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Synthesis and Anti-inflammatory Activity of 4-Substituted-2,5-Disubstituted Indolyl Azetidine-3-yl/Thiazolidin-1-yl-Substituted Triazoles

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Abstract. A new series of 4-[2′-(substituted phenyl)-5′-methoxy indolyl azetidine-1-yl/thiazolin-1-yl-3-(substituted phenyl)-5-mercapto-1,2,4-triazoles were designed, synthesized and tested for anti-inflammatory and analgesic activities. All compounds were screened *in vitro* for anti-inflammatory activity against carrageenan induced rat paw oedema and tested for their analgesic activity against phenyl quinone induced pain syndrome in mice at a dose of 50 mg/kg p.o. All the compounds of this series have been analyzed and confirmed by elemental (C, H, N) and spectral methods, i.e. I.R., ^{1}H-NMR, ^{13}C NMR and mass spectrometry data.

Keywords: 1,2,4-triazole, indolylazetidinoyl, indolylthiazolidinoyl, anti-inflammatory activity, analgesic activity

Introduction

Non steroidal anti-inflammatory drugs (NSAIDS) are a heterogeneous family of pharmacologically active compounds used in the treatment of acute and chronic inflammation, pain and fever. Heterocyclics, bearing a symmetrical 1,2,4-triazole moiety, are reported to possess a broad spectrum of pharmacological properties such as anti-inflammatory (Braccio *et al*., 2008; Metwally *et al*., 2008), analgesic (Goksen *et al*., 2007), antimicrobial (Kavegoudae *et al*., 2008) and anticonvulsant (Srivastava *et al*., 2002). A survey of literature revealed that 1,2,4-triazole has received much attention during recent years on account of their prominent utilization as antifungal (Reddy *et al*., 2008), analgesic (Mohd *et al*., 2007) and anti-inflammatory agents (Dunder *et al*., 2007). Substitution at third and fourth position of 1,2,4-triazole heterocyclic ring by aromatic/heterocyclic moieties plays a pivotal role in modulating the anti-inflammatory activity. Moreover, the substitution of indolyl/azetidinonyl/thiazolidinonyl moieties at different heterocyclic nuclei remarkably change the anti-inflammatory activity. Hence, synthesis of some new derivatives of 1,2,4-triazole was undertaken by incorporating indolyl/azetidinonyl/thiazolidinonyl moieties in a singular frame in the hope of finding better anti-inflammatory agents.

Chemistry

The target 1,2,4-triazole derivatives were synthesized according to Scheme 1. The reaction of substituted acid hydrazides with hydrazine hydrate in ethanol afforded the corresponding substituted potassium di-thiocarbazinates in high yields (85-90%). The di-thiocarbazinates were converted to 1-amino-5-mercapto-1,2,4-triazole **(3a-d)** using hydrazine hydrate in water (63-70%). 4-((Amino methylene)-(2′-substituted phenyl)-5′′-methoxyindol-3′-yl)-3(substituted phenyl)-5-mercapto-1,2,4-triazole **(4a-h)** were prepared by the reaction of substituted 1,2,4-triazoles with 2-substituted phenyl-5-meythoxy indol-3-aldehydes in absolute ethanol (50-60%). To reaction mixture of compounds **(4a-h)** in dry benzene and chloroacetyl chloride triethylamine was added and 4-((5′′-methoxy-2′′-substituted phenylindole-3′′yl)-(3′-chloro-2′-oxoazetidin-1′yl))-3-substituted phenyl-5-mercapto-1,2,4-triazoles **(5a-h)** (41-48%) was obtained. 4-(5′′-methoxy-2′′-substituted phenyl indole-3′′yl)-(2'-oxothiazolin-1′yl)-3-substituted phenyl-5-mercapto-1,2,4-triazoles **(6a-h)** were synthesized by the mixture of compounds **4a-h** and thioglycolic acid in the presence of a pinch of anhydrous zinc chloride in methanol (35-45%). The purities of all synthesized compounds were determined by thin layer chromatography using several solvent systems of different polarity.

Materials and Methods

All reagents and solvents were generally used as received from the commercial supplier. Reactions were routinely performed in oven dried glassware. Melting points were determined with an electro-thermal melting point apparatus and are uncorrected. The homogeneity of all newly synthesized compounds was checked by thin layer chromatography (TLC) on silica gel G coated plates. The eluent was a mixture of different solvents in different proportions and spots were visualized under iodine chamber.

General procedure for the preparation of substituted acid hydrazides (1). The ester of substituted acids (0.1 mol) was dissolved in ethanol (10 ml) and hydrazine hydrate (0.1 mol)

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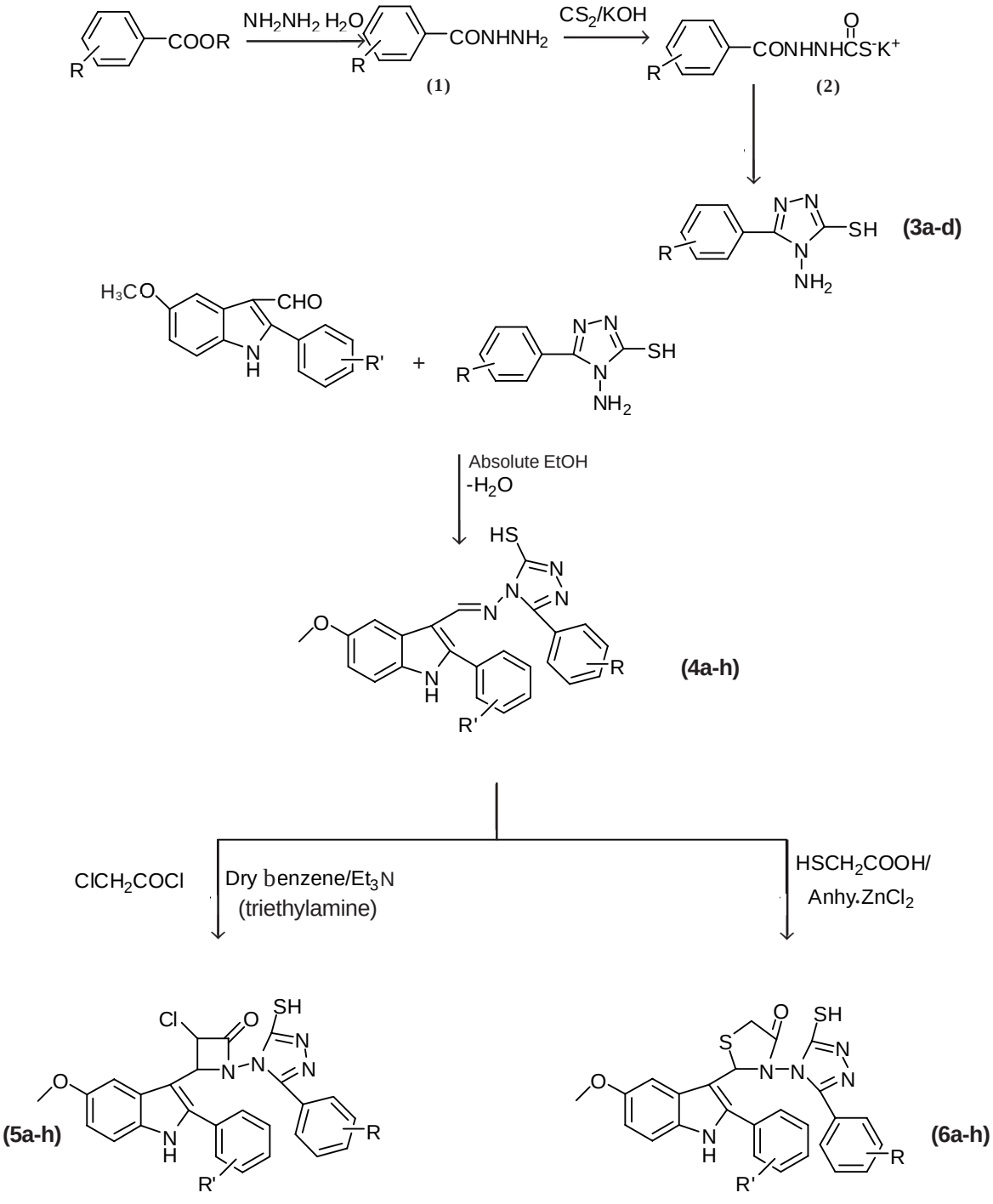
was added drop wise to the solution with stirring. The resulting mixture was allowed to reflux for 6 hs; the excess ethanol was distilled off and the contents were allowed to cool. The crystals formed were filtered, washed thoroughly with water and dried. Progress of the reaction was monitored on TLC using silica gel G coated plates while ethyl acetate and petroleum ether (1:1) were used as eluent. The plates were observed in UV light and substituted acid hydrazides were obtained.

