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Review Article

FUROXAN DERIVATIVES AS NITRIC OXIDE DONORS AND THEIR THERAPEUTIC POTENTIAL

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ABSTRACT

Nitric oxide synthesized in endothelial cells that line blood vessels, was first described in 1980 as an endothelium derived vascular relaxing factor. It is an important signalling molecule in various pathological and physiological processes. Dysfunction of NO formation has been implicated in the pathogenesis of a number of disorders. Exogenous NO sources constitute a powerful way to supplement NO when the body cannot generate enough for normal biological functions. Furoxan, 1,2,5-oxadiazole 2-oxide, has been a very important scaffold in Medicinal Chemistry as nitric oxide (NO) donor. This article explores some of the most promising recent advances in NO donor drug development. Major focus is placed on recently developed Furoxan derivatives as NO donors and their pharmacological actions.

Keywords: Nitric oxide, Furoxan, NSAIDs, anticancer, vasodilatory.

INTRODUCTION

The free radical, nitric oxide (NO), was discovered in 1980 as a critical signalling molecule, with various functions in the cardiovascular, nervous and immune systems. It is a physiological messenger that is almost ubiquitous in human tissues. It is synthesized from L-arginine under the action of a family of enzymes called NO synthase (NOS). It directly diffuses to the target or is transported there as metal complex or nitrosothiol. Nitric oxide displays diverse potent physiological actions.[1] Dysfunction of NO formation has been implicated in the pathogenesis of a number of disorders. Exogenous NO sources constitute a powerful way to supplement NO when the body cannot generate enough for normal biological functions.[2] The administration of physiological amounts of NO in the bloodstream or at the site of the local tissue and injured cells to improve diminished supplies of NO for the maintenance of cardiovascular homeostasis is considered as an emerging therapeutic strategy. Organic nitrates and nitrites are the most commonly used NO donor drugs in cardiovascular therapy. Glyceryl trinitrate (GTN) and amyl nitrite were proposed in the nineteenth century as antianginal drugs. Later drug discovery effort in 1950s led to the development of isosorbide dinitrate (ISDN), which is a stable nitrate that has a longer duration of action than GTN. Likewise, sodium nitroprusside (SNP) (Figure 1) was introduced as therapeutic agent more than 50 years ago and has been used for the treatment of hypertension.

However, these classical NO donors are characterized by side effects such as marked hypotension, reflex tachycardia and headache. Moreover, they undergo tolerance over a repeated administration regimen.

During the last decade, the search for new NO donors with reduced side effects and improved oral bioavailability has greatly intensified. Several reviews have been published illustrating the various chemical approaches which have been used to improve the pharmaceutical profile of NO donors. Recent medicinal chemistry approaches attempt to exploit the tissue protective function of NO against NSAID-induced gastric injury. Thus the idea of synthesizing multiple ligand drugs based on the conjugation between conventional NSAIDs and NO donating moieties became attractive. These efforts have culminated in the development of COX-inhibiting nitric oxide donors (CINODs), one of the most promising approaches for the design of anti-inflammatory drugs which are devoid of the adverse cardiovascular effects associated with the use of both selective COX-2 inhibitors, and non-selective NSAIDs; and which elicit a decreased ulcerogenicity relative to that frequently observed on long-term use of traditional NSAIDs. Fiorucci *et al*. demonstrated that NO donating agents could exert strong anti-inflammatory effects as well as reduce gastrointestinal damage.[3]

Loretta *et al*. found that NO could both inhibit bone resorption and increase bone formation which will be very beneficial to osteoporosis patients.[4] There is much interest today in drugs related to nitric oxide, especially in structures able to release NO. These products are collectively called NO donors.[5] One of the important NO donors, furoxan is discussed in this article.

Furoxan or 1,2,5-oxadiazole 2-oxide (Figure 2) is a heterocycle of the isoxazole family and an amine oxide derivative of furazan. Both 1,2,5-oxadiazole[6] and 1,2,4 oxadiazole[7] derivatives have been a very important scaffold in Medicinal Chemistry. Many furoxan derivatives have been reported in the literature showing diverse biological properties. Furoxan derivatives are stable compounds capable of producing NO in physiological solution, under the action of thiol cofactors. Studies have shown that furoxan derivatives generate NO or related N-oxide species in a controlled manner, the furoxan derivatives CAS 1609 and CHF 2206 (Figure 3) being the notable examples which were found to exert potent vasodilating activity. These findings suggested that furoxan ring can be a vital moiety in the design of NO releasing drugs.[6]

1. Anti- inflammatory activity

Fang *et al*. (2007) synthesized a series of furoxan-based nitric oxide-releasing glucocorticoid derivatives. The pharmacological evaluation of three compounds 4a, 4b, and 4c, (Figure 4) indicated the anti-inflammatory activity. Furthermore compared with the leading compound hydrocortisone the safety of 4a was greatly improved. Due

to releasing NO *in vivo* the side effects of glucocorticoids, including hypertension and osteoporosis, were effectively avoided.[8]

Yadav *et al*. (2007) synthesized a series of 3,4-diaryl-1,2,5-oxadiazoles and 3,4-diaryl-1,2,5-oxadiazole-*N*-oxides (Figure 5) and evaluated their COX-2 and COX-1 binding affinity *in vitro* and anti-inflammatory activity by the rat paw edema method. *p*-Methoxy (*p*-OMe) substituted compounds showed COX-2 enzyme inhibition higher than that showed by compounds with other substituents.[9]

Lazzarato *et al*. (2011) synthesized a new group of furoxans and furazans derivatives of salicylic acid (Figure 6) and evaluated them as new aspirin-like molecules. Phenylsulfonyl and cyano-substituted furoxans inhibited platelet aggregation induced by collagen in human platelet-rich plasma through a cGMP (cyclic guanosine monophosphate) dependent mechanism. Furoxan derivatives displayed cGMP-dependent vasodilator activities. All compounds showed anti-inflammatory activity comparable to that of aspirin.[10]

Cena *et al*. (2003) synthesized a novel series of NSAIDs in which aspirin is joined by an ester linkage to furoxan moieties with different ability to release NO and tested them for NO-releasing, anti-inflammatory, anti-aggregatory, and ulcerogenic properties. Compounds 7a and 7b (Figure 7) showed maximum activities.[11]

A new series of non-steroidal anti-inflammatory drugs (NSAIDs) was synthesized by linking ibuprofen to selected furoxan moieties and to related furazans (Figure. 8). The synthesized compounds were tested for their anti-inflammatory, anti-aggregatory, and ulcerogenic properties. All the derivatives were endowed with anti-inflammatory activity comparable to that of ibuprofen, but, unlike this drug, they displayed reduced acute gastrotoxicity.[12]

Hernandez *et al*. (2012) synthesized furoxanyl N-acylhydrazones (furoxanyl-NAH) (Figure. 9) and evaluated their analgesic and anti-inflammatory activities. Among them, furoxanyl-NAH, (9a), benzofuroxanyl-derivative, (9b), and furoxanyl-NAH derivative, (9c), showed orally analgesic and anti-inflammatory activities with lower toxicities.[13]

Rahma *et al*. (2012) reported the synthesis of a group of novel nitric oxide (NO) donating chalcone (Figure. 10). Most of the synthesized compounds showed significant anti-inflammatory activity in comparison to indomethacin with lower gastric toxicity due to the incorporation of the NO-donating group into the parent chalcone.[14]

