Biological Activities of 2, 5-Disubstituted – 1, 3, 4-Oxadiazoles

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ABSTRACT

The heterocyclic compound has been known for several years and investigations in field have been indentified due to the large no. of uses & application in most diverse area. Heterocyclic compounds has been an interesting area for the study of synthesis and biological activity of novel oxadiazole derivatives for a long time.Oxadiazole are the major compound of heterocyclic nucleus for the development of new drugs and the drugs of oxadiazole were the first effective chemotherapeutic agent to be employed systemically for the prevention & cure of bacterial infection. Oxadiazole have accelerated interest in various field like medicinal chemistry, polymer industry, etc. Literature survey reveals that the compound are well known to have a no. of broad spectrum biological activities like as antibacterial, anti-inflammatory, anticonvulsant, anticancer, anti-tubercular, anti-diabetic, antihelmintic, analgesic etc.Therefore, the synthesis of new 2,5-di-substituted 1,3,4-oxadiazole derivatives that possess a promising biological activity for the future development to get a safer & effective compounds

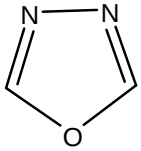
KEYWORDS : Heterocyclic, 1,3,4-oxadiazole and biological activities.

INTRODUCTION

In heterocyclic compounds the rings are not entirely composed of carbon atoms. There may be present one or more hetero atoms in rings. Heterocyclic system in drugs generally have certain substitutions & functionalisation.[1]

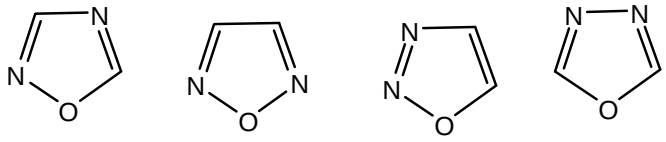
Heterocyclic compounds are those compounds whose ring contain beside carbon, one or more atoms of other element. The non-carbon atoms in such ring are reffered to as hetero atoms. The common hetero atoms are nitrogen, oxygen & sulphur. The important of heterocyclic compounds are present in most of the members of vit- B complex, antibiotics, alkaloids, amino acid, drugs, dyes, enzyme & genetic material DNA and having therapeutics use.[2]

Heterocyclic compounds having five membered rings containing two carbon atom, one oxygen, two nitrogen & two double bond such as oxadiazole.



1,3,4-Oxadiazole

The oxadiazole drug were the first effective chemotherapeutics agents to be employed systemically for the prevention and cure of bacterial infection in human beings. the sequence of these atoms may be different as 1,2,4-oxadiazole (a), 1,2,5-oxadiazole (b), 1,2,3-oxadiazole (c) and 1,3,4-oxadiazol(d).[3]



(a) (b) (c) (d)

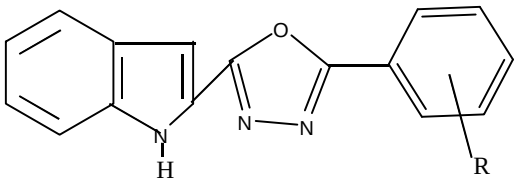
A large no. of drugs used clinically have oxadiazole ring as a structural building block. Literature survey reveals that the derivatives of the 1,3,4-oxadiazoles played an vital role in the medicinal chemistry. the derivative of 1,3,4-oxadiazole with suitable substitution at 2,5-position are becoming an important member in the heterocyclic family not only because of their wide range usages as photosensitive & electrical materials but also because of their broad spectrum in biological activities like as_ Antibacterial, anti-inflammatory, anticonvulsant, anticancer, anti-tubercular, anthelmintic, analgesic, CNS depressant & other activities.[4] A literature summary of biologically active of 1,3,4-oxadiazoles is presented in this review.

