Scientific paper

Multi-component Reactions of Cyclohexan-1,3-diketones to Produce Fused Pyran Derivatives with Antiproliferative Activities and Tyrosine Kinases and Pim-1 Kinase Inhibitions

Rafat Milad Mohareb,[1,*] Rehab Ali Ibrahim[2] and Ensaf Sultan Alwan[1,2]

[1] *Department of chemistry, Faculty of science, Cairo University, Giza, A. R. Egypt*

[2] *Higher Institute of Engineering and Technology, El-Tagammoe El-Khames, New Cairo, Egypt*

[3] *Department of Quality Assurance, Yemen Drug Company for Industry and Commerce (YEDCO), Sana'a, Yemen*

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

Received: 05-06-2020

Abstract

In this work the multi-component reactions of either of the arylhydrazocyclohexan-1,3-dione derivatives **3a–c** with either of benzaldehyde (**4a**), 4-chlorobenzaldehyde (**4b**) or 4-methoxybenzaldehyde (**4c**) and either malononitrile (**5a**) or ethyl cyanoacetate (**5b**) giving the 5,6,7,8-tetrahydro-4*H*-chromene derivatives **6a–r**, respectively, are presented. The reaction of two equivalents of cyclohexan-1,3-dione with benzaldehyde gave the hexahydro-1*H*-xanthene-1,8(2*H*)-dione derivative **7**. On the other hand, the multi-component reactions of compound **1** with dimedone and benzaldehyde gave **13**. Both of **7** and **13** underwent heterocyclization reactions to produce fused thiophene, pyran and thiazole derivatives. Selected compounds among the synthesized compounds were tested against six cancer cell lines where most of them gave high inhibitions; especially compounds **3b**, **3c**, **6b**, **6c**, **6d**, **6f**, **6i**, **6m**, **6n**, **8b**, **14a**, **15** and **16** being the most cytotoxic compounds. Further tests against the five tyrosine kinases c-Kit, Flt-3, VEGFR-2, EGFR, and PDGFR and Pim-1 kinase showed that compounds **3c**, **6c**, **6d**, **6f**, **6n**, **14a** and **15** were the most potent of the tested compounds toward the five tyrosine kinases and compounds **3c**, **6c**, **6d**, **6n** and **15** displayed the highest inhibitions toward Pim-1 kinase.

Keywords: Cyclohexan-1,3-dione; dimedone; thiophene; pyran; thiazole; antitumor activity; tyrosine kinases

1. Introduction

Pyran derivatives are known as important class of compounds that exist in nature and have many applications[1] especially fused pyrans are important core units comprising many natural products. Due to their various kinds of biological activities pyrans and their fused derivatives attracted the attention within the last few years. It was reported that benzo[*b*]pyran derivatives were excellent anticancer compounds that give good results at very low concentrations.[2] Many 2-amino-4*H*-pyran derivatives have various applications within industry like their uses as photoactive materials,[3] pigments,[4] and potentially biodegradable agrochemicals.[5] In addition, naphthopyrans have many application with optical studies due to their ability to generate a yellow color on being irradiated with UV light (van). In addition, pyranochalcones have many applications like antimutagenic, antimicrobial, antiulcer, and antitumor activities.[6–8] Pyrans and their fused derivatives showed different kinds of biological activities. The attachments of heterocyclic ring to the pyran ring improve many of the biological effects of the resulting molecules. Especially the 4*H*-pyran derivatives exhibited wide range of biological activities with great interests such as antimicrobial,[9] antiviral,[10,11] mutagenicity,[12] antiproliferative,[13] sex pheromone,[14] antitumor,[15] cancer therapy,[16] and central nervous system activity.[17] Some of these compounds were applied in industrial chemistry as they can be used in many cosmetic manufacturing and through the field of agrochemicals.[18] Such high importance of pyrans and their derivatives together with the ease of their synthesis with high yields direct many works through their synthesis.

This encouraged our research group to be attracted toward the synthesis of pyran derivatives through the uses of β-diketones. The produced compounds showed high anti-proliferative activities against cancer cell lines together with high inhibitions toward tyrosine kinases.[19–25] Through our present work we adopted multi-component reactions of either arylhydrazonocyclohexan-1,3-dione, aromatic aldehydes and cyanometylene derivatives together with using the produced molecule as a suitable starting material for subsequent heterocyclization to obtain a variety of fused derivatives. The anti-proliferative activities of the synthesized compounds and their inhibitions toward tyrosine kinases were determined.

2. Experimental

For newly synthesized compounds melting points were determined and are given as uncorrected values. For all compounds the IR spectra (KBr discs) were measured using a FTIR plus 460 or PyeUnicam SP-1000 spectrophotometer. The ^{1}H NMR spectra were measured using Varian Gemini-300 (300 MHz) and Jeol AS 500 MHz instruments. Measurements were performed in DMSO-d_6 as the solvent using TMS as the internal standard and chemical shifts are expressed as δ ppm. The MS spectra (EI) were measured using Hewlett Packard 5988 A GC/MS system and GCMS-QP 1000 Ex Shimadzu instruments. The microanalytical CHN data were obtained from the Micro-analytical Data Unit at Cairo University and were performed on Vario EL III Elemental analyzer. Screening of compounds against the cancer cell lines and tyrosine kinases were performed through The National Cancer Institute at Cairo University.

2. 1. Synthesis of the Arylhydrazone Derivatives 3a–c

A solution of either the diazonium salts (0.01 mol) [prepared by the addition of a solution of sodium nitrite (0.70 g, 0.01 mol) in water (10 mL) to a cold solution of either aniline (0.93 g, 0.01 mol), 4-methylaniline (1.07 g, 0.01 mol) or 4-chloroaniline (1.27 g, 0.01 mol) dissolved in concentrated hydrochloric acid (10 mL, 18 mol) with continuous stirring] was added to a cold solution of any of the compounds **1** (1.12 g, 0.01 mol), in ethanol (50 mL) containing sodium acetate (3.0 g) with stirring. The whole reaction mixture was left at room temperature for 2 h and the formed solid product was collected by filtration.

2-(2-Phenylhydrazono)cyclohexane-1,3-dione (3a)

Yellow crystals from ethanol, yield 1.51 g (70%). Mp 145–147 °C. IR (KBr) ν_{max} (cm^{-1}): 3472–3328 (NH), 3055 (CH, aromatic), 1705, 1688 (2C=O), 1640 (C=N), 1634 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.67–1.70 (m, 4H, 2CH_2), 2.38–2.45 (m, 2H, CH_2), 7.26–7.59 (m, 5H, C_6H_5), 8.36 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.8, 34.6, 38.2, (3CH_2), 120.2, 122.4, 125.8, 127.6 (C_6H_5), 164.3 (C=N), 166.2, 168.6 (2C=O). Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.56; H, 5.59; N, 12.96. Found: C, 66.80; H, 5.73; N, 13.06. MS: *m/z* 216 (M^+, 36%).

2-(2-(*p*-Tolyl)hydrazono)cyclohexane-1,3-dione (3b)

Brown crystals from ethanol, yield 1.51 g (66%). Mp 170–172 °C. IR (KBr) ν_{max} (cm^{-1}): 3493–3342 (NH), 3055 (CH, aromatic), 1703, 1689 (2C=O), 1638 (C=N), 1632 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.64–1.72 (m, 4H, 2CH_2), 2.36–2.43 (m, 2H, CH_2), 2.74 (s, 3H, CH_3), 7.26–7.59 (m, 4H, C_6H_4), 8.38 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.5, 34.8, 38.6 (3CH_2), 39.4 (CH_3), 120.6, 123.8, 126.5, 128.3 (C_6H_4), 164.3 (C=N), 166.7, 168.4 (2C=O). Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 68.21; H, 6.08; N, 12.36. MS: *m/z* 230 (M^+, 48%).

2-(2-(4-Chlorophenyl)hydrazono)cyclohexane-1,3-dione (3c)

Orange crystals from ethanol, yield 1.85 g (74%). Mp 180–183 °C. IR (KBr) ν_{max} (cm^{-1}): 3485–3326 (NH), 3055 (CH, aromatic), 1701, 1687 (2C=O), 1636 (C=N), 1634 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.62–1.70 (m, 4H, 2CH_2), 2.34–2.46 (m, 2H, CH_2), 7.24–7.40 (m, 4H, C_6H_4), 8.38 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.5, 34.8, 38.6 (3CH_2), 39.4 (CH_3), 120.6, 123.8, 126.5, 128.3 (C_6H_4), 164.3 (C=N), 166.7, 168.4 (2C=O). Anal. Calcd. for $C_{12}H_{11}ClN_2O_2$: C, 57.49; H, 4.42; N, 11.17. Found: C, 57.62; H, 4.73; N, 11.29. MS: *m/z* 250 (M^+, 24%).

2. 2. General Procedure for the Synthesis of the 5,6,7,8-Tetrahydro-4*H*-chromene Derivatives 6a–r

Each of either benzaldehyde (1.06 g, 0.01 mol), 4-chlorobenzaldehyde (1.40 g, 0.01 mol) or 4-methoxybenzaldehyde (1.36 g, 0.01 mol) and either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) were added to a solution of either **3a** (2.16 g, 0.01 mol), **3b** (2.30 g, 0.01 mol) or **3c** (2.50 g, 0.01 mol) in 1,4-dioxane (50 mL) containing triethylamine (1.00 mL). The whole 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-7-oxo-4-phenyl-8-(2-phenylhydrazono)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6a)

Yellow crystals from 1,4-dioxane, yield 2.51 g (68%). Mp 95–98 °C. IR (KBr) ν_{max} (cm^{-1}): 3485–3341 (NH_2, NH), 3054 (CH, aromatic), 2220 (CN), 1689 (C=O), 1642 (C=N), 1636 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.83–2.94 (2t, 4H, 2CH_2), 4.82 (s, 2H, D_2O exchangeable NH_2), 5.08 (s, 1H, pyran H-4), 7.23–7.48 (m, 10H, 2C_6H_5),

8.28 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 37.9, 42.1 ($2CH_2$), 51.2 (pyran C-4), 117.3 (CN), 120.4, 121.3, 121.8, 122.0, 123.6, 124.3,125.8, 126.8 ($2C_6H_5$), 130.2, 131.6, 134.8, 136.1 (pyran C), 166.8 (C=N), 167.2 (C=O). Anal. Calcd. for $C_{22}H_{18}N_4O_2$: C, 71.37; H, 4.90; N, 15.13.Found: C, 71.52; H, 5.13; N, 15.29. MS: *m/z* 370 (M^+, 28%).

2-Hydroxy-7-oxo-4-phenyl-8-(2-phenylhydrazono)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6b)

Yellow crystals from 1,4-dioxane, yield 2.59 g (70%). Mp 117–120 °C. IR (KBr) ν_{max} (cm^{-1}): 3528–3330 (OH, NH), 3055 (CH, aromatic), 2220 (CN), 1688 (C=O), 1640 (C=N), 1632 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.81–2.98 (2t, 4H, $2CH_2$), 5.05 (s, 1H, pyran H-4), 7.25–7.46 (m, 10H, $2C_6H_5$), 8.26 (s, 1H, D_2O exchangeable, NH), 10.27 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 37.6, 42.5 ($2CH_2$), 51.1 (pyran C-4), 116.3 (CN), 120.2, 120.6, 121.9, 122.3, 123.9, 125.2,125.5, 126.3 ($2C_6H_5$), 130.4, 131.1, 133.8, 136.5 (pyran C), 166.3 (C=N), 168.4 (C=O). Anal. Calcd. for $C_{22}H_{17}N_3O_3$: C, 71.15; H, 4.61; N, 11.31. Found: C, 70.93; H, 4.82; N, 11.42. MS: *m/z* 371 (M^+, 36%).

