New Approaches for the Synthesis of Heterocyclic Compounds Derived from Cyclohexan-1,3-dione with Anti-proliferative Activities

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Received: 06-11-2020

Abstract

In the present work a series of heterocyclization reactions were adopted using cyclohexan-1,3-dione through its reaction with either furan-2-carbaldehyde or thiophene-2-carbaldehyde to give the corresponding ylidene derivatives **3a,b**. The latter compounds underwent heterocyclization reactions to give thiophene and pyran derivatives **5a–d** and **6a–d**, respectively. Moreover, compounds **3a,b** reacted with elemental sulfur and phenyl isothiocyanate to give the fused thiazole derivatives **8a,b**. In addition, the reaction with either of hydrazine hydrate or phenylhydrazine has given the 4-hydrazono-4,5,6,7-tetrahydro-2H-indazole derivatives **10a–d**, respectively. Similarly, the reaction of either **3a** or **3b** with hydroxylamine hydrochloride gave the 6,7-dihydrobenzo[c]isoxazol-4(5H)-one oxime derivatives **12a** and **12b**, respectively. Other fused heterocyclic compounds were produced and their structures were elucidated. Evaluation of the synthesized compounds against selected cancer cell lines was performed. The most active compounds were further evaluated against tyrosine kinases and Pim-1 kinase inhibitions.

Keyword: Cyclohexan-1,3-dione, thiophene, pyrazole, isoxazole, cytotoxicity

1. Introduction

Within the last few years the synthesis of heterocyclic compounds attracted the attention due to the wide spectrum of their high biological activities. In addition, many compounds were considered as good synthons for fused systems that were characterized by different pharmaceutical applications.^{1–10} Therefore, organic chemists have been making extensive efforts to produce heterocyclic compounds by developing new and efficient synthetic transformations. Within the field of pharmaceutical chemistry, many pyrazoles, thiophenes and thiazoles were reported with a wide spectrum of biological activities that included potent analgesic, anti-convulsant, anti-inflammatory and anti-bacterial, anti-pyretic, anti-tumor, anti-parasitic, anti-microbial, anti-histaminic (H1), anti-anxiety activities in tests in mice, anti-arrhythmic and as serotonin antagonists.^{11–23} The present work is dealing with the current application of pyrazole, thio-

phene, pyrimidine and oxazine cores in the designing of anticancer agents within tumor progression. In our research it was possible to verify that such compounds are readily applicable to provide new insights and valuable inspiration in the research of new drugs and in their development as well as to contribute to the management of cancer. This encouraged our group to be attracted toward the synthesis of pyran derivatives research through the uses of β -diketones. The produced heterocyclic compounds showed high anti-proliferative activities against cancer cell lines together with high inhibitions toward tyrosine kinases.^{24–26} Based on such importance of heterocyclic compounds, therefore, we studied the reaction of cyclohexan-1,3-dione with some heterocyclic aldehydes and cyanomethylene reagents followed by heterocyclization of the products. Additionally, the anti-tumor evaluations of the resulting compounds towards cancer cell lines are reported.

2. Experimental

2. 1. General

The melting points of the obtained compounds were determined using Electrothermal digital melting point apparatus and are uncorrected. IR spectra (KBr discs) were measured on an FTIR plus 460 or PyeUnicam SP-1000 spectrophotometer (PyeUnicam, UK, Cambridge). ^1H NMR spectra were obtained using Varian Gemini-300 (300 MHz, Varian UK) using DMSO- d_6 as the solvent and tetramethylsilane (TMS) as the internal standard; chemical shifts are expressed as δ ppm. The mass spectra were measured with Hewlett Packard 5988 A GC/MS system (Hewlett-Packard, Agilent, USA) instrument.

2. 1. 1. General Procedure for the Synthesis of the 2-Methylenecyclohexane-1,3-dione Derivatives 3a,b

Either of furan-2-carbaldehyde (0.96 g, 0.01 mol) of thiophene-2-carbaldehyde (1.12 g, 0.01 mol) was added to a solution of cyclohexane-1,3-dione (1) (1.12 g, 0.01 mol) in absolute ethanol (40 mL) containing piperidine (0.50 mL). The reaction mixture, in each case, was heated under reflux for 3 h then poured onto ice/water containing a few drops of hydrochloric acid and the formed solid product was collected by filtration.

2-(Furan-2-ylmethylene)cyclohexane-1,3-dione (3a)

Yellow crystals from ethanol, yield 1.46 g (77%), m.p. 185–188 °C. IR (KBr) ν_{max} (cm^{-1}) 3053 (CH, aromatic), 1704, 1687 (2 CO), 1632 (C=C); ^1H NMR (DMSO- d_6 , 300 MHz) δ 1.45–1.69 (m, 2H, CH_2), 2.63–2.76 (m, 4H, 2CH_2), 6.82 (s, 1H, CH), 6.80–7.83 (m, 3H, furan H); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 16.4, 36.5, 39.2 (3CH_2), 112.4, 158.1 (C=CH), 135.8, 140.2, 142.6, 146.1 (furan C), 177.1, 179.4 (2CO). Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{O}_3$: C, 69.46; H, 5.30. Found: C, 69.31; H, 5.52. MS: m/z 190 (M^+ , 28%).

2-(Thiophen-2-ylmethylene)cyclohexane-1,3-dione (3b)

Orange crystals from ethanol, yield 1.44 g (70%), m.p. 201–204 °C. IR (KBr) ν_{max} (cm^{-1}) 3055 (CH, aromatic), 1703, 1689 (2 CO), 1630 (C=C); ^1H NMR (DMSO- d_6 , 200 MHz) δ 1.43–1.68 (m, 2H, CH_2), 2.61–2.74 (m, 4H, 2CH_2), 6.80 (s, 1H, CH), 6.82–7.88 (m, 3H, thiophene H); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 16.8, 36.2, 39.1 (3CH_2), 112.6, 158.8 (C=CH), 135.6, 140.5, 142.3, 146.2 (thiophene C), 177.6, 179.2 (2CO). Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{O}_2\text{S}$: C, 64.05; H, 4.89; S, 15.55. Found: C, 63.80; H, 4.73; S, 15.38. MS: m/z 206 (M^+ , 32%).

2. 1. 2. General Procedure for the Synthesis of the 6,7-Dihydrobenzo[*b*]thiophen-5(4*H*)-one Derivatives 5a–d

Either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.07 g, 0.01 mol) was added to a solution of

either compound 3a (1.90 g, 0.01 mol) or 3b (2.06 g, 0.01 mol) in ethanol (40 mL) containing triethylamine (0.50 mL). The reaction mixture was heated under reflux for 3 h then poured onto ice/water mixture containing a few drops of hydrochloric acid and the formed solid product was collected by filtration.

2-Amino-4-(furan-2-ylmethylene)-5-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (5a)

Pale yellow crystals from ethanol, yield 1.94 g (70%), m.p. 130–132 °C. IR (KBr) ν_{max} (cm^{-1}) 3482–3353 (NH_2), 3056 (CH, aromatic), 2220 (CN), 1686 (CO), 1630 (C=C); ^1H NMR (DMSO- d_6 , 300 MHz) δ 2.62–2.78 (2t, 4H, 2CH_2), 4.73 (s, 2H, D_2O exchangeable, NH_2), 6.84 (s, 1H, CH), 6.82–7.86 (m, 3H, furan H); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 16.6, 36.3, 39.5 (3CH_2), 112.6, 158.4 (C=CH), 116.8 (CN), 135.4, 140.6, 141.4, 142.2, 142.7, 144.8, 145.6, 146.5 (thiophene, furan C), 179.3 (CO). Anal. Calcd for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_2\text{S}$: C, 62.21; H, 3.73; N, 10.36; S, 11.86. Found: C, 62.36; H, 3.80; N, 10.41; S, 12.04. MS: m/z 270 (M^+ , 32%).

Ethyl 2-Amino-4-(furan-2-ylmethylene)-5-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (5b)

Yellow crystals from ethanol, yield 2.21 g (70%), m.p. 125–127 °C. IR (KBr) ν_{max} (cm^{-1}) 3494–3368 (NH_2), 3058 (CH, aromatic), 2931, 2972 (CH_2 , CH_3), 1689, 1688 (2 CO), 1630 (C=C); ^1H NMR (DMSO- d_6 , 300 MHz) δ 1.12 (t, 3H, $J = 7.28$ Hz, CH_3), 2.68–2.74 (2t, 4H, 2CH_2), 4.21 (q, 2H, $J = 7.28$ Hz, CH_2), 4.76 (s, 2H, D_2O exchangeable, NH_2), 6.86 (s, 1H, CH), 6.84–7.92 (m, 3H, furan H); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 16.3 (OCH_2CH_3), 16.4, 36.8, 39.3 (3CH_2), 52.8 (OCH_2CH_3), 112.3, 158.6 (C=CH), 135.6, 18.0, 140.8, 141.6, 142.3, 143.5, 144.2, 146.7 (thiophene, furan C), 164.8, 178.3 (2CO). Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{NO}_4\text{S}$: C, 60.55; H, 4.76; N, 4.41; S, 10.10. Found: C, 60.80; H, 4.83; N, 4.60; S, 10.26. MS: m/z 317 (M^+ , 38%).

2-Amino-5-oxo-4-(thiophen-2-ylmethylene)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (5c)

Orange crystals from ethanol, yield 1.94 g (68%), m.p. 202–205 °C. IR (KBr) ν_{max} (cm^{-1}) 3459–3342 (NH_2), 3058 (CH, aromatic), 2221 (CN), 1688 (CO), 1630 (C=C); ^1H NMR (DMSO- d_6 , 300 MHz) δ 2.64–2.75 (2t, 4H, 2CH_2), 4.74 (s, 2H, D_2O exchangeable, NH_2), 6.88 (s, 1H, CH), 6.80–7.87 (m, 3H, thiophene H); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 16.3, 39.8 (2CH_2), 112.3, 158.8 (C=CH), 116.9 (CN), 134.2, 138.6, 140.3, 142.4, 143.1, 143.6, 145.2, 146.7 (two thiophene C), 179.8 (CO). Anal. Calcd for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{OS}_2$: C, 58.72; H, 3.52; N, 9.78; S, 22.39. Found: C, 58.36; H, 3.80; N, 9.68; S, 22.41. MS: m/z 286 (M^+ , 46%).