Tang *et al*. (2014) modified Brusatol, a biologically active natural product, in four distinct positions through the covalent attachment of a furoxan moiety, which acts as a nitric oxide (NO) donor. Compounds synthesized were evaluated for their inhibitory effects on excess NO biosynthesis in activated macrophages. Among them, compound 11 (Figure. 11) demonstrated inhibition (IC_{50} = 0.067 μM) comparable to that of brusatol but were less cytotoxic. More importantly, even at very low doses (2 μmol/kg/day), compound 11 also showed substantial inhibitory efficacy against chronic obstructive pulmonary disease (COPD)-like inflammation in the mouse model induced by cigarette smoke (CS) and lipopolysaccharide (LPS). Particularly, this compound was over 100-fold less toxic (LD_{50} > 3852 μmol/kg) than brusatol and could be a promising lead for further studies. Notably, the improved properties of this derivative were associated with its NO-releasing capability.[15]

Turnbull *et al*. (2006) studied furoxan for their anti-inflammatory activity. They examined the effects of furoxan upon TNF-α release from lipopolysaccharide (LPS)-stimulated human monocytes and monocyte-derived macrophages and investigated a potential mechanism of action through effects on LPS-stimulated nuclear factor-κ B (NF-κ B) activation. Compound furoxan-aspirin (Figure. 12) significantly reduced TNF-α release from LPS-treated macrophages and suggested that inhibition of NF-κ B activation is a likely mechanism for the effect.[16]

Velazquez *et al*. (2005) synthesized a group of 3,4-diphenyl-1,2,5-oxadiazole-2-oxides (3,4-diphenylfuroxans), evaluated as hybrid cyclooxygenase (COX) inhibitor/nitric oxide donor agents. The methanesulfonyl regioisomers 13a, 13b and aminosulfonyl regioisomers 13c (Figure. 13) were potent *in vitro* COX-2 inhibitors with a good COX-2 selectivity index.[17]

2. Cardiovascular activity

Gasco *et al*. (2004) focussed attention on furoxan derivatives (Figure. 14) as NO donors. The *in vitro* antiaggregatory activities and the *in vitro* and *in vivo* vasodilating properties of a number of furoxans were examined with particular reference to involvement of NO in these actions. The compound showed prevalent calcium channel blocking properties.[18]

Boschi *et al*. (2000) synthesized and evaluated vasodilating activity of different furoxan derivatives (Figure. 15). The amide analogues of Nicorandil displayed feeble vasorelaxing action not involving the activation of K^+ channels, while in the guanidine analogues, this mechanism seemed to underlie the action.[19]

Ovchinnikov *et al*. (2003) synthesized a series of N-alkylamide derivatives of 4-amino-3-furoxancarboxylic acids and their oxidation products, the azo derivatives (Figure. 16) and studied them for their vasodilating properties. Experiments carried out in the presence of oxyhaemoglobin (HbO_2) suggested the involvement of NO in the vasodilation.[20]

Gasco *et al*. (1993) synthesized a series of l,l-dinitroethyl substituted furoxans. All compounds were evaluated for their vasodilatory properties. The most active derivative of the series was 3-(l,l-dinitroethyl)-4-phenylfuroxan (Figure. 17). Its vasodilatory property was found to be similar to that of glyceryl trinitrate. In addition, this compound was a more potent platelet aggregation inhibitor than sodium nitroprusside.[21]

A series of α-tocopherol mimetics with NO-releasing capacity were synthesized and were evaluated for their *in vitro* NO-releasing capacities, vasodilating properties and mammal cytotoxic activities. New hybrid furoxan and phenol derivatives (Figure. 18) were reported and found to possess good vasodilating activity.[22]

A new class of arylsulphinyl and arylsulphonyl substituted furoxans compounds (Figure. 19) was evaluated by Ferioli *et al*. (1993) for their vasodilating and antiaggregatory activities. The compounds 4-methyl-3-(p-methoxyphenylsulphonyl) furoxan, 3-phenyl-4-phenylsulphonylfuroxan (19a), 4-phenyl-3-phenylsulphonylfuroxan (19b) and 3,4-bis(phenyl-sulphonyl)furoxan (19c) displayed very good activity.[23]

A novel series of bisphosphonates bearing the nitrogen-containing NO-donor furoxan ring was synthesized by Lolli *et al*. (2010) and evaluated for vasodilator activities. The synthesized compounds were found to relax contracted vascular tissue in a concentration dependent manner. Compound 20 (Figure. 20) was found to be most active.[24]

Boschi *et al*. (2001) synthesized compounds containing NO-donor furoxan moieties at the 3-positioned basic lateral chain of 1,4-DHPs (1,4-dihydropyridine) related to nicardipine (Figure. 21).They studied their vasodilating activity and their lipophilic behaviour. It was found that nitrogen containing lateral chain at the 3-position is a suitable molecular region to be modified in order to obtain well-balanced furoxan NO-donor 1,4-DHPs.[25]

Cena *et al*. (2001) synthesized a series of "hybrid" 1,4-dihydropyridines (1,4-DHPs), bearing NO-donating furoxan moieties on the 3-positioned lateral ester chain (Figure. 22) and evaluated their vasodilating activity. Some hybrid compounds (22a and 22b) displayed vasodilating activity depending predominantly on their Ca^{2+} channel blocker properties. By contrast, some others (derivatives 22c and 22d) behaved as well-balanced hybrids with mixed Ca^{2+}channel blocking and NO-dependent vasodilating activities.[26]

Stilo *et al*. (1998) synthesized a series of 4-phenyl-1,4-dihydropyridines substituted at the ortho and meta positions of the phenyl ring with NO releasing furoxan moieties (Figure. 23) and evaluated for vasodilator activity. The compounds belonging to the *ortho* series displayed higher Ca^{2+} channel-blocker potency than the corresponding compounds of the *meta* series.[27]

Boschi *et al*. (1997) synthesized a series of derivatives having a propranolol-like moiety linked to NO-donor furoxan (Figure. 24) and evaluated their vasodilating and β-blocking activities. All compounds showed well balanced "hybrids" displaying NO-dependent vasodilating and β-blocking properties in the same concentration range.[28]

Fruttero *et al*. (1995) synthesized furoxan derivative of Prazosin (Figure. 25). Their biological activity showed that when the 4-furoxanylcarbonyl system, bearing an ester or an amide function at the 3-position was present, hybrids (25a, b) with predominant α1-antagonist activity were obtained. By contrast, in the derivative 25c, in which the nitrile function was linked to the 3-position of the furoxan ring, the NO-mediated vasodilating properties were predominant. The (furoxanylsulfonyl)piperidine derivatives 25d showed NO vasodilation and α_1-antagonist activities in an appropriate balance.[29]

Dong *et al*. (2010) synthesized nine furoxan derivatives of chalcones and evaluated their vasorelaxant activities. All of these compounds showed preferable vasorelaxant activities which were more potent than their parent compounds (Figure. 26). The most potent compound, was found to be promising structural template for the development of novel vasorelaxant agents.[30]

Sorba *et al*. (1997) reported the synthesis, characterization, NO donor properties, and in vitro vasodilating activity of a series of water soluble furoxans. All of the compounds released NO when treated with a large excess of cysteine under physiological conditions (pH 7.4; 37 °C). The vasodilating potency (EC_{50}) of all the derivatives was assessed on rat aortic strips precontracted with noradrenalin. Compound 27a, 27b and 27c (Figure. 27) showed maximum activity.[31]

Tambolia *et al*. (2012) described a new class of NO-donor hypoglycemic products obtained by joining tolbutamide, a typical hypoglycemic sulfonylurea, with a NO-donor moiety through a hard link. As NO-donors they chose either furoxan (1,2,5-oxadiazole 2-oxide) derivatives or the classical nitrooxy function. A preliminary biological characterization of these compounds, including stimulation of insulin release from cultured rat pancreatic β-cells and *in vitro* vasodilator and anti-aggregatory activities, was reported. Among all synthesised compound 28a and 28b (Figure. 28) showed very good activity.[32]

Ferioli *et al*. (1995) evaluated the vasodilator activity of a series of R-substituted and di-R-substituted phenylfuroxans. Phenyl-cyano isomers (Figure. 29) and the 3,4-dicyanofuroxan showed maximal potency and they were also able to inhibit collagen-induced platelet aggregation.[33]

