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Synthesis, characterization, molecular docking study and antimicrobial activity of new 1,3,4-oxadiazoles bearing isomeric pyridyl and thiazolyl scaffolds

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In search of new antimicrobial agents, herein is reported a series new isomeric 2-pyridinyl substituted thiazolyl-5-aryl-1,3,4-oxadiazoles **2a-4g**, using pyridine nitriles as starting compounds, following multistep synthetic route. An intermediate, pyridinyl substituted thiazolyl acid hydrazide when condensed with different *para*-substituted benzoic acids in the presence of $POCl_3$ yields better to excellent yields of the title compounds. All the synthesized compounds **2a-4g** have been screened for their *in vitro* antimicrobial activity. Amongst them, 3-pyridynyl and 4-pyridynyl derivatives are found to be more active than 2- pyridynyl derivatives.

Keywords: 1,3,4-Oxadiazoles, Pyridine, Thiazole, Antimicrobial activity

In continuation of our previous work the present work deals with an additional heterocyclic unit 1,3,4-oxadiazole along with pyridine and thiazole. Compounds containing five-membered heterocycle 1,3,4-oxadiazole have been shown to exert anti-inflammatory[1], antimicrobial[2], anticonvulsant[3] and hypoglycaemic activities[4]. A brief literature summary of biological activity of 1,3,4-oxadiazoles containing pyridine and thiazole is presented below.

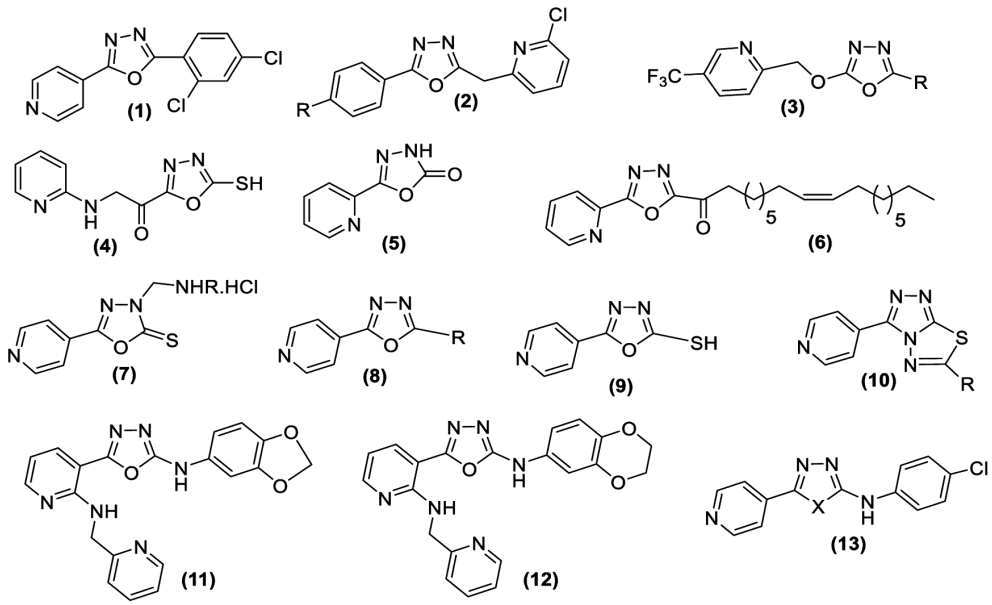
Amir *et al*.[5] studied the analgesic activity of compound **(1)** which showed a maximal activity of (70.37 ± 1.67%), almost equivalent to that of the ibuprofen standard (73.52 ± 1.00%). The synthesized derivative evaluated for anti-inflammatory, analgesic ulcerogenic and lipid peroxidation properties of ibuprofen type derivatives.

Holla *et al*.[6] studied the insecticidal activity of a number of substituted 1,3,4-oxadiazoles analogues derived from 2-chloropyridine-5-acetic acid **(2).** Cao *et al*.[7] designed and synthesized eight 2-(5-(trifluromethyl)-pyridyloxymethyl)-1,3,4-oxadiazoles **(3)** for their insecticidal activity. Two of these oxadiazoles exhibited significant insecticidal activity on armyworm, *Leucania separate walker* at 500 mg/L.

Salimon *et al*.[8] synthesized 1-(5-Mercapto-1,3,4-oxadiazol-2-yl)-2-(pyridine-2-ylamino) ethanone **(4)** has from 2-(pyridine-2-ylamino) acetohydrazide. This compound was found to have significant antimicrobial activity against some pathogenic microorganisms: *S. aureus*, *Streptococcus viridians* and *E. coli*. From structure-activity relationships, introduction of the 1,3,4-oxadiazole ring into compound significantly increases their biological activity. Belkadi *et al*.[9] synthesized oxadiazole derivative **(5)** from picolinic acid has relatively lower inhibition effect on *S. aureus* and *E. coli* but exhibited more effect on *P. aeruginosa*.

Garfunkle and co-workers[10] identified the most potent α-ketoheterocycle inhibitors of fatty acid amide hydrolase inhibitor, 5-aminopyrimidinone R-keto-1,3,4-oxadiazole (ONO-6818) which is the representative of orally active nonpeptidic reversible inhibitors of Human Neutrophil Elastase (HNE), with potent Ki values in the nanomolar range (0.003uM)[11,12]. The molecule **(6)** also exhibited potent oral *in vivo* efficacy potentiating the cytotoxic agent temozolomide in a B16F10 murine melanoma model[13].

Singh *et al*.[14] synthesized 5-(4-pyridyl)-3-(substituted aminomethyl)-1,3,4-oxadiazoline-2-thione hydrochloride (**7**) that possesses anti-inflammatory activity. Gilani *et al*.[15] also evaluated anti-inflammatory activity of a series of 6-substituted-1, 2,4-triazolo- [3,4-b]-1, 3,4-thiadiazole **(10)** and 1, 3, 4-oxadiazole derivatives of isoniazid **(8,9)**. Compound, 2-(2,4-dichlorophenyl-5- (pyridin-4-yl)-1, 3, 4-oxadiazole



Molecules containing pyridine-oxadiazoles

Scheme 1 — Molecules containing pyridine-oxadiazoles

showed maximum anti-inflammatory. It revealed that triazolo thiadiazole and 1,3,4-oxadiazole derivatives of isoniazid might afford a safer alternative to isoniazid for the treatment of inflammatory disease.

Ouyang and co-workers[16] synthesized derivatives of oxadiazoles and evaluated for their ability to inhibit tubulin polymerization and to arrest mitotic division of tumor cells. Among the synthesized compounds,**(11)** showed potent activity. Tuma and co-workers[17] synthesized and evaluated various 1,3,4-oxadiazole derivatives as to their ability to inhibit tubulin polymerization and block the mitotic division of tumor cells. Compound **(12)** exhibited potent activity. *In vitro* studies of compound **(12)** indicated that at nano-concentrations it interrupted mitotic division in breast carcinoma and squamous cell tumors, which included multi-drug resistant cells (Scheme 1).

Mohammad Shaharyar and co-workers[18] synthesized a series of five membered heterocycles **(13)**. From the synthesized compounds 2-(4-chlorophenyl)amino-5-(4-pyridyl)-1,3,4-thiadiazole (X=S) and 2-(4-chlorophenyl)amino-5-(4-pyridyl)-1,3,4-oxadiazole (X = O) showed potent anticonvulsant activity.

Results and Discussion

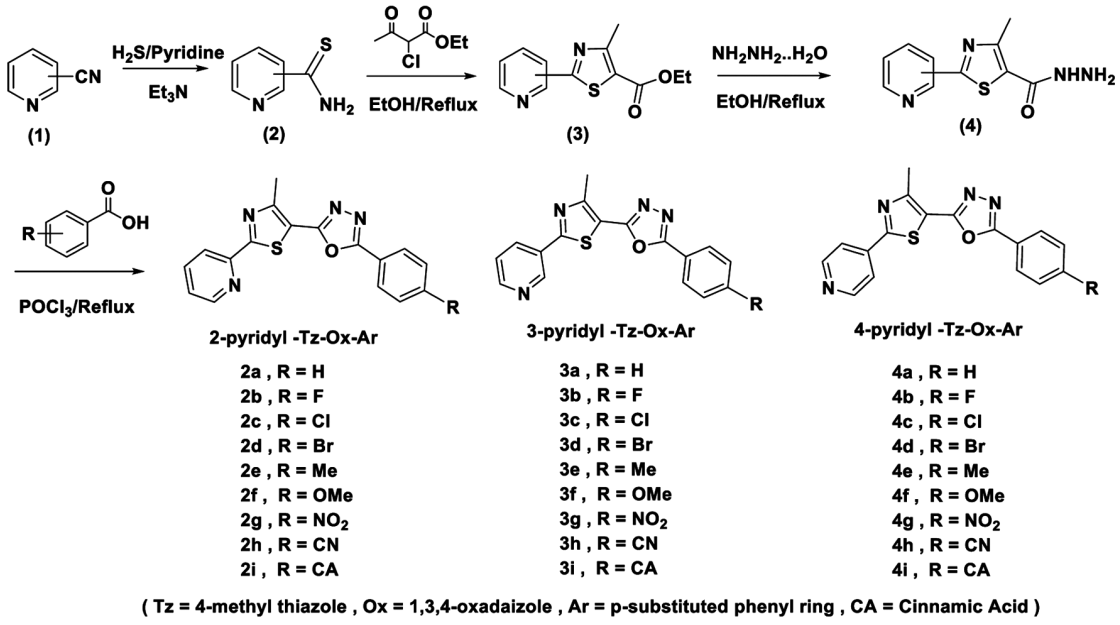
Present work

In this work thiazole ring is 2,4,5-tri-substituted, carbon number 2 of thiazole carries isomeric pyridyl rings, at carbon 3 methyl group is present whereas carbon 5 of the thiazole ring is having 1,3,4-oxadiazole ring. Literature reveals that there is a scanty information on the molecules having scaffolds like thiazole, 1,3,4-oxadiazole and pyridine in one molecular framework. Literature reveals that 1,3,4-oxadiazoles clubbed with thiazole and pyridyl moiety are not reported. The synthetic strategies adopted to obtain the oxadiazole substituted heterocyclic compounds is depicted in Scheme 2.

