Glycomics & Lipidomics

Extended Abstract

Synthesis and hypolipidemic properties of novel N-(4-benzoylphenyl) pyrrole-2-carboxamide derivatives

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Abstract

Hyperlipidemia is involved in development of atherosclerosis and coronary heart disease. We synthesized two novel pyrrole carboxamide derivatives N-(4-benzoylphenyl)-4-bromo-2,5-dihydro-1H-pyrrole-2 carboxamide (1) and 4- Amino-N-(4-benzoylphenyl)-1-methyl-1H- pyrrole-2carboxamide (2) and tested them as anti-hyperlipidemic agents. The synthesized compounds were characterized using IR and NMR. Biological evaluation of compound 1 and 2 showed that compound 1 significantly decreased TG, LDL-C and TC, and mild increase in HDL-C in plasma. Contrarily, compound 2 appeared to be less potent when compared to 1; it moderately decreased TG, LDL-C and TC with mild increase of HDL-C. The NH pyrrole mediates H-bond interaction of 1 with the backbone of the target(s) protein(s) and this corresponds to the high potency of 1. The lower activity of 2 confirms that the presence of H-bond is essential to induce high activity. The finding of this work suggests that this scaffold might be promising as antihyperlipidemic agents for future work.

Substituted thiazole compounds play an important role in nature and have a diverse range of biological effects such as antitumor [1–3] antibacterial [4], antimicrobial [5], anti-viability [6], anti-inflammatory [7], Syk inhibitor [8], antiviral [9], antiproliferative [10], and anticandidal activity [11]. In past decades, amide containing heterocycles are reported as a class of compounds displaying extensive biological activities, which consist of a large number of natural and synthetic products and are extremely versatile building blocks for the manufacture of bioactive compounds in pharmaceutical drug design and agrochemical industry [12–18]. We noticed that most optimizations focused on the pyridine [19], pyrazole [20], piperazine [21] and oxadiazole [22] heterocycles, but the thiazole ring, as an active moiety widely used in pesticides and medicine, has not been fully reported. For example, phthalic diamides [23] and anthranilic diamides [24] were reported by Nihon Nohyaku (Tokyto, Japan), Bayer CropScience (Monheim, Genmany) and DuPont (Delaware, USA), respectively. In view of all these facts and as continuation of our research on bioactive compounds [25–37], the promising bioactive diversity of this class of heteroaryl compounds encourage us to synthesize and biologically evaluate a series of novel structural variants of 2-phenyl-4-trifluoromethyl thiazole-5-carboxamide derivatives and related intermediates. Their antitumor activity was tested in A-549 lung cancer cell lines, Bel7402 liver cancer cell lines and HCT-8 intestine cancer cell lines.

A series of thiazole derivatives 1 - 4 were synthesized employing simple one-pot reaction pathway and characterized via Fourier Transform Infrared (FTIR), Proton Nuclear Magnetic Resonance (1 H NMR), Ultraviolet-Visible (UV-Vis) and Gas Chromatography-Mass Spectrometry (GC-MS). The newly synthesized compounds were evaluated for their in vitro antimicrobial properties against several bacterial strains including Gram-positive and Gram-negative as well as fungus using broth microdilution method . The results revealed that all of the compounds exhibited good activity with a range of MIC values between 1.25-5.0 mg/mL. From the MIC and MBC results, compound 1 exhibited good activities with same MIC value of 1.25 mg/mL and MBC value of 5 mg/mL against B. cereus and S. flexneri . In order to support antimicrobial results, the molecular docking studies were carried out for inhibition of the GlcN-6-P synthase as the target. Out of four compounds underwent for molecular docking studies, 5-acetyl-4-methyl-2-(4-aminobiphenyl)-1,3-thiazole (1) shows the lowest minimum binding energy at -7.32 kcal/mol as compared to 2 , 3 and 4 with -7.31, -7.20 and -6.76 kcal/mol, respectively which are in agreement with antimicrobial assay results. In conclusion, 2, 4, 5-trisubstituted-1,3- thiazole derivatives could be considered as promising antimicrobial in drug discovery candidates.

A series of novel 2-phenyl-4-trifluoromethyl thiazole-5-carboxamide derivatives have been synthesized and evaluated for their anticancer activity against A-549, Bel7402, and HCT-8 cell lines. Among the tested compounds, highest activity (48%) was achieved with the 4-chloro-2-methylphenyl amido substituted thiazole containing the 2-chlorophenyl group on the two position of the heterocyclic ring. Other structurally similar compounds displayed moderate activity. The key intermediates have been fully characterized

The oncogenic potential of phosphatidylinositol 3-kinase (PI3Kα) has made it an attractive target for anticancer drug design. In this work, we describe our efforts to optimize the lead PI3Kα inhibitor 2-hydroxy-1,2-diphenylethanone (benzoin). A series of 2-oxo-1,2-diphenylethyl benzoate analogs were identified as potential PI3Kα inhibitors. Docking studies confirmed that the aromatic interaction is mediating ligand/protein complex formation and identified Lys802 and Val851 as H-bonding key residues. Our biological data in

human colon carcinoma HCT116 showed that the structure analogs inhibited cell proliferation and induced apoptosis.

A series of 1,2-bis(4-methoxyphenyl)-2-oxoethyl benzoates was synthesized and characterized by means of FT-IR, 1H and 13C NMR, and by elemental analysis. Biological investigation demonstrated that the newly synthesized compounds exhibit antiproliferative activity in human colon adenocarcinoma (HCT-116), breast adenocarcinoma (MCF-7), and breast carcinoma (T47D) cell lines possibly via inhibition of PI3Kα and estrogen receptor alpha (ERα).

Additionally, results revealed that these compounds exert selective inhibitory activity, induce apoptosis, and suppress VEGF production. Compound 3c exhibited promising antiproliferative activity in HCT-116 interrogating that hydrogen bond-acceptor mediates ligand/PI3Kα complex formation on m- position. Compounds 3e and 3i displayed high inhibitory activity in MCF-7 and T47D implying a wide cleft discloses the o-attachment. Furthermore, compound 3g exerted selective inhibitory activity against T47D. Glide docking studies against PI3Kα and ERα demonstrated that the series accommodate binding to PI3Kα and/or ERα.

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