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ORIGINAL ARTICLE

SYNTHESIS, CHARACTERIZATION, MOLECULAR DOCKING STUDIES AND ANTIBACTERIAL EVALUATION OF CHALCONE BASED PYRAZOLINES AS DNA GYRASE INHIBITORS

C. Manivannan and *N. Santhi
Department of Chemistry, Government Arts College, C .Mutlur, Chidambaram, Tamilnadu, India

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ABSTRACT

(E)-1-(4-fluorophenyl)-3-substitutedphenylprop-2-en-1-one **(3-7)** were ultrasonically prepared by the reaction of 4-fluoroacetophenone with different aromatic aldehydes in the presence of alkali . Reaction of the prepared chalcones (3-7) with 3,4,5-trimethoxybenzohydrazide **(8)** afforded the corresponding substituted pyrazoline **(9-13).** All the prepared compounds have been characterized by FT-IR and ^{1}H-NMR spectra. Docking studies were carried out against DNA Gyrase receptor. Docking scores were compared with the scores of standard drugs ciprofloxacin Majority of the synthesized compounds showed good fitting with the active site of all the docked targets. The synthesized compounds were screened for their antibacterial against five bacterial strains by disc diffusion method.

Keywords: chalcone , pyrazoline, Biological assay, ultrasonic irradiation, molecular docking, DNA Gyrase

1.INDRODUCTION

A classical synthesis of these compounds involves the base-catalyzed aldol condensation reaction of aromatic ketones and aldehydes to give α,β- unsaturated ketones (chalcones), which undergo a subsequent cyclization reaction with hydrazides affording 2- pyrazolines. In this method, hydrazones are formed as intermediates, which can be subsequently cyclized to 2- pyrazolines in the presence of a suitable cyclizing reagent like acetic acid.

The treatment of infectious diseases caused by bacteria, parasites, viruses and fungi always remains a global health problem because of increasing number of multi-drug resistant pathogenic microbial strains (Narang et al., 2012). Despite the availability of large number of antibiotics for clinical use, the emergence of antibiotic resistance in recent years against Grampositive and Gram-negative bacterial and fungal strains constitutes an urgent need for the discovery of new class of antimicrobial agents (Perez et al., 2014; Narasimhan et al., 2009). Various sulfur and/or nitrogen containing heterocyclics belonging to the class of alkaloids, vitamins, pigments etc. possessing biological activities are reported in the literature (Ozdemir et al., 2007).

Compounds with pyrazoline ring have received widespread attention in recent years. They have been reported as possessing a wide range of biological activities such as anti-inflammatory, anti-microbial, antiandrogenic, and anti-thrombotic properties (Fioravanti et al., 2010; Rani et al., 2011; El-Wahab et al., 2011; Amr et al., 2006; Casimiro-Garcia et al., 2006). Several 1,3,5-triaryl-2-pyrazoline derivatives were also used as scintillation solutes [Wiley et al, 1958]. Pyrazoline derivatives with a phenyl group at the 5-position have been shown to possess good film-forming properties and exhibit excellent characteristics of blue photoluminescence, fluorescence and electroluminescence [Zhang et al, 2000]. Of all the synthesized pyrazoline derivatives, the 1,3,5 tri-substituted derivatives are of particular importance. Prasad et al. (2005) reported that the compounds possessing electron-releasing groups on both aromatic rings in positions 3 and 5 of substituted pyrazolines. Laboratory techniques for drug discovery are very time-consuming and expensive. Each candidate drug must be synthesized and assayed for activity on the target protein, as well as cross-reactivity with non-targets. There is therefore a great deal of interest in developing computational techniques to assist with this stage of drug development. One such method is the docking of the drug molecule with the receptor. On the other hand computer docking technique plays an important role in the drug design as well as in the mechanistic study by placing a molecule into the binding site of the target macromolecule in a non-covalent fashion [El-Gamal et al., 2010]. Docking Server program enable us to predict favourable protein-ligand complex structures with reasonable accuracy and speed. The docking technique will undoubtedly continue to play an important role in drug discovery [16]. So, we docked the designed compounds into DNA Gyrase active site in order to predict their binding

Corresponding* author: ***Dr. N.Santhi,* *Department of Chemistry, Government Arts College, C.Mutlur, Chidambaram, Tamilnadu, India*

modes, their binding affinities and orientation of the designed compounds at the active site of the DNA Gyrase.

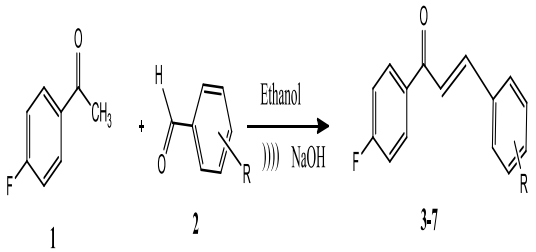
Ultrasound irradiation has been utilized to accelerate a number of synthetically useful reactions during the last few years. Cavitation is the formation, growth and collapse of bubbles in an irradiated liquid. This effect induces very high local pressure and temperatures inside the bubbles and enhances mass transfer and turbulent flow in the liquid[Cravotto et al, 2006]. Ultrasound has been utilized to accelerate a number of synthetically useful reactions, especially in heterocyclic chemistry[Mamaghani et al, 2011; Pereira et al, 2007]. Ultrasound assisted re- actions have resulted in better yields and faster reaction time of the desired products than when prepared under conven- tional conditions. Based on the above facts and our interest for search for new antibacterial agents, we have reported a facile method for the synthesis of novel, 1,3,5-trisubstituted pyrazoline derivatives (9-13) as antibacterial agents under microwave irradiation. In present study, we have also reported molecular docking properties of the synthesized compounds. The results suggest that the compounds could be exploited as an antibacterial drug.

