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Synthesis and antiinflammatory activity of some pyrimidines and thienopyrimidines using 1-(2-Benzo[*d*][1,3]dioxol-5-yl)vinyl)-4-mercapto-6-methylpyrimidine-5-yl)ethan-2-one as a starting material

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Abstract In continuation to our search for new heterocyclic systems based antiinflammatories, the suggestion and synthesis of some pyrimidines, thienopyrimidines, and their derivatives, were herein realized. The pharmacological screening showed that many of these compounds have good antiinflammatory activity. The structure assignments of the new compounds are based on chemical and spectroscopic evidence. The detailed synthesis, spectroscopic data, and pharmacological properties are reported.

Keywords Pyrimidines; Thienopyrimidine; Thiopyranopyrimidine; Antiinflammatory activity.

Introduction

In connection to our or previous work on pyrimidines [1–6] we tried to synthesize new fused substituted pyrimidines of expected biological activity. Numerous publications have appeared describing the synthesis of arylvinyl derivatives condensed with pyrimidines possessing a variety of pharmacological activities, such as anticonvulsant [7], antiinflammatory [8], bactericidal [9], fungicidal [10], and antifertility [11]. On the other hand, thienopyrimidine and thioxopyrimidine derivatives have promising biological [12, 13], anticancer activities [14, 15] and inhibitor of VEGFR-2 kinase activity [16, 17]. Recently, some new pyridine, pyrimidine and their derivatives have been synthesized and used as analgesic, anticonvulsant, and antiparkinsonian agents [18–23]. In addition, *Atheral et al*. [24] have synthesized a novel series of thieno[2,3-*d*]pyrimidines which can be used in combatting fungi in plants to inhibit the growth of cancer cells [25, 26]. In view of these observations and in continuation of our previous work in pyridimidine chemistry, we synthesized some new pyrimidine and thieno[2,3-*d*]pyrimidine derivatives and tested their antiinflammatory activity.

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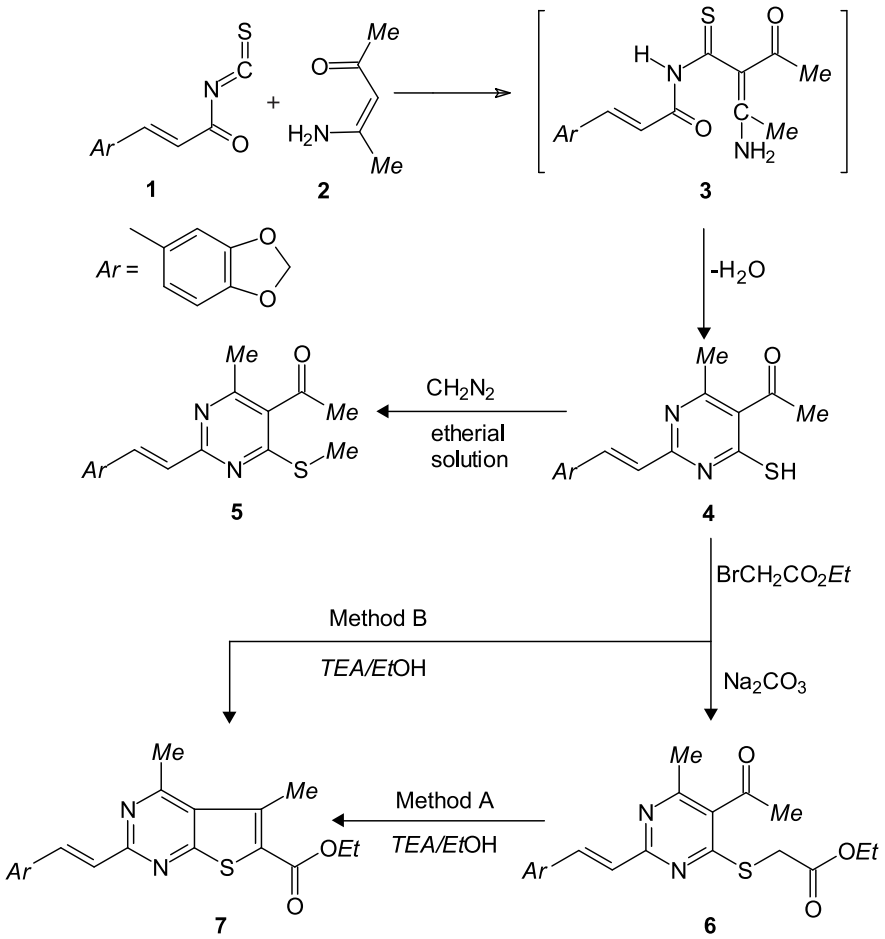
Results and discussion

Chemistry

The starting material **4** was prepared from the addition of enaminic carbon of enaminone **2** to the electrophilic carbon of isothiocyanate **1** *via* the non isolable intermediated **3** according to literature methods [27]. Alkylation of **4** to the corresponding 4-substituted-mercaptopyrimidine derivatives **5** and **6** was achieved by the action of diazomethane in ethereal solution or ethyl bromoacetate in the presence of sodium carbonate. Cyclization of **6** was achieved by



