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Synthesis, and analgesic and antiparkinsonian activities of thiopyrimidine, pyrane, pyrazoline, and thiazolopyrimidine derivatives from 2-chloro-6-ethoxy-4-acetylpyridine

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Abstract A series of substituted pyridine derivatives were prepared from 2-chloro-6-ethoxy-4-acetylpyridine, which was prepared from the corresponding citrazinic acid as starting material. Reaction of acetylpyridine with thiophene-2-carboxaldehyde afforded the 2-chloro-6-ethoxy-4-β-(2-thienyl)acryloylpyridine, which was reacted with malononitrile in refluxing ethanol in the presence of piperidine as a catalyst to afford the cyanoaminopyrane derivative. Acryloylpyridine was treated with urea or guanidine hydrochloride in refluxing ethanolic potassium hydroxide to give the corresponding pyrimidinone and aminopyrimidine derivatives. The latter was condensed with hydrazine hydrate or phenyl hydrazine to give pyrazoline and *N*-phenylpyrazoline derivatives. Finally, cycloaddition reaction of acryloylpyridine with thiourea yielded thioxopyrimidine, which was treated with 2-bromopropionic acid, 3-bromopropionic acid, or bromoacetic acid to yield methylthiazolo-, thiazino-, and thiazolopyrimidine derivatives. The arylmethylene derivative was prepared by reacting thiazolopyrimidine with benzaldehyde or by reacting thioxopyrimidine with benzaldehyde and bromoacetic acid in one step. The pharmacological screening showed that many of these compounds have good analgesic and antiparkinsonian activities comparable to Valdecoxib® and Benzatropine® as reference drugs.

Keywords Citrazinic acid; 2-Chloro-6-ethoxy-4-acetylpyridine; Thiazolopyrimidine; Analgesic; Antiparkinsonian.

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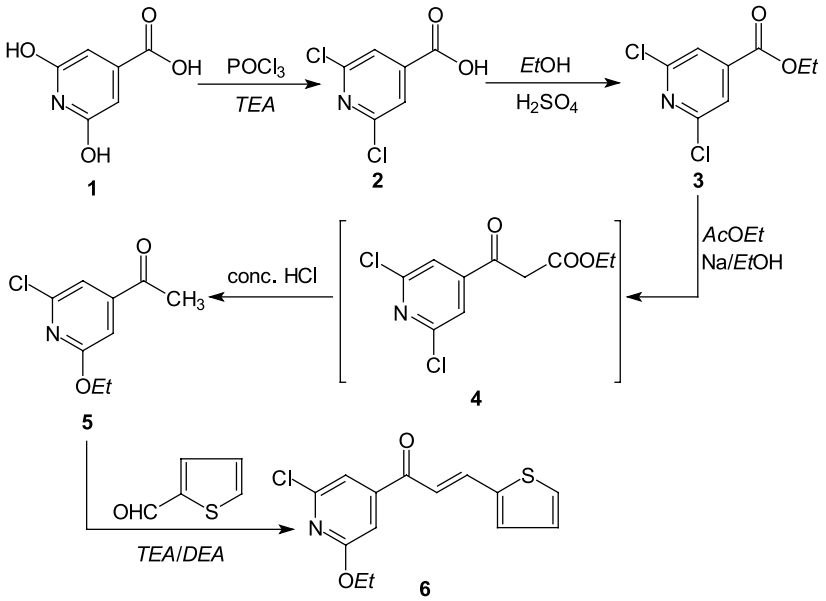
Introduction

In previous work we have reported that certain substituted pyridines and their chiral macrocyclic derivatives have antimicrobial [1–5], anticancer [6, 7], analgesic, and anticonvulsant [8, 9] activities. In addition, the biological and antiandrogenic activities of many heterocyclic compounds have been reviewed [10, 11]. On the other hand, thioxopyrimidine and thiazolopyrimidine derivatives have promising biological activities, *e.g.*, anticancer properties [12–16] and androgenic anabolic activities [17]. Recently, some new thienopyrimidinone derivatives have been synthesized and tested for their analgesic, anticonvulsant, antiparkinsonian [18, 19], and antiinflammatory [20–23] activity. In view of these observations and in continuation of our previous work in heterocyclic chemistry, we synthesized some new thiopyrimidine, pyrane, pyrazoline, and thiazolopyrimidine derivatives using citrazinic acid as starting material and tested their analgesic and antiparkinsonian activities.



