Research in Pharmaceutical Sciences, October 2017; 12(5): 425-433
Received: November 2016
Accepted: May 2017

School of Pharmacy & Pharmaceutical Sciences
Isfahan University of Medical Sciences

Original Article

Docking study, synthesis and antimicrobial evaluation of some novel 4-anilinoquinazoline derivatives

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Abstract

A series of novel 4-anilinoquinazoline derivatives were designed and synthesized from benzoic acid through ring closure, chlorination or nucleophilic substitution. The structures of compounds were characterized by IR, ^{1}H-NMR and mass spectroscopy. All synthesized derivatives were screened for their antimicrobial activities against Gram-positive *(Staphylococcus aurous, Bacillus subtilis, Listeria monocitogenes)* and Gram-negative *(Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella entritidis*) bacteria and also for antifungal activities against *Candida albicans* using the conventional micro dilution method. Most of the compounds have shown good antibacterial activities, especially compound **4c** having highest activities against *E. coli* at 32 µg/mL concentration while the tested compounds did not exhibited remarkable antifungal activities. The potential DNA gyrase inhibitory activity of these compounds was investigated *in silico* using molecular docking simulation method. All compounds showed good results especially compound **4c** which showed the lowest ΔG_{bind} results (-8.16 Kcal/mol).

Keywords: 4-Anilinoquinazoline; Synthesis; Antimicrobial activity; Antifungal activity; Molecular docking

INTRODUCTION

The increasing rates of resistance to antimicrobial agents have caused severe health problems. Consequently, there is a rapid need of design and synthesis of newer antimicrobial agents (1). Some of the useful approaches for the discovery of new drugs are based on investigations of drug targets like enzymes or receptors (2,3). DNA gyrase is one of the attractive targets in *E. coli* which is involved in replication and transcription. This enzyme contains an ATPase activity which introduces negative supercoiling of circular DNA. The enzyme belongs to a superfamily of ATPases which is a known target for antibacterial agents since its blocking induces bacterial death (4,5). Quinazolines are a class of fused pyrimidine derivatives, which show a wide range of biological activities and used widely in the pharmaceutical industry, medicine and agriculture (6-11). Quinazolines act as an important backbone for a range of inhibitors of enzymes such as tyrosine kinase, thymidylate synthase and dihydrofolate reductase (12-14). In this heterocyclic family, 4-anilinoquinazoline derivatives have been reported as potent and selective inhibitors of protein kinases, such as epidermal growth factor receptor (EGFR). For example gefitinib and erlotinib are as dual EGFR- human epidermal growth factor receptor 2 (HER2) inhibitors, which are used for certain breast, lung and other cancers (15). Docking technique is a very important tool in the rational design of drugs which helps to predict the interactions between a ligand and a receptor molecule in order to predict the affinity and the activity of the small molecules. To the best of our knowledge, docking studies of 4-anilinoquinazoline derivatives with DNA-gyrase have not yet been studied (16).

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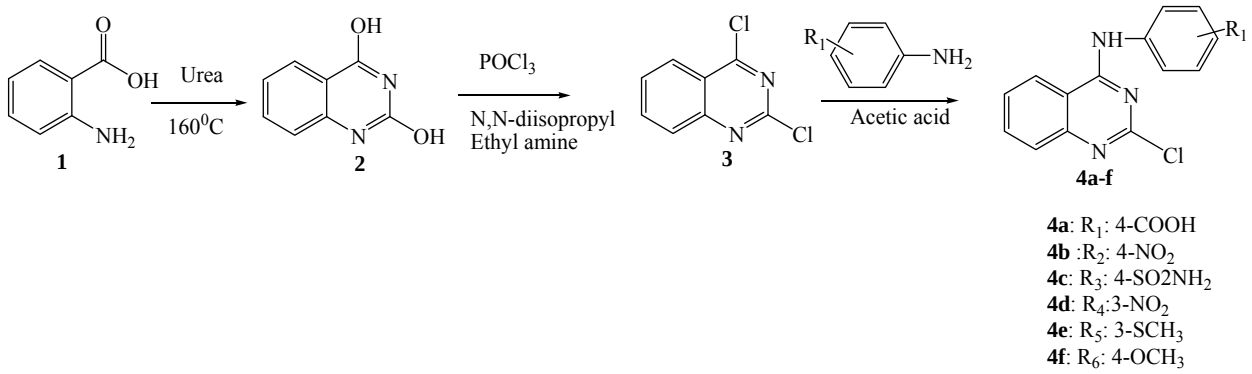
Website: http://rps.mui.ac.ir

