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Synthesis and Anti-inflammatory Activity of Indole Derivatives

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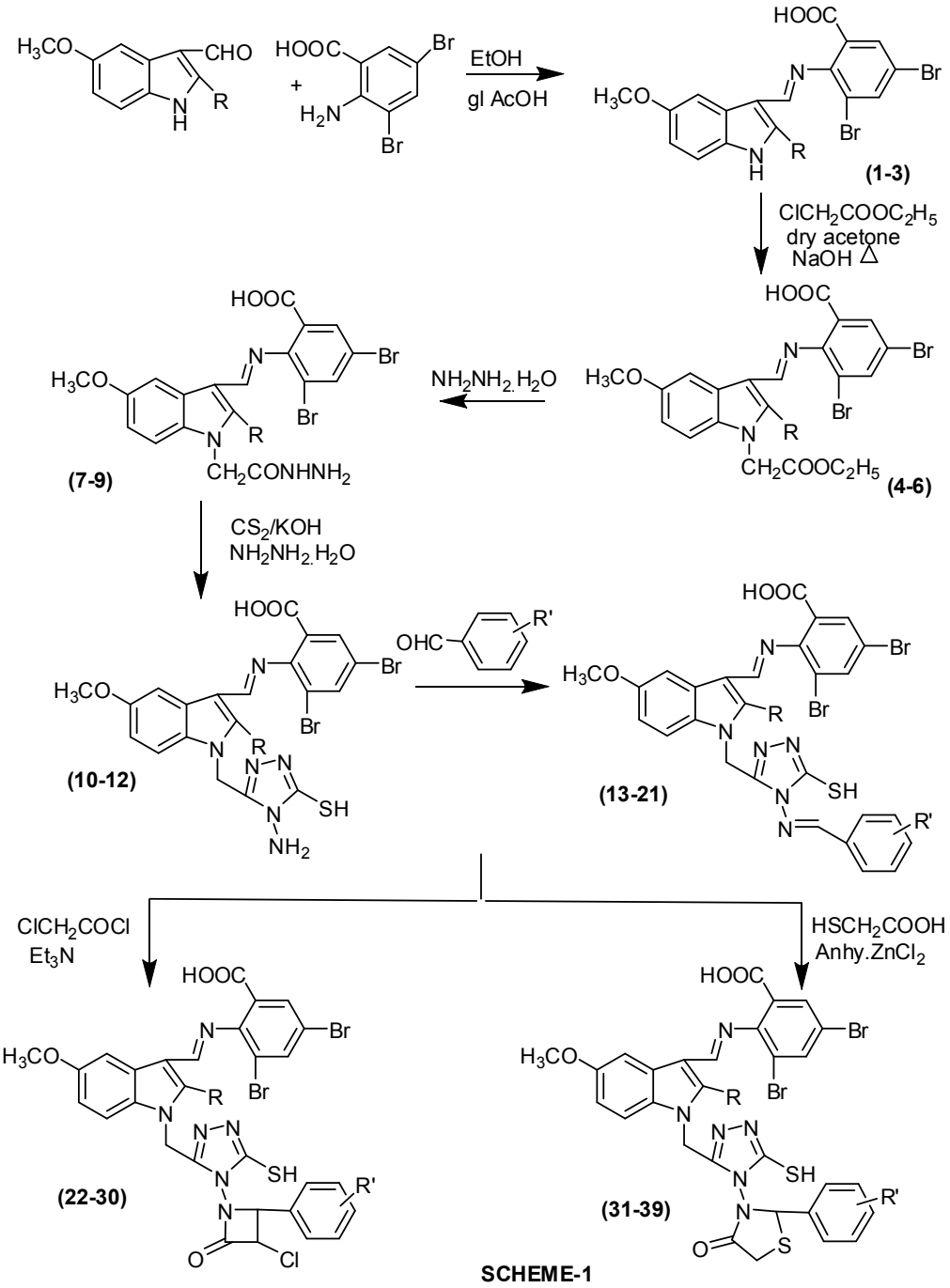
ABSTRACT: The present investigation is concerned with synthesis of new substituted indole derivatives **1-39** with the objective of discovering novel and potent anti-inflammatory agent. The structure of all the synthesized compounds were elucidated by spectral (IR, ^{1}HNMR and mass) and elemental (C, 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

INTERODUCTION

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 antibacterial[1,2], antifungal[3], anti-inflammatory[4-8] and analgesic[9]. 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, triazole[10-13] compounds with another heterocyclic ring are significant agents for the treatment of inflammation. It is evident from chemical literature that thiazolidinones[14-17] and azetidinones[18-21] 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 in $\pm$ 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 ^{1}H spectra were recorded on a DPX-300 MHz, Bruker FT-NMR spectrometer. The chemical shifts were reported as parts per million (δ ppm).



SCHEME-1

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^{o}C; IR (KBr) ν_{max} in cm^{-1}; 3005 (N-H), 3030 (C-H aromatic), 1710 (C=O), 1585 (C=N), 578 (C-Br).

^{1}HNMR ($CDCl_3$) δ in ppm : 9.68 (s, 1H, Ar-COO<u>H</u>), 8.75 (s, 1H, N<u>H</u> exchangeable), 8.44 (s, 1H, N=C<u>H</u>), 6.92-7.58 (m, 10H, Ar-<u>H</u>), 3.35 (s, 3H, OC<u>H</u>$_3$). Anal.Calcd. for $C_{23}H_{16}N_2O_3Br_2$: 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) ν_{max} in cm^{-1};3010 (NH), 3033 (C-H aromatic), 1705 (C=O), 1588 (C=N), 785 (C-Cl), 570 (C-Br). ^{1}HNMR ($CDCl_3$) δ in ppm : 9.65 (s, 1H, Ar-COOH), 8.75 (s, 1H, NH exchangeable), 8.39 (s, 1H, N=CH), 6.88-7.65 (m, 9H, Ar-H), 3.32 (s, 3H, OCH_3).Anal Calcd. for $C_{23}H_{15}N_2O_3ClBr_2$: C, 49.10 ; H, 2.69 ; N, 4.98 ; Found : C, 49.87 : H, 2.10 ; N, 5.05 ; MS : $[M]^+$at m/z 562.64.

