CHAPTER-2
CHAPTER- 2

Synthesis of 5-((5-(2-(phenylsulfonyl) ethyl)-1H-indol-3-yl) Methyl) thiazolidine-2, 4-Dione

2.1 INTRODUCTION:

Thiazolidinones are the derivatives of thiazolidine, which belong to important group of heterocyclic compounds, containing sulfur and nitrogen in a five member ring. Many thiazolidinedione and their derivatives serve as basic pharmacophore for various biological profiles i.e. antidiabetic [117] anticancer [118] antimalarial [119] and anti inflammatory [120]. Thiazolidine-2, 4-dione analogues such as ciglitazone [121], troglitazone [122] and englitazone [123] are well known for their anti diabetic activity. The interesting chemistry and various pharmacological activities associated with thiazolidine-2, 4-dione led to the discovery of various drugs such as rosiglitazone [124] pioglitazone [125] and netoglitazone [126]. These observations promoted us to synthesize a new series of thiazolidinedione derivatives and check the biological activity.

2.2 LITERATURE SURVEY

Weller et.al. reported [127] the condensation of indole-3-carboxaldehyde (2) with thiosemicarbazide in methanol–AcOH resulting in the formation of the corresponding thiosemicarbazones derivatives (3). The latter was found to posses anti–tubercular activity (Scheme-2.1)
Gallent et al. reported [128] N-phenylmaleimide (4b) was prepared starting from maleic anhydride (4a) and phenyl amine, followed by chlorination of 4b with thionyl chloride afforded 3,4-dichloro-N-phenylmaleimide (4c). Reaction of 4c with indole or substituted indole (1a-c) on Grignard reagent gave indole adducts (5a-c) (Scheme-2.2).

Ogilive et al. [129] reported the synthesis of anti-migraine drug eletriptan, starting from 5-bromo indole (1a-b) in the following reaction using phenylvinylsulphone in the presence of triorthotolylphosphene and palladium acetate as a catalyst giving 3-substituted -5-(β-sulfonylviny1) indole (8) 80 % yield (Scheme-2.3)
Dubey et al. reported [130] the Knoevenagel condensation of indole-3-carboxyaldehyde (2) and their N-substituted derivatives (11) with the active methylene compound, i.e., 3-cyanoacetylindole (9), affording novel substituted olefins (10) and (12) respectively. The latter products reacted with DMS in the presence of PEG-600 to afford the corresponding N, N dimethylated derivatives (13) (Scheme-2.4).

... Scheme-2.3

... Scheme-2.4
Lohary et al. reported [131] the Knoevenagel condensation of aldehyde (14) with 2,4-thiazolidinedione (15) in the presence of piperidinium benzoate in refluxing toluene with azeotropic removal of water to give benzyldine compound (16). Reduction of olefinic double bond by using excess of Pd/C gave the target 5-[4-(2-indol-1-yl-ethoxy)-benzyl]-thiazolidine-2,4-dione (17). (Scheme-2.5)

Swan et al. reported [132] the synthesis of 1-(3-indolymethyl) -N, N-diethylpipecolamide hydrochloride (20) starting from indole (18) with N,N-diethyl pipecolamide hydrochloride (19) and 37% aq. formaldehyde in the presence of methanol at RT. (Scheme-2.6).

Pradasni et al. reported [133] the Knoevenagel type condensation of 5-bromoindole-2,3-dione (21) with substituted
thiazolidine (22) in ethanol media to give 5-bromoindole-3-(substituted thiazolidinone)-2-one (23). (Scheme-2.7).

\[
\begin{align*}
\text{Reflux / 6-7hrs} & \quad \text{C}_2\text{H}_5\text{OH} \\
\text{R} & \quad \text{21a: X=NH, RBr} \\
\text{22} & \quad \text{23a: X=S, Y=S, R=H} \\
\text{23b: X=S, Y=S, R=Me} \\
\end{align*}
\]

...Scheme-2.7

2.3 PRESENT WORK:

The present chapter deals with the synthesis of Knovenagel condensation products based on 5-bromoindole-3-carboxyaldehyde. Condensation between different indole-3-carboxylaldehyde and active methylene group containing compound of thiazolidine-2,4-dione PTSA in toluene media to gave different indole-3-yl-methylene-thiazoline-2,4-dione derivatives. 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.

2.4 RESULTS AND DISCUSSIONS:

Formylation of 5-bromoindole (1a-b) (i.e., 1a, R=H; 1b, R= -CH3) under Vilsmeier-Hack formylation conditions using POCl₃ and DMF as a reagents under cooling conditions (0-5 °C) followed by simple processing, gave a 5-bromoindole-3-carboxyaldehyde (2a-b). (i.e., 2a,
\( R=H; \) 2b, \( R=\text{-CH3} \) which have been characterized on the basis of its spectral and analytical data. Thus, its IR (KBr) spectrum showed a very broad band of medium to strong intensity in the region 3216-3220 cm\(^{-1}\) assignable to \(-\text{NH-}\) stretching. Other absorptions were obtained in the IR spectrum at 1642 cm\(^{-1}\) as a strong peak and very sharp peak assignable to the carbonyl group as a diagnostic absorption. Its \(^1\)H-NMR spectrum (DMSO \( d_6 / \text{TMS} \) showed signals at \( \delta \) 7.34-7.3 (d, 1H, indole ring proton); 9.89 (s, 1H, -CHO); 12.3 (s, 1H, -NH-, \( D_2O \) exchangeable NH). Its CI mass spectrum in Q+2 mode showed a molecular ion peak at 226 (base peak) corresponding to a molecular mass of 224; (Scheme- 2.8)

![Scheme 2.8](image)