DOI: 10.4103/1735-5362. 213988



Scheme 1. General reaction schemes for the synthesis of the target compounds **2, 3** and **4a-f**.

In the present work, we have focused on the effect of substitution of different aniline derivatives at the 4th position of the quinazoline ring and also on the antibacterial activities of these compounds. Compounds were prepared through the routine synthetic procedure in which anthranilic acid was cyclized with urea to yield quinazoline-2, 4-dione (17). The synthesis of 2, 4-dichloroquinazoline as the key intermediate was performed by reaction of quinazoline-2, 4-dione with phosphorus oxychloride (18). Aniline substitution occurred selectively at position 4 through nucleophilic aromatic substitution (Scheme 1). All 2-chloro-4-anilino-quinazoline derivatives were purified and structurally confirmed by mass spectrometry, infrared spectroscopy and ^{1}H nuclear magnetic resonance (^{1}H-NMR). Antimicrobial effects were evaluated using the serial dilution method against three Gram-positive bacteria (*Staphylococcus aureu*, *Bacillus subtilis, and Listeria monocitogenes)* and three Gram-negative bacteria *(Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella entritidis*) and also on the *Candida albicans*as, an yeast-like fungi strain. Synthesized analogues were docked into the binding pocket of DNA gyrase protein and their binding energies were calculated.

MATERIALS AND METHODS

All commercially available reagents and solvents used in this study were purchased from Merck Co (Merck, Germany). The reactions were monitored by thin-layer chromatography (TLC) on silica gel (F245 Merck plates). Melting points of the synthesized compounds were determined in open capillaries using electrothermal 9200 melting point apparatus (England) and uncorrected. ^{1}H-NMR spectra were obtained on a Bruker 400 MHz spectrometer (Germany) using TMS as internal reference with chemical shifts are reported in δ scale (ppm). Mass spectra were recorded on the Shimadzu Mass Spectrometer (Japan). IR spectra in KBr were recorded on a WQF-510 FT-IR spectrophotometer (China).

Antibacterial studies

The *in vitro* antimicrobial activity of the synthesized compounds were carried out by the serial dilution method against microorganism obtained from the Persian Type Culture Collection. Sabouraud dextrose agar and Mueller Hinton agar were used to culture fungal strains and bacterial strains, respectively. Standard antibacterial drug (ciprofloxacin) and antifungal drug (ketoconazole) were used for comparison.

Molecular docking studies

Molecular docking studies were performed in order to predict the interaction of synthesized compounds with the binding sites of DNA-gyrase (19,20). The crystal structure of the enzyme (PDB code 1KZN) with resolution 2.3 Å was chosen as the protein model for the current study. The structures of ligands were optimized using the HyperChem 7.0 software (http://www.hyper.com) as was explained previously (21). Auto Dock Tools

were used to prepare the molecules and parameters before submitting it for docking analysis with Auto Dock (21).

Polar hydrogen atoms were added while non-polar hydrogen atoms were merged and then, Gasteiger partial atomic charges were assigned to the ligands.

All rotatable bonds of ligands, defined by default of the program, were allowed to rotate during the automated docking process and then prepared protein and ligand structures were saved in the PDBQT format suitable for calculating energy grid maps. A grid box size of 46 × 46 × 46 Å points with a grid spacing of 0.375 Å was considered.

Lamarckian genetic algorithm (LGA) program with an adaptive whole method search in the Auto Dock was chosen to calculate the different ligand conformers (21,22). After 200 independent docking runs for each ligand, a cluster analysis was done. In according to the root mean square deviation (RMSD) tolerance of 2.0 Å conformations were clustered and were ranked by energy of which the conformation with the best scored pose with the lowest binding energy was selected for these ligands (22).

