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Research Article

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Synthesis and anticonvulsant activity of thiazolidione thiourea of 4-methyl quinoline

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ABSTRACT

New thiazolidione thiourea of 4-methylquinoline derivatives were synthesized from 2-nitroacetophenone by bromination followed by reduction of nitro group and cyclization to obtain the quinoline nucleus . the structures of synthesized compounds were identified by IR, NMR and physical data . The newly synthesized products were tested for their anticonvulsant activities by PTZ induced convulsion method. All the derivatives showed moderate to significant anticonvulsant activity at 10 mg/kg of the dose and compound 5(a) and 5(c) showed less percent of mortality over duration of 24 h.

Keywords: Quinolines, Thiazolidiones, thiourea, anticonvulsant.

INTRODUCTION

Epilepsy is a common neurologic disorder characterized by excessive temporary neuronal discharge that affects about 1% of the world's population [1]. Despite the availability of many antiepilepticdrugs (AEDs), there is still an urgent need for the development of more effective and safer AEDs, since about 30% of epileptic patients are not seizure-free with the existing AEDs [2]. Besides, many AEDs such as phenobarbital, phenytoin, carbamazepine,vigabatrin, valproate, felbamate, and lamotrigine, are effective toward only 60-80% of patients and have some undesirable side effects, such as headache, nausea, anorexia, ataxia, hepatotoxicity, drowsiness, gastrointestinal disturbance, gingival hyperplasia, and hirsutism [3-6]. Thus, there is an enormous need for the development ,of novel AEDs with fewer side effects and more effectives. Thiazolidinone has been considered as a magic moiety (wonder nucleus) which posses almost all types of biological activities. Indeed, several Thiazolidiones have been reported to possess various activities which includes anti-microbial [8], anti-diabetic activities [9], antihypertensive activities[10], anti-HIV activity[11], cardiovascular effects[12], Hypolipidemic Agents[13]and anti-tumor[14]. Quinoline nucleus has been associated for anti convulasnt ,antihypertensive CNS , antitumor activities [15-18]. In view of the aforementioned facts, it seemed most interesting to synthesize some thiazolidone thiourea of 4-methylquinoline derivatives with the aim to evaluate their anticonvulsant activity.

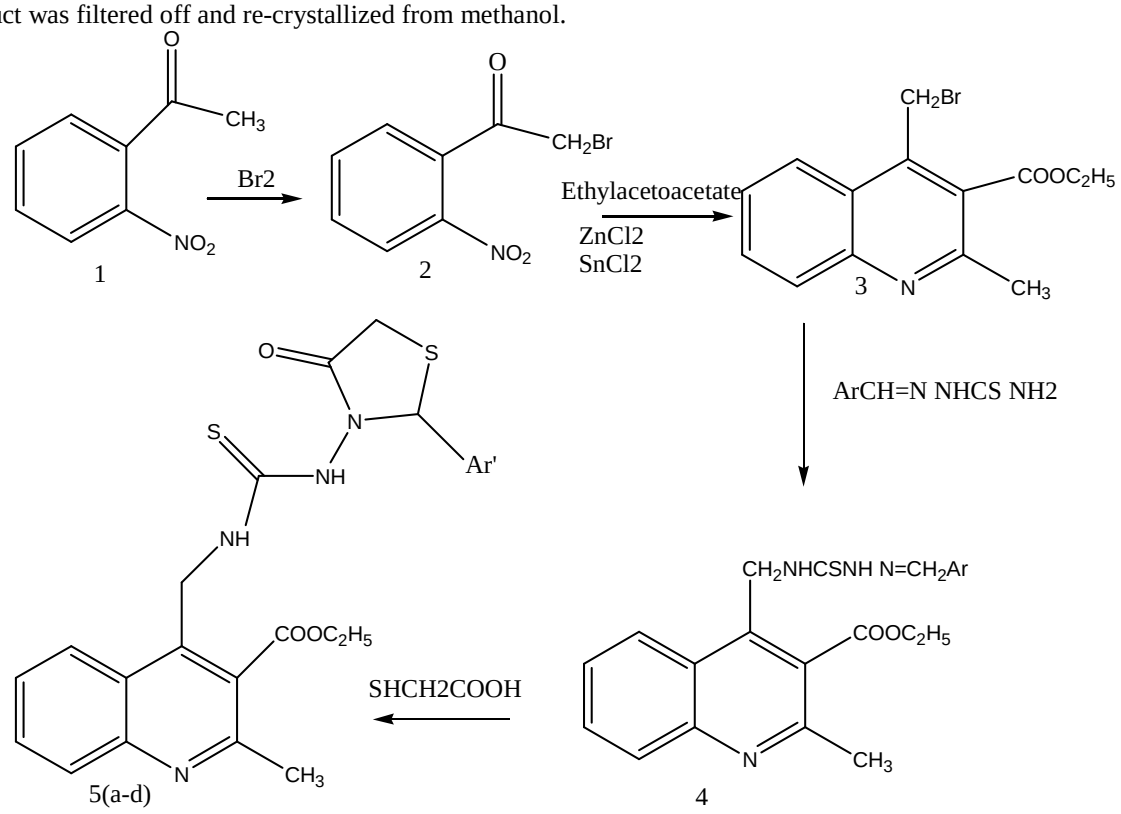
EXPERIMENTAL SECTION

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 FT-IR spectra were recorded on Perkin Elmer spectrophotometer using KBr pellets, values are given in cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Spectrospin DPX 300 MHz using DMSO as solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ (ppm) scale . 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 institute.

