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# Synthesis, characterization and biological evaluation of novel Indole- mannich bases containing azetidin-2-one and thiazolidin-4-one moieties

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**Abstract:** The synthesis and characterization of new series of novel indole derivatives have been presented. The structures were confirmed by elemental analysis, IR spectral, H1- NMR spectral, C13-NMR spectral and mass spectral data. All the compounds were screened for invitro antibacterial and antifungal activities. The antibacterial activity was tested against *Staphylococcus aureus*(Gram positive), *Bacillus cereus* (Gram positive), *Escherichia coli* (Gram negative) and *Pseudomonas aeruginosa* (Gram negative). The antifungal activity was tested against *Aspergillusniger* and *Candida albicans*. All the compounds showed considerable antimicrobial activity against the microorganism studied. Based on the nature of substituent present, the structure-activity correlation of novel compounds was discussed.
**Key words** Indole ; azetidinone;thiazolidinone; antibacterial activity and antifungal activity.

## Introduction

The wide range of biological activities exhibited by azetidin-2-ones, thiazolidin-4-ones and indole, it was our aim is to prepare derivatives of azetidin-2-ones and thiazolidin-4-ones incorporated with indole ring system in a molecular frame work and to explore the therapeutic advantage of this combination. 4-Thiazolidinone ring system contains sulphur and nitrogen heterogenous at position 1 and 3 respectively and keto group at position 4. Azetidinones are the carbonyl derivatives of azetidines containing carbonyl group at the position-2. Indole derivatives constitute an important class of therapeutic agents in medicinalchemistry including anticancer [1], anti oxidant [2], anti rheumatoidal [3] and anti-HIV [4] and also play a vital role in the immune system [5] and potent scavenger of free radicals [6].

The azetidinone nucleus is a pharmacophoric scaffold and represents a class of heterocycles with a wide range of biological applications. Many of them are widely used as anti-inflammatory [7,8], antitubercular [9], antiproliferative [10], DNA cleavage [11], cholesterol absorption inhibitors [12], Antiplasmodial [13], antidepressant [14] and antimicrobial [15-17]. The study of indole derivatives is of considerable current interest as a result of their important biological properties.Thiazolidinones have a broad spectrum of pharmacological properties viz. anti HIV, anti fungal , anti psychotic, anti convulsant activity[18], hypnotic[19] , antitubercular[20],anticancer[21] ,and antiviral activity[22] etc.

This prompted us to synthesize new compounds containing both azitidin-2-one and thiazolidin-4-one moieties in anticipation of improved biological activity. In view of their biological importance , the authors tried to integrate these nuclei in a single entity to result in compounds that demonstrate better therapeutical activities. The present article is an effort in that direction and reports the synthesis, characterization and biological evaluation of some novel indole derivatives containing azetidin-2-one and thiazolidin-4-one moieties.

## Materials and methods

All chemicals and reagents were obtained from Merck IndiaLimited. Melting points were determined in

open capillarytubes and were uncorrected (in degree Celsius). The infraredspectra of the compounds were recorded in KBr discson FT-IR (Spectrum ONE) spectrometer manufactured by Perkin-Elmer. The $^{1}$H-NMR spectra were recorded on a JOEL(300 MHz) spectrometer using TMS as an internal standard(chemical shifts in δ). The 13CNMR Spectra were recorded on a Brucker 75MHz spectrophotometer. The Mass spectra were recorded on varian MATCH-7 mass spectrometer at 70ev instrument (m/z in %). Nutrient broth, nutrient agar and 5 mm diameter antibiotic assay discs were obtained from Hi-Media Laboratories Limited, India. The standard bacterial and fungal strains were procured from NationalCentre for Cell Science (NCCS), Pune, India.

## Experimental

**Synthesis of Ethyl 2-(5-chloro-1H-indol-3-yl)acetate (2)**

A mixture of 5-chloro-1H-indole (0.02mol, 3.03g) and anhydrous K2CO3 (0.03mol), Chloro ethyl acetate (0.03mol, 3.6g) and DMF was added and the mixture is stirred at room temperature for 8 hours, the reaction mixture was diluted with icecold water . The progress of the reaction was monitored by TLC with acetone: ethyl acetate (7:3) as elutent .The separated solid was identified as ethyl 2-(5-chloro-1H-indol-3-yl)acetate (2). This was collected by filtration and recrystallized from ethanol.

**Synthesis of 2-(5-chloro-1H-indol-3-yl)acetohydrazide (3)**

A solution of Ethyl 2-(5-chloro-1H-indol-3-yl)acetate (2) (0.01mol, 2.37g) and hydrazine hydrate (0.02 mol) in ethanol (20ml) was refluxed for 5 hours. The progress of the reaction was monitored by TLC with acetone: ethyl acetate (7:3) as elutent . The reaction mixture was cooled and poured on to ice cold water with stirring .The separated solid was filtered, washed with water and recrystallized from ethanol to afford 2-(5-chloro-1H-indol-3-yl)acetohydra zide (3).

**Synthesis of 2-(5-chloro-1-(Morpholine/N-methyl piparazine-1-ylmethyl)-1Hindol-3-yl) aceto hydrazide (4a-b)**

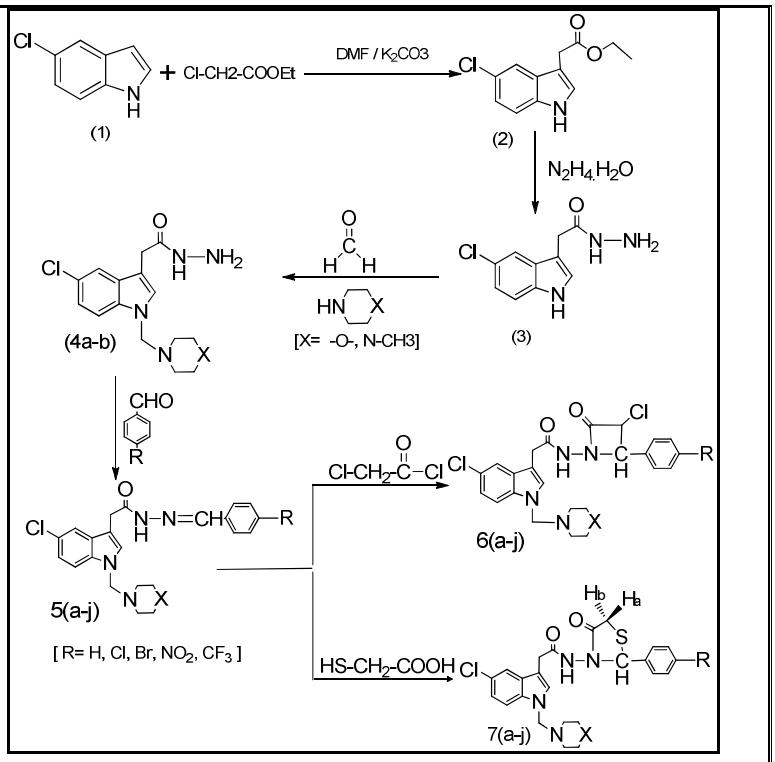
A solution of (3) (0.01mol, 2.23g) in absolute ethanol-dioxane mixture (20ml) was treated with formaldehyde (40%, 1.5ml).Later, the appropriate amine(0.02ml) in ethanol (10ml) was added with stirring and the reaction mixture was stirred over night at room temperature. The progress of the reaction was monitored by TLC with acetone: ethyl acetate (7:3) as elutent . The precipitated mannich base was collected by filtration and dried. Recrystallisation was done from Ethanol-DMF mixture to give 2-(5-chloro-1-(morpholinomethyl)-1H-indol-3-yl) acetohydrazide (4a). The reaction procedure leading to 4a was then extended to the synthesis of compound(4b).

**Synthesis of 2-(5-chloro-1-( Morpholine/N-methyl piparazine -1-ylmethyl)-1Hindol-3-yl)-N'- (4-Substituted benzylidene)acetohydrazide (5a-j)**

To a solution of 2-(5-chloro-1-(morpholinomethyl)-1H-indol-3-yl) acetohydrazide (4a) (1.3mmol, 451.8mg) in hot methanol (25ml), benzaldehyde (3mmol) and a drop of glacial acetic acid were added. The solid that separated on refluxing for 3hrs was filtered wash with cold methanol and recrystallised from methanol to afforded Schiff's derivative N'- benzy lidene-2-(5-chloro-1-(morpho linomethyl)-1H-indol-3-yl)acetohydrazide(5a). The reaction procedure leading to (5a) was then extended to the synthesis of (5b-j) from 4(a-b) and para substituted benzaldehyde.