2. EXPERIMENTAL

The melting points were taken in open capillary tube and are uncorrected. Infrared spectra (KBr, 4000-400 cm^{-1}) were recorded on AVATAR-300 Fourier transform spectrophotometer ^{1}H-NMR spectra were recorded on 400 MHz-BRUCKER using $CDCl_3$ as solvent. The chemical shifts are reported as parts per million downfield from tetra methyl silane (Me_4Si). The spectral data are presented in Table 1.

General procedure for preparation of (E)-1-(4-fluorophenyl)-3 substitutedphenylprop-2-en-1-one (3-7)

4-Fluoroacetophenone (2.5mmol), Substituted benzaldehydes (2.5 mmol) 95% Ethanol (20 ml) and 2N NaOH (3 ml) were taken into a 100 ml conical flask. The mixture was irradiated in ultrasonic generator at room temperature for 3 min. The product was filtered with suction on a Buchner funnel, washed with cold water until the washings were neutral to litmus and then with ice cold ethanol. The crude product was recrystallized from ethanol.



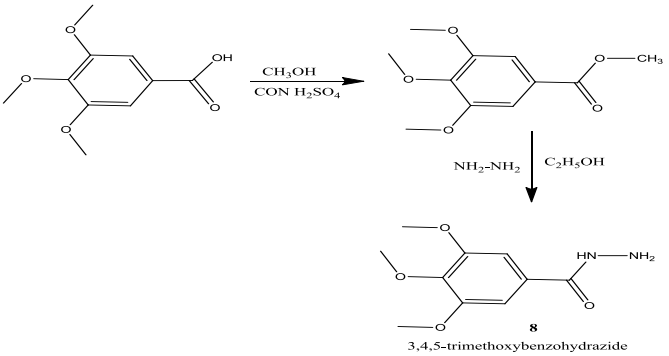
3.RESULTS

Synthesis of methyl 3,4,5-trimethoxybenzoate

3,4,5-trimethoxy Benzoic acid (0.01 mole) in 20 ml of methanol and 0.5 ml conc. Sulphuric acid were taken into a 100 ml conical flask. The mixture was irradiated in ultrasonic generator at room temperature for 10 min. The product was filtered with suction on a Buchner funnel, washed with cold water. The product was isolated and treated with standard sodium bicarbonate solution to give desired compounds.m.p:81-83^{0}C

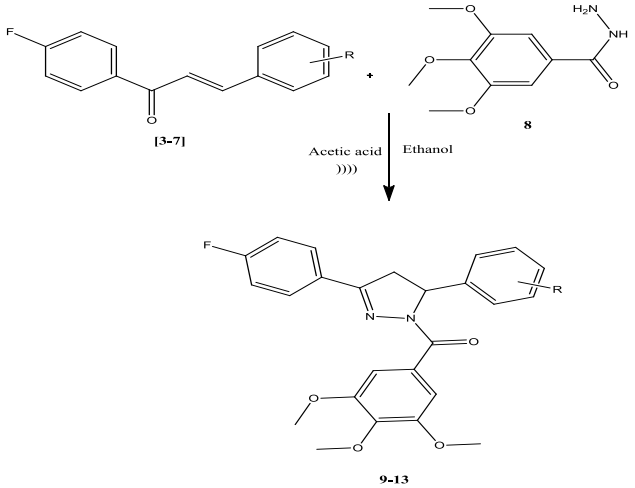
Synthesis of 3,4,5-trimethoxybenzohydrazide (8)

washed with cold water. The product was isolated and crystallized from ethanol. m.p = 156-160^{0}C; Mol. Formula: $C_8H_{10}N_2O_2$; Mol.wt: 166; IR (cm^{-1}): 3170 (NH str.), 3043 (Aromatic C-H str.), 1641(C=O str.), 2926 (Ali C-H str.),



General procedure for preparation of (3-(4-fluorophenyl)-5-substitutedphenyl-4,5-dihydro-1H-pyrazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (9-13)

Substituted chalcones (3-7) (2.5mmol), 3,4,5-trimethoxybenzohydrazide (2.5mmol) and glacial acetic acid (20 ml) were taken into a 100 ml conical flask. This reaction flask was suspended at the center of the ultrasonic cleaning-bath to get the maximum ultrasound energy and sonicated until crystals appeared or starting chalcone disappeared. The reaction-mixture was poured into crushed ice and left overnight. The precipitate was separated by filtration, washed well with water, dried and recrystallized from ethanol



Synthesis of (Z)-N'-(3,3-dimethyl-2,6-diphenylpiperidin-4-ylidene)-4-methoxybenzohydrazide [8]

Mol. Formula : $C_{25}H_{23}FN_2O_4$; Mol.wt : 434.46; m.pt: 122-124 ^{0}C; **IR (KBr) (cm^{-1})**: 3062(Aro-C-H stretching), 2931 (Ali-C-H stretching), 1657 (C=O stretching), 1589 (C=N stretching) ;) 1506 (C=C stretching) **^{1}H NMR(400 MHz, $CDCl_3$, δ,(ppm)**: 7.21.7.82 (m, Ar-H), 3.29 (dd, 1H, H_A), 3.46 (dd, 1H, H_B), 4.30 (dd, 1H, H_X), 3.54 (s, 9H, OCH_3),

