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RESEARCH ARTICLE

Synthesis, antibacterial activities, binding mode analysis and predictive ADME studies of novel 1-(aryl)-2-(1H-imidazol-1-yl)methanones

Priyanka Chandra*,Swastika Ganguly, Rajdeep Dey and Biswatrish Sarkar

ABSTRACT

Introduction: In the present study a novel series of twelve 1-(aryl)-2-(1H-imidazol-1-yl)methanones 3(a-l) were synthesized and characterised by physicochemical and spectral analysis,viz. elemental analysis, IR spectroscopy, NMR spectroscopy. The antibacterial property of the compounds were examined, in order to develop new broad spectrum antibiotics.

Methods: The compounds 3(a-l) were synthesised by reacting the corresponding 2-(aryl)-1H-imidazoles 2 with substituted benzoyl chlorides. Binding mode analysis of the most active compound was carried out. Predictive ADME studies were carried out for all the compounds.

Results and Discussions: Among the synthesized compounds, (2-(3-nitrophenyl) (2,4-dichlorophenyl) -1Himidazol-1-yl) methanone 3i exhibited highest antibacterial activity. Binding mode analysis of the highest active compound was carried out in the active site of glucosamine-6-phosphate synthase (2VF5).

Keywords: ADME, Antibacterial activity, Benzoyl chlorides, Docking, Imidazoles, Synthesis.

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INTRODUCTION

Compounds containing the imidazole(**1**) moiety have exhibited antibacterial,[1-3] antifungal,[4] anti HIV[5]and miscellaneous other activities. Imidazoles play an important role in the clinical practice as antimicrobial agents and are widely used in the treatment of giardiasis, amoebiasis, and *Balantidium infections*.[6-7] Current therapeutic drugs containing imidazole nucleus having good systemic activity against antimicrobial infections are, bifonazole, oxiconazole, luliconazole, azomycin, metronidazole, tinidazole, nimorazole, panidazole, ornidazole.[7] With the advent of Human Immunodeficiency virus which causes full blown AIDS, the immune system of the patients affected by HIV has been compromised and opportunistic infections like bacterial and fungal infections are increasing at an alarming rate. In view of this and in continuation of our previous work on diaryl imidazoles,[8] a series of 1-(aryl)-2-(1H-imidazol-1-yl)methanones **3(a-l)** were synthesized. All the analogs were evaluated for their antibacterial activities. Binding mode analysis of the most active compound in the series was carried out in the active site of glucosamine 6-phosphate synthase (PDB ID 2VF5).[9]

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MATERIALS AND METHODS

All the chemicals and solvents for synthesis were purchased from Sigma Aldrich. Unless otherwise mentioned the solvents were used without purification. All solvents used were of commercial grade. Reactions were monitored by TLC on precoated silica gel plates (Kieselgel 60 F 254, Merck) and the spots were detected under UV light (254 nm). Melting points were checked using Optimelt, Stanford research systems, California. CHN elemental analysis was performed by using Carlo Erba 1108. Infrared (IR) spectra were taken on a FTIR Spectrophotometer IR Prestige -21 (Shimadzu Corporation, Japan) from 4000–400 cm-1 using KBr discs. 1H nuclear magnetic resonance (NMR) spectra were recorded at 400 MHz on Varian, Palo Alto, CA using $CDCl_3$/ dimethyl sulfoxide (DMSO) – d_6 as a solvent.

Preparation of 1-(aryl)-2-(1H-imidazol-1-yl) methanones (3)

General Procedure

To a mixture of 2-(aryl)-1H-imidazole (**2**),0.157g (0.002mol) of appropriately substituted benzoyl chloride in 25 mL of dichloromethane (DCM) was added and stirred for 3 hours at 5-10ºC followed by stirring for 48 hours in room temperature. The solvent was further evaporated to obtain a solid residue. The solid residue was then

Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology and Sciences, Mesra, Ranchi, India.

Corresponding Author: Priyanka Chandra, Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology and Sciences, Mesra, Ranchi, India., E-mail: priyankachandra78@gmail.com

treated with ethanol and filtered. The ethanol layer on concentration yielded white crystals of **(3)**.

(4-methoxyphenyl)(2-phenyl-1H-imidazol-1-yl) methanone (3a)

3a: IR (KBr)cm-1 : 648.10 (C-N-C bending), 717.45 (mono substituted benzene), 801.25 (p-disubstituted Benzene), 991.44 (C-C stretching), 1072.69 (C-C-N bending), 1290.85 (C-N aromatic amine), 1483.96 (CH_2 aliphatic stretching), 1583.69 (benzene ring in aromatic compound), 1675.85 (C=O stretching), 2955.64 (CH_3& CH_2 aliphatic).
1HNMR (DMSO-d_6, 400MHz): δ ppm : 8.42-6.46 (m,11H, Ar-H), 2.55-2.02 (s, 3H of OCH_3). [Found: C, 73.65; H, 5.03; N, 10.16 $C_{17}H_{14}N_2O$ requires C, 73.37; H, 5.07; N,10.07]. The 1H NMR spectra of compound 3a is given in Figure 1.

