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Review article

A review on antioxidant potential of bioactive heterocycle benzofuran: Natural and synthetic derivatives

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ABSTRACT

The majority of heterocycle compounds and typically common heterocycle fragments present in most pharmaceuticals currently marketed, alongside with their intrinsic versatility and unique physicochemical properties, have poised them as true cornerstones of medicinal chemistry. In this context, oxygen heterocycles exhibit diverse biological and pharmacological activities due in part to the similarities with many natural and synthetic molecules with known biological activity. Among oxygen containing heterocycles, benzofuran (synthetic and natural isolated) and its derivatives have attracted medicinal chemists and pharmacologists due to their pronounced biological activities and their potential applications as pharmacological agents such as antioxidant, antitumor, antiplatelet, antimalarial, antiinflammatory, antidepressant and anticonvulsant properties. There are also an amazing number of approved benzofuran-containing drugs in the market as well as compounds currently going through different clinical phases or registration statuses. Due to the wide range of biological activities of benzofurans, their structure activity relationships have generated interest among medicinal chemists, and this has culminated in the discovery of several lead molecules in numerous disease conditions. Recently, this scaffold has emerged as a pharmacophore of choice for designing antioxidant drug development as their derivatives have shown excellent results through different mechanism of action. This review focused on the recent development of benzofuran derivatives as antioxidant agents (including natural products) and their antioxidant activities; summarize the structure property, hoping to inspire new and even more creative approaches. Also, this study systematically provides a comprehensive report on current developments in benzofuran-based compounds as antioxidant agents and is also helpful for the researchers working on a substitution pattern around the nucleus, with an aim to help medicinal chemists to develop structure activity relationships (SAR) on these derivatives as antioxidant drugs.

Abbreviations: AAPH, 2,2′-azobis(2-amidinopropane hydrochloride); AChEs, Acetyl cholinesterase inhibitors; AD, Alzhiemer's disease; ADP, adenosine diphosphate; AO, antioxidant; AOA, antioxidant activity; APB, 6-(2-aminopropyl)benzofuran; BHA, butylated hydroxyanisole; CAT, catalase; CNS, central nervous system; DBO, 2,3-diazabicyclo [2.2.2]oct-2-ene; DNA, deoxyribonucleic acid; DPPH, 2,2-diphenyl-1-picrylhydrazyl; EC_{50}, effective concentration 50; FDA, food and drug administration; FRAP, ferric reducing ability of plasma; GR, glutathione reductase; LDL, low density lipoprotein; LOX, lipid peroxidation; IC_{50}, inhibitory concentration 50; β-CLAMS, inhibition of degradative oxidation of β-carotene) assays; IPL, lipid peroxidation; iNOS, inducible nitric oxide synthase; μM, micro molar; mg, Milligram; MPx, myeloperoxidase; NADPH, Nicotinamide adenine dinucleotide phosphate; NOR, nitric oxide radical scavenging; OIT, oxidation induction time; ORAC, oxygen radical anti-oxidant capacity; PPK, plasma pyruvate kinase (); ppm, part per million; PP, polypropylene; ROCK, Rho-associated protein kinase; RNA, ribonucleic acid; ROS, reactive oxygen species; SAR, structure activity relationship; TBA, thiobarbituric acid; TE, trolox equivalents; TEAC, trolox equivalent antioxidant capacity; UA, Usnic acid; XOD, xanthine oxidase.

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Contents

Introduction 282
Benzofuran or 2,4-dihydrobenzofuran derivatives as antioxidant 282
Benzofuran-based natural products as antioxidants 283
Synthetic benzofuran derivatives as antioxidants 288
Conclusions and future aspects 293
Conflict of interest 293
Acknowledgements 293
References 293

Introduction

Oxygen and its importance in living beings are well known as it plays vital role in several biological processes. However, during oxidative stress, oxygen can leads to formation of free radicals (electrically charged molecules having unpaired electron) including superoxide radical ($O_2^{-\bullet}$), hydroxyl radical ($OH^{\bullet}$), hydrogen peroxide (H_2O_2), and lipid peroxide radicals, on interacting with certain molecules of body during natural processes. Free radicals so formed are also essential at low to moderate concentration for production of energy to fuel biological processes in most living organismsbut when they are generated in higher concentration are very harmful to body as they damage or modified the major components of a cell, such as deoxyribonucleic acid (DNA), ribonucleic acid (RNA), proteins, cell membranes, enzymes etc., and form grounds of various neurodegenerative (Alzheimer, and Parkinson) diseases. Moreover ageing and degenerative diseases of ageing such as cancer, diabetes, rheumatoid arthritis, cardiovascular diseases (atherosclerosis), inflammation, ocular and pulmonary diseases also occur due to uncertain death of the cell or alteration of structure or abnormal function of membranes which is caused by the sequences of chain reactions of free radicals with lipids. The process is known as lipid peroxidation (LPO) which is responsible not only for alteration of the structure or odd function of membranes, but also leads for generation of highly toxic by-products which are responsible for several diseases [1].

