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Research Article

SYNTHESIS, BIOLOGICAL EVALUATION AND MODELING STUDIES OF 2-(4-((1H-1,2,3-TRIAZOL-4-YL)METHOXY)PHENYL)BENZO[D]OXAZOLE AND 2-(4-((2-ALKYL-2H-TETRAZOL-5-YL)METHOXY)PHENYL) BENZO[D]OXAZOLES AS A NOVEL ANTIMICROBIAL AGENTS

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ABSTRACT

*A series of triazole **(6a-f)** and tetrazole **(7a-f)** derivatives were synthesized and their structures were confirmed by IR, 1HNMR and mass spectroscopic studies. All the compounds have been screened for their antibacterial activity against Staphylococcus aureus, Pseudomonas aeruginosa and Escherichia coli and antifungal activity against Aspergillus fumigates Aspergillus niger and Candida albicans. Evaluation of antimicrobial activity considering the MIC value calculated by the serial dilution method revealed that several compounds exhibits good to moderate activity. Further to understand the interaction of the compounds with the bacterial and fungal protein receptor binding sites, docking studies are conducted using biotin protein ligase (BPL) (3V7R) from Staphylococcus aureus and dihydrofolate reductase (DHFR) (PDB ID 4HOF) from Candida albicans. Among the all compounds, compound 6d of triazole derivative and compound 7f of tetrazole derivative showed high docking energy. This investigation has open up the scope for development of a new class of antimicrobial agents.*

KEYWORDS: *Benzoxazole, Triazole, Tetrazole, Molecular Docking and Antimicrobial activity.*

INTRODUCTION

The expanding microbial resistance to currently available antimicrobial drugs has grown into a serious human health complication and is the major cause of morbidity and mortality throughout the world. Infections bring about by these resistant microorganisms such as bacteria, fungi parasites and viruses decline the relevant common medications, resulting in persistence and spreading of infections [1-3]. Most of these microbes are the human pathogens accompanying the surrounding habitat, may be allied to the progress of these severe infections with continued illness and greater risk of deaths. The most prevailing are the bacterial and fungal pathogens, for the most part associate with hospital and community-acquired infections primarily in immunocompromised conditions. They are liable for common infections of urinary tract, bloodstream, skin and pneumonia to high percentage of hospital acquired infectious diseases, especially among patients immunocompromised due to AIDS, diabetic, organ transplantation, severe burns, chemotherapy or other invasive procedures [1, 3-6]. Despite the availability of large number of antimicrobials for clinical use and their resistance against some fungal and bacterial strains, the emergence in the designing new, more effective, and safe antimicrobial agents has opened up an intense research for medicinal chemists. These efforts are mainly implemented for controlling not only serious infections, but also the prevention and treatment of complications associated with infections of other therapeutic modalities such as cancer chemotherapy and surgery. Besides developing completely new agents with chemical characteristics that clearly differ from those of existing ones, the combination therapy is another approach fusing two or more biologically active heterocyclic systems to a single molecular scaffold. In this context, the pharmacologically important azole derivatives possessing diverse activity are of intense research in the antimicrobial therapy [1, 3, 7, 8].

The five membered azoles are heterocyclic compounds with two or more heteroatoms in which at least one is nitrogen. Their natural existence provides a source for wider biological applications in treating various diseases and is mainly considered as integral structural feature for the synthesis and development of new medicinal agents. Research on these azole heterocycles, especially triazole-tetrazole chemistry, has gained considerable interest owing to their pharmacological importance as antimicrobial, analgesic, anti-inflammatory, anticancer, anticonvulsant and antimalarial agents. As a result, a variety of new improved compounds are established varying the substitution on the triazole and tetrazole nucleus [7-9]. The importance of triazole derivatives lie in the field that these have occupied a unique position in heterocyclic chemistry due to their agricultural, industrial, and biological activities, along with the application of the concept of "click-synthesis" for their efficient and quick synthesis [10-12]. Triazoles have also been incorporated in a wide variety of therapeutically interesting drugs including H1/H2 histamine receptor blockers, CNS stimulants, anti-anxiety agents and sedatives. The 1,2,3- triazole system has been well reported with wide spread uses of antitubercular, antimalarial, analgesic, antimicrobial, local anaesthetic, antineoplastic, antiinflammatory, anticonvulsant, antiviral, antiproliferative, anticancer and antioxidant activities [13-21]. This triazole moiety is stable to metabolic degradation and capable of hydrogen bonding, which could be favourable in binding bimolecular targets as well as increasing solubility. Moreover, they can function as attractive linker units which could connect two pharmacophores to give some innovative bifunctional drugs, thus have become increasingly useful and important in constructing bioactive and functional molecules [10, 12, 22-25].

On the other hand, Tetrazoles are class of synthetic organic heterocyclic compounds, possessing broad spectrum of activities in major areas such as medicine, agriculture and imaging technology, and are very stimulating heterocycles from an academic viewpoint [26-31]. In general, this nitrogen rich ring system is used in propellants, explosives, and in pharmaceuticals. In addition, tetrazoles are important synthons

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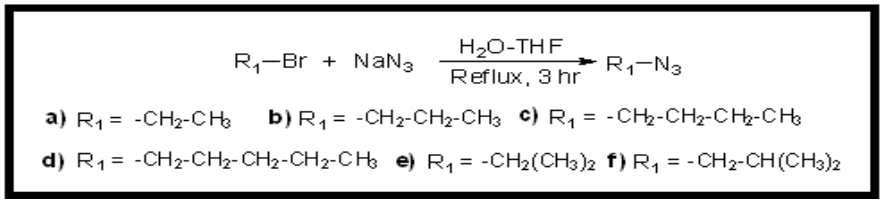
in synthetic organic chemistry and also used as precursors of carbenes in flash vacuum pyrolysis. Tetrazole, an aromatic azapyrrole group, is metabolically stable and has acidic characteristics closely similar to that of the carboxylic group. Various tetrazole based compounds have also shown good coordination properties and are able to form stable complexes with several metal ions. Furthermore, the tetrazole ring has strong electron withdrawing property, have been successfully used in organic synthesis as derivatising agents for the chemical modification [32-36]. Tetrazoles are incorporated in a large number of drugs to achieve a wide spectrum of biological activities and their derivatives have been reported as antibacterial, antifungal, antiviral, herbicidal, antitumor, anticonvulsant, analgesic, antiinflammatory, antitubercular, anticancer and antihypertensive activities [37-43].

