ABSTRACT

The thesis entitled***"Synthesis of Substituted heterocyclic ring systems ß-hydroxy 1,2,3-triazoles, pyrrolo[1,2-a]quinoxalines, 3,5-disubstituted 1,2,4-thiadiazoles and1,2-benzisoxazole based hybrid molecules "***has been divided into four chapters.

Chapter I: Multicomponent click chemistry approach to Functionalized β-hydroxy 1, 2, 3-triazoles

ChapterII: Expeditious Synthesis of 1-methylpyrrolo [1, 2-*a*] quinoxalines via SP^3-CH activation

Chapter III: Practical approach for the Synthesis of 3,5-diaryl-1,2,4- Thiadiazoles

Chapter IV: This chapter further divided into **two** sections:

Section A: Synthesis and biological evaluation of novel 1, 2-benzisoxazoles derived Triazole hybrids.

Section B: Synthesis and biological evaluation of novel 1, 2-benzisoxazoles derived isoxazole hybrids

CHAPTER-1: Multi-component Click chemistry approach to Functionalized β-hydroxy 1, 2, 3-triazoles via heterogeneous catalysis.

The term ***Click chemistry*** introduced by Sharpless and co-workers is a newer approach to the synthesis of drug-like molecules that can accelerate the drug discovery process by utilizing a few practical and reliable reactions. The Click reaction has wide scope and is easy to perform, uses only readily available reagents and is insensitive towards oxygen and water. Nowadays this concept has found wide use in drug discovery processes and biochemistry. Of the reactions comprising Click chemistry, the perfect example is the Huisgen1,3-dipolar cycloadditionof alkynes to azides to form 1,4-disubstituted-1,2,3-triazoles. The copper (I) catalyzed reaction is mild and very efficient. The azide and alkyne functional groups are largely inert towards biological molecules and aqueous environments which allows the use of Huisgen1,3-dipolar cycloaddition in target guided synthesis and activity based protein profiling. The products of the reactions, 1,2,3-triazoles have similarities to the ubiquitous amide moiety found in nature, but unlike amides, is not susceptible to cleavage. Additionally, they are nearly impossible to be oxidized or reduced. Thus they have been widely used as synthetic intermediates and in industrial applications, such as dyes, anti corrosive agents, photo stabilizers, photographic materials and agrochemicals.

1,2,3-triazole structural scaffold exhibits interesting biological properties such as antifungal, antibacterial, antiviral, antiepileptic, and anti-allergic activities. In particular, 1,4-disubstituted-1,2,3-triazoles can be used to selectively open calcium channels in cells, to regulate plant growth and to inhibit enzymes, as well as exhibit significant antiproliferative action against a various human cancer cell lines. *β-hydroxy* 1,2,3-triazoles ring systems are present in peptide surrogates of HIV-1 protease inhibitors AB_2, AB_3 (Figure-7) and also useful in drugs and pharmaceuticals.

Heterogeneous catalyst:The major limitations of existing procedures can be realized as handling of unstable, toxic organic azides and using homogeneous catalysts which cannot be separated easily from the reaction system. In view of this, it is desirable to use *heterogeneous catalysts*, which have several advantages, such as faster and simpler isolation of the catalyst from reaction products by filtration, as well as easy recovery and recyclability. For this reason, immobilization

of transition metals on various supports such as alumina, Amberlyst and zeolites as well as copper nanoparticles on charcoal have generated remarkable attention because of their green and efficient roles in catalyzed reactions. A number of chitosan-supported metal complexes such as CS-supported Pdcatalyst , CS-supported Cu catalyst , CS-supported Rh catalyst and CS-supported Ti catalyst, have been reported recently.

We have developed a new protocol by using Chitosan supported, recyclable, and inexpensive copper catalyst for the construction of functionalized β-hydroxy 1,2,3-triazoles. This heterogeneous catalyst is easily recoverable and reused several times.

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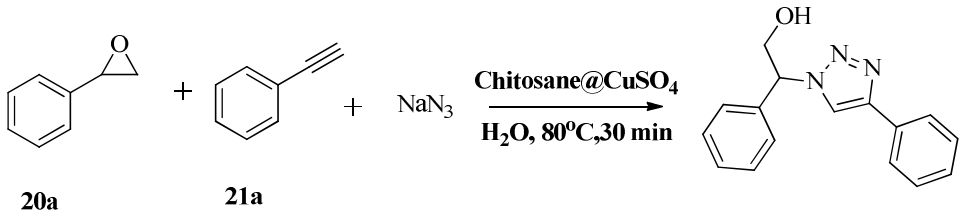

Major advantage of the catalyst is reusability, recyclability and easily isolated, which make them green catalysts especially considering from an environmental point of view. Along with known examples we synthesized functionalized β-hydroxy 1,2,3-triazoles in following path.

