INTERNATIONAL JOURNAL OF CURRENT RESEARCH IN CHEMISTRY AND PHARMACEUTICAL SCIENCES
(p-ISSN: 2348-5213: e-ISSN: 2348-5221)
www.ijcrcps.com
DOI:10.22192/ijcrcps Coden: IJCROO(USA) Volume 3, Issue 11 - 2016

Research Article

DOI: http://dx.doi.org/10.22192/ijcrcps.2016.03.11.008

Synthesis, Structure-based molecular design of some novel (E)-N'-(3,3-dimethyl-2,6-diarylpiperidin-4-ylidene) -4-methoxybenzohydrazide as DNA gyrase inhibitors

G. Sundaraselvan and S. Darlin Quine*

Department of Chemistry, Government Arts College, C.Mutlur, Chidambaram-608102, India
*Corresponding Author: sdarlinquine@gmail.com

Abstract

A novel series of (E)-N'-(3,3-dimethyl-2,6-diarylpiperidin-4-ylidene)-4-methoxybenzohydrazide (**DMMs**) derivatives have been designed, synthesized by using FT-IR, ^{1}H, ^{13}C NMR and Mass spectral studies. The antibacterial activity of the **DMMs** evaluated against different bacteria *viz*. *Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus* and *Streptococcus pyogenes*. Among them, compounds **10** and **11** were found to be the most potent than the others. Different docking programs (Auto-Dock and molecular docking server) have been used to assess the accuracy of virtual screening methods against DNA gyrase target. An analysis provides us which functions perform well and feasibility of two docking approaches. In connection with these efforts we conclude that Auto Dock program gives us more accuracy and scoring reliability of the selected docking approaches. From these results, we report analogue **10** and **11** as promising candidates for the discovery of well-balanced compounds.

Keywords: DMMs, FT-IR, antibacterial activity, DNA gyrase.

Introduction

Piperidin-4-one moiety plays a vital role in diverse biological activities and is a key feature of some of the most interesting and important classes of compounds. Many piperidin-4-one scaffold containing compounds are biological activities like antiviral [1,2], antitumor [3], anti-inflammatory [4], central nervous system [5], anticancer [6] and antibacterial activity [7]. Inspired by the growing importance of piperidin-4-one heterocyclic rings and the wide range of biological importance of heterocycles containing piperidin-4-one framework, we have devised a synthesis for the construction of piperidin-4-one ring systems incorporating a hydrazone framework with oxygen heterocycles. In view of the importance of piperidin-4-one and hydrazone in the field of medicinal chemistry and also to explore the scope of these motifs, we have focused in this work was to incorporate these five independently biologically active moieties into one molecule to generate compounds with better biological activities.

In studying the various properties associated with protein-ligand interactions, docking is a powerful tool. Since molecules in nature have a tendency to be found in their lowest energy form, the final configuration should also be of low energy [6]. Understanding these properties is crucial in the ration al design of potent inhibitors. Molecular Docking is an effective and competent tool for *in silico* screening. It is playing an important and ever increasing role in rational drug design [7,8]. It is usually known that molecular binding of one molecule (the ligand) to the pocket of another molecule (the receptor), which is commonly a protein, is responsible for accurate drug activity. Molecular docking has been proved very gifted tool for novel drug discovery

for targeting protein. Among different types of docking, protein-ligand docking is of special interest, because of its application in medicine industry [10]. Protein ligand docking refers to search for the accurate ligand conformations within a targeted protein when the structure of proteins is known [11,12]. In the current scenario the use of computational approach is very important in the field of computer aided drug designing to elucidate the molecular level interaction and active site residues property in relation to activity. Therefore, we elicit synthesis, biological evaluation and comparative docking study with extensively used programs such as AutoDock [13,14], and Molecular docking server [15] of (*E*)-*N*'-(3,3-dimethyl-2,6-diarylpiperidin-4-ylidene)-4-methoxybenzohydrazide as DNA gyrase inhibitor .

Experimental details

Synthesis of 3,3-Dimethyl-2,6-diarylpiperidin-4-ones (1-5)

Dry ammonium acetate (100 mmol), 3-methyl-2-butanone (100 mmol) and appropriate substituted benzaldehyde (200 mmol) in ethanol were just heated to boil and allowed to stand at room temperature overnight. The reaction mixture was diluted with ether (100 mL) and treated with Conc. HCl (20 mL). The precipitated hydrochloride was washed with ethanol–ether. The hydrochloride was suspended in acetone and neutralized with aqueous ammonia. Dilution with water gave the free base which was recrystallized from ethanol.

Synthesis of ethyl 4-methoxybezoate (6) and 4-methoxybezo hydrazide (7)

4-methoxybezoate (**6**) and 4-methoxybezo hydrazide (**7**) were synthesized as per the procedure described in literature [16].

