OXADIAZOLE: A PROMISING HETEROCYCLIC NUCLEUS FOR DRUG DEVELOPMENT

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Abstract

A molecular framework containing Nitrogen atom display diverse medicinal application, Oxadiazole rings was introduced in drug discovery as a mandatory part of the pharmacophore, contributing to ligand binding. Oxadiazole moieties also act as a flat, aromatic linker to place substituents in the appropriate orientation as well as modulating molecular properties in the periphery of the Oxadiazole molecule. Oxadiazole is versatile lead molecules for designing potent bioactive drugs with Biological and Therapeutic activities, such as "Anti-microbial", "Anti-inflammatory", and "Anti-tubulin", "Anti-Convulsant", "Anti-cancer", "Anti-HIV", "Tyrosine Inhibitor" and "Anti-Tumor activity", "Proliferation of Cells", "Tuberculosis, Allergy", "Viral diseases" [1].

Keywords: Drug Design and Development, heterocyclic drugs, Oxadiazole**.**

Introduction

Oxadiazole are a series of synthetic compounds of medicinal importance, having a 5 member ring with 2N atoms and 1O atom. Oxadiazole is a weak base due to the inductive effect of the heteroatom. The replacement of 2 – CH groups in Furan ring by 2 pyridine type nitrogen group (–N) reduces aromatic character of Oxadiazole ring to an extent that it exhibits character of a (conjugated) diene. Because of the low electron density on C atom, it is extremely resistant to electrophilic substitutions. The attack of electrophile occurs at N, if substituted with electron releasing groups. The nucleophilic attack is little difficult in oxadiazoles; as the halogen substituted Oxadiazole undergo nucleophilic substitution with the replacement of "Halogen" atom by nucleophilic group[2].

Marketed Drugs Containing Oxadiazole Moiety [3]

RALTEGRAVIR (Anti-retroviral drug) **Merck & Co** The first of a new class of integrase inhibitors to receive such approval

Mechanism: It targets the enzyme integrase which is used by the HIV to integrate the viral genetic material to a human chromosome. The drug is metabolized via Glucuronidation.

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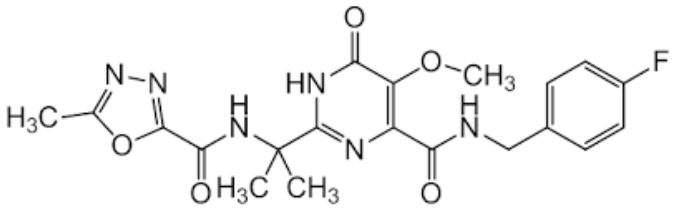
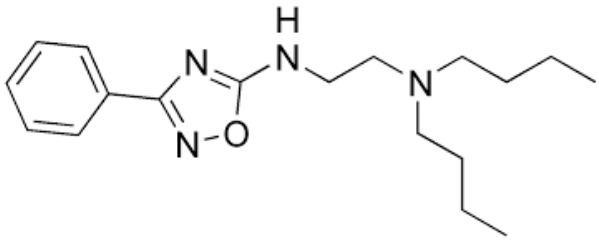
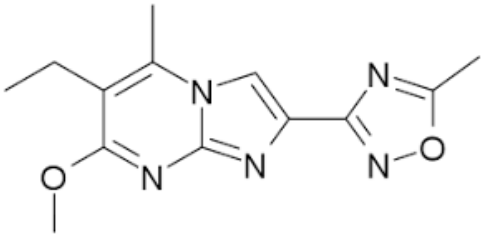


BUTALAMINE (Vasodilator)



FASIPLON (Anti-Anxiety)



Mechanism: Fasiplon binds very strongly to “benzodiazepine” sites on the “GABA” receptor and produces Anxiolytic Effect.

