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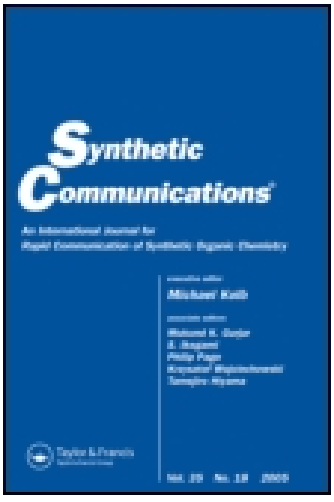

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Copper-Catalyzed Coupling Reaction of 2-Thioxo-4-quinazolinone and Thieno[3,2-d]pyrimidin-4-one Methane Sulphonamide with Aryl Iodides: Preparation of Potential COX-2 Selective Inhibitors

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Copper-Catalyzed Coupling Reaction of 2-Thioxo-4-quinazolinone and Thieno[3,2-*d*] pyrimidin-4-one Methane Sulphonamide with Aryl Iodides: Preparation of Potential COX-2 Selective Inhibitors

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Abstract: Thio-aryl methane sulfonamide derivatives of 4-quinazolinone and thieno[2,3-*d*]pyrimidin-4-one were synthesized using powdery copper/copper(I) iodide as catalyst; their structural elucidation is also reported. These derivatives were planned as sulfur bioisosteres of selective COX-2 inhibitor drugs.

Keywords: copper catalyst, COX-2 selective inhibitors, sulphonamides, thio-aryl derivatives

INTRODUCTION

In the search for new anti-inflammatory drugs acting as specific COX-2 inhibitors (coxibs) through modifications of well-known selective agents, two new series of potential selective COX-2 inhibitors have been designed by bioisosterically replacing the C═C bond[1,2] in the coxibs stilbene scaffold with a sulfur atom or molecular hybridization using the 4-quinazolinone or thieno-pyrimidin-4-one heterocyclic systems[3–5] (Fig. 1).

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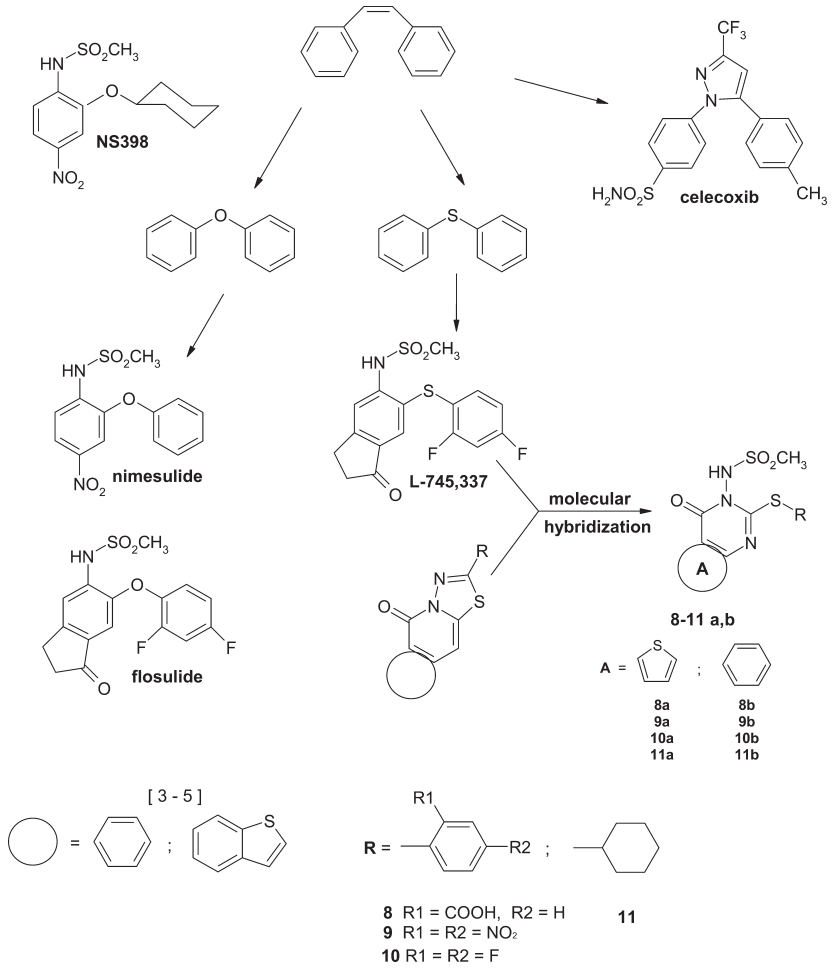

Figure 1. Rational drug design—coxibs stilbene scaffold.

Among the derivatives synthesized were difluorobenzene and thiocycloesyl derivatives with structural features of leads L-745,337 and NS398 respectively (Fig. 1).

The thio-aryl derivatives could be realized with satisfactory yields through the use of powdery copper/copper(I) iodide as catalyst in the reaction of aryl iodides with the thiolic form of the heterocyclic systems. This catalyzed reaction was conducted at reflux in common solvents, water and ethanol, and following previous reactions from our laboratories[6] on other heterocyclic systems, it is the simplest method to form aryl sulphur bonds in heterocycles containing the 2-thioxo-4-pyrimidinone system.

