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Design, Synthesis, Molecular Docking and Antioxidant Evaluation of Benzimidazole-1,3,4 oxadiazole Derivatives

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Highlights

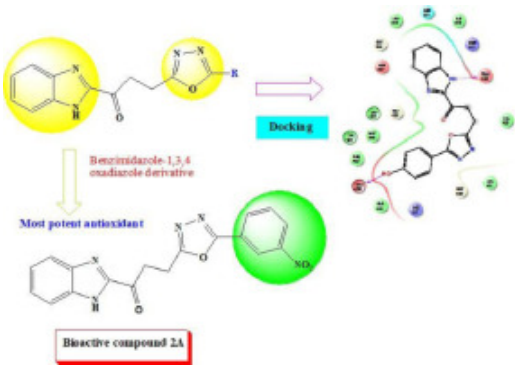
- Design of NME.
- Docking.
- ADMET predictions.
- Synthesis.
- Free radical scavenging activity.

Abstract

In this research, we synthesised novel benzimidazole-1,3,4 oxadiazole derivatives and studied their antioxidant properties using the DPPH Radical Scavenging Assay. A significant class of substances

with a broad range of biological activities is the 1,3,4-benzimidazole family. Furthermore, enabling for various biological activities are the five-membered heterocyclic moieties. Thus, a number of benzimidazole derivatives have been created, there in vitro antioxidant activity has been evaluated, and they have been characterized by FTIR and ^{1}H NMR spectral studies. Compounds **1A, 2A** and **3A** have the highest G-score i.e., - 7.575 kcal/mol, -6.932 kcal/mol, -6.911 kcal/mol, as compared to standards propyl gallate and Ascorbic acid, which had glide scores of -4.757 kcal/mol and -4.50 kcal/mol respectively. The benzimidazole-1,3,4 oxadiazole containing compounds that were created demonstrated impressive antioxidant activity. When compared to the reference standard, ascorbic acid, (IC_{50}-11.51±0.31 µg/ml) Compound 2A demonstrated the strongest antioxidant activity with an IC_{50} value (53.00±1.31 µg/ml) respectively.

Graphical Abstract



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Introduction

Antioxidants are one of the body's many defences against oxidative/nitrosative damage [1]. Being a highly reactive atom, oxygen may mix with other elements to create "free radicals," which are potentially dangerous molecules. Free radicals, which may damage nucleic acids, proteins, carbohydrates, and lipids, are molecules or molecular fragments having one or more unpaired electrons in atomic or molecular orbitals [2]. Early ageing, carcinogenesis, atherosclerosis, cardiovascular disease, moderate cognitive impairment, diabetes mellitus, ischemia, Alzheimer's disease, Parkinson's disease, liver injury, inflammation, skin damages, and arthritis are just a few of the disorders that can result from this [3], [4], [5], [6], [7], [8], [9], [10], [11]. Regular bodily processes result in the production of free radicals and other reactive oxygen species (ROS), vital metabolic activities or by external factors such exposure to X-rays, ozone, tobacco smoke, air pollution, and industrial toxins [12]. Both enzymatic and non-enzymatic processes result in the constant formation of free radicals in cells [13]. Reactive oxygen species (ROS) such as hydroxyl HO·, superoxide O2·,

peroxide ROO·, alkoxyl RO· and nitroxyl NO· radicals cause the oxidative destruction of all organic materials [14]. In general, human physiology involves reactive oxygen species (ROS) and reactive nitrogen species (RNS), two types of free radicals linked to the oxygen atom (O) or their equivalents that are more reactive with other molecules than with oxygen [15,16]. About 5% or more of the oxygen that is breathed in is converted by univalent reduction of oxygen into ROS such superoxide, hydrogen peroxide, and hydroxyl radicals [17]. Because they may scavenge these free radicals to avoid cellular damage by ultimately reducing oxidative stress, antioxidants have a beneficial effect on human health [18]. As a result, oxidation processes may produce free radicals, which harm cells by initiating chain reactions. Antioxidants stop these chain reactions by neutralising or stabilising free radicals, and by self-oxidizing, they prevent subsequent oxidation processes [19]. There have been two suggested primary mechanisms of action for antioxidants [20]. The principal antioxidant donates an electron to the first step, which breaks a chain by providing a free radical in the system with that electron [21]. The role of antioxidants is it aids in lowering free radicals. Normal cell growth is stimulated, and cells are protected against premature and aberrant ageing [22]. Several synthetic antioxidants, such as butylated hydroxy anisole (BHA), tert-butylated hydroquinone (TBHQ), propyl gallate, and butylated hydroxy toluene (BHT), are routinely used as food additives to prevent lipid peroxidation [23,24]. Natural anti-oxidants found in plants and mushrooms have been shown to have crucial roles in both boosting health and curing a variety of diseases, including infectious and cancerous conditions [25].

