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Synthesis, antimicrobial assays and docking study of new triazolo cum tetrazolo quinoline derivatives.

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Abstract A series of triazolo cum tetrazolo quinoline derivatives *viz* 4-((4-phenyl 1*H*-1,2,3 triazol 1 yl)-methyl) tetrazolo [1,5-a] quinoline derivatives **(4a-g)** were synthesized utilizing 1,3-dipolar cycloaddition (click chemistry) reaction of 4-(azido-methyl) tetrazolo [1,5-a] quinoline derivatives **(3a-3g)** with alkyne hydrocarbon containing a phenyl group using copper (I) catalyst has been achieved in good yield. *In vitro* antimicrobial assays of all corresponding synthesized derivatives were performed. Significant antimicrobial activity observed against all the tested strains for majority of the synthesized compounds. From the results of biological activity and docking study it is observed that the Novel triazolo cum tetrazolo quinoline derivatives 4b, 4d and 4f can serve as important lead moiety for further exploration.

Keywords: Huisgen Cycloaddition, Tetrazole, Triazole, Antimicrobial Assays, Molecular Docking

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1. Introduction

Tetrazole[1] ring is used extensively in pharmaceuticals. The combination of hetero cyclic functionality in medicinal chemistry and good pharmacokinetic profile of tetrazole chemistry is observed over the past period of decade.[2,3] Tetrazoles have excellent therapeutic application in the field of drugs with minimal side effects.

The well-known terminology Click Chemistry discovered by K. B. Sharpless which depicts reactions that provides products in excellent selectivities and in high yields by carbon-hetero bond arrangement reactions. The Huisgen 1,3-dipolar [3+2] cycloaddition[4] of azides and alkynes is among the different reactions that fulfill this click chemistry criteria. For making possible to

strongly connect two substrates, oxidation/reduction of 1,2,3-triazole ring possible in this type of cycloaddition.

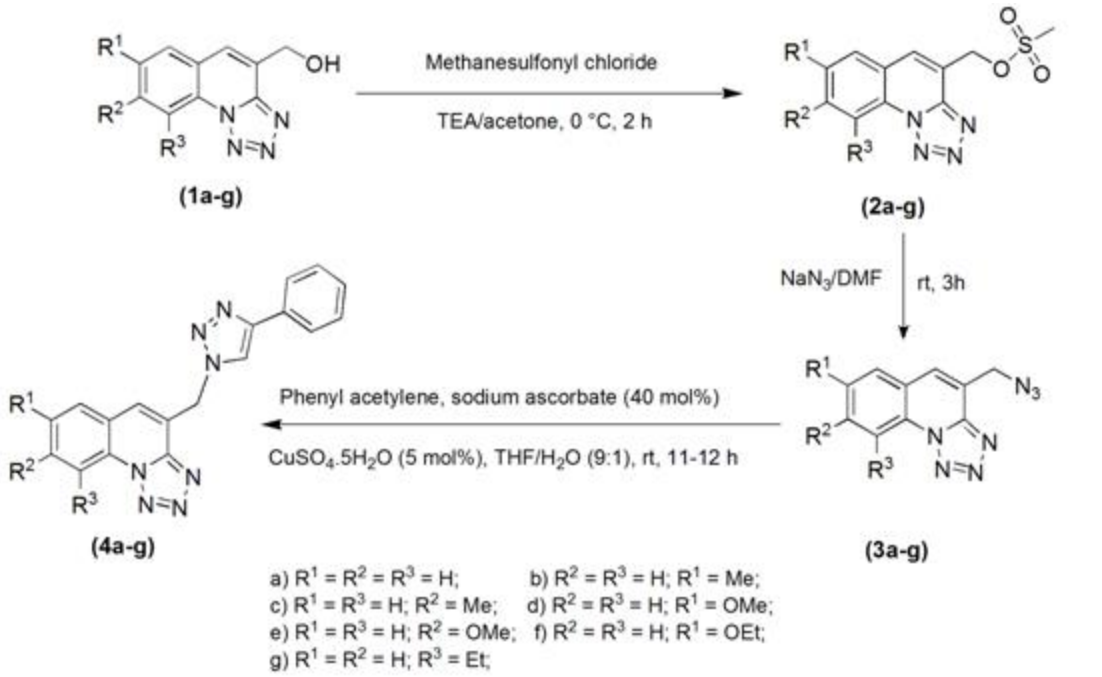
In the discovery of biologically functional scaffolds, 1,2,3-triazoles have remarkably wider and considerable application as advantaged structure. Various synthetic utilities of 1,2,3-triazoles like key building block in organic compounds and materials synthesis and direct group in transition metal catalyzed reactions.[5-9] 1,2,3-triazole moieties were prepared and applied[10-13] to uphold quick and extensive infiltration to integrative fields can predominantly be endorsed to the happening of forceful synthetic techniques toward this heterocyclic compound. With multiple substitution patterns,[14-19] cycloaddition of azides with activated di-polar-ophiles were acknowledged as trustworthy approaches to admit 1,2,3-triazole derivatives.