Scheme 1

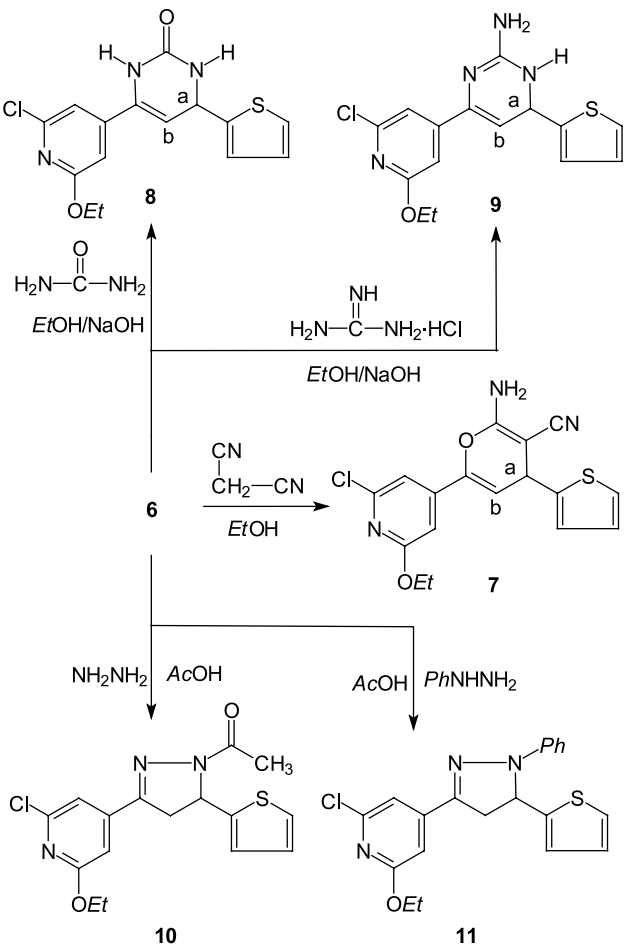
Results and discussion

Synthesis

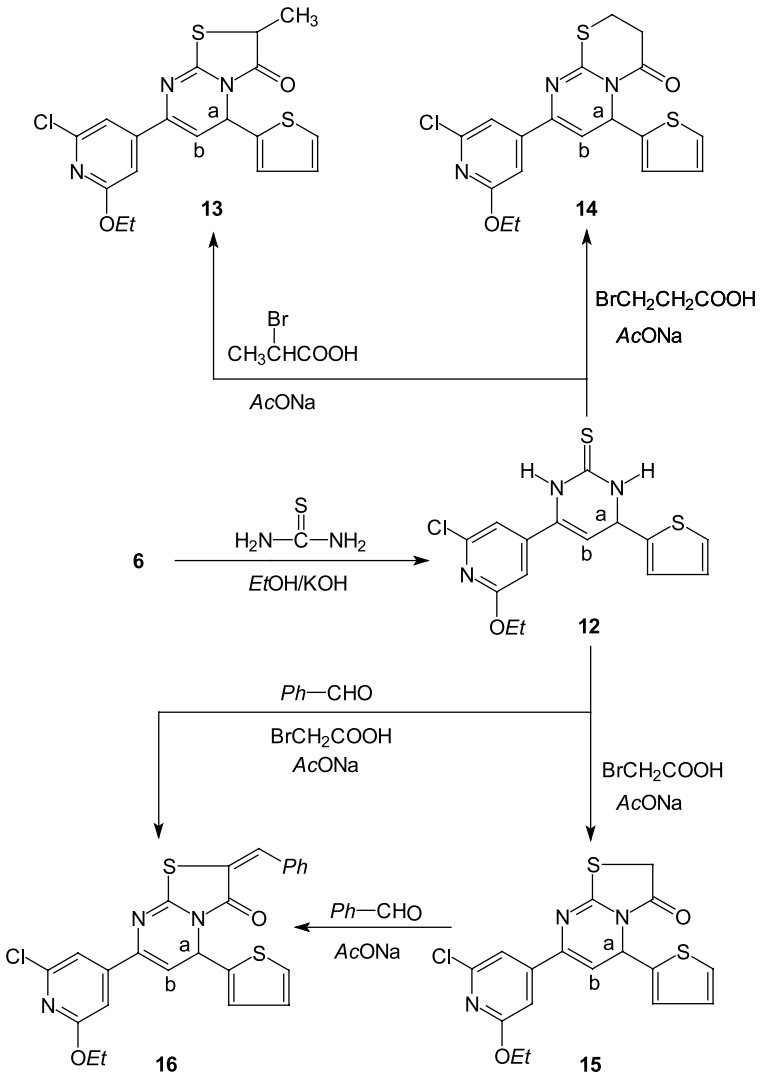
In previous work we have reported the synthesis and a preliminary biological activity screening of several pyridine derivatives based on 4-β-(2-thienyl)acryloylpyridine (**6**) [24], which was prepared as starting material from the corresponding 2,6-dihydroxyisonicotinic acid (citrazinic acid) (**1**) *via* 2,6-dichloroisonicotinic acid ethyl ester (**3**) and the corresponding 2-chloro-6-ethoxy-4-acetylpyridine (**5**) according to literature methods [4, 24] (Scheme 1).

Treatment of **6** with malononitrile in refluxing ethanol with a small amount of piperidine gave the cyanoaminopyrane **7**, but, it was condensed with diamines, namely, urea or guanidine hydrochloride in refluxing ethanolic potassium hydroxide to afford the 2-carbonyl- **8** and 2-aminopyrimidines **9** (Scheme 2). Compound **6** was treated with hydrazine hydrate or phenyl hydrazine in refluxing glacial acetic acid to give *N*-acetylpyrazoline **10** and *N*-phenylpyrazoline **11** (Scheme 2).

Also, compound **6** was condensed with thiourea in ethanol and dry HCl gas to give thioxopyrimidine **12**, which was condensed with 2-propionic acid, 3-propionic acid, or chloroacetic acid in a mixture of acetic acid/acetic anhydride in the presence of anhydrous sodium acetate to yield the corresponding methylthiazolo-, thiazino-, and thiazolopyrimidines



Scheme 2



Scheme 3

13–**15**. Compound **15** contains an active methylene group. As such it condensed with benzaldehyde in the presence of anhydrous sodium acetate and glacial acetic acid/acetic anhydride mixture to yield the arylmethylene **16**. However, the latter was also prepared directly from **12** by the action of chloroacetic acid, benzaldehyde, and anhydrous sodium acetate in the presence of an acetic acid/acetic anhydride mixture (Scheme 3).

Pharmacological screening

Initially, the acute toxicity of the compounds was assayed by the determination of their LD_{50} (Table 1).

Table 1 Acute toxicity LD_{50} of the synthesized and starting compounds

Compound no.	LD_{50}/mg kg^{-1}
Valdecoxib®	1.68
6	1.80
7	2.05
8	1.79
9	2.53
10	3.62
11	2.45
12	1.77
13	1.81
14	2.97
15	2.45
16	2.35

