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Microwave Assisted Synthesis, Docking and Antimicrobial Studies of Tetrazole linked *N*-Acyl Hydrazone Derivatives

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Novel Schiff bases of 2-(1*H*-tetrazole-5-yl)acetohydrazide were synthesized by employing microwave assisted green synthesis using substituted aldehydes. The structural characterization of the synthesized compounds was done by elemental, FT-IR, ^{1}H NMR and mass spectrometry. The antimicrobial activity was investigated against Gram-positive and negative bacteria such as *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa*. The ADME properties and protein binding studies of the test compounds were computed by using SwissADME and AutoDock software. Among all the compounds, compound **HNTAC** demonstrated stronger binding affinity (-10.37 kcal/mol) than the control cefazolin (-7.2 kcal/mol) for 4OR7. The excellent results of antimicrobial, molecular docking and ADME (*in silico*) studies enhanced the potential of the compounds under study as candidates for further research exploration.

Keywords: 2-(1*H*-Tetrazol-5-yl)acetohydrazide Schiff bases, Antimicrobial activity, Docking studies, Swiss ADME.

INTRODUCTION

The tetrazole moiety is a preferred ring for potential drug discovery due to its high metabolic stability, its ability to accept as well as donate π-electrons and its pyrrole type nitrogen is isosteric with carboxylic acids [1]. The nitrogen rich tetrazole heterocyclic ring has continued to fascinate scientists with its multipurpose applications as enzyme inhibitors [1,2], energetic coordination compounds [3], potential anticancer drug molecules [4] and polydentate ligands for metal coordination [5]. Tetrazoles are highly versatile compounds in chemistry, prized for their stability and diverse chemical properties, such as acidity, basicity and the ability to form coordination complexes. They can exist in multiple tautomeric forms, most commonly 1*H*- and 2*H*-tetrazoles. Due to their polar nature, driven by the presence of multiple nitrogen atoms, tetrazoles can engage in hydrogen bonding and coordinate with metal ions [6].

In pharmaceuticals, tetrazoles are often used as bioisosteres for carboxylic acids becuase of their acidic properties and ability to mimic carboxyl groups enhance the pharmacokinetic and pharmacodynamic profiles of drugs [7]. Significant examples include losartan, an angiotensin II receptor antagonist for hypertension and cefazolin, an antibiotic. Tetrazoles demonstrate various biological activities, including antimicrobial, antiviral, anti-inflammatory and anticancer effects [8,9]. They also form stable complexes with metal ions, which is advantageous in developing metal-based drugs and imaging agents, often with efficient anticancer activity and enzyme inhibition properties [10,11]. Additionally, tetrazole rings are integral in the design of peptidomimetics–molecules that mimic the structure and function of peptides, which are crucial in drug design, particularly for inhibiting protein-protein interactions [12]. In bioorthogonal chemistry, tetrazoles facilitate reactions within living systems without disrupting natural biochemical processes, making them valuable for labeling and tracking biological molecules. Moreover, their stability and efficacy make tetrazoles promising candidates in agrochemicals as herbicides, fungicides and plant growth regulators [13].

Many novel synthetic pathways have evolved for tetrazole ring synthesis, majority of them using either sodium azide

(NaN_3) or azido-*n*-butyl stannane (n-Bu_3SnN_3) [14,15]. Jawad *et al.* [16] discussed the numerous applications of tetrazole ring derivatives in medicinal chemistry with potential antibacterial, antifungal, antiviral, anticancer, analgesic, antioxidant and anti-inflammatory activities.

The N-acyl hydrazone moiety is bioisosteric with amide linkage [17] and metabolically more stable than a peptide bond. This moiety has been explored by medicinal chemists in designing new drug molecules [18,19]. Narang *et al.* [20] discussed extensively the biological activities and synthetic routes of hydrazone derivatives in their review article. Keeping in view the broad significance of tetrazole derivatives, in present study, 2-(1*H*-tetrazol-5-yl)acetohydrazide has been condensed with substituted aldehydes to give novel N-acyl hydrazones which have been investigated for their bactericidal propensities.

EXPERIMENTAL

The chemicals and reagents used in this work were of AR grade and obtained from various commercial suppliers such as Sigma-Aldrich, Molychem and Himedia. The silica gel G used for analytical chromatography (TLC) was obtained from E. Merck India Ltd. The chemicals were purified by distillation before use. The elemental analysis (C, H, N & S) of compounds under study were carried out on Perkin-Elmer 240C elemental analyzer. UV-vis spectra were scanned on Perkin-Elmer 240 C (USA) Bruker at room temperature. IR spectra (KBr) were recorded on a Perkin-Elmer 435 spectrophotometer in the range of 4000-400 cm^{-1}. ^1H NMR spectra were recorded on Bruker 400 MHz spectrometer in DMSO-d_6 solvent. ^{13}C NMR spectra were recorded on Bruker 400 MHz spectrometer in DMSO-d_6 solvent. Mass spectra were measured on LC-MSD-Trap-SL instrument by ESI method.