Table 1: Physical Properties of (E)-1-(4-fluorophenyl)-3 substitutedphenylprop-2-en-1-one (3-7)

Compound	X	Molecular formula	Molecular weight	Melting point	IR DATA
1	H	$C_{15}H_{11}FO$	226	80-82	C=C: 1597, C=O:1627, C-F:1002
2	Cl	$C_{15}H_{10}ClFO$	260	121-122	C=C: 1604, C=O:1654, C-F:902
3	F	$C_{15}H_{10}F_2O$	244	111-113	C=C: 1602, C=O:1660, C-F:1002
4	CH_3	$C_{16}H_{13}FO$	240	132-134	C=C: 1593, C=O:1654, C-F:987
5	OCH_3	$C_{16}H_{13}FO_2$	256	142-144	C=C: 1591, C=O:1653, C-F:1018

Table2: Energy values of docked Diethyl (3-(4-fluorophenyl)-5-substitutedphenyl-4,5-dihydro-1H-pyrazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (9-13) ligand with DNA Gyrase

Compound	Binding Energy kcal/mol	Docking Energy kcal/mol	Inhibition Constant µM	Intermolec.Energy kcal/mol
9	-4.97	-6.72	228.6	-6.81
10	-5.65	-7.58	2.54	-7.82
11	-5.34	-7.24	122.34	-7.17
12	-4.88	-6.66	264.03	-6.73
13	-5.03	-7.18	204.9	-7.36
Ciprofloxacin	-7.82	-7.03	1.85	-8.74

Table – 3 Antibacterial activity of Diethyl (3-(4-fluorophenyl)-5-substitutedphenyl-4,5-dihydro-1H-pyrazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (9-13)

S. No.	Bacteria	Ciprofloxacin	Zone of inhibition mm in diameter				
			9	10	11	12	13
1	*Bacillus subtilis*	22	20	12	15	13	11
2	*Escherichia coli*	26	18	13	10	8	12
3	*Pseudomonas aeruginosa*	25	10	12	6	8	9
4	*Staphylococcus aureus*	27	5	8	13	12	11
5	*Streptococcus pyogenes*	28	16	14	10	16	12

Mol. Formula : $C_{25}H_{22}ClFN_2O_4$; Mol.wt : 468.9; m.pt: 251-53 ^{0}C; **IR (KBr) (cm^{-1})**: 3053(Aro-C-H stretching), 2931 (Ali-C-H stretching), 1687 (C=O stretching), 1591 (C=N stretching) ; 1508 (C=C stretching) **^{1}H NMR(400 MHz, $CDCl_3$, δ,(ppm)**: 7.26-8.01 (m, Ar-H), 3.01 (dd, 1H, H_A), 3.13 (dd, 1H, H_B), 4.58 (dd, 1H, H_X), 3.50 (s, 9H, OCH_3),

Synthesis of (Z)-N'-(2,6-bis(4-hydroxyphenyl)-3,3-dimethylpiperidin-4-ylidene)-4-methoxybenzohydrazide [10]

Mol. Formula : $C_{25}H_{22}F_2N_2O_4$; Mol.wt : 452.15; m.pt: 203-206 ^{0}C**; IR (KBr) (cm^{-1})**: 3062(Aro-C-H stretching), 2937 (Ali-C-H stretching), 1695 (C=O stretching), 1587 (C=N stretching) ; 1510 (C=C stretching) **^{1}H NMR(400 MHz, $CDCl_3$, δ,(ppm)**: 7.28-8.18 (m, Ar-H), 2.38 (dd, 1H, H_A), 2.54 (dd, 1H, H_B), 3.22 (dd, 1H, H_X), 3.68 (s, 9H, OCH_3),

Synthesis of (Z)-N'-(3,3-dimethyl-2,6-di-p-tolylpiperidin-4-ylidene)-4-methoxybenzohydrazide [11]

Mol. Formula : $C_{26}H_{25}FN_2O_4$; Mol.wt : 448.49; m.pt: 190-192^{0}C; **IR (KBr) (cm^{-1})**: 3091(Aro-C-H stretching), 2924 (Ali-C-H stretching), 1666 (C=O stretching), 1589 (C=N stretching) ; 1519 (C=C stretching) **^{1}H NMR(400 MHz, $CDCl_3$, δ,(ppm)**: 7.28-8.18 (m, Ar-H), 2.19 (dd, 1H, H_A), 3.37 (dd, 1H, H_B), 3.53 (dd, 1H, H_X), 3.68 (s, 9H, OCH_3), 2.61 (s, 3H, -CH_3),