2-(4-Methylphenyl)-3-(4',6'-dibromo-2'-carboxyphenyliminomethyl)-5-methoxy-indole (3).
Yield (72%), (Acetone), m.p. 240°C; IR (KBr) ν_{max} in cm^{-1};3005 (NH), 3028 (C-H aromatic), 1715 (COOH), 1580 (C=N), 575 (C-Br). ^{1}HNMR ($CDCl_3$) δ in ppm : 9.62 (s, 1H, Ar-COOH), 8.72 (s, 1H, NH exchangeable), 8.42 (s, 1H, N=CH), 6.90-7.60 (m, 9H, Ar-H), 2.19 (s, 3H, CH_3) , 3.33 (s, 3H, OCH_3).Anal.Calcd.for $C_{24}H_{18}N_2O_3Br_2$: C, 53.16; H, 3.35; N, 5.17; Found : C, 53.75: H, 3.95; N, 5.29; MS : $[M]^+$ at m/z 542.22.

2-Phenyl-1-carboxymethyl-3-(4',6'-dibromo-2'-carboxyphenyliminomethyl)-5-methoxy-indole (4).
A mixture of compound **1** (0.01 mole), ethyl chloroacetate (0.01 mole), anhydrous acetone (90 ml) and NaOH (8 g) was heated under reflux of 22 hours. After cooling, it was wash with excess of water the solid was filtered and dried, again washed with ethanol. The solid was obtained and recrystallized from ethanol to yield compound **4** (73%). m.p: 265°C; IR (KBr) ν_{max} in cm^{-1}; 3035 (C-H aromatic), 2925 (C-H aliphatic) 1778 (COOEt), 1710 (COOH), 1570 (C=N), 575 (C-Br), ^{1}HNMR ($CDCl_3$) δ in ppm: 9.60 (s, 1H, Ar-COOH), 8.43 (s, 1H, N=CH), 6.90-7.75 (m, 10H, Ar-H), 4.70 (s, 2H, N-CH_2), 4.44 (q, J=7 Hz, 2H ester CH_2), 1.55 (t, J=7 Hz, 3H, ester CH_3), 3.36 (s, 3H, OCH_3). Aanl.Calcd. for $C_{27}H_{22}N_2O_5Br_2$; C, 52.79; H, 3.61; N, 4.56; Found : C, 52.72; H, 3.95; N, 4.66; MS : $[M]^+$ at m/z 614.28.
The following compounds **(5-6)** were prepared using a similar procedure described for compound **(4).** The physical and spectral data of these compounds are giving below.

2-(4-Chlorophenyl)-1-carboxymethyl-3-(4',6'-dibromo-2'-carboxyphenylimino methyl) -5-methoxy indole (5).
Yield (71%), (Methanol), m.p: 253° C; IR (KBr) ν_{max} in cm^{-1};3030 (C-H aromatic), 2920 (C-H aliphatic), 1772 (COOEt), 1712 (COOH), 1575 (C=N), 788 (C-Cl), 572 (C-Br); ^{1}HNMR ($CDCl_3$) δ in ppm: 9.60 (s, 1H, Ar-COOH), 8.40 (s, 1H, N=CH), 6.95-7.85 (m, 9H, Ar-H), 4.75 (s, 2H, N-CH_2), 4.41 (q, J=7 Hz, 2H ester CH_2), 1.50 (t, J=7 Hz, 3H, ester CH_3), 3.30 (s, 3H, OCH_3). Aanl.Calcd. for $C_{27}H_{21}N_2O_5ClBr_2$; C, 49.99 ; H, 3.26 ; N, 4.32 ; Found : C,49.63 ; H, 3.62 ; N, 4.11 ; MS : $[M]^+$ at m/z 648.73.

2-(4-Methylphenyl)-1-carboxymethyl-3-(4',6'-dibromo-2'-carboxy phenylimino methyl)-5-methoxy indole (6).
Yield (66%), (Ethylacetate), m.p: 297°C; IR (KBr) ν_{max} in cm^{-1}; 3028 (C-H aromatic), 2926 (C-H aliphatic), 1775 (COOEt), 1715 (COOH), 1570 (C=N), 575 (C-Br); ^{1}HNMR ($CDCl_3$) δ in ppm: 9.57 (s, 1H, Ar-COOH), 8.44 (s, 1H, N=CH), 6.90-7.78 (m, 9H, Ar-H), 4.72 (s, 2H, N-CH_2), 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 $C_{28}H_{24}N_2O_5Br_2$; 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) ν_{max} in cm^{-1}; 3310 (N-H), 3030 (C-H aromatic), 2920 (C-H aliphatic), 1715 (COOH), 1650 (C=O amide), 1572 (C=N), 575 (C-Br); ^{1}HNMR ($CDCl_3$) δ in ppm: 9.65 (s, 1H, COOH), 8.45 (s, 1H, N=CH), 6.87-7.79 (m, 10H, Ar-H), 5.60 (br, 1H, NH exchangeable), 4.70 (s, 2H, N-CH_2), 4.58 (hump, 2H, NH_2 exchangeable), 3.35 (s, 3H, OCH_3).Anal. Calcd.for $C_{25}H_{20}N_4O_4Br_2$: C, 50.02; H, 3.36; N, 9.33; Found : C, 50.79; H, 3.81; N, 9.13; 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 giving below.