General procedure for the preparation of substituted acid potassium dithio-carbazinates (2). Potassium hydroxide (0.15 mol) was dissolved in absolute ethanol (200 ml). To the



Scheme 1

above solution, substituted acid hydrazides (0.2 mol) were added. The solution was cooled in ice and carbon disulphide (0.15 mol) was added to it in small quantities with constant stirring. The reaction mixture was stirred continuously for a period of 15 hs. It was then diluted with anhydrous ether. The precipitated potassium dithio carbazinate was collected by filtration. The precipitate was further washed with anhydrous ether (100 ml) and dried under vacuum. The potassium salt thus obtained was in quantitative yield and was used in the next step without further purification. Other substituted compounds (**2a-2h**) were prepared similarly.

General procedure for the preparation of 3-substituted-4-amino-5-mercapto-1,2,4-triazole (3a-h). Suspensions of potassium dithiocarbazinates of respective aromatic esters (0.1 mol) in water (5 ml) (0.3 mol) were refluxed for 6-7 hs with occasional shaking The colour of the reaction mixtures changed to green with the evolution of hydrogenous reaction mixtures which were obtained during the reaction process. The reaction mixtures were cooled to room temperature and diluted with concentrated hydrochloric acid. The triazoles formed were precipitated, filtered, washed thoroughly with cold water and recrystallized from ethanol. Progress of the reaction was monitored on TLC by using silica gel G coated plates while ethyl acetate and petroleum ether (1:1) were used as the eluent. The plates were observed in UV light.

3-(2-Hydroxyphenyl)-4-amino-5-mercapto-1,2,4 triazole (3a). Yield: 65%; mp: 215 °C; IR (KBr): ν(cm^{-1}) (3420 (OH), 3130 (aromatic C-H), 2972, 2810 (methyl C-H str), 2584(S-H) 1608(C=N), 1545 (C=C aromatic ring), 1280(N-N); ^{1}H NMR: δ(ppm) 3.65 (s, 1H, 3H), 5.73(s, 2H,NH2), 7.18-8.10(m, 4H, ArH), 10.85(s,1H,OH exchangeable). ^{13}C NMR($CDCl_3$) δ:117.8, 118.5, 121.9, 130. 5, 132.1, 148.1, 154.1, 167.1, Mass, M^+at m/z 208. Anal. Calcd. for $C_8H_8N_4OS$: C, 46.15; H, 3.87; N, 26.91. Found: C, 46.40; H, 3.72; N, 26.98.

4-Amino-3-(4-N,N-dimethylaminophenyl)-5-mercapto1,2,4-triazole (3b). Yield: 63%; mp: 243-244 °C; IR (KBr): ν(cm^{-1}) 3313 (NH stretching), 2978, 2813 (methyl C-H str), 2586(S-H), 1609(C=N), 1540(C=C stretching)1322(C-N stretching); ^{1}HNMR: δ(ppm) 2.98(s, 6H, $N(CH_3)_2$), 5.72 (s,2H,NH_2), 6.82-7.96 (d, 4H, Ar-H), 13.65(s, 1H, SH). ^{13}C NMR($CDCl_3$) δ: 40.2, 40.2, 112.7, 113.1, 12 0.1, 128. 4, 1289.5, 148.1, 155.3, 167.1. Mass, M^+at m/z 235. Anal. Calcd. for $C_{10}H_{13}N_5S$: C, 51.10; H, 5.56; N, 29.76. Found: C, 50.26; H, 5.66; N, 29.85.

4-Amino-3-(2-chlorophenyl)-5-mercapto-1,2,4-triazole (3c). Yield: 70%; mp: 258 °C; IR (KBr): ν(cm^{-1}) 3310 (NH stretching), 2970, 2815 (methyl C-H str), 2565 (S-H),1610(C=N), 1552 (C=C stretching); ^{1}H NMR: δ(ppm) 5.73(s,2H,NH_2), 6.90-7.98(m, 4H, Ar-H), 13.58(s,1H,SH). ^{13}C NMR ($CDCl_3$) δ:127.3, 128.9, 129.3, 130.5, 132.8, 139.6, 148.1, 161.1. Mass, M^+at m/z 226 Anal. Calcd. for $C_8H_7N_4SCl$: C, 42.33; H, 3.33; N, 24.68. Found: C, 42.62; H, 3.25; N, 24.64.

4-Amino-3-(2-methoxyphenyl)-5-mercapto-1,2,4-triazole (3d). Yield: 67%; mp: 238-239 °C; IR (KBr): ν(cm^{-1}) 3315 (NH stretching), 2970, 2810(methyl C-H str), 2567(S-H), 1616(C=N), 1550(C=C stretching); ^{1}HNMR: δ(ppm) 3.40 (s, 3H, OCH_3), 5.70(s, 2H, NH_2), 6.85-7.93(m,4H, ArH), 13.55(s, 1H, SH). ^{13}C NMR ($CDCl_3$) δ:56.1, 116.2, 116.8, 121.5, 129.7, 131.8, 148.4, 157.5, 167.1. Mass, M^+at m/z 250 Anal. Calcd. for $C_8H_{10}N_4SO$: C, 45.70; H, 4.79; N, 26.65. Found: C, 45.82; H, 4.72; N, 26.73.

General procedure for the preparation of 4-(amino methylene-2′-substituted phenyl)-5-mercapto-1,2,4-triazole (4a-h). An equimolar (0.01 mol) mixture of 2-substituted phenyl-5-methoxy-indol-3-aldehyde and substituted triazoles **3(a-d)** in absolute ethanol (100 ml) containing 2-3 drops of glacial acetic acid were refluxed for 4 hs and excess solvent removed. The solid was separated, filtered and recrystallized from appropriate solvent.

4-(Aminomethylene)-2′-(4″-chlorophenyl)-5′-methoxy indol-3′yl))-3-(2-hydroxyphenyl)-5-mercapto-1,2,4 triazole (4a). Yield: 58%; mp: 170 °C; IR (KBr): ν(cm^{-1})3425(O-H stretching), 3132(aromatic C-H stretching), 3350(NH stretching), 2580 (S-H), 1618(C=N), 1560 C=C stretching), 1280 (N-N stretching); ^{1}H NMR: δ(ppm) 3.43 (s, 3H, OCH_3), 6.72(s, 1H, CH=N-N), 6.80-7.90(m, 11H, ArH), 9.10(s, 1H, NH, indolic exchangeable), 10.96(s, 1H, phenolic), 13.50 (s,1H, SH).^{13}C NMR($CDCl_3$) δ:55.8, 102.2, 104.5, 112, 112.4, 118.5, 123.7, 123.9, 127.5, 129.9, 131.1, 134.3, 148.2, 148.5, 154, 156.5. Mass, M^+at m/z 475. Anal. Calcd. for $C_{24}H_{18}N_5SO_2Cl$: C, 60.56; H, 3.81; N, 14.71. Found: C, 60.62; H, 3.76; N, 14.76.

