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Synthesis, Reactions, and Pharmacological Activities of Some Pyrimidines Using (*N*-Methylindolyl)acetic Acid as Synthon

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Summary. A series of pyrimidinones, thienopyrimidines, and their derivatives were synthesized using *N*-methylindolyl acetic acid as a starting material. Sixteen new heterocyclics containing a pyrimidine ring were thus prepared. 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 assignments of the new compounds based on chemical and spectroscopic evidence. The detailed synthesis, spectroscopic data, and pharmacological properties are reported.

Keywords. Indole acetic acid; Pyrimidines; Thienopyrimidines, Antimicrobial agents.

Introduction

Pyrimidines and fused pyrimidines, being an integral part of *DNA* and *RNA*, play an essential role in several biological processes and have considerable chemical and pharmacological importance, particularly, the pyrimidine ring can be found in nucleoside antibiotics, antibacterials, cardio-vascular as well as agro chemical and veterinarian products [1–9]. In view of these observations and in continuation of our interest in developing efficient syntheses of polyfunctionally substituted heterocycles we used the readily obtainable pyrimidines as starting materials [10–13]. Pyrimidines present an interesting group of compounds many of which possess wide-spread pharmacological properties such as analgesic, antiarrhythmic, and anticancer activities [14–16]. Recently, some new substituted pyrimidine derivatives have been synthesized, which exhibit analgetic, antiinflammatory, antiparkinsonian, and androgenic-anabolic activities [17–22]. In view of these observations and as continuation of our previous work on pyrimidine chemistry, we synthesized some new compounds containing pyrimidine and indole moieties, and tested their analgesic and antiparkinsonian activities in comparison to Voltarene® and Benzatropine® as reference drugs.

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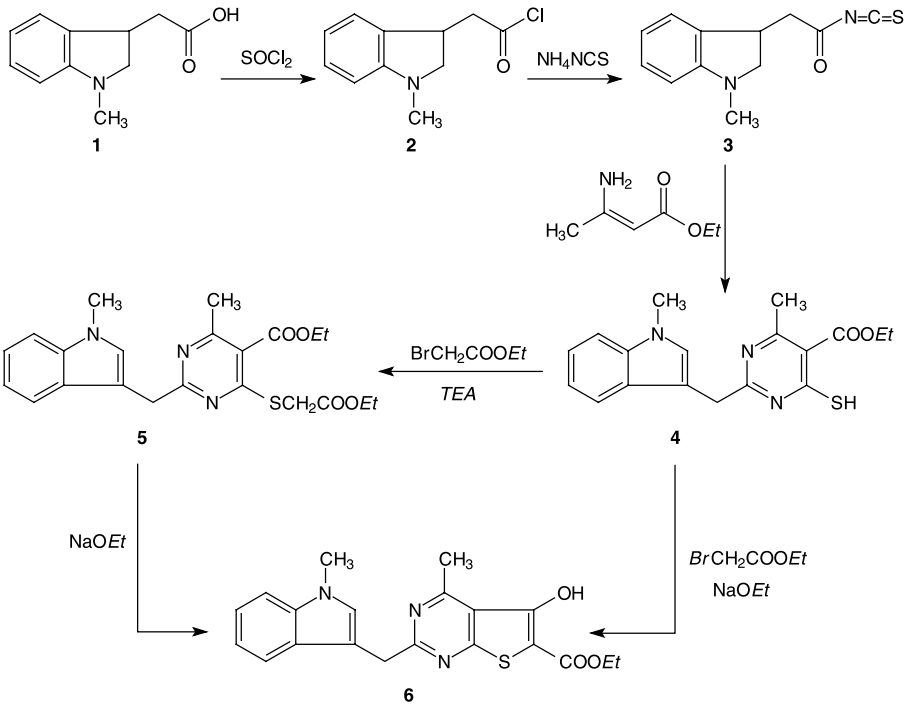
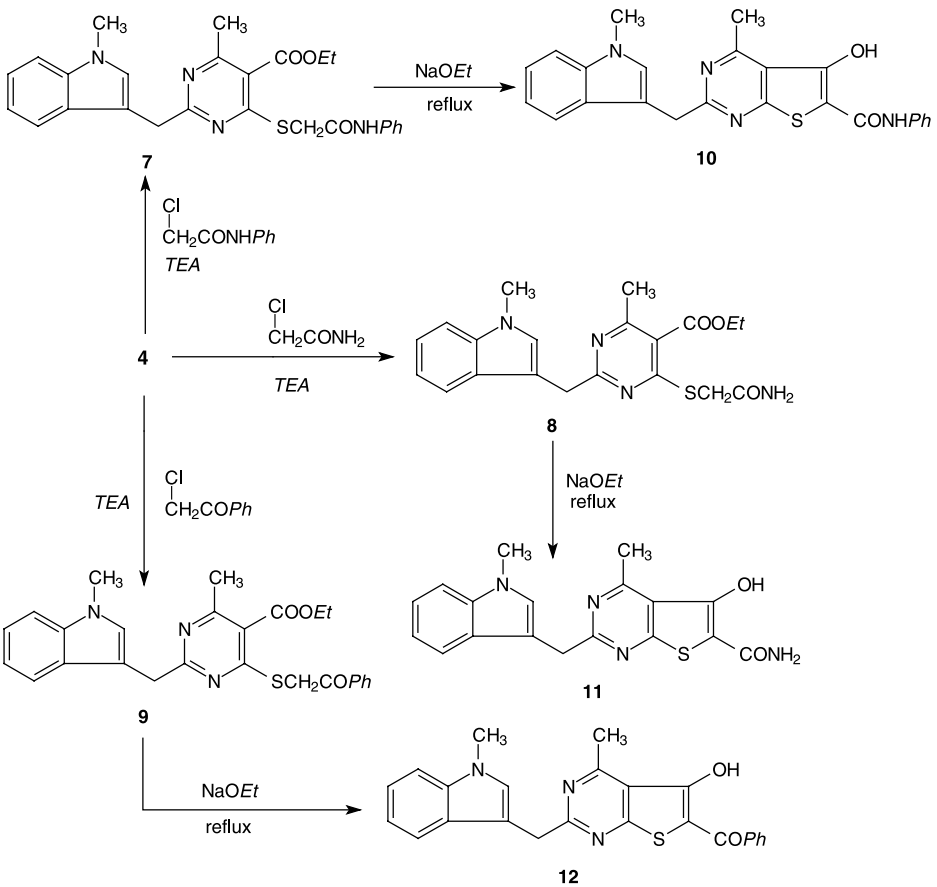
Results and Discussion