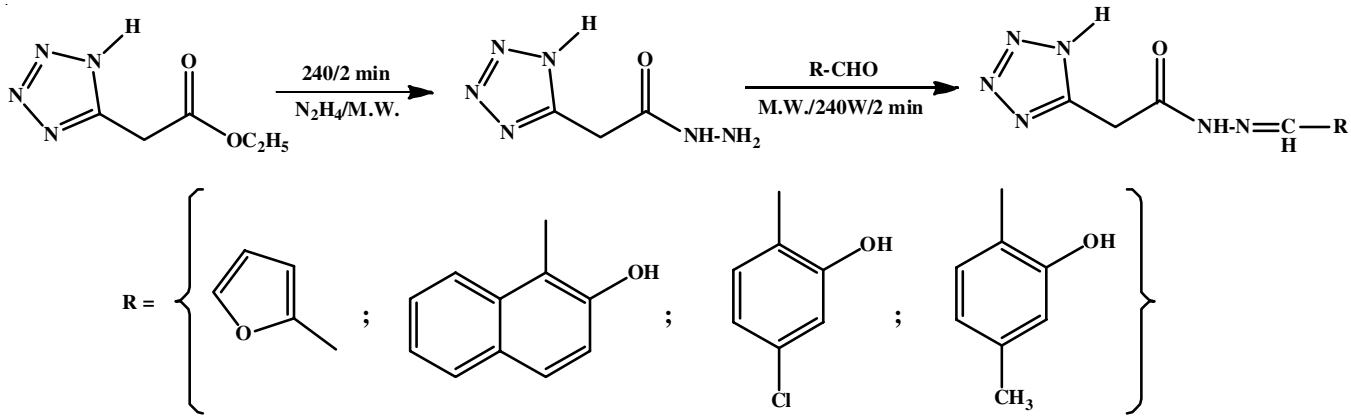
Synthesis of 2-(1*H*-tetrazole-5-yl)acetohydrazide: 2-(1*H*-Tetrazole-5-yl)acetohydrazide was synthesized by the reported procedure [21]. In brief, a mixture of ethyl-1*H*-tetrazole acetate and hydrazine hydrate in 1:3 ratio was heated in a microwave at Pmax: 240W for 1-2 min. The colourless hydrazide obtained was stirred well at 0 ºC and washed with ethanol. The progress of the reaction was monitored and purity was checked by TLC (m.p.: 159-161 ºC).

Synthesis of Schiff bases of 2-(1H-tetrazole-5-yl)-acetohydrazide: The Schiff bases were synthesized by mixing 2-(1*H*-tetrazole-5-yl)acetohydrazide (4 equiv.) and substituted aldehydes (1 equiv.) in solvent methanol. The reaction mixture was irradiated at Pmax: 240W for 1-2 min. The resulting compounds obtained were stirred well at 0 ºC and washed thoroughly with methanol (**Scheme-I**). The products were dried in hot air oven and their purity was checked with TLC.

N-(Furan-2-ylmethlene)-2-(1*H*-tetrazol-5-yl)acetohydrazide (FTAC): Yield: 90%, m.p.: 240-242 ºC; Anal. analysis of calcd. (found) % for $C_8H_8N_6O_2$: C, 43.64 (44.56); H, 3.66 (3.71); N, 38.17 (39.15); O, 14.53 (15.41). IR (KBr, ν_{max}, cm^{-1}): 3112.67 (N-H *str.*), 1670.11 (NH-CO amide), 1563.26 (N=CH imine); 1464, 1441 (C=C), 1017 & 1053 (C-O *str.*). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 4.36 (2H, s, -CH_2); 6.6-7.23 (3H, m, furan); 7.93 (1H, s, N=CH (imine); 8.10 (1H, s, amide) (D_2O); 11.69 (1H, s, N-H) (D_2O). ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 35.50 (t, -CH_2-), 112.54 (d, C_3 of furan), 114.36 (d, C_3 of furan), 134.67 (d, N=CH), 145.83 (d, C_5 of furan), 149.46 (s, C_2 of furan), 162.85 (s, tetrazole carbon) and 168.57 (s, C=O). HRMS (ESI) *m/z* 221.1 (M+1).

***N*-(2-Hydroxynaphthalen-1-yl)methylene)-2-(1*H*-tetrazol-5-yl)acetohydrazide (HNTAC):** Yield: 85%, m.p.: 251-253 ºC, Anal. analysis calcd. (found) % for $C_{14}H_{12}N_6O_2$: C, 56.75 (57.71); H, 4.08 (4.56); N, 28.36 (29.23); O, 10.80 (10.84); IR (KBr, ν_{max}, cm^{-1}): 3585 (Ar-OH *str.*), 3205 (N-H *str.*). 2925 (Ar-CH *str.*), 1681.14 (NH-CO amide), 1621.13 (N=CH imine), 1598, 1466, 1413 (C=C). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 4.13 (2H, s, CH_2);7.43-8.87 (6H, m, ring); 7.21 (1H, s, N=CH (imine); 9.17 (1H, s, amide) (D_2O); 11.68 (1H, s, N-H (D_2O); 12.32 (1H, Ar-OH) (D_2O); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 36.08 (s, CH_2-), 107.51 (s), 108.94 (d), 119.12 (d), 121.61 (d), 123.36 (s), 128.02 (d), 129.32 (d), 131.92 (d), 133.60 (s), 147.12 (d), 162.92 (s), 168.97 (s, C=O). HRMS (ESI) *m/z* 297.1 (M+1).