**Scheme 1. Synthetic route for preparation of the target compounds (6 a-j) and (7 a-j). Synthesis of 2-(5-chloro-1-(Morpholine/N-methyl piparazine-1-ylmethyl)-1Hindol-3-yl)-N-(3-chloro-2-oxo-4-(4-Substituted phenylazetidin-1-yl)acetamide(6a-j)**

To a solution of Schiff's Base N'-benzylidene-2-(5-chloro-1-(morpholino methyl)-1H-indol-3-yl)aceto hydrazide (5a) (0.73mmol, 300mg) in acetone, triethylamine (5mmol, 0.75 ml) was added. To this, a solution of chloroacetylchloride (2mmol, 1.13 ml) was added drop wise with stirring. The mixture was refluxed up to12h. The progress of the reaction was monitored by TLC with acetone: ethyl acetate (7:3) as elutent . The triethyl amine hydrochloride formed was filtered and washed several times with acetone. The filtrate and washings were mixed and concentrated under reduced pressure. The residue obtained was washed with petroleum ether (40-60$^{0}$C) to remove the unreacted Schiff's base and the solid obtained was recrystallized from ethanol to afford 2-(5-chloro-1-(morpholinomethyl)-1H-indol-3-yl)-N-(3-chloro-2-oxo-4-phenyl azetidin-1-yl) acetamide (6a). The reaction procedure leading to (6a) was then extended to the synthesis of (6b-j).




| Compound | R | X |
|---|---|---|
| 6a / 7a | -H | -O |
| 6b / 7b | -Cl | -O |
| 6c / 7c | -Br | -O |
| 6d / 7d | $-NO_2$ | -O |
| 6e / 7e | $-CF_3$ | -O |
| 6f / 7f | -H | $-NCH_3$ |
| 6g / 7g | -Cl | $-NCH_3$ |
| 6h / 7h | -Br | $-NCH_3$ |
| 6i / 7i | $-NO_2$ | $-NCH_3$ |
| 6j / 7j | $-CF_3$ | $-NCH_3$ |

**Synthesis of 2-(5-chloro-1-( Morpholine/N-methyl piparazine-1ylmethyl) -1H-indol-3-yl) -N-(4- oxo-2-Substituted phenylthiazolidin-3-yl)acetamide (7a-j)**

A mixture of N'-benzylidene-2-(5-chloro-1(morpholino methyl)-1H-indol-3-yl) aceto hydrazide (5a) (0.73mmol,300mg) and thioglycolic acid (2mmol)dissolved in dioxane(20 ml),anhydrous zinc chloride (0.5 mg) was added and taken in a 100 ml beaker and the reaction mixture was refluxed for 15 hours. The progress of the reaction was monitored by TLC with acetone: ethyl acetate (7:3) as elutent . The reaction mixture was then cooled and poured into ice-cold water. the resulting solid was filtered, washed with sodium bicarbonate solution and recrystallised from absolute alcohol to afford 2-(5-chloro-1-(morpholinomethyl)-1H-indol-3-yl)-N-(4-oxo-2-phenylthi azolidin-3-yl)acetamide (7a).The reaction procedure leading to (7a)was then extended to the synthesis of (7b-j) from (5b-j) and thioglycolic acid.

## Results and discussion

**Characterisation of Ethyl 2-(5-chloro-1H-indol-3-yl)acetate (2)**

Molecular formula: $C_{12}H_{12}ClNO_2$, yield: 70%, M.P:164-6 $^0$C, element found%

(calculated%): C 60.24(60.64); H 4.91 (5.09);Cl 14.54(14.92);N 5.40 (5.89); O 13.16 (13.46), IR $\upsilon_{max}$ in $cm^{-1}$ (Group): 3250 $cm^{-1}$ (-NH of secondary amine); 2980 $cm^{-1}$ (aliphatic -$CH_{2\ str.}$); 2960 $cm^{-1}$ (-$CH_{3\ str.}$),1695$cm^{-1}$ (-C=O of ester) , 1310(C-O-C of ester) and 722$cm^{-1}$ (-C-Cl), $^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 10.80(brs,1H-NH of indole),7.10-7.45(m,4H of Indole ring), 4.35(s,2H,-CH2CO),3.85(q,2H,-CH2 of ethyl),1.29(t,3H,-CH3 of ethyl gp).

**Characterisation of 2-(5-chloro-1H-indol-3-yl)acetohydrazide (3)**

Molecular formula: $C_{10}H_{10}ClN_3O$, yield: 67%, M.P:167-9 $^0$C, element found%

(calculated%): C 53.34(53.70); H 4.23 (4.51);Cl 15.54(15.85);N 18.40 (18.79); O 6.96(7.15), IR $\upsilon_{max}$ in $cm^{-1}$ (Group): 3495 $cm^{-1}$ and 3420 $cm^{-1}$ (2-bands of -NH2); 3205 $cm^{-1}$ (-NH);3050 $cm^{-1}$ (-CH of aromatic); 1690$cm^{-1}$ (-C=O of amide) and 722$cm^{-1}$ (-C-Cl), $^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 2.10(s,2H,-NH2); 4.35(s,2H, -CH2-CO); 6.98-7.34(m,4H -CH of indole ring); 9.72 (s, 1H,-CONH); 11.20(brs,s,1H -NH of indole).

**Characterisation of (4a-b)**

4a : Molecular formula: $C_{15}H_{19}ClN_4O_2$ , yield: 68%, M.P:172-4$^0$C, element found%

(calculated%): C 55.42(55.81); H 5.61 (5.93);Cl 10.64(10.98);N 17.08 (17.36); O 9.62(9.91), IR $\upsilon_{max}$ in $cm^{-1}$(Group): 3485 $cm^{-1}$ and 3410 $cm^{-1}$ (2-bands of -NH2); 3210 $cm^{-1}$ (-NH);3040$cm^{-1}$ (=CH of aromatic); 1690$cm^{-1}$ (-C=O of amide); 1250 $cm^{-1}$ (C-N)and 722$cm^{-1}$ (-C-Cl), $^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 9.72(s,1H, -CONH); 7.10-7.40(m,4H of indol ring); 4.78(s,1H,-NCH2); 4.35(s,2H,-CH2-CO); 3.62-3.66 (t, CH2-O-CH2 of morpholine ring); 2.47-2.50(t,4H,-CH2-N-CH2 of morpholine ring); 2.30(s,2H,-NH2).

4b : Molecular formula: $C_{16}H_{22}ClN_5O$ , yield: 67%, M.P:175-6$^0$C, element found%

(calculated%): C 56.92(57.22); H 6.43(6.60); Cl 10.21(10.56); N 20.41(20.85); O 4.37(4.76), IR $\upsilon_{max}$ in $cm^{-1}$(Group): 3480 $cm^{-1}$ and 3400 $cm^{-1}$ (2-bands of -NH2); 3205 $cm^{-1}$ (-NH);3035$cm^{-1}$ (=CH of aromatic); 1685$cm^{-1}$ (-C=O of amide); 1245 $cm^{-1}$ (C-N)and 720$cm^{-1}$ (-C-Cl), $^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 9.73(s,1H, -CONH), 7.10-7.55(m,4H,=CH of indol ring),4.77(s,1H,-NCH2 attached to indol ring), 4.33 (s,2H,-CH2-CO), 2.45-2.48(m,8H,-CH2-N-CH2 of piperazine ring), 2.31(s,2H,-NH2), 2.23(s, 3H,N-CH3 of piperazine ring).

**Characterisation of (5a-j)**

5a : Molecular formula: $C_{22}H_{23}ClN_4O_2$ , yield: 62%, M.P:176-8$^0$C, element found%

(calculated%): C 64.12(64.31); H 5.38(5.64); Cl 8.46(8.63); N 13.43(13.64); O 7.52(7.79), IR $\upsilon_{max}$ in $cm^{-1}$(Group): 3225$cm^{-1}$ (–NH of amide); 3050$cm^{-1}$ (=CH aromatic stretching); 1625$cm^{-1}$ (-C=N); 1685$cm^{-1}$ (-C=O of amide); 1256$cm^{-1}$ (-C-N);1180$cm^{-1}$ (C-O-C) and 722 $cm^{-1}$ (C-Cl), $^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 9.72(s,1H, -CONH), 8.45(s,1H, N=CH of benzylidene ring),6.85-7.85 (m,9H, 4H of indol and 5H C6H5 ring) , 4.79(s,2H,N-CH2 attached to indol),4.35(s,2H,-CH2 C=O),3.60(t,4H,CH2-O-CH2 of morpholine),2.47(t,4H,-CH2-N-CH2 of morpholine).

5b : Molecular formula: $C_{22}H_{22}Cl_2N_4O_2$ , yield: 65%, M.P:184-6$^0$C, element found%

(calculated%): C 59.06(59.33); H 4.68(4.98); Cl 15.63(15.92); N 12.26(12.58); O 6.92(7.19)IR $\upsilon_{max}$ in $cm^{-1}$(Group): 3052$cm^{-1}$ (=CH aromatic stretching); 1683$cm^{-1}$ (-C=O of amide); 1258 $cm^{-1}$ (-C-N); 722 $cm^{-1}$(C-Cl), $^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 9.73(s,1H, -CONH), 8.49 (s,1H, N=CH of benzylidenering), 6.90 - 7.78(m,8H 4H of indol and 4H C6H4 ring), 4.77(s, 2H,-NCH2 attached to indole ring), 4.32 (s,2H,-CH2-CO), 3.62(t, 4H, CH2-O-CH2 of morpho line), 2.47(t,4H,-CH2-N-CH2 of morpholine ring ).

