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Synthesis and anti-convulsant activity of triazothiole/thiazolyl thiazolidinone derivatives of indole

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ABSTRACT

The pharmacological interesting activities of indole and of triazole and thiazolidinones promoted us to synthesis indole ucleus fused with sulphur and nitrogen conataining hetrocyles and to eluavate a their anticonvulsant activities. New heterocyclic derivatives of Indole were synthesized initially from the bromination of 3-acetyl indole, which was further treated with semicarbazones / thiosemicarbazones to obtain the titled derivatives. The synthesized compounds were identified by spectral data and were tested for their anti-convulsant activities by PTZ induced convulsions in mice at 10mg/kg.IR absorption at 3350 cm-1 (N-H), aromatic C-H stretching at 3147.61 cm-1 and C-C stretching at 1531.37 cm-1 were observed, confirming the indole nucleus, the chemical shift seen in 1HNMR at δ 7.01 to 7.54 and at δ 169 of 13C NMR confirmed the presence of oxo group and protons of the heteroaromatic nucleus. Compounds 5a, 5b, 5c, 5d, 6a, 6b, 6c were found to have moderate to significant anti convulsant activity.

Key words: indole, thiazolidinones, triazthiole, anticonvulsant

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INTRODUCTION

Convulsion is a symptom of an epileptic seizure. Epilepsy is a neurological disorder characterized by unprovoked seizures, and affects at least 50 million people worldwide. Barbuituric acid derivatives such as phenobarbitone and mephobarbitone have found effective in treatment [1]. Improvement in treatment of convulsion is essential for drugs having minimal side effect side effects. Various substituted / hetrocylic substituted indole molecules have been reported for anticonvulsion activity [2, 3], and other pharmacological activities anticancer, [4], antiviral[5] , Antileshmanial activity[6] The sulphur and nitrogen containing hetrocyclic thiazole have exhibited wide range of bilological effect anticonvulsant [7]antitumor, [8-9] ,antimicrobial [10] thiazolidinones derivatives have a great potential in exhibiting anticancer, anti HIV, antimicrobial and anti inflammatory and anticonvulsion effect[11]. Hence with these aspects we propose to synthesize indole molecule by assimilating triathiazolyl and thiazolidinones nucleus and evaluate for anti convulsion activity.

MATERIALS AND METHODS

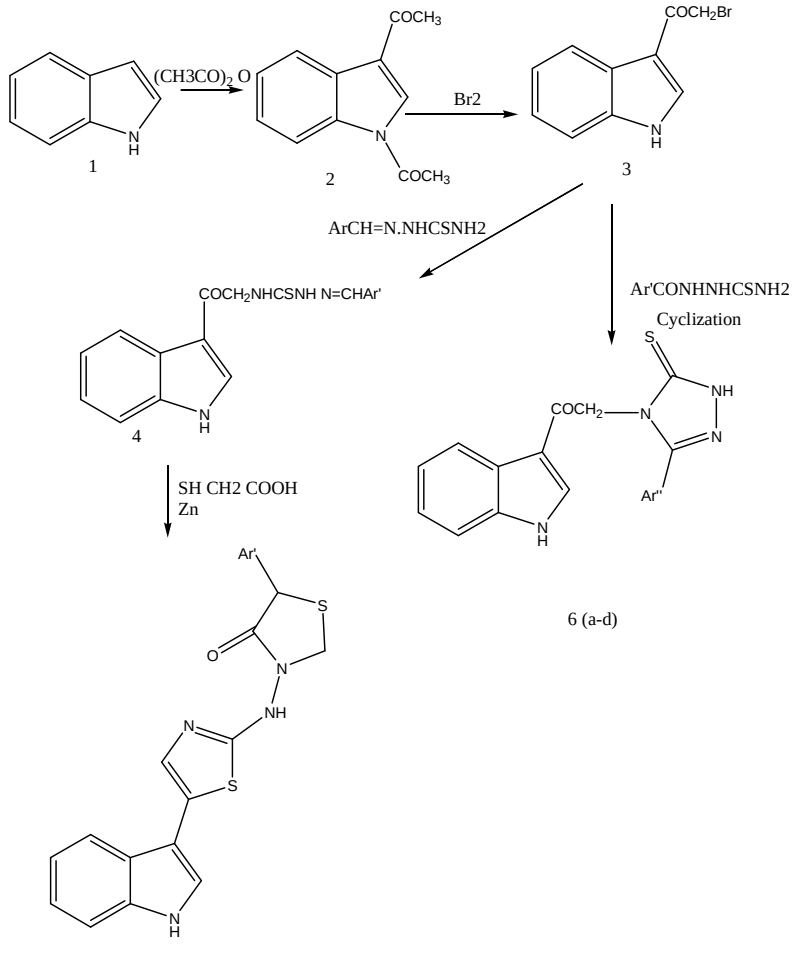
General experimental- The FT-IR spectra were recorded on Perkin Elmer spectrophotometer using KBr pellets values are given in cm^{-1}. ^1H NMR spectra was recorded on Bruker Spectrospin DPX 300 MHz using $CDCl_3$ as solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ (ppm) scale. Melting points were determined by open tube capillary method and are uncorrected. Purity of the compounds was checked by thin layer chromatography (TLC) plates (silica gel G) which were visualized by exposing to iodine vapours and UV light. The experimental protocol for anticonvulsant activity was approved from ethical committee of Krupanidhi College of Pharmacy, Bangalore. Albino mice were obtained from animal house of the pharmacy college .

