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Synthesis and evalution of some newer indole derivatives as anticonvulsant agents

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ABSTRACT

A new series of 3-(1-(3''-(Substitutedphenyl-5''-mercapto-1'',2'',4''-triazolyl)-2'-oxo-3'-(2-chlorophenoxy)-1-azetidinoyl)-4'-indoles **(6a-e)** was synthesized for anticonvulsant activity. Compound **(6c)** found to be most potent compound of this series. All compounds were screened *in vivo* for their anticonvulsant activity and acute toxicity studies. The structural assignment of these compounds has been made on the basis of elemental analysis, IR and ^{1}H-NMR and Mass spectroscopic data.

KEYWORDS

1,2,4-Triazole;
Indolyl azetidinonyl;
Anticonvulsant activity;
Toxicity studies.

INTRODUCTION

Indole is the most beneficial heterocyclic nucleus which has gained prominence in medicinal chemistry due to its diverse biological activities such as anticonvulsant[1-6], anti-inflammatory[7], antipsychotic[8] activities. It is interesting to note from chemical literature that triazole[9-13] and azetidinone[14-15] 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 triazolyl and azetidinonyl moieties in single molecular frame work with the hope to possess better anticonvulsant agents.

Chemistry

The target 3-substituted indoles derivatives were synthesized are given in SCHEME. The reaction of substituted acid hydrazides **(1a-e)** with carbon disulphide and potassium hydroxide in ethanol afforded the corresponding substituted potassium dithiocarbazinates **(2a-e)**. The dithio carbazinates were converted to substituted-4-amino-5-mercapto-1,2,4 triazole **(3a-e)** using hydrazine hydrate in water 3-(2′-(Substitutedphenyl-5′-mercapto-″,2″,4″-triazolyl) amino methyllenyl indoles **(4a-e)** were prepared by the reaction of substituted 1,2,4 triazoles with indol-3-carboxaldehyde in absolute ethanol.The reaction mixture of compounds **(4a-e)** in dry benzene and chloro acetyl chloride were added triethyl amine yielded 3-(1-(3″-(Substitutedphenyl -5″-mercapto-1″,2″,4″-triazolyl)-2′-oxo-3′-chloro-1-azetidinoyl)-4′-indoles **(5a-e)**. 3-(1-(3″-(Substituted phenyl-5″-mercapto-1″,2″,4″-triazolyl)-2′-oxo-3′-(2-chlorophenoxy)-1-azetidinoyl)-4′-indoles **(6a-e)** were synthesized by the mixture of compounds **(5a-e)** and 2-chlorophenol. The purity of all synthesized compounds were determined by thin layer chromatography using several solvent systems of different polarity.

EXPERIMENTAL

The melting points of compounds were determined in open capillaries and thin layer chromatography was done on Silica gel-G plates. The eluent was a mixture

of different polarity in different proportion and spots were located by iodine. Elemental analysis (C,H,N) of these newly synthesized compounds were done on Carlo Erba-1108 elemental analyzer. The IR spectra were recorded on Bruker IFS-66 V FI-IR (ν max in cm^{-1}). The ^1H NMR spectra were recorded by Bruker DRX-400 FT-NMR instrument using $CDCl_3$ as solvent, tetramethyl silane (TMS) as internal reference standard. Chemical shift (δ) value recorded in ppm.

General procedure for the preparation of Substituted acid hydrazides (1a-e)

Dissolved the ester of substituted acids (0.1 mol) in ethanol (10 ml) and hydrazine hydrate (0.1 mol) were added drop wise in the mixture with stirring. The resulting mixture were allowed to reflex for 6 h excess ethanol were distilled out and the contents were allowed to cool. The crystals formed were filtered, washed, thoroughly with water and dried. The completion of the section was mentioned on TLC by using silica gel G coated plated by using ethyl acetate and petroleum ether as eluent and spots were observed in iodine chamber and substituted acids hydrazides **(1a-e)** were obtained.

General procedure for the preparation of Substituted acid Potassium dithio carbazinates (2a-e)

Potassium hydroxide (0.15 mol) was dissolved in absolute ethanol (200 ml) in the above solution substituted acid hydrazide (0.2 mol) was added and cooled the solution in ice. To the carbon disulfide (0.15 mol),substituted acid hydrazide solution was added in small portion with constant stirring.The reaction mixture was agitated continuously for a period of 15 h. It was then diluted with anhydrous ether. The precipitated potassium dithio carbazinates was collected by filtration. The precipitates was further washed with anhydrous ether (100 ml) and dried under vacuum. The potassium salt thus obtained was in quantitative yield and acid potassium dithio carbazinates **(2a-e)** were obtained.