Mu *et al*. (2000) synthesized a series of hybrid compounds incorporating the furoxan and nicorandil moieties (30a-d), (Figure. 30) and evaluated their cardiovascular and cerebrovascular activities. The results suggested that the furoxan-nicorandil derivatives are a useful lead in the design of NO-donor compounds for hypertension.[34]

Bohn *et al*. (1995) reported the cardiovascular effects of CAS 1609 (4-hydroxymethyl-furoxan-3-carboxamide) (Figure. 31) *in vitro* as well as *in vivo* in various animal models. In the anaesthetized pig, it significantly lowered blood pressure and in dogs it decreased mortality rate in acute heart failure. Studies revealed that CAS 1609 is a potent, long-lasting orally active donor of NO, devoid of tolerance development.[35]

A series of benzofurazanyl-l,4-dihydropyridines and benzofuroxanyl analogues (Figure. 32) was synthesized by Gasco *et al*. (1996) and was evaluated for calcium blocking activity. All the synthesized compounds displayed high potency. The potency of the two most active compounds 32a and 32b was comparable to Nifedipine.[36]

Visentin *et al*. (2004) synthesized a novel series of calcium channel agonists structurally related to Bay K8644, containing NO donor furoxans (Figure. 33). All the synthesized compounds were found to be potent calcium channel agonists. The cyanofuroxan displayed Ca^{2+}-dependent positive inotropic and NO-dependent vasodilating activity.[37]

3. Antioxidant Activity

Cena *et al*. (2006) synthesized novel hybrid compounds (Figure. 34) by incorporating different antioxidant phenolic moieties to the furoxan substructure in CHF2363 and evaluated their antioxidant and vasodilating properties. Their IC_{50} and EC_{50} values showed that in the series of products the vasodilating action prevailed over the antioxidant activity.[38]

Buonsanti *et al*. (2007) synthesized a series of furoxan NO-donor moieties by joining with fenoterol, a β_2-adrenoceptor agonist (Figure. 35) and evaluated their antioxidant activity. The synthesized furoxan derivatives displayed antioxidant activity higher than that of fenoterol.[39]

Cena *et al*. (2008) synthesized a new class of products in which NO-donor moieties are linked to either the 3-OH (36a-c) or 2-OH group (36d) of ascorbic acid (ASA) (Figure. 36). All the compounds were tested for their antioxidant activity on lipid peroxidation induced by Fe^{3+}-ADP/NADPH in lipids of microsomal membranes of rat hepatocytes. Only 3-*O* series displayed antioxidant activity and it seemed to be principally dependent on the lipophilicity. Both series triggered *in vitro* NO-dependent vasodilator properties.[40]

Iwasaki *et al*. (2011) synthesized compounds by the reaction between Chlorogenic acid (ChA) or caffeic acid (CaA) in coffee and $NaNO_2$ in artificial gastric juice. The identified phenolic compounds and nitrated phenolic compounds were assessed for their anti-oxidant, pro-oxidant, and nitration activities by performing an *in vitro* assay. The nitrated phenolic compounds seemed to show increased anti-oxidant activity and decreased prooxidant activity. However, one nitrated CaA compound (Figure. 37) that has a furoxan ring showed the ability to release NO_2 in the neutral condition.[41]

A novel series of polyvalent compounds were synthesized by linking edaravone with NO-donor moieties and were evaluated for their biological properties (Figure. 38). All compounds displayed high antioxidant activity alongwith NO-dependent vasodilator properties.[42]

4. Antiplatelet Activity

Turnbull *et al*. (2008) reported the synthesis of furoxan derivatives of aspirin and evaluated for NO-release patterns and antiplatelet effects

of novel furoxan derivatives of aspirin (39a and 39b) (Figure. 39) in comparison to existing antiplatelet agents. The furoxan derivatives of aspirin (39a and39b) significantly inhibited COX activity *in vitro* and caused aspirin-independent, cGMP-dependent inhibition of collagen-induced platelet aggregation in WP. 39a was more potent of the series.[43]

Calvino *et al*. (1992) reported the synthesis of a series of 4-methyl-3-(arylthio)furoxans by oxidation of 1-(arylthio)-2-methylglyoxymes with dinitrogen tetroxide. Reduction with trimethyl phosphite of the furoxan derivatives afforded the corresponding furazans. All the furoxan and furazan derivatives showed activity as inhibitors of platelet aggregation. 4-Methyl-3-(arylsulfonyl)furoxan (Figure. 40) were the most potent derivatives of the series.[44]

Lopez *et al*. (2005) synthesized a series of α-tocopherol analogs with NO-releasing capacity and tested their *in vitro* NO-releasing capacities, vasodilating properties, and antiplatelet activity. The synthesized compounds were also capable of preventing LDL (Low Density Lipoprotein) oxidation. The LDL-protective activity of derivative 41 (Figure. 41) suggested the potential use of these compounds for prevention of atherosclerosis disease.[45]

5. Anticancer activity

Cerecetto *et al*. (2006) reported the synthesis and characterization of thiol-containing 1,2,5-oxadiazole *N*-oxide derivatives (Figure. 42) and evaluated as anticancer drug. Result revealed that furoxan containing compound showed anticancer properties with lower gastrointestinal activity.[46]

Zhang *et al*. (2011) developed furoxan-based nitric oxide-releasing derivative of oleanolic acid ($ZCVI_4$-2) (Figure. 43). It exhibited strong cytotoxicity against human hepatocellular carcinoma (HCC) *in vitro* and significantly inhibited the growth of HCC tumors *in vivo*. However, its low aqueous solubility and toxicity due to the fast release of nitric oxide (NO) in blood challenged its formulation.[47]

Ling *et al*. (2011) synthesized novel furoxan-based nitric oxide (NO) releasing derivatives of farnesylthiosalicylic acid (FTS). Compound 44 (Figure. 44) displayed the strongest inhibition on the proliferation of human hepatocellular carcinoma (HCC) cells *in vitro*, superior to FTS, sorafenib, and furoxan moiety, selectively induced high frequency of HCC cell apoptosis, and produced high levels of NO in HCC cells but not in non-tumor liver cells.[48]

Lai *et al*. (2010) designed and synthesized a series of novel furoxan-based nitric oxide (NO)-releasing derivatives of glycyrrhetinic acid (GA) and evaluated their *in vitro* cytotoxicity against human hepatocellular carcinoma (HCC) and non-tumor liver cells. Five compunds, 45b-d, 45f, and 45g, displayed potent cytotoxicity against HCC cells but had a little effect on the growth of LO2 cells, indicating that these compounds had selective cytotoxicity against HCC cells.[49]

Ling *et al*. (2010) synthesized novel furoxan-based nitric oxide (NO)-releasing derivatives of farnesylthiosalicylic acid (FTA) (Figure. 46) and evaluated for their anti-tumor activities most of the compound showed superior antitumor activity than to FTA and sorafenib in most cancer cells tested.[50]

Chen *et al*. (2008) synthesized novel furoxan-based nitric oxide (NO) releasing derivatives of oleanolic acid (OA) and were evaluated for potential therapy of liver cancers. Six compounds produced high levels of NO in human hepatocellular carcinoma (HCC) cells and exhibited strong cytotoxicity selectively against HCC *in vitro*. Treatment with 47a or 47b significantly inhibited the growth of HCC tumors *in vivo*. These data provide a proof-in-principle that furoxan/OA hybrids may be used for therapeutic intervention of human liver cancers.[51]

