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Synthesis, physicochemical characterization, cytotoxicity, antimicrobial, anti-inflammatory and psychotropic activity of new *N*-[1,3-(benzo)thiazol-2-yl]-ω-[3,4-dihydroisoquinolin-2(1*H*)-yl] alkanamides

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ABSTRACT

A series of new *N*-[(benzo)thiazol-2-yl]-2/3-[3,4-dihydroisoquinolin-2(1*H*)-yl]ethan/propanamide derivatives was synthesized and characterized by ^{1}H, ^{13}C NMR and IR spectroscopy and mass-spectrometry. A single crystal X-ray study of *N*-(1,3-benzothiazol-2-yl)-2-[3,4-dihydroisoquinolin-2(1*H*)-yl]ethanamide is reported to determine its conformational feature. The investigated compounds were found to be active in psychotropic *in vivo*, anti-inflammatory *in vivo* and cytotoxicity *in vitro* screening. They possess marked sedative action, reveal high anti-inflammatory activity, have selective cytotoxic effects and NO-induction ability concerning tumour cell lines. Some of the compounds synthesized demonstrate antimicrobial action. An attempt was made to correlate the biological results with their structural characteristics and physicochemical parameters. Some specific combinations of types of activities for the synthesized compounds have been revealed.

1. Introduction

Among pharmacologically important heterocyclic compounds, thiazole and tetrahydroisoquinoline derivatives have been well known in medicinal chemistry because of their wide spectrum of biological activities and the presence of their structural moieties in molecules of naturally occurring compounds.

Thiazole core is present in many biologically relevant molecules, which are in therapeutical use, such as Sulfathiazole (antimicrobial drug), Ritonavir (antiretroviral drug), Abafungin (antifungal drug), Tiazofurin (antineoplastic agent), Meloxicam (non-steroidal anti-inflammatory drug), Nitazoxanide (antiprotozoal agent) etc. Many natural products containing thiazole ring were isolated and most of them exhibit considerable cytotoxicity and antitumour potential [1–4]. Thiazole and its derivatives are found to be associated with various biological activities such as anti-inflammatory [5–7], antimicrobial [8–12], antitubercular [13], antitumour activities [14–18], enzyme inhibition [19,20] and also find application in the drug development for the treatment of allergies [21], schizophrenia [22] and as hypnotics [23]. Some coumarins incorporating thiazolyl semicarbazones act as anticonvulsant agents [24]. Thiazole derivatives were reported to possess antidegenerative activity and coupling with other heterocyclic system form new biologically active compounds [25–27].

The tetrahydroisoquinoline ring system is an important structural motif [28,29], which is commonly encountered in naturally occurring alkaloids with interesting biological activities. Typical examples include indenoisoquinoline (topoisomerase I inhibitor) [30], saframycin-B [31], narciclasine [32] and ecteinascidin-743 (antitumour agents) [33]. In this regard, the tetrahydroisoquinoline framework has become widely identified as a “privileged” structure with representation in several medicinal agents of diverse therapeutic action and are the potential drug candidates [34–37]. Tetrahydroisoquinoline derivatives have been discussed as affine

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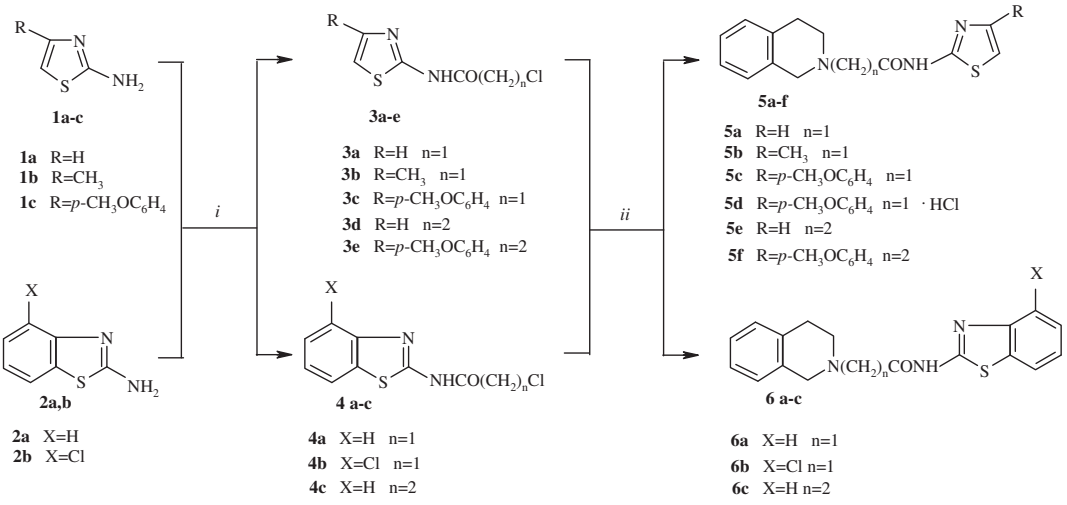

i: $Cl(CH_2)_nCOCl/C_6H_6/80^oC$

ii: $Et_3N/C_6H_6/80^oC$ (A); $K_2CO_3/EtOH/78^oC$ (B); [**3** or **4**]:[Tetrahydroisoquinoline] = 1:2.5/$C_6H_6/80^oC$ (C)

Scheme 1. Synthesis of *N*-[1,3-(benzo)thiazol-2-yl]-ω-[3,4-dihydroisoquinolin-2(1*H*)-yl]alkanamides (**5a**–**f** and **6a**–**c**).

ligands for CNS receptors [38–41] and possess sedative [42–44] and antitumour properties [45–47]. Besides hydrogenated quinoline moieties are present as structural fragments in Amsacrine, Bruneomycinum, Vincristine and Vinblastinum widely used in oncology [14,48].