General procedure for the preparation of 3-substituted -4-amino-5-mercapto-1,2,4-triazole (3a-e)

Suspension of potassium dithio carbazinates of respective aromatic esters (0.1 mol) in water (6 ml) was refluxed for 4-7 h with occasional shaking. The colors of the reaction mixture changed to green with the evolution of hydrogenous reaction mixtures were obtained during the reaction process. The reaction mixture was cooled to room temperature and diluted with concentrated hydrochloric acid, the required triazole was precipitated, it was filtered,washed thoroughly with cold water and recrystallized from suitable solvent.The competition by the reaction was monitored on TLC by using silica gel G coated plate by using ethyl acetate and petroleum ether as the eluent and spots was observed in iodine chamber.

3-(2-Hydroxyphenyl)-4-amino-5-mercapto-1,2,4-triazole (3a)

Yield 75% (Ethanol), mp: 215^0C. IR (KBr) νcm^{-1}: 3420 (O-H), 3130 (C-H aromatic), 2972, 2810 (C-H structure methyl), 2584 (SH), 1608 (C=N),1545 (C=C aromatic),1280 (N-N).: ^1H NMR ($CDCl_3$) δ ppm : 5.73 (s,2H,NH_2),7.18-8.10 (m, 4H,Ar-H),10.85 (s,1H, OH exchangeable),13.65 (s, 1H, SH). Anal. Calcd for $C_8H_8N_4OS$: C, 46.14,H, 3.87, N, 26.90.Found: C, 46.23; H, 3.76, N, 26.84.MS: m/z. 208.04(100.0%).

3-(4-Hydroxyphenyl)-4-amino-5-mercapto-1,2,4-triazole (3b)

Yield 65% (Ethanol), mp: 243^0C. IR (KBr) νcm^{-1}: 3422(O-H), 3131(C-H aromatic), 2970, 2811(C-H structure methyl), 2580 (SH), 1612 (C=N),1546(C=C aromatic),1285 (N-N).: ^1H NMR ($CDCl_3$) δ ppm. 5.70 (s,2H,NH_2),7.15-8.12 (m, 4H,Ar-H),10.88 (s,1H,OH exchangeable), 13.62 (s, 1H, 3H).: Anal. Calcd for $C_8H_8N_4OS$: C, 46.14,H, 3.87, N, 26.90.Found: C, 46.33; H, 3.66, N, 26.88. MS : m/z 208.04(100.0%).

3-(2-Chlorophenyl)-4-amino-5-mercapto-1,2,4-triazole (3c)

Yield 60% (Methanol), mp: 250^0C. IR (KBr) νcm^{-1}: 3129 (C-H aromatic), 2975, 2810 (C-H structure methyl), 2582 (SH), 1615(C=N),1548 (C=C aromatic),1282(N-N),710(C-Cl). : ^1H NMR ($CDCl_3$) δ ppm. 5.65 (s,2H,NH_2),7.25-8.15 (m, 4H,Ar-H), 13.55 (s, 1H, SH), Anal. Calcd for $C_8H_7ClN_4S$: C, 42.39,H, 3.11, N, 24.72.Found: C, 42.53; H, 3.16, N, 24.88. MS: m/z 226.69(100.0%).

3-(4-Chlorophenyl)-4-amino-5-mercapto-1,2,4-triazole (3d)

Yield 55% (Benzene), mp: 239^0C. IR (KBr) νcm^{-1}:

3120(C-Haromatic), 2972, 2814(C-H structuremethyl), 2581(SH), 1620(C=N),1540(C=C aromatic),1281 (N-N),712 (C-Cl): ^{1}H NMR ($CDCl_3$) δ ppm. 5.61 (s,2H,NH2),7.20-8.11 (m, 4H,Ar-H), 13.52 (s, 1H, SH), Anal. Calcd for $C_8H_7Cl N_4S$: C, 42.39,;H, 3.11, N, 24.72.Found: C, 4230; H, 2.96, N, 24.58. MS : m/z 226.69(100.0%).