4-((Aminomethylene)-2′-(4″-chlorophenyl)-5'-methoxy indol-3′yl))-3-(4-N,N-dimethyl aminophenyl)-5-mercapto-1,2,4 triazole (4b). Yield: 55%; mp: 184 °C; IR (KBr): ν(cm^{-1}) 3350 (NH stretching), 3135(aromatic C-H stretching), 2584(S-H), 1620(C=N), 1556 (C=C stretching), 1282(N-N stretching); ^{1}HNMR: δ(ppm)2.95(s, 6H, $N(CH_3)_2$, 3.40(s, 3H, OCH_3), 6.60(s, 1H, CH=N-N), 6.82-7.92 (m, 11H, ArH), 9.12(s, 1H, NH indolic exchangeable), 13.55(s, 1H, SH). ^{13}C NMR($CDCl_3$) δ:40.5, 40.8, 55.6, 102.4, 104.5, 112.8, 112.9, 118.5, 119, 123.7, 123.9, 129.9, 130.1, 134.3, 148.2, 147.5, 154, 155, 155.5. Mass, M^+at m/z 503. Anal. Calcd. for $C_{26}H_{23}N_6SOCl$: C, 62.21; H, 4.60; N, 16.70. Found: C, 62.27; H, 4.52; N, 16.78.

4-((Aminomethylene)-2′-(4″-chlorophenyl)-5′-methoxyindol-3′yl))-3-(2-chlorophenyl)-5-mercapto-1,2,4 triazole (4c). Yield: 52%; mp: 206-208 °C; IR(KBr): ν(cm^{-1}) 3352(NH stretching), 2586(S-H), 1622(C=N), 1558(C=C stretching), 1285(N-N

stretching); ^{1}H NMR δ(ppm). 3.41 (s, 3H, OCH_3), 6.74(s, 1H, CH=N-N), 6.86-7.95(m, 11H, Ar-H), 9.15(s, 1H, NH, indolic exchangeable), 13.52(s, 1H, SH). ^{13}C NMR($CDCl_3$) δ:55.8, 102.4, 104.5, 112.6, 112.9, 118.9, 119, 123.7, 123.9, 129.3, 131.1, 132.3, 138.5, 148.2, 148.5, 154, 155, 156.9. Mass, M^+at m/z 462. Anal. Calcd. for $C_{24}H_{17}N_5SOCl_2$: C, 62.33; H, 3.70; N, 15.14. Found: C, 62.28; H, 3.65; N, 15.22.

4-((Aminomethylene)-2′-(4″-chlorophenyl)-5′-methoxy indol-3′yl))-3-(2-methoxyphenyl)-5-mercapto-1,2,4 triazole (4d). Yield: 56%; mp: 182 °C; IR(KBr): ν(cm^{-1}) 3348(N-H stretching), 2580(S-H), 1625(C=N), 1555(C=C stretching), 1284(N-N stretching); ^{1}H NMR: δ(ppm) 3.30(s,6H, 2 $XOCH_3$), 6.70(s, 1H, CH=NN), 6.88-7.82(m, 11H, ArH), 9.13(s, 1H, NH, indolic exchangeable), 13.46(s, 1H, SH). ^{13}C NMR($CDCl_3$) δ:55.4, 56.1, 102.6, 104.8, 112.6, 112.9, 116, 116.7, 118.9, 119, 123.7, 123.9, 129.3, 131.1, 132.3, 138.5, 148.2, 148.5, 154, 155, 156.9, 157.3. Mass, M^+at m/z 490. Anal. Calcd. for $C_{25}H_{20}N_5SO_2Cl$: C, 61.28; H, 4.11; N, 14.29. Found: C, 61.34; H, 4.15; N, 14.34.

4-((Aminomethylene)-2′-(4″-bromophenyl)-5′-methoxyindol-3′yl))-3-(2-hydroxyphenyl)-5-mercapto-1,2,4 triazole (4e). Yield: 50%; mp: 168 °C; IR (KBr): ν(cm^{-1}) 3425(O-H stretching), 3132(aromatic C-H stretching), 3350 (NH stretching), 2580(S-H), 1618(C=N), 1560 (C=C stretching), 1280(N-N stretching); ^{1}H NMR: δ(ppm) 3.43 (s, 3H, OCH_3), 6.72(s, 1H, CH=N-N), 6.80-7.90(m, 11H, ArH), 9.10(s, 1H, NH, indolic exchangeable), 10.96(s, 1H, phenolic), 13.50(s, 1H, SH). ^{13}C NMR ($CDCl_3$) δ:102.6, 104.8, 112.8, 112.9, 116, 116.7, 118.9, 119, 123.7, 123.9, 129.3, 131.1, 132.1, 132.2, 138.5, 148.2, 148.5, 154, 155, 156.9. Mass, M^+at m/z 534. Anal. Calcd. for $C_{24}H_{18}N_6SO_2Br$: C, 53.94; H, 3.39; N, 15.72. Found: C, 53.81; H, 3.42; N, 15.75.

4-((Aminomethylene)-2′-(4″-bromophenyl)-5′-methoxyindol-3′yl))-3-(4-N,N-dimethylaminophenyl)-5-mercapto-1,2,4-triazole (4f). Yield: 53%; mp: 180 °C; IR(KBr): ν(cm^{-1}) 3350 (NH stretching), 3135(aromatic C-H stretching), 2584(S-H), 1620(C=N), 1556(C=C stretching), 1282(N-N stretching); ^{1}H NMR: δ(ppm)2.95 (s, 6H, $N(CH_3)_2$), 3.40(s, 3H, OCH_3), 6.60 (s, 1H, CH =N-N), 6.82-7.92(m, 11H, Ar-H), 9.12(s, 1H, NH indolic exchangeable), 13.55(s, 1H, SH). ^{13}C NMR($CDCl_3$) δ:40, 40.4, 55.4, 55.1, 102.6, 104.8, 112.5, 112.9, 116, 116.5, 118.9, 119, 122.7, 123.9, 128.3, 131.1, 132.3, 135.5, 144.2, 145.5, 154, 155, 156.9, 155. Mass, M^+at m/z 547. Anal. Calcd. for $C_{26}H_{23}N_6SOBr$: C, 57.04; H, 4.23; N, 15.35. Found: C, 57.12; H, 4.29; N, 15.30.

4-((Aminomethylene)-2′-(4″-bromophenyl)-5′-methoxy indol-3′yl))-3-(2-chlorophenyl)-5-mercapto-1,2,4 triazole (4g). Yield: 60%; mp: 200-201 °C; IR (KBr): ν(cm^{-1}) 3352 (NH stretching), 2586(S-H), 1622(C=N), 1558(C=C stretching), 1285(N-N stretching); ^{1}H NMR: δ(ppm). 3.41(s, 3H, OCH_3), 6.74(s, 1H, CH=N-N), 6.86-7.95(m, 11H, Ar-H), 9.15(s, 1H, NH indolic exchangeable), 13.52(s, 1H,SH). ^{13}C NMR ($CDCl_3$) δ:55.8, 102. 6, 104.6, 112.6, 112.9, 116, 116.7, 118.5, 119, 123.7, 123.9, 129.5, 131.1, 132.6, 138.8, 148, 148.5, 155.2, 156.6. Mass, M^+at m/z 618 Anal. Calcd. for $C_{24}H_{17}N_5SOClBr_2$: C, 46.58; H, 2.77; N, 11.32. Found: C, 46.52; H, 2.85; N, 11.37.