Ethyl 2-Amino-5-oxo-4-(thiophen-2-ylmethylene)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (5d)

Pale yellow crystals from ethanol, yield 2.13 g (66%), m.p. 189–192 °C. IR (KBr) ν_{max} (cm^{-1}) 3486–3342 (NH_2), 3054 (CH, aromatic), 2938, 2893 (CH_2 , CH_3), 1689, 1686 (2

CO), 1630 (C=C); ^1H NMR (DMSO- d_6 , 300 MHz) δ 1.13 (t, 3H, $J = 7.59$ Hz, CH_3), 2.64–2.78 (2t, 4H, 2CH_2), 4.23 (q, 2H, $J = 7.59$ Hz, CH_2), 4.79 (s, 2H, D_2O exchangeable, NH_2), 6.84 (s, 1H, CH), 7.29–7.85 (m, 3H, thiophene H); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 16.1 (OCH_2CH_3), 16.5, 36.4, 39.7 (3CH_2), 52.3 (OCH_2CH_3), 112.1, 158.4 (C=CH), 135.3, 136.7, 138.3, 140.5, 141.5, 142.0, 143.8, 144.6, 146.8 (two thiophene C), 164.5, 178.9 (2CO). Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{NO}_3\text{S}_2$: C, 57.64; H, 4.53; N, 4.20; S, 19.23. Found: C, 57.80; H, 4.71; N, 4.38; S, 19.46. MS: m/z 333 (M^+ , 26%).

2. 1. 3. General Procedure for the Synthesis of the 2H-Chromen-5-one Derivatives 6a–d

Either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) was added to a solution of either compound **3a** (1.90 g, 0.01 mol) or **3b** (2.06 g, 0.01 mol) in absolute ethanol (40 mL) containing triethylamine (1.0 mL). The reaction mixture, in each case, was heated under reflux for 3 h then the excess solvent was removed under vacuum. The remaining product was triturated with diethyl ether and the formed solid product was collected by filtration.

2-Amino-4-(furan-2-yl)-5-oxo-5,6,7,8-tetrahydro-2H-chromene-3-carbonitrile (6a)

Pale yellow crystals from ethanol, yield 1.66 g (69%), m.p. 194–196 °C. IR (KBr) ν_{max} (cm^{-1}) 3470–3328 (NH_2), 3055 (CH, aromatic), 2220 (CN), 1632 (C=C); ^1H NMR (DMSO- d_6 , 300 MHz) δ 1.41–1.66 (m, 4H, 2CH_2), 2.61–2.76 (m, 4H, 2CH_2), 4.71 (s, 2H, D_2O exchangeable, NH_2), 6.04 (s, 1H, pyran H-4), 6.87–7.83 (m, 3H, furan H); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 16.1, 36.3, 37.2, 39.5 (4CH_2), 116.8 (CN), 134.3, 141.5, 141.8, 142.6, 143.1, 143.8, 145.2, 146.4 (pyran, furan C), 178.4 (CO). Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.38; H, 5.92; N, 11.29. MS: m/z 242 (M^+ , 28%).

4-(Furan-2-yl)-2-hydroxy-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6b)

Pale brown crystals from ethanol, yield 1.79 g (74%), m.p. 198–200 °C. IR (KBr) ν_{max} (cm^{-1}) 3568–3339 (OH), 3055 (CH, aromatic), 2222 (CN), 1630 (C=C); ^1H NMR (DMSO- d_6 , 300 MHz) δ 1.32–1.68 (m, 4H, 2CH_2), 2.63–2.74 (m, 4H, 2CH_2), 6.02 (s, 1H, pyran H-4), 6.84–7.85 (m, 3H, furan H), 9.80 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 16.3, 36.5, 37.1, 39.3 (4CH_2), 116.7 (CN), 134.1, 138.0, 140.2, 141.7, 142.3, 142.9, 143.3, 146.6 (furan, pyran C). Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{NO}_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.92; H, 5.42; N, 5.58. MS: m/z 243 (M^+ , 36%).

2-Amino-4-(thiophen-2-yl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6c)

Brown crystals from ethanol, yield 1.85 g (72%), m.p. 211–214 °C. IR (KBr) ν_{max} (cm^{-1}) 3445–3372 (NH_2), 3055 (CH, aromatic), 2220 (CN), 1630 (C=C); ^1H NMR

(DMSO- d_6 , 200 MHz) δ 1.41–1.64 (m, 4H, 2CH_2), 2.61–2.77 (m, 4H, 2CH_2), 4.73 (s, 2H, D_2O exchangeable, NH_2), 6.07 (s, 1H, thiophene H-4), 6.91–7.73 (m, 3H, thiophene H); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 16.3, 36.6, 37.2, 39.8 (4CH_2), 116.4 (CN), 134.6, 138.7, 140.2, 141.6, 142.3, 142.8, 143.6, 146.2 (thiophene, pyran C). Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$: C, 65.09; H, 5.46; N, 10.84; S, 12.41. Found: C, 64.90; H, 5.62; N, 10.68; S, 12.58. MS: m/z 258 (M^+ , 40%).

2-Hydroxy-4-(thiophen-2-yl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6d)

Orange crystals from ethanol, yield 1.96 g (76%), m.p. 177–179 °C. IR (KBr) ν_{max} (cm^{-1}) 3542–3329 (OH), 3055 (CH, aromatic), 2220 (CN), 1688 (CO), 1630 (C=C); ^1H NMR (DMSO- d_6 , 300 MHz) δ 1.34–1.66 (m, 4H, 2CH_2), 2.61–2.76 (m, 4H, 2CH_2), 6.04 (s, 1H, pyran H-4), 6.76–7.89 (m, 3H, furan H), 9.83 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 16.1, 36.3, 37.4, 39.6 (4CH_2), 116.9 (CN), 134.4, 139.2, 140.8, 141.5, 143.7, 144.3, 145.2, 146.8 (furan, pyran C), 178.6 (CO). Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{NO}_2\text{S}$: C, 64.84; H, 5.05; N, 5.40; S, 12.36. Found: C, 64.72; H, 5.24; N, 12.59. MS: m/z 259 (M^+ , 42%).

2. 1. 4. General Procedure for the Synthesis of 2-Thioxohexahydrobenzo[d]thiazole Derivatives 8a,b

Each of elemental sulfur (0.32 g, 0.01 mol) and phenyl isothiocyanate (1.30 g, 0.01 mol) were added to a solution of either compound **3a** (1.90 g, 0.01 mol) or **3b** (2.06 g, 0.01 mol) in 1,4-dioxane (40 mL) containing triethylamine (1.0 mL). The reaction mixture was heated under reflux for 2 h then was left to cool and the formed solid product, in each case, was collected by filtration.

4-(Furan-2-ylmethylene)-3-phenyl-2-thioxo-2,3,6,7-tetrahydrobenzo[d]thiazol-5(4H)-one (8a)

Yellow crystals from ethanol, yield 2.50 g (74%), m.p. 168–169 °C. IR (KBr) ν_{max} (cm^{-1}) 3055 (CH, aromatic), 1688 (CO), 1630 (C=C), 1205 (C=S); ^1H NMR (DMSO- d_6 , 300 MHz) δ 2.63–2.78 (2t, 4H, 2CH_2), 6.87 (s, 1H, CH), 6.82–7.85 (m, 8H, C_6H_5 , furan H); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 16.1, 36.6, 39.5 (3CH_2), 112.1, 158.4 (C=CH), 120.3, 122.6, 124.8, 127.2, 134.6, 140.8, 142.2, 143.2, 143.8, 146.9 (C_6H_5 , furan, thiazole C), 179.6 (CO), 181.3 (C=S). Anal. Calcd for $\text{C}_{18}\text{H}_{13}\text{NO}_2\text{S}_2$: C, 63.69; H, 3.86; N, 4.13; S, 18.89. Found: C, 63.80; H, 3.69; N, 4.32; S, 19.18. MS: m/z 339 (M^+ , 48%).

3-Phenyl-4-(thiophen-2-ylmethylene)-2-thioxo-2,3,6,7-tetrahydrobenzo[d]thiazol-5(4H)-one (8b)

Pale yellow crystals from 1,4-dioxane, yield 2.84 g (80%), m.p. 222–225 °C. IR (KBr) ν_{max} (cm^{-1}) 3055 (CH, aromatic), 1689 (CO), 1630 (C=C), 1205 (C=S); ^1H NMR (DMSO- d_6 , 300 MHz) δ 2.61–2.79 (2t, 4H, 2CH_2), 6.88 (s, 1H, CH), 6.96–7.89 (m, 8H, C_6H_5 , thiophene H); ^{13}C

NMR (DMSO- d_6 , 75 MHz) δ 16.5, 39.7 (2CH₂), 112.4, 158.6 (C=CH), 120.7, 122.5, 124.3, 126.8, 136.2, 140.6, 141.3, 142.6, 143.4, 146.6 (C₆H₅, thiophene, thiazole C), 179.3 (CO), 181.3 (C=S). Anal. Calcd for C₁₈H₁₃NOS₃: C, 60.81; H, 3.69; N, 3.94; S, 27.06. Found: C, 60.69; H, 3.74; N, 4.12; S, 26.86. MS: m/z 355 (M⁺, 59%).

2. 1. 5. General Procedure for the Synthesis of the 4-Hydrazono-4,5,6,7-tetrahydro-2H-indazole Derivatives 10a–d

Either hydrazine hydrate (0.1 mL, 0.02 mol) or phenylhydrazine (2.16 g, 0.02 mol) was added to a solution of either of compound **3a** (1.90 g, 0.01 mol) or **3b** (2.06 g, 0.01 mol) in 1,4-dioxane (40 mL). The reaction mixture was heated under reflux for 3 h then poured onto ice/water mixture containing a few drops of hydrochloric acid and the formed solid product was collected by filtration.

3-(Furan-2-yl)-4-hydrazono-4,5,6,7-tetrahydro-2H-indazole (10a)

Yellow crystals from ethanol, yield 1.55 g (72%), m.p. 158–161 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3472–3328 (NH, NH₂), 3055 (CH, aromatic), 1658 (exocyclic C=N), 1630 (C=C); ¹H NMR (DMSO- d_6 , 300 MHz) δ 1.32–1.64 (m, 2H, CH₂), 2.60–2.78 (m, 4H, 2CH₂), 4.86 (s, 2H, D₂O exchangeable, NH₂), 7.14–7.84 (m, 3H, furan H), 8.28 (s, 1H, D₂O exchangeable, NH); ¹³C NMR (DMSO- d_6 , 75 MHz) δ 16.5, 36.3, 39.7 (3CH₂), 112.4, 158.6 (C=CH), 136.4, 138.0, 139.2, 140.3, 143.8, 146.2 (furan, pyrazole C), 168.3, 172.8 (2C=N). Anal. Calcd for C₁₁H₁₂N₄O: C, 61.10; H, 5.59; N, 25.91. Found: C, 60.93; H, 5.29; N, 25.77. MS: m/z 216 (M⁺, 36%).