Oxobenzimidazoles are very useful synthetic intermediates which are reported for a myriad of applications in the area of therapeutics. Oxobenzimidazole analogues were designed by the structural modifications of the three potent structures of the AR antagonist [26]. Many research studies have reported oxadiazole compounds as a medicinal agent with an intent to discover novel chemical scaffold compounds with low toxicity, high bioactive and excellent pharmacokinetic property. The oxadiazoles are the important moieties that show more effective inhibition against various cancer cell lines such as breast cancer (MCF-7, MDA- MB231), skin cancer (HaCaT), cervical cancer (HeLa), liver cancer (HepG2), colorectal cancer (SW1116), human lung cancer cells (L2987, A549) and stomach cancer (BGC823) [27].

In recent years, the structural activity relationship with target structures and their mechanism used for the drug design and oxadiazole has been reported with various biological activities such as antitubercular, antiviral, antifungal, antibacterial, antimicrobial, antidiabetic and anticancer activities, in particular, 1,3,4-oxadiazole is an important moiety that exhibits more potent and selective inhibitory activity against various cancer cell lines [28]. Recently, there are reports of correlation of antioxidants with protection of the human body from free radicals which facilitated retardation of the progress of many chronic diseases. Earlier reports also demonstrate promising antioxidant properties of the plant extracts, which are mainly due to the presence of ‘polyphenols’ and phenolic compounds [29]. Recent study on 4-(4-benzoylaminophenoxy) phenol (BAPP) derivatives suggested that the presence of tri-fluoromethyl substitution in the phenyl ring appears to strongly enhance the anticancer activities in the prostate cancer cell lines and Ph-X-Ph skeleton

with amide substitutions shows the exciting AR antagonistic activity in LNCaP cell lines [30].

The antioxidant capacities of the synthesized compounds were evaluated using the free radical scavenging test by using 1,1-diphenyl-2-picrylhydrazyl (DPPH). Protein tyrosine kinase-2beta (PTK-2 β), a regulator of cell regulatory pathways and signal transduction activities, was selected for docking studies [31]. The capacity of peptides to convert ferric iron to ferrous, bind metals (metal chelation), scavenge free radicals (1,1-diphenyl-2 picrylhydrazyl, hydroxyl, and superoxide) and prevent lipid oxidation in-vitro accounts for the majority of their antioxidant activities.

Section snippets

Chemicals

O-Phenylene diamine, alpha-ketoglutaric acid, hydrochloric acid, 3-nitrobenzoic acid,3,4-dichlorobenzoic acid, para-hydroxy benzoic acid, 3,4-dimethoxy benzoic acid, 3,5-dinitrobenzoic acid, POCl3, hydrazine hydrate.…

Reagents

1,1-Diphenyl-2-Picrylhydrazyl (DPPH), ethanol, Dimethyl sulfoxide (DMSO), ascorbic acid.…

Instruments

Prior to usage, all the solvents were thoroughly purified by distillation and were of lab reagents from E. Merck. Pre-coated silica gel was used to monitor the thin layer chromatography process,…

1-(1H-benzo[d]imidazol-2-yl)-3-(5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)-propan-1-one,1A

Brown coloured powder; Yield 45%; Rf 0.65 (toluene: ethyl acetate: formic acid (5:4:1)); λmax 517 nm; FTIR (KBr, cm-1): 3106.45 (O-H), 3443 (N-H), 2929.60 (C-H, Ar-H), 2972(C-H, CH2), 1734.37 (C=O), 1655 (C=N), 1591 (C=C), 1195 (C-O).;1H NMR (500MHz, DMSO) δ 8.71 (s, 1H), 7.88 – 7.78 (m, 3H), 7.69 – 7.62 (m, 1H), 7.39 – 7.30 (m,2H), 6.96 – 6.90 (m, 2H), 4.17 (t, J=9.3 Hz, 2H), 3.48 (t, J=9.3 Hz, 2H). 13C NMR (125MHz, DMSO) δ 193.61, 167.76, 164.27, 159.93, 150.48, 140.35, 137.90, 128.31,…

Conclusion

The careful evaluation of results of molecular docking studies (dry lab work) and anti-oxidant screening assay result, we conclude that the most potent compound 2A was found to show g- score

of 7.575 (docking result) and IC_{50} of 53.60 ± 1.31 µg/ml indicating that results of dry lab were endorsed by wet lab result. Second most potent anti-oxidant compound was found to be compound 3A (IC_{50} =78.4 ± 1.46, g-score -6.911). Compound 4A was found to be 3rd most potent anti-oxidant compound (IC_{50}=…

Credit author statement

1. Shashikant V. Bhandari All results and discussion was redrafted, responses were drafted to reviewers comments. Whole Manuscript was edited, revised and verified.…
2. Om G. Nagras Molecular docking studies, DFT studies, ADMET prediction, Synthesis, references were checked and verified.…
3. Pranali V. Kuthe MS editing, Typographical and grammatical errors, references were checked.…
4. Aniket P. Sarkate Manuscript editing and interpretation of IR, UV and ^{1}H NMR.…
5. Kaustubh S. Waghmare Structure elucidation, free…

…

Declaration of Competing Interest

The authors declare no conflict of interest, financial or otherwise.…

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