



Synthesis, reactions and pharmacological studies of new series of selenolo [2,3-b]tetrahydroquinoline

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Abstract

A novel series of selenolo [2, 3-b] tetrahydroquinoline derivatives were synthesized by the reaction of NaSeH with 2-chloro-3-cyano-4-(4-methoxyphenyl)-5, 6, 7, 8-tetrahydroquinoline 2 followed by reactions with chloro acetone, chloro acetonitrile, ethyl chloroacetate and chloro acetamide to yield 9 and 11a-c respectively. Reactions of 11c with acetic anhydride, cyclohexanone and aromatic aldehyde affording derivatives 12-14 respectively. Spectroscopic (IR, ¹HNMR, ¹³CNMR and MS) were confirmed the structure of the synthesized compounds. Compounds 5a-c, 9, 11a-c, 12, 13 and 14 were investigated for their anti-inflammatory and analgesic activities; in addition, the most active compounds were tested for their acute toxicity.

Keywords: Tetrahydro Quinolines; Pharmacological Screening; Pyrimidoselenolo Tetrahydroquinolines; Spirocyclohexanepyrimidoselenolo Tetrahydroquinoline.

1. Introduction

Tetrahydroquinolines are used as a precursor for synthetic many of heterocyclic compounds for examples their use in the synthesis of pyrazolo[3,4-b]quinolines and benzo[b][1,8] naphthyridines derivatives [1-6] which possess antitumor, trypanocidal and DNA binding properties [7,8] and are antimicrobial agents [9]. While pyrazolo[3,4-b]quinoline derivatives are used as pharmaceutical agents and as inhibitors of oncogenic Ras [10,11]. A literature survey indicates that incorporation of a selenium atom in the quinoline nucleus posses' anti-inflammatory and analgesic activities; in addition, pyrimidoselenolo quinoline derivatives were saver concerning ulcerogenicity in animals: they showed ranging from 50% to 33% activity, for the applied doses, compared to indomethacin (100%) and nontoxic at doses up to 160 mg/kg [12]. Consequently, synthesis and biological screening of bearing selenium onto tetrahydroquinoline derivatives may discover new useful compounds for the treatment of inflammatory diseases and may act as drugs. In this paper we investigated selenophene and tetrahydroquinoline systems combined with a fused ring and screened these compounds for their inflammatory and analgesic effects.

2. Results and discussion

To attempt our target, we start with 2-oxo-4-(4-substituedphenyl)-1, 2, 5, 6, 7, 8-hexahydroquinoline-3-carbonitrile (5a-c) which were prepared as according to known method [1]. Reaction of 5c with POCl₃ affording 2- Chloro-4-(4-methoxyphenyl)-5, 6, 7, 8-tetrahydro quinoline-3-carbonitrile (6) and reacted directly with sodium hydrogen selenide in ethanol to give 4-(4-methoxyphenyl)-5, 6, 7, 8-tetrahydroquinoline-2(1H) selenone-3-carbonitrile (7).

Refluxing of compound 7 with chloro acetone or chloro acetonitrile or ethyl chloroacetate or chloro acetamide in ethanol in the presence of sodium acetate as a basic catalyst followed by sodium ethoxide afforded compounds 9 and

11a-c respectively in excellent yields, via the intermediates 8 and 10a-c respectively. Furthermore reaction of compounds 11c with acetic anhydride, cyclohexanone and aromatic Aldehyde (anisaldehyde) gave the corresponding compounds 12, 13 and 14 respectively. The structures of the synthesized compounds were characterized by their physical, analytical and spectral data. The results were displayed in (Table 1 and 2).

Table 1: Physical Properties and Elemental Analyses of the New Compounds.

