

Scientific paper

Synthesis of Heterocyclic Compounds Derived From Dimedone and Their Anti-tumor and Tyrosine Kinase Inhibitions

Rafat M. Mohareb,^{1,*} Fatma M. Manhi² and Amal Abdelwahab²¹ Department of Chemistry, Faculty of Science, Cairo University, Giza, A. R. Egypt² National Organization for Drug Control & Research, P.O. 29, Cairo, A. R. Egypt

* Corresponding author: E-mail: raafat_mohareb@yahoo.com

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Abstract

The reaction of dimedone with arylaldehydes gave the benzylidene derivatives **3a–c**, the latter underwent a series of heterocyclization reactions to give fused thiophene, pyrazole isoxazole and pyridazine derivatives. The synthesized compounds were evaluated against different kinds of cancer cell lines together tyrosine kinases and Pim-1 kinase inhibitions. All the synthesized compounds were assessed for the inhibitory activities against A549 (non-small cell lung cancer), H460 (human lung cancer), HT-29 (human colon cancer) and MKN-45 (human gastric cancer) cancer cell lines together with foretinib as the positive control by a MTT assay. The promising compounds were **3c**, **5b**, **5e**, **5f**, **7c**, **7f**, **9c**, **11b**, **12c**, **12d**, **13b**, **13d**, **14b**, **16c** and **16d** among the tested compounds. On the other hand, compounds **5b**, **5e**, **5f**, **7c**, **11b**, **12c**, **12d**, **13d**, **14b**, **16c** and **16d** were the most effective inhibitors against tyrosine kinases and compounds **5b**, **11b**, **12d**, **13d**, **14b** and **16c** were the most potent against Pim-1 kinase.

Keywords: Dimedone; thiophene; pyrazole; isoxazole; antitumor; tyrosine kinase

1. Introduction

As typical reactive 1,3-dicarbonyl compounds, cyclohexane-1,3-dione and its analog 5,5-dimethyl cyclohexane-1,3-dione (dimedone) have been widely used in versatile synthetic reactions.^{1,2} Dimedone is not only a typical reagent for Knoevenagel condensation, but also adds easily to electron-deficient alkenes *via* Michael addition. On the other hand, its one or two carbonyl groups could take part in substitution and cyclization reactions through the tautomeric enolate form. Thus, the cascade reactions of addition, elimination and substitution could be achieved in many reactions involving dimedone. The reactions of cyclohexane-1,3-dione or dimedone with aldehydes have been extensively studied in the past years, from which several types of compounds have been produced according to the reaction conditions.^{3,4} The normal Knoevenagel condensations of cyclohexane-1,3-dione or dimedone with aldehydes have been conducted with numerous methods including promotion *via* amines,⁵ Lewis acids,⁶ surfactants,^{7,8} zeolites,⁹ ionic liquids.¹⁰ The use of environmentally benign methods, such as aqueous medi-

um¹¹ or in the absence of solvents¹² and the usage of ultrasound or microwave heating¹³ have also been developed in recent years. The reactions usually proceed further through Michael addition reaction of the second molecule of dimedone to yield tetraketones as main products.¹⁴ On the other hand, tetraketones could be easily converted to 9-substituted 1,8-dioxoxanthenes by dehydration step.¹⁵ According to our previous work a large number of heterocyclic compounds with anti-proliferative and anti-inflammatory activities were recently synthesized by our research group.^{16,17} Recently, our research group was involved in the synthesis and determination of the anti-proliferative properties of a large number of heterocyclic compounds.^{18,19} In addition, according to our continued interest in the design of new multicomponent reactions and the application in the synthesis of heterocyclic compounds we found some unprecedented reaction patterns in the reaction of dimedone (**1**) with aromatic aldehydes **2a–c**, to produce the benzylidene derivatives **3a–c** and with aromatic diazonium salts **10a,b** to produce products which underwent heterocyclization reactions to give compounds with potential antitumor activities.

2. Experimental

Dry solvents were used throughout this work. All melting points of the synthesized compounds were recorded on Büchi melting point apparatus D-545. The IR spectra (KBr discs) were recorded on Bruker Vector 22 instrument. ^{13}C NMR and ^1H NMR spectra were measured on Bruker DPX200 instrument in $\text{DMSO}-d_6$ with TMS as the internal standard. Mass spectra were measured using EIMS (Shimadzu) and ESI-esquire 3000 Bruker Daltonics instrument. Elemental analyses were measured using the Micro-analytical Data center at Cairo University. All reactions were monitored by TLC on 2×5 cm pre-coated silica gel 60 F254 plates of thickness of 0.25 mm (Merck) for determining when the reactions were complete.

2.1. General Procedure for the Synthesis of the Benzylidene Derivatives 3a–c

To a solution of dimedone (1.40 g, 0.01 mol) in absolute ethanol (40 mL) containing piperidine (0.50 mL) any of the aldehydes: benzaldehyde (1.05 g, 0.01 mol), 4-methoxybenzaldehyde (1.36 g, 0.01 mol) or 4-chlorobenzaldehyde (1.40 g, 0.01 mol), were added. Subsequently, the mixture was heated using the reflux conditions for 1 h, then poured onto ice/water containing a few drops of hydrochloric acid, the solid was collected by filtration, dried and crystallized from ethanol to get the 3a–c.

2.1.1. 2-Benzylidene-5,5-dimethylcyclohexane-1,3-dione (3a)

Orange crystals from ethanol; m.p. 190–192 °C; yield 78%. IR (KBr) cm^{-1} : 3054, 2986, 1689, 1687, 1632. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.42–7.23 (m, 5H, C_6H_5), 6.02 (s, 1H, CH), 2.31, 2.28 (2s, 4H, 2CH_2), 1.09, 1.06 (2s, 6H, 2CH_3); ^{13}C NMR ($\text{DMSO}-d_6$, 75 MHz) δ 166.2, 164.8 (C-1, C-3), 127.3, 126.6, 124.3, 121.2 (C_6H_5), 108.6, 103.2 (CH=C), 50.6 (C-4), 36.2 (C-5), 24.4 (2CH_3); EIMS: m/z 228 $[\text{M}]^+$ (28%); Anal. Calcd for $\text{C}_{15}\text{H}_{16}\text{O}_2$ (228.29): C, 78.92; H, 7.06%. Found: C, 78.24; H, 6.83%.

2.1.2. 2-(4-Methoxybenzylidene)-5,5-dimethylcyclohexane-1,3-dione (3b)

Pale yellow crystals from ethanol; m.p. 140–142 °C; yield 78%. IR (KBr) cm^{-1} : 3055, 2984, 1689, 1688, 1630. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.47–7.26 (m, 4H, C_6H_4), 6.06 (s, 1H, CH), 3.68 (s, 3H, OCH_3), 2.36, 2.24 (2s, 4H, 2CH_2), 1.07, 1.06 (2s, 6H, 2CH_3); ^{13}C NMR ($\text{DMSO}-d_6$, 75 MHz) δ 166.8, 164.5 (C-1, C-3), 127.0, 126.9, 123.7, 121.6 (C_6H_4), 108.3, 103.6 (CH=C), 50.3 (C-4), 50.1 (OCH_3), 36.7 (C-5), 24.2 (2CH_3); EIMS: m/z 258 $[\text{M}]^+$ (32%); Anal. Calcd for $\text{C}_{16}\text{H}_{18}\text{O}_3$ (258.31): C, 74.39; H, 7.02%. Found: C, 74.48; H, 6.95%.

2.1.3. 2-(4-Chlorobenzylidene)-5,5-dimethylcyclohexane-1,3-dione (3c)

Pale yellow crystals from ethanol; m.p. 125–127 °C; yield 80%. IR (KBr) cm^{-1} : 3055, 2984, 1690, 1688, 1630. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.49–7.22 (m, 4H, C_6H_4), 6.07 (s, 1H, CH), 2.38, 2.21 (2s, 4H, 2CH_2), 1.08, 1.05 (2s, 6H, 2CH_3); ^{13}C NMR ($\text{DMSO}-d_6$, 75 MHz) δ 166.5, 164.2 (C-1, C-3), 128.3, 126.5, 123.2, 121.3 (C_6H_4), 108.8, 103.3 (CH=C), 50.6 (C-4), 36.8 (C-5), 24.5 (2CH_3); EIMS: m/z 262 $[\text{M}]^+$ (28%); Anal. Calcd for $\text{C}_{15}\text{H}_{15}\text{ClO}_2$ (262.73): C, 68.57; H, 5.75%. Found: C, 68.39; H, 6.02%.

2.2. General Procedure for the Synthesis of the 6,7-Dihydrobenzo[b]thiophene Derivatives 5a–f

To a solution of any of 3a (2.28 g, 0.01 mol), 3b (2.58 g, 0.01 mol) or 3c (2.62 g, 0.01 mol) in 1,4-dioxan (40 mL) containing triethylamine (0.50 mL) each of elemental sulfur (0.32 g, 0.01 mol) and either of malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.07 g, 0.01 mol) were added. The reaction mixture was heated under reflux for 1 h then left to cool. The formed solid product was collected by filtration, dried and crystallized from ethanol to give 5a–f, respectively.

2.2.1. 2-Amino-4-benzylidene-7,7-dimethyl-5-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (5a)

Yellow crystals from ethanol; m.p. 199–202 °C; yield 80%. IR (KBr) cm^{-1} : 3487–3348 (NH_2), 3055, 2985, 1688, 1632. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.40–7.25 (m, 5H, C_6H_5), 6.06 (s, 1H, CH), 4.30 (s, 2H, D_2O exchangeable, NH_2), 2.32 (s, 2H, CH_2), 1.08, 1.06 (2s, 6H, 2CH_3); ^{13}C NMR ($\text{DMSO}-d_6$, 75 MHz) δ 166.0 (C-1), 138.6, 136.0, 135.2, 130.7, 127.8, 125.4, 124.3, 121.0 (C_6H_5 , thiophene C), 116.9 (CN), 108.9, 103.5 (CH=C), 50.8 (C-4), 36.7 (C-5), 24.6 (2CH_3); EIMS: m/z 308 $[\text{M}]^+$ (22%); Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{OS}$ (308.40): C, 70.10; H, 5.23; N, 9.08; S, 10.40%. Found: C, 70.06; H, 5.39; N, 9.29; S, 10.31%.

2.2.2. Ethyl 2-Amino-4-benzylidene-7,7-dimethyl-5-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (5b)

Yellow crystals from ethanol; m.p. 117–120 °C; yield 72%. IR (KBr) cm^{-1} : 4682, 3367 (NH_2), 3055, 2985, 1702, 1688, 1632. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.43–7.27 (m, 5H, C_6H_5), 6.05 (s, 1H, CH), 4.35 (s, 2H, D_2O exchangeable, NH_2), 4.21 (q, 2H, $J = 7.26$ Hz, OCH_2CH_3), 2.35 (s, 2H, CH_2), 1.12 (t, 3H, $J = 7.26$ Hz, OCH_2CH_3), 1.07, 1.03 (2s, 6H, 2CH_3); ^{13}C NMR ($\text{DMSO}-d_6$, 75 MHz) δ 166.3, 164.2 (C-1, CO ester), 138.3, 136.5, 135.8, 130.3,

127.4, 125.8, 124.1, 121.6 (C₆H₅, thiophene C), 108.6, 103.3 (CH=C), 52.6 (OCH₂CH₃), 50.4 (C-4), 36.3 (C-5), 24.5 (2CH₃), 16.2 (OCH₂CH₃); EIMS: *m/z* 355 [M]⁺ (28%); Anal. Calcd for C₂₀H₂₁NO₃S (355.45): C, 67.58; H, 5.95; N, 3.94; S, 9.02%. Found: C, 67.70; H, 5.64; N, 4.16; S, 8.86%.

