Comparative Computational Studies on Selective CytochromeP450 1B1 Inhibitors

Mohd Usman Mohd Siddique[1,2,*], Azim Ansari[2], Barij Nayan Sinha[1], Venkatesan Jayaprakash[1]

[1]*Department of Pharmaceutical Sciences and Technology*
Birla Institute of Technology
Mesra, Ranchi-835215, India
E-mails: palladiumsalt@gmail.com, bnsinha@bitmesra.ac.in, drvenkatesanj@gmail.com

[2]*Shri Vile Parle Kelavani Mandal's Institute of Pharmacy*
Dhule-424001, Maharashtra, India
E-mail: azimchem313@gmail.com

[*]*Corresponding author*

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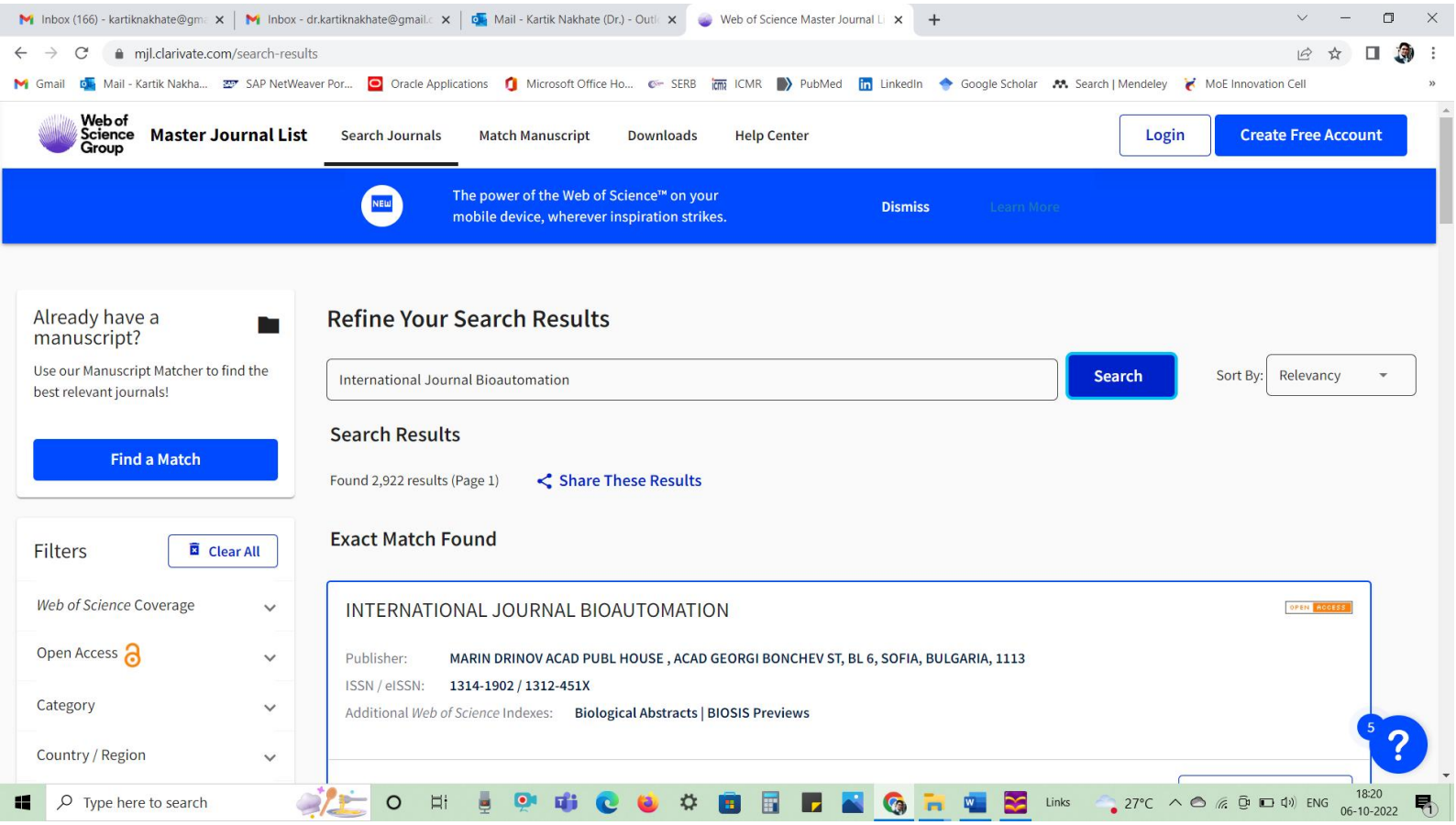
Abstract: *Selective inhibitors of CYP isoforms gaining importance in the treatment of cancers caused by hormonal imbalance. Metabolites of estradiol and polyaromatic hydrocarbons generated due to CYP1B1 activity were reported to be oncogenic. The selective CYP1B1 inhibitors could have the potential therapeutic utility in controlling the cancer due to these oncogens. Due to the CYP isoforms high sequence similarity the design of selective CYP inhibitor is difficult. Recently our group has reported two novel chemical classes (scaffolds) that are specific towards CYP1B1. The chemical architecture of these compounds should give valuable information for its selectivity and potency against CYP1B1. Overlay of our compounds and ANF by Shape and electrostatic based similarity and molecular docking displayed different orientations. Moreover the study has shown the overlay of three atom bridge of selective inhibitor superimposed on –O-CH- linking aryl groups rather than –CO-CH=CH- of ANF. Molecular docking simulation revealed that the selective inhibitors are either establishing H-bonding interaction with Asp333 or π-π staking interaction Phe231 and Phe268. Molecular docking simulation has provided much more information rather than simple shape and electrostatic based similarity study. Crucial H-bonding interactions and π-π staking interactions responsible for selectivity towards CYP1B1 were identified. Two atom linker between the aryl groups matter, cyclization simply ensures the planarity of ANF and quinazolines.*

Keywords: *CYP1B1, Selective inhibitors, Similarity search, Docking, Druggability, ADME.*

Introduction

Cytochrome P450 (CYP) enzymes are present in various organs of the human body, comprise of a large family of detoxification enzymes. The cytochrome P450 1B1 isoform (CYP1B1) is a heme-thiolate monooxygenase which causes the hydroxylation of steroids, estrogens and fatty acids. Unlike other CYPs, CYP1B1 is not present in normal healthy tissues but significant expression of the protein has been reported in most hormonal cancers including that of the ovary, prostate, uterus, mammary, pituitary, regardless of the cancer's genetic origin. Recent studies revealed that CYP1B1 plays a major role in the genesis of hormone-mediated prostate and breast cancers [14-16]. In both cancerous and precancerous cells of mammary, prostate and ovarian tissues, the regio-specific metabolism of estradiol by CYP1B1 produces '4-hydroxy estradiol (4-OHE_2)', while CYP1A1 and CYP1A2 produces '2-hydroxy estradiol (2-OHE_2)'. Amongst these two metabolites 4-OHE_2 has been reported to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