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BENZOTRIAZOLE - OXADIAZOLE HYBRIDS AS MEDICINAL AGENTS – THE SIGNIFICANCE IN UNITY IS AN ETERNAL WONDER

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ABSTRACT

Azole is an important class of organic compound having diverse applications in the therapeutic field. Benzotriazole and oxadiazole are two important azole heterocyclic nuclei used in many marketted pharmaceutical formulations such as Vorozole, Alizapride, Raltegravir etc. The aim of the present review work is to conduct a detailed survey on various synthetic strategies for joining these two bioactive nuclei- benzotriazole and oxadiazoleand the pharmacological actions of the hybrid molecules. Hopefully, this review work will be beneficial to develop highly bioactive benzotriazole-oxadiazole hybrid drugs with low toxicity and side effects.

INTRODUCTION

Azole heterocyclic compounds exerts a wide spectrum of therapeutic applications in the treatment of various diseases.[1] Compounds holding a benzotriazole nucleus linked with a heterocyclic system are of broad significance by virtue of their divergent biological activities.[2] Benzotriazole is an important class of heterocyclic compound holding three nitrogen atoms fused with a benzene ring. It is reported to exhibit a wide spectrum of pharmacological activities such as antimicrobial[3-8], antitubercular[9-10], anti-inflammatory, anticonvulsant[11], DNA cleavage[12]& antiviral[13] etc. Oxadiazoles are the heterocyclic compounds containing one oxygen and two nitrogen atoms in a five membered ring.

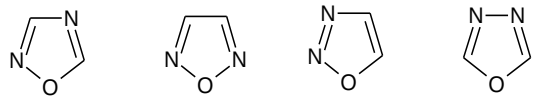
It possess a wide variety of pharmacological activities such as antimicrobial[14,15,19,24], antimycobacterial[16-17], Anti-inflammatory18-20,[27], analgesic[20], anticonvulsant[21], antiproliferative[22-23], antiprotozoal[24], antidiabetic[25], anthelmintic[26-27], antiallergic[28], enzyme inhibitor[29-30], anticancer[30-31], CNS depressant[32] etc. Benzotriazole moiety attached to an oxadiazole ring is reported to possess anticonvulsant[33],antimicrobial[33-36], antifungal[37], anticancer[38-39], antitubercular[40]activities etc. Thus by combining these two heterocyclic nucleuses, novel heterocycles which are more biologically active than individual nucleus containing compounds have been developed.

CHEMISTRY

Benzotriazole nucleus holds a larger conjugated system to form π-π stacking interactions, and the three nitrogen atoms makes it easy to form hydrogen bonds and coordination bonds. As a result, the benzotriazole derivatives readily binds with a variety of enzymes and receptors in biological system via diverse non-covalent interactions & results in a broad spectrum of biological activities.[1] Benzotriazole (C_6HN_3) is a nitrogen heterocycle derivative containing three nitrogen atoms, each with an unshared lone pair of electrons, forming a five-membered ring that can exist in the following tautomeric form.[41]

I II

Oxadiazoles are heterocyclic compounds containing one oxygen and two nitrogen atom in a five membered ring. The sequence of these atoms may be different .i.e. 1,2,4-oxadiazole(a), 1,2,5-oxadiazole(b), 1,2,3-oxadiazole(c) and 1,3,4-oxadiazole(d).



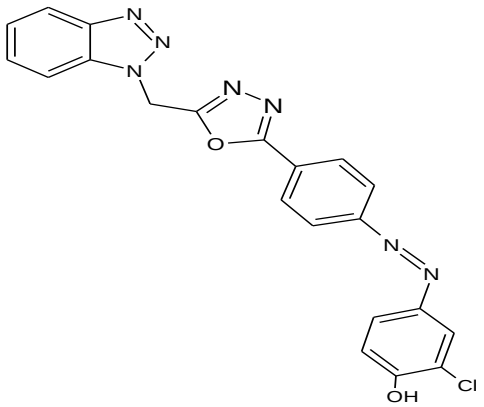
(a) (b) (c) (d)

This molecule exhibits least drug resistance when the nucleus has been properly substituted at second and fifth position.[40]

