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Synthesis and molecular docking of novel *N*-((2-chloroquinolin-3-yl) methylene)-4-methylbenzenamine derivatives as anti-HIV-1 reverse transcriptase inhibitors

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Abstract

In this research work, a proficient method has been developed for the preparation of novel *N*-((2-chloroquinolin-3-yl) methylene)-4-methylbenzenamine derivatives from 2-chloroquinoline-3-carbaldehyde derivatives and *p*-toluidine in ethanol as solvent and using catalytic amount of acetic acid under reflux conditions to obtain desired products in good yields. The identification of all the synthesized compounds was confirmed by melting point, FT-IR, ^{1}H NMR, and ^{13}C NMR. Also, in the present work, all the synthesized compounds were evaluated for their molecular docking as anti-HIV-1 reverse transcriptase inhibitors using GOLD 5.2. software. The results of molecular docking showed that all the compounds established 'π–π' interactions with side chain of amino acid.

Keywords: *N*-((2-chloroquinolin-3-yl) methylene)-4-methylbenzenamine; mlecular docking; *p*-toluidine; 2-chloroquinoline-3-carbaldehyde; anti-HIV; Vilsmeier-Haack reagent.

Introduction

Quinolines and their analogs are very important derivatives of nitrogen-containing heterocycles. They have attracted considerable attention in recent years due to their important applications such as biological activities and medicinal properties [1-3]. Several quinoline derivatives are reported to have useful biological effects, such as anti-asthmatic, anti-inflammatory, anti-bacteria and antihypertensive HIV-1 Integrase Inhibitors [4-6]. Moreover, among the various quinoline derivatives, chloroquinolines are used for the treatment of malaria [7]. Moreover, quinolines are used as solvents for terpenes and resin.

There are several methods for synthesizing substituted quinolines. Vilsmeier-Haack reagent was generated *in situ* by the treatment of $POCl_3$ with DMF [8-10]. This reagent undergoes a lot of synthetic transformations including: formylation [11,12], cyclohaloaddition [13] and cyclization [14]. Therefore, Vilsmeier-Haack

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reagent can be regarded as an efficient and mild reagent for the synthesis of 2-chloro-3-formyl quinolines from acetanilide derivatives. 2-chloro-3-formyl quinolines can be converted into *N*-((2-chloroquinolin-3-yl) methylene)-4-methylbenzenamine derivatives.

HIV stands for human immunodeficiency virus. If left untreated HIV would lead to the disease AIDS (acquired immunodeficiency syndrome). It is estimated that 34 million people worldwide are infected with HIV. There is no vaccine for HIV, so, drugs are the only therapeutic tools that can be used to treat HIV-1. In recent years, synthesis and characterization of anti-HIV compounds have attracted much attention.

Currently, the majority of available drugs for HIV treatment are Reverse Transcriptase (RT) Inhibitors. The reverse transcriptases (RTs) are a diverse group of enzymes; however they share two common functions: (1) a DNA polymerization function which is capable of using either DNA or RNA as a template, and (2) an RNase H function which serves to hydrolyze the RNA strand within an RNA/DNA hybrid. Both the polymerase and RNase H activities are essential for viral replication [15]. Reverse transcriptase (RT) plays a key role in the replication of HIV by converting single-stranded genomic RNA into double-stranded DNA and represents one of the main targets for the development of AIDS therapy [16].

Docking technique plays an important role in drug design. Docking is a computational method which predicts the preferred conformation, orientation, affinity, and activity of small molecules into the active site of target protein.

Due to the significant drug effects of quinolines and their application in anti HIV drugs, we report the synthesis and docking a new series of molecular scaffold containing *N*-((2-chloro quinolin-3-yl) in which methylbenzenamine can provide HIV-1 Reverse Transcriptase inhibitor activity.

Experimental

General: Starting materials and solvents were purchased from Merck and Fluka Chemical Companies. IR spectra were run on a Shimadzu model 8300 FT-IR spectrophotometer. NMR spectra were recorded on a BrukerAvance DPX-250 in $CDCl_3$ as a solvent and TMS as an internal standard. The purity of the products and the progress of the reactions were measured by TLC on silica-gel polygram SILG/UV254 plates. Elemental analyses were performed on Eager 300. Melting points (uncorrected) were determined in open capillary tubes on a Kruss KSP 1N apparatus.

