World Academy of Science, Engineering and Technology
International Journal of Chemical and Molecular Engineering
Vol:15, No:10, 2021

Synthesis of a Library of Substituted Isoquinolines Based on a Triazolization Strategy, and Their Anti-HIV and C-X-C Chemokine Receptor Type 4 Antagonist Activity

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Abstract : Since CXCR4 is the main coreceptor of HIV-1 and plays an important role in human immunodeficiency virus (HIV) entry, numerous efforts were directed towards the discovery of new classes of small molecules that act as CXCR4 antagonists. In addition, CXCR4 antagonists are potentially useful in the treatment of several other disorders, such as cancer cell metastasis, leukemia cell proliferation, rheumatoid arthritis, and pulmonary fibrosis. Since AMD3100 (plerixafor) is the only CXCR4 antagonist which obtained approval by the Food and Drug Administration (FDA), we were motivated to investigate a new category of molecules as CXCR4 antagonists. Most of the scaffolds which have been studied so far as CXCR4 antagonists are based on the tetrahydroquinoline (THQ) moiety in which AMD11070 (mavorixafor), GSK-812394, and TIQ15 displayed the most potent CXCR4 antagonism. Due to the high potency of these scaffolds, two different series of compounds were prepared in this work. In the first set, the THQ moiety is coupled to an amine chain and various isoquinoline derivatives (prepared by an in-house developed triazolization strategy), of which the upper part of molecules is identical to AMD11070 and TIQ15. In the second category of compounds, the THQ moiety was simplified by the synthesis of a substituted pyridine moiety. In order to investigate if CXCR4 antagonism requires the presence of an isoquinoline moiety, the corresponding pyridine analogues were also prepared. In both series of compounds, potent CXCR4 antagonism was noticed.

Keywords : CXCR4 coreceptor, CXCR4 antagonists, HIV inhibitor, tetrahydroquinoline
Conference Title : ICOCDDDA 2021 : International Conference on Organic Chemistry of Drug Design and Drug Action
Conference Location : Baku, Azerbaijan
Conference Dates : October 04-05, 2021