SYNTHETIC ROUTES AND BIOLOGICAL ACTIVITIES

Benzotriazole-oxadiazole hybrids are generally prepared by esterifying benzotriazole(1) with ethylchloroacetate to produce ethyl-1,2,3-benzotriazol-1-ylacetate(2), followed by conversion into 1,2,3-benzotriazol-1-ylacetohydrazide(3) by treating with hydrazine hydrate in presence of ethanol. Cyclisation of hydrazide to oxadiazole ring can be achieved by various routes giving rise to a number of benzotriazole-oxadiazole hybrid derivatives with various biological activities.[33-34,37-40](scheme 1)

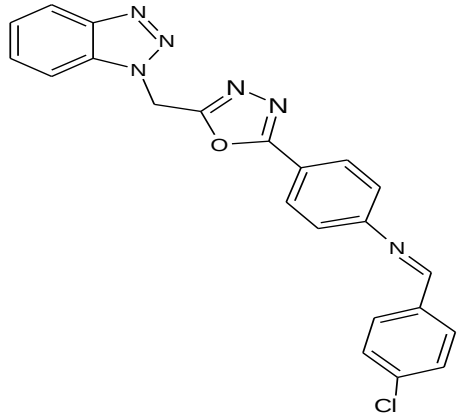
1,2,3-benzotriazol-1-ylacetohydrazide(3) when refluxed with p-amino benzoic acid in the presence of phosphorus oxy chloride yields 5-(benzotriazole-1-yl-methyl)-1,3,4-oxadiazole-2yl)benzenamine(4). From this a series of novel 5-(Benzotriazole-1-ylmethyl)-2-Phenyl-1,3,4-oxadiazole azo compounds(4a) were synthesised by treating it with sodium nitrite & Hydrochloric acid in the presence of a suitable coupling reagent. Among these compounds, 4-(5((1h-benzo[d][1,2,3]triazol-1-yl)methyl)-1,3,4oxadiazol-2yl)-N-phenzyl)diazenyl)2-chlorophenol was found to possess potent antimicrobial activity due to the presence of electron withdrawing group as a part of the molecule.[34]



4-(5((1h-benzo[d][1,2,3]triazol-1-yl)methyl)-1,3,4oxadiazol-2yl)-N-phenzyl)diazenyl)2-chlorophenol

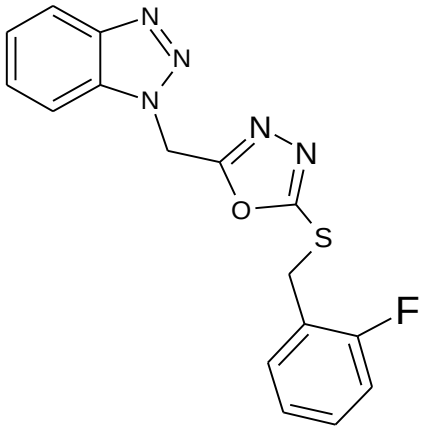
Preparation of various benzotriazole schiff bases(4b) can be achieved by refluxing different aromatic aldehyde with compound (4). Among them, 4-(5((1h-benzo[d][1,2,3]triazol-1-yl)methyl)-1,3,4-oxadiazol-2-yl)-n-(4-chlorobenzylidene)phenylimino)methyl)phenol showed excellent anti-microbial activities through its zone of inhibition (mm) against *E. coli, S.aureus, B. subtilis, P. vulgaris, C. albicans and A. niger* and

offered 82.15% of protection against pentylenetetrazole induced convulsion effect.[33]



