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باللغة الانجليزية:(٥)

Design, Synthesis and Mechanistic Study of Novel Diarylpyrazole Derivatives as Anti-Inflammatory Agents with Reduced Cardiovascular Side Effects

Novel diarylpyrazole (**5a-d**, **6a-e**, **12**, **13**, **14**, **15a-c** and **11a-g**) derivatives were designed, synthesized and evaluated for their dual COX-2/sEH inhibitory activities via recombinant enzyme assays to explore their anti-inflammatory activities and cardiovascular safety profiles. Comprehensively, the structures of the synthesized compounds were established via spectral and elemental analyses, followed by the assessment of both their *in vitro* COX inhibitory and *in vivo* anti-inflammatory activities. The most active compounds as COX inhibitors were further evaluated for their *in vitro* 5-LOX and sEH inhibitory activities, alongside with their *in vivo* analgesic and ulcerogenic effects. Compounds **6d** and **11f** showed excellent inhibitory activities against both COX-2 and sEH (COX-2 IC_{50} = 0.043 and 0.048 μM; sEH IC_{50} = 83.58 and 83.52 μM, respectively). Moreover, the compounds demonstrated promising results as anti-inflammatory and analgesic agents with considerable ED_{50} values and gastric safety profiles. Remarkably, the most active COX inhibitors **6d** and **11f** possessed improved cardiovascular safety profiles, if compared to celecoxib, as shown by the laboratory evaluation of both essential cardiac biochemical parameters (troponin-1, prostacyclin, tumor necrosis factor-α, lactate dehydrogenase, reduced glutathione and creatine kinase-M) and histopathological studies. On the other hand, docking simulations confirmed that the newly synthesized compounds displayed sufficient structural features required for binding to the target COX-2 and sEH enzymes. Also, *in silico* ADME studies prediction and drug-like properties of the compounds revealed favorable oral bioavailability results. Collectively, the present work could be featured as a promising future approach towards novel selective COX-2 inhibitors with declined cardiovascular risks.