***N*-(4-Chloro-2-hydroxybenzylidene)-2-(1*H*-tetrazol-5-yl)acetohydrazide (CHTAC):** Yield: 85%; m.p.: 220-221 ºC; Anal. analysis calcd. (found) % for $C_{10}H_9N_6O_2Cl$: C, 42.79 (42.86); H, 3.23 (3.42); Cl, 12.63 (13.56); N, 29.94 (30.81); O, 11.40 (11.57). IR (KBr, ν_{max}, cm^{-1}); 3550 (Ar-OH *str.*), 3220 (N-H *str.*), 2922 (Ar-CH *str.*), 1683.21 (NH-CO amide), 1620.27 (N=CH imine) 1557, 1478 (C=C), 710 (C-Cl *str.*). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 4.41 (2H, s, CH_2); 6.96-8.74 (3H, Ar-H); 7.73 (1H, s, N=CH (IMINE); 8.97 (1H, s, amide) (D_2O); 11.41



Scheme-I

(1H, Ar-OH) (D_2O); 11.73 (1H, s, N-H) (D_2O); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 167.11 (s), 159.98 (s, C-OH), 157.29 (s), 146.66 (d, N=CH), 132.47 (C-Cl), 127.98 (C_6 of benzene), 120.08 (C_5 of benzene), 118.28 (C_3 of benzene), 116.82 (C_1 of benzene). HRMS (ESI): *m/z* 281.1 (M+1).

N-(2-Hydroxy-4-methylbenzylidene)-2-(1*H*-tetrazol-5-yl)acetohydrazide (HMTAC): Yield: 88%, m.p.: 241-243 ºC; Anal. analysis calcd. (found) % for $C_{11}H_{12}N_6O_2$: C, 50.77 (51.56); H, 4.65 (4.68); N, 32.29 (33.57); O, 12.29 (13.57). IR (KBr, ν_{max}, cm^{-1}); 3203 (N-H *str.*), 2921 (Ar-CH *str.*), 2852 (alkyl C-H *str.*), 1677.02 (NH-CO amide),1610.09 (N=CH imine), 1556, 1507 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.25 (3H, Ar-methyl); 4.01 (2H, s, CH_2); 6.68-7.52 (3H, m, ring); 8.39 (1H, s, N=CH (imine); 10.94 (1H, s, amide) (D_2O); 11.60 (1H, s, N-H) (D_2O); 12.01 (1H, Ar-OH) (D_2O); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 21.31 (q, -CH_3, 36.6 (t, -CH_2-), 116.48 (C_1 of benzene), 118.28 (C_3 of benzene), 120.74 (C_5 of benzene), 129.71 (C_6 of benzene), 142.36 (C_4 of benzene), 148.22 (N=CH), 157.88 (tetrazole carbon), 162.28 (C_2 of benzene), 168.26 (C=O). HRMS (ESI): *m/z* 261.1 (M+1).

Microbial analysis: A pour plate method of antibacterial assay was carried out by performing pour plate method [5]. The *Staphylococcus aureus* and *Bacillus subtilis* were chosen as Gram-positive bacteria, *Escherichia coli* and *Pseudomonas aeruginosa* as Gram-negative bacteria. The antifungal assay was performed by using *Candida albicans* and *Aspergillus niger*. Potato dextrose agar and yeast extract peptone agar media were used.

***In silico* studies:** The computational studies including molecular docking was performed using AutoDock suite 1.5.6 software. The three-dimensional structures of both synthesized compounds and standard were drawn by using ChemDraw Professional 16.0 and the 3D protein *Klebsiella pneumoniae* dihydrofolate reductase (PDB ID: 4OR7) sdf file was download from RSCB Protein Data Bank. After completion of docking the results and images have been analyzed by Biovia Discovery Studio 2021 Client Version and Binding effinity was expressed in kcal/mol. The *in silico* physico-chemical properties and egg boiled model were analyzed using SwissADME (http://www.swissadme.ch/).

RESULTS AND DISCUSSION

Antibacterial activity: The *in vitro* antibacterial studies of the Schiff base compounds *viz.* **FTAC**, **HNTAC**, **CHTAC** and **HMTAC** were tested against Gram-positive *Bacillus subtilis*, *Staphylococcus aureus* and Gram-negative *Escherichia coli* and *Pseudomonas aeruginosa* species. Compounds **FTAC** and **HMTAC** were found to be inactive against both Gram-positive as well as negative bacterial species, whereas compounds **HNTAC** and **CHTAC** exhibited mild activity against both Gram-positive and Gram-negative species, compared to control antibiotic streptomycin (Table-1). These results suggest that compounds **HNTAC** and **CHTAC** exhibit broad spectrum of bactericidal activity against the antibiotic resistant bacterial species.

Compounds **HNTAC** and **CHTAC** were assayed for their minimum inhibitory concentrations (MIC) by loading 25 µL, 50 µL, 75 µL, 100 µL of samples diluted with water/solvent to make up the volume up to 100 µL in each well of the plate respectively. In this assay, 10 mg/mL samples were used and respective dilutions were made. The results of MIC assays are tabulated in Table-2. *In vitro* antibacterial study demonstrated that the compound exhibited significant antibacterial activity against both Gram-positive and Gram-negative bacteria, with MIC values with higher concentration. When compared to the standards test compound showed marginal variation of efficacy, however, these were less potent than standard drugs.

