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ARTICLE

Synthesis, DFT Calculations, DNA Binding and Molecular Docking Studies on Biologically Active *N*-((3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)naphthyl Derivatives

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Asian Journal of Organic & Medicinal Chemistry

Volume: 6 Year: 2021
Issue: 4 Month: October–December
pp: 292–301
DOI: https://doi.org/10.14233/ajomc.2021.AJOMC-P351

Received: 30 November 2021
Accepted: 24 December 2021
Published: 31 December 2021

ABSTRACT

The biologically active pyrazole clubbed imino naphthyl derivatives have been designed and synthesized from 1-phenyl-3-methoxy phenyl-1*H*-pyrazol-4-carboxaldehyde and substituted naphthyl amines *via* acid catalyzed condensation reaction. All the synthesized compounds were well characterized by different spectroscopic and mass spectral techniques. The *in vitro* antibacterial, antifungal and antituberculosis studies were carried out. The molecular docking study was also done with the software Arguslab 4.0.1. The studied compounds showed moderate to good biological activities both experimentally and theoretically. Geometry optimization, DNA binding interaction and FMO analysis were also investigated with the help of Gaussian 16 package at B3LYP/6-31G(d,p) level.

KEYWORDS

Pyrazole derivatives, Imino naphthyl derivatives, Biological activities, Molecular docking, DNA binding.

INTRODUCTION

One of the most important heterocyclic frameworks in the medicinal chemistry is pyrazole and its derivatives, widely observed in natural products such as vitamins, hormones and alkaloids [1,2], possessing a broad spectrum of biological profiles such as NOS inhibitor [3], monoamine oxidase inhibitor [4], antibacterial [5], antiamoebic [6], anti-inflammatory [7], antiviral [8], antitumor [9], antidepressant, anticonvulsant [10], antimicrobial [11], antibacterial, antifungal [12], anticancer [13], antihistaminic activities, proton pump inhibitor, antioxidant, antihypertensive, anticoagulant [14] and agrochemical agents [15]. During the last few years, several well-known drugs possessing pyrazole scaffold like celecoxib, viagra, fipronil, *etc*. are in clinical use as therapeutic agents [16-18]. Therefore, pyrazole nucleus served as a valuable structure for the exploration of lead molecules.

Literature confirm that *N*-phenyl pyrazole derivatives show an increased activity among phenyl derivatives against antitumor screening as well as antimicrobial [19]. Recently these pyrazole derivatives have reported potent applications in the development of pesticides, insecticides and herbicides [20]. These activities introduced pyrazole attached derivative as an important compound in the novel drug development process.

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Recently, 1*H*-pyrazoles are having special attention as they constitute an important class of natural and synthetic products, most of which exhibit versatile biological activities. The success of this scaffold having pharmacological efficiency encouraged us to synthesize new pyrazole derivatives and examine its biological activities.

On the other hand, interesting physiological and chemotherapeutic properties of imino or azomethine moiety make them promising pharmacophore to design and develop new potentially useful therapeutic agents. Moreover, several imino derivatives with pharmacological activities such as inhibition of DNA and RNA, protein synthesis, carcinogenesis [21] and nitrogen fixation have been reported. In addition, the imino compounds have many applications in the field of hypnotic drugs for nervous system as well as having biological activities against bacteria and fungus [22].

It is expected that the presence of pyrazole ring together with imino moiety may facilitate it's *in vitro* antibacterial and antifungal activities. Promoted from the above observation, a simple and efficient method is developed for the synthesis of biologically active pyrazole terminated imino naphthyl derivatives. Apart from this, the presence of different substituents on imino naphthyl ring also influence its potential as chemotherapeutics. Herein, we synthesized *N*-phenyl-*C*-methoxy phenyl terminated imino naphthyl derivatives, characterized using IR, NMR, mass spectroscopy and elemental analysis techniques. *In vitro* biological activities like antimicrobial, antibacterial and antifungal were investigated. Docking studies have been performed to determine the plausible protein-ligand interactions.

EXPERIMENTAL

All the chemicals and solvents were purchased from Sigma-Aldrich and Merck and used as received. All reagents used were commercial products of analytical grade and were used as such without any purification. Melting points were taken on a Yanaco MP-S3 microscopic melting point apparatus. Infrared spectrum of the compound spectra was recorded in KBr pellets on a Brucker Equinox-55 FT-IR apparatus. Both ^{1}H NMR and ^{13}C NMR spectra were scanned on an INOVA-400 (using TMS as internal standard, DMSO-d_6 as solvent).

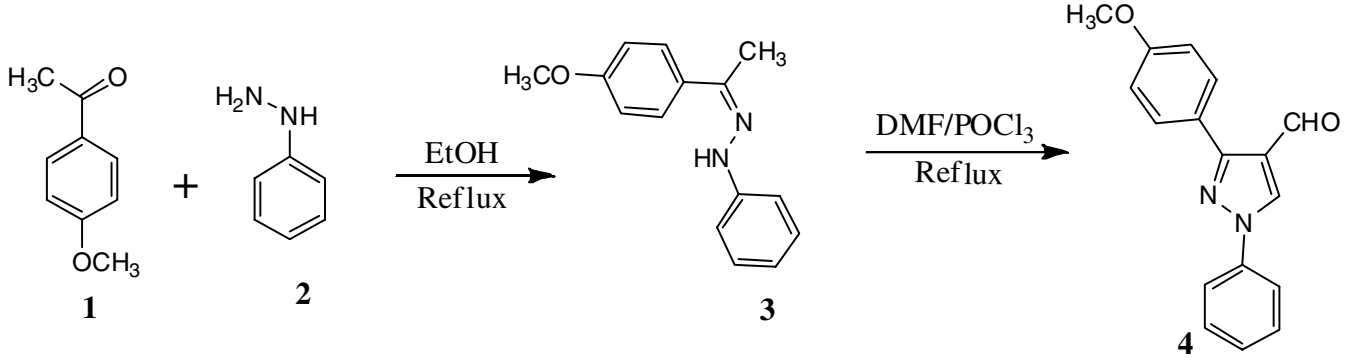
General procedure: Compound 1-phenyl-3-methoxy phenyl pyrazol-4-carboxaldehyde (**3**) was synthesized from 4-methoxy acetophenone (**1**) and phenyl hydrazine (**2**) and followed by Vilsmeir-Haack reaction as shown in **Scheme-I**. The formed pyrazole-4-carboxaldehyde on condensation the reaction with *p*-substituted naphthalene to afford the title compounds (**4a-f**) as illustrated in **Scheme-II**.