2. 2. 3. 2-Amino-4-(4-methoxybenzylidene)-7,7-dimethyl-5-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (5c)

Yellow crystals from ethanol; m.p. 193–196 °C; yield 80%. IR (KBr) cm⁻¹: 3473–3368 (NH₂), 3055, 2985, 2220, 1688, 1630. ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.46–7.21 (m, 4H, C₆H₄), 6.09 (s, 1H, CH), 4.36 (s, 2H, D₂O exchangeable, NH₂), 3.64 (s, 3H, OCH₃), 2.36 (s, 2H, CH₂), 1.07, 1.04 (2s, 6H, 2CH₃); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 166.3 (C-1), 138.2, 136.4, 135.6, 130.9, 128.5, 126.3, 123.8, 120.8 (C₆H₅, thiophene C), 116.8 (CN), 108.7, 103.5 (CH=C), 52.8 (OCH₃), 50.6 (C-4), 36.5 (C-5), 24.6 (2CH₃); EIMS: *m/z* 338 [M]⁺ (28%); Anal. Calcd for C₁₉H₁₈N₂O₂S (338.42): C, 67.43; H, 5.36; N, 8.28; S, 9.47%. Found: C, 67.72; H, 5.41; N, 8.16; S, 9.63%.

2. 2. 4. Ethyl 2-Amino-4-(4-methoxybenzylidene)-7,7-dimethyl-5-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (5d)

Orange crystals from ethanol; m.p. 188–190 °C; yield 67%. IR (KBr) cm⁻¹: 4673, 3359 (NH₂), 3055, 2985, 1689, 1688, 1630. ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.46–7.24 (m, 4H, C₆H₄), 6.03 (s, 1H, CH), 4.38 (s, 2H, D₂O exchangeable, NH₂), 4.22 (q, 2H, *J* = 7.19 Hz, OCH₂CH₃), 3.68 (s, 3H, OCH₃), 2.38 (s, 2H, CH₂), 1.13 (t, 3H, *J* = 7.19 Hz, OCH₂CH₃), 1.08, 1.01 (2s, 6H, 2CH₃); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 166.6, 164.8 (C-1, CO ester), 138.3, 136.5, 135.8, 130.3, 128.6, 126.2, 123.5, 121.4 (C₆H₅, thiophene C), 108.2, 103.4 (CH=C), 52.8 (OCH₃), 52.6 (OCH₂CH₃), 50.2 (C-4), 36.5 (C-5), 24.8 (2CH₃), 16.2 (OCH₂CH₃); EIMS: *m/z* 385 [M]⁺ (32%); Anal. Calcd for C₂₁H₂₃NO₄S (385.48): C, 65.43; H, 6.01; N, 3.63; S, 8.32%. Found: C, 65.59; H, 5.94; N, 3.80; S, 8.42%.

2. 2. 5. 2-Amino-4-(4-chlorobenzylidene)-7,7-dimethyl-5-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (5e)

Yellow crystals from ethanol; m.p. 170–172 °C; yield 75%. IR (KBr) cm⁻¹: 3480–3359 (NH₂), 3055, 2985, 2220, 1688, 1630. ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.43–7.23 (m, 4H, C₆H₄), 6.05 (s, 1H, CH), 4.34 (s, 2H, D₂O exchangeable, NH₂), 2.38 (s, 2H, CH₂), 1.07, 1.04 (2s, 6H, 2CH₃); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 166.6 (C-1), 138.3, 135.9, 134.6, 130.3, 128.2, 126.7, 123.5, 120.4 (C₆H₅, thiophene C), 116.9 (CN), 108.3, 103.2 (CH=C), 50.3

(C-4), 36.2 (C-5), 24.7 (2CH₃); EIMS: *m/z* 342 [M]⁺ (35%); Anal. Calcd for C₁₈H₁₅ClN₂OS (342.84): C, 63.06; H, 4.41; N, 8.17; S, 9.35%. Found: C, 63.29; H, 4.69; N, 8.31; S, 9.42%.

2. 2. 6. Ethyl 2-amino-4-(4-chlorobenzylidene)-7,7-dimethyl-5-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (5f)

Yellow crystals from ethanol; m.p. 126–128 °C; yield 76%. IR (KBr) cm⁻¹: 4673, 3368 (NH₂), 3055, 2983, 1703, 1688, 1630. ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.46–7.23 (m, 4H, C₆H₅), 6.02 (s, 1H, CH), 4.39 (s, 2H, D₂O exchangeable, NH₂), 4.23 (q, 2H, *J* = 6.72 Hz, OCH₂CH₃), 2.35 (s, 2H, CH₂), 1.13 (t, 3H, *J* = 6.72 Hz, OCH₂CH₃), 1.09, 1.053 (2s, 6H, 2CH₃); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 166.6, 164.5 (C-1, CO ester), 138.2, 136.3, 135.6, 130.4, 127.3, 125.2, 124.6, 121.3 (C₆H₅, thiophene C), 108.2, 103.5 (CH=C), 52.4 (OCH₂CH₃), 50.6 (C-4), 36.8 (C-5), 24.5 (2CH₃), 16.2 (OCH₂CH₃); EIMS: *m/z* 389 [M]⁺ (32%); Anal. Calcd for C₂₀H₂₀ClNO₃S (389.90): C, 61.61; H, 5.17; N, 3.59; S, 8.22%. Found: C, 61.49; H, 5.36; N, 3.69; S, 8.38%.

2. 2. 7. General Procedure for the Synthesis of the 4,5,6,7-Tetrahydro-2H-indazole Derivatives 7a–f

To a solution of any of **3a** (2.28 g, 0.01 mol), **3b** (2.58 g, 0.01 mol) or **3c** (2.62 g, 0.01 mol) in ethanol (40 mL) either of hydrazine hydrate (0.1 mL, 0.02 mol) or phenylhydrazine (3.16 g, 0.02 mol) was added. The reaction mixture, in each case, was heated under reflux for 3 h then was left to cool and the formed solid product was collected by filtration upon pouring onto ice/water mixture containing a few drops of hydrochloric acid.

2. 2. 7. 1. 4-Hydrazono-6,6-dimethyl-3-phenyl-4,5,6,7-tetrahydro-2H-indazole (7a)

Pale yellow crystals from ethanol; m.p. 175–177 °C; yield 68%. IR (KBr) cm⁻¹: 3497–3336 (NH, NH₂), 3055, 2985, 1663, 1632. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.26 (s, 1H, D₂O exchangeable, NH), 7.43–7.26 (m, 5H, C₆H₅), 5.29 (s, 2H, D₂O exchangeable, NH₂), 2.41, 2.38 (2s, 4H, 2CH₂), 1.07, 1.06 (2s, 6H, 2CH₃); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 172.3 (C-4), 140.6, 138.3, 127.8, 125.4, 124.3, 121.0 (C₆H₅, C-3, C-4), 34.6 (C-6), 36.8, 24.9, (C-7, C-5) 24.3 (2CH₃); EIMS: *m/z* 254 [M]⁺ (28%); Anal. Calcd for C₁₅H₁₈N₄ (254.33): C, 70.84; H, 7.13; N, 22.03%. Found: C, 70.69; H, 6.93; N, 21.79%.

2. 2. 7. 2. 4-Hydrazono-3-(4-methoxyphenyl)-6,6-dimethyl-4,5,6,7-tetrahydro-2H-indazole (7b)

Orange crystals from ethanol; m.p. 189–192 °C; yield 70%. IR (KBr) cm⁻¹: 3474–3353 (NH, NH₂), 3055,

2985, 1660, 1630. ^1H NMR (300 MHz, DMSO- d_6) δ 8.28 (s, 1H, D₂O exchangeable, NH), 7.48–7.23 (m, 4H, C₆H₄), 5.27 (s, 2H, D₂O exchangeable, NH₂), 3.52 (s, 3H, OCH₃), 2.46, 2.32 (2s, 4H, 2CH₂), 1.09, 1.06 (2s, 6H, 2CH₃); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 172.6 (C-4), 140.3, 138.6, 127.4, 126.6, 123.1, 120.8 (C₆H₅, C-3, C-4), 50.2 (OCH₃), 34.8 (C-6), 36.6, 24.8, (C-7, C-5) 24.1 (2CH₃); EIMS: m/z 284 [M]⁺ (30%); Anal. Calcd for C₁₆H₂₀N₄O (284.36): C, 67.58; H, 7.09; N, 19.70%. Found: C, 67.39; H, 6.84; N, 19.66%.

2. 2. 7. 3. 3-(4-Chlorophenyl)-4-hydrazono-6,6-dimethyl-4,5,6,7-tetrahydro-2H-indazole (7c)

Yellow crystals from 1,4-dioxan; m.p. 185–187 °C; yield 77%. IR (KBr) cm⁻¹: 3493–3342 (NH, NH₂), 3057, 2985, 1662, 1630. ^1H NMR (300 MHz, DMSO- d_6) δ 8.27 (s, 1H, D₂O exchangeable, NH), 7.52–7.25 (m, 4H, C₆H₄), 5.25 (s, 2H, D₂O exchangeable, NH₂), 2.43, 2.36 (2s, 4H, 2CH₂), 1.08, 1.03 (2s, 6H, 2CH₃); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 172.8 (C-4), 140.1, 138.4, 128.3, 125.5, 122.6, 120.2 (C₆H₅, C-3, C-4), 34.6 (C-6), 36.3, 24.5, (C-7, C-5) 24.3 (2CH₃); EIMS: m/z 288 [M]⁺ (24%); Anal. Calcd for C₁₅H₁₇ClN₄ (288.78): C, 62.39; H, 5.93; N, 19.40%. Found: C, 62.58; H, 6.15; N, 19.52%.

2. 2. 7. 4. 6,6-Dimethyl-2,3-diphenyl-4-(2-phenylhydrazono)-4,5,6,7-tetrahydro-2H-indazole (7d)

Pale yellow crystals from ethanol; m.p. 171–173 °C; yield 60%. IR (KBr) cm⁻¹: 3482–3346 (NH, NH₂), 3055, 2985, 1665, 1632. ^1H NMR (300 MHz, DMSO- d_6) δ 8.28 (s, 1H, D₂O exchangeable, NH), 7.46–7.22 (m, 15H, 3C₆H₅), 2.42, 2.38 (2s, 4H, 2CH₂), 1.09, 1.07 (2s, 6H, 2CH₃); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 172.6 (C-4), 140.4, 138.1, 129.6, 129.3, 128.5, 127.8, 127.4, 126.1, 126.5, 126.9, 125.6, 125.2, 124.0, 121.2 (3C₆H₅, C-3, C-4), 34.8 (C-6), 36.4, 24.7 (C-7, C-5) 24.5 (2CH₃); EIMS: m/z 406 [M]⁺ (24%); Anal. Calcd for C₂₇H₂₆N₄ (406.52): C, 79.77; H, 6.45; N, 13.78%. Found: C, 79.84; H, 6.62; N, 13.53%.

