Bioactive Benzofuran Derivatives: A Review

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Original article

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ABSTRACT

In nature's collection of biologically active heterocycles, benzofuran derivatives constitute a major group. The broad spectrum of pharmacological activity in individual benzofurans indicates that this series of compounds is of an undoubted interest. Benzofuran and its derivatives have attracted medicinal chemists and pharmacologists due to their pronounced biological activities and their potential applications as pharmacological agents. 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. The outstanding development of benzofuran derivatives in diverse diseases in very short span of time proves its magnitude for medicinal chemistry research. The present review is endeavour to highlight the progress in the various pharmacological activities of benzofuran derivatives in the current literature with an update of recent research findings on this nucleus.

1. Introduction

Heterocycles occupy a central position in organic chemistry [1–3]. These compounds are an integral part of the chemical and life sciences and a considerable amount of the modern research is being currently pursued on such kinds of compounds throughout the world. Heterocyclic ring systems have emerged as powerful scaffolds for many biological evaluations [4]. These compounds play an important role in the design and discovery of new physiological/pharmacologically active molecules [5]. Heterocyclic compounds provide scaffolds on which pharmacophores can arrange to yield potent and selective drugs [6]. These are of particular interest and significant importance in the search for new bioactive molecules in both the agrochemical and pharmaceutical industries. Indeed, with particular reference to the pharmaceutical industry, heterocyclic motifs are especially prevalent with over 60% of the top retailing drugs containing at least one heterocyclic nucleus as part of the overall topography of the compound [7]. Furthermore, compounds that contain heterocyclic moieties often exhibit improved solubilities and can facilitate salt formation properties, both of which are known to be important for oral absorption and bioavailability [8]. 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 [9]. Benzofuran scaffolds (oxygen heterocycles) have drawn considerable attention over the last few years due to their profound physiological and chemotherapeutic properties as well as their widespread occurrence in nature [10]. Benzofuran derivatives are versatile biodynamic agents that can be used to design and develop new potentially useful therapeutic agents [11]. These are of special interest to researchers for their wide range of biological activities and potential applications as pharmacological molecules. Benzofuran derivatives display potent biological properties including antihyperglycemic [12], analgesic [13], antiparasitic [14], antimicrobial [15], antitumor and kinase inhibitor [16,105] activities. In addition substituted benzofurans find application such as of fluorescent sensor [17], oxidant [18], antioxidants, brightening agents, a variety of drugs and in other field of chemistry and agriculture [19]. Moreover benzofurans occur in a great number of natural products. Many of the natural benzofurans have physiological, pharmacological and toxic properties. There are well known natural products having related benzofuran ring structures, which are particularly isolated from *Machilus glaucescens, Ophryosporus charua, Ophryosporus lorentzii, Krameria ramosissima*, and *Zanthoxylum ailanthoidol* [20]. The most recognized benzofurans are *ailanthoidol, amiodarone* and *bufuralol* compounds. *Ailanthoidol*, a neolignan with a 2-arylbenzofuran skeleton, has been reported to possess a variety of biological activities such as anticancer, antiviral, immunosuppressive, antioxidant, antifungal and antifeedant activities [21]. *Amiodarone* is a

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highly effective antiarrhythmic agent with class III activity [22]. *Bufuralol* is a nonselective β-adrenoceptor antagonist developed by Hoffman–La Roche. This compound is a good substrate of cytochrome P450 (CYP) and undergoes enantioselective and regioselective oxidations in liver [23]. Benzofuran containing structures have been found among naturally occurring furocoumarins, such as psoralen and methoxalen isolated from the seed of *Ammi majus L.* and used for the treatment of psoriasis and other dermal diseases [24,25]. In order to explore diverse biological activities, investigating various methods for synthesis and structural modification of benzofuran ring have now become important goal of several research groups. Thus, benzofuran moiety can be taken as lead compound for the synthesis of novel derivatives with a variety of biological activities.

2. Chemistry

Benzofuran is a heterocyclic compound consisting of fused benzene and furan ring (Fig. 1). This colorless liquid is a component of coal tar. Benzofuran is the "parent" of many related compounds with more complex structures. These heterocyclic compounds show a wide range of pharmacological properties, and change of their structure offers a high degree of diversity that has proven useful for the search of new therapeutic agents. The broad spectrum of pharmacological activity in individual benzofuran indicates that this series of compounds is of an undoubted interest. From this point of view, synthetic methods may be of very useful aid in the production of specific structures characterized by given pharmacological qualities [26]. Moreover from a drug discovery perspective, synthesis of substituted benzofurans could be more interesting because they might constitute starting materials for the production of biologically active compounds. A diversity of synthetic routes can be applied to the synthesis of benzofurans. A convenient metal-free cyclization of *ortho*-hydroxystilbenes into 2-arylbenzofurans and 2-arylnaphthofurans is mediated by hypervalent iodine reagents. Using stoichiometric (diacetoxyiodo) benzene in acetonitrile, desired products can be isolated in good yields [27]. A one-pot synthesis of benzofurans which utilizes a palladium-catalyzed enolate arylation demonstrates broad substrate scope and provides differentially substituted benzofurans in moderate yields. The utility of the method is further demonstrated by the synthesis of the natural product eupomatenoid in three steps [28]. Substituted benzofurans can be synthesized from their corresponding substituted 1-allyl-2-allyloxybenzenes using ruthenium-catalyzed *C*- and *O*-allyl isomerization followed by ring-closing metathesis [29]. An effective, Ru-catalyzed cycloisomerization of benzannulated homo- and bis-homopropargylic alcohols affords benzofurans and isochromenes chemo- and regioselectively (5-, and 6-endo cyclizations). The presence of an amine/ammonium base–acid pair is crucial for the catalytic cycle [30]. Alkali-metal salts of a large number of electron-rich, electron-poor, and sterically hindered aryl- and heteroaryl silanols undergo efficient cross-coupling with a wide range of aromatic bromides and chlorides under mild condition to afford the benzofuran derivatives. The critical feature for the success of these coupling reactions and their considerable scope is the use of bis (tri-*tert*-butylphosphine) palladium [31]. A palladium-catalyzed addition of potassium aryltrifluoroborates to aliphatic nitriles leads to a wide range of alkyl aryl ketones with good yields. The scope of the developed approach is successfully explored toward the one-step synthesis of 2-arylbenzo[*b*]furans *via* sequential addition and intramolecular annulation reactions. The methodology accepted a wide range of substrates and is applicable to library synthesis [32]. A well-defined cationic Ru–H complex catalyzes the dehydrative C–H alkylation reaction of phenols with alcohols to form *ortho*-substituted phenol products. The reaction with diols delivers benzofuran derivatives *via* dehydrative C–H alkenylation and annulation reaction. The catalytic C–H coupling method employs cheap starting materials, exhibits a broad substrate scope, and liberates water as the only by product [33]. Reaction of *O*-aryl hydroxylamine hydrochlorides with either cyclic or acyclic ketones in the presence of methanesulfonic acid leads directly to the benzofuran derivative *via* a proposed one-pot condensation-rearrangement-cyclisation reaction sequence in good to excellent yields [34]. An effective and mild microwave-assisted route to 2-substituted benzofurans directly from carboxylic acids allows the preparation of α-alkyl-2-benzofuranmethanamines from N-protected α-amino acids without racemization in good yields [35]. 2,3-Disubstituted benzo[*b*]furans are readily prepared under very mild reaction conditions by the Sonogashira coupling of various *O*-iodoanisoles and terminal alkynes, followed by an electrophilic cyclization. Aryl- and vinylic-substituted alkynes give cyclization products in excellent yields [36] (Scheme 1).

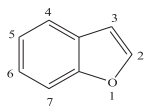

Fig. 1. Chemical structure of Benzofuran.

3. Pharmacological activity of Benzofuran analogs

Benzofuran and its derivatives are central pharmacophores and privileged structures in medicinal chemistry and have featured in a number of clinically used drugs. Recent studies revealed that benzofuran anologs tolerate a broad spectrum of pharmacological activities (Fig. 2) which can be classified into the following categories:

3.1. Anticancer agents

Cancer remains one of the most difficult diseases worldwide to treat and is the leading cause of human mortality exceeded only by cardiovascular diseases [37]. The International Agency for Research on Cancer (IARC), the specialized cancer agency of the World Health Organization, released (Lyon/Geneva, 12 December 2013) the latest data on cancer incidence, mortality, and prevalence worldwide. According to new version of IARC's online database, GLOBOCAN 2012, an estimated 14.1 million new cancer cases and 8.2 million cancer-related deaths occurred in 2012 [38]. Although there is enormous discovery and development of various anticancer drugs yet they are not met the needs for eradicating so incorrigible and crafty cancer cells. Search of new effective anticancer agents are still urgent for human's battling against cancer. Therefore, development of new anticancer drugs and more effective treatment strategies for cancer is of importance [39]. Recently, benzofurans have been identified to exhibit potent cytotoxic activities against human breast cancer cells and ovarian cancer cells [40,41]. Wan et al. [42] prepared a series of novel benzofuran derivatives and evaluated *in vitro* against a panel of human tumor cell lines. It was found that the existence of 2-methylimidazole or 2-ethylimidazole ring and substitution of the imidazolyl-3-position with a naphthylacyl or methoxyphenacyl group were essential for modulating cytotoxic activity. In particular, hybrid compound **1** was found to be the most potent compound against five strains human tumor cell lines and more active than cisplatin (DDP), while hybrid compound **2** was more selective toward colon carcinoma (SW480) and breast carcinoma (MCF-7) with IC_{50} value 44.0- and 36.8-fold more

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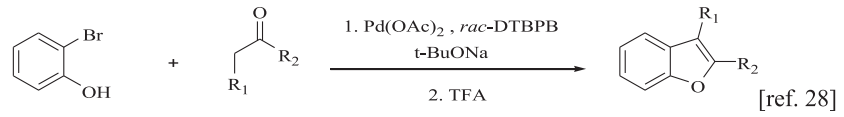
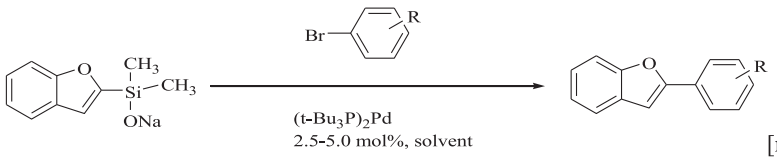


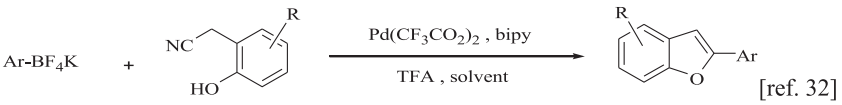
[ref. 28]

(R_1 = Me, H, Et; R_2 = Ph, 3,5-diOMe-C_6H_3, etc.)



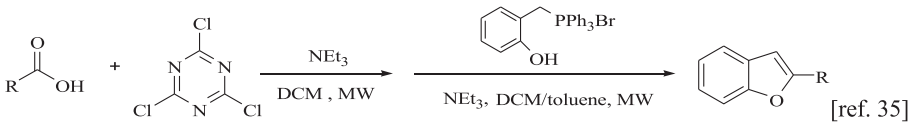
[ref. 31]

(R = 4-OCH_3, 4-OTBS, 3-CH_2OTBS, 2-CH_3, 4-NO_2, 4-CN)



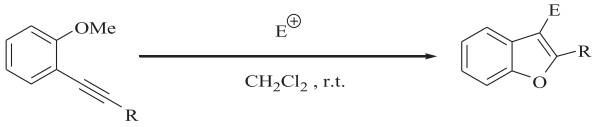
[ref. 32]

(R = OMe, Me, Cl, H, Br; Ar = Ph, 4-Br-C_6H_4, 4-OMe-C_6H_4 , etc..)



[ref. 35]

(R = Ph, t-Bu, etc.)