***N*-((3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-methylene)naphthalen-1-amine (4a):** Compound **4a** was obtained when 3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde condensed with 1-naphthylamine. Yield: 50%, appearance, red coloured solid, m.p.: 192 ºC; IR (KBr, ν_{max}, cm^{-1}): 3062 (Ar-CH *str.*), 1467 (ArC=C *str.*), 1638 (C=N *str.*), 1242 (C-N *str.*); ^{1}H NMR (δ ppm): 10.36 (s, 1H, HC=N), 9.59 (s, 1H, CH of pyrazole ring), 7.37-8.21 (m, 16H, aromatic H), 2.98 (s, 3H, OCH_3); ^{13}C NMR (ppm): 113-150.6 (all aromatic carbons), 164.24 (HC=N, imino carbon), 19.61 (methoxy carbon); MS: *m/z* 403 (M^+).

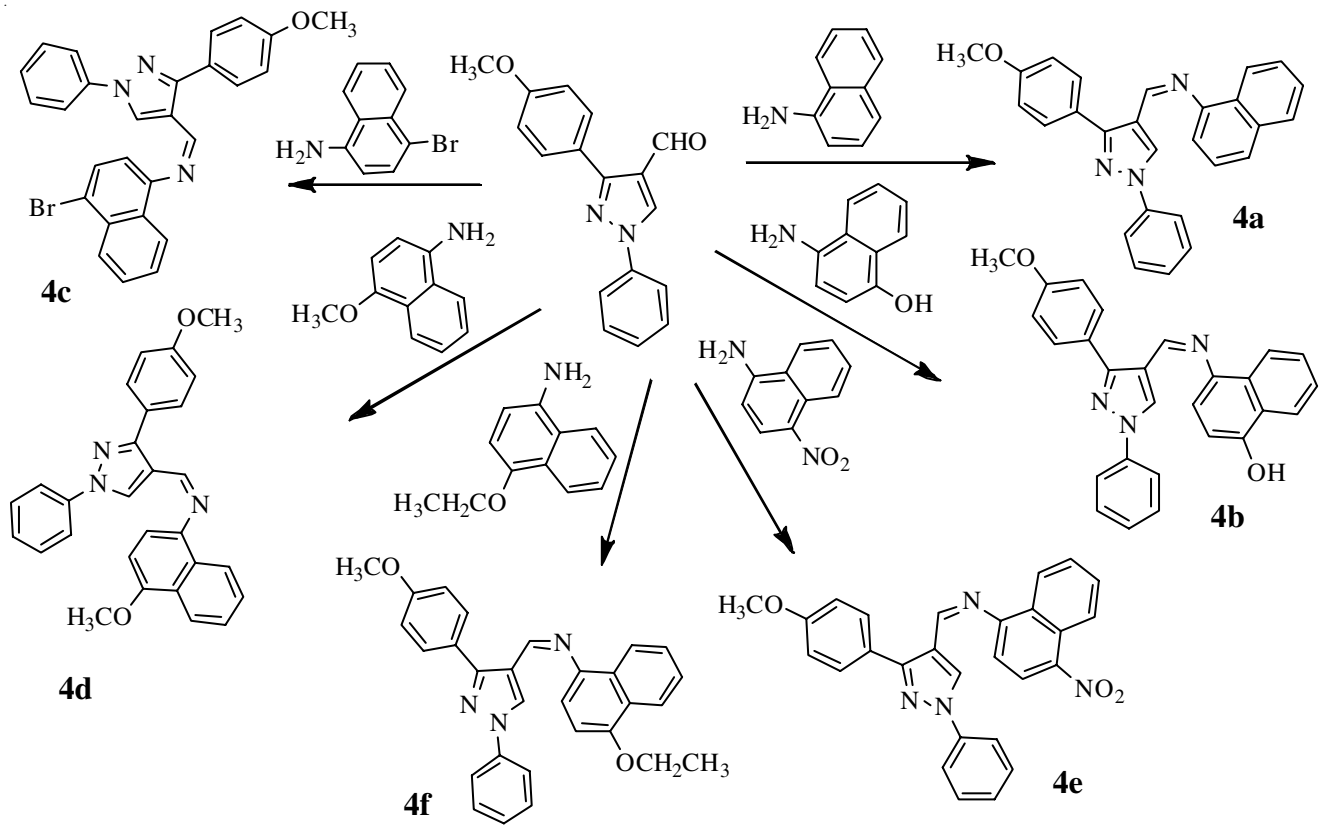
4-(((3-(4-Methoxyhenyl)-1-phenyl-1*H*-pyrazol-4-yl)-methylene)amino)naphthalen-1-ol (4b): Compound **4b** was prepared by the reaction between 3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde with 4-aminonaphthol. Yield 44 %, brown solid, m.p.: 160 ºC, IR (KBr, ν_{max}, cm^{-1}): 3413 (OH *str.*), 3043 (ArCH *str.*), 1464 (ArC=C *str.*), 1632 (C=N *str.*), 1231 (C-N *str.*); ^{1}H NMR (δ ppm): 3.81 (s, 3H, OCH_3), 5.41 (s, 1H, OH), 9.05 (s, 1H, HC=N), 9.84 (s, 1H, CH of pyrazole ring), 7.32-8.94 (m, 15H, aromatic H), ^{13}C NMR (δ ppm): 104-137 (all aromatic carbons), 17.04 (methoxy carbon), MS: *m/z* 419 (M^+).

4-Bromo-*N*-((3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)naphthalen-1-amine (4c): Compound **4c** was synthesized by the condensation reaction between 3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde with 4-bromoaniline. Yield 57 %, reddish brown solid, m.p.: 148 ºC, IR (KBr, ν_{max}, cm^{-1}): 3031 (ArCH *str.*), 1432 (ArC=C *str.*), 1604 (C=N *str.*), 1215 (C-N *str.*), 736 (C-Br *str.*); ^{1}H NMR (δ ppm): 3.81 (s, 3H, CH_3), 9.32 1H, HC=N), 8.97 (s, 1H, CH of pyrazole), 7.24-8.93 (m, 15H, aromatic H), ^{13}C NMR (δ ppm): 113-151 (all aromatic carbons), 14.04 (methoxy carbon), MS: *m/z* 482 (M^+).

