European Journal of Medicinal Chemistry 100 (2015) 119–128

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

Synthesis of 1*H*-1,2,3-triazole linked aryl(arylamidomethyl) – dihydrofurocoumarin hybrids and analysis of their cytotoxicity

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ARTICLE INFO

Article history:
Received 22 January 2015
Received in revised form
30 April 2015
Accepted 11 May 2015
Available online 12 May 2015

Keywords:
Azides
Alkynes
1,2,3-Triazoles
Click chemistry
Cytotoxicity

ABSTRACT

A series of 2-(4-R-triazolyl)substituted 3-oxo-2,3-dihydrofurocoumarins have been synthesized by a regioselective cycloaddition of 2-azidooreoselone **1** or 2-azido-9-[(4-methylpiperazin-1-yl)methyl] oreoselone **2** with various alkynes in the presence of Cu(II)/ascorbate in water/methylene chloride reaction medium. The structure of 2-azidooreoselone was established by X-ray structure analysis. The cytotoxicity of 2-substituted dihydrofurocoumarins was determined against three cancer cell lines (CEM-13, MT-4, U-937) using the conventional MTT assays. Among the tested molecules, most of the analogs displayed better cytotoxic activity then the parent natural furocoumarin peucedanin **3**. The activity and selectivity to the cell line increased even further in the series of 2-(4-{2,3-dihydrobenzo[*b*][1,4]dioxine} triazolyl)-3-oxo-2,3-dihydrofurocoumarins and 2-(4-aryltriazolyl)-3-oxo-2,3-dihydrofurocoumarins having the (4-methylpiperazin-1-ylmethyl) substituent in the 9-th position. The most active compound **20** contain the 4-hydroxy-3-methoxybenzamidomethyl substituent in the *4*-th position at the triazole ring of 2-(triazol-1-yl)dihydrofurocoumarins. The obtained 2-triazolyl substituted dihydrofurocoumarins were studied as inhibitors of phosphodiesterase (PDE-4B) using docking experiments. As a result of virtual screening 3 compounds are selected based on minimum binding energy. The interactions of the most active compound and amino acid residues in the binding site were studied.

1. Introduction

Linear furocoumarins (psoralens) exhibit photosensitizing activities and were used for the treatment of autoimmune or hyperproliferative skin diseases, including psoriasis and vitiligo in combination with UVA irradiation therapy. They induce many biological effects, such as photocycloadditions to DNA, immune system modulation, reactions with proteins, RNA and lipids [1–3]. The accepted mode of action of psoralen ultraviolet radiation therapy has been the intercalation of DNA, followed by photoactivated cross linking of the 5,6-double bond and the 2,3-double bond of the psoralen with pyrimidine base pairs in the DNA forming mono- and biscyclobutane dimers [4]. There also arose a series of side effects especially via possible cross linking of two DNA molecules by one molecule of psoralen, which causes genotoxicity, skin cancer, and other neoplastic diseases [2,3].

In the last decade many new potential therapeutic applications for linear furocoumarins were revealed. For instance, some psoralen derivatives were found to induce erythroid differentiation in different cellular models [5] or were characterized as HIV-1 integrase inhibitors [6]. Several psoralen derivatives we able to inhibit NF-κB/DNA interactions [7–9]. The substituents in the furan ring was found to be responsible for identification of candidates with inflammatory activity [9]. A number of psoralen derivatives have been evaluated for their ability to inhibit phosphodiesterase 4 (PDE 4) [10,11]. A comparison among the coumarins revealed that lipophilicity and the substituents at *2*-th or *3*-th position are two important factors in the phosphodiesterase inhibitory activity of furocoumarins [10]. Recently, prenylated coumarins were found to shown strong inhibitory activity on phosphodiesterase-4 (PDE4)

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http://dx.doi.org/10.1016/j.ejmech.2015.05.016
0223-5234/

[12]. Several reports on PDE-4 enzymes shown that PDE 4B subtype is involved in the orchestra of events which includes inflammation [13], cancers [14] and psoriatic arthritis [15]. Accordingly, in view of PDE 4B inhibiting of 1,2,3-triazole class of compounds [16,17], we became interest in a targeted preparation and investigation of new modified dihydrofurocoumarins, in particular, compounds, containing a 1,2,3-triazole linked with aryl(arylamidomethyl) substituent in 2-th position. 1,2,3-Triazoles have been the nuclei of choice in recent years because of their excellent pharmacokinetic characteristics, favorable safety profile, latent ability for the formation of hydrogen bonds, moderate dipole character, rigidity and stability under *in vivo* conditions on the synthesized hybrids [18,19]. A library of coumarin derivatives conjugated with 1,2,3-triazole in the *3*-th, *4*-th or *7*-th position with 1,2,3-triazole were synthesized and proved to possess different bioactivity. Novobiocin analogs with 1,2,3-triazole at the 3-position of coumarin displayed potent cytotoxic activity against brest cancer cell lines [20]. 4-[(1,2,3-Triazole-1yl)methyl]coumarins [21] and 7-[(1,2,3-triazole-1yl)methylamino]-4-methylcoumarin [22] exhibited obvious anti-cancer activity throught inducing apoptosis of the cell lines. 4-(1,2,3-Triazole-1-yl)coumarins [23] display attractive antitumor activities through arresting G_2/M cell-cycle and inducing apoptosis. 4,7-Bis-Coumarinyl-triazoles [24] and chalcone-coumarin hybrids with a triazole linker [25] are of interest as potential anti-cancer and antimycobacterial agents. All the coumarin derivatives were obtained using click chemistry approach.