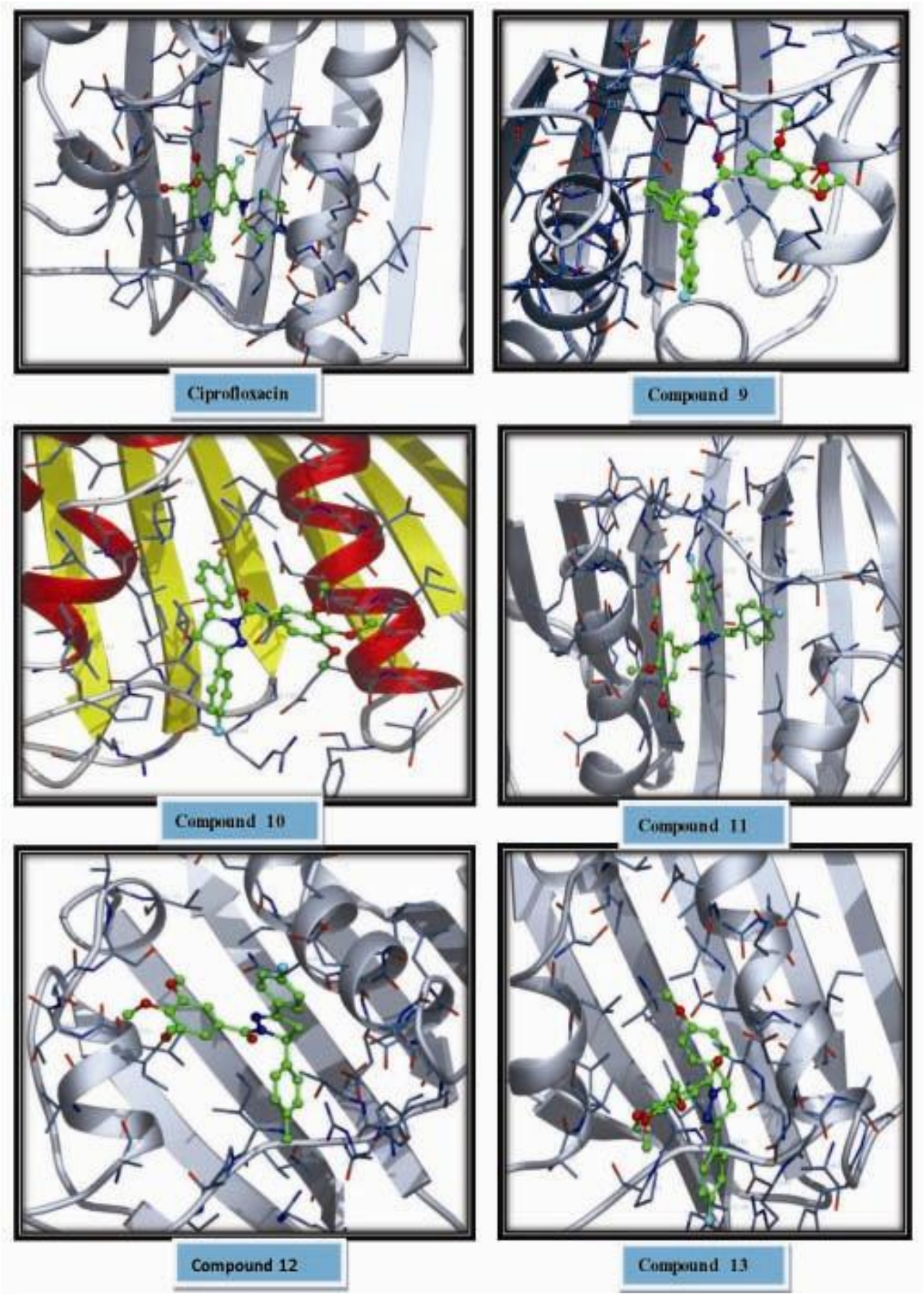


Figure 1: Docked image showing protein and ligand (9-13) interaction

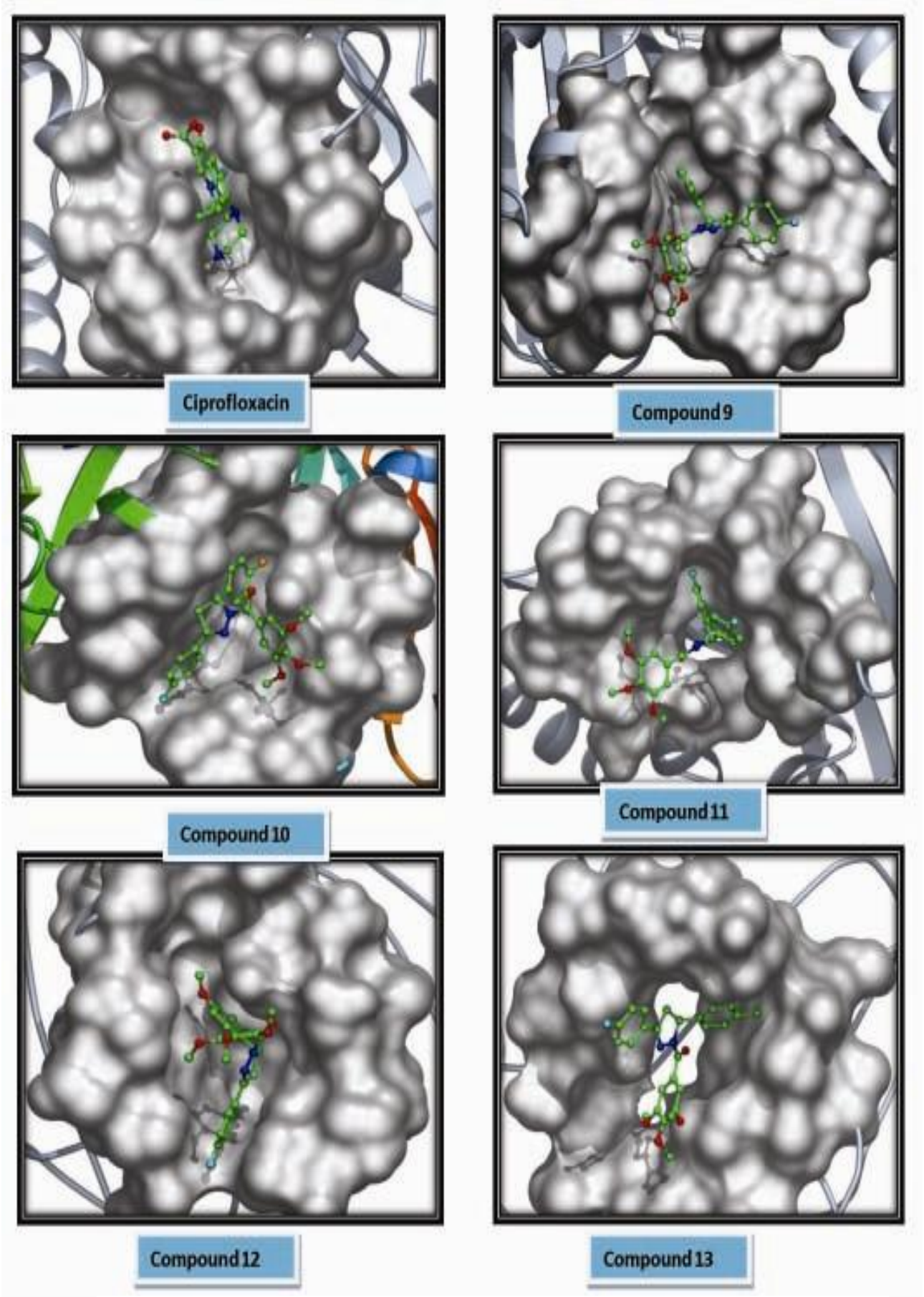


Figure 2:The surface cavity with