Synthesis of (E)-N'-(3,3-dimethyl-2,6-diarylpiperidin-4-ylidene)-4-methoxybenzohydrazide (8-12)

A mixture of 3,3-Dimethyl-2,6-diarylpiperidin-4-ones (1 mmol), 4-methoxybezo hydrazide (1.5 mmol) in ethanol and a few drops of acetic acid was added and refluxed for 2–4 h. On completion of the reaction time, a solid mass was formed, which was then cooled to room temperature. The precipitate was filtered off and washed with ice-cooled water– ethanol mixture. The crude product was recrystallized from ethanol. Synthetic routes of compounds are given in scheme 1.

(E)-N'-(3,3-dimethyl-2,6-diphenylpiperidin-4-ylidene)-4-methoxybenzohydrazide (8)

Pale Yellow solid; Yield 65%., M.P: 191°C, MF: $C_{27}H_{29}N_3O_2$; elemental analysis: Calcd (%): C, 75.85; H, 6.84; N, 9.83; O, 7.48; found (%):C, 75.74; H, 6.86; N, 9.79; IR (KBr, cm^{-1}): 3464 (N-H), 3068 (Ar-C-H), 2935 (AliC-H), 1647 (C=O); ^{1}H-NMR ($CDCl_3$) 7.26-8.01 (m, Ar-**H**), 2.14 (1H, N-**H**), 7.26 (1H, N-**H**), 3.01 (1H, H5ax,), 3.13 (1H, H5eq), 3.88 (1H, H2), 3.54 (1H, H6), 3.50 (3H, OC**H**$_3$), 1.62 (3H, C**H**$_3$); 13C NMR (100 MHz, CDCl3, δ, ppm):180.09 (C=O), 153.56 (C=O), 122.18-144.35 (Ar-C), 62.75 C(2), 56.40 C(6), 44.74C(3), 34.15C(5), 61.25 (OCH3), 26.06 (CH3);Mass (m/z): 426 (M+), 350, 265, 164, 107, 96, 77.

(E)-N'-(2,6-bis(4-fluorophenyl)-3,3-dimethyl-2,6-diphenylpiperidin-4-ylidene)-4-methoxybenzohydrazide (9)

Yellow solid; Yield 63%., M.P: 204°C, MF: $C_{27}H_{27}F_2N_3O_2$; elemental analysis: Calcd (%):C, 69.96; H, 5.87; F, 8.20; N, 9.07; O, 6.90 ; found (%):C, 69.665; H, 5.83; N, 9.03; IR (KBr, cm^{-1}): 3477 (N-H), 3064 (Ar-C-H), 2920 (AliC-H), 1674 (C=O); ^{1}H-NMR ($CDCl_3$) 6.84-7.75 (m, Ar-**H**), 2.14 (1H, N-**H**), 7.28 (1H, N-**H**), 2.18 (1H, H5ax,), 2.54 (1H, H5eq), 4.36 (1H, H2), 4.00 (1H, H6), 3.91 (3H, OC**H**$_3$), 1.61 (3H, C**H**$_3$); 13C NMR (100 MHz, CDCl3, δ, ppm): 186.38 (C=O), 156.29 (C=O), 113.19-144.00 (Ar-C), 65.96 C(2), 56.98C(6), 43.51 C(3), 39.22 C(5), 64.50 (OCH3), 14.43 (CH3); Mass (m/z): 462 (M+), 368, 328, 273, 150, 107.

(E)-N'-(2,6-bis(4-hydroxyphenyl)-3,3-dimethyl-2,6-diphenylpiperidin-4-ylidene)-4-methoxybenzohydrazide (10)

Pale Yellow solid; Yield 66%., M.P: 189°C, MF: $C_{27}H_{27}Cl_2N_3O_2$; elemental analysis: Calcd (%):C, 65.32; H, 5.48; Cl, 14.28; N, 8.46; O, 6.45 ; found (%):C, 65.302; H, 5.45; N, 8.43; IR (KBr, cm^{-1}): 3427 (N-H), 3059 (Ar-C-H), 2927 (AliC-H), 1653 (C=O); ^{1}H-NMR ($CDCl_3$) 7.47-8.18 (m, Ar-**H**), 1.97 (1H, N-**H**), 7.28 (1H, N-**H**), 2.37 (1H, H5ax,), 2.54 (1H, H5eq), 3.19 (1H, H2), 4.78 (1H, H6), 3.68 (3H, OC**H**$_3$), 1.66 (3H, C**H**$_3$); 13C NMR (100 MHz, CDCl3, δ, ppm): 164.63 (C=O), 162.30 (C=O), 113.97-147.32 (Ar-C), 65.05 C(2), 55.59 C(6), 44.98 C(3), 42.83 C(5), 61.33 (OCH3), 14.93 (CH3); Mass (m/z): 458 (M+), 444, 352, 324, 282, 135, 93.