(4-chlorophenyl)(2-phenyl-1H-imidazol-1-yl) methanone (3b)

3b:IR (KBr) cm-1: 645.10 (C-N-C bending), 781.20 (C-Cl stretching), 720.45 (mono substituted benzene), 801.25 (p-disubstituted Benzene), 991.44 (C-C stretching), 1072.69 (C-C-N bending), 1290.85 (C-N aromatic amine), 1583.69 (benzene ring in aromatic compound), 1675.85 (C=O stretching), 1697.11(C=O stretching).
1H NMR (DMSO-d_6, 400MHz) δ ppm: 8.45-6.87 (m, 11H, Ar-H), 6.78.-6.60 (s, 1H,NH of imidazole).

[Found: C, 54.66; H, 3.33; N, 7.35 $C_{16}H_{11}ClN_2O$ requires C, 67.97; H, 3.92; Cl, 12.54; N, 9.91;]

(2,4-dichlorophenyl)(2-phenyl-1H-imidazol-1-yl) methanone (3c)

3c:IR (KBr) cm-1: 725.26 (C-Cl stretching), 815.69 (mono substituted Benzene), 995.20 (C-C-N bending), 1198.26 (C-C stretching), 1699.34 (C=O stretching).
1H NMR (DMSO-d_6, 400MHz) δ ppm: 8.55-6.70 (m, 11H, Ar-H), 6.75.-6.60 (s, 1H, NH of imidazole).

[Found: C, 60.75; H, 3.14; N, 8.75 $C_{16}H_{10}Cl_2N_2O$ requires C, 60.59; H, 3.18; Cl, 22.36; N, 8.83]

(2-(4-ethylphenyl)-1H-imidazol-1-yl) (4-methoxyphenyl)methanone (3d)

3d:IR (KBr) cm-1: 717.54 (C-Cl stretching), 756.12 (mono substituted benzene), 991.24 (C-C-N bending), 1197.65 (C-N aromatic amine stretching), 1697.41 (C=O stretching), 2997.40cm-1 (=CH in aromatic and unsaturated hydrocarbon).
1H NMR (DMSO-d_6, 400MHz) δ ppm: 8.55-6.70 (m, 11H, Ar-H), 6.75.-6.60 (s, 1H, NH of imidazole) 2.56-2,44(d, 2H, CH_2CH_3), 2.02-2.00 (s,3H of OCH_3),1.20(s, 3H, CH_2CH_3). The 1H NMR spectra of compound 3d is given in Figure 2.

[Found C, 74.57; H, 5.22; N, 9.57 $C_{19}H_{18}N_2O_2$ requires C, 74.49; H, 5.92; N, 9.14]

(4-chlorophenyl)(2-(4-ethylphenyl)-1H-imidazol-1-yl)methanone (3e)

3e:IR (KBr) cm-1: 670.46 (C-Cl stretching), 812.73 (mono substituted Benzene), 990.21 (C-C-N bending),1390.43 (CH_2 aliphatic stretching), 1670.48 (C=O stretching), 2950.48 (CH_3&CH_2 aliphatic).
1H NMR (DMSO-d_6,400MHz) δ ppm: 8.45- 7.801 (m, 11H, Ar-H), 2.60-2.53(d, 2H CH_2CH_3),1.20(s,3H, CH_2CH_3).

[Found: C, 69.55; H, 4.17; N, 9.34 $C_{18}H_{15}ClN_2O$ requires C, 69.57; H, 4.86; N, 9.01]

(2,4-dichlorophenyl)(2-(4-ethylphenyl)-1H-imidazol-1-yl)methanone (3f)

3f:IR (KBr) cm-1: 675.36 (C-Cl stretching), 660.96 (mono. subs. Benzene), 1200.63 (C-N aromatic amine stretching), 1570.26 (benzene ring in aromatic comp.), 1680.36 (C=O stretching), 2940.06 (CH_3& CH_2 aliphatic), 2990.97 (CH aromatic).
1H NMR (DMSO-d_6,400MHz) δ ppm: 8.55-7.901 (m, 10H, Ar-H);2.53-2.50(d, 2H CH2CH3),1.25(s, 3H, CH_2CH_3).

