Asian Journal of Chemistry; Vol. 26, No. 23 (2014), 8202-8206

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2014.17921

Synthesis and Characterization of Some Novel Substituted Thiazolo[3,2-a]pyridine and Thioxopyrimido[4,5-d]pyrimidine Derivatives

NAGY M. KHALIFA[1,2], ADEL A.-H. ABDEL-RAHMAN[3], AMINA A. ABD EL GWAAD[2] and MOHAMED A. AL-OMAR[1]

[1]Pharmaceutical Chemistry Department, Drug Exploration and Development Chair, College of Pharmacy, king Saud University, Riyadh 11451, Saudia Arabia
[2]Therapeutical Chemistry Department, Pharmaceutical and Drug Industries Division, National Research Centre, Dokki 12622, Cairo, Egypt
[3]Chemistry Department, Faculty of Science, El-Menoufia University, Shebin El-Kom, Egypt

*Corresponding author: E-mail: nagykhalifa@hotmail.com

Received: 30 April 2014; *Accepted*: 10 July 2014; *Published online*: 15 November 2014; AJC-16325

Some novel substituted thiazolo[3,2-a]pyridine (**2-8**) and thioxopyrimido[4,5-d]pyrimidine (**10-12**) derivatives have been synthesized by initial reactions of 2-[(5-methylfuran-2-yl)methylene]malononitrile with 2-mercaptoacetic acid and thiourea, respectively. Their cyclization with HCl/AcOH, formamide and formic acid afforded a series of polycyclic heterocycles. The structures of the target compounds were confirmed by elemental analyses and spectral data.

Keywords: Fused pyrimidine derivatives, Thiazolo[3,2-a]pyridine, Pyrido[2,3-d]pyrimidines, Thioxopyrimido[4,5-d]pyrimidines derivatives.

INTRODUCTION

Thiazolopyridine ring system is found in a broad range of biologically active compounds[1]. Specifically, thiazolo[3,2-a]pyridine derivatives are found to exhibit a broad spectrum of potent anticancer activity and are useful for chemotherapy of various cancers, such as leukemia, lung cancer and melanoma[2]. Also, thiazolo[3,2-a]pyridines have many important bioactivities such as inhibiting β-amyloid production[3], potent CDK2-cyclin A inhibitor[4], a-glucosidase inhibitor[5], potential uterus stimulant[6], antibacterial and antifungal activities[7,8]. Due to their biological importance, thiazolo[3,2-a]pyridine derivatives have become synthetic targets for many organic and medicinal chemists[9-14]. In addition, pyrimidines and fused pyrimidines represent a broad class of compounds, which have received considerable attention due to their wide range of biological activities. Among them, the pyrimido[4,5-d]pyrimidines represents an attractive target due to the interesting pharmacological activities as antioxidant[15], antiviral[16], antiallergic[17], antihypertensive[18], antifungal[19], hepatoprotective[20] and anticancer[21,22] agents. There are also numerous examples in the literature with diverse biological profiles shown by the pyrido[2,3-d]pyrimidine nucleus. The family based on pyrido[2,3-d]pyrimidines has been developed and these compounds show great specificity for individual subgroups of receptor tyrosine kinases[23,24]. Other members of this family inhibit non-receptor tyrosine kinases such as Abl[25,26], Akt[27] or cyclin kinases[28]. Another target for these derivatives is dihydrofolate reductase inhibition, *e.g.* piritrexim[29], as well as cell cycle modulation[30]. Thus, the efficient and novel synthesis of such compounds is of prime interest and represents a highly pursued target.

EXPERIMENTAL

All melting points were uncorrected and were taken on a Boetius melting point microscope. The infrared (IR) spectra were recorded on a Bruker-Vector 22, Germany, using KBr discs at the microanalytical center, Cairo University. ^{1}H NMR spectra were performed on a Varian Gemini 300 MHz spectrometer and JEOL EX-270 MHz at the Central Services Laboratory, National Research Centre, Cairo, Egypt, using tetramethylsilane (TMS) as internal standard. All chemical shifts are quoted in d values using parts per million scale (ppm) downfield from tetramethylsilane. Mass spectra were recorded on a Hewlett-Packard 5988 A (1,000 Hz) instrument and Shimadzu GCMS-QP-1000EX mass spectrometer at 70 eV at Cairo University. Elemental analysis were performed by microanalytical unit at Cairo University and the found values agreed favourably with the calculated ones. All reactions were monitored by TLC using precoated aluminum sheet silica gel Merck 60F254 plates and detection of the components was made by short and long UV light.

