Synthesis and Reactions of Some New Substituted Pyridine and Pyrimidine Derivatives as Analgesic, Anticonvulsant and Antiparkinsonian Agents

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A series of substituted pyridine and pyrimidine derivatives were synthesized as analgesic, anticonvulsant, and antiparkinsonian agents by using compounds **1**, **2**, and **9** as starting materials. Pyridino-imide derivative **3** was prepared by condensation of **1** with tetrachlorophthalic anhydride and compounds **4** and **5** were also obtained by reaction of compound **1** with 1,2,4,5-benzene-tetracarboxylic dianhydride and 1,4,5,8-naphthalenetetracarboxylic dianhydride, respectively. Similarly, compound **2** was reacted with previous anhydrides to afford the corresponding imide **6** and *bis*-imide derivatives **7** and **8**, respectively. *Bis*-arylmethylene derivatives **9** were treated with hydrogen peroxide to afford the corresponding *bis*-oxiranocycloalkanone derivatives **10**, which condensed with thiourea to give the corresponding thioxopyrimidine derivatives **11**. Treatment of compound **11** with chloroacetic acid in the presence of anhydrous sodium acetate afforded the corresponding thiazolopyrimidine derivative **12** which condensed with aromatic aldehydes in acetic acid/acetic anhydride to give arylmethylene derivative **13**. Also, compounds **13** could be prepared by reaction of compounds **11** with chloroacetic acid, aromatic aldehydes, and sodium acetate in a mixture of acetic acid and acetic anhydride. The pharmacological screening showed that many of these obtained compounds have good analgesic, anticonvulsant, and antiparkinsonian activities comparable to Valdecoxib, Carbamazepine, and Benzatropine as reference drugs.

Keywords: Pyridine derivatives; Thiazolopyrimidine; Analgesic; Anticonvulsant; Antiparkinsonian

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Introduction

In previous work we have found that certain substituted pyridine derivatives show antimicrobial, anti-inflammatory [1−6], and antitumor activities [7−9]. In addition, the biological and analgesic activities of many heterocyclic compounds containing a sulfur atom have been reviewed [10−12]. On the other hand, thioxopyrimidine and thiazolopyrimidine derivatives have promising biological activities, e.g. anticancer properties [13−16]. Recently, some new thienopyrimidinone derivatives have been synthesized and tested for their analgesic, anticonvulsant, and antiparkinsonian activities [17]. In view of these observations and in continuation of our previous work in pyridine and pyrimidine chemistry, we synthesized some new heterocyclic compounds containing the pyridine or pyrimidine moiety and tested their biological activities.

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Results and discussion

Chemistry

6-Amino-6′-chloro-2′-ethoxy-4-thien-2-yl-[2,4′]bipyridinyl-5-carbonitrile (**1**) [6] and ethyl-2-amino-5,6,7,8-tetrahydro-4*H*-cyclohepta[b]thiophene-3-carboxylate (**2**) were prepared according to the published methods [18]. Condensation of compound **1** with acid anhydrides, namely, 3,4,5,6-tetrachlorophthalic anhydride, 1,2,4,5-benzenetetracarboxylic dianhydride, and 1,4,5,8-naphthalene tetracarboxylic dianhydride in refluxing acetic acid afforded the corresponding 6′-chloro-2′-ethoxy-6-(4,5,6,7-tetrachloro-1,3-dioxo-1,3-dihydroisoindol-2-yl)-4-thien-2-yl-[2,4′]bipyridinyl-5-carbonitrile (**3**), 2,6-*bis*-[substituted-bipyridinyl]pyrrolo[3,4-f]isoindole-1,3,5,7-tetraone derivative (**4**), and 2,7-*bis*-[substituted-bipyridinyl]benzo[l,m,n][3,8]phenanthroline-1,3,6,8-tetraone derivative (**5**), respectively (Scheme 1). The IR spectra of compounds **3**−**5** showed the absence of ν (NH_2) at 3450−3310 cm^{-1} for compound **1**, the presence of bands at 1690−1685 cm^{-1} corresponding to n (C=O, imide), and bands at 2220−2210 cm^{-1} corresponding to ν (C≡N).

Similarly, condensation of ethyl-2-amino-5,6,7,8-tetrahydro-4*H*-cyclohepta[b]thiophene-3-carboxylate (**2**) with the pre-

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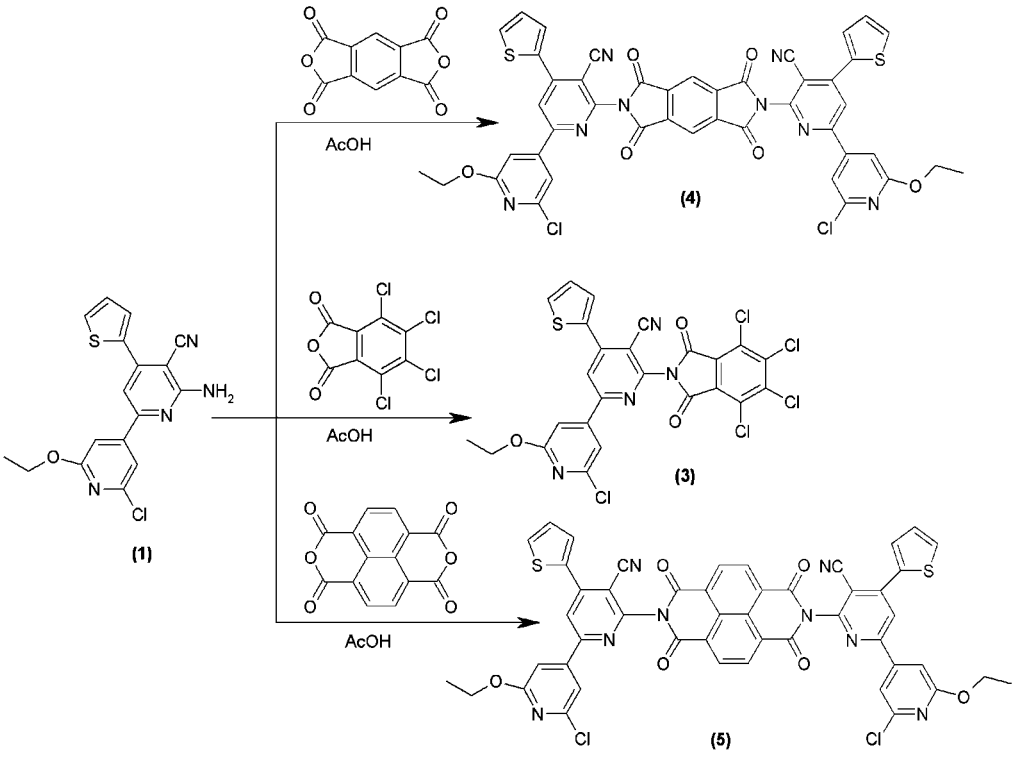


