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ORIGINAL ARTICLE

Synthesis, characterization, antibacterial and antiepileptic studies of some novel thiazolidinone derivatives

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Abstract In the quest of finding new drug leads with potential antibacterial and antiepileptic activities, synthesis of thiazolidinone derivatives **6(a–c)** is reported which are obtained from 5-(4-chlorobenzylidine)-3-[4-(7-chloroquinoline-4-ylamino]propyl)-2-imino-thiazolidin-4-one derivatives by applying appropriate synthetic route. These compounds **6(a–c)** were evaluated for antibacterial and antiepileptic activities. Compound **6a** having good lipophilicity is found to be most active.

1. Introduction

Thiazolidinone derivatives are the subject of renowned interest because they have been found to be useful intermediates for the synthesis of various heterocyclic compounds (Singh et al., 1981). The most important results of extensive studies (synthesis, spectral, structural characterization and applications in various biological systems) of thiazolidinone derivatives are reviewed (Metzger et al., 1984). Thiazolidinone derivatives are associated with multifarious biological activities such as analgesic (Hosni and Abdulla (2008), anti-inflammatory (Vigorita et al., 2001), antimicrobial (Sharma and Jain (2008), tuberculo-static, hormone receptor (Pelletier et al. (2005), CNS stimulant (Chaudhary et al. (1976), antiproliferative (Ottana et al. (2005), anti-HIV Monforte et al. (2001), Ali et al. (2007), anticonvulsant Gursoy and Terzioglu (2005), antihistaminic Vittoria et al. (1992), etc.

Epilepsy is a neurological disorder characterized by unprovoked seizures, and affects at least 50 million people worldwide. There is a continuing demand for new anticonvulsant agents as it has not been possible to control every kind of seizure with the currently available antiepileptic drugs. Phenobarbital and mephobarbital are well-known barbituric acid derivatives which are used for the treatment of epilepsy. These drugs are very effective in controlling the seizures but they suffer from major side effects such as sedation, and hypnosis. So there is an urge for the development of effective anticonvulsant drugs with less or no side effects. Ralitoline (Fig. 1) is one of the compounds which possesses a thiazolidinone moiety and found to be effective in preclinical anticonvulsant models.

Based on these literature evidences we thought to synthesize some thiazolidinone derivatives having anticonvulsant activity. These compounds were obtained from 5-(4-chlorobenzylidene)-

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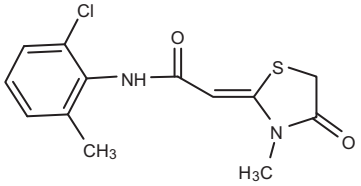


Figure 1 Ralitoline.

3-[4-(7-chloroquinoline-4-ylamino] propyl)-2-imino-thiazolidin-4-one derivatives **5**(**a**–**c**), following the synthetic strategy as shown in Scheme 1. The structure of the newly synthesized compounds is proved using spectroscopic methods such as IR, ^{1}HNMR and mass spectral data.