Scheme 1

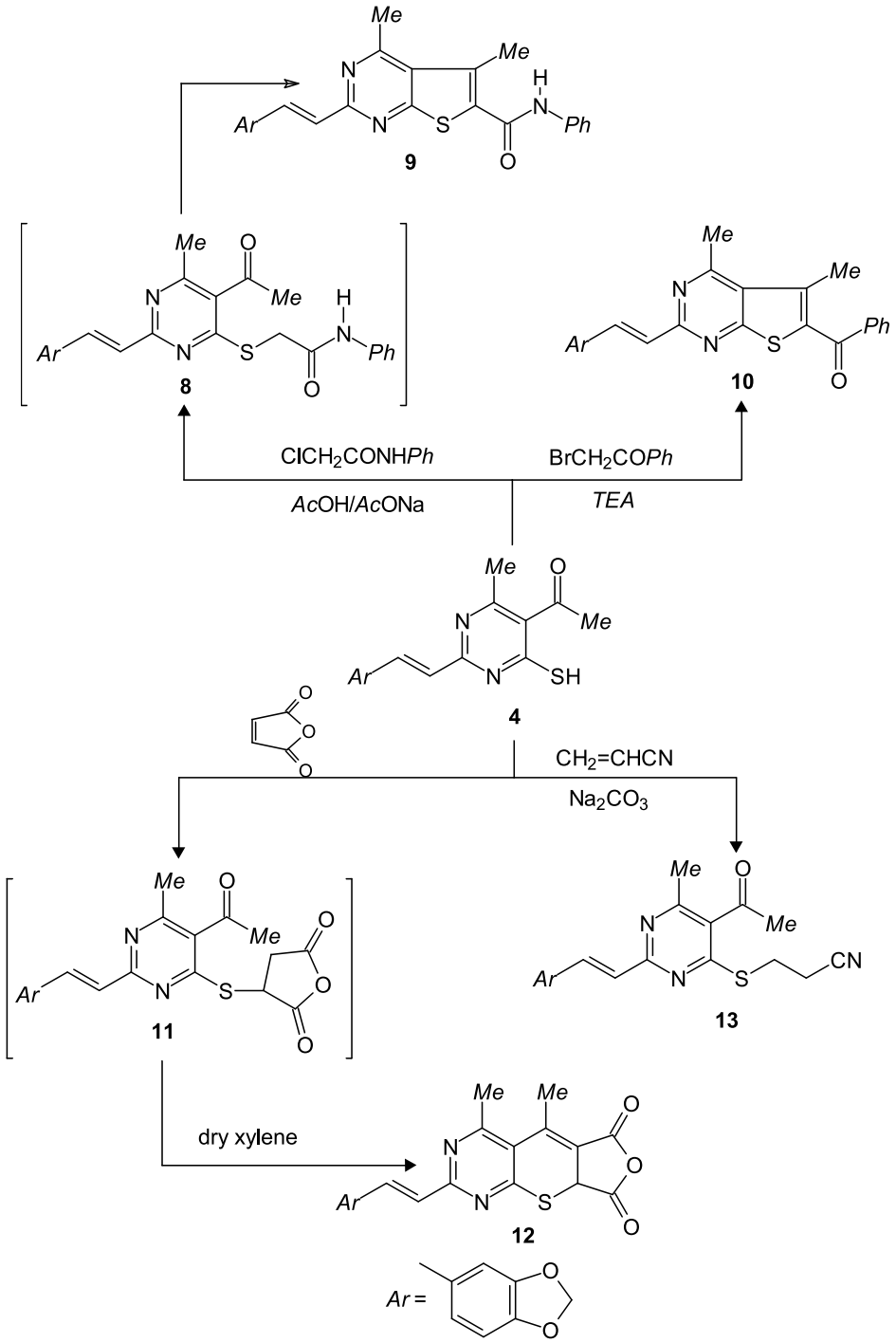
refluxing in ethanol in the presence of *TEA* afforded thienopyrimidine **7** [Method A], which was prepared directly from **4** with ethyl bromoacetate in the presence of triethylamine in refluxing ethanol [Method B] (Scheme 1).

Condensation of **4** with *N*-phenylchloroacetamide in the presence of anhydrous sodium acetate gave the thienopyrimidine **9**, *via* the non-isolated intermediate **8**. While, **4** was reacted with phenacylbromide in the presence of *TEA* in refluxing ethanol. The reaction of **4** with maleic anhydride in refluxing xylene in the presence of *TEA* yielded the thiopyrano[2,3-*d*]pyrimidine **12** presumably through *Michael* type product **11**. Also, **4** was reacted with acrylo-nitrile in the presence of Na_2CO_3 to afford 4-cyanoethylene-mercaptopyrimidine derivative **13** (Scheme 2).

The reaction of ethyl ester **7** with refluxing hydrazine hydrate afforded the corresponding hydrazide **14**, which was condensed with aldehydes, namely, benzaldehyde, *p*-methoxy-benzaldehyde, *p*-chlorobenzaldehyde, or *p*-nitrobenzaldehyde in refluxing ethanol yielded the corresponding *Schiff*'s base **15a**–**15d**; but when fused with acetylacetone to give pyrrazolo derivative **16**. On the other hand, compound **17** was obtained by stirring of **14** with 2,5-hexandione in glacial acetic acid at room temperature, but, **14** was treated with carbon disulfide in absolute ethanol in the presence of KOH to afford oxadiazole **18** (Scheme 3).

