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Year 2022-2023

3.3.2 Number of research papers per teachers in the Journals notified on UGC website during the year

molecules

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Article

Virtual Screening, Synthesis, and Biological Evaluation of Some Carbohydrazide Derivatives as Potential DPP-IV Inhibitors

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Abstract: Dipeptidyl peptidase-4 (DPP-IV) inhibitors are known as safe and well-tolerated antidiabetic medicine. Therefore, the aim of the present work was to synthesize some carbohydrazide derivatives (**1a**–**5d**) as DPP-IV inhibitors. In addition, this work involves simulations using molecular docking, ADMET analysis, and Lipinski and Veber's guidelines. Wet-lab synthesis was used to make derivatives that met all requirements, and then FTIR, NMR, and mass spectrometry were used to confirm the structures and perform biological assays. In this context, in vitro enzymatic and in vivo antidiabetic activity evaluations were carried out. None of the molecules had broken the majority of the drug-likeness rules. Furthermore, these molecules were put through additional screening using molecular docking. In molecular docking experiments (PDB ID: 2P8S), many molecules displayed more potent interactions than native ligands, exhibiting more hydrogen bonds, especially those with chloro- or fluoro substitutions. Our findings indicated that compounds **5b** and **4c** have IC_{50} values of 28.13 and 34.94 µM, respectively, under in vitro enzymatic assays. On the 21st day of administration to animals, compound **5b** exhibited a significant reduction in serum blood glucose level (157.33 ± 5.75 mg/dL) compared with the diabetic control (Sitagliptin), which showed 280.00 ± 13.29 mg/dL. The antihyperglycemic activity showed that the synthesized compounds have good hypoglycemic potential in fasting blood glucose in the type 2 diabetes animal model (T2DM). Taken all together, our findings indicate that the synthesized compounds exhibit excellent hypoglycemic potential and could be used as leads in developing novel antidiabetic agents.

Keywords: DPP-IV; in vivo; carbohydrazide; 2P8S; ADMET; molecular docking

1. Introduction

Hyperglycemia and many other alterations of carbohydrate and protein metabolisms are symptoms of diabetes mellitus, often known as "DM", a chronic metabolic disorder. The

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Letters in Drug Design & Discovery, 2022, *19*, 160-174

RESEARCH ARTICLE

Synthesis, Characterization and Screening of Some Novel 2-Methyl-N'-[(Z)-Substituted-Phenyl ethylidene] Imidazo [1, 2-a] Pyridine-3-Carbohydrazide Derivatives as DPP-IV Inhibitors for the Treatment of Type 2 Diabetes Mellitus

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Abstract: ***Background***: One of the leading global metabolic diseases marked by insulin resistance and chronic hyperglycemia is type 2 diabetes mellitus (T2DM). Since the last decade, DPP-4 enzyme inhibition has proven to be a successful, safe, and well-established therapy for the treatment of T2DM.

Objective: The present work reports the synthesis, characterization, and screening of some novel 2-methyl-N'-[(Z)-substituted-phenyl ethylidene] imidazo [1, 2-a] pyridine-3-carbohydrazide derivatives as DPP-IV inhibitors for the treatment of T2DM.

Methods: The molecular docking was performed to study these derivatives' binding mode in the enzyme's allosteric site. All the synthesized compounds were subjected for DPP-IV enzyme assay and *in vivo* antihyperglycemic activity in STZ-induced diabetic rats.

Results: The synthesized derivatives exhibited potent antidiabetic activity as compared to the standard drug Sitagliptin. Out of sixteen compounds, A1, A4, B4, C2, C3, and D4 have shown promising antidiabetic activity against the DPP-IV enzyme. The most promising compound, C2, showed a percentage inhibition of 72.02±0.27 at 50 µM concentration. On the 21st-day, compound C2 showed a significant reduction in serum blood glucose level, *i.e*., 156.16±4.87 mg/dL, then diabetic control, which was 280.00±13.29 mg/dL whereas, standard Sitagliptin showed 133.50±11.80 mg/dL. In the *in vivo* antihyperglycemic activity, the compounds have exhibited good hypoglycemic potential in fasting blood glucose in the T2DM animal model. All the docked molecules have exhibited perfect binding affinity towards the active pocket of the enzyme. The synthesized derivatives were screened through Lipinski's rule of five for better optimization, and fortunately, none of them violated the rule.

