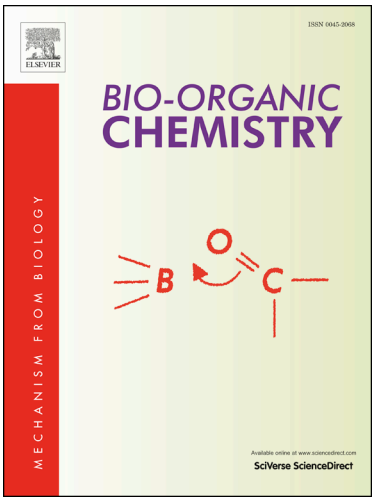


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# Synthesis of C-2 and C-3 substituted quinolines and their evaluation as anti-HIV-1 agents

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**Abstract**

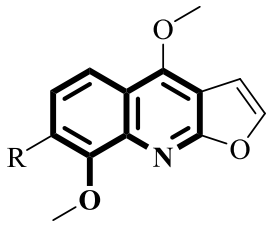
A plenty of natural products and synthetic derivatives containing quinoline moiety have been reported to possess various pharmacological activities. Quinolines such as 2-styrylquinolines and 8-hydroxyquinolines are extensively studied for their anti-HIV-1 activity and found to act mainly through HIV-1 integrase enzyme inhibition. In continuation of our efforts to search for newer anti-HIV-1 molecules, thirty-one quinoline derivatives with different linkers to ancillary phenyl ring were synthesized and evaluated for *in vitro* anti-HIV-1 activity using TZM-bl assays. Compound **31** showed higher activity in TZM-bl cell line against HIV-$1_{VB59}$ and HIV-$1_{UG070}$ cell associated virus ($IC_{50}$ 3.35±0.87 and 2.57±0.71 μM) as compared to other derivatives. Compound **31** was further tested against cell free virus HIV-$1_{VB59}$ and HIV-$1_{UG070}$ ($IC_{50}$ 1.27±0.31 and 2.88±1.79 μM, TI 42.20 and 18.61, respectively). This lead molecule also showed good activity in viral entry inhibition assay and cell fusion assay defining its mode of action. The activity of compound **31** was confirmed by testing against HIV-$1_{VB51}$ in activated peripheral blood mononuclear cells (PBMCs). Binding interactions of **31** were compared with known entry inhibitors.

**Keywords**

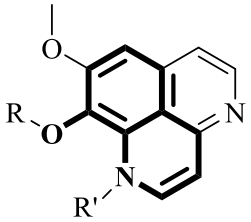
Quinoline, $\alpha,\beta$-Unsaturated amide, 1,3,4-Oxadiazole, Anti-HIV-1, Entry inhibition, Fusion inhibition

## 1. Introduction

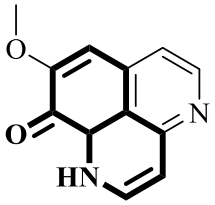
A large number of biologically important natural products and synthetic derivatives containing quinoline moiety have been reported to possess anti-bacterial, anti-fungal, anti-parasitic, anti-viral, anti-protozoal, anti-neoplastic, cytotoxic, anti-inflammatory and immunosuppressive activities [1]. Amongst the anti-viral profile, quinoline derivatives with various substituents have been reported for *in vitro* anti-HIV activity through various mechanisms [2-9]. Some of the natural products with 8-oxygenated quinoline as substructure possessing anti-HIV-1 activity are depicted in Figure 1.