Compd.	Mp. (°C) Yield (%)	Formula (Mwt)	Solvent of crystallization	Analysis % Calcd. (Found)			
				C	H	N	Cl
5a	290 (90)	C ₁₇ H ₁₆ N ₂ O ₂ (280.32)	Ethanol	72.84 (72.66)	5.75 (5.68)	9.99 (9.79)	
5b	260 (85)	C ₁₆ H ₁₃ ClN ₂ O (284.74)	Ethanol	67.49 (67.20)	4.60 (4.50)	9.84 (9.66)	12.45 (12.30)
5c*	275 (reported)	C ₁₆ H ₁₄ N ₂ O (250.30)	Ethanol	76.78 (77.02)	5.64 (5.82)	11.19 (11.46)	
6	170 (85)	C ₁₇ H ₁₅ ClN ₂ O (298.77)	Ethanol	68.34 (68.11)	5.06 (4.88)	9.38 (9.11)	11.87 (11.75)
7	190-192 (70)	C ₁₇ H ₁₆ N ₂ OSe (343.28)	Dioxane	59.48 (59.22)	4.70 (4.65)	8.16 (8.00)	
8	105-107 (80)	C ₂₀ H ₂₀ N ₂ O ₂ Se (399.34)	Ethanol	60.15 (60.00)	5.05 (4.89)	7.01 (6.88)	
9	215-217 (65)	C ₂₀ H ₂₀ N ₂ O ₂ Se (399.34)	DMF/H ₂ O	60.15 (59.95)	5.05 (4.77)	7.01 (6.96)	
10a	194 – 196 (75)	C ₁₉ H ₁₇ N ₃ OSe (382.32)	Ethanol	59.69 (59.61)	4.48 (4.19)	10.99 (10.74)	
10b	145 – 146 (55)	C ₂₁ H ₂₂ N ₂ O ₃ Se (429.37)	Ethanol	58.74 (58.22)	5.16 (4.88)	6.52 (6.23)	
10c	250 – 252 (60)	C ₁₉ H ₁₉ N ₃ O ₂ Se (400.33)	Ethanol	57.00 (56.79)	4.78 (4.25)	10.50 (10.29)	
11a	>300 (65)	C ₁₉ H ₁₇ N ₃ OSe (382.32)	DMF/H ₂ O	59.69 (59.48)	4.48 (4.32)	10.99 (10.89)	
11b	280 – 282 (40)	C ₂₁ H ₂₂ N ₂ O ₃ Se (429.37)	DMF/H ₂ O	58.74 (58.46)	5.16 (5.00)	6.52 (6.34)	
11c	270 – 272 (55)	C ₁₉ H ₁₉ N ₃ O ₂ Se (400.33)	DMF/H ₂ O	57.00 (56.99)	4.78 (4.44)	10.50 (10.29)	
12	>300 (70)	C ₂₁ H ₁₉ N ₃ O ₂ Se (424.35)	DMF/H ₂ O	59.44 (59.11)	4.51 (4.33)	9.90 (9.80)	
13	>300 (45)	C ₂₅ H ₂₇ N ₃ O ₂ Se (480.46)	DMF/H ₂ O	62.50 (62.22)	5.66 (5.33)	8.75 (8.45)	
14	>300 (50)	C ₂₇ H ₂₅ N ₃ O ₃ Se (518.47)	DMF/H ₂ O	62.55 (62.32)	4.86 (4.69)	8.10 (7.88)	

*Reported as previously described [1]

Table 2: Physical Properties and Elemental Analyses of the New Compounds

Compd.	IR (cm ⁻¹)	¹ H and ¹³ C-NMR (δ, ppm)
5a	3123 (NH), 2220 (CN), 1646 (CO).	DMSO-d ₆ :1.55-2.55 (m, 8H, 4CH ₂); 3.90 (s, 3H, OCH ₃); 6.95-7.10 (m, 4H, Ar-H); 8.00 (s, 1H, NH); ¹³ C: 22.6, 23.5, 25.2, 30.5 (4CH ₂); 55.5 (OCH ₃); 115.3 (C-CN); 115.9 (CN); 149.6 (C4-quinoline); 119.5 (C5-quinoline); 136.5 (C6-quinoline); 114.3, 127.3, 129.5, 129.5, 129.5, 136.4 (Ph), 169.2 (C=O)
		DMSO-d ₆ :1.60-2.55 (m, 8H, 4CH ₂); 7.20-7.30 (m, 4H, Ar-H); 8.00 (s, 1H, NH)
5b	3190 (NH), 2220 (CN), 1650 (CO)	DMSO-d ₆ :1.64-1.98 (m, 8H, 4CH ₂); 7.13-7.35 (m, 5H, Ar-H).8.10 (s, 1H, NH)
5c*	3226 (NH), 2215 (CN), 1717 (CO).	DMSO-d ₆ :1.55-2.55 (m, 8H, 4CH ₂); 3.90 (s, 3H, OCH ₃); 6.95-7.10 (m, 4H, Ar-H); 12.5 (s, 1H, SeH) ¹³ C: 22.6, 23.5, 25.2, 30.5 (4CH ₂); 55.5 (OCH ₃); 110.3 (C-CN); 117.9 (CN); 149.6