target molecule (9-13) at the active pocket of the

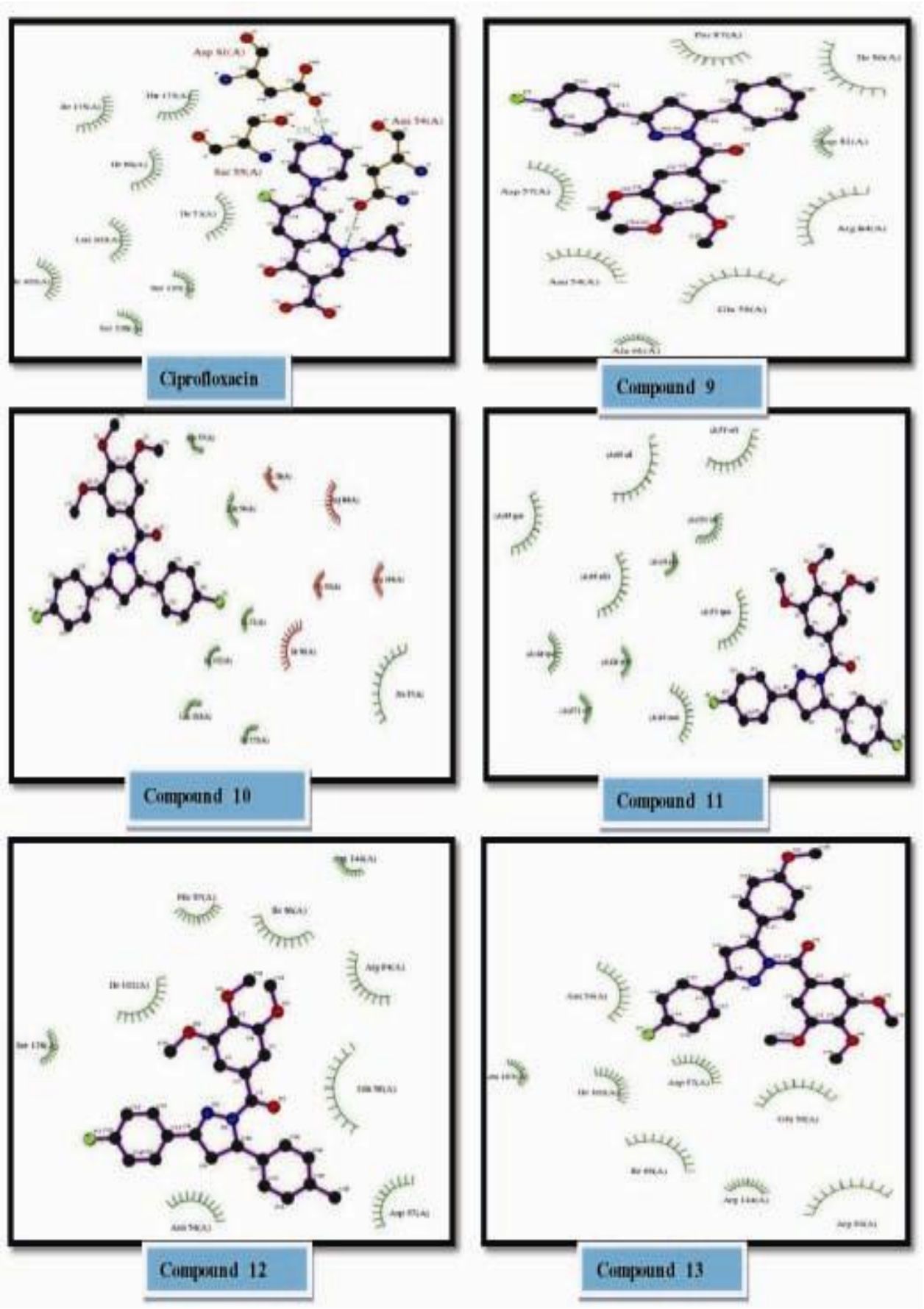


Figure 3: 2D plot of hydrogen bond forming amino acids with target ligand for compound (9-13)