Antiinflammatory activity

From Table 1 it appeared that the hydrazones **15a**–**15d** have significant antiinflammatory activities. Among the hydrazones, the substituted 4-methoxy-**15b**, 4-nitro- **15d**, and 4-chloro- **15c** derivatives have antiinflammatory activities higher than that of **15a** with an unsubstituted benzaldehyde group. Here, the lipophilicity plays an important role. The most active



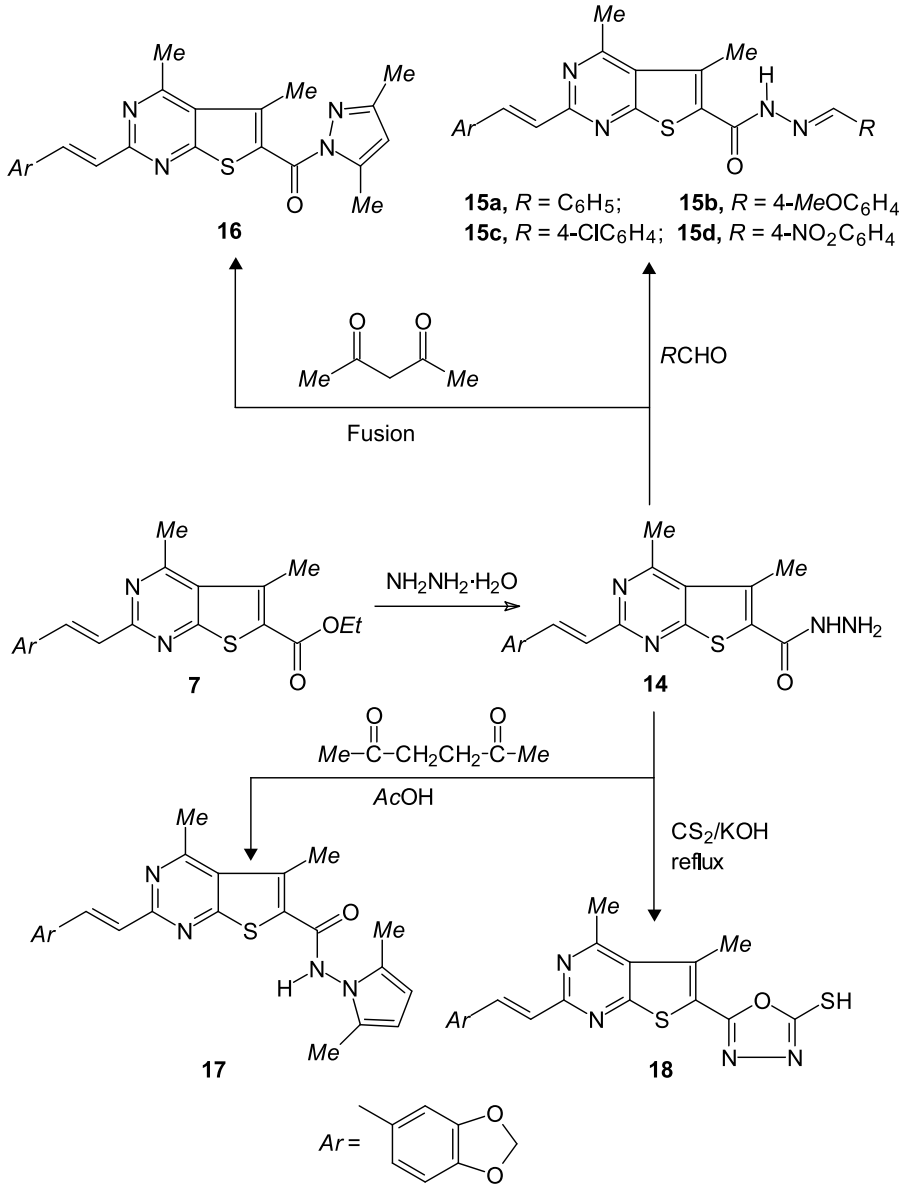
Scheme 2

compounds **15b**–**15d** and the standard drug flurbiprofen were found to exhibit essentially equipotent antiinflammatory activity. The oxadiazole **18** was found to have lower antiinflammatory activities, while the pyrrole **17** showed no significantly as antiinflammatory activities.

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 agree-



Scheme 3

Table 1 Antiinflammatory activity of some synthesized compounds **15a**–**15d**, **17**, and **19** (% reduction in edema induced by yeast)

Compound	Post treatment 3 h/%	Post treatment 6 h/%
15a	7.2	18.0
15b	26.6	34.4
15c	17.2	30.0
15d	24.2	34.2
18	18.2	26.8

ments with the calculated values. The IR spectra (*KBr*) were recorded on a PYE UNICAM spectrophotometer. The ^{1}H and ^{13}C 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).

