CHAPTER-3
CHAPTER-3
SYNTHESIS OF SOME 3, 5-SUBSTITUTED INDOLE DERIVATIVES

3.1 INTRODUCTION:

Indole, the basic pharmacodynamic nucleus has been reported to possess a wide variety of biological properties such as antiviral agents which inhibits of Herpes Simplex Virus replication [134-136], fungicidal [137], anti-inflammatory [138], anticonvulsant [139] and antibacterial [140]. Other compound derived from 3-acetylindole used in the treatment of gastrointestinal [141], antiproliferative agent[142,143], potential antiviral agents [144] cardiovascular and central nervous system (CNS) disorders [145] and also used as Herpes Simplex type-1(HIV) integrase inhibitors [146].

Among these, 3-substitutedindoles represent an emerging structural class of alkaloids based upon their high degree of biological activity. The substituent at 3-position of the indole ring is often an additional heterocyclic ring: imidazole nortopsentins [147] and toposentins [148]); oxazole martefragan [149], amazol [150], oxadiazine, alboinon [151] and some of indole alkaloids, meridian [152] A-E (32 & 33) have been isolated from the tinicate aplidium meridianum. These alkaloids, which show cytotoxicity towards murine tumor cell lines, have a brominated and hydroxylated indole nucleus with a pyrimidine ring as substituent at 3-position.
3-Substituted 5-(β-sulfonyl vinyl) indoles are useful intermediates for variety products of impartent pharmacologically active and are fabricated by Heck reaction between phenylvinylsulfone and the corresponding 5-halo indoles [153]. Phenyl vinylsulfone, though being a versatile reagent which is used in a wide spectrum of organic syntheses. 5-Alkyl-3-substituted indoles e.g. naratriptan (34) and eletriptan (35) on the other hand have been reported as 5-HT\textsubscript{1B/1D} receptor agonists for the potential treatment of migraine headache [154].

Keeping this in view, the present chapter deals with the synthesis of new 3, 5-substituted indole derivatives.
3.2 LITERATURE BACKGROUND:

Mariosechi et.al. reported [155] a synthetic approaches for preparation of target indole derivative compounds 37a-f and 39a-f by claisen condensation of substituted 2-acetyl and 3-acetyl indoles with diethyl oxalate and sodiummethoxide in methanol to give substituted 2 and 3- β-diketo esters (Scheme-3.1)

Stefania et.al. reported[156] the synthesis of diketo ester derivatives (41) from N-benzyl derivative of 3-acetyl-7-methoxy indole (40) reaction with diethyloxalate using dry sodium methoxide, THF, two separate steps under the same conditions mw; 2 min, at continuous temperature (50 °C), 250Watt; providing a mixture of tautomers (41) (Scheme-3.2)
Chaudhari et al. reported [157] the cyclocondensation reaction of indole-3-carboxyaldehyde (2), urea or thiourea (42) and ethylacetoacetate (43) in the presence of acid catalyst by refluxing in ethanol to afford indoledihydropyrimidines (44) and the compound evaluated for antimicrobial activity. (Scheme-3.3).

Pilar et al. reported [158] the marine natural products of meridians 3-(2-amino-pyrimidin-4-yl)-1H-indol-4-ol (48) and 3-(2-amino-pyrimidin-4-yl)-7-bromo-1H-indol-4-ol (49) have been synthesized for the first time starting from the appropriate N-tosyl-3-acetyl indole (45). A facile two-step conversion of N-tosyl-3-acetyl indole (45) to the corresponding meridians by treatment with dimethylformamide dimethylacetal (DMF-DMA) and further cyclization of the resulting enamine (46) with guanidine is described. (Scheme-3.4).
Arya et.al. reported [159] the synthesis of anti depressant activity of some 2,3-disubstituted indoles (22), reaction of 3-(chloroacetyl)-2,5-substituted indole (50) and thiourea (51) to obtained containing aminothiazole moiety at the 3-position indole derivative (52) (Scheme-3.5).

...Scheme-3.4

...Scheme-3.5
3.3 PRESENT WORK:

It is obvious from the literature citations that not much work has been carried out on the derivative of 4-[5-bromo-1H-indole-3-yl]-2-hydroxy-4-oxo-but-2-enoic acid ethyl ester. The present chapter deals with the studies on condensation of α, β-unsaturated esters with different aromatic as well as aliphatic nucleophiles such as hydrazinesulfate, phenylhydrazine, 1,2-diaminobenzene, cyanoguanidine, 2-aminophenol, hydroxylamine hydrochloride and acetamidine hydrochloride. The products formed in the proceeding reaction are further subjected to Heck reaction studies with phenylvinylsulfone in the presence of triorthotolylphosphene using palladium acetate as a catalyst in DMF to yield new indole derivatives.

3.4 RESULTS AND DISCUSSIONS:

Condensation of 5-bromo-3-acetyl indole (53a-b) (i.e., 53a, R=H; 53b, R= -CH3) with diethyl oxalate (54) in presence of sodiumethoxide in THF, under reflux conditions, gave α, β-unsaturated ester of 4-[5-bromo-1H-indole-3-yl]-2-hydroxy-4-oxo-but-2-enoic acid ethyl ester (55a-b), (i.e., 55a, R_1=Br, R=H; 55b, R_1=Br, R=-CH3), which has been characterized on the basis of its spectral and analytical data. Thus, its IR (KBr) spectrum showed (figure-3.1) at 3432 (broad, -NH, stretching); 3255 (strong, -OH, stretching); 1716 (strong, -C=O, ester carbonyl stretching); 1592 (strong, γ-carbonyl); cm⁻¹ assignable to –NH- or –OH-, stretching. Its ¹H-NMR spectrum (DMSO d₆/TMS) showed (figure-3.2) signals at δ1.3 (t, 3H, -CH₂-CH₃);
4.20 (q, 2H, -O-CH₂-); 4.2 (q, 2H, J=7.2Hz, -O-CH₃); 7.03 (s, 1H, -CH=); 7.4 (dd, 1H, J=8.4Hz, Ar-H ring); 7.48 (d, 1H, J=8.4Hz, Ar-H ring); 8.36 (s, 1H, J=8.21, Ar-H ring); 8.80 (s, 1H, indole ring); 12.60 (s, 1H, -NH-, D₂O exchangeable NH); 15.50 (s, 1H, D₂O exchangeable –OH). ¹³C-NMR (DMSO d₆/TMS) showed (figure-3.3) signals at δ=188.92 (-C=O, ester carbonyl); 162.55 (-C=O, γ-carbonyl); 62.28 (-OCH₂-, in ester); 34.10 (-N-CH₃, in indole ring); 14.40 (OCH₂CH₃); Its Mass spectrum, when recorded in the CI method, showed in Q+1 mode (figure-3.4), the molecular ion peak at 340, corresponding to a molecular mass of 339. (Scheme- 3.6).