2-Amino-4-(4-chlorophenyl)-7-oxo-8-(2-phenylhydrazono)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6c)

Yellow crystals from 1,4-dioxane, yield 3.21 g (79%). Mp 93–95 °C. IR (KBr) ν_{max} (cm^{-1}): 3468–3359(NH_2, NH), 3055 (CH, aromatic), 2220 (CN), 1688 (C=O), 1646 (C=N), 1630 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.81–2.97 (2t, 4H, $2CH_2$), 4.84 (s, 2H, D_2O exchangeable NH_2), 5.13 (s, 1H, pyran H-4), 7.24–7.58 (m, 9H, C_6H_5, C_6H_4), 8.32 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 37.5, 42.3 ($2CH_2$), 51.6 (pyran C-4), 117.2 (CN), 120.1, 120.5, 121.5, 122.3, 123.8, 125.1,125.9, 126.3 (C_6H_5, C_6H_4), 130.4, 131.6, 133.8, 1358 (pyran C), 166.6 (C=N), 167.8 (C=O). Anal. Calcd. for $C_{22}H_{17}ClN_4O_2$: C, 65.27; H, 4.23; N, 13.84. Found: C, 65.42; H, 4.33; N, 14.09. MS: *m/z* 404 (M^+, 72%).

4-(4-Chlorophenyl)-2-hydroxy-7-oxo-8-(2-phenylhydrazono)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6d)

Yellow crystals from1,4-dioxane, yield 2.63 g (65%). Mp 122–125 °C. IR (KBr) ν_{max} (cm^{-1}): 3542–3348 (OH, NH), 3055 (CH, aromatic), 2220 (CN), 1701 (C=O), 1645 (C=N), 1632 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.83–2.97 (2t, 4H, $2CH_2$), 5.07 (s, 1H, pyran H-4), 7.22–7.55 (m, 9H, C_6H_5, C_6H_4), 8.23 (s, 1H, D_2O exchangeable, NH), 10.29 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 37.2, 42.8 ($2CH_2$), 51.6 (pyran C-4), 117.8 (CN), 120.4, 121.8, 122.2, 122.6, 124.3, 125.6, 125.8, 126.0 (C_6H_5, C_6H_4), 130.4, 132.8, 134.8, 135.2 (pyran C), 166.7 (C=N), 168.8 (C=O). Anal. Calcd. for $C_{22}H_{16}ClN_3O_3$: C, 65.11; H, 3.97; N, 10.35. Found: C, 65.29; H, 4.16; N, 10.53. MS: *m/z* 405 (M^+, 26%).

2-Amino-4-(4-methoxyphenyl)-7-oxo-8-(2-phenylhydrazono)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6e)

Brown crystals from 1,4-dioxane, yield 2.40 g (60%). Mp 86–88 °C. IR (KBr) ν_{max} (cm^{-1}): 3478–3338 (NH_2, NH), 3055 (CH, aromatic), 2222 (CN), 1687 (C=O), 1643 (C=N), 1630 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.83–2.95 (2t, 4H, $2CH_2$), 3.70 (s, 3H, OCH_3), 4.86 (s, 2H, D_2O exchangeable NH_2), 5.09 (s, 1H, pyran H-4), 7.22–7.52 (m, 9H, C_6H_5, C_6H_4), 8.33 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 37.3, 42.6 ($2CH_2$), 50.2 (OCH_3), 51.2 (pyran C-4), 117.4 (CN), 120.2, 121.0, 121.8, 122.7, 123.2, 125.3,125.6, 126.1 (C_6H_5, C_6H_4), 130.1, 132.8, 134.5, 136.2 (pyran C), 166.8 (C=N), 167.9 (C=O). Anal. Calcd. for $C_{23}H_{20}N_4O_3$: C, 68.99; H, 5.03; N, 13.99. Found: C, 68.79; H, 4.93; N, 14.27. MS: *m/z* 400 (M^+, 68%).

2-Hydroxy-4-(4-methoxyphenyl)-7-oxo-8-(2-phenylhydrazono)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6f)

Yellow crystals from 1,4-dioxane, yield 3.00 g (75%). Mp 121–123 °C. IR (KBr) ν_{max} (cm^{-1}): 3552–3329 (OH, NH), 3054 (CH, aromatic), 2220 (CN), 1696 (C=O), 1642 (C=N), 1630 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.81–2.99 (2t, 4H, $2CH_2$), 3.69 (s, 3H OCH_3), 5.13 (s, 1H, pyran H-4), 7.24–7.59 (m, 9H, C_6H_5, C_6H_4), 8.24 (s, 1H, D_2O exchangeable, NH), 10.32 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 37.5, 42.9 ($2CH_2$), 50.2 (OCH_3), 51.6 (pyran C-4), 116.9 (CN), 120.3, 121.6, 122.8, 123.4, 124.7, 125.4, 125.2, 126.4 (C_6H_5, C_6H_4), 130.7, 133.2, 134.5, 135.8 (pyran C), 166.8 (C=N), 168.9 (C=O). Anal. Calcd. for $C_{23}H_{19}N_3O_4$: C, 68.82; H, 4.77; N, 10.47. Found: C, 68.93; H, 4.80; N, 10.54. MS: *m/z* 401 (M^+, 34%).

2-Amino-7-oxo-4-phenyl-8-(2-(*p*-tolyl)hydrazono)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6g)

Brown crystals from 1,4-dioxane, yield 2.84 g (74%). Mp 110–113 °C. IR (KBr) ν_{max} (cm^{-1}): 3492–3326 (NH_2, NH), 3055 (CH, aromatic), 2221 (CN), 1687 (C=O), 1641 (C=N), 1630 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.68–2.93 (2t, 4H, $2CH_2$), 2.80 (s, 3H, CH_3), 4.86 (s, 2H, D_2O exchangeable NH_2), 5.13 (s, 1H, pyran H-4), 7.24–7.58 (m, 9H, C_6H_5, C_6H_4), 8.33 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 37.6, 42.8 ($2CH_2$), 36.8 (CH_3), 51.3 (pyran C-4), 117.3 (CN), 120.4, 121.5, 122.4, 122.9, 123.6, 125.8, 125.1, 126.4 (C_6H_5, C_6H_4), 130.1, 133.7, 134.8, 135.6 (pyran C), 166.5 (C=N), 167.8 (C=O). Anal. Calcd. for $C_{23}H_{20}N_4O_2$: C, 71.86; H, 5.24; N, 14.57. Found: C, 71.72; H, 5.43; N, 14.39. MS: *m/z* 384 (M^+, 42%).

2-Hydroxy-7-oxo-4-phenyl-8-(2-(*p*-tolyl)hydrazono)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6h)

Dark brown crystals from1,4-dioxane, yield 2.31 g (60%). Mp 177–179 °C. IR (KBr) ν_{max} (cm^{-1}): 3539–3342

(OH, NH), 3055 (CH, aromatic), 2220 (CN), 1692 (C=O), 1645 (C=N), 1631 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.83–2.96 (2t, 4H, $2CH_2$), 2.72 (s, 3H CH_3), 5.11 (s, 1H, pyran H-4), 7.21–7.47 (m, 9H, C_6H_5, C_6H_4), 8.26 (s, 1H, D_2O exchangeable, NH), 10.31 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 38.1, 42.3 ($2CH_2$), 36.2 (CH_3), 51.4 (pyran C-4), 117.8 (CN), 120.1, 120.9, 121.3, 122.8, 124.3, 125.6, 126.1, 126.8 (C_6H_5, C_6H_4), 130.9, 132.6, 134.8, 136.4 (pyran C), 166.7 (C=N), 168.5 (C=O). Anal. Calcd. for $C_{23}H_{19}N_3O_3$: C, 71.67; H, 4.97; N, 10.90. Found: C, 71.82; H, 4.74; N, 11.25. MS: *m/z* 385 (M^+, 40%).

2-Amino-4-(4-chlorophenyl)-7-oxo-8-(2-(*p*-tolyl)hydrazono)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6i)

Pale brown crystals from 1,4-dioxane, yield 2.92 g (70%). Mp 114–116 °C. IR (KBr) ν_{max} (cm^{-1}): 3463–3351 (NH_2, NH), 3055 (CH, aromatic), 2220 (CN), 1689 (C=O), 1640 (C=N), 1630 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.65–2.91 (2t, 4H, $2CH_2$), 2.76 (s, 3H, CH_3), 4.88 (s, 2H, D_2O exchangeable NH_2), 5.08 (s, 1H, pyran H-4), 7.21–7.50 (m, 8H, $2C_6H_4$), 8.34 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 37.8, 42.9 ($2CH_2$), 36.8 (CH_3), 51.6 (pyran C-4), 117.0 (CN), 120.6, 121.8, 122.1, 122.5, 123.4, 125.2, 125.5, 126.1 ($2C_6H_4$), 130.3, 132.6, 134.6, 136.1 (pyran C), 166.8 (C=N), 168.1 (C=O). Anal. Calcd. for $C_{23}H_{19}ClN_4O_2$: C, 65.95; H, 4.57; N, 13.38. Found: C, 65.73; H, 4.73; N, 13.42. MS: *m/z* 418 (M^+, 28%).

4-(4-Chlorophenyl)-2-hydroxy-7-oxo-8-(2-(*p*-tolyl)hydrazono)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6j)

Yellow crystals from1,4-dioxane, yield 2.31 g (55%). Mp 153–155 °C. IR (KBr) ν_{max} (cm^{-1}): 3539–3342 (OH, NH), 3055 (CH, aromatic), 2221 (CN), 1692 (C=O), 1645 (C=N), 1631 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.83–2.96 (2t, 4H, $2CH_2$), 2.72 (s, 3H CH_3), 5.11 (s, 1H, pyran H-4), 7.21–7.47 (m, 8H, $2C_6H_4$), 8.26 (s, 1H, D_2O exchangeable, NH), 10.31 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 38.4, 42.8 ($2CH_2$), 36.2 (CH_3), 51.2 (pyran C-4), 117.6 (CN), 120.0, 120.6, 122.8, 123.2, 125.0, 125.2, 126.0, 126.5 ($2C_6H_4$), 130.2, 132.8, 134.8, 136.5 (pyran C), 166.8 (C=N), 168.5 (C=O). Anal. Calcd. for $C_{23}H_{18}ClN_3O_3$: C, 65.79; H, 4.32; N, 10.01. Found: C, 65.81; H, 4.29; N, 9.82. MS: *m/z* 419 (M^+, 58%).