1-((2-Benzo[d][1,3]dioxol-5-yl)vinyl)-4-mercapto-6-(methyl-pyrimidine-5-yl)ethan-2-one (**4**, $C_{16}H_{14}N_2O_3S$)

A mixture of 0.23 g **1** (1 mmol) and 0.1 g enaminone **2** (1 mmol) in 50 cm^3 dioxane was refluxed for 1 h. The reaction mixture was evaporated under reduced pressure, the obtained yellow precipitate was collected by filtration and crystallized from ethanol to give 0.18 g **4** (60%). Mp 118°C; IR (film): $\bar{\nu} = 1718$ (C=O), 1615 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.40$ (s, CH_3), 2.60 (s, CH_3), 3.10 (s, SH, exchangeable with D_2O), 5.90 (s, CH_2), 6.60–6.90 (m,

CH=CH, *Ar*H) ppm; MS (EI, 70 eV): $m/z = 314$ (M^+, 100, base peak).

1-(2-((Benzo[d][1,3]dioxol-5-yl)vinyl)-6-methyl-4-(methylthio)pyrimidine-5-yl)ethanone (**5**, $C_{17}H_{16}N_2O_3S$)
To a solution of 0.31 g **4** (1 mmol) in 20 cm^3 dry ether, ethereal solution of diazomethane (1.5 mmol) was added at −5°C. The reaction mixture was stirred at the same temperature for 1 h, the solid obtained was filtered off and crystallized from methanol to give 0.21 g **5** (65%). Mp 105°C; IR (film): $\bar{\nu} = 1720$ (C=O), 1622 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.38$ (s, CH_3), 2.61 (s, CH_3), 2.72 (s, CH_3), 5.88 (s, CH_2), 6.65–6.96 (m, CH=CH *Ar*H); ^{13}C NMR (*DMSO*-d_6): $\delta = 126.00$, 163.40, 166.30, 167.20 (pyrimid-C), 112.80, 133.40 (CH=CH), 111.60, 115.20, 119.70, 128.50, 148.00, 148.70, (benzene-C), 199.80 (C=O), 14.90, 18.10, 28.60 ($3CH_3$), 161.20 (CH_2) ppm; MS (EI, 70 eV): $m/z = 328$ (M^+, 6) and at 147 (100, base peak).

Ethyl (2-(5-acetyl-2-(benzo[d][1,3]dioxol-5-yl)vinyl)-6-(methylpyrimidin-4-yl)-sulfanyl)acetate (**6**, $C_{20}H_{20}N_2O_5S$)
To a solution of 0.31 g **4** (1 mmol) and 0.1 g sodium carbonate (1 mmol) in 30 cm^3 water, 0.2 g of ethyl bromoacetate (1 mmol) was added. The reaction mixture was stirred for 1 h, the precipitate obtained was filtered off, washed with water, methanol and crystallized from ethanol to give 0.28 g **6** (70%). Mp 125°C; IR (film): $\bar{\nu} = 1717$ (C=O), 1615 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.50$ (t, $J = 7.10$ MHz, CH_3), 2.42 (s, CH_3), 2.58 (s, CH_3), 3.80 (s, S–CH_2), 4.10 (q, $J = 7.20$ MHz, CH_2), 5.92 (s, CH_2), 6.68–7.05 (m, CH=CH, *Ar*H) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 126.05$, 163.38, 166.26, 167.18 (pyrimid-C), 112.78, 133.43 (CH=CH), 111.56, 115.24, 119.72, 128.51, 148.05, 148.74, (benzene-C), 169.48, 199.76 (2C=O), 14.14, 18.12, 28.63 ($3CH_3$), 32.47, 60.62 ($2CH_2$), 101.15 (O–CH_2–O) ppm; MS (EI, 70 eV): $m/z = 400$ (M^+, 16) and at 340 (100, base peak).

Ethyl (2-(benzo[d][1,3]dioxol-5-yl)vinyl)-4,5-dimethylthieno[2,3-d]pyrimidine-6-carboxylate (**7**, $C_{20}H_{18}N_2O_4S$)
Method A: A mixture of 0.4 g **6** (1 mmol) and few drops of *TEA* in 20 cm^3 ethanol was heated under reflux for 2 h. The solid obtained during reflux was filtered off and crystallized from dimethylformamide/water to give 0.26 g **7** (70%). Mp 176°C; IR (film): $\bar{\nu} = 1735$ (C=O, ester), 1620 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.50$ (t, $J = 7.05$ MHz, CH_3), 2.20 (s, CH_3), 2.44 (s, CH_3), 4.30 (q, $J = 7.20$ MHz, CH_2), 5.89 (s, CH_2), 6.65–6.96 (m, CH=CH, *Ar*H) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 130.80$, 156.50, 163.80, 166.80 (pyrimid-C), 112.82, 133.41 (CH=CH), 111.62, 115.23, 119.68, 128.47, 148.05, 148.72 (benzene-C), 136.12, 147.46 (thiophene-C), 160.60 (C=O), 23.02, 13.20, 16.10 ($3CH_3$), 60.90 (CH_2), 101.16 (O–CH_2–O) ppm; MS (EI, 70 eV): $m/z = 382$ (M^+, 12) and at 337 (100, base peak).

Method B: A mixture of 0.31 g **4** (1 mmol), 0.17 g ethyl bromoacetate (1 mmol) and 3 drops of triethylamine in 100 cm^3 ethanol was refluxed for 1 h. The reaction mixture was concentrated under reduced pressure, the solid obtained was filtered off and crystallized from *DMF*/H_2O to afford 0.26 g **7** (65%) which was identified by comparison with authentic samples from Method A.

