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# *Molecular Docking and Quinolone Derivatives Synthesis and Antibacterial Activity*

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## *Abstract*

The quinolone antibiotics arose in the early 1960s, with the first examples possessing a narrow spectrum of activity with unfavourable pharmacokinetic properties. Over time, the development of new quinolone antibiotics has led to improved analogues with an expanded spectrum and high efficacy. Nowadays, quinolones are widely used for treating a variety of infections. Quinolones are broad-spectrum antibiotics that are active against both Gram-positive and Gram-negative bacteria, including mycobacteria, and anaerobes. They exert their actions by inhibiting bacterial nucleic acid synthesis through disrupting the enzymes topoisomerase IV and DNA gyrase, and by causing breakage of bacterial chromosomes. However, bacteria have acquired resistance to quinolones, like other antibacterial agents, due to the overuse of these drugs. Mechanisms contributing to quinolone resistance are mediated by chromosomal mutations and/or plasmid gene uptake that alter the topoisomerase targets, modify the quinolone, and/or reduce drug accumulation by either decreased uptake or increased efflux. This research discusses the synthesis of novel derivatives of quinolones by novel strategy and their molecular docking studies.

***Keywords:*** *Quinolone, Antibacterial, Naphthyridines, Agar dilution*

## *Introduction*

The quinolones are a family of antibiotics containing a bicyclic core structure related to the compound 4-quinolone (Figure 1). Since their discovery in the early 1960s, they have gained increasing importance as key therapies to treat both community-acquired and severe hospital-acquired infections. The first quinolone antibiotic is generally considered to be nalidixic acid, which was reported in 1962 as part of a series of 1-alkyl-1,8-naphthyridines prepared at the Sterling- Winthrop Research Institute. However, a 2015 perspective that examined the origins of quinolone antibiotics in greater detail points out that the author of the 1962 publication (George Lesher) described the isolation of-chloro-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid in the late 1950s as a by-product of chloroquine synthesis, with modest antibacterial activity leading to further work on analogues, including nalidixic acid. Around the same time, Imperial Chemical Industries (ICI) published patent applications with anti- bacterial quinolones, including a 6-fluoroquinolone.

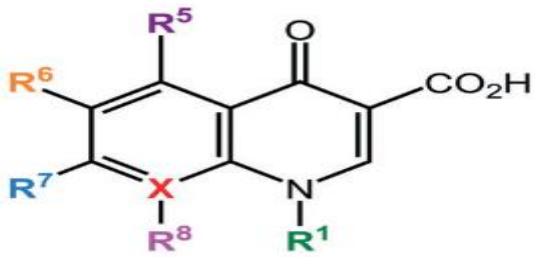


**Figure 1: Core structure of quinolone antibiotics. There are 6 important positions for modifications to improve the activity of the drug: R1, R5, R6, R7, R8, and X. X =C defines quinolones, X=N defines naphthyridones.**

Nalidixic acid is a narrow-spectrum agent against enteric bacteria used for treating uncomplicated urinary tract infections (UTIs) [1-5]. During the 1970s–1980s, the coverage of the quinolone class was expanded significantly by the breakthrough development of fluoroquinolones, which show a much broader spectrum of activity and improved pharmacokinetics compared to the first-generation quinolone. Those fluoroquinolones, such as ciprofloxacin and ofloxacin, are active against both Gram-negative and Gram-positive pathogens; importantly, they are also active against the causative agent of tuberculosis, Mycobacterium tuberculosis. Quinolones have been favoured as antibiotics for more than five decades because of their high potency, broad spectrum of activity, favourable bioavailability, convenient formulations, and high serum concentrations, as well as a comparatively low incidence of side effects [6-8]. Quinolones are widely prescribed for several different types of human infections, with side effects including gastrointestinal reactions, CNS reactions, genotoxicity, photo-toxicity, and some minor adverse effects. The quinolone class of antibiotics inhibits the DNA synthesis of bacteria by disrupting the bacterial topoisomerase type II, inhibiting the catalytic activity of DNA gyrase and topoisomerase IV. These two enzymes are critical bacterial enzymes that regulate the chromosomal supercoiling required for DNA synthesis. Over time, quinolone resistance has become a serious problem among many emerging resistant pathogens. The mutations generated by the bacteria against quinolones are generally located on the target enzyme binding sites in DNA gyrase and topoisomerase IV [9-11].