General procedure for synthesis of Arylacetamides (1a-1g)

Arylacetamides were prepared using the published method [17]. Aniline derivatives (20 mL) were cooled in an ice bath, and then acetic anhydride (30 mL) was added drop wise. Upon completion of addition, the reaction mixture was stirred for 30 min at room temperature. Afterward, H_2O (100 mL) was added to the reaction mixture, and the precipitated was separated with a simple filtration. The filtered product was dried in oven at 40 °C for 4 h.

General procedure for synthesis of 2-choloro-3-quinolinecarbaldehydes (2a-2g)

2-Choloro-3-quinolinecarbaldehydes were prepared according to the literature procedure [18]. Firstly, DMF (3 mL) was added to a stirred $POCl_3$ (12 mL) in ice bath (0 °C). After that,

arylacetamide (3 mmol) was added. Then, the reaction was taken out of the cooling bath and heated at 90 °C. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, and the precipitated solid was collected by filtration. The crude product was purified by recrystallization from ethyl acetate to give desired compounds.

General procedure for the preparation of *N*-((2-chloroquinolin-3-yl) methylene)-4-methylbenzenamines (3a-3g).

2-Chloroquinoline-3-carbaldehydes (3 mmol, 0.573 g), *p*-toluidine (3 mmol, 0.321 g) and 2-3 drops glacial acetic acid and EtOH (30 mL) were added to a round-bottom flask. The reaction mixture was stirred for appropriate time in reflux temperature. Afterwards, the progress of the reaction was monitored by TLC. After completion of the reaction, the resulting product was separated by filtration and recrystallized from ethanol in order to afford pure product.

***N*-((2-chloroquinolin-3-yl) methylene)-4-methylbenzenamine (3a)**

IR (KBr) υ cm^{-1}: 2854 (CH aliphatic), 1600 (C=N imine), 1573 (C=N quinoline), 1504 (C=C quinoline), 1500(C=C phenyl), 1049(C-Cl quinolone ring); ^{1}H NMR (250 MHz, $CDCl_3$, ppm) δ: 2.34 (s, 3H, CH_3), 7.24 (m, 4H, ArH, overlapped with solvent),7.60 (t, 1H, *J* = 6.7 Hz, ArH), 7.77 (t, 1H, *J* = 5.7 Hz, ArH), 7.95 (d, 1H, *J*= 7.75 Hz, ArH), 8.04 (d, 1H, *J*= 8.2 Hz, ArH), 8.98 (s, 1H, HC=N), 9.03 (s, 1H, quinoline ring H); ^{13}C NMR (62 MHz, $CDCl_3$, ppm) δ: 21.60, 114.51, 122.67, 127.23, 127.50, 127.64, 128.00, 134.03, 136.56, 137.61, 144.17, 146.96, 152.07, 153.43, 159.01; Anal. Calcd. For $C_{17}H_{13}ClN_2$: C, 72.73; H, 4.64; N, 9.98; Found: C, 72.97; H, 4.86; N, 10.23.

***N*-((2-chloro-6-methylquinolin-3-yl) methylene) -4-methyl benzenamine (3b)**

IR (KBr) υ cm^{-1}: 2916 (CH aliphatic), 1610 (C=N imine), 1577 (C=N quinoline), 1504 (C=C quinoline), 1500 (C=C phenyl), 1053(C-Cl quinolone ring); ^{1}H NMR (250 MHz, $CDCl_3$, ppm) δ: 2.4 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 7.25 (m, 4H, ArH, overlapped with solvent), 7.61 (d, 1H, *J* = 7.5 Hz, ArH), 7.69 (s, 1H, ArH), 7.93 (d, 1H, *J*= 8.5 Hz, ArH), 8.93 (s, 1H, HC=N), 8.97(s, 1H, quinoline ring H); ^{13}C NMR (62 MHz, $CDCl_3$, ppm) δ: 21.56, 22.67, 115.92, 121.63, 126.97, 132.10, 132.44, 132.94, 134.83, 136.76, 137.63, 143.92, 147.16, 148.89, 153.63, 160.05; Anal. Calcd. For $C_{18}H_{15}ClN_2$: C, 73.34; H, 5.13; N, 9.58; Found: C, 73.05; H, 5.24; N, 9.83.

