Journal of Saudi Chemical Society (2017) **21**, 495–503

King Saud University

Journal of Saudi Chemical Society

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Synthesis and biological evaluation of fluorine substituted pyrazolo[4,3-e][1,2,4]triazines as purine analogues

Reda M. Abdel-Rahman *, **Rihab F. Angawi, Aisha R. Al-Mehmadi**

Department of Chemistry, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia

Received 18 September 2016; revised 21 November 2016; accepted 21 November 2016
Available online 2 December 2016

KEYWORDS

4-Aminoantipyrine;
Purine analogues;
Fluorinated pyrazolotriazines;
Cellobaise activity

Abstract Some more new fluorine substituted pyrazolo[4,3-e][1,2,4]triazine derivatives **(2–5)**, **7**, **10**, **14**, **17** have been synthesized derived from hydrazinolysis of N-acyl/aroyl/dithioic formamido-2,3-dimethyl-1-phenyl-pyrazolo-5-ones which are obtained from 4-aminoantipyrine **1**. The enzymatic assays (cellobaise activity) of the new products have been evaluated.

1. Introduction

4-Aminoantipyrine is one of the most important biological active [1–3] classes of heterocyclic nitrogen systems as anti-inflammatory, antipyretic, analgesic, antimicrobial agents [4]. Also 1,2,4-triazine derivatives received a significant attention in the biological and pharmacological fields [5,6]. On the other hand, pyrazolotriazines were found to inhibit some enzymes of purine metabolism like xanthine oxidase or bacterial purine-nucleoside phosphorylase with inhibition constant values ranging from 10^{-3} to 10^{-5} M [7].

It is known that, introduction of fluorine atoms to a type of heterocyclic nitrogen systems, often improves their pharmacological and physical properties [8,9]. These observation promoted us to synthesize some new fluorine substituted pyrazolo[4,3-e][1,2,4]triazine derivatives as purine analogues starting from 4-N-(acyl/aroyl)-amino-antipyrines in view of their effect in cellobaise activity (enzymatic action) towards E.coli microorganism.

2. Experimental

2.1. Material and methodology

All the chemical and organic solvents used were produced by BDH company. The enzymatic study of the new products was carried out in the Department of Biochemistry, Faculty of Science, Ain Shams University, Cairo, Egypt.

Melting point was determined with an electrothermal bib by Stuart Scientific Melting Point SMPI (UK). Spectrometer Electronic absorption spectra were recorded on Shimadzu Multi Spec-1501 UV–VIS spectrophotometer. Elemental analysis was determined to be preformed in Micro Analytical Center, Cairo University, Egypt. Infra-red spectra were recorded

* Corresponding author.
E-mail addresses: rm_rahman1951@yahoo.com (R.M. Abdel-Rahman), aisha-raja@hotmail.com (A.R. Al-Mehmadi).
Peer review under responsibility of King Saud University.

ELSEVIER Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jscs.2016.11.004
1319-6103 Production and hosting by Elsevier B.V. on behalf of King Saud University.

in the region 4000–400 cm^{-1} on a Perkin Elmer spectrometer 100 FT-IR, using samples suspended in dry KBr disk. Nuclear Magnetic resonance (NMR) spectroscopy spectra were recorded at advance Dpx 600 MHz on a Bruker instrument under normal working condition using deuterated $CDCl_3$ solution with tetramethylsilane TMS as an internal reference. The mass spectra were recorded using a GCMS-Q 1000 Ex mass spectrometer.

2.2. Chemistry

2.2.1. 2,3-Dimethyl-1-phenyl-4-trifluoroacetylamido-pyrazol-5-one (2)

A mixture of compound **2** (0.01 mol) and trifluoroacetic acid (0.015 mol) in THF (100 ml) was warmed for 1 h, then cooled. The solid obtained was filtered off and crystallized from THF to give **2** as faint yellow crystals. Yield: 79%, m.p. 190–192 °C for $C_{13}H_{12}N_3F_3O_2$ (299). Anal. Calcd: C, 52.17; H, 4.01; N, 14.04; F, 19.06%. Found: C, 51.95; H, 3.95; N, 13.87; F, 18.86%. UV: 316 nm. IR: 3250 (NH); 3015, 2990 (aromatic & aliphatic CH); 1720, 1680 (2C═O); 1610 (C═N); 1235 (C─F). M/S = (m/e, Inti.%): 300 (M + 1, 1.55); 230 (18.55), 202 (5.31), 176 (4.00), 116 (100, $C_7H_8N_2$ as Me-N═N-ph).