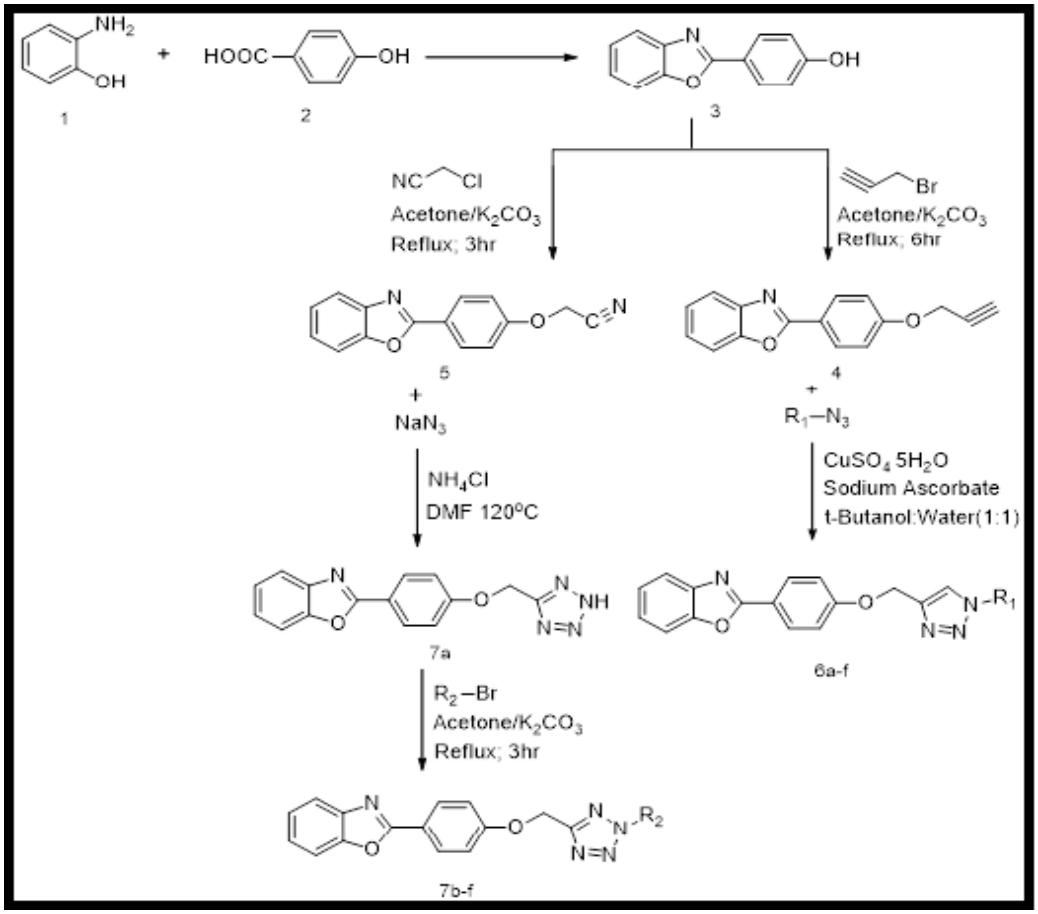
In view of these considerations, in the present study a new series of triazole and tetrazole derivatives were synthesized and evaluated for in vitro antimicrobial activities.

Chemistry:

Scheme-1:



Scheme-2



6a *R1= Ethyl;* ***6b*** *R1= Propyl;* ***6c*** *R1= Butyl;* ***6d*** *R1= Pentyl;* ***6e*** *R1= Isopropyl;* ***6f*** *R1= Isobutyl*
7a *R2= H;* ***7b*** *R2= Ethyl;* ***7c*** *R2= Propyl;* ***7d*** *R2= Butyl;* ***7e*** *R2= Isopropyl;* ***7f*** *R2= Isobutyl*

General procedure for synthesis:

1. Synthesis of alkyl azides **(a-f):**

Sodium azide reacted with alkyl bromide **(a-f)** at reflux temperature in water: THF solvent system for 3 hr to yield corresponding alkyl azides **(a-f)**. The N_3 peak of alkyl azides (**a-f**) observed in the IR spectrum in the range of 2082-2116 cm^{-1}.

Synthesis of 4-(Benzoxazole-2-yl)phenol **(3):**

o-Amino phenol **(1)** (2.18g, 20mmol) and p-hydroxy benzoic acid **(2)** (3.32g, 24mmol) were taken in a round bottom flask in xylene (90ml) refluxed for 12hr by adding p-toluenesulfonic (21.00g, 50mmol). Ethyl acetate (180ml) was added to the mixture, and then washed with saturated sodium bicarbonate solution. The organic phase was dried over Na_2SO_4 and filtered. The filtrate crude product was purified by column with pet ether: ethyl acetate (80:20) to get 4-(Benzoxazole-2-yl)phenol **(3)** [44].

2. Synthesis of 2-(4-(prop-2-yn-1-yloxy) phenyl) benzo[d]oxazole **(4):**

4-(Benzoxazole-2-yl)phenol **(3)** (2.0g, 9.0mmol) dissolved in dry acetone and refluxed over anhydrous potassium carbonate for 6hrs on water bath by adding propargyl bromide (1.05ml, 9.0mml). After completion of the reaction was monitored by TLC acetone was removed under reduced pressure and crushed ice was added to the residue. The product 2-(4-(prop-2-yn-1-yloxy)phenyl)benzo[d]oxazole **(4)** was filtered washed with water and recrystallized from chloroform.

3. 2-(4-(benzo[d]oxazol-2-yl)phenoxy)acetonitrile **(5):**

4-(benzo[d]oxazol-2-yl)phenol **(3)** (2.0g, 9.0mmol) and Chloroacetonotrile (0.67ml, 9.0mmol) were dissolved in dry acetone

and refluxed over anhydrous potassium carbonate for 3hrs on water bath to get the products 2-(4-(benzo[d]oxazol-2-yl)phenoxy) acetonitrile **(5)** which was purified on column chromatography with pet.ether:ethylacetate (80:20) gave as white solid.