**1**: R=H, $EC_{50}$ <0.44 μM
**2**: R=OH, $EC_{50}$ 2.58 μM



**3**: R=$CH_3$, R'=H; $EC_{50}$ 1.3 μM
**4**: R=H, R'=$CH_3$; $EC_{50}$ 0.6 μM



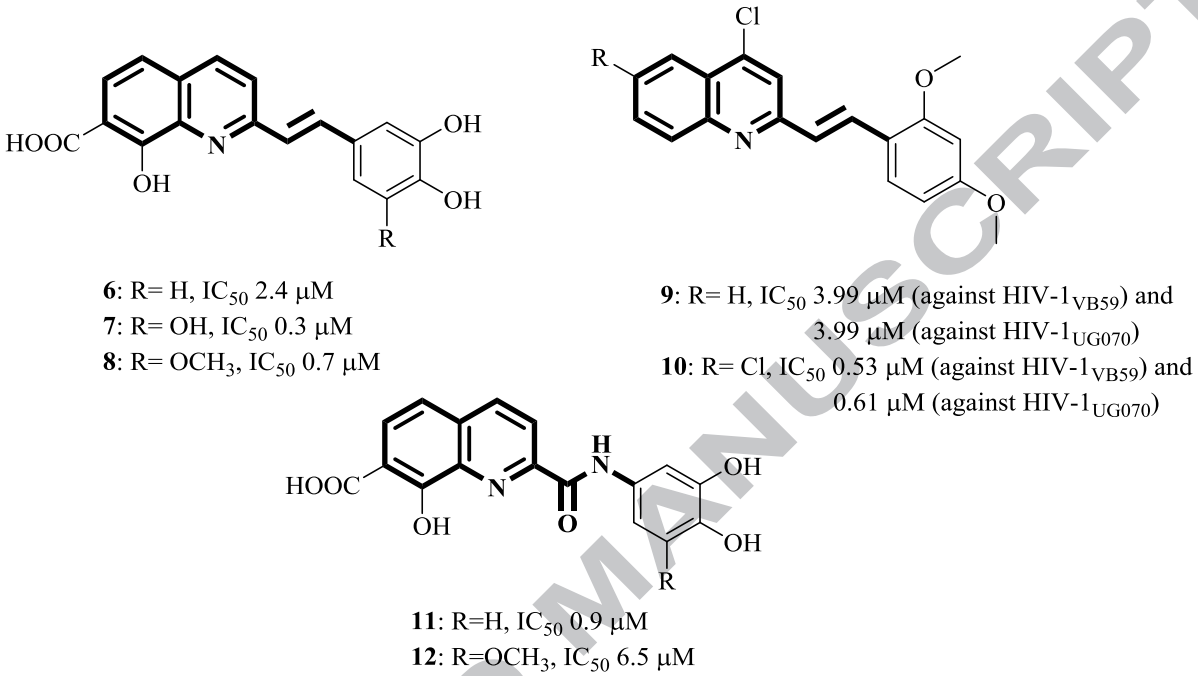
**5**: $EC_{50}$ 0.34 μM

**Figure 1.** Naturally occurring 8-oxygenated quinolines with anti-HIV-1 activity.

γ-Fagarine **(1)** and haplopine **(2)** are furoquinoline class of alkaloids isolated from root bark of *Zanthoxylum ailanthoides*. γ-Fagarine has been reported to possess potent anti-HIV activity with $EC_{50}$ and TI values of <0.44 μM and >231, respectively. Haplopine, which has a hydroxy (–OH) group at C-7 position, showed $EC_{50}$ and TI values of 2.58 μM and 36.7, respectively [10]. Marine alkaloids aaptamine **(3)**, isoaaptamine **(4)** and demethyl(oxy)aaptamine **(5)**, containing a rare 1*H*-benzo[*de*]-1,6-naphthyridine skeleton, have been reported for anti-HIV-1 activity with $EC_{50}$ of 1.3, 0.6 and 0.34 μM, respectively These aaptamines were isolated from sea sponge *Aaptos aaptos* [11, 12].

Quinoline derivatives such as 2-styrylquinolines and 8-hydroxyquinolines are extensively studied for their anti-HIV-1 activity and found to act through inhibition of HIV-1 integrase enzyme [13-17]. Some of them (**6**, **7**, **8**) are shown in Figure 2. Our previous efforts in the

search of anti-HIV agents with styrylquinolines also led to the identification of two lead molecules (**9** and **10**, Figure 2) [9]. Schiff bases have also been reported for anti-HIV activity [18].




