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FUROXAN DERIVATIVES AS POTENTIAL NITRIC OXIDE DONOR

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ABSTRACT

A vast majority of heterocyclic derivatives containing oxygen and nitrogen have been used as versatile scaffolds in drug development. Furoxan is a five-membered nitrogen and oxygen containing ring with two active oxygen atoms. Furoxan (1,2,5-oxadiazole 2-oxide) are very important scaffold in medicinal chemistry as NO donors, which releases high levels of NO *in vitro*. Compounds containing furoxan ring show a variety of biological activities. Due to its potent and significant biological activities it has great pharmaceutical importance; hence, synthesis of this compound is of considerable interest. This review work focuses on the research work reported in the scientific literature on Furoxan compounds.

KEYWORDS

Furoxan, NO donors and Biological activities etc.

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INTRODUCTON

Furoxan derivatives are of current interest because of their diverse pharmacological activities such as anti-cancer, anti-leishmanial, anti-trypanosoma cruzi, anti-aggregant, anti-platelet, anti-thrombotic, anti-inflammatory, anti-malarial, anti-glaucoma, anti-schistosomal activities. Nitric oxide releasing ability of Furoxan was discovered by Gasco *et al*, and other research groups. It has been proposed that furoxan is one of the NO-reservoirs within organisms[1]. Single furoxan compounds are precursors for synthesis of various poly-furoxan and macrocycle-furoxan derivatives which plays a role in the development of Furoxan- based energetic

meterials[2]. Strategies for the synthesis of Furoxan compounds include dimerization of nitrile N-oxides, dehydration of α-nitro oximes, thermolysis of α -nitro-azides, oxidation of α –dioximes, reaction of alkenes with N_2O_3, $NaNO_2$, $NOBF_4$ etc[3].

FUROXAN DERIVATIVES

Nadezhda E *et al*,[4] Reported the antiaggregant activity of 3-cyano-4-phenylfuroxan (Structure- 1) and 3-nitro-4-phenylfuroxan (Structure- 2) which was studied *in vitro* using platelet rich plasma (PRP). Four platelet agglutination inducers, namely collagen, ristocetin, adenosine diphosphate and adrenaline were applied for experiment.

Gamal E *et al*,[5] Synthesized N-[4-(arylacryloyl)phenyl]-2-(2-oxy-4-phenylfurazan-3-ylmethoxy) acetamides by binding various amino chalcones with NO donating moiety. Some of the synthesized compounds showed significant anti-inflammatory activity using carrageenan-induced rat paw edema method when compared with Indomethacin. It was revealed that the incorporation of the NO-donating group into the parent chalcone derivatives caused a moderate increase in the anti-inflammatory activity. (Scheme.1)

Luiz A *et al*,[6] Described new resveratrol derivatives with nitric oxide (NO) release properties. The combination of resveratrol derivatives effects with NO activity enhance both platelet aggregation inhibition and antithrombotic effects. (Scheme.2; a- Hydroxybenzaldehyde, DBU, CH_2Cl_2) and (Scheme.3; b- Aminobenzohydrazide derivative, ethanol, acetic acid).

Ricardo A *et al*,[7] Designed compounds which are hybrids of N-acylhydrazone, potential inhibitor of cruzain and furoxan, a NO donor for anti-Trypanosoma cruzi activity. These hybrid bioisoster compounds containing N-acylhydrazones and furoxan groups having different substituted and non-substituted aromatic rings, and methyl or phenyl substituent on furoxan ring. (Structure- 3)

Ganesha R *et al*,[8] Synthesized 4-phenyl -3-cyano furoxan derivatives as antischistosomal agents. The classical synthesis of the compound involves treatment of the requisite cinnamyl alcohol with sodium nitrate and acetic acid at room temperature to form the 4-phenyl -3- furoxan methanol derivatives. Formation of oxime was carried out using hydroxylamine hydrochloride in the presence of sodium acetate in ethanol. Dehydration was carried out using $SOCl_2$ in DMF to form the 4-phenyl-3-cyano derivatives. (Scheme.4)