6		(C4-quinoline); 119.5 (C5-quinoline); 136.5 (C6-quinoline); 114.3, 127.3, 129.5, 129.5, 129.5, 136.4 (Ph), 161.2 (C-SeH)
7	2217 (CN)	CDCl ₃ :1.55-2.55 (m, 8H, 4CH ₂); 2.40 (s, 3H, CH ₃); 3.90 (s, 3H, OCH ₃); 4.2 (s, 2H, CH ₂); 6.95-7.10 (m, 4H, Ar-H)
	3195 (NH), 2223 (CN)	DMSO-d ₆ :1.55-2.55 (m, 8H, 4CH ₂); 2.35 (s, 3H, CH ₃); 3.95 (s, 3H, OCH ₃); 5.9 (s, 2H, NH ₂); 7.50-8.10 (m, 4H, Ar-H)
		CDCl ₃ :1.55-2.55 (m, 8H, 4CH ₂); 3.90 (s, 3H, OCH ₃); 4.5 (s, 2H, CH ₂); 7.70-8.10 (m, 4H, Ar-H)
8		CDCl ₃ :1.55-2.55 (m, 8H, 4CH ₂); 1.6 (t,3H, CH ₃); 3.90 (s, 3H, OCH ₃); 4.0 (s, 2H, CH ₂); 4.5 (q, 2H, CH ₂); 7.50-8.10 (m, 4H, Ar-H)
9	2200 (CN); 1690 (CO)	CDCl ₃ :1.55-2.55 (m, 8H, 4CH ₂); 3.90 (s, 3H, OCH ₃); 4.20 (s, 2H, CH ₂); 7.10 (broad, 2H, NH ₂); 7.50-8.20 (m, 4H, Ar-H)
10a	3300,3400 (NH ₂);1645 (C=O)	DMSO-d ₆ :1.55-2.55 (m, 8H, 4CH ₂); 3.90 (s, 3H, OCH ₃); 7.30 (s, 2H, NH ₂); 7.80-8.00 (m, 4H, Ar-H)
		DMSO-d ₆ :1.55-2.55 (m, 8H, 4CH ₂); 1.28 (t, 3H CH ₃); 3.90 (s, 3H, OCH ₃); 4.00 – 4.20 (q, 2H CH ₂); 6.10 (s, 2H NH ₂); 7.90 – 8.00 (m, 4H Ar-H);
10b	2200 (CN)	DMSO-d ₆ :8.70 (s,2H CONH ₂); 7.90 – 8.00 (m, 4H Ar-H); 7.10 (s, 2H NH ₂); 3.80 (s, 3H OCH ₃); 1.55-2.55 (m, 8H, 4CH ₂)
10c	2217 (CN); 1720 (C=O ester)	DMSO-d ₆ :8.50 (d,1H NH); 7.50 – 8.10 (m, 4H Ar-H); 3.50 (s, 3H OCH ₃); 1.95 (s, 3H CH ₃); 1.55-2.55 (m, 8H, 4CH ₂)
11a		DMSO-d ₆ :8.30 (s, 1H NH); 7.30 – 8.00 (m, 4H Ar-H); 6.00 (s, 1H NH); 3.90 (s, 3H OCH ₃); 1.5 – 2.4 (m, 10Hcyclohexane); 1.55-2.55 (m, 8H, 4CH ₂)
11b	3300,3430 (NH ₂); 1680 (C=O); 2200 (CN)	DMSO-d ₆ :9.40 (s, 1H NH); 7.00 – 8.50 (m, 8H Ar-H); 6.50 (d, 1H CH); 5.8 (d, 1H NH); 3.90 (s, 3H OCH ₃); 3.70 (s, 3H OCH ₃); 1.55-2.55 (m, 8H, 4CH ₂)
11c	3390,3280 (NH ₂);2200 (CN)	
	3400,3200 (NH ₂);1665 (C=O ester)	
12		
13	3500,3450, 3300, 3250 (NH ₂); 1660 (C=O)	
	3190 (NH); 1675 (C=O)	
14	3350, 3150 (2NH);1670 (C=O)	
	3350, 3150 (2NH);1670 (C=O)	