4-((Aminomethylene)-2′-(4″-bromophenyl)-5′-methoxy indol-3′yl))-3-(2-methoxyphenyl)-5-mercapto-1,2,4-triazole (4h). Yield: 54%; mp: 174 -175 °C; IR (KBr): ν(cm^{-1}) 3348 (N-H stretching), 2580(S-H), 1625(C=N), 1555(C=C stretching), 1284(N-N stretching); ^{1}H NMR: δ(ppm) 3.30(s, 6H, 2$XOCH_3$), 6.70(s, 1H, CH=N-N), 6.88-7.82(m, 11H, Ar-H), 9.13(s,1H,NH indolic exchangeable), 13.46(s, 1H, SH). ^{13}C NMR($CDCl_3$) δ:56.1, 102.6, 104.8, 112.6, 112.9, 116, 116.7, 118.9, 119, 123.7, 123.9, 129.5, 132.1, 132.5, 138.5, 148.7, 148.9, 154, 155, 156.9, 157.5. Mass, M^+at m/z 534. Anal. Calcd. for $C_{25}H_{20}N_5SO_2Br$: C, 56.19; H, 3.77; N, 13.10. Found: C, 56.26; H, 3.70; N, 13.16.

General procedure for the preparation of 4-((5′′-methoxy-2′′-substituted phenyl indole-3′′yl)-(3′-chloro-2′-oxoazetidin-1′yl))-3-substituted phenyl-5-mercapto-1,2,4-triazoles 5(a-h). To a solution of **(4a-h)** (0.005 mol) in dry benzene (50 ml), chloroacetyl chloride (0.005 mol) was added followed by the addition of tertiary amine (0.006 mol). The reaction mixtures were refluxed for 4 hs, excess solvent was removed and the residue was treated with petroleum ether at 60-80 °C followed by water. The solid thus obtained was filtered and recrystallized from the appropriate solvent.

4-((5′′-methoxy-2′′-(4′′′-chlorophenyl indole-3′′yl)-(3′-chloro-2′-oxoazetidin-1′yl))-3-(hydroxyphenyl)-5-mercapto-1,2,4-triazoles (5a). Yield: 47%; mp: 220 °C; IR (KBr): ν(cm^{-1}) 3345 (N-H stretching), 3142(aromatic C-H stretching), 3050, 2850(methylene C-H str), 2584(S-H), 1710(C=O), 1650(N-C=O), 1610(C=N), 1285(N-N stretching); ^{1}H NMR: δ(ppm) 3.30(s, 3H, OCH_3), 4.65(s, 1H, COCHCl), 6.60 (s, 1H, CH=N-N), 6.85-7.80(m, 11H, Ar-H), 9.10(s, 1H, NH indolic exchangeable), 13.50 (s, 1H, SH). ^{13}C NMR ($CDCl_3$) δ:55.5, 102.6, 104.6, 112.8, 1 12.9, 116, 117.7, 118.93, 121, 123.7, 127.9, 128.3, 129, 130.1, 131.8, 134.2, 138.5, 147.2, 148.5, 154, 154.4. Mass, M^+at m/z 552. Anal. Calcd. for $C_{26}H_{19}N_5SO_3Cl_2$: C, 56.52; H, 3.46; N, 12.67. Found: C, 56.58; H, 3.40; N, 12.74.

4-((5′′-methoxy-2′′-(4′′′-chlorophenylindole-3′′yl)-(3′-chloro-2′-oxoazetidin-1′yl))-3-(4-N,N-dimethylaminophenyl)-5-mercapto-1,2,4-triazoles (5b). Yield: 41%; mp: 245-246 °C; IR (KBr): ν(cm^{-1}) 3340 (N-H stretching), 3140(aromatic C-H stretching), 3045, 2845(methylene C-H str), 2582(S-H), 1712(C=O), 1645(N-C=O), 1612(C=N), 1280(N-N stretching); ^{1}H NMR; δ(ppm) 2.90(s, 6H, $N(CH_3)_2$), 3.32(s, 3H, OCH_3), 4.62(s, 1H, COCHCl), 6.64(s, 1H, CH=NN), 6.82, 7.805 (m, 11H, ArH), 9.12(s, 1H, NH indolic exchangeable), 13.45 (s, 1H,SH). ^{13}C NMR

($CDCl_3$) δ:40.5, 40.4, 56.5, 102.3, 104.6, 1 12.6, 112.8, 116.2, 117.2, 118.9, 121.5, 123.7, 127.9, 128.3, 129.8, 130.1, 131.8, 134.2, 138.5, 147.2, 148.5, 151.5. Mass, M+at m/z 579. Anal. Calcd. for $C_{28}H_{24}N_6SO_2Cl_2$: C, 58.02; H, 4.17; N, 14.50. Found: C, 58.10; H, 4.13; N, 14.57.

4-((5′′-methoxy-2′′-(4′′′-chlorophenylindole-3′′yl)-(3′-chloro-2′-oxoazetidin-1′yl))-3-(2-chlorophenyl)-5-mercapto-1,2,4-triazoles (5c). Yield: 44%; mp: 248 °C; IR (KBr): ν(cm^{-1}) 3135(aromatic C-H stretching), 3045,2840(methylene C-H stretching), 2586 (S-H), 1715 (C=O), 1615(C=N), 1280(N-N stretching); ^{1}H NMR: δ(ppm) 3.32 (s, 3H, OCH_3), 4.60 (s, 1H, COCHCl), 6.70 (s, 1H, CH=N-N), 6.82-7.85(m, 11H, Ar-H), 9.05(s, 1H, NH indolic exchangeable), 13.52(s, 1H, SH). ^{13}C NMR($CDCl_3$) δ:55.8, 104.8, 112.5, 112.9, 123.4, 123.9, 127.3, 129.4, 129.7, 131.1, 132.4, 132.2, 138.8, 148.2, 148.3, 154, 156.4. Mass, M^+at m/z 570. Anal. Calcd. for $C_{26}H_{18}N_5SO_2Cl_3$: C, 54.78; H, 3.18; N, 12.84. Found: C, 54.72; H, 3.25; N, 12.80.

4-((5′′-methoxy-2′′-(4′′′-chlorophenylindole-3′′yl)-(3′-chloro-2′-oxoazetidin-1′yl))-3-(2-methoxyphenyl)-5-mercapto-1,2,4-triazoles (5d). Yield: 46%; mp: 235 °C; IR (KBr): ν(cm^{-1}) 3330 (N-H stretching), 3135(aromatic C-H stretching), 3040, 2852(methylene C-H str), 2586(S-H), 1712(C=O), 1652(N-C=O), 1618(C=N), 1281(N-N stretching); ^{1}H NMR: δ(ppm) 3.30(s, 3H, OCH_3), 3.25(s, 3H, Ar CH_3), 4.62 (s, 1H, COCHCl), 6.65(s, 1H, CH=N-N), 6.80-7.70(m, 11H, Ar-H), 9.02(s, 1H, NH indolic exchangeable), 13.40(s, 1H, SH). ^{13}C NMR($CDCl_3$) δ:55.5, 56.2, 104, 112.8, 112.9, 116, 116.5, 123, 123.4, 127.3, 129.4, 129.8, 131.1, 132.1, 134.2, 138.5, 148.2, 148.5, 154, 155, 156.9, 157.3. Mass, M^+at m/z 566. Anal. Calcd. for $C_{27}H_{21}N_5SO_3Cl_2$: C, 57.24; H, 3.73; N, 12.36. Found: C, 57.32; H, 3.78; N, 12.31.