The plausible way of reaction seems to follow the mechanism shown below:
Cyclization of **55a-b** with phenyl hydrazine (**56**) in methanol as a solvent under reflux, followed by simple processing gave 5-[5-bromo-1H-indol-3yl]-2-phenyl-2H-pyrazole-4-carboxylic acid ethyl ester (**57a-b**) i.e., **57a**, $R_1=\text{Br}$, $R=\text{H}$; **57b**, $R_1=\text{Br}$, $R=\text{-CH}_3$), which has been characterized on the basis of spectral and analytical data. Thus, its IR (KBr) spectrum showed (figure-3.5) in the region 3318 (broad band,-NH stretching); 1726 (strong, -C=O, ester carbonyl stretching); cm$^{-1}$ assignable to –NH- stretching vibrations and a very strong, sharp peak assignable to the carbonyl group. Its $^1$H-NMR spectrum (DMSO d$_6$/TMS) showed (figure-3.6) signals at $\delta$ 1.3 (t, 3H, -CH$_2$CH$_3$); 4.30 (q, 2H, -O-CH$_2$-); 7.04 (s, 1H, -CH=C-); 7.12-7.27 (m, 3H, Ar-H ring); 7.33-7.39 (m, 6H, 5H in Ar-H ring & 1proton indole ring); 11.65 (s, 1H, -NH-, D$_2$O exchangeable NH). $^{13}$C-NMR (DMSO d$_6$/TMS) showed (figure-3.7) signals at $\delta$ 162.19(-C=O, ester carbonyl); 60.92 (-OCH$_2$-, in ester); 33.37 (-N-CH$_3$ in indole ring) 14.71 (-OCH$_2$CH$_3$, in ester); Its Mass spectrum, when recorded in the CI method, showed in Q+2 mode (figure-3.8), the molecular ion peak at 412 corresponding to the molecular ion peak at 410 (Scheme- 3.7).
The plausible way of above reaction seems to follow the mechanism shown below:

Cyclization of 55a-b with o-phenylenediamine (58) in methanol as a solvent under reflux, followed by simple processing gave 4-(5-Bromo-1H-indol-3-yl)-1H-benzo[b][1,4]diazepine-2-carboxylic acid (59a-b) i.e., 59a, R₁=Br, R=H; 59b, R₁=Br, R=-CH₃). During the cyclisation indole-3-diketo ester with bidentate nucleophiles, it was observed that the formation of seven membered heterocycles resulted in the spontaneous hydrolysis of the corresponding ester. This has been characterized on the basis of spectral and analytical data. Thus, its IR (KBr) spectrum showed (figure-3.9) at 3414 (strong, acid, -OH, stretching); 3226.30 (broad band, -NH); 3046 (broad, indole, -NH); 1682.0 (strong, -C=O, acid carbonyl); Its ¹H-NMR spectrum (DMSO d₆/TMS) showed (figure-3.10) signals at δ 6.69 (s, 1H, -CH=C-); 7.02-
7.08 (m, 3H, Ar-H protons); 7.30 (d, 1H, Ar-H ring); 11.80 (s, azaepine proton); 12.13 (s, 1H, -NH-, D$_2$O exchangeable NH); 13.29 (s, 1H, acid proton D$_2$O exchangeable). Its Mass spectrum, when recorded in the Q+2 mode, showed (figure-3.11) the molecular ion peak at 384 corresponding to a molecular mass of 382. (Scheme -3.8).

Treatment of 55a-b with o-aminophenol (60) in methanol as a solvent under reflux, followed by simple processing gave 8-(5-Bromo-1H-indol-3-yl)-5-oxa-9-aza-benzocycloheptene-6-carboxylic acid (61a-b) i.e., 61a, R$_1$=Br, R=H; 61b, R$_1$=Br, R=-CH$_3$) Thus, its IR (KBr) spectrum showed at 3334 cm$^{-1}$ assignable to –OH- stretching vibrations and a very strong, sharp peak in the region 1740 cm$^{-1}$ assignable to the carbonyl group. Its $^1$H-NMR spectrum (DMSO d$_6$/TMS) showed signals at $\delta$ 6.75 (s, 1H, -CH=C); 7.01 (t, 1H, Ar-H ring); 7.12-7.17 (m, 2H, one proton in Ar-H ring & one proton in indole ring); 12.19 (s, 1H, -NH- proton D$_2$O exchangeable NH); 12.53 (s, 1H, acid proton D$_2$O exchangeable –COOH) Its Mass spectrum,
when recorded in the Q+2 mode, showed the molecular ion peak at 385 corresponding to a molecular mass of 383 (Scheme -3.9).

\[ \text{OH} \quad \text{NH}_2 \]
\[ \text{MeOH / Reflux} \]

\[ \text{HO} \quad \text{COOC}_2\text{H}_5 \]
\[ \text{N} \quad \text{R} \quad \text{1} \]
\[ \text{O} \quad \text{R} \quad \text{R} \quad \text{2} \]
\[ \text{55a-b} \]

\[ \text{R}_1 \]
\[ \text{R} \]

\[ \text{60} \]

\[ \text{MeOH / Reflux} \]

\[ \text{R}_1 \]
\[ \text{R} \]

\[ \text{61a-b} \]

