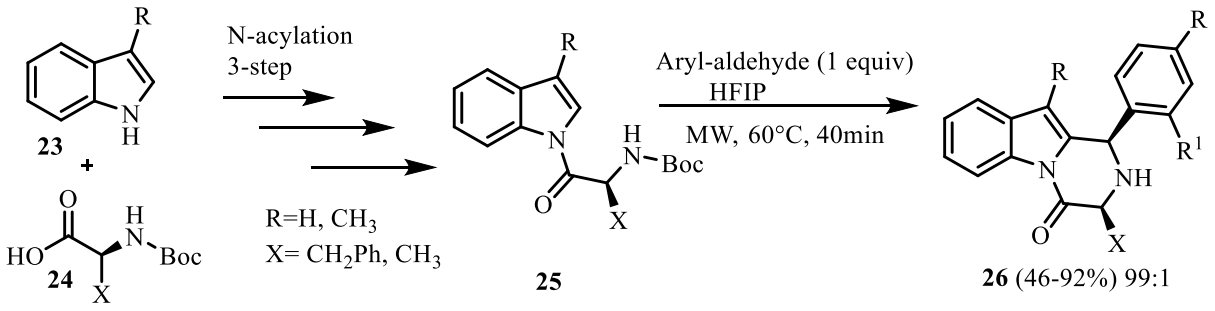
Annulation of trifluoromethyl functionalised pyrazinoindole derivatives was achieved by acid-catalysed domino reaction with moderate to good yields. The TFA-promoted reaction demonstrated tricyclic ring formation in the *N*-substituted indole/pyrrole **18, 19** substrates with trifluoroacetaldehyde methyl hemiacetal **20** in the presence of trifluoracetic acid at room temperature. The introduction of the -CF_3 group into the vicinal position indicates a lower basicity potential of the amine. This method is useful for the synthesis of indole and pyrrole fused piperazines respectively, with the benefits of trifluoracetic acid as a catalyst for the domino transformation of 88% **21**. The reaction condition provides a high yield for various substituted indole over the pyrrole moieties [15].



18 **19** **20** **21** **22**

Scheme 4

Stereoselective one-pot access to pyrazinoindole synthesis is challenging under appropriate reaction conditions and similarly, acidic conditions are unfavourable for good yield and isolation techniques. Therefore, the synthesis of pyrazinoindole via scheme 5 was studied under various acidic conditions as the initial study examined *N*-substituted indole **25**, which was synthesised from indole derivative **23** and Boc-protected amino acid **24** using several coupling reagents (see Table 1). The intermediate **25** was charged with aryl aldehyde under the optimised reaction condition in the presence of HFIP to obtain intramolecular cyclisation of stereospecific pyrazinoindole **26**. The reaction was tolerant to several substituents in the indole and N-Boc protected moieties which afforded a good yield with time efficiency. Aryl aldehyde containing both electron-donating groups (Me, OMe) an electron-withdrawing group (nitro, fluorine, chlorine, bromine) also achieved excellent yields [16].

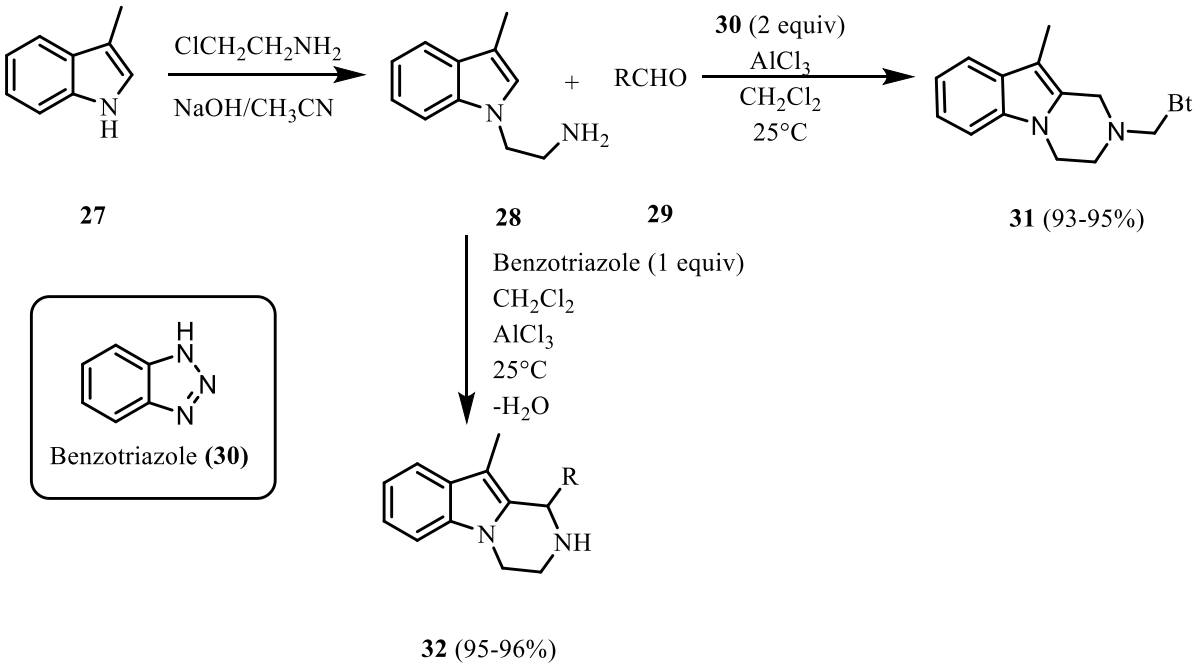


Scheme 5

Table 1. Reaction optimisation with various coupling reagents

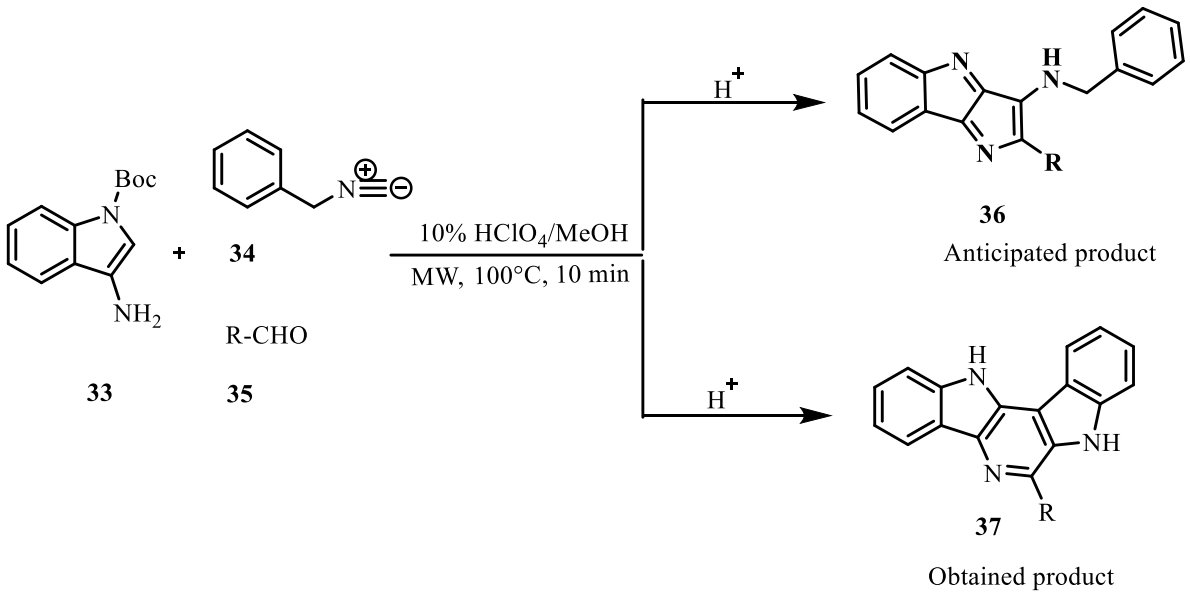
Entry	**Reaction conditions**	**product**
1)	20% TFA in DCM; PTSA (2.0eq); DCE; rt 2−12 h	0%
2)	20% TFA in DCM; Cat. $AlCl_3$, Benzotriazole; DCE; rt 2−12 h	18%
3)	HIFP, 60−65°C, MW, 40 min	92%

Tetrahydropyrazino[1,2-*a*]indole derivatives were obtained under the catalytic Lewis acid conditions, with intermediate 2-(3-Methyl-1*H*-indol-1-yl) ethylamine **28** achieved by treatment of 2-chloroethylamine with skatole **27** in acetonitrile in the presence of PTC reagents NaOH and Bu_4NHSO_4[17]. 2-(1*H*-1,2,3,4-benzotriazolylmethyl)-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole **31 (**yield 93-95%) was synthesised by cyclocondensation of 2-(3-methyl-1*H*-indol-1-yl)ethylamine **28** in presence of $AlCl_3$, benzotriazole **30** (2 equiv) and aldehyde **29.** However, under similar reaction conditions, if the amount of benzotriazole was reduced up to 1 equiv., cyclocondensation product **32 (**yield 95−96%) without linkage of benzotriazole was obtained. An in vitro antibacterial activity study using the disk diffusion method found that compound **32** has strong activity against *P. aeruginosa* compared to compound **31** [18].



Scheme 6

The novel three-component domino reaction produces a 6-membered annulated indole assisted by microwave irradiation under acidic conditions. The scheme consists of a novel process of three components involving Boc-protected 3-amino indoles **33**, benzyl isocyanide **34**, and aldehyde **35** to synthesise pyridodiindole **37** [19]. Pyrroloindole **36** is formed by Schiff base generation between 3-amino indole and aldehyde in intermediate steps, the reaction proceeds with isonitrile moiety under thermal conditions in the presence of catalytic amount of acid. However, since Boc-protected 3-amino indole **33** demonstrates unique properties in the post-Ugi domino reaction, 5-membered cyclised product **36** is not observed. Surprisingly, a 6-membered pyridodiindole **37** was obtained**.** Optimization of the three-component reaction was performed in methanol and various acids and stirred overnight at room temperature but did not produce a good yield of the product. Alternatively, microwave irradiation at 100°C improved the yield using $HClO_4$ treatment. Specifically, aldehyde moiety was unrestricted to the aromatic compounds when alkyl aldehyde was used in the reaction. The MW-promoted reaction was well tolerated with various substrates to obtain moderate to good yields. The optimised reaction condition was evaluated for the synthesis of substituted pyridodiindoles [20].

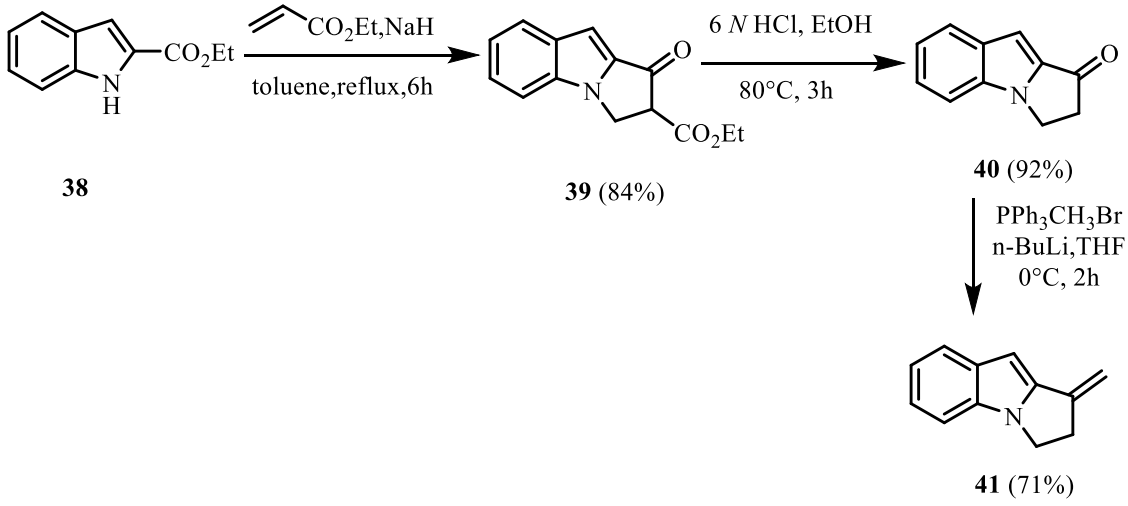


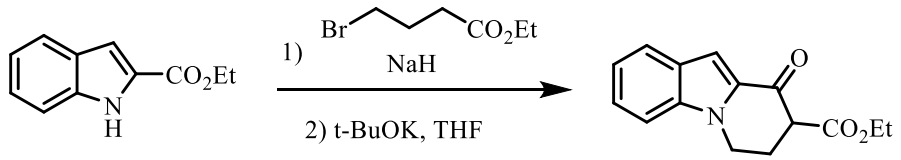
Scheme 7

2.4. Anionic domino reactions

2.4.1. 5-membered annulated indole

There are limited reports of the synthesis of 5-membered indole annulation via anionic cascade approaches. Fused 5-membered 2-vinylindole **41** was synthesised as per scheme 8. The synthesis involves a tandem-Michael coupling reaction of indole-2-carboxylate **38** with ethyl acrylate using sodium hydride base under reflux to produce 84% of cyclic tricyclic ketoester **39**, followed by ester hydrolysis and decarboxylation in 6*N* HCl to yield 92% of tricyclic keto compound **40**. The next step of Wittig olefination yields 2-vinylindole **41.** The optimised reaction conditions reported for intermediate **39** and **40** notably yield only the keto form but when reaction conditions were used to expand the 6- or 7-membered ring, then product **42** was obtained by forming a tautomeric keto-enol mixture in a 1:1 ratio [21].

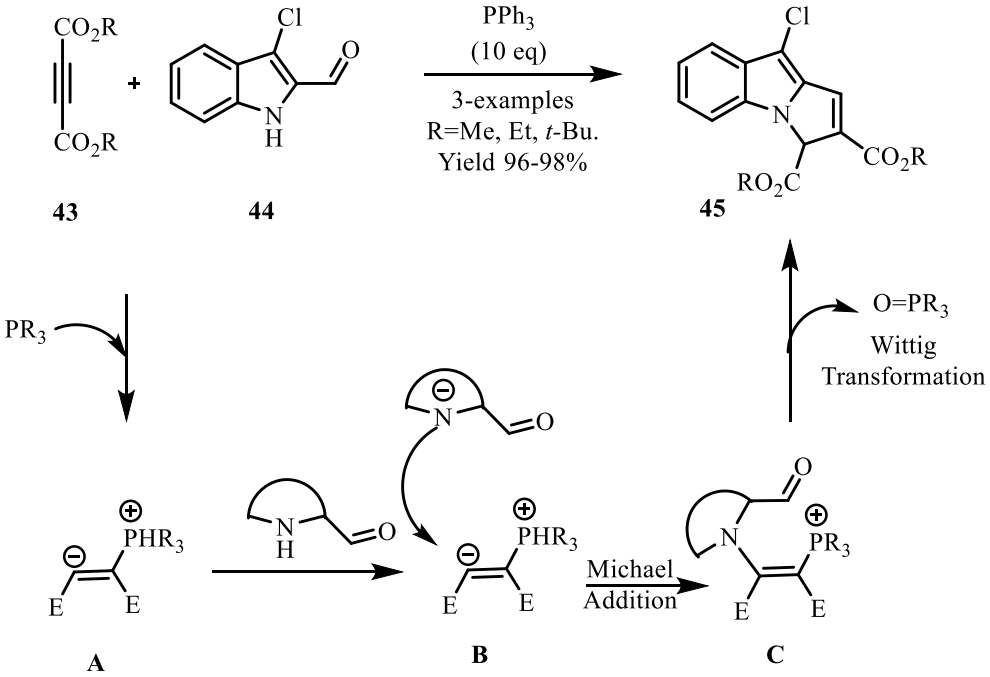




38 **42** (Keto-enol) 1:1

Scheme 8

The intramolecular reaction of 3-chloroindole-2-carbaldehyde **44** with acetyl esters **43** in the presence of triphenylphosphine proceeds in dichloromethane at room temperature to obtain a high yield of dialkyl 3*H*-pyrrolo[1,2-a]indole-2,3-dicarboxylates **45** (Scheme 9). The reaction begins with the addition of a stoichiometric amount of phosphine to dialkyl acetylene dicarboxylate to convert into zwitter ionic compounds **A,** followed by deprotonation of intermediate substrate indole carboxylate and the Michael addition corresponding to the vinyl phosphonium adduct (likely called phosphorus ylide) in step **A** to **C** before cyclisation. The reaction condition was applied to various acetyl esters and all esters afforded a high yield (96−98%) [22].

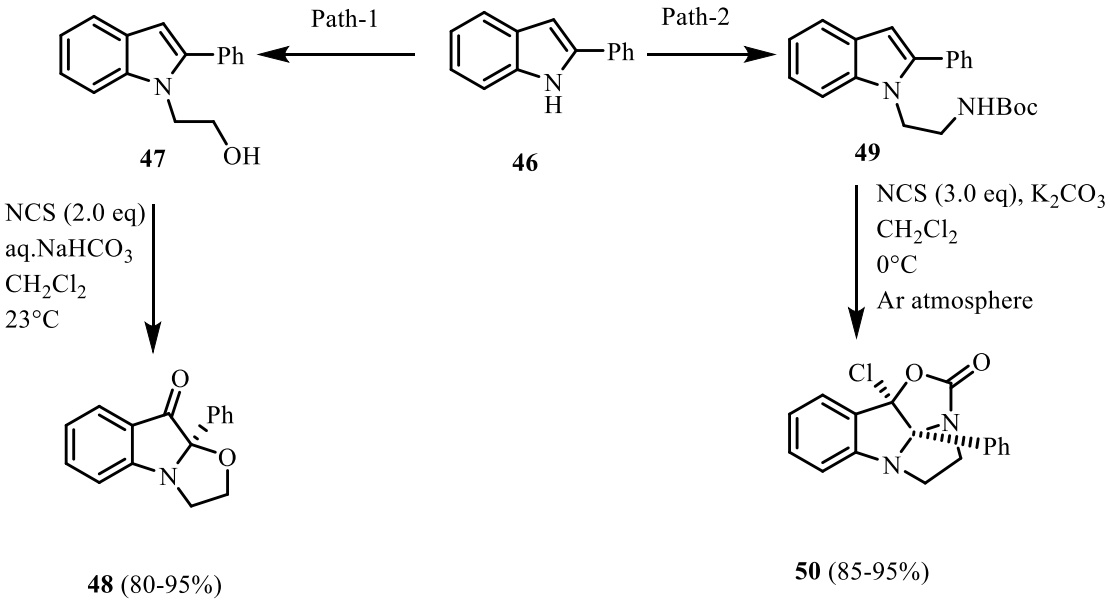


Scheme 9

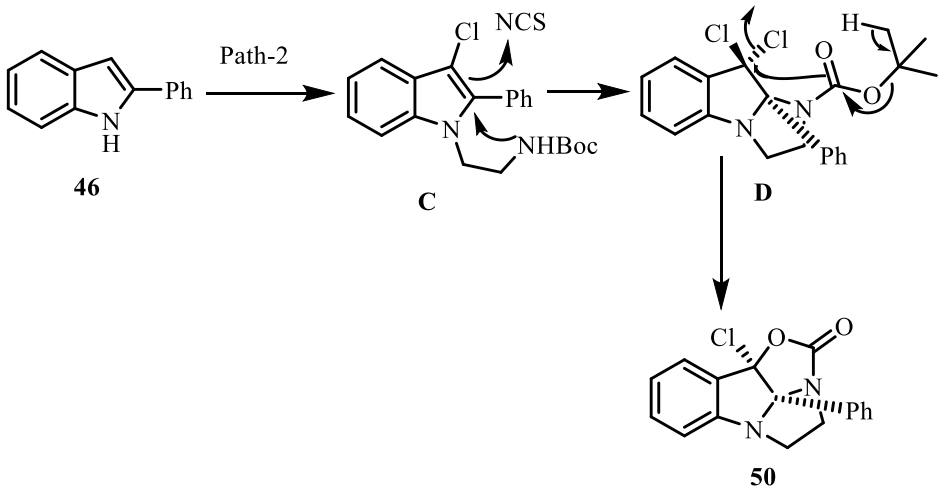
An efficient intramolecular nitrogen and oxygen nucleophile promoted cyclisation using 2-arylindole **46** to obtain excellent yields of 2-aza-3-oxaindoline **48** and 3-indolinone **50.** The synthetic method provides convenient access to the nuclei annulation of imidazo[1,2-*c*]oxazolidinone, oxazolidinone or tetrahydro-1,3-oxazine under mild reaction conditions, and the

reaction has been studied via two pathways for reactivity profile of *O/N* nucleophile. Pathway 1 studied involved halogenation/cyclisation through an oxygen-containing nucleophile to yield 94% of 3-oxazolidine **48** in the presence of aqueous solution $NaHCO_3$ and NCS (2.0 eq)in CH_2Cl_2 at 23°C. The aqueous solution of base and ambient temperature enhanced the reactivity of the *O*-nucleophile to improve productivity. The electronic nature of the substrate does not affect the yield of electron withdrawing and electronic donating groups.

The reactivity of the *N*-nucleophile bearing indole derivative **49** was studied using a similar reaction condition in pathway 2, which produced a low yield of differently orientated product. Furthermore, the development of reaction conditions in the presence of K_2CO_3 and NCS (3.0 eq) in CH_2Cl_2 at 0°C in an Ar atmosphere affords 95% of product **50.** Interestingly, the polycyclic indoline derivative contains the expected imidazolidine ring along with the annulated oxazolidinone functionality. In scheme 11, NCS-promoted intramolecular cyclisation through N-Boc group extrution of isobutene **D** produces cyclised product **50**[23].



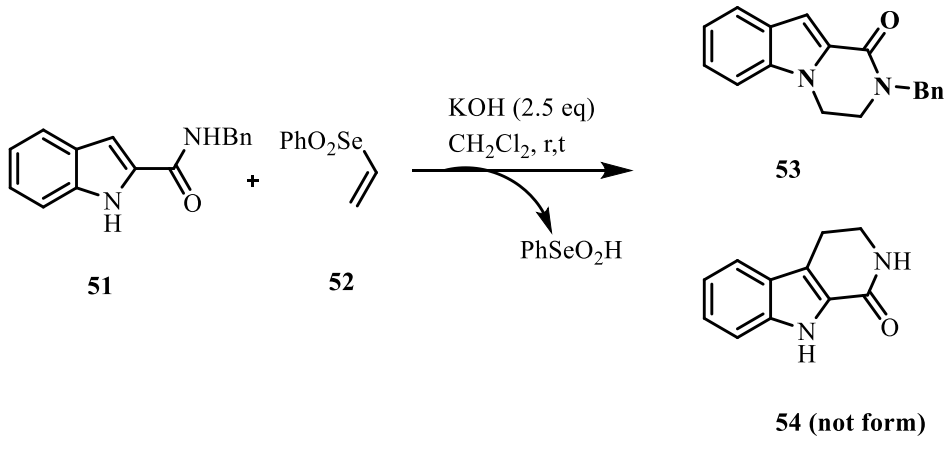
Scheme 10



Scheme 11

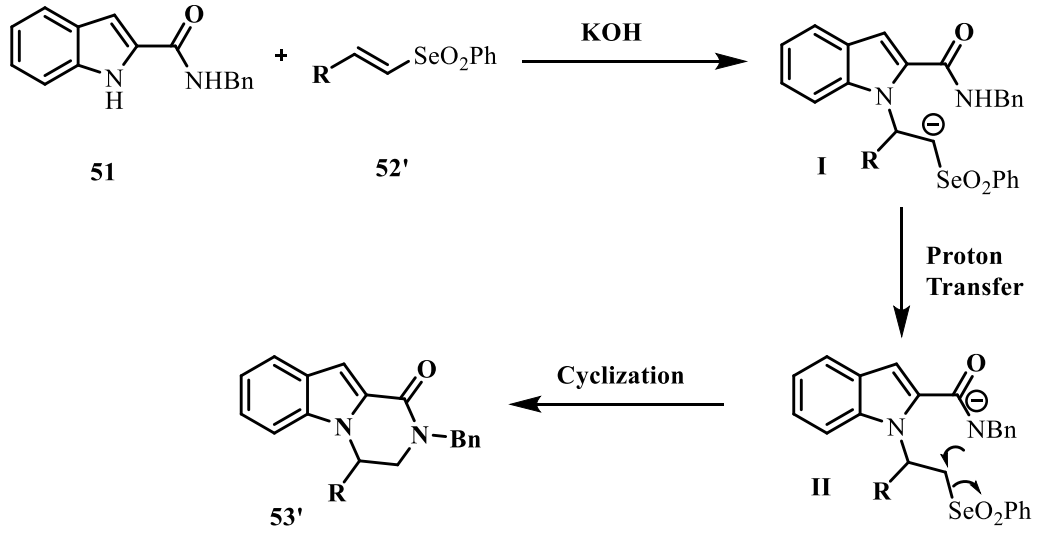
2.4.2. 6-membered annulated indole

An efficient synthetic approach was developed to produce biologically relevant 3,4-dihydropyrazino[1,2-a]indol-1(2*H*)one molecule via an intramolecular domino nucleophilic substitution pathway in the presence of potassium hydroxide in dichloromethane. Various substituted 1*H*-indole-2-carboxamides and vinyl selenones were successfully used in chemo-selective processes. The introduction of the amino acid over the amide function is well tolerated without any racemisation. Indol carboxamides are easily synthesised through coupling reactions starting with the corresponding carboxylic acids with amines or amino esters. The preliminary experiment was performed with *N*-benzyl-1*H*-indole-2-carboxamide **51** and vinyl selenone **52** to obtain cyclisation of 3,4-dihydropyrazino[1,2-a]indol-1(2*H*)-one **53** using excess potassium hydroxide in dichloromethane at room temperature. The presence of the base promoted both Michael addition and domino cyclisation sequentially. The best result was obtained by using an excess of KOH and other inorganic bases produced moderate to good yields.



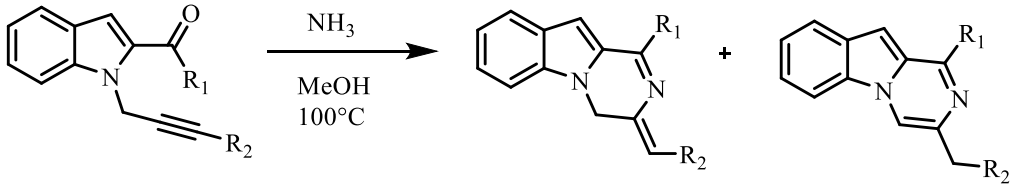
Scheme 12

Product **54** was not formed due to chemoselective attack by favourable acidity of the N-H (higher pKa for the N-H indole) compared to the C3 position of the hydrogen, followed by a proton transfer step and cyclisation [24].



Scheme 13

Synthesis of the pyrazino[1,2-a]indole derivatives was performed by intramolecular cyclisation of 2-carbonyl-1-propargylindole **55** in the presence of ammonia. The treatment of the 1-propargyl derivative in a sealed tube at 100°C with 2 M ammonia in methanol produced pyrazino[1,2-a]indoles **57a, 57b,** and **57c,** while 1-alkynyl derivatives afforded a mixture of isomeric pyrazino[1,2-a]indoles **56d** and **57d**. Moreover, the cyclisation of newly obtained 2-benzoyl indole core derivatives gave very low yields. As anticipated, **56a-c** was not isolated due to the stability of the pyrazine ring but substituted alkynyl derivatives **56d** afforded a low yield.



55a = R_1 = H, R_2= H.
55b = R_1 = CH_3, R_2= H.
55c = R_1 = Ph, R_2= H.
55d = R_1 = H, R_2= Ph.

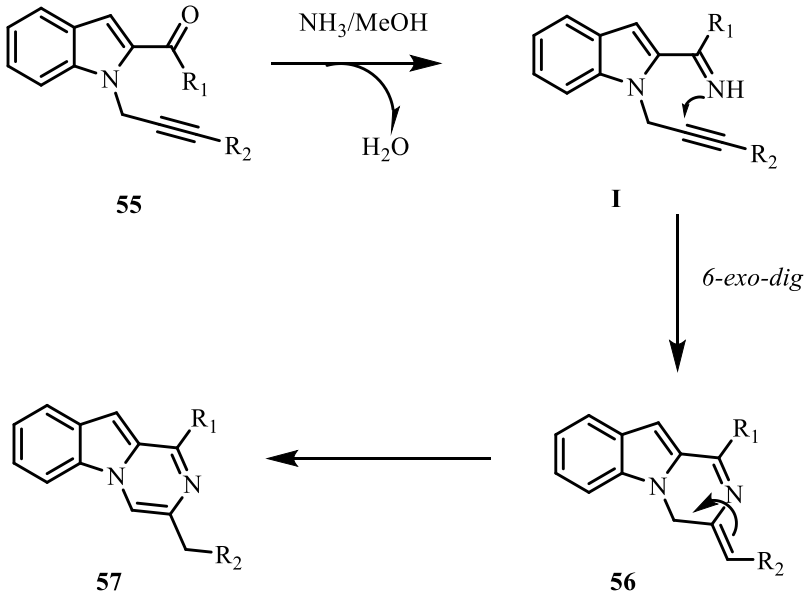
56a = R_1 = H, R_2= H.(0%)
56b = R_1 = CH_3, R_2= H.(0%)
56c = R_1 = Ph, R_2= H.(0%)
56d = R_1 = H, R_2= Ph.(35%)

57a = R_1 = H, R_2= H.(80%)
57b = R_1 = CH_3, R_2= H.(73%)
57c = R_1 = Ph, R_2= H.(14%)
57d = R_1 = H, R_2= Ph.(12%)

Scheme 14

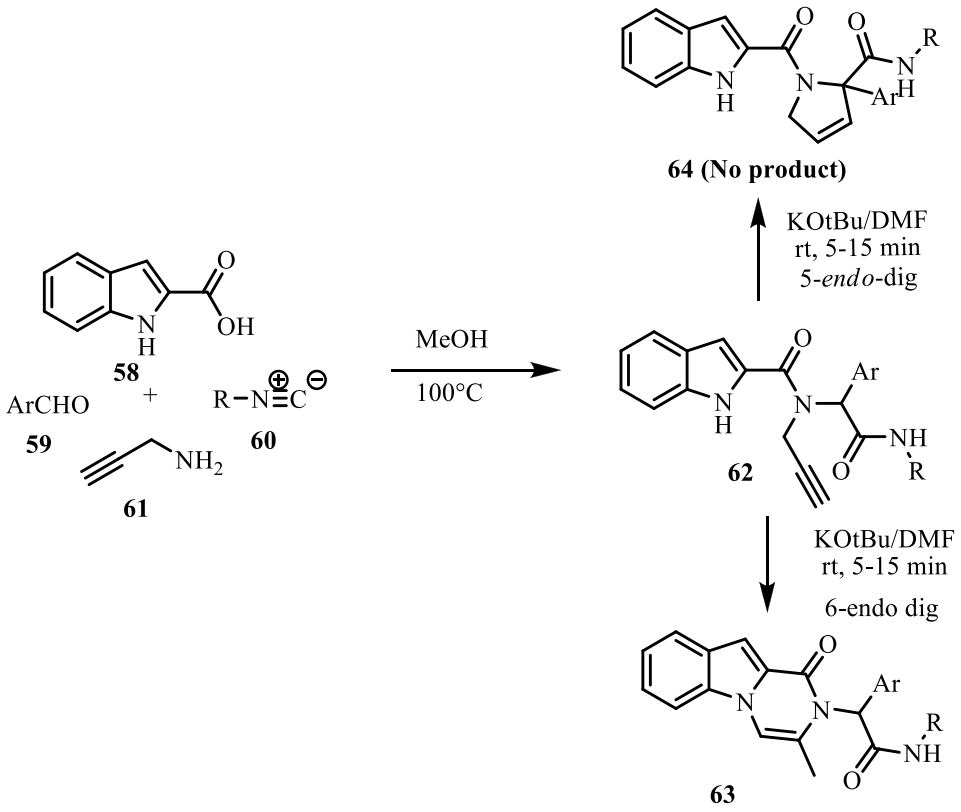
Scheme 15 involves the formation of an intermediate imine which undergoes 6-exo-dig cyclisation to 3,4-dihydropyrazinoindole **56,** followed by aromatisation to produce pyrazinoindole

57. There was experimental evidence of the mutual stability of pyrazinoindoles compared to dihydropyrazino derivatives and the discrepancy in the reaction time required for various substituted substrates. The formation of dihydropyrazino derivatives is a kinetically controlled process while pyrazinoindoles are thermodynamically controlled [25, 26].



Scheme 15

The novel analogue of oxopyrazino[1,2-*a*]indole **63** was synthesised through a two-step method including an Ugi-four component reaction and transition metal-free intramolecular hydroamination using KO*t*-Bu in DMF at room temperature. The Ugi-adduct **62** was synthesised by a simultaneous reaction between indole-2-carboxylic acid **58**, aromatic aldehyde **59**, isocyanide **60** and propargylamine **61** in methanol at room temperature without a transition metal. The Ugi-adduct **62** treated with KO*t*-Bu in DMF at room temperature formed a cyclised product with moderate to good yield as well as various substituted Ugi-adducts. An intramolecular hydroamination reaction occurred via the 6-exo-dig ring followed by a [1,3]-H shift to give product **63** and no product **64** was generated via the 5-endo-dig ring closure [27].

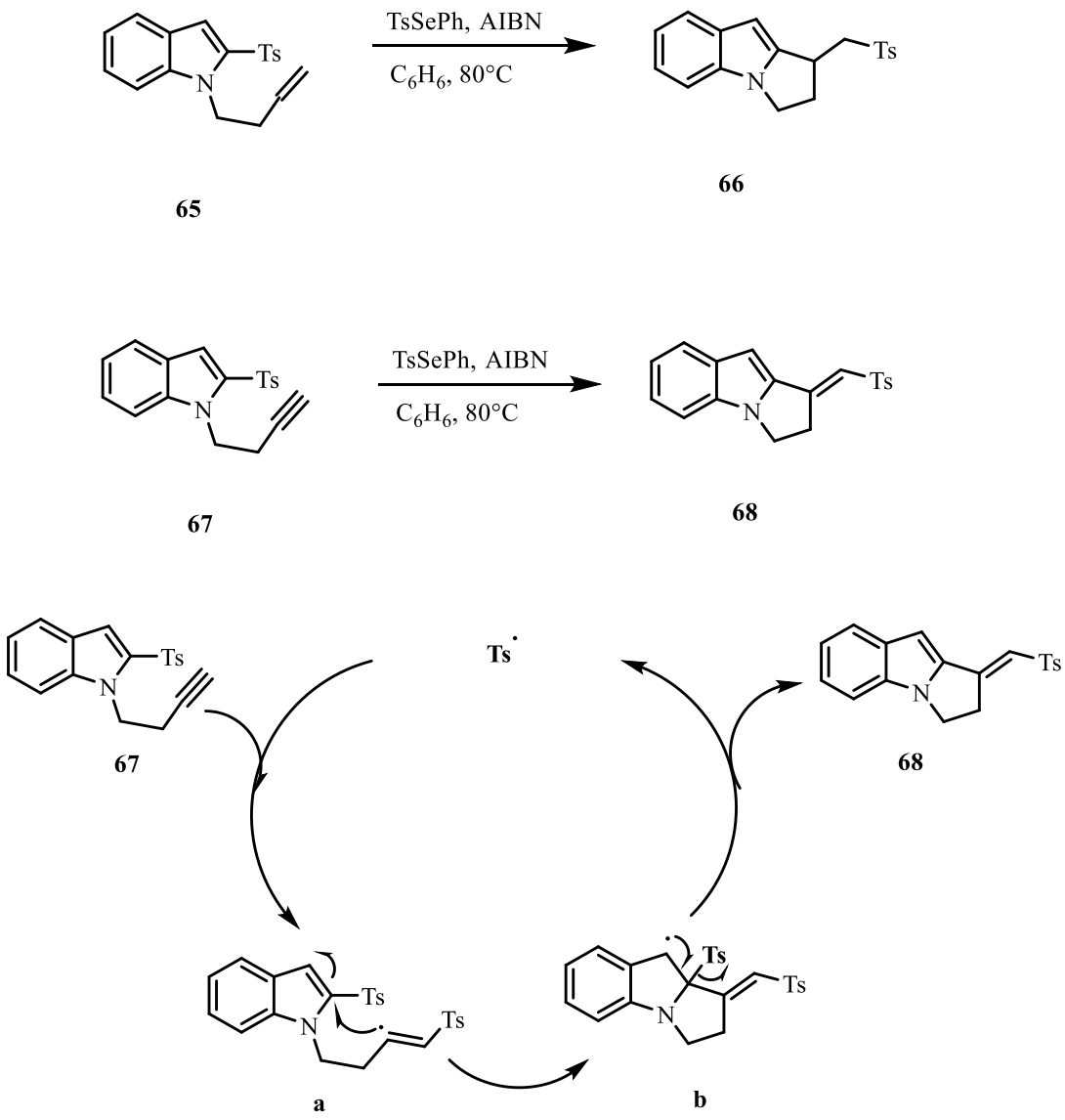


Scheme 16

2.5. Radical domino reactions

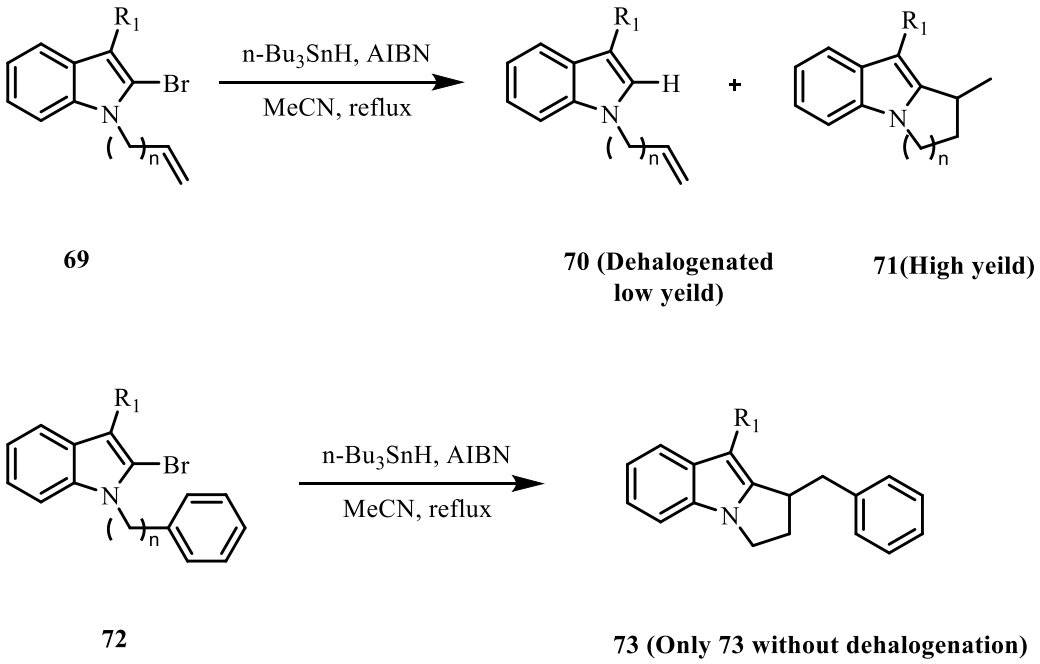
2.5.1. 5-membered ring annulation

Free-radical processes have been exploited in contemporary organic synthesis and investigated to develop new substitution reactions to synthesise annulated heterocyclic sulphone derivatives. The *N*-alkenyl **65** and *N*-alkynyl **67** derivatives of 2-*p*-toluenesulfonylindoles are useful substrates for this novel methodology and the syringe-pump addition of TsSePh and AIBN to a solution of *N*-alkynyl substrate at 80°C in the presence of benzene furnished 72–89% of product **68**. The isolation of **68** is noteworthy in that the presence of the sulphonyl group appears to maintain the 'diene character' of the product. In the case of *N*-alkenyl **65,** optimised reaction conditions yielded 76% of cyclised product **66** [28].



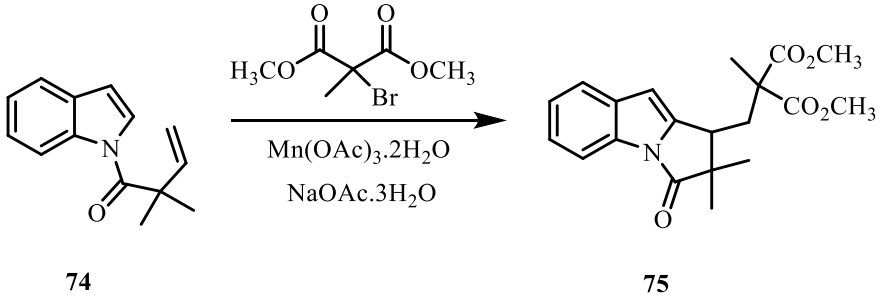
Scheme 17

The scheme demonstrated intramolecular cyclisation of the indolyl-2-radical to achieve fused [1,2-*a*]indoles in the presence of TBTH and AIBN radicals. Substrate **69** was synthesised from indole by the reported method [29], followed by *N*-alkylation of 2-bromoindole in the presence of K_2CO_3 and alkyl/aryl bromide. The radical precursors were subjected to the normal radical reaction conditions of TBTH with catalytic AIBN as an initiator under refluxing in acetonitrile for 12 hours. However, 5-membered and 6-membered cyclised **71** major products were formed exclusively along with the dehalogenated byproduct **70** (ring formation cyclopentane via 5-*exo* cyclisation and cyclohexane via 6-*endo* cyclization). Interestingly, in the case of the aryl radical **72**, only 5-membered (5-*exo*) ring formation **73** occurred without any byproduct, possibly due to the bond angle in the 5-membered ring. The chain length was not extended during cyclisation [30].