2. Experimental

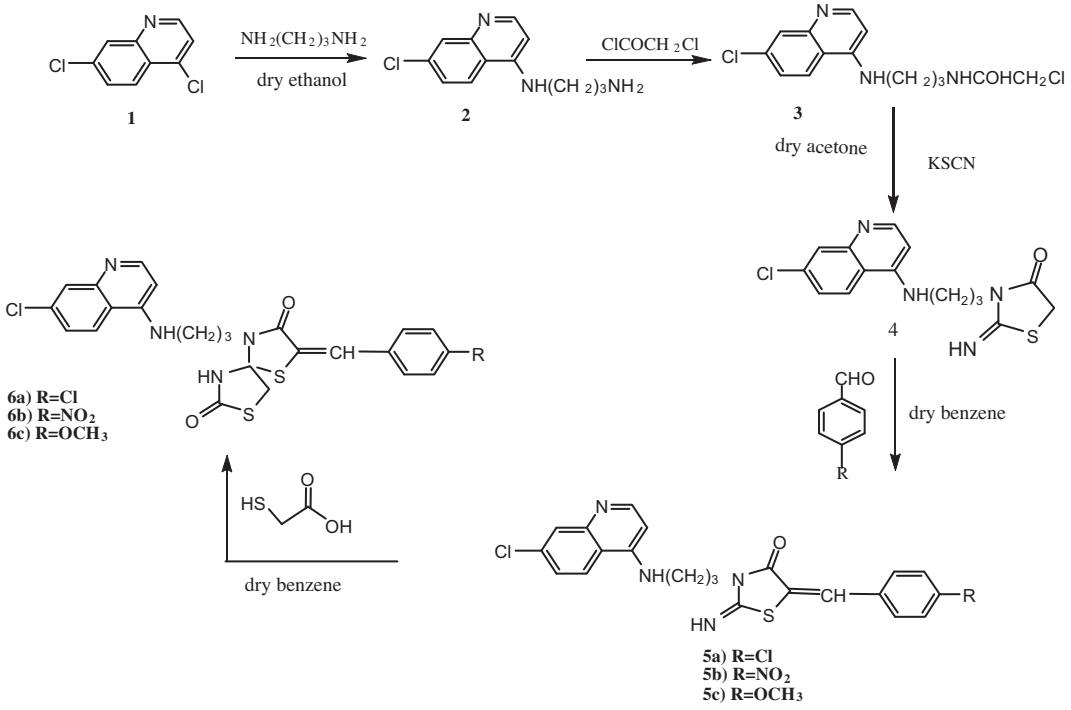
The entire chemicals were purchased from Aldrich Chemical Company (USA) and were used after purification by distillation. The reactions were monitored by precoated aluminum silica gel 60F 254 thin layer plates procured from Merck (Germany). All melting points were measured by a capillary apparatus and are uncorrected. All the compounds were routinely checked by IR, ^{1}H-NMR and mass spectrometries. IR spectra were recorded in KBr on a Perkin–Elmer model 8201 FTIR spectrophotometer. ^{1}H-NMR spectra were recorded at ambient temperature using a Brucker spectroscopin DPX-300 MHz spectrophotometer in DMSO. The following abbreviations were used to indicate the peak multiplicity as s – singlet, d – doublet, t – triplet, and m – multiplet. FAB mass spectra were recorded on a JEOL SX102 mass spectrometer using Argon/Xenon (6 kV, 10 mB) gas. Column chromatography was performed on silica gel (Merck). Anhydrous sodium sulfate was used as a drying agent for the organic phase.

*2.1. Synthesis of N-(7-chloroquinolin-4-yl) propane 1, 2-diamine (**2**)*

A mixture of 4-7-dichloroquinoline (2.97 g, 0.59 mol) and 1-2-diaminopropane (0.89 g, 0.07 mol) in ethanol was refluxed with stirring for 8 h. It was cooled and distilled in the solvent. Solid product was dissolved in DCM (80 ml), washed with 5% of sodium bicarbonate and brine solution. The organic layer was filtered and dried over Na_2SO_4. The solid product was recrystallized from EtOH to give compound **2** (yield 55%) m.p. 97–98 °C. IR (KBr) cm^{-1} 3272 [NH str.], 2928[C–H str. Ar. H], 1552 [C–N str.], 815 [C–Cl str.], 1485 [C–H bend. CH_2], 1197 [C–C str.]. ^{1}H-NMR ($CDCl_3$) δ 8.64(d, 1H, CH), 8.5(s, 1H,CH), 8.3 (m, 2H,CH), 7.43 (q, NH), 6.49 (d, 1H,CH), 4.12(s,1H, NH) 2.0 (t,2H, CH), 1.7 (q, 2H,CH). MS: [*m*/*z*] 235.71 (M + 1) Anal. Calculated/found for $C_8H_{14}ClN_3$: C, 16.59/16.04; N, 19.83/19.06.