2-((Benzo[d][1,3]dioxol-5-yl)vinyl)-4,5-dimethyl-N-phenylthieno[2,3-d]pyrimidine-6-carboxamide (**9**, $C_{24}H_{19}N_3O_3S$)
A mixture of 0.31 g **4** (1 mmol), 0.17 g *N*-phenyl chloroacetamide (1 mmol), and 0.3 g sodium acetate in 100 cm^3 acetic acid was refluxed for 20 h. After cooling, the precipitate was collected by filtration and crystallized from acetic acid to give 0.20 g **9** (50%). Mp 180°C; IR (film): $\bar{\nu} = 3200$–3350 (NH), 1670 (C=O), 1610 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.22$ (s, CH_3), 2.41 (s, CH_3), 5.94 (s, CH_2), 6.65–7.00 (m, CH=CH, *Ar*H), 8.10 (s, NH, exchangeable with D_2O) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 131.02$, 157.12, 164.00, 166.92 (pyrimid-C), 112.81, 133.38 (CH=CH), 135.10, 147.50 (thiophene-C), 161.90 (C=O), 111.60, 115.21, 119.70, 128.50, 148.00, 148.70 (benzene-C), 121.60, 124.40, 129.00, 135.90 (*Ph*–C), 11.80, 23.00 ($2CH_3$), 101.22 (O–CH_2–O) ppm; MS (EI, 70 eV): $m/z = 429$ (M^+, 8) and at 307 (100, base peak).

2-((Benzo[d][1,3]dioxol-5-yl)vinyl)-4,5-dimethylthieno[2,3-d](pyrimidin-6-yl)(phenyl)methanone (**10**, $C_{24}H_{18}N_2O_3S$)
A mixture of 0.31 g **4** (1 mmol), 0.2 g phenacyl bromide (1 mmol) and one drop of *TEA* in 25 cm^3 ethanol was refluxed for 1 h. The solid obtained was filtered off, dried and crystallized from acetic acid to give 0.27 g **10** (65%). Mp 170°C; IR (film): $\bar{\nu} = 1660$ (C=O), 1600 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.18$ (s, CH_3), 2.38 (s, CH_3), 5.92 (s, CH_2), 6.68–7.80 (m, CH=CH, *Ar*H); ^{13}C NMR (*DMSO*-d_6): $\delta = 131.17$, 157.52, 163.85, 166.88 (pyrimid-C), 112.80, 133.40 (CH=CH), 111.62, 115.24, 119.69, 128.52, 148.04, 148.67 (benzene-C), 139.35, 147.50 (thiophene-C), 183.68 (C=O), 124.40, 129.65, 132.70, 135.40 (*Ph*–C), 12.30, 23.00 ($2CH_3$), 101.17 (O–CH_2–O) ppm; MS (EI, 70 eV): $m/z = 414$ (M^+, 8) and at 307 (100, base peak).

2-(Benzo[d][1,3]dioxol-5-yl)-4,5-dimethylthieno[2,3-d]-pyrimidine-6,7-dicarboxylic acid anhydride
(**12**, $C_{20}H_{14}N_2O_5S$)
A mixture of 0.31 g **4** (1 mmol) and 0.98 g maleic anhydride (1 mmol) in 30 cm^3 dry xylene was refluxed for 16 h. The obtained solid was filtered off and crystallized from benzene to give 0.20 g **12** (50%). Mp 290°C; IR (film): $\bar{\nu} = 1725$ (C=O), 1616 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.70$ (s, CH_3), 2.21 (s, CH_3), 4.15 (s, CH), 5.92 (s, CH_2), 6.65–6.98 (m, CH=CH, *Ar*H) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 125.40$, 158.90, 164.70, 166.26 (pyrimid-C), 112.78, 133.38 (CH=CH), 166.08, 169.10 (2C=O), 111.60, 115.22, 119.70, 128.50, 148.02, 148.69 (benzene-C), 48.10, 124.90, 147.30 (thine-C); 14.60, 19.00 ($2CH_3$), 101.20 (O–CH_2–O) ppm; MS (EI, 70 eV): $m/z = 394$ (M^+, 100, base peak).

3-((5-Acetyl-2-(benzo[d][1,3]dioxol-5-yl)vinyl)-6-(methylpyrimidine-4-yl)(sulfanyl)propanenitrile (**13**, $C_{19}H_{17}N_3O_3S$)
A mixture of 0.31 g **4** (1 mmol), 0.1 g acrylonitrile (1 mmol) and 0.11 g sodium carbonate (1 mmol) in 20 cm^3 ethanol, was stirred at room temperature for 1 h. The solid formed was filtered off and crystallized from ethanol to afford 0.24 g **13**

(65%). Mp 135°C; IR (film): $\bar{\nu} = 2225$ (C≡N), 1720 (C=O), 1605 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.42$ (s, CH_3), 2.58 (s, CH_3), 3.40–3.42 (m, $2CH_2$), 5.94 (s, CH_2), 6.63–6.99 (m, CH=CH, *Ar*–H) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 166.30$, 167.20, 126.00, 163.40 (pyrimid-C), 112.80, 133.40 (CH=CH), 111.55, 115.20, 119.65, 128.52, 148.00, 148.72 (benzene-C), 117.70 (C≡N), 199.76 (C=O), 18.10, 28.60 ($2CH_3$), 30.40, 19.30 ($2CH_2$), 101.16 (O–CH_2–O) ppm; MS (EI, 70 eV): $m/z = 367$ (M^+, 22) and at 146 (100, base peak).