$\overset{\oplus}{E}$ = ICl, I_2 , PhSeCl, or *p*-$O_2NC_6H_4SCl$ [ref. 36]

(R = Ph, 4-OMe-C_6H_4, 2-AcO-C_6H_4, cyclohexenyl)

Scheme 1. Synthetic routes for benzofuran derivatives.

sensitive to DDP. Hranjec et al. [43] prepared a series of novel heteroaromatic benzofuran-2-carboxamide derivatives. It was observed that replacement of benzo[*b*]thiophene with benzo[*b*] furan seems to be detrimental for the antitumor activity. All the newly synthesized compounds were evaluated for the anti-proliferative potency *in vitro* on human tumor cell lines and normal (diploid) human fibroblasts. The compounds showed non-selective effects on all tested cells and stronger antitumor activities were detected only in the highest tested concentrations. The results revealed a potential for three compounds as selective anti-proliferative compounds. In particular, 2-imidazolynyl substituted compound **3** showed good selectivity on SK-BR-3 cell line while 2-*N*-acetamidopyridyl substituted amide (**4**) and 2-imidazolynyl substituted compound **5** showed selective concentration-dependent antiproliferative effects on MiaPaCa-2 and SW620 cell lines, respectively in the micromolar range. Substitution of a sulphur atom instead of nitrogen at position 1, caused increased antiproliferative activity of 2-imidazolynyl substituted benzimidazole amide (**3**) as compared to the structurally related 2-imidazolynyl substituted benzothiazole amide. The compounds (Fig. 3) exerted different antiproliferative mechanisms, i.e. compounds **4** and **3** induced apoptosis through activation of caspases that might be indicative for activation of death receptors along with the intrinsic apoptotic pathway. Contrary to this, antiproliferative effect of compound **5** relied on a cell death mechanism other than apoptosis, i.e. mitotic catastrophe. Current cancer chemotherapy indeed, aims to activate apoptosis in cancer cells where the concomitant induction of the intrinsic apoptotic pathway plays a crucial role in chemotherapy potency towards tumor cells.

3.1.1. *Farnesyltransferase inhibitors*

Membrane-bound GTP binding proteins (G-proteins) act as molecular switches to regulate cell growth by cycling between the inactive GDP-bound state and the active GTP-bound state. In tumor cells, the constitutive activation of some G-proteins contributes to their malignant growth properties. In normal cells, this switching

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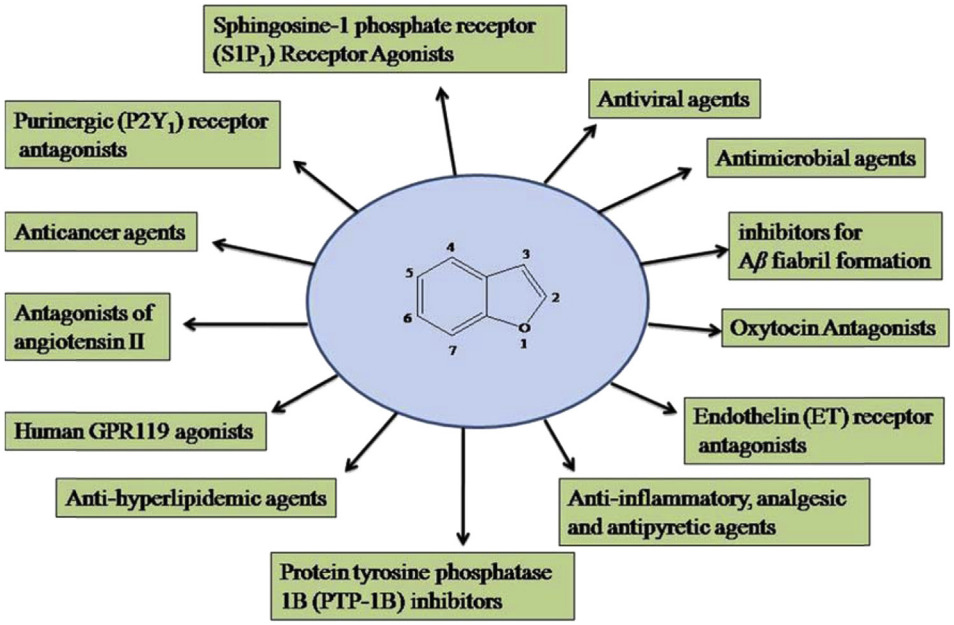

Fig. 2. The biological activity spectrum of benzofuran derivatives.

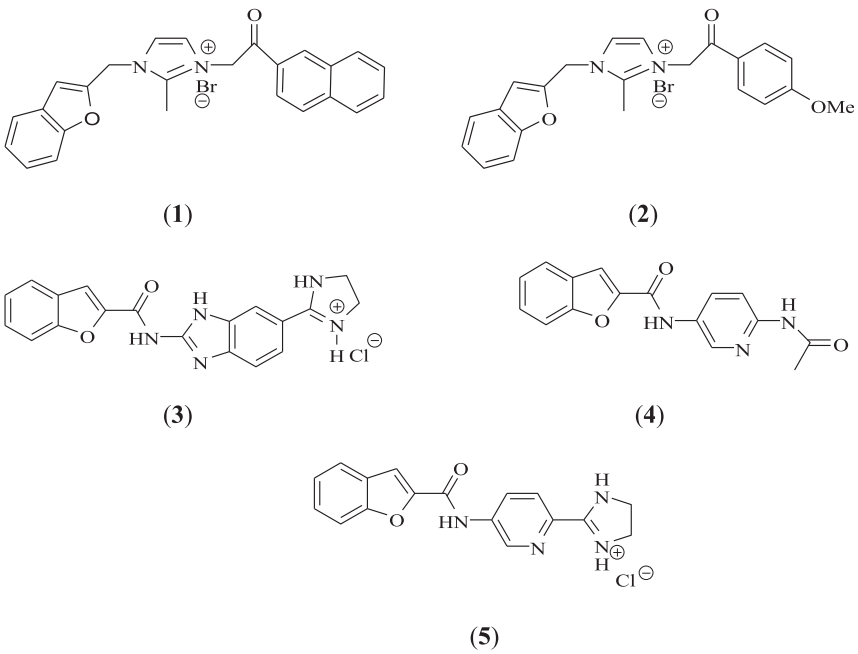

Fig. 3. Benzofuran derivatives as antitumor agents [ref. [42,43]].

mechanism is highly regulated and G-proteins are found predominantly in their inactive GDP-binding state. All of these G-proteins originally have the CAAX tetrapeptide motif (C: Cys, A: an aliphatic amino acid, X: Ser, Met, Gln, Ala) at their C-terminal [44]. Farnesyltransferase (FTase) enzymes recognize this CAAX tetrapeptide motif and transfer the farnesyl group to the cysteine thiol. This farnesylation is critical for membrane binding and the biological function of G-proteins [45]. In the last decade, many classes of FTase inhibitors have been reported and discussed as antitumor agents [46]. Asoh et al. [47] reported design and synthesis of the series of benzofuran-based FTase inhibitors using the X-ray structure of human FTase. The enzyme inhibitory activity (FTase/K-ras) and antiproliferative activity against human non-small cell lung carcinoma (QG56) of compounds were evaluated [48]. The results from compounds showed that introduction of a cyano group (**7**) or a nitro group (**8**) on the A-ring resulted in significant increase of enzyme inhibitory activities (6.4 and 30 nM respectively). A cyano group at the para-position of the A-ring showed excellent FTase inhibition. Substituent of the functional group at the B-ring increased antiproliferative activity against human cancer cell lines. After evaluation of several parameters including solubility, biological stability, and pharmacokinetics, compound **6** was identified as a clinical candidate (enzyme inhibitory activity, IC_{50} = 1.1 nM) (Fig. 4). Compound **6**, showed strong tumor regression in the QG56

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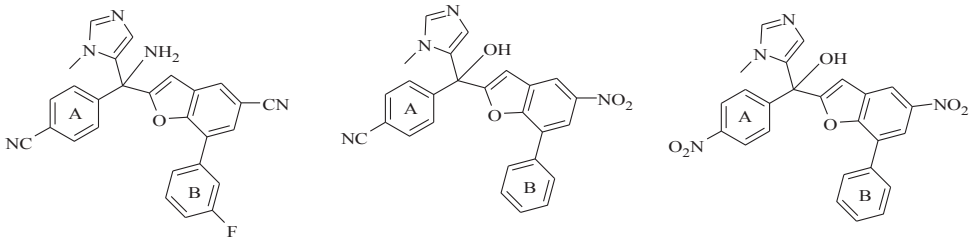


(6) (7) (8)

Fig. 4. Farnesyltransferase inhibitors [ref. [47]].

human NSCLC xenograft model with no noticeable body weight loss.

3.1.2. Angiogenesis inhibitors

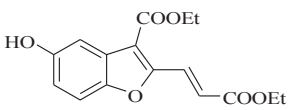
Angiogenesis is the process of development of new blood supply system in early developed tumors. Angiogenesis is responsible for the critical growth of a tumor as well as for the recurrence and metastasis of a tumor [49]. Because of these reasons, the effective inhibition of tumor angiogenesis can block tumor progression, growth and metastasis to other organs [50]. Benzofuran scaffold represents a promising structural core to discover a new class of active and selective angiogenesis inhibitors. It is known that dihydrobenzofuran scaffold actually exists in some anti-angiogenesis agents like cryptotanshinone [51], lignans [52] and A-3922 [53]. A series of benzofuran derivatives were synthesized and evaluated against HUVEC (Human umbilical vein endothelial cell) A549, Bel-7402 and MCF-7 proliferation by Chen et al. [54]. The compounds showed remarkable preference for their inhibitory activity against HUVEC proliferation and absence of the inhibitory activity to cancer cells of A549, Bel-7402 and MCF-7. Among all the compounds, compound **9** (Fig. 5) exhibited good inhibitory activity and remarkable selectivity to HUVEC. The studies suggested that the presence of methyl, acrylate and carboxylate groups in benzofuran scaffold was the basic requirement for inhibitory activity against HUVEC proliferation.

3.1.3. Pim-1 inhibitors

The Pim-1 serine/threonine kinases and its two other family members, Pim-2 and Pim-3 are associated with several oncogenic processes [55]. The pim-1 proto-oncogene was initially identified as a frequent site of integration for slowly transforming Maloney murine leukemia virus in murine T cell lymphomas [56]. Pim-1 overexpression is observed in a range of human lymphomas and acute leukemia [57], whereas Pim-2 overexpression is associated with chronic lymphocytic leukemia and non-Hodgkin lymphoma [58]. The pleiotropic roles of Pim family kinases in proliferation and survival pathways have attracted interest of many investigators to the discovery of inhibitors as potential therapeutics. In the last few years, a number of potent Pim-1 inhibitors have been reported in the literature [59]. Xiang et al. discovered novel benzofuran-2-carboxylic acids as potent Pim-1 inhibitors using fragment based screening followed by X-ray structure guided medicinal chemistry optimization [60]. The compounds demonstrated potent inhibition against Pim-1 and Pim-2 in enzyme assays. X-ray structures of the inhibitor/Pim-1 binding complex revealed important saltbridge and hydrogen bond interactions mediated by the compound's carboxylic acid and amino groups. The authors identified a potent Pim-1 inhibitor **10** (Fig. 6) by adding a *cis*-diaminocyclohexanyl group at the 7-position of the benzofuran core. X-ray structure of the bound complex of **10** indicated that the terminal amino group which formed salt-bridge, interacted with *D128* and *E171* of the ribose binding site. The concise and rigid *cis*-diaminocyclohexanyl ring looked possessing an ideal shape to position the terminal amino residue in the right distance and orientation, allowing for strong interactions with *D128* and *E171*. The spatial arrangement could likely be the cause which made the relatively small size molecule (**10**), capable of strong binding and inhibition of both Pim-1 and Pim-2 as demonstrated by IC_{50}'s of 0.001 μM and 0.004 μM, respectively. The LE (Ligand efficiency) of compound **10** was obtained as 0.59, which showed significant increment from the LE of the original hit molecule (without *cis*-diaminocyclohexanyl group) (0.48). Thus the discovery of potent and selective Pim kinase inhibitors provided useful tools for the further evaluation of the role of this kinase family in the context of disease states and possible interventions in the treatment of cancer or other diseases.

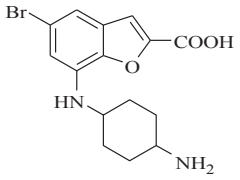
3.1.4. Anti-estrogen breast cancer agents

Breast cancer is the most frequently diagnosed cancer and the second leading cause of cancer deaths among women which is after lung cancer, accounting for 23% of total cancer cases in women, and 14% of cancer deaths [61]. Estrogen receptor (ER) and aromatase are two major targets in the treatment of breast cancer. The ER subtype ERα which is predominantly expressed in breast cancer cells is an important target. ERα antagonists directly block the active site of ERα to prevent binding of estrogen to it as well as to stop the function of hormone. In breast cancer cell, estrogen activates ERα by binding to its active site, which induces conformational changes that allow co-activators to attach on the complex. As a result, several effects are stimulated, which causes cell proliferation in the



(9)

Fig. 5. Angiogenesis inhibitor [ref. [54]].



