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Non-carboxylic acid inhibitors of aldose reductase based on N-substituted thiazolidinedione derivatives

Mohd Usman Mohd Siddique [a, f, 1], Abhishek Thakur [b, 1], Deepak Shilkar [a, 1], Sabina Yasmin [a, g, 1], Dominika Halakova [c], Lucia Kovacikova [c], Marta Soltesova Prnova [c], Milan Stefek [c, **], Orlando Acevedo [b], Gayathri Dasararaju [d], Velmurugan Devadasan [d], Susanta Kumar Mondal [e], Venkatesan Jayaprakash [a, *]

[a] Department of Pharmaceutical Sciences & Technology, Mesra, Ranchi, 835215, (JH), India
[b] Department of Chemistry, University of Miami, Coral Gables, Florida, 33146, USA
[c] Institute of Experimental Pharmacology and Toxicology, CEM, Slovak Academy of Sciences, Bratislava, Slovak Republic
[d] Centre of Advanced Study in Crystallography and Biophysics, University of Madras, Guindy Campus, Chennai, 600025, (TN), India
[e] TCG Life Sciences Ltd, Block-EP & GP, BIPL, Tower-B, Saltlake, Sector-V, Kolkata, 700091, (WB), India
[f] Department of Pharmaceutical Chemistry, Shri Vile Parle Kelavani Mandal's Institute of Pharmacy, Dhule, 424001, (MH), India
[g] Department of Pharmaceutical Chemistry, College of Pharmacy, King Khalid University, Abha, 61441, Saudi Arabia

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ABSTRACT

In search of dually active PPAR-modulators/aldose reductase (ALR2) inhibitors, 16 benzylidene thiazolidinedione derivatives, previously reported as partial PPARγ agonists, together with additional 18 structural congeners, were studied for aldose reductase inhibitory activity. While no compounds had dual property, our efforts led to the identification of promising inhibitors of ALR2. Eight compounds (**11**, **15**–**16**, **20**–**24**, **30**) from the library of 33 compounds were identified as potent and selective inhibitors of ALR2. Compound **21** was the most effective and selective inhibitor with an IC_{50} value of 0.95 ± 0.11 and 13.52 ± 0.81 μM against ALR2 and aldehyde reductase (ALR1) enzymes, respectively. Molecular docking and dynamics studies were performed to understand inhibitor-enzyme interactions at the molecular level that determine the potency and selectivity. Compound **21** was further subjected to *in silico* and *in vitro* studies to evaluate the pharmacokinetic profile. Being less acidic (p*Ka* = 9.8), the compound might have a superior plasma membrane permeability and reach the cytosolic ALR2. This fact together with excellent drug-likeness criteria points to improved bioavailability compared to the clinically used compound Epalrestat. The designed compounds represent a novel group of non-carboxylate inhibitors of aldose reductase with an improved physicochemical profile.

1. Introduction

Drastic changes in lifestyle habits in the past few decades have raised the incidence of diabetes mellitus worldwide. According to an estimate by the International Diabetes Federation, the global prevalence of diabetes is set to increase from the current figure of 451 million individuals worldwide to 693 million by 2045 [1]. As diabetes mellitus is a multifactorial disease, drugs targeting proteins in different biochemical pathways leading to the pathogenesis of diabetes mellitus are required. Accordingly, there are different classes of oral antidiabetic agents available. However, each class of drug is associated with a set of problems related to potency, pharmacokinetic profile and toxicity. Hence, there is a need to develop a novel candidate with a better profile. In addition,

Abbreviations: ALR1, Aldehyde Reductase; ALR2, Aldose Reductase 2; BCS, Biopharmaceutical Classification System; CG, Conjugate Gradient; MD, Molecular Dynamics; NADP, Nicotinamide-Adenine-Dinucleotide Phosphate; PBS, Phosphate Buffer Solution; RMSD, Root-Mean-Square Deviations; RMSF, Root-Mean-Square Fluctuation.

* Corresponding author.
** Corresponding author.
E-mail addresses: palladiumsalt@gmail.com (M.U. Mohd Siddique), axt651@miami.edu (A. Thakur), deepakshilkar@live.com (D. Shilkar), Sabinayasmin20@gmail.com (S. Yasmin), dominika.halakova@gmail.com (D. Halakova), lucia.kovacikova@savba.sk (L. Kovacikova), marta.prnova@savba.sk (M.S. Prnova), milan.stefek@savba.sk (M. Stefek), orlando.acevedo@miami.edu (O. Acevedo), drdgayathri@gmail.com (G. Dasararaju), shirai2011@gmail.com (V. Devadasan), susanta.mondal@tcgls.com (S.K. Mondal), venkatesanj@bitmesra.ac.in (V. Jayaprakash).
[1] Authors contributed equally Email & ORCiD IDs of contributing authors.