Scheme 1. Synthesis routes to compounds **3**–**5**.

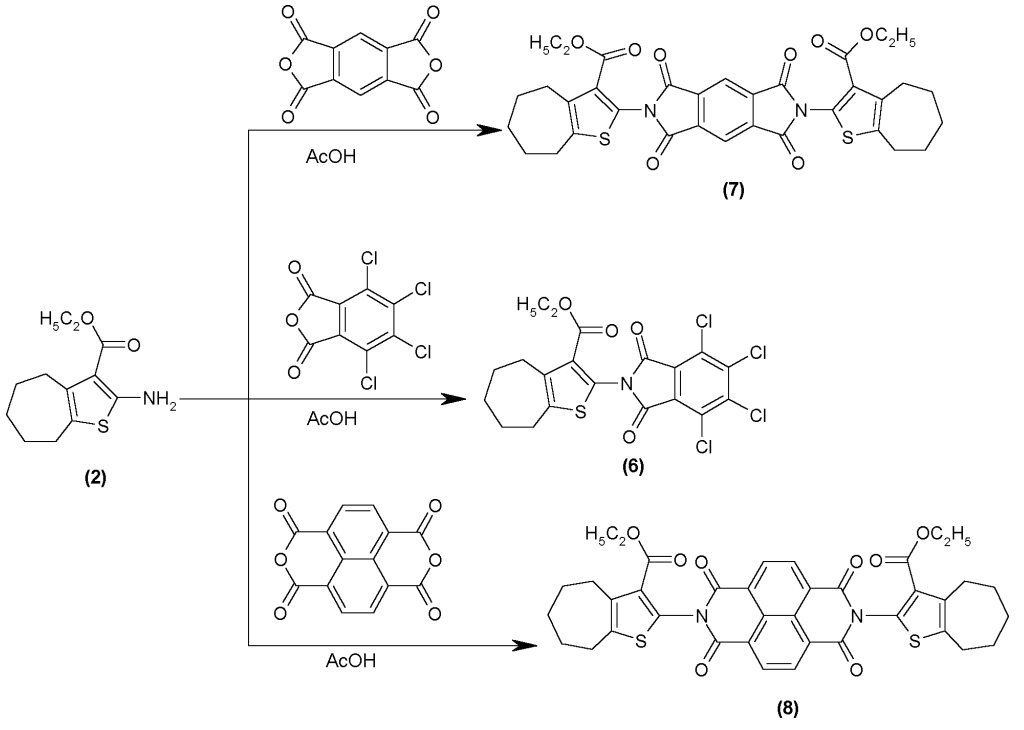
vious acid anhydride in refluxing acetic acid yielded the corresponding 2-(4,5,6,7-tetrachloro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-5,6,7,8-tetrahydro-4*H*-cyclohepta[b]thiophene-3-carboxylic acid ethyl ester (**6**), 2,6-*bis*-[substituted cyclohepta[b]thien]pyrrolo[3,4-f]isoindole-1,3,5,7-tetraone derivative (**7**) and 2,7-*bis*-[substituted cyclohepta[b]thien]-benzol-[l,m,n][3,8]phenanthroline-1,3,6,8-tetraone derivative (**8**), respectively (Scheme 2). The IR spectra of compounds **6**–**8** showed the absence of n (NH_2) at 3360–3300 cm^{-1} for compound **2** and the presence of bands at 1680–1675 cm^{-1} and 1725–1715 cm^{-1} corresponding to ν (C=O, imide) and n (C=O, ester), respectively.

Bis-arylmethylene cycloalkanone derivatives (**9a-f**) [19] required for the synthesis of the corresponding *bis*-(aryl)-1,6-dioxa-dispirodecane-4-one derivatives (**10a**–**f**) were obtained by treatment with hydrogen peroxide (30%) in the presence of sodium hydroxide (Scheme 3). The IR (KBr) of compounds **10a**–**f** showed bands at 1713–1729 cm^{-1} corresponding to ν (C=O) and also, the bands at 1700–1703 cm^{-1} (C=O in the α,β-unsaturated system) in compounds **9a**–**f** are not observed.

