Research Article

Synthesis, molecular docking and antimicrobial evaluation of some novel quinoline-3-carbaldehyde derivatives

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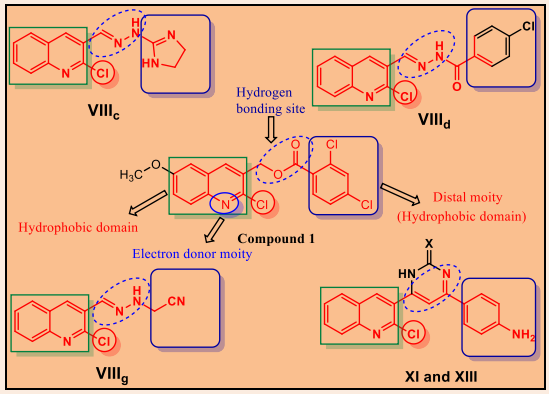
Abstract

Vilsmeier formulation of acetanilide afforded 2-chloroquinoline-3-carbaldehyde (II). Condensation of II with 4-aminoacetophenone produced chalcone III. Cyclocondensation of chalcone III with hydrazine hydrate, hydroxylamine hydrochloride, thiourea, guanidine hydrochloride, urea, metformine hydrochloride, and malononitrile produced the corresponding compounds IX-XV. Treating II with hydroxylamine hydrochloride produced 2-chloroquinoline-3-carbonitrile (IV). Treatment of IV with thiourea yielded 2-mercaptoquinoline-3-carbonitrile (V) that was reacted with alkyl halides and chloroacetanilides to afford thioether derivatives VI_{a-d} and acetanilide derivatives VII_{a-d} respectively. Compound II was condensed with different primary amines or substituted hydrazide to give $VIII_{a-j}$. All of the synthesized compounds were subjected to *in vitro* antimicrobial screening. The molecular docking was performed for all synthesized compounds to assess their binding affinity towards GlcN-6-P synthase enzyme in order to rationalize their antimicrobial activity in a qualitative way. The obtained data from the molecular modeling was strongly correlated with those obtained from the biological screening. The highest binding affinities were noticed for compounds XIII, $VIII_c$, $VIII_g$ and VI_d which showed the highest antimicrobial activities of this series.



Keywords: Quinoline, Vilsmeier–Haack, Chalcone, Antimicrobial, Molecular docking

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1. Introduction

Infectious and parasitic diseases are responsible for 23% of global deaths and the second ranking cause of death according to the World Health Organization. The other issues related to infectious diseases are their emerging resistance to most of the available antimicrobial agents.[1] Therefore, the need to the discovery of new antimicrobial agents is a necessity. Quinolines are a class of compounds well known for a long time and they have attracted the scientist's attention in the past decades, mainly due to their variety of applications in different fields particularly as organic synthesis[2,3] and pharmaceuticals.

Many reports showed that compounds containing quinoline subunit have been described as a scaffold to design new prototypes of drug-candidates with different biological activities and are used in different diseases as infectious diseases,[4] tuberculosis,[5] tumors,[6] multiple myeloma,[7] inflammatory diseases,[8] asthma,[9] hyperlipidemia,[10] diabetes,[11] convulsion,[12] and depression.[13] Glucosamine-6-phosphate synthase (L-glutamine:D-fructose-6-phosphate amidotransferase; GlcN-6-P synthase) catalyzes the formation of D-glucosamine 6-phosphate from D-fructose-6-phosphate using L-glutamine as the ammonia source.[14,15] Because *N*-acetylglucosamine is an essential building block of both bacterial cell walls and fungal cell wall chitin, the

enzyme is a potential target for antibacterial and antifungal agents.[16] Many 2-chloroquinoline derivatives have been docked and proved to be potent GlcN-6-P synthase (1XFF) inhibitors e.g. compound 1 (Figure 1).[17]

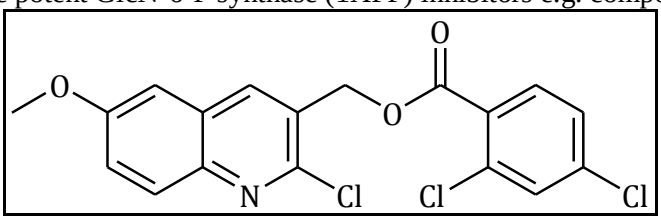


Figure 1 Compound 1 potent GlcN-6-P synthase (1XFF) inhibitor.

Based on the previous outcomes[18,19], we synthesized a series of quinoline derivatives attached to various functionalities that have been proved to possess antibacterial and antifungal activities aiming to synergize the antimicrobial activity. The newly synthesized derivatives were then evaluated for their antimicrobial activity against different gram-negative, gram-positive bacteria and fungi. Therefore, there is an urgent need for novel chemical entities that are particularly effective against gram-positive pathogens.[20,21] In continuation of our efforts in developing heterocycles of biological interest[22] and considering the significant role of quinoline in biological applications, we wish to report here the synthesis of a new derivatives containing quinoline moiety and evaluate their antimicrobial activities.

2. Results and discussion

2.1. Rationale and structure-based design

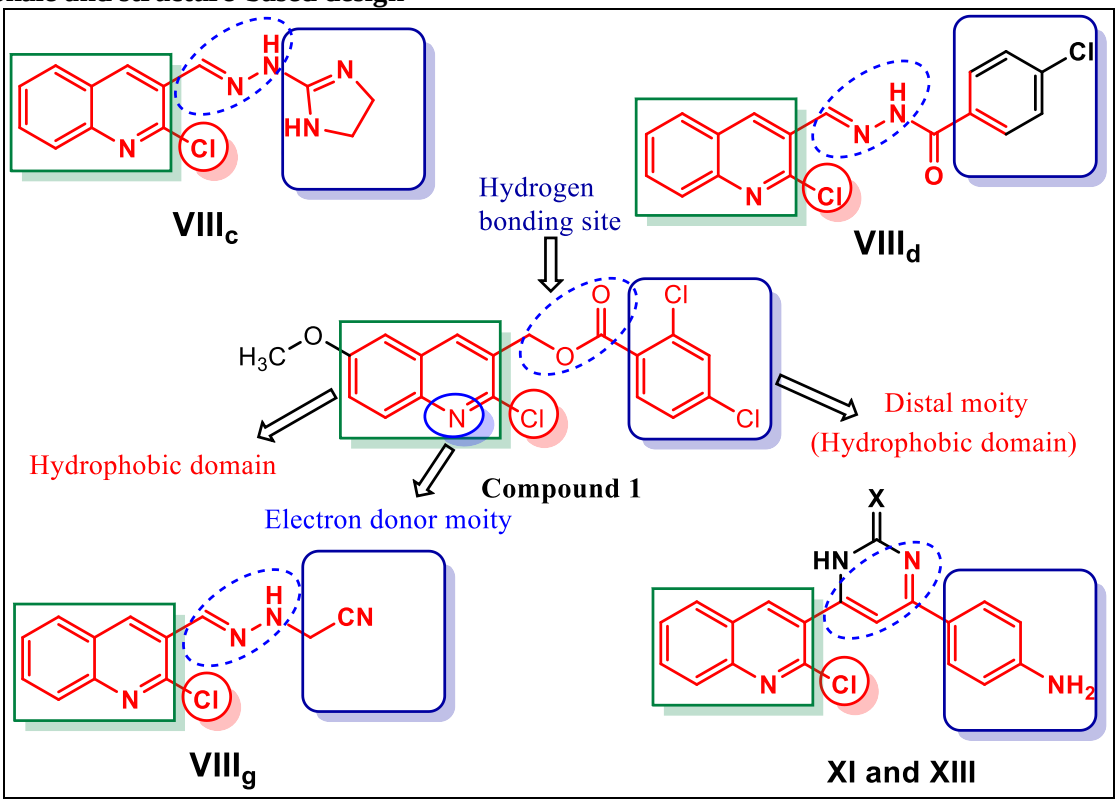


Figure 2 Structural similarities and pharmacophoric features of reported and selected designed quinolines as antimicrobials

Tabassum *et al*[17] synthesized many 2-chloroquinoline derivatives as GlcN-6-P synthase (1XFF) inhibitors. Compound 1 was proved to be the most active GlcN-6-P synthase (1XFF) inhibitor of this series. Figure (2) represents the structural similarities and pharmacophoric features of the reported antimicrobial quinoline and our designed compounds. Based on the previously mentioned fact, it appeared to us that considerable promise for discovering new antimicrobial might be found through the synthesis of structural analogs of this compound.

Figure (2) shows that structure of some designed final compounds fulfilled all the pharmacophoric structural requirements. These requirements include: the presence of 2-chloroquinoline moiety as hydrophobic portion, N as electron donor system, the presence of the linker of side chain as hydrogen bonding site and the distal moiety as

hydrophobic domain in many derivatives and CN in compound $VIII_g$ which stabilized by formation of four hydrogen bonds. The distal moiety is responsible for controlling the pharmacokinetic properties of the antimicrobial activity.

The present study was carried out to prepare the target compounds as hybrid molecules. These molecules formed of 2-chloroquinoline ring system joined, through linker atoms, with distal moiety (aromatic ring in many compounds) with different electronic environments to study the SAR of these compounds and the effect of each substituent on their antimicrobial activity hoping to obtain more potent antimicrobial agents.

2.2. Molecular docking study

In the present work, all the target compounds were subjected to docking study to explore their binding mode to GlcN-6-P synthase receptor, since GlcN-6-P synthase is a target for a remarkable variety of antimicrobial agents[17]. All modeling experiments were performed using Molsoft (ICM-Pro) program which provides a unique set of tools for the modeling of protein / ligand interactions. It predicts how small flexible molecule such as substrates or drug candidates bind to a protein of known 3D structure represented by grid interaction potentials. Each experiment used the biological target GlcN-6-P synthase downloaded from the Brookhaven Protein Databank. In order to qualify the docking results in terms of accuracy of the predicted binding conformations in comparison with the experimental procedure, the reported GlcN-6-P synthase inhibitor (compound 1) was used as a reference ligand. The docking study has been conducted to predict the binding mode and to rationalize the observed biological activity.

The obtained results indicated that all studied ligands have similar position and orientation inside the putative binding site of GlcN-6-P synthase receptor (PDB code 1XFF) which reveals a large space bounded by a membrane-binding domain which serves as an entry channel for substrate to the active site (Figure 3). In addition, the affinity of any small molecule can be considered as a unique tool in the field of drug design. There is a relationship between the affinity of organic molecules and the free energy of binding. This relationship can contribute in prediction and interpretation of the activity of the organic compounds toward the specific target protein.[23] The obtained results of the free energy of binding (ΔG) explained that most of these compounds had good binding affinity toward the receptor and the computed values reflected the overall trend (Table 1).

The proposed binding mode of compound 1 (Figure 3) **(**affinity value of -67.66 kcal/mol) revealed 3 H-bonds where, the N-group of 2-chloroquinoline formed one hydrogen bond with *Tryptophan74* (–NH group) with a distance of 2.62 Å. The carbonyl group of the linker formed one hydrogen bond with *Serine176* (–OH group) with distances of 2.76 Å. Furthermore 6-methoxy group at quinoline moiety formed one hydrogen bond with *Threonine76* (–OH group) with a distance of 2.01 Å. In addition the 2-chloroquinoline moiety occupied the hydrophobic pocket formed by *Tryptophan74*, *Isoleucine100*, *Cysteine1*, *Arginine73*, *Histidine71*, Alanine75, Asparagine98, Glycine99, Isolucine100 and *Threonine76*. On the other hand the 2,6-dichlorophenyl distal moiety occupied the hydrophobic pocket formed by *Serine176*, *Proline177*, *Lucine178*, *Valine179* and *Arginine26*. These interactions of compound 1 may explain the highest binding free energy and antimicrobial activity.

