Chem. Biodiversity

Synthesis of Camphecene and Cytisine Conjugates Using Click Chemistry Methodology and Study of Their Antiviral Activity

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A series of camphecene and quinolizidine alkaloid (-)-cytisine conjugates has been obtained for the first time using "click" chemistry methodology. The cytotoxicity and virus-inhibiting activity of compounds were determined against MDCK cells and influenza virus A/Puerto Rico/8/34 (H1N1), correspondingly, in *in vitro* tests. Based on the results obtained, values of 50% cytotoxic dose (CC_{50}), 50% inhibition dose (IC_{50}) and selectivity index (SI) were determined for each compound. It has been shown that the antiviral activity is affected by the length and nature of linkers between cytisine and camphor units. Conjugate **13**, which contains cytisine fragment separated from triazole ring by -C_6H_{12}- aliphatic linker, showed the highest activity at relatively low toxicity (CC_{50}=168 μmol, IC_{50}=8 μmol, SI=20). Its selectivity index is appeared higher than that of reference compound, rimantadine. According to theoretical calculations, the antiviral activity of a lead-compound **13** can be explained by its influence on the functioning of neuraminidase.

Keywords: azides, heterocyclization, (+)-camphor, (-)-cytisine, "click" chemistry, terpenoids, 1,2,3-triazoles, camphecene

Introduction

Functionalization of natural compounds by the synthesis of hybrid molecules containing at least two natural fragments and connected by molecular linkers of different length and nature is one of efficient approaches to designing biologically active compounds. The scope of natural substrates is rather wide and may include alkaloids, steroids, mono- and diterpenoids, etc. Among the noted natural compounds, especial attention is attracted to terpenoids, which are the main components of essential oils and exhibit a wide spectrum of biological activity.[1] For example, the introduction of pharmacophoric groups into camphor [2,3] and fenchone [4] molecules leads to formation of compounds showing antituberculous activity. Oxygen-containing monoterpenes proved to be efficient against influenza virus [5,6] and Marburg virus.[7] Although the 1,2,3-triazole moiety does not exist in nature, it has attracted interest as a candidate anticancer drug, particularly for the production of '1,2,3-triazole-natural compound' hybrids.[8] The introduction of 1,3-thiazole heterocycle into camphor molecule leads to compounds showing antibacterial and antifungal activity.[9]

It was shown previously that a product resulting from the reaction of camphor and aminoethanol and called camphecene exhibits a wide spectrum of antiviral activity and low toxicity.[10,11] Recently, we prepared a new series of compounds derived from camphecene showing expressed antiviral activity.[12] The strategy for the modification of natural compounds of terpene series using click chemistry methodology attracts a considerable attention of experts in organic and medicinal chemistry. For example, rupestonic acid derivatives containing 1,2,3-triazole fragment were described and studied as AH1N1 influenza virus inhibitors;[13] a large series of oleanolic and betulinic acid conjugates with esters of L-ascorbic acid was obtained using the noted methods, these agents showed activity toward A H1N1 influenza virus.[14]