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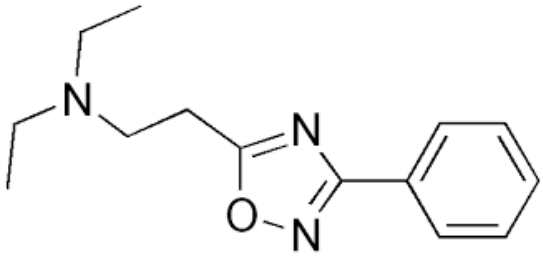
OXOLAMINE (Cough Suppressant)



Mechanism: Pleconaril binds to a hydrophobic pocket in VP1, the major protein which comprises the capsid (the outer "shell") of picornaviruses. In enteroviruses, this prevents the virus from exposing its RNA, and in rhinoviruses, it also prevents the virus from attaching itself to the host cell.

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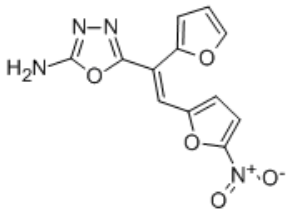
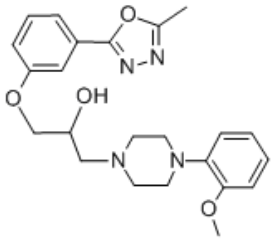
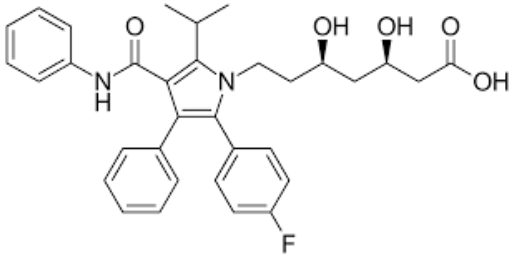
FURAMIZOLE



NESAPIDIL (Antihypertensive agents, anti-microbial, anticancer activity)

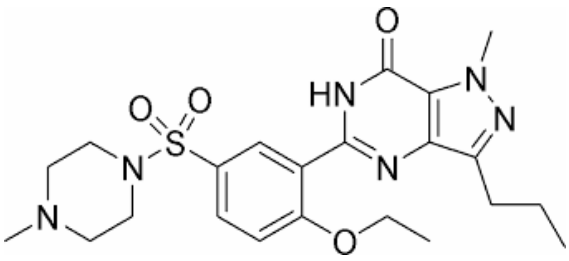


ATORVASTATIN (Pfizer)



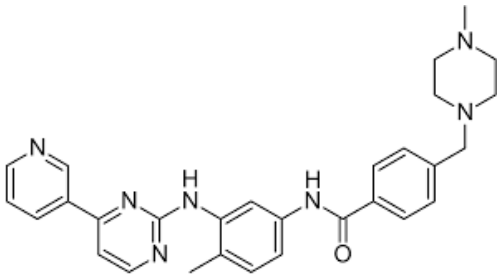
Mechanism of Action: A Statin inhibit "HMG-CoA reductase", enzyme that plays important role in the production of cholesterol.

SILDENAFIL DRUG (Pfizer)



Mechanism of Action: A "PDE5' inhibitor was used clinically in the treatment of "Erectile Dysfunction"

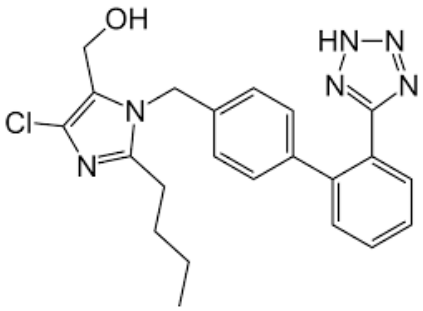
IMATINIB (Novartis)



"2-phenylamino-pyrimidine" derivative, functions as a specific inhibitor of "tyrosine kinase" enzyme.

Imatinib is a drug treat "Chronic Myelogenous Leukemia" and "Cancer".

