CHAPTER 4

SYNTHESIS OF 5-(2-BENZENSULFONYL ETHYL)-3-(3-BENZYL-3H-IMIDAZOL-4-YL)-1H-INDOLE.

4.1 INTRODUCTION:

Imidazole belongs to an important group of heterocyclic compound containing two nitrogen atoms in a five member ring. Imidazoles are a common component of a large number of natural products and pharmacologically active molecules [160] and these bioactive metabolites are nortopsentins [161] and topsentins [162] possessing an imidazole spacer between the two indole residues. Imidazo-indole derivatives exhibit antidiabetic [163], aldose reductctase inhibitory activity [164], antidepressant, analgesics [165], 5-NT₃ receptor antagonists [166], light –dependent TNF-α antagonists [167] and antifungal [168] activities. These observations promoted us to synthesize a new series of imidazole derivatives in order to understand pharmacological activities.

4.2 LITERATURE BACKGROUND

Sisko et.al. [169] published a procedure wherein the imine (74) is formed in situ and thereafter reacted with an aryl substituted TosMIC (75) reagent to yield 1,4,5-trisubstituted imidazoles (76). In this sequence by first reacting 3-formyl indole with benzyl amine and then adding TosMIC (75) and triethylamine yielded 1,4,5-trisubstituted imidazoles (76) [Scheme-4.1].
Borgne et al. reported[170] the reduction of the 3-formyl (77) group was carried out by using sodiumborohydride in methanol to give carbinols (78), followed by reaction with 1,1'-carbonyldiimidazole (CDI) in THF yielded 3-(1-Azolyl methyl) -1H-indoles (79) (Scheme-4.2).

Nagarathanam et al. reported[171] the utility of indole-1,3-substituted phosphonate ester (80) for the synthesis of 3-vinyl indole (82) was demonstrated by the Witting-Horner reaction with pyridine-3-carboxyaldehyde (81) using sodium hydride as the base to give 3-[2-(3-pyridyl)-vinyl] indole (82) (Scheme-4.3).
Pedro et.al. reported[172] the synthesis of 3-[(2-amino)-pyrimidin-4-yl]-7-azaindole (85) starting from 3-acetyl indole (83a) followed by N-protection with p-toluenesulfonyl chloride provided the N-tosyl-3-acetyl-7-aza-indole (83b) and formation of enamine (84) by using dimethylformamide-dimethylacetal followed by cyclization with guanidine hydrochloride with N-deprotection to give desired compound(85). (Scheme-4.4).

Pilar et.al. reported [173] the conversion of ketoamide (86) into the corresponding 2, 4-disubstitued imidazoles (87) involved the use of ammonium acetate and heating of the resulting mixture. (Scheme-4.5).
Javier et al. [174] studied the reaction of 7-azaindolecarboxyaldehyde with tosylmethylisocyanate (TosMIC) in order to synthesize fused indole derivative (89). Instead of 89, 7-azaindole-3-(oxazole) (90) was formed by means of a simple condensation of appropriate 7-azaindolecarboxyaldehyde (88a) and TosMIC, but not only with (88a), and also with 2-indolecarboxyaldehyde (88b) (Scheme-4.6).
4.3 PRESENT WORK:

It is obvious from the literature citations, given above, that not much work has been done on the condensation of 5-bromo-3-formyl indole with benzyl amine and further reaction with aldimine. The present chapter deals with the studies on the synthesizing 3-(imidazolyl)-indoles. There are two main ways of synthesizing 3-(imidazolyl)-indoles. One starts with an imidazole and then indole moiety is built from there and the other with an existing indole derivatives. As tosylmethylisocyanate (TosMIC) has been used successfully to synthesize imidazoles, the choice of starting from the 3-formylindole was commercially available product and an excellent starting material for this 3-(imidazolyl)methyl indole containing bromine was subjected to Heck reaction, followed by hydrogenation to get the targeted indole derivatives.

4.3 RESULTS AND DISCUSSIONS:

Treatment of 5-bromo indole-3-carboxyaldehyde (2a-b) (i.e., 2a, R=H; 2b, R= -CH\textsubscript{3}) with benzyl amine (91) in presence of TBAB (tetra butyl ammonium bromide) as a catalyst in THF, stirring at room temperature for maintained for 18 hrs., obtained a product benzyl-(5-bromo-1H-indolmethylene)amine (92a-b) (i.e., 92a, R=H; 92b, R=-CH\textsubscript{3}) which was characterized on the basis of spectral and analytical data. Thus, its IR (KBr) spectrum showed (figure-4.1) a very broad band of medium to strong intensity in the region 3056 (broad, –NH, stretching); 1631 (strong, –CH=N-, stretching); 1524 (strong, -N-CH\textsubscript{2});
$^{1}$H-NMR (DMSO d$_{6}$/TMS) signals showed (figure-4.2) at $\delta$ 4.71 (s, 2H, -N-CH$_2$); 7.21-7.24 (d, 1H, indole ring); 7.25-7.33 (m, 5H, Ar-H ring); 7.34-7.42 (d, 1H, indole ring); 7.87 (s, 1H, -CH=N); 8.38 (s, 1H, indole ring); 8.56 (s, 1H, indole ring); 11.74 (s, 1H, -NH, indole ring);

$^{13}$C-NMR (DMSO d$_{6}$/TMS) signals showed (figure-4.3) at $\delta$ 157.0, 141.0, 136.1, 133.0, 128.8, 128.1, 127.1, 125.54, 124.42, 114.3, 113.5, 65.1. Its CI mass spectrum in the Q+1 mode showed (figure-4.4) a molecular ion peak at 315.1 (base peak) corresponding to a molecular mass of 314. (Scheme -4.7)