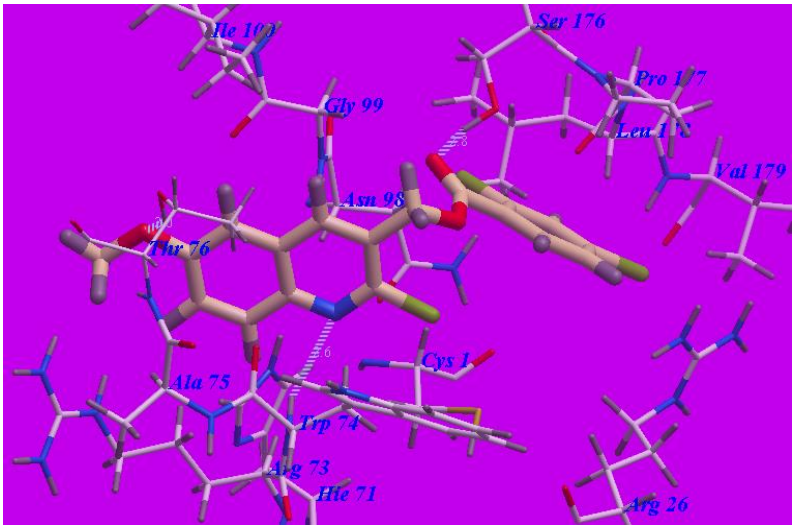


Figure 3 Predicted binding mode for compound 1 with 1XFF receptor. H-bonds are indicated by dotted lines.

The proposed binding mode of compound VIIIg (affinity value of -86.92 kcal/mol and 9 H-bonds) is virtually the same as that of compound 1 (Figure 4) where the N-group of 2-chloroquinoline formed one hydrogen bond with *Tryptophan74* (–NH group) with a distance of 2.72 Å. The NH of the linker formed two hydrogen bonds with *Threonine124* (–OH group) with distances of 2.03 Å and 2.52 Å, one hydrogen bond with *Aspartate123* (–O group) with a distance of 2.45 Å and fourth hydrogen bond with *Histidine86* (–NH group) with a distance of 2.59 Å. Furthermore CN distal moiety was stabilized by formation of four hydrogen bonds. It formed two hydrogen bonds with *Threonine76* (–NH and –OH group) with distances of 1.38 Å and 2.31 Å respectively, one hydrogen bond with *Arginine73* (–NH group) with a distance of 2.11 Å and fourth hydrogen bond with *Histidine77* (–NH group) with a distance of 1.66 Å. The 2-chloroquinoline moiety occupied the hydrophobic pocket formed by *Tryptophan74, Isoleucine100, Cysteine1*, *Arginine73, Histidine71*, Alanine75, Asparagine98, Glycine99, Isolucine100 and *Threonine76*. These interactions of compound VIIIg may explain the highest binding free energy and antimicrobial activity.

Moreover the proposed binding mode of compound VIIIc (affinity value of -74.89 kcal/mol and 3 H-bonds) is virtually the same as that of compound 1 and compound VIIIg (Figure 5) where the N-group of 2-chloroquinoline formed one hydrogen bond with *Tryptophan74* (–NH group) with a distance of 1.88 Å. The N of the linker formed one hydrogen bond with *Glycine99* (–NH group) with a distance of 2.24 Å. Furthermore the distal imidazole moiety formed one hydrogen bond with *Serine176* (–OH group) with distances of 3.68 Å. In addition the 2-chloroquinoline moiety occupied the hydrophobic pocket formed by *Tryptophan74, Isoleucine100, Cysteine1*, *Arginine73, Histidine71*, Alanine75, Asparagine98, Glycine99, Isolucine100 and *Threonine76*. On the other hand the distal imidazole moiety occupied the hydrophobic pocket formed by *Alanine172, Serine176, Proline177, Lucine178, Valine179* and *Arginine26*. These interactions of compound VIIIc may explain the highest binding free energy and antimicrobial activity.

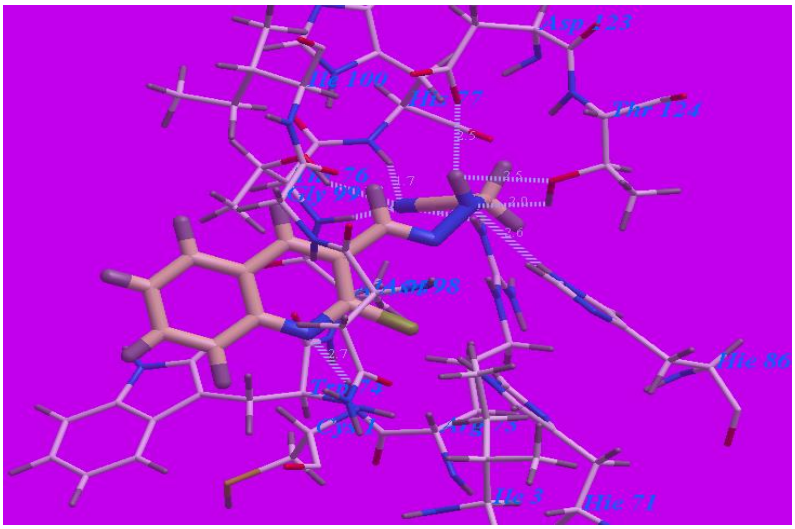


Figure 4 Predicted binding mode for $VIII_g$ with 1XFF receptor. H-bonds are indicated by dotted lines

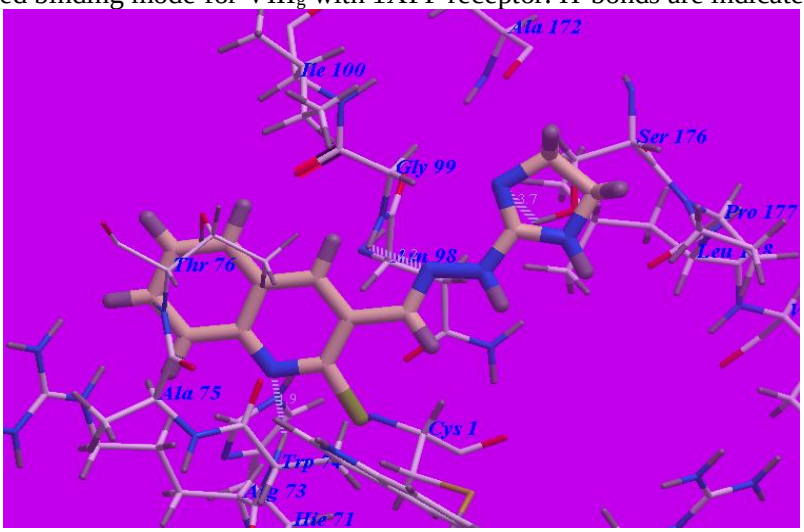


Figure 5 Predicted binding mode for compound $VIII_C$ with 1XFF receptor

It was noticed that: the exchange of the O-C=O group of the linker (e.g. compound 1) by N-N moiety (e.g. most of our target compounds) leading to increase of number of hydrogen bonds and subsequently increase in binding affinity leading to increase in antimicrobial activity which explain the design and structures of our target compounds.

Table 1 The calculated ΔG (free energy of binding) and binding affinities for the ligands

Compound	ΔG [kcal mol^{-1}]	Compound	ΔG [kcal mol^{-1}]
III	-56.94	**VIII$_e$**	-70.18
IV	-49.04	**VIII$_f$**	-52.12
V	- 47.81	**VIII$_g$**	-86.92
VI$_a$	-66.78	**VIII$_h$**	-53.18
VI$_b$	-65.29	**VIII$_i$**	-60.50
VI$_c$	-69.21	**VIIIj**	-60.48
VI$_d$	-69.33	**IX**	-64.41
VII$_a$	-69.76	**X**	-64.45
VII$_b$	-59.77	**XI**	-74.81
VII$_c$	-54.40	**XII**	-67.93
VII$_d$	-57.39	**XIII**	-76.83
VIII$_a$	-70.08	**XIV**	-70.50
VIII$_b$	-54.88	**XV**	-72.26
VIII$_c$	-74.89	**Compound 1**	-67.66
VIII$_d$	-74.55		

2.3. Chemistry

All melting points were carried on Gallen Kamp point apparatus and are uncorrected. The infrared spectra were recorded on Brucker- Vector-22-F T-IR spectrophotometer using the potassium bromide disc technique. The ^{1}HNMR spectra were recorded on varian-Gemini-300-MHz spectrophotometer using DMSO-d6 as a solvents and TMS as internal reference. The chemical shift values were recorded in δ ppm downfield the TMS signal. The Mass spectra were recorded on AZH-ph-AR-XO2 Mass spectrometer. Elemental analyses were performed on CHN analyzer. All spectral measurements have been performed at the Micro Analytical Center, Cairo University, Egypt. Following reported procedures, 2-chloroquinoline-3-carbaldehyde II,[24] 2-chloroquinoline-3-carbonitrile IV,[25] 2-mercapto quinoline-3-carbonitrile[26] were prepared.

2.3.1. Experimental

Synthesis of 2-(Alkylthio)quinoline-3-carbonitrile derivatives (VI$_{a-h}$).

A suspension of 2-mercaptoquinoline-3-carbonitrile (V) (1.86 g, 10 mmol) and anhyd. Sodium acetate (1.25g, 15 mmol) in ethanol (30 ml), an appropriate alkyl halide (Ethyl bromide, Butyl bromide, n-decyl bromide and allyl bromide) (10 mmol) was added. The reaction mixture was heated to reflux for 4 hours. On cooling, the precipitate product was collected by filtration and recrystallized from ethanol to afford the titled compounds. The physical characters and spectral data of compounds VI$_{a-d}$ are listed below:

2-(Ethylthio) quinoline-3-carbonitrile (VI$_a$).

White solid. Yield: 83%; m.p. 120 °C. IR (KBr) cm^{-1}: 3070 (CH aromatic), 2985 (CH aliphatic), 2210 (CN). ^{1}H NMR (DMSO-d6) δ ppm: 8.96 (s, 1H, quinoline-H4), 8.01 (d, 1H, J = 8 Hz, quinoline- H5), 7.94 (t, 1H, J = 9 Hz, quinoline- H6), 7.91 (t, 1H, J = 9 Hz, quinoline-H7), 7.66 (d, 1H, J = 8 Hz, quinoline- H8), 3.39 (q, 2H, J = 7.2 Hz, S-CH$_2$), 1.4 (t, 3H, J = 9 Hz, CH$_3$). MS (m/z): 214 ($C_{12}H_{10}N_2S$, 70.4%, M+), 180 ($C_{10}H_5N_2S$, 100%), 153 ($C_{10}H_5N_2$, 33%). Anal. Calc. for: ($C_{12}H_{10}N_2S$) (M.W. = 214): C, 67.26; H, 4.70; N, 13.07; Found: C, 66.93; H, 4.61; N, 12.95%.

2-(Butylthio) quinoline-3-carbonitrile (VI$_b$).

Yellow solid. Yield: 93%; **m.p.** 185 °C. IR (KBr) cm^{-1}: 3080 (CH aromatic), 2954 (CH aliphatic), 2215 (CN). ^{1}H NMR (DMSO-*d*$_6$) δ ppm: 8.94 (s, 1H, quinoline-H4), 8.00 (d, 1H, *J* = 9 Hz, quinoline- H5), 7.91 (t, 1H, *J* = 9 Hz, quinoline- H6), 7.64 (t, 1H, *J* = 9 Hz, quinoline-H7), 7.60 (d, 1H, *J* = 8 Hz, quinoline- H8), 3.4 (t, 2H, *J* = 5.7 Hz, S-CH$_2$), 1.7 (pent, 2H, *J* = 7.2 Hz, CH$_2$), 1.48 (pent, 2H, *J* = 7.5 Hz, CH$_2$), 0.97 (t, 3H, *J* = 5.5 Hz, CH$_3$). MS (m/z): 242 ($C_{14}H_{14}N_2S$, 22.18%, M$^+$), 200 ($C_{11}H_7N_2S$, 92.86%), 186 ($C_{10}H_5N_2S$, 100%), 153 ($C_{10}H_5N_2$, 53%). Anal. Calc. for: ($C_{14}H_{14}N_2S$) (M.W. = 228): C, 69.39; H, 5.8; N, 11.57; Found: C, 69.11; H, 5.4; N, 11.36%.

