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Design, Synthesis, Docking Study & Antibacterial Evaluation of 1,3-Diarylpyrazolyl Substituted Indolin-2-ones

Sumit Bansal[*1], Sharad Kumar[1], Vaibhav Aggarwal[2], Alex Joseph[1*]

[1] *Department of Pharmaceutical Chemistry, Manipal College of Pharmaceutical Sciences, Manipal-576104, India*

[2] *Department of Pharmacy, Jaypee University of Information Technology, Solan, Himachal Pradesh,India*

Address for Correspondance: bansalsumit50@gmail.com

ABSTRACT: In the present investigation, a series of novel 3-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)indolin-2-one was synthesized by the Claisen-Schmidt condensation of indolin-2-one with substituted diaryl formylpyrazoles using alcoholic sodium hydroxide. The chemical structures of the newly synthesized compounds were characterized by IR, ^{1}HNMR, and mass spectroscopy. The title compounds were evaluated for qualitative (zone of inhibition) and quantitative antibacterial activity (MIC) by agar diffusion and broth microdilution MIC (minimum inhibitory concentration) methods, respectively against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Klebsiella pneumoniae*. All the synthesized compounds were found active against Gram-positive bacteria, while showed very weak activity against Gram-negative bacteria. Docking study was performed to check interaction of synthesized compounds with the target DNA gyrase.

KEYWORDS: Pyrazoles; Indolin-2-ones; Antibacterial; Docking; DNA Gyrase.

INTRODUCTION

Increasing number of multi-drug resistant microbial pathogens and emerging infectious diseases are the major challenging problems for the clinicians. There is an urgent need to develop new class of potent antimicrobial agents. Heterocyclic compounds play an important role in designing of a new class of structural entities of medicinal importance with new mechanisms of action. These heterocyclic compounds are well known to possess diverse pharmacological properties, *viz.* antimicrobial, analgesic, anti-inflammatory, anticancer, anticonvulsant, and antimalarial [1].

Pyrazole and its derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activities. During the past years, considerable evidence has been accumulated to demonstrate the efficacy of pyrazole derivatives including antimicrobial [2], antitumor [3,4], antiproliferative agents [5], GABA receptor antagonists and insecticides [6], anti-inflammatory [7] etc. Pyrazoles have been reported to possess antibacterial activity and inhibitor activity against DNA gyrase and topoisomerase IV at their respective ATP-binding sites [8-10].

Quinolone moiety is of great importance to chemists as well as biologists as it is found in a large variety of naturally occurring compounds possessing diverse biological activities such as antimicrobial [11], antiproliferative [12], antithrombotic [13], anti-hepatitis B [14], anti-HIV [15], anti-tumor [16], and antioxidative activity [17]. Several 2-quinolone derivatives are also nitric oxide production inhibitors [18], 5-HT_{1B}/5-HT_{2A} receptor antagonists [19], Rho-kinase inhibitors [20], and androgen receptors [21]. Quinolones are known to inhibit DNA synthesis by promoting cleavage of bacterial DNA gyrase and type-IV topoisomerase, resulting in rapid bacterial death [22]. Quinolones exhibit a wide spectrum of activity *in vitro* because these essential targets are highly conserved in virtually all bacteria. However, the diverse nature of substituents on the quinolone nucleus affords variable target activity or affinity (for DNA gyrase

and/or topoisomerase IV), permeability, efflux, and overall antibacterial activity [23].

Considering these perspectives and our ongoing efforts to develop therapeutically active agent using a hybrid pharmacophore approach [24,25], we decided to incorporate proved biologically active moieties into single hybrid system and investigated their antibacterial activity against both Gram-positive and Gram-negative bacteria. Since both moieties are enabled to inhibit DNA gyrase, we also decided to explore the interaction of this hybrid pharmacophore with the active site of DNA gyrase.