## *Experimental section*

Chemical reagents and all solvents used in this study were purchased from Glenmark and Ranbaxy Chemicals. 2-Bromo1-(naphthalen-2-yl) ethanone (7) was prepared according to the literature method. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The IR spectra were obtained on a Shimadzu 470 spectrophotometer (potassium bromide disc). NMR spectra were recorded on a Bruker 500 spectrometer and chemical shifts are reported in parts per million relatives to tetramethylsilane (TMS) as an internal standard. Elemental analyses were carried out on a CHN-O rapid elemental analyzer (GmbH-Germany) for C, H and N, and the results were within ± 0.4% of the theoretical values. Merck silica gel 60 F254 plates were used for analytical TLC.

### *General procedure for the synthesis of 7-[4-[2-(naphthalen-2-yl)-2-oxoethyl] piperazinylquinolones (5a-c)*

A mixture of 2-bromo-1-(naphthalen-2-yl) ethanone 7 (0.55 mmol), quinolone 1-3 (0.5 mmol) and NaHCO3 (0.5 mmol) in DMF (5 ml), was stirred at room temperature for 72 h. After consumption of quinolone, water (20 ml) was added and the precipitate was filtered, washed with water, and crystallized from methanol-chloroform (9:1) to give compounds 5a-c.

### *1-Cyclopropyl-6-fluoro-1,4-dihydro-7-[4-[2-(naphthalen-2-yl)-2-oxoethyl] piperazin-1-yl]-4-oxo-3-quinoline carboxylic acid (5a)*

Yield: 60%; m.p.: 175-177 ºC; IR (KBr, cm-1), 1680 and 1721 (C=O), 3441 (OH); 1 H NMR (DMSO-d6) : 1.01-1.31 (m, 4H, cyclopropyl), 2.75-2.89 (m, 4H, piperazine), 3.25-3.38 (m, 4H, piperazine), 3.75-3.86 (m, 1H, cyclopropyl), 4.11 (s, 2H, COCH2), 7.55- 7.72 (m, 3H, H-8 quinolone, H-6 and H-7 naphthyl), 7.90 (d, 1H, J=13.32 Hz, H-5 quinolone), 7.94-8.07 (m, 3H, H-4, H-5 and H-8 naphthyl), 8.12 (d, 1H, J=8.05 Hz, H-3 naphthyl), 8.65 (s, 1H, H-1 naphthyl), 8.72 (s, 1H, H-2 quinolone), 15.20

### *General procedure for the synthesis of 7-[4-[2-(naphthalen-2-yl)-2-hydroxyimino ethyl]piperazinyl-quinolones (5d-f)*

A solution of 2-bromo-1-(naphthalen-2-yl) ethanone 7 (249 mg, 1.0 mmol) and hydroxylamine hydrochloride (209 mg, 3.0 mmol) in methanol (5 ml) was stirred at room temperature for 24 h. Water (25 ml) was added and the precipitate was filtered and washed with water to give 2-bromo-1-(naphthalen-2-yl) ethanone oxime (8a) which was used without further purification for next step. Yield: 80%; m.p.: 164-165ºC; IR (KBr, $cm^{-1}$) max: 1615 (C=N), 3250 (OH). A mixture of compound 8a (0.55 mmol), quinolone 1-3 (0.5 mmol) and NaHCO3 (0.5 mmol) in DMF (5 ml) was stirred at room temperature for 72 h. After consumption of quinolone, water (20 ml) was added and the precipitate was filtered, washed with water and crystallized from methanol chloroform (9:1) to give compounds 5d-f.

### *General procedure for the synthesis of 7-[4-[2-(naphthalen-2-yl)-2-methoxyimino ethyl]piperazinyl quinolones (5g-i)*

To a stirred solution of 2-bromo-1-(naphthalen-2-yl) ethanone 7 (498 mg, 2.0 mmol) in methanol (8 ml) at room temperature, was added 25% solution of O-methyl hydroxyl ammonium chloride in diluted HCl (1002 mg, 3.0 mmol). After 3 days stirring at room temperature, water (25 ml) was added and the precipitated solid was filtered, washed with water, and dried to give 2-bromo-1-(naphthalen2-yl) ethanone O-methyl oxime (8b) which was used without further purification for next step. Yield: 46%; m.p.: 45-46 ºC; IR (KBr, cm-1) max: 1616 (C=N). A mixture of compound 8b (0.55 mmol), quinolone 1-3 (0.5 mmol) and NaHCO3 (0.5 mmol) in DMF (5 ml), was stirred at room temperature for 72 h. After consumption of quinolone, water

(20 ml) was added and the precipitate was filtered, washed with water and crystallized from methanol-chloroform (9:1) to give compounds 5g-i.