2-(Decylthio)quinoline-3-carbonitrile (VI_c).
Brownish solid. Yield: 82%; **m.p**. 270 °C. IR (KBr) cm^{-1}: 3050 (CH aromatic), 2950 (CH aliphatic), 2200 (CN). ^1H NMR (DMSO-d_6) δ ppm: 8.94 (s, 1H, quinoline-H4), 8.00 (d, 1H, *J* = 8 Hz, quinoline- H5), 7.90 (t, 1H, *J* = 9 Hz, quinoline- H6), 7.88 (t, 1H, *J* = 9 Hz, quinoline- H7), 7.64 (d, 1H, *J* = 8 Hz, quinoline- 8H), 3.39 (t, 2H, *J* = 6.75 Hz, S-CH_2), 1.73 (pent, 2H, *J* = 6.75 Hz, CH_2), 1.46 (pent, 2H, *J* =6.75 Hz, CH_2), 1.22 (s, 10H, *J* =5.5 Hz, CH_2), 0.83 (t, 3H, *J* = 6.75 Hz, CH_3). MS (m/z): 326 ($C_{20}H_{26}N_2S$, 18.76%, M^+), 199 ($C_{11}H_7N_2S$, 78.86%), 185 ($C_{10}H_5N_2S$, 100%), 153 ($C_{10}H_5N_2$, 25%). Anal. Calc. for: ($C_{19}H_{24}N_2S$) (M.W. = 312): C, 73.57; H, 8.03; N, 8.58; Found: C, 73.11; H, 7.94; N, 8.26%.

2-(Allylthio)quinoline-3-carbonitrile (VI_d).
White solid. Yield: 90%; **m.p.** 185 °C. IR (KBr) cm^{-1}: 3075 (CH aromatic), 2985 (CH aliphatic), 2210 (CN). ^1H NMR (DMSO-d_6) δ ppm: 8.97 (s, 1H, quinoline-H4), 8.02 (d, 1H, *J* =8 Hz, quinoline- H5), 7.92 (t, 1H, *J* = 9 Hz, quinoline- H6), 7.68 (t, 1H, *J* = 9 Hz, quinoline- H7), 7.65 (d, 1H, *J* = 8 Hz, quinoline- H8), 6.02 (quin, 1H, *J* = 1.8 Hz, CH alkene), 5.46 (dd, 1H, *J* = 17, 1.8 Hz, CH alkene trans H), 5.15 (dd, 1H, *J* = 10, 1.8 Hz, CH alkene cis H), 4.07 (d, 2H, *J* = 6.2 Hz, S-CH_2). MS (m/z): 226 ($C_{13}H_{10}N_2S$, 48.96%, M^+), 214 ($C_{12}H_{10}N_2S$, 100%), 199 ($C_{11}H_7N_2S$, 14.29%). Anal. Calc. for: ($C_{13}H_{10}N_2S$) (M.W. = 226): C, 69.00; H, 4.45; N, 12.38; Found: C, 68.93; H, 4.41; N, 11.99%.

Synthesis of *N*-(Substituted phenyl) 2-[(3-Cyanoquinolin-2-yl) thio]acetamide derivatives (VII_{a-d}).
A suspension of 2-mercaptoquinoline-3-carbonitrile (**V)** (1.86 g, 10 mmol) and anhydrous sodium acetate (1.25g, 15 mmol) in absolute ethanol (30 ml), the appropriate chloroacetanilides (4-chloro acetanilide, 2-chloro acetanilide, 4-methyl acetanilide and 4-methoxy acetanilide) (10 mmol) was added. The reaction mixture was heated under reflux for 4 hours. After cooling down to room temperature, the precipitate was collected and recrystallized from absolute ethanol to provide the desired products. The physical properties and spectral data of compounds **VII_{a-d}** are listed below:

N-(4-Chlorophenyl)-2-[(3-cyanoquinolin-2-yl)thio]acetamide (VII_a).
Yellowish white solid. Yield: 85%; m.p. 235 °C. IR (KBr) cm^{-1}: 3295 (NH), 3080 (CH aromatic), 2900 (CH aliphatic), 2222 (CN), 1675 (C=O). ^1H NMR (DMSO-d_6) δ ppm: 10.27 (s, 1H, N-H, D2O-exchangeable), 8.8 (s, 1H, quinoline-H4), 8.01 (d, 1H, *J* =8 Hz, quinoline- H5), 7.94 (t, 1H, *J* = 9 Hz, quinoline- H7), 7.91 (t, 1H, *J* = 8 Hz, quinoline-H6), 7.56 (d, 1H, *J* = 8 Hz, quinoline- H8), 7.49 (d, 2H, *J* = 6.9 Hz, phenyl-H2, H6), 7.4 (d, 2H, *J* = 6.9, phenyl-H-3,H-5), 4.25 (s, 2H, S-CH_2). MS (m/z): 355 ($C_{18}H_{12}ClN_3OS$, 0.37%, M+2), 353 ($C_{18}H_{12}ClN_3OS$, 0.9%, M^+), 228 ($C_{12}H_8N_2OS$, 100%), 229 ($C_{12}H_9N_2OS$, 89%), 199 ($C_{11}H_7N_2S$, 9%), 153 ($C_{10}H_5N_2$, 25%), 75 (C_6H_3, 8%). Anal. Calc. for: ($C_{18}H_{12}ClN_3OS$) (M.W. = 353): C, 61.10; H, 3.42; N, 11.88%; Found: C, 61.47; H, 3.25; N, 11.76%.

***N*-(2-Chlorophenyl)-2-[(3-cyanoquinolin-2-yl)thio]acetamide (VII_b).**
Yellowish white solid. Yield: 80%; **m.p**. 229 °C. IR (KBr) cm^{-1}: 3295 (NH), 3080 (CH aromatic), 2900 (CH aliphatic), 2222 (CN), 1675 (C=O). ^1H NMR (DMSO-d_6) δ ppm: 10.1 (s, 1H, N-H, D_2O-exchangeable), 9.15 (s, 1H, quinoline-H4), 7.9 (d, 1H, *J* = 8 Hz, quinoline- H5), 7.9 (t, 1H, *J* = 8 Hz, quinoline- H7), 7.77 (t, 1H, *J* = 8 Hz, quinoline-H6), 7.66 (d, 1H, *J* = 8 Hz, quinoline-H8), 7.5-7.2 (m, 4H aromatic protons), 4.35 (s, 2H, S-CH_2).MS (*m/z*): 355 ($C_{18}H_{12}ClN_3OS$, 0.37%, M+2), 353 ($C_{18}H_{12}ClN_3OS$, 0.9%, M^+), 228 ($C_{12}H_8N_2OS$, 100%), 229 ($C_{12}H_9N_2OS$, 89%), 199 ($C_{11}H_7N_2S$, 9%), 153 ($C_{10}H_5N_2$, 25%), 75 (C_6H_3, 8%). Anal. Calc. for: ($C_{18}H_{12}ClN_3OS$) (M.W. = 353): C, 61.10; H, 3.42; N, 11.88%; Found: C, 61.47; H, 3.25; N, 11.54%.

***N*-(4-methyl phenyl)-2-[(3-cyanoquinolin-2-yl)thio]acetamide (VII_c).**
Brown solid. Yield: 85%; **m.p**. 222 °C. IR (KBr) cm^{-1}: 3300 (NH), 3122 (CH aromatic), 2900 (CH aliphatic), 2221 (CN), 1665 (C=O). ^1H NMR (DMSO-d_6) δ ppm: 10.27 (s, 1H, N-H, D_2O-exchangeable), 9.1 (s, 1H, quinoline-H4), 8.01 (d, 1H, *J* = 8 Hz, quinoline- H5), 7.9 (t, 1H, *J* = 9 Hz, quinoline- H7), 7.81 (t, 1H, *J* = 8 Hz, quinoline-H6), 7.66 (d, 1H, *J* = 8 Hz, quinoline- H8), 7.6 (d, 2H, *J* = 6.9 Hz, phenyl-H2, H6), 7.4 (d, 2H, *J* = 6.9, phenyl-H3, H5), 4.2 (s, 2H, S-CH_2), 2.6 (s, 3H, CH_3). MS (m/z): 333 ($C_{19}H_{15}N_3OS$, 10.5%, M^+), 257 ($C_{12}H_8N_2OS$, 100%), 229 ($C_{12}H_9N_2OS$, 75.7%), 199 ($C_{11}H_7N_2S$, 9.3%), 153 ($C_{10}H_5N_2$, 17.8%), 75 (C_6H_3, 1.3%). Anal. Calc. for: ($C_{19}H_{15}N_3OS$) (M.W. = 333): C, 68.45; H, 4.53; N, 12.60%; Found: C, 68.12; H, 4.41; N, 12.07%.

***N*-(4-methoxy phenyl)-2-[(3-cyanoquinolin-2-yl)thio]acetamide (VII_d)**
Grey solid. Yield: 85%; **m.p**. 230 °C.IR (KBr) cm^{-1}: 3261 (NH), 3071 (CH aromatic), 2900 (CH aliphatic), 2225 (CN), 1666 (C=O). ^{1}H NMR (DMSO-d_6) δ ppm: 10.28 (s, 1H, N-H, D2O-exchangeable), 9 (s, 1H, quinoline-H4), 8.01 (d, 1H, *J* = 8 Hz, quinoline-H5), 7.9 (t, 1H, *J* = 9 Hz, quinoline-H7), 7.91 (t, 1H, *J* = 8 Hz, quinoline-H6), 7.66 (d, 1H, *J* = 8 Hz, quinoline- H8), 7.6 (d, 2H, *J* = 6.9 Hz, phenyl-H2, H6), 7.4 (d, 2H, *J* = 6.9, phenyl-H3, H5), 4.25 (s, 2H, S-CH_2), 3.99 (s, 3H, OCH_3). MS (m/z): 349 ($C_{19}H_{15}N_3O_2S$, 10.5%, M^+), 257 ($C_{12}H_8N_2OS$, 100%), 229 ($C_{12}H_9N_2OS$, 75.7%), 199 ($C_{11}H_7N_2S$, 9.3%), 153 ($C_{10}H_5N_2$, 17.8%), 75 (C_6H_3, 1.3%). Anal. Calc. for: ($C_{19}H_{15}N_3O_2S$) (M.W. = 349): C, 65.31; H, 4.33; N, 12.03%; Found: C, 65.02; H, 4.10; N, 11.97%.

Synthesis of (*E*)-3-(((2-chloroquinolin-3-yl)methylene)amino)-2-methylquinazolin-4(3*H*)-one ($VIII_a$)
2-Chloroquinoline-3-carbaldehyde (**II)** (1.91 g, 0.01mole) was dissolved in absolute ethanol (30 ml) and then added 2-amino-3-methylquinazolin-4(3H)-one (1.75 g, 0.01 mol) in the presence of conc. sulfuric acid (0.5 ml). The reaction mixture was reflux for 12 hours, cooled and the obtained solid was filtered off, washed with absolute ethanol (10 ml) and air dried to give the desired product as light yellow powder in yield 90%. **m.p.:** 285 °C.^{1}H NMR (DMSO-d_6) δ ppm: 9.57 (s, 1H, quinoline-H4), 9.27 (s, 1H, CH=N), 8.31 (d, 1H, *J* = 9 Hz, quinoline- H5, quinazolin-H5), 8.18 (d, 1H, *J* = 9 Hz, quinoline- H8), 7.97 (t, 1H, *J* = 9 Hz, quinoline- H7, quinazolin-H7), 7.77 (t, 1H, *J* = 9 Hz, quinoline- 6H, quinazolin-H6), 2.6 (s, 3H, CH_3). MS (m/z): 350 ($C_{19}H_{13}ClN_4O$, 0.64%, M+2), 348 ($C_{19}H_{13}ClN_4O$, 1.89%, M^+), 313 ($C_{19}H_{13}N_4O$, 25.13%), 298 ($C_{18}H_{11}N_4O$, 19.12%), 160 ($C_{10}H_{10}N_2$, 100%). Anal. Calc. for: ($C_{19}H_{13}ClN_4O$) (M.W. = 348): C, 65.43; H, 3.76; N, 16.06; Found: C, 65.23; H, 3.35; N, 15.96%.