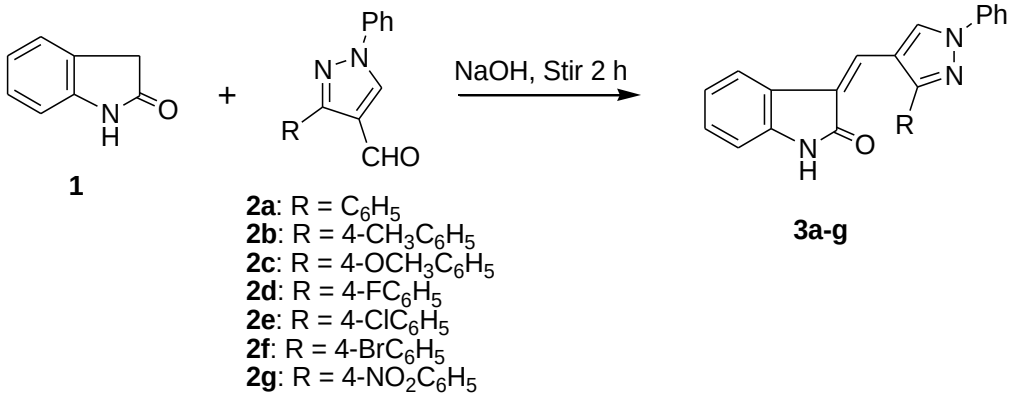
MATERIALS & METHODS

1. General

All reagents were purchased from spectrochem, merck and used as received. Melting points were determined by Shital Scientific Industries capillary melting point apparatus. Infrared spectra were obtained on a Shimadzu FTIR-8310 (Shimadzu, Japan) using potassium bromide discs. All the NMR spectra were measured using Bruker AVANCE II 400 MHz spectrophotometer (Bruker, USA). ^{1}H NMR spectra measured in d_6-DMSO at 400 MHz with TMS as internal reference. The purity of all compounds was established by single spot on the pre-coated TLC plates (Merck, Germany). Iodine vapor was used as developing agent. Hexane: ethyl acetate (3:7) was used as a solvent system.

2. General procedure for the synthesis of compounds 3a-g [26]

The final compounds (**3a-g**) were prepared by continuous stirring of indolin-2-one (**1**, 0.1 mole) in alcoholic solution (80%, 25 ml), containing 2% sodium hydroxide with appropriate formylpyrazoles (0.1 mol) (**2a-g**), in ice cold conditions for about 2 h (Scheme 1). The progress of reaction was monitored by TLC. The mixtures obtained were refrigerated for about 10 h and were neutralized by pouring into 20%, 200 ml HCl with continuous stirring. The solids precipitated out were filtered off, washed with water and recrystallized from ethanol.



Scheme 1. Synthesis of novel 3-((1,3-diaryl-1*H*-pyrazol-4-yl)methylene)indolin-2-one (3a-g)

a) 3-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)indolin-2-one (3a): Yellow solid, yield: 88%; mp 142-143 ºC. IR (KBr, cm^{-1}): 3180 (N-H), 1696 (C=O), 1595 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6, ppm): 10.50 (s, 1H, -NH- of indole ring), 8.41 (s, 1H, =CH- of pyrazole ring), 7.37 (s, 1H, =CH-), 7.32-7.85 (m, 14H, Ar-H). ESI-MS *m/z*: 364 ($C_{24}H_{17}N_3O$, $[M+H]^+$).

b)3-((1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)methylene)indolin-2-one (3b): Yellow solid, yield: 85%; mp 155-156 ºC. IR (KBr, cm^{-1}): 3175 (N-H), 1692 (C=O), 1585 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6, ppm): 10.45 (s, 1H, -NH- of indole ring), 8.47 (s, 1H, =CH- of pyrazole ring), 7.31 (s, 1H, =CH-), 7.12-7.77 (m, 13H, Ar-H), 2.47 (s, 3H, CH_3). ESI-MS *m/z*: 378 ($C_{25}H_{19}N_3O$, $[M+H]^+$).

c)3-((3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)indolin-2-one (3c): Yellow solid, yield: 82%; mp 135-136 ºC. IR (KBr, cm^{-1}): 3186 (N-H), 1710 (C=O), 1560 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6, ppm): 10.34 (s, 1H, -NH- of indole ring), 8.51 (s, 1H, =CH- of pyrazole ring), 7.41 (s, 1H, =CH-), 6.85-7.76 (m, 13H, Ar-H), 3.72 (s, 3H, OCH_3). ESI-MS *m/z*: 394 ($C_{25}H_{19}N_3O_2$, $[M+H]^+$).