...Scheme- 3.9

Condensation of 55a-b with hydroxyl amine hydrochloride (62) in methanol as a solvent under reflux, followed by simple processing gave 3-(5-bromo-1H-indol-3-yl)-isoxazole-5-carboxylic acid ethyl ester (63a-b) i.e., 63a, \( R_1=\text{Br}, \ R=\text{H} \); 63b, \( R_1=\text{Br}, \ R=\text{-CH}_3 \). Thus, its IR (KBr) spectrum showed in the region 3234 cm\(^{-1}\) assignable to \(-\text{NH}\)-stretching vibrations and a very strong, sharp peak in the region 1743 cm\(^{-1}\) assignable to the carbonyl group. Its \(^1\text{H-NMR}\) spectrum (DMSO \( \text{d}_6 \)/TMS) showed signals at \( \delta \) 1.3 (t, 3H, \(-\text{CH}_2-\text{CH}_3\)); 4.4 (q, 2H, O-\text{CH}_2-); 7.23 (s, 1H, \text{CH}=-\text{C}-); 12.17 (s, 1H, \text{NH} proton D\text{O} exchangeable \text{NH}). Its Mass spectrum, when recorded in the Q+3 mode, showed the molecular ion peak at 333 corresponding to a molecular mass of 330 (Scheme- 3.10).
Treatment of 55a-b with hydrazine sulphate (64) in methanol under reflux, followed by simple processing gave 3-(5-bromo-1H-indol-3-yl)-pyrazole-3-carboxylic acid ethyl ester (65a-b) i.e., 65a, \( R_1=Br, R=H \); 65b, \( R_1=Br, R=-CH_3 \). Thus, its IR (KBr) spectrum showed at 3377 cm\(^{-1} \) assignable to –NH- stretching vibrations and a very strong, sharp peak in the region 1723 cm\(^{-1} \) assignable to the carbonyl group. Its \(^1\)H-NMR spectrum (DMSO d\(_6\)/TMS) showed signals at \( \delta \) 1.31-1.35 (t, 3H, -CH\(_2\)-C\(_6\)H\(_5\)); 4.35 (q, 2H, O-CH\(_2\)-) 7.1 (s, 1H, CH=C-); 11.63 (s, 1H, NH- proton D\(_2\)O exchangeable NH). Its Mass spectrum, when recorded in the Q+1 mode, showed the molecular ion peak at 334 corresponding to the molecular ion peak at 333 (Scheme- 3.11).
Reaction of 55a-b with acetamidinehydrochloride (66) in methanol under reflux, followed simple processing gave 4-[5-bromo-1H-indol-3-yl]-2-methyl-pyrimidine-5-carboxylic acid ethyl ester (67a-b) (i.e., 67a, R₁=Br, R=H; 67b, R₁=Br, R=-CH₃). Thus, its IR (KBr) spectrum showed in the region 3380 cm⁻¹ assignable to –NH- stretching vibrations and a very strong, sharp peak in the region 1680 cm⁻¹ assignable to the carbonyl group. Its ¹H-NMR spectrum (DMSO d₆/TMS) showed signals at δ 1.18-1.29 (t, 3H, -CH₂CH₃); 2.1-2.2 (s, 3H, -C-CH₃, pyrimidine ring); 4.23-4.28 (q, 2H, -O-CH₂); 6.98 (s,1H, -CH= proton in pyrimidine ring); 7.35-7.38 (d, 1H, indole ring); 7.43-7.45 (d, 1H, indole ring); 8.31 (s, 1H, Ar-H ring); 8.7 (s, 1H, indole ring); 12.5 (s, 1H, -NH, proton, indole ring); when recorded in the Q+2 showed the molecular ion peak at 362 corresponding to a molecular mass of 360 (Scheme- 3.12).

Cyclization of 55a-b with cyanoguanidine (68) in methanol under reflux, followed by simple processing gave 4-(5-bromo-1H-indol-3-yl)-2-cyanoamino-pyrimidine-5-carboxylic acid ethyl ester (69a-b) i.e., 69a, R₁=Br, R=H; 69b, R₁=Br, R=-CH₃. Thus, its IR (KBr) spectrum showed a very broad band of medium to strong
intensity in the region 3383 cm$^{-1}$ assignable to $-\text{NH}$- stretching vibrations and a very strong, sharp peak in the region 1638 cm$^{-1}$ assignable to the carbonyl group. Its $^1$H-NMR spectrum (DMSO d$_6$/TMS) showed (figure-3.13) signals at 1.18-1.29 (t, 3H, $-\text{CH}_2\text{CH}_3$); 4.23-4.28 (q, 2H, $-\text{O-CH}_2$); 6.98 (s, 1H, $-\text{CH}=\text{proton in pyrimidine ring}$); 7.35-7.38 (d, 1H, indole ring); 7.43-7.45 (d, 1H, indole ring); 8.31 (s, 1H, Ar-$\text{H}$ ring); 8.75 (s, 1H, indole ring); 12.55 (s, 1H, $-\text{NH}$, proton, indole ring); 15.2 (s,1H. $-\text{NH}-\text{CN}$); $^{13}$C-NMR (DMSO d$_6$/TMS) showed (figure-3.14) $\delta$ 189.7, 163.27, 162.64, 162.26, 137.44, 136.32, 127.38, 126.61, 124.16, 118.89, 115.73, 115.16, 114.75, 101.05, 62.30, 14.40. Its mass spectrum, when recorded in the Q+6 mode showed (figure-3.15) the molecular ion peak at 392 corresponding to the molecular mass of 386. (Scheme -3.13).
SUMMARY OF THE REACTIONS (Scheme-3.14):

\[
\begin{align*}
(53a-b) & \quad \text{Na / EtOH / THF} \quad (\text{COOEt})_2 \quad (54) \\
(55a-b) & \quad \text{MeOH/Reflux} \\
R=\text{Br}, \text{R}_1=\text{H, CH}_3
\end{align*}
\]
3.5. All the above synthesized compounds coupled with phenylvinylsulfone by heck reaction method.