4-(Methoxy-*N*-((3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)naphthalen-1-amine (4d): The condensation reaction was performed between 3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde and 4-methoxyaniline to obtain compound **4d**. Yield 54 %, yellow solid, m.p.: 143 ºC, IR (KBr, ν_{max}, cm^{-1}): 3032 (ArCH *str.*), 1446 (ArC=C *str.*), 1610 (C=N *str.*), 1219 (C-N *str.*), ^{1}H NMR (δ ppm): 3.07 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3) 9.12 (s, 1H, HC=N), 8.97 (s, 1H, CH of pyrazole), 7.08-8.39 (m, 15H,



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



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

aromatic H), ^{13}C NMR (δ ppm): 107-143 (all aromatic carbons), 28 (methoxy carbon) MS: *m/z* 433 (M^+).

4-(Ethoxy-*N*-((3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)naphthalen-1-amine (4e): The condensation reaction was under gone between 3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde with 4-ethoxyaniline to obtain compound **4e**. Yield 51 %, yellow powder, m.p.: 147 ºC, IR (KBr, ν_{max}, cm^{-1}): 3032 (ArCH *str.*), 1445 (ArC=C *str.*), 1616 (C=N *str.*), 1221 (C-N *str.*), ^{1}H NMR (δ ppm): 1.079 (t, 3H, CH_3), 3.67 (s, 3H, OCH_3), 4.74 (q, 2H, CH_2), 9.14 (s, 1H, HC=N), 8.96 (s, 1H, CH of pyrazole), 7.15-8.86 (m, 15H, aromatic H), ^{13}C NMR (δ ppm): 109-151 (all aromatic carbons), 63.5, 51.7 and 13.09 (aliphatic carbons); MS: *m/z* 449 (M^+).

***N*-((3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl) methylene)-4-nitronaphthalen-1-amine (4f):** Compound **4f** was obtained by the reaction between 3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde with 4-nitronaphthylamine. Yield: 40%, reddish brown solid, m.p.: 148 ºC, IR (KBr, ν_{max}, cm^{-1}): 3048 (ArCH *str.*), 1446 (ArC=C *str.*), 1619 (C=N *str.*), 1218 (C-N *str.*), 1392 and 1546 (NO *str.*); ^{1}H NMR (ppm): 9.68 (s, 1H, HC=N), 8.39 (s, 1H, CH of pyrazole ring), 7.08-8.19 (m, 15H, aromatic H), 3.05 (s, 3H, OCH_3); ^{13}C NMR (ppm): 109-142 (all aromatic carbons), 164.3 (HC=N, imino carbon); 20.3 (methoxy carbon) Ms: *m/z*: 450 (M^+).

RESULTS AND DISCUSSION

The title compounds were synthesized successfully by the condensation of 4-methoxy acetophenone with phenyl hydrazine followed by Vilsmeir-Haack reaction to yield 3-(4-methoxy phenyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde. The formed C-methoxy phenyl *N*-phenyl pyrazol-4-carboxaldehyde again underwent condensation reaction with substituted naphthyl amines to form pyrazole terminated imino naphthyl derivatives and all were well characterized by different spectroscopic techniques.

Antimicrobial activity: Among the pyrazole terminated substituted imino naphthyl derivatives, *S. aureus* is found to be more active against compounds **4c** and **4f** and moderately active against compounds **4a** and **4e**. Compounds **4b**, **4c**, **4d** and **4f** are active against *E. coli* and moderately active against compounds **4a** and **4e**. *P. aerugivosa* is showing excellent activity against almost all the compounds. *S. pyrogenes* showed more activity against compounds **4b**, **4c** and **4f** and a moderate activity against compounds **4a**, **4d** and **4e**. All the above activities are compared with that of ciprofloxacin, which is considered as the standard for the present study and tabulated in Table-1 and summarizes that all our compounds are exhibiting good to moderate antibacterial activity. Subsequently, the phenyl and naphthyl derivatives of pyrazoles are showing an outstanding antifungal activity with MIC 0.2 µg/mL against *A. niger* than fluconazole and it is independent of the substituents on phenyl and naphthyl scaffolds. All exhibiting a good antifungal activity against *C. albicans* (MIC 50 µg/mL) and. Here also these compounds are less active than standard antifungal fluconazole (MIC 30 µg/mL).

Structure activity relationship (SAR): Presence of either electron releasing or electron withdrawing group on imino naphthyl moiety extends the conjugation and this will affect

TABLE-1
ANTIBACTERIAL, ANTIFUNGAL AND ANTITUBERCULOSIS ACTIVITIES OF PYRAZOLE CLUBBED PHENYL DERIVATIVES (INHIBITION ZONE IN mm)

Compound	*S. aureus*	*E. coli*	*P. aerugi*	*S. pyrogenes*	*A. niger*	*C. albicans*	*M. tuberculosis*
4a	15	15	16	15	0.2	100	100
4b	13	17	20	18	0.2	75	100
4c	21	21	22	22	0.2	100	30.2
4d	12	19	16	17	0.2	100	30.2
4e	17	15	15	15	0.2	100	100
4f	22	21	22	21	0.2	50	30.2
Ciprofloxacin	24	22	23	23	–	–	–
Fluconazole	–	–	–	–	30	30	–
Isonicotyl hydrazone	–	–	–	–	–	–	0.4