Chemistry

The synthetic route for the novel compounds is shown in Scheme 1**.** Synthesis of novel 4-anilino quinazoline derivatives was initiated from benzoic acid in three steps ring closure, chlorination and nucleophilic substitution.

The compounds **2** and **3** were synthesized in accordance with a previously reported method (17,18). Compound **3** as the key intermediate was treated with different substituted aniline derivatives in the presence of acetic acid to form title compound **4a-f** in high yield in order to obtain biologically active compounds.

*Synthesis of quinazoline-2, 4-dione (**2**)*

A mixture of 2-aminobenzoic acid (**1**) (68.5 g, 0.5 mol) and urea (210 g, 3.5 mol) was stirred at 160 ^{0}C for 12 h. The reaction mixture was filtered and the filtrate was washed with water to afford title compound (**2)** as a white solid in 90% yield (17).

Synthesis of 2, 4-dichloroquinazoline (***3***)

In a flask equipped with a reflux condenser, the reaction mixture containing the quinazolinone **2** (48.6 g, 0.3 mol) and excess amount of $POCl_3$ (200 mL) was stirred at room temperature, and then N,N-Diisopropyl-ethylamine (DIPEA) (77.6 g, 0.3 mol) was added dropwise to the mixture. The reaction was monitored by TLC and after complete consumption of quinazolinone **2** the product was triturated with *n*-hexane and isolated by filtration to yield compound **3** as light yellow crystals in 80% yield (17,18).

*General procedure for synthesis of new 4-anilino quinazoline derivatives (**4a-f**)*

Aniline derivatives (1 mmol) and 2, 4-dichloroquinazoline (**3)** (1 mmol) were dissolved in acetic acid and stirred at room temperature. Through the progress of reaction an insoluble product was produced which had a different R_f in TLC plate. The precipitate was collected by filtration, recrystallized in ethanol and characterized by different techniques.

Antibacterial evaluation

Following approach was used to demonstrate the minimal inhibitory concentrations (MICs) of the synthesized compounds using Microplate Alamar Blue Assay (MABA) method. All synthesized compounds were dissolved in DMSO and diluted with water to obtain concentration of 5120 µg/mL as a stock solution. The stock solution was diluted to obtain 2560 to 320 µg/mL concentrations. Mueller Hinton broth was used as a medium for bacterial growth and 96-well microtiter plates with U-shaped wells were used in this method. Each well was inoculated with 20 µL of each concentration with the exception of those wells acting as a growing control. After adding Alamar Blue reagent, the plates were sealed with parafilm and incubated at 37 ^{0}C for 24 h for bacteria and 48 h at 25 ^{0}C for the fungus (23,24). The MIC was defined as the lowest concentration that shows no growth by visual reading, which avoids discoloration from blue to pink. MBC and MFC results were obtained from each well that show no growth by Mueller Hinton agar plates and Sabouraud Dextrose agar for bacteria and fungi, respectively (25).

RESULTS

All synthesized compounds were docked into the active site of DNA gyrase B subunit and then were analyzed for binding free energy and their interactions with the receptor. Table 1 summarizes the binding free energy in Kcal/mole and interactions between 6 synthesized compounds and DNA-gyrase. In this table, all ligands interact through hydrogen bonding with the DNA-gyrase binding site. The distance of hydrogen bonds was shorter than 3.5 Å.

The best conformations from the docking procedure with the best scored pose and the lowest binding energy (~-7 – -8 kcal/mol) were selected for these ligands **(4a-f)** (Figs. 1-4).

The designed compounds were synthesized through conventional synthetic procedures and characterized by different methods. Structural properties of synthesized compounds are shown below.

