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Comprehensive Review On The Chemistry Of 1,3,4-Oxadiazoles And Their Applications

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Abstract: 1,3,4-Oxadiadoles have created interest in synthetic organic and medicinal chemistry as surrogates of carboxylic acid. They are an important class of heterocyclic compounds that have a wide range of pharmaceutical and biological applications. Attracted by the their broad spectrum of biological activity and as useful synthons in organic synthesis, researchers across the globe are working on this moiety and consequently have been instrumental in the advancement of 1,3,4-oxadiazole chemistry. This review article provides up to date information about developments, exploration of new methods, techniques adopted for the synthesis of 1,2,4-oxadiazoles and their varied biological activities. Now 1,2,4-oxadizoles are not limited to their synthesis and their biological applications, and is extended to study their physical properties. They are known to exhibit anticorrosion, liquid crystal, optical brightening and fluorescent properties was described.

Key words: Hydrazide, phosphoryl, oxadiazoles, antitumour, antioxidant, antiinflammatory.

INTRODUCTION

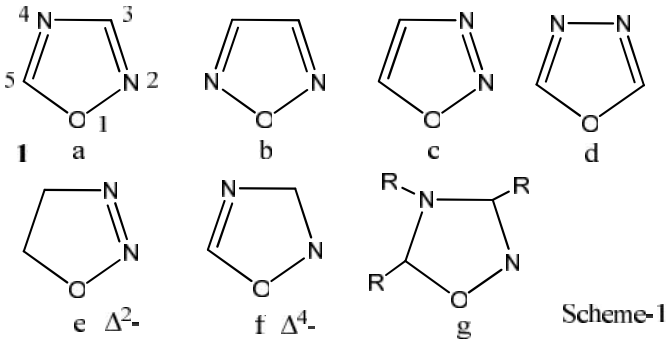
Oxadiazoles and their derivatives can be considered as simple five membered heterocycles possessing one oxygen and two nitrogen atoms. The oxadiazoles exist in different isomeric forms such as 1,2,4-, 1,2,5-, 1,2,3- and 1,3,4-oxadiazoles (**1a-d**). Oxadiazoles are numbered by designating heteroatoms as shown in scheme-1. Here the ring system of the type (**1a**) are termed as azoximes and (**1b**) are commonly called furoxans.[1] The position of the double bonds in partially reduced rings is designated as Δ^2- or Δ^4- with the terminal ending –oline (**1e-f**), the fully saturated ring is described by the terminal ending –olidine. Substituents may be referred to as occupying position C-3(R), *N*-4(R') or C-5(R) (**1g**).[2]

The five-member heterocyclic compounds; particularly nitrogen and oxygen heterocycles oxadiazoles have been successfully tested against several diseases and therefore received special attention in pharmaceutical chemistry due to their diverse medicinal potential. Among the oxadiazoles; 1,2,4-oxadiazoles continuously draws interest for development of newer drug moiety. They have demonstrated a broad spectrum of biological properties in both pharmaceutical and agrochemical fields. Substituted 1,3,4-oxadiazole derivatives have demonstrated a broad spectrum of biological properties in both pharmaceutical and agrochemical fields. They have known to exhibit diverse biological activities such as virucidal[3], CNS depressant[4], genotoxic[5], anticonvulsant[6], insecticidal[7], antitubercular[8], anti-HIV[9], herbicidal[10], anti-inflammatory[11]. They have also known to exhibit antimalarial[12], muscle relaxants[13], antitumour[14], lipid peroxidation inhibitor[15], antimicrobial[16,17], and remarkable analgesic, anti-convulsant, diuretic, hypnotic and sedative properties[18]. Therefore, 1,3,4-oxadiazoles have attracted the researchers all over the world to