BIOLOGICAL ACTIVITIES :

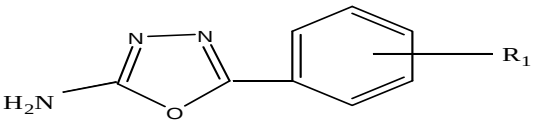
1-Antimicrobial activity

Antimicrobial is an antibacterial agent. These agents are the greatest contribution of the 20th century to therapeutics. Their advent changed the outlook of the physician about the power drugs can have on diseases. Antimicrobial drugs are designed to inhibit or kill the infecting organism & to have no or minimal effect on the recipient. Antibiotic are the substances produced by micro-organism, which suppress the growth of or kill other micro-organism at very low concentration.[5]

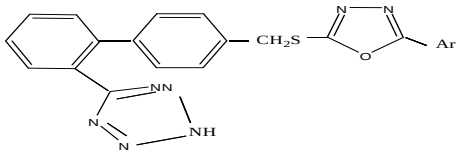
a-2 phenyl 5-indole 1,3,4-oxadiazoles were synthesized & characterized & the study of antimicrobial activity of the compound was evaluated.[6]



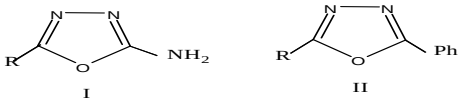
b-A series of 3(1,3,4-oxadiazole-2-yl)quinazolin-4(3H)-ones were synthesized for their in vitro antimicrobial activity. The antimicrobial activity of this compound were examined against gram positive bacteria S. aureus & gram negative bacteria A. Niger using the broth micro-dilution method.[7]



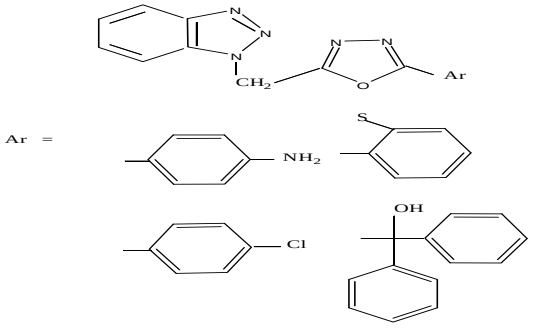
c-The series of several new 5-[4'-(5 phenyl-1,3,4-oxadiazole-2 yl sulfonylmethyl)-biphenyl-2-yl]-tetrazoles derivatives were synthesized & these compound evaluated for their antimicrobial activity against Bacillus subtilis & E. coli at the conc. Of 100ug/mL in N.agar media. These compound showed a better inhibitory of these bacterial growth.[8]



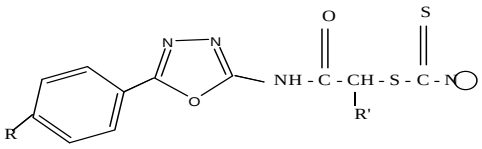
The newly synthesized compounds 5 – (alkenyl -2- amino and 2- (alkenyl) -5 phenyl - 1,3,4- oxadiazoles were screened for their antibacterial activity.The 5-alkenyl-2-amino 1,3,4-oxadiazoles showed antibacterial activity against E. coli & 2 (alkenyl-5 phenyl 1,3,4-oxadiazoles showed activity against all the bacteria such as S. typhi, S. aureus at the conc. of 50 ug/mL & 100 ug/mL in N. agar media as compare with standard antibiotic chloromycetine.[9]



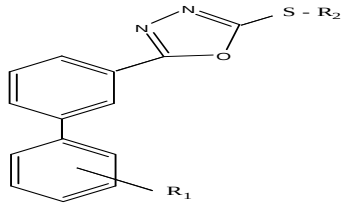
d-The antimicrobial activity has been reported in 2-(substituted)-5-(benzotriazomethyl) 1,3,4-oxadiazole derivatives & these compounds possessing a good anti-fungal activity on agar plate using saboraunds method by cup-plate technique.[10]



