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Synthesis and Reactions of Some Fused Oxazinone, Pyrimidinone, Thiopyrimidinone, and Triazinone Derivatives with a Thiophene Ring as Analgesic, Anticonvulsant, and Antiparkinsonian Agents

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Summary. A series of 2,6-disubstituted pyridine ester derivatives and the corresponding amides were prepared. The esters were hydrolysed to the sodium salts, which were treated with acetic anhydride to afford oxazinone derivatives. These were treated with ammonium acetate to afford 2-methylpyrimidinone derivatives, which were methylated to yield 2,3-dimethylpyrimidinone derivatives. In addition, they were reacted with aniline or hydrazine hydrate to give 3-phenyl- or 3-aminopyrimidinone derivatives. The latter reacted with 2-thiophenecarbaldehyde or phthalic anhydride to afford the corresponding *Schiff*'s base and imide derivatives. Diazotization of amides gave thienotriazinone derivatives, which were treated with ethyl iodide to afford the corresponding 3-ethyltriazinone derivatives. Also, they were reacted with phenyl isothiocyanate to give the corresponding thiopyrimidinone derivatives, which were alkylated with ethyl iodide or chloroacetic acid to afford the corresponding thioethyl- or thioglycolic acid pyrimidinone derivatives.

The pharmacological screening showed that many of these obtained compounds have good analgesic, anticonvulsant, and antiparkinsonian activities comparable to Voltarene®, Carbamazepine®, and Benzotropene® as reference drugs.

Keywords. 2,6-Disubstituted pyridine; Oxazinone; Pyrimidinone; Analgesic; Anticonvulsant; Antiparkinsonian.

Introduction

In previous work we have found that certain substituted pyridine and their amide derivatives show antimicrobial [1–4] and antitumor activities [5–7]. In addition,

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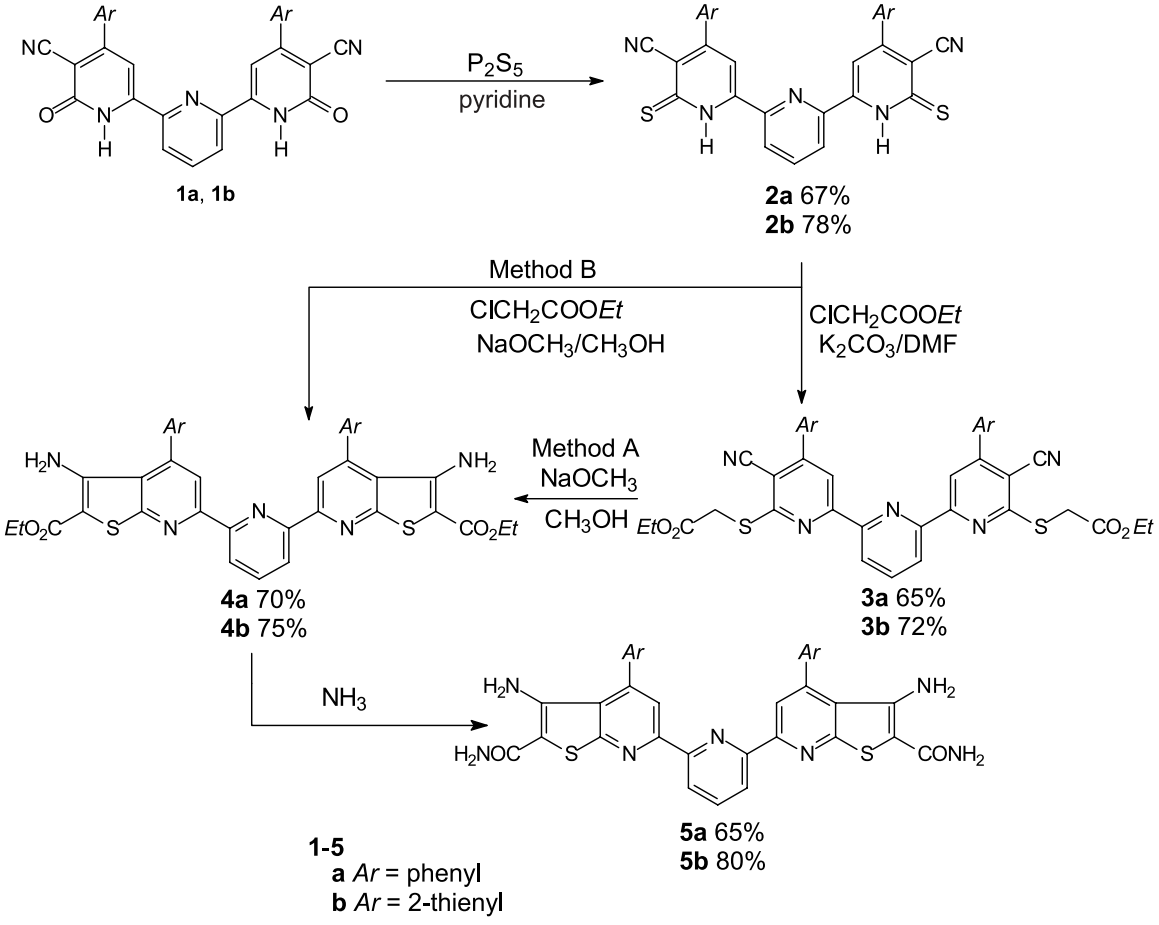
the biological and antianalgesic activities of many heterocyclic compounds containing a sulfur atom have been reviewed [8–10]. On the other hand, thienopyrimidine and thioxopyrimidine derivatives have promising biological [11, 12] and anticancer activity [13, 14]. Recently, some new thienopyrimidinone derivatives have been synthesized [15]. In view of these observations and in continuation of our previous work in pyridine chemistry, we synthesized some new heterocyclic compounds containing the thieno[2,3-*b*]pyridine moiety fused with a pyridine, oxazinone, pyrimidinone, or triazinone nucleus and tested their biological activity.