Conclusion: The above results indicate that compound C2 is a relatively active and selective hit molecule that can be structurally modified to enhance the DPP-IV inhibitor's potency and overall pharmacological profile. From the present work, it has been concluded that substituted pyridine-3-carbohydrazide derivatives possess excellent DPP-IV inhibitory potential and can be better optimized further by generating more *in vivo, in vitro* models.

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Keywords: DPP-IV inhibitors, Type 2 diabetes mellitus, T2DM, pyridine-3-carbohydrazides, enzyme assay, molecular docking.

1. INTRODUCTION

The worldwide public health issue for type 2 diabetes mellitus (T2DM) is rising continuously. One of the leading global metabolic diseases marked by insulin resistance and chronic hyperglycemia is T2DM [1]. In India, about 70 million persons have diabetes, and about 1.6 million people are at risk of developing the condition [2]. The sum of people who will have diabetes by 2040 is estimated to be 123.5 million, as per the international diabetes federation (IDF) [2]. More than 23 million people in the US are diabetic (approximately 8 percent of the total population) [3]. Diabetes has numerous clinical problems, including cardiovascular disease, nephropathy, retinopathy, and neuropathy [4-6]. Present oral care therapies for type 2 diabetes are intended to reduce the synthesis of hepatic glucose, promoting the secretion of glucose, reducing glucose ingestion, and increasing the use of residual glucose [1, 7, 8]. Commonly, T2DM is

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Journal of Science and Arts Volume 22, Issue 3, pp. 735-754, 2022

ORIGINAL PAPER

FORMULATION DEVELOPMENT AND EVALUATION OF IMMEDIATE RELEASE TABLET OF PARACETAMOL AND ORPHENADRINE CITRATE BY DIRECT COMPRESSION METHOD

BHARAT ASHOK NIKAM[1], AMOL U. GAYKE[1,*]

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Abstract. *The objective of this research work was to formulate, develop and evaluate immediate release tablet of paracetamol and orphenadrine citrate by direct compression method. Paracetamol which is antipyretic and orphenadrine citrate is skeletal muscle relaxant. The drug paracetamol and orphenadrine citrate was taken and formulated with different concentration of cross-povidone, mannitol, micro-crystalline cellulose, magnesium stearate and talc. Where cross-povidone as a superdisintegrant, mannitol as diluent, micro-crystalline cellulose as binder, magnesium stearate as lubricant and talc as a glidant used. the preformulation parameters such as bulk density, tapped density, compressibility index and hausner's ratio were analysed. The thickness, hardness, friability, weight variation, disintegration time & drug content uniformity was evaluated. the in-vitro drug release studied were performed in the usp type (ii) paddle using 0.1N HCl as a dissolution media at 75 rpm speed and temperature of 37±0.5°C. The % drug release at different time interval was estimated using UV method. Based on the evaluation result f9 trial was selected as the best formulation. The in-vitro drug release profile of the drugs was compared with marketed reference product. All the evaluated result was found to be satisfied with the reference products.*

Keywords: *Paracetamol; orphenadrine citrate; direct compression.*

1. INTRODUCTION

For decades, oral drug delivery has been recognised as the most widely used route of administration among all the routes that have been investigated for the systemic delivery of drugs via various pharmaceutical products in various dosage forms. The oral route's popularity may be due in part to its ease of administration, as well as the traditional belief that the drug is well absorbed along with the gastrointestinal tract and food stuff when administered orally. It is the most desirable and preferred method of administering therapeutic agents for their systemic effects. Furthermore, oral medication is widely regarded as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, owing to patient acceptance, ease of administration, and a cost-effective manufacturing process [1-3].