5-Amino-3,7-dihydro-7-(5-methylfuran-2-yl)-3-oxo-2*H*-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (2): A solution of compound **1** (10 mmol) and thioglycolic acid (10 mmol) in ethanol (50 mL) and a catalytic amount of piperidine was refluxed for 5 h. The solvent was concentrated and the solid product was collected by filtration and recrystallized from ethanol to give the title compound **2** in 91 % yield; m.p. 220-222 °C; IR (KBr, ν_{max}, cm^{-1}): 3489 (NH_2), 2203 (CN). 1633 (C=O); ^{1}H NMR (DMSO-d_6) δ: 2.26 (s, 3H, CH_3), 4.12 (s, 2H, CH_2), 4.75 (s, 2H, NH_2), 6.01 (s, 1H, CH), 6.28, 7.62 (2d, 2H, furan ring); MS *m/z* (%): 298 (M^+). Anal. Calcd. For $C_{14}H_{10}N_4O_2S$ (298.32): Calcd. C 56.37, H 3.38, N, 18.78; found C 56.19, H 3.21, N 18.58.

(2*E*)-Ethyl-3-(6,8-dicyano-3,7-dihydro-7-(5-methylfuran-2-yl)-3-oxo-2*H*-thiazolo-[3,2-a]pyridin-5-ylamino)-but-2-enoate (3): A mixture of compound **2** (5 mmol) and ethylacetoacetate (5 mmol) in dry benzene (50 mL) in presence of *p*-toluene sulphonic acid (0.29 mmol) was azeoptrically refluxed for 2 h. After completion (TLC), the reaction mixture was cooled, poured into ice/water and the solid formed was filtered off, dried and crystallized from MeOH to give compound **3** in 87 % yield, m.p. 232-234 °C (d); IR (KBr, ν_{max}, cm^{-1}): 3231 (NH), 2209 (CN), 1623 (C=O); ^{1}H NMR (DMSO-d_6) δ: 1.12 (t, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 4.09 (s, 2H, CH_2), 4.23 (q, 2H, CH_2), 5.19 (s, 1H, CH), 6.11 (s, 1H, CH), 6.24, 7.65 (2d, 2H, furan ring); MS *m/z* (%): 410 (M^+). Anal. Calcd. For $C_{20}H_{18}N_4O_4S$ (410.45): Calcd. C 58.53, H 4.42, N, 13.65; found C 58.36, H 4.25, N 13.47.

(2*E*)-5-Amino-2-substituted benzylidene-3,7-dihydro-7-(5-methylfuran-2-yl)-3-oxo-2*H* thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (4a-f)

General method: Equimolar amounts of compound **2** and appropriate aromatic aldehydes (10 mmol) dissolved in absolute ethanol (50 mL), the reaction mixture was heated under reflux for 5-8 h. The solvent was concentrated under reduced pressure and the obtained residue was filtered, dried and crystallized from the proper solvent to give the title compounds **4a-f**.

(2*E*)-5-Amino-2-benzylidene-3,7-dihydro-7-(5-methylfuran-2-yl)-3-oxo-2*H*-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (4a): Yield 72 %, m.p. 150-152 °C (AcOH); IR (KBr, ν_{max}, cm^{-1}): 3433 (NH_2), 2200 (CN), 1705 (C=O); ^{1}H NMR (DMSO-d_6) δ: 2.29 (s, 3H, CH_3), 4.39 (s, 2H, NH_2), 6.05 (s, 1H, CH), 6.38, 6.49 (2d, 2H, furan ring), 6.94 (s, 1H, =CH), 7.12-7.62 (m, 5H, Ar); MS *m/z* (%): 386 (M^+). Anal. Calcd. For $C_{21}H_{14}N_4O_2S$ (386.43): Calcd. C 65.27, H 3.65, N, 14.50; found C 65.09, H 3.48, N 14.31.

(2*E*)-2-(4-Chlorobenzylidene)-5-amino-3,7-dihydro-7-(5-methylfuran-2-yl)-3-oxo-2*H*-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (4b): Yield 68 %, m.p. 170-172 °C (AcOH); IR (KBr, ν_{max}, cm^{-1}): 3465 (NH_2), 2217 (CN), 1701 (C=O); ^{1}H NMR (DMSO-d_6) δ: 2.25 (s, 3H, CH_3), 4.45 (s, 2H, NH_2), 6.15 (s, 1H, CH), 6.36, 6.48 (2d, 2H, furan ring), 6.85 (s, 1H, =CH), 7.18-7.52 (m, 4H, Ar); MS *m/z* (%): 421 (M^+). Anal. Calcd. For $C_{21}H_{13}ClN_4O_2S$ (420.87): Calcd. C 59.93, H 3.11, N, 13.31; found C 59.74, H 2.96, N 13.16.

(2*E*)-2-(4-methoxybenzylidene)-5-amino-3,7-dihydro-7-(5-methylfuran-2-yl)-3-oxo-2*H*-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (4c): Yield 61 %, m.p. 174-176 °C (DMF/H_2O); IR (KBr, ν_{max}, cm^{-1}): 3478 (NH_2), 2210 (CN), 1703 (C=O); ^{1}H NMR (DMSO-d_6) δ: 2.28 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 4.86 (s, 2H, NH_2), 6.25, 6.48 (2d, 2H, furan ring), 6.12 (s, 1H, CH), 6.95-7.54 (m, 5H, Ar + =CH); MS *m/z* (%): 416 (M^+). Anal. Calcd. For $C_{22}H_{16}N_4O_3SCl$ (416.45): Calcd. C 63.45, H 3.87, N, 13.45; found C 63.23, H 3.69, N 13.28.