Results and Discussion

Synthesis

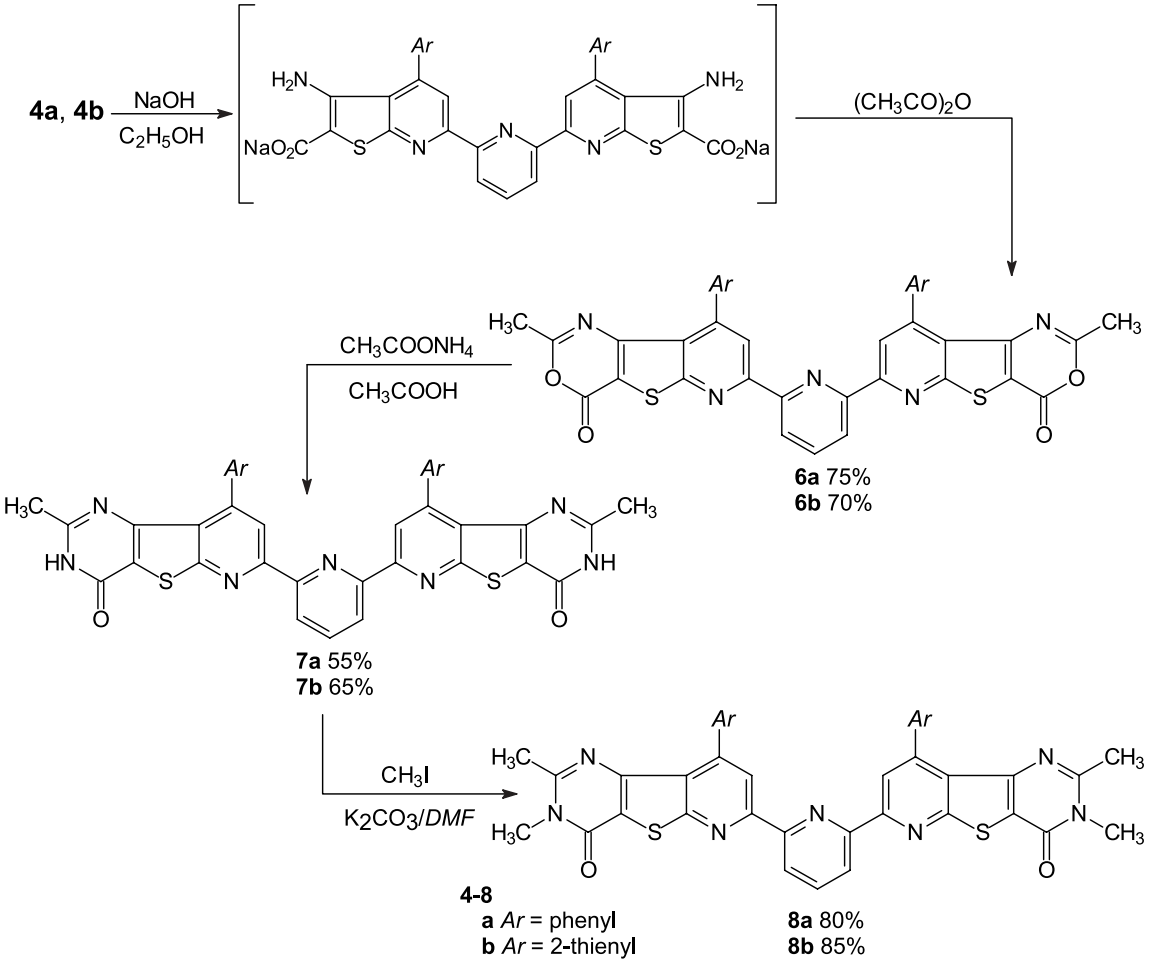
The 2,6-di(4-aryl-3-cyano-2-oxopyridin-6-yl)pyridine derivatives **1a** and **1b** were prepared according to literature [1]. Thionation of **1a** and **1b** to the corresponding thione derivatives **2a** and **2b** were achieved by the action of P_2S_5 in dry pyridine.



Scheme 1

Condensation of **2a** and **2b** with ethyl chloroacetate in the presence of anhydrous K_2CO_3 gave **3a** and **3b**, which were cyclized by sodium methoxide in methanol to give the amino ester derivatives **4a** and **4b** (method A). The latter compounds were also obtained from **2a** and **2b** with ethyl chloroacetate and sodium methoxide in methanol (method B). Aminolysis of **4a** and **4b** by ammonia gave **5a** and **5b** (Scheme 1). The IR spectra of **4a** and **4b** showed the absence of $\bar{\nu}$(C≡N) at 2219, 2220 cm^{-1} for **3a** and **3b** and the presence of broad bands at 3439 – 3310 cm^{-1} corresponding to $\bar{\nu}(NH_2)$. Correspondingly, the IR spectra of **5a** and **5b** showed the absence of $\bar{\nu}$(C=O, ester) at 1738, 1732 cm^{-1} of **4a** and **4b** and the presence of bands at $\bar{\nu}$ = 1680, 1675 cm^{-1} corresponding to $\bar{\nu}$(C=O, amide).

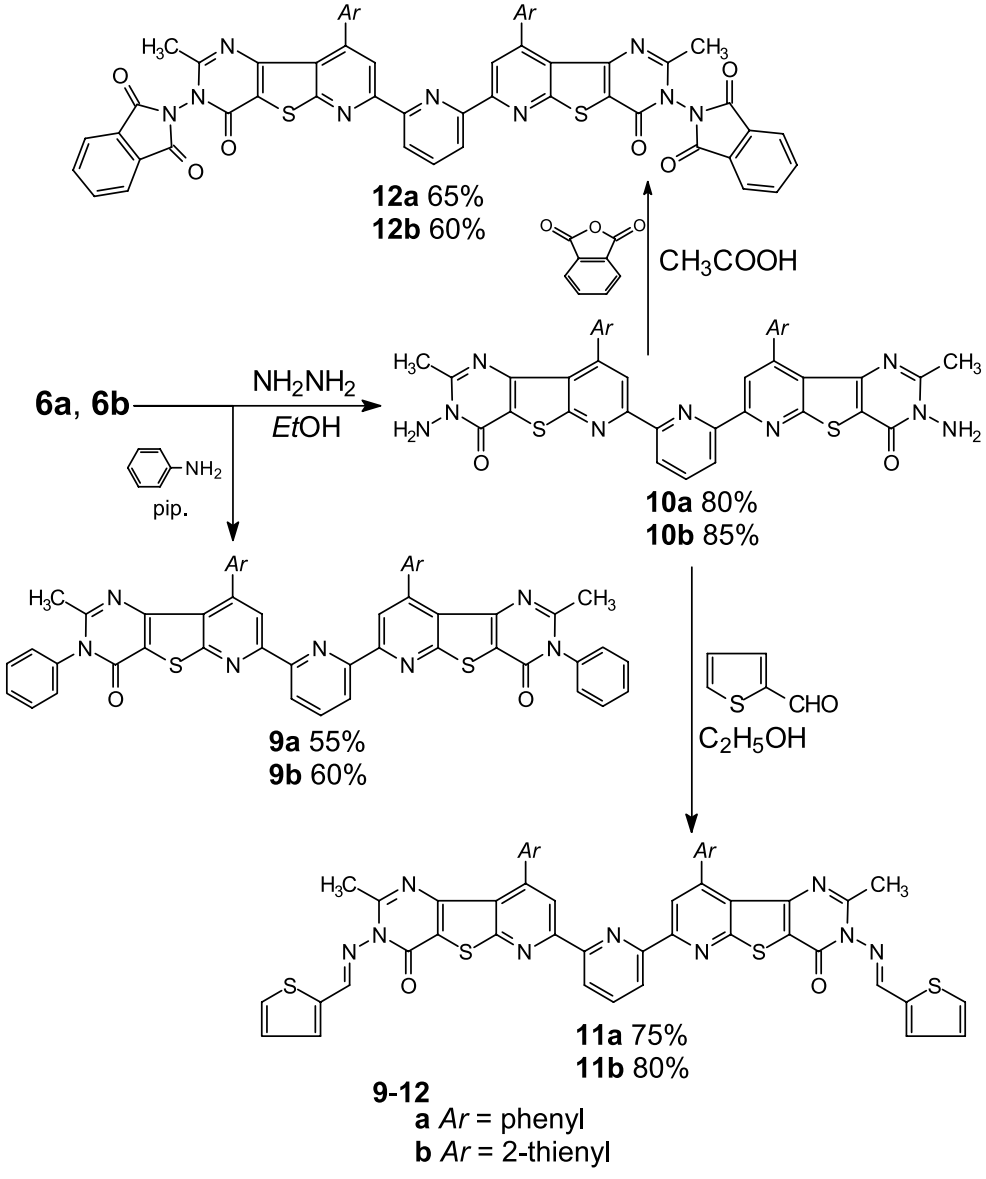
Compounds **4a** and **4b** were hydrolyzed by refluxing with ethanolic NaOH solution to their sodium salts, which were treated with acetic anhydride to give the oxazinone derivatives **6a** and **6b**. Reaction of **6a** and **6b** with ammonium acetate in acetic acid afforded the corresponding pyrimidinone derivatives **7a**