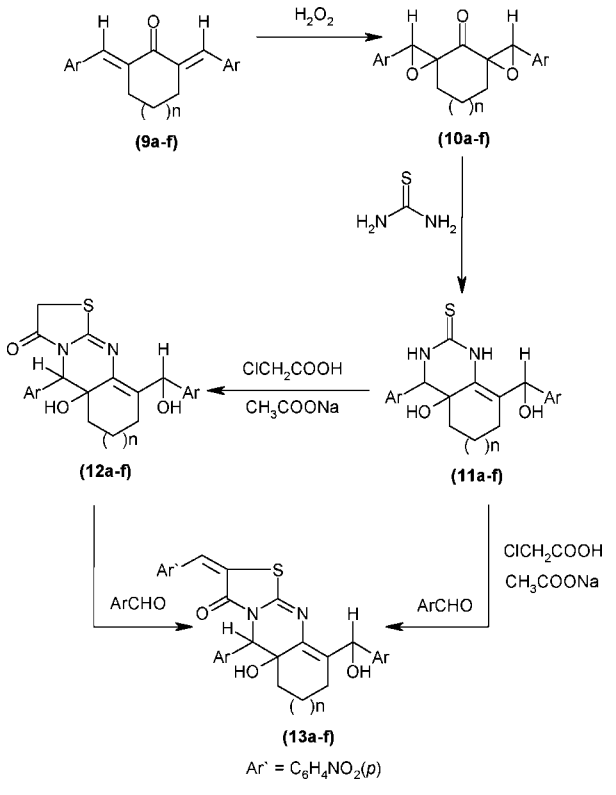
Thioxopyrimidine derivatives (**11a**–**f**) were obtained from the reaction of the oxirane derivatives (**10a**–**f**) with thiourea in ethanolic potassium hydroxide according to a published procedure [20, 21] (Scheme 3). The IR spectra of compounds **11a**–**f** showed bands at 3100–3250 cm^{-1} and at 3350–3400 cm^{-1} corresponding to ν (NH) and n (OH), respectively, while bands corresponding to ν (C=O) and ν (NH_2, thiourea) are not observed.

The thioxopyrimidine derivatives (**11a**–**f**) synthesized by the above procedure, were condensed with chloroacetic acid in a mixture of acetic acid/acetic anhydride in the presence of anhydrous sodium acetate to yield the corresponding thiazolopyrimidine derivatives (**12a**–**f**) (Scheme 3). The IR spectra of compounds **12a**–**f** showed bands at 3310–3390 cm^{-1} and at 1683 cm^{-1} corresponding to ν (OH) and ν (C=O), respectively, while, the bands corresponding to ν (NH) and ν (C=S) presented in the IR spectra of **11** are not observed.

Condensation of **12a**–**f** with *p*-nitrobenzaldehyde in refluxing acetic acid/acetic anhydride mixture afforded the corresponding arylmethylene derivatives **13a**–**f**. However, the arylmethylene derivatives **13a-f** could also be prepared directly from **11a**–**f** by reaction with chloroacetic acid, sodium acetate, and *p*-nitrobenzaldehyde in an acetic acid/acetic anhydride mixture [15,21] (Scheme 3). The IR spectra of compounds **13a**–**f** showed bands at 1700–1705 cm^{-1} and at 3300–3450 cm^{-1} corresponding to ν (C=O) and ν (OH), respectively, while bands corresponding to ν (NH) are not observed.



Scheme 2. Synthesis routes to compounds **6**–**8**.



Scheme 3. Synthesis routes to compounds **10**–**13**.

Pharmacological Screening

The tested three pharmacological properties namely, analgesic, anticonvulsant, and antiparkinsonian all have despite of their different biological receptors a neurological basis. Ten representative compounds (**3**, **4**, **7**, **10a**, **10d**, **11c**, **11e**, **12b**, **12f**, and **13a**) were studied with respect on these properties.

Analgesic activity

All compounds tested exhibited analgesic activities in a hot plate assay (Table 1). The most potent are compounds **12f** and **13a** showing higher activities than that of Valdecoxib by nearly 140–160% (compound **12f** showed the most pronounced effect). Also, the analgesic activities of **3**, **4**, **7**, **10a**, **10d**, **11c**, **11e**, and **12b** approached those of Valdecoxib, and showed 61–83% activity as compared to Valdecoxib (= 100%) (Table 1).

Anticonvulsant activity

Antagonism against yohimbine-induced clonic seizures in mice is considered to be a predictive model of potential anticonvulsant and *GABA*-mimetic [22]. Compounds **7**, **10a**, and **10e** are devoid of anticonvulsant activity in the yohimbine-induced clonic seizures assay, in which they provide no protection against yohimbine-induced clonic seizures. Compounds **3**, **11b** showed interesting anticonvulsant activities.

Table 1. Analgesic activities of selected compounds in a hot plate assay.

Compound	Analgesic activity related to Valdecoxib after						
	10 min. ± SE	20 min ± SE	30 min ± SE	45 min ± SE	60 min ± SE	90 min ± SE	120 min ± SE
Valdecoxib	1.0 ± 0.01	1.0 ± 0.01	1.0 ± 0.01	1.0 ± 0.01	1.0 ± 0.01	1.0 ± 0.01	1.0 ± 0.01
3	0.88 ± 0.011	0.89 ± 0.011	0.89 ± 0.011	0.91 ± .017	0.92 ± 0.016	0.93 ± 0.015	0.91 ± 0.017
4	0.66 ± 0.012	0.63 ± 0.012	0.88 ± 0.012	0.88 ± 0.016	0.88 ± 0.021	0.89 ± 0.017	0.89 ± 0.018
7	0.77 ± 0.012	0.85 ± 0.014	0.84 ± 0.012	0.87 ± 0.015	0.88 ± 0.018	0.84 ± 0.012	0.83 ± 0.019
10a	0.61 ± 0.013	0.73 ± 0.012	0.79 ± 0.001	0.81 ± 0.015	0.84 ± 0.016	0.84 ± 0.016	0.84 ± 0.035
10d	0.82 ± 0.014	0.91 ± 0.015	0.93 ± 0.017	0.95 ± 0.021	0.95 ± 0.032	0.94 ± 0.018	0.94 ± 0.026
11c	0.61 ± 0.013	0.65 ± 0.011	0.74 ± 0.012	0.75 ± 0.018	0.77 ± 0.011	0.77 ± 0.011	0.77 ± 0.013
11e	0.91 ± 0.011	0.92 ± 0.009	0.93 ± 0.016	0.88 ± 0.019	0.83 ± 0.021	0.79 ± 0.016	0.65 ± 0.012
12b	0.63 ± 0.010	0.64 ± 0.017	0.73 ± 0.013	0.73 ± 0.018	0.74 ± 0.019	0.75 ± 0.016	0.78 ± 0.013
12f	1.29 ± 0.18	1.45 ± 0.16	1.45 ± 0.13	1.44 ± 0.20	1.41 ± 0.32	1.41 ± 0.29	1.39 ± 0.28
13a	0.97 ± 0.013	0.98 ± 0.015	1.40 ±0.14	1.55 ± 0.21	1.56 ± 0.35	1.61 ± 0.34	1.42 ± 0.45