Cyclization of 92a-b (i.e., 92a, R=H; 92b, R= -CH$_3$) with tosylmethyisocyanate (TosMIC) (75) in the presence of mixture of methanol & THF at 65-70 $^\circ$C for 6 hrs gave a product which was characterized as 3-(3-benzyl-3H-imidazole-4yl)-5-bromo indole (93a-b) (i.e., 93a, R=H; 93b, R= -CH$_3$) on the basis of its analytical and spectral data. Thus, the compound in its IR (KBr) spectrum showed (figure-4.5) a very broad band of medium to strong intensity in the region 3424 (broad –NH stretching); 1512 (strong, –N-CH$_2$, stretching); $^{1}$H-NMR (DMSO d$_{6}$/TMS) signals showed (figure-4.6) at $\delta$ 5.26 (s, 2H, -NCH$_2$); 6.93-6.95 (d, 2H, indole ring); 7.13 (s, 1H,
imidazole ring); 7.19-7.28 (m, 4H, Ar-H ring); 7.34-7.39 (m, 2H, 1H in Ar-H & 1H in imidazole ring); 7.55 (s, 1H, indole ring); 7.85 (s, 1H, indole ring); 11.56 (s, 1H, -NH, indole ring); \(^{13}\)C-NMR (DMSO d\(_6\)/TMS) signals showed [figure-4.7] at \(\delta\) 139.07, 138.40, 135.06, 129.05, 128.71, 128.20, 127.80, 126.78, 126.08, 125.99, 124.77, 121.45, 114.28, 112.74, 103.78, 48.17. Its mass spectrum, when recorded in the Q+2 mode, showed [figure-4.8] the molecular ion peak at 354 corresponding to a molecular mass of 352 (Scheme-4.8).

The plausible way of reaction seems to follow the mechanism shown below:
Debenzylation of 93a in the presence of hydrogen gas and 10% palladium-carbon in methanol heating at 45-50 °C for 8 hrs gave 5-bromo-3-(3H-imidazol-4-yl)-1H-indole (94a) (94a, i.e., R= H) which has been characterized on the basis of spectral and analytical data. thus, its IR (KBr) spectrum showed a peak at 3424 (broad, –NH, stretching in indole ring); 3350 (broad, –NH, stretching, imidazole ring); 1H-NMR (DMSO d$_6$/TMS) signals showed (figure-4.9) at δ 4.39-4.42 (s, 1H, -NH, imidazole ring); 7.2 (s, 1H, imidazole ring); 7.3 (d, 2H, indole ring); 7.37-7.41 (s, 1H, indole ring); 7.72 (s, 1H, imidazole ring); 7.80 (s, 1H, indole ring); 10.07 (s, 1H, -NH, indole ring); Its Cl mass spectrum in the Q+1 mode showed (figure-4.10) a molecular ion peak at 263.1 (base peak) corresponding to a molecular mass of 262; (Scheme- 4.9).

Benzylation of 94b with benzyl chloride in DMF, in the presence of potassium carbonate, stirring at room temperature for 10-30 min, followed by warming at 105 °C and maintained for 10-12 hrs., yielded 3-(3-benzyl-3H-imidazol-4-yl)-5-bromo-1-methyl-1H-indole (93b) (93b, i.e., R=CH$_3$,) which has been characterized on the basis of spectral and analytical data. thus, its IR (KBr) spectrum showed at 3324
(broad, –NH, stretching); 1512 (strong, –N-CH2, stretching); 1H-NMR (DMSO d6/TMS) δ 5.26 (s, 2H, -NCH2); 6.93-6.95 (s, 2H, indole ring); 7.13 (s, 1H, imidazole ring); 7.19-7.28 (m, 4H, Ar-H ring); 7.34-7.39 (m, 2H, 1H in Ar-H & 1H in imidazole ring); 7.55 (s, 1H, indole ring); 7.85 (s, 1H, indole ring); 11.56 (s, 1H, -NH, indole ring); 13C-NMR (DMSO d6/TMS) signals δ 139.07-103.78, aryl carbons); 48.17 (-NCH2 in imidazole ring); 33.54 (-N-CH3, in indole ring); when recorded in the CI method, showed the molecular ion CI mass spectrum in Q+2 mode showed a molecular ion peak at 354 (base peak) corresponding to a molecular mass of 352; (Scheme- 4.10).

Treatment of 93a-b (i.e., 93a, R=H; 93b, R=-CH3) with 25 in the presence of palladium acetate as a catalyst in DMF as a solvent heating at 100-105 °C for 16 hrs gave 5-(2-benzenesulfonyl-vinyl)-3-(3-benzyl-3H-imidazol-4yl)-1H-indole (96a-b) (i.e., 96a, R=H; 96b, R=-CH3) which has been characterized on the basis of spectral and analytical data. Thus, its IR (KBr) spectrum showed a very broad band of medium to strong intensity in the region 3362 (broad, –NH, stretching); 1143 (braod, -NCH2); 1H-NMR (DMSO d6/TMS) δ 5.19-
5.43 (s, 2H, -NCH₂); 6.90-6.92 (d, 3H, 2H indole ring & 1H in –CH=); 7.18-7.22 (d, 3H, 1H in SCH= & two H in benzyl ring); 7.37-7.43 (m, 4H, three H in benzyl ring & 1H in Ar-H ring); 7.55-7.67 (m, 6H, four protons in Ar-H ring & two protons in imidazole in ring); 7.88-7.89 (s, 1H, indole ring); 8.41-8.51 (s, 1H, indole ring); 11.76-11.78 (s, 1H, -NH-); when recorded in the CI method, showed the molecular ion peak at 440.1 corresponding to a molecular mass of 439.0 (Scheme- 4.11).

