Synthesis and Anti-inflammatory Activity of Indole Derivatives

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ABSTRACT: The present investigation is concerned with synthesis of new substituted indole derivatives 1-39 with the objective of discovering novel and potent anti-inflammatory agent. The structure of all the synthesized compounds were elucidated by spectral (IR, ¹H NMR and mass) and elemental (C, H, N) analysis. The obtained compounds were screened for their anti-inflammatory as well as analgesic activities at the dose of 50 mg/kg p.o. The compound 2-(p-Chlorophenyl)-1-[4’-[2”-(p-chlorophenyl)-4”-oxo-thiazolidin-3”-yl]-5’-mercapto-1’,2’,4’-triazol-3’-yl-methyl]-3-(4”’,6”’-bromo-2”’-carboxyphenyl iminomethyl]-5-methoxy-indole 35 showed better anti-inflammatory and analgesic activities at the three graded dose of 25, 50 and 100 mg/kg p.o.

KEY WORDS: Indoles, Thiazalidinones, Azetidinone, Anti-inflammatory, Analgesic Activities

INTRODUCTION

The discovery of indomethacin, ethodolac and tenidap, as potent anti-inflammatory agents, has led to the exploration of indole nucleus. Indole derivatives have been found to possess potent wide spectrum of biological activities especially antibacterial¹², antifungal³, anti-inflammatory⁴-⁸ and analgesic⁹. Further, it has been reported that substitution of different heterocyclic or aromatic moieties at 2 or 3-position of indole nucleus modulates the anti-inflammatory activity of such substituted indole derivatives. Besides these, triazole¹⁰-¹³ compounds with another heterocyclic ring are significant agents for the treatment of inflammation. It is evident from chemical literature that thiazolidinones¹⁴-¹⁷ and azetidinones¹⁸-²¹ were also found to possess wide spectrum of biological activities in different heterocyclic nuclei. It is therefore thought worthwhile to synthesize some new indole derivatives by incorporating azetidinonyl and thiazolidinonyl moieties in single molecular frame work with the hope to possess better anti-inflammatory activity.

MATERIAL AND METHOD

Melting points were taken in open capillaries on Thomas Hoover melting point apparatus and are uncorrected. Elemental analysis (C, H, N) was performed on a Perkin-Elmer 2400 analyzer and values were with ± 0.4% of the calculated. The IR spectra (cm⁻¹) were recorded in film or in potassium bromide disks on a Perkin-Elmer 398 spectrometer. The ¹H spectra were recorded on a DPX-300 MHz, Bruker FT-NMR spectrometer. The chemical shifts were reported as parts per million (δ ppm).
2-(Phenyl)-3-(4',6'-dibromo-2'-carboxyphenyl iminomethyl)-5-methoxy-indole (1).
A mixture of 3-carboxyaldehyde -5-methoxy 2-phenyl indole (0.01 mole) and 2,5-dibromo anthranilic acid (0.01 mole) in absolute ethanol (90 ml) containing few drops of glacial acetic acid was refluxed for 28 hours, and excess of solvent was distilled off. The solid thus obtained was filtered, dried and recrystallized from ethyl acetate to yield compound (1) (72%) m.p: 247°C; IR (KBr) $\nu_{\text{max}}$ in cm$^{-1}$: 3005 (N-H), 3030 (C-H aromatic), 1710 (C=O), 1585 (C=N), 578 (C-Br).

$\text{^1}H NMR$ (CDCl$_3$) $\delta$ in ppm : 9.68 (s, 1H, Ar-COOH), 8.75 (s, 1H, NH exchangeable), 8.44 (s, 1H, N=CH), 6.92-7.58 (m, 10H, Ar-H), 3.35 (s, 3H, OCH$_3$).

Anal. Calcd. for C$_{23}$H$_{16}$N$_2$O$_3$Br$_2$: C, 52.30; H, 3.05; N, 5.30; Found : C, 52.25 : H, 3.47; N, 5.51: MS : [M]$^+$ at m/z 552.95.

The following compounds (2-3) were prepared using a similar procedure described for compound (1). The physical and spectral data of these compounds are giving below.
2-(4-Chlorophenyl)-3-(4′,6′-dibromo-2′-carboxyphenyliminomethyl)-5-methoxy-indole (2).

Yield (74%), (Ethanol), m.p: 272°C; IR (KBr) \( \square_{\max} \) in cm\(^{-1}\): 3010 (NH), 3033 (C-H aromatic), 1705 (C=O), 1588 (C=N), 785 (C=Cl), 570 (C-Br). \(^{1}\)HNMR (CDCl\(_3\)) \( \square \) in ppm: 9.65 (s, 1H, Ar-COOH), 8.75 (s, 1H, NH exchangeable), 8.39 (s, 1H, N=CH\(_2\)), 6.88-7.65 (m, 9H, Ar-H), 3.32 (s, 3H, OCH\(_3\)). Anal. Calcd. for C\(_{25}\)H\(_{20}\)N\(_2\)O\(_4\)Br\(_2\): C, 52.79; H, 3.61; N, 4.98; Found: C, 52.72; H, 3.61; N, 4.95. MS: [M]\(^+\) at m/z 648.73.