5c : Molecular formula: $C_{22}H_{22}BrClN_4O_2$ , yield: 63%, M.P:193-5$^0$C, element found%

(calculated%): C 53.67(53.95); H 4.26(4.53); Br 16.07(16.31); Cl 7.05(7.24); N 11.15(11.44); O 6.24(6.53), IR $\upsilon_{max}$ in $cm^{-1}$(Group): 3051$cm^{-1}$ (=CH aromatic stretching); 1682$cm^{-1}$ (-C=O of amide); 1257 $cm^{-1}$ (-C-N); 721 $cm^{-1}$(C-Cl), $^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 9.72(s,1H, -CONH), 8.50(s,1H, N=CH of benzylidene ring),6.95-7.60(m,8H 4H of indol and 4H C6H4 ring),4.77(s,2H,-NCH2 attached to indol ring) 4.30(s,2H,-CH2-CO),3.62(t,4H,CH2-O-CH2 of morpholine ring),2.47(t, 4H,-CH2-N-CH2 of morpholine).

5d : Molecular formula: $C_{22}H_{22}ClN_5O_4$ , yield: 63%, M.P:213-5$^0$C, element found%

(calculated%): C 57.68(57.96); H 4.59(4.86); Cl 7.43(7.78); N 15.12(15.36); O 13.89(14.04),IR $\upsilon_{max}$ in cm$^{-1}$(Group): 3055cm$^{-1}$ (=CH aromatic stretching); 1686cm$^{-1}$ (-C=O of amide); 1252 cm$^{-1}$ (-C-N); 725 cm$^{-1}$(C-Cl), $^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 9.75(s,1H,-CONH), 8.55(s,1H, N=CH of benzylidenering), 7.05-7.80 (m,8H 4H of indol and 4H C6H4 ring),4.79(s,2H,-NCH2 attached to indol ring),4.30 (s,2H,-CH2-CO),3.62(t,4H,CH2-O-CH2 of morpholine ring), 2.47(t,4H,-CH2-N-CH2 of morpholine).

5e : Molecular formula: $C_{22}H_{22}ClF_3N_4O_2$ , yield: 71%, M.P:210-2$^0$C, element found%

(calculated%): C 57.41(57.68); H 4.39(4.63); Cl 7.18(7.40); F 11.65(11.90); N 11.47(11.70); O 6.42(6.68), IR $\upsilon_{max}$ in cm$^{-1}$(Group): 3045cm$^{-1}$ (=CH aromatic stretching); 1684cm$^{-1}$ (-C=O of amide); 1251 cm$^{-1}$ (-C-N); 723 cm$^{-1}$(C-Cl), $^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 9.74 (s, 1H, -CONH), 8.5(s,1H, N=CH of benzylidene ring), 7.10-7.85(m,8H 4H of indol and 4H C6H4 ring),4.78(s,2H,-NCH2 attached to indol ring),4.28 (s,2H,-CH2-CO) 3.62(t,4H,CH2-O-CH2 of morpholine ring),2.47(t,4H,-CH2-N-CH2 of morpholine).

5f : Molecular formula: $C_{23}H_{26}ClN_5O$, yield: 62%, M.P:167-9$^0$C, element found%

(calculated%): C 64.92(65.16); H 6.05(6.18); Cl 8.11(8.36); N 16.34(16.52); O 3.45(3.77),IR $\upsilon_{max}$ in cm$^{-1}$(Group): 3050cm$^{-1}$ (=CH aromatic stretching); 1685cm$^{-1}$ (-C=O of amide); 1250cm$^{-1}$ (-C-N); 722cm$^{-1}$(C-Cl), $^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 9.72(s,1H, -CONH), 8.45(s,1H, N=CH of benzylidene ring),7.10-7.83 (m,9H, 4H of indol and 5H C6H5 ring),4.79 (s,2H, N-CH2 attached to indol ring),4.65(s,2H,-CH2 attached to C=O), 2.42 (t,8H,-CH2-N-CH2 of N-methyl piperazine), 2.23(s,3H, -CH3 of N-methyl piperazine).

5g : Molecular formula: $C_{23}H_{25}Cl_2N_5O$, yield: 66%, M.P:177-9$^0$C, element found%

(calculated%): C 60.07(60.27); H 5.32(5.50); Cl 15.21(15.47); N 15.12(15.28); O 3.24(3.49), IR $\upsilon_{max}$ in cm$^{-1}$(Group): 3052cm$^{-1}$ (=CH aromatic stretching); 1683cm$^{-1}$ (-C=O of amide); 1248cm$^{-1}$ (-C-N); 720cm$^{-1}$(C-Cl), $^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 9.73(s,1H, -CONH), 8.49(s,1H, N=CH of benzylidene ring), 7.10-7.90(m,8H 4H of indol and 4H C6H4 ring),4.77 (s,2H,-NCH2 attached to indol ring),4.67(s,2H,-CH2-CO),2.42(t,8H,-CH2-N-CH2 of N-methyl piperazine ring),2.23(s,3H, -CH3 of N-methyl piperazine).

5h : Molecular formula: $C_{23}H_{25}BrClN_5O$, yield: 64%, M.P:190-2$^0$C, element found%

(calculated%): C 54.67(54.94); H 4.87(5.01); Br 15.52(15.89); Cl 6.84(7.05); N 13.62(13.93); O 3.04(3.18), IR $\upsilon_{max}$ in cm$^{-1}$(Group): 3051cm$^{-1}$ (=CH aromatic stretching); 1682cm$^{-1}$ (-C=O of amide); 1247cm$^{-1}$ (-C-N); 721cm$^{-1}$(C-Cl), $^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 9.72 (s, 1H, -CONH), 8.50(s,1H, N=CH of benzylidene ring), 7.10-7.91(m,8H 4H of indol and 4H C6H4 ring),4.77(s,2H,-NCH2 attached to indol ring), 4.67(s,2H,-CH2-CO),2.42(t,8H,-CH2-N-CH2 of N-methyl piperazine ring),2.23(s,3H,-CH3 of N-methyl piperazine).

5i : Molecular formula: $C_{23}H_{25}ClN_6O_3$ , yield: 68%, M.P:217-9$^0$C, element found%

(calculated%): C 58.67(58.91); H 5.13(5.37); Cl 7.32(7.56); N 17.69(17.92); O 10.05(10.24),IR $\upsilon_{max}$ in cm$^{-1}$(Group): 3055cm$^{-1}$ (=CH aromatic stretching); 1686cm$^{-1}$ (-C=O of amide); 1252cm$^{-1}$ (-C-N); 725cm$^{-1}$(C-Cl), $^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 9.75(s,1H, -CONH), 8.55(s,1H, N=CH of benzylidene ring), 7.10-7.75(m,8H 4H of indole and 4H of C6H4 ring),4.79(s,1H,-NCH2 attached to indol ring),4.65(s,2H,-CH2- CO) 2.42(t,8H,-CH2-N-CH2 of N-methyl piperazine ring),2.23(s,3H , -CH3 of N-methyl piperazine).

5j : Molecular formula: $C_{24}H_{25}ClF_3N_5O$ , yield: 70%, M.P:214-6$^0$C, element found%

(calculated%): C 58.42(58.60); H 4.95(5.12); Cl 7.02(7.21); F 11.35(11.59); N 14.03(14.24); O 3.09(3.25), IR $\upsilon_{max}$ in cm$^{-1}$(Group): 3045cm$^{-1}$ (=CH aromatic stretching); 1684cm$^{-1}$ (-C=O of amide); 1251cm$^{-1}$ (-C-N); 723cm$^{-1}$(C-Cl), $^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 9.74(s, 1H, -CONH), 8.5(s,1H, N=CH of benzylidene ring), 7.10-7.85(m,8H 4H of indol and 4H C6H4 ring),4.78(s,1H,-NCH2 attached to indol ring),4.60(s,2H,-CH2-CO), 2.42(t,8H,-CH2-N-CH2 of N-methyl piperazine ring),2.23(s,3H,N-CH3 of N-methyl piperazine ring).