2-Amino-4-(4-methoxyphenyl)-7-oxo-8-(2-(*p*-tolyl)hydrazono)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6k)

Brown crystals from 1,4-dioxane, yield 2.92 g (71%). Mp 93–95 °C. IR (KBr) ν_{max} (cm^{-1}): 3463–3351 (NH_2, NH), 3055 (CH, aromatic), 2220 (CN), 1689 (C=O), 1640 (C=N), 1630 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.65–2.91 (2t, 4H, $2CH_2$), 2.76 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.88 (s, 2H, D_2O exchangeable NH_2), 5.08 (s, 1H, pyran H-4), 7.21–7.50 (m, 8H, $2C_6H_4$), 8.34 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 37.8, 42.9 ($2CH_2$), 36.8 (CH_3), 50.8 (OCH_3), 51.6 (pyran C-4), 116.8 (CN), 120.6, 121.8, 122.1, 122.5, 123.4, 125.2, 125.5, 126.1 ($2C_6H_4$),130.3, 132.4, 134.8, 136.1 (pyran C), 166.8 (C=N), 168.1 (C=O). Anal. Calcd. for $C_{24}H_{22}N_4O_3$: C, 69.55; H, 5.35; N, 13.52. Found: C, 69.70; H, 5.72; N, 13.68. MS: *m/z* 414 (M^+, 44%).

2-Hydroxy-4-(4-methoxyphenyl)-7-oxo-8-(2-(*p*-tolyl)hydrazono)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6l)

Orange crystals from1,4-dioxane, yield 2.82 g (68%). Mp 82–84 °C. IR (KBr) ν_{max} (cm^{-1}): 3548–3328 (OH, NH), 3055 (CH, aromatic), 2221 (CN), 1692 (C=O), 1641 (C=N), 1631 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.86–2.99 (2t, 4H, $2CH_2$), 2.75 (s, 3H CH_3), 3.67 (s, 3H, OCH_3), 5.08 (s, 1H, pyran H-4), 7.26–7.54 (m, 8H, 2 C_6H_4), 8.26 (s, 1H, D_2O exchangeable, NH), 10.30 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 38.8, 42.7 ($2CH_2$), 36.8 (CH_3), 50.6 (OCH_3), 51.8 (pyran C-4),117.3 (CN), 120.3, 120.9, 122.6, 123.4, 124.8, 125.6, 126.4, 126.9 ($2C_6H_4$), 130.1, 133.2, 134.2, 136.4 (pyran C), 166.5 (C=N), 168.8 (C=O). Anal. Calcd. for $C_{24}H_{21}N_3O_4$: C, 69.39; H, 5.10; N, 10.11. Found: C, 69.52; H, 4.85; N, 9.96. MS: *m/z* 415 (M^+, 65%).

2-Amino-8-(2-(4-chlorophenyl)hydrazono)-7-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6m)

Brown crystals from 1,4-dioxane, yield 2.86 g (71%). Mp 101–103 °C. IR (KBr) ν_{max} (cm^{-1}): 3480–3338 (NH_2, NH), 3055 (CH, aromatic), 2223 (CN), 1688 (C=O), 1643 (C=N), 1632 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.68–2.96 (2t, 4H, $2CH_2$), 4.82 (s, 2H, D_2O exchangeable NH_2), 5.13 (s, 1H, pyran H-4), 7.24–7.47 (m, 9H, C_6H_5, C_6H_4), 8.36 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 37.4, 42.3 ($2CH_2$), 51.2 (pyran C-4), 116.8 (CN), 120.2, 120.9, 121.6, 122.8, 123.0, 124.6, 125.2, 126.8 (C_6H_5, C_6H_4), 130.4, 133.0, 134.6, 136.8 (pyran C), 167.2 (C=N), 168.8 (C=O). Anal. Calcd. for $C_{22}H_{17}ClN_4O_2$: C, 65.27; H, 4.23; N, 13.84. Found: C, 65.40; H, 4.32; N, 13.79. MS: *m/z* 404 (M^+, 60%).

8-(2-(4-Chlorophenyl)hydrazono)-2-hydroxy-7-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6n)

Yellow crystals from 1,4-dioxane, yield 3.03 g (75%). Mp 107–110 °C. IR (KBr) ν_{max} (cm^{-1}): 3528–3358 (OH, NH), 3054 (CH, aromatic), 2223 (CN), 1696 (C=O), 1640 (C=N), 1633 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.83–2.98 (2t, 4H, $2CH_2$), 5.15 (s, 1H, pyran H-4), 7.23–7.50 (m, 9H, C_6H_5, C_6H_4), 8.28 (s, 1H, D_2O exchangeable, NH), 10.35 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 38.5, 42.0 ($2CH_2$), 51.8 (pyran C-4), 117.6 (CN), 120.6, 120.8, 121.5, 122.7, 123.7, 124.9,

125.8, 126.2 (C_6H_5, C_6H_4), 130.4, 133.7, 134.0, 136.0 (pyran C), 166.9 (C=N), 168.6 (C=O). Anal. Calcd. for $C_{22}H_{16}ClN_3O_3$: C, 65.11; H, 3.97; N, 10.35. Found: C, 65.08; H, 4.16; N, 10.22. MS: *m/z* 405 (M^+, 48%).

2-Amino-4-(4-chlorophenyl)-8-(2-(4-chlorophenyl)hydrazono)-7-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6o)

Orange crystals from 1,4-dioxane, yield 2.76 g (63%). Mp 128–131 °C. IR (KBr) ν_{max} (cm^{-1}): 3489–3325 (NH_2, NH), 3053 (CH, aromatic), 2222 (CN), 1688 (C=O), 1641 (C=N), 1633 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.61–2.97 (2t, 4H, $2CH_2$), 4.87 (s, 2H, D_2O exchangeable NH_2), 5.15 (s, 1H, pyran H-4), 7.23–7.56 (m, 8H, $2C_6H_4$), 8.36 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 37.3, 42.8 ($2CH_2$), 51.2 (pyran C-4), 117.7 (CN), 120.3, 121.5, 122.0, 122.9, 123.6, 124.1, 125.8, 126.6 ($2C_6H_4$), 130.6, 133.8, 134.2, 136.0 (pyran C), 166.9 (C=N), 168.4 (C=O). Anal. Calcd. for $C_{22}H_{16}Cl_2N_4O_2$: C, 60.15; H, 3.67; N, 12.75. Found: C, 59.79; H, 3.59; N, 12.90. MS: *m/z* 439 (M^+, 42%).

4-(4-Chlorophenyl)-8-(2-(4-chlorophenyl)hydrazono)-2-hydroxy-7-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6p)

Pale yellow crystals from 1,4-dioxane, yield 3.43 g (78%). Mp 181–184 °C. IR (KBr) ν_{max} (cm^{-1}): 3550–3329 (OH, NH), 3054 (CH, aromatic), 2222 (CN), 1689 (C=O), 1643 (C=N), 1633 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.80–2.96 (2t, 4H, $2CH_2$), 5.11 (s, 1H, pyran H-4), 7.25–7.56 (m, 8H, 2 C_6H_4), 8.29 (s, 1H, D_2O exchangeable, NH), 10.31 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 38.5, 42.0 ($2CH_2$), 51.6 (pyran C-4), 117.9 (CN), 120.1, 120.6, 121.8, 122.7, 123.2, 124.3, 125.5, 126.8 ($2C_6H_4$), 130.5, 133.8, 134.8, 136.1 (pyran C), 166.6 (C=N), 168.9 (C=O). Anal. Calcd. for $C_{22}H_{15}Cl_2N_3O_3$: C, 60.02; H, 3.43; N, 9.54. Found: C, 60.19; H, 3.80; N, 9.69. MS: *m/z* 440 (M^+, 60%).

2-Amino-8-(2-(4-chlorophenyl)hydrazono)-4-(4-methoxyphenyl)-7-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6q)

Yellow crystals from 1,4-dioxane, yield 2.95 g (68%). Mp 86–88 °C. IR (KBr) ν_{max} (cm^{-1}): 3472–3351 (NH_2, NH), 3055 (CH, aromatic), 2224 (CN), 1689 (C=O), 1643 (C=N), 1636 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.60–2.99 (2t, 4H, $2CH_2$), 3.66 (s, 3H, OCH_3), 4.84 (s, 2H, D_2O exchangeable NH_2), 5.12 (s, 1H, pyran H-4), 7.24–7.59 (m, 8H, $2C_6H_4$), 8.34 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 37.6, 42.4 ($2CH_2$), 50.3 (OCH_3), 51.4 (pyran C-4), 116.9 (CN), 120.1, 120.8, 121.6, 122.7, 123.4, 124.3, 124.9, 126.2 ($2C_6H_4$), 130.3, 133.7, 134.6, 136.0 (pyran C), 166.8 (C=N), 168.6 (C=O). Anal. Calcd. for $C_{23}H_{19}ClN_4O_3$: C, 63.52; H, 4.40; N, 12.88. Found: C, 63.71; H, 4.27; N, 12.73. MS: *m/z* 434 (M^+, 50%).

8-(2-(4-Chlorophenyl)hydrazono)-2-hydroxy-4-(4-methoxyphenyl)-7-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (6r)

Pale yellow crystals from1,4-dioxane, yield 3.43 g (79%). Mp 85–87 °C. IR (KBr) ν_{max} (cm^{-1}): 3550–3329 (OH, NH), 3054 (CH, aromatic), 2223 (CN), 1689 (C=O), 1643 (C=N), 1633 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.80–2.96 (2t, 4H, $2CH_2$), 3.70 (s, 3H, OCH_3), 5.11 (s, 1H, pyran H-4), 7.25–7.56 (m, 8H, 2 C_6H_4), 8.29 (s, 1H, D_2O exchangeable, NH), 10.31 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 38.5, 42.0 ($2CH_2$), 50.1 (OCH_3), 51.6 (pyran C-4), 118.0 (CN), 120.1, 120.6, 121.8, 122.7, 123.2, 124.3, 125.5, 126.8 ($2C_6H_4$), 130.7, 132.8, 134.8, 136.1 (pyran C), 166.6 (C=N), 168.9 (C=O). Anal. Calcd. for $C_{23}H_{18}ClN_3O_4$: C, 63.38; H, 4.16; N, 9.64. Found: C, 63.47; H, 3.93; N, 9.83. MS: *m/z* 435 (M^+, 58%).

2. 3. 9-Phenyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (7)

Benzaldehyde (1.06 g, 0.01 mol) was added to a solution of compound **1** (2.24 g, 0.02 mol) in absolute ethanol (40 mL) containing piperidine (1.0 mL). The whole 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.

White crystals from ethanol, yield 2.35 g (80%). Mp 214–217 °C. IR (KBr) ν_{max} (cm^{-1}): 3056 (CH, aromatic), 1702, 1689 (C=O), 1631 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.59–1.80 (m, 8H, $4CH_2$), 2.58–2.73 (m, 4H, $2CH_2$), 5.09 (s, 1H, pyran H-4), 7.25–7.41 (m, 5H, C_6H_5); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 26.3, 28.4, 32.6 ($6CH_2$), 50.9 (pyran C-4), 120.6, 121.4, 123.6, 125.8 (C_6H_5), 168.9 (2C=O). Anal. Calcd. for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.80; H, 6.29. MS: *m/z* 294 (M^+, 100%).

2. 4. General Procedure for the Synthesis of the Dithieno[3,2-*a*:2',3'-*j*]xanthenes Derivatives 8a,b

Each of elemental sulfur (0.64 g, 0.02 mol) and either malononitrile (1.32 g, 0.02 mol) or ethyl cyanoacetate (2.26 g, 0.02 mol) were added to a solution of compound **7** (2.94 g, 0.01 mol) in 1,4-dioxane (40 mL) containing triethylamine (1.00 mL). The reaction mixture was heated under reflux for 3 h then poured onto ice/water mixture and the precipitated product was collected by filtration.

