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Synthesis and docking analysis of new 2-chloro-3-((2,2-dimethylhydrazono) methyl)quinoline derivatives as non-nucleoside human HIV-1 reverse transcriptase inhibitors

Sohrab Ghanei[a], Hossein Eshghi[b]*, Jalil Lari[a] and Mohammad Saadatmandzadeh[b]

[a]*Department of Chemistry, School of Sciences, Payam Nour University of Mashhad, Mashhad, Iran*
[b]*Department of Chemistry, School of Sciences, Ferdowsi University of Mashhad, Mashhad, Iran*

ABSTRACT

*In recent years, the chemistry of 2-chloroquinoline-3-carbaldehydeshave received considerable attention owing to their synthetic and effective biological importance which exhibits a wide variety of biological activity, and 2-chloro-3-((2,2-dimethylhydrazono)methyl)quinoline derivatives that synthesized from 2-chloroquinoline-3-carbaldehydes may have biological effects as non-nucleoside Human HIV-1 Reverse Transcriptase Inhibitors. A group of 2-chloro-3-((2,2-dimethylhydrazono)methyl) quinolone derivatives were synthesized, and theoretically evaluated for their inhibitory as non-nucleoside Human HIV-1 Reverse Transcriptase Inhibitors via docking process. The docking calculation was done in GOLD 5.2.2 software using Genetic algorithm. Compounds**3g** and **3b** showed the best inhibitory potency by GOLD score value of 79.24 and 78.34 respectively.* Some *of the best models formed strong hydrogen bonds with Lys 103via quinoline moiety. It was found that pi-pi interaction between Lys 103,Lys 101, Trp229, Trp 181, Tyr 181, Tyr 188, and Phe 227 side chain and quinolin moiety was one of the common factors in enzyme-inhibitor junction. It was found that both hydrogen bonding and hydrophobic interactions are important in the structure and function of biological molecules, especially for inhibition in a complex.*

Keywords: Human HIV-1, Reverse Transcriptase inhibitors, Docking Analysis, Heterocyclic compound, Quinoline derivatives.

INTRODUCTION

The human immunodeficiency virus (HIV) is a lentivirus (a subgroup of retrovirus) that causes the acquired immunodeficiency syndrome (AIDS) [1, 2],a condition in humans in which progressive failure of the immune system allows life-threatening opportunistic infections and cancers to thrive. Without treatment, average survival time after infection with HIV is estimated to be 9 to 11 years, depending on the HIV subtype [3]. Infection with HIV occurs by the transfer of blood, semen, vaginal fluid, pre-ejaculate, or breast milk. Within these bodily fluids, HIV is present as both free virus particles and virus within infected immune cells.

HIV infects vital cells in the human immune system such as helper T cells (specifically CD4+ T cells), macrophages, and dendritic cells [4]. HIV infection leads to low levels of CD4+ T cells through a number of mechanisms, including apoptosis of uninfected bystander cells [5], direct viral killing of infected cells, and killing of infected CD4+ T cells by CD8 cytotoxic lymphocytes that recognize infected cells [6]. When CD4+ T cell numbers decline below a critical level, cell-mediated immunity is lost, and the body becomes progressively more susceptible to opportunistic infections.

Reverse transcriptase (RT)plays a key role in the replication of HIV by converting single-stranded genomic RNA into double-stranded proviral DNA and represents one of the main targets for the development of AIDS therapy. Most inhibitors of RT described in the past years, whether nucleoside analogues or non-nucleoside inhibitors target

the polymerase activity of RT but present some limitations including toxicity and the emergence of resistant strains [7–9].
Docking is an important trend in the study of protein ligand interaction properties such as binding energy, geometry complementarity, hydrogen bond donor acceptor, hydrophobicity, electron distribution and polarizability thus it plays a major role in the drug discovery for the identification of suitable molecular scaffold and distinguishing selectivity for the target protein [10].