[Found: C, 62.29; H, 4.16; N, 8.52 $C_{18}H_{14}Cl_2N_2O$ requires C, 62.62; H, 4.09; N, 8.11]

(4-methoxyphenyl)(2-(3-nitrophenyl)-1H-imidazol-1-yl)methanone (3g)

3g:IR (KBr) cm-1: 540.26 (C-CO-C stretching), 1240 (C-N

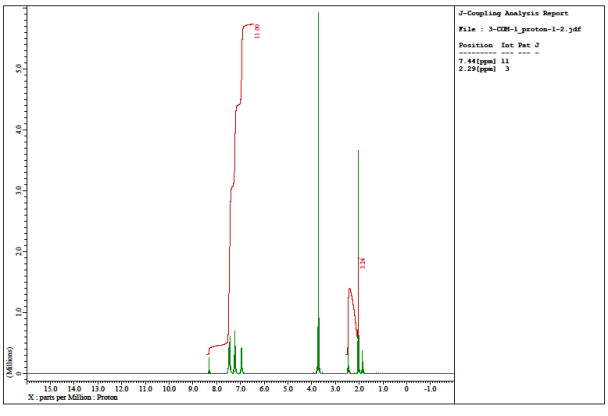


Figure 1: 1H NMR of the synthesised compound 3a.

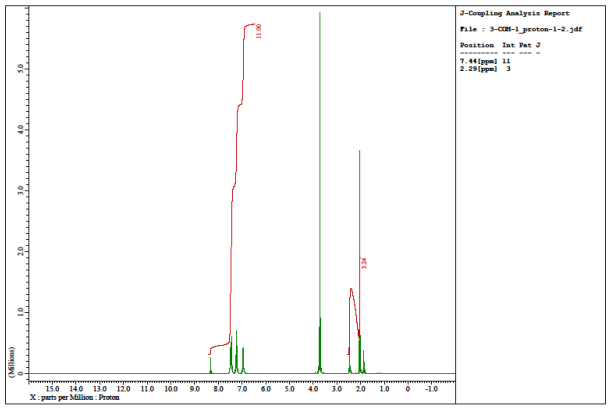


Figure 2: 1H NMR of the synthesised compound 3d.

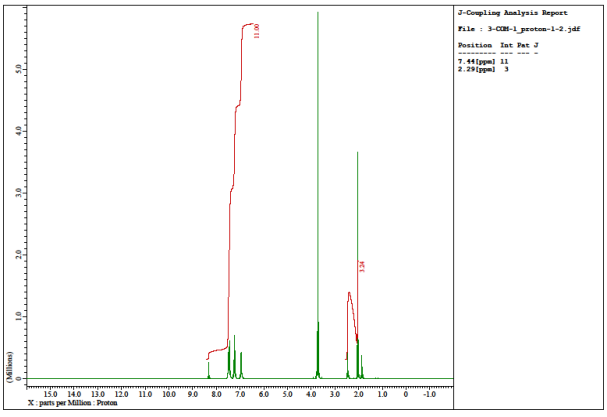


Figure 3: 1H NMR of the synthesised compound 3g.

aromatic amine stretching), 1416.98 (C-N aliphatic stretching), 1610.26 (benzene ring in aromatic comp.), 1680.36 (C=O stretching).
1H NMR(DMSO-d_6,400MHz) δ ppm: 7.58-7.56 (m, 11H, Ar-H), 2.32-2.00 (s, 3H of OCH_3). The 1H NMR spectra of compound 3g is given in Figure 3.

[Found: C, 63.25; H, 4.22; N, 13.43 $C_{17}H_{13}N_3O_4$ requires C, 63.16; H, 4.05; N, 13.00]

(3-nitrophenyl)(2-(4-chlorophenyl)-1H-imidazol-1-yl)methanone (3h)

3h:IR (KBr)cm-1: 780.65 (C-Cl stretching), 820.50 (C-CO-C bending), 950.24 (C-C-N bending), 1725.46 (C=O stretching), 1580.65 (NO_2 in aromatic nitro compound), 2990.56 (C-H alkanes).
1H NMR (300MHz, $CDCl_3$) δ ppm: 7.85-7.50 (m, 11H, Ar-H), 6.70-6.40 ((s, 1H, NH).

[Found C, 59.32; H, 3.07; N,12.58 $C_{16}H_{10}ClN_3O_3$ C, 58.64; H, 3.08; N, 12.82]

(2-(3-nitrophenyl) (2,4-dichlorophenyl) -1H-imidazol-1-yl)methanone (3i)

3i: IR (KBr) cm-1: 549.33 (C-N-C bending), 783.65 (C-Cl stretching), 812.06 (mono. subs. benzene), 1012.63 (C-N aromatic amine stretching), 1583.67 (NO_2 in aromatic nitro compound), 1685.36 (C=O stretching).
1H NMR (300 MHz, $CDCl_3$) δ ppm: 7.56 (m, 10H, Ar-H), 6.64-6.30 ((s, 1H, NH).
[Found: C, 57.22; H, 3.56; N, 8.45 $C_{19}H_{17}ClN_2O$ requires C, 57.56; H, 3.66; N, 8.55] (Figure 4).

