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Synthesis, Molecular Docking and DFT Studies of Biologically Active *N*-((3-(4-Nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)aniline Derivatives

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Some biologically active pyrazole clubbed imino molecules have been designed and synthesized from 1-phenyl-3-nitro phenyl-1*H*-pyrazol-4-carboxaldehyde and substituted aromatic amines *via* acid catalyzed condensation reaction. All the synthesized molecules were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral techniques. The *in vitro* antibactericidal property of the synthesized compounds was screened and compared with the results of theoretical molecular docking. Optimization of molecular geometry, DNA binding interaction and FMO analysis were also investigated by computational studies using Gaussian 16 package at B3LYP/6-31G(d,p) level. All the synthesized compounds exhibited moderate to good biological activities both experimentally and theoretically.

Keywords: Pyrazole derivatives, Antibacterial activity, Molecular docking, DNA binding, DFT studies.

INTRODUCTION

Several important classes of biologically active compounds contain pyrazole ring and have been found large applications in pharmaceuticals. Many pyrazole derivatives are well known for their high and wide activities such as NOS inhibitor [1], monoamine oxidase inhibitor [2], antibacterial [3], antiamoebic [4], anti-inflammatory [5], antiviral [6], antitumor [7], antidepressant, anticonvulsant [8], antimicrobial [9] antibacterial, antifungal [10], anticancer [11], antihistaminic activities, proton pump inhibitor, antioxidant, antihypertensive, anticoagulant [12] and agrochemical agents [13]. Furthermore *N*-phenyl pyrazole derivatives show an increased activity among phenyl derivatives against antitumor screening as well as antimicrobial [14]. These pyrazole derivatives also have applications in the development of pesticides, insecticides and herbicides [15]. These activities make pyrazole attached compounds for the novel drug development process.

From the literature, it was observed that the compounds with imino group act as an important pharmacore in the discovery of drug for inhibition of DNA and RNA, protein synthesis, carcinogenesis [16] and nitrogen fixation. Imino compounds also found application as hypnotic drugs for nervous system as well as in biological activities against bacteria and fungus [15].

Accepting the importance of these two groups, *N*-phenyl pyrazole and imino group, in biological activity, we focused on the synthesis of compounds containing both pyrazole and imino group. Herein, we synthesized some *N*-phenyl pyrazole clubbed substituted phenyl imino compounds by a simple and efficient method by treating nitro acetophenone phenyl hydrazone with DMF/$POCl_3$ complex and functionalized by substituted amino compounds. All the synthesized compounds were characterized by spectroscopic techniques and investigated their antimicrobial activities. Molecular docking calculations, DNA binding nature and FMO analysis were also performed.

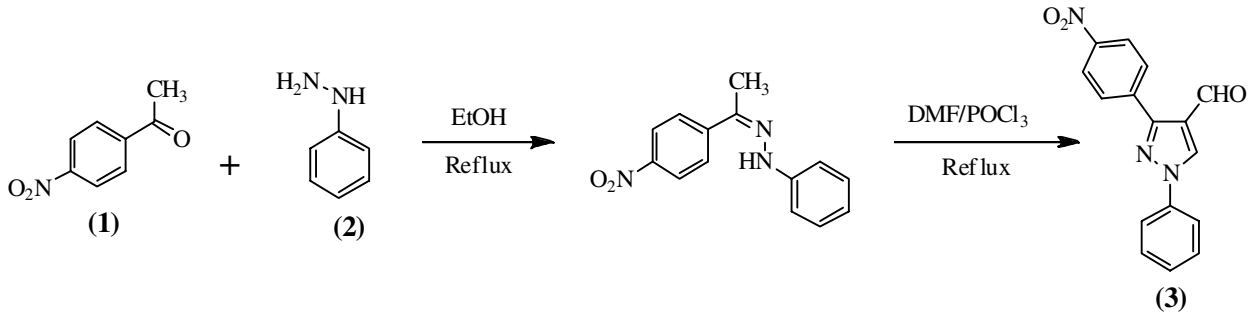
EXPERIMENTAL

Melting points of the synthesized compounds were determined on a Yanaco MP-S3 microscopic melting point apparatus. The FT-IR spectra were obtained in KBr pellets on a Brucker Equinox-55 FT-IR apparatus. The ^{1}H & ^{13}C nuclear magnetic resonance spectra were taken down on NMR-JEOL GSX-400 spectrophotometer, tetramethyl silane was used as the internal