3-(Furan-2-yl)-2-phenyl-4-(2-phenylhydrazono)-4,5,6,7-tetrahydro-2H-indazole (10b)

Pale yellow crystals from 1,4-dioxane, yield 2.50 g (68%), m.p. 177–180 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3463–3341 (NH), 3055 (CH, aromatic), 1652 (exocyclic C=N), 1630 (C=C); ¹H NMR (DMSO- d_6 , 300 MHz) δ 1.31–1.67 (m, 2H, CH₂), 2.63–2.77 (m, 4H, 2CH₂), 7.26–7.89 (m, 13H, 2C₆H₅, furan H), 8.30 (s, 1H, D₂O exchangeable, NH); ¹³C NMR (DMSO- d_6 , 75 MHz) δ 16.2, 36.1, 39.4 (3CH₂), 120.2, 121.6, 123.2, 123.8, 124.0, 126.3, 128.3, 1290.1, 136.4, 140.3, 140.8, 141.2, 143.4, 146.8 (2C₆H₅, pyrazole, furan C), 176.2, 178.3 (2C=N). Anal. Calcd for C₂₃H₂₀N₄O: C, 74.98; H, 5.47; N, 15.21. Found: C, 75.19; H, 5.31; N, 15.02. MS: m/z 368 (M⁺, 41%).

4-Hydrazono-3-(thiophen-2-yl)-4,5,6,7-tetrahydro-2H-indazole (10c)

Pale yellow crystals from 1,4-dioxane, yield 1.76 g (76%), m.p. 233–236 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3458–3342 (NH, NH₂), 3055 (CH, aromatic), 1656 (exocyclic C=N), 1630 (C=C); ¹H NMR (DMSO- d_6 , 300 MHz) δ 1.33–1.67 (m, 2H, CH₂), 2.62–2.75 (m, 4H, 2CH₂), 4.80 (s, 2H, D₂O

exchangeable, NH₂), 6.96–7.88 (m, 3H, thiophene H), 8.28 (s, 1H, D₂O exchangeable, NH); ¹³C NMR (DMSO- d_6 , 75 MHz) δ 16.5, 36.3, 39.7 (3CH₂), 112.4, 158.6 (C=CH), 136.6, 138.4, 139.2, 140.1, 143.5, 146.4 (thiophene, pyrazole C), 176.4, 178.6 (2C=N). Anal. Calcd for C₁₁H₁₂N₄S: C, 56.87; H, 5.21; N, 24.12; S, 13.80. Found: C, 56.93; H, 5.30; N, 24.31; S, 13.98. MS: m/z 232 (M⁺, 28%).

2-Phenyl-4-(2-phenylhydrazono)-3-(thiophen-2-yl)-4,5,6,7-tetrahydro-2H-indazole (10d)

Orange crystals from ethanol, yield 2.61 g (68%), m.p. 180–184 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3484–3326 (NH), 3055 (CH, aromatic), 1655 (exocyclic C=N), 1630 (C=C); ¹H NMR (DMSO- d_6 , 300 MHz) δ 1.32–1.69 (m, 2H, CH₂), 2.60–2.78 (m, 4H, 2CH₂), 7.23–7.85 (m, 13H, 2C₆H₅, thiophene H), 8.29 (s, 1H, D₂O exchangeable, NH); ¹³C NMR (DMSO- d_6 , 75 MHz) δ 16.4, 36.6, 39.4 (3CH₂), 120.8, 122.2, 123.6, 123.9, 125.8, 126.6, 128.1, 129.7, 135.8, 140.6, 142.6, 142.9, 143.1, 146.5 (2C₆H₅, pyrazole, thiophene C), 176.4, 178.6 (2C=N). Anal. Calcd for C₂₃H₂₀N₄S: C, 71.85; H, 5.24; N, 14.57; S, 8.34. Found: C, 72.13; H, 5.42; N, 14.38; S, 8.62. MS: m/z 384 (M⁺, 26%).

2. 1. 6. General Procedure for the Synthesis of the 6,7-Dihydrobenzo[c]isoxazol-4(5H)-one Oxime Derivatives 12a,b

Hydroxylamine hydrochloride (1.40 g, 0.02 mol) was added to a solution of either compound **3a** (1.90 g, 0.01 mol) or **3b** (2.06 g, 0.01 mol) in 1,4-dioxane (40 mL) containing sodium acetate (2.0 g). The reaction mixture was heated under reflux for 3 h then poured onto ice/water mixture and the formed solid product, in each case, was collected by filtration.

3-(Furan-2-yl)-6,7-dihydrobenzo[c]isoxazol-4(5H)-one Oxime (12a)

Yellow crystals from 1,4-dioxane, yield 1.52 g (70%), m.p. 177–180 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3524–3376 (OH), 3055 (CH, aromatic), 1655 (exocyclic C=N), 1630 (C=C); ¹H NMR (DMSO- d_6 , 300 MHz) δ 1.31–1.68 (m, 2H, CH₂), 2.63–2.77 (m, 4H, 2CH₂), 6.93–7.81 (m, 3H, furan H), 10.29 (s, 1H, D₂O exchangeable, OH); ¹³C NMR (DMSO- d_6 , 75 MHz) δ 16.2, 36.3, 39.2 (3CH₂), 132.3, 135.1, 140.6, 141.5, 142.8, 143.6 (isoxazole, furan C), 176.1, 178.4 (2C=N). Anal. Calcd for C₁₁H₁₀N₂O₃: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.39; H, 4.80; N, 12.93. MS: m/z 218 (M⁺, 32%).

3-(Thiophen-2-yl)-6,7-dihydrobenzo[c]isoxazol-4(5H)-one Oxime (12b)

Pale yellow crystals from 1,4-dioxane, yield 1.52 g (65%), m.p. 222–225 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3551–3349 (OH), 3055 (CH, aromatic), 1653 (exocyclic C=N), 1630 (C=C); ¹H NMR (DMSO- d_6 , 300 MHz) δ 1.32–1.65 (m, 2H, CH₂), 2.61–2.74 (m, 4H, 2CH₂), 7.22–7.80 (m, 3H,

thiophene H), 10.29 (s, 1H, D₂O exchangeable, OH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 16.4, 36.6, 39.8 (3CH₂), 132.1, 134.3, 138.8, 140.9, 141.6, 144.2 (isoxazole, thiophene C), 176.0, 178.6 (2C=N). Anal. Calcd for C₁₁H₁₀N₂O₂S: C, 56.39; H, 4.30; N, 11.96; S, 13.69. Found: C, 56.42; H, 4.49; N, 12.05; S, 13.83 MS: *m/z* 234 (M⁺, 42%).

2. 1. 7. 2-(Ethoxymethylene)cyclohexane-1,3-dione (14)

Ethyl orthoformate (1.68 g, 0.01 mol) was added to a solution of cyclohexan-1,3-dione (1.12 g, 0.01 mol) in acetic acid (40 mL). The reaction mixture was heated under reflux for 2 h then evaporated in vacuum and the remaining product was triturated with ethanol and the formed solid product was collected by filtration.

Yellow crystals from ethanol, yield 1.27 g (76%), m.p. 282–258 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 2980 (CH₂), 1689, 1686 (CO), 1632 (C=C); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 1.28 (t, 3H, *J* = 6.83 Hz, CH₃), 1.49–1.67 (m, 2H, CH₂), 2.65–2.73 (m, 4H, 2CH₂), 3.89 (q, 2H, *J* = 6.83 Hz, CH₂), 6.79 (s, 1H, CH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 16.3 (OCH₂CH₃), 16.2, 36.8, 39.0 (3CH₂), 62.8 (OCH₂CH₃), 112.3, 158.2 (C=CH), 177.3, 179.2 (2CO). Analysis Calcd for C₉H₁₂O₃ (168.19): C, 64.27; H, 7.19%. Found: C, 64.08; H, 7.33%. MS: *m/z* 168 (M⁺, 22%).

2. 1. 8. General Procedure for the Synthesis of the 2-(Aminomethylene)cyclohexane-1,3-dione Derivatives 16a–c

Equimolar amounts of aniline (0.93 g, 0.01 mol), 4-methylaniline (1.08 g, 0.01 mol) or 4-methoxyaniline (1.34 g, 0.01 mol) and compound **14** (1.68 g, 0.01 mol) in 1,4-dioxane (50 mL) were refluxed for 4 h. The reaction mixture was evaporated under vacuum and the remaining product was triturated with ethanol and the solid product formed, in each case, was collected by filtration.

2-((Phenylamino)methylene)cyclohexane-1,3-dione (16a)

Yellow crystals from ethanol, yield 1.24 g (58%), m.p. 165–167 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3480–3363 (NH), 3055 (CH aromatic), 2980 (CH₂), 1688, 1686 (2CO), 1632 (C=C); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 1.42–1.69 (m, 2H, CH₂), 2.63–2.75 (m, 4H, 2CH₂), 6.05 (s, 1H, CH), 7.28–7.39 (s, 5H, C₆H₅), 8.28 (s, 1H, D₂O exchangeable, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 16.5, 36.8, 39.4 (3CH₂), 94.3 (CH), 120.3, 123.1, 124.8, 126.4 (C₆H₅), 177.1, 179.8 (2CO). Anal. Calcd for C₁₃H₁₃NO₂ (215.25): C, 72.54; H, 6.09; N, 6.51%. Found: C, 72.31; H, 6.29; N, 6.38%. MS: *m/z* 215 (M⁺, 35%).

2-((Phenylamino)methylene)cyclohexane-1,3-dione (16b)

Yellow crystals from ethanol, yield 1.67 g (73%), m.p. 214–217 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3459–3341 (NH), 3054 (CH aromatic), 2982, 2886 (CH₃, CH₂), 1688, 1686 (2CO),

1631 (C=C); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 1.43–1.67 (m, 2H, CH₂), 2.61–2.76 (m, 4H, 2CH₂), 2.88 (s, 3H, CH₃), 6.08 (s, 1H, CH), 7.24–7.45 (s, 4H, C₆H₄), 8.26 (s, 1H, D₂O exchangeable, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 16.3, 36.6, 39.5 (3CH₂), 23.8 (CH₃), 90.6 (CH), 120.8, 122.9, 123.4, 127.9 (C₆H₄), 177.3, 179.5 (2CO). Analysis Calcd for C₁₄H₁₅NO₂ (229.27): C, 73.34; H, 6.59; N, 6.11%. Found: C, 73.29; H, 6.41; N, 6.26%. MS: *m/z* 229 (M⁺, 40%).