12,10-Diamino-12-phenyl-5,7,8,12-tetrahydro-4*H*-dithieno[3,2-*a*:2',3'-*j*]xanthene-1,11-dicarbonitrile (8a)

Orange crystals from 1,4-dioxane, yield 2.81 g (62%). Mp 144–146 °C. IR (KBr) ν_{max} (cm^{-1}): 3468–3369 (NH_2), 3055 (CH, aromatic), 2223, 2220 (2CN), 1630 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.84–3.39 (m, 8H, $4CH_2$), 4.89, 5.13 (2s, 4H, D_2O exchangeable, $2NH_2$), 5.12 (s, 1H,

pyran H-4), 7.26–7.43 (m, 5H, C_6H_5); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 39.2, 45.8 ($4CH_2$), 116.8, 116.9 (2CN), 120.3, 120.5, 123.9, 125.3 (C_6H_5), 130.6, 131.6, 132.7, 134.6, 137.8, 139.2, 140.5, 141.2 (pyran, two thiophene C). Anal. Calcd. for $C_{25}H_{18}N_4OS_2$: C, 66.06; H, 3.99; N, 12.33; S, 14.11. Found: C, 65.93; H, 4.13; N, 12.29; S, 14.30. MS: *m/z* 454 (M^+, 58%).

Diethyl 2,10-Diamino-12-phenyl-5,7,8,12-tetrahydro-4*H*-dithieno[3,2-*a*:2',3'-*j*]xanthene-1,11-dicarboxylate (8b)

Orange crystals from 1,4-dioxane, yield 3.61 g (66%). Mp 118–121 °C. IR (KBr) ν_{max} (cm^{-1}): 3479–3339 (NH_2), 3055 (CH, aromatic), 1633 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.12, 1.14 (2t, 6H, J_1 = 5.90 Hz, J_2 = 6.48 Hz, two $OCH_2\underline{CH_3}$), 2.87–3.42 (m, 8H, $4CH_2$), 4.22, 4.24 (2q, 4H, J_1 = 5.90 Hz, J_2 = 6.48 Hz, two $O\underline{CH_2}CH_3$), 4.82, 5.14 (2s, 4H, D_2O exchangeable, $2NH_2$), 5.11 (s, 1H, pyran H-4), 7.25–7.42 (m, 5H, C_6H_5); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.5, 16.8 (two OCH_2CH_3), 39.6, 45.5 ($4CH_2$), 50.8 (pyran C-4), 52.6, 52.9 (two OCH_2CH_3), 120.5, 120.3, 124.7, 125.8 (C_6H_5), 130.2, 131.6, 132.4, 132.8, 133.8, 137.2, 138.7, 140.3 (pyran, thiophene C). Anal. Calcd. for $C_{29}H_{28}N_2O_5S_2$: C, 63.48; H, 5.14; N, 5.14; S, 11.69. Found: C, 63.62; H, 5.41; N, 5.08; 11.73. MS: *m/z* 548 (M^+, 76%).

2,12-Diamino-4,10,14-triphenyl-5,6,8,9,10,14-hexahydro-4*H*-dipyrano[2,3-*a*:3',2'-*j*]xanthene-3,11-dicarbonitrile (9)

Each of benzaldehyde (2.12 g, 0.02 mol) and malononitrile (1.32 g, 0.02 mol) were added to a solution of compound **7** (2.94 g, 0.01 mol) in 1,4-dioxane (40 mL) containing triethylamine (1.00 mL). The reaction mixture was heated under reflux for 3 h then poured onto ice/water mixture and the precipitated product was collected by filtration.

Pale yellow crystals from 1,4-dioxane, yield 4.69 g (78%). Mp 189–202 °C. IR (KBr) ν_{max} (cm^{-1}): 3453–3326 (NH_2), 3055 (CH, aromatic), 2223, 2220 (2CN), 1630 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.82–3.42 (m, 8H, $4CH_2$), 4.95, 5.16 (2s, 4H, D_2O exchangeable, $2NH_2$), 5.08, 5.12, 5.14 (3s, 3H, pyran H-4), 7.22–7.58 (m, 15H, $3C_6H_5$); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 39.2, 45.7 ($4CH_2$), 51.2, 51.6 (threepyran C-4), 116.6, 117.2 (2CN), 120.1, 120.8, 122.1, 122.5, 123.0, 123.5, 123.8, 124.2, 124.6, 125.3, 125.8, 126.8 ($3C_6H_5$), 130.3, 133.5, 134.6, 135.0, 136.7, 137.0, 137.6, 139.8 (three pyran C). Anal. Calcd. for $C_{39}H_{30}N_4O_3$: C, 77.72; H, 5.02; N, 9.30. Found: C, 77.90; H, 4.79; N, 9.42. MS: *m/z* 602 (M^+, 42%).

1,11,12-Triphenyl-4,5,7,8-tetrahydro-1*H*-xantheno[1,2-*d*:8,7-*d*']bis(thiazole)-2,10(11*H*,12*H*)-dithione (11)

Each of elemental sulfur (0.64 g, 0.02 mol) and phenylisothiocyanate (2.60 g, 0.02 mol) were added to a solution of compound **7** (2.94 g, 0.01 mol) in 1,4-dioxane (40 mL) containing triethylamine (1.00 mL). The reaction mixture was heated under reflux for 2 h then poured onto ice/water mixture and the precipitated product was collected by filtration.

Orange crystals from1,4-dioxane, yield 3.96 g (67%). Mp > 300 °C. IR (KBr) ν_{max} (cm^{-1}): 3055 (CH, aromatic), 1632 (C=C), 1208 (C=S); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.96–3.41 (m, 8H, $4CH_2$), 5.08 (s, 1H, pyran H-4), 7.23–7.49 (m, 15H, $3C_6H_5$); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 37.6, 42.5 ($2CH_2$), 51.1 (pyran C-4), 120.2, 120.8, 121.2, 121.6, 122.0, 122.3, 123.1, 123.9, 124.8, 125.1, 125.5, 126.8 ($3C_6H_5$), 130.2, 131.3, 132.6, 136.5, 139.4, 140.8 (pyran, two thiazole C), 180.3 (2C=S). Anal. Calcd. for $C_{33}H_{24}N_2OS_4$: C, 66.86; H, 4.08; N, 4.73; S, 21.64. Found: C, 66.93; H, 4.19; N, 4.90; S, 21.47. MS: *m/z* 592 (M^+, 18%).

3,3-Dimethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (13)

Each of benzaldehyde (1.06 g, 0.01 mol) and dimedone (1.40 g, 0.01 mol) was added to a solution of compound **1** (1.12 g, 0.01 mol) in absolute ethanol (40 mL) containing piperidine (1.0 mL). The whole reaction mixture was heated under reflux for 1 h then poured onto ice/water mixture containing a few drops of hydrochloric acid and the formed solid product was collected by filtration.

White crystals from1,4-dioxane, yield 2.25 g (70%). Mp 149–152 °C. IR (KBr) ν_{max} (cm^{-1}): 3054 (CH, aromatic), 1704, 1689 (2C=O), 1635 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.06, 1.08 (2s, 6H, $2CH_3$), 1.68–1.96 (m, 6H, $3CH_2$), 2.79, 2.83 (2s, 4H, $2CH_2$), 5.13 (s, 1H, pyran H-4), 7.26–7.46 (m, 5H, C_6H_5); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.4 ($2CH_3$), 26.5, 28.8, 32.9, 36.5, 42.1 ($5CH_2$), 50.8 (pyran C-4), 120.3, 121.8, 122.4, 124.2 (C_6H_5), 168.8, 170.3 (2C=O). Anal. Calcd. for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 78.40; H, 6.68. MS: *m/z* 322 (M^+, 60%).

2. 5. General Procedure for the Synthesis of the Dithieno[3,2-*a*:2',3'-*j*]xanthenes Derivatives 14a,b

Each of elemental sulfur (0.64 g, 0.02 mol) and either malononitrile (1.32 g, 0.02 mol) or ethyl cyanoacetate (2.26 g, 0.02 mol) were added to a solution of compound **13** (3.22 g, 0.01 mol) in 1,4-dioxane (40 mL) containing triethylamine (1.00 mL). The reaction mixture was heated under reflux for 3 h then poured onto ice/water mixture and the precipitated product was collected by filtration.

2,10-Diamino-4,4-dimethyl-12-phenyl-5,7,8,12-tetrahydro-4*H*-dithieno-[3,2-*a*:2',3'-*j*]xanthene-1,11-dicarbonitrile (14a)

Yellow crystals from 1,4-dioxane, yield 2.89 g (60%). Mp 138–141 °C. IR (KBr) ν_{max} (cm^{-1}): 3476–3337 (NH_2), 3055 (CH, aromatic), 2224, 2220 (2CN), 1633 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.06, 1.09 (2s, 6H, $2CH_3$),

2.86–3.42 (m, 4H, $2CH_2$), 3.62 (s, 2H, CH_2), 4.87, 5.15 (2s, 4H, D_2O exchangeable, $2NH_2$), 5.14 (s, 1H, pyran H-4), 7.28–7.40 (m, 5H, C_6H_5); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.7 ($2CH_3$), 39.8, 44.6, 48.3 ($3CH_2$), 51.2 (pyran C-4),116.6, 117.3 (2CN), 120.2, 120.8, 123.3, 124.1 (C_6H_5), 132.3, 134.2, 135.1, 135.6, 136.3, 138.3, 138.7, 139.4, 140.2, 141.2, 142.0, 142.6 (pyran, two thiophene C). Anal. Calcd. for $C_{27}H_{22}N_4OS_2$: C, 67.19; H, 4.59; N, 11.61; S, 13.29. Found: C, 66.93; H, 4.75; N, 11.82; 13.05. MS: *m/z* 482 (M^+, 58%).

Diethyl 2,10-Diamino-12-phenyl-5,7,8,12-tetrahydro-4*H*-dithieno[3,2-*a*:2',3'-*j*]xanthene-1,11-dicarboxylate (14b)

Pale white crystals from 1,4-dioxane, yield 4.32 g (75%). Mp 175–179 °C. IR (KBr) ν_{max} (cm^{-1}): 3449–3326 (NH_2), 3055 (CH, aromatic), 11695, 1689 (2CO), 633 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.07, 1.09 (2s, 6H, $2CH_3$), 1.12, 1.13 (2t, 6H, J_1 = 6.77 Hz, J_2 = 6.92 Hz, two $OCH_2\underline{CH_3}$), 2.89–3.48 (2t, 4H, $2CH_2$), 3.70 (s, 2H, CH_2), 4.22, 4.23 (2q, 4H, J_1 = 6.77 Hz, J_2 = 6.92 Hz, two $O\underline{CH_2}CH_3$), 4.82, 5.14 (2s, 4H, D_2O exchangeable, $2NH_2$), 5.11 (s, 1H, pyran H-4), 7.25–7.42 (m, 5H, C_6H_5); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.5, 16.8 (two $OCH_2\underline{CH_3}$),24.4 ($2CH_3$), 39.4, 45.8, 47.2 ($3CH_2$), 51.3 (pyran C-4), 52.6, 52.7(two $O\underline{CH_2}CH_3$),120.3, 122.8, 124.6, 125.7 (C_6H_5), 130.1, 131.8, 132.6, 131.1, 133.5, 136.6, 137.2, 138.9, 139.4, 140.3, 141.2, 142.6 (pyran, two thiophene C). Anal. Calcd. for $C_{31}H_{32}N_2O_5S_2$: C, 64.56; H, 5.59; N, 4.86; S, 11.12. Found: C, 64.41.; H, 5.79; N, 5.16; 11.30. MS: *m/z* 576 (M^+, 76%).