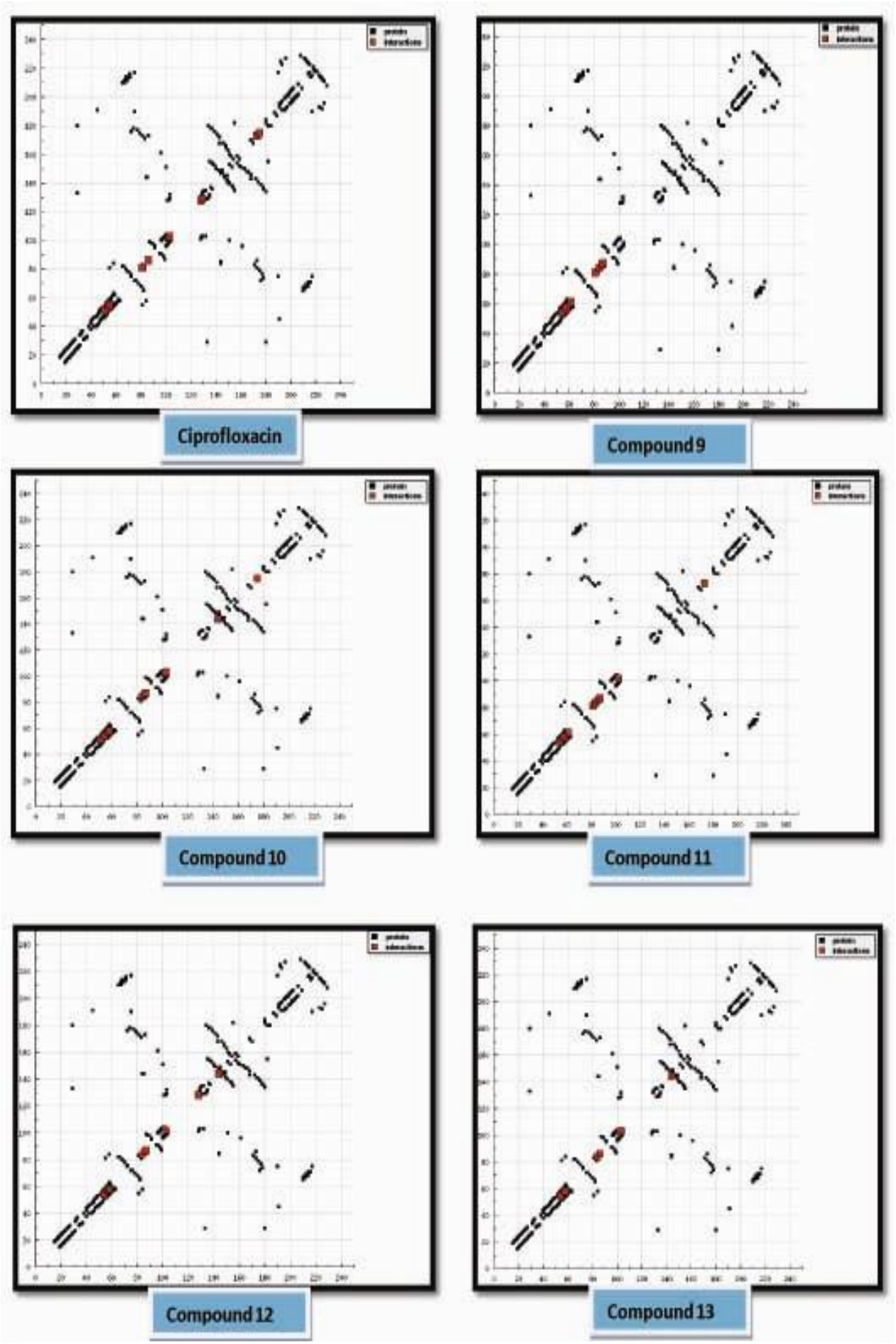


Figure 4: Hydrogen Binding Plot of interacted residues in protein with compound (9-13

Synthesis of (Z)-N'-(2,6-bis(4-methoxyphenyl)-3,3-dimethylpiperidin-4-ylidene)-4-methoxybenzohydrazide [12]

Mol. Formula : $C_{26}H_{25}FN_2O_5$; Mol.wt : 464.49; m.pt: 141-143 ^{0}C; **IR (KBr) (cm^{-1})**: 3032(Aro-C-H stretching), 2927 (Ali-C-H stretching), 1660 (C=O stretching), 1589 (C=N stretching) ; 1471 (C=C stretching) **^{1}H NMR(400 MHz, $CDCl_3$, δ,(ppm)**: 7.02-7.39 (m, Ar-H), 3.74 (dd, 1H, H_A), 4.02 (dd, 1H, H_B), 4.28 (dd, 1H, H_X), 3.99 (s, 12H, OCH_3).

4.DISCUSSION

MOLECULAR DOCKING

Docking calculations were carried out using DockingServer (*Bikadi, Hazai, 2009*). Gasteiger partial charges were added to the ligand atoms. Non-polar hydrogen atoms were merged, and rotatable bonds were defined. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools (*Morris, Goodsell et al., 1998*). Affinity (grid) maps of ×× Å grid points and 0.375 Å spacing were generated using the Autogrid program (*Morris, Goodsell et al., 1998*). AutoDock parameter set- and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively.

Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method (*Solis and Wets, 1981*). Initial position, orientation, and torsions of the ligand molecules were set randomly. All rotatable torsions were released during docking. Each docking experiment was derived from 10 different runs that were set to terminate after a maximum of 250000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied.