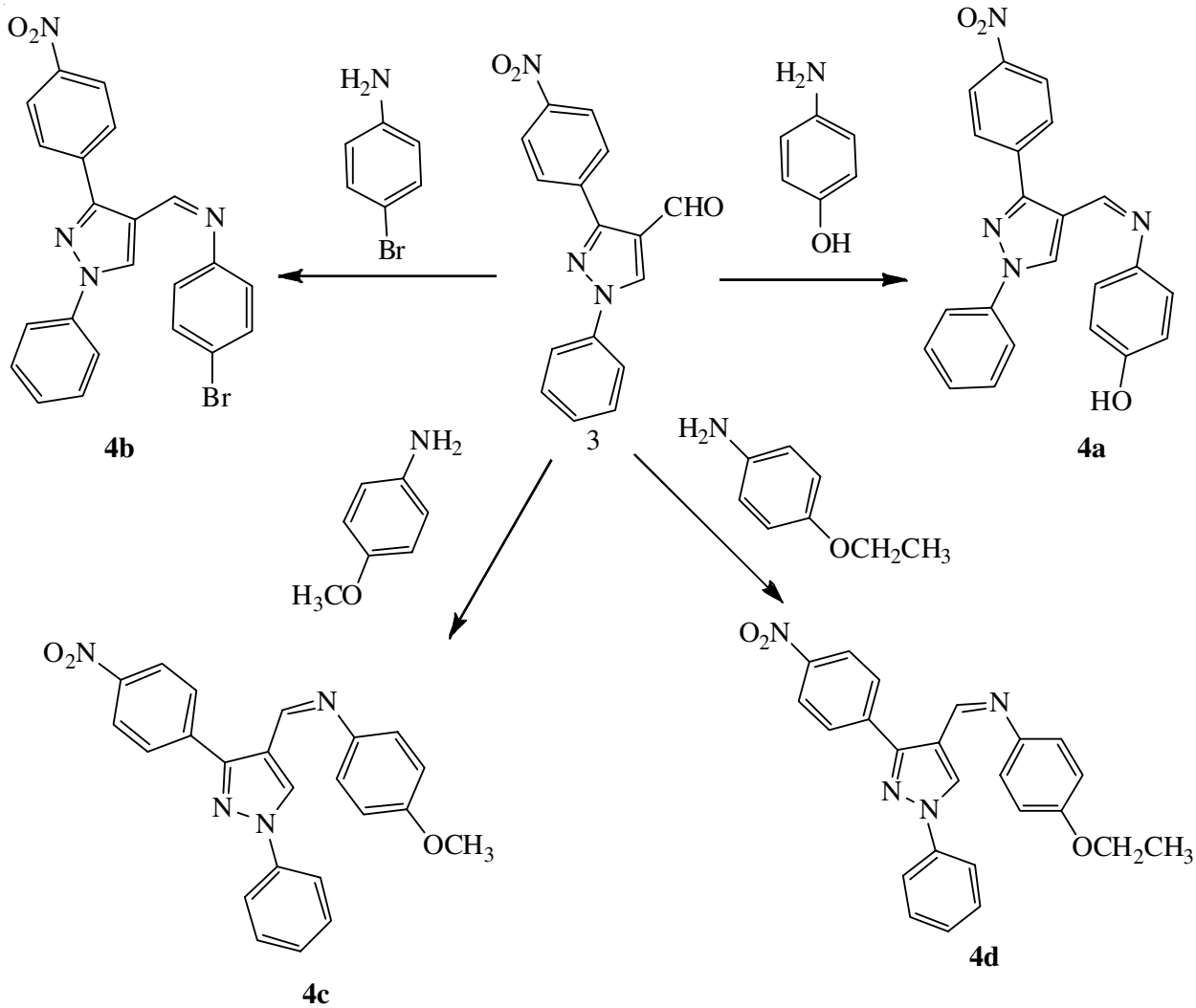
reference and $CDCl_3$ as solvent. Mass spectra were recorded on an HP 1100 LC-MS (ESI). All the chemicals and reagents used were of commercial grade and can be used without further purification.

General procedure: The intermediate 3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole -4-carboxaldehyde (**3**) was synthesized from 4-nitroacetophenone (**1**) and phenyl hydrazine (**2**) followed by Vilsmeir-Haack reaction as shown in **Scheme-I**. The formed diphenyl pyrazole-4-carboxaldehyde underwent condensation reaction with *p*-substituted aromatic amines to afford *N*-((3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)aniline derivatives (**4a-d**) (**Scheme-II**).