d)3-((3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)indolin-2-one (3d): Yellow solid, yield: 75%; mp 164-165 ºC. IR (KBr, cm^{-1}): 3199 (N-H), 1702 (C=O), 1566 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6, ppm): 10.44 (s, 1H, -NH- of indole ring), 8.54 (s, 1H, =CH- of pyrazole ring), 7.33 (s, 1H, =CH-), 7.05-7.85 (m, 13H, Ar-H). ESI-MS *m/z*: 382 ($C_{24}H_{16}FN_3O$, $[M+H]^+$).

e)3-((3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)indolin-2-one (3e): Yellow solid, yield: 79%; mp 173-174 ºC. IR (KBr, cm^{-1}): 3192 (N-H), 1690 (C=O), 1567 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6, ppm): 10.42 (s, 1H, -NH- of indole ring), 8.49 (s, 1H, =CH- of pyrazole ring), 7.41 (s, 1H, =CH-), 7.31-7.68 (m, 13H, Ar-H). ESI-MS *m/z*: 398 ($C_{24}H_{16}ClN_3O$, $[M+H]^+$).

f)3-((3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)indolin-2-one (3f): Yellow solid, yield: 81%; mp

185-186 ºC. IR (KBr, cm^{-1}): 3182 (N-H), 1694 (C=O), 1562 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6, ppm): 10.37 (s, 1H, -NH- of indole ring), 8.43 (s, 1H, =CH- of pyrazole ring), 7.49 (s, 1H, =CH-), 7.43-7.88 (m, 13H, Ar-H). ESI-MS *m/z*: 444 ($C_{24}H_{16}BrN_3O$, $[M+H]^+$).

g) 3-((3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)indolin-2-one (3g): Yellow solid, yield: 72%; mp 195-196 ºC. IR (KBr, cm^{-1}): 3178 (N-H), 1687 (C=O), 1559 (C=C). ^{1}H-NMR (400 MHz, DMSO-d_6, ppm): 10.39 (s, 1H, -NH- of indole ring), 8.47 (s, 1H, =CH- of pyrazole ring), 7.39 (s, 1H, =CH-), 7.29-8.26 (m, 13H, Ar-H). ESI-MS *m/z*: 409 ($C_{24}H_{16}N_4O_3$, $[M+H]^+$).

3. Biological activity

3.1. Antibacterial activity (Agar diffusion method) [27]

The antibacterial activity of the synthesized molecules (**3a**-**g**) was determined by agar diffusion method using four organisms such as *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumonia*e and a standard drug, Ampicillin. This method was based on diffusion of antibacterial component from reservoir bore to the surrounding inoculated nutrient agar medium so that the growth of microorganisms was inhibited as circular zone around the bore. The concentration of test compounds was100mg/ml. It was prepared in 20% water in DMSO. The test samples and standard drugs were placed in a bore made in petri dishes which contained different organisms and incubated at 37ºC for 24 h. The zone of inhibition around the bore was measured after 24 h. The antibacterial activity data of 3-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)indolin-2-ones (**3a**-**g**) are recorded in Table 1.

3.2 Determination of MIC [28]

The determination of minimum inhibitory concentration was done with four isolates of *B. subtilis*, *S. aureus*, *E. coli*, and *K. pneumoniae* which were inoculated into Luria broth medium containing 1% tryptone, 0.5% yeast extract, and 0.5% sodium chloride. The pH of the medium was adjusted to 7.2 with sterile phosphate buffered saline and incubated at 37ºC for 24 h. The optical density of the bacteria from mid-log phase of growth was measured at 540 nm and diluted in fresh medium so as to get an optical density of 0.004 (corresponding to 5×10^5 colony forming units/ml). To each well of the ELISA plate, 200µl of diluted bacterial suspension was added and graded concentrations (0.2–500µg/ml) of the synthesized promising compounds and a standard antibiotic (Ampicillin) in 20% water in DMSO were added and incubated at 37ºC for 24 h. At the end of incubation the effect of the drugs on the growth of organisms was monitored by measuring the optical density at 540 nm using ELISA reader (BIOTEK EL X800-MS). The results of MIC data of 3-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)indolin-2-ones (**3a**-**g**) are recorded in Table 1.