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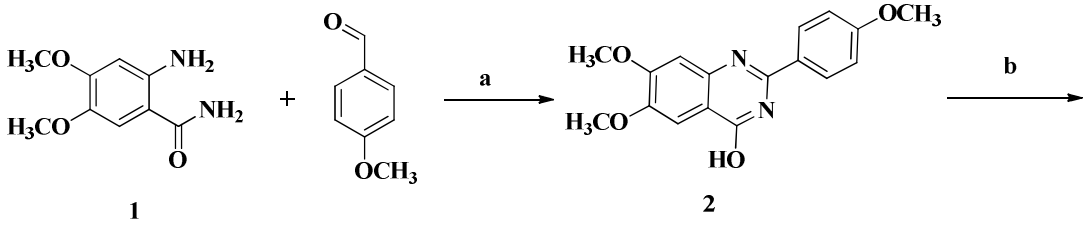

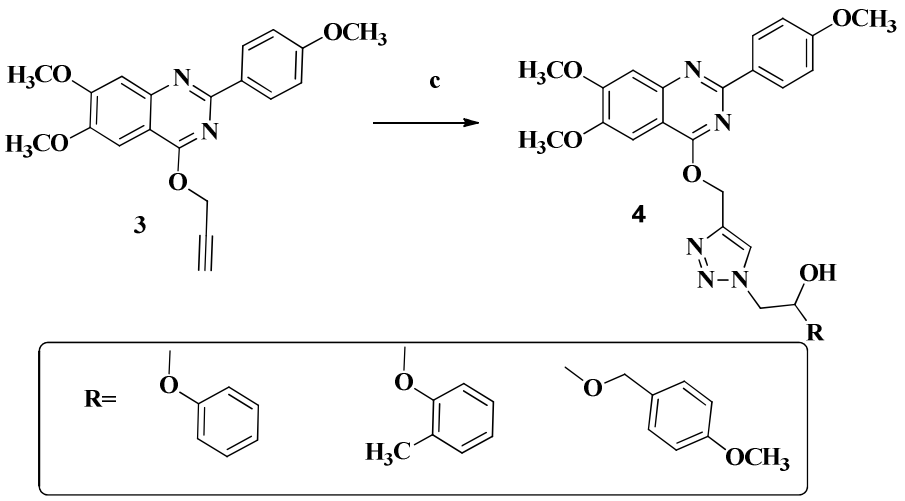

Reagents and conditions: a) $NaHSO_3$, DMA, 150°C, 12 h; b)Propargyl bromide/ K_2CO_3, r.t, 12 h; c) epoxide, NaN_3, CS@$CuSO_4$,80°C,3 h.

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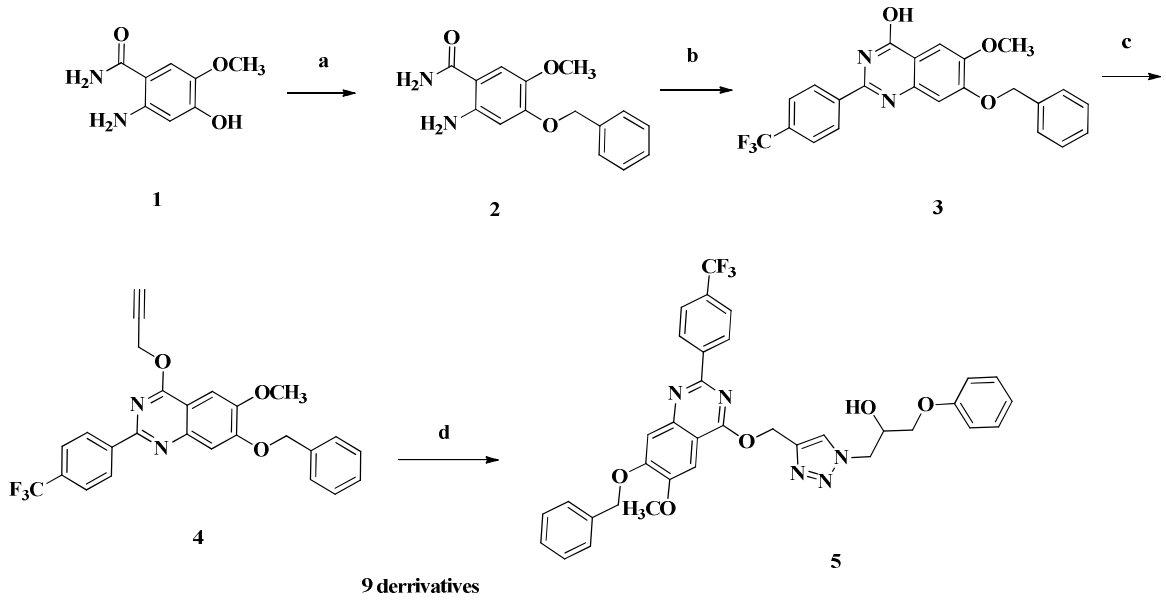