On the other hand, pharmaceutical dosage forms such as tablets, capsules, suppositories, creams, ointments, liquids, aerosols, and injectables have been used to deliver drugs to patients for the treatment of a variety of diseases. Even today, conventional dosage forms are the most common pharmaceutical vehicles in the prescription and over-the-counter

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Current Medicinal Chemistry, XXXX, *XX*, 1-00 1

RESEARCH ARTICLE

The Efficient Activity of Glabridin and its Derivatives Against EGFR--mediated Inhibition of Breast Cancer

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Abstract: ***Background*:** Breast cancer (BC) is one of the most typical causes of cancer death in women worldwide. Activated epidermal growth factor receptor (EGFR) signaling has been increasingly associated with BC development and resistance to cytotoxic drugs. Due to its significant association with tumour metastasis and poor prognosis, EGFR-mediated signaling has emerged as an attractive therapeutic target in BC. Mainly in all BC cases, mutant cells over-expresses EGFR. Certain synthetic drugs are already used to inhibit the EGFR-mediated pathway to cease metastasis, with several phytocompounds also revealing great chemopreventive activities.

***Methods*:** This study used chemo-informatics to predict an effective drug from some selected phytocompounds. The synthetic drugs and the organic compounds were individually screened for their binding affinities, with EGFR being the target protein using molecular docking techniques.

***Results*:** The binding energies were compared to those of synthetic drugs. Among phytocompounds, Glabridin (phytocompound of *Glycyrrhiza glabra*) manifested the best dock value of -7.63 Kcal/mol, comparable to that of the highly effective anti-cancer drug Afatinib. The glabridin derivatives also exhibited comparable dock values.

***Conclusion*:** The AMES properties deciphered the non-toxic features of the predicted compound. Pharmacophore modeling and *in silico* cytotoxicity predictions also exhibited a superior result assuring their drug likeliness. Therefore, Glabridin can be conceived as a promising therapeutic method to inhibit EGFR-mediated BC.

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#These authors contributed equally to this work.

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Prerana B. Jadhav et al/ Design, Synthesis and Antibacterial Evaluation of some new 2, 5-disubstituted 1, 3, 4-oxadiazole derivatives

Design, Synthesis and Antibacterial Evaluation of some new 2, 5-disubstituted 1, 3, 4-oxadiazole derivatives

Prerana B. Jadhav[1]*, Sunayana R. Vikhe[2], Pooja S. Jadhav[1], SonaliN. Valate[1], SonaliS. Jadhav[1]
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ABSTRACT
Compounds containing 1,3,4-Oxadiazole nucleus investigated for CYP51 inhibitory activity. Current research work describes the designing, molecular docking, synthesis and structural elucidation of certain new 2,5-disubstituted 1,3,4-Oxadiazole derivatives investigated for antimicrobial activity. Series of the 2,5-disubstituted 1,3,4-Oxadiazole derivatives were designed and show good *in silico* ADME properties. The molecular docking study was done by Autodockvina software exploring better interaction with target protein and could be the potent inhibitor of ergosterol biosynthesis. The novel 2,5-disubstituted 1,3,4-Oxadiazole derivatives synthesized by conventional heating method as well as microwave irradiation method. The microwave assisted synthesis remarkely higher yield at less time compared to conventional synthesis. Structural elucidation was done by FTIR, ^{1}H NMR and Mass spectroscopy. The synthesized compounds subjected to *in vitro* antimicrobial activity by agar diffusion method and all compounds show good inhibition of bacterial growth.
Keywords: *In silico*ADME, Molecular Docking, Synthesis, 1,3,4- Oxadiazole, Antimicrobial Activity.
DOINumber:10.48047/nq.2022.20.22.NQ10196 **NeuroQuantology2022;20(22):2077-2093**