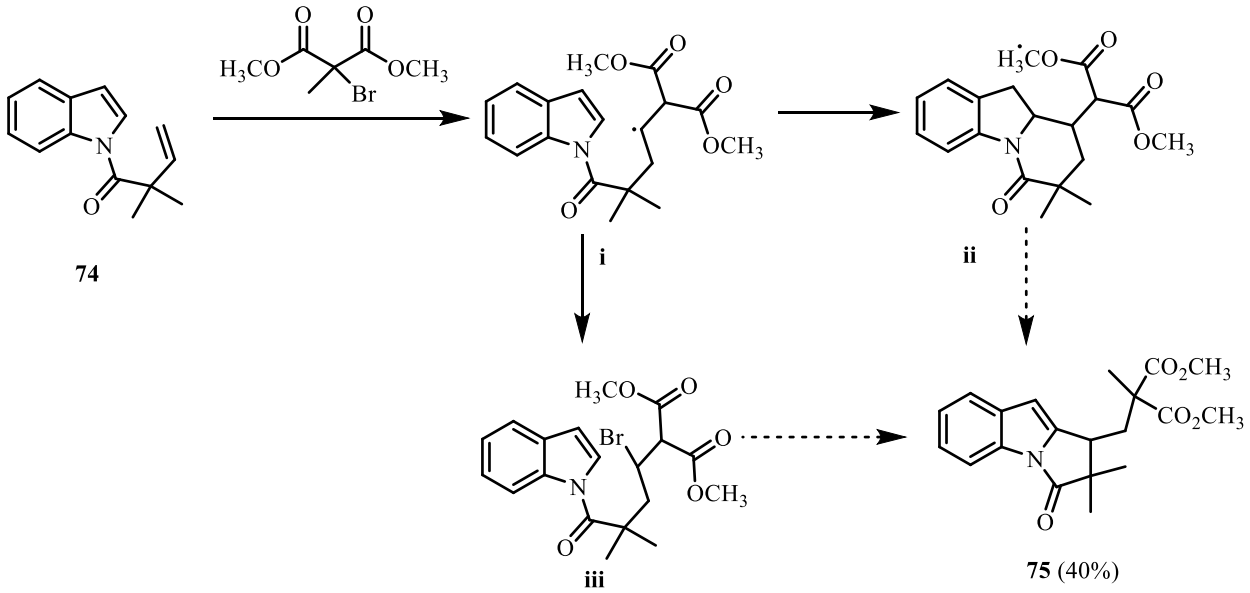


Scheme 18

The new Mn-promoted radical aromatic substitution assisted domino intermolecular addition to the olefin substrate in indole core, followed by rearomatization is a novel approach to synthesise 1,2- and 2,3-fused indoles. The substrate **74** reacts with dimethyl bromomethylmalonate (Scheme 19) in the presence of $Mn(OAc)_3.2H_2O$ and $NaOAc.3H_2O$ in acetic acid overnight run affords **75**. The potential reaction pathway, the dimethyl methylmalonate radical presumably adds in substrate **74** to generate the intermediate radical **(i)** (Scheme 20) and undergoes prior cyclisation toward atom transfer and rearomatisation. In the second pathway, Br transfer occurs before cyclisation generating the atom transfer product **(ii)**, which subsequently undergoes intramolecular electrophilic substitution on the indole ring along with oxidative addition to yield 40% **75**. The Mn(III) oxidative addition is the elaborated atom transfer method in this scheme and improves the yield [31].



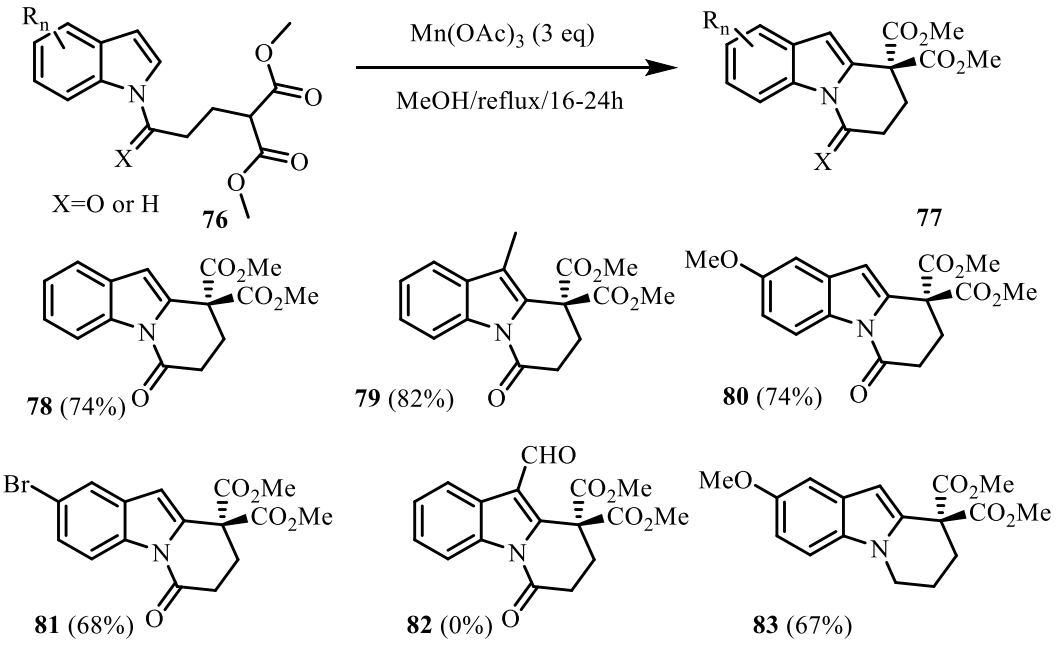
Scheme 19



Scheme 20

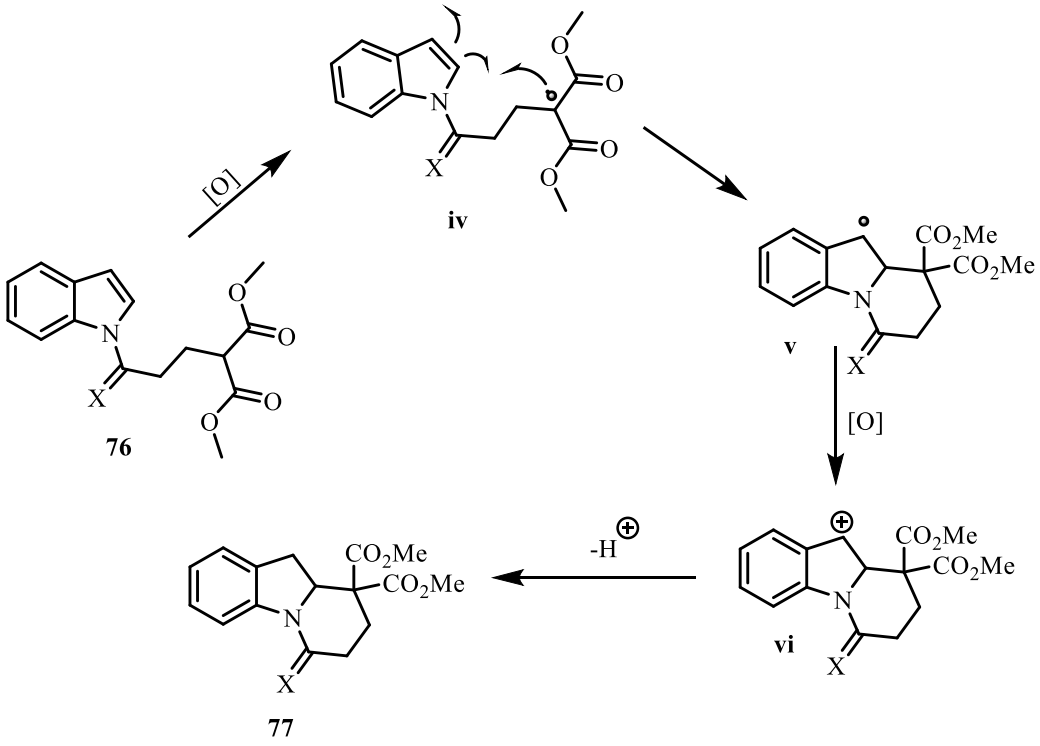
2.5.2 6-membered ring annulation

Mn(III)-mediated oxidative cyclisation yields 1,2-annulated indole **77** when indole derivatives of the N-atom substrate have the pendant malonyl group. The various commercially available substituted indoles are acylated or alkylated with malonyl chains to give compounds **76**, which were further subjected to oxidative cyclisation with $Mn(OAc)_3$ in CH_3OH offering **77** in good yield. The oxidative radical cyclization of *N*-acylindoles and *N*-alkyl derivatives yielded good yields of **78-83.** Moreover, methanol and acetic acid were appropriate solvents for the transformation via the $Mn(OAc)_3$ reaction. More complex substrates will likely be more tolerant of methanol than acetic acid [32].



Scheme 21

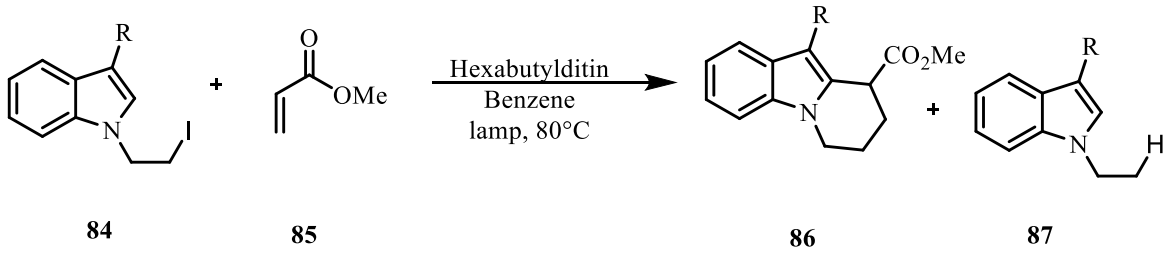
Mn(OAc)3-mediated cyclisation proceeds through the oxidation of a malonic enolate derived from **76** to yield a malonic radical **(iv)** (Scheme 22). Cyclisation occurred on the 2-position of the indole to produce a resonance stabilised radical **(v)** which may undergo further oxidation to the carbonium ion **(vi),** and aromatisation via proton loss gives rise to product **77**.



Scheme 22

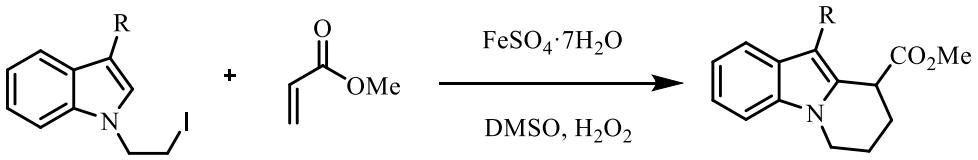
The benzindolizidine **86** system scaffolds were obtained in moderate to good yields by prominent radical addition/cyclization/oxidation methods from substituted 1-(2-iodoethyl)indole **84** with methyl acrylate **85** via Fenton-type conditions. Cyclopenta[*b*]indole ring system was developed by a similar radical domino process comprising intramolecular 2 and 3-indolylacyl radical oxidative addition in the presence of n-Bu_6Sn_2 and benzene at 80°C. However, there were drawbacks due to the high toxicity of hexa(n-butyl)ditin and to overcome this toxicity problem, alternative Fenton-type conditions were developed to obtain oxidative radical cyclisation on indole systems. Fenton technology not only works in a Tin-free environment but also resolves the re-aromatisation step which comes through Tin-mediated reactions. The reaction conditions were tolerated by pyrrole and its derivatives [33].

a) Toxicity concerns with hexa(n-butyl)ditin.



84 **85** **86** **87**

b) Fenton technology (tin-free environment/without dehalogenation).

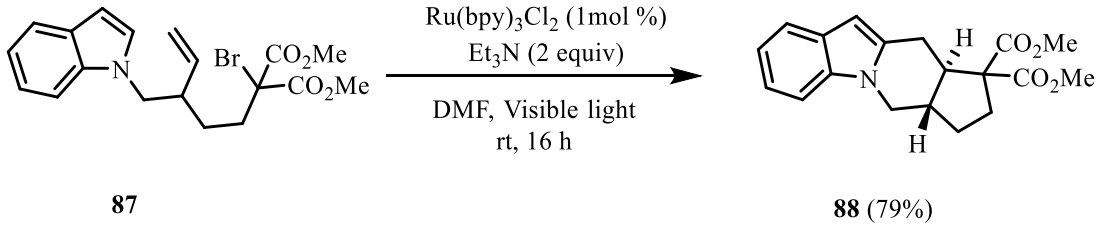


84 **85** **86**

Scheme 23

Photoredox catalysis is the most effective method for free radical generation. Recently, the annulated indoles and pyrroles have been synthesised via the domino process. Photoredox catalyst tris(2,2'-bipyridyl)ruthenium dichloride can be exposed to a light source for radical cyclization at room temperature. Activated free radical intermediates are generated through the reduction of carbon-halogen bonds by a single electron reductant Ru(I) to induce the photo-catalytical cycle under visible light. The initial investigations of substrate *N*-substituted indole **87** treated with iPr_2NEt (2 equiv), $Ru(bpy)_3Cl_2$ (2.5 mol %), and DMF in the presence of visible light irradiation **88** yielded 52% of the desired product, as well as a major dehalogenated byproduct. Triethylamine base was used as an electron donor for reductive quenching of photoinduced excited Ru(II)* to

avoid the dehalogenated product. Various amines were tested including Ph_3N, Et_3N, Me_3N, and $(HOCH_2CH_2)_3N$ but Et_3N had the best reactivity and selectivity towards cyclisation into **88** during dehalogenation yielding 79% conversion[34].

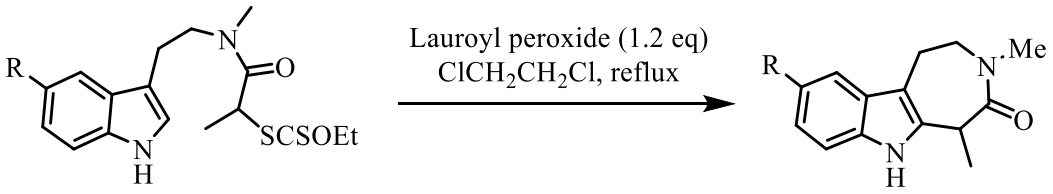


87 **88** (79%)

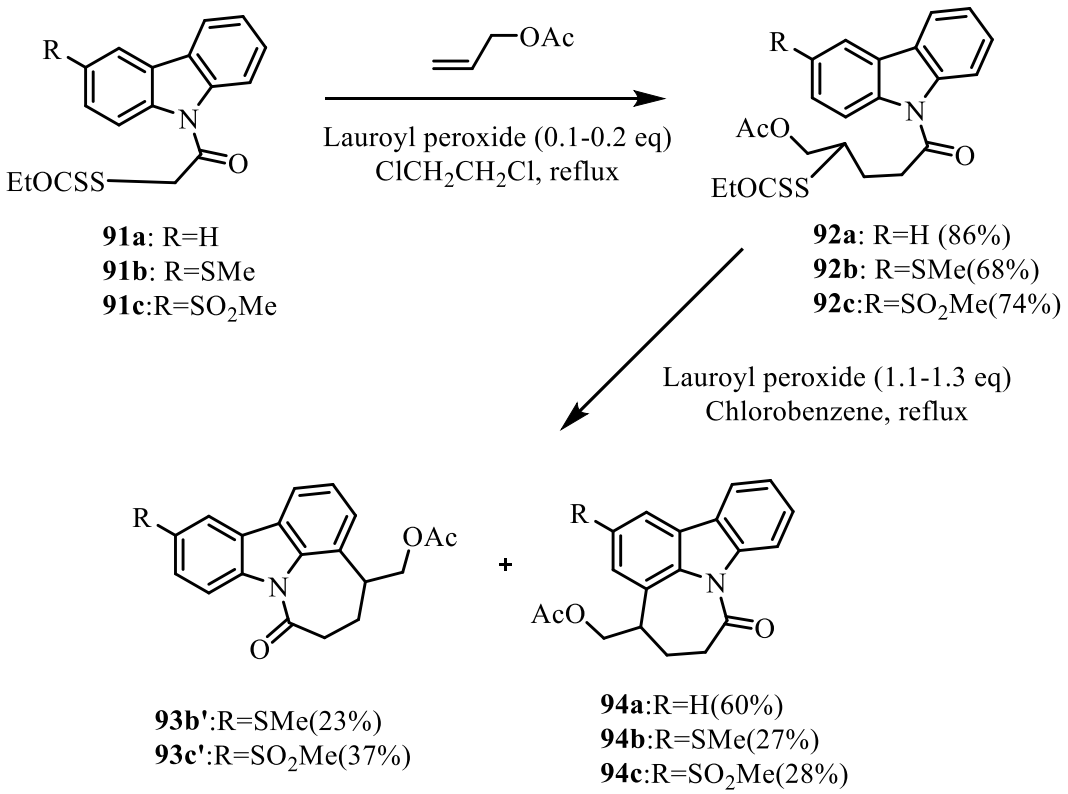
Scheme 24

2.5.3. Medium-sized ring annulation

There are few reports of preparation of medium-sized ring annulated indoles through a radical method due to several challenges such as interfering with cyclisation due to the stability of the radical ion, the activity profile of the substrate and slow product formation with low yield. Annulation of the medium-sized ring to an aromatic nucleus gives access to several novel structures like indoline, oxindole, indanes, and tetralones. The reported Scheme 25 describes the use of lauryl peroxide in the presence of a chlorinated solvent to prepare xanthate carrying substrate **89** to afford cyclisation of **90** in the presence of radical precursors and heat with moderate to good yields. The optimised reaction condition was suitable for various substituted indole analogues e.g., carbazole substrate **91a** produced the tetracyclic carbazole moiety yielding 60% **94a** but sulphide **91b** and sulphone **91c** affords equal quantities of two isomers **93b-94b** and **93c-94c** [35].



89 **90** (54%)



91a: R=H
91b: R=SMe
91c:R=SO_2Me

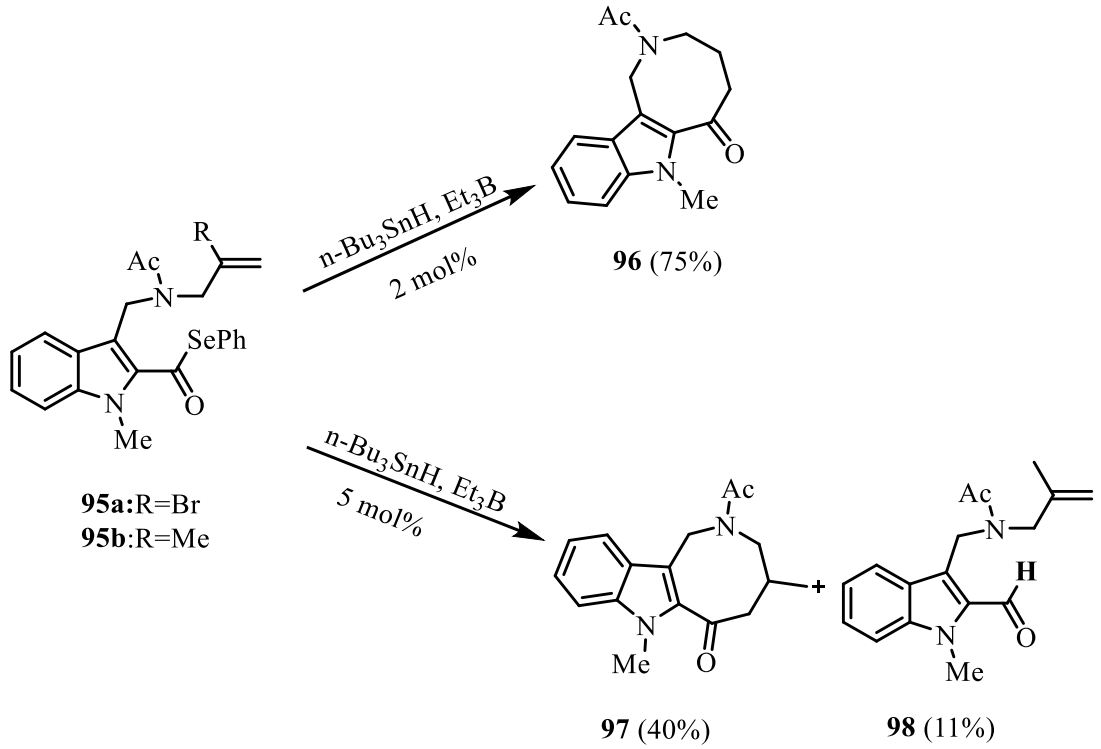
92a: R=H (86%)
92b: R=SMe(68%)
92c:R=SO_2Me(74%)

93b':R=SMe(23%)
93c':R=SO_2Me(37%)

94a:R=H(60%)
94b:R=SMe(27%)
94c:R=SO_2Me(28%)

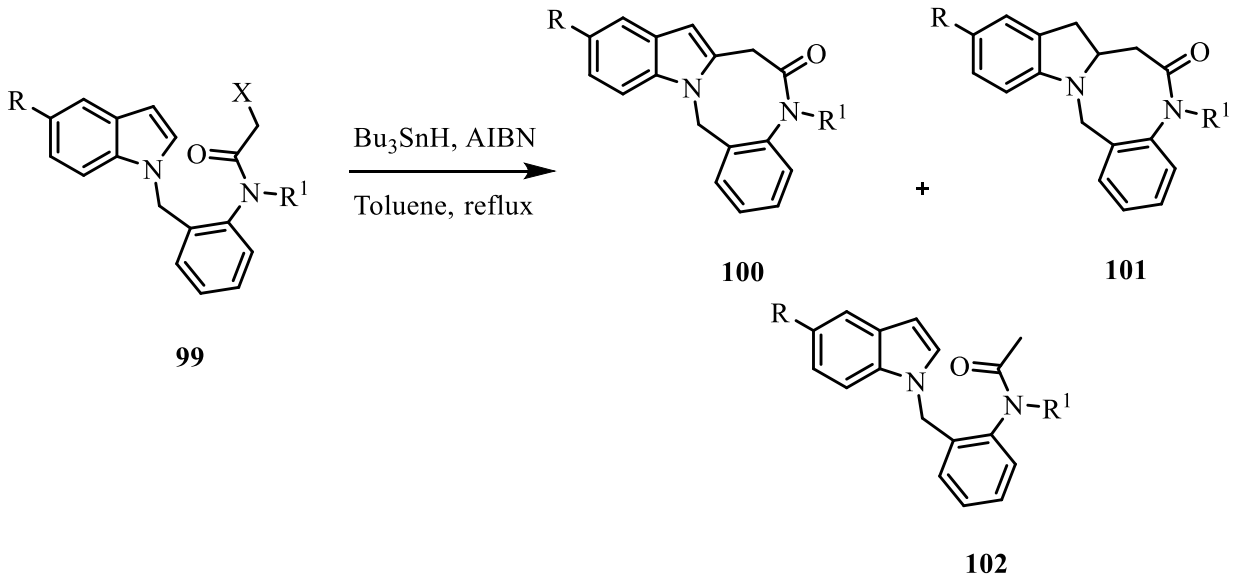
Scheme 25

Novel regioselective azocino[4,3-*b*]indole synthesis derived from 2-indolylacyl radicals on amino-connected alkenes and selenoester functionality in the presence of n-Bu_3SnH with Et_3B with high yields. These tricyclic subunits are present in indole alkaloids apparicine and mercicarpine. The 8-endo mode cyclization was elaborated when the alkene acceptor was substituted at the internal position by a bromine atom or by methyl group. Interestingly, for the competitive 7-exo attack, both substituents are sterically prevented. The halogen atom containing the substrate benefited 8-membered cyclization faster compared to others due to activation of the double bond to obtain the apparicine substructure **96** (yield 75%) from (bromovinyl) substituted selenoether **95a** using n-Bu_3SnH in Et_3B 2 mol%). Meanwhile, selenoester incorporated with the (2-methyl-2-propenyl)amino moiety **95b** gave 40% azocinoindole **97**and a minor product obtained with aldehyde moiety **98.** The medium sized ring (7- and 8-endo cyclization) products were produced from suitable substituted 2-indolylacyl radicals under viable reaction conditions in the presence of radical precursors [36].



Scheme 26

A free radical cyclisation approach has been developed to obtain indolo[2,1-*d*][1,5]benzodiazocine derivatives **100** from *N*-substituted indole derivatives **99** with appropriately positioned haloacetamide functional groups. The substrate was developed from indole *N*-alkylation with the appropriate alkyl halides, benzyl halides followed by acylation of the resulting amines with acyl halide to produce a haloacetamide moiety. Cyclisation of the haloacetamides occurred by using a 40 mol% solution of tributyltin hydride (Bu_3SnH) in the presence of azobisisobutyronitrile (AIBN) in appropriate solvents at reflux. Slow addition of tributyltin hydride to haloacetamides afforded an eight-membered ring product fused with indole derivatives **100** and **101** with the minor **102** product observed [37].

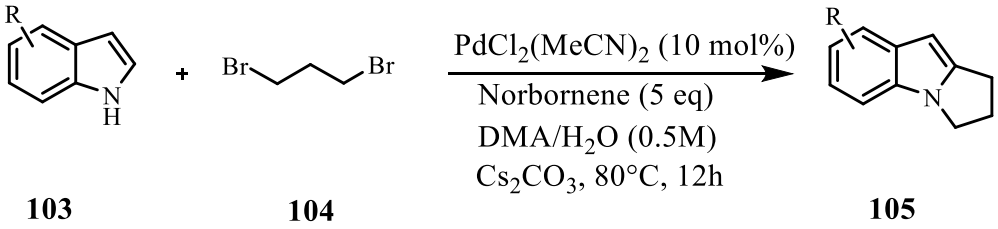


Scheme 27

2.6. Transition metal-catalysed annulations

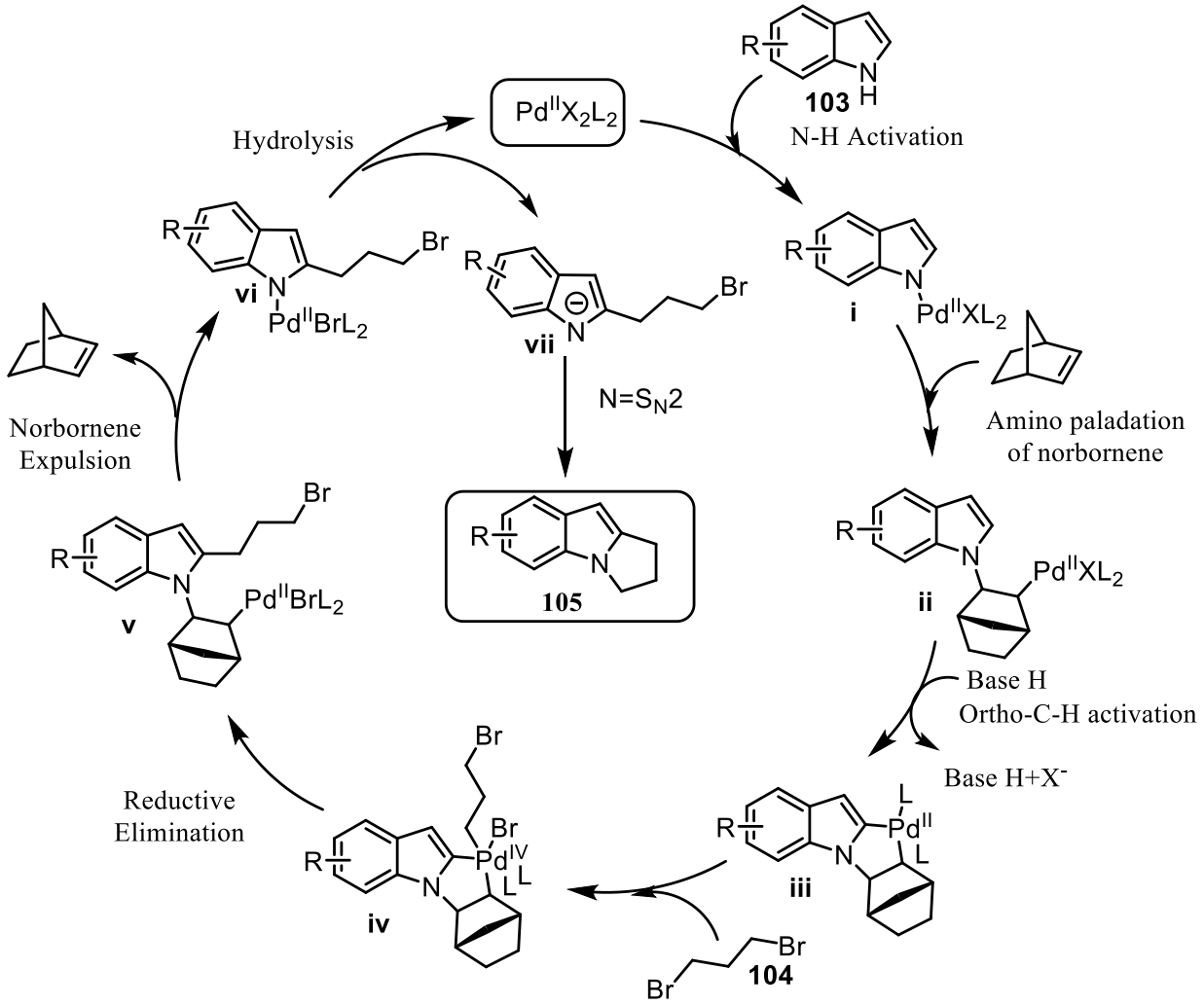
2.6.1 5-membered ring annulation

Organometallic chemistry has explored a wide range of applications in inter and intramolecular indole annulation. The novel one step synthesis of annulated indole (Scheme 28) was developed through a palladium-catalysed double alkylation between indole and dibromo alkane compound also significantly elaborated oxidative addition of the halides, reductive elimination, norbornene extrusion, hydrolysis of C2-functionalised indole followed by Pd(II) catalyst regeneration The initial reaction proceeds in the presence of Pd-catalyst ($PdCl_2(MeCN)_2$ 10 mol%) along with norbornene-mediated indole **103** *N*-alkylation with dibromo propane **104** subsequent regioselective cyclization to obtained 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole **105**. The optimised reaction condition was appropriate for various substituted indole derivatives as well as diborane compound. Interestingly, the dibromo alkanes play an important role in the annulation of various rings.



Scheme 28

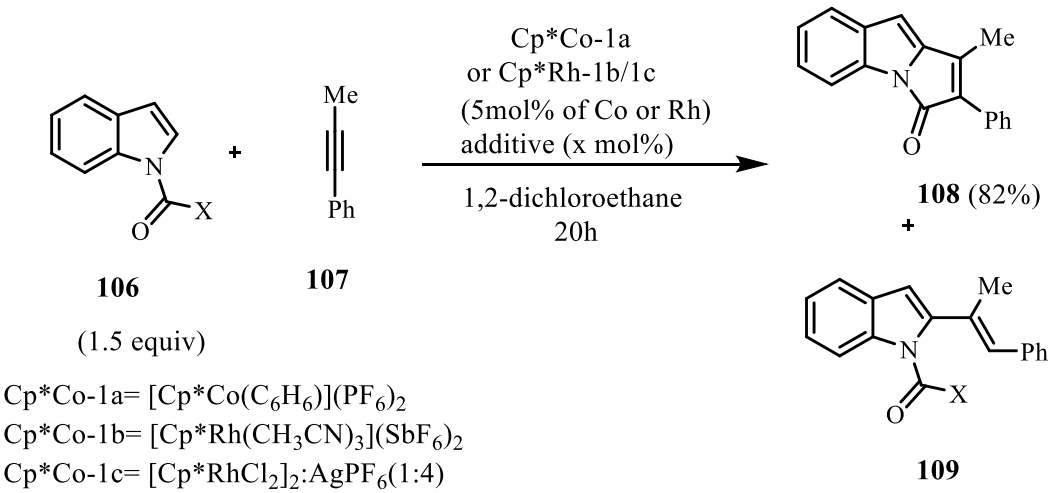
The proposed catalytic cycle in Scheme 29 has initial step, *N*-palladation of indoles, and aminopalladation of norbornene followed by formation of Pd(II) in **ii**, which undergoes ortho C-H activation to provide the Pd cyclic complex **iii**. Therefore, oxidative addition of dibromoalkanes, reductive elimination, and norbornene extrusion generates the 2-alkyl *N*-palladaindole species **vi,** which is subsequently hydrolysed to the 2-alkylated indole intermediate **vii** and retains Pd(II) catalyst. The intermediate **vii** underwent direct intramolecular *N*-nucleophilic substitution to affords the [*a*]-annulated indole **105** [38].



Scheme 29

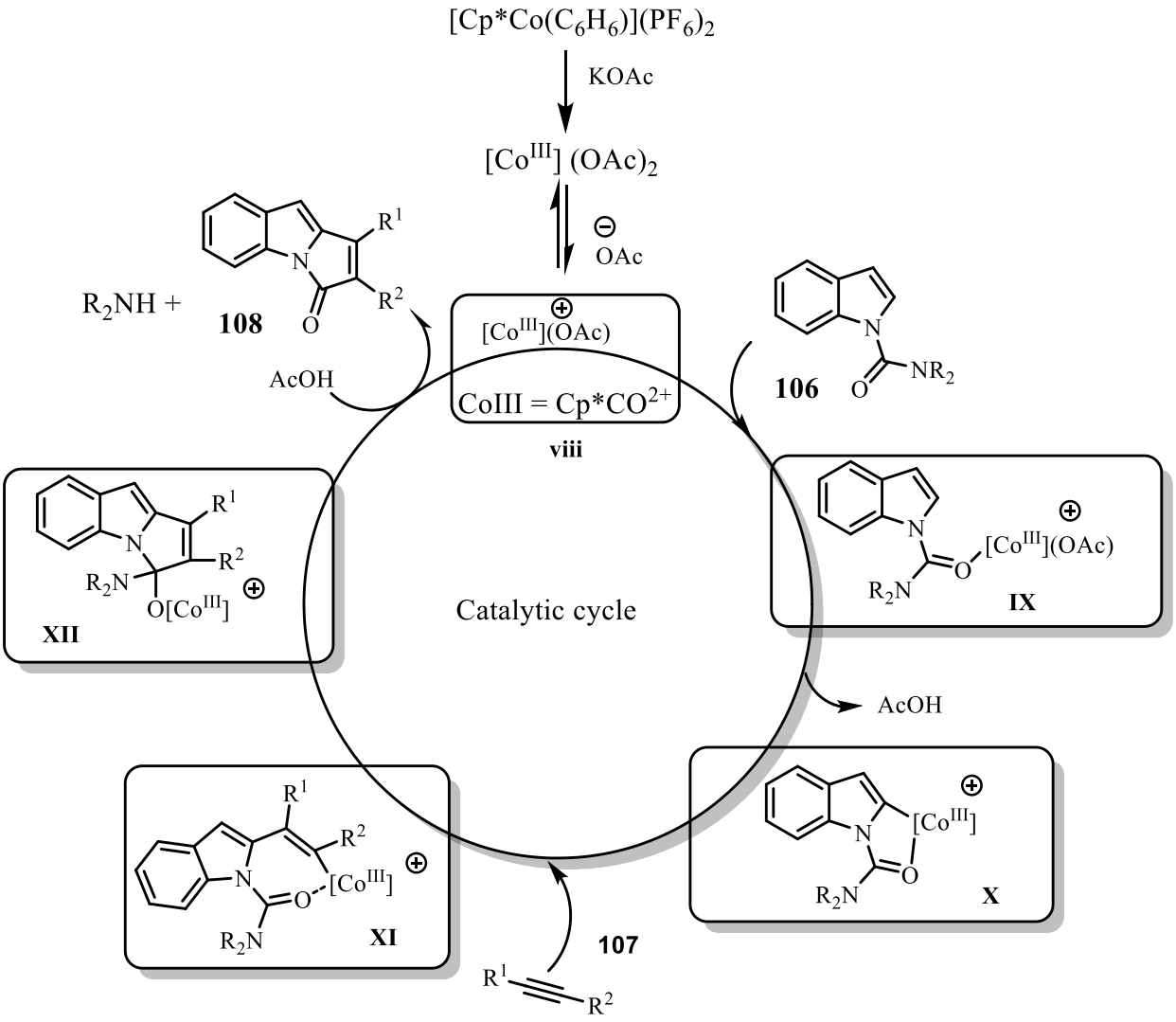
The unique use of the Cp*Co^{III} catalyst in indole annulation compared to the Cp*Rh^{III} catalyst is described in Scheme 30. The C-2 selective indole alkenylation and annulation sequence occurs with a catalytic amount of the [Cp*Co^{III}(C_6H_6)](PF_6)$_2$ (**1a)** complex in the presence of KOAc. Intramolecular addition of the alkenyl Cp*Co complex to the carbamoyl moiety affords pyrroloindolones in an one-pot process with moderate to good yields. The initial optimisation study was performed with various metal complexes (**1a, 1b, 1c)** but only **1a** gave outstanding

results over various reactive complexes. The desired pyrroloindolone **108** (yield 82%) was obtained from the reaction of *N*-dimethylcarbamoyl indole **106** with substituted alkyne **107** moiety in the presence of 5 mol% $[Cp^*Co^{III}(C_6H_6)](PF_6)_2$ and KOAc in DCE at 80°C, while the simple alkylated product **109** was also observed in small (yield 8%). However, increasing the loading of KOAc (20 mol%) and raising the temperature to 130°C afforded an excellent yield of the desired product **108** and the C2-selective alkenylation/indole annulation sequence was better in the presence of high loading KOAc and Cp*Co over Cp^*Rh^{III} .



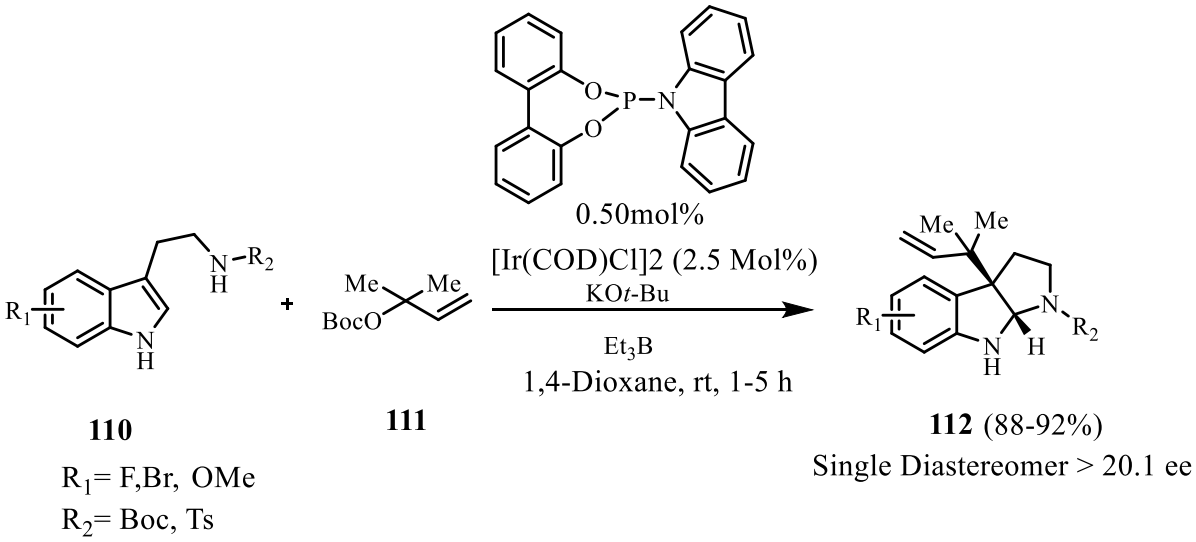
Scheme 30

In the initial step, thermal dissociation of the (C_6H_6) ligand of $[Cp^*Co(C_6H_6)]$-$(PF_6)_2$ exchanges to acetate generates the catalytically active monocationic species **viii** in equilibrium with a resting neutral di-acetate complex. Coordination of the carbamoyl group of indole **IX** is followed by regioselective C−H metalation at the C2-position via concerted metalation-deprotonation mechanics to afford indolyl-Co species **X**. Therefore, insertion of alkyne **107** generates the key alkenyl-Co intermediate **XI** and annulation of **XII** produces **108** [39]**.**



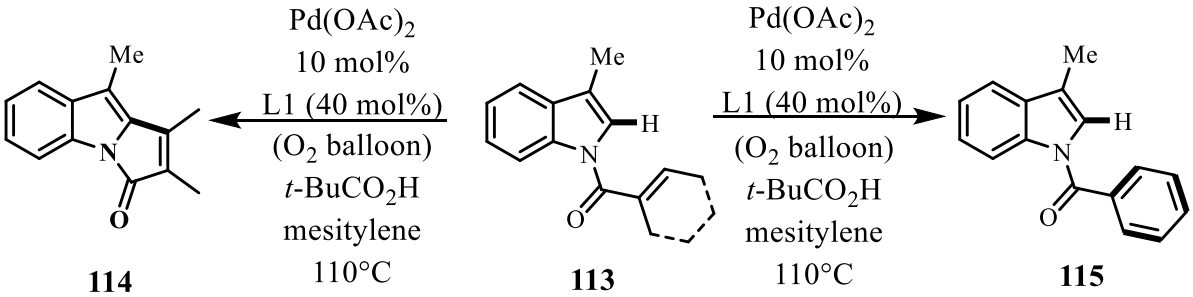
Scheme 31

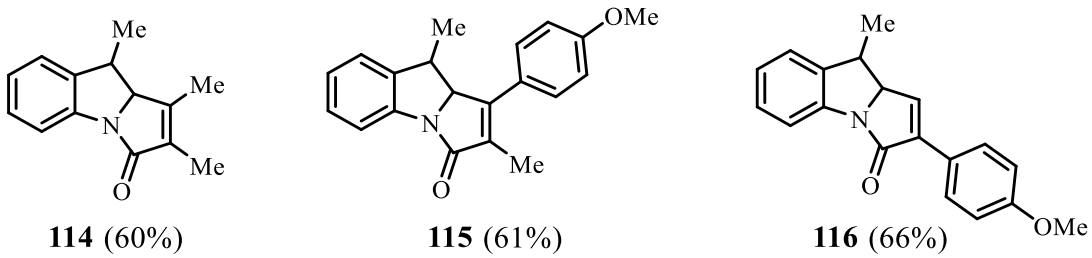
Scheme 32 demonstrated Ir-catalysed selective reverse prenylation of 3-substituted-1*H*-indoles at C3 position for the synthesis of various annulated indoles and the reaction proceeds with high branched to linear selectivity (>20:1) for a variety of indoles. The concept of reverse prenylation of methyl tryptophan ester demonstrated the synthetic utility of biologically active (-)-brevicompanin B. The methodological investigations began from *N*-protected tryptamine **110**, Boc-protected carbonate **111** in the presence of catalyst (generated *in situ* from phosphoramidite ligand in presence of [{Ir(cod)Cl}$_2$]) to obtain the desired product **112** (88-92%). The reaction with KO*t*-Bu and Et_3B as additives serves to activate indole through the formation of an *N*-borylated intermediate. Various substituted indoles (electronic withdrawing and donating substrate) were used to increase the scope of C-3 position indole annulation and resulted in a moderate to good yield [40].



