Bioorganic & Medicinal Chemistry Letters 19 (2009) 4143–4147

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis and antitumor activity of substituted triazolo[4,3-*a*]pyrimidin-6-sulfonamide with an incorporated thiazolidinone moiety

Hend N. Hafez *, Abdel-Rahman B. A. El-Gazzar

National Research Centre, Photochemistry Department (Heterocyclic & Nucleoside Unit), Dokki, 12622 Cairo, Egypt

ARTICLE INFO

Article history:
Received 26 February 2009
Revised 15 May 2009
Accepted 30 May 2009
Available online 6 June 2009

Keywords:
Triazolo[4,3-*a*]pyrimidine
Thioglycolic acid
Thiazolidinone
Anti-tumor

ABSTRACT

Chlorosulfonation of 3-methyl[1,2,4]triazolo[4,3-*a*]pyrimidine with chlorosulfonic acid in the presence of thionyl chloride was studied. When triazolo[4,3-*a*]pyrimidines are used as substrates, the substitution occurs at C-6. Also the reactivity of the hydrazides (**7**) towards aldehydes, thioglycolic acid and amines were studies. The newly prepared compounds **10a,d** and **11a,d** demonstrated inhibitory effects on the growth of a wide range of cancer cell lines generally at 10^{-5} M level and in some cases at 10^{-7} M concentrations.

Cancer encompasses many disease states generally characterized by abnormally proliferating cell and is a major and often fatal disease. A variety of anticancer drugs are currently in clinical use. Some of these compounds can be applied successfully for the treatment of several neoplastic diseases such as leukemias or testicular cancer. However, the effect of anticancer drugs on solid tumors has been poor. Because the response of solid tumors to available anticancer chemotherapy has been reduced, new drugs with improved efficacy are desired.

Pyrimidines nucleus are a pharmacophoric scaffold and represents a class of heterocyclic compounds with a wide range of biological applications. Many of them are widely used as anticonvulsant,[1] analgesic,[2] sedative,[3] anti-depressive,[4] anti-pyretic agents.[5] Some heterocycles containing pyrimidine moiety were reported to possess anti-inflammatory,[6] antiviral,[7] anti-HIV-1,[8] antimicrobial,[9] and anti-tumor activities.[10,11] Other than their biological importance, pyrimidine derivatives are valuable for the preparation of fused ring compounds, such as triazolopyrimidines,[12] thieno-pyrimidines,[13] thiazolo-pyrimidines,[14] and pyridopyrimidines.[15] It has been noticed that introduction of an additional ring to the pyrimidines core tends to exert profound influence in conferring novel biological activities in these molecules. Although many methods for synthesizing triazolopyrimidines ring systems have been reported, they continue to receive a great deal attention.[16–18]

Another class of heterocyclic compounds used as scaffold in medicinal chemistry is devoted to sulfonamide derivatives.[19] They exhibit useful pharmacological properties and clinical applications. In addition to these considerable biological applications, triazolopyrimidines are important intermediates and final products in organic synthesis. In the course of our research and as part of our program involving the synthesis of heterocyclic compounds having potential biological interest, we have already reported the synthesis of many pyridopyrimidine,[20] pyrimido[4,5-*b*]quinoline and its tricyclic derivatives.[21–23]

In pursuance of our interests for investigating the reactivity of pyrimidine-2-thione towards electrophile reagents we now extend the scope of this reactivity towards other active reagents. Also, sulfochlorination reactions are widely used in organic chemistry. Sulfonyl chlorides are intermediates in syntheses of active and dispersible dyes, herbicides, and fungicides.[24] Among six-membered heterocyclic compounds containing two nitrogen atoms, a prominent place is occupied by pyrimidine derivatives used as drugs (sulfamide drug such as sulfadimethoxine, sulfamonomethoxine; antitumor agent fluorouracil; antibiotic Amecytin, etc.).[25] Moreover, triazolo[4,3-*a*]pyrimidin-6-sulfonoamide derivatives were utilized as new pharmacophoric tool for the development of more efficacious antitumor agent. On the basis of the above observations, the development of novel heteroaromatic sulfonamide as potential antitumor agents is very attractive.

