AI/ML AND VIRTUAL HUMAN PLATFORMS FOR THREAT AGENT HAZARD ASSESSMENT AND MEDICAL COUNTERMEASURE DISCOVERY AND DRUG DEVELOPMENT

The Use Of O-alkylation To Enhance Structural Stability And Biological Activity Of Rotigotine

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Approximately one-third of all Food and Drug Administration (FDA) approved drugs mediate their effects through G protein coupled receptors (GPCRs). Notably, Rotigotine activates GPCR pathways to support continuous dopaminergic stimulation (CDS). Rotigotine is used as a therapeutic drug to treat a range of neurodegenerative disorders such as Willis-Ekbom disease (Restless Leg Syndrome) and Parkinson's disease. Two forms of Rotigotine exist: Form I is the metastable structure typically used as the transdermal patch (Neupro). Neupro can undergo changes in spatial arrangement within the crystalline lattice when exposed to elevated temperatures (above 10°C) thus, giving Form II a relatively stable structure. However, during 2008, the transdermal patch was recalled due to poor absorption from crystallization. Thus, Form II is a relatively stable structure. It has been proposed that the difference between structures account for the change in biological activity. Reports of oxidation and instability indicate the vital need for structural changes to ensure product quality. The goal is to identify and design a series of promising Rotigotine derivatives to enhance compound stability and biological activity. Moreover, the derivatives must effectively minimize the amount of impurities encountered during product synthesis or product storage. The Rotigotine derivatives are generated via O-alkylation to create an unreactive ether analog to change intrinsic properties such as solubility and overall reactivity. Several reaction conditions were explored to identify the fastest, lowest cost, and highest yielding reaction. A set of conditions were found to afford an analog in good yield and this will be applied to synthesize other O-alkylated Rotigotine derivatives. This research has implications to establish Quantitative Structure-Activity Relationship (QSAR) models that can provide a rational design for defense against current and next generation chemical agents.

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