Scheme 32

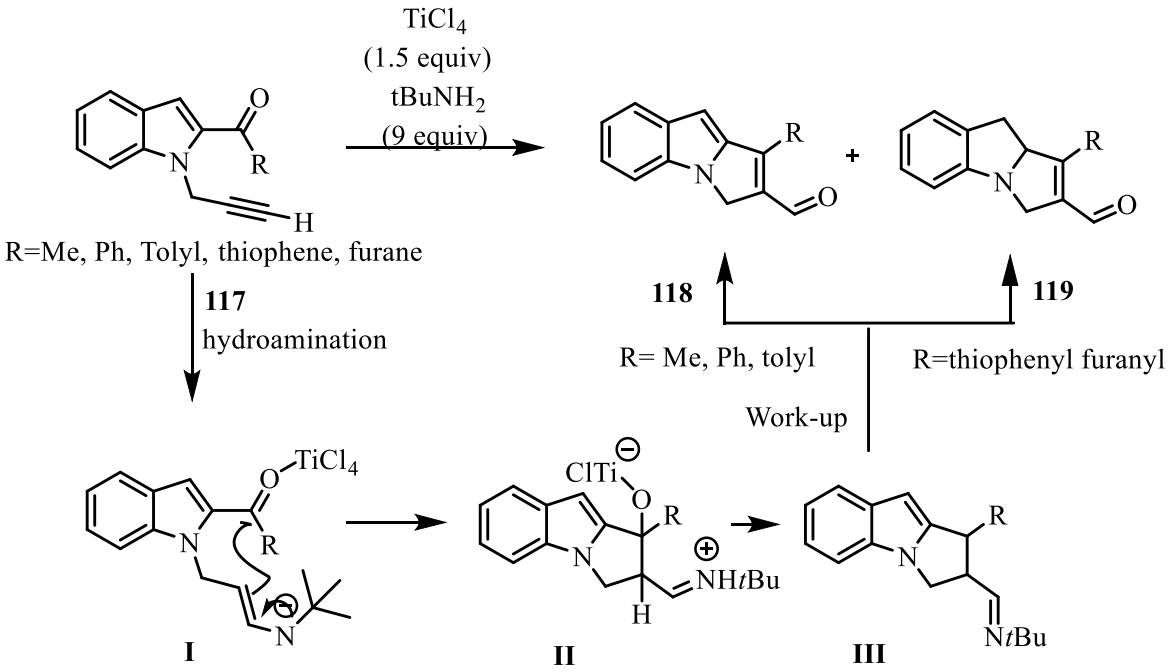
The *N*-vinyl group containing indole **113** is catalysed in the presence of $Pd(OAc)_2$ and various bases to achieve 5-membered annulated indole. Nicotinitrile (L1) or pivalic acid (L2) have been used as effective additives for domino-aerobic indole 5-membered annulation and this synthetic route offers a step-by-step entry to achieve diastereoselective C2-alkenylation of indol product **114**. Interestingly, cyclohexene connected fragment produced dehydroaromatisation **115** instead of annulation with the existing catalytic system. The substrate was suitable to synthesise various cyclised products yielding moderate to good yields [41].





Scheme 33

$TiCl_4$/t-$BuNH_2$-mediated hydroamination or domino annulation of δ-Keto-acetylenes in the presence of toluene offers annulated indoles. $TiCl_4$ acts as an effective multiactivity reagent: catalyst/Lewis acid/water scavenger. The initial investigation began with preparation of various 2-carbonyl groups containing an indole substrate which react with propargyl bromide under 50% NaOH, TBAB and toluene at room temperature to produce an excellent yield (89−98%) **117.** Therefore, the reaction of propargyl 2-acetyl indole substrate **117** treated with *t*-$BuNH_2$ 9 (equiv) in the presence of $TiCl_4$ (1.5 eq) resulted in a moderate yield of **118** which was better than that obtained with 2-benzoyl and tolyl propargyl indole. The reaction also allows for a heteroaryl substituent on C=O group but in the interaction of thiophen-2-yl and furan2-yl derivatives, gave only another isomer product conversion **119** [42].

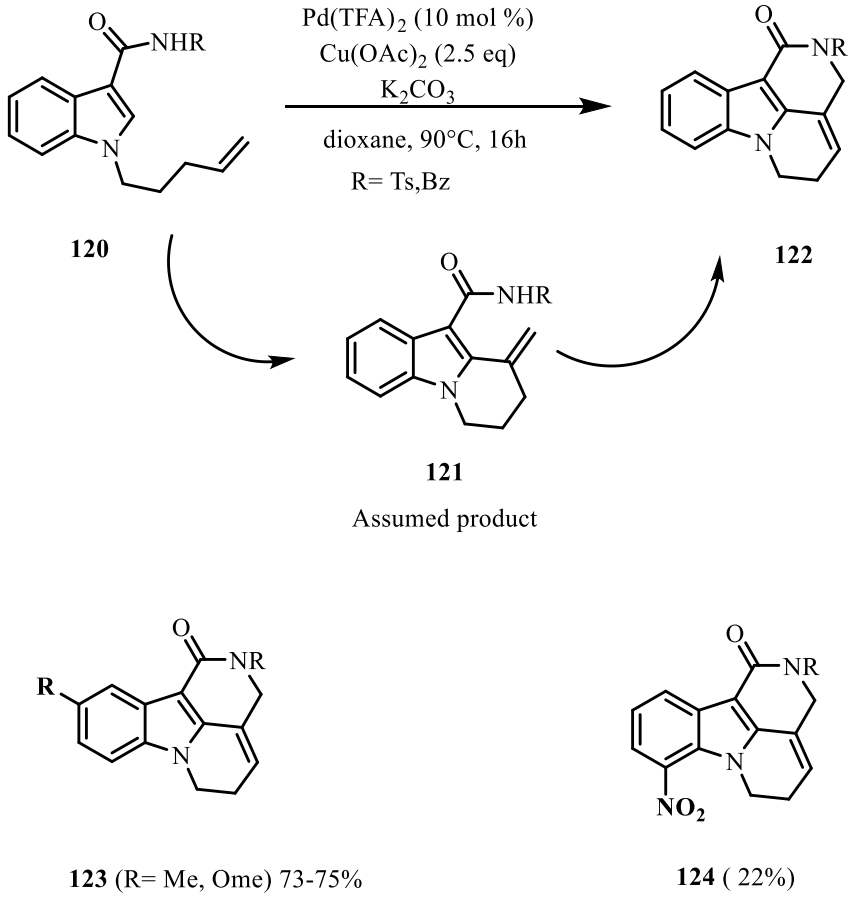


Scheme 34

2.6.2. 6-membered annulation

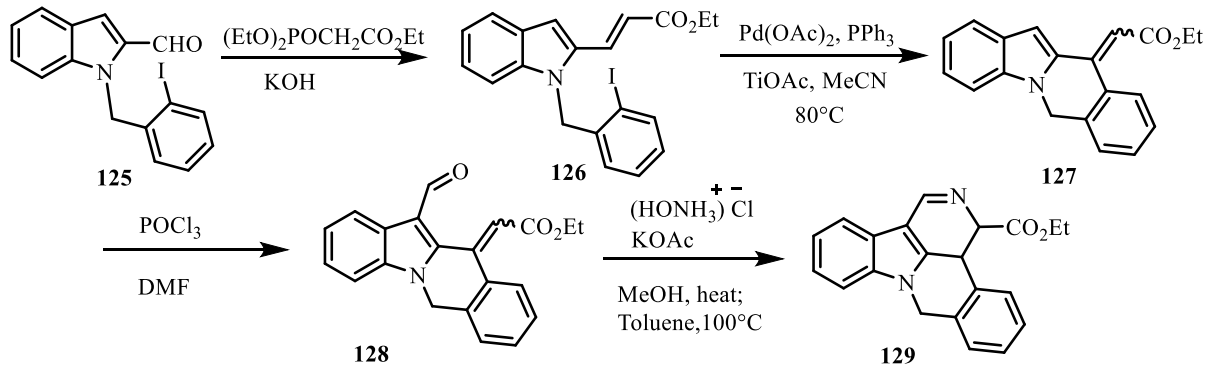
Pd-catalysed 6-membered annulation has been developed for both indole and pyrrole substrates. The transformation occurred in the presence of a Pd catalyst and $Cu(OAc)_2$ to form a 6-membered ring. The reaction proceeds with the help of Pd (II) catalysed C–H activated Heck coupling followed by a second Pd(II) catalysed aza-Wacker reaction with the Cu(II)-mediated Pd(0) sequence. The substrate **120** was synthesised by *N*-alkylation with 3-amide functionalities. Moreover, it was predicted that the oxidative Heck cyclised product **121** is synthesised via beta hydride elimination. Interestingly, when **120** was treated with 10 Mol % of Pd $(OAc)_2$, $Cu(OAc)_2$ (acts as oxidant), and K_2CO_3 in presence of toluene at 90°C, a better yield of the polycyclic

compound **122** was obtained. The substrate was well tolerated with the electron-donating substrates over the electron-withdrawing substrates [43].



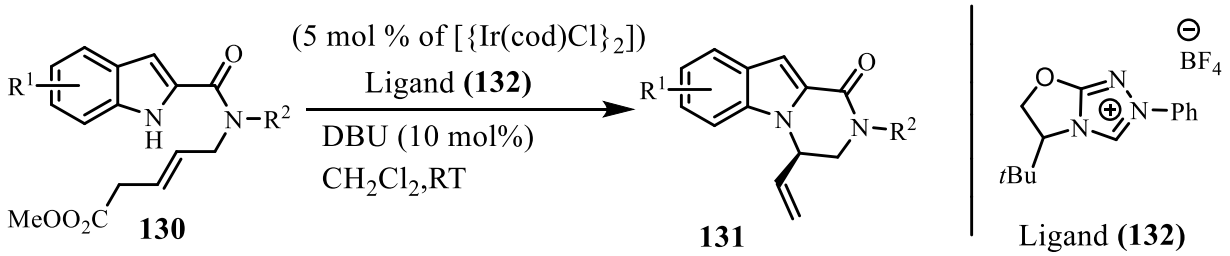
Scheme 35

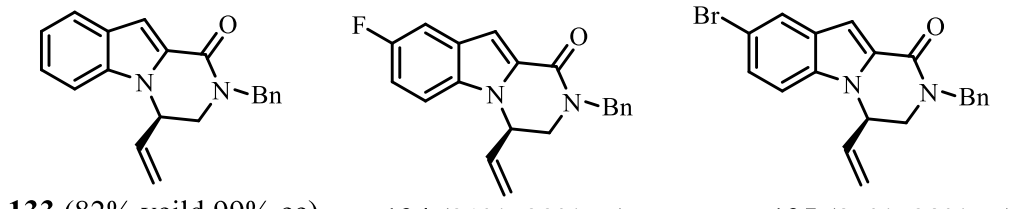
Pd-catalysed intramolecular cyclisation through the Heck reaction to obtain indole annulation has been reported. The synthetic intermediate was prepared by a derivative of the 2-position aldehyde with *N*-halogen containing aromatic ring indole substrate **125** favourably transformed into the alpha-beta unsaturated ester **126** with good yield under Wadsworth-Emmons reaction conditions. Intramolecular cyclisation of occurred under Heck reaction conditions in the presence of $Pd(OAc)_2$, PPh_3, and TiOAc to obtain tetracyclic ester **127,** followed by Vilsmeier-Haack formylation giving a mixture of stereoisomers **128** in the presence of methanol with reagents to afford a good yield of the pentacyclic desired product **129** [44].



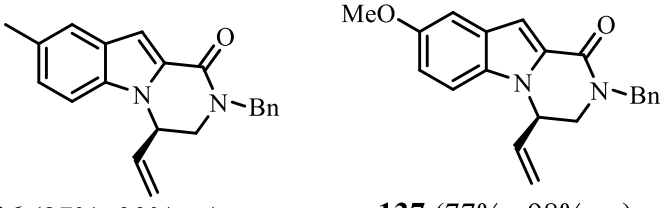
Scheme 36

Chiral iridium (I) mediated *N*-heterocyclic carbene complex with highly enantioselective intramolecular allylic amination and cyclization has been reported. The various unsubstituted indole substrates and chiral triazolium salts were examined for asymmetric transformations. The use of the model indole substrate **130** made it possible to obtain the desired allyl amination product **131** in (75-92%) yield and 92-99% *ee* in the presence of 5 mol% of [{Ir(cod)Cl}$_2$], 10 mol% of Ligand **132**, 10 mol% of DBU, and CH_2Cl_2 at room temperature without Friedel-Crafts alkylation reaction at C3 of the indole. Substrates bearing an electron-withdrawing group (5-F, 5-Cl, 5-Br, 6-Cl, 6-Br) or an electron donor group (5-Me, 5-MeO, 6-MeO) obtained a good yield of the corresponding desired product indole piperazinone (77–91%) with excellent enantioselectivity (97–99% ee) [45].





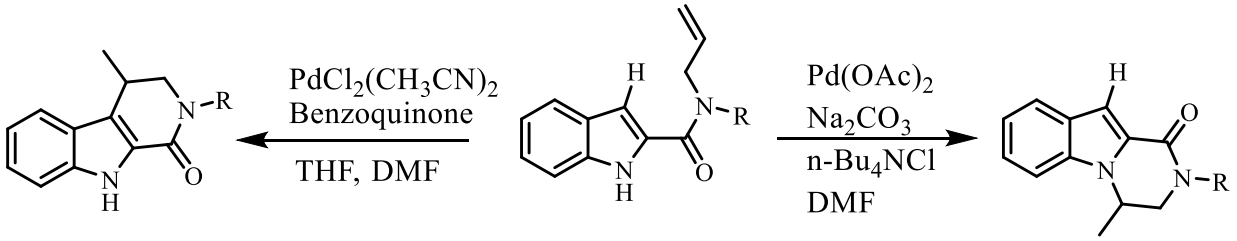
133 (82% yeild 99% ee) **134** (91%, 99% ee) **135** (87%, 98% ee)



136 (87%, 99% ee) **137** (77% , 98% ee)

Scheme 37

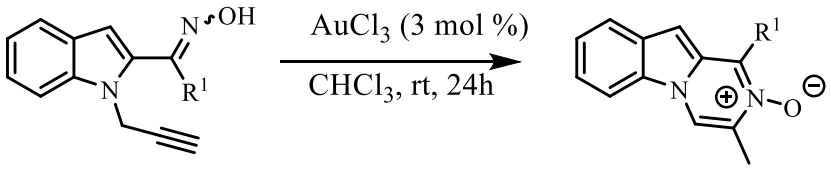
β-Carbolinones or pyrazino[1,2-*a*]indoles were synthesised by different reaction pathways in the presence of palladium-catalyst from indole-2-carboxamide derivatives **138** and complete regioselectivity was obtained in the different reaction conditions. The selective synthesis began with 1H-indole-2-carboxylic acid allylmethylamide with $Pd(OAc)_2$ (10 mol %), Ph_3P (15 mol %), tetrapropylammonium bromide (Pr_4NBr) (1.0 equiv), and Na_2CO_3 (4.0 equiv) in DMF at 90°C for 5 h affording pyrazino[1,2-*a*]indole derivatives **140**. The $PdCl_2(CH_3CN)_2$ catalyst with Benzoquinone (BQ) as a reoxidant reaction was switched to the alternative cyclisation pathway to afford *β-carbolinones* as the predominant product **139** with 90% yield. The cyclisation goes through an oxidation process and C-C bond formation in intermediate steps [46].



139 (90%) **138** **140** (79%)

Scheme 38

The reactivity of gold catalyst towards *N*-propargyl indole substrates to achieve desired domino annulation via oxime intermediate formation has been described. The substrate oxime derivatives were synthesized using 2- carbonyl functional group indole derivatives treated with propargyl bromide followed by hydroxylamine in the presence of a base and alcohol solvent. Interestingly, two isomers *E* and *Z* oxime derivatives **141** were obtained in good yields. Further domino cyclisation was performed in the presence of Au catalyst (3 mol%) and chloroform affords the *N*-oxide **142** derivative of pyrazine [47].



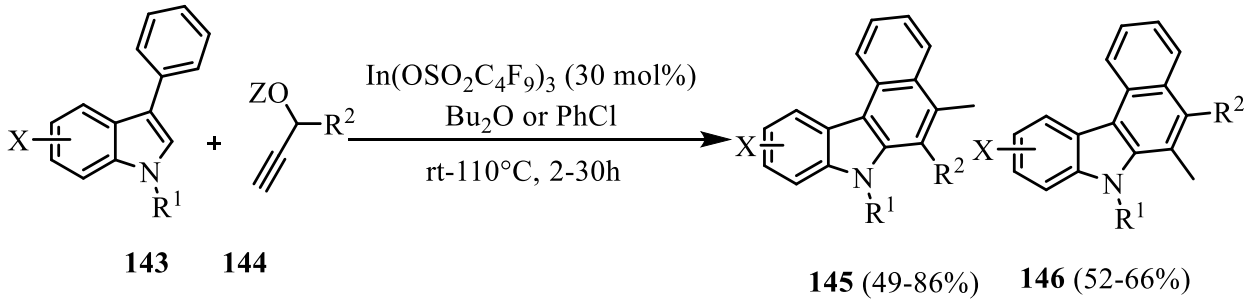
141 a R^1= H
141 b R^1= Me

142a R^1 =97%
142b R^1 =67%

Scheme 39

Heteroaryl indoles and various propargyl esters were studied in the presence of an indium catalyst for the synthesis of annulated indole via the domino pathway.

3-Aryl and 3-heteroarylindoles **143** were reacted with different propargyl ethers **144** under indium-catalysed reaction conditions to obtain regioisomers **145** and **146**. The regioselectivity depends on the strong leaving group connected with propargyl ether. The substrate **143** was treated with **144** (HCCCH(R)OZ), (R = H, Me, n-C_5H_{11}: Z = H, Me, TMS) in presence of $In(OSO_2C_4F_9)_3$ (30 mol%) with $(Bu)_2O$ or Ph-Cl at room temperature to 110°C to achieve **146** (yield 52−66%) but product **145** was obtained through the addition of an indolyl C-H bond to inactive alkyne bond followed by intramolecular cyclisation [48].



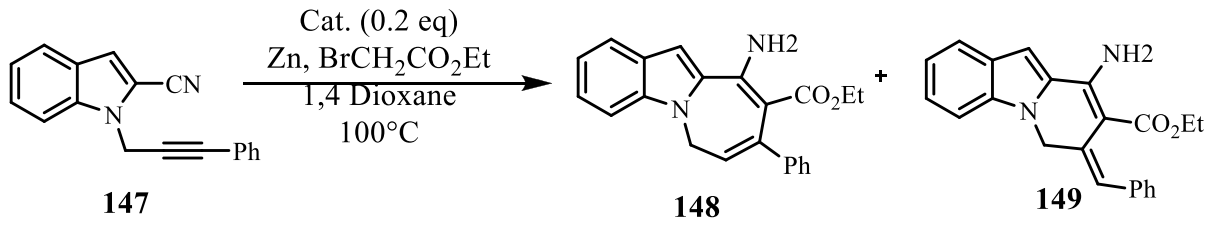
143 **144** **145** (49-86%) **146** (52-66%)

R^1=H, Me, Ph,4-$MeOC_6H_4$
X=H , 3-Me, 10-mw, 3MeO, 10-Br
R^2= H, Me, n-C_5H_{11}
Z=H, Me, TMS, CO_2Et

Scheme 40

2.6.3. Metal-catalysed medium-sized ring annulation

Zink and scandium Lewis acid-promoted medium-sized ring annulation of cyano indole derivatives through the Reformatsky reagent has been reported. The substrate 2-cyano-1-propargylindole **147** was produced from 2-cyano indole through *N*-substitution with various substituted propargyl bromides under base, followed by treatment with the Reformatsky reagent (prepared from ethyl bromoacetate with activated Zn) and Lewis acid hafnium triflate to produce a good yield of the medium-sized ring annulation product **148** with byproduct **149.** Various Lewis acids were used to optimise the reaction but only scandium triflate catalyst exclusively furnishes medium-sized azepino[1,2-*a*]indole annulation with the best yield of 99% [49].



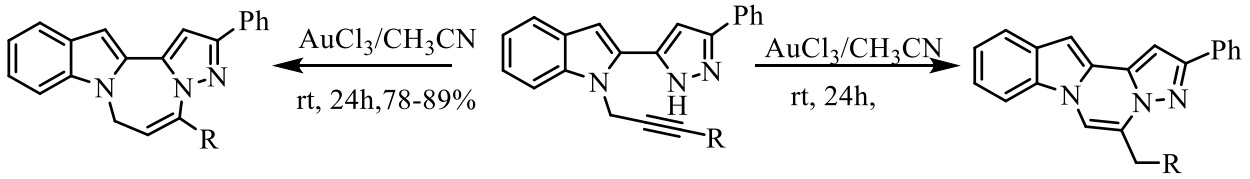
147 **148** **149**

Scheme 41

Table 2. Reaction optimization

Entry	Lewis acids	Time (h)	Yields (148)	Yields (149)
1	-	5	46	38
2	$Hf(OTf)_4$	1	46	20
3	$In(OTf)_3$	2.5	37	0
4	$Yb(OTf)_3$	2	31	24
5	$Sc(OTf)_3$	0.5	99	-

Gold-catalysed intramolecular cyclisation of *N*-propargyl indole derivatives with pyrazole affords a 7-membered ring formation. Various alkynes were introduced to indole including Sonogashira cross coupling reaction products. The optimisation of the gold catalysed reaction introduced into indole C-2 connected pyrazole with alkyne affording *6-exo-dig* and *7-endo-dig* internal cyclisation. The synthetic approach was achieved by using $AuCl_3$ gold complex salt as it plays important role for electrophilic activation followed by nucleophilic reaction. $AuCl_3$ was used for intramolecular cyclisation of substrate **150** carrying terminal alkyne via electrophilic activation of triple bonds followed by *6-exo-dig* cyclisation of H-shift affords **152** (87% yield). However, intermediate alkyne goes through *7-endo-dig* cyclisation to produce **151 a-c** under the same reaction condition [50].



151

151a = 83%
151b = 89%
151c = 80%

150

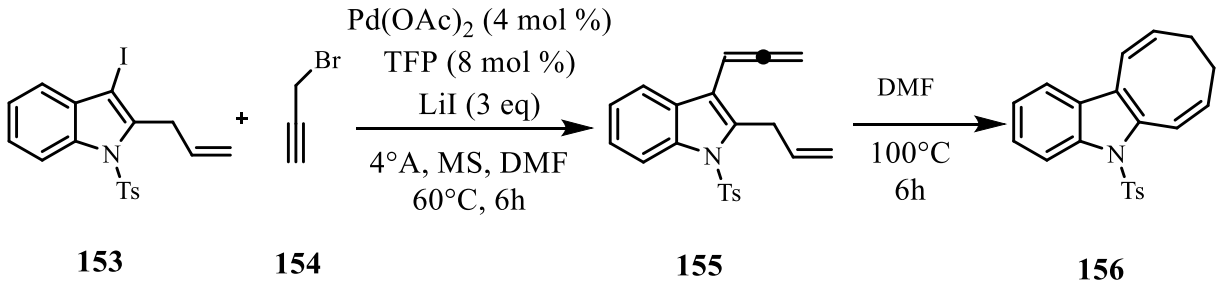
150a R= Ph
150b R=CH_3
150c R=p-C_6H_6-CH_3

152, R=H (87%)

Scheme 42

One-pot synthesis of dihydrocycloocta[*b*]indoles via a Pd-catalyst was discussed in Scheme 43. The intramolecular cyclisation has effective yield of annulated indole derivatives to obtain various sized rings with the respective indole core. The one pot synthesis of dihydrocycloocta[*b*]indole **156** from 2-allyl-3-iodo-1-tosyl-1*H*-indole **153** with propargyl bromide **154** under Pd(II) phosphine ligand complex produces the cross coupled intermediate **155** with

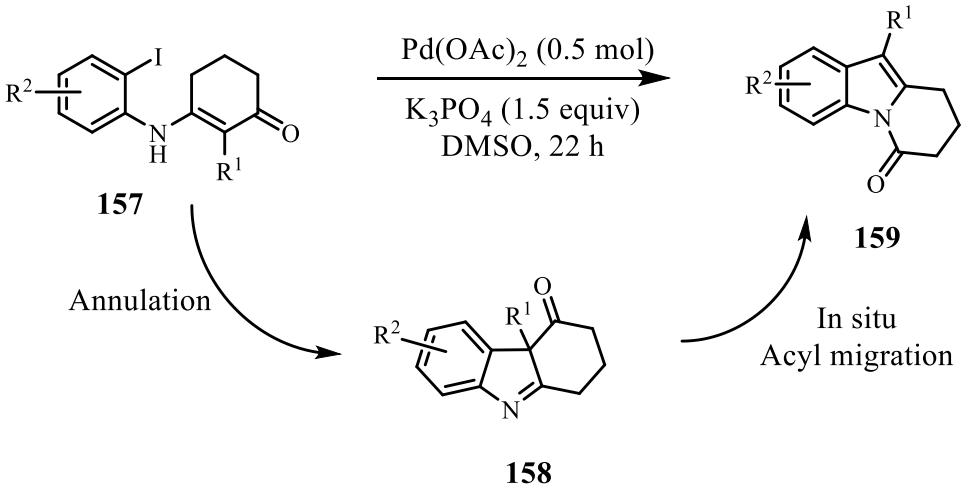
connection of alkene double bonds followed by reaction at 100°C for 6–8 h, high temperature promotes intermolecular cyclisation to obtain 61% product **154** [51].



Scheme 43

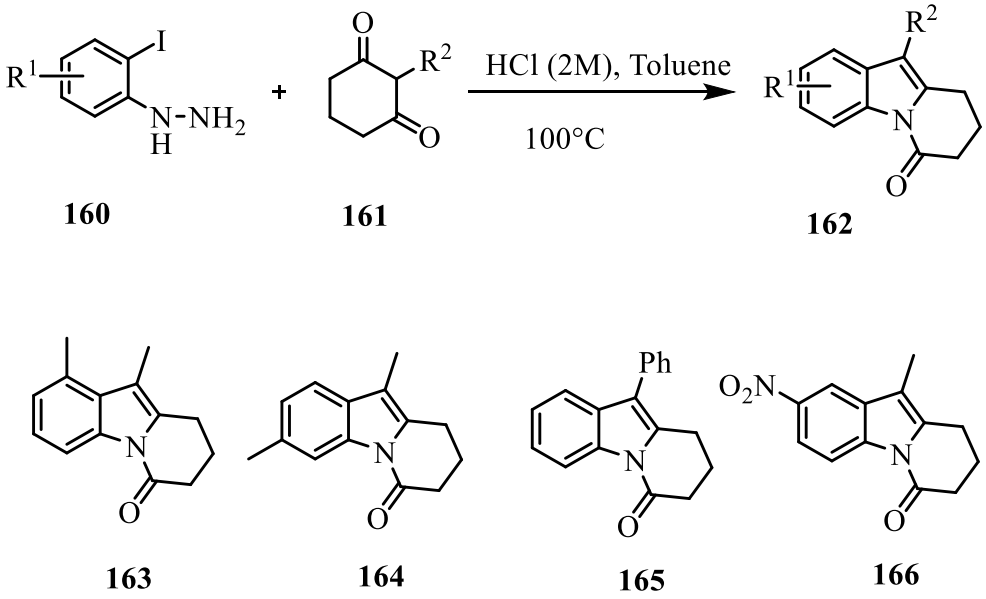
2.7. Miscellaneous domino transformations

The efficient synthetic method has been utilised for annulation under Pd-catalysed as well as acyl migration domino sequence. The optimal reaction conditions access a wide range of useful applications for readily available indole scaffolds to annulation. $Pd(OAc)_2$ achieved the desired product under specific reaction conditions, although Pd and different ligand complexes have been used for reaction optimisation. The treatment of **157** with 0.5 mol % Pd in DMSO at 120 C affords **159** with good yield. The more rare but more desirable protocol has developed with significantly reduced valuable metal loading in a ligand-free process which turns carbonyl group migration over aryl and alkyl group of indolenines. Scheme 45 was extended through the traditional Fischer synthetic method vs novel developed optimised reaction conditions, showing that the Pd-catalysed reaction results in a higher yield [52].



Scheme 44

Comparison of Fischer indole synthesis with the optimised Pd-catalysed method.

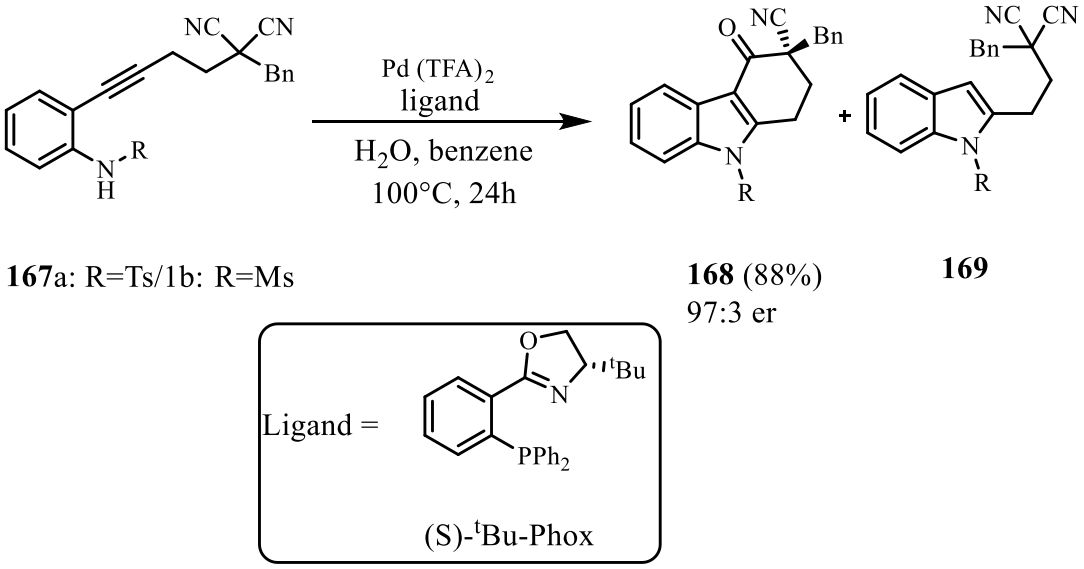


Scheme 45

Table 3. Yields via various methods.

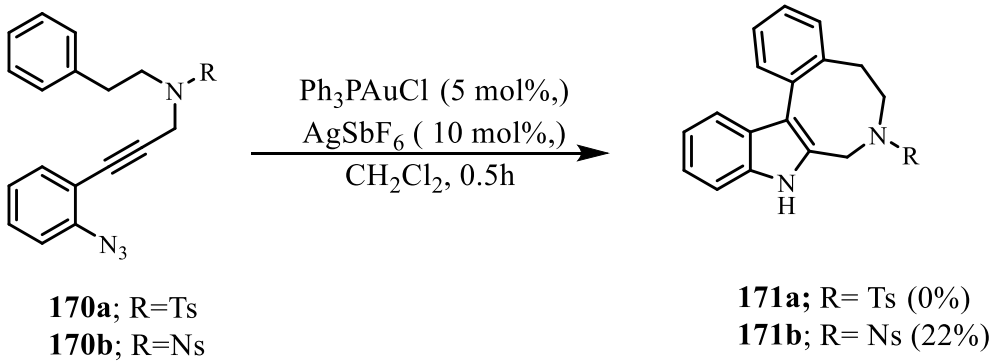
Methods	163	164	165	166
Fischer method	55%	55%	61%	5%
Pd-Cat method	68%	84%	67%	72%

The development of enantioselective annulated indole derivatives under a metal-catalyst has wide ranging scope in novel biological analogues. The authors examined and discussed various chemical properties and the development of a novel domino synthetic Pd-catalysed method to assemble a carbazolone analogue while rearranging the α-quaternary carbon centre to activate new disconnections achieving complex molecules to develop highly enantioselective α-quaternary carbazolone (98:2 er). Various derivatisations were described and a novel method was developed to construct β-ketonitriles containing a quaternary carbon centre, as well as desymmetrising ideology by forming alkyne connected mononitriles to afford the desired product **167**. The transformation involved the formation of trans-amino-palladium substrate, followed by insertion onto nitrile groups under hydrolysis to afford 88% **168** (97:3 er) along with the byproduct **169** [53].



Scheme 46

Assembling medium-sized annulation of indole under gold(I) catalysed reactions through azido-alkynes has been developed. The initial approach involved the synthesis of substrate **170a**, followed by substrate were used to obtain an eight membered ring product **171a** using $Ph_3PAuCl/AgSbF_6$ catalyst in CH_2Cl_2 but resulted in polymerisation due to substrate with Ts-group has strong electron withdrawing character as substrate. **170b** has Ns-(*o*-nitrobenzenesulfonyl) group access to form the eight membered ring (azocine) product **171b** in 22% yield. Ns-group reacts with the alpha-imino(gold) carbene in the electrophilic arylation to form eight membered ring [54].



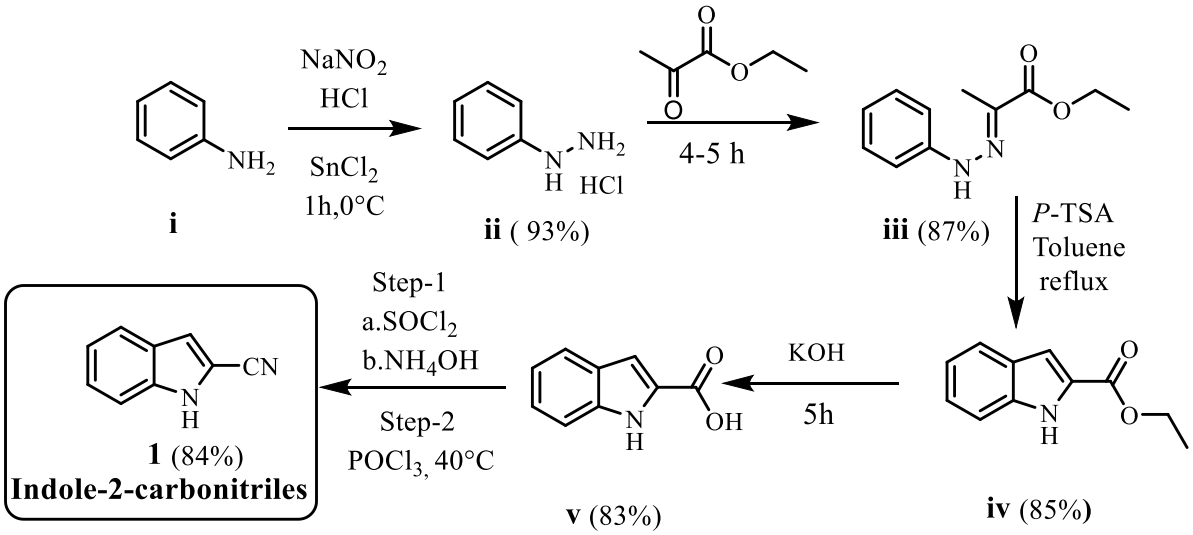
Scheme 47

Despite numerous examples of the preparation of annulated indoles, it is of note that nitriles are rarely used for domino cyclisation in indole series, so there are opportunities for future developments in the field of domino transformations of nitriles.

3. Results and discussions

Study of N-(propargyl)indole-2-carbonitriles towards O, C, and N-nucleophiles to achieve various annulated indoles through domino reaction.

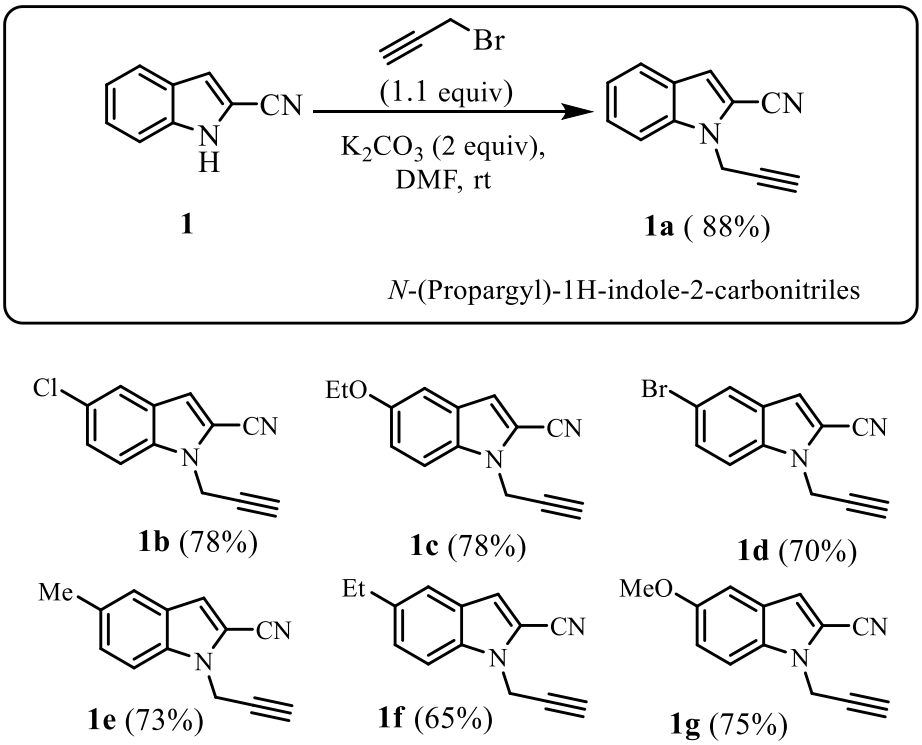
According to the literature survey on domino syntheses of annulated indoles, the nitrile-substituted indoles are an understudied class of compounds. As far as an appropriate substrate selection is the most important task in designing effective synthetic strategies, we hypothesized the substrate *N*-(propargyl)indole-2-carbonitriles **1a** can give significant output for the development of synthetic methodologies towards annulated indoles. The desired useful substrate was obtained by the following synthetic route (Scheme 1) The initial synthesis began from the simple substituted aniline **i** diazotization process to obtain hydrazine **ii** with 93% yield, followed by the reaction with ethyl pyruvate to obtain hydrazone **iii** (yield 87%) further, the cyclization of the hydrazone was carried out through Fischer indole synthesis to obtain cyclized indole-2-carboxylate **iv.** Then, ester hydrolysis was performed by KOH in ethanol to get indole-2-carboxylic acids **v.** Formation of amide substrate was achieved in two steps: acid was treated with thionyl chloride at reflux to obtain acid chloroanhydride substrate, which was treated with ammonia solution, delivering amide derivative. The latter was used for the reaction with $POCl_3$ to deliver indole-2-carbonitriles **1** (yield 84%).



Scheme 1

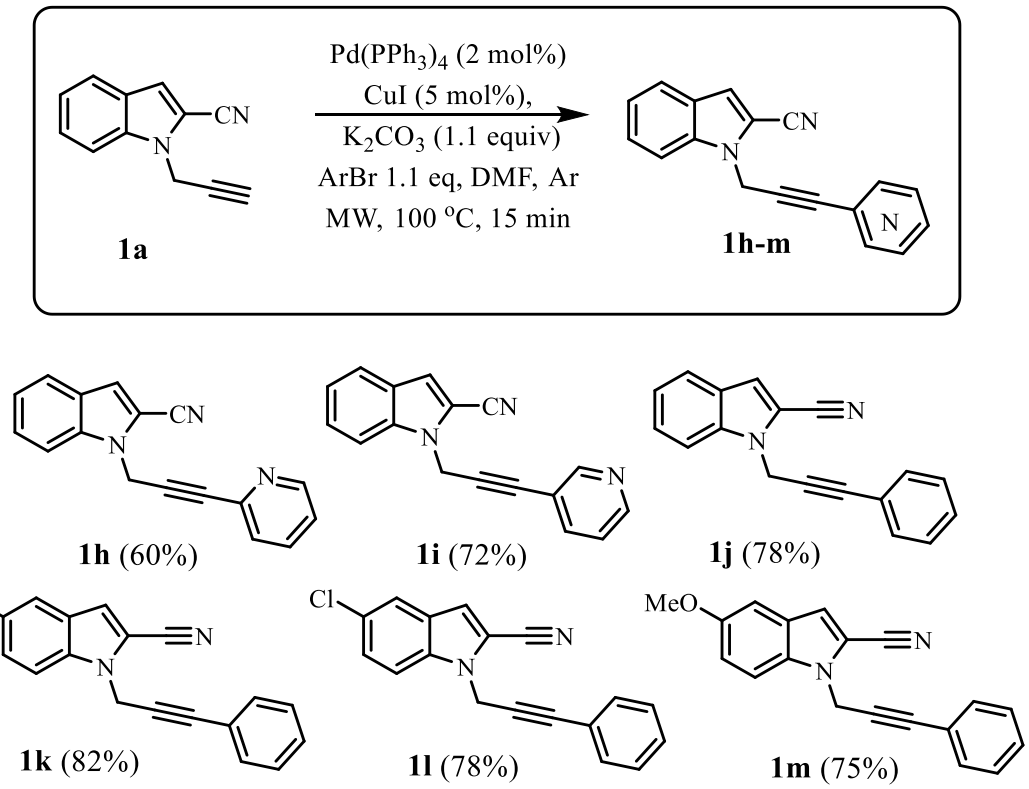
3.1. Synthesis of substituted *N*-(Propargyl)-*1H*-indole-2-carbonitriles.

Then, we synthesized 1-(propargyl)indol-2-carbonitriles (Scheme 2) by alkylating the corresponding indol-2-carbonitriles using propargyl bromide in the presence of K_2CO_3 in DMF at 60°C.



Scheme 2

Substrate scope extension was performed under Sonogashira coupling with various aryl halides including heterocyclic aryl halides to achieve useful substrates (Scheme 3).

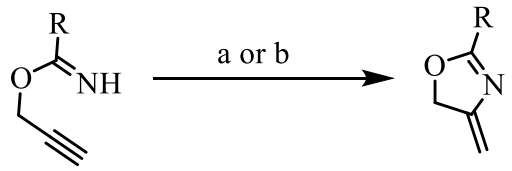


Scheme 3

3.2. Chemical properties of *O*-Nucleophiles towards *N*-(Propargyl)-*1H*-indole-2-carbonitriles.

3.2.1. Alkyne- imidate Cyclization.

Alkynes are highly pertinent to organic synthesis [55] and are widely used to construct diverse heterocyclic compounds [56]. The addition of various *N*-nucleophiles to alkynes is well established, [57] while hydroamination using imidates is less studied. Overman and co-workers reported a thermal- or DBU-promoted cyclization of propargyl imidates, affording oxazolines [58] (a). Recently, an analogous transformation was performed via copper iodide catalysis [59] (b).

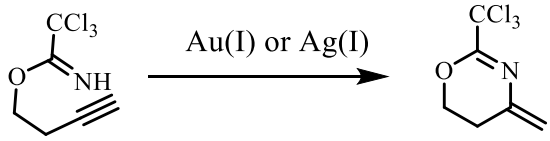


i **ii**

(a) DBU(1eq), reflux, 48h, 2 examples.