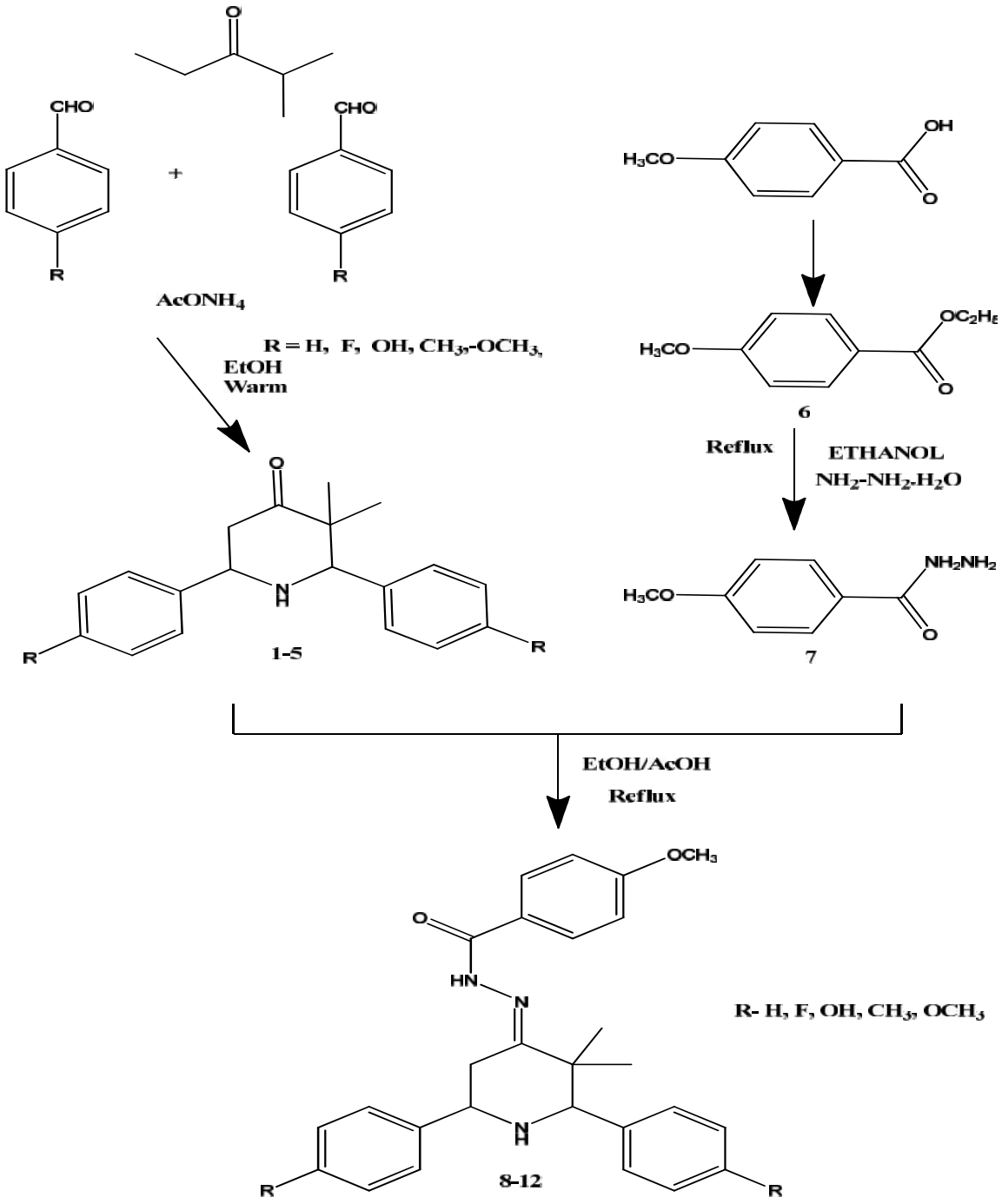
(E)-N'-(3, 3-dimethyl-2,6-di-p-tolylpiperidin-4-ylidene)-4-methoxybenzohydrazide (11)

Pale Yellow solid; Yield 60%., M.P: 214°C, MF: $C_{29}H_{33}N_3O_2$; elemental analysis: Calcd (%):C, 76.45; H, 7.30; N, 9.22; O, 7.02; found (%):C, 76.30; H, 7.29; N, 9.12; IR (KBr, cm^{-1}): 3464 (N-H), 3068 (Ar-C-H), 2918 (AliC-H), 1597 (C=O); ^{1}H-NMR ($CDCl_3$) 7.05-7.60 (m, Ar-**H**), 2.15 (1H, N-**H**), 6.75 (1H, N-**H**), 2.48 (1H, H5ax,), 2.66 (1H, H5eq), 3.65 (1H, H2), 3.65 (1H, H6), 3.45 (3H, OC**H**$_3$), 1.62 (3H, C**H**$_3$); 13C NMR (100 MHz, CDCl3, δ, ppm): 184.95 (C=O), 155.89 (C=O),

122.56-155.90 (Ar-C), 67.05 C(2), 55.24 C(6), 53.09 C(3), 50.40 C(5), 64.52 (OCH3), 19.92,20.15 (CH3); Mass (m/z): 454 (M+), 440, 349, 329, 293, 135.