Synthesis of (*E*)-5-(((2-chloroquinolin-3-yl)methylene)amino)-1-phenyl-1*H*-pyrazole-4-ethyl carboxylate ($VIII_b$)
2-chloroquinoline-3-carbaldehyde (II) (1.91 g, 0.01mole) was dissolve in absolute ethanol (30 ml) and then added 5-amino-1-phenyl-1H-pyrazole-4-ethyl carboxylate (2.31 g, 0.01 mol) in the presence of glacial acetic acid (0.5 ml). The reaction mixture was reflux for 22 hours, cooled and the obtained solid was filtered off, washed with absolute ethanol (10 ml) and air dried to give the desired product as light yellow powder in yield 90%. *m.p.: 285 °C.IR (KBr) cm-1: 3122 (CH aromatic), 2900 (CH aliphatic), 1750 (-OC=O), 1665 (C=N). 1H NMR (DMSO-d6) δ ppm: 9.00 (s, 1H, quinoline-H4), 8.55 (s, 1H, CH=N), 8.30 (d, 1H J = 9 Hz, quinoline- H5), 8.28 (s, 1H, pyrazol-H3), 8.14 (d, 1H, J = 9 Hz, quinoline- H8, phenyl- H2, H6), 7.98 (d, 1H, J = 8 Hz, quinoline- 7H), 7.86 (t, 1H, J = 8, quinoline- H6), 7.7 (m, 3H, phenyl-H3, H4, H5) 4.24 (quar, 2H, J = 6.7 Hz, O-CH_2), 1.28 (t, 3H, J = 6.5 Hz, CH_3). Anal. Calc. for: ($C_{22}H_{17}ClN_4O$) (M.W. = 404): C, 65.27; H, 4.23; N, 13.84; Found: C, 65.03; H, 3.99; N, 13.86%.

Synthesis of (*E*)-2-chloro-3-((2-(4,5-dihydro-1H-imidazol-2-yl)Hydrazono)methyl)quinoline ($VIII_c$)
2-Chloroquinoline-3-carbaldehyde (**II)** (1.91 g, 0.01mole) was dissolve in absolute ethanol (30 ml) and then added 2-hydrazinyl-4,5-dihydro-1*H*-imidazole hydro-bromide (1.8 g, 0.01 mol) in the presence of glacial acetic acid (0.5 ml). The reaction mixture was reflux for 22 hours, cooled and the obtained solid was filtered off, washed with cooled ethanol (10 ml) and air dried to give the desired product as light yellow powder in yield 75%. **m.p.:** 260 °C.^{1}H NMR (DMSO-d_6) δ ppm: 12.7 (s, 1H, NH, D_2O-exchaneable), 9.22 (s, 1H, quinoline-H4), 8.96 (s, 1H , NH, D_2O-exchangeable), 8.66 (s, 1H, CH=N), 8.06 (d, 1H, *J* = 8 Hz, quinoline-H5), 7.97 (d, 1H, *J* = 8 Hz, quinoline-H8), 7.87 (t, 1H, *J* = 8 Hz, quinoline-H7), 7.77 (t, 1H, *J* = 8 Hz, quinoline-H6), 3.8 (s, 4H, -$2CH_2$). **MS** (*m/z*): 275 ($C_{13}H_{12}ClN_5$, 1.64%, M^{+2}), 273 ($C_{13}H_{12}ClN_5$, 4.86%, M^+), 238 ($C_{13}H_{12}N_5$, 51.2%), 200 ($C_{10}H_5N_3Cl$, 73.66%), 185.99 ($C_{10}H_5N_2Cl$, 100%). Anal. Calc. for: ($C_{13}H_{12}ClN_5$) (M.W. = 273): C, 57.02; H, 4.42; N, 25.59%; Found: C, 57.37; H, 4.19; N, 25.43%.

Synthesis of (*E*)-4-chloro-*N*`-((2-chloroquinolin-3-yl)methylenebenzohydrazide ($VIII_d$)
2-Chloroquinoline-3-carbaldehyde (**II)** (1.91 g, 0.01 mole) was dissolve in absolute ethanol (30 ml) and then added 4-chlorobenzohydrazide (1.7 g, 0.01 mole) in the presence of glacial acetic acid (0.5 ml). The reaction mixture was reflux for 23 hours, cooled and the obtained solid was filtered off, washed with cooled ethanol (10 ml) and air dried to give the desired product as light yellow powder in yield 70%. **m.p.:**270 °C.^{1}H NMR(DMSO-d_6) δ ppm: 12.32 (s, 1H, OH, D_2O-exchaneable), 10.62 (s, 1H, NH, D_2O-exchaneable), 8.97 (s, 1H, quinoline-H4), 8.22 (s, 1H, CH=N), 8.01 (d, 1H, *J* = 8 Hz, quinoline-H5), 7.99 (d, 1H, *J* = 8 Hz, quinoline-H8, phenyl-H2, H6), 7.87 (t, 1H, *J* = 8 Hz, quinoline-H7), 7.69 (t, 1H, *J* = 8 Hz, quinoline-H6), 7.62 (d, 2H, *J* = 6 Hz, phenyl-H3, H5). **MS** (*m/z*): 345 ($C_{17}H_{11}Cl_2N_3O$, 1.54%, M^{+2}), 343 ($C_{17}H_{11}Cl_2N_3O$, 2.37%, M^+), 308 ($C_{17}H_{11}ClN_3$, 7.08%), 189 ($C_{10}H_6ClN_2$, 100%). Anal. Calc. for: ($C_{17}H_{11}Cl_2N_3$) (M.W. = 343): C, 59.32; H, 3.22; N, 12.21%; Found: C, 59.31; H, 3.19; N, 12.43%.

Synthesis of (E)-N-(((2-chloroquinolin-3-yl)methylene)amino)Phenyl)-4-ethylbenzamide ($VIII_e$)
2-Chloroquinoline-3-carbaldehyde (**II)** (1.91 g, 0.01 mole) was dissolve in absolute ethanol (30 ml) and then added *N*-(4-aminophenyl)-4-ethylbenzamide (2.4 g, 0.01 mole) in the presence of glacial acetic acid (0.5 ml). The reaction mixture was reflux for 22 hours, cooled and the obtained solid was filtered off, washed with cooled ethanol (10 ml) and air dried to give the desired product as light yellow powder in yield 65%. ***m.p.:** 290 °C.^{1}H NMR (DMSO-d_6) δ ppm: 10.38 (s, 1H, NH, D_2O-exchaneable), 9.04 (s, 1H, quinoline-H4), 8.88 (s, 1H, CH=N), 8.14 (d, 1H, *J* = 8 Hz, quinoline-H5), 7.99 (d, 1H, *J* = 8 Hz, quinoline-H8, phenyl-H2, H6), 7.87 (t, 1H, *J* = 8 Hz, quinoline-H7), 7.69 (t, 1H, *J* = 8 Hz, quinoline-H6), 7.62 (d, 2H, *J* = 6 Hz, phenyl-H3, H5), 2.8 (quar, 2H, *J* = 6.7 Hz, CH_2), 1.2 (t, 3H, *J* = 6.5 Hz, -CH_3). **MS** (*m/z*): 415 ($C_{25}H_{20}ClN_3O$, 1.24%, M^{+2}), 413 ($C_{25}H_{20}ClN_3O$, 3.72%, M^+), 378 ($C_{25}H_{20}N_3O$, 22.2%), 189 ($C_{10}H_6ClN_2$, 100%). Anal. Calc. for: ($C_{25}H_{20}ClN_3O$) (M.W. = 413): C, 72.55; H, 4.87; N, 10.15%; Found: C, 72.31; H, 4.89; N, 10.43%.

Synthesis of (*E*)-1-(2-chloroquinolin-3-yl)-*N*-(thiazol-2-yl) methanimine ($VIII_f$)
2-Chloroquinoline-3-carbaldehyde (**II)** (1.91 g, 0.01 mole) was dissolve in absolute ethanol (30 ml) and then added thiazole-2-amine (1 g, 0.01 mole) in the presence of glacial acetic acid (0.5 ml). The reaction mixture was reflux for 24 hours, cooled and the obtained solid was filtered off, washed with cooled ethanol (10 ml) and air dried to give the desired product as light yellow powder in yield 65%. **m.p.:** 210 °C.^{1}H NMR (DMSO-d_6) δ ppm: 9.04 (s, 1H, quinoline-H4), 8.88 (s, 1H, CH=N), 8.14 (d, 1H, *J* = 8 Hz, quinoline-H5), 7.99 (d, 1H, *J* = 8 Hz, quinoline-H8, phenyl-H2, H6), 7.87 (t, 1H, *J* = 8 Hz, quinoline-H7), 7.69 (t, 1H, *J* = 8 Hz, quinoline-H6), 7.62 (d, 2H, *J* = 6 Hz, thiazol-H2,H3). **MS** (*m/z*): 275 ($C_{13}H_8ClN_3S$, 1.16%, M^{+2}), 273 ($C_{13}H_8ClN_3S$, 4.51%, M^+), 238 ($C_{13}H_8N_3S$, 12.2%), 189 ($C_{10}H_6ClN_2$, 100%). Anal. Calc. for: ($C_{13}H_8ClN_3S$) (M.W. = 273): C, 57.04; H, 2.95; N, 15.35%; Found: C, 57.31; H, 2.89; N, 15.43%.

Synthesis of (*E*)-2-(2-chloroquinolin-3-yl)methylene)hydrazinyl)Acetonitrile ($VIII_g$)
2-Chloroquinoline-3-carbaldehyde (**II)** (1.91 g, 0.01 mole) was dissolve in absolute ethanol (30 ml) and then added 2-hydrazinyl acetonitrile (0.71g, 0.01 mole) in the presence of *anhyd.* Lithium chloride (0.5 g). The reaction mixture was reflux for 22 hours, cooled and the obtained solid was filtered off, washed with cooled ethanol (10 ml) and air dried to give the desired product as light yellow powder in yield 65%. ***m.p.:** 135 °C.IR (KBr) cm^{-1}: 3295 (NH), 3080 (CH, aromatic), 2900 (CH aliphatic), 2222 (CN). ^{1}H NMR (DMSO-d_6) δ ppm: 9.2 (s, 1H, quinoline-H4), 8.97 (s, 1H, CH=N), 8.44 (d, 1H, *J* = 8 Hz, quinoline-H5), 8.01 (d, 1H, *J* = 8 Hz, quinoline-H8), 7.83 (t, 1H, *J* = 8 Hz, quinoline-H7), 7.67 (t, 1H, *J* = 8 Hz, quinoline-H6), 7.2 (s, 1H, NH, D_2O-exchaneable), 4.2 (s, 2H, -CH_2). **MS** (*m/z*): 246 ($C_{12}H_9ClN_4$, 2.43%, M^{+2}), 244 ($C_{12}H_9ClN_4$, 7.18%, M^+), 209 ($C_{12}H_9N_4$, 29.2%), 189 ($C_{10}H_6ClN_2$, 100%). Anal. Calc. for: ($C_{12}H_9ClN_4$) (M.W. = 244): C, 58.90; H, 3.71; N, 22.90%; Found: C, 58.41; H, 3.89; N, 22.43%.

Synthesis of (*E*)-*N*-(benzo[d]thiazol-2-yl)-1-(2-chloroquinolin-3-yl)methanimine ($VIII_h$)
2-Chloroquinoline-3-carbaldehyde (**II)** (1.91 g, 0.01 mole) was dissolve in absolute ethanol (30 ml) and then added benzo[d]thiazol-2-amine (1.5 g, 0.01 mole) in the presence of glacial acetic acid (0.5 ml). The reaction mixture was reflux for 27 hours, cooled and the obtained solid was filtered off, washed with cooled ethanol (10 ml) and air dried to give the desired product as light yellow powder in yield 59%. ***m.p.:** 190 °C.^{1}H NMR (DMSO-d_6) δ ppm: 9.05 (s, 1H, CH=N), 8.86 (s, 1H, quinoline-H4), 8.53 (d, 1H, *J* = 8 Hz, benzothiazol-H4), 7.99 (d, 1H, *J* = 8 Hz, quinoline-H5), 7.95 (d, 1H, *J* = 8 Hz, benzothiazol-H7), 7.89 (d, 1H, *J* = 8 Hz, quinoline-H8), 7.76 (t, 1H, *J* = 8 Hz, quinolin-H7), 7.7 (t, 1H, *J* = 8 Hz, quinolin-H6), 7.5 (d, 2H, *J* = 6.8 Hz, benzothiazol-H5,H6). **MS** (*m/z*): 325 ($C_{17}H_{10}ClN_3S$, 2.66%, M^{+2}), 323 ($C_{17}H_{10}ClN_3S$, 7.66%, M^+), 288 ($C_{17}H_{10}N_3S$, 32.2%), 177 ($C_{10}H_8ClN$, 100%). Anal. Calc. for: ($C_{17}H_{10}ClN_3S$) (M.W. = 323): C, 63.06; H, 3.11; N, 12.98%; Found: C, 63.31; H, 2.99; N, 12.73%.