2-Bromo-2'-Nitroacetophenone (2)
A solution of bromine (0.837 mol) in dioxane (12.5 ml) is added drop wise over a 2 h period to a solution of *o*-nitroacetophenone (0.83mol) in dioxane (25 ml). The oily residue 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.

Ethyl 4-(bromomethyl) -2-methyl quinoline-3- carboxylate (3)
2-Bromo-2'-nitroacetophenone (66.2 mmol), ethylacetoacetate (66.2 mmol), and anhydrous zinc chloride (18.0 g, 132 mmol) is stirred in presence of 10 grams of 3Å molecular sieves and anhydrous methanol. The flask is flushed with a stream of nitrogen and with stirring, heated to an internal temperature of 67 °C for 1 h. Tin chloride (331 m mol) is then slowly added to the flask over five min in equal portions. the reaction mixture is stirred at 67 °C for 12 h. The solution is then allowed to cool to room temperature. A solution of potassium carbonate (331 m mol), is added to the reaction until alkaline. To this slurry, diethyl ether is added and separated organic layer is washed with brine. The organic phase is dried over magnesium sulphate and the ester is obtained yellow oil [19].

Ethyl 2-methyl-4-((3-(4-oxo-2-phenylthiazolidine-3-yl) thiouredo)methyl) quinoline carboxylate (5 a-d)
A mixture of respective thiosemicarbazide (5mmole), thioglycollic acid (5mmloe) was added to the synthesized ethyl 4- (bromo methyl) -2-methyl quinoline -3- carboxylate (5mmole) and refluxed in anhydrous dioxane (20ml) for 24h . Reaction was cooled to room temperature and was neutralized with sodium bicarbonate. The formed product was filtered off and re-crystallized from methanol.



Ar '

5(a) p-OCH3
5(b) p-OH
5 (c) p-Cl
5(d) p-OH and m-OC2H5

Ethyl 2-methyl-4-((3-(4-oxo-2-(4-methoxyphenyl) thiazolidine)thiouredo)methyl)quinoline 3- crboxylate (**5a**) – an yellow solid , yield 58 % , M. P. 180°C ^{1}HNMR(DMSO) (δ ppm) 8.08 (,s, ArH, 1H); 7.9- 7.7 (m, ArH, 3H); 6.9-7.02 (m, ArH, 5H);5.8(s, 2H, CH_2); 4.7 (s, 2H, CH_2) ; 4.2 (q,2 H, CH_2);3.2 (s, 2H, CH_2); 2.5(s, 3H, CH_3) 2.0 (d, 2H,

NH); 1.07(t, 3H, CH3) ; ^{13} C NMR (DMSO) 169 C= O; 167 C=O OC_2H_5; 160 C-OCH_3; 150-114 Ar C;56 OCH_3; 41 CH_2; 39 CH_2; 62 $COOCH_2$; 18. CH_3; 14.5 CH_3 ; I. R (KBr) (cms ^{1}) C=C (1590.82), C=O (1728.85),C- N(1402.28), N-H (3431.84), C-H Ar (3143.24), C-H(ali) (3069), C-S(1162),C-O (1190).

Ethyl2-methyl-4-((3-(4-oxo-2-(3-ethoxy-hydroxyl)phenylthiazolidone-3yl)thiouredo)methyl)quinoline-3-carboxy - late **(5b)** –yield 56 %, brown yellow, solid, MP 190°C ; ^{1}HNMR(DMSO) (δ ppm) 8.08 (,s, ArH, 1H); 7.9- 7.7 (m, ArH, 3H); 7.1 -7.7 (m, ArH, 5H);5.8(s, 2H, CH_2); 4.7 (s, 2H, CH_2) ; 4.2 (q,2 H, CH_2);3.2 (s, 2H, CH_2); 2.5(s, 3H, CH_3) 2.0 (d, 2H, NH); 1.07(t, 3H, CH_3) ; IR (KBr) (cms $^{-1}$) C=C (1592.82), C=O (1722.85),C- N(1402.28), N-H (3429.84), C-H Ar (3901.24),C-H(ali) (2951), C-S(1162); ^{13}CNMR 169 C= O; 167 C=O OC_2H_5; 160 C-OCH_3; 150-114 Ar C;56 OCH_3; 58 CH; 41 CH_2; 39 CH2;62 $COOCH_2$; 20 CH_3; 14.5 CH_3