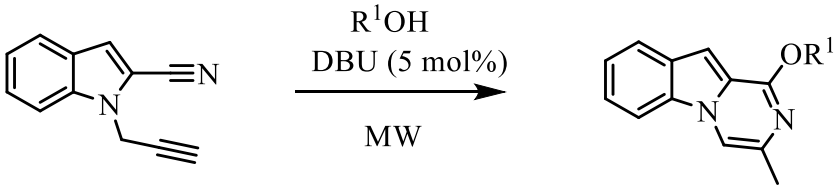
(b) CuI (5 mol), rt, 24 h.

The formation of six-membered rings was restricted to trichloroacetimidates and occurred via gold [60] or silver catalysis [61].



iii **iv**

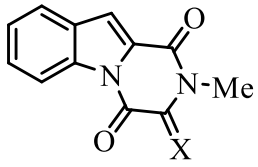
The hydroamination of alkynes (with imidates generated *in situ*) resulting in pyrazine ring formation was hitherto unknown.



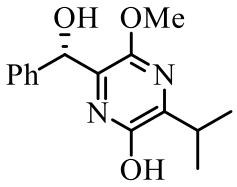
v **vi**

The pyrazino[1,2-*a*]indole scaffold exhibits wide-ranging biological activity against a multitude of targets. Recently reported examples include arenavirus, [62] Dengue virus, [63] phosphodiesterase [64] inhibition, and potentiating agonist [3H]CPPA binding to the A1 receptor [65]. Compounds derived from this scaffold have intra-arterial cardiovascular, [66] antifungal,

[67] seratoninergic, [68] anti-inflammatory, [69] and antiproliferative [70] activities, are a 5-HT2A and 5-HT2C agonist, [71] and are ligands for the histamine H3 receptor. [72] Regarding natural occurrence, secondary metabolites of marine flora and fauna exhibiting antibacterial and antiproliferative activities incorporate pyrazino[1,2-*a*]indole [73] and methoxypyrazine [74] moieties (Figure 1).



vii (Marine fungi metabolites) X=O, CH_2



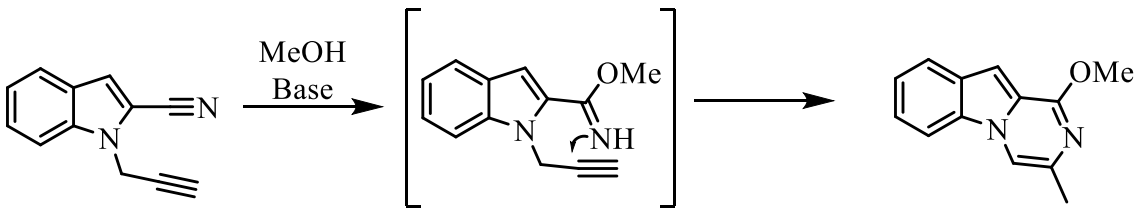
viii (terezine A)

Figure 1

The aforementioned properties render pyrazinoindoles an interesting synthesis target. [75] Recent synthesis examples include alkyne hydroamination, [76] a two-step Ugi−alkyne hydroamination reaction sequence, [77] and bromolactamization of *N*-allylindole-2-carbamide. [78] Additional work includes allylic aminations catalyzed by an iridium *N*-heterocyclic carbene complex [79] or palladium, [80] and dinitrile cyclization [81].

3.2.2. Reaction Optimization

We presumed that *O*-nucleophiles towards *N*-(propargyl)-1*H*-indole-2-carbonitriles can cyclize to deliver pyrazino[1,2-*a*]indoles under MeOH, base and CuI reaction condition. Unfortunately, reaction results concludes low yield of the desired product **2a** through Cu-catalyzed reaction.



1a

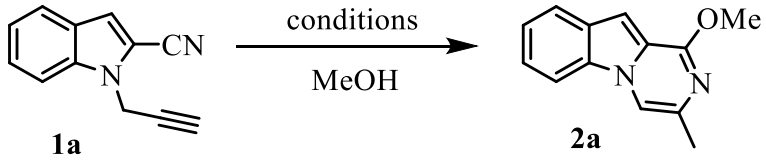
2a

Endo-Double bond aromatic, more stable

Scheme 4

Further reaction optimization we envisaged that using CuI, a well-known catalyst for hydroamination reactions, and Et_3N as a base would facilitate the preparation of desired pyrazino[1,2-*a*]indoles **2a** (Scheme 4). Unfortunately, the reaction was not triggered at rt in methanol and gave a complex mixture upon heating (Table 1, entries 1 and 2). Therefore in

presence of K_2CO_3 with Cu (Table 1, entry 3) failed to obtained desired product. Presuming that copper acetylenide formation may aggravate cyclization, we carried out the reaction without copper salt. Further, in DMSO and K_2CO_3 solution heated at 80°C obtained 40% yield (Table 1, entry 4). To our delight, heating nitrile **1a** in a methanol–DMSO mixture in the presence of Cs_2CO_3 for 18 h afforded **2a** in 50% yield (Table 1, entry 5). The use of DBU raised the yield to 79% (Table 1, entry 6). Performing the reaction in a microwave reactor at 150 °C reduced the reaction time to 30 min and furnished the cyclized product in 80% yield (Table 1, entry 7). The quantity of DBU may be reduced to 5 mol % without a loss in yield (Table 1, entries 8–11). We have also noticed that extended exposure of the product to silica led to its degradation, and silica was first neutralized with ammonia prior for use in column chromatography purifications, giving cyclized product **2a** in 88% yield (Table 1, entry 12). Heating nitrile **1a** in methanol at 150 °C without DBU (Table 1, entry 12) no desired product obtained.



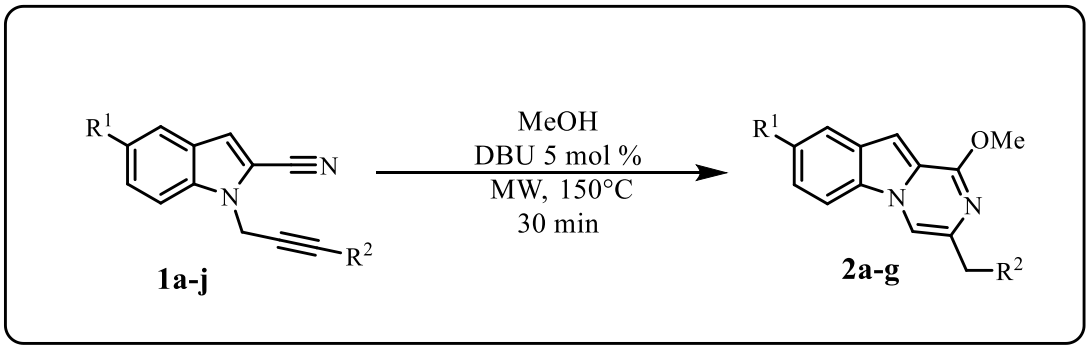
1a **2a**

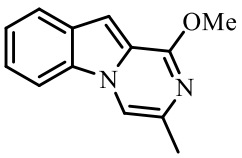
Table.1 Reaction optimization. 1a (0.3 mmol) in MeOH (2 mL).

Entry	**Base**	**Conditions**	**Yields (2a)**
1	Et_3N (1 eq)	CuI (0.1 eq), rt, 40 h	0
2	Et_3N (1 eq)	CuI (0.1 eq), reflux, 18 h	0
3	K_2CO_3 (1 eq)	CuI (0.1 eq), rt, 40 h	0
4	K_2CO_3 (2.eq)	DMF, 80°C, 8 h	40
5	Cs_2CO_3 (2 eq)	DMSO, 80°C, 18 h	50
6	DBU (1 eq)	Reflux, 18 h	79
7	DBU (1 eq)	MW, 150°C, 30 min	80
8	DBU (0.2 eq)	MW, 150°C, 30 min	80
9	DBU (0.1 eq)	MW, 150°C, 30 min	80
10	DBU (0.05 eq)	MW, 150°C, 30 min	80
11	DBU (0.02 eq)	MW, 150°C, 30 min	60
12	**DBU (0.05 eq)**	**MW, 150°C, 30 min**	**88**
13	-	MW, 150°C, 30 min	0

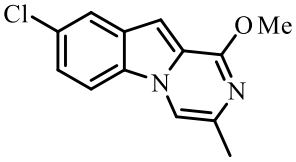
(Yields are given for isolated products after column chromatography. (Table 1, entry 12) reactions were run in microwave reactor Monowave 300 (Anton Paar GmbH) in a closed vial, and the reaction temperature was monitored by an IR sensor and yield obtained after column chromatography on silica that was first neutralized by ammonia.)

3.2.3. Methanol Scope towards substituted N-(propargyl)-1H-indole-2-carbonitriles.

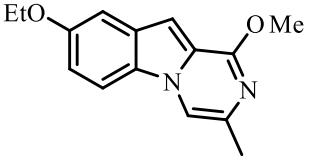




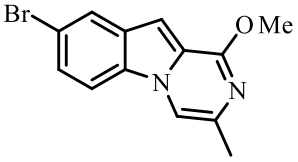
2a (88%)



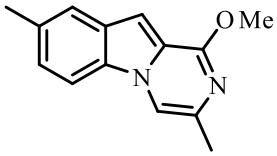
2b (85%)



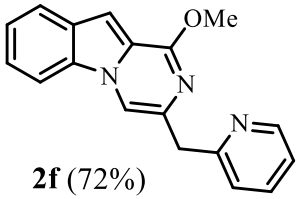
2c (85%)



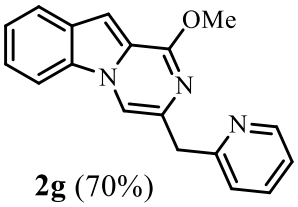
2d (83%)



2e (80%)



2f (72%)

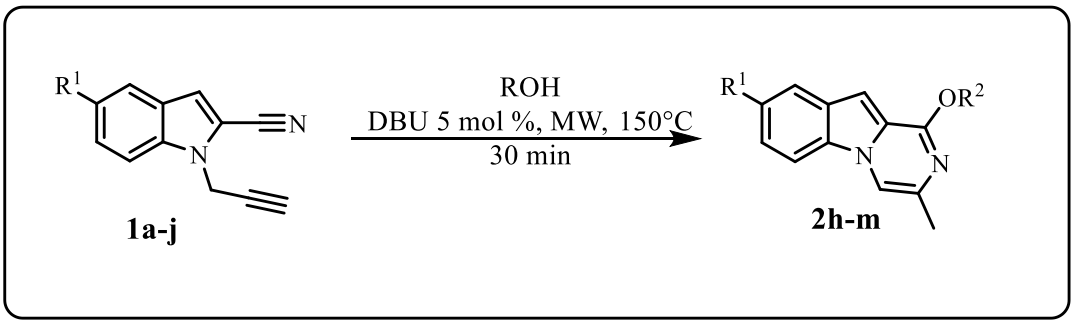


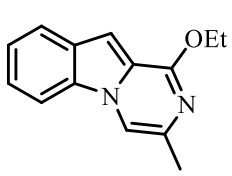
2g (70%)

Scheme 5

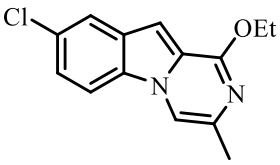
We readily transformed indole-2-carbonitriles **1b**–**e** into 1-methoxypyrazino[1,2-*a*]indoles **2b**–**e** under optimized conditions in very good yields (Scheme 5). The reactions of pyridine-substituted alkynes were also successful, affording corresponding products **2f** and **2g** in 72 and 70% yields.

3.2.4. Different primary alcohols scope towards substituted N-(propargyl)-1H-indole-2-carbonitriles.

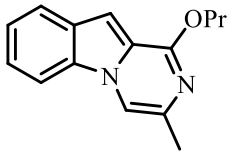




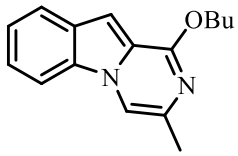
2h (60%)



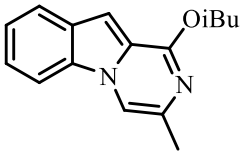
2i (83%)



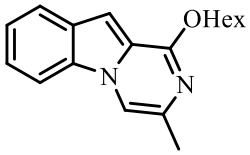
2j (52%)



2k (65%)



2l (78%)



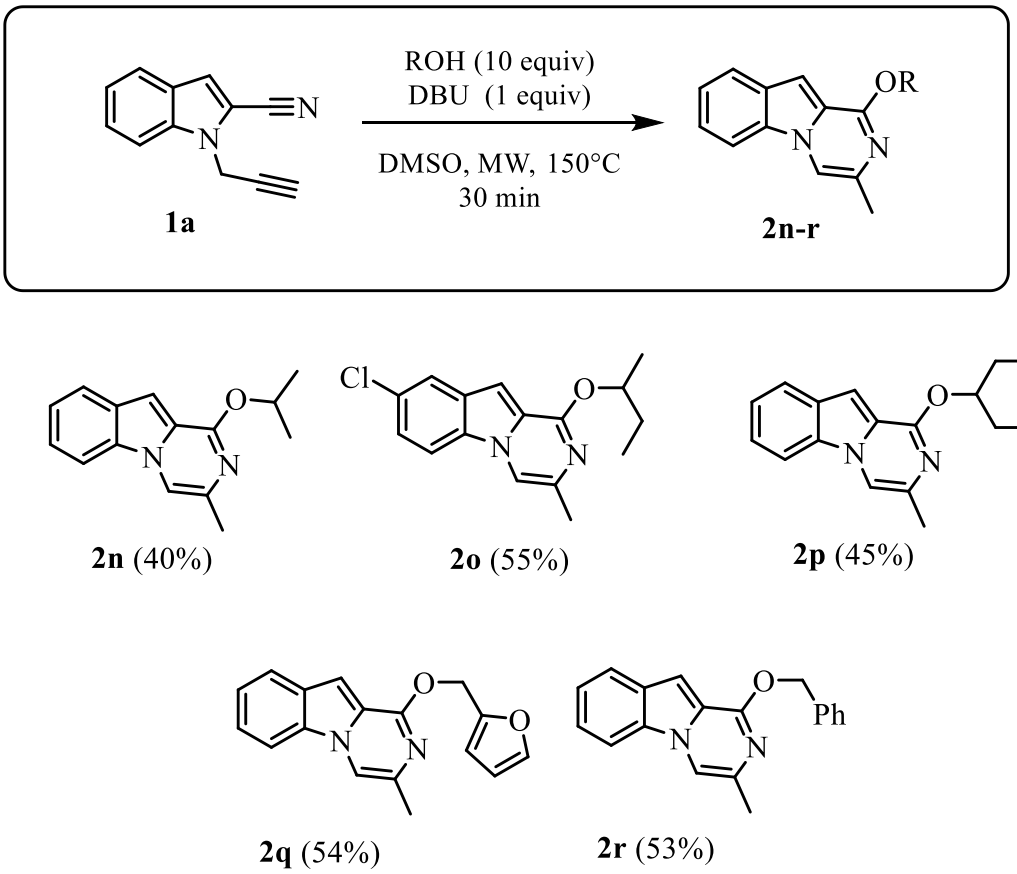
2m (53%)

Scheme 6

To better understand the scope of the reaction, we tested different alcohols. When we performed the reaction in ethanol, propanol, butanol, *iso*-butanol, or hexanol as solvents, we isolated the corresponding alkoxy-substituted **2h**–**m** in good to excellent yields (Scheme 6). Neither secondary *iso*-propanol nor cyclohexanol solvent afforded the intended product.

3.2.5. Secondary and aromatic alcohols scope towards substituted N-(propargyl)-1H-indole-2-carbonitriles.

In an effort to overcome the limitations of alcohol solvents, we performed the reaction in toluene. Heating **1a** with 1 equiv of MeOH and 5 mol % DBU in a microwave reactor at 150 °C for 30 min afforded **2a** in 20% yield.

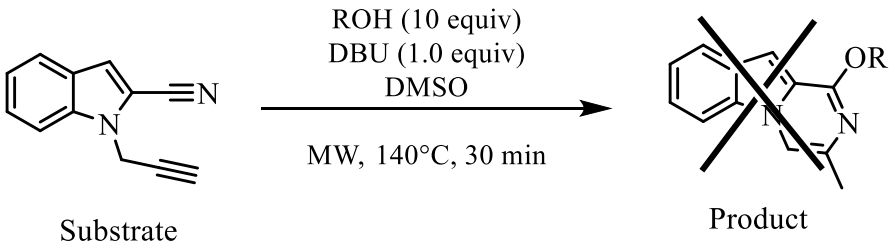


Scheme 7

Gradually increasing the amount of MeOH to 10 equiv and DBU to 1 equiv afforded the desired product in 73% yield, close to that of experiments performed in methanol. The change of the solvent to DMSO increased the yield, giving product **2a** in 80%. To our great satisfaction, analogous reactions were also successful for *iso*-propanol, butanol-2, cyclohexanol, and furfuryl and benzyl alcohols, producing compounds **2n**–**r** in moderate yields.

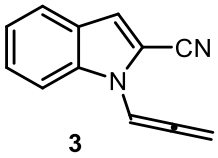
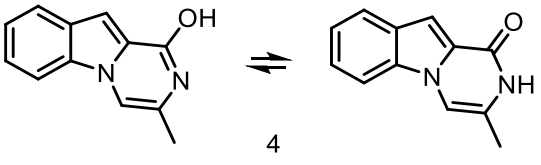
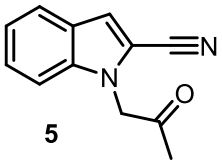
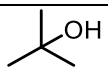
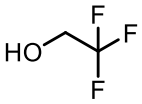
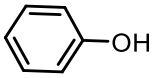
3.2.6. Tertiary alcohols, phenol and trifluoroethanol scope towards substituted N-(propargyl)-1H-indole-2-carbonitriles.

Non-nucleophilic *tert*-butanol, trifluoroethanol and phenol solvents afforded respectively allene **3,** hydrolyzed product **4** and ketone indole derivative **5**. An increase in neither the reaction time nor the temperature led to the desired compounds due to non-nucleophilic character of respective alcohols.



Scheme 8

Table 2. Product formation under treatment of non-nucleophilic Alcohols

Alcohols	**Products**		
R-OH	 **3**	 4	 **5**
	50%	50%	--
	80%	--	--
	20%	30%	20%

We assumed that the reaction of tert-alcohol cannot proceed towards alkyne and nitriles functional group due to the low nucleophilic character of the alcohol. Allene has been interpreted by ^{1}H NMR, peaks signals at δ= **5.85** (2H, d, J = 7.1) and ^{13}CNMR at δ= **203.80**.

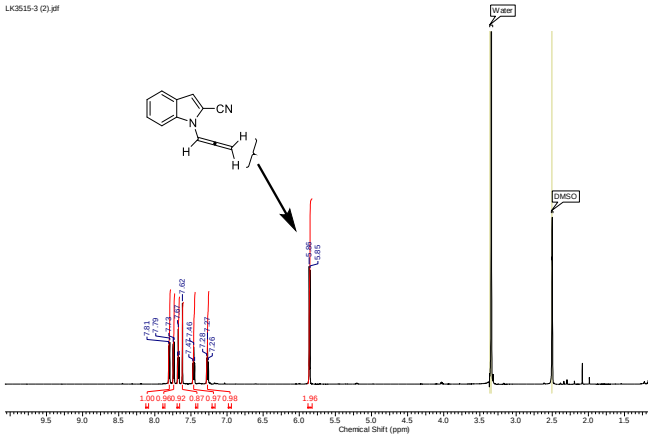


Figure 2. NMR Spectra

3.2.7. Structure determination by X-ray determination.

The structure of compound **2e** was unambiguously determined by a single-crystal X-ray diffraction study (**CCDC 1840160**).

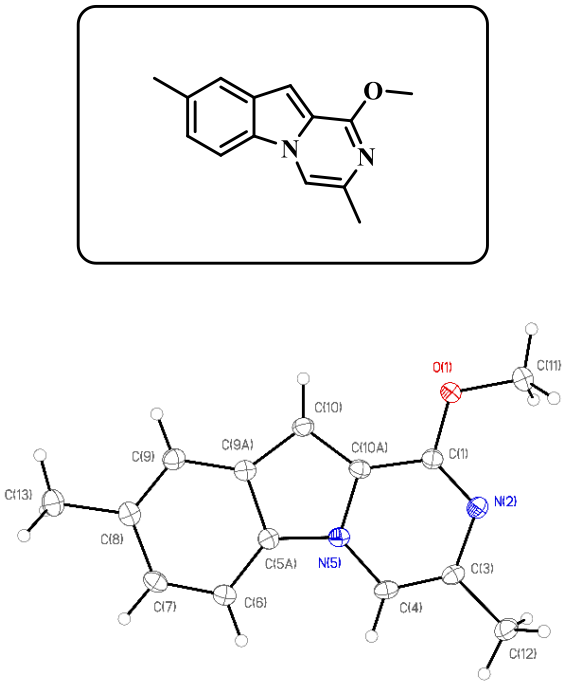
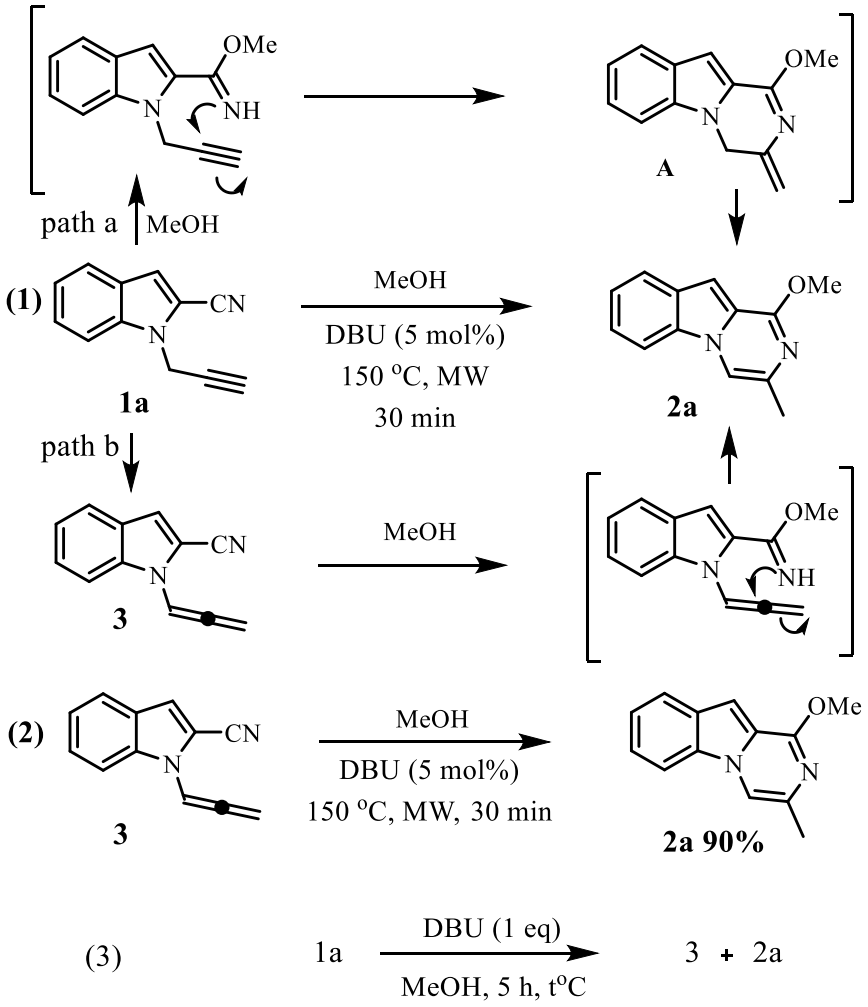


Figure 3. single crystal X-ray structure

3.2.8. Proposed Reaction Mechanism and Control Experiments.

We see two possible mechanistic pathways for the discovered process. First, the reaction may start with the formation of an imidate, which can undergo an intramolecular hydroamination, resulting in ring closure and followed by an aromatization of intermediate **A** to complete the reaction sequence (Scheme 9,eq 1, path a). As far as an allene, **3** was isolated previously, and we presumed another possible pathway to start with an alkyne to allene rearrangement, followed by imidate formation and nucleophilic cyclization (Scheme 9, eq 1, path b). A forementioned **3** was found to be an intermediate of the reaction, as it can be transformed to pyrazino[1,2-*a*]indole **2a** in 90% yield when treated with a nucleophilic alcohol (Scheme 9, eq 2). In an effort to isolate the imidate intermediate, we have performed the reaction between starting indole **1a** and MeOH under different temperatures (Scheme 9 eq 3). No reaction occurred at rt. An analysis of the reaction mixture after 5 h of reflux showed the conversion of **1a** to **2a**, and after 5 h at 40 °C the mixture contained 25% allene **3**. As no imidate intermediate could be noticed, we suggest imidate formation to be the rate-limiting step and assume path b to be more viable. It is also important that, in the absence of DBU, neither allene **3** nor nitrile **1a** afforded the desired cyclic compound.



Scheme 9

Table 3. Yield determination 1a,3,2a

t°C	1a	3	2a
20°C	99%	0%	0%
40°C	30%	25%	30%
60°C	25%	0%	60%

(Proposed Reaction Mechanism and Control Experiments reactions were run on a 0.5 mmol scale in MeOH (2 mL). reactions were carried out under microwave irradiation in a closed vial, and the reaction temperature was monitored by an IR sensor as shown in the scheme 9. Isolated yields as shown in the Table 3)

3.3 Chemical properties of C-Nucleophiles towards *N*-(Propargyl)-*1H*-indole-2-carbonitriles.

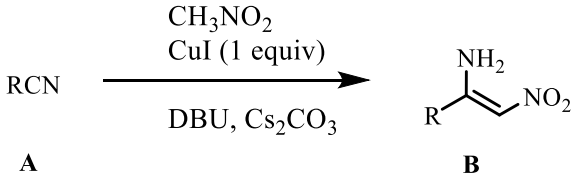
3.3.1. Alkyne-enamine cyclization.

According to the previous scheme of *O*-nucleophiles study, we switch to work on *C*-nucleophile's chemical properties towards *N*-(propargyl)-1*H*-indole-2-carbonitriles. previous study we conclude that *O*-nucleophile reactivity towards substrate cyclization affords pyrazinoindole. Throughout investigation of literature surveys we found that the reaction between

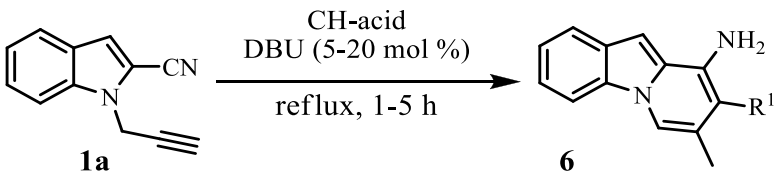
nitriles and C-nucleophiles can offer an appealing alternative for the preparation of various enamines, especially valuable for annulated heterocycle synthesis.

The development of novel methodologies towards the preparation of pyrido[1,2-*a*]indole systems is a needful task, recently attracting extensive attention from scientists. Recent examples of the pyrido[1,2-*a*]indole syntheses through the construction of a pyrrole ring include aza-Nazarov-type rearrangement of aryl(dipyrid-2-yl)methanols,[82-84] 1,2,4-triazine transformations in the presence of aryne precursors,[85-87] Pd-catalyzed cyclization of *o*-picolyl bromides,[88] and In-catalyzed recyclization of triazolopyridines.[89] The preparation of pyrido[1,2-*a*]indoles via pyridine ring closure has been reported to be conducted via transition metal-catalyzed annulations of dienes and alkynes with indoles, [90–92] and ring-closing metathesis reactions. [93] Elegant approaches for the simultaneous construction of both cycles have also been recently reported: either through azepine ring-contraction, [94] or through a multicomponent reaction of electron-deficient alkynes with enamines. [95] Still, general and efficient methods for the synthesis of 9-aminopyrido[1,2-*a*]indoles have not been reported to date. The reaction between nitriles and C-nucleophiles can offer an appealing alternative for the preparation of various enamines,[96–99] especially valuable for heterocyclic synthesis.[100-101].

Yoshimatsu and co-workers recently developed an efficient copper-mediated aza-Henry reaction on nitriles, leading to the formation of push–pull enamines (Scheme 10 eqn (1)) [102]. This reaction caught our attention and prompted us to conduct a domino sequence of Aza-Henry reaction, followed by cyclization. Previously employed *N*-propargylindole-2-carbonitriles **1a** [103] seemed to be perfect substrates for the formation of pyrido[1,2-*a*]indoles. Herein, we report a domino reaction of CH-acids with alkynylnitriles as a route towards 9-aminopyrido[1,2-*a*]indoles **6** with remarkable optical properties (Scheme 10, eqn (2)) While this experiments were under progress, a paper by Verma and co-workers was published [104]. Their work employs stoichiometric KOH for nitromethane-induced nitrile–alkyne cyclization, giving naphtylamines.



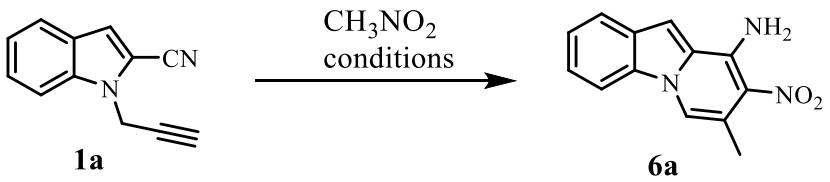
Scheme 10 equation (1)



Scheme 10 equation (2)

3.3.2. Aza-Henry reaction on nitriles to archives pyrido[1,2-a]indole

Under aza-Henry reaction conditions, developed by Yoshimatsu, *N*-propargylindole-2-carbonitrile **1a** was smoothly converted into the corresponding pyrido[1,2-*a*]indole **6a** in 82% yield (Table 4 , entry 1). It turned out that the amount of CuI could be reduced to 10 mol% and product **6a** was isolated with 89% yield (Table 4 , entry 2). Surprisingly, the reaction without copper and with stoichiometric amounts of Cs_2CO_3 and DBU furnished the target product in an excellent 92% yield (Table 4 , entry 3). The use of DBU solely led to the isolation of the desired pyrido[1,2-*a*]indole with 93% yield, while full conversion was achieved in 30 min (Table 4 , entry 4). To our delight, the reaction could be successfully performed with catalytic loadings of DBU as low as 5 mol% (Table 4 , entries 5 and 6). Without the addition of DBU, no conversion was observed (Table 4 , entry 7). The use of other nitrogen bases including TEA or DIPEA was less efficient (Table 4 , entries 8 and 9) an well as K_2CO_3 and DBU in presence CuI affords 45% (Table 4, entry 10) , KOH and NaOH in DMSO was unsuccessful (Table 4, entry 11)



Scheme 11

Table 4. Optimization of aza-Henry/cyclization reaction.

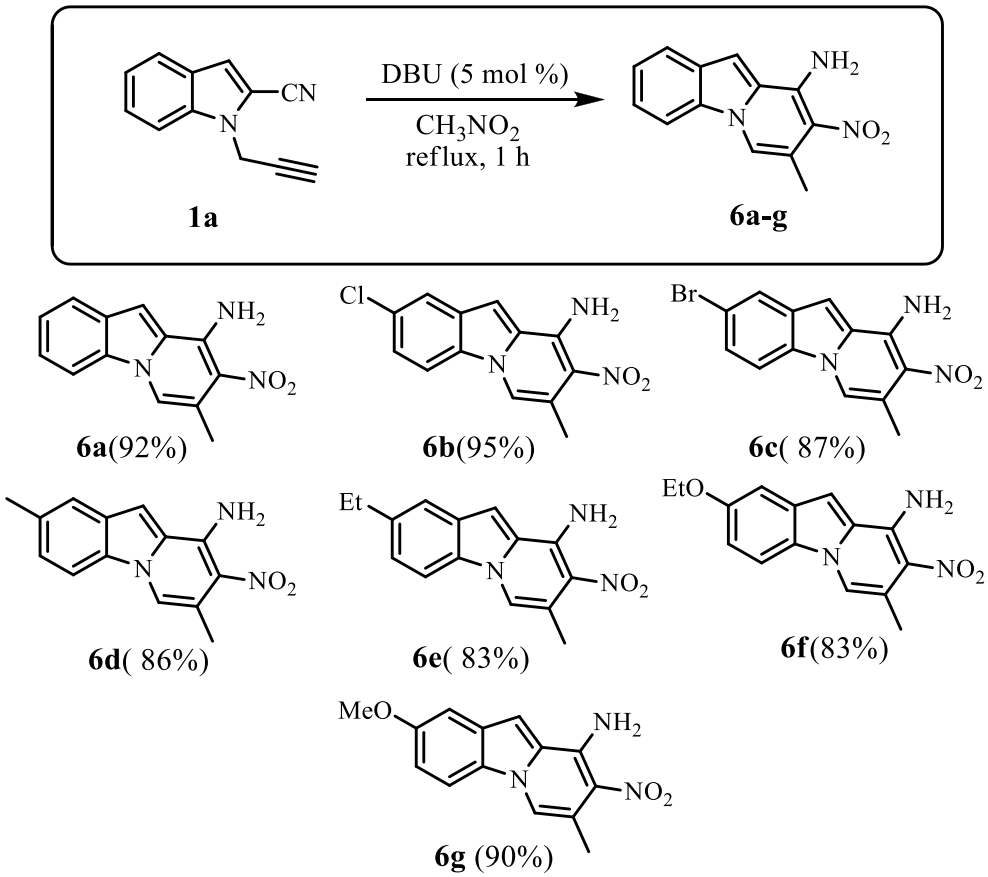
Entry	**Reaction Conditions**	**Yields**
1	CuI (1 equiv), Cs_2CO_3 (1 equiv), DBU (1 equiv), reflux, 3 h	82
2	CuI (10 mol %), Cs_2CO_3 (1 equiv), CuI (10 mol %),	89
3	Cs_2CO_3 (1 equiv), DBU (1 equiv), reflux, 1 h	92
4	DBU (1 equiv), reflux, 30 min	93
5	DBU (20 mol %), reflux, 40 min	92
6	DBU (5 mol %), reflux, 1 h	92
7	no base, reflux, 1 h	0
8	TEA (5 mol %), reflux, 8 h	25
9	DIPEA (5 mol %), reflux, 8 h	33
10	K_2CO_3 (1.5 equiv), DBU (1 equiv), CuI (10 mol %),	45

11	KOH/ NaOH (1.5 equiv), DMSO, rt, 5 h	0

*(Table 4, General conditions: indole **1a** (0.55 mmol) and additives were heated under reflux in CH_3NO_2. Yields after column chromatography)*

3.3.3. Scope of various substituted indoles under aza-Henry/cyclization through domino sequence.

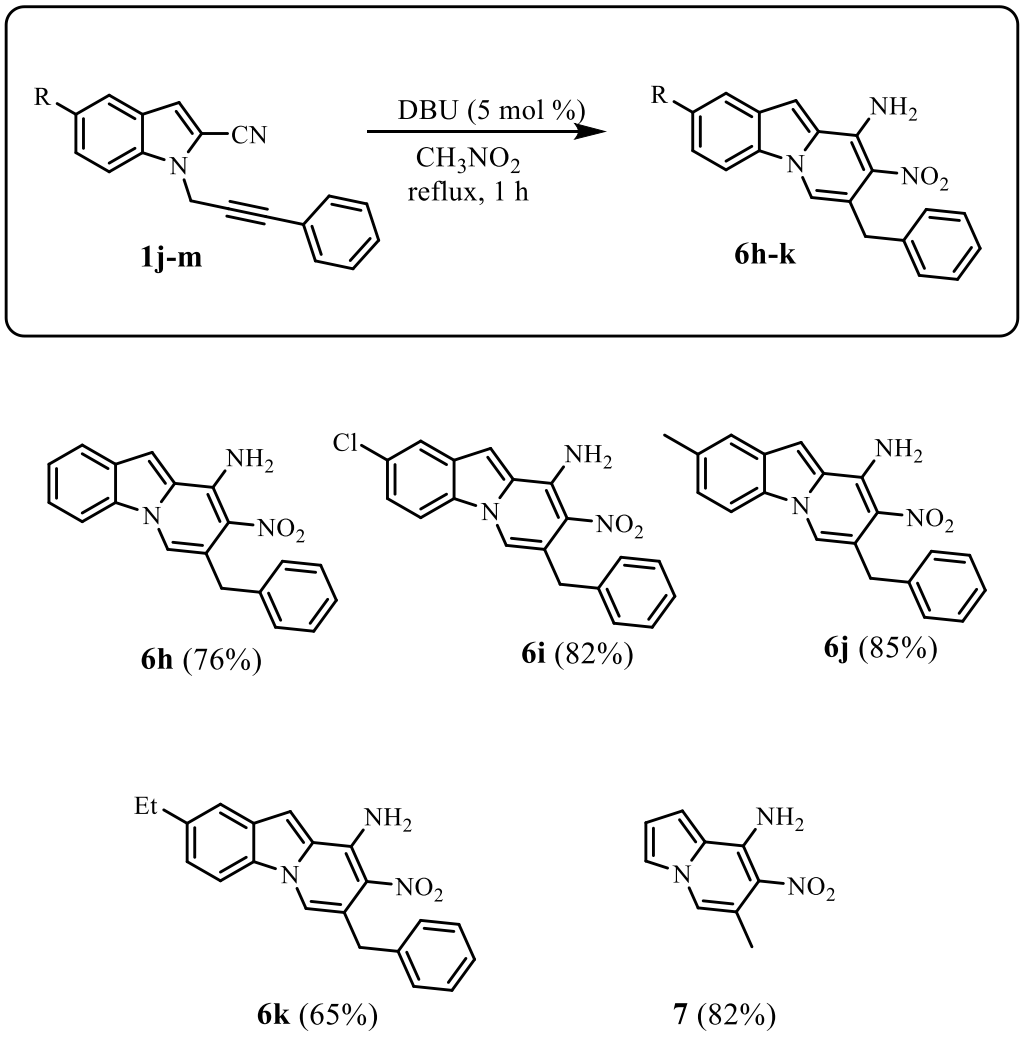
It is worth noting that the resulting pyridoindoles **6a**, containing amino and nitro groups, were found to have high water solubility. Hence, the extraction step should be performed with care, otherwise severe product loss could be observed. Luckily, under copper-free conditions, water treatment-extraction could be avoided, and the reaction mixture could be directly subjected to chromatography, resulting in product **6a** in excellent yield. Optimized conditions were used to evaluate the scope of the aza-Henry/cyclization domino sequence. Chloro-, bromo-, methyl-, ethyl-, ethoxy-, and methoxy-substituted indoles could be successfully converted into the corresponding pyrido[1,2-*a*]indoles **6b**–**g** in very good to excellent 83–95% yields (Scheme 12 *N*-(Propargyl)indole-2-carbonitrile reaction with nitromethane. General conditions: indole **1a** (0.55 mmol) and DBU (0.0275 mmol) were heated under reflux in CH_3NO_2 (2 mL) for 1 h (TLC tracking). Products were isolated by column chromatography.



Scheme 12

3.3.4. Scope of the various internal alkyne substituted indoles with nitromethane.

In this case, slightly reduced yields of products **6h**–**k** were obtained. The reaction of *N*-(propargyl)pyrrole-2-carbonitrile with nitromethane under standard conditions furnished indolizine **7** with 82% yield, verifying the methodology for different heterocyclic scaffolds (Scheme 13).

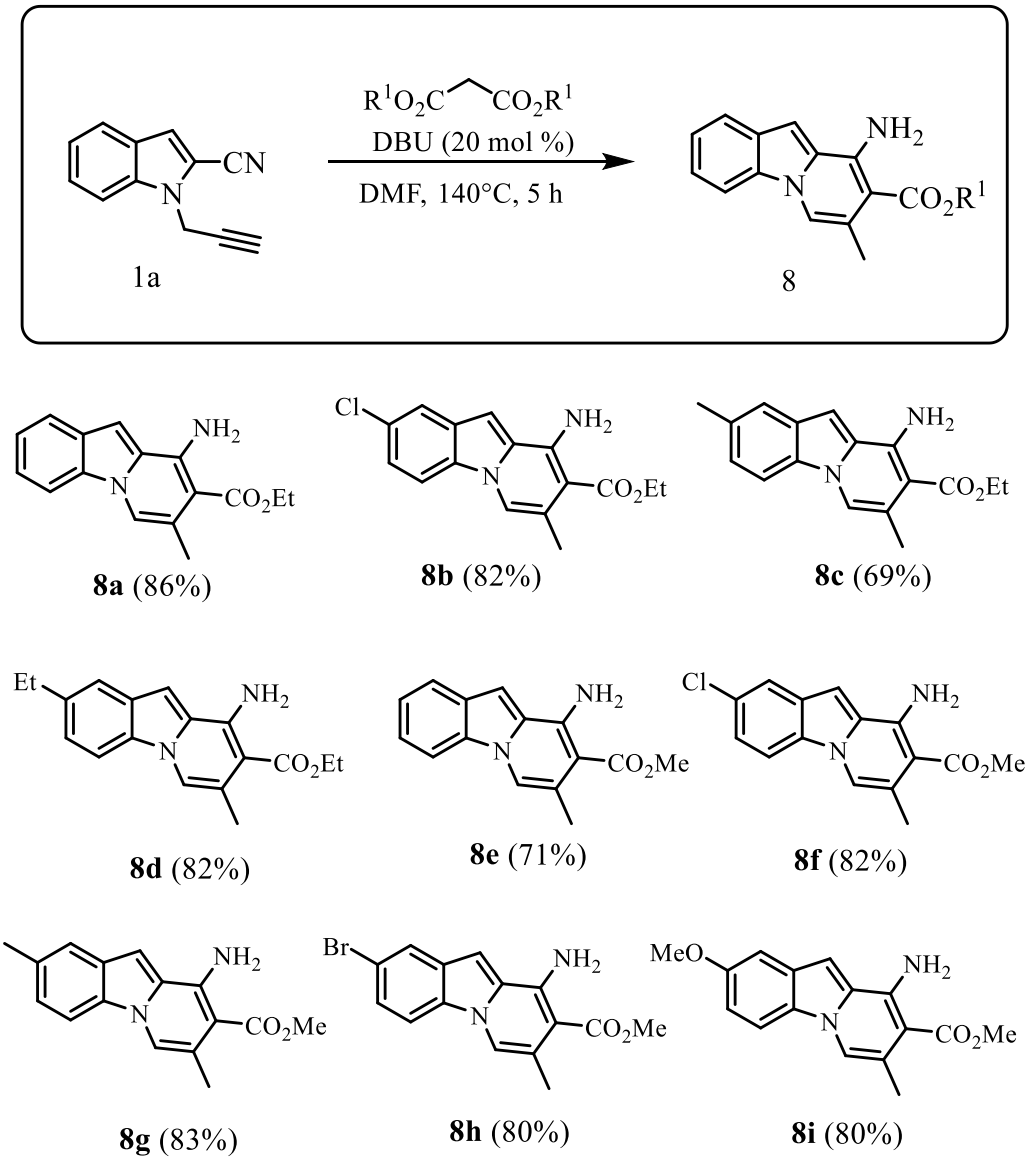


Scheme 13

3.3.5. Scope of C-H acids towards N-(Propargyl)indole-2-carbonitrile under Aza-Knoevenagel/cyclization domino sequence.

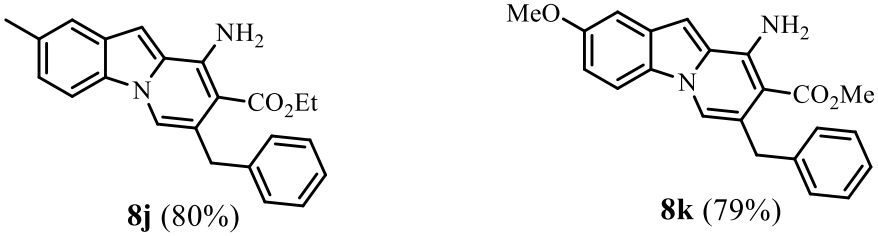
To better understand the limitations and scope of the proposed methodology, the use of other CH-acids was investigated. Firstly, the reaction with diethyl malonate was performed. Though the desired product **8a** of aza Knoevenagel/cyclization/decarboxylation could be isolated under standard conditions with malonate being used as a solvent, the workup was tedious and required certain modifications. Product **8a** was obtained in 86% yield after the reaction of the starting indole **1a** and diethylmalonate (10 equiv) in DMF in the presence of DBU (20 mol%)

(Scheme 14). Accordingly, products **8b**–**d** from the correspondingly substituted chloro, methyl, and ethyl indoles were isolated with 69–82% yields. Dimethyl malonate could also be employed, and products **8e**–**i** could also be prepared in 71–83% yields.