Reagents and conditions: a) BnCl, K_2CO_3,Acetone; b) $NaHSO_3$, DMA, 150°C, 12 h; c)Propargyl bromide/ K_2CO_3, r.t; 12 h; d) 2-(phenoxymethyl)oxirane, NaN_3, CS@$CuSO_4$, 80°C, 3 h.

CHAPTER-2:Expeditious synthesis of pyrrolo [1, 2-*a*] quinoxalines via Dehydrogenativeintramolecular cyclization of Sp^3 C-H activation

Nitrogen-containing heterocycles are widely found in natural products and biologically active molecules.Among the various classes of heterocyclic compounds, ***Quinoxalines*** are a class of N-containing heterocycles, form an important component of many pharmacologically active compounds.So due to diversity in biological activity, it attracts the researchers to find out more its biological activity. Quinoxalines constitute an important group of heterocyclic compounds with basic skeleton **1**, (Figure-1) in which benzene ring is condensed with pyrazine ring also called as benzopyrazine, is a weekly basic compound. Quinoxalines are also termed as benzopyrazines and 1,4-diazanaphthalenes. These can be conveniently classified into natural and synthetic Quinoxalines.

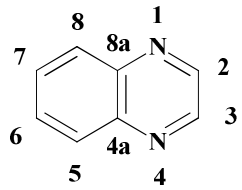
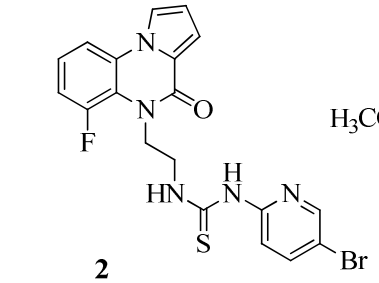
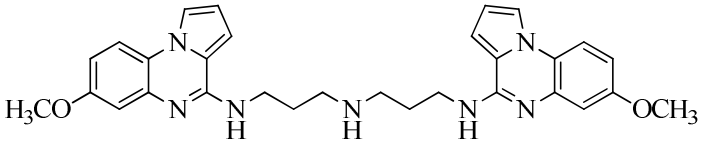


Figure-1

Pyrrolo [1,2-*a*]quinoxalines are an important quinoxaline derivatives, which are conjugated tricyclic ring systems and exhibiting various biological activity such as antimicrobial, anti-HIV agents, antimalarial agents and anticancer agents.



2
Anti-HIV agents



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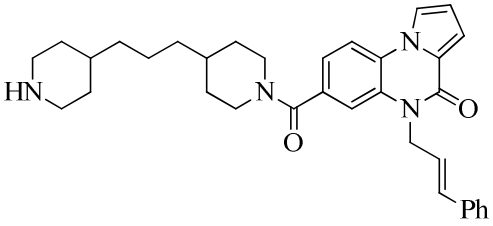
Antimalarial agents



4
Anticancer agents

we have developed a highly efficient synthesis of novel pyrrolo (1,2-*a*)quinoxalines from different functionalized N-arylpyrroles (2-(2,5-dimethyl-1*H*-pyrrol-1-yl)benzenamines)via transition metal catalyzed intramolecular SP^3 C-H activation by 2,3-dichloro, 5,6-dicyano-1,4-benzoquinone(DDQ).