4. Molecular docking studies [29]

The designed ligands were docked into the active site of DNA gyrase (PDB ID: 1KZN) (Fig. **1**). Before virtual screening studies, water molecules and hetero atoms were removed, and hydrogens were added to the protein. The structures of compounds in PDB format were prepared using CS ChemDraw Ultra 8.0. AutoDock 4.2 was used for molecular docking analysis. The grid box was set at dimensions 40 Å × 40 Å × 40 Å and center x = 20, y = 24, z = 38 with grid point spacing of 0.375Å. Lamarckian genetic algorithm was applied to find the conformations of lowest binding energy. The results of molecular docking analysis are expressed as estimated free energy of binding in kcal/mol.

RESULTS & DISCUSSION

Chemistry

All 1,3-diaryl pyrazolyl substituted indolin-2-ones (**3a**-**g**) were synthesized by stirring oxindole (indolin-2-one) (**1**) with different formylpyrazoles (**2a**-**g**) in presence of alcoholic NaOH according to Claisen-Schimdt condensation. The structures of compounds were confirmed by IR, ^{1}HNMR and Mass spectral techniques. The IR spectra showed characteristics peaks of N-H, C =O, and C=C groups. The ^{1}HNMR spectra showed signals correspond to protons in the structure of compound. In ^{1}HNMR, we observed a singlet of -NH- of indole ring, singlet of =CH- of pyrazole ring and multiplet from aromatic protons. ESI-MS spectra showed characteristic molecular $(M+H)^+$ ion peaks corresponding to the molecular weight of synthesized compounds.

Antibacterial evaluation

All the synthesized compounds (**3a**-**g**) were tested *in vitro* for their antibacterial activity against two Gram-positive bacteria namely; *S. aureus*, *B. subtilis*, and two Gram-negative bacteria namely; *E. coli*, and *K. pneumoniae*.

The zone of inhibition and MICs of all compounds are presented in Table 1. Ampicillin was used as standard drug for comparison with test compounds. All the tested compounds showed good antibacterial activity against Gram-positive strains. Among tested compounds, **3a** showed significant MIC at 19.6 and 22.5 µg/ml against *B. subtilis* and *S. aureus*, respectively and found moderate active against both Gram-negative strains *E. coli* and *K. pneumonia*. Any type of substitution on phenyl ring of pyrazole resulted in significant loss of activity. Compound possessing electron withdrawing nitro group (**3g**) and halogens particularly chloro group (**3e**) showed moderate activity against both Gram-positive bacteria when compared to other derivatives in the series (Table 1).

Table 1 *In vitro* antibacterial activity data of compounds 3a-g

Compounds	Zone of inhibition in mm (MIC in µg/ml)			
	S. aureus	*B. Subtilis*	*E. coli*	*K. pneumonia*
3a	19(22.5)	18(19.6)	11(40.5)	10(42.8)
3b	13(30.8)	12(35.6)	-	-
3c	12(41.5)	12(45.5)	-	-
3d	14(38.4)	12(43.2)	-	-
3e	15(27.6)	16(25.4)	-	-
3f	13(38.3)	14(39.4)	-	-
3g	16(28.4)	17(24.5)	09(62.5)	09(73.6)
Ampicillin	29(3.5)	30(3.2)	31(4.0)	29(4.0)

Molecular docking analysis

All the compounds were docked into the active site of DNA gyrase. Among the ligands virtually screened to the DNA gyrase (**3a-g**), **3a** emerged as lead compound with estimated free energy of binding –5.45 kcal/mol. Estimated inhibition constant (*K*i) of **3a** was found to be 101.72 µM against DNA gyrase, whereas final intermolecular energy of **3a** observed was –5.75 kcal/mol. Stereoview of docked complex showed that **3a** and Gly-117 residue of DNA gyrase interacted by means of hydrogen bonding, where hydrogen atom of oxindole moiety was 2.3 Å away from carboxylic oxygen of Gly-117 (N−H…O=C−C, 2.3Å) (Fig. **2** & **3**). Apart from hydrogen bonding, hydrophobic and van der Waals interactions were also detected between lead molecule **3a** and DNA gyrase. The entire 1-phenylpyrazol substituted oxindole scaffold was projected into the hydrophobic pocket of DNA gyrase defined by Val-43, Val-89, Ile-90, Met-91, Val-93, Leu-94, Val-118, Val-120, and Val-122 amino acid residues of the target protein (Fig. **2** & **3**).

