CONVENIENT SYNTHESIS OF SOME NEW PURINE ANALOGUES INCORPORATING FURAN NUCLEUS

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Sodium 3-(furan-2-yl)-3-oxoprop-1-en-1-olate was used as precursor for synthesis of some novel derivatives of various fused heterocyclic ring systems namely pyrazolo[1,5-α]pyrimidines, triazolo[1,5-α]pyrimidines, benzo[4,5]imidazo[1,2-α]pyrimidines, pyrazolo[5,1-c]triazines, 1,2,4-triazolo[4,3-c]triazines, benzo[4,5]imidazo[2,1-c]triazines. The structures of the newly synthesized compounds were established on the basis of their spectral data, elemental analyses and alternate synthetic routes wherever possible.

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Introduction

Pyrazolo[1,5-α]pyrimidines which are purine analogues proved to have wide varieties of useful pharmaceutical activities such as antitrypanosomal activity,1 antischistosomal activity,2 activity as HMG-CoA reductase inhibitors,3 COX-2 selective inhibitors,4 AMP phosphodiesterase inhibitors,5 KDR kinase inhibitors,6 selective peripheral benzodiazepine receptor ligands7 and as antianxiety agents.8 Other pharmaceutical activities, such as agents for the treatment of sleep disorders9 and as oncolgical agents10 have been reported. Also, several pyrazolotriazines and triazolotriazines, as adenine analogues, were used as antagonists, antischistosomal and antitumor agents.11-17 Such utilities have stimulated recent interest in the synthesis of these ring systems. Also, A large number of heterocyclic compounds containing pyridine rings are associated with diverse pharmacological properties such as antimicrobial,18,19 antitumor,20 anticonvulsant,21 antiviral,22 anti-HIV,23 antifungal and antimycobacterial activities.24 In continuation of our interest in the synthesis of heterocycles,15,25,26 we report herein a convenient general method for synthesis of various zoloazines namely pyrazolo[1,5-α]pyrimidines, triazolo[1,5-α]pyrimidines, benzo[4,5]imidazo[1,2-α]pyrimidines, pyrazolo[5,1-c]1,2,4-triazines, 1,2,4-triazolo[3,4-c]1,2,4-triazines, benzo[4,5]imidazo[2,1-c]1,2,4-triazines containing furan moiety.

EXPERIMENTALS

All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Nicolet Avatar 370 CSL FT-IR 8201 PC spectrophotometer. 1H & 13C NMR spectra were recorded in CDCl3 and (CD3)2SO solutions on a Varian Gemini 300 MHz and 400 MHz spectrometer and chemical shifts are expressed in δ units using TMS as an internal reference. Mass spectra were recorded on a GC-MS QP1000 EX Shimadzu. Elemental analyses were carried out at the Micro analytical Center of Cairo University. The calculation of heat of formation, ΔH, for compounds 19a and 22a was carried out by Hyper Chem. program.

Sodium 3-(furan-2-yl)-3-oxoprop-1-en-1-olate (3)

A solution of 2-acetylfurane (1) (5.25 g, 25 mmol) in ether (25 mL) was added dropwise to a mixture of sodium methoxide and ethyl formate (2) (25 mmol for each) in dry ether (50 mL) with stirring in ice-bath at 0-5 °C, for 2 h. The resulting solid collected to give 3 without crystallization.

Pyrazolo[1,5-α]pyrimidines (8a, 8b), triazolo[1,5-α]pyrimidine (14) and imidazo[1,2-α]pyrimidine (15)

General procedure

A mixture of the sodium salt of 3 (1.6 g, 10 mmol) and the appropriate heterocyclic amines 5a-d (10 mmol for each), in a solution consisting of pipidrene (2.5 mL), water (5 mL) and acetic acid (2 mL), were heated under reflux for about 10 min, acetic acid (1.5 mL) was added to the reaction mixture while boiling, then the mixture was cooled and the resulting solid was collected and recrystallized from the proper solvent to give 8a, 8b, 14 and 15, respectively.

Alternate synthetic route for 8a

Method A: A mixture of 2-acetylfurane (1) (9.5 mmole) and N,N-dimethyl-N’-(3-phenyl-1H-pyrazol-5-yl)formamidine (13) (1.06 g, 5 mmol) in ethanol (10 mL) was heated under reflux for 3 h. The resulting solid was collected and recrystallized from ethanol gave product identical in all aspects (m.p., mixed m.p. and spectra) with 8a

Method B: Equimolecular amounts of 3-(dimethylamino)-1-(furan-2-yl)prop-2-en-1-one (12) (0.82 g, 5 mmole), the appropriate heterocyclic amines 5a-d (5 mmol) in acetic acid (10 mL) containing ammonium acetate (0.32 g, 5
7-(Furan-2-yl)-2-phenylpyrazolo[1,5-a]pyrimidine (8a)