2,12-Diamino-5,5-dimethyl-4,10,14-triphenyl-5,6,8,9,10,14-hexahydro-4*H*-dipyrano[2,3-*a*:3',2'-*j*]xanthene-3,11-dicarbonitrile (15)

Each of benzaldehyde (2.12 g, 0.02 mol) and malononitrile (1.32 g, 0.02 mol) were added to a solution of compound **13** (3.22 g, 0.01 mol) in 1,4-dioxane (40 mL) containing triethylamine (1.00 mL). The reaction mixture was heated under reflux for 3 h then poured onto ice/water mixture and the precipitated product was collected by filtration.

Pale yellow crystals from1,4-dioxane, yield 4.69 g (78%). Mp 136–138 °C. IR (KBr) ν_{max} (cm^{-1}): 3453–3326 (NH_2), 3055 (CH, aromatic), 2223, 2220 (2CN), 1630 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.07, 1.08 (2s, 6H, $2CH_3$), 2.82–2.96 (2t, 4H, $2CH_2$), 3.11–3.42 (s, 2H, CH_2), 4.95, 5.16 (2s, 4H, D_2O exchangeable, $2NH_2$), 5.09, 5.11, 5.14 (3s, 3H, threepyran H-4), 7.22-7.58 (m, 15H, $3C_6H_5$); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.5 ($2CH_3$), 39.2, 45.7 ($4CH_2$), 51.6 (pyran C-4), 116.6, 117.2 (2CN), 120.8, 122.5, 123.5, 123.8, 124.6,125.3, 125.8, 126.8 ($3C_6H_5$), 130.3, 131.2, 131.9, 132.3, 133.5, 134.6, 135.0, 136.7, 137.0, 137.6, 138.4, 139.8 (three pyran C). Anal. Calcd. for $C_{41}H_{34}N_4O_3$: C, 78.07; H, 5.43; N, 8.88. Found: C, 77.86; H, 5.60; N, 9.02. MS: *m/z* 630 (M^+, 32%).

4,4-Dimethyl-1,11,12-triphenyl-4,5,7,8-tetrahydro-1*H*-xantheno[1,2-*d*:8,7-*d*']bis(thiazole)-2,10(11*H*,12*H*)-dithione (16)

Each of elemental sulfur (0.64 g, 0.02 mol) and phenylisothiocyanate (2.60 g, 0.02 mol) were added to a solution of compound **13** (3.22 g, 0.01 mol) in 1,4-dioxane (40 mL) containing triethylamine (1.00 mL). The reaction mixture was heated under reflux for 2 h then poured onto ice/water mixture and the precipitated product was collected by filtration.

Yellowish white crystals from 1,4-dioxane, yield 4.24 g (68%). Mp 147–149 °C. IR (KBr) ν_{max} (cm^{-1}): 3054 (CH, aromatic), 1632 (C=C), 1209 (C=S); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.05, 1.08 (2s, 6H, $2CH_3$), 2.82–2.98 (2t, 4H, $2CH_2$), 3.07–3.40 (s, 2H, CH_2), 5.12 (s, 1H, pyran H-4), 7.23–7.57 (m, 15H, $3C_6H_5$); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.6 ($2CH_3$), 37.8, 42.7, 44.2 ($3CH_2$), 51.5 (pyran C-4), 120.1, 120.9, 121.1, 121.8, 122.3, 122.7, 123.5, 123.8, 124.3, 125.6, 126.0, 126.5 ($3C_6H_5$), 130.2, 131.3, 132.6, 136.5, 138.0, 139.4, 141.3, 142.6 (pyran, two thiazole C), 179.2, 180.1 (2C=S). Anal. Calcd. for $C_{35}H_{28}N_2OS_4$: C, 67.71; H, 4.55; N, 4.51; S, 20.66. Found: C, 67.80; H, 4.48; N, 4.72; S, 20.82. MS: *m/z* 620 (M^+, 32%).

2. 6. Biology Section

2. 6. 1. Cell Proliferation Assay

Most of the newly synthesized compounds were screened against the six cancer cell lines namely A549, HT-29, MKN-45, U87MG, SMMC-7721, and H460 using the standard MTT assay *in vitro*, with foretinib as the positive control.[26–28] Their anti-proliferative activities against the six cancer cell lines and the mean values of three independent experiments, expressed as IC_{50} values, are presented in Table 1. Most of the synthesized compounds exhibited potent anti-proliferative activity with IC_{50} values less than 30 μM. Generally, the variations of substituents within the thienopyridine moiety together with the heterocyclic ring being attached have a notable influence on the anti-proliferative activity.

2. 6. 2. Structure-Activity Relationship

Table 1 shows the cytotoxicity of most of the synthesized compounds toward the six cancer cell lines A549, H460, HT-29, MKN-45, U87MG, and SMMC-7721. The reaction of cyclohexan-1,3-dione with the aryldiazonium salts **2a**–**c** produced the arylhydrazono derivatives **3a**–**c**, respectively. The two compounds **3b** (X = CH_3) and **3c** (X = Cl) showed the highest cytotoxicity among these three compounds toward the six cancer cell lines. The multicomponent reactions of either of **3a**–**c** with either of the arylaldehydes **4a**–**c** and either malononitrile or ethyl cyanoacetate gave the 4*H*-chromenone derivatives **6a**–**r**, respectively. Eleven compounds of this series were selected for screening against the six cancer cell lines and their ac-

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

Compound No	IC_{50} ± SEM (μM)					
	A549	H460	HT29	MKN-45	U87MG	SMMC-7721
3a	6.26 ± 2.86	8.36 ± 3.24	5.69 ± 1.39	6.58 ± 1.37	9.62 ± 3.15	6.43 ± 2.25
3b	0.28 ± 0.12	0.33 ± 0.18	0.53 ± 0.13	0.33 ± 0.17	0.61 ± 0.28	0.52 ± 0.16
3c	0.43 ± 0.31	0.51 ± 0.25	0.49 ± 0.28	0.63 ± 0.39	0.82 ± 0.27	0.93 ± 0.39
6b	1.38 ± 0.91	2.46 ± 1.16	1.52 ± 0.92	1.63 ± 0.78	1.54 ± 0.85	2.53 ± 1.06
6c	1.34 ± 0.79	2.41 ± 1.20	1.35 ± 0.84	1.52 ± 0.71	2.58 ± 1.23	2.63 ± 1.17
6d	0.56 ± 0.32	0.29 ± 0.26	0.48 ± 0.22	0.41 ± 0.26	0.35 ± 0.12	0.53 ± 0.23
6e	2.16 ± 1.02	3.27 ± 1.38	3.38 ± 1.80	2.80 ± 1.38	2.32 ± 1.09	4.64 ± 1.42
6f	1.64 ± 0.36	1.52 ± 0.85	1.43 ± 0.75	2.60 ± 0.89	1.46 ± 0.63	1.63 ± 0.45
6g	4.36 ± 1.20	3.45 ± 1.81	2.61 ± 1.59	6.83 ± 2.28	4.60 ± 1.52	6.50 ± 2.63
6h	3.28 ± 1.48	5.83 ± 1.39	4.60 ± 1.24	6.80 ± 1.79	5.53 ± 1.61	6.45 ± 2.23
6i	1.25 ± 1.06	2.34 ± 1.13	2.32 ± 1.16	2.29 ± 1.71	1.29 ± 0.47	1.36 ± 0.95
6m	1.37 ± 0.71	0.50 ± 0.29	1.96 ± 1.19	1.80 ± 0.88	1.69 ± 0.82	1.33 ± 0.86
6n	0.46 ± 0.09	0.73 ± 0.44	0.85 ± 0.34	0.63 ± 0.41	0.52 ± 0.24	0.30 ± 0.26
6o	4.41 ± 1.49	6.72 ± 1.53	6.41 ± 2.49	6.29 ± 2.17	8.09 ± 2.17	5.19 ± 1.29
6q	2.34 ± 1.21	3.63 ± 1.32	4.58 ± 1.56	6.28 ± 2.39	5.32 ± 2.43	3.36 ± 1.28
8a	3.48 ± 1.09	2.63 ± 1.19	3.64 ± 1.26	4.38 ± 0.84	2.48 ± 0.89	2.23 ± 1.27
8b	1.13 ± 0.59	2.28 ± 0.72	3.29 ± 1.85	2.26 ± 1.79	3.62 ± 1.29	1.81 ± 0.84
9	4.13 ± 1.29	5.09 ± 1.36	6.16 ± 2.93	6.92 ± 1.37	5.82 ± 1.39	7.27 ± 1.92
11	2.32 ± 1.18	2.35 ± 1.08	3.42 ± 1.26	2.46 ± 0.98	1.26 ± 0.63	2.39 ± 0.98
14a	1.29 ± 0.59	1.39 ± 0.79	2.42 ± 1.08	1.36 ± 0.62	1.72 ± 0.98	1.42 ± 0.63
14b	4.69 ± 1.22	5.48 ± 2.21	6.42 ± 2.20	5.37 ± 1.19	4.49 ± 1.28	6.52 ± 1.28
15	0.35 ± 0.22	0.44 ± 0.16	0.62 ± 0.26	0.35 ± 0.16	0.62 ± 0.45	0.38 ± 0.16
16	0.29 ± 0.03	0.46 ± 0.23	0.46 ± 0.26	0.33 ± 0.20	0.59 ± 0.29	0.48 ± 0.21
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

tivites varied from moderate to high. Compounds **6b** (X = Y = H, R' = OH), **6c** (X = H, Y = Cl, R' = NH_2), **6f** (X = H, Y = OCH_3, R' = OH) and **6i** (X = CH_3, Y = Cl, R' = NH_2) showed moderate inhibitions. However, compounds **6d** (X = H, Y = Cl, R' = OH) and **6n** (X = Cl, Y = H, R' = OH) showed the highest inhibitions among the eleven compounds. On the other hand, compounds **6e**, **6g**, **6h**, **6o** and **6q** had declining inhibition activities. The reaction of compound **7** with two folds of elemental sulfur and either malononitrile or ethyl cyanoacetate gave the dithieno[3,2-*a*:2',3'-*j*]xanthene derivatives **8a**,**b**. It is obvious from Table 1 that compound **8b** (R = COOEt) was more cytotoxic than compound **8a** (R = CN); it seemsd that the oxygen content in **8b** was responsible for its high inhibition activity. Surprisingly, the dipyrano[2,3-*a*:3',2'-*j*]xanthene derivative **9** and the xantheno[1,2-*d*:8,7-*d*']bis(thiazole) derivative **11** exhibited low inhibition values. Considering the dithieno[3,2-*a*:2',3'-*j*] xanthene-2,10-diamine derivatives **14a** and **14b**, it is clear that compound **14a** (R = CN) showed higher inhibitions than **14b** (R = COOEt). Finally both of the 5,6,8,9,10,14-hexahydro-4*H*-dipyrano[2,3-*a*:3',2'-*j*]xanthene derivative **15** and the 4,5,7,8-tetrahydro-1*H*-xantheno[1,2-*d*:8,7-*d*']bis(thiazole)-2,10(11*H*,12*H*)-dithione derivative **16** exhibted high inhibitions against the six cancer cell lines. It is of great importance to note from Table 1 that compounds **3b**, **3c**, **6d**, **6n**, **15** and **16** showed the highest cytotoxicity among the tested compounds against the six cancer cell lines, while compounds **6b**, **6c**, **6f**, **6i, 6m**, **8b**, and **14a** exhibited moderate inhibitions. The high inhibition compounds together with those of moderate inhibitions were selected to be tested against tyrosine kinases.