(2-(4-nitrophenyl)(4-methoxyphenyl) 1H-imidazol-1-yl) methanone (3j)

3j: IR (KBr) cm-1: 549.33 (C-N-C bending), 810.06 (mono. subs. benzene), 1015.63 (C-N aromatic amine stretching), 1580.70 (NO_2 in aromatic nitro compound), 1680.40 (C=O stretching).
1H NMR (300 MHz, $CDCl_3$) δ ppm: 8.01 (m; 11H; Ar-H), 2.34-2.00 (s, 3H of OCH_3), 6.50-6.30 ((s, 1H, NH).

[Found: C, 68.20; H, 4.56; N, 9.23; $C_{17}H_{13}N_3O_4$ requires C, 68.81; H, 4.42; N, 9.44]

(2-(4-nitrophenyl)-(4-chlorophenyl)1H-imidazol-1-yl)methanone(3k)

3k: IR (KBr) cm-1: 550.33 (C-N-C bending), 669.32 (C-Cl stretching), 810.06 (mono. subs. benzene), 1010.54 (C-N aromatic amine stretching), 1585.65 (NO_2 in aromatic nitro compound), 1675.20 (C=O stretching).
1H NMR (300 MHz, $CDCl_3$) δ ppm: 8.58 (m; 11H; Ar-H), 6.32 (s; 1H; NH of imidazole)

[Found: C, 68.20; H, 4.56; N, 9.23; $C_{17}H_{13}N_3O_4$ requires C, 68.81; H, 4.42; N, 9.44]

(2-(4-nitrophenyl)-(2,4-chlorophenyl)1H-imidazol-1-yl)methanone(3l)

3l: IR (KBr) cm-1: 556.33 (C-N-C bending), 670.54 (C-Cl stretching), 815.06 (mono. subs. benzene), 1005.65 (C-N aromatic amine stretching), 1590.53 (NO_2 in aromatic nitro compound), 1670.10 (C=O stretching).
1H NMR (300 MHz, $CDCl_3$) δ ppm: 8.66 (m; 10H; Ar-H), 6.40 (s; 1H; NH of imidazole)

[Found: C, 68.20; H, 4.56; N, 9.23; $C_{17}H_{13}N_3O_4$ requires C, 68.81; H, 4.42; N, 9.44]

Antibacterial Studies

The microbial strains of the organisms used in this study were procured from MTCC-IMTECH Chandigarh, and NCIM- National Chemical Laboratory, Pune. Screening of the test compounds **3(a-l)** was done for their *in-vitro* antibacterial activity against standard organisms [Gram-positive bacteria: *Staphylococcus aureus* NCIM 2901, *Bacillus subtilis* MTCC 441; Gram-negative bacteria: *Salmonella typhi* NCIM 2501, *Escherichia coli* NCIM 2810 and *Pseudomonas aeruginosa* NCIM 2036, by by two-fold serial broth dilution method.[10,15] Ciprofloxacin was used as the standard. Single strength nutrient broth was used as the medium. This method depends upon the inhibition of growth of a microbial culture in a uniform solution of antibiotic in a liquid medium that is favourable to its rapid growth in the absence of the antibiotic. Determination of the Minimum Inhibitory Concentration (MIC) of the synthesized compounds was done. The MIC is the lowest concentration of tested compounds that completely inhibited the growth of the test organisms after 24 hrs of incubation at 37°C. The test compounds 3a-l were studied at concentrations of 100, 50, 25, 12.5, 6.25, 3.125 µg/ml respectively. The medium used was Muller-Hilton Agar media.

Computational Studies

All computational studies were carried out using Autodock v 4.5.6,[11] installed in a HP Precision workstation

(Radeon Graphics) with an Intel Core 3 quad processor and 8 GB of RAM with Operating system as Windows 10. The binding mode of the compound **3i** into the active site of glucosamine 6-phosphate synthase was investigated and is shown in Figure 5.

Protein structure preparation

The X-ray crystal structures of protein (PDB ID: 2VF5) were obtained from the protein data bank- Research Collaboratory for Structural Bioinformatics (RCSB).[9] The protein was prepared using the AutoDock 4.5.6 in which chain A has been selected for the docking studies. By removing the ligand, deleting water molecules, polar hydrogen's were added and Gasteiger charges were assigned.

After that the file was saved in -.pdbqt format.

Ligand Structure Preparation

The test compound 1 which was showing significant activity was selected for the docking studies. The ligand structure was prepared via PRODRG Server[12] followed by clean up the structure, energy minimization and saving it in - .pdbqt format.

Docking Protocol and their validation

The molecular docking studies were carried out using Autodock 4.5.6.