2-(4-Chlorophenyl)-1-(hydrazinocarbonylmethyl)-3-(4',6'-dibromo-2'-carboxyphenyl-iminomethyl)-5-methoxy-indole (8).
Yield (65%), (Ethanol), m.p:175°C; IR (KBr) ν_{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 ($CDCl_3$) δ in ppm : 9.58 (s, 1H, COOH), 8.42 (s, 1H, N=CH), 6.89-7.81 (m, 9H, Ar-H), 5.55 (br, 1H, NH exchangeable), 4.75 (s, 2H, N-CH_2), 4.56 (hump, 2H, NH_2 exchangeable), 3.33 (s, 3H, OCH_3). Anal Calcd.for $C_{25}H_{19}N_4O_4ClBr_2$: 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'-dibromo2'-carboxyphenyl-iminomethyl)- 5-methoxy-indole (9).
Yield (60%), (Acetone), m.p:196°C; IR (KBr) ν_{max} in cm^{-1}; 3308 (NH), 3040 (C-H aromatic), 2930 (C-H aliphatic), 1715 (COOH), 1646 (C=O amide), 1573 (C=N), 576 (C-Br); ^{1}HNMR ($CDCl_3$) δ in ppm: 9.55 (s, 1H, COOH), 8.46 (s, 1H, N=CH), 6.83-7.77 (m, 9H, Ar-H), 5.58 (br, 1H, NH exchangeable), 4.76 (s, 2H, N-CH_2), 4.52 (hump, 2H, NH_2 exchangeable), 2.26 (s, 3H, CH_3), 3.38 (s, 3H, OCH_3). Anal.calcd. for $C_{26}H_{22}N_4O_4Br_2$: C, 50.84; H, 3.61; N, 9.12; Found : C, 50.48; H, 3.74; N, 9.81; MS: $[M]^+$ at m/z 612.29.

2-Phenyl-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'-carboxy phenyl imino 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 for 4 hours till the evolution of H_2S ceased. The reaction mixture was poured into ice-cold water. The separated solid was filtered washed with water, dried and recrystallized from acetic acid to yield compound **10** (60%). m.p: 204°C; IR (KBr) ν_{max} in cm^{-1} ; 3305 (N-H), 3030 (C-H aromatic), 2925 (C-H aliphatic), 1708 (COOH), 1570 (C=N), 1525 (N-N), 576 (C-Br); ^{1}HNMR ($CDCl_3$) δ in ppm: 9.58 (s, 1H, COOH), 8.46 (s, 1H, N=CH), 6.86-7.79 (m, 10H, Ar-H), 4.69 (s, 2H, N-CH_2), 4.58 (hump, 2H, NH_2 exchangeable), 2.58 (s, 1H, SH), 3.39 (s, 3H, OCH_3). Anal.Calcd. for $C_{26}H_{20}N_6O_3Br_2S$: C, 47.58; H, 3.07; N, 12.80 ;Found : C, 47.38 ; H, 3.41 ; N, 12.40 ; MS: $[M]^+$ at m/z. 656.35.
The following compounds **(11-12)** were prepared using a similar procedure described for compound **(10).**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 (11).
Yield(66%),(Ethanol), m.p. 198°C; IR (KBr) ν_{max} 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); ^{1}HNMR ($CDCl_3$) δ 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-CH_2), 4.55 (hump, 2H, NH_2 exchangeable), 2.55 (s, 1H, SH) , 3.40 (s, 3H, OCH_3). Anal.Calcd.for $C_{26}H_{19}N_6O_3Br_2SCl$: 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-(4-Methylphenyl)-1-(4'-amino-5'-mercapto-[1',2',4']-triazol-3'-yl-methyl)-3-(4",6"-dibromo-2"-carboxyphenyliminomethyl}-5-methoxy-indole (12).
Yield (59%), (Ethyl acetate), m.p: 209°C; IR (KBr) ν_{max} in cm^{-1}; 3310 (N-H), 3030 (C-H aromatic), 2925 (C-H aliphatic), 1710 (COOH), 1570 (C=N), 1525 (N-N), 572 (C-Br); ^{1}HNMR ($CDCl_3$) δ in ppm: 9.56 (s, 1H, COOH), 8.39 (s, 1H, N=CH), 6.79-7.68 (m, 9H, Ar-H), 4.75 (s, 2H, N-CH_2), 4.51 (hump, 2H, NH_2 exchangeable), 2.58 (s, 1H, SH), 2.28 (s, 3H, CH_3), 3.37 (s, 3H, OCH_3). Anal.Calcd. for $C_{27}H_{22}N_6O_3Br_2S$: C, 48.37; H, 3.31; N, 12.54: Found : C, 48.04 ; H, 3.31; N, 12.12; MS: $[M]^+$ at m/z. 670.37.