In this article, by click approach, we are going to report for the exceptional synthesis of new scaffolds for the consideration of expanding our ongoing research work[20].

2. Results and discussion

2.1 Chemistry

In the present act of drawing near to triazolo cum tetrazolo quinoline derivatives *viz* 4-((4-phenyl 1*H*-1,2,3 triazol 1 yl)-methyl) tetrazolo [1,5-a] quinoline derivatives, we have achieved Huisgen cycloaddition reaction to synthesise 4-(azido-methyl)-tetrazolo-[1,5-a]-quinolyl part compounds **(3a-3g)** containing terminal $–N_3$ and phenyl acetylene (Ph-C≡CH) in the occurrence of Copper-I as a catalyst to figure out new 4-((4-phenyl-1*H*-1,2,3-triazol-1-*yl*)methyl)tetrazolo[1,5-a]quinoline compounds **(4a-4g)** shown in Scheme 1. Consequently, we have firstly done synthesis of (tetrazolo[1,5-a]quinolin-4-yl)methanol derivatives **(1a-1g)** by known method,[20]. Further reaction of (**1a-1g)** compounds with methanesulphonylchloride in the occurrence with triethylamine (TEA) in acetone at 0°C to yield the analogous (tetrazolo[1,5-a]quinolin-4-yl)methyl methane-sulfonate compounds **(2a-2g)**. Further these derivatives **(2a-2g)** utilized with sodiumazide in dimethyl-formide at ambient temperature to get derivatives **(3a-3g)** in excellent yields.



Scheme 1: Synthesis of new 4-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)tetrazolo[1,5-a]quinoline derivatives

2.2 Spectroscopic investigation

Infrared spectrum of compounds **(2a-2g)** have evidences like selective functional groups observed in the range of 1321 to 1353 cm^{-1} and 1140 to 1163 cm^{-1} due to asymmetric (-S=O) and symmetric (-S=O) stretching respectively(Table 1).

Table 1: Synthesis of (tetrazolo [1, 5 - a] quinolin – 4 – yl) methyl methane-sulfonate derivatives **(2a-2g)**.

Compound	$-R^1$	$-R^2$	$-R^3$	M. P. (in °C)	Yield (%)[a]	Infrared Spectra (Potassium Bromide, ν max/cm)	
						Asymmetric -S=O Stret.	Symmetric -S=O Stret.
2a	-H	-H	-H	127-129	88	1321	1145
2b	-Me	-H	-H	135-127	84	1341	1143
2c	-H	-Me	-H	102-104	90	1342	1163
2d	-OMe	-H	-H	98-100	78	1353	1155
2e	-H	-OMe	-H	88-90	86	1353	1149
2f	-OEt	-H	-H	78-80	84	1341	1143

2g	-H	-H	-Et	90-92	77	1332	1140

[a]Isolated Yields

At δ 4.78 ppm resonance analogues to (Aromatic -CH_2) gr. was seen in ^{1}H Nuclear Magnetic Resonance spectrum. Corresponding to (-O-SO_2-C) and (Aromatic -C-OSO_2) at δ 44.3 ppm and δ 56.6 ppm are observed for compound **(2a)** respectively carbons in ^{13}C NMR spectra. An IR spectrum in the range of 2105 to 2128 cm-1 (Table 2) confirms the occurrence of (–N_3) group in the derivatives **(3a-3g)**.

Table 2: Synthesis of *4 - (azido-methyl) tetrazolo [1,5 - a] quinolines* **(3a-3g)**.

Compound	-R^1	-R^2	-R^3	M. P.(in °C)	Yield (%)[a]	Infrared Spectra (Potassium Bromide, ν max/cm)
						(-N_3) gr.
3a	-H	-H	-H	45-47	92	2105
3b	-Me	-H	-H	44-46	96	2111
3c	-H	-Me	-H	74-746	94	2124
3d	-OMe	-H	-H	69-71	91	2110
3e	-H	-OMe	-H	72-74	94	2128
3f	-OEt	-H	-H	65-67	82	2123
3g	-H	-H	-Et	68-70	78	2109

[a]Isolated Yields

For ^{1}H N.M.R. spectrum, at δ 4.68 ppm value point outs the occurrence of (Aromatic -CH_2) gr. At δ 51.8 ppm observed (Aromatic -C-N_3) carbon in the ^{13}C N.M.R. spectra for the derivative **(3a)**.