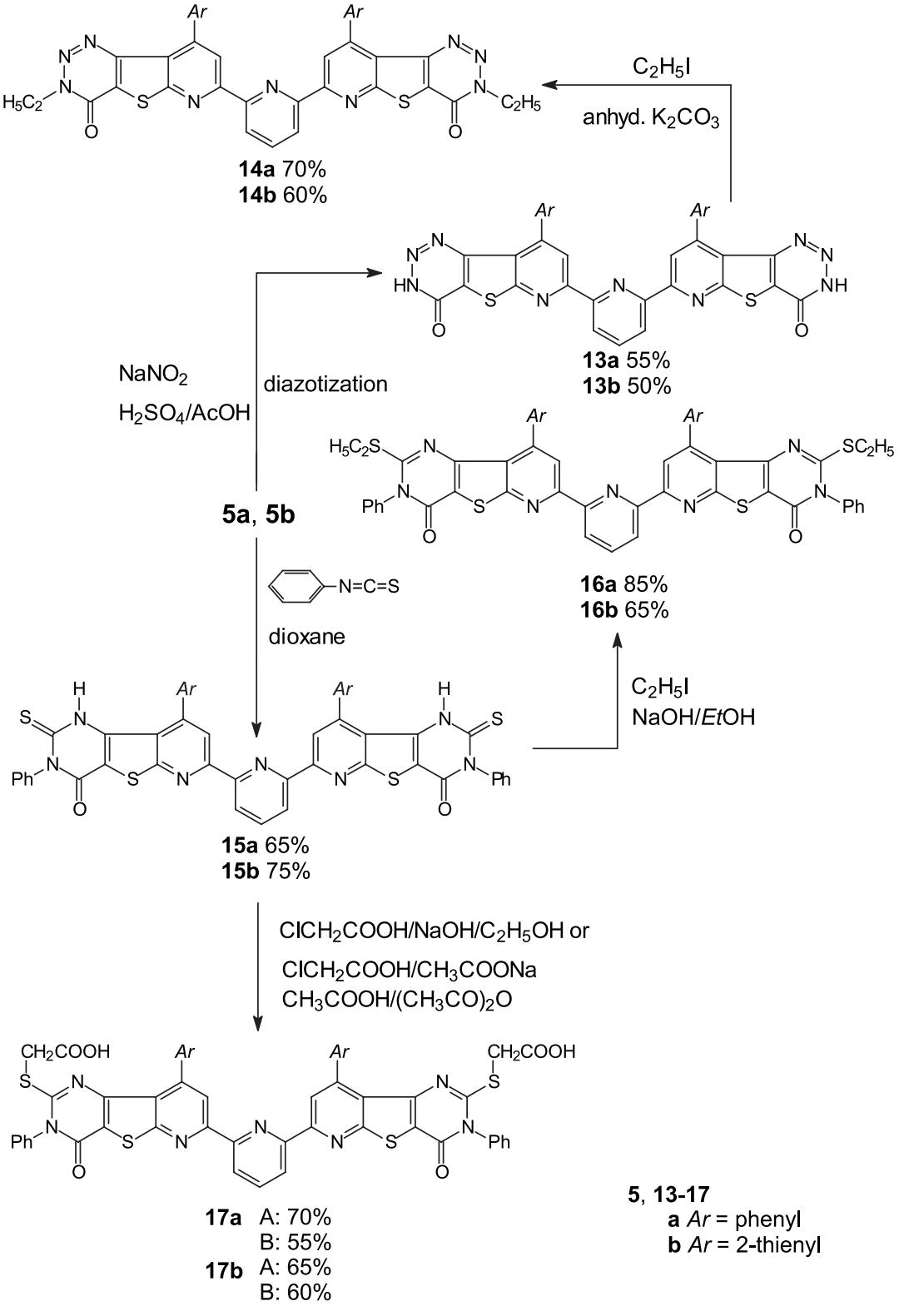
Scheme 2

and **7b**, which were reacted with methyl iodide in *N*,*N*-dimethylformamide in the presence of anhydrous K_2CO_3 to yield the 3-methylpyrimidinone derivatives **8a** and **8b** (Scheme 2).

Similarly, reaction of oxazinone derivatives **6a** and **6b** with aniline in acetic acid or hydrazinehydrate in ethanol under reflux afforded **9a** and **9b** and **10a** and **10b**. Condensation of **10a** and **10b** with 2-thiophenecarbaldehyde in refluxing ethanol containing a few drops of piperidine yielded the corresponding *Schiff*'s bases **11a** and **11b**. Also, the reaction of **10a** and **10b** with phthalic anhydride in refluxing acetic acid gave the corresponding 3-imido-pyrimidinone derivatives **12a** and **12b** (Scheme 3).



Scheme 3


Ar
H_5C_2
C_2H_5
C_2H_5I
anhyd. K_2CO_3
14a 70%
14b 60%
HN
NH
13a 55%
13b 50%
$NaNO_2$
H_2SO_4/AcOH
diazotization
5a, 5b
H_5C_2S
SC_2H_5
Ph
16a 85%
16b 65%
N=C=S
dioxane
C_2H_5I
NaOH/*Et*OH
15a 65%
15b 75%
$ClCH_2COOH/NaOH/C_2H_5OH$ or
$ClCH_2COOH/CH_3COONa$
$CH_3COOH/(CH_3CO)_2O$
CH_2COOH
17a A: 70%
B: 55%
17b A: 65%
B: 60%
5, 13-17
a *Ar* = phenyl
b *Ar* = 2-thienyl

Scheme 4

Diazotization of **5a** and **5b** gave the corresponding triazinone derivatives **13a** and **13b**, which were treated with ethyl iodide in the presence of K_2CO_3 to give the corresponding 3-ethyltriazinone derivatives **14a** and **14b** (Scheme 4). Moreover, the reaction of **5a** and **5b** with phenyl isothiocyanate in refluxing dioxane gave the 3-phenyl-2-thioxopyrimidin-4-one derivatives **15a** and **15b**, which were reacted with ethyl iodide in ethanolic sodium hydroxide to give the corresponding 2-thioethylpyrimidinone derivatives **16a** and **16b**. Similarly, reaction of **15a** and **15b** with chloroacetic acid in refluxing ethanolic NaOH gave the corresponding 2-thioglycolic acids **17a** and **17b** (Scheme 4).

