

Short Note

Ethyl (1,3-diphenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5-yl)acetate

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Abstract: Novel ethyl (1,3-diphenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5-yl)acetate (**5**), was prepared *via* heating of 5-amino-1,3-diphenyl-4,5-dihydro-4-imino-1*H*-pyrazolo[3,4-*d*] pyrimidine (**1**) and diethyl malonate (**2**) under reflux. The structure of the synthesized compound was assigned on the basis of its elemental analysis, IR, ¹H-NMR and mass spectral data.

Keywords: pyrazolo[3,4-*d*]pyrimidine; pyrazolo-triazolo-pyrimidine

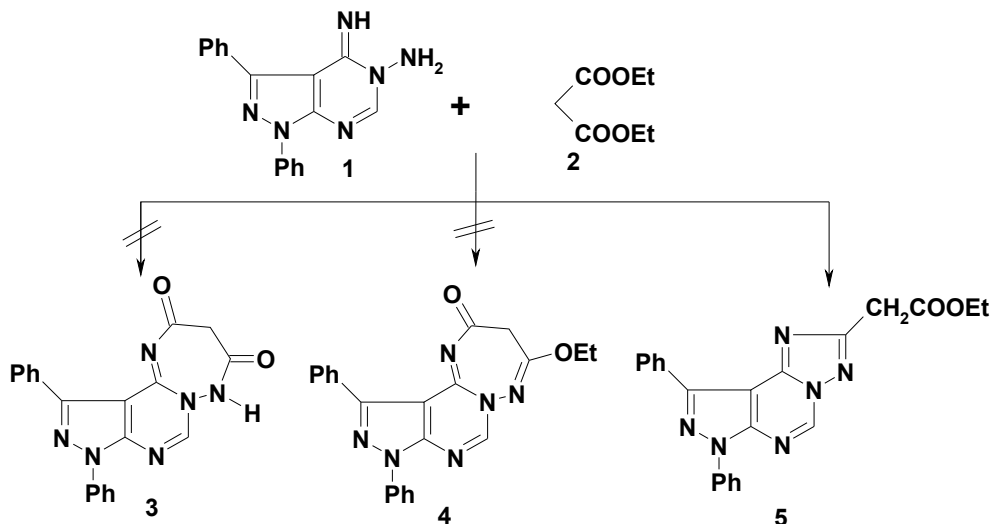
Pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine exhibits interesting pharmacological activities such as glycogen synthase kinase-3 inhibitors [1], xanthine oxidase (XO) inhibitors [1] and adenosine receptor antagonists [2-11]. These observations led us to synthesize a new pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine from 5-amino-1,3-diphenyl-4,5-dihydro-4-imino-1*H*-pyrazolo[3,4-*d*]pyrimidine and diethyl malonate.

Results and Discussion

5-Amino-1,3-diphenyl-4,5-dihydro-4-imino-1*H*-pyrazolo[3,4-*d*]pyrimidine (**1**) [12] was allowed to react with diethyl malonate (**2**) under reflux. The expected product of this reaction was structure 9,11-diphenylpyrazolo[3',4':4,5]pyrimido[1,6-*b*][1,2,4]triazepin-2,4-dione (**3**) or 4-ethoxy-9,11-diphenylpyrazolo[3',4':4,5]pyrimido[1,6-*b*][1,2,4]triazepin-2-one (**4**) or its isomeric ethyl (1,3-diphenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5-yl)acetate (**5**) (Scheme 1). MS, ¹H NMR, IR and elemental analyses data of the isolated product were in full agreement with the structure **5** not the isomeric structures **3** or **4**. The IR spectrum of the isolated product showed bands at 1735 cm⁻¹ characteristic for ester carbonyl group. Its ¹H NMR spectrum showed a singlet signal at δ 4.12 for the

acyclic CH₂ protons, in addition to triplet and quartet signals at δ 1.25 and 4.22 due to the protons of ethyl group.

Scheme 1. Synthesis of the title compound (**5**).



*Synthesis of ethyl (1,3-diphenyl-1H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-5-yl)acetate (**5**).* A mixture of 5-amino-1,3-diphenyl-4-iminopyrazolo[3,4-b]pyrimidine (**1**) [12] (3.02 g, 10 mmol) and diethyl malonate (**2**) (2.4 g, 15 mmol) was heated under reflux for 2 h. After cooling, the solid precipitated was collected and crystallized from ethanol/dioxane mixture (1:1).

Yield: 96%; Yellow crystals; m.p. 200–202 °C.

GC-MS m/z (%): 399 ($M^+ + 1$, 12), 398 (M^+ , 50), 326 (43), 256 (4), 127 (8), 77 (100), 51 (65).

IR (KBr) $\nu_{\max}$ cm⁻¹: 1735 (C=O).

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 1.25 (t, J = 7 Hz, 3H, CH₃), 4.12 (s, 2H, CH₂), 4.22 (q, J = 7 Hz, 2H, CH₂), 7.47–7.70 (m, 10H, Ar-H), 9.69 (s, 1H, pyrimidine-H).