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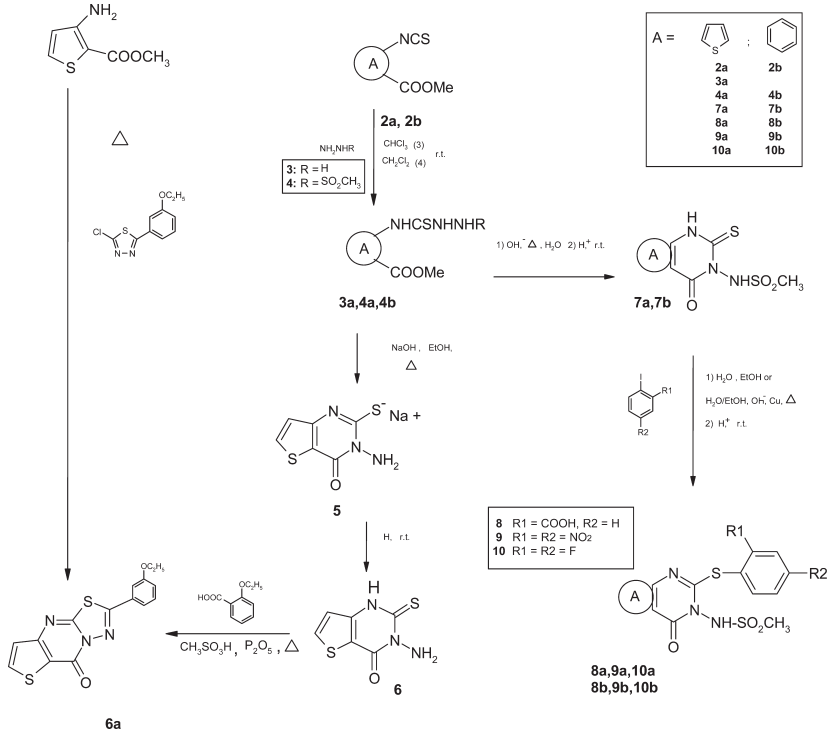
RESULTS

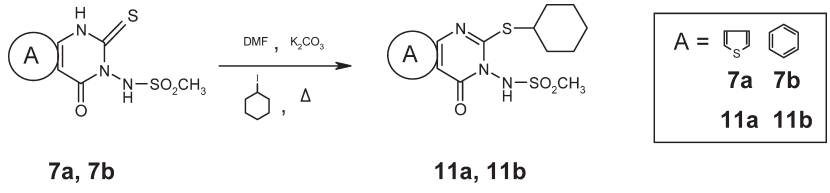
Starting compounds were 3-isothiocyanate-thiophene **2a** and 2-isothiocyanate methyl anthranilate **2b**, prepared in acetone at room temperature without the production of pollutants from the reaction of the corresponding amino esters and thiophosgene (Scheme 1).

The reaction at room temperature of isothiocyanate **2a** and **2b** with hydrazine or mesylhydrazine and the subsequent treatment of the resulting thiosemicarbazide **3a** or methylsulfonyl hydrazino **4a** or **4b**, according to the methods reported by Wamhoff,[7] with refluxing hydroxide ethanolic or aqueous solution afforded the amino-thioxo sodium salt **5** and aqueous or ethanolic solution of sodium or potassium salt of sulphonamide derivative **7a** and **7b**; acidification with hydrochloric acid gave the amino-thioxo derivative **6** and the thioxo-methanesulfonamides **7a** and **7b**, respectively (Scheme 1).

The pyrimidine structure, instead of a seven-membered ring, of the amino-thioxo derivatives **5** and **6** was confirmed by independent preparations of 2-ethoxyphenyl derivative of 5*H*-[1,3,4]thiadiazolo[3,2-*a*]thieno[3,2-*d*]



Scheme 1.

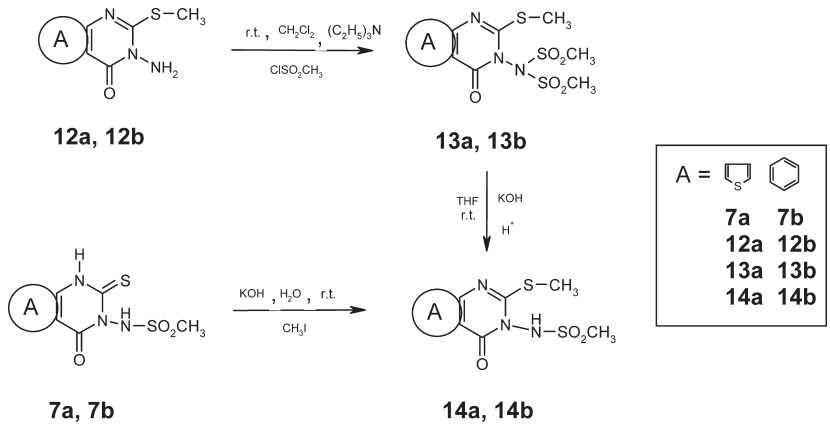


Scheme 2.

pyrimidin-5-one **6a**, a new heterocyclic system. The thioaryl derivatives **8a**, **8b**, **9a**, **9b**, **10a**, and **10b** were obtained in satisfactory yield by coupling the thioxo derivatives **7a** or **7b** and suitable aryl iodides in refluxing slightly basic water/ethanol solution in the presence of powdery copper/copper(I) iodide (Scheme 1).