Synthesis of (*E*)-1-(2-chloroquinolin-3yl)-*N*-morpholinoMethanimine ($VIII_i$)
2-chloroquinoline-3-carbaldehyde (II) (1.91 g, 0.01 mole) was dissolve in absolute ethanol (30 ml) and then added morpholin-4-amine (1g, 1 ml, 0.01 mole) in the presence of lithium chloride anhydrous (0.5 g). The reaction mixture was reflux for 16 hours, cooled and the obtained solid was filtered off, washed with cooled ethanol (10 ml) and air dried to give the desired product as light yellow powder in yield 75%. *m.p.: 105 °C.1H NMR (DMSO-d6) δ ppm: 9.2 (s, 1H, quinoline-H4), 8.5 (s, 1H, CH=N), 8.44 (d, 1H, J = 8 Hz, quinoline-H5), 8.01 (d, 1H, J = 8 Hz, quinoline-H8), 7.83 (t, 1H, J = 8 Hz, quinoline-H7), 7.67 (t, 1H, J = 8 Hz, quinoline-H6). 3.75 (t, 4H, J = 6 Hz, aliphatic O-$(CH_2)_2$), 3.1 (t, 4H, J = 6 Hz, aliphatic N-$(CH_2)_2$). MS (m/z): 277 ($C_{14}H_{14}ClN_3O$, 9.66%,

M^{+2}), 275 ($C_{14}H_{14}ClN_3O$, 29.59%, M^+), 240 ($C_{14}H_{14}N_3O$, 23.2%), 189 ($C_{10}H_6ClN_2$, 100%). Anal. Calc. for: ($C_{14}H_{14}ClN_3O$) (M.W. = 275): C, 60.98; H, 5.12; N, 15.28%; Found: C, 60.91; H, 4.98; N, 15.43%.

Synthesis of (*E*)-1-(2-chloroquinolin-3-yl)-*N*-(4-methylpiperazin-1-yl)methanimine ($VIII_j$)

2-Chloroquinoline-3-carbaldehyde (**II)** (1.91 g, 0.01 mol) was dissolve in absolute ethanol (30 ml) and then added 4-methylpiperazin-1-amine (1.15 g, 1 ml, 0.01 mol) in the presence of lithium chloride anhydrous (0.5 g). The reaction mixture was reflux for 16 hours, cooled and the obtained solid was filtered off, washed with cooled ethanol (10 ml) and air dried to give the desired product as light yellow powder in yield 75%. ***m.p.:** 105 °C.^{1}H NMR (DMSO-d_6) δ ppm: 9.2 (s, 1H, quinoline-H4), 8.5 (s, 1H, CH=N), 8.44 (d, 1H, *J* = 8 Hz, quinoline-H5), 8.01 (d, 1H, *J* = 8 Hz, quinoline-H8), 7.83 (t, 1H, *J* = 8 Hz, quinoline-H7), 7.67 (t, 1H, *J* = 8 Hz, quinoline-H6). 3.11 (t, 4H, *J* = 6 Hz, aliphatic N-$(CH_2)_2$), 2.34 (t, 4H, *J* = 6 Hz, aliphatic N-$(CH_2)_2$), 1.89 (s, 3H, CH_3). **MS** (*m/z*): 290 ($C_{15}H_{17}ClN_4$, 11.66%, M^{+2}), 288 ($C_{15}H_{17}ClN_4$, 35.66%, M^+), 253 ($C_{15}H_{17}N_4$, 25.2%), 189 ($C_{10}H_6N_2Cl$, 100%). Anal. Calc. for: ($C_{15}H_{17}ClN_4$) (M.W. = 288): C, 62.39; H, 5.93; N, 19.40%; Found: C, 62.39; H, 5.99; N, 19.23%.

Synthesis of (*E*)-1-(4-aminophenyl)-3-(2-chloroquinolin-3-yl)Prop-2-en-1-one (III)

To a stirred and ice-cooled aqueous solution of sodium hydroxide (10 mmole, 50% w/w) and absolute methanol (25 ml), 2-chloroquinoline-3-carbadehyde (**II**) (1.91 g, 10 mmole) was added portion wise followed by 4-aminoacetophenone (1.35 g, 10 mmole). The reaction mixture was vigorously stirred for 3 hours while temperature was maintained below 20°C until the reaction mixture became thick. The reaction mixture was left in the refrigerator overnight. The formed precipitate was filtered off under vacuum and washed with copious amount of water until the filtrates became neutral to litmus paper, washed with ice-cold ethanol (20 ml), and then recrystallized from ethanol to afford compound **III** as a yellow solid.Yield: 85%; **m.p.** 130 °C. IR (KBr) cm^{-1}: 3050 (CH aromatic), 1650 (C=O). ^{1}H NMR (DMSO-d_6) δ ppm: 9.21 (s, 1H, quinoline-H4), 8.12 (d, 1H, *J* = 8 Hz, quinoline-H5), 7.99 (d, 1H, *J* = 8 Hz, quinoline-H8, d, 2H *J* = 6 phenyl-H2, H6 proton), 7.87 (t, 1H, *J* = 8 Hz, quinoline-H7),7.73 (d, 1H, *J* =15 Hz, CH alkene β proton), 7.63 (d, 1H, *J* = 15 Hz, CH alkene α proton), 7.45 (t, 1H, *J* = 9 Hz, quinoline-H7), 6.76 (d, 2H, *J* = 9 Hz, phenyl-H3, H5 protons), 4.1 (s, 2H, NH_2, D_2O-exchaneable). **MS** (*m/z*): 310 ($C_{18}H_{13}ClN_2O$, 3.7%, M^{+2}), 308 ($C_{18}H_{13}ClN_2O$, 1.2%, M^+), 273 ($C_{18}H_{13}N_2O$, 78%), 188 ($C_{11}H_7ClN$, 3.8%), 77 (C_6H_6, 100%). Anal. Calc. for: ($C_{18}H_{13}ClN_2O$) (M.W. = 308): C, 70.02; H, 4.24; N, 9.07%; Found: C, 70.20; H, 4.56; N, 9.03%.

Synthesis of 2-Chloro-3-[3-(4-aminophenyl)-4,5-dihydro-1*H*-pyrazol-5-yl]quinoline (IX)

A mixture of chalcone (**III)** (3 g, 10 mmole) and hydrazine hydrate (1 ml, 20mmole) was stirred in ethanol (20 ml) and heated at reflux for 22 hours. After completion of the reaction, the mixture was concentrated by evaporating out the solvent under reduced pressure, and then poured onto ice water. The obtained precipitate was filtered off, washed by water and recrystallized from ethanol to afford compound **IX** as white needles.Yield: 60%; m.p. 105 °C. IR (KBr) cm^{-1}: 3290 (NH), 3300 (NH_2) 3050 (CH aromatic), 2950 (CH aliphatic). ^{1}H NMR (DMSO-d_6) δ ppm: 8.53 (s, 1H, NH, D_2O-exchaneable), 8.19 (s, 1H, quinoline-H4), 8.07 (d, 1H, *J* = 9 Hz, quinoline-H8), 7.97 (t, 1H. *J* = 9 Hz, quinoline-H7), 7.85 (d, 2H, *J* = 9 Hz, phenyl- H2,H6), 7.76 (d, 1H, *J* = 9 Hz, quinoline-H5), 7.3 (t, 1H, *J* = 9 Hz, quinoline- H6), 6.55 (d, 2H, *J* = 9 Hz, phenyl-H3,H5), 5.1 (t, 1H , *J* = 9.2 Hz, pyrazole-H5), 4.1 (s, 2H, NH_2, D_2O-exchaneable), 3.6 (dd, 1H, *J* = 16, 9.2 Hz, pyrazole- H4 axial proton), 2.9 (dd, 1H, *J* = 16.4, 9.2 Hz, pyrazole-H4 equatorial proton). **MS** (*m/z*): 324 ($C_{18}H_{15}ClN_4$, 15%, M^{+2}), 322 ($C_{18}H_{15}ClN_4$, 47.9%, M^+), 287 ($C_{18}H_{15}N_4$, 10%), 155 ($C_{10}H_7N_2$, 27%), 135 ($C_{10}H_6N$, 100%). Anal. Calc. for: ($C_{18}H_{15}ClN_4$) (M.W. = 322): C, 66.98; H, 4.68; N, 17.36%; Found: C, 66.91; H, 4.39; N, 17.53%.

Synthesis of 5-(2-Chloroquinolin-3-yl)-3-(4-aminophenyl)-4,5-dihydroisoxazole (X)

A mixture of chalcone (**III)** (3 g, 10 mmole) and hydroxylamine hydrochloride (0.69 g, 10 mmole) was stirred in ethanol (20 ml), and then sodium hydroxide (0.8 g, 20 mmole) was added. The reaction mixture was heated to reflux for 24 hours, and then the solvent was evaporated under reduced pressure and poured into ice water. The obtained precipitate was filtered off, washed with copious amount of water and recrystallized from ethanol to afford the compound **X** as reddish solid.Yield: 65%; **m.p.** 140 °C. IR (KBr) cm^{-1}: 3050 (CH aromatic), 2950 (CH aliphatic), 1590 (C=N). ^{1}H NMR (DMSO-d_6) δ ppm: 8.87 (s, 1H, quinoline-H4), 8.15 (d, 1H, *J* = 9 Hz, quinoline-H8), 7.95 (t, 1H. *J* = 9 Hz, quinoline-H7), 7.84 (d, 2H, *J* = 9 Hz, phenyl- H2,H6), 7.75 (d, 1H, *J* =9 Hz, quinoline-H5), 7.4 (t, 1H, *J* = 9 Hz, quinoline- H6), 6.66 (d, 2H, *J* = 9 Hz, phenyl-H3,H5), 6.2 (t, 1H, *J* = 14 Hz, isoxazole-H5), 4 (dd, 1H, *J* = 11, 5 Hz, isoxazole-H4 axial proton), 4.1 (s, 2H, NH_2, D_2O-exchaneable), 2.9 (dd, 1H, *J* = 17, 4.8 Hz, isoxazole-H4 equatorial proton). **MS** (*m/z*): 325 ($C_{18}H_{14}ClN_3O$, 15%, M^{+2}), 323

($C_{18}H_{14}ClN_3O$, 42%, M^+), 231 ($C_{12}H_8ClN_2O$, 19%), 200 ($C_{11}H_8N_2O_2$, 33%), 118 (C_9H_{10}, 100%). Anal. Calc. for: ($C_{18}H_{14}ClN_3O$) (M.W. = 323): C, 66.77; H, 4.36; N, 12.80%; Found: C, 66.63; H, 4.27; N, 12.60%.

Synthesis of 4-(4-aminophenyl)-6-(2-chloroquinolin-3-yl) pyrimidine-2(1*H*)-thione (XI)

A mixture of chalcone **(III)** (3 g, 10 mmole) and thiourea (2.28 g, 30 mmole) was stirred in ethanol (20 ml) and then sodium hydroxide (1.2 g, 30mmole) was added to it and the mixture was heated at reflux for 24 hours. After completion of the reaction the solvent was concentrated by evaporation under reduced pressure and poured into ice water. The obtained precipitate was filtered, washed and recrystallized from ethanol to give the titled compound as a dark yellow solid.Yield: 40%; **m.p**. 150 °C. IR (KBr) cm^{-1}: 3290 (NH), 3350 (NH_2) 3050 (CH aromatic). ^{1}HNMR (DMSO-d_6) δ ppm: 12.3 (s,1H, NH, D_2O-exchangeable proton), 8.5 (s, 1H, quinoline-H4), 8.3 (d, 1H, *J* = 15 Hz, quinoline-H5), 8.1 (d, 1H, *J* = 15 quinoline-H8), 7.98 (t, 1H, *J* = 15 Hz, quinoline-H7), 7.88 (d, 2H, *J* = 9 Hz, phenyl-H2,H6), 7.4 (t, 1H, *J* = 15 Hz, quinoline-H6), 7.1 (d, 2H, *J* = 9 Hz, phenyl-H3,H5), 6.5 (s, 1H, pyrimidine-thion), 4.1 (s, 2H, NH, D_2O-exchangeable proton). MS (*m/z*): 366 ($C_{19}H_{13}ClN_4S$, 0.15%, M^{+2}), 364 ($C_{19}H_{13}ClN_4S$, 0.5%, M^+), 329 ($C_{19}H_{13}N_4S$, 4%), 77 (C_6H_5, 100%). Anal. Calc. for: ($C_{19}H_{13}ClN_4S$) (M.W. = 364): C, 62.55; H, 3.59; N, 15.36%; Found: C, 62.96; H, 3.31; N, 15.78%.