Condensation of \( 2a-b \) (i.e., 2a, \( R=H; \) 2b, \( R=\text{-CH3} \)) with thiaoozolidine-2,4-dione (15) in toluene as a solvent in the presence of PTSA & TBAB as a phase transfer catalyst under stirring initially at room temperature for 10-30 min., then slowly raise the temperature to 105 °C and maintained for 12-15 hrs obtained a product of 5-(5-bromo-IH-indol-3-yl methylene)-thiaoozidine-2,4-dione (24a-b) (i.e., 24a, \( R=H; \) 24b, \( R=\text{-CH3} \)) which is homogeneous on TLC and has been characterized on the basis of spectral and analytical data. Thus,
its IR (KBr) spectrum showed at 3134 cm\(^{-1}\) assignable to \(-\text{NH}\)-, stretching vibrations \textit{indole} ring, 3025 cm\(^{-1}\) \textbf{(figure-2.1)} assignable to \(-\text{NH}\)- stretching vibrations \textit{thiazolidine} ring and a very strong, sharp peak in the region 1736 cm\(^{-1}\) assignable to the carbonyl group. Its \(^1\text{H}\)-NMR spectrum (DMSO \textit{d}_6/TMS) showed \textbf{(figure-2.2)} signals at \(\delta\) 7.35 (d, 1H, \textit{Ar-H} ring); 7.76 (s, 1H, \(-\text{CH}=\text{C}-\)); 12.25 (s, 1H, \(-\text{NH}-\textit{indole}\) ring \(\text{D}_2\text{O}\) exchangeable \textit{NH}); 12.37 (s, 1H, \(-\text{NH}-\textit{thiazolidine}\) \(\text{D}_2\text{O}\) exchangeable \textit{NH}). \(^{13}\text{C}\)-NMR (DMSO \textit{d}_6/TMS) showed \textbf{(figure-2.3)} signals at \(\delta\) 168.26, 168.08, 135.38, 129.98, 129.06, 126.03, 124.39, 121.59, 117.78, 114.83, 114.15, 110.60, Its CI mass spectrum in \(\text{Q}+1\) mode showed \textbf{(figure-2.4)} a molecular ion peak at 338 (base peak) corresponding to a molecular mass of 337. (\textbf{Scheme- 2.9})

\[\text{Reaction of 24a-b with phenylvinylsulfone (25) under Heck condition using palladium acetate as a catalyst in DMF at 100-105 \degree\text{C} for 16 hrs gave 5-[5-(2-benzenesulfonyl-vinyl)-1H-indol-3-ylmethylene]-thiazolidine-2,4-dione (28a-b) (i.e., 28a, R=H; 28b, R= -CH3) while on heck reaction, starting with out N-protection of compound, we observed the two major spots from residue and} \]
identified as monomer and dimer by $^1$H NMR & $^{13}$C NMR of phenylvinylsulfone derivatives.

The structure of the compound characterized on the basis of spectral and analytical data. Thus, its IR (KBr) spectrum showed \textbf{(figure-2.5)} in the region 3197 (broad $–\text{NH}$, stretching, \textit{indole} ring); 3044 (broad, $–\text{NH}$, stretching, \textit{thiazolidine} ring); 1723 (very strong, carbonyl, \textit{thiazolidine} ring); 1680 (very strong, \textit{thiazolidine} carbonyl ring); $^1$H-NMR (DMSO d$_6$/TMS) showed \textbf{(figure-2.6)} signals at $\delta$ 7.50 (s, 1H, \textit{indole} ring); 7.60-7.78 (m, 7H, 5 proton in \textit{Ar-H} ring & 2 proton, -SCH=CH-); 7.93-7.95 (d, 2H, \textit{indole} ring); 8.1 (s, 1H, \textit{indole} ring); 8.49 (s, 1H, \textit{indole} ring); 12.31 (s, 2H, -NH, 1proton in \textit{indole} ring & 1proton in \textit{thiazolidine} ring D$_2$O exchangeable NH); Its CI mass spectrum showed in Q-1 mode, \textbf{(figure-2.7)} the molecular ion peak at 409 (M-1), corresponding to a molecular mass of 410 (\textbf{Scheme- 2.10}).

\textbf{Scheme- 2.10}

On reduction of \textbf{28a-b} in the presence of hydrogen gas, palladium-carbon by using catalytic amount acetic acid medium in
methanol at 45-50 °C gave 5-[5-(2-benzenesulfonyl-ethyl)-1H-indol-3-ylmethylene]-thiazolidine-2,4-dione (31a-b) (i.e., 31a, R=H; 31b, R=-CH3) which has been characterized on the basis of spectral and analytical data. Thus, its IR (KBr) spectrum showed (figure-2.8) at 3299 cm\(^{-1}\) assignable to \(-\text{NH- thiazolidine}\) stretching vibrations, 3149 cm\(^{-1}\) broad \(-\text{NH- indole}\) ring and a very strong, sharp peak in the region 1675 cm\(^{-1}\) assignable to the carbonyl group. Its \(^1\)H-NMR spectrum (DMSO d\(_6\)/TMS) showed (figure-2.9) signals at \(\delta\) 2.93-2.98 (m, 2H, -CH\(_2\)_2, ethyl); 3.66-3.70 (m, 2H, -SCH\(_2\)_2); 7.02 (d, 1H, -indole ring); 7.33 (d, 1H, indole ring); 7.60 (s, 1H, -CH=); 7.62, (s, 1H, indole ring); 7.64 (t, 1H, Ar-H ring); 7.77 (t, 2H, Ar-H ring); 7.93 (d, 2H, Ar-H ring); 7.99 (s, 1H, indole ring); 12.01 (s, 1H, -NH, proton); 12.25 (s, 1H, -NH, thiazolidine, proton); \(^13\)C-NMR (DMSO d\(_6\)/TMS) showed (figure-2.10) signals at \(\delta\) 167.14, 165.28 (-C=O, thiazolidine ring), 138.99, 109.51 (-CH=), 51.48 (S-CH\(_2\)_2), 35.77 (-NCH\(_3\), indole ring), 33.98 (SCH\(_2\)_2-CH\(_2\))_. Its CI mass spectrum in Q+1 mode showed (figure-2.11) a molecular ion peak at 411 (base peak) corresponding to a molecular mass of 410; (Scheme- 2.11).
Alternative synthesis of 31a-b.

