Chapter IV

Greener One-pot Synthesis of 3-Substituted Indoles using L-Ascorbic acid in water as green eco-friendly catalyst and alternatively using PEG-300 in catalyst-free condition

IV.A. Introduction

Structural motif of Indole has been familiar universally as a privileged structure in chemistry of medicinal field due to presence of heterocyclic scaffold in plentiful therapeutic agents and natural products. This demonstrates wide range of biological[1-5] and pharmacological properties[6-12] such as antioxidative, antibacterial, anticancer, antimicrobial and insecticidal activities, and an array of derivatives of indole have been also used as antibiotics in pharmaceuticals[13-14]. Indole nucleus[15] is present in a number of drugs available in market currently. Most of these drugs belong to 3-substituted indole family, as an important intermediate for chemical synthesis.

Drugs like Frovatriptan, Sumatriptan, Zolmitriptan and Rizatriptan are utilized as anti-migraine headaches[16-18] is made of 3-substituted indole as main structural unit. Whereas azolylbenzyl indole is used as a breast cancer inhibitor[19] and bis-indole is used as HIV-1 integrase inhibitor[20] (Figure IV.1).

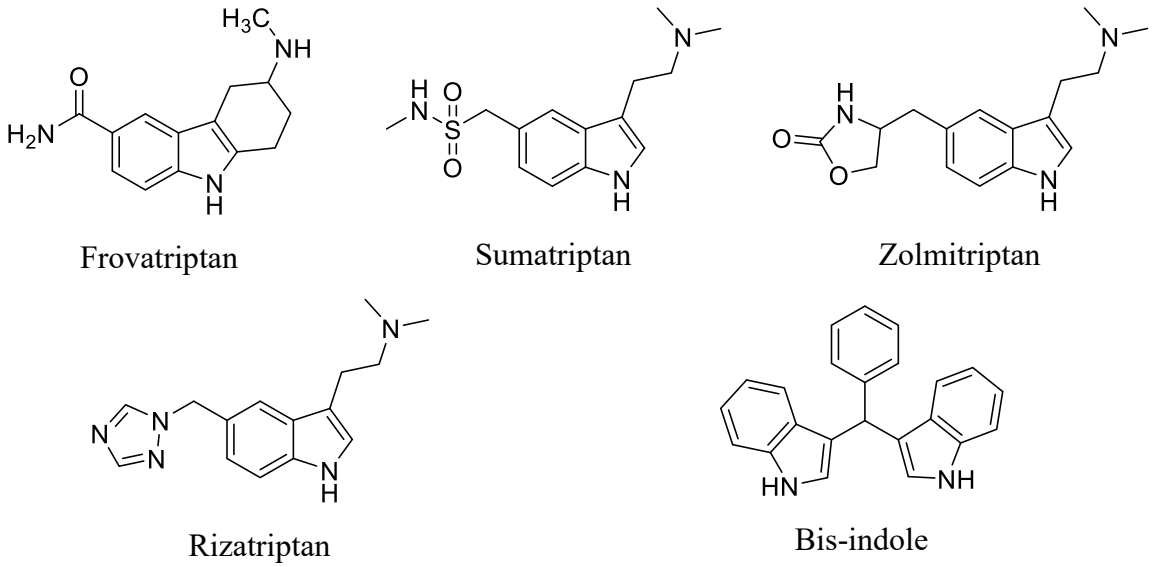


Figure IV.1. Biologically active 3-substituted indoles.

IV.B. Background and objectives

Indole is also addressed as benzopyrrole containing benzenoid nucleus and has ten π-electrons and hence aromatic in nature. Therefore, electrophilic substitutions occur readily as pi ring cloud is present over it. Regioselective functionalization of indole ring at the 3-position can be carried out exploiting a Friedel–Crafts process. For this process use of electron poor alkenes activated by bronsted or lewis acid is widely used[21]. There are various ways to perform the alkylation of indolyl compounds, with the main modifications lying in the nature of the electrophile utilized. Among the different methods 1,2-addition of arenes to carbonyl compounds, Micheal type condensation between Arenes and electron deficit C=C bonds,

opening of ring of epoxides and aziridines are some of the established methods. Transition metal catalyzed allylic substitution known as Tsuji-Trost reaction is also applicable[22]. A few substitutions of indole core is represented in Figure IV.2.

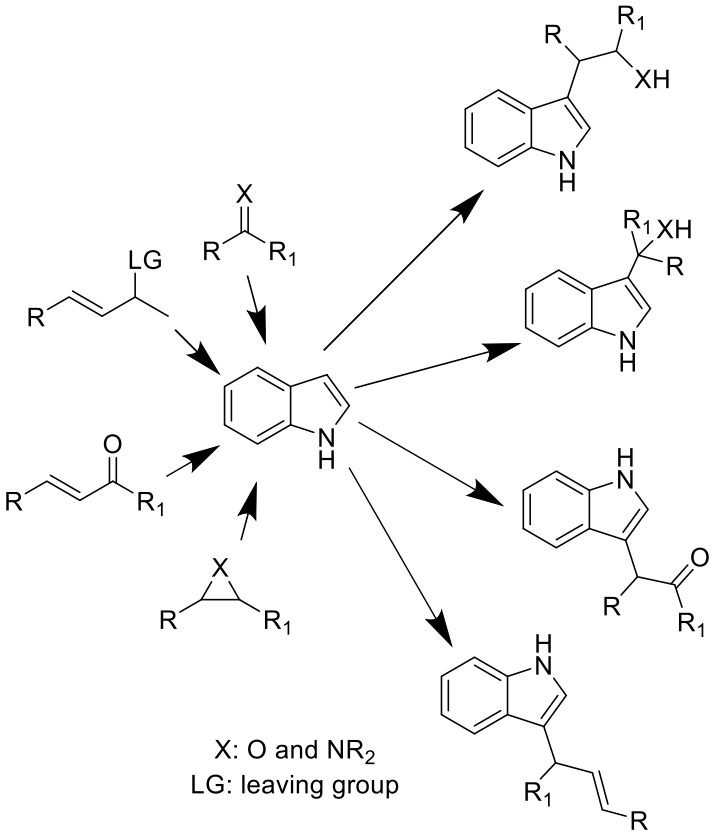
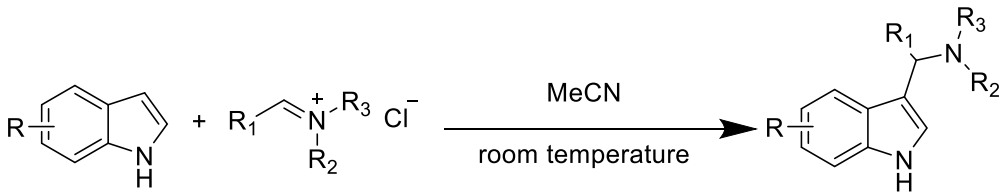


Figure IV.2. Different approaches for the Friedel–Crafts alkylation of indoles.

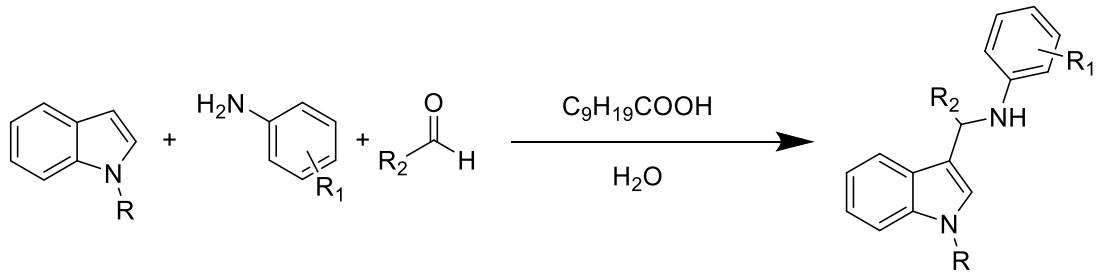
IV.B.1. Specialized methods for synthesis of 3-substituted amino indoles

Many advancements have been reported for synthesis of 3-substituted amines and their derivatives. In 1996, Nikolaus Risch *et al.* had synthesized 3-amino alkylated indoles[23-25] using indole and the iminium salt of the aromatic aldehyde in a Mannich based reaction (Scheme IV.1). Acetonitrile has been used as solvent in this process at room temperature. Various indoles; like *N*-methyl, *N*-benzyl, 1*H*, *N,N*-dimethylaniline, indoles are employed for this method with good yield. Se of toxic acetonitrile is a limitation of this process and reaction time reported up to 48 hours in some cases.



Scheme IV.1. 3-substituted amino indole synthesis using acetonitrile.