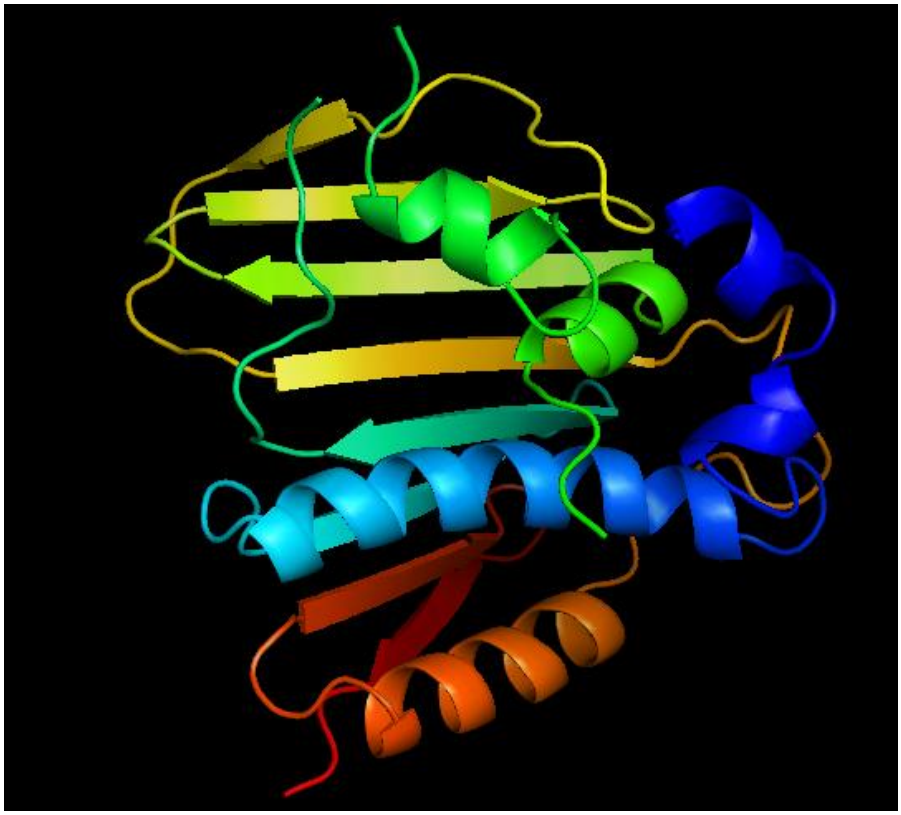


Fig. 1.Stereoview of 3-D crystal structure of DNA gyrase (PDB ID: 1KZN)