This compound was obtained as pale yellow crystals from AcOH. Yield: 79 %, m.p.: 127-30 °C. FT-IR (KBr, cm⁻¹): 3059 ν(CH), 1611 ν(C≡N), 1565 ν(C=C). ¹H NMR (300 MHz, DMSO-d₆): δ = 5.99 (s, 1H, pyrazole H-5), 6.84 (d, 1H, J = 4 Hz, furan H-4), 7.00 (d, 1H, J = 4 Hz, furan H-3), 7.42-7.39 (m, 7H, ArH's and furan H-5), 8.75 (s, 1H, pyrimidine H-4). ¹³C NMR: δ = 100.89, 102.23, 120.12, 125.90, 127.30, 128.85, 130.57, 132.68, 134.42, 144.49, 146.21, 149.98, 154.23. MS (EI, m/z (%)): 262 (M+1, 34.2 %), 261 (M⁺, 100.0 %), 244 (21.9 %), 232 (21.9 %), 207 (5.3 %), 142 (14.0 %), 130 (14.9 %), 103 (22.8 %), 92 (20.2 %), 77 (76.3 %), 76 (42.1 %), 75 (26.3 %), 64 (21.9 %). Calcd. for C₁₁H₁₉N₄O (251.28) C, 73.55; H, 4.24; N, 16.16 %.

7-(Furan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitile (8b)

This compound was obtained as white crystals from EtOH. Yield: 70 %, m.p.: 196-200 °C. FT-IR (KBr, cm⁻¹): 3059 ν(CH), 2228 ν(CN), 1632 ν(C=N), 1572 ν(C=C). ¹H NMR (300 MHz, DMSO-d₆): δ = 6.75 (d, 1H, J = 4 Hz, furan H-4), 7.10 (d, 1H, J = 4 Hz, furan H-3), 7.60 (d, 1H, ArH), 7.74 (d, 1H, J = 4 Hz, furan H-5), 8.27 (s, 1H, pyrazole H-4), 9.12 (d, 1H, J = 4 Hz, pyrimidine H-4). ¹³C NMR: δ = 102, 113, 119, 125, 133, 135, 145, 146, 153. MS (EI, m/z (%)): 210 (M⁺, 100.0 %), 181 (29.9 %), 104 (11.5 %), 94 (13.8 %), 76 (23.0 %), 65 (33.3 %). Calcd. for C₁₁H₁₉N₃O₂ (261.29) C, 62.86; H, 2.88; N, 26.66 Found: C, 63.00; H, 2.71; N, 26.75 %.

5-(Furan-2-yl)-1,2,4-triazolo[4,3-a]pyrimidine (14)

Brown crystals from EtOH. Yield: 70 %, m.p.: 181-84 °C. FT-IR (KBr, cm⁻¹): 3059 ν(CH), 1616 ν(C≡N), 1570 ν(C=C). ¹H NMR (300 MHz, DMSO-d₆): δ = 6.73 (d, 1H, J = 4 Hz, furan H-4), 7.51 (d, 1H, J = 4 Hz, furan H-3), 7.75 (d, 1H, ArH), 8.18 (d, 1H, J = 4 Hz, furan H-5), 8.57 (s, 1H, pyrazole H-4), 8.82 (d, 1H, J = 4 Hz, pyrimidine H-4). ¹³C NMR: δ = 111, 123, 131, 145, 146, 145, 152, 159. MS (EI, m/z (%)): 186 (M⁺, 33.3 %), 130 (60.0 %), 53 (50.0 %), 64 (40.0 %), 62 (35.3 %). Calcd. for C₁₀H₇N₅O (186.17) C, 58.06; H, 3.25; N, 30.09 Found: C, 58.18; H, 3.34; N, 29.85 %.}

7-(Furan-2-yl)-7-phenylpyrazolo[1,2,4-triazole-8-carbonitrile (22b)

This compound was obtained as yellowish brown crystals from AcOH. Yield: 80 %, m.p.: > 300 °C. FT-IR (KBr, cm⁻¹): 3059 ν(CH), 1638 ν(C≡N), 1569 ν(C=C). ¹H NMR (300 MHz, DMSO-d₆): δ = 6.75 (d, 1H, J = 4 Hz, furan H-4), 7.45-7.62 (m, 4H, ArHs, and pyrazole H-4), 7.74 (d, 1H, J = 4 Hz, furan H-3), 7.90-7.93 (m, 2H, ArHs), 8.10 (d, 1H, J = 4 Hz, furan H-5), 9.20 (s, 1H, ArH). ¹³C NMR: δ = 102.23, 114.89, 121.19, 124.21, 125.96, 127.40, 128.53, 129.88, 133.44, 144.98, 146.67, 154.58, 154.67. MS (EI, m/z %): 186 (M⁺, 38.4 %), 130 (50.7 %), 93 (26.5 %), 77 (24.1 %). Calcd. for C₁₄H₁₄N₃O₂ (262.27) C, 68.69; H, 3.84; N, 21.36 Found: C, 68.74; H, 4.00; N, 21.52 %.