Highly active = 20-30, moderately active = 15-20, weakly active = 11-15, less than 11 inactive

the bioactivity and thus exhibiting a broad-spectrum of biological activity. It is predicted that bioactivity for these compounds may be due to the combination of many factors such as differently substituted pyrazole ring, the presence of the imino linkage, steric hindrance, extend of conjugation, the presence of aryl rings on pyrazole moiety and the number of phenyl groups on pyrazole ring. Moreover, one of the important properties of heterocyclic compounds is its pharmacological behaviour and it was true in present case also. Structure activity relationship (SAR) studies were carried out for understanding the effect of different substitution on imino naphthyl ring and electronic effect on microbial strain [23]. Here, the substituents were selected to establish different electronic environment on the new molecules such as methoxy and ethoxy groups were electron donating groups to aromatic ring and hydroxy, nitro and bromo groups were electron withdrawing groups [24]. It was gathered from experiment the compounds with electron withdrawing groups (on imino naphthyl ring) showed a marked biological activity. Also, the hydrophobic substituents at the 4th positions of naphthyl ring giving a positive impact on antimicrobial activity and its physiochemical properties. From the outcome of antibacterial studies it is concluded that activity order of the different pyrazole derivatives (substituent at 4th position of the imino naphthyl ring) follows as $NO_2 > Br > OH > H > OCH_3 > OCH_2CH_3$ [25]. It was observed from the literature the chain length is inversely proportional to the inhibitory activity, generally decreasing and in present case also the compound with methoxy group was much more active than ethoxy compounds [26]. The *in vitro* activity against *E. coli* can be increased by the incorporation of electron withdrawing groups such as bromo, nitro and hydroxy groups. Similarly, activity against *S. aureus*, electron withdrawing groups at 4th position of imino naphthyl ring showed a positive impact on inhibition (MIC = 12.5 µg/mL) and activity against *S. pyogenes* at 50 µg/mL MIC.

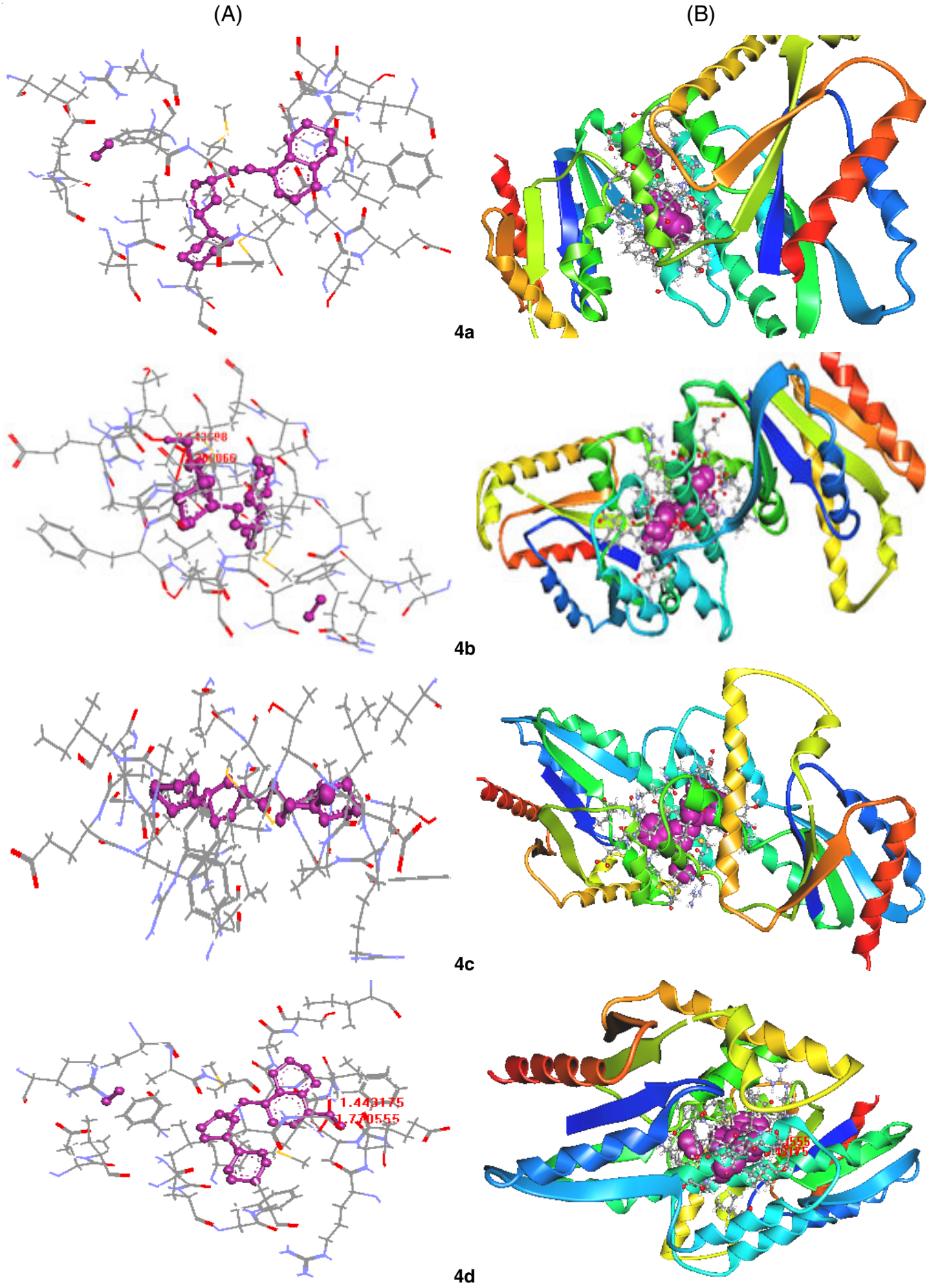
Molecular docking studies with protein: The working mechanism of antibacterial drugs generally includes either inhibition of cell wall synthesis or inhibition of protein synthesis or inhibition of nucleic acid synthesis and antimetabolism [27]. The actual action is the interaction with the specific proteins, which are responsible for the above-mentioned routes. We selected thymidylate kinase (TMPK) as our target protein, which contains 50 monophosphate kinase and the essential enzyme present in this protein catalysis the biosynthesis of DNA of bacterial cell. Moreover, this protein generates dTTP for the above cell wall synthesis [28]. The action of commonly used antibacterial drug ciprofloxacin is the inhibition of the DNA gyrase, which is necessary for the separation of the bacterial DNA synthesis and thus inhibits the cell wall division.

The synthesized imino naphthyl pyrazole derivatives (**4a-f**) were docked in the active site of the target protein TMPK using the software Arguslab 4.0.1 and tabulated the minimum binding energy and H-bond lengths (Table-2, Fig. 1). The active site of docking was created by autodock by which the ligands were forced to bind within the active site of the protein TMPK.