TABLE-1
ZONE OF INHIBITION (mm) DATA OF SYNTHESIZED TETRAZOLE LINKED N-ACYL HYDRAZONE DERIVATIVES

Compound	Gram-positive: Bacterial pathogens		Gram-negative: Bacterial pathogens	
	Staphylococcus aureus	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*
FTAC	Not detected	Not detected	Not detected	Not detected
HNTAC	8	12	10	8
CHTAC	8	12	8	9
HMTAC	Not detected	Not detected	Not detected	Not detected
Streptomycin (standard)	15	16	15	14

TABLE-2
MIC ASSAY DATA OF SYNTHESIZED TETRAZOLE LINKED N-ACYL HYDRAZONE DERIVATIVES AGAINST SOME BACTERIAL SPECIES

Compound	Bacterial species	Minimum inhibitory concentration (MIC, mm)				MIC of sample (µL)
		25 µL	50 µL	75 µL	100 µL	
HNTAC	*Staphylococcus aureus*	–	–	8	10	75
CHTAC		–	–	7	8	75
HNTAC	*Bacillus subtilis*	–	–	8	12	75
CHTAC		–	–	–	10	100
HNTAC	*Escherichia coli*	–	–	–	8	100
CHTAC		–	–	8	10	75
HNTAC	*Pseudomonas aeruginosa*	–	–	–	8	100
CHTAC		–	–	8	12	75

Antifungal activity: The antifungal studies of compounds **FTAC**, **HNTAC**, **CHTAC** and **HMTAC** were tested against *Candida albicans* and *Aspergillus niger*. Compounds **FTAC** and **HMTAC** were found to be inactive against both fungi (Table-3), whereas compounds **HNTAC** and **CHTAC** exhibited mild activity against both, compared to control antibiotic streptomycin. Compounds **HNTAC** and **CHTAC** were also assayed for their minimum inhibitory concentrations (MIC) by loading 25 µL, 50 µL, 75 µL and 100 µL of samples diluted with water/solvent to make up the volume up to 100 µL in each well of the plate. The results of MIC assays are tabulated in Table-4.

Structure activity relationship (SAR) studies: The SAR studies in the present investigation revealed that tetrazole ring, amide carbonyl, amide nitrogen and substitution on olefinic (imine) carbon are essential for activity and play a key role in binding interactions with the receptor 4OR7 varying 'R' group with various aromatic and hetero-aromatic rings on imine carbon four analogues were chosen in this investigation (Fig. 1). The key interactions of these analogues with receptor 4OR7 are (i) amide carbonyl and NH are involved in hydrogen bonding interactions with the receptor active site; (ii) tetrazole ring nitrogens are important in binding to the receptor with hydrogen bonding; (iii) pyrrole ring oxygen in compound **FTAC** is involved in hydrogen bonding interactions; (iv) the bulky naphthalene ring in compound **HNTAC** is twisting the molecule out of plane and bringing -OH on the naphthalene ring close to the receptor site for hydrogen bonding interactions. Increase in the binding affinity for this analogue indicates better conformation is obtained to bind with the receptor; and (v) aromatic and hetero-aromatic rings are involved in van der Waal's and hydrophobic interactions with the receptor [22-25].

TABLE-3
ANTIFUNGAL ACTIVITY DATA OF SYNTHESIZED TETRAZOLE LINKED N-ACYL HYDRAZONE DERIVATIVES

Compound	Fungal pathogens	
	Candida albicans	*Aspergillus niger*
FTAC	Not detected	Not detected
HNTAC	8 mm	8 mm
CHTAC	8 mm	8 mm
HMTAC	Not detected	Not detected
Standard	15 mm	12 mm

In silico activity studies

Molecular docking study: Molecular docking studies were conducted to determine the binding mode and interactions between the most active compounds of the tetrazole series of Schiff bases of 2-(1*H*-tetrazole-5-yl)acetohydrazide *viz.* **FTAC**, **HNTAC**, **CHTAC**, **HMTAC** and the proteins 4OR7 *Klebsiella*

TABLE-4
MIC ASSAY OF SYNTHESIZED COMPOUNDS HNTAC AND CHTAC AGAINST FUNGAL SPECIES

Compound	Fungal species	Minimum inhibitory concentration (MIC, mm)				MIC of sample (µL)
		25 µL	50 µL	75 µL	100 µL	
HNTAC	*Candida albicans*	–	–	7	8	75
CHTAC		–	–	8	10	75
HNTAC	*Aspergillus niger*	–	–	–	8	100
CHTAC		–	–	8	12	75