(2*E*)-2-[4-(Dimethylamino)benzylidene]-5-amino-3,7-dihydro-7-(5-methylfuran-2-yl)-3-oxo-2*H*-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (4d) Yield 61 %, m.p. 163-165 °C (DMF/H_2O); IR (KBr, ν_{max}, cm^{-1}): 3387 (NH_2), 2204 (CN), 1707 (C=O); ^{1}H NMR (DMSO-d_6) δ: 2.27 (s, 3H, CH_3), 2.81 (s, 6H, $2CH_3$), 4.70 (s, 2H, NH_2), 6.28, 6.46 (2d, 2H, furan ring), 6.11 (s, 1H, CH), 7.10-7.66 (m, 5H, Ar + =CH); MS *m/z* (%): 429 (M^+). Anal. Calcd. For $C_{23}H_{19}N_5O_2S$ (429.49): Calcd. C 64.32, H 4.46, N, 16.31; found C 64.17, H 4.31, N 16.22.

(2*E*)-2-(3,4-Dimethoxybenzylidene)-5-amino-3,7-dihydro-7-(5-methylfuran-2-yl)-3-oxo-2*H*-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (4e): Yield, 65 %, m.p. 160-162 °C (DMF/H_2O); IR (KBr, ν_{max}, cm^{-1}): 3381 (NH_2), 2204 (CN), 1707 (C=O), ^{1}H NMR (DMSO-d_6) δ: 2.22 (s, 3H, CH_3), 3.83, 3.86 (2s, 6H, $2OCH_3$), 6.09 (s, 1H, CH), 5.15 (s, 1H, NH_2), 6.97-7.62 (m, 4H, Ar + =CH). MS *m/z* (%): 446 (M^+). Anal. Calcd. For $C_{23}H_{18}N_4O_4S$ (446.48): Calcd. C 61.87, H 4.06, N, 12.55; found C 61.63, H 3.86, N 12.38.

(2*E*)-2-(3,4,5-Trimethoxybenzylidene)-5-amino-3,7-dihydro-7-(5-methylfuran-2-yl)-3-oxo-2*H*-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (4f): Yeild, 71 %, m.p. 166-168 °C (DMF/H_2O); IR (KBr, ν_{max}, cm^{-1}): 3435 (NH_2), 2218 (CN), 1705 (C=O); ^{1}H NMR (DMSO-d_6) δ: 2.21 (s, 3H, CH_3), 3.81, 3.86 (2s, 9H, $3OCH_3$), 4.96 (s, 2H, NH_2), 6.07 (s, 1H, CH), 6.27, 6.95 (2d, 2H, furan ring), 7.15-7.71 (m, 3H, Ar + =CH); MS *m/z* (%): 476 (M^+). Anal. Calcd. For $C_{24}H_{20}N_4O_5S$ (476.5): Calcd. C 60.49, H 4.23, N, 11.76; found C 60.32, H 4.07, N 11.53.

(2*Z*)-5-Amino-7-(5-methylfuran-2-yl)-2-[(5-methyl-furan-2-yl)methylidene]-3-oxo-2,3-dihydro-7*H*-[1,3]thia-zolo[3,2-a]pyridine-6,8-dicarbonitrile (5)[31]

(8*Z*)-2-methyl-5-(5-methylfuran-2-yl)-8-[(5-methyl-furan-2-yl)methylidene]-4,9 dioxo-3,5,8,9-tetrahydro-4*H*-[1,3]thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carbonitrile (6): Compound **5** (10 mmol) was refluxed in a mixture of hydrochloric acid (3 mL) and acetic acid (9 mL) for 3 h. The reaction mixture was cooled, poured into ice/water and the solid formed was filtered off, dried and recrystallized from dioxane to give the title compound **6** in 94 % yield, m.p. 260-262 °C; IR (KBr, ν_{max}, cm^{-1}): 3390 (NH), 2204 (CN), 1707, 1623 (2 C=O); ^{1}H NMR (DMSO-d_6) δ: 1.23 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 6.10 (s, 1H, CH), 6.14, 6.31 (2d, 4H, furan ring), 7.74 (s, 1H, =CH), 9.34 (s, 1H, NH); MS *m/z* (%): 432 (M^+). Anal. Calcd. For $C_{22}H_{16}N_4O_4S$ (432.45): Calcd. C 61.10, H 3.73, N, 12.96; found C 66.91, H 3.59, N 12.83.