5- (Furan-2-yl)-[1,2,4]triazolo[4,3-a]pyrimidine (15)

Dark brown crystals from AcOH. Yield: 75 %, m.p.: > 300 °C. FT-IR (KBr, cm⁻¹): 3059 ν(CH), 1635 ν(C≡N), 1569 ν(C=C). ¹H NMR (300 MHz, DMSO-d₆): δ = 6.75 (d, 1H, J = 4 Hz, furan H-4), 7.10 (d, 1H, J = 4 Hz, furan H-3), 7.60 (d, 1H, ArH) 7.74 (d, 1H, J = 4 Hz, furan H-5), 8.27 (m, 4H, ArHs), 9.12 (d, 1H, J = 4 Hz, pyrimidine H-4). ¹³C NMR: δ = 109, 111, 113, 115, 121, 123, 126, 129, 131, 140, 144, 146, 157, 159. MS (EI, m/z %): 235 (M⁺, 13.2 %), 234 (M⁻, 21.1 %), 148 (26.3 %), 133 (26.3 %), 112 (34.2 %), 100 (23.7 %), 95 (73.7 %), 84 (36.8 %).

4-Furan-2-yl-benzo[4,5]-imidazo[1,2-a]pyrimidine (17)

A solution of 1,2,4-triazole-3-diazonium nitrate (16c) (5 mmol) (which is prepared from 3-amino-1,2,4-triazole and sodium nitrite in nitric acid at 0-5 °C), was added to a mixture of the appropriate 3 or 12 (5 mmol for each) and sodium acetate (0.41 gm, 5mmole) in ethanol (40 mL) at 0-5 °C, while stirring for 30 min. The reaction mixture was stirred for 3 h. The resulting solid was collected and recrystallized from the proper solvent to give 22a and 22b, respectively.

A solution of benzimidazol-2-diazonium sulphate (16d) (5 mmol) (which is prepared from 2-aminobenzimidazole and sodium nitrite in sulphuric acid at 0-5 °C), was added dropwise to a mixture of the appropriate arenediazonium chloride (5 mmole), was refluxed for 4 h. The resulting solid, so formed, after cooling was recrystallized from the proper solvent to give the corresponding redish brown crystals. Yield 96 %, m.p.: 156-58 °C. FT-IR (KBr, cm-1): 3111 ν(NH), 3058 ν(CH), 1651 ν(C=N), 1652 ν(C=O). 1H NMR (300 MHz, CDCl3): δ = 8.68 (d, 1H, J = 4 Hz, furan H-4), 7.32 (m, 2H, ArH's), 7.75 (m, 1H, ArH), 7.80 (d, 1H, J = 4 Hz, furan H-5), 8.01 (d, 1H, J = 8Hz ArH), 8.70 (d, 1H, J = 8 Hz, ArH), 9.62 (s, 1H, triazine H-6). MS (EI, m/z (%)): 236 (M+, 23.6 %), 181 (4.26 %), 95 (100.0 %), 66 (10.66 %); Calcd. for C13H10N2O3 (242.23) C, 64.46; H, 4.16; N, 16.90 %. Found: C, 65.81; H, 4.72; N, 16.00 %.

2-(2-Arylhydrazono)-3-(furan-2-yl)-3-oxopropanal 26a-d

The appropriate of benzenediazonium chloride (25a), 4-methylbenzenediazonium chloride (25b), 4-nitrobenzenediazonium chloride (25c) or 2,4-dinitrobenzenediazonium chloride (25d) (5 mmole) was added drop wise with continuous cooling and stirring to a solution of the sodium salt of 1-(furan-2-yl)-3-hydroxyprop-2-en-1-one (3) or 3-(dimethylamino)-1-(furan-2-yl)prop-2-en-1-one (11) (5 mmole), in ethanol (15 mL) at 0-5 °C. Sodium acetate was used as a buffer. The reaction mixture was stirred for another 3 h. Then, it was kept in a refrigerator overnight; the resulting solid was collected, washed with water and recrystallized from the proper solvent to give the corresponding 26a-d, respectively.