2-(4-Methylphenyl)-1-carboxymethyl-3-(4′,6′-dibromo-2′-carboxyphenylimino methyl)-5-methoxy indole (6).

Yield (66%), (Ethylacetate), m.p: 297°C; IR (KBr) \( \square_{\max} \) in cm\(^{-1}\): 3028 (C-H aromatic), 2926 (C-H aliphatic), 1775 (COOEt), 1715 (COOH), 1570 (C=N), 575 (C-Br); \(^{1}\)HNMR (CDCl\(_3\)) \( \square \) in ppm: 9.57 (s, 1H, Ar-COOH), 8.44 (s, 1H, N=CH\(_2\)), 6.90-7.78 (m, 9H, Ar-H), 4.72 (s, 2H, N-CH\(_3\)), 4.46 (q, J=7 Hz, 2H ester CH\(_2\)), 2.26 (s, 3H, CH\(_3\)), 1.50 (t, J=7 Hz, 3H, ester CH\(_3\)), 3.37 (s, 3H, OCH\(_3\)). Anal. Calcd. for C\(_{28}\)H\(_{26}\)N\(_2\)O\(_4\)Br\(_2\): C, 53.52; H, 3.85; N, 4.46; Found: C, 53.04; H, 3.22; N, 4.18. MS: [M]\(^+\) at m/z 628.25.

2-Phenyl-1-(hydrazinocarbonylmethyl)-3-(4′,6′-dibromo-2′-carboxy phenyl imino methyl)-5-methoxy indole (7).

A mixture of compound 4 (0.01 mole) and hydrazine hydrate (0.02 mole) in absolute ethanol (80 ml) was refluxed for 20 hours. It was then cooled and poured on crushed ice and separated solid was filtered, washed with cold water, dried and recrystallized from ethyl acetate to yield compound 6 (60%), m.p: 187°C; IR (KBr) \( \square_{\max} \) in cm\(^{-1}\): 3310 (N-H), 3030 (C-H aromatic), 2920 (C-H aliphatic), 1710 (COOH), 1650 (C=O amide), 1572 (C=N), 575 (C-Br); \(^{1}\)HNMR (CDCl\(_3\)) \( \square \) in ppm: 9.65 (s, 1H, COOH), 8.45 (s, 1H, N=CH\(_2\)), 8.45-7.79 (m, 10H, Ar-H), 5.60 (br, 1H, NH exchangeable), 4.50 (t, J=7 Hz, 2H ester CH\(_2\)), 4.42 (q, J=7 Hz, 2H, NH exchangeable), 3.37 (s, 2H, OCH\(_3\)). Anal. Calcd. for C\(_{28}\)H\(_{26}\)N\(_2\)O\(_4\)Br\(_2\): C, 53.52; H, 3.85; N, 4.46; Found: C, 53.04; H, 3.22; N, 4.18. MS: [M]\(^+\) at m/z 600.00.

The following compounds (8-9) were prepared using a similar procedure described for compound (7). The physical and spectral data of these compounds are given below.

2-(4-Chlorophenyl)-1-carboxymethyl-3-(4′,6′-dibromo-2′-carboxyphenyliminomethyl)-5-methoxy indole (8).

Yield (65%), (Ethanol), m.p: 175°C; IR (KBr) \( \square_{\max} \) in cm\(^{-1}\): 3300 (NH), 3035 (C-H aromatic), 2925 (C-H aliphatic), 1710 (COOH), 1645 (C=O amide), 1570 (C=N), 790 (C-Cl), 570 (C-Br); \(^{1}\)HNMR (CDCl\(_3\)) \( \square \) in ppm: 9.58 (s, 1H, COOH), 8.42 (s, 1H, N=CH\(_2\)), 6.89-7.81 (m, 9H, Ar-H), 5.55 (br, 1H, NH exchangeable), 4.75 (s, 2H, N-CH\(_3\)), 4.56 (hump, 2H, NH exchangeable), 3.33 (s, 3H, OCH\(_3\)). Anal. Calcd. for C\(_{25}\)H\(_{19}\)N\(_2\)O\(_4\)Cl\(_2\): C, 47.31; H, 3.02; N, 8.83; Found: C, 47.70; H, 3.12; N, 8.65; MS: [M]\(^+\) at m/z 634.70.
2-(4-Methylphenyl)-1-(hydrazinocarbonylmethyl)-3-(4′,6′-dibromo-2′-carboxyphenyl-iminomethyl)-5-methoxy-indole (9).

Yield (60%), (Acetone), m.p: 196°C; IR (KBr) νmax in cm⁻¹: 3308 (NH), 3040 (C-H aromatic), 2930 (C-H aliphatic), 1715 (COOH), 1646 (C=O amide), 1573 (C=N), 1525 (N-N), 785 (C-Cl), 576 (C-Br); νmax in cm⁻¹: 1710 (COOH), 1575 (C=N), 1520 (N-N), 788 (C-Cl), 565 (C-Br).