Antioxidants are the radical scavenger which helps in delaying or prevention of oxidation by trapping the free radicals. The normal vital concentration of the free radicals or reactive oxygen species (ROS) in living organisms is maintained by the enzymatic antioxidants such as glutathione peroxidise, superoxide dismutase, glutathione reductase, catalase, and non-enzymic antioxidants like alpha-tocopherol, glutathione, and ascorbic acid, which provides protection to the organism against free radical induced oxidative damage [2]. Sometimes these enzymes present in our body are not able to maintain the proper balance of actual required concentration of free radicals due to its unlimited or uncontrolled production and leads to several health problems [3,4]. In such cases additional antioxidants from outside are required to supply to maintain the proper balance between free radicals and enzymatic antioxidants in the body. Many natural and synthetic compounds such as polyphenols, flavonoids, Vitamins C, E, and terpenoids, have been reported as antioxidants due to their ability to donate a hydrogen atom or an electron to chelate redoxactive metals and inhibit lipoxygenases [5,6]. Some of them are available as drugs for the treatment of different diseases related to oxidative stress [7,8]. Thus, discovery of antioxidants that can maintain health in human is of great interest to scientists across the world over the last decades.

Heterocyclic compounds are widely distributed in nature and consumed by mammals through dietary materials. They are essential for health and life as they provide the basic skeletons for most of the existing available drugs. Among these benzofuran (**1**) and its derivatives has emerged as potent source in the area of drug discovery. They are also found in many eatable plants [9–11] and possess a wide spectrum of biological activities including antiviral [12], anti-inflammatory [13], antimicrobial [14], anticancer [15], anti-Alzheimer's [16], antihyperlipidemic [17], anticonvulsant [18], antitubercular [19], analgesic [20], antipyretic [21], CNS regulants [22] and selective enzyme inhibitory activities [23]. The active research on benzofuran begins dates back to the 19th century, when Perkin [24,25] reported synthesis of coumarilic acid (**2**, later given name as benzofuran-2-carboxylic acid) from 3-halocoumarins by treatment with alkali through rearrangement reaction. Few years later after synthesis of benzofuran-2-carboxylic acid, Mustapha et al., [26] isolated first benzofuran based molecule from natural source named khellin (**3**) bearing benzofuran and chromone skeletons simultaneously, from ancient Arabian medicinal plant Khella. Since then a large number of related compounds containing benzofuran moiety has been either synthesized or isolated from the natural sources and became subject of interest due to its diverse biological properties. A number of drugs containing benzofuran skeleton such as saprisartan [27] (**4**, used in the treatment of hypertension and heart failure), benzbromarone (**5**, used in the treatment of gout), vilazodone (**6**, used for the treatment of depressive disorder in adults), 6-(2-aminopropyl)benzofuran or 6-APB (**7** used as psychoactive drug), amiodarone and dronedarone (**8** & **9** respectively, used for treatment of arrhythmia), psoralen, methoxsalen, and trioxsalen (**10**, **11** & **12** respectively, used for treatment of psoriasis, eczema, vitiligo, cutaneous lymphomas, pigment enhancement) has already been released in the clinical world while many more are under clinical trials (Fig. 1). Till date more than thirty four drugs containing benzofuran or 2,4-dihydrobenzofuran skeleton have been approved by Food and Drug Administration (FDA) [28]. Apart from medicinal properties, benzofuran derivatives serve as viable synthons for dyes [29,30], silver photography [31,32], polymer chemistry [33,34], and are also used as brightening agents in textiles, wool, paper, cellulose and nylon [35].

Therefore, the vast range of biological effects associated with this scaffold has resulted in the benzofuran ring system being considered as a privileged structure. The biological potential of benzofuran derivatives has been reported by us previously [28,36]. However no one has described its antioxidant properties briefly. Therefore in this review, we have compiled and discussed specifically on naturally as well synthetic benzofuran derivatives to provide an insight of its antioxidant potential, so that collective information could be helpful to researchers for gaining knowledge and further which could serve as a platform for medicinal chemists to design better antioxidant drugs.

Benzofuran or 2,4-dihydrobenzofuran derivatives as antioxidant

In the development of newer antioxidant agents after flavonoids, benzofuran nucleus has been identified as newer target in medicinal chemistry. In this regard a large number of benzofuran derivatives either synthetic or naturally occurring have