Binding energy evaluation: Assessment of binding free energy of the ligand within the active site of the protein assist to understand the accuracy of binding affinity between the target protein and the docking models. The pyrazole ring with two attached phenyl groups was incorporated in the design to establish a favourable hydrophobic interaction. From the literature, the lower the value of binding energy more will be the binding strength of the ligand within the protein. To figure out the binding strength of the synthesized compounds, the ligand-protein docked complexes were studied and computed the minimum binding energy values, ligand interaction (hydrogen/hydrophobic) pattern and H-bond length. The output revealed that the studied compounds were possessing good binding energy values ranging from -10.21 to -11.23 Kcal/mol

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

Compound	Binding energy (Kcal/mol)	H bond length (Å)
4a	-11.23	–
4b	-11.09	2.14 (265 THR with O of OH), 2.30 (269 LEU with O of OH)
4c	-10.87	–
4d	-10.77	1.77 (268 MET with O of OCH_3 of naphthyl group), 1.44 (269 LEU with O of OCH_3 of naphthyl group)
4e	-10. 92	2.09 (269 LEU with O of OCH_2CH_3), 1.94 (268 MET with O of OCH_2CH_3)
4f	-10.21	1.77 (268 MET with N of NO_2), 1.35 (269 LEU with N of NO_2)


(A)
(B)
4a
4b
4c
4d

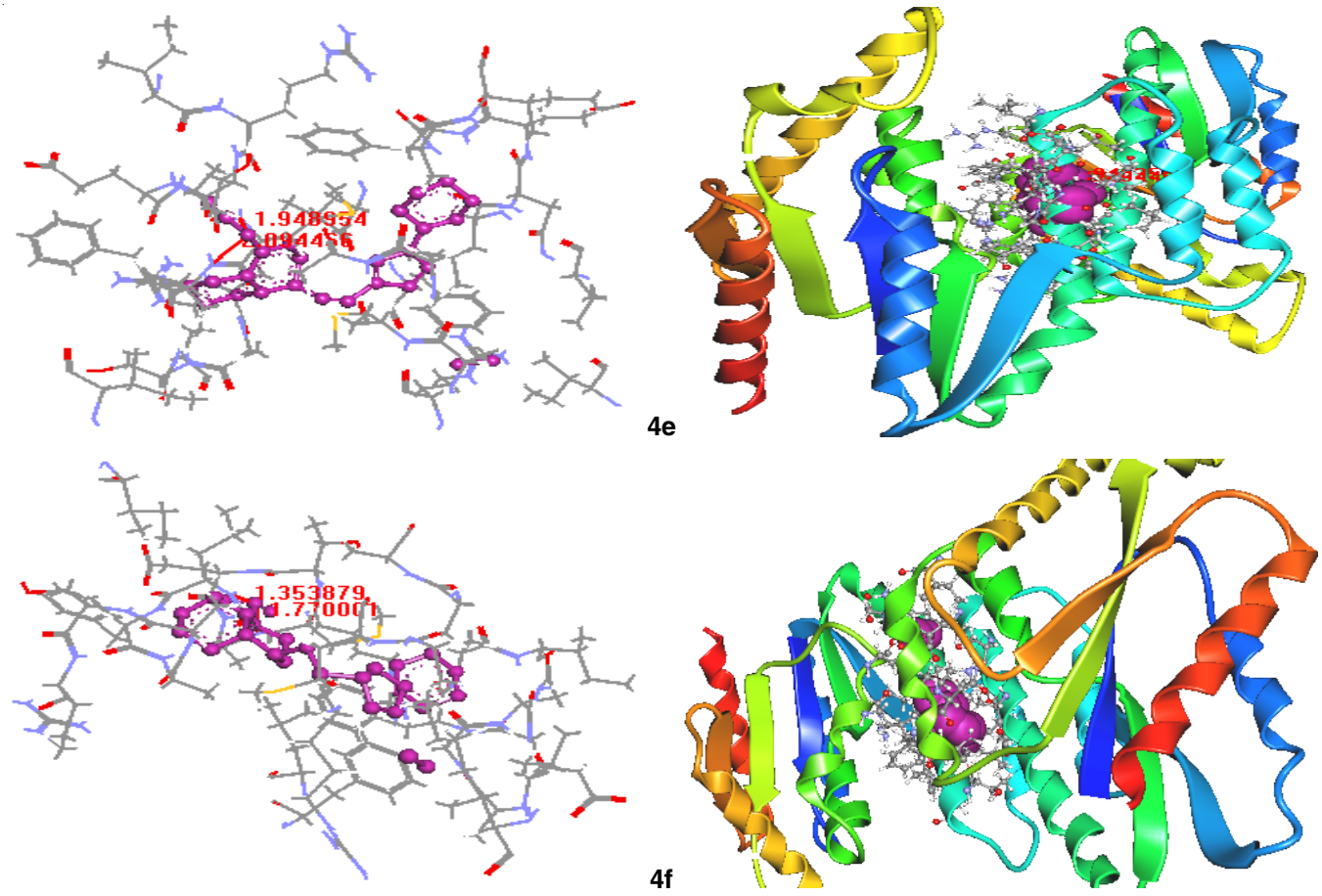


Fig. 1. Docked pose of the compounds (**4a-f**, purple colour) in the active site of the target protein (grey and blue colour) (A) and its cartoon view (protein as ribbon) (B)

as shown in Table-2. It was also obtained from literature that the predicted binding energy values were not higher than 2.5 Kcal/mol indi-cating the synthesized compounds were well fitted in the active pocket of the targeted protein.

Binding pocket and structure activity relationship analysis: The docking studies help to know how strongly the ligand is bonded within the active site of the target protein and shown in Fig. 2. Since all the compounds are biologically active (from the antibacterial activity studies), compound **4d** is selected here to check its binding profile against target protein. From the docking conformation, we came to know that the compound **4d** firmly binds within the binding pocket of TMPK and thus inhibit the function of TMPK for DNA synthesis**.** The amino acid residues 68 ALA, 67 ALA, 119 ALA, 116 ASN, 115 LEU, 322 PHE, 319 LEU, 271 ALA, 60 ARG, 319 LEU, 322 PHE and 115 LEU binds with the ligand compound **4d** through electrostatic interaction. Other amino acids like 265 THR, 269 LEU, 266 GLU and 270 PHE binds with compound **4d** through π-σ bonding. There are two H bond interactions, one with the amino acid 268 MET and the other with 269 LEU with OCH_3 moiety of naphthyl ring with bond distance 1.77 and 1.44 Å respectively. The molecular docking studies supported that the structure of the synthesized compounds could be used as therapeutic agent for bacterial infections.