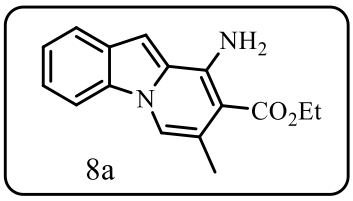
Scheme 14

Internal alkynes with a phenyl group (Scheme 15) delivered the corresponding products with 80 and 79% yields.



Scheme 15

The structure of compound **8a** was unambiguously determined by single crystal X-ray diffraction study.



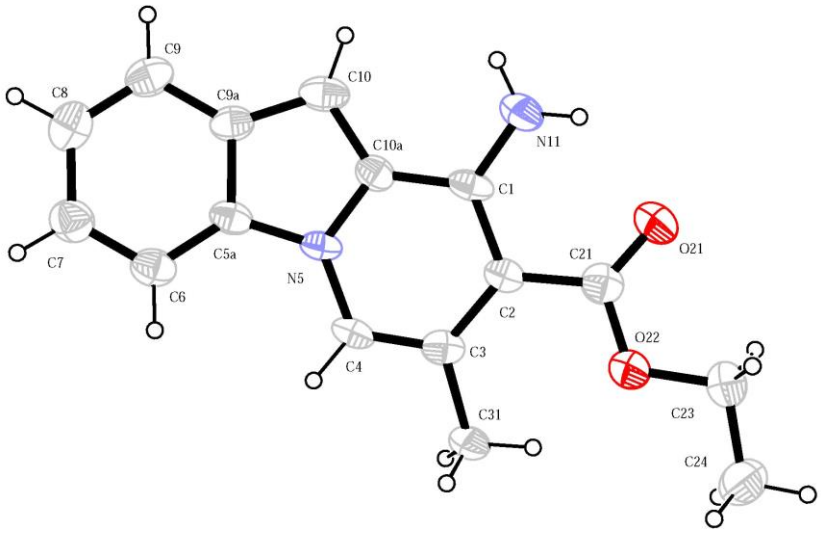
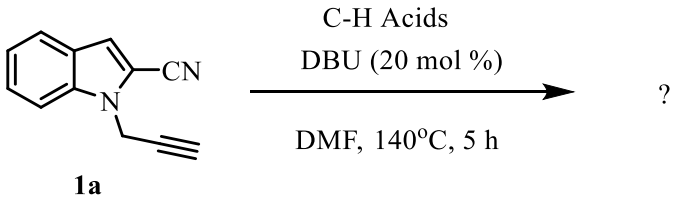


Figure 4. X-ray structure (for details, see CCDC #1966123).

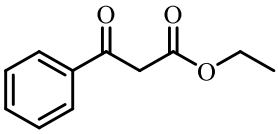
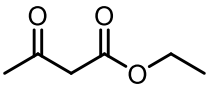
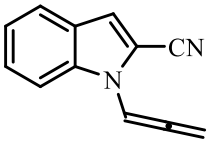
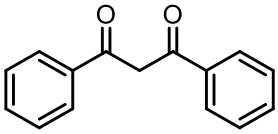
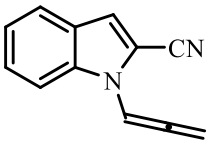
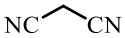
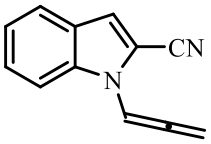
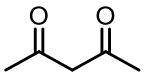
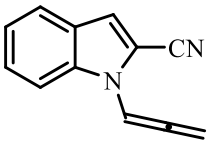
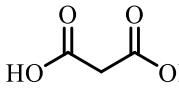
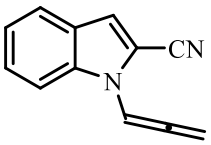
3.3.6. Scope of different C-H acids towards N-(Propargyl)indole-2-carbonitrile.

Interestingly, when the unsymmetrical CH-acid benzoylacetate was employed, ethyl carboxylate **8a** was isolated (63% yield). Complex mixtures were formed when acetylacetone, dibenzoylmethane, malononitriles or acetophenone was employed.



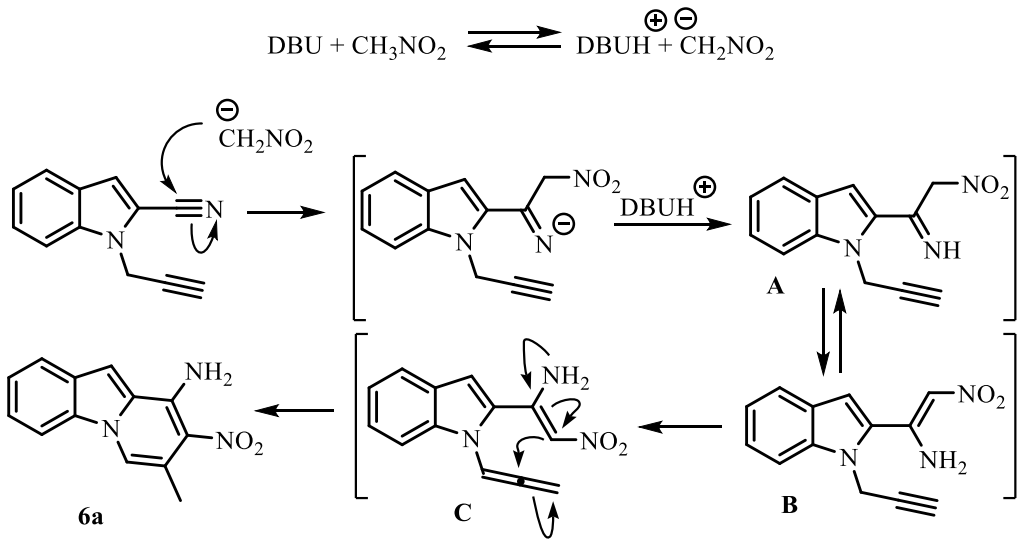
1a

Table 5. Unreacted C-H acids towards *N*-(Propargyl)indole-2-carbonitrile

C-H Acids	Results	Side Product
	**8a**	--
	No desired Product	
	No desired Product	
	No desired Product	
	No desired Product	
	No desired Product	

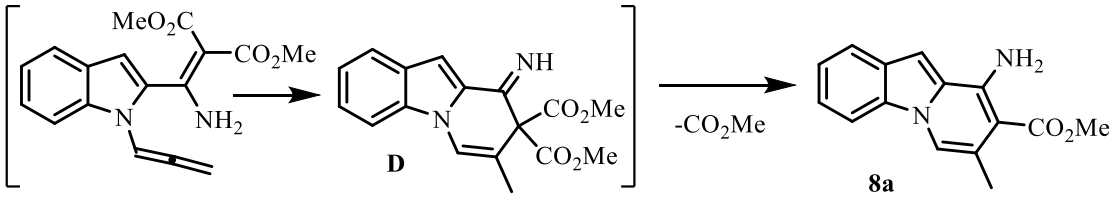
3.3.7. Proposed reaction pathway

According to our previous experience with *N*-(propargyl)indol-2-carbonitriles **1a**, a plausible reaction mechanism for the transformation is proposed (Scheme 16). Firstly, the CH-acid, deprotonated by DBU, attacks the nitrile, giving imine **A**, which tautomerizes to a more stable push–pull enamine **B**. This enamine can undergo a DBU-catalyzed alkyne–allene rearrangement to provide allene **C**. An intramolecular nucleophilic attack of the enamine on the *β*-carbon of the allene gives a cyclic compound, which is readily aromatized by tautomerization.



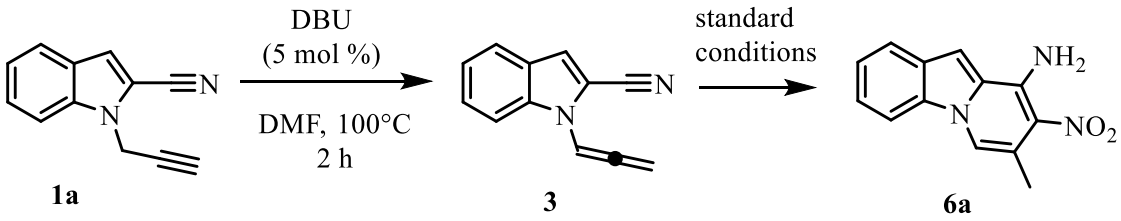
Scheme 16

When the malonates are used as CH-acids, the aromatization of intermediate **D** is reached via decarboxylation (Scheme 17).



Scheme 17

N-Allenylindole **3** was previously shown to be formed under heating in the presence of DBU. The viability of the proposed pathway was proven by the conversion of allene **3** into the target product **6a** under standard conditions (Scheme 18).



Scheme 18

3.3.8. Optical properties study.

The resulting compounds were found to exhibit important optical properties. To better understand the potential of the pyrido[1,2-*a*]indole system for the field of organic electronics, absorbance and emission spectra of selected compounds **6b, (8a**, **b**, **e**, **f**, **j)**were obtained. Nitro-

substituted pyrido[1,2-*a*]indole exhibited two absorption maxima – at 338 nm and 485 nm, while the maxima of carboxylates **8** lay in the 409–415 nm region (Fig. 4).

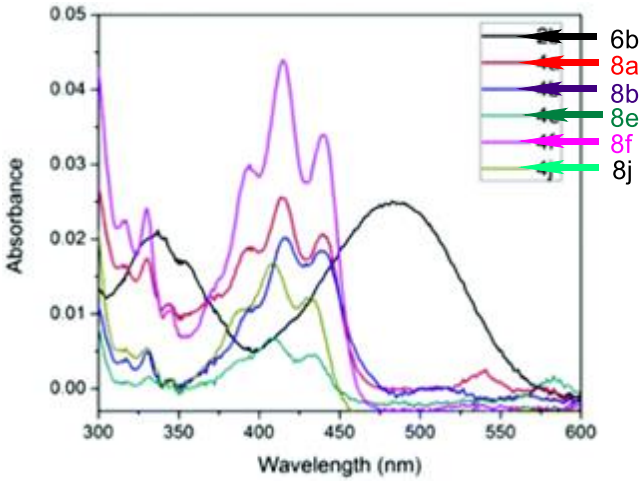


Figure 5. The absorption spectra of the synthesized compounds in EtOH.

Emission spectra also showed great distinction between the nitro-substituted compound **6b** and carboxylates **6**. Emission maxima of **6b** at 438 and 672 nm were found to be of low intensity. In turn, carboxylates **8a**, **b**, **e**, **f**, and **j** exhibited fluorescence with high quantum yields of up to 63% and the emission bands were located in the region of 475–490 nm (Figure 5). The photophysical properties of the compounds **6b**, **8a**, **b**, **e**, **f**, and **j** are summarized in (Figure 6).

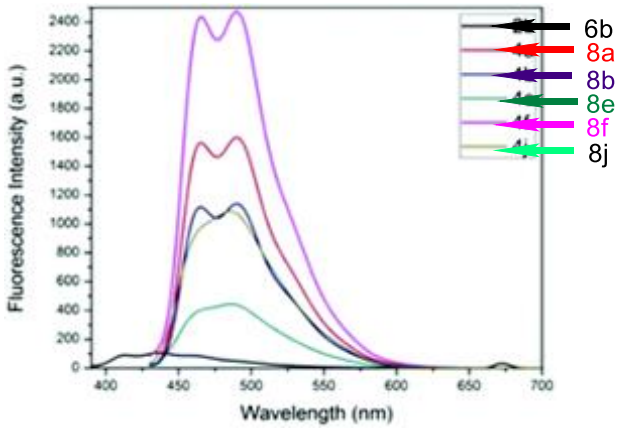


Figure 6. Photophysical properties of the synthesized compounds in EtOH

In conclusion, a novel transition metal-free protocol for the synthesis of valuable pyrido[1,2-*a*]indoles was developed. The reaction starts with a DBU-catalyzed addition of a CH-acid to nitrile to generate a reactive push–pull enamine, prone to intramolecular cyclization. To the best of our knowledge, these are the first examples of organocatalyzed aza-Henry and aza-Knoevenagel reactions on nitriles. The resulting compounds exhibit interesting optical properties with 9-amino-8-nitropyrido[1,2-*a*]indoles **6** being dyes, and 9-aminopyrido[1,2-*a*]indole-8-carboxylates **8** being fluorescent dyes.

Table 6. Photophysical properties of the synthesized compounds in EtOH.

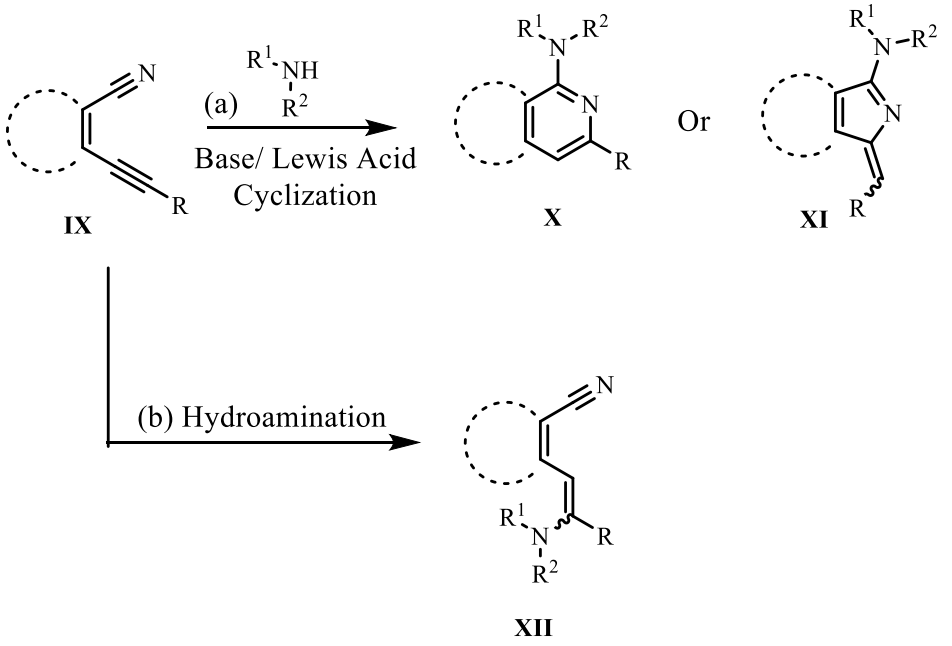
Compound	Abs[a] [nm]	ε^b [(M cm)$^{-1}$ (10^7)]	Em[a]	QY	Stokes shift
6b	338, 485	6.76, 9.70	438	6	6754, 5581
8a	413	8.26	490	51	3804
8b	415	8.30	489	47	3646
8e	409	8.18	486	45	3873
8f	415	8.30	475	63	3043
8j	408	8.16	486	57	3933

[a] Peak maximum. [b] Molar extinction coefficient.

3.4. Chemical properties of *N*-Nucleophiles towards *N*-(Propargyl)-*1H*-indole-2-carbonitriles.

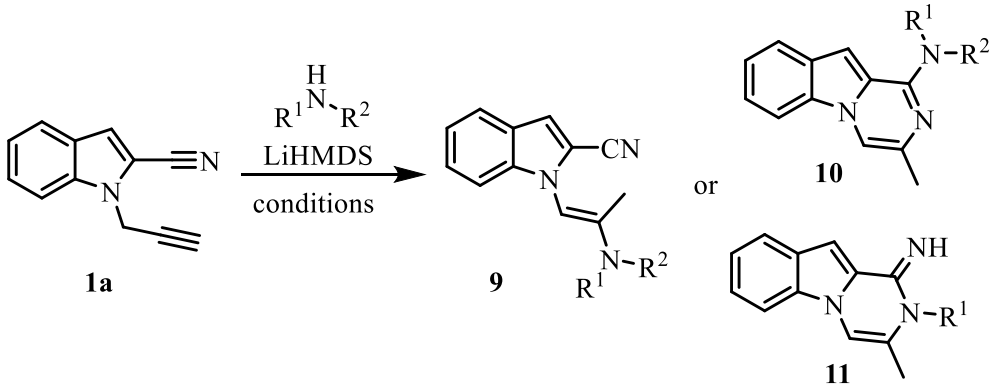
3.4.1. Amidine- alkyne cyclization / Alkyne-Hydroamination Cyclization.

As per our investigation of *O*- and *C*- Nucleophile we focused on the *N*-Nucleophile reaction towards *N*-(propargyl)indole-2-carbonitrile under base or Lewis acids. Transformations of the same material into various compounds, depending on the conditions, catalyst, etc., are known as chemodivergent reactions and have emerged as an attractive way for achieving chemical diversity. [105] Alkynyl nitriles might become valuable compounds for developing chemodivergent processes, but the chemoselectivity remains uncontrollable in most cases. When nitrogen nucleophiles are involved, the reactions usually start with the nucleophilic addition to a nitrile group, while the carbon−carbon triple (Scheme 19 (a)) bond reacts subsequently [106−111]. Separately, the hydroamination of alkynes is a well-established process [112], as well as amidine formation from nitriles [113], but in the case of alkynyl nitriles, only few examples allowing reactivity switch is known (Scheme 19 (b)) [114,115].



Scheme 19 (a-b)

Moreover, to the best of our knowledge, the condition-dependent switch between amine addition to nitrile or to alkyne is yet unknown (Scheme 20).

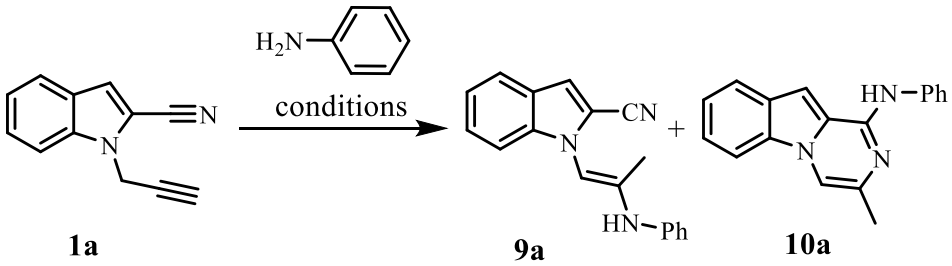


Scheme 20

We report the chemoselective reactions of nitrogen nucleophiles with *N*-(propargyl)indole-2-carbonitriles. Promoted by lithium hexamethyldisilazane (LiHMDS), the reactions are condition- and additive-controlled, leading to the selective formation of three interesting compound classes, which can be obtained from the same starting material. It was found that LiHMDS-promoted reactions lead to the mixture of two product types, originating from an initial attack onto CC or CN triple bonds. Performing the reaction at reduced temperature and in the presence of catalytic amounts of LiHMDS, delivered alkyne hydroamination products exclusively. On the contrary, one-pot reaction of *N*-(propargyl)indole-2-carbonitriles with methanol and LiHMDS on heating, followed by addition of nitrogen nucleophile, allowed a selective domino cyclization sequence towards 1-aminopyrazino[1,2-*a*]indoles. Anilines and nitrogen heterocycles

could be employed as nucleophiles to obtain products of both types. Moreover, an alternative one-pot route towards third product type has been developed. When *N*-(propargyl)indole-2-carbonitrile was firstly combined with aniline and LiHMDS at reduced temperature, further heating of the *in situ* generated hydroamination product led to the intramolecular cyclization into 1-imino-2-phenylpyrazino[1,2-*a*]indoles. Thus, chemodivergent transformations of the same starting material into three compound classes were investigated. The possible reaction routes were studied, and *N*-(allenyl)indole-2-carbonitrile was identified as a key intermediate. Acyclic and cyclic products are exhibiting fluorescence emission in blue to green range.

3.4.2. Study of N-(propargyl)indole-2-carbonitrile interaction with aniline.



Scheme 21 (Optimization)

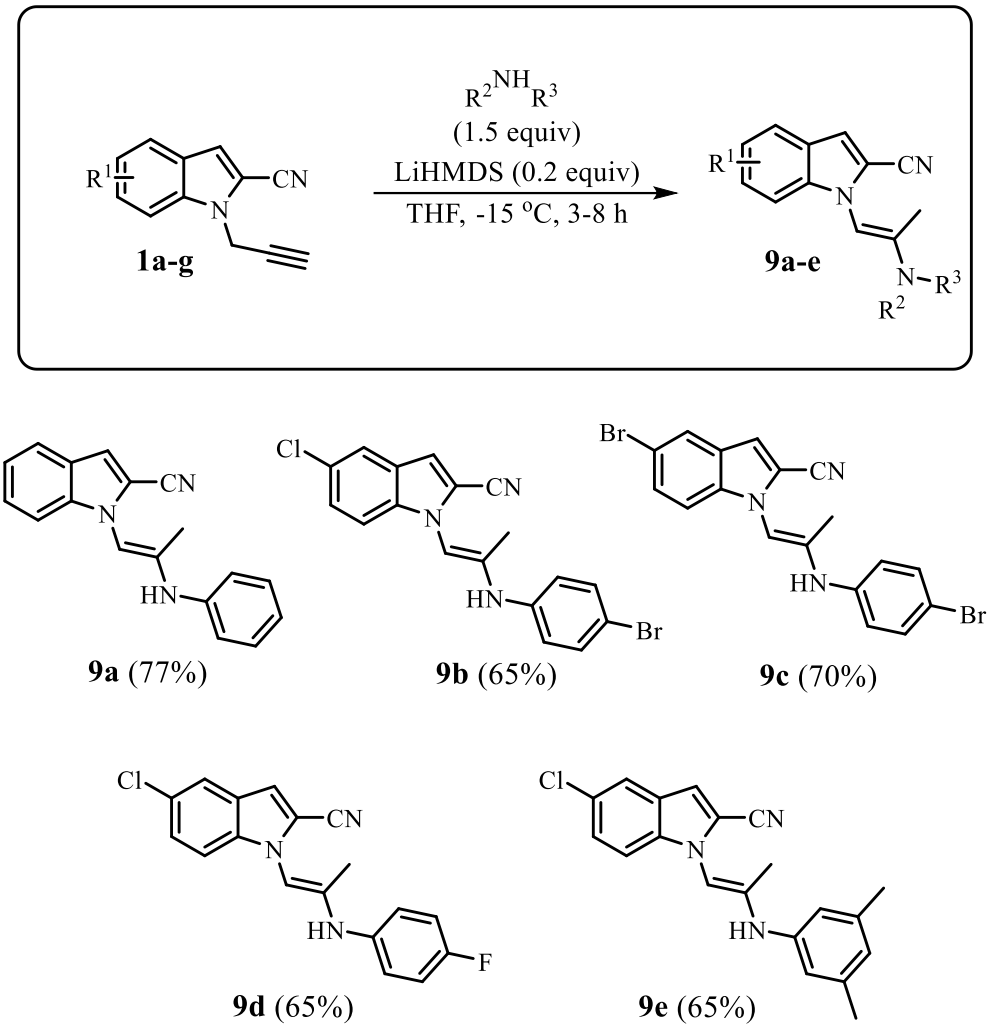
Table 7. Reaction optimization of aniline towards aromatic amine.

Entry	**Conditions**	**Yield 2a,**	**Yield 3a**
1	LiHMDS (2 equiv), THF, rt, 30 min	50	6
2	LiHMDS (2 equiv), THF, reflux, 30 min	50	15
3	LiHMDS (2 equiv), THF, 0^{o}C, 4 h	55	2
4	LiHMDS (2 equiv), THF, -15^{o}C, 24 h	77	0
5	LiHMDS (0.2 equiv), THF, -15^{o}C, 24 h	77	0
6	MeOH (2 equiv), LiHMDS (2.5 equiv), THF, reflux, 6 h	35	15
7	1) MeOH (2 equiv), LiHMDS (2.5 equiv), THF, 5 min 2) $PhNH_2$ (2.5 equiv), reflux, 6 h	35	82
8	No base, reflux in DMF, THF or neat	0	0
9	DBU, reflux in DMF.	0	0
10	*t*-BuOK, dry THF, rt to reflux, 8h	0	0
11	Cs_2CO_3, dry THF, rt. 6 h	0	0
12	K2CO3, dry THF, reflux, 8 h.	0	0

*(General conditions: N-(propargyl)indole-2-carbonitrile **1a** (0.32 mmol) was added to a stirred solution of aniline (0.49 mmol) and LiHMDS in THF under argon atmosphere. The reaction mixture was stirred at specified temperature and for specified time. Yields after column chromatography)*

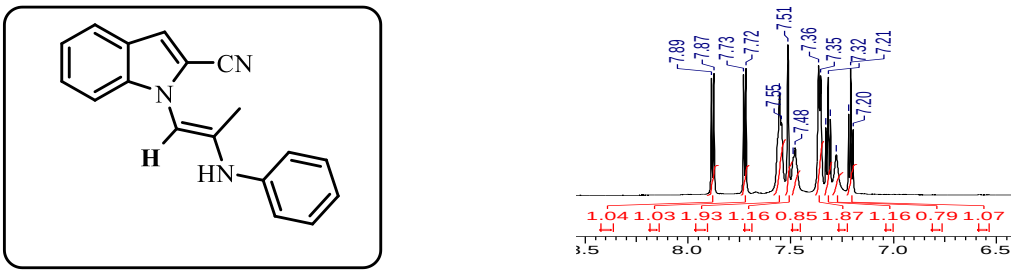
As far as hexamethyldisilazane lithium salt is known to promote amine addition to nitriles to form amidines [116], thus, we initiated our study with the employment of this base. Surprisingly, after treating the mixture of *N*-(propargyl)indole-2-carbonitrile **1a** and aniline with LiHMDS solution (2 equiv.) in THF at rt, we isolated an alkyne hydroamination product **9a** with 50% yield, while a cyclized pyrazino[1,2-*a*]indole **10a** was isolated with tenuous 6% yield (Table 7, Entry 1). Performing the reaction at reflux increased the yield of the cyclized product **10a** to 15% yield (Table 7, Entry 2). When the reaction was performed at reduced temperature, hydroamination product **9a** could be isolated with 65% yield (Table 7, Entry 3). At -15^{o}C, hydroamination became an exclusive process, and the corresponding product **9a** was obtained chemoselectively with a good 77% yield (Table 7, Entry 4). Fortunately, the same yield could be achieved carrying out the reaction with catalytic amounts of LiHMDS (0.2 equiv.) (Table 7, Entry 5). Our further endeavors focused on obtaining the cyclization product **10a**. Tan, Wang and co-workers [117] developed an elegant HMDS metal salt-catalyzed nucleophilic substitution of methoxy group in aromatic substrates with amines. We have previously developed an efficient synthesis of alkoxypyrazino[1,2-*a*]indoles by treatment of *N*-(propargyl)indole-2-carbonitriles with alcohols. [118] In that case, the nucleophilic addition to a CN moiety was exclusive, we did not witness any alkoxide addition to a CC triple bond. Moreover, the methoxy derivative was obtained with excellent 92% yield. We further presumed that the desired amine-containing pyrazino[1,2-*a*]indole **10a** could be obtained by nucleophilic substitution of a methoxy group. Indeed, addition of methanol to a reaction mixture formidably increased the yield of **10a** to 55% (Table 7, Entry 6). The sequential addition of the reagents to firstly generate the methoxy derivative solved the issue, and the target cyclized product **10a** was selectively obtained with 82% yield (Table 7, Entry 7). It needs noting, that when DBU, *t*-BuOK, K_2CO_3 as well as Cs_2CO_3 were used as a base, or no base was used at all, neither hydroamination, or cyclization reactions started (Table 7, Entry 8-12).

3.4.3. LiHMDS-catalyzed hydroamination of N-(propargyl)indole-2 carbonitriles with Nitrogen nucleophiles (aromatic amine).



Scheme 22

With the optimized conditions in hand, we firstly set up for scope studies of hydroamination reaction. We were pleased to find that anilines, bearing bromo, fluoro or methyl groups gave corresponding products **9a-e** with 65-77% yields (Scheme 22). In the isolation process we had several problems due to less stability of desired product. We have developed chromatography with neutral silica with flash chromatographic techniques. Due to long period of time exposure of compounds leads to convert into polymerization or some brown sticky materials. During scope study with O-trifluoromethyl aniline we have obtained undesired compounds, as per NMR analysis. as well as we thoroughly monitored TLC in the polar eluent system. according to ^{1}H NMR we found vinyl proton at **9a** (^{1}H NMR = ***7.51 ppm***) figure.6.



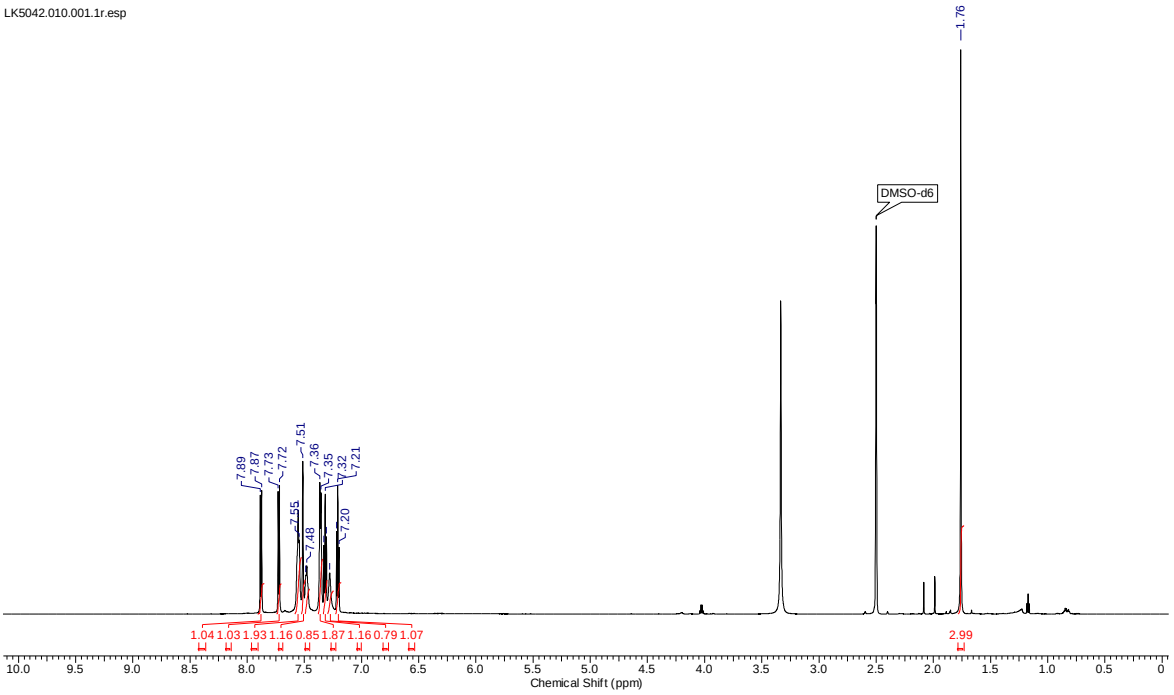
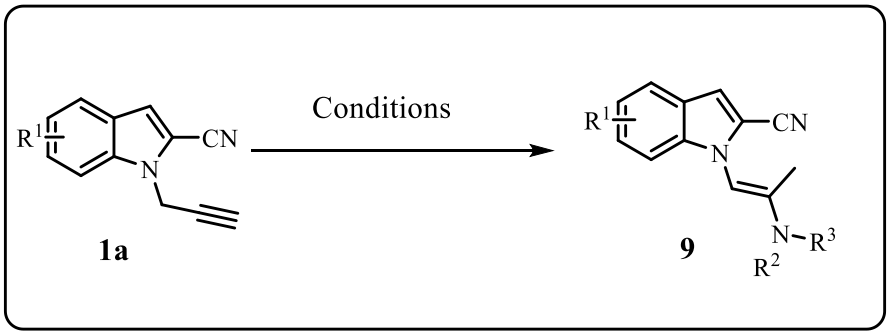


Figure 7. NMR data

3.4.4. LiHMDS-catalyzed hydroamination of N-(propargyl)indole-2 carbonitriles with Nitrogen nucleophiles (Nitrogen containing heterocycles).



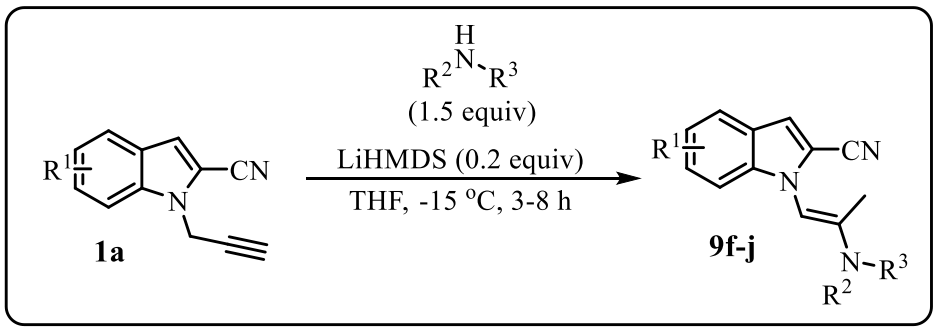
Scheme 23

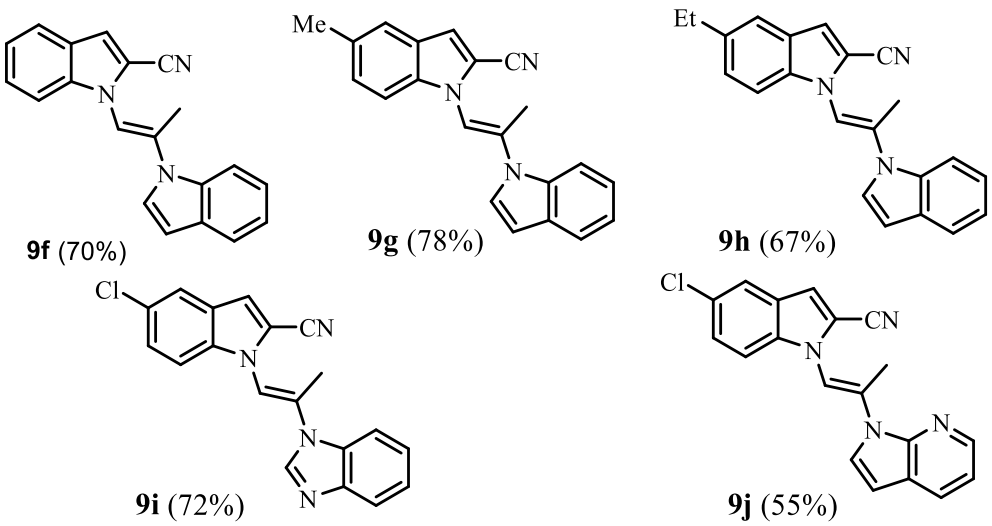
Table 8. reaction Optimization.

Entry	Conditions	Yields
1	K_2CO_3,(2.5 equiv), dry THF, rt, 8h	0%
2	*t*-BuOK,(2.5 equiv), dry THF, reflux, 1h	65%
3	DBU, dry THF, rt, 8 h	0
4	LiHMDS (2 equiv.), THF, -15^{o}C, 3h	70%
5	LiHMDS (0.2 equiv.), THF, -15^{o}C, 3h	70

As per reaction condition (Scheme 23) we investigated that, treatment with potassium carbonate in dry THF (Table 8, Entry 1) reaction could not generate desired product. As well treatment of *t*-BuOK in dry THF (Table 8, Entry 2) we have obtained significant yields 65%, In case of DBU (Table 8, Entry 3) obtained complex mixture. Followed by using LiHMDS and catalytic amount of base has delivered 70% yields (Table 8, Entry 4-5).

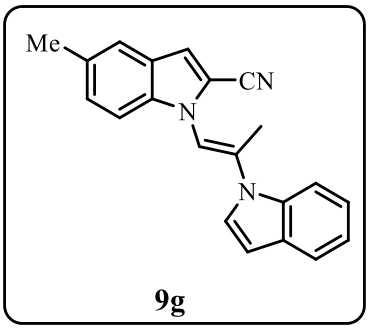
3.4.5. Scope for heterocycles towards substituted N-(propargyl)indole-2-carbonitriles





Scheme 24

Indole and its derivatives were successfully used as nucleophiles, giving products **9f-h** with 67-78% yields. Interestingly, other nitrogen heterocycles could be used in this reaction. Benzimidazole furnished hydroamination product **9i** with 72% yield. Luckily, the reaction also worked smoothly with 7-azaindole as a nucleophile, and the corresponding indolylazaindolyl propylene **9j** was isolated with 55% yield. Structure **9g** determination done by X-ray crystallography.



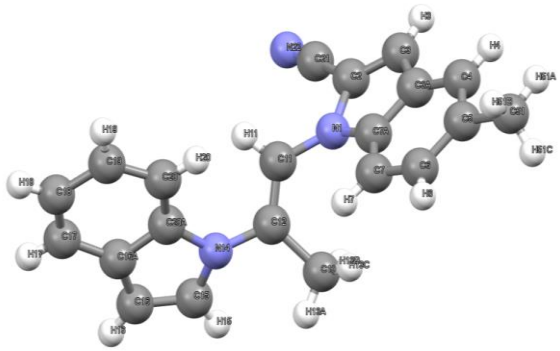
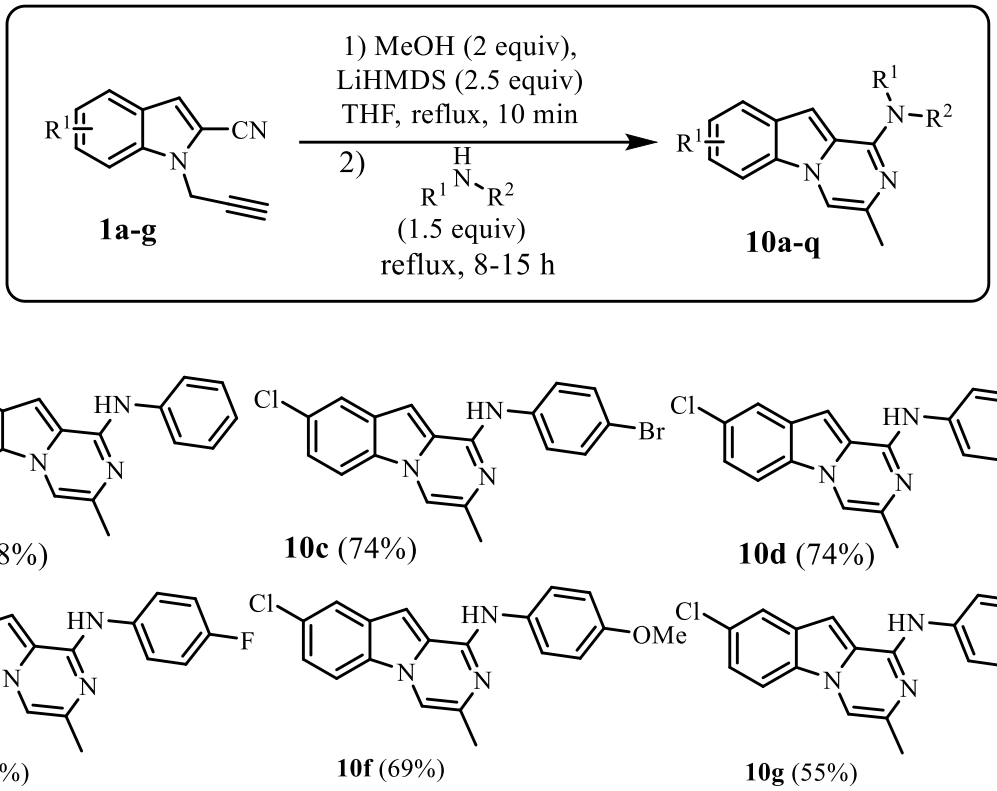


Figure 8. X-ray crystal structure

3.4.6. LiHMDS-promoted cyclization of N-(propargyl)indole-2-carbonitriles with nitrogen nucleophiles.

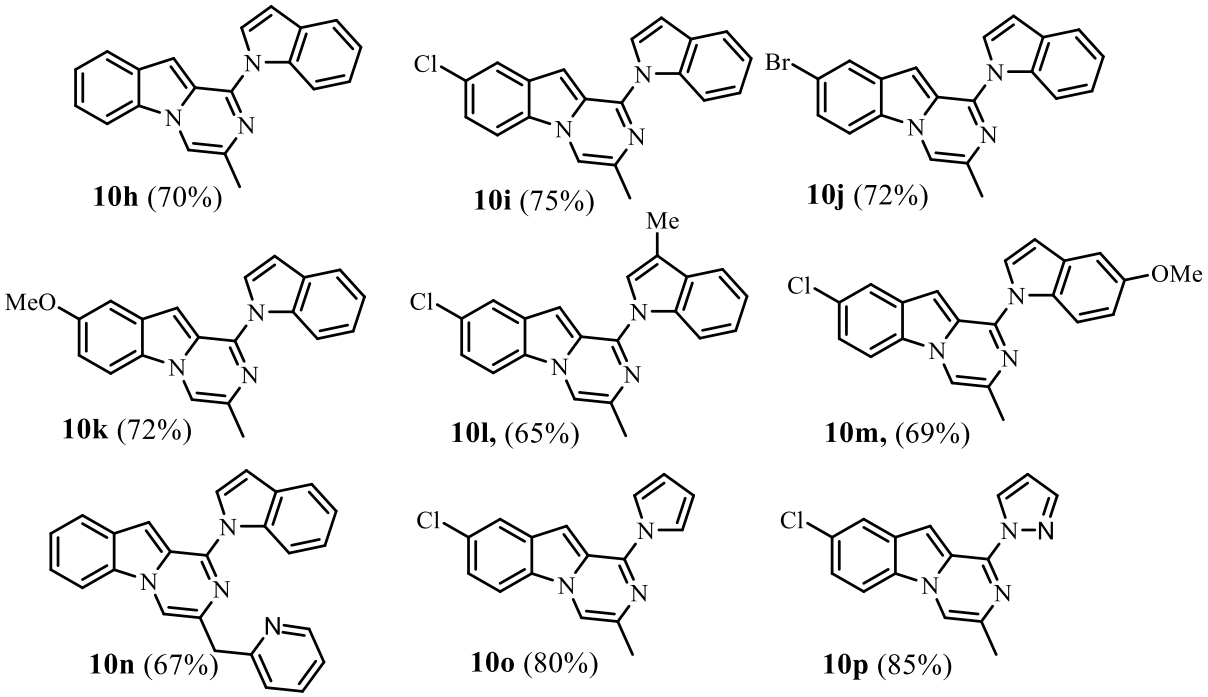
The cyclization was performed in a sequential manner. The initial reaction with methanol was very fast and effective, the starting indole **1a-g** was fully consumed after 5-10 min. The subsequent nucleophilic substitution of methoxy group with a nitrogen nucleophile took more time, and the full conversion was achieved in 8 to 15 hours reflux. Anilines, bearing bromo-,

methyl-, fluoro-, and methoxy-substituents were smoothly transformed into 1-aminophenyl-3-methylpyrazino[1,2-*a*]indoles **10b-f** with moderate to good 60-78% yields. 3,5-Dimethoxyaniline could be successfully employed too, giving product **10g** with 55% yield. Various indoles were further used to synthesize uncommon indolyl-substituted pyrazino[1,2-*a*]indoles **10h-m**.