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 benzaldehyde (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) ν_{max} in cm^{-1}; 3030 (C-H aromatic), 2925 (C-H aliphatic), 1712 (COOH), 1573 (C=N), 1517 (N-N), 575 (C-Br); ^{1}HNMR ($CDCl_3$), δ in ppm: 9.60 (s, 1H, COOH), 8.40 (s, 2H, 2 X N=CH), 6.78-7.79 (m, 15H, Ar-H), 4.72 (s, 2H, N-CH_2), 2.56 (s, 1H, SH), 3.35 (s, 3H, OCH_3). Anal.Calcd. for $C_{33}H_{24}N_6O_3Br_2S$: C, 53.24; H, 3.15; N, 11.29: Found: C, 53.95; H, 3.33; 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'-(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) ν_{max} 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). ^{1}HNMR ($CDCl_3$), δ in ppm : 9.62 (s, 1H, COOH), 8.42 (s, 2H, 2X N=CH), 6.80-7.89 (m, 14H, Ar-H), 4.75 (s, 2H, N-CH_2), 2.54 (s, 1H, SH), 3.36 (s, 3H, OCH_3). Anal.Calcd.for $C_{33}H_{23}N_6O_3ClBr_2S$: C, 50.89; H, 2.98 ; N, 10.79

:;Found : C, 50.28 ; H, 2.28 ; N, 10.39 ; MS: $[M]^+$ at m/z. 778.90.

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) ν_{max} 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). ^{1}HNMR ($CDCl_3$), δ in ppm : 9.65 (s, 1H, COO<u>H</u>), 8.42 (s, 2H, 2X N=CH), 6.77-7.91 (m, 14H, Ar-H), 4.75 (s, 2H, N-C<u>H</u>$_2$), 3.42 (s, 6H, 2 X OC<u>H</u>$_3$), 2.54 (s, 1H, S<u>H</u>). Anal.Calcd.for $C_{34}H_{26}N_6O_4Br_2S$: 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'-(benzylidine)-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) ν_{max} 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). ^{1}HNMR ($CDCl_3$), δ in ppm : 9.62 (s, 1H, COO<u>H</u>), 8.45 (s, 2H, 2X N=CH), 6.80-7.89 (m, 14H, Ar-H), 4.75 (s, 2H, N-C<u>H</u>$_2$), 2.54 (s, 1H, S<u>H</u>), 3.36 (s, 3H, OC<u>H</u>$_3$). Anal.Calcd.for $C_{33}H_{23}N_6O_3ClBr_2S$: C, 50.89; H, 2.98 ; N, 10.79: Found : C, 50.38 ; H, 2.30 ; N, 10.38 ;MS: $[M]^+$ at m/z. 778.90.

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) ν_{max} 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). ^{1}HNMR ($CDCl_3$), δ in ppm : 9.60 (s, 1H, COO<u>H</u>), 8.45 (s, 2H, 2X N=CH), 6.77-7.76 (m, 13H, Ar-H), 4.72 (s, 2H, N-C<u>H</u>$_2$), 2.56 (s, 1H, S<u>H</u>), 3.38 (s, 3H, OC<u>H</u>$_3$). Anal.Calcd.for $C_{33}H_{22}N_6O_3Cl_2Br_2S$: 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) ν_{max} in cm^{-1}; 3030 (C-H aromatic), 2926 (C-H aliphatic), 1715 (COOH), 1585 (C=N), 1525 (N-N), 1172 (C-O-C), 785 (C-Cl), 565 (C-Br). ^{1}HNMR ($CDCl_3$), δ in ppm: 9.59 (s, 1H, COO<u>H</u>), 8.40 (s, 2H, 2X N=CH), 6.82-7.93 (m, 13H, Ar-H), 4.72 (s, 2H, N-C<u>H</u>$_2$), 3.45 (s, 6H, 2 X OC<u>H</u>$_3$), 2.51 (s, 1H, S<u>H</u>). Anal.Calcd. for $C_{34}H_{25}N_6O_4Cl\ Br_2S$: 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-Methylphenyl)-1-{4'-(benzylidine)-amino-5'-mercapto-[1',2',4']-triazol-3'-yl-methyl-3-(4",6"-dibromo-2"-carboxyphenyliminomethyl}-5-methoxy-indole (19).

