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PII: S0960-894X(16)30855-1
DOI: http://dx.doi.org/10.1016/j.bmcl.2016.08.034
Reference: BMCL 24160

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 14 June 2016
Revised Date: 11 August 2016
Accepted Date: 12 August 2016

Please cite this article as: Al-Hourani, B.J., Al-Awaida, W., Matalka, K.Z., El-Barghouthi, M.I., Alsoubani, F., Wuest, F., Structure-activity relationship of novel series of 1,5-disubstituted tetrazoles as cyclooxygenase-2 inhibitors: Design, synthesis, bioassay screening and molecular docking studies, *Bioorganic & Medicinal Chemistry Letters* (2016), doi: http://dx.doi.org/10.1016/j.bmcl.2016.08.034

Structure-activity relationship of novel series of 1,5-disubstituted tetrazoles as cyclooxygenase-2 inhibitors: Design, synthesis, bioassay screening and molecular docking studies

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Abstract

A novel class of modified 1,5-disubstituted tetrazoles was designed and synthesized, their biological activity as cyclooxygenases inhibitors was screened, and their molecular docking studies were performed. The structural modifications of the first category included the 4-methylsulfonyl phenyl at C-1 of the central moiety and the linkers (–OH, $–CH_2OH$, $–CH_2CH_2OH$) with different lengths at the para position of the N-1 phenyl group. For the second category, the 4-methylsulfonyl phenyl group at C-1 was replaced with 4-aminosulfonyl phenyl. While for the third category, a methylene unit was inserted between the C-1 of the tetrazole central ring and the 4-(methylsulfonyl)phenyl group, keeping the same linkers of various extensions at the para position of the N-1 phenyl group. Among the screened compounds, tetrazole **4i** showed the best inhibition potency and selectivity values for both COX-2 enzyme (IC_{50} = 3 μM, SI > 67) and COX-1 isoenzyme (IC_{50} > 200 μM). Compounds **4e**, **4h**, and **4i**, which have the highest inhibition potency toward COX-2 were selected for the molecular docking studies to verify their inhibition and selectivity for COX-2 over COX-1 with their modified structure. The obtained theoretical studies are in agreement with the in vitro bioassay screening results, which supports the importance of the structural modifications for our studied compounds.

Keywords 1,5-Disubstituted tetrazoles; COX-2 Inhibitors; COX-1 Inhibitors; Molecular docking; Structure-activity relationship; Methylsulfonyl; Aminosulfonyl

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