Reaction of 57a-b with 25 in the presence of palladium acetate as a catalyst in DMF, heating at 100-105 °C., gave 5-[5-(2-benzenesulfonyl-vinyl)-1H-indol-3-yl]-2-phenyl-2H-pyrazole-4-carboxylic acid ethyl ester (70a-b) (i.e., 70a, R=H; 70b, R=-CH3) which has been characterized on the basis of spectral and analytical data. Thus, its IR (KBr) spectrum showed (figure-3.16) a very broad band of medium to strong intensity in the region 3312 cm\(^{-1}\) assignable to \(-\text{NH}\)- stretching vibrations and a very strong, sharp peak in the region 1721 cm\(^{-1}\) assignable to the carbonyl group. Its \(^1\)H-NMR spectrum (DMSO d\(_6\)/TMS) showed (figure-3.17) signals at δ 1.32-1.35 (t, 3H, -CH\(_2\)CH\(_3\)); 4.32-4.38 (q, 2H, -O-CH\(_2\)); 7.18-7.20 (m, 2H, -CH=CH, proton in vinyl); 7.33-7.51 (m, 8H, five protons in N-phenyl ring & proton in \(-\text{CH}=\text{H}\), in pyrazole ring & two protons in indole ring); 7.63-7.7.7 (m, 5H, phenyl sulfonyl ring); 7.91-7.93 (d, 2H, indole ring); 11.7 (s, 1H, -NH, indole ring); \(^{13}\)C-NMR (DMSO d\(_6\)/TMS) showed (figure-3.18) signals at δ 162.30 (-C=O, ester carbonyl); 109.5 (-SCH-); 105.1 (-SCH=CH-); 60.87 (-OCH\(_2\)-, in ester); 14.74 (-OCH\(_2\)CH\(_3\)). Its mass spectrum, when recorded in the Q+1 showed (figure-3.19) the molecular ion peak at 498, corresponding to a molecular mass of 497 (scheme- 3.15).
Treatment of 59a-b with 25 in the presence of palladium acetate as a catalyst in DMF as a solvent heating at 100-105 °C., gave 4-[5-(2-benzenesulfonyl-vinyl)-1H-indol-3-yl]-1H-benzo[b][1,4]diazepine-2-carboxylic acid (71a-b) (i.e., 71a, R=H; 71b, R=-CH₃) which has been characterized on the basis of spectral and analytical data. Thus, its IR (KBr) spectrum at 3436 cm⁻¹ assignable to –NH- stretching vibrations and a very strong, sharp peak in the region 1672 cm⁻¹ assignable to the carbonyl group. Its ¹H-NMR spectrum (DMSO d₆/TMS) showed signals at δ 4.37-4.41 (t, 2H, -SCH₂); 6.56 (s, 1H, -C=, benzoezapine ring); 7.05-7.06 (d, 2H, benzoezapine ring); 7.35-7.37 (t, 1H, bezoezapine ring); 7.39 (m, 2H, 1 proton in Ar-H &1 proton bezoezapine ring); 7.48-7.50 (d, 1H, Ar-H ring); 7.61-7.65 (t, 2H, phenyl ring); 7.72 (t, 1H, Ar-H ring); 7.90-7.92 (d, 2H, indole ring); 8.4 (s, 1H, indole ring); 8.48 (s, 1H, indole ring); 13.19 (s, 1H, acid proton); when recorded in the CI method, showed in Q mode, the molecular ion peak at 471, corresponding to a molecular mass of 471(scheme- 3.16).
Reaction of 61a-b with 25 in the presence of palladium acetate as a catalyst in DMF as a solvent heating at 100-105 °C., gave 8-[5-(2-benzenesulfonyl-vinyl)-H-indol-3yl]-5-oxa-9-aza-benzocycloheptane-6-carboxylic acid (72a-b) (i.e., 72a, R=H; 72b, R=-CH₃) which has been characterized on the basis of spectral and analytical data. Thus, its IR (KBr) spectrum showed in the region 3434 cm⁻¹ assignable to –COOH stretching vibrations and a very strong, sharp peak in the region 1753 cm⁻¹ assignable to the carbonyl group. Its ¹H-NMR spectrum (DMSO d₆/TMS) showed signals at δ6.75 (s, 1H, -C=H, benzoxapine ring); 7.05-7.09 (td, 1H, benzoxapine ring); 7.18-7.23 (m, 2H, benzoxapine ring); 7.4-7.52 (d,2H, CH=CH, proton in vinyl); 7.62-7.76 (m, 6H, 5proton in Ar-H ring & proton benzoxapine ring); 7.97-7.99 (d, 2H, indole ring); 8.6-8.63 (d, 2H, indole ring); 12.59 (s,1H, acid proton); when recorded in the CI method, showed in Q mode, the molecular ion peak at 450, corresponding to a molecular mass of 450 (scheme -3.17).
Treatment of 63a-b, with 25 in the presence of palladium acetate as a catalyst in DMF, heating at 100-105°C, gave 3-[5-(2-benzenesulfonyl-vinyl)-1H-indol-3-yl]-isoxazole-5-carboxylic acid ethyl ester (73a-b) (i.e., 73a, R=H; 73b, R=-CH3) which has been characterized on the basis of spectral and analytical data. Thus, its IR (KBr) spectrum showed (figure-3.20) at 3325 cm⁻¹ assignable to –NH-stretching vibrations and a very strong, sharp peak in the region 1733 cm⁻¹ assignable to the carbonyl group. Its ¹H-NMR spectrum (DMSO d₆/TMS) showed (figure-3.21) signals at δ1.31-1.34(t, 3H, -CH₂C₃H₃); 4.35-4.40 (q, 2H, OCH₂); 7.35 (s, 1H, -CH=, oxazole ring); 7.49-7.51(d, 1H, -CH=C=H, proton in vinyl); 7.56-7.68 (m, 5H, Ar-H ring); 7.83-7.86 -SCH=, proton in vinyl); 7.90-7.92 (d, 2H, indole ring); 8.20 (s, 1H, indole ring); 8.38(s, 1H, indole ring); 12.17(s, 1H, -NH, indole ring); ¹³C-NMR (DMSO d₆/TMS) showed (figure-3.22) δ 168.28, 160.27, 157.01, 144.19, 141.87, 138.33, 133.80, 130.04, 128.74, 127.43, 126.22, 125.84, 124.14, 123.28, 122.78, 113.52, 104.15, 98.41, 62.23, 14.50., when recorded in the CI method,
showed (figure-3.23) the molecular ion peak at 423(M+1) corresponding to a molecular mass of 422 (scheme- 3.18).

...Scheme- 3.18

The over all sequence of the reactions given in Scheme-3.19.
TOTAL SUMMARY OF THE SCHEMES (Scheme-3.19)

\[ R = \text{Br, } R_1 = \text{H, CH}_3 \]

\[ \text{Palladium acetate /DMF} \]

\[ \text{Tri-orthotolyl phosphene} \]

\[ 100-105 \, ^\circ \text{C} \]
3.6. EXPERIMENTAL SECTION

GENERAL: The reagents which are used in the synthesis i.e. phenyl hydrazine, 2-aminoaniline, 2-aminophenol, hydrazinesulfate, cyanoguanidine, hydroxylamine hydrochloride, and acetamidine hydrochloride etc. were purchased from commercial suppliers and used as it is.

Preparation of 53a from 5-Bromo indole:

A mixture of THF (125.0ml) and 5-bromoindole (0.127 moles) was stirred at 25-30 °C for 15.0min. then cool to 0 °C and add drop wise of 20% ethyl magnesium bromide solution in THF (200.0ml, 0.299 moles as 100%) at 0-10 °C for 0.5-1.0hr, then stir for 1.0hr at 0-10 °C and add the acetyl chloride (0.191moles) at 0-10 °C in 1.0hr, then slowly raise the temperature to 60 °C and maintain for 10-12hr at 60-65 °C, cool to RT, then quenched the mass into chilled 10% hydrochloric acid solution (125.0ml) and extracted with ethyl acetate (2X150.0ml) and residue was collected by solvent distillation and chromatographic on silica gel column using ethyl acetate/hexane (3:7) as eluent to give pure compound 3-actyl-5-bromo indole (53a).

(53a): off white solid; M.R: 159-169 °C. IR (KBr): 3124.23 (strong, –NH, stretching); and 1728 (strong, -C=O); ¹H-NMR (DMSO d₆/TMS) δ 2.43 (s, 3H, -CH₃); 7.32 (dd, 1H, Ar-H ring); 7.4 (d, 1H, Ar-H ring); 8.29 (s, 1H, Ar-H ring); 8.36 (s, 1H, indole ring); 12.1 (s, 1H, -NH, proton); MS m/z = 240 (M+2).
Preparation of 53b from 53a

To a well stirred solution of 53a (0.084 moles) in DMF (100ml), add lot wise of sodium hydride 50 % (0.084 moles) at 0-5 °C in .5-1.0hr and charge methyl iodide (1.2moles). Then maintained for 0.5hr at 0-10 °C, then add methanol (100ml) and stir for 15.0min., at the same temperature, then distilled the solvent completely under vacuum and charge the DM water (100ml), then stir for 0.5hr at RT, filter the mass and wash with water, dry the material and crystallized in hot methanol and get the of pure compound N-methyl-3-acetyl indole (53b).