(8*Z*)-5-(5-Methylfuran-2-yl)-8-[(5-methylfuran-2-yl)methylidene]-4,9-dioxo-3,5,8,9-tetrahydro-4*H*-[1,3]thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carbonitrile (7): A mixture of compound **5** (1 mmol) and formic acid was refluxed for 3 h. The solid formed on cooling at room temperature was filtered off, dried and crystallized from dioxane to give compound **7** in 78 % yeild, m.p. 197-199 °C; IR (KBr, ν_{max}, cm^{-1}):

3319 (NH), 2226 (CN), 1701, 1648 (2 C=O); ^{1}H NMR (DMSO-d_6) δ: 2.23 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 5.98 (s, 1H, CH), 6.05 (d, 1H, CH), 6.26 (d, 1H, CH), 6.46 (d, 1H, CH), 7.11 (d, 1H, CH), 7.20 (s, 1H, =CH), 7.96 (s, 1H, CH pyrimidine), 8.72 (s, 1H, NH exchangeable with D_2O); MS *m/z* (%): 418 (M^+). Anal. Calcd. For $C_{21}H_{14}N_4O_4S$ (418.43): Calcd. C 60.28, H 3.37, N, 13.39; found C 60.12, H 3.15, N 13.26.

(2*E*)-Ethyl-3-((3*E*)-6,8-dicyano-3,7-dihydro-7-(5-methylfuran-2-yl)-2-((5-methyl furan-2-yl)methylene)-3-oxo-2*H*-thiazolo[3,2-a]pyridin-5-ylamino)but-2-enoate (8): A mixture of compound **5** (5 mmol) and ethylacetoacetate (5 mmol) in dry benzene (50 mL) in presence of *p*-toluene sulphonic acid (0.29 mmol) were refluxed for 2 h. The reaction mixture was cooled, poured into ice/water and the solid formed was filtered off, dried and recrystallized from AcOH to give the title compound **8** in 77 % yield, m.p. 230-232 °C (d); IR (KBr, ν_{max}, cm^{-1}): 3423 (NH), 2363 (CN), 1701, 1641 (2 C=O); ^{1}H NMR (DMSO-d_6) δ: 1.15 (t, 3H, CH_3), 1.78 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 4.25 (q, 2H, CH_2), 5.22 (s, 1H, CH), 6.05 (s, 1H, CH), 6.23 (d, 1H, CH), 6.32 (d, 1H, CH), 6.46 (d, 1H, CH), 7.10 (d, 1H, CH), 7.49 (s, 1H, =CH), 8.95 (s, 1H, NH exchangeable with D_2O). Analysis for: $C_{26}H_{22}N_4O_5S$ (502.54) Calcd C 62.14, H 4.41, N 11.15 found; C 61.96, H 4.23, N 10.89.

4-Amino-1,2-dihydro-6-(5-methylfuran-2-yl)-2-thioxopyrimidine-5-carbonitrile (9): A mixture of compound **1** (10 mmol), thiourea (10 mmol) and anhydrous K_2CO_3 (10 mmol) in ethanol (30 mL) were refluxed for 9 h. After completion (TLC), the reaction mixture was allowed to cool to room temperature and the solid obtained on cooling was filtered off, washed with water, air dried and crystallized from MeOH to give the title compound **9** in 89 % yield, m.p: 267-269 °C; IR (KBr, ν_{max}, cm^{-1}): 3486 (NH_2), 3355 (NH), 2190 (CN); ^{1}H NMR (DMSO-d_6) δ: 2.27 (s, 3H, CH_3), 4.95 (s, 2H, NH_2), 6.27, 7.61 (2d, 2H, furan ring), 10.87 (s, 1H, NH exchangeable with D_2O); MS *m/z* (%): 232 (M^+). Anal. Calcd. For $C_{10}H_8N_4OS$ (232.26): Calcd. C 51.71, H 3.47, N, 24.12; found C 51.35, H 3.50, N 23.80.

6,7-Dihydro-2-methyl-5-(5-methylfuran-2-yl)-7-thioxopyrimido[4,5-d]pyrimidin 4(3*H*)-one (10): Compound **9** (0.01 mol) was refluxed in a mixture of hydrochloric acid (3 mL) and acetic acid (9 mL) for 3 h. The reaction mixture was cooled, poured into water and the solid formed was filtered off, dried and recrystallized from DMF/H_2O to give compound **10** in 57 % yield. m.p.: 300 °C; IR (KBr, ν_{max}, cm^{-1}): 3320 (NH), 1668 (CO); ^{1}H NMR (DMSO-d_6) δ: 1.27 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 6.24, 7.58 (2d, 2H, furan ring), 10.36 (s, 1H, NH exchangeable with D_2O); MS *m/z* (%): 274 (M^+). Anal. Calcd. For $C_{12}H_{10}N_4O_2S$ (274.3): Calcd. C 52.54, H 3.67, N, 20.43; found C 52.35, H 3.49, N 20.26.