(E)-l'-(2,6-bis(4-methoxyphenyl)-3,3-dimethyl-2,6-diphenylpiperidin-4-ylidene)-4-methoxybenzohydrazide (12)

Pale Yellow solid; Yield 61%., M.P: 231°C, MF: $C_{29}H_{33}N_3O_4$; elemental analysis: Calcd (%):C, 71.44; H, 6.82; N, 9.22; O, 13.13 ; found (%):C, 71.43; H, 6.70; N, 9.12; IR (KBr, cm^{-1}): 3462 (N-H), 3070 (Ar-C-H), 2920 (AliC-H), 1656 (C=O); ^{1}H-NMR ($CDCl_3$) 6.75-7.32 (m, Ar-**H**), 2.17 (1H, N-**H**), 6.90 (1H, N-**H**), 2.70(1H, H5ax,), 3.06 (1H, H5eq), 3.82 (1H, H2), 3.44 (1H, H6), 3.88 (3H, OC**H**$_3$), 1.68 (3H, C**H**$_3$); 13C NMR (100 MHz, CDCl3, δ, ppm): 163.37 (C=O), 154.75 (C=O), 116.47-139.90 (Ar-C), 61.09 C(2), 56.99 C(6), 50.50 C(3), 45.16 C(5), 58.71 (OCH3), 14.89 (CH3); Mass (m/z): 486 (M+), 472, 456, 380, 352, 349, 164, 111.



Scheme .1 Synthetic routes of compounds **8-12**

Spectral measurements

The FT-IR spectrum of the synthesized **DDMs** was measured in the range 4000-500 cm^{-1} on a AVATAR-330 FT-IR spectrometer (Thermo Nicolet) using KBr (pellet form). ^{1}H NMR spectrum was recorded at 400 MHz on a BRUKER model using $CDCl_3$ as solvent. Tetramethylsilane (TMS) was used as internal reference for all NMR spectra, with chemical shifts reported in δ units (parts per million) relative to the standard.

Biology studies

Antibacterial activity by disc diffusion method

Nutrient agar plates were prepared under sterile conditions and incubated overnight to detect contamination. About 0.2 mL of working stock culture was transferred into separate nutrient agar plates and spread thoroughly using a glass spreader. Whatmann No.1 discs (6 mm in diameter) were impregnated with the test compounds dissolved in DMSO (200 mg/mL) for about half an hour. Commercially available drug disc *(Ciprofloxacin* 10 µg/disc) was used as positive reference standard. Negative controls were also prepared by impregnating the disc of same size with DMSO solvent. The discs were placed on the inoculated agar plates and incubated at 37 ± 1°C for about 18-24 hrs. Antibacterial activity was evaluated by measuring the zone of inhibition against the test organism.

Methods

DNA gyrase inhibitor

Crystal structures of the protein complex used in this study were obtained from the the protein data bank (www.rcsb.org/pdb). PDB code: 3U2D [18]

Docking Studies

The test set of complexes described above was used in the evaluation. DNA gyrase was docked back into the corresponding binding site. In order to get accurate results, all the docking experiments were performed with the default parameters. Doc ing with was performed on a Autodock 4.2 and Molecular docking server with an Intel Pentium D process or (3.0 GHz) and 4 GB of R A M was run on windows 7. The following paragraphs describe the search algorithm and scoring methods used in the three programs. For each program, details of the calculations performed in this study are provided.

Auto Dock 4.2

For AutoDock 4.2, ligand molecules were drawn in ChemBioDraw Ultra 12.0 and converted to their three-dimensional structures in Chem Bio3D Ultra 12.0 and saved as in pdb format. The prepared ligands were used as input files for AutoDock 4.2 in the next step. Lamarckian genetic algorithm method [18] was employed for docking simulations. The standard docking procedure was used for a rigid protein and a flexible ligand whose torsion angles were identified (for 10 independent runs per ligand). A grid of 60, 60, and 60 points in x, y, and z directions was built with a grid spacing of 0.375 A˚ and a distance dependent function of the dielectric constant were used for the calculation of the energetic map. The default settings were used for all other parameters. At the end of docking, the best poses were analyzed for hydrogen bonding/π–π interactions and root mean square deviation (RMSD) calculations using Discovery Studio Visualizer 4.2 (Accelrys Software Inc.) and Pymol (The PyMOL Molecular Graphics System) programs. From the estimated free energy of ligand binding energy, the inhibition constant (Ki) for each ligand was calculated and reproduced in Table 2.

Molecular docking server

Docking calculations were carried out using DockingServer [19,20]. Gasteiger partial charges were added to the ligand atoms. Non-polar hydrogen atoms were merged, and rotatable bonds were defined. Docking calculations were carried out on DNA gyrase protein model. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of Auto-Dock tools [18]. Affinity (grid) maps of ×× Å grid points and 0.375 Å spacing were generated using the Autogrid program [18]. Auto-Dock parameter set- and distance-dependent dielectric functions were used in the calculation of the vander Waals and the electrostatic terms, respectively. Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method [21]. 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 2 different runs that were set to terminate after a maximum of 250000 energy evaluations. The population size was set to 1 50. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied.