To complete the pharmacological profile of the series, thio-cycloexyl derivatives **11a** and **11b** were prepared in dimethylformamide at 80°C, in the presence of potassium carbonate, from the reaction of sulfolnylamide derivatives **7a** and **7b**, respectively, with cycloexyl iodide (Scheme 2).

The proposed structures were confirmed by elemental analysis, IR, and ^{1}H and ^{13}C NMR spectra. ^{1}H NMR spectra at 6.45 ppm for compound **5** and 6.36 ppm for compound **6** gave the signal attributable to amino group NH_2 and showed the signal attributable to NH of methylsulfonamide group in the region of 11.0–11.6 ppm; the NMR spectra of thio-aryl derivatives showed the chemical shifts of multiplet aromatic signals. In the ^{1}H NMR spectrum, cycloesyl derivatives **11a** and **11b** showed the multiplet of ten methylenes in the region of 1.3–2.0 ppm and the multiplet of proton bonded to carbon adjacent to sulfur at position at 3.5–3.8 ppm.



Scheme 3.

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The reaction of methyl derivative **12a** or **12b** with methanesulfonyl chloride gave the disulfonate **13a** and **13b** (Scheme 3) that with subsequent alkaline hydrolysis gave the monomesyl derivatives **14a** and **14b**, identical to those obtained from methylation of methanesulfonamide derivatives **7a** and **7b**, respectively. The two independent preparations of **14a** and **14b** confirmed the proposed sulphonamide structure **7a** and **7b** and also that sulfur was more reactive than nitrogen adjacent to the sulphonic group.

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EXPERIMENTAL

Chemistry

^{1}H and ^{13}C NMR spectra were recorded at 200 MHz on a Varian Gemini 200 spectrometer; chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane as internal standard. Coupling constants (J) are in hertz (Hz). IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR in potassium bromide disks. Microanalyses for C, H, N, and S were obtained from an EA 1108 elemental analyzer Fisons Carlo-Erba instrument. Analyses indicated by the symbols of the elements or functions were within $\pm 0.4\%$ of the theoretical values. Melting points are uncorrected and were determined in open capillary tubes on an SMP1 apparatus (Stuart Scientific, Staffordshire). The melting points of all crude compounds were within 3°C of the pure product: therefore, as synthetic intermediates, they could be used without further purification. The purity of compounds was checked by thin-layer chromatography (TLC) on Merck silica-gel 60 F-254 plates. All commercial chemicals were purchased from Aldrich, Fluka, Merk, Lancaster, and Carlo Erba and were used without further purification.

Methyl 3-Isothiocyanatothiophene-2-carboxylate (2a)

A solution of methyl 3-amino-2-thiophenecarboxylate (1.7 g, 99%, 10.8 mmol) in acetone (20 ml) was added slowly dropwise at room temperature to a stirred solution of thiophosgene (0.8 ml, 97%, d = 1.508, 10.15 mmol) in acetone (10 ml). After 20 min of stirring at room temperature, water was added (200 ml); the solid separated was collected, washed first with 5% sodium hydroxide and then with water, dried, and crystallized from petroleum ether to give isothiocyanate **2a** as yellow microcrystals. Yield 80%; mp 54–56°C. The isothiocyanate preparation with a different method was reported by Gutschow and Powers[8] and referenced herein. IR (KBr): 2145 and 2095 (NCS), 1710 (C═O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.82 (s, 3H, OCH_3), 7.96 (d, $J =$ 5.2 Hz, 1H, H-thiophene), 7.24 (d, $J = 5.2$ Hz, 1H, H-thiophene).

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Methyl 3-[(Hydrazinocarbonothioyl)amino]thiophene-2-carboxylate (3a)

Isothiocyanate **2a** (1.20 g, 6.0 mmol) in chloroform (15 ml) was added dropwise to a stirred solution of hydrazine hydrate (0.35 ml, 7.0 mmol) in dichloromethane (15 ml) at room temperature. After the addition was complete, the mixture was stirred at room temperature for 2 h. The resulting solid was collected, washed with dichloromethane, dried, and crystallized from ethanol to give **3a** as a white powder. Yield 90%; mp 225–228°C dec. IR (KBr): 3340, 3260 and 3165 (NH_2 or NH), 1680 (C═O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.81 (s, 3H, CH_3), 4.94 (s, 2H, NH_2), 7.81 (d, $J = 5.4$ Hz, 1H, H-thiophene), 8.93 d, $J = 5.4$ Hz, 1H, H-thiophene), 9.61 (s, 1H, NH), 11.80 (s br, 1H, NH).