2-(2-Phenylhydrazono)-3-(furan-2-yl)-3-oxopropanal (26a)

This compound was obtained as yellow crystals from EtOH, Yield: 93 %, m.p.: 140-42 °C. FT-IR (KBr, cm-1): 3125 ν(NH), 3058 ν(CH), 1667 ν(CO), 1615 ν(C=N). 1H NMR (300 MHz, CDCl3): δ = 6.83 (d, 1H, J = 4 Hz, furan H-4), 7.25-7.73 (m, 6H, ArH's and furans protons), 7.74 (d, 1H, J = 4 Hz, furan H-3), 7.09-8.94 (m, 5H, ArH's and furans protons), 9.93 (s, 1H, CHO), 14.08 (s, br., 1H, NH). 13C NMR: δ = 120.50, 117.24, 123.82, 128.39, 145.24, 146.38, 147.58, 149.21, 152.22, 179.88, 192.54. MS (EI, m/z (%)): 286 (M-1, 30.0 %), 258 (M-2, 100.0 %), 260 (50.0 %), 177 (25.0 %), 176 (45.0 %), 165 (65.0 %), 137 (70.0 %), 122 (45.0 %), 108 (65 %), 91 (80.0 %), 77 (55 %), 76 (60.0 %), 75 (65.0 %), 64 (40 %), 62 (80 %). Calcd. for C13H11N3O5 (287.23) C, 54.36; H, 3.16; N, 14.63 Found: C, 54.57; H, 3.30; N, 14.48 %.

2-(2,4-Dinitrophenylhydrazono)-3-(furan-2-yl)-3-oxopropanal (26d)

This compound was obtained as yellow brown crystals from AcOH, Yield: 96 %, m.p.: 207-209 °C. FT-IR (KBr, cm-1): 3111 ν(NH), 3058 ν(CH), 1651 ν(C=N), 1625 ν(C=O). 1H NMR (300 MHz, CDCl3): δ = 6.83 (d, 1H, J = 4 Hz, furan H-4), 7.25-7.73 (m, 5H, ArH's and furans protons), 7.74 (d, 1H, J = 4 Hz, furan H-3), 9.93 (s, 1H, CHO), 14.08 (s, br., 1H, NH). 13C NMR: δ = 112.50, 117.24, 123.82, 128.39, 145.24, 146.38, 147.58, 149.21, 152.22, 179.88, 192.54. MS (EI, m/z (%)): 286 (M-1, 30.0 %), 258 (M-2, 100.0 %), 177 (25.0 %), 176 (45.0 %), 165 (65.0 %), 137 (70.0 %), 122 (45.0 %), 108 (65 %), 91 (80.0 %), 77 (55 %), 76 (60.0 %), 75 (65.0 %), 64 (40 %), 62 (80 %). Calcd. for C13H11N3O5 (287.23) C, 54.36; H, 3.16; N, 14.63 Found: C, 54.57; H, 3.30; N, 14.48 %.
This document appears to be a research paper discussing the synthesis and properties of new purine analogues containing furan nuclei. The text includes detailed descriptions of the chemical reactions used to prepare these compounds, along with their spectral data and physical properties. The text is rich with chemical equations, spectral data (NMR, IR), and analytical data (mass spectrometry and elemental analysis). The paper covers a range of compounds, each described in a similar format, indicating a systematic approach to the synthesis and characterization of these furan-containing purine analogues.
3-(Furan-2-yl)-1H-pyrazole (28a)

This compound was obtained as white crystals from water, Yield: 51 %, m.p.: 101-103 °C. FT-IR (KBr, cm⁻¹): 3149 (v(NH), 3033 ν(CH), 1634 ν(C=C), 1165 ν(C=C). ¹H NMR (300 MHz, CDCl₃): δ = 6.49 (d, 1H, J = 4 Hz), 6.61 (d, 1H, J = 4Hz), 6.69 (d, 1H, J = 4 Hz, furan-H), 4.12 (q, 2H, J = 7.5 Hz), 2.12 (s, 3H, CH₃), 1.33 (t, 3H, J = 7.5 Hz), 2.72 (s, 3H, CH₃), 4.22 (q, 2H, J = 7.5 Hz, CH₂), 6.49 (d, 1H, J = 4 Hz, furan-H-4), 6.51 (d, 1H, J = 4Hz, furan-H-3), 6.69 (d, 1H, J = 4 Hz, furan-H), 7.96 (d, 1H, J = 4Hz), 6.51 (d, 1H, J = 4Hz, furan-H-3), 6.69 (d, 1H, J = 4 Hz, furan-H-4), 6.51 (d, 1H, J = 4Hz, furan-H-3), 6.69 (d, 1H, J = 4 Hz, furan-H-5), 7.63-8.00 (m, 2H, ArH's), 7.26 (d, 1H, J = 4 Hz), 7.29-7.85 (m, 4H, ArH's), 7.48 (d, 1H, J = 4 Hz, furan H-5), 7.54 (d, 1H, J = 4 Hz, furan H-4). MS (EI, m/z (%)): 231 (M +, 2.6 %), 186 (50 %), 65 (25 %), 61 (18 %), 59 (14 %).