3-Acetyl indole from 1,3-diacetylindole (2)
1,3-Diacetyl indole (1 g) was suspended in ethanol and sodium hydroxide (10 ml) of 2 N. The mixture was stirred and warmed until the diacetyl indole dissolved, the product after being precipitated by dilution with water, was collected and crystallized from ethanol.

Bromination of 3-acetyl indole (3)
A solution of bromine (0.837 mol) in dioxane is added drop wise over a 2 h period to a 3-acetyl indole (0.835 mol) in dioxane . The oily residue thus obtained is dissolved in ether and the solution washed successively with a 10 % solution of sodium bicarbonate and brine until neutral. The organic layer is dried over magnesium sulphate and evaporated. Crystallization of the crude mixture in 95% ethanol afforded pure 2-bromo-1-(1*H*-indol-3-yl) ethanone .

3-[5-(1*H*-Indol-3-yl)-thiazol-2-ylamino]-5-phenylthiazolidin- 4-one (5a-d)
A mixture of Thiosemicarbazide (5 mmol), thioglycollic acid (5 mmol), 3-bromo acetylindole (5 mmol) and pinch of anhydrous zinc chloride is refluxed in dry dioxane for 24 hrs. Cooled to room temperature and mixture was neutralized with sodium bicarbonate. Formed product is filtered off and re-crystallized from methanol .

1-(1*H*-Indol-3-yl)-2-(5-thioxo-1,5-dihydro[1,2,4]triazol-4-yl)ethanone (6a-d)
A solution of acylthiosemicarbazone (2 mmol) in ethanol was added to a suspension of anhydrous sodium acetate (2.2mmol) in 10ml of ethanol and stirred for 15 min. Subsequently 3-bromo acetylindole (3mmol) was added at room temperature and the reaction stirred and refluxed for 24 h, the solvent was completely removed and crushed ice was added. The precipitate formed was filtered and washed with 0.1M of potassium bisulphate and water, re-crystallize from absolute ethanol .



Ar'
(a) C6H5
(b) p- C6H4Cl
(c) p-C6H4(OCH3)
(d)-C6H4(p-OCH3)(o-OH)

Ar''
(a)C6H5
(b)C6H4OCH3)
(c)C6H4(OH)

All the synthesized compounds were subjected for spectral analysis see table 1 for ^{1}H NMR, IR and for physical properties.