2-(((4-Methoxyphenyl)amino)methylene)cyclohexane-1,3-dione (16c)

Yellow crystals from 1,4-dioxane, yield 1.47 g (60%), m.p. 193–196 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3463–3329 (NH), 3055 (CH aromatic), 2982, 2886 (CH₃, CH₂), 1689, 1686 (2CO), 1630 (C=C); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 1.41–1.69 (m, 2H, CH₂), 2.61–2.78 (m, 4H, 2CH₂), 3.68 (s, 3H, OCH₃), 6.06 (s, 1H, CH), 7.27–7.48 (s, 4H, C₆H₄), 8.28 (s, 1H, D₂O exchangeable, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 16.3, 36.6, 39.5 (3CH₂), 50.3 (OCH₃), 90.2 (CH), 120.3, 122.4, 125.6, 128.7 (C₆H₄), 177.1, 179.3 (2CO). Analysis Calcd for C₁₄H₁₅NO₃ (245.27): C, 68.56; H, 6.16; N, 5.71%. Found: C, 68.80; H, 6.24; N, 5.93%. MS: *m/z* 245 (M⁺, 38%).

2. 1. 9. General Procedure for the Synthesis of the 6,7-Dihydrobenzo[*b*]thiophen-5(4*H*)-one Derivatives 17a–f

Either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.07 g, 0.01 mol) was added to a solution of either compound **16a** (2.15 g, 0.01 mol), **16b** (2.29 g, 0.01 mol) or **16c** (2.45 g, 0.01 mol) in ethanol (40 mL) containing triethylamine (0.50 mL). The reaction mixture was heated under reflux for 3 h then poured onto ice/water mixture containing a few drops of hydrochloric acid and the formed solid product was collected by filtration.

2-Amino-5-oxo-4-((phenylamino)methylene)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (17a)

Pale yellow crystals from ethanol, yield 2.06 g (70%), m.p. 127–129 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3472–3353 (NH₂, NH), 3055 (CH, aromatic), 2220 (CN), 1686 (CO), 1630 (C=C); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.60–2.79 (2t, 4H, 2CH₂), 4.78 (s, 2H, D₂O exchangeable, NH₂), 6.89 (s, 1H, CH), 7.26–7.42 (m, 5H, C₆H₅), 8.39 (s, 1H, D₂O exchangeable, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 36.0, 39.8 (2CH₂), 112.2, 158.4 (C=CH), 116.8 (CN), 121.6, 122.4, 124.8, 127.2, 132.7, 134.2, 138.0, 142.6 (C₆H₅, thiophene C), 179.6 (CO). Anal. Calcd for C₁₆H₁₃N₃OS: C, 65.06; H, 4.44; N, 14.23; S, 10.86. Found: C, 65.18; H, 4.60; N, 14.19; S, 11.17. MS: *m/z* 295 (M⁺, 38%).

Ethyl 2-Amino-5-oxo-4-((phenylamino)methylene)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (17b)

Yellow crystals from ethanol, yield 2.18 g (64%), m.p. 96–98 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3486–3351 (NH₂), 3058

(CH, aromatic), 2930, 2972 (CH₂, CH₃), 1689, 1686 (2 CO), 1630 (C=C); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 1.13 (t, 3H, *J* = 7.08 Hz, CH₃), 2.68–2.76 (2t, 4H, 2CH₂), 4.22 (q, 2H, *J* = 7.08 Hz, CH₂), 4.77 (s, 2H, D₂O exchangeable, NH₂), 6.86 (s, 1H, CH), 7.22–7.40 (m, 5H, C₆H₅), 8.33 (s, 1H, D₂O exchangeable, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 16.3 (OCH₂CH₃), 36.8, 39.6 (2CH₂), 52.5 (OCH₂CH₃), 112.4, 158.8 (C=CH), 121.3, 123.6, 125.2, 126.8, 132.9, 133.3, 138.0, 142.7 (C₆H₅, thiophene C), 164.2, 179.8 (2CO). Anal. Calcd for C₁₈H₁₈N₂O₃S: C, 63.14; H, 5.30; N, 8.18; S, 9.36. Found: C, 62.91; H, 5.49; N, 8.25; S, 9.60. MS: *m/z* 342 (M⁺, 27%).

2-Amino-5-oxo-4-((*p*-tolylamino)methylene)-4,5,6,7-tetrahydrobenzo-[c]thiophene-3-carbonitrile (17c)

Orange crystals from 1,4-dioxane, yield 2.31 g (75%), m.p. 177–179 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3493–3323 (NH₂, NH), 3055 (CH, aromatic), 2220 (CN), 1688 (CO), 1630 (C=C); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.62–2.77 (2t, 4H, 2CH₂), 2.79 (s, 3H, CH₃), 4.77 (s, 2H, D₂O exchangeable, NH₂), 6.82 (s, 1H, CH), 7.28–7.46 (m, 4H, C₆H₄), 8.37 (s, 1H, D₂O exchangeable, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 36.0, 39.6 (2CH₂), 24.3 (CH₃), 112.0, 158.6 (C=CH), 116.9 (CN), 120.3, 123.7, 124.8, 128.9, 132.9, 134.7, 138.3, 142.2 (C₆H₄, thiophene C), 179.3 (CO). Anal. Calcd for C₁₇H₁₅N₃OS: C, 66.00; H, 4.89; N, 13.58; S, 10.36. Found: C, 65.85; H, 4.91; N, 13.70; S, 10.42. MS: *m/z* 309 (M⁺, 24%).

Ethyl 2-Amino-5-oxo-4-((*p*-tolylamino)methylene)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (17d)

Brown crystals from 1,4-dioxane, yield 2.45 g (69%), m.p. 203–206 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3459–3337 (NH₂), 3055 (CH, aromatic), 2930, 2970 (CH₂, CH₃), 1689, 1687 (2 CO), 1630 (C=C); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 1.12 (t, 3H, *J* = 6.59 Hz, CH₃), 2.65–2.78 (2t, 4H, 2CH₂), 2.80 (s, 3H, CH₃), 4.24 (q, 2H, *J* = 6.59 Hz, CH₂), 4.79 (s, 2H, D₂O exchangeable, NH₂), 6.83 (s, 1H, CH), 7.21–7.45 (m, 4H, C₆H₄), 8.36 (s, 1H, D₂O exchangeable, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 16.1 (OCH₂CH₃), 36.3, 39.7 (3CH₂), 23.9 (CH₃), 52.1 (OCH₂CH₃), 112.2, 158.7 (C=CH), 120.1, 123.8, 124.9, 128.3, 134.8, 137.2, 140.2, 142.6 (C₆H₅, thiophene C), 164.3, 179.5 (2CO). Anal. Calcd for C₁₉H₂₀N₂O₃S: C, 64.02; H, 5.66; N, 7.86; S, 9.00. Found: C, 63.91; H, 5.53; N, 8.01; S, 9.26. MS: *m/z* 356 (M⁺, 32%).

2-Amino-4-(((4-methoxyphenyl)amino)methylene)-5-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (17e)

Yellow crystals from ethanol, yield 2.30 g (71%), m.p. 166–169 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3474–3329 (NH₂, NH), 3055 (CH, aromatic), 2220 (CN), 1688 (CO), 1630 (C=C); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.61–2.77 (2t, 4H, 2CH₂), 3.68 (s, 3H, OCH₃), 4.75 (s, 2H, D₂O exchangeable, NH₂),

6.87 (s, 1H, CH), 7.24–7.46 (m, 4H, C₆H₄), 8.35 (s, 1H, D₂O exchangeable, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 16.1, 36.2, 39.4 (3CH₂), 50.2 (OCH₃), 112.5, 158.4 (C=CH), 116.7 (CN), 120.1, 122.9, 125.3, 127.6, 132.2, 134.7, 137.6, 143.3 (C₆H₄, thiophene C), 179.6 (CO). Anal. Calcd for C₁₇H₁₅N₃O₂S: C, 62.75; H, 4.65; N, 12.91; S, 9.85. Found: C, 62.53; H, 4.79; N, 12.83; S, 10.01. MS: *m/z* 325 (M⁺, 32%).

Ethyl 2-Amino-4-(((4-methoxyphenyl)amino)methylene)-5-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (17f)

Yellow crystals from ethanol, yield 2.40 g (65%), m.p. 203–206 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3459–3337 (NH₂), 3055 (CH, aromatic), 2930, 2970 (CH₂, CH₃), 1689, 1687 (2 CO), 1630 (C=C); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 1.13 (t, 3H, *J* = 7.59 Hz, CH₃), 2.62–2.75 (2t, 4H, 2CH₂), 3.61 (s, 3H, OCH₃), 4.22 (q, 2H, *J* = 7.59 Hz, CH₂), 4.79 (s, 2H, D₂O exchangeable, NH₂), 6.83 (s, 1H, CH), 7.24–7.48 (m, 4H, C₆H₄), 8.34 (s, 1H, D₂O exchangeable, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 16.1 (OCH₂CH₃), 36.3, 39.7 (3CH₂), 50.2 (OCH₃), 52.2 (OCH₂CH₃), 112.2, 158.7 (C=CH), 120.2, 122.2, 124.3, 128.1, 134.6, 136.7, 138.1, 140.8 (C₆H₅, thiophene C), 164.1, 179.7 (2CO). Anal. Calcd for C₁₉H₂₀N₂O₄S: C, 61.27; H, 5.41; N, 7.52; S, 8.61. Found: C, 60.91; H, 5.23; N, 7.39; S, 8.59. MS: *m/z* 372 (M⁺, 36%).

2. 1. 10. General Procedure for the Synthesis of the 6,7-Dihydrobenzo[*b*]thiophen-3-carboxamide Derivatives 19a–c

Either of compounds **18a** (1.12 g, 0.01 mol), **18b** (1.74 g, 0.01 mol) or **18c** (1.94 g, 0.01 mol) was added to a solution of cyclohexane-1,3-dione (**1**) (1.12 g, 0.01 mol) in 1,4-dioxane (40 mL) containing triethylamine (0.50 mL). The reaction mixture was heated under reflux for 3 h then poured onto ice/water mixture containing a few drops of hydrochloric acid and the formed solid product was collected by filtration.