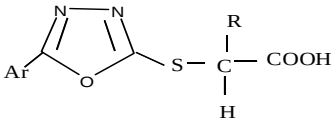
e-A series of novel 5-aryl -2 [N, N- di- substituted thiocarbamoylthio)calamine]-1,3,4-oxadiazole derivatives were synthesized for their antimicrobial activity against various micro-organism such as S. aureus, S. epidermidis using disc diffusion method.[11]



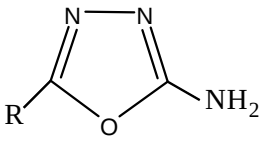
f-A novel series of 5-[substituted –(1,1-biphenyl)-3-yl]-1,3,4-oxadiazole-2 (3H)-thiones & its 5- alkyl derivatives were synthesized for their antimicrobial activity against various bacterial strains namely S. aureus, P.aeruginosa by using cup-plate method & analgesic activity by using Eddy'shot plate method.[12]



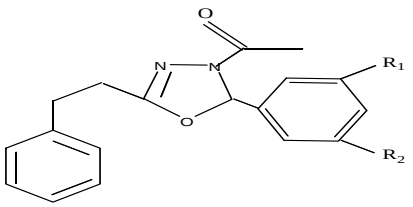
g-The study of some new 2-[5-(aryl)-[1,3,4-oxadiazole-2-yl sulfonyl]alkanoic acid were synthesized & exhibited a good in vitro antibacterial activity and their minimum inhibitory conc. (MIC) were determined.[13]



h-Several derivatives showed better to moderate antimicrobial activity against the gram positive bacteria B.subtilis and gram negative bacteria E. coli & marked antifungal activity against A. niger & C. albicans.The antibacterial & antifungal activities were reported in newly synthesized derivatives of 5- substituted -2-amino-1,3,4-oxadiazole.[14]



i-The study of a new series 1-(2-aryl-5-phenethyl-1,3,4-oxadiazole-3(2H)-yl)ethanones was synthesized & found to exihibit good antibacterial & antifungal activity.These newly synthesized compound were shown the maximum activity against the strains of micro-organism S. aureus, P. aeruginosa. And enhance the activity of synthesized oxadiazoles by concluding the para substitution.[15]

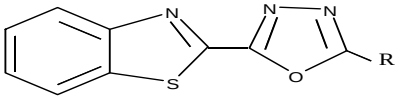


R_1 = H , H, OH, H, H

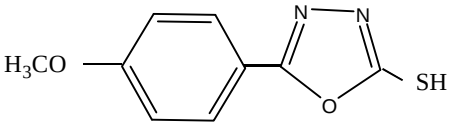
R_2 = $N(CH_3)_2$, Cl, OH, OH, H

j-Antimicrobial activity was reported in some new 2-(5-substituted-1,3,4-oxadiazole-2-yl)-1,3-benzothiazole.Several derivatives exhibited promising in vitro antibacterial activity against bacterial strains such

as B. subtilis, B. pumilus, E. coli, at conc. 100ug/ml by using disc diffusion method as compare with standard antibiotic ciprofloxacin.[16]



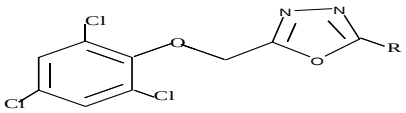
k-Another series of 5-(3,4,5-trimethoxy phenyl)-2-sulphonyl-1,3,4-oxadiazole derivatives were synthesized & screened for their antifungal activity against G.zeae, B.cinerea, S.sclerotiorum using the mycelia growth rat test.[17]