6-(Furan-2-yl)-2-methylpyridine-3-carboxylic acid (29)

A mixture of ethyl 6-(furan-2-yl)-2-methylpyridine-3-carboxylate (29) (1.15 g, 5 mmol) and hydrazine hydrate (1 mL) in ethanol (10 mL) were boiled under reflux for 4 h. The resulting solid, was cooled and recrystallized to give 31 as dark brown crystals from AcOH, Yield: 97 %, m.p.: > 300 °C. FT-IR (KBr, cm⁻¹): 3429, 3317 ν(NH, NH₂), 3064, 2982 ν(CH), 1715 ν(CO), 1635 ν(C=C), 1583 ν(C=C). ¹H NMR (300 MHz, CDCl₃): δ = 2.52 (s, 3H, CH₃), 6.49 (d, 1H, J = 4 Hz, furan-H-4), 6.51 (d, 1H, J = 4Hz, furan-H-3), 6.69 (d, 1H, J = 4 Hz, furan-H-5), 7.63-8.00 (m, 2H, ArH's), 9.75 (s, br., 3H, NH₂, NH). Calcd. for C₁₁H₁₉N₄O₂ (277.27) C, 57.00; H, 8.00; N, 28.36; 26.9 %.

Ethyl 6-(furan-2-yl)-2-methylpyridine-3-carboxylate (29) and 1-(6-(furan-2-yl)-2-methylpyridin-3-yl)-3-phenylurea (33a)

General procedure: Equimolecular amounts of 3- (dimethylamino)-1-(furan-2-yl)prop-2-en-1-one (11) and ethyl acetoacetate or acetylacetone (5 mmol, each) in acetic acid (10 mL) and ammonium acetate (5 mmol) were boiled under reflux for 4 h. The resulting solid, was collected and recrystallized from the proper solvent to give 32 and 33, respectively.

Ethyl 6-(furan-2-yl)-2-methylpyridine-3-carboxylate (29)

This compound was obtained as dark brown crystals from benzene, Yield: 77 %, m.p.: 78-81 °C. FT-IR (KBr, cm⁻¹): 3058, 2929 ν(CH), 1715 ν(CO, ester),1646 ν(C≡N), 1582 ν(C=C). ¹H NMR (300 MHz, CDCl₃): δ = 1.33 (t, 3H, J = 7.5 Hz, CH₂CH₃), 2.72 (s, 3H, CH₃), 4.22 (q, 2H, J = 7.5 Hz, CH₂), 6.49 (d, 1H, J = 4 Hz, furan-H-4), 6.51 (d, 1H, J = 4Hz, furan-H-3), 6.69 (d, 1H, J = 4 Hz, furan-H), 7.96 (d, 2H, J = 4 Hz, ArH's), 1592 (C=O). ¹H NMR (300 MHz, CDCl₃): δ = 2.52 (s, 3H, CH₃), 6.49 (d, 1H, J = 4 Hz, furan-H-4), 6.51 (d, 1H, J = 4Hz, furan-H-3), 6.69 (d, 1H, J = 4 Hz, furan-H), 7.54 (d, 1H, J = 8 Hz, ArH), 7.89 (d, 1H, J = 8 Hz, ArH). MS (EI, m/z (%)): 202 (M+1, 50 %), 186 (50 %), 65 (25 %), 61 (18 %), 59 (14 %), 57 (10 %), 55 (45 %), 50 (25 %). Calcd. for C₁₁H₁₉N₄O₂ (277.27) C, 57.00; H, 8.00; N, 28.36; 26.9 %.

Synthesis of new purine analogous containing furan nucleus

Section A-Research paper


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203 (22.41 %), 186 (100.0 %), 158 (23.33 %), 130 (16.81 %), 107 (37.07 %), 103 (40.36 %), 94 (11.84 %), 91 (19.42 %), 77 (29.39 %), 60 (26.39 %). Calcd. for C17H13N5O6 (383.32) C, 53.27; H, 3.42; N, 18.27 %.

1-(6-(Furan-2-yl)-2-methylpyridin-3-yl)-3-p-tolyurea (33b)

This compound was obtained as dark brown crystals from DMF. Yield: 91 %, m.p.: > 300 °C. FT-IR (KBr, cm⁻¹): 3365 ν(CH), 1704 ν(CO), 1600 ν(C=C). ¹H NMR (300 MHz, CDCl₃): δ = 2.12 (s, 3H, CH₃), 2.35 (s, 3H, CH₃), 6.49 (d, 1H, J = 4 Hz, furan H-4), 6.51 (d, 1H, J = 4Hz, furan H-5), 6.13-7.17 (m, 3H, ArH's), 7.26 (d, 1H, J = 4 Hz), 7.29-7.85 (m, 3H, ArH's), 8.49 (s, br., 2H, NH). Calcd. for C17H15N3O2 (293.32) C, 70.45; H, 5.15; N, 13.85 %.