*Reported as previously described [1]

3. Pharmacological results and discussion

3.1. Anti-inflammatory activity

Anti-inflammatory activity of the tested synthesized compounds (5a-c, 7, 9, 11a-c, 12-14) was evaluated by carrageenan induced paw edema method of Winter et al [13]. The data are taken at 0.5,1,2,3,4 and 5h interval .The compounds were tested at doses of 10 mg/ kg .The results are listed in Table (3) and showed that after 3h all the tested compounds gave inhibition activity against carrageenan –induced inflammation in rats. Compounds (5a, 7, 11c, 12 and 13) displayed strong activity and showed inhibition percentage ranged from (45.3-89%) of that standard drug Indomethacin (100 %), while after 5h inhibition percentage ranged from (64.6-87.7%). On the other hand, compounds (5c, 9 and 11b) showed moderate activity ranged from (40.6-50.2%) less than of that Indomethacin. Finally, from the resulted data compounds (5b, 11a and 14) appeared weak activity with inhibition percentage ranged from (36.0-8.1%). Generally, it was noticed that the tested synthesized compounds after 5h interval and highly anti-inflammatory activity of the first group 7, 11c, 12 and 13 may be due to the presence of selenium and methoxyphenyl substituted in 4-postion in compound7 and the activity increased with selenium atom in cyclic structures.

3.2 Analgesic activity

The tested synthesized compounds (5a-c, 7, 9, 11a-c, 12-14) were tested for their analgesic properties relative to acetyl salicylic acid as reference drug at a dose level of 0.028 mol/kg according to the reported procedures [14]. The results are given in (Table 4). The results showed that after 3h, compounds (5a, 7, 11c, 12 and 13) are the most active ranging from 60.4 to112.3% compared to the reference drug, while compounds 5c and 11b showed moderate activity with 45.6 % and 57 % respectively compared to the reference drug. The rest compounds 5b 9, 11a and 14 showed very weak activity as compared the standard drug Aspirin. Generally, the most active inflammatory compounds gave the same trends as analgesic activity.

Table 4: Analgesic Activities of the Test Compound (On the Hot Plate)

Compound	Time					
	0.5h	1h	2h	3h	4h	5h
5a	20.8	29.1	32.3	26.6	23.2	20.1
5b	5.1	5.9	6.7	4.5	4.2	4.0
5c	14.9	19.5	20.5	16.6	15.8	15.2
7	22.6	28.9	26.4	25.7	22.5	20.7
9	9.4	13.6	15.2	10.0	9.7	8.6
11a	8.3	11.7	12.5	9.4	8.7	8.0
11b	18.0	24.7	23.9	21.4	19.3	19.0
11c	31.7	43.5	49.5	45.0	38.7	33.8
12	39.1	51.9	59.8	56.8	42.5	37.4
13	29.8	41.4	46.3	39.9	33.8	30.3
14	4.8	5.4	6.7	5.1	4.6	4.5
Control	18.1	18.6	19.0	19.5	20.2	18.9