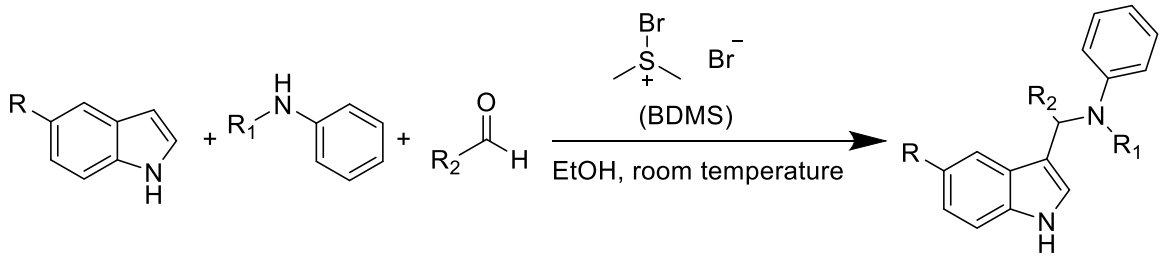
Later Kobayashi *et. al.* reported synthesis of 3-substituted indole derivatives by using Aza Friedel Craft's reactions. This process is catalyzed by carboxylic acid and developed by reactiong aldehyde, primary amines and indoles in water. But the reaction had only employed *o*-anisidine depicting it has substrate limitations[26] (Scheme IV.2).



Scheme IV.2. Synthetic Scheme of 3-Substituted Indoles using carboxylic acid.

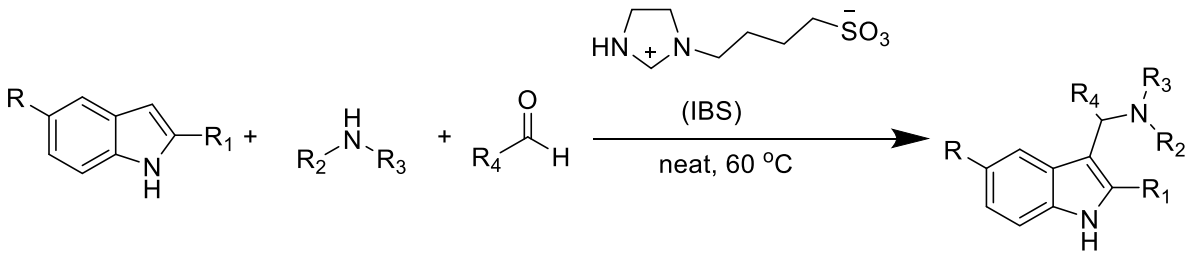
IV.B.2. Modern approach towards 3-substituted amino indoles

In 2010, S. Yadav *et al.* reported a facile synthesis of 3-substituted indoles via multi-component synthesis of substituted indoles, aldehydes and substituted amines[27]. In this method bromodimethylsulfonium bromide (BDMS) is used as catalyst in ethanol medium at room temperature (Scheme IV.3).



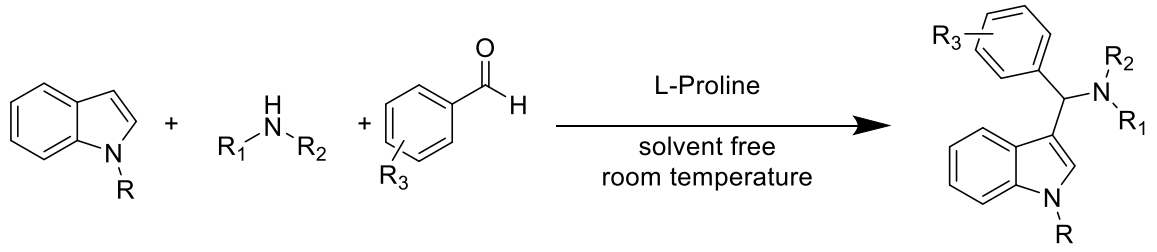
Scheme IV.3. Synthesis of 3-aminoalkylated indoles using bromodimethylsulfonium bromide.

Another multicomponent reaction for synthesis of 3-amino indole is reported by A. Hajra *et al.*[28]. In the three-component coupling they have used indole, aldehyde and amines. Catalytic amount of zwitterionic-type molten salt, 4-(1-imidazolium)-butane sulfonate (IBS) is used for the reaction under solvent-free condition at 60 ºC temperature (Scheme IV.4).



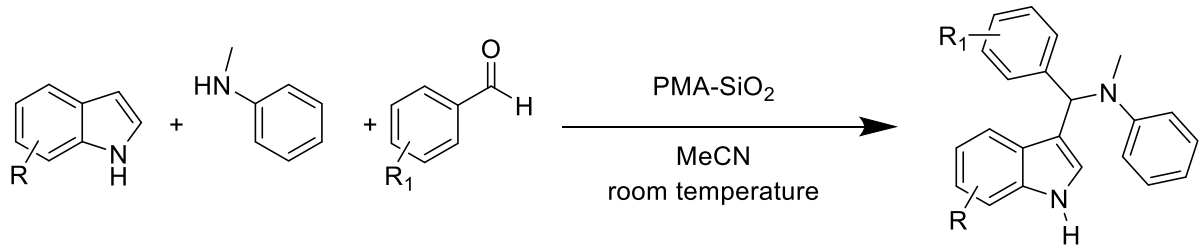
Scheme IV.4. Synthesis of 3-aminoalkylated indoles using 4-(1-imidazolium)-butane sulfonate.

L-proline is also employed as catalyst for synthesis of 3-amino alkylated indoles by M. Kumar *et al.*[29]. The reaction progressed through multi-component mannich type reaction. Secondary amines, aldehydes and indoles are condensed in a solvent -free reaction condition at room temperature. Several aldehydes with electron releasing and withdrawing groups produce good yield of corresponding 3-amino alkylated indole in this reaction condition (Scheme IV.5).



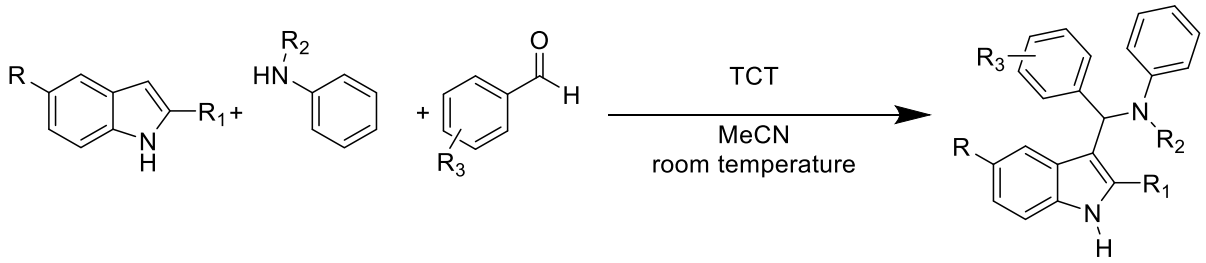
Scheme IV.5. Synthesis of 3-amino alkylated indole by L-proline.

J.S. Yadav *et al.* reported another multi-component one-pot synthesis of 3-substituted indoles[30]. Solid supported phosphomolybdic acid (PMA) with silica (SiO_2) is used as catalyst. The reaction is performed in acetonitrile as solvent and at room temperature to yield desired 3-substituted indoles with various aldehydes and amines in good yield (Scheme IV.6).



Scheme IV.6. Synthesis of 3-amino alkylated indole using PMA-SiO_2.

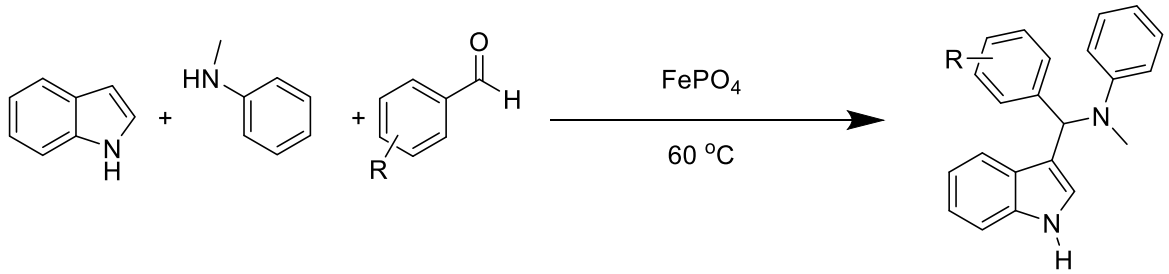
Another interesting method for formation of 3-amino alkylated indole is described by K. Damodar *et al.*[31]. In this reaction multi-component condensation of substituted indole, aldehydes and amines is attempted using 2,4,6-trichloro-1,3,5-triazine (TCT) as catalyst (Scheme IV.7). Acetonitrile is used as solvent for the process at room temperature. This method is applicable for various aldehydes and ketones.



Scheme IV.7. Synthesis of 3-[(*N*-Alkylanilino)(aryl)methyl]indoles Using TCT.