LOSARTAN (Merck & Co)



Mechanism of Action: Antagonist activity of "Angiotensin II" type 1 receptor (AT_1), used for the treatment of Hypertension.

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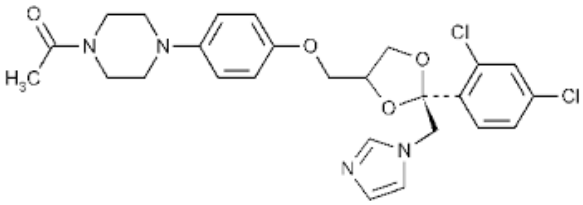
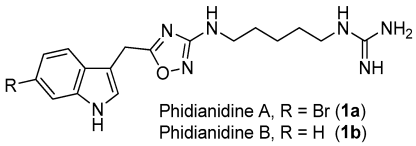
KETOCONAZOLE

An "imidazole" Antifungal that inhibit enzyme responsible for fungal "Ergosterol biosynthesis", 14α-demethylase.



Naturally Occurring Oxadiazole

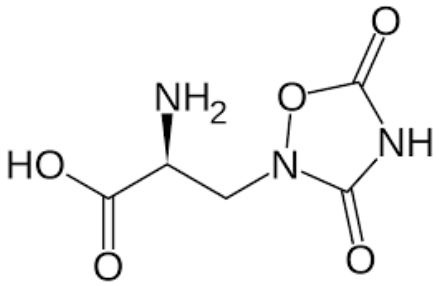
PHIDIANIDINES A AND B



Phidianidine A, R = Br (**1a**)
Phidianidine B, R = H (**1b**)

Selective inhibitors of Dopamine Transporter "DAT" and partial agonists of the "μ opioid receptor". These molecules were isolated from the aeolid opisthobranch Phidiana militaris.

QUISQUALIC ACID isolated from the seeds of Quisqualis indica and Q. fructus.



Agonist for "AMPA" (α-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid) receptors and metabotropic glutamate receptors.

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Biological Importance of Functionalized Oxadiazoles

POTASSIUM CHANNEL OPENER

Romine et al. 3-[(5-chloro-2- hydroxyphenyl) methyl]-5-[4(trifluoromethyl)phenyl]-1,3,4-oxadiazole-2(3H)-one (5) demonstrated clinically efficient opener of large-conductance "Ca2+-activated K channel" [4].

SELECTIVE PROTEASOME INHIBITORS

Rydzewski et. al. Vinyl sulfones (VS) were evaluated as inhibitors of the "chymotrypsin" like activity of the 20S proteasome. P4-P3-P2 sequence was evaluated for novel proteasome inhibitor warhead, "2-keto-1,3,4-oxadiazoles" (6) (KOD), to produce reversible, "Subnanomolar Proteasome Inhibitors" that were 1000-fold selective versus "Cathepsin B" (CatB), cathepsin S (CatS), and trypsin-like and PGPH-like proteasome activity[5].

MUSCLE RELAXANT

Yale et al. "2-amino-5substituted-1,3,4-oxadiazoles" was highly potent in producing a "profound flaccid paralysis" in Animals [6].

HYPOGLYCEMIC ACTIVITY

O'Neal et. al. "5-alkyl-2-arylsulfonamido-l,3,4-oxadiazoles" and "2(p-substituted-sulfonamido)-5-substituted1,3,4-oxadiazoles" were synthesized with powerful hypoglycemic activity [7].

ANTIALLERGIC ACTIVITY

Musser J.H et. al. "2-(2,3-dihydro-2-oxo-1,3,4-oxadiazol-5y1) benzo heterocycle" were tested for inhibitors of "Antigen-Induced Release Of Histamine" (AIR) in-vitro for rat peritoneal mast cells (RMC), inhibitors of IgE-mediated rat passive cutaneous anaphylaxis (PCA) in the rat also Showed Anti-allergic Agents with good activity in assay of RMC [8].