2. 2. 7. 5. 3-(4-Methoxyphenyl)-6,6-dimethyl-2-phenyl-4-(2-phenylhydrazono)-4,5,6,7-tetrahydro-2H-indazole (7e)

Orange crystals from ethanol; m.p. 128–130 °C; yield 76%. IR (KBr) cm⁻¹: 3486–3336 (NH), 3055, 2985, 1660, 1630. ^1H NMR (300 MHz, DMSO- d_6) δ 8.31 (s, 1H, D₂O exchangeable, NH), 7.53–7.26 (m, 14H, C₆H₅, 2C₆H₄), 3.61 (s, 3H, OCH₃), 2.48, 2.36 (2s, 4H, 2CH₂), 1.08, 1.07 (2s, 6H, 2CH₃); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 172.8 (C-4), 140.7, 138.3, 128.8, 129.3, 128.5, 127.8, 127.3, 126.1, 126.8, 125.9, 125.6, 124.3, 123.7, 120.2 (2C₆H₅, C₆H₄, C-3, C-4), 50.2 (OCH₃), 34.1 (C-6), 36.6, 24.3 (C-7, C-5) 24.2 (2CH₃); EIMS: m/z 436 [M]⁺ (38%); Anal. Calcd for C₂₈H₂₈N₄O (436.55): C, 77.04; H, 6.46; N, 12.83%. Found: C, 77.25; H, 6.58; N, 12.64%.

2. 2. 7. 6. 3-(4-Chlorophenyl)-6,6-dimethyl-2-phenyl-4-(2-phenylhydrazono)-4,5,6,7-tetrahydro-2H-indazole (7f)

Pale yellow crystals from ethanol; m.p. 126–128 °C; yield 66%. IR (KBr) cm⁻¹: 3492–3327 (NH), 3055, 2985, 1660, 1630. ^1H NMR (300 MHz, DMSO- d_6) δ 8.26 (s, 1H, D₂O exchangeable, NH), 7.47–7.21 (m, 14H, 2C₆H₅, C₆H₄), 2.46, 2.38 (2s, 4H, 2CH₂), 1.08, 1.04 (2s, 6H, 2CH₃); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 172.4 (C-4), 140.1, 138.6, 129.3, 129.1, 128.4, 127.5, 127.4, 126.3, 126.5, 126.7, 125.4, 125.2, 124.0, 121.0 (2C₆H₅, C₆H₄, C-3, C-4), 34.5 (C-6), 36.4, 24.7 (C-7, C-5) 24.8 (2CH₃); EIMS: m/z 440 [M]⁺ (36%); Anal. Calcd for C₂₇H₂₅ClN₄ (440.97): C, 73.54; H, 5.71; N, 12.71%. Found: C, 73.58; H, 5.68; N, 12.86%.

2. 2. 8. General Procedure for the Synthesis of the Dihydrobenzo[c]isoxazole Derivatives 9a–c

To a solution of any of **3a** (2.28 g, 0.01 mol), **3b** (2.58 g, 0.01 mol) or **3c** (2.62 g, 0.01 mol) in ethanol (40 mL) containing sodium acetate (1.00 g) hydroxylamine hydrochloride (1.40 g, 0.02 mol) was added. The reaction mixture was heated under reflux for 2 h then poured onto ice/water and the formed solid product was collected by filtration.

2. 2. 8. 1. 6,6-Dimethyl-3-phenyl-6,7-dihydrobenzo[c]isoxazol-4(5H)-one oxime (9a)

Pale yellow crystals from 1,4-dioxan; m.p. 183–185 °C; yield 68%. IR (KBr) cm⁻¹: 3572–3326 (OH), 3055, 2985, 1663, 1631. ^1H NMR (300 MHz, DMSO- d_6) δ 9.52 (s, 1H, D₂O exchangeable, OH), 7.42–7.26 (m, 5H, C₆H₅), 2.47, 2.33 (2s, 4H, 2CH₂), 1.08, 1.05 (2s, 6H, 2CH₃); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 175.3 (C-4), 140.1, 137.6, 127.8, 126.5, 124.0, 121.2 (C₆H₅, C-3, C-4), 34.3 (C-6), 36.8, 24.5 (C-7, C-5), 24.8 (2CH₃); EIMS: m/z 256 [M]⁺ (30%); Anal. Calcd for C₁₅H₁₆N₂O₂ (256.30): C, 70.29; H, 6.29; N, 10.93%. Found: C, 70.31; H, 6.37; N, 11.25%.

2. 2. 8. 2. 3-(4-Methoxyphenyl)-6,6-dimethyl-6,7-dihydrobenzo[c]isoxazol-4(5H)-one oxime (9b)

Pale yellow crystals from ethanol; m.p. 177–180 °C; yield 58%. IR (KBr) cm⁻¹: 3529–3336 (OH), 3055, 2985, 1663, 1631. ^1H NMR (300 MHz, DMSO- d_6) δ 9.40 (s, 1H, D₂O exchangeable, OH), 7.48–7.26 (m, 4H, C₆H₄), 3.52 (s, 3H, OCH₃), 2.42, 2.35 (2s, 4H, 2CH₂), 1.09, 1.04 (2s, 6H, 2CH₃); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 172.8 (C-4), 140.7, 138.1, 126.9, 125.6, 125.6, 120.8 (C₆H₄, C-3, C-4), 50.8 (OCH₃), 34.4 (C-6), 36.9, 24.3 (C-7, C-5) 24.8 (2CH₃); EIMS: m/z 286 [M]⁺ (30%); Anal. Calcd for C₁₆H₁₈N₂O₃ (286.33): C, 67.12; H, 6.34; N, 9.78%. Found: C, 67.26; H, 6.26; N, 9.80%.

2. 2. 8. 3. 3-(4-Chlorophenyl)-6,6-dimethyl-6,7-dihydrobenzo[c]isoxazol-4(5H)-one oxime (9c)

Pale yellow crystals from 1,4-dioxan; m.p. 201–203 °C; yield 77%. IR (KBr) cm⁻¹: 3552–3361 (OH), 3055,

2985, 1664, 1630. ^1H NMR (300 MHz, DMSO- d_6) δ 9.53 (s, 1H, D₂O exchangeable, OH), 7.46–7.23 (m, 4H, C₆H₄), 2.49, 2.31 (2s, 4H, 2CH₂), 1.06, 1.02 (2s, 6H, 2CH₃); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 175.5 (C-4), 140.3, 137.2, 127.6, 125.8, 123.3, 120.9 (C₆H₅, C-3, C-4), 34.1 (C-6), 36.6, 24.2 (C-7, C-5), 24.3 (2CH₃); EIMS: m/z 290 [M]⁺ (26%); Anal. Calcd for C₁₅H₁₅ClN₂O₂ (290.74): C, 61.97; H, 5.20; N, 9.64%. Found: C, 62.79; H, 4.86; N, 9.80%.

2. 2. 9. General Procedure of the Synthesis of the Hydrazone Derivatives 11a,b

To a cold solution (0–5 °C) of compound **1** (1.40 g, 0.01 mol) in ethanol (40 mL) containing sodium acetate (3.0 g) either 4-methylnaphthalen-1-diazonium salt (0.01 mol) or 4-chloronaphthalen-1-diazonium salt [prepared by the addition of sodium nitrite solution (0.70 g, 0.01 mol) to a cold solution (0–5 °C) of either of 4-methylnaphthalen-1-amine (1.57 g, 0.01 mol) or 4-chloromethylnaphthalen-1-amine (1.77 g, 0.01 mol) with continuous stirring] was added with continuous stirring. The reaction mixture, in each case was stirred at room temperature for an additional 2 h and the formed solid product was collected by filtration.

2. 2. 9. 1. 5,5-Dimethyl-2-(2-(4-methylnaphthalen-1-yl)hydrazono)cyclohexane-1,3-dione (11a)

Pale yellow crystals from ethanol; m.p. 220–223 °C; yield 68%. IR (KBr) cm^{-1} : 3468–3334 (NH), 3055, 2985, 1689, 1687, 1663, 1630. ^1H NMR (300 MHz, DMSO- d_6) δ 8.29 (s, 1H, D₂O exchangeable, NH), 7.48–7.23 (m, 6H, naphthalene H), 2.41, 2.38 (2s, 4H, 2CH₂), 2.89 (s, 3H, CH₃), 1.07, 1.06 (2s, 6H, 2CH₃); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 172.8 (C-2), 166.2, 164.8 (C-1, C-3), 138.6, 135.2, 133.1, 129.6, 126.5, 126.1, 124.7, 123.9, 122.3, 120.6 (naphthalene C), 34.8 (C-6), 36.5, 32.8 (CH₃), 24.3 (C-7, C-5) 24.5 (2CH₃); EIMS: m/z 308 [M]⁺ (21%); Anal. Calcd for C₁₉H₂₀N₂O₂ (308.37): C, 74.00; H, 6.54; N, 9.08%. Found: C, 73.96; H, 6.82; N, 8.79%.

2. 2. 9. 2. 2-(2-(4-Chloronaphthalen-1-yl)hydrazono)-5,5-dimethylcyclohexane-1,3-dione (11b)

Pale yellow crystals from ethanol; m.p. 211–213 °C; yield 74%. IR (KBr) cm^{-1} : 3493–3358 (NH), 3055, 2985, 1688, 1687, 1663, 1630. ^1H NMR (300 MHz, DMSO- d_6) δ 8.32 (s, 1H, D₂O exchangeable, NH), 7.56–7.25 (m, 6H, naphthalene H), 2.46, 2.33 (2s, 4H, 2CH₂), 1.08, 1.06 (2s, 6H, 2CH₃); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 172.9 (C-2), 166.7, 164.8 (C-1, C-3), 138.8, 135.6, 134.41, 129.2, 127.8, 125.3, 124.2, 123.7, 122..1, 120.4 (naphthalene C), 34.8 (C-6), 36.8, 24.3 (C-7, C-5) 24.2 (2CH₃); EIMS: m/z 328 [M]⁺ (18%); Anal. Calcd for C₁₈H₁₇ClN₂O₂ (328.79): C, 65.75; H, 5.21; N, 8.52%. Found: C, 65.49; H, 5.06; N, 8.63%.

2. 2. 10. General Procedure for the Synthesis of the 6,7-Dihydrobenzo[b]thiophene Derivatives 12a–d

To a solution of either of **11a** (3.08 g, 0.01 mol), **11b** (3.28 g, 0.01 mol) in 1,4-dioxan (40 mL) containing triethylamine (0.50 mL) each of elemental sulfur (0.32 g, 0.01 mol) and either of malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.07 g, 0.01 mol) were added. The reaction mixture was heated under reflux for 1 h then left to cool. The formed solid product was collected by filtration, dried and crystallized from ethanol to give **12a–d**, respectively.