***N*-((2-chloro-6-methoxyquinolin-3-yl) methylene) -4-methyl benzenamine (3c)**

IR (KBr) υ cm^{-1}: 2916 (CH aliphatic), 1616 (C=N imine), 1573 (C=N quinoline), 1504 (C=C quinoline), 1500 (C=C phenyl), 1053 (C-Cl quinolone ring); ^{1}H NMR (250 MHz, $CDCl_3$, ppm) δ: 2.4 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 7.17 (s, 1H, ArH),7.24 (m, 4H, ArH, overlapped with solvent), 7.42 (dd, 1H, J_1= 9.25 Hz, J_2= 2.5 Hz, ArH), 7.93 (d, 1H, *J*= 8.5 Hz, ArH), 8.92 (s, 1H, HC=N), 8.97(s, 1H, quinoline ring H); ^{13}C NMR (62 MHz, $CDCl_3$, ppm) δ: 21.06, 55.63, 105.82, 121.12, 124.71, 127.70, 128.29, 129.73, 129.93, 136.15, 136.95, 144.63, 147.75, 148.74, 154.94, 158.44; Anal. Calcd. For $C_{18}H_{15}ClN_2O$: C, 69.57; H, 4.86; N, 9.01; Found: C, 69.31; H, 5.09; N, 9.31.

***N*-((2-chloro-6-ethoxyquinolin-3-yl) methylene))-4-methyl benzenamine (3d)**

IR (KBr) υ cm^{-1}: 2916 (CH aliphatic), 1620 (C=N imine), 1573 (C=N quinoline), 1504 (C=C quinoline), 1500 (C=C phenyl), 1283 (C-O), 1053 (C-Cl quinolone ring); ^{1}H NMR (250 MHz, $CDCl_3$, ppm) δ: 1.5 (t, 3H, *J* = 7 Hz, CH_3), 2.4 (s, 3H, CH_3), 4.15 (q, 2H, *J* = 7 Hz, CH_2), 7.16 (d, 1H, *J* = 8.5 Hz, ArH), 7.26 (m, 4H, ArH, overlapped with solvent), 7.42 (dd, 1H, J_1 = 9.25 Hz, J_2 = 2.25 Hz, ArH), 7.92 (d, 1H, *J* = 9.25 Hz, ArH), 8.90 (s,1H, HC=N), 8.97 (s, 1H, quinoline ring H). Anal. Calcd; ^{13}C NMR (62 MHz, $CDCl_3$, ppm) δ: 15.01, 21.62, 61.26, 106.52, 114.51, 122.67, 124.07, 125.14, 128.15, 128.93, 134.03, 136.56, 137.61, 142.37, 147.14, 152.83, 158.97; For $C_{19}H_{17}ClN_2O$: C, 70.26; H, 5.87; N, 8.62; Found: C, 70.59; H, 6.15; N, 9.06.

***N*-((2,6 - di chloro quinolin-3-yl) methylene) -4-methyl benzenamine (3e)**

IR (KBr) υ cm^{-1}: 2783 (CH aliphatic), 11615 (C=N imine), 1593 (C=N quinoline), 1515 (C=C quinoline), 1485(C=C phenyl), 1053 (C-Cl quinolone ring); ^{1}H NMR (250 MHz, $CDCl_3$, ppm) δ: 2.4 (s, 3H, CH_3), 7.24 (m, 4H, ArH, overlapped with solvent), 8.97 (d, 1H, *J* = 9 Hz, ArH), 7.92 (s, 1H, ArH), 7.98 (d, 1H, *J* = 9 Hz, ArH), 8.94 (s, 1H, HC=N), 8.97 (s, 1H, quinoline ring H); ^{13}C NMR (62 MHz, $CDCl_3$, ppm) δ: 21.81, 118.90, 120.16, 123.62, 124.35, 126.13, 128.15, 129.75, 136.84, 138.96, 142.00, 145.80, 147.75, 154.94, 160.93; Anal. Calcd. For $C_{17}H_{12}Cl_2N_2$: C, 64.78; H, 3.84; N, 8.89; Found: C, 65.05; H, 4.17; N, 8.99.