2-Amino-5-oxo-*N*-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (19a)

Pale yellow crystals from ethanol, yield 2.14 g (75%), m.p. 120–123 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3484–3337 (NH₂, NH), 3055 (CH, aromatic), 2220 (CN), 1689, 1686 (2 CO), 1630 (C=C); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.62–2.79 (2t, 4H, 2CH₂), 3.02 (s, 2H, CH₂), 4.75 (s, 2H, D₂O exchangeable, NH₂), 7.28–7.40 (m, 5H, C₆H₅), 8.38 (s, 1H, D₂O exchangeable, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 16.3, 36.6, 40.3 (3CH₂), 116.6 (CN), 120.8, 122.2, 125.3, 127.3, 132.2, 134.5, 138.0, 142.9 (C₆H₅, thiophene C), 164.3, 179.6 (2CO). Anal. Calcd for C₁₅H₁₄N₂O₂S: C, 62.92; H, 4.93; N, 9.78; S, 11.20. Found: C, 63.22; H, 4.75; N, 9.59; S, 11.36. MS: *m/z* 286 (M⁺, 42%).

2-Amino-5-oxo-*N*-(*p*-tolyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (19b)

Yellow crystals from ethanol, yield 1.98 g (66%), m.p. 194–196 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3449–3327 (NH₂, NH), 3055 (CH, aromatic), 2220 (CN), 1689, 1687 (2 CO), 1630 (C=C); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.63–2.77 (2t, 4H, 2CH₂), 2.80 (s, 3H, CH₃), 3.06 (s, 2H, CH₂), 4.78 (s, 2H, D₂O exchangeable, NH₂), 7.26–7.46 (m, 4H, C₆H₄), 8.38 (s, 1H, D₂O exchangeable, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 16.3, 36.6, 40.3 (3CH₂), 116.6 (CN), 120.8, 122.2, 125.3, 127.3, 132.7, 134.7, 138.4, 142.6 (C₆H₄, thiophene C), 164.3, 179.6 (2CO). Anal. Calcd for C₁₆H₁₆N₂O₂S: C, 63.98; H, 5.37; N, 9.33; S, 10.67. Found: C, 63.72; H, 5.75; N, 9.59; S, 10.36. MS: *m/z* 300 (M⁺, 36%).

2-Amino-*N*-(4-chlorophenyl)-5-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (19c)

Brown crystals from 1,4-dioxane, yield 2.49 g (78%), m.p. 205–208 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3473–3351 (NH₂, NH), 3055 (CH, aromatic), 2220 (CN), 1689, 1686 (2 CO), 1630 (C=C); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.64–2.76 (2t, 4H, 2CH₂), 3.06 (s, 2H, CH₂), 4.79 (s, 2H, D₂O exchangeable, NH₂), 7.23–7.48 (m, 4H, C₆H₄), 8.36 (s, 1H, D₂O exchangeable, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 16.1, 36.4, 40.6 (3CH₂), 116.9 (CN), 120.2, 123.5, 125.8, 128.6, 132.3, 134.7, 138.0, 142.7 (C₆H₄, thiophene C), 164.3, 179.8 (2CO). Anal. Calcd for C₁₅H₁₃ClN₂O₂S: C, 56.16; H, 4.08; N, 8.73; S, 10.00. Found: C, 56.29; H, 4.26; N, 8.93; S, 10.26. MS: *m/z* 320 (M⁺, 28%).

2. 1. 11. General Procedure for the Synthesis of the Tetrahydrobenzo[*b*]thiophene-3-carboxamide Derivatives 20a–c

A mixture of either **19a** (2.86 g, 0.01 mol), **19b** (3.00 g, 0.01 mol) or **19c** (3.20 g, 0.01 mol) in *N,N*-dimethylformamide (30 mL) and ethyl cyanoacetate (1.07 g, 0.01 mL) was heated under reflux for 3 h. The solid product, formed in each case, produced upon pouring onto ice/water mixture, was collected by filtration.

2-(2-Cyanoacetamido)-5-oxo-*N*-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (20a)

Dark brown crystals from ethanol, yield 3.28 g (78%), m.p. 118–120 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3469–3329 (NH), 3054 (CH, aromatic), 2256 (CN), 1690–1686 (3 CO), 1630 (C=C); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.61–2.82 (2t, 4H, 2CH₂), 3.08 (s, 2H, CH₂), 3.68 (s, 2H, CH₂), 7.29–7.42 (m, 5H, C₆H₅), 8.24, 8.34 (2s, 2H, D₂O exchangeable, 2NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 16.6, 36.2, 40.5 (3CH₂), 60.3 (CH₂), 170.1 (CN), 120.3, 123.5, 125.9, 126.5, 132.8, 133.3, 138.6, 142.8 (C₆H₅, thiophene C), 164.3, 166.1, 179.6 (3CO). Anal. Calcd for C₁₈H₁₅N₃O₃S: C, 61.18; H, 4.28; N, 11.89; S, 9.07. Found: C, 61.31; H, 4.29; N, 11.68; S, 8.85. MS: *m/z* 353 (M⁺, 20%).

2-(2-Cyanoacetamido)-5-oxo-*N*-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (20b)

Brown crystals from ethanol, yield 2.27 g (62%), m.p. 211–214 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3453–3340 (NH), 3055 (CH, aromatic), 2256 (CN), 1693–1685 (3 CO), 1630 (C=C); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.63–2.80 (2t, 4H, 2CH₂), 2.70 (s, 3H, CH₃), 3.10 (s, 2H, CH₂), 3.62 (s, 2H, CH₂), 7.25–7.38 (m, 4H, C₆H₄), 8.23, 8.38 (2s, 2H, D₂O exchangeable, 2NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 16.3, 36.4, 40.8 (3CH₂), 60.5 (CH₂), 168.3 (CN), 120.6, 122.1, 126.4, 127.1, 132.8, 134.2, 138.6, 142.9 (C₆H₄, thiophene C), 164.2, 166.1, 179.8 (3CO). Anal. Calcd for C₁₉H₁₇N₃O₃S: C, 62.11; H, 4.66; N, 11.44; S, 8.73. Found: C, 62.26; H, 4.48; N, 11.52; S, 8.90. MS: *m/z* 367 (M⁺, 28%).

N-(4-Chlorophenyl)-2-(2-cyanoacetamido)-5-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (20c)

White crystals from ethanol, yield 2.12 g (55%), m.p. 118–121 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3470–3338 (NH), 3055 (CH, aromatic), 2256 (CN), 1691–1685 (3 CO), 1630 (C=C); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.62–2.82 (2t, 4H, 2CH₂), 3.12 (s, 2H, CH₂), 3.62 (s, 2H, CH₂), 7.22–7.49 (m, 4H, C₆H₄), 8.26, 8.32 (2s, 2H, D₂O exchangeable, 2NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 16.1, 36.6, 40.4 (3CH₂), 60.2 (CH₂), 168.9 (CN), 120.4, 124.2, 125.1, 128.6, 132.5, 134.9, 138.4, 142.6 (C₆H₄, thiophene C), 164.4, 166.3, 179.6 (3CO). Anal. Calcd for C₁₈H₁₄ClN₃O₃S: C, 55.74; H, 3.64; N, 10.83; S, 8.27. Found: C, 55.80; H, 3.80; N, 11.01; S, 8.38. MS: *m/z* 387 (M⁺, 30%).

2. 1. 12. General Procedure for the Synthesis of the Phenylthioureido Derivatives 21a–c

Equimolar amounts of either **19a** (2.86 g, 0.01 mol), **19b** (3.00 g, 0.01 mol) or **19c** (3.20 g, 0.01 mol) and phenyl isothiocyanate (1.30 g, 0.01 mol) in ethanol (40 mL) containing triethylamine (1.0 mL) were heated under reflux for 3 h then left to cool. The formed solid crystals, in each case, were collected by filtration.

5-Oxo-*N*-phenyl-2-(3-phenylthioureido)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (21a)

Yellow crystals from ethanol, yield 2.52 g (60%), m.p. 115–117 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3464–3331 (NH), 3054 (CH, aromatic), 1689, 1687 (2 CO), 1632 (C=C), 1205 (C=S); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.63–2.84 (2t, 4H, 2CH₂), 3.66 (s, 2H, CH₂), 7.28–7.40 (m, 10H, 2C₆H₅), 8.21, 8.23, 8.38 (3s, 3H, D₂O exchangeable, 3NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 16.1, 36.6, 40.6 (3CH₂), 120.8, 122.4, 125.8, 126.0, 126.3, 127.5, 127.9, 128.2, 131.9, 133.8, 139.3, 142.9 (2C₆H₅, thiophene C), 164.2, 179.2 (2CO), 180.2 (C=S). Anal. Calcd for C₂₂H₁₉N₃O₂S₂: C, 62.68; H, 4.54; N, 9.97; S, 15.21. Found: C, 62.77; H, 4.49; N, 10.21; S, 15.49. MS: *m/z* 421 (M⁺, 32%).

5-Oxo-2-(3-phenylthioureido)-N-(p-tolyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (21b)

Pale yellow crystals from 1,4-dioxane, yield 2.70 g (60%), m.p. 205–208 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3485–3329 (NH), 3055 (CH, aromatic), 1689, 1687 (2 CO), 1638 (C=C), 1208 (C=S); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.61–2.89 (2t, 4H, 2CH₂), 2.80 (s, 3H, CH₃), 3.67 (s, 2H, CH₂), 7.23–7.48 (m, 9H, C₆H₅, C₆H₄), 8.26, 8.21, 8.36 (3s, 3H, D₂O exchangeable, 3NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 16.5, 36.6, 40.6 (3CH₂), 30.6 (CH₃), 120.2, 121.6, 124.5, 126.7, 126.8, 128.1, 128.7, 129.3, 133.5, 135.2, 138.6, 142.6 (C₆H₅, C₆H₄, thiophene C), 164.6, 179.4 (2CO), 180.6 (C=S). Anal. Calcd for C₂₃H₂₁N₃O₂S₂: C, 63.42; H, 4.86; N, 9.65; S, 14.72. Found: C, 63.52; H, 4.68; N, 9.74; S, 14.80. MS: *m/z* 435 (M⁺, 28%).

N-(4-Chlorophenyl)-5-oxo-2-(3-phenylthioureido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (21c)

Yellow crystals from ethanol, yield 2.95 g (65%), m.p. 200–203 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3442–3338 (NH), 3054 (CH, aromatic), 1689, 1685 (2 CO), 1630 (C=C), 1208 (C=S); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.62–2.86 (2t, 4H, 2CH₂), 3.68 (s, 2H, CH₂), 7.22–7.48 (m, 9H, C₆H₅, C₆H₄), 8.22, 8.25, 8.41 (3s, 3H, D₂O exchangeable, 3NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 16.0, 36.6, 40.9 (3CH₂), 120.3, 124.6, 125.5, 126.6, 127.2, 128.3, 128.7, 128.9, 132.5, 134.7, 138.0, 142.6 (C₆H₅, C₆H₄, thiophene C), 164.5, 179.8 (2CO), 180.5 (C=S). Anal. Calcd for C₂₂H₁₈ClN₃O₂S₂: C, 57.95; H, 3.98; N, 9.22; S, 14.06. Found: C, 57.63; H, 3.77; N, 9.39; S, 14.26. MS: *m/z* 455 (M⁺, 28%).