Min *et al*. (2009) synthesised a new class of potent hybrid compounds by joining NO-donor furoxanyl moieties, through an appropriate spacer arm and evaluated their antitumor activity using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) assay based on four different cancer cell lines (BGC-1, HL60-1, SMMC-1, and A549-1). The results suggested that different length of spacer arm in the hybrid compounds did have an impact on the molecules' capability to inhibit cancer cell growth to various degrees. Among all the synthesized hybrids, compound 48 showed the strongest inhibitory activity against all the tested cell lines.[52]

Moharram *et al*. (2004) synthesized a group of substituted 3′-O- and 5′-O-(3-benzenesulfonylfuroxan-4-yl)-2′-deoxyuridines (Figure. 49). The synthesized compounds were evaluated as hybrid anticancer agents that have the ability to simultaneously release cytotoxic NO.[53]

A new series of nitric oxide-releasing tamibarotene derivatives were synthesized by coupling NO donors with tamibarotene through different spacers (Figure. 50), and were evaluated for their antiproliferative activities against human leukemic HL-60, NB4 and K562 cell lines *in vitro*. The three compounds (50a, 50b and 50c) were found to be more potent antileukemic agents than the control tamibarotene.[54]

A series of furoxan-based nitric oxide-releasing matrine derivatives (Figure. 51) were synthesized by He *et al*. (2010). Their biological evalution revealed that compounds 51a, 51b and 51c were more cytotoxic than 5-fluorouracil against human hepatoma cells (HepG2) *in vitro*.[55]

Kong *et al*. (2008) synthesized a series of new NO-donating six alkoxyl biphenyl derivatives by reacting furoxan with alkoxyl biphenyl skeleton using amino acids as the spacers, and evaluated their cytotoxicity against HepG2 cells *in vitro*. Compounds 52a-f (Figure. 52) were found to be more potent than 5-flurouracil.[56]

A series of novel NO releasing derivatives was synthesized by coupling furoxan and nitric oxide with irbesartan analogue (Figure. 53) and their cytotoxicity against BEL-7402 cells *in vitro* were evaluated by MTT method. The results suggested that these hybrids of AT1 antagonists and NO donor had beneficial effects on tumor progression.[57]

6. Antimalarial Activity

Galli *et al*. (2005) synthesized furoxan derivatives bearing a sulfone moiety at 3 or 4 position (Figure. 54) and evaluated their antimalarial action on the chloroquine-sensitive D10 and the chloroquine-resistant W2 strains of *Plasmodium falciparum*. Compounds having -SO_2R groups at the 3-position of the furoxan system were found to be most active. [58]

Bertinaria *et al*. (2011) synthesized a series of novel compounds by conjugating amodiaquine with moieties containing either furoxan or nitrooxy NO-donor substructures. The synthesized compounds were tested *in vitro* against the chloroquine sensitive, D10 and the chloroquine resistant, W-2 strains of *Plasmodium falciparum*. Most of the compounds showed good antiplasmodial activity. Compound 55 was found to be a potent and fast amodiaquine-derived NO donor, when compared with amodiaquine.[59]

7. Antihisatminic activity

Tosco *et al*. (2005) synthesized and pharmacologically evaluated a series of NO-donor furoxan ring. The whole series of products was found to display reversible histamine H_3-antagonistic activity on guinea-pig ileum. 4-(4-(3-(1H-Imidazol-4-yl)propoxy)phenyl) furoxan-3-carbonitrile (Figure. 56) was also able to induce partial

relaxation of the guinea-pig ileum during the study of its H_3-antagonistic properties.[60]

Bertinaria *et al*. (2003) reported the synthesized a series of compounds by coupling the H_3-antagonist SKF 91486 through appropriate spacers with the NO-donor 3-phenylfuroxan-4-yloxy and 3-benzenesulfonylfuroxan-4-yloxy moieties and furazan derivatives. All the products were tested for their H_3-antagonistic and H_2-agonistic properties on electrically-stimulated guinea-pig ileum segments and guinea-pig papillary muscle, respectively. The whole series of compounds displayed good H_3-antagonist behaviour and feeble partial H_2-agonist activity. Among furoxan derivatives, the benzenesulfonyl hybrid (Figure. 57), a good NO-donor, triggered a dual NO-dependent muscle relaxation and H_3-antagonistic effect on guinea-pig intestine.[61]

8. Anti HIV activity

Takayama *et al*. (1996) synthesized furoxan derivatives and evaluated their HIV activity. Results revealed that 4-aryl-l,2,5-oxadiazole-3-yl N,N-dialkylcarbamate (Figure. 58) exhibited potent anti-HIV-I activity.[62]

Persichini *et al*. (1999) reported the modulation of the HIV-1 reverse transcriptase activity by NO, released by the NO-donors 3, 3-bis(aminoethyl)-1-hydroxy-2-oxo-1-triazene (NOC-18), (+/-)-(E)-4-ethyl-2-[(E)-hydroxyimino]-5-nitro-3-hexenamide (NOR-3), 3-morpholinosydnonimine (SIN-1), 4-(phenylsulfonyl)-3-((2-(dimethylamino) ethyl)thio)furoxan oxalate (SNO-102), and sodium nitroprusside (SNP). NO inhibited dose-dependently the HIV-1 reverse transcriptase activity, likely due to oxidation of Cys residue(s). Results provided a new insight into the modulation mechanism of the HIV-1 reverse transcriptase activity.[63]

10. Other activities

Nirode *et al*. (2006) synthesized a series of symmetrically substituted dibenzoyl furoxans (Figure. 59) and investigated their potential to release nitric oxide, which plays a key role in the nervous and cardiovascular systems.[64]

Schiefer *et al*. (2012) synthesized a new series of furoxan derivatives and evaluated their neuroprotective activity. Compound 60 showed maximum activity (Figure. 60).[65]

Novel furoxan-based NO-releasing DDB derivatives were synthesized and were evaluated as potential Pgp (P-glycoprotein)-mediated MDR (Multidrug resistance) reversal agents in MCF-7/Adr cells by Tang *et al*. (2012). Results revealed that compounds 61a and 61b (Figure. 61) significantly reversed the resistance of MCF-7/Adr cells to doxorubicin and markedly increased the intracellular accumulation of doxorubicin probably via inhibiting Pgp-mediated intracellular drug efflux alongwith down-regulating doxorubicin-induced Pgp expression.[66]

A series of furoxan-based nitric oxide-releasing chrysin derivatives (Figure. 62) were synthesized by Zou *et al*. (2011). Pharmacological assays indicated that all synthesized derivatives exhibited *in vitro* inhibitory activities against aldose reductase and advanced glycation end-product formation. Some derivatives were also found to increase the glucose consumption of HepG2 cells. These hybrid derivatives offered a mutual prodrug design concept for the development of therapeutic or preventive agents for vascular complications due to diabetes.[67]

Rai *et al*. (2009) synthesized several 1,2,5-oxadiazole-2-oxide (Furoxan) analogues (Figure. 63) in an effort to probe the SAR around the phenyl substituent and oxadiazole core toward thioredoxin-glutathione reductase (TGR) inhibition and antischistosomal activity.[68]

Jorge *et al*. (2011) designed a set of benzofuroxan derivatives as antimicrobial agents exploring the physicochemical properties of the related substituents. Topliss' decision tree approach was applied to select the substituent groups. The minimal inhibitory concentration method was employed to evaluate the activity against multidrug-resistant *Staphylococcus aureus* strains. The most active compound was 4-nitro-3-(trifluoromethyl)[*N*-(benzofuroxan-5-yl)methylene] benzhydrazide (Figure. 64) with MIC range 12.7–11.4 µg/mL, pointing out that the antimicrobial activity was indeed influenced by the hydrophobic and electron-withdrawing property of the substituent groups 3-CF_3 and 4-NO_2, respectively.[69]