Molecular docking studies were conducted in order to validate the obtained pharmacological data and to provide understandable evidence for the observed antibacterial activity of all synthesized compounds. Molecular docking study is a well-established technique to determine the interaction of two molecules and find the best orientation of ligand would form a complex with overall minimum energy. All the synthesized compounds (9-13) were docked Structure of DNA Gyrase

The structure of the protein mentioned above [PDB:3U2D] was retrieved from the Protein Data Bank [www.rcsb.org(DOI:10.2210/pdb3b6o/pdb)] and further modified for docking calculations. The ligand molecules were drawn and analysed using Chem Draw Ultra 8.0. 3D, coordinates were prepared using dock server. Based on the in vitro antibacterial studies, it is worthwhile to do in silico studies; it supports the in vitro activity.

In silico studies revealed all the synthesized molecules showed good binding energy toward the target protein ranging from -5.65 to -4.48 kcal/mol. The docking results revealed that compound **1** showed maximum binding energy of -5.65 kcal/mol, which is due to hydrophobic and hydrogen bond interaction with amino acids of targeted protein. The other compounds like 2 and 3 having significant antibacterial activity are also found to have good binding energy shown in Table 2. The acting forces of this binding mode is mainly depends on hydrogen bonding , electrostatic forces, van-der Waals forces and hydrophobic interaction due to non-polar residue interaction and water structure effect alteration.

Docked ligand molecule 9 to 13 with the secondary structure solid and ribbon model is depicted in Fig 1. 2D plot of hydrogen bond forming amino acid with target ligand, HB plot of interacted residues in protein and molecular interaction with compound 9 to 13 is depicted in Figure 4 respectively.

ANTIBACTERIAL ACTIVITY

The antibacterial activity of the synthesized compounds (9-13) was studied systematically against five different strains of bacteria *Staphylococcus aureus, Bacillus subtillis, Streptococcus pyogenes* (Gram-positive), and *Escherichia coli, Pseudomonas aerugenosa* (Gram-negative) by using disc diffusion method[Barry, 1976]. The test organisms were subcultured using nutrient agar medium. The tubes containing sterilized medium were inoculated with the respective bacterial strain. After incubation at 37ºC ±1ºC for 18 hours, they were stored in a refrigerator. The nutrient agar medium was sterilized by autoclaving at 121ºC for 15 min. The petriplates, tubes and flasks plugged with cotton were sterilized in hot-air oven at 160 ºC, for an hour. Into each sterilized petriplate (20 cm diameter), was poured about 125 ml of molten nutrient agar medium which was already inoculated with the respective strain of bacteria (5 ml of inoculum to 250 ml of nutrient agar medium) aseptically. The plates were left at room temperature aseptically to allow the solidification. After solidification, the paper discs containing the derivatives were placed at different areas on the surface of each plate and labelled accordingly.

Each test compound (5 mg) was dissolved in dimethylsulfoxide (5 ml Annular grade) to give a concentration of 1000 µg/ml. Ciprofloxacin solution was also prepared to give a concentration of 1000 µg/ml in sterilized distilled water. The pH of all the test solutions and control was maintained in between 2 to 3 by using conc.HCl. All the compounds were tested at dose levels of 1000 µg and DMSO used as a control. The solutions of each test compound, control and reference standard were added separately in the cups and the plates were kept undisturbed for at least 2 hours in a refrigerator to allow diffusion of the solution properly into nutrient agar medium. Petri dishes were subsequently incubated at 37±1 ^{0}C for 24 hours. After incubation, the diameter of zone of inhibition surrounding each of the cups was measured with the help of an antibiotic zone reader. The results are presented in Tables and Figures.

Table 3 shows the invitro antibacterial activities of the Diethyl (3-(4-fluorophenyl)-5-substitutedphenyl-4,5-dihydro-1H-pyrazol-1-yl)(3,4,5-trimethoxyphenyl)methanone (9-13) derivatives. From the results, it was noticed that, Compound **9,10 and 11** showed significant antibacterial activity at 15mg concentration level when compared with standard ciprofloxacin . Compounds possessed maximum activity which may be due to the presence of halogen group at C-4 on aromatic ring-B

The screening results indicate that compounds **(11)** and **(12)** were found to be active against *S. aureus*. vCompounds **(13)** was found to moderately active against *S. aureus*, whereas Compounds **(10)** and **(12)** was found to be moderately active

against *B. subtilis*. Compounds **(9)** and **(10)** was found to be moderately active against *E. coli*, whereas all other compounds were found to be less active against *E. coli* . Compound (2) and **(4)** was found to be active against S.pyogenes

5.CONCLUSION

In summary, a new series of Diethyl (3-(4-fluorophenyl)-5-substitutedphenyl-4,5-dihydro-1H-pyrazol-1-yl)(3,4,5-trimethoxyphenyl)methanone derivatives were synthesized and characterized by FT-IR, 1H NMR spectral analyses. All the molecules were studied for their interactions with DNA Gyease by molecular docking protocol. Among the tested molecules, compound 10 and 11 exhibited a good binding energy value of -5.65 and -5.34. In vitro antibacterial activity of the tested compounds shows improved activity against all the microorganisms used. In particular compound 9 and 10 exhibits marked activity against two microorganisms.