The physical and spectral data of these compounds are giving below.

2-(4-Chlorophenyl)-1-(4′-amino-5′-mercapto-[1′,2′,4′]-triazol-3′-yl-methyl)-3-(4″,6″-dibromo-2″-carboxyphenyliminomethyl)-5-methoxy-indole (10).

To the ice cold mixture of compound 2-Phenyl-1-(hydrazinocarbonylmethyl)-3-(4′,6′-dibromo-2′-carboxyphenylimino methyl)-5-methoxy-indole (7) (0.01 mole) and KOH (0.04 mole) in dry ethanol (80 ml), carbon disulphide (0.01 mole) was added with magnetic stirring. The reaction mixture was stirred further at room temperature for 25 hours. The separated solid was filtered washed with dry ether and dried. It was further magnetically stirred with hydrazine hydrate (0.015 moles) on boiling water bath then poured into ice water. The separated solid was filtered and recrystallized from ethanol to yield compound.

The following compounds (11-12) were prepared using a similar procedure described for compound (10).

2-Phenyl-1-(4′-benzylidine)-amino-5′-mercapto-[1′,2′,4′]-triazol-3′-yl-methyl)-3-(4″,6″-dibromo-2″-carboxyphenyliminomethyl)-5-methoxy-indole (13).

A solution of compound 10 (0.01 mole) in methanol (50 ml) was refluxed with benzoaldehyde (0.01 mole) in the presence of glacial acetic acid (4 ml) for 11 ours. The reaction mixture was concentrated, cooled and then poured into ice water. The separated solid was filtered and recrystallized from ethanol to yield compound (13) (62%), m.p: 222°C; IR (KBr) νmax in cm⁻¹: 3303 (C-H aromatic), 2925 (C-H aliphatic), 1712 (COOH), 1573 (C=N), 1517 (C=N), 572 (C-Br); HNMR (CDCl₃) ν in ppm: 9.56 (s, 1H, COOH), 8.40 (s, 2H, 2 X N=CH), 6.78-7.79 (m, 15H, Ar-H), 4.72 (s, 2H, N-CH₂), 2.56 (s, 3H, OCH₃). Anal.Calcd. for C₁₃H₁₂N₃O₁₃S₄: C, 39.24; H, 2.90; N, 11.19 ; MS: [M]+ at m/z. 744.46. The following compounds (14-21) were prepared using a similar procedure described for compound (13). The physical and spectral data of these compounds are giving below.

2-Phenyl-1-(4′-chlorobenzylidine)-amino-5′-mercapto-[1′,2′,4′]-triazol-3′-yl-methyl)-3-(4″,6″-dibromo-2″-carboxyphenyliminomethyl)-5-methoxy-indole (14).

Yield (58%), (Ethyl acetate), m.p: 226°C; IR (KBr) νmax in cm⁻¹: 3303 (C-H aromatic), 2920 (C-H aliphatic), 1710 (COOH), 1575 (C=N), 1520 (N-N), 788 (C-Cl), 565 (C-Br); HNMR (CDCl₃) ν in ppm: 9.62 (s, 1H, COOH), 8.42 (s, 2H, 2 X N=CH), 6.78-7.89 (m, 14H, Ar-H), 4.75 (s, 2H, N-CH₂), 2.54 (s, 1H, SH), 3.36 (s, 3H, OCH₃). Anal.Calcd. for C₁₃H₁₂N₃O₁₃S₄: C, 58.99; H, 2.98 ; N, 10.79

The physical and spectral data of these compounds are giving below.

2-Phenyl-1-(4′-amino-5′-mercapto-[1′,2′,4′]-triazol-3′-yl-methyl)-3-(4″,6″-dibromo-2″-carboxyphenyliminomethyl)-5-methoxy-indole (11).

Yield(66%), (Ethanol), m.p: 198°C; IR (KBr) νmax in cm⁻¹: 3305 (N-H), 3032 (C-H aromatic), 2920 (C-H aliphatic), 1712 (COOH), 1572 (C=N), 1520 (N-N), 785 (C-Cl), 570 (C-Br); HNMR (CDCl₃) ν in ppm: 9.60 (s, 1H, COOH), 8.42 (s, 1H, N=CH), 6.84-7.75 (m, 9H, Ar-H), 4.73 (s, 2H, N-CH₂), 4.55 (hump, 2H, NH₂ exchangeable), 2.55 (s, 1H, SH) , 3.40 (s, 3H, OCH₃). Anal.Calcd. for C₁₃H₁₂N₃O₁₃S₄: C, 45.21; H, 2.77; N, 12.17; Found : C, 45.12; H, 2.96; N, 12.57 ; MS: [M]+ at m/z. 690.71.
2-Phenyl-1-{4'- (4-methoxybenzylidine)-amino-5'-mercapto-[1',2',4']-triazol-3'-yl-methyl-3-(4",6"-dibromo-2'-carboxyphenyliminomethyl)-5-methoxy-indole (15).
Yield (57%), (Ethanol), m.p: 235°C; IR (KBr) in cm⁻¹: 3035 (C-H aromatic), 2928 (C-H aliphatic), 1715 (COOH), 1578 (C=N), 1525 (N-N), 1170 (C-O-C), 565 (C-Br).
¹HNMR (CDCl₃), δ in ppm : 9.65 (s, 1H, COOH), 8.42 (s, 2H, 2X N=CH), 6.77-7.91 (m, 14H, Ar-H), 4.75 (s, 2H, N-CH₃), 3.42 (s, 6H, 2X OCH₃), 2.54 (s, 1H, SH). Anal.Caled.for C₃₅H₂₁N₂O₅Br₂S : C, 52.73; H, 3.38; N, 10.85: Found : C, 52.49; H, 3.15; N, 10.58; MS: [M⁺] at m/z. 774.48.