Synthesis

In the present work we report the synthesis and a preliminary biological activity screening of several pyrimidine derivatives based on 2-[(*N*-methylindolyl)methyl]-4-methyl-5-ethoxycarbonyl-6-mercaptopyrimidine (**4**), which was prepared from *N*-methylindolyl-3-acetic acid (**1**) according to Ref. [23] (Scheme 1). The reaction of 6-mercaptopyrimidine **4** with ethyl bromoacetate in the presence of triethylamine (*TEA*) produced ethoxycarbonylmethyl-mercaptopyrimidine **5**, which was refluxed with ethanolic sodium ethoxide to yield the corre-



Scheme 1



Scheme 2

sponding thieno[2,3-*d*]pyrimidine **6**. However, the latter was also prepared directly from **4** by refluxing with ethyl bromoacetate in the presence of sodium ethoxide (Scheme 1).

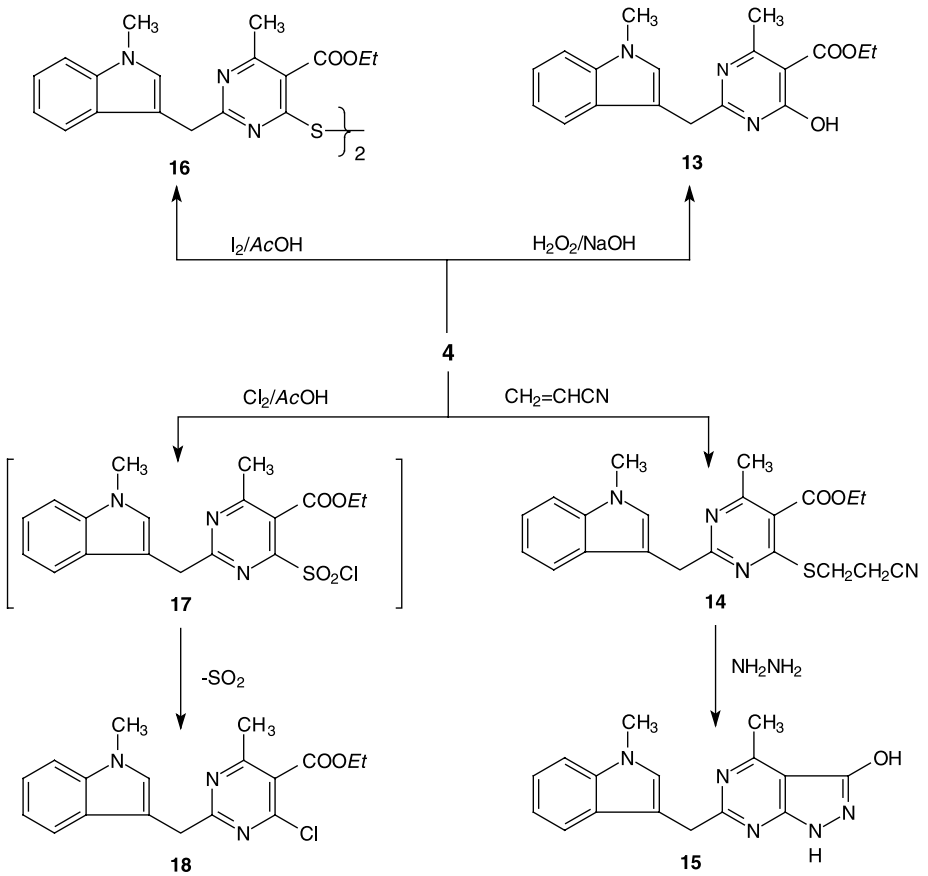
Reaction of **4** with chloro reagents, namely, chloro-*N*-phenylacetamide, chloro-acetamide, and phenacylchloride in refluxing ethanol containing triethylamine as a catalyst afforded the 2-(*N*-phenylacetamido)mercapto-, 2-acetamidomercapto-, and 2-benzoylmethyl-mercaptopyrimidines **7**–**9**. The latter **7**–**9** undergo intramolecular cyclization using sodium ethoxide affording the corresponding fused thienopyrimidines **10**–**12** (Scheme 2).

The reaction of **4** with hydrogen peroxide in sodium hydroxide solution affording the 6-hydroxypyrimidine **13**. *Michael* addition of acrylonitrile in refluxing ethanol gave the 6-mercaptoethyl carbonitrile **14**, which was treated with hydrazine hydrate to afford 3-hydroxypyrazolopyrimidine **15**. Oxidation of **4** with iodine in acetic acid gave the disulfide **16**. Chlorination of **4** with chlorine in acetic acid yielded **18** *via* the formation of **17** as intermediate.