**6**: R= H, $IC_{50}$ 2.4 μM
**7**: R= OH, $IC_{50}$ 0.3 μM
**8**: R= $OCH_3$, $IC_{50}$ 0.7 μM

**9**: R= H, $IC_{50}$ 3.99 μM (against HIV-$1_{VB59}$) and 3.99 μM (against HIV-$1_{UG070}$)
**10**: R= Cl, $IC_{50}$ 0.53 μM (against HIV-$1_{VB59}$) and 0.61 μM (against HIV-$1_{UG070}$)

**11**: R=H, $IC_{50}$ 0.9 μM
**12**: R=$OCH_3$, $IC_{50}$ 6.5 μM

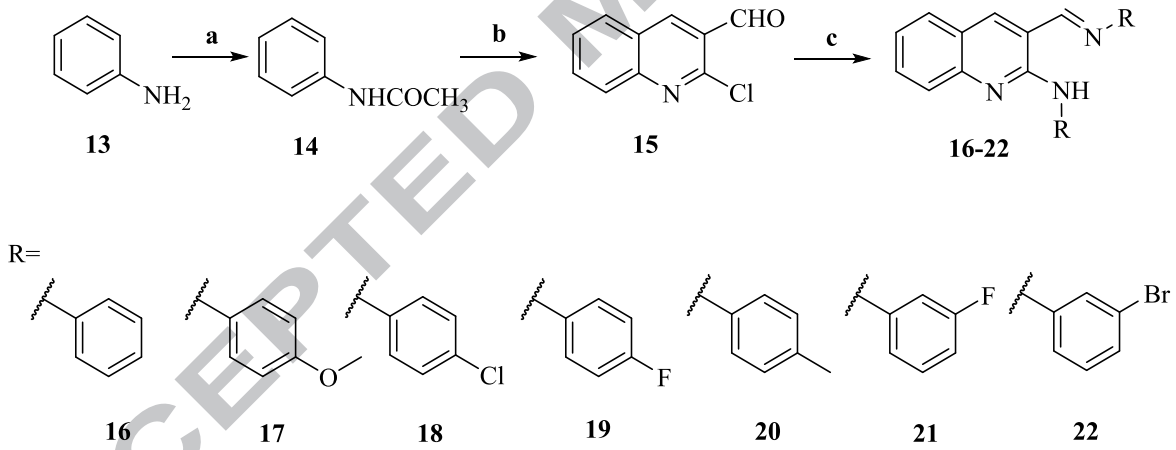
**Figure 2.** Synthetic quinoline derivatives containing styryl and amide linkers possessing anti-HIV-1 activity.

In continuation of search for newer anti-HIV molecules, 2,3-disubstituted quinoline derivatives (**16-22**) were synthesized using differently substituted anilines, leading to imine moiety at C-3 position and substituted amine moiety at C-2 position. However, these derivatives did not show any effect against both the studied HIV-1 strains. Further based on the literature, 8-methoxyquinoline scaffold was explored by modifying its C-2 position. Substituted amide derivatives of quinoline (**11** and **12**, Figure 2) are reported to exhibit anti-HIV activity by inhibiting HIV-1 integrase [2]. Recently, oxadiazoles containing molecules have also been reported for anti-HIV activity and being privileged structures, can be used as linkers [19]. Here, combining the above structural features, C-2 position of 8-methoxyquinoline was substituted with $\alpha,\beta$-unsaturated amides (**27-31**) and 2,5-disubstituted-1,3,4-oxadiazoles (**34-47**) by replacing the styryl functionality to investigate the effect on the anti-HIV-1 potential.