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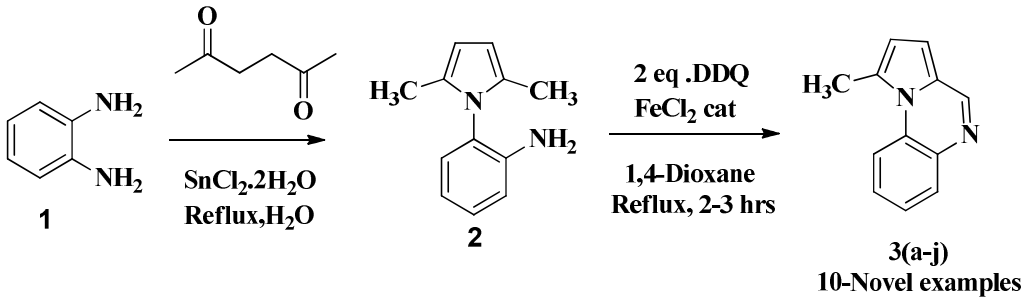
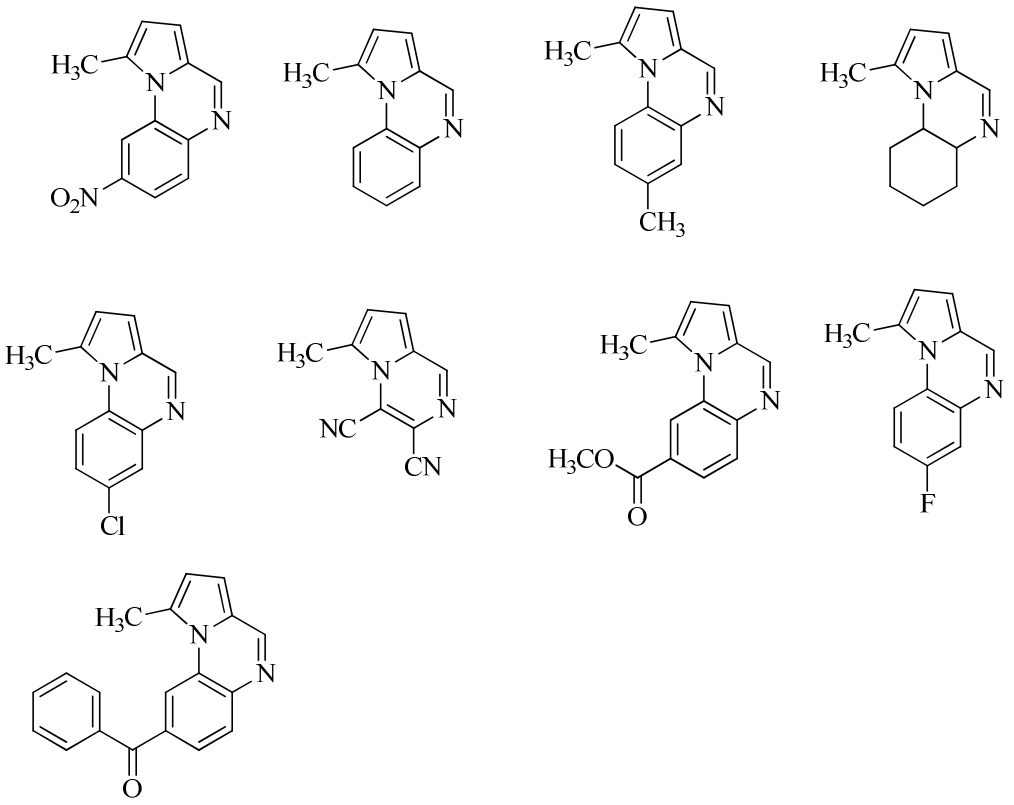


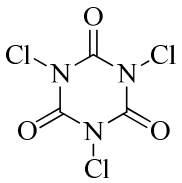


To explore the scope of this methodologyunder the optimized conditions various N-Aryl Pyrroles were converted to 1-methylpyrrolo [1, 2-*a*] quinoxalines and isolated yields up to 75 to 89%.

Pyrrolo [1, 2-*a*] quinoxaline derivatives described above have been evaluated for their antimicrobial and anti-*candida* activity in vitro against different microbial and *candida* strains and the data illustrated that some of these compounds showed good antifungal effects with minimum inhibitory concentration (MIC).The excellent growth inhibitory effects of compound **20c**against Candida albicans MTCC 3017 prompted us to further test this compound against thirteen more fungal strains andthe results are shown in Table 3. As evident from the results, the compound **20c** showed excellent to good antifungal activitywith effective MIC values ranging between 2.34 to37.5μg mL^{-1}

CHAPTER-3:Practical approach for the synthesis of 3,5-diary 1,2,4-thiadiazole via oxidative dimerization.