2-(4-Chlorophenyl)-1-{4'-(benzylidene)-amino-5'-mercapto-[1',2',4']-triazol-3'-yl-methyl-3-(4",6"-dibromo-2'-carboxyphenyliminomethyl)-5-methoxy-indole (16).
Yield (61%), (Ethyl acetate), m.p: 225°C; IR (KBr) in cm⁻¹: 3033 (C-H aromatic), 2920 (C-H aliphatic), 1710 (COOH), 1575 (C=N), 1520 (N-N), 788 (C-Cl), 565 (C-Br). ¹HNMR (CDCl₃), δ in ppm : 9.62 (s, 1H, COOH), 8.45 (s, 2H, 2X N=CH), 6.80-7.89 (m, 14H, Ar-H), 4.75 (s, 2H, N-CH₃), 2.54 (s, 1H, SH), 3.36 (s, 3H, OCH₃). Anal.Caled.for C₃₅H₂₁N₂O₅Br₂S : C, 50.89; H, 2.98; N, 10.79: Found : C, 50.38; H, 2.30; N, 10.38; MS: [M⁺] at m/z. 774.90.

2-(4-Chlorophenyl)-1-{4'-(4-chlorobenzylidine)-amino-5'-mercapto-[1',2',4']-triazol-3'-yl-methyl-3-(4",6"-dibromo-2'-carboxyphenyliminomethyl)-5-methoxy-indole (17).
Yield (57%), (Acetone), m.p: 233°C; IR (KBr) in cm⁻¹: 3033 (C-H aromatic), 2920 (C-H aliphatic), 1710 (COOH), 1575 (C=N), 1520 (N-N), 788 (C-Cl), 565 (C-Br). ¹HNMR (CDCl₃), δ in ppm : 9.60 (s, 1H, COOH), 8.45 (s, 2H, 2X N=CH), 6.77-7.76 (m, 13H, Ar-H), 4.72 (s, 2H, N-CH₃), 2.56 (s, 1H, SH), 3.38 (s, 3H, OCH₃). Anal.Caled.for C₃₅H₂₁N₂O₅ClBr₂S : C, 48.73; H, 2.73; N, 10.33; Found : C, 48.66; H, 2.88; N, 10.71; MS: [M⁺] at m/z. 813.35.

2-(4-Chlorophenyl)-1-{4'-(4-methoxybenzylidine)-amino-5'-mercapto-[1',2',4']-triazol-3'-yl-methyl-3-(4",6"-dibromo-2'-carboxyphenyliminomethyl)-5-methoxy-indole (18).
Yield (64%), (Ethanol), m.p: 218°C; IR (KBr) in cm⁻¹: 3030 (C-H aromatic), 2926 (C-H aliphatic), 1715 (COOH), 1585 (C=N), 1525 (N-N), 785 (C-Cl), 565 (C-Br). ¹HNMR (CDCl₃), δ in ppm : 9.59 (s, 1H, COOH), 8.40 (s, 2H, 2X N=CH), 6.82-7.93 (m, 13H, Ar-H), 4.72 (s, 2H, N-CH₃), 3.45 (s, 6H, 2X OCH₃), 2.51 (s, 1H, SH). Anal.Caled.for C₃₅H₂₁N₂O₅Br₂S : C, 50.48; H, 3.12; N, 10.39: Found : C, 50.68; H, 3.41; N, 10.45; MS: [M⁺] at m/z. 808.83.

2-(4-Methylphényl)-1-{4'-(benzylidene)-amino-5'-mercapto-[1',2',4']-triazol-3'-yl-methyl-3-(4",6"-dibromo-2'-carboxyphenyliminomethyl)-5-methoxy-indole (19).
Yield (64%), (Methanol), m.p: 224°C; IR (KBr) in cm⁻¹: 3035 (C-H aromatic), 2925 (C-H aliphatic), 1712 (COOH), 1578 (C=N), 1524 (N-N), 560 (C-Br). ¹HNMR (CDCl₃), δ in ppm : 9.65 (s, 1H, COOH), 8.46 (s, 2H, 2X N=CH), 6.84-7.94 (m, 14H, Ar-H), 4.72 (s, 2H, N-CH₃), 2.54 (s, 1H, SH), 2.23 (s, 3H, CH₃), 3.41 (s, 3H, OCH₃). Anal.Caled.for C₃₅H₂₃N₂O₅Br₂S : C, 53.84; H, 3.46; N, 11.08; Found : C, 53.33; H, 3.76; N, 11.62; MS: [M⁺] at m/z. 758.48.