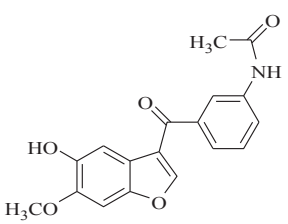
(10)

Fig. 6. Pim-1 inhibitor [ref. [60]].

breast [62]. As a ligand inducible nuclear receptor, ERα plays a critical physiological role as mediator of the actions of the estrogen hormones [63]. Therefore, it is an attractive pharmaceutical target for the development of novel therapeutic agents for the treatment of breast cancer. The link between estrogen and breast cancer suggested that 'antiestrogenic strategies' [64] might have potential as therapeutic agents [65]. In fact, many existing chemotherapies are ERα antagonists. Tamoxifen [66] is well known to remain the first line therapy for estrogen receptor positive breast cancer since the 1980s, [67,68]. Li et al. [69] reported the application of 3-acyl-5-hydroxybenzofurans as a scaffold to develop potential drugs for breast cancer. They synthesized seven novel derivatives by using a microwave-assisted method. Those compounds exhibited different antiproliferation against human breast cancer MCF-7 cells, with the best activity of IC_{50} = 43.08 μM for compound **11** (Fig. 7). To investigate the binding interactions between compounds and estrogen receptor alpha (ERα), a Quantum Mechanics Polarized Ligand Docking (QPLD) study was carried out. A detailed analysis indicated that compound **11** possesses the highest Van der Waals and hydrogen bond interactions and good inhibitor and can be used as attractive scaffold for designing new anti-cancer agents.

3.1.5. Tubulin polymerization inhibitors

The microtubule system of eukaryotic cells plays important roles in regulating cell architecture. Since microtubules are a key component of the mitotic spindle, it has an essential role in cell division, [70]. The biological importance of microtubules in mitosis and cell division makes them an interesting target for the development of anticancer agents. Small molecules such as benzofurans are attractive as inhibitors of tubulin polymerization. Romagnoli et al. [71] synthesized a new class of inhibitors of tubulin polymerization based on the 2-(3′,4′,5′-trimethoxybenzoyl)benzofuran molecular skeleton, and evaluated for antiproliferative activity, inhibition of tubulin polymerization and cell cycle effects. The SAR studies revealed that the introduction of methyl at the C-3 position of the benzofuran moiety resulted in increased activity compared with the corresponding 3-amino counterpart, thus revealing that this latter substituent is not essential for activity. Most of the compounds showed excellent activity as inhibitors of tubulin polymerization, and were found to be more potent than CA4 in this assay. The interaction with tubulin leads to cell cycle arrest in the G2–M phase and to an apoptotic cell death. Structure–activity relationship study indicated that a methoxy group located at the C-6 position of the benzofuran ring yielded the most active compound. Changing its position from C-6 to C-4, C-5 or C-7 led to a reduction in potency. Compound **12** (Fig. 8) was the most potent analog, with IC_{50} values ranging from 1.2 to 6.3 nM, in the same range as the values obtained with CA4. Compound **12** also had excellent potency as an inhibitor of tubulin polymerization (IC_{50} = 0.43 μM). It interacted strongly with tubulin by binding to the colchicine site. At the 2-position of the benzofuran, the carbonyl linker was found to be much more effective than a carbinol, methoxymethyl or simple methylene group. A thiocarbonyl linker, however, was compatible with good activity.



(11)

Fig. 7. Anti-estrogen breast cancer agent [ref. [69]].

Pieters et al. [72] obtained a series of 19 related dihydrobenzofuran lignans and benzofurans by a biomimetic reaction sequence. Anticancer activities of all compounds were evaluated in an *in vitro* human disease oriented tumor cell line screening panel developed at the NCI. It was observed that Leukemia and breast cancer cell lines were relatively more sensitive to these agents than were the other cell lines. Compound **13** (methyl (*E*)-3-[2-(3,4-dihydroxyphenyl)-7-hydroxy-3-methoxycarbonyl-2,3-dihydro-1-benzofuran-5-yl]prop-2-enoate) (Fig. 8), the dimerization product of caffeic acid methyl ester, containing a 3′,4′-dihydroxyphenyl moiety and a hydroxyl group in position 7 of the dihydrobenzofuran ring, showed promising activity. The average GI_{50} value (the molar drug concentration required for 50% growth inhibition) of **13** was 0.3 μM, **13** had a GI_{50} value of <10 nM against three breast cancer cell lines. It was interesting to note that methylation, reduction of the double bond of the C3-side chain, reduction of the methoxycarbonyl functionalities to primary alcohols, or oxidation of the dihydrobenzofuran ring to a benzofuran system resulted in a decrease or loss of cytotoxic activity. Compound **13** appeared to inhibit mitosis at micromolar concentrations in cell culture through a relatively weak interaction at the colchicine binding site of tubulin. *In vitro* it inhibited tubulin polymerization by 50% at a concentration of 13 ± 1 μM. The 2*R*,3*R*-enantiomer of **13** was found to be twice as active as the racemic mixture, while the 2*S*,3*S*-enantiomer had minimal activity as an inhibitor of tubulin polymerization. These dihydrobenzofuran lignans (2-phenyldihydrobenzofuran derivatives) constitute a new group of antimitotic and potential antitumor agents that inhibit tubulin polymerization. Further modification of substituents and/or the core structure of the molecule will yield more active agents, including compounds that will have antitumor activity.

3.1.6. Glycogen synthase kinase 3β inhibitors

It is well established that GSK-3 (Glycogen synthase kinase) affects a variety of biological processes such as cell cycle progression, proliferation, apoptosis, signalling, and transcription by phosphorylation of many different substrates. In mammals, GSK-3 consists of two distinct isoforms, α and β [73]. Recent studies have demonstrated that glycogen synthase kinase 3β (GSK-3β) is overexpressed in human colon and pancreatic carcinomas, and these play a role to cancer cell proliferation and survival. Gaisina et al. [74] reported synthesis, and screening of benzofuran-3-yl-(indol-3-yl) maleimides as potent GSK-3β inhibitors. Some compounds showed profound inhibitory activity towards GSK-3β and an enhanced selectivity against cyclin-dependent kinase 2 (CDK-2). Selected GSK-3β inhibitors were tested in the pancreatic cancer cell lines MiaPaCa-2, BXPC-3, and HupT3. It was demonstrated that most of the compounds showed antiproliferative activity against some or all of the pancreatic cancer cells at low micromolar to nanomolar concentrations. Treatment of pancreatic cancer cells with GSK-3β inhibitors **14** and **15** (Fig. 9**)** resulted in suppression of GSK-3β activity and a distinct decrease of the X-linked inhibitor of apoptosis (XIAP) expression, leading to significant apoptosis. The data suggested a possible role for GSK-3β inhibitors in cancer therapy.

3.1.7. Multidrug resistance-reversing activity

The development of multiple drug resistance represents a growing problem in cancer treatment as well as in antimicrobial therapy. Within the past decade several mechanisms of pleiotropic drug resistance of tumor cells have been identified [75]. One type of multidrug resistance (MDR) has been shown to be mediated by an

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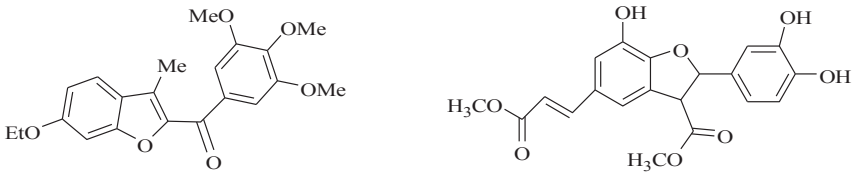
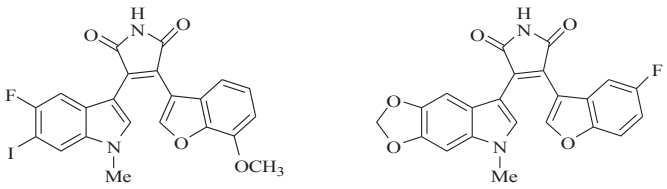


(12) (13)

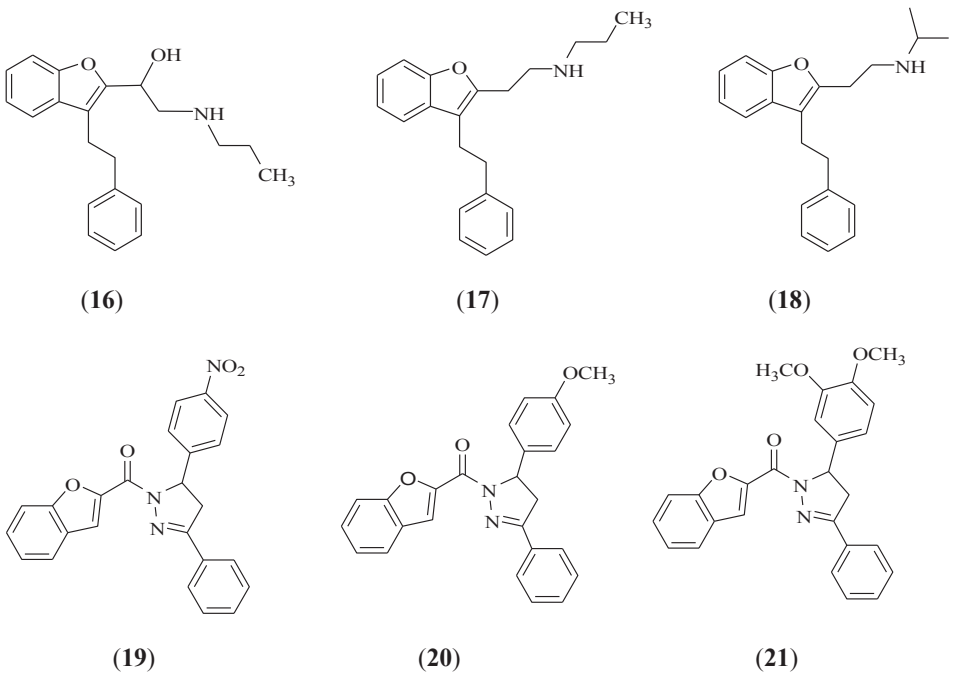
Fig. 8. Benzofuran derivatives as tubulin polymerization inhibitors [ref. [71,72]].



(14) (15)

Fig. 9. Glycogen synthase kinase 3β inhibitors [ref. [74]].

energy dependent, membrane-bound efflux pump termed P-glycoprotein (PGP) [76]. PGP represents a member of the ATP-binding cassette 3 with low substrate specificity. A broad range of cytostatic drugs such as anthracyclines, epipodophyllotoxins, actinomycin D, vinca alkaloids, colchicines, and taxol are eliminated *via* PGP-mediated efflux [77]. Within the past few years a variety of substances have been shown to inhibit PGP-mediated drug efflux and thereby re-establish sensitivity toward chemotherapeutic agents [78]. A series of propafenone analogs were identified as effective inhibitors of PGP [79]. Propafenone is in clinical use as an antiarrhythmic agent due to its ability to block cardiac sodium channels. The substance also has weak β-adrenoreceptor-blocking activity. Rhodamine-123 as well as daunomycin efflux studies on a series of closely related structural homologs of propafenone showed a highly significant correlation between lipophilicity and MDR-reversing ability. Ecker et al. [80] synthesized a series of benzofuran analogs propafenone and evaluated for multidrug resistance-reversing activity in two *in vitro* assay systems. They tested for their chemosensitizing potency with diminished flexibility in both rhodamine-123 efflux studies and daunomycin cytotoxicity assays in order to gain further insights into structural features required for good PGP-inhibitory activity of propafenone-type MDR modulators. As for propafenones, an excellent correlation of biological data with calculated lipophilicity values was found for benzofurans, whereby the latter generally had lower activity/lipophilicity ratios. Almost identical slopes of the regression lines were obtained for both propafenones and benzofurans. Multiple linear regression analysis of the complete data set yielded an equation with excellent predictive power ($r^2_{\text{cross-valid}} = 0.968$). Thus, incorporation of the ether oxygen of propafenone into a benzofuran moiety and simultaneous removal of the carbonyl group leads to a remarkable decrease in activity, whereby lipophilicity retains its predictive character. Results obtained for the enantiomers of **16** and for the deshydroxy analogs **17** and **18** (Fig. 10) showed that the hydroxyl group did not contribute to PGP interaction. Synthesis of desphenyl derivatives of propafenones as well as benzofurans demonstrated that the phenyl ring contributes to pharmacological activity only by influencing lipophilicity.



(16) (17) (18)

(19) (20) (21)

Fig. 10. Multidrug resistance (MDR) reversal agents [80,81].

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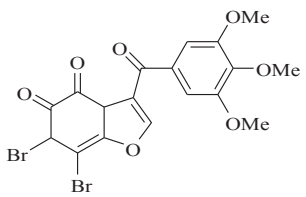
Membrane interaction measurements using NMR spectroscopy showed benzofurylethanolamines mainly interact within the region of the aryl ether oxygen, whereas the deshydroxy benzofuran derivative **17** exhibits a strong interaction over the whole (phenylethyl)benzofuryl region. Nevertheless, this difference was not reflected in the MDR modulating ability of the compounds.