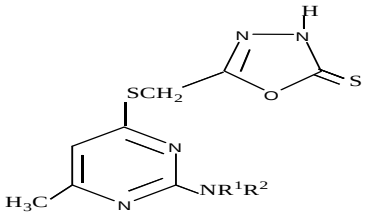
2-Anti-inflammatory activity

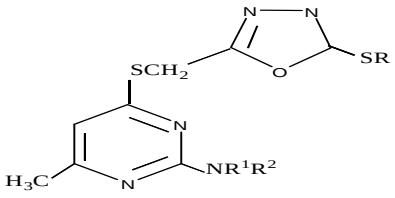
NSAIDS have a clinical use for the prevention & cure of inflammation and pain including musculoskeletal disorders such as rheumatical arithiritis, osteoarthritis etc. all drugs grouped in this class have analgesic, antipyretic, anti-inflammation. These agents are used to relieve swelling, redness, pain and fever associates with inflamed joints is an for long time.[1]NSAIDS agents inhibit the cycloxygenase steps (COX 1 extensively, besides COX 2) thereby preventing the formation of prostaglandin endoperoxidase (PGG_2 & PGH_2) & TXA_2. & other prostaglandins and consequently reducing the sign & symptoms of inflammation.[18]

a. Some new 2-substituted aryl -5- (2,4,6-trichloro phenoxy methyl)- 1,3,4-oxadiazole derivatives were synthesized and evaluated for their in vitro anti-inflammatory activity by using carrageenan induced rat paw edema method.[19]

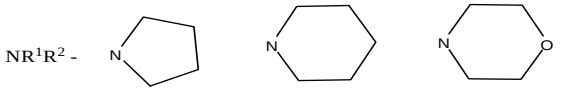


b. A few better example of 1,3,4-oxadiazole derivatives belonging to a series of 5-[(2-disubstitutedamino -6-methyl –pyrimidine-4-yl)-sulfonylmethyl]-3H-1,3,4-oxadiazole-2-thiones were synthesized & these synthesized compound were tested for their anti-inflammatory activity by using the method of carrageenan & bentonite induced paw edema in rats, these compound were found to be much more potent than ibuprofen. Compound (b) showed moderate anti-inflammatory activity.[20]

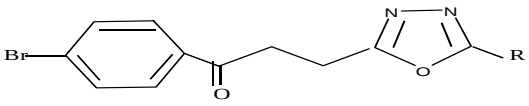




(a) **(b)**

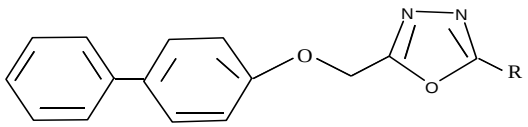


C.A new series of 2-[3-(4-bromophenyl)propane-3-ones]-5-(substituted phenyl)-1,3,4-oxadiazoles were synthesized for their anti-inflammatory activity as compare to the standard drug indomethacin.[21]

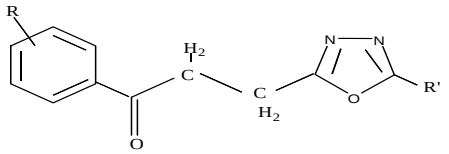


R- C_6H_5 , 2-ClC_6H_4, 4-ClC_6H_4, 2-HOC_6H_4, 4-$NO_2C_6H_4$, 4-FC_6H_4 etc.

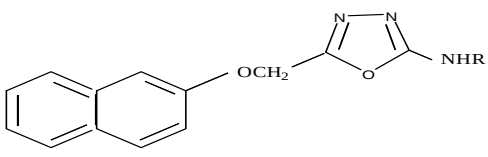
d.Another series of 1,3,4-oxadiazole derivatives of biphenyl-4-yloxy acetic acid were synthesized & screened for their potent anti-inflammatory activity by using carrageenan induced rat paw edema. The lead compound having much more anti-inflammatory activity (81.81%) than the reference drug flurbiprofen (79.54%).[22]



e. potent anti-inflammatory activity has been reported in 2,5 disubstituted-1,3,4-oxadiazoles derivatives based on Aroylpropionic acid.These synthesized compound showed anti-inflammatory activity 81,46% & 81.48% respectively against to the standard drug ibuprofen.[23]