2-(4-Methylphényl)-1-{4'-(4-chlorobenzylidene)-amino-5'-mercapto-[1',2',4']-triazol-3'-yl-methyl-3-(4",6"-dibromo-2'-carboxyphenyliminomethyl)-5-methoxy-indole (20).
Yield (57%), (Acetone), m.p: 232°C; IR (KBr) in cm⁻¹: 3035 (C-H aromatic), 2928 (C-H aliphatic), 1715 (COOH), 1578 (C=N), 1525 (N-N), 792 (C-Cl), 560 (C-Br). ¹HNMR (CDCl₃), δ in ppm : 9.64 (s, 1H, COOH), 8.39 (s, 2H, 2X N=CH), 6.83-7.95 (m, 13H, Ar-H), 4.72 (s, 2H, N-CH₃), 2.51 (s, 1H, SH), 2.25 (s, 3H, CH₃), 3.42 (s, 3H, OCH₃). Anal.Caled.for C₃₅H₂₃N₂O₅ClBr₂S : C, 51.50; H, 3.18; N, 10.60; Found : C, 51.92; H, 3.59; N, 10.72; MS: [M⁺] at m/z. 792.93.

2-(4-Methylphényl)-1-{4'-(4-methoxybenzylidene)-amino-5'-mercapto-[1',2',4']-triazol-3'-yl-methyl-3-(4",6"-dibromo-2'-carboxyphenyliminomethyl)-5-methoxy-indole (21).
Yield (61%), (Ethyl acetate), m.p: 237°C; IR (KBr) in cm⁻¹: 3030 (C-H aromatic), 2922 (C-H aliphatic), 1718 (COOH), 1585 (C=N), 1525 (N-N), 1175 (C-O-C), 565 (C-Br). ¹HNMR (CDCl₃), δ in ppm : 9.59 (s, 1H, COOH), 8.44 (s, 2H, 2X N=CH), 6.82-7.96 (m, 13H, Ar-H), 4.71 (s, 2H, N-CH₃), 3.42 (s, 6H, 2X OCH₃), 2.51 (s, 1H, SH), 2.22(s, 3H, CH₃). Anal.Caled.for C₃₅H₂₃N₂O₅Br₂S : C, 53.31; H, 3.58; N, 10.66; Found : C, 53.17; H, 3.52; N, 10.73; MS: [M⁺] at m/z. 788.51.

2-Pheny1-1-{4'-(benzylidene)-amino-5'-(2-chloroacetylthio)-[1',2',4']-triazol-3'-yl-methyl-3-(4",6"-dibromo-2'-carboxyphenyliminomethyl)-5-methoxy-indole (22).
Take the solution of chloroacetyl chloride (0.01 mole) in dry dioxane (50 ml), was added drop wise during 2
hours to a well stirred solution of compound 13 (0.01 mole) in dry dioxane. The reaction mixture was stirred continuously 4 hours, cooled and poured it into water. A solid was obtained, filtered and washed with water and recrystallized from acetone to yield compound 22 (54%) m.p. 212°C; IR (KBr) max in cm⁻¹: 3035 (C-H aromatic), 2922 (C-H aliphatic), 1745 (C-O), 1578 (C=N), 1528 (N=N), 660 (C=O). ¹H NMR (CDCl₃) δ in ppm: 9.62 (s, 1H, COOH), 8.41 (s, 2H, 2 X N=CH), 6.82-7.93 (m, 15H, Ar-H), 4.75 (s, 2H, N-CH₂), 3.44 (s, 2H, CH₂Cl), 3.35 (s, 3H, OCH₃). Anal. Calcd. for C₃₅H₃₅N₅O₇BrCl₂S: C, 51.21; H, 3.07; N, 10.24; Found: C, 51.68; H, 3.35; N, 10.46; MS: [M⁺] at m/z 820.94.

The following compounds (23–30) were prepared using a similar procedure described for compound (22). The physical and spectral data of these compounds are given below.

2-Phenyl-1-{[4′-(4-chlorobenzylidine)-amino-5′-(2-chloroacetylthio)-[1′,2′,4′]-triazol-3′-yl-methyl-3-(4′,6′-dibromo-2-carboxyphenyliminomethyl)-5-methoxy-indole (23).

Yield (50%), (Ethanol), m.p: 216°C; IR (KBr) max in cm⁻¹: 3033 (C-H aromatic), 2925 (C-H aliphatic), 17445 (C-O), 1710 (COOH), 1570 (C=N), 1524 (N=N), 788 (C-Cl), 565 (C-Br). ¹H NMR (CDCl₃) δ in ppm: 9.64 (s, 1H, COOH), 8.41 (s, 2H, 2 X N=CH), 6.79-7.88 (m, 14H, Ar-H), 4.75 (s, 2H, N-CH₂), 3.45 (s, 2H, CH₂Cl), 3.38 (s, 3H, OCH₃). Anal. Calcd. for C₃₅H₃₅N₅O₇BrCl₂S: C, 50.21; H, 2.83; N, 9.82; Found: C, 49.81; H, 3.11; N, 9.69; MS: [M⁺] at m/z 885.38.

