Chemistry of Heterocyclic Compounds, Vol. 46, No. 9, 2010

SYNTHESIS AND ANTIVIRAL EVALUATION OF 1,3-DIMETHYL-6-(1H-1,2,3-TRIAZOL-1-YL)PYRIMIDINE-2,4(1H,3H)-DIONE DERIVATIVES

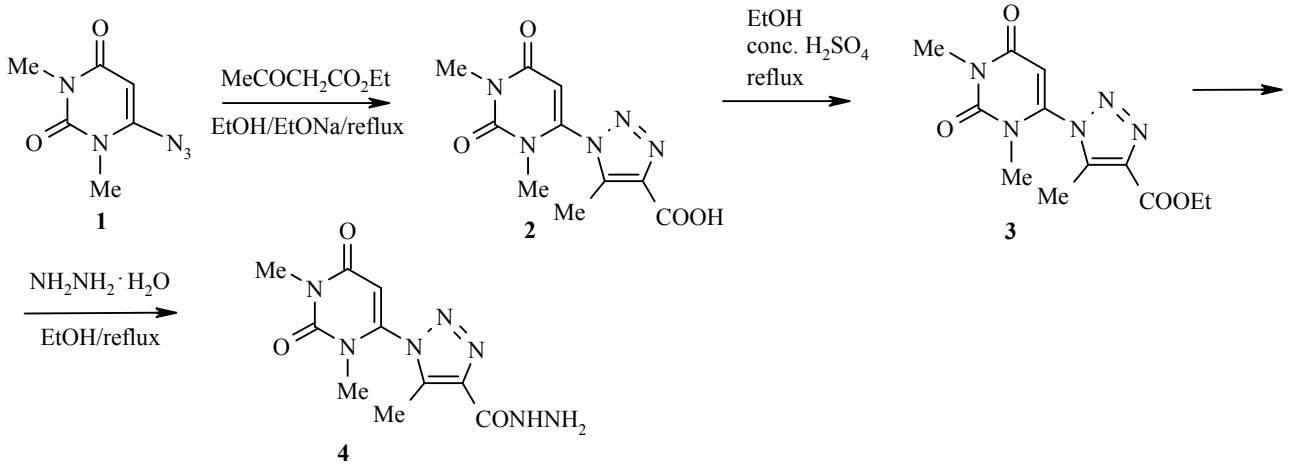
A. Sh. El-Etrawy[1] and A. A.-H. Abdel-Rahman[2]*

Some 6-(1H-1,2,3-triazol-1-yl)pyrimidine-2,4(1H,3H)-dione derivatives were synthesized via the reaction of 6-azido-1,3-dimethyluracil with ethyl acetoacetate in the presence of sodium ethoxide. The antiviral activities of these compounds against Hepatitis A virus (HAV, MBB-cell culture adapted strain) and Herpes simples virus type-1 (HSV-1) were tested.

Keywords: pyrimidine derivatives, 1,2,3-triazoles, anti hepatitis A virus, cycloaddition.

The chemistry of azides has attracted the attention of many chemists, since many of these compounds play an important role in organic chemistry [1–3]. One of the more useful synthetic applications of azides is the preparation of 1,2,3-triazoles *via* cycloaddition reactions [4–6]. 1,2,3-Triazoles have also received much attention because of their chemotherapeutic value [7]. Moreover, 1,2,3-triazole derivatives show significant

Scheme 1



1 **2** **3** **4**

* To whom correspondence should be addressed, e-mail: adelnassar63@hotmail.com.

[1]Department of Organic Chemistry, College of Pharmacy, Misr University for Science and Technology, 6th October City, Egypt.

[2]Department of Chemistry, Faculty of Science, Menoufia University, Shebin El-Koam, Egypt.

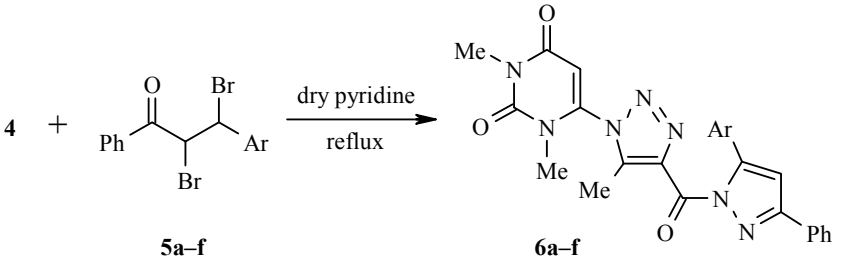
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, 1372-1375, September, 2010. Original article received December 02, 2009.

antimicrobial, cytostatic, virostatic, and anti-inflamatory activities [8-10]. The versatile biological properties of pyrimidine derivatives and 1,2,3-triazoles prompted us to investigate the synthesis and antiviral activity of modified pyrimidine with the 1,2,3-triazolyl moiety at the 6-position of the pyrimidine.