2. 2. 10. 1. 2-Amino-7,7-dimethyl-4-(2-(4-methylnaphthalen-1-yl)hydrazono)-5-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (12a)

Pale yellow crystals from ethanol; m.p. 218–220 °C; yield 68%. IR (KBr) cm^{-1} : 3480–3350 (NH, NH₂), 3055, 2985, 2220, 1688, 1663, 1630. ^1H NMR (300 MHz, DMSO- d_6) δ 8.37 (s, 1H, D₂O exchangeable, NH), 7.48–7.23 (m, 6H, naphthalene H), 4.85 (s, 2H, D₂O exchangeable, NH₂), 2.86 (s, 3H, CH₃), 2.42 (s, 2H, CH₂), 1.09, 1.06 (2s, 6H, 2CH₃); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 175.7 (C-2), 166.2, (C-3), 138.8, 136.6, 133.8, 129.3, 126.2, 126.4, 124.2, 123.3, 122.8, 120.2 (naphthalene C), 116.8 (CN), 34.6 (C-6), 32.3 (CH₃), 24.1 (C-7, C-5), 24.8 (2CH₃); EIMS: m/z 388 [M]⁺ (28%); Anal. Calcd for C₂₂H₂₀N₄OS (388.49): C, 68.02; H, 5.19; N, 14.42; S, 8.25%. Found: C, 67.83; H, 5.27; N, 8.39; S, 8.36%.

2. 2. 10. 2. Ethyl 2-Amino-7,7-dimethyl-4-(2-(4-methylnaphthalen-1-yl)hydrazono)-5-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (12b)

Pale yellow crystals from ethanol; m.p. 177–179 °C; yield 73%. IR (KBr) cm^{-1} : 3468–3342 (NH, NH₂), 3055, 2985, 1689, 1687, 1663, 1630. ^1H NMR (300 MHz, DMSO- d_6) δ 8.39 (s, 1H, D₂O exchangeable, NH), 7.56–7.25 (m, 6H, naphthalene H), 4.88 (s, 2H, D₂O exchangeable, NH₂), 4.21 (q, 2H, $J = 6.72$ Hz, OCH₂CH₃), 2.86 (s, 3H, CH₃), 2.41 (s, 2H, CH₂), 1.13 (t, 3H, $J = 6.72$ Hz, OCH₂CH₃), 1.09, 1.07 (2s, 6H, 2CH₃); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 175.8 (C-2), 166.7, (C-3), 138.2, 137.3, 133.2, 129.7, 126.4, 126.2, 124.1, 123.6, 123.2, 120.0 (naphthalene C), 52.4 (OCH₂CH₃); 34.7 (C-6), 36.8, (CH₃), 32.1, 24.5 (C-7, C-5), 24.4 (2CH₃), 16.2 (OCH₂CH₃); EIMS: m/z 435 [M]⁺ (46%); Anal. Calcd for C₂₄H₂₅N₃O₃S (435.54): C, 66.18; H, 5.79; N, 9.65; S, 7.36%. Found: C, 66.84; H, 5.50; N, 9.19; S, 7.47%.

2. 2. 10. 3. 2-Amino-4-(2-(4-chloronaphthalen-1-yl)hydrazono)-7,7-dimethyl-5-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (12c)

Pale yellow crystals from ethanol; m.p. 136–139 °C; yield 78%. IR (KBr) cm^{-1} : 3469–3332 (NH, NH₂), 3055, 2985, 2220, 1689, 1663, 1630. ^1H NMR (300 MHz, DMSO- d_6) δ 8.39 (s, 1H, D₂O exchangeable, NH), 7.51–7.23 (m,

6H, naphthalene H), 4.88 (s, 2H, D₂O exchangeable, NH₂), 2.40 (s, 2H, CH₂), 1.09, 1.07 (2s, 6H, 2CH₃); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 175.7 (C-2), 166.2, (C-3), 138.8, 136.6, 133.8, 129.3, 126.2, 126.4, 124.2, 123.3, 122.8, 120.2 (naphthalene C), 116.8 (CN), 34.6 (C-6), 32.3 (CH₃), 32.6, 24.1 (C-7, C-5), 24.8 (2CH₃); EIMS: *m/z* 408 [M]⁺ (40%); Anal. Calcd for C₂₁H₁₇ClN₄OS (408.90): C, 61.68; H, 4.19; N, 13.70; S, 7.84%. Found: C, 61.93; H, 4.26; N, 13.82; S, 7.94%.

2. 2. 10. 4. Ethyl 2-Amino-4-(2-(4-chloronaphthalen-1-yl)hydrazono)-7,7-dimethyl-5-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (12d)

Pale brown crystals from acetic acid; m.p. 205–207 °C; yield 68%. IR (KBr) cm⁻¹: 3442–3329 (NH, NH₂), 3055, 2985, 1689, 1687, 1663, 1630. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.35 (s, 1H, D₂O exchangeable, NH), 7.53–7.21 (m, 6H, naphthalene H), 4.84 (s, 2H, D₂O exchangeable, NH₂), 4.22 (q, 2H, *J* = 7.41 Hz, OCH₂CH₃), 2.41 (s, 2H, CH₂), 1.13 (t, 3H, *J* = 7.41 Hz, OCH₂CH₃), 1.08, 1.05 (2s, 6H, 2CH₃); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 175.3 (C-2), 166.5 (C-3), 138.6, 137.6, 133.5, 129.3, 126.1, 126.0, 124.5, 123.2, 122.7, 120.3 (naphthalene C), 52.5 (OCH₂CH₃), 34.8 (C-6), 32.4, 24.2 (C-7, C-5), 24.4 (2CH₃), 16.3 (OCH₂CH₃); EIMS: *m/z* 455 [M]⁺ (22%); Anal. Calcd for C₂₃H₂₂ClN₃O₃S (455.96): C, 60.59; H, 4.86; N, 9.22; S, 7.03%. Found: C, 60.52; H, 5.08; N, 9.13; S, 7.24%.

2. 2. 11. General Procedure for the Synthesis of the Cyclohexane-(1,2,3-triylidene)tris(hydrazine) Derivatives 13a–d

To a solution of either **11a** (3.08 g, 0.01 mol), **11b** (3.28 g, 0.01 mol) in ethanol (40 mL) either of hydrazine hydrate (1.0 mL, 0.02 mol) or phenylhydrazine (3.60 g, 0.02 mol) was added. 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. 2. 11. 1. (5,5-Dimethyl-2-(2-(4-methylnaphthalen-1-yl)hydrazono)cyclohexane-1,3-diylidene)bis(hydrazine) (13a)

Pale yellow crystals from ethanol; m.p. 220–224 °C; yield 60%. IR (KBr) cm⁻¹: 3473–3326 (NH, NH₂), 3055, 2985, 1665, 1660, 1630. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.26 (s, 1H, D₂O exchangeable, NH), 7.54–7.26 (m, 6H, naphthalene H), 4.51, 5.16 (2s, 4H, D₂O exchangeable, 2NH₂), 2.80 (s, 3H, CH₃), 2.52, 2.43 (2s, 4H, 2CH₂), 1.08, 1.07 (2s, 6H, 2CH₃); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 176.1, 172.5, 170.3 (C-1, C-2, C-3), 138.3, 137.2, 133.1, 128.5, 126.6, 126.1, 124.8, 123.1, 122.2, 120.3 (naphthalene C), 50.8 (CH₃), 34.3 (C-6), 32.6 (CH₃), 32.8, 24.3 (C-7, C-5), 24.6 (2CH₃); EIMS: *m/z* 336 [M]⁺ (35%); Anal. Calcd for C₁₉H₂₄N₆ (336.43): C, 67.83; H, 7.19; N, 24.98%. Found: C, 67.61; H, 6.93; N, 25.25%.

2. 2. 11. 2. (2-(2-(4-Chloronaphthalen-1-yl)hydrazono)-5,5-dimethylcyclohexane-1,3-diylidene)bis(hydrazine) (13b)

Pale yellow crystals from ethanol; m.p. 210–212 °C; yield 63%. IR (KBr) cm⁻¹: 3486–3348 (NH, NH₂), 3056, 2985, 1687, 1665, 1660, 1630. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.23 (s, 1H, D₂O exchangeable, NH), 7.47–7.22 (m, 6H, naphthalene H), 4.53, 5.18 (2s, 4H, D₂O exchangeable, 2NH₂), 2.52, 2.43 (2s, 4H, 2CH₂), 1.08, 1.07 (2s, 6H, 2CH₃); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 176.1, 172.5, 170.3 (C-1, C-2, C-3), 138.3, 137.2, 133.1, 128.5, 126.6, 126.1, 124.8, 123.1, 122.2, 120.3 (naphthalene C), 34.6 (C-6), 32.8, 24.5 (C-7, C-5), 24.8 (2CH₃); EIMS: *m/z* 356 [M]⁺ (28%); Anal. Calcd for C₁₈H₂₁ClN₆ (356.85): C, 60.58; H, 5.93; N, 23.55%. Found: C, 60.74; H, 6.15; N, 23.68%.

2. 2. 11. 3. 2,2'-(5,5-Dimethyl-2-(2-(4-methylnaphthalen-1-yl)hydrazono)-cyclohexane-1,3-diylidene)bis(1-phenylhydrazine) (13c)

Pale brown crystals from 1,4-dioxan; m.p. 205–207 °C; yield 68%. IR (KBr) cm⁻¹: 3492–3348 (NH, NH₂), 3055, 2986, 1666, 1660, 1630. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.36, 8.28, 8.25 (3s, 3H, D₂O exchangeable, 3NH), 7.56–7.23 (m, 16H, 2C₆H₅, naphthalene H), 2.83 (s, 3H, CH₃), 2.56, 2.41 (2s, 4H, 2CH₂), 1.09, 1.06 (2s, 6H, 2CH₃); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 176.6, 172.8, 170.4 (C-1, C-2, C-3), 138.6, 137.1, 133.0, 128.6, 126.4, 126.1, 125.3, 125.1, 124.8, 124.6, 123.6, 123.1, 122.6, 122.2, 121.5, 121.2, 120.3, 119.5 (2C₆H₅, naphthalene C), 50.4 (CH₃), 34.6 (C-6), 32.6, 24.5 (C-7, C-5), 24.7 (2CH₃); EIMS: *m/z* 488 [M]⁺ (40%); Anal. Calcd for C₃₁H₃₂N₆ (488.63): C, 76.20; H, 6.60; N, 17.20%. Found: C, 76.36; H, 6.39; N, 17.48%.

2. 2. 11. 4. 2,2'-(2-(2-(4-Chloronaphthalen-1-yl)hydrazono)-5,5-dimethyl-cyclohexane-1,3-diylidene)bis(1-phenylhydrazine) (13d)

Pale brown crystals from 1,4-dioxan; m.p. 188–191 °C; yield 68%. IR (KBr) cm⁻¹: 3472–3326 (NH, NH₂), 3055, 2985, 1664, 1660, 1630. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.38, 8.23, 8.22 (3s, 3H, D₂O exchangeable, 3NH), 7.58–7.24 (m, 16H, 2C₆H₅, naphthalene H), 2.54, 2.46 (2s, 4H, 2CH₂), 1.09, 1.03 (2s, 6H, 2CH₃); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 176.8, 172.5, 170.3 (C-1, C-2, C-3), 138.8, 137.7, 133.1, 128.2, 126.9, 126.3, 125.8, 125.1, 124.3, 124.6, 123.9, 123.3, 122.6, 122.2, 122.0, 121.8, 120.3, 119.5 (2C₆H₅, naphthalene C), 34.8 (C-6), 32.3, 24.7 (C-7, C-5), 24.5 (2CH₃); EIMS: *m/z* 509 [M]⁺ (26%); Anal. Calcd for C₃₀H₂₉ClN₆ (509.04): C, 70.78; H, 5.74; N, 16.51%. Found: C, 70.64; H, 5.59; N, 16.72%.