Synthesis of 4-(2-chloroquinazolin-4-yl amino) benzoic acid (**4a**)

White solid (79%). M.p: 260-261 ^{0}C, (MS: m/z (%): 298 (M, 100), 300 (M+2), $C_{14}H_9N_4O_2Cl$ M.W. 299, ν_{max}, 3423.99 (N-H), 2923.56 (CH-arom), 1685.48 (C=O), 1606.41 (C=N), 758.85 (C-Cl) cm^{-1}; δ_H (400 MHz; DMSO-d_6): 7.8 (1H, t, J = 8 Hz, H-Qu), 7.9 (1H, d, J = 8 Hz, H-Qu), 8.0 (1 H, t, J = 8 Hz, H-Qu), 8.2 (2 H, d, J=8 Hz, H-Ar), 8.4 (2 H, d, J = 8 Hz, H-Ar), 8.7 (1 H, d, J = 8 Hz, H-Qu), 10.6 (1 H, s, NH-Ph, exchangeable with D_2O).

Table 1. Energy-based interactions for 6 novel 4-anilinoquinazoline derivatives docked into DNA gyrase.

Compound	Estimated free energy of binding (kcal/mol)	Hydrogen bond
4a	-7.97	Asp73 (3.07 Å), Arg136 (2.80 Å)
4b	-8.12	Asp73 (3.12 Å), Arg136 (2.83 Å)
4c	-8.16	Asp73 (3.21 Å), Glu50 (2.89 Å), Arg76 (2.94 Å)
4d	-7.07	Asp73 (3.23 Å), Gly77 (2.92 Å)
4e	-7.82	-
4f	-7.64	Asp73 (3.13 Å)
Clorobiocin	-6.48	Asp73 (2.54 Å), Arg136 (2.51 Å)

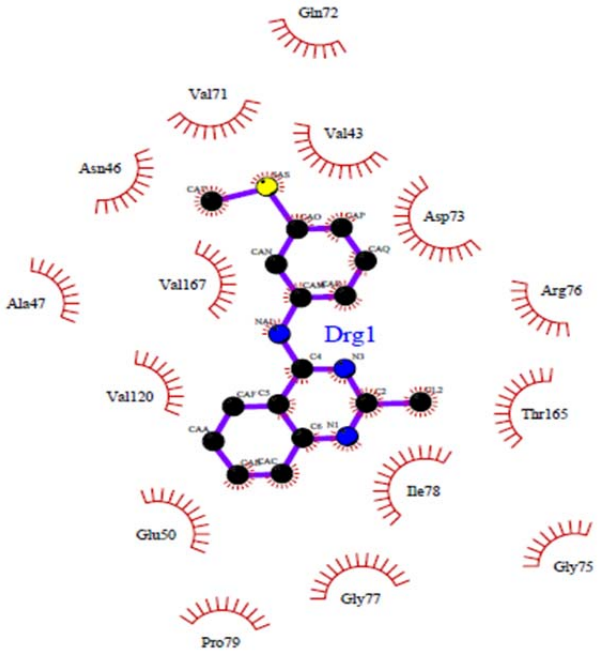


Fig. 1. Docked conformations of ligand structure **4e** in the binding site of DNA gyrase.

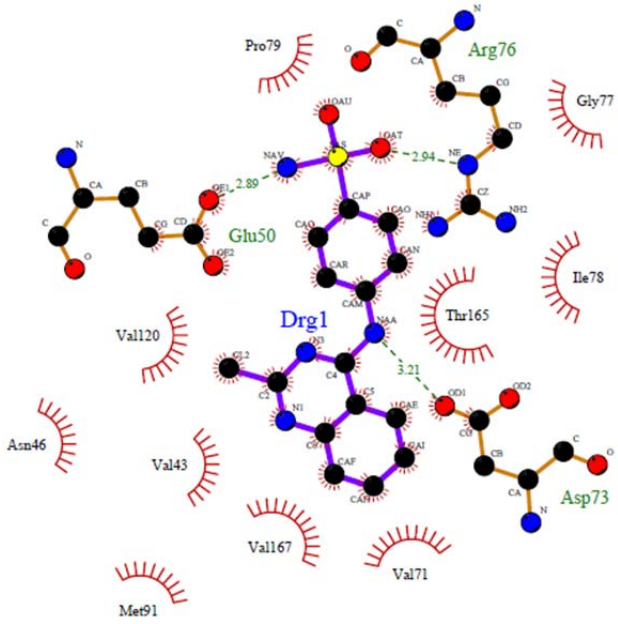


Fig. 2. Docked conformations of ligand structure **4c** in the binding site of DNA gyrase. Hydrogen bonds are shown by green dashed line.

