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Synthesis, Analgesic, and Antiparkinsonian Profiles of Some Pyridine, Pyrazoline, and Thiopyrimidine Derivatives

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Summary. A series of substituted pyridine, pyrazoline, and thiopyrimidine derivatives were synthesized from 3-acetylpyridine, which was prepared from nicotinic acid as a naturally starting material. The pharmacological screening showed that many of these compounds have good analgesic and antiparkinsonian activities comparable to Voltarene® and Benzatropine® as reference drugs. The structure assignment of the new compounds is based on chemical and spectroscopic evidence. The detailed synthesis, spectroscopic data, and pharmacological properties for synthesized compounds are reported.

Keywords. Nicotinic acid; Pyrazolines; Thiopyrimidine; Analgesic; Antiparkinsonian.

Introduction

Nicotinic acid and its derivatives constitute an important class of naturally occurring compounds, minute amounts of nicotinic acid occur in all living cells [1], and it exhibits a wide spectrum of biological activities [2, 3]. Previous work reported that certain substituted pyridines and their chiral macrocyclic derivatives have antidepressant, antimacrobial, anticancer, analgesic, and anticonvulsant activities [4–10]. Pyrazolines present an interesting group of compounds many of which possess wide-spread pharmacological properties, such as analgesic, antipyretic, and antirheumatic activities [11, 12]. These derivatives are also well known for their pronounced anti-inflammatory activity [13, 14] and are used as potent antidiabetic agents [15, 16]. In addition, the pharmacological and antitumor activities of many compounds containing pyrazoline rings have been reviewed [17–19]. Recently, these heterocyclic nitrogen derivatives have been shown to exhibit a general ionophoric potency for divalent cations [20] and have been used as a novel thiocyanate-selective membrane sensor [21]. 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, pyrazoline, or thiopyrimidine moiety and tested their analgesic and antiparkinsonian activities in comparison to Voltarene® and Benzatropine® as reference drugs.

Results and Discussion

Synthesis

In the present work we report on the synthesis and a preliminary biological activity screening of several pyridine derivatives based on 3-β-[(*p*-methoxyphenyl)acryloyl]pyridine (**2**). 3-Acetylpyridine (**1**) prepared from nicotinic acid according to Ref. [17] was reacted with *p*-methoxybenzaldehyde in refluxing ethanol in the presence of a mixture of triethylamine and diethylamine as a catalyst to yield 3-β-[(*p*-methoxyphenyl)acryloyl]pyridine (**2**). Condensation of **2** with hydroxylamine hydrochloride in refluxing

