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Pyrimidine and cumene derivatives functionalized by hydroxy and methoxy: Computational insights in drug-likeness, ADM, and toxicity studies

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ABSTRACT

The –OH and –OCH_3 functionalized isopropyl cumene and isopropyl pyrimidine derivatives were designed and, explored in terms of the ADM, and possible toxic effects in view of the medicinal and environmental. For this goal, the geometry optimizations and structural confirmations were conducted by the G09W package at B3LYP/6-311G** level of theory. The verified geometries were used for further computations and analyses. The bioavailability features such as lipophilicity, water solubility, and drug-likeness, pharmacokinetics were determined by SwissADME tools. Also, ADMETLab computations were used to predict the absorption, distribution, metabolism, and toxicity of the data set. The FMO and NBO analyses were performed to determine the –OH and –OCH_3 function effect on the cumene and pyridine structures and then the electronic properties underlying the bioavailability and toxicity properties. Accordingly, the –OCH_3 function on the structure l seems to be important to rise the inhibitory or substrate potency in the enzyme metabolism for both series. For the pyrimidine series, the anomeric interactions ($n \rightarrow \sigma^*$) in addition to the resonance interactions ($n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$) also would have a role in molecular stability and affect the charge distribution on the molecular surface, which could play of remarkable role in the bioavailability and ADM. In terms of electronic structure and physicochemical properties, and possible bioactivity or toxicity relationship, the results obtained in the study will be an important reference source for the research on exploring/developing/improving future biocompatible molecular structures.

Introduction

The heterocyclic skeleton is a constituent of natural dyes, herbicides, and pesticides [1], as well as the traditional agents used for medicinal purposes [2,3]. Also, heterocyclic compounds in synthetic chemistry, especially those having aromatic and/or fused rings, are of great place in the different scientific areas due to the capability of a flexible application. In this perspective, the pyrimidine scaffold is also a constituent of natural-based compounds such as thiamine, alloxan, cytosine, etc., as ring-fused compounds [4–6] and substituted components. Unlike benzene, nitrogen atoms in 1- and 3- positions in its six-membered ring structure provide a significant structural advantage to pyrimidine compounds, which are widely members of the N-heterocyclic compounds, for use in medical fields. For this reason, the functionalized pyrimidines have a main place in synthetic chemistry, and still, research goes on to concentrate on the pyrimidine process of obtaining pyrimidine by a shorter, efficient, low toxicity, and facile route [7–9]. A promising work for the green synthetic process has been published to form the Schiff bases in the framework of the pyrimidine by using traditional and microwave techniques and authors suggested that the yields of the substituted pyrimidines synthesized by microwave tools are quite higher than those of the traditional approaches [10]. Furthermore, a series of pyrimidine derivatives were synthesized by DABCO (1,4-diazabicyclo[2.2.2]octane) catalysis with a one-pot domino method, and then its antibacterial properties were investigated [11]. In that research, the authors [11] have determined that the diazepine-substituted pyrimidine carboxylic acid methyl ester compound has a remarkable antibacterial activity against *S. aureus* and *E. coli*. Zhang and coworkers [12] have designed novel Arylpyrazole derivatives in the core of pyrimidine to develop fungicidal compounds and suggested that one of the new compounds promises a higher activity against CDM than has already been used in commercial fungicides (Scheme 1).

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