Table 2. Anticonvulsant activities of selected compounds (as ED_{50} values) needed to antagonize yohimbine-induced clonic seizure and compared to the anticonvulsant activity of Carbamazepine.

Compound	**ED_{50} [mg/kg]/± SE**	**Relative potency compared to Carbamazepine ± SE**
Control	0	0
Carbamazepine	29 ± 0.31	1.0 ± 0.01
3	53 ± 0.41	0.67 ± 0.008
5	30 ± 0.32	0.954 ± 0.0091
7	No protection	No protection
10a	No protection	No protection
10e	No protection	No protection
11b	34 ± 0.34	0.74 ± 0.0068
11f	12 ± 0.11	2.31 ± 0.019
12d	11 ± 0.112	2.53 ± 0.021
13a	14 ± 0.117	2.01 ± 0.023
13c	16 ± 0.123	1.83 ± 0.0178

Their relative potencies to Carbamazepine (1.0) are 0.67 and 0.74, respectively. Compounds **11f**, **12d**, **13a**, and **13c** are more potent than Carbamazepine where their relative potencies are 2.31, 2.53, 2.01, and 1.83, respectively (Table 2). ED_{50} was estimated via determining the dose, which protected 5% of the tested animals against the convulsant induced by yohimbine.

Antiparkinsonian activity

The muscarinic agonists Tremorine and Oxotremorine induce parkinsonian signs such as tremor, ataxia, spasticity, salivation, lacrimation, and hypothermia. Antiparkinsonian agents antagonize these signs. The antiparkinsonian activity measured by the ability of compounds to protect animals against the parkinsonian like signs induced by agonists. Compounds **11a**, **11d**, **12b**, and **12f** showed nearly no antiparkinsonian activities. While compounds **8**, **10c**, and **10d** showed moderate antiparkinsonian activities (relative potencies to Benzatropine (= 1.0) are 0.64, 0.60 and 0.40). Compounds **10b**, **13a**, and **13d** are the most potent antiparkinsonian agents (0.80 relative potencies) (Table 3).

Experimental

Chemistry

Melting points were determined on open glass capillaries using an Electrothermal IA 9000 SERIES digital melting point apparatus (Electrothermal, Essex, U.K.) and are uncorrected. Elemental analyses were performed with all final compounds on Elementar, Vario EL, Microanalytical Unit, National Research Centre, Cairo Egypt and were found within ± 4% of the theoretical values. Infrared (IR) spectra were recorded on a Pye Unicam SP-1000 spectrophotometer (Pye Unicam. Ltd., Papakura, New Zealand) using the KBr disc technique. ^{1}H-NMR spectra were recorded on Varian EM-360-270 MHz spectrometer (DMSO-d_6 or $CDCl_3$) (Varian, Palo Alto, CA, USA) and the chemical shifts are given in δ (ppm) downfield from tetramethylsilane (TMS) as an internal standard. Splitting patterns were designated as follows: s singlet; d doublet; t triplet; m multiplet. The mass spectra (MS) were measured using VG 2AM-3F mass spectrometer (Thermo electron corporation, Madison, WI, USA). Follow up of the reactions and checking the purity of the compounds were made by TLC on silica gel-precoated aluminum sheets (Type 60 F254, Merck, Darmstadt, Germany) and the spots were detected by exposure to UV lamp at λ 254 nm for few seconds.

*Synthesis of 6-Amino-6′-chloro-2′-ethoxy-4-thien-2-yl-[2,4′]bipyridinyl-5-carbonitrile (**1**)*

A mixture of 2-chloro-6-ethoxy-4-acetylpyridine (0.2g, 1 mmol), 2-thiophencarbaldehyde (0.1g, 1 mmol), malononitrile (0.066g, 1 mmol) and ammonium acetate (0.6 g, 8 mmol) in absolute ethanol (25 mL) was heated under reflux for 3 h. The reaction mixture was cooled, the formed solid was then filtered off, washed with and crystallized from ethanol to give compound **1**: mp. 184−186 °C (Lit. mp. 186−188 °C [6]).

Table 3. Antiparkinsonian activities of selected compounds compared to that of Benzatropine.

Compound	Salivation and lacrimation score	Tremors score	Decrease of Oxotremerine rectal temperature [%] ± SE	Relative potency compared to Benzatropine mesilate ± SE
Control	0	0	0	0
Benzatropine	1	1	25 ± 0.41	1.00 ± 0.09
8	1	1	16 ± 0.31	0.64 ± 0.07
10b	1	1	20 ± 0.38	0.80 ± 0.075
10c	2	2	15 ± 0.28	0.60 ± 0.059
10d	2	2	10 ± 0.11	0.40 ± 0.031
11a	3	3	4.0 ± 0.01	0.16 ± 0.014
11d	3	3	3.0 ± 0.012	0.12 ± 0.013
12b	3	3	4.0 ± 0.013	0.16 ± 0.012
12f	3	3	3.0 ± 0.016	0.12 ± 0.011
13a	1	1	20.0 ± 0.51	0.80 ± 0.06
13d	1	1	20.0 ± 481	0.80 ± 0.071

Table 4. Physico-chemical data of newly synthesized compounds.