A novel series of heteroaryl nitrones, 1-7, bearing furoxanyl and thiadiazolyl moieties were synthesized and evaluated for their free radical-trapping properties. The 4-furoxanyl nitrone (FxBN), a(Z)-(3-methylfuroxan-4-yl)-N-tert-butylnitrone (Figure. 65), was found to act as spin trap in a specific biological system, that is, in the free radical production of experimental anti-trypanosomatid drugs using *Trypanosoma cruzi* microsomes as biological system.[70]

Boiani *et al*. (2008) reported the study of a series of over hundred furoxans, alkylnitrates and related compounds as growth inhibitors of the two major kinetoplastids of Latin America, *Trypanosoma cruzi and Leishmania* sp., *in vitro* assays. The most active compounds showed 50% inhibitory doses of the same order of that of Nifurtimox and Miltefosine, reference drugs used to treat Chagas Disease and Leishmaniasis respectively. Among the studied compounds derivative 66 (Figure. 66), presenting excellent inhibitory activity against the tryposmastigote and amastigote forms of T. cruzi, emerged as a lead compound.[71]

Boschi *et al*. (2003) synthesized new NO-donor R1-antagonists by joining a recent uroselective α_1-adrenoceptor antagonist, REC15/2739 with nitrooxy and furoxan NO-donor moieties. All the compounds studied proved to be potent and selective ligands of human cloned α_{1A} -receptor subtype. Derivatives 67a and 67b (Figure. 67) were able to relax the prostatic portion of rat vas deferens contracted by (-)-noradrenaline because of both their α_{1A}-antagonist and their NO-donor properties.[72]

Fruttero *et al*. (2010) synthesized a series of furoxan derivatives and studied their ability to interact with P-gp and MRP1 transporters in MDCK cells overexpressing these proteins. 3-Phenylsulfonyl substituted furoxans emerged as the most interesting compounds. All of them were capable of inhibiting P-gp, and a few also were capable of inhibiting MRP1. When compounds 68a and 68b (Figure. 68) were coadministered with doxorubicin, they restored a high degree of the activity of the antibiotic.[73]

Santos *et al*. (2012) designed and synthesized phthalimide derivatives containing furoxanyl subunits as nitric oxide (NO)-donors and evaluated them *in vitro* and *in vivo* for their potential uses in the oral treatment of sickle cell disease symptoms. Compound 69 (Figure. 69) emerged as a new leading drug candidate with multiple beneficial effects for the treatment of sickle cell disease symptoms and provides an alternative to hydroxyurea treatment.[74]

Serafim *et al*. (2014) designed and synthesized fifteen hybrid bioisostere compounds containing *N*-acylhydrazone and furoxan groups (Figure. 70) and evaluated their potential of NO releasing, trypanocidal activity. The most active compounds (70**a**, 70**b**) were submitted to permeability, cytotoxicity and cruzain inhibition tests. SAR indicated the mode of interaction of the overall structures with the target is interfering more than the R_2 substituent. Due to the nature of the general scaffold, a dual mechanism of action, NO releasing and cruzain inhibition, was expected. Compounds 70**a** and 70**b** presented

lower trypanocidal activities compared with the reference drug benznidazole (Bzd). The potential of NO releasing seemed to have no direct correlation with the activity, but a synergic effect could be present. Cruzain assay showed both compounds can be inhibitors, derivative 70a being the most active. Those compounds were found to be less cytotoxic in human cells than (Bzd).[75]

Guglielmo *et al*. (2014) synthesized a new class of NO-donor PZQ (praziquantel) hybrids by joining NO-donor furoxan moieties to different areas of the PZQ structure (Figure. 71) by. The inhibitory activity of these products, and that of the related *des*-NO furazan derivatives, was evaluated against recombinant *S. mansoni* TGR (Thioredoxin Glutathione Reductase); their antiparasitic action against *ex vivo* adult *S. mansoni* worms was likewise evaluated. Some products emerged as potent antischistosomal agents, endowed with both PZQ-like and NO-dependent antiparasitic activity.[76]

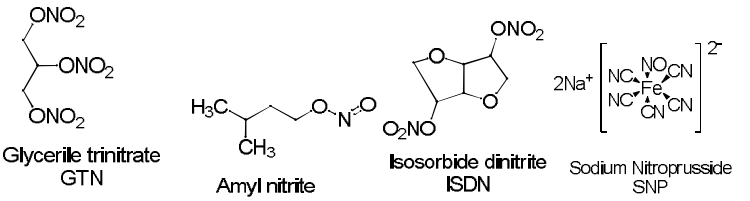


Figure 1: Organic nitrates and nitrites

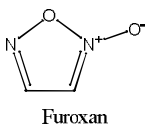


Figure 2: Furoxan

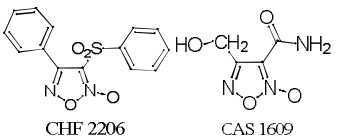


Figure 3: CHF2206 and CAS1609

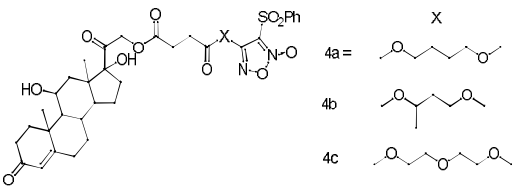


Figure 4: Compounds 4a,4b,4c

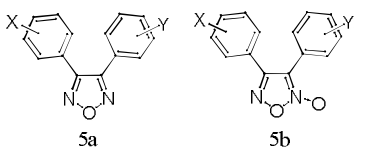


Figure 5: Compounds 5a and 5b

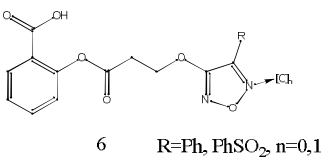


Figure 6: Compound 6

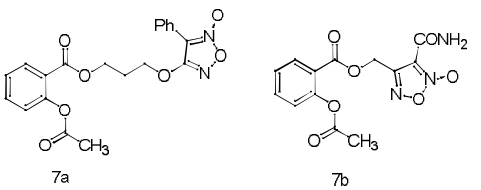


Figure 7: Compounds 7a and 7b

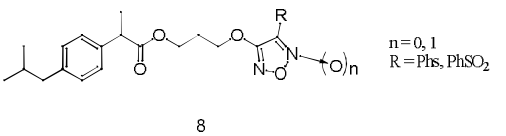


Figure 8: Compound 8

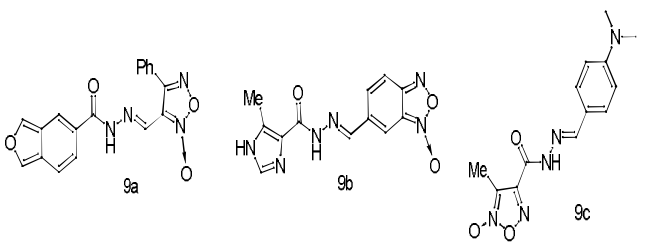


Figure 9: Compounds 9a, 9b and 9c

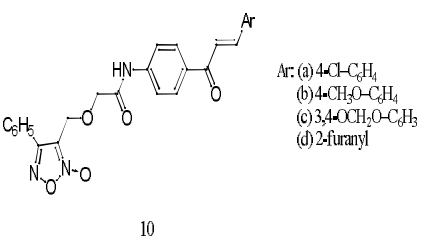
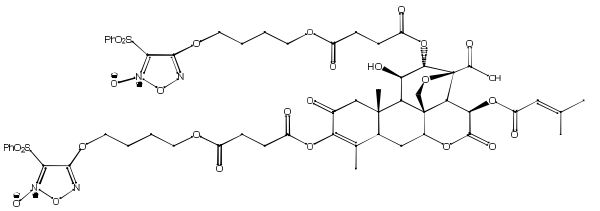
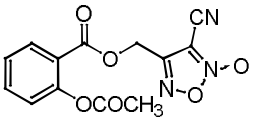