3-(2-Methoxy phenyl)-4-amino-5-mercapto-1,2,4-triazole (3e)

Yield 52%(Acetone). mp: 232^{0}C. IR (KBr) νcm^{-1}: 3122(C-H aromatic), 2975, 2819(C-H structure methyl), 2585(SH), 1625(C=N),1538(C=C aromatic),1275(N-N),1225(OCH_3). :^{1}H NMR ($CDCl_3$) δ ppm. 3.25 (s, 3H, OCH_3), 5.60 (s,2H,NH_2),7.22-8.15 (m, 4H,Ar-H), 13.55 (s, 1H, SH), Anal. Calcd for $C_9H_{10}N_4OS$: C, 48.63, H, 4.53, N, 25.21.Found: C, 48.75; H, 4.66, N, 25.11. MS : m/z 222.06(100.0%).

General procedure for the preparation of 3-(2′-(Substitutedphenyl-5′-mercapto-1″,2″,4-triazolyl) aminomethylenyl)indoles (4a-e)

An equimolar (0.01 mol) mixture of indol-3-carboxaldehyde and compounds **(3a-e)** in absolute ethanol (100 ml) containing 2-3 drops of glacial acetic acid were refluxed for 4 h and excess solvent removed. The solid separated, filtered and recrystallized from appropriate solvent to gave **(4a-e)**.

3-(2′-(2′-hydroxyphenyl-5'-mercapto-1″,2″,4″-triazolyl)aminomethylenyl)indole (4a)

Yield 68% (Ethanol), mp: 170^{0}C. IR (KBr) νcm^{-1}: 3425(O-H), 3132(C-H aromatic),2580 (SH),1612 (C=N),1280 (N-N).:^{1}H NMR ($CDCl_3$) δ ppm. 7.18-8.18(m,9H,Ar-H), 8.86 (s,1H,C<u>H</u>=N), 9.92(s,1H,N-H indole exchangeable), 11.00 (s,1H,OH exchange able),13.50 (s,1H, SH).Anal.Calcd for $C_{17}H_{13}N_5OS$: C, 60.88, H, 3.91, N, 20.88.: Found: C, 60.68; H, 3.82, N,20.65. MS: m/z 335.08(100.0%).

3-(2′-(4′-hydroxyphenyl-5'-mercapto-1″,2″,4″-triazolyl)aminomethyleneyl) indole (4b)

Yield 65% (Benzene), mp: 183^{0}C. IR (KBr) cm^{-1}: 3422 (O-H), 3130 (C-H aromatic), 2582(SH),1615 (C=N), 1282 (N-N).: ^{1}H NMR ($CDCl_3$) δ ppm. 7.19-8.20 (m,9H,Ar-H), 8.81 (s,1H,C<u>H</u>=N), 9.85(s,1H,N-H indole exchangeable),10.88(s,1H,OH exchangeable), 13.52(s,1H,SH).Anal. Calcd for $C_{17}H_{13}N_5OS$: C, 60.88; H, 3.91, N, 20.88.: Found: C, 60.98; H, 3.72, N,20.98. MS: m/z 335.08(100.0%).

3-(2′-(2′-Chlorophenyl-5′-mercapto-1″,2″,4″-triazolyl)aminomethylenyl)indole (4c)

Yield55%(Methanol),mp: 206-208^{0}C.IR(KBr) νcm^{-1}: 3131 (C-H aromatic), 2580(SH), 1618(C=N), 1281(N-N), 712(C-Cl).: ^{1}H NMR ($CDCl_3$) δ ppm. 7.19-8.25 (m,9H,Ar-H), 8.85 (s,1H,C<u>H</u>=N), 9.85 (s,1H,N-H indole exchangeable), 13.55(s,1H,SH). Anal.Calcd for $C_{17}H_{12}ClN_5S$: C, 57.71; H, 3.42, N, 19.79: Found: C, 57.88; H, 3.52, N, 19.98.MS: m/z 353.83(100.0%).

3-(2′-(4′-Chlorophenyl-5′-mercapto-1″,2″,4″-triazolyl)aminomethylenyl)indole (4d)

Yield 52% (Ethanol), mp: 168^{0}C. IR (KBr) νcm^{-1}: 3130 (C-H aromatic),2582(SH),1619(C=N),1282 (N-N), 715 (C-Cl). :^{1}H NMR ($CDCl_3$) δ ppm. 7.18-8.26 (m,9H,Ar-H), 8.89 (s,1H,C<u>H</u>=N), 9.90(s,1H,N-H indole exchangeable), 13.50(s,1H,SH). Anal. Calcd for $C_{17}H_{12}ClN_5S$: C, 57.71; H, 3.33, N, 19.55.: Found: C, 57.58; H, 3.12, N, 19.62.MS: m/z 353.83 (100.0%).