*2.2. Synthesis of N-(7-chloroquinolin-4-yl) propane 1, 2-diamine (**2**) [microwave method]*

A mixture of 4-7-dichloroquinoline (2.97 g, 0.59 mol) and 1-2-diaminopropane (0.89 g, 0.07 mol) in ethanol was placed in a 100 ml borosil flask ice fitted with a funnel as a loose top. The reaction mixture was subjected to microwave irradiation, at 20% (360 W) for 10 min. Completion of reaction was checked by TLC and UV. The reaction mixture was cooled and the resulting solid was filtered, washed with ethanol, dried and recrystallized from ethanol to give compound **2** (yield 40.45%).



Scheme 1

*2.3. Synthesis of 2-chloro-N-(2-(7-chloroquinoline-4-ylamino)propyl) chloroacetanilides (**3**)*

Compound N-(7-chloroquinoline-4-yl) propane-1, 2-diamine (**2**) (2.35 g, 10 mmol), triethyl amine (1 ml, 1.01 mmol) and chloroacetyl chloride (0.75 ml, 10 mmol) were dissolved in dry ethanol (25 ml). The mixture was stirred for 30 min on ice bath then refluxed with stirring for 4–6 h. Reaction mixture was cooled and solvent was evaporated. Now, the solid product was dissolved in DCM and water. The organic layer was filtered and dried over Na_2SO_4. The solid product was recrystallized from EtOH to give compound **3** (yield 40%), m.p. 102–104 °C. IR (KBr) cm^{-1} 3419 [NH str.], 3008[C–H str. Ar. H], 1200 [C–N str.], 1002 [C–Cl str.], 3352 [C–C str.]. ^{1}H-NMR ($CDCl_3$) δ 8.9(d, 1H,CH), 8.7 (d, 1H,CH), 8.3 (m, 2H,CH), 8.0 (m,NH), 7.4 (q,NH), 6.49 (d, 1H,CH), 2.5 (s,1H, NH) 2.08 (t,2H, CH), 1.7 (q, 2H,CH). MS: [*m*/*z*] 235.71 (M + 1) Anal. Calculated/found for $C_{14}H_{15}Cl_2N_3O$: C, 12.84/12.04; N, 55.06/54.92.

*2.4. Synthesis of 3-(2-(7-chloroquinoline-4-ylamino)propyl)-2-iminothiazolidi-4-one (**4**)*

Compound 2-chloro-N-(2-(7-chloroquinoline-4-ylamino)propyl) chloroacetanilides (3) (0.78 g,2.5 mmol) and potassium thiocyanate (0.78 g, 1.1 mmol) were mixed in dry acetone followed by refluxing on water bath for about 8 h. Progress of reaction was checked by TLC. Reaction mixture was cooled and solvent was evaporated. Now, the solid product was dissolved in DCM and water. The organic layer was filtered and dried over Na_2SO_4. The solid product was recrystallized from EtOH to give compound **3** (yield 45%), m.p. 150–151 °C.

*2.5. Synthesis of 5-(4-chlorobenzylidene)-3-[4-(7-chloroquinoline-4-ylamino] propyl)-2-imino- thiazolidin-4-one (**5a**)*

A mixture of 3-(2-(7-chloroquinoline-4-ylamino)propyl) -2-iminothiazolidi-4-one (**4**) (0.78 g, 2.5 mmol) and p-chloro benzaldehyde (0.78 g, 1.1 mmol) was dissolved in dry benzene and refluxed for about 8 h. After completion of reaction, it was cooled. After evaporation of the solvent yielded a solid product which was purified over the column of silica gel and eluted with ethanol to give compound **5a** (yield 65%), m.p. 125-126 °C. IR (KBr) cm^{-1} 3200 [NH str.], 3124[C–H str. Ar. H], 1209 [C–N str.], 1022 [C–Cl str.], 3002 [C–C str.], 1144 and 690 (C–S of thiazolidinone ring). ^{1}H-NMR ($CDCl_3$) δ 8.9 (s, 1H,NH), 8.7(d, 1H,CH) 8.3 (d, 1H,CH), 8.1 (m, 4H,CH), 7.8 (s,NH), 7.4 (d,1H), 6.49 (d, 1H,CH), 3.3 (d,2H, CH) 2.5 (d,2H, CH), 1.6(m, 6H,CH).