Scheme 25

Various indoles were further used to synthesize uncommon indolyl-substituted pyrazino[1,2-*a*]indoles (Scheme 26) **10h-m**. When pyridine-substituted alkyne was used, corresponding product **10n** was isolated with 67% yield. Pyrrole and pyrazole were found to be successful nucleophiles either, generating compounds **10o-p** with 80-85% yields.



Scheme 26

General conditions: *N*-(propargyl)indole-2-carbonitrile **1a** (0.38 mmol), LiHMDS (0.5 equiv.) and MeOH (2 equiv) were stirred at reflux in THF for 10 min under argon atmosphere. After 10 min, nucleophile (1.5 equiv) and LiHMDS (2 equiv) were added. The reaction mixture was refluxed for 8-15 h (TLC tracking). The products were isolated by column chromatography. the yield of the reaction, performed on 2 mmol scale of indole **1a**. Structure of compound **10j** was unambiguously determined via single crystal X-ray diffraction study fig.5 (CCDC #2158198)

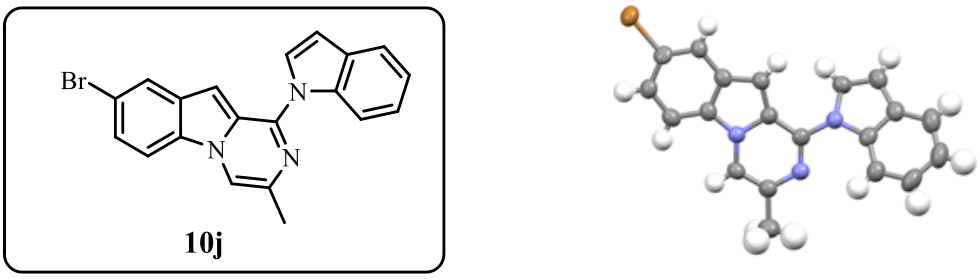
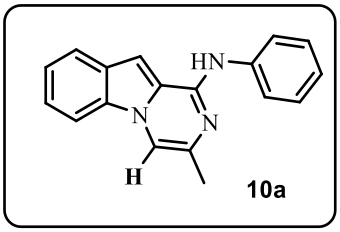


Figure 9. X-ray crystal structure

According to chemical structural formula mass determination was challenging but we have found pyrazine ring proton signals at **10a** *(^1H NMR = 8.16 ppm)*



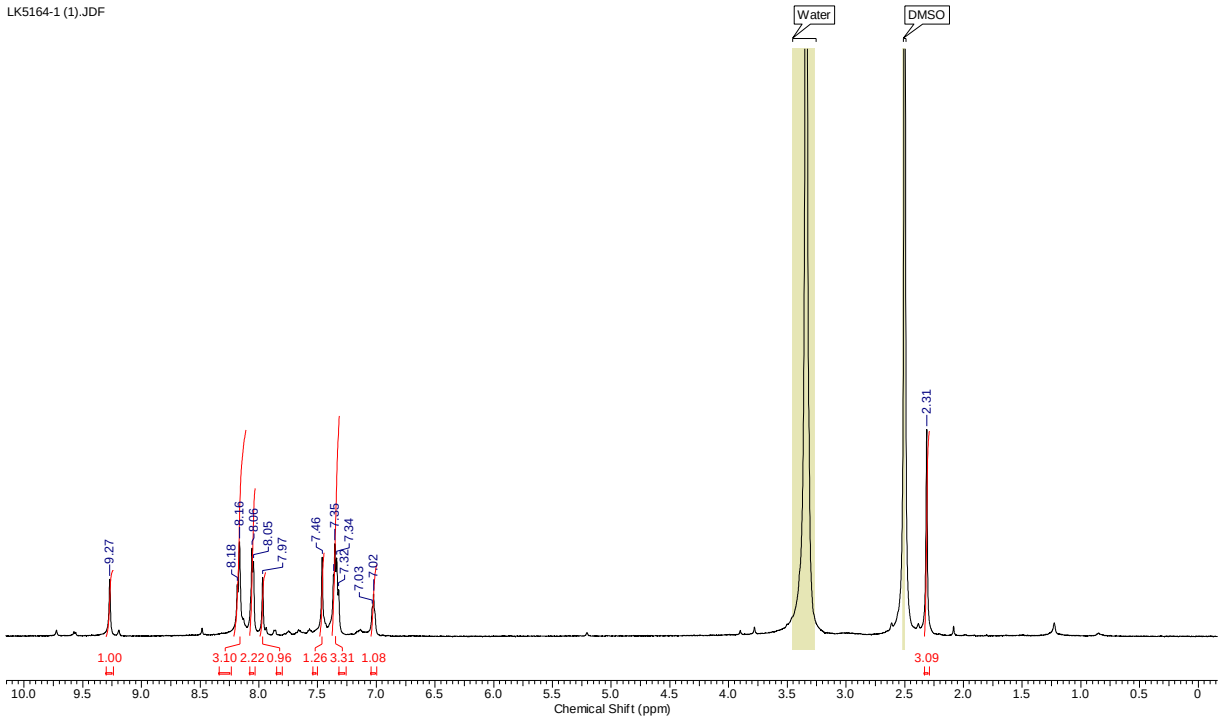
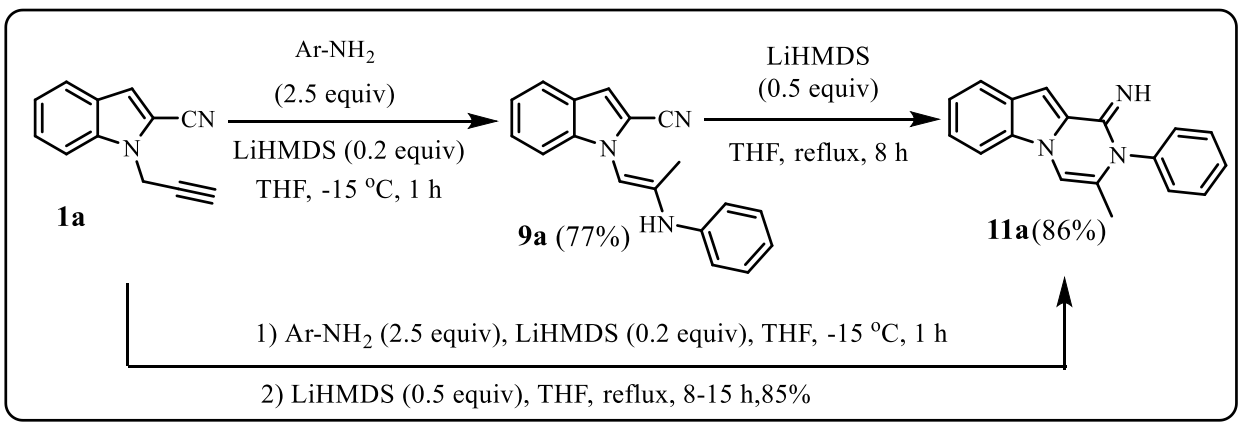
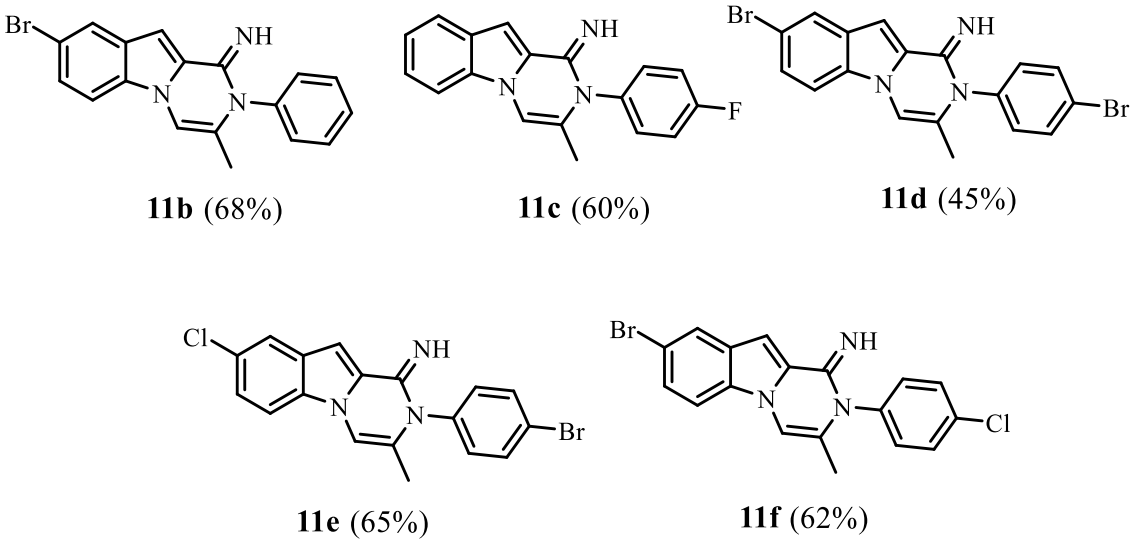


Figure 10. NMR data

3.4.7. An alternative cyclization of N-(propargyl)indole-2-carbonitriles with nitrogen nucleophiles.

We became interested in converting the aniline-derived hydroamination products **9** into alternatively cyclized heterocycles. Luckily, refluxing **9a** with LiHMDS in THF led to a smooth formation of the desired compound **11a** with a very good 86% yield (Scheme 27). To elaborate the success, a series of compounds **11** were synthesized in a one-pot manner. Initially, hydroamination product **9** was generated at reduced temperature, while further heating the reaction mixture to reflux led to an intramolecular cyclization into 1-imino-2-phenylpyrazino[1,2-*a*]indoles **11b-f**.



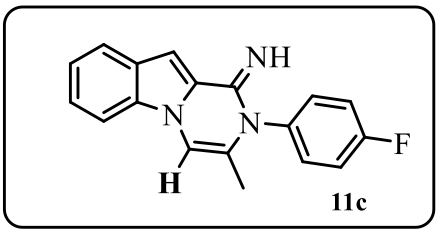


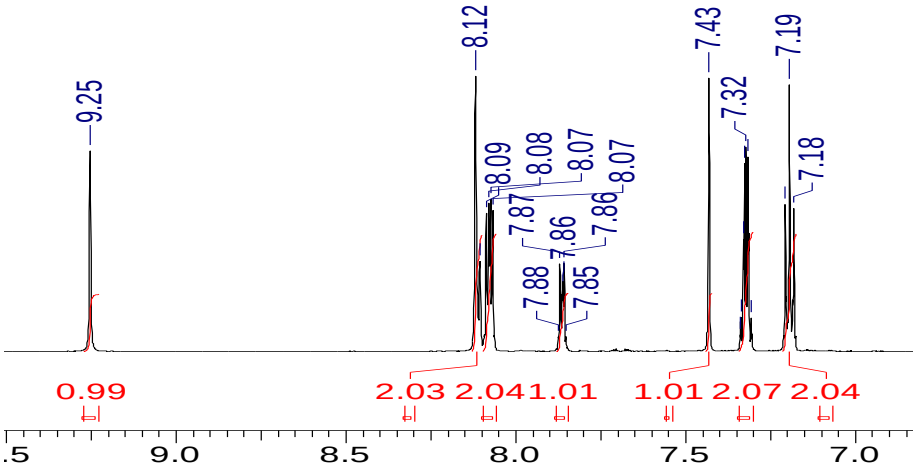
11b (68%) **11c** (60%) **11d** (45%)

11e (65%) **11f** (62%)

Scheme 27

N-(propargyl)indole-2-carbonitrile **1a** (0.32 mmol) was added to a stirred solution of aniline (0.49 mmol) and LiHMDS (0.2 equiv) in THF at -15 ^{o}C under argon atmosphere. The reaction mixture was stirred at -15 ^{o}C for 1 h (TLC tracking). Then, LiHMDS (2 equiv) was added, and the rection was refluxed for 8-15 h. The products were isolated by column chromatography. Purification method was quite challenging for cyclized product due to instability of product. NMR interpretation was challenging to identify products.as per TLC we have identified different spot in parallel with hydroamination products through TLC and by NMR analysis we have found pyrazine ring protons at **11c** *(^{1}H NMR =* ***8.12 ppm*** *).*





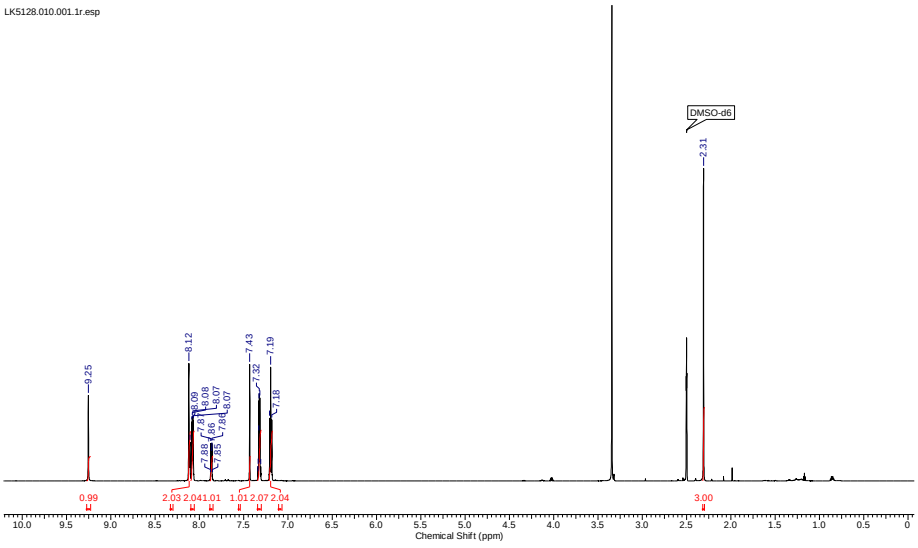
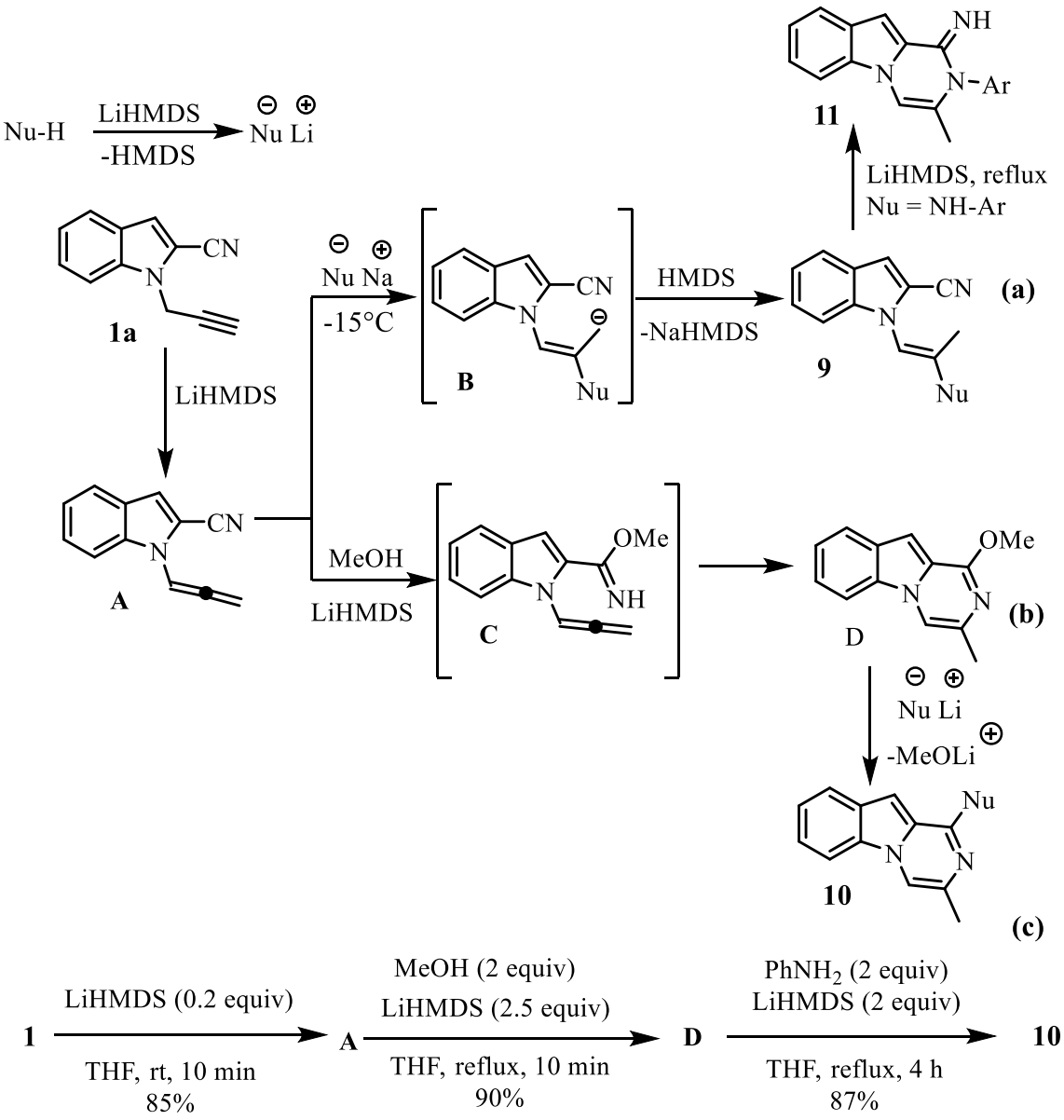


Figure 11. NMR interpretation

3.4.8. Proposed reaction pathway and control experiments.

Following possible mechanism we proposed for hydroamination of alkane and cyclic products under different condition. The following mechanistic pathway can be suggested for the developed protocols. [119,120] The reactions might start with LiHMDS-catalyzed alkyne-allene rearrangement of compound **1**, giving allene **A** (Scheme 28).



Scheme 28

In hydroamination, deprotonated by LiHMDS nucleophile adds to an allene moiety (Scheme 28**(a)**). The resulting anion **B** recycles the catalyst by deprotonating HMDS and transforms into target molecule **9**. When compound **9** is treated with a strong base, E-Z isomerization, followed by intramolecular cyclization gives cyclic imine derivatives **11**. When methanol is present in the reaction mixture, LiHMDS-catalyzed addition of methoxide anion forms imidate **C**, which undergoes an intramolecular cyclization to deliver methoxypyrazino[1,2-*a*]indole **D** (Scheme 28**(b)**).The latter undergoes nucleophilic substitution by lithium amide to form the desired compound **10**. The given pathways were proven by the following experiments (Scheme 28 **(c)**). Firstly, alkyne **1** was transformed into allene **A** under reaction conditions with 85% yield. Refluxing allene **A** in THF in the presence of MeOH and LiHMDS for 10 min resulted in the formation of 1-methoxypyrazino[1,2-*a*]indole **C** with 90% yield. The latter was further

transformed into amine **9a** under the action of aniline in the presence of NaHMDS with 87% yield. Thus, all the steps of the domino sequence could be performed independently, proving the suggested pathway.

3.4.9. Optical properties study.

The synthesized compounds **9, 10** and **11** showed intense emission when subjected to UV-light. Therefore, we decided to investigate the optical properties of the products to better understand their practical potential. The absorption and emission spectra were registered, and the fluorescence quantum yields were determined. The data for compounds **9g**, **9e**, **10o**, and **11b** is presented in Table 9. The fluorescence of hydroamination product **9e** was the most efficient with 24% FQY. Interestingly, hydroamination products **9**, as well as cyclic imines **11**, showed large Stokes shifts up to 9504 cm^{-1}.

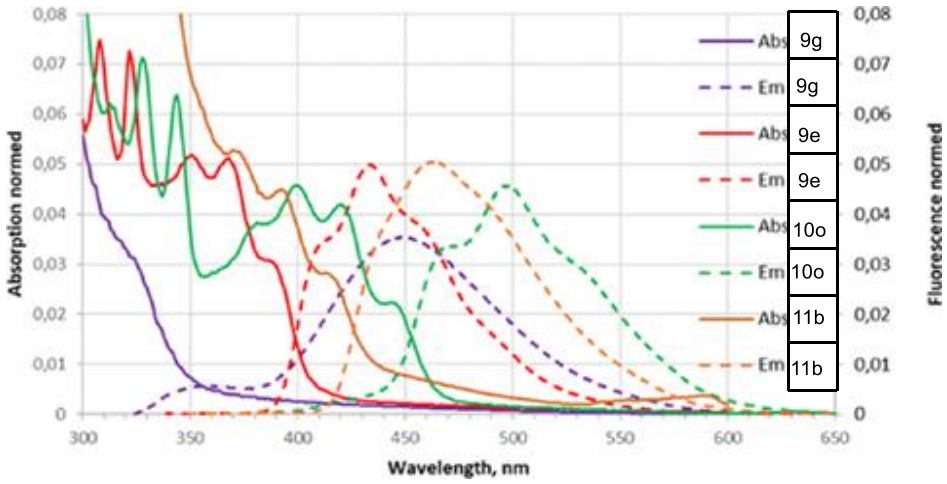


Figure 12. Absorption and emission spectra

Table 9. Absorption and emission spectra of selected compounds in EtOH.

Compound	**Abs (nm)**	**Em (nm)**	**Stokes shift (cm^{-1})**	**FQY %**
9g	315	450	9224	10
9e	350	434	7262	24
10o	400	496	6417	17
11b	372	464	9504	9

Fluorescence quantum yield was determined with quinine sulfate as a standard.

Fluorescence quantum yield was determined with coumarin 153 as a standard.

demonstrating minimal or absence of absorption and emission spectra overlap, like **9g**, are of special interest for applications in organic electronics due to the avoidance of self-reabsorption and inner-filter effects.[121].

4. Experimental section

4.1 General Information.

Solvents were distilled and dried according to standard procedures. 1H and 13C nuclear magnetic resonance (NMR) spectra were acquired on 400 or 600 MHz spectrometers and referenced to the residual signals of the solvent (for 1H and 13C). The solvents used for NMR were DMSO (DMSO-d6) and CDCl3. Chemical shifts are reported in parts per million (δ/ppm). Coupling constants are reported in Hertz (J/Hz). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; dd, doublet of doublets; br s, broad singlet. Infrared spectra were recorded on a Fourier transform infrared instrument. The wavelengths are reported in reciprocal centimeters (λmax/cm–1). High-resolution mass spectrometry (HRMS) spectra were recorded on Bruker MicroTOF-Q II. Microwave (MW)-assisted reactions were carried out in a Monowave 300 MW reactor from Anton Paar GmbH; the reaction temperature was monitored by an infrared (IR) sensor. Standard 10 mL G10 reaction vials, sealed with silicone septa, were used for the MW irradiation experiments. The reaction progress was monitored by TLC and the spots were visualized under UV light (254 or 365 nm). Column chromatography was performed using silica gel (230–400 mesh) and neutralized with ammonia, and the mixture of hexane with ethyl acetate was used as the mobile phase. Melting points were determined on a SMP-10 apparatus.

General procedure for preparation of propargylated indoles (1a-g):

The solution of corresponding 1*H*-indole-2-carbonitrile (1.00 g, 7.0 mmol) in 10 mL of anhydrous DMF was treated with K_2CO_3 (1.06 g, 7.7 mmol) and stirred at RT for 10 min. Propargyl bromide solution in toluene (0.58 mL, 7.0 mmol) was added dropwise, the reaction mixture was heated at 60ºC for 3h. Reaction progress was monitored by TLC. After completion, the reaction mixture was treated with 50 mL of water and extracted with ethyl acetate (20 mL X 2). Organic layer was washed with brine (20 mL) and dried over sodium sulfate, evaporated under high-vacuum to get crude product, which was purified by column chromatography using 100-200 mesh silica and eluted with 20% ethyl acetate in hexane solution.

1-(Prop-2-yn-1-yl)-1*H*-indole-2-carbonitrile (1a)

White solid, yield 1.11 g (88%), mp 131–132 °C. ^{1}H NMR ($CDCl_3$, 600 MHz, δ): 2.41 (1H, t, *J* = 2.5), 5.04 (2H, d, *J* = 2.5), 7.21 (1H, s), 7.24–7.26 (1H, m), 7.45–7.48 (1H, m), 7.52 (1H, d, *J* = 8.2), 7.69 (1H, d, *J* = 8.1). ^{13}C NMR ($CDCl_3$, 150 MHz, δ): 34.4, 73.8, 76.1, 109.2, 110.3, 112.8, 113.8, 121.8, 122.3, 126.0, 126.2, 136.9. HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{12}H_9N_2$ [(M + H)$^+$], 181.0760; found, 181.0764. IR (KBr): 3111, 2911, 2224 (CN).

5-Chloro-1-(prop-2-yn-1-yl)-1*H*-indole-2-carbonitrile (1b)

White solid, yield 474 mg (78%), mp 124–125 °C. ^{1}H NMR ($CDCl_3$, 600 M + Hz, δ): 2.43 (1H, t, *J* = 2.5), 5.02 (2H, d, *J* = 2.5), 7.14 (1H, s), 7.41 (1H, dd, *J* = 8.7, 2.0), 7.45 (1H, d, *J* = 8.7), 7.67 (1H, d, *J* = 2.0). ^{13}C NMR ($CDCl_3$, 150 MHz, δ): 14.1, 22.7, 31.8, 35.0, 74.5, 75.9, 111.7, 113.2, 121.7, 121.8, 126. 3, 135.4. HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{12}H_8N_2Cl$ [(M + H)$^+$], 215.0370; found, 215.0374. IR (KBr): 3285, 3124, 2958, 2866, 2211, 1899, 1520.

5-Ethoxy-1-(prop-2-yn-1-yl)-1*H*-indole-2-carbonitrile (1c)

Pale-yellow solid, yield 469 mg (78%), mp 141–142 °C. ^{1}H NMR (DMSO-d_6, 600 MHz, δ): 1.21 (3H, t, *J* = 7.6, CH_2CH_3), 2.69 (2H, q, *J* = 7.6, CH_2CH_3), 3.46 (1H, d, *J* = 2.5), 5.21 (2H, d, *J* = 2.5, CH_2), 7.33 (1H, dd, *J* = 8.6, 1.8), 7.43 (1H, s), 7.50–7.51 (1H, m), 7.63 (1H, d, *J* = 8.6). ^{13}C NMR (DMSO-d_6, 150 MHz, δ): 16.5, 28.4, 34.6, 76.4, 78.4, 108.9, 111.4, 113.6, 114.4, 120.5, 126.3, 127.4, 136.1, 137.6. HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{14}H_{13}N_2O$ [(M + H)$^+$], 225.1022; found, 225.1018. IR (KBr): 3247, 3089, 2926, 2857, 1674, 1636.

5-Bromo-1-(prop-2-yn-1-yl)-1*H*-indole-2-carbonitrile (1d).

White solid, yield 398 mg (68%), mp 119–120 °C. ^{1}H NMR ($CDCl_3$, 600 MHz, δ): 2.43 (1H, t, *J* = 2.5), 5.02 (2H, d, *J* = 2.5), 7.14 (1H, s), 7.40 (1H, dd, *J* = 9.0, 1.7), 7.45 (1H, d, *J* = 9.0), 7.66 (1H, d, *J* = 2.0). ^{13}C NMR ($CDCl_3$, 150 MHz, δ): 34.9, 75.0, 75.9, 110.7, 111.7, 112.5, 113.2, 121.6, 126.8, 127.3, 127.8, 135.4. HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{12}H_8N_2Br$ [(M + H)$^+$], 258.9865; found, 258.9869. IR (KBr): 3273, 2921, 2218, 2125, 1873, 1590, 1525.

5-Methyl-1-(prop-2-yn-1-yl)-1*H*-indole-2-carbonitrile (1e).

White solid, yield 453 mg (73%), mp 144–145 °C. ^{1}H NMR (DMSO-d_6, 600 MHz, δ): 2.39 (3H, s), 3.46 (1H, t, *J* = 2.5), 5.21 (2H, d, *J* = 2.5), 7.27–7.29 (1H, m), 7.41 (1H, s), 7.48 (1H, s), 7.60 (1H, d, *J* = 8.5). ^{13}C NMR (DMSO-d_6, 150 MHz, δ): 21.7, 34.0, 76.4, 78.5, 108.4, 111.2, 113.6, 114.2, 121.7, 126.4, 128.4, 131.0, 136.0. HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{13}H_{11}N_2$ [(M + H)$^+$], 195.0916; found, 195.0921. IR (KBr): 3285, 2958, 2986, 2866, 2211, 1899, 1520.

5-Ethyl-1-(prop-2-yn-1-yl)-1*H*-indole-2-carbonitrile (1f)

White solid, yield 485 mg (79%), mp 152°C; ^{1}H NMR (DMSO-d6, 600 MHz): 1.21 (3H, t, J=7.0), 7.68-7.72 (2H, m), 3.45 (1H s), 5.21 (2H, d, J=2.5), 7.32 (1H, d, J=8.5), 7.45 (1H, s), 7.50 (1H, s), 7.62 (1H, d, J= 8.5).

5-Methoxy-1-(prop-2-yn-1-yl)-1*H*-indole-2-carbonitrile (1g). White solid, yield 1.00 g (68%). mp 118-119°C. ^{1}H NMR (CDCl3, 600 MHz): δ 7.45 (d, 1H, J = 6.3), 7.11 (d, 2H, J = 6.9), 7.06 (s, 1H), 5.01 (d, 2H, J = 2.3), 3.86 (s, 3H), 2.40 (t, 1H, J = 2.5). ^{13}C{1H} NMR (CDCl3, 150 MHz): δ 132.5. 126.9, 117.9, 117.8, 113.3, 113.2, 111.5, 109.5, 102.4, 76.4, 74.0, 55.7, 34.8. HRMS (TOF ES$^+$) m/z: [M+H]$^+$ Calcd for $C_{13}H_{11}N_2O$ 211.0866; Found 211.0868.

1-(3-(Pyridin-2-yl)prop-2-yn-1-yl)-1*H*-indole-2-carbonitrile (1h)

A mixture of compound **1a** (0.500 g, 2.76 mmol), 2-bromopyridine (0.474 g, 3.0 mmol) and K_2CO_3 (0.414 g, 3.0 mmol) in 5 ml of DMF was degassed by using Ar for 10 min. Then, $Pd(PPh_3)_4$ (64 mg, $5.5*10^{-5}$ mol), and CuI (26 mg, $1.37*10^{-4}$ mol) were added, flushed with Ar for 5 min and the reaction mixture was heated in a closed vial in microwave reactor to 100 °C for 15 min. Reaction was monitored by TLC. Resulting mixture was diluted with water, extracted with ether (3x25mL), organic layer dried over sodium sulfate and evaporated; the residue was purified by flash column chromatography (ethyl acetate/hexane) to produce 426 mg (60%) of the coupled product **1h** as a white solid.

Light-brown solid, yield 85 mg (60%), mp 151–152 °C. ^{1}H NMR ($CDCl_3$, 600 MHz, δ): 5.30 (2H, s), 7.23–7.27 (3H, m), 7.43–7.47 (2H, m), 7.61 (1H, d, *J* = 8.5), 7.65–7.769(2H, m), 8.58 (1H, s). ^{13}C NMR ($CDCl_3$, 150 MHz, δ): 35.5, 82.4, 84.5, 109.6, 110.8, 114.3, 114.3, 122.0, 122.1, 122.6, 122.5, 126.5, 127.8, 136.7, 137.4, 141.9, 149.8. HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{17}H_{12}N_3$ [(M + H)$^+$], 258.1025; found, 258.1029. IR (KBr): 3110, 2911, 2224, 1583, 1466.

1-(3-(Pyridin-3-yl)prop-2-yn-1-yl)-1*H*-indole-2-carbonitrile) (1i).

Light-brown solid, yield 102 mg (72%), mp 158–160 °C. ^{1}H NMR ($CDCl_3$, 600 MHz, δ): 5.31 (2H, s), 7.24–7.27 (2H, m), 7.42–7.47 (2H, m), 7.59 (1H, d, *J* = 8.5), 7.69 (1H, t, *J* = 7.5), 7.69 (1H, d, *J* = 8.0), 8.57 (1H, s). ^{13}C NMR ($CDCl_3$, 150 MHz, δ): 35.1, 82.0, 84.3, 109.2, 110.42, 112.0, 113.9, 121.6, 122.2, 123.3, 126.1, 126.6, 127.3, 136.3, 137.4, 141.5, 149.4. HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{17}H_{12}N_3$ [(M + H)$^+$], 258.1025; found, 258.1029. IR (KBr): 3111, 2912, 2224, 1583, 1466.

General Procedure for preparation of 1-(3-phenylprop-2-ynyl)-1*H*-indole-2-carbonitrile (1j)

To the solution of Compound Propargylated Indole (0.5gm, 2.76mmol), Iodobenzene (0.62gm, 3.0 mmol) was added in 5.0 ml of Triethylamine and purged nitrogen for 10 min, further was added Pd catalyst (mg, 0.055mmol) and CuI (26 mg,0.135) were added, purged nitrogen for 10 min, and heat reaction mixture for 1 hrs. at 80°C. Reaction was monitored by TLC. Reaction mixture was diluted with water, extracted with Ethyl acetate (2x20mL), organic layer was dried over sodium sulfate and evaporated to obtained crude compound. Crude compound was purified over silica gel with help of column chromatography and eluted in 20% ethyl acetate in hexane.

White solid, yield 565 mg (80%); ^{1}H NMR (DMSO-d6, 600MHz): 5.51 (2H, s), 7.24 (1H, t, *J*=7.5), 7.34 -7. 41(5H, m) 7.47 (2H, d, *J*=7.5), 7.54 (1H, s) 7.73 (1H, d, *J*= 8.0), 7.80 (1H, d, *J*= 8.5).

5-methyl-1-(3-phenylprop-2-ynyl)-1*H*-indole-2-carbonitrile (1k)

White solid, yield 570 mg (82%); ^{1}H NMR (DMSO-d6, 600MHz): 2.40 (3H, s), 5.47 (2H, s), 7.30 (1H, d, *J*=8.58), 7.34-4.40 (5H, m) 7.43 (1H, s), 7.49 (1H, s), 7.68 (1H, d, *J*=8.58).

5-chloro-1-(3-phenylprop-2-ynyl)-1*H*-indole-2-carbonitrile (1l)

White Solid, yield 525 mg (78%); ^{1}H NMR (DMSO-d6, 600MHz): 5.54 (2H, s), 7.34-7.38 (3H, m), 7.39-7.41 (2H, m), 7.49 (1H, dd, *J* = 9.0. 1.8), 7.52 (1H, s), 7.82 (1H, d, *J* = 1.7), 7.86 (1H, d, *J* = 9.1).

5-chloro-1-(3-phenylprop-2-ynyl)-1*H*-indole-2-carbonitrile (1m).

White Solid, yield 510 mg (75%); ^{1}H NMR (DMSO-d6, 600MHz): 3.79 (3H, s), 5.47 (2H, s), 7.12 (1H, dd, *J* = 9.0, 2.5), 7.18 (1H, d, *J* = 2.0), 7.35-7.42 (6H, m), 7.71 (1H, d, *J* = 9.0).

General procedure for preparation of 1-alkoxypyrazino[1,2-*a*]indoles (2):

The solution of a propargylated indole **1a-f** (1 mmol) and DBU (7.5 μL, 5.0 .x10^{-5} mol) in 4.0 ml of a corresponding alcohol was heated in a closed vial under microwave irradiation at 150°C for 30 min. The reaction progress was monitored by TLC. After the completion, the reaction mass was diluted with 20 mL of water and extracted with ethyl acetate (3x20mL). Organic layer was dried over sodium sulfate and evaporated to get crude product. Purification of the product was performed using column chromatography on silica (preliminary neutralized with ammonia), and eluting with 2% ethyl acetate in hexane

1-Methoxy-3-methylpyrazino[1,2-a]indole (2a)

White solid, yield 186 mg (88%), mp 71°C. ^{1}H NMR (DMSO-d_6, 600MHz): 2.31 (3H, s, CH_3), 4.04 (3H, s, OCH_3), 6.94 (1H, s), 7.33-7.35 (2H, m), 7.83 (1H, d, *J* = 7.5), 8.14 (1H, d, *J* = 7.5), 8.30 (1H, d, *J* = 2.5).^{13}C NMR (DMSO-d_6, 150 MHz): δ_C ppm = 20.4, 53.3, 93.1, 109.4, 111.7, 121.5, 121.8. 121.8, 122.8, 127.3, 129.3, 130.0, 155.4. HRMS (TOF ES$^+$): m/z calcd for $C_{13}H_{13}N_2O$ [$(M+H)^+$], 213.1022; found, 213.1017IR (KBr): 2937, 2852, 1634, 1519.

8-Chloro-1-methoxy-3-methylpyrazino[1,2-*a*]indole (2b)

Pale-yellow solid, yield 209 mg (85%), mp 170–171 °C. ^{1}H NMR (DMSO-d_6, 600 MHz, δ): 2.31 (3H, s, CH_3), 4.04 (3H, s, CH_3), 6.92 (1H, s), 7.35 (1H, d, *J* = 8.5), 7.90 (1H, s), 8.20 (1H, d, *J* = 8.5), 8.34 (1H, s). ^{13}C NMR (DMSO-d_6, 150 MHz, δ): 20.4, 53.5, 92.9, 109.6, 109.6, 109.5, 113.6, 120.7, 126.0, 128.2, 128.4, 130.1, 155.3. HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{13}H_{12}ClN_2O$ [$(M + H)^+$], 247.0633; found, 247.0638. IR (KBr): 3123, 2953, 1633, 1523, 1449.

8-Ethoxy-1-methoxy-3-methylpyrazino[1,2-*a*]indole (2c)

Pale yellow solid, yield 217 mg (85%), mp 103–105 °C. ^{1}H NMR (DMSO-d_6, 600 MHz, δ): 1.25 (3H, t, *J* = 7.5), 2.31 (3H, s, CH_3), 2.75 (2H, q, *J* = 7.5), 4.03 (3H, s), 6.86 (1H, s), 7.22 (1H, dd, *J* = 8.0, 1.1), 7.61 (1H, s), 8.04 (1H, d, *J* = 8.0), 8.26 (1H, s). ^{13}C NMR (DMSO-d_6, 150 MHz, δ): 16.1, 20.4, 28.5, 53.2, 92.7, 109.5, 111.6, 119.6, 121.6, 122.9, 127.6, 128.8, 129.2, 138.4, 155.3. HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{15}H_{17}N_2O_2$ [$(M + H)^+$], 257.1284; found, 257.1278. IR (KBr): 2953, 1634, 1521, 1312.

8-Bromo-1-methoxy-3-methylpyrazino[1,2-*a*]indole (2d)

White solid, yield 239 mg (82%), mp 71–72 °C. ^{1}H NMR (DMSO-d_6, 600 MHz, δ): 2.32 (3H, s, CH_3), 4.05 (3H, s, CH_3), 6.93 (1H, s), 7.48 (1H, dd, *J* = 8.0, 1.5), 8.07 (1H, d, *J* = 1.5), 8.15 (1H, d, *J* = 8.0), 8.35 (1H, s). ^{13}C NMR (DMSO-d_6, 150 MHz, δ): 20.0, 53.1, 92.4, 109.1, 113.5, 113.6, 115.2, 122.0, 123.6, 124.1, 128.2, 129.7, 154.9. HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{13}H_{12}BrN_2O$ [(M + H)$^+$], 291.0127; found, 291.0129. IR (KBr): 3121, 2951, 2853, 1633, 1520.

1-Methoxy-3,8-dimethylpyrazino[1,2-*a*]indole (2e)

White solid, yield 188 mg (83%), mp 74–75 °C. ^{1}H NMR (DMSO-d_6, 600 MHz, δ): 2.30 (3H, s, CH_3), 2.45 (3H, s, CH_3), 4.03 (3H, s, CH_3), 6.84 (1H, s), 7.18 (1H, dd, *J* = 8.0, 1.1), 7.59 (1H, s), 8.02 (1H, d, *J* = 8.0), 8.25 (1H, s). ^{13}C NMR (DMSO-d_6, 150 MHz, δ): −20.4, 21.4, 53.3, 92.6, 109.5, 111.5, 120.9, 121.6, 123.9, 127.6, 128.6, 129.2, 131.9, 155.4. HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{14}H_{15}N_2O$ [(M + H)$^+$], 227.1179; found, 227.1184. IR (KBr): 3061, 2937, 1589, 1519, 1369.

1-Methoxy-3-(pyridin-2-ylmethyl)pyrazino[1,2-*a*]indole (2f)

White solid, yield 208 mg (72%), mp 176–177 °C. ^{1}H NMR (DMSO-d_6, 600 MHz, δ): 3.98 (3H, s, CH_3), 4.09 (2H, s, CH_2), 6.97 (1H, s), 7.22–7.24 (1H, m), 7.34–7.41 (3H, m), 7.72 (1H, td, *J* = 7.5, 2.0), 7.85 (1H, d, *J* = 7.0), 8.19 (1H, d, *J* = 8.0), 8.47–8.51 (2H, m). ^{13}C NMR (DMSO-d_6, 150 MHz, δ): 42.4, 53.0, 93.2, 110.8, 111.6, 121.3, 121.8, 122.9, 123.3, 127.2, 127.5,129.7, 130.0, 130.8, 136.2, 148.7, 155.4, 159.2. HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{18}H_{16}N_3O$ [(M + H)$^+$], 290.1288; found, 290.1297. IR (KBr): 3062, 2937, 1589, 1519. 1305.