Characterization

2-Pyridyl series

^{1}H and ^{13}C NMR spectra of compound **2b** were recorded in $CDCl_3$. In ^{1}H NMR spectrum of the representative compound **2b**, the most downfield signal of Ha of pyridine skeleton was appeared at δ_H 8.64-8.66 as doublet with coupling constant J = 4.76 Hz. Downfield chemical shift is due to the presence of more electronegative nitrogen atom at *ortho* position. H-b of pyridine skeleton was appeared in downfield region at δ_H 8.22-8.24 as doublet with coupling constant J = 7.84 Hz. H-d of pyridine was appeared at δ_H 7.82 - 7.86 as doublet of doublet of doublet with coupling constant J = 7.8 Hz, 5.04Hz and 1.6Hz. Similarly the H-f proton of pyridine also appeared as doublet of doublet of doublet with coupling constant J = 7.52 Hz, 5.0Hz and 1.68Hz at δ_H 7.37 - 7.41. The characteristic singlet of H-g of methyl group was



Scheme 2 — Synthesis of 1,3,4-oxadiazoles bearing pyridyl and thiazolyl scaffolds

appeared at δ_H 2.94-2.97. Amongst the four protons of *para* substituted phenyl ring the two H-c protons appeared in downfield region as doublet of doublet of doublet at δ_H 8.01-8.07 with J = 8.7 Hz, 10.6 Hz. The remaining two protons of phenyl ring H-e appeared as doublet of doublet at δ_H 7.52 - 7.56 with J = 8.7 Hz and 6.7 Hz (Spectrum 1).

^{13}C NMR broad band decoupled spectrum displayed total fifteen carbon signals, including eight quaternary, six methine and one methyl carbon (Spectrum 2).

HRMS of compound **2b** (Spectrum 3) showed the molecular ion peak [M+1] at *m/z* 339.0718 with a composition of $C_{17}H_{12}FN_4OS$ which confirmed the formation of the desired molecule.

3-Pyridyl series

^{1}H and ^{13}C NMR spectra of compound **3e** were recorded in DMSO-d_6. In ^{1}H NMR spectrum of the representative compound **3e**, downfield signal of H-a of pyridine skeleton was appeared at δ_H 9.22 as doublet with coupling constant J = 1.6Hz (Spectrum 4). Downfield chemical shift is due to the presence of more electronegative nitrogen atom at *ortho* position. H-b of pyridine skeleton was appeared in downfield region at δ_H 8.71-8.72 as doublet of doublet with coupling constant J = 3.48Hz and 1.6Hz. H-c of pyridine was appeared at δ_H 8.27 - 8.30 as doublet of doublet of doublet with coupling constant J = 3.92Hz, 2Hz and 1.92Hz. H-e of pyridine skeleton is most shielded at δ_H 7.68 and appeared as doublet of doublet with J = 4.8Hz and J = 4.76Hz. Amongst the four protons of phenyl ring the two H-d protons appeared in downfield region as doublet at δ_H 7.99-8.01 with J = 8.2Hz. The remaining two protons of phenyl ring H-f appeared in upfield region as doublet at δ_H 7.34 - 7.36 as doublet with J = 7.96Hz (Spectrum 4). The characteristic singlet of H-g (thiazole) and H-h (phenyl) of methyl moiety was appeared at δ_H 2.94 and 2.45 respectively.

^{13}C NMR broad band decoupled spectrum displayed total sixteen carbon signals, including eight quaternary, six methine and two methyl carbon (Spectrum 5).

HRMS of compound **3e** (Spectrum 6) showed the molecular ion peak [M+1] at *m/z* 335.0968 with a composition of $C_{18}H_{15}N_4OS$ which confirmed the formation of the desired molecule.

4-Pyridyl series

^{1}H and ^{13}C NMR spectra of compound **4a** were recorded in $CDCl_3$. In ^{1}H NMR spectrum of the representative compound **4a**, downfield signal of H-a protons of pyridine skeleton was appeared at δ_H 8.74 - 8.75 as doublet with coupling constant J = 4Hz (Spectrum 7). Downfield chemical shift is due to the presence of more electronegative nitrogen atom at *ortho* position. H-b protons of pyridine skeleton was appeared in downfield region at δ_H 8.10-8.11 as doublet with coupling constant J = 4Hz. Amongst the five protons of phenyl ring the two H-c protons

appeared in downfiled region as doublet at δ_H 7.83 with J = 8Hz. The remaining three protons of phenyl ring H-d appeared in upfield region as multiplet at δ_H 7.54 - 7.56. The methyl protons was appeared as singlet at δ_H 2.94.

^{13}C NMR broad band decoupled spectrum displayed total thirteen carbon signals, including seven quaternary, five methine and one methyl carbon (Spectrum 8).

HRMS of compound **4a** (Spectrum 9) showed the molecular ion peak [M+1] at *m/z* 321.0815 with a composition of $C_{17}H_{13}N_4OS$ which confirmed the formation of the desired molecule.

Molecular docking study

In order to see the sights of binding energy, binding affinity, binding mode and molecular interactions of synthesised derivatives molecular docking study was carried out with bacterial DNA gyrase B subunit and fungal cytochrome P450 14α-demethylase (CYP51). Bacterial DNA gyrase is an essential enzyme for the survival of bacterial species and that is also known as topoisomerase II. It is ATP dependant enzyme which catalyses various important function in the bacterial cell such as transcription, replication and chromosomal segregation process. DNA gyrase composed of four subunits and also called as tetramer where it has on dimer as GyrA and another dimer as GyrB[19-23]. DNA gyrase B is very variable drug target for many antibacterial agents. The various classes of natural products, synthetic and screened libraries of chemical compounds has found to be has excellent inhibitory potential towards the bacterial GyrB[24-26].

Cytochrome family of the enzyme as catalyses the oxidation reaction and also known as monoxides present in all the living organisms. The CYP51 is one of the most prominent members of CYP family of enzyme also known as Erg11[27]. The fungal membrane is mostly made up of sterols which are important for maintaining membrane permeability and fluidity. The fungal cytochrome P450 14α-demethyase (CYP51). One of the important sterol in sterol biosynthesis that is lanosterol which is the key precursor for the synthesis of ergosterol. There are many classes of azoles, broad and narrow spectrum antibiotics which inhibits the fungal cytochrome P450 14α-demethyase (CYP51) and shown antifungal activity[28,29]

All these functions bacterial DNA gyrase B subunit and fungal cytochrome P450 14α-demethyase (CYP51) serve as best attractive target for the antimicrobial drug discovery. To perform molecular docking three dimensional X-ray crystal structure of DNA gyrase of E. coli 24kDa Domain in Complex with Clorobiocin (PDB ID: 1KZN Resolution 2.30 Å) and Crystal structure of sterol 14-alpha demethylase (CYP51B) from Aspergillus fumigatus in complex with the VNI derivative N-(1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethyl)-4-(5-(2-fluoro-4-(2,2,2-trifluoroethoxy)phenyl)-1,3,4-oxadiazol-2-yl) benzamide (PDB ID: 6CR2 Resolution 2.38 Å) was used[30-32].

The detail analysis of binding affinity (Free Energy of Binding) values and molecular interactions of synthesized derivatives (Table 1) such as **2e** (-6.240), **3g** (-6.436) and **4e** (-6.144) suggesting that they are the most active among all the synthesised derivatives when docked in binding site of DNA Gyrase B. The most active synthesized derivatives such as **3g** (-6.436), **2e** (-6.240) and **4e** (-6.144) shown efficient binding mode and penetrating active site cavity by forming the hydrogen bond interactions and π interactions with active site residues.

The most active synthesized derivatives **3g** (-6.436Kcal/Mol) forms interactions with polar amino

Table 1 — Docking energy score of the synthesized derivatives

Synthesized derivative	Free Energy of binding (pdb id 1KZN Kcal/mol)	Free Energy of binding (pdb id 6CR2 Kcal/mol)
2a	–5.8453	–5.2384
2b	–6.015	–4.3476
2c	–4.9586	–4.6295
2d	–4.8392	–5.0003
2e	–6.2407	–6.2571
2f	–5.672	–5.2561
2g	–5.3197	–4.8587
2h	–4.78	–4.803
3a	–5.6177	–4.916
3b	–5.3243	–5.0114
3c	–5.8984	–5.4882
3d	–5.352	–4.5203
3e	–5.4218	–5.0446
3f	–6.1111	–5.994
3g	–6.4368	–4.3728
3h	–5.4391	–4.4077
4a	–5.4208	–5.7491
4b	–5.4008	–5.1028
4c	–5.0473	–4.8222
4d	–5.9998	–5.9279
4e	–6.1443	–5.5503
4f	–5.1289	–5.8951
4g	–4.2133	–4.8198
4h	–5.3503	–5.3187

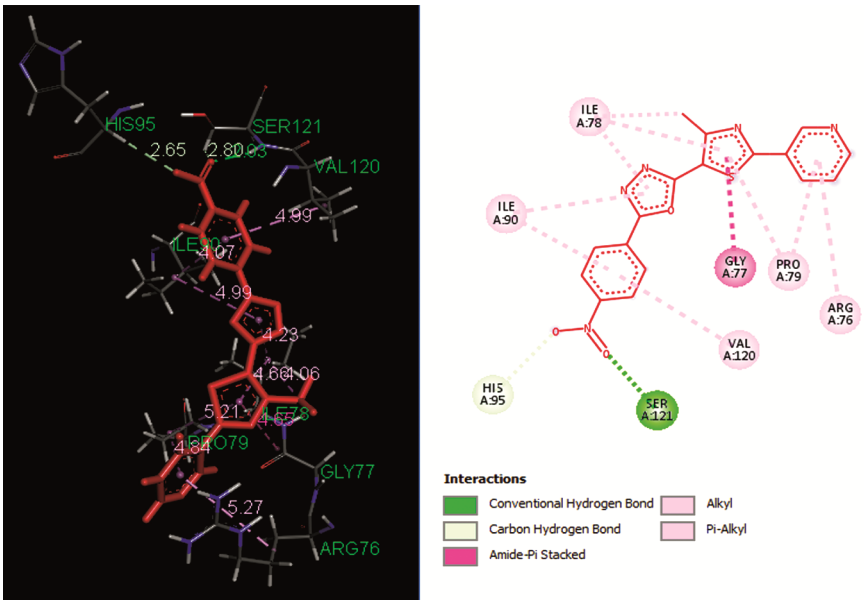


Fig. 1 — Binding Pose and molecular interactions of **3g** into the active site of DNA Gyrase B

acid residues SER121 and HIS95 were it forms conventional hydrogen bond and Carbon hydrogen bond interactions with oxygen atoms of nitro atoms of nitrobenzene ring distance 2.03 and 2.80 Å respectively. The Positively charged and aliphatic Amino acid residues ARG76, GLY77, ILE78, PRO79, ILE90 and VAL120. The active site amino acids such as HIS192, ALA237 and VAL30 forms π interactions such as amide- π stacked, π-Alkyl and Alkyl-Alkyl with nitrobenzene, 1,3,4-oxadiazole, 1,3-thiazole and pyridine rings shown in Fig. 1.

