Abstract

Ten new substituted 2-amino-5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazole were synthesized and evaluated for pharmacological and biological activities. 5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazole-2-amine (I) was synthesized by reaction of ibuprofen and thiosemicarbazide in presence of polyphosphoric acid (80-90 °C/8h.). Compound (I) was acetylated to 2-Chloro-N-(5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazole-2-yl) acetamide, using chloroacetyl chloride. Later the chloroacetyl chloride derivative was converted to the substituted acetylamino (acetamide-) derivatives (AS01-AS08), utilizing the secondary amines. The compound AS09 (N-(5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazole-2-yl) acetamide) was prepared by acetylation of compound (I), using the acetic anhydride in dry condition. Compound AS10 (2-(1-(4-isobutylphenyl)ethyl)-N-(5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazole-2-yl)-propanamide) was prepared by utilizing ibuprofen and 5-(1-(4-isobutylphenyl)ethyl)-1,3,4-thiadiazole-2-amine in presence of DCC.

Synthesized compounds were characterized using IR, NMR and Mass spectroscopic techniques. The physiochemical parameters were recorded and reported in thesis. Synthesized compounds were evaluated for pharmacological and biological activities. Results indicated that the all the synthesized compounds produce peripheral analgesic activity (p<0.01). The significant analgesic activity (P<0.001) was produced by compound AS09. So far as anti-inflammatory activity is concerned, compound AS10, produce significant activity (156% as compared to diclofenac sodium). Other compounds like AS06 (N-methyl-N-cyclohexyl amino, 138%), AS05 (morpholinino, 131%), AS03 (Dipropylamino, 107%) and AS07 (4-methyl piperidino derivative, 105%) inhibit the carrageenan-induced edema.

Regarding the anticholinergic activity, compound AS04 (dibutyl amino) and AS01 (dimethyl amino) produce significant activity. IC50 of AS04 and AS01 were 13.5±1.5 μg/ml and 25.1±1.1 respectively against acetylcholine (2.5 x 10⁻⁸ g/ml).

These new compounds were also evaluated for antibacterial activities in-vitro. The compounds AS02, AS04, AS05 and AS07 exhibited significant activity against S. aureus and B. subtilis. While the compounds AS01, AS03, AS06, AS09 and AS10 showed moderate activity. Regarding the activity against E. coli, compounds AS06 and AS02 were producing good activity.

In general these new thia diazole derivatives are producing significant activities. Molecular modeling and docking studies suggests that COOH group can be replaced with 1,3,4-thiadiazole for achieving NSAID activity. The 1,3,4-thiadiazole and the CO-group of the side chain produced several interaction with amino acid of COX-2 (INT1) protein. More structural modification is required to optimize the pharmacological activities.

Graphical Abstract

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Author(s) : Shkair, Anas M. Hikmat (author) | Shakya, Ashok K. (supervisor)

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Detailed view of the monograph

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