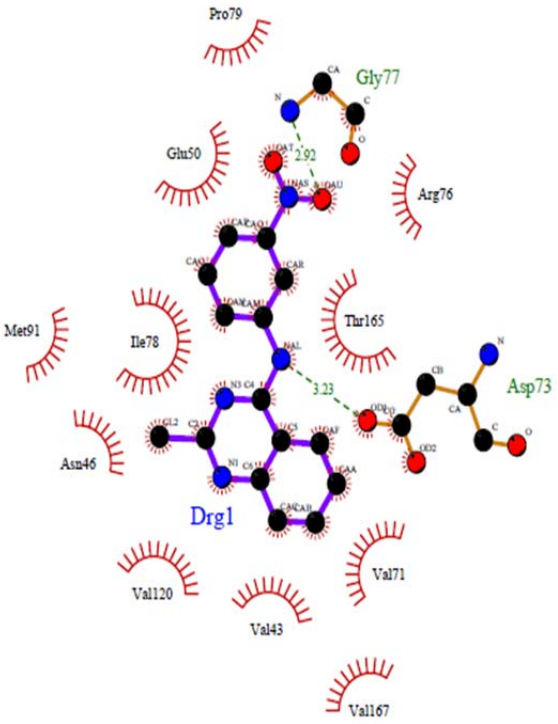


Fig. 3. Docked conformations of ligand structure **4d** in the binding site of DNA gyrase. Hydrogen bonds are shown by green dashed line.

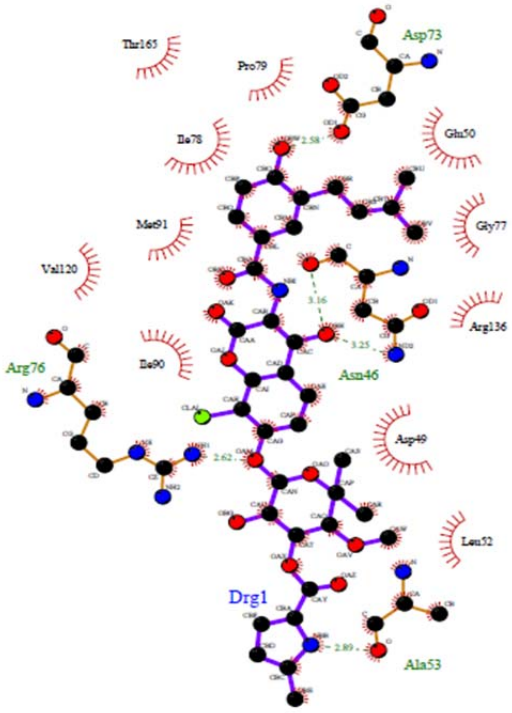


Fig. 4. Redocking results of clorobiocin the active site of DNA gyrase. Hydrogen bonds are shown by green dashed line.

Table 2. Minimum inhibitory concentration and minimum bactericidal concentration results of synthesized compounds against bacteria.

Compounds	Gram-negative bacteria (µg/mL)						Gram-positive bacteria (µg/mL)					
	Escherichia coli		*Pseudomonas aeruginosa*		*Salmonella entritidis*		*Staphylococcus aureus*		*Bacillus subtilis*		*Listeria monocitogens*	
	MIC	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**
4a	512	G	32	64	512	G	64	NA	512	G	512	G
4b	256	512	64	G	512	G	64	G	256	512	256	G
4c	32	64	128	256	512	G	128	NA	256	512	512	G
4d	64	NA	256	512	512	G	256	NA	512	G	512	G
4e	256	NA	512	G	128	256	512	G	128	256	256	512
4f	512	NA	512	G	512	G	512	NA	512	G	512	G

G, growth; MIC, minimum inhibitory concentration; MBC, minimum bactericidal concentration; NA, not applicable. Ciprofloxacin (standard antibacterial agent).