### *1-Cyclopropyl-6-fluoro-1,4-dihydro-7-[4-[2-(naphthalen-2-yl)-2-methoxyimino ethyl]piperazin-1-yl]-4- oxo-3-quinoline carboxylic acid (5g)*

Z-isomer; Yield: 43%; m.p.: 220-221ºC; IR (KBr, $cm^{-1}$) max: 1634, 1731 (C=O), 3452 (OH); 1 H NMR (CDCl3):1.11-1.19 (m, 2H, cyclopropyl), 1.30-1.35 (m, 2H, cyclopropyl), 2.74-2.82 (m, 4H, piperazine), 3.25-3.32 (m, 4H, piperazine), 3.45-3.50 (m, 1H, cyclopropyl), 3.86 (s, 2H, N=C-CH2), 4.05 (s, 3H, NOCH3), 7.28 (d, 1H, J=7.00 Hz, H-8 quinolone), 7.47-7.51 (m, 2H, H-6 and H-7 naphthyl), 7.80-7.90 (m, 3H, H-4, H-5 and H-8 naphthyl), 7.97 (dd, 1H, J=8.50 and 1.5 Hz, H-3 naphthyl), 7.98 (d, 1H, J=13.00 Hz, H-5 quinolone), 8.27 (d, 1H, J=1.4 Hz, H-1 naphthyl), 8.73 (s, 1H, H-2 quinolone), 15.18 (s, 1H, COOH). 13C NMR (125 MHz, DMSO-d6): 8.00, 36.30, 49.86, 50.90, 52.93, 62.44, 107.00, 107.14, 111.23, 111.42, 119.04, 119.10, 124.43, 126.86, 126.93, 127.21, 127.96, 128.00, 128.99, 132.74, 133.08, 133.62, 139.58, 145.67, 148.43, 152.50, 154.63, 166.42, 176.81.12

### *Antibacterial Activity*

Agar-dilution method was utilized for determination of MIC. Compounds 5a-l were evaluated for their antibacterial activity using agar-dilution method. Twofold serial dilutions of the compounds and reference drugs 1-3 were prepared in Mueller-Hinton agar. Drugs (10.0 mg) were dissolved in DMSO (1 ml) and the solution was diluted with water (9 ml). Further progressive double dilution with melted Mueller Hinton agar was performed to obtain the required concentrations of 100, 50, 25, 12.5, 6.25, 3.13, 1.56, 0.78, 0.39, 0.19, 0.098, 0.049, 0.025, 0.013, 0.006, 0.003 and 0.0015 µg $ml^{-1}$. The bacteria inocula were prepared by suspending overnight colonies from Mueller-Hinton agar media in 0.85% saline. The inocula were adjusted photometrically at 600 nm to a cell density equivalent to approximately 0.5 McFarland standard (1.5 ×108 CFU/ml). The suspensions were then diluted in 0.85% saline to give 107 CFU/ml. Petri dishes were spot inoculated with 1 µl of each prepared bacterial suspension (104 CFU/spot) and incubated at 35-37 ºC for 18 h. The minimum inhibitory concentration (MIC) was the lowest concentration of the test compound, which resulted in no visible growth on the plate. To ensure that the solvent had no effect on bacterial growth, a control test was performed with test medium supplemented with DMSO at the same dilutions as used in the experiment (Table 1) [12,13].

**Table 1. In vitro antibacterial activities of compounds 5a-l Against Selected Strains (MICs in g ml-1).**

| Compound | X | Y | R | *S.a.*[a] | MRSA I | MRSA II | *S. e.* | *B. s.* | *E. c.* | *K. p* | *P. a.* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 5a | CH | O | C-Pr | 0.19 | 0.19 | 0.19 | 0.39 | 0.098 | 0.006 | 0.003 | 0.39 |
| 5b | CH | O | Et | 0.78 | 1.56 | 1.56 | 1.56 | 0.78 | 0.049 | 0.024 | 1.56 |
| 5c | N | O | Et | 0.78 | 0.78 | 0.78 | 0.78 | 0.39 | 0.098 | 0.049 | 0.78 |
| 5d | CH | NOH | c-Pr | 0.098 | 0.098 | 0.098 | 0.098 | 0.049 | 0.098 | 0.098 | 6.25 |
| 5e | CH | NOH | Et | 0.39 | 0.098 | 0.098 | 0.39 | 0.049 | 0.098 | 0.049 | 3.13 |
| 5f | N | NOH | Et | 0.78 | 0.78 | 0.78 | 0.78 | 0.19 | 3.13 | 0.39 | >100 |
| 5g | CH | NOMe | c-Pr | 0.78 | 0.78 | 0.78 | 0.39 | 0.19 | 0.78 | 0.19 | 50 |
| 5h | CH | NOMe | Et | 1.56 | 3.13 | 3.13 | 1.56 | 0.78 | 0.39 | 0.19 | 12.5 |
| 5i | N | NOMe | Et | 3.13 | 3.13 | 3.13 | 3.13 | 0.78 | 1.56 | 0.78 | 100 |
| 5j | CH | NOBn | c-Pr | >100 | >100 | >100 | 100 | 50 | 12.5 | 6.25 | >100 |
| 5k | CH | NOBn | Et | >100 | >100 | >100 | >100 | >100 | 50 | 1.56 | >100 |