GOLD, the first algorithm to be evaluated on a large data set of complex posse, an empirical free energy scoring function that estimates the free energy of binding permitting inhibition constant for protein ligand complex. It is a package of program for structure visualization and manipulation for docking, the post processing and visualization of the results [11]. The objective of the present work is to study the in silico of Human HIV-1 Reverse Transcriptase inhibitory activity of some new2-chloro-3-((2,2-dimethylhydrazono)methyl)quinoline.

Quinoline and its derivatives have always attracted both synthetic and biological chemist because of its diverse chemical and pharmacological properties [12]. For example quinine has been used for the treatment of malaria [13], dynemicin A and streptonigrin, naturally occurring members of the class of antitumor antibiotic [14, 15]. According to the best of our review the literature we find that compounds containing quinoline [16-19],have been reported to exhibit anti-inflammatory activity[20].To study the combined effect of these two moieties (quinoline and diimine) in a single network, there is an interest in the synthesis of 2-chloro-3-((2,2-dimethylhydrazono)methyl) quinoline**(3a-3g).** Therefore, we studied our compound as a potential inhibitor for Human HIV-1 Reverse Transcriptase enzyme.

EXPERIMENTAL SECTION

2.1 Experimental

The products were characterized by spectroscopic data (IR, ^{1}H NMR, and mass spectroscopy). The purity determinations of the products were accomplished by TLC on silica gel polygram STL G/UV 254 plates. Melting points were determined with an Electrothermal Type 9100 melting point apparatus. Elemental analyses were made by a Thermo Finning Flash EA1112 CHNO-S analyzer and agreed with the calculated values. The FTIR spectra were recorded on an Avatar 370 FTIR Therma Nicolet spectrometer. The NMR spectra were recorded on a Bruker Avance 100 and 400 MHz instrument in $CDCl_3$. Mass spectra were recorded on Agilent Technology (HP) Model 5973Network Mass Selective Detector.

2.2 General experimental procedure for the preparation of2-chloro-3-((2,2-dimethylhydrazono) methyl) quinoline(3a-g).

A mixture of 2-chloroquinoline-3-carbaldehydes (3 mmol, 0.5734g) **(1)**, 1,1-dimethylhydrazine(3 mmol, 0.1803ml) **(2)**, few drops glacial acetic acid and 40 mL EtOH in a 100 mL flask was stirred at reflux for 4 hours . After completion of the reaction (monitored by TLC, ethyl acetate/n-hexane, 1/1), 80 mL of distilled water was added to the reaction mixture, the resulting solid was separated by filtration, and recrystallized from ethanol to afford pure product.

2.2.1 2-Chloro-3-((2,2-dimethylhydrazono)methyl)quinoline(3a)

Yield: 70%; mp 97-99 °C; IR (KBr)υ cm^{-1}:3000-3100(CH aromatic), 2854(CH aliphatic), 1581 (C=N imine), 1550 (C=N quinoline), 1481 (C=C quinoline), 1470(C=C phenyl), 1045(C-Cl quinolone ring). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, ppm) δ: 3.12 (s, 6H, CH_3, N-CH_3), 7.47 (s, 1H, HC=N),7.50 (t, J=7.5Hz,1H, ArH), 7.63(t, J=7.5Hz, 1H, ArH),7.81 (d, 1H, J=8Hz,ArH), 7.95 (d,1H, J=8.2Hz, ArH), 8.59(s, 1H, quinoline ring H). Anal. Calcd. for $C_{12}H_{12}ClN_3$: C, 61.67; H, 5.18; Cl, 15.17; N, 17.98; Found: C, 61.62; H, 5.15; N, 17.99. Mass (m/z): 233.2(M^+)

2.2.2 2-Chloro-3-((2,2-dimethylhydrazono)methyl)-6-methylquinoline (3b)

Yield: 72%; mp 105 °C; IR (KBr)υ cm^{-1}:3000-3150 (CH aromatic), 2850(CH aliphatic), 1610 (C=N imine), 1546 (C=N quinoline), 1540 (C=C quinoline), 1480(C=C phenyl), 1045(C-Cl quinoline ring). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, ppm) δ: 2.50 (s, 3H, CH_3);3.10 (s, 6H, CH_3,N-CH_3), 7.40-7.50 (m, 2H), 7.56 (s, 1H,ArH), 7.83(d, 1H, J=8.5Hz, ArH), 8.50(s, 1H, quinoline ring H). Anal. Calcd. for Anal. Calcd. for $C_{13}H_{14}ClN_3$: C, 63.03; H, 5.70; Cl, 14.31; N, 16.96; Found: C, 63.05; H, 5.68; N, 16.94.