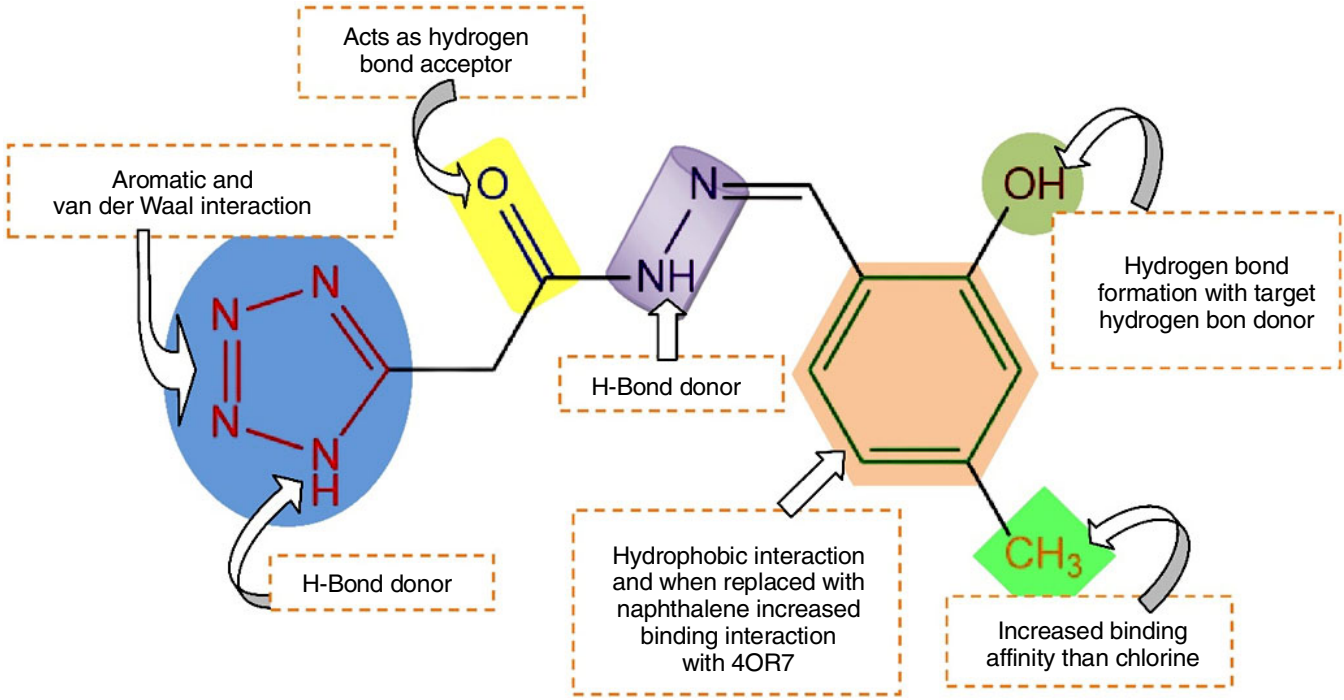
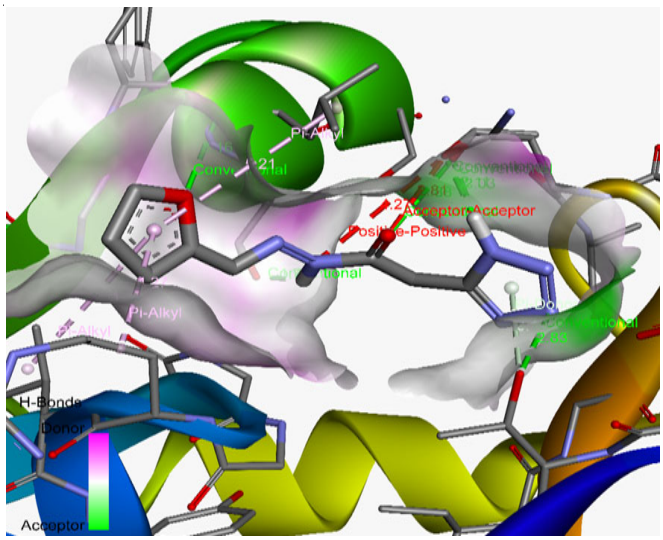


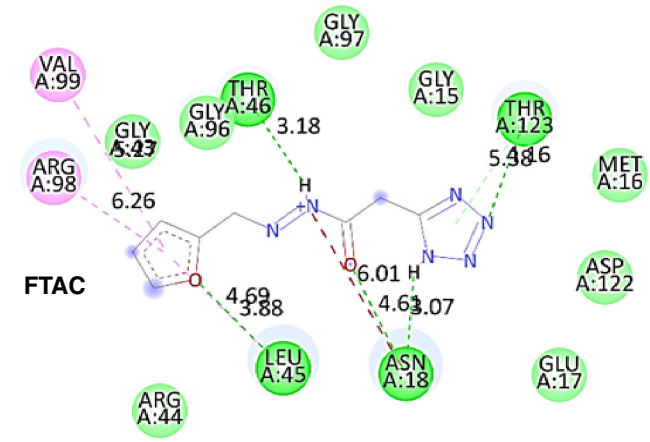
Fig. 1. SAR studies of tetrazole linked N-acyl hydrazone derivatives

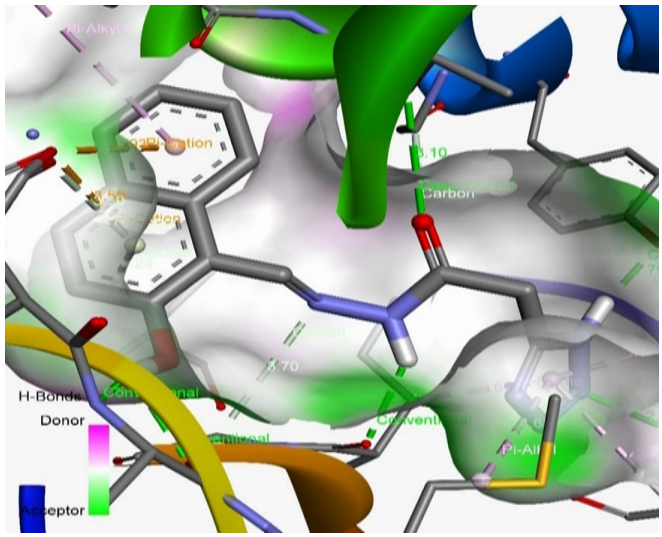
pneumoniae dihydrofolate reductase using AutoDock Vina 1.5.6. The results obtained were compared with the molecular docking models of the reference compound cefazolin. The docking behaviour of synthesized compounds **FTAC**, **HNTAC**, **CHTAC**, **HMTAC** and the control cefazolin were examined using the proteins 4OR7 *via* AutoDock1.5.6 program. Here, naphthalene derivative showed better binding affinity (-10.37 kcal/mol) than the control cefazolin (-7.2 kcal/mol) for 4OR7. Indeed, hydrogen bonding seemed to be pivotal in stabilizing the protein–ligand bonding interactions, thereby ensuring a favourable bond distance of less than 3.5 Å between the H-donor and the H-acceptor atoms (Table-5). Compound **HNTAC** exhibited five hydrogen bonds with Ala7, Ile14, Ala19, Thr46 and Tyr100. Compound **HMTAC** formed five hydrogen-bonding interactions with the receptor 4OR7. Here, the residue Ala7, Ile14, Ala19, Thr46 and Tyr100 with bond lengths of 2.81 Å, 2.24 Å, 2.33 Å, 3.10 Å and 1.79 Å was involved in the aforementioned interactions. Also, residues Asn18, Leu45, Thr123, Met20, Ala6, Gly15, Gly96 exhibit various categories of interactions. The control cefazolin formed two hydrogen-bonding interactions with 4OR7 (Fig. 2). The overall bonding connections of the respective amino acid residues in 4OR7 protein, when analyzed using tetrazole scaffolds and cefazolin, are shown in Fig. 2.