2. 1. 13. General Procedure for the Synthesis of the Hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-6(5*H*)-one Derivatives 22a–c

A suspension of either compound **21a** (4.21 g, 0.01 mol), **21b** (4.35 g, 0.01 mol), **21c** (4.55 g, 0.01 mol) in sodium ethoxide [prepared through dissolving metallic sodium (0.46 g, 0.02 mol) in absolute ethanol (50 mL)] was heated in a boiling water bath for 6 h. The reaction mixture was poured onto ice/water mixture then triturated with hydrochloric acid (till pH 7) and the formed solid product was collected by filtration.

3-Phenyl-4-(phenylimino)-2-thioxo-1,2,3,4,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-6(5*H*)-one (22a)

Yellow crystals from ethanol, yield 3.14 g (78%), m.p. 111–113 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3458–3324 (NH), 3055 (CH, aromatic), 1688 (CO), 1632 (C=C), 1205 (C=S); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.61–2.86 (2t, 4H, 2CH₂), 3.68 (s, 2H, CH₂), 7.28–7.40 (m, 10H, 2C₆H₅), 8.21 (s, 1H, D₂O exchangeable, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 16.1, 36.6, 40.6 (3CH₂), 120.8, 122.4, 125.8, 126.0, 126.3, 127.5, 127.9, 128.2, 132.2, 134.7, 137.2, 142.9 (2C₆H₅,

thiophene C), 179.1 (CO), 180.3 (C=S). Anal. Calcd for C₂₂H₁₇N₃OS₂: C, 65.48; H, 4.25; N, 10.41; S, 15.89. Found: C, 65.63; H, 4.19; N, 10.32; S, 15.74. MS: *m/z* 403 (M⁺, 38%).

3-Phenyl-2-thioxo-4-(p-tolylimino)-1,2,3,4,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-6(5*H*)-one (22b)

Brown crystals from ethanol, yield 2.46 g (59%), m.p. 273–275 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3479–3336 (NH), 3055 (CH, aromatic), 1688 (CO), 1631 (C=C), 1209 (C=S); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.60–2.88 (2t, 4H, 2CH₂), 2.93 (s, 3H, CH₃), 3.65 (s, 2H, CH₂), 7.22–7.45 (m, 9H, C₆H₅, C₆H₄), 8.25 (s, 1H, D₂O exchangeable, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 16.4, 36.8, 40.9 (3CH₂), 32.6 (CH₃), 120.2, 122.6, 125.5, 125.9, 126.9, 127.7, 127.3, 128.1, 132.2, 134.9, 137.6, 142.3 (C₆H₅, C₆H₄, thiophene C), 179.6 (CO), 180.8 (C=S). Anal. Calcd for C₂₃H₁₉N₃OS₂: C, 66.16; H, 4.59; N, 10.06; S, 15.36. Found: C, 66.39; H, 4.42; N, 10.15; S, 15.80. MS: *m/z* 417 (M⁺, 42%).

4-((4-Chlorophenyl)imino)-3-phenyl-2-thioxo-1,2,3,4,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-6(5*H*)-one (22c)

Pale yellow crystals from ethanol, yield 3.49 g (80%), m.p. 119–122 °C. IR (KBr) $\nu_{\max}$ (cm⁻¹) 3459–3328 (NH), 3054 (CH, aromatic), 1688, 1685 (2CO), 1630 (C=C), 1210 (C=S); ¹H NMR (DMSO-*d*₆, 200 MHz) δ 2.62–2.88 (2t, 4H, 2CH₂), 3.68 (s, 2H, CH₂), 7.22–7.48 (m, 9H, C₆H₅, C₆H₄), 8.22 (s, 1H, D₂O exchangeable, NH); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 16.0, 36.6, 40.9 (3CH₂), 120.3, 124.6, 125.5, 126.6, 127.2, 128.3, 128.7, 128.9, 132.8, 134.3, 137.2, 142.9 (C₆H₅, C₆H₄, thiophene C), 164.8, 179.4 (2CO), 180.2 (C=S). Anal. Calcd for C₂₂H₁₆ClN₃OS₂: C, 60.33; H, 3.68; N, 9.59; S, 14.64. Found: C, 60.26; H, 3.49; N, 9.41; S, 14.52. MS: *m/z* 437 (M⁺, 32%).

2. 2. Biology Section**2. 2. 1. Cell Proliferation Assay**

Foretinib was used as the positive control^{127–29} during measuring the anti-proliferative activities of the newly synthesized compounds (Table 1). The newly synthesized compounds were evaluated against the six cancer cell lines A549, HT-29, MKN-45, U87MG, and SMMC-7721 and H460 using the standard MTT assay *in vitro*.

The IC₅₀ values were measured through three independent experiments and the data are shown in Table 1. It is clear that many of the tested compounds showed potent anti-proliferative activity with IC₅₀ values less than 6.00 μ M. Generally, the variations of substituents within the aryl moiety together with the heterocyclic ring being attached had a notable effect and a positive impact on the anti-proliferative activity.

Table 1. *In vitro* growth inhibitory effects $IC_{50} \pm SEM$ (μM) of the newly synthesized compounds against cancer cell lines

Compound	$IC_{50} \pm SEM$ (μM)					
	A549	H460	HT29	MKN-45	U87MG	SMMC-7721
3a	6.62 $\pm$ 2.34	5.42 $\pm$ 2.31	7.73 $\pm$ 2.59	6.72 $\pm$ 2.21	6.82 $\pm$ 1.73	5.01 $\pm$ 2.32
3b	0.40 $\pm$ 0.25	0.39 $\pm$ 0.17	0.29 $\pm$ 0.16	0.24 $\pm$ 0.16	0.19 $\pm$ 0.17	0.42 $\pm$ 0.23
5a	4.16 $\pm$ 1.49	4.18 $\pm$ 1.26	5.43 $\pm$ 2.71	5.32 $\pm$ 1.41	6.53 $\pm$ 2.51	6.80 $\pm$ 1.49
5b	1.07 $\pm$ 0.68	1.17 $\pm$ 0.63	2.04 $\pm$ 0.95	2.27 $\pm$ 1.33	1.95 $\pm$ 0.49	2.17 $\pm$ 0.52
5c	0.19 $\pm$ 0.07	0.26 $\pm$ 0.11	0.37 $\pm$ 0.21	0.26 $\pm$ 0.08	0.52 $\pm$ 0.23	0.62 $\pm$ 0.25
5d	0.39 $\pm$ 0.15	0.36 $\pm$ 0.21	0.27 $\pm$ 0.18	0.29 $\pm$ 0.17	0.36 $\pm$ 0.22	0.35 $\pm$ 0.18
6a	6.41 $\pm$ 2.26	5.73 $\pm$ 2.17	6.42 $\pm$ 2.31	8.92 $\pm$ 3.41	6.22 $\pm$ 2.73	5.82 $\pm$ 1.39
6b	1.08 $\pm$ 0.69	0.82 $\pm$ 0.26	0.63 $\pm$ 0.37	0.38 $\pm$ 0.26	1.82 $\pm$ 0.79	0.63 $\pm$ 0.31
6c	0.32 $\pm$ 0.21	0.37 $\pm$ 0.19	0.40 $\pm$ 0.15	0.25 $\pm$ 0.07	0.62 $\pm$ 0.14	0.51 $\pm$ 0.23
6d	0.32 $\pm$ 0.15	0.42 $\pm$ 0.26	0.16 $\pm$ 0.09	0.26 $\pm$ 0.14	0.37 $\pm$ 0.17	0.28 $\pm$ 0.08
8a	0.33 $\pm$ 0.12	0.28 $\pm$ 0.15	0.28 $\pm$ 3.19	6.28 $\pm$ 1.08	7.89 $\pm$ 2.63	9.39 $\pm$ 2.37
8b	0.65 $\pm$ 0.18	0.29 $\pm$ 0.12	0.43 $\pm$ 0.25	0.36 $\pm$ 0.19	0.26 $\pm$ 0.18	0.56 $\pm$ 0.18
10a	6.48 $\pm$ 1.54	7.60 $\pm$ 2.42	6.63 $\pm$ 2.29	6.16 $\pm$ 2.59	5.26 $\pm$ 1.83	6.29 $\pm$ 2.28
10b	2.48 $\pm$ 1.01	3.80 $\pm$ 1.18	2.47 $\pm$ 1.14	4.52 $\pm$ 2.16	0.93 $\pm$ 0.42	2.83 $\pm$ 1.02
10c	0.26 $\pm$ 0.18	0.43 $\pm$ 0.18	0.41 $\pm$ 0.20	0.38 $\pm$ 0.16	0.46 $\pm$ 0.26	0.38 $\pm$ 0.13
10d	0.65 $\pm$ 0.32	0.58 $\pm$ 0.21	1.08 $\pm$ 0.62	0.73 $\pm$ 0.32	0.46 $\pm$ 0.29	0.53 $\pm$ 0.25
12a	1.82 $\pm$ 0.78	1.06 $\pm$ 0.62	0.84 $\pm$ 0.38	0.61 $\pm$ 0.19	0.72 $\pm$ 0.36	0.59 $\pm$ 0.16
12b	0.22 $\pm$ 0.15	0.36 $\pm$ 0.12	0.43 $\pm$ 0.19	0.29 $\pm$ 0.16	0.42 $\pm$ 0.25	0.58 $\pm$ 0.24
14	8.68 $\pm$ 2.59	6.70 $\pm$ 2.63	7.28 $\pm$ 1.62	5.63 $\pm$ 1.26	6.92 $\pm$ 2.37	7.29 $\pm$ 2.62
16a	4.91 $\pm$ 1.56	5.41 $\pm$ 1.28	3.52 $\pm$ 1.15	3.30 $\pm$ 1.86	5.02 $\pm$ 2.80	4.69 $\pm$ 1.38
16b	6.53 $\pm$ 2.38	7.24 $\pm$ 2.49	6.80 $\pm$ 1.92	7.49 $\pm$ 2.63	5.60 $\pm$ 1.32	8.05 $\pm$ 3.26
16c	0.76 $\pm$ 0.39	0.68 $\pm$ 0.27	0.43 $\pm$ 0.26	0.51 $\pm$ 0.23	0.60 $\pm$ 0.29	0.39 $\pm$ 0.24
17a	4.83 $\pm$ 1.53	6.28 $\pm$ 2.54	6.22 $\pm$ 2.26	3.42 $\pm$ 1.60	5.23 $\pm$ 1.21	4.72 $\pm$ 1.38
17b	3.41 $\pm$ 1.25	4.61 $\pm$ 1.28	4.82 $\pm$ 1.52	2.16 $\pm$ 0.73	2.37 $\pm$ 1.29	3.42 $\pm$ 1.53
17c	3.42 $\pm$ 1.80	2.63 $\pm$ 1.03	4.81 $\pm$ 1.68	3.68 $\pm$ 1.29	3.62 $\pm$ 1.26	2.46 $\pm$ 1.82
17d	1.02 $\pm$ 0.71	1.65 $\pm$ 0.83	0.93 $\pm$ 0.42	0.85 $\pm$ 0.31	0.72 $\pm$ 0.29	0.69 $\pm$ 0.23
17e	0.82 $\pm$ 0.18	0.51 $\pm$ 0.23	0.42 $\pm$ 0.19	0.31 $\pm$ 0.25	0.39 $\pm$ 0.13	0.58 $\pm$ 0.13
17f	0.21 $\pm$ 0.09	0.33 $\pm$ 0.17	0.48 $\pm$ 0.31	0.35 $\pm$ 0.12	0.59 $\pm$ 0.23	0.23 $\pm$ 0.17
19a	7.28 $\pm$ 2.62	8.29 $\pm$ 2.17	6.39 $\pm$ 1.02	5.86 $\pm$ 2.23	7.43 $\pm$ 2.49	6.32 $\pm$ 2.34
19b	2.34 $\pm$ 1.14	2.28 $\pm$ 0.82	3.51 $\pm$ 1.50	3.46 $\pm$ 1.63	3.68 $\pm$ 1.23	2.18 $\pm$ 1.02
19c	0.24 $\pm$ 0.13	0.32 $\pm$ 0.17	0.48 $\pm$ 0.23	0.29 $\pm$ 0.36	0.26 $\pm$ 0.15	0.43 $\pm$ 0.29
20a	8.52 $\pm$ 3.50	7.62 $\pm$ 2.40	6.39 $\pm$ 3.60	7.80 $\pm$ 2.68	5.18 $\pm$ 2.70	6.48 $\pm$ 2.37
20b	4.26 $\pm$ 1.05	5.72 $\pm$ 2.83	6.93 $\pm$ 2.40	4.70 $\pm$ 1.52	5.94 $\pm$ 1.29	1.04 $\pm$ 0.89
20c	0.37 $\pm$ 0.16	0.35 $\pm$ 0.18	0.46 $\pm$ 0.261	0.51 $\pm$ 0.28	0.24 $\pm$ 0.63	0.28 $\pm$ 0.18
21a	8.24 $\pm$ 3.51	6.39 $\pm$ 2.73	4.46 $\pm$ 1.28	5.34 $\pm$ 1.60	6.70 $\pm$ 2.93	5.45 $\pm$ 1.69
21b	1.42 $\pm$ 0.98	1.64 $\pm$ 0.52	0.68 $\pm$ 0.31	1.25 $\pm$ 0.79	2.35 $\pm$ 1.06	3.36 $\pm$ 1.20
21c	6.43 $\pm$ 2.53	8.69 $\pm$ 2.64	7.16 $\pm$ 1.69	8.69 $\pm$ 2.26	8.53 $\pm$ 2.38	8.76 $\pm$ 2.49
22a	6.42 $\pm$ 2.26	8.25 $\pm$ 2.13	5.29 $\pm$ 2.30	3.27 $\pm$ 1.04	5.52 $\pm$ 1.31	4.50 $\pm$ 1.46
22b	2.43 $\pm$ 1.16	2.37 $\pm$ 1.28	3.45 $\pm$ 1.19	2.26 $\pm$ 1.16	4.58 $\pm$ 1.14	3.27 $\pm$ 3.16
22c	0.42 $\pm$ 0.23	0.29 $\pm$ 0.15	0.54 $\pm$ 0.29	0.19 $\pm$ 0.04	0.59 $\pm$ 0.31	0.42 $\pm$ 0.63
Foretinib	0.08 $\pm$ 0.01	0.18 $\pm$ 0.03	0.15 $\pm$ 0.023	0.03 $\pm$ 0.0055	0.90 $\pm$ 0.13	0.44 $\pm$ 0.062