Figure 10: Compound 10



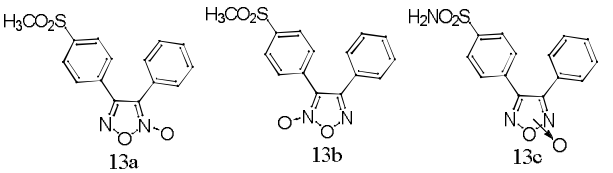
11

Figure 11: Compound 11



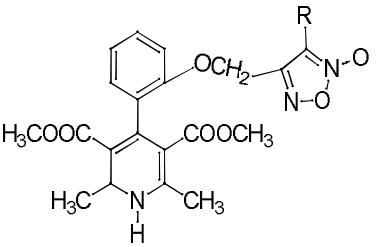
12

Figure 12: Compound 12



13a 13b 13c

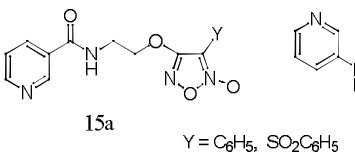
Figure 13: Compounds 13a, 13b and 13c



14

R = 2: CH_3, 3: $CONH_2$; 4: CN

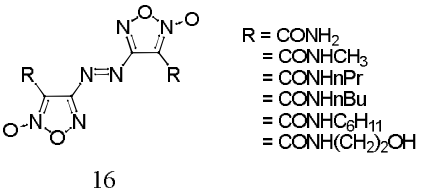
Figure 14: Compound 14



15a 15b

Y = C_6H_5, $SO_2C_6H_5$

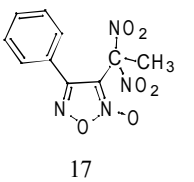
Figure 15: Compounds 15a and 15b



16

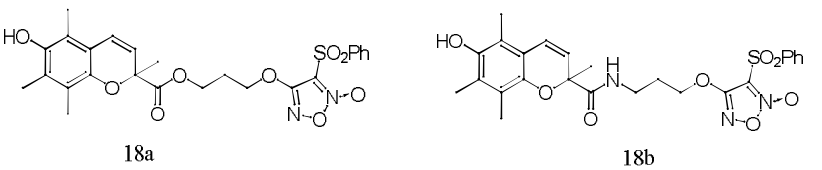
R = $CONH_2$
= $CONHCH_3$
= CONHnPr
= CONHnBu
= $CONHC_6H_{11}$
= $CONH(CH_2)_2OH$

Figure 16: Compound 16



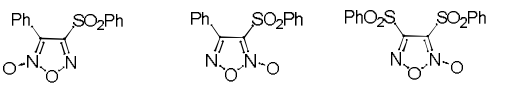
17

Figure 17: Compound 17



18a 18b

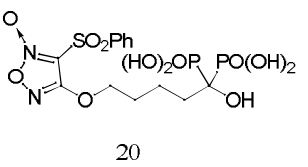
Figure 18: Compounds 18a and 18b



19a 19b 19c

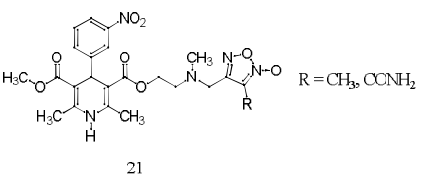
n	R
0	C_6H_5
1	C_6H_5
2	C_6H_5
2	p-CH_3-C_6H_4
2	p-CH_3O-C_6H_4
2	p-FC_6H_5
2	p-ClC_6H_5