Yield (64%),(Mthanol), m.p: 224°C ;IR (KBr) ν_{max} in cm^{-1}; 3035 (C-H aromatic), 2925 (C-H aliphatic), 1712 (COOH), 1578 (C=N), 1524 (N-N), 560 (C-Br). ^{1}HNMR ($CDCl_3$), δ in ppm : 9.65 (s, 1H, COO<u>H</u>), 8.46 (s, 2H, 2 X N=CH), 6.84-7.94 (m, 14H, Ar-H), 4.72 (s, 2H, N-C<u>H</u>$_2$), 2.54 (s, 1H, S<u>H</u>), 2.23 (s, 3H, C<u>H</u>$_3$) , 3.41 (s, 3H, OC<u>H</u>$_3$); Anal.Calcd. for $C_{34}H_{26}N_6O_3Br_2S$: 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-Methylphenyl)1-{4'-(4-chlorobenzylidine)-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) ν_{max} 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). ^{1}HNMR ($CDCl_3$), δ in ppm : 9.64 (s, 1H, COO<u>H</u>), 8.39 (s, 2H, 2 X N=CH), 6.83-7.95 (m, 13H, Ar-H), 4.72 (s, 2H, N-C<u>H</u>$_2$), 2.51 (s, 1H, S<u>H</u>), 2.25 (s, 3H, C<u>H</u>$_3$) , 3.42 (s, 3H, OC<u>H</u>$_3$). Anal.Calcd or $C_{34}H_{25}N_6O_3ClBr_2S$: 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-Methylphenyl)-1-{4'-(4-methoxybenzylidine)-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) ν_{max} 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). ^{1}HNMR ($CDCl_3$), δ in ppm : 9.59 (s, 1H, COO<u>H</u>), 8.44 (s, 2H, 2 X N=CH), 6.82-7.96 (m, 13H, Ar-<u>H</u>), 4.71 (s, 2H, N-C<u>H</u>$_2$), 3.42 (s, 6H, 2 X OC<u>H</u>$_3$), 2.51 (s, 1H, SH), 2.22(s, 3H, C<u>H</u>$_3$). Anal.Calcd. for $C_{35}H_{28}N_6O_4Br_2S$: 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-Phenyl-1-{4'-(benzylidine)-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%) mp. 212°C ; IR (KBr) ν_{max} in cm^{-1}; 3035 (C-H aromatic), 2922 (C-H aliphatic), 1745 (C=O), 1710 (COOH), 1578 (C=N), 1528 (N-N), 660 (C-Cl), 560 (C-Br). ^{1}HNMR ($CDCl_3$) δ in ppm: 9.62 (s, 1H, COO<u>H</u>), 8.41 (s, 2H, 2 X N=CH), 6.82-7.93 (m, 15H, Ar-<u>H</u>), 4.75 (s, 2H, N-C<u>H</u>$_2$), 3.44(s, 2H, C<u>H</u>$_2$Cl), 3.35 (s, 3H, OC<u>H</u>$_3$). Anal.Calcd. for $C_{35}H_{25}N_6O_4ClBr_2S$: 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 giving 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) ν_{max} in cm^{-1};3033 (CH aromatic), 2925 (CH aliphatic), 17445 (C=O), 1710 (COOH), 1570 (C=N), 1524 (N-N), 788 (C-Cl), 565 (C-Br). ^{1}HNMR ($CDCl_3$) δ in ppm: 9.64 (s, 1H, COO<u>H</u>), 8.41 (s, 2H, 2 X N=CH), 6.79-7.88 (m, 14H, Ar-<u>H</u>), 4.75 (s, 2H, N-C<u>H</u>$_2$), 3.45 (s, 2H, C<u>H</u>$_2$Cl), 3.38 (s, 3H, OC<u>H</u>$_3$). Anal.Calcd. for $C_{35}H_{24}N_6O_4Cl_2Br_2S$: C, 49.14; H, 2.83; N, 9.82; Found: C, 49.81; H, 3.11 ; N, 9.69 ;MS : $[M]^+$ at m/z 855.38.

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) ν_{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). ^{1}HNMR ($CDCl_3$) δ in ppm: 9.61 (s, 1H, COO<u>H</u>), 8.40 (s, 2H, 2 X N=CH), 6.80-7.91 (m, 14H, Ar-<u>H</u>), 4.72 (s, 2H, N-C<u>H</u>$_2$), 3.46 (s, 2H, C<u>H</u>$_2$Cl), 3.43 (s, 6H, 2 X OC<u>H</u>$_3$). Anal.Calcd.for $C_{36}H_{27}N_6O_5ClBr_2S$: 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) ν_{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). ^{1}HNMR ($CDCl_3$) δ in ppm: 9.64 (s, 1H, COO<u>H</u>), 8.39 (s, 2H, 2 X 1H, N=C<u>H</u>), 6.79-7.91 (m, 14H, Ar-<u>H</u>), 4.75 (s, 2H, N-C<u>H</u>$_2$), 3.46 (s, 2H, C<u>H</u>$_2$Cl), 3.36 (s, 3H, OC<u>H</u>$_3$) Anal.Calcd. for $C_{35}H_{24}N_6O_3Cl_2Br_2S$: 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.

2-(4-Chlorophenyl)-1-{4'-(p-chlorobenzylidine)amino-5'-(2-chloroacetylthio)-[1',2',4']-triazol-3'-yl-methyl-3-(4",6"-dibromo-2"-carboxyphenyliminomethyl]-5-methoxy-indole (26).

Yield (46%), (Pet/ether), m.p: 256°C; IR (KBr) ν_{max} in cm^{-1}; 3035 (C-H aromatic), 2920 (C-H aliphatic), 1740 (C=O), 1712 (COOH), 1575 (C=N), 1520 (N-N), 790 (C-Cl), 560 (C-Br). ^{1}HNMR ($CDCl_3$) δ in ppm: 9.60 (s, 1H, COO<u>H</u>), 8.43 (s, 2H, 2 X N=CH, 6.82-7.93 (m, 13H, Ar-<u>H</u>), 4.78 (s, 2H, N-C<u>H</u>$_2$), 3.46 (s, 2H, C<u>H</u>$_2$Cl), 3.35 (s, 3H, OC<u>H</u>$_3$). Anal.Calcd. for $C_{35}H_{23}N_6O_4Cl_3Br_2S$: C, 47.24; H, 2.61; N, 9.44; Found: C, 47.95 ; H, 2.88 ; N, 9.65 ; MS : $[M]^+$ at m/z 889.83.

2-(4-Chlorophenyl)-1-{4'-(p-methoxybenzylidine)-amino-5'-(2-chloroacetylthio)-[1',2',4']-triazol-3'-yl-methyl-3-(4",6"-dibromo-2"-carboxy phenyl iminomethyl]-5-methoxy-indole (27).

Yield (45%), (Methanol), m.p: 235°C; IR (KBr) ν_{max} in cm^{-1}; 3030 (C-H aromatic), 2925 (C-H aliphatic), 1745 (C=O), 1714 (COOH), 1570 (C=N), 1524 (N-N), 1178 (C-O-C), 785 (C-Cl), 560 (C-Br). ^{1}HNMR ($CDCl_3$) δ in ppm: 9.58 (s, 1H, COO<u>H</u>), 8.41 (s, 2H, 2 X N=CH), 6.84-7.94 (m, 13H, Ar-<u>H</u>), 4.75 (s, 2H, N-C<u>H</u>$_2$), 3.44 (s, 6H, 2 X OC<u>H</u>$_3$), 3.41 (s, 2H, C<u>H</u>$_2$Cl). Anal.Calcd. for $C_{36}H_{26}N_6O_5Cl_2Br_2S$: C, 48.83; H, 2.96; N, 9.49: Found: C, 50.29; H, 3.23; N, 7.79 : MS $[M^+]$ at m/z 885.41.