2. 6. 3. Inhibitions of the Most Active Compounds Against Tyrosine Kinases

Compounds **3b**, **3c**, **6b**, **6c**, **6d**, **6f**, **6m**, **6n**, **14a**, **15** and **16** that showed from moderate to high inhibitions against the six cancer cell lines were further evaluated

Table 2. Inhibitions of tyrosine kinases [Enzyme IC_{50} (nM)] by compounds **3b**, **3c**, **6b**, **6c**, **6d**, **6f**, **6m**, **6n**, **14a**, **15** and **16**

Compound	c-Kit	Flt-3	VEGFR-2	EGFR	PDGFR
3b	2.83	3.25	2.16	0.73	0.52
3c	0.21	0.34	0.23	0.46	0.29
6b	1.32	1.08	1.69	0.43	1.02
6c	0.82	0.63	0.36	0.69	0.42
6d	0.25	0.31	0.47	0.24	0.29
6f	0.53	0.21	0.53	0.39	0.22
6m	1.16	0.29	0.42	1.80	2.01
6n	0.46	0.25	0.31	0.37	0.27
14a	0.82	0.29	0.37	0.44	0.29
15	0.33	0.21	0.47	0.35	0.26
16	2.09	1.28	1.62	1.59	2.42

against other five tyrosine kinases (c-Kit, Flt-3, VEGFR-2, EGFR, and PDGFR) using the same screening method (Table 2). These receptor tyrosine kinases (RTKs) have been implicated in vascular development by affecting the proliferation and migration of endothelial cells or pericytes. It is clear from Table 2 that compounds **3c**, **6c**, **6d**, **6f**, **6n**, **14a** and **15** were the most potent against the five tyrosine kinases. Compound **6b** showed high inhibitions towards EGFR kinase with IC_{50} 0.43 nM, while it showed moderate inhibition towards c-Kit, Flt-3, VEGFR-2 and PDGFR with IC_{50} 1.32, 1.08, 1.69 and 1.02 nM, respectively. Compound **6m** showed high inhibitions toward Flt-3 and VEGFR-2 tyrosine kinases with IC_{50} 0.29 and 0.42 nM, respectively. On the other hand, compound **3b** showed high inhibitions against EGFR and PDGFR kinases with IC_{50} 0.73 and 0.52 nM, respectively. Compounds **3c**, **6d** and **15** were the most active toward c-Kit tyrosine kinase with IC_{50} 0.21, 0.25 and 0.33 nM, respectively. Compounds **3b** and **16** showed the lowest potency among the tested compounds.

2. 6. 4. Inhibitions of Selected Compounds Against Pim-1 Kinase

Compounds **3c**, **6c**, **6d**, **6f**, **6n**, **14a** and **15** were selected to examine their Pim-1 kinase inhibition activity (Table 3) as these compounds showed high inhibition against the tested cancer cell lines at a range of 10 concentrations and the IC_{50} values were calculated. Compounds **3c**, **6c**, **6d**, **6n** and **15** most potently inhibited Pim-1 kinase with IC_{50} values of 0.24, 0.27, 0.24, 0.28 and 0.32 μM, respectively. On the other hand, compounds **6f** and **14a** were less effective (IC_{50} > 10 μM). These profiles in combination with cell growth inhibition data of compounds **3c**, **6c**, **6d**, **6f**, **6n**, **14a** and **15** are listed in Table 3, indicating that Pim-1 is a potential target of these compounds where SGI-1776 was used as the positive control with IC_{50} 0.048 μM in the assay.

Table 3. The inhibitions of compounds **3c**, **6c**, **6d**, **6f**, **6n**, **14a** and **15** against Pim-1 kinase.

Compound	Inhibition ratio at 10 μM	IC_{50} (μM)
3c	94	0.24
6c	90	0.27
6d	94	0.24
6f	20	> 10
6n	90	0.28
14a	31	>10
15	86	0.32
SGI-1776	–	0.048

2. 6. 5. Pan Assay Interference Compounds (PAINS)

Good antitumor drugs should give false positive results when evaluated within Pan Assay Interference Compounds (PAINS).[29,30] Compounds can be regarded as false positives due their binding interactions by forming aggregates[31–33] by being protein-reactive entities[34–36] or by directly interfering with assay signaling. Pan Assay Interference Compounds (PAINS) are chemical entities that are frequently false positive in HTS. PAINS have a tendency to non-specifically react with several biological targets moderately, then specifically disturbing one preferred target.[37] A number of disorderly functional groups are collected by numerous PAINS.[38] Unwanted compounds may negatively influence not only enzyme assays but also phenotypic

Table 4. Drug-like character of different compounds and standard drugs foretinib and SGI-1776

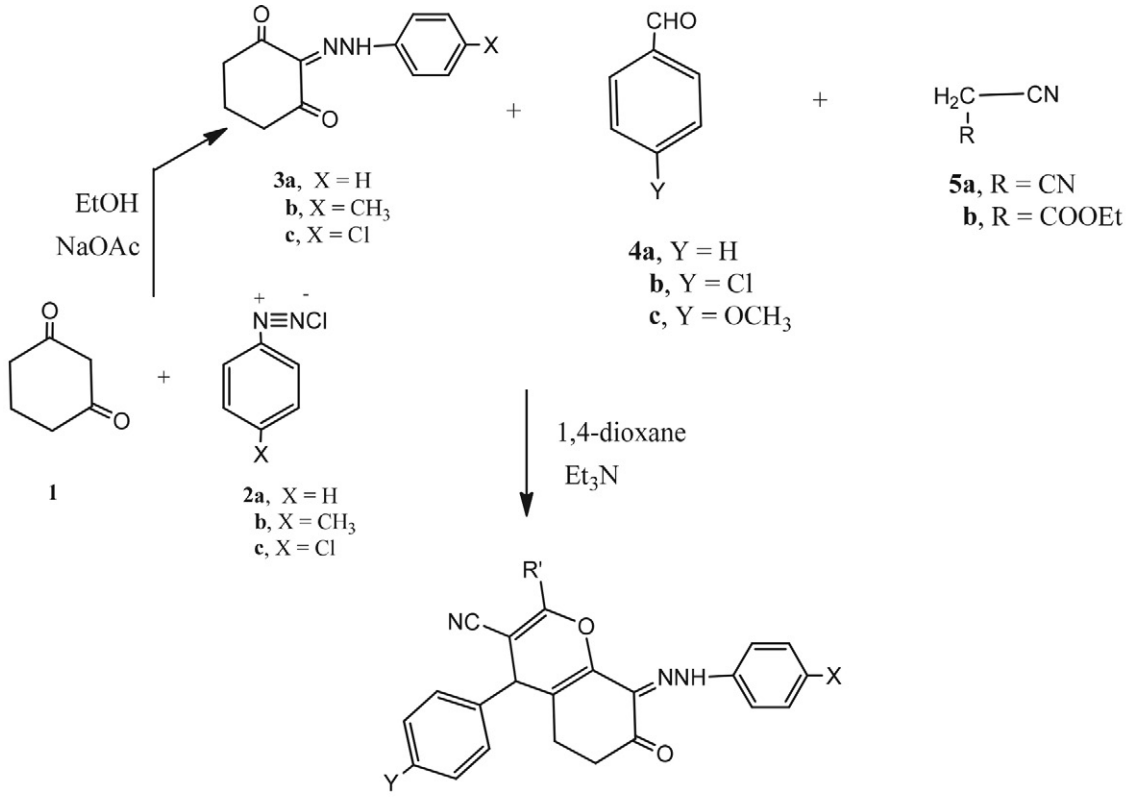
Compound	Drug-likeness Rule			Medicinal Chemistry Rules	
	Lvio.[a]/No. of vio.[a]	Vvio.[b]/No. of vio.[b]	Gvio.[c]/No. of vio.[c]	Lead likeliness /No. alert[d] of vio.	PAINS
3b	None	None	None	None	0
3c	None	None	None	None	0
6b	None	None	None	3	1
6c	None	None	None	2	0
6d	None	None	None	3	0
6f	None	None	None	None	0
6m	None	None	None	2	0
6n	None	None	None	3	0
14a	None	None	None	3	0
15	None	None	None	2	0
16	None	None	None	None	1
Foretinib	None	None	None	None	0
SGI-1776	None	None	None	None	0

[a] Lvio. = Lipinski's rule. [b] Vvio. = Veber Rules. [c] Gvio. = Ghose filter. [d] PAINS = Pan Assay Interference Compounds Analysis.

screens and show biological activity for the wrong reason.[39] PAINS violations of proposed compounds and reference drugs are given in Table 4. Almost all the compounds showed zero PAINS alert and can be used as good anticancer agents in the future without side effects.

3. Results and Discussion

Initially 2-arylhydrazonocyclohexan-1,3-dione was chosen as the model substrate for the synthesis of fused heterocyclic compounds through studying its multi-component reactions with aromatic aldehydes and cyanomethylene reagents to give biologically active fused pyran derivatives. The arylhydrazone derivatives **3a–c** were obtained through the coupling reaction between cyclohexane-1,3-dione (**1**) and either benzenediazonium chloride (**2a**), 4-methylbenzenediazonium chloride (**2b**) or 4-chlorobenzenediazonium chloride (**2c**) in ethanol solution containing the appropriate amount of sodium acetate. The multi-component reactions of either **3a**, **3b** or **3c** with either of benzaldehyde (**4a**), 4-chlorobenzaldehyde (**4b**) or