The X-ray co-crystal structure (Protein Data Bank entry code 2VF5) GLP was used as the initial structure for the computational studies. All the residues within 20 Å core from GLP were used to define the Binding Pocket.

Autodock 4.5.6 was used to explore the binding conformation of GLP and for the other test molecules.

Initially the ligand and water molecules from the X-ray co-crystal structure of 2VF5 were discarded, polar hydrogen atoms were added to the protein and later Gasteiger charges were assigned. All the non-polar hydrogens were merged.

The protein was saved in PDBQT format. The AutodockTools package version 4.5.6 was employed to generate the docking input files and to analyze the docking results. For the docking, a grid spacing of 0.200 Å and 100 x 100 x 100 number of points was used. The grid was centered on the allosteric site, using the GLP crystallographic position as reference.

The AutoGrid program generated separate grid maps for all atom types of the ligand structures plus one for electrostatic interactions. Autodock generated 50 possible binding conformations, i.e., 50 runs, for each docking by using Lamarckian Genetic Algorithm (LGA) searches. A default protocol was applied, with an initial population of 150 randomly placed individuals, a maximum number of 2.5 x 105 energy evaluations, and a maximum number of 2.7 x 104 generations. A mutation rate of 0.02 and a crossover rate of 0.8 were used.

The docking pose of the reference ligand (GLP) is shown in Figure 5.

Predictive ADME Studies

Predictive ADME studies were performed by using Swiss tools.[16] It is an online tool that requires the structure or the smiles for calculating the parameters.

The test compounds were built within the window by using the drawing tools of the online server else smiles can be directly copied instead of drawing structures. Predictive ADME studies were calculated on the basis of Lipinski's rule of five[17] which is essential to ensure drug like pharmacokinetic profile while using rational drug design.

RESULTS AND DISCUSSION

Chemistry

Firstly, 2-(aryl)-*1H*-imidazoles **2** were prepared following the method of *Ganguly et al.*[13] Next, the 1-(aryl)-2-(1Himidazol-1-yl)methanones **3a-l** were prepared by the method reported for imidazoles[14] by the treatment of 2-(aryl)-*1H*-imidazoles) **3** with appropriate benzoyl chlorides. The reactions leading to the formation of compounds **3** is outlined in Scheme 1 (Figure 1).

The physical data of all the newly synthesized compounds **3** are depicted in Table 1.

Antibacterial activity

All the synthesized compounds **3(a-l)** were evaluated for their *in vitro* antibacterial activity against- Gram-positive bacteria: *Staphylococcus aureus* NCIM 2901, *Bacillus subtilis* MTCC 441; Gram-negative bacteria: *Escherichia coli* NCIM 2810, *Pseudomonas aeruginosa* NCIM2036 and *Salmonella typhi* NCIM 2501 by by two-fold serial broth dilution method.[12] Compound **3i** showed reasonably high activity against the panel of bacteria (Minimum Inhibitory Concentration (MIC) =12.5µg/ml)**.** Compounds **3c**, and **3h** showed varied degrees of activity against all the bacterial strains. The results are summarized in Table 2.

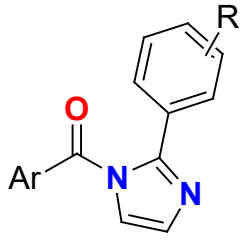


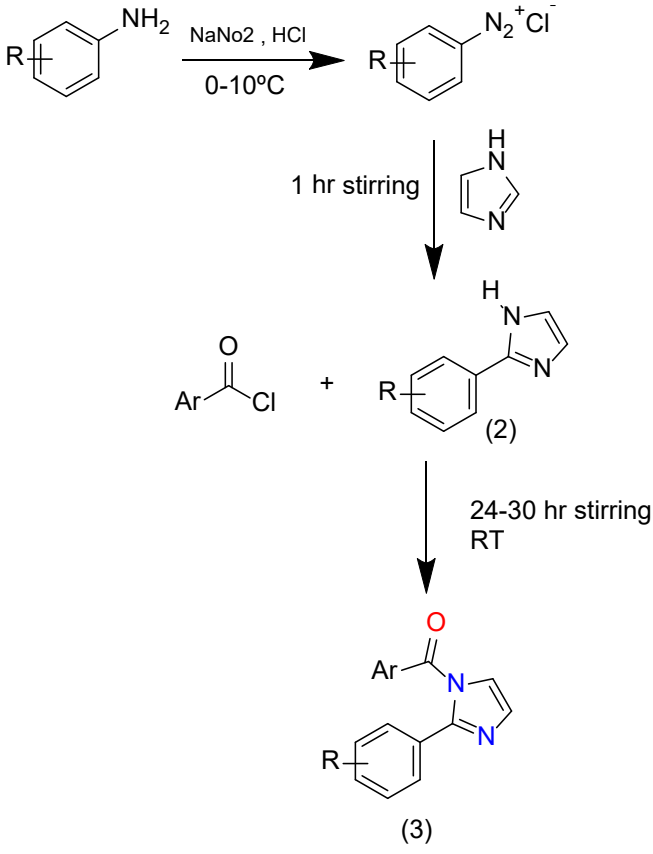
Figure 4: Structure of Compound 3i

Molecular Docking Studies

Binding Mode Analysis

Considering the best *in vitro* results, it was thought worthy to investigate the binding mode of the highest active compound **3i** in the active site of glucosamine-6-phosphate synthase (PDB ID: 2VF5).