1-(6-(Furan-2-yl)-2-methylpyridin-3-yl)-3-(4-nitrophenoxy)urea (33c)

This compound was obtained as deep red crystals from AcOH. Yield: 82 %, m.p.: > 300 °C. FT-IR (KBr, cm⁻¹): 3365 ν(NH), 3058 ν(CH), 1708 ν(CO), 1615 ν(C=N), 1562, 1370 ν(NO₂). ¹H NMR (300 MHz, CDCl₃): δ = 2.12 (s, 3H, CH₃), 6.49 (d, 1H, J = 4 Hz, furan H-4), 6.51 (d, 1H, J = 4Hz, furan H-5), 7.21-7.28 (m, 5H, ArH's and furan H-5), 7.92 (d, 1H, J = 8 Hz, ArH), 8. (d, 1H, J = 8 Hz, ArH), 9.13 (s, br., 2H, NH). Calcd. for C₁₇H₁₄N₄O₄ (338.32) C, 60.35; H, 7.92 (d, 1H, J = 8 Hz, furan H-4), 6.51 (d, 1H, J = 4Hz, furan H-5), 6.39-7.35 (m, 6H, ArH's and furan H-5), 7.92 (d, 1H, J = 8 Hz, ArH), 9.56 (s, br., 1H, NH). MS (EI, m/z (%)): 339 (M⁺, 62.2 %), 247 (100.0 %), 158 (19.6 %), 152 (24.5 %), 131 (14.0 %), 130 (23.2 %), 118 (18.1 %), 109 (6.7 %), 93 (14.2 %), 77 (30.3 %), 67 (21.3 %), 51 (8.3 %). Calcd. for C₁₇H₁₄N₄O₄ (339.3) C, 60.18; H, 3.86; N, 12.38 Found: C, 60.25; H, 4.00; N, 12.45 %.

2,4,6-trinitrophenyl 6-(furan-2-yl)-2-methylpyridin-3-ylocarbamate (34c)

This compound was obtained as yellowish brown crystals from AcOH. Yield: 83 %, m.p.: > 300 °C. FT-IR (KBr, cm⁻¹): 3438 ν(NH), 3090 ν(CH), 1716 ν(CO), 1612 ν(C=N), 1561, 1384 ν(NO₂). ¹H NMR (300 MHz, CDCl₃): δ = 2.12 (s, 3H, CH₃), 6.49 (d, 1H, J = 4 Hz, furan H-4), 6.51 (d, 1H, J = 4Hz, furan H-5), 7.20 (d, 1H, J = 4Hz, furan H-5), 6.39 (d, 1H, J = 8 Hz, ArH), 7.92 (d, 1H, J = 8 Hz, ArH), 9.15 (s, 2H, ArH's), 9.56 (s, br., 1H, NH). MS (EI, m/z (%)): 429 (M⁺, 12.5 %), 389 (86.7 %), 134 (13.4 %), 127 (10.1 %), 121 (100.0 %). Calcd. for C₁₇H₁₂N₂O₃ (429.3) C, 47.56; H, 2.58; N, 16.31 Found: C, 47.67; H, 2.62; N, 16.55 %.

Ethylen 2-amino-6-(furan-2-yl)pyridine-3-carboxylate (35)

A mixture of 3-(dimethylamino)-1-(furan-2-yl)prop-2-en-one (11) (0.83, 5 mmol), ethyl cyanoacetate (0.56 g, 5 mmol) and ammonium acetate (0.35 g 5 mmol) in acetic acid (10 mL) was refluxed for 4 h. The solid resulting after cooling was collected and recrystallized from acetic acid to give 35 as white crystals from AcOH. Yield: 69 %, m.p.: 333-36 °C. FT-IR (KBr, cm⁻¹): 3378 ν(NH), 3058 ν(CH), 1694 ν(CO), 1644 ν(C=C), 1562 ν(C=C). ¹H NMR (300 MHz, CDCl₃): δ = 1.27 (t, 3H, J = 7.5 Hz, CH₂CH₃), 2.12 (q, 2H, J = 7.5 Hz, CH₂CH₃), 6.49 (d, 1H, J = 4 Hz, furan H-4), 6.51 (d, 1H, J = 4Hz, furan H-5), 7.20 (d, 1H, J = 4Hz, furan H-5), 7.25 (d, 1H, J = 8Hz, ArH), 7.92 (d, 1H, J = 8 Hz, ArH), 12.58 (s, br., 1H, NH). MS (EI, m/z (%)): 232 (M⁺, 5.9 %), 203 (64.4 %), 189 (13.9 %), 187 (28.9 %), 160 (13.9 %), 132 (12.8 %), 105 (25 %), 77 (23.3 %), 65 (12.8 %). Calcd. for C₁₇H₁₂N₂O₃ (232.24) C, 62.06; H, 5.21; N, 12.06 Found: C, 61.92; H, 4.95; N, 9.68 %.
(2-Amino-6-(furan-2-yl)pyridin-3-yl)(phenyl)methanone (36)