Synthesis of 4-(((3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)amino)phenol (4a): The compound was obtained by the reaction between 3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde with 4-aminophenol. Yield: 48 %, dark brown solid, m.p. 154 ºC, IR (KBr, cm^{-1}): 3420 (OH *str.*), 3054 (ArCH *str.*), 1471 (ArC=C *str.*), 1646 (C=N *str.*), 1239 (C-N *str.*), 1561 and 1414 (NO_2 asymmetric and symmetric *str.*); ^1H NMR (δ ppm): 5.04 (s, 1H, OH), 8.94 (s, 1H,



Scheme-I: Schematic representation of synthesis of 3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde



Scheme-II: Schematic representation of synthesis of compounds **4a-d**

HC=N), 8.54 (s, 1H, CH of pyrazole ring), 6.98-8.13 (m, 13H, aromatic H); ^{13}C NMR (δ ppm): 109-142 (all aromatic carbons), MS: *m/z* 384 (M^+).

Synthesis of 4-bromo-*N*-((3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)aniline (4b): The compound was obtained by the reaction between 3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole -4- carboxaldehyde with 4-bromoaniline. Yield: 62%, brown solid, m.p.: 143 ºC, IR (KBr, cm^{-1}): 3038 (ArCH *str.*), 1449 (ArC=C *str.*), 1611 (C=N *str.*), 1222 (C-N *str.*), 1551 and 1398 (NO_2 asymmetric and symmetric *str.*), 744 (C-Br *str.*); ^{1}H NMR (δ ppm): 9.13 (s, 1H, HC=N), 8.62 (s, 1H, CH of pyrazole), 7.02-8.38 (m, 13H, aromatic H); ^{13}C NMR (δ ppm): 114-152 ppm (all aromatic carbons), MS: *m/z* 448 (M^+).

Synthesis of 4-(methoxy-*N*-((3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)aniline (4c): The condensation reaction was carried out between 3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde with 4-methoxyaniline to obtain **4c**. Yield: 46%, yellow solid, m.p. 132 ºC, IR (KBr, cm^{-1}): 3035 (ArCH *str.*), 1449 (ArC=C *str.*), 1612 (C=N *str.*), 1221 (C-N *str.*), 1550 and 1400 (NO_2 asymmetric and symmetric *str.*); ^{1}H NMR (δ ppm): 3.01 (s, 3H, OCH_3), 9.05 (s, 1H, HC=N), 8.87 (s, 1H, CH of pyrazole), 7.02-8.22 (m, 13H, aromatic H), ^{13}C NMR (δ ppm): 107-143 ppm (all aromatic carbons), 78 ppm (methoxy carbon) MS: *m/z* 398 (M^+).

Synthesis of 4-(ethoxy-*N*-((3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)aniline (4d): The condensation reaction was carried out between 3-(4-nitrophenyl)-1-phenyl-1H-pyrazole -4-carboxaldehyde with 4-ethoxyaniline to obtain **4d**. Yield: 44%, yellow powder, m.p. 135 ºC, IR (KBr, cm^{-1}): 3041 (ArCH *str.*), 1453 (ArC=C *str.*), 1620 (C=N *str.*), 1228 (C-N *str.*), 1557 and 1408 (NO_2 asymmetric and symmetric *str.*); ^{1}H NMR (δ ppm): 0.99 (t, 3H, CH_3), 4.34 (q, 2H, CH_2) 9.01 (s, 1H, HC=N), 8.94 (s, 1H, CH of pyrazole), 7.02-8.02 (m, 13H, aromatic H); ^{13}C NMR (δ ppm): 109-142 ppm (all aromatic carbons), 68.5 and 14.08 ppm (methoxy carbon); MS: *m/z* 412 (M^+).

Antibacterial activity: All the synthesized compounds have been screened for their antibacterial activity (*in vitro*) by adopting standard protocols available in the literature [17,18]. The antibacterial activity studies were caried out against two-Gram-negative bacterial strains such as *Escherichia coli* MTCC-443 and *Pseudomonas aeruginosa* MTCC1688 and two Gram-positive strains *viz. Staphylococcus aureus* MTCC96 and *Streptococcus pyogenes* MTCC442. The ciprofloxacin drug was chosen as the standard antibacterial drug.

Antifungal activity: Antifungal activity was investigated against two fungal strains *viz. Candida albicans* MTCC227 and *Aspergillus niger* MTCC282, and the drug fluconazole was chosen as the standard. The broth micro-dilution method was adopted to measure the minimal inhibitory concentration (MIC) according to National Committee for Clinical Laboratory Standards (NCCLS) [19].