The enzyme, glucosamine-6-phosphate synthase (GLP), is a new target for antibacterials and antifungals, GlcN-6-P synthase catalyzes the first step in hexosamine metabolism, converting fructose 6-phosphate (Fru6P) into glucosamine 6-phosphate (GlcN6P) in the presence of glutamine. The reaction catalyzed by GlmS is irreversible, and is therefore considered as a committed step. The end product of the pathway, N-acetyl glucosamine, is an essential building block of bacterial and fungal cell walls. It has been found that even a short time inactivation of GlmS is lethal for fungal cells. It is well established that small modifications in the structure of the targets can alter their biological character as well as their physiochemical properties.



Scheme 1: General reaction procedure of synthesized compounds 3a-l.

Initially the docking of the glucosamine-6-phosphate in the active site of glucosamine-6-phosphate synthase was performed in Autodock 4.5.6 10 to test the reliability of the docking formalism for our purposes. The docking of Glucosamine phosphate (GLP)(**4**) in the binding pocket of glucosamine phosphate synthase (PDB ID-2VF5) was performed to ensure the validity of docking calculations, reliability and reproducibility of the docking parameters for our study. It was evident that the docked pose of the redocked ligand of GLP was almost superimposed. A hydrogen bond interaction (1.905 Å) was observed between the hydrogen atom of NH_3^+ of GLP and LYS 103(NHGLP ··· COLYS103 = 1.905 Å).

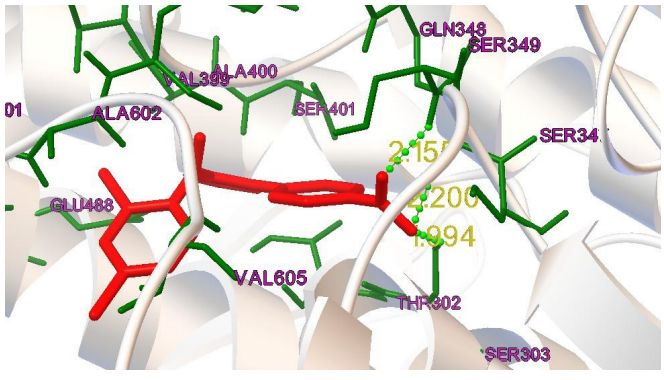


Figure 5: Redocking of co-crystallized ligand GLP(4) in the binding pocket of Glucosamine-Fructose-6-Phosphate Synthase (2VF5). Ligand is shown as orange line model and the amino acid residues interacting with the ligands are shown as green line model. Hydrogen bond interaction with amino acid residue of Glucosamine-Fructose-6-Phosphate Synthase is shown as green dotted spheres.

Table 1: Characterization data of compounds 3a-l

Compd	*Molecular Formula*	*R*	*X*	*M.P. (°C)*	*(%) Yield*
3a	$C_{17}H_{14}N_2O_2$	H	4-OCH_3	133-134	60
3b	$C_{16}H_{11}ClN_2O$	H	4-Cl	129-130	62
3c	$C_{16}H_{10}Cl_2N_2O$	H	2,4-diCl	100-101	50
3d	$C_{19}H_{18}N_2O_2$	4-C_2H_5	4-OCH_3	110-111	70
3e	$C_{18}H_{15}ClN_2O$	4-C_2H_5	4-Cl	113-114	76
3f	$C_{18}H_{14}C_{l2}N_2O$	4-C_2H_5	2,4-di Cl	138-139	66
3g	$C_{17}H_{13}N_3O_4$	3-NO_2	4-OCH_3	119-120	52
3h	$C_{16}H_{10}ClN_3O_3$	3-NO_2	4 - Cl	94-95	60
3i	$C_{16}H_9Cl_2N_3O_3$	3-NO_2	2,4-di Cl	144-145	50
3j	$C_{17}H_{13}N_3O_4$	4-NO_2	4-OCH_3	131-132	60
3k	$C_{16}H_{10}ClN_3O_3$	4-NO_2	4 - Cl	127-128	70
3l	$C_{16}H_9Cl_2N_3O_3$	4-NO_2	2,4-di Cl	154-155	65

Table 2: MIC value of the compounds 3a-l against Gram-positive bacteria: *Bacillus subtilis* MTCC441, *Staphylococcus aureus* NCIM 2901 and Gram-negative bacteria: *Pseudomonas aeruginosa* NCIM 2036, *Salmonella typhi* NCIM 2501, *Escherichia coli* NCIM 2810.

