Abstract

Herein we describe our efforts to develop novel anti-inflammatory/analgesic agents devoid of known cardiovascular drawbacks. In doing so, two 1,5-diarylpyrazole series of urea linked (**9a-f**) and amide linked (**11a-f)** compounds were synthesized and evaluated *in vitro* as dual COX-2/sEH inhibitors using recombinant enzyme assays. The *in vivo* anti-inflammatory and analgesic activities were then examined using reported animal models. Compounds **9b** and **9c** showed the highest inhibitory activities against both COX-2 and sEH (IC_{50} of COX-2 = 1.85 and 1.24 µM; sEH = 0.55 and 0.40 nM, respectively), besides showing the best activity as anti-inflammatory agents. Interestingly, the cardiovascular profile of the two compounds **9b** and **9c** was evaluated through measuring some biochemical parameters such as prostacyclin (PGI_2), lactate dehydrogenase (LDH), troponin-1 (Tn-1), tumor necrosis factor- α (TNF-α), creatine kinase-M (CK-M) and reduced glutathione (GSH) in addition to a histo-pathological study to investigate the changes in the heart muscle. The results confirmed that compounds **9b** and **9c** have a more favorable cardio-profile than celecoxib with much less cardiovascular risks associated with the common selective COX-2 inhibitors. Finally, the current work provided a promising approach that can be optimized to serve as a lead project to overcome the cardiovascular toxicity related to the traditional selective COX-2 inhibitors.