## 2. Results and discussion

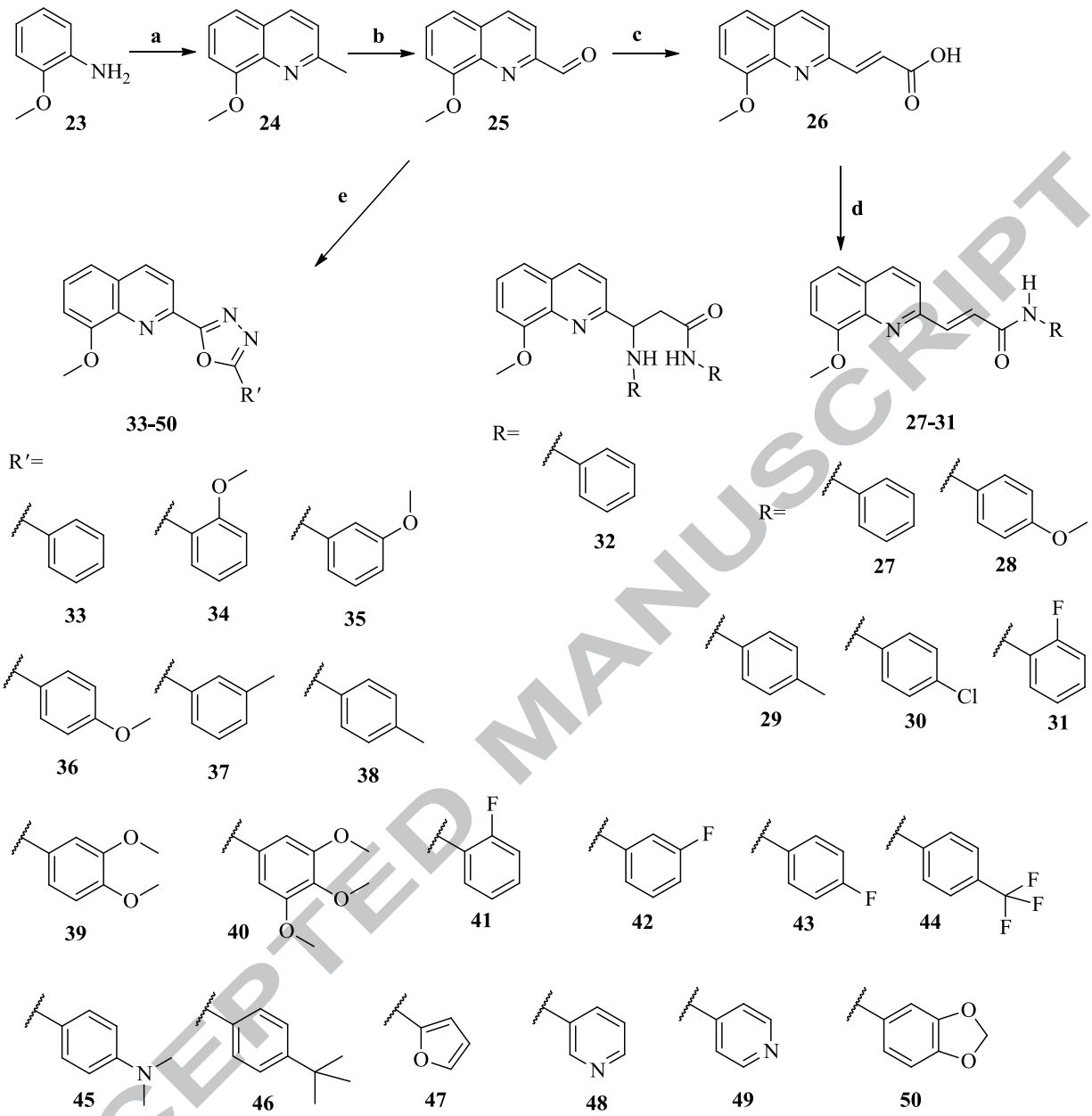
### 2.1. Synthesis

The overall synthetic strategies are depicted in Schemes 1 and 2. As shown in Scheme 1, aniline (**13**) was first acetylated using acetic anhydride to yield acetanilide (**14**) in 88 % yield, which on refluxing with $POCl_3$ in DMF resulted in 2-chloro-quinoline-3-carbaldehyde (**15**) via Vilsmeier-Haack reaction [20]. 2-Chloro-quinoline-3-carbaldehyde (**15**) was used as penultimate compound for the synthesis of 2,3-disubstituted quinoline derivatives (**16-22**) using substituted anilines in moderate to good yields. All the derivatives (**16-22**) showed N-H stretching absorption band in the region of 3300-3100 $cm^{-1}$ in IR spectra and N-H proton signal in the range of 11-12 ppm in $^1$H NMR spectra. Apart from this, imine proton CH=N was observed in the range of 8-9 ppm in $^1$H NMR spectra.




**Scheme 1.** Synthesis of 2,3-disubstituted quinoline derivatives: **Reagents and conditions: (a)** acetic anhydride, 40 °C, 10 min, 88%; **(b)** $POCl_3$, DMF, 80 °C, 8 h, 65%; **(c)** substituted anilines, DMF, 75 °C, 7 h, 40-61%.