Pharmacological Screening

The tested three pharmacological activities namely, analgesic, anticonvulsant, and antiparkinsonism despite of their different biological receptors yet all of a neurological. Seven representative compounds **2a**, **4b**, **6a**, **8a**, **10a**, **10b**, and **13a** were studied with respect to analgesic, anticonvulsant, and antiparkinsonian activities.

Analgesic Activity

All tested compounds exhibited analgesic activities (Table 1). The most potent one is **13a** that showed the same activity as Voltarene® after 45 min and it had even higher activity than Voltarene® after 60, 90, and 120 min. Also the analgesic activities of **4b** and **8a** approached those of Voltarene®, and **10b** had 31–47% activity as compared with Voltarene® (Table 1).

Anticonvulsant Activity

Compounds **4b** and **6b** are devoid of any anticonvulsant activity where they provide no protection against yohinobine-induced clonic seizures. Compounds **2a**, **8a**, and **10a** showed interesting anticonvulsant activities, their relative potencies to Carbamazebene® are 0.58, 0.94, and 0.7. Compounds **10b** and **13a** are even more potent than Carbamazebene® (1.93 and 2.23, relative potency).

Table 1. Analgesic activity of the new compounds as compared with Voltarene® in mice

Comp. no.	Analgesic activity after						
	10 min	20 min	30 min	45 min	60 min	90 min	120 min
Voltarene®	1	1	1	1	1	1	1
2a	0.59	0.61	0.69	0.71	0.77	0.81	0.80
4b	0.79	0.83	0.87	0.88	0.88	0.88	0.91
6b	0.54	0.56	0.58	0.55	0.51	0.49	0.47
8a	0.81	0.89	0.88	0.91	0.93	0.94	0.94
10a	0.61	0.63	0.71	0.73	0.74	0.74	0.74
10b	0.31	0.40	0.40	0.42	0.45	0.43	0.47
13a	0.97	0.98	0.99	1.07	1.12	1.21	1.41

Table 2. Anticonvulsant activity of the new compounds and Carbamazepine® *via* ED_{50} needed to antagonize yohimbine seizure

Comp. no.	ED_{50} value/mg/kg	Relative potency to Carbamazepine®
Control	0	0
Carbamazepine®	29	1
2a	50	0.58
4b	No protection	–
6b	No protection	–
8a	31	0.935
10a	35	0.70
10b	15	1.933
13a	13	2.23

Table 3. Antiparkinsonian activity of the new compounds as compared with Benzotropene®

Comp. no.	Salivation & lacrimation score	Tremors score	% decrease from Oxotremerine® rectal temp.	Relative potency to Benzotropene®
Control	0	0	0	0
Benzotropene	1	1	25	1
2a	2	2	10	0.4
4b	3	3	3	0.12
6b	3	3	4	0.16
8a	2	2	11	0.44
10a	2	2	15	0.6
10b	1	1	20	0.8
13a	1	1	20	0.8

Antiparkinsonian Activity

Compounds **2a**, **8a**, and **10a** showed moderate activity (relative potencies to Benzotropene® 0.40, 0.44, and 0.6). Compounds **10b** and **13a** are the most potent antiparkinsonic agents (0.8 relative potency) (Table 3).

Experimental

Melting points are uncorrected and were recorded on an Electrothermal IA 9000 SERIES Digital Melting Point Apparatus. Analytical data were obtained from the Microanalytical unit, National Research Center, Cairo, Egypt. Their results were found to be in good agreement with the calculated values. The IR spectra (KBr) were recorded on a FT IR-8201 PC Spectro-photometer (Shimadzu). The ^{1}H NMR spectra were measured with Jeol 270 MHz in *DMSO*-d_6 and the chemical shifts were recorded in ppm relative to *TMS*. The Mass spectra were run at 70 eV with a Finnigan SSQ GC/MS spectrometer using EI. The reactions were followed by TLC (Silica gel, aluminum sheets 60 F_{254}, Merck). Starting materials **1a** and **1b** were prepared according to published procedures [1].

*Synthesis of **2a** and **2b***

A mixture of 1 mmol of **1a** or **1b** and 4.45 g of P_2S_5 (20 mmol) in 50 cm^3 of dry pyridine was heated under reflux for 6 h with stirring. The reaction mixture was cooled, then poured into ice-water, the separated solid was collected by filtration, washed with water, dried, and crystallized.

2,6-Bis(3-cyano-4-phenyl-2-thioxopyridin-6-yl)pyridine (**2a**, $C_{29}H_{17}N_5S_2$)

Mp 228–230°C (dioxane); IR (film): $\bar{\nu} = 3330$ (NH), 2210 (C≡N) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 6.90$–7.50 (m, 10 Ar-H), 8.10–8.20 (m, 3pyridine-H), 8.55 (s, 2C-5′-H), 10.68 (s, 2NH, exchangeable with D_2O); MS (EI, 70 eV): $m/z = 499$ [M^+].

2,6-Bis(3-cyano-4-(2-thienyl)-2-thioxopyridin-6-yl)pyridine (**2b**, $C_{25}H_{13}N_5S_4$)

Mp 235–237°C (dioxane); IR (film): $\bar{\nu} = 3324$ (NH), 2216 (C≡N) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 6.80$–7.15 (m, 6thiophene-H), 8.00–8.25 (m, 3pyridine-H), 8.35 (s, 2C-5′-H), 10.55 (s, 2NH, exchangeable with D_2O); MS (EI, 70 eV): $m/z = 511$ [M^+].

*Synthesis of **3a** and **3b***

A mixture of 1 mmol of **2a** or **2b** and 0.27 g of anhydrous K_2CO_3 (2 mmol) in 25 cm^3 of *N*,*N*-dimethylformamide was stirred at room temperature for 1/2 h, then 2.16 g of ethyl chloroacetate (2 mmol) were added with stirring. The reaction mixture was heated at 60°C for 2 h and after cooling poured into ice. The solid formed was collected by filtration and crystallized.

2,6-Bis(3-cyano-2-ethylthioglycolate-4-phenylpyridin-6-yl)pyridine (**3a**, $C_{37}H_{29}N_5O_4S_2$)

Mp 175–177°C (*Et*OH); IR (film): $\bar{\nu} = 2220$ (C≡N), 1735 (C=O, ester) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 1.20$ (t, $2CH_2CH_3$), 3.85 (q, $2CH_2CH_3$), 4.90 (s, $2S-CH_2$), 6.95–7.65 (m, 10phenyl-H), 8.10–8.25 (m, 3pyridine-H), 8.55 (s, 2C-5′-H); MS (EI, 70 eV): $m/z = 671$ [M^+].