2-((Benzo[d][1,3]dioxol-5-yl)vinyl)-4,5-dimethylthieno[2,3-d]-pyrimidine-6-carbo-hydrazide (**14**, $C_{18}H_{16}N_4O_3S$)
A solution of 0.4 g, **7** (1 mmol) in 0.4 cm^3 hydrazine hydrate (8 mmol, 98%) was refluxed for 6 h. The reaction mixture was evaporated under reduced pressure, the resultant solid was filtered off and crystallized from ethanol to give 0.27 g **14** (74%). Mp 192°C; IR (film): $\bar{\nu} = 3350$–3180 (NH, NH_2), 1680 (C=O), 1610 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta =$ 2.19 (s, CH_3), 2.43 (s, CH_3), 4.25 (s, NH_2, exchangeable with D_2O), 5.91 (s, CH_2), 6.62–6.98 (m, CH=CH, *Ar*H), 8.05 (s, NH, exchangeable with D_2O) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 131.20$, 158.50, 163.80, 166.80 (pyrimid-C), 112.74, 133.33 (CH=CH), 111.58, 115.19, 119.68, 128.52, 148.03, 148.70 (benzene-C), 135.16, 147.48 (thiophene-C), 160.70 (C=O), 12.70. 23.00 ($2CH_3$), 101.20 (O–CH_2–O) ppm; MS (EI, 70 eV): $m/z = 368$ (M^+, 100, base peak).

2-((Benzo[d][1,3]dioxol-5-yl)vinyl)-4,5-dimethylthieno[2,3-d]-pyrimidine-6-carbohydrazones ***15a–15d***
To a solution of 0.37 g **14** (1 mmol) in 10 cm^3 absolute ethanol, the appropriate aromatic aldehydes, namely, benzaldehyde, *p*-methoxybenzaldehyde, *p*-chlorobenzaldehyde or *p*-nitrobenzaldehyde (1 mmol) was added. The reaction mixture was refluxed for 5 h and the obtained solid was filtered off, dried and crystallized from ethanol to give 0.38 g **15a** (82%), 0.40 g **15b** (85%), 0.40 g **15c** (83%) and 0.50 g **15d** (98%).

2-((Benzo[d][1,3]dioxol-5-yl)vinyl)-4,5-dimethylthieno[2,3-d]-pyrimidine-6-carbophenylhydrazone (**15a**, $C_{25}H_{20}N_4O_3S$)
Mp 262°C; IR (film): $\bar{\nu} = 3330$–3150 (NH), 1690 (C=O), 1620 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.20$ (s, CH_3), 2.40 (s, CH_3), 5.92 (s, CH_2), 6.66–7.65 (m, CH=CH, *Ar*–H), 8.24 (s, NH, exchangeable with D_2O), 8.12 (s, CH=N) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 131.25$, 158.54, 163.79, 166.84 (pyrimid-C), 112.85, 133.46 (CH=CH), 111.60, 115.22, 119.70, 128.50, 148.00, 148.70 (benzene-C), 135.18, 147.50 (thiophene-C), 170.06 (C=O), 128.90, 129.20, 131.10, 133.80 (*Ph*–C), 11.70, 23.00 ($2CH_3$), 101.20 (O–CH_2–O), 143.05 (N=CH) ppm; MS (EI, 70 eV): $m/z = 465$ (M^+, 5) and at 147 (100, base peak).

2-((Benzo[d][1,3]dioxol-5-yl)vinyl)-4,5-dimethylthieno[2,3-d]-pyrimidine-6-carbo-(p-methoxyphenyl)hydrazone
(**15b**, $C_{26}H_{22}N_4O_4S$)
Mp 297°C; IR (film): $\bar{\nu} = 3300$–3180 (NH), 1680 (C=O), 1614 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.21$ (s, CH_3), 2.42 (s, CH_3), 3.70 (s, CH_3), 5.92 (s, CH_2), 6.70–7.50 (m, CH=CH, *Ar*H's), 8.18 (s, NH, exchangeable with D_2O), 8.25 (s, CH=N) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 131.22$, 158.50, 163.80, 166.82 (pyrimid-C), 112.86, 133.24 (CH=CH), 111.58, 115.21, 119.72, 128.48, 148.02, 148.71 (benzene-C), 135.18, 147.56 (thiophene-C), 126.18, 128.30, 129.20, 134.90 (*Ph*–C), 170.00 (C=O), 142.97 (N=CH), 12.70, 23.00 ($2CH_3$), 43.10 (OCH_3), 101.24 (O–CH_2–O) ppm; MS (EI, 70 eV): $m/z = 486$ (M^+, 100, base peak).