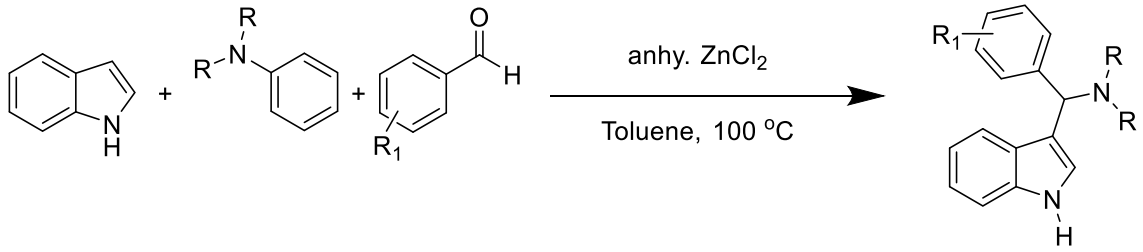
In recent time, F.K. Behbahani *et al.* reported a multi-component one-pot synthesis of 3-amino alkyl indoles[32]. Iron (III) phosphate is used as catalyst in this process at 60 ºC by combination

of aromatic aldehydes, *N*-methyl aniline and indole as precursor (Scheme IV.8). No solvent is used in this method of 3-amino alkylated indole preparation.



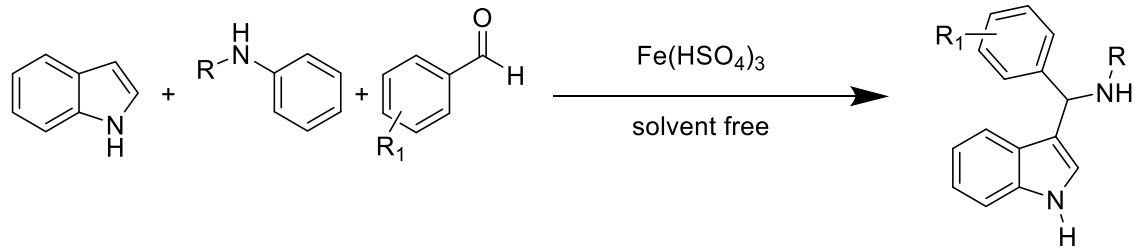
Scheme IV.8. Three-component synthesis of 3-aminoalkylindoles using iron (III) phosphate.

Ganesan *et al.* reported another one-pot synthesis of 3-arylmethyl and diarylmethyl indoles via multi-component synthesis[33]. The reaction is mediated by anhydrous $ZnCl_2$ in toluene at 100 °C temperature (Scheme IV.9). The reaction takes up to 5 hours in some cases.



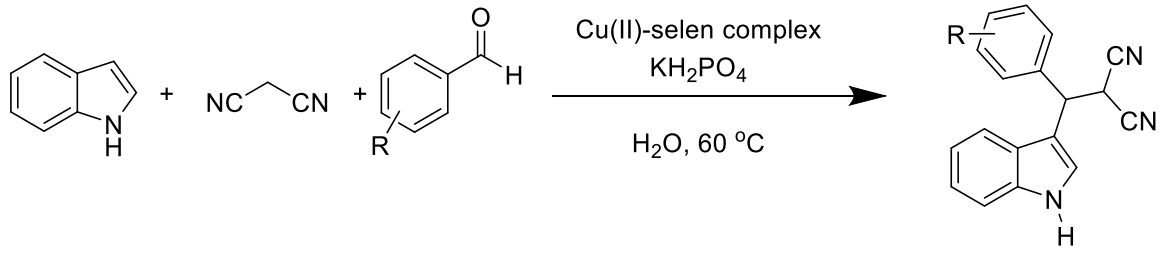
Scheme IV.9. Synthesis of 3-arylmethylindole using $ZnCl_2$.

M. Gholizadeh *et al.* reported one-pot method for synthesis of *tert*-indolylmethane amine derivatives[34]. In this multi-component coupling between aldehyde, *N*-alkyl aniline and indole is catalyzed by $Fe(HSO_4)_3$ in solvent -free condition at 45 °C temperature (Scheme IV.10). The metal catalyst has reusability property up to six times. Reaction time is up to 2.5 hours in ideal cases.



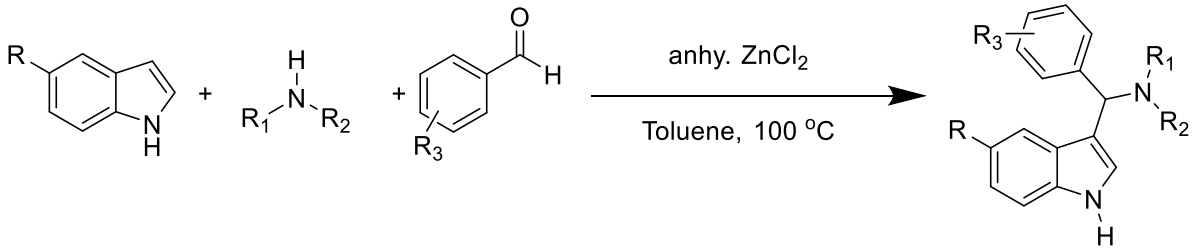
Scheme IV.10. Solvent-free synthesis of 3-substituted indole derivatives by $Fe(HSO_4)_3$.

An interesting effort towards synthesis of 3-indole derivatives is reported by X. Zhou *et al.* in water[35]. Copper acetate combining with sulfonato salen complex successfully yielded desired 3-substituted indole product in good yield from indole, aldehyde, and malononitrile (Scheme IV.11). Weak acid KH_2PO_4 is beneficial for the increase in yield of the reaction.



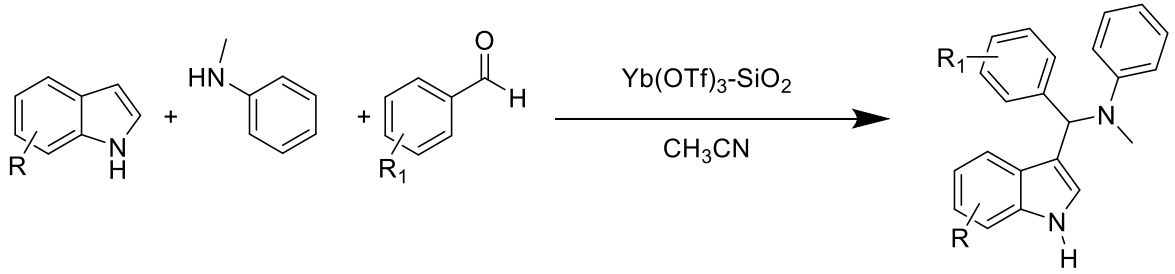
Scheme IV.11. Synthesis of 3-indole derivatives by copper sulfonato salen catalyst.

A. Kumar *et al.* reported an unique micelle promoted multicomponent synthesis of 3-amino alkylated indoles via a Mannich-type reaction[36]. In this reaction secondary amines, aldehydes and indoles combine to form desired 3-amino alkyl indoles (Scheme IV.12). The advantage of using micelle is it stabilizes the intermediate iminium ions, which eventually undergo to give 3-amino alkylated indole. SDS is used as surfactant at 80 °C for the reaction.



Scheme IV.12. Micelle promoted multicomponent synthesis of 3-amino alkylated indoles.

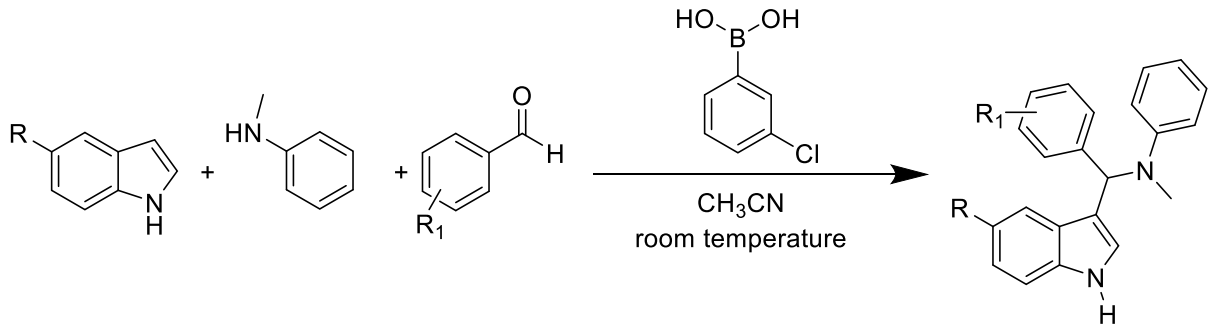
In an effort of finding anticancer and src kinase inhibitory activities of 3-substituted indoles A. Kumar *et al.* reported one-pot synthesis of 3-substituted indoles by multi-component condensation catalyzed by $Yb(OTf)_3$–SiO_2[37]. Acetonitrile is used as solvent in the reaction at room temperature for up to 2 hours (Scheme IV.13). All the synthesized compounds were estimated for inhibition of cell proliferation of human ovarian adenocarcinoma (SK-OV-3), human colon carcinoma (HT-29) and c-Src kinase activity.



Scheme IV.13. Synthesis of 3-substituted indoles by one-pot three-component coupling using $Yb(OTf)_3$–SiO_2.