The Thiadiazole ring systems are a class of heterocyclic five-membered organic compounds containing two nitrogen atoms and a sulfur atom. Currently,Cefozopran is the commercial available drug containing 1,2,4-thiadiazole ring, along with this number of synthetic products related to this system with a broad range of biological activities, such that anti-inflammatory, cardiovascular and antibiotic activity.Thiadiazolesarean important precursorfor the synthesis of many bioactive molecules belonging to various therapeutic categories, such asanti-microbial agents,fungicideand herbicides. Here we reported an inexpensive and eco-friendly preparative protocol for the highly efficient synthesis of structurally diverse 3,5-diaryl-1,2,4-thiadiazoles from primary thioamides at room temperature water used as a solvent. In this transformation Trichloroisocyanuric acid (TCCA) is an effective promoter of oxidative dimerization of thioamides to yield 3,5-disubstituted 1,2,4-thiadiazoles , it is inexpensive and widely available.



Trichloroisocyanuric acid

In recent years, Trichloroisocyanuric acid (1,3,5-triazinane-2,4,6-trione, TCCA) is used widely as an industrial disinfectant, bleaching agent, and innocuous oxidant with high stability. Herein, we reported an efficient and practical method by employing TCCA-Water as a new promoter system for the one pot synthesis of 3,5-diaryl, 1,2,4-thiadiazoles. Water plays an essential role in life processes; however its use as a solvent has been limited in organic synthesis. Water is an abundant, inexpensive and environmentally friendly solvent but also exhibit new reactivity and selectivity, which is different from conventional solvents. The use of water as a medium for organic reactions is one of the latest challenges for modern organic chemist.

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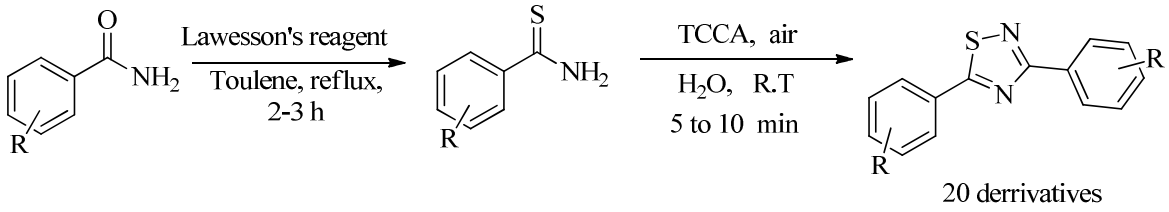
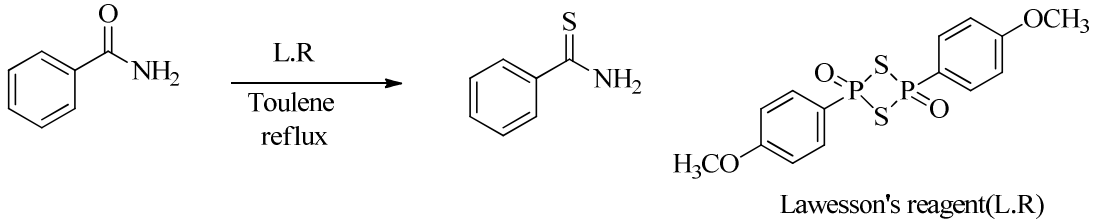


Based on the literature reports, we proposed that a tentative mechanism for the condensation of the aryl thioamidesto give 3,5-disubstituted 1,2,4-thiadiazoles via nucleophilic attack by sulfur of another molecule of thioamide gives a intermediate, which on further oxidation obtained the product.Each TCCA molecule releases three chloride ions so that 0.3 eq is enough to convert 1 equiv. of thioamide into product. After completion of the total reaction Cyanuricacid formed as a side product and it reconvert to Trichloroisocyanuric acid by passing chlorine gas in presence of base.

Preparation of benzothioamide:



CHAPTER-4:

Section-A: Synthesis and biological evaluation of Novel 1, 2-benzisoxazole derived 1, 2, 3-triazole.

Hybrid molecules:

One of the main goals of the organic synthesis from its very inception has been search for new compounds that exhibit novel physical, chemical and biological properties.[1] in this quest

human intuition and leads from nature have played a pivotal role. Nature makes natural products of bewildering diversity and complexity and these are generally derived through specific biosynthetic pathways like shikimate, polyketide or mevalonate leading to a particular class of compounds.[2]Many biologically active natural products are also derived through mixed biological synthesis. This may involve either integration of the different biosynthetic pathways to generate complex, enmeshed structures or eventuate in straightforward covalent linkage between components derived through pathways.