Antimycobacterial activity: The *in vitro* antitubercular activity was investigated against *M. tuberculosis* H37Rv by microplate alamar blue assay method [20]. Isonicotinic acid hydrazide (INH) was selected as the standard antituberculosis drug, and all the synthesized compounds were screened.

DFT studies: The ground state geometry of the synthesized molecules was optimized at B3LYP/6-31G(d,p) level using the Gaussian 16 package. The atomic orbital contributions of the FMOs were predicted by Chemcraft_B595A software.

Molecular docking: We used the Arguslab 4.0.1 version software for docking to prepare input file. First, we optimized the structures of all the compounds, after that its binding conformations in the active site of the selected protein thymidylate kinase (TMPK) (PDB Id: 4QGG downloaded from PDB database) were prepared. Before docking all the miscellaneous residues, water molecules and heterocyclic compounds present in the crystallographic structure of TMPK were removed to activate the binding sites of protein only for the synthesized compounds and subsequently hydrogen atoms were added to all its amino acids. The docking process was carried out by assuming that the ligand molecule is flexible (all the rotatable bonds of ligands are considered) and protein is rigid. The calculation box was created and placed at the centre of the binding site residues with 60 × 60 × 60 grid points in XYZ directions. The docking study was carried out with standard precision with default values.

RESULTS AND DISCUSSION

The synthesis of the title compounds was performed by the condensation of nitro acetophenone with phenyl hydrazine followed by Vilsmeir-Hack reaction to yield 3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde, which on again undergo condensation with *p*-substituted amino compound to form imino compounds (**4a-d**). All the synthesized compounds were well characterized by different spectroscopic techniques.

Biological studies

Antimicrobial activity: Among the synthesized compounds **4a** and **4b** are active against *S. aureus* and compounds **4c** and **4d** are inactive (Table-1). All compounds show activity (weak to high activity) against *E. coli*. However, against *P. aeruginosa* the compounds **4b** is highly active, **4a** and **4c** are exhibiting weak activity and **4d** is inactive. Compounds **4a** and **4b** are moderately active against *S. pyrogenes*, compounds **4c** and **4d** are less active. All the synthesized compounds displayed an outstanding antifungal activity with MIC 0.2 µg/mL against *A. niger* than fluconazole and this activity is found to be indep-endent of the substituents on phenyl ring. Against *C. albicans*, compound **4a** exhibited good antifungal activity (MIC 50 µg/mL) than rest of the compounds. However, they all were less active than standard drug fluconazole (MIC 30 µg/mL).

Structure activity relationship (SAR): The biological studies point out that the presence of electron releasing or withdrawing group on imino phenyl ring extensively increases the conjugation and this will influence the bioactivity and exhibit broad-spectrum of antimicrobial activity. It is supposed that the bioactivity for these compounds due to the combination of the factors such as phenyl substitution on the pyrazole ring, the presence of the imino bond, steric hindrance, and substituents at the imino phenyl ring. SAR study would help to under-

TABLE-1
ANTIMICROBIAL ACTIVITY OF PYRAZOLE CLUBBED PHENYL DERIVATIVES (INHIBITION ZONE MEASURED IN mm)

Compound	*S. aureus*	*E. coli*	*P. aerugi*	*S. pyrogenes*	*A. niger*	*C. albicans*	*M. tuberculosis*
4a	15	17	13	16	0.2	70	100
4b	19	20	20	19	0.2	100	51.2
4c	8	15	12	11	0.2	100	51.2
4d	5	12	8	8	0.2	100	51.2
Ciprofloxacin	24	22	23	23	–	–	–
Fluconazole	–	–	–	–	30	30	–
INH	–	–	–	–	–	–	0.4

Highly active = 20-30, Moderately active = 15-20, Weakly active = 11-15, Less than 11 inactive.

stand the effect of different substitutions on imino phenyl and electronic effect on microbial strain [21]. The substituents have been carefully chosen to establish different electronic environment on the new molecules. Methoxy and ethoxy groups were selected as electron donating groups on aromatic ring and hydroxy and bromo groups are electron withdrawing groups from the aromatic system [22]. The *in vitro* antimicrobial activity studies revealed that the compounds with electron withdrawing groups on imino phenyl ring show enhanced activity. Furthermore, the hydrophobic substituents at 4th position of phenyl ring attached to imino group provide a positive impact on antimicrobial activity and its physico-chemical properties. From our observation, the activity order follows as the compounds with Br > OH > OCH_3 > OCH_2CH_3 [23]. It was also true in the present case as the chain length increases the inhibitory activity generally decrease, compound with methoxy group was more active than corresponding ethoxy compounds [24]. Compounds with *N*-atom in the heterocyclic systems are having better pharmacological activities than the simple benzene analogue.