The second most active synthesized derivatives **2e** (-6.240 Kcal/Mol) interact with positively charged amino acid ARG136 by forming conventional hydrogen bond interactions with nitogen and sulfur atoms of 1,3-thiazole and pyridine rings acids with distance of 2.83 and 2.25 Å respectively. Aliphatic amino acid GLY77 interact with nitrogen and sulfur atoms of 1,3,4-oxadiazole, 1,3-thiazole ring to form conventional hydrogen bond interactions with distance of 2.93 and 2.83 Å respectively. Polar amino acid residue THR165 interact with nitrogen of 1,3,4-oxadiazole ring to form conventional hydrogen bond interactions with distance of 2.07 Å. The positively charged ARG76 and aliphatic amino acid residue ILE78 interact with Nitrogen atoms of 1,3,4-oxadiazole and pyridine ring to form carbon hydrogen bond interactions with the distance of 2.96 and 2.76 Å respectively. The aliphatic, nonpolar and charged amino acid residues such as VAL43, ALA47, ARG76, GLY77, ILE78 and PRO79 are forming Sulfur-X, π-Lone pair, π-Alkyl and alkyl interactions with phenyl, 1,3,4-oxadiazole, 1,3-thiazole and pyridine rings shown in Fig. 2.

The synthesized derivatives **4e** (-6.144Kcal/Mol) interact with aliphatic amino acid residue VAL120 by forming conventional hydrogen bond interactions with distance of 2.63 Å with nitrogen atom of 1,3-thiazole ring. Positively charged amino acid HIS195 interact with nitrogen atom of pyridine ring to form carbon hydrogen bond interactions with distance of 2.34 Å. Aliphatic amino acid GLY119 is interact with pyridine ring to form van der waals interactions. Aliphatic, polar, nonpolar amino acid residues such as ILE78, PRO79, ILE90, MET91and VAL118 interact with phenyl, 1,3,4-oxadiazole, 1,3-thiazole and pyridine rings to form π- amide stacked, π-Alkyl and alkyl interactions shown in Fig. 3.

The molecular docking study also carried out against fungal cytochrome P450 14α-demethylase (CYP51) in order to understand mechanism of inhibition and the inhibition potential of synthesized derivatives. The most active shown efficient binding mode and penetrating active site cavity by forming the hydrogen bond interactions and π and various forms of π- π interactions with active site residues.

The most active synthesized derivatives against CYP51 is **2e** (-6.257Kcal/Mol) which interact with hydrophobic active site amino acid residue PHE234 where it forms π-sulfur interactions with π- electron

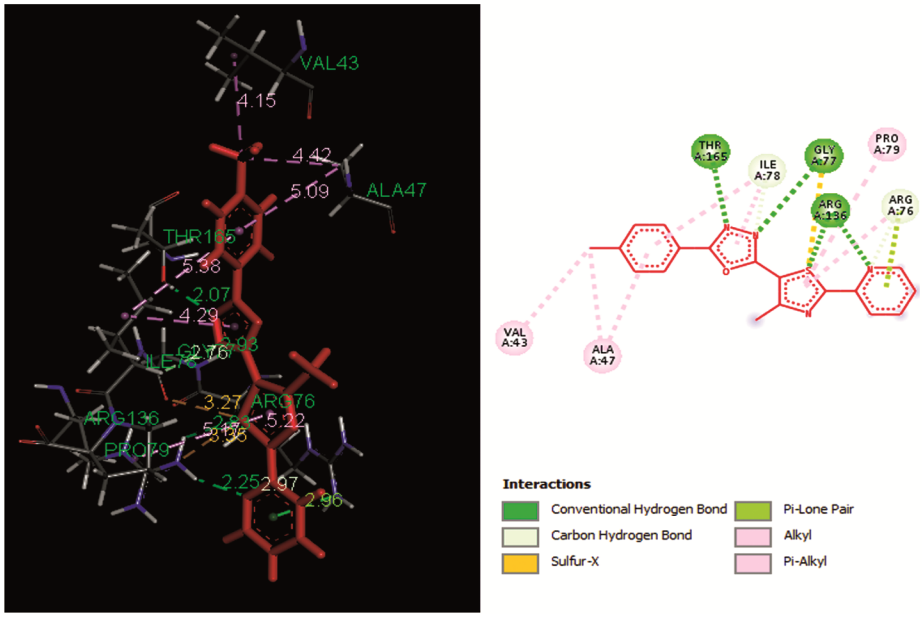


Fig. 2 — Binding Pose and molecular interactions of **2e** into the active site of DNA Gyrase B

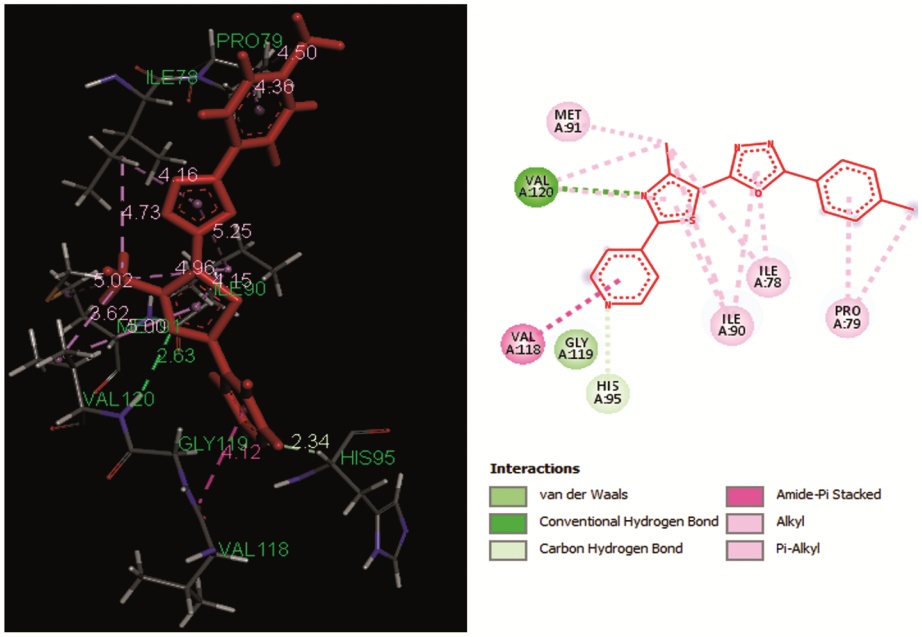


Fig. 3 — Binding Pose and molecular interactions of **4e** into the active site of DNA Gyrase B

clouds of 1,3-thiazole ring. The aliphatic amino acid residue LEU91 interacts with π-electron clouds of pyridine ring to form π-sigma interactions. The aliphatic and hydrophobic Amino acid LEU92, TYR122, TYR136, PHE234 and LEU503 forms π-sigma, π-alkyl and alkyl bond interaction with phenyl, 1,3,4-oxadiazole, 1,3-thiazole and pyridine rings shown in Fig. 4.

The synthesized derivatives **4d** (-5.927 Kcal/Mol) interact with aliphatic amino acid ALA307 to form carbon hydrogen bond interactions with hydrogen atom of pyridine ring with distance of 2.77 Å. The hydrophobic amino acid residue PHE504 interacts with π electron clouds of aromatic ring to form π-sulfur interactions of 4.93 Å. Another hydrophobic amino acid residue TYR122 interact with π- electron clouds to form π- π stacked interactions with 1,3,4-oxadiazole ring. The π electron cloud of phenyl, 1,3,4-oxadiazole, 1,3-thiazole and pyridine rings interact with ailphatic and hydrophobic amino acids to

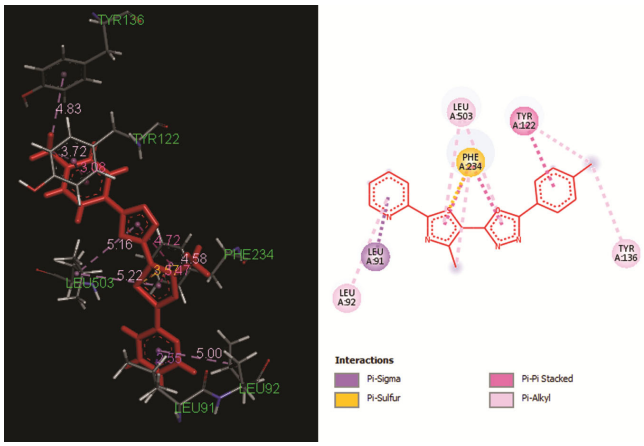


Fig. 4 — Binding Pose and molecular interactions of **2e** into the active site of CYP51

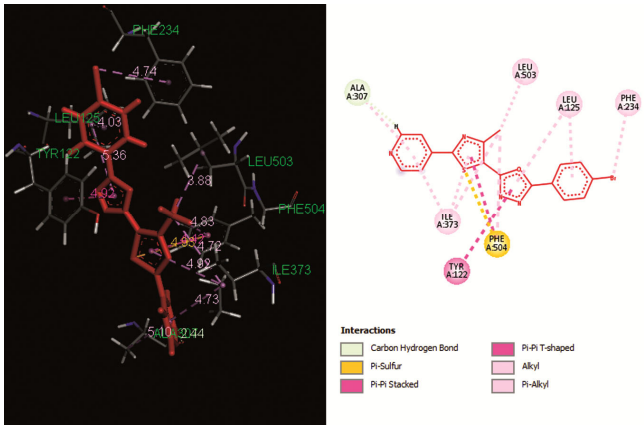


Fig. 5 — Binding Pose and molecular interactions of **4d** into the active site of CYP51

form π- π stacked, π- π T shaped, π –alkyl and alkyl interactions at various shown in Fig. 5.