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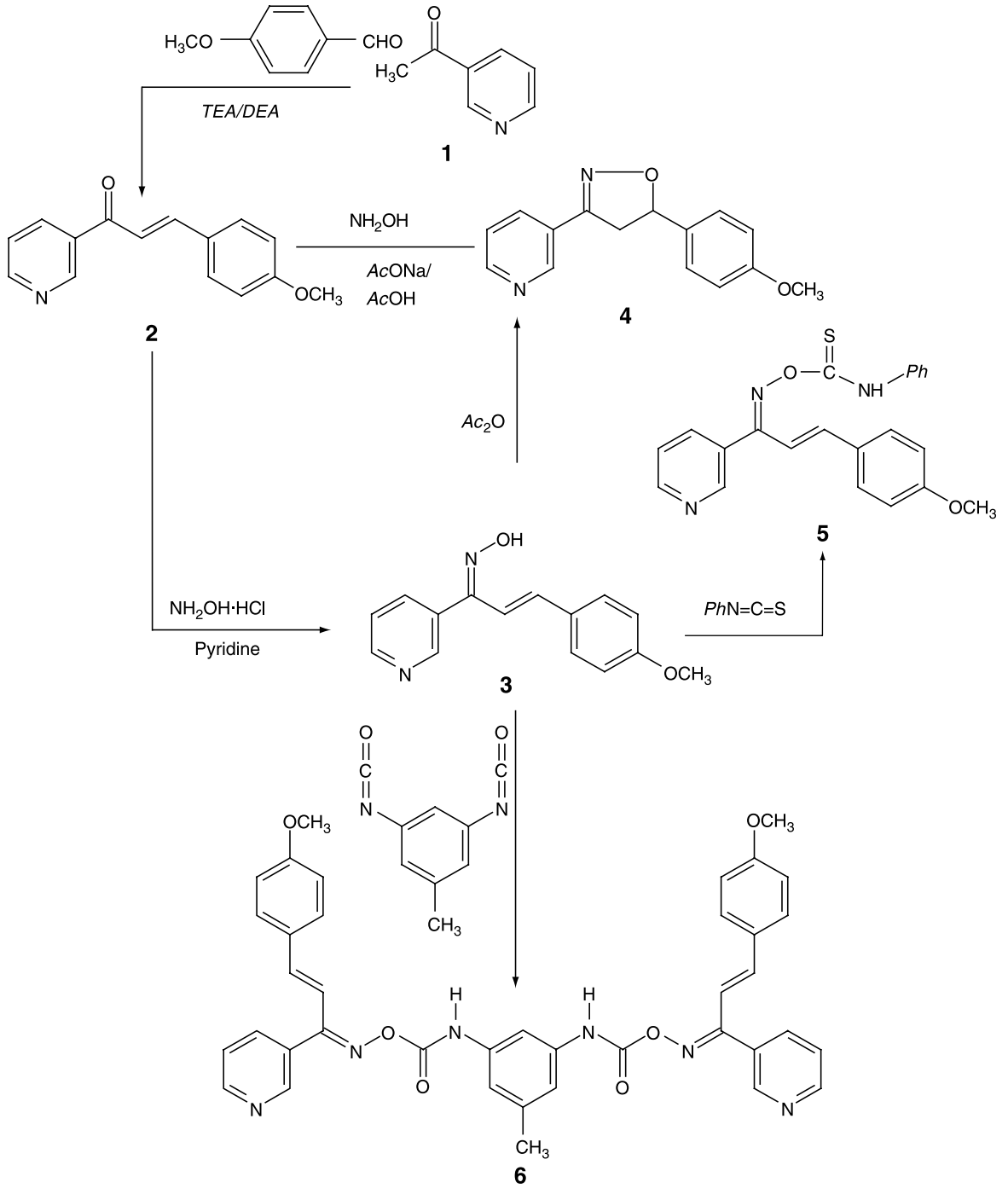
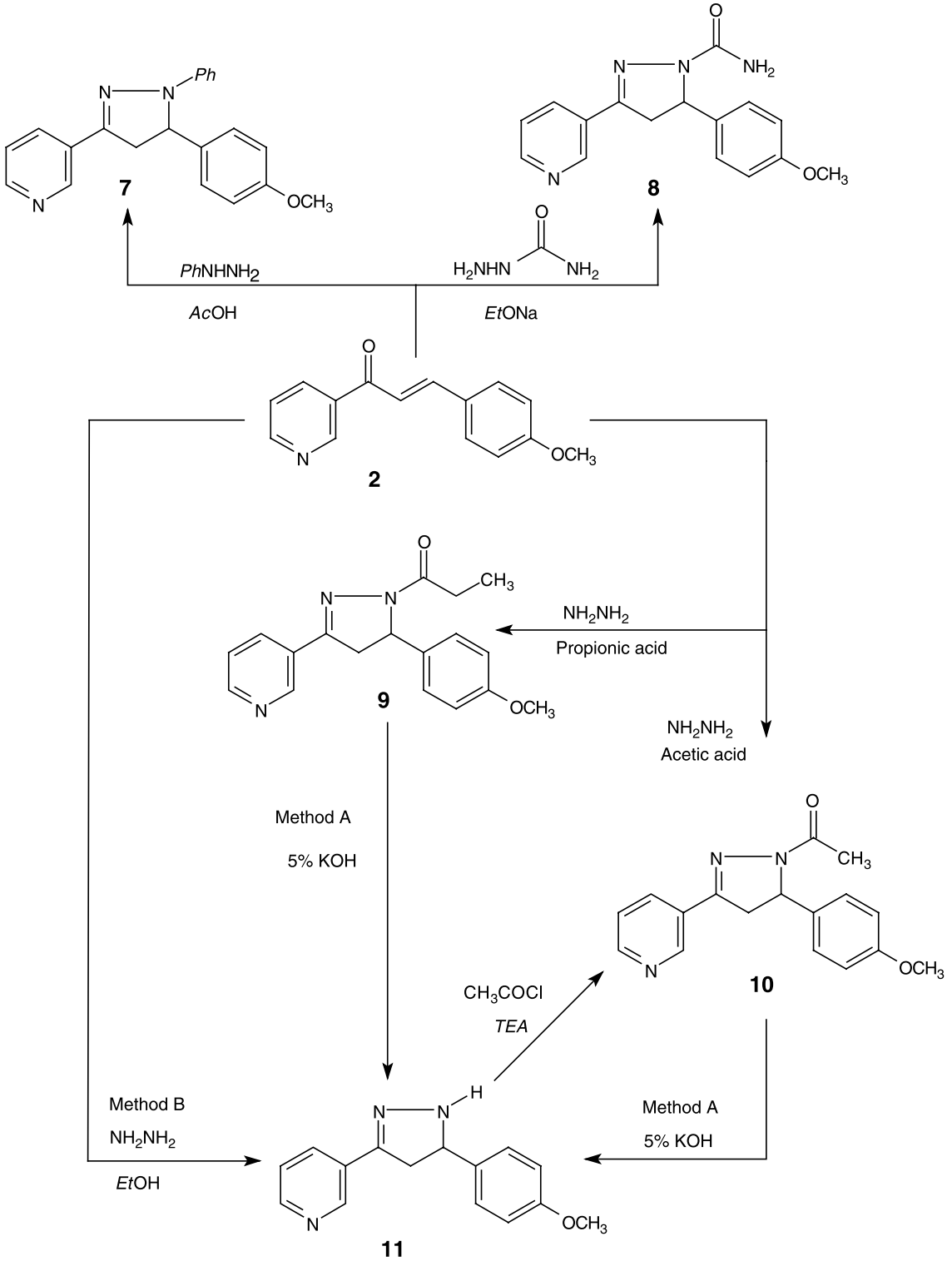


Scheme 1

pyridine with stirring afforded the corresponding 3-β-(*p*-methoxyphenyl)acryloylpyridine oxime **3** (Scheme 1). The latter was cyclized with refluxing acetic anhydride to the oxazole **4**, which was also prepared directly from **2** by reaction with hydroxylamine hydrochloride in the presence of anhydrous sodium acetate in refluxing acetic acid. Oxime **3** was treated with phenyl isothiocyanate or toluene-3,5-diisocyanate in refluxing dioxane to afford the phenyl thiosemicarbazide **5** and bissemicarbazide **6** (Scheme 1).

Condensation of **2** with phenylhydrazine in refluxing glacial acetic acid gave the *N*-phenylpyrazoline **7**, while **2** was reacted with semicarbazide hydrochloride to give the *N*-aminocarbonylpyrazoline **8**

(Scheme 2). Compound **2** was condensed with hydrazine hydrate in refluxing propionic acid or glacial acetic acid to afford the *N*-substituted pyrazolines **9** and **10**, which were hydrolyzed by refluxing in alcoholic potassium hydroxide to yield pyrazoline **11** (method A). The latter was obtained directly by con-