In this investigation, reaction of 6-azido-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (**1**) [11] with ethyl acetoacetate in the presence of sodium ethoxide under reflux afforded 6-(4-carboxy-5-methyl-1H-1,2,3-triazol-1-yl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (**2**) in 80% yield. Esterification of compound **2** with ethanol in the presence of conc. H_2SO_4 at reflux temperature afforded 6-(4-ethoxycarbonyl-5-methyl-1H-1,2,3-triazol-1-yl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (**3**) in 95% yield. The acid hydrazide derivative **4** was obtained in 93% yield by boiling compound **3** with hydrazine hydrate in ethanol (Scheme 1).

Refluxing of the acid hydrazide **4** with dibromochalcone derivatives **5a-f** [12] in dry pyridine gave the substituted pyrazole derivatives **6a-f** in 77–88% yields (Scheme 2).

Scheme 2



5a–f **6a–f**

5, 6 a Ar = phenyl, **b** Ar = 2-bromophenyl, **c** Ar = 4-bromophenyl,
d Ar = 2,4-dibromophenyl, **e** Ar = 2-fluorophenyl, **f** Ar = 3-nitrophenyl

The structures of compounds **2**–**6** were confirmed by ^{1}H NMR and mass spectrometry. In the ^{1}H NMR spectra of the synthesized compounds we observed all proton signals of the aromatic ring, heterocyclic ring, and methyl group.

Plaque infectivity assay [13] was carried out to test the prepared compounds for antiviral activity. The test was performed to include three possibilities for antiviral activity – virucidal effect, virus adsorption, and effect on virus replication for both *Hepatitis A* virus (HAV-27) and *Herpes simples* virus type 1 (HSV-1).

For the antiviral activity against HAV-27 it was noticed that, at both concentrations 10 and 20 μg/10^5 cells, compounds **6a**,**c** revealed the highest antiviral activity in this series of compounds, and compounds **6e**,**f** revealed high activity at 10 μg/10^5 cells using Amantadine (maximum concentration) as a control. Compound **2** showed moderate activity, while at a concentration of 20 μg/10^5 cells, compound **3** revealed little antiviral activities.

For the antiviral activity against HSV-1, the results revealed that compounds **2** and **6a–f** showed the highest effect on HSV-1 at concentration 10 μg/10^5 cells, while compounds **3** and **4** showed moderate activity.

In conclusion, new 6-(1,2,3-triazol-1-yl)pyrimidine derivatives were synthesized in order to increase the number of tested compounds screened for antiviral activity. Some of them displayed promising activities.

EXPERIMENTAL

Melting points were determined using a Büchi apparatus. ^{1}H NMR spectra were recorded with a Varian Gemini spectrometer at 200 (compounds **2–4**) and 300 MHz (compounds **6a-f)** in DMSO-d_6 with TMS as internal standard. The microanalyses were performed at the microanalytical unit, Tokyo University, Japan. The

progress of the reactions was monitored by TLC using aluminum silica gel plates 60 F_{245}. EI-mass spectra were recorded with a HP D5988 A 1000 MHz instrument (Hewlett-Packard, Palo Alto, CA, USA).

6-(4-Carboxy-5-methyl-1H-1,2,3-triazol-1-yl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (2). 6-Azido-1,3-dimethyluracil **1** [11] (5.43 g, 30 mmol) in absolute ethanol (20 ml) was treated with sodium ethoxide in ethanol (0.15 M, 10 ml) with stirring at room temperature. Ethyl acetoacetate (4.55 g, 35 mmol) was added to the reaction mixture, which was then refluxed for 6 h. The reaction mixture was left to cool and then neutralized with Amberlite IR-120(H^+) resin and filtered, and the resin was washed with ethanol. The combined filtrates were evaporated under reduced pressure, and the residue was recrystallized from ethanol to afford compound **2** (6.36 g, 80%) as a pale-yellow powder; mp 270-272ºC. ^{1}H NMR spectrum, δ, ppm: 2.33 (3H, s, CH_3); 3.20 (3H, s, CH_3); 3.39 (3H, s, CH_3); 6.66 (1H, s, H-5); 11.04 (1H, br. s, OH). Mass spectrum, *m/z* (*I*, %): 265 [M^+] (45). Found, %: C 45.11; H 4.05; N 26.33. $C_{10}H_{11}N_5O_4$. Calculated, %: C 45.28; H 4.18; N 26.41.