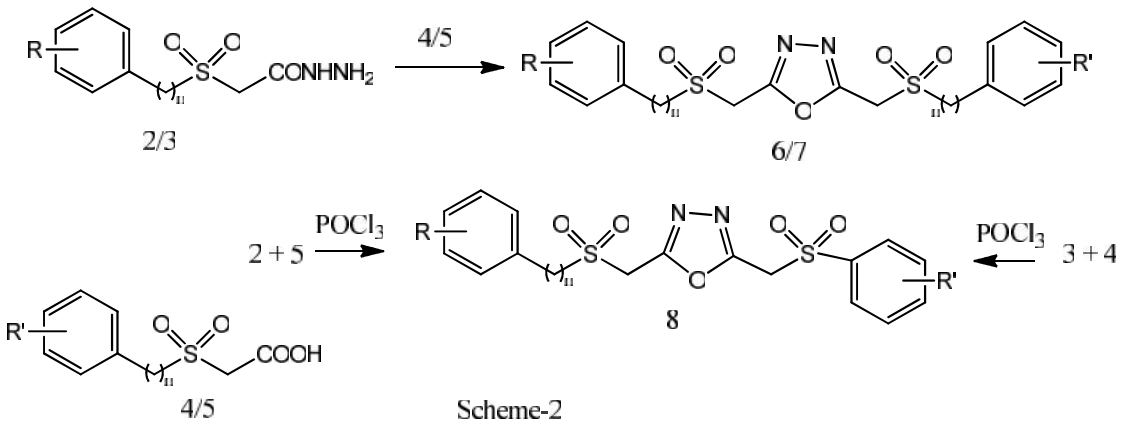
work in this area of new drug development. An enormous amount of research was undertaken to synthesize these classes of compounds by employing traditional methods, introducing new innovative methods and techniques, to reach the target molecules and study their biological applications.

Synthesis of 1,3,4-oxadiazoles:

The conventional method of synthesis of 1,3,4-oxadiazole involves intermolecular condensation of acid hydrazides with carboxylic acids in the presence of cyclising reagents such as phosphorus oxychloride, polyphosphoric acid, acetic anhydride. For instance, acid hydrazides of arylsulfonylacetic acid (**2)** and arylmethanesulfonylacetic acid (**3)** were used as an useful intermediates in the synthesis of symmetric and unsymmetric 1,3,4-oxadiazoles. The symmetrical 2,5-bis(arylsulfonylmethyl)-1,3,4-oxadiazoles (**6)** were prepared by the cyclocondensation of arylsulfonylacetic acid (**4)** with (**2)** in the presence of phosphorus oxychloride. Similarly, 2,5-bis(benzylsulfonyl methyl)-1,3,4-oxadiazoles (**7)** were obtained by the reaction of benzylsulfonylacetic acid (**3**) with (**5)** in the presence of phosphorus oxychloride. The unsymmetrical 1,3,4-oxadiazoles (**8**) were prepared by the reaction 2 + 5 or 3 + 4 in the presence of phosphorus oxychloride (Scheme-2)[19].