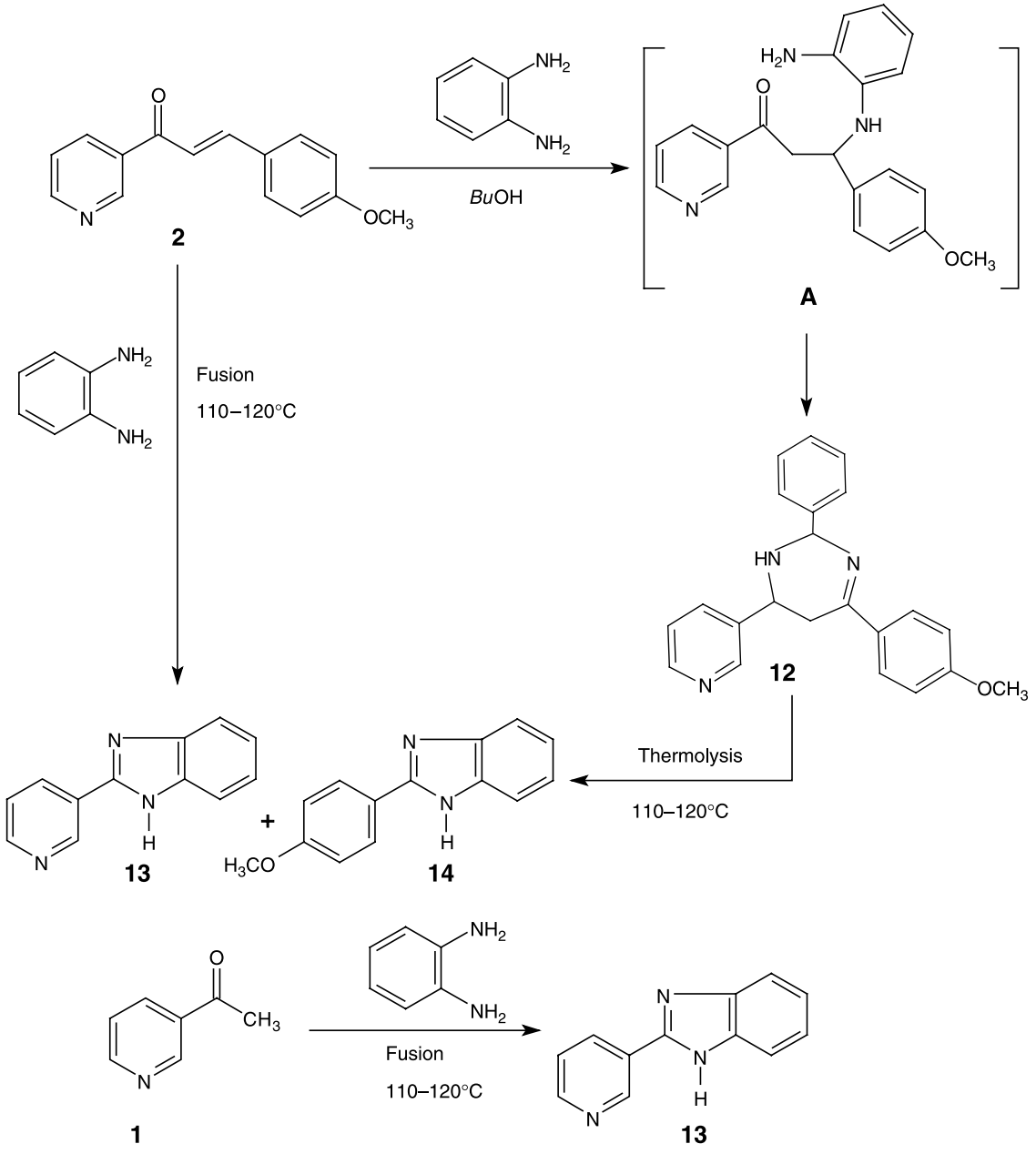


Scheme 2

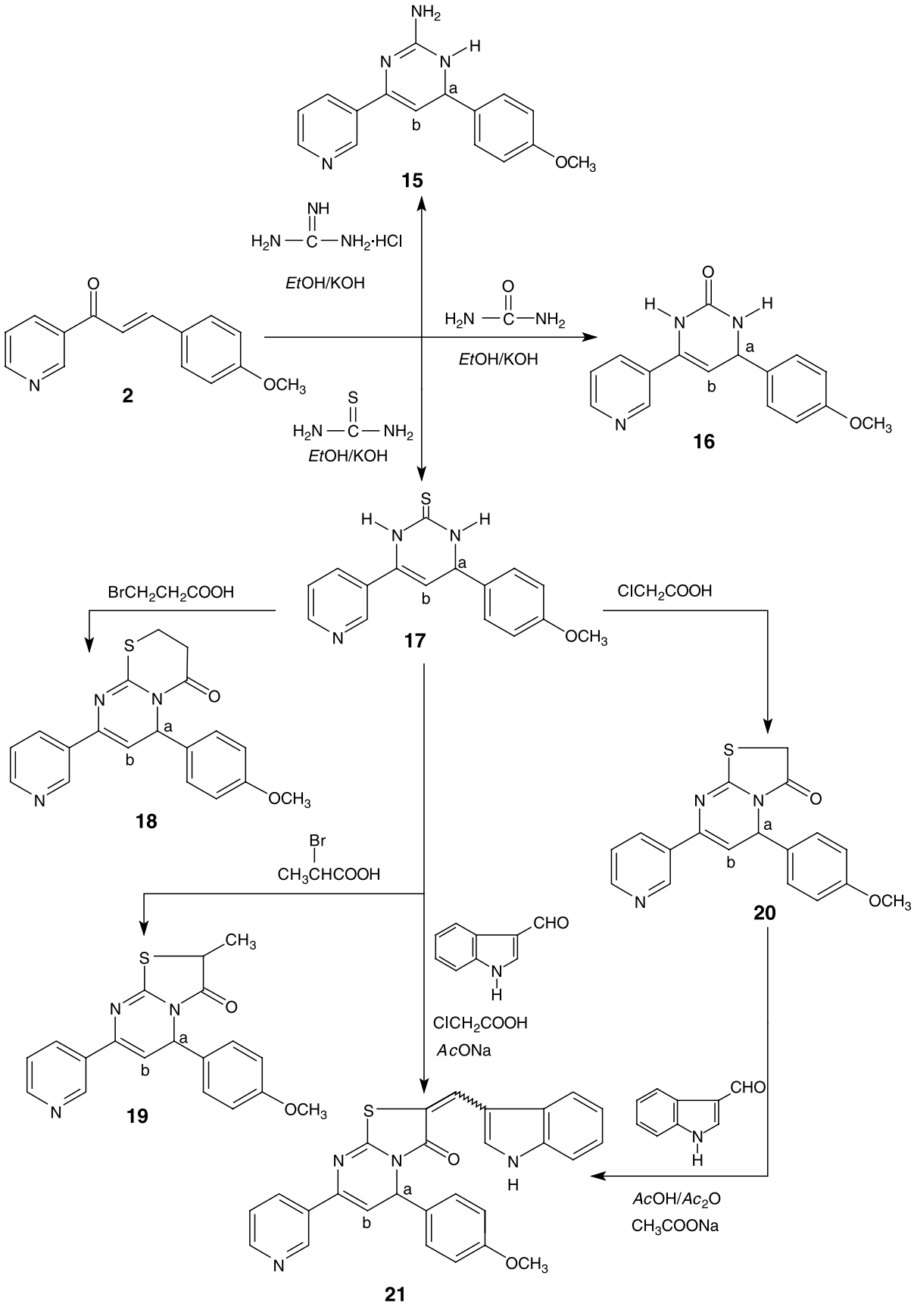
densation of acryloylpyridine **2** with hydrazine hydrate in refluxing ethanol (method B) (Scheme 2).

