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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF SOME NEWLY 1, 2, 4-TRIAZOLE DERIVATIVES

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Keywords:

1,2,4-triazoles, Indoles, Azetidinones, Thiazolidinones, Antibacterial activity, Antifungal activity

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ABSTRACT: A series of 1-(2-(4H-1,2,4-triazol-4-yl)ethylamino)-3-chloro-4-(5-methoxy/ehthoxy-2-substituted alkyl/aryl-1H-indol-3-yl)azetidinones (4a-4h) and 1-(2-(4H-1,2,4-triazol-4-yl) ethylamino)-3-chloro-4-(5-methoxy/ethoxy-2-substituted alkyl/aryl-1H-indol-3-yl) thiazolidinones (5a-5h) have been synthesized by the reaction of 3-((2-(2-(4H-1,2,4-triazol-4-yl)ethyl)hydrazono)methyl)-5-methoxy/ethoxy-2-substituted-1H-indoles (3a-3h) with chloroacetyl chloride and thioglycolic acid respectively. All the newly synthesized compounds were screened for their antibacterial activity against *S. aureus*, *E. coli*, *P. vulgaris*, *K. pneumonia* and antifungal activity against *A. fumigatus*, C. albicans, C. albicans ATCC and *C. krusei* G03. The antibacterial activity of newly synthesized compounds compared with standard drug gatifloxacin and ciprofloxacin against different bacteria and antifungal activity of new compounds compared with standard drug fluconazole against different fungi. The compounds 5d, 5e, 5g, and 5h exhibited good antibacterial activity while compounds 4g, 5g, and 5h also showed notable antifungal activity. The purity of the newly synthesized compounds was checked by thin-layer chromatography (TLC) on silica gel-G coated plates using different solvent systems. The structure of all the compounds was established by the elemental (C, H, N) and spectral (IR, ^{1}HNMR, and mass) analysis.

INTRODUCTION: The triazole ring is an important pharmacophore in modern drug discovery. The chemistry and pharmacology of triazoles have been of great interest to medicinal chemistry because its derivatives possessed various biological activities such as antimicrobial [1-3], anti-inflammatory [4], anticancer [5], anti-histaminic [6].

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Triazole derivatives having indole moiety are found to possess a wide spectrum of antimicrobial activity. A large number of indole derivatives [7-9] having substitution at 2, and 5 position increases the antimicrobial activity. Penicillins are the family of antimicrobial drugs which are derivatives of azetidinone [10].

Azetidinone derivatives have been reported to show a variety of antimicrobial [11-12], antituberculosis [13]. Thiazolidinone moiety with triazole ring increases the antimicrobial activity [14-16]. These all activities showed that the minor change in the substitution batter activities of azetidine and thiazolidine derivatives had enhanced dramatically, so our

research group decides to synthesized a new series azeti/thiazolidine derivatives with several substitutions.

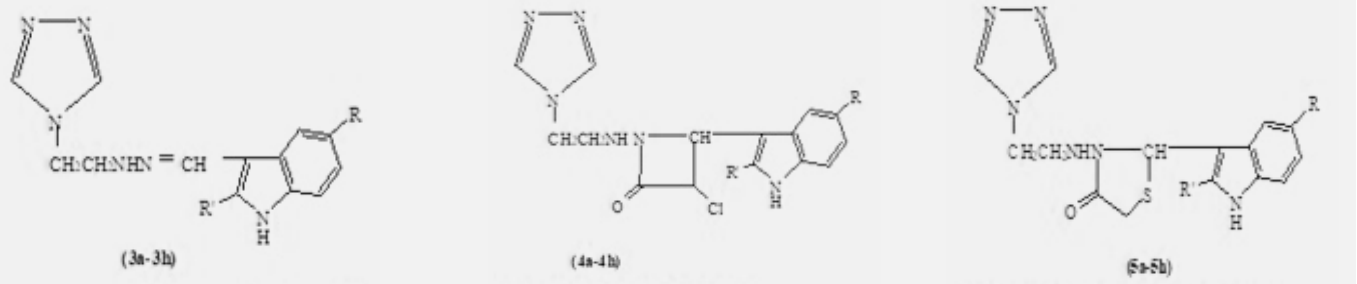
MATERIAL AND METHODS:

Antimicrobial Activity: All the newly synthesized compounds 3a-3h, 4a-4h, and 5a-5h were tested for their antimicrobial activity. The effects of unknown compounds were compared with the standard drug; gatifloxacin and ciprofloxacin for bacteria and fluconazole for fungi. The antimicrobial activity was assayed by using cup plate method Chuinkshank *et al.*, [17] by using the inhibition zones in mm. Antibacterial activity was performed against *Staphyloccus aureus, Escherischia coli, Proteus vulgaris, Klebsiella pneumoniae* and antifungal activity against *Aspergillus fumigatus, Candida albicans, Candida albicans* ATCC and *Candida krusei*.

Chemistry: All reagents and solvents were of analytical grade and used directly. Reactions were routinely performed in oven-dried borosil glassware. The melting points of compounds were determined in open capillaries with the help of thermonic melting point apparatus and were uncorrected. The homogeneity of all newly synthesized compounds was routinely checked by thin-layer chromatography (TLC) on silica gel G plates, and spots were located by using iodine chamber. Elemental analysis (C, H, N) of all the synthesized compounds were determined by Perkin-Elmer 2400 elemental analyzer, and results were found within the ± 0.4% of theoretical values. The IR spectra were recorded on a Beckman Acculab-10 spectrometer (ν max in cm^{-1}), and the ^1H NMR spectra were recorded by Brucker DPX-300 MHz using $CDCl_3$ as the solvent. Mass spectra were determined on VG-70-S instrument.