(53b): off white solid; M.R: 161-163 °C. IR (KBr): 1633 (strong, -C=O); 1530.67(strong, -N-CH₃); 1H-NMR (DMSO d₆/TMS) δ 2.43 (s, 3H, -CH₃); 3.84 (s, 3H, -N-CH₃); 7.41 (d, 1H, Ar-H ring), 7.53(d, 1H, Ar-H ring); 8.29 (s, 1H, Ar-H ring); 8.37 (s, 1H, indole ring); MS m/z = 254(M+2).

Preparation of 55a-b from 53a-b:

In ethanol (100.0ml) was dissolved of sodium metal (0.136 moles) under heating. The ethanol was evaporated under reduced pressure and the residue was suspended in THF (200.0ml) and also the THF was evaporated under pressure. To the suspension was added at room temperature of 53a-b (0.05 moles) and addition diethyl oxalate (54) (0.05 moles), then maintained for 3 hr at RT and raise the temperature to 60 °C, then maintained for 17.0hr at 60-65 °C, the reaction monitored by TLC, then cool the mass to RT and quenched the mass in to chilled 10% hydrochloric acid (120.0ml) and stir for
30.0min at RT and extract with ethyl acetate (2X150.0ml), distilled the solvent completely and residue was crystallized in hot acetone to give pure compound 55a-b.

55a: (R=Br, R₁=H) Yellow color solid; M.R: >260 °C. IR (KBr) : 3432 (brad, -NH); 3256 (strong, -OH); 1717 (strong, -C=O, ester carbonyl); 1592 (strong, γ-carbonyl); 1H-NMR (DMSO d₆/TMS) δ 1.3 (t, 3H, J=7.2Hz, -CH₃); 4.2 (q, 2H, J=7.2Hz, -O-CH₂); 7.03 (s, 1H, -CH=); 7.4 (dd, 1H, J=8.4Hz, Ar-H ring); 7.48 (d, 1H, J=8.4Hz, Ar-H ring); 8.36 (s, 1H, J=8.21, Ar-H ring); 8.80 (s, 1H, indole ring); 12.6 (s, 1H, -NH, indole ring); 15.5 (s, 1H, =C-OH); 13C-NMR (DMSO d₆/TMS) δ 189.72, 162.64, 162.25, 137.48, 136.33, 127.40, 126.61, 124.16, 115.73, 115.17, 114.75, 101.07, 62.30, 14.41.; MS m/z=340(M+1).

55b : (R=Br, R₁=CH₃) Yellow color solid; M.R: 152-154 °C. IR (KBr): 3113 (strong, -OH); 1732 (strong, -C=O, ester carbonyl); 1608 (strong, γ-carbonyl); 1H-NMR (DMSO d₆/TMS) δ 1.33 (t, 3H, J=7.2Hz, -CH₃); 3.9 (s, 3H, -NCH₃); 4.2-4.40 (q, 2H, -OCH₂); 6.92 (s, 1H, -CH=), 7.49 (dd, 1H, J=8.4Hz, Ar-H ring); 7.61 (d, 1H, J=8.4Hz, Ar-H ring); 8.35 (s, 1H, J=8.21, Ar-H ring); 8.80 (s, 1H, indole ring); 15.5 (s, 1H, =C-OH); 13C-NMR (DMSO d₆/TMS) δ 188.92, 162.55, 162.02, 140.54, 136.98, 127.61, 126.47, 124.17, 116.21, 113.71, 113.45, 100.90, 62.28, 34.10, 14.40.; MS m/z = 354(M+1).

Preparation of 57a-b from 55a-b:

A Mixture of 55a-b (0.006 moles), 56 (0.007 moles) and catalytic amount of acetic acid in methanol was stirred at reflux for 16.0hr then monitored the reaction by TLC, cool to 10°C and stir for 30.0min,
then filter the solid and wash with diethyl ether and dried obtain the pure compound 57a-b.

57a: (R=Br, R₁=H), off white solid; M.R: >260 °C. IR (KBr): 3318 (broad, -NH); 1726 (strong, -C=O, ester carbonyl); 1446, 1229; 1H-NMR (DMSO d₆/TMS) δ 1.3 (t, 3H, -CH₃); 4.3 (q, 2H, -O-CH₂); 7.04 (s, 1H, -CH=); 7.12-7.27 (m, 3H, Ar-H ring); 7.33-7.39 (m, 6H, 5H in Ar-H ring & 1 proton indole ring); 11.65 (s, 1H, -NH proton); ¹³C-NMR (DMSO d₆/TMS) δ 162.23, 144.05, 140.09, 139.23, 135.05, 129.65, 129.07, 127.87, 127.35, 125.87, 124.93, 121.43, 114.46, 113.04, 109.39, 103.67, 60.91, 14.73., MS m/z = 412 (M+1).

57b: (R=Br, R₁=CH₃), off white solid; M.R: 170-171 °C. IR (KBr): 1727 (strong, -C=O, ester carbonyl); 1500 (very strong, -N-CH₃ stretching); 1H-NMR (DMSO d₆/TMS) δ 1.3 (t, 3H, -CH₃); 3.7 (s, 3H, -N-CH₃); 4.27-4.33 (q, 2H, -OCH₂); 7.01 (s, 1H, N=CH, pyrazole ring); 7.19-7.24 (m, 3H, Ar-H ring); 7.31-7.40 (m, 6H, five H in Ar-H ring & proton indole ring); ¹³C-NMR (DMSO d₆/TMS) δ 162.19, 144.10, 140.04, 138.85, 135.63, 131.61, 129.65, 129.02, 127.48, 125.67, 124.91, 121.67, 113.34, 112.93, 109.62, 102.82, 60.92, 33.37, 14.71., MS m/z=424(M+1).

Preparation of 59a-b from 55a-b:

Condensation of 55a-b (0.05 moles), with 58 (0.06moles) by using catalytic amount of acetic acid in methanol was stirred at reflux for 16.0hr. Then monitored the reaction by TLC Cool to 10 °C and stir for 30.0min, then filter the solid and wash with diethyl ether and dried obtain the pure compound 59a-b.
59a: (R=Br, R₁=H), off white solid; M.R: > 260 °C. IR (KBr): 3414 (strong, acid, -OH); 3226 (broad, -NH); 3046 (broad, indole –NH); 1682 (strong, -C=O, acid carbonyl); 1H-NMR MSO d₆/TMS) δ 6.69 (s, 1H, -CH₃); 7.02-7.08 (m, 3H, one proton in Ar-H ring & two proton in indole); 7.3 (d, 1H, Ar-H ring); 7.40-7.44 (t, 2H, Ar-H ring); 8.4 (s, 1H, indole ring); 8.5 (s, 1H, indole ring); 11.8(s, 1H, -NH, ezapine proton); 12.13 (s, 1H, -NH, indole ring); 13.29 (s, 1H, acid proton); MS m/z=384 (M+2).