3.2.1. Acute toxicity (LD₅₀)

The median lethal dose (LD₅₀) of the most active inflammatory and analgesic compounds (11c, 12 and 13) in addition compound 7 were determined (i.p) in mice according to reported procedures [15]. The animals got injection (i.p) of a certain grade .The results showed that the (LD₅₀) of tested compounds were non-toxic at doses up to 400 mg /kg

4. Experimental

4.1. General

Melting points were determined by using the Kofler melting point apparatus, and were uncorrected. IR (KBr, cm⁻¹) spectra were recorded on a Pye-Unicam SP3–100 instrument at Taif University. ¹H NMR spectra were obtained on a Varian (400 MHz) EM 390 USA instrument at Cairo University by using TMS as internal reference. ¹³C NMR spectra were recorded on a GEMINI-200 NMR200 at Cairo University. Elemental analyses were obtained on an Elementar Vario EL 1150C analyzer (Heraeus, Germany). Mass spectra were recorded on a JEOL-JMS-AX 500 at Cairo National Research Center, Cairo, Egypt. Purity of the compounds was checked by thin layer chromatography (TLC) using silica gel plates.

2-Oxo-4-(4-substitutedphenyl)-1, 2, 5, 6, 7, 8-hexahydroquinoline-3-carbonitrile (5a-c), were prepared as according to previously procedure [1]. See physical properties and elemental analyses (Table 1). Also, IR, ^1H - and ^{13}C -NMR of the new compounds 5a and 5b and reported compound 5c (See Table 2).

2-Chloro-4-(4-methoxyphenyl)-5, 6, 7, 8-tetrahydroquinoline-3-carbonitrile (6)

A mixture of the corresponding 2-Oxo-4-(methoxyphenyl)-1, 2, 5, 6, 7, 8-hexahydroquinoline-3-carbonitrile derivative 5a (2.80 g, 10 mmol) and POCl_3 (30 mmol) was refluxed for 3 h at 70 °c. The mixture was cooled and poured onto crushed ice. The solid precipitate was filtered, dried, and recrystallized from proper solvent.

4-(4-methoxyphenyl)-5, 6, 7, 8-tetrahydroquinoline-2(1H) selenone-3-carbonitrile (7)

A mixture of the corresponding chlorotetrahydroquinoline derivative 6 (2.99 g, 10 mmol), selenium metal (1.0 g, 12 mmol) and sodium borohydride (1.2 g, 32 mmol) was refluxed in ethanol (50 mL) for 6 h. The mixture was cooled and poured in cold HCl. The solid precipitate was filtered, dried, and recrystallized from proper solvent. Mass spectrum of compound.

7 exhibited molecular ion peak at m/z, (%) 343 (M, 55%)

3-Cyano-4-(4-methoxyphenyl)-2-substituted selenotetrahydroquinolines (8 and 10a-c)

General procedure:

A mixture of 7 (3.43 g, 10 mmol), fused sodium acetate (0.98 g, 12 mmol), and chloroacetone chloroacetonitrile or ethyl chloroacetate or chloroacetamide (12 mmol), respectively, in 30 mL ethanol was heated under reflux for 1 h. The reaction mixture was allowed to cool and was then poured into 50 mL of ice water. The precipitate was collected by filtration and recrystallized from proper solvent.

3-Amino-2-acetyl-4-(methoxyphenyl) selenolo [2, 3-b]-5, 6, 7, 8-tetrahydroquinoline; 3-Amino-4-(4-methoxyphenyl) selenolo [2, 3-b]-5, 6, 7, 8-tetrahydroquinoline-2-carbonitrile; Ethyl- 3-Amino-4-(4-methoxyphenyl) selenolo [2, 3-b]-5, 6, 7, 8-tetrahydroquinoline-2-carboxylate; 3-Amino-4-(4-methoxyphenyl) selenolo [2, 3-b]-5, 6, 7, 8-tetrahydroquinoline-2-carboxamide (9 and 11a-c)

General procedure: Compounds 8 or 10a-c (10 mmol) and EtONa (0.5 g, Na in 10 mL EtOH) were refluxed for 10 min. and then cooled. The solid product was collected and recrystallized from proper solvent.