Compound **4b** forms two different H bonds with the amino acid moiety 265 THR and 269 LEU with O of OH of the compound with bond length 2.14 and 2.30 Å respectively, the

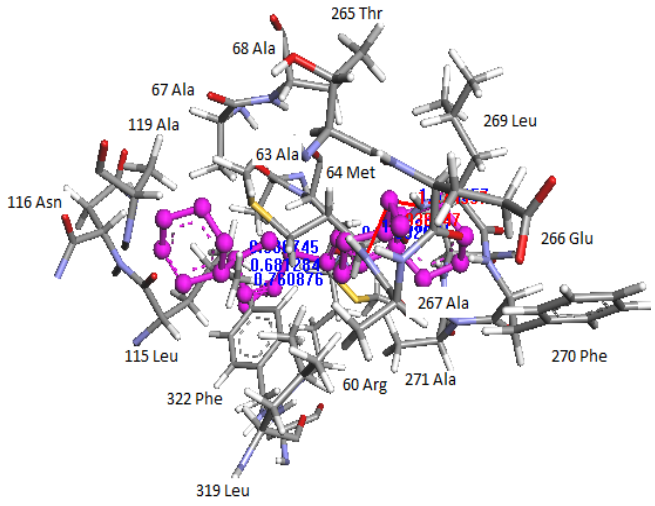


Fig. 2. Closer view of the docking compound **4d** (purple colour) to justify the interaction behaviour in the binding pocket of the target protein (light grey and blue colour). The red colour bond is H bond in Å. The above interactions contributed towards the stability of the compound **4b** docking complex

compound **4e** is forming two different H bonds with 269 LEU with bond lengths 2.09 and 268 MET with bond length 1.94 Å with O of OCH_2CH_3 and the compound **4f**, the amino acid moiety 268 MET and 269 LEU with bond length 1.77 and 1.35 Å, respectively. Compounds **4a** and **4c** are not showing H-bond interaction.

Molecular docking with DNA: Molecular docking analysis with DNA allows to characterize the nature of drug-DNA interaction for the synthesis of the drug and its design as a new chemotherapeutic drug as well as in the study of its mechanism when this drug molecule introduced into the binding site of the specific region of the DNA target in a non-covalent manner [32]. Moreover, there are different structural properties to elucidate the binding modes, here we concentrated and exercised 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 the forces responsible for the stability of DNA-intercalator complex include van der Waals, hydrogen bonding, hydrophobic, charge transfer and electrostatic complementarity [30,31]. The power of the molecule to act as a biologically active drug lies on its favourable conformation and binding location within the DNA. The DNA binding conformations of compounds **4a-f** had been done with CT-DNA duplex of sequence d(CGCGAATTCGCG)2 dodecamer (PDB ID: 355D) and the most favourable docked poses are given in Fig. 3. All the compounds could effectively bind