RESULTS AND DISCUSSION: All the newly synthesized compounds 3a-3h, 4a-4h, and 5a-5h, were tested for their antimicrobial activity. The pharmacological data of all the compounds have been reported in **Table 1**. The results revealed that the majority of the synthesized compounds showed varying degree of inhibition against the tested microorganism. The alkyl, phenyl and chlorophenyl substitution is beneficial for the antibacterial as well as antifungal activities. The methoxy and ethoxy substituent's on the indole nucleus increase the antimicrobial activity. Compounds having azetidinone and thiazolidinone moiety exhibited better antimicrobial activities. It can be seen in **Table 1,** although all the compounds are not as active as standard drugs. Compounds 5g was found more potent antibacterial agents against different bacteria with standard drug gatifloxacin and ciprofloxacin. Compounds 4e, 4g, 5a, 5b, 5d, 5e, 5f and 5h showed moderate activity and rest compounds showed less activity against all the strains. Compounds 5g (against *C. albicans*), 5h (against *C. albicans* ATCC), 4g, 5g and 5h (against *C. krusei* GO3) showed good antifungal activity compared with fluconazole.

TABLE 1: ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY OF THE COMPOUNDS 3a-3h, 4a-4h AND 5a-5h



Comp. no.	R	R'	Bacterial growth inhibition (diameter)				Fungal growth inhibition (diameter)			
			S. aureus	*E. coli*	*P. vulgaris*	*K. pneumoniae*	*A. fumigatus*	*C. albicans*	*C. albicans* ATCC	*C. krusei* G03
4a	OCH_3	H	16	-	18	17	-	18	16	-
4b	OC_2H_5	H	17	-	-	16	18	-	16	15
4c	OCH_3	CH_3	20	21	-	-	20	-	-	18
4d	OC_2H_5	CH_3	19	17	20	-	19	18	-	-
4e	OCH_3	C_6H_5	22	-	21	19	-	21	20	19
4f	OC_2H_5	C_6H_5	-	20	-	20	-	-	-	18
4g	OCH_3	C_6H_4Cl	21	-	-	-	20	-	-	20
4h	OC_2H_5	C_6H_4Cl	19	20	18	18	17	19	20	-

5a	OCH_3	H	22	-	19	-	-	20	-	19
5b	OC_2H_5	H	20	21	-	20	-	19	18	-
5c	OCH_3	CH_3	21	20	18	-	18	-	20	18
5d	OC_2H_5	CH_3	23	-	19	17	-	24	-	-
5e	OCH_3	C_6H_5	24	21	-	20	19	22	20	-
5f	OC_2H_5	C_6H_5	-	20	20	-	21	-	22	19
5g	OCH_3	C_6H_4Cl	28	24	21	22	-	30	23	21
5h	OC_2H_5	C_6H_4Cl	26	26	20	20	-	278	26	20
Ciprofloxacin			20	22	20	21	-	-	-	-
Gatifloxacin			25	22	20	21	-	-	-	-
Fluconazole			-	-	-	-	-	29	25	19

CONCLUSION: From this study, we may conclude that:

1. Compounds (5a-5h) containing thiazolidinone ring exhibited better antibacterial activity than compounds (4a-4h) having azetidinone ring.

2. Para chlorophenyl substituted indole derivatives showed more efficiency due to the presence of more electronegative atom.

Experimental Procedure: The synthetic route of the title compounds is outlined in Scheme 1, which are mentioned below as follows.

Synthesis of 4-(2-chloroethyl)-4H-1,2,4-triazole (1): A mixture of 1,2,4-triazole (1.0 mol) and 1-bromo-2-chloroethane (1.0 mol) was dissolved in acetone at room temperature. The reaction mixture was continuously stirred on a magnetic stirrer for about 8 h. The product was filtered, dried, and recrystallized from ethanol at room temperature to yield compound 1.

Yield 87%; mp 135 ºC; IR (KBr): 771 (C-Cl), 1261 (N-CH_2), 1298 (N-N), 1507 (C-N), 1680 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 3.47 (t, 2H, -CH_2Cl), 3.76 (t, 2H, -N-CH_2), 8.58 (s, 2H, -N=CH); MS: $[M]^+$ at m/z 131.56. Elemental analysis found (calculated) for $C_4H_6ClN_3$: C, 36.51 (36.52); H, 4.62 (4.60); N, 31.92 (31.94)%.

Synthesis of 4-(2-hydrazinylethyl)-4H-1,2,4-triazole (2): A mixture of compound **1** (1.0 mol) and hydrazine hydrate (1.0 mol) in methanol was refluxed on a steam bath for 4 h the excess solvent was removed under reduced pressure and the product crystallized from methanol to obtain compound 2.