3-(2′-(2′-Methoxyphenyl-5′-mercapto-1″,2″,4″-triazolyl)aminomethylenyl)indole (4e)

Yield 58% (Acetone), mp: 172^{0}C. IR (KBr) νcm^{-1}: 3132 (C-H aromatic),2580 (SH),1622(C=N), 1285(N-N), 1228(OCH_3).: ^{1}H NMR ($CDCl_3$) δ ppm. 3.22 (s,3H, OCH_3), 7.15-8.22 (m,9H,Ar-H), 8.91 (s,1H,C<u>H</u>=N), 9.86(s,1H,N-H indole exchangeable), 13.45(s,1H,SH). Anal. Calcd for $C_{18}H_{15}N_5OS$: C, 61.87, H, 4.33, N, 20.04.: Found: C, 61.98; H, 4.20, N, 20.12. MS: m/z 349.10(100.0%).

General procedure for the preparation of 3-(1-(3″-(Substitutedphenyl-5″-mercapto-1″,2″,4″-triazolyl) -2'-oxo-3'-2-chloro-1-azetidinoyl)-4'-indoles (5a-e)

To a solutions of **(4a-e)** (0.005 mol) in dry benzene (50 ml), chloro acetyl chloride (0.005 mol) was added followed by the addition of triethyl amine (0.006 mol). The reaction mixture was refluxed for 4 h. Excess of solvent removed and the residue treated with petroleum ether 60-80^{0}C. The solid thus obtained were filtered and recrystallized from appropriate solvent to gave **(5a-e)**.

3-(1-(3″-(2″-Hydroxyphenyl-5″-mercapto-1″,2″, 4″-triazolyl)-2′-oxo-3′-2-chloro-1-azetidinoyl)-4′-indole (5a)

Yield 62% (DMF/Water),mp: 185^{0}C. IR (KBr) νcm^{-1}: 3445 (O-H), 3245 (N-H), 3050(C-H of aromatic), 2850(C-H of aliphatic),2589 (SH), 1610 (C=N), 1245 (N-N): ^{1}H NMR ($CDCl_3$) δ ppm. 4.65 (d,1H, COCHCl), 6.75 (d,1H,CH-N), 6.88-7.40(m,9H,Ar-H), 8.45 (s,1H,N-H indole exchangeable),11.25(s, 1H,OH exchangeable),13.66(s,1H,SH). Anal. Calcd for $C_{19}H_{14}N_5O_2SCl$: C, 55.41; H, 3.43, N, 20.00.: Found: C, 55.38; H, 3.38, N,20.05.MS: m/z 411.06 (100.0%).

3-(1-(3″-(4″-Hydroxyphenyl-5″-mercapto-1″,2″, 4″-triazolyl)-2′-oxo-3′-2-chloro-1-azetidinoyl)-4′-indole (5b)

Yield 60% (Methanol), mp: 245^{0}C. IR (KBr) νcm^{-1}: 3442 (O-H), 3241(N-H), 3051(C-H of aromatic), 2852(C-H of aliphatic), 2585 (SH),1652,1645, 1612 (C=N), 1250 (N-N). : ^{1}H NMR ($CDCl_3$) δ 4.65 (d,1H, COCHCl), 6.70 (d,1H,CH-N), 6.82-7.45(m,9H,Ar-H), 8.41 (s,1H,N-H indole exchangeable),11.30 (s, 1H,OHexchangeable), 13.62(s,1H,SH). Anal. Calcd for $C_{19}H_{14}N_5O_2SCl$: C, 55.41, H, 3.43, N, 20.00.: Found: C, 55.38; H, 3.38, N,20.05. MS: m/z 411.06 (100.0%).

3-(1-(3″-(2″-Chlorophenyl-5″-mercapto-1″,2″,4″-triazolyl)-2'-oxo-3'-2-chloro-1-azetidinoyl)-4'-indole (5c)

Yield 58% (Ethanol), mp: 248^{0}C. IR (KBr) νcm^{-1}: 3240 (N-H), 3053(C-H of aromatic),2845(C-H of aliphatic), 2562 (SH), 1615 (C=N), 1255(N-N),713(C-Cl).:^{1}H NMR($CDCl_3$) δ 4.60 (d,1H,COCHCl), 6.78 (d,1H, CH-N), 6.80-7.42(m,9H,Ar-H), 8.40 (s,1H,N-H indole exchangeable),13.60(s,1H,SH). Anal. Calcd for $C_{19}H_{13}N_5OSCl_2$: C, 53.03, H, 3.05, N, 16.28.: Found: C, 53.18; H, 3.12, N,16.15.MS:m/z 430.31(100.0%).