Comp.	Ar	n	Yield [%]	Mp. [°C]	Color and solvent for crystallization	Mol. Formula* (Mol. wt)
3	–	–	60	240–2	white DMF/H_2O (2:1)	$C_{25}H_{11}Cl_5N_4O_3S$ (624.71)
4	–	–	72	225–7	White AcOH/H_2O (2:1)	$C_{44}H_{24}Cl_2N_8O_6S_2$ (895.75)
5	–	–	75	232–4	Yellow DMF/H_2O (2:1)	$C_{48}H_{26}Cl_2N_8O_6S_2$ (945.80)
6	–	–	80	189–91	White EtOH	$C_{20}H_{15}Cl_4NO_4S$ (507.20)
7	–	–	82	196–8	White AcOH	$C_{34}H_{32}N_2O_8S_2$ (660.70)
8	–	–	65	210–2	White AcOH	$C_{38}H_{34}N_2O_8S_2$ (710.80)
10a	C_6H_5	1	80	148–49	Yellow EtOH	$C_{20}H_{18}O_3$ (306.30)
10b	C_6H_4-*p*-CH_3	1	75	178–9	Orange EtOH	$C_{22}H_{22}O_5$ (366.04)
10c	C_6H_4-*p*-Cl	1	80	155–6	Pale yellow MeOH	$C_{20}H_{16}Cl_2O_3$ (375.20)
10d	C_6H_5	2	65	135–6	brown MeOH/H_2O (2:1)	$C_{21}H_{20}O_3$ (320.40)
10e	C_6H_4-*p*-OCH_3	2	70	185–6	Orange MeOH	$C_{23}H_{24}O_5$ (380.40)
10f	C_6H_4-*p*-Cl	2	75	142–3	Yellow EtOH	$C_{21}H_{18}Cl_2O_3$ (389.30)
11a	C_6H_5	1	60	173–4	White MEOH	$C_{21}H_{22}N_2OS$ (366.50)
11b	C_6H_4-*p*-OCH_3	1	65	200–2	White Dioxane	$C_{23}H_{26}N_2O_4S$ (426.50)
11c	C_6H_4-*p*-Cl	1	70	192–3	Yellow MeOH	$C_{21}H_{20}Cl_2N_2O_2S$ (435.40)
11d	C_6H_5	2	60	188–9	White Dioxane	$C_{22}H_{24}N_2O_2S$ (380.50)
11e	C_6H_4-*p*-OCH_3	2	63	236–7	Brown Dioxane	$C_{24}H_{28}N_2O_4S$ (440.50)
11f	C_6H_4-*p*-Cl	2	68	207–8	Orange Dioxane	$C_{22}H_{22}C_{l2}N_2O_2S$ (449.40)

Table 4. (*continued*).

Comp.	Ar	n	Yield [%]	Mp. [°C]	Color and solvent for crystallization	Mol. Formula* (Mol. wt)
12a	C_6H_5	1	55	148–50	Yellow MeOH	$C_{23}H_{22}N_2O_3S$ (406.50)
12b	C_6H_4-*p*-OCH_3	1	58	172–3	Red MeOH	$C_{25}H_{26}N_2O_5S$ (466.50)
12c	C_6H_4-*p*-Cl	1	62	164–5	Pale yellow EtOH	$C_{23}H_{20}Cl_2N_2O_3S$ (475.40)
12d	C_6H_5	2	50	157–8	White MeOH	$C_{24}H_{24}N_2O_3S$ (420.50)
12e	C_6H_4-*p*-OCH_3	2	54	189–90	Orange MeOH	$C_{26}H_{28}N_2O_5S$ (480.60)
12f	C_6H_4-*p*-Cl	2	60	178–9	Brown Dioxane	$C_{24}H_{22}Cl_2N_2O_3S$ (489.40)
13a	C_6H_5	1	62	196–8	White Benzene	$C_{30}H_{25}N_3O_5S$ (539.60)
13b	C_6H_4-*p*-OCH_3	1	65	227–8	Yellow MeOH	$C_{32}H_{29}N_3O_7S$ (599.60)
13c	C_6H_4-*p*-Cl	1	70	209–10	Orange EtOH	$C_{30}H_{23}Cl_2N_3O_5S$ (608.50)
13d	C_6H_5	2	57	231–2	Yellow Dioxane	$C_{31}H_{27}N_3O_5S$ (553.60)
13e	C_6H_4-*p*-OCH_3	2	63	268–9	White Dioxane	$C_{33}H_{31}N_3O_7S$ (613.70)
13f	C_6H_4-*p*-Cl	2	70	253–4	Yellow Dioxane	$C_{31}H_{25}Cl_2N_3O_5S$ (622.50)

* Confirmed by elemental analysis showing values within ± 0.4% of the theoretical values unless otherwise stated.

*Synthesis of Ethyl 2-amino-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-3-carboxylate (**2**)*

A mixture of cycloheptanone (1.12 g, 10 mmol), ethyl cyanoacetate (1.13 g, 10 mmol) and sulfur (0.48 g, 15 mmol) in 50 mL of absolute ethanol was stirred and a few drops of pyridine were added. The reaction mixture was stirred at room temperature for 12 hr. The excess ethanol was evaporated under reduced pressure, the residue was triturated with diethyl ether and *n*-hexane (1:1, ratio) to give compound **2**: 1.2 g, 50% yield, mp. 117–118°C (Lit. mp. 118–119°C [18]).