Synthesis of4-(2-Chloroquinolin-3-yl)-6-(4-aminophenyl)pyrimidin-2-amine (XII)

A mixture of chalcone (**III)** (3 g, 10 mmole) and guanidine hydrochloride (2.85 g, 30 mmole) was stirred in absolute ethanol (20 ml), and then sodium hydroxide (1.2 g, 30 mmole) was added. The reaction mixture was heated at reflux for 21 hours. After completion of reaction, the solvent was concentrated under reduced vaccum, and then poured into ice water (50 ml). The obtained solid was filtered off, washed and recrystallized from ethanol to afford the desired compound **XII**as yellow solid. Yield: 60%; **m.p**. 195 °C. IR (KBr) cm^{-1}: 3300 (NH_2), 3050 (CH aromatic-H's). ^{1}H NMR (DMSO-d_6) δ ppm: 8.73 (s, 1H, quinoline-H4), 8.17 (d, 1H, *J* = 9 Hz, quinoline-H5), 8.1 (s, 1H, pyrimidine-H5), 7.9 (d, 1H, *J* = 9 Hz, quinoline-H8), 7.59 (t, 1H, *J* = 9 Hz, quinoline-H7), 7.5 (t, 1H, *J* = 9 Hz, quinoline-H6), 7.4 (d, 2H, *J* = 9 Hz, phenyl-H2, H6), 7.1 (d, 2H, *J* = 9 Hz, phenyl-H3, H5), 6.5 (s, 2H, NH_2 of pyrimidine, D_2O-exchangeable protons), 5.5 (s, 2H, NH_2 of phenyl, D_2O-exchangeable protons). **MS** (*m/z*): 349 ($C_{19}H_{14}ClN_5$, 1.3%, M^{+2}), 347 ($C_{19}H_{14}ClN_5$, 4.01%, M^+) 312 ($C_{19}H_{14}N_5$, 9.15%, M^+), 215 ($C_{13}H_{10}ClN$, 16%), 118 (C_9H_{10}, 100%), Anal. Calc. for: ($C_{19}H_{14}ClN_5$) (M.W. = 347): C, 65.61; H, 4.06; N, 20.14%; Found: C, 65.95; H, 3.96; N, 20.03%.

Synthesis of 6-(2-Chloroquinolin-3-yl)-4-(4-aminophenyl)pyrimidin-2(1*H*)-one (XIII)

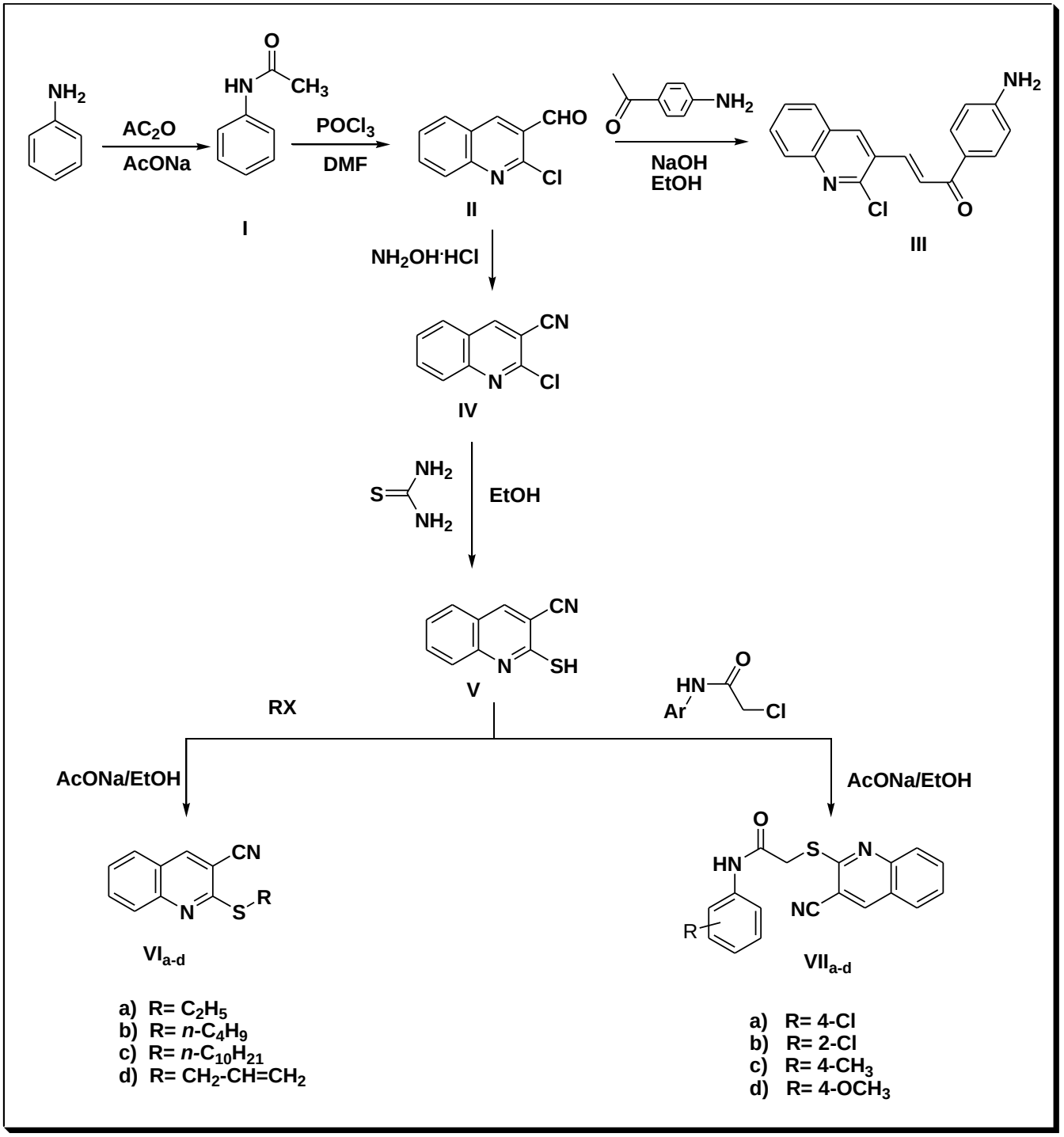
A mixture of chalcone (**III)** (3 g, 10 mmole) and urea (1.8 g, 30 mmole) was stirred in ethanol (20 ml), and then hydrochloric acid (3 ml) was added. The mixture was heated at reflux for 12 hours. After completion the reaction, the solvent was concentrated under reduced pressure and poured into ice water (50 ml). The obtained precipitate was filtered off, washed and recrystallized from ethanol to yield the titled compound as brown solid.Yield: 60%; **m.p**. 180 °C. IR (KBr) cm^{-1}: 3300 (NH_2) 3290 (NH), 3050 (CH aromatic). ^{1}H NMR (DMSO-d_6) δ ppm: 11.99 (s, 1H, NH, D_2O-exchangeable proton), 8.53 (s, 1H, quinoline-H4), 8.33 (s, H, pyrimidinone-H5), 8.23 (d, 1H, *J* = 15 Hz, quinoline-H5), 7.86 (d, 1H, *J* = 9 Hz, quinoline-H8), 7.73 (t, 1H, *J* = 9 Hz, quinoline-H7), 7.5 (d, 2H, *J* = 7 Hz, phenyl-H2, H6), 7.4 (t, 1H, *J* = 9 Hz, quinoline-H6), 6.65 (d, 2H, *J* = 9 Hz, phenyl-H3, H5), 6.14 (s, 2H, NH_2, D_2O-exchangeable proton). **MS** (*m/z*): 350 ($C_{19}H_{13}ClN_4O$, 1.6%, M^{+2}), 348 ($C_{19}H_{13}ClN_4O$, 4%, M^+), 313 ($C_{19}H_{13}N_4O$, 4%), 77 (C_6H_5, 100%). Anal. Calc. for: ($C_{19}H_{13}ClN_4O$) (M.W. = 348): C, 65.43; H, 3.76; N, 16.06%; Found: C, 65.96; H, 3.81; N, 16.08%.

Synthesis of 3-[4-(2-Chloroquinolin-3-yl)-6-(4-aminophenyl)pyrimidin-2-yl]-1,1-dimethylguanidine (XIV)

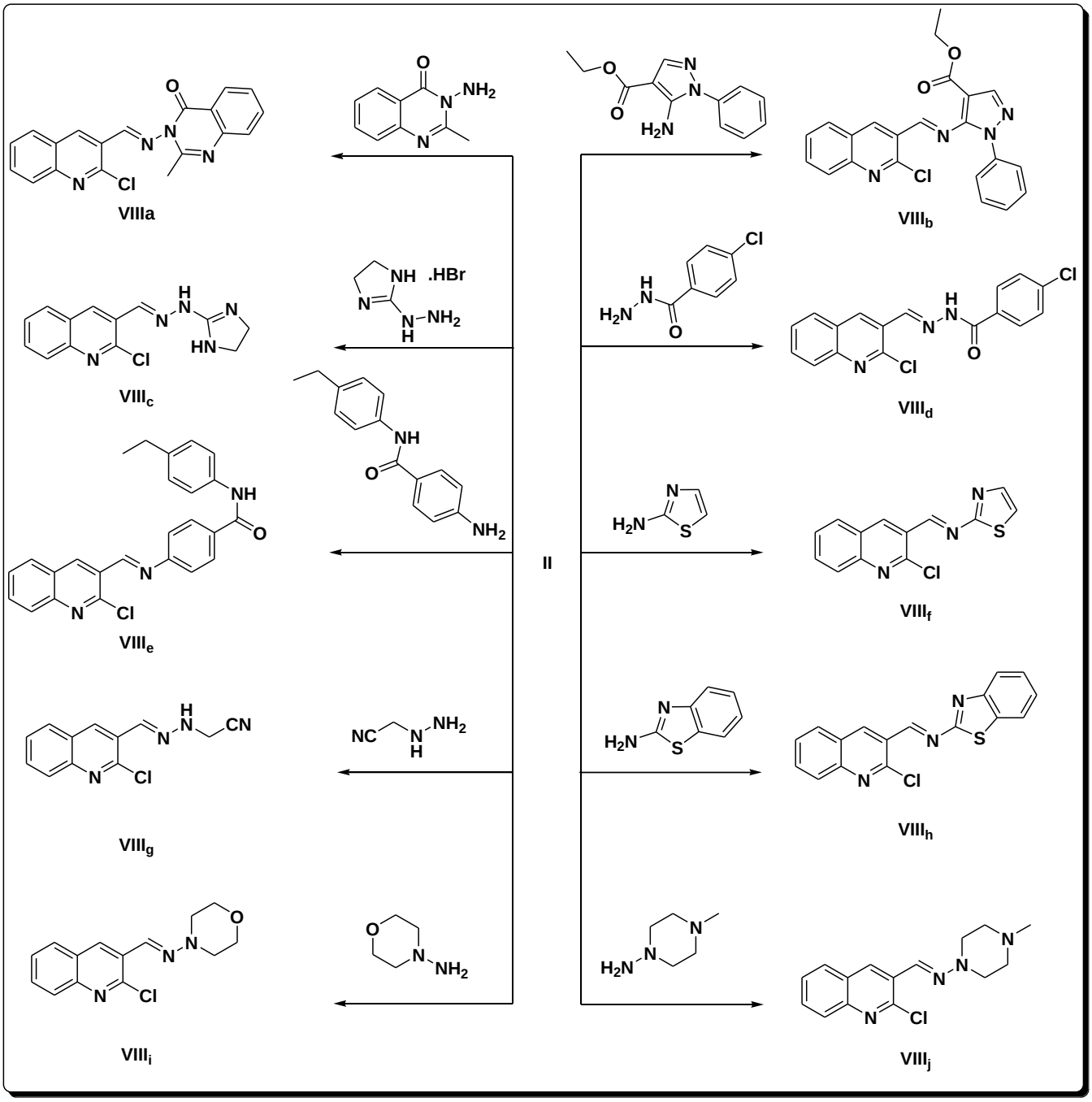
A mixture of chalcone (**III)** (3 g, 10 mmole) and metformine hydrochloride (4.95 g, 30 mmole) was stirred in ethanol (25 ml), and then sodium hydroxide (1.2 g, 30 mmole) was added. The mixture was heated at reflux for 23 hours. After completion of the reaction, the solvent was concentrated under vaccum and poured into ice water (50 ml). The obtained precipitate was filtered off, washed and recrystallized from ethanol to afford compound **XIV** as a buff solid.Yield: 65%; **m.p**. 131 °C. IR (KBr) cm^{-1}: 3350 (NH_2), 3290 (NH), 3050 (CH aromatic). ^{1}H NMR (DMSO-d_6) δ ppm: 9.3 (s, 1H, NH, D_2O exchangeable H), 8.53 (s, 1H, quinoline-H4), 8.45 (s, 1H, pyrimidine-H5), 8.23 (d, 1H, *J* = 9 Hz, quinoline-H5), 7.86 (d, 1H, *J* = 9 Hz, quinoline-H8), 7.5 (t, 1H, *J* = 9 Hz, quinoline-H7), 7.4 (t, 1H, *J* = 9 Hz, quinoline-H6), 7.3 (d, 2H, *J* = 9 Hz, phenyl-H2, H6), 6.9 (d, 2H, *J* = 9 Hz, phenyl-H3,H5), 5.6 (s, 2H, NH_2 of C=NH, D_2O-exchangeable proton), 2.8 (s, 6H, $2CH_3$). **MS** (*m/z*): 419 ($C_{22}H_{20}ClN_7$, 2.3%, M^{+2}), 417 ($C_{22}H_{20}ClN_7$, 7.6%, M^+) 382 ($C_{19}H_{14}N_7$, 4.15%), 215 ($C_{13}H_{10}ClN$, 16%), 118 (C_9H_{10}, 100%), Anal. Calc. for: ($C_{22}H_{19}ClN_7$) (M.W. = 417): C, 63.23; H, 4.82; N, 23.46%; Found: C, 63.65; H, 4.76 N, 23.93%.