5-Amino-4-(5-methylfuran-2-yl)pyrimido[4,5-d]pyrimidine-2(3*H*)-thione (11): A mixture of compound **9** (1 mmol) and formamide (5 mL) was reflux for 9 h, the solid obtained after cooling was filtered off, washed with water, air dried and crystallized from DMF/H_2O to give compound **11** in 78 % yeild, m.p. 137-139 °C; IR (KBr, ν_{max}, cm^{-1}): 3465 (NH_2), 3290 (NH); ^{1}H NMR (DMSO-d_6) δ: 2.21 (s, 3H, CH_3), 4.80 (s, 2H, NH_2), 6.26, 7.54 (2d, 2H, furan ring), 11.02 (s, 1H, NH exchangeable with D_2O); MS *m/z* (%): 259 (M^+). Anal. Calcd. For $C_{11}H_9N_5OS$ (259.29): Calcd. C 50.95, H 3.50, N, 27.01; found C 50.71, H 3.46, N 26.89.

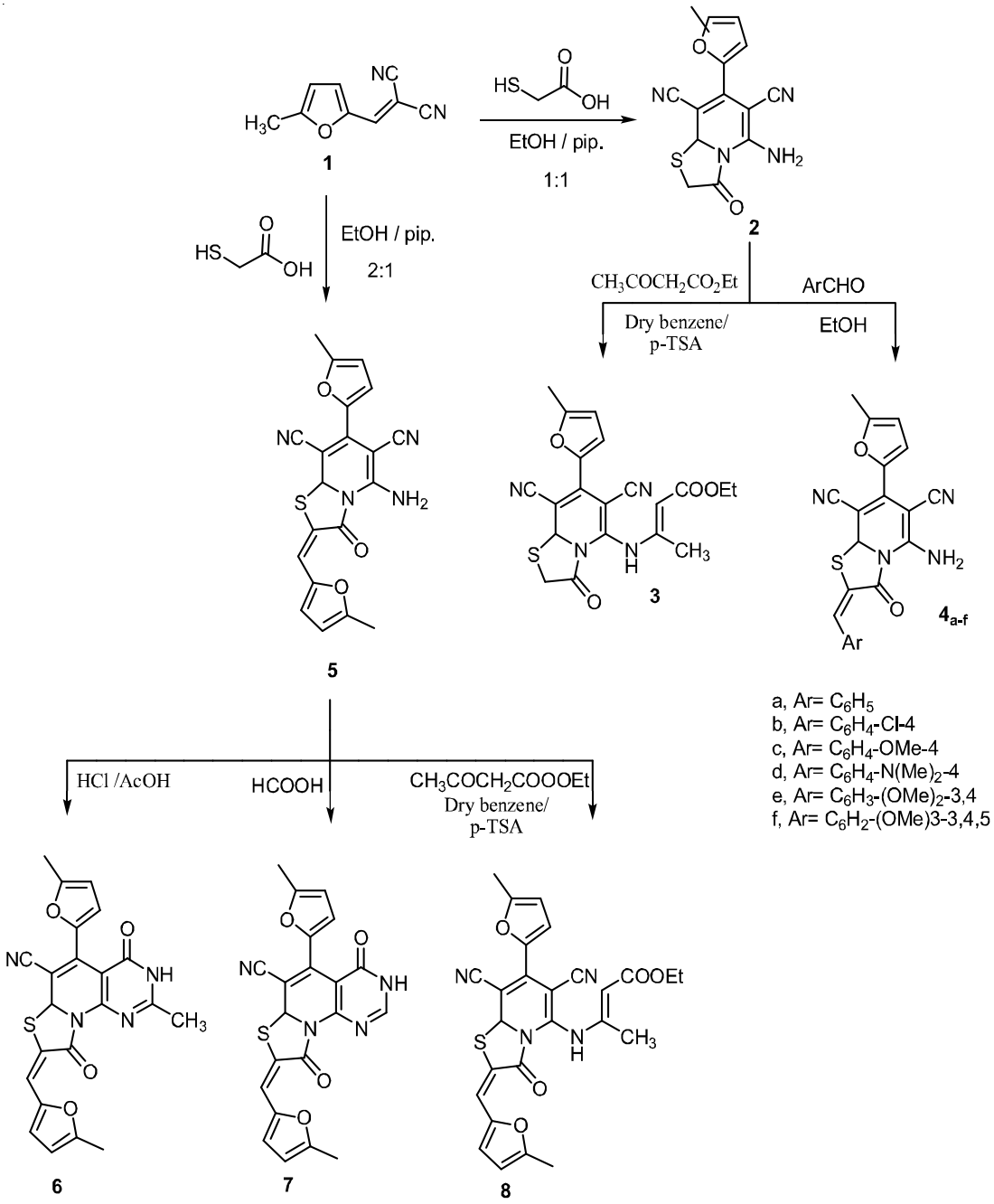
6,7-Dihydro-5-(5-methylfuran-2-yl)-7-thioxopyrimido-[4,5-d]pyrimidin-4(3*H*)-one (12): A mixture of compound **9** (2 mmol) and formic acid (5 mL) was reflux for 9 h, the solid obtained on cooling to room temperature was filtered off, dried and crystallized from DMF/H_2O to give compound **12** in yield of 78 %, m.p. 148-150 °C; IR (KBr, ν_{max}, cm^{-1}): 3245 (NH), 1665 (CO); ^{1}H NMR (DMSO-d_6) δ: 2.23 (s, 3H, CH_3), 6.29, 7.55 (2d, 2H, furan), 7.81 (s, 1H, pyrimidine), 10.37 (s, 1H, NH exchangeable with D_2O); MS *m/z* (%): 260 (M^+). Anal. Calcd. For $C_{11}H_8N_4O_2S$ (260.27): Calcd. C 50.76, H 3.10, N, 21.53; found C 50.62, H 3.01, N 21.38.