***N*-((2, 7-di chloro quinolin-3-yl) methylene) -4-methyl benzenamine (3f)**

IR (KBr) υ cm^{-1}: 2858 (CH aliphatic), 1604 (C=N imine), 1593 (C=N quinoline), 1515 (C=C quinoline), 1473 (C=C phenyl), 1049(C-Cl quinolone ring); ^{1}H NMR (250 MHz, $CDCl_3$, ppm) δ: 2.41 (s, 3H, CH_3), 7.25 (m, 4H, ArH, overlapped with solvent), 7.56 (d, *J* = 8.75 Hz, 1H, ArH), 7.89 (d, 1H, *J* = 8.75 Hz, ArH), 8.04 (s, 1H, ArH), 8.97 (s, 1H, HC=N), 9.01(s, 1H, quinoline ring H); ^{13}C NMR (62 MHz, $CDCl_3$, ppm) δ: 21.45, 119.06, 120.65, 122.82, 123.34, 126.52, 129.15, 133.02, 136.66, 138.26, 139.84, 140.91, 146.22, 156.75, 160.53; Anal. Calcd. For $C_{17}H_{12}Cl_2N_2$: C, 64.78; H, 3.84; N, 8.89; Found: C, 64.38; H, 4.07; N, 9.01.

***N*-((2-chloro-7-methylquinolin-3-yl) methylene))-4-methyl benzenamine (3g)**

IR (KBr) υ cm^{-1}: 2858 (CH aliphatic), 1604 (C=N imine), 1593 (C=N quinoline), 1508 (C=C quinoline), 1473 (C=C phenyl), 1049(C-Cl quinolone ring); ^{1}H NMR (250 MHz, $CDCl_3$, ppm) δ: 2.41 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 7.26 (m, 4H, ArH, overlapped with solvent), 7.44 (dd, J_1= 8 Hz, J_2 = 1.25 Hz, 1H, ArH), 7.85 (d, 1H, *J* = 8.75 Hz, ArH), 7.86 (s,1H, HC=N), 8.07(s, 1H), 8.98(s, 1H, quinoline ring H); ^{13}C NMR (62 MHz, $CDCl_3$, ppm) δ: 20.64, 21.56, 116.76, 125.48, 125.98, 126.65, 131.72, 132.44, 135.24, 136.44, 137.33, 140.31, 144.47, 147.56, 153.44, 160.64; Anal. Calcd. For $C_{18}H_{15}ClN_2$: C, 73.34; H, 5.13; N, 9.5; Found: C, 73.69; H, 5.3; N, 9.04.

Molecular docking

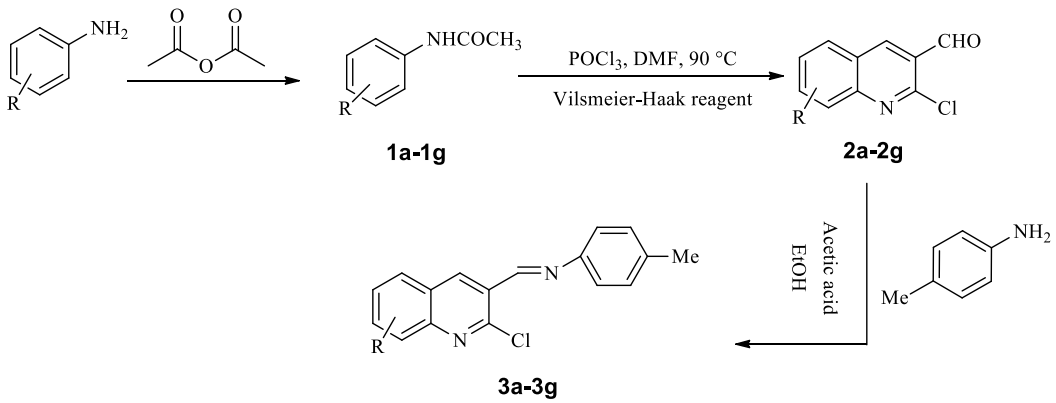
Docking was carried out using GOLD 5.2 (Genetic optimization for Ligand Docking) software based on the Gold Score fitness function using the Genetic algorithm (GA). All water molecules and hetero atoms were omitted from the protein to evaluate the two scoring functions in GOLD. For each of the 25

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. It is worth mentioning that the best ranked solutions were always among the first 50 GA runs, and further analyzing of the conformation of molecules was performed on the best fitness score. The docking procedure was validated by redocking of the Human HIV-1 Reverse Transcriptase crystal structure 1RT1.