Clearly confirms compounds **(4a-4g)** as we observed absorption due to (-C≡N) stretch in the range 1018 to 1049 per cm (Table No. 3) in I.R. spectrum.

(Aromatic -CH_2) site protons for all **(4a-4g)** derivatives have been observed in the range of δ 5.84 to 5.87 ppm and proton (-H) in triazole ring extensively seen in the range of δ 8.67-8.76

ppm. In ^{13}C N.M.R. spectrum, Aromatic-C-triazole carbon was observed in the region of δ 50.4 to 51.4 ppm for all **(4a-4g)** derivatives.

Table 3: Synthesis of compounds **(4a-4g)**.

Compound	-R^1	-R^2	-R^3	M. P.(in °C)	Yield (%)[a]	Infrared Spectra (Potassium Bromide, ν max/cm)
						-C≡N Stretching
4a	-H	-H	-H	148-150	90	1035
4b	-Me	-H	-H	138-140	92	1049
4c	-H	-Me	-H	144-146	96	1049
4d	-OMe	-H	-H	106-108	91	1018
4e	-H	-OMe	-H	122-124	88	1031
4f	-OEt	-H	-H	190-192	82	1034
4g	-H	-H	-Et	118-120	83	1047

[a]Isolated Yields

2.3 Antimicrobial assays

Method used for Biological assays of newly synthesized triazolo cum terazolo quinoline derivatives (**4a-4g**)[20]

Invitro antimicrobial assays were screened by considering zone of inhibition of growth. Newly produced triazolo cum tetrazolo quinoline derivatives **(4a-4g)** were monitored with their diverse concentrations using standard antibiotics such as Streptomycin (Strepto.) (05 µg per mL) and Griseofluvin (Griseo.) (05 µg per mL) (Table 4.). The outcomes showed that the majority of our premeditated derivatives had judicious antibacterial and antifungal activities in between 10.40-18.20 µg per mL. Minimum inhibitory concentration values against standard antibiotics *invitro* are presented in Table 4. Derivatives **4c** (-R^1 = -R^3 = -H; -R^2 = -Me), **4d** (-R^2 = -R^3 = -H; -R^1 = -OMe), **4e** (-R^1 = -R^3 = -H; -R^2 = -OMe), **4f** (-R^1 = -OEt; -R^3 = -R^2 = -H) and **4g** (-R^1 = -R^2 = -H; -R^3 = -Et) have the zone of inhibition (ZI) (16.8, 17.5, 15.0, 16.6 and 18.2 m.m. respectively) as

that of the standard Strepto. (17.1 m.m.) against *Bacillus subtilis.* Derivative **4g** showed better result than standard. Against *Escherichia coli* the compounds **4d** (-R^2 = -R^3 = -H; -R^1 = -OMe), **4e** (-R^1 = -R^3 = -H; -R^2 = -OMe), **4f** (-R^1 = -OEt; -R^3 = -R^2 = -H) and **4g** (-R^1 = -R^2 = H; -R^3 = -Et) showed (16.7, 16.3, 16.9 and 16.7m.m.) zone of inhibition correspondingly as that of the standard Strepto. (17.5 m.m.). The statistics demonstrates that a change in the substituent might also influence the antibacterial assay of entitle derivatives **(4a-4g)**. Comparison of biological assays between **(4a-4g)** displayed functional grs. as -R^1 = -OMe, -R^2 = -Me/-OMe and -R^3 = -Et to be potentially more active against *Bacillus subtilis.* Also antibacterial potency of compounds among **(4a-4g)** shows functional groups as -R^1 = -OMe/-OEt, -R^2 = -OMe and -R^3 = -Et displayed more active against *Escherichia coli*.

In antifungal assays, compounds **4a** (-R^1 = -R^2 = -R^3 = -H), **4b** (-R^2 = -R^3 = -H; -R^1 = -Me), **4c** (-R^1 = -R^3 = -H; -R^2 = -Me), **4d** (-R^2 = -R^3 = -H; -R^1 = -OMe), **4e** (-R^1 = -R^3 = -H; -R^2 = -OMe), **4f** (-R^1 = -OEt; -R^3 = -R^2 = -H) and **4g** (-R^1 = -R^2 = -H; -R^3 = -Et) have displayed (16.3, 17.7, 17.4, 16.7, 15.2, 16.8, 15.3 m.m.) ZI against *Candida albicans* which might be signals that the functional grs (-R^1 = -R^2 = -R^3 = -H), -R^1 = -Me/-OMe/-OEt, -R^2 = -Me/-OMe and -R^1 = -OEt occupy in the antifungal potency of relevant derivatives as that of stand. Griseofluvin (17.8 m.m.). In opposition to *Aspergillus niger* (17.4, 16.2, 17,5 and 16.8 m.m.) ZI of derivatives **4b** (-R^2 = -R^3 = -H; -R^1 = -Me), **4c** (-R^1 = -R^3 = -H; -R^2 = -Me), **4d** (-R^2 = -R^3 = -H; -R^1 = -OMe) and **4f** (-R^1 = -OEt; -R^3 = -R^2 = -H) respectively indicate that the functional groups at -R^1 = -Me/-OMe/-OEt and -R^2 = -Me position interferes in the antifungal potency of title derivatives **(4a-4g)** as that of stand. Griseofluvin (17.4 m.m.).