2-Amino-4,5-dihydro-4-(5-methylfuran-2-yl)-5-oxo-1*H*-indeno[1,2-b]pyridine-3-carbonitrile (13): Equimolar amounts of compound **1**, 1,3-indanedione and ammonium acetate (10 mmol) in absolute ethanol (50 mL) were heated under reflux for 6 h. After cooling, the solvent was concentrated under reduced pressure and the obtained residue was filtered, dried and crystallized from AcOH to give the title compound **13** in 61 % yield, m.p. 140 °C; IR (KBr, ν_{max}, cm^{-1}): 3490 (NH_2), 3315 (NH), 2219 (CN), 1698 (CO); ^{1}H NMR (DMSO-d_6) δ: 2.27 (s, 3H, CH_3), 4.73 (s, 2H, NH_2), 6.11 (s, 1H, CH), 6.26 (1d, 1H, furan), 7.22-751 (m, 4H, Ar), 7.59 (1d, 1H, furan), 9.67 (s, 1H, NH exchangeable with D_2O); MS *m/z* (%): 303 (M^+). Anal. Calcd. For $C_{18}H_{13}N_3O_2$ (303.31): Calcd. C 71.28, H 4.32, N, 13.85; found C 71.14, H 4.23, N 13.57.

RESULTS AND DISCUSSION

The synthetic route to the target compounds **2-13** is depicted in **Scheme-I**. Synthesis of the target compounds was carried out by refluxing the starting material 2-[(5-methylfuran-2-yl)methylene]malononitrile (**1**) with thioglycolic acid in a molar ratio of 1:1 in ethanol in the presence of a catalytic amount of piperidine gave 5-amino-3,8a-dihydro-7-(5-methylfuran-2-yl)-3-oxo-2*H*-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (**2**). Reaction of compound **2** with ethylacetoacetate in dry benzene yielded (2*E*)-ethyl-3-(6,8-dicyano-3,8a-dihydro-7-(5-methylfuran-2-yl)-3-oxo-2*H*-thiazolo[3,2-a]pyridin-5-ylamino)but-2- enoate (**3**). Condensation of compound **2** with different aromatic aldehydes namely, benzaldehyde, *p*-chloro benzaldehyde, anisaldehyde, *p*-N,N-dimethylamino benzaldehyde, 3,4-dimethoxy benzaldehyde and 3,4,5-trimethoxy benzaldehyde gave (2*E*)-5-amino-2-substituted benzylidene-3,8a-dihydro-7-(5-methylfuran-2-yl)-3-oxo-2*H* thiazolo[3,2-a]pyri-dine-6,8-dicarbonitrile **4a-f**.

On the other hand, treatment of compound **1** with thioglycolic acid in a molar ratio of 2:1 in ethanol in the presence of a catalytic amount of piperidine gave thiazolo[3,2-a]pyridine-6,8-dicarbonitrile derivative (**5**). Cyclization of compound **5** to the pyridopyrimidine derivatives **6** and **7** occurred on reaction with a mixture of hydrochloric acid/acetic acid and formic acid, respectively. When compound **5** was treated with ethylacetoacetate in dry benzene, it afforded (2*E*)-ethyl-3-((3*E*)-6,8-dicyano-3,8a-dihydro-7-(5-methylfuran-2-yl)-2-((5-methylfuran-2-yl) methylene)-3-oxo-2*H*-thiazolo-[3,2-a]pyridin-5ylamino)but-2-enoate (**8**) (**Scheme-I**). Furthermore, the starting material 2-[(5-methylfuran-2-yl)methylene]-malononitrile (**1**) can reacted with thiourea in ethanol in presence