*Synthesis of tetrachlorodioxo-isoindolyl derivatives **3** and **6***

A mixture of compound **1** or **2**, respectively (1 mmol) and 1,2,3,4-tetrachlorophthalic anhydride (0.285 g, 1 mmol) in glacial acetic acid (50 mL) was refluxed for 6 h. The solvent was evaporated under reduced pressure and the obtained residue solidified with dry ether, the crude product was collected by filtration and purified by recrystallization from DMF/H_2O and EtOH, respectively, to yield the corresponding compounds **3** and **6**, respectively (Table 4).

*6′-Chloro-2′-ethoxy-6-(4,5,6,7-tetrachloro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-4-thien-2-yl-[2,4′]bipyridinyl-5-carbonitrile (**3**)*

IR (KBr, cm^{-1}): 2220 (C≡N), 1690 (C=O, imide), 1640 (C=N). ^{1}H-NMR (DMSO-d_6) δ: 1.85 (t, 3H, CH_3), 3.80 (q, 2H, CH_2), 6.90–7.50 (m, 3H, thiophene-H), 8.25–8.40 (m, 3H, pyridyl-H). MS m/z (%): 625 (M^+, 18) corresponding to the molecular formula $C_{25}H_{11}Cl_5N_4O_3S$ and at 296 (100, base peak).

*2-(4,5,6,7-Tetrachloro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-5,6,7,8-tetrahydro-4H-cyclohepta[b]-thiophene-3-carboxylic acid ethyl ester (**6**)*

IR (KBr, cm^{-1}): 1725 (C=O, ester), 1680 (C=O, imide). ^{1}H-NMR ($CDCl_3$) δ: 1.25–2.00 (m, 10H, 5 × CH_2, cycloheptyl-H), 2.10 (t, 3H, CH_3), 4.10 (q, 2H, 2 × CH_2). MS m/z (%): 507 (M^+, 100, base peak) corresponding to the molecular formula $C_{20}H_{15}Cl_4NO_4S$.

*Synthesis of Bis-[substituted bipyridinyl or cyclohepta[b]thien]pyrroloisoindolyl derivatives **4** and **7***

A mixture of compound **1** or **2** (2 mmol) and benzene tetracarboxylic dianhydride (0.218 g, 1 mmol) in glacial acetic acid (50 mL) was heated under reflux for 6 h. The residue formed was filtered off and crystallized from AcOH/H_2O (2:1) and AcOH, respectively, to yield the corresponding compounds **4** and **7** (Table 4).

*2,6-Bis-[2′-chloro-6′-ethoxy-4-thien-2-yl-[2,4′]bipyridinyl-5-carbonitril-6-yl]pyrrolo[3,4-f]isoindole-1,3,5,7-tetraone (**4**)*

IR (KBr, cm^{-1}): 2210 (C≡N), 1688, 1665 (two C=O), 1632 (C=N). ^{1}H-NMR (DMSO-d_6) δ: 1.90 (t, 6H, 2 × CH_3), 3.75 (q, 4H, 2 × CH_2), 7.25–7.75 (m, 6H, 2 × thiophene-H), 7.80 (s, 2H, Ar-H), 8.25–8.35 (m, 6H, pyridyl-H). MS m/z (%): 895 (M^+, 8.5) corresponding to the molecular formula $C_{44}H_{24}Cl_2N_8O_6S_2$ and at 296 (100, as base peak).

*2,6-Bis-[3′-ethyl-5′,6′,7′,8′-tetrahydro-4′H-cyclohepta[b]thien-carboxylate-2′-yl]pyrrolo[3,4-f]isoindole-1,3,5,7-tetraone (**7**)*

IR (KBr, cm^{-1}): 1723 (C=O, ester), 1677 (C=O, imide). ^{1}H-NMR (DMSO-d_6) δ: 1.30-1.95 (m, 20H, 10 × CH_2, cycloheptyl ring), 2.05 (t, 6H, 2 × CH_3), 4.25 (q, 4H, 2 × CH_2), 7.90 (s, 2H, Ar-H). MS m/z (%): 660 (M^+, 35) corresponding to the molecular formula $C_{34}H_{32}N_2O_8S_2$ and at 514 (100, base peak).

*Synthesis of 2,7-Bis-[substituted bipyridinyl or cyclohepta[b]thien]-benzo[l,m,n][3,8]phen-anthroline Derivatives **5** and **8***

A mixture of compound **1** or **2** (2 mmol) and naphthalene tetracarboxylic dianhydride (0.268 g, 1 mmol) in glacial acetic acid (50 mL) was heated under reflux for 6 h. The obtained solid was filtered off, washed with acetic acid, and crystallized from DMF/H_2O (2:1) and AcOH, respectively, to afford the corresponding derivatives **5** and **8** (Table 4).

*2,7-Bis-[2′′-chloro-6′′-ethoxy-4′-thien-2′-yl-[2′,4′′]bipyridinyl-5′-carbonitril-6′-yl]benzo[l,m,n]phenanthroline-1,3,6,8-tetraone (**5**)*

IR (KBr, cm^{-1}): 2215 (C≡N), 1685 (two C=O), 1636 (C=N). MS m/z (%): 945 (M^+, 15) corresponding to the molecular formula $C_{48}H_{26}Cl_2N_8O_6S_2$ and at 296 (100, base peak).