Results and discussion

Although there are many methods for the synthesis of functionalized quinoline, it seems that the Vilsmeier-Haack method to be the best one. Thus, in this paper, we reported synthesis of 2-choloro-3-quinolinecarbaldehydes **2a-2g** and transformation of them into *N*-((2-chloroquinolin-3-yl) methylene)-4-methylbenzenamine derivatives **3a-3g** with the aim of exploring their anti HIV activity.

To develop an efficient procedure to prepare *N*-((2-chloroquinolin-3-yl) methylene)-4-methylbenzenamine derivatives **3a-3g**, we initially needed acetanilide derivatives and 2-choloro-3-quinolinecarbaldehydes. The synthetic method is illustrated in scheme 1. First, in order to optimize the reaction conditions, we studied reaction of aniline and acetic anhydride as a model.



Scheme 1. Synthesis of *N*-((2-chloroquinolin-3-yl) methylene)-4-methylbenzenamine derivatives

Initially, acetanilide **1** was simply prepared *via* the reaction of aniline with acetic anhydride. When the reaction was complete, water was added to the reaction mixture, and the precipitation was separated with a simple filtration and recrystallized from water. The reaction was preceded in less than one hour with good yield. To develop an efficient procedure to prepare 2-choloro-3-quinolinecarbaldehyde **2**, we selected Vilsmeier-Haack reaction of acetanilide **1** adding DMF and $POCl_3$ at 0 °C followed by heating to 85-90 °C. As expected, we observed the desired product in 88% yield after 2 h.

2-Choloro-3-quinolinecarbaldehyde which has formyl functional group can be converted to other functional groups

such as imine. However, new quinolones are obtained which are important in anti HIV drugs. Therefore, corresponding *N*-((2-chloroquinolin-3-yl) methylene)-4-methylbenzenamine. Thus, *p*-toluidine, and 2-choloro-3-quinolinecarbaldehyde were refluxed for 2 h in the presence of acetic acid as a catalyst and ethanol as a solvent. We observed that the reaction did not proceed without the addition of acetic acid.

According to the obtained results, acetic acid activated formyl group, and, then, we have the nucleophilic attacks of the amino group in *p*-toluidine on the formyl group. Finally, by the removal of a water molecule, the imine bond is achieved.

After this success, in order to determine the generality of this reaction, we used various anilines with electron-withdrawing and electron-donating groups (Table 1).

the formyl group in 2-choloro-3-quinolinecarbaldehyde was transformed into imine group to afford the

We observed that anilines with electron-donating groups provide corresponding products as compared to the electron-withdrawing groups. All the products were characterized and confirmed by their spectroscopic and elemental analysis data. The IR spectrum of **3a** showed characteristic absorption bands at 1600 cm^{-1}, which is due to the HC=N functional group. The ^1H NMR spectrum of **3a** showed a singlet signal for CH_3 at 2.34 ppm. The four protons of the aromatic ring resonated as a singlet at 7.24 ppm and five protons of the quinoline ring resonated as two triplets at δ 7.60 and 7.77 ppm, two doublets at δ 7.95 and 8.04, and a singlet signal at δ 9.03 ppm. Besides, their ^1H NMR spectrum showed the presence of a singlet signal at δ 8.98 ppm corresponding to imine hydrogen of product.

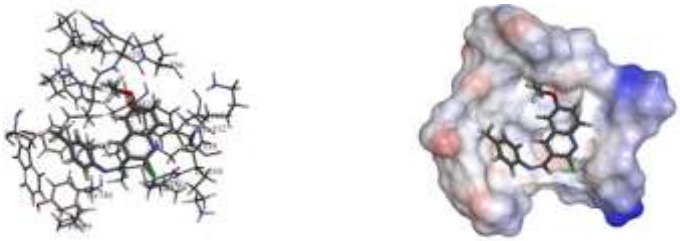
Table1. Synthesis of *N*-((2-chloroquinolin-3-yl) methylene)-4-methylbenzenamine derivatives