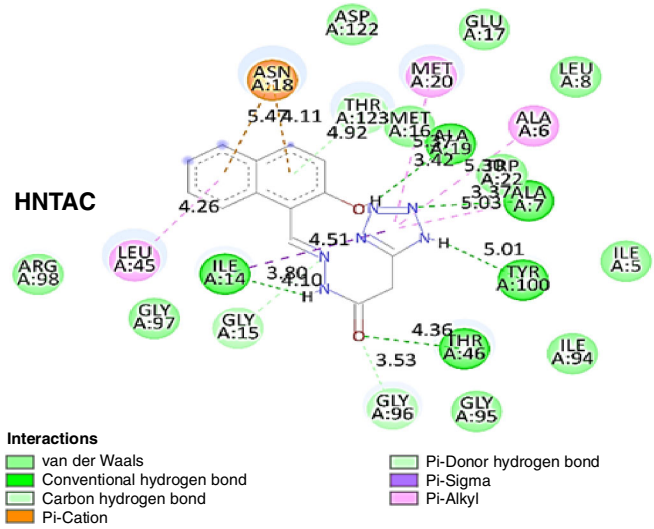
TABLE-5
BINDING AFFINITY AND INTERACTION DATA OF AMINO ACID RESIDUES WITH SYNTHESIZED TETRAZOLE LINKED N-ACYL HYDRAZONE DERIVATIVES

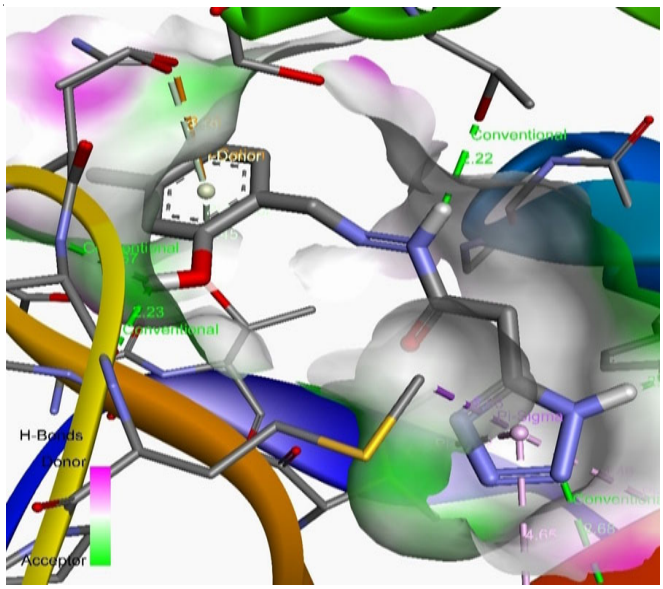
Compound	Binding affinity (kcal/mol)	Number of hydrogen bonds	Interacting amino acid residues
FTAC	-7.83	01	Asn18, Lue45, Thr46, Arg98, Val99 & Thr123
HNTAC	-10.37	05	Ala6, Ala7, Ile14, Gly15, Asn18, Ala19, Met20, Leu45, Thr46, Gly96, Tyr100 & Thr123
CHTAC	-8.81	03	Ala6, Ala7, Ile14, Asn18, Ala19, Met20, Thr46, Gly96, Tyr100 & Thr123
HMTAC	-9.19	05	Ala6, Ala7, Ile14, Asn18, Ala19, Met20, Thr46, Tyr100 & Thr123
Cefazolin (std.)	-7.2	02	Ile14, Asn18, Met20, Leu45, Thr46, Ser49, Gly97, Arg98, Tyr100 & Thr123