Table 3. Minimum inhibitory concentration (µg/mL) and minimum fungicidal concentration **(**µg/mL**)** results of synthesized compounds against fungi.

Compound		**4a**	**4b**	**4c**	**4d**	**4e**	**4f**
Candida albicans	MFC	NA**	G*	512	G	512	G
	MIC	512	512	256	NA	256	512

G*, growth; NA**, not applicable

2-chloro-N-(4-nitrophenyl) quinazolin-4-amine **(4b)**

Light yellow crystals (88%). M.p: 235-236 ^{0}C, (MS: m/z (%): 300 (M+, 100), 302 (M+2), $C_{14}H_9N_4O_2ClM.W.$ 300, ν_{max}, 3397.96 (N-H), 3050.83 (CH-arom), 2923.56 (CH-aliph), 1566.88 (C=N), 759.81 (C-Cl) cm^{-1}; δ_H (400 MHz; DMSO-d_6): 7.0 (1 H, d, J = 6.8 Hz, H-Ar), 7.70 (1 H, d, J = 6.8 Hz, H-Ar), 7.72 (1 H, t, J = 8 Hz, H-Qu), 7.76 (1 H, d, J = 8 Hz, H-Qu), 7.9 (1 H, t, J = 8 Hz, H-Qu), 8.6 (1 H, d, J = 8 Hz, H-Qu), 10.2 (1 H, s, NH-ph,exchangeable with D_2O).

4-amino-N-(2-chloroquinazolin-4-yl) benzene-sulfonamide **(4c)**

White crystal (90%). M.p. 250-251 ^{0}C, (MS:334 m/z (%): 335 (M+, 100), 337 (M+2), $C_{14}H_{11}N_4SO_2Cl$, M.W. 334, ν_{max}, 3354.57 (N-H), 3276.47 (CH-arom), 2925.48 (CH-aliph), 1571.7 (C=N), 1238.08 (C=S), 1147.44 (SO_2), 766.56 (C-Cl) cm^{-1}; δ_H (400 MHz; DMSO-d_6): 7.4 (1 H, s, NH-ph, exchangeable with D_2O), 7.7 (1 H, t, J = 7.6 Hz, H-Qu), 7.8 (1 H, d, J = 7.6 Hz, H-Qu), 7.9 (1 H, d, J = 8.8 Hz, H-Ar), 8.0 (1 H, t, J = 7.2 Hz, H-Qu), 8.06 (1 H, d, J = 6.8 Hz, H-Ar), 8.6 (1 H, d, J = 8 Hz, H-Qu), 10.5 (1 H, s, SO_2NH, exchangeable with D_2O).

2-chloro-N-(3-nitrophenyl) quinazolin-4-amine **(4d)**

Yellow crystal (90%). M.p. 195-196 ^{0}C. (MS: m/z (%): 301 (M+, 100), 303 (M+2), $C_{14}H_9N_4O_2Cl$ M.W. 300). ν_{max}, 3395.07 (N-H), 2920.66 (CH-arom), 2574.5 (CH-aliph), 1623.77 (C=N), 1530.24 (NO_2) 765.60 (C-Cl) cm^{-1}; δ_H (400 MHz;$CDCl_3$): 7.6 (2 H, t, J = 8Hz, H-Qu), 7.7 (1 H, s, NH-Ph, exchangeable with D_2O), 7.8 (3 H, d, J = 8 Hz, H-Qu,Ar), 8.0 (1 H, d, J = 8.0 Hz, H-Qu), 8.3 (1 H, d, J = 8 Hz, H-Ar), 8.5 (1 H, s, H-Ar).

