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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>

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## 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<sub>2</sub>OH, –CH<sub>2</sub>CH<sub>2</sub>OH) 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<sub>50</sub> = 3 μM, SI > 67) and COX-1 isoenzyme (IC<sub>50</sub> > 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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