4-((5′′-methoxy-2′′-(4′′′-bromophenylindole-3′′yl))-(3′-chloro-2′-oxoazetidin-1′yl))-3-(hydroxy phenyl)-5-mercapto-1,2,4-triazoles (5e). Yield: 48%; mp: 218 °C; IR (KBr): ν(cm^{-1}) 3345 (N-H stretching), 3142(aromatic C-H stretching), 3050, 2850 (methylene C-H str), 2584(S-H), 1710(C=O), 1650(N-C=O), 1610(C=N), 1285(N-N stretching); ^{1}H NMR: δ(ppm) 3.30(s, 3H, OCH_3), 4.65(s, 1H, COCHCl), 6.60(s, 1H, CH=N-N), 6.85-7.80(m, 11H, Ar-H), 9.10(s, 1H, NH indolic exchangeable), 13.50(s, 1H, SH); ^{13}C NMR($CDCl_3$) δ:102, 104.8, 112.8, 112.9, 116, 117.7, 118.3, 119, 121.7, 123.9, 129.3, 131.1, 132.1, 132.2, 138.5, 148.2, 148.5, 154.4, 155, 155.9. Mass, M^+at m/z 596. Anal. Calcd. for $C_{26}H_{19}N_5SO_3ClBr$: C, 52.31; H, 3.20; N, 11.73. Found: C, 52.26; H, 3.25; N, 11.67.

4-((5′′-methoxy-2′′-(4′′′-bromophenylindole-3′′yl))-(3′-chloro-2′-oxoazetidin-1′yl))-3-(4-N,N-dimethylaminophenyl)-5-mercapto-1,2,4-triazoles (5f). Yield: 45%; mp: 238 °C; IR (KBr): ν(cm^{-1}) 3340 (N-H stretching), 3140(aromatic C-H stretching), 3045, 2845(methylene C-H str), 2582(S-H), 1712(C=O), 1645(N-C=O), 1612(C=N), 1280(N-N stretching); ^{1}H NMR: δ(ppm) 2.90(s, 6H, $N(CH_3)_2$), 3.32(s, 3H, OCH_3), 4.62(s, 1H, COCHCl), 6.64(s, 1H, CH=N-N), 6.82-7.85(m, 11H, Ar-H), 9.12(s, 1H, NH indolic exchangeable), 13.45(s, 1H, SH). ^{13}C NMR ($CDCl_3$) δ:44.5, 4 0.8, 102.4, 104.8, 112.8, 112.9, 116, 116.7, 118.9, 119, 123.1, 123.8, 129.3, 131.1, 132.2, 132.4, 138.5, 148.2, 148.5, 154, 154, 155.9. Mass, M^+at m/z 624. Anal. Calcd. for $C_{28}H_{24}N_6SO_2Cl$ Br: C, 53.89; H, 3.88; N, 13.47. Found: C, 53.96; H, 3.81; N, 13.42.

4-((5′′-methoxy-2′′-(4′′′-bromophenylindole-3′′yl)-(3′-chloro-2′-oxoazetidin-1′yl))-3-(2-chlorophenyl-5-mercapto-1,2,4-triazoles (5g). Yield: 42%; mp: 240 °C; IR (KBr): ν(cm^{-1}) 3135 (aromatic C-H stretching), 3045, 2840(methylene C-H stretching), 2586(S-H), 1715(C=O), 1615(C=N), 1280(N-N stretching); ^{1}H NMR: δ(ppm) 3.32(s, 3H, OCH_3), 4.60(s, 1H, C OCHCl), 6.70(s, 1H, CH=N-N), 6.82-7.85 (m, 11H, Ar-H), 9.05(s, 1H, NH indolic exchangeable), 13.52(s, 1H,SH); ^{13}C NMR ($CDCl_3$) δ:55. 7, 102, 104.8 , 112.5, 112.7 , 116, 116.7, 118.9, 119, 123.7, 123.9, 129.3, 131.1, 132.1, 132.2, 138.5, 145.2, 147.5, 154, 154.8, 154.9. Mass, M^+at m/z 615. Anal. Calcd. for $C_{26}H_{18}N_5SO_2Cl_2$ Br: C, 50.74; H, 2.95; N, 11.38. Found: C, 50.82; H, 2.90; N, 11.42.

4-((5′′-methoxy-2′′-(4′′′-bromophenylindole-3′′yl)-(3′-chloro-2′-oxoazetidin-1′yl))-3-(2-methoxyphenyl)-5-mercapto-1,2,4-triazoles (5h). Yield: 43%; mp: 215 °C; IR (KBr): ν(cm^{-1}) 3330 (N-H stretching), 3135(aromatic C-H stretching), 3040, 2852 (methylene C-H str), 2586(S-H), 1712(C=O), 1652(N-C=O), 1618(C=N), 1281(N-N stretching); ^{1}H NMR: δ(ppm) 3.30(s, 3H, OCH3), 3.25(s, 3H, Ar CH3), 4.62(s, 1H, COCHCl), 6.65(s, 1H, CH=N-N), 6.80-7.70(m, 11H, Ar-H), 9.02(s, 1H, NH indolic exchangeable), 13.40(s, 1H, SH). ^{13}C NMR ($CDCl_3$) δ: 55, 56.1, 102.2, 1 04.8, 112.8, 112.9, 116.2, 116.7, 118.9, 119, 123.7, 123.9, 129.4, 131.1, 132.1, 132.2, 138.5, 148.2, 148.5, 154, 156, 157.9. Mass, M^+at m/z 610. Anal. Calcd. for $C_{27}H_{21}N_5SO_3Cl$ Br: C, 53.08; H, 3.46; N, 11.46. Found: C, 53.15; H, 3.37; N, 11.52.

General procedure for the preparation of 4-((5′′-methoxy-2′′ substituted phenyl indole-3′′yl)-(-2′-oxo thiazolin-1′yl))-3-substituted phenyl-5-mercapto-1,2,4-triazoles (6a-h). The mixtures of compounds **4(a-h)** (0.01 mol) and thioglycolic acid (0.01 mol) in the presence of a pinch of anhydrous zinc chloride in methanol were refluxed and poured in ice cold water, the products were filtered and recrystallized from appropriate solvent.

4-((5′′-methoxy-2′′-(4′′′-chlorophenylindole-3′′yl)-(2′-oxothiazolin-1′yl))-3-(2-hydroxyphenyl)-5-mercapto-1,2,4-triazoles (6a). Yield: 45%; mp: 300-302 °C; IR (KBr): ν(cm^{-1}) 3440(O-H), 3225(N-H stretching), 3135(aromatic C-H stretching) 3040, 2830(methylene C-H str), 2570(S-H), 1695(C=O),

1645(N-C=O), 1600(C=N), 1282(N-N), 770(C-S); ^{1}H NMR: δ(ppm) 3.25(s, 3H, OCH_3), 4.05 (s, 2H, CH_2 of thiazolidenone ring), 6.65(s, 1H, CH=N-N), 6.75-7.70(m, 11H, Ar-H), 9.08(s, 1H, N-H of indole exchangeable), 11.24(s, 1H, OH exchangeable), 13.42(s, 1H, SH). ^{13}C NMR ($CDCl_3$) δ:31.8, 5 6.8, 100.5, 112.4, 112.9, 12 1.5, 123.4, 128.5, 129, 130.1, 131.1, 134.2, 154, 156, 167.9, 171. Mass, M$^+$at m/z 550 Anal. Calcd. for $C_{26}H_{20}N_5S_2O_3Cl$: C, 56.77; H, 3.66; N, 12.73. Found: C, 56.82; H, 3.60; N, 12.78.