***4. 2-(4-((1-alkyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)benzo[d] oxazole* (6a-f):**

2-(4-(prop-2-yn-1-yloxy)phenyl)benzo[d]oxazole **(4)** (2.0g, 8.03mmol) and equimoles of alkyl azides **(a-f)** were suspended in 1:1 mixture of water and tertiary butanol followed by freshly prepared 1M sodium ascorbate solution in water and copper sulphate in water was added. The heterogeneous reaction mixture was stirred for 6-9 hr at room temperature to yield 2-(4-((1-ethyl-1H-1,2,3-triazol-4-yl) methoxy)phenyl)benzo[d]oxazole **(6a)**.

***2-{4-[(1-ethyl-1H-1,2,3-triazol-4-yl)methoxy]phenyl}-1,3-benzoxazole* (6a):**

IR (KBr): υ 1733 (C=C of triazole), 1609 (C=N of benzaxazole) cm^{-1}. ***^{1}H-NMR (CDCl$_3$, 400MHz):*** δ 7.61-7.76 δ (m, 4H, 2'-H, 6'-H, 5-H, 6-H), 7.24 (s, 1H, 5''-H), 6.92-7.04 (m, 4H, 4-H, 7-H, 3'-H, 5'-H), 5.26 (s, 2H, -OCH_2), 3.76 (q, 2H, J=7.6Hz, 1''-CH_2), 1.20 δ (t, 3H, J=7.6Hz, 2'''-CH_3). ***^{13}C-NMR (CDCl$_3$, 100MHz):*** δ 160.9 (C-2), 158.4 (C-4'), 149.1 (C-7a), 140.9 (C-4''), 140.2 (C-4), 126.2 (C-5''), 123.3 (C-5), 122.2 (C-6), 121.4 (C-1'), 117.4 (C-3a), 114.1 (C-2', C-6'), 113.2 (C-3', C-5'), 109.8 (C-7), 71.0 (-OCH_2), 48.1 (C-1'''), 13.6 (C-2'''). ***Mass (ES):*** *m/z* 321.1 $[M+H]^+$, M.P: 172 ^{0}C, Yield: 72 %.

***2-{4-[(1-propyl-1H-1,2,3-triazol-4-yl)methoxy]phenyl}-1,3-benzoxazole* (6b):**

IR (KBr): υ 1728 (C=C of triazole), 1605 (C=N of benzaxazole) cm^{-1}. ***^{1}H-NMR (CDCl$_3$, 400MHz):*** δ 7.72-7.83 (m, 4H, 2'-H, 6'-H, 5-H, 6-H), 7.28 (s, 1H, 5''-H), 6.96-7.07 (m, 4H, 4-H, 7-H, 3'-H, 5'-H), 5.29 (s, 2H, -OCH_2), 3.81 (t, 2H, J=7.2Hz, 1''-CH_2), 1.82-1.93 (m, 2H, 2'''-CH_2), 1.09 (t, 3H, J=7.2Hz, 3'''-CH_3). ***^{13}C-NMR (CDCl$_3$, 100MHz):*** δ 161.9 (C-2), 159.3 (C-4'), 151.1 (C-7a), 141.2 (C-4''), 140.6 (C-4), 126.2 (C-5''), 122.8 (C-5), 121.7 (C-6), 120.4 (C-11), 117.0 (C-3a), 114.3 (C-2', C-6'), 113.0 (C-3', C-5'), 109.8 (C-7), 70.0 (-OCH_2), 49.1 (C-1'''), 19.5 (C-2'''), 12.0 (C-3'''). ***Mass (ES):*** *m/z* 335.1 $[M+H]^+$, M.P: 186 ^{0}C, Yield: 70 %.

***2-{4-[(1-butyl-1H-1,2,3-triazol-4-yl)methoxy]phenyl}-1,3-benzoxazole* (6c):**

IR (KBr): υ 1682 (C=C of triazole), 1598 (C=N of benzaxazole) cm^{-1}. ***^{1}H-NMR (CDCl$_3$, 400MHz):*** δ 7.66-7.81 (m, 4H, 2'-H, 6'-H, 5-H, 6-H), 7.26 (s, 1H, 5''-H), 6.93-7.06 (m, 4H, 4-H, 7-H, 3'-H, 5'-H), 5.27 (s, 2H, -OCH_2), 3.80 (t, 2H, J=7.6Hz, 1'''-CH_2), 1.84-1.96 (m, 2H, 2'''-CH_2), 1.29-1.37 (m, 2H, 3'''-CH_2), 1.01 (t, 3H, J=7.2Hz, 3'''-CH_3). ***^{13}C-NMR (CDCl$_3$, 100MHz):*** δ 160.0 (C-2), 158.2 (C-4'), 149.6 (C-7a), 141.2 (C-4''), 140.1 (C-4", 139.2 (C-4), 125.8 (C-5''), 123.2 (C-5), 120.6 (C-1'), 117.0 (C-3a), 113.7 (C-2', C-6'), 113.0 C-3', C-5'), 108.7 (C-7), 71.3 (-OCH_2), 48.4 (C-1'''), 28.2 (C-2'''), 19.0 (C-3'''), 14.6 (C-4'''). ***Mass (ES):*** *m/z* 349.6 $[M+H]^+$, M.P: 176 ^{0}C, Yield: 84 %.

