20872 | Pyrazoles as potential modulators of inflammation through the inhibition of COX-2 activity and human leukocytes' oxidative burst

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Abstract

The inflammatory process is a complex and tightly regulated cascade of events that involves the production of prostaglandins (PG) by the inducible isoform cyclooxygenase 2 (COX-2) and the production of reactive pro-oxidant species. When the production of these mediators becomes excessive, it can lead to chronic inflammation and associated diseases such as diabetes, rheumatoid arthritis, and cancer. Unfortunately, many existing anti-inflammatory agents are associated with unwanted side effects. Therefore, there is a critical need to discover new and effective compounds that can modulate the inflammatory cascade.

In this study, an extensive panel of structurally related pyrazoles holding diverse structures and substitutions were tested *in vitro* against human COX-2, and ex vivo in human whole blood, through the measurement of prostaglandin E_2 (PGE_2) production. Their potential inhibitory effect against human leukocytes' oxidative burst was also studied.

The results showed that some of the tested compounds had a significant inhibitory effect on COX-2 activity, and pyrazoles 4 and 11 (Figure 1) excelled as the most potent inhibitors, with $IC_{50} < 25$ µM. Nonetheless, among the tested compounds only 1 was able to inhibit both the COX-2 activity and the PGE_2 production. The tested pyrazoles, namely pyrazole 4, also demonstrated a potential inhibitory effect ($IC_{50} < 5$ µM) against human leukocytes' oxidative burst. These results represent a significant contribution for the design and development of new anti-inflammatory molecules.

Keywords: Pyrazoles, Cyclooxygenase 2, Inflammation.

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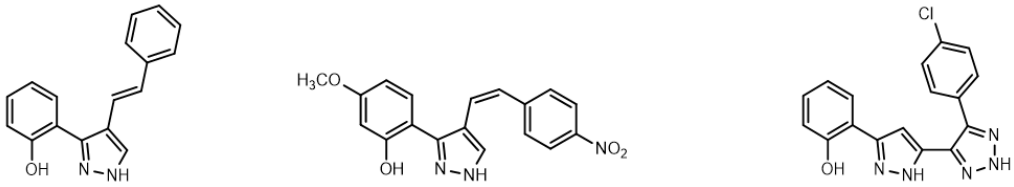

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Figure 1: Chemical structure of some of the studied pyrazoles.