Antituberculosis activity: All the title compounds exhibited a very slight tubercular activity (Table-1). The poor antitubercular activity may be due to the lower lipophilicity as indicated by their Clog P values, which resulted in the reduced cell wall permeation.

Molecular docking studies with protein: Action of the drug antibiotic generally includes the inhibition of cell wall synthesis, inhibition of protein synthesis, inhibition of nucleic acid synthesis and anti-metabolism [25]. That is the antibiotics attack the specific proteins which are responsible for the above-mentioned routes. Thymidylate kinase (TMPK) is a nucleotide contains 50 monophosphate kinase and the essential enzyme present in it catalyzes the biosynthesis of DNA of bacterial cell. This protein is usually generating dTTP for the above cell wall synthesis [26]. The selected standard antibacterial drug ciprofloxacin usually inhibits the DNA gyrase, which is necessary to separate the bacterial DNA and thus resulting the inhibition of the cell wall division. The H-bond length and minimum ligand pose energy of the title compounds within the active site of the target proteins were measured and tabulated in Table-2. The lowest energy conformation and its binding pose of all the compounds is shown in Fig. 1.

The binding free energy helps to evaluate the accuracy of affinity between target protein and the docking models. From the literature it is suggested that the lower the value of binding energy more will be the binding strength of the ligand in the active site of the target protein and the binding energy values ranging from -8.40 to -9.40 Kcal/mol. The predicted binding energy values were not higher than 2.5 Kcal/mol, indicated that all the synthesized compounds were well fitted in the active pocket of the targeted protein. Compound **4a** is forming three different H bond interactions such as the amino acid moiety 266 GLU, 265 THR and 269 LEU with O of OH with bond length 1.845, 2.247 and 1.796 Å, respectively. In compound **4c**, 269 LEU amino acid moiety formed H bond with O of OCH_3 with bond length 1.800 Å and 270 PHE with O of OCH_3 with bond length 2.892 Å. In compound **4d**, there is two H-bond interactions, 270 PHE and 269 LEU with O of OCH_2CH_3 with bond length 2.720 and 1.688 Å, respectively.

Frontier molecular orbital (FMO) calculation: The energy values of HOMO, LUMO, the HOMO – LUMO energy gap and global reactivity descriptors are summarized in Table-3. The HOMO, LUMO plots for the synthesized compounds are depicted in Fig. 2. Using Koopman's theorem equations the global reactivity descriptors such as chemical potential (μ) and hardness (η), were calculated: Hardness is given by $\eta = I - A/2$; chemical potential is given by $\mu = -(I+A)/2$. The electronegativity is given by $\chi = (I+A)/2$; where I is the electron affinity ($I = -E_{HOMO}$) and A is the ionization potential ($A = -E_{LUMO}$). The negative chemical potential indicates non-spontaneous decomposition. The energy gap for **4b** is maximum and equal to 3.6164 eV and minimum is for **4d** equal to 3.5073. Compounds with electron donating substituents are having lower energy gap compared to compounds with electron withdrawing groups and its order is **4b** > **4a** > **4c** > **4d**. The iso density in HOMO of **4a** is spread over the entire scaffold (including the OH substituent), and that of **4b**, **4c** and **4d** are distributed over

TABLE-2
BINDING ENERGY OF THE COMPOUND AND H-BOND LENGTH CALCULATED USING ARGUS LAB 4.0.1

Entry	Binding energy (Kcal/mol)	H bond length (Å)
4a	-8.68	1.845 (266 GLU with O of OH), 2.247 (265 THR with O of OH), 1.796 (269 LEU with O of OH)
4b	-9.40	–
4c	-8.40	1.800 (269 LEU with O of OCH_3), 2.892 (270 PHE with O of OCH_3)
4d	-9.15	2.720 (270 PHE with O of OCH_2CH_3), 1.688(269 LEU with O of OCH_2CH_3)