### *Results and Discussion*

The efficient synthetic route to obtain N-[2-(2-naphthyl)ethyl]piperazinyl quinolones 5a-l is outlined in Figure 2. The starting compound 2-acetylnaphthalene 6 was converted to 2-(bromoacetyl) naphthalene 7 by treating with $Br_2$ in $CHCl_3$. Compound 7 was converted to oxime 8a by stirring with 3 equivalents of hydroxylamine hydrochloride in methanol at room temperature. Similarly, the oxime ethers 8b, c was prepared by reaction of compound 7 with methoxylamine hydrochloride or O-benzylhydroxylamine hydrochloride. Reaction of quinolones (1, 2 or 3) with bromoketone 7 or bromooxime derivatives 8a-c in DMF, in the presence of NaHCO3 at room temperature afforded corresponding ketones 5a-c and oxime derivatives 5d-l, respectively. In the reaction of piperazinyl quinolones 1-3 with bromooxime derivatives 8a-c, compounds 5e, 5g-j and 5l were isolated as pure Z-isomer while compounds 5d, 5f and 5k were obtained as a mixture of E- and Z-isomers, predominantly in the E-configuration. The stereochemical assignment of the oxime derivatives 5d-l was elucidated by $^{1}H$ and $^{13}C$ NMR spectroscopy. It is known from the literature that the assignment of geometry in substituted ethanone oximes is possible based on the chemical shifts of the methylene attached to the imino-group. The selected $^{1}H$

and $1^3$C NMR spectroscopic data of Z and E-isomers are presented in Table 2. In Z-isomers, the methylene protons are deshielded by the presence of the proximal oxygen of oxime function and appeared lower field at 3.81-3.89 ppm compared to the corresponding E-isomers (3.51-3.54 ppm).