Taking into account the importance of heterocyclic compounds in creating drug [49], the successful application of fragment-based analysis in the design of new biologically active substances [50] and regarding the pharmacological properties of tetrahydroquinoline and thiazole derivatives, it was envisaged to synthesize some new bis-heterocyclic compounds as possible prodrugs and to evaluate their biological potentials. Coupling of tetrahydroquinoline and thiazole ring in a single frame for the development of new chemical entities, in which the one could reinforce or modify the biological effects of the other, was carried out by using peptide link as a spacer.

This approach, called "dual action prodrug approach" or "mutual prodrug approach" [51,52] has several advantages, such as synchronous delivery of active agents, slower development of resistance, improved formulation, improved chemical stability, reduced potential steric and/or electronic issues associated with biological target interaction and decreased toxicity [53].

In this paper, we propose the synthesis of novel *N*-[(benzo) thiazol-2-yl]-ω-[3,4-dihydroisoquinolin-2(1*H*)-yl]alkanamide derivatives, in order to generate compounds with high biological activity and low toxicity, and evaluation of their biological action, namely, *in vitro* inhibiting properties on tumour cells (human fibrosarcoma HT-1080 and mouse hepatoma MG-22A), normal mouse fibroblasts (NIH 3T3), bacterial (two Gram-positive, *Staphylococcus aureus* and *Bacillus cereus*, and three Gram-negative, *Escherichia coli*, *Pseudomonas aeruginosa* and *Proteus mirabilis*) and fungal strains (*Candida albicans* and *Aspergillus niger*), as well as their *in vivo* anti-inflammatory properties against carrageenin mouse paw oedema and psychotropic activity along a number of tests. In addition, we report on a single crystal X-ray study of *N*-(1,3-benzothiazol-2-yl)-2-[3,4-dihydroisoquinolin-2(1*H*)-yl]ethanamide to understand its conformational feature and supramolecular assembly. It helps in understanding the mechanism of action of the drug and also in docking studies with various receptors. An attempt was made to correlate the biological results with their structural characteristics and physicochemical parameters.

2. Results and discussion

As mentioned above, the aim of our work is to get potential dual action prodrugs with low toxicity by combining conventional pharmacophores in one molecule. New compounds, containing two biologically active heterocycles (1,2,3,4-tetrahydroisoquinoline and 1,3-thiazole), namely, 2(3)-[3,4-dihydroisoquinolin-2(1*H*)-yl]-*N*-(1,3-thiazol-2-yl)- and -(1,3-benzothiazol-2-yl)ethan/propanamides have been synthesized, characterized by various physicochemical methods and evaluated for some types of biological action.

2.1. Chemistry

The synthesis of the title compounds is outlined in Scheme 1.

The strategy for the synthesis of *N*-[1,3-(benzo)thiazol-2-yl]-ω-[3,4-dihydroisoquinolin-2(1*H*)-yl]alkanamides (**5a**–**f** and **6a**–**c**) involved the preparation of the ethanamido **3a**–**e** and propanamido intermediates **4a**–**c** [54], which were further used as alkylating agents in reaction with 1,2,3,4-tetrahydroisoquinoline to afford a series of the desired compounds.

Initially, three different synthetic modifications were followed for the synthesis of 2-[3,4-dihydroisoquinolin-2(1*H*)-yl]-*N*-(1,3-thiazol-2-yl)ethanamide (**5a**): interaction of equimolar amounts of the 1,2,3,4-tetrahydroisoquinoline and 2-chloro-*N*-(1,3-thiazol-2-yl)ethanamide (**3a**) in boiling benzene in presence of triethylamine (A), alkylation of the appropriate amine in boiling alcohol in presence of potassium carbonate with a little access of the amine (B) and reaction between the reactants in boiling benzene using 2.5 molar excess of the amine (C). The yields of product **5a** along the methods A, B and C were 31, 24 and 44%, correspondingly. Taking into account the possibility to recover the heterocyclic amine from the reaction mixture, method C was the optimal alkylation procedure among the examined ones. Therefore, the latter reaction conditions were applied for the synthesis of all the other title compounds. The yields of the synthesized *N*-[1,3-(benzo)thiazol-2-yl]-ω-[3,4-dihydroisoquinolin-2(1*H*)-yl]alkanamides ranged from moderate to high (44–87%).

The structure of the compounds was confirmed by element analysis, IR, ^1H and ^{13}C NMR spectroscopy, GC- and LC-mass-