Several publications [22–24] have reported the reaction of 1,2-diamines with α,β-unsaturated ketones and the nature of the products varied according to the experimental conditions. The present work reports the reaction between **2** and *o*-phenylenediamine under different conditions. The uncatalysed reaction of **2** with *o*-phenylenediamine in refluxing butanol afforded the diazepine **12**. Formation of **12** was believed to proceed through the initial addition of the diamine to the ethylenic double bond of **2** followed by intramolecular condensation of the amino group with the carbonyl function affording **12** as the sole product (Scheme 3).

On the other hand, when equimolar amounts of **2** and *o*-phenylenediamine were fused together without solvent at 200–220°C, 2-(3-pyridyl)benzimidazole (**13**) was isolated as the main product along with 2-(*p*-methoxyphenyl)benzimidazole (**14**) [25] (Scheme 3). Moreover, thermolysis of the benzodiazepine derivative **12** at 200–220°C afforded the same



Scheme 3


15
2
16
17
18
19
20
21
EtOH/KOH
EtOH/KOH
EtOH/KOH
BrCH2CH2COOH
ClCH2COOH
CH3CHCOOH
ClCH2COOH
AcONa
AcOH/Ac2O
CH3COONa

Scheme 4

benzimidazoles **13** and **14** as identified by TLC. In addition, compound **13** was independently prepared for TLC comparison by fusion of acetyl derivative **1** with *o*-phenylenediamine at the same temperature (Scheme 3).

Condensation of **2** with diamines, namely, guanidine hydrochloride, urea, and thiourea in refluxing ethanolic potassium hydroxide afforded the 2-amino-, 2-carbonyl-, and 2-thiopyrimidines **15**–**17** (Scheme 4). Compound **17** was condensed with 3-bromopropionic acid, 2-bromopropionic acid, or chloroacetic acid in a mixture of acetic acid/acetic anhydride in the presence of anhydrous sodium acetate to yield the corresponding thiazino-, methylthiazolo-, and thiazolopyrimidines **18**–**20**. Compound **20** contains an active methylene group. As such it condensed with indole-3-carboxaldehyde in the presence of anhydrous sodium acetate and glacial acetic acid/acetic anhydride mixture to yield the arylmethylene **21**. However, the latter was also prepared directly from **17** by the action of chloroacetic acid, indole-3-carboxaldehyde, and anhydrous sodium acetate in the presence of acetic acid/acetic anhydride mixture (Scheme 4).

Pharmacological Screening

We tested two pharmacological activities namely, analgesic and antiparkinsonian, despite of their different biological receptors. Yet both are of neurological origin. Seven representative compounds **6**, **8**, **10**, **12**, **15**, **17**, and **21** were studied.

Analgesic Activity

All tested compounds exhibited analgesic activities (Table 1), the most potent one is **12** 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 **6** and **21** approached those of Voltarene®, and **8** had 31–47% activity as compared with Voltarene® (Table 1).

Antiparkinsonian Activity

Compounds **6**, **10**, and **15** showed moderate activity (relative potencies to Benzotropene® 0.44, 0.60, and 0.40). Compounds **8** and **12** are the most potent antiparkinsonic agents (0.80 relative potency) (Table 2).

Table 1. Analgesic activity of several 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
6	0.81	0.89	0.88	0.91	0.93	0.94	0.94
8	0.31	0.40	0.40	0.42	0.45	0.43	0.47
10	0.61	0.63	0.71	0.73	0.74	0.74	0.74
12	0.97	0.98	0.99	1.07	1.12	1.21	1.41
15	0.59	0.61	0.69	0.71	0.77	0.81	0.80
17	0.54	0.56	0.58	0.55	0.51	0.49	0.47
21	0.79	0.83	0.87	0.88	0.88	0.88	0.91

Table 2. Antiparkinsonian activity of several compounds as compared with Benzotropene®

Comp. no.	Salivation and lacrimation score	Tremors score	% Decrease from Oxotremerine® rectal temp.	Relative potency to Benzotropene®
Control	0	0	0	0
Benzotropene®	1	1	25	1
6	2	2	11	0.44
8	1	1	20	0.80
10	2	2	15	0.60
12	1	1	20	0.80
15	2	2	10	0.40
17	3	3	4	0.16
21	3	3	3	0.12

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, Centre of Molecular and Macromolecular Studies, Polish Academy of Science, Poland. The mass spectra were performed using a VG 2AB-3F spectrometer (70 eV). All reactions were followed by TLC (silica gel, aluminum sheets 60 F_{254}, Merck).