Condensation of 1a-b with 25 in the presence of palladium acetate as a catalyst in DMF as a solvent heating at 100-105 °C gave 5-(2-benzenesulfonyl-vinyl)-1H-indole (26a-b) (i.e., 26a, R=H; 26b, R= -CH3) which has been characterized on the basis of spectral and analytical data. Thus, its IR (KBr) spectrum showed in the region 3401 cm⁻¹ assignable to –NH- stretching vibrations and a very strong, sharp peak in the region 1604 cm⁻¹ assignable to the -C=C- group. Its ¹H-NMR spectrum (DMSO d₆/TMS) showed signals at δ 6.45 (s, 1H, indole ring), 7.37 (d, 1H, indole ring); 7.47 (d, 1H, -CH=); 7.37 (d, 1H, -SCH-); 11.36 (s, -NH-, proton); Its CI mass spectrum in Q+1 mode showed a molecular ion peak at 284 (base peak) corresponding to a molecular mass of 283; (scheme- 2.12)

Formylation of 26a-b under Vilsmeier-Hack conditions using POCl₃ and DMF as a reagent under cooling conditions (0-5 °C) followed by simple processing gave, 5-(2-benzenesulfonyl-vinyl)-1H-indole-3-carbaldehyde (27a-b) (i.e., 27a, R=H; 27b, R= -CH3), which has been characterized on the basis of its spectral data. Thus, its IR
(KBr) spectrum showed in the region 3268 cm\(^{-1}\) assignable to \(-\text{NH}-\) stretching, 2823 cm\(^{-1}\) very strong \(-\text{CHO}\), other absorptions were obtained in the IR spectrum at 1644 cm\(^{-1}\) as a strong peak and very sharp peak assignable to the carbonyl group as a diagnostic absorption. Its \(^1\text{H}-\text{NMR}\) spectrum (DMSO \(d_6\)/TMS) showed signals at \(\delta\) 7.51-7.60 (d, 1H, -CH=C); 7.61 (d, 1H, indole ring); 7.73 (d, 1H, -SCH=C); 9.95 (s, 1H, -CHO); 12.34 (s, 1H, -NH-, D\(_2\)O exchangeable NH). Its CI mass spectrum in Q+2 mode showed a molecular ion peak at 326 (base peak) corresponding to a molecular mass of 324;

(Scheme-2.13)

![](image)

...Scheme -2.13

The \(27\text{a-b}\) also prepared from \(2\text{a-b}\) with \(25\) in the presence of palladium acetate as a catalyst in DMF, at 100-105 \(^\circ\)C obtained the compound \(27\text{a-b}\) (i.e., \(27\text{a}, R=H; 27\text{b}, R=\text{-CH}_3\)) identical with all respect obtained compound earlier. (Scheme-2.14).
Condensation of 27a-b with 15 in toluene as a solvent in the presence of PTSA & TBAB as a phase transfer catalyst stirring, initially at room temperature for 10-30 mints, then slowly to a the temperature 105 °C, for 12-15 hrs., yielded a product 28a-b (i.e., 28a, R=H; 28b, R= -CH3) which has been characterized on the basis of spectral and analytical data and identical with all respect obtained compound earlier. (Scheme- 2.15).

Reduction of 26a-b in the presence of hydrogen gas, using palladium-carbon as catalyst and used catalytic amount acetic acid in methanol and heating at 45-50 °C for 8 hrs gave the new intermediate 29a-b (i.e., 29a, R=H; 29b, R= -CH3) which have been characterized on the basis of spectral and analytical data. Thus, its IR (KBr) spectrum showed in the region 3361 cm⁻¹ assignable to –NH-
**indole** ring. Its \(^1\)H-NMR spectrum (DMSO \(d_6/TMS\)) showed signals at \(\delta\) 2.86-2.90 (m, 2H, -CH\(_2\)-); 3.56-3.60 (m, 2H, -S-CH\(_2\)-); 6.28 (s, 1H, **indole** ring); 10.97 (s, 1H,-NH- proton); Its CI mass spectrum in Q+1 mode showed a molecular ion peak at 285, corresponding molecular ion peak at 286 (Scheme- 2.16).

Formylation of 29a-b with POCl\(_3\) in DMF as a solvent under cooling conditions (0-5 \(^\circ\)C) gave a 5-(2-benzenesulfonyl-ethyl)-1H-indole-3-carboxyalydehyde (30a-b) (i.e., 30a, R=H; 30b, R= -CH\(_3\)) which has been characterized on the basis of its spectral data. Thus, its IR (KBr) spectrum showed in the region 3434 cm\(^{-1}\) assignable to –NH- stretching, 2830 cm\(^{-1}\) very strong -CHO Other absorptions were obtained in the IR spectrum at 1660 cm\(^{-1}\) as a strong peak and very sharp peak assignable to the carbonyl group as a diagnostic absorption. Its \(^1\)H-NMR spectrum (DMSO \(d_6/TMS\)) showed signals at \(\delta\) 2.85-2.95 (m, 2H, -CH\(_2\), ethyl); 3.59-3.63 (m, 2H, -SCH\(_2\)-); 7.05-7.08 (d, 1H, **indole** ring); 7.34-7.36 (d, 1H, **indole** ring); 7.60-7.64 (t, 2H, Ar-H ring); 7.69-7.73 (t, 1H, Ar-H ring); 7.83 (s, 1H, **indole** ring); 7.91-7.93 (d, 2H, Ar-H ring); 8.2 (s, 1H, **indole** ring); 9.85 (s, 1H, **formyl** proton); 12.01 (s, 1H,-NH-, D\(_2\)O exchangeable NH). Its CI mass
spectrum in Q+1 mode showed a molecular ion peak at 314 (base peak) corresponding to a molecular mass of 313; (Scheme -2.17)