Entry	Product	R	Time (h)	Yield (%)	M.p. (°C)
1	**3a**	H	2	61	116-118
2	**3b**	6-Me	3.5	59	140-142
3	**3c**	6-OMe	2.5	52	174-176
4	**3d**	6-OEt	2.5	71	155-157
5	**3e**	6-Cl	4.5	61	161-163
6	**3f**	7-Cl	4	72	180-182
7	**3g**	7-Me	3	69	172-174

Molecular docking studies

After the success of synthesis and characterization of the *N*-((2-chloroquinolin-3-yl) methylbenzenamine derivatives, we carried out *in silico* studies. Molecular docking is a useful tool for drug discovery. It is used to predict binding interaction of a protein receptor with its ligand *via* hydrogen bond, non-bonded 'π–π' and 'π–$^+$' interactions. Molecular docking of *N*-((2-chloroquinolin-3-yl) methylbenzenamine derivatives **3a-3g** to the HIV-1 RT was evaluated to investigate their binding styles. All docking and Gold scores, binding

energy and Ki were performed and the results are summarized in Table 2. Docking of all ligands with HIV-1 RT exhibit bonds with amino acids present in the active pocket of the receptor.



A B

Figure 1. Three dimensional view of the binding interaction of 3d with active site of HIV-1 reverse transcriptase

To explain the results, we performed binding mode of **3d** to the active site of HIV-1 RT. At first, we optimized geometry of compound **3d** (Figure 1). As illustrated in Figure 2, amino acid residues, Leu 228, Val 108, Tyr188, Gln 222, Lys 223, Glu 224, Phe 227, Trp 229 are interacting with **3d** compound. Docking studies revealed intermolecular Van der Waals interaction with Glu 224 and Leu 228, *via* oxygen atom of the methoxy moiety and nitrogen of imine group. Amongst the synthetic compounds, 3a showed the lowest Gold score while **3d** possessed the highest score.

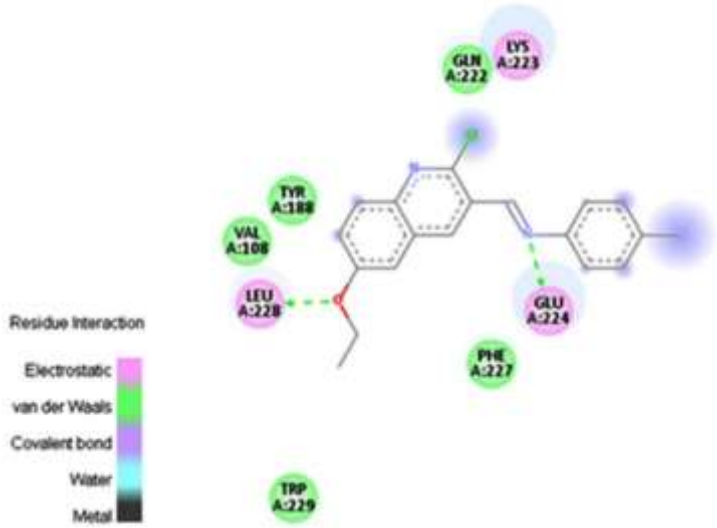


Figure 1. Two dimensional view of the binding interaction of **3d** with active site of HIV-1 reverse transcriptase

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

Entry	Compound	Gold Score	ΔG (kJ/mol)	Ki(1/k)
1	**3a**	89.23	-45.2762	1.1664E-08
2	**3b**	97.12	-48.6444	3.0072E-09
3	**3c**	91.05	-45.2608	1.1758E-08
4	**3d**	99.55	-46.9421	5.9705E-09
5	**3e**	96.96	-46.6593	6.6845E-09
6	**3f**	92.68	-46.191	8.08E-09
7	**3g**	93.30	-45.5576	1.0418E-08

Conclusion

In conclusion, we have demonstrated an efficient procedure for the synthesis of some new *N*-((2-chloroquinolin-3-yl) methylbenzenamines using 2-chloroquinoline-3-carbaldehydes and *p*-toluidine in the presence of acetic acid. The reactions afforded acceptable yields under mild condition.

Molecular docking studies were done using GOLD 5.2 software. Docking showed that 3d compound exhibited significant anti HIV-1 Reverse Transcriptase activity. The obtained results show that 3d compound is connected to Leu 228 and Glu 224 amino acids van der Waals interaction.

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