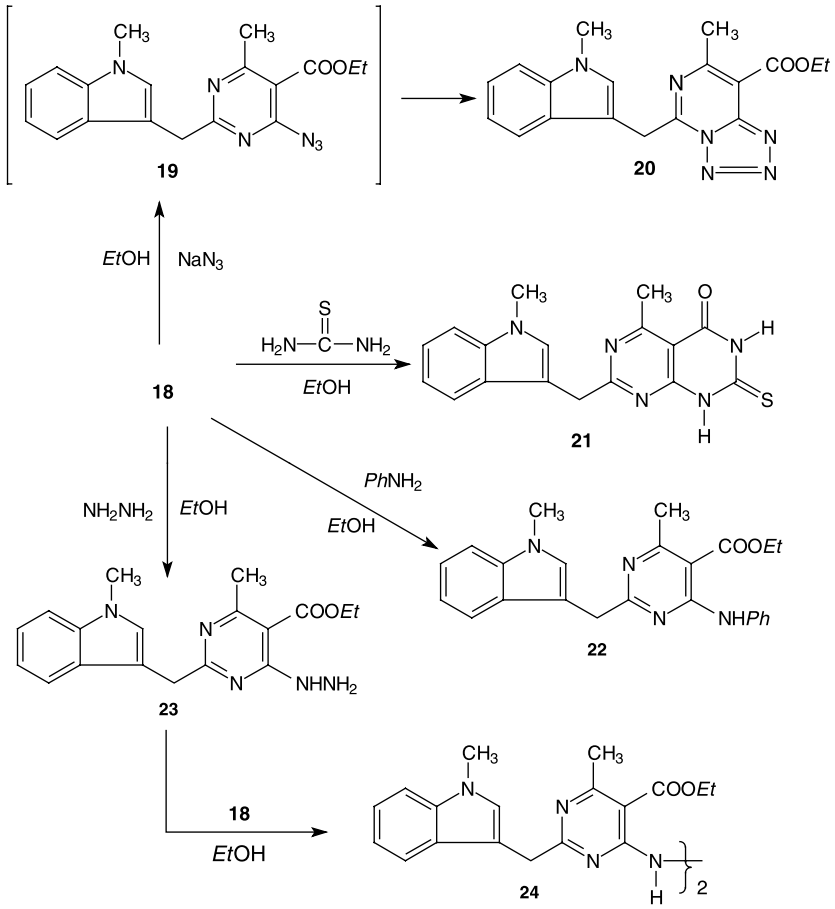
Treatment of **18** with sodium azide in refluxing ethanol gave the corresponding tetrazolopyrimidine **20** *via* the formation of azide form **19**. Compound **18** was reacted with thiourea, aniline, and hydrazine hydrate in refluxing ethanol to afforded the corresponding pyrimidopyrimidine **21**, 6-phenylaminopyrimidine **22**, and 6-hydrazinopyrimidine **23**. The latter compound was reacted with another molecule of **18** to give the corresponding bis-pyrimidine derivative **24**.

Pharmacological Screening

Two pharmacological activities namely, analgesic and antiparkinsonism were tested despite their different biological receptors. Yet both are of neurological origin. Seven representative compounds **6**, **7**, **11**, **12**, **15**, **21**, and **24** were studied with repect to their analgesic and antiparkinsonian activities.



Scheme 3



Scheme 4

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	0.80	0.90	0.88	0.91	0.93	0.94	0.94
7	0.32	0.41	0.41	0.42	0.45	0.43	0.47
11	0.62	0.63	0.73	0.73	0.74	0.74	0.74
12	0.96	0.99	0.99	1.07	1.13	1.20	1.42
15	0.58	0.62	0.69	0.71	0.77	0.81	0.80
21	0.55	0.57	0.58	0.55	0.51	0.49	0.47
24	0.79	0.82	0.87	0.88	0.88	0.88	0.91

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 **24** approached those of Voltarene®, and **8** had 31–47% activity (Table 1).

Antiparkinsonian Activity

Compounds **6**, **11**, and **15** showed moderate activity (relative potencies to Benzotropene® 0.44, 0.60, and

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	26	1
6	2	2	12	0.45
7	1	1	19	0.81
11	2	2	16	0.61
12	1	1	21	0.82
15	2	2	11	0.43
21	3	3	5	0.17
24	3	3	4	0.14

0.40). Compounds **7** and **12** are the most potent antiparkinsonic agents (0.80 relative potency) (Table 2).

Experimental

Synthesis

All melting points were taken on Electrothermal IA 9000 series digital melting point apparatus. Elemental analytical data were obtained from the microanalytical unit, Cairo University, Cairo, Egypt; the results were in favorable agreements with the calculated values. The IR spectra (KBr) were recorded on a Perkin-Elmer model 1430 spectrophotometer. The ^{1}H NMR spectra were recorded at 270 MHz on a Perkin-Elmer R12B Spectrometer using *TMS* as an internal standard. 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)

2-[(N-Methylindolyl)methyl]-4-methyl-5-ethoxycarbonyl-6-ethoxycarbonylmethylmercaptopyrimidine (**5**, $C_{22}H_{25}N_3O_4S$)

A mixture of 0.34 g **4** (1 mmol) and 0.17 g ethyl bromoacetate (1 mmol) in the presence of 3 drops *TEA* as catalyst in 25 cm^3 absolute ethanol was refluxed for 30 min. The reaction mixture was cooled and poured into water, the obtained precipitate was collected by filtration, and crystallized from methanol to give 0.26 g **5** (60%). Mp 110°C; IR (film): $\bar{\nu} = 1736$ (C=O, ester), 1520 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.20$, 1.24 (2t, $J = 7.05$ Hz, 2 CH_3), 2.30 (s, CH_3), 2.38 (s, N–CH_3), 3.55 (s, CH_2), 3.72 (s, CH_2), 4.10 (q, $J = 7.18$ Hz, CH_2), 4.30 (q, $J = 7.20$ Hz, CH_2), 6.85–7.60 (m, *Ar*–H) ppm; MS (EI, 70 eV): m/z (%) = 427 (M^+, 62) and at 337 (100, base peak).