Methyl 3({[2(Methylsulfonyl)hydrazino]carbonothioyl}amino)-thiophene-2-carboxylate (4a)

Isothiocyanate **2a** (1.8 g, 9.0 mmol) in dichloromethane (20 ml) was added dropwise to a stirred solution of methanesulfonyl hydrazide (0.90 g, 98%, 8.0 mmol) in dichloromethane (25 ml) at room temperature. After the addition was complete, the mixture was stirred at room temperature for 2 h. The resulting solid was collected, washed with dichloromethane, dried, and recrystallized from ethanol to give **4a** as colorless microcrystals. Yield 55%; mp 202–204°C dec. IR (KBr): 3300 and 3230 (NH_2 or NH), 1675 (C═O), 1315 and 1150 (SO_2-N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.10 (s, 1H, CH_3), 3.85 (s, 1H, CH_3), 7.90 (d, $J =$ 5.6 Hz, 1H, H-thiophene), 8.84 (d, $J = 5.6$ Hz, 1H, H-thiophene), 9.96, 10.62, and 11.41 (s, 1H, NH).

3-Amino-2-thioxo-2,3-dihydrothieno[3,2-*d*]pyrimidin-4(1*H*)-one (6) from Its Sodium Salt (5)

A mixture of hydrazino-thioxo **3a** (1.0 g, 4.3 mmol) in a solution of sodium hydroxide (0.180 g, 4.5 mmol) in ethanol (60 ml) was refluxed under stirring for 1 h; the resulting solid was collected while hot, washed with warm dioxane, and dried to give **5** as white powder. Yield 80%; mp 285–288°C dec. IR (KBr): 3409 and 3260 (NH_2), 1641 (C═O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.45 (s, 2H, NH_2), 6.90 (d, $J = 5.4$ Hz, 1H, H-thiophene), 7.73 (d, $J = 5.4$ Hz, 1H, H-thiophene).

Concentrated hydrochloric acid was added dropwise to a mixture of sodium salt **5** (0.4 g, 1.8 mmol) in water (40 ml) under stirring until pH 3–4; the mixture was stirred for 1 h. The resulting solid was collected, washed with water, and recrystallized from dimethylformamide/water to give **6** as a white powder. Yield 90%; mp 234–237°C dec. IR (KBr): 3285

and 3165 (NH_2 or NH), 1650 (C═O); ^{1}H NMR (DMSO-d_6): δ 6.36 (s, 2H, NH_2), 7.03 (d, $J =$ 5.3 Hz, 1H, H-thiophene), 8.15 (d, $J = 5.3$ Hz, 1H, H-thiophene), 13.62 (s br, 1H, NH).

2-(2-Ethoxyphenyl)-5*H*-[1,3,4]thiadiazolo[3,2-*a*]thieno[3,2-*d*] pyrimidin-5-one (6a)

From Amino Ester **1**

A mixture of 2-chloro-5-(2-ethoxyphenyl)-1,3,4-thiadiazole[9] (0.19 g, 0.8 mmol) and amino ester **1** (0.125 g, 99%, 0.8 mmol) was heated in an oil bath at 220°C until the evolution of hydrochloric acid was complete. After cooling, the reaction mixture was treated with warm ethanol and filtered. The resulting solid was treated with $NaHCO_3$ 5%, collected, washed with water, dried, and crystallized from dimethylformamide/water to give **7** as a white powder. Yield 40%; mp 264–266°C. IR (KBr): 1695 (C═O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.52 (t, $J = 6.8$ Hz, 3H, CH_3), 3.34 (s, 3H, CH_3), 4.33 (q, $J = 6.8$ Hz; 2H, CH2), 7.29–8.30 (m, 6H, Ar-H, and 2 × H-thiophene).

From Amino-thioxo Derivative **6**

A mixture of amino-thioxo derivative **6** (0.27 g, 1.38 mmol), phosphorus pentoxide (0.3 g), methasulfonic acid (0.6 ml), and 2-ethoxybenzoic acid (2.0 g, 98%, 11.8 mmol) was heated at 130°C for 2 h. After cooling to room temperature, the reaction mixture was treated with ice water, and 5% sodium hydroxide was added until pH 9–10. The resulting solid was collected, washed with water, dried, and crystallized from dimethylformamide/water to give **7** as a white powder. Yield 50%. The spectral and analytical data of the two samples were identical, and the mixture melting point was not depressed.

N-(4-Oxo-2-thioxo-1,4-dihydrothieno[3,2-*d*]pyrimidin-3(2*H*)-yl) methanesulfonamide (7a)

A solution of mesyltiosemicarbazide **4a** (0.7 g, 2.3 mmol) and sodium hydroxide (0.180 g, 4.6 mmol) in water (40 ml) was refluxed under stirring for 2 h. After cooling to room temperature, the solution was filtered and acidified with concentrated hydrochloric acid until pH 3–4. The resulting solid was collected, washed with water, dried, and crystallized from dimethylformamide/water to give **7a** as white microcrystals. Yield 75%; mp 276–278°C dec. IR (KBr): 3250 and 3170 (NH), 1665 (C═O), 1335 and 1155

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(SO_2-N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.26 (s, 3H, CH_3), 7.04 (d, $J = 5.2$ Hz; 1H, H-thiophene), 8.24 (d, $J = 5.2$ Hz, 1H, H-thiophene), 10.46 (s, 1H, NH), 13.66 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 44.49, 114.15, 117.49, 138.97, 145.13, 155.38, 176.32.