3-[β-(p-Methoxyphenyl)acryloyl]pyridine (**2**, $C_{15}H_{13}NO_2$)
A mixture of 0.12 g 3-acetylpyridine (**1**) (1 mmol), 0.14 g *p*-methoxybenzaldehyde (1 mmol), and 3 cm^3 triethylamine/diethylamine in 50 cm^3 absolute ethanol was heated under reflux for 4 h. The reaction mixture was evaporated under reduced pressure to dryness. The obtained solid was triturated with diethyl ether, filtered off, air-dried, and crystallized to afford 0.18 g (78%) **2**. Mp 230–232°C (*Ac*OH/H_2O); IR (film): $\bar{\nu} = 1682$ (C=O), 1610 (C=C) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 3.65$ (s, OCH_3), 6.42 (d, $J = 14.65$ Hz, CH-olefinic), 6.85 (d, $J = 14.65$ Hz, CH-olefinic), 7.10–7.45 (m, *Ar*-H), 7.78–8.30 (m, pyrid-4,5,6), 8.70 (s, pyrid-2) ppm; MS (EI, 70 eV): m/z (%) = 239 [M^+, 25], 161 [100, base peak].

3-[β-(p-Methoxyphenyl)acryloyl]pyridine oxime
(**3**, $C_{15}H_{14}N_2O_2$)
A mixture of 0.24 g **2** (1 mmol) and ~0.1 g hydroxylamine hydrochloride (1 mmol) in 30 cm^3 dry pyridine was refluxed for 6 h. The reaction mixture was cooled, poured into ice, and neutralized with 1 *N* HCl. The obtained solid was filtered, dried (under vacuum), and crystallized to give 0.21 g (82%) **3**. Mp 198–199°C *Et*OH/H_2O); IR (film): $\bar{\nu} = 3540$–3360 (OH), 1675 (C=N), 1610 (C=C) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.50$ (s, OH, exchangeable with D_2O), 3.62 (s, OCH_3), 6.38 (d, $J = 14.58$ Hz, CH-olefinic), 6.86 (d, $J = 14.60$ Hz, CH-olefinic), 6.95–7.35 (m, *Ar*-H), 7.75–8.25 (m, pyrid-4,5,6), 8.72 (s, pyrid-2) ppm; MS (EI, 70 eV): m/z (%) = 254 [M^+, 100, base peak].

2-(3-Pyridyl)-4-(p-methoxyphenyl)oxazole (**4**, $C_{15}H_{14}N_2O_2$)
Method A: A solution of 0.24 g **2** (1 mmol) in 50 cm^3 acetic anhydride was refluxed for 10 h. After cooling, the reaction mixture was poured into ice, the obtained solid was filtered off, washed with water, dried under reduced pressure, and crystallized to give 0.19 g (74%) **4**. Mp 176–178°C (*Ac*OH); IR (film): $\bar{\nu} = 1670$ (C=N), 1610 (C=C) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.50$–1.85 (m, CH_2-oxazole), 3.62 (s, OCH_3), 4.20 (m, CH-oxazole), 6.92–7.45 (m, *Ar*-H), 7.82–8.32 (m, pyrid-4,5,6), 8.72 (s, pyrid-2) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 55.90$ (OCH_3), 42.15, 77.75, 154.90 (oxazole-C), 114.30, 127.70, 134.86, 157.65 (*Ph*-C), 122.75, 125.10, 136.15, 149.50, 150.90 (pyridine-C) ppm; MS (EI, 70 eV): m/z (%) = 254 [M^+, 35], 122 [100, base peak].

Method B: A mixture of 0.24 g **2** (1 mmol), ~0.1 g hydroxylamine hydrochloride (1 mmol), and 0.082 g anhydrous sodium acetate (1 mmol) in 30 cm^3 glacial acetic acid was heated under reflux for 6 h. The reaction mixture was cooled, poured into ice, the obtained solid was collected by filtration, washed with water, air dried, and crystallized to give 0.17 g (66%) **4**, as identified by m.p. and TLC in comparison with an authentic sample from method A.

Thiosemicarbazide and Bissemicarbazide ***5*** and ***6***
A mixture of 0.254 g **3** (1 mmol) and phenyl isothiocyanate or toluene-3,5-diisocyanate (1 mmol) in 50 cm^3 dry dioxane containing 1 cm^3 triethylamine was heated under reflux for ~8 h. The solvent was evaporated under reduced pressure, and the obtained residue was solidified with *n*-hexane. The obtained solid was filtered off, washed with diethyl ether, air dried, and crystallized to give 0.26 g (68%) thiosemicarbazide **5** and 0.37 g (55%) biscarbazide **6**.

3-[β-(p-Methoxyphenyl)acryloyl phenyl thiosemicarbazide]pyridine (**5**, $C_{22}H_{19}N_3O_2S$)
Mp 213–215°C (dioxane); IR (film): $\bar{\nu} = 3336$–3250 (NH), 1665 (C=N), 1228 (C=S) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 3.60$ (s, OCH_3), 4.15–4.25 (bs, NH-CS, exchangeable with D_2O), 6.35 (d, $J = 14.60$ Hz, CH-olefinic), 6.52 (d, $J = 14.65$ Hz, CH-olefinic), 6.95–7.35 (m, *Ar*-H), 7.88–8.42 (m, pyrid-4,5,6), 8.86 (s, pyrid-2) ppm; MS (EI, 70 eV): m/z (%) = 389 [M^+, 32], 136 [100, base peak].

3,5-Bis{3-[β-(p-methoxyphenyl)acryloylsemicarbazide] pyridine}toluene (**6**, $C_{39}H_{34}N_6O_6$)
Mp 188–189°C (dioxane); IR (film): $\bar{\nu} = 3390$–3260 (NH), 1705–1695 (C=O), 1675–1665 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.25$ (s, CH_3), 3.64 (s, OCH_3), 6.25 (d, $J = 14.60$ Hz, 2CH-olefinic), 6.55 (d, $J = 14.65$ Hz, 2CH-olefinic), 6.85–7.40 (m, *Ar*-H), 7.82–8.40 (m, 2 pyrid-4,5,6), 8.65 (s, NHCO, exchangeable with D_2O), 8.86 (s, 2 pyrid-2) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 18.65$ (CH_3), 55.90 (OCH_3), 110.85, 114.65, 116.18, 127.32, 127.86, 135.80, 137.60, 158.76 (*Ph*-C), 122.75, 125.18, 136.32, 150.50, 150.95 (pyridine-*C*), 137.28, 142.55 (CH=CH), 152.80 (C=O), 163.15 (C=N) ppm; MS (EI, 70 eV): m/z (%) = 682 [M^+, 10], 237 [100, base peak].