Table 2 Analgesic activities of selected compounds in a hot plate assay

Compound no.	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
7	1.29 ± 0.175	1.42 ± 0.16	1.45 ± 0.130	1.46 ± 0.200	1.40 ± 0.320	1.40 ± 0.290	1.41 ± 0.279
8	0.89 ± 0.010	0.88 ± 0.011	0.90 ± 0.011	0.92 ± 0.017	0.93 ± 0.016	0.92 ± 0.015	0.90 ± 0.017
9	0.65 ± 0.011	0.64 ± 0.011	0.88 ± 0.011	0.89 ± 0.016	0.90 ± 0.021	0.90 ± 0.017	0.89 ± 0.018
10	0.78 ± 0.011	0.86 ± 0.014	0.85 ± 0.012	0.87 ± 0.015	0.88 ± 0.017	0.85 ± 0.012	0.84 ± 0.018
11	0.62 ± 0.012	0.74 ± 0.012	0.80 ± 0.001	0.83 ± 0.015	0.86 ± 0.016	0.85 ± 0.015	0.85 ± 0.036
12	0.99 ± 0.012	0.98 ± 0.014	1.40 ± 0.138	1.57 ± 0.210	1.56 ± 0.350	1.59 ± 0.340	1.44 ± 0.450
13	0.83 ± 0.013	0.92 ± 0.014	0.94 ± 0.017	0.96 ± 0.021	0.96 ± 0.032	0.95 ± 0.018	0.95 ± 0.025
14	0.60 ± 0.012	0.67 ± 0.011	0.75 ± 0.012	0.76 ± 0.018	0.78 ± 0.011	0.79 ± 0.011	0.78 ± 0.013
15	0.92 ± 0.010	0.93 ± 0.009	0.93 ± 0.015	0.89 ± 0.019	0.84 ± 0.021	0.80 ± 0.016	0.66 ± 0.012
16	0.65 ± 0.010	0.66 ± 0.017	0.75 ± 0.013	0.74 ± 0.017	0.76 ± 0.017	0.76 ± 0.016	0.79 ± 0.012

The tested two pharmacological activities namely, analgesic and antiparkinsonian despite of their different biological receptors yet all of a neurological. Ten representative compounds **7**–**16** were studied with respect to analgesic and antiparkinsonian activities.

Analgesic activity

All compounds tested exhibited analgesic activities in a hot plate assay (Table 2). The most potent are compounds **7** and **12** showing higher activity than Voldecoxib® by nearly 140–160% (compound **7** showed the most pronounced effect). Also, the analgesic activities of **8**–**11** and **13**–**16** approached those of Valdecoxib®, and showed 62–84% activity as compared to Valdecoxib® (=100%) (Table 2).

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 **8**, **13**, **14**, and **15** showed nearly no antiparkinsonian activities. While compounds **9**, **10**, and **11** showed moderate antiparkinsonian activities (relative potencies to Benzatropine® (= 1.0) are 0.64, 0.60, and 0.40). Compounds **7**, **12**, and **16** are the most potent antiparkinsonian agents (0.80 relative potencies) (Table 3).

Table 3 Antiparkinsonian activities of synthesized compounds as compared with Benzatropine®

Compound no.	Salivation and lacrimation score	Tremors score	Decrease from oxotremorine rectal temperature/% ±SE	Relative potency compared to benzatropine mesilate ±SE
Control	0	0	0	0
Benzatropine®	1	1	25.0 ± 0.400	1.00 ± 0.09
7	1	1	21.0 ± 0.370	0.80 ± 0.075
8	3	3	5.0 ± 0.012	0.17 ± 0.012
9	2	2	16.0 ± 0.290	0.59 ± 0.059
10	2	2	11.0 ± 0.100	0.41 ± 0.031
11	1	1	17.0 ± 0.300	0.65 ± 0.07
12	1	1	21.0 ± 0.140	0.80 ± 0.06
13	3	3	4.0 ± 0.011	0.13 ± 0.013
14	3	3	4.0 ± 0.015	0.13 ± 0.011
15	3	3	5.0 ± 0.010	0.15 ± 0.014
16	1	1	21.0 ± 0.480	0.80 ± 0.071

Experimental

All melting points were taken on Electrothermal IA 9000 series digital melting point apparatus. Elemental analytical data (in accord with the calculated values) were obtained from the microanalytical unit, Cairo University, Cairo, Egypt. The IR spectra (KBr) were recorded on a Pye Unicam SP-1000 spectrophotometer. The ^{1}H NMR spectra were recorded at 270 MHz on Varian EM-360 Spectrometer using *TMS* as an internal standard. The Central Services Laboratory, Cairo University, Egypt. The mass spectra were performed using VG 2AB-3F spectrometer (70 eV). All reactions were followed by *TLC* (silica gel, aluminum sheets 60 F_{254}, Merck). Starting materials **2**–**6** were prepared from citrazinic acid (**1**) according to published procedures [4, 24].