Figure 19: Compounds 19a, 9b and 19c



20

Figure 20: Compound 20



21

Figure 21: Compound 21

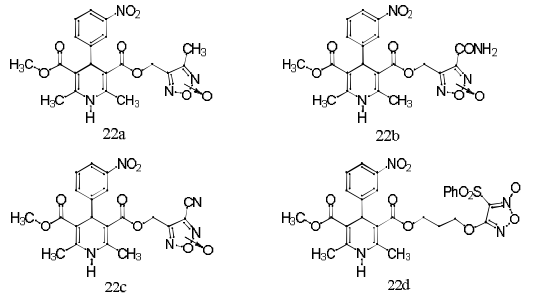


Figure 22: Compounds 22a-d

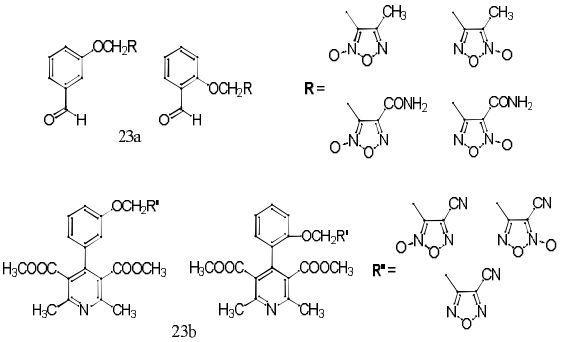


Figure 23: Compounds 23a and 23b

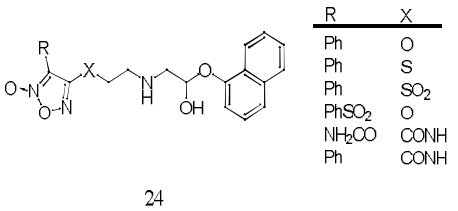


Figure 24: Compound 24

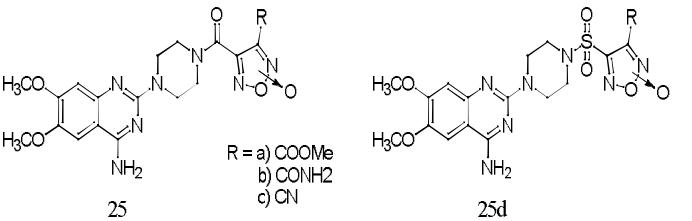


Figure 25: Compounds 25a-d

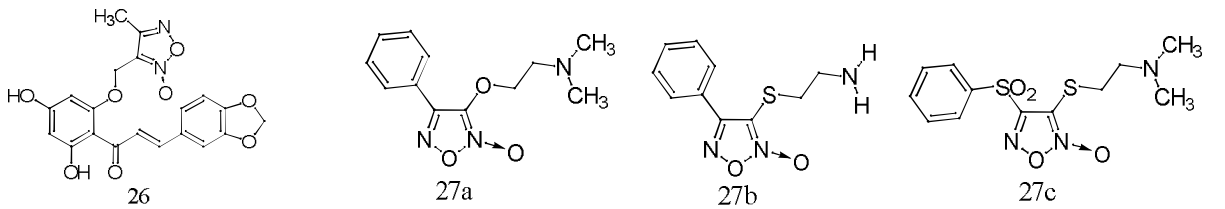


Figure 26: Compound 26

Figure 27: Compounds 27a-c

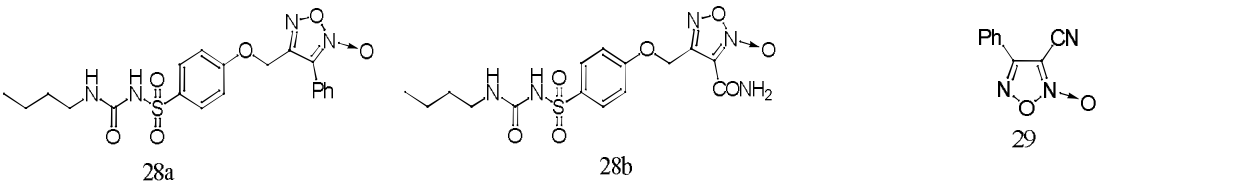


Figure 28: Compounds 28a and 28b

Figure 29: Compound 29

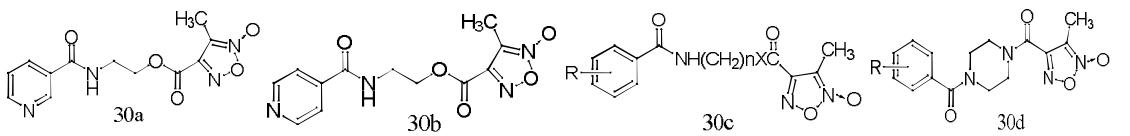


Figure 30: Compound 30a-d

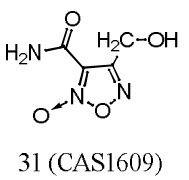


Figure 31: CAS 1609

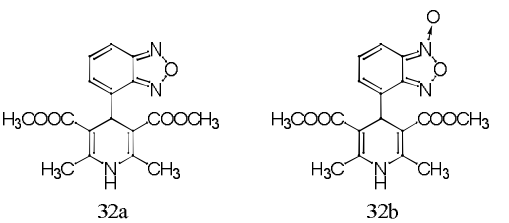


Figure 32: Compounds 32a and 32b

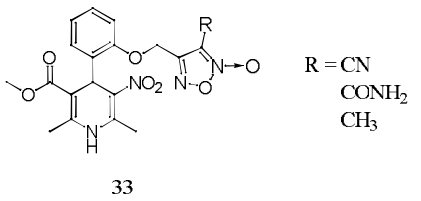


Figure 33: Compound 33

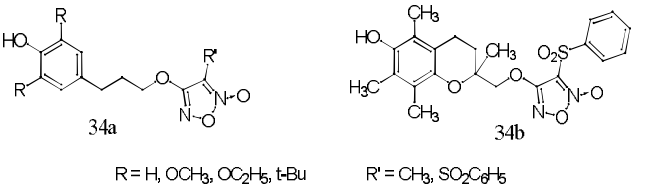


Figure 34: Compound 34 a and 34b

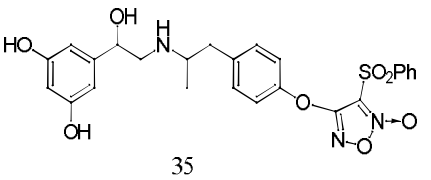


Figure 35: Compound 35

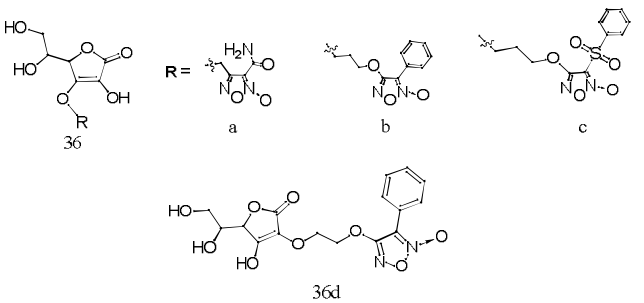


Figure 36: Compound 36a-d

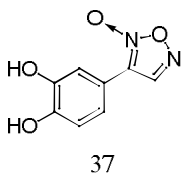


Figure 37: Compound 37

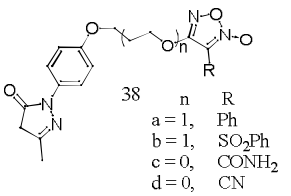


Figure 38: Compound 38a-d

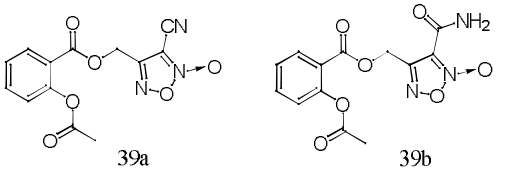


Figure 39: Compound 39a and 39b

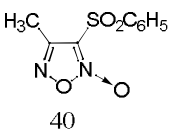


Figure 40: Compound 40

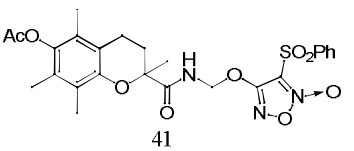


Figure 41: Compound 41

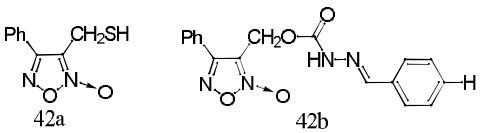


Figure 42: Compound 42a and 42b

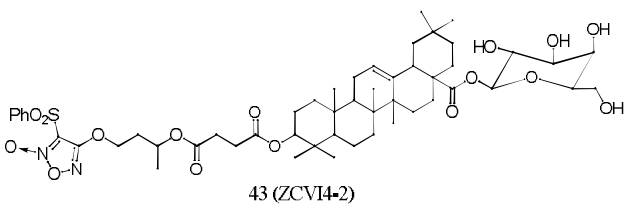


Figure 43: Compound 43

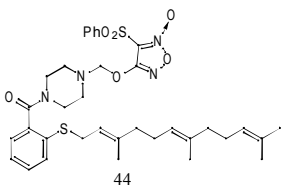


Figure 44: Compound 44

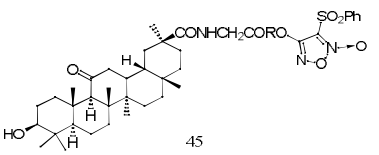


Figure 45: Compounds 45a-g

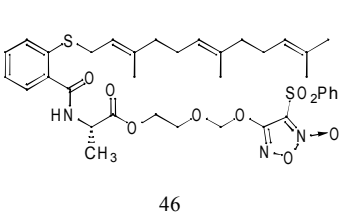


Figure 46: Compound 46

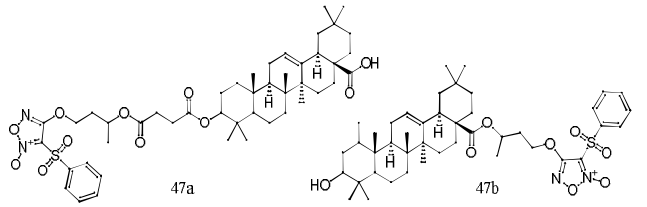


Figure 47: Compounds 47a and 47b

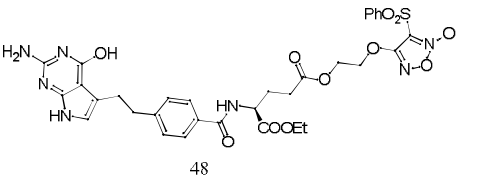


Figure 48: Compound 48

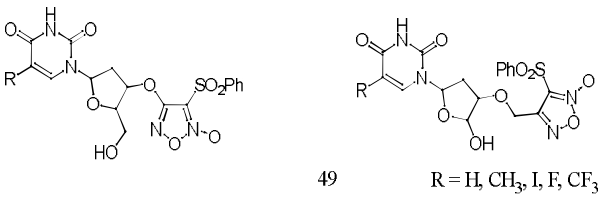
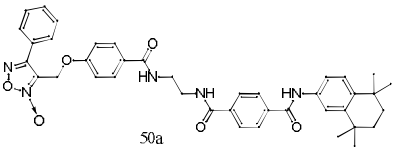