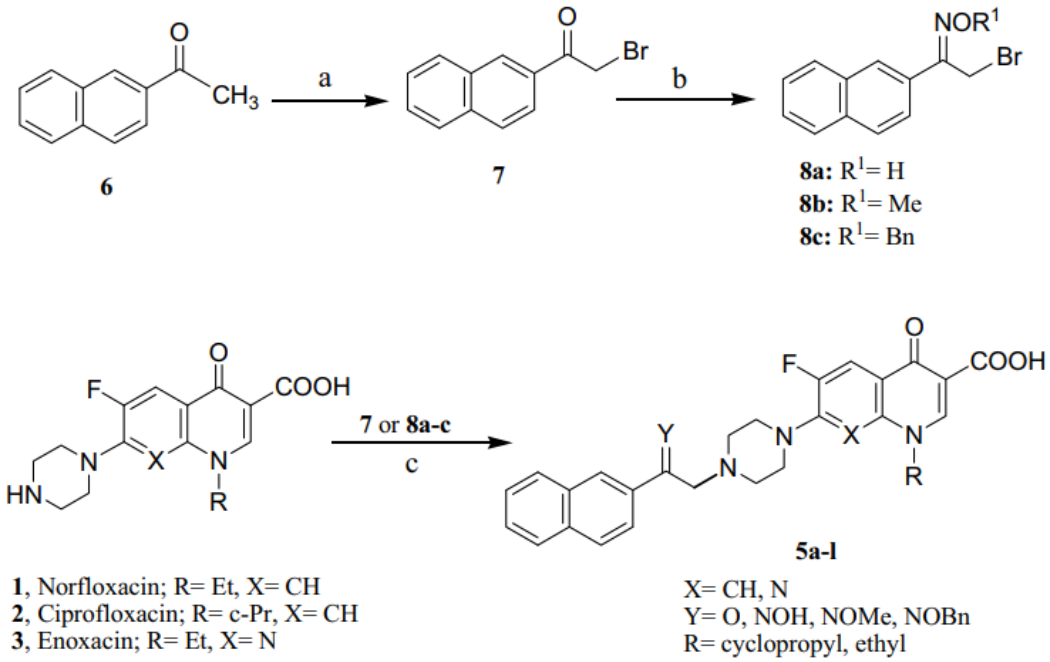


**Figure 2: Synthesis of N-[2-(2-naphthyl) ethyl] piperazinyl quinolones 5a-l. Reagents and conditions: (a) Br2, CHCl3, r.t. (b) appropriate hydroxylamine hydrochloride derivative, MeOH, r.t.; (c) DMF, NaHCO3**

**Table 2: Selected 1H and 13C NMR spectroscopic data related to methylene group attached to C=N of Z- and E-Oxime derivatives 5d-l.**

| Compound | X | R | R | Z-isomer | E-isomer | Z-isomer | E-isomer |
|---|---|---|---|---|---|---|---|
| 5d | CH | c-Pr | H | 3.85 | 3.54 | 52.56 | 61.39 |
| 5e | CH | Et | H | 3.86 | - | 52.54 | - |
| 5f | N | Et | H | 3.82 | 3.51 | 52.38 | 61.3 |
| 5g | CH | c-Pr | Me | 3.86 | - | 52.93 | - |
| 5h | CH | Et | Me | 3.84 | - | 52.5 | - |
| 5i | N | Et | Me | 3.81 | - | - | - |
| 5j | CH | c-Pr | Bn | 3.89 | - | 52.47 | - |
| 5k | CH | Et | Bn | 3.89 | Obscured | - | - |
| 5l | N | Et | Bn | 3.86 | - | 52.48 | - |

## *Molecular docking studies*

Molecular interactions play a key role in all biological reactions. Drugs are either mimicking or mitigating the effect of natural ligands binding to the receptor by exerting the pharmacological reactions. Computational methods are used to understand this mode of binding of ligands to their receptors which is called as Molecular Docking. It is an attempt to find out the "best" binding between different a set of molecules: a receptor and a ligand.

Molecular docking was conducted to study the potential binding interaction of derivatives with double-strand DNA. The crystallographic structure of the double-strand DNA was down- loaded from the Protein Data Bank (PDB ID: 1QC1). The conformation corresponding to the lowest binding free energy was selected as the most probable binding conformation. Herein, the calculation results showed that three molecules interacted with dsDNA in different sites and diverse properties. As shown in Figures 3 and Figure 4, for, the whole molecule structure was inserted into the major groove constituted by G15–G17 and G6– G7, with the energy of 5.24 kcal mol/1, through hydrogen bonding force. For 1, the main ligand intercalated into the minor groove based on C4–G6 and C18–G20, with the

energy of 5.84 kcal mol/1, through electrostatic binding effect. For 2, the main ligand was inserted into the minor groove composed of G13–G16 and G9–G10, with the energy of 6.04 kcal mol/1, through electrostatic binding and hydrogen bonding force. These results suggested that the presence of methyl groups in dipyridyl units was beneficial to the derivative interaction with DNA.