***2-{4-[(1-pentyl-1H-1,2,3-triazol-4-yl)methoxy]phenyl}-1,3-benzoxazole* (6d):**

IR (KBr): υ 1696 (C=C of triazole), 1602 (C=N of benzaxazole) cm^{-1}. ***^{1}H-NMR (CDCl$_3$, 400MHz):*** δ 7.69-7.80 (m, 4H, 2'-H, 6'-H, 5-H, 6-H), 7.28 (s, 1H, 5''-H), 6.95-7.07 (m, 4H, 4-H, 7-H, 3'-H, 5'-H), 5.29 (s, 2H, -OCH_2), 3.82 (t, 2H, J=7.6Hz, 1'''-CH_2), 1.86-1.95 (m, 2H, 2'''-CH_2), 1.27-1.38 (m, 2H, 3'''-CH_2), 0.89 (t, 3H, J=7.2Hz, 5'''-CH_3). ***^{13}C-NMR (CDCl$_3$, 100MHz):*** δ 161.0 (C-2), 159.3 (C-4'), 151.3 (C-7a), 141.3 (C-4''), 127.1 (C-5''), 122.9 (C-5), 121.9 (C-6), 120.8 (C-1'), 120.6 (C-1'), 117.4 (C-3a), 114.7 (C-2', C-6'), 113.0 (C-3', C-5'), 109.5 (C-7), 70.6 (-OCH_2), 49.7 (C-1'''), 29.9 (C-2'''), 27.8 (C-3'''), 18.7 (C-4'''), 11.9 C-5'''). ***Mass (ES):*** *m/z* 363.8 $[M+H]^+$, M.P: 158 ^{0}C, Yield: 88 %.

***2-(4-{[1-(propan-2-yl)-1H-1,2,3-triazol-4-yl]methoxy}phenyl)-1,3-benzoxazole* (6e):**

IR (KBr): υ 1678 (C=C of triazole), 1594 (C=N of benzaxazole) cm^{-1}. ***^{1}H-NMR (CDCl$_3$, 400MHz):*** δ 7.63-7.78 (m, 4H, 2'-H, 6'-H, 5-H, 6-H), 7.24 (s, 1H, 5''-H), 6.92-7.05 (m, 4H, 4-H, 7-H, 3'-H, 5'-H), 5.27 (s, 2H, -OCH_2), 4.08- δ 4.22 (m, 1H,1'''-CH), 1.67 (d, H, J=6.8Hz, 2'''-$(CH_3)_2$). ***^{13}C-NMR (CDCl$_3$, 100MHz):*** δ 160.7 (C-2), 158.9 (C-4'), 149.5 (C-7a), 140.6 (C-4''), 139.7 (C-4), 125.9 (C-5''), 123.2 (C-5), 122.3 (C-6), 120.9 (C-1'), 117.3 (C-3a), 13.8 (C-2', C-6'), 113.1 (C-3', C-5'), 108.9 (C-7), 71.5 (-OCH_2), 52.8 (C-1'''), 32.4 (C-2'''). ***Mass (ES):*** *m/z* 335.2 $[M+H]^+$, M.P: 164 ^{0}C, Yield: 82 %.

***2-(4-{[1-(2-methylpropyl)-1H-1,2,3-triazol-4-yl]methoxy}phenyl)-1,3-benzoxazole* (6f):**

IR (KBr): υ 1676 (C=C of triazole), 1602 (C=N of benzaxazole) cm^{-1}. ***^{1}H-NMR (CDCl$_3$, 400MHz):*** δ 7.72-7.84 (m, 4H, 2'-H, 6'-H, 5-H, 6-H), 7.25 (s, 1H, 5''-H), 6.97-7.07 (m, 4H, 4-H, 7-H, 3'-H, 5'-H), 5.28 (s, 2H, -OCH_2), 3.87 (d, 2H, J=6.8Hz, 3''' $(CH_3)_2$), 1.28 (d, 2H, J=6.8Hz, 3'''-$(CH_3)_2$), 4.08-4.22 (m, 1H, 1'''-CH), 1.67 (d, H, J=6.8Hz, 2'''-$(CH_3)_2$). ***^{13}C-NMR (CDCl$_3$, 100MHz):*** δ 160.9 (C-2), 159.1 (C-4'), 150.2 (C-7a), 141.6 (C-4''), 140.1 (C-4), 127.2 (C-5''), 123.4 (C-5), 122.1 (C-6), 121.9 (C-1'), 117.3 (C-3a), 117.6 (C-2', C-6'), 112.7 (C-3', C-5'), 109.2 (C-7), 70.8 (-OCH_2), 46.6 (C-1'''), 22.7 (C-2'''), 13.8 (C-3'''). ***Mass (ES):*** *m/z* 349.6 $[M+H]^+$, M.P: 142 ^{0}C, Yield: 78 %.

***2-(4-((2H-tetrazol-5-yl) methoxy) phenyl) benzo[d]oxazole* (7a):**

A mixture of 2-(4-(benzo[d]oxazol-2-yl)phenoxy)acetonitrile **(5)** (2.0g, 8.0mmol), sodium azide (0.52g, 8.0mmol) and NH_4Cl (0.42g, 8.0mmol) in DMF (15ml) was heated for 8hr at 120^{0}C. The reaction mixture was cooled to room temperature and added crushed ice, and then a cream colour precipitate was obtained. It was collected by filtration and washed with water, dried at 50^{0}C to get crude compound which was purified on column chromatography with pet. ether: ethylacetate (70:30) gave as **(7a)** as light cream solid.

***2-{4-[(2H-tetrazol-5-yl)methoxy]phenyl}-1,3-benzoxazole* (7a):**

IR (KBr): υ 1661 (C=N of tetrazole) cm^{-1}. ***^{1}H-NMR (CDCl$_3$, 400MHz):*** δ 7.76-7.88 (m, 4H, 2'-H, 6'-H, 5-H, 6-H), 6.95-7.08 (m, 4H, 4-H, 7-H, 3'-H, 5'-H), 5.21 (s, 2H, -OCH_2). ***^{13}C-NMR (CDCl$_3$, 100MHz):*** δ 161.0 (C-2), 159.6 (C-5''), 113.1 (C-2', C-6'), 159.2 (C-4'), 112.4 (C-3', C-5'), 148.3 (C-7a), 109.7 (C-7), 137.4 (C-3a), 69 (-OCH_2), 121.9 (C-5), 120.4 (C-6), 119.8 (C-1'), 118.4 (C-4). ***Mass (ES):*** *m/z* 294.10 $[M+H]^+$, M.P: 258 ^{0}C, Yield: 68 %.