A new series of benzofuran derivatives were synthesized by Parekh et al. [81]. The effect of synthesized compounds was examined against human cancer cell lines for their antiproliferative activity and reversal of multidrug resistance on human MDR1-gene transfected mouse lymphoma cells *in vitro*. Most of the compounds had significant MDR inhibitory effect on MDR cells in the flow cytometric experiment measuring the accumulation of R123 fluorescent dye with FAR values above 10 when applying the compounds in 20 μg/mL final concentration. The antiproliferative effect of the compounds was different. Among the 24 compounds, **19** and **20** (Fig. 10) showed good antiproliferative activity. The lowest IC_{50} value was found 4.569 μg/mL (**20**) while some compounds were ineffective even at the applied 50 μg/mL concentration. Position of the substitutions may affect the antiproliferative activity, however, it is difficult to evaluate the connection between chemical structures and affectivity of benzofuran methanones. Further investigations are essential to clarify the effects of several functional groups at different positions. The possible correlation between the FAR values and the chemical structure of the compounds need some QSAR evaluation related to rational drug design. The majority of compounds were found good resistance modifiers according to their higher FAR values in comparison with the positive control verapamil. Interestingly, compounds **21** and **20** (Fig. 10) were found to be the most active MDR reversal agent with FAR value of 29.9 and 26.77 respectively in the flow cytometric experiment. The studies suggested that the antiproliferative effects, the IC_{50} values of the compounds were similar, concentration however the inhibitory action on the function of over expressed ABC transporter in cancer cells were strictly dependent on the chemical structures of benzofuran methanones, resulting in increased rhodamine accumulation in cancer cell model.

3.1.8. Inhibitors of human peptide deformylase (hspdf)

It has been observed that human peptide deformylase (HsPDF) inhibition by actinonin and actinonin analogs or by specific siRNA knockdown of expression is associated with antiproliferative effect in cancer cells [82]. Thus HsPDF inhibitors can be considered as a new class of antitumor agents. Antczak et al. [83] identified the benzofuran-4,5-diones as the first known selective HsPDF inhibitors and described their selectivity profile in a panel of metalloproteases. The structure–activity relationships were studied for antitumor activity in a panel of cancer cell lines. The efficacy of the compounds was assessed in a mouse xenograft model. To verify the hypothesis that HsPDF inhibitors can be a potential novel anticancer agents, the cytotoxicity profile of the 13 novel benzofuran-4,5-dione derivatives was studied in a panel of nine cancer cell lines (HL-60, HL-60/RV+, Jurkat, Molt-3, ALL-3, CWR22, HEK293, Y79, Meso47). It was observed that all the benzofuran-4,5-dione derivatives have cytotoxic activity towards at least five out of nine of the cancer cell lines tested, with an IC_{50} ranging from 2.8 to 74 μM. Interestingly, the most potent HsPDF inhibitor (compound **22,** Fig. 11) was also the most potent compound in the viability assay. It was found to be active across all the cancer cell lines tested, with IC_{50} ranging from 2.8 to 37 μM, including the multidrug resistant cell line HL-60/RV+ (IC_{50} = 12 μM). In a pilot study, the *in vivo* efficacy of compound **22** was assessed in a mouse xenograft model using human promyelocytic leukemia HL-60 cells. The tested compound delayed the growth of HL-60 tumors by up to 40%.To put this result in perspective, actinonin-which has a reported IC_{50} of 43 nM toward HsPDF [82]-must be administered twice a day for 2 weeks at the large dose of 250 mg/kg to delay tumor growth [82]. This difference in potency could be attributed to a better bioavailability compared to the peptidomimetic actinonin but further studies are needed to address this question. The observed results were encouraging considering that **22**, a benzofuran-4,5-dione derivative of first generation, was potent *in vivo* at a dose of 15 mg/kg. These findings strongly suggested that derivatives of the benzofuran-4,5-dione scaffold could constitute a new class of potent antitumor agents selective for HsPDF.



(**22**)

Fig. 11. Inhibitor of human peptide deformylase (hspdf) [ref. [83]].

3.1.9. Inhibitors of mTOR signalling

The mammalian Target of Rapamycin (mTOR) is a key protein that controls cell growth, metabolism, autophagy and angiogenesis [84,85]. Its signaling is one of the most frequently altered in cancer cells, which makes mTOR an important target in oncology. In their quest to identify inhibitors of mTOR signalling, William Sellers, Pamela Silver and coworkers at Harvard University identified the hit **23** by high-throughput screening [86,87]. Recently it was demonstrated that the replacements of the dimethylamine and benzyl moieties of **23** by a 4-piperidinopiperidine and a phenyl (compound **24**) significantly improved cytotoxicity [88]. The results showed that the compound **24** interacted with the complex mTORC1 to inhibit its activity. A series of 32 derivatives and isosteres of the mTOR inhibitor **24** were synthesized by Salomé et al. [89]. The cytotoxicity of the compounds was compared in radioresistant SQ20B cancer cell line. The seven isosteric replacement of the benzofuran scaffold were detrimental to the activity. It was observed that methylation of the phenolic hydroxyl and replacement of the 4-piperidinopiperidine by a 4-dimethylaminopiperidine was well tolerated. Essentially, substitution of the phenyl by a benzyloxy significantly improved the cytotoxicity in cancer cells. Combination of these data resulted in compound **25**, which showed IC_{50} 10 fold lower than **24**. Both compounds displayed a similar profile of cytotoxicity on a panel of human cancer cell lines, suggesting a related mechanism of action. Importantly, **25** was shown to inhibit both mTORC1 and Akt signalling, suggesting that it should overcome the resistance associated to Akt overactivation observed with rapamycin derivatives currently used in clinic (Fig. 12).

3.2. Antimicrobial agents (antibacterial and antifungal)

Infections caused by multi-drug resistant bacteria are major health problem worldwide. Methicillin- and vancomycin-resistant *Staphylococcus aureus* strains are responsible for most infections of this type [90,91]. Due to serious side effects observed in recently developed antibiotics, imminent development of structurally diversified chemical entities is believed to be the key to the discovery of new antibiotics [92]. Moreover, Tuberculosis constitutes today a serious threat to human health worldwide, aggravated by the increasing number of identified multi-drug resistant strains of

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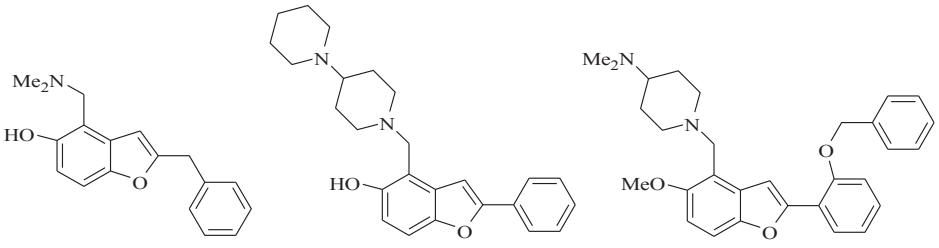

(23) (24) (25)

Fig. 12. Benzofuran derivatives as cytotoxic and inhibitors of mTOR signalling agents [ref. [89]].

Mycobacterium tuberculosis (Mtb), its causative agent, as well as by the lack of development of novel mycobactericidal compounds for the last few decades. In recent years, there has been an increased interest in 2-substituted benzofurans as anti-mycobacterial agents. Highly substituted pyrazine as a 2-substituent on benzofuran has given a useful anti-mycobacterial series, with the most active compound showing MIC of 1.2 μg/mL [93]. Substituted purines have also been tried on 2-position of benzofuran ring to form another useful anti-mycobacterial series [94]. A novel series of benzofuran-3-carbohydrazide and its analogs was synthesized by Telveka et al. [95]. All the compounds were evaluated for *in vitro* inhibitory activity against *M. tuberculosis* H37Rv strains by using resazurin assay utilizing microtiterplate method (REMA) using isoniazid as the standard. The newly synthesized compounds also showed good antifungal activity against *Candida albicans*. The synthesized N′-benzylidene benzofuran-3-carbohydrazide and its analogs showed promising anti-mycobacterial and anti-fungal activity. Compounds (**26** and **27**) were found to be most active compounds with MIC of 8 and 2 μg/mL respectively. It was observed that *ortho*-hydroxyl and protected hydroxyl groups substitution on benzylidene group showed good antitubercular activity. In addition, unsubstituted benzylidene and electron withdrawing groups on benzofuran ring was also important for antitubercular activity. For antifungal activity when the benzofuran ring was unsubstituted, a highly substituted side chain attached to hydrazide appeared to be more active. When benzofuran ring was substituted, a highly substituted side chain was found to decrease activity. Bulky side chain attached to hydrazide was required for activity. Substitution on benzofuran ring along with bulky side chain proved to be the most potent compound **29** with a MIC of less than 15.62 μg/mL.The inhibition of Mtb at concentrations as low as 2 and 8 μg/mL by compounds **27** and **26** respectively indicated that these compounds could act as leads for development of newer anti-TB and antifungal agents.

A series of novel natural product like 2-substituted-3*H*-benzofurobenzofurans designed by molecular hybridization were synthesized by Yempala et al. [96]. The key reactions involved in the synthesis were iodination of 2-dibenzofuranol using iodine monochloride followed by palladium–copper catalyzed Sonogashira-coupling of 1-iododibenzofuran-2-ol with various alkyl and aryl acetylenes. The compounds were screened for *in vitro* anti-mycobacterial activity against *M. tuberculosis* H37Rv. Among them 2-(4-methoxy-2-methyl phenyl)-3*H*-benzofuro [3,2-*e*] benzofuran (**29**) was found to be most active with MIC 3.12 μg/mL and exhibited lower cytotoxicity with good therapeutic index. Mehdi et al. [97] performed synthesis of new benzofuran derivatives. Antimicrobial activity of all the synthesized compounds was evaluated against Gram positive (*Bacillus subtilis, Bacillus cereus, S. pneumonia, S. aureus*) and Gram negative (*Klebsiella pneumonia, S. flexneri, Pseudomonas aeruginosa, E. aerogenes, Escherichia coli*) bacterial and fungal (*C. albicans*) strains using microdilution method. The compounds showed potential antimicrobial activity comparable to that of clinically used antimicrobial agents against selected microorganisms. In general, MIC values of the compound against all test microorganisms were between 0.5 and 1 μg/mL. Such values were compared with those of standard antibiotics. The compounds also showed selective and moderate inhibitory activity on butyryl cholinesterase enzyme and could serve as potential lead compound for synthesis of more bioactive derivatives. In order to investigate antimicrobial activity Kirilmis et al. [98] synthesized novel class of mesitylene substituted benzofurans. The compounds were tested for antimicrobial activity against *S. aureus*, *E. coli* and *C. albicans*. The minimal inhibitory concentration (MIC) of the synthesized compounds was determined using a standard broth dilution technique. The obtained data reported that compounds were able to inhibit the growth of the selected microorganisms *in vitro* showing MIC values between 4 and 256 μg/mL. Among the synthesized compounds, (*E*)-1-(1-benzofuran- 2-yl)-2-mesitylethanone-*O*-benzoyloxime (**30**) was found to be the most active derivative against *S. aureus* and *E. coli* at MIC values of 4 and 32 μg/mL, respectively. Other compounds exhibited moderate activity against the test microorganisms.