*2.6. Synthesis of 5-(4-chlorobenzylidene)-3-[4-(7-chloroquinoline-4-ylamino] propyl)-2-imino- thiazolidin-4-one (**5a**) [microwave method]*

A mixture of 3-(2-(7-chloroquinoline-4-ylamino)propyl) -2-iminothiazolidi-4-one (**4**) (0.78 g, 2.5 mmol) and *p*-chloro benzaldehyde (0.78 g, 1.1 mmol) dissolved in dry benzene was placed in a 100 ml borosil flask ice fitted with a funnel as a loose top. Reaction mixture was subjected to microwave irradiation at 360 W for 15 min. Completion of reaction was checked by TLC and UV. After cooling the reaction mixture a solid was obtained which was recrystallized from ethanol to give compound **5a**.

*2.7. Synthesis of 2-(4-chlorobenzylidene)-4-(2[7-chloroquinolin-4-ylamine]propyl) 1,6-dithia-4,9-diazaspiro[4,4]nonane-3,8-dione (**6a**)*

A mixture of compound **5a** (0.18 g, 0.429 mol) and thioglycolic acid (0.276 g, 0.03 mol) was dissolved in dry benzene and refluxed on water bath for 24 h. After completion of reaction it was cooled and neutralized with an aqueous solution of sodium bicarbonate. The organic layer was separated followed by evaporation. Resultant solid was purified over the column of silica gel and eluted with ethanol to give compound **6a** (Yield 60%), m.p. 165–166 °C. IR (KBr) cm^{-1} 3407 [NH str.], 3359 [C–H str. Ar. H], 1313 [C–N str.], 1035 [C–Cl str.], 3002 [C–C str.], 1708 [C═O], 1144 and 690 (C–S of thiazolidinone ring). ^{1}H-NMR ($CDCl_3$) δ 8.3(d, 1H,), 8.1(d, 1H,CH), 7.8 (d, 1H,CH), 7.4 (m, 4H,CH), 6.49 (d, 1H,CH),4.4 (s, 1H, NH), 3.3 (t,2H, CH) 2.3 (d,2H, CH), 1.3 (m, 6H,CH).

3. Antiepileptic activity

Male Wistar albino mice having weight 80–130 g were kept in quarantine for 10 days under standard husbandry conditions

Table 1 Antiepileptic activity of synthesized spirothia-zolidinone derivatives using maximal electroshock seizure (MES) induced seizure in mice.

Time duration (s)				
Treatment	Tonic flexion (mean ± SEM)	Tonic extension (mean ± SEM)	Clonic stupor (mean ± SEM)	Mortality (mean ± SEM)
Control	245 ± 1.80	170 ± 4.90	200 ± 4.9*	100
Diazepam 4 mg/kg	3.6 ± 6.1*	05 ± 1.9*	03 ± 1.73*	00
Comp (**6a**) 100 mg/kg propane	40.3 ± 5.7*	30.0 ± 4.8*	32 ± 5.5*	20.2
Comp II (**6b**) 100 mg/kg propane	120.2 ± 4.7*	80 ± 5.3*	60.6 ± 5.5*	22.00
Comp III (**6c**) 100 mg/kg propane	150.3 ± 5.7*	120 ± 5.3*	127.6 ± 5.3*	24.2

* $P < 0.05$, compared with control, No. of animals ($n = 6$) in each group.