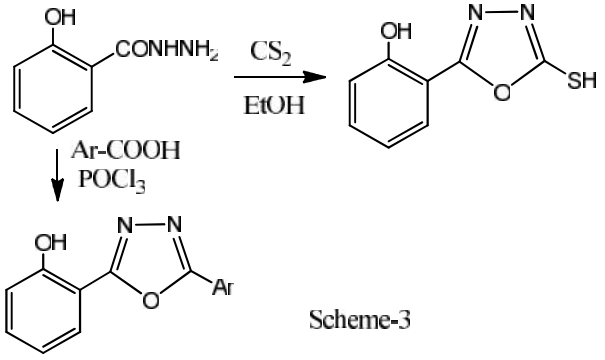


Scheme-1



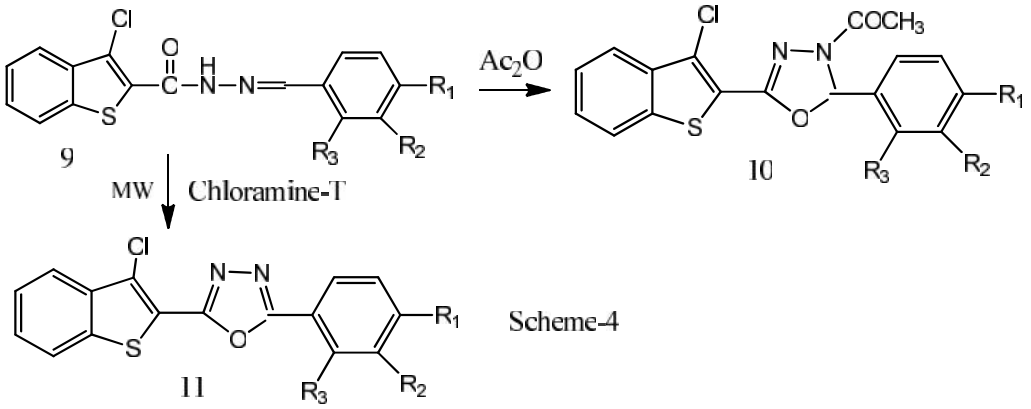
Scheme-2

A mixture of carboxylic acid, semicarbazide and phosphorus oxychloride initially on heating at 60 °C for 1hr and then at 95°C for an additional 2hr yielded 2-Amino-5-aryl-1,3,4-oxadiazoles, and were reported to show promising antimicrobial activity[20]**.** In the development of a synthetic approach to the vinca alkaloids based on the cycloaddition reactions of electron-deficient heterocyclic azadienes, a systematic exploration of the intramolecular [4+2]/[3+2] cycloaddition cascade of 1,3,4-oxadiazoles in which the scope and utility of the reaction are well described[21]. 2-Hydroxy benzohydrazide on heating with carbon disulphide in the presence of KOH in alcohol produced 5-(2-hydroxyphenyl)-2-mercapto-1,3,4-oxadiazole, and with benzoic acid in phosphorus oxychloride gives 5-(2-hydroxyphenyl)-2-phenyl-1,3,4-oxadiazole relatively in good yield (Scheme-3)[22].



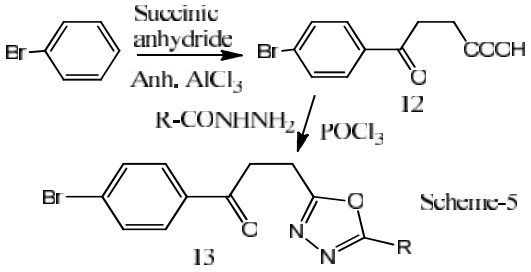
Scheme-3

Treatment of a suspension of salicylic hydrazide in toluene with acetic anhydride or an acid chloride in the presence of an equimolecular amount of methanesulfonic acid at room temperature, and then heating to reflux temperature gave 1,3,4-oxadiazoles in yields ranging from 43 to 68%. Similarly, thiosalicylic hydrazide afforded the corresponding 1,3,4-oxadiazoles in 31 to 36%. The treatment of salicylic semicarbazides under Appel's dehydration condition ($Ph_3P/CCl_4/Et_3N$) smoothly afforded 1,3,4-oxadiazoles (47-85%) *via* carbodiimide intermediates followed by intramolecular cyclization reaction and hydride shift. The method is observed to be advantageous over the usual method, as it this method is cheaper, nontoxic, stable, and easy to handle. The drawback of the method is it has its limitations as regards to the low yields of 1,3,4-oxadiazoles having thiophenol group[23]. A carbohydrazide (**9**) on heating with excess of acetic anhydride for about 4 hrs afforded 3-acetyl-5-(3-chloro-1-benzo [*b*]thiophen-2-yl)-2-substituted phenyl-2,3-dihydro-1,3,4-oxadiazoles (**10**), while the mixture of same carbohydrazide and chloramine-T in ethyl alcohol on microwave irradiation at 300 W intermittently at 30 sec intervals for specified time produced 2-(3-chloro-1-benzo[*b*]thiophen-2-yl)-5-substitutedphenyl-1,3,4-oxadiazoles (**11**), the products exhibited antimicrobial activity (Scheme-4)[24].



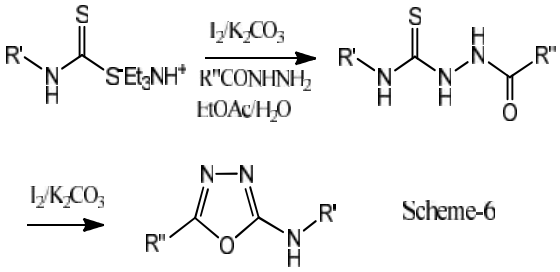
Scheme-4

With the aim to get better anti-inflammatory and analgesic agents with minimum or without side effects (ulcerogenicity), a series of 2-[3-(4-bromophenyl)propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazoles (**13**) have been synthesized from 3-(4-bromobenzoyl)propionic acid (**12**) and several aryl acid hydrazides in phosphorous oxychloride. The synthesised compounds were evaluated for their anti-inflammatory, analgesic, ulcerogenic and antibacterial activities. Antibacterial activity was expressed as the corresponding minimum inhibitory concentration (*MIC*). A fair number of compounds were found to have significant anti-inflammatory and analgesic activities, while a few compounds showed appreciable antibacterial activity. The newly synthesized compounds showed very low ulcerogenic action. The results indicated that; the cyclization of the carboxylic group of (**12**) into novel 1,3,4-oxadiazole nucleus resulted in increased anti-inflammatory and analgesic activities with a significant decrease of ulcerogenic activity (Scheme-5)[25].