2,6-Bis(3-cyano-2-ethylthioglycolate-4-(2-thienyl)pyridin-6-yl)pyridine (**3b**, $C_{33}H_{25}N_5O_4S_4$)

Mp 182–184°C (*Et*OH); IR (film): $\bar{\nu} = 2219$ (C≡N), 1728 (C=O, ester) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 1.15$ (t, $2CH_2CH_3$), 3.70 (q, $2CH_2CH_3$), 4.75 (s, $2S-CH_2$), 6.80–7.35 (m, 6thiophene-H), 7.95–8.15 (m, 3pyridine-H), 8.40 (s, 2C-5′-H); MS (EI, 70 eV): $m/z = 683$ [M^+].

*Synthesis of **4a** and **4b***

Method A: A mixture of 1 mmol of **3a** or **3b** in 20 cm^3 of a sodium ethoxide solution (2%) was refluxed for 1 h on a water bath at 70°C with stirring. The reaction mixture was evaporated under reduced pressure, the obtained residue was dissolved in CH_2Cl_2, washed with H_2O, 10 cm^3 1*N* HCl and then H_2O. The solvent was dried over anhydrous $CaCl_2$, evaporated under reduced pressure, and the product was crystallized.

Method B: Compounds **4a** and **4b** were also prepared from compounds **2a** and **2b** according to the literature method [19] in yields 55 and 65%, respectively. The obtained products were identified by mp and TLC in comparison with authentic samples from Method A.

2,6-Bis(3-amino-2-carbethoxy-4-phenylthieno[2,3-b]pyridin-6-yl)pyridine
(**4a**, $C_{37}H_{29}N_5O_4S_2$)

Mp 208–210°C (*Et*OH); IR (film): $\bar{\nu} = 3419 - 3360$ (NH_2), 1732 (C=O, ester) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 0.95$ (t, $2CH_2CH_3$), 4.10 (q, $2CH_2CH_3$), 4.65 (brs, $2NH_2$, exchangeable

with D_2O), 7.00–7.55 (m, 10phenyl-H), 8.15–8.30 (m, 3pyridine-H), 8.60 (s, 2C-5′-H); MS (EI, 70 eV): $m/z = 671$ [M^+].

2,6-Bis(3-amino-2-carbethoxy-4-(2-thienyl)thieno[2,3-b]pyridin-6-yl)-pyridine
(**4b**, $C_{33}H_{25}N_5O_4S_4$)

Mp 198–200°C (*Et*OH); IR (film): $\bar{\nu} = 3439$–3310 (NH_2), 1738 (C=O, ester) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 0.90$ (t, $2CH_3$), 3.90 (q, $2CH_2$), 4.60 (brs, $2NH_2$, exchangeable with D_2O), 6.90–7.25 (m, 6thiophene-H), 8.10–8.35 (m, 3pyridine-H), 8.50 (s, 2C-5′-H); MS (EI, 70 eV): $m/z = 683$ [M^+].

*Synthesis of **5a** and **5b***

Compounds **4a** or **4b** (1 mmol) were suspended in 100 cm^3 of ethanol, then a current of NH_3 was passed through at 0°C till saturation, the reaction mixture was left overnight at −4°C, evaporated under reduced pressure, and the residue obtained was triturated with *n*-hexane, the formed solid was filtered off, washed with H_2O, and crystallized.

2,6-Bis(3-amino-2-carboxamido-4-phenylthieno[2,3-b]pyridin-6-yl)pyridine
(**5a**, $C_{33}H_{23}N_7O_2S_2$)

Mp 214–216°C (*Ac*OH); IR (film): $\bar{\nu} = 3415$–3309 (NH_2), 1680 (C=O, amide) cm^{-1}; MS (EI, 70 eV): $m/z = 613$ [M^+].

2,6-Bis(3-amino-2-carboxamido-4-(2-thienyl)thieno[2,3-b]pyridin-6-yl)pyridine
(**5b**, $C_{29}H_{19}N_7O_2S_4$)

Mp 224–226°C (dioxane); IR (film): $\bar{\nu} = 3460$–3380 (NH_2), 1675 (C=O, amide) cm^{-1}; MS (EI, 70 eV): $m/z = 625$ [M^+].

*Synthesis of **6a** and **6b***

A mixture of 1 mmol of **4a** or **4b** in 100 cm^3 of ethanolic NaOH (5%) was heated under reflux for 4 h. The corresponding sodium salt precipitated and was filtered off and dried. It was dissolved in 100 cm^3 of acetic anhydride and refluxed for 6 h. The reaction mixture was concentrated and allowed to cool. The obtained solid was collected and crystallized.

2,6-Bis(2-methyl-4-oxo-9-phenylpyrido[3′,2′:4,5]thieno[3,2-d]oxazin-7-yl)pyridine
(**6a**, $C_{37}H_{21}N_5O_4S_2$)

Mp 186–188°C (*DMF*/H_2O); IR (film): $\bar{\nu} = 1750$ (C=O) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 2.09$ (s, $2CH_3$), 7.20–7.60 (m, 10phenyl-H), 7.95–8.10 (m, 3pyridine-H), 8.45 (s, 2C-5′-H); MS (EI, 70 eV): $m/z = 663$ [M^+].

2,6-Bis(2-methyl-4-oxo-9-(2-thienyl)pyrido[3′,2′:4,5]thieno[3,2-d]oxazin-7-yl)pyridine
(**6b**, $C_{33}H_{17}N_5O_4S_4$)

Mp 212–214°C (*DMF*/H_2O); IR (film): $\bar{\nu} = 1745$ (C=O) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 1.85$ (s, $2CH_3$), 6.75–7.25 (m, 6thiophene-H), 8.10–8.25 (m, 3pyridine-H), 8.35 (s, 2C-5′-H); MS (EI, 70 eV): $m/z = 675$ [M^+].

*Synthesis of **7a** and **7b***

A mixture of 1 mmol of **6a** or **6b** and 0.6 g of ammonium acetate (4 mmol) in 100 cm^3 of glacial acetic acid was refluxed for 6 h. The reaction mixture was concentrated under reduced pressure, then poured into H_2O, and the solid formed was collected by filtration and crystallized.

2,6-Bis(2-methyl-4-oxo-9-phenyl-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d] pyrimidin-7-yl)-pyridine (**7a**, $C_{37}H_{23}N_7O_2S_2$)

Mp 245–247°C (*DMF*/H_2O); IR (film): $\bar{\nu} = 3420$ (NH), 1650 (C=O) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 2.30$ (s, $2CH_3$), 7.10–7.70 (m, 10phenyl-H), 8.0–8.20 (m, 3pyridine-H), 8.50 (s, 2C-5′-H), 9.20 (s, 2NH, exchangeable with D_2O); MS (EI, 70 eV): $m/z = 661$ [M^+].