Lei F *et al*,[9] Reported a series of furoxan based nitric oxide releasing glucocorticoid derivatives. In this study a group of NO releasing derivatives of hydrocortisone was described. Benzenesulfonyl-substituted furoxans, which can donate two molecules of NO *in vivo* under the action of thiol cofactors was incorporated to the 21 position of hydrocortisone through various spacers. By releasing NO *in vivo* anti-inflammatory activity of these derivatives was enhanced. (Structure- 4)

Zhi-hong Z *et al*,[10] Synthesized furoxan-based nitric oxide-releasing derivatives of tetrahydroisoquinoline (Structure- 5) for their cytotoxic activities and effects in reversing multidrug resistance. The synthesized compounds shown moderate cytotoxic effects as well as multidrug resistance reversal effects.

Leonid L *et al*,[11] Have synthesized close analogues, triazolylfuroxans, by the cycloaddition of azidofuroxans to terminal and internal acetylenes. Classical synthesis of 4-azido-3-phenylfuroxan involves nucleophilic substitution of the nitro group in 4-nitro-3-phenylfuroxan under the action of NaN_3 in DMSO at room temperature. (Scheme.5)

Leonid L *et al*,[12] Reported the synthesis of 4-amino-3-(1H-tetrazol-5-yl) furoxan from 4-amino-3-cyanofuroxan on treatment with NaN_3 in water in the presence of $ZnBr_2$, as well as the synthesis of 3,4-bis(1H-tetrazol-5-yl) furoxan by the reaction of 3,4-dicyanofuroxan with NaN_3 in DMF at 80^0C in the presence of NH_4Cl. (Scheme.6)

Alexander A *et al*,[13] Developed a method for the preparation of (chlorohydroxamoyl) furoxans from cyanofuroxans using a two-step, via their reaction with hydroxylamine and transformation of the resulting (aminohydroxamoyl) furoxans into chlorides by the action of $NaNO_2$ in the presence of HCl. (Scheme.7)

Tamara I *et al*,[14] Performed synthesis of unsubstituted furoxan and investigated some of the

physical and chemical properties of this compound. (Scheme.8)

Yaoqing H *et al*,[15]Synthesized novel furoxan-based nitric oxide (NO) releasing hybrids of 16,17-pyrazoannulated steroidal derivatives (Structure- 6) and evaluated them against the MDA-MB-231, HCC1806, SKOV-3, DU145, and HUVEC cell lines for their *in vitro* anti-proliferative activity.

Hiromitsu T *et al*,[16] Have reinvestigated the features of the classical Wieland reaction and applied this to the synthesis of 4-aryl-1,2,5-oxadiazole-3-yl N,N-dialkylcarbamate derivatives (Structure- 7) which shown potent anti-HIV activity.

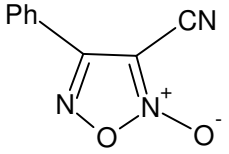
Massimo C *et al*,[17] Reported synthesis of 1,2,5-oxadiazole-*N*-oxides from α-nitro-ketoximes using acidic alumina as catalyst. (Scheme.9)

Leonid L *et al*,[18] Synthesized 3-aryl-4-hydroxyfuroxans by nucleophilic substitution of the nitro group in 3-aryl-4-nitrofuroxans using NaOH in H_2O-THF. The methylation reaction of hydroxyfuroxanswas studied using three different methylating reagents: CH_2N_2, MeI, and $(MeO)_2SO_2$ which showed that 3-aryl-4-hydroxyfuroxans are prone to side-chain prototropic tautomerism. (Scheme.10)

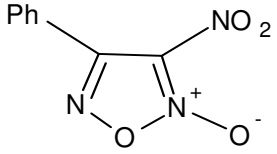
Gasco A *et al*,[19] Reported the synthesis of a series of 1, 1 -dinitroethyl substituted furoxans (Structure- 8) for vasodilatory and platelet aggregation inhibitor properties. Their vasodilatory properties was evaluated on isolated rings of rabbit thoracic aorta precontracted with noradrenaline, and their ability to inhibit the collagen induced aggregation in human platelet-rich plasma, was reported.