Scheme-5

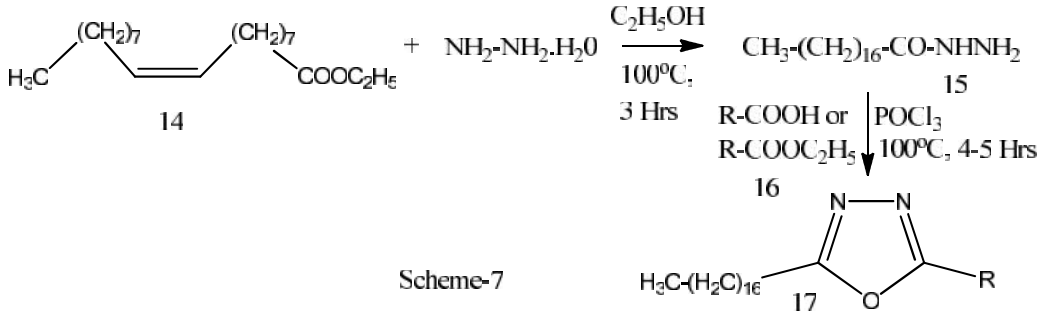
A novel series of 2-[3-(4-chloro phenyl)propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazole and 2-[3-(4-ethylphenyl)propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazole were synthesized and have been tested for their antiinflammatory, analgesic, ulcerogenic and antibacterial actions. A fair number of compounds were found to have very good antiinflammatory activity in carrageenan induced rat paw edema test, while a few compounds showed significant analgesic activity in acetic acid induced writhing test. The new synthesized compounds showed very low ulcerogenic action and moderate antibacterial action[26]. A one-pot synthesis of 3-amino-1,3,4-oxadiazoles has been achieved from the corresponding dithiocarbamate salt, employing the thiophilic property of molecular iodine. The precursor thiosemicarbazides could be derived *in situ* which underwent an intramolecular cyclodesulfurization in the presence of iodine to afford 3-amino-1,3,4-oxadiazoles exclusively. Apart from being milder and environmentally sustainable, this method involves a simple, reliable approach to give excellent yields of the desired products and is compatible with a wide range of functional groups (Scheme-6)[27].



Scheme-6

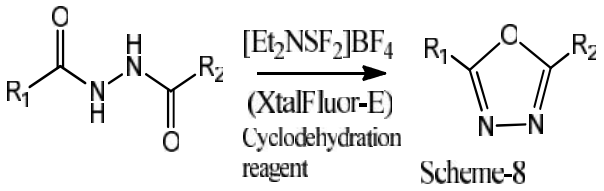
The reaction of *p*-bromoanilino acetohydrazide with aromatic aldehydes in alcohol yielded 2-[4-bromo aniline] N-substituted benzylidine hydrazides, which in presence of yellow mercuric oxide and iodine in DMF, yielded corresponding 4-bromo[(N-5-substituted 1,3,4 oxadiazole-2-yl)methyl]aniline. The some of the synthesized compounds have showed remarkable antibacterial, antifungal and anti-inflammatory activities[28]. A series of isatin-3-ylidene and arylthiazolyl-1,3,4-oxadiazole-2-thione derivatives derived from arylthiazolyl carbohydrazide analogs were synthesized. The synthesized compounds were assayed against HIV-1 and HIV-2 in MT-4 cells, some of the compounds showed inhibition of HIV-1 with EC_{50} = 2.34 μg mL^{-1}, and 1.12 μg mL^{-1} with therapeutic indexes (SI) of 9 and <1, respectively[29].

Symmetric and unsymmetric 1,3,4-oxadiazoles were synthesized *in situ* from hydrazine hydrate and the corresponding 2-acyl-4,5-dichloropyridazin-3-ones as acylating agents in PPA[30]. Fatty acid hydrazides are used as cheap starting materials in the synthesis of important biologically active 1,3,4-oxadiazoles using cyanogen bromide and benzoyl chloride or benzoic acid as reagents respectively[31]. Recently, Ajay kumar and co-workers reported the synthesis of 1,3,4-oxadiazoles, in an attempt to synthesise alkenyl substituted oxadiazoles, they observed that the during the conversion of ethyl oleate to oleic acid hydrazide, the double bond present in C_9-C_{10} positions of ethyl oleate underwent reduction leading to the formation of unusual stearic acid hydrazide instead of the expected oleic acid hydrazide, then they converted the stearic acid hydrazide to a series of new 2,5-substituted 1,3,4-oxadiazoles by the reaction of stearic acid hydrazide with different carboxylic acids and their ethyl esters in phosphorus oxychloride (Scheme-7)[32].