2-Phenyl-3-(p-methoxyphenyl)-3,4-dihydro-5-(3-pyridyl) pyrazoline (**7**, $C_{21}H_{19}N_3O$)
A mixture of 0.24 g **2** (1 mmol) and 0.16 g phenylhydrazine (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 reduced pressure, and crystallized to give 0.25 g (76%) **7**. Mp 215–217°C (*Me*OH/H_2O); IR (film): $\bar{\nu} = 1672$ (C=N), 1612 (C=C) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.70$–2.05 (m, CH_2-pyrazoline), 3.60 (s, OCH_3), 3.85 (m, CH-pyrazoline), 6.65–7.35 (m, *Ar*-H), 7.66–8.652 (m, pyrid-4,5,6), 8.85 (s, pyrid-2) ppm; MS (EI, 70 eV): m/z (%) = 329 [M^+, 35], 221 [100, base peak].

2-Aminocarbonyl-3-(p-methoxyphenyl)-3,4-dihydro-5-(3-pyridyl)pyrazoline (**8**, $C_{16}H_{16}N_4O_2$)
A solution of 0.24 g **2** (1 mmol) and 1.5 g semicarbazide hydrochloride (1.5 mmol) in sodium ethoxide [460 mg sodium metal (20 mmol) in 25 cm^3 absolute ethanol] was refluxed for 8 h. The reaction mixture was acidified with 1 *N* hydrochloric acid. The obtained solid was filtered off, washed with water, air dried, and crystallized to give 0.26 g (88%) **8**. Mp 155–157°C (dioxane); IR (film): $\bar{\nu} = 3340–3215$ (NH_2), 1670 (C=O), 1656 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.80–2.00$ (m, CH_2-pyrazoline), 3.62 (s, OCH_3), 3.95 (m, CH-pyrazoline), 5.45 (s, NH_2, exchangeable with D_2O), 6.95–7.25 (m, *Ar*-H), 7.68–8.35 (m, pyrid-4,5,6), 8.86 (s, pyrid-2) ppm; MS (EI, 70 eV): m/z (%) = 296 [M^+, 15], 172 [100, base peak].

*2-Substituted Pyrazolines **9** and **10***
A mixture of 0.24 g **2** (1 mmol) and 0.4 cm^3 hydrazine hydrate (8 mmol) in 15 cm^3 propionic acid or glacial acetic acid was heated under reflux for ~7 h. The reaction mixture was poured onto ice, then neutralized with sodium bicarbonate. The formed precipitate was collected by filtration, washed with water, air dried, and crystallized to give 0.2 g (65%) **9** and 0.22 g (75%) **10**.

2-Acetyl-3-(p-methoxyphenyl)-3,4-dihydro-5-(3-pyridyl)pyrazoline (**9**, $C_{18}H_{19}N_3O_2$)
Mp 245–246°C (*Et*OH/H_2O); IR (film): $\bar{\nu} = 1715$ (C=O), 1660 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.15$ (t, CH_3), 1.75–2.05 (m, CH_2-pyrazoline), 2.15 (m, CH_2), 3.65 (s, OCH_3), 3.88 (m, CH-pyrazoline), 7.05–7.30 (m, *Ar*-H), 7.70–8.25 (m, pyrid-4,5,6), 8.85 (s, pyrid-2) ppm; MS (EI, 70 eV): m/z (%) = 309 [M^+, 10], 172 [100, base peak].

2-Ethylcarbonyl-3-(p-methoxyphenyl)-3,4-dihydro-5-(3-pyridyl)pyrazoline (**10**, $C_{17}H_{17}N_3O_2$)
Mp 186–188°C (MeOH/H_2O); IR (film): $\bar{\nu} = 1718$ (C=O), 1662 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.80$ (s, CH_3), 1.90–2.15 (m, CH_2-pyrazoline), 3.66 (s, OCH_3), 3.86 (m, CH-pyrazoline), 7.00–7.35 (m, *Ar*-H), 7.68–8.15 (m, pyrid-4,5,6), 8.84 (s, pyrid-2) ppm; MS (EI, 70 eV): m/z (%) = 295 [M^+, 45], 174 [100, base peak].

3-(p-Methoxyphenyl)-3,4-dihydro-5-(3-pyridyl)pyrazoline (**11**, $C_{15}H_{15}N_3O$)
Method A: A solution of **9** or **10** (1 mmol) in 15 cm^3 ethanolic potassium hydroxide (5%) was refluxed for 4–6 h. The reaction mixture was acidified with 1 *N* HCl, the obtained solid was filtered off, washed with water, dried, and crystallized to give 0.22 g (88%) **11**. Mp 156–158°C *Me*OH); IR (film): $\bar{\nu} = 3335–3225$ (NH), 1665 (C=O), 1658 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.78–2.05$ (m, CH_2-pyrazoline), 3.63 (s, OCH_3), 3.86 (m, CH-pyrazoline), 6.55 (s, NH, exchangeable with D_2O), 6.98–7.35 (m, *Ar*-H), 7.78–8.25 (m, pyrid-4,5,6), 8.96 (s, pyrid-2) ppm; MS (EI, 70 eV): m/z (%) = 253 [M^+, 25], 121 [100, base peak].

Method B: A mixture of 0.24 g **2** (1 mmol) and 0.4 cm^3 hydrazine hydrate (8 mmol) in 25 cm^3 ethanol was refluxed for ~5 h. The solvent was evaporated under reduced pressure to dryness, the residue was solidified with water, filtered off, washed with water, dried, and crystallized to give 0.14 g (55%) **11**, as identified by m.p. and R_f values in comparison with authentic samples from the above method A.