2-(4-Methylphenyl)-1-{4'-(benzylidine)-amino-5'-(2-chloroacetylthio)-[1',2',4']-triazol-3'-yl-methyl-3-(4",6"-dibromo-2"-carboxyphenyliminomethyl]-5-methoxy-indole(28).

Yield (47%), (Ethanol), m.p: 235°C; IR (KBr) ν_{max} in cm^{-1}; 3038 (C-H aromatic), 2925 (C-H aliphatic), 1745 (C=O), 1715 (COOH), 1571 (C=N), 1525 (N-N), 565 (C-Br). ^{1}HNMR ($CDCl_3$) δ in ppm: 9.63 (s, 1H, COO<u>H</u>), 8.46 (s, 2H, 2 X N=CH), 6.84-7.99 (m, 14H, Ar-<u>H</u>), 4.75 (s, 2H, N-C<u>H</u>$_2$), 3.45 (s, 2H, C<u>H</u>$_2$Cl), 2.20 (s, 3H, C<u>H</u>$_3$) , 3.30 (s, 3H, OC<u>H</u>$_3$). Anal.Calcd. for $C_{36}H_{27}N_6O_4ClBr_2S$: C, 51.78; H, 3.36; N, 10.07; Found : C, 51.62 ; H, 3.59 ; N, 10.63 ; MS : $[M]^+$ at m/z 833.98.

2-(4-Methylphenyl)1-{4'-(4-chlorobenzylidine)-amino-5'-(2-chloroacetylthio)-[1',2',4']-triazol-3'-yl-methyl-3-(4",6"-dibromo-2"-carboxyphenyl iminomethyl]-5-methoxy-indole (29).

Yield (51%), (Pet/ether), m.p: 243°C ; IR (KBr) ν_{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-Cl), 565 (C-Br). ^{1}HNMR ($CDCl_3$) δ in ppm: 9.64 (s, 1H, COOH), 8.41 (s, 2H, 2 X N=CH), 6.81-7.95 (m, 13H, Ar-H), 4.77 (s, 2H, N-CH_2), 3.44 (s, 2H, CH_2Cl), 2.23 (s, 3H, CH_3), 3.28 (s, 3H, OCH_3). Anal.Calcd.for $C_{36}H_{26}N_6O_4Cl_2Br_2S$: C, 49.73; 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-methoxybenzylidine)-amino-5'-(2-chloroacetylthio)-[1',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) ν_{max} in cm^{-1}; 3030 (CH aromatic), 2925 (CH aliphatic), 1744 (C=O), 1710 (COOH), 1571 (C=N), 1525 (N-N), 1178 (C-O-C), 560 (C-Br). ^{1}HNMR ($CDCl_3$) 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-CH_2), 3.44 (s, 6H, 2 X OCH_3), 3.48 (s,2H, CH_2Cl), 2.19 (s, 3H, CH_3). Anal.Calcd. for $C_{37}H_{29}N_6O_5ClBr_2S$: 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-Phenyl-1-{4'-(benzylidine)-amino-5'-(2-aminothiazol-4-ylthio)-[1',2',4']-triazol-3'-yl-methyl}-3-(4",6"-bromo-2"-carboxyphenyl iminomethyl]- 5-methoxy-indole (31).

To a solution of compound **22** (0.01mole) in hot absolute ethanol (250 ml) was reacted with a solution of thiourea (0.01mole) in absolute ethanol (50ml) then refluxed the reaction mixture for 14 hours. The reaction mixture which is in the form of HCl is saturated with $NaHCO_3$ 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) ν_{max} in cm^{-1}; 3320 (NH_2), 3033 (C-H aromatic), 2920 (C-H aliphatic), 1722 (C=O), 1714 (COOH), 1570 (C=N), 1524 (N-N), 685 (C-S-C), 560 (C-Br). ^{1}HNMR ($CDCl_3$) 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, -NH_2 exchangeable with D_2O), 4.78 (s, 2H, N-CH_2), 4.60 (s, 1H, N-CH-Ar), 3.37 (s, 3H, OCH_3). Anal.Calcd. for $C_{36}H_{26}N_8O_3Br_2S_2$: 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 giving below.