2. 2. 12. General Procedure for the Synthesis of the Cyclohexane-1,3-dione Dioxime 14a,b

To a solution of either **11a** (3.08 g, 0.01 mol), **11b** (3.28 g, 0.01 mol) in ethanol (40 mL) containing sodium

acetate (2.0 g) hydroxylamine hydrochloride (1.440 g, 0.02 mol) was added. The reaction mixture in each case was heated under reflux for 4 h then poured onto ice/water and the formed solid product was collected by filtration.

2. 2. 12. 1. 5,5-Dimethyl-2-(2-(4-methylnaphthalen-1-yl)hydrazono)cyclohexane-1,3-dione Dioxime (14a)

Pale yellow crystals from 1,4-dioxan; m.p. 212–214 °C; yield 78%. IR (KBr) cm^{-1} : 3563–3347 (OH, NH), 3055, 2985, 1663, 1660, 1630. ^1H NMR (300 MHz, DMSO- d_6) δ 9.68, 10.04 (2s, 2H, D₂O exchangeable, 2OH), 8.28 (s, 1H, D₂O exchangeable, NH), 7.53–7.28 (m, 6H, naphthalene H), 2.83 (s, 3H, CH₃), 2.56, 2.40 (2s, 4H, 2CH₂), 1.09, 1.07 (2s, 6H, 2CH₃); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 176.8, 173.3, 171.8 (C-1, C-2, C-3), 138.6, 137.4, 133.8, 128.2, 126.1, 125.7, 124.8, 123.6, 122.4, 120.1 (naphthalene C), 34.2 (C-6), 32.6 (CH₃), 32.5, 24.1 (C-7, C-5), 24.8 (2CH₃); EIMS: m/z 338 [M]⁺ (26%); Anal. Calcd for C₁₉H₂₂N₄O₂ (338.40): C, 67.44; H, 6.55; N, 16.56%. Found: C, 67.64; H, 6.41; N, 16.73%.

2. 2. 12. 2. 2-(2-(4-Chloronaphthalen-1-yl)hydrazono)-5,5-dimethylcyclohexane-1,3-dione Dioxime (14b)

Pale yellow crystals from 1,4-dioxan; m.p. 190–193 °C; yield 70%. IR (KBr) cm^{-1} : 3533–3329 (OH, NH), 3055, 2985, 1665, 1662, 1630. ^1H NMR (300 MHz, DMSO- d_6) δ 10.06, 9.65 (2s, 2H, D₂O exchangeable, 2OH), 8.25 (s, 1H, D₂O exchangeable, NH), 7.50–7.24 (m, 6H, naphthalene H), 2.58, 2.43 (2s, 4H, 2CH₂), 1.09, 1.06 (2s, 6H, 2CH₃); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 176.5, 173.6, 171.8 (C-1, C-2, C-3), 138.8, 137.1, 133.5, 128.0, 126.7, 125.3, 124.8, 123.4, 122.6, 120.1 (naphthalene C), 34.5 (C-6), 32.5, 24.3 (C-7, C-5), 24.5 (2CH₃); EIMS: m/z 358 [M]⁺ (32%); Anal. Calcd for C₁₈H₁₉ClN₄O₂ (358.82): C, 60.25; H, 5.34; N, 15.61%. Found: C, 60.19; H, 5.28; N, 15.80%.

2. 2. 13. General Procedure for the Synthesis of the 2,3,5,6,7,8-Hexahydrocinnoline Derivatives 16a–d

To a solution of either of **11a** (3.08 g, 0.01 mol), **11b** (3.28 g, 0.01 mol) in ethanol (40 mL) containing triethylamine either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.07 g, 0.01 mol) was added. 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. 2. 13. 1. 3-Imino-6,6-dimethyl-2-(4-methylnaphthalen-1-yl)-8-oxo-2,3,5,6,7,8-hexahydrocinnoline-4-carbonitrile (16a)

Pale brown crystals from 1,4-dioxan; m.p. 188–191 °C; yield 70%. IR (KBr) cm^{-1} : 3478–3337 (NH), 3055,

2985, 2220, 1687, 1666, 1660, 1630. ^1H NMR (300 MHz, DMSO- d_6) δ 8.25 (s, 1H, D₂O exchangeable, NH), 7.53–7.24 (m, 6H, naphthalene H), 2.86 (s, 3H, CH₃), 2.53, 2.42 (2s, 4H, 2CH₂), 1.09, 1.07 (2s, 6H, 2CH₃); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 176.4 (C-3), 165.8 (C-8), 138.9, 136.3, 135.4, 128.1, 126.5, 125.3, 124.8, 123.6, 122.4, 120.4 (naphthalene C), 117.0 (CN), 34.6 (C-6), 32.8 (CH₃), 32.2, 24.3 (C-7, C-5), 24.8 (2CH₃); EIMS: m/z 356 [M]⁺ (32%); Anal. Calcd for C₂₂H₂₀N₄O (356.42): C, 74.14; H, 5.66; N, 15.72%. Found: C, 74.03; H, 5.79; N, 15.84%.

2. 2. 13. 2. 6,6-Dimethyl-2-(4-methylnaphthalen-1-yl)-3,8-dioxo-2,3,5,6,7,8-hexahydrocinnoline-4-carbonitrile (16b)

Pale yellow crystals from 1,4-dioxan; m.p. 203–206 °C; yield 65%. IR (KBr) cm^{-1} : 3055, 2985, 2220, 1689, 1666, 1660, 1630. ^1H NMR (300 MHz, DMSO- d_6) δ 7.56–7.23 (m, 6H, naphthalene H), 2.84 (s, 3H, CH₃), 2.56, 2.40 (2s, 4H, 2CH₂), 1.09, 1.08 (2s, 6H, 2CH₃); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 176.6 (C-3), 165.5 (C-8), 138.4, 137.1, 135.2, 127.4, 126.5, 125.1, 124.8, 123.6, 122.2, 120.4 (naphthalene C), 116.8 (CN), 34.6 (C-6), 32.5 (CH₃), 32.0, 24.6 (C-7, C-5), 24.5 (2CH₃); EIMS: m/z 357 [M]⁺ (28%); Anal. Calcd for C₂₂H₁₉N₃O₂ (357.41): C, 73.93; H, 5.36; N, 11.76%. Found: C, 73.61; H, 5.49; N, 11.83%.

2. 2. 13. 3. 2-(4-Chloronaphthalen-1-yl)-3-imino-6,6-dimethyl-8-oxo-2,3,5,6,7,8-hexahydrocinnoline-4-carbonitrile (16c)

Pale yellow crystals from 1,4-dioxan; m.p. 180–183 °C; yield 65%. IR (KBr) cm^{-1} : 3459–3341 (NH), 3055, 2985, 2220, 1689, 1664, 1660, 1630. ^1H NMR (300 MHz, DMSO- d_6) δ 8.23 (s, 1H, D₂O exchangeable, NH), 7.56–7.23 (m, 6H, naphthalene H), 2.56, 2.42 (2s, 4H, 2CH₂), 1.09, 1.07 (2s, 6H, 2CH₃); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 176.6 (C-3), 165.9 (C-8), 138.5, 137.8, 135.3, 127.6, 126.2, 125.1, 124.8, 123.4, 122.1, 120.5 (naphthalene C), 116.8 (CN), 34.4 (C-6), 32.0, 24.7 (C-7, C-5), 24.5 (2CH₃); EIMS: m/z 376 [M]⁺ (32%); Anal. Calcd for C₂₁H₁₇ClN₄O (376.84): C, 66.93; H, 4.55; N, 14.87%. Found: C, 67.27; H, 4.74; N, 15.04%.

2. 2. 13. 4. 2-(4-Chloronaphthalen-1-yl)-6,6-dimethyl-3,8-dioxo-2,3,5,6,7,8-hexahydrocinnoline-4-carbonitrile (16d)

Pale yellow crystals from 1,4-dioxan; m.p. 210–213 °C; yield 70%. IR (KBr) cm^{-1} : 3055, 2985, 2220, 1689, 1686, 1663, 1660, 1630. ^1H NMR (200 MHz, DMSO- d_6) δ 7.58–7.21 (m, 6H, naphthalene H), 2.54, 2.43 (2s, 4H, 2CH₂), 1.09, 1.08 (2s, 6H, 2CH₃); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 176.8 (C-3), 165.3 (C-8), 138.6, 137.5, 135.2, 127.8, 126.2, 125.6, 124.3, 123.4, 122.1, 120.1 (naphthalene C), 116.8 (CN), 34.4 (C-6), 32.2, 24.3 (C-7, C-5), 24.5 (2CH₃); EIMS: m/z 377 [M]⁺ (30%); Anal. Calcd for C₂₁H₁₆ClN₃O₂ (377.82): C, 66.76; H, 4.27; N, 11.12%. Found: C, 66.92; H, 4.58; N, 11.43%.

2. 3. Biology Section

2. 3. 1. *In vitro* Cell Assays

All the synthesized compounds were assessed for the inhibitory activities against A549 (non-small cell lung cancer), H460 (human lung cancer), HT-29 (human colon cancer) and MKN-45 (human gastric cancer) cancer cell lines together with foretinib as the positive control by a MTT assay. Furthermore, all compounds were further evaluated against U87MG (human glioblastoma) and SMMC-7721 (human liver cancer) cell lines. The results expressed as IC₅₀ are summarized in Table 2. The IC₅₀ values are the average of at least three independent experiments. The data listed in Table 2 reveal that the compounds possess moderate to strong cytotoxicity against the five tested cell lines in the single-digit nM range, and high selectivity for inhibition against A549, H460 and MKN-45 cells. The promising compounds were **3c**, **5b**, **5e**, **5f**, **7c**, **7f**,

9c, **11b**, **12c**, **12d**, **13b**, **13d**, **14b**, **16c** and **16d** among the tested compounds.

