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Rajnibhai V. Patel
PharmInnova Award
Best M. Pharm Thesis

WINNER

Winner

Ms. Krishna A Gajjar

Research Guide

Dr. Anuradha K. Gajjar

Subject:
Pharmaceutical Chemistry

Thesis Title :
Design, synthesis & Pharmacological evaluation of 2-Aminothiophene derivatives as Antidiabetic agents

College:
Institute of Pharmacy, Nirma University, Ahmedabad

Chemical synthesis of new anti-diabetic drug

Outcome of Research

PTP1B (protein-tyrosine phosphatase 1B) is an intracellular enzyme found on endoplasmic reticulum. PTP1B is a negative regulator of the insulin signaling pathway and is considered a promising potential therapeutic target for the treatment of diabetes. This study successfully designed and synthesized 2-aminothiophene derivatives based on docking studies (Computational simulation of a ligand binding to a receptor) on PTP1B allosteric site. Synthesis of compounds were carried out, keeping in mind twelve principles of green chemistry. In vivo evaluation of the selected compound was done using the oral glucose tolerance test. The molecules exhibited good control of both, fasting and post meal glucose levels in experimental animals, validating the results of docking studies.

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ABSTRACT

According to International Diabetes Federation (IDF), India is the World Diabetes Capital with a current figure of 50.8 million. Globally, by 2030 an estimated 435 million people are expected to suffer from this disease. Several strategies are being pursued to improve the pharmacological properties of PTP1B inhibitors. After review of public domain literature, research strategy is focused on combining sulphonylurea with known PTP1B inhibitor scaffold 2-aminothiophene. Sulfonylurea acts as insulin secretagogues and control postprandial glucose. PTP1B is an enzyme involved in insulin signalling. It is reported that peripheral insulin resistance is due to over activity of this enzyme. So inhibitor of PTP1B may improve peripheral insulin resistance and hence fasting glucose control. By attempting such strategy it will serve as pharmacophore for both insulin secreatagauges action as well as PTP1B inhibition. The extensive literature search was carried out to know the available chemical space, possible modifications and based on its analysis the new strategy were planned. Virtual library was designed to maintain the essential features required for both actions..Docking studies were performed in order to determine PTP1B inhibition potential of molecules. Co-crystal structure of PTP1B enzyme are 1T49, 1T4J and 1L8G PDB codes. Docking simulations were carried out using Surflex-Dock program interfaced with SYBYLX-1.2. KG-2 binds with Asn-193, KG-6 binds with Asn-193 & Leu-192, KG-7 binds with Asn-193 & Ala-189, KG-13 binds with Asn-193, Leu-193 and Phe196 on allosteric site. Based on the docking results, synthesis of compounds was carried out keeping in mind principles of green chemistry. Multicomponent Reactions were carried out in **Gewald reaction** with different methods like photochemical, microwave, ultra-sonication, solvent-free. It is difficult to have amide coupling reactions with good yield by using coupling reagents.To avoid hazardous reagents like HoBt, BOP **Schotten–Baumann reactionwas carried out** this was our another approach towards developing green chemistry. **Suzuki-Miyaura reaction** was carried out to synthesize Biaryl Ring system and in ^{1}H NMR spectra of the desired product there is no interference of paramagnetic substance. Structures of synthesized and purified compounds were established by IR, Mass and ^{1}H NMR spectral data. Some of the impurities were characterized and quantified based on the ^{1}H NMR spectral data. HPTLC was used for assigning the purity of the selected compounds. The merged impurities were visualized by performing three-dimensional thin layer chromatography. The compounds which gave the highest score were further evaluated for in-vivo activity. Oral glucose tolerance test (OGTT) for no diabetic rats were performed according to the standard method. The molecules showed both the actions i.e. postprandial glucose control via and fasting blood glucose control. Compounds KG-7 at Higher Dose (25mg/kg) showed excellent decrease than in Metformin and good decrease than Glibenclamide in the post-prandial

glucose control test. The key finding of this research work is, selected compounds are well docked at allosteric site which will address the selectivity. The prodrug approach improved the drug likeness. The in vivo results concludes that New Design Strategy, Docking Studies for prioritization of designed compounds for synthesis(focussed synthesis) , application of principles of green chemistry and correct interpretation of spectral data to assign the structure of the synthesised compounds to develop antidiabetic agents worked well.

Keywords: 2 Amino-thiophene, PTP1B, green Chemistry, Sulfsonylurea, OGTT, docking