2-Phenyl-1-{[4′-(4-methoxybenzylidine)-amino-5′-(2-chloroacetylthio)-[1′,2′,4′]-triazol-3′-yl-methyl-3-(4′,6′-dibromo-2-carboxyphenyliminomethyl)-5-methoxy-indole (24).

Yield (52%), (Ethanol), m.p: 218°C; IR (KBr) max in cm⁻¹: 3035 (C-H aromatic), 2925 (C-H aliphatic), 1745 (C-O), 1710 (COOH), 1571 (C=N), 1525 (N-N), 1171 (C-O-C), 562 (C-Br). ¹H NMR (CDCl₃) δ in ppm: 9.61 (s, 1H, COOH), 8.40 (s, 2H, 2 X N=CH), 6.80-7.91 (m, 14H, Ar-H), 4.72 (s, 2H, N-CH₂), 3.46 (s, 2H, CH₂Cl), 3.43 (s, 3H, OCH₃). Anal. Calcd. for C₃₅H₃₅N₅O₇BrCl₂S: C, 50.81; H, 3.20; N, 9.88; Found: C, 50.48; H, 3.53; N, 9.73; MS: [M⁺] at m/z 850.96.

2-(4-Chlorophenyl)-1-{[4′-(benzylidine)-amino-5′-(2-chloroacetylthio)-[1′,2′,4′]-triazol-3′-yl-methyl-3-(4′,6′-dibromo-2-carboxyphenyliminomethyl)-5-methoxy-indole (25).

Yield (55%) (Ethyl acetate) m.p: 215°C; IR (KBr) max in cm⁻¹: 3030 (C-H aromatic), 2922 (C-H aliphatic), 1745 (C-O), 1715 (COOH), 1570 (C-N), 1524 (N-N), 790 (C-Cl), 564 (C-Br). ¹H NMR (CDCl₃) δ in ppm: 9.64 (s, 1H, COOH), 8.39 (s, 2H, 2 X 1H, N=CH), 6.79-7.91 (m, 14H, Ar-H), 4.75 (s, 2H, N-CH₂), 3.46 (s, 2H, CH₂Cl), 3.36 (s, 3H, OCH₃). Anal. Calcd. for C₃₅H₃₅N₅O₇BrCl₂S: C, 49.14; H, 2.83; N, 9.82; Found: C, 49.87; H, 2.42; N, 9.55; MS: [M⁺] at m/z 855.38.
Yield (51%), (Pet ether), m.p: 243°C; IR (KBr) δ max in cm⁻¹: 3033 (C-H aromatic), 2924 (C-H aliphatic), 1745 (C=O), 1717 (COOH), 1578 (C=N), 1522 (N-N), 785 (C-CI), 565 (C-Br). ¹HNMR (CDCl₃) δ in ppm: 9.64 (s, 1H, COOH aliphatic), 8.41 (s, 2H, 2 X N=CH), 6.81-7.95 (m, 13H, Ar-H), 4.77 (s, 2H, N-CH₃), 3.44 (s, 2H, CH₂Cl), 2.23 (s, 3H, CH₃), 3.28 (s, 3H, OCH₃). Anal.Calcd. for C₃₆H₂₃N₄O₇Br₂Sₐ: C, 51.73; H, 3.01; N, 9.67; Found: C, 49.46 ; H, 3.32 ; N, 9.39 ; MS: [M]+ at m/z 869.41.

2-(4-Methylphenyl)-1-[4¢-(4-methoxybenzylidene)-amino-5¢-(2-chloroacetlythio)-1'2,2',4'-triazol-3'-yl-methyl-3(4¢,6¢-dibromo-2'-carboxyphenyl iminomethyl)-5-methoxy-indole (30).

Yield (50%), (DMF/water), m.p: 249°C. IR (KBr) δ max in cm⁻¹: 3030 (CH aromatic), 2925 (C-H aliphatic), 1744 (C=O), 1710 (COOH), 1571 (C=N), 1525 (N-N), 1178 (C-O-C), 560 (C-Br). ¹HNMR (CDCl₃) δ in ppm: 9.62 (s, 1H, COOH), 8.44 (s, 2H, 2 X N=CH), 6.78-7.93 (m, 13H, Ar-H), 4.74 (s, 2H, N-CH₃), 3.44 (s, 6H, 2 X OCH₃), 3.48 (s, 2H, CH₂Cl), 2.19 (s, 3H, CH₃). Anal.Calcd. for C₃₇H₂₉N₆O₇ClBr₂S: C, 51.38; H, 3.38; N, 9.72; Found: C, 51.09; H, 3.70; N, 9.57; MS: [M]+ at m/z 864.99.

