In silico design and molecular docking study of some novel flutamide analogues in the management of prostate cancer

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The androgen receptor (AR) plays a crucial role in the development of sexual functions in men, as well as the overexpression of androgenic hormones that contribute to prostate cancer (PC) development. Therefore, AR is an essential target for PC research. The aryl group of flutamide has been used as a replacement site in the present study to design newer and safer analogues using a bioisosteric approach with reduced toxicity. To design flutamide analogues, MolOpt was used along with ADMETlab 2.0 to determine their pharmacokinetic and toxicity properties. Additionally, OSIRIS Property Explorer was used to eliminate drug-likeness and drug score. Docking of the newly designed analogues was carried out using ArgusLab 4.0.1 based on Hartree–Fock calculations. The docking score ranged from –8.12 to –11.06 kcal/mol for all the ligands. A good binding score was observed for ligands 008, 009, 012, 016, 018 and 020, which had significantly better binding features than the other ones. Results from the *in silico* approaches (docking and ADMET study) suggest that these compounds 008 and 020 may have the potential as anti-androgen for prostate cancer. The hypothesis may be tested by synthesizing and evaluating the compounds for anti-androgen activity using *in vitro* and *in vivo* approaches.

Keywords: Anti-androgen agent, bioisosteric approach, flutamide, molecular docking, prostate cancer.

AR is divided into three domains: the DNA-binding domain (DBD), the ligand-binding domain (LBD) and the N-terminal domain (NTD). DBD and LBD are involved in the translocation of AR from the cytoplasm to the nucleus, whereas NTD contains amino acids like polyglutamine and polyglycine to regulate transcription[6]. As a result of the overexpression of AR, testosterone may be transported more readily into tumour cells, causing DNA transcription and proliferation, which may lead to PC. Currently, PC is treated by a single or combination of approaches, including castration (removal of the testicles), radiation implant and hormonal treatment (AR antagonists). The disease is treated with flutamide, bicalutamide and nilutamide. These treatments become resistant to the AR antagonists after 2–4 years because of mutation in the AR[7,8].

Flutamide is a nonsteroidal antiandrogen drug which is chemically 2-methyl-*N*-[4-nitro-3-(trifluoromethyl)phenyl]-propanamide (Figure 1)[9,10]. It is frequently used to treat PC by blocking the AR after binding and is also effective for the treatment of polycystic ovary syndrome caused by an excess of androgen in women[11–13]. Recently, it has been used in the treatment of hyperandrogenism in women[14]. Flutamide is rapidly absorbed from the oral route, and in the liver, it is converted into the active metabolite 2-hydroxyflutamide (Figure 1)[15,16]. Idiosyncratic hepatotoxicity can be caused by flutamide due to the formation of