The synthesized derivatives **4f** (-5.895Kcal/ Mol) interact with hydrophobic amino acid TYR122 with nitrogen atom of 1,3-thiazole ring to form carbon hydrogen bond interactions with distance of 2.52 Å. The aliphatic and hydrophobic amino acids such as LEU91, LEU125,PHE234 and LEU503 are forming π- π-stacked, π- π- shaped, π-Alkyl and Alkyl with phenyl, 1,3,4-oxadiazole, 1,3-thiazole and pyridine rings shown in Fig. 6.

In vitro antimicrobial screening

The zone of inhibition, MIC against microorganisms tested is reported in Table 2 and Table 3 respectively. As shown in Table 2 most of the compounds were active against gram positive and gram negative bacteria as well as both the fungi species**.** The results of antimicrobial screening were found satisfactory for all the synthesized derivatives as shown in Table 2. 3-pyridyl and 4-pyridyl derivatives are found to be more active than the 2-pyridyl derivatives. Many of the synthesized derivatives was found to have inhibition zone above 10mm for the two fungal species (A. Niger and C. Albicans) and two bacterial species (S. Aureus and E. Coli). Amongst 2-pyridyl derivatives compound **2b** (F) was found to have good antifungal activity. Compound **2a** (H), **2c** (Cl) and **2e** (Me) was found to have moderate antifungal activity. In 3-pyridyl series compound **3f** (OMe) and **3g** (NO_2) was found to have broad spectrum antibiotic activity possessing both antibacterial and antifungal activity. Compound **3b** (F), **3c** (Cl), **3d** (Br), **3e** (Me) was found to have good antifungal activity. Amongst 4-pyridyl derivatives compound **4d** (Br) and **4e** (Me) was found to have broad spectrum antibiotic activity possessing both antibacterial and antifungal activity. Compound **4a** (H) and **4b** (F) was found to have good antifungal activity whereas compound **4f** (OMe) was found to have good antibacterial activity.

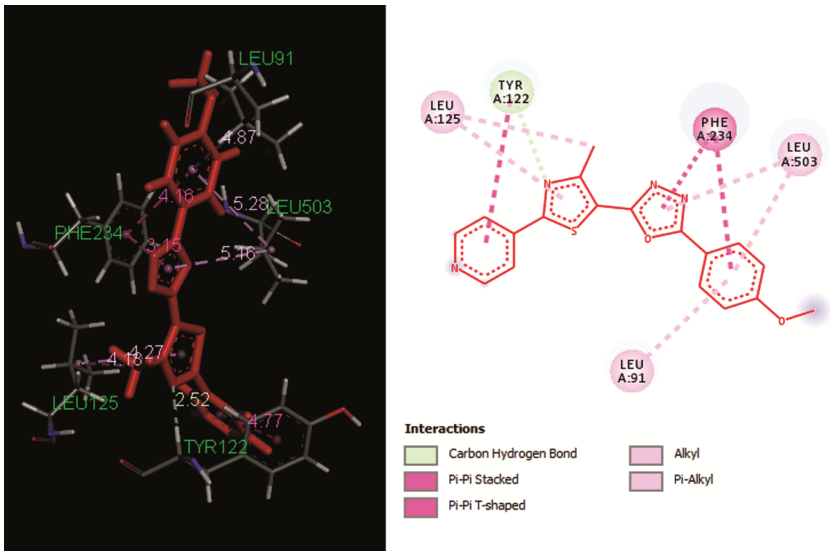


Fig. 6 — Binding Pose and molecular interactions of **4f** into the active site of CYP51

Table 2 — Antimicrobial screening of the synthesized compound **2a**-**4h** (zone diameter of growth inhibition in mm)

Compd	*Aspergillus niger* (NCIM 545)	*Candida albicans* (MTCC 277)	*Staphylococcus aureus* (ATCC 29737)	*Escherchia coli* (ATCC 25922)
2a	13.5	13.2	12.4	12.6
2b	14.1	13.7	11.6	11.8
2c	12.9	12.6	12.7	13.2
2d	11.8	11.4	12.3	11.9
2e	12.3	12.1	11.4	12.3
2f	11.0	10.5	10.9	10.2
2g	10.6	9.5	9.8	9.9
2h	10.6	10.3	10.2	10.3
3a	11.2	10.5	8.2	9.9
3b	13.8	11.4	12.1	13.7
3c	13.6	12.3	12.4	11.5
3d	12.5	12.7	11.6	11.8
3e	13.1	11.9	11.3	10.6
3f	14.4	13.3	14.8	12.9
3g	13.7	13.1	14.4	12.6
3h	10.2	10.3	10.3	10.2
4a	12.2	12.6	11.8	11.3
4b	14.2	13.8	13.9	12.1
4c	11.4	10.8	11.2	10.6
4d	13.7	13.1	14.4	13.4
4e	12.6	13.5	14.1	12.5
4f	11.8	11.2	12.5	11.9
4g	11.5	10.7	11.7	11.1
4h	10.3	10.3	10.0	10.2
Control	09±0.3	08±0.6	08±0.8	08±0.2
Fluconazole	15±0.7	14±0.5	–	–
Gentamycin	–	–	15±0.6	14±0.4

Gentamycin (40 µg/disc), Fluconazole (40 µg/disc) were used as reference; synthesized compounds (40µg/well). Bold values indicate the values of more active compounds in the series.

Table 3 — *In vitro* antifungal and antibacterial activity of synthesized compounds **2a**-**4h** [MIC ug/mL (μM)]

Compd	Mol. wt.	*Aspergillusniger* (NCIM 545)	*Candida albicans* (MTCC 277)	*Staphylococcus aureus*(ATCC 29737)	*Escherchia coli*(ATCC 25922)
			MIC μg/mL (μM)		
2a	320.37	40 (0.124)	40 (0.124)	20 (0.062)	40 (0.124)
2b	338.36	20 (0.059)	20 (0.059)	20 (0.059)	20 (0.059)
2c	354.81	40 (0.112)	40 (0.112)	20 (0.056)	40 (0.112)
2d	399.26	40 (0.100)	40 (0.100)	20 (0.050)	40 (0.100)
2e	334.39	40 (0.119)	40 (0.119)	20 (0.059)	40 (0.119)
2f	350.39	80 (0.228)	80 (0.228)	80 (0.228)	80 (0.228)
2g	365.37	80 (0.218)	80 (0.218)	80 (0.218)	80 (0.218)
2h	345.38	80 (0.231)	80 (0.231)	80 (0.231)	80 (0.231)
3a	320.37	80 (0.249)	80 (0.249)	80 (0.249)	80 (0.249)
3b	338.36	20 (0.059)	10 (0.029)	20 (0.059)	40 (0.118)
3c	354.81	80 (0.225)	80 (0.225)	80 (0.225)	80 (0.225)
3d	399.26	40 (0.100)	40 (0.100)	40 (0.100)	40 (0.100)
3e	334.39	80 (0.239)	80 (0.239)	80 (0.239)	80 (0.239)
3f	350.39	40 (0.114)	40 (0.114)	20 (0.057)	40 (0.114)
3g	365.37	40 (0.109)	40 (0.109)	40 (0.109)	40 (0.109)
3h	345.38	80 (0.231)	80 (0.231)	80 (0.231)	80 (0.231)
4a	320.37	80 (0.249)	80 (0.249)	80 (0.249)	80 (0.249)
4b	338.36	40 (0.118)	40 (0.118)	10 (0.029)	40 (0.118)
4c	354.81	80 (0.225)	80 (0.225)	80 (0.225)	80 (0.225)
4d	399.26	40 (0.100)	40 (0.100)	40 (0.100)	40 (0.100)
4e	334.39	40 (0.119)	80 (0.239)	40 (0.119)	80 (0.239)
4f	350.39	80 (0.228)	80 (0.228)	80 (0.228)	80 (0.228)
4g	365.37	80 (0.218)	80 (0.218)	80 (0.218)	80 (0.218)
4h	345.38	80 (0.231)	80 (0.231)	80 (0.231)	80 (0.231)
Fluconazole	306.27	40 (0.130)	40 (0.130)	–	–
Gentamycin	477.59	–	–	40 (0.083)	40 (0.083)

Bold values indicate the values of more active compounds in the series.

Careful analysis of the MICs in Table 3 provides some lead molecules with good antibacterial and antifungal activity. Of the compounds **2a-4g** tested, compound with electron-withdrawing F at the phenyl ring expressed a moderate to good activity against most of the tested pathogens, they inhibited the Gram positive pathogens equally. Compound **3b** (F) required about 20 μg/mL against Gram positive bacteria and 10 μg/mL against the fungi species, whereas **4b** (F) required 10 μg/mL against *S. aureus*.

Structure activity relationship (SAR)

The results of the *in vivo* and *in vitro* antimicrobial screening demonstrated the following assumptions about the structural activity relationship (SAR).

1. It is noteworthy to point out that substituted 2-pyridyl and 4-pyridyl derivatives in general showed good antimicrobial activity than 2-pyridyl derivatives. The order of their activity is 4-pyridyl > 2-pyridyl > 3-pyridyl.
2. The derivative **4d** (Br), **4e** (Me) and **4f** (OMe) of 4-pyridyl series showed better binding energy. Amongst the 3-pyridyl series the only derivative **3g** (NO_2) and of 2-pyridyl series the derivative **2e** (Me) showed best binding capacity.
3. The in-silico results are matching with the *in vitro* antimicrobial screening showing that the derivative **3g** (NO_2), **4d** (Br) and **4e** (Me) possess broad spectrum of activity against fungal as well as bacterial species.
4. The synthesized derivative **4b** (F) showed the least MIC 10(0.0290) for the bacterial species *S. Aureus* and **3b** (F) showed the least MIC 10(0.0290) for the fungal species *C. albicans*.

5. The derivative **3g** (NO_2) and **4d** (Br) are found to be the best antifungal agent's on the basis of *in silico* as well as *in vitro* screening.

Experimental Section

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. All the reactions were monitored by thin layer chromatography (TLC) on pre-coated silica gel 60 F254(mesh); spots were visualized with UV light. Merck silica gel(60-120 mesh) was used for column chromatography. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Brucker Avance II 400 MHz NMR spectrometer in $CDCl_3$/DMSO-d_6 solution using tetramethylsilane as an internal standard. All chemical shifts were recorded in δ (ppm) and the following abbreviations are used: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet. The mass spectra were recorded on Waters, Q-TOF Micromass /ESI-MS at 70eV.

