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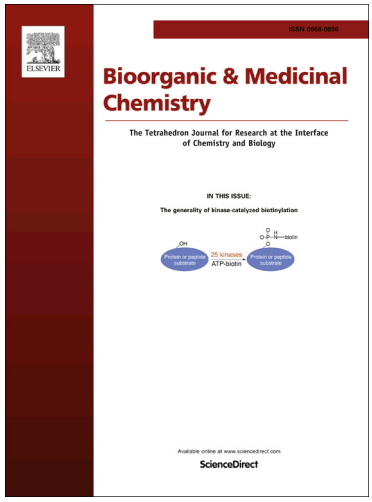

Computer design, synthesis, and bioactivity analyses of drugs like Fingolimod used in the treatment of Multiple Sclerosis

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Computer design, synthesis, and bioactivity analyses of drugs like Fingolimod used in the treatment of Multiple Sclerosis

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Abstract

Multiple Sclerosis (MS) is a very common disease of vital importance. In the MS treatment, some drugs such as fingolimod which help to protect nerves from damage are used. The main goal of the drug therapy in MS is to take control of the inflammation which leads to the destruction of myelin and axons in nerve cell and thus prevent and stop the progression of the disease. Fingolimod (**FTY720**) is an orally active immunomodulatory drug that has been used for the treatment of relapsing-remitting multiple sclerosis. It is a sphingosine-1-phosphate receptor modulator which prevents lymphocytes from contributing to an autoimmune reaction by inhibiting egress of lymphocytes them from lymph nodes. In this study, we have computer designed, synthesized and characterized two novel derivatives of **FTY720**, **F1-12h** and **F2-9**, and have determined their underlying mechanism of their beneficial effect in SH-SY5Y, SK-N-SH, and U-118MG cell lines. For this purpose, we first determined the regulation of the cAMP response element (CRE) activity and cAMP concentration by **F1-12h** and **F2-9** together with **FTY720** using pGL4.29 luciferase reporter assay and cAMP immunoassay, respectively. Then, we have determined their effect on MS- and GPCR-related gene expression profiles using custom arrays along with **FTY720** treatment at non-toxic doses (EC10). It was found that both derivatives significantly activate CRE and increase cAMP concentration in all three cell lines, indicating that they activate cAMP pathway through cell surface receptors as **FTY720** does. Furthermore, **F1-12h** and F2-9 modulate the expression of the pathway related genes that are important in inflammatory signaling, cAMP signaling pathway, cell migration as well as diverse receptor and transcription factors. Expression of the genes involved in myelination was also increased by the treatment with **F1-12h** and **F2-9**. In summary, our data demonstrate that the two novel **FTY720** derivatives act as anti-inflammatory ultimately by influencing the gene expression