Ethyl2-methyl-4-((3-(4-oxo-2-(4-chloro phenylthiazolidone3yl)thiouredo)methyl)quinoline carboxylate **(5c**) yield 62 %; yellow solid, MP 204 °C ; ^{1}HNMR (DMSO) (δppm) -8.08 (,s, ArH, 1H); 7.9- 7.7 (m, ArH, 3H); 7.1 -7.7 (m, ArH, 5H);5.8(s, 2H, CH_2); 4.7 (s, 2H, CH2) ; 4.2 (q,2 H, CH_2);3.2 (s, 2H, CH2); 2.5(s, 3H, CH_3) 2.0 (d, 2H, NH); 1.07(t, 3H, CH_3); ^{13}CNMR 169 C= O; 167 C=O OC_2H_5; 132 C-Cl; 150-124 Ar C; 58 CH; 41 CH_2; 39 CH_2;62 $COOCH_2$; 18. CH_3; 14.5 CH_3; IR KBr (cms^{-1}) C=C (1590.82), C=O (1728.85),C- N(1402.28), N-H (3481.84), C-H Ar (3901.24),C-H(ali) (2951), C-S(1162) OH (3303.0)

Ethyl2-methyl-4-((3-(4-oxo-2-(4-hydroxyphenylthiazolidine-3-yl)thiourediomethyl)quinoline carboxylate **(5d**)-198^{0}C; brown solid ;yield 56 % ; HNMR (DMSO) 8.08 (,s, ArH, 1H); 7.9- 7.7 (m, ArH, 3H); 6.9 -7.5 (m, ArH, 5H);5.9(s, 2H, CH_2); 4.7 (s, 2H, CH_2) ; 4.2 (q,2 H, CH_2);3.2 (s, 2H, CH_2); 2.5(s, 3H, CH_3) 2.0 (d, 2H, NH); 1.07(t, 3H, CH_3); ^{13}CNMR (DMSO)-169 C= O; 167 C=O OC_2H_5; 160 C-OCH_3; 150-114 Ar C;56 OCH_3; 58 CH; 41 CH_2; 39 CH_2;62 $COOCH_2$; 18.0 CH_3; 14.5 CH_3; IR KBr (cms^{-1}) C=C (1590.82), C=O (1728.85),C- N (1402.28), N-H (3481.84), C-H Ar (3901.24),C-H(ali) (2951), C-S(1162) OH (3303.0)

Anticonvulsant Activity

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

RESULTS AND DISCUSSION

Anticonvulsant activity against PTZ induced convulsions in mice at dose 10 mg/kg compound **(5c)** showed very significant ($p<0.001$) with respective to control,(s table 1) with delayed onset of action and showing 88% mortality while others showed moderate activity with respective to control.

Table 1 - Anticonvulsant activity of titled compounds in PTZ convulsion model

Treatment Dose (mg/kg)	Onset of convulsion (sec)	% protection (24 h)
Control PTZ(80)	185± 17.3	0
Standard (diazepam) (4)	Absent	100
5a (10)+ PTZ (80)	435± 28 .0*	83.3
5b (10)+ PTZ (80)	390± 38.7*	66.6
5c (10)+ PTZ (80)	540 ±34.6*	83.3
5d (10)+ PTZ (80)	390 ± 37.6*	66

*Values are expressed as mean ±SEM, from 6 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*

The methylene proton shift at δ 4.9 as singlet in ^{1}H NMR together with absorption at 2951cm^{-1} confirmed the presence of methylene ,further quinoline nucleus protons were observed at δ 8.02 and 8.6 , which confirmed the formation of 4-bromomethyl quinoline **(3)** . The basic quinoline nucleus **(3)** on treatment with aryl semicarbazone and thioglycollic acid on 24 h reflux yielded thiazolidinone derivatives **(5a-d)**; the presence of thiourea was confirmed by the presence of peak at δ 8.45(s, H, NH), δ8.85(s, H, NH) in proton spectra and C-S showing absorption at 1162 cm^{-1},similarly chemical shift at δ5.50 as singlet for methylene protons supported by ^{13}CNMR peak at δ 39, and of thiazolidione ring and methine proton was observed at δ 3.70 and at δ 41in carbon spectra further IR absorption showed peak at 1728.85 cm^{-1} for carbonyl oxygen and C-S 1162 cm^{-1} thus confirming the formation of thiazolidione. Compounds **5(a-d)** were evaluated for anticonvulsant activity in PTZ induced animal model, compounds **(5c)** and **(5a)** showed statistically significant activity while **5b** and **5d** showed moderate activity.

The enhanced activity of **5c** would be attributed due to presence of electronegative aryl chlorine substituted on the thiazolidione nucleus and **5a** has an electron donating methoxy substituent, while **5b** and **5d** having electron donating group showed moderate activity. The study suggests compounds electron withdrawing group would be more responsible for activity.

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