![Scheme-2.17]

The 30a-b also prepared by the reducing of 27a-b in the presence of hydrogen gas, palladium-carbon in methanol containing catalytic amount of acetic acid and heating at 45-50 °C for 8 hrs gave 30a-b (i.e., 30a, R=H; 30b, R= -CH3) which has been characterized on the basis of spectral and analytical data and identical with all respect obtained compound earlier. (Scheme- 2.18).

![Scheme- 2.18]

Condensation of 30a-b with 15 in toluene as a solvent in the presence of PTSA & TBAB as a phase transfer catalyst stirring at room temperature for 10-30 mints, then slowly raise the temperature to 105 °C and maintained for 12-15 hrs, obtained a product 31a-b (i.e., 31a, R=H; 31b, R= -CH3), which has been characterized on the basis of spectral and analytical data. Thus, its IR (KBr) spectrum showed in the region 3299 cm⁻¹ assignable to –NH- stretching vibrations thiazolidine ring, 3149 cm⁻¹ assignable to –NH- stretching vibrations
indole ring and a very strong, sharp peak in the region 1718 cm$^{-1}$ assignable to the carbonyl group. Its $^1$H-NMR spectrum (DMSO d$_6$/TMS) showed signals at $\delta$ 2.93-2.98 (m, 2H, -CH$_2$-, ethyl), 3.62-3.70 (m, 2H, -SCH$_2$); 7.60 (s, 1H, -CH=C); 12.01 (s, 1H, -NH-indole, D$_2$O exchangeable NH); 12.25(s, 1H,-NH-, D$_2$O exchangeable NH). Its CI mass spectrum in Q+1 mode showed a molecular ion peak at 411 (base peak) corresponding to a molecular mass of 410; (Scheme-2.19)

The over all sequence of the reactions given in Scheme-2.20.
SUMMARY OF THE SCHEME-2.20

\[
\begin{align*}
(1a-b) & \xrightarrow{DMF} (2a-b) & (2a-b) & \xrightarrow{POCl_3} (3a-b) & (3a-b) & \xrightarrow{Toluene/PTSA/TBAB/105-110^\circ C} (4a-b) \\
& \xrightarrow{Tri-ortho toyl phosphene/105-110^\circ C} (5a-b) & (5a-b) & \xrightarrow{Pd-C/H_2/MeOH/AcOH} (6a-b) \\
& \xrightarrow{Tri-ortho toyl phosphene/105-110^\circ C} (7a-b) & (7a-b) & \xrightarrow{Pd-C/H_2/MeOH/AcOH} (8a-b) \\
& \xrightarrow{Tri-ortho toyl phosphene/105-110^\circ C} (9a-b) & (9a-b) & \xrightarrow{Pd-C/H_2/MeOH/AcOH} (10a-b) \\
& \xrightarrow{Tri-ortho toyl phosphene/105-110^\circ C} (11a-b) & (11a-b) & \xrightarrow{Pd-C/H_2/MeOH/AcOH} (12a-b) \\
& \xrightarrow{Tri-ortho toyl phosphene/105-110^\circ C} (13a-b) & (13a-b) & \xrightarrow{Pd-C/H_2/MeOH/AcOH} (14a-b) \\
& \xrightarrow{Tri-ortho toyl phosphene/105-110^\circ C} (15a-b) & (15a-b) & \xrightarrow{Pd-C/H_2/MeOH/AcOH} (16a-b) \\
& \xrightarrow{Tri-ortho toyl phosphene/105-110^\circ C} (17a-b) & (17a-b) & \xrightarrow{Pd-C/H_2/MeOH/AcOH} (18a-b) \\
& \xrightarrow{Tri-ortho toyl phosphene/105-110^\circ C} (19a-b) & (19a-b) & \xrightarrow{Pd-C/H_2/MeOH/AcOH} (20a-b) \\
& \xrightarrow{Tri-ortho toyl phosphene/105-110^\circ C} (21a-b) & (21a-b) & \xrightarrow{Pd-C/H_2/MeOH/AcOH} (22a-b) \\
& \xrightarrow{Tri-ortho toyl phosphene/105-110^\circ C} (23a-b) & (23a-b) & \xrightarrow{Pd-C/H_2/MeOH/AcOH} (24a-b) \\
& \xrightarrow{Tri-ortho toyl phosphene/105-110^\circ C} (25a-b) & (25a-b) & \xrightarrow{Pd-C/H_2/MeOH/AcOH} (26a-b) \\
& \xrightarrow{Tri-ortho toyl phosphene/105-110^\circ C} (27a-b) & (27a-b) & \xrightarrow{Pd-C/H_2/MeOH/AcOH} (28a-b) \\
& \xrightarrow{Tri-ortho toyl phosphene/105-110^\circ C} (29a-b) & (29a-b) & \xrightarrow{Pd-C/H_2/MeOH/AcOH} (30a-b) \\
& \xrightarrow{Tri-ortho toyl phosphene/105-110^\circ C} (31a-b) & (31a-b) & \xrightarrow{Pd-C/H_2/MeOH/AcOH} (32a-b) \\
\end{align*}
\]

R = H, CH₃
2.4. EXPERIMENTAL SECTION

GENERAL: The reagents used in the synthesis i.e. Phenylvinylsulfone, tri-orthotolylphosphine, thiazolidine-2,4-dione, palladium acetate, Pd-C, etc., were purchased from commercial suppliers and used as it is without any purification.