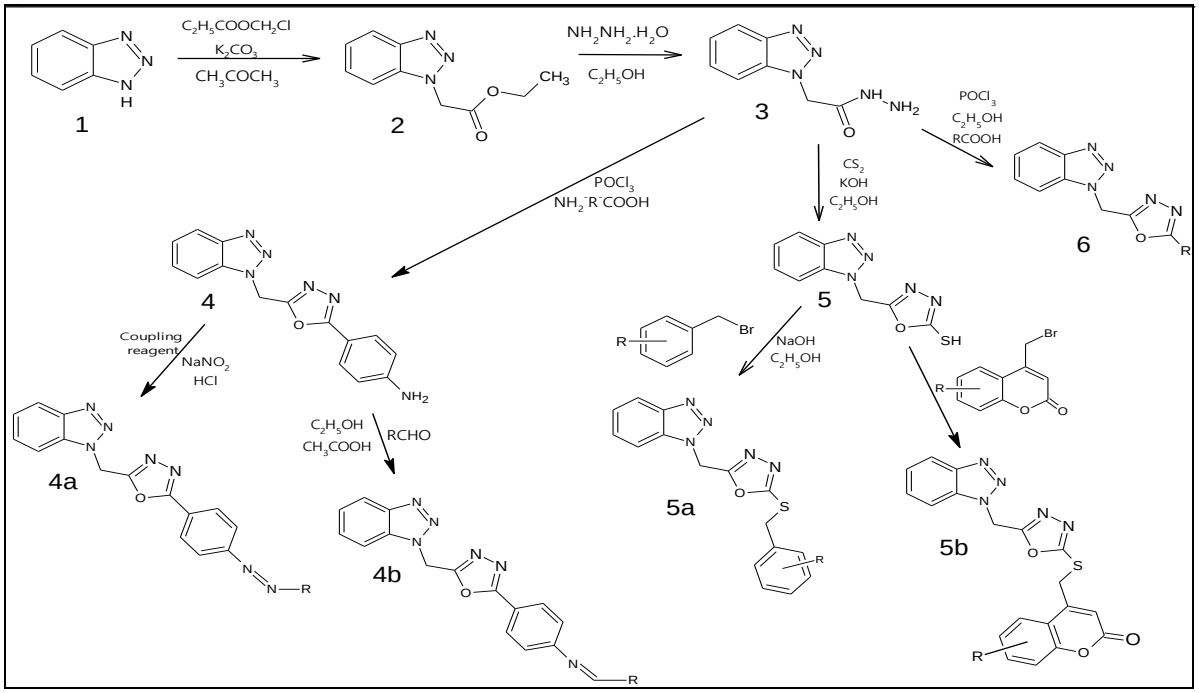
4-(5((1h-benzo[d][1,2,3]triazol-1-yl)methyl)-1,3,4-oxadiazol-2-yl)-n-(4-chlorobenzylidene)phenylimino)methyl)phenol

5-[(1H-benzotriazol-1-yl)methyl]-1,3,4-oxadiazole-2-thiol (5) was prepared by refluxing ethanolic solution of compound (3) with Carbondisulphide in presence of Potassium carbonate. From this, a series of halogen substituted 1-{[5-(benzylsulfanyl)-1,3,4-oxadiazol-2-yl]methyl}-1H-benzotriazole derivatives(5a) were prepared by refluxing with halogen substituted benzyl bromide in the presence of sodium hydroxide in anhydrous ethanol and investigated the anticancer activity. The bioactivity assay results showed that out of the nineteen derivatives synthesised, 2-((1H-benzo[d][1,2,3]triazol-1-yl)methyl)-5-(2-fluorobenzylthio)-1,3,4-oxadiazole exhibited the most potent inhibitory activity for Focal adhesion kinase(FAK) and good activity against human breast cancer cell MCF-7than other compounds.[38]



2-((1H-benzo[d][1,2,3]triazol-1-yl)methyl)-5-(2-fluorobenzylthio)-1,3,4- oxadiazole

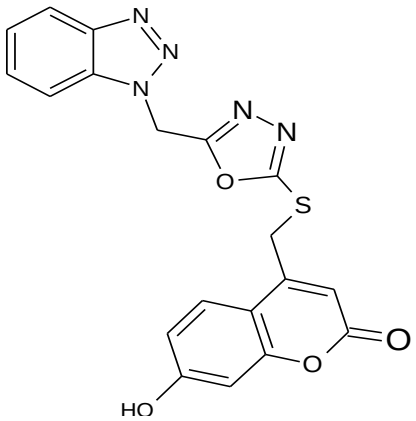
(Scheme 1)