4-((5′′-methoxy-2′′-(4′′′-chlorophenylindole-3′′yl)-(2′-oxo thiazolin-1′yl))-3-(4-N,N-dimethylaminophenyl)-5-mercapto-1,2,4-triazoles (6b). Yield: 46%; mp: 316-318 °C; IR (KBr): ν(cm^{-1}) 3322 (N-H stretching), 3130(aromatic C-H stretching) 3035, 2840(methylene C-H str), 2567(s-H), 1690(C=O), 1642 (N-C=O), 1602(C=N), 1281(N-N), 760(C-S); ^{1}H NMR: δ(ppm) 2.72 (s, 6H, $N(CH_3)_2$, 3.22(s, 3H, OCH_3), 4.00(s, 2H, CH_2 of thiazolidenone ring), 6.62(s, 1H, CH=N-N), 6.75-7.72(m, 11H, Ar-H), 9.06(s, 1H, N-H of indole exchangeable), 13.40(s, 1H, SH); ^{13}C NMR ($CDCl_3$) δ: 42.4, 44.1, 55, 100.2, 102.2, 104, 112, 112.4, 121.5, 123.6, 128.2, 129.2, 130.4, 130.3, 134.5, 154.5, 156, 167.9, 171.8. Mass, M$^+$at m/z 545. Anal. Calcd. for $C_{28}H_{25}N_6S_2O_2Cl$: C, 61.67; H, 4.62; N, 15.42. Found: C, 61.64; H, 4.67; N, 15.54.

4-((5′′-methoxy-2′′-(4′′′-chlorophenylindole-3′′yl)-(2′-oxothiazolin-1′yl))-3-(2-chlorophenyl)-5-mercapto-1,2,4-triazoles (6c). Yield: 44%; mp: 320 °C; IR (KBr): ν(cm^{-1}) 3324 (N-H stretching), 3132(aromatic C-H stretching) 3036, 2840(methylene C-H str), 2569(S-H), 1700(C=O), 1644(N-C=O), 1605(C=N), 1285(N-N), 765(C-S); ^{1}H NMR: δ(ppm) 3.25(s, 3H, OCH_3), 4.08 (s, 2H, CH_2 of thiazolidenone ring), 6.60(s, 1H, CH=N-N), 6.78-7.76(m, 11H, Ar-H), 9.10(s, 1H, NH indole exchangeable), 13.42(s, 1H, SH). ^{13}C NMR ($CDCl_3$) δ:55.8, 100.6, 102.2, 104, 112, 112.4, 121.5, 123.6, 127.3, 128.2, 129.2, 130.4, 130.3, 134.5, 138, 154.5, 156, 167.4, 171.6. Mass, M$^+$at m/z 568. Anal. Calcd. for $C_{26}H_{19}N_5S_2O_2Cl_2$: C, 54.62; H, 3.37; N, 12.32. Found: C, 54.67; H, 3.31; N, 12.25.

4-((5′′-methoxy-2′′-(4′′′-chlorophenylindole-3′′yl)-(2′-oxothiazolin-1′yl))-3-(2-methoxyphenyl)-5-mercapto-1,2,4-triazoles (6d). Yield: 42%; mp: 307 °C; IR (KBr): ν(cm^{-1}) 3320 (N-H stretching), 3128(aromatic C-H stretching) 3030, 2835 (methylene C-H str), 2560(S-H), 1685(C=O), 1640(N-C=O), 1602(C=N), 1280(N-N), 762(C-S); ^{1}H NMR: δ(ppm)3.24(s, 3H, OCH_3), 3.34 (s, 3H, CH_3), 4.02(s, 2H, CH_2 of thiazolidenone ring), 6.62(s, 1H, CH=N-N), 6.75-7.80 (m, 11H, Ar-H), 9.00 (s, 1H, N-H of indole exchangeable), 13.34(s, 1H, SH). ^{13}C NMR ($CDCl_3$) δ:56.8, 100.7, 102.2, 104, 112.4, 112.8, 121.6, 12 3, 123.6, 12 7.5, 128.3, 129.8, 130.1, 130.7, 134.8, 138, 154.8, 156.4, 167.2, 171. Mass, M$^+$at m/z 564. Anal. Calcd. for $C_{27}H_{22}N_5S_2O_3Cl$: C, 57.49; H, 3.93; N, 12.41. Found: C, 57.42; H, 3.97; N, 12.49.

4-((5′′-methoxy-2′′-(4′′′-bromophenylindole-3′′yl)-(2′-oxothiazolin-1′yl))-3-(2-hydroxyphenyl)-5-mercapto-1,2,4-triazoles (6e). Yield: 40%; mp: 298 °C; IR (KBr): ν(cm^{-1}) 3440(O-H), 3225(N-H stretching), 3135(aromatic C-H stretching) 3040(cm^{-1}), 2830 (methylene C-H str), 2570(S-H), 1695(C=O), 1645(N-C=O), 1600(C=N), 1282(N-N), 770(C-S); ^{1}H NMR: δ(ppm) 3.25(s, 3H, OCH_3), 4.05 (s, 2H, CH_2 of thiazolidenone ring), 6.65 (s, 1H, CH=N-N), 6.75-7.70 (m, 11H, Ar-H), 9.08(s, 1H, N-H of indole exchangeable), 11.24(s, 1H, OH exchangeable), 13.42(s, 1H,SH). ^{13}C NMR ($CDCl_3$) δ:31.8, 36, 50.4, 55.4, 100.1, 102. 2, 104, 112, 112.4, 117.5, 118, 121.5, 123.4, 127.3, 128.2, 129.2, 130.6, 131.8, 148, 154.2, 167.4, 171. Mass, M$^+$at m/z 594. Anal. Calcd. for $C_{26}H_{20}N_5S_2O_3Br$: C, 52.53; H, 3.39; N, 11.78. Found: C, 52.57; H, 3.32; N, 11.84.

4-((5′′-methoxy-2′′-(4′′′-bromophenylindole-3′′yl)-(2′-oxo thiazolin-1′yl))-3-(4-N,N-dimethylaminophenyl)-5-mercapto-1,2,4-triazoles (6f). Yield: 37%; mp: 294 °C; IR (KBr): ν(cm^{-1}) 3322(N-H stretching), 3130(aromatic C-H stretching) 3035, 2840 (methylene C-H str), 2567(S-H), 1690(C=O), 1642(N-C=O), 1602(C=N), 1281(N-N), 760(C-S); ^{1}H NMR: δ(ppm) 2.72(s, 6H, $N(CH_3)_2$), 3.22(s, 3H, OCH_3), 4.00(s, 2H, CH_2 of thiazolidenone ring), 6.62(s, 1H, CH=N-N), 6.75-7.72(m, 11H, Ar-H), 9.06(s, 1H, N-H of indole exchangeable), 13.40(s, 1H, SH); ^{13}C NMR ($CDCl_3$) δ:31.8, 35.6, 40.2, 40.5, 50.4, 55.4, 100, 102.2, 104, 112, 112.4, 118, 121, 123.4, 127.3, 128.2, 129.2, 130.2, 130.6, 131.8, 148, 153.2, 167.4, 171. Mass, M$^+$at m/z 621 Anal. Calcd. for $C_{28}H_{25}N_6S_2O_2Br$: C, 54.10; H, 4.05; N, 13.52. Found: C, 54.18; H, 4.07; N, 13.58.