Compound 96a-b (i.e., 96a, R=H; 96b, R=-CH₃) was reduced to 5-(2-Benzene sulfonyl-ethyl)-3-(3-benzyl-3H-imidazol-4-yl)-1H-indole (98a-b) (i.e., 98a, R=H; 98b, R=-CH₃) using palladium-carbon as a catalyst in presence of acid medium in methanol at 45-50 °C for 8 hrs. The structure of 98a-b was conformed by its analytical and spectral data thus, the compound in IR (KBr) spectrum showed (figure-4.11) at 1293 (very strong N–CH₃, in indole ring); 1148 (very strong, -CH₂-N, in benzylimidazole ring); Its 1H-NMR (DMSO d₆/TMS) signals showed (figure-4.12) at § 2.92-2.95 (t, 2H, -CH₂, ethyl); 3.60-3.64 (t, 2H, -SCH₂); 3.78 (s, 3H, N-CH₃, in indole ring); 5.44(s,2H, -N-CH₂, in
benzyl ring); 7.05-7.11 (m, 3H, benzyl ring); 7.26-7.29 (m, 4H, 2H in benzyl ring & 2H in Ar-H ring); 7.42-7.44 (d, 1H, indole ring); 7.58 (d, 1H, indole ring); 7.64-7.67 (m, 2H, Ar-H ring); 7.75 (d, 1H, Ar-H ring); 7.89-7.94 (m, 3H, 2H in imidazole ring & 1H in indole ring); 9.30 (s, 1H, indole ring); $^{13}$C-NMR (DMSO d$_6$/TMS) signals showed at $\delta$ 139.5, 136.4, 135.83, 135.37, 134.25, 131.21, 130.27, 129.89, 129.22, 128.64, 128.62, 128.19, 127.74, 126.88, 123.69, 118.64, 118.44, 110.97, 98.73, 56.47, 50.23, 33.33, 28.72, When recorded in the CI method, showed the molecular ion peak at 456.1(q+1), corresponding to a molecular mass of 455 (Scheme- 4.12).

Condensation of 27a-b (i.e., 27a, R=H; 27b, R=-CH$_3$) (already prepared in chapter-2) with 91 in THF as a solvent in the presence of TBAB as a catalyst stirring at room temperature for 10-30 mints, then maintained for 18 hrs., yielded of [5-(2-benzenesulfonyl-vinyl)-1H-indol-3-yl methylene]-benzyl amine (95a-b) (i.e., 95a, R=H; 95b, R=-CH$_3$) which has been characterized on the basis of spectral and analytical data. Thus, its IR (KBr) spectrum showed in the region
3268 (broad, –NH, stretching indole ring), 1292 (very strong, -N-CH₂, stretching); \(^1\)H-NMR (DMSO d₆/TMS) δ 4.33-4.38(s, 2H, -N-CH₂, N-benzyl); 7.18-7.20 (d, 2H, S-CH=CH-); 7.32-7.43 (m, 8H, 5H in benzyl ring + 2H in indole ring + 1H –CH=N); 7.63-7.70 (m, 5H, Ar-H ring); 7.91-7.93 (d, 2H, indole ring); 11.71 (s, 1H, -NH, proton in indole ring); when recorded in the CI method, showed the molecular ion peak at 401.2 corresponding to a molecular mass of 400.  

(Scheme- 4.13).

\[
\text{N} \quad \text{CHO} \\
\text{N} \quad \text{S} \quad \text{O} \\
\text{O} \quad \text{R} \\
\text{THF / TBAB/Benzyl amine(91)} \\
25-30^\circ\text{C/18hrs.} \\
\text{CHO} \\
\text{N} \quad \text{S} \quad \text{O} \\
\text{O} \quad \text{R} \\
\text{(95a-b)} \\
\text{Scheme- 4.13}
\]

Cyclization of 95a-b with 75 in methanol: THF at 65-70 °C for 6 hrs gave 5-(2-benzenesulfonyl-vinyl)-3-(3-benzyl-3H-imidazol-4yl)-1H-indole (96a-b) (i.e., 96a, R=H; 96b, R=-CH₃), which has been characterized on the basis of spectral and analytical data. Thus, its IR (KBr) spectrum showed a very broad band of medium to strong intensity in the region 3362 (broad, –NH, stretching); 1521 (braod,-NCH₂); \(^1\)H-NMR (DMSO d₆/TMS) δ 5.19-5.43 (s, 2H, -NCH₂); 6.90-6.92 (d, 3H, 2H indole ring +1H in –CH=); 7.18-7.22 (d, 3H, 1H in SCH= + 2H in benzyl ring); 7.37-7.43 (m, 4H, 3H in benzyl ring + 1H in Ar-H ring); 7.55-7.67 (m, 6H, 4 proton in Ar-H ring + 2 proton in imidazole in ring); 7.88-7.89 (s, 1H, indole ring); 8.41-8.51 (s, 1H, indole ring);
11.76-11.78 (s, 1H, -NH-); when recorded in the CI method, showed the molecular ion peak at corresponding to a molecular mass of (Scheme -4.14).