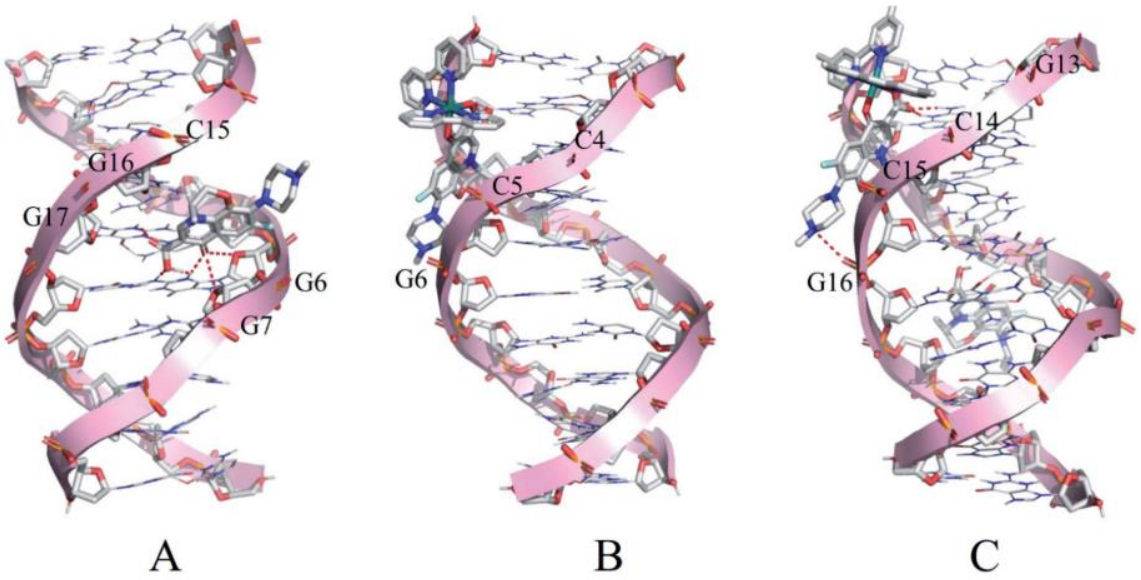


**Figure 3: Molecular docking studies.**

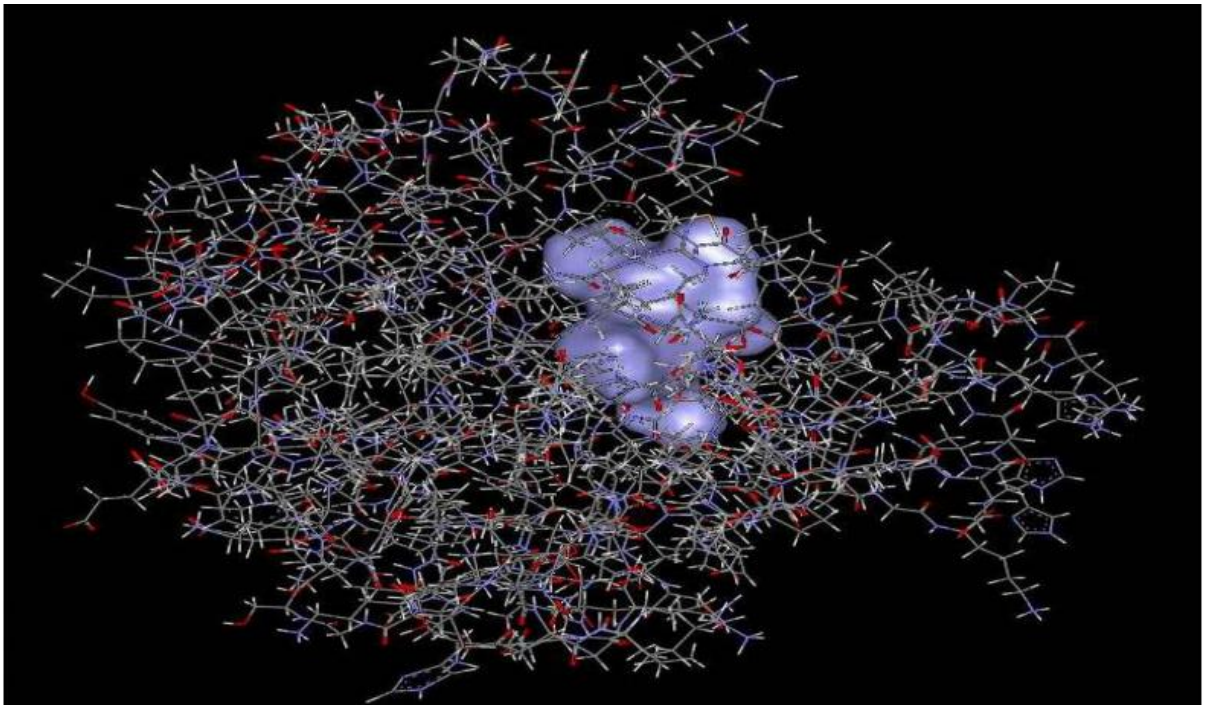

**Figure 4: Receptor drug interactions.**

## *Conclusion*

In this research article several quinolone derivatives were synthesised, and efficient yields was obtained by optimizing the reaction conditions. Molecular docking studies was executed, and the antibacterial activity of the synthesised compounds was carried out. Some of the new N-[2-(2-naphthyl)ethyl]piperazinyl quinolones containing a carbonyl related functional groups (oxo- or oxyimino-) on the ethyl spacer showed good antibacterial activity and modification of the position 8 and N-1 substituent on quinolone ring, and ethyl spacer functionality produced significant changes in activity against Gram-positive and Gram-negative bacteria.

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