6-[(N-Methylindolyl)methyl]-4-methyl-2-ethoxycarbonyl-3-hydroxythienopyrimidine (**6**, $C_{20}H_{19}N_3O_3S$)

Method A: A mixture of 0.42 g **5** (1 mmol) and ~0.1 g sodium ethoxide (1 mmol) in 50 cm^3 ethanol was heated under reflux for 30 min. The reaction mixture was cooled, acidified with HCl, the formed solid was filtered off, and crystallized from ethanol to give 0.22 g **6** (58%). Mp 140°C; IR (film): $\bar{\nu} = 3448$–3250 (br, OH), 1732 (C=O, ester) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.25$ (t, $J = 7.10$ Hz, CH_3), 2.36 (s, CH_3), 2.41 (s, N–CH_3), 3.58 (s, CH_2), 4.15 (q, $J = 7.15$ Hz, CH_2), 6.90–7.95 (m, *Ar*–H), 12.20 (s, OH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 381 (M^+, 15) and at 336 (100, base peak).

Method B: A mixture of 0.34 g **4** (1 mmol), 0.17 g ethyl bromoacetate (1 mmol) and ~0.1 g sodium ethoxide (1 mmol) in 10 cm^3 ethanol was refluxed for 2 h. After cooling, acidification with 3 cm^3 HCl (1 *N*), the precipitate was collected and crystallized from ethanol to give 0.23 g **6** (60%).

*Synthesis of Substituted Pyrimidines **7–9***

A mixture of 0.34 g **4** (1 mmol), 1 mmol appropriate chlorinating agent, and 3 drops of *TEA* in 25 cm^3 ethanol was refluxed for 30 min. The reaction mixture was cooled, poured into water, the solid formed was filtered off, and crystallized to give 0.34 g **7** (72%), 0.27 g **8** (68%) and 0.26 g **9** (56%).

2-[(N-Methylindolyl)methyl]-4-methyl-5-ethoxycarbonyl-6-mercapto-N-phenylacetamidopyrimidine (**7**, $C_{26}H_{26}N_4O_3S$)

Mp 245°C (*Ac*OH); IR (film): $\bar{\nu} = 3397$–3280 (NH), 1735 (C=O, ester), 1660 (C=O, amide) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.30$ (t, $J = 7.00$ Hz, CH_3), 2.32 (s, CH_3), 2.40 (s, N–CH_3), 3.54 (s, CH_2), 3.74 (s, CH_2), 4.16 (q, $J = 7.20$ Hz, CH_2), 6.98–7.65 (m, *Ar*–H), 8.80 (s, NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 474 (M^+, 44) and at 263 [100, base peak].

2-[(N-Methylindolyl)methyl]-4-methyl-5-ethoxycarbonyl-6-mercaptoacetamidopyrimidine (**8**, $C_{20}H_{22}N_4O_3S$)

Mp 233°C (*Et*OH); IR (film): $\bar{\nu} = 3360$ (NH_2), 1735 (C=O, ester), 1705 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.28$ (t, $J = 6.98$ Hz, CH_3), 2.35 (s, CH_3), 2.42 (s, N–CH_3), 3.56 (s, CH_2), 3.73 (s, CH_2), 4.18 (q, $J = 7.16$ Hz, CH_2), 6.05 (s, NH_2, exchangeable with D_2O), 6.94–7.60 (m, *Ar*–H) ppm; MS (EI, 70 eV): m/z (%) = 398 (M^+, 48) and at 281 (100, base peak).