2-Phenyld-1-[4¢-(benzylidene)-amino-5¢-(2-aminothiol-4-ythio)-1'2,2',4'-triazol-3'-yl-methyl-3(4¢,6¢-dibromo-2'-carboxyphenyl iminomethyl)-5-methoxy-indole (31). To a solution of compound 22 (0.01 mole) in hot absolute ethanol (250 ml) was reacted with a solution of thiourea (0.01 mole) in absolute ethanol (50 ml) then refluxed the reaction mixture for 14 hours. The reaction mixture which is in the form of HCl is saturated with NaHCO₃ solution to release the base and extract the base with methylene chloride. Dry the organic extract and distilled off the solvent, and recrystallized from ethanol to yield compound 31 (45%), m.p: 235°C; IR (KBr) δ max in cm⁻¹: 3320 (NH₂), 3033 (C-H aromatic), 2924 (C-H aliphatic), 1722 (C=O), 1714 (COOH), 1570 (C=N), 1524 (N-N), 685 (C-S-C), 560 (C-Br). ¹HNMR (CDCl₃) δ in ppm: 9.61 (s, 1H, COOH), 8.42 (s, 2H, 2 X N=CH), 6.82-7.96 (m, 16H, Ar-H), 6.30 (s, 2H, -NH₂ exchangeable with D₂O), 4.78 (s, 2H, N-CH₃), 4.60 (s, 1H, N-CH₂Ar), 3.37 (s, 3H, OCH₃). Anal.Calcd. for C₃₇H₂₉N₆O₇Br₂S: C, 51.31; H, 3.11; N, 13.30; Found: C, 51.72; H, 3.41; N, 13.79; MS: [M]+ at m/z 842.58.

The following compounds 32-39 were prepared using a similar procedure described for compound (31). The physical and spectral data of these compounds are given below.

2-Phenyl-1-[4¢-(4-chlorobenzylidene)-amino-5¢-(2-aminothiol-4-ythio)-1'2,2',4'-triazol-3'-yl-methyl-3(4¢,6¢-dibromo-2'-carboxyphenyl iminomethyl)-5-methoxy-indole (32).

Yield (46%), (Ethanol), m.p: 243°C; IR (KBr) δ max in cm⁻¹: 3322(NH₂), 3030 (C-H aromatic), 2920 (C-H aliphatic), 1723 (C=O), 1717 (COOH), 1570 (C=N), 1524 (N-N), 785 (C-CI), 695 (C-S-C), 568 (C-Br). ¹HNMR (CDCl₃) δ in ppm: 9.64 (s, 1H, COOH), 8.40 (s, 2H, 2 X N=CH), 6.82-7.95 (m, 15H, Ar-H), 6.30 (s, 2H, -NH₂ exchangeable with D₂O), 4.82 (s, 2H, N-CH₂Ar), 4.61 (s, 1H, N-CH₂Ar), 3.38 (s, 3H, OCH₃). Anal.Calcd. for C₃₇H₂₉N₆O₇ClBr₂S: C, 49.30; H, 2.87; N, 12.78; Found: C, 49.63; H, 2.35; N, 12.38; MS: [M]+ at m/z 877.00.

2-Phenyl-1-[4¢-(4-methoxybenzylidene)-amino-5¢-(2-aminothiol-4-ythio)-1'2,2',4'-triazol-3'-yl-methyl-3(4¢,6¢-dibromo-2'-carboxyphenyl iminomethyl)-5-methoxy-indole (33).

Yield (48%), (Ethyl acetate), m.p: 278°C; IR (KBr) δ max in cm⁻¹: 3318 (NH₂), 3033 (C-H aromatic), 2924 (C-H aliphatic), 1723 (C=O), 1714 (COOH), 1570 (C=N), 1523 (N-N), 1170 (C-O-C), 690 (C-S-C), 562 (C-Br). ¹HNMR (CDCl₃) δ in ppm: 9.61 (s, 1H, COOH), 8.42 (s, 2H, 2 X N=CH), 6.82-7.94 (m, 15H, Ar-H), 6.30 (s, 2H, -NH₂ exchangeable with D₂O), 4.82 (s, 2H, N-CH₂Ar), 4.61 (s, 1H, N-CH₂Ar), 3.44 (s, 6H, 2 X OCH₃). Anal.Calcd. for C₃₇H₂₉N₆O₇ClBr₂S: C, 50.93; H, 3.23; N, 12.84; Found: C, 50.65; H, 3.75; N, 12.39; MS: [M]+ at m/z 872.61.

2-(4-Chlorophenyl)-1-[4¢-(benzylidene)-amino-5¢-(2-aminothiol-4-ythio)-1'2,2',4'-triazol-3'-yl-methyl-3(4¢,6¢-dibromo-2'-carboxyphenyl iminomethyl)-5-methoxy-indole (34).