***2-(4-((2-alkyl-2H-tetrazol-5-yl) methoxy) phenyl) benzo[d]oxazole* (7b-f):**

2-(4-((2H-tetrazol-5-yl)methoxy)phenyl)benzo[d]oxazole **(7a)** (1g, 3.41mmol) dissolved in dry acetone and Ethyl bromide (0.36ml, 3.41mmol) was added, refluxed over anhydrous potassium carbonate for 3 hrs on water bath. Reaction was monitored by TLC, acetone was removed under reduced pressure and crushed ice was added to the residue, compound was filtered and washed with plenty of water. The compounds were purified on column chromatography with pet. ether: ethylacetate (85:15) gave 2-(4-((2-alkyl-2H-tetrazol-5-yl) methoxy)phenyl)benzo[d]oxazole **(7b)** as white solid.

***2-{4-[(2-ethyl-2H-tetrazol-5-yl)methoxy]phenyl}-1,3-benzoxazole* (7b):**

IR (KBr): υ 1672 (C=N of tetrazole) cm^{-1}. ***^{1}H-NMR (CDCl$_3$, 400MHz):*** δ 7.76-7.81 (m, 4H, 2'-H, 6'-H, 5-H, 6-H), 6.95-7.08 (m, 4H, 4-H, 7-H, 3'-H, 5'-H), 5.23 (s, 2H, -OCH_2), 3.44 (q, 2H, J=7.2Hz, 1'''-CH_2), 1.22 (t, 3H, J=7.2 Hz, 2'''-CH_3). ***^{13}C-NMR (CDCl$_3$, 100MHz):*** δ 161.8 (C-2), 160.1 (C-5''), 113.5 (C-2', C-6'), 159.8 (C-4'), 112.9 (C-3', C-5'), 149.3 (C-7a), 110.0 (C-7), 136.8 (C-3a), 69.2 (-OCH_2), 121.3 (C-5), 52.7 (C-1'''), 120.4 (C-6), 13.4 (C-2'''), 119.1 (C-1'), 117.4 (C-4). ***Mass (ES):*** *m/z* 322.12 $[M+H]^+$, M.P: 212 ^{0}C, Yield: 72 %.

***2-{4-[(2-propyl-2H-tetrazol-5-yl)methoxy]phenyl}-1,3-benzoxazole* (7c):**

IR (KBr): υ 1628 (C=N of tetrazole) cm^{-1}. ***^{1}H-NMR (CDCl$_3$, 400MHz):*** δ 7.72-7.86 (m, 4H, 2'-H, 6'-H, 5-H, 6-H), 6.89-6.98 (m, 4H, 4-H, 7-H, 3'-H, 5'-H) 5.28 (s, 2H, -OCH_2), 3.58 (t, 2H, J=7.6Hz, 1'''-CH_2), 1.81-1.92 (m, 2H, 2'''-CH_2), 1.11 (t, 3H, J=7.6Hz, 3'''-CH_3). ***^{13}C-NMR (CDCl$_3$, 100MHz):*** δ 161.2 (C-2), 159.2 (C-5''), 109.3 (C-7), 158.7 (C-4'), 136.9 (C-3a), 68.7 (-OCH_2), 22.2 (C-5), 56.6 (C-1'''), 120.1 (C-6), 10.4 (C-3'''), 119.2 (C-1'), 18.6 (C-4). ***Mass (ES):*** *m/z* 336.21 $[M+H]^+$, M.P: 198 ^{0}C, Yield: 72 %.

***2-{4-[(2-butyl-2H-tetrazol-5-yl)methoxy]phenyl}-1,3-benzoxazole* (7d):**

IR (KBr): υ 1660 (C=N of tetrazole) cm^{-1}. ***^{1}H-NMR (CDCl$_3$, 400MHz):*** δ 7.62-7.74 (m, 4H, 2'-H, 6'-H, 5-H, 6-H), 6.73-6.85 (m, 4H, 4-H, 7-H, 3'-H, 5'-H), 5.24 (s, 2H, -OCH_2), 3.46 (t, 2H, J=7.6Hz, 1'''-CH_2), 1.76-1.88 (m, 2H, 2'''-CH_2), 1.28-1.39 (m, 2H, 3'''-CH_2), 0.94 (t, 3H, J=6.8 Hz, 4'''-

CH_3). ***^{13}C-NMR ($CDCl_3$, 100MHz):*** δ 161.5 (C-2), 159.4 (C-5''), 158.9 (C-4'), 147.96 (C-7a), 137.2 (C-3a), 122.4 (C-5), 120.6 (C-6), 119.2 (C-1'), 118.4 (C-4), 113.4 (C-2', C-6'), 112.1 (C-3', C-5'),110.2 (C-7), 68.7 (-OCH_2), 54.8 (C-1'''), 28.4 (C-2'''), 18.6 (C-3'''), 13.9 (C-4'''). ***Mass (ES):*** *m/z* 350.15 $[M+H]^+$, M.P: 192 ^{0}C, Yield: 76 %.

***2-(4-{[2-(propan-2-yl)-2H-tetrazol-5-yl]methoxy}phenyl)-1,3-benzoxazole* (7e):**

IR (KBr): υ 1690 (C=N of tetrazole) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400MHz): δ 7.69-7.77 (m, 4H, 2'-H, 6'-H, 5-H, 6-H), 6.74-6.85 (m, 4H, 4-H, 7-H, 3'-H, 5'-H), 5.28 (s, 2H, -OCH_2), 3.88-3.96 (m, 2H, 1'''-CH), 1.84 (d, 6H, J=7.2Hz, 2'''- $(CH_3)_2$). ***^{13}C-NMR ($CDCl_3$, 100MHz):*** δ 161.5 (C-2), 158.6 (C-5''), 157.4 (C-4'), 148.2 (C-7a), 137.9 (C-3a), 122.0 (C-5, C-6), 120.0 (C-1'), 118.4 (C-4), 113.8 (C-2', C-6'), 112.4 (C-3', C-5'), 109.6 (C-7), 70.1 (-OCH_2), 63.2 (C-1'''), 25.3 (C-2'''). ***Mass (ES):*** *m/z* 336.08 $[M+H]^+$, M.P: 202-205 ^{0}C, Yield: 65 %.