2-({3-[(Methylsulfonyl)amino]-4-oxo-3,4-dihydrothieno[3,2-*d*] pyrimidin-2-yl}thio)benzoic Acid (8a)

Methane sulfonamide **7a** (0.185 g, 0.67 mmol) was dissolved in water (30 ml) and KOH (75 mg, 1.34 mmol). 2-Jodobenzoic acid (0.17 g, 98%, 0.67 mmol), dissolved in a small amount of 5% sodium hydroxide, and powdery copper (30 mg)/copper(I) iodide (20 mg) were added to the stirred solution. The mixture was heated at reflux under stirring for 7 h and then filtered while hot; the resulting solution was cooled to room temperature and acidified with concentrated hydrochloride acid until pH 4–5. The white solid separated was collected, washed with water, dried and crystallized from water/dioxane to give **8a** as a white powder. Yield 40%; mp 219–222°C. IR (KBr): 3310 (NH), 1690 (C=O), 1340 and 1150 (SO_2-N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.36 (s, 3H, CH_3), 7.07 (d, $J = 4.6$ Hz, 1H, H-thiophene), 7.35–7.88 (m, 4H, Ar-H), 8.16 (d, $J = 4.6$ Hz, 1H, H-thiophene), 11.49 (s br, 1H, NH), 13.22 (s br, 1H, COOH). ^{13}C NMR (DMSO-d_6): δ 43.93, 118.55, 124.78, 128.19, 129.93, 130.46, 131.82, 136.08, 136.94, 137.38, 155.35, 155.95, 162.34, 176.53.

N-[2-[(2,4-Dinitrophenyl)thio]-4-oxothieno[3,2-*d*]pyrimidin-3(4*H*)-yl] methanesulfonamide (9a)

Methane sulfonamide **7a** (0.25 g, 0.9 mmol) was dissolved in ethanol/water (20 ml/20 ml) and KOH (0.1 g, 1.8 mmol). 2,4-Dinitroiodobenzene (0.27 g, 98%, 0.9 mmol) and powdery copper (30 mg)/copper(I) iodide (20 mg) were added to the stirred solution. The mixture was heated at reflux under stirring for 7 h and filtered while hot; after cooling to room temperature, the solution was poured in water (150 ml). The solution was filtered and acidified with concentrated hydrochloric acid until pH 3–4: a yellow solid mass separated that was collected, washed with water, dried, and crystallized from ethanol /water to give **9a** as a yellow powder. Yield 40%; mp >112°C dec. IR (KBr): 3225 (NH), 1695 (C=O), 1345 and 1155 (SO_2-N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.36 (s, 3H, CH_3), 7.11 (d, $J = 5.2$ Hz, 1H, H-thiophene), 8.18–8.88 (m, 3H, Ar-H), 8.23 (d, $J = 5.2$ Hz, 1H, H-thiophene), 11.66 (s br, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 43.77, 120.48, 124.61, 126.63, 127.20, 131.55, 132.18, 133.00, 144.92, 146.61, 154.22, 164.71, 170.01.

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N-[2-[(2,4-Difluorophenyl)thio]-4-oxothieno[3,2-*d*]pyrimidin-(4*H*)-yl] methanesulfonamide (10a)

Methane sulfonamide **7a** (0.25 g, 0.9 mmol) was dissolved in ethanol/water (20 ml/20 ml) and KOH (0.1 g, 1.8 mmol). 2,4-Difluoroiodobenzene (0.22 g, 98%, 0.12 ml, 0.9 mmol, d = 2.006) and powdery copper (30 mg)/ copper(I) iodide (20 mg) were added to the stirred solution. The mixture was heated at 80°C under stirring for 7 h; after cooling to room temperature, the mixture was filtered. The solution was poured in water (150 ml); the resulting solution was filtered and acidified with concentrated hydrochloric acid until pH 3–4. The mixture was held at room temperature for 4 h, and the separated white solid was collected, washed with water, dried, and crystallized from ethanol/water to give **10a** as a white powder. Yield 50%; mp 210–122°C. IR (KBr): 3215 (NH), 1700 (C═O), 1350 and 1160 (SO_2-N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.37 (s, 3H, CH_3), 7.11 (d, $J = 5.2$ Hz, 1H, H-thiophene), 7.18–7.79 (m, 3H, Ar-H), 8.20 (d, $J = 5.2$ Hz, 1H, H-thiophene), 11.52 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 44.09, 105.21 (t, $J = 26.15$), 114.40 (d, $J = 14.6$), 112.65 (d, 18.25), 118.76, 124.81, 137.68, 138.95 (d, $J = 9.75$), 155.33, 155.90, 160.71, 161.84, 166.83.

N-[2-(Cyclohexylthio)-4-oxothieno[3,2-*d*]pyrimidin-3(4*H*)yl]-methanesulfonamide (11a)

A mixture of methane sulfonamide **7a** (0.180 g, 0.65 mmol), cyclohexyl iodide (0.2 ml, 98%, d 1.625), and potassium carbonate (0.18 g) in dimethylformamide (2 ml) was heated at 80°C under stirring for 12 h; after cooling to room temperature, the mixture was acidified with hydrochloric acid and then poured in water (100 ml). The resulting solid was collected, washed with water, dried, and crystallized from petroleum ether to give **11a** as a white power. Yield 45%; mp 92–95°C dec. IR (KBr): 3195 (NH), 1695 (C═O), 1350 and 1155 (SO_2-N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.34–2.02 (m, 10H, cycloexyl), 3.28 (s, 3H, CH_3), 3.66 (s, 1H, S-CH_3), 7.33 (d, $J = 5.2$ Hz, 1H, H-thiophene), 8.24 (d, $J = 5.2$ Hz, 1H, H-thiophene), 11.15 (s br, 1H, NH).

