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Synthesis and pharmacological properties of some quinoline derivatives

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Abstract

A series of 2-(2-thienyl)cinchoninic acids **3**, their derivatives **5** and 4-(3-substituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazolo-6-yl)-2-(2-thienyl)quinolines **6** were synthesized. The structures of the newly synthesized compounds are confirmed by analytical, IR, NMR and mass spectral data. The newly synthesized compounds were evaluated for their anti-inflammatory, analgesic and anthelmintic activity. The results indicated that dinitrothiophene derivatives **5** are more active.

Keywords: Thiophene derivatives; Anti-inflammatory activity; Analgesic activity; Anthelmintic activity; Quinoline derivatives

1. Introduction

Chemotherapeutic activity of nitro heterocycles is almost always associated with compounds having the nitro group attached to C-5 of the five-membered heterocycle [1] containing appropriate substituents at C-2. The 1,3,4-thiadiazole nucleus is associated with a broad spectrum of biological activities, possibly by virtue of the toxophoric >N–C–S moiety [2,3]. These thiadiazoles find a variety of applications as antitumor and anti-inflammatory agents. Quinoline and its derivatives are well known for their antimalarial and therapeutic properties [4]. A quinoline ring fused with the heterocyclic system is also found in natural products. Prompted by the above observations and as part of the general search for chemotherapeutically important nitrogen- and sulfur-containing heterocycles [5–7], a project was undertaken to synthesize and to study the biological activity of quinoline carboxylic acid of type **3**, nitrothiophene derivatives **5** and thiadiazole derivatives **6** (Scheme 1). The results of such studies are reported in this paper. Some of the newly synthesized compounds were subjected to anti-inflammatory, analgesic and anthelmintic activity studies.

2. Chemistry

The Pfitzinger [8] reaction of substituted isatins **1** with 2-acetylthiophene **2** provides a convenient method for the preparation of 2-(2-thienyl)cinchoninic acids **3**. In the present investigation 5-methylisatin, 5-bromoisatin, 5-chloroisatin, and 5,7-dichloroisatin were prepared according to the literature methods [9]. 5-Bromoisatin was prepared by the bromination of isatin. Isatin was obtained commercially. 2-Acetylthiophene was prepared by acetylation of thiophene [10]. 2-(2-Thienyl)cinchoninic acids **3** were then condensed with 3-substituted-4-amino-5-mercapto-1,2,4-triazoles **4** in the presence of phosphorus oxychloride to give 4-(3-substituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole-6-yl)-2-(2-thienyl)quinolines **6**. Nitration of **3** using concentrated nitric acid and concentrated sulfuric acid gave 2-(3,5-dinitro-2-thienyl)cinchoninic acid **5**. The triazoles **4** carrying alkyl, aryl and aryloxymethyl substituents at position **3** were prepared according to literature procedures [11–13].

The characterization data of compounds **3** and **5** are given in Table 1. The IR spectra of **3** showed an absorption band at 1700 and 2870–3070 cm^{-1} characteristic of the carboxyl functional group. The mass spectrum of **3a** showed the molecular ion peak at *m/z* 255 consistent with the molecular formula $C_{14}H_9NO_2S$, which is also found to be the base peak. The other prominent peak was observed at *m/z* 211 which can be attributed to the loss of the CO_2 group from the molecular ion. Nitration of cinchoninic acids **3** with concentrated nitric acid and sulfuric acid at 0°C gave 2-(3,5-dinitro-2-thienyl)cinchoninic acids **5**. In the IR spectra of **5** the absorption bands due to the $-CO_2H$ group appeared in the regions 1680–1720 and 2780–3050 cm^{-1}. In a typical example in the proton magnetic resonance (PMR) spectra of **5d**, a 3-proton singlet appeared at δ 2.6 for the methyl group. The thiophene 4H proton appeared as a singlet at δ 8.5. The aromatic protons appeared as multiplets at δ 7.8–8.3 integrating for four pro-