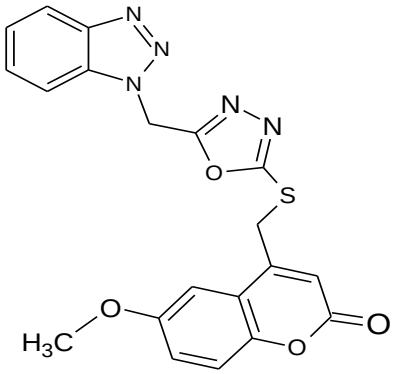
Structure-activity relationship (SAR) studies revealed that compounds with electron-withdrawing group showed stronger activity than those with electron-donating group. The potency order was F (fluorine) > Cl (chlorine) > Br (bromine) > NO_2 (nitro-group) > OCH_3 (methoxy group) > CH_3 (methyl).When the substituent is methoxy group, the potency order is ortho > meta > para.[38]

5-((1H-benzo[d][1,2,3]triazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiol-tethered substituted 4-(bromomethyl)-7-methyl-2H-chromen-2-one derivatives (5b) were synthesised from compound (5) under three different reaction conditions.

- Reaction Condition A
  Solution of Sodium metal in absolute ethanol refluxed with compound (5) and substituted 4-bromo methyl coumarins for 18-24 h.
- Reaction Condition B
  Solution of compound (5) in absolute ethanol stirred with dried K_2CO_3 for 1 h, followed by addition of substituted 4-bromo methyl coumarins and refluxed for 18-24 h.
- Reaction Condition C
  Compound (5), N,N-Diisopropylethylamine and substituted 4-bromo methyl coumarins were mixed in acetone : dichloromethane(DCM) (80:20) solvent in round bottom flask and stirred at room temperature for 30-36 h under nitrogen atmosphere.



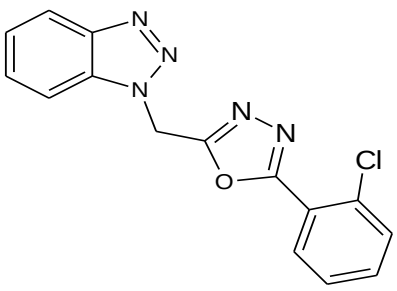
4-((5-((1H-benzo[d][1,2,3]triazol-1-yl)methyl)-1,3,4-oxadiazol-2-ylthio)methyl)7-hydroxy-2H-chromen-2-one



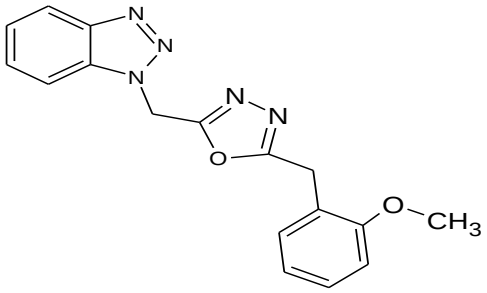
4-((5-((1H-benzo[d][1,2,3]triazol-1-yl)methyl)-1,3,4-oxadiazol-2-ylthio)methyl)6-methoxy-2H-chromen-2-one

Among these reaction conditions, use of diisopropylethylamine (DIPEA) was found to be more efficient when compared to other conditions (i.e.reaction condition C). Anti - Tubercular activity of these new Coumarin-Benzotriazole Hybrids were investigated against the Mtb H37Rv strain using Alamar Blue assay.Among the 14 novel oxadiazole-coumarin-triazole derivatives, 4-((5-((1H-benzo[d][1,2,3]triazol-1-yl)methyl)-1,3,4-oxadiazol-2-ylthio)methyl)7-hydroxy-2H-chromen-2-one and 4-((5-((1H-benzo[d][1,2,3]triazol-1-yl)methyl)-1,3,4-oxadiazol-2-ylthio)methyl)6-methoxy-2H-chromen-2-one displayed good antimycobacterial activity towards M. tuberculosis with an MIC value of 15.5 µM.[40]

