Vol. 2, Issue: 2, February 2014
ISSN:(P) 2347-5404 ISSN:(O)2320 771X

Oxadiazole Core as a Good Drug Candidate and Its Synthetic Methods

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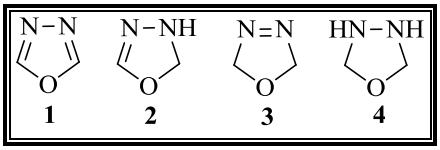
Abstract:
1,3,4-Oxadiazole is a heterocyclic molecule with oxygen atom at 1 and two nitrogen atoms at 3 and 4 position. They have been known for about 80 years, it is only in the last decade that investigations in this field have been intensified. This is because of large number of applications of 1,3,4-oxadiazoles in the most diverse areas. It also contains broad range of therapeutic activity. In this article biological importance of oxadiazole and its synthetic methods have been discussed thoroughly.

Keywords: *Antiviral, Heterocyclic chemistry, Medicinal chemistry, Oxadiazole, anticancer*

1. Introduction

Oxadiazoles belong to an important group of heterocyclic compounds having –N=C-O- linkage. 1,3,4-oxadiazole(**1**) is a thermally stable aromatic heterocycle and exist in two partially reduced forms; 2,3-dihydro-1,3,4-oxadiazole(1,3,4-oxadiazoline)(**2**) and 2,5-dihydro-1,3,4-oxadiazole(1,3,4-oxadiazoline)(**3**) depending on the position of the double bond. The completely reduced form of the 1,3,4-oxadiazole is known as 2,3,4,5-tetrahydro-1,3,4-oxadiazole (1,3,4-oxadiazolidine)(4)[1]

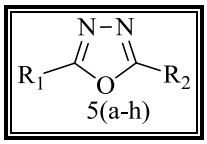


1,3,4-Oxadiazole is a heterocyclic molecule with oxygen atom at 1 and two nitrogen atoms at 3 and 4 position. They have been known for about 80 years, it is only in the last decade that investigations in this field have been intensified. This is because of large number of applications of 1,3,4-oxadiazoles in the most diverse areas viz. drug synthesis, dye stuff industry, heat resistant materials, heat resistant polymers and scintillators. Reviews of the relevant literature prior to 1965 are available.

Bactericidal and/or fungicidal activity was reported for oxadiazole (5a), aminooxadiazole (5b)[2] and oxadiazolinethiones (6a).[3] The tin derivatives (6b) is an effective fungicide and antimicrobial activity is shown by thiones (6c).[4] Antiinflammatory, sedative and analgesic properties were reported for aryloxadiazoles (5c).[5] Amino-oxadiazoles (5d) show analgesic activity and amino-oxadiazoles (5e) exhibit both anti-inflammatory and antiproteolytic properties[6]. Anticonvulsant and nervous system depressant activity was reported for amino-oxadiazoles (5f), where R is quinazolin-3-yl group.[7] Aminooxadiazole (5g) show local anaesthetic activity.[8] The oxadiazolinone (6d) is an orally active antiallergic agent, for example in the treatment of asthma and allergy disease and is claimed to be more potent than sodium cromoglycate.[9] Examples of the many oxadiazolones for the many herbicidal activity (week killers) are (6e,6f) and

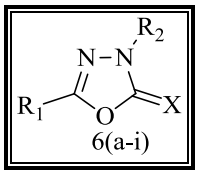
"oxadiazon"(6g), which is the subject of many regular reports in the literature. Insecticidal activity is shown by oxadiazolones (6h, 6i the later is an aphicide), and oxadiazole (5h)

	R^1		R^2
5a	Ar		$CH_2CONHCONHR$
5b	AR		OCH_2 NHCOR
5c	trimethoxy	or	3,4-dimethoxyphenyl
5d	2-pyridyl		NR_2HCl
5e	4-biphenylylmethyl		NHAr
5f	Ar		$NHCH_2CONHR$
5g	Ar		$NHCO(CH_2)nNRR'HCl(n=2or3)$



5(a-h)

	R^1	R^2	X
6a	heteroarylOCH_2	H	S
6b	1-methylcyclopropyl	$Sn(Ph)_3$	O
6c	5-Cl-2-phenylindol-3-ylNH	H	S
6d	3-Cl-benzo[b]thiophen-2-yl	H	O
6e	4-cyclohexylphenoxy	H	O
6f	2,4-diCl-phenoxymethyl	Bn	O
6g	*t*-Bu	2,4-diCl--5-isopropoxyphenyl	O
6h	OCH_3	*o*-methoxyphenyl	O
6i	CH_3NH	2,3-diH-2,2,4-triMebenzofuran-7-yl	O