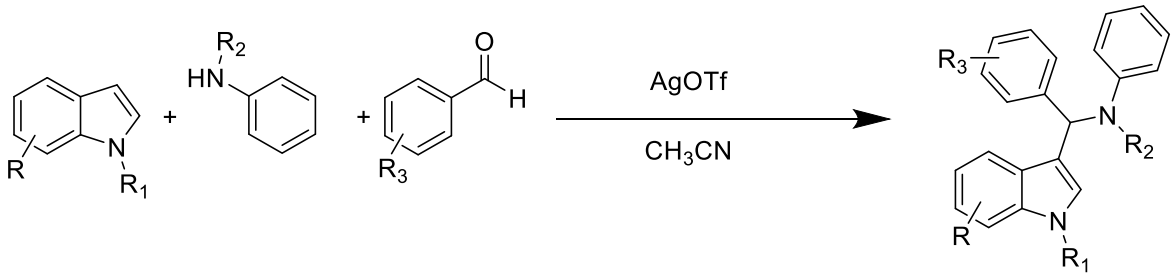
S.R. Bhusare *et al.* reported another one-pot three component synthesis of 3-aminoalkylated indoles[38]. 3-chlorophenylboronic acid is used as organo catalyst in this reaction in acetonitrile at room temperature in this method (Scheme IV.14). Three components indoles, aromatic

aldehydes and *N*-methyl aniline forms corresponding 3-aminoalkylated indoles in good yield in this method.



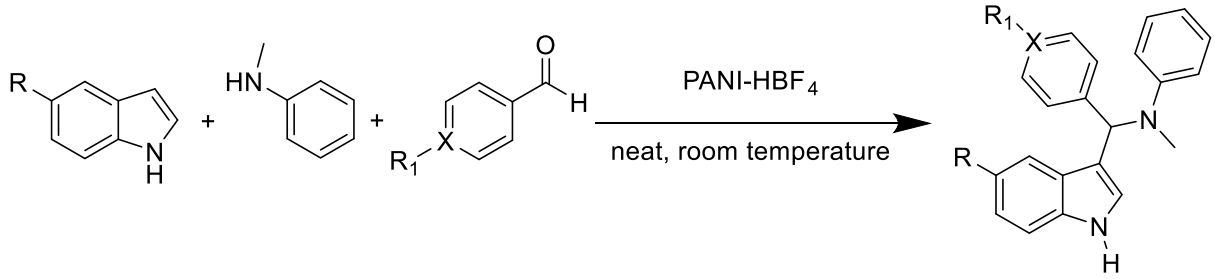
Scheme IV.14. Synthesis of 3-aminoalkylated indoles using 3-chlorophenylboronic acid.

A. Kumar *et al.* advanced their study for synthesis of 3-aminoalkylated indoles using Silver triflate as catalyst[39]. In this method they used acetonitrile as solvent too (Scheme IV.15). One-pot multi-component coupling of aldehydes, *N*-methylanilines, and indoles produced good yield of corresponding product. Further, 3-aminoalkylated indoles was examined for their antibacterial activities against Gram-negative and Gram-positive bacteria respectively.



Scheme IV.15. Synthesis of 3-aminoalkylated indoles using silver triflate.

S. Palaniappan *et al.* reported synthesis of multi-component synthesis of 3-substituted amino methyl indoles under solvent-free conditions[40] (Scheme IV.16). Polyaniline salt is used as polymer-based catalyst in this process and this three-component synthesis yields desired product in good yield even at room temperature. Reusability of the polymer catalyst is also explored in this reaction.



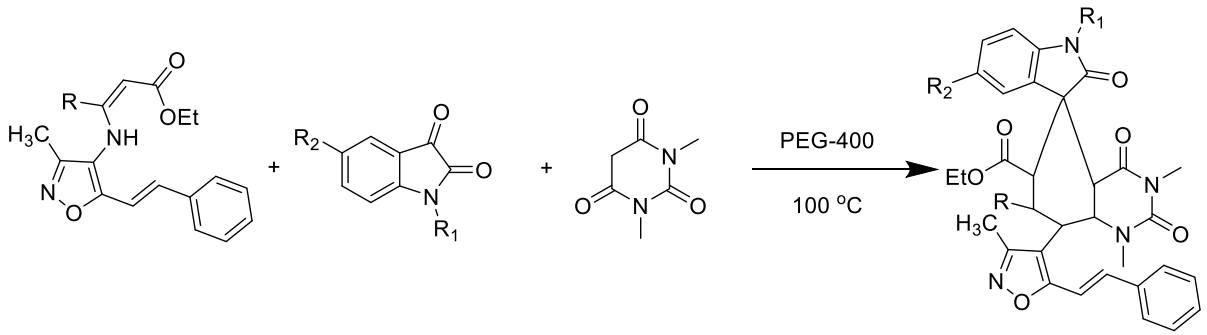
Scheme IV.16. Three-component one-pot synthesis of 3-substituted amino methyl indoles using PANI-HBF_4.

IV.B.3. Background of PEG 300 in organic synthesis

In organic synthesis, a major concern is with solvents due to wide range of environmental hazards caused by them. Major disadvantages incorporate their volatile nature, pyrophoric property and less recoverability. Develop solvent -free protocols was attempted in many cases, which to some extent have been successful for a few reactions[41]. However, solvent plays a significant role in organic transformations by providing homogeneous phase to the reactants and enhancing the molecular interactions. To solve the critical concerns and developing efficient catalyst systems, utilizing PEG as reaction medium is highly looked-for in terms of environmentally benign condition as well as atom economy.

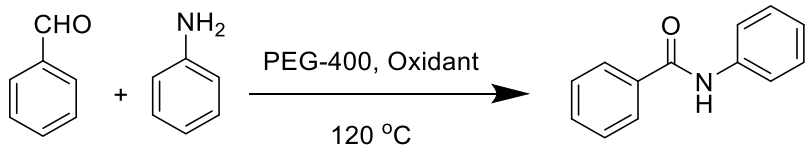
Meanwhile, water as a green solvent has also been well cited for many years. Though, the practical utilization is limited because of the hydrophobic nature of organic compounds and the sensitivity of various catalysts to moisture. Now a day, an alternate reaction media polyethylene glycol (PEG)[42] is more popular, due to their attractive properties like non-toxicity, bio-compatibility and bio-degradability. Moreover, PEG is considered as a high boiling, environmentally benign, inexpensive, easily separable, safe, recyclable, bio-degradable, non-flammable solvent.

PEG mediated synthesis is getting notable appreciation in recent times. P.K. Pittala *et al.* reported one-pot synthesis of isoxazole substituted spirooxindole derivatives in PEG-400 medium[43] (Scheme IV.17). This method is advantageous as it is a toxic metal -free synthesis which elevates its scope. Excellent yield of product is reported by this method for synthesis of various functionalized isoxazoles.



Scheme IV.17. PEG-400 facilitated synthesis of substituted spirooxindole derivatives.

Z.C. Shang *et al.* reported recently oxidative amidation with aldehyde and amines in a one-pot synthesis[44]. PEG-400 is used as catalyst as well as reaction medium at 120°C temperature. *N*-substituted amides are produced in good yield in this method (Scheme IV.18).

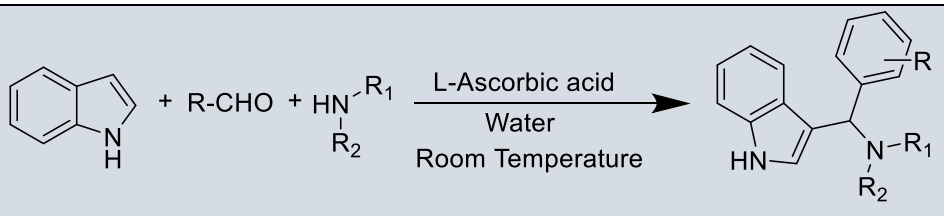


Scheme IV.18. Synthesis of *N*-substituted amide in PEG-400/oxidant system.

IV.C. Present Work

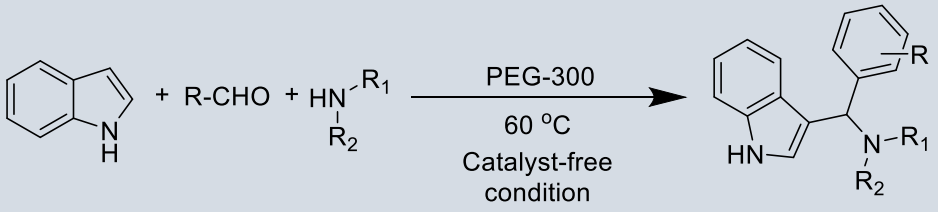
Our strategy for synthesis of 3-amino alkylated indoles involves a multi-component mannich type reaction[20] in metal -free condition. L-ascorbic acid has been proven to be a very useful mild and economical reagent in our previous findings of synthesis of 2-Substituted-2,3-dihydroquinazolin-4(1*H*) one and 2-Substituted Quinazolin-4(3*H*)-one in water[21] and synthesis of substituted 1*H*-tetrazoles from organic nitrile precursors. Therefore, we continued our study for synthesis of 3-amino indole with L-ascorbic acid in water which produced good yield (Scheme 1). According to green chemistry, water is considered as an economic and environmentally benign solvent. Though, water is a poor solvent for organic synthesis mainly due to poor solubility of reactants in it, still we observed sizable yield of product while observing our scheme in water as solvent and that is worth exploring. Further we extended the scope of the reaction with PEG-300 taking inspiration from success of various sustainable organic synthesis[22].PEG-300, a bio-degradable solvent which itself acted as a catalyst produced 3-amino indole in considerable amount (Scheme 2). It is well known that PEG is less basic than other hydroxylic solvents such as water, ethanol or methanol, ethers. Thus, it results in the hydrogen atoms of PEG being more positive (acidic) to activate electron rich carbonyl oxygen. The oxygen atom of PEG may activate acidic proton to initiate the iminium ion formation and then attacking of indole on iminium ion, followed by proton abstraction from indole moiety to yield the final product.