3-Amino-2-(methylthio)thieno[3,2-*d*]pyrimidin-4(3*H*)-one (12a)

A mixture of sodium salt **5** (0.2 g, 0.85 mmol) and methyl iodide (0.16 ml, 99%, d = 2.27) in water (30 ml) was stirred at room temperature for 1.5 h. The resulting solid was collected, washed with water, dried, and crystallized from ethanol to give **12a** as pale microneedles. Yield 60%; mp 223–225°C. IR (KBr): 3310 and 3250 (NH_2), 1680 (C═O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.40 (s, 3H, CH_3), 5.81 (s, 2H, NH_2), 7.30 (d, $J = 5.2$ Hz, 1H, H-thiophene), 8.13 (d, $J = 5.2$ Hz, 1H, H-thiophene).

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N-(Methylsulfonyl)-N-[2-(methylthio)-4-oxothieno[3,2-*d*]pyrimidin-3(4*H*)-yl]methanesulfonamide) (13a)

A solution of methanesulfonyl chloride (0.22 ml, 2.85 mmol, 99.5%, d = 1.480) in dichloromethane (10 ml) was added slowly dropwise at room temperature to a stirred solution of methyl derivative **12a** (0.170 g, 0.8 mmol) and triethylamine (1 ml) in dichloromethane (20 ml). The mixture was stirred at room temperature for 3 h; the organic phase was washed with water, dried on sodium sulphate, and concentrated under vacuum to give a solid that was collected and washed with diethyl ether to give derivative **13a** as a yellow solid (resulted pure on TLC). Yield 66%; mp 195–197°C. IR (KBr): 1705 (C═O), 1380 and 1165 (SO_2-N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.59 (s, 3H, CH_3), 3.77 (s, 6H, 2 × CH_3-SO_2), 7.42 (d, J = 5.3 Hz, 1H, H-thiophene), 8.37 (d, J = 5.3 Hz, 1H, H-thiophene).

N-[2-(Methylthio)-4-oxothieno[3,2-d]pyrimidin-3(4*H*)-yl] methanesulfonamide (14a)

From Hydrolysis of Dimesyl Derivative **13a**

A mixture of dimesyl derivative **13a** (81 mg, 0.22 mmol) in a solution of potassium hydroxide (1 M) in water (10 ml) and tetrahydrofuran (90 ml) was stirred for 1 h at room temperature; the resulting solution was acidified with concentrated hydrochloric acid until pH 4–5 and then extracted with ethyl acetate. The organic phase was concentrated under vacuum to give a residue that was collected and dissolved in sodium hydroxide 10%. The resulting solution was filtered and acidified with concentrated hydrochloric acid until pH 4–5. The solid separated was collected, washed with water, and dried to give the monomesyl derivative **14a** as a white powder (resulted pure at TLC). Yield 35%; mp 197–200°C. IR (KBr): 3110 (NH), 1650 (C═O), 1355 and 1165 (SO_2-N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.46 (s, 3H, CH_3), 3.31 (s, 3H, CH_3), 7.36 (d, J = 5.3 Hz, 1H, H-thiophene), 8.26 (d, J = 5.3 Hz, 1H, H-thiophene), 11.23 (s, 1H, NH).

From Monomesyl Derivative **7a**

Methyl iodide (0.15 g, 99%, d = 2.27) was added to a solution of tioxo-monomesyl derivative **7a** (0.17 g, 0.6 mmol) in water (20 ml) and KOH (46 mg, 0.82 mmol), and the mixture was stirred at room temperature for 1.5 h. The mixture was filtered, and the filtrate was acidified with concentrated hydrochloride acid until pH 4–5. The solid separated was collected, washed with water, and dried to give **14a** as a white powder (resulted pure at TLC).

Yield 55%; the spectral and analytical data of the two samples were identical, and the mixture melting point was not depressed.

Methyl 2-({[2-(Methylsulfonyl)hydrazino]carbonothioyl}amino) benzoate (4b)

Methyl 2-isothiocyanatobenzoato (**2b**)[10] (2.0 g, 10.4 mmol) in dichloromethane (20 ml) was added dropwise at room temperature to a stirred solution of methanesulfonyl hydrazide (1.0 g, 98%, 8.9 mmol) in dichloromethane (25 ml). After the addition was complete, the mixture was stirred at room temperature for 4 h. The resulting solid was collected, washed with dichloromethane, dried, and recrystallized from ethanol to give **4b** as an amorphous white solid. Yield 50%; mp 188–190°C. IR (KBr): 3240 and 3155 (NH), 1695 (C═O), 1355 and 1155 (SO_2-N) cm^{-1}; ^{1} H NMR (DMSO-d_6): δ 3.09 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 7.21–7.95 (m, 3H, Ar-H), 8.80 (d, 1H, Ar-H), 9.86 (s, 1H, NH), 10.39 (s, 1H, NH), 11.36 (s, 1H, NH).