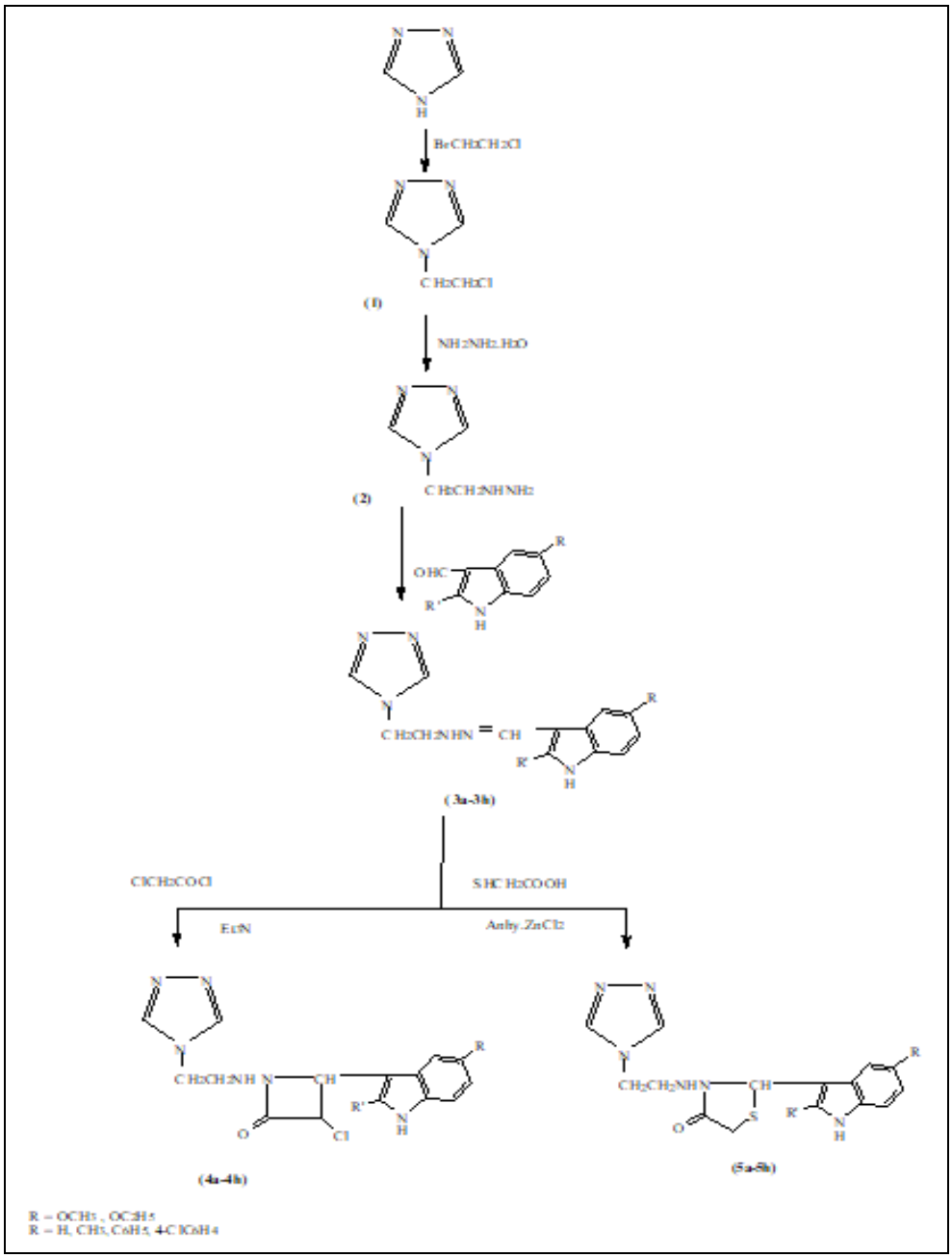
Yield 86%; mp 147 ºC; IR (KBr): 1261 (N-CH_2), 1298 (C-N), 1507 (N-N), 1682 (C=N) cm^{-1}; 1H-NMR (DMSO-d6 δ ppm): 3.32 (q, 2H, $NCH_2C\underline{H_2}$), 4.54 (t, 2H, -N-CH_2), 5.69 (d, 2H, NH_2), 7.60 (m, 1H, NH) 8.61 (s, 2H, -N=CH). MS: $[M]^+$ at m/z 127.15. Elemental analysis found (calclated) for $C_4H_9N_5$: C, 37.76 (37.79); H, 7.12 (7.13); N, 55.06 (55.08)%.

General procedure for the synthesis of 3-((2-(2-(4H-1,2,4-triazol-4-yl)ethyl)hydrazono)methyl)-5-methoxy/ethoxy-2-substituted-1H-indoles (3a-3h): In the ethanolic solution of compound 2 (0.8 mol) several substituted aryl/alkyl-5-methoxy/ ethoxy indol-3-aldehydes (1.0 mol) was added in the presence of glacial acetic acid. The reaction mixture was refluxed for 8-10 h. The completion of the reaction was checked by TLC. The excess of ethanol was distilled off. The reaction mixture was poured into ice water, filtered, washed with water, dried and recrystallized from ethanol to give title compounds.

3-((2-(2-(4H-1,2,4-triazol-4-yl)ethyl)hydrazono) methyl)-5-methoxy-1H-indole (3a): Yield 85%; (Acetone); mp 147 ºC; IR (KBr): 1261 (N-CH_2), 1298 (C-N), 1507 (N-N), 1576 (-N=CH), 1682 (C=N), 3323 (-C-NH) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 3.45 (s, 3H, OCH_3), 3.32 (q, 2H, $NCH_2C\underline{H_2}$), 4.56 (t, 2H, -N-CH_2), 7.50 (d, 1H, C-CH of pyrole ring of indole), 7.60 (m, 1H, CH_2NH), 7.69 (d, 1H, NH of indole), 7.71-8.31 (m, 3H, ArH), 8.61 (s, 2H, -N=CH of triazole), 8.85 (s, 1H, N=CH-indole); MS: $[M]^+$ at m/z 284.32. Elemental analysis found (calculated) for $C_{14}H_{16}N_6O$: C, 59.16 (59.14); H, 5.69 (5.67); N, 29.57 (29.56)%.

3-((2-(2-(4H-1,2,4-triazol-4-yl)ethyl)hydrazono) methyl)-5-ethoxy-1H-indole (3b): Yield 83%; (Methanol); mp 155 ºC; IR (KBr): 1263 (N-CH_2), 1297 (C-N), 1509 (N-N), 1577 (-N=CH), 1685 (C=N), 3324 (-C-NH) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 3.25 (s, 5H, OC_2H_5), 3.31 (q, 2H, NCH_2CH_2), 4.58 (t, 2H, -N-CH_2), 7.52 (d, 1H, C-

CH of pyrole ring of indole), 7.63 (m, 1H, CH_2NH), 7.66 (d, 1H, NH of indole), 7.71-8.30 (m, 3H, ArH), 8.63 (s, 2H, -N=CH of triazole), 8.83 (s, 1H, N=CH-indole); MS: $[M]^+$ at m/z 298.34. Elemental analysis found (calculated) for $C_{15}H_{18}N_6O$: C, 60.37 (60.39); H, 6.07 (6.08); N, 28.15 (28.17)%.