General procedure for the synthesis of pyridine thioamides, 2

A solution of pyridine carbonitrile (5 g/5 mL) in pyridine (15 mL) and triethyl amine (3 mL) was stirred for 15min. H_2S gas was then passed into the reaction mixture. The reaction was monitored on TLC. After stirring for about 2 hrs the solution turns to greenish yellow solid. On completion of the reaction, the mixture was poured into crushed ice and stirred for the complete precipitation. The crude thioamide product was filtered and washed extensively with water. The product was re-crystallized from ethanol to obtain almost pure product. Yield: 80-90%.

General procedure for the synthesis of ethyl - 4 - methyl-2-(pyridyl) thiazole-5-carboxylate, 3

Thioamide (2) (10gm,1mmol) was then condensed with 2-chloroethylacetoacetate (11 mL,1mmol) in refluxed ethanol at 80°C in an oil bath for about 5-6 hrs. The oil was then poured onto petri dish to evaporate the solvent. The sticky mass was then washed using hexane and obtained 5-carboethoxy-4-methyl(pyridyl-2-yl) thiazole **(3)**

General procedure for the synthesis of 4-methyl - 2 - (pyridyl) thiazole - 5 –carbohydrazide, 4

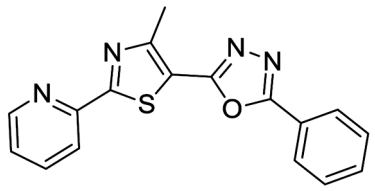
A mixture of hydrazine hydrate and the 5-carboethoxy-4-methyl (pyridyl - 2 - yl) thiazole (**3**) was dissolved in ethanol and the solution was refluxed for 2-3 hrs for getting the respective acid hydrazide.

General procedure for the synthesis of 2-pyridinylsubstituted thiazolyl-5-aryl-1,3,4-oxadiazoles

Appropriate pyridyl acid hydrazide (**4**) (1 mmol) was dissolved in phosphorous oxychloride (5 mL) and different 4-substituted benzoic acids (**3**) (1 mmol) was added. The reaction mixture, after refluxing for 5 hrs, was cooled to RT and poured onto crushed ice. On neutralization of the contents with sodium bicarbonate solution (20%), a solid separated out and was filtered, washed with water and dried. It was crystallized from ethanol to give title compounds, 2-pyridinylsubstituted thiazolyl-5-aryl-1,3,4-oxadiazoles with moderate to better yields.

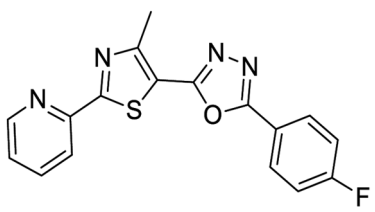
Spectral data

2-(4-Methyl-2-(pyridin-2-yl)thiazol-5-yl)-5-phenyl-1,3,4-oxadiazole, 2a:



Yield 89%. Yellow. m.p.198°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62-8.64 (d, *J* = 5.2Hz, 1H, pyridine), 8.20-8.22(d, *J* = 8.2Hz, 1H, pyridine), 8.15-8.17 (ddd, *J* = 7.9, *J* = 4.5, *J* = 1.6Hz,1H, pyridine), 8.10-8.11 (ddd, *J* = 8Hz, 5.2Hz, *J* = 1.7Hz, 1H, Pyridine), 7.90 (d, *J* = 8.1Hz, 2H, phenyl), 7.92-7.93(m, 3H, phenyl), 2.85(s, 3H, methyl thiazole); ^{13}C NMR(100MHz, $CDCl_3$): δ 164.52, 162.48, 161.28, 157.44, 152.48, 149.22, 137.22, 133.79, 129.52, 128.76, 127.92,127.50, 124.24, 123.62,17.52.

2-(4-Fluorophenyl)-5-(4-methyl-2-(pyridin-2-yl)thiazol-5-yl)-1,3,4-oxadiazole, 2b:

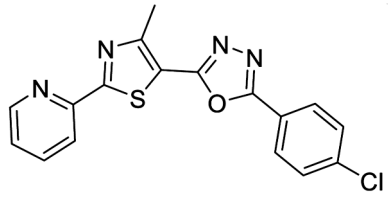


Yield 62%. White. m.p.172°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.64-8.66 (d, *J*=4.76Hz, 1H, pyridine),8.22-

8.24 (d, *J*= 7.84Hz, 1H, pyridine), 8.01-8.07 (ddd, *J* = 8.68Hz, *J* = 4.64Hz, *J* = 1.8Hz,1H, phenyl), 7.82-7.86 (ddd, *J* = 7.8Hz, *J* = 5.64Hz, *J*= 1.6Hz, 1H, Pyridine), 7.52-7.56 (dd, *J* = 8.56Hz, *J* = 4.84Hz, 2H, phenyl), 7.37-7.41 (ddd,*J* = 7.52Hz, *J* = 1.68, *J* = 1Hz, 2H, phenyl), 2.95 (s, 3H, methyl thiazole)

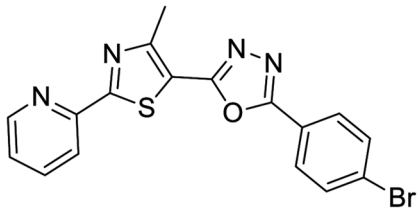
^{13}C NMR (100 MHz, $CDCl_3$): δ 164.54, 162.98, 162.88, 160.19, 157.44, 149.66, 142.55, 138.30,137.21,129.61, 128.23, 125.39, 122.16, 120.11,17.54; MS: *m/z* (70 eV) 339.0718 [M+1], for the molecular formula $C_{17}H_{12}FN_4OS$.

2-(4-Chlorophenyl)-5-(4-methyl-2-(pyridin-2-yl)thiazol-5-yl)-1,3,4-oxadiazole, 2c:



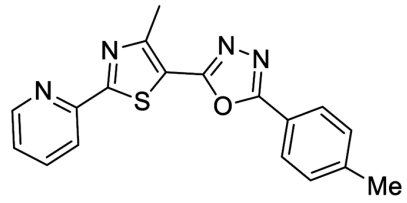
Yield 60%. Brown. m.p.200-205°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.66-8.67 (d, *J* = 3.24Hz, 1H, pyridine), 8.19-8.21 (d, *J* = 7.36Hz, 1H, pyridine), 8.12-8.17 (dd, *J* = 5.24Hz, *J* = 4.36Hz, 1H, pyridine), 7.95-7.98 (dd, *J* = 8.2Hz, *J* = 7.4Hz, 1H, Pyridine), 7.41 (d, *J* = 8.32Hz, 2H, phenyl), 7.37 (d, *J* = 8.76Hz, 2H, phenyl), 2.89 (s, 3H, methyl thiazole); ^{13}C NMR (100MHz, $CDCl_3$): δ 164.54, 162.88, 161.28,157.42, 152.44, 149.22, 137.22, 134.33, 129.39, 128.92, 127.96, 124.23, 124.12, 123.61, 17.54; MS: *m/z* (70 eV) 355.0419 [M+1], 357.0389 [M+2] for the molecular formula $C_{17}H_{12}ClN_4OS$.

2-(4-Bromophenyl)-5-(4-methyl-2-(pyridin-2-yl)thiazol-5-yl)-1,3,4-oxadiazole, 2d:



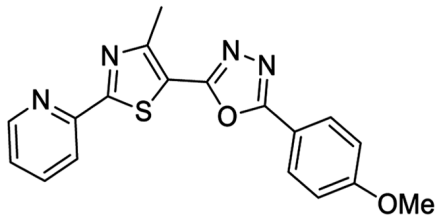
Yield 66%. White. m.p.140-142°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.60-8.62 (d, *J* = 4.9Hz, 1H, pyridine), 8.18-8.19(d, *J* = 7.9Hz, 1H, pyridine), 7.98-7.99 (ddd, *J* = 7.5Hz, 4.2Hz, 1.5Hz,1H,pyridine), 7.58-7.60 (ddd, *J* = 8.0Hz, 5.6Hz, 2.1Hz, 1H, Pyridine), 7.43 (d, *J* = 8.3Hz, 2H, phenyl), 7.34 (d, *J* = 8.3Hz, 2H, phenyl), 2.86 (s, 3H, methyl thiazole). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.75, 162.54, 161.14, 157.54, 152.46, 149.26, 137.26, 134.33, 129.65,128.54, 127.57, 124.85, 124.54, 123.57, 17.52.

2-(4-Methyl-2-(pyridin-2-yl)thiazol-5-yl)-5-(*p*-tolyl)-1,3,4-oxadiazole, 2e:



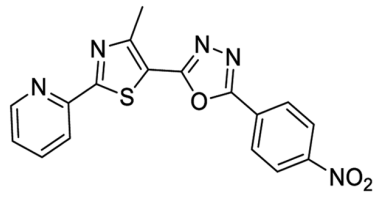
Yield 78%. Yellowish green. m.p.190°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.66 - 8.67(d, *J* = 4Hz, 1H, pyridine), 8.19-8.20(d, *J* = 8Hz, 1H, pyridine), 7.97-7.98 (ddd, *J* = 8Hz, 3.92Hz, 1.8Hz, 1H, pyridine), 7.51-7.54 (ddd, *J* = 8Hz, 3.80Hz,1.6Hz, 1H, Pyridine), 7.84 (d, *J* = 8Hz, 2H, phenyl), 7.41-7.43 (d, *J* = 8Hz, 2H, phenyl), 2.87 (s, 3H, methyl thiazole), 2.52 (s, 3H, methyl). ^{13}C NMR(100MHz, $CDCl_3$): δ 169.39, 164.55, 163.77, 162.84, 159.13, 152.46, 149.71, 142.29, 137.65, 131.73, 129.81, 126.49, 125.68, 119.50, 21.21,17.37; MS: *m/z* (70 eV) 335.0971 [M+1], for the molecular formula $C_{18}H_{15}N_4OS$.