2.2.3 2-Chloro-3-((2,2-dimethylhydrazono)methyl)-6-methoxyquinoline (3c)

Yield: 75%; mp 122 °C; IR (KBr)υ cm^{-1}:3100 (CH aromatic), 2877 (CH aliphatic), 1620 (C=N imine), 1585 (C=N quinoline), 1562 (C=C quinoline), 1500(C=C phenyl),1230(C-O), 1041(C-Cl quinolone ring).^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, ppm) δ: 3.10 (s, 6H, CH_3,N-CH_3), 3.90 (s, 3H, OCH_3),7.05 (d, 1H, J=2.75Hz,ArH), 7.28 (dd, 1H, J=9.5, 2.5Hz, ArH), 7.45(s, 1H,ArH), 7.83 (d, 1H, J=9.5Hz, ArH), 8.49(s, 1H, quinoline ring H).for Anal. Calcd.

for $C_{13}H_{14}ClN_3O$: C, 59.21; H, 5.35; Cl, 13.44; N, 15.93; O, 6.07; Found: C, 59.23; H, 5.33; N, 15.95.

2.2.4 2,6-Dichloro-3-((2,2-dimethylhydrazono)methyl)quinoline (3d)

Yield: 69%; mp 135-137°C; IR (KBr)υ cm^{-1}: 3100-3200(CH aromatic), 2900-3000(CH aliphatic), 1585 (C=N imine), 1546 (C=N quinoline), 1530 (C=C quinoline), 1481(C=C phenyl), 1049(C-Cl quinolone ring). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, ppm) δ: 3.08 (s, 6H, CH_3,N-CH_3), 7.40 (s, 2H, HC=N),7.54 (dd,1H,J=8.25, 2Hz), 7.77 (d, 1H, J=1.75Hz, ArH), 8.48(s, 1H, quinoline ring H). for Anal. Calcd. for $C_{12}H_{11}Cl_2N_3$: C, 53.75; H, 4.13; Cl, 26.44; N, 15.67; Found: C, 53.78; H, 4.15; N, 15.66

2.2.5 2-Chloro-3-((2,2-dimethylhydrazono)methyl)-7-methylquinoline (3e)

Yield: 80%; mp 109 °C; IR (KBr)υ cm^{-1}: 2900-3100(CH aromatic), 2850(CH aliphatic), 1650 (C=N imine), 1545 (C=N quinoline), 1510 (C=C quinoline), 1490(C=C phenyl), 1041(C-Cl quinolone ring). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, ppm) δ: 2.51(s, 3H, CH_3), 3.08 (s, 6H, CH_3, N-CH_3), 7.31 (d, 1H, J=8.25Hz, ArH), 7.46 (s, 1H, HC=N), 7.69 (d,J=9Hz, 1H,ArH), 7.70 (s, 1H, ArH),8.52(s, 1H, quinoline ring H). for Anal. Calcd. for $C_{13}H_{14}ClN_3$: C, 63.03; H, 5.70; Cl, 14.31; N, 16.96; Found: C, 63.00; H, 5.71; N, 16.95

2.2.6 2-Chloro-3-((2,2-dimethylhydrazono)methyl)-6-isopropylquinoline (3f)

Yield: 70%; mp 98 °C; IR (KBr)υ cm^{-1}:3000-3100(CH aromatic), 2900(CH aliphatic), 1585 (C=N imine), 1546 (C=N quinoline), 1505 (C=C quinoline), 1481(C=C phenyl), 1049(C-Cl quinolone ring).^{1}H NMR (400 MHz, DMSO, 25 °C, ppm) δ: 1.37 (d, 6H, J=6.75, CH_3, Isopropyl), 2.11 (m, 1H,CH Isopropyl), 7.40-7.50 (m, 2H), 7.56 (s, 1H, ArH), 7.83(d, 1H, J=8.5Hz, ArH), 8.49 (s, 1H, quinoline ring H). for Anal. Calcd. for $C_{15}H_{18}ClN_3$: C, 65.33; H, 6.58; Cl, 12.86; N, 15.24; Found: C, 65.35; H, 6.59; N, 15.26**.**