**Characterisation of (6a-j)**

6a : Molecular formula: $C_{24}H_{24}Cl_2N_4O_3$ , yield: 65%, M.P:177-9$^0$C, element found%

(calculated%): C 58.92(59.14); H 4.68(4.96); Cl 14.32(14.55); N 11.27(11.50); O 9.58(9.85)IR $\upsilon_{max}$ in $cm^{-1}$(Group): 3430 $cm^{-1}$ (-NH), 2947 and 2887 $cm^{-1}$(2 bands.)(-CH aliphatic),1730 $cm^{-1}$(-CO of azetidinone),1690$cm^{-1}$(-CO of amide), 1450$cm^{-1}$ (-CN) and 676$cm^{-1}$ (-C-Cl), $^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 9.65 (s,1H, -CONH), 6.75-7.42 (m,9H, 4H of indol ring and 5H of C6H5 phenyl ring), 5.45(d, 1H,-CH of azitidine attached to –Cl ) 5.05(d,1H, N-CH of azitidine ring proton),4.75(s,2H,N-CH2 attached to indol ring), 4.35 (s,2H,-CH2-CO), 3.63 (t,4H, CH2-O-CH2 of morpholine ring), 2.50 (t,4H,-CH2-N-CH2 of morpholine ring). $^{13}$C-NMR spectra(75MHz, DMSO-d6)δ: 127,112,121,128,123,115,134,129,39,173,168, 67,71,139,124,126.5,124.5,85,55,69 These are due to C1, C2, C3, C4, C5, C6, C7, C8, C9,C10,

C11,C12, C13,C14,C15&C19,C16& C18, C17, C20,C21&C24,C22&C23 carbon atoms respectively.

6b : Molecular formula: $C_{24}H_{24}Cl_2N_4O_3$ , yield: 68%, M.P:185-7$^0$C, element found%

(calculated%): C 55.07(55.24); H 4.16(4.44); Cl 20.14(20.38); N 10.42(10.74); O 9.03(9.20) IR $\upsilon_{max}$ in $cm^{-1}$(Group): 3415 $cm^{-1}$ (-NH), 2925 and 2853 $cm^{-1}$(2 bands.)(-CH aliphatic),1733 $cm^{-1}$(-CO of azetidinone), 1452$cm^{-1}$ (-CN) and 680$cm^{-1}$ (-C-Cl), $^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 2.50(t,4H,-CH2-N-CH2of morpholine), 3.63(t, 4H, CH2-OCH2 of morpholine), 4.37 (s,2H,-CH2-CO),4.75(s, 2H, NCH2 attached to indol ),508(d,1H, N-CH of azitidine ring proton), 5.50(d,1H,-CH of azitidine attached to –Cl ), 7.10-7.85 (m,8H, 4H of indol, 4H of C6H4), 9.65 (s,1H, -CONH). $^{13}$C-NMR spectra(75MHz, DMSO-d6)δ: 127, 112, 121, 128, 123, 115,134, 129, 39,173,168, 67,71,141,128,130,133,85,55, 69 These are due to C1, C2, C3, C4, C5, C6, C7, C8, C9,C10,C11,C12,C13,C14,C15&C19,C16&C18, C17, C20,C21&C24,C22&C23 carbon atoms respectively.

6c : Molecular formula: $C_{24}H_{23}BrCl_2N_4O_3$ , yield: 66%, M.P:193-5$^0$C, element found%

(calculated%): C 50.75(50.90); H 3.92(4.09); Br 13.90(14.11); Cl 12.31(12.52); N 9.62(9.89); O 8.26(8.48) , IR $\upsilon_{max}$ in $cm^{-1}$(Group): 3412 $cm^{-1}$ (-NH), 2921 and 2852 $cm^{-1}$(2 bands.)(-CH aliphatic),1735 $cm^{-1}$(-CO of azetidinone), 1451$cm^{-1}$ (-CN) and 677$cm^{-1}$ (-C-Cl),$^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 2.50 (t,4H,-CH2-N-CH2 of morpholine), 3.63(t, 4H, CH2-OCH2 of morpholine), 4.36 (s,2H,-CH2-CO), 4.75(s, 2H, NCH2 attached to indol), 4.95(d,1H, N-CH of azitidine ring proton), 5.50(d,1H,-CH of azitidine attached to –Cl ), 7.10-7.90 (m,8H, 4H of indol , 4H of C6H4 of phenyl ring attached to -Br), 9.65 (s,1H, -CONH). $^{13}$C-NMR spectra (75MHz, DMSO-d6)δ: 127,112, 121, 128, 123, 115,134, 129, 39,173,168,67,71, 143,128, 132, 122, 85,55, 69 These are due to C1,C2,C3,C4,C5, C6,C7, C8, C9 ,C10, C11,C12,C13, C14,C15 &C19,C16&C18, C17, C20,C21&C24,C22&C23 carbon atoms respectively.

6d : Molecular formula: $C_{24}H_{23}Cl_2N_5O_5$ , yield: 70%, M.P:216-8$^0$C, element found%

(calculated%): C 54.02(54.15); H 4.16(4.35); Cl 13.12(13.32); N 13.03(13.15); O 14.89 (15.03), IR $\upsilon_{max}$ in $cm^{-1}$(Group): 3421 $cm^{-1}$ (-NH), 2925 and 2854 $cm^{-1}$(2 bands.)(-CH aliphatic),1736 $cm^{-1}$(-CO of azetidinone), 1455$cm^{-1}$ (-CN) and 695$cm^{-1}$ (-C-Cl),$^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 2.50 (t,4H,-CH2-N-CH2 of morpholine ring), 3.63(t, 4H,CH2-O-CH2 of morpholine ring), 4.39 (s,2H,-CH2-CO), 4.75(s, 2H, N-CH2 attached to indol ring), 5.03 (d, 1H, NCH of azitidine ring proton), 5.55(d,1H,-CH of azitidine attached to –Cl ), 7.10-7.95 (m,8H, 4H of indol,4H of C6H4 phenyl ring attached to –NO2), 9.65 (s,1H, -CONH).$^{13}$C-NMR spectra(75MHz, DMSO-d6)δ: 127,112,121,128,123,115,134,129,39,173,168,67,71,147,124,125,148,85,55,69 These are due to C1,C2,C3,C4,C5, C6,C7, C8, C9 ,C10, C11, C12,C13,C14,C15&C19,C16&C18, C17, C20, C21 & C24,C22&C23 carbon atoms respectively.

6e : Molecular formula: $C_{25}H_{23}Cl_2F_3N_4O_3$ , yield: 72%, M.P:212-4$^0$C, element found%

(calculated%): C 53.92(54.07); H4.06 (4.17); Cl 12.52(12.77); F 10.07(10.26); N 9.95(10.09) ;O 8.47(8.64), IR $\upsilon_{max}$ in $cm^{-1}$(Group): 3417 $cm^{-1}$ (-NH), 2924 and 2853 $cm^{-1}$(2 bands.)(-CH aliphatic),1737 $cm^{-1}$(-CO of azetidinone), 1454$cm^{-1}$ (-CN) and 690$cm^{-1}$ (-C-Cl),$^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 2.50 (t,4H,-CH2-N-CH2 of morpholine ring), 3.63(t, 4H,CH2-O-CH2 of morpholine ring), 4.33 (s,2H,-CH2-CO),4.75(s, 2H, N-CH2 attached to indol ring), 5.02 (d, 1H, NCH of azitidine ring proton), 5.54(d,1H,-CH of azitidine attached to –Cl ),7.10-7.97 (m, 8H, 4H of indol,4H of C6H4 phenyl ring attached to –CF3), 9.65 (s,1H, -CONH). $^{13}$C-NMR spectra(75MHz, DMSO-d6)δ: 127,112,121,128,123,115,134,129,39,173,168,67,71,146, 126, 129,144,85,55,69 These are due to C1,C2,C3,C4,C5, C6,C7, C8, C9 ,C10, C11, C12, C13 ,C14, C15 &C19,C16&C18, C17, C20, C21 ,C22 &C25, C23 &C24 carbon atoms respectively.

6f : Molecular formula: $C_{25}H_{27}Cl_2N_5O_2$ , yield: 72%, M.P:212-4$^0$C, element found%

(calculated%):C 59.82(60.00); H 5.27(5.44); Cl 14.03(14.17); N 13.82(13.99); O 6.18(6.39),IR $\upsilon_{max}$ in $cm^{-1}$(Group): 3420 $cm^{-1}$ (-NH), 2920 and 2850 $cm^{-1}$(2 bands.)(-CH aliphatic),1734 $cm^{-1}$(-CO of azetidinone), 1450$cm^{-1}$ (-CN) and 675$cm^{-1}$ (-C-Cl), $^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 2.23(s,3H,N-CH3 of piperazine ring), 2.43 (t, 8H,-CH2-NCH2 of piperazine ring), 4.30(s,2H, -CH2 attached to C=O),4.70(s,2H, N-CH2 attached to indol ring), 5.01(d,1H, N-CH of azitidine ring proton), 5.45(d,1H,-CH of azitidine attached to -Cl ) 7.10-7.80 (m,9H, 4H of indol and 5H of C6H5 phenyl ring), 9.72 (s,1H, -CONH). $^{13}$C-NMR spectra(75MHz, DMSO-d6)δ: 127,112,121, 128,123,115,134,129, 39,173,168,67,71,141,123, 124,126,78, 55,62,45 These aredue to C1,C2,C3,C4,C5, C6,C7,C8,C9 ,C10,C11, C12,C13,C14, C15&C19,C16& C18,C17, C20,C21 & C24,C22 & C23 and C25 carbon atoms respectively.