6-(4-Ethoxycarbonyl-5-methyl-1H-1,2,3-triazol-1-yl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (3). Acid derivative **2** (2.65 g, 10 mmol) in absolute ethanol (30 ml) was treated, carefully dropwise, with conc. H_2SO_4 (5 ml) with stirring at room temperature. The reaction mixture was refluxed for 1 h and then cooled to room temperature. The solvent was concentrated and cooled to afford a pale-yellow crystals (2.78 g, 95%); mp 211-213ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30 (3H, t, *J* = 6.5, $C\underline{H}_3CH_2$); 2.37 (3H, s, CH_3); 3.17 (3H, s, CH_3); 3.40 (3H, s, CH_3); 4.20 (2H, q, *J* = 6.5, $CH_3C\underline{H}_2$); 6.61 (1H, s, H-5). Mass spectrum, *m/z* (*I*, %): 293 [M^+] (32). Found, %: C 48.98; H 5.02; N 23.79. $C_{12}H_{15}N_5O_4$. Calculated, %: C 49.14; H 5.16; N 23.88.

6-(4-Carbohydrazide-5-methyl-1H-1,2,3-triazol-1-yl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (4). Compound **3** (2.93 g, 10 mmol) in absolute ethanol (20 ml) was treated with hydrazine hydrate (5 ml) with stirring under reflux for 3 h and then cooled to room temperature. The solid was filtered off and dried to give **4** (2.59 g, 93%); mp 245-247ºC. ^{1}H NMR spectrum, δ, ppm: 2.11 (2H, br. s, NH_2); 2.34 (3H, s, CH_3); 3.19 (3H, s, CH_3); 3.37 (3H, s, CH_3); 6.65 (1H, s, H-5); 8.00 (1H, br. s, NH). Mass spectrum, *m/z* (*I*, %): 279 [M^+] (24). Found, %: C 42.88; H 4.55; N 34.90. $C_{10}H_{13}N_7O_3$. Calculated, %: C 43.01; H 4.69; N 35.11.

Preparation of the Pyrazole Derivatives 6a-f (General Method). A mixture of compound **4** (0.279 g, 1 mmol) and dibromochalcone derivatives **5a-f** [12] (1 mmol) in dry pyridine (15 ml) was refluxed for 7-10 h. The solvent was evaporated under reduced pressure and coevaporated with toluene (4×5 ml). The residue was recrystallized from ethanol to afford **6a-f** in 77-88% yields as pale-yellow powders.

6-[4-(3,5-Diphenyl-1H-pyrazole-1-carbonyl)-5-methyl-1H-1,2,3-triazol-1-yl]-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (6a). Yield 0.41 g (88%); mp 195-197ºC. ^{1}H NMR spectrum, δ, ppm: 2.30 (3H, s, CH_3); 3.18 (3H, s, CH_3); 3.28 (3H, s, CH_3); 6.60 (1H, s, H-5); 7.10 (1H, s, H-4 pyrazole); 7.41-7.79 (8H, m, H Ar); 8.00-8.15 (2H, m, H Ar). Mass spectrum, *m/z* (*I*, %): 467 [M^+] (15). Found, %: C 64.07; H 4.44; N 20.72. $C_{25}H_{21}N_7O_3$. Calculated, %: C 64.23; H 4.53; N 20.97.

6-{4-[5-(2-Bromophenyl)-3-phenyl-1H-pyrazole-1-carbonyl]-5-methyl-1H-1,2,3-triazol-1-yl}-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (6b). Yield 0.43 g (80%); mp 205-207ºC. ^{1}H NMR spectrum, δ, ppm: 2.33 (3H, s, CH_3); 3.16 (3H, s, CH_3); 3.29 (3H, s, CH_3); 6.66 (1H, s, H-5); 7.13 (1H, s, H-4 pyrazole); 7.30-7.62 (7H, m, H Ar); 8.01–8.07 (2H, m, H Ar). Mass spectrum, *m/z* (*I*, %): 545/547 [M^+] (12). Found, %: C 54.80; H 3.50; N 17.77. $C_{25}H_{20}BrN_7O_3$. Calculated, %: C 54.96; H 3.69; N 17.94.

6-{4-[5-(4-Bromophenyl)-3-phenyl-1H-pyrazole-1-carbonyl]-5-methyl-1H-1,2,3-triazol-1-yl}-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (6c). Yield 0.44 g (82%); mp 219–221ºC. ^{1}H NMR spectrum, δ, ppm: 2.30 (3H, s, CH_3); 3.19 (3H, s, CH_3); 3.32 (3H, s, CH_3), 6.62 (1H, s, H-5), 7.10 (1H, s, H-4 pyrazole), 7.50-7.80 (7H, m, H Ar); 8.03-8.09 (2H, m, H Ar). Mass spectrum, *m/z* (*I*, %): 545/547 [M^+] (17). Found, %: C 54.77; H 3.47; N 17.79. $C_{25}H_{20}BrN_7O_3$. Calculated, %: C 54.96; H 3.69; N 17.94.