¹³C NMR (75 MHz, DMSO-*d*₆): 13.99, 34.64, 60.83, 100.62, 122.0, 127.04, 127.31, 128.43, 129.01, 137.73, 138.71, 140.00, 143.83, 145.10, 146.58, 148.14, 161.19, 168.41.

Anal. Calcd. for C₂₂H₁₈N₆O₂(398.15): C, 66.32; H, 4.55; N, 21.09. Found: C, 66.18; H, 4.42; N, 20.89%.

References and Notes

1. Nagamatsu, T.; Fujita, T. Facile and general syntheses of 3- and/or 5-substituted 7H-pyrazolo[4,3-*e*]-1,2,4-triazolo[4,3-*c*]pyrimidines as a new class of potential xanthine oxidase inhibitors. *Chem. Commun.* **1999**, 1461–1462.
2. Ongini, E.; Monopoli, A.; Cacciari, B.; Baraldi, P.G. Selective adenosine A_{2A} receptor antagonists. *Il Farmaco* **2001**, 56, 87–90.

3. Kishore, D.P.; Balakumar, C.; Rao, A.R.; Roy, P.P.; Roy, K. QSAR of adenosine receptor antagonists: Exploring physicochemical requirements for binding of pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine derivatives with human adenosine A₃ receptor subtype. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 818–823.
4. Baraldi, P.G.; Manfredini, S.; Simoni, D.; Zappaterra, L.; Zocchi, C.; Dionisotti, S.; Ongini, E. Synthesis of new pyrazolo[4,3-*e*]1,2,4-triazolo[1,5-*c*]pyrimidine and 1,2,3-triazolo[4,5-*e*]1,2,4-triazolo[1,5-*c*]pyrimidine displaying potent and selective activity as A_{2A} adenosine receptor antagonists. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2539–2544.
5. Kumar, T.S.; Mishra, S.; Deflorian, F.; Yoo, L.S.; Phan, K.; Kecskés, M.; Szabo, A.; Shinkre, B.; Gao, Z.-G.; Trenkle, W.; Jacobson, K.A. Molecular probes for the A_{2A} adenosine receptor based on a pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5-amine scaffold. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2740–2745.
6. Dolzhenko, A.V.; Pastorin, G.; Dolzhenko, A.V.; Chui, W.K. A new synthesis of 2,8-disubstituted pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines. *Tetrahedron Lett.* **2009**, *50*, 5617–5621.
7. Baraldi, P.G.; El-Kashef, H.; Farghaly, A.; Vanelle, P.; Fruttarolo, F. A new synthesis of 2,8-disubstituted pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines and related heterocycles. *Tetrahedron* **2004**, *60*, 5093–5104.
8. Harris, J.M.; Neustadt, B.R.; Zhang, H.; Lachowicz, J.; Cohen-Williams, M.; Varty, G.; Hao, J.; Stamford, A.W. Potent and selective adenosine A_{2A} receptor antagonists: [1,2,4]Triazolo[4,3-*c*]pyrimidin-3-ones. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2497–2501.
9. Baraldi, P.G.; Bovero, A.; Fruttarolo, F.; Romagnoli, R.; Tabrizi, M.A.; Preti, D.; Varani, K.; Borea, P.A.; Moorman, A.R. New strategies for the synthesis of A₃ adenosine receptor antagonists. *Bioorg. Med. Chem.* **2003**, *11*, 4161–4169.
10. Michielan, L.; Bolcato, C.; Federico, S.; Cacciari, B.; Bacilieri, M.; Klotz, K.-N.; Kachler, S.; Pastorin, G.; Cardin, R.; Sperduti, A.; Spalluto, G.; Moro, S. Combining selectivity and affinity predictions using an integrated Support Vector Machine (SVM) approach: An alternative tool to discriminate between the human adenosine A_{2A} and A₃ receptor pyrazolo-triazolo-pyrimidine antagonists binding sites. *Bioorg. Med. Chem.* **2009**, *17*, 5259–5274.
11. Paeshuyse, J.; Letellier, C.; Froeyen, M.; Dutartre, H.; Vrancken, R.; Canard, B.; De Clercq, E.; Gueffier, A.; Teulade, J.-C.; Herdewijn, P.; Puerstinger, G.; Koenen, F.; Kerkhofs, P.; Baraldi, P.G.; Neyts, J. A pyrazolotriazolopyrimidinamine inhibitor of bovine viral diarrhea virus replication that targets the viral RNA-dependent RNA polymerase. *Antiviral Res.* **2009**, *82*, 141–147.
12. Shawali, A.S.; Fahmi, A.A.; Albar, H.A.; Hassaneen, H.M.; Abdelhamid, H.A. A facile synthesis of some pyrazolo analogues of tricyclic purine derivatives *via* hydrazonoyl halides. *J. Chem. Res. (S)* **1994**, *6*, 1040–1049.