6g : Molecular formula: $C_{25}H_{26}Cl_3N_5O_2$ , yield: 69%, M.P:182-4$^0$C, element found%

(calculated%):C 55.96(56.14); H 4.73(4.90); Cl 19.68(19.89); N 12.91(13.09); O 5.74(5.98), IR $\upsilon_{max}$ in $cm^{-1}$(Group): 3415 $cm^{-1}$ (-NH), 2925 and 2853 $cm^{-1}$(2 bands.)(-CH aliphatic),1736 $cm^{-1}$(-CO of azetidinone), 1451$cm^{-1}$ (-CN) and 680$cm^{-1}$ (-C-Cl), $^1$H-NMR (300 MHz, DMSO -$d_6$) δppm: 2.23(s,3H,N-CH3 of piperazine ring), 2.43 (t, 8H,-CH2-NCH2 of piperazine ring), 4.34 (s, 2H, -CH2 attached to C=O),4.77(s,2H, N-CH2 attached to indol ring), 5.03(d,1H,N-CH of azitidine ring proton), 5.52(d,1H,-CH of azitidine attached to -Cl ), 7.10-7.85 (m,8H, 4H of indol and 4H of $C_6H_4$ phenyl ring attached to -Cl), 9.72 (s,1H, -CONH). $^{13}$C-NMR spectra(75MHz, DMSO-d6)δ: 127,112,121,128,123,115, 134, 129, 39, 173,168,67, 71, 142,127,128, 133,78,55,62,45 These are due to C1,C2,C3,C4,C5, C6,C7, C8, C9 ,C10,C11, C12,C13,C14,C15 & C19,C16 & C18,C17,C20,C21 & C24,C22&C23andC25 carbon atoms respectively.

6h : Molecular formula: $C_{25}H_{26}BrCl_2N_5O_2$ , yield: 67%, M.P:191-3$^0$C,element found%

(calculated%):C 51.65(51.83); H 4.38(4.52); Br 13.56(13.79); Cl 12.07(12.24); N 11.91 (12.09); O 5.36(5.52), IR $\upsilon_{max}$ in $cm^{-1}$(Group): 3412 $cm^{-1}$ (-NH), 2921 and 2852 $cm^{-1}$(2 bands.)(-CH aliphatic),1735 $cm^{-1}$(-CO of azetidinone), 1452$cm^{-1}$ (-CN) and 677$cm^{-1}$ (-C-Cl), $^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 2.23(s,3H,N-CH3 of piperazine ring), 2.43 (t, 8H,-CH2-NCH2 of piperazine ring), 4.34(s, 2H, -CH2 attached to C=O),4.79(s,2H, N-CH2 attached to indol ring), 5.03(d,1H, N-CH of azitidine ring proton), 5.54(d,1H,-CH of azitidine attached to –Cl ), 7.10-7.90 (m,8H, 4H of indol and 4H of $C_6H_4$ phenyl ring attached to -Br), 9.72 (s, 1H, -CONH). $^{13}$C-NMR spectra(75MHz, DMSO-d6)δ: 127,112,121,128, 123,115, 134,129,39,173, 168,67,71,141,126,131,123, 78,55,62,45 These are due to C1,C2,C3,C4,C5, C6,C7, C8, C9 ,C10, C11,C12,C13,C14,C15&C19,C16 & C18,C17,C20,C21& C24,C22&C23andC25 carbon atoms respectively.

6i : Molecular formula: $C_{25}H_{26}Cl_2N_6O_4$ , yield: 68%, M.P:218-9$^0$C, element found%

(calculated%): C 54.87(55.05); H 4.63(4.80);Cl 12.87(13.00); N 15.24(15.41);O 11.52(11.73) IR $\upsilon_{max}$ in $cm^{-1}$(Group): 3421 $cm^{-1}$ (-NH), 2925 and 2854 $cm^{-1}$(2 bands.)(-CH aliphatic),1736 $cm^{-1}$(-CO of azetidinone), 1455$cm^{-1}$ (-CN) and 695$cm^{-1}$ (-C-Cl), $^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 2.23(s,3H,N-CH3 of piperazine ring), 2.43 (t, 8H,-CH2-NCH2 of piperazine ring), 3.70(s, 2H, -CH2 attached to C=O),4.76(s,2H, N-CH2 attached to indol ring), 4.95(d,1H, N-CH of azitidine ring proton),5.55(d,1H,-CH of azitidine attached to -Cl), 7.10-7.95 (m,9H, C8H4 of indol ring and $C_6H_4$ of phenyl ring attached to –NO2), 9.72 (s,1H, -CONH). $^{13}$C-NMR spectra(75MHz, DMSO-d6)δ: 127,112,121,128, 123,115,134,129, 39, 173,168,67,71,149,123,124, 147,78,55, 62,45 These are due C1,C2,C3,C4,C5, C6,C7,C8,C9 , C10,C11, C12,C13,C14,C15 & C19,C16 & C18,C17, C20, C21 & C24,C22&C23andC25 carbon atoms respectively.

6j : Molecular formula: $C_{26}H_{26}Cl_2F_3N_5O_2$ , yield: 68%, M.P:218-9$^0$C, element found%

(calculated%):C 54.78(54.94); H 4.49(4.61); Cl 12.28(12.47); F 9.87(10.03); N 12.14(12.32); O 5.46(5.63), IR $\upsilon_{max}$ in $cm^{-1}$(Group): 3417 $cm^{-1}$ (-NH), 2924 and 2853 $cm^{-1}$(2 bands.)(-CH aliphatic),1737 $cm^{-1}$(-CO of azetidinone), 1454$cm^{-1}$ (-CN) and 694$cm^{-1}$ (-C-Cl), $^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 2.23(s,3H,N-CH3 of piperazine ring), 2.43 (t, 8H,-CH2-NCH2 of piperazine ring),4.35(s, 2H, -CH2 attached to C=O), 5.05(s,2H, N-CH2 attached to indol ring), 4.95(d,1H, N-CH of azitidine ring proton),5.54(d,1H,-CH of azitidine attached to -Cl), 7.10-7.97 (m,8H, 4H of indol and 4H of $C_6H_4$ phenyl ring attached to -CF3), 9.72 (s,1H, -CONH). $^{13}$C-NMR spectra(75MHz, DMSO-d6)δ: 127,112,121,128,123,115,134,129,39, 173,168,67,71,147, 125,124, 128,125, 78,55,62,45 These are due to C1,C2,C3, C4,C5,C6, C7, C8, C9,C10, C11,C12,C13,C14,C15 & C19,C16 & C18,C17,C20,C21,C22 & C25,C23 & C24andC26 atoms respectively.

**Characterisation of (7a-j)**

7a : Molecular formula: $C_{24}H_{25}ClN_4O_3S$, yield: 64%, M.P:175-7$^0$C, element found%

(calculated%):C 59.31(59.43); H 5.04(5.20); Cl 7.10(7.31); N 11.41(11.55); O 9.72(9.90); S 6.40(6.61), IR $\upsilon_{max}$ in cm$^{-1}$(Group): 3340cm$^{-1}$(-NH), 2947cm$^{-1}$(-$CH_2$S),1710cm$^{-1}$( -C=O of thiazolidinone), 1184cm$^{-1}$,(C-N) 720cm$^{-1}$ (C-Cl) and 690 cm$^{-1}$ (C-S-C), $^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 2.45(t,4H, CH2-N-CH2 of morpholin ring), 4.30(s,2H, of-CH2CO), 3.55 (t, 4H,CH2-O-CH2 of morpholin ring), 3.95and 3.85(s,2H,Ha and Hb of –CH2S), 4.75(s,2H, of –NCH2-N), 5.45(s,1H, of –CH-N), 7.05-7.45(m, 9H, 4H of indol and 5H of -C6H5 nucleus), 9.85(s, 1H, CONH). $^{13}$C-NMR spectra(75MHz, DMSO-$d_6$)δ: 128,112,121, 127,123, 114, 134,129,39,173,170,37, 67, 139, 124, 127,125, 85,56, 68 These are due to C1, C2, C3, C4, C5, C6, C7, C8, C9, C10,C11, C12, C13, C14, C15&C19, C16& C18, C17, C20,C21&C24, C22&C23 carbon atoms respectively.

7b : Molecular formula: $C_{24}H_{24}Cl_2N_4O_3S$, yield: 68%, M.P:181-3$^0$C, element found%

(calculated%): C 55.32(55.49); H 4.51 (4.66); Cl 13.43(13.65); N 10.51(10.79); O 9.05 (9.24) ; S 6.03(6.17), IR $\upsilon_{max}$ in cm$^{-1}$(Group): 3342cm$^{-1}$(-NH), 2946cm$^{-1}$(-$CH_2$S),1707cm$^{-1}$( -C=O of thiazolidinone), 1186cm$^{-1}$(C-N) 722cm$^{-1}$ (C-Cl) and 686 cm$^{-1}$ (C-S-C), $^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 2.45(t,4H, CH2-N-CH2 of morpholin ring),4.34(s,2H, of -CH2CO), 4.33(t,4H,CH2-O-CH2 of morpholin ring), 3.97 and 4.00(s, 2H,Ha , Hb of–CH2S),4.75(s,2H, of -N-CH2-N attached to indol ring), 5.40(s,1H, of –CH-N),7.15-7.65(m, 8H, 4H of indol and 4H of -C6H5 nucleus),9.83(s,1H,-CONH). $^{13}$C-NMR spectra(75MHz, DMSO-$d_6$)δ: 128,112, 121,127,123,114,134,129,39,173,170,37, 67, 139, 131, 129, 132,85,56, 68 These are due to C1, C2, C3, C4, C5, C6, C7, C8, C9, C10, C11, C12, C13, C14, C15&C19, C16 &C18, C17, C20, C21 & C24, C22&C23 carbon atoms respectively.