(27.3 °C, relative humidity 65 ± 10%) for 12 h in dark and light cycles respectively and were given standard food and water ad. libitum. The project proposal was approved by the Institutional Animal Ethics Committee (ref. no. PBRI/11/IAEC/223). The outcome of this study is presented in Table 1.

3.1. Acute oral toxicity study

Acute oral toxicity test was performed for substituted [spiro-4-thiazolidinone] **6(a–c)** compounds following the OECD guideline – 420. Starting with the least dose of these synthesized compounds **6(a–c)** increasing doses, up to 2000 mg/kg body weight, were administered to different groups of mice and their mortality was determined. (Fisher, 1989). Substituted [spiro-4-thiazolidinone] **6(a–c)** were screened for their antiepileptic potential using maximum electroshock (MES) induced seizure. (Ecobichon, 1997).

3.2. Experimental setup

The animals were divided into 5 groups of 6 numbers each and were administered as follows:

Group I received vehicle
Group II received Diazepam 4 mg/kg
Group III received Compound **6(a)**30 mg/kg suspended in Tween 80
Group IV received Compound **6(b)** 30 mg/kg suspended in Tween 80
Group V received Compound **6(c)** 30 mg/kg suspended in Tween 80

Diazepam (4 mg/kg) was used as reference standard. All these compounds were administered by intraperitoneal route (i.p.) 30 min before application of electroshock (42 MA, 0.2 s) using corneal electrode. The mice were observed for the reduction in duration of tonic flexion, extension and clonic stupor convulsions.

4. Antimicrobial activity

The in vitro antimicrobial activity of compounds **5a**, **5b**, **5c** and **6a**, **6b**, **6c** was performed using the disk diffusion method (Hassan et al. (1998), Patel and Trivedi (1977). Ciprofloxacin for bacteria and fluconazole for fungal were used as standard

Table 2 Antimicrobial activities of the synthesized compounds **3**, **5** (**a–c**), **6(a–c)**.

S. No.	Conc. (μg/ml)	*E. coli*		*B. subtilis*		*A. niger*		*A. flavus*	
		Zone of inhibition (mm)	% activity compared to the standard	Zone of inhibition (mm)	% activity compared to the standard	Zone of inhibition (mm)	% activity compared to the standard	Zone of inhibition (mm)	% activity compared to the standard
5 (a)	400	14	50.00	16	53.33	53	81.53	16	55.17
	200	12	54.55	11	47.82	44	73.33	11	47.82
	100	10	62.50	7	41.17	–	–	8	44.44
5 (c)	400	20	71.82	25	83.33	54	83.07	18	62.06
	200	17	77.27	17	73.91	46	76.66	13	56.52
	100	11.5	71.80	11	64.70	–	–	9	50.00
6 (c)	400	18	64.28	20	66.67	38	58.46	23	79.31
	200	16	72.72	13	56.52	26	43.33	16	69.56
	100	9	56.25	9	52.94	–	–	11	61.11
5 (b)	400	20	71.42	22	73.33	49	75.38	20	68.96
	200	14	63.64	15	62.21	36	60.00	13	56.52
	100	9	56.25	9	25.94	–	–	905	52.78
6 (a)	400	22	78.51	27	90.00	49	75.33	24	82.75
	200	18	81.81	18	78.26	38	63.33	17	73.91
	100	12	75.00	11.5	67064	–	–	11.5	63.88
6 (b)	400	13	46.42	19	63.33	46	70.46	26	89.65
	200	11	50.00	13.5	58.69	369	60.00	18	78.26
	100	7.5	46.87	835	50.00	–	–	12	66.67
3	400	18	64.28	18	60.00	59	90.76	19	65.51
	200	13	59.09	13	56.52	44	73.33	13.5	58369
	100	9	56.25	8	47.05	–	–	9.0	50.00
*	400	28	100	30	100				
Std.	200	22	100	23	100				
antibact.	100	16	100	17	100				
*									
Std.									
antifungal.	400					65	100	29	100
	200					60	100	23	100
	100					–	–	18	100