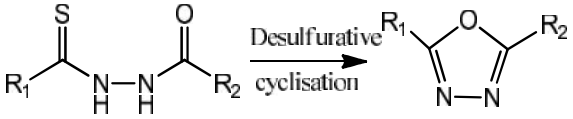
Scheme-7

In recent years, multicomponent reactions (MCRs) have become important tools in modern preparative synthetic chemistry; because these reactions increase efficiency by combining several operational steps without any isolation of intermediates or changes in the conditions. For instance, the 1:1 iminium intermediate generated by the addition of a secondary amine to aromatic bis-aldehydes is trapped by the *N*-isocyaniminotriphenylphosphorane in the presence of aromatic carboxylic acid derivative, which lead to the formation of corresponding iminophosphorane intermediate. Then the disubstituted 1,3,4-oxadiazole derivatives are formed via intramolecular aza-Wittig reaction of the iminophosphorane intermediates. The reactions were completed in neutral conditions at room temperature and the corresponding disubstituted 1,3,4-oxadiazole derivatives were produced in excellent yields[33]. 1,2-Diacylhydrazines have been converted to various functionalized 1,3,4-oxadiazoles effectively using XtalFluor-E ($[Et_2NSF_2]BF_4$) as cyclodehydration reagent, the use of acetic acid as an additive in a reaction generally improved the yields (Scheme-8)[34].



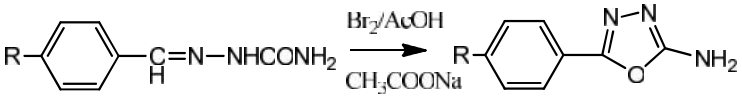
Scheme-8

The iminium intermediate generated by the reaction between a secondary amine and cinnamaldehyde was reacted with *N*-isocyanimino-triphenylphosphorane in the presence of benzoic acid derivatives to form the corresponding iminophosphorane intermediate, whose intramolecular aza-Wittig reaction led to disubstituted 1,3,4-oxadiazole derivatives. The syntheses were completed under neutral conditions at room temperature to give excellent yields[35]. In recent times, solid phase organic synthesis (SPOS) has considered as an efficient route in organic synthesis. The technique is effectively used for the synthesis of 1,3,4-oxadiazoles involving cyclodesulphurisation reactions of acyldithiocarbazate resin (Scheme-9)[36].



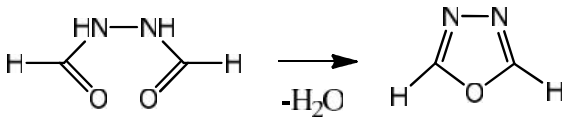
Scheme-9

A series of 3-(5-phenyl-1,3,4-oxadiazole-2-yl)-2-(substituted styryl)-quinazoline-4(3*H*)-ones were synthesized by reacting 2-methyl-3-(5-phenyl-1,3,4-oxadiazole-2-yl)-quinazoline-4(3*H*)-one 2 and substituted benzaldehydes in glacial acetic acid. 2-methyl-3-(5-phenyl-1,3,4-oxadiazole-2-yl)-quinazoline-4(3*H*)-one was obtained by refluxing 2-methylbenzoxazin-4(3*H*)-one with the 2-amino-5-phenyl-1,3,4-oxadiazole. 2-Amino-5-phenyl-1,3,4-oxadiazole was prepared by oxidative cyclization of benzaldehyde semicarbazone and bromine in the presence of glacial acetic acid[37]. Aromatic aldehyde semicarbazides on oxidative cyclisation with bromine in acetic acid in the presence of sodium acetate was reported to produce 2,5-disubstituted 1,3,4-oxadiazoles (Scheme-10)[38].