2-Amino-4-(2-thienyl)-6-[4-(2′-chloro-6′-ethoxypyridinyl)]-3-carbonitrile (**7**, $C_{17}H_{14}ClN_3O_2S$)
A solution of 0.293 g **6** (1 mmol), and 0.06 g malononitrile (1 mmol) in 30 cm^3 absolute ethanol in the presence of 2 cm^3 piperidine was stirred at room temperature for 3 h. The solvent was concentrated under reduced pressure, the formed product was collected by filtration, washed with water, dried, and crystallized to give 0.27 g (76%) **7**. Mp 214–216°C (*Et*OH); IR (film): $\bar{\nu} = 3405$–3345 (NH_2), 2226 (CN) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.32$ (t, CH_3, $J = 6.95$ Hz), 3.78 (q, CH_2, $J = 6.95$ Hz), 4.46 (d, H-a pyrane), 4.72 (s, NH_2 exchangeable with D_2O), 6.95–7.18 (m, 3 thiophene-H + H-b pyrane), 8.12–8.26 (m, 2 pyr-H) ppm; MS (EI, 70 eV): $m/z = 360$ [M^+, 18] and at 161 [100, base peak].

*Substituted pyrimidines **8** and **9***
Diamino compounds, namely, urea or guanidine hydrochloride (1 mmol) were added to 0.293 g **6** (1 mmol) in 100 cm^3 ethanolic sodium hydroxide (1%). The reaction mixture was refluxed for 4–6 h and then poured gradually with stirring onto cold water. The solid formed was filtered off, washed with H_2O, and crystallized to give **8** and **9**.

6-[(2-Chloro-6-ethoxypyridin-4-yl)]-1,2,3,4-tetrahydro-2-oxo-4-(2-thienyl)pyrimidine (**8**, $C_{15}H_{14}ClN_3O_2S$)
Yield 0.22 g (65%); mp 146–148°C (*Et*OH/H_2O); IR (film): $\bar{\nu} = 3338$–3268 (NH), 1670 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.30$ (t, CH_3, $J = 6.98$ Hz), 3.80 (q, CH_2, $J = 6.98$ Hz), 5.36 (d, H-a, pyrimidine), 6.98–7.22 (m, 3 thiophene-H + H-b pyrimidine), 8.06–8.24 (m, 2 pyr-H), 8.34 and 8.48 (2s, 2 NH-exchangeable with D_2O) ppm; MS (EI, 70 eV): $m/z = 336$ [M^+, 12], and at 290 [100, base peak].

2-Amino-6-[(2-chloro-6-ethoxypyridin-4-yl)-3,4-dihydro-4-(2-thienyl)pyrimidine (**9**, $C_{15}H_{15}ClN_4OS$)
Yield 0.24 g (75%); mp 232–234°C (*Ac*OH/H_2O); IR (film): $\bar{\nu} = 3444$–3318 (NH, NH_2) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.33$ (t, CH_3, $J = 6.95$ Hz), 3.79 (q, CH_2, $J = 6.95$ Hz), 4.52 (s, NH_2 exchangeable with D_2O), 5.26 (d, H-a, pyrimidine), 6.95–7.16 (m, 3 thiophene-H + H-b pyrimidine), 8.10–8.18 (m, 2 pyr-H), 8.49 (s, NH- exchangeable with D_2O) ppm; MS (EI, 70 eV): $m/z = 335$ [M^+, 24], and at 273 [100, base peak].