N-(4-Oxo-2-thioxo-1,4-dihydroquinazolin-3(2*H*)-yl)methane Sulfonamide (7b) from Its Dipotassium Salt of N-(4-Oxo-2-thioxo-1,4-dihydroquinazolin-3(2*H*)-yl)methanesulfonamide (4b)

A solution of mesyltiosemicarbazide **4b** (1.0 g, 3.3 mmol) and potassium hydroxide (0.45 g, 8.0 mmol) in ethanol (20 ml) was refluxed under stirring for 3 h; after cooling to room temperature, the resulting precipitate was collected, washed with warm ethanol, and dried to give the potassium salt of **7b** as a white amorphous solid. Yield 90%; mp 280–283°C. The compound was hygroscopic and was immediately kept in a dessicator. IR (KBr): 1680 (C═O) cm^{-1}; ^{1}H NMR (DMSO-d_6): d 2.92 (s, 3H, CH_3), 6.85–7.75 (m, 4H, ArH).

Concentrated hydrochloric acid was added to a stirred solution of potassium salt of **7b** (0.3 g, 0.86 mmol) in water (30 ml) until pH 3–4. The resulted precipitate was collected, washed with water, dried, and crystallized from dioxane/water to give **7b** as white powder. Yield 79%, mp 263–264°C dec. IR (KBr): 3225 (NH), 1665 (C═O), 1335 and 1150 (SO_2-N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.27 (s, 3H, CH_3), 7.33–8.01 (m, 4H, ArH), 10.42 (s, 1H, NH), 13.20 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 45.11, 115.28, 115.98, 124.89, 127.78, 136.31, 138.90, 158.66, 175.98.

2-({3-[(Methylsulfonyl)amino]-4-oxo-3,4-dihydroquinazolin-2-yl}thio)benzoic Acid (8b)

Methane sulphonamide **7b** (0.16 g, 0.57 mmol) was dissolved in water (30 ml), and KOH (64 mg, 1.14 mmol), 2-jodobenzoic acid (0.14 g, 98%,

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0.57 mmol) (dissolved in a small amount of 5% of sodium hydroxide), and powdery copper (30 mg)/copper(I) iodide (20 mg) were added. The mixture was heated at reflux under stirring, and after 7 h, it was filtered while hot. The resulting solution was cooled to room temperature and acidified with concentrated hydrochloride acid until pH 4–5. The white solid separated was collected, washed with water, dried, and crystallized from dioxane/water to give **8b** as a white powder. Yield 79%; mp 212–215°C. IR (KBr): 3310 (NH), 1705 (C═O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.28 (s, 3H, CH_3), 7.21–8.05 (m, 8H, Ar-H), 11.37 (s, 1H, NH), 13.01 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6): δ 47.78, 119.36, 126.36, 126.46, 126.73, 129.81, 130.39, 131.66, 135.51, 136.85, 138.40, 146.13, 159.60, 160.04, 168.71.

N-2-[(2,4-Dinitrophenyl)thio]-4-oxoquinazolin-3(4*H*)-yl] Methanesulfonamide (9b)

Methanesulphonamide **7b** (0.27 g, 0.98 mmol) was dissolved in ethanol/water (20 ml/20 ml) and KOH (0.110 g, 1.96 mmol). 2,4-Dinitroiodobenzene (0.27 g, 98%, 0.9 mmol) and powdery copper (30 mg)/copper(I) iodide (20 mg) were added to the stirred solution; the mixture was heated at reflux under stirring for 7 h and filtered while hot. After cooling to room temperature, the solution was poured in water (150 ml); the resulting solution was filtered and acidified with concentrated hydrochloric acid until pH 3–4. The yellow solid separated was collected, washed with water, dried, and crystallized from ethanol/water to give **9b** as a yellow powdery. Yield 40%, mp 149–151°C dec. IR (KBr): 3220 (br, NH), 1705 (C═O), 1345 and 1155 (SO_2-N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.16 (s, 3H, CH_3), 7.13–7.61 (m, 3H, Ar-H), 8.05–8.80 (m, 4H, Ar-H), 11.60 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 45.10, 119.95, 120.67, 125.10, 125.59, 126.13, 126.57, 133.28, 135.08, 138.41, 145.88, 147.36, 151.86, 160.44, 161.01.

N-[2-[(2,4-Difluorophenyl)thio]-4-oxoquinazolin-3(4*H*)-yl] Methanesulfonamide (10b)

Methane sulphonamide **7b** (0.16 g, 0.57 mmol) was dissolved in ethanol/water (20 ml/20 ml) and KOH (64 mg, 1.15 mmol). 2,4-Difluoroiodobenzene (0.15 g, 98%, 0.075 ml, 0.6 mmol, d = 2.006) and copper powder (30 mg)/copper(I) iodide (20 mg) were added to the stirred solution. The mixture was heated at 80°C under stirring for 7 h; after cooling to room temperature, the mixture was filtered, and the solution was poured in water (150 ml). The resulting solution was filtered and acidified with concentrated hydrochloric acid until pH 3–4. The white solid separated was collected, washed with water, dried, and crystallized from ethanol/water to give **10b** as a white powder. Yield 40%; mp 229–230°C. IR (KBr): 3275 (NH), 1695 (C═O),

1335 and 1150 (SO_2-N) cm^{-1}; ^1H NMR (DMSO-δ_6): δ 3.37 (s, 3H, CH_3), 7.2–8.10 (m, 7H, Ar-H), 11.46 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 43.87, 105.06 (t, $J = 26.75$), 112.50 (d, $J = 22.45$), 119.29, 126.44, 126.74, 126.84, 135.66, 139 (d, $J = 10.30$), 146.10, 158.09, 159.56, 160.50, 165.50.