2.4.1 Preparation of 31a-b:

2.4.2. Preparation of 2a-b from 1a-b:

To a stirred ice cold solution of DMF (80ml) was added POCl₃ (0.045 moles) at 0-5 °C, over a period of 30-45 min. The solution was maintained at 0-5 °C for 15 min until the reaction mass was formed. To this mass a solution of 1a-b (0.05 moles) in DMF (20 ml) was added over period of 0.5-1.0 hr at 0-5 °C, then maintained for 0.5 hr at the same temperature. Then slowly raise the temperature to 45 °C, and maintained for 6-8 hrs at 45-50 °C. The progress of reaction was monitored by TLC and on completion, the reaction mass was cool to 20 °C and stir for 15.0 min., at 20-25 °C and charge water (50 ml) at the same temperature, then adjust pH to 9-9.5 with 50% sodium hydroxide solution at 20-30 °C, then stir for 1.0 hr 20-25 °C. Filter the mass and wash with water (50 ml) and pressed dry. The crude product (2a-b) was recrystallized from ethanol to pure compound 2a-b.

2a: (i.e., R=H) Yield 10.5 gm (92.5 %); off white solid. M.R: 200-203 °C. IR (KBr): 3216 (strong –NH, stretching), and 2838 (very strong, formyl); 1643 (strong, -C=O); ¹H-NMR (DMSO d₆/TMS) δ 7.34-7.36 (d, 1H); 7.44-7.46 (d, 1H, Ar-H ring); 8.18 (s, 1H, Ar-H ring); 8.31 (s, 1H,
indole ring); 9.89 (s, 1H, formyl proton); 12.3 (s, 1H, -NH, proton); MS m/z = 226 (M+2).

2b: (i.e., R=CH₃) Yield 10 gm (95%); white solid, M.R: >260 °C. IR (KBr): 2924 (strong –CH, stretching); and 1660 (very strong, -CHO, formyl carbonyl); 1535 (strong, -CH₃); ³H-NMR (DMSO d₆/TMS) δ 3.88 (s, 3H, -CH₃); 7.45-7.47 (d, 1H, Ar-H ring); 7.56-7.58 (d, 1H, Ar-H ring); 8.22 (s, 1H, Ar-H ring); 8.32 (s, 1H, indole ring); 9.88 (s, 1H, -CHO proton); MS m/z= 240 (M+2).

2.4.3. Preparation of 24a-b from 2a-b:

A mixture of toluene (50ml), 2a-b (0.22 moles), thiazolidine-2,4-dione (15) (1.2eq.) and PTSA & TBAB (as catalysts) was stirred for 10.0min at 25-30 °C, then slowly raise the temperature to 105 °C and maintained for 12-15hrs at 105-110 °C. Then monitored the reaction by TLC and cooled to 20-25 °C and charged water (50ml) and stir for 1.0hr at 20-25 °C, filter the mass and wash with water (10ml) and obtained the pure material 24a-b.

24a: (i.e., R=H), Yield 6.2 gm (86.11 %); off white to light yellow color solid M.R >260 °C, IR (KBr): 3134 (broad –NH stretching); 3025 (broad, –NH, stretching, thiazolidine ring); 1736 (very strong, carbonyl); 1680 (very strong, carbonyl); ³H-NMR (DMSO d₆/TMS) δ 7.35 (d, 1H, Ar-H ring); 7.46 (d, 1H, Ar-H ring); 7.76 (s, 1H, -CH=); 8.05 (s, 1H, Ar-H ring); 8.14 (s, 1H, indole ring); 12.25 (s, 1H, -NH, indole ring); 12.37 (s, 1H, -NH proton, thiazolidine); ¹³C-NMR (DMSO d₆/TMS) δ 168.26, 168.08, 135.38, 129.98, 129.06, 126.03, 124.39, 121.59, 117.78, 114.83, 114.15, 110.60, MS m/z= 323 (M).
24b: (i.e., R=CH₃) Yield 7.0 gm (95 %); off white solid, M.R: 250-255 °C. IR (KBr): 3435 (broad –NH stretching, thiazolidine ring); 1737 (very strong, carbonyl, stretching); 1680 (very strong, carbonyl, stretching); 1594.0 (strong, -CH₃); 1H-NMR (DMSO d₆/TMS) δ 3.86 (s, 3H, -N-CH₃); 7.36-7.38 (d, 1H, Ar-H ring); 7.47-7.49 (d, 1H, Ar-H ring); 7.76 (s, 1H, -CH=); 7.9 (s, 1H, Ar-H ring); 8.13 (s, 1H, indole ring); 12.27 (s, 1H, -NH); 13C-NMR (DMSO d₆/TMS) δ 168.07, 167.60, 135.94, 133.54, 129.40, 126.05, 124.08, 121.66, 117.24, 114.62, 113.24, 109.56, 33.88., MS m/z = 338 (M+1).

2.4.4. Preparation of 28a-b from 24a-b;

Charge DMF (50ml), palladium acetate (0.2gm,) and tri-orthotolylphosphine (0.06moles) was stirred at 20-25 °C and slowly add a mixture of 24a-b (1.2eq), 25 (1.2eq) and triethylamine (2.eq) 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 28a-b. by using solvent ratio hexane: ethyl acetate (7:3).