Herein we report synthesis of 3-amino alkylated indoles involving a multi-component mannich type reaction by L-ascorbic acid and water at room temperature. Also, we are reporting an alternate approach for synthesis of 3-amino indole in PEG-300 at 60 °C temperature under catalyst-free condition.



1 2 3 4

Scheme IV.19. L-Ascorbic acid catalysed multi-component synthesis of the 3-amino indole in water.



1 2 3 4

Scheme IV.20. Multi-component synthesis of the 3-amino indole in PEG-300 without any catalyst.

Where, R = Alkyl, Phenyl, Substituted phenyl. R_1= Alkyl, Phenyl. R_2= H, Alkyl.

IV.C.1. Result and discussion

We started our investigation with mild acid, L-ascorbic acid for formation of initial iminium ion by nucleophilic attack of substituted amine on substituted aldehyde which further trapped by indole to provide 3-amino alkyl indoles. Stronger bronsted acids like PTSA (Table IV.1, entry 1), TFA (Table IV.1, entry 2) produces large amount of bis-indole as by product. None of the silica supported acids viz., SiO_2-Cl (Table IV.1, entry 4), $HClO_4$-SiO_2 (Table IV.1, entry 3) etc. too were found to be efficient to yield desired compound. We also turned our attention to organo catalysts like amino acids due to their inexpensiveness and recyclability for various organic reactions. Basic amino acids like L-histidine (Table IV.1, entry 5) and L-lysine (Table IV.1, entry 6) were found ineffective to form the desired product. But acidic amino acids like L-aspartic acid (Table IV.1, entry 7) and L-glutamic acid (Table IV.1, entry 8) were found to be delivering 3-amino indoles but in poor yield. L-proline (Table IV.1, entry 9) provided better yield of our desired product in ethanol but still fails to meet the yield achieved by L-Ascorbic acid in water medium (Table IV.1, entry 10).

Table IV.1. [a]Optimization of acid catalysts for synthesis of 3-amino indole.

Entry	Acid Catalyst	[b]Yield(%)
1	PTSA	20
2	TFA	17

3	$HClO_4$-SiO_2	Trace
4	SiO_2-Cl	Trace
5	L-histidine	-
6	L-lysine	-
7	L-aspartic acid	32
8	L-glutamic acid	35
9	L-proline	62
10	**L-ascorbic acid**	**88**

The bold signifies most optimized condition.

[a] Reaction of Indole (1 mmol), 4-methoxybenzaldehyde (1.2 mmol) and aniline (1.2 mmol) in presence of acid catalyst and 5 ml of water as solvent at room temperature.

[b] Isolated yield

We also tried various mild solvents with L-ascorbic acid like ethanol (Table IV.2, entry 3,4), methanol (Table IV.2, entry 1, entry 2), DCM (Table IV.2, entry 12), Benzene (Table IV.2, entry 5), DMF (Table IV.2, entry 6), DMSO (Table IV.2, entry 7), THF (Table IV.2, entry 8) and in solvent-free condition too (Table IV.2, entry 10). Ethanol (Table IV.2, entry 4) and methanol (Table IV.2, entry 2) produces very close yield of 3-amino indoles compared to water (Table IV.2, entry 11). But considering its availability and economical advantage over the other solvents, water is selected as most competent solvent with L-Ascorbic acid (Table IV.2).

Table IV.2. [a]Optimization of solvent and time for synthesis of 3-amino indole.

Entry	Solvents	Time (hours)	Yield[%][b]
1	MeOH	10	82
2	MeOH	3	80
3	EtOH	10	86
4	EtOH	3	83
5	Benzene	10	56
6	DMF	10	45
7	DMSO	10	67
8	THF	10	Trace
9	Water	10	92
10	Solvent -free	10	26
11	**Water**	**3**	**88**
12	DCM	10	Trace

The bold signifies most optimized condition.

[a] Reaction of Indole (1 mmol), 4-methoxybenzaldehyde (1.2 mmol) and aniline (1.2 mmol) in presence of L-Ascorbic acid and 5 ml of solvent at room temperature.

[b] Isolated yield

We have developed an alternate approach to this 3-amino indole formation as well using PEG-300 only in a catalyst-free condition (Table IV.3, entry 8). This reaction opportunity is explored using various catalyst -free conditions using DMSO (Table IV.3, entry 1), DMF (Table IV.3, entry 2), CH_3CN (Table IV.3, entry 6), Toluene (Table IV.3, entry 3), EtOH (Table IV.3, entry 5), Water (Table IV.3, entry 4), PEG-600 (Table IV.3, entry 10, entry 11), Glycerol (Table IV.3, entry 12, entry 13) and PEG-300 (Table IV.3, entry 8, entry 9). Among all these solvents PEG-600 (Table IV.3, entry 10) produced middling yield but a higher temperature requirement is a drawback. Glycerol (Table IV.3, entry 12) also shown considerable yield but PEG-300 (Table IV.3, entry 8) produced the best yield among all the solvents (Table IV.3).

Table IV.3. [a]Optimization of solvent and temperature for synthesis of 3-amino indole under catalyst-free condition

Entry	Solvent	Temp (^oC)	Yield[%][b]
1	DMSO	120	30
2	DMF	120	25
3	Toluene	110	33
4	Water	reflux	53
5	EtOH	reflux	50
6	CH_3CN	70	26
7	PEG-300	120	89
8	**PEG-300**	**60**	**86**
9	PEG-300	RT	68
10	PEG 600	120	78
11	PEG 600	60	60
12	Glycerol	120	72
13	Glycerol	60	66

The bold signifies most optimized condition.

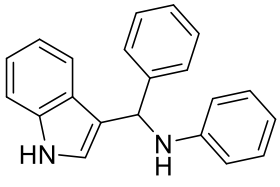
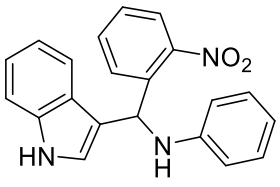
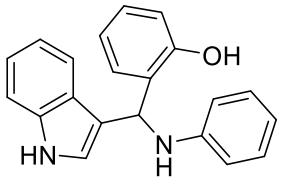
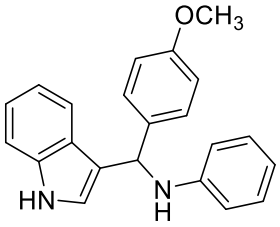
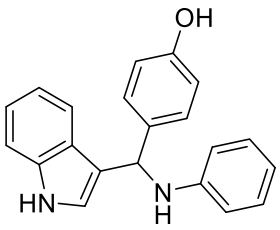
[a] Reaction of Indole (1 mmol), 4-methoxybenzaldehyde (1.2 mmol) and aniline (1.2 mmol) in presence of 5 ml of solvent at various temperature under catalyst-free condition for 3 hours.

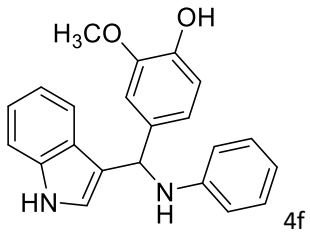
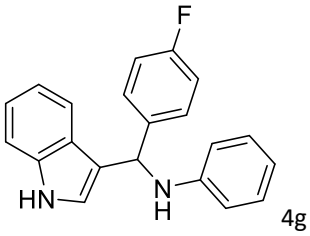
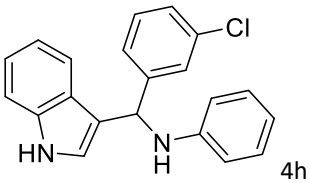
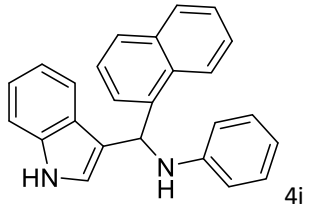
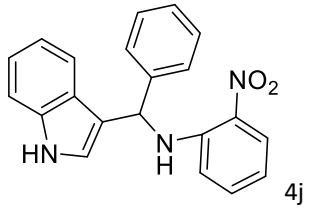
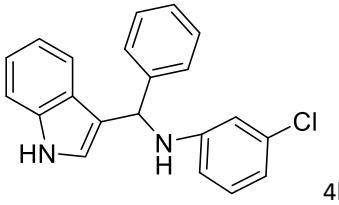
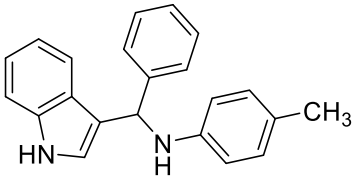
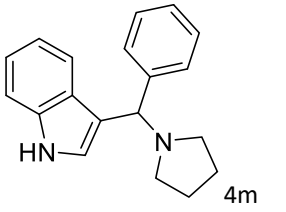
[b] Isolated yield