*N-substituted pyrazolines **10** and **11***
A mixture of 0.293 g **6** (1 mmol) and 0.4 cm^3 hydrazine hydrate (8 mmol) or 1.6 g phenyl hydrazine (1.5 mmol) in 15 cm^3 glacial acetic acid was heated under reflux for 5 h. The reaction mixture was poured into ice, the obtained solid was filtered off, washed with water, dried under pressure, and crystallized to give 0.25 g (72%) **10** and 0.26 g (68%) **11**.

2-Acetyl-3-(2-thienyl)-3,4-dihydro-5-[(2-chloro-6-ethoxypyridin-4-yl)pyrazoline (**10**, $C_{16}H_{16}ClN_3O_2S$)
Mp 186–188°C (*Me*OH/H_2O); IR (film): $\bar{\nu} = 1718$ (C=O), 1668 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.29$ (t, CH_3, $J = 6.96$ Hz), 1.90–2.10 (m, CH_2-pyrazoline), 3.65 (s, $COCH_3$), 3.81 (q, CH_2, $J = 6.96$ Hz), 3.86–3.88 (m, CH-pyrazoline), 6.98–7.20 (m, 3 thiophene-H), 8.10–8.22 (m, 2 pyr-H) ppm; MS (EI, 70 eV): $m/z = 350$ [M^+, 16], and at 179 [100, base peak].

2-Phenyl-3-(2-thienyl)-3,4-dihydro-5-[(2-chloro-6-ethoxypyridin-4-yl)pyrazoline (**11**, $C_{20}H_{18}ClN_3OS$)
Mp 176–178°C (*Me*OH/H_2O); IR (film): $\bar{\nu} = 1674$ (C=N), 1616 (C=C) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.31$ (t, CH_3, $J = 6.98$ Hz), 1.88–2.12 (m, CH_2-pyrazoline), 3.79 (q, CH_2, $J = 6.98$ Hz), 3.84–3.87 (m, CH-pyrazoline), 6.94–7.36 (m, 3 thiophene-H + *Ph*-H), 8.09–8.24 (m, 2 pyr-H) ppm; MS (EI, 70 eV): $m/z = 384$ [M^+, 24], and at 226 [100, base peak].

6-[(2-Chloro-6-ethoxypyridin-4-yl)-1,2,3,4-tetrahydro-2-thioxo-4-(2-thienyl)pyrimidine (**12**, $C_{15}H_{14}ClN_3OS_2$)
Dry hydrogen chloride gas was passed through a mixture of 0.293 g **6** (1 mmol) and 0.076 g thiourea (1 mmol) in 25 cm^3 absolute ethanol at room temperature for 6 h. The reaction mixture was poured gradually with stirring onto cold water. The solid formed was filtered off, washed with water, dried under pressure, and crystallized to give 0.3 g (85%) **12**. Mp > 265°C (*Ac*OH/H_2O); IR (film): $\bar{\nu} = 3376$–3265 (NH), 1218 (C=S) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.33$ (t, CH_3, $J = 6.95$ Hz), 3.80 (q, CH_2, $J = 6.95$ Hz), 5.35 (d, H-a, pyrimidine), 6.94–7.28 (m, 3 thiophene-H + H-b pyrimidine), 8.16–8.22 (m, 2 pyr-H), 8.35 and 8.49 (2s, 2 NH exchangeable with D_2O) ppm; MS (EI, 70 eV): $m/z = 352$ [M^+, 100, base peak].

*Methylthiazolo-, thiazino-, and thiazolopyrimidines **13–15***
A mixture of 0.352 g **12** (1 mmol) and halo compounds, namely, 2-bromopropionic acid, 3-bromopropionic acid, or bromoacetic acid (1 mmol) was dissolved in 40 cm^3 of a mixture of *Ac*OH/Ac_2O (1/3) in the presence 3 g anhydrous sodium acetate was refluxed for 6–7 h. The reaction mixture was cooled and poured onto cold water with stirring, the solid formed was filtered off and crystallized to give 0.27 g (66%) **13**, 0.28 g (70%) **14**, and 0.3 g (75%) **15**.