SCHEME 1: SYNTHETIC ROUTE OF TRIAZOLE DERIVATIVES

3-((2-(2-(4H-1,2,4-triazol-4-yl)ethyl)hydrazono) methyl)-5-methoxy-2-methyl 1H-indole (3c): Yield 82%; (Acetone); mp 157 ºC; IR (KBr): 1261 (N-CH_2), 1298 (C-N), 1507 (N-N), 1576 (-N=CH), 1682 (C=N), 2850 (CH_3 of indole), 3323 (-C-NH) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 2.23 (s, 3H, CH_3 of indole), 3.45 (s, 3H, OCH_3), 3.30 (q, 2H, NCH_2CH_2), 4.49 (t, 2H, -N-CH_2), 7.60 (m, 1H, CH_2NH), 7.68 (d, 1H, NH of indole), 7.70-8.31 (m, 3H, ArH), 8.65 (s, 2H, -N=CH of triazole), 8.84 (s, 1H, N=CH-indole); MS: $[M]^+$ at m/z 298.34. Elemental analysis found (calculated) for $C_{15}H_{18}N_6O$: C, 60.36 (60.39); H, 6.05 (6.08); N, 28.14 (28.17)%.

3-((2-(2-(4H-1,2,4-triazol-4-yl)ethyl)hydrazono) methyl)-5-ethoxy-2-methyl 1H-indole (3d): Yield 83%; (Ethanol); mp 165 ºC; IR (KBr): 1261 (N-

CH_2), 1298 (C-N), 1507 (N-N), 1576 (-N=CH), 1682 (C=N), 2850 (CH_3 of indole), 3323 (-C-NH) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 2.23 (s, 3H, CH_3 of indol), 3.45 (s, 5H, OC_2H_5), 3.31 (q, 2H, NCH_2CH_2), 4.50 (t, 2H, -N-CH_2), 7.62 (m, 1H, CH_2NH), 7.67 (d, 1H, NH of indole), 7.70-8.31 (m, 3H, ArH), 8.63 (s, 2H, -N=CH of triazole), 8.85 (s, 1H, N=CH-indole); MS: $[M]^+$ at m/z 312.37. Elemental analysis found (calculated) for $C_{15}H_{20}N_6O$: C, 61.50 (61.52); H, 6.43 (6.45); N, 26.91 (26.90)%.

3-((2-(2-(4H-1,2,4-triazol-4-yl)ethyl)hydrazono) methyl)-5-methoxy-2-phenyl 1H-indole (3e): Yield 82%; (Methanol); mp 172 ºC; IR (KBr): 1261 (N-CH_2), 1298 (C-N), 1507 (N-N), 1576 (-N=CH), 1610 (C=C of aromatic ring), 1682 (C=N), 3150 (CH aromatic), 3323 (-C-NH) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 3.45 (s, 3H, OCH_3), 3.31 (q, 2H, NCH_2CH_2), 4.51 (t, 2H, -N-CH_2), 7.60 (m, 1H, CH_2NH), 7.69 (d, 1H, NH of indole), 7.71-8.32 (m, 8H, ArH), 8.62 (s, 2H, -N=CH of triazole), 8.86 (s, 1H, N=CH-indole); MS: $[M]^+$ at m/z 360.41. Elemental analysis found (calculated) for $C_{20}H_{20}N_6O$: C, 66.67 (66.65); H, 5.57 (5.59); N, 23.30 (23.32)%.

3-((2-(2-(4H-1,2,4-triazol-4-yl)ethyl)hydrazono) methyl)-5-ethoxy-2-phenyl 1H-indole (3f): Yield 80%; (Acetone); mp 180 ºC; IR (KBr): 1261 (N-CH_2), 1298 (C-N), 1507 (N-N), 1576 (-N=CH), 1610 (C=C of aromatic ring), 1682 (C=N), 3150 (CH aromatic), 3323 (-C-NH) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 3.45 (s, 5H, OC_2H_5), 3.31 (q, 2H, NCH_2CH_2), 4.51 (t, 2H, -N-CH_2), 7.68 (d, 1H, NH of indole), 7.59 (m, 1H, CH_2NH) 7.70-8.31 (m, 8H, ArH), 8.63 (s, 2H, -N=CH of triazole), 8.84 (s, 1H, N=CH-indole); MS: $[M]^+$ at m/z 374.44. Elemental analysis found (calculated) for $C_{21}H_{22}N_6O$: C, 67.38 (67.36); H, 5.90 (5.92); N, 22.43 (22.44)%.

3-((2-(2-(4H-1,2,4-triazol-4-yl)ethyl)hydrazono) methyl)-5-methoxy-2-(4-chlorophenyl)1H-indole (3g): Yield 80%; (Ethanol); mp 195 ºC; IR (KBr): 770 (C-Cl), 1261 (N-CH_2), 1298 (C-N), 1507 (N-N), 1576 (-N=CH), 1610 (C=C of aromatic ring), 1682 (C=N), 3150 (CH aromatic), 3323 (-C-NH) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 3.45 (s, 3H, OCH_3), 3.34 (q, 2H, NCH_2CH_2), 4.57 (t, 2H, -N-CH_2), 7.60 (m, 1H, CH_2NH), 7.68 (d, 1H, NH of indole), 7.72-8.30 (m, 7H, ArH), 8.63 (s, 2H, -N=CH of triazole), 8.83 (s, 1H, N=CH-indole); MS: $[M]^+$ at m/z 394.86. Elemental analysis found (calculated) for $C_{20}H_{19}ClN_6O$: C, 60.82 (60.84); H, 4.83 (4.85); N, 21.26 (21.28)%.