Scheme-I: Synthetic route to compound **2-8**

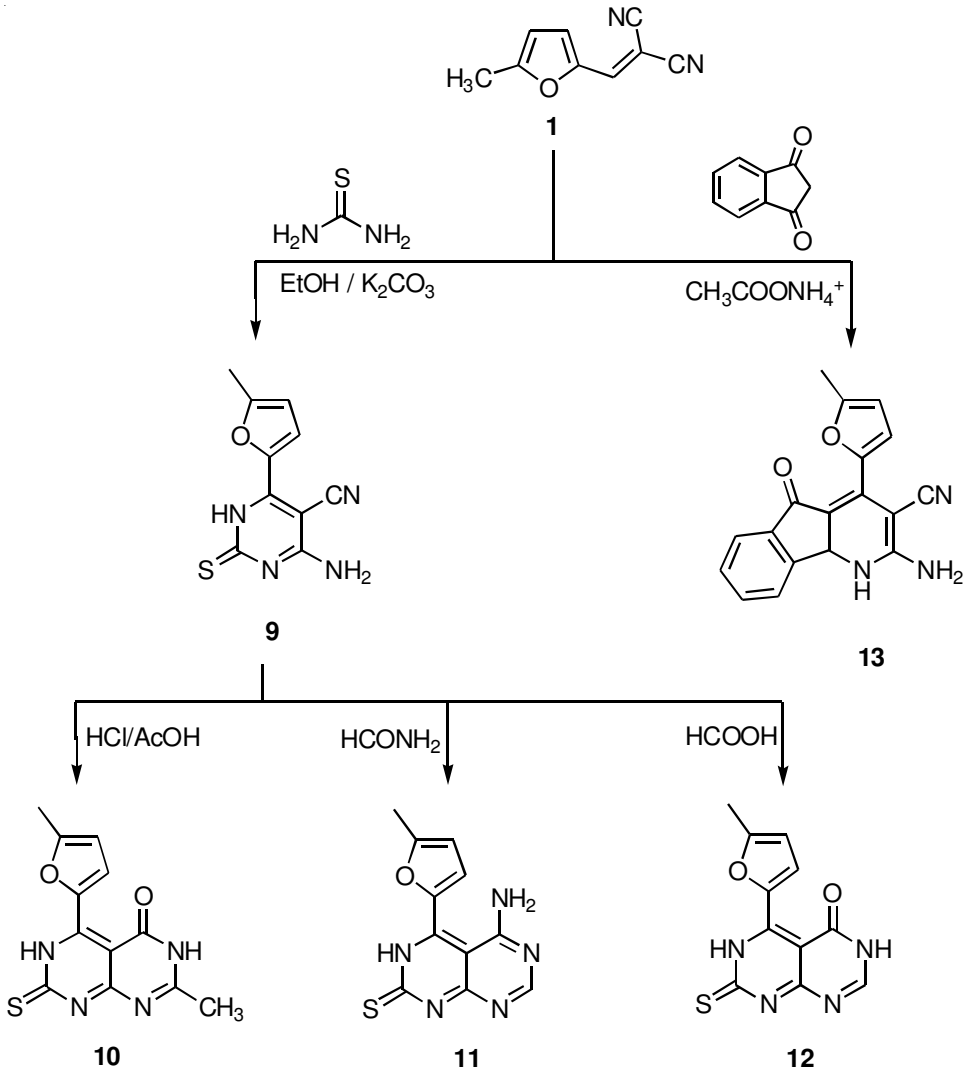
of anhydrous potassium carbonate to afford 2-thioxo-pyrimidine derivatives **9**. The latter compound **9** can be reacted with HCl/AcOH mixture, formamide and formic acid at reflux temperature to give thioxopyrimido-[4,5-d]pyrimidin-4(3*H*)one derivatives **10, 11** and **12**, respectively. Meanwhile, the formation of indeno[1,2-b]pyridine-3-carbonitrile derivative **13** took place *via* the heating of compound **1** with indanedione in presence of ammonium acetate (**Scheme-II**).

ACKNOWLEDGEMENTS

The authors would like to extend their sincere appreciation to the Deanship of Scientific Research at King Saud University for its funding of this research through the Research Group project no. RGP-VPP-320.

REFERENCES

1. A. El-Gaby, G. Al-Sehemi, A. Mohamed and A. Ammar, *Phosphorus Sulfur Silicon Relat. Elem.*, **181**, 631 (2006).
2. Y. Isobe, J. Goto, S. Chiba and Y. Matsuda, *Jpn. Kokai Tokkyo Koho,* JP 08157363 [96157363] (1996); *Chem. Abstr.*, **125**, 195649y (1996).
3. J. Mullan, D. Paris and P. Bakshi, WO 2008070875 (2008); *Chem. Abstr.*, **149**, 45259 (2008).
4. S. Vadivelan, N. Sinha, J. Irudayam and P. Jagarlapudi, *J. Chem. Inf. Model.*, **47**, 1526 (2007).
5. H. Park, Y. Hwang, H. Oh, H. Kim, Y. Lee and K. Kim, *Bioorg. Med. Chem.*, **16**, 284 (2008).
6. Manhi and A. Soliman, *Bull. Fac. Pharm.*, **31**, 265 (1993); *Chem. Abstr.*, **121**, 50029 (1993).
7. G. El-Hag Ali, A. Khalil, R. Lamphon and A. El-Maghraby, *Phosphorus Sulfur Silicon Relat. Elem.*, **180**, 1909 (2005).
8. A.A. El-Maghraby, G.A.M.E.-H. Ali, A.H.A. Ahmed and M.S.A. El-Gaby, *Phosphorus Sulfur Silicon Relat. Elem.*, **177**, 293 (2002).