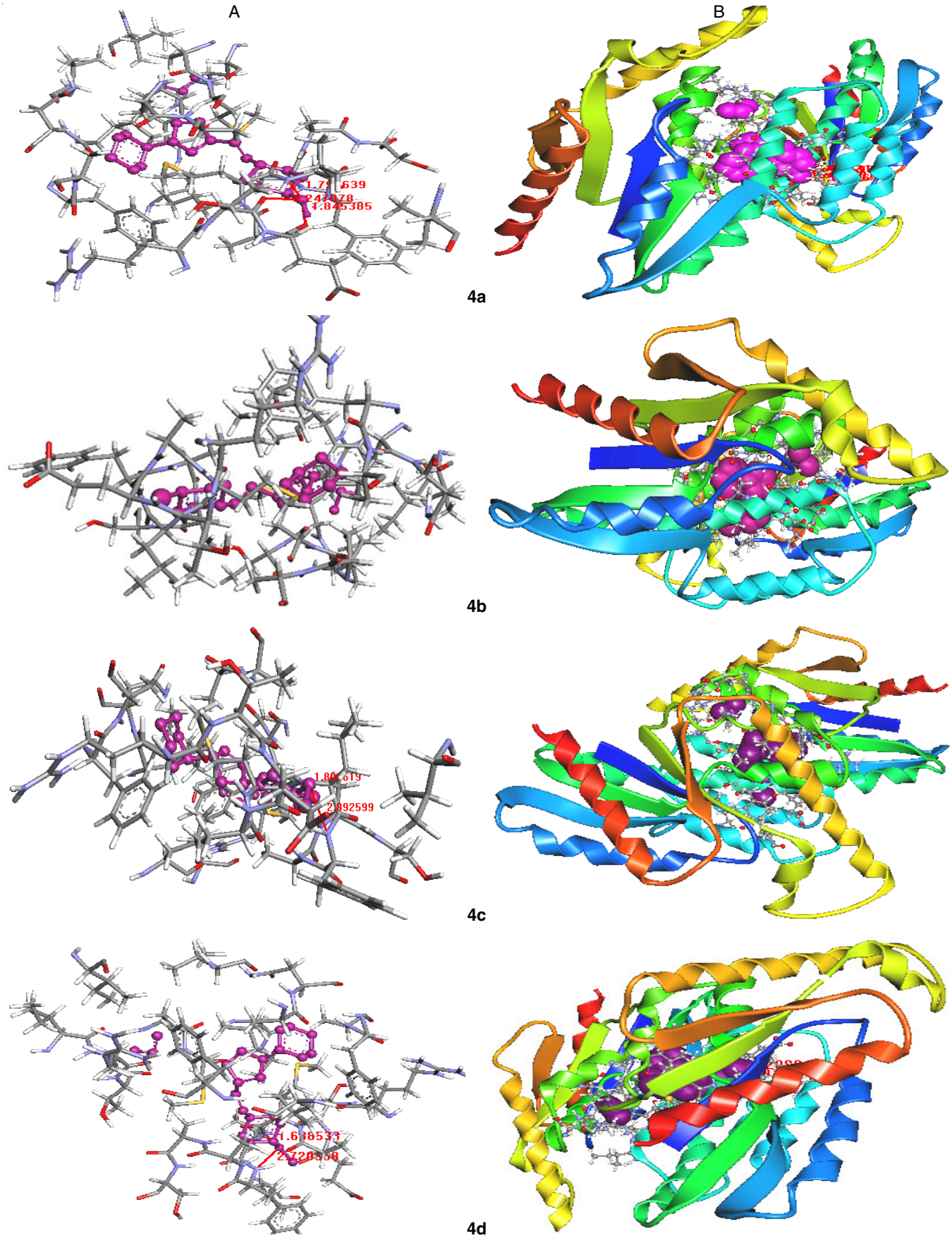


Fig. 1. Docked pose of the compounds (**4a-d**, purple colour) in the active site of the target protein (grey and blue colour (A) and its cartoon view (protein as ribbon) (B)