Benzisoxazole are an important class of organic compounds of medicinal significance due to their recognized biological and therapeutic activities. As such these heterocycles constitute key structural units that exhibit a wide range of biological properties such as typical antipsychotics (Risperidone), anticonvulsant (Zonisamide) and anticancer prodrugs.

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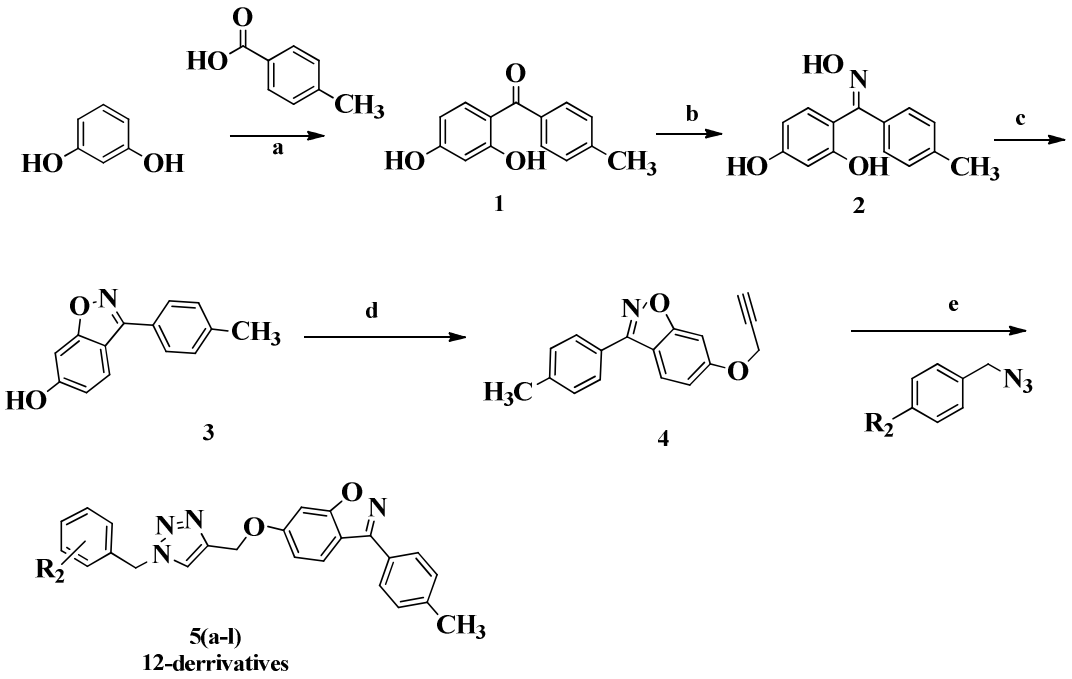

Reagents and conditions: a) BF_3-OEt_2, 95°C, 2 h; b) NH_2OH. HCl, NaOAC, EtOH/H_2O, 2h, reflux; c) Diethylazodicarboxylate, PPh_3, THF, RT; d) Propargylbromide, K_2CO_3, Acetone, RT, 12 h; e) $CuSO_4.5H_2O$, Sodium ascorbate, t-BuOH/H_2O, 28°C.

The construction of new analogues of heterocyclic compounds represents a major challenge in synthetic organic and medicinal chemistry. Due totheir broad spectrum of biological

interest, we have prepared novel benzisoxazole-triazole hybrids and evaluated for antifungal activity, and some of the hybrids showed effective anti fungal activity towards the wide range of *candida*strains.

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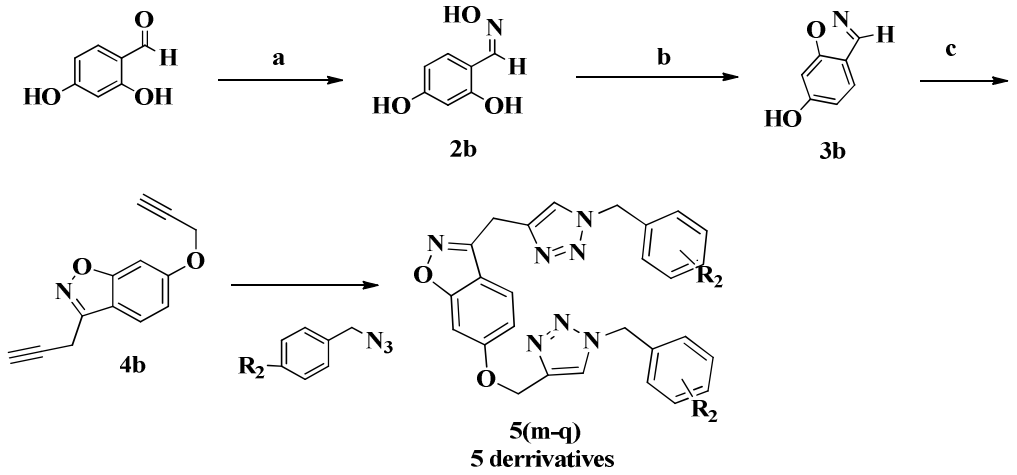