Compound 3 when treated with different aromatic carboxylic acids in the presence of phosphoryl chloride yields various 2-(substituted)-5-(benzotriazomethyl)-1,3,4-oxadiazole derivatives (6). Out of the synthesised derivatives, 5-(Benzotriazole-1-yl-methyl)-2-(2-chloro phenyl)-1,3,4-oxadiazole shows most potent antifungal activity & 2-((1H-Benzo[d]1,2,3]triazol-1-yl)methyl)-5-(2methoxybenzyl)-1,3,4-oxadiazole displayed the most potent antitumor activity against HeLa cells.[37,39]



5-(Benzotriazole-1-yl-methyl)-2-(2-chloro phenyl)-1,3,4-oxadiazole

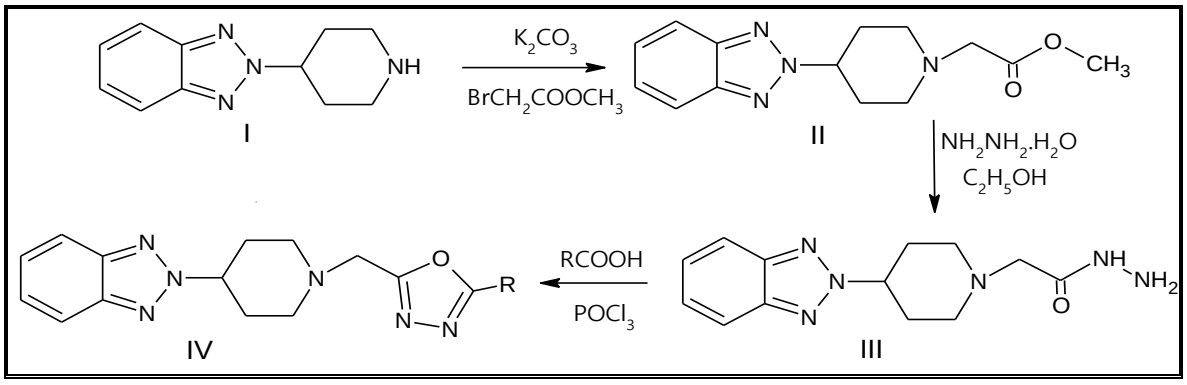


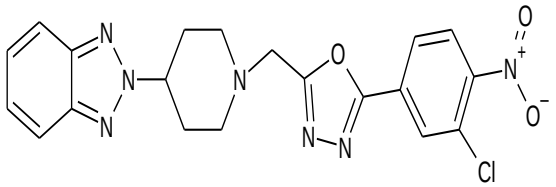
2-((1H-Benzo[d]1,2,3]triazol-1-yl)methyl)-5-(2methoxybenzyl)-1,3,4-oxadiazole

A series of 2-((4-(2Hbenzo[d] [1,2,3] triazol-2-yl) piperidin-1-yl)methyl)-5substituted phenyl-1,3,4-oxadiazoles(IV) were synthesized by esterification of 4-benzotriazol-2-yl-piperidine (I) with methylbromoacetate followed by hydrazination & cyclization with aromatic carboxylic acid in the presence of Phosphorus oxychloride (scheme 2) & antimicrobial activity was evaluated.[36]

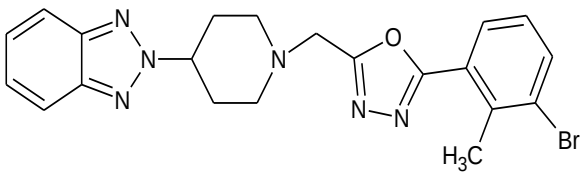
The compound with 3-chloro,4 nitro phenyl and 3-bromo-2-methyl phenyl substituents i.e. 2-(1-((5-(3-Chloro-4-nitrophenyl)-1,3,4-oxadiazol-2yl)methyl)piperidin-4-yl)2H-benzo[d] [1,2,3] triazole & 2-(1-((5-(3-Bromo-2-methylphenyl)-1,3,4-oxadiazol-2yl)methyl)piperidin-4-yl)2H-benzo[d] [1,2,3] triazole exhibited higher activity against *E. coli* & *K. pneumonia*. The compound with 3,5-ditert-butyl hydrophobic substituent .i.e. 2-(1-((5-(3, 5-Di-tert-butylphenyl)-1,3,4-oxadiazol-2yl)methyl)piperidin-4-yl)2H-benzo[d] [1,2,3] triazole showed highest activity than standard drug itrazole against the fungi.[36]