For the synthesis of C-2-substituted 8-methoxyquinoline derivatives (Scheme 2), 8-methoxy-2-quinaldine (**24**) was synthesized using modified Skraup quinoline synthesis, by refluxing *o*-anisidine (**23**) in 6M HCl and crotonaldehyde in toluene [21]. This compound **24** was oxidised to 8-methoxyquinoline-2-carbaldehyde (**25**) by refluxing with selenium dioxide in anhydrous 1,4-dioxane [22], which upon reaction with malonic acid in pyridine yielded (*E*)-3-(8-methoxyquinolin-2-yl)acrylic acid (**26**). The acid (**26**) was further coupled with different substituted anilines using HOBt and DIC to yield various $\alpha,\beta$-unsaturated amide derivatives




**Scheme 2.** Synthesis of 2-substituted quinoline derivatives: **Reagents and conditions: (a)** 6M HCl, toluene, crotonaldehyde, 110°C, 3 h, 61%; **(b)** $SeO_2$, anhydrous 1,4-dioxane, 110 °C, 2 h, 81%; **(c)** malonic acid, pyridine, 70 °C, 2 h, 65%; **(d)** substituted anilines, DIC, HOBt, DMF, $N_2$, 40 °C, 12 h, 56-69%, **(e)** *i.* acylhydrazines, absolute ethanol, 80 °C, 3 h; *ii.* $I_2$, $K_2CO_3$, DMSO, 110 °C, 6-10 h, 50-93%.

(**27-31**). All the derivatives (**27-31**) showed an N-H stretching absorption band in the region of 3300 to 3100 $cm^{-1}$ in IR spectra and N-H proton signal in the range of 7-9 ppm in $^1H$ NMR spectrum. Moreover, two protons with coupling constants >15 Hz in $^1H$ NMR, revealed the presence of *trans* protons. An exceptional result was obtained with aniline, which yielded **32** in addition to **27**. This was due to Michael addition to the $\alpha,\beta$-unsaturated carbonyl group.

Compound **32** also showed N-H stretching absorption band in the region of 3300-3100 $cm^{-1}$ in IR spectra and two N-H proton signals at 9.79 and 6.41 ppm in $^{1}H$ NMR spectrum.

For the synthesis of oxadiazoles, compound **25** was refluxed with various substituted acylhydrazines in ethanol to produce acyl hydrazides of 8-methoxyquinoline-2-carbaldehyde. These acyl hydrazides were directly converted to 1,3,4-oxadiazoles (**33-50**) using $I_2/K_2CO_3$ mediated oxidative cyclisation [23]. All the derivatives (**33-50**) showed characteristic peaks of 1,3,4-oxadiazole *i.e.* 1650-1580 $cm^{-1}$ (C=N), 1300-1200 $cm^{-1}$ (C-O-$C_{asymm}$), 1050-950 $cm^{-1}$ (C-O-$C_{symm}$) in IR spectra.

All the synthesized compounds were confirmed using $^{1}H$-NMR, $^{13}C$-NMR, HRESI-MS and IR. Percentage purity of all synthesized compounds were determined using HPLC and observed at their respective $\lambda_{max}$ values.

2.2. *In vitro* evaluation for anti-HIV-1 activity

All the synthesized compounds were first screened for cytotoxicity in TZM-bl cell line using MTT assay and $CC_{50}$ (Concentration showing 50% cytotoxicity) values were determined. The non-cytotoxic concentration of compounds were screened for *in vitro* anti-HIV-1 activity against cell-associated primary isolates HIV-$1_{VB59}$ (R5, Subtype C) and HIV-$1_{UG070}$ (X4, Subtype D) in TZM-bl cell line and $IC_{50}$ (concentration showing 50% inhibition of HIV-1 replication in cell culture) values were determined [9]. In this assay, the TZM-bl cells were initially infected with HIV-1 and allowed for integration in the cell and subsequently the test compound was added. Therapeutic indices (TI) were calculated using $CC_{50}$ and $IC_{50}$ values. Azidothymidine was kept as a positive control throughout the study. Results are shown in Table 1. The primary aim of the study was to identify new molecules against global subtype which is majorly subtype C. Therefore, HIV-1 Indian subtype C strain was used for the study.

For mechanistic study, due