Paulo S *et al*,[20] Synthesized 1-Oxy-benzo[1,2,5]oxadiazol-5-ylmethyl [2-(2,6-dichloro-phenylamino)-phenyl]-acetate by the reaction of sodium diclofenac and 5-bromomethyl-benzo[1,2,5]oxadiazole 1-oxide. (Structure- 9) This modified diclofenac derivative shown anti-inflammatory activity similar to its parent compound.

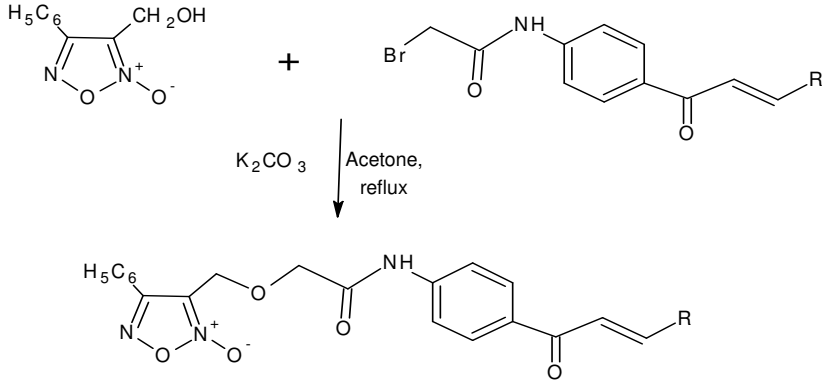
Mai A *et al*,[21] Synthesized a group of nitric oxide (NO) donating chalcone derivatives by binding amino chalcones with furoxans. (Scheme.11) The synthesized compounds were screened for anticancer activity. Selected NO-donating compounds exhibited mild to strong cytotoxic activity.