59b: (R=Br, R₁=CH₃), Yellow color solid; M.R: 260 °C. IR (KBr): 3435 (strong, acid, -OH); 3046 (broad, -NH); 1681 (strong, -C=O, acid carbonyl); 1H-NMR MSO d₆/TMS) δ 3.88-3.90 (s, 3H, -N-CH₃); 6.64 (s, 1H, -CH₃); 7.02-7.11 (m, 3H, Ar-H ring ); 7.40-7.42 (d, 2H, 1proton indole ring & Ar-H ring); 7.53-7.55 (d, 1H, indole ring); 8.5-8.54 (s, 2H, indole ring); 11.9 (s, 1H, COOH, acid proton); 13.2 (s, 1H, -NH proton); MS m/z = 398 (M+1).

Preparation of 61a-b from 55a-b:

Treatment of 55a-b (0.05 moles), with 60 (0.06 moles) by using catalytic amount of acetic acid in methanol was stirred at reflux for 16.0hr then monitored the reaction by TLC, cool to 10 °C and stir for 30.0min, then filter the solid and wash with diethyl ether and dried obtain the pure compound 61a-b.

61a: (R=Br, R₁=H), yellowish orange solid; M.R: > 260 °C. IR (KBr): 3334 (strong, -OH); 3226 (broad, -NH); 1740 (strong, -C=O, acid carbonyl); 1H-NMR MSO d₆/TMS) δ 6.75 (s, 1H, -CH₃); 7.01 (t, 1H, Ar-H); 7.12-7.17 (m, 2H, one proton in Ar-H + one proton indole ring);
7.32 (d, 1H, indole ring); 7.39 (d, 1H, Ar-H ring); 7.46 (d, 1H, Ar-H ring); 8.49 (s, 1H, indole ring); 8.53 (s, 1H, indole ring); 12.19 (s, 1H, -NH, proton); 12.53 (s, 1H, acid proton); MS m/z = 385 (M+2).

61b: (R=Br, R₁=CH₃), yellowish orange solid; M.R: > 260 °C. IR (KBr): 3120 (strong, -OH); 1753 (strong, -C=O, acid carbonyl); 1524 (very strong, -N-CH₃, stretching); 1H-NMR DMSO d₆/TMS δ 3.83 (s, 3H, -N-CH₃); 6.67 (s, 1H, -CH=); 6.99-7.03 (t, 1H, Ar-H ring); 7.12-7.17 (m, 2H, Ar-H ring); 7.37-7.39 (dd, 1H, Ar-H ring); 7.44-7.46 (d, 1H, indole ring); 7.48-7.51 (d, 1H, indole ring); 8.48-8.56 (s, 2H, indole ring); 12.46 (s, 1H, acid proton); MS m/z = 399 (M+1).

Preparation of 63a-b from 55a-b:

Reaction of 55a-b (0.05 moles), with 62 (0.06 moles) and catalytic amount of acetic acid in methanol was stirred at reflux for 16.0hr then monitored the reaction by TLC and cool to 10 °C and stir for 30.0min, then filter the solid and wash with diethyl ether and dried obtain the pure compound 63a-b.

63a: (R=Br, R₁=H), off white solid; M.R: 206-209 °C. IR (KBr): 3234 (brad, -NH); 1743 (strong, -C=O, ester carbonyl); 1H-NMR DMSO d₆/TMS δ 1.3 (t, 3H, -CH₃); 4.4 (q, 2H, -O-CH₂); 7.23 (s, 1H, -CH=); 7.39 (d, 1H, Ar-H ring); 7.51 (d, 1H, indole ring); 8.1 (s, 1H, Ar-H ring); 8.2 (s, 1H, indole ring); 12.17 (s, 1H, -NH, proton); MS m/z=333(M-2).

63b: (R=Br, R₁=CH₃), off white solid; M.R: 154-156 °C. IR (KBr): 1724 (strong, -C=O, ester carbonyl); 1531 (strong, -NCH₃); 1H-NMR DMSO d₆/TMS δ 1.34-1.37 (t, 3H, -CH₃); 3.88 (s, 3H, -N-CH₃); 4.37-4.43 (q,
2H, -O-CH\(_2\)); 7.21 (s, 1H, -CH=); 7.43-7.45 (d, 1H, **indole** ring); 7.57-7.59 (d, 1H, **indole** ring); 8.16 (s, 1H, **indole** ring); 8.22-8.24 (s, 1H, **indole** ring); MS m/z = 351(M+2).

**Preparation of 65a-b from 55a-b:**

Reaction of **55a-b** (0.05 moles), with **64**(0.06 moles) and catalytic amount of acetic acid in methanol was stirred at reflux for 16.0hr. Then monitored the reaction by TLC and cool to 10 °C and stir for 30.0min, then filter the solid and wash with diethyl ether and dried to obtain the pure compound **65a-b**.

**65a:** (R=Br, R\(_1=\)H), off white solid; M.R: 160-170 °C. IR (KBr): 3377 (brad, -NH, indole ring); 3237 (broad, -NH, stretching in **pyrazole** ring); 1722 (strong, -C=O, **ester** carbonyl); 1H-NMR (DMSO d\(_6\)/TMS) δ 1.32-1.35 (t, 3H, -CH\(_2\)CH\(_3\)); 4.32-4.35 (q, 2H, -O-CH\(_2\)); 5.8 (s,1H, -NH proton in **pyrazole** ring); 7.10 (s, 1H, -CH=); 7.27-7.29 (d, 1H, **indole** ring); 7.41-7.43 (d, 1H, **indole** ring); 7.92-7.93 (s, 1H, **Ar-H** ring); 8.15 (s, 1H, **indole** ring); 11.63 (s, 1H, -NH, proton); MS m/z = 336(M+2).

**65b:** (R=Br, R\(_1=\)CH\(_3\)), off white solid; M.R: 236-237 °C. IR (KBr): 3225 (broad,-NH, stretching in **pyrazole** ring); 1724 (strong, -C=O, **ester** carbonyl); 1524 (very strong,-N-CH\(_3\)); 1H-NMR (DMSO d\(_6\)/TMS) δ 1.27-1.31 (t, 3H, -CH\(_2\)CH\(_3\)); 3.79-3.85 (s, 3H, -N-CH\(_3\)); 4.26-4.31 (q, 2H, OCH\(_2\)); 7.03 (s, 1H, -CH=); 7.30-7.32 (d, 1H, **indole** ring); 7.45-7.47 (d, 1H, **indole** ring); 7.85 (s, 1H, **Ar-H** ring); 8.24 (s, 1H, **indole** ring); 13.77 (s, 1H, -NH, proton **pyrazole** ring); MS m/z=350(M+2).
Preparation of 67a-b from 55a-b:

A Mixture of 55a-b (0.05 moles), 67 (0.08 moles) and catalytic amount of acetic acid in methanol was stirred at reflux for 16.0hr then monitored the reaction by TLC and cool to 10 °C and stir for 30.0min, then filter the solid and wash with diethyl ether and dried obtain the pure compound 67a-b

67a: (R=Br, R₁=H), off white solid; M.R: > 260 °C (decompose). IR (KBr): 3383 (broad, -NH); 1638 (strong, C=O, ester carbonyl); 1H-NMR (DMSO d₆/TMS) δ 1.18-1.29 (t, 3H, -CH₂CH₃); 2.1-2.2 (s, 3H,-C-CH₃, pyrimidine ring), 4.23-4.28 (q, 2H, -O-CH₂); 6.98 (s,1H, -CH= proton in pyrimidine ring); 7.35-7.38 (d, 1H, indole ring); 7.43-7.45 (d, 1H, indole ring); 8.31 (s, 1H, Ar-H ring); 8.7 (s, 1H, indole ring); 12.5 (s, 1H, -NH, proton, indole ring); MS m/z = 360 (M).