2.2.7 2,7-Dichloro-3-((2,2-dimethylhydrazono)methyl)quinoline (3g)

Yield: 69%; mp 119 °C; IR (KBr)υ cm^{-1}: 3000-3100(CH aromatic), 2900-3000(CH aliphatic), 1604 (C=N imine), 1542 (C=N quinoline), 1527 (C=C quinoline), 1473(C=C phenyl), 1041(C-Cl quinolone ring). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, ppm) δ: 3.11 (s, 6H, CH_3,N-CH_3), 7.40-7.50(m, 2H, ArH), 7.73 (d, 1H, J=8.25Hz, ArH), 7.93(s, 1H, HC=N), 8.54(s, 1H, quinoline ring H). for Anal. Calcd. for $C_{12}H_{11}C_{l2}N_3$: C, 53.75; H, 4.13; Cl, 26.44; N, 15.67; Found: C, 53.74; H, 4.12; N, 15.66.

2.3 Structure optimization

Three dimensional structures of the compounds **3a-g** were simulated in Hyper Chem7.5 using MM+ method (RMS gradient = 0.1 kcal mol^{-1}) (HyperChem® Release 7, Hypercube Inc., http://www.hyper.com/). In the second optimization, output files were minimized under Semi empirical AM1 methods (Convergence limit = 0.01; Iteration limit = 50; RMS gradient = 0.1 kcal mol^{-1}; Polak-Ribiere optimizer algorithm) [20, 21].

Crystal structures of Human HIV-1 Reverse Transcriptase (EC.2.7.7.49) were retrieved from RCSB Protein Data Bank (PDBentry: 1RT1).

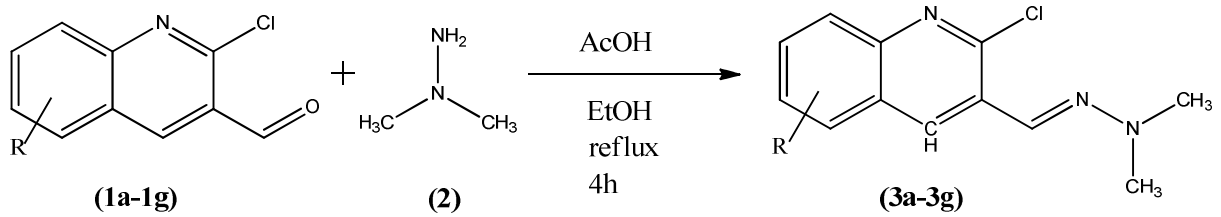
2.4 Molecular docking

Docking was carried out using GOLD 5.2 (Genetic optimization for Ligand Docking) software based on the Gold Score fitness function, that uses the Genetic algorithm (GA). All water molecules and hetero atoms were omitted from the protein to evaluate the two scoring functions in GOLD. For each of the 25 independent GA runs, a maximum number of 100000 GA functions were established on a set of five groups with a population size of 100 individuals. Mutation, migration and operator weights for crossover were set to 95, 10, and 95, respectively. Default cutoff values of 4.0 A for van der Waals distance and 2.5 A (dH-X) for hydrogen bonds were employed. When the top three solutions achieved RMSD values enough 1.5 A, GA docking was terminated. The RMSD values for the docking computations are based on the RMSD matrix of the ranked solutions and observed that the best ranked solutions were always among the first 50 GA runs, and further analyzing of the conformation of molecules performed on the best fitness score. The docking procedure was validated by redocking of the Human HIV-1 Reverse Transcriptase crystal structure 1RT1.

RESULTS

3.1 Chemistry

To formation the products **(3a-3g)**, the reaction took place between 2-chloroquinoline-3- carbaldehydes **(1a-1g)** and 1,1-dimethylhydrazine**(2)**as the starting materials, in ethanol reflex condition,(Scheme1).



