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Design and synthesis of 1,3,4-oxadiazole derivatives as a new kappa opioid receptor ligands

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Introduction: Selective agonists of kappa opioid receptors are potent analgesics without causing complications such as euphoria, mental and physical dependency, usually occur during administration.In the current study, Tifluadom, a known agonist of kappa-receptors was used as a lead compound to design and synthesis 1,3,4-oxadiazole derivatives (a,b) as kappa selective agonists.

Methods and Materials: Compound d was synthesized from 2,4-dichlorobenzoic acid (c) through Aromatic Nucleophilic Substitution mechanism and estherified afterwards. Then the esther reacted with Hydrazine hydrate to form the related Hydrazine acid. From the reaction between Hydrazine acid and chloroacetyl chloride the intermediate compound, Benzoyl hydrazine, was synthesized. In the next step the oxadiazol ring was formed and compound e produced. Eventually, compound d was obtained throughout the Nucleophilic Substitution SN2 mechanism from compound e.

Results: Molecular structures of Target compounds were characterized by Mass, H-NMR and IR spectroscopic methods. The conformational optimization of the obtained compounds was studied by MM +force field method and conformations were exactly optimized by semi empirical method, AMI.

Discussion: First step of synthesis (figure1) was the most challenging part of this study due to the naturally low yield rate of Aromatic Nucleophilic Substitution reactions. Nonetheless, with carrying out modifications to reaction condition, it is accomplished to synthesis compound d with significantly high yield (75%). Furthermore, Tifluadom has antagonistic activity against CCK-B receptors therefore the superimposition of compounds a-b on L-365260, a known antagonist of CCK-B receptors, was studied as well as Tifluadom. The results of conformational analysis indicated that well-superimposition existed between pharmacophors of compounds a-b and the lead compounds. Accordingly, the obtained compounds are expected to be selective agonists of kappa receptors and antagonizing CCK-B receptors may contribute to their analgesic activity.

Biography

Masoumeh Behnami was graduated from School of pharmacy, Shaheed Beheshti University of Medical Sciences and Health Services with PharmD degree. She found her interest in designing compounds with novel structure resulting in unique pharmacologic properties. She has been active in scientific fields other than medicinal chemistry and published papers in reputed domestic journals.

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