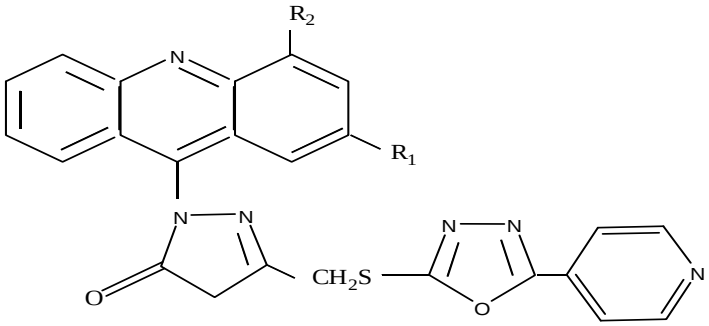


f. A novel series of 2-(2-napthyloxymethyl)-5-substitutedamino-1,3,4-oxadiazole derivatives has been found to possess considerable anti-inflammatory property.[24]



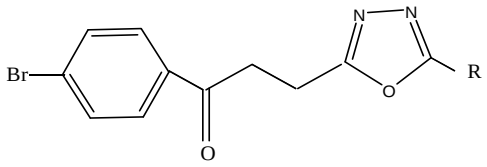
R - CH_3, C_2H_5, C_6H_5, CH_2-CH-CH_2

g. A new series of 1-(2',4'-chloroacridine-9'yl)-3-(5'- pyridine-4-yl)-(1,3,4-oxadiazole-2-yl-thiomethyl)-pyrazole-5-one were synthesized & evaluated for their anti-inflammatory activity as compare with reference drug phenylbutazone & aspirin.[25]

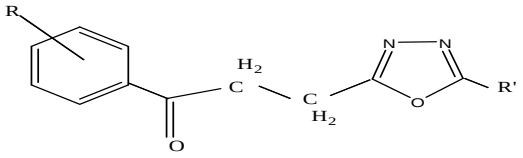


3-Analgesic Activity

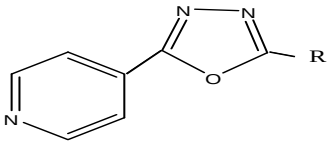
a-Some 2-[3-(4-bromophenyl) propane-3-ones]-5-(substituted phenyl)-1,3,4-oxadiazoles were synthesized with the aim to get a better analgesic activity.The analgesic activity was screened by acetic acid induced writhing method.[26]



b-Aroylpropionic acid based 2,5-di-substituted-1,3,4-oxadiazoles were synthesized & tested for their strong analgesic activity.[27]



c-Some novel 2,5 di-substituted-1,3,4-oxadiazole & their synthetic analogs have been found to possess analgesic activity by using acetic acid induced writhing method as compare to the standard drug diclofenac.[28]

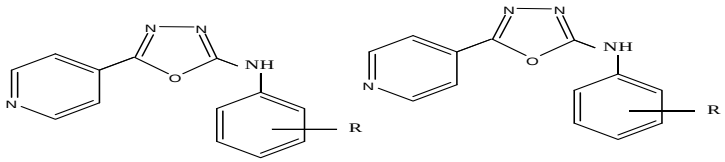


Potent analgesic activity has been reported in 1,3,4-oxadiazole bearing bis(heterocycle) derivatives.[29]

4- Anticonvulsant Activity

Anticonvulsants are agents which selectively depress the CNS. The term epilepsy (seize) is characterized by abnormal & excessive electroencephalographic discharge & a disturbance or loss of consciousness. These agents are used in the prevention & control of epileptic seizures.[18]

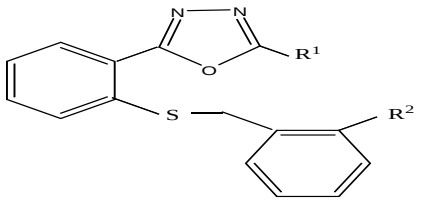
a-Anticonvulsant activity provide protection against convulsion induced by electroconvulsometer.The newly synthesized compounds 2-(4-chlorophenyl)amino-5-(4-pyridyl)-1,3,4-oxadiazole were tested for their anticonvulsant activity by MES (maximal electroshock) method, the range of all compounds showed activity in 33-100%. Compound (a) showed maximal activity & compound (b) showed good activity.[30]