2. 3. 1. 1. Structure Activity Relationship

From Table 1 it is clear that most of compounds showed high cytotoxicities against the six cancer cell lines. In most cases the high inhibitions was due to the presence of electronegative substituent through the aryl or the heterocyclic rings. Considering the benzylidene derivatives **3a–c**, it is obvious that compound **3a** (X = H) is of low inhibitions relative to **3b** (X = OCH₃) and **3c** (X = Cl). In addition, compound **3b** showed moderate inhibitions and **3a** with highest inhibitions among the three compounds. Considering the thiophene derivatives **5a–f**, it is clear that compounds **5d** (X = OCH₃, R = COOEt), **5e** (X = Cl, R = CN) and **5f** (X = Cl, R = COOEt) were the most cytotoxic compounds. On the other hand, for the 4,5,6,7-tetrahydro-2H-indazole derivatives **7a–f**, where compounds **7c**

Table 1. *In vitro* growth inhibitory effects IC₅₀ ± SEM (μM) of the newly synthesized compounds towards cancer cell lines

Compound No	IC ₅₀ ± SEM (μM)					
	A549	H460	HT29	MKN-45	U87MG	SMMC-7721
3a	8.32 ± 2.57	8.68 ± 2.60	7.93 ± 2.49	8.73 ± 2.71	8.48 ± 2.90	8.29 ± 2.09
3b	2.63 ± 1.14	2.64 ± 0.95	1.63 ± 0.59	1.47 ± 0.69	2.16 ± 0.96	1.53 ± 0.87
3c	0.29 ± 0.12	0.34 ± 0.18	0.62 ± 0.36	0.26 ± 0.19	0.35 ± 0.22	0.41 ± 0.13
5a	5.23 ± 1.47	4.82 ± 1.36	2.58 ± 0.926	3.62 ± 1.21	5.78 ± 1.30	5.39 ± 1.15
5b	6.88 ± 1.23	4.83 ± 2.05	5.64 ± 2.11	4.52 ± 2.18	2.38 ± 2.21	4.20 ± 1.19
5c	4.56 ± 1.25	6.72 ± 1.81	6.23 ± 2.32	5.88 ± 1.41	5.22 ± 2.30	2.34 ± 1.29
5d	1.20 ± 0.74	1.47 ± 0.47	1.23 ± 0.63	2.22 ± 1.15	1.60 ± 0.86	2.96 ± 1.63
5e	0.41 ± 0.22	0.87 ± 0.53	0.52 ± 0.25	0.43 ± 0.21	0.39 ± 0.16	0.48 ± 0.25
5f	0.26 ± 0.17	0.31 ± 0.15	0.42 ± 0.32	0.26 ± 0.15	0.40 ± 0.26	0.38 ± 0.15
7a	8.90 ± 3.60	9.53 ± 2.06	8.31 ± 2.70	6.16 ± 1.93	6.49 ± 2.52	8.24 ± 3.19
7b	2.36 ± 1.06	1.48 ± 0.69	2.40 ± 1.13	1.05 ± 0.72	1.28 ± 0.69	2.59 ± 1.06
7c	0.43 ± 0.24	0.57 ± 0.16	0.42 ± 0.19	0.58 ± 0.21	0.35 ± 0.22	0.28 ± 0.09
7d	3.25 ± 1.19	2.36 ± 0.92	3.50 ± 1.56	2.87 ± 1.40	3.42 ± 1.82	1.92 ± 0.89
7e	1.28 ± 0.42	1.67 ± 0.83	2.61 ± 0.76	1.88 ± 0.42	2.26 ± 0.80	1.53 ± 0.80
7f	0.24 ± 0.11	0.31 ± 0.16	0.38 ± 0.27	0.41 ± 0.12	0.25 ± 0.08	0.52 ± 0.16
9a	8.38 ± 2.72	7.29 ± 2.60	8.53 ± 2.30	7.93 ± 2.27	8.09 ± 1.74	6.92 ± 1.79
9b	1.18 ± 0.30	0.86 ± 0.53	0.69 ± 0.40	0.83 ± 0.27	0.59 ± 0.31	0.63 ± 0.25
9c	0.32 ± 0.17	0.52 ± 0.13	0.44 ± 0.15	0.23 ± 0.13	0.23 ± 0.42	0.63 ± 0.30
11a	1.03 ± 0.36	1.43 ± 0.39	0.96 ± 1.42	0.78 ± 0.35	0.68 ± 0.34	0.80 ± 0.35
11b	0.28 ± 0.19	0.36 ± 0.18	0.41 ± 0.27	0.31 ± 0.13	0.28 ± 0.15	0.50 ± 0.21
12a	2.25 ± 0.68	2.70 ± 0.61	1.09 ± 0.79	1.17 ± 0.40	1.58 ± 0.54	1.80 ± 0.93
12b	4.27 ± 1.12	3.55 ± 1.25	2.38 ± 1.16	3.42 ± 1.38	2.25 ± 1.68	3.51 ± 1.09
12c	0.46 ± 0.18	0.39 ± 0.17	0.72 ± 0.23	0.84 ± 0.26	0.34 ± 0.18	0.34 ± 0.29
12d	0.63 ± 0.24	0.22 ± 0.13	0.47 ± 0.17	0.68 ± 0.16	0.37 ± 0.24	0.52 ± 0.20
13a	6.09 ± 1.26	7.83 ± 1.84	8.39 ± 2.53	6.73 ± 1.80	8.53 ± 2.06	5.27 ± 1.73
13b	0.98 ± 0.32	0.45 ± 0.25	0.69 ± 0.32	0.38 ± 0.16	0.50 ± 0.17	0.68 ± 0.42
13c	4.48 ± 1.23	5.59 ± 1.27	3.27 ± 1.24	4.25 ± 1.56	2.82 ± 1.04	3.53 ± 1.51
13d	0.34 ± 0.26	0.39 ± 0.25	0.60 ± 0.42	0.52 ± 0.20	0.28 ± 0.19	0.26 ± 0.15
14a	6.23 ± 1.38	5.39 ± 1.13	5.09 ± 1.25	4.78 ± 2.21	5.42 ± 2.32	6.26 ± 2.63
14b	0.79 ± 0.35	0.85 ± 0.28	0.84 ± 0.31	0.59 ± 0.36	0.80 ± 0.31	0.48 ± 0.24
16a	7.28 ± 2.09	8.26 ± 3.16	9.26 ± 2.41	6.27 ± 1.89	8.47 ± 2.53	6.61 ± 1.75
16b	4.33 ± 1.70	4.16 ± 1.72	2.46 ± 1.29	4.59 ± 1.25	3.72 ± 1.47	4.64 ± 1.63
16c	0.28 ± 0.18	0.43 ± 0.15	0.34 ± 0.12	0.45 ± 0.22	0.39 ± 0.28	0.39 ± 0.132
16d	0.23 ± 0.12	0.44 ± 0.20	0.32 ± 0.17	0.28 ± 0.08	0.20 ± 0.14	0.19 ± 0.017
foretinib	0.08 ± 0.01	0.18 ± 0.03	0.15 ± 0.023	0.03 ± 0.0055	0.90 ± 0.13	0.44 ± 0.062

(R = H, X = Cl) and **7f** (R Ph, X = Cl) were the most cytotoxic compounds. For the isoxazole derivatives **9a–c**, compound **9c** (X = Cl) was the most cytotoxic compound among the three compounds. While compound **9b** (X = OCH₃) has high cytotoxicity against the five cancer cell lines H460, HT29, MKN-45, U87MG and SMMC-7721 with IC₅₀ values 0.86, 0.69, 0.83, 0.59 and 0.63 μM, respectively. For the arylhydrazone derivatives **11a,b**, compound **11b** with Y = Cl was more cytotoxic than **11a** with Y = CH₃. Considering the fused thiophene derivatives **12a–d**, it is obvious that compounds **12c** (Y = Cl, R = CN) and **12d** (Y = Cl, R = COOEt) were more cytotoxic than compounds **12a** and **12b** although compound **12a** has moderate cytotoxicity. In case of the trihydrazone derivatives **13a–d**, compounds **13b** (R = H, Y = Cl) and **13d** (R = Ph, Y = Cl) were the most cytotoxic compounds, it is clear that the presence of Cl group was responsible for such high cytotoxicity. The same was also observed in the case of **14a,b** where compound **14b** (Y = Cl) was more cytotoxic than **14a** (Y = CH₃). Finally, for the fused pyridazine derivatives **16a–d**, it is clear that compounds **16c** (Y = Cl, R' = NH) and **16d** (Y = Cl, R' = O) were the most cytotoxic compounds among the four compounds.

2. 3. 2. Inhibition of Tyrosine Kinases (Enzyme IC₅₀ (nM))

Compounds **3c**, **5b**, **5e**, **5f**, **7c**, **7f**, **9c**, **11b**, **12c**, **12d**, **13b**, **13d**, **14b**, **16c** and **16d** were the most potent compounds against the selected six cancer cell lines and were further tested toward the five tyrosine kinases c-kit, Flt-3, VEGFR-2, EGFR and PDGFR and the data are shown in Table 2.

The selection of the five tyrosine kinases was based on the fact that these contain seven, five and three Ig-like domains in the extracellular domain, respectively.²⁰ These RTKs have been implicated in vascular development by

affecting the proliferation and migration of endothelial cells or parricides. Among them, VEGFR is a major regulator of tumor angiogenesis *via* endothelial cell proliferation and the permeability of blood vessels.^{21,22} VEGFR is expressed in most human cancers such as breast, kidney and colon and patients with tumors showing elevated VEGFR expression have a poor prognosis.²³ It is clear that compounds **5b**, **5e**, **5f**, **7c**, **11b**, **12c**, **12d**, **13d**, **14b**, **16c** and **16d** are the most inhibitory compounds.

2. 3. 4. Inhibition of Selected Compounds Towards Pim-1 Kinase

Furthermore, compounds **5b**, **5e**, **5f**, **7c**, **11b**, **12c**, **12d**, **13d**, **14b**, **16c** and **16d** were selected to examine their Pim-1 kinase inhibition activity (Table 3) as these compounds showed high inhibition toward the tested cancer cell lines at a range and high inhibitions toward the five

Table 3. Inhibition of Pim-1 kinase by compounds **5b**, **5e**, **5f**, **7c**, **11b**, **12c**, **12d**, **13d**, **14b**, **16c** and **16d**

Compound	Inhibition ratio at 10 μM	IC ₅₀ (μM)
5b	96	0.31
5e	26	> 10
5f	22	> 10
7c	28	> 10
11b	86	0.68
12c	28	>10
12d	92	0.42
13d	94	0.38
14b	89	0.46
16c	95	0.34
16d	23	>10
SGI-1776	-	0.048

Table 2. Inhibition of tyrosine kinases (Enzyme IC₅₀ (nM)) by compounds **3c**, **5b**, **7c**, **7f**, **9c**, **11b**, **12c**, **12d**, **13b**, **13d**, **14b**, **16c** and **16d**