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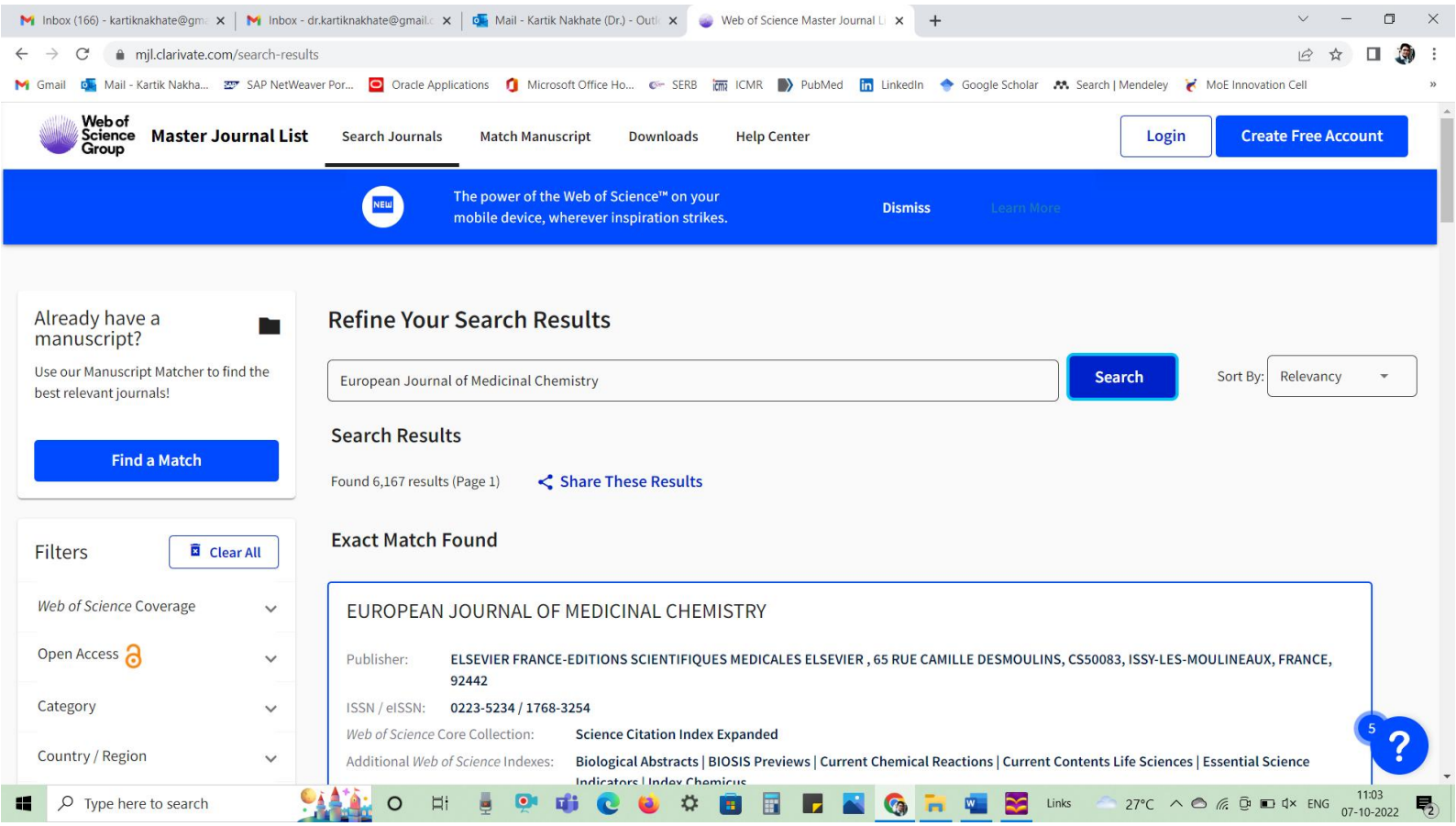
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