28a: (i.e., R=H) Yield 6.4 gm (91 %); off white to light yellow color solid M.R: 260 °C, IR (KBr): 3197 (broad –NH, stretching); 3044 (broad, –NH, stretching, thiazolidine ring); 1723. (very strong, carbonyl, stretching); 1680.8 (very strong, carbonyl, stretching); 1H-NMR (DMSO d₆/TMS) δ 7.50 (s, 1H, indole ring); 7.60-7.78 (m, 7H,
five proton in \textbf{Ar-H} ring & two protons, -\textit{SCH=CH}-); 7.93-7.95 (d, 2H, \textit{indole} ring); 8.1 (s, 1H, \textit{indole} ring); 8.49 (s, 1H, \textit{indole} ring); 12.31 (s, 2H, -NH, proton \textit{indole} ring & proton in \textit{thiazolidine} ring); MS m/z = 410.9 (M+1).

\textbf{28b}: (i.e., R=CH$_3$); Yield 5.8 gm (88 %); off white to light yellow color solid M.R >260 0°C, IR (KBr): 3044 (broad, –NH, stretching, \textit{thiazolidine} ring); 1723. (very strong, carbonyl);1680.8 (very strong, carbonyl); 1521 (very strong, -N-CH$_3$); \textsuperscript{1}H-NMR (DMSO d$_6$/TMS) δ 3.8 (s, 3H, -N-CH$_3$); 7.50 (s, 1H, \textit{indole} ring); 7.60-7.78 (m, 7H, 5 proton in \textbf{Ar-H} ring + 2 proton, -\textit{SCH=CH}-); 7.93-7.95 (d, 2H, \textit{indole} ring); 8.1 (s, 1H, \textit{indole} ring); 8.49 (s, 1H, \textit{indole} ring); 12.31 (s, 1H, -NH, \textit{thiazolidine} ring); MS m/z = 425 (M+1).

\textbf{2.4.5. Preparation of 31a-b from 28a-b; (METHOD-1)}

Reduction of \textbf{28a-b} (0.012 mole) in the presence of hydrogen gas, palladium-carbon(10%) by using catalytic amount of acetic acid medium in methanol by heating at 45-50 0°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 obtained pure compound of \textbf{31a-b}.

\textbf{2.4.6. Preparation of 31a-b from 30a-b; (METHOD-2)}

A mixture of Toluene (50ml.), \textbf{30a-b} (0.22 moles), (\textbf{15}) (1.2eq) and catalytic amount of PTSA & TBAB was stirred for 10.0min at 25-30 0°C, then slowly raise the temperature to 105 0°C and maintained for 12-15hrs at 105-110 0°C. The progresses of the reaction monitored by
TLC and cooled to 20-25 °C and charged water (50ml) and stir for 1.0hr at 20-25 °C, filter the mass and wash with DM Water (10ml) and obtained the pure material 31a-b.

31a: (i.e., R=H) Yield = 5.10 gm (78%); off white solid, M.R: >260 °C. IR (KBr): 3299 (-NH, stretching, thiazolidine); 3149 (br, -NH, indole ring); 1718.7 (very strong, carbonyl, stretching); and 1675 (very strong, carbonyl, stretching); 1H-NMR (DMSO d6/TMS) δ 2.93-2.98 (m, 2H, -CH2, ethyl); 3.62-3.70 (m, 2H, -SCH2); 7.02 (d, 1H, -indole ring); 7.33 (d, 1H, indole ring); 7.60 (s, 1H, -CH=); 7.62, (s, 1H, indole ring); 7.64 (t, 1H, Ar-H ring); 7.77 (t, 2H, Ar-H ring); 7.93 (d, 2H, Ar-H ring); 7.99 (s, 1H, indole ring); 12.01 (s, 1H, -NH, proton); 12.25 (s, 1H, -NH, thiazolidine, proton); 13C-NMR (DMSO d6/TMS) δ 168.15, 167.69, 139.52, 135.47, 134.23, 130.84, 129.86, 129.23, 128.20, 127.58, 125.06, 124.44, 118.32, 116.39, 112.72, 110.71, 56.24, 28.76,. MS m/z= 411 (M-1).

31b: (i.e., R=CH3) Yield = 5.8 gm (79%); off white solid, M.R: 214-217 °C., IR (KBr): 3446.73 (-NH, stretching, thiazolidine); 1728.7 (very strong, carbonyl, stretching); and 1675.5 (very strong, carbonyl, stretching); 1H-NMR (DMSO d6/TMS); δ 3.69-3.72 (m, 2H, -CH2, ethyl); 3.86 (m, 2H, -SCH2); 3.88 (s, 3H, -N-CH3, indole ring); 7.39-7.41 (d, 1H, indole ring); 7.50-7.52 (d, 1H, indole ring); 7.64 (t, 2H, Ar-H ring); 7.70 (t, 1H, Ar-H ring); 7.82 (s, 1H, indole ring); 7.89 (d, 2H, Ar-H ring); 8.09 (s, 1H, -CH=); 8.21 (s, 1H, indole ring); 12.25 (s, 1H, -NH, thiazolidine, proton); 13C-NMR (DMSO d6/TMS) δ 167.14,
165.28, 138.99, 136.02, 134.64, 133.97, 130.02, 129.43, 128.14, 126.22, 125.62, 121.82, 114.84, 114.43, 113.97, 109.51, 51.48, 35.77, 33.98. MS m/z = 427 (M+1).