Table 4: Antibacterial and antifungal assays of derivativs **(4a-4g)**

Compound	*BS*[a]	*EC*[b]	*CA*[c]	*AN*[d]
	Z.I.[e](M.I.C.)[f]	Z.I.(M.I.C.)	Z.I.(M.I.C.)	Z.I.(M.I.C.)
4a	13.10 (15.00)	12.20 (15.00)	**16.30 (15.00)**	10.40 (20.00)
4b	11.80 (25.00)	14.70 (15.00)	**17.70 (15.00)**	**17.40 (10.00)**
4c	**16.80 (10.00)**	14.20 (15.00)	**17.40 (10.00)**	**16.20 (15.00)**
4d	**17.50 (10.00)**	**16.70 (15.00)**	**16.70 (15.00)**	**17.50 (15.00)**
4e	**15.00 (10.00)**	**16.30 (10.00)**	**15.20 (15.00)**	11.60 (20.00)
4f	**16.60 (10.00)**	**16.90 (15.00)**	**16.80 (10.00)**	**16.80 (15.00)**
4g	**18.20 (10.00)**	**16.70 (15.00)**	**15.30 (15.00)**	14.40 (20.00)
Strept.	17.10 (05.00)	17.50 (05.00)	n.t.[g]	n.t.
Gris.	n.t.	n.t.	17.80 (05.00)	17.40 (05.00)

[a] *Bacillus subtilis (BS),* [b]*Escherichia coli (EC),* [c]*Candida albicans (CA),* [d]*Aspergillus niger (AN)* [e]zone of inhibition (Z.I.) in mm, [f]minimum inhibitory concentration (M.I.C.) in µg/mL [g]n. t. not tested

2.4 Molecular Modelling Study[21]:

2.4.1 Comparative modelling

While selection of template structure, there are two key parameters *viz* the series identity and atomic resolution which was 44% and 2.8 Å respectively, which satisfy the basic criteria for comparative modeling. The final model was subjected for structure validation tool like Procheck, ProSA and SPDBV were 99.7% of residue followed in allowed region, overall quality of model was evaluated using Prosa were Z-score is -3.2 and Cα deviation is 0.45 Å respectively. The validation study of model suggested it was perfect for further computation study.

2.4.2 Molecular docking study[21]

The synthesized derivatives (**4a-4g**) and standard drug was docked in active site of modeled CACYP51 with Autodock vina docking tool. Outcomes of docking are revealed in Table 5. In investigation of docking interaction it was found that triazole ring are mainly responsible for interaction.

Table 5: *Invitro* antifungal, antibacterial assays and molecular docking of synthesized derivatives (**4a-4g**)

Compd.	Z.I.(M.I.C.) values in µg/mL				Free Binding Energy (Kcal/mol)
	Bacillus subtilis	*Escherichia coli*	*Candida albicans*	*Aspergillus niger*	
4a	13.10 (15.00)	12.20 (15.00)	**16.30 (15.00)**	10.40 (20.00)	-5.598
4b	11.80 (25.00)	14.70 (15.00)	**17.70 (15.00)**	**17.40 (10.00)**	-6.696
4c	**16.80 (10.00)**	14.20 (15.00)	**17.40 (10.00)**	**16.20 (15.00)**	-5.267
4d	**17.50 (10.00)**	**16.70 (15.00)**	**16.70 (15.00)**	**17.50 (15.00)**	-6.323
4e	**15.00 (10.00)**	**16.30 (10.00)**	**15.20 (15.00)**	11.60 (20.00)	-5.937
4f	**16.60 (10.00)**	**16.90 (15.00)**	**16.80 (10.00)**	**16.80 (15.00)**	-6.271
4g	**18.20 (10.00)**	**16.70 (15.00)**	**15.30 (15.00)**	14.40 (20.00)	-6.023
Miconazole	NA	NA	NA	NA	-5.26

The synthesized triazolo cum tetrazolo quinoline derivatives **4b, 4d** and **4f** reproduced similar result as that of *invitro* activity data. All active compounds proficiently bind in the active site residues like ALA501, HIS504, PHE499, PRO410, PRO442, CYS506, PRO498, GLY500, HIS504 and ALA150, LYS179, ILE507, ALA343, ILE167, TYR168.