7c : Molecular formula: $C_{24}H_{24}BrClN_4O_3S$, yield: 67%, M.P:184-6$^0$C, element found%

(calculated%): C 50.94(51.12); H 4.12(4.29); Br 14.03(14.17); Cl 6.12(6.29); N 9.78(9.94); O 8.35 (8.51) ; S 5.42(5.69), IR $\upsilon_{max}$ in cm$^{-1}$(Group): 2955cm$^{-1}$(-$CH_2$S), 1705cm$^{-1}$( -C=O of thiazolidinone), 1185cm$^{-1}$(C-N) 722cm$^{-1}$ (C-Cl) and 676 cm$^{-1}$ (C-S-C), $^1$H-NMR (300 MHz, DMSO-$d_6$) δppm: 2.44(t,4H, CH2-N-CH2 of morpholin ring), 4.32(s,2H, of -CH2CO), 3.55(t, 4H,CH2-O-CH2 of morpholin ring), 3.97 and 4.00(s, 2H,Ha , Hb of–CH2S), 4.75(s, 2H, of -N-CH2-N attached to indol ring), 5.40(s,1H, of –CH-N), 7.10-7.85(m, 9H, 8H, 4H of indol and 4H of -C6H5 nucleus),9.82(s,1H,-CONH). $^{13}$C-NMR spectra(75MHz, DMSO-$d_6$)δ: 128,112,121,127,123,114,134,129,39,173,170,37, 67, 138, 130, 132, 122, 85,55, 68 These are due to C1, C2, C3, C4, C5, C6, C7, C8, C9, C10,C11, C12, C13, C14, C15&C19, C16& C18, C17, C20,C21&C24, C22&C23 carbon atoms respectively.

7d : Molecular formula: $C_{24}H_{24}ClN_5O_5S$, yield: 70%, M.P:215-7$^0$C, element found%

(calculated%): C 54.23(54.39); H 4.39(4.56); Cl 6.42(6.69); N 13.03(13.21); O 14.89 (15.09); S 5.87(6.05), IR $\upsilon_{max}$ in cm$^{-1}$(Group): 2962cm$^{-1}$(-$CH_2$S), 1712cm$^{-1}$( -C=O of thiazo lidinone), 1188cm$^{-1}$(C-N) 725cm$^{-1}$ (C-Cl) and 673 cm$^{-1}$ (C-S-C), $^1$H-NMR (300 MHz, DMSO -$d_6$) δppm: 2.43(t,4H, CH2-N-CH2 of morpholin ring), 4.36(s,2H, of -$CH_2$CO), 4.35(t, 4H,CH2-O-CH2 of morpholin ring), 3.97 and 4.00(s, 2H, Ha,Hb of–CH2S),4.75(s,2H, of –N-CH2-N attached to indol ring), 5.40(s,1H, of –CH-N), 7.10-7.95(m, 9H, 8H, 4H of indol and 4H of -C6H5 nucleus),9.83(s,1H,CONH). $^{13}$C-NMR spectra(75MHz, DMSO-$d_6$)δ:128, 112, 121, 127, 123, 114,134, 129, 39,173,170,37,67,145,127,125,148,85,55,68 These are due to C1, C2, C3, C4, C5, C6, C7, C8, C9, C10,C11, C12, C13, C14, C15&C19, C16& C18, C17, C20,C21&C24, C22&C23 carbon atoms respectively.

7e : Molecular formula: $C_{25}H_{24}ClF_3N_4O_3S$, yield: 72%, M.P:212-4$^0$C, element found%

(calculated%): C 54.12(54.30); H 4.15(4.37); Cl 6.24(6.41); F 9.95(10.31); N 9.94(10.13); O 8.43(8.68); S 5.62(5.80), IR $\upsilon_{max}$ in cm$^{-1}$(Group): 2960cm$^{-1}$(-$CH_2$S), 1709cm$^{-1}$( -C=O of thiazo lidinone), 1187cm$^{-1}$(C-N) 723cm$^{-1}$ (C-Cl) and 670 cm$^{-1}$ (C-S-C), $^1$H-NMR (300 MHz, DMSO -$d_6$) δppm: 2.45(t,4H, CH2-N-CH2 of morpholin ring), 4.33(s,2H, of -CH2CO), 4.34(t, 4H,CH2-O-CH2 of morpholin ring), 3.97 and 4.00(s, 2H, Ha,Hb of–CH2S),4.75(s,2H, of –N-CH2-N attached to indol ring), 5.40(s,1H, of –CH-N), 7.05-7.75(m, 9H, 8H, 4H of indol and 4H of -C6H5 nucleus),9.85(s,1H,CONH). $^{13}$C-NMR spectra(75MHz, DMSO-$d_6$)δ: 128, 112, 121,127,123,114,134,129,39,173,168,37,67,143,127,124,127.5,123,85,55,69 These are due to to C1,C2,C3,C4,C5,C6,C7,C8, C9, C10,C11,C12,C13,C14,C15&C19,C16&C18,C17,C20,C21 , C22&C25,C23 &C24 carbon atoms respectively.

7f : Molecular formula: $C_{25}H_{28}ClN_5O_2S$, yield: 62%, M.P:177-9$^0$C, element found%

(calculated%): C 60.07(60.29); H 5.52(5.67); Cl 6.95(7.12); N 13.86(14.06); O 6.23(6.42); S 6.27(6.44), IR $\upsilon_{max}$ in cm$^{-1}$(Group): 2953cm$^{-1}$(-$CH_2$S), 1698cm$^{-1}$( -C=O of thiazo lidinone), 1187cm$^{-1}$(C-N) 721cm$^{-1}$ (C-Cl) and 667 cm$^{-1}$ (C-S-C), $^1$H-NMR (300 MHz, DMSO -$d_6$) δppm: 2.23(s,3H,N-CH3 of piperazine ring), 2.43 (t, 8H,-CH2-NCH2 of piperazine ring), 3.97 and 4.0 (s,2H, H, H of CH2S of thiazolidinone ring ), 4.75 (s, 2H of N-CH2-N attached to indole ring),7.10-7.80 (m,9H, 4H of indol and 5H of -C6H5 nucleus), 9.80 (s,1H, -CONH). $^{13}$C-NMR spectra(75MHz, DMSO-$d_6$)δ:128,112,121,127,123,114,134,129,39,173,17137.5,66,139,125,128, 127.5,75,55,58,43 These are due to C1,C2,C3,C4,C5,C6,C7,C8,C9,C10, C11, C12,C13,C14,C15 & C19,C16&C18,C17, C20,C21&C24,C22&C23 and C25 carbon atoms respectively.

7g : Molecular formula: $C_{25}H_{27}Cl_2N_5O_2S$, yield: 65%, M.P:185-7$^0$C, element found%

(calculated%): C 56.21(56.39); H 4.93(5.11); Cl 13.12(13.32); N 13.03(13.15); O 5.87 (6.01); S 5.85(6.02), IR $\upsilon_{max}$ in cm$^{-1}$(Group): 2956cm$^{-1}$(-$CH_2$S), 1700cm$^{-1}$( -C=O of thiazo lidinone), 1186cm$^{-1}$(C-N) 722cm$^{-1}$ (C-Cl) and 668 cm$^{-1}$ (C-S-C), $^1$H-NMR (300 MHz, DMSO -$d_6$) δppm: 2.23(s,3H,N-CH3 of piperazine ring), 2.43 (t, 8H,-CH2-NCH2 of piperazine ring), 3.95 and 4.0 (s,2H, H, H of CH2S of thiazolidinone ring ), 4.73 (s, 2H of N-CH2-N attached to indole ring), 7.10-7.85 (m,8H, 4H of indol and 4H of -C6H4 phenyl ring attached to -Cl), 9.80 (s,1H, -CONH). $^{13}$C-NMR spectra(75MHz, DMSO-$d_6$)δ: 128,112, 121,127,123, 115,134, 129,39,173,171,37.5,66,136,131,127,131,78,55,58,43 These are due to C1,C2,C3, C4, C5, C6, C7,C8,C9,C10,C11,C12,C13,C14,C15&C19,C16&C18, C17, C20, C21&C24,C22&C23 andC25 carbon atoms respectively.