A series of thirteen new benzofuran derivatives bearing aryl substituents at its C-3 position through methanone linker, were synthesized by Jiang et al. [99]. All the compounds were screened for their antibacterial and antifungal activities against four bacteria *E. coli, Staphylococcus aureus, Methicillin-resistant S. aureus, B. subtilis*, and a fungus *C. albicans*. Preliminary anti-microorganism tests with the compounds established some interesting structure-activity relationships. Compound **31**, with a hydroxyl group at C-4′, displayed the excellent antibacterial activity against *S. aureus* and MRSA with MIC_{80} values of 0.39 and 0.78 μg/mL, respectively, as compared to the positive control drugs. Its activities against *E. coli* and *B. subtilis* were found to be comparable to that of sodium penicillin against *E. coli* and that of cefotaxime against *B. subtilis*, respectively. Compounds **32** and **33**, with additional substituents at C-3′ position, exhibited medium antimicrobial activities with MIC_{80} values from 0.78 to 3.12 μg/mL against *E. coli* and *B. subtilis*. The presence of hydroxyl group at C-3′ position, also had similar activities against all four bacteria as compound **31** (MIC_{80} = 0.39–0.78 μg/mL). Unexpectedly, presence of hydroxyl group at C-2′ position, imparted no activity against the bacteria (MIC_{80} > 200 μg/mL). On the other hand, compounds with the methylation of the hydroxyl group would reduce the solubility and decrease their antimicrobial abilities. Much different from the natural products, some compounds with the halogen atom substituents showed no antibacterial activity. All of the tested compounds were found to be inactive against *C. albicans*. Abdel-Wahab et al. [100] synthesized new benzofuran derivatives for antimicrobial evaluation. The synthesized compounds were tested, at 100 mg concentration, for their *in vitro* antimicrobial activity against the

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Gram-positive (*Staphylococcus aureus*, *B. subtilis*), Gram-negative bacteria (*E. coli*) and fungi (*C. albicans* and *Aspergillus niger*). The primary screening was carried out by agar disc-diffusion method using nutrient agar medium. Amoxicillin and fluconazole were used as control drugs. The results of preliminary antibacterial testing of the compounds revealed that majority of the synthesized compounds showed varying degrees of inhibition against the tested microorganisms. In general, the inhibitory activity against the Gram-negative bacteria was higher than that of the Gram-positive bacteria. The compounds showed remarkable activity against *C. albicans*. Most of the tested compounds showed none or weak antifungal activity against *A. niger*. Compounds **34, 35** were found to be more active (against *C. albicans*) than the reference sample fluconazole. According to structure–activity relationships (SAR), it can be concluded that benzofuran, pyrazoline, and thiazole moieties are essential for the antimicrobial activity.

Liu et al. [101] observed that the benzofuran derivatives bearing aryl substituents at the C-3 position through a methanone linker (Fig. 13) exhibited high antibacterial activities against Gram-negative and Gram-positive bacteria [99]. In addition, the hydroxyl groups on the aromatic ring at C-3 position significantly enhanced such activities. Based on these observations they reported the synthesis and antibacterial evaluation of a new series of 3-methanone-6-substituted-benzofuran derivatives with hydroxyl or (5-methyl-2-phenyloxazol-4-yl)ethyloxy at C-6 position of benzofuran. All the seventeen compounds were screened for their antibacterial activities against *E. coli, Staphylococcus aureus, Methicillin-resistant S. aureus, B. subtilis,* and *P. aeruginosa*. Among them seven compounds exhibited excellent antibacterial activities against all five tested strains with MIC_{80} value comparable to those of cefotaxime and sodium penicillin. Compounds **36** and **37** displayed specific activity (MIC_{80} = 3.12–12.5 μg/mL) against *S. aureus*. The anti-microorganism tests with benzofuran derivatives established some interesting structure activity relationships (SAR). The substitutions at C-6 and C-3 positions of these derivatives were found to greatly impact on the antibacterial activity and strains specificity, respectively.

Compounds bearing a hydroxyl group at C-6 (**38**, **39**) offered excellent antibacterial activities against all the strains (MIC_{80} = 0.78–3.12 μg/mL). Compounds with phenyl, 5-methylfuran-2-yl, and 4-methoxyphenyl groups at C-2 position of benzofuran showed good antibacterial activity with MIC_{80} values between 0.78 and 6.25 μg/mL, comparable to those of control drugs. In contrast, compounds in which hydroxyl group was blocked at the C-6 position of benzofuran, exhibited no antibacterial activity to any of tested strains, indicating the hydroxyl group at C-6 position of benzofuran was requisite for the activity. The strain-specificity was also observed in compounds **36** and **37**. C-6 position was fixed with a 5-methyl-2-phenyloxazole-4-ethyloxy group and the C-3 position was occupied by either a 3,4,5-trimethoxybenzoyl group (**36**) or an imine group (**37**). These two compounds displayed antibacterial activities only against *S. aureus* with MIC_{80} values of 12.5 μg/mL and 3.12 μg/mL, respectively. It was speculated that the strain-specificity may be owe to the methanone group or imine group between the 3,4,5-trimethoxyphenyl and benzofuran nucleus, which may play a specific role with the biological target of *S. aureus*. Moreover, the strain-specific lost when the double bond was introduced between the 3,4,5-trimethoxyphenyl and methanone or the imine was reduced to amine.

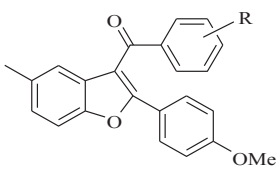

Fig. 13. 3-Benzoylbenzofuran.

Manna et al. [102] reported microwave assisted synthesis of new indophenazine 1,3,5-trisubstituted pyrazoline derivatives of benzofuran. The antibacterial activity was screened against multi-drug resistant Escherichia coli, Pseudomonas aeruginosa, Streptococcus pneumoniae, Streptococcus agalactiae, Salmonella typhi, Streptococcus aureus, and Streptococcus pyogenes by cylinder and well method. The MICs were determined using Mueller–Hinton Broth (MHB) culture media. The antifungal activity was screened against *Candida albicans* using agar couture medium. Among the 14 compounds some compounds exhibited good antibacterial activity with MICs bellow 10 μg/mL against *Escherichia coli, Pseudomonas aeruginosa* and *Streptococcus aureus*, which can be compared with sparfloxacin and norfloxacin. Benzofuran-5-ols are an interesting sub-group of benzofurans which could metabolize to benzoquinone derivatives with a quinonoid structure in fungi. Quinonoid compounds display potent biological properties including antifungal, antimalarial, and antibacterial activity [103]. Ryu et al. assumed that benzofuran-5-ols could have similar biological activities with those of the quinonoid compounds. Based on this speculation, they synthesized benzofuran-5-ol derivatives to elucidate their contribution to the antifungal activity against *Candida, Aspergillus* species, and *Cryptococcus neoformans* [104]. The MIC (minimum inhibitory concentration) values were determined by comparison with fluconazole and 5-fluorocytosine as standard agents. Most benzofuran-5-ols showed potent antifungal activity against all tested organisms. The antifungal activity of compounds **40** and **41**, was superior or comparable to those of 5-fluorocytosine. These compounds completely inhibited the growth of all tested fungal species at the MIC level of 1.6–12.5 μg/mL. Many of 2-amino-4-arylthio-5-hydroxybenzofurans also showed potent antifungal activity against *Candida krusei*, *C. neoformans*, and *Aspergillus niger*. The results suggested that benzofuran-5-ol scaffolds would be promising leads for the development of antifungal agents. Moreover, these observations encouraged the synthesis of benzofuran-5-ol analogs for improving antifungal properties.

Benzofurans with substituent (s) at C-2 and/or C-3 have attracted strong interest due to their widespread in a large number of natural products and for their useful biological and pharmacological properties [14,105,106]. A huge number of natural and synthetic benzofurans have established potency as antifungal agents [107,108] such as the fungistatic benzofuran derivative Griseofulvin. Abdel-Aziz et al. [109] performed synthesis of benzofuran-based (1*E*)-1-(piperidin-1-yl)-N^2-arylamidrazones. All the synthesized compounds were screened for their antifungal and antibacterial activities against two filamentous fungi (*Aspergillus fumigatus* and *Syncephalastrum racemosum*), two yeast (*C. albicans* and *Geotrihum candidium*), two Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) and two Gram-negative (*E. coli* and *P. aeruginosa*) bacteria. Griseofulvin and amoxicilline were used as a standard antifungal and antibacterial agent, respectively. Most of active compounds exhibited significant antifungal potency more than antibacterial potency. Compound **42** was found to be promising antifungal agent. Some compounds also showed excellent antimicrobial activities with respect to the control drugs. The authors also studied the effect of most potent antifungal compound **42** on morphological features of *A. fumigatus* and *C. albicans* using image analyzer. Furthermore, the effect of **42** on the ultra-structures of the latter fungi was occurred by transmission electron microscope. It can be concluded that, newly synthesized benzofuran-based (1*E*)-1-(piperidin-1-yl)-N^2-arylamidrazones can

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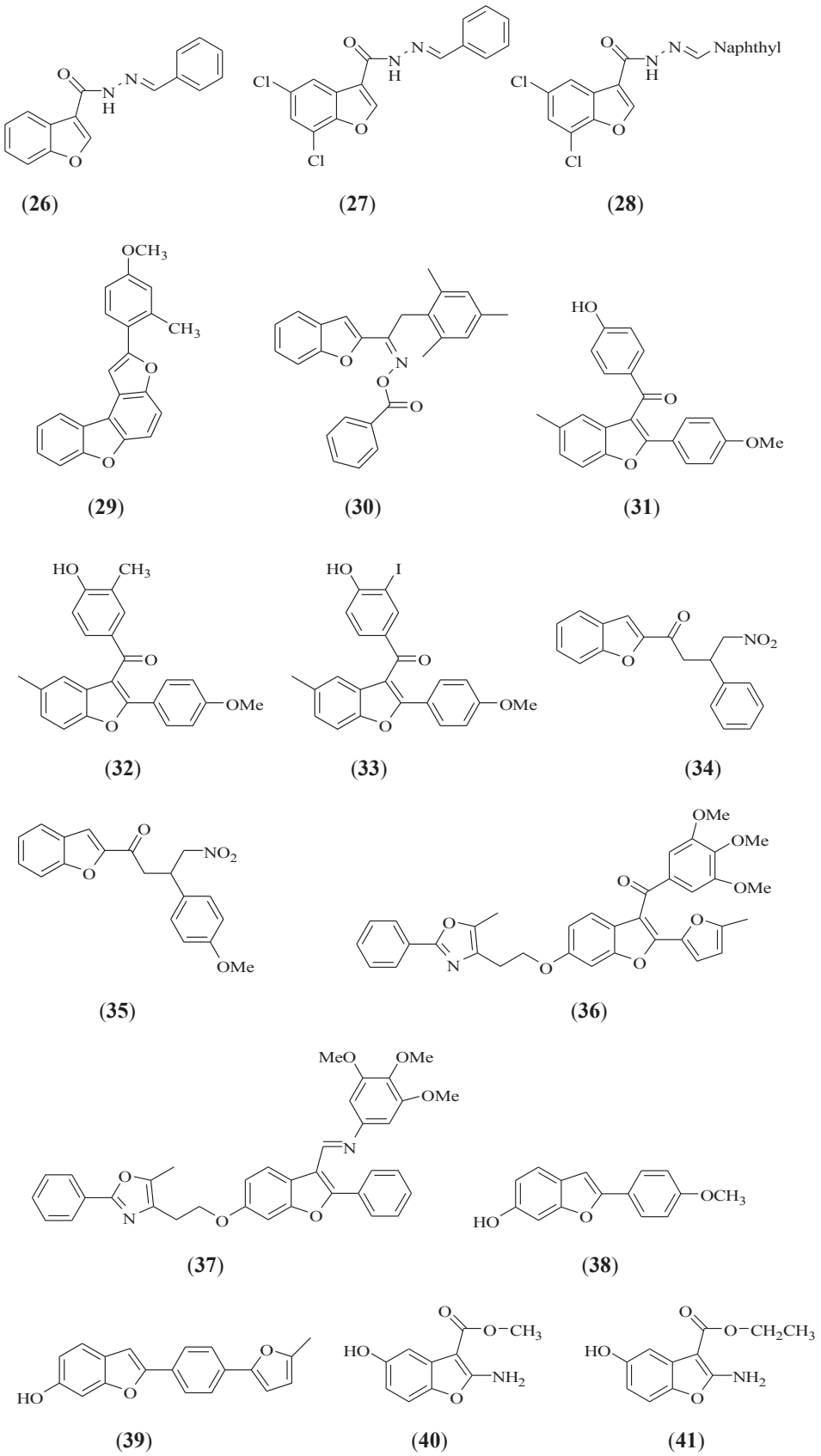

Fig. 14. Benzofuran derivatives as antimicrobial agents [ref. [95,96,98–101,104,109,111]].