6-{4-[5-(2,4-Dibromophenyl)-3-phenyl-1H-pyrazole-1-carbonyl]-5-methyl-1H-1,2,3-triazol-1-yl}-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (6d). Yield 0.48 g (78%); mp 228-230ºC. ^{1}H NMR spectrum, δ, ppm: 2.32 (3H, s, CH_3); 3.17 (3H, s, CH_3); 3.30 (3H, s, CH_3); 6.64 (1H, s, H-5); 7.13 (1H, s, H-4 pyrazole); 7.52–7.70 (5H, m, H Ar); 8.03-8.07 (3H, m, H Ar). Mass spectrum, *m/z* (*I*, %): 624/626 [M^+] (7).

6-{4-[5-(2-Fluorophenyl)-3-phenyl-1H-pyrazole-1-carbonyl]-5-methyl-1H-1,2,3-triazol-1-yl}-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (6e). Yield 0.38 g (80%); mp 210-212ºC. ^{1}H NMR spectrum, δ, ppm: 2.28 (3H, s, CH_3); 3.16 (3H, s, CH_3); 3.29 (3H, s, CH_3); 6.66 (1H, s, H-5); 7.14 (1H, s, H-4 pyrazole); 7.28-7.77 (7H, m, H Ar); 8.00–8.05 (2H, m, H Ar). Mass spectrum, *m/z* (*I*, %): 485 [M^+] (21). Found, %: C 61.66; H 4.10; N 20.07. $C_{25}H_{20}FN_7O_3$. Calculated, %: C 61.85; H 4.15; N 20.20.

1,3-Dimethyl-6-{5-methyl-4-[5-(3-nitrophenyl)-3-phenyl-1H-pyrazole-1-carbonyl]-1H-1,2,3-triazol-1-yl}-pyrimidine-2,4(1H,3H)-dione (6f). Yield 0.39 g (77%); mp 233-235ºC. ^{1}H NMR spectrum, δ, ppm: 2.31 (3H, s, CH_3); 3.19 (3H, s, CH_3); 3.32 (3H, s, CH_3); 6.64 (1H, s, H-5); 7.12 (1H, s, H-4 pyrazole); 7.41-7.75 (4H, m, H Ar); 8.09-8.45 (5H, m, H Ar). Mass spectrum, *m/z* (*I*, %): 512 [M^+] (8). Found, %: C 58.44; H 3.77; N 21.68. $C_{25}H_{20}N_8O_5$. Calculated, %: C 58.59; H 3.93; N 21.87.

REFERENCES

1. S. Patai (editor), *The Chemistry of the Azido Group*, Interscience, New York, 1971.
2. N. A. Ridois, *J. Heterocycl. Chem.*, **21**, 1169 (1984).
3. E. F. V. Scriven and K. Turnbull, *Chem. Rev.*, **88**, 297 (1988).
4. T. Gilchrist, G. E. Gymer, A. R. Katritzky, and J. A. Boulton, *Adv. Heterocycl. Chem*., **16**, 33 (1974).
5. D. I. Patei and R. K. Smalley, *J. Chem. Soc. Perkin I*, 2587 (1984).
6. B. Loubinoux, J. N. Colin, and S. Tabbache, *J. Heterocycl. Chem.*, **21**, 1669 (1984).
7. B. K. Sanghvi, G. D. Bhattacharya, S. S. Kini, S. B. Matsumoto, W. B. Larson, R. K. Jolley, G. R. Robins, and G. R. Revankar, *J. Med. Chem.*, **33**, 336 (1990).
8. K. M. Banu and A. Dinakar, C. Ananthanarayanan, *Indian J. Pharm. Sci.*, **4**, 202 (1999).
9. M. D. Chen, S. J. Lu, G. P. Yuag, S. Y. Yang, and X. L. Du, *Heterocycl. Commun.*, **6**, 421 (2000).
10. E. A. Sherement, R. I. Tomanov, E. V. Trukhin, and V. M. Berestovitskaya, *Russ. J. Org. Chem.*, **40**, 594 (2004).
11. W. Pfleiderer and K. H. Schündhütte, *Liebigs Ann. Chem*., **612**, 158 (1958).
12. A. A.-H. Abdel-Rahman, A. E.-S. Abdel-Megied, M. A. M. Hawata, E. R. Kasem, and M. T. Shabaan, *Monatsh. Chem.*, **138**, 889 (2007).
13. R. S. Farag, A. S. Shalaby, G. A. El-Baroty, and N. A. Ibrahim, *Phytother. Res.*, **18**, 30(2004).