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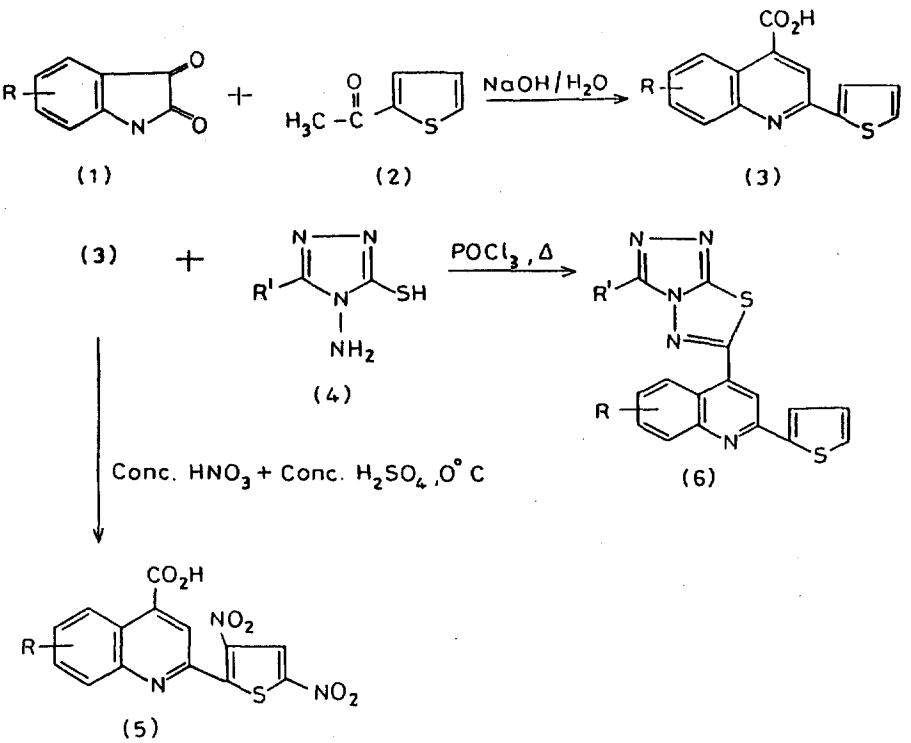

Scheme 1. Quinoline carboxylic acid **3**, nitrothiophen derivatives **5** and thiadiazole derivatives **6**.

Table 1
Characterization data of 2-(2-thienyl)cinchoninic acids **3** and 2-(3,5-dinitro-2-thienyl)cinchoninic acids **5**

Comp.	R (M.p. (°C))	Yield (%) (M.p. (°C))	Colour and crystal form	Molecular formula	Anal.: found (calc.) (%)		
					C	H	N
3a	H (218 [14–16])	80 (210–212) [a]	yellowish green crystals	$C_{14}H_9NO_2S$	65.5 (65.88)	3.42 (3.53)	5.46 (5.50)
3b	6-chloro (261 [16])	82 (261–262) [b]	pale yellow silky needles	$C_{14}H_8ClNO_2S$	58.22 (58.13)	2.58 (2.77)	4.62 (4.84)
3c	6-bromo (256 [16])	76 (248–249) [b]	yellow shiny needles	$C_{14}H_8BrNO_2S$	50.24 (50.45)	2.36 (2.40)	4.22 (4.20)
3d	6-methyl (222 [16])	84 (222–23) [b]	yellow silky needles	$C_{15}H_{11}NO_2S$	66.73 (66.91)	4.00 (4.08)	5.18 (5.20)
3e	6,8-dichloro	81 (283–284) [b]	yellow shiny needles	$C_{14}H_7Cl_2NO_2S$	51.88 (52.01)	2.15 (2.17)	4.36 (4.33)
5a	H	85 (171–173) [b]	yellow powder	$C_{14}H_7N_3O_6S$	48.78 (48.69)	2.00 (2.03)	12.22 (12.17)
5b	6-chloro	88 (289–291) [b]	pale yellow flakes	$C_{14}H_6ClN_3O_6S$	44.22 (44.33)	1.50 (1.58)	11.00 (11.08)
5c	6-bromo	68 (282–283) [b]	yellow shiny crystals	$C_{14}H_6BrN_3O_6S$	39.67 (39.72)	1.35 (1.42)	9.72 (9.93)
5d	6-methyl	70 (240–42) [b]	pale yellow crystals	$C_{15}H_9N_3O_6S$	50.22 (50.14)	2.43 (2.51)	11.58 (11.70)
5e	6,8-dichloro	78 (279–281) [b]	yellow shiny flakes	$C_{14}H_5Cl_2N_3O_6S$	40.56 (40.67)	1.25 (1.21)	10.22 (10.17)

Solvent of crystallization: [a] ethanol; [b] acetic acid.

tons. Further evidence in support of the dinitro product is obtained by mass spectral studies. The mass spectrum of **5b** showed the molecular ion peak at *m/z* 379 consistent with the molecular formula $C_{14}H_6ClN_3O_6S$. The chlorine isotope peak was observed at *m/z* 381. The other prominent peaks observed were at *m/z* 335 which can be attributed to the loss of the CO_2 group and at *m/z* 333 due to the loss of the NO_2 radical from the molecular ion. Similarly, the mass spectra of **5c** and **5d** were recorded and are also in conformity with the assigned structure.