Synthesis of 2-amino-6-(4-aminophenyl)-4-(2-chloroquinoline-3-yl)Nicotinonitrile (XV)

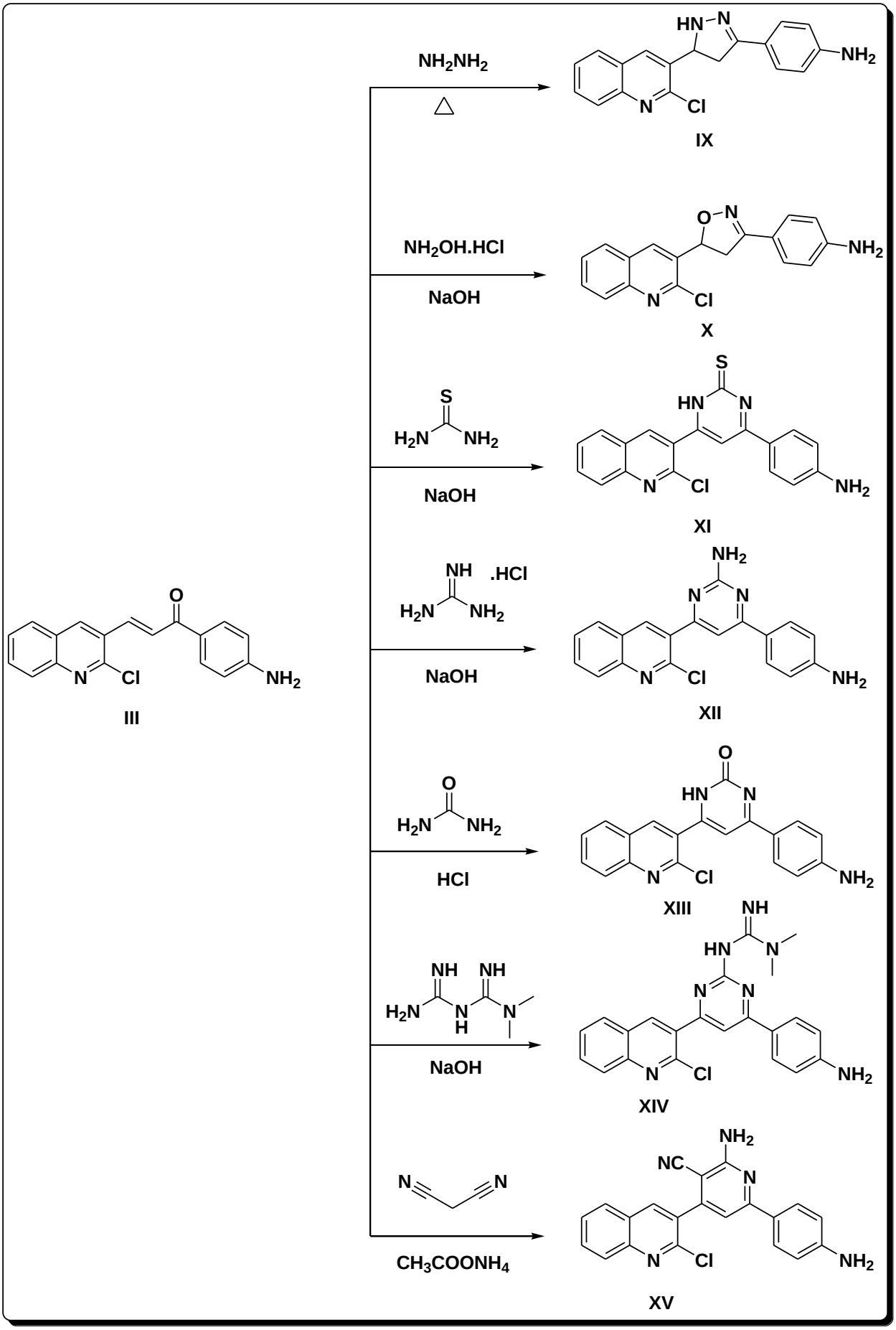
A mixture of chalcone (**III)** (3 g, 10 mmole) and malononitrile (1.32 g, 20 mmole), was stirred in ethanol (20 ml), and then *anhyd.* ammonium acetate (2.31 g, 30 mmole), was added. The reaction mixture was heated at reflux for 22 hours. After completion the reaction, the solvent was concentrated by vaporization under reduced pressure, and poured onto ice water (50 ml), the obtained precipitate was filtered off, washed and recrystallized from ethanol to afford compound **XV** as brownish solid. Yield: 60%;**m.p.** 160 °C. ^{1}H NMR (DMSO-d_6) δ ppm: 8.7 (s, 1H, quinoline-H4), 8.3 (d, 1H, *J* = 9 Hz, quinoline-H5), 8 (d, 2H, *J* = 9 Hz, phenyl-H2, H6), 7.7 (d, 1H, *J* = 9 Hz, quinoline-H8), 7.5 (s, 1H, *J* = 9 Hz , pyridine-H5) 7.3 (t, 1H, *J* = 9 Hz, quinoline-H7), 7.2 (t, 1H, *J* = 9 Hz, quinoline-H6), 7.1 (s, 2H, NH_2, D_2O exchangeable proton), 6.99 (d, 2H, *J* = 9 Hz, phenyl-H3, H5), 5.5 (s, 2H, NH_2, D_2O exchangeable proton). **MS** (*m/z*): 373 ($C_{21}H_{14}ClN_5$, 3.6%, M^{+2}), 371 ($C_{21}H_{14}ClN_5$, 10.4%, M^+), 338 ($C_{21}H_{14}N_5$, 4%), 299 ($C_{20}H_{17}N_3$, 100%), 286 ($C_{20}H_{18}N_2$, 2.85%). Anal. Calc. for: ($C_{21}H_{14}ClN_5$) (M.W. = 371): C, 67.83; H, 3.80; N, 18.84%; Found: C, 67.49; H, 3.93; N, 18.93%.



Scheme 1 Synthesis of compounds **III, VI$_{a-d}$ and VII$_{a-d}$**



Scheme 2 Synthesis of compounds **VIII$_{a-j}$**



Scheme 3 synthesis of compounds **IX** and **X**

2.4. Antimicrobial Activity

Antibacterial and antifungal activities of all newly synthesized compounds were tested by measuring the inhibitory effect of such compounds against some Gram-positive, Gram-negative bacteria and some fungi using agar diffusion technique.[27] The newly synthesized compounds were evaluated for their in vitro antibacterial activity against Gram-positive namely *Staphylococcus aureus* (SA) and *Bacillus subtilis* (BS) and Gram-negative *Pseudomonas aeuroginosa* (PA) and *Escherichia coli* (EC). They were also evaluated for their in vitro antifungal activity against *Aspergillus fumigatus* (AF), *Geotricum candidum*(GC), *Syncephalasterum racemosum* (SR),*Candida albicans* (CA). Ampicillin was the standard used for the evaluation of antibacterial activity against gram positive bacteria and Gentamicin was used as a standard in assessing the activity of the tested compounds against gram negative bacteria, while Amphotericin B was taken as a reference for the antifungal effect. The inhibitory effects of the synthetic compounds against these organisms are given in Tables 2 and 3, Figures 6- and Figure 7.

Tested organisms **Sample**	***Aspergillusfumigatus***	***Syncephalastrumracemosum***	***Geotriucumcandidum***	***Candida albicans***
Lead compound	13.2± 0.58	13.9± 0.24	14.4± 0.72	NA
III	17.7± 0.38	16.9± 0.23	19.8± 0.34	NA
VI_a	17.2± 0.58	19.3± 0.19	21.9± 0.58	NA
VI_b	16.3± 0.58	18.4± 0.19	21.4± 0.58	NA
VI_c	15.4± 0.58	17.3± 0.63	22.2± 0.78	NA
VI_d	18.6± 0.63	21.2± 0.72	22.4± 0.58	NA
VIIa	19.8.± 0.58	18.7± 0.58	17.6± 0.63	NA
VII_b	15.3± 0.44	18.4± 0.58	19.1± 0.37	NA
VII_c	15.7± 0.19	14.8± 0.19	13.9± 0.37	NA
VII_d	18.6± 0.58	17.3± 0.25	16.3± 0.38	NA
$VIII_a$	20.6± 0.44	22.1± 0.58	22.9± 0.37	NA
$VIII_b$	16.3± 0.58	17.4± 0.63	17.6± 0.63	NA
$VIII_c$	22.3± 0.58	22.8±0.44	24.1±0.53	NA
$VIII_d$	20.3± 0.72	21.4± 0.72	23.6± 0.72	NA
$VIII_e$	20.3± 0.72	21.6± 0.72	24.6± 0.72	NA
$VIII_f$	12.3± 0.72	14.3± 0.72	17.1± 0.72	NA
$VIII_g$	24.3± 0.72	26.2± 0.72	28.3± 0.72	NA
$VIII_h$	11.3± 0.72	14.3± 0.72	15.9± 0.72	NA
$VIII_i$	18.3± 0.72	20.3± 0.72	21.5± 0.72	NA
$VIII_j$	15.4± 0.63	16.2± 0.58	22.1± 0.72	NA
IX	18.2± 0.72	20.4± 0.72	21.3± 0.72	NA
X	20.3± 0.58	21.2± 0.58	22.1± 0.58	NA
XI	22.3± 0.58	24.9± 0.58	25.4± 0.58	NA
XII	21.7± 0.58	22.3± 0.58	22.6± 0.58	NA
XIII	23.4± 0.72	25.3± 0.52	26.7± 0.72	NA
XIV	20.3± 0.72	21.3± 0.52	24.6± 0.72	NA
XV	22.7± 0.72	23.7± 0.72	24.7± 0.72	NA
Amphotricin B	23.7± 0.63	19.7± 0.72	28.7± 0.58	25.4± 0.63