Reaction of 30a-b (i.e., 30a, R=H; 30b, R=-CH₃) (already prepared in chapter-2) with 91 in THF as a solvent in the presence of TBAB as a catalyst stirring at room temperature for 10-30 mints, then maintained for 18 hrs., yielded a crude product [5-(2-benzenesulfonyl-ethyl)-1H-indol-3-yl methylene]-benzyl amine (97a-b) (i.e., 97a, R=H; 97b, R=-CH₃). The crude product 97a-b was used in the next step. The cyclization of crude 97a-b with 75 in the mixture of methanol & THF heating at 65-70 °C for 6 hrs gave 5-(2-benzenesulfonyl-ethyl)-3-(3-benzyl-3H-imidazol-4yl)-1H-indole (98a-b) (i.e., 98a, R=H; 98b, R=-CH₃) which has been characterized on the basis of spectral and analytical data. Thus, its IR (KBr) spectrum showed at 3441 (very strong N–H, stretching in indole ring); 1148 (very strong, -CH₂-N-, in benzylimidazole ring); ¹H-NMR (DMSO d₆/TMS) δ 2.92-2.95 (t, 2H, -CH₂, ethyl); 3.60-3.64 (t, 2H, -SCH₂); 5.44 (s, 2H, -N-CH₂, in benzyl
ring); 7.05-7.11 (m, 3H, benzyl ring); 7.26-7.29 (m, 4H, 2H in benzyl ring + 2H in Ar-H ring); 7.42-7.44 (d, 1H, indole ring); 7.58 (d, 1H, indole ring); 7.64-7.67 (m, 2H, phenyl ring); 7.75 (d, 1H, Ar-H ring); 7.89-7.94 (m, 3H, 2H in imidazole ring + 1H in indole ring); 9.30 (s, 1H, indole ring); 11.56 (s, 1H, -NH, in indole ring); $^{13}$C-NMR (DMSO d$_6$/TMS) signals δ 56.47 (-SC$_2$H); 50.23 (-NCH$_2$, in imidazole ring); 33.33 (-NCH$_3$, in indole ring); 28.72 (-SCH$_2$CH$_2$); when recorded in the CI method, showed in Q+1 mode, the molecular ion peak at 352 corresponding to a molecular mass of 351 (Scheme -4.15).

Condensation of 30b (30b, i.e., R=CH$_3$) (already reported the preparation in chapter-2) with 2,2-dimethoxy ethylamine in THF as a solvent in the presence of TBAB as a catalyst stirring at room temperature for 10-30 mints, then maintained for 18 hrs., yielded the product [6-(2-benzenesulfonyl-ethyl)-3H-indole-1-ylmethylenec]-
2,2-dimethoxy-ethyl)amine (99b) \( (99b, \text{ i.e., } R=\text{CH}_3) \). This has been characterized on the basis of spectral and analytical data. Thus, its IR (KBr) spectrum showed in the region 1641 (strong, \(-\text{C}=-\text{N}\), stretching); 1290 (strong, \(-\text{N}-\text{CH}_3\)); 1195 (very strong, \(-\text{C}-\text{OCH}_3\), in dimethoxyethylamine); \(^1\text{H}-\text{NMR} \) (DMSO d\(_6\)/TMS) \( \delta \) 2.94-2.98 (t, 2H, S-\text{CH}_2-\text{CH}_2\); 3.35 (s, 6H, \(-\text{OCH}_3\)_2); 3.63-3.67 (t, 2H, -S-\text{CH}_2, ethyl); 3.84 (s, 3H, N-\text{CH}_3, in indole ring); 4.25-4.26 (d, 2H, -N-\text{CH}_2); 4.54-4.55 (t, 1H, -N-\text{CH}_2-\text{CH}_-); 7.11-7.13 (d, 1H, indole ring); when recorded in the CI method, showed the molecular ion peak at 415.2, corresponding to a molecular mass of 415(Scheme -4.16).

Cyclization of 99b with 75 in a mixture of methanol & THF and heating at 65-70 °C for 6 hrs gave 5-(2-benzenesulfonyl-ethyl)-3-[3-(2,2-dimethoxy-ethyl)-3H-imidazol-4-yl]-1H-indole (100b) \( (100b, \text{ i.e., } R=\text{CH}_3) \), which has been characterized on the basis of spectral and analytical data. Thus, its IR (KBr) spectrum showed (figure-4.15) at 1294 (strong, \(-\text{NCH}_3\), stretching, indole ring); 1146 (strong, \(-\text{C}-\text{OCH}_3\), in dimethoxyethylamine); \(^1\text{H}-\text{NMR} \) (DMSO d\(_6\)/TMS) signals showed (figure-4.16) at \( \delta \) 2.94-2.98 (t, 2H, -CH\(_2\), ethyl); 3.35 (s, 6H, \(-\text{OCH}_3\)_2); 3.63-3.67 (t, 2H, -S-\text{CH}_2, ethyl); 3.84 (s, 3H, -N-\text{CH}_3, in
in indole ring; 4.25-4.26 (d, 2H, -N-CH2); 4.55 (t, 1H, -CH- in ethyl); 7.11-7.13 (d, 1H, in indole ring); 7.35 (s, 1H, imidazole ring); 7.45-7.47 (d, 1H, indole ring); 7.62-7.66 (t, 2H, Ar-H ring); 7.73-7.74 (m, 2H, 1H in Ar-H ring & 1H in indole ring); 7.80 (s, 1H, imidazole ring); 7.91-7.93 (d, 2H, Ar-H ring); 9.19 (s, 1H, indole ring); 13C-NMR (DMSO d_6/TMS) signals showed (figure-4.17)  at δ 98.64 (-CH(OCH_3)_2); 56.45 (-SCH_2); 55.10 (-OCH_3); 48.06 (-NCH_2, in imidazole ring); 33.41 (-N-CH_3, in indole ring) 28.76 (-SCH_2CH_2); when recorded in the CI method, showed (figure-4.18) the molecular ion peak at 454.1, corresponding to a molecular mass of 453(Scheme-4.17).