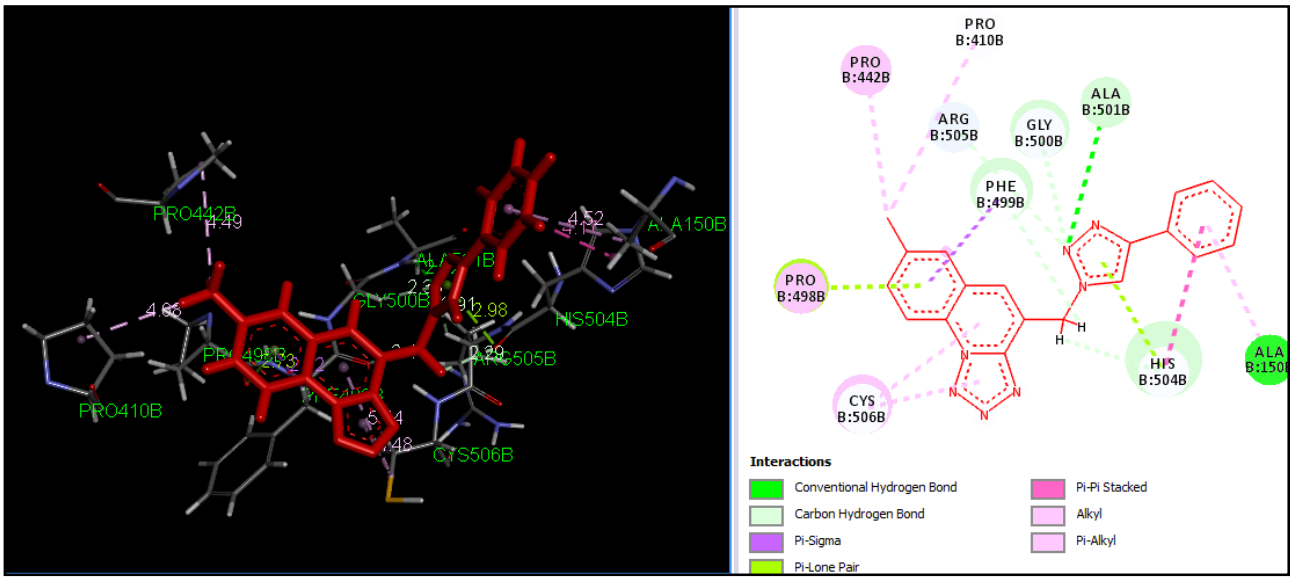


Fig. 1: Binding Pose and molecular interactions of 4b in the active site of cytochrome P450 lanosterol 14α-demethylase

The triazolo cum tetrazolo quinoline derivative **4b (-6.696 Kcal/Mol)** interact with aliphatic amino acid residues ALA501 where it interact with nitrogen atom of triazole ring with the distance of 2.62 Å to form conventional hydrogen bond interactions. The polar and hydrophobic amino acid residues HIS504 and PHE499 forms carbon hydrogen bond with –**CH_2** bridge of tetrazolo and triazole ring with distance of 2.29 and 4.77 Å. Whereas hydrophobic amino acid PRO410 and PRO442 interact with –CH3 group of tetrazolo[1,5-a]quinoline ring to form Alkyl interactions. Polar, Hydrophobic aliphatic amino acid residues of active site such as CYS506, PRO498, GLY500, HIS504 and ALA150 interact with Pi-electron cloud of aromatic ring to form Pi-Pi T shaped, Pi-lone pair, Pi-Pi Stacked and Pi-alkyl interaction shown in figure 1.

The triazolo cum tetrazolo quinoline derivative **4b (-6.323 Kcal/mol)** interact with polar and non polar amino acid of active site. The polar amino acid LYS179 interacts with nitrogen atom of tetrazole ring to form conventional hydrogen bond interactions with distance of 2.11 Å. The Pi electron cloud of triazole and aromatic phenyl ring interact with alkyl group of polar and aliphatic amino acid CYS506, ILE507 and ALA343 to form Pi-alkyl interaction of various distance. Pi electron cloud of tetrazolo[1,5-a]quinoline interact with aliphatic, hydrophobic and polar amino acid ILE167,TYR168 and LYS 179 to form Pi-Pi stacked and Pi-alkyl interactions of various distance shown in figure 2.