A mixture of 3-(dimethylamino)-1-(furan-2-yl)prop-2-en-1-one (11) (0.85, 5 mmol), benzoylecyanonitrile (0.74 g, 5 mmol) and ammonium acetate (0.35 g 5 mmol) in acetic acid (10 mL) was refluxed for 4 h. The solid resulting on cooling was collected and recrystallized from diluted acetic acid to give 36 as pale brown crystals from AcOH. Yields: 80 %, m.p.: 210-14 °C. FT-IR (KBr, cm⁻¹): 3370, 3167 ν(C=O), 3058 ν(CH), 1648 ν(CO, conjugated), 1615 ν(C≡N), 1571 ν(C=C). ¹H NMR (300 MHz, CDCl₃): δ = 6.49 (d, 1H, J = 4 Hz, furan H-4), 6.51 (d, 1H, J = 4Hz, furan H-3), 7.20 (d, 1H, NH₂), 7.61-7.85 (m, 7H, ArH’s), 9.85 (s, br., 2H, NH₂) MS (EI, m/z (%)): 264 (M⁺, 73.1 %), 256 (100.0 %), 248 (42.3 %), 218 (26.9 %), 185 (42.3 %), 161 (26.9 %), 105 (19.2 %), 77 (88.2 %), 66 (42.3 %) Calcd. for C₁₆H₁₂N₂O₂ (264.28) C, 72.72; H, 4.58; N, 10.84 %.

Results and Discussion

Treatment of sodium 3-(furan-2-yl)-3-oxoprop-1-en-1-olate (3) with sodium methoxide gave 4-(furan-2-yl)-7-(furan-2-yl)-1,2,4-triazolo-[1,5-a]pyrimidine (8a) in good yield (Scheme 1).

Scheme 1. Synthesis of 7-(furan-2-yl)-2-phenylpyrazolo[1,5-a]pyrimidine (8a)
Scheme 2. Synthesis of pyrazolo[1,5-a]pyrimidine (8b), 1,2,4-triazolo[1,5-a]pyrimidine (14) and benzo[4,5]imidazo[1,2-a]pyrimidine (15).

For example, its infrared spectrum revealed no bands between in the region 1650-2000 cm⁻¹ due to the absence of any carbonyl group. Its mass spectrum showed m/z = 262. On the basis of these results, the structure 19 was ruled out.

The formation of 22a seems to occur via coupling of diazonium chloride 16a with 3 to form the intermediate 20 which then cyclized to give intermediate 21, which in turn undergoes elimination of formic acid to give 22a as the end product. Also, the formation of 22a rather than 19a is also evidenced by our finding that the calculated heat of formation of 22a (ΔH = 170.581 kcal mol⁻¹) is higher than of 19a (ΔH = 145.961 kcal mol⁻¹).

Reaction of 3-(dimethylamino)-1-(furan-2-yl)prop-2-en-1-one (12) with 16a in ethanolic sodium acetate solution gave a product identical in all aspects (m.p., mixed m.p. and spectra) with 22a isolated above from the reaction of 16a with 3 (Scheme 3).

Analogously, coupling of the diazotized 5-amino-4-cyanopyrazole (16b), 3-amino-1,2,4-triazole (16c) and 2-aminobenzimidazole (16d) with the appropriate 3 or 12 in ethanolic sodium acetate afforded 4-(furan-2-yl)pyrazolo[5,1-c]1,2,4-triazine-8-carbonitrile (22b), 4-(furan-2-yl)-1,2,4-triazolo[5,1-c]1,2,4-triazine (24) and 4-furan-2-yl-benzo[4,5]imidazo[2,1-c]1,2,4-triazine (25), respectively (cf. Scheme 3).

