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Design, synthesis, and biological evaluation of novel pyrrolizine derivatives as safe anti-inflammatory agents

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Background & Aim: NSAIDs are one of the most frequently used drugs worldwide. The use of NSAIDs is usually associated with multiple side effects in many organs in human body. Erosions and bleeding of GIT is the most common side effects with a bad prognosis lead to death. GIT toxicity of NSAIDs is mediated by two mechanisms; the first is the direct necrotic effect of the acidic NSAIDs on the gastric mucosa. The second mechanism of GIT toxicity is mediated through the inhibition of the cytoprotective PGs biosynthesis through inhibition of COX enzymes. Several strategies were used to overcome the aforementioned implications. In this study, we have focused on the synthesis of novel safe non-acidic NSAIDs aiming to get antiinflammatory agents with low GIT side effects.

Methods: Several compounds were designed through structural manipulation of the Aza(6-amino-N-(4-bromophenyl)-7-cyano-pyrrolizine-5-carboxmide). The differential binding affinities of the designed analogs into COX-1/2 enzymes were evaluated by molecular docking using AutoDock 4.2. Seven of these compounds which revealed the highest binding affinities to COX-2 enzymes were synthesized. Structural elucidation of the new compounds was done using different spectral analyses. *In vitro* and *in vivo* anti-inflammatory and analgesic activities of the new compounds in addition to the GIT toxic effects of the most potent compounds were screened.

Results: Evaluation of the antiinflammatory activities of the new compounds using rat paw edema method revealed that the pyrrolizine-5-carboxamide has comparable analgesic and anti-inflammatory activities to that of ibuprofen. The 6-(4-methylphenylsulfonamido)-pyrrolizine-5-carboxamide exhibited higher analgesic and anti-inflammatory activities than ibuprofen. The hybrid of ibuprofen with pyrrolizine-5-carboxamide showed better GIT safety profile although it was slowly acting.

Conclusion: In the light of these promising results; the new compounds warrant further development as potential analgesic antiinflammatory agents with low GIT side effects.

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