Table 2
Characterization data of 4-(3-ethyl/*o*-chlorophenyl/*p*-chlorophenoxymethyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole-6-yl)-2-(2-thienyl)quinolines **6**

Comp.	R	R^1	Yield (%) (M.p. (°C))	Colour and crystal form	Molecular formula	Anal.: found (calc.) (%)		
						C	H	N
6a	H	ethyl	67 (140–142)	pale yellow powder	$C_{18}H_{13}N_5S_5$	58.94 (59.50)	3.48 (3.58)	19.23 (19.28)
6b	H	*o*-chlorophenyl	65 (>300)	pale yellow powder	$C_{22}H_{12}ClN_5S_2$	59.20 (59.33)	2.56 (2.70)	15.63 (15.73)
6c	H	*p*-chlorophenoxymethyl	65 (220–222)	pale yellow micro crystals	$C_{23}H_{14}ClN_5S_2$	58.00 (58.10)	2.78 (2.95)	14.63 (14.74)
6d	6-bromo	ethyl	70 (280–282)	pale yellow shiny needles	$C_{18}H_{12}BrN_5OS_2$	48.72 (48.98)	2.53 (2.72)	15.72 (15.87)
6e	6-bromo	*o*-chlorophenyl	58 (268–270)	dark yellow micro crystals	$C_{22}H_{11}BrClN_5S_2$	50.22 (50.48)	2.00 (2.10)	13.26 (13.38)
6f	6-methyl	*o*-chlorophenyl	60 (210–212)	yellow shiny crystals	$C_{23}H_{14}ClN_5S_2$	60.00 (60.13)	3.00 (3.05)	15.18 (15.25)
6g	6-methyl	*p*-chlorophenoxymethyl	68 (182–184)	pale green micro crystals	$C_{24}H_{16}ClN_5OS_2$	58.68 (58.90)	3.12 (3.27)	14.28 (14.31)
6h	6,8-dichloro	ethyl	64 (182–184)	yellow shiny micro needles	$C_{18}H_{11}Cl_2N_5S_2$	50.20 (50.12)	2.32 (2.55)	16.18 (16.24)
6i	6,8-dichloro	*o*-chlorophenyl	68 (184–186)	yellow micro crystals	$C_{22}H_{10}Cl_3N_5S_2$	51.32 (51.46)	2.00 (1.95)	13.58 (13.64)
6j	6,8-dichloro	*p*-chlorophenoxymethyl	68 (242–244)	yellow crystals	$C_{23}H_{12}Cl_3N_5OS_2$	50.48 (50.83)	2.22 (2.21)	12.88 (12.90)

Solvent of crystallization: 2:1 mixture of ethanol and dimethylformamide.

Cinchoninic acids **3**, on condensation with triazoles **4** in the presence of phosphorus oxychloride gave triazolothiadiazolylquinolines **6**. The characterization data of these condensation products **6** are given in Table 2. The structures assigned to compounds **6** were confirmed by analytical and spectral data. In the IR spectra of these compounds the absorption bands characteristic of the $-CO_2H$ and $-NH_2$ groups were absent, thereby indicating the involvement of the amino group of triazole and the carboxylic group of cinchoninic acid in the condensation reaction. In the PMR spectrum of **6c**, a two-proton singlet appeared at δ 5.68 for the $-OCH_2$ group. The signals due to aromatic and thiophene protons mingled together and appeared as a multiplet at δ 7.15–8.45 integrating for 12 protons. The mass spectrum of **6d** showed the molecular ion peak at *m/z* 441, consistent with the molecular formula $C_{18}H_{12}BrN_5S_2$. The bromine isotope peak was observed at *m/z* 443 as intense as that of the molecular ion peak. The molecular ion underwent fragmentation to give a peak at *m/z* 314–316 corresponding to the formation of 2-thienyl-4-cyano-6-bromoquinoline. Similarly, the mass spectrum of **6e**, **6g** and **6j** were also recorded and are in conformity with the assigned structure.

3. Experimental

3.1. Chemistry

All melting points are uncorrected. IR spectra (KBr disc) were recorded on a Shimadzu IR spectrophotometer. ^1H NMR spectra of a few selected compounds were recorded on a 90 MHz NMR spectrometer using tetramethylsilane (TMS) as internal standard and mass spectra were recorded on a V.G. Micromass model 7070F mass spectrometer.