2.2.2. 2,3-Dimethyl-1-phenyl-4H-5-trifluoromethyl-pyrazolo [4,3-e][1,2,4]triazine (3)

A mixture of compound **2** (0.01 mol) and hydrazine hydrate (0.01 mol) in absolute ethanol-THF (1:1, 100 ml) was refluxed for 4 h then cooled. The solid thus produced was filtered off and crystallized from EtOH to give **3**, as yellowish ppt, yield: 77%, m.p. 168–170 °C for $C_{13}H_{12}N_5F_3$ (295). Anal. Calcd: C, 52.88; H, 4.06; N, 23.72; F, 19.32%. Found: C, 52.38; H, 4.00; N, 23.45; F, 19.08%. UV: 296 nm. IR: 3105 (NH); 3010, 2988 (aromatic & aliphatic CH); 1610 (C═N); 1488, 1440 (deformation of CH_3); 1235 (C─F). ^{1}H NMR ($CDCl_3$) δ ppm: 9.53 (s, 1H, NH); 7.47–7.29 (m, 5H, phenyl protons); 3.09, 2.05 (each s, 3H, N-Me, 3H, C-Me). ^{13}C NMR: 150.62, 134.58, 129.54, 127.47, 125.02, 108.7, 77.07, 35.93, 23.05, 12.29.

2.2.3. 2,3-Dimethyl-1-phenyl-4-(4′-fluorobenzoyl)pyrazol-5-one (4)

Equimolar mixture of compound **1** and 4-flourobenzoyl chloride in DMF (20 ml) was warmed for 1 h, cooled then poured onto ice. The solid was produced, filtered off and crystallized from AcOH to give **4**. Yield: 81%, m.p. 188–190 °C for $C_{18}H_{16}N_3FO_2$ (325). Anal. Calcd: C, 66.46; H, 4.92; N, 12.92; F, 5.84%. Found: C, 65.78; H, 4.80; N, 12.75; F, 5.75%. UV: 304 nm. IR: 3095 (NHCO─); 1580 (CONH); 1660 (C═O); 1610 (C═C); 1490, 1435 (deformation CH_3); 1238 (C-F); 800, 780 cm^{-1} (p-substituted phenyl).

2.2.4. 2,3-Dimethyl-5-(4′-fluorophenyl)-6-(4′-chlorophenyl)-1-phenyl-pyrazolo [4,3-e][1,2,4]triazine (5)

A mixture of **4** (0.01 mol) and 4-chlorophenyl hydrazine hydrochloride (0.01 mol) in DMF (100 ml) was refluxed for 4 h, then cooled and poured onto ice. The solid obtained was filtered off and crystallized from EtOH to give **5** as orange crystals, yield: 79%, m.p. 170–172 °C for $C_{24}H_{19}N_5FCl$ (432). Anal. Calcd: C, 66.66; H, 4.39; N, 16.20; F, 4.39; Cl, 8.33%. Found: C, 65.92; H, 4.33; N, 15.98; F, 4.33; Cl, 8.12%. UV: 290 nm. IR: 3010, 2982 (aromatic & aliphatic CH); 1608, 1598 (C═N); 1488, 1445 (deformation CH_3); 1235 (C-F); 700 (C─Cl). ^{1}H NMR (DMSO) δ ppm: 8.071–7.33 (m, 13H, aryl + phenyl protons); 3.35, 2.18 (each s, 3H, N-Me, 3H, C-Me). ^{13}C NMR: 152.98, 135.08, 130.32, 130.22, 129.09, 126.23, 123.50, 115.38, 115.24, 107.52, 40.03, 35.99.