2-(Pyridin-3-yl)-4-(p-methoxyphenyl)benzo[b]diazipene (**12**, $C_{21}H_{19}N_3O$)
A mixture of 0.24 g **2** (1 mmol) and 0.11 g *o*-phenylenediamine (1 mmol) in 30 cm^3 dry butanol was heated under reflux and followed up by TLC. The reaction was completed after 18 h and the solvent was evaporated under reduced pressure to dryness. The oily product was triturated with petroleum ether (40–60°C) and the separated solid was filtered off, washed with petroleum ether (40–60°C), dried, and crystallized to give 0.24 g (74%) **12**. Mp 165–167°C (*Et*OH/*n*-hexane); IR (film): $\bar{\nu} = 3380–3342$ (NH), 1605 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 3.15$ (d, CH_2-diazepine), 3.68 (s, OCH_3), 4.05 (m, CH-diazepine), 6.78–7.60 (m, *Ar*-H), 7.76-8.45 (m, pyrid-4,5,6), 8.65 (s, pyrid-2), 10.15 (s, NH-diazepine, exchangeable with D_2O) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta =$ 42.30 (CH_2), 55.80 (OCH_3), 58.25 (CH), 113.80, 113.95, 117.65, 122.10, 125.68, 127.10, 129.75, 137.54, 144.25 162.40, (*Ar*-C), 122.75, 126.65, 136.48, 149.75, 151.05 (pyridine-*C*), 161.05 (C=N) ppm; MS (EI, 70 eV): m/z (%) = 329 [M^+, 15], 312 [100, base peak].

*Formation of Benzimidazoles **13** and **14***
Equimolar amounts of 0.24 g **2** (1 mmol) and 0.11 g *o*-phenylenediamine (1 mmol) were fused together in an oil bath at 200–220°C for 6 h. The obtained solid was crushed and extracted with hot benzene. The benzene extract was evaporated under reduced pressure to dryness and the residue was solidified with petroleum ether (40–60°C) to give 0.07 g (36%) 2-(3-pyridyl)benzimidazole (**13**), mp 133–135°C. The undissolved residue left after extraction with benzene was dissolved in a mixture of ethanol/methanol. The solution was evaporated under reduced pressure, and the obtained residue was solidified with *n*-hexane to give 0.1 g (45%) 2-(*p*-methoxyphenyl)benzimidazole (**14**), mp 215–217°C (Lit. mp 214–216°C) [25].

*Thermolysis of Benzodiazipine **12***
Benzodiazipine **12** (0.33 g, 1 mmol) was heated in an oil bath at 200–220°C for 6 h. The dark mass was crushed and extracted with boiling benzene. The benzene extract was evaporated to dryness and crystallized from benzene/petroleum ether (40–60°C) to give 0.05 g (28%) **13**. The residue left after extraction with benzene was dissolved in ethanol/methanol. The solution was evaporated under reduced pressure, and the obtained residue was crystallized from ethanol/petroleum ether (40–60°C) to give 0.08 g (35%) **14**. The obtained products were identified by m.p. and R_f values in comparison with authentic samples from the above method.

2-(3-Pyridyl)benzimidazole (**13**, $C_{12}H_9N_3$)
A mixture of 0.12 g **1** (1 mmol) and 0.11 g *o*-phenylenediamine (1 mmol) was fused in an oil bath at 200–220°C for

6 h. The obtained residue was solidified with methanol, filtered off, and crystallized to give 0.1 g (55%) **13**. The product was identified by its mp and R_f value in comparison with an authentic sample. Mp 133–135°C (*Et*OH/pet. ether]; IR (film): $\bar{\nu} = 3380–3342$ (NH), 1610 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 7.15–7.65$ (m, *Ar*-H), 7.75–8.55 (m, pyrid-4,5,6), 8.76 (s, pyrid-2), 8.62 (s, NH-imidazole, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 195 [M^+, 100, base peak].

Substituted Pyrimidines ***15–17***

General Procedure

Diamino compounds, namely, guanidine hydrochloride, urea, and thiourea (1 mmol) were added to 0.24 g **2** (1 mmol) in 100 cm^3 ethanolic potassium hydroxide (1%). The reaction mixture was refluxed for 4–6 h and then poured gradually with stirring into cold water. The solid formed was filtered off, washed with H_2O, and crystallized to give **15–17**.

2-Amino-6-(pyridin-3-yl)-3,4-dihydro-4-(p-methoxyphenyl) pyrimidine (**15**, $C_{16}H_{16}N_4O$)

Yield 0.19 g (68%); mp 240–242°C (*Ac*OH/H_2O); IR (film): $\bar{\nu} = 3440–3320$ (NH, NH_2) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.62$ (s, OCH_3), 4.55 (s, NH-pyrimidine, exchangeable with D_2O), 5.15 (d, H-a, pyrimidine), 6.75–7.25 (m, *Ar*-H + H-b pyrimidine), 6.60 (bs, NH_2, exchangeable with D_2O), 7.76–8.45 (m, pyrid-4,5,6), 8.74 (s, pyrid-2) ppm; MS (EI, 70 eV): m/z (%) = 280 [M^+, 15], and at 233 [100, base peak].

6-(Pyridin-3-yl)-1,2,3,4-tetrahydro-2-oxo-4-(p-methoxyphenyl) pyrimidine (**16**, $C_{16}H_{15}N_3O_2$)

Yield 0.18 (66%); mp 246–248°C (*DMF*/H_2O); IR (film): $\bar{\nu} = 3348–3265$ (NH), 1668 (C=O) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.66$ (s, OCH_3), 5.35 (d, H-a, pyrimidine), 6.80–7.20 (m, *Ar*-H + H-b pyrimidine), 7.86–8.64 (m, pyrid-4,5,6), 8.30 and 8.55 (2s, 2NH-pyrimidine, exchangeable with D_2O), 8.78 (s, pyrid-2) ppm; MS (EI, 70 eV): m/z (%) = 281 [M^+, 100, base peak].