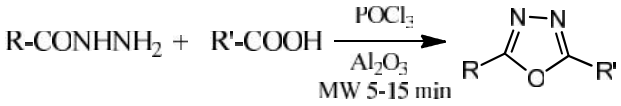


Scheme-10

An improved method for the synthetic approaches to 1,3,4-oxadiazole have been investigated, which involves dehydration of *N,N'*-diformylhydrazine with P_2O_5 in polyphosphoric acid (Scheme-11)[39]. Microwave radiation provides an alternative tool to conventional heating as it utilizes the ability of liquids or solids to transform electromagnetic energy into heat. Chemical transformations that took hours, or even days, to complete can now be accomplished in minutes. Microwave energy offers numerous benefits for performing synthesis including increased reaction rates, yield enhancements, and cleaner chemistries. However, for the sake of safety measurements, it has been advised that only the microwave ovens designed for organic synthesis be used. 2,5-Disubstituted-1,3,4-oxadiazoles were synthesized under microwave irradiation, the reaction afforded the products in relatively good yield (Scheme-12)[40].



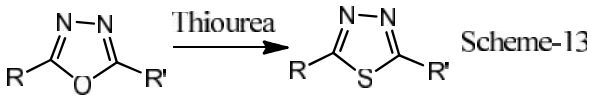
Scheme-11



Scheme-12

Reactions of 1,3,-4-oxadiazoles:

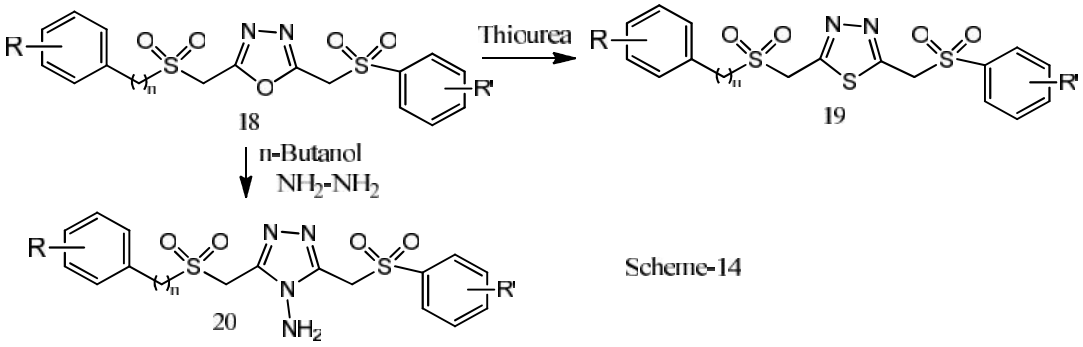
Rai and co-workers introduced thiourea as a new reagent for the direct conversion of 2.5-diaryl- 1,3,4-oxadiazole to 2.5-diaryl-1,3,4-thiadiazole. They observed that, when the reaction of 1,3,4-oxadiazoles with thiourea was carried out at retlux temperature for 3 to 4 days, only 2 to 5% of oxadiazoles gets converted to thiadiazoles. In order to reduce the reaction time and to increase the yield, they carried out in a sealed tube at water bath temperature for 10-15 hr and obtained the yield in 65-72% (Scheme-13)[41]. Their method of using thiourea as thionating agent for the transformation of oxadiazoles to thiadiazoles has been widely accepted and implemented.



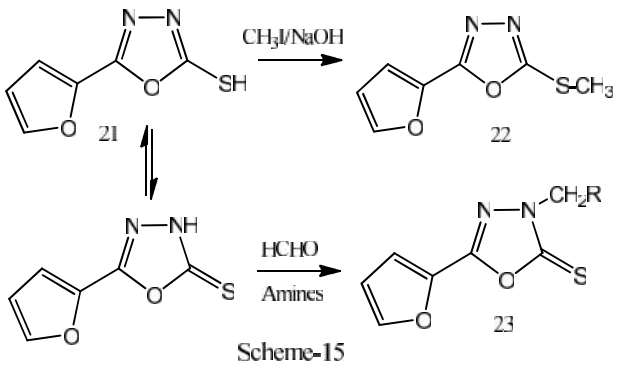
Scheme-13

The unsymmetrical 1,3,4-oxadiazole (**18**) when treated with two fold excess thiourea in tetrahydrofuran produced 2-(benzylsulfonylmethyl)-5-(arylsulfonylmethyl)-1,3,4-thiadiazole (**19**). On the other hand, treatment of (**18**) with excess hydrazine hydrate gave 3-(benzylsulfonylmethyl)-5-(arylsulfonyl methyl)-4-amino-1,3,4-triazole (**20**) (Scheme-14)[19].