Results and Discussion

Synthesis of compounds 8-12

The structure of formed **DMMs** derivatives was elucidated with the help of various spectral techniques such as IR, ^{1}H NMR, ^{13}C NMR and mass data. For compound 8 taken as representative, In this the IR spectrum shows sharp peak appeared at 3466 cm^{-1} corresponds to the piperidine ring N–H stretching, the strong peak at 1647 cm^{-1} corresponds to C=O stretching and the peak at 1572 cm^{-1} corresponds to C=N stretching. In the 1H NMR, signals around

7.26-8.01 ppm, as multiplet is due to aromatic protons in phenyl ring at C-2, C-6 and hydrazone group.The downfield signal at 3.88 ppm quartet is assigned to H-2a and H-6a benzylic proton is appeared at 3.54 ppm. The signal at 3.13 ppm, quartet is assigned to H5eq proton. Consequently, the signal at 3.01 ppm is assigned to methylene proton of H5ax. Obviously, the signal at 2.14 ppm is due to N-H proton in piperidine ring. The most downfield singlet at 7.26 ppm is assigned to NH proton of hydrazone group. The signal at 3.50 ppm is corresponds to methoxy protons in synthesized compound. The upfield signal at 1.62 ppm is due to methyl protons at C-3 position. In the 13C NMR, the chemical shift at 26.06 ppm is assigned to methyl carbon at C-3. The most downfield signal around 180.09 ppm is assigned to C=O carbon in hydrazone unit. C-4 could readily be distinguished from other heterocyclic ring carbons by their characteristic downfield signal observed at 153.56 ppm and also by their low intensities. The signals at 66.75 and 56.40 ppm are due to benzylic carbons at C-2 and C-6 and the remaining signals at 44.74 and 34.15 ppm are due to C-3 and C-5 carbons.

Antibacterial activity

To examine the structure activity relationship (SAR) of the newly synthesized compounds were evaluated for their antibacterial activity against five bacterial strains by adopting disc diffusion method [22,23]. *Ciprofloxin* was used as a standard reference drug. To achieve better affinity and further potency of the new candidates, the *para* position in phenyl was subjected to a variety of new different electron donating and deactivating functional groups including moieties of fuoro (**9**), hydroxyl (**10**) methyl (**11**) and methoxy (**12**).

The anti bacterial activity of the synthesized compounds exhibited significant zones of inhibition against tested Gram positive and Gram negative strains at 200 µg/mL. The zone of inhibition (mm) of synthesized molecules at 200 µg/mL concentration was shown in Figure 1. Among the synthesized compounds, compounds **10** and **11** were found to be the most potent compounds (17 and 18 µM, respectively) and were more active than **8, 11** and **12** against *Escherichia coli*. Among, the tested compounds, compound **11** exhibited highest activities against *Staphylococcus aureus* and *Streptococcus pyogenes* 16 and 17 mm zone of inhibition, respectively and also compound **11** exhibited significant antibacterial activity with zone of inhibition 13 mm against *Bacillus subtili*s and 12 mm against *Escherichia coli* and *Pseudomonas aeruginosa*. On the other hand, compound **12** also exhibited significant antibacterial activity with zone of inhibition 14 mm against *Streptococcus pyogenes. Bacillus subtilis* and *Staphylococcus aureus* shows 13 mm zone of inhibition and 12 mm against Escherichia coli and Pseudomonas aeruginosa. From the above results it is clear that the compounds **11** and **12** are found to exhibit greater inhibition efficiency against various strains. Apart from these, compound **8**-**12** also showed significant to moderate antibacterial activity to *Bacillus subtilis*. With respect to structure activity relationship, the data in Table 1 show that the compounds **10** and **9** possess more activity against *Escherichia coli* than the **8, 11** and **12**.

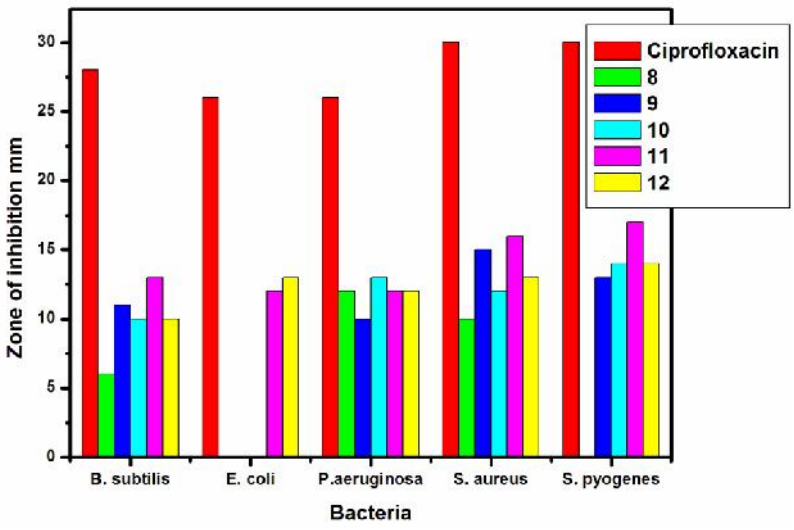


Fig. 1 protective effect of **8-12** against *Ciprofloxacin*

Table 1 Antibacterial activity of **DMMs**

S. No.	Bacteria	*Ciprofloxacin*	Zone of inhibition mm in diameter					
			8	**9**	**10**	**11**	**12**	Control (DMSO)
1	*Bacillus subtilis*	28	06	11	10	13	10	-
2	*Escherichia coli*	26	-	-	-	12	13	-
3	*Pseudomonas aeruginosa*	26	12	10	13	12	12	-
4	*Staphylococcus aureus*	30	10	15	12	16	13	-
5	*Streptococcus pyogenes*	30	-	13	14	17	14	-

Among the designed candidates in the order of activity is 4-OHC_6H_4 > 4-FC_6H_4 >4-$OCH_3C_6H_4$ > 4-$CH_3C_6H_4$ > C_6H_5. In series of **8-12**, the presence of hydroxy atom in the phenyl ring at para-position enhanced the antibacterial activity and this was followed by weakly deactivating group fluorine derivatives. Electron donating groups like methoxy and methyl reduced the activity.