2-((Benzo[d][1,3]dioxol-5-yl)vinyl)-4,5-dimethylthieno[2,3-d]-pyrimidine-6-carbo-(p-chloro-phenyl)hydrazone
(**15c**, $C_{25}H_{19}ClN_4O_3S$)
Mp 293°C; IR (film): $\bar{\nu} = 3310$–3150 (NH), 1690 (C=O), 1610 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.23$ (s, CH_3), 2.39 (s, CH_3), 5.89 (s, CH_2), 6.70–7.60 (m, CH=CH, *Ar*H's), 8.16 (s, NH, exchangeable with D_2O), 8.24 (s, CH=N) ppm; MS (EI, 70 eV): $m/z = 491$ (M^+, 32) and at 309 (100, base peak).

2-((Benzo[d][1,3]dioxol-5-yl)vinyl)-4,5-dimethylthieno[2,3-d]-pyrimidine-6-carbo-(p-nitrophenyl)hydrazone
(**15d**, $C_{25}H_{19}N_5O_5S$)
Mp 288°C; IR (film): $\bar{\nu} = 3380$–3180 (NH), 1680 (C=O), 1608 (C=N), 1520–1350 (NO_2) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.20$ (s, CH_3), 2.40 (s, CH_3), 5.90 (s, CH_2), 6.65–8.20 (m, CH=CH, N=CH, *Ar*H's), 8.30 (s, NH, exchangeable with D_2O) ppm; MS (EI, 70 eV): $m/z = 501$ (M^+, 22) and at 192 (100, base peak).

2-((Benzo[d][1,3]dioxol-5-yl)vinyl)-4,5-dimethylthieno[2,3-d]-(pyrimidine-6-yl)(3,5-dimethyl-1H-pyrazol-1-yl)methanone
(**16**, $C_{23}H_{20}N_4O_3S$)
A mixture of 0.43 g **14** (1 mmol) and 0.1 cm^3 acetylacetone (1 mmol) was heated in an oil bath at 120°C for 1 h. The reaction mixture was cooled and the obtained solid was filtered off and crystallized from ethanol to give 0.26 g **16** (60%). Mp 201°C; IR (film): $\bar{\nu} = 1714$ (C=O), 1612 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.20$ (s, CH_3), 2.40 (s, CH_3), 2.70 (s, $2CH_3$), 5.92 (s, CH_2), 6.60–6.90 (m, CH=CH, *Ar*–H) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 131.20$, 158.54, 163.78, 166.82 (pyrimid-C), 112.80, 133.40 (CH=CH), 111.60, 115.20, 119.70, 128.49, 148.00, 148.72 (benzene-C), 135.65, 147.66 (thiophene-C), 184.00 (C=O), 105.00, 143.20, 144.30 (pyrazole-C), 12.80, 14.00, 17.70, 23.00 ($4CH_3$), 101.26 (O–CH_2–O) ppm; MS (EI, 70 eV): $m/z = 432$ (M^+, 24) and at 285 (100, base peak).

2-((Benzo[d][1,3]dioxol-5-yl)vinyl)-4,5-dimethylthieno[2,3-d]-pyrimidine-6-yl)(2,5-dimethyl-1H-pyrazol-1)carboxamide
(**17**, $C_{24}H_{22}N_4O_3S$)
A mixture of 0.43 g **16** (1 mmol) and 0.125 cm^3 2,5-hexanedione (1 mmol) in 5 cm^3 acetic acid was stirred at room temperature for 12 h. The reaction mixture was cooled, poured onto water, the obtained solid was filtered off, dried and crystallized from ethanol to give 0.34 g **17** (77%). Mp 255°C; IR (film): $\bar{\nu} = 3350$–3195 (NH), 1680 (C=O), 1610 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.23$ (s, CH_3), 2.35 (s, $2CH_3$), 2.42 (s, CH_3), 5.60 (m, pyrrole-H), 5.94 (s, CH_2), 6.60–7.05 (m, CH=CH, *Ar*–H), 8.00 (s, NH, exchangeable with D_2O) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 130.99$, 157.05, 163.75, 166.82 (pyrimid-C), 112.74, 133.35 (CH=CH), 111.55, 115.24,

119.68, 128.55, 148.10, 148.76 (benzene-C), 135.50, 147.30 (thiophene-C), 161.00 (C=O), 106.66, 106.75, 131.70, 132.00 (pyrole-C), 12.99, 13.50, 14.95, 23.0 ($4CH_3$), 101.26 (O–CH_2–O) ppm; MS (EI, 70 eV): $m/z = 446$ (M^+, 100, base peak).

5-(2-(Benzo[d][1,3]dioxol-5-yl)vinyl)-4,5-dimethylthieno-[2,3-d](pyrimidine-6-yl)1,3,4-oxadiazole-2-thiol
(**18**, $C_{19}H_{14}N_4O_3S_2$)
A mixture of 0.43 g **14** (1 mmol) and 0.1 g KOH (1 mmol) in 50 cm^3 ethanol was stirred at room temperature until a clear solution was obtained. 0.108 g Carbon disulphide (1.5 mmol) was added dropwise during 20 min with stirring. The reaction mixture was refluxed for 5 h, then evaporated under reduced pressure, diluted with cold water and acidification with HCl. The obtained solid was filtered off and crystallized from ethanol to give 0.32 g **18** (78%). Mp 249°C; IR (film): $\bar{\nu} = 2680$ (SH), 1609 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.20$ (s, CH_3), 2.40 (s, CH_3), 3.00 (s, SH, exchangeable with D_2O), 5.90 (s, CH_2), 6.62–6.98 (m, CH=CH, *Ar*–H) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 130.95$, 156.86, 163.72, 166.81 (pyrimid-C), 112.85, 133.43 (CH=CH), 135.65, 147.30 (thiophene-C), 111.60, 115.20, 119.70, 128.50, 148.05, 148.72 (benzene-C), 101.18 (O–CH_2–O), 13.40, 23.00 ($2CH_3$), 156.70, 161.20 (oxadiazole-C) ppm; MS (EI, 70 eV): $m/z = 410$ (M^+, 100, base peak).