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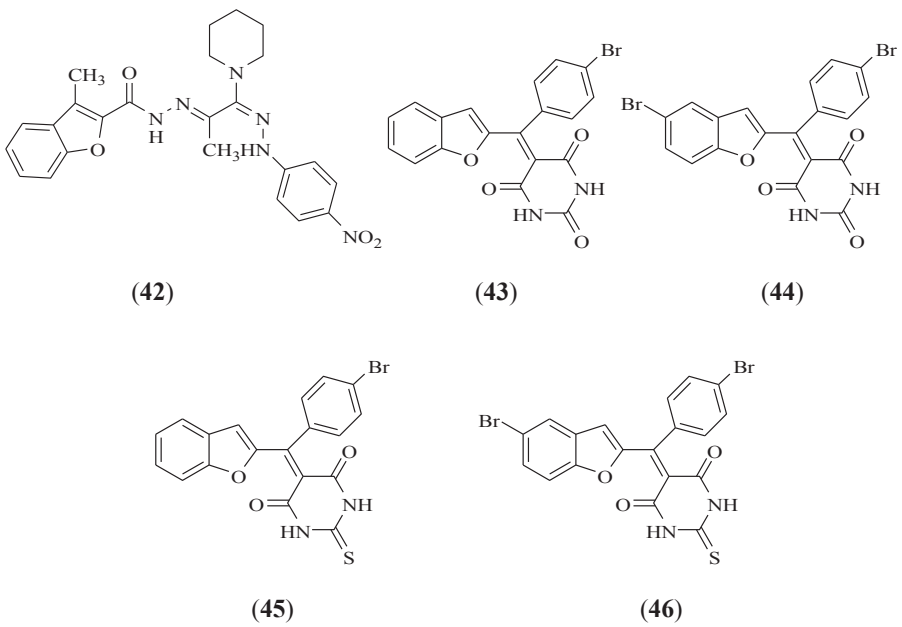
be considered as very promising in the perspective of new drugs discovery with respect to the medical importance of the tested fungal strains.

Barbituric acid (BA) derivatives are versatile reagents, capable of condensing with a wide range of carbonyl compounds [110]. They also possess various chemical and pharmacological properties. Therefore, it is envisaged that chemical entities with benzofuran and barbituric/thiobarbituric moieties would result in compounds of interesting biological activities. In view of these findings, Kenchappa et al. [111] synthesized novel series of benzofuran derivatives, containing barbitone and thiobarbitone moiety. These compounds were screened for the antimicrobial and antioxidant activities against five bacterial strains *Pseudomonas syringae*, *Salmonella tyhphi*, *B. subtilis*, *K. pneumonia*, *E. coli*, and four fungal strains *Asperigillus flavous*, *C. albicans*, *Microspora griseus*, and *Asperigillus terus*. The investigation of antimicrobial screening revealed that, test compounds showed varying degree of activity against all the tested micro-organisms. All the compounds exhibited a varied degree (MIC, 11.38–199.10 μmol/L) of antibacterial activity against all the tested bacterial strains. SAR studies revealed that structural changes played a key role in determining activity. It was observed that electron withdrawing groups in the *ortho* position of benzofuran ring and in the *para* position of aryl ring have a tendency to increase the potency while compounds containing electron donating groups were found to weaken the antimicrobial activity. Compounds **44**, **46** having two bromo substituents on C-5 of benzofuran and C-4 of phenyl ring, respectively were found to exhibit excellent antibacterial activity against all the tested bacterial strains with MIC value of 29.76–31.96 μmol/L. Compounds bearing –Br substituent on C-4 position of the aryl ring showed good ability to inhibit *S. tyhphi* at MIC 36.61–37.92 μmol/L; the same compounds showed good activity against *P. syringae* with MIC 37.20–38.50 μmol/L. In case of compounds having hydroxyl and bromo-substituent, exhibited moderate to good activity against *S. tyhphi* with MIC value 36.08–36.73 μmol/L. The MIC of antifungal activity of the compounds indicated that, compounds **43** and **45** exhibited remarkable activity against the tested organisms with MIC value 14.90–29.92 μmol/L. Further, the synthesized compounds were studied for docking on the enzyme, Glucosamine-6-phosphate synthase. The compounds **44** and **46** emerged as an active antimicrobial agent with least binding energy (−5.27 and −4.85 kJ mol^{-1}) (Fig. 14).

3.3. Antiviral agents

Antiviral properties of various benzofuran derivatives have been studied using different virus strains, such as hepatitis C virus (HCV), influenza, and HIV. The enzyme reverse transcriptase (RT) is used by retroviruses to transcribe their single-stranded RNA genome into single-stranded DNA and to subsequently construct a complementary strand of DNA, providing a DNA double helix capable of integration into host cell chromosomes. Reverse transcriptase is multifunctional enzyme. Functional HIV1-RT is a heterodimer contains two domains, the N-terminal polymerase domain and the C-terminal RNase H domain [112]. Because of the importance of RT to HIV replication, inhibitors of this enzyme are potential therapeutic agents in the battle against HIV. In addition the NS3-4A serine protease of hepatitis C virus (HCV) is essential for viral replication and therefore has been one of the most attractive targets for developing specific antiviral agents against HCV. Galal et al. [113] designed and synthesized new transition metal complexes of benzofuran derivatives. HIV and HIV reverse transcriptase inhibitory activity besides the hepatitis C virus (HCV) NS3-4A protease inhibitory activity was also discussed. The HIV inhibitory studies (EC_{50} values) showed that, all of tested compounds were more potent than atevirdine. Moreover, the benzoimidazolylpyrrole derivative **47** ($EC_{50} = 9 \times 10^{-6}$ μM) had higher therapeutic index than the standard. The HIV-1 RT inhibitory activity showed that all of the tested compounds showed significant potency but none of them showed higher activity than atevirdine. The HCV NS3-4A protease inhibitor activity of the tested compounds revealed that the complex formation had great positive effect on the bioactivity, where the Fe-complex, **48** was the most potent compound with higher therapeutic index than VX-950, the standard. Also, the cytotoxicity of the synthesized compounds on hepatocyte cell lines, showed that Cu-complex, **49** was the most potent compound with potency nearly to that of the standard. Studying the median lethal dose LD_{50} showed that the complex formation have positive effect on the



(42) (43) (44)

(45) (46)

Fig. 14. (*continued*).

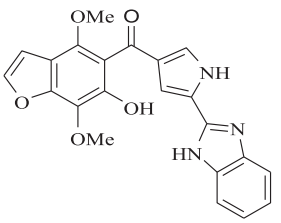
reduction of toxicity of free ligands. Malpani et al. [114] performed synthesis of 3*H*,3′*H*-spiro[benzofuran-2,1′-isobenzofuran]-3,3′-diones and tested them against influenza virus type A *viz*., A/Taiwan/1/86 (H1N1), A/Hong Kong/8/68 (H3N2) and type B *viz*., B/Panama/45/90, B/Taiwan/2/62, B/Lee/40, B/Brisbane/60/2008. Among 31tested compounds, some of them showed good activity (selective index values>10) against these influenza viruses preferentially for type B. The SAR analysis showed that the presence of chloride or methyl substitutions at position-1 of the phenolic ring gave a potent antiviral activity without any cytotoxicity. In particular, the presence of dimethyl group at positions-2 and 3 on the ring exhibited the most enhanced activity (**50**). The most active compound **50** showed activity in 3.0–16.1 μM range without any cytotoxicity at 500 μM with a selectivity index value between 30 and 166 against these type B viruses, in which it was comparable to the antiviral agent favipiravir. Also, **50** was found to be inactive against other enveloped viruses (*viz*., HIV and HSV) showing its specificity for influenza viruses. It is expected that compound **50** could be further optimized to be a candidate for development of a novel and specific therapeutics inhibiting influenza B viruses which are not sensitive to adamantanes, as well as influenza A virus to some extent Fig. 15.

3.4. Miscellaneous

3.4.1. Alzheimer's disease (inhibitors for Aβ fibril formation)

Alzheimer's disease (AD) is a neurodegenerative disorder of the brain that is characterized by dementia, cognitive impairment, and memory loss [115,116]. A major hallmark of AD is the formation and accumulation of fibrillar β-amyloid (Aβ) peptides in the brain [117,118]. Of the two most abundant forms of Aβ, Aβ42 are aggregated into oligomers, protofibrils, and fibrils more readily than relatively soluble Aβ40 [119,120]. To prevent Aβ fibril formation in the brain, are now a days being targeted as potential therapies for AD and many compounds are under clinical trials [121,122]. Various promising approaches to develop ligands exhibiting specific high binding affinity to Aβ fibrils have been proposed by Byun et al. [123]. They designed and synthesized a novel series of aminostyrylbenzofuran analogs and described their inhibitory activities for Aβ fibril formation. All the synthesized compounds were found to interfere with the fibrillization of Aβ as determined by thioflavin T (ThT) assay. Among them, compounds **51** and **52** (Fig. 16) exhibited excellent inhibitory activities (IC_{50} = 0.07 and 0.08 μM, respectively) than those of curcumin (IC_{50} = 0.80 μM) and IMSB (IC_{50} = 8.00 μM) as reference compounds.

The quantitative evaluation of Aβ aggregates in the brain with noninvasive techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) would allow a presymptomatic diagnosis and the monitoring of putative effects of neuroprotective treatments. Thus, great efforts have been made to develop radiotracers that bind to β-amyloid plaques *in vivo* [124–126]. Recent success in developing radiolabeled agents targeting Aβ aggregates has provided a window of opportunity to improve the diagnosis of AD. A series of fluorinated benzofuran derivatives were synthesized by Cheng et al. [127] and evaluated *in vitro* and *in vivo* as potential tracers for positron emission tomography (PET) targeting β-amyloid plaques in the brains of patients with Alzheimer's disease (AD). The derivatives were produced using an intramolecular Wittig reaction. In experiments *in vitro*, all displayed high affinity for Aβ(1–42) aggregates with Ki values in the nanomolar range. Radiofluorinated **53**, **[^{18}F] 53**, in particular labeled β-amyloid plaques in sections of Tg2576 mouse brain and displayed high uptake (5.66% ID/g) at 10 min postinjection, sufficient for PET imaging. In addition, *in vivo* β-



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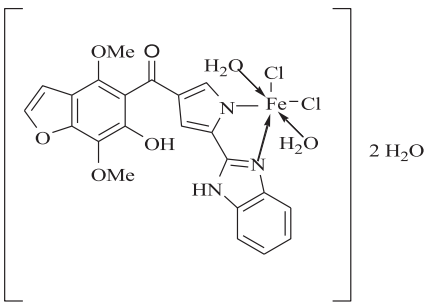

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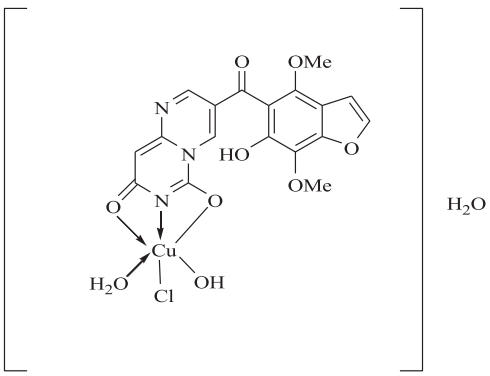

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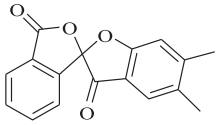

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Fig. 15. Antiviral agents [ref. [113,114]].

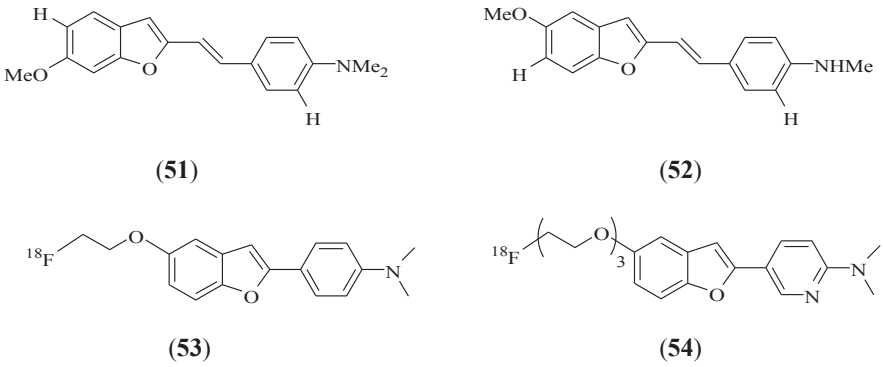


Fig. 16. Benzofuran derivatives as inhibitors of Aβ fibril formation [ref. [123,127,128]].

amyloid plaque labeling can be clearly demonstrated with **[^{18}F]53** in Tg2576 mice. Thus, **[^{18}F]53** may be useful for detecting β-amyloid plaques in patients with AD. Cheng et al. also synthesized FPYBF-1(5-{2-[2-(fluoroethoxy) ethoxy]ethoxy}benzofuran-2-yl)-*N*,*N*-dimethylpyridin-2-amine), **(54)** (Fig. 16) as a potential probe for PET targeting β-amyloid plaques in Alzheimer's disease (AD) brain [128]. In experiments *in vitro*, FPYBF-1 displayed high affinity for Aβ(1–42) aggregates (Ki = 0.9 nM), and substantial labeling of β-amyloid plaques in sections of postmortem AD brains but not control brains. And in *in vivo* experiments, [^{18}F]FPYBF-1 displayed good initial uptake (5.16%ID/g at 2 min postinjection) and rapid washout from the brain (2.44%ID/g at 60 min postinjection) in normal mice, and excellent binding to β-amyloid plaques in a murine model of AD. Furthermore, the specific labeling of plaques was observed in autoradiographs of autopsied AD brain sections. The results showed that [^{18}F]FPYBF-1 may be a useful probe for imaging β-amyloid plaques in living brain tissue. In addition, ^{99m}Tc-labeled pyridyl benzofuran derivatives and corresponding rhenium complexes were synthesized and tested as potential probes for imaging β-amyloid plaques using single photon emission computed tomography (SPECT) [129]. All Re complexes showed affinity for Aβ(1–42) aggregates (Ki = 13.6–149.6 nM). Biodistribution experiments in normal mice revealed that the ^{99m}Tc-labeled derivatives displayed sufficient uptake in the brain (1.41–1.80% ID/g at 2 min postinjection). Conspicuously, [**^{99m}Tc**]BAT-Bp-2 showed a good initial uptake (1.80% ID/g at 2 min) and a reasonable washout from the brain (0.79% ID/g at 60 min). *Ex vivo* autoradiography with [^{99m}Tc]BAT-Bp-2 revealed considerable labeling of β-amyloid plaques in sections of brain tissue from Tg2576 transgenic mice but not in the age-matched controls.