4-((5′′-methoxy-2′′-(4′′′-bromophenylindole-3′′yl)-(2′-oxothiazolin-1′yl))-3-(2-chlorophenyl)-5-mercapto-1,2,4-triazoles (6g). Yield: 35%; mp: 304-306 °C; IR(KBr): ν(cm^{-1}) 3324 (N-H stretching), 3132(aromatic C-H stretching), 3036, 2840(methylene C-H str), 2569(S-H), 1700(C=O), 1644(N-C=O), 1605(C=N), 1285(N-N), 765(C-S); ^{1}H NMR: δ(ppm) 3.25(s, 3H, OCH_3), 4.08(s, 2H, CH_2 of thiazolidenone ring), 6.60(s, 1H, CH=N-N), 6.78-7.76(m, 11H, Ar-H), 9.10(s, 1H, N-H of indole exchangeable), 13.42(s, 1H, SH); ^{13}C NMR($CDCl_3$) δ:35.8, 35.6, 50.8, 55.8, 100.7, 102.2, 104, 117.5, 118, 121.5, 123.4, 127.3, 128.2, 129.2, 13 0.2, 130.6, 131.8, 138, 148, 154.2, 167.4, 171. Mass, M$^+$at m/z 612. Anal. Calcd. for $C_{26}H_{19}N_5S_2O_2Cl$ Br: C, 50.94; H, 3.12; N, 11.42. Found: C, 50.82; H, 3.24; N, 11.48.

4-((5′′-methoxy-2′′-(4′′′-bromophenylindole-3′′yl)-(2′-oxothiazolin-1′yl))-3-(2-methoxyphenyl)-5-mercapto-1,2,4-triazoles (6h). Yield: 40%; mp: 282 °C; IR (KBr): ν(cm^{-1}) 3320 (N-H stretching), 3128(aromatic C-H stretching) 3030, 2835(methylene C-H str), 2560(S-H), 1685(C=O), 1640(N-C=O), 1602(C=N), 1280(N-N), 762(C-S): ^{1}H NMR: δ(ppm)3.24(s, 3H, OCH_3), 3.34(s, 3H, CH_3), 4.02(s, 2H, CH_2 of thiazolidenone

ring), 6.62(s, 1H, CH=N-N), 6.75-7.80(m, 11H, Ar-H), 9.00(s, 1H, N-H of indole exchangeable), 13.34(s, 1H, SH); ^{13}C NMR ($CDCl_3$) δ:35.8, 50.8, 55.6, 100.5, 102.2 , 104, 112, 112.4, 116.5, 116.6, 118, 121.5, 123.4, 125.4, 128.2, 129.8, 130.2, 130.6, 131.8, 148, 154.2, 157.1, 167.4, 171. Mass, M^+ at m/z 608. Anal. Calcd. for $C_{27}H_{22}N_5S_2O_3Br$: C, 53.29; H, 3.64; N, 11.50. Found: C, 53.20; H, 3.60; N, 11.44.

Biological methods. The compounds were tested for their anti-inflammatory and analgesic activities as well as for acute toxicity. The test compounds were suspended in 0.5% gum acacia in water and administered orally. The experiments were performed with albino rats of Charles-Foster strain of either sex, excluding pregnant females, 60 to 90 days old weighing 100 to 120 g. Food (chaw pallet) and water was given to the animals *ad libidum*. The tested compounds were dissolved in propylene glycol. Phenyl butazone and aspirin were used as reference drugs for the comparison of anti-inflammatory and analgesic activities.

Anti-inflammatory activity. Anti-inflammatory activity against carrageenan-induced rat paw oedema was determined by the method of Winter *et al*. (1962). This study was conducted on albino rats of either sex (100-150 g). The rats were divided into groups of five animals each. Compounds were screened for anti-inflammatory activity at 50 mg/kg p.o. The percentage of anti-inflammatory activity was calculated according to the following formula.

Anti-inflammatory activity (%) = $(1-V_t / V_c) \times 100$

Where, V_t and V_c are the volume of oedema in drug treated and control group, respectively.

Analgesic activity. This activity was determined by the method of Berkowitz *et al*. (1977), which is based on the property of the test compound to antagonize the phenyl quinone-induced pain syndrome in mice. Groups of five mice were injected intraperitonially with 0.25 ml of 0.02% solution of phenyl-quinone in ethanol (5%) one h after oral administration of the test compound. The number of writhes induced in each mice

Table 1. Physical and analytical data of compounds **3a-3d**, **4a-4h**, **5a-5h** and **6a-6h***

Compound	R1	R2	m.p. (°C)	Yield (%)	Molecular formula	Molecular weight
3a	2-OH	-	215	60	$C_8H_8N_4OS$	208.17
3b	4N$(CH_3)_2$	-	243-244	63	$C_{10}H_{13}N_5S$	235.30
3c	2-Cl	-	258	70	$C_8H_7N_4SCl$	226.95
3d	2-OCH_3	-	238-239	90	$C_8H_{10}N_4SO$	210.24
4a	2-OH	4-Cl	170	72	$C_{24}H_{18}N_5SO_2Cl$	475.99
4b	4N$(CH_3)_2$	4-Cl	184	92	$C_{26}H_{23}N_6SOCl$:	503.07
4c	2-Cl	4-Cl	206-208	68	$C_{24}H_{17}N_5SOCl_2$	462.44
4d	2-OCH_3	4-Cl	182	70	$C_{25}H_{20}N_5SO_2Cl$	490.02
4e	2-OH	4-Br	168	79	$C_{24}H_{18}N_6SO_2Br$	534.39
4f	2-Cl	4-Br	180	75	$C_{26}H_{23}N_6SOBr$	547.46
4g	4N$(CH_3)_2$	4-Br	200-201	60	$C_{24}H_{17}N_5SOClBr_2$	618.81
4h	2-OCH_3	4-Br	174-175	70	$C_{25}H_{20}N_5SO_2Br$	534.42
5a	2-OH	4-Cl	220	52	$C_{26}H_{19}N_5SO_3Cl_2$	552.53
5b	4N$(CH_3)_2$	4-Cl	245-246	54	$C_{28}H_{24}N_6SO_2Cl_2$	579.60
5c	2-Cl	4-Cl	248	55	$C_{26}H_{18}N_5SO_2Cl_3$	570.04
5d	2-OCH_3	4-Cl	235	50	$C_{27}H_{21}N_5SO_3Cl_2$	566.56
5e	2-OH	4-Br	218	48	$C_{26}H_{19}N_5SO_3ClBr$	596.93
5f	2-Cl	4-Br	238	45	$C_{28}H_{24}N_6SO_2ClBr$	624.00
5g	4N$(CH_3)_2$	4-Br	240	42	$C_{26}H_{18}N_5SO_2Cl_2Br$	615.44
5h	2-OCH_3	4-Br	215	40	$C_{27}H_{21}N_5SO_3ClBr$	540.92
6a	2-OH	4-Cl	300-302	45	$C_{26}H_{20}N_5S_2O_3Cl$	550.08
6b	2-Cl	4-Cl	316-318	46	$C_{28}H_{25}N_6S_2O_2Cl$	545.10
6c	4N$(CH_3)_2$	4-Cl	320	44	$C_{26}H_{19}N_5S_2O_2Cl_2$	568.60
6d	2-OCH_3	4-Cl	307	42	$C_{27}H_{22}N_5S_2O_3Cl$	564.11
6e	2-OH	4-Br	298	40	$C_{26}H_{20}N_5S_2O_3Br$	594.48
6f	2-Cl	4-Br	294	30	$C_{28}H_{25}N_6S_2O_2Br$	621.55
6g	4N$(CH_3)_2$	4-Br	304-306	35	$C_{26}H_{19}N_5S_2O_2ClBr$	612.99
6h	2-OCH_3	4-Br	282	32	$C_{27}H_{22}N_5S_2O_3Br$	608.51