Showing maximum activity.
Showing minimum activity.

drugs. The compounds **5a**, **5b**, **5c** and **6a**, **6b**, **6c** were tested for their anti-bacterial and anti-fungal activities by disk-diffusion method using nutrient broth medium [contained (g/l): beef extract 3 g; peptone 5 g; pH 7.0] for bacteria and potato dextrose broth medium [contained (g/l): beef extract 3 g; peptone 5 g; pH 7.0] for fungi. The Gram-positive bacteria and Gram-negative bacteria utilized in this study consisted of *E. coli*, and *B. subtilis* for bacterial species and *A. niger* and *A. flavus* for the fungal species. In the disk-diffusion method, sterile paper disks (0.5 mm) impregnated with compound dissolved in dimethylsulfoxide (DMSO) at concentrations 100, 200 and 400 μg/ml were used. Then, the paper disks impregnated with the solution of the tested compounds were placed on the surface of the media inoculated with the micro-organism. The plates were incubated at 35 °C for 24 h. After incubation, the growth inhibition zones and activity were checked out. The outcome of this study is presented in Table 2.

5. Results and discussion

A rapid simple and efficient method has been developed for the synthesis of some novel benzylidene spiro thiazolidinone derivatives under conventional and microwave conditions. The thiazolidinone derivatives were synthesized and evaluated for their physical, analytical and spectral data. Characteristic IR bands provide significant indications for the formation of thiazolidinone derivatives. IR spectra of all the compounds showed 1500–1578 cm^{-1} (NH str.), 1735–1770 cm^{-1} (C═O str.), 1600–1475 cm^{-1}(C═C str.), 1144 and 690 (C–S of thiazolidinone ring), which confirmed the formation of thiazolidinone derivatives. Structures of thiazolidinone derivatives were further confirmed by ^{1}H-NMR spectra, which proved as a diagnostic tool for the positional elucidation of the proton. Assignments of the signals are based on chemical shift and intensity pattern. The ^{1}H-NMR spectra showed multiplates in the region 1.5–2.0 ppm for (CH_2) and doublets in the region 8.14–7.3 ppm for aromatic proton in all spectra respectively. Characteristic peaks were observed in the mass spectra of all compounds which followed the similar fragmentation pattern. The spectra of compounds showed molecular ion peak (M^+) at m/z which confirmed the molecular weight of the thiazolidinone derivatives.

The synthesized compounds **3**, **5(a–c)** and **6(a–c)** were screened for antibacterial activity against two pathogenic strains (*E. coli* and *B. subtilis*).The antibacterial screening against *E. coli* showed that among the compounds **3**, **5(a–c)** and **6(a–c)** the compound **6a** displayed highest activity. Contrary to this observation, compound **5a** showed highest activity among all the compounds screened for this activity against *B. subtilus*. Similarly the antifungal activity was evaluated against two pathogenic strains (*A. niger and A. flavus*). The zone of inhibition and activity index were determined by comparison with the standard drug flucanazole. The compound **6a** displayed highest activity against *A. niger*. Contrary to this observation, compounds **3** and **6b** showed highest activity among all the compounds screened for this activity against *A.flavus*.

All the compounds **6a–c** were tested for their antiepileptic activities using maximum electro seizure method and results are shown in Table 1. Diazepam (4 mg/kg) was used as standard for this study. The tonic flexion and extension along with clonic stupor was observed for control synthesized compound and standard and **6a** was found to be more potential among all the derivatives tested. The probable cause of potentiality of **6a** is due to greater lipophilicity of chloro group which in turn is responsible for greater penetrability of the compound in the cell.

In conclusion, the present study throws light on the identification of this structural class as antiepileptic agent which can be of interest for further detailed preclinical investigations.

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