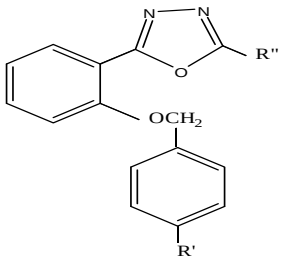
R - H
(a)

R - pCl
(b)

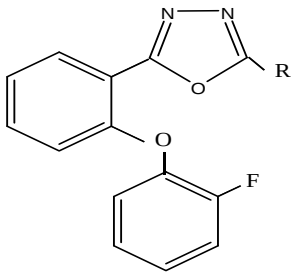
a-some new series of 2-substituted-5-{2-[(2-halobenzyl)thio)phenyl}-1,3,4-oxadiazoles were designed, synthesized and evaluated for their anticonvulsant activity in MES method.The synthesized compounds contains main essentials pharmacophore for binding to the benzodiazepine receptor .[31]



b-Another series of 2-substituted -5-(2-benzyloxyphenyl)-1,3,4-oxadiazole derivatives were synthesized & screened for their potene activity of anticonvulsant.[32]



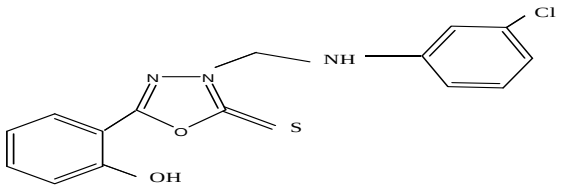
c-A few good example of 2-substituted-5-[2-(2-fluorophenoxy)phenyl]-1,3,4-oxadiazoles & -1,2,4-triazoles were synthesized for their considerable anticonvulsant activity in PTZ & MES model.[33]



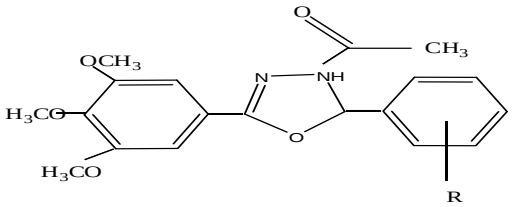
5-Anticancer Activity

Anticancer refers to a group of disease caused by several agents like as chemical compound, radiant energy. Cancer is characterized by an abnormal & uncontrolled division of cell exhibiting varying degree of malignancy which produce tumor & invade adjacent normal tissue. These agents are used for treatment of cancer or either kill cancer cells or modify their growth.[18]

a-The promising anticancer activity of a new series of 5-(2-hydroxyphenyl)-2-substituted -2,3-dihydro-1,3,4-oxadiazole-2-thione derivatives were reported.These compound have been selecte for anticancer testing against a 60-cells panel assay & promising activity against all cancer cells lines. The anticancer activity of these compounds as compare to the reference drugs 5-fluorouracil & cyclophasphamide.[34]



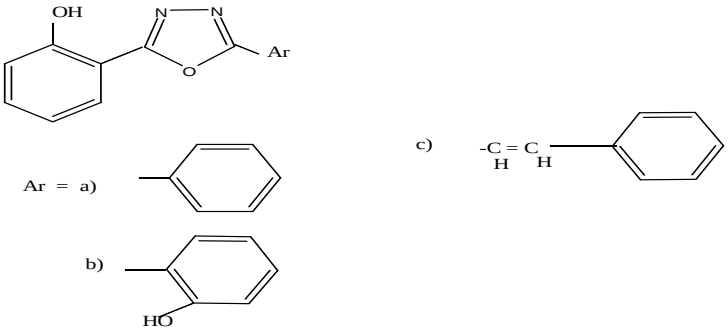
b-The 3-ac etyl-2-substituted phenyl -5-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1,3,4-oxadiazole derivatives were characterized & synthesized & these compound were screened for their in vitro antitumor activities against PC3, BGC823, & Bcap-37 by MTT method.[35]