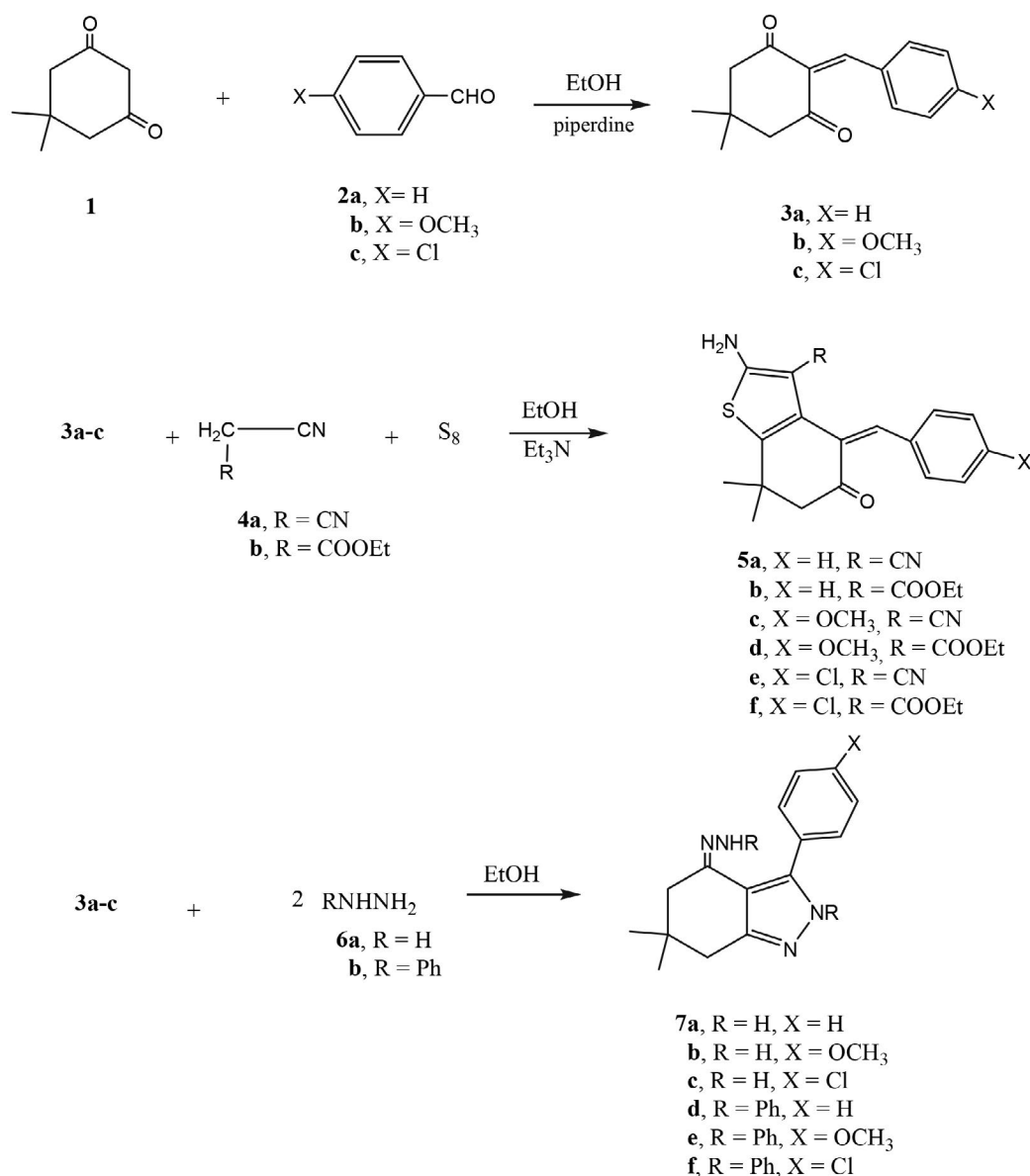
Compound	c-Kit	Flt-3	VEGFR-2	EGFR	PDGFR
3c	1.61	0.96	1.36	1.42	1.17
5b	0.35	0.27	0.21	0.36	0.42
5e	0.28	0.19	0.36	0.25	0.46
5f	0.37	0.24	0.42	0.39	0.48
7c	0.42	0.36	0.51	0.28	0.26
7f	1.09	1.24	1.31	0.96	0.30
9c	1.16	1.27	1.40	1.16	0.52
11b	0.28	0.50	0.19	0.33	0.26
12c	0.26	0.38	0.51	0.39	0.27
12d	0.30	0.35	0.19	0.43	0.60
13b	1.01	0.82	1.07	1.53	1.32
13d	0.38	0.26	0.63	0.62	0.47
14b	0.47	0.56	0.32	0.53	0.61
16c	0.24	0.26	0.38	0.41	0.37
16d	0.72	0.69	0.93	0.52	0.73

tyrosine kinases. Compounds **5b**, **11b**, **12d**, **13d**, **14b** and **16c** were the most potent to inhibit Pim-1 activity with IC_{50} value of 0.31, 0.68, 0.42, 0.38, 0.46 and 0.34 μM , while **7c**, **5e**, **5f**, **12c** and **16d** were less effective ($IC_{50} > 10 \mu\text{M}$). SGI-1776 was used as the positive control with IC_{50} 0.048 μM in the assay. These profiles in combination with cell growth inhibition data of the tested compounds are listed in Table 3 indicating that Pim-1 was a potential target of these compounds.

3. Results and Discussion

The synthetic route to prepare a new class of biologically active molecules using dimedone as the key starting compound is illustrated in Schemes 1–3. The reaction of

dimedone (**1**) with any of the aromatic aldehydes **2a–c** gave the benzylidene derivatives **3a–c**, respectively. Compounds **3a–c** were appropriate for Gewald's thiophene synthesis^{24–26} through the reaction of any of compounds **3a–c** with either of malononitrile (**4a**) or ethyl cyanoacetate (**4b**) and elemental sulfur gave the 6,7-dihydrobenzo[*b*]thiophen-5(4*H*)-one derivatives **5a–f**, respectively. The structures of compounds **5a–f** were based on their analytical and spectral data. Thus, the ^1H NMR spectrum of compound **5a** (as an example) showed the presence of one NH_2 group at δ 4.30 ppm (D_2O exchangeable) and a singlet at δ 2.32 ppm indicating one CH_2 group. The ^{13}C NMR spectrum revealed the presence of a signal at 166.0 due to the presence of $\text{C}=\text{O}$ group and signals at δ 138.6, 136.0, 135.2, 130.7, 127.8, 125.4, 124.3, 121.0 due to the phenyl and thiophene carbons. On the other hand, the reaction of any of



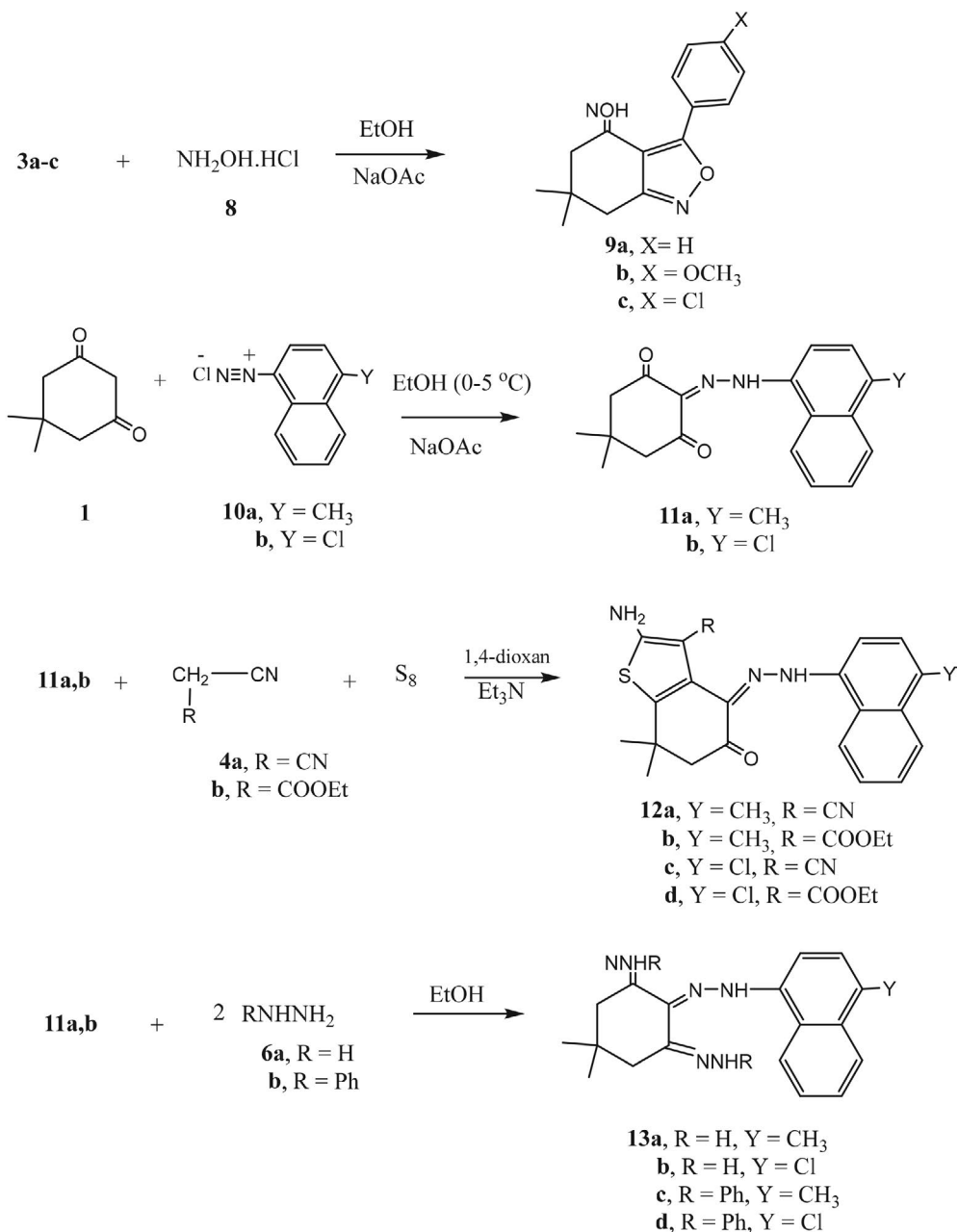
Scheme 1. Synthesis of compounds **3a–c**, **5a–f** and **7a–f**.

compounds **3a-c** with either of hydrazine hydrate (**6a**) or phenylhydrazine (**6b**) gave the 4,5,6,7-tetrahydro-2*H*-indazole derivatives **7a-f**, respectively (Scheme 1).

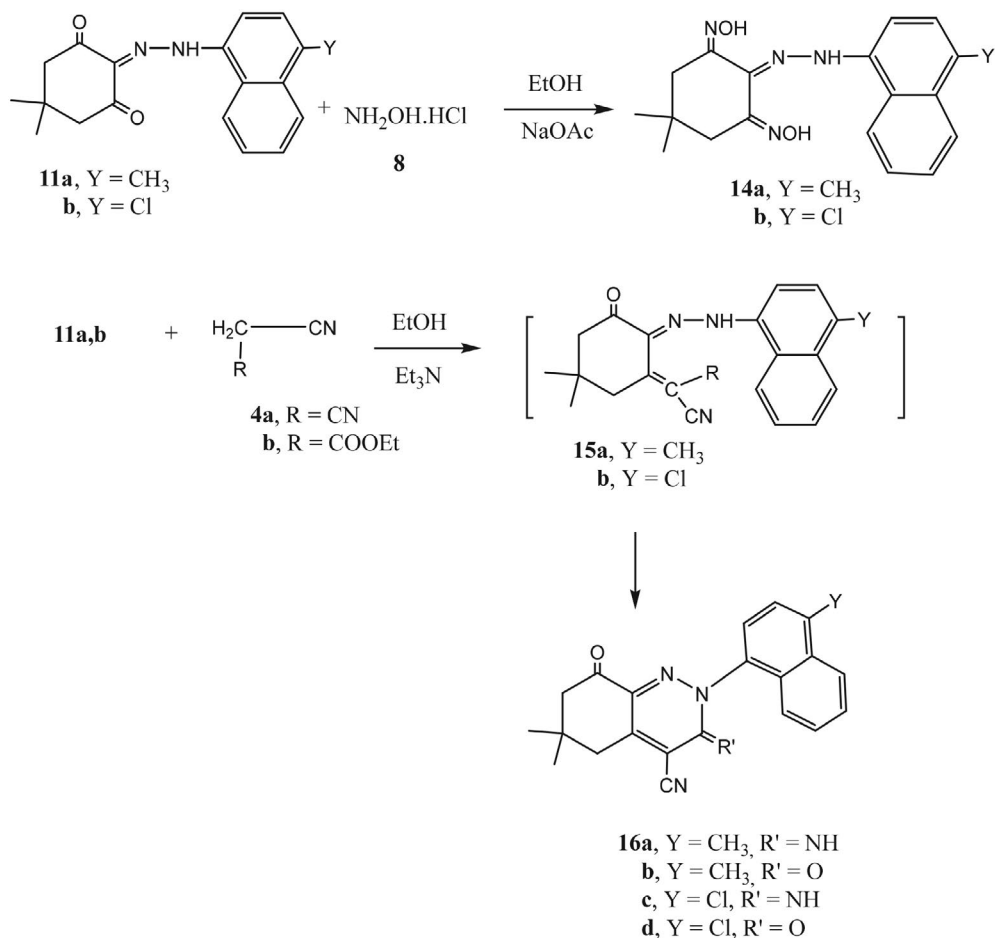
The reaction of any of compounds **3a-c** with two moles of hydroxylamine hydrochloride (**8**) in ethanol containing sodium acetate gave the 4,5,6,7-tetrahydrobenzo[*c*]isoxazol-3-yl)benzene derivatives **9a-c**, respectively. The structures of compounds **9a-c** were established on the basis of analytical and spectral data. Thus, the ¹H NMR spectrum of **9a** (as an example) showed the presence of the OH group at δ 9.52 ppm (D₂O exchangeable) and two singlets at δ 2.47 and 2.33 ppm due to the presence of the two CH₂ groups. On the other hand, the ¹³C NMR spectrum