2. 2. 2. Structure Activity Relationship

It is clear from Table 1 that most of the compounds exhibited high cytotoxicities against the six cancer cell lines A549, HT-29, MKN-45, U87MG, and SMMC-7721 and H460. Where in the most of the cases the presence of electronegative substituents is responsible for the high inhibitions. Considering the 2-ylidene-cyclohexane-1,3-dione derivatives **3a,b** it is clear that compound **3b** (X = S) showed higher cytotoxicities than compound **3a** (X = O). For the 4,5,6,7-tetrahydrobenzo[*b*]thiophene derivatives **5a–d**, compound **5a** (X = O, R = CN) exhibited relatively low inhibitions while

compound **5b** (X = O, R = COOEt) showed moderate inhibitions. On the other side, compounds **5c** (X = S, R = CN) and **5d** (X = S, R = COOEt) showed extensively high inhibitions toward the six cancer cell lines. Similarly, for the 5,6,7,8-tetrahydro-4*H*-chromene derivatives **6a–d**, it is obvious that compound **6a** (X = O, Y = NH₂) showed low inhibitions, compound **6b** (X = O, Y = OH) displayed moderate inhibitions and compounds **6c** (X = S, Y = NH₂) and **6d** (X = S, Y = NH₂) showed high inhibitions. Considering the 2,3,6,7-tetrahydrobenzo[*d*]thiazole derivatives **8a,b**, where both of the two compounds exhibited high cytotoxicities, this is at-

tributed to the presence of the thiazole moiety in both compounds. For the 4,5,6,7-tetrahydro-2*H*-indazole derivatives **10a–d** it is clear that compound **10a** (X = O, R = H) showed low inhibitions, compound **10b** with high inhibition only toward U87MG cell line with IC₅₀ = 0.93 μ M and moderate inhibitions toward the other five cell lines A549, H460, HT29, MKN-45 and SMMC-7721. Compounds **10c** (X = S, R = H) and **10d** (X = S, R = Ph) revealed high inhibitions toward the six cancer cell lines. On the other hand, the 6,7-dihydrobenzo[*c*]isoxazole derivatives **12a** and **12b** showed high inhibitions. Compound **14** the 2-(ethoxymethylene)cyclohexane-1,3-dione showed low inhibitions toward the six cancer cell lines. Considering the 2-(arylamino)methylene)cyclohexane-1,3-dione derivatives **16a–c** where compound **16c** (X = OCH₃) showed the highest inhibitions among the three compounds although compound **16a** (X = H) showed relatively higher inhibitions than compound **16b** (X = CH₃). For the 6,7-dihydrobenzo[*b*]thiophene derivatives **17a–f**, it is clear from Table 1 that compounds **17a**, **17b** and **17c** showed low inhibitions while compounds **17d** (X = CH₃, R = COOEt), **17f** (X = OCH₃, R = CN) and **17d** (X = OCH₃, R = COOEt) showed high inhibitions. Within the 6,7-dihydrobenzo[*b*]thiophene derivatives **19a–c** and **20a–c**, compounds **19c** (Y = Cl) and **20c** (X = Cl) showed the highest inhibitions among the six compounds. Surprisingly, for compounds **21a–c** where compound **21b** (Y = CH₃) showed higher inhibitions than **21a** (Y = H) and **21c** (Y = Cl). Finally for the 1,2,3,4,7,8-hexahydrobenzo[4,5]thien[2,3-*d*]pyrimidine derivatives **22a–c**, where compound **22a** (Y = H) showed low inhibitions, compound **22b** (Y = CH₃) displayed moderate inhibitions and compound **22c** (Y = Cl) showed high inhibitions. It is of great value to mention that compounds **3b**, **5c**, **5d**, **6b**, **6c**, **6d**, **8a**, **8b**, **10c**, **10d**, **12a**, **12b**, **16c**, **17d**, **17e**, **17f**, **19c**, **20c** and **22c** were the most cytotoxic compounds among the tested compounds.

2. 2. 3. Inhibition of Tyrosine Kinases

Compounds **3b**, **5c**, **5d**, **6b**, **6c**, **6d**, **8a**, **8b**, **10c**, **10d**, **12a**, **12b**, **16c**, **17d**, **17e**, **17f**, **19c**, **20c** and **22c** were selected for inhibition of the five tyrosine kinases c-Kit, Flt-3, VEGFR-2, EGFR, and PDGFR. It is clear from Table 2 that compounds **3b**, **5d**, **6b**, **6d**, **8a**, **8b**, **10c**, **12a**, **12b**, **16c**, **17e**, **17f** and **19c** were the most potent of the tested compounds towards the five tyrosine kinases. Compound **5c** showed high potency towards the two kinases c-EGFR and PDGFR with IC₅₀ 0.96 and 0.68 nM, respectively. In addition the 2-(((4-methoxyphenyl)amino)methylene)cyclohexane-1,3-dione (**16c**) showed activity towards the five kinases with IC₅₀ 0.14, 0.32, 0.21, 0.36 and 0.40 nM, respectively. Compounds **6c**, **10d**, **20c** and **22c** showed the lowest potency among the tested compounds.