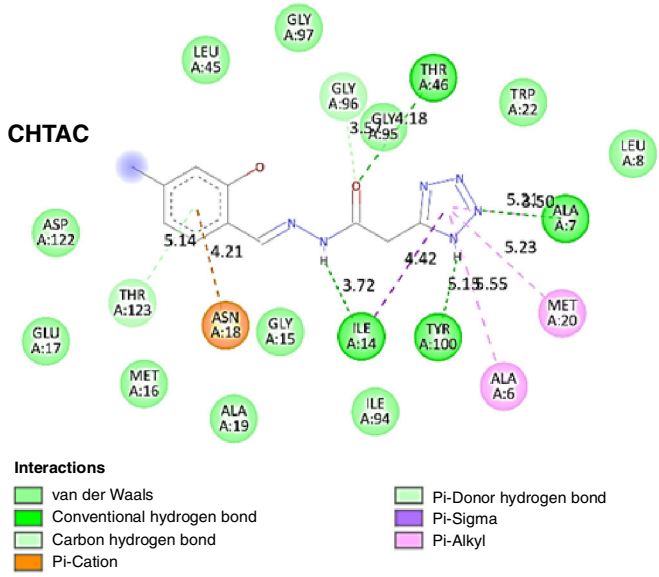


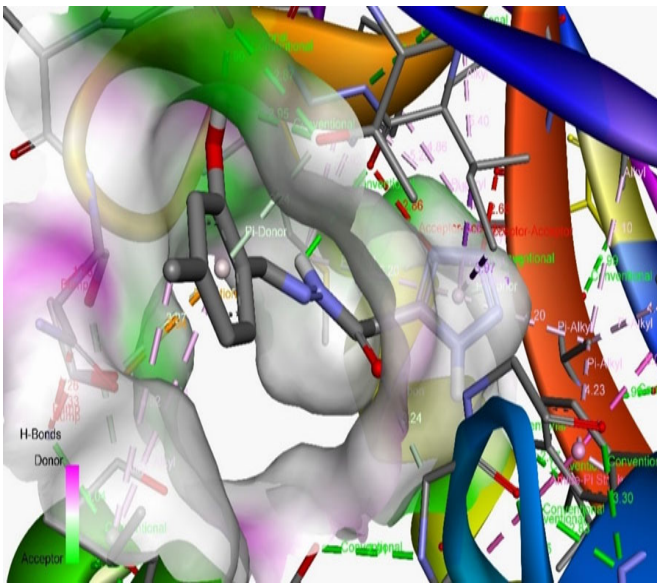


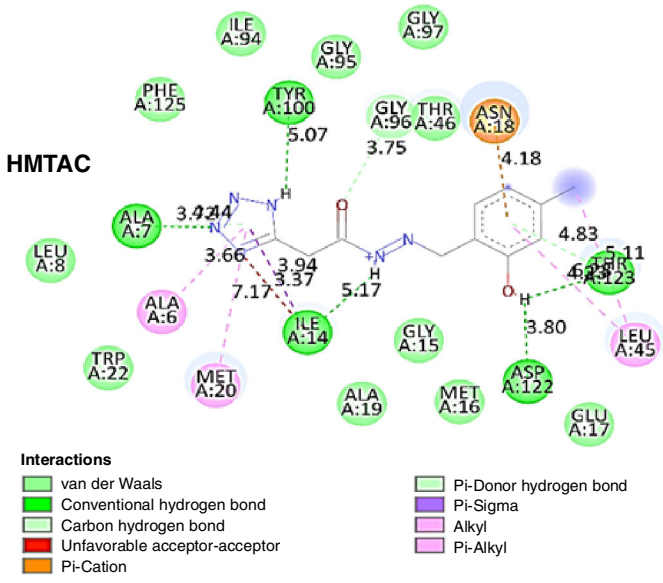


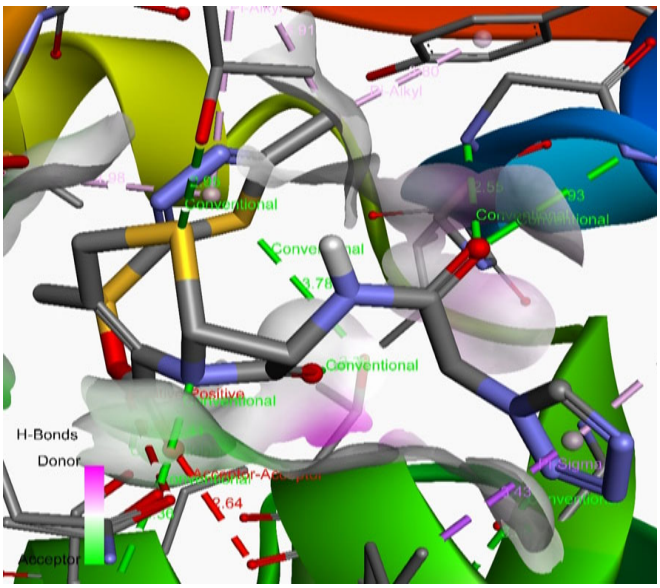












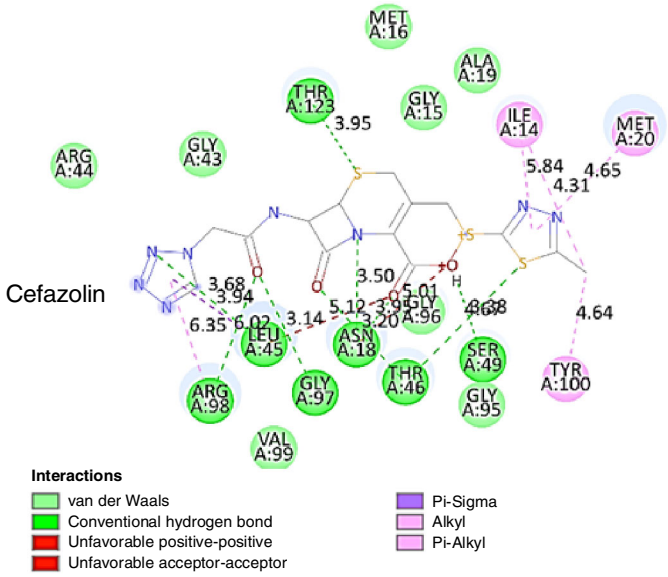


Fig. 2. 2D and 3D docking images of tetrazole linked N-acyl hydrazone derivatives (FTAC) with protein *K. pneumoniae* dihydrofolate reductase (PDB ID:4OR7)