3-((2-(2-(4H-1,2,4-triazol-4-yl)ethyl)hydrazono) methyl)-5-ethoxy-2-(4-chlorophenyl) 1H-indole (3h): Yield 78%; (Methanol); mp 178 ºC; IR (KBr): 770 (C-Cl), 1261 (N-CH_2), 1298 (C-N), 1507 (N-N), 1576 (-N=CH), 1610 (C=C of aromatic ring), 1682 (C=N), 3150 (CH aromatic), 3323 (-C-NH) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 3.45 (s, 5H, OC_2H_5), 3.31 (q, 2H, NCH_2CH_2), 4.55 (t, 2H, -N-CH_2), 7.60 (m, 1H, CH_2NH), 7.68 (d, 1H, NH of indole), 8.63 (s, 2H, -N=CH of triazole), 7.70-8.31 (m, 7H, ArH), 8.84 (s, 1H, N=CH-indole); MS: $[M]^+$ at m/z 408.88 Elemental analysis found (calculated) for $C_{21}H_{21}ClN_6O$: C, 61.67 (61.69); H, 5.16 (5.18); N, 20.57 (20.55)%.

General procedure for the synthesis of 1-(2-(4H-1,2,4-triazol-4-yl)ethylamino)-3-chloro-4-(5-methoxy/ethoxy-2-substituted alkyl/aryl-1H-indol-3-yl)azetidin-2-ones (4a-4h): A mixture of compounds 3a-3h (0.6 mol), dry dioxane (100 ml) and triethylamine (0.8 mol) were taking in round bottom flask. The reaction was stirred on an ice bath and when temperature dropped below 0-5 ºC, then chloroacetylchloride (0.10 mol) was added dropwise with stirring. After completion of addition, the stirring was further continued for 6 h. at room temperature. The reaction mixture was then kept a side for 48 h. Finally, the reaction mixture was added to ice cold water to obtain the desired product. The products were dried and purified by recrystallization from methanol to yield title compounds.

1-(2-(4H-1,2,4-triazol-4-yl)ethylamino)-3-chloro-4-(5-methoxy-1H-indol-3-yl)azetidin-2-one (4a): Yield 76%; (Acetone); mp 197 ºC; IR (KBr): 772 (C-Cl), 1261 (N-CH_2), 1298 (C-N), 1507 (N-N), 1576 (-N=CH), 1682 (C=N), 1755 (C=O), 3323 (-C-NH) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 3.32 (q, 2H, NCH_2CH_2), 3.45 (s, 3H, OCH_3), 4.56 (t, 2H, -N-CH_2), 4.60 (s, 1H, CH-Cl), 7.60 (m, 1H, CH_2NH), 7.69 (d, 1H, NH of indole), 7.50 (d, 1H, C-CH of pyrole ring of indole), 7.71-8.31 (m, 3H, ArH), 8.61 (s, 2H, -N=CH of triazole), 8.85 (s, 1H, N-CH-azetidinone); MS: $[M]^+$ at m/z 360.80

Elemental analysis found (calculated) for $C_{16}H_{17}ClN_6O_2$: C, 53.28 (53.26); H, 4.74 (4.75); N, 23.25 (23.29)%.

1-(2-(4H-1,2,4-triazol-4-yl)ethylamino)-3-chloro-4-(5-ethoxy-1H-indol-3-yl)azetidin-2-one (4b): Yield 73%; (Ethanol); mp 189 ºC; IR (KBr): 772 (C-Cl), 1261 (N-CH_2), 1298 (C-N), 1507 (N-N), 1576 (-N=CH), 1682 (C=N), 1755 (C=O), 3323 (-C-NH) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 3.32 (q, 2H, NCH_2CH_2), 3.45 (s, 5H, OC_2H_5), 4.56 (t, 2H, -N-CH_2), 4.60 (s, 1H, CH-Cl), 7.60 (m, 1H, CH_2NH) 7.65 (d, 1H, NH of indole), 7.50 (d, 1H, C-CH of pyrole ring of indole), 7.71-8.31 (m, 3H, ArH), 8.61 (s, 2H, -N=CH of triazole), 8.85 (s, 1H, N-CH-azetidinone); MS: $[M]^+$ at m/z 374.82 Elemental analysis found (calculated) for $C_{17}H_{19}ClN_6O_2$: C, 54.49 (54.47); H, 5.10 (5.11); N, 22.43 (22.42)%.

1-(2-(4H-1,2,4-triazol-4-yl)ethylamino)-3-chloro-4-(5-methoxy-2-methyl-1H-indol-3-yl)azetidin-2-one (4c): Yield 71%; (Methanol); mp 187 ºC; IR (KBr): 772 (C-Cl), 1261 (N-CH_2), 1298 (C-N), 1507 (N-N), 1576 (-N=CH), 1682 (C=N), 1755 (C=O), 2854 (CH_3), 3323 (-C-NH) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 2.28 (s, 3H, CH_3 of indole), 3.32 (q, 2H, NCH_2CH_2), 3.45 (s, 3H, OCH_3), 4.50 (t, 2H, -N-CH_2), 4.60 (s, 1H, CH-Cl), 7.60 (m, 1H, CH_2NH), 7.66 (d, 1H, NH of indole), 7.70-8.31 (m, 3H, ArH), 8.63 (s, 2H, -N=CH of triazole), 8.87 (s, 1H, N-CH-azetidinone); MS: $[M]^+$ at m/z 374.82 Elemental analysis found (calculated) for $C_{17}H_{19}ClN_6O_2$: C, 54.48 (54.47); H, 5.12 (5.11); N, 22.41 (22.42)%.