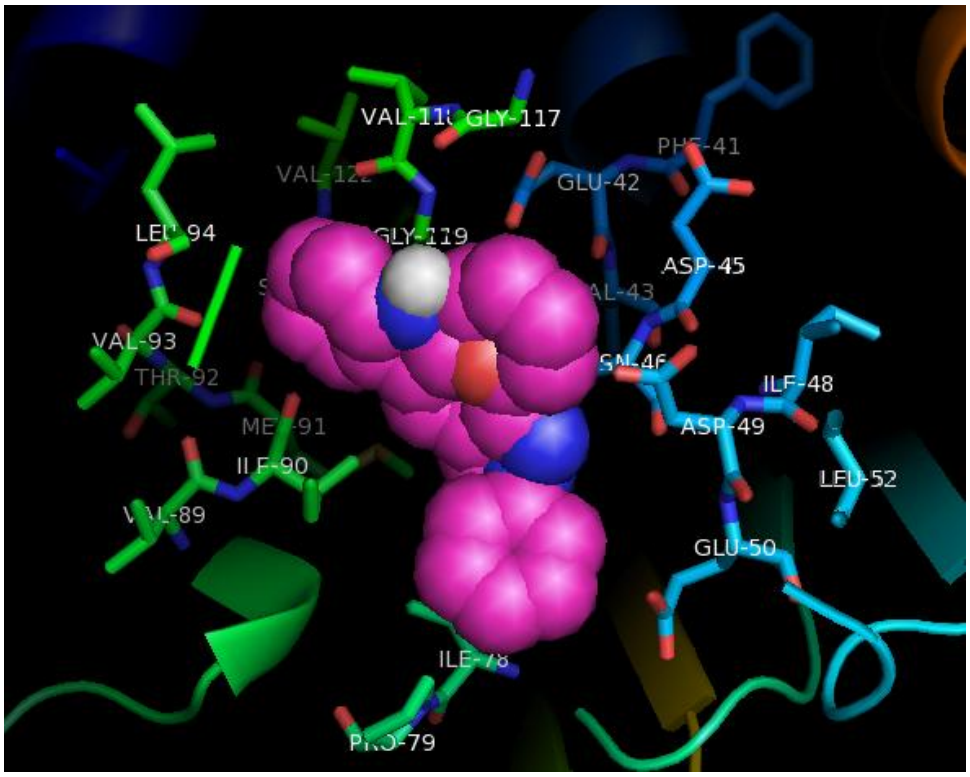


Fig. 2. Docking of compound 3a (shown as spheres) into the active site of DNA gyrase. The amino acids involved in hydrogen, hydrophobic and van der Waals interactions are highlighted.

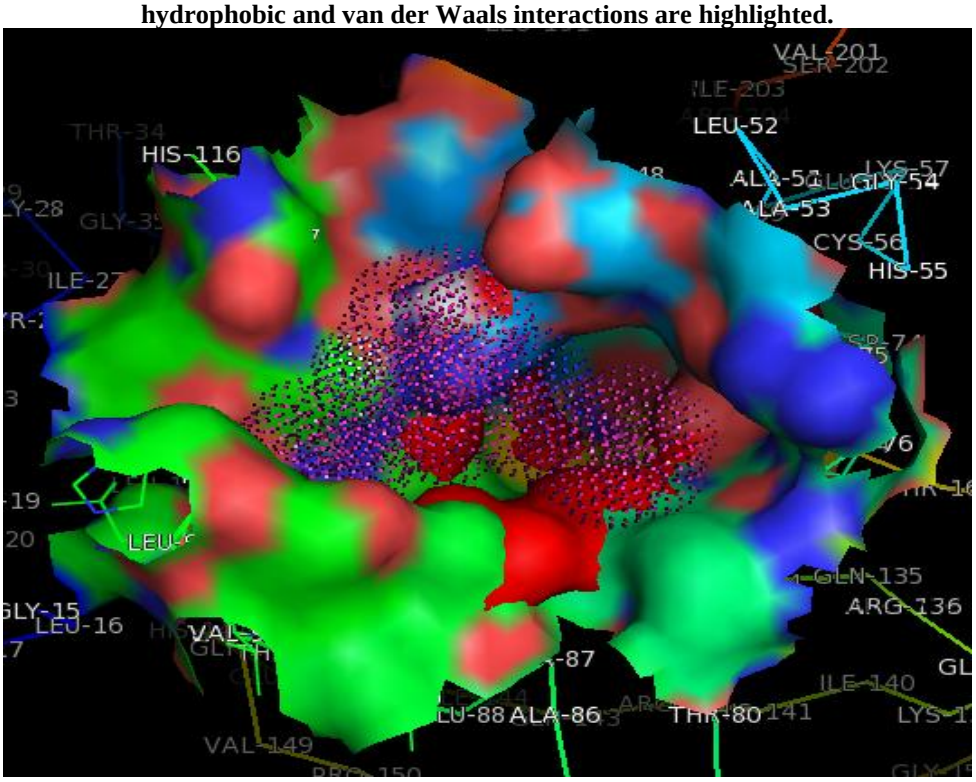


Fig. 3. The orientation of docked compound 3a in the active site of DNA gyrase (PDB ID: 1KZN). Protein is shown as surface, while compound 3a is displayed in dots.

The 3-phenylpyrazol ring also exhibited hydrophobic and weak van der Waals interactions with Ile-78 residue of the DNA gyrase. Estimated free energy of binding of docked series of compounds ranged between –4.34 and –5.75 kcal/mol.

CONCLUSION

A new series of substituted 3-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)indolin-2-one derivatives has been synthesized by Claisen-Schimdt condensation and characterized by spectral analysis. The pharmacological study was undertaken to evaluate the effects of substituents on the antibacterial activity. All the synthesized compounds exhibited good antibacterial activity towards Gram-positive bacteria. However, these compounds did not show any promising activity towards Gram-negative bacteria. It is worth mentioning that minor changes in molecular configuration of these compound profoundly influence the activity. Further synthetic modification is required to enhance the potency of pyrazolyl substituted quinolones by changing molecular configuration.

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