2-chloro-N-(3-(methylthio) phenyl) quinazolin-4-amine **(4e)**

White solid (90%), M.p. 169-170 ^{0}C, (MS: m/z (%):300 (M+, 100), 302 (M+2), ($C_{15}H_{12}N_3Cl$ M.W. 300). ν_{max}, 3322.75 (N-H), 2921.63 (CH-arom), 2493.51 (CH-aliph), 1573.63 (C=N), 766.56 (C-Cl) cm^{-1};δ_H (400 MHz; DMSO-d_6): 3.4 (s, 3H, SCH_3), 7.1 (1H, d, J = 8 Hz, H-Ar), 7.4 (1H, t, J = 8 Hz, H-Ar), 7.6 (1 H, d, J = 8 Hz, H-Ar), 7.75 (1 H, t, J = 8 Hz, H-Qu), 7.78 (1 H, d, J = 8 Hz, H-Qu), 7.8 (1 H, s, H-Ar), 7.9 (1 H, t, J = 8 Hz, H-Qu), 8.6 (1 H, d, J = 8 Hz, H-Qu), 10.2 (s, 1 H, NH-ph, exchangeable with D_2O).

2-chloro-N-(4-methoxyphenyl) quinazolin-4-amine **(4f)**

Yellow solid (80%). M.p. 178-180 ^{0}C, (MS: m/z (%):286 (M+, 100), 288 (M+2), ($C_{15}H_{12}N_3OCl$ M.W. 285) ν_{max}, 3421.1 (N-H), 3252.36 (CH-arom), 2964.05 (CH-aliph), 1575.56 (C=N), 759.81 (C-Cl) cm^{-1}; δ_H (400 MHz; DMSO-d_6): 2.0 (s, 3H, OCH_3), 7.7 (1 H, t, J = 8 Hz, H-Qu), 7.8 (1 H, d, J = 8 Hz, H-Qu), 7.9 (1 H, t, J = 8 Hz, H-Qu), 8.0 (4 H, s, H-Ar), 8.7 (1 H, d, J = 8 Hz, H-Qu).

All synthesized compounds were tested for antibacterial activity against Gram-positive *(Staphylococcus aurous, Bacillus subtilis, Listeria monocitogenes),* Gram-negative bacteria *(Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella entritidis*) and also for antifungal activities against *Candida albicans*. The results of biological effects are shown in Tables 2 and 3.

DISCUSSION

In the majority of the structures, hydrophobic sites of the ligands are conserved. The residue that interacts with the acceptor/donor site of the ligand through a hydrogen bonding differs depending on the ligand. The binding patterns of different ligands are also slightly different.

The nitrogen atom in the middle ring of all compounds except **4e** can form a strong hydrogen bond with Asp73 at distance 2.54 Å-3.23 Å, which is consistent with the decomposition analysis of the electrostatic interaction (Fig. 1). It is interesting that more complex stabilization might result from the hydrogen bonds between these ligands and Arg136 via electron withdrawing substitution on the phenyl ring. Although these interactions were also recognized for these derivatives, these are different from those present in **4c** (Glu50, Arg 76) and **4d** (Gly 77) and may be responsible for the activity changes (Figs. 2 and 3). These results are compatible with the X-ray cocrystal structure and earlier studies prove the important roles of those residues (26-28).

No hydrogen bond interaction between the **4e** compound and discussed residues was predicted. Because of the long distance (more than 3.5 Å) between the nitrogen atom at the middle ring of **4e** and the oxygen atom of Asp73, this ligand in the best pose with the lowest binding energy could not form a hydrogen bonding interaction, but in other compounds such as **4c** and **4d** could establish a hydrogen bond with Glu50, Arg76 **(4c)** and Gly77 **(4d)**.

These compounds also significantly preserve the DNA gyrase through hydrophobic contacts with Asn40, Val43, Val71, Arg76, Gly77, Ile78, Pro79, Met91, Val120, Thr163, Thr165 and Val167 that are important in hydrophobic interactions.

In all compounds it is clear that the hydrophobic pocket of the inhibitor binding site was occupied by 4-anilinoquinazoline or phenyl plus the groups substituted on these rings (28-30).