TYROSINASE INHIBITORY

Khan et. al. "2,5-disubstituted-1,3,4-oxadiazoles" were studied for inhibition patterns and structure-activity relationship (SAR) against the enzyme "Tyrosinase", multifunctional copper-containing enzyme and catalyzes the o-hydroxylation of monophenols, also the oxidation of "O-Diphenols to O-Quinones". It was concluded for a better inhibition of tyrosinase[9].

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ANTICANCER ACTIVITY

Aboraia et. al. "5-(2hydroxyphenyl)-3-substituted-2,3-dihydro-1,3,4-oxadiazole2-thione" derivatives and evaluated for their Anticancer Activity. [10].

THIOCARBAZATE CATHEPSIN-L INHIBITOR

Esser R.E et. al. The cathepsins show primary function (i.e., protein degradation) in normal cellular homeostasis. The cathepsin L with abnormal activity has been implicated in Osteo-Arthritis and Rheumatoid Arthritis [11].

CARBONIC ANHYDRASE INHIBITORS

Folkman, J et. al. The carbonic Anhydrase are Metalloenzymes. A series of mercapto-1,3,4-oxadiazole were evaluated as inhibitors of 3 physiologically isoforms of zinc enzyme "carbonic anhydrase" (CA), i.e., the Cytosolic CA I and II, and the tumor-associated, trans-membrane isozyme[12].

VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR-2 (VEGFR-2 KINASE) INHIBITORS Vascular **Cai, Zhen-Wei et. al.** "Endothelial growth factor receptor-2" (VEGFR2) is a protein tyrosine kinase that drives Angiogenesis required for tumor growth and metastasis [13].

COMPETITIVE MONOAMINE OXIDASE INHIBITORS

Mazouz et al. New "5-aryl-1, 3, 4oxadiazol-2(3H)-one" derivatives and its sulfur analogs were evaluated for in-vitro for inhibitory properties on MAO-A and MAO-B. The most active compounds have **IC50(MAO B)** values in the range of 1.4-4.6 nM and its selectivity, estimated by the ratio of IC50 values, are from 3200 to >71400[14].

CALCIUM- AND CALMODULIN-ANTAGONISTS

Manhold et. al. A compound with 5-position of "dihydropyridine" (Elnadipine) is substituted with a 1,3,4-oxadiazole ring. Lipophilic substituents of the oxadiazole resulted in increased calmodulin (CaM) antagonist property and decreased $Ca2^{+}$antagonistic potency[15].

DUAL INHIBITORS OF CYCLOOXYGENASE AND 5LIPOXYGENASE

Boschelli et al. The replacement of the carboxylic acid with "1,3,4-oxadiazole" heterocycle resulted in the conversion of NSAIDs to inhibitors of COX and 5-LOX[16].

ANTI-INFLAMMATORY

Palaska, E et. al. "3-heterocyclyl-1,2-benoisothiazoles" having 1,3,4-oxadiazole ring system attached at position Third of the "1,2-benzisothiazole" nucleus were evaluated for "Anti-Inflammatory Activity" with standard drug Ibuprofen [17].

ANTIBACTERIAL, ANTIMYCOBACTERIAL AND ANTIFUNGAL ACTIVITIES

Mamolo et al. "5-(pyridine-4yl)-3H-1,3,4-oxadiazol-2-thione and 5-(pyridin-4-yl)-3H1,3,4-oxadiazol-2-one" derivatives, in which the N at the 3- position is linked by a methylene bridge to a cyclic Amine[18].

ANTICONVULSANT ACTIVITY

Zarghi et al. Anticonvulsant Activity of new "2-substituted-5-(2-benzyloxyphenyl)-1,3,4-oxadiazoles" was evaluated[19].

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SPASMOLYTIC AND HYPOTENSIVE ACTIVITY

Mishra et al. reported Spasmolytic Activity and Hypotensive Activity of "2-(substituted acetyl) amino-5-alkyl1,3,4-oxadiazoles"[20].

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