Mass spectrum of compound 9 exhibited molecular ion peak at m/z, (%) 399 (M^+ , 65%)

Mass spectrum of compound 11a exhibited molecular ion peak at m/z, (%) 382(M^+ , 60%)

Mass spectrum of compound 11b exhibited molecular ion peak at m/z, (%) 429 (M^+ , 75%)

Mass spectrum of compound 11c exhibited molecular ion peak at m/z, (%) 400 (M^+ , 100%)

2-Methyl-4-(4-methoxyphenyl) pyrimido[4',5': 4,5]selenolo[2,3-b]-5, 6, 7, 8-tetrahydroquinoline -11(1H)-one (12)

Compound 11c (1.0 g, 25 mmol) and redistilled acetic anhydride (20 mL) were heated under reflux for 10 hrs, and then left to cool. The precipitate was filtered and crystallized from proper solvent. Mass spectrum of compound 12 exhibited molecular ion peak at m/z, (%) 423 (M^+ -1, 50%)

Spirocyclohexane-4-(4-methoxyphenyl)-3(H) pyrimido[4',5': 4,5]selenolo[2,3-b]-5, 6, 7, 8-tetrahydroquinoline - 11(1H)-one; 2 (4'-methoxyphenyl)-4-(4-methoxyphenyl)-3(H) pyrimido[4',5': 4,5]selenolo[2,3-b]-5, 6, 7, 8-tetrahydroquinoline -11(1H)-one (13 and 14)

General procedure: A mixture of 11c (1.0 g, 25 mmol) and the corresponding aromatic aldehyde or cyclohexanone (33 mmol) was heated under reflux in glacial acetic acid (20 mL) for 5–7 h, the solid was collected by filtration and recrystallized from acetic acid.

Mass spectrum of compound 13 exhibited molecular ion peak at m/z, (%) 480 (M^+ , 100%)

Mass spectrum of compound 14 exhibited molecular ion peak at m/z, (%) 518 (M^+ , 70%)

5. Biological screening

The biological screening was carried out at the Department of Biochemistry Faculty of Agriculture Cairo University, Giza, Egypt. Animals were obtained from the animal house of the Central Laboratory of Agricultural Pesticides, Dokki, Egypt. The experiments were performed with albino rats of wister strain of either sex, weighing (100-130g) .The animals were maintained at 25+ 2C and 50+ 2% relative humidity, 12h light/ dark cycle .Food and water were freely available up to the time of experiments. The test compounds were dissolved in 1% carboxy methyl cellulose (CMC) solution.

6.1. Anti-inflammatory activity

The anti-inflammatory of eleven synthesized compounds (5a-c,7,9,11a-c,12-14) were evaluated according to the method described by Winter et al [13], where a pedal inflammation in rat paws induced by sub-plantar injection of 0.2 ml carrageenan (0.2%) suspension into the right hind of the rats. Male adult albino rats (100-130g) were divided into twelve groups, each of five animals. The thickness of rat paw was measured by a plethysmeter before and after 1h of carrageenan injection to detect the inflammation induced by carrageenan. Test compounds at doses of 10 mg/ kg were injected i.p to fifteen groups of rats 1h after injection of carrageenan control group received the vehicle (5% gum acacia), while reference group received Indomethacin at 10 mg /kg. The difference between the thicknesses of two paws

was taken as a measure of edema. The measurement was carried out at 0.5,1,2,3,4 and 5h, after injection of the test compounds, the reference drug and the vehicle. The percent of anti-inflammatory activity was calculated according to the formula given below. % Anti-inflammatory activity = $(v_c - v_t/v_c) \cdot 100$, where v_t represents the mean increase in paw volume in rats treated with the test compounds and v_c represents the mean increase in paw volume in control group of rats. The results are displayed in Table 3.