Antiinflammatory activity [28, 29]
Six compounds **15a**–**15d**, **17**, and **18** were evaluated for their antiinflammatory activity. Mature albino rats (95) of both sexes weighing 50–200 g divided into nineteen equal groups were used. Oedema in the rat paw was induced by injection of 0.1 cm^3 of 20% *Brewer's* yeast suspended in physiological saline solution in the paw skin of the hind limb. After 4 h the thickness of the paw was measured using a skin caliber to detect the inflammation induced by the yeast. The first group was left as control while the second group was injected intrapretenoal (I.P.) with dimethyl sulfoxide (*DMSO*) and the third group was injected (I.P.) with Flurbiprofen (20 mg/kg). The remaining groups were treated with the tested compounds dissolved in *DMSO* in a dose of 100 mg/kg. The paw thickness was measured after *Scand* 6 h post injection.

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References

1. Ouf NH (2004) Bull Chim Farm Anno 143:275
2. Assy MG, Youssif ShA, Ouf NH (1995) Polish J Chem 69:896
3. Assy MG, Out NH, Fikry RM (1995) Polish J Chem 69:892
4. Amr AE, Sabry NM, Abdulla MM (2007) Monatsh Chem 138:699
5. Amr AE, Mohamed AM, Mohamed SF, Abdel-Hafez NA, Hammam AG (2007) Bioorg Med Chem 14:5481
6. Amr AE, Hegab MI, Ibrahiem AA, Abdulla MM (2003) Monatsh Chem 134:1395
7. Doria C, Passarotti C, Arcari G, Battinoni A (1983) Belgian Patent 893, 835; (1983) Chem Abstr 99:70749
8. Tripathi S, Ahmad S, Barthwal YP, Tangri KK, Kishore K, Bhargava KP (1981) Ind J Exp 19:630
9. Zhikhareva GP, Mastafanova LL, Evstratova ML, Polukina LM, Pustikina TV, Pershin GN, Yakhontov LN (1982) Khim Farm Zh 183; (1982) Chem Abstr 96:199625
10. Zhikaren GP, Promina EVM, Golovanova EA, Pershin GN, Novitshaya NA, Zykova TN, Gus'Kova TA, Yakhontav LN (1976) Khim Farm Zh 10:62; (1976) Chem Abstr 85:123848
11. Manhas MS, Amin SG, Sharma SD, Dayal B, Bese KA (1979) J Heterocycl Chem 16:371
12. DeClercq E (1986) Anticancer Res 6:549
13. DeClercq E (1986) J Med Chem 29:156
14. Hammam AG, Sharaf M, Abdel-Hafez NA (2001) Ind J Chem 40B:213
15. Hammam AG, Fahmy AFM, Amr AE, Mohamed AM (2003) Ind J Chem 42B:1985
16. Miceal JM, Jean SP, Jeffery MC, Beth AC, Jonathan LD, Carla RH, Stephen MH, Catherine IS, Elisabeth AK, Matthew AM, Ann MKR, Susan BS, Jianmin S (2004) Bioorg Med Chem Lett 14:21
17. Abdel-Fattah B, Kandeel MM, Abdel-Hakeem M, Fahmy ZM (2006) J Chin Chem Soc 53:403
18. Nehad AA, Amr AE, Alhusain AI (2007) Monatsh Chem 138:559
19. Amr AE, Abdel-Latif NA, Abdalla MM (2006) Bioorg Med Chem 14:273
20. Amr AE, Sayed HH, Abdulla MM (2005) Arch Pharm Chem Life Sci 338:433
21. Amr AE (2005) Z Naturforsch 60b:90
22. Amr AE, Abou-Galia MH, Abdulla MM (2006) Z Naturforsch 61b:1335
23. Amr AE, Abdulla MM (2006) Arch Pharm Chem Life Sci 339:88
24. Atherall JF, Hough TL, Linjell SA, Mahony MJ, Anne ES (2003) US Patent 6, 541, 630B
25. Wang YD, Johnson S, Powell D, McGinnis JP, Miranda M, Rabindran SK (2005) Bioorg Med Chem Lett 15:3763
26. Jenning LD, Kincaid SL, Wang YD, Krishnamurthy G, Beyer CF, McGinnis JP, Miranda M, Discafani CM, Rabindran SK (2005) Bioorg Med Chem Lett 15:4731
27. Ouf NH, Amr AE, Fayed AA (2007) Monatsh Chem (Accepted 6-8-2007)
28. VanDyke K, Peden D, VanDyke C, Jones G, Castranova V, Ma J (1982) Inflammation 6:113
29. Alpermann H (1972) Bericht über Pharmakologische Untersuchunger mit Fibendazole. Abt Pharm 863:1

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