6(a-i)

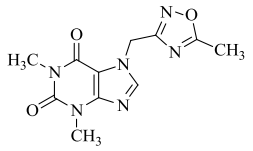
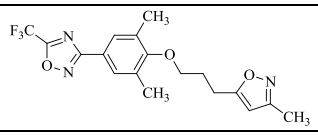
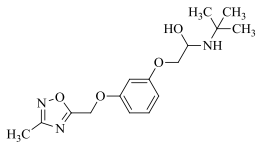
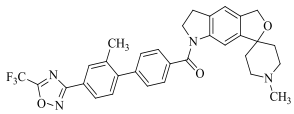
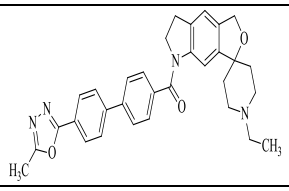
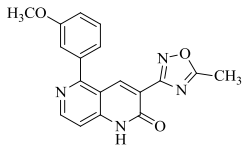
2. Pharmacology

1,3,4-Oxadiazole derivatives have been tested for various pharmacological activities, which have been summarized as under.

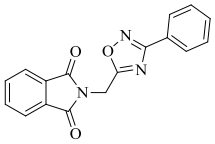
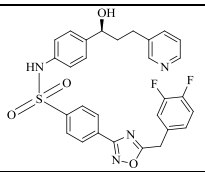
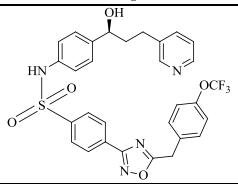
1. Antibacterial[10]	6. Anticonvulsant[15]	11. Hypoglycemic[20]
2. Antiinflammatory11	7. Antiproliferative[16]	12. Hypnotic and Sedative[21]
3. Analgesic12	8. Antifungal[17]	13. MAO inhibitor[22]
4. Antiviral and anticancer13	9. Cardiovascular[18]	14. Insecticidal[23]
5. Antihypertensive14	10. Herbicidal[19]	

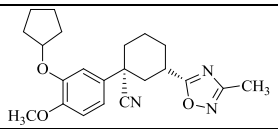
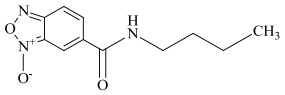
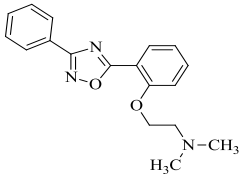
1,3,4-Oxadiazole is a versatile scaffold and is being consistently used as a building block in organic chemistry as well as in heterocyclic chemistry for the synthesis of different heterocycles. The synthetic versatility of 1,3,4-oxadiazole has led to the extensive use of this compound in organic synthesis.

Some oxadiazole drugs & derivatives under Preclinical/Phase clinical trials.

Sr.	Chemical structure	Activity	Phase	Originator
1		Antitussive, Bronchodilator	Phase-I	Sanofi-Synthlabo
2		Antirhinoviral, Antiviral	Phase-III	Viro pharma
3		Antihypertensive, Antianginal, Antiglaucoma agent, Beta-adrenoceptor antagonist	Phase-II	Center for Chemistry of Drugs
4		Antidepressants, Anxiolytic, 5-HT1D Antagonist	Biological testing	Smithkline Beecham
5		Antidepressants, Anxiolytic, 5-HT1D Inverse agonist	Preclinical	Smithkline Beecham
6		Cognition enhancing drug, GABA(A) receptor modulator, GABA(A) B2 site inverse agonist	Preclinical	Dainoppon pharma