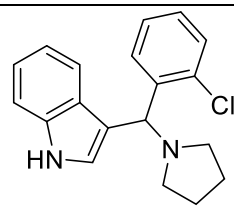
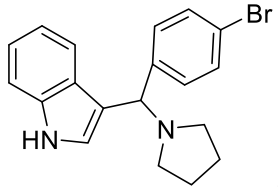
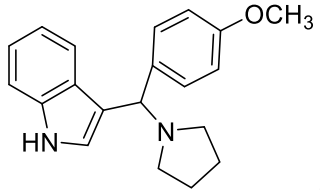
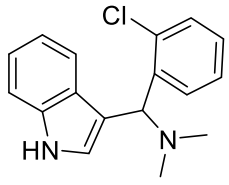
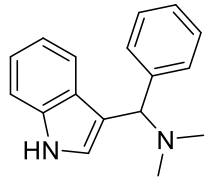
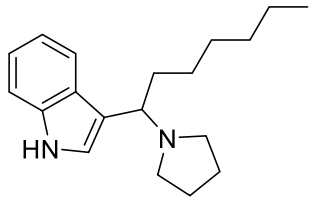
Generally, the 3-aminoalkylation reaction occurs at the C3 position of the indole ring. But when the C3 position is covered by a group, the reaction did not proceed to C2 position. In free C3 indoles the reaction proceeded smoothly with aromatic aldehydes, anilines and secondary

amines containing different functional groups as alkoxy, hydroxy, nitro, bromo, fluoro, chloro, alkyl. Aromatic aldehydes and aniline containing electron donating group produces good yield (Table IV.4, entry 4c, 4d, 4e, 4h, 4k, 4l, 4o, 4p), whereas electron deficit aromatic aldehydes also provided considerable yield but lesser in amount (Table IV.4, entry 4b, 4j). Presence of naphthalene group in aldehyde also yields satisfactory result (Table IV.4, entry 4i). Further the reaction was not very successful under same condition with aliphatic aldehydes (Table IV.4, entry 4s) and unsuccessful with *N*,*N*-diphenylamine. The prospect of this reaction is demonstrated with respect to various aromatic aldehydes and amines and the results are presented in Table IV.4.

Table IV.4. [a]Synthesis of 3-amino indole under catalyst-free condition.

Entry	Product	Yield[%] (With L-Ascorbic acid/water)[b]	Yield[%] (With PEG-300)[c]
1	 4a	86	84
2	 4b	76	72
3	 4c	85	81
4	 4d	88	86
5	 4e	87	83

6	 4f	81	77
7	 4g	82	76
8	 4h	84	82
9	 4i	77	71
10	 4j	78	73
11	 4k	84	75
12	 4l	86	85
13	 4m	83	81

14	 4n	82	78
15	 4o	85	83
16	 4p	86	85
17	 4q	72	75
18	 4r	78	75
19	 4s	58	52

[a]Reaction conditions: indole (1 mmol), aldehyde (1.2 mmol) and amine (1.2 mmol) in presence of [b]L-Ascorbic acid in water as the solvent (5 mL) and in presence of [c]PEG-300 (5 mL) at room temperature. Isolated yield of product measured by column chromatography.

IV.D. Conclusion

In conclusion we have developed a simple, relevant, benign and eco-friendly facile strategy for synthesis of 3-amino indole and its derivatives using L-ascorbic acid and water (Scheme IV.19). Use of water as solvent further enhances the advantage of the protocol. Replacement of expensive and toxic metal catalysts by environment friendly L-ascorbic acid is the highlight of this protocol. Further achievement of good yield and production of 3-amino indoles and its derivatives in less reaction time and at room temperature has added further advantages to this protocol. Alternatively, we extended the scope with catalyst -free condition using only PEG-

300. It provides higher environmental compatibility and sustainability factors as it is a catalyst -free greener process. Therefore, we expect this protocol to achieve wide application in natural product synthesis and in pharmaceutical industry.

IV.E. Experimental

IV.E.1. General Information

All the compounds were purchased from commercial suppliers and used without further purification. All the products were purified by column chromatography on silica gels (60−120 mesh, SRL, India). For TLC, Merck plates coated with silica gel 60, F_{254} were used. ^{1}H NMR and ^{13}C NMR were recorded using 400 MHz, 300 MHz and 100 MHz, 75 MHz respectively on Bruker AV 400 and 300 NMR spectrometer using TMS as internal standard.

IV.E.2. General Procedure

In a typical experiment, the aldehyde (1.2 mmol), amine (1.2 mmol), indole (1 mmol) and L-ascorbic acid (1 mmol) and 5 mL of water were placed in a 25 ml round-bottom flask. The reaction mixture was stirred at room temperature until the reaction was complete (monitored by TLC). After completion the reaction mixture was diluted with water and extracted with ethyl acetate, dried over sodium sulphate and evaporated under vacuum to give the crude product, which was purified by silica gel (60-120 mesh) column chromatography to afford the corresponding product. All products were characterized by ^{1}H NMR and ^{13}C NMR.

IV.E.3. Spectroscopy data

1. *N*-((1*H*-indol-3-yl)(phenyl)methyl)aniline: (Table IV.4, entry 4a)

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.82 (s, 1H), 6.45 (s, 2H), 6.96 (t, *J* = 7.6 Hz, 2H), 7.12 (t, *J* = 7.6 Hz, 2H), 7.15-7.24 (m, 5H), 7.29 (d, *J* = 7.6 Hz, 2H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.55 (s, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 39.7, 110.7, 118.8, 119.1, 119.5, 121.5, 123.2, 125.7, 126.6, 127.8, 128.3, 136.2, 143.6, 147.0.

2. *N*-((1*H*-indol-3-yl)(4-methoxyphenyl)methyl)aniline: (Table IV.4, entry 4d)

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.80 (s, 3H), 5.87 (s, 1H), 6.53 (s, 2H), 6.85 (d, *J*=6.0 Hz, 2H), 7.07 (t, *J*= 5.4 Hz, 2H), 7.13-7.44 (m, 6H), 7.45 (d, *J*= 6 Hz, 2H), 7.65 (s, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 29.3, 38.9, 54.8, 55.1, 110.7, 113.2, 113.5, 114.6, 118.8, 119.5, 119.6, 121.5, 121.9, 123.3, 126.6, 129.1, 129.3, 130.8, 133.6, 133.8, 135.9, 136.2, 157.4.

3. 4-((1*H*-indol-3-yl)(phenylamino)methyl)-2-methoxyphenol: (Table IV.4, entry 4f)

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.86 (s, 3H), 5.77 (s, 1H), 6.52 (s, 2H), 6.78 (d, *J*= 8 Hz, 2H), 6.84 (s, 1H), 6.97 (t, *J*= 7.6 Hz, 2H), 7.12 (t, *J*= 7.6 Hz, 2H), 7.26 (d, *J*= 8.4 Hz, 2H), 7.37 (d, *J* = 8 Hz, 2H), 7.83 (s, 2H), 10.73 (s, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 39.4, 55.4, 110.7, 110.8, 111.1, 113.6, 118.7, 118.9, 119.3, 119.4, 120.2, 120.8, 121.4, 121.6, 121.8, 122.2, 123.2, 126.6, 135.8, 136.3, 143.3, 145.9.

4. 3-(phenyl(pyrrolidin-1-yl)methyl)-1*H*-indole: (Table IV.4, entry 4m)[45]

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.75 (s, 4H), 2.51 (d, *J*=6.5 Hz, 4H), 4.59 (s, 1H), 7.04-7.15(m, 4H), 7.21-7.26 (m, 3H), 7.54 (d, *J*=7.2Hz, 2H), 7.82 (d, *J*=7.5 Hz, 1H), 8.10 (br, s, 1H);

^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 144.41, 136.08, 128.16, 127.69, 126.53, 122.0, 121.79, 119.73, 119.39, 119.30, 111.01, 67.97, 53.68, 23.51.

5. 3-((2-chlorophenyl)(pyrrolidin-1-yl)methyl)-1*H*-indole (Table IV.4, entry 4n)[45]

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.72 (s, 4H), 2.53 (d, *J*=3.2 Hz, 4H), 5.15 (s, 1H), 6.98-7.23 (m, 7H), 7.93(d, *J*=7.2 Hz, 2H), 8.07 (br, s, 1H);

^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 141.25, 135.89, 132.81, 129.40, 129.33, 127.39, 126.83, 126.42, 122.83, 121.74, 119.73, 119.33, 117.75, 111.05, 62.89, 53.41, 23.47;

6. 3-((4-bromophenyl)(pyrrolidin-1-yl)methyl)-1*H*-indole (Table IV.4, entry 4o)[46]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.06, (br s, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 8.7 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.19–7.14 (m, 2H), 7.08 (t, *J* = 7.3 Hz, 1H), 4.56 (s, 1H), 2.51 (d, *J* = 8.0 Hz, 4H), 1.77 (s, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 143.82, 136.43, 131.59, 129.72, 126.56, 122.33, 120.47, 119.97, 119.80, 119.21, 111.46, 67.63, 53.94, 23.83.