Scheme-II: Synthetic route to compounds **9-13**

9. J. Valenciano, E. Sanchez-Pavon, M. Cuadro, J. Vaquero and J. Alvarez-Builla, *J. Org. Chem.*, **66**, 8528 (2001).
10. I. Ungureanu, P. Klotz, A. Schoenfelder and A. Mann, *Chem. Commun.*, 958 (2001).
11. J. Tejeda, R. Reau, F. Dahan and G. Bertrand, *J. Am. Chem. Soc.*, **115**, 7880 (1993).
12. V. Nair, S. Menon, R. Sreekanth, N. Abhilash and T. Biju, *Acc. Chem. Res.*, **39**, 520 (2006).
13. V. Nair, R. Sreekanth, N. Abhilash, M. Bhadbhade and C. Gonnade, *Org. Lett.*, **4**, 3575 (2002).
14. V. Nair, R. Sreekanth, T. Biju and P. Rath, *Tetrahedron Lett.*, **44**, 729 (2003).
15. J.P. de la Cruz, T. Carrasco, G. Ortega and F.S. de la Cuesta, *Lipid*, **27**, 192 (1992).
16. S. Sanghvi, B. Larson, S. Matsumoto, D. Nord, F. Smee, C. Willis, H. Avery, K. Robins and R. Revankar, *J. Med. Chem.*, **32**, 629 (1989).
17. N. Kitamura and A. Onishi, European Patent 163599 (1984); *Chem. Abstr.*, **104**, 186439 (1984).
18. P. Raddatz and R. Bergmann, German Patent 360731 (1988); *Chem. Abstr.*, **109**, 54786 (1988).
19. S. Furuya and T. Ohtaki, European Patent 608565 (1994); *Chem. Abstr.*, **121**, 205395w (1994).
20. G. Singh, K. Yadav and K. Mishraa, *Indian J. Chem.*, **41B**, 430 (2002).
21. D. Prajapati, M. Gohain and A. Thakur, *J. Bioorg. Med. Chem. Lett.*, **16**, 3537 (2006).
22. N.J. Curtin, H.C. Barlow, K.J. Bowman, A.H. Calvert, R. Davison, B.T. Golding, B. Huang, P.J. Loughlin, D.R. Newell, P.G. Smith and R.J. Griffin, *J. Med. Chem.*, **47**, 4905 (2004).
23. X.N. Guo, L. Zhong, J.Z. Tan, J. Li, X.M. Luo, H.L. Jiang, F.J. Nan, L.P. Lin, X.W. Zhang and J. Ding, *Cancer Biol. Ther.*, **4**, 1125 (2005).
24. J. Caballero, M. Fernández, M. Saavedra and F.D. González-Nilo, *Bioorg. Med. Chem.*, **16**, 810 (2008).
25. N.C. Wolff, D.R. Veach, W.P. Tong, W.G. Bornmann, B. Clarkson and R.L. Ilaria, *Blood*, **105**, 3995 (2005).
26. C. Antczak, D.R. Veach, C.N. Ramírez, M.A. Minchenko, D. Shum, P.A. Calder, M.G. Frattini, B. Clarkson and H. Djaballah, *Bioorg. Med. Chem. Lett.*, **19**, 6872 (2009).
27. Z. Wu, R.G. Robinson, S. Fu, S.F. Barnett, D. Defeo-Jones, R.E. Jones, A.M. Kral, H.E. Huber, N.E. Kohl, G.D. Hartman and M.T. Bilodeau, *Bioorg. Med. Chem. Lett.*, **18**, 2211 (2008).
28. F. Graf, B. Mosch, L. Koehler, R. Bergmann, F. Wuest and J. Pietzsch, *Mini Rev. Med. Chem.*, **10**, 527 (2010).
29. D. Chan, H. Fu, R. Forsch, S. Queener and A. Rosowsky, *J. Med. Chem.*, **48**, 4420 (2005).
30. O. Hashimoto, M. Shinkawa, T. Torimura, T. Nakamura, K. Selvendiran, M. Sakamoto, H. Koga, T. Ueno and M. Sata, *BMC Cancer*, **6**, 292 (2006).
31. N. Khalifa, A. Abdel-Rahman, S. Abd-Elmoez, O. Fathalla and A. Abd El-Gwaad, *Res. Chem. Intermed.*, doi:10.1007/s11164-013-1347-1.