Table 1- Spectral and physical properties of the synthesized compounds

Compound code	^{1}HNMR $CDCl_3$ (δ ppm)	IR cm^{-1}	% yield	Melting point (^{0}C)
5a	10.01 (s, 1 H, NH), 8.6 (s, 1H, Ar H), 8.2(s, 1H, Ar H), 7.50 (d, 1H, Ar H), 7.5(m, 4H, Ar H), 7.10(s, 1H, CH). 6.5(m, 1H, Ar H), 3.95(m, 2H, $2CH_2$), 3.9(m, 1H, NH).	C=C (1598.88), C-C (1249.79), CH (1027.99), C=O (1542.95), CS (746.40), N-H (3305.76), C-H Ar (3055.03).	56	256-257
5b	10.02(s, 1 H, NH), 8.7(s, 1H, Ar H), 8.1(s, 1H, Ar H), 7.40(d, 1H, Ar H), 7.6(m, 4H, Ar H), 7.20(s, 1H, CH), 6.6(m, 1H, Ar H), 3.95(m, 2H, $2CH_2$), 3.9(m, 1H, NH).	C=C (1600.81), C-C (1105.14), C-Cl (815.83), C=O (1497.87), C-S (746.40), N-H (3434.98), C-H Ar (3278.76).	54	260-261
5c	10.0(s, 1 H, NH), 8.4(s, 1H, Ar H), 8.3(s, 1H, Ar H), 7.40(d, 1H, Ar H), 7.5(m, 4H, Ar H), 7.25(s, 1H, CH), 6.61(m, 1H, Ar H), 3.97(m, 2H, $2CH_2$), 3.8(m, 1H, NH).	C=C (1685.67), C-C (1168.78), CS (833.19), C=O (1701.10), O-H (748.33), N-H (3359.77), C-H Ar (3064.68).	62	346-347
5d	10.01(s, 1 H, NH), 8.35(s, 1H, Ar H), 8.2(s, 1H, Ar H), 7.45(d, 1H, Ar H), 7.7(m, 4H, Ar H), 7.3(s, 1H, CH), 6.65(m, 1H, Ar H), 3.96(m, 2H, CH_2), 3.8(m, 1H, NH), 1.32(t, 3H, CH_3).	C=C (1672.59), C-C (1267.14), S (750.26), C=O (1701.10), OC_2H_5 (1124.42), N-H (3392.55), C-H Ar (3062.24).	64	283-284
6a	10.1(s, 1H, NH), 8.2(m, 2H, Ar H), 7.54(m, 3H, ArH), 7.46(d, 2H, ArH), 7.02(d, 2H, ArH), 7.01(s, 1H, NH), 5.8(s, 2H, CH_2).	C=C (1531.37), C-C (1199.21), C=O (1600.81), C-S (829.33), N-H (3417.63), C-H (3147.61), C-H (2904.6).	64	270-273
6b	10.15(s, 1H, NH), 8.25(m, 2H, Ar H), 7.58(m, 3H, ArH), 7.47(d, 2H, ArH), 7.1(d, 2H, ArH), 7.02(s, 1H, NH), 5.9(s, 2H, CH_2), 3.8(s, 3H, CH_3).	C=C (1600.81), C-C (1184.21), C=O (1703.91), C-S (746.40), N-H (3274.90), C-H (3056.96), C-H (2935.16).	63	337-338
6c	10(s, 1H, NH), 8.4(m, 1H, Ar H), 8.2(m, 1H, ArH), 7.57(m, 3H, ArH), 7.4(m, 3H, ArH), 7.19(m, 3H, ArH), 7.0(s, 1H, NH), 7.03(s, 1H, CH=CH).	C=C (1649.02), C-C (1130.21), C-S (752.19), C=O (1708.81), N-H (3419.56), C- H Ar (3055.03).	62	278-280

Anticonvulsant activity

Albino mice of either sex with a body weight between 18 and 22g were divided into nine groups (n=5). The test compound and the reference drug were orally administered. Group I served as control. One hour after oral administration of test compound (10 mg/kg), PTZ 80 mg/kg was given orally. Each animal was placed into an individual plastic cage for observation lasting 1h.Seizures and tonic clonic convulsions were recorded 12] .