2,6-Bis(2-methyl-4-oxo-9-(2-thienyl)-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d] pyrimidin-7-yl)pyridine (**7b**, $C_{33}H_{19}N_7O_2S_4$)

Mp 234–236°C (*DMF*/H_2O); IR (film): $\bar{\nu} = 3400$ (NH), 1660 (C=O) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 2.10$ (s, $2CH_3$), 7.50–7.80 (m, 6thiophene-H), 8.15–8.30 (m, 3pyridine-H), 8.65 (s, 2C-5′-H), 8.85 (s, 2NH exchangeable with D_2O); MS (EI, 70 eV): $m/z = 673$ [M^+].

*Synthesis of **8a** and **8b***

A solution of 1 mmol of **7a** or **7b** in 20 cm^3 of *DMF* was stirred with 0.55 g of anhydrous K_2CO_3 (4 mmol) for 10 min at room temperature, then 0.56 g of methyl iodide (4 mmol) in 5 cm^3 of *DMF* were added. The reaction mixture was heated at 60°C for 4 h, after cooling poured into H_2O, and the precipitate was filtered off and crystallized.

2,6-Bis(2,3-dimethyl-4-oxo-9-phenyl-3,4-dihydropyrido[3′,2:4,5]thieno[3,2-d] pyrimidin-7-yl)pyridine (**8a**, $C_{39}H_{27}N_7O_2S_2$)

Mp 210–212°C (*Ac*OH/H_2O); IR (film): $\bar{\nu} = 1665$ (C=O) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 2.20$ (s, $2CH_3$), 3.45 (s, 2N-CH_3), 6.80–7.40 (m, 10phenyl-H), 8.00–8.20 (m, 3pyridine-H), 8.55 (s, 2C-5′-H); MS (EI, 70 eV): $m/z = 689$ [M^+].

2,6-Bis(2,3-dimethyl-4-oxo-9-(2-thienyl)-3,4-dihydropyrido[3′,2′:4,5]thieno [3,2-d]pyrimidin-7-yl)pyridine (**8b**, $C_{35}H_{23}N_7O_2S_4$)

Mp 205–207°C (*DMF*/H_2O); IR (film): $\bar{\nu} = 1658$ (C=O) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 2.00$ (s, $2CH_3$), 3.25 (s, 2N-CH_3), 6.55–7.10 (m, 6thiophene-H), 8.10–8.25 (m, 3pyridine-H), 8.40 (s, 2C-5′-H); MS (EI, 70 eV): $m/z = 701$ [M^+].

*Synthesis of **9a** and **9b***

A mixture of 1 mmol of **6a** or **6b** and 0.4 cm^3 of aniline (4 mmol) in 50 cm^3 of glacial acetic acid was heated under reflux for 6 h. The reaction mixture was concentrated, poured onto ice, and the formed solid was filtered off and crystallized.

2,6-Bis(2-methyl-4-oxo-3,9-diphenyl-3,4-dihydropyrido[3′,2′:4,5]thieno [3,2-d]pyrimidin-7-yl)pyridine (**9a**, $C_{49}H_{31}N_7O_2S_2$)

Mp 264–266°C (*DMF*/H_2O); IR (film): $\bar{\nu} = 1665$ (C=O) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 2.0$ (s, $2CH_3$), 6.75–7.50 (m, 20phenyl-H), 8.05–8.20 (m, 3pyridine-H), 8.35 (s, 2H, 2C-5′-H); MS (EI, 70 eV): $m/z = 813$ [M^+].

2,6-Bis(2-methyl-4-oxo-3-phenyl-9-(2-thienyl)-3,4-dihydropyrido[3′,2′:4,5]thieno [3,2-d]-pyrimidin-7-yl)pyridine (**9b**, $C_{45}H_{27}N_7O_2S_4$)

Mp 254–256°C (*DMF*/H_2O); IR (film): $\bar{\nu} = 1680$ (C=O) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 1.95$ (s, $2CH_3$), 6.90–7.60 (m, 16phenyl-H + thiophene-H), 8.10–8.25 (m, 3pyridine-H), 8.40 (s, 2C-5′-H); MS (EI, 70 eV): $m/z = 825$ [M^+].

*Synthesis of **10a** and **10b***

A mixture of 1 mmol of **6a** or **6b** and 0.8 cm^3 of hydrazine hydrate (16 mmol) in 100 cm^3 of absolute ethanol was refluxed for 4 h. After cooling the solid formed was collected and crystallized.

2,6-Bis(3-amino-2-methyl-4-oxo-9-phenyl-3,4-dihydropyrido[3′,2′:4,5]thieno [3,2-d]pyrimidin-7-yl)pyridine (**10a**, $C_{37}H_{25}N_9O_2S_2$)

Mp 244–246°C (*DMF*/H_2O); IR (film): $\bar{\nu} = 3340$–3280 (NH_2), 1658 (C=O) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 2.10$ (s, $2CH_3$), 4.75 (s, $2NH_2$, exchangeable with D_2O), 6.90–7.35 (m, 10phenyl-H), 8.15–8.30 (m, 3pyridine-H), 8.45 (s, 2C-5′-H); MS (EI, 70 eV): $m/z = 691$ [M^+].

2,6-Bis(3-amino-2-methyl-4-oxo-9-(2-thienyl)-3,4-dihydropyrido[3′,2′:4,5]thieno [3,2-d]-pyrimidin-7-yl)pyridine (**10b**, $C_{33}H_{21}N_9O_2S_4$)

Mp 238–240°C (*DMF*/H_2O); IR (film): $\bar{\nu} = 3365$–3300 (NH_2), 1670 (C=O) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 2.30$ (s, $2CH_3$), 4.80 (s, $2NH_2$, exchangeable with D_2O), 7.10–7.55 (m, 6thiophene-H), 8.10–8.25 (m, 3pyridine-H), 8.60 (s, 2C-5′-H); MS (EI, 70 eV): $m/z = 703$ [M^+].

*Synthesis of **11a** and **11b***

A mixture of 1 mmol of **10a** or **10b** and 0.22 g of 2-thiophenecarbaldehyde (2 mmol) in 25 cm^3 of absolute ethanol was refluxed for 6 h (a solid was formed after 1 h). The obtained solid was filtered off, washed with ethanol, and crystallized.

2,6-Bis(2-methyl-4-oxo-3-(2-thienylmethylidene)amino)-9-phenyl-3,4-dihydropyrido [3′,2′:4,5]-thieno[3,2-d]pyrimidin-7-yl)pyridine (**11a**, $C_{47}H_{29}N_9O_2S_4$)

Mp >300°C (*DMF*/H_2O); IR (film): $\bar{\nu} = 1670$ (C=O) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 2.35$ (s, $2CH_3$), 6.75–7.10 (m, 10phenyl-H), 7.30–7.60 (m, 6thiophene-H), 7.95–8.10 (m, 3pyridine-H), 8.45 (s, 2C-5′-H), 9.20 (s, 2CH=N); MS (EI, 70 eV): $m/z = 880$ [M^+].