![Scheme 4.17](image)

The over all sequence of the reactions given in Scheme-4.18
SUMMERY OF THE SCHEME-4.18
4.4. EXPERIMENTAL SECTION

GENERAL: The reagents which are used in the synthesis i.e. benzyl amine, TBAB (tetra butyl ammonium bromide) tosylmethylisocyanate (TosMIC), phenylvinylsulfone, tri-orthotolylphosphi ne, palladium acetate, Pd-C, ect, were purchased from commercial suppliers and used as with purification.

4.4.1. Preparation of 98 a-b:

4.4.2. Preparation of 92 a-b from 2a-b;

A mixture of THF (50ml), 2a-b (0.02 moles), 91 (1.2eq.) and TBAB (tetra butyl ammonium bromide) as a catalyst was stirred for 24.hr at 25-30 °C, then monitored the reaction by TLC and cooled to 20-25 °C and charged water (100ml) and stir for 1.0hr at 10-15 °C, filter the mass and wash with water (25ml) and obtained the pure material 92a-b.

92a: (i.e., R=H), Yield 6.2 g (86.11%). Off white color solid M.R: 175-177 °C, IR (KBr): 3056 (broad –NH, stretching); 1631 (strong, –CH=N- stretching); 1524 (strong, -N-CH2); 1H-NMR (DMSO d6/TMS) δ 4.71 (s, 2H, -N=CH2); 7.21-7.24 (d, 1H, indole ring); 7.25-7.33 (m, 5H, Ar-H ring); 7.34-7.42 (d, 1H, indole ring); 7.87 (s, 1H, indole ring); 8.38 (s, 1H, indole ring); 8.56 (s, 1H, indole ring); 11.74 (s, 1H, -NH, indole ring);

13C-NMR (DMSO d6/TMS) δ 157.0, 141.0, 136.1, 133.0, 128.8, 128.1, 127.1, 125.54, 124.42, 114.3, 113.5, 65.1., MS m/z = 315.1 (M+1).

92b: (i.e., R= -CH3) Yield 7.0 g (95 %); off white solid, M.R: 117-120 °C. IR (KBr): 1633. (strong, –CH=N-, stretching); 1562 (strong, -N-CH3); 1535 (broad, –N-CH2, stretching); 1H-NMR (DMSO d6/TMS) δ
3.78 (s, 3H, -NCH$_3$); 4.68 (s, 2H, -NCH$_2$); 7.19-7.21 (d, 1H, indole ring); 7.22-7.34 (m, 5H, Ar-H ring); 7.44-7.46 (d, 1H, indole ring); 7.82 (s, 1H, -CH=); 8.33-8.34 (s, 1H, indole ring); 8.51 (s, 1H, indole ring); $^{13}$C-NMR (DMSO d$_6$/TMS) δ 156.5, 141.0, 136.7, 136.4, 128.7, 128.1, 127.4, 127.0, 125.4, 124.3, 113.9, 113.2, 112.7, 65.1, 33.4., MS m/z = 329.1 (M+1).

4.4.3. Preparation of 93a-b from 92a-b;

A solution of THF (50ml), methanol (25), triethyl amine (2.0eq.), 92a-b (0.015 moles), and 75 (1.2eq.) was stirred at 25-30°C for 15.0min and raise the temperature to 65 °C, then maintained for 6.0hrs at 65-70 °C, then monitored the reaction by TLC cool to 25 °C and quenched the mass into ice cold water below 10 °C, then adjust the pH to 4.5-5.0 with acetic acid and extract with ethyl acetate(2X100ml), evaporate the solvent completely and obtained residue was run column chromatography and collect the pure compound 93a-b by using solvent ratio hexane: ethyl acetate(7:3) and confirm the compound by $^1$H NMR & $^{13}$C NMR.

4.4.4. Preparation of 93a from 94b;

A mixture of DMF (50ml), 94b (0.05moles), potassium carbonate(1.3eq.) and was stirred at 20-25 °C and slowly add a mixture benzyl chloride (1.2 eq.), at 20-25 °C for 30.0min and raise the temperature to 100 °C, then maintained for 10-12.0hrs at 100-105 °C, then monitored the reaction by TLC, cool to 40 °C and distilled the mass below 60 °C, the obtained residue was run column
chromatography and collect the pure compound by using solvent ratio
hexane: ethyl acetate(7:3), identified by IR, $^1$H NMR & $^{13}$C NMR.

**93a: (i.e., R=H);** off white color solid M.R: 187.6-191 °C, IR (KBr):
3424 (broad, –NH, stretching); 1512 (strong, –N-CH$_2$, stretching); $^1$H-
NMR (DMSO d$_6$/TMS) δ 5.26 (s, 2H, -NCH$_2$); 6.93-6.95 (d, 2H, indole
ring); 7.13 (s, 1H, imidazole ring ); 7.19-7.28 (m, 4H, Ar-H ring);
7.34-7.39 (m, 2H, 1H in Ar-H & 1H in imidazole ring); 7.55 (s, 1H,
indole ring); 7.85 (s, 1H, indole ring); 11.56 (s, 1H, -NH, indole ring);
$^{13}$C-NMR (DMSO d$_6$/TMS) signals δ 139.07, 138.40, 135.06, 129.05,
128.71, 128.20, 127.80, 126.78, 126.08, 125.99, 124.77, 121.45,
114.28, 112.74, 103.78, 48.17., MS m/z = 354 (M+2).