The docking procedure in this research was validated by redocking of chlorobiocin as a well-known inhibitor to the energy minimized DNA gyrase protein. The residues Asp73, Asn46 and Arg136 are important in developing hydrogen bond (Fig. 4) (30-32). The same is mainly true for our quinazoline derivatives, the only exception is the relatively weak hydrogen bond with Asn46. The best molecule in these series **(4c)** showed a high dock score of -8.16 kcal/mol in docking protocol. Rest of molecules showed an appropriate dock score ranging from –7.07 to -8.16 kcal/mol. So, the binding mode reported here suggests that these 4-anilinoquinazoline compounds act as DNA-gyrase inhibitors and show some key structural points to be considered in future optimization. The synthetic pathways to the intermediates and final compounds **(2-4f)** are presented in Scheme 1.

At first, anthranilic acid **1** was condensed with urea to produce quinazoline-2, 4-dione. Amino group in anthranilic acid acts as a nucleophile and attacks to carbonyl group of urea to produce the intermediate upon elimination of ammonia group. Simultaneous nucleophilic attacks of amino group in urea resulted in the production of the product **2** upon elimination of water molecule (33,34). Chlorination reaction was performed with $POCl_3$ to form intermediate **3**. In this reaction, diisopropyl ethylamine was used as a strong base (35). Finally the addition of different aniline derivatives provided the compound **4a-f** through S_NA_r reaction as presented in Scheme 1. The reaction was initiated by the nucleophilic attack of NH_2 to the fourth position of the quinazoline ring to displace the chlorine moiety (36).

All synthesized compounds were tested for antibacterial activity against Gram-positive (*Staphylococcus aurous, Bacillus subtilis, Listeria monocitogenes*) and Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella entritidis*) and also for antifungal activities against (*Candida albicans*).

Most of the synthesized compounds showed good activity against both the Gram-positive and Gram-negative bacterial species. Obtained results of screened compounds against Gram-negative organisms showed that compounds **4a**, **4b** and **4c** had the highest activities against *E. coli* at 32 μg/mL concentration. In case of Gram-positive bacteria, compounds **4a** and **4b** showed acceptable activity results against *Staphylococcus aureus*. Antibacterial study revealed that compounds showed better bacteriostatic activity than bactericidal activity.

Structure–activity relationship study based on the observed results indicated that in **4a-f**, the type of aryl substitution plays a controlling role in developing the exhibited biological properties. It has been noticed that, substitution on the phenyl group with an electron-withdrawing group such as a COOH, NO_2 or a sulfonamide group **4a**, **4b**, **4c** and **4d** (MIC:512, 256, 32 and 64 μg/mL) seems more favorable for enhancing the antibacterial activity than substitution with an electron-donating group such as methylthio and methoxy groups **4e**, **4f** (MIC:, 256 and 512 μg/mL). Compound with the COOH group in the para position of the phenyl ring showed high activity which could be due to the participation in hydrogen bonding interactions and improved solubility. NO_2 substitution at the para position of phenyl ring has also resulted in high activity against the bacteria. Compound with a sulfonamide group has also good effect against the bacteria which might be due to the increasing of ionization of the N-H group. Interestingly, introducing of SCH_3 group at the meta position, reduced antibacterial activity. This might be attributed to the donation of electrons to the benzene ring through inductive effect. Similarly, the compound containing OCH_3 group in para position has the least effect (37-39). Results of

antifungal study showed that almost all of the screened compounds have no antifungal activity against *C. albicans*, except compound **4e** which showed moderate activity at 256 µg/mL (Table 3).

CONCLUSION

In this study, in silico design, synthesis and evaluation of antimicrobial activity of six novel 4-anilinoquinazoline derivatives were reported. All compounds showed good antibacterial activity, especially against *E. coli* at 32 µg/mL concentration while no remarkable antifungal activities were observed for these compounds. Careful investigation in this series gave the compound **4c** as the most promising inhibitor of DNA-gyrase based on the docking score energies, hydrogen bonds distances and antimicrobial evaluation. Further developments are in progress to optimize new 4-anilinoquinazoline derivatives as potential antibiotic drug candidates in the future.

ACKNOWLEDGEMENTS

The content of this paper is extracted from the Ph.D thesis (No. 394158) submitted by Rezvan Rezaee Nasab which was financially supported by the Isfahan University of Medical Sciences, Isfahan, Iran.

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