5-furan-2-yl[1,3,4]oxadiazole-2-thiol (**21**) was synthesized by the ring closure reaction of furan-2-carboxylic acid hydrazide with carbon disulfide. Then the compound 5-furan-2-yl[1,3,4]oxadiazole-2-thiol (**21**) was converted to thiomethyl derivative (**22**) by its reaction with Methyl iodide in the presence of sodium hydroxide. On the other hand, the compound 5-furan-2-yl[1,3,4]oxadiazole-2-thiol (**21**) was converted to a series of Mannich bases of 5-furan-2-yl[1,3,4]oxadiazole-2-thiol (**23**) by its reaction with suitably substituted amines and formaldehyde in ethanol (Scheme-15)[42]. The 2-furoyl thiosemicarbazide employed in these reactions was obtained by refluxing the corresponding furan-2-carboxylic acid hydrazide with ammonium thiocynate in presence of aq. hydrochloric acid.



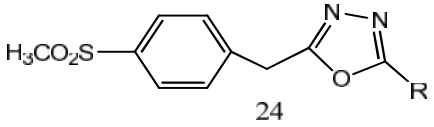
Scheme-14



Scheme-15

Applications of 1,3,4-oxadiazoles:

A series of substituted 1,3,4-oxadiazole derivatives were synthesized by cyclo desulfurization of the corresponding thio semicarbazides using dicyclohexyl carbodiimide DCC were investigated for their antiinflammatory activity on histamine-induced edema in rat abdomen. Results revealed that some of the compounds proved to be more potent antiinflammatory agents at 200 mg/kg po than ibuprofen, some showed significant antiinflammatory activity but less than ibuprofen at the same dose level. The low toxicity of the most potent compounds was reflected by their higher LD_{50} value, ranging from ~1000 to 1500 mg/kg, as well as the lower ulcerogenic liability at 200 mg/kg po. Some of the compounds were better analgesics than the reference drug as observed from the percentage writhing inhibition in the p-benzoquinone (PBQ)-induced writhing test in mice[43]. A series of new 2-[4-(alkylsulfonyl) benzyl]-5-substituted-1,3,4-oxadiazoles (**24**) synthesized from 4-(alkyl thio)phenyl actetonitrile through a multi step reaction have showed antioxidant activity[44].



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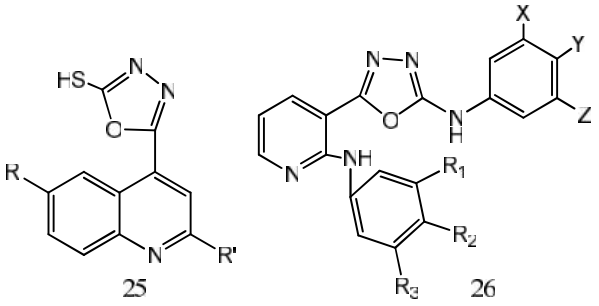
Some novel calixarene based heterocyclic compounds in which 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives have been coupled with 5,11,17,23-tetra-*tert*-butyl-25,27-bis(chlorocarbonyl-methoxy)-26,28-dihydroxy calix[4]arene. All the final scaffolds have been subjected to antioxidant activity, *in vitro* antimicrobial screening against bacterial and fungal strains, they also showed antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$[45]. Indolyl-1,3,4-oxadiazole derivatives were prepared as reversible monoamine oxidase inhibitors. The compound 5-(3-methylindolyl)-1,3,4-oxadiazol-2(3*H*)one was shown to be a good monoamine oxidase B inhibitor[46]. The compounds 5-(4-nitrophenyl)-2-(4-chlorophenyl)-1,3,4-oxadiazole and 5-(4-nitrophenyl)-2-(4-nitro phenyl)-1,3,4-oxadiazole synthesized were found to be the most promising compounds of the series in antidepressant, anticonvulsant and antianxiety activity with no neurotoxicity when compared with standard[47].

A series of novel 1,3,4-oxadiazole derivatives based on structural and electronic overlap with combretastatins have been designed and synthesized. Initially, we tested all new compounds in vivo using the phenotypic sea urchin embryo assay to yield a number of agents with anti-proliferative, anti-mitotic, and microtubule destabilizing activities. The experimental data led to identification of 1,3,4-oxadiazole derivatives with isothiazole and phenyl pharmacophores featuring activity profiles comparable to that of combretastatins, podophyllotoxin and nocodazole. Cytotoxic effects of the molecules were further confirmed and evaluated by conventional assays with the A549 human cancer cell line including cell proliferation, cell cycle arrest at the G2/M phase, cellular microtubule distribution, and finally in vitro microtubule assembly with purified tubulin. The modeling results using 3D similarity (ROCS) and docking (FRED) correlated well with the observed activity of the molecules. Docking data suggested that the most potent molecules are likely to target the colchicine binding site[48].