2.5. Alternate preparation of 31a-b:

2.5.1. Preparation of 26a-b from 1a-b:

Stir the mixture of DMF (50ml.), palladium acetate (0.2gm,) and tri-orthtolylphosphine (1.2eq) at 20-25 °C and slowly add a mixture of 1a-b (0.05 moles), 25 (1.2eq) and triethylamine (2.0eq.) 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 26a-b by using solvent ratio hexane: ethyl acetate (7:3).

26a: (i.e., R=H) Yield =2.2 gm. (77%), off white solid, M.R: 126-130 °C, IR (KBr): 3401 (strong –NH, stretching); and 1604 (very strong, -C=, sulfonyl vinyl); 1H-NMR (DMSO d_6/TMS) δ 6.45 (s, 1H, indole ring); 7.35 (d, 1H, indole ring); 7.37 (d, 1H, indole); 7.39 (d, 1H, indole ring); 7.47 (d, 1H, -CH=); 7.62 (d, 1H, SCH-); 7.66 (t, 1H, Ar-H ring); 7.69 (t, 2H, Ar-H ring); 7.88 (d, 2H, Ar-H ring); 7.90 (d, 1H, indole ring); 11.36 (s, -NH proton); MS m/z = 284 (M+1).

26b: (i.e., R=CH_3) Yield = 1.84 gm (88%), off white solid; M.R: 129-131 °C. IR (KBr): 1446 (very strong –CH_3); 1H-NMR (DMSO d_6/TMS) δ 3.76 (s, 3H, -CH_3); 6.45 (s, 1H, indole ring); 7.35 (d, 1H, indole ring); 7.36 (d, 1H, indole ring); 7.39 (d, 1H, indole ring); 7.46 (d, 1H, -CH=);
7.62 (d, 1H, SCH); 7.66 (t, 1H, Ar-H ring); 7.69 (t, 2H, Ar-H ring); 7.88 (d, 2H, Ar-H ring); 7.90 (d, 1H, indole ring); MS m/z = 298 (M+1).

2.5.2. Preparation of 27a-b from 26a-b;

To an ice cold solution of DMF (80ml), was added POCl₃ (0.06 moles) at 0-5 °C, over a period of 30-45 min. The solution was maintained for 15 min. at the same temperature until a reaction mass syrupy liquid was formed. To this, 26a-b (0.05 moles, in 10 vol. of DMF) was added for 0.5-1.0 hr at 0-5 °C. Then maintained for 0.5 hr at the same temperature. Then slowly raise the temperature to 45 °C, and maintained for 6-8 hrs at 45-50 °C. The reaction was monitored by TLC. After completion of reaction cool to 20 °C and stir for 15.0 min at 20-25 °C and charge DM water (50 ml) at the same temperature, then adjust pH to 9-9.5 with 50% sodium hydroxide solution at 20-30 °C, then stir for 1.0 hr 20-25 °C, filter the mass the and wash with water (50.0 ml) and obtained the material 27a-b.

27a: (i.e., R=H), Yield = 5.45 gm (95%); off white solid M. R: >260 °C, IR (KBr): 3268 (broad -NH stretching); 2823 (very strong-CHO, formyl stretching); and 1644 (very strong, -CHO, formyl carbonyl stretching); ¹H-NMR (DMSO d₆/TMS) δ 7.51-7.60 (d, 1H, -CH=); 7.61 (d, 1H, indole ring proton); 7.66 (d, 1H, indole ring protons); 7.71 (t, 1H, Ar-H ring); 7.73 (d, 1H, -SCH proton); 7.64 (t, 2H, Ar-H ring); 7.93 (d, 2H, Ar-H ring); 8.30 (s, 1H, indole ring); 8.36 (s, 1H, indole ring); 9.95 (s, 1H, formyl proton); 12.34 (s, 1H, -NH, proton); MS m/z= 311 (M+1).
27b: (i.e., R=CH₃) Yield = 5.51 gm (96%); off white solid, M.R : >260 °C IR (KBr): 3056 (strong -CH, vinyl stretching); 2821 (-CH, vinyl, stretching ); 1651 (very strong, -CHO, formyl carbonyl); and 1535 (strong, methyl); ¹H-NMR (DMSO d₆/TMS) δ 3.86 (s, 3H, -CH₃); 7.53-7.60 (d, 1H, -CH=); 7.61 (d, 1H, indole ring proton); 7.66 (d, 1H, indole ring protons); 7.71 (t,1H, Ar-H ring); 7.73 (d, 1H, -SCH, proton); 7.74 (t, 2H, Ar-H ring); 7.93 (d, 2H, Ar-H ring); 8.30 (s, 1H, indole ring); 8.36 (s, 1H, indole ring); 9.8 (s, 1H, formyl proton); MS m/z = 326 (M+1).

2.5.3. Preparation of 28a-b from 2a-b;

On reduction of 27a-b (0.012 mole) in the presence of palladium-carbon(10%) and hydrogen gas by using catalytic amount of acetic acid in methanol at 45-50 °C under stirring for 8 hrs. The reaction was monitored by TLC, after completion of reaction cool to RT and filter the mass through hyflo bed, take filtrate and concentrated and obtained pure compound of 28a-b.