Click chemistry of natural products has acquired great importance in recent years [26,27]. 1,4-Disubstituted triazoles were synthesized by copper-catalyzed azide alkyne cycloaddition (CuAAC) reaction using sodium ascorbate as reducing agents [28]; synthesis of the some compounds with 1,5-substitution triazoles was achieved by using ruthenium catalyst [29].

In continuation of our pursuit of the synthesis of biologically potent 2-substituted dihydrofurocoumarins [30] we present herein the regoselective synthesis of a series of hybrids of aryl – dihydrofurocoumarin and arylamidomethyl – dihydrofurocoumarin types with 1*H*-1,2,3-triazolyl linker and their *in vitro* evaluation of cytotoxicity. For completing the knowledge of the structure activity relationships, derivatives with an additional N-methylpiperazinyl substituent in the *9*-th position of the furocoumarin scaffold were taken into account. Moreover, we tried to join the useful aspect of molecular docking to derive a binding site for triazolyl substituted furocoumarin derivatives by *in silico* evaluation of their PDE4B inhibiting properties.

2. Results and discussion

2.1. Chemistry

The key step of our synthetic strategy to 1,4-disubstituted triazoles relied on the preparation of oreoselone azides **1**, **2** (Scheme 1). 2-Azidooreoselone **1** was synthesized from the accessible plant furocoumarin peucedanin **3** through the step of preparation 2-bromooreoselone **4** and its reaction with sodium azide as described in our previous paper [31]. The Mannich reaction of compound **1** with 4-methylpyperazine and formaldehyde in conditions of our previous studies [32], resulted in the formation of 2-azido-9-(4-methylpiperazin-1-ylmethyl)oreoselone **2** in 65% yield after the purification by column chromatography.

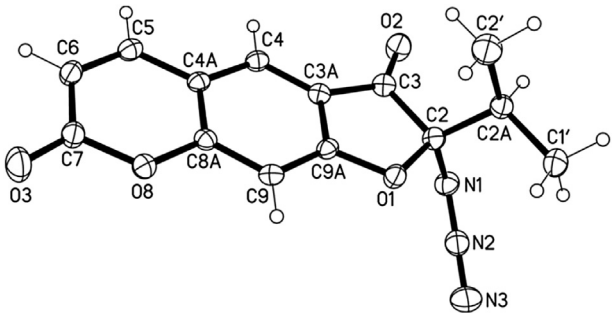
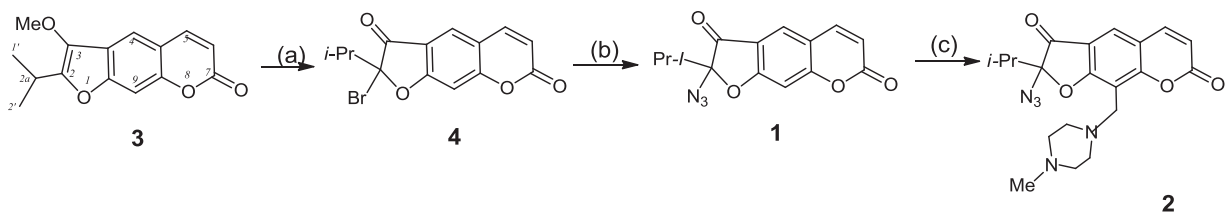


Fig. 1. View of the molecule **1**. Displacement ellipsoids are drawn at the 50% probability level.

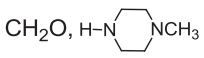
The structure of 2-azidooreoselone **1** was established by X-ray structure analysis. The refined molecule is shown in Fig. 1. The crystal parking and selected hydrogen bond parameters are presented in Fig. 2 and Table 1, respectively.

The bond lengths and bond angles are the same as the statistical means [33]. According to the of X-ray diffraction data of the 1,3-dihydrofurochromene-3,7-dione core of the molecule **1** is perfectly planar in the crystal. The standard deviations from the mean plane are 0.026 E. In the crystall packing molecules of **1** form stacks due to the π … π interaction of the furochromene fragments appurtenanted the neighboring molecules (Fig. 2) with distance between ring centroids Cg … Cg 3.632(1), 3.630(1) E and plane-to-plane 3.453(1) E. Additionally to the π … π interaction, the C–O … π interaction of the C7–O3 bond of one molecule with phenyl ring of another is observed, the atom-to-plane distance is 3.552(2) E. The lateral intermolecular H-bond C–H … O and C–H … N with parameters in Table 1 led to formation of 2D networks.

The azido groups of compounds **1** and **2** were reacted with different alkynes by CuAAC reactions (Schemes 2 and 3). Reaction of compound **1** with 1 equivalent of aryl alkynes **3**–**7** in the presence of sodium ascorbate (15 mol%) and $CuSO_4$ (5 mol%) in 1:1 CH_2Cl_2-water medium (the conditions used in our previous studies [31]) gave the 2-(4-aryl-1*H*-1,2,3-triazol-1-yl)-3-oxo-2,3-dihydrofurocoumarins **8**–**12** in 80–88% yields (Scheme 2). By using of the mentioned CuAAC conditions for reacting of azide **1** with



Scheme 1. Synthesis of 2-azidooreoselons **1**, **2**: a) BR_2, $CHCl_3$, 25 °C; b) NaN_3, DMF, 40 °C, 8 h; c)



, MeOH, reflux, 10 h.