(1a-1g) **(2)** **(3a-3g)**

Scheme1

The completion of the reaction was monitored by TLC, and the disappearance of the starting material was catalyzed with few drops of acetic acid and observed within 4 hrs. In order to study the generality of this method, we extended our studies to synthesis of some 2-chloro-3-((2,2-dimethylhydrazono)methyl)quinoline derivatives **(3a-3g).** The reactions proceeded very efficiently in relatively high yields as shown in Table 1. All the products were characterized and confirmed by their spectroscopic and elemental analysis data.

Table1:Synthesis of 2-chloro-3-((2,2-dimethylhydrazono)methyl)quinolone derivatives

Product	*R*	*Yield (%)*[a]	*mp °C*
3a	H	70	97-99
3b	6-Me	72	105
3c	6-OMe	75	122
3d	6-Cl	69	135-137
3e	7-Me	80	109
3f	6-Isopropyl	70	98
3g	7-Cl	69	119

a) Isolated yield

3.2 Docking

The receptor 1RT1 is a complex structure of enzyme. The possible active site was identified using Accelrys DS Visualizer. Eight active site residues as Leu 100, Lys 101, Lys 102, Tyr 181, Tyr 182, Gly 190, Phe 227, Tyr 318 were found. Therefore it is chosen as a most biologically favorable site for docking. Some of the best models formed strong hydrogen bonds with Lys103, via quinoline moiety and nitrogen of quinolone ring (Figure 1). pi - pi Interaction between Lys103, Trp 229, Tyr 181, Tyr 188 and Phe 227 and quinoline moiety was one of the common factor in enzyme-inhibitor junction. Amongst the synthetic compounds, **3c** showed the lowest score while **3f** possessed the highest score. The estimated inhibitory constant of the docked compounds are outlined in Table2.

Table 2: **Estimated inhibitory constant (Ki), free energy of binding, gold score and amino acids involved in hydrogen binding with synthetic compounds**

compound	Gold Score	ΔG (kJ/mol)	Ki	Residues involved in hydrogen binding
3a	78.30	-36.54	3.96381E-07	Tyr 188,Lys 103
3b	78.34	-40.39	8.38657E-08	Lys 103
3c	69.97	-32.24	2.24637E-6	Tyr 181
3d	77.81	-40.36	8.48869E-08	Phe 227
3e	70.69	-32.65	1.90394E-06	Lys 103, Trp 229
3f	79.24	-40.3168	8.62678E-08	Lys 103
3g	74.16	-36.52	3.99592E-07	Tyr 188, Tyr 181
Co crystall	97.12	-36.79	3.58354E-07	Lys 101, Leu 100, Tyr 181, Tyr 188

DISCUSSION

The complete spectral and elemental analytical data of the products confirmed the formation of new 2-chloro-3-((2,2-dimethylhydrazono)methyl)quinolone derivatives **(3a-3g)**.The ^{1}H NMR spectrum of **3a** consist of three singlet signals at δ 3.11, 7.26, 8.59 due to six hydrogen of CH_3 and one imine hydrogen and one hydrogen of quinolone ring that posse nitrogen respectively. The two doublet signal at δ 7.81 and 7.95 due to the two hydrogen on the aromatic ring of quinolines and two triplet for the two hydrogens on the aromatic ring of quinolines at δ 7.50, and 7.63ppm were confirmed to the structure. The mass spectrum shows the molecular ion at 233.2 *m/z*. Also the absence of the stretching vibration band at 1689 cm^{-1} due to the carbonyl group (C=O) in IR spectrum confirmed the structure of **3a.** Comparison of the elemental analyses data of this compound which was in good agreement with calculated data was the final proof for this structure.