2-(4-Methoxyphenyl)-5-(4-methyl-2-(pyridin-2-yl)thiazol-5-yl)-1,3,4-oxadiazole, 2f:



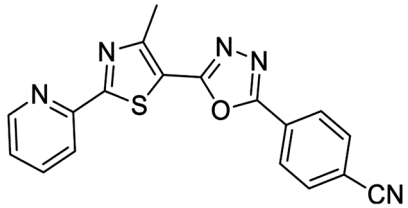
Yield 64%. Green. m.p.170°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.63-8.65 (d, *J* = 3.9Hz, 1H, pyridine), 8.20-8.22 (d, *J* = 8.9Hz, 1H, pyridine), 7.85 - 7.87 (ddd, *J* = 7.9Hz, 4.1Hz, 1.62Hz, 1H, pyridine), 7.65-7.67 (ddd, *J* = 8.1Hz, 4.9Hz, 1.8Hz, 1H, Pyridine), 7.34 (d, *J* = 7.9Hz, 2H, phenyl), 7.30 (d, *J* = 7.9Hz, 2H, phenyl), 3.86 (s, 3H, methoxy), 2.82 (s, 3H, methyl thiazole). ^{13}C NMR(100MHz, $CDCl_3$): δ 164.55, 162.84, 161.24, 157.44, 152.46, 149.27, 142.21, 137.26, 131.73, 127.95, 127.54, 126.37, 124.25, 123.54, 55.57, 17.52.

2-(4-Methyl-2-(pyridin-2-yl)thiazol-5-yl)-5-(4-nitrophenyl)-1,3,4-oxadiazole, 2g:



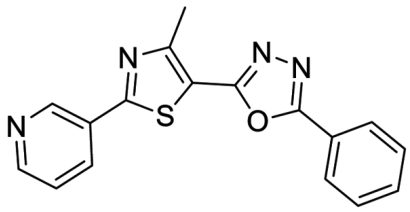
Yield 52%. Red. m.p.200-202°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.62-8.64 (d, *J* = 5Hz, 1H, pyridine), 8.21-8.24 (d, *J* = 7.9Hz, 1H, pyridine), 8.15-8.17 (ddd, *J* = 8Hz, 5.6Hz, 2.3Hz, 1H, pyridine), 7.87-7.89 (ddd, *J* = 8.5Hz, 4.30Hz, 2.1Hz, 1H, Pyridine), 7.66 (d, *J* = 7.95Hz, 2H, phenyl), 7.42 (d, *J* = 7.92Hz, 2H, phenyl), 2.89 (s, 3H, methyl thiazole). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.58, 162.98, 161.42, 157.94, 152.48, 149.92, 147.95, 137.72, 132.79, 130.52, 128.46, 127.43, 124.44, 123.6,17.5.

4-(5-(4-Methyl-2-(pyridin-2-yl)thiazol-5-yl)-1,3,4-oxadiazol-2-yl)benzonitrile, 2h:



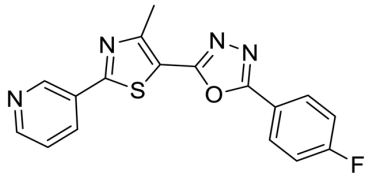
Yield 54%. White. m.p.180°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.61-8.65 (d, *J* = 4.7Hz, 1H, pyridine), 8.24-8.26 (d, *J* = 7.8Hz, 1H, pyridine), 8.20-8.22 (ddd, *J* = 8.4Hz, 4.7Hz, 2.1Hz, 1H, pyridine), 7.98-8.10 (ddd, *J* = 7Hz, 3.9Hz, 1.6Hz, 1H, Pyridine), 7.90 (d, *J* = 8.23Hz, 2H, phenyl), 7.46 (d, *J* = 8.68Hz, 2H, phenyl), 2.82 (s, 3H, methyl thiazole). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.48, 162.88, 161.22, 157.44, 152.48, 149.22, 137.22, 132.28, 130.40, 128.79, 127.52, 124.46, 123.38, 118.63, 17.44.

2-(4-Methyl-2-(pyridin-3-yl)thiazol-5-yl)-5-phenyl-1,3,4-oxadiazole, 3a:



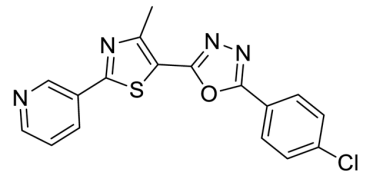
Yield 72%. Yellow. m.p.198°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 9.17-9.18 (d, *J* = 1.8Hz, 1H, pyridine), 8.68-8.69 (dd, *J* = 4.7Hz, 1.5Hz, 1H, pyridine), 8.45-8.47 (ddd, *J* = 7.9, 4.8, 1.9Hz, 1H, pyridine), 8.03-8.10 (dd, *J* = 8.1Hz, 7.5Hz, 1H, Pyridine), 7.85-7.89 (m, 5H, phenyl), 2.86 (s, 3H, methyl thiazole); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.58, 161.22, 153.64, 152.48, 148.92, 147.95, 134.72, 133.79, 133.42, 129.26, 128.73, 127.94, 127.56, 124.50, 17.53.

2-(4-Fluorophenyl)-5-(4-methyl-2-(pyridin-3-yl)thiazol-5-yl)-1,3,4-oxadiazole, 3b:



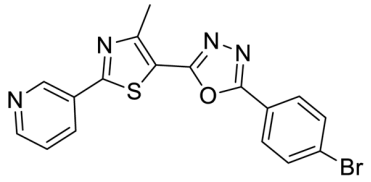
Yield 65%. Dark yellow. m.p.198°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 9.18 - 9.20 (d, *J* = 1.7Hz, 1H, pyridine), 8.72- 8.73 (dd, *J* = 5Hz,1.8Hz,1H,pyridine), 8.50-8.51 (ddd, *J* = 8.2Hz, 5.1Hz, 2.1Hz, 1H, pyridine), 8.18-8.20 (dd, *J* = 8.1Hz, 6.1Hz, 1H, Pyridine), 8.10-8.11 (dd, *J* = 7.8Hz, 5.1Hz, 2H, phenyl), 7.99-8.02 (dd, *J* = 11Hz,7.9Hz,2H, phenyl), 2.92 (s, 3H, methyl thiazole); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.54, 162.98, 161.88, 153.44, 152.48, 148.92, 147.92, 134.02,133.45, 129.19,127.92, 124.46, 121.71,116.03,17.54.

2-(4-Chlorophenyl)-5-(4-methyl-2-(pyridin-3-yl)thiazol-5-yl)-1,3,4-oxadiazole, 3c:



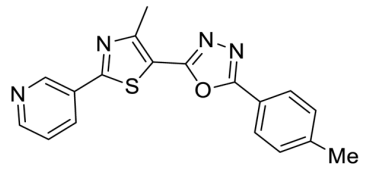
Yield 87%. Yellowish green. m.p.198°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 9.12 (d, *J* = 1.96Hz, 1H, pyridine), 8.72-8.73 (dd, *J* = 4.8Hz,1.6Hz, 1H, pyridine), 8.37 - 8.40 (ddd, *J* = 7.8Hz,5.76Hz,1.92Hz,1H, pyridine), 8.09-8.14 (d, *J* = 8.56Hz, 2H, Phenyl),7.68-7.70 (d, *J* = 8.56Hz, 2H, phenyl),7.57-7.60 (dd, *J* = 7.8Hz, 4.96Hz, 1H, pyridine), 2.88(s,3H,methyl thiazole); ^{13}C NMR (100MHz, $CDCl_3$): δ 164.54, 161.28, 153.62, 152.44, 148.92, 147.92, 134.33, 134.09, 133.42, 129.36, 128.93,127.92, 124.21,124.04, 17.5; MS: *m/z* (70 eV) 355.0418 [M+1], 357.0387 [M+2] for the molecular formula $C_{17}H_{12}ClN_4OS$.

2-(4-Bromophenyl)-5-(4-methyl-2-(pyridin-3-yl)thiazol-5-yl)-1,3,4-oxadiazole, 3d:



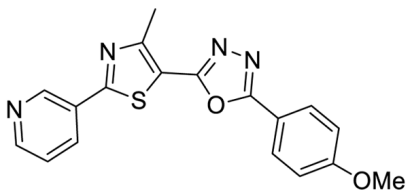
Yield 87%. Yellowish green. m.p.198°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 9.12 (d, *J* = 1.96Hz, 1H, pyridine), 8.72-8.73 (dd, *J* = 4.8Hz, 1.6Hz, 1H, pyridine), 8.37-8.40 (ddd, *J* = 7.8Hz, 5.76Hz, 1.92Hz, 1H, pyridine), 8.09-8.14 (d, *J* = 8.56Hz, 2H, Phenyl), 7.68-7.70 (d, *J* = 8.56Hz, 2H, phenyl), 7.57-7.60 (dd, *J* = 7.8Hz, 4.96Hz, 1H, pyridine),2.88 (s, 3H, methyl thiazole); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.55, 161.24, 153.54, 152.46, 148.96, 147.26, 134.33, 132.65, 129.54, 127.57, 125.85, 124.04, 123.17,17.52.

2-(4-Methyl-2-(pyridin-3-yl)thiazol-5-yl)-5-(*p*-tolyl) -1,3,4-oxadiazole, 3e:



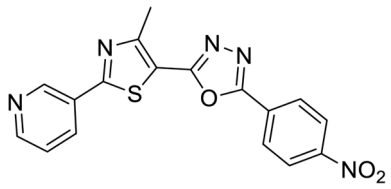
Yield 87%. Yellowish green. m.p.198°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 9.22 (d, *J* = 1.6Hz, 1H, pyridine), 8.71-8.72 (dd, *J* = 3.48Hz,1.16Hz, 1H, pyridine), 8.27-8.30 (ddd, *J* = 3.92Hz, 2Hz, 1.92Hz, 1H, pyridine), 7.99-8.01(d, *J* = 8.2Hz, 2H, Phenyl), 7.68 (dd, *J* = 4.8Hz, 4.76Hz, 1H, pyridine), 7.34-7.36 (d, *J* = 7.96Hz, 2H, phenyl), 2.94 (s, 3H, methyl thiazole), 2.45 (s,3H,tolyl); ^{13}C NMR (100MHz, $CDCl_3$): δ 165.45, 157.13, 153.74, 152.46, 151.66, 148.97, 147.89, 142.72, 133.87, 129.92, 126.97, 123.90, 120.61, 115.44, 21.73, 17.61; MS: *m/z* (70 eV) 335.0968 [M+1], for the molecular formula $C_{18}H_{15}N_4OS$.