7. 3-((4-methoxyphenyl)(pyrrolidin-1-yl)methyl)-1*H*-indole (Table IV.4, entry 4p)[46]

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.02 (br s, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 2H), 7.06 (t, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 2H), 4.55 (s, 1H), 3.74 (s, 3H), 2.56–2.46 (m, 4H), 1.76 (s, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 158.53, 137.03, 136.47, 129.07, 126.84, 122.14, 120.10, 120.05, 119.62, 113.84, 111.36, 67.61, 55.48, 54.00, 23.86.

8. 1-(2-chlorophenyl)-1-(1*H*-indol-3-yl)-*N*,*N*-dimethylmethanamine (Table IV.4, entry 4q)[45]

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.27 (s, 6H), 5.05 (s, 1H), 7.03-7.26 (m, 7H), 7.87(br, s, 2H), 8.19 (br, s, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 137.32, 136.89, 133.97, 132.19, 130.41, 130.30, 128.35, 127.71, 127.00, 122.13, 121.14, 120.14, 115.97, 113.48, 73.71, 41.64.

9. 1-(1*H*-indol-3-yl)-*N*,*N*-dimethyl-1-phenylmethanamine (Table IV.4, entry 4q)[47]

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.70 (s, 6H), 4.98 (s, 1H), 6.59-6.74 (m, 2H), 6.83-6.85 (m, 3H), 6.94- 7.03 (m, 4H), 7.20 (s, 1H), 7.42 (d, *J* = 6.8 Hz, 1H);

^{13}C, NMR (50 MHz, $CDCl_3$) δ (ppm): 137.32, 136.43, 129.61, 129.24, 128.77, 128.12, 127.00, 122.13, 121.15, 120.14, 115.35, 113.49, 74.28, 41.64.

IV.E.4. Scanned copies of ^{1}H and ^{13}C NMR

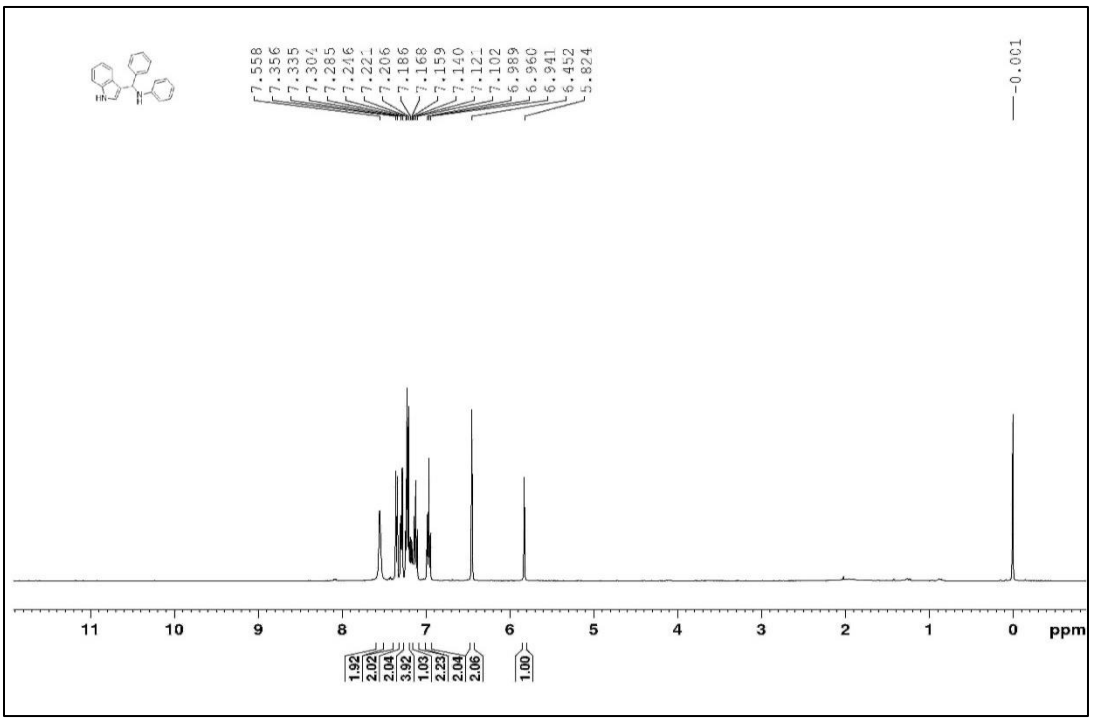


Figure IV.3. Scan copy of ^{1}H NMR of *N*-((1*H*-indol-3-yl)(phenyl)methyl)aniline.

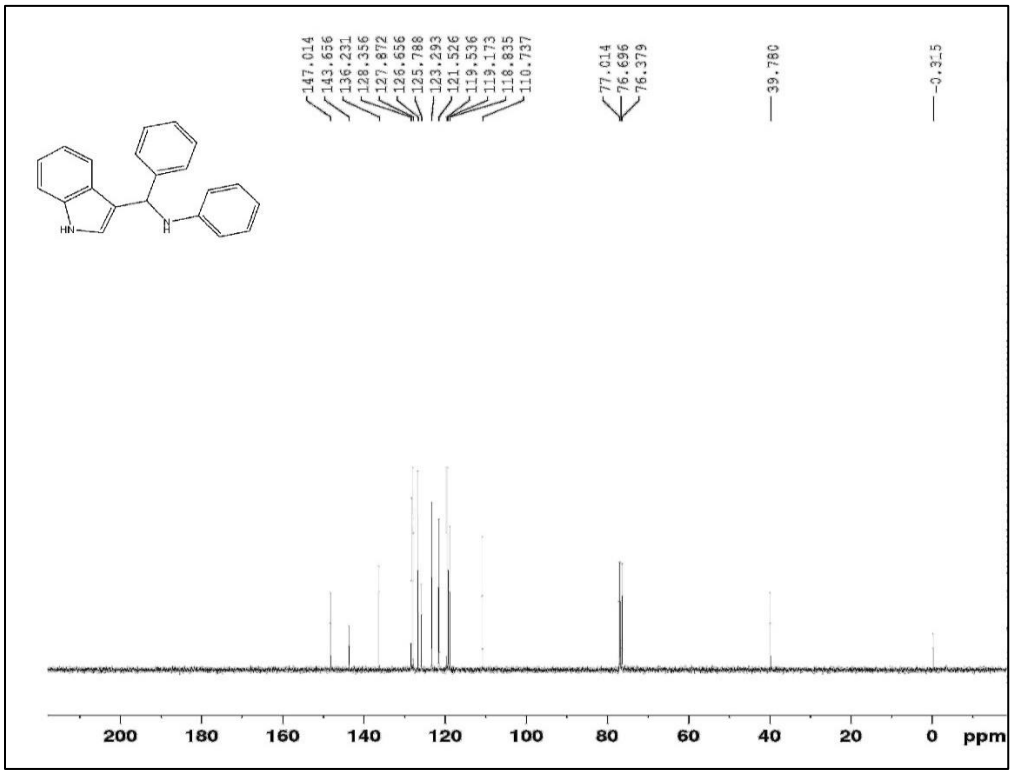


Figure IV.4. Scan copy of ^{13}C NMR of *N*-((1*H*-indol-3-yl)(phenyl)methyl)aniline.