	MIC(µg/ml)				
Compounds	*B.subtilis*	*S.aureus*	*E.coli*	*P.aeruginosa*	*S.typhi*
3a	-	-	-	-	-
3b	-	-	-	-	-
3c	25	25	25	25	25
3d	-	-	-	-	-
3e	-	-	-	-	-
3f	-	-	-	-	-
3g	-	-	-	-	-
3h	50	50	50	50	50
3i	12.5	12.5	12.5	12.5	12.5
3j	-	-	-	-	-
3k	-	-	-	-	-
3l	-	-	-	-	-
Ciprofloxacin	6.25	6.25	6.25	6.25	6.25

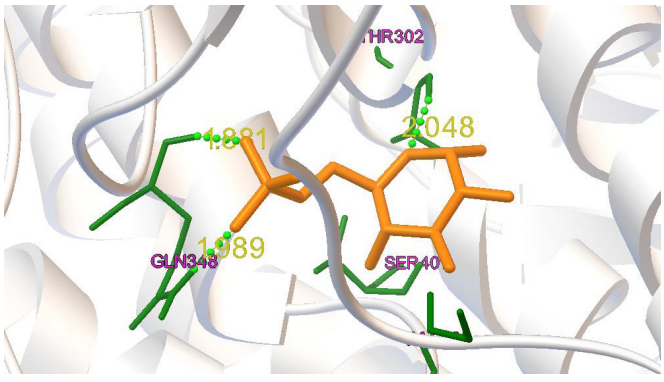
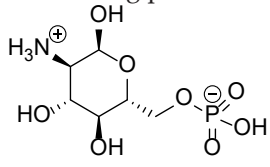


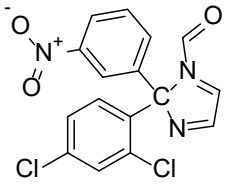
Figure 6: Binding mode of highest active compound **3i** the binding pocket of Glucosamine-Fructose-6-Phosphate Synthase (2VF5). Ligand is shown as red stick model and the amino acid residues interactingwith the ligands are shown as green line model. Hydrogen bond interaction with amino acid residue of Glucosamine-Fructose-6-Phosphate Synthase is shown as green dotted spheres.

Autodock was able to reproduce the experimental binding conformation of GLP within a minimal root mean square deviation (RMSD= 1.834 Å). (Figure 2). The estimated binding free energy and for GLP (**4**) was -4.78 kcal/mol. The estimated binding free energy for the active compound **3i** was -7.17 kcal/mol. It was interesting to note that the experimental results of the compound **3i** correlated well with the estimated binding free energy of the cocrystallized ligand GLP, in that the compound **3i** showed only moderate inhibitory activity, lesser than that of Ciprofloxacin.

An investigation of the binding mode of compound **3i** (Figure 6) revealed that the centroid imidazole ring was surrounded by the residues Ala602, Val399, Ala400, Gly301, Thr302, Ser303, Cys300, Gln348, Ser349, Thr352, Ser347 and Lys603. The hydrophilic linker group Ph-NO2 interacted favourably with the residues of SER303, SER349 and GLN348 of 2VF5. Three hydrogen bond interactions were observed between the macromolecule and the compound **3i** such as (N-O- ··· COSER303 = 1.994Å), (N=O ···COGLN348 = 2.200Å) and (N-O- ··· COSER349 = 2.155Å). Thus, these interactions and orientations may explain the reasonable minimum inhibitory concentration of the compound **3i** in the binding pocket of 2VF5.



4



3i

Predictive ADME studies

Analysis of physicochemically significant descriptors and pharmacokinetically relevant properties of all the compounds (**3a to l**) using SWISSPROT[16] tools was carried out, among which major descriptors reported here are required for predicting the drug-like properties of molecules.

These properties are

- Molecular weight (mol MW) (150–650)
- Octanol/water partition coefficient (Log Po/w) (-2–6.5)
- Hydrogen Bond Donour (≤5)
- Hydrogen Bond Acceptor (≤10)
- Percent human oral absorption (≥80% is high, ≤25% is poor)

All the compounds **3(a-l)** showed significant values for the properties analyzed and exhibited drug-like characteristics based on Lipinski's rule of five.[17]

CONCLUSION

A series of twelve analogs of imidazole substituted with phenyl ring **3(a-l)** were synthesised, their structures were characterized by IR and NMR, elemental analysis were done for each of the compounds. All the new analogs were evaluated for their antimicrobial (antifungal and antibacterial) activities. The compound showing the highest activity was subjected to molecular docking studies at the active site of glucosamine-6-phosphate synthase (PDB ID: 2VF5), binding mode analysis was carried out of the docked conformer. From the antimicrobial studies and the docking studies it must be concluded that the activity is due to the presence of electron withdrawing groups and electronegative groups at different positions of the phenyl rings linked to the imidazole moiety of the test compound. The study inspires us to consider a new molecular skeleton of ortho and para substituted imidazolyl methanones as potential entity for the development of broad spectrum antimicrobial agents.