2-(4-Methoxyphenyl)-5-(4-methyl-2-(pyridin-3-yl)thiazol-5-yl)-1,3,4-oxadiazole, 3f:



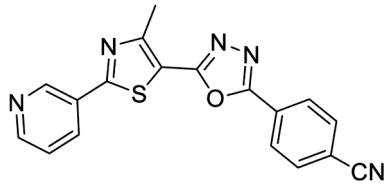
Yield 87%. Yellowish green. m.p.198°C. ^{1}H NMR(400MHz, $CDCl_3$): δ 9.20 (d, *J* = 1.7Hz, 1H, pyridine), 8.67-8.68 (dd, *J* = 4.2Hz,1.8Hz, 1H, pyridine), 8.34-8.36 (ddd, *J* = 4.6Hz, 2.5Hz, 1.52Hz, 1H, pyridine), 8.13 (d, *J* = 7.9Hz, 2H, Phenyl), 7.94 (dd, *J* = 5Hz, 4.7Hz, 1H, pyridine), 7.40 (d, *J* = 7.9Hz, 2H, phenyl), 3.89 (s, 3H, methoxy), 2.87 (s, 3H, methyl thiazole); ^{13}C NMR (100MHz, $CDCl_3$): δ 164.55, 161.24, 160.64, 153.66, 152.47, 148.91, 147.96, 134.73, 133.95, 129.54, 127.97, 124.25, 115.54, 114.80, 55.57,17.52.

2-(4-Methyl-2-(pyridin-3-yl)thiazol-5-yl)-5-(4-nitrophenyl)-1,3,4-oxadiazole, 3g:



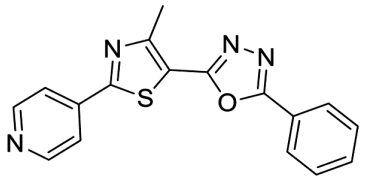
Yield 87%. Yellowish green. m.p.198°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 9.23-9.25 (d, *J* = 1.9Hz, 1H, pyridine), 8.77-8.79 (dd, *J* = 5Hz, 2Hz, 1H, pyridine), 8.63-8.65 (ddd, *J* = 5.6Hz, 2.3Hz, 1.9Hz, 1H, pyridine), 8.58 (dd, *J* = 5.6Hz, 5.2Hz, 1H, Pyridine), 8.56 (d, *J* = 8.2Hz, 2H, phenyl), 8.36-8.40 (d, *J* = 8.2Hz, 2H, phenyl), 2.90 (s, 3H, methyl thiazole); ^{13}C NMR(100MHz, $CDCl_3$): δ 164.58, 161.22, 153.94, 152.48, 148.92, 147.98, 147.90, 134.72, 133.79, 132.52, 130.46, 128.83, 127.44,124.64,17.5.

4-(5-(4-Methyl-2-(pyridin-3-yl)thiazol-5-yl)-1,3,4-oxadiazol-2-yl)benzonitrile, 3h:



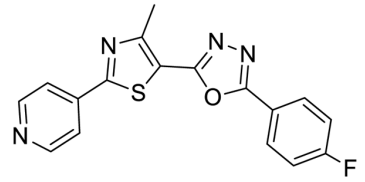
Yield 70%. Yellow. m.p.170-172°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 9.22-9.24 (d, *J* = 1.8Hz, 1H, pyridine), 8.85-8.86 (dd, *J* = 5.6Hz, 2.3Hz, 1H, pyridine), 8.68-8.70 (ddd, *J* = 6.2Hz, 3.5Hz, 1.9Hz, 1H, pyridine), 8.60-8.61 (dd, *J* = 5.8Hz, 5.2HZ,1H, Pyridine), 8.59 (d, *J* = 7.9Hz, 2H, phenyl), 8.45-8.47 (d, *J* = 7.9Hz, 2H, phenyl), 2.89 (s, 3H, methyl thiazole); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.48, 161.22, 153.64, 152.48, 148.92, 147.92, 134.28, 133.40, 132.7, 130.41, 128.29, 127.92, 124.46, 118.63, 112.36, 17.54.

2-(4-Methyl-2-(pyridin-4-yl)thiazol-5-yl)-5-phenyl-1,3,4-oxadiazole, 4a:



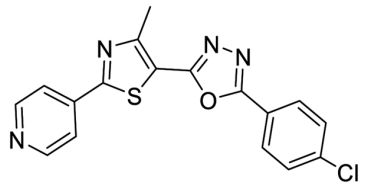
Yield 75%. Red. m.p.135-137°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.74-8.75 (d, *J* = 4Hz, 2H, pyridine), 8.10-8.11 (d, *J* = 4Hz, 2H, pyridine), 7.83(d, *J* = 8Hz, 2H, phenyl), 7.54-7.56 (m, 3H, phenyl), 2.94 (s, 3H,methyl thiazole); ^{13}C NMR (100MHz, $CDCl_3$): δ 164.54, 161.22, 153.64, 152.48, 149.82, 143.72, 133.79, 129.22, 128.76,127.95, 127.55, 121.33, 17.51; MS: *m/z* (70 eV) 321.0815 [M+1], for the molecular formula $C_{17}H_{13}N_4OS$.

2-(4-Fluorophenyl)-5-(4-methyl-2-(pyridin-4-yl)thiazol-5-yl)-1,3,4-oxadiazole, 4b:



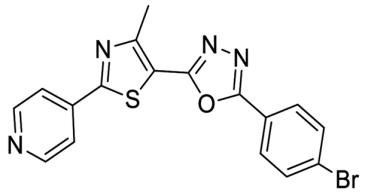
Yield 68%. White. m.p.150-152°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.75-8.76 (d, *J* = 6.8Hz, 2H, pyridine), 8.13-8.16 (ddd, *J* = 15.04Hz, 5.24Hz, 3.6Hz, 2H, phenyl), 7.91-7.92(d, *J* = 6.08Hz, 2H, pyridine), 7.36-7.40 (dd, *J* = 8.80Hz, 8.56Hz, 2H, phenyl), 2.91 (s, 3H, methyl thiazole); ^{13}C NMR (100MHz, $CDCl_3$): δ 164.54, 161.22, 153.64, 152.48, 149.82, 143.72, 133.79, 129.22, 128.76,127.95, 127.55, 121.33, 17.51; MS: *m/z* (70 eV) 339.0716 [M+1], for the molecular formula $C_{17}H_{12}FN_4OS$.

2-(4-Chlorophenyl)-5-(4-methyl-2-(pyridin-4-yl)thiazol-5-yl)-1,3,4-oxadiazole, 4c:



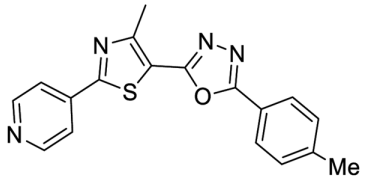
Yield 72%. Yellow. m.p.170-172°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.73-8.75 (d, *J* = 4.3Hz, 2H, pyridine), 8.11-8.12 (d, *J* = 4.2Hz, 2H, pyridine), 7.85-7.87 (d, *J* = 7.9Hz, 2H, phenyl), 7.60-7.62 (d, *J* = 7.8Hz, 2H, phenyl), 2.90 (s, 3H, methyl thiazole); ^{13}C NMR (100MHz, $CDCl_3$): δ 164.54, 161.22, 153.64, 152.48, 149.82, 143.72, 134.79, 129.22, 128.76,127.95, 124.55, 121.33, 17.51

2-(4-Bromophenyl)-5-(4-methyl-2-(pyridin-4-yl)thiazol-5-yl)-1,3,4-oxadiazole, 4d:



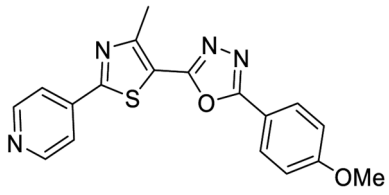
Yield 62%. White. m.p.160-165°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.70 - 8.72 (d, *J* = 4.5Hz, 2H, pyridine), 7.94 - 7.96 (d, *J* = 4.6Hz, 2H, pyridine), 7.92 - 7.93 (d, *J* = 7.8Hz, 2H, phenyl), 7.52 - 7.55 (d, *J* = 8Hz, 2H, phenyl), 2.97 (s, 3H, methyl thiazole); ^{13}C NMR (100MHz, $CDCl_3$): δ 164.54, 161.22, 153.64, 152.48, 149.82, 143.72, 132.79, 129.22, 127.95, 125.55, 123.33,121.32, 17.51

2-(4-Methyl-2-(pyridin-4-yl)thiazol-5-yl)-5-(*p*-tolyl)-1,3,4-oxadiazole, 4e:



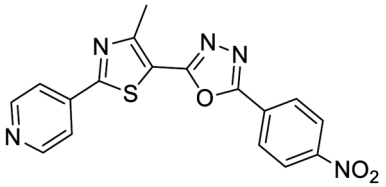
Yield 84%. White. m.p.150-155°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.75 (d, *J* = 4.2Hz, 2H, pyridine), 7.90 - 7.91 (d, *J* = 4.2Hz, 2H, pyridine), 7.96 - 7.98 (d, *J* = 7.5Hz, 2H, phenyl), 7.40 - 7.41 (d, *J* = 7.5Hz, 2H, phenyl), 2.9 (s, 3H, methyl thiazole), 2.4 (s, 3H, tolyl methyl); ^{13}C NMR (100MHz, $CDCl_3$): δ 164.54, 161.22, 153.64, 152.48, 149.82, 143.72, 142.79, 131.22, 127.95, 127.55, 126.33,121.32, 21.36, 17.51; MS: *m/z* (70 eV) 335.0973 [M+1], for the molecular formula $C_{18}H_{15}N_4OS$.

2-(4-Methoxyphenyl)-5-(4-methyl-2-(pyridin-4-yl)thiazol-5-yl)-1,3,4-oxadiazole, 4f:



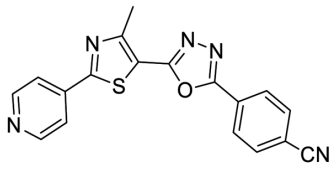
Yield 63%. Yellow. m.p.196-198°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.72 (d, *J* = 4.8Hz, 2H, pyridine), 7.90 - 7.91 (d, *J* = 4.8Hz, 2H, pyridine), 7.81 - 7.83 (d, *J* = 7.9Hz, 2H, phenyl), 7.37 - 7.39 (d, *J* = 7.9Hz, 2H, phenyl), 3.87 (s, 3H, methoxy), 2.50 (s, 3H, methyl thiazole); ^{13}C NMR (100MHz, $CDCl_3$): δ 164.54, 160.22, 153.64, 152.48, 149.82, 143.72, 129.23, 127.95, 121.32, 115.95, 114.82, 55.36, 17.51.