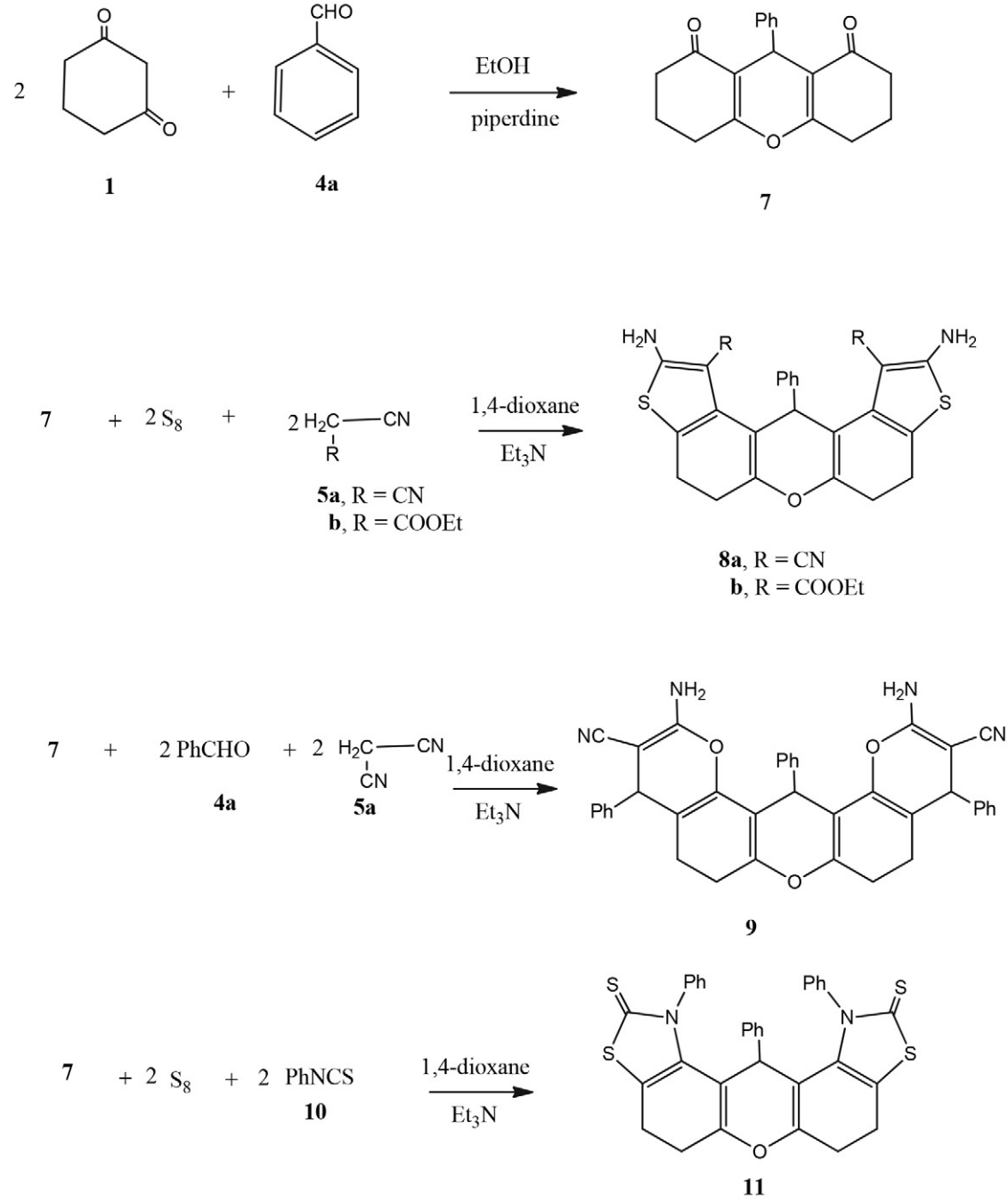


6	a	b	c	d	e	f	g	h	i
X	H	H	H	H	H	H	CH_3	CH_3	CH_3
Y	H	H	Cl	Cl	OCH_3	OCH_3	H	H	Cl
R'	NH_2	OH	NH_2	OH	NH_2	OH	NH_2	OH	NH_2
6	**j**	**k**	**l**	**m**	**n**	**o**	**p**	**q**	**r**
X	CH_3	CH_3	CH_3	Cl	Cl	Cl	Cl	Cl	Cl
Y	Cl	OCH_3	OCH_3	H	H	Cl	Cl	OCH_3	OCH_3
R'	OH	NH_2	OH	NH_2	OH	NH_2	OH	NH_2	OH

Sheme 1. Synthesis of compounds **3a–c** and **6a–r.**

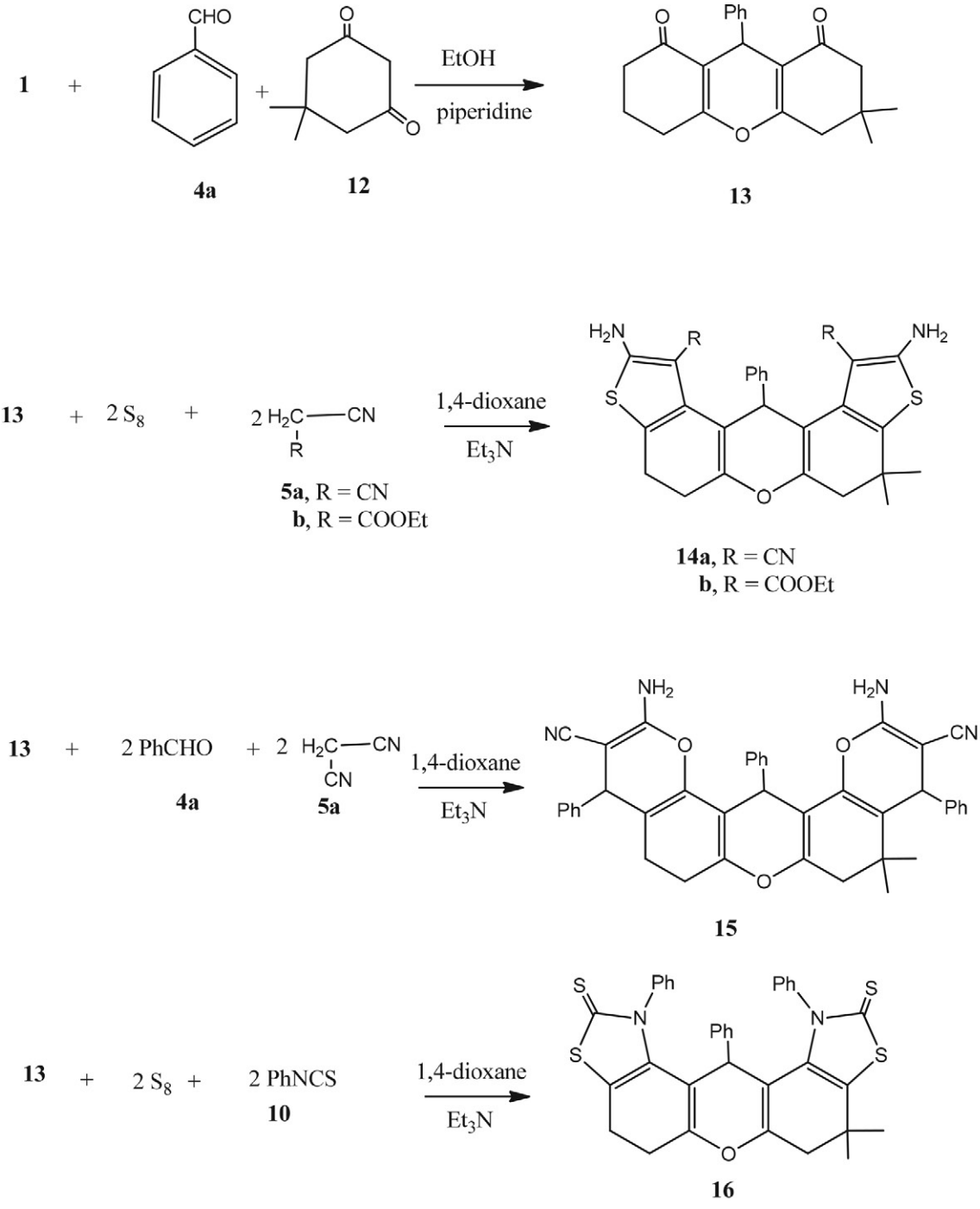
4-methoxybenzaldehyde (**4c**) and either malononitrile (**5a**) or ethyl cyanoacetate (**5b**) in 1,4-dioxane solution containing a catalytic amount of triethylamine gave the 5,6,7,8-tetrahydro-4*H*-chromene derivatives **6a**–**r**, respectively (Scheme 1). The chemical structures of new compounds were assured by spectral data (IR, ^{1}H, ^{13}C NMR, MS). Thus, the ^{1}H NMR spectrum of compound **6a** (as an example) showed (beside the expected signals) signals at δ 4.82 ppm (D_2O exchangeable) indicating the presence of the NH_2 group, a multiplet at δ 7.23–7.48 ppm for the two phenyl groups. In addition, the ^{13}C NMR spectrum revealed the presence of a signal at 51.2 due to the pyran C-4, one signal-at δ 117.3 for CN groups, signals at δ 130.2, 131.6, 134.8, 136.1 for the pyran carbons and two signals at δ 166.8 and 167.2 for the C=N and C=O groups.

Next, we studied the reaction of two-fold amount of cyclohexan-1,3-dione with benzaldehyde in ethanol containing a catalytic amount of triethylamine to give the 9-phenyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**7**). The analytical and spectral data of compound **7**



Sheme 2. Synthesis of compounds **7; 8a,b; 9** and **11.**

were in agreement with the proposed structure. Thus, the ^{1}H NMR spectrum showed the presence of two multiplets at δ 1.59–1.80 and 2.58–2.73 ppm equivalent to the six CH_2 groups, a singlet at δ 5.09 ppm for the pyran H-4 and a multiplet at δ 7.25–7.41 ppm corresponding to the C_6H_5 group. In addition, the ^{13}C NMR spectrum showed signals at δ 26.3, 28.4, 32.6 equivalent to the six CH_2 groups, signal at 50.9 due to the pyran C-4, four signals at δ 120.6, 121.4, 123.6 and 125.8 for the phenyl carbons and a signal at δ 168.9 for the two symmetric C=O groups. Compound **7** showed interesting reactivity toward heterocyclization reactions through its reactions with some reagents. It was ready to undergo Gewald's thiophene[40–42] reaction to produce biologically active fused thiophene derivatives. Thus, the reaction of compound **7** with two folds of either malononitrile (**5a**) or ethyl cyanoacetate (**5b**) and elemental sulfur gave the dithieno[3,2-*a*:2',3'-*j*]xanthene derivatives **8a** and **8b**, respectively. On the other hand, compound **7**



Sheme 3. Synthesis of compounds **13, 14a,b; 15** and **16.**

underwent multi-component reactions with two folds of benzaldehyde (**4a**) and malononitrile (**5a**) affording the hexahydro-4*H*-dipyrano[2,3-*a*:3',2'-*j*]xanthene derivative **9**. Its structure was established on the basis of its analytical and spectral data (see experimental section). In addition, the reaction of compound **7** with two folds of elemental sulfur and phenylisothiocyanate (**10**) in 1,4-dioxane solution containing a catalytic amount of triethylamine gave the xantheno[1,2-*d*:8,7-*d'*]bis(thiazole)-dithione derivative **11** (Scheme 2). Compounds **8**, **9** and **11** were obtained in pure state and high yields and promising structure identification were obtained thus encouraging us to carry similar reactions using cyclohexan-1,3-dione in one side and dimedone in the other side. Therefore, the multi-component reactions of cyclohexan-1,3-dione with benzaldehyde (**4a**) and dimedone gave the 3,3-dimethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**13**).

Compound **13** showed interesting reactivity toward heterocyclization reactions through its reactions with some reagents. Thus, the reaction of compound **13** with two folds of either malononitrile (**5a**) or ethyl cyanoacetate (**5b**) and elemental sulfur gave the 4,4-dimethyl-5,7,8,12-tetrahydro-4*H*-dithieno[3,2-*a*:2',3'-*j*]xanthenes derivatives **14a** and **14b**, respectively. On the other hand, compound **13** underwent multi-component reactions with two folds of benzaldehyde (**4a**) and malononitrile (**5a**) affording the 2,12-diamino-5,5-dimethyl-4,10,14-triphenyl-5,6,8,9,10,14-hexahydro-4*H*-dipyrano[2,3-*a*:3',2'-*j*]xanthene derivative **15**. In addition, the reaction of compound **13** with two folds of elemental sulfur and phenylisothiocyanates (**10**) in 1,4-dioxane solution containing a catalytic amount of triethylamine gave the 4,4-dimethyl-4,5,7,8-tetrahydro-1*H*-xantheno[1,2-*d*:8,7-*d'*]bis(thiazole)-dithione derivative **16** (Scheme 3).