Table 2. Inhibition of tyrosine kinases (enzyme IC₅₀ in nM) by compounds **3b**, **5c**, **5d**, **6b**, **6c**, **6d**, **8a**, **8b**, **10c**, **10d**, **12a**, **12b**, **16c**, **17d**, **17e**, **17f**, **19c**, **20c** and **22c**

Compound	c-Kit	Flt-3	VEGFR-2	EGFR	PDGFR
3b	0.80	0.37	0.42	0.58	0.38
5c	1.03	2.63	1.82	0.96	0.68
5d	0.23	0.26	0.42	0.69	0.72
6b	0.48	0.27	0.62	0.49	0.52
6c	1.42	2.58	1.61	1.80	2.31
6d	0.16	0.24	0.57	0.34	0.28
8a	0.58	0.42	0.38	0.27	0.19
8b	0.29	0.48	0.68	0.52	0.40
10c	0.16	0.13	0.28	0.31	0.28
10d	2.07	1.24	1.30	1.28	1.72
12a	0.36	0.24	0.62	0.18	0.24
12b	0.18	0.53	0.61	0.53	0.42
16c	0.14	0.32	0.21	0.36	0.40
17d	1.85	1.64	1.52	2.83	1.18
17e	0.26	0.23	0.37	0.28	0.46
17f	0.55	0.80	0.92	0.16	0.27
19c	0.26	0.42	0.31	0.50	0.62
20c	1.27	1.43	2.60	2.88	1.69
22c	2.49	2.61	1.96	2.37	3.39

2. 2. 4. Inhibition of Selected Compounds Towards Pim-1 Kinase

Compounds **3b**, **5d**, **6b**, **6d**, **8a**, **8b**, **10c**, **12a**, **12b**, **16c**, **17e**, **17f** and **19c** were selected to examine their Pim-1 kinase inhibition activity (Table 3) as these compounds showed high inhibition towards the tested cancer cell lines at a range of 10 concentrations and the IC₅₀ values were calculated. Compounds **5d**, **6b**, **6d**, **10c**, **12a**, **17e** and **17f** were the most potent to inhibit Pim-1 activity with IC₅₀ values of 0.24, 0.41, 0.30, 0.28, 0.45, 0.23 and 0.25 μ M, respectively. On the other hand, compounds **3b**, **8a**, **8b**, **12b**, **16c**, and **19c** were less effective (IC₅₀ > 10 μ M). SGI-1776 was used as the positive control with IC₅₀ 0.048 μ M in the assay. These profiles in combination with cell growth inhibition data of compounds **3b**, **5d**, **6b**, **6d**, **8a**, **8b**, **10c**, **12a**, **12b**, **16c**, **17e**, **17f** and **19c** are listed in Table 3 indicating that Pim-1 is a potential target of these compounds.

3. Results and Discussion

The synthesis of the 2-(hetero-2-ylmethylene)cyclohexane-1,3-dione derivatives **3a,b** has been accomplished as outlined in Scheme 1 starting from cyclohexan-1,3-dione (**1**). Compounds **3a** and **3b** were obtained through the reaction of **1** with either of furan-2-carbaldehyde or thiophene-2-carbaldehyde. The reaction of either of compound **3a** or **3b** with elemental sulfur and either of malononitrile (**4a**) or ethyl cyanoacetate (**4b**) gave the 6,7-dihydrobenzo[*b*]thiophen-5(4*H*)-one derivatives **5a–**

Table 3. The inhibitory activity of compounds **3b**, **5d**, **6b**, **6d**, **8a**, **8b**, **10c**, **12a**, **12b**, **16c**, **17e**, **17f** and **19c** toward Pim-1 kinase.

Compound	Inhibition ratio at 10 μ M	IC ₅₀ (μ M)
3b	16	> 10
5d	96	0.24
6b	90	0.41
6d	89	0.30
8a	26	> 10
8b	24	> 10
10c	92	0.28
12a	0.88	0.45
12b	28	> 10
16c	26	> 10
17e	92	0.23
17f	90	0.25
19c	18	> 10
SGI-1776	–	0.048

d, respectively. The structures of the latter products were established on the analytical and spectral data. Thus, the ¹H NMR spectrum of compound **5a** (as an example) showed the presence of two triplets at δ 2.62–2.78 ppm for the two CH₂ groups, a singlet at δ 4.73 ppm (D₂O exchangeable) indicating the presence of the NH₂ group, a singlet at δ 6.84 for the pyran H-4 and a multiplet at δ 6.82–7.86 ppm for the furan protons. In addition, the ¹³C NMR spectrum revealed three signals at δ 16.6, 36.3 and 39.5 equivalent to the three CH₂ groups, two signals at δ 112.6 and 158.4 for the C=CH group, a signal at δ 116.8 for the CN group, eight signals at δ 135.4, 140.6, 141.4, 142.2, 142.7, 144.8, 145.6, 146.5 for the thiophene and furan carbons and a signal at δ 179.3 indicating the CO group. The reaction of either compound **3a** or **3b** with either of malononitrile (**4a**) or ethyl cyanoacetate (**4b**) in ethanol containing a catalytic amount of triethylamine gave the 2*H*-chromen-5-one derivatives **6a–d**, respectively (Scheme 1).

Scheme 1. Synthesis of compounds **3a,b**; **5a–d** and **6a–d**.

The reactivity of compounds **3a** and **3b** toward thiazole synthesis was studied. Thus, the reaction of either compound **3a** or **3b** with elemental sulfur and phenyl isothiocyanate (**7**) gave the 2-thioxohexahydrobenzo[*d*]thiazole derivatives **8a** and **8b**, respectively.

The reaction of either of compound **3a** or **3b** with either hydrazine hydrate (**9a**) or phenylhydrazine (**9b**) gave the 4-hydrazono-4,5,6,7-tetrahydro-2*H*-indazole derivatives **10a–d**, respectively. Similarly, the reaction of either **3a** or **3b** with hydroxylamine hydrochloride (**11**) gave the 6,7-dihydrobenzo[*c*]isoxazol-4(5*H*)-one oxime derivatives **12a** and **12b**, respectively (Scheme 2).

Next, we moved toward studying the use of 2-(ethoxymethylene)cyclohexane-1,3-dione (**14**), obtained according to the reported work³⁰ via the reaction of cyclohexane-1,3-dione (**1**) with ethyl orthoformate in acetic acid solution, through different heterocyclization reactions.

Thus, the reaction of compound **3** with any of the aromatic amines namely aniline (**15a**), 4-methylaniline (**15b**) or 4-methoxyaniline (**15c**) gave the 2-(aminomethylene)cyclohexane-1,3-dione derivatives **16a–c**, respectively. Structures of compounds **16a–c** were confirmed on the basis of their respective analytical and spectral data (see experimental section). Compounds **16a–c** were used to synthesize thiophene derivatives using the Gewald's thiophene synthesis.^{31–33} Thus, the reaction of any of compounds **16a**, **16b** or **16c** with elemental sulfur and either of malononitrile (**4a**) or ethyl cyanoacetate (**4b**) gave the 6,7-dihydrobenzo[*b*]thiophene derivatives **17a–f**, respectively.

The reaction of cyclohexane-1,3-dione (**1**) with elemental sulfur and any of cyanoacetanilide (**19a**), cyano-4-methylacetanilide (**19b**) or cyano-4-methoxyacetanilide (**19c**) gave the 6,7-dihydrobenzo[*b*]thiophene

Scheme 2. Synthesis of compounds **8a,b**; **10a–d** and **12a,b**.

Scheme 3. Synthesis of compounds **14**, **16a-c**; **17a-f** and **19a-c**.

derivatives **19a-c**, respectively (Scheme 3). The analytical and spectral data of the latter compounds were consistent with their respective structures. Thus, the ^1H NMR of compound **19a** showed the presence of two triplets at δ 2.62–2.79 ppm equivalent to the two CH_2 groups, a singlet for the third CH_2 group, a singlet at δ 4.75 ppm (D_2O exchangeable) for the NH_2 group, a multiplet at δ 7.28–7.40 ppm for the phenyl protons and a singlet at δ 8.38 ppm (D_2O exchangeable) indicating the NH group. Moreover, the ^{13}C NMR spectrum showed the presence of three sig-

nals at δ 16.3, 36.6, 40.3 corresponding to the three CH_2 groups, a signal at δ 116.6 indicating the presence of the CN group, signals at δ 120.8, 122.2, 125.3, 127.3, 132.2, 134.5, 138.0, 142.9 for the C_6H_5 and thiophene carbons and two signals at δ 164.3, 179.6 confirming the presence of two CO groups.

Compounds **19a-c** were ready to form amide derivatives through their reactions with cyanomethylene esters. Thus, the reaction of either compounds **19a-c** with ethyl cyanoacetate in *N,N*-dimethylformamide solution

Scheme 4. Synthesis of compounds **20a-c**; **21a-c** and **22a-c**.

took place to form the 4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)acetamide derivatives **20a-c**, respectively. On the other hand, the reaction of either compounds **19a**, **19b** or **9c** with phenyl isothiocyanate gave the corresponding *N*-phenylthiourea derivatives **21a-c**, respectively. The analytical and spectral data of compounds **21a-c** were consistent with their respective structures. Compounds **20a-c** were ready for further cyclization to form biologically active annulated compounds. Thus, heating of either compound **21a**, **21b** or **21c** in sodium ethoxide solution in a boiling water bath afforded the hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine derivatives **22a-c**, respectively (Scheme 4). Their structures were based on the analytical and spectral data (see experimental section).

4. Conclusion

Forty novel heterocyclic compounds bearing cyclohexanone moiety were designed and synthesized. Their structures were confirmed by multiple techniques. The synthesized compounds were screened for cytotoxic activity against a panel of six human cancer cell lines using MTT assay. Some intriguing structure-activity relationships were found and discussed and the most active compounds were selected for further screening against tyrosine kinases, Pim-1 kinase and the results indicated that these compounds are good candidates as anti-cancer agents that will encourage further work in the future.

Human and Animal Rights

No Animals/Humans were used for studies that are basis of this research.

Consent for Publication

This work is consent for publication through the Journal formats.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

5. References

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Povzetek

V prispevku opisujemo serijo heterociklizacijskih reakcij, ki smo jih izvedli na cikloheksan-1,3-dionu s furan-2-karbaldehidom ali tiofen-2-karbaldehidom pri čemer sta nastala ustrezna ilidenska derivata **3a,b**; ti dve spojini sta bili izhodišče za nadaljnje heterociklizacijske reakcije, ki so vodile do tiofenskih in piranskih derivatov **5a–d** oz. **6a–d**. Ob reakciji spojin **3a,b** z elementarnim žveplom in fenil izotiocianatom sta nastala pripojena tiazolska derivata **8a,b**. Pri reakciji s hidrazin hidratom ali fenilhidrazinom pa so nastali 4-hidrazono-4,5,6,7-tetrahidro-2*H*-indazolski derivati **10a–d**. Podobno sta pri reakciji med **3a** ali **3b** s hidroksilamin hidrokloridom nastala 6,7-dihidrobenzo[*c*]izoksazol-4(5*H*)-on oksima **12a** in **12b**. Pripravili smo še več drugih heterocikličnih spojin in določili njihove strukture. Pripravljenim spojinam smo določili citotoksične aktivnosti na izbrane celične linije raka. Za najbolj aktivne spojine smo v nadaljevanju določili še inhibitorne lastnosti proti tirozin kinazam in Pim-1 kinazi.

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