***2-(4-{[2-(2-methylpropyl)-2H-tetrazol-5-yl]methoxy}phenyl)-1,3-benzoxazole* (7f):**

IR (KBr): υ 1683 (C=N of tetrazole) cm^{-1}. ***^{1}H-NMR ($CDCl_3$, 400MHz):*** δ 7.74-7.88 (m, 4H, 2'-H, 6'-H, 5-H, 6-H), 6.88-7.02 (m, 4H, 4-H, 7-H, 3'-H, 5'-H), 5.30 (s, 2H, -OCH_2), 1.98-2.09 (m, 2H, 1'''-CH), 1.01 (d, 6H, J=7.2Hz, 3'''- $(CH_3)_2$). ***^{13}C-NMR ($CDCl_3$, 100MHz):*** δ 160.9 (C-2), 158.4 (C-5''), 157.9 (C-4'), 147.6 (C-7a), 137.0 (C-3a), 121.8 (C-5), 120.2 (C-6), 119.4 (C-1'), 118.1 (C-4), 114.0 (C-2', C-6'), 112.9 (C-3', C-5'), 109.9 (C-7), 69.4 (-OCH_2), 24.0 (C-2'''), 16.3 (C-3'''). ***Mass (ES):*** *m/z* 350.16 $[M+H]^+$, M.P: 206-209 ^{0}C, Yield: 65 %.

Antimicrobial screening:

The synthesized compounds were screened *in vitro* antimicrobial activities using agar well diffusion method. The compounds were tested against Gram positive bacteria -*Staphylococcus aureus* and Gram negative bacteria -*Pseudomonas aeruginosa* and *Escherichia coli for* antibacterial activity and against the fungal species *Candida albicans, Aspergillus fumigates and Aspergillus niger* for antifungal activity. The minimum inhibitory concentration (MIC) in µg/mL was determined by the serial dilution method. The respective test compounds were dissolved in DMSO to obtain 1 mg/mL stock solution. Seeded broth (broth containing microbial spores) was prepared in nutrient broth (NB) from 24-h-old bacterial cultures on nutrient agar at 37 ± 1°C, while fungal spores from 1- to 7-day-old Sabouraud agar slant cultures were suspended in Sabouraud dextrose broth (SDB). The number of colony forming units (cfu) of the seeded broth were determined by the plating technique, and adjusted in the range of 10^4-10^5 cfu/mL. The final inoculum size was 10^5 cfu/mL for the antibacterial assay and 1.1-1.5× 10^2 for the antifungal assay. Testing was performed at pH 7.4 ± 0.2 for bacteria (NB) and at pH 5.6 for fungi (SDB). Exactly 0.4 mL of the solution of the test compound was added to 1.6 mL of seeded broth to form the first dilution. One milliliter of this was diluted with a further 1 mL of seeded broth to give the second dilution, and so on, till six such dilutions were obtained. A set of assay tubes containing only seeded broth were kept as control. The tubes were incubated in BOD (biochemical oxygen demand) incubators at 37 ± 1°C for bacteria and 28 ± 1°C for fungi. The MICs were recorded by visual observation after 24 h (for bacteria) and 72–96 h (for fungi) of incubation. Ciprofloxacin was used as the standard for bacterial studies and Fluconazole as the standard drug for fungal studies.

Molecular Docking Studies:

To investigate the binding pattern of the synthesized compounds respect to their binding affinity, docking experiments were performed using Discovery Studio. Molecular docking is a technique which serves to verify binding integrity and interaction poses of ligands within the binding pocket of target proteins. To validate and specify the target for anti-fungal and anti-bacterial activity of newly synthesized compounds, target proteins *i.e.*, biotin protein ligase (BPL) (3V7R) from Staphylococcus aureus and dihydrofolate reductase (DHFR) (PDB ID 4HOF) from *C. albicans* were selected as bacterial and fungal target.

The bacterial drug target BPL catalyzes the ATP-dependent addition of biotin onto specific carboxylases that require the cofactor for activity. The BPL in S. aureus (SaBPL) has two such substrates, acetyl-CoA carboxylase and pyruvate carboxylase that without biotinylation are totally inactive. BPL as a potential antibacterial target, as acetyl-CoA carboxylase is required for membrane lipid biosynthesis (9-11). This metabolic pathway is important in *S. aureus*, as the bacteria can only derive 50% of their membrane phospholipids from exogenous fatty acids.

The fungal target, Dihydrofolate reductase (DHFR) catalyzes the reaction of 7,8-dihydrofolate and NADPH to form 5,6,7,8-tetrahydrofolate and $NADP^+$. Tetrahydrofolate is essential for the biosynthesis of purines, thymidylate, and several amino acids. Because of its metabolic importance, DHFR has been extensively studied as targets for many diseases.

Preparation of the proteins:

The structures of target proteins *i.e.*, biotin protein ligase (BPL) (3V7R) from Staphylococcus aureus and dihydrofolate reductase (DHFR) (PDB ID 4HOF) from *C. albicans*, are retrieved from the PDB database. After importing in to the Discovery Studio 2.5 (DS), using the clean Protein protocol, the proteins are prepared for correcting the lack of hydrogen atoms, missing atoms and residues, incorrect atom order in amino acids, protonation states of ionizable side-chains and terminal groups by using predicted pKs, to complete the protein chain. Water molecules and all the hetero atoms are removed and CHARMm force field is applied for energy minimization using different algorithms till the protein reaches a convergence gradient 0.001 kcal/mol. After energy minimization, the binding pockets of the receptor are predicted by the receptor cavity method (Eraser algorithm). Using Define and Edit Binding Site tools in DS, the binding site of the target proteins is determined based on the occupied volume of the known ligands in the active site. The ligand is first selected and a sphere is created around the residues comprising binding site at a radius of 9 Å using define sphere from the selection option.

Ligand generation and optimization:

Using ACD/ ChemSketch (12.0) the 2D structures of all the synthesized compounds are drawn and saved in mol file format. These saved compounds are later imported in to DS and ligand preparation with constraint parameters such as consistency of ionization states, tautomer and isomer generation, removal of duplicate structures, conversion of 2D to 3D structures using catalyst algorithm is done and are energy minimized until a convergence gradient of 0.001 k.cal/ mol is reached.