*2,7-Bis-[3′-ethyl-5′,6′,7′,8′-tetrahydro-4′H-cyclohepta[b]thien-carboxylat-2′-yl]benzo[l,m,n][3,8]phenanthroline-1,3,6,8-tetraone (**8**)*

IR (KBr, cm^{-1}): 1715 (C=O, ester), 1675 (C=O, imide). ^{1}H-NMR (DMSO-d_6) δ: 1.25−1.85 (m, 20H, 10 × CH_2, cycloheptyl ring), 2.15 (t, 6H, 2 × CH_3), 4.05 (q, 4H, 2 × CH_2), 7.85 (d, 4H, Ar-H). MS m/z (%): 710 (M^+, 100) corresponding to the molecular formula $C_{38}H_{34}N_2O_8S_2$ and also as base peak.

*Synthesis of 2,7-Bis-(aryl)-1,6-dioxa-dispirodecane-4-one Derivatives **10a−f***

To a mixture of *bis*-arylmethylene derivatives (**9a−f**) [19] (100 mmol) in acetone/dioxane (50 mL, 3:2 ratio) and sodium hydroxide (2 g) in few drops of water, hydrogen peroxide (6 mL, 30%) was added dropwise with stirring for 15 min. The reaction mixture was stirred for further 8 h at room temperature, then left overnight at −5 °C. The solid formed was collected by filtration and crystallized from proper solvent to give the corresponding *bis*-spiro compounds **10a−f**, respectively (Table 4).

*2,6-Bis-(4-methoxyphenyl)-1,6-dioxadispiro[2.1.2.3]decan-4-one (**10b**)*

IR (KBr, cm^{-1}): 1729 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.15−2.10 (m, 6H, 3 × CH_2), 3.65 (s, 2H, 2 × CH-Ar), 3.95 (s, 6H, 2 × OCH_3), 7.35−7.75 (m, 8H, 2 × Ar-H). MS m/z (%): 366 (M^+, 100), as base peak and corresponds to the molecular formula $C_{22}H_{22}O_5$.

*2,7-Bis-(4-methoxyphenyl)-1,6-dioxadispiro[2.1.2.4]undecan-4-one (**10e**)*

IR (KBr, cm^{-1}): 1713 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.10−2.20 (m, 8H, 4 × CH_2), 3.60 (s, 2H, 2 × CH-Ar), 3.90 (s, 6H, 2 × OCH_3), 7.20−7.80 (m, 8H, 2 × Ar-H). MS m/z (%): 380 (M^+, 16) corresponding to the molecular formula $C_{23}H_{24}O_5$ and at 348 (100, base peak).

*Synthesis of Thioxopyrimidine Derivatives **11a**−f*

A mixture of compounds **10a−f** (10 mmol), thiourea (1.34 g, 20 mmol) and potassium hydroxide (1 g) in ethanol (50 mL) was refluxed for 3 h. The solvent was evaporated under reduced pressure, the residue was dissolved in water and neutralized with 1N hydrochloric acid. The solid formed was collected by filtration and crystallized from the proper solvent to give the corresponding thioxopyrimidines **11a−f**, respectively (Table 4).

*4a-Hydroxy-8-[hydroxyl-(4-methoxyphenyl)methyl]-4-(4-methoxyphenyl)-3,4,4a,5,6,7-hexahydro-1H-quinazolin-2-thione (**11b**)*

IR (KBr, cm^{-1}): 3400−3100 (OH, NH), 1195 (C=S). ^{1}H-NMR (DMSO-d_6) δ: 0.95−2.15 (m, 6H, 3 × CH_2), 3.70 (s, 1H, CH-Ar), 3.85 (s, 6H, 2 × OCH_3), 4.46 (bs, 1H, OH, which is exchangeable with D_2O), 5.40 (s, 1H, CH-pyrimidine), 7.10−7.65 (m, 8H, Ar-H), 7.85 (bs, 1H, NH which is exchangeable with D_2O), 10.10 (bs, 1H, OH, which is exchangeable with D_2O), 10.20 (br, 1H, NH). MS (m/z,%): 426 (M^+, 28) corresponding to the molecular formula $C_{23}H_{26}N_2O_4S$ and at 319 (100, base peak).

*4a-Hydroxy-9-[hydroxyl-(4-methoxyphenyl)methyl]-4-(4-methoxyphenyl)-1,3,4,4a,5,6,7,8-octa-hydrocycloheptapyrimidine-2-thione (**11e**)*

IR (KBr, cm^{-1}): 3380−3200 (OH, NH), 1198 (C=S). ^{1}H-NMR ($CDCl_3$) δ: 1.20-2.10 (m, 8H, 4 × CH_2), 3.50 (s, 1H, CH-Ar), 3.90 (s, 6H, 2 × OCH_3), 4.30 (bs, 1H, OH, which is exchangeable with D_2O), 5.20 (s, 1H, CH-pyrimidine), 6.80−7.30 (m, 8H, Ar-H), 7.80 (bs, 1H, NH which is exchangeable with D_2O), 9.80 (bs, 1H, OH, which exchangeable with D_2O), 10.50 (br, 1H, NH). MS m/z (%): 440 (M^+, 18) corresponding to the molecular formula $C_{24}H_{28}N_2O_4S$ and at 318 (100, base peak).

*Synthesis of Thiazolopyrimidine Derivatives **12a−f***

A mixture of compounds **11a−f** (10 mmol), chlororacetic acid (0.95 g, 10 mmol) and anhydrous sodium acetate (1.72 g, 20 mmol) in glacial acetic acid (30 mL) and acetic anhydride (10 mL) was refluxed for 3 h. The reaction mixture was poured into water, the formed solid was filtered off and crystallized from the proper solvent to give the corresponding thiazolopyrimidine derivatives **12a−f**, respectively (Table 4).