3.1.1. General procedure for 2-(2-thienyl)cinchoninic acid 3

A solution of sodium hydroxide (2 g, 0.05 mol) and the appropriate isatin (**1**, 0.01 mol) in water (25 ml) was heated till a clear solution was obtained. 2-Acetylthiophene (**2**, 1.26 g, 0.01 mol) was added to it in small portions with occasional shaking and heating was continued for another 2 h. The reaction mixture was chilled in an ice bath. The solid mass formed was collected by filtering through a sintered glass crucible (G-4). The sodium salt of cinchoninic acid thus obtained was dissolved in water (100 ml). The cinchoninic acid was precipitated by neutralizing this solution with glacial acetic acid.

3.1.2. General procedure for 2-(3,5-dinitro-2-thienyl)-cinchoninic acid 5

The powdered cinchoninic acid (**3**, 0.01 mol) was added, in small portions with stirring, to concentrated sulfuric acid (15 ml) at 0°C. When the addition was complete, a cold solution of a mixture of concentrated nitric acid (1.5 ml) and concentrated sulfuric acid (1.5 ml) was added dropwise to the cold suspension of cinchoninic acid. Stirring continued for an hour at 0°C. The contents were then poured onto crushed ice with vigorous stirring. The crude precipitate formed was collected by filtration, washed with water, dried and recrystallized from glacial acetic acid.

3.1.3. General procedure for 4-(3-substituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazol-6-yl)-2-(2-thienyl)-quinolines 6

A mixture of triazole (**4**, 0.01 mol), cinchoninic acid (**3**, 0.01 mol) and phosphorus oxychloride (10 ml) was heated over a water bath for 2 h. The reaction mixture was allowed to cool to room temperature and poured onto crushed ice. The solid mass formed was collected by filtration, washed with sodium bicarbonate (5%) solution, then with water and dried. It was recrystallized from a 2:1 mixture of ethanol and dimethyl formamide.

3.2. Pharmacology

The anti-inflammatory activity studies were carried out according to the method of Winter et al. [17].

3.2.1. Analgesic activity

The acetic acid induced writhing test in mice was carried out employing the method of Collier et al. [18]. Albino mice weighing 20–25 g were used for this test. A day prior to drug testing these mice were given an injection of 0.6% acetic acid intraperitonially; only those which produced a positive writhing episode were selected. The results are given in Table 4.

3.2.2. Anthelmintic activity

The anthelmintic activity studies were carried out against earthworms (*Pontoscolex corethrusus*) according to the method of Garg and Atal [19]. Six earthworms of approximately the same size were placed in each Petri dish containing a 50 ml suspension of the sample of specific concentration at 28 ± 1°C. Simultaneously, a control comprising six worms in distilled water and Tween® 80 (0.5%) was kept. The drug concentrations were 0.1% and 0.2% (wt./vol.) for both the

Table 3
Analgesic activity [a] data of compounds **3**, **5** and **6**

Comp.	Dose (mg/kg)	No. of animals tested	Mean no. of writhings in 20 min ± SE	Protection (%)
3a	100	5	28.00 ± 0.98	26.32
3b	100	5	34.00 ± 1.64	10.53
3d	100	5	36.00 ± 0.79	5.26
5a	100	5	30.00 ± 1.09	21.05
5b	100	5	36.00 ± 2.16	5.26
5d	100	5	32.00 ± 3.02	15.79
6a	100	5	28.00 ± 1.19	26.32
6e	100	5	33.00 ± 1.25	13.16
6g	100	5	31.00 ± 0.65	18.42
Control (0.6% acetic acid, 10 ml/kg)		5	38.00 ± 0.02	
Standard (Ibuprofen)	100	5	10.00 ± 2.43	73.68

[a] Index for analgesic activity. Method: acetic acid induced writhings; animals: albino mice (20–25 g); No. of animals per group: 5; route of administration: intraperitonially; standard: Ibuprofen (100 mg/kg); test compounds: 100 mg/kg; SE: standard error.