(Scheme 2)

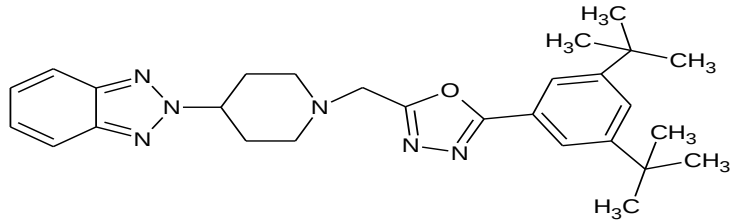




2-(1-((5-(3-Chloro-4-nitrophenyl)-1,3,4-oxadiazol-2yl)methyl)piperidin-4-yl)2H-benzo[d] [1,2,3] triazole



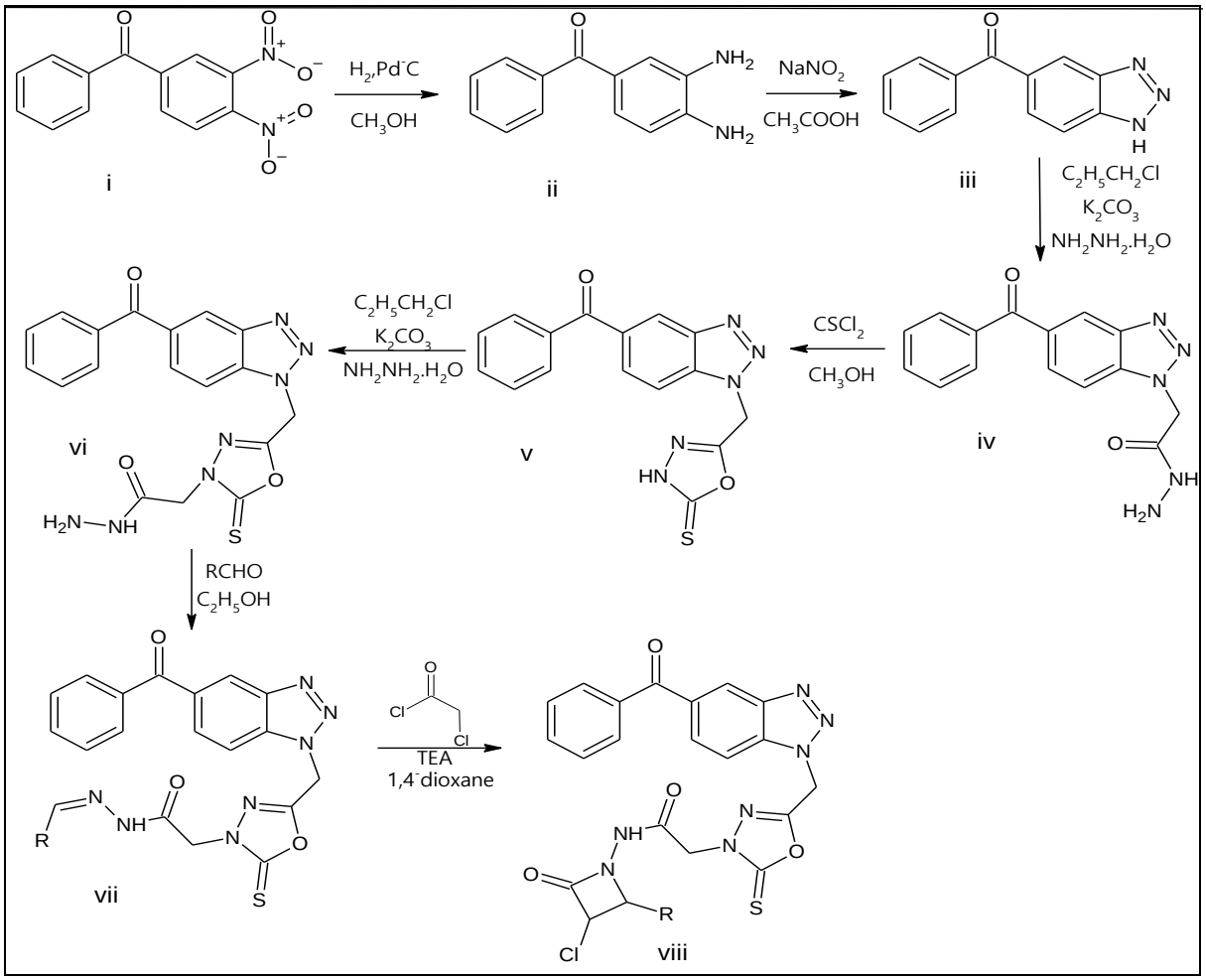
2-(1-((5-(3-Bromo-2-methylphenyl)-1,3,4-oxadiazol-2yl)methyl)piperidin-4-yl)2H-benzo[d] [1,2,3] triazole