2,6-Bis(2-methyl-4-oxo-3-(2-thienylmethylidene)amino)-9-(2-thienyl)-3,4-dihydropyrido [3′,2′:4,5]thieno[3,2-d]pyrimidin-7-yl)pyridine (**11b**, $C_{43}H_{25}N_9O_2S_6$)

Mp 285–287°C (*DMF*/H_2O); IR (film): $\bar{\nu} = 1678$ (C=O) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): 2.20 (s, $2CH_3$), 7.10–7.65 (m, 12thiophene-H), 8.00–8.20 (m, 3pyridine-H), 8.35 (s, 2C-5′-H), 8.95 (s, 2CH=N); MS (EI, 70 eV): $m/z = 892$ [M^+].

*Synthesis of **12a** and **12b***

A mixture of 1 mmol of **10a** or **10b** and 0.29 g of phthalic anhydride (2 mmol) was refluxed in 50 cm^3 of glacial acetic acid for 6 h. The reaction mixture was cooled, the obtained product was collected by filtration, dried, and crystallized.

2,6-Bis(2-methyl-4-oxo-3-(phthalimido)-9-phenyl-3,4-dihydropyrido [3′,2′:4,5]thieno[3,2-d]-pyrimidin-7-yl)pyridine (**12a**, $C_{53}H_{29}N_9O_6S_2$)

Mp >300°C (*DMF*/*Et*OH); IR (film): $\bar{\nu} = 1680$ (C=O) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 2.35$ (s, $2CH_3$), 6.80–7.60 (m, 18Ar-H), 8.00–8.20 (m, 3pyridine-H), 8.4 (s, 2C-5′-H); MS (EI, 70 eV): $m/z = 951$ [M^+].

2,6-Bis(2-methyl-4-oxo-3-(phthalimido)-9-(2-thienyl)-3,4-dihydropyrido [3′,2′:4,5]thieno[3,2-d]pyrimidin-7-yl)pyridine (**12b**, $C_{49}H_{25}N_9O_6S_4$)

Mp >300°C (*DMF*/*Et*OH); IR (film): $\bar{\nu} = 1680$ (C=O) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 2.20$ (s, $2CH_3$), 6.75–7.10 (m, 8Ar-H), 7.25–7.75 (m, 6thiophene-H), 8.05–8.25 (m, 3pyridine-H), 8.45 (s, 2C-5′-H); MS (EI, 70 eV): $m/z = 964$ [M^+].

*Synthesis of **13a** and **13b***

A mixture of 1 mmol of **5a** or **5b**, 10 cm^3 of conc. H_2SO_4, and 20 cm^3 of glacial acetic acid was stirred for 15 min at −5°C. Then 0.2 g of $NaNO_2$ (3 mmol) in 10 cm^3 of H_2O were added dropwise with constant stirring during 10 min. The reaction mixture was stirred for 1 h at 0°C and then diluted with H_2O. The obtained product was filtered off, washed with water, and crystallized.

2,6-Bis(4-oxo-9-phenyl-3,4-dihydropyrido[3′,2′:4,5]thieno [3,2-d]-[1,2,3]-triazin-7-yl)-pyridine (**13a**, $C_{33}H_{17}N_9O_2S_2$)

Mp 215–217°C (*Ac*OH); IR (film): $\bar{\nu} = 3300$–2600 (NH), 1660 (C=O) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 6.80$–7.40 (m, 10phenyl-H), 7.90–8.10 (m, 3pyridine-H), 8.50 (s, 2C-5′-H), 8.90 (s, 2NH, exchangeable with D_2O); MS (EI, 70 eV): $m/z = 635$ [M^+].

2,6-Bis(4-oxo-9-(2-thienyl)-3,4-dihydropyrido[3′,2′:4,5]thieno [3,2-d]-[1,2,3]-triazin-7-yl)-pyridine (**13b**, $C_{29}H_{13}N_9O_2S_4$)

Mp 196–198°C (*Ac*OH); IR (film): $\bar{\nu} = 3380$–2300 (NH), 1680 (C=O) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 7.20$–7.60 (m, 6thiophene-H), 8.10–8.30 (m, 3pyridine-H), 8.55 (s, 2C-5′-H), 9.10 (s, 2NH, exchangeable with D_2O); MS (EI, 70 eV): $m/z = 647$ [M^+].

*Synthesis of **14a** and **14b***

A solution of 1 mmol of **13a** or **13b** in 20 cm^3 of *DMF* was stirred with 0.55 g of anhydrous K_2CO_3 (4 mmol) for 10 min at room temperature. Then 0.62 g of ethyl iodide (4 mmol) were added. The reaction mixture was heated at 60°C for 4 h. After cooling the mixture was poured into H_2O. The formed solid was filtered off and crystallized.

2,6-Bis(3-ethyl-4-oxo-9-phenyl-3,4-dihydropyrido[3′,2′:4,5]thieno [3,2-d]-1,2,3-triazin-7-yl)-pyridine (**14a**, $C_{37}H_{25}N_9O_2S_2$)

Mp 223–225°C (*DMF*/*Et*OH); IR (film): $\bar{\nu} = 1670$ (C=O) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 1.60$ (t, $2CH_3$), 4.6 (q, $2CH_2$), 6.85–7.35 (m, 10phenyl-H), 8.00–8.20 (m, 3pyridine-H), 8.45 (s, 2C-5′-H); MS (EI, 70 eV): $m/z = 691$ [M^+].

2,6-Bis(3-ethyl-4-oxo-9-(2-thienyl)-3,4-dihydropyrido[3′,2′:4,5]thieno [3,2-d]-1,2,3-triazin-7-yl)pyridine (**14b**, $C_{33}H_{21}N_9O_2S_4$)

Mp 218–220°C (*DMF*/*Et*OH); IR (film): $\bar{\nu} = 1665$ (C=O) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 1.50$ (t, $2CH_3$), 4.35 (q, $2CH_2$), 7.10–7.60 (m, 6thiophene-H), 8.10–8.35 (m, 3pyridine-H), 8.55 (s, 2C-5′-H); MS (EI, 70 eV): $m/z = 703$ [M^+].

*Synthesis of **15a** and **15b***

A mixture of 1 mmol of **5a** or **5b** and 2.7 g of phenyl isothiocyanate (2 mmol) in 25 cm^3 of dioxane was refluxed for 6 h. The reaction mixture was evaporated under reduced pressure, the obtained residue was solidified with *n*-hexane, filtered off and crystallized.

2,6-Bis(4-oxo-3,9-diphenyl-1,2,3,4-tetrahydro-2-thioxopyrido[3′,2′:4,5]thieno [3,2-d]pyrimidin-7-yl)-pyridine (**15a**, $C_{47}H_{27}N_7O_2S_4$)

Mp 242–244°C (*DMF*/H_2O); IR (film): $\bar{\nu} = 3320$ (NH), 1680 (C=O), 1200 (C=S) cm^{-1}; MS (EI, 70 eV): $m/z = 850$ [M^+].