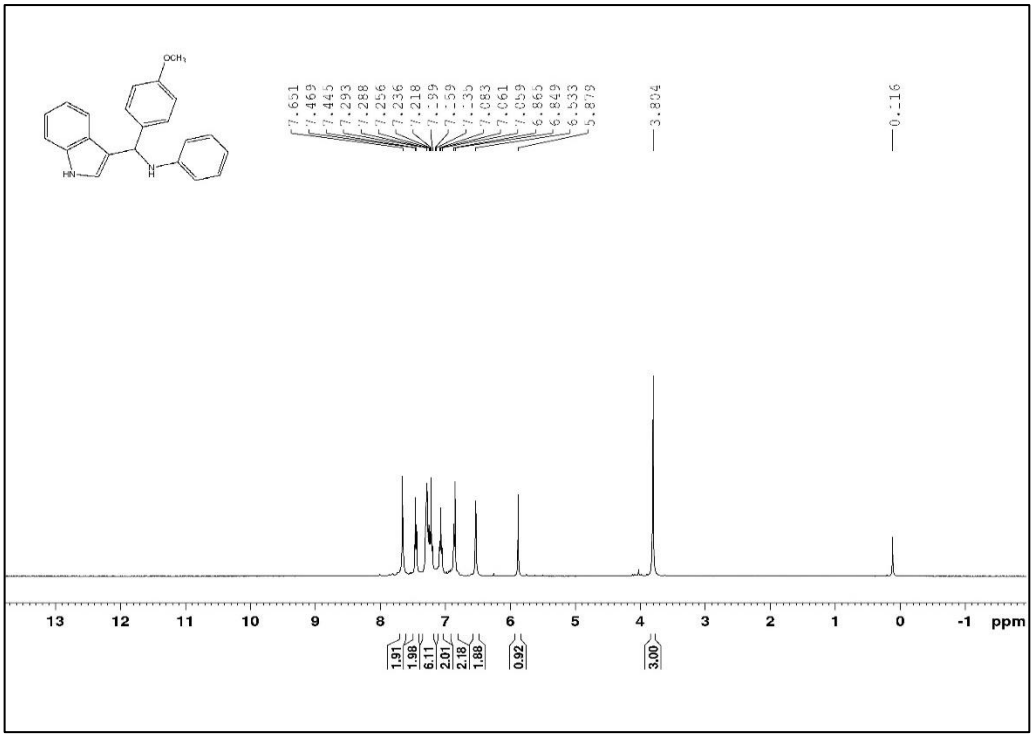


Figure IV.5. Scan copy of ^{1}H NMR of *N*-((1*H*-indol-3-yl)(4-methoxyphenyl)methyl)aniline.

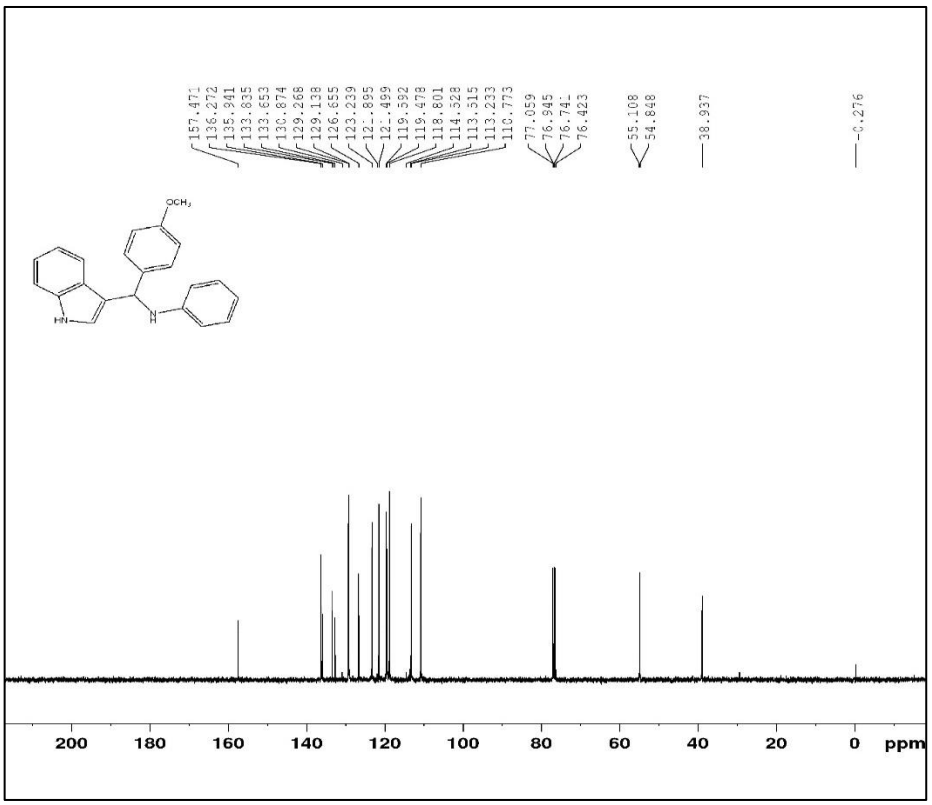


Figure IV.6. Scan copy of ^{13}C NMR of *N*-((1*H*-indol-3-yl)(4-methoxyphenyl)methyl)aniline.

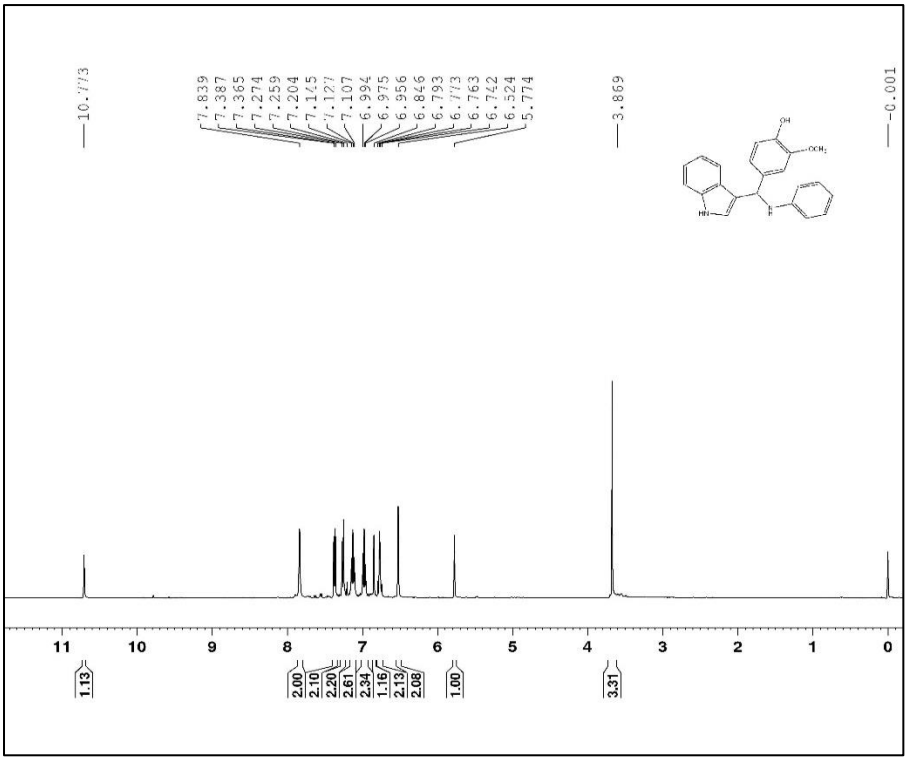


Figure IV.7. Scan copy of ^{1}H NMR of 4-((1*H*-indol-3-yl)(phenylamino)methyl)-2-methoxyphenol.

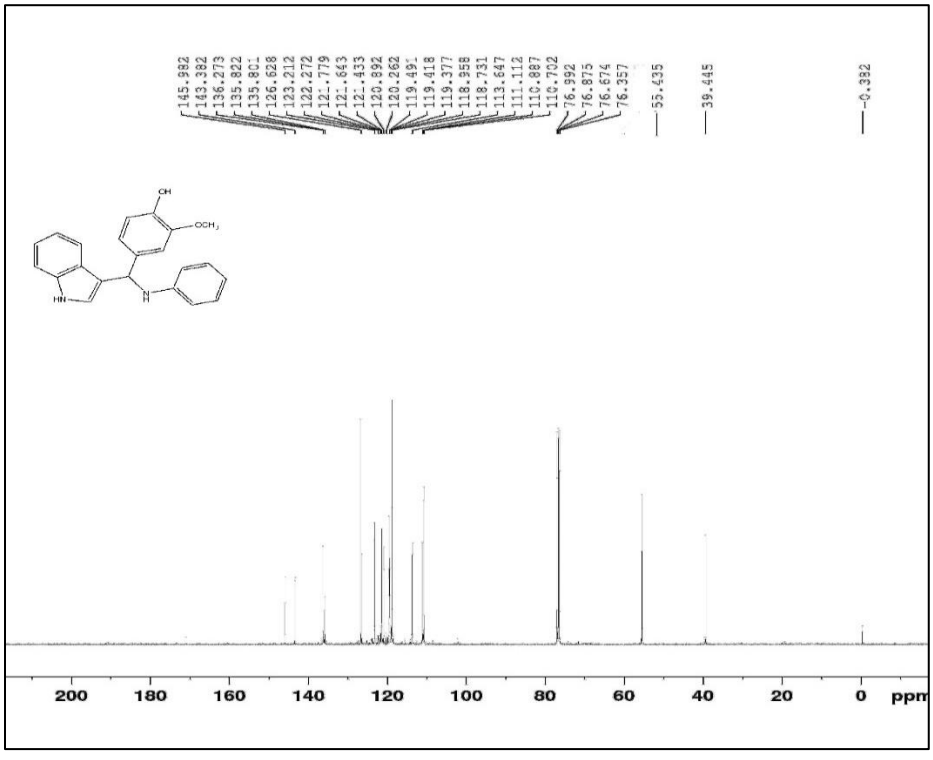


Figure IV.8. Scan copy of ^{13}C NMR of 4-((1*H*-indol-3-yl)(phenylamino)methyl)-2-methoxyphenol.

IV.F. Reference

References are given in BIBLOGRAPHY under Chapter IV.