gave signals at δ 140.1, 137.6, 127.8, 126.5, 124.0, 121.2 due to the phenyl and two isoxazole carbons.

The reaction of compound **1** with either 4-methyl-1-naphthalen-1-diazonium salt (**10a**) or 4-chloro-1-naphthalen-1-diazonium salt (**10b**) gave the naphthylhydrazo derivatives **11a** and **11b**, respectively. Compounds **11a,b** reacted with elemental sulfur and either of malononitrile (**4a**) or ethyl cyanoacetate (**4b**) to give the naphthalen-1-yl)hydrazono)-6,7-dihydrobenzo[*b*]thiophene derivatives **12a-d**, respectively. Compounds **11a,b** were appropriate for Gewald's thiophene synthesis, thus the reaction of either of **11a** or **11b** with elemental sulfur and either of malononitrile (**4a**) or ethyl cyanoacetate (**4b**) gave



Scheme 2. Synthesis of compounds **9a-c**, **11a,b**, **12a-d** and **13a-d**.



Scheme 3. Synthesis of compounds **14a,b** and **16a–d**.

the 6,7-dihydrobenzo[*b*]thiophene derivatives **13a–d**, respectively (Scheme 2).

The reaction of either of **11a** or **11b** with hydroxylamine hydrochloride gave the cyclohexane-1,3-dione di-oxime derivatives **14a** and **14b**, respectively. On the other hand, the reaction of either of compound **11a** or **11b** with either of malononitrile (**4a**) or ethyl cyanoacetate (**4b**) gave the 2,3,5,6,7,8-hexahydrocinnoline derivatives **16a–d**, respectively (Scheme 3). The structures of the latter products were based on their respective analytical and spectral data. Thus, the ¹H NMR spectrum of **16a** (as an example) showed the presence of a singlet at δ 8.25 ppm due to the presence of the NH group, a multiplet at δ 7.53–7.24 ppm due to the presence of the naphthalene protons. In addition the ¹³C NMR spectrum showed the presence of signals at δ 138.9, 136.3, 135.4, 128.1, 126.5, 125.3, 124.8, 123.6, 122.4, 120.4 due to the naphthalene carbons and two signals at δ 32.2, 24.3 for the two CH₂ groups.

4. Conclusion

In conclusion, an efficient and practical synthesis of new series of heterocyclic compounds derived from dime-

done was carried out and the prepared compounds were characterized and their anti-proliferative activities were evaluated against the six cancer cell lines A549, HT-29, MKN-45, U87MG, SMMC-7721 and H460. The results showed that compounds **3c**, **5b**, **5e**, **5f**, **7c**, **7f**, **9c**, **11b**, **12c**, **12d**, **13b**, **13d**, **14b**, **16c** and **16d** were the most potent compounds. On the other hand, compounds **5b**, **5e**, **5f**, **7c**, **11b**, **12c**, **12d**, **13d**, **14b**, **16c** and **16d** were the most inhibitory active compounds against tyrosine kinases and compounds **5b**, **11b**, **12d**, **13d**, **14b** and **16c** were the most potent against Pim-1 kinase.

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5. References

- L. G. Dutra, C. Saibert, D. S. Vicentini, M. M. Sa, *J. Mol. Catal. A: Chemical* **2014**, 386, 35–41.
DOI:10.1016/j.molcata.2014.02.011

2. J. S. Yadav, B. V. Subba, R. Rao, R. Narender, *Tetrahedron Lett.* **2009**, *50*, 3963–3965. DOI:10.1016/j.tetlet.2009.04.088
3. R. Kumar, K. Raghuvanshi, R. K. Verma, M. S. Singh, *Tetrahedron Lett.* **2010**, *51*, 5933–5936. DOI:10.1016/j.tetlet.2010.09.017
4. V. Nadaraj, S. T. Selvi, S. Mohan, *Eur. J. Med. Chem.*, **2009**, *44*, 976–980. DOI:10.1016/j.ejmech.2008.07.004
5. M. L. Deb, P. J. Bhuyan, *Tetrahedron Lett.* **2005**, *46*, 6453–6456. DOI:10.1016/j.tetlet.2005.07.111
6. S. Chassaing, S. Specklin, J. M. Weibel, P. Pale, *Tetrahedron* **2012**, *68*, 7245–7273. DOI:10.1016/j.tet.2012.05.107
7. A. Amoozadeh, E. Tabrizian, S. Rahmani, *Comptes Rend. Chim.* **2015**, *18*, 848–857. DOI:10.1016/j.crci.2014.11.003
8. A. Ilangovan, S. Malayappasamy, S. Muralidharan, *Chem. Cent.* **2011**, *5*, 81. DOI:10.1186/1752-153X-5-81
9. A. M. Al-Majid, M. S. Islam, S. Barakat, N. J. Al-Qahtani, S. Yousef, M. I. Choudhary, *Arab J. Chem.* **2017**, *10*, 185–193. DOI:10.1016/j.arabjc.2014.04.008
10. J. M. Khurana, D. Magoo, *Tetrahedron Lett.* **2009**, *52*, 7300–7303. DOI:10.1016/j.tetlet.2009.10.032
11. H. Naeimi, Z. S. Nazif, *J. Ind. Engin. Chem.* **2014**, *20*, 1043–1049. DOI:10.1016/j.jiec.2013.06.041
12. K. Nikoofar, F. M. Yielzoleh, *J. Saudi Chem. Soc.* **2018**, *22*, 715–741. DOI:10.1016/j.jscs.2017.12.005
13. A. A. Abdelhamid, S. K. Mohamed, A. M. Maharramov, A. N. Khlalilov, M. A. Allahverdiev, *J. Saudi Chem. Soc.* **2014**, *18*, 474–478. DOI:10.1016/j.jscs.2011.10.005
14. M. L. Silva, R. R. Teixeira, L. A. Santos, F. T. Martins, T. C. Ramahho, *J. Mol. Struct.* **2018**, *1156*, 700–711. DOI:10.1016/j.molstruc.2017.11.105
15. C. Jiao, Y. J. Chao-guo, *Chem. Res. Chin. Univ.* **2011**, *27*, 49–53.
16. R. M. Mohareb, T. M. Klapötke, E. Reinhardt, *Med. Chem. Research* **2018**, *27*, 2494–2511. DOI:10.1007/s00044-018-2252-3
17. R. M. Mohareb, F. Al-Omran, M. A. Abdelaziz, R. A. Ibrahim, *Acta Chim. Slov.* **2017**, *64*, 349–364. DOI:10.17344/acsi.2017.3200
18. R. M. Mohareb, P. A. Halim, *Acta Chim. Slov.* **2018**, *65*, 554–568. DOI:10.17344/acsi.2017.4146
19. R. M. Mohareb, N. Y. Abdo, F. O. Al-Farouk, *Acta Chim. Slov.* **2017**, *64*, 117–128. DOI:10.17344/acsi.2016.2920
20. P. B. Jensen, T. Hunter, *Nature* **2001**, *411*, 355–365. DOI:10.1038/35077225
21. J. DiSalvo, M. L. Bayne, G. Conn, P. W. Kwok, P. G. Trivedi, D. D. Soderman, T. M. Palisi, K. A. Sullivan, K. A. Thomas, *J. Biol. Chem.* **1995**, *270*, 7717–7723. DOI:10.1074/jbc.270.13.7717
22. D. R. Senger, S. J. Galli, A. M. Dvorak, C. A. Perruzzi, V. S. Harvey, H. F. Dvorak, *Science* **1983**, *219*, 983–985. DOI:10.1126/science.6823562
23. N. Ferrara, *Nat. Rev. Cancer*, **2002**, *2*, 795–803. DOI:10.1038/nrc909
24. R. M. Mohareb, W. W. Wardakhan, R. A. Ibrahim, *Med. Chem. Res.* **2016**, *25*, 2187–2204. DOI:10.1007/s00044-016-1654-3
25. A. M. Abdallah, R. M. Mohareb, E. M. Khalil, M. A. M. Elshamy, *Chem. Pharm. Bull.* **2017**, *65*, 469–477. DOI:10.1248/cpb.c16-00925
26. W. Zhang, T. Ma, S. Li, Y. Yang, J. Guo, W. Yu, L. Kong, *Eur. J. Med. Chem.* **2017**, *125*, 538–550. DOI:10.1016/j.ejmech.2016.09.068

Povzetek

Pri reakciji dimedona z arilaldehidi so nastali benzilidenski derivati **3a–c**, ki smo jih v naslednji stopnji s heterociklizacijsko reakcijo pretvorili v pripojene tiofenske, pirazol izoksazolske in piridazinske derivate. Pripravljenim spojinam smo določili učinek na različne rakave celične linije ter tudi morebitno inhibicijo tirozin kinaze in Pim-1 kinaze. Za vse sintetizirane spojine smo določili inhibitorno aktivnost na A549 (nemikrocelični pljučni rak), H460 (človeški pljučni rak), HT-29 (rak človeškega debelega črevesa) in MKN-45 (rak človeškega želodca); foretinib smo uporabili kot pozitivno kontrolo pri MTT testiranju. Kot obetavne so se izkazale spojine **3c**, **5b**, **5e**, **5f**, **7c**, **7f**, **9c**, **11b**, **12c**, **12d**, **13b**, **13d**, **14b**, **16c** in **16d**. Po drugi strani so se spojine **5b**, **5e**, **5f**, **7c**, **11b**, **12c**, **12d**, **13d**, **14b**, **16c** in **16d** pokazale kot najbolj učinkoviti inhibitorji tirozin kinaze, spojine **5b**, **11b**, **12d**, **13d**, **14b** in **16c** pa so bile najbolj aktivne proti Pim-1 kinazi.



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