2-Phenyl-1-{4'-(4-chlorobenzylidine)-amino-5'-(2-aminothiazol-4-ylthio)-[1',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) ν_{max} in cm^{-1}; 3322(NH_2), 3030 (C-H aromatic), 2920 (C-H aliphatic), 1723 (C=O), 1717 (COOH), 1570 (C=N), 1524 (N-N), 785 (C-Cl), 695 (C-S-C), 568 (C-Br). ^{1}HNMR ($CDCl_3$) 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,-NH_2 exchangeable with D_2O), 4.82 (s, 2H, N-CH_2), 4.61 (s, 1H, N-CH-Ar), 3.38 (s, 3H, OCH_3). Anal.Calcd. for $C_{36}H_{25}N_8O_3Cl\ Br_2S_2$: 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-methoxybenzylidine)-amino-5'-(2-aminothiazol-4-ylthio)-[1',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) ν_{max} in cm^{-1}; 3318 (NH_2), 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). ^{1}HNMR ($CDCl_3$) 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, -NH_2 exchangeable with D_2O), 4.82 (s, 2H, N-CH_2), 4.61 (s, 1H, N-CH-Ar), 3.44 (s, 6H, 2 X OCH_3). Anal.Calcd. for $C_{37}H_{28}N_8O_4Br_2S_2$: 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'-(benzylidine)-amino-5'-(2-aminothiazol-4-ylthio)-[1',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) ν_{max} in cm^{-1}; 3325 (NH_2), 3030 (C-H aromatic), 2921(C-H aliphatic), 1728 (C=O), 1715 (COOH), 1585 (C=N), 1525 (N-N), 792 (C-Cl), 688 (C-S-C), 561 (C-Br). ^{1}HNMR ($CDCl_3$) 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,-NH_2 exchangeable with D_2O),4.83 (s, 2H, N-CH_2) 4.61 (s, 1H, N-CH-Ar, 3.39 (s, 3H, OCH_3). Anal.Calcd: for $C_{36}H_{25}N_8O_3ClBr_2S_2$: 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-chlorobenzylidine)amino-5'-(2-aminothiazol-4-ylthio)-[1',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) ν_{max} in cm^{-1}; 3323 (NH_2), 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). ^{1}HNMR ($CDCl_3$) □ in ppm: 9.65 (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_2O), 4.80 (s, 2H, N-CH_2) 4.63 (s, 1H, N-CH-Ar), 3.40 (s, 3H, OCH_3).Anal.Calcd. for $C_{36}H_{24}N_8O_3Cl_2Br_2S_2$: C, 47.44; H, 2.65 ; N, 12.29 ; Found : C, 47.75 ; H, 2.27 ; N, 12.63 ; MS : $[M]^+$ at m/z 911.47.

2-(4-Chlorophenyl)-1-{4'-(4-mthoxybenzylidine)-amino-5'-(2-aminothiazol-4-ylthio)-[1',2',4']-triazol-3'-yl-methyl-3-(4",6"-dibromo-2-carboxyphenyl imino methyl}-5-methoxy-indole (36).

Yield (44%), (Ethanol), m.p: 273°C; IR (KBr) □$_{max}$ in cm^{-1}; 3318 (NH_2), 3035 (CH aromatic), 2928 (CH aliphatic), 1725 (C=O), 1717 (COOH), 1575 (C=N), 1520 (N-N), 1174 (C-O-C), 790 (C-Cl), 690 (C-S-C), 565 (C-Br). ^{1}HNMR ($CDCl_3$) □ in ppm : 9.65 (s, 1H, COOH), 8.42 (s, 2H, 2 X N=CH), 6.85-7.89 (m, 14H, Ar-H), 6.30 (s, 2H, -NH_2 exchangeable with D_2O), 4.80 (s, 2H, N-CH_2), 4.63 (s, 1H, N-CH-Ar), 3.44 (s, 6H, 2 X OCH_3). Anal.Calcd. for $C_{37}H_{27}N_8O_4Cl\ Br_2S_2$: C, 48.99; H, 3.00; N, 12.35; Found: C, 48.52; H, 3.23; N, 12.65; MS: $[M]^+$ at m/z 907.05.

2-(4-Methylphenyl)-1-{4'-(benzylidine)-amino-5'-(2-aminothiazol-4-ylthio)-[1',2',4']-triazol-3'-yl-methyl-3-(4",6"-dibromo-2"-carboxyphenyl iminomethyl}-5-methoxy-indole(37).

Yield (48%), (Methanol), m.p: 258°C ; IR (KBr) □$_{max}$ in cm^{-1}; 3316 (NH_2), 3035 (C-H aromatic), 2930 (C-H aliphatic), 1725 (C=O), 1715 (COOH), 1570 (C=N), 1525 (N-N), 688 (C-S-C), 560 (C-Br). ^{1}HNMR ($CDCl_3$) □ in ppm : 9.64 (s, 1H, COOH), 8.41 (s, 2H, 2 X N=CH), 6.83-7.98 (m, 15H, Ar-H), 6.30 (s, 2H, -NH_2 exchangeable with D_2O), 4.82 (s, 2H, N-CH_2) 4.60 (s, 1H, N-CH-Ar), 2.23 (s, 3H, CH_3), 3.42 (s, 3H, OCH_3). Anal .Calcd .for $C_{37}H_{28}N_8O_3Br_2S_2$: C, 51.88; H, 3.29; N, 13.08; Found: C, 51.19; H, 3.65; N, 13.69; MS: $[M]^+$ at m/z 856.61.

2-(4-Methylphenyl)1-{4'-(4-chlorobenzylidine)-amino-5'-(2-aminothiazol-4-ylthio)-[1',2',4']-triazol-3'-yl-methyl-3-(4",6"-dibromo-2"-carboxyphenyl imino methyl}-5-methoxy-indole (38).

Yield (45%), (Acetone), m.p: 280°C ; IR (KBr) □$_{max}$ in cm^{-1}; 3324 (NH_2), 3035 (C-H aromatic), 2928 (C-H aliphatic), 1725 (C=O), 1715 (COOH), 1578 (C=N), 1525 (N-N), 785 (C-Cl), 685 (C-S-C), 570 (C-Br). ^{1}HNMR ($CDCl_3$) □ in ppm : 9.64 (s, 1H, COOH), 8.43 (s, 2H, 2 X N=CH), 6.84-7.92 (m, 14H, Ar-H), 6.30 (s, 2H, -NH_2 exchangeable with D_2O), 4.83 (s, 2H, N-CH_2) 4.61 (s, 1H, N-CH-Ar), 2.20 (s, 3H, CH_3) , 3.34 (s, 3H, OCH_3). Anal.Calcd. for $C_{36}H_{27}N_6O_4ClBr_2S_2$: C, 49.87; H, 3.05; N, 12.58; Found: C, 49.66; H, 3.34; N, 12.96; MS : $[M]^+$ at m/z 891.05.