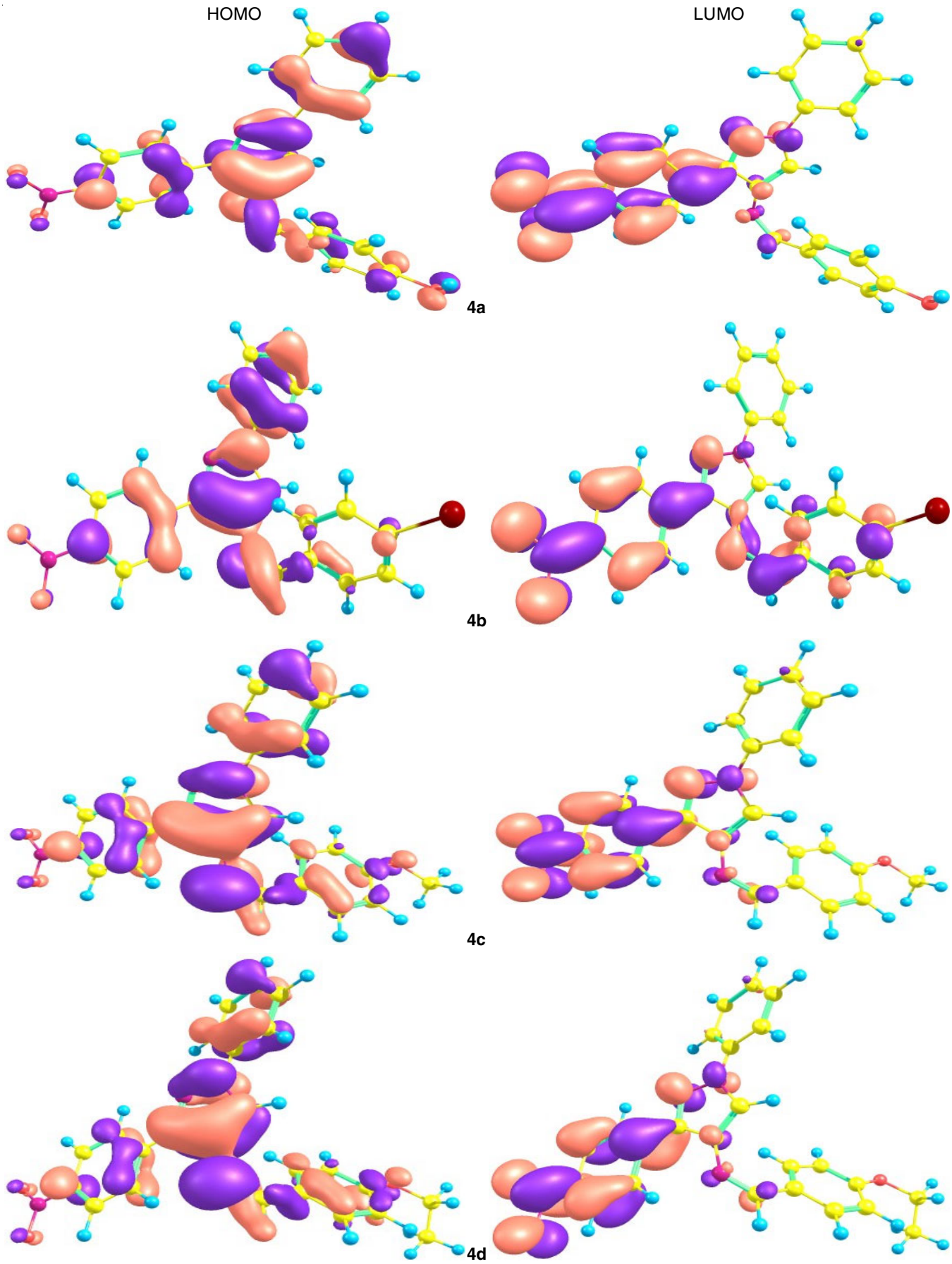


Fig. 2. HOMO-LUMO (the frontier molecular orbitals) plots of compounds **4a-d**

TABLE 3
ELECTRONIC ENERGY CALCULATION VALUES OF SYNTHESIZED **4a-d**

Compound	E_{HOMO} (eV)	E_{LUMO} (eV)	Energy gap	η	μ	χ
4a	-5.7528	-2.2038	3.5490	1.7745	-3.9783	3.9783
4b	-5.9299	-2.3135	3.6164	1.8082	-4.1217	4.1217
4c	-5.6831	-2.1625	3.5206	1.7603	-3.9228	3.9228
4d	-5.6597	-2.1524	3.5073	1.7536	-3.9060	3.9060

*η is the hardness, *μ is the chemical potential indicating spontaneous decomposition, *χ is the electronegativity.

the entire molecule, but not to the substituent of phenyl ring of imino group. The iso-density of LUMO of all the compounds mainly distributed along nitrophenyl pyrazole core.

Molecular docking with DNA: Even though there are different structural properties to determine the binding modes, here we concentrated on the shape of the molecule for DNA binding to bind either in major groove or minor groove as binding site for the synthesized compounds. Literature reports show that the forces maintaining the stability of DNA-intercalator complex include van der Waals, hydrogen bonding, hydrophobic, charge transfer and electrostatic complementarity [27-29]. The efficiency of the molecule to act as a biologically active drug depends on its favourable conformation and binding location within the DNA. The DNA binding conformations for compounds **4a-d** were performed with CT-DNA duplex of sequence d(CGCGAATTCGCG)2 dodecamer (PDB ID: 355D) and the most favourable docked poses are given in Fig. 3. It can be seen from Fig. 3, all the synthesized compounds could bind with DNA in an interactive fashion near the minor groove. The planarity of the compounds enhances binding of these compounds *via* partial intercalation with DNA. From literature usually small molecules prefer to interact with minor groove due to little steric hindrance [30]. Furthermore, presence of aromatic ring connected by single bonds allow for torsional strain to facilitate the curvature of the groove with displacement of water molecules. Presence of heterocyclic ring in the molecule makes favorable stacking interactions between DNA base pairs, resulting van der Waals interactions and hydrophobic contacts with DNA functional groups that define the groove [18,31]. Thus, present molecular modeling studies raise light on the binding modes through which these compounds interact with DNA.