2-[(N-Methylindolyl)methyl]-4-methyl-5-ethoxycarbonyl-6-mercaptophenacylpyrimidine (**9**, $C_{26}H_{25}N_3O_3S$)

Mp 156°C (*Ac*OH); IR (film): $\bar{\nu} = 1736$ (C=O, ester), 1700 (C=O), 1540 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.32$ (t, $J = 7.00$ Hz, CH_3), 2.34 (s, CH_3), 2.43 (s, N–CH_3), 3.53 (s, CH_2), 3.76 (s, CH_2), 4.14 (q, $J = 7.20$ Hz, CH_2), 6.84–7.70 (m, *Ar*–H) ppm; MS (EI, 70 eV): m/z (%) = 459 (M^+, 12) and at 308 (100, base peak).

*Synthesis of Thienopyrimidines **10–12***

A mixture of **7–9** (1 mmol) and ~0.1 g sodium ethoxide (1 mmol) in 25 cm^3 ethanol was heated under reflux for 1 h. The reaction mixture was cooled, acidified with HCl, the solid was filtered off and crystallized to give 0.3 g **10** (70%), 0.23 g **11** (64%), and 0.24 g **12** (58%).

6-[(N-Methylindolyl)methyl]-4-methyl-2-(N-phenylamido)-3-hydroxythienopyrimidine (**10**, $C_{24}H_{20}N_4O_2S$)

Mp 218°C (*Et*OH); IR (film): $\bar{\nu}$ = 3440–3120 (NH, OH), 1707 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): δ = 2.37 (s, CH_3), 2.44 (s, N–CH_3), 3.53 (s, CH_2), 6.88–7.68 (m, *Ar*–H), 8.76 (s, NH, exchangeable with D_2O), 12.28 (s, OH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 428 (M^+, 36) and at 192 (100, base peak).

6-[(N-Methylindolyl)methyl]-4-methyl-2-amido-3-hydroxythienopyrimidine (**11**, $C_{18}H_{16}N_4O_2S$)

Mp 236°C (*Me*OH); IR (film): $\bar{\nu}$ = 3460–3210 (OH, NH_2), 1704 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): δ = 2.36 (s, CH_3), 2.45 (s, N–CH_3), 3.54 (s, CH_2), 6.15 (s, NH_2, exchangeable with D_2O), 6.85–7.65 (m, *Ar*–H), 12.32 (s, OH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 352 (M^+, 35) and at 320 (100, base peak).

6-[(N-Methylindolyl)methyl]-4-methyl-2-benzoyl-3-hydroxythienopyrimidine (**12**, $C_{24}H_{19}N_3O_2S$)

Mp 256°C (*Ac*OH); IR (film): $\bar{\nu}$ = 3418–1325 (OH), 1720 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): δ = 2.35 (s, CH_3), 2.43 (s, N–CH_3), 3.58 (s, CH_2), 6.90–7.74 (m, *Ar*–H), 12.28 (s, OH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 413 (M^+, 46) and at 252 (100, base peak).

2-[(N-Methylindolyl)methyl]-4-methyl-5-ethoxycarbonyl-6-hydroxypyrimidine (**13**, $C_{18}H_{19}N_3O_3$)

A mixture of 0.34 g **4** (1 mmol), 60 cm^3 hydrogen peroxide (30%), and 20 cm^3 sodium ethoxide (5%) was stirred for 1 h at room temperature. The reaction mixture was cooled, acidified with HCl, the solid formed was filtered off, and crystallized from ethanol to give 0.21 g **13** (65%). Mp 170°C; IR (film): $\bar{\nu}$ = 3540–3350 (OH), 1695 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): δ = 1.24 (t, J = 7.04 Hz, CH_3), 2.30 (s, CH_3), 2.38 (s, N–CH_3), 3.55 (s, CH_2), 4.16 (q, J = 7.21 Hz, CH_2), 6.85–7.60 (m, *Ar*–H), 11.40 (s, OH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 325 (M^+, 75) and at 362 (100, base peak).

2-[(N-Methylindolyl)methyl]-4-methyl-5-ethoxycarbonyl-6-mercaptoethylcarbonitrilepyrimidine (**14**, $C_{21}H_{22}N_4O_2S$)

A mixture of 0.34 g **4** (1 mmol), ~0.1 g acrylonitrile (1.9 mmol), and 3 drops of *TEA* in 10 cm^3 ethanol was heated under reflux for 1 h. After cooling the precipitate was collected and crystallized from ethanol to give 0.27 g **14** (68%). Mp 115°C; IR (film): $\bar{\nu}$ = 2218 (C≡N), 1734 (C=O, ester), 1595 (C=N) cm^{-1}; MS (EI, 70 eV): m/z (%) = 394 (M^+, 16) and at 362 (100, base peak).