Synthetic pathway depicted in Scheme 1 outlines the chemistry of the present work. The key intermediate 7-amino-3-methyl-5*H*-[1,2,4]triazolo[4,3-*a*]pyrimidin-5-one (**3**) was prepared by treating of 2-hydrazino-6-aminopyrimidin-4(4*H*)-one (**2**) with glacial acetic acid. The latter 2-hydrazino compound **2** was obtained from the action of hydrazine hydrate on 2-aminothiouracil (**1**). The reaction of compound **3** with aromatic aldehydes in ethanol and cata-

* Corresponding author.
E-mail address: hendnagah2000@yahoo.com (H.N. Hafez).

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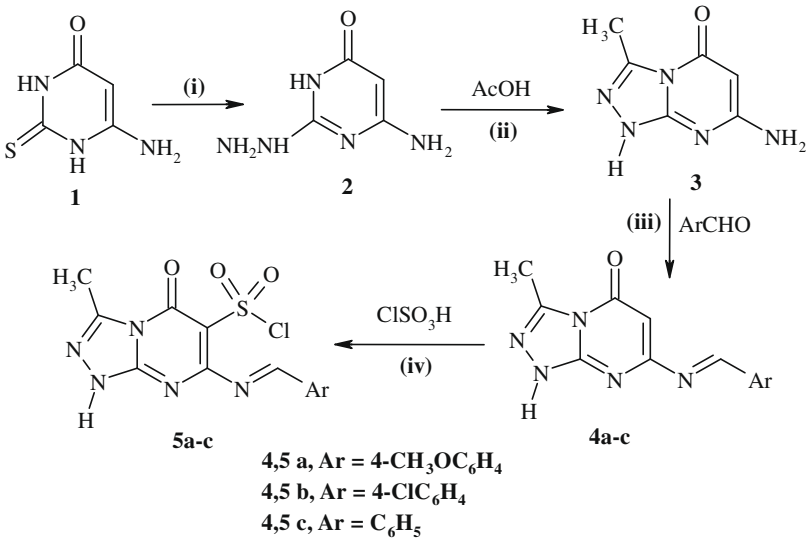
doi:10.1016/j.bmcl.2009.05.126



Scheme 1. Reagents and conditions: (i) EtOH (100 mL), $NH_2.NH_2$ (25 mL, 99%), 12 h; (ii) AcOH (30 mL), 16 h; (iii) Ar-CHO, EtOH (30 mL), AcOH (1 mL), 4 h; (iv) $ClSO_3H$, stirring at rt (20–30 min), heated at 75–85 °C for 5–6 h, cooled to 0 °C.

lytic amount of acetic acid yielded triazolo[4,3-*a*]pyrimidine (**4a–c**). According to the literature, the data on chlorosulfonation of pyrimidines are relatively few. As shown in the chemical abstract,[26] uracil and substituted pyrimidines react with a tenfold excess of chlorosulfonic acid to form uracil-6-sulfonyl chloride and 6-methyluracil-5-chlorosulfonyl. We reported here a develop and more efficient procedure for preparation of 7-aryl-methyleneamino-3-methyl-6-chlorosulfonyl[1,2,4]triazolo[4,3-*a*]pyrimidin-5-one (**5a–c**). Chlorosulfonic acid in combination with thionyl chloride (1.5:1) considerably increases the rate of formation and yields of (**5a–c**).