2-(4-Methyl-2-(pyridin-4-yl)thiazol-5-yl)-5-(4-nitrophenyl)-1,3,4-oxadiazole, 4g:



Yield 81%. Yellow. m.p.165°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.76 - 8.77 (d, *J* = 4.9Hz, 2H, pyridine), 8.09 - 8.10 (d, *J* = 8.2Hz, 2H, phenyl), 7.96 - 7.98 (d, *J* = 4.9Hz, 2H, pyridine), 7.60 - 7.63 (d, *J* = 8.2Hz, 2H, phenyl), 2.95 (s, 3H, methyl thiazole); ^{13}C NMR (100MHz, $CDCl_3$): δ 164.54, 161.22, 153.64, 152.48, 149.82, 143.72, 132.23, 130.25, 128.82, 127.95, 121.32, 17.51.

4-(5-(4-Methyl-2-(pyridin-4-yl)thiazol-5-yl)-1,3,4-oxadiazol-2-yl)benzonitrile, 4h:



Yield 59%. Red-Brown. m.p.189°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.78 (d, *J* = 5Hz, 2H, pyridine), 8.11-8.13 (d, *J* = 8.3Hz, 2H, phenyl), 7.95-7.97 (d, *J* = 5Hz, 2H, pyridine), 7.71 - 7.74 (d, *J* = 8.3Hz, 2H, phenyl), 2.96 (s, 3H, methyl thiazole); ^{13}C NMR (100MHz, $CDCl_3$): δ 164.54, 161.22, 153.64, 152.48, 149.82, 143.72, 132.73, 130.45, 128.82, 127.95, 121.32,118.62,112.62, 17.51.

Molecular docking study

The AutoDockTools 1.5.4 (ADT) was used to prepare the input files for docking[34]. All water molecules and Ions were removed from the protein crystallographic structures, polar hydrogens were added and partial atomic charges were assigned by Kollmanunited charges method[35,36]. The pK_a values of the residues in the enzyme were calculated to determine if any of them were likely to adopt nonstandard ionization states, using PROPKA 2.0 (Ref. 37). The side chains of the lysine, arginine, and histidine residues were protonated, while the carboxylic groups of glutamic acid and aspartic acid were deprotonated. For each ligand, nonpolar hydrogens were merged, Gasteiger charges were assigned, and rotatable bonds were setup. The structures were then saved in the corresponding pdbqt file required by Autodock. A grid box ofm 40×40×40 Å (*x*, *y*, and *z*) was created around the enzymes active pocket with the spacing of1nm in each dimension to evaluate the ligand–protein interactions. The center of the grid box was set to the average coordinates of the crystallography ligand in the pdb structure. Other vina docking parameters were set to default.

Antimicrobial activity

The *in vitro* antibacterial activity of all the synthesized compounds was done by the disc diffusion method against the standard strains Gram-positive bacteria, *Staphylococcus aureus* (ATCC 29737) and Gram-negative bacteria, *Escherichia coli* (ATCC 25922). All cultures were maintained at 4ºC over nutrient agar slants throughout the experiment. The cultures incubated overnight at 37ºC in nutrient broth before using for antibacterial activity. Five hundred microliters of overnight old bacterial suspension were spread over the nutrient agar plates using a sterile cotton swab in order to get a uniform microbial growth. The synthesized compounds were dissolved in DMSO. A standard disc containing Gentamycin was used as positive control. The plates were left for 30 min at RT to allow the diffusion of synthesized compounds and then incubated at 37 ºC for 24 hours. The antimicrobial activity was evaluated by measuring the zone of inhibition using vernier calliper against the tested microorganism. All experiments were carried in triplicates.

The synthesized compounds were screened for their antifungal activity against *Candida albicans* (MTCC 277) and *Aspergillus niger* (NCIM 545). The test cultures were grown separately in Sabouards Dextrose broth (SDB) (Hi Media, India) at RT for 48 h. After checking the purity of the test culture, 10 µl of test cultures were spread on Sabouards Dextrose Agar plates (SDA). Using cork bore 6mm diameter, wells were made on plates. The test compounds were dissolved in DMSO. Each well was filled with 40 µg/mL of test compound. The DMSO used as

negative control and Flucanozole of 10 µg/mL concentration used as positive control. Inoculated plates were kept at RT for 48 h. Each plate was then observed for inhibition zones.

Conclusion

In conclusion, several 2-pyridinylsubstituted thiazolyl-5-aryl-1,3,4-oxadiazoles were successfully synthesized. The *in silico* molecular docking study highlights that **2e** (Me), **3g** (NO_2), **4d** (Br), **4e** (Me) and **4f** (OMe) are the most active forms of synthesized derivatives and have the strong potential to act against microorganism drug targets. The pharmacological study was undertaken to evaluate effect of substituent on the antibacterial and antifungal activities. Many of the synthesized derivatives exhibited good antimicrobial activity. In conclusion, derivative **2b**, **3b** and **4b** of the series containing fluorine as a common substituent was noticeably found to have good antifungal activity. The derivatives of 3-pyridyl and 4-pyridyl was found to have better activity than the isomeric 2-pyridyl series. Derivative **3g** (NO_2), **4d** (Br) and **4e** (Me) was found to have broad spectrum antimicrobial activity. 4-pyridyl position is found to possess better future scope than the 2-pyridyl and 3-pyridyl position on the basis of the above results.

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References

1 Amir M & Shawano S, *Ind J Het Chem*, 8 (1998) 107.
2 Ashour F A & Al Mazoroa S A, *J Pharm Sci*, 4 (1990) 29.
3 Nassar O M, *Indian J Het Chem*, 7 (1997) 105.
4 Mohamed N A, *Poly Der*, *44* (1994) 33.
5 Amir M & Kumar S, *Acta Pharm*, 57 (2007) 31.
6 Holla B S, Prasanna C S, Poojary B, Rao K S, Shridhara K & Bhat U G, *Ind J Chem*, 43 (2004) 864
7 Cao S, Qian X, Song G & Huang Q, *J Flu Chem*, 117 (2002) 63
8 Salimon J, Salih N, Hussien H, *Sains Malaysiana*, 40 (2011) 445.
9 Belkadi M, Othman A A, *ARKIVOC*, XI (2006) 183.
10 Garfunkle J, Ezzili C, Rayl TJ, Hochstatter DG, Hwang I & Boger D L, *J Med Chem*, 51 (2008) 4392.
11 Ohmoto K, Yamamoto T, Horiuchi T, Imanishi H, Odagaki Y, Kawabata K, Sekioka T, Hirota Y, Matsuoka S & Nakai H, *J Med Chem*, 43 (2000) 4927.
12 Ohmoto K, Yamamoto T, Okuma M, Horiuchi T, Imanishi H, Odagaki Y, Kawabata K, Sekioka T, Hirota Y & Matsuoka S, *J Med Chem*, 44 (2001) 1268.
13 Zeng H, Zhang H, Jang F, Zhao L, Zhang J, *Chem Biol Drug Des*, 78 (2011) 333.
14 Singh I P, Saxena A K & Shankar K, *Eur J Med Chem*, 21 (1986) 267.
15 Gilani S J, Khan S A & Siddiqui N, *Bioorg Med Chem Lett,* 20 (2010) 4762.
16 Ouyang X, Piatnitski E L, Pattaropong V, Chen X, He H Y, Kiselyov A S, Velankar A, Kawakami J, Labelle M, Smith L, *Bioorg Med Chem Lett,,* 16 (2006) 1191.
17 Tuma M C, Malikzay A, Ouyang X, Surgulazde D, Fleming J, Mitelman S, Camara M, Finnerty B, Doody J & Chekler E L P, *Trans Oncol*, 3 (2010) 318.
18 Shaharyar M & Mohammad W A, *Acta Pol Pharm Drug Res*, 66 (2009) 393.
19 Collin F, Karkare S & Maxwell A, *Appl Micro Biotech*, 92 (2011) 479.
20 Schoeffler A J & Berger J M, *Rev Biophy*, 1 (2008) 41.
21 Merino A, Madden K R, Lane W S, Champoux J J & Reinberg D, *Nature*, 365 (1993) 227.
22 Yeh Y C, Liu H F, Ellis C A & Lu A L, *J Biol Chem*, 269 (1994) 15498.
23 Heide L, *Biotech Adv*, 27 (2009) 1006.
24 Pozzi R, Simone M, Mazzetti C, Maffioli S, Monciardini P, Cavaletti L, Bamonte R, Sosio M & Donadio S, *J Antibio*, 64 (2011) 133.
25 Bryskier A, *Antimicrobial Agents: Antibacterials and Antifungals*, (John Wiley & Sons, Inc), 2005, p. 13.
26 L Heide, *Int J Med Microbio*, 304 (2014) 31.
27 Khan T, *Biomed Pharm*, 103 (2018) 923.
28 Daum G, Lees N D, Bard M & Dickson R, *Yeast*, 14 (1998) 1471.
29 Zhang H Z, Gan L L, Wang H & Zhou C H, *Mini Rev Med Chem*, 17 (2017) 122.
30 Sheehan D J, Hitchcoch C A & Sibley C M, *Clin Micro Rev*, 12 (1999) 40.
31 Lafitte D, *Biochem*, 41 (2002) 7217.
32 Friggeri L, *J Med Chem*, 61 (2018) 5679.
33 Desai N, *Eur J med Chem*, 196 (2021) 569.
34 Oleg T & Olson A J, *J Comp Chem*, 31 (2010) 455.
35 Morris G M, Huey R, Lindstrom W, Sanner M F, Belew R K, Goodsell D S & Olson A J, *J Comp Chem*, 30 (2009) 2785.
36 M F Sanner, *J Mol Graph Mod*, 17 (1999) 57.
37 Bas D C, Rogers D M & Jensen J H, *Proteins*, 73 (2008) 765.