Docking analysis

Different database docking programs (Auto Dock, Molecular docking server) have been used to assess the accuracy of virtual screening methods against DNA gyrase targets of known three-dimensional structure. The number and categories in which the dock poses fall are summarized in Table 2. Using above-cited docking programs, we first addressed the docking accuracy of each tool. As seen in from Table 2, Auto Dock was found to be the best for carrying out docking. It generated higher binding energy than molecular docking server.

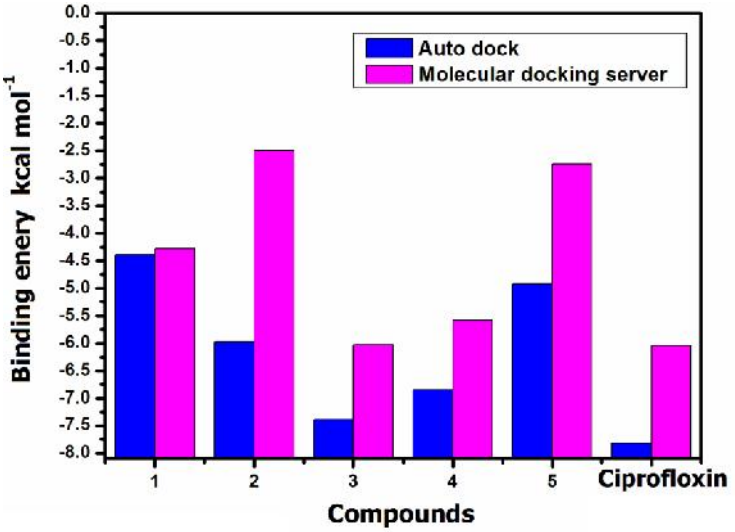


Fig. 2 Binding energy of **8-12**

Table 2 Docking results of **DMMs** with DNA gyrase (PDB code: 3CU2D)

S.NO	Compounds	Binding energy Kca/mol^{-1}		Vdw_hb_desolv_ energy Kca/mol^{-1}		Inhibition constant (µm)		Intermol energy Kca/mol^{-1}		Hydrogen bonding		Residues involving interactions	
		Auto Dock 4.2	Docking Server	Auto Dock 4.2	Docking Server	Auto Dock 4.2	Docking Server	Auto Dock 4.2	Docking Server	Auto Dock 4.2	Docking Server	Auto Dock 4.2	Docking Server
1	S	-4.39	-4.28	-4.13	-5.20	608.44	728.29	-4.69	-5.88	-	1	-	ASN54
F	F	-5.97	-2.50	-6.06	-3.65	65.34	14.76	-6.6	-4.42	3	3	VAL B:130 ASN B:54 LYS A:1163	ASN54 VAL131 VAL130
3	OH	-7.38	-6.03	-4.66	-5.41	54.29	35.41	-7.12	-4.66	4	2	GLU B:58 ASP B:81 GLY B:85 THR B:173	ARG84 VAL131
M	ME	-6.85	-5.58	-5.33	-7.25	37.97	9.52	-6.21	-7.30	-	2	-	SER129 GLU50
5	MEO	-4.92	-2.74	-5.1	-4.27	37.97	9.83	-6.21	-4.89	2	3	LYS A:154 APR B:198	VAL130 VAL131 ARG84
	CIP	-7.82	-6.05	6.63	-7.03	36.54	1.85	-5.57	-8.74	2	2	ASP A:161 ASP B:57	ASN54 SER55

Table 3 Average docking times (s) of algorithms

Molecule	Auto dock	Molecular docking server
8	51	391
9	29	291
10	98	620
11	88	624
12	110	353

This variation might be because of the algorithms employed by the routines, grid box specification and active site residue specification. Overall results, molecular docking server showed relatively poor performance than auto dock. These results were surprisingly low, indicating the docking programs often failed to find the correct binding mode. Evaluation of docking accuracy of docking programs requires the programs run at approximately comparable speeds. The average time required for carrying out the docking calculation using different docking routines of a single ligand is shown in Table 3. According to Table 3 in the context of the average time required for docking a single ligand, auto-dock is the fastest algorithm with average 75.2 se c than molecular docking server 455.2 sec. In connection with these efforts we conclude that Auto Dock program gives us more accuracy and scoring reliability of the selected docking approaches.