3.4.2. Antagonists of angiotensin II

There is good evidence that antagonists of angiotensin II will be useful in the treatment of hypertension [130]. This area of research has been the focus of much effort over the last few years and many clinical candidates have been identified [131]. To compete successfully with other forms of treatment such compounds will have to be suitable for once-a-day oral administration. Consequently any clinical candidates should be well absorbed after oral administration, be metabolically stable and have low plasma clearance. Despite having good metabolic stability and low plasma clearance many of the early non-peptide antagonists of angiotensin II are only poorly absorbed. Thus identification of antagonists of angiotensin II with improved oral absorption over that of first clinical candidate GRl 17,289 [132] has been necessary. A series of imidazopyridinylbenzofurans have been identified as potent, non-peptide antagonists of angiotensin II by Judd et al. [133]. Several of these compounds, caused marked fall in blood pressure in the renal artery ligated rat model of hypertension after oral administration. In particular, two compounds (**55**, **56**) (Fig. 17) showed high bioavailability and low plasma clearance with high metabolic stability in rats.

3.4.3. Anti-inflammatory, analgesic and antipyretic agents

Benzofurans have drawn considerable attention over the last few years due to their profound physiological and chemotherapeutic properties. Natural and synthetic products possessing the 2-benzylbenzofuran moiety exhibit wide range of biological activities [134]. Yadav et al. [135] synthesized new benzofuran derivatives and they studied anti-inflammatory activity of the prepared compounds using mouse paw edema bioassay. All the synthesized compounds were evaluated for their anti-inflammatory activity by biochemical COX (COX-1 & COX-2) inhibitory assay. Docking study was performed to study the interaction of molecules with the active site of COX-2 (cyclooxygenase). The ratio of IC_{50} of COX-2 to IC_{50} of COX-1 (COX-2/COX-1) suggested the selectivity of the compound and hence its gastric liability [136–138]. Among synthesized compounds, **57** (Fig. 18) exhibited good anti-inflammatory activity, and optimal COX-2 inhibitory potency (IC_{50} = 4.2 μM). Molecular modeling indicated that benzofuran analogs interact with COX-2 active site by forming classical hydrogen bonding and this interaction increase the residence time of ligand in the active site consequently augmenting anti-inflammatory activity of compounds.

Xie et al. [13] obtained the library of benzofuran-2-carboxamide derivatives and discussed their *in vivo* anti-inflammatory, analgesic and antipyretic activities in details. Anti-inflammatory activity was evaluated against carrageenan induced paw edema method in Wistar rats [139]. The standard drug diclofenac sodium was administered at dose of 20 mg/kg p.o. which gave 74% inhibition of inflammation at 4 h. Among the newly synthesized benzofuran-2-carboxamide derivatives, compound **58** showed significant anti-inflammatory activity (65% inhibition) compared to other scaffolds. The results indicated that the methyl group at 5-position of

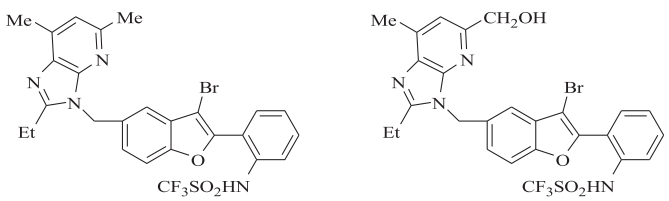
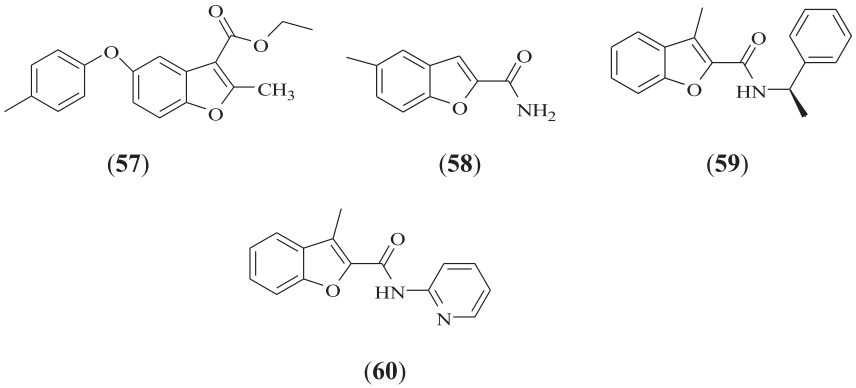


Fig. 17. Antagonists of angiotensin II [ref. [133]].



(57) (58) (59)

(60)

Fig. 18. Anti-inflammatory, analgesic and antipyretic agents [ref. [13,135]].

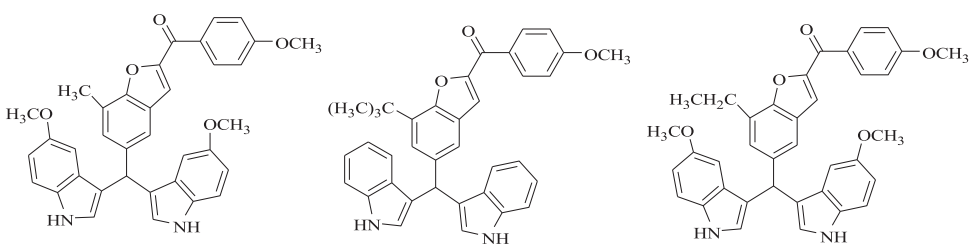
benzofuran ring might be responsible for the anti-inflammatory activity. Radiant heat tail-flick method in rats was used to screen the analgesic activity [140]. Most of the synthesized compounds showed significant analgesic activity with 134–172% increase in reaction after 1 h treatment. While, the antipyretic activity was evaluated against brewer's yeast induced method [141]. Paracetamol was used as standard drug at a dose of 150 mg/kg p.o. The percentage reduction in temperature after 5 h, indicated that the compounds **58**, **59**, and **60** (Fig. 18) exhibit potent antipyretic activity causing more than 58% reduction in rectal temperature. The results gave an interesting insight, into the validity of employing benzofuran analogs as good anti-inflammatory, analgesic and antipyretic agents.

3.4.4. Anti-hyperlipidemic agents

Hyperlipidemia, a key feature of the metabolic syndrome and is the major cause of heart disease, stroke and death in most industrialized world [142]. It is estimated that nearly 31.9 million US adults have total serum cholesterol levels ≥240 mg/dL, and 13.8% are with a prevalence of cardiovascular risk and this is set to rise in future [143]. The typical characteristics of hyperlipidemia are high plasma triglyceride (TG) concentration, low high density lipoprotein cholesterol (HDL-C) concentration and increased concentration of small density lipoprotein cholesterol (LDL-C) particles [144]. Current available therapies for hyperlipidemia include statins, fibrates, niacin/nicotinic acid and bile acid sequestrants [145]. Due to multifactorial nature of the metabolic syndrome, it is envisaged that compounds endowed with both hypolipidemic and antioxidant properties will be able to offer a better therapeutic benefit. Benzofuran containing natural products tourefolic acids A and B have shown potent anti-lipid-peroxidative properties [146]. Furthermore, a literature survey revealed that benzofuran ring containing moiety, exhibit antihyperlipidemic activity [147]. These studies, suggested that compounds containing this ring might have a potential lipid lowering effect. Sashidhara et al. [148] performed synthesis of different benzofuranebisindole hybrids and evaluated *in vitro* for their antioxidant and *in vivo* for antidyslipidemic activity in triton WR-1339 induced hyperlipidemic rats. The pathological investigation revealed that the novel compounds **61**, **62** and **63** (Fig. 19) showed significant decrease in plasma levels of total cholesterol (TC), phospholipids (PL) and triglycerides (TG) followed by increase in post heparin lipolytic activity (PHLA). Furthermore, the synthesized compounds **61** and **63** exhibited potent antioxidant properties and increased the plasma lecithin cholesterol acyltransferase (LCAT) activity, which plays a key role in lipoprotein metabolism contributing to an increased level of HDL-C in serum. The obtained results strongly suggested that novel hybrid prototypes (with unique chemical structures) with improved lipid abnormalities would be a potential new leads against dyslipidemia.

3.4.5. Protein tyrosine phosphatase 1B (PTP-1B) inhibitors

The complex metabolic syndrome, diabetes mellitus, is a major human health problem of the world. Although treatment with highly active thiazolidinedione (TZD) [149] class of drugs has significantly improved the clinical situation, but suffers with adverse side effects of hepatotoxicity, weight gain and edema. The alarming situation emphasized the need to explore the new molecular targets and strategies to develop novel antihyperglycemic agents. One such strategy is to design and synthesize inhibitors for protein tyrosine phosphatase-1B (PTP-1B), which is a legitimate target for the treatment of Type 2 diabetes by attenuating insulin resistance. PTP-1B, a cytosolic PTP, is thought to function as a negative regulator of insulin signal transduction and directly interacts with activated insulin receptor or insulin receptor substrate-1 (IRS-1) to dephosphorylate phosphotyrosine residue, resulting in down-regulation of insulin action [150]. Studies have shown that



(61) (62) (63)

Fig. 19. Benzofuran derivatives as anti-hyperlipidemic agents [ref. [148]].

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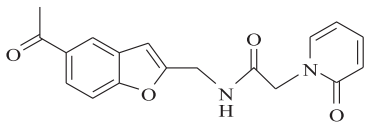
PTP-1B knockout mice showed increased insulin sensitivity in muscle and liver as well as resistance to obesity. Dixit et al. [151] synthesized various nature-mimicking hydroxybenzofuran methyl ketones and their dimers as well as linear and angular furanochalcones and flavones and evaluated their protein tyrosine phosphatase-1B inhibitory activity. The results showed that screened compounds displayed good inhibitory activity. Benzofuran dimers **64** and **65** (Fig. 20) showed good inhibitory activity (IC_{50} = 58.8 and 56.3 μM respectively) against PTP-1B compared to their monomers. The linear furanoflavonoids showed better inhibition (67.5%, 75.6%) against PTP-1B compared to their angular isomers (21%, 22%).

3.4.6. Oxytocin antagonists

Wyatt et al. [152] synthesized benzofuran derivatives and studied their oxytocin antagonist activity and pharmacokinetic parameters. The compound **66** (Fig. 21) was used as a lead to identify potent and selective oxytocin antagonists *in vitro*. Investigations demonstrated that much of the molecule was intolerant to modification. However, a significant increase in activity and improvement of pharmacokinetic parameters was achieved by optimisation of the pyridone moiety of **66**. The *in vivo* activity of the compounds was significantly lower than their *in vitro* activity, possibly due to protein binding. This loss of activity was paralleled *in vitro* by the addition of human serum albumin to the hOT binding screen, allowing selection of candidates for *in vivo* evaluation. The findings demonstrated that the benzofuran derivatives can be valuable in the design of oxytocin antagonists with potent *in vivo* activity.