Table 3: Inhibitory Effect of the Test Compounds and Indomethacin upon Carrageenan Induced Paw Edema in Rats (% Edema Inhibition)

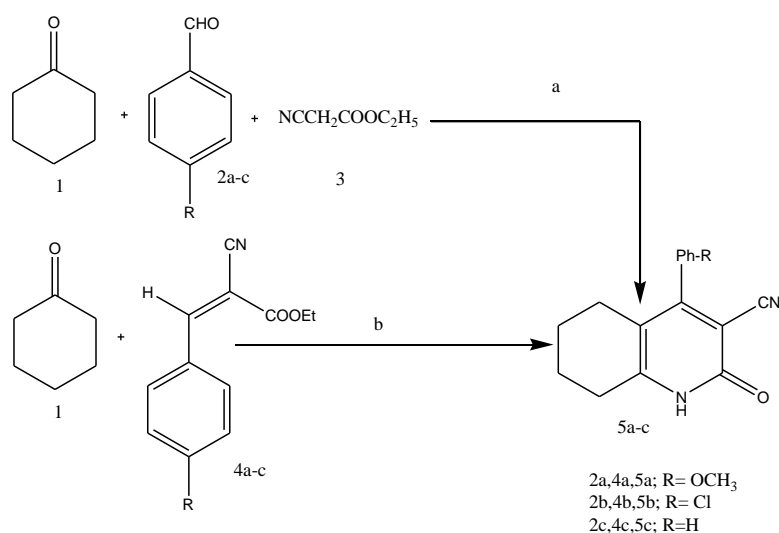
Compound	Time					
	0.5h	1h	2h	3h	4h	5h
5a	2.5	8	16.7	19.2	33.0	38.4
5b	0.4	2.3	3.3	4.5	6.0	6.4
5c	1.7	6.0	11.4	14.5	20.5	24.1
7	2.7	8.8	18	22.7	31.8	40.5
9	1.4	5.1	9.4	10.1	18.5	26.3
11a	1.0	4.0	8.2	9.3	19.8	21.4
11b	2.2	7.4	14.8	17.9	24.1	29.8
11c	4.2	14	28.9	32.2	42.2	52.1
12	4.7	14.8	30.6	37.9	48.5	50.3
13	3.9	12.7	25.9	29.6	39.8	47.2
14	0.5	2.6	3.1	4.2	5.1	4.8
Indomethacin	6.1	19.3	32.2	42.4	52.0	59.4

6.2. Analgesic activity

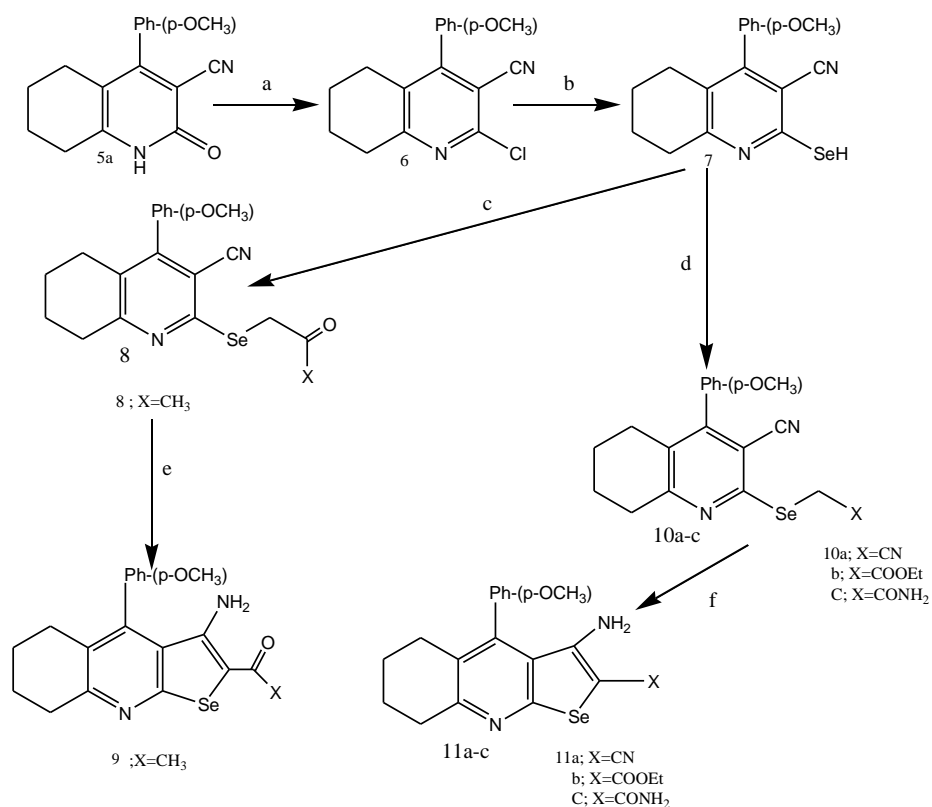
The analgesic activity of compounds (5a-c, 7, 9, 11a-c, 12-14) was determined in mice using the hot plate method [14] in comparison to Aspirin. In this method, the time taken by the mouse to lick its feet or to jump within a Plexiglas cylinder placed on a hot plate surface (55°C) was determined. This reaction time was taken as the end point and the increase in hot plate latency was taken as a measure of the analgesic activity. Male adult albino mice (25-30 g) were divided into thirteen groups, each of five animals. Eleven test compounds and the reference drug were injected i.p. at dose level of 10 mg /kg into mice. Control group of animals was similarly treated with 5% gum acacia .The reaction time was evaluated directly after 0.5, 1, 2, 3, 4, and 5h of injection. % Analgesic activity = $(n - n'/n) \cdot 100$; where n' represents the mean number of writhes of the test compounds and n represents the mean number of writhes of control group of rats .The results are displayed in (Table 4)