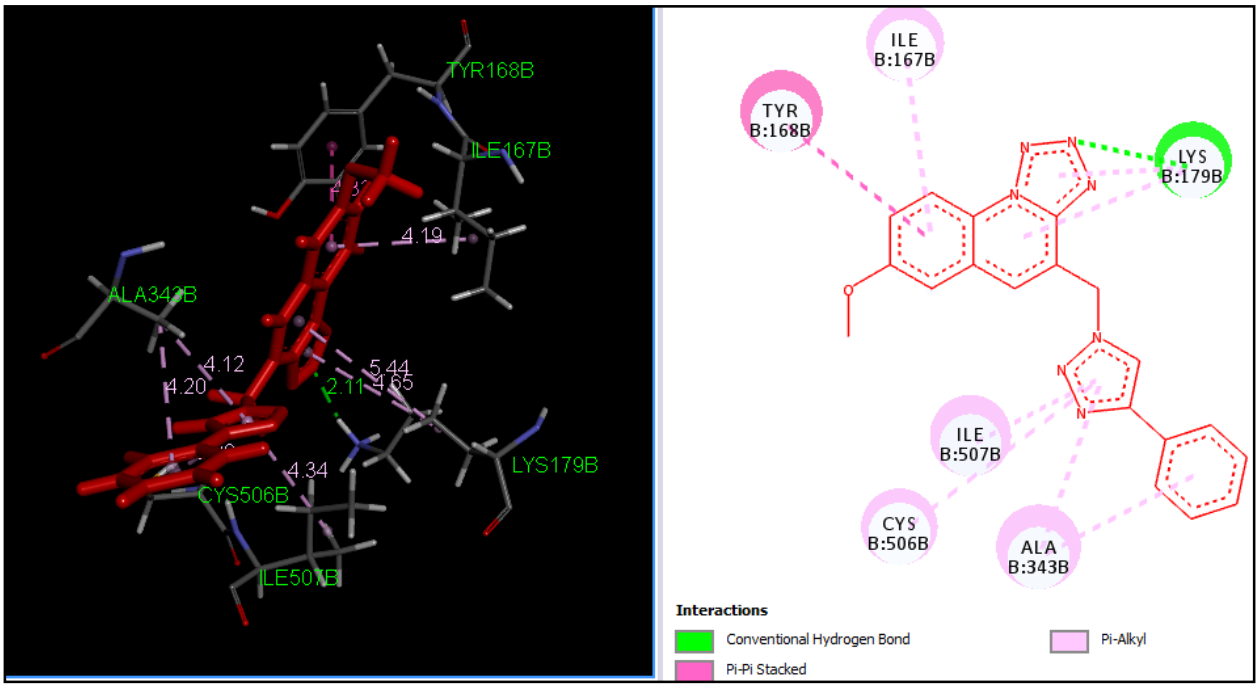


Fig. 2: Binding Pose and molecular interactions of **4d** in the active site of cytochrome P450 lanosterol 14α-demethylase

4. Conclusion

New triazolo cum terazolo quinoline derivatives have been synthesized and evaluated for their antimicrobial assays. All produced compounds were exhibit effective inhibition against all the strains examined. Significant feature of this effort remains in the probability that the new derivatives might be further effective drugs against bacteria and fungi, which could be useful in deceitful more potent antibacterial and antifungal representatives for medicinal exploit.

New triazolo cum terazolo quinoline derivatives **4b, 4d and 4f** can serve as important escort moiety as they replicating *invitro* activity in the inhibition assay and *Insilico* molecular docking study. They can use in scaffold hoping for the design and development of new lead as antifungal agents.

5. Experimental

Required chemicals and solvents acquired from Lancaster, Sigma-Aldrich, Spectrochem and S. D. Fine Chem companies. All physical constants i.e. melting points were determined in open capillaries at atmospheric pressure and uncorrected. Anhydrous sodium sulfate was used to dry Organic layers. Thin Layer Chromatography analyses were passed on readymade GF-254 TLC plate (Make-Merck). Chromatographic separations were done; Silicon Oxide was used as the stationary phase. Infrared spectra were recorded on FT/IR-410 type A spectrophotometer in potassium bromide and adsorptions are expressed in cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were measured in DMSO-d6 solution on a Bruker spectrophotometer at 400 MHz.

5.1 General procedure for the synthesis of derivatives **(2a-2g)**

Tetrazolo methanol compound **1** (1 equiv) was added at 0 °C to a mixture of acetone and TEA (2 equiv). Drop wise addition of methane sulphonyl chloride (1.5 equiv) in acetone was done in 10 min at 0 °C in above mixture which was stirred for 6 h. The development of the reaction was checked by means of TLC. After conclusion of the reaction, the reaction mixture was discharged on crushed ice. The solid compound obtained which was extracted with chloroform (5×75 mL) and washed down with brine (2×25 mL). Thus organic layer was removed, dried out over

anhydrous Sodium Sulfate. The solvent was removed under reduced pressure. The obtained crude product was purified by column chromatography on silica gel by Ethyl Acetate: Petrolium Ether (3:7) as an eluant to obtain untainted products **2**.