Hence, we compare the binding affinity of the synthesized analogues with Auto Dock results. Table 2 show the solutions with the highest predicting binding affinity for DNA gyrase. Table 2, revealed that the more active compounds **10** and **11** are showing nice docking scores -7.38 and -6.85, respectively. Among this compound **10** is having binding affinity within the DNA gyrase in comparison to **11**. These *in-silico* findings are well supported by results of *in-vitro* antibacterial activity. The binding pattern of **10** with DNA gyrase was depicted in Figs 3,4 and clearly raveled that the compound **10** showed major bonding interactions with Glu 58, Asp 81 and Thr 173. The standard drug *Ciprofloxin* showed binding interactions with Asp 161 and Asp 57 with binding energy -7.82 (Table 2) which is close to docking score of compound **10.** Generally, substitution of functional groups such as F, OH, CH_3 and OCH_3 at phenyl group positions increases the free energy of binding [24]. Interestingly, OH substituted compounds show higher binding energy values compare with unsubstituted compounds.

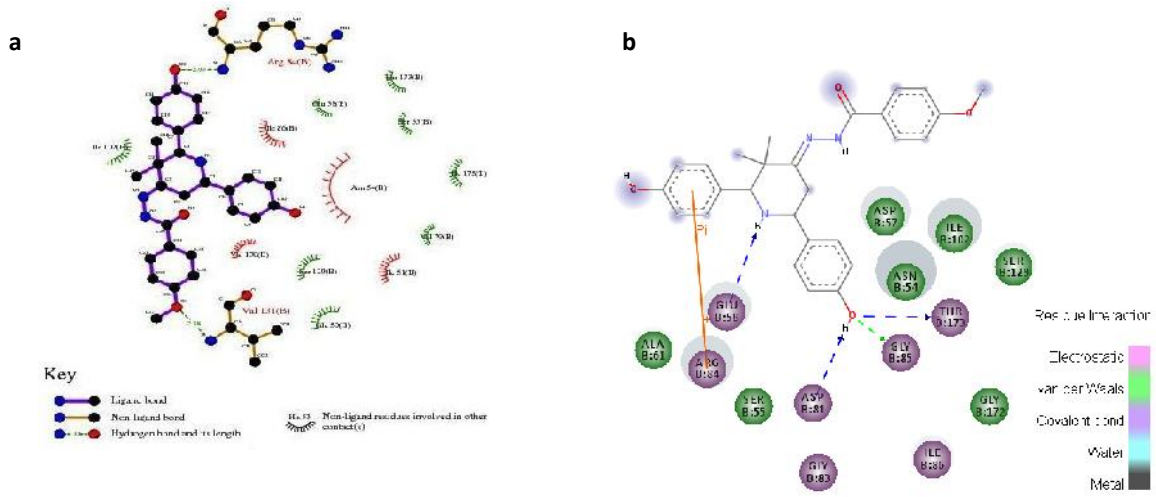


Fig. 3 Docked conformation of most active compound **10** with hydrogen bonding view in form of 2-D [(**a**) molecular docking server (**b**) Auto-dock 4.2]

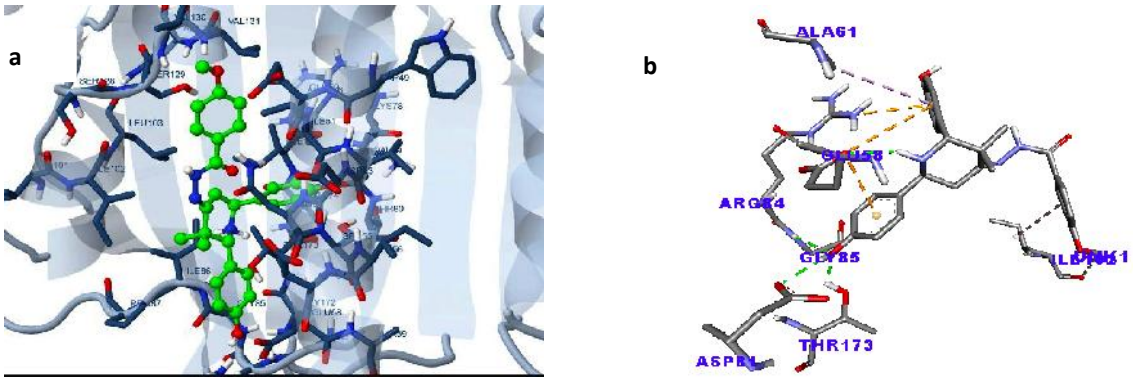


Fig. 4 Docking of representative ligands compound **10** into the binding site of DNA gyrase (PDB:3CU2D). [(**a**) molecular docking server (**b**) Auto-dock 4.2]

Conclusions

From all the above it could be concluded that, reaction of 3,3-Dimethyl-2,6-diarylpiperidin-4-ones with 4-methoxybezo hydrazide in ethanol in the presence of sufficient small of acetic acids smoothly affording (E)-N'-(3, 3- dimethyl- 2, 6- diarylpiperidin – 4 - ylidene)-4-methoxybenzohydrazide in good yields. The synthesized compounds exhibit promising antibacterial properties especially, **10** and **11**which reveal the best antibacterial activity among all the prepared analogues. Auto-Dock and molecular docking server have been used to assess the predictive power of each docking and scoring function. Our results suggest that all docking programs studied here do a reasonable job in docking and should aid significantly the drug discovery process. However, Auto-Dock consistently outperformed as compared to other program and was found to be relatively more useful than molecular docking server. Auto-dock result clearly revealed that the compound **10** showed major bonding interactions with Glu 58, Asp 81 and Thr 173. So compound **10** is able to enter next phase of drug development.