Some oxadiazole drugs & derivatives under Preclinical/Phase clinical trials

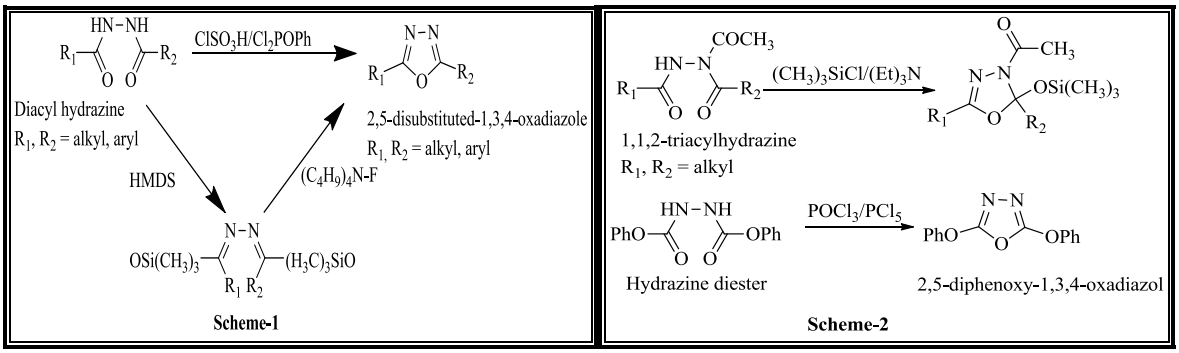
Sr.	Chemical structure	Activity	Phase	Originator
1		Analgesic	Preclinical	Universidade federal pernambuco
2		Antiobesity drug, Antidiabetic drug, Beta3 adrenoce tor agonist	Preclinical	Merck
3		Antiobesity drug, Antidiabetic drug, Beta3 adrenoceptor agonist	Preclinical	Merck

4		Bronchodilator, Phosphodiesterase Inhibitor	Preclinical	Smithkline Beecham
5		Antitrypanosomal	Preclinical	Universidad de larepublica
6		Antiepileptic drug,Neuronal Injury Inhibitor, AMPA antagonist,Sodium channel blocker	Preclinical	Boehringer Ingelaeim

3. Synthetic methods

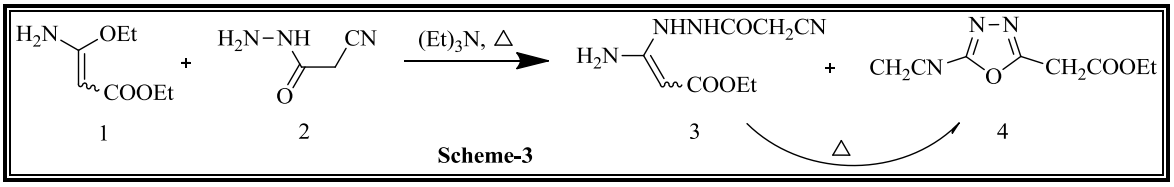
There were several routes for the synthesis of 1,3,4-oxadiazoles reported in the literature among which the most important aspects of synthesis were discussed as under.

2,5-Disubstituted 1,3,4-oxadiazole can be accomplished by cyclodehydration of 1,2-diacylhydrazine either by using chlorosulphonic acid[24] or phenyl dichorophosphite in dimethylformamide. A nonaqueous, nonacedic, route involves treatment of hydrazine with hexamethyl disilazane (HMDS) and tetrabutylammoniumfluoride, the last step presumably being fluoride catalyzed cyclization of intermediate bis silyl ether[25,26] (Scheme-1)



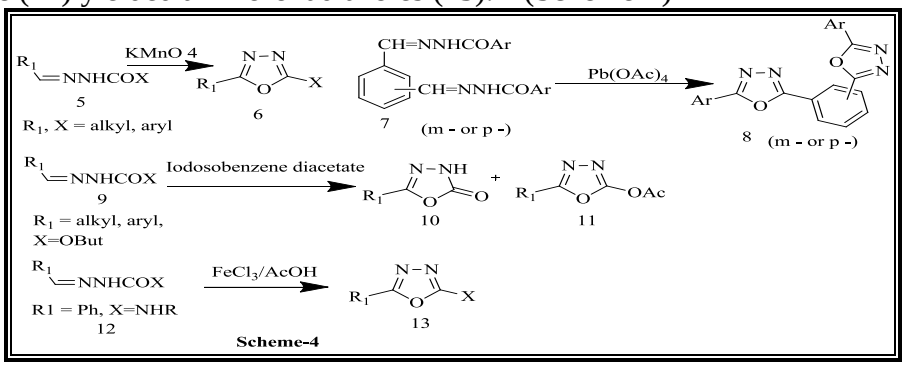
In a related reaction, 1,1,2-triacetylhydrazine with trimethylsilylchloride/triethylamine gave oxadiazolinyl silylether.[27] Cyclodehydration ($PCl_5/POCl_3$) of hydrazinyl diester gave the diphenyloxyoxadiazole.[28] (Scheme-2)

The malonate derivative (1) reacted with acylhydrazine (2) to give a mixture of diacylhydrazine monoamine (3) and oxadiazole (4). The later was also formed from (3) by heating.[29] (Scheme-3)