RESULTS AND DISCUSSION

The new derivatives were obtained in different steps, 3-acetyl indole was prepared by treating indole and acetic anhydride in presence of phosphoric acid, bromonation of 3- acetylindole was carried out by treating with bromine in dioxane, where bromine was added drop wise over a 2 h period. After the addition is completed, the solvent and hydrobromic acid formed are evacuated by evaporation; thiazolidones derivatives were prepared by reacting thiosemicarbazide, thioglycollic acid, 3-bromo acetylindole and pinch of zinc chloride was refluxed in anhydrous dioxane for 24 h, triazothiole derivatives were prepared by treating solution of arylthiosemicarbazone in ethanol in presence of anhydrous sodium acetate in ethanol . From the result of spectra analysis it is concluded that the various derivatives that were synthesized the IR exhibited an absorption at 3350cm-1 indicating the presence of N-H, supported by the aromatic C-H stretching at 3147.61 cm-1 and C-C stretching at 1531.37 cm- confirming the indole nucleus which was confirmed by the chemical shift seen in ^{1}HNMR at δ 7.01 to 7.54, further presence of signlet peak at δ 7.2 and absorption peak seen at 1286.43cm -1 for C=N confirms the formation of thiazolidine ring and broad multiplet peak at δ 3.9 supported by IR (3305.76cm-1)indicating NH group that links thiazolidine ring to thiazolidinone ring.; the cyclization of latter nuleus is supported from chemical shift values seen at δ 3.95 for methylene protons depicting as mutiplet ,and from absorption peak observed at 1542.95 cm-1 for carbonyl group.C-S peak seen at 746 cm-1.the from peaks obsreved at C=O (1703.91 cm-1),and singlet peak at δ 5.9 for sp3 proton support the acyl group ; 746.40) cm-1 indicates C-S formation of triazole nucleus was confirmed which was Table 2 represent anti convulsant activity for all synthesized compound in mice. At of dose 10 mg /kg, significant activity ($p<0.001$) was observed from compounds **5(a-d)** moderate activity was seen from compounds **6a** and **6c.**

Among Triazothioles of indole derivatives , compound **6a** showed significant activity probably due presence of electron releasing methoxy and animal recovery from compounds **6a-c** was 80 %similarly among thiazolyl thiazolidone indole compounds **(5b &5c)** thiazolidione, ring substituted with electron releasing hydroxy and ethoxy group showed very significant activity, at the dose given all animals recovered from convulsion effect from **5a-d** series was cent percent.

Table 2 –Anticonvulsant activity of synthesized indole derivatives

Treatment (mg/kg)	Time taken for onset of Convulsion (min)	Recovery(min)	Lethality
Control + PTZ (80)	3.5 ± 0.2887	23.25 ± 3.304	0/5
5a (10) + PTZ (80)	7.5 ± 0.2883	32.25 ± 1.708**	0/5
5 b (10) + PTZ (80)	7.5 ± 0.6455	45.75 ± 4.391**	1/5
5c (10) + PTZ (80)	8.5 ± 0.6453	38.75 ±2.980**	0/5
5d(10) + PTZ (80)	9.75 ± 0.4787	45.0 ± 2.160**	0/5
6a (10) + PTZ (80)	7.0 ± 0.9129	48.75 ± 2.90*	1/5
6b (10) + PTZ (80)	6.5 ± 0.6455	49.5 ± 4.040	2/5
6c (10) + PTZ (80)	7.0 ± 1.08	39.25 ± 2.500*	1/5

*Values are expressed as mean ±SEM, from 5 mice. Significant at **p<0.01 and ***p<0.001 as compare to control using one-way ANOVA followed by Tukey Kramer Multiple Comparison Test*

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