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Analgesic And Anti-Inflammatory Effects Of 1,5-Diarylpyrazole-3-Propanoic Acid Derivates

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Nonsteroidal anti-inflammatory drugs (NSAIDs) clinically exhibit analgesic, anti-inflammatory and antipyretic effects with certain main side effects such as gastrointestinal irritation and kidney toxicity. It is known that the clinical profiles of the various pyrazole derivatives depending on the variations in their chemical structures exhibit relative differences like low anti-inflammatory, high analgesic and antipyretic effects. Likewise, recent studies showed that the novel synthesis of ester and amide derivatives of known NSAIDs, were also obtained as more potent anti-inflammatory compounds with low side effects. The aim of this study was to investigate the analgesic and anti-inflammatory properties of newly synthesized ester and amide derivatives of 1,5-diarylpyrazole-3-propanoic acid and their potential degree in ulcer development.

Male Swiss albino mice (25-35g) were maintained in a temperature (22^{o}C±1) and humidity (55%±10) controlled room under a 12 h light-dark cycle. The animals were separated into 6 groups randomly (in each group n=7-9). DMSO (dimethlysulfoxide) used as the control group and, ibuprofen (IBU-reference drug group) and groups of 4 different test compounds (TEP422, TEP424, TEP425 and SNTZ39 - dissolved in DMSO) were chosen as of treatment. All test compounds were administrated 30 min. before p-benzoquinone (PBQ) and carrageenan (CG) injection. Anti-inflammatory activity of derivatives was evaluated with model of CG-induced paw edema (intraplantar, 25µL/paw, 0,5mg/25µL CG was solved in SF). Thickness of paw edema of mice was measured by compass at 0, 90, 180, 270 and 360 minutes after CG injection. % Anti-inflammatory activity was calculated by using thickness of paw edema. The analgesic activity of four derivatives of 1,5-diarylpyrazole-3-propanoic acid was evaluated with PBQ-induced writhing test (i.p 2,5 mg/kg, PBQ was solved in SF). % Analgesic activity was calculated by using quantity of writhing. Four hours after analgesic activity experiments, certain mice were anesthetized and their esophagus, stomach and duodenum were removed and fixed in 1,5 ml 10% formalin solutions for the assessment of development of ulcerogenic activity. Mortality incidences were also followed in live mice. For statistical analyses, one-way ANOVA and the appropriate post-hoc tests were performed.

Our results showed that all the derivatives have antinociceptive activity as of IBU (For TEP422, TEP424, TEP425, SNTZ39 and IBU: 69,4±7,4%; 58,1±12,7%; 42,3±16,8%; 65,9±11,7% and 67,9±6,50% respectively, $p<0.01$-0.0001). TEP424, SNTZ39 and TEP422 exhibit relative equivalent potencies when compared with IBU. In anti-inflammatory activity experiments, all substances inhibited paw edema as compared to DMSO group (For TEP422, TEP424, TEP425, SNTZ39 and IBU: 29,82±5,2; 63,16±5,92; 23,68±6,62; 47,37±5,44 and 57,89±5,14, respectively, $p<0.001$-0.0001). But TEP424 and SNTZ39 have relative equivalent potency with IBU. The compounds did not produce any ulcerogenic and acute toxicity effects and no mortality were observed during 48 hours after the termination of the experiments.

These results suggest that synthesis of 1,5-Diarylpyrazole-3-Propanoic Acid derivatives may represent a potentially novel group with substantial analgesic and anti-inflammatory activities and less gastrointestinal side-effects.