6-(Pyridin-3-yl)-1,2,3,4-tetrahydro-2-thioxo-4-(p-methoxyphenyl) pyrimidine (**17**, $C_{16}H_{15}N_3OS$)

Yield 0.23 (79%); mp >250°C (*Ac*OH/H_2O); IR (film): $\bar{\nu} = 3368–3255$ (NH), 1665 (C=O), 1215 (C=S) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.63$ (s, OCH_3), 5.18 (d, H-a, pyrimidine), 6.85–7.26 (m, *Ar*-H + H-b pyrimidine), 7.82–8.46 (m, pyrid-4,5,6), 8.28 and 8.45 (2s, 2NH-pyrimidine, exchangeable with D_2O), 8.76 (s, pyrid-2) ppm; MS (EI, 70 eV): m/z (%) = 297 [M^+, 5], and at 112 [100, base peak].

Thiazino- and Thiazolopyrimidines ***18–20***

General Procedure

A mixture of 0.297 g **17** (1 mmol) and halo compounds, namely 3-bromopropionic acid, 2-bromopropionic acid, and chloroacetic 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 and then refluxed for 6–7 h. The reaction mixture was cooled and poured into cold water with stirring, the solid formed was filtered off and crystallized to give 0.24 g (68%) **18**, 0.29 g (82%) **19**, and 0.27 g (80%) **20**.

3-(6-p-Methoxyphenyl-2,3-dihydro-6H-thiazino[3,2-a]pyrimidin-4-one-8-yl)pyridine (**18**, $C_{19}H_{17}N_3O_2S$)

Mp 235–237°C (*Ac*OH/H_2O); IR (film): $\bar{\nu} = 1725$ (C=O) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.40–3.55$ (m, $2CH_2$ thiazine ring), 3.64 (s, OCH_3), 5.36 (d, H-a, pyrimidine), 6.72–7.15 (m, *Ar*-H + H-b pyrimidine), 7.79–8.48 (m, pyrid-4,5,6), 8.84 (s, pyrid-2) ppm; MS (EI, 70 eV): m/z (%) = 351 [M^+, 12], 166 [100, base peak].

7-(Pyridin-3-yl)-5-(p-methoxyphenyl)-2,3-dihydro-5H-3-methylthiazolo[3,2-a]pyrimidine (**19**, $C_{19}H_{17}N_3O_2S$)

Mp 224–246°C (*DMF*/H_2O); IR (film): $\bar{\nu} = 1705$ (C=O) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.36$ (s, 3H, CH_3), 3.55 (m, 1H, thiazole), 3.64 (s, OCH_3), 5.45 (d, H-a, pyrimidine), 6.82–7.18 (m, *Ar*-H + H-b pyrimidine), 7.84–8.65 (m, pyrid-4,5,6), 8.82 (s, pyrid-2) ppm; MS (EI, 70 eV): m/z (%) = 351 [M^+, 10], 152 [100, base peak].

7-(Pyridin-3-yl)-5-(p-methoxyphenyl)-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine (**20**, $C_{18}H_{15}N_3O_2S$)

Mp 210–212°C (*Ac*OH/H_2O); IR (film): $\bar{\nu} = 1712$ (C=O) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.66$ (s, OCH_3), 3.74 (s, CH_2-thiazole), 5.24 (d, H-a, pyrimidine), 6.80–7.15 (m, *Ar*-H + H-b pyrimidine), 7.78–8.52 (m, pyrid-4,5,6), 8.81 (s, pyrid-2) ppm; MS (EI, 70 eV): m/z (%) = 337 [M^+, 5], 152 [100, base peak].

7-(Pyridin-3-yl)-2-(indolylmethylene)-5-(p-methoxyphenyl)-2,3-dihydro-5-thiazolo[3,2-a]pyrimidine (**21**, $C_{27}H_{20}N_4O_2S$)

Method A: A mixture of 0.297 g **17** (1 mmol), 0.094 g chloroacetic acid (1 mmol), 1.5 g anhydrous sodium acetate in 40 cm^3 of a mixture of *Ac*OH/Ac_2O (1/3) and 0.145 g indole-3-carboxaldehyde (1 mmol) was refluxed for 6 h. The reaction mixture was cooled and poured into ice-water, the obtained solid was collected by filtration and crystallized to give 0.39 g (84%) **21**. Mp 232–234°C (*Et*OH/H_2O); IR (film): $\bar{\nu} = 3355–3325$ (NH), 1716 (C=O) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.64$ (s, OCH_3), 5.55 (d, H-a, pyrimidine ring), 6.70–7.45 (m, indole-H + H-b pyrimidine ring + *Ar*-H + benzylic proton), 7.80–8.45 (m, pyrid-4,5,6), 8.72 (s, pyrid-2), 9.68 (s, NH-indole, exchangeable with D_2O) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 45.05$ (C-a), 55.86 (OCH_3), 119.65 (C-b), 110.15, 111.35, 118.10, 119.22, 121.34, 122.94, 126.15, 135.80 (indole-C), 113.65, 127.12, 134.67, 157.26 (*Ph*-C), 141.10, 162.20 (pyrimidine-C), 141.38 (CH-benzylic-C), 120.85 (thiazole-C), 122.86, 126.32, 130.12, 149.58, 150.81 (pyridine-*C*), 165.65 (C=O) ppm; MS (EI, 70 eV): m/z (%) = 464 [M^+, 100, base peak].

Method B: A mixture of 0.337 g **20** (1 mmol) and 0.145 g indole-3-carboxaldehyde (1 mmol) in 40 cm^3 of a mixture of *Ac*OH/Ac_2O (1/3) was refluxed for 5 h, allowed to cool, then poured into water, and the solid formed was collected by filtration and crystallized to yield 0.33 g (72%) **21**, as identified by its m.p., mixed m.p., and R_f value on TLC by comparison with an authentic sample from method A.

Pharmacology Screening

Analgesic Activity

Sixty mice of both sexes weighting from 20 to 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 **6**, **8**, **10**, **12**, **15**, **17**, and **21** (SC administration). Mice were dropped gently in a dry glass beaker of one liter capacity maintained at 55–55.5°C. Normal reaction times 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) [26]. Relative potencies to Voltarene® were determined (Table 1).

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 male 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) [27] 1 h prior the administration of 0.5 mg/kg of Oxotremerine® SC. 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 2).

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