**93b: (i.e., R=-CH$_3$);** off white solid M.R: >260 °C, IR (KBr): 1588.
(broad, -NCH$_2$); 1544 (strong, -N-CH$_3$); $^1$H-NMR (DMSO d$_6$/TMS) δ 3.8
(s, 3H, -N-CH$_3$); 5.41 (s, 2H, -NCH$_2$); 7.02 (m, 2H, Ar-H ring); 7.22-
7.23 (m, 3H, Ar-H ring); 7.32-7.34 (d, 1H, indole ring); 7.48-7.51 (d, 1H,
indole ring); 7.58 (s, 1H, imidazole ring); 7.65 (s, 1H, imidazole
ring); 7.91 (s, 1H, indole ring); 9.35 (s, 1H, indole ring); $^{13}$C-NMR
(DMSO d$_6$/TMS) signals δ 136.61, 135.57, 135.30, 132.57, 129.17,
128.63, 128.58, 127.75, 125.35, 121.42, 118.87, 113.80, 113.09,
98.64, 50.22, 33.54, MS m/z= 368.3 (M+2).

**4.4.5. Preparation of 94a from 93a;**

Reduction of **93a** (0.012 mole) in the presence of palladium-
carbon(10%) hydrogen gas in methanol, heating at 45-50 °C for 8 hrs,
reaction monitored by TLC, after completion of reaction cool to RT and
filter the mass through hyflo bed, take filtrate and concentrated and recrystalized in acetonitrile and obtained pure compound of 94a.

94a: (i.e., R=H), off white color semi solid, IR (KBr): 3424.36 (broad –NH, stretching in indole ring); 3350 (broad, –NH, stretching, imidazole ring); 1H-NMR (DMSO d$_6$/TMS) δ 4.39-4.42 (s, 1H, -NH, imidazole ring); 7.2 (s, 1H, imidazole ring); 7.3 (d, 2H, indole ring); 7.37-7.41 (s, 1H, indole ring); 7.72 (s, 1H, imidazole ring); 7.80 (s, 1H, indole ring); 10.07 (s, 1H, -NH, indole ring); MS m/z = 263.1 (M+1).

4.4.6. Preparation of 96a-b from 93a-b;

A mixture of DMF (50ml), palladium acetate (0.2gm,) and tri-orthotolylphosphine (1.2eq.) was stirred at 20-25°C and slowly add a mixture of 93a-b (0.06 moles), 25 (1.15eq) and triethylamine (2.0eq.) at 20-25°C. Stirr the reaction mixture for 15.0min at 20-25°C and raise the temperature to 100°C, then maintained for 16.0hrs at 100-105°C, then monitored the reaction by TLC and cool to 40°C and distilled the mass below 60°C, the obtained residue was run column chromatography and collect the pure compound 96a-b by using solvent ratio hexane : ethyl acetate(7:3) and identified by 1H NMR & 13C NMR of phenylvinylsulfone derivatives.

4.4.7. Preparation of 96a-b from 95a-b;

A solution of THF (20 vol.), methanol (10.vol), triethylamine (2.0eq.), 95a-b(0.015 moles), and 75 (1.2eq.) was stirred at 25-30°C for 15.0min and raise the temperature to 65°C, then maintained for 6.0hrs at 65-70°C, then monitored the reaction by TLC and cool to 25
C and quenched the mass into ice cold water below 10 °C, then adjust the pH to 4.5-5.0 with acetic acid and extract with ethyl acetate(2X100ml), evaporate the solvent completely and obtained residue was run column chromatography and collect the pure compound 96a-b by using solvent ratio hexane : ethyl acetate(7:3) and conform the compound by \textsuperscript{1}H NMR & \textsuperscript{13}C NMR.

96a: (i.e., R=H), off white color solid M.R: >260 °C, IR (KBr): 3362 (broad, –NH, stretching); 1143 (strong, -NCH\textsubscript{2}, benzyl imidazole); \textsuperscript{1}H-NMR (DMSO d\textsubscript{6}/TMS) \(\delta\) 5.19-5.43 (s, 2H, -NCH\textsubscript{2}); 6.90-6.92 (d, 3H, 2H, indole ring & 1H in –CH=); 7.18-7.22 (d, 3H, 1H in SCH= & 2H in benzyl ring); 7.37-7.43 (m, 4H, 3H in benzyl ring & 1H in Ar-H ring); 7.55-7.67 (m, 6H, 4 proton in Ar-H ring & 2 proton in imidazole); 7.88-7.89 (s, 1H, indole ring); 8.41-8.51 (s, 1H, indole ring); 11.76-11.78 (s, 1H, -NH-); MS m/z = 440.1 (M+1).