Docking strategy:

The docking program LibDock module in Discovery Studio have been employed to generate the bioactive binding poses of synthesized compounds in the active site of protein. LibDock uses protein site features called HotSpots" that are resolved with a grid fixed in active site which counts the hotspot map for polar and apolar cluster and further used for the alignment of the ligand conformations to the protein interaction sites. All other docking and consequent scoring parameters used were kept at their default settings. Finally, at the end of the docking process, it returns all the minimized ligand poses and their rankings. Among all the obtained poses of each ligand, the ligand binding in a receptor cavity is evaluated based on the LibDock top score, which uses a simple pair-wise method. The ligands with high LibDock scores are preferred for estimating binding energies of the protein-ligand complex. The complex pose with the best binding energy is used for further binding mode analysis. In addition, all docked poses were scored by applying Analyze Ligand Poses sub protocol in Discovery Studio.

RESULTS AND DISCUSSION

Antibacterial activity and Antifungal activity:

The synthesized compounds were assessed to elicit there in *vitro* antibacterial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli* and were found to possess activities against the microorganisms. The antibacterial potency of the synthesized compounds was compared with Ciprofloxacin using their minimum inhibitory concentration (MIC) values that are summarized in table-1. According to the observed MIC values, all the compounds exhibited moderate to good bacterial inhibition against all the tested bacterial strains. Among the synthesized compounds it was clear that compound 7d and 6b showed very good antibacterial activity against all the bacterial strains. Compound 7d exhibited maximum inhibition activity against S. aureus and E. coli with a MIC value of 16µg/ml and

10µg/ml respectively and compound 6b showed maximum inhibition against *Pseudomonas aeruginosa* with a MIC value of 7µg/ml.

In *vitro* antifungal activity against *Candida albicans, Aspergillus fumigates and Aspergillus niger.* The antifungal potency of the synthesized compounds was compared with Fluconazole using their minimum inhibitory concentration (MIC) values that are summarized in table-1. The results indicate that compound 7b has excellent antifungal activity against *Aspergillus fumigates and* Candida *albicans* with a MIC value of 18µg/ml and 12µg/ml respectively. And against the *Aspergillus niger,* compound 6c showed maximum inhibition with a MIC value of 16 µg/ml.

Table No. 1: In *vitro* antimicrobial activity and docking scores of the top ranked poses of the synthesized triazole (6a-f) and tetrazole (7a-f) derivatives

	Minimum inhibitory concentration (MIC) in µg/mL						LibDock score	
	Anti-microbial activity			Anti-fungal activity			BPL	DHFR
Compound	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Escherichia coli.*	*Aspergillus fumigates*	*Aspergillus niger*	*Candida albicans*	*Staphylococcus aureus*	*Candida albicans*
6a	17	17	19	22	23	15	121.721	129.801
6b	16	7	11	24	36	32	125.683	129.945
6c	34	18	26	21	16	18	130. 398	138.163
6d	31	16	28	19	15	21	130. 769	142.376
6e	20	26	31	41	46	54	123.453	133.124
6f	28	31	31	18	27	12	125.215	133.254
7a	22	31	56	25	54	57	113.845	128.215
7b	16	16	10	33	45	31	117.443	138.207
7c	20	19	15	31	48	23	120.737	131.851
7d	22	28	23	27	40	21	126.884	135.551
7e	27	25	19	20	29	19	122.737	133.629
7f	28	15		24	23	18	135.378	140.959
Standard		**120**			**126**			

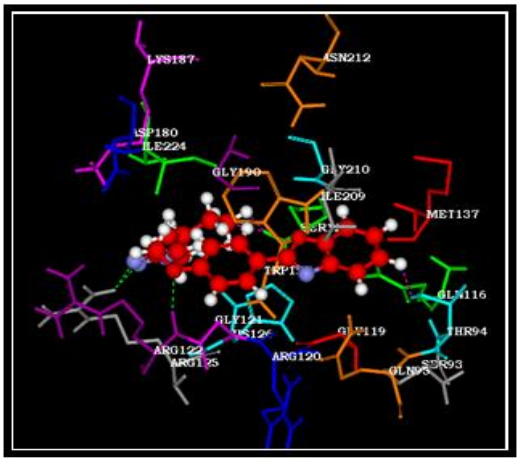
Docking Studies:

The antimicrobial potency of all the newly synthesized compounds were subjected for further docking studies to explore the binding pattern against biotin protein ligase (BPL) (3V7R) from Staphylococcus aureus and dihydrofolate reductase (DHFR) (PDB ID 4HOF) from *C. albicans.*

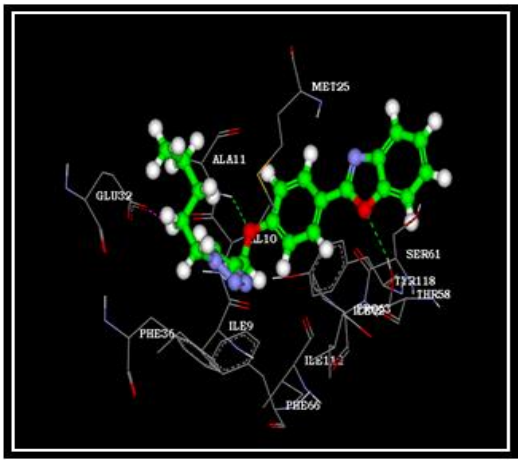
Conformational search of these ligands along with the standard drugs ciproflaxacin against bacterial and fluconazole against fungal were investigated *via Libdock* program of DS. In this study, ten conformers were generated for each ligand producing their corresponding docking scores using default parameters. Of all the conformations generated for each compound, the compound with the highest LibDock score is taken for interaction analysis of the hydrogen bonding. The Summary of docking scores of the top ranked poses of each compound are tabulated in Table-1.