ABBREVIATIONS

A°: Angstrom, cm: Centimetre, °C: Degree Centigrade, DMF: Dimethyl Formamide, DMSO: Dimethyl sulfoxide, *et al:* All Others, FTIR: Fourier Transform Infrared, g: Gram, h: Hour, IR: Infrared Spectroscopy, *m:* meta, MIC: Minimum Inhibitory Concentration, mg: Miligram, μL: Microlitre, mL: Millilitre, Mol: Molar, MIC: Minimum Inhibitory Concentration, NMR: Nuclear Magnetic Resonance, NRTIs: Nucleoside ReverseTranscriptase Inhibitors, NNRTIs: Non Nucleoside ReverseTranscriptase Inhibitors, PDB: Protein Data Bank.

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REFERENCES

1. Butler, K; Howes, H.L; Lynch, J.E.; Pirie, D.K. Nitroimidazole derivatives. Relationship between structure and antitrichomonal activity. *J. Med. Chem.***1967**, *10*, 891-897.
2. Maeda, K; Osato, T; Umezawa, H. A new antibiotic, azomycin. *J. Antibiot.* **1953**, *6*,182-182.
3. Demirayak, S.; Karaburun, A.C.Kiraz, N.; Synthesis and antibacterial activities of some 1-[2-(substituted pyrrol-1-yl) ethyl]-2-methyl-5-nitroimidazole derivatives.*Eur. J. Med. Chem.***1999**, *34*, 275-278
4. Zaprutko, L. Synthesis of some N-substituted nitroimidazole derivatives as potential antioxidant and antifungal agents, *Eur. J. Med. Chem.* **2009**, *44*, 645–652.
5. Ganguly, S., Vithlani, V.V., Kesharwani, A.K., Kuhu, R., Baskar, L., Mitramazumder, P., Sharon, A., Dev, A. Synthesis, antibacterial and potential anti-HIV activity of some novel imidazole analogs, *Acta Pharm.* **2011**, *61*, 187–201.
6. Mital, A. Synthetic Nitroimidazoles: Biological Activities and Mutagenicity Relationships. *Sci. Pharm.* **2009**, *77* (3), 497–520.
7. Black, J. H., and John, M.; Beale, Jr.;Wilson and Gisvold's textbook of Organic Medicinal and Pharmaceutical Chemistry. **2004**, 504.
8. Swastika Ganguly S; Shaw P; Synthesis, Antimicrobial Activity and Binding Mode Analysis of Some New Diaryl Imidazole Derivatives, *Ind. J.Het. Chem.* **2019**, *29* , 5-10.
9. http://www.rcsb.org/pdb last accessed on 2019 July 22nd.
10. India Ministry of health and Family Welfare, *Indian Pharmacopoeia.* Vol.2, Controller of Publications, New Delhi. 1996, p 88.
11. Lindstrom, W.; Morris, G. M.; Weber, C.; Huey, R. AutoDock 4. The Scripps Research institute,Molecular Graphics Laboratory, California, USA 2008.
12. http://davapc1.bioch.dundee.ac.uk/prodrg/index.html accessed on 2019 July 22nd.
13. Ganguly S., Mishra S., Sankrityayan I. , Dev A. *Ind. J.Het. Chem.* **2015 ,** *24*,373-380.
14. Olender, D; Zwawiak, J; Lukianchuk, V; Lesyk, R; Kropacz, A; Fojutowski, A; Zaprutko, L. Synthesis of some N-substituted nitroimidazole derivatives as potential antioxidant and antifungal agents. *Eur. J. Med. Chem.* **2009**, *44*, 645-652.
15. Kus, C.; Sozudonmez, F.; Altanlar, N.; Synthesis and antimicrobial activity of some novel 2-[4-(Substitutedpiperazin/ piperidin-1-ylcarbonyl) phenyl]-1H-benzimidazole derivatives. *Arch. Pharm. Life. Sci.* **2009**, *342*, 54-60.
16. http://www.swissadme.ch/index.php last accessed on 2019 March 13th
17. Lipinski, C. A. Lead and drug like compounds: the rule of five revolution. *Drug Discov. Today.* **2004**, *1(4)*, 337-341.