7h : Molecular formula: $C_{25}H_{27}BrClN_5O_2S$, yield: 63%, M.P:188-9$^0$C, element found%

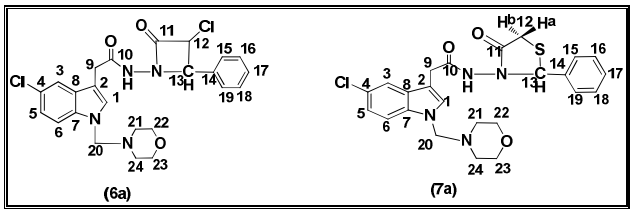
(calculated%): C 51.89(52.05); H 4.56(4.72); Br 13.67(13.85); Cl 6.02(6.15); N 11.97(12.14); O 5.38(5.55); S 5.40(5.56), IR $\upsilon_{max}$ in cm$^{-1}$(Group): 2955cm$^{-1}$(-$CH_2$S), 1705cm$^{-1}$( -C=O of thiazo lidinone), 1185cm$^{-1}$(C-N) 722cm$^{-1}$ (C-Cl) and 667 cm$^{-1}$ (C-S-C), $^1$H-NMR (300 MHz, DMSO -$d_6$) δppm: 2.23(s,3H,N-CH3 of piperazine ring), 2.43 (t, 8H,-CH2-NCH2 of piperazine ring), 3.96 and 4.0 (s,2H, H, H of -CH2S of thiazolidinone ring ), 4.73 (s, 2H of N-CH2-N attached to indole ring), 7.10-7.90 (m, 8H, 4H of indol and 4H of -C6H4 phenyl ring attached to -Br), 9.80(s,1H, -CONH). $^{13}$C-NMR spectra(75MHz, DMSO-$d_6$)δ:128, 112, 121,127,123,115,134,129,39,173,171,37.5,66,139,131,133,123,78,55,58,43 These are due to C1,C2,C3,C4, C5,C6,C7, C8, C9, C10, C11,C12,C13,C14,C15&C19,C16&C18, C17, C20, C21&C24,C22&C23andC25 carbon atoms respectively.

7i : Molecular formula: $C_{25}H_{27}ClN_6O_4S$, yield: 68%, M.P:217-9$^0$C, element found%

(calculated%): C 55.13(55.29); H 4.87(5.01); Cl 6.41(6.53); N 15.32(15.48); O 11.53(11.79); S 5.72(5.90), IR $\upsilon_{max}$ in cm$^{-1}$(Group): 2962cm$^{-1}$(-$CH_2$S), 1712cm$^{-1}$( -C=O of thiazo lidinone), 1188cm$^{-1}$(C-N) 725cm$^{-1}$ (C-Cl) and 673 cm$^{-1}$ (C-S-C), $^1$H-NMR (300 MHz, DMSO -$d_6$) δppm: 2.23(s,3H,N-CH3 of piperazine ring), 2.43 (t, 8H,-CH2-NCH2 of piperazine ring), 3.97 and 4.0 (s,2H, H, H of CH2S of thiazolidinone ring ), 4.76 (s, 2H of N-CH2-N attached to indole ring), 7.10-7.95 (m, 8H, 4H of indol and 4H of -C6H4 phenyl ring attached to -NO2), 9.80(s,1H, -CONH). $^{13}$C-NMR spectra(75MHz, DMSO-$d_6$)δ:128,112, 121,127, 123, 115, 134,129,39,173,171,37.5,66,146,127,122,148,78,55,58,43 These are due to C1,C2,C3,C4, C5,C6,C7, C8, C9, C10, C11,C12,C13,C14,C15&C19,C16&C18, C17, C20, C21&C24,C22&C23andC25 carbon atoms respectively.

7j : Molecular formula: $C_{26}H_{27}ClF_3N_5O_2S$, yield: 71%, M.P:213-5$^0$C, element found%

(calculated%): C 55.02(55.17); H 4.64(4.81); Cl 6.07(6.26); F 9.89(10.07); N 12.21(12.37); O 5.46(5.65); S 5.43(5.66), IR $\upsilon_{max}$ in cm$^{-1}$(Group): 2960cm$^{-1}$(-$CH_2$S), 1709cm$^{-1}$( -C=O of thiazo lidinone), 1187cm$^{-1}$(C-N) 723cm$^{-1}$ (C-Cl) and 670 cm$^{-1}$ (C-S-C), $^1$H-NMR (300 MHz, DMSO -$d_6$) δppm: 2.23(s,3H,N-CH3 of piperazine ring), 2.43 (t, 8H,-CH2-NCH2 of piperazine ring), 3.94 and 4.0 (s,2H, H, H of CH2S of thiazolidinone ring ), 4.75 (s, 2H of N-CH2-N attached to indole ring), 7.10-7.97 (m, 8H, 4H of indol and 4H of -C6H4 phenyl ring attached to -CF3), 9.80(s,1H, -CONH). $^{13}$C-NMR spectra(75MHz, DMSO-$d_6$)δ:128,112, 121, 127, 123,115,134,129,39,173,171,37.5,66,144,127,124,130,125,78,55,58,45These are due to C1,C2,C3,C4, C5,C6,C7,C8,C9,C10,C11,C12,C13,C14,C15&C19,C16&C18,C17,C20, C21, C22& C25, C23 &C24andC26 atoms respectively.




**Mass spectral details of compound 6a & compound 7a**

The mass spectra of 2-(5-chloro-1-(morpholinomethyl)-1H-indol-3-yl)-N-(3-chloro-2-oxo -4-phenylazetidin-1-yl)acetamide (6a) exhibited the molecular ion ($M^{+\bullet}$) peak at m/z = 486.12. The m/z value of molecular ion indicates that molecule is having even number of nitrogens. Base peak was at m/z=386.0(100%). The other prominent peaks were appeared at m/z 249 (77.5%), 263 (31.3%), 291(11.6% ), 306 (22.1%), 400 (26.4%), 409 (8.4%). Primery mass fragmentation pattern is shown in chart-I.

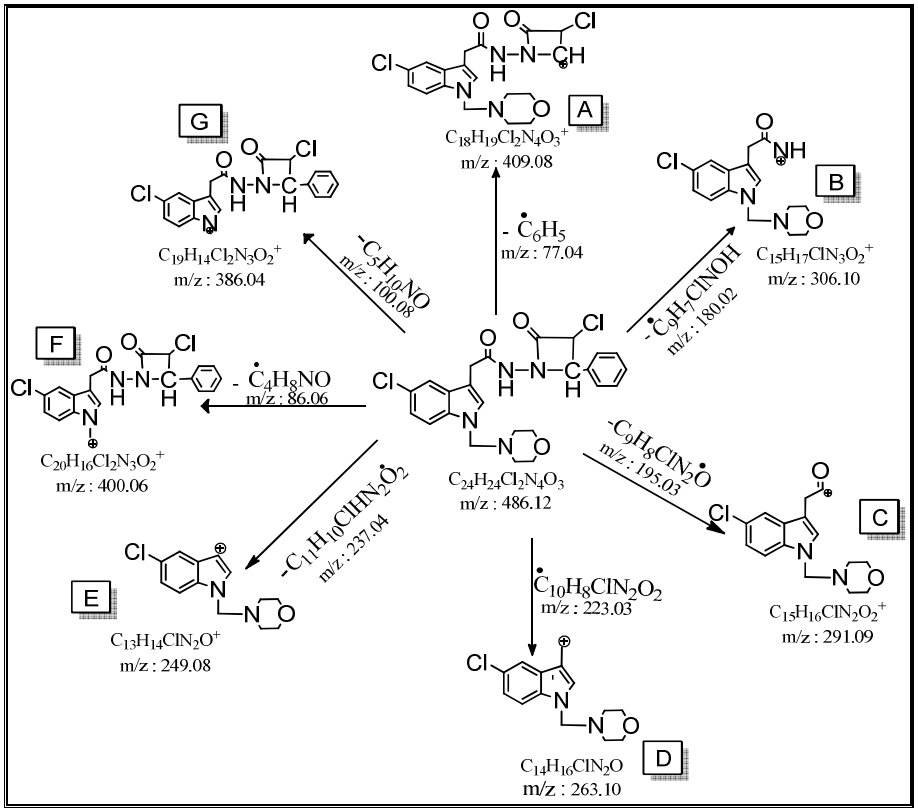



**Chart-I : Primery mass fragmentation pattern of 2-(5-chloro-1-(morpholinomethyl)-1H-indol-3-yl)-N-(3-chloro-2-oxo-4-phenylazetidin-1-yl)acetamide (6a)**