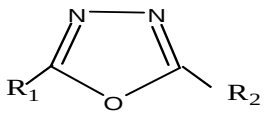
6-Anti-tubercular Activity

Tuberculosis is a chronic granulomatous disease and a major health problem in developing country about 1/3rd of worlds population is infected with mycobacterium tuberculosis. These agents that either kill the growth of mycobacterium tuberculosis[5]

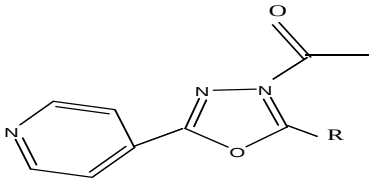
a-Some novel 1,3,4-oxadiazole derivatives & pyrazole derivatives have synthesized & evaluated for their anti-tubercular activity by middle brook 7H9 agar medium against H37Rv strain as compare to the standard drug streptomycine. Compound 1 (a) have shown promising activity and compound 1 (b,c) have shown moderate activity.[36]



b-The in-vitro anti-tubercular activity have been reported in the newly series of 2,5 di-substituted-1,3,4-oxadiazole derivatives.These synthesized compound showed a better activity against a strain of mycobacterium tuberculosis H37Rv.[28]



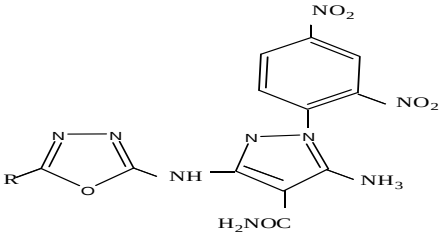
c-Some novel series of 2,5-di-subsitituted 1,3,4-oxadiazoles were synthesized & the newly synthesized compound have been found to exhibit good anti-tubercular activity by using REMA plate method.[37]



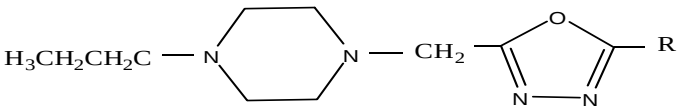
7-Anthelmintic Activity

The parasitic disease constitute a major health hazard world over.[1] anthelmintics are drugs that either kill (vermicide) or expel (vermifuge) infesting helminthes & treat parasitic infection due to flat worm & round worm.[5]

a-The 3-amino-1-(2,4-dinitro phenyl)-5-[(5-substituted-1,3,4-oxadiazole-2 yl)amino]-1-H-pyrazole-4-carboxamide have been synthesized & screened for their anthelmintic activity as compare to the reference drug Albendazole of 0.075%, 0.150%. The synthesized compounds have been shown a better activity against pherituma posthuma.[3]

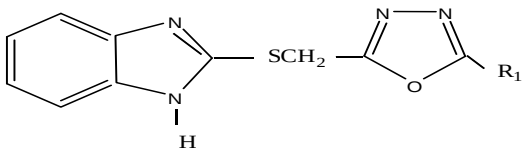


b-A newly synthesized compounds 1-[(5-substituted-1,3,4-oxadiazole-2-yl)methyl]-4-propylpiperazines derivatives was designed and synthesized for their anthelmintic activity.[38]



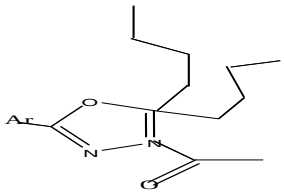
8. Anti-diabetic Activity

a-A group of 1,3,4-oxadiazole containing 2-mercepto benzimidazole moiety were synthesized & tested for anti-diabetic activity using oral glucose tolerance test (OGTT).[39]



9. Mono amino oxidase- inhibitors

a-A novel series of 1,3,4-oxadiazole-3(2H)-carboxamide derivatives were synthesized as potential novel MOA inhibitor



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