67b: (R=Br, R₁=CH₃), off white solid; MR: 260 °C (decompose). IR (KBr): 1638 (strong, C=O, ester carbonyl); and 1525; 1H-NMR (DMSO d₆/TMS) δ 1.18-1.29 (t, 3H, -CH₂CH₃); 2.1-2.2 (s, 3H,-C-CH₃, pyrimidine ring), 3.8 (s, 3H, -N-CH₃, indole ring); 4.23-4.28 (q, 2H, -O-CH₂); 6.98 (s, 1H, -CH= proton in pyrimidine ring); 7.35-7.38 (d, 1H, indole ring); 7.43-7.45 (d, 1H, indole ring); 8.31 (s, 1H, Ar-H ring); 8.7 (s, 1H, indole ring); MS m/z = 374 (M).

Preparation of 69a-b from 55a-b:

Condensation of 55a-b (0.05 moles) with 68 (0.08moles) by using catalytic amount of acetic acid in methanol was stirred at reflux for 16.0hr then monitored the reaction by TLC and cool to 10 °C and stir
for 30.0 min, then filter the solid and wash with diethyl ether and dried obtain the pure compound 69a-b.

69a: (R=Br, R₁=H), off white solid; M.R: 199-200 °C (decompose). IR (KBr): 3333 (broad, -NH, indole ring); 3383 (broad, -NH, stretching in -NH-CN); 2207 (strong, -CN); 1638 (strong, C=O, ester carbonyl); 1H-NMR (DMSO d₆/TMS) δ 1.18-1.29 (t, 3H, -CH₂CH₃); 4.23-4.28 (q, 2H, -O-CH₂); 6.98 (s, 1H, -CH=N proton in pyrimidine ring); 7.35-7.38 (d, 1H, indole ring); 7.43-7.45 (d, 1H, indole ring); 8.31 (s, 1H, Ar-H ring); 8.7 (s, 1H, indole ring); 15.2 (s, 1H, -NH-CN); 13C-NMR (DMSO d₆/TMS) showed δ 189.7, 163.27, 162.64, 162.26, 137.44, 136.32, 127.38, 126.61, 124.16, 118.89, 115.73, 115.16, 114.75, 101.05, 62.30, 14.40. MS m/z = 392(M+6).

69b: (R=Br, R₁=CH₃), off white solid; M.R: >260 °C. IR (KBr): 3383.5 (broad, -NH, stretching in -NH-CN); 2207 (strong, -CN); 1638 (strong, C=O, ester carbonyl); 1525; 1H-NMR (DMSO d₆/TMS) δ 1.18-1.29 (t, 3H, -CH₂CH₃); 3.8 (s, 3H, -NH₃); 4.23-4.28 (q, 2H, -O-CH₂); 6.98 (s, 1H, -CH=N proton in pyrimidine ring); 7.35-7.38 (d, 1H, indole ring); 7.43-7.45 (d, 1H, indole ring); 8.31 (s, 1H, benzene ring); 8.7 (s, 1H, indole ring); 15.2 (s, 1H, -NH-CN); MS m/z = 405(M+5).

Preparation of 70a-b from 57a-b

A solution of DMF (10 vol.) and tri-orthotolylphosphene (0.06 moles) was stirred at 20-25 °C and slowly add a mixture of 57a-b (0.05 mole) 25 (0.06 moles) and triethylamine (0.2 moles) at 20-25 °C. Stirr the reaction mixture for 15.0 min 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 70a-b by using solvent ratio hexane: ethyl acetate (7:3).

70a: (R=H), pale yellow solid; M.R: 168-169 °C. IR (KBr): 3312 (broad, -NH, indole ring); 1721 (strong, C=O, ester carbonyl); 1H-NMR (DMSO d₆/TMS) δ 1.32-1.35 (t, 3H, -CH₂CH₃); 4.32-4.38 (q, 2H, -O−CH₂); 7.18-7.20 (m, 2H, -CH=CH, proton in vinyl); 7.33-7.51 (m, 8H, 5proton in N-phenyl ring & 1proton in –CH= pyrazole & two protons indole ring); 7.63-7.7.7 (m, 5H, phenyl sulfonyl ring); 7.91-7.93 (d, 2H, indole ring); 11.7 (s, 1H, -NH. indole ring); ¹³C-NMR (DMSO d₆/TMS) signals δ 162.30, 144.20, 144.08, 141.93, 140.22, 139.20, 137.80, 133.75, 130.0, 129.54, 129.01, 127.63, 127.40, 126.12, 125.96, 125.17, 125.03, 122.82, 122.17, 113.03, 109.52, 105.10, 60.87, 14.74., MS m/z = 498 (M+1).

70b: (R= -CH₃), pale yellow solid; M.R: >260°C. IR (KBr): 1721 (strong, C=O, ester carbonyl); 1524; 1H-NMR (DMSO d₆/TMS) δ 1.32-1.35 (t, 3H, -CH₂CH₃); 3.8 (s, 3H, -NH₃); 4.32-4.38 (q, 2H, -O−CH₂); 7.18-7.20 (m, 2H, -CH=CH, proton in vinyl); 7.33-7.51 (m, 8H, five proton in N-phenyl ring & 1proton in –CH= pyrazole & 2 proton indole ring); 7.63-7.7.7 (m, 5H, phenylsulfonyl ring); 7.91-7.93 (d, 2H, indole ring); MS m/z = 512 (M+1).
Preparation of 71a-b from 59a-b:

A mixture of DMF (10 vol.) and tri-orthotolylphosphine (0.06) was stirred at 20-25 °C and slowly add a mixture of 59a-b (0.05mole) 25 (0.06moles) and triethylamine (0.2 moles) at 20-25 °C. Stir 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 71a-b by using solvent ratio hexane: ethyl acetate(7:3)

71a: (R=H), pale yellow solid; M.R: > 260°C. IR (KBr): 3436 (broad, –NH, stretching benzeazpine ring); 3107 (broad -COOH, stretching); 1672 (strong, -C=O, acid carbonyl); 1H-NMR (DMSO d6/TMS) δ 3.69-3.73 (t, 2H, CH2, ethyl); 4.37-4.41 (t,2H, -SCH2); 6.56 (s,1H,-CH=, benzoazapine ring); 7.05-7.06 (d, 2H, benzoazapine ring); 7.35-7.37 (t, 1H, bezoezapine ring); 7.39 (m, 2H, 1 proton in Ar-H + 1proton bezoezapine ring); 7.48-7.50 (d, 1H, Ar-H ring); 7.61-7.65 (t, 2H, Ar-H ring); 7.72 (t, 1H, Ar-H ring); 7.90-7.92 (d, 2H, indole ring); 8.4 (s,1H, indole ring); 8.48 (s, 1H, indole ring); 13.19 (s,1H, acid proton); MS m/z = 471(M).