3-(1-(3″-(4″-Chlorophenyl-5″-mercapto-1″,2″,4″-triazolyl)-2'-oxo-3'-2-chloro-1-azetidinoyl)-4'-indole (5d)

Yield 58% (Methanol), mp: 232^{0}C. IR (KBr) νcm^{-1}: 3235(N-H), 3056(C-H of aromatic),2853(C-H of aliphatic),2562(SH),1612 (C=N), 1259 (N-N),712(C-Cl).:^{1}H NMR ($CDCl_3$) δ4.62 (d,1H,COCHCl), 6.70 (d,1H,CH-N), 6.82-7.45(m,9H,Ar-H), 8.45 (s,1H,N-H indole exchangeable), 13.61(s,1H,SH). Anal. Calcd for $C_{19}H_{13}N_5OSCl_2$: C, 53.03, H, 3.05, N, 16.28.: Found: C, 52.90; H, 3.15, N,16.10.MS: m/z 430.31 (100.0%).

3-(1-(3″-(2″-Methoxyphenyl-5″-mercapto-1″,2″, 4″-triazolyl)-2′-oxo-3′-2-chloro-1-azetidinoyl)-4′-indole (5e)

Yield 58% (DMF/Water), mp: 219^{0}C. IR (KBr)νcm^{-1}: 3235 (N-H), 3056(C-H of aromatic),2850(C-H of aliphatic), 2855,2562 (SH), 1259(N-N), 1231 (OCH_3). :^{1}H NMR ($CDCl_3$) δ ppm. 3.24 (s, 3H, OCH_3), 4.60 (d,1H,COCHCl), 6.80 (d,1H,CH-N), 6.82-7.48 (m,9H,Ar-H), 8.40 (s,1H,N-H indole exchangeable), 13.55(s,1H,SH). Anal. Calcd for $C_{20}H_{16}N_5O_2SCl$: C, 56.40; H, 3.79, N, 16.44.: Found: C, 56.51; H, 3.85, N,16.61.MS: m/z 430.31 (100.0%).

General procedure for the preparation of 3-(1-(3″-(Substitutedphenyl-5″-mercapto-1″,2″,4-triazolyl)-2′-oxo-3′-(2-chlorophenoxy)-1-azetidinoyl)-4′-indoles (6a-e)

An equimolar mixtures of compounds **(5a-e)** (0.0025 mol) and 2-chloro phenol in dry benzene (25ml) containing triethyl amine (0.003 mol) were refluxed for 6h solvent removed and residue treated with water. The solid obtained were recrystallized from appropriate solvent to gave **(6a-e)**.

3-(1-(3″-(2″-Hydroxyphenyl-5″-mercapto-1″,2″, 4″-triazolyl)-2′-oxo-3′-(2-chlorophenoxy)-1-azetidinoyl)-4′-indole (6a)

Yield 61% (Ethanol), mp: 300^{0}C. IR (KBr) νcm^{-1}: 3445 (O-H), 3255(N-H), 3065 (C-H aromatic),2854 (C-H of aliphatic),2585(SH),1648(C=N), 1590 (C=C of aromatic).: ^{1}H NMR ($CDCl_3$) δ ppm. 4.60 (d,1H, COCHCl), 6.89 (d,1H,CH-N), 6.70-7.48(m,13H,Ar-H), 8.35 (s,1H,N-H indole exchangeable),11.40 (s, 1H,OH exchangeable), 13.65(s,1H,SH). Anal. Calcd for $C_{25}H_{18}N_5O_3SCl$: C, 59.58, H, 3.60, N, 13.90.: Found: C, 59.68; H, 3.76, N,13.82. MS: m/z 503.08 (100.0%).