3.4.7. Endothelin (ET) receptor antagonists

Endothelin (ET), a peptide of 21-amino acids, was initially identified from endothelial cells as a potent vasoconstrictor [153,154]. It is a small peptide hormone that is believed to play a critical role in the control of blood flow and cell growth. Elevated ET blood levels are associated with several cardiovascular disease conditions [155]. The ETs function by binding to transmembrane G-protein-coupled receptors of which two major subtypes, ET_A and ET_B, have been identified [156,157]. Screening of the Parke–Davis compound library identified two benzofuran carboxylic acid derivatives that showed potent selectivity for the ETA receptor (IC_{50} = 11–3.8 μM) [158]. The previous report of structure and activity relationship of benzofuran carboxylic acid derivatives indicated that 3-methyl group and the carboxyl group were essential for ETA binding affinity. Therefore, Cai et al. [159] introduced some other substituents in 4-position, such as longer aliphatic chains, substituted benzene rings and benzothiadiazoles, which were pharmacophores of some known ETA antagonists in former report [160]. They screened antagonism effect of newly synthesized compounds on ET-1-induced contraction in the rat thoracic aortic ring. Some target compounds demonstrated significant inhibitory activity, especially benzothiadiazole and benzoxadiazole compounds **67** and **68** (Fig. 22) exhibited potent inhibition percentage



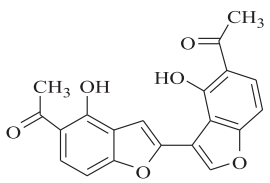
(66)

Fig. 21. Oxytocin antagonist [ref. [152]].

higher than the contrast compound BQ123. Further affinity and selectivity for ET binding assay showed that **67** demonstrated a dual ET_A/ET_B antagonism activity in nanomole level. Moreover, compound **68** was effective in relieving hypoxia-induced pulmonary arterial hypertension.

3.4.8. Human GPR119 agonists

Type 2 diabetes mellitus (T2DM) is a chronic disease characterized by elevated blood glucose levels in the context of insulin resistance and relative insulin deficiency. Impairments in both insulin production and insulin sensitivity result in a chronic demand for greater β-cell insulin production, which ultimately leads to the gradual loss of pancreatic β-cell function as diabetes progresses. Despite current available treatments glycemic control represents a significant unmet medical need, due to both the increasing patient population and the ineffectiveness of the above antidiabetic agents over years of treatment. G-protein-coupled receptor 119 (GPR119) is a rhodopsin-like, class A Gs-coupled GPCR, which is predominately expressed in human pancreatic β-cells, where it mediates insulin secretion, and in gastrointestinal L-cells, where it mediates GLP-1 release. The activation of GPR119 increases the intracellular accumulation of cyclic adenosine monophosphate (cAMP), leading to enhanced glucose-dependent insulin secretion from pancreatic β-cells and increased release of the gut hormones such as GLP-1 (glucagon-like peptide 1), GIP (glucose-dependent insulinotropic peptide) and PYY (polypeptide YY) from enteroendocrine cells. This dual mechanism of action might produce favorable effects on glucose homeostasis and β-cell preservation, along with other beneficial effects such as reduced food intake and body weight [161,162]. Scientific evidence has been published by various laboratories demonstrating the capability of small synthetic GPR119 agonists to lower glucose in a variety of animal models [163]. In addition, Overton et al. reported that OEA (oleoylethanolamide, an endogenous agonist of GPR119) and PSN632408 (a synthetic GPR119 agonist) reduced body weight, white adipose tissue depots, and food intake in diet-induced obese rats [164]. Several pharmaceutical companies have entered clinical trials with small molecule GPR119 agonists. This includes: Johnson & Johnson/Arena JNJ-38431055 [165a,b], Metabolex/Sanofi-Aventis MBX-2982 [165b,c], GlaxoSmithKline GSK1292263 [165b,d], and Astellas Pharma PSN8216 [165b,e]. The available clinical data demonstrated the ability of GPR119 agonists to promote incretin release and reduce postprandial glucose excursion [166]. All these results have made



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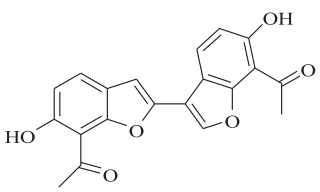
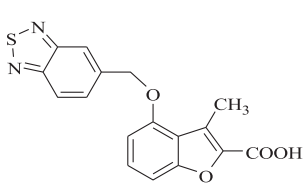


(65)

Fig. 20. Protein tyrosine phosphatase 1B (PTP-1B) inhibitors [ref. [151]].



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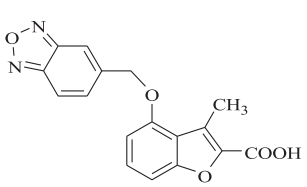


(68)

Fig. 22. Endothelin (ET) receptor antagonists [ref. [159]].

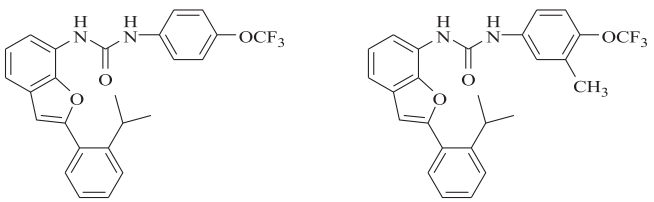
GPR119 an attractive drug target for treating diabetes and possibly obesity, with a low propensity to cause hypoglycemia. Ye et al. [167] synthesized various benzofuran derivatives (Fig. 23) and analyzed them as GPR119 agonists. The results showed that compounds **69** and **70** were found to exhibit most of the characteristics desirable for an effective GPR119 agonist, including GPR119 *in vitro* potency, liver microsomal stability, high PAMPA permeability, low PXR transactivation, weak CYP inhibition, etc. The most significant issue for this chemotype was the poor aqueous solubility (generally <1 μg/mL at pH 6.5). It was envisioned that a prodrug strategy might solve this issue. After surveying several polar functional groups such as−OH and $-NH_2$ at the various positions of the molecule, it was found that an −OH group in the sulfonamide side chain was best suited for retention of *in vitro* potency. The SAR of the hydroxyl sulfonamide analogs in three different dihydrobenzofuran cores showed that both primary and tertiary alcohols are active *in vitro*, with minimal potency differences due to the length of the side chain. Compound **71** was found to be potent human GPR119 agonism activity and reasonable metabolic stability in both human and mouse microsomes. Conspicuously, the hydroxyl group in **71** could serve as suitable functionality for several different types of prodrugs such as phosphate and glycine ester, which could enhance aqueous solubility and improve pharmacokinetic profiles.

3.4.9. Purinergic ($P2Y_1$) receptor antagonists

Purinergic receptor antagonists have recently demonstrated therapeutic potential for the treatment of a variety of diseases, including thrombosis, diabetes, cystic fibrosis, and cancer [168]. The $P2Y_1$ and $P2Y_{12}$ receptors play key roles in platelet aggregation and thrombus formation [169]. Inhibition of the $P2Y_{12}$ receptor is a well-established strategy for anti-thrombotic therapy; Plavix®(-clopidogrel), an irreversible $P2Y_{12}$ receptor antagonist, is the number one selling drug on the market for antiplatelet therapy [170]. However, $P2Y_1$ is a relatively new target being explored for anti-thrombotic therapies. Several studies have shown that exclusive inhibition of the $P2Y_1$ receptor can effectively prevent platelet aggregation and thrombus formation both *in vitro* [171] and *in vivo* [172] Therefore, $P2Y_1$ receptor antagonists offer great potential as novel anti-thrombotic agents. Thalji et al. [173] identified benzofuran-substituted urea analogs as novel $P2Y_1$ receptor antagonists that affect ADP-mediated platelet activation. All compounds were initially evaluated in the $P2Y_1$ FLIPR assay. Hits were then followed up in a competitive binding assay employing radiolabeled ADP ([^{33}P]-2-SMe-ADP) to confirm $P2Y_1$ specific activity. Most of the compounds showed improved potency. Analogs **72** and **73** (Fig. 24) showed significant inhibition of P-selectin expression demonstrating that this class of $P2Y_1$ inhibitor is functionally active. Structure− activity relationship studies showed that a large, relatively non-polar *ortho*-phenyl substituent on the benzofuran ring is required for optimal activity. It was observed that alkyl-substituted aryl groups are optimal substituents on the urea.

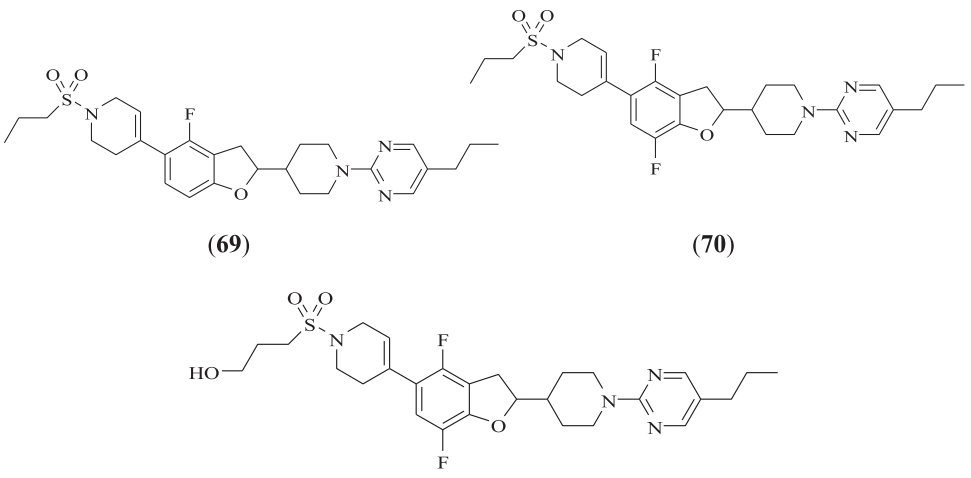
3.4.10. Sphingosine-1 phosphate ($S1P_1$) receptor agonists

Current therapeutic options for multiple sclerosis (MS) are all injectable, and a need for an effective oral agent exists. Myelin reactive T cells (lymphocytes) in the peripheral immune system play a key role in MS [174–176]. Regulation of sphingosine-1 phosphate receptor subtype-1 ($S1P_1$), a G-protein-coupled receptor (GPCR) expressed on T lymphocytes, could produce a new class of immunomodulators with a novel mechanism of action. Lymphocyte egress from lymphoid tissues requires the lipid mediator $S1P_1$ and is required for the emigration of lymphocytes from the thymus and the trafficking of lymphocytes in secondary lymphoid organs [177,178]. The pro-drug FTY-720 upon phosphorylation activates the $S1P_1$ receptor [179]. It was successful in advanced clinical trials for relapsing-remitting MS and was recently recommended for approval by an FDA advisory committee for relapsing MS [180]. It is, however, a nonselective S1P receptor agonist with potent affinity for four of five S1P receptor subtypes. Agonism of $S1P_3$ is believed to cause chronotropic side effects [181]. Saha



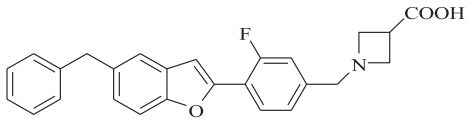
(72) (73)

Fig. 24. Benzofuran derivatives as purinergic ($P2Y_1$) receptor antagonists [ref. [173]].



(69) (70) (71)

Fig. 23. Benzofuran derivatives as human GPR119 agonists [ref. [167]].



(74)

Fig. 25. Sphingosine-1 phosphate ($S1P_1$) receptor agonist [ref. [182]].

et al. [182] discovered novel benzofuran-based potent and selective $S1P_1$ receptor agonists. 1-{[4-(5-Benzylbenzofuran-2-yl)-3-fluorophenyl]methyl}azetidine-3-carboxylic acid (**74**) (Fig. 25) was found to be a potent $S1P_1$ agonist with >1000 × selectivity over $S1P_3$. It established a good *in vitro* ADME profile and excellent oral bioavailability across species. Oral dosing of compound **74** in rats (1 mg/kg) resulted in a statistically significant reduction in circulating lymphocytes 24 h postdose, as well as efficacy in the mice EAE model of MS. The overall profile of compound **74** led to nomination for preclinical development including follow-on GLP toxicology studies. Such studies revealed pro-convulsive activity at doses of 40 mg/kg and higher. Optimization efforts toward scaffolds that avoid such toxic properties can be solved in further investigations.

4. Conclusion

Benzofuran scaffolds display potent biological properties such as antihyperglycemic, analgesic, anti-inflammatory, antibacterial, antifungal, antitumor, antiviral, antipyretic activities including enzyme inhibitors. Several benzofuran ring systems bearing various substituents at the C-2 position are widely distributed in nature. There are well known natural products having related benzofuran ring structures. Many of the natural benzofurans have physiological, pharmacological and toxic properties. The most recognized of the benzofurans are amiodarone, angelicin xanthotoxin, bergapten, nodekenetin and usnic acid compounds. The present review is an attempt to highlight the medicinal importance along with chemistry of benzofuran derivatives. In addition, important insights about the structural requirement for various pharmacological activities have also been reviewed. It is concluded that a wide spectrum of biological activities exhibited by the scaffold will certainly serve the purpose to be used as efficient chemotherapeutics. This information may endow with an opportunity to scientific community to design selective, optimized as well as poly-functional benzofuran analogs for the treatment of multifactorial diseases.

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