1-Methoxy-3-(pyridin-2-ylmethyl)pyrazino[1,2-*a*]indole (2g)

White solid, yield 110 mg (70%), mp 180–181 °C. ^{1}H NMR (DMSO-d_6, 600 MHz, δ): 3.95 (2H, s, CH_2), 4.00 (3H, s, CH_3), 6.97 (1H, s), 7.32–7.40 (3H, m), 7.78 (1H, d, *J* = 8.1), 7.85 (1H, d, *J* = 8.1), 8.15 (1H, d, *J* = 8.0), 8.43 (1H, d, *J* = 4.0), 8.50 (1H, s), 8.62 (1H, s). ^{13}C NMR (DMSO-d_6, 150 MHz, δ): 42.6, 53.2, 93.4, 111.0, 111.0, 111.8, 121.5, 121.6, 121.9, 122.1, 123.0, 123.2, 127.4, 130.0, 136.4, 148.9, 155.6, 159.4. HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{18}H_{16}N_3O$ [(M + H)$^+$], 290.1287; found, 290.1291. IR (KBr): 3247, 2925, 1635, 1579, 1464.

1-Ethoxy-3-methylpyrazino[1,2-*a*]indole (2h)

White oil, yield 136 mg (60%), R/F (0.5/9.5 EtOAc/hexane) = 0.78. ^{1}H NMR (DMSO-d_6, 600 MHz, δ): 1.42 (3H, t, *J* = 7.0, CH_3), 2.31 (3H, s, CH_3), 4.51 (2H, q, *J* = 7.0, CH_2), 6.93 (1H, s), 7.32–7.36 (2H, m), 7.83 (1H, dd, *J* = 7.5, 1.0), 8.14 (1H, d, *J* = 7.5), 8.29 (1H, s). ^{13}C NMR (DMSO-d_6, 150 MHz, δ): 14.6, 20.7, 61.8, 93.4, 109.5, 112.0, 121.9, 122.1, 122.7, 123.1, 127.5, 129.7, 130.2, 155.3. HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{14}H_{15}N_2O$ [(M + H)$^+$], 227.1179; found, 227.1183. IR (KBr): 3057, 2935, 1519, 1409.

8-Chloro-1-ethoxy-3-methylpyrazino[1,2-*a*]indole (2i)

Yellow solid, yield 116 mg (85%), mp 170–171 °C. ^{1}H NMR (DMSO-d_6, 600 MHz, δ): 1.41 (3H, t, J = 7.0, CH_3), 2.29 (3H, s, CH_3), 4.50 (2H, q, J = 7.0, CH_2), 6.90 (1H, s), 7.34 (1H, dd, J = 7.0, 2.0), 7.88 (1H, d, J = 2.0), 8.18 (1H, d, J = 8.5), 8.30 (1H, s). ^{13}C NMR (DMSO-d_6, 150 MHz, δ): 14.2, 20.4, 61.7, 92.8, 109.3, 113.6, 120.7, 121.9, 122.7, 126.0, 128.1, 128.4, 130.07, 154.8. HRMS (TOF ES$^+$): m/z calcd for $C_{14}H_{14}ClN_2O$ [(M + H)$^+$], 261.0789; found, 261.0792. IR (KBr): 2982, 2921,1519, 1477, 1306.

3-Methyl-1-propoxypyrazino[1,2-*a*]indole (2j)

White solid, yield 125 mg (52%), mp 97–98 °C. ^{1}H NMR (DMSO-d_6, 600 MHz, δ): 1.03 (3H, t, J = 7.5, CH_3), 1.80–1.86 (2H, m), 2.30 (3H, s, CH_3), 4.41 (2H, t, J = 6.5), 6.94 (1H, s), 7.32–7.36 (2H, m), 7.83 (1H, dd, J = 7.5, 1.5), 8.14 (1H, d, J = 7.5), 8.29 (1H, s). ^{13}C NMR (DMSO-d_6, 150 MHz, δ): 10.2, 20.2, 21.5, 68.6, 92.8, 109.0, 111.5, 121.4, 121.6, 122.6, 127.0, 127.1, 129.2, 129.8, 154.9. HRMS (TOF ES$^+$): m/z calcd for $C_{15}H_{17}N_2O$ [(M + H)$^+$], 241.1335; found, 241.1343. IR (KBr): 2969, 2945, 2880, 1631, 1519, 1314, 1292.

1-Butoxy-3-methylpyrazino[1,2-*a*]indole (2k)

White solid, yield 132 mg (52%), mp 96–97 °C. ^{1}H NMR (DMSO-d_6, 600 MHz, δ): 0.97 (3H, t, J = 7.5, CH_3), 1.46–1.53 (2H, m), 1.78–1.82 (2H, t, J = 8.0), 2.31 (3H, s, CH_3), 4.47 (2H, t, J = 6.0), 6.94 (1H, s), 7.32–7.36 (2H, m), 7.83 (1H, dd, J = 7.0, 1.5), 8.14 (1H, d, J = 7.5), 8.29 (1H, s). ^{13}C NMR (DMSO-d_6, 150 MHz, δ): 13.7, 18.8, 20.4, 30.4, 30.6, 65.3, 93.1, 109.2, 111.7, 121.6, 129.8, 122.8, 127.3, 129.4, 130.0, 155.1. HRMS (TOF ES$^+$): m/z calcd for $C_{16}H_{19}N_2O$ [(M + H)$^+$], 255.1492; found, 255.1493. IR (KBr): 2924, 2855, 1633, 1516, 1458, 1302.

1-(2-Methylpropoxy-1)-3-methylpyrazino[1,2-*a*]indole (2l)

White solid, yield 198 mg (78%), mp 121–122 °C. ^{1}H NMR (DMSO-d_6, 600 MHz, δ): 1.0 (6H, d, J = 7.1), 2.11–2.16 (1H, m), 2.30 (3H, s, CH_3), 4.23 (2H, d, J = 6.5, CH_2) 6.95 (1H, s), 7.31–7.36 (2H, m), 7.83 (1H, dd, J = 7.5, 1.5), 8.13 (1H, d, J = 7.5), 8.28 (1H, s). ^{13}C NMR (DMSO-d_6, 150 MHz, δ): 18.7, 20.1, 27.1, 71.2, 92.7, 109.0, 111.4, 111.3, 121.2, 121.5, 122.5, 127.0, 127.2, 129.1, 129.7, 154.9. HRMS (TOF ES$^+$): m/z calcd for $C_{16}H_{19}N_2O$ [(M + H)$^+$], 255.1492; found, 255.1488. IR (KBr): 3360, 2976, 1710, 1514, 1302.

1-Hexyloxy-3-methylpyrazino[1,2-*a*]indole (2m)

White solid, yield 149 mg (53%), mp 71–72 °C. ^{1}H NMR (DMSO-d_6, 600 MHz, δ): 0.86–0.90 (3H, m), 1.28–134 (4H, m), 1.45 (2H, d, J = 7.5), 1.77–1.80 (2H, m), 2.30 (3H, s, CH_3), 4.44 (2H, t, J = 6.5), 6.92 (1H, s), 7.31–7.36 (2H, m), 7.83 (1H, dd, J = 7.0, 1.5), 8.14 (1H, d, J = 8.0), 8.28 (1H, s). ^{13}C NMR (DMSO-d_6, 150 MHz, δ): 13.8, 20.1, 22.0, 25.2, 28.2, 30.9, 65.8, 93.0, 109.2, 111.7, 121.6, 121.7, 121.8, 122.7, 127.3, 129.4, 130.0, 155.1. HRMS (TOF ES$^+$): m/z calcd for $C_{18}H_{23}N_2O$ [(M + H)$^+$], 283.1732; found, 283.1734. IR (KBr): 3136, 2924, 1717, 1633, 1516, 1302.

General experimental procedure for preparation of 1-alkoxypyrazino[1,2-*a*]indoles from aromatic and secondary alcohols.

To a solution of propargylated indole (0.1gm, 0.5 mmol) in 10 eq of a corresponding alcohol and 2 ml of DMSO, it was treated with DBU (84 mg 0.5mmol) and heat reaction mass under microwave at 150°C for 30 min. reaction progress monitored by TLC. It shows completion of starting material. reaction mass diluted with 10 ml water and extracted with ethyl acetate 20 ml x 1. Organic layer was dried over sodium sulfate and evaporated. The product was purified by using Silica 100 mesh and eluted in 2% ethyl acetate in hexane. (Silica was neutralized by ammonia solution and this purification method improved yield).

1-Isopropoxy-3-methylpyrazino[1,2-a]indole (2n)

White amorphous solid, yield 53 mg (40%), R/F = 0.78 (0.5/9.5 EtOAc/hexane). ^{1}H NMR (DMSO-d_6, 600 MHz, δ): 1.40 (6H, d, *J* = 6.0), 2.30 (3H, s), 5.5 (1H, h, *J* = 6.0), 6.9 (1H, s), 7.31–7.35 (2H, m), 7.81 (1H, t, *J* = 7.5), 8.12 (1H, d, *J* = 7.5), 8.26 (1H, s). ^{13}C NMR (DMSO-d_6, 150 MHz, δ): 20.2, 21.5, 67.9, 88.4, 92.8, 108.7, 111.5, 115.7, 121.6, 122.2, 122.7, 126.2, 129.7, 136.3, 154.3. HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{15}H_{17}N_2O$ [(M + H)$^+$], 241.1335; found, 241.1343. IR (KBr): 2982.

1-(Butoxy-2)-3-methylpyrazino[1,2-*a*]indole (2o)

White solid, yield 77 mg (55%), mp 131–133 °C. ^{1}H NMR (DMSO-d_6, 600 MHz, δ): 0.96 (3H, t, *J* = 7.5), 1.37 (3H, d, *J* = 6.0), 1.70–1.80 (2H, m), 2.30 (3H, s), 5.32–5.37 (1H, m), 6.92 (1H, s), 7.31–7.35 (2H, m), 7.82 (1H, d, *J* = 7.0), 8.13 (1H, *J* = 7.6), 8.28 (1H, s). ^{13}C NMR (DMSO-d_6, 150 MHz, δ): 9.8, 19.4, 20.7, 28.6, 72.9, 93.3, 109.2, 112.0, 122.0, 122.0, 122.2, 123.0, 127.5, 129.7, 130.2, 155.1. EI-MS, *m*/*z* (%); HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{16}H_{19}N_2O$ [(M + H)$^+$], 255.1491; found, 255.1494. IR (KBr): 3101, 2949, 2845, 1709, 1607.

1-(Cyclohexyloxy)-3-methylpyrazino[1,2-*a*]indole (2p)

White amorphous solid, yield 69 mg (45%), R/F = 0.80 (0.5/9.5 EtOAc/hexane). ^{1}H NMR (DMSO-d_6, 600 MHz, δ): 0.87–0.90 (2H, m), 1.31–1.34 (4H, m), 1.43–1.47 (2H, m), 1.78–1.82 (2H, m), 2.30 (3H, s), 4.41–4.47 (1H, m), 6.93 (1H, s), 7.32–7.36 (2H, m), 7.83 (1H, d, *J* = 8.58), 8.13 (1H, d, *J* = 7.57), 8.28 (1H, s). ^{13}C NMR (DMSO-d_6, 150 MHz, δ): 13.7, 20.2, 21.8, 25.0, 28.1, 30.8, 39.0, 65.5, 92.9, 109.1, 111.6, 121.5, 121.5, 127.1, 129.3, 129.3, 129.8, 155.0. EI-MS, *m*/*z* (%); HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{18}H_{21}N_2O$ [(M + H)$^+$], 281.1648; found, 281.1644. IR (KBr): 3101, 2949, 2845, 1709, 1607.

1-(Furfuryloxy)-3-methylpyrazino[1,2-*a*]indole (2q)

White solid, yield 150 mg (54%), mp 141–142 °C. ^{1}H NMR (DMSO-d_6, 600 MHz, δ): 2.35 (3H, s, CH_3), 5.52 (2H, s, CH_2), 6.51 (1H, t, *J* = 3.0,), 6.6 (1H, d, *J* = 3.0), 6.93 (1H, s), 7.32–7.37 (2H,

m), 7.74 (1H, d, *J* = 1.8), 7.81 (1H, d, *J* = 7.6), 8.15 (1H, d, *J* = 8.0), 8.35 (1H, s). ^{13}C NMR (DMSO-d_6, 150 MHz, δ): 20.5, 59.2, 93.5, 109.9, 110.9, 111.3, 111.9, 121.4, 122.0, 122.1, 123.1, 127.5, 129.3, 130.2, 143.9, 149.9, 154.5. HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{17}H_{15}N_2O_2$ [(M + H)$^+$], 279.1128; found, 279.1132. IR (KBr): 3247, 3089, 2925, 2856, 1535, 1579.

1-(Benzyloxy)-3-methylpyrazino[1,2-*a*]indole (2r)

White solid, yield 152 mg (53%), mp 188–190 °C. ^{1}H NMR (DMSO-d_6, 600 MHz, δ): 2.33 (3H, s, CH_3), 5.56 (2H, s, CH_2), 6.99 (1H, s), 7.32–7.37 (3H, m), 7.42 (2H, t, *J* = 7.5), 7.55 (2H, d, *J* = 7.5), 7.84 (1H, d, *J* = 7.3), 8.15 (1H, d, *J* = 7.5), 8.34 (1H, s). ^{13}C NMR (DMSO-d_6, 150 MHz, δ): 20.4, 66.9, 93.3, 109.7, 111.8, 121.5, 121.87, 121.94, 122.9, 127.4, 127.9, 128.0, 128.4, 128.5, 129.3, 129.7, 130.1, 136.7, 154.8. HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{19}H_{17}N_2O$ [(M + H)$^+$], 289.1335; found, 289.1333. IR (KBr): 3057, 2914, 1702, 1635, 1517, 1302.

1-(Propa-1,2-diene-1-yl)-1*H*-indole-2-carbonitrile (3)

White amorphous solid, yield 108 mg (60%), R/F = 0.72 (0.5/9.5 ethyl acetate/hexane). ^{1}H NMR (DMSO-d_6, 600 MHz, δ): 5.85 (2H, d, *J* = 7.1), 7.27 (1H, t, *J* = 7.1), 7.46 (1H, t, *J* = 7.0*)*, 7.62 (1H, s), 7.67 (1H, t, *J* = 6.9), 7.74 (1H, d, *J* = 8.2), 7.80 (1H, d, *J* = 8.3). ^{13}C NMR (DMSO-d_6, 150 MHz, δ): 89.3, 95.3, 108.3, 111.9, 113.3, 116.3, 122.5, 122.8, 126.4, 126.8, 136.6, 203.8. HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{12}H_9N_2$ [(M + H)$^+$], 181.0760; found, 181.0764. IR (KBr): 3111, 2911, 2224, 1583, 1465, 1342.

3-methylpyrazino[1,2-a]indol-1-ol (4)

White solid, yield 95 mg (85%), R/F = 0.72 (0.5/9.5 ethyl acetate/hexane).^{1}H NMR (DMSO-d_6, 600MHz): 2.12 (3H, s, CH_3), 7.17 (1H, s, H-10), 7.25 (1H, t, *J*= 7.57, H-8), 7.36 (1H, t, *J= 8.0,* H-7), 7.64(1H, s, H-4), 7.78 (1H, d, *J*= 8.0, H-6), 7.97(1H, d, *J*=8.58, H-9), 10.5(1H, s, OH).^{13}C NMR (DMSO-d_6, 150 MHz): δ_C ppm = 20.2, 46.5, 93.1, 109.30, 111.17, 118.2, 121.86, 122.84, 127.31, 129.84, 145.4, 155.05.HRMS (TOF ES$^+$): m/z calcd for $C_{12}H_{10}N_2O$ [(M+H) $^+$] 199.0793 found, 199.0865.IR (KBr): 3474, 2927.

1-(2-oxopropyl)-1*H*-indole-2-carbonitrile (5)

White solid, yield 111g (82%), mp 141–142 °C. ^{1}H NMR ($CDCl_3$, 600 MHz, δ): 2.32 (3H, s), 4.48 (2H, d, *J* = 2.5), 7.29 (1H, s), 7.26–7.28 (1H, m), 7.48–7.51 (1H, m), 7.55 (1H, d, *J* = 8.2), 7.75 (1H, d, *J* = 8.1). ^{13}C NMR ($CDCl_3$, 150 MHz, δ): 27.0, 53.5, 73.8, 109.5, 111.3, 113.8, 121.7, 123.5, 125.0, 128.7, 137.2, 201.1. HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{12}H_{10}N_2O$ [(M + H)$^+$], 198.1760; found, 198.1964. IR (KBr): 3111, 2911, 2224 (CN).

General procedure for the preparation of 7-methyl-8-nitropyrido[1,2-a]indol-9-amines 6a-k and indolizine 7:

The Solution of a Propargylated Indole (100mg, 0.55 mmol), DBU (4.2 mg, 0.0277 mmol), was added 2.0 ml Nitromethane, (addition of DBU turns reaction colour brown to dark brown) reaction was heated under dry condition at 145°C for 2.0 hrs. The reaction progress was monitored by TLC. After completion, the reaction mass was evaporated to get crude compound. Purification of crude compound was performed by column chromatography and eluted with 50% ethyl acetate in hexane.

7-Methyl-8-nitropyrido[1,2-a]indol-9-amine (6a)

Brown solid, yield 122 mg (92%), mp 129°C; ^{1}H NMR (DMSO-d6, 600MHz): 2.44 (3H, s), 7.29-7.31 (1H, m), 7.36-7.38 (1H, m), 7.65 (1H, s), 7.80 (1H, d, J = 8.0), 7.97 (1H, s), 8.09 (1H, d, J = 8.0), 8.62 (2H, s). ^{13}C NMR (DMSO-d6, 150 MHz): δC ppm = 19,1, 99.1, 111.5, 111.7, 113.5, 121.2, 121.4, 121.7, 122.6, 123.0, 127.4, 131.3, 141.9. HRMS (TOF ES^{+}): m/z calcd for $C_{13}H_{10}N_3O_2$ [(M-H)$^{-}$], 240.0778; found, 240.0781. IR (KBr): 3275, 3120, 1518, 1453, 1444, 1400, 1368, 1332, 1273, 1216, 1156, 1137, 1064.

2-Chloro-7-methyl-8-nitropyrido[1,2-a]indol-9-amine (6b)

Brown solid, yield 144 mg (95%), mp 146°C; ^{1}H NMR (DMSO-d6, 600 MHz): 2.41 (3H, s, CH3), 7.32 (1H, d, J = 8.1), 7.58 (1H, s), 7.86 (1H, s), 7.92 (1H, s), 8.08 (1H, d, J = 8.0), 8.56 (2H, s). ^{13}C NMR (DMSO-d6, 150 MHz): δC ppm = 19.0, 98.4, 112.4, 113.2, 113.4, 120.3, 121.5, 112.8, 127.2, 128.1, 128.6, 129.6, 141.3. HRMS (TOF ES^{+}): m/z calcd for $C_{13}H_9ClN_3O_2$ [(M-H) –] 274.0389; found, 274.0391. IR (KBr): 3428, 3312, 3115, 1592, 1529, 1454, 1408.

2-Bromo-7-methyl-8-nitropyrido[1,2-a]indol-9-amine (6c)

Brown solid, yield 153 mg (87%), mp 170°C; ^{1}H NMR (DMSO-d6, 600MHz): 2.42 (3H, s, CH3), 7.46 (1H, dd, J = 8.5, 1.1), 7.61 (1H, s), 7.97 (1H, s), 8.05 (1H, d, J = 1.2), 8.08 (1H, d, J = 8.5), 8.57 (2H, s). ^{13}C NMR (DMSO-d6, 150 MHz): δC ppm = 19.0, 98.3, 112.5, 113.4, 113.6, 115.4, 121.6, 123.5, 125.3, 128.5, 128.8, 129.8, 141.3. HRMS (TOF ES^{+}): m/z calcd for $C_{13}H_9BrN_3O_2$ [(M-H)$^{-}$] 317.9884; found, 317.9887. IR (KBr): 3451, 3362, 3347, 3026, 2974, 1678, 1590, 1492, 1454, 1426.

2,7-Dimethyl-8-nitropyrido[1,2-a]indol-9-amine (6d)

Brown solid, yield 121 mg (86%), mp 166°C; ^{1}H NMR (DMSO-d6, 600MHz):): 2.43 (3H, s), 2.45 (3H, s), 7.19 (1H, d, J = 8.2), 7.55 (1H, s), 7.57 (1H, s), 7.91 (1H, s), 7.96 (1H, d, J = 8.3), 8.57 (2H, s). ^{13}C NMR (DMSO-d6, 150 MHz): δC ppm = 19.1, 21.2, 98.6, 111.2, 111.5, 113.6, 120.5, 121.2, 125.0, 127.3, 127.7, 129.9, 131 7, 141.9. HRMS (TOF ES^{+}): m/z calcd for $C_{14}H_{12}N_3O_2$ [(M-H)$^{-}$] 254.0935; found, 254.0936. IR (KBr): 3489, 3336, 2982, 2935, 2906, 1659, 1631, 1583, 1469, 1428, 1281, 1259.

2-Ethyl-7-methyl-8-nitropyrido[1,2-a]indol-9-amine (6e).

White solid, yield 123 mg (83%), mp 151°C; ^{1}H NMR (DMSO-d6, 600MHz): 1.26 (3H, t, J = 7.5), 2.43 (3H, s), 2.75 (2H, q, J = 7.5), 7.24 (1H, d, J = 7.5), 7.56-7.58 (2H, m), 7.92 (1H, s), 7.99 (1H, d, J = 8.5), 8.57 (2H, s). ^{13}C NMR (DMSO-d6, 150 MHz): δC ppm = 16.0, 19.1, 28.3, 98.8, 111.3, 111.5, 129.2, 129.6, 121.2, 124.0, 127.3, 127.7, 130.1, 138.3, 141.9. HRMS (TOF ES^{+}): m/z calcd for $C_{15}H_{14}N_3O_2$ [(M-H)$^{-}$] 268.1092; found, 268.1095. IR (KBr): 3489, 3336, 2982, 2935, 2906, 1659, 1631, 1583, 1469, 1428.

2-Ethoxy-7-methyl-8-nitropyrido [1,2-a]indol-9-amine (6f)

Brown solid, yield 130 mg (83%), mp 165°C; ^{1}H NMR (DMSO-d6, 600MHz):): 1.25 (3H, t, J = 7.5), 2.43 (3H, s), 2.73 (2H, q, J = 7.5), 7.22 (1H, d, J = 8.5), 7.56-7.58 (2H, m), 7.89 (1H, s), 7.96 (1H, d, J = 8.5), 8.57 (2H, s). ^{13}C NMR (DMSO-d6, 150 MHz): δC ppm – 16.0, 19.1, 28.3, 98.7, 111.2, 111.5, 113.6, 119.2, 121.2, 124.0, 127.3, 127.7, 130.1, 138.2, 141.9. HRMS (TOF ES^{+}): m/z calcd for $C_{15}H_{14}N_3O_3$ [(M-H)$^{-}$] 284.1041; found, 284.1044. IR (KBr) - 3451, 1520, 1455, 1444, 1400, 1368, 1332, 1273, 1216, 1064.

2-Methoxy-7-methyl-8-nitropyrido[1,2-a]indol-9-amine (6g)

Brown solid, yield 134 mg (90%), mp 170°C ^{1}H NMR (DMSO-d6, 600MHz): 2.43 (3H, s), 3.83 (3H, s), 6.99 (1H, d, J = 8.5), 7.23 (1H, s), 7.55 (1H, s), 7.91 (1H, s), 7.98 (1H, d, J = 8.5), 8.54 (2H, s). ^{13}C NMR (DMSO-d6, 150 MHz): δC ppm = 19.1, 55.3, 98.6, 101.0, 111.5, 112.5, 113.1, 114.7, 121.2, 126.8, 127.5, 128.1, 141.5, 155.76. HRMS (TOF ES^{+}): m/z calcd for $C_{14}H_{13}N_3O_3$ [(M+H) $^{+}$] 270.0884; found, 270.0887. IR (KBr): 3450, 3336, 1659, 1631, 1583, 1468, 1428, 1281, 1260, 1147, 1112, 1060.

7-Benzyl-8-nitropyrido[1,2-a]indol-9-amine (6h).

Brown solid, yield 133 mg (76%), mp 173°C ^{1}H NMR (DMSO-d6, 600MHz): 4.25 (2H, s), 7.13-7.16 (3H, m), 7.23 (2H, t, J = 7.0), 7.41 (1H, dd J = 8.5, 1.5), 7.66 (2H, s), 7.93 (1H, d, J = 1.5), 8.16 (1H, d, J = 8.5), 8.22 (1H, s). 8.53 (2H, s). ^{13}C NMR (DMSO-d6, 150 MHz): δC ppm = 37.4, 98.9, 78.1, 113.4, 115.0, 120.5, 120.7, 123.1, 125.9, 126.8, 127.4, 128.0, 128.1, 128.2, 128.4, 128.9, 130.0, 140.3, 141.7. HRMS (TOF ES^{+}): m/z calcd for $C_{19}H_{14}N_3O_2$ [(M-H)$^{-}$] 316.1092; found, 316.1093. IR (KBr): 3433, 3310, 3061, 1599, 1552, 1531.

7-Benzyl-2-chloro-8-nitropyrido [1,2-a]indol-9-amine (6i).

Brown solid, yield 159 mg (82%), mp 222°C ^{1}H NMR (DMSO-d6, 600MHz): 4.25 (2H, s, CH2), 7.12-7.16 (3H, m), 7.23 (2H, t, J = 7.0), 7.40 (2H, dd, J = 8.5, 2.0), 7.66 (1H, s), 7.93 (1H, d, J = 2.0), 8.16 (1H, d J = 8.5), 8.21 (2H, s). ^{13}C NMR (DMSO-d6, 150 MHz): δC ppm = 37.4, 59.7, 99.0, 113.4, 115.1, 120.5, 120.5, 120.5, 120.7, 123.1, 125.9, 127.4, 128.0, 128.4, 128.9, 130.0, 140.3, 141.7, 170.3. HRMS (TOF ES^{+}): m/z calcd for $C_{19}H_{13}ClN_3O_2$ [(M-H)$^{-}$] 350.0703 found, 350.0701 IR (KBr): 3478, 3346, 3291, 3108, 1729, 1601, 1551, 1535, 1452, 1416, 1369, 1264.

7-Benzyl-2-methyl-8-nitropyrido [1,2-a]indol-9-amine (6j)

Yellow solid, yield 155 mg (85%), mp 170°C. ^{1}H NMR (DMSO-d6, 600MHz): 2.46 (3H, s), 4.25 (2H, s), 7.13-7.16 (3H, m), 7.21-7.23 (3H, m), 7.6 (2H, s), 7.99 (1H, d, J =8.5), 8.14 (1H, s), 8.52 (2H, s). ^{13}C NMR (DMSO-d6, 150 MHz): 21.4, 37.0, 99.1, 111.2, 114.2, 115.2, 120.3, 120.6, 125.2, 125.9, 127.4, 127.8, 127.8, 127.9, 128.1, 128.2, 130.2, 131.9, 140.6, 142.2. HRMS (TOF ES^{+}): m/z calcd for $C_{20}H_{16}N_3O_2$ [(M-H)$^{-}$] 330.1248; found, 330.1249. IR (KBr): 3429, 3314, 3117, 2973, 2930, 1720, 1592, 1529, 1454, 1408, 1382, 1332, 1262, 1240.

7-Benzyl-2-ethyl-8-nitropyrido[1,2-a]indol-9-amine (6k).

Brown solid, yield 123 mg (65%), mp 173°C ^{1}H NMR (DMSO-d6, 600MHz): 1.26 (3H, t, J = 7.0), 2.74-2.77 (2H, q, J = 7.0), 4.26 (2H, s), 7.13-7.15 (3H, m), 7.22 (2H, d, J = 7.6), 7.27 (1H, d, J = 8.2), 7.62 (2H, s), 8.01 (1H, d, J = 8.6), 8.14 (1H, s), 8.54 (2H, s). ^{13}C NMR (DMSO-d6, 150 MHz): δC ppm = 16.1, 28.4, 37.5, 99.4, 111.4, 114.2, 115.2, 119.2, 119.4, 120.3, 124.3, 124.2, 125.9, 127.5, 127.8, 127.9, 128.1, 130.4,138.4, 140.6, 142.2. HRMS (TOF ES^{+}): m/z calcd for $C_{21}H_{18}N_3O_2$ [(M-H)$^{-}$] 344.1404; found, 344.1407. IR (KBr): 3429, 3315, 3117, 2982, 2935, 2906, 1659, 1631, 1583, 1469, 1428, 1382, 1332, 1262, 1240.

6-Methyl-7-nitroindolizin-8-amine (7)

Brown solid, yield 86 mg (82%). mp 114°C ^{1}H NMR (DMSO-d6, 600MHz): 2.35 (3H, s), 6.64-6.65 (1H, m), 7.31-7.33 (1H, m), 7.38-7.40 (1H, m), 7.49 (1H, s), 8.42 (2H, s). ^{13}C NMR (DMSO-d6, 150 MHz): δC ppm = 19.4, 107.7, 113.2, 115.1, 118.9, 119.9, 119.4, 122.4, 141.9. HRMS (TOF ES^{+}): m/z calcd for $C_9H_8N_3O_2$ [(M-H)$^{-}$] 190.0622 found, 190.0616 IR (KBr): 3480, 3115, 1580, 1516, 1332.

General procedure for preparation of Ethyl 9-amino-7-methylpyrido [1, 2-a]indole-8-carboxylate.

The Solution of a Propargylated Indole **1** (100mg, 0.55 mmol), DBU (17 mg, 0.111 mmol), (888 mg, 5.5 mmol), diethyl malonate was added in 2 ml of DMF, reaction was heated under dry condition at 150°C for 5.0 hrs. The reaction progress was monitored by TLC. After completion, the reaction mass was diluted with water (30 mL) and extracted with ethyl acetate (2x20 mL). Organic layer was dried over sodium sulfate and evaporated under reduced pressure. The product was purified by column chromatography on silica eluting with 40 % EtOAc /hexane.

Ethyl 9-amino-7-methylpyrido [1,2-a]indole-8-carboxylate (8a).

Yellow solid, yield 127 mg (86%), mp 128°C; ^{1}H NMR (DMSO-d6, 600MHz): 1.33 (3H, t, J = 7.0), 2.39 (3H, s), 4.28 (2H, q, J = 7.0), 7.24 (1H, s), 7.26- 7.28 (2H, m), 7.58 (2H, s), 7.75-7.77 (1H, m), 7.90 (1H, s), 8.06-8.08 (2H, m). ^{13}C NMR (DMSO-d6, 150 MHz): δC ppm = 14.20, 20.6, 59.7, 93.8, 96.5, 111.3, 112.1, 116.1, 120.9, 121.1, 122.1, 127.3, 128.4, 130.3, 144.8, 168.2. HRMS

(TOF ES$^+$): m/z calcd for $C_{16}H_{17}N_2O_2$ [(M+H) $^+$] 269.1284; found, 269.1287. IR (KBr), - 3330, 3295, 3120, 3051, 2930, 1697,146, 1194, 1143, 1049, 1026, 1004.

Ethyl 9-amino-2-chloro-7-methylpyrido[1,2-a]indole-8-carboxylate (8b).

Yellow solid, yield 153 mg (92%), mp 129°C; ^{1}H NMR (DMSO-d6, 600MHz): 1.33 (3H, t, J = 7.0), 2.38 (3H, s), 4.28 (2H, q, J = 7.0), 7.23 (1H, s), 7.24- 7.25-7.27 (1H, m), 7.58 (2H, s), 7.84 (1H, d, J = 2.0), 7.94 (1H, s), 8.11-8.13 (1H, m). ^{13}C NMR (DMSO-d6, 150 MHz): δC ppm = 14.1, 20.5, 59.8, 93.4, 97.1, 112.1, 113.1, 116.9, 119.8, 121.0, 126.8, 128.1, 128.8, 129.7, 144.4, 168.1. HRMS (TOF ES$^+$): m/z calcd for $C_{16}H_{16}ClN_2O_2$ [(M+H)$^+$] 303.0895 found, 303.0892. IR (KBr): 3325, 3291, 3115, 3048, 1520, 1449, 1346, 1246, 1190, 1143, 1122.

Ethyl 9-amino-2,7-dimethylpyrido[1,2-a]indole-8-carboxylate (8c).

Yellow solid, yield 107 mg (69%), mp 135°C; ^{1}H NMR (DMSO-d6, 600MHz): 1.33 (3H, t, J = 7.0), 2.37 (3H, s), 2.44 (3H, s), 4.28 (2H, q, J = 7.0), 7.09 (1H, s), 7.14 (1H, s), 7.53 (2H, d, J = 7.5), 7.85 (1H, s), 7.94 (1H, d, J = 7.5). ^{13}C NMR (DMSO-d6, 150 MHz): δC ppm = 14.2, 20.6, 21.3, 59.6, 93.2, 96.4, 111.0, 112.1, 115.8, 120.0, 123.0, 127.6, 128.5, 128.9, 131.0, 144.8, 168.3. HRMS (TOF ES$^+$): m/z calcd for $C_{17}H_{19}N_2O_2$ [(M+H)$^+$] 283.1441; found, 283.1442. IR (KBr): 3329, 3295, 3277, 2931, 1697, 1616, 1521, 1452, 1402, 1346, 1246, 1194.

Ethyl 9-amino-2-ethyl-7-methylpyrido[1,2-a]indole-8-carboxylate (8d).

Yellow solid, yield 134 mg (82%), mp 129°C; ^{1}H NMR (DMSO-d6, 600MHz): 1.26 (3H, t, J = 7.5), 1.33 (3H, t, J = 7.5), 2.38 (3H, s), 2.74 (2H, q, J = 7.5), 4.28 (2H, q, J = 7.5), 7.13-7.15 (2H, m), 7.52-7.55 (3H, m), 7.85 (1H, s), 7.96 (1H, d, J = 8.5). ^{13}C NMR (DMSO-d6, 150 MHz): δC ppm = 14.2, 16.1, 20.6, 28.4, 59.6, 93.4, 96.4, 111.1, 112.1, 115.8, 118.8, 122.0, 127.6, 128.4, 129.12, 137.6, 144.8, 168.3, HRMS (TOF ES$^+$): m/z calcd for $C_{18}H_{21}N_2O_2$ [(M+H)$^+$] 297.1597; found, 297.1599. IR (KBr): 3329, 3295, 3277, 3120, 3053, 2931, 1697, 1616, 1521, 1452, 1402, 1346, 1246, 1194.

Methyl 9-amino-7-methylpyrido[1,2-a]indole-8-carboxylate (8e).

Yellow solid, yield 99 mg (71%), mp 124°C; ^{1}H NMR (DMSO-d6, 600MHz): 2.37 (3H, s), 3.80 (3H, s), 7.26-7.28 (3H, m), 7.57 (1H, s) 7.75-7.77 (1H, m), 7.90 (1H, s), 8.06-8.08 (2H, m). ^{13}C NMR (DMSO-d6, 150 MHz): δC ppm = 20.5, 59.8, 93.4, 97.1, 112.1, 113.1, 116.9, 119.8, 121.0, 126.8, 128.1, 128.8, 129.7, 144.4, 168.1. HRMS (TOF ES$^+$): m/z calcd for $C_{15}H_{15}N_2O_2$ [(M+H)$^+$] 255.1128; found, 255.1131. IR (KBr): 3330, 3295, 3120, 3051, 2930, 1697,146, 1194, 1049.

Methyl 9-amino-2-chloro-7-methylpyrido[1,2-a]indole-8-carboxylate (8f).

Yellow solid, yield 138 mg (87%), mp 132°C; ^{1}H NMR (DMSO-d6, 600MHz): 2.35 (3H, s), 3.80 (3H, s) 7.24-7.26 (2H, m), 7.57 (2H, s), 7.84 (1H, d, J = 1.5) 7.94 (1H, s), 8.09-8.11 (1H, m). ^{13}C NMR (DMSO-d6, 150 MHz): δ C ppm = 20.4, 51.0, 93.5, 97.1, 112.1, 113.1, 116.8, 119.8, 121.0, 126.8, 128.2, 128.8, 129.7, 144.3, 166.5. HRMS (TOF ES$^+$): m/z calcd for $C_{15}H_{14}ClN_2O_2$ [(M+H)$^+$

] 289.0738; found, 289.0741. IR (KBr): 3325, 3291, 3115, 3048, 1520, 1449, 1346, 1246, 1190, 1143.

Methyl 9-amino-2,7-dimethylpyrido[1,2-a]indole-8-carboxylate (8g)

Yellow solid, yield 122 mg (83%), mp 124°C; ^{1}H NMR (DMSO-d6, 600MHz): 2.35 (3H, s), 2.44 (3H, s), 3.79 (3H, s), 7.09 (1H, d, J = 8.5), 7.15 (1H, s) 7.52-7.54 (3H, m), 7.85 (1H, s), 7.94 (1H, d, J = 8.1). ^{13}C NMR (DMSO-d6, 150 MHz): δC ppm = 20.5, 21.4, 59.8, 93.4, 97.1, 112.1, 113.1, 116.9, 119.8, 121.0, 126.8, 128.1, 128.8, 129.7, 144.4, 168.1. HRMS (TOF ES^{+}): m/z calcd for $C_{16}H_{17}N_2O_2$ [(M+H)$^{+}$] 269.1284; found, 269.1287. IR (KBr): 3439, 1665, 1643.

Methyl 9-amino-2-bromo-7-methylpyrido[1,2-a]indole-8-carboxylate (8h).

Yellow solid, yield 147 mg (80%), m.p. 138°C; 1H NMR (DMSO-d6, 600MHz): 2.35 (3H, s), 3.80 (3H, s) 7.24-7.26 (2H, m), 7.57 (2H, s) 7.84 (1H, d, J = 1.5) 7.93 (1H, s), 8.12 (1H, d, J = 8.5). ^{13}C NMR (DMSO-d6, 150 MHz): δC ppm = 20.4, 51.0, 93.5, 97.0, 112.1, 113.1, 116.8, 119.8, 121.0, 126.8, 128.2, 128.8, 129.6, 144.3, 168.5. HRMS (TOF ES^{+}): m/z calcd for $C_{15}H_{14}BrN_2O_2$ [(M+H)$^{+}$] 333.0233; found, 333.0236. IR (KBr): 3324, 3292, 3115, 3048, 1520, 1449, 1346, 1246.

Methyl 9-amino-2-methoxy-7-methylpyrido[1,2-a]indole-8-carboxylate (8i).

Yellow solid, yield 125 mg (80%), mp 138°C; ^{1}H NMR (DMSO-d6, 600MHz): 2.35 (3H, s), 3.80 (3H, s), 3.82, (3H, s), 6.89 (1H, dd, J = 6.5, 2.5), 7.15 (1H, s), 7.18 (1H, d, J = 2.5), 7.50 (2H, s), 7.85 (1H, s), 7.6 (1H, d, J = 7.0). ^{13}C NMR (DMSO-d6, 150 MHz): δC ppm = 20.4, 50.9, 55.2, 93.5, 96.4, 100.8, 112.1, 112.2, 112.5, 115.8, 125.8, 128.0, 128.6, 144.4, 155.5, 168.7, HRMS (TOF ES^{+}): m/z calcd for $C_{16}H_{17}N_2O_3$ [(M+H) $^{+}$] 285.1234; found, 285.1235. IR (KBr): 3330, 3295, 3115, 3048, 2931, 1520, 1449, 1346, 1246, 1190, 1140, 1122.

Ethyl 9-amino-7-benzyl-2-methylpyrido[1,2-a]indole-8-carboxylate (8j).

Yellow solid, yield 158 mg (80%), mp 165°C; ^{1}H NMR (DMSO-d6, 600MHz): 1.08 (3H, t, J = 7.0), 2.41 (3H, s), 4.02 (2H, q, J = 7.0), 4.19 (2H, s), 7.09- 7.14 (4H, m), 1.03 (1H, s), 7.25 (2H, t, J = 7.6), 7.40 (2H, s), 7.56 (1H, s), 7. 95 (1H, d, J = 8.6), 8.04 (1H, s). ^{13}C NMR (DMSO-d6, 150 MHz): δC ppm = 13.8, 21.3, 38.5, 59.5, 93.5, 96.1, 111.0, 113.8, 118.1, 120.1, 123.2, 125.5, 127.7, 127.8, 128.0, 128.2, 128.6 (2C), 129.2, 131.2, 141.8, 144.6, 167.7. HRMS (TOF ES^{+}): m/z calcd for $C_{23}H_{23}N_2O_2$ [(M+H)$^{+}$] 359.1754; found, 359.1757. IR (KBr): 3329, 3295, 3277, 2930, 1697, 1616, 1521, 1452, 1402, 1346, 1246, 1190.

Methyl 9-amino-7-benzyl-2-methoxypyrido[1,2-a]indole-8-carboxylate (8k)

Yellow solid, yield 156 mg (79%), mp 146°C; ^{1}H NMR (DMSO-d6, 600MHz): 2.46 (3H, s), 3.58 (3H, s), 4.15 (2H, s), 7.11- 7.40 (4H, m) 7.18 (1H, s), 7.23 (1H, t, J = 7.5), 7.38 (2H, s), 7.56 (1H, s), 7.97 (2H, d, J = 8.5), 8.07 (1H, s) ^{13}C NMR (DMSO-d6, 150 MHz): δC ppm = 21.4, 38.6, 50.8, 93.6, 95.8, 111.0, 113.8, 118.5, 120.1, 123.2, 125.6, 125.8, 128.0 (2C), 128.5 (2C), 129.2, 131.2, 131.3, 141.6, 144.6, 168.1 HRMS (TOF ES^{+}): m/z calcd for $C_{22}H_{21}N_2O_3$ [(M+H) $^{+}$] 361.1547;

found, 361.1543. IR (KBr): 3330, 3295, 3115, 3048, 2931, 1520, 1449, 1346, 1246, 1190, 1140, 1122.

General procedure A for the preparation of hydroamination products 9.

The solution of aniline (67 mg, 0.58 mmol, 1.5 eq) and LiHMDS (0.08 ml of 1M THF solution, 0.2 eq) stirred in dry THF for 5-10 min at -15° C, then, propargylated indole **9a-e** (0.38 mmol) was added, and the reaction mixture was stirred at -15°C for 3-8 hours). The reaction progress was monitored by TLC. After completion, the reaction mass was evaporated to get crude compound. Purification of the crude compound was performed by column chromatography, eluting with ethyl acetate/hexane system.