2-(4-Methylphenyl)-1-{4'-(4-methoxybenzylidine)-amino-5'-(2-aminothiazol-4-ylthio)-[1',2',4']-triazol-3'-yl-methyl-3-(4",6"-bromo-2-carboxyphenylimino methyl}-5-methoxy-indole(39).

Yield (50%), (Ethanol), m.p: 292°C; IR (KBr) □$_{max}$ in cm^{-1}; 3326 (NH_2), 3033 (C-H aromatic), 2920 (C-H aliphatic), 1724 (C=O), 1718 (COOH), 1572 (C=N), 1525 (N-N), 1174 (C-O-C), 690 (C-S-C), 562 (C-Br). ^{1}HNMR ($CDCl_3$) □ in ppm : 9.64 (s, 1H, COOH), 8.43 (s, 2H, 2 X N=CH), 6.81-7.89 (m, 14H, Ar-H), 6.30 (s, 2H, -NH_2 exchangeable with D_2O), 4.82 (s, 2H, N-CH_2), 4.61 (s, 1H, N-CH-Ar), 3.48 (s, 6H, 2 X OCH_3), 2.21 (s, 3H, CH_3). Anal.Calcd. for $C_{38}H_{30}N_8O_4Br_2S_2$: C, 51.48, H, 3.41; N, 12.64 ; Found: C, 51.72 ; H, 3.94 ; N, 12.24 ; MS : $[M]^+$ at m/z 884.63.

PHATRMACOLOGICAL STUDIES

All the newly synthesized compounds **3-39** were tested in vivo in order to evaluate their anti-inflammatory and analgesic activities by using student's t test. 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 9.3-33.9 % and analgesic activity evolution varying degree 6.4-36.2% are given in (Table 1).

The characteristic feature of this series is the substituents by the substituted phenyl at presence of moiety at second position of indol nucleus. It was obsereved that compound **35** showed maximum anti-inflammatory 33.9% inhibition of oedema and analgesic 36.2% activities. This compound showed better anti-inflammatory activity and equipotent analgesic activity than standard drug phenyl butazone at the dose of 25, 50 and 100 mg/kg p.o.

CONCLUSION

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

2. The azetidinones showed better anti-inflammatory and analgesic activities than parent compounds but less than thiazalidinones.

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PHARMACOLOGICAL EVOLUTION

The experiments were performed with albino rats of the Charles-Foster strain of either sex, excluding pregnant females, of 70 to 95 days weighing 120 to 175 g. Acute toxicity was tested in albino mice (15-25 g). Food (chaw pallet) and water was given to the animals ad libitum. The compounds were dissolved in propylene glycol. Phenylbutazone drug was used as reference drug.

Anti-inflammatory activity

This study was done by following the procedure of Winter et al[22]. 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, 1hr 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.

Percentage of inhibition of oedema = $(1-V_t/V_c) \times 100$

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

Analgesic activity

Acetic acid writhing test was performed on mice by following the method of Davis at el [23]. Test compounds were given to the animals at the dose of 50 mg/kg, 30 min later the animals were injected inter peritoneally 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 at el[24] . 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[25].

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 obsereved 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 phenyl butazone 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.

Table- I: Anti inflammatory, analgesic, ulcorogenic and toxicity data of compounds 4-39.

Comp. No.	Dose (mg/kg p.o.)	Anti inflammatory activity % oedema inhibition relative to control.	Analgesic activity % decrease of writhes in 60 min after treatment relative to control	UD_{50}	ALD_{50}
4	50	9.3*	6.4*	-	>1000
5	50	10.2***	7.7*	-	>1000
6	50	11.6**	9.8*	-	>1000
7	50	10.9**	8.9*	-	>1000

8	50	12.5***	10.4**	-	>1000
9	50	13.6**	11.2**	-	>1000
10	50	14.7*	13.9*	-	>1000
11	50	19.8*	21.2*	-	>1000
12	50	17.3*	16.5*	-	>1000
13	50	18.4*	19.6**	-	>1000
14	50	22.2**	21.8**	-	>1000
15	50	20.1*	19.1**	-	>1000
16	50	22.6**	22.6*	-	>1000
17	50	27.2***	25.7**	-	>1000
18	50	25.7**	23.2**	-	>1000
19	50	18.6*	19.5*	-	>1000
20	50	24.5***	22.3**	-	>1000
21	50	23.8**	20.7*	-	>1000
22	50	21.5**	21.1**	-	>1000
23	50	26.2***	26.3**	-	>1000
24	50	24.3**	24.5**	-	>1000
25	50	25.8**	26.7**	-	>1000
26	50	33.9***	32.8***	-	>1000
27	50	31.6***	29.2***	-	>1000
28	50	24.1**	24.1**	-	>1000
29	50	31.3***	28.9***	-	>1000
30	50	26.4**	26.4**	-	>1000
31	50	25.4***	25.6**	-	>1000
32	50	29.8***	29.1***	-	>1000

33	50	27.2***	27.2***	-	>1000
34	50	29.2**	30.5***	-	>1000
35	25 50 100	15.6** 37.4*** 67.9***	14.9** 33.9*** 69.6***	192.5	>1000
36	50	35.3***	32.4***	-	>1000
37	50	29.5**	28.3**	-	>1000
38	50	30.1***	34.7***	-	>1000
39	50	31.8***	30.6***	-	>1000
Phenylbutazone	25 50 100	17.6** 36.3*** 65.6***	18.4* 34.1*** 68.8 ***	65.46	
Indo-methacin	5 7.5 10	52.2 63.1 93.2			

*P < 0.05, **P < 0.01, ***P < 0.001.

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