3-(1-(3″-(4″-Hydroxyphenyl-5″-mercapto-1″,2″,4″-triazolyl)-2′-oxo-3′-(2-chlorophenoxy)-1-azetidinoyl)-4-indole (6b)

Yield 61% (Methanol), mp: 316^{0}C. IR (KBr) νcm^{-1}:

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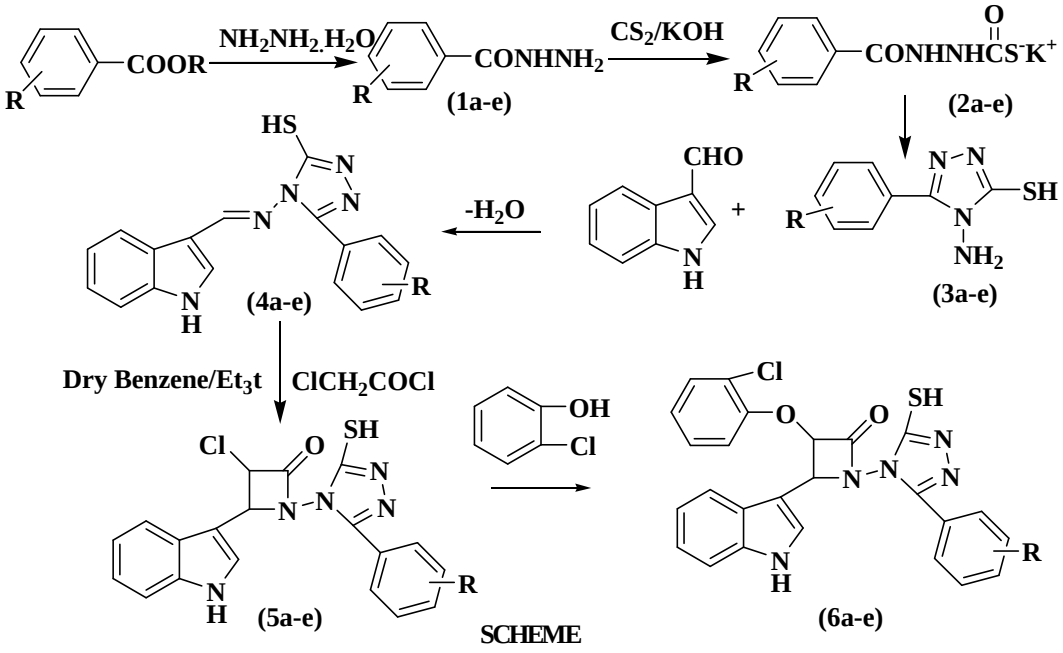

SCHEME

3450(O-H), 3255 (N-H), 3065(C-H of aromatic), 2860(C-H of aliphatic),2585 (SH).:^{1}H NMR ($CDCl_3$) δ ppm. 4.62 (d,1H,COCHCl), 6.84 (d,1H,CH-N), 6.75-7.48(m,13H,Ar-H), 8.40 (s,1H,N-H indole exchangeable),11.45 (s, 1H,OH exchangeable),13.60 (s,1H,SH). Anal. Calcd for $C_{25}H_{18}N_5O_3SCl$: C, 59.58, H, 3.60, N, 13.90.: Found: C, 59.42; H, 3.56, N,13.62. MS: m/z 503.08(100.0%).

3-(1-(3″-(2″-Chlorophenyl-5″-mercapto-1″,2″,4″-triazolyl)-2′-oxo-3′-(2-chlorophenoxy)-1-azetidinoyl)-4′-indole (6c)

Yield 65% (Acetone), mp: 290^{0}C. IR (KBr) νcm^{-1}: 3250,3155, 3060 (C-H of aromatic),2855(C-H of aliphatic),2585 (SH), 1615 (C=N).: ^{1}H NMR ($CDCl_3$) δ ppm. 4.68 (d,1H,COCHCl), 6.80 (d,1H,CH-N), 6.78-7.45(m,13H,Ar-H), 8.49 (s,1H,N-H indole exchangeable),13.55(s,1H,SH)..Anal. Calcd for $C_{25}H_{17}N_5O_2SCl_2$: C, 57.48; H, 3.28, N, 13.41.: Found: C, 57.58; H, 3.36, N,13.55. MS: m/z 521.05 (100.0%).

3-(1-(3″-(4″-Chlorophenyl-5″-mercapto-1″,2″,4″-triazolyl)-2′-oxo-3′-(2-chlorophenoxy)-1-azetidinoyl)-4′-indole (6d)

Yield 61% (Ethanol), mp: 320^{0}C. IR (KBr) νcm^{-1}: 3255(C-H of aromatic),2854(C-H of aliphatic),2581 (SH), 1620(C=N). :^{1}H NMR ($CDCl_3$) δ ppm. 4.61(d,1H,COCHCl), 6.82 (d,1H,CH-N), 6.75-7.48 (m,13H,Ar-H), 8.42 (s,1H,N-H indole exchangeable), 13.61(s,1H,SH). Anal. Calcd for $C_{25}H_{17}N_5O_2SCl_2$: C, 57.48, H, 3.28, N, 13.41.: Found: C, 57.38; H, 3.16, N,13.52. MS :m/z 521.05 (100.0%).