1-(2-(4H-1,2,4-triazol-4-yl)ethylamino)-3-chloro-4-(5-ethoxy-2-methyl-1H-indol-3-yl)azetidin-2-one (4d): Yield 69%; (Acetone); mp 201 ºC; IR (KBr): 772 (C-Cl), 1261 (N-CH_2), 1298 (C-N), 1507 (N-N), 1576 (-N=CH), 1682 (C=N), 1755 (C=O), 3323 (-C-NH) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 2.28 (s, 3H, CH_3 of indole), 3.32 (q, 2H, NCH_2CH_2), 3.35 (s, 5H, OC_2H_5), 4.56 (t, 2H, -N-CH_2), 4.60 (s, 1H, CH-Cl), 7.60 (m, 1H, CH_2NH), 7.69 (d, 1H, NH of indole), 7.71-8.30 (m, 3H, ArH), 8.61 (s, 2H, -N=CH of triazole), 8.84 (s, 1H, N-CH-azetidinone); MS: $[M]^+$ at m/z 388.85.

Elemental analysis found (calculated) for $C_{18}H_{21}ClN_6O_2$: C, 55.62 (55.60); H, 5.46 (5.44); N, 21.62 (21.61)%.

1-(2-(4H-1,2,4-triazol-4-yl)ethylamino)-3-chloro-4-(5-methoxy-2-phenyl-1H-indol-3-yl)azetidin-2-one (4e): Yield 67%; (Ethanol); mp 195 ºC; IR (KBr): 772 (C-Cl), 1261 (N-CH_2), 1298 (C-N), 1507 (N-N), 1576 (-N=CH), 1610 (C=C of aromatic ring), 1682 (C=N), 1755 (C=O), 3153 (CH Aromatic), 3323 (-C-NH) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 3.35 (q, 2H, NCH_2CH_2), 3.45 (s, 3H, OCH_3), 4.56 (t, 2H, -N-CH_2), 4.60 (s, 1H, CH-Cl), 7.50 (m, 1H, CH_2NH), 7.64 (d, 1H, NH of indole), 7.73-8.31 (m, 8H, ArH), 8.61 (s, 2H, -N=CH of triazole), 8.83 (s, 1H, N-CH-azetidinone); MS: $[M]^+$ at m/z 436.89. Elemental analysis found (calculated) for $C_{22}H_{21}ClN_6O_2$: C, 60.49 (60.48); H, 4.83 (4.84); N, 19.26 (19.24)%.

1-(2-(4H-1,2,4-triazol-4-yl)ethylamino)-3-chloro-4-(5-ethoxy-2-phenyl-1H-indol-3-yl)azetidin-2-one (4f): Yield 65%; (Acetone); mp 225 ºC; IR (KBr): 775 (C-Cl), 1262 (N-CH_2), 1297 (C-N), 1507 (N-N), 1576 (-N=CH), 1610 (C=C of aromatic ring), 1682 (C=N), 1755 (C=O), 3153 (CH Aromatic), 3323 (-C-NH) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 3.25 (s, 5H, OC_2H_5), 3.52 (q, 2H, NCH_2CH_2), 4.76 (t, 2H, -N-CH_2), 4.60 (s, 1H, CH-Cl), 7.60 (m, 1H, CH_2NH), 7.69 (d, 1H, NH of indole), 7.71-8.31 (m, 8H, ArH), 8.61 (s, 2H, -N=CH of triazole), 8.86 (s, 1H, N-CH-azetidinoe); MS: $[M]^+$ at m/z 450.92. Elemental analysis found (calculated) for $C_{23}H_{23}ClN_6O_2$: C, 61.24 (61.26); H, 5.16 (5.14); N, 18.62 (18.64)%.

1-(2-(4H-1,2,4-triazol-4-yl)ethylamino)-3-chloro-4-(5-methoxy-2-chlorophenyl-1H-indol-3-yl) azetidin-2-one (4g): Yield 65%; (Methanol); mp 211 ºC; IR (KBr): 770 (C-Cl), 1265 (N-CH_2), 1293 (C-N), 1502 (N-N), 1575 (-N=CH), 1615 (C=C of aromatic ring), 1684 (C=N), 1753 (C=O), 3152 (CH Aromatic), 3321 (-C-NH) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 3.31 (q, 2H, NCH_2CH_2), 3.47 (s, 3H, OCH_3), 4.57 (t, 2H, -N-CH_2), 4.72 (s, 1H, CH-Cl), 7.60 (m, 1H, CH_2NH), 7.67 (d, 1H, NH of indole), 7.70-8.30 (m, 7H, ArH), 8.62 (s, 2H, -N=CH of triazole), 8.83 (s, 1H, N-CH-azetidinone); MS: $[M]^+$ at m/z 471.34. Elemental analysis found (calculated) for $C_{22}H_{20}Cl_2N_6O_2$: C, 56.04 (56.06); H, 4.27 (4.28); N, 17.81 (17.83)%.