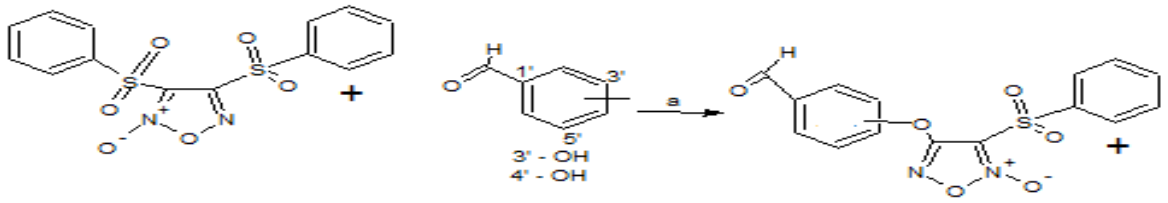
Structure- 1



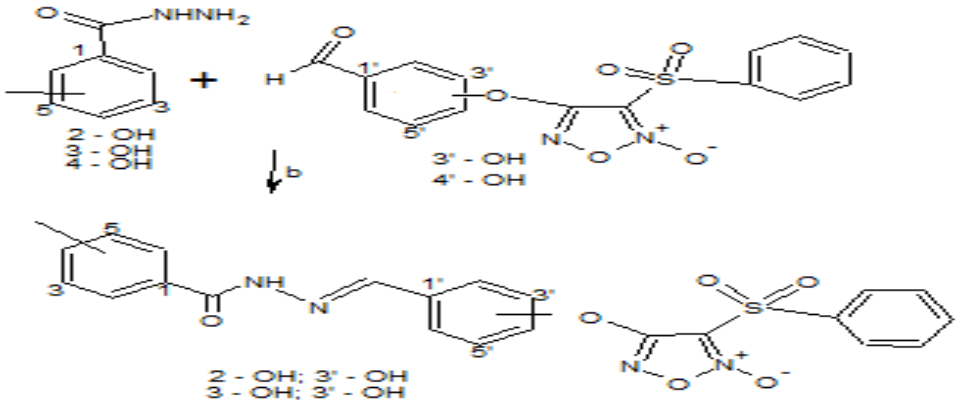
Structure- 2



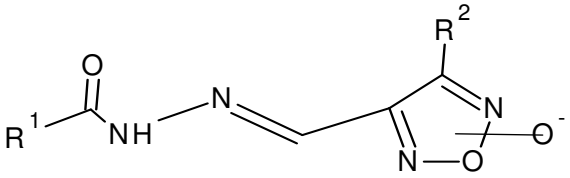
Scheme.1



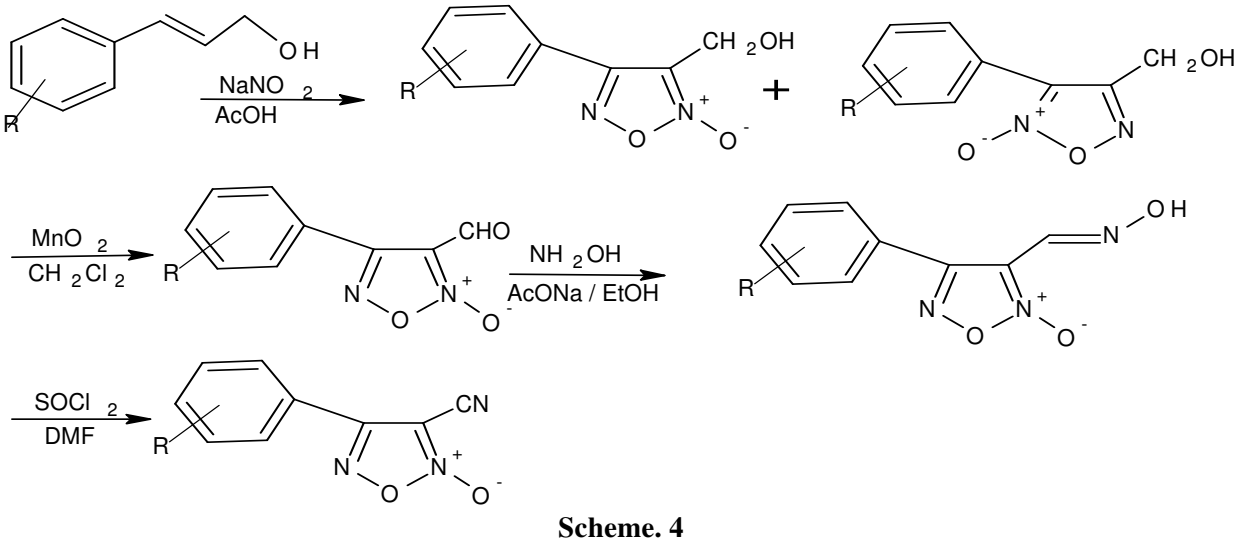
Scheme. 2



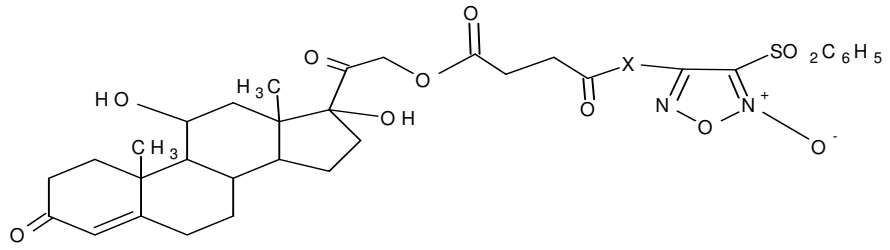
Scheme. 3



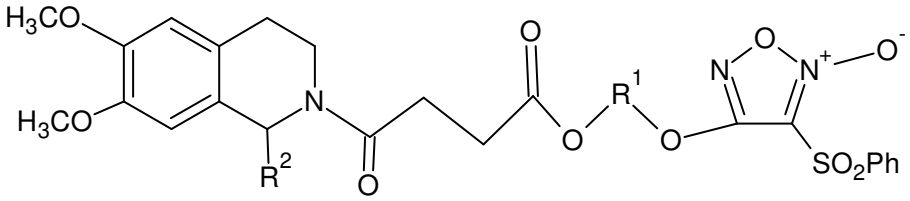
Structure- 3



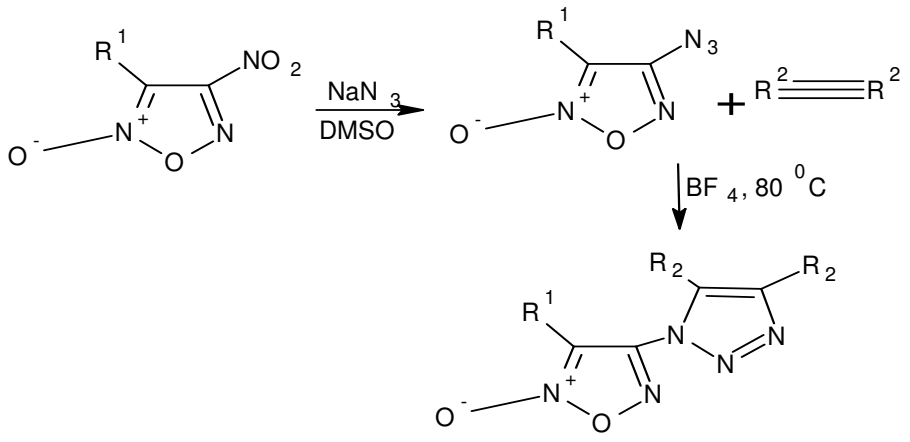
Scheme. 4



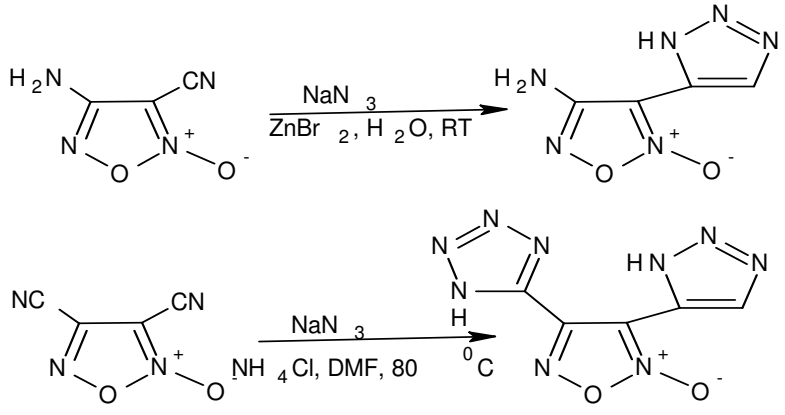
Structure- 4