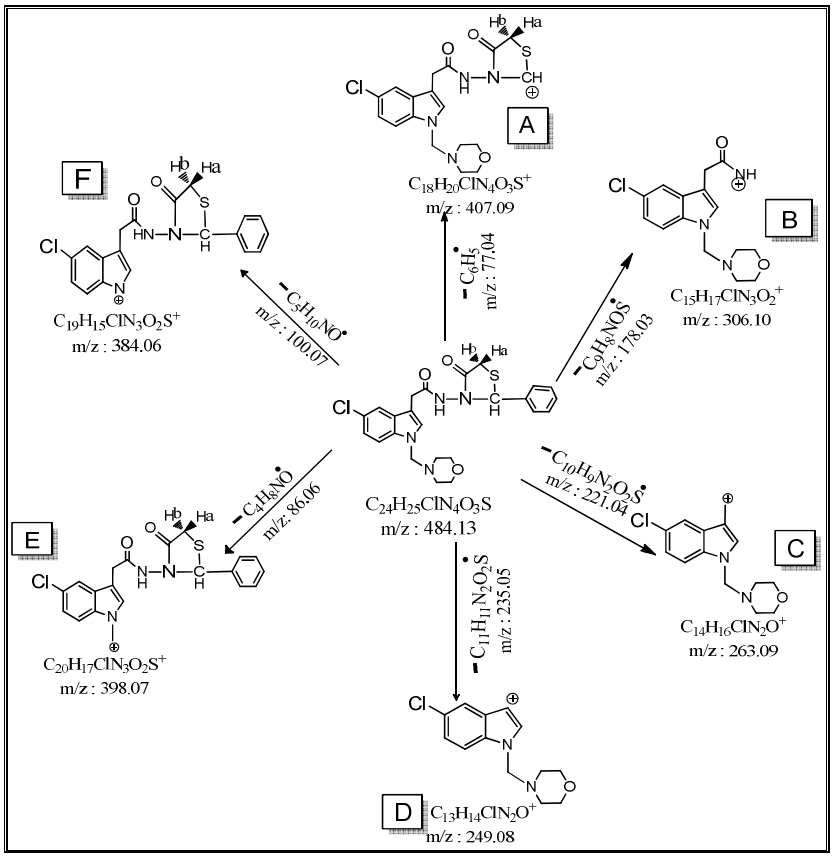



**Chart-II : Primery mass fragmentation pattern of 2-(5-chloro-1-(morpholinomethyl)-1H- indol-3-yl)-N-(4-oxo-2-phenylthiazolidin-3-yl)acetamide (7a)**

The mass spectra of 2-(5-chloro-1-(morpholinomethyl)-1H-indol-3-yl)-N-(4-oxo-2-phenylthiazolidin-3-yl)acetamide (7a) exhibited the molecular ion ($M^{+\bullet}$) peak at m/z = 484.13. The m/z value of molecular ion indicates that molecule is having even number of nitrogens. Base peak was at m/z= 384.06 (100%). The other prominent peaks were appeared at m/z 249 (77.7%), 263 (32.3%), 306 (9.5%), 398 (16.2%), 407 (12.4%). Primery mass fragmentation pattern is shown in chart-II.

**Antibacterial activity**

The antibacterial activity of synthesized compounds was studied by the disc diffusion method against the following pathogenic organisms. The gram +ve bacteria screened were Staphylococcus aureus (S.A) NCCS 2079 and Bacillus cereus (B.C) NCCS 2106. The gram _ve bacteria screened were Escherichia coli (E.Coli) NCCS 2065 and Pseudomonas aeruginosa (P.A) NCCS2200. The synthesized compounds were used at the concentration of 250 µg/ml using DMSO as a solvent. The amoxicillin 10 µg/disc and cefaclor 10 µg/disc were used as a standard (Himedia laboratories limited. Mumbai).

**Disc Diffusion Method**

A suspension of Staphylococcus aureus was added sterile nutrient agar at 45ºC. The mixture was transferred to sterile Petri dishes to give a depth of 3 to 4 mm and allowed to solidify. Precautions were observed to reduce uniform layer of medium on the plate. Sterile discs 5mm in diameter (made from Whatman Filter paper) were immersed in the solutions of synthesized compounds (250 µg/ml) and maintain an untreated control sample for comparison.Leave the plates to stand for 1hour at room temperature as a period of preincubation diffusion to minimize the effects of variations in different time. Then the plates were incubated at 37ºC for 24 hours and observed for antibacterial activity. The diameter of the zone of inhibition was measured for each plate in which the zone of inhibition was observed. The average zone of inhibition was calculated and compared with that of standard. A similar procedure was adopted for studying the antibacterial activity against the other organisms.

**Antifungal activity**

The antifungal activity of synthesized compounds were studied by disc diffusion method against the organisms of Aspergillus Niger (A.N) NCCS 1196 and Candida albicans (C.A) NCCS 3471. Compounds were treated at the concentrations of 250 µg/ml DMSO as a solvent. The standard used was ketoconazole 50 µg/ml against both the organisms.

**Table 1 Antimicrobial activity by disc diffusion method for Indole mannich bases having azetidin-2-one (4 a-j), thiazolidin-4-one (5 a-j).**

| S. No. | Compd. | Zone of Inhibition (mm) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Anti bacterial activity | | | | Anti fungal activity | |
| | | Staphylococcus aureus NCCS 2079 | Bacillus Cereus NCCS 2106 | EscherichiaColi NCCS 2065 | Pseudomonas Aeruginosa NCCS 2200 | Aspergillus niger NCCS 1196 | Candida albicans NCCS 3471 |
| 1) | 4a | 09 | 10 | 11 | 09 | 10 | 09 |
| 2) | 4b | 13 | 12 | 13 | 12 | 12 | 11 |
| 3) | 4c | 11 | 11 | 10 | 11 | 11 | 10 |
| 4) | 4d | 17 | 16 | 17 | 16 | 18 | 17 |
| 5) | 4e | 16 | 15 | 16 | 14 | 16 | 16 |
| 6) | 4f | 10 | 09 | 09 | 08 | 09 | 10 |
| 7) | 4g | 12 | 11 | 12 | 12 | 11 | 12 |
| 8) | 4h | 11 | 10 | 10 | 09 | 10 | 11 |
| 9) | 4i | 16 | 15 | 17 | 16 | 17 | 16 |
| 10) | 4j | 14 | 13 | 15 | 14 | 15 | 14 |
| 11) | 5a | 08 | 09 | 10 | 10 | 09 | 09 |
| 12) | 5b | 14 | 13 | 13 | 12 | 12 | 11 |
| 13) | 5c | 10 | 09 | 11 | 11 | 10 | 10 |
| 14) | 5d | 18 | 17 | 16 | 17 | 16 | 18 |
| 15) | 5e | 16 | 15 | 14 | 15 | 14 | 15 |
| 16) | 5f | 09 | 10 | 09 | 08 | 10 | 08 |
| 17) | 5g | 12 | 13 | 13 | 11 | 12 | 10 |
| 18) | 5h | 11 | 12 | 11 | 10 | 11 | 11 |
| 19) | 5i | 17 | 18 | 17 | 16 | 17 | 16 |
| 20) | 5j | 15 | 16 | 15 | 14 | 16 | 15 |
| 21) | Amoxicillin | 21 | 27 | 24 | 22 | -- | -- |
| 22) | Cefaclor | 19 | 22 | 19 | 20 | -- | -- |
| 23) | Ketoconazole | -------- | ------- | ------- | --------- | 23 | 26 |

**Disc Diffusion Method**

A suspension of Aspergillus Niger NCCS 1196 was added to sterile sabouraud dextrose agar at 45ºC. The mixture was transferred to sterile Petri dishes and allowed to solidify. Sterile discs 5 mm in diameter (made from Whatmann Filter paper) immersed in the solutions of synthesized compounds and control were placed on the surface of agar medium with forceps and pressed gently to ensure even contact. Leave the plates to stand for 1 hour at room temperature as a period of preincubation diffusion to minimize the effects of variation at 37ºC for 48 hours and observed for antibacterial activity. The diameters of the zone of inhibition were measured for the plates in which the zone of inhibition was observed. The average zone of inhibition was calculated with that of standard. A similar procedure was carried out for studying the antifungal activity the other organisms (Candida albicans).

In this series morpholin ring containing 4-nitro (4d / 5d) , 4-trifluoro methyl (4e / 5e) azitidinone and thiazolidinone compounds having high antibacterial and high antifungal activity than N-methyl piperizine ring containing compounds. Substituents activity $-NO_2$ > $-CF_3$ > -Cl > -Br > -H . It can be seen from **Table 1** that introduction of electron withdrawing group has significantly increases antimicrobial activity.

## Conclusion

A series of new class of novel indole mannich bases bearing β-lactone moiety/ thiazolidinone moiety have been reported. The compounds were characterized by elemental analysis data, IR, $H^1$-NMR, $^{13}C$- NMR and mass spectral data. The novel heterocycles were evaluated for THEIR antimicrobial profile. The mannich bases demonstrate to good antimicrobial activity against selected bacterial and fungal stains. It appeared from the preliminary investigations that the mannich bases with electron withdrawing substituents show high antimicrobial activity when compare to electron donating groups. The order of anti bacterial activity was 4d > 4e ≥ 4i > 4j > 4b ≥ 4g > 4c ≥ 4h > 4a >4f / 5d > 5e ≥ 5i > 5j > 5b ≥ 5g > 5c ≥ 5h > 5a >5f . The similar order for antifungal activity also.

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