28a: (i.e., R=H) Yield = 5.3 gm (92%), off white to light yellow color solid M.R: >260 °C, IR (KBr): 3197 (broad -NH, stretching); 3044 (broad, -NH, stretching, thiazolidine ring); 1723. (very strong, carbonyl, stretching ); 1680 (very strong, carbonyl, stretching); ¹H-NMR (DMSO d₆/TMS) δ 7.50 (s, 1H, indole ring); 7.60-7.78 (m, 7H, five protons in Ar-H ring & two protons, -SCH=CH-); 7.93-7.95 (d, 2H, indole ring); 8.1 (s, 1H, indole ring); 8.49 (s, 1H, indole ring); 12.31 (s, 2H, -NH, proton indole ring & proton in thiazolidine ring); MS m/z = 410.9 (M+1).
28b: (i.e., $R=CH_3$); Yield = 5.25 gm (89%); off white to light yellow color solid M.R: >260 °C, IR (KBr): 3044 (broad, –NH, stretching, thiazolidine ring); 1723 (very strong, carbonyl, stretching); 1680.8 (very strong, carbonyl, stretching); 1521 (very strong, -N-CH₃); ¹H-NMR (DMSO d₆/TMS) δ 3.8 (s, 3H, -N-CH₃); 7.50 (s, 1H, indole ring); 7.60-7.78 (m, 7H, five protons in Ar-H ring & two proton, -SCH=CH-); 7.93-7.95 (d, 2H, indole ring); 8.1 (s, 1H, indole ring); 8.49 (s, 1H, indole ring); 12.31 (s, 1H, -NH, thiazolidine ring); MS m/z = 425 (M+1).

2.5.4. Preparation of 29a-b from 26a-b:

The reduction of 26a-b (0.012 moles) in the presence of palladium-carbon(10%) and hydrogen gas by using acid medium in methanol stirring 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 obtained pure compound of 29a-b.

29a: (i.e., $R=H$) Yield = 4.63 gm(92%), off white solid, M. R:104-106 °C, IR (KBr): 3361 (strong, –NH, stretching); ¹H-NMR (DMSO d₆/TMS) δ 2.86-2.90 (m, 2H, -CH₂, ethyl); 3.56-3.60 (m, 2H, -SCH₂); 6.28 (s, 1H, indole ring); 6.84-6.86 (d, 1H, indole ring); 7.22- (d, 1H, indole ring); 7.25 (d, 1H, indole ring ); 7.28 (d, 1H, indole ring); 7.61-7.64, (t, 2H, Ar-H ring); 7.73 (t, 1H, Ar-H ring); 7.92-7.94 (d, 2H, Ar-H ring); 10.97 (s, 1H, -NH proton); MS m/z = 286 (M+1).
29b: (i.e., R=CH₃), Yield = 4.96 gm(95%); off white solid, M.R: 78-80 °C, IR (KBr): 1447 (very strong, –CH₃); ¹H-NMR (DMSO d₆/TMS) δ 2.87-2.90 (m, 2H, -CH₂, ethyl); 3.56-3.60 (m, 2H, -SCH₂); 3.69 (s, 3H, -CH₃); 6.27 (d, 1H, indole ring); 6.91-6.94 (d, 1H, indole ring); 7.23 (d, 1H indole ring); 7.25 (s, 1H, indole ring); 7.29 (d, 1H, indole ring); 7.6 (t, 2H, Ar-H ring); 7.70 (t, 1H, Ar-H ring); 7.93 (d, 2H, Ar-H ring); MS m/z= 300 (M+1).

2.5.5. Preparation of 30a-b from 29a-b;

To an ice cold solution of DMF (80.0ml), was added POCl₃ (0.045moles) at 0-5 °C, in a period of 30-45min. The solution was maintained for 15min. at the same temperature until a reaction mass syrupy liquid was formed. To this, 29a-b (5.0gm) (0.05moles), in DMF (20ml) was added for 0.5-1.0hr at 0-5 °C. Then maintained for 0.5hr at the same temperature. Then slowly raise the temperature to 45 °C, and maintained for 6-8hrs at 45-50 °C. The reaction was monitered by TLC. After completion of reaction, cool to 20 °C and stir for 15.0min at 20-25 °C and charge water (50ml) at the same temperature, then adjust pH to 9-9.5 with 50% sodium hydroxide solution at 20-30 °C, then stir for 1.0hr 20-25 °C. Filter the mass and wash with water (50ml) and obtained the pure material 30a-b.

30a: (i.e., R=H), Yield = 5.25 gm(96%); off white solid, M.R: 130-135 °C IR (KBr): 3434 (strong, –NH, stretching); 2830 (formyl stretching); and 1660 (very strong, -C=O, carbonyl); ¹H-NMR (DMSO d₆/TMS) δ 2.85-2.95 (m, 2H, -CH₂, ethyl); 3.59-3.63 (m, 2H, -SCH₂); 7.05-7.08
(d, 1H, indole ring); 7.34-7.36 (d, 1H, indole ring); 7.60-7.64 (t, 2H, phenyl ring); 7.69-7.73 (t, 1H, Ar-H ring); 7.83 (s, 1H, indole ring); 7.91-7.93 (d, 2H, Ar-H ring); 8.2 (s, 1H, indole ring); 9.85 (s, 1H, formyl proton); 12.01 (s, 1H, -NH proton); MS m/z = 314 (M+1).

30b: (i.e., R=CH₃) Yield = 4.96 gm (96%); off white solid, M.R: 136.0-138.0 ⁰C., IR (KBr): 2926 (formyl, stretching); 1653 (very strong formyl carbonyl); and 1535 (very strong, –CH₃); ¹H-NMR (DMSO d₆/TMS) δ 2.96-2.99 (m, 2H, -CH₂, ethyl); 3.64-3.69 (m, 2H, -SCH₂); 3.85 (s, 3H, -CH₃); 7.19 (d, 1H, indole ring); 7.48 (d, 1H, indole ring); 7.6, (t, 1H, Ar-H ring); 7.7 (t, 2H, Ar-H ring); 7.8 (s, 1H, indole ring); 7.96 (d, 2H, Ar-H ring); 8.2 (s, 1H, indole ring); 9.85 (s, 1H, formyl proton); MS m/z = 328 (M+1).