6-[(N-Methylindolyl)methyl]-4-methyl-3-hydroxypyrazolopyrimidine (**15**, $C_{16}H_{15}N_5O$)

A mixture of 0.4 g **14** (1 mmol) and 0.5 cm^3 hydrazine hydrate (8 mmol) in 20 cm^3 ethanol was refluxed for 2 h. The precipitate obtained upon cooling was collected and crystallized from ethanol to give 0.20 g **15** (67%). Mp 130°C; IR (film): $\bar{\nu}$ = 3520, 3200, 3140 (NH, OH) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): δ = 2.30 (s, CH_3), 2.42 (s, N–CH_3), 3.55 (s, CH_2), 6.92–7.75 (m, *Ar*–H), 11.10 (s, NH, exchangeable with D_2O), 12.19 (s, OH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 293 (M^+, 22) and at 148 (100, base peak).

6,6′-Bis-{2-[(N-methylindolyl)methyl]-4-methyl-5-ethoxycarbonylpyrimidino}sulfide (**16**, $C_{36}H_{36}N_6O_4S_2$)

To a solution of 0.34 g **4** (1 mmol) in 20 cm^3 acetic acid, 0.25 g iodine (1 mmol) was added portion-wise with stirring at room temperature. The solid formed was collected by filtration and crystallized from ethanol to give 0.37 g **16** (55%). Mp 220°C; IR (film): $\bar{\nu}$ = 1735, 1733 (2C=O, ester) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): δ = 1.24 (t, J = 7.10 Hz, 2 CH_3), 2.30 (s, 2CH_3), 2.38 (s, 2N–CH_3), 3.55 (s, 2CH_2), 4.16 (q, J = 7.20 Hz, 2CH_2), 6.85–7.60 (m, *Ar*–H) ppm; MS (EI, 70 eV): m/z (%) = 680 (M^+, 42) and at 295 (100, base peak).

2-[(N-Methylindolyl)methyl]-4-methyl-5-ethoxycarbonyl-6-chloropyrimidine (**18**, $C_{18}H_{18}ClN_3O_2$)

Chlorine gas was bubbled through a suspension of 0.34 g **4** (1 mmol) in 50 cm^3 acetic acid for about 3 h. The resulting colorless precipitate was filtered off, washed with water, dried and crystallized from ethanol to give 0.20 g **18** (60%). Mp 125°C; IR (film): $\bar{\nu}$ = 1739 (C=O, ester) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): δ = 1.28 (t, J = 7.02 Hz, CH_3), 2.32 (s, CH_3), 2.40 (s, N–CH_3), 3.56 (s, CH_2), 4.15 (q, J = 7.14 Hz, CH_2), 6.87–7.68 (m, *Ar*–H) ppm; MS (EI, 70 eV): m/z (%) = 344 (M^+, 38) and at 298 (100, base peak).

7-[(N-Methylindolyl)methyl]-5-methyl-4-ethoxycarbonyltetrazolopyrimidine (**20**, $C_{18}H_{18}N_6O_2$)

A mixture of 0.34 g **18** (1 mmol) and ~0.1 g sodium azide (1.5 mmol) in 30 cm^3 ethanol was refluxed for 4 h. The reaction mixture was cooled, poured into water, the solid was filtered off, and crystallized from ethanol to give 0.21 g **20** (60%). Mp > 300°C; IR (film): $\bar{\nu}$ = 1735 (C=O, ester) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): δ = 1.30 (t, J = 7.00 Hz, CH_3), 2.35 (s, CH_3), 2.39 (s, N–CH_3), 3.54 (s, CH_2), 4.12 (q, J = 7.20 Hz, CH_2), 6.90–7.78 (m, *Ar*–H) ppm; MS (EI, 70 eV): m/z (%) = 350 (M^+, 100, base peak).