5.1.1 Spectroscopic data for (tetrazolo[1,5-a]quinolin-4-yl)methyl methanesulfonate ***(2a)***

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.32 (s, 3H, CH_3), 4.78 (s, 2H, Ar-CH_2), 7.64 (t, 1H, *J* = 7.43 Hz, Ar-H), 7.86 (t, 1H, *J* = 7.43 Hz, Ar-H), 7.86 (d, 1H, *J* = 7.8 Hz, Ar-H), 8.13 (d, 1H, *J* = 8.3 Hz, Ar-H), 8.31 (s, 1H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 44.3(O-SO_2-C), 56.6 (Ar-C-OSO_2), 127.3 127.7 127.8, 128.4 129.2 131.2, 138.7, 148.2 149.7 (Ar-C).

5.2 General procedure for the synthesis of derivatives and **(3a-3g)**

To a solution of tetrazolo methanesulfonate compound **2** (1.5 equivalent) in dry Dimethylformamide, sodium azide (2 equiv) was added. Then it was stirred at rt for 4 h. The development of the reaction was supervised on thin layer chromatography. After conclusion of reaction, reaction mixture was poured on crushed ice. The solid obtained was extracted with ethyl acetate (2×50 mL). The organic extract was swabbed with water and brine. The solvent was separate under reduced pressure to afford crude product **3**, which was purified by column chromatography on silica gel by n-hexane: ethyl acetate (7:3) as an eluant.

5.2.1 Spectroscopic data for 4-(azidomethyl)tetrazolo[1,5-a]quinoline ***(3a)***

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 4.68 (s, 2H, Ar-CH_2), 7.59 (t, 1H, *J* = 7 Hz, Ar-H), 7.69-7.75 (m, 2H, Ar-H), 8.01 (d, 1H, *J* = 9 Hz, Ar-H), 8.10 (s, 1H, Ar-H)

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 51.8 (Ar-C-N_3), 126.7, 127.4, 127.7, 127.8, 127.9, 130.5, 137.3, 146.79, 149.4 (Ar-C).

5.3 General procedure for the synthesis of new triazolo cum terazolo quinoline derivatives ***(4a-4g)***

The (–N_3) derivatives **(3a-3g)** (1.5 equivalent) and phenyl acetylene (1.2 equiv) were dissolved in Tetrahydrofuran-Water (8:2). To this solution, Penta hydrate copper sulphate (0.03 equivalent) and sodium ascorbate (0.42 equivalent) were mixed. The reaction mixture was stirred for 09-14 hr at rt. After completion of reaction, reaction mixture was poured on crushed ice. The solid

compound obtained was extracted with ethyl acetate (2×50 mL). The organic extract was washed with H_2O and brine (high-concentration solution of salt in water). The solvent was separated under reduced pressure to afford crude product **3**. Further it was purified by column chromatography on silica gel by Methyl Alcohol: Dichloro Methane (3:7) as an eluant to achieve compounds **(4a-4g)**.

*Spectroscopic data for new triazolo cum terazolo quinoline derivatives **(4a-4g)***

*5.3.1 2-Chloro-3-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)quinoline **(4a)***

^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 5.6 (s, 2H, Ar-CH_2), 7.27-7.85 (m, 7H, Ar-H), 7.92 (d, 1H, *J* = 9 Hz, Ar-H), 8.04 (d, 1H, *J* = 6 Hz, Ar-H), 8.33 (s, 1H, Ar-H), 8.65 (s, 1H, Triazole-H);

^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 50.9 (Ar-C-Triazole), 122.1, 125.4, 126.7, 127.6, 127.8, 127.9, 128.1, 128.3, 128.7, 130.5, 131.3, 133.5, 137.4, 139. 7, 146.2, 146.8, 149.1 (Ar-C)

*5.3.2 7-methyl-4-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)tetrazolo[1,5-a]quinoline **(4b)***

^{1}H NMR (300 MHz, DMSO-d_6, δ ppm):): 2.47 (s, 3H, CH_3), 5.84 (s, 2H, Ar-CH_2), 7.36-7.88 (m, 8H, Ar-H), 8.54 (s, 1H, Ar-H), 8.67 (s, 1H, Triazole-H).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 23.0 (CH_3), 50.7 (Ar-C-Triazole), 121.8, 122.4, 125.7, 126.6, 127.3, 127.4, 127.8, 128.6, 129.3, 129.7, 130.5, 133.6, 137.4, 139.3, 145.6, 146.7, 148.1 (Ar-C).