6.REFERENCES

1. Fioravanti, R., Bolasco, A., Manna, F., Rossi, F., Orallo, F., Ortuso, F., Alcaro, S., & Cirilli, R. (2010). Synthesis and biological evaluation of N-substituted-3,5-diphenyl-2-pyrazoline derivatives as cyclooxygenase (COX-2) inhibitors. European Journal of Medicinal Chemistry, 45, 6135–6138.
2. Rani, M., Yusuf, M., Khan, S. A., Sahota, P. P., & Pandove, G. (2011). Synthesis, studies and in-vitro antibacterial activity of N-substituted 5-(furan-2-yl)-phenyl pyrazolines. Arabian Journal of Chemistry, in press
3. El-Wahab, A. H. F. A., Al-Fifi, Z. I. A., Bedair, A. H., Ali, F M., Halawa, A. H. A., & El-Agrody, A. M. (2011). Synthesis, reactions and biological evaluation of some new naphtho[2,1- b]furan derivatives bearing a pyrazole nucleus. Molecules, 16, 307–318.
4. Amr, A. E. E., Abdel-Latif, N. A., & Abdalla, M. M. (2006). Synthesis and antiandrogenic activity of some new 3- substituted androstano[17,16-c]-5'-aryl-pyrazoline and their derivatives. Bioorganic & Medicinal Chemistry, 14, 373–384
5. Casimiro-Garcia, A., Dudley, D. A., Heemstra, R. J., Filipski, K. J., Bigge, C. F., & Edmunds, J. J. (2006). Progress in the discovery of factor Xa inhibitors. Expert Opinion on Therapeutic Patents, 16, 119–145.
6. Wiley, R.H.; Jarboe, C.H.; Hayes, F.N.; Hansbury, E.; Nielsen, J.T.; Callahan, P.X.; Sellars, M. 1,3,5-Triaryl-2-pyrazolines for use as scintillation solutes. *J. Org. Chem.* 1958, *23*, 732–738.
7. Zhang, X.H.; Wu, S.K.; Gao, Z.Q.; Lee, C.S.; Lee, S.T.; Kwong, H.L. Pyrazoline derivatives for blue color emitter in organic electroluminescent devices. *Thin Solid Films* 2000, *371*, 40–46.
8. Prasad, Y. R., Rao, A. L., Prasoona, L., Murali, K., & Kumar, P. R. (2005). Synthesis and antidepressant activity of some 1,3,5-triphenyl-2-pyrazolines and 3-(2''-hydroxy naphthalen- 1''-yl)-1,5-diphenyl-2-pyrazolines. Bioorganic & Medicinal Chemistry Letters, 15, 5030–5034.
9. Narang R, Narasimhan B, Sharma S, (Naphthalen-1-yloxy)- acetic acid benzylidene/(1-phenyl-ethylidene)-hydrazide derivatives: Synthesis, antimicrobial evaluation and QSAR studies. Med Chem Res, 2012; 21:2526-2547
10. Perez KK, Olsen RJ, Musick WL, Cernoch PL, Davis JR, Peterson LE, Musser JM. Integrating rapid diagnostics and antimicrobial stewardship improves outcomes in patients with antibiotic resistant Gramnegative bacteremia. J Infect, 2014; 69:216-225.
11. Narasimhan B, Ohlan S, Ohlan R, Judge V, Narang R. Hansch analysis of veratric acid derivatives as antimicrobial agents. Eur J Med Chem, 2009; 44:689-700.
12. Ozdemir A, Turan-Zitouni G, Kaplancikli ZA, Revial G, Güven K. Synthesis and antimicrobial activity of 1-(4-aryl-2-thiazolyl)-3-(2- thienyl)-5-aryl-2-pyrazoline derivatives. Eur J Med. Chem 2007; 42:403- 409.
13. Cravotto G and Cintas P. Power ultrasound in organic synthesis moving cavitational chemistry from academic to innovative and large-scale application. Chem Soc Rev. 2006;35:180
14. Mamaghani M, Loghmanifar A and Taati MR. An efficient one-pot synthesis of new 2-imino-1,3-thiazolidin-4-ones under ultrasonic conditions. Ultrason Sonochem. 2011;18:45.
15. Pereira CMP, Stefanil HA, Guzen KP and Orfao ATG. Improved synthesis of benothiazoles and 1-acylbenzotriazoles by ultrasound irradiation. Lett Org Chem. 2007;4:43.
16. Bikadi, Z., Hazai, E. Application of the PM6 semi-empirical method to modeling proteins enhances docking accuracy of AutoDock J. Cheminf. 1, 15 (2009)
17. T. A. Halgren *Merck molecular force field. I. Basis, form, scope, parametrization, and performance of MMFF94* Journal of Computational Chemistry 17 (5-6), 490-519 (1998)
18. G. M. Morris, D. S. Goodsell, et al. *Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function* Journal of Computational Chemistry 19 (14), 1639-1662 (1998)
19. F. J. Solis and R. J. B. Wets *Minimization by Random Search Techniques* Mathematics of Operations Research 6 (1), 19-30 (1981)
20. Barry, A.L., in: *The antimicrobial susceptibility test: Principle and Practice, Lea and Febiger*, Philadelphia, 180 (1976).
21. El-Gamal MI, Bayomi SM, El-Ashry SM, Said SA, Abdel-Aziz AA-M, Abdel-Aziz NI (2010) Synthesis and anti-inflammatory activity of novel (substituted)benzylidene acetone oxime ether derivatives: molecular modeling study. Eur J Med Chem 45: 1403–1414
22. Wang, R., Lu, Y. and Wang, S. (2003): Comparative evaluation of 11 scoring functions for molecular docking. J. Med. Chem., 46: 2287- 303.

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