*Synthesis of Pyrimidopyrimidine **21** and Substituted Pyrimidines **22** and **23***

A mixture of 0.34 g **18** (1 mmol) and amino reagents, namely, thiourea, aniline (1 mmol) or hydrazine hydrate (8 mmol) in 30 cm^3 ethanol in the presence of 3 drops *TEA* was refluxed for 3 h. The reaction mixture was poured into water, the separated solid was collected and crystallized to give 0.28 g **21** (82%), 0.24 g **22** (60%), and 0.25 g **23** (75%).

7-[(N-Methylindolyl)methyl]-5-methyl-4-oxo-2-mercaptopyrimidopyrimidine (**21**, $C_{17}H_{14}N_5O_5$)

Mp 130°C (*Et*OH); IR (film): $\bar{\nu}$ = 3465 (NH), 1705 (C=O), 1230 (C = S) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): δ = 2.31 (s, CH_3), 2.38 (s, N–CH_3), 3.57 (s, CH_2), 6.89–7.80 (m, *Ar*–H), 8.45,

9.70 (2s, 2NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 336 (M^+, 18) and at 192 (100, base peak).

2-[(N-Methylindolyl)methyl]-4-methyl-5-ethoxycarbonyl-6-phenylaminopyrimidine (**22**, $C_{24}H_{24}N_4O_2$)
Mp 214 (*Et*OH); IR (film): $\bar{\nu}$ = 3455 (NH), 1734 (C=O, ester) cm^{-1}; ^1H NMR (*DMSO*-d_6): δ = 1.32 (t, J = 7.02 Hz, CH_3), 2.33 (s, CH_3), 2.39 (s, N–CH_3), 3.57 (s, CH_2), 4.16 (q, J = 7.20 Hz, CH_2), 6.45 (s, NH, exchangeable with D_2O), 6.84–7.66 (m, *Ar*–H) ppm; MS (EI, 70 eV): m/z (%) = 400 (M^+, 8) and at 235 (100, base peak).

2-[(N-Methylindolyl)methyl]-4-methyl-5-ethoxycarbonyl-6-hydrazinopyrimidine (**23**, $C_{18}H_{21}N_5O_2$)
Mp 224°C (*Et*OH); IR (film): $\bar{\nu}$ = 3455–3265 (NH, NH_2), 1736 (C=O, ester) cm^{-1}; ^1H NMR (*DMSO*-d_6): δ = 1.29 (t, J = 7.00 Hz, CH_3), 2.30 (s, CH_3), 2.36 (s, N–CH_3), 3.54 (s, CH_2), 4.12 (q, J = 7.22 Hz, CH_2), 6.25 (s, NH_2, exchangeable with D_2O), 6.92–7.76 (m, Ar–H), 9.45 (s, NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 339 (M^+, 100, base peak).

6,6′-Bis-{2-[(N-methylindolyl)methyl]-4-methyl-5-ethoxycarbonylpyrimidino}imide (**24**, $C_{36}H_{38}N_8O_4$)
A mixture of 0.34 g **18** (1 mmol) and 0.33 g of **23** (1 mmol) in 50 cm^3 ethanol in the presence of 3 drops *TEA* was refluxed for 5 h. The separated solid was collected and crystallized from ethanol to give 0.49 g **24** (62%). Mp 132–134°C; IR (film): $\bar{\nu}$ = 3446 NH, 1750 (C=O) cm^{-1}; ^1H NMR (*DMSO*-d_6): δ = 1.35 (t, J = 7.04 Hz, 2 CH_3), 2.34 (s, 2 CH_3), 2.42 (s, 2 N–CH_3), 3.54 (s, 2 CH_2), 4.18 (q, J = 7.20 Hz, 2 CH_2), 6.87–7.70 (m, *Ar*–H), 10.10 (s, 2 NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): m/z (%) = 646 (M^+, 100, base peak).

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 (gum acacia), and the third one received Voltarene® as a reference drug, whereas the other groups received **6**, **7**, **11**, **12**, **15**, **21**, and **24** (SC administration). Mice were dropped gently in a dry glass beaker of 1 dm^3 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 animal licks its feet or jamb out of the beaker (dose 5 mg/kg) [24]. Relative potencies to Voltarene® were determined (Table 1).

Antiparkinsonian Activity

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

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) [25] 1 h *prior* the administration of 0.5 mg/kg of Oxotremerine® S.C. Rectal temperature was measured before administration of the compounds and 1 h 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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