2,6-Bis(4-oxo-3-phenyl-9-(2-thienyl)-1,2,3,4-tetrahydro-2-thioxopyrido[3′,2′:4,5]thieno [3,2-d]pyrimidin-7-yl)pyridine (**15b**, $C_{43}H_{23}N_7O_2S_6$)

Mp 236–238°C (*DMF*/*Et*OH); IR (film): $\bar{\nu} = 3345$ (NH), 1680 (C=O), 1195 (C=S) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 6.90$–7.30 (m, 10phenyl-H), 7.40–7.60 (m, 6thiophene-H), 7.90 (s, 2NH, exchangeable with D_2O), 8.00–8.25 (m, 3pyridine-H), 8.60 (s, 2C-5′-H); MS (EI, 70 eV): $m/z = 862$ [M^+].

*Synthesis of **16a** and **16b***

To a solution of 1 mmol of **15a** or **15b** in 100 cm^3 of alcoholic NaOH (5%) 0.62 g of ethyl iodide (4 mmol) were added with stirring. The reaction mixture was refluxed for 8 h, then the excess solvent was evaporated under reduced pressure, and the residue was poured onto H_2O. The obtained solid was collected by filtration and crystallized.

2,6-Bis(4-oxo-3,9-diphenyl-3,4-dihydro-2-(ethylthio)pyrido[3′,2′:4,5]thieno [3,2-d]pyrimidin-7-yl)pyridine (**16a**, $C_{51}H_{35}N_7O_2S_4$)

Mp 186–188°C (*Ac*OH/H_2O); IR (film): $\bar{\nu} = 1668$ (C=O) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 1.10$–1.20 (t, $2CH_3$), 2.4–2.60 (q, $2CH_2$), 7.10–7.65 (m, 20phenyl-H), 8.10–8.25 (m, 3pyridine-H), 8.55 (s, 2C-5′-H); MS (EI, 70 eV): $m/z = 906$ [M^+].

2,6-Bis-(2-(ethylthio)-4-oxo-3-phenyl-9-(2-thienyl)-3,4-dihydropyrido [3′,2′:4,5]thieno[3,2-d]-pyrimidin-7-yl)pyridine (**16b**, $C_{47}H_{31}N_7O_2S_6$)

Mp 210–212°C (*Ac*OH/H_2O); IR (film): $\bar{\nu} = 1675$ (C=O) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 0.95$–1.20 (t, $2CH_3$), 2.60–2.85 (q, $2CH_2$), 6.65–7.60 (m, 16phenyl-H + thiophene-H), 8.00–8.25 (m, 3pyridine-H), 8.60 (s, 2C-5′-H); MS (EI, 70 eV): $m/z = 918$ [M^+].

*Synthesis of **17a** and **17b***

Method A: A solution of 1 mmol of **15a** or **15b** in 100 cm^3 of ethanolic NaOH (20%) was stirred at room temperature for 1 h and 0.19 g of chloroacetic acid (2 mmol) were added. The reaction mixture

was refluxed for 12 h, concentrated, and then poured onto ice. The formed solid was collected by filtration and crystallized.

Method B: A mixture of 1 mmol of **15a** or **15b**, 0.19 g of chloroacetic acid (2 mmol), and 0.25 g of anhydrous sodium acetate (3 mmol) in 40 cm^3 of glacial acetic acid/acetic anhydride (3/1, v/v) was refluxed for 6 h, then allowed to cool, and poured gradually with stirring into cold H_2O. The formed solid was filtered off and crystallized.

2,6-Bis(2-ethylthioglycolole-4-oxo-3,9-diphenyl-3,4-dihydropyrido [3′,2′:4,5]thieno[3,2,-d]pyrimidin-7-yl)pyridine (**17a**, $C_{51}H_{31}N_7O_6S_4$)

Mp >300°C (*DMF*/H_2O); IR (film): $\bar{\nu} = 3560–3440$ (br, OH), 1723 (C=O, acid), 1675 (C=O) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): $\delta = 4.20$ (s, $2CH_2$), 7.20–7.60 (m, 20phenyl-H), 8.05–8.30 (m, 3pyridine-), 8.60 (s, 2C-5′-H), 10.60 (s, 2OH, exchangeable with D_2O); MS (EI, 70 eV): $m/z = 966$ [M^+].

2,6-Bis(2-ethylthioglycolole-4-oxo-3-phenyl-9-(2-thienyl)-3,4-dihydropyrido [3′,2′:4,5]thieno[3,2-d]pyrimidin-7-yl)pyridine (**17b**, $C_{47}H_{27}N_7O_6S_6$)

Mp >300°C (*DMF*/H_2O); IR (film): $\bar{\nu} = 3520–3435$ (br, OH), 1726 (C=O, acid), 1680 (C=O) cm^{-1}; ^1H NMR (270 MHz, *DMSO*-d_6): 3.95 (s, $2CH_2$), 6.85–7.10 (m, 10phenyl-H), 7.20–7.65 (m, 6thiophene-H), 8.15–8.35 (m, 3pyridine-H), 8.55 (s, 2C-5′-H), 10.75 (s, 2OH, exchangeable with D_2O); MS (EI, 70 eV): $m/z = 978$ [M^+].

Pharmacology

Analgesic Activity

Sixty mice of both sexes weighting from 20–25 g were divided into 10 groups. One group was kept as control (received saline), the second group received vehicle (Gumacaccia), and the third one received Voltarene® as a reference drug, whereas the other groups received **2a**, **4b**, **6a**, **8a**, **10a**, **10b**, and **13a** (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 were 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 jamb out of the beaker (dose 5 mg/kg). Relative potencies to Voltarene® were determined (Table 1).

Anticonvulsant Activity

Purpose and Rationale

Antagonism against yohimbine-induced seizures in mice is considered to be a predictive model of potential anxiolytic and *GABA*-mimetic [16].

Procedure

Male *Webster* mice (20–30 g) were individually placed in clear plastic cylinder and the tested compounds were administered intrapretonial (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. Evaluation ED_{50} values of compounds with 95% confidence limit were calculated for the antagonism of yohimbine-induced clonic seizures by means of the *Lichtfield-Wilcoxon* procedure [17] (Table 2).

Antiparkinsonian Activity

Purpose and Rationale

The muscarinic agonists Tremorine® and Oxotremorine® induce parkinisonisin-like signs such as tremor, attaxia, spasticity, salivation, lacrimation, and hypothermia. These signs are antagonized by antiparkinsonian agents.

Procedure

Groups of eight mail mice (18–20 g) were used. They were dosed orally with the tested compounds (5 mg/kg) or the standard (Benzotropene® mesilate, 5 mg/kg) [18] 1 h prior the administration of 0.5 mg/kg of Oxotremerine® S.C. Rectal temperature was measured before administration of the compounds and one hour after Oxotremerine® dosage. The scores for the recorded signs are zero (absent), one (slight), two (medium), and three (high) (Table 3).

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