*5.3.3 2-Chloro-7-methyl-3-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)quinoline **(4c)***

^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 2.23(s, 3H, CH_3), 5.85 (s, 2H, Ar-CH_2), 7.28-7.86 (m, 8H, Ar-H), 8.54 (s, 1H, Ar-H), 8.76 (s, 1H, Triazole-H);

^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 21.6 (CH_3), 51.4 (Ar-C-Triazole), 120.5, 122.3, 124.1, 126.4, 127.3, 127.5, 127.8, 129.1, 129.2, 129.6, 130.2, 133.5, 137.3, 138.5, 146.1, 146.2, 150.4 (Ar-C)

*5.3.5 2-Chloro-6-methoxy-3-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)quinoline **(4d)***

^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 3.75 (s, 3H, OCH_3), 5.84 (s, 2H, Ar-CH_2), 7.24-7.96 (m, 8H, Ar-H), 8.25 (s, 1H, Ar-H), 8.68 (s, 1H, Triazole-H);

^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 50.4 (Ar-C-Triazole), 55.3 (OCH_3), 106.5, 119.4, 120.6, 121.7, 122.1, 124.3, 125.4, 127.8, 128.5, 129.8, 130.3, 135.5, 139.8, 146.8, 148.5, 149.8, 161.6 (Ar-C)

5.3.6 2-Chloro-7-methoxy-3-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)quinoline ***(4e)***

^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 3.34 (s, 3H, OCH_3), 5.84 (s, 2H, Ar-CH_2), 7.32-7.83 (m, 8H, Ar-H), 8.09 (s, 1H, Ar-H), 8.76 (s, 1H, Triazole-H);

^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 51.1 (Ar-C-Triazole), 55.4 (OCH_3), 105.7, 120.7, 121.1, 121.4, 122.6, 124.7, 125.9, 127.0, 128.7, 129.3, 130.9, 135.6, 140.7, 145.7, 147.9, 149.6, 159.8 (Ar-C)

5.3.7 2-Chloro-6-ethoxy-3-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)quinoline ***(4f)***

^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 1.37 (t, 3H, J = 6 Hz, C$\underline{H}_3$-OCH_2), 4.17 (q, 2H, J = 6 Hz, OCH_2), 5.87 (s, 2H, Ar-CH_2), 7.32-7.87 (m, 8H, Ar-H), 8.12 (s, 1H, Ar-H), 8.68 (s, 1H, Triazole-H);

^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 14.4 ($\underline{C}H_3$-CH_2), 50.7 (Ar-C-Triazole), 63.5 ($\underline{C}H_2$-CH_3), 105.1, 106.7, 119.3, 120.6, 121.2, 122.3, 123.5, 125.3, 127.7, 127.8, 128.3, 128.8, 130.3, 135.7, 137.5, 142.7, 157.5 (Ar-C);

5.3.8 2-Chloro-8-ethyl-3-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)quinoline ***(4g)***

^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 1.25(t, 3H, J = 6 Hz, C$\underline{H}_3$-CH_2), 3.13 (q, 2H, J = 6 Hz, CH_3-C$\underline{H}_2$), 5.87 (s, 2H, Ar-CH_2), 7.25-7.83 (m, 8H, Ar-H), 8.34 (s, 1H, Ar-H), 8.67 (s, 1H, Triazole-H);

^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 15.3 ($\underline{C}H_3$-CH_2), 23.6 ($\underline{C}H_2$-CH_3) 50.8 (Ar-C-Triazole), 106.3, 120.6, 121.5, 122.3, 125.4, 126.6, 127.4, 127.8, 128.0, 128. 4, 129.7, 130.4, 140.5, 141.3, 145.6, 146.4, 148.6 (Ar-C).

6. Molecular Modelling Study[21]

6.1 Homology modelling:

The Homology modelling technique was employed to build 3D model structure of cytochrome P450 lanosterol 14α-demethylase of *C. albicans* with help of VLifeMDS 4.3 Promodel molecular modelling tool. The protein sequence was retrieved from UniprotKB database

(Accession Number: P10613). The homologues template sequence search was carried out against the Protein structure database (http://www.rcsb.org/) by using BlastP. The based on default parameters identity and positive criteria appropriate template crystal structure of human lanosterol 14α-demethylase (CYP51) complexed with ketocanazole (3LD6_B). The secondary structure assignment and sequence realignment was carried out to build final modeled structure of fungal CYP51.

The modeled structure was subjected for various checks like phi-psi, Z score and Cα deviation.

6.2 Molecular docking study:

The model protein structure and 3D structure of sketched synthesized compound was prepared for molecular docking using Autodock vina docking tool [3]. Molecular docking study of synthesized compounds 4a to 4g was carried out using final modeled structure of fungal CYP51 to understand this mechanism of action of inhibitors molecular interactions were analyzed.

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