7-[(2-Chloro-6-ethoxypyridin-4-yl)-5-(2-thienyl)-2,3-dihydro-5H-3-methylthiazolo[3,2-a]-pyrimidine (**13**, $C_{18}H_{16}ClN_3O_2S_2$)
Mp 198–200°C (*Ac*OH/H_2O); IR (film): $\bar{\nu} = 1715$ (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.32$ (t, CH_3, $J = 7.05$ Hz),

1.36 (d, CH_3), 3.55 (m, CH-thiazole), 3.80 (q, CH_2, $J=$ 7.05 Hz), 5.45 (d, H-a, pyrimidine), 6.88–7.28 (m, 3 thiophene-H + H-b pyrimidine), 8.10–8.23 (m, 2 pyr-H) ppm; MS (EI, 70 eV): $m/z=406$ [M^+, 14], and at 310 [100, base peak].

2-Chloro-6-ethoxy-4-[6-(2-thienyl)-2,3-dihydro-6H-thiazino-[3,2-a]pyrimidin-4-one-8-yl)]pyridine (**14**, $C_{18}H_{16}ClN_3O_2S_2$)
Mp 215–217°C (*Ac*OH/H_2O); IR (film): $\bar{\nu}=1718$ (C=O) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta=1.30$ (t, CH_3, $J=6.96$ Hz), 3.40–3.55 (m, 2 CH_2-thiazine ring), 3.81 (q, CH_2, $J=$ 6.96 Hz), 5.36 (d, H-a, pyrimidine), 6.78–7.16 (m, 3 thiophene-H + H-b pyrimidine), 8.14–8.26 (m, 2 pyr-H) ppm; MS (EI, 70 eV): $m/z=406$ [M^+, 32], and at 249 [100, base peak].

7-[(2-Chloro-6-ethoxypyridin-4-yl)-5-(2-thienyl)-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine (**15**, $C_{17}H_{14}ClN_3O_2S_2$)
Mp 218–220°C (*Ac*OH/H_2O); IR (film): $\bar{\nu}=1709$ (C=O) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta=1.34$ (t, CH_3, $J=6.95$ Hz), 3.74 (s, CH_2-thiazole), 3.78 (q, CH_2, $J=6.95$ Hz), 5.38 (d, H-a, pyrimidine), 6.82–7.18 (m, 3 thiophene-H + H-b pyrimidine), 8.11–8.24 (m, 2 pyr-H) ppm; MS (EI, 70 eV): $m/z=$ 392 [M^+, 5], and at 152 [100, base peak].

7-[(2-Chloro-6-ethoxypyridin-4-yl)-2-(phenylmethylene)-5-(2-thienyl)-2,3-dihydro-5-thiazolo[3,2-a]pyrimidine
(**16**, $C_{24}H_{18}ClN_3O_2S_2$)
Method A: A mixture of 0.352 g **12** (1 mmol), 0.138 g bromoacetic acid (1 mmol), 1.5 g anhydrous sodium acetate in 40 cm^3 a mixture of *Ac*OH/Ac_2O (1/3) and 0.106 g benzaldehye (1 mmol) was refluxed for 6 h. The reaction mixture was cooled and poured onto ice–water, the obtained solid was collected by filtration and crystallized to give 0.4 g (82%) **16**. Mp 242–244°C (*Ac*OH/H_2O); IR (film): $\bar{\nu}=3365$–3298 (NH), 1712 (C=O) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta=1.32$ (t, CH_3, $J=6.98$ Hz), 3.80 (q, CH_2, $J=6.98$ Hz), 5.42 (d, H-a, pyrimidine), 6.78–7.44 (m, 3 thiophene-H + H-b pyrimidine + benzylic-H + *Ph*-H), 8.12–8.24 (m, 2 pyr-H) ppm; MS (EI, 70 eV): $m/z=478$ [M^+, 100, base peak].

Method B: A mixture of 0.292 g **15** (1 mmol) and 0.106 g benzaldehyde (1 mmol) in 40 cm^3 a mixture of *Ac*OH/Ac_2O (1/3) was refluxed for 5 h, allowed to cool, then poured onto water the solid formed was collected by filtration and crystallized to yield 0.35 g (74%) **16**, as identified by its mp; mixed mp and R_f value on TLC by comparison with authentic sample from method A.