4. Conclusion

The main result of these studies is the synthesis of a series of novel heterocyclic derivatives synthesized from arylhydrazonocyclohexan-1,3-dione followed by screening of the newly synthesized compounds against six cancer cell lines. Compounds **3b**, **3c**, **6b**, **6c**, **6d**, **6f**, **6m**, **6n**, **14a**, **15** and **16** were the most cytotoxic. Screening against the five tyrosine kinases c-Kit, Flt-3, VEGFR-2, EGFR, and PDGFR showed that compounds **3c**, **6c**, **6d**, **6f**, **6n**, **14a** and **15** were the most active compounds. On the other hand, inhibition against Pim-1 kinase indicated that compounds **3c**, **6c**, **6d**, **6n** and **15** were of the highest inhibitions.

5. References

1. T. Moriguchi, H. Matsuura, Y. Itakura, H. Katsuki, H. Saito, N. Nishiyama, *Life Sci.* **1997**, *61*, 1413–1420. **DOI:**10.1016/S0024-3205(97)00687-5
2. G. H. Abou El-Fotooh, O. I. Abd El-Salam, M. M. Ashraf, A. H. Nagla, *Ind. J. Chem.* **2005**, *44B*, 1887–1893.
3. D. Armesto, W. M. Horspool, N. Martin, A. Ramos, C. Seoane, *J. Org. Chem.***1989**, *54*, 3069–3072. **DOI:**10.1021/jo00274a021
4. J. A. Rideout, I. R. Smith, M. D. Sutherland, *Aust. J. Chem.* **1976**,*29*, 1087–1089. **DOI:**10.1071/CH9761087
5. D. Kumar, V. B. Reddy, S. Sharad, U. Dube, K. A. Suman, *Eur. J. Med. Chem.***2009**, *44*, 3805–3809. **DOI:**10.1016/j.ejmech.2009.04.017
6. Y. R. Lee, X. Wang, L. Xia, *Molecules* **2007**, *12*, 1420–1429. **DOI:**10.3390/12071420
7. M. M. Khafagy, A. H. F. El-Wahas, F. A. Eid, A. M. El-Agrody, *Il Farmaco* **2002**, *57*, 715–722. **DOI:**10.1016/S0014-827X(02)01263-6
8. W. P. Smith, L. S. Sollis, D. P. Howes, C. P. Cherry, D. I. Starkey, N. K. Cobley, H. Weston, J. Scicinski, A. Merritt, A. Whittington, P. Wyatt, N. Taylor, D. Green, R. Bethell, S. Madar, R. J. Fenton, P. J. Morley, T. Pateman, A. J. Beresford, *Med. Chem.* **1998**, *41*, 787–797. **DOI:**10.1021/jm970374b
9. A. G. Martinez, L. J.Marco, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3165–3170. **DOI:**10.1016/S0960-894X(97)10165-2
10. K. Hiramoto, A. Nasuhara, K. Michiloshi, T. Kato, K. Kikugawa, *Mutat. Res.***1997**, *395*,47–56. **DOI:**10.1016/S1383-5718(97)00141-1
11. C. P. Dell, C. W. Smith, *Eur. Pat. Appl.* **1993**, *537*, 949. *Chem. Abstr.* **1993**, *119*, 139102d.
12. G. Bianchi, A.Tava, *Agric. Biol. Chem.* **1987**, *51*, 2001–2002. **DOI:**10.1271/bbb1961.51.2001
13. S. J. Mohr, M. A. Chirigos, F. S. Fuhrman, J. W. Pryor, *Cancer Res.* **1975**, *35*, 3750–3754.
14. J. Skommer, D. Wlodkowic, M. Matto, M. Eray, J. Pelkonen, *Leukemia Res.* **2006**, *30*, 322–331. **DOI:**10.1016/j.leukres.2005.08.022
15. D. R. Anderson, S. Hegde, E. Reinhard, L. Gomez, W. F. Vernier, L. Lee, S. Liu, A. Sambandam, P. A. Snider, L. Masih, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1587–1590. **DOI:**10.1016/j.bmcl.2005.01.067
16. J. L. Wang, D. Liu, Z. Zhang, S. Shan, X. Han, S. M. Srinvasula, C. M. Croce, E. S. Alnemeri, Z. Huang, *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 7124–7129. **DOI:**10.1073/pnas.97.13.7124
17. F. Eiden, F. Denk, *Arch. Pharm. (Weinheim, Germany)* **1991**, *324*, 353–354. **DOI:**10.1002/ardp.19913240606
18. E. A. A. Hafez, M. H. Elnagdi, A. G. A. Elagamey, F. M. A. El-Taweel, *Heterocycles* **1987**, *26*, 903–907. **DOI:**10.3987/R-1987-04-0903
19. R. M. Mohareb, N. Y. Abdo, K. A. EL-Sharkawy, *Anticancer Agent in Med. Chem.* **2018**, *18*, 1736–1749. **DOI:**10.2174/1871520618666180604091358
20. R. M. Mohareb, E. M. Samir, P. A. Halim, *Bioorg.Chem.* **2019**, *83*, 402–413. **DOI:**10.1016/j.bioorg.2018.10.067
21. R. M. Mohareb, K. A. El-Sharkawy, F. O. El-Farouk, *Med. Chem. Res.* **2019**, *28*, 1885–1900. **DOI:**10.1007/s00044-019-02421-6
22. R. M. Mohareb, A. E. M. Abdallah, M. A. Abelaziz, *Med. Chem. Res.* **2014**, *23*, 564–597. **DOI:**10.1007/s00044-013-0664-7

23. R. M. Mohareb, W. W. Wardakhan, F. I. Hamid, *Med. Chem. Res.* **2015**, *24*, 2043–2054. **DOI:**10.1007/s00044-014-1273-9
24. R. M. Mohareb, F. M. Manhi, A. Abdelwahab, *Acta Chim. Slov.* **2020**, *67*, 83–95. **DOI:**10.17344/acsi.2019.5224
25. R. M. Mohareb, P. A. Halim, *Acta Chim. Slov.* **2018**, *65*, 554–568. **DOI:**10.17344/acsi.2017.4146
26. L. Liu, A. Siegmund, N. Xi, P. Kaplan-Lefko, K. Rex, A. Chen, J. Lin, J. Moriguchi, L. Berry, L. Y. Huang, Y. Teffera, Y. J. Yang, Y. H. Zhang, S. F. Bellon, M. Lee, R. Shimanovich, A. Bak, C. Dominguez, M. H. Norman, J. C. Harmange, I. Dussault, T. S. Kim, *J. Med. Chem.* **2008**, *51*, 3688–3691. **DOI:**10.1021/jm800401t
27. M. L. Peach, N. Tan, S. J. Choyke, A. Giubellino, G. Athauda, T. R. Burke, M. C. Nicklaus, D. P. Bottaro, *J. Med. Chem.* **2009**, *52*, 943–951. **DOI:**10.1021/jm800791f
28. F. D. Bacco, P. Luraghi, E. Medico, G. Reato, F. Girolami, T. Perera, P. Gabriele, P. M. Comoglio, C. Boccaccio, *J. Natl. Cancer Inst.* **2011**, *103*, 645–661. **DOI:**10.1093/jnci/djr093
29. J. B. Bael, G. A. Holloway, *J. Med. Chem.***2010**, *53*, 2719–2740. **DOI:**10.1021/jm901137j
30. S. L. McGovern, E. Caselli, N. Grigorieff, B. K. Shoichet, *J. Med.Chem.* **2002**, *45*, 1712–1722. **DOI:**10.1021/jm010533y
31. S. L. McGovern, B. K. Shoichet, *J. Med. Chem.* **2003**, *46*, 1478–1483. **DOI:**10.1021/jm020427b
32. B. Y. Feng, A. Shelat, T. N. Doman, R. K. Guy, B. K. Shoichet, *Nat. Chem. Biol.* **2005**, *1*, 146–148. **DOI:**10.1038/nchembio718
33. B. Y. Feng, B. K. Shoichet, *J. Med. Chem.***2006**, *49*, 2151–2154. **DOI:**10.1021/jm060029z
34. J. T. Metz, J. R. Huth, P. J. Hajduk, *J. Computer-Aided Mol. Des.* **2007**, *21*, 139–144. **DOI:**10.1007/s10822-007-9109-z
35. J. R. Huth, D. Song, R. R. Mendoza, C. L. Black-Schaefer, J. C. Mack, S. A. Dorwin, U. S. Ladror, J. M. Severin, K. A.Walter, D. M. Bartley, P. Hajduk, *Chem. Res. Toxicol.* **2007**, *20*, 1752–1759. **DOI:**10.1021/tx700319t
36. B. B. Jonathan, A. W. Michael, *Nature* **2014**, *513*, 481–483. **DOI:**10.1038/513481a
37. L. D. Jayme, A. W. Michael, *Futu. Med.Chem.* **2014**, *6*, 1265–1290. **DOI:**10.4155/fmc.14.60
38. P. Martin, J. Stephane, *J. Med. Chem.* **2016**, 59, 497–503. **DOI:**10.1021/acs.jmedchem.5b00361
39. F. Cheng, A. W. Li, *J. Chem. Inf. Mod.***2012**, *52*, 3099–3105. **DOI:**10.1021/ci300367a
40. B. P. McKibben, C. H. Cartwright, A. L. Castelhano, *Tetrahedron Lett.* **1999**, *40*, 5471–5474. **DOI:**10.1016/S0040-4039(99)01108-9
41. R. Mishra, K. K. Jha, S. Kumar, I. Tomer, *A review Der Pharma Chemica* **2011**, *3*, 38–54.
42. K. Wang, D. Kim, A. Dömling, *J. Comb.Chem.* **2010**, *12*, 111–118. **DOI:**10.1021/cc9001586

Povzetek

V prispevku predstavljamo večkomponentne reakcije med arilhidrazocikloheksan-1,3-dionskimi derivati **3a**–**c** in benzaldehidom (**4a**), 4-klorobenzaldehidom (**4b**) ali 4-metoksibenzaldehidom (**4c**) ter malononitrilom (**5a**) ali etil cianoacetatom (**5b**), ki vodijo do nastanka 5,6,7,8-tetrahidro-4*H*-kromenskih derivatov **6a**–**r**. Pri reakciji dveh ekvivalentov cikloheksan-1,3-diona z benzaldehidom je nastal heksahidro-1*H*-ksanten-1,8(2*H*)-dionski derivat **7**. Po drugi strani pa večkomponentna reakcija med spojino **1** in dimedonom ali benzaldehidom daje produkt **13**. Obe spojini **7** in **13** lahko sodelujeta v reakcijah heterociklizacij, pri katerih nastanejo pripojeni tiofenski, piranski in tiazolski derivati. Izmed pripravljenih spojin smo nekatere uporabili za določevanje potencialne inhibitorne aktivnosti proti šestim rakavim celičnim linijam; rezultati so bili obetavni, spojine **3b**, **3c**, **6b**, **6c**, **6d**, **6f**, **6i**, **6m**, **6n**, **8b**, **14a**, **15** in **16** so se izkazale kot še posebej citotoksične. Nadaljnje testiranje na petih tirozin kinazah (c-Kit, Flt-3, VEGFR-2, EGFR in PDGFR) ter Pim-1 kinazi je pokazalo, da so spojine **3c**, **6c**, **6d**, **6f**, **6n**, **14a** in **15** najbolj aktivne proti prvim petim tirozin kinazam, medtem ko so spojine **3c**, **6c**, **6d**, **6n** in **15** najbolj aktivne proti Pim-1 kinazi.

Except when otherwise noted, articles in this journal are published under the terms and conditions of the Creative Commons Attribution 4.0 International License