3-(1-(3″-(2″-Methoxyphenyl-5″-mercapto-1″,2″,4″-triazolyl)-2′-oxo-3′-(2-chlorophenoxy)-1-azetidinoyl)-4′-indole (6e)

Yield 61% (Acetone), mp: 307^{0}C. IR (KBr) νcm^{-1}: 3250(C-H of aromatic),2862(C-H of aliphatic),2585 (SH), 1632(C=N).: ^{1}H NMR ($CDCl_3$) δ ppm. 3.20 (s, 3H, OCH_3), 4.68 (d,1H,COCHCl), 6.74 (d,1H,CH-N), 6.75-7.48(m,13H,Ar-H), 8.40 (s,1H,N-H indole exchangeable), 13.65 (s,1H,SH). Anal. Calcd for $C_{26}H_{20}N_5O_3SCl$: C, 60.29; H, 3·89, N, 13.52.: Found: C, 60.42; H, 3.76, N,13.61. MS: m/z 517.99 (100.0%).

RESULTS AND DISCUSSION

All the newly synthesized compounds were studied for their anticonvulsant activity against maximal electroshock induced seizures. All the compounds were tested at the dose of 30 mg/kg i.p. and have shown varying degree (30 to 90%) of anticonvulsant activity. The results are given in TABLE 1. The compounds **(3a-e)** exhibited (30-70%) anticonvulsant activity. It was observed that compound **(3a)** which was substituted

TABLE 1: Anticonvulsant activity of compounds (3a-3e, 4a-e, 5a-e and 6a-e)

Compd. no.	R	X	Dose (mg/kg i.p.)	Anticonvulsant activity (SMES[C]) No. of animals exhibiting convulsions	% Seizure protection	ALD_{50} (mg/kg i.p.)
	P.G.[a]		2 ml	10	0	
	Phenytoin sodium[b]		30	2	80***	
(3a)	2-OH	-	30	7	30	> 1000
(3b)	4-OH	-	30	5	50**	>1000
(3c)	2-Cl	-	30	4	60***	> 1000
(3d)	4-Cl	-	30	3	70**	>1000
(3e)	2-OCH_3	-	30	4	60*	>1000
(4a)	2-OH	-	30	6	40	>1000
(4b)	4-OH	-	30	5	50**	>1000
(4c)	2-Cl	-	30	4	60*	>1000
(4d)	4-Cl	-	30	5	50*	>1000
(4e)	2-OCH_3	-	30	3	70**	>1000
(5a)	2-OH	-	30	4	60	> 1000
(5b)	4-OH	-	30	5	50**	> 1000
(5c)	2-Cl	-	30	2	80**	> 1000
(5d)	4-Cl	-	30	4	60*	> 1000
(5e)	2-OCH_3	-	30	4	60*	> 1000
(6a)	2-OH	2-Cl	30	5	50*	> 1000
(6b)	4-OH	2-Cl	30	5	50	> 1000
			7.5	7	30	
(6c)	2-Cl	2-Cl	15	1	90***	> 2000
			30	3	70**	
(6d)	4-Cl	2-Cl	30	4	60**	>1000
(6e)	2-OCH_3	2-Cl	30	5	50*	> 1000

***P < 0.05,*P< 0.01, ***P < 0.001, [a]P.G.- Propylene glycol standard for control, [b]Phenytoin sodium reference standard drug for anticonvulsant activitym, [c]Supramaximal electroshock seizure pattern test**