1-(2-(4H-1,2,4-triazol-4-yl)ethylamino)-3-chloro-4-(5-ethoxy-2-chlorophenyl-1H-indol-3-yl)azetidin-2-one (4h): Yield 63%; (Ethanol); mp

227^0C; IR (KBr): 772 (C-Cl), 1261 (N-CH_2), 1298 (C-N), 1507 (N-N), 1576 (-N=CH), 1610 (C=C of aromatic ring), 1682 (C=N), 1755 (C=O), 3153 (CH Aromatic), 3323 (-C-NH) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 3.32 (q, 2H, NCH_2CH_2), 3.40 (s, 5H, OC_2H_5), 4.53 (t, 2H, -N-CH_2), 4.67 (s, 1H, CH-Cl), 7.55 (m, 1H, CH_2NH), 7.69 (d, 1H, NH of indole), 7.71-8.31 (m, 7H, ArH), 8.61 (s, 2H, -N=CH of triazole), 8.85 (s, 1H, N-CH-azetidinone); MS: $[M]^+$ at m/z 485.37. Elemental analysis found (calculated) for $C_{23}H_{22}Cl_2N_6O_2$: C, 56.90 (56.92); H, 4.59 (4.57); N, 17.30 (17.31)%.

General procedure for the synthesis of 3-(2-(4H-1,2,4-triazol-4-yl)ethylamino)-2-(5-methoxy/ ethoxy-2-substituted alkyl/aryl-1H-indol-3-yl) thiazolidin-4-ones (5a-5h): In a ethonolic solution of compounds (4a-4h) (0.4 mol), thioglycolic acid (0.8 mol) was added in the presence of anhydrous zinc chloride. The reaction mixture was refluxed for 15 h. The excess of solvent was distilled off and separated solid was poured into ice water, filtered, washed with water and recrystallized from ethanol to yield title compounds.

3-(2-(4H-1,2,4-triazol-4-yl)ethylamino)-2-(5-methoxy-1H-indol-3-yl)thiazolidin-4-one (5a): Yield 61%; (Methanol); mp 239 ºC; IR (KBr): 684 (C-S-C), 1260 (N-CH_2), 1296 (C-N), 1509 (N-N), 1575 (-N=CH), 1685 (C=N), 1758 (C=O), 3155 (CH Aromatic), 3321 (-C-NH) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 3.45 (s, 3H, OCH_3), 3.60 (q, 2H, NCH_2CH_2), 3.75 (s, 2H, CH_2 of thiazolidinone), 4.75 (t, 2H, -N-CH_2), 6.64 (s, 1H, N-CH of thiazolidinone), 7.62 (m, 1H, CH_2NH), 7.68 (d, 1H, NH of indole), 7.70-8.30 (m, 3H, ArH), 8.61 (s, 2H, -N=CH of triazole), 8.84 (s, 1H, N-CH-indole); MS: $[M]^+$ at m/z 358.42. Elemental analysis found (calculated) for $C_{16}H_{18}N_6O_2S$: C, 53.64 (53.62); H, 5.07 (5.06); N, 23.48 (23.45)%.

3-(2-(4H-1,2,4-triazol-4-yl)ethylamino)-2-(5-ethoxy -1H-indol-3-yl)thiazolidin-4-one (5b): Yield 60%; (Ethanol); mp 253 ºC; IR (KBr): 686 (C-S-C), 1263 (N-CH_2), 1296 (C-N), 1503 (N-N), 1576 (-N=CH), 1685 (C=N), 1751 (C=O), 3152 (CH Aromatic), 3321 (-C-NH) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 3.35 (s, 5H, OC_2H_5), 3.42 (q, 2H, NCH_2CH_2), 3.73 (s, 2H, CH_2 of thiazolidinone), 4.76 (t, 2H, -N-CH_2), 6.68 (s, 1H, N-CH of thiazolidinone), 7.52 (m, 1H, CH_2NH), 7.65 (d, 1H, NH of indole), 7.71-8.31 (m, 3H, ArH), 8.64 (s, 2H, -N=CH of triazole), 8.85 (s, 1H, N-CH-indole); MS: $[M]^+$ at m/z 372.44. Elemental analysis found (calculated) for $C_{17}H_{20}N_6O_2S$: C, 54.80 (54.82); H, 5.40 (5.41); N, 22.58 (22.56)%.

3-(2-(4H-1,2,4-triazol-4-yl)ethylamino)-2-(5-methoxy-2-methyl-1H-indol-3-yl)thiazolidin-4-one (5c): Yield 58%; (Acetone); mp 247 ºC; IR (KBr): 683 (C-S-C), 1265 (N-CH_2), 1298 (C-N), 1507 (N-N), 1576 (-N=CH), 1682 (C=N), 1755 (C=O), 2857 (CH_3), 3158 (CH Aromatic), 3323 (-C-NH) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 2.26 (s, 3H, CH_3), 3.32 (q, 2H, NCH_2CH_2), 3.42 (s, 2H, CH_2 of thiazolidinone), 3.67 (s, 3H, OCH_3), 3.79 (t, 2H, -N-CH_2), 6.65 (s, 1H, N-CH of thiazolidinone), 7.50 (m, 1H, CH_2NH), 7.66 (d, 1H, NH of indole), 7.73-8.31 (m, 3H, ArH), 8.61 (s, 2H, -N=CH of triazole); MS: $[M]^+$ at m/z 372.44. Elemental analysis found (calculated) for $C_{17}H_{20}N_6O_2S$: C, 54.81 (54.82); H, 5.43 (5.41); N, 22.55 (22.56)%.

3-(2-(4H-1,2,4-triazol-4-yl)ethylamino)-2-(5-ethoxy-2-methyl-1H-indol-3-yl)thiazolidin-4-one (5d): Yield 57%; (Methanol); mp 252 ºC; IR (KBr): 685 (C-S-C), 1261 (N-CH_2), 1294 (C-N), 1505 (N-N), 1573 (-N=CH), 1686 (C=N), 1758 (C=O), 2856 (CH_3), 3154 (CH Aromatic), 3320 (-C-NH) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 2.27 (s, 3H, CH_3), 3.35 (s, 5H, OC_2H_5), 3.45 (q, 2H, NCH_2CH_2), 3.55 (s, 2H, CH_2 of thiazolidinone), 4.68 (t, 2H, -N-CH_2), 6.65 (s, 1H, N-CH of thiazolidinone), 7.61 (m, 1H, CH_2NH), 7.67 (d, 1H, NH of indole), 7.72-8.30 (m, 3H, ArH), 8.64 (s, 2H, -N=CH of triazole); MS: $[M]^+$ at m/z 386.47. Elemental analysis found (calculated) for $C_{18}H_{22}N_6O_2S$: C, 55.93 (55.94); H, 5.75 (5.74); N, 21.73 (21.75)%.