An alternative procedure for the preparation of hydroamination products

The solution of a propargylated indole (0.55 mmol) and a nucleophile (0.82 mmol) with *t*-BuOK (124 mg, 1.1 mmol, 2.0 eq) in 3.0 ml of dry THF was heated for 1 h at 150°C. The reaction progress was monitored by TLC. After completion, the reaction mass was evaporated to get crude compound. Purification of the crude compound was performed by column chromatography, eluting with ethyl acetate/hexane system. The yields of the products **9i-p** were approximately the same as for the general procedure A.

1-[(1*E*)-2-(phenylamino)prop-1-en-1-yl]-1*H*-indole-2-carbonitrile (9a)

White solid, yield 88 mg (83 %), mp 119°C; ^{1}H NMR (DMSO-d_6, 600MHz): 1.76 (3H, s, CH_3), 7.21 (1H, t, *J* = 7.4), 7.28 (1H, s), 7.32 (1H, t, *J* = 7.4), 7.35 (2H, d, *J* = 8.1), 7.48-7.49 (1H, m), 7.51 (2H, s), 7.53-7.57 (2H, m), 7.72 (1H, d, *J* =7.9), 7.87 (1H, d, *J* = 7.8); ^{13}C NMR (DMSO-*d*$_6$, 150 MHz): δ_C ppm = 18.1, 99.86, 99.89, 100.9, 110.1 (2C), 121.4, 121.5, 122.9, 123.0, 127.0, 129.4, 129.5, 129.61, 129.63, 129.7, 130.0 (2C), 131.8; HRMS (TOF ES$^+$): m/z calcd for $C_{18}H_{16}N_3$ $[M+H]^+$ 274.1339; found, 274.1342. IR (KBr): 3276, 3120, 2220, 1518, 1459, 1444, 1333.

(*E*)-1-(2-((4-bromophenyl)amino)prop-1-en-1-yl)-5-chloro-1*H*-indole-2-carbonitrile (9b)

White solid, yield 81 mg (65%), mp 110°C; ^{1}H NMR (DMSO-*d*$_6$, 600 MHz): 1.72 (3H, s), 7.30-7.36 (4H, m), 7.55 (1H, s), 7.72 (2H, d, *J* = 8.6), 7.81 (1H, s), 7.92 (1H, d, *J* = 9.3); ^{13}C NMR (DMSO-*d*$_6$, 150 MHz): δ_C ppm = 18.0, 99.6, 101.0, 112.7, 120.5 (2C), 123.1, 123.3, 126.1, 127.8, 130.2, 132.2, 132.3 (2C), 132.4, 132.44, 132.49, 132.5. HRMS (TOF ES$^+$): m/z calcd for $C_{18}H_{13}BrClN_3$ $[M+H]^+$ 384.9981; found, 386.0059. IR (KBr): 3220, 3272, 3119, 2221, 1646, 1517, 1114.

(*E*)-1-(2-((4-bromophenyl)amino)prop-1-en-1-yl)-5-bromo-1*H*-indole-2-carbonitrile (9c)

White solid, yield 81 mg (70 %), mp 119°C; ^{1}H NMR (DMSO-*d*$_6$, 600 MHz): 1.76 (3H, s), 7.30-7.36 (2H, m), 7.43 (1H, d, *J* = 8.7), 7.53 (1H, s), 7.67-7.75 (1H, m), 7.88 (1H, d, *J* = 8.6), 7.95

(1H, d, *J* = 1.5), ^{13}C NMR (DMSO-*d*$_6$, 150 MHz): δ_C ppm = 18.0, 99.5, 101.0, 113.1, 113.2, 114.2, 114.3, 123.6 (2C), 125.5, 128.5, 130.5, 127.8, 132.3 (2C), 132.38, 132.40, 132.45 HRMS (TOF ES$^+$): m/z calcd for $C_{18}H_{14}Br_2N_3$ $[M+H]^+$ 429.9549; found, 429.9554. IR (KBr): 3313, 3048, 2228, 1671, 1596, 1488, 1203.

(*E*)-5-chloro-1-(2-((4-fluorophenyl)amino)prop-1-en-1-yl)-1*H*-indole-2-carbonitrile (9d)

White solid, yield 87 mg (82%), mp 138°C; ^{1}H NMR (DMSO-*d*$_6$, 600MHz): 1.77 (3H, s), 7.19-7.23 (1H, m), 7.30-7.34 (2H, m), 7.36-7.43 (4H, m), 7.51 (1H, s), 7.72 (1H, d, *J* = 8.1), 7.87 (1H, d, *J* = 8.1); ^{13}C NMR (DMSO-*d*$_6$, 150 MHz): δ_C ppm = 18.0, 99.9, 100.9, 110.9, 121.39, 121.40, 121.41, 122.9 (2C), 122.97, 123.0, 127.0, 131.7, 131.8 (2C), 132.06, 132.08, 132.11. HRMS (TOF ES$^+$): m/z calcd for $C_{18}H_{14}ClFN_3$ $[M+H]^+$, 325.0782; found, 325.0788; IR (KBr): 3313, 3048, 2225, 1671, 1596, 1355.

(*E*)-5-chloro-1-(2-((2,6-dimethylphenyl)amino)prop-1-en-1-yl)-1*H*-indole-2-carbonitrile (9e)

Brown solid, yield 70 mg (65%), mp 138°C; ^{1}H NMR (DMSO-*d*$_6$, 600MHz): 1.70 (3H, s), 1.91 (3H, s), 2.33 (3H, s), 7.12 (1H, bs), 7.30-7.35 (4H, m), 7.40 (1H, s), 7.62 (1H, bs), 7.82 (1H, s), 7.95 (1H, d, *J* = 8.0); ^{13}C NMR (DMSO-*d*$_6$, 150 MHz): δ_C ppm = 13.5, 17.5, 20.0, 99.7, 112.7 (2C), 112.81, 112.85, 120.6 (2C), 122.22, 122.26, 123.1, 126.22, 126.6, 126.7, 127.2, 127.9, 130.2, 130.31, 130.34, 130.38. HRMS (TOF ES$^+$): m/z calcd for $C_{20}H_{19}ClN_3$ $[M+H]^+$, 336.1262; found, 336.1266; IR (KBr): 3282, 3104, 2978, 2223, 1680, 1551, 1469.

(*E*)-1-(2-(1H-indol-1-yl)prop-1-en-1-yl)-1*H*-indole-2-carbonitrile (9f)

White solid, yield 122 mg (70%), mp 129°C; ^{1}H NMR (DMSO-*d*$_6$, 600MHz): 2.14 (3H, s), 6.74 (1H, d, *J* = 3.1), 7.17 (1H, t, *J* = 7.6), 7.27-7.31 (2H, m), 7.35 (1H, s), 7.50 (1H, t, *J* = 7.2), 7.55 (1H, d, *J* = 8.4), 7.66 (1H, d, *J* = 7.8), 7.69 (1H, s), 7.78 (1H, d, *J* = 2.1), 7.80 (1H, d, *J* = 4.0), 7.87 (1H, d, *J* = 7.9);^{13}C NMR (DMSO-*d*$_6$, 150 MHz): δ_C ppm = 16.9, 104.1, 110.1, 111.6, 111.7, 113.7, 114.7, 116.1, 120.6, 120.9, 122.0, 122.4, 122.6, 125.8, 126.5, 127.5, 129.2, 135.2, 137.6, 139.9; HRMS (TOF ES$^+$): m/z calcd for $C_{20}H_{16}N_3$ $[M+H]^+$, 298.1339; found, 298.1342. IR (KBr): 3137, 2898, 2689, 2226, 1856, 1687, 1556.

(*E*)-1-(2-(1*H*-indol-1-yl)prop-1-en-1-yl)-5-methyl-1*H*-indole-2-carbonitrile (9g)

White solid, yield 144 mg (78%), mp 146°C; ^{1}H NMR (DMSO-*d*$_6$, 600 MHz): 2.13 (3H, s, CH_3), 2.43 (3H, s), 6.73 (1H, d, *J* = 3.14), 7.16 (1H, t, *J* = 6.8), 7.27 (1H, t, *J* = 6.5), 7.31-7.33 (2H, m), 7.44 (1H, d, *J* = 8.0), 7.56 (1H, s), 7.58 (1H, s), 7.66 (1H, d, *J* = 7.7), 7.77 (1H, d, *J* = 3.3), 7.85 (1H, d, *J* = 7.4);

^{13}C NMR (DMSO-*d*$_6$, 150 MHz): δ_C ppm = 17.4, 21.4, 104.5, 110.4, 111.9, 112.1, 114.2, 114.6, 116.7, 121.1, 121.4, 122.0, 123.0, 126.5, 128.04, 128.8, 129.7, 131.5, 135.7, 136.6, 140.1 HRMS (TOF ES$^+$): m/z calcd for $C_{21}H_{18}N_3$ $[M+H]^+$ 312.1495; found, 312.1498. IR (KBr):3210, 2895, 2656, 2229, 1658, 1590, 1250.

(*E*)-1-(2-(1*H*-indol-1-yl)prop-1-en-1-yl)-5-ethyl-1*H*-indole-2-carbonitrile (9h)

White solid, yield 153 mg (67%), mp 170°C; ^{1}H NMR (DMSO-d_6, 600MHz): 1.24 (3H, t, J = 7.2), 2.14 (3H, s), 2.73 (2H, q, J = 7.2), 7.74 (1H, d, J = 3.5), 7.16 (1H, t, J = 7.4), 7.27 (1H, t, J = 7.7), 7.32 (1H, s), 7.36 (1H, d, J = 8.4), 7.46 (1H, d, J = 8.2), 7.58 (1H, s), 7.60 (1H, s), 7.66 (1H, d, J = 7.5), 7.77 (1H, d, J = 3.1), 7.85 (1H, d, J = 8.3); ^{13}C NMR (DMSO-d_6, 150 MHz): δ_C ppm = 16.1, 16.9, 28.1, 101.0, 109.9, 111.6, 111.6, 113.8, 114.3, 116.2, 120.3, 120.6, 120.9, 122.6, 126.0, 127.4, 127.5, 129.2, 135.2, 136.3, 137.6, 139.6. HRMS (TOF ES$^+$): m/z calcd for $C_{22}H_{20}N_3$ $[M+H]^+$ 326.1652; found, 326.1655. IR (KBr):3147, 2825, 2287, 1857,1635, 1579, 1464.

(*E*)-1-(2-(1*H*-benzo[d]imidazol-1-yl)prop-1-en-1-yl)-5-chloro-1*H*-indole-2-carbonitrile (9i)

White solid, yield 111 mg (72%), mp 166°C; ^{1}H NMR (DMSO-d_6, 600MHz):): 2.23 (3H, s), 7.35 (1H, t, J = 6.4), 7.41 (1H, t, J = 7.5), 7.51 (1H, dd, J = 7.30, 2.0), 7.53 (1H, d, J = 1.5), 7.67 (2H, t, J = 8.9), 7.79 (1H, d, J = 8.1), 7.88 (1H, d, J = 8.1), 7.90 (1H, d, J = 1.8), 8.69 (1H, s); ^{13}C NMR (DMSO-d_6, 150 MHz): δ_C ppm = 16.6, 115.5, 111.9, 113.1, 113.7, 114.4, 117.0, 120.0, 121.5, 122.8, 123.7, 126.6, 126.7, 126.8, 132.6, 136.0, 137.6, 142.9, 143.0. HRMS (TOF ES$^+$): m/z calcd for $C_{19}H_{14}ClN_4$ $[M+H]^+$ 333.0902; found, 333.0905. IR (KBr): 3025, 2953, 2221, 1854, 1634, 1521, 1312.

(*E*)-1-(2-(1*H*-pyrrolo [2,3-b]pyridin-1-yl)prop-1-en-1-yl)-5-chloro-1*H*-indole-2-carbonitrile (9j)

White solid, yield 104 mg (55 %), m.p. 125°C; ^{1}H NMR (DMSO-d_6, 600MHz): 2.25 (3H, s, CH_3), 6.76 (1H, d, J = 3.5), 7.26-7.28 (1H, m), 7.48 (1H, d, J = 8.8), 7.57 (1H, d, J = 9.0), 7.64 (1H, s), 7.89 (1H, d, J = 1.4), 7.94 (1H, d, J = 3.8), 8.05 (1H, s), 8.12 (1H, dd, J = 7.8, 1.1), 8.40 (1H, d, J = 4.5); ^{13}C NMR (DMSO-d_6, 150 MHz): δ_C ppm: 15.8, 102.3, 111.7, 113.1, 113.55, 113.57, 114.0, 117.4, 121.48, 121.5, 122.1, 126.6, 126.7, 128.1, 129.4, 136.2, 139.8, 143.3, 147.6 HRMS (TOF ES$^+$): m/z calcd for $C_{19}H_{14}ClN_4$ $[M+H]^+$ 333.0902; found, 333.0905. IR (KBr): 3396, 2951, 2927, 2218, 1703, 1519, 1456.

General procedure for the preparation of cyclized products (10)

The solution of a propargylated indole-2-carbonitrile **1a-e** (0.38 mmol), LiHMDS in THF solution (0.1 mL, 0.5 eq) and MeOH (2.0 eq) were stirred for 10-15 min. A solution of nucleophile (1.5 eq) was combined with LiHMDS (2.0 eq) and added to the reaction mixture, stirred for 8-15 hours under reflux. The reaction progress was monitored by TLC. After completion, the reaction mass was evaporated to get crude compound. Purification of the crude compound was performed by column chromatography, eluting with 2-5% ethyl acetate in hexane.

3-Methyl-*N*-phenylpyrazino[1,2-a]indol-1-amine (10a)

Yellow solid, yield 74 mg (78%), mp 183°C; ^{1}H NMR (DMSO-*d*$_6$, 600MHz): 2.31 (3H, s), 7.02 (1H, m), 7.32-7.36 (3H, m), 7.46 (1H, s), 7.97 (1H, s), 8.05 (2H, m), 8.16 (3H, m), 9.41 (1H, s); ^{13}C NMR (DMSO-*d*$_6$, 150 MHz): δ_C ppm = 20.9, 92.6, 106.8, 113.3, 120.0 (2C), 120.6, 121.6, 122.0, 122.3, 127.0, 127.9, 128.4, 128.5 (2C), 128.6, 131.3, 146.9. HRMS (TOF ES$^+$): m/z calcd for $C_{18}H_{16}N_3$ [M+H]$^+$, 274.1339; found, 274.1343; IR (KBr): 3345, 2925, 2899, 1956, 1875, 1645, 1520.

8-Chloro-3-methyl-*N*-phenylpyrazino[1,2-a]indol-1-amine (10b)

Yellow solid, yield 474 mg (78%), mp 183°C; ^{1}H NMR (DMSO-*d*$_6$, 600MHz): 2.31 (3H, s), 7.02 (2H, t, *J* = 5.7), 7.27-7.40 (3H, m), 7.46 (1H, s), 7.96 (1H, s,), 8.05 (1H, d, *J* = 7.3); 8.14-8.17 (2H, m); 9.26 (1H, s); ^{13}C NMR ($CDCl_3$, 150 MHz): δ_C ppm = 20.8, 92.6, 106.7, 113.3, 119.9 (2C), 120.5, 121.5, 122.0, 123.2, 127.0, 127.9, 128.4, 128.4 (2C), 131.2, 140.5, 146.9; HRMS (TOF ES$^+$): m/z calcd for $C_{18}H_{15}ClN_3$ [M+H]$^+$, 308.0949; found, 308.0954; IR (KBr): 3325, 3025, 2958, 2866, 1823, 1625, 1520.

***N*-(4-bromophenyl)-8-chloro-3-methylpyrazino[1,2-a]indol-1-amine (10c)**

Yellow solid, yield 92 mg (74%), mp 156°C; ^{1}H NMR (DMSO-*d*$_6$, 600 MHz): 2.32 (3H, s, CH_3), 7.33 (1H, dd, *J* = 7.1, 2.0), 7.45 (1H, s), 7.52 (2H, d, *J* = 8.6), 7.98 (1H, d, *J* = 2.0), 8.05 (2H, d, *J* = 9.2), 8.18 (2H, d, *J* = 9.5), 9.41 (1H, s); ^{13}C NMR (DMSO-*d*$_6$, 150 MHz): δ_C ppm = 20.7, 92.8, 99.5, 107.2, 113.36, 113.44, 120.6, 121.8 (2C), 123.1, 127.1, 127.9, 128.4, 131.1, 131.2 (2C), 140.0, 146.7; HRMS (TOF ES$^+$): m/z calcd for $C_{18}H_{14}BrClN_3$ [M+H]$^+$, 386.0054; found, 386.0057; IR (KBr): 3098, 3064, 2920, 1715, 1625, 1525, 1449.

8-Chloro-3-methyl-*N*-(p-tolyl)pyrazino[1,2-a]indol-1-amine (10d)

Yellow solid, yield 77 mg (74%), mp 178°C; ^{1}H NMR (DMSO-*d*$_6$, 600 MHz): 2.28 (3H, s), 2.29 (3H, s), 7.15 (2H, d, *J* = 7.6), 7.31 (1H, dd , *J* = 8.1, 2.4), 7.43 (1H, s), 7.91 (2H, d, *J* = 8.7), 7.95 (1H, d, *J* = 1.6), 8.12 (1H, s), 8.15 (1H, d, *J* = 8.7), 9.19 (1H, s); ^{13}C NMR (DMSO-*d*$_6$, 150 MHz): δ_C ppm = 20.4, 20.8, 92.5, 108.4, 113.2, 120.1 (2C), 120.5, 121.4, 123.2, 127.0, 127.9, 128.3, 128.8 (2C), 130.9, 131.3, 138.0, 146.9; HRMS (TOF ES$^+$): m/z calcd for $C_{19}H_{17}ClN_3$ [M+H]$^+$, 322.1106; found, 322.1110; IR (KBr): 3319, 2923, 1731, 1604, 1508, 1477, 1404.

8-Chloro-*N*-(4-fluorophenyl)-3-methylpyrazino[1,2-a]indol-1-amine (10e)

Yellow solid, yield 83 mg (79%), mp 145°C; ^{1}H NMR (DMSO-*d*$_6$, 600MHz): 2.30 (3H, s), 7.16-7.23 (2H, m), 7.31 (1H, dd, *J* = 7.1, 1.6), 7.42 (1H, s), 7.96 (1H, d, *J* = 1.4), 8.04-8.10 (2H, m), 8.13-8.20 (2H, m), 9.32 (1H, s); ^{13}C NMR (DMSO-*d*$_6$, 150 MHz): δ_C ppm = 20.8, 92.6, 106.8, 113.3, 114.9, 115.0, 120.5, 121.6 (2C), 123.1, 127.0, 127.9, 128.41, 131.2, 136.9, 146.8, 156.7, 158.0; HRMS (TOF ES$^+$): m/z calcd for $C_{18}H_{14}ClFN_3$ [M+H] $^+$, 326.0855; found, 326.0860; IR (KBr): 3341, 3014, 2957, 2866, 1956, 1699, 1545.

8-Chloro-*N*-(4-methoxyphenyl)-3-methylpyrazino[1,2-a]indol-1-amine (10f)

Yellow solid, yield 75 mg (69%), mp 148°C; ^{1}H NMR (DMSO-*d*$_6$, 600MHz): 2.28 (3H, s), 3.75 (3H, s), 6.94 (2H, d, *J* = 8.8), 7.30 (1H, dd, *J* = 8.2, 1.4), 7.40 (1H, s), 7.92 (2H, d, *J* = 8.8), 7.94 (1H, s), 8.09 (1H, s), 8.14 (1H, d, *J* = 8.8), 9.16 (1H, s); ^{13}C NMR (DMSO-*d*$_6$, 150 MHz): δ_C ppm = 20.1, 55.1, 92.4, 106.2, 113.2, 113.6 (2C), 120.5, 121.4, 121.8 (2C), 123.2, 126.9, 127.9, 128.3, 131.4, 133.6, 147.0, 154.6 HRMS (TOF ES$^+$): m/z calcd for $C_{19}H_{17}ClN_3O$ $[M+H]^+$, 338.1055; found, 338.1062; IR (KBr): 3424, 2924, 1633, 1547, 1501, 1450, 1218.

***N*-(3,5-dimethoxyphenyl)-3-methylpyrazino[1,2-a]indol-1-amine (10g)**

Yellow solid, yield 70 mg (55%), mp 138°C; ^{1}H NMR (DMSO-*d*$_6$, 600MHz): 2.33 (3H, s), 3.77 (6H, s), 6.18 (1H, s), 7.30-7.36 (2H, m), 7.45-7.46 (3H, m), 7.86-7.87 (1H, m), 8.12-8.14 (2H, m), 9.13 (1H, s); ^{13}C NMR (DMSO-*d*$_6$, 150 MHz): δ_C ppm = 20.8, 55.0, 92.7, 94.1, 98.0, 107.0, 111.5 (2C), 121.4, 121.5, 121.6, 122.1, 122.6 (2C), 127.1, 129.9, 130.4, 142.4, 147.0, 160.3;HRMS (TOF ES$^+$): m/z calcd for $C_{20}H_{20}N_3O_2$ $[M+H]^+$, 334.1550; found, 334.1554; IR (KBr): 3355, 3121, 2908, 2201, 1723, 1654, 1532.

1-(1*H*-indol-1-yl)-3-methylpyrazino[1,2-a]indole (10h)

Yellow solid, yield 80 mg (70 %), mp 128°C; ^{1}H NMR (DMSO-*d*$_6$, 600MHz): 2.51 (3H, s), 6.86 (1H, d, *J* = 3.3), 7.11 (1H, s), 7.23 (1H, t, *J* = 7.1), 7.87 (1H, d, *J* = 7.8), 7.44 (2H, m) , 7.71 (1H, d , *J* = 7.8), 7.92 (1H, d, *J* = 7.8), 8.14 (1H, d, *J* = 8.1), 8.17 (1H, d, *J* = 3.3) , 8.32 (1H, d, *J* = 8.3), 8.73 (1H, s); ^{13}C NMR ($CDCl_3$, 150 MHz): δ_C ppm = 20.2, 95.5, 105.4, 112.1, 112.56, 112.58, 113.9, 120.8, 121.7, 122.1, 122.5, 122.9, 123.7, 127.1, 127.8, 129.4, 129.8, 130.3, 135.3, 144.61. HRMS (TOF ES$^+$): m/z calcd for $C_{20}H_{16}N_3$ $[M+H]^+$, 298.1339; found, 298.1344; IR (KBr): 3398, 3130, 2920, 1730, 1604, 1508, 1445.

8-Chloro-1-(1*H*-indol-1-yl)-3-methylpyrazino[1,2-a]indole (10i)

Yellow solid, yield 81 mg (75%), mp 124°C; ^{1}H NMR (DMSO-*d*$_6$, 600MHz): 2.45 (3H, s), 6.82 (1H, d, *J* = 3.5), 7.10 (1H, s), 7.19 (1H, t, *J* = 7.5), 7.25 (1H, t, *J* = 7.7), 7.41 (1H, d, *J* = 9.0) 7.67 (1H, d, *J* = 8.0); 7.93 (1H, s), 8.07-8.10 (2H, m), 8.31 (1H, d, *J* = 8.5), 8.69 (1H, s); ^{13}C NMR (DMSO-*d*$_6$, 150 MHz): δ_C ppm = 20.2, 95.1, 105.5, 112.7, 113.8, 113.9, 120.8, 120.8, 121.7, 122.6, 123.0, 124.01, 127.0, 128.2, 128.2, 128.5, 129.4, 130.9, 135.3, 144.4; HRMS (TOF ES$^+$): m/z calcd for $C_{20}H_{15}ClN_3$ $[M+H]^+$, 332.0949; found, 332.0955; IR (KBr): 3064, 2958, 2919, 1714, 1603, 1494, 1449.

8-Bromo-1-(1*H*-indol-1-yl)-3-methylpyrazino[1,2-a]indole (10j)

Yellow solid, yield 72 mg (72%), mp 122°C; ^{1}H NMR (DMSO-*d*$_6$, 600MHz): 2.49 (3H, s), 6.86 (1H, d, *J* = 3.3), 7.15 (1H, s), 7.23 (1H, t, *J* = 7.3), 7.28 (1H, t, *J* = 8.1), 7.55 (1H, dd, *J* = 8.8, 1.6), 7.71 (1H, d, *J* = 7.8), 8.09-8.16 (3H, m), 8.30 (1H, d, *J* = 8.8), 8.78 (1H, s); ^{13}C NMR (DMSO-*d*$_6$, 600MHz): δC ppm = 20.21, 95.08, 105.5, 112.7, 113.8, 114.2, 116.4, 120.8, 121.7, 123.0, 123.8, 124.0, 125.0, 127.0, 128.5, 129.2, 129.4, 130.9, 135.2, 144.5; HRMS (TOF ES$^+$): m/z calcd for

$C_{20}H_{15}BrN_3$ $[M+H]^+$, 376.0444; found, 376.0447; IR (KBr): 2951, 2919, 1703, 1540, 1498, 1450, 1398.

1-(1*H*-indol-1-yl)-8-methoxy-3-methylpyrazino[1,2-a]indole (10k)

Yellow solid, yield 72 mg (72%), mp 122°C; ^{1}H NMR (DMSO-*d*$_6$, 600MHz): 2.48 (3H, s), 3.82 (3H, s), 6.79 (1H, d, *J* = 3.6), 6.91 (1H, dd, *J* = 7.7, 2.6), 7.19 (1H, s), 7.22 (1H, d, *J* = 2.8), 7.45 (1H, dd, *J* = 7.6, 2.6), 7.99 (1H, d, *J* = 2.2), 8.08 (1H, d, *J* = 9.4) , 8.14 (1H, d, *J* = 3.6), 8.35 (1H, d, *J* = 8.1), 8.72 (1H, s); ^{13}C NMR (DMSO-*d*$_6$, 600MHz): δC ppm = 20.2, 55.3, 95.3, 102.7, 105.6, 112.4, 112.5, 112.6, 113.9, 114.9, 120.9, 122.6, 127.3, 127.4, 128.1, 128.3, 128.6, 130.2, 130.2, 130.9, 144.4; HRMS (TOF ES$^+$): m/z calcd for $C_{21}H_{17}N_3O$ $[M+H]^+$, 327.1372; found, 328.1449; IR (KBr): 3272, 3119, 1714, 1636, 1516, 1401, 1331.

8-Chloro-3-methyl-1-(3-methyl-1*H*-indol-1-yl)pyrazino[1,2-a]indole (10l)

Yellow solid, yield 73 mg (65%), mp 138°C; ^{1}H NMR (DMSO-*d*$_6$, 600MHz): 2.39 (3H, s), 2.48 (3H, s), 7.22 (1H, s), 7.24 (1H, t, *J* = 8.1), 7.29 (1H, t, *J* = 7.5), 7.44 (1H, dd, *J* = 7.7, 1.9), 7.65 (1H, d, *J* = 5.9), 7.97 (1H, s), 7.99 (1H, d, *J* = 1.5), 8.16 (1H, d, *J* = 8.1), 8.36 (1H, d, *J* = 8.8), 8.71 (1H, s); ^{13}C NMR (DMSO-*d*$_6$, 150 MHz): δ_C ppm = 9.4, 20.2, 95.3, 112.2, 113.9, 114.0, 114.3, 118.9, 120.8, 121.4, 122.6, 123.2, 124.0, 128.1, 128.2, 128.3, 128.5, 130.1, 130.9, 135.5, 144.4; HRMS (TOF ES$^+$): m/z calcd for $C_{21}H_{17}ClN_3$ $[M+H]^+$, 346.1106; found, 346.1110; IR (KBr): 3485, 3124, 2858, 2861, 1856, 1705, 1555.

1-(5-methoxy-1*H*-indol-1-yl)-3-methylpyrazino[1,2-a]indole (10m)

Yellow solid, yield 104 mg (82 %), mp 122°C; ^{1}H NMR (DMSO-d$_6$, 600MHz): 2.49 (3H, s), 3.84 (3H, s), 7.85 (1H, d, *J* = 3.1), 7.05 (1H, s), 7.09 (1H, dd, *J* = 8.8, 2.1), 7.22 (1H, t, *J* = 7.2), .7.27 (1H, t, *J* = 7.3), 7.31 (1H, d, *J* = 1.8), 7.71 (1H, d, *J* = 8.0), 8.09 (1H, d, *J* = 8.5), 8.13 (1H, d, *J* = 3.0), 8.22 (1H, d, *J* = 9.1), 8.69 (1H, s); ^{13}C NMR (DMSO-*d*$_6$, 600MHz): δ_C ppm = 20.1, 55.3, 94.9, 101.0, 105.2, 112.7, 113.2, 113.8, 114.3, 114.7, 120.8, 121.6, 122.9, 123.4, 125.4, 127.1, 128.1, 129.4, 130.1, 135.3, 144.5. HRMS (TOF ES$^+$): m/z calcd for $C_{21}H_{17}N_3O$ $[M+H]^+$, 328.1444; found, 328.1448; IR (KBr): 3010, 2934, 1703, 1657, 1620, 1520, 1454.

1-(1*H*-indol-1-yl)-3-(pyridin-2-ylmethyl)pyrazino[1,2-a]indole (10n)

Yellow solid, yield 58 mg (40%), mp 165°C; ^{1}H NMR (DMSO-*d*$_6$, 600MHz): 4.08 (2H, s), 6.83 (1H, s), 7.08-7.13 (2H, m), 7.14 (1H, t, *J* = 7.3), 7.25 (1H, t, *J* = 7.1), 7.31 (1H, d, *J* = 8.5), 7.32-7.37 (2H, m), 7.39-7.45 (2H, m), 7.67 (1H, d, *J* = 7.8), 7.69 (1H, s), 7.79 (1H, d, *J* = 8.1), 8.15 (1H, d, *J* = 3.3), 8.22 (1H, d, *J* = 8.5), 8.85 (1H, s); ^{13}C NMR (DMSO-*d*$_6$, 600MHz): δ_C ppm = 21.4, 95.1, 105.4, 111.7, 113.1, 114.0, 120.7, 121.0, 121.6, 122.8, 122.9, 124.8, 126.2, 126.8, 128.3, 128.3 (2C), 129.1 (2C), 129.2, 133.0, 133.4, 135.3, 140.0, 144.7; HRMS (TOF ES$^+$): m/z calcd for $C_{25}H_{19}N_4$ $[M+H]^+$, 375.1604; found, 375.1609; IR (KBr): 3401, 2953, 2923, 2854, 1718, 1601, 1509.

8-Chloro-3-methyl-1-(1*H*-pyrrol-1-yl)pyrazino[1,2-a]indole (10o)

Yellow solid, yield 72 mg (80 %), mp 122°C; ^{1}H NMR (DMSO-d_6, 600MHz): 2.42 (3H, s), 6.43 (2H, s,), 7.33 (1H, s), 7.43 (1H, dd, *J* = 7.3, 1.6), 7.70-7.74 (2H, m), 7.97 (1H, d, *J* = 1.6), 8.33 (1H, d, *J* = 8.8), 8.69 (1H, s); ^{13}C NMR (DMSO-d_6, 600MHz): δ_C ppm = 20.1, 95.2, 111.2 (2C), 112.7, 113.9, 120.0 (2C), 120.1, 120.9, 122.7, 122.7, 128.2, 128.6, 130.7, 143.7; HRMS (TOF ES$^+$): m/z calcd for $C_{16}H_{13}ClN_3$ $[M+H]^+$, 282.0793; found, 282.0798; IR (KBr): 3063, 2919, 1714, 1625, 1525, 1449, 1449.

8-Chloro-3-methyl-1-(1*H*-pyrazol-1-yl)pyrazino[1,2-a]indole (10p)

Yellow solid, yield 78 mg (85%), mp 119°C; ^{1}H NMR (DMSO-d_6, 600MHz): 2.45 (3H, s), 6.69-6.70 (1H, m), 7.42 (1H, dd, *J* = 7.0, 2.0), 7.85 (1H, s), 8.02 (1H, s), 8.05 (1H, d, *J* = 1.6), 8.33 (1H, d, *J* = 8.6), 8.74 (1H, s), 8.76 (1H, d, *J* = 2.5); ^{13}C NMR (DMSO-d_6, 150 MHz): δ_C ppm = 20.1, 93.5, 108.4, 113.4, 113.8, 121.1, 121.6, 122.6, 128.0, 128.1, 128.6, 128.8, 129.9, 143.0, 143.0; HRMS (TOF ES$^+$): m/z calcd for $C_{15}H_{12}ClN_4$ $[M+H]^+$, 283.0745; found, 283.0751; IR (KBr): 3154, 3130, 2976, 2920, 1730, 1604, 1508.

General procedure for the preparation of hydroamination/cyclization reaction sequence products 11

The solution of a propargylated indole **1** (70 mg, 0.41 mmol) and aniline (53 mg, 0.57 mmol) with 1M LiHMDS solution in THF (0.38 mL, 0.41 mmol, 1.0 eq) stirred at -15°C for 3 hours. Reaction was monitored by TLC to achieve full conversion. Further, additional LiHMDS solution in THF (0.57 mL, 0.62mmol, 1.5 eq) was added, and the reaction was stirred at reflux for 8 hours. After completion, reaction mixture was diluted with 20 ml ethyl acetate. Purification of the crude compound was performed by column chromatography, eluting with 5-10 % ethyl acetate in hexane.

3-methyl-2-phenylpyrazino[1,2-a]indol-1(2*H*)-imine (11a)

Brown solid, yield 78 mg (85%), mp 151°C; ^{1}H NMR (DMSO-d_6, 600MHz): 2.31 (3H, s), 7.00-7.06 (2H, m), 7.30-7.37 (4H, m), 7.46 (1H, s), 7.97 (1H, s), 8.01-8.08 (2H, m), 8.16 (1H, s), 8.17 (1H, d, *J* = 9.5), 9.27 (1H, s); ^{13}C NMR (DMSO-d_6, 150 MHz): δ_C ppm = 20.8, 92.6, 106.8, 113.3, 119.9 (2C), 120.5, 121.5, 122.0, 123.2, 127.0, 127.9, 128.4 (2C), 128.7, 131.2, 140.5, 146.9. HRMS (TOF ES$^+$): m/z calcd for $C_{18}H_{16}N_3$ $[M+H]^+$ 274.1338; found, 274.1343. IR (KBr):3210, 2970, 1819, 1635, 1540, 1470.

8-Bromo-3-methyl-2-phenylpyrazino[1,2-a]indol-1(2*H*)-imine (11b)

White solid, yield 65 mg (68%), mp 151°C; ^{1}H NMR (DMSO-d_6, 600MHz): 2.31 (3H, s), 7.02 (1H, t, *J* = 6.9), 7.33-7.37 (2H, m), 7.43 (1H, dd, *J* = 8.6, 1.7), 7.46 (1H, s), 8.03-8.07 (2H, m),

8.10-8.14 (2H, m), 8.16 (1H, s), 9.27 (1H, s). ^{13}C NMR (DMSO-d_6, 150 MHz): δ_C ppm = 21.3, 93.0, 107.2, 114.1, 115.7, 120.4, 120.9, 122.5, 123.5, 124.1, 124.4, 128.9 (2C), 129.07, 129.2, 131.7, 141.0, 147.4. HRMS (TOF ES$^+$): m/z calcd for $C_{18}H_{15}BrN_3$ $[M+H]^+$ 352.0444; found, 352.0449. IR (KBr):3145, 2875, 1923, 1765, 1610, 1564.

2-(4-fluorophenyl)-3-methylpyrazino[1,2-a]indol-1(2*H*)-imine (11c)

White solid, yield 67 mg (60%), mp 112°C; ^{1}H NMR (DMSO-d_6, 600MHz): 2.31 (3H, s, CH_3), 7.19 (2H, t, *J* = 9.0), 7.31-7.34 (2H, m), 7.43 (1H, s), 7.85-7.88 (1H, m), 8.08 (2H, dd, *J* = 9.0, 4.5), 8.10-8.14 (2H, m), 9.25 (1H, s);^{13}C NMR (DMSO-d_6, 150 MHz): δ_C ppm = 20.8, 92.8, 106.8, 111.5, 115.0 (2C), 121.5 (2C), 121.6, 122.0, 122.6, 127.1, 129.9, 130.5, 137.1, 147.0, 156.6, 158.0; HRMS (TOF ES$^+$): m/z calcd for $C_{18}H_{15}FN_3$ $[M+H]^+$ 292.1244; found, 292.1248. IR (KBr): 3124, 2730, 1964, 1747, 1655, 1535.

8-Bromo-2-(4-bromophenyl)-3-methylpyrazino[1,2-a]indol-1(2*H*)-imine (11d)

White solid, yield 52 mg (45%), mp 151°C; ^{1}H NMR (DMSO-d_6, 600MHz): 2.31 (3H, s, CH_3), 7.43-7.46 (2H, m), 7.50-7.54 (2H, m), 8.05 (2H, d, *J* = 9.2), 8.11-8.15 (2H, m), 8.16 (1H, s), 9.41 (1H, s). ^{13}C NMR (DMSO-d_6, 150 MHz): δ_C ppm = 20.7, 92.6, 107.1, 113.4, 113.7, 115.4, 121.7 (2C), 122.9, 123.8, 124.1, 128.6, 131.0, 131.2 (2C), 131.7, 139.9, 146.7. HRMS (TOF ES$^+$): m/z calcd for $C_{18}H_{14}Br_2N_3$ $[M+H]^+$ 429.9549; found, 429.9554. IR (KBr):3247, 2879, 1987, 1675, 1565, 1480.

8-Bromo-2-(4-methoxyphenyl)-3-methylpyrazino[1,2-a]indol-1(2*H*)-imine (11e)

White solid, yield 81 mg (65%), mp 151°C; ^{1}H NMR (DMSO-d_6, 600MHz): 2.32 (3H, s), 7.33 (1H, dd, *J* = 6.6, 2.1), 7.45 (1H, s), 7.52 (2H, d, *J* = 8.9), 7.98 (1H, d, *J* = 1.8), 8.05 (2H, d, *J* = 8.8), 8.16-8.20 (2H, m), 9.40 (1H, s). ^{13}C NMR (DMSO-d_6, 150 MHz): δ_C ppm = 20.7, 92.7, 107.2, 113.3, 116.4, 120.6, 121.7 (2C), 123.1, 126.7, 127.1, 127.2, 128.5, 131.2 (2C), 132.7, 138.6, 146.7. HRMS (TOF ES$^+$): m/z calcd for $C_{18}H_{14}BrClN_3$ $[M+H]^+$ 386.0054; found, 386.0061. IR (KBr):3189, 2876, 1889, 1635, 1579, 1464.

8-bromo-2-(4-chlorophenyl)-3-methylpyrazino[1,2-a]indol-1(2*H*)-imine (11f)

White solid, yield 64 mg (62%), mp 151°C; ^{1}H NMR (DMSO-d_6, 600MHz): 2.31 (3H, s), 7.39 (2H, d, *J* = 8.9), 7.43 (2H, d, *J* = 7.5), 8.10-8.13 (4H, m), 8.16 (1H, s), 9.41 (1H, s). ^{13}C NMR (DMSO-d_6, 150 MHz): δ_C ppm = 20.7, 92.6, 107.1, 113.6, 115.3, 121.3 (2C), 122.9, 123.7, 124.1, 125.4, 128.3 (2C), 128.5, 128.6, 131.1, 139.5, 146.7. HRMS (TOF ES$^+$): m/z calcd for $C_{18}H_{14}BrClN_3$ $[M+H]^+$ 386.0054; found, 386.0059. IR (KBr): 3224, 2945, 1954, 1620, 1512, 1421.

5. Conclusions

We have investigated effective methods for the transformation of *N*-(propargyl)indole-2-carbonitriles to O, N, C-nucleophiles to achieve various annulated indoles through the domino reaction. The chemical properties of the different nucleophiles were investigated in-depth for various reaction conditions to produce several classes of annulated indoles, showing that O-nucleophile reactivity to develop an effective microwave-assisted route toward the alkoxypyrazino[1,2-*a*]indole scaffold through a DBU-catalysed isomerisation/double nucleophilic addition reaction sequence in an alcohol medium is possible. The reaction tolerated a wide range of indoles and primary alcohols. We also elaborated the analogous transformation for secondary alcohols and alcohols which were difficult to use as solvents. It is anticipated that this reaction will be applicable in the field of medicinal chemistry for the synthesis of drug structures. Furthermore, the reaction between nitriles and C-nucleophiles offers an alternative for the preparation of various enamines, particularly heterocyclic synthesis. Therefore, the scope was extended towards C nucleophiles to achieve the synthesis of valuable pyrido[1,2-*a*]indoles through a transition metal-free protocol. The reaction was initiated with the DBU-catalysed addition of CH-acid to nitrile to generate a reactive push-pull enamine prone to intramolecular cyclization. To the best of our knowledge, these are the first examples of organocatalyzed aza-Henry and aza-Knoevenagel reactions on nitriles. The resulting compounds exhibit interesting optical properties with 9-amino-8-nitropyrido[1,2-*a*]indoles being dyes, and 9-aminopyrido[1,2-*a*]indole-8-carboxylates being fluorescent dyes. The *N*-nucleophile elaborated chemoselective transformations of *N*-(propargyl)indole-2-carbonitriles were extended into three different systems and when the reactions were performed at reduced temperature, chemo- and regioselective alkyne hydroamination occurs to form *N*-(propylene)indoles and the process is LiHMDS-catalysed. When the transformations are performed in the presence of methanol at reflux, 1-methoxypyrazino[1,2-*a*]indole is formed initially. The latter undergoes LiHMDS-promoted nucleophilic substitution of a methoxy group to produce the corresponding pyrazino[1,2-*a*]indoles with an amine moiety at C(1). The hydroamination products may undergo an intramolecular cyclisation to produce distinct cyclic imines. We believe that the designed approach is applicable to numerous alkynyl nitrile systems allowing chemodivergent transformations. Furthermore, the synthesised compounds demonstrated intense fluorescence with emission in the blue/green range.

6. References

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7. List of abbreviations

The following table describes the significance of various abbreviation and acronyms used throughout thesis.

Abbreviation	Definition
ACN	Acetonitrile
AIBN	Azobisisobutyronitrile
BQ	1,4-Benzoquinone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIPEA	*N*,*N*-Diisopropylethylamine
DMF	Dimethylformamide
HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
HMDS	Hexamethyldisilazane
LiHMDS	Lithium bis(trimethylsilyl)amide
NaHMDS	Sodium bis(trimethylsilyl)amide
NCS	*N*-Chlorosuccinimide
PTSA	*p*-Toluenesulfonic acid
TBAB	Tetrabutylammonium bromide

TBTH	Tributyltin hydride
TEA	Triethylamine
TMS	Tetramethylsilane
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TFA	Trifluoroacetic acid
TFP	tris(2-furyl)phosphine
Ts	4-toluenemethanesulfonyl

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