Scheme 3. Synthesis of 4-(furan-2-yl)pyrazolo[5,1-c]1,2,3-triazine-8-carbonitrile (21b), 4-(furan-2-yl)-1,2,4-triazolo[5,1-c]1,2,4-triazine (24) and 4-furan-2-yl-benzo[4,5]imidazo[2,1-c]1,2,4-triazine (25).
Reactions of 3 or 11 with benzenediazonium chloride (25a) in ethanol containing sodium acetate as a buffer solution yielded 2-(2-phenylhydrazono)-3-(furan-2-yl)-3-oxopropanal (26a) (Scheme 4). Structure of 26a was confirmed by elemental analysis, spectral data and chemical transformations. \(^1\)H-NMR spectrum of 26a showed signal at \(\delta = 6.61\) (d, 1H, furan-H-4), 7.25-7.73 (m, 6H, ArH's and furans protons), 7.74 (d, 1H, furan-H-3), 6.69 (d, 1H, Furan H-5), 7.96 (s, 2H, ArH's and furans protons), 7.25-7.73 (m, 6H, ArH's and furans protons), 7.74 (d, 1H, furan-H-3), 6.69 (d, 1H, Furan H-5), 7.96 (s, 2H, ArH's and furans protons). Compound 26a was refluxed with hydrazine hydrate in ethanol to give 1-(3-(furan-2-yl)-4H-pyrazol-4-ylidene)-2-phenylhydrazine (27a). Further, compound 11 reacts with hydrazine hydrate to give 3-(furan-2-yl)-1H-pyrazole (28). The compound 28 reacted with benzenediazonium chloride in ethanolic sodium acetate solution to afford a product identical in all aspect (m.p., mixed m.p. and spectra) with 27a which was prepared as described in Scheme 4. Similarly, treatment of the appropriate arylenaadiazonium chlorides (25b-d) with 3 or 11 in cold ethanolic sodium acetate solution gave the corresponding (26b-f) respectively.

Reaction of 3-(dimethylamino)-1-(furan-2-yl)prop-2-en-1-one (11) with ethyl acetoacetate or acetylacetone in boiling acetic acid containing ammonium acetate under reflux gave ethyl 6-(furan-2-yl)-2-methylpyridine-3-carboxylate (29) and 1-(6-(furan-2-yl)-2-methylpyridin-3-yl)methanone (30), respectively (Scheme 5). Structures of (29) and (30) were confirmed by elemental analysis, spectral data and chemical transformation. \(^1\)H-NMR spectrum of 29 showed signals at \(\delta = 1.33\) (t, 3H, CH\(_2\)CH\(_3\)), 2.72 (s, 3H, CH\(_3\)), 4.22 (q, 2H, \(J = 7.5\) Hz, CH\(_2\)CH\(_3\)), 6.49 (d, 1H, furan-H-4), 6.51 (d, 1H, furan-H-5), 7.96 (s, 2H, ArH's). Thus, treatment of compound (29) with hydrazine hydrate gave 6-(furan-2-yl)-2-methylpyridine-3-carboxyhydrazide (31), which is converted to azido(6-(furan-2-yl)-2-methylpyridin-3-yl)methanone (32) by aqueous sodium nitrite in hydrochloric acid (6 M) in an ice-bath.

Structure of 32 was confirmed by elemental analysis, spectral data and chemical transformation. Further, compound 32 reacted separately with the appropriate aromatic amines (aniline, p-toluidine, 4-nitroaniline, 2,4-dinitroaniline) in dry dioxan or with phenols (phenol, 4-nitrophenol, 2,4,6-trinitrophenol) in dry benzene to afford substituted urea (33a-d) and aryl carbamates (34a-c) respectively.

Finally, treatment of the enaminoine 11 separately with ethyl cyanoacetate and benzoylacetonitrile gave ethyl 2-amino-6-(furan-2-yl)pyridine-3-carboxylate (35) and 2-amino-6-(furan-2-yl)pyridin-3-yl)(phenyl)methanone (36), respectively (Scheme 5).

In conclusion, compounds of type 3 and 12 proved to be useful precursors for synthesis of various fused heterocycles via their reactions with 5-aminopyrazoles, 3-aminotriazoles, 2-aminobenzimidazole and diazotized heterocyclic amines. The structures of the newly synthesized compounds were confirmed by spectral data, alternate synthesis and elemental analyses.

References


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Scheme 4. Synthesis of hydrazones (26) and pyrazoles (27) and (28)

Scheme 5. Synthesis of hydrazides (31), azides (32), urea derivatives (33 a-d), aryl carbamates (34) and pyridines (35 and 36).

Conclusion

In conclusion, compounds of type 3 and 12 proved to be useful precursors for synthesis of various fused heterocycles via their reactions with 5-aminopyrazoles, 3-aminotriazoles, 2-aminobenzimidazole and diazotized heterocyclic amines. The structures of the newly synthesized compounds were confirmed by spectral data, alternate synthesis and elemental analyses.
Synthesis of new purine analogous containing furan nucleus

Section A - Research paper


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