2.2.5. 2,3-Dimethyl-1-phenyl-4H-5-(pyridin-4′-yl)-pyrazolo [4,3-e][1,2,4]triazine (6)

An equimolar of compound **1** and isonicotinic acid hydrazide in absolute ethanol (100 ml) with a few drops of glacial acetic acid (1 ml) was refluxed for 4 h then cooled. The solid was thus obtained, filtered off and crystallized from EtOH to give **6** as white ppt. yield: 83%, m.p. 226–227 °C for $C_{17}H_{16}N_6$ (304). Anal. Calcd: C, 67.10; H, 5.26; N, 27.63%. Found: C, 66.63; H, 5.13; N, 27.29%. UV: 280 nm. IR: 3382 (NH); 3183, 2944 (aromatic and aliphatic CH); 1646 (C═N). ^{1}H NMR (DMSO) δ ppm: 10.84 (s, 1H, NH); 7.58–9.04 (m, 9H, Ar─H); 3.32, 2.09 (each s, 3H, N-Me, 3H, C-Me) respectively. ^{13}C NMR: 150.19, 148.70, 136.45, 133.75, 129.88, 128.62, 128.21, 126.21, 126.39, 121.42, 107.09, 77.44, 77.23, 77.02, 35.45, 11.959.

2.2.6. 2,3-Dimethyl-1-phenyl-4-trifluoroacetyl-pyrazolo[4,3-e] [1,2,4]triazine (7)

A mixture of compound **6** (0.01 mol) and trifluoroacetic acid (0.015 mol) in THF (100 ml) was refluxed for 2 h, then cooled. The solid produced was filtered off and crystallized from THF to give **7**. Yield: 85%; m.p. 200–201 °C for $C_{19}H_{15}N_6F_3O$ (400). Anal. Calcd: C, 57.00; H, 3.75; N, 21.00; F, 14.25%. Found: C, 56.71; H, 3.70; N, 20.75, F, 14.07%. UV: 295 nm. IR: 3015, 2985 (aromatic & aliphatic CH); 1685 (C═O); 1608 (C═N); 1490, 1442 (deformation of CH_3); 1235 (C-F). ^{13}C NMR: 164.45, 152.60, 150.50, 148.41, 135.23, 128.05, 123.73, 121.29, 40.02, 39.91, 39.77, 39.63, 39.40, 39.35, 39.21, 39.07, 30.66. M/S (m/e, Intr.%): 401(M + 1, 1.10), 198 (100), 147 (15.35), 120(3.01), 96 (5.51), 80 (35.80), 78(8.11).

2.2.7. Potassium 4-dithioic-formamido-2,3-dimethyl-1-phenyl-pyrazol-5-one (8)

To compound **1** (0.01 mol) in aqueous KOH (5%, 100 ml), CS_2 (0.015 mol) was added by stir at room temperature along 4 h to give **8** (as liquid).

2.2.8. N-aryl-N′-(2,3-dimethyl-1-phenyl-5-oxo-pyrazol-4-yl) thioureas (9a-c)

Equimolar mixture of compound **1** and the selection isothiocyanates in DMF (50 ml) was warmed for 1 h then cooled and poured onto ice. The solid thus obtained was frittered off and crystallized from benzene to give **9a-c**.

9a: C_6H_6; yield 85%, m.p. 198–200 °C for $C_{18}H_{18}N_4SO$ (338). Anal. Calcd: C, 63.90; H, 5.35; N, 16.56; S, 9.46%. Found: C, 63.53; H, 5.28; N, 16.34; S, 9.26%.

9b: C_6H_6; yield 90%, m.p. 188–190 °C for $C_{18}H_{17}N_4ClSO$ (373). Anal. Calcd: C, 57.90; H, 4.55; N, 15.01; Cl, 9.65; S, 8.57%. Found: C, 27.78; H, 4.49; N, 14.81; Cl, 9.52; S, 8.46%.

9c: C_6H_6; yield 83%, m.p. 150–152 °C for $C_{18}H_{17}N_4FSO$ (356). Anal. Calcd: C, 60.67; H, 4.77; N, 15.73, F, 5.33; S, 8.98%. Found: C, 59.94; H, 4.71; N, 15.35; F, 5.26; S,