N-[2-(Cyclohexylthio)-4-oxoquinazolin-3(4*H*)yl] methanesulfonamide (11b)

A mixture of **7b** (0.18 g, 0.67 mmol), cyclohexyl iodide (0.2 ml, 98%, d = 1.625), and potassium carbonate (0.18 g) in dimethylformamide (2 ml) was heated at 80°C under stirring for 12 h. After cooling to room temperature, the mixture was acidified with hydrochloric acid and then poured in water (100 ml). The resulting solid was collected, washed with water, dried, and crystallized from petroleum ether to give **11b** as a white power. Yield 30%; mp 176–178°C. IR (KBr): 3215 (NH), 1710 (C═O), 1325 and 1150 (SO_2N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.45–2.05 (m, 10H, cycloexyl), 3.29 (s, 3H, CH_3), 3.72 (s, 1H, S-CH), 7.38–8.10 (m, 4H, Ar-H), 11.14 (s br, 1H, NH).

3-Amino-2-(methylthio)quinazolin-4(3*H*)-one (12b)

A mixture of potassium salt of 3-amino-2,3-dihydro-2-thioxo-4(1H)-quinazolinone[11] (1.0 g g, 4.3 mmol) and methyl iodide (0.85 ml, 99%, d = 2.27) in water (50 ml) was stirred at room temperature for 1.5 h. The resulting solid was collected, washed with water, dried, and crystallized from ethanol/water to give **12b** as amorphous white solid. Yield 50%; mp 153–154°C. IR (KBr): 3315 and 3210 (NH_2), 1680 (C═O) cm^{-1}; ^1H MNR (DMSO-d_6): δ 2.43 (s, 3H, CH_3), 5.77 (s, 2H, NH_2), 7.37–8.08 (m, 4H, Ar-H).

N-(Methylsulfonyl)-N-[2-(methylthio)-4-oxoquinazolin3(4*H*)yl] methanesulfonamide (13b)

A solution of methanesulfonyl chloride (0.22 ml, 2.85 mmol, 99.5%, d = 1.480) in dichloromethane (10 ml) was added slowly dropwise at room temperature to a stirred solution of methyl derivative **12b** (0.165 g, 0.8 mmol) and triethylamine (1 ml) in dichloromethane (20 ml). The mixture was stirred at room temperature for 3 h; the organic phase was washed with water, dried on sodium sulphate, and concentrated under vacuum to give a solid, which was collected and washed with diethyl ether to give derivative **13b** as a pale yellow solid (resulted pure on TLC). Yield 73%; mp 167–169°C dec. IR (KBr): 1710 (C═O), 1380 and 1160 (SO_2-N)

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cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.59 (s, 3H, CH_3), 3.77 (s, 6H, 2 × CH_3-SO_2), 7.47–8.05 (m, 4H, Ar-H).

N-[2-(Methylthio)-4-oxoquinazolin-3(4*H*)-yl] methanesulfonamide (14b)

From Hydrolysis of Dimesyl Derivative **13b**

A mixture of dimesyl derivative **13b** (0.08 g, 0.22 mmol) in a solution of potassium hydroxide (1 M) in water (10 ml) and tetrahydrofuran (90 ml) was stirred for 1 h at room temperature; the resulting solution was acidified with concentrated hydrochloric acid until pH 4–5 and then extracted with ethyl acetate. The organic phase was concentrated under vacuum to give a residue that was collected and dissolved in sodium hydroxide 10%. The resulting solution was filtered and acidified with concentrated hydrochloric acid until pH 4–5. The solid separated was collected, washed with water, and dried to give the monomesyl derivative **14b** as a white powder (resulted pure at TLC). Yield 86%; mp 193–95°C. IR (KBr): 3245 (NH), 1695 (C═O), 1345 and 1155 (SO_2-N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.46 (s, 3H, CH_3), 3.31 (s, 3H, CH_3), 7.45–8.11 (m, 4H, Ar-H), 11.16 (s, 1H, NH).

From Monomesyl Derivative **7b**

Methyl iodide (0.4 ml, 99%, d = 2.27) was added to a solution of **7b** (0.16 g, 0.6 mmol) and potassium hydroxide (46 mg, 0.82 mmol) in water (20 ml). The mixture was stirred at room temperature for 12 h. The mixture was filtered, and the filtrate was acidified with concentrated hydrochloride acid until pH 4–5. The solid separated was collected, washed with water, and dried to give **14b** as a white powder (resulted pure at TLC). Yield 24%. The spectral and analytical data of the two samples were identical, and the mixture melting point was not depressed.

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