From the observed docking results, almost all the compounds exhibited better binding affinity with both of the protein targets. Docking analysis of synthesized triazole compounds revealed that the compound 3d fitted well in the active site of the bacterial target BPL and fungal target DHFR showing the best docking scores of 130.769 and 142.376 respectively. The best conformation with H-bond interactions obtained for these compounds is shown in figure 1. From the Figure 1a it is revealed that three hydrogen bonds are formed with the protein BPL and compound 6d. A hydrogen bond is formed between the hydrogen atom of the amino acid Arginine122 and 16th oxygen atom of compound 7(AA: Arg122:HN-Comp6d: O16) with a hydrogen bond distance of 2.333 Å. The second hydrogen bond is formed between the hydrogen atom of Arginine125 and 21 nitrogen atom of compound 6d (AA: Arg125:HN-Comp6d: N21) with a hydrogen bond distance of 1.984 Å. Third hydrogen bond is formed between the hydrogen atom of Arginine125 and 20th nitrogen atom of compound 7 (AA: Arg125:HN-Comp6d: N20) with a hydrogen bond distance of 1.737 Å. Some close contacts are also formed between the protein and the compound 6d that is formed with hydrogen atom of the compound 6d and the hydrogen atom of the amino acid threonine94 (Comp6d:H30-A: Thr94:HG1) with a distance of 1.737 Å.

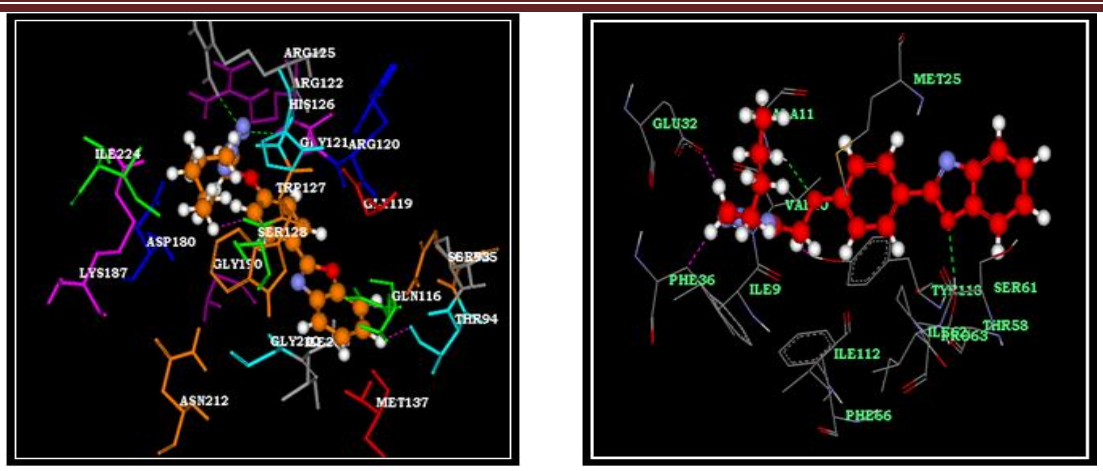
From the Figure 1 (b) it is revealed that two hydrogen bonds are formed with the protein DHFR and compound 6d. A hydrogen bond is formed between the hydrogen atom of the amino acid Tyrosine118 and oxygen atom of compound 6d (AA: Tyr118: OH-O2:Comp6d) with a hydrogen bond distance of 2.125 Å. The second hydrogen bond is formed between the hydrogen atom of Valine10 and oxygen atom of compound 7 (AA: Val10:HN-O1:Comp6d) with a hydrogen bond distance of 2.098 Å. Close contact is formed with oxygen atom of the compound 6d and the hydrogen atom of the amino acid glutamine (Comp6d:O-HG1:Glu32) with a distance of 1.689 Å.



a. BPL



b. DHFR



c. BPL **d. DHFR**

Fig. 1: Hydrogen bond interactions of compound 6d with a. BPL and b. DHFR, 7f with c. BPL and d. DHFR

Docking analysis of synthesized tetrazole compounds revealed that the compound 7f fitted well in the active site of the bacterial target BPL and fungal target DHFR showing the high docking scores of 135.378 and 140.959 respectively. The hydrogen bond interaction of the proteins and the compound 7f are shown in figure 1. From the Figure c it is revealed that two hydrogen bonds are formed with the protein BPL and compound 7f. A hydrogen bond is formed between the hydrogen atom of the amino acid Argine125 and nitrogen atom of compound 7f (AA: Arg125:HH11- Comp7f: N21) with a hydrogen bond distance of 2.121 Å. The second hydrogen bond is formed between the hydrogen atom of Argine122 and nitrogen atom of compound 7f (AA: Arg122:HN-Comp7f: N21) with a hydrogen bond distance of 2.118 Å. Close contact is formed with oxygen atom of the compound 4f and the hydrogen atom of the amino acid glutamine (Comp7f: O-HG1:Glu32) with a distance of 1.689 Å. Some close contacts are also formed between the protein and the compound 7f. They are formed with hydrogen atom of the compound 7f and the hydrogen atom of the amino acid threonine94 (Comp7f:H30-A: Thr94:HG1) and other with the compound 7f and the hydrogen atom of the amino acid Serine128 with a distances of 1.742 Å and 1.713 Å respectively.

From the Figure 1d it is revealed that two hydrogen bonds are formed with the protein DHFR and compound 7f. A hydrogen bond is formed between the hydrogen atom of the amino acid Alanine11 and oxygen atom of compound 7f (AA: Ala11:HN-Comp7f: O16) with a hydrogen bond distance of 2.228 Å. The second hydrogen bond is formed between the oxygen atom of glutamine and hydrogen atom of compound 7f (AA: GLu32:OE1-Comp7f:H39) with a hydrogen bond distance of 1.879 Å. Some close contacts are also formed between the protein and the compound 7f. They are formed with hydrogen atom of the compound 4f and the hydrogen atom of the amino acid tyrosine118 (Comp7f:H36-A: Tyr118: HH) and other with the amino acid Valine10 and the hydrogen atom of compound 7f with a distances of 1.685 Å and 1.645 Å respectively.

CONCLUSION

A new series of novel triazole **(6a-f)** and tetrazole **(7a-f)** have been synthesized and evaluated for them in vitro antibacterial and antifungal activities. The antimicrobial activity results indicated that some of the tested compounds showed the most promising antibacterial and antifungal activities. All the molecules were studied for their interactions with the bacterial target BPL and fungal target DHFR enzymes by molecular docking protocol. Among the tested molecules, compound 6d and 7f exhibited good docking scores of 130.769 and 135.378 against bacterial target and 142.376 and 140.959 against fungal target. The results of antimicrobial activity are supported by docking analysis. These observations may promote a further development of our research in this field.

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