Pharmacological screening
All animals were obtained from Animal House Colony, Research Institute of Ophthalmology, Giza, Egypt.

Determination of acute toxicity (LD_{50})
The LD_{50} for compounds were determined by injected different gradual increased doses of the tested compounds to adult mail albino rats, then calculate the dose cause 50% animal death, according to *Austen* and *Brocklehurst* [25] (Table 1).

Analgesic activity
Sixty *Webster* 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 (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) [26], relative potencies to Valdecoxib® were determined (Table 2).

Antiparkinsonian activity
Groups of eight mail mice (18–20 g) were used. They were dosed orally with the tested compounds (5 mg/kg) or the standard (Benzatropine®, 5 mg/kg) [27] 1 h prior to the administration of 0.5 mg/kg of Oxotremorine® S.C. Rectal temperature was measured before administration of the compounds and 1 h after Oxotremorine® dosage. The score for the recorded signs are zero (absent), one (slight), two (mediums), and three (highs) (Table 3).

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References

1. Amr AE, Mohamed AM, Ibrahim AA (2003) Z Naturforsch 58b:861
2. Amr AE, Abo-Ghalia MH, Mohamed MA (2006) Z Naturforsch 61b:1335
3. Amr AE, Abdel-Salam OI, Attia A, Stibor I (1999) Collect Czech Chem Commun 64:288
4. Amr AE (2000) Ind J Heterocyc Chem 10:49
5. Attia A, Abdel-Salam OI, Amr AE (1997) Egypt J Chem 40:317
6. Abo-Ghalia MH, Amr AE (2004) Amino Acids 26:283
7. Amr AE, Ashraf MM, Salwa FM, Naglaa AA, Abu El-Fotooh GH (2006) Bioorg Med Chem 14:5481
8. Amr AE (2005) Z Naturforsch 60b:990
9. Nehad AA, Amr AE, Alhusien AI (2007) Monatsh Chem 138:559
10. Amr AE, Abdel-Latif NA, Abdalla MM (2006) Acta Pharm 56:203
11. Amr AE, Abdel-Latif NA, Abdalla MM (2006) Bioorg Med Chem 14:273
12. Hammam AG, Fahmy AF, Amr AE, Mohamed AM (2003) Ind J Chem Sec B 42B:1985
13. Hammam AG, Naglaa AA, Wanda MH, Marian M (2000) Z Naturforsch 55b:417
14. Ali MI, Hammam AG (1981) J Chem Eng Data 26:352

15. Hammam AG, Mohie AS, Naglaa AA (2001) Ind J Chem Sec B 40B:213
16. Hammam AG, Hussain SM, Kotob IR (1990) Phosphorus Sulfur Silicon 47:47
17. Amr AE, Abdulla MM (2002) Ind J Heterocycl Chem 12:129
18. Amr AE, Hegab MI, Ibrahim AA, Abdulla MM (2003) Monatsh Chem 134:1395
19. Amr AE, Sayed HH, Abdulla MM (2005) Arch Pharm Chem Life Sci 338:433
20. Abo-Ghalia MH, Amr AE, Abdulla MM (2003) Z Naturforsch 58b:903
21. Amr AE, Abdalla MM (2006) Bioorg Med Chem 14:4341
22. Amr AE, Abdalla MM (2006) Arch Pharm Chem Life Sci 339:88
23. Amr AE, Nermien MS, Mohamed MA (2007) Monatsh Chem 138:699
24. Attia A, Abdel-Salam OI, Abou-GHalia MH, Amr AE (1995) Egypt J Chem 38:543
25. Austen KF, Brocklehurst WE (1961) J Exp Med 113:521
26. Tgolsen A, Rofland GH, Berge OG, Hole K (1991) J Pharmacol Ther 25:241
27. Tyahr MD (1976) The Basal Ganginia. Raven Press, New York, p 293

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