Conclusion

A series of four new 1-phenyl-3- nitrophenyl pyrazole clubbed imino phenyl derivatives were synthesized and characterized. Their antibacterial activity was investigated against Gram-negative bacterial strains such as *Escherichia coli* MTCC-443 and *Pseudomonas aeruginosa* MTCC1688 and two Gram-positive strains *viz*. *Staphylococcus aureus* MTCC96 and *Streptococcus pyogenes* MTCC442. Their antifungal and anti-tuberculosis activities were also evaluated. Most of the synthesized compounds were found very active, which might be due to the greater lipophilicity of three different phenyl groups present in the molecule and electron withdrawing substituent present at 4th position of the imino phenyl ring also enhanced the biological activity. Running molecular docking analysis using the software Arguslab 4.0.1, minimum ligand pose binding energy and H-bond information of all the synthesized compounds in the protein TMPK were also investigated. The DFT frontier orbital analysis determined the global reactivity descriptors. The molecular docking with DNA results supported non-covalent interactions into the groove binding mode.

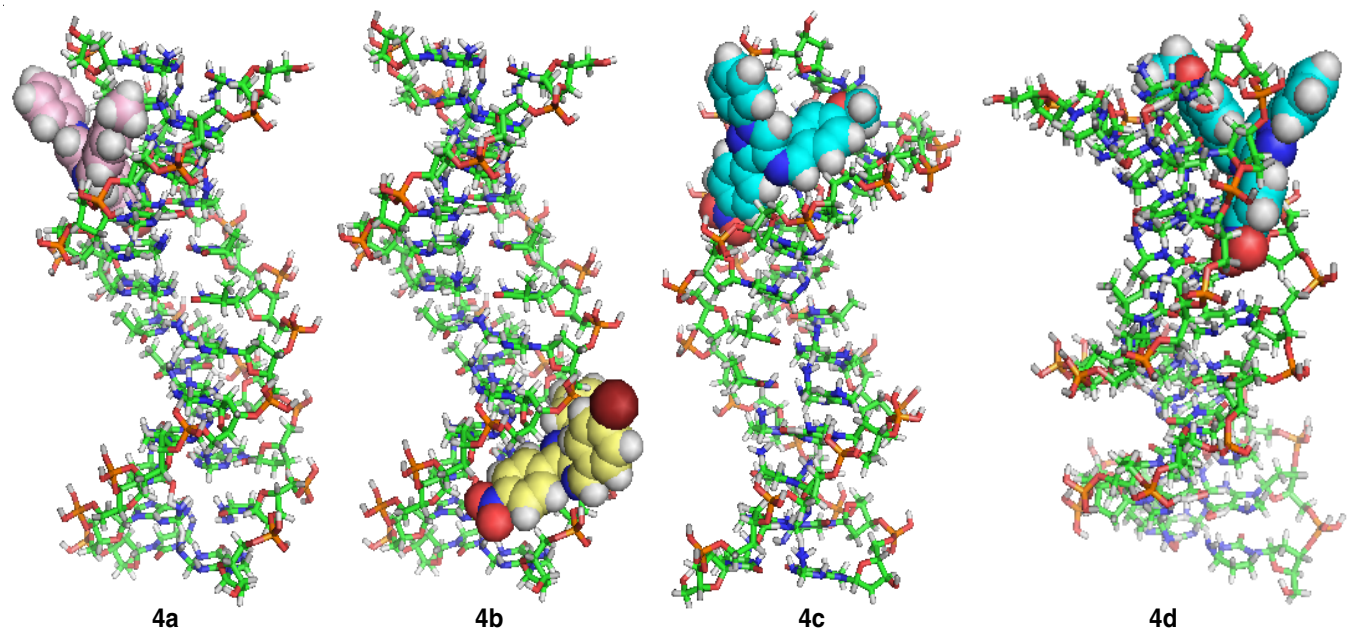


Fig. 3. Molecular docked model of compounds **4a-d** with DNA dodecamer duplex of sequence d(CGCGAATTCGCG)2(PDB ID: 1BNA)

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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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