Reagents and conditions: a) NH_2OH. HCl, NaOAC, $EtOH/H_2O$, 2h, reflux; b) Diethylazodicarboxylate, PPh_3, THF, r.t; c) Propargylbromide, K_2CO_3, acetone, r.t, 12 h; d) $CuSO_4.5H_2O$, Sodium ascorbate, t-$BuOH/H_2O$, 28 ^oC

Section-B:Synthesis and biological evaluation of novel 1, 2-benzisoxazoles derived isoxazole hybrids

Isoxazole are an important class of five membered heterocyclic compound containing oxygen and nitrogen atoms in the 1, 2 positions, which are largely employed in the area of pharmaceuticals and therapeutics such as insecticidal, antibacterial, antibiotic, antitumour, antifungal, antituberculosis, anticancer and ulcerogenic.Due to their broad spectrum of biological interest, we have prepared novel benzisoxazole-isoxazole hybrids and evaluated for antibacterial activity. By considering previous results of isoxazole moiety exhibits antibacterial activity so that we are interested to make isoxazole hybrids and studied their biological activity.

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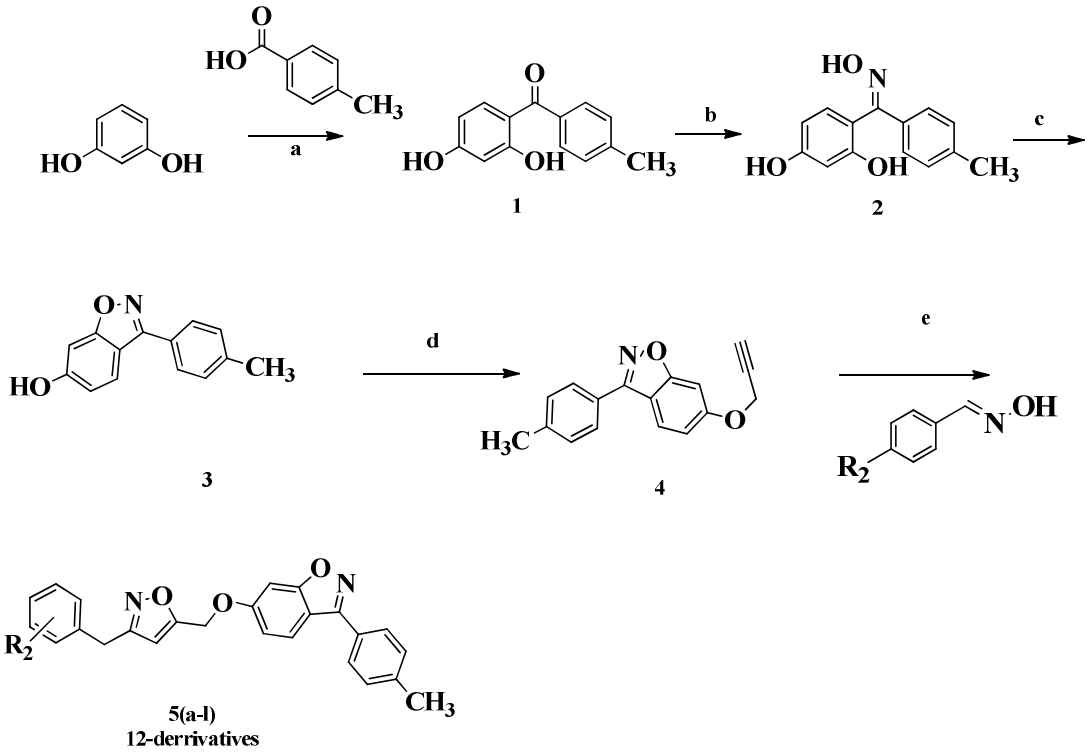
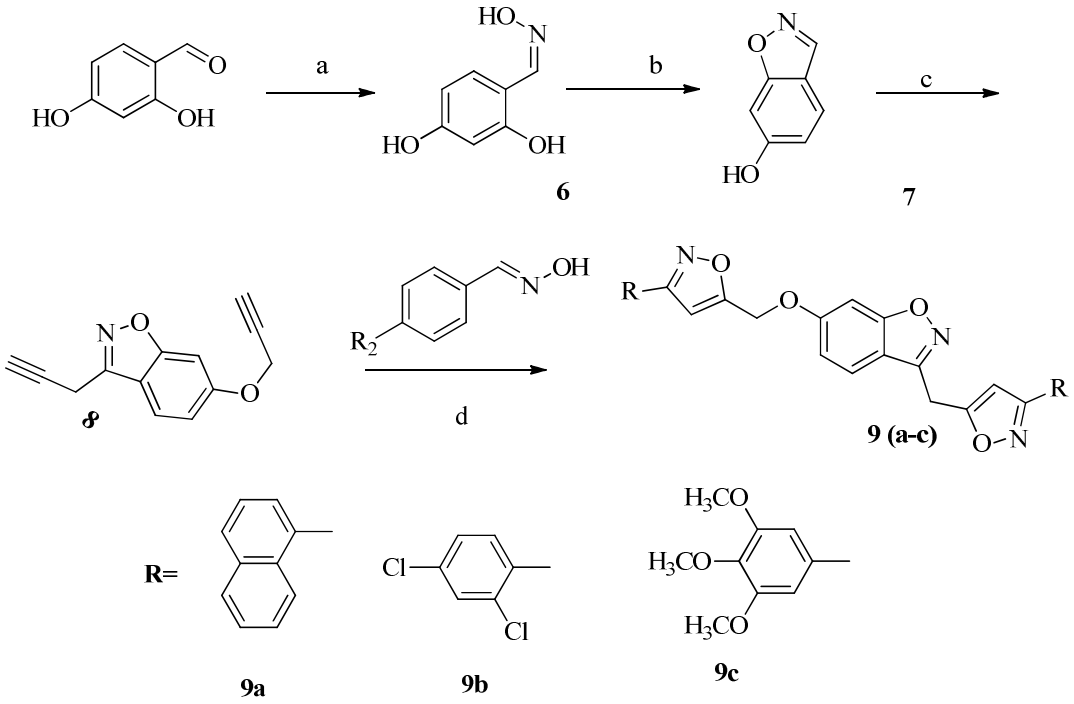