with 2-hydroxyphenyl group exhibited (30%) activity. Compounds **(3b, 3c, 3d and 3e)** substituted with 4-hydroxyphenyl ring **(3b)**, 2-chlorophenyl ring **(3c)**, 4-chlorophenyl ring **(3d)** and 2-methoxy phenyl ring **(3e)** exhibited 50%,70%, 60% and 60% inhibition of seizures respectively. Further, compounds **(4a-e)** of this series were characterized by the presence of substituted indole ring in addition to triazolyl ring. The compound **(4e)** substituted with 2-methoxyphenyl ring have shown activity (70%).Compound **(4a)** substituted with 2-hydroxyphenyl ring exhibited (40%) activity and compound **(4b)** substituted with 4-hydroxyphenyl ring showed (60%) protection against seizure, while compound **(4c)** and **(4d)** substituted with 2-chlorophenyl ring and 4-chlorophenyl ring exhibited (60%) and (50%) inhibition of seizures respectively. Moreover compounds **(5a-e)** varying degree of protection (50% to 80%) in which compound **(5c)** substituted with 2-chlorophenyl ring have shown equipotent activity to phenytoin sodium (80%) and compounds **(5a,5b,5d,5e)** exhibited (60% 50% 60% 60%) inhibition of seizure respectively. In the next step compounds **(6a-e)** characterized by the Indolyl azetidinonyl ring in addition to 2-chlorophenol ring, while **(6a)** substituted with 2-hydroxyphenyl ring exhibited (50%) activity. However compound **(6c)** substituted with 2-chlorophenyl ring have shown interesting anticonvulsant activity (90%) as this compound have shown good percentage of protection against seizures. It was further studied in details at three graded doses (7.5, 15,30 mg/kg, i.p.) exhibited better anticonvulsant activity than standard drug. Compound **(6b)** and **(6e)** exhibited same percent inhibition (50%), of seizures while compound **(6d)** substituted with 4-chlorophenyl group exhibited (60%) activity. The newly synthesized compounds were also tested for approximate lethal dose (ALD_{50}) and were found to exhibit a higher value of ALD_{50} i.e. more than 1000 mg/kg,i.p. except compound **(6c)** which exhibited ALD_{50} of more than 2000 (maximum dose tested) thus indicating the safer nature of these compounds.

Pharmacological evolution

The anticonvulsant activity was performed accord-

ing the method of Toman et al.[16] on Charles foster rats of either sex weighing, between in 90-150 g. Rats were divided into groups of ten animal each. The rats were treated with different doses of test drugs or phenytoin sodium 30 mg/kg i.p. After 1 h they were subjected to a shock of 150 m.A by convulsiometer through ear electrodes for 0.2 s and the presence or absence of extensor response was noted. Animals in which extensor response was abolished were taken as protected rats. The compounds were also investigated for their acute toxicity (ALD_{50}) in mice by following the method of smith[17].

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REFERENCES

[1] I.S.Biradar, S.Y.Manjunath; Indian J.Chem., **43B**, 389 **(2004)**.
[2] S.S.Panda, P.V.R.Chawdary; J.of Pharma Sci., **70**, 208 **(2008)**.
[3] G.S.Singh, Siddiquin; Boll.Chem.Form., **133**, 76 **(1994)**.
[4] J.L.Stanton, M.H.Ackerman; J.of Med Chem., **26**, 986 **(1983)**.
[5] K.Kaminnski, J.Obniska; Bioorganic and Med.Chem., **16**, 4921 **(2008)**.
[6] Archana, P.Rani, K.Bajaj, V.K.Srivastava, A. Kumar; Arzneim Forsch/Drug Research, **53**, 301 **(2003)**.
[7] S.Sharma, V.K.Srivastava, A.Kumar; Indian J.Chemistry, **41B**, 2647 **(2002)**.
[8] K.Bajaj, V.K.Srivastava,S.Lata, R.Chandra, A. Kumar; Indian J.Chem., **42B**, 1723 **(2003)**.
[9] A.K.Sengupta, K.C.Agarwal; Indian.J.Chem., **17B**, 184 **(1979)**.
[10] J.M.Kane, B.M.Baron, M.W.Dudley, S.M. Sorensen, M.A.Staeger; J.Med.Chem., **33**, 2772 **(1990)**.
[11] F.Melane, L.Cecchi, V.Colotta, D.Catarzi, G. Filacchioni; J.Hetrocyclic Chem., **29**, 819 **(1992)**.
[12] S.D.Srivastava, T.R.Rawat; Indian J.of Chem., **38B**, 623 **(1999)**.
[13] S.K.Srivastava,S.Srivastava, S.D.Srivastava; Indian J.of Chem., **41B**, 2357 **(2002)**.
[14] S.K.Srivastava, S.Srivastava, S.D.Srivastava; Indian J.Chem., **38B**, 183 **(1999)**.
[15] A.Rajasekaran,S.Murugesan; J.of Pharmacy and Biosources, **2**, 162 **(2005)**.
[16] J.E.P.Toman, E.A.Swinyard, L.S.Goodman; J.Neurophysiology, **9**, 231 **(1946)**.
[17] Q.E.Smith; Butterworths London, **1**, 1 **(1960)**.