Yield (50%), (Methanol), m.p: 255°C; IR (KBr) δ max in cm⁻¹: 3325 (NH₂), 3030 (C-H aromatic), 2921(C-H aliphatic), 1728 (C=O), 1715 (COOH), 1585 (C=N), 1525 (N-N), 792 (C-CI), 688 (C-S-C), 561 (C-Br). ¹HNMR (CDCl₃) δ in ppm: 9.62 (s, 1H, COOH), 8.42 (s, 2H, 2 X N=CH), 6.81-7.92 (m, 15H, Ar-H), 6.30 (s, 2H, -NH₂ exchangeable with D₂O), 4.83 (s, 2H, N-CH₂Ar), 4.61 (s, 1H, N-CH₂Ar), 3.39 (s, 3H, OCH₃). Anal.Calcd. for C₃₇H₂₉N₆O₇ClBr₂S: C, 49.30; H, 2.87; N, 12.78; Found: C, 50.69; H, 2.19; N, 12.36; MS: [M]+ at m/z 877.00.

2-(4-Chlorophenyl)-1-[4¢-(4-chlorobenzylidene)amino-5¢-(2-aminothiol-4-ythio)-1'2,2',4'-triazol-3'-yl-methyl-3(4¢,6¢-dibromo-2'-carboxyphenylimino methyl)-5-methoxy-indole (35).

Yield (48%), (Ethanol), m.p: 270°C; IR (KBr) δ max in cm⁻¹: 3323 (NH₂), 3033 (C-H aromatic), 2925 (C-H aliphatic), 1720 (C=O), 1710 (COOH), 1575 (C-N),
1520 (N-N), 790 (C-Cl), 690 (C-S-C), 565 (C-Br).

\[ \text{IR (KBr)} \quad \text{max} \] in cm\(^{-1}\): 8.16 (s, 1H, COOH), 8.40 (s, 2H, 2 X N=CH), 6.85-7.89 (m, 14H, Ar-H), 6.30 (s, 2H, -NH\(_2\) exchangeable with D\(_2\)O), 4.80 (s, 2H, -NH\(_2\) exchangeable with D\(_2\)O), 4.82 (s, 2H, N-CH\(_3\)), 4.60 (s, 1H, N-CH=Ar), 3.42 (s, 3H, OCH\(_3\)).

**Conclusion**

Further more the substitution with phenyl group having a chloro group at p-position showed better activities than other group.

The azetidinones showed better anti-inflammatory and analgesic activities than parent compounds but less than thiazalidinones.
Antioxidant activity
This study was done by following the procedure of Winter et al. The rats were divided into three groups (control, drugs treated and standard drugs) of six animals each. A freshly prepared suspension of carrageenan (1% in 0.9% saline), 0.05 mL was injected under the planter aponeurosis of the right hind paw of each rat. The compound and standard drug were administered orally to the animals of drug treated groups and the standard drug group, respectively, 1 hr before the carrageenan injection. The paw volume of each rat was measured before 1 hr and after 3 hr of carrageenan treatment with the help of a Plethysmometer. The percent anti-inflammatory activity was calculated according to the formula given below.

\[
\text{Percentage of inhibition of oedema} = \left(1 - \frac{V_t}{V_c}\right) \times 100
\]

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

Analgesic activity
Acetic acid writhing test was performed on mice by following the method of Davis et al. Test compounds were given to the animals at the dose of 50 mg/kg. 30 min later the animals were injected intraperitoneally with 0.25 mL /mouse of 0.5% acetic acid. The mean number of writhes for each experimental groups and percentage decrease compared with the control group was calculated after 60 min.

Ulcerogenic activity
Ulcerogenic liabilities of newly synthesized compounds were checked by the method of Verma et al. Albino rats were fasted for 24 hr prior to drug administration. All animals were sacrificed 8 hr after drug treatment and then their stomachs and small intestines were microscopically examined to assess the incidence of hyperaemia, shedding of epithelium, petechial and frank haemorrhages and erosion or discrete ulceration with or without perforation. The presence of any one of these criteria was considered to be an evidence of ulcerogenic activity.

Acute toxicity
Acute Lethal dose (ALD\(_{50}\)) of all the compounds were investigated by the method of Smith, Q.E.

RESULTS AND DISCUSSION
All the newly synthesized compounds 3-39 were tested in vivo in order to evaluate their anti-inflammatory and analgesic activities. These compounds were screened for their anti-inflammatory and analgesic activities at a dose of 50 mg/kg p.o. exhibited substantive anti-inflammatory activity of varying degree from 9.3-37.4% and analgesic activity of varying degree 6.4-33.9% are given in Table 1.

The characteristic feature of this series is substituted phenyl moiety at second position of indole nucleus. It was observed that compound 35 showed maximum anti-inflammatory 37.4% inhibition of oedema and inhibition of 33.9% of writhes. This compound showed better anti-inflammatory and analgesic activities than standard drug phenylbutazone at the three graded doses of 25, 50 and 100 mg/kg p.o. but showed lesser activity than reference drug indomethacin. Further more the substitution with chloro group at 2nd position of phenyl ring showed better activities than other groups. ALD\(_{50}\) of all compounds is > 1000 mg/kg p.o.

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<th>Analgesic activity % decrease of writhes in 60 min after treatment relative to control</th>
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