96b: (i.e., R= -CH\textsubscript{3}); off white color solid M.R: >260 °C, IR (KBr): 1143 (very strong, -NCH\textsubscript{2}); 1286 (strong, -N-CH\textsubscript{3}, in indole ring); \textsuperscript{1}H-NMR (DMSO d\textsubscript{6}/TMS) \(\delta\) 3.7 (s, 3H, -N-CH\textsubscript{3}, in indole ring); 5.19-5.43 (s, 2H, -NCH\textsubscript{2}); 6.90-6.92 (d, 3H, 2H indole ring & 1H in –CH=); 7.18-7.22 (d, 3H, 1H in SCH= + 2H in benzyl ring); 7.37-7.43 (m, 4H, 3H in benzyl ring & 1H in Ar-H ring); 7.55-7.67 (m, 6H, 4 proton in Ar-H ring & 2 proton in imidazole); 7.88-7.89 (s, 1H, indole ring); 8.41-8.51 (s, 1H, indole ring); MS m/z = 454.1 (M+1).
4.4.8. Preparation of 98a-b from 96a-b;

Reduction of 96a-b (0.012 ml) in the presence of palladium-carbon and hydrogen gas by using acid medium in methanol by heating at 45-50 °C for 8 hrs, reaction monitored by TLC, after completion of reaction cool to RT and filter the mass through hyflo bed, take filtrate and concentrated and recrystalized in methanol obtained pure compound of 98(a-b).

4.5. Alternate preparation of 98a-b:

4.5.1. Preparation of 98a-b from 30a-b;

A mixture of THF (50ml), 30a-b (0.02 moles), 91 (1.2eq.) and TBAB (tetra butyl ammonium bromide) as catalyst was stirred for 24.hr at 25-30 °C, then monitored the reaction by TLC and cooled to 20-25 °C and charged water (100ml) and stir for 1.0hr at 10-15 °C, filter the mass and wash with water (25ml) and obtained the crude material 97a-b.

A solution of THF (50ml), methanol (25ml), triethyl amine (2.0eq.), 97(a-b) (0.015 moles), and 75 (1.2eq.) was stirred at 25-30 °C for 15.0min and raise the temperature to 65 °C, then maintained for 6.0hrs at 65-70 °C, then monitored the reaction by TLC, cool to 25 °C and quenched the mass into ice cold water below 10 °C, then adjust the pH to 4.5-5.0 with acetic acid and extract with ethyl acetate(2X100ml), evaporate the solvent completely and obtained residue was run column chromatography and collect the pure
compound **98a-b** by using solvent ratio hexane : ethyl acetate(7:3) and conform the compound by $^1$H NMR & $^{13}$C NMR.

**98a: (i.e., R=H)** Yield = 4.63 gm (92%); off white solid, M.R: 155-160°C, IR (KBr): 3441 (very strong N–H, stretching in indole ring); 1148 (very strong, -CH$_2$N-, in benzylimidazole ring); $^1$H-NMR (DMSO d$_6$/TMS) $\delta$ 2.92-2.95 (t, 2H, -CH$_2$, ethyl); 3.60-3.64 (t, 2H, -SCH$_2$); 5.44 (s, 2H, -N-CH$_2$, in benzyl ring); 7.05-7.11 (m, 3H, benzyl ring); 7.26-7.29 (m, 4H, 2H in benzyl ring & 2H in Ar-H ring); 7.42-7.44 (d, 1H, indole ring); 7.58 (d, 1H, indole ring); 7.64-7.67 (m, 2H, phenyl ring); 7.75 (d, 1H, Ar-H ring); 7.89-7.94 (m, 3H, 2H in imidazole ring & 1H in indole ring); 9.30 (s, 1H, indole ring); 11.56 (s, 1H, -NH, in indole ring); MS m/z = 442 (M+1).

**98b: (i.e., R= -CH$_3$)**, Yield = 4.96 gm (95%); Off white solid, M.R: 178-183 °C, IR (KBr): 1294 (very strong N–CH$_3$, in indole ring); 1148 (very strong, -CH$_2$N-, in benzylimidazole ring); $^1$H-NMR (DMSO d$_6$/TMS) $\delta$ 2.92-2.95 (t, 2H, -CH$_2$, ethyl); 3.60-3.64 (t, 2H, -SCH$_2$); 3.78 (s, 3H, N-CH$_3$, in indole ring); 5.44 (s, 2H, -N-CH$_3$, in benzyl ring); 7.05-7.11 (m, 3H, benzyl ring); 7.26-7.29 (m, 4H, 2H in benzyl ring & 2H in Ar-H ring); 7.42-7.44 (d, 1H, indole ring); 7.58 (d, 1H, indole ring); 7.64-7.67 (m, 2H, Ar-H ring); 7.75 (d, 1H, Ar-H ring); 7.89-7.94 (m, 3H, 2H in imidazole ring & 1H in indole ring); 9.30 (s, 1H, indole ring); $^{13}$C-NMR (DMSO d$_6$/TMS) $\delta$ 139.5, 136.4, 135.83, 135.37, 134.25, 131.21, 130.27, 129.89, 129.22, 128.64, 128.62, 128.19, 127.74, 126.88, 123.69, 118.64, 118.44, 110.97, 98.73, 56.47, 50.23, 33.33, 28.72,. MS m/z = 456.1 (M+1).
4.5.2. Preparation of 95a-b from 27a-b;

A mixture of THF (50ml), 27a-b (0.02 moles), 91 (1.2eq.) and TBAB (tetra butyl ammonium bromide) as a catalyst was stirred for 24.hr at 25-30 °C, then monitored the reaction by TLC and cooled to 20-25 °C and charged water (100ml) and stir for 1.0hr at 10-15 °C, filter the mass and wash with water (25ml) and obtained the pure material 95a-b.