*Satisfactory analysis for C, H, N was obtained for all the compounds within ± 0.4% of the theoretical values

Table 2. Pharmacological evaluation of the synthesized compounds **3a-3d**, **4a-4h**, **5a-5h** and **6a-6h**

Comp. no.	R	R′	Dose (mg/kg p.o.)	Antiinflammatory activity (% oedema inhibition relative to control)	Dose (mg/kg p.o.)	Analgesic activity (% decrease of writhes in 60 min after treatment relative to control)	ALD_{50}
3a	2-OH	-	50	16.3*	50	9.1*	>1000
3b	$4N(CH_3)_2$	-	50	13.5*	50	6.2**	>1000
3c	2-Cl	-	50	19.5**	50	11.3**	>1000
3d	$2OCH_3$	-	50	15.6*	50	8.2*	>1000
4a	2-OH	4-Cl	50	23.4**	50	16.6**	>1000
4b	$4N(CH_3)_2$	4-Cl	50	19.6**	50	13.6**	>1000
4c	2-Cl	4-Cl	50	25.8***	50	18.5***	>1000
4d	$2\text{-}OCH_3$	4-Cl	50	21.9**	50	15.1**	>1000
4e	2-OH	4-Br	50	22.5**	50	15.5**	>1000
4f	$4N(CH_3)_2$	4-Br	50	19.1**	50	12.3**	>1000
4g	2-Cl	4-Br	50	24.6**	50	17.4**	>1000
4h	$2\text{-}OCH_3$	4-Br	50	20.7**	50	14.4**	>1000
5a	2-OH	4-Cl	50	31.1**	50	29.9**	>1000
5b	$4N(CH_3)_2$	4-Cl	50	26.7**	50	24.8**	>1000
5c	2-Cl	4-Cl	25	33.5***	25	23.8***	
			50	51.3***	50	38.2***	
			100	76.4***	100	57.5***	>1600
5d	$2\text{-}OCH_3$	4-Cl	50	30.8**	50	28.4**	>1000
5e	2-OH	4-Br	50	31.7**	50	27.6**	>1000
5f		4-Br	50	24.2**	50	23.2**	>1000
5g	2-Cl	4-Br	50	38.1**	50	35.7**	>1000
5h	$2\text{-}OCH_3$	4-Br	50	28.6**	50	27.6**	>1000
6a	2-OH	4-Cl	50	34.1***	50	30.5***	>1000
6b	$4N(CH_3)_2$	4-Cl	25	27.2***	50	25.5***	>1000
6c	2-Cl	4-Cl	25	34.3***	25	25.6***	>1600
			50	53.6***	50	42.1***	
			100	72.2***	100	60.4***	
6d	$2\text{-}OCH_3$	4-Cl	50	31.2***	50	29.5***	>1000
6e	2-OH	4-Br	50	31.5***	50	28.6***	>1000
6f	$4N(CH_3)_2$	4-Br	50	25.6***	50	26.2***	>1000
6g	2-Cl	4-Br	50	38.5***	50	33.3***	>1000
6h	$2\text{-}OCH_3$	4-Br	50	32.6***	50	30.4***	>1000
Phenyl butazone			25	31.4***	25	18.8***	
			50	40.6***	50	32.5***	
			100	63.4***	100	42.6***	
Aspirin			25	30.25***	25	30.2***	
			50	34.4***	50	45.5***	
			100	60.8***	100	59.3***	

was counted for 5 min after injection of an irritant. The analgesic effect was expressed as percent protection in comparison to control.

Protection (%) = (1-mean no. of writhes in mice of test groups/ mean number of writhes in mice of control group) × 100

Acute toxicity. Acute Lethal Dose (ALD_{50}) of all the compounds were investigated by the method of Smith (1960).

Results and Discussion

Physical and analytical data of all the newly synthesized compounds (3a-3d, 4a-4h, 5a-5h and 61-6h are given in Table 1. All the synthesized compounds were screened for their anti-inflammatory activity and analgesic activities. All the compounds have shown anti-inflammatory activity ranging from 13.5-53.6% at the dose of 50 mg/kg, p.o. In addition to the anti-inflammatory activity, these compounds also exhibited analgesic activity ranging from 6.2-42% at the dose of 50 mg/kg i.p. (Table 2). When the compounds were substituted with 4-chlorphenyl group at the 2-position of indole nucleus, they showed better anti-inflammatory and analgesic activities than 4-bromophenyl group. The anti-inflammatory and analgesic activities of compounds **3a-d** were 13.5-19.5% and 6.2-11.2%, respectively, while those of compounds **4a-h** ranged between 19.1-25.8% and 12.3-18.5%, respectively. Among the compounds **3a-d** and **4a-h**, compound **4c** which was substituted with 2-chlorophenyl at 3-position of triazole ring exhibited 25.8% protection against carrageenan-induced oedema. In addition to anti-inflammatory activity, this compound exhibited 18.6% protection against phenyl quinine-induced analgesia. Cyclization of compounds **4a-h** into azetidinones **5a-h** and thiazolidinones **6a-h** have shown better anti-inflammatory and analgesic activities than their corresponding parent compounds. Azetidinones (**5a-h**) exhibited anti-inflammatory and analgesic activities ranging from 24.2-51.3% and 23.2-38.2%, respectively. Among the azetidinones (**5a-h**), compound **5c** showed potent anti-inflammatory (51.3%) and analgesic (38.2%) activities. However, compound **5f** exhibited lesser degree of inhibition of oedema 24.2% as well as analgesia 23.2% due to the presence of N, N-dimethyl group at 4-position of phenyl ring. Thiazolidinones **6a-h**, generally, showed better anti-inflammatory and analgesic activities than azetidinones **5a-h**. Out of the eight synthesized thiazolidinones **6a-h**, the compound **6c** exhibited the most potent anti-inflammatory (34.3, 53.6, 72.2%) activity at the three graded doses of 25, 50 and 100 mg/kg, p.o., respectively. This compound was also associated with analgesic activity 25.6, 42.1 and 60.4% at the three graded dose, of 25, 50 and 100 mg/kg, p.o., respectively. The compounds **5c** and **6c** were compared with reference drugs phenylbutazone and aspirin. At all the three doses, this compound elicited both activities better than the reference drugs.

Conclusions

- It can be concluded that the compounds **4a-h** having an azomethyne (-N=CH-) group between the substituted triazole rings and substituted indoles show good anti-inflammatory and analgesic activities.
- The cyclization of compounds **4a-h** into the four membered heterocyclic ring i.e. azetidinones **5a-h** show better activity than the parent compounds.
- The conversion of compounds **4a-h** into five membered ring thiazolidinone ring compounds **6a-h** show much better activity than **5a-h** and **4a-h**.
- The substitution of fourth position of triazole nucleus by substituted indole azetidinonyl and substituted indole thiazolidinonyl moieties remarkably increase the activities.
- The results show that chloro-substituted analogues are more potent than the other derivatives.

Statistical analysis. Statistical analysis of the anti-inflammatory activity of the synthesized compounds by level of significance was determined using Student's 't' Method.

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