NA= No activity. Table (2): Antifungal activities of compounds III- XV

Table 3 Antibacterial activities against Gram-positive and gram- negative organisms of compounds III- XV

Tested organisms / Sample	*Streptococcus pneumoniae*	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Escherichia coli*
Lead compound	14.3± 0.63	16.2± 0.24	NA	12.1± 0.72
III	18.2± 0.19	19.8± 0.47	NA	18.2± 0.58
VI_a	20.2± 0.55	21.9± 0.52	NA	20.3± 0.58
VI_b	19.3± 0.37	21.3± 0.72	NA	19.8± 0.63
VI_c	17.4± 0.37	19.3± 0.63	NA	16.9± 0.63
VI_d	21.2± 0.63	23.2± 0.58	NA	21.1± 0.58
VIIa	20.3± 0.72	21.2± 0.58	NA	22.6± 0.58
VII_b	15.9± 0.44	16.3± 0.58	NA	13.9± 0.63
VII_c	20.9± 0.37	21.5± 0.28	NA	20.6± 0.44
VII_d	20.3± 0.43	21.4± 0.53	NA	16.3± 0.25
$VIII_a$	22.1± 0.44	22.8± 0.25	NA	20.5± 0.44
$VIII_b$	17.4± 0.63	18.6± 0.58	NA	15.3± 0.58
$VIII_c$	25.3± 0.72	27.7± 0.63	NA	22.2± 0.72
$VIII_d$	22.4± 0.72	25.2± 0.72	NA	21.6± 0.72
$VIII_e$	11.4± 0.44	14.2± 0.67	NA	10.4± 0.46
$VIII_f$	17.4± 0.25	16.2± 0.63	NA	15.9± 0.44
$VIII_g$	25.4± 0.27	31.6± 0.58	NA	23.3± 0.25
$VIII_h$	17.6± 0.18	17.8± 0.19	NA	20.8± 0.19
$VIII_i$	12.6± 0.26	14.3± 0.27	NA	12.6± 0.57
$VIII_j$	16.3± 0.72	17.8± 0.72	NA	15.2± 0.72
IX	19.3± 0.72	19.9± 0.72	NA	16.3± 0.72
X	20.4± 0.72	20.8± 0.72	NA	17.6± 0.72
XI	16.5± 0.72	18.7± 0.72	NA	20.3± 0.72
XII	19.8± 0.72	20.6± 0.72	NA	21.3± 0.72
XIII	22.2± 0.72	23.8± 0.72	NA	21.9± 0.72
XIV	20.6± 0.72	23.8± 0.72	NA	20.6± 0.72
XV	21.8± 0.2	23.8± 0.58	NA	22.3± 0.58
Gentamicin	23.8± 0.2	32.4± 0.58	17.3± 0.63	21.3± 0.58

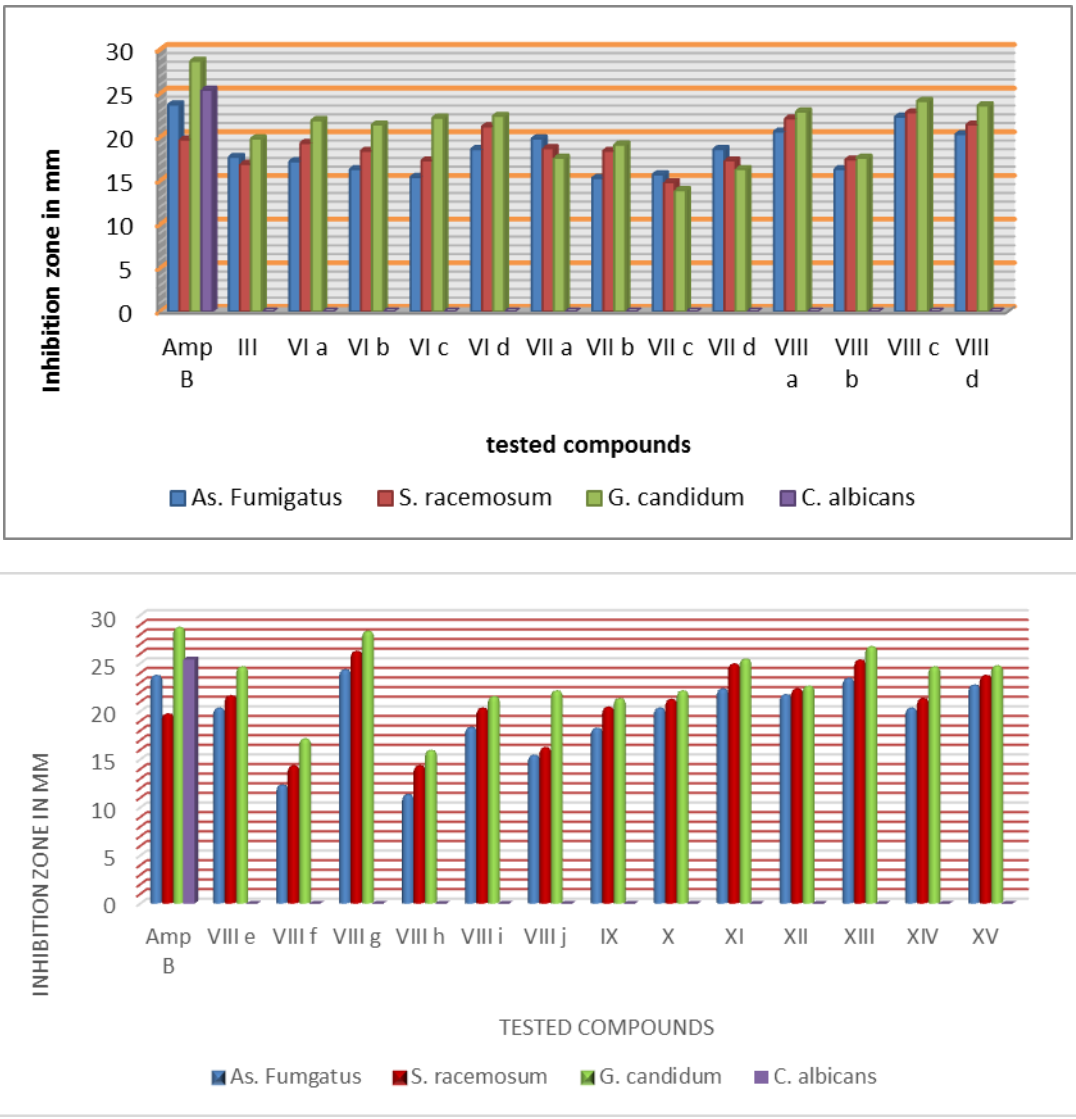
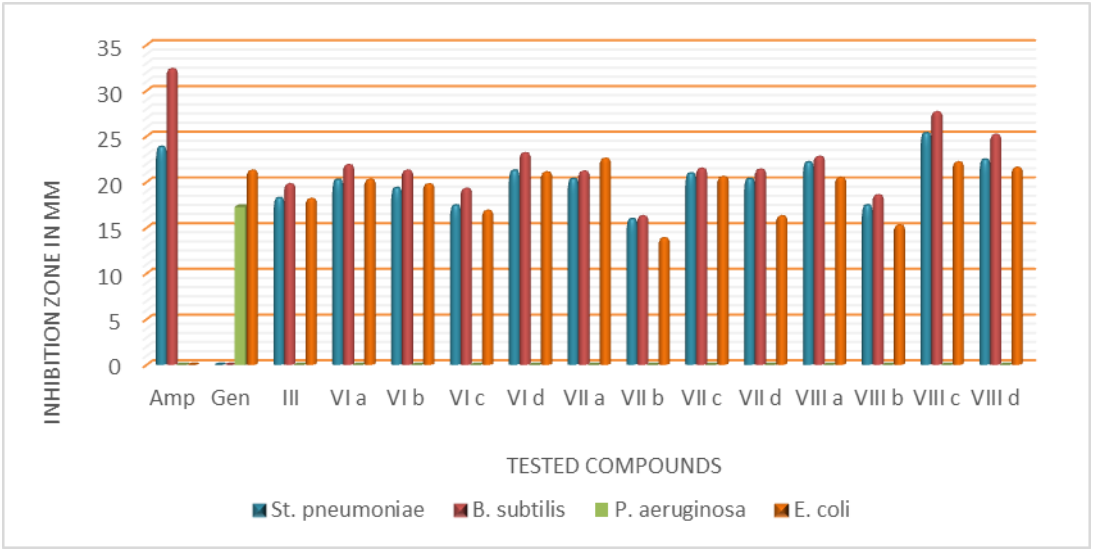


Figure 6 Antifungal activities of compounds III-XV



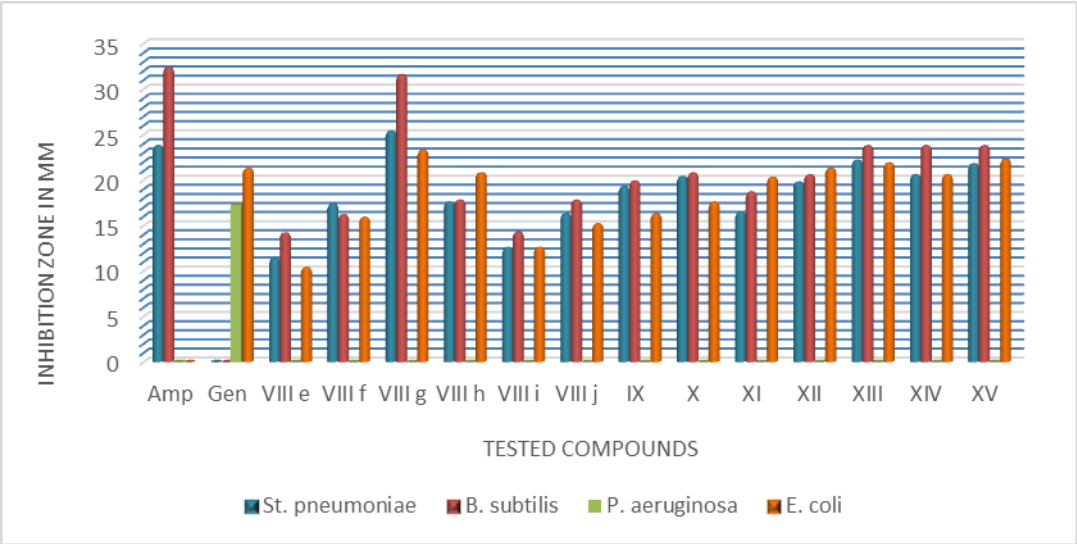


Figure 7 Antibacterial activities of compounds III-XV

3. Conclusion

In the present work, we synthesized novel series of 2-chloroquinolin-3-carboxaldehyde derivatives with different reagents. Screening for some selected compounds was carried for their potential antibacterial, antifungal activity. Most of the tested compounds revealed better activity against the Gram-positive rather than the Gram negative bacteria. All test compounds were found to be inactive against *Pseudomonas aeuroginosa*. Compounds **$VIII_g$**, **$VIII_c$**, **$VIII_d$** and **XIII** exhibited excellent activity against *Staphylococcus aureus*, *Bacillus subtilis* and *Escherichia coli* compared with the standards drugs, while compounds **$VIII_g$**, **XIII** and **XI** have strong antifungal activity against *Aspergillus fumigatus, Syncephalasterum racemosum, and Geotricum candidum, comparable to* Amphotericin B. Finally, none of the synthesized compounds gave any activity against *Candida albicans*.

The results of this study demonstrated that some derivatives possessed good antimicrobial activity, specially, compounds **$VIII_g$**, **XIII**, **$VIII_c$**, **XI** and **$VIII_d$** showed the highest antimicrobial activities of this series. The obtained results showed that compounds VIIIg, XIII, VIIIc, XI and VIIId could be useful as a template for future design, optimization, and investigation to produce more active analogs.

The molecular design was performed to assess the binding mode of the proposed compounds with GlcN-6-P synthase (1XFF) receptor. The obtained data from the docking studies showed that; all the synthesized derivatives had considerable high affinity towards the GlcN-6-P synthase receptor in comparing to compound 1 as a reference ligand. The data obtained from the biological screening fitted with that obtained from the molecular modeling.

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