95a (i.e., R=H) Yield = 5.31 gm (94%); off white solid M. R: >260 °C , IR (KBr): 3268 (broad, –NH stretching indole ring), 1292 (very strong, -N-CH₂, stretching); ¹H-NMR (DMSO d₆/TMS) δ 4.33-4.38(s, 2H, -N-CH₂, N-benzyl); 7.18-7.20 (d, 2H, S-CH=CH-); 7.32-7.43 (m, 8H, 5H in benzyl ring & 2H in indole ring & 1H –CH=N); 7.63-7.70 (m, 5H, Ar-H ring); 7.91-7.93 (d, 2H, indole ring); 11.71 (s, 1H, -NH, proton in indole ring); MS m/z = 401.2 (M+1).

95b (i.e., R= -CH₃), 5.4 gm (94%), off white solid M.R: >260 °C, IR (KBr): 1535 (very strong –CH₃); 1292 (very strong, -N-CH₂, stretching); ¹H-NMR (DMSO d₆/TMS) δ 3.8 (s, 3H, -N-CH₃ in indole ring); 4.33-4.38 (s, 2H, -N-CH₂ , N-benzyl); 7.18-7.20 (d, 2H, S-CH=CH-); 7.32-7.43 (m, 8H, 5H in benzyl ring & 2H in indole ring & 1H –CH=N); 7.63-7.70 (m, 5H, Ar-H ring ); 7.91-7.93 (d, 2H, indole ring); MS m/z = 4015.2 (M+1).
4.6. Preparation of 100a-b:

4.6.1. Preparation of 99b from 30b;

A mixture of THF (50ml), 30b (0.02 moles), 2,2-dimethoxy ethylamine (1.2eq.) and TBAB as catalyst was stirred for 24 hr at 25-30 °C, then monitored the reaction by TLC and cooled to 20-25 °C and charged water (100ml) and stir for 1.0 hr at 10-15 °C, filter the mass and wash with water (50ml) and obtained the pure material 99b.

99b: (i.e., R= -CH₃) Yield = 2.5 gm (82%) orange color semi solid, M. R: semi solid; IR (KBr): 1641 (strong, -C=N-, stretching); 1290 (strong,-N-CH₃); 1195 (very strong, -C-OCH₃, in dimethoxyethylamine); ¹H-NMR (DMSO d₆/TMS) δ 2.94-2.98 (t, 2H, S-CH₂-CH₂); 3.35 (s, 6H, (OCH₃)₂); 3.63-3.67 (t, 2H, -S-CH₂, ethyl); 3.84 (s, 3H, N-CH₃, in indole ring); 4.25-4.26 (d, 2H, -N-CH₂); 4.54-4.55 (t, 1H, -N-CH₂-CH₂); 7.11-7.13 (d, 1H, indole ring); 7.35 (s, 1H, -CH=N); 7.45-7.47 (d, 1H, indole ring); 7.62-7.66 (t, 2H, Ar-H ring); 7.71-7.80 (m, 2H, Ar-H ring); 7.91-7.93 (s, 1H, indole ring); 9.19 (d, 2H, 1H in Ar-H ring + 1H in indole ring); MS m/z = 315 (M+1).

4.6.2. Preparation of 100b from 99b;

A solution of THF (50ml), methanol (25ml), triethyl amine (2.0eq.), 99b(0.015 moles), and 75 (1.2eq.) was stirred at 25-30 °C for 15.0 min and raise the temperature to 65 °C, then maintained for 6.0 hrs at 65-70 °C, then monitored the reaction by TLC and cool to 25 °C, then quenched the mass into ice cold water below 10 °C, then adjust the pH to 4.5-5.0 with acetic acid and extract with ethyl acetate(2X100ml), evaporate the solvent completely and obtained
residue was run column chromatography and collect the pure compound (102b) by using solvent ratio hexane: ethyl acetate (7:3) and conform the compound by $^1$H NMR & $^{13}$C NMR.

**100b:** (i.e., $R= -\text{CH}_3$) Yield = 2.0 gm (93%), off white solid, M.R: 194-195 °C; IR (KBr): 1294 (strong, -NCH$_3$, stretching, indole ring); 1146 (strong, -C-OCH$_3$, in dimethoxyethylamine); $^1$H-NMR (DMSO d$_6$/TMS) $\delta$ 2.94-2.98 (t, 2H, -CH$_2$, ethyl); 3.35 (s, 6H, (-OCH$_3$)$_2$); 3.63-3.67 (t, 2H, -S-CH$_2$, ethyl); 3.84 (s, 3H, -N-CH$_3$, in indole ring); 4.25-4.26 (d, 2H, -N-CH$_2$); 4.55 (t, 1H, -CH, in ethyl); 7.11-7.13 (d, 1H, in indole ring); 7.35 (s, 1H, Ar-H ring); 7.45-7.47 (d, 1H, indole ring); 7.62-7.66 (t, 2H, Ar-H ring); 7.73-7.74 (m, 2H, 1H in Ar-H ring & 1H in indole ring); 7.80 (s, 1H, imidazole ring); 7.91-7.93 (d, 2H, Ar-H ring); 9.19 (s, 1H, indole ring); $^{13}$C-NMR (DMSO d$_6$/TMS) $\delta$ 139.47, 136.59, 135.93, 134.26, 131.51, 130.39, 129.8, 128.89, 128.19, 127.02, 123.76, 118.58, 117.70, 111.06, 101.64, 98.64, 56.45, 55.10, 48.06, 33.41, 28.76,. MS m/z = 454.1 (M+1).