References

[1] A.R. Kartrizky, Compere. Heteocycl. Chem., 5 **(1995)** 20–24

[2] H.I.E.L. Subbagh, S.M. Abu-Zaid, M.A. Mahran, F.A. Badria, A.M. Alafaid, J. Med. Chem., 43 **(2000)** 2915–2921.

[3] A.A. Watsona, G.W.J. Fleet, N. Asano, R.J. Molyneux, R.J. Nugh, Phytochemistry., 56 **(2001)** 265–295.

[4] N. Rameshkumar, A. Veena, R. Ilavarasan, M. Adirja, P. Shanmugapandian, S.K. Sridhar, Biol. Pharm. Bull., 26 **(2003)** 188–193.

[5] C.R. Ganellin, R.G.W. Spickett, J. Med. Chem., 8 **(1965)** 619–625.

[6] M.X. Wei, L. Feng, X.Q. Li, X.Z. Zhou, Z.H. Sho, Eur. J. Med. Chem., 44 **(2009)** 3340–3344.

[7] P. Parthipan, G. Aridoss, P. Rathika, V. Ramkumar, S. Kabilan, Bioorg. Med.Chem. Lett., 19 **(2009)** 6981–6985.

[8] S. Pyne , P. Gayathri ,Bioinformatics Ind. J., 3 (**2005**), 11 –12.

[9] DI. Kuntz, Science., 257 **(1992)** 1078–1082.

[10] J. Drews, Science., 287 **(2000)** 1960–1964.

[11] I. Muegge , M. Rarey, Rev Comp Chem., 17 **(2001)** 1 –60.

[12] SF.Sousa, PA. Fernandes, MJ.Ramos, Struct Funct Bioinf., 65 **(2006)** 15–26.

[13] D.S Goodsell , GM. Morris , AJ. Olson , J Mol Recognit., 9 **(1996)** 1-5.

[14] F. Osterberg , GM. Morris , MF. Sanner , AJ. Olson , DS. Goodsell, Proteins-Structure Function and Bioinformatics., 46 **(2002)** 34-40.

[15] A. Subhasri and C. Anbuselvan, Anal. Methods., 6 **(2014)** 5596–5609.

[16] G. Thiyagarajan, P. Anjana, P. Nithya, P. Ashutosh, Int. J. Org. Chem., 1 **(2011)** 71.

[17] A.E Eakin, O. Green, N. Hales, G.K. Walkup, S. Bist, A. Singh, G. Mullen, J. Bryant, K. Embrey, N. Gao, A. Breeze, D. Timms, B. Andrews, M. Uria-Nickelsen, J. Demeritt, J.T. Loch, K. Hull, A. Blodgett, R.N Illingworth, B. Prince, P.A Boriack-Sjodin, S. Hauck, L.J Macpherson, H. Ni, B. Sherer, Antimicrob.Agents Chemother., 56 **(2012)** 1240-1246.

[18] GM. Morris, DS. Goodsell, RS. Halliday, R. Huey, WE. Hart, RK. Belew, AJ. Olson, J. Comp. Chem., 19 **(1998)** 1639–1662.

[19] Bikadi, Z., Hazai, E. J. Cheminf., 1 **(2009)** 15.

[20] T. A. Halgren, J. Com. Chem., 17 **(1998)** 490-519.

[21] F. J. Solis and R. J. B. Wets, Mathematics of Operations Research, 6 **(1981)** 19-30.

[22] G. James, N. Sherman, Microbiology, A Laboratory Manual, 3rd ed., The Benjamin Publishing Company, California., **(1992)** 77.

[23] R. Murray, E.J. Baron, M.A. Pfaller, F.C. Tenover, R.H. Yolke, Manual of Cilinical Biology, ASM, Washington DC., **(1995)** 6.

[24] S. Shahavar Sulthana, S. Arul Antony, C. Balachandran, S. Syed Shafi, Bioorg. Med. Chem. Lett., 25 **(2015)** 2753–2757.

Access this Article in Online	
	Website: www.ijcrcps.com
	Subject: Chemistry
Quick Response Code	
DOI: 10.22192/ijcrcps.2016.03.11.008	

How to cite this article:

G. Sundaraselvan and S. Darlin Quine. (2016). Synthesis, Structure-based molecular design of some novel (E)-N'-(3,3-dimethyl-2,6-diarylpiperidin-4-ylidene) -4-methoxybenzohydrazide as DNA gyrase inhibitors. Int. J. Curr. Res. Chem. Pharm. Sci. 3(11): 47-55. **DOI:** http://dx.doi.org/10.22192/ijcrcps.2016.03.11.008