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Design of fluoxetine derivatives for the treatment of Rett syndrome

Rett syndrome is a genetic disorder affecting the development of both brain and nervous system, primarily impacting girls. It's a rare and orphan disease, meaning it has a prevalence of 1 in 10,000 to 15,000 girls, and furthermore, there's no enough development of therapeutic drugs to improve its symptoms [1]; it has recently been reported that the molecule fluoxetine has the capacity to reduce motor coordination deficits present in this syndrome [2]. Therefore, the present work will present a theoretical study on how chemical modification of this drug can improve its absorption, distribution, metabolism, excretion, toxicity, synthetic accessibility (ADMET-SA) properties, as well as its physicochemical properties, antioxidant capacity, and improved interaction with receptors involved in this syndrome, thereby enhancing fluoxetine's therapeutic effect.

Figure 1 (attached)

The present study was carried out using the CADAMA-Chem computational methodology [3], which is summarized in the following steps: 1) Fluoxetine derivatives (see Figure 1) were obtained through single or double functionalization with the functional groups -NH2, -OH, -OCH3, -SH, and -C=OH at the different sp2 carbons of the pristine molecule. 2) Subsequently, the ADMET-SA properties of over 600 derivatives were calculated, and 5 were chosen, which showed improved properties compared to pristine fluoxetine. Then, 3) for the 4 best derivatives, a conformational search was performed using semi-empirical potentials. Subsequently, using calculations with the DFT approximation, the acidity constant values and thus the acid-base equilibrium of each derivative were theoretically evaluated. For each ionic species of each derivative, 4) a primary antioxidant capacity study was conducted, and for those favored species, 5) a molecular docking interaction study of these derivatives with receptors relevant to this syndrome was performed. This study contributes to the design of drugs for orphan diseases, also provides a hope to improve the quality of life for those suffering from this illness.

[1] U. Petriti & et al. (2023), "Global prevalence of rett syndrome: systematic review and meta-analysis," Systematic Reviews 12, 5. [2] C. Villani & et al. (2020), "Fluoxetine rescues rotarod motor deficits in mecp2 heterozygous mouse model of rett syndrome via brain serotonin", Neuropharmacology 176, 108221. [3] E. G. Guzman-Lopez & et al (2022), "CADMA-chem: A computational protocol based on chemical properties aimed to design multifunctional antioxidants", International Journal of Molecular Sciences 23.

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