3-(2-(4H-1,2,4-triazol-4-yl)ethylamino)-2-(5-methoxy-2-phenyl-1H-indol-3-yl)thiazolidin-4-one (5e): Yield 54%; (Ethanol); mp 243 ºC; IR (KBr): 680 (C-S-C), 1264 (N-CH_2), 1289 (C-N), 1509 (N-N), 1574 (-N=CH), 1615 (C=C of aromatic ring), 1682 (C=N), 1758 (C=O), 3156 (CH Aromatic), 3328 (-C-NH) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 3.40 (s, 3H, OCH_3), 3.50 (q, 2H, NCH_2CH_2) 3.74 (s, 2H, CH_2 of thiazolidinone), 4.74 (t, 2H, -N-CH_2), 6.69 (s, 1H, N-CH of thiazolidinone), 7.60 (m, 1H, CH_2NH), 7.67 (d, 1H,

NH of indole), 7.71-8.33 (m, 8H, ArH), 8.63 (s, 2H, -N=CH of triazole); MS: $[M]^+$ at m/z 434.51. Elemental analysis found (calculated) for $C_{22}H_{22}N_6O_2S$: C, 60.80 (60.81); H, 5.12 (5.10); N, 19.36 (19.34)%.

3-(2-(4H-1,2,4-triazol-4-yl)ethylamino)-2-(5-ethoxy-2-phenyl-1H-indol-3-yl)thiazolidin-4-one (5f): Yield 52%; (Acetone); mp 224 ºC; IR (KBr): 683 (C-S-C), 1265 (N-CH_2), 1294 (C-N), 1501 (N-N), 1574 (-N=CH), 1615 (C=C of aromatic ring), 1686 (C=N), 1759 (C=O), 3158 (CH Aromatic), 3324 (-C-NH) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 3.20 (s, 5H, OC_2H_5), 3.39 (q, 2H, NCH_2CH_2) 3.70 (s, 2H, CH_2 of thiazolidinone), 4.75 (t, 2H, -N-CH_2), 6.65 (s, 1H, N-CH of thiazolidinone), 7.53 (m, 1H, CH_2NH), 7.65 (d, 1H, NH of indole), 7.70-8.31 (m, 8H, ArH), 8.63 (s, 2H, -N=CH of triazole); MS: $[M]^+$ at m/z 448.54. Elemental analysis found (calculated) for $C_{23}H_{24}N_6O_2S$: C, 61.57 (61.59); H, 5.37(5.39); N, 18.76 (18.74)%.

3-(2-(4H-1,2,4-triazol-4-yl)ethylamino)-2-(5-methoxy-2-chlorophenyl-1H-indol-3-yl)thiazolidin-4-one (5g): Yield 50%; (Methanol); mp 169 ºC; IR (KBr): 681 (C-S-C), 772 (C-Cl), 1261 (N-CH_2), 1298 (C-N), 1507 (N-N), 1576 (-N=CH), 1610 (C=C of aromatic ring), 1682 (C=N),1755 (C=O), 3153 (CH Aromatic), 3323 (-C-NH) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 3.32 (q, 2H, NCH_2CH_2), 3.45 (s, 3H, OCH_3), 3.72 (s, 2H, CH_2 of thiazolidinone), 4.56 (t, 2H, -N-CH_2), 6.68 (s, 1H, N-CH of thiazolidinone), 7.56 (m, 1H, CH_2NH), 7.66 (d, 1H, NH of indole), 7.71-8.31 (m, 7H, ArH), 8.61 (s, 2H, -N=CH of triazole); MS: $[M]^+$ at m/z 468.96. Elemental analysis found (calculated) for $C_{22}H_{21}ClN_6O_2S$: C, 56.34 (56.35); H, 4.53 (4.51); N, 17.91 (17.92)%.

3-(2-(4H-1,2,4-triazol-4-yl)ethylamino)-2-(5-ethoxy-2-chlorophenyl-1H-indol-3-yl)thiazolidin-4-one (5h): Yield 47%; (Ethanol); mp 178 ºC; IR (KBr): 682 (C-S-C), 770 (C-Cl), 1260 (N-CH_2), 1295 (C-N), 1504 (N-N), 1572 (-N=CH), 1612 (C=C of aromatic ring), 1680 (C=N),1753 (C=O), 3151 (CH Aromatic), 3321 (-C-NH) cm^{-1}; ^{1}H-NMR (DMSO-d6 δ ppm): 3.26 (s, 5H, OC_2H_5), 3.36 (q, 2H, NCH_2CH_2), 3.71 (s, 2H, CH_2 of thiazolidinone), 3.74 (t, 2H, -N-CH_2), 6.67 (s, 1H, N-CH of thiazolidinone), 7.56 (m, 1H, CH_2NH), 7.68 (d, 1H, NH of indole),7.72-8.30 (m, 7H, ArH), 8.60 (s, 2H, -N=CH of triazole); MS: $[M]^+$ at m/z 482.99. Elemental analysis found (calculated) for $C_{23}H_{23}ClN_6O_2S$: C, 57.22 (57.20); H, 4.81 (4.80); N, 17.42 (17.40) %.

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