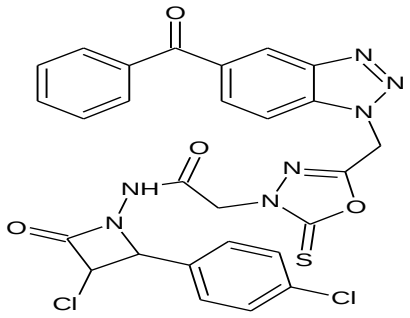


2-(1-((5-(3, 5-Di-tert-butylphenyl)-1,3,4-oxadiazol-2yl)methyl)piperidin-4-yl)2H-benzo[d] [1,2,3] triazole

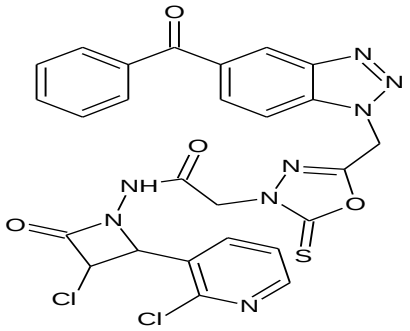
A series of heterocyclic derivatives containing azetidinone, benzotriazole & 1,3,4-oxadiazole (viii) were synthesised(scheme 3) and evaluated for antibacterial activity. Out of the 14 derivatives synthesised, 2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)N-(3-chloro-2-(4-chlorophenyl)-4-oxoazetidin1-yl)acetamide , 2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)yl)-N-(3-chloro-2-(2-chloropyridin-4-yl)-4oxoazetidin-1-yl)acetamide & 2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)yl)-N-(2-(2-bromopyridin-4-yl)-3-chloro-4oxoazetidin-1-yl)acetamide exhibited potent antibacterial activity against gram positive and gram-negative bacteria.[35]

(Scheme 3)

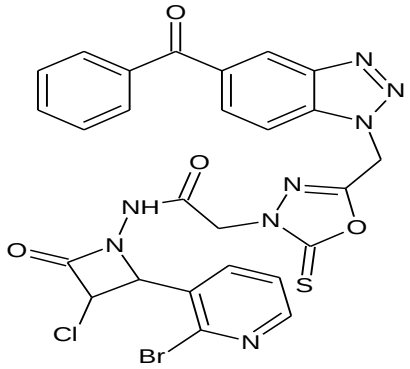




2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)N-(3-chloro-2-(4-chlorophenyl)-4-oxoazetidin1-yl)acetamide



2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)yl)-N-(3-chloro-2-(2-chloropyridin-4-yl)-4oxoazetidin-1-yl)acetamide



2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)yl)-N-(2-(2-bromopyridin-4-yl)-3-chloro-4oxoazetidin-1-yl)acetamide

CONCLUSION

Benzotriazole & oxadiazole nucleus individually has a very high therapeutic effect in the medicinal field. The electron-rich benzotriazole ring is an attractive molecular skeleton, which can be employed to combine with other bioactive fragments to afford more active compounds with remarkable physicochemical properties. Thus, benzotriazole- oxadiazole hybrids are promising drug molecules with wide spectrum of pharmacological activities such as anticancer, antimycobacterial, antimicrobial, anti-inflammatory, anticonvulsant activities etc. In the future, benzotriazole-oxadiazole hybrid molecules can be expected to appear as active pharmaceutical agent in marketed formulations.

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