Table 4
Anti-inflammatory activity [a] data of compounds **3**, **5** and **6**

Comp.	No. of animals tested	Paw volume ± SE (ml) after			Inhibition (%) of edema after		
		1 h	3 h	5 h	1 h	3 h	5 h
3a	5	0.71 ± 0.01	0.79 ± 0.05	0.98 ± 0.03	7.79	15.05	20.96
3b	5	0.73 ± 0.03	0.81 ± 0.03	0.99 ± 0.04	5.19	12.90	20.16
3d	5	0.72 ± 0.01	0.71 ± 0.02	0.68 ± 0.04	6.49	23.65	45.16
5a	5	0.71 ± 0.02	0.71 ± 0.02	0.70 ± 0.04	7.79	23.65	43.54
5b	5	0.72 ± 0.02	0.72 ± 0.02	0.72 ± 0.01	6.49	22.58	41.93
5d	5	0.72 ± 0.12	0.72 ± 0.01	0.71 ± 0.02	6.49	23.65	42.74
6a	5	0.71 ± 0.03	0.71 ± 0.01	0.70 ± 0.01	7.79	23.65	43.54
6e	5	0.71 ± 0.02	0.69 ± 0.01	0.68 ± 0.01	7.79	25.80	45.16
6g	5	0.72 ± 0.24	0.71 ± 0.02	0.70 ± 0.02	6.49	23.65	43.54
Control (2% acacia mucilage)	5	0.77 ± 0.03	0.93 ± 0.44	1.24 ± 0.01			
Standard (Ibuprofen)	5	0.63 ± 0.12	0.55 ± 0.03	0.51 ± 0.03	18.18	40.86	58.87

[a] Index for anti-inflammatory activity. Model: acute inflammatory; method: formalin induced edema test; animals: albino rats; No. of animals per group: 5; route of administration: intraperitonially; standard: Ibuprofen (20 mg/kg); test compounds: 20 mg/kg; SE: standard error.

Table 5
Anthelmintic activity [a] data of compounds **3**, **5** and **6**

Comp.	No. of earthworms tested	Conc. (wt./vol.) (mg)	Mean paralysis time ± SE (min)	Mean death time ± SE (min)
3a	6	100	64.20 ± 2.46	83.42 ± 0.36
	6	200	44.18 ± 1.30	102.10 ± 2.09
3b	6	100	88.40 ± 1.40	126.14 ± 3.16
	6	200	56.24 ± 1.36	82.36 ± 2.10
3d	6	100	72.48 ± 2.16	84.32 ± 3.16
	6	200	40.24 ± 1.22	62.18 ± 2.18
5a	6	100	28.32 ± 2.14	32.00 ± 2.12
	6	200	25.10 ± 1.36	30.18 ± 3.10
5b	6	100	20.14 ± 0.40	25.12 ± 0.68
	6	200	16.10 ± 1.42	21.18 ± 0.96
5d	6	100	34.12 ± 2.46	48.16 ± 3.02
	6	200	28.18 ± 2.05	34.32 ± 2.50
6a	6	100	44.20 ± 1.36	68.12 ± 1.46
	6	200	32.16 ± 2.42	40.10 ± 1.30
6c	6	100	28.12 ± 2.42	34.36 ± 1.42
	6	200	20.16 ± 0.68	32.16 ± 2.16
6g	6	100	30.42 ± 3.04	38.26 ± 3.16
	6	200	25.44 ± 2.42	34.28 ± 2.48
Piperazine citrate	6	100	22.48 ± 2.30	46.28 ± 2.42
	6	200	20.32 ± 1.48	28.30 ± 1.26
Mependazole	6	100	16.24 ± 2.46	55.32 ± 3.42
	6	200	12.10 ± 1.40	33.18 ± 2.26
Control	6	100	N.E.	N.E.
	6	200	N.E.	N.E.

[a] Index for anthelmintic activity. Earthworm: Sp. *Portoscoplex corethrusus*; amount of sample: 100 and 200 mg; standard drugs: piperazine citrate and mependazole; control: distilled water + 0.5% Tween® 80; N.E.: no effect; SE: standard error.

standard and the test sample. The times required for paralysis (movement stopped) and death of the worms were noted using a stopwatch.

4. Results

From the data obtained and reported in Table 3 it is clear that none of the compounds showed any significant analgesic activity.

The results presented in Table 4 demonstrated that dinitrocinchoninic acids **5** showed better anti-inflammatory activity than cinchoninic acids **3**. Further, most of the compounds showed anti-inflammatory activity in the 3rd and 5th hours.

The results for anthelmintic activity are given in Table 5. The data indicate that although the cinchoninic acids **3** did not show any marked anthelmintic activity, the nitrated compounds **5** showed significant activity at lower doses; with **5b** the activity was slightly higher than that of the standard drug. Similarly, the triazolothiadiazoles **6e** and **6g** showed significant activity, even at lower doses, although lower compared with the standard.

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