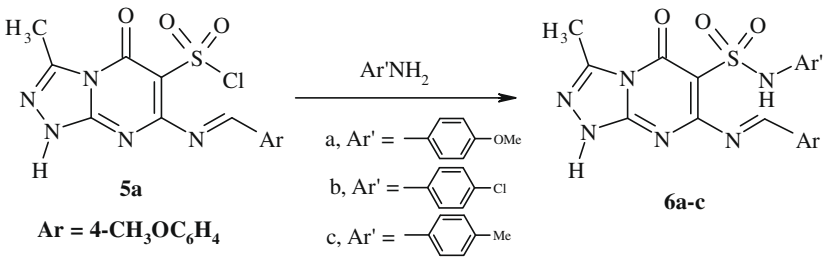
Compounds (**5a–c**) were synthesized by chlorosulfonation of 7-arylmethylene-amino-3-methyl[1,2,4]triazolo[4,3-*a*]pyrimidin-5-one (**4a–c**). *C*-Sulphonyl chloride in position 6 of the triazolopyrimidine ring was performed at atmospheric pressure by treatment of **4** with chlorosulphonic acid and thionyl chloride (1.5:1). Treatment of compound **5a** with aryl amine in dry benzene under reflux afforded 7-(4-methoxyphenylmethyleneamino)-3-methyltriazolo[4,3-*a*]pyrimidin-6-*N*-aryl-sulfonoamide (**6a–c**), (Scheme 2). Postulated structures of the newly synthesized compounds **3**, **4**, **5** and **6** are in agreement with their IR, ^{1}H NMR spectral and elemental analysis data.

Simultaneously, the reaction of compound **5a** with hydrazine hydrate (99%) was completed in 5 h, the pure sulphonyl hydrazide **7** was obtained in good yield. The latter hydrazide was treated with aryl aldehydes at room temperature in absolute ethanol affording the corresponding aryl hydrazone derivatives **8a–d** (Scheme 3). The NMR spectrum of **8a**, as an example showed three singlet signals at δ 2.31, 3.93 and 4.00 corresponding to the methyl and two methoxy groups, showed also the aromatic protons at δ 7.52 (d, 2H, J = 8.01 Hz), 7.80 (d, 2H, J = 8.00 Hz), 8.22 (d, 2H, J = 8.01 Hz) and 8.38 (d, 2H, J = 8.00 Hz), the two azomethain protons (–N=CH–) appear at δ 8.81, 8.96 ppm, finally two broad bands corresponding to 2 NH at δ 9.50 and 11.40 which are D_2O exchangeable.

The syntheses of 3-methyltriazolo[4,3-*a*]pyrimidin-6-sulfono[(4-methylpiperazine/or morpholine-1-yl-methyl)-4-oxo-2-(arylthiazolidin-3-yl]amide derivatives (**10** and **11**) were carried out as shown in Scheme 3. The intermediate compounds **9a–d** was synthesized by the nucleophilic cycloaddition of thioglycolic acid in dry benzene under reflux in a water-bath. The structure of **9** was assigned to the isolated products **9a–d** on the basis of elemental analysis, IR and in particular NMR spectra: the latter compound revealed the absence of –CH=N– and appeared the absorption signal corresponding to the methylene proton around δ 4.40 ppm and the singlet signal due to the N–CH–S of thiazolidine proton around δ 8.80 ppm.

6-(4-Methylpiprazin or morpholin)-1-yl-methyl)-derivatives were prepared by the reaction of intermediate **9** with a mixture of paraformaldehyde and *N*-methyl piperazine or morpholine in absolute ethanol. The mixture was refluxed for 7–10 h and left it at room temperature under stirring for 3 days. The structure of compounds **10a–d** and **11a–d** were conformed on the basis of their correct elemental analyses as well as compatible spectral data (general).[31] The ^{1}H NMR spectra of compounds **10** and **11** revealed the absence of the $-CH_2-$ absorption signal of thiazolidine ring and appeared the multiplet absorption signals of the methylene protons (4–CH_2) of piperazine and morpholine.

Evaluation of anticancer activity on thiazolopyrimidines **6–11** was performed at the National Cancer Institute (NCI). First, all



Scheme 2. Reagents and conditions: Ar′-NH_2, dry benzene (50 mL), reflux 3 h.