Figure 49: Compound 49



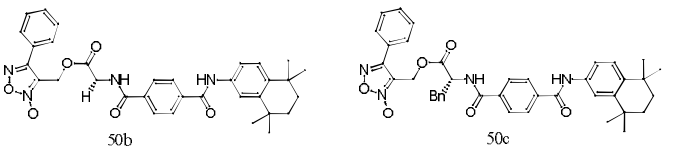


Figure 50: Compounds 50a-c

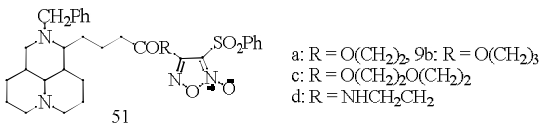


Figure 51: Compounds 51a-c

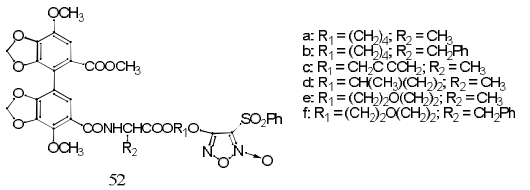


Figure 52: Compounds 52a-f

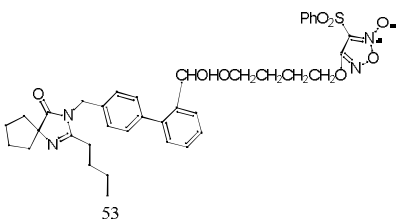


Figure 53: Compound 53

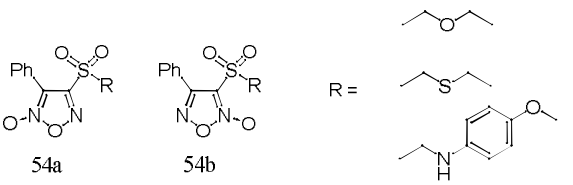


Figure 54: Compound 54a and 54b

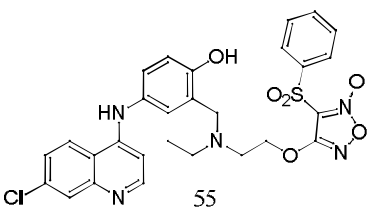


Figure 55: Compound 55

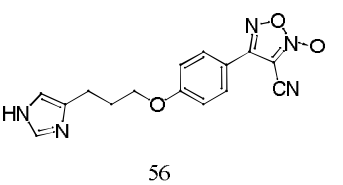


Figure 56: Compound 56

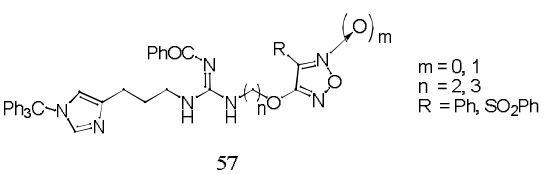


Figure 57: Compound 57

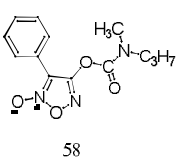


Figure 58: Compound 58

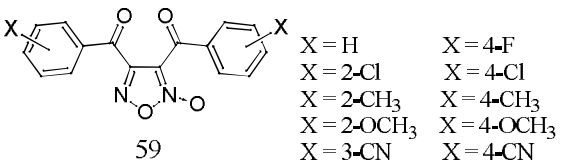


Figure 59: Compound 59

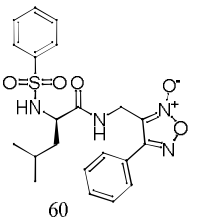


Figure 60: Compound 60

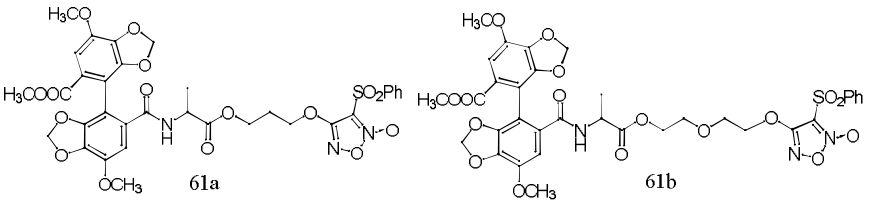


Figure 61: Compound 61a and 61b

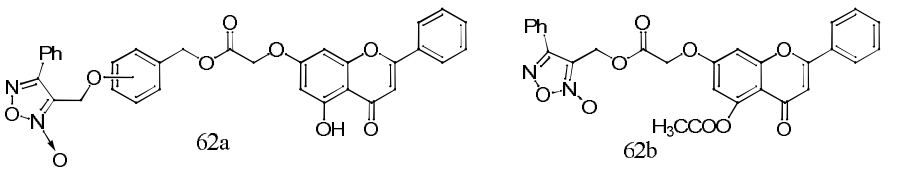
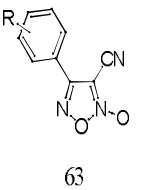


Figure 62: Compounds 62a and 62b



R = 4-F, 4-Cl, 4-Br, 3-OMe, 3-OH, 2-OMe, 4-CF_3, 4-F, 3-Br, 4-NO_2, 4-Cl, 3-NO_2, 4-OMe, 3-CF_3, 5-CF_3, 4-OH, 3,4,5-OMe, 4-Me, 3,4-OCH_2O, 4-Phe, napthyl, furan, thiophene, 3-Cl, 2-NO_2-furan, 1,4-thiophene-bis-furoxan, 3-F,5-furoxan

Figure 63: Compound 63

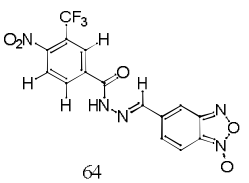


Figure 64: Compound 64

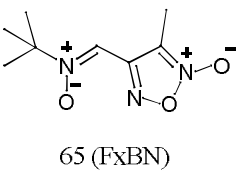


Figure 65: Compound 65

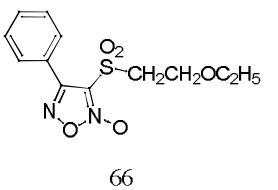


Figure 66: Compound 66

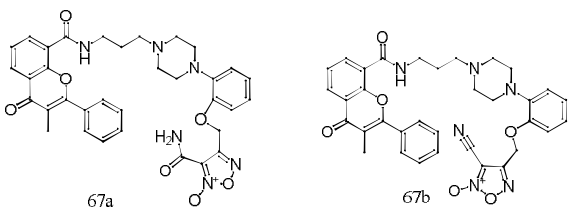


Figure 67: Compounds 67a and 67b

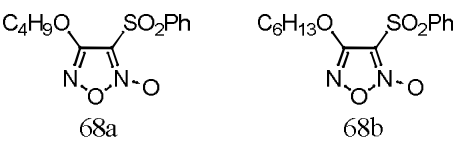
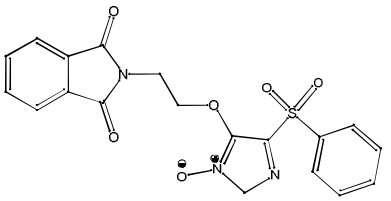
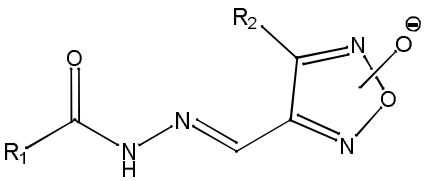


Figure 68: Compounds 68a and 68b



69

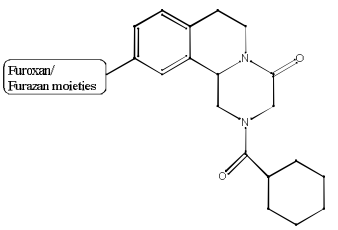
Figure 69: Compound 69



70

a, R_1=-C_6H_5 NO_2 R_2=-CH_3
b, R_1=-C_6H_5 NO_2 R_2=-C_6H_5

Figure 70: Compounds 70a and 70b



71

Figure 71: Compound 71

CONCLUSION

This review unveiled various biological applications of furoxan derivatives, in particular, anticancer, anti-inflammatory, vasodilatory, anti-HIV, antioxidant, antimalarial, antiplatelet, antimicrobial activities with low toxicity and good bioavailability. All these have strongly suggested the infinite potential of furoxan derivatives in medicinal field. There is much scope in this promising moiety owing to its different molecular targets. Future investigations of this scaffold could give some more encouraging results in the field of medicine. Advances in this field will require analyses of the structure-activity relationships of furoxan derivatives, as well as the mechanisms of action of these compounds. It is anticipated that this information would give rise to design of better molecules with enhanced biological properties and higher specificity.

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