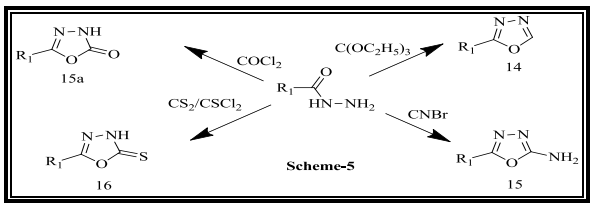


Oxidation of acylhydrazones derived (5) from aldehydes has been developed into a useful route to disubstituted oxadiazoles (6). The use of potassium permanganate with acetone as solvent was claimed to give better yields than the use of other oxidizing agents (e.g.halogens).[30] An improved synthesis of bis-oxadiazolylbenzenes (8) involved oxidation of bishydrazones (7) with lead tetraacetate.[31] Acylhydrazones (9) were oxidized by iodosobenzene diacetate to oxadiazolinones (10), with acetates (11) also being formed in some cases. A similar oxidation of ethyl esters (9,

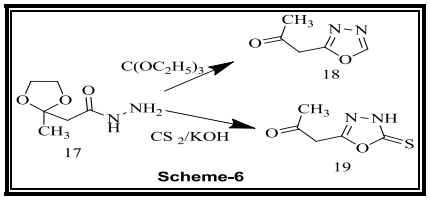
X=OEt) gave oxadiazolyl ethers (11, X=OEt).[32] Oxidative cyclization($FeCl_3$/AcOH) of semicarbazone (12) yielded amino-oxadiazoles (13).[33] (Scheme-4)



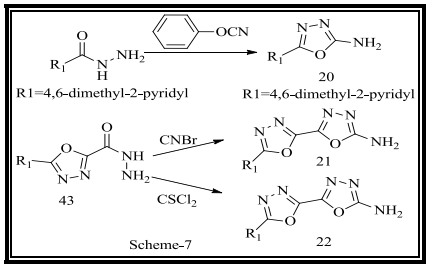
Important routes to monosubstituted oxadiazoles (14), aminooxadiazoles (15), oxadiazolinones (15a) and oxadiazolinethiones (16) involve reaction of hydrazides ($R_1CONHNH_2$) with triethyl orthoformate, cyanogen bromide, phosgene, or carbon disulphide (or $CSCl_2$) respectively. (Scheme-5)



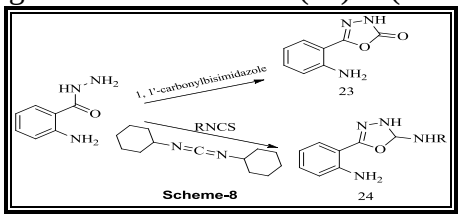
Reaction of hydrazide (17) with triethylorthoformate, or with CS_2/KOH, allowed the synthesis of oxadiazolyl methyl ketones (18) and (19), respectively, after hydrolysis of the acetal group.[34] (Scheme-6)



An alternative to cyanogenbromide is phenyl cyanate (PhOCN), which reacted with hydrazines ($R_1CONHNH_2$) to give aminooxadiazoles (R_1= 4,6- dimethyl-2-pyrimidyl).[35] From oxadiazol-2-carbohydrazides (20) bioxadiazolyls (21) and (22) were prepared using cyanogen bromide[36] or thiophosgene[37] respectively. (Scheme-7)

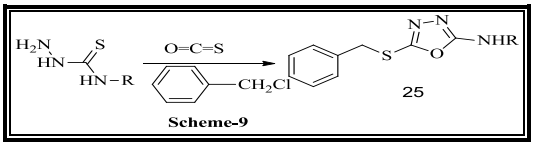


It has been shown that *o*-aminobenzoylhydrazine reacted with (i) 1,1'-carbonyl- bis-imidazole(a variation of the use of phosgene) to give oxadiazolinone(23)[38] & (ii)1,3 dicyclohexylcarbodiimide and an isothiocyanate RNCS to give aminooxadiazole (24).[39] (Scheme-8)



A variation of the oxidative cyclization of acyl-thiosemicarbazides to aminooxadiazoles.[40]A variation of the reaction of acylhydrazines and carbon disulfide forming oxadiazolinethiones, is

the reaction of thiosemicarbazide ($RNHCSNHNH_2$) with carbon oxysulfide and benzyl chloride, which yields amino-oxadiazolyl thioethers(25).[41] (Scheme-9)



Scheme-9

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