BACKGROUND AND AIM OF THE WORK

Microbial infections treatments is increasingly complicated by the ability of bacteria to develop resistance to antimicrobial agents (1). Microorganisms have become resistant to currently used antibiotics due to poor infection treatment, over-prescription of antibiotics, and their inappropriate use by patients. This challenges treatment even though previously used antibiotics or antimicrobial drugs are no longer effective, and infections become progressively difficult to treat (2).Drug-resistant bacteria that have spread and developed new resistance mechanisms, resulting to bacterial resistance, continues to cause serious harm to our capacity to treat common diseases. The increasing global development bacterial resistant, which spread disease that are not treatable with the existing antimicrobial medications such as antibiotics (3). 1,3,4-oxadiazole heterocyclic ring shows a lots of therapeutic and biological activities like antimicrobial, anticonvulsant, antitcancer, antipyretic, anti-viral, spasmolytic, antioxidant, anti-inflammatory, insecticidal, CNS stimulant, antiemetic, antidepressant, anthelmintic activities, vasodilator activity and antihypertensive activities (4) The presence of toxophoric –N=C–O– linkage might be responsible for potent pharmacological activities. 2,5-disubstituted-1,3,4-oxadiazole derivatives are stable in which 2,5-diaryl-1,3,4-oxadiazoles are more stable than the 2,5-dialkyl derivatives (5). The 2,5-disubstituted 1,3,4-Oxadiazole derivatives were designed by considering its pharmacophore properties. The various substitutions were used at position 2 and 5 to synthesize 2,5-disubstituted 1,3,4-Oxadiazole

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SOLUBILITY ENHANCEMENT OF BSN WITH PVP AS CARRIER FOR FORMATION OF NANOCOMPOSITES BY MICROWAVE ASSISTED TECHNIQUE

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Abstract
In the present work solubility enhancement of BSN with PVP as carrier for formation of Nanocomposites by microwave assisted technique. The Nanocomposite was prepared in various ratios of drug to polymer. One of the best ratios was selected on the basis of solubility and powder dissolution data for optimization of formulation. The optimized Nanocomposites were subjected to FTIR, DSC, XRD and SEM studies to know the mechanism by which the solubility and dissolution has enhanced. Through characterization can be concluded that the drug has been converted into Nanocompposities and responsible for solubility enhancement. Characterization also confirms that there was no interaction in drugs and polymer. *In-vitro* assessment of optimized formulations has further confirmed the use of Nanocomposites for enhancing solubility and dissolution by use of PVP.
Key-words: Nanocompposities, Solubility enhancement, FTIR, DSC, XRD.

Introduction
The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion. From a patient"s perspective, swallowing a dosage form is a comfortable and a familiar means of taking medication (1,2). Although the oral route of administration is preferred, for many drugs it can be a problematic and inefficient mode of delivery for a number of reasons. Limited drug absorption resulting in poor bioavailability is paramount amongst the potential problems that can be encountered when delivering an active agent via the oral route. (3-5) Drug absorption from the gastrointestinal (GI) tract can be limited by a variety of factors with the most significant contributors being poor aqueous solubility and/or poor membrane permeability of the drug molecule. When delivering an active agent orally, it must first dissolve in gastric and/or intestinal fluids before it can then permeate the membranes of the GI tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs. So, solid dispersion technologies is used to improve the dissolution characteristics of poorly water-soluble drugs and in turn their oral bioavailability.(6)
Solubility is defined as the concentration of the un-dissolved solid in a solvent under a given set of conditions. The solution becomes saturated and the dissolved solute is in equilibrium with the excess un dissolved solute. Poorly water-soluble drugs are increasingly becoming a problem in terms of obtaining the satisfactory dissolution within the gastrointestinal tract that is necessary for good bioavailability. It is not only existing drugs that cause problems but it is the challenge of medicinal chemists to ensure that new drugs are not only active pharmacologically but have enough solubility to ensure fast enough dissolution at the site of administration, often gastrointestinal tract (8). Dissolution of solid dosage forms in gastrointestinal fluids is a prerequisite to the delivery of the drug to the systemic circulation following oral administration. Dissolution depends on the solubility of the drug substance in the surrounding medium. Surface area of drug particle is another parameter that influences drug dissolution and in turn drug absorption, particle size is a determinant of surface area (9).