1, 3, 4-oxadiazole derivatives (**25**)[49] were obtained from 6-phenyl-2-substituted quinoline-4-carbohydrazide and a mixture of carbon disulphide and potassium hydroxide have reported to exhibit antifungal and antibacterial activities. A series of 2-anilinonicotinyl linked 1,3,4-oxadiazoles (**26**)[50] was synthesized and evaluated for their antitumour activity against various cancer cell lines, inhibition of tubulin polymerization and cell cycle effects. Some of these compounds showed good antiproliferative activity with GI_{50} values ranging from 4.57 to 97.09 μM in the human cancer cell lines and one of the compounds 5m showed potent antitumour efficacy in the entire cell lines tested. This compound also inhibited tubulin polymerization under both *in vitro* and *in vivo* conditions. Analysis of tubulin by Western blot experiments demonstrated that 5m depolymerizes microtubules by causing disturbances in the ratio of soluble *versus* polymerized tubulin in cells, leading to the cell cycle arrest at G2/M phase of the cell cycle followed by activation of caspase-3 activity and apoptotic cell death.



2,5-disubstituted-1,3,4-oxadiazoles[51] have been synthesized by the condensation of 4-methoxybenzohydrazide with different aromatic acids in presence of phosphoryl chloride. The synthesized compounds have reported to exhibit inhibiting activity against different strains of bacteria and fungi, and were also showed antiinflammatory activity against carrageenan-induced rat paw oedema of about 50% inflammation inhibitory activity at a dose of 50 mg/kg po. 2,5-Disubstituted 1,3,4-oxadiazoles synthesized by cyclisation of 3-aroylpropionic acid hydrazides in the presence of phosphorous oxychloride showed anti-inflammatory and analgesic effects with reduced gastric irritation[52].

A new 1,3,4-oxadiazole-based fluorescence chemosensor, *N*-(2-ethoxy-2-oxoethyl)-*N*-(5-(2-hydroxy-3,5-di-*tert*-butyl phenyl)-[1,3,4]oxadiazol-2-yl)glycine ethyl ester has been designed and synthesized. Its fluorescence properties and selectivity for various metal ions were investigated, A prominent fluorescence enhancement only for Zn^{2+} was found in aqueous acetonitrile solution[53].

A new series of 1,3,4-oxadiazole derivatives containing 2-fluoro-4-methoxy phenyl were synthesized by refluxing mixture of acid hydrazide with different aromatic carboxylic acids in phosphorous oxychloride. The open-aperture z-scan experiment was employed to measure the optical nonlinearity of the samples at 532 nm, using 5 ns laser pulses. The measurements indicate that 1,3,4-oxadiazole that contains bromine as substituent, behaves as an optical limiter at this wavelength, with potential applications in optoelectronics[54]. The synthesis of novel liquid-crystalline heteroaromatic compounds incorporating the five membered 1,3,4-oxadiazole ring is described. Due to the bent molecular structure of the oxadiazole ring their mesophase stability is low if the heterocyclic ring occupies a central position, but it is increased if this ring is shifted to a terminal position. Dielectric measurements indicate that the 2-*N*-alkylthio substitutes 1,3,4-oxadiazole derivatives change the sign of the dielectric anisotropy at the phase transition from the nematic to the smectic A phase. This effect is explained by the increase of the antiparallel correlation of the molecules on formation of the smectic layers[55].

2,5-disubstituted-1,3,4-oxadiazoles[56] have been investigated by various corrosion monitoring techniques for their corrosion inhibitor properties. Results reveal that these compounds are very good inhibitors and behave better in 1 M HCl. The influence of oxadiazole derivatives on the corrosion inhibition of steel in 2M H_3PO_4 solution is studied using weight-loss and electrochemical polarisation measurements. The results show that 2,5-bis(4-methoxyphenyl)-1,3,4-oxadiazole is the best inhibitor and its inhibition efficiency increases with the increase of concentration to attain 76% at 5×10^{-4} M. Potentiodynamic polarisation studies clearly reveal that the oxadiazole derivatives act essentially as cathodic inhibitors[57]. The review article on 1,3,4-oxadiazole appeared recently, emphasizes the pharmacological applications associated with 1,3,4-oxadiazole derivatives[58].

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