*5a-Hydroxy-9-[hydroxyl-4-(4-methoxyphenyl)methyl]-5-(4-methoxyphenyl)-5a,6,7,8-tetrahydro-5H-thiazolo[2,3-b]quinazolin-3-one (**12b**)*

IR (KBr, cm^{-1}): 3390−3310 (OH), 1683 (C=O). MS m/z (%): 466 (M^+, 100, base peak) corresponding to the molecular formula $C_{25}H_{26}N_2O_5S$.

*4a-Hydroxy-9-[hydroxyl-4-(4-methoxyphenyl)methyl]-5-(4-methoxyphenyl)-4,4a,5,6,7,8-hexa-hydro-1-thia-3a,10-diaza-cyclohepta-[f]inden-3-one (**12e**)*

IR (KBr, cm^{-1}): 3375−3290 (OH), 1680 (C=O). MS m/z (%): 480 (M^+, 100, base peak) corresponding to the molecular formula $C_{26}H_{28}N_2O_5S$.

*Synthesis of thiazoloarylarylmethylene derivatives **13a−f***

Method A: To a mixture of compounds **11a-f** (10 mmol), chloroacetic acid (0.95 g, 10 mmol) and anhydrous sodium acetate (1.72 g, 20 mmol) in glacial acetic acid (30 mL)/acetic anhydride (10 mL) and *p*-nitrobenzaldehyde (1.51 g, 10 mmol) was added. The reaction mixture was heated under reflux for 3 h, then cooled and poured into water. The solid formed was collected by filtration and crys-

tallized from the proper solvent to yield the corresponding thiazoloarylmethylene derivatives **13a**−**f**, respectively (Table 4).

Method B: A mixture of compounds **12a**−**f** (10 mmol) and *p*-nitrobenzaldehyde (1.51 g, 10 mmol) in glacial acetic acid/acetic anhydride (40 mL, 3:1) was refluxed for 3 h, allowed to cool down, and then poured into water. The solid formed was collected by filtration and crystallized from the proper solvent to give compounds **13a**−**f**, respectively. The crystallized products were identified by mp., mixed mp. and TLC in comparison with authentic samples from Method A. It should be notified that Method A generally resulted in higher yields than Method B.

*5a-Hydroxy-9-[hydroxyl-4-(4-methoxyphenyl)-2-(4-nitrobenzylidene)-5a,6,7,8-tetrahydro-5H-thiazolo[2,3-b]quinazolin-3-one (**13b**)*

IR (KBr, cm^{-1}): 3450−3360 (OH), 1700 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.30−1.80 (m, 6H, 3 × CH_2), 3.50 (s, 1H, CH-Ar), 3.80 (s, 6H, 2 × OCH_3), 4.60 (bs, 1H, OH, which is exchangeable with D_2O), 5.50 (s, 1H, CH-pyrimidine), 6.80−7.90 (m, 12H, Ar-H), 8.10 (s, 1H, benzylic proton), 9.30 (s, 1H, OH, which is exchangeable with D_2O). MS m/z (%): 599 (M^+, 13) corresponding to molecular formula $C_{32}H_{29}N_3O_7S$ and at 467 (100, base peak).

*4a-Hydroxy-9-[hydroxyl-4-(4-methoxyphenyl)methyl]-4-(4-nitrobenzylidene)-4,4a,5,6,7,8-hexahydro-1-thia-3a,10-diaza-cyclohepta-[f]indin-3-one (**13e**)*

IR (KBr, cm^{-1}): 3400−3350 (OH), 1705 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.25-1.95 (m, 8H, 4 × CH_2), 3.60 (s, 1H, CH-Ar), 3.90 (s, 6H, 2 × OCH_3), 4.65 (bs, 1H, OH, which is exchangeable with D_2O), 5.70 (s, 1H, CH-pyrimidine), 7.10−7.90 (m, 12H, Ar-H), 8.25 (s, 1H, benzylic proton), 9.45 (s, 1H, OH, which is exchangeable with D_2O). MS m/z (%): 613 (M^+, 100) corresponding the molecular formula $C_{33}H_{31}N_3O_7S$ and also as base peak.

Pharmacological screening

Analgesic activity

Sixty Webster mice of both sexes weighting from 20−25 g were divided into 10 groups. (All animals were obtained from the Animal House Colony, Research Institute of Ophthalmology, Giza, Egypt) One group was kept as control (received saline), the second group received vehicle (Gum acacia), and the third one received Valdecoxib as a reference drug, whereas the other groups received tested compounds (SC administration). Mice were dropped gently in a dry glass beaker of one-liter capacity maintained at 55−55.5°C. Normal reaction time in seconds for all animals was determined at time intervals of 10, 20, 30, 45, 60, 90, and 120 min. This is the interval extending from the instant the mouse reaches the hot beaker till the animals licks its feet or jump out of the beaker (dose 5 mg/kg) [23], relative potencies to that of Valdecoxib were determined (Table 1).

Anticonvulsant activity

Male Webster mice (20-30 g) were individually placed in clear plastic cylinder and the tested compounds were administrated intraperitoneally (5 mg/kg), 30 min prior to a dose of 45 mg/kg of yohimbine-HCl. The animals were observed for onset and number of clonic seizures [24] (Table 2). Evaluation of ED_{50} values for compounds with 95% confidence limits were calculated for the antagonism of yohimbine-induced clonic seizure according to Austen et al. [25].

Antiparkinsonian activity

Groups of eight male mice (18−20 g) were used. They were dosed orally with the tested compounds (5 mg/kg) or the standard (Benzatropine, 5 mg/kg) [26] one hour prior to the administration of 0.5 mg/kg of Oxotremorine s.c. Rectal temperature was measured before administration of the compounds and one hour after Oxotremorine application. The score for the recorded signs are zero (absent), one (slight), two (mediums), and three (highs) (Table 3).

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