Reagents and conditions: a) BF_3-OEt_2, 95°C, 2 hr; b) NH_2OH. HCl, NaOAC, EtOH/H_2O, 2h reflux; c) Diethylazodicarboxylate (DEAD), PPh_3, THF, RT ; d) Propargylbromide, K_2CO_3, Acetone, RT, 12 h; e) Aldoxime, NaOCl drop wise, r.t, 2 h, CH_2Cl_2.

Here along with *O*-propargylation active-CH position on benzisoxazole ring also propargylated and formed di propargyl ether compound **29,** if we use 1 equivalent of propargyl bromide ***O*-**propargylation takes place along with traces of di-propargylated product, instead of 1 equivalent if we use excess of propargyl bromide exclusively di-propargylation taken place



Reagents and conditions: a) NH_2OH. HCl, NaOAC ,EtOH/H_2O, 2h, reflux; b) Diethylazodicarboxylate, PPh_3, THF, r.t; c) Propargylbromide, K_2CO_3,Acetone,RT,12 h; d) Aldoxime,NaOCl drop wise,RT,2 h,CH_2Cl_2.

The synthesized compounds were evaluated for their antifungal activity against various anti fungal strains like *C. albicans MTCC 183, C. albicans MTCC 227, C. albicans MTCC 227, C. albicans MTCC 1637, C. albicans MTCC 3018, C. albicans MTCC 3958, C. albicans MTCC 4748, C. albicans MTCC 7315., C. parapsilosis MTCC 1744, C. aaseri MTCC 1962, C. glabrata MTCC 3019 and C. krusei MTCC 3020*, and were comparable Miconazole, standard drug. Along with the anti fungal activity we also screened for anti bacterial activity against several anti bacterial strains such that *S.aureu MTCC 96 ,S. aureus MTCC 2940, B. subtilis MTCC 121, E. coli MTCC 739, P.Aeruginsa MTCC 2453 and K. planticola MTCC 530,* comparable to Ciprofloxacin, standard drug. From the above some of them showed good effects on bacterial strains with MIC value of range 7.8 to 31.2 *µg/ml*