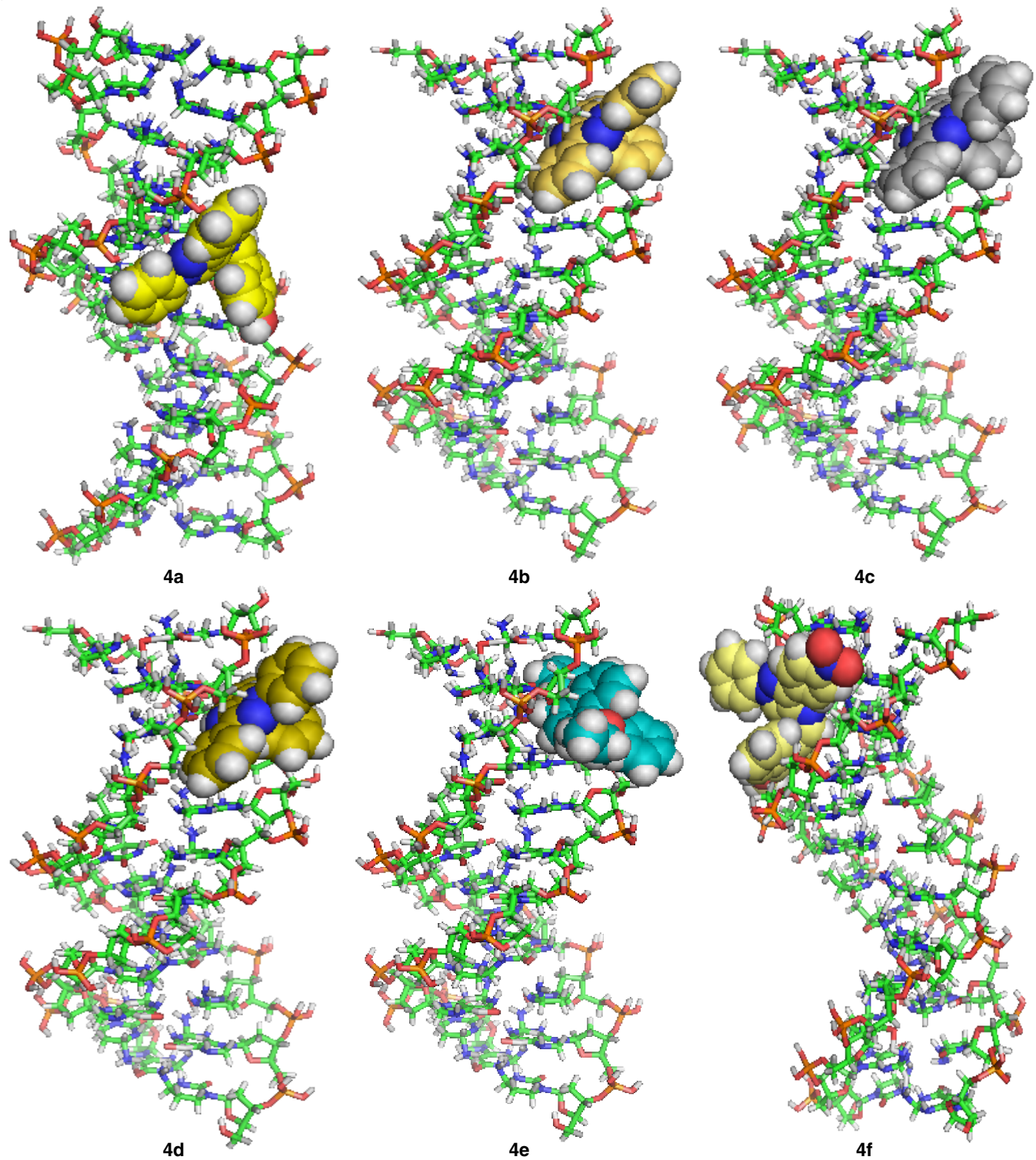


Fig. 3. Molecular docked model of compounds **4a-f** with DNA dodecamer duplex of sequence d(CGCGAATTCGCG)2 (PDB ID: 1BNA)

with DNA in an interactive fashion near the minor groove. Moreover, the planarity of the compounds also strengthens the binding of the compounds *via* partial intercalation with DNA. Normally the small molecules like to interact with minor groove due to little steric hindrance [32]. Furthermore, presence of aromatic ring connected by single bonds grant for torsional strain to facilitate the curvature of the groove with displacement of water molecules. The presence of heterocyclic ring in the molecule contributes a favourable stacking interaction between DNA base pairs, resulting van der Waals interactions and hydrophobic contacts with DNA functional groups that define the groove [33]. Thus, molecular modelling studies focus on the binding modes through which the compounds are interacting with DNA.

Frontier molecular orbital (FMO) calculation: Most widely accepted frontier molecular orbitals are highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), which explain the electronic as well as the optical properties of the compound. The value of HOMO energy level means the electron donating abilities while that of LUMO is the electron accepting ability. The HOMO and LUMO energy values, energy gap (HOMO–LUMO) and global reactivity descriptors are tabulated in Table-3. The HOMO and LUMO sketches for the synthesized compounds are outlined in Fig. 4. Considering Koopman's theorem of equations the global reactivity descriptors such as chemical potential (μ) and hardness (η), were calculated as:

The hardness is given by

$$\eta = \frac{I - A}{2}$$

The chemical potential is given by:

$$\mu = -\frac{(I + A)}{2}$$

The electronegativity can be calculated by:

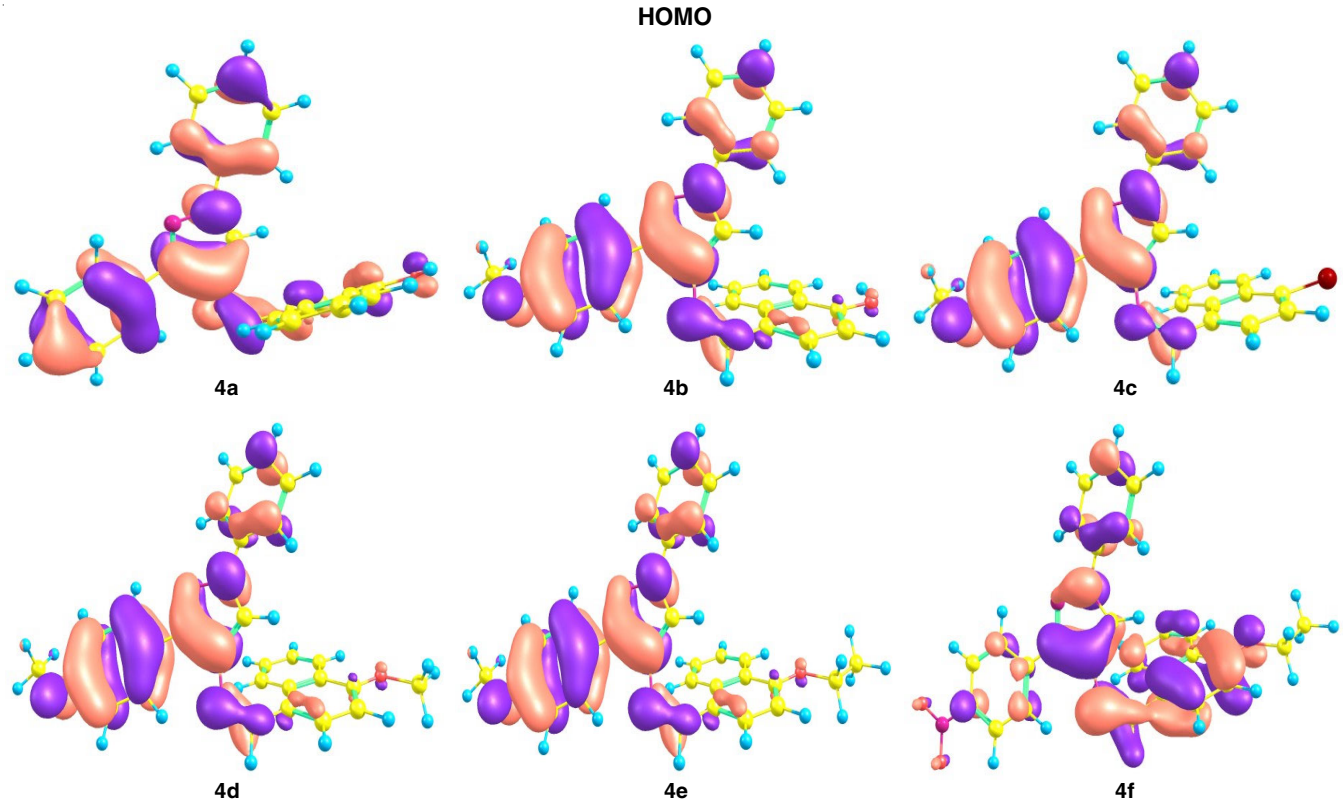
$$\chi = \frac{(I + A)}{2}$$

where I is the electron affinity ($I = -E_{HOMO}$) and A is the ionization potential ($A = -E_{LUMO}$). The negative chemical potential defines non-spontaneous decomposition. The energy gap value of compound **4f** is maximum and equal to 3.7595 eV and compound **4b** has minimum value equal to 3.4175.