71b: (R= -CH3), Pale yellow solid; M.R: 260°C. IR (KBr): 3436 (broad, –NH, stretching, benzeazapine ring); 3107 (broad -COOH, stretching); 1672 (strong, -C=O, acid carbonyl); 1521 (strong , -N-CH3); 1H-NMR (DMSO d6/TMS) δ 3.69-3.73 (t, 2H, CH2, ethyl); 3.83 (s, 3H, -N-CH3); 4.37-4.41 (t, 2H, -SCH2); 6.56 (s, 1H, -CH=, benzoazapine ring); 7.05-7.06 (d, 2H, benzoazapine ring); 7.35-7.37 (t, 1H, bezoezapine ring);
7.39 (m, 2H, 1 proton in Ar-H + 1proton bezoozapine ring); 7.48-7.50 (d, 1H, Ar-H ring); 7.61-7.65 (t, 2H, Ar-H ring); 7.72 (t, 1H, Ar-H ring); 7.90-7.92 (d, 2H, indole ring); 8.4 (s, 1H, indole ring); 8.48 (s, 1H, indole ring); 13.19 (s, 1H, Acid proton); MS m/z = 485 (M).

**Preparation of 72a-b from 61a-b:**

A solution of DMF (10 vol.) and tri-orthotolylphosphine (0.06) was stirred at 20-25°C and slowly add a mixture of 61a-b (0.05mole) 25 (0.06moles) and triethylamine (0.2 moles) 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 72a-b by using solvent ratio hexane: ethyl acetate (7:3)

**72a: (R=H),** pale yellow solid; M.R: >260°C. IR (KBr): 3434 (broad, -COOH, stretching); 1753 (strong, C=O, acid carbonyl); 1H-NMR (DMSO d_6/TMS) δ 6.75 (s, 1H, -CH=, bezoozapine ring); 7.05-7.09 (td, 1H, bezoozapine ring); 7.18-7.23 (m, 2H, bezoozapine ring); 7.4-7.52 (d, 2H, CH=CH, proton in vinyl); 7.62-7.76 (m, 6H, 5proton in Ar-H ring + 1proton bezoozapine ring); 7.97-7.99 (d, 2H, indole ring); 8.6-8.63 (d, 2H, indole ring); 12.1 (s, 1H, -NH, indole ring); 12.59 (s, 1H, acid proton); MS m/z = 450(M).

**72b: (R = -CH3),** pale yellow solid; M.R: >260°C. IR (KBr): 3434 (broadm, -COOH, stretching); 1753 (strong, C=O, acid carbonyl); 1525 (strong, -N-CH3); 1H-NMR (DMSO d_6/TMS) δ 3.87-3.89 (s, 3H, -
N-CH₃); 6.75 (s, 1H, -CH₃, bezoxapine ring); 7.05-7.09 (td, 1H, bezoxapine ring); 7.18-7.23 (m, 2H, bezoxapine ring); 7.4-7.52 (d, 2H, CH=CH, proton in vinyl); 7.62-7.76 (m, 6H, 5proton in Ar-H ring + 1proton bezoxapine ring); 7.97-7.99 (d, 2H, indole ring); 8.6-8.63 (d, 2H, indole ring); 12.59 (s, 1H, acid proton); MS m/z = 464(M).

Preparation of 73a-b from 63a-b:

A mixture of DMF (10 vol.) and tri-orthotolylphosphine (0.06) was stirred at 20-25 °C and slowly add a mixture of 63a-b (0.05mole) 25 (0.06moles) and triethylamine (0.2 moles) at 20-25 °C. Stir 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. Cool to 40 °C and distilled the mass below 60 °C, the obtained residue was run column chromatography and collect the pure compound 73a-b by using solvent ratio hexane:ethyl acetate(7:3).

73a: (R = H), pale yellow solid; M.R: 212-216 °C; IR (KBr): 3325 (broad, -NH, stretching); 1733 (strong, -C=O, ester carbonyl); 1H-NMR (DMSO d₆/TMS) δ 1.31-1.34(t, 3H, -CH₂C₂H₃); 4.35-4.40 (q, 2H, OCH₂); 7.35 (s, 1H, -CH=, oxazole ring); 7.49-7.51 (d, 1H, -CH=CH, proton in vinyl); 7.56-7.68 (m, 5H, phenyl ring); 7.83-7.86 (d,1HY, -SCH=, in vinyl); 7.90-7.92 (d, 2H, indole ring); 8.20 (s, 1H, indole ring); 8.38 (s, 1H, indole ring); 12.17 (s, 1H, -NH, indole ring); 13C-NMR (DMSO d₆/TMS) showed δ 168.28, 160.27, 157.01, 144.19, 141.87, 138.33, 133.80, 130.04, 128.74, 127.43, 126.22, 125.84, 124.14, 123.28, 122.78, 113.52, 104.15, 98.41, 62.23, 14.50., MS m/z = 423(M+1).
**73b: \((R = -\text{CH}_3)\)**, pale yellow solid; M.R: 196-210 °C. (decompose); IR (KBr): 1716 (strong, \text{C=O, ester carbonyl}); 1515 (strong, \text{-N-CH}_3); 1H-NMR (DMSO d$_6$/TMS) \(\delta\) 1.30-1.34 (t, 3H, \text{-CH}_2\text{CH}_3); 3.86 (s, 3H, \text{-N-CH}_3); 4.35-4.40 (q, 2H, O\text{CH}_2); 7.35 (s, 1H, \text{-CH=, oxazole ring}); 7.61-7.70 (m, 4H, \text{-Ar-H ring}); 7.72-7.84 (m, 2H, \text{CH=CH, proton in vinyl}); 7.88-7.92 (m, 3H, 1proton in \text{-Ar-H ring} & 2 proton \text{indole ring}); 8.21 (s, 1H, \text{indole ring}); 8.39 (s, 1H, \text{indole ring}); \(^{13}\text{C-NMR (DMSO d}_6$/TMS\) signals \(\delta\) 167.75, 160.23, 157.05, 144.00, 141.79, 138.69, 133.85, 132.37, 130.08, 127.46, 126.41, 126.05, 124.31, 123.20, 122.88, 112.10, 103.17, 98.38, 62.25, 33.70, 14.50., MS m/z = 437.2(M+1).