ADME studies: A molecule must exhibit favourable pharmacokinetics and biological activity to act as a viable therapeutic candidate. In this study *in silico* tools such as violation of Lipinski's rule, polar surface area, hydrogen bond acceptors, donors and synthetic accessibility were employed to access drug-likeness metrics [26-30]. All tested compounds met the criteria indicating promising drug like characteristics as outlined in Table-6. Fig. 3 illustrated the egg-boiled model of test compounds alongside regular cefazolin, revealing that the test compounds were primarily contained in the albumin region. The yolk (yellow area) indicates a high likelihood of BBB permeability, while the albumin portion (white region) suggests a favourable probability of absorption in the human intestine. The figure represents that all the synthyesized compounds are primarily concentrated in the albumin region indicating strong potential for gastrointestinal absorption.

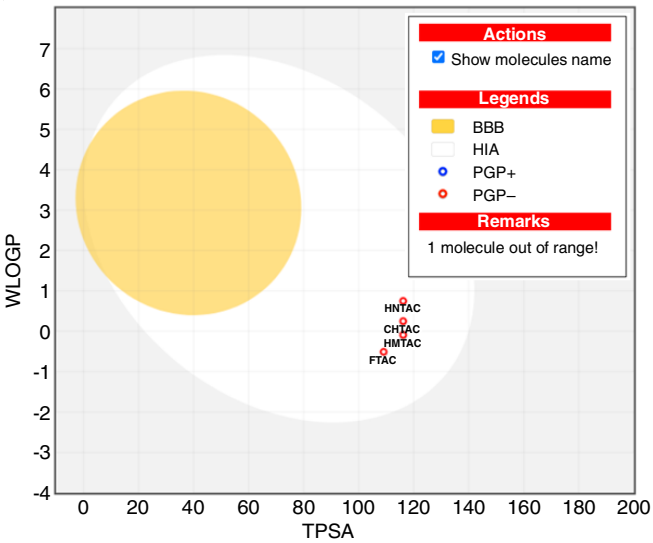


Fig. 3. The egg-boiled model of tetrazole linked N-acyl hydrazone derivatives and standard cefazolin

The compounds having molecular weight less than 500 are considered to be an ideal range for drug likeliness. The fact that the Log P value for compounds **FTAC** and **CHTAC** was less than 1 suggests that these compounds are too hydrophilic. Such compounds might have poor membrane permeability and may not effectively cross cell membranes, potentially leading to poor absorption and bioavailability. The compounds **HNTAC**, **HMTAC** and cefazolin displayed multiple Log P values, indicating a balance between hydrophilicity and lipophilicity, which is crucial for optimal gastrointestinal absorption and bioavailability.

In SWISSADME, TPSA is one of the key factors used to predict a compound's drug-likeness and potential success as an orally active or CNS-targeted drug. All the compounds exhibiting a TPSA of ≤ 140 Å^2 is considered to be favourable for oral bioavailability. The number of rotatable bonds in every compound was 5, which suggests that a drug candidate should have 10 or fewer rotatable bonds to ensure good oral bioavailability. Molar refractivity (MR) is a physico-chemical property that reflects the polarizability of a molecule, which is related to the volume occupied by the molecule's electrons. The molecular refractivity of all the synthesized compounds ranged from 30 to 140 cm^3/mol, which was generally advantageous for drug-likeness and biological activity.

Conclusion

Novel Schiff bases of 2-(1*H*-tetrazole-5-yl)acetohydrazide *viz*. **FTAC**, **HNTAC**, **CHTAC** and **HMTAC** were synthesized by unconventional microwave method and characterized by infrared, mass, NMR and CHN analyses. Compounds **HNTAC** and **CHTAC** exhibited mild activity against both Gram-positive and negative species, compared to control antibiotic streptomycin, whereas compounds **FTAC** and **HMTAC** were found to be inactive against both fungi and compounds **HNTAC** and **CHTAC** exhibited mild activity against both, compared to control antibiotic streptomycin. The molecular docking and ADME (*in silico*) studies enhanced the potential of the synthesized compounds under study as candidates for further therapeutic exploration.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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TABLE-6
In silico ADME PROPERTIES OF SYNTHESIZED TETRAZOLE LINKED N-ACYL HYDRAZONE DERIVATIVES

Compound	MW	Violation of Lipinski's rule	The polar surface area (TPSA)	No. of hydrogen bond acceptors	No. of hydrogen bond donors	Log P	Synthetic accessibility
FTAC	220.19	No	109.06 Å^2	6	2	0.48	3.07
HNTAC	296.28	No	116.15 Å^2	3	3	1.21	2.85
CHTAC	280.67	No	116.15 Å^2	6	3	0.75	2.68
HMTAC	260.25	No	116.15 Å^2	6	3	1.02	2.71
Cefazolin (std.)	454.51	Yes	234.93 Å^2	9	2	1.11	4.62

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