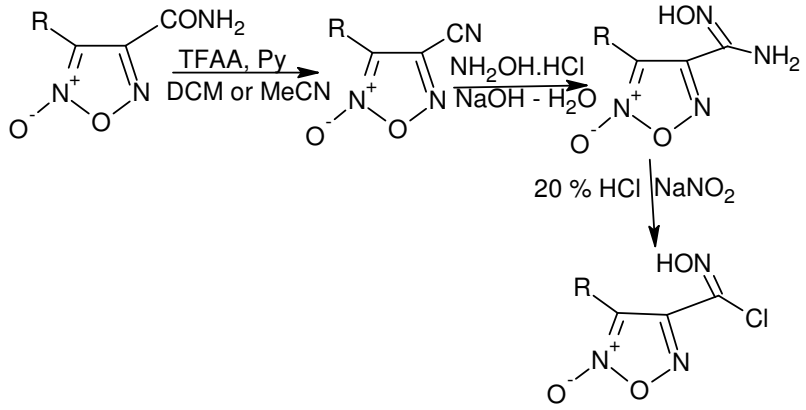
Structure- 5



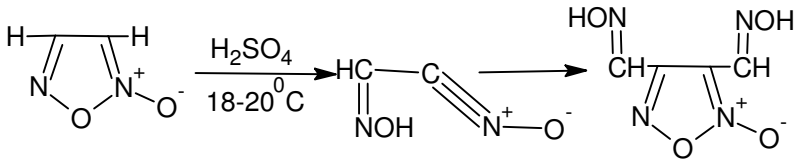
Scheme. 5



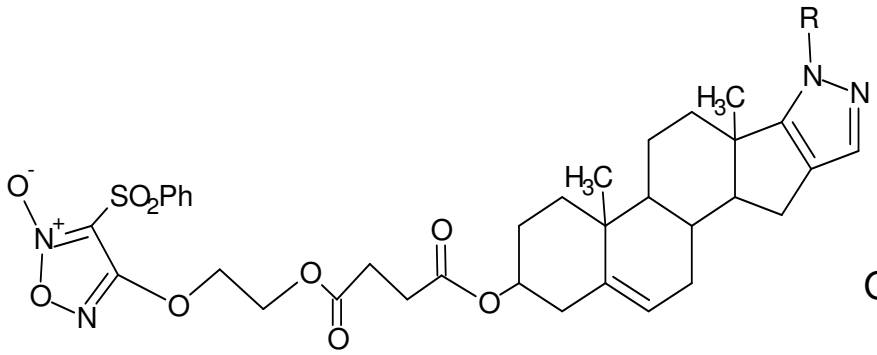
Scheme. 6



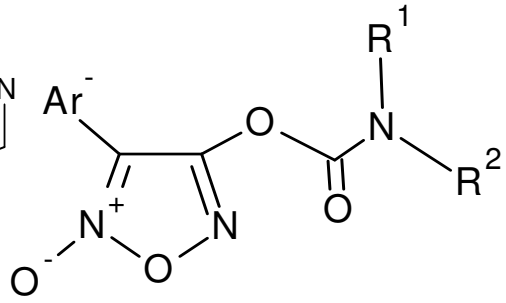
Scheme. 7



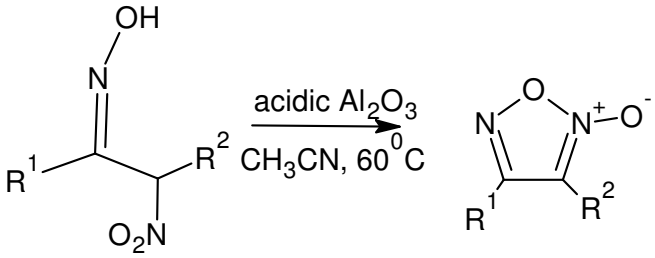
Scheme. 8



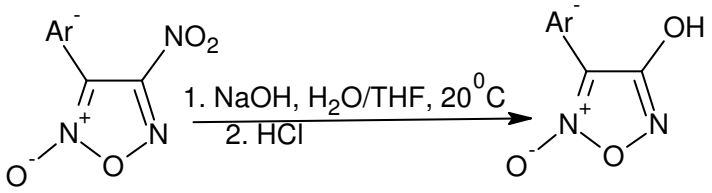
Structure- 6



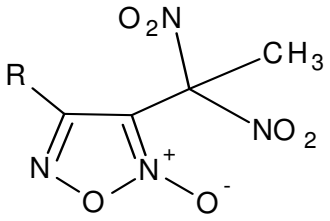
Structure- 7



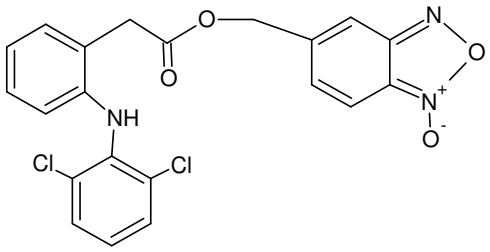
Scheme. 9