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

Compound	E_{HOMO} (eV)	E_{LUMO} (eV)	Energy gap	η	μ	χ
4a	-5.0363	-1.3785	3.6578	1.8289	-3.2074	3.2074
4b	-5.1993	-1.7818	3.4175	1.7087	-3.4905	3.4905
4c	-5.0131	-1.3434	3.6697	1.8348	-3.1782	3.1782
4d	-4.9979	-1.3173	3.6806	1.8403	-3.1576	3.1576
4e	-4.9978	-1.3140	3.6838	1.8419	-3.1559	3.1559
4f	-6.0567	-2.2972	3.7595	1.8797	-4.1769	4.1769

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



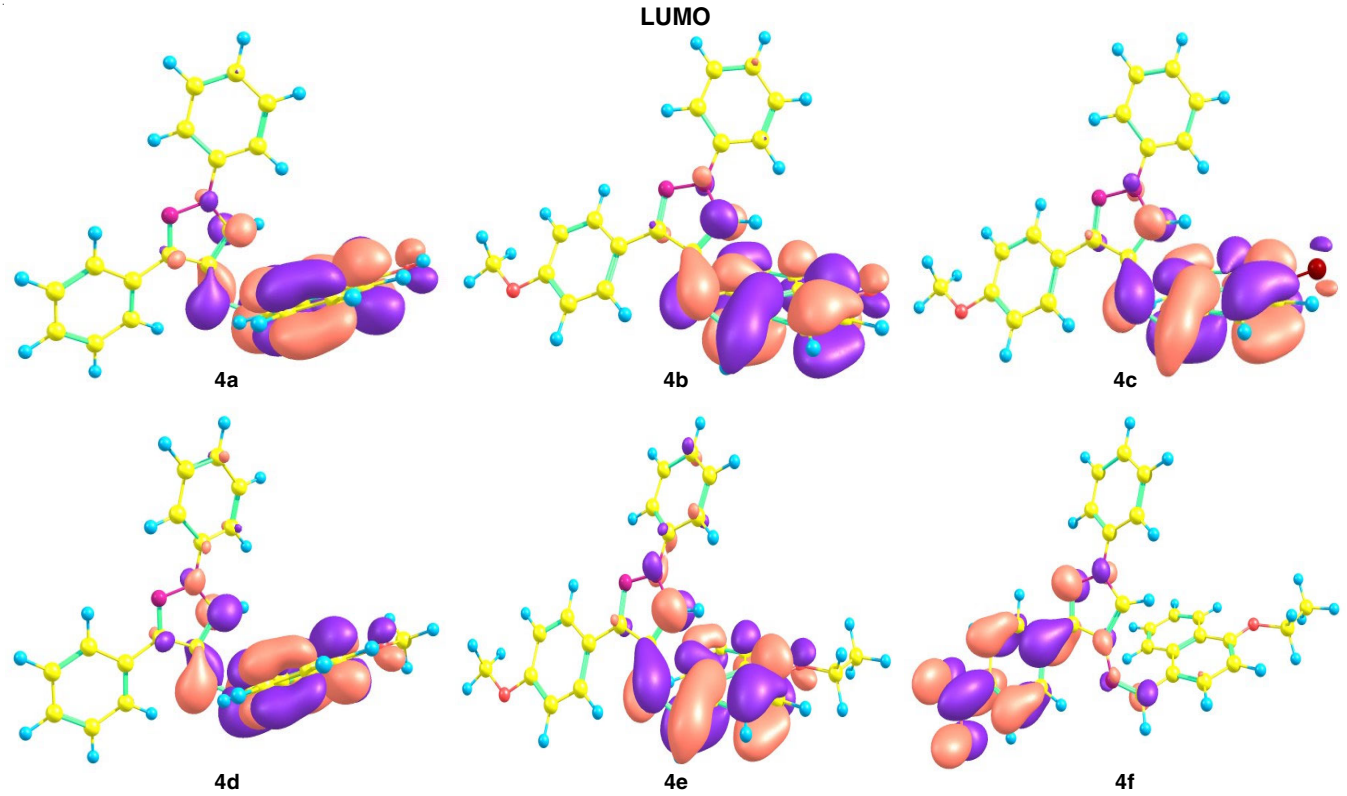


Fig. 4. HOMO-LUMO (the frontier molecular orbitals) plots of compounds **4a-f**

Compounds of electron donating substituents showed higher energy gap than that of compounds with electron withdrawing group and its order is **4f** > **4e** > **4d** > **4c** > **4a** > **4d**. Since all the compounds are having similar structures, the iso density lobes of HOMO of all the compounds are distributed mainly along the entire molecule except that of bromo derivative (**4c**). In compound **4c**, the HOMO lobes are not distributed along the imino bromo naphthyl group. The iso-density of LUMO of all the compounds except compound **4f** scattered mainly along imino naphthyl moiety. Compound **4f**, imino nitro naphthyl derivative it is the LUMO is spread along the *N*-phenyl group attached to the pyrazole entity.

Conclusion

A series of six new 1,3-diphenyl pyrazole linked imino naphthyl derivatives were synthesized, characterized and investigated their *in vitro* antibacterial activity against Gram-negative bacterial strains such as *E. coli* MTCC-443 and *P. aeruginosa* MTCC-1688 and two Gram-positive strains as *S. aureus* MTCC-96 and *S. pyogenes* MTCC-442. Antifungal and antituberculosis activities were also monitored. The titled compounds were active, which might be due to the greater lipophilicity of two different phenyl and one naphthyl groups attached to the pyrazole entity. It is noticed that the electron withdrawing substituent present at 4th position of the imino naphthyl ring enhanced its biological activity. By conducting the molecular docking studies, minimum ligand pose binding energy and H-bond length information of all the synthesized compounds in the protein TMPK were noted. The molecular docking with DNA also holds up the non-covalent interactions into the minor groove binding mode. The DFT frontier molecular orbital analysis helped to calculate the global reactivity descriptors.

ACKNOWLEDGEMENTS

One of the authors (PVS) acknowledge the financial support from the University Grants Commission, New Delhi, India.

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