6.3. Determination of acute toxicity (LD₅₀)

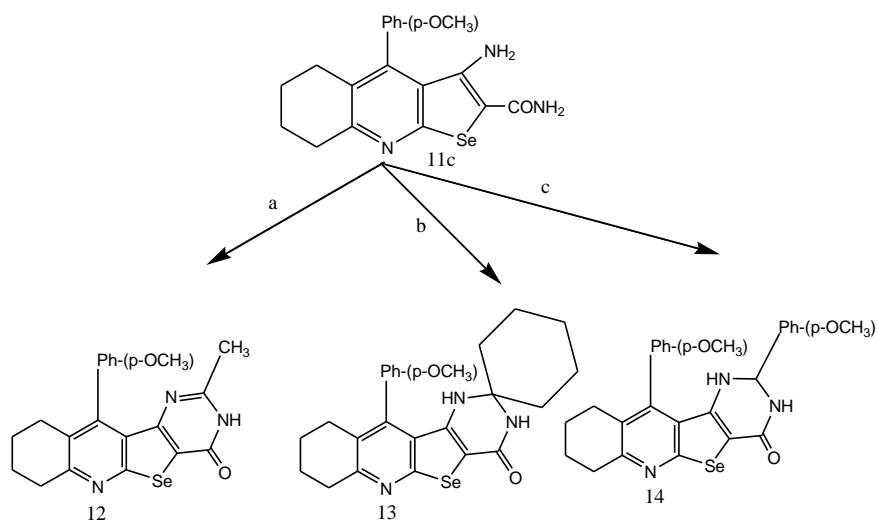
The median lethal dose (LD₅₀) of the test compounds were determined in mice .A group of male albino mice of five animals (25-30 g) was injected (i.p) at a certain grade .The percentage of mortality was determined 72 h after injection. Computation of LD₅₀ was processed by a graphical method [15].



Scheme 1: a, CH₃COONH₄/EtOH/reflux 30 hrs; b, CH₃COONH₄/EtOH/reflux hrs



Scheme 2: a=POCl₃/reflux 6 hrs; b=NaSeH/EtOH/reflux 3hrs; C= ClCH₂COCH₃/CH₃COONa/reflux 1 hr; d= ClCH₂X/CH₃COONa/reflux 1 hr; e,f= NaOEt/EtOH/reflux 1 hr.



Scheme3: a= Ac₂O/reflux/10 hrs; b= cyclohexanone/gl.acetic acid/reflux 6 hrs; p-anisaldehyde/gl.acetic acid /reflux 6 hrs

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