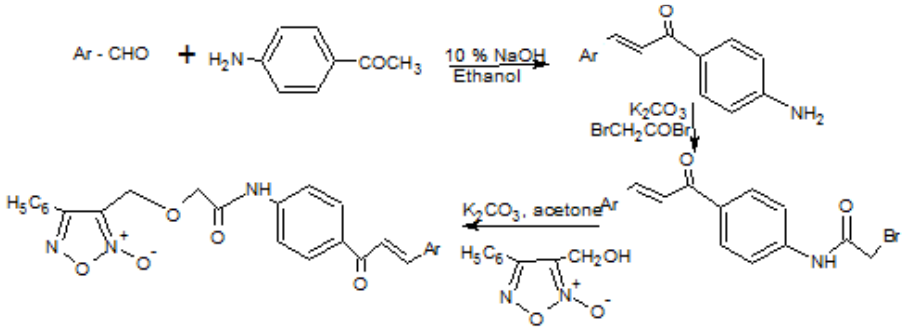
Scheme. 10



Structure- 8



Structure- 9



Scheme. 11

CONCLUSION

Extensive literature survey was carried out on furoxan derivatives. It is reported that the furoxan (1,2,5-oxadiazole 2-oxide) is nitric oxide donor which releases high level of nitric oxide *in vitro* and result into enhancement of activity.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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