Docking of 2-chloro-3-((2,2-dimethylhydrazono)methyl)quinolone with Human HIV-1 Reverse Transcriptase was performed by using of GoldScore fitness function. The algorithm exhaustively searches the entire rotational and translational space of the ligand with respect to the receptors. The various solutions valuated by a score, which is

equivalent to the absolute value of the total energy of the ligand in the protein environment. For each compound the best docking solutions of GOLD score was considered. GoldScore carry out a force field based scoring function and is made up of four components: 1) Ligand internal van der Waals energy (internal vdw); 2) Ligand intermolecular hydrogen bond energy (internal-H-bond); 3) Protein- ligand hydrogen bond energy (external H-bond); 4) Protein-ligand van der Waals energy (external vdw). When the total fitness score is computed the external vdw score is multiplied by a factor of 1.375. This is an empirical correction to persuade protein-ligand hydrophobic interaction. The fitness function has been optimized for the divination of ligand binding positions. GoldScore = $S_{(hb\_ext)}$ + $S_{(vdw\ ext)}$ + $S_{(hb\ int)}$ + $S_{(vdw\ int)}$where $S_{(hb\ ext)}$ is the protein- ligand hydrogen bond score, $S_{(vdw\_ext)}$ is the protein-ligand Van der Waals score, $S_{(hb\_int)}$ is the score from intermolecular hydrogen bond in the ligand and $S_{(vdw\_int)}$ is the score from intermolecular strain in the ligand. Redocking of6-Benzyl-1-ethoxymethyl-5-isopropyl uracil (co crystal)resulted ΔG = -36.79 and Ki = 3.58E-07, bonding model of the mentioned molecule was similar to which was reported in the crystal structure of 1RT1. It was noted that GOLD scores of **3f** and **3b** are 79.24 and 78.34, respectively, which are greater than the other scores as shown in Table 2.

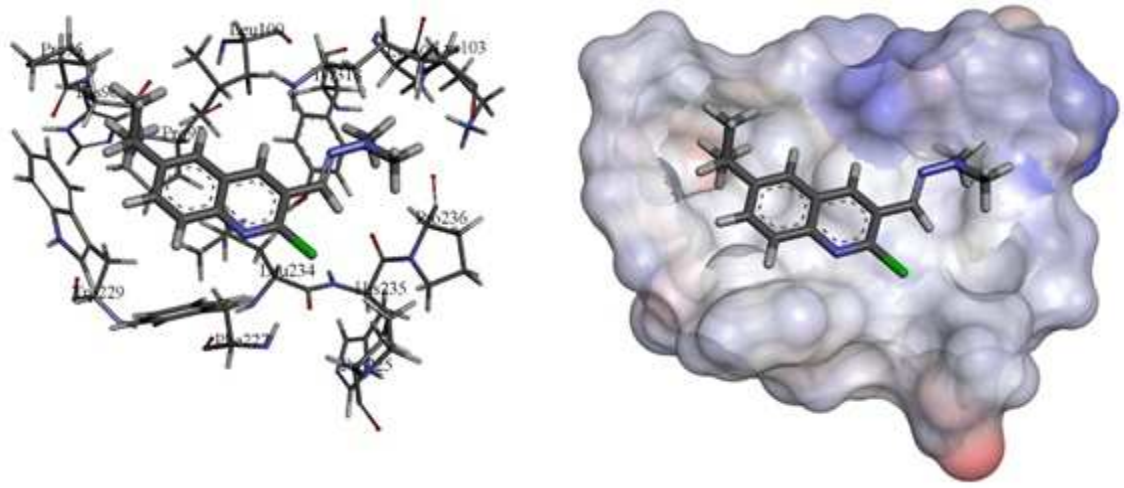


Figure 1: The best docked structure of 3f in the active site pocket of Human HIV-1 Reverse Transcriptase (PDB entry: 1RT1) in stick (left) and solvent surface (right) views

CONCLUSION

In summary we have described an efficient and convenient synthesis of 2-chloro-3-((2,2-dimethylhydrazono)methyl)quinoline involving condensation reaction of 2- chloroquinoline-3-carbaldehydes and 1,1-dimethylhydrazinein acid catalyst condition. Docking was carried out using GOLD 5.2. It was found that both hydrogen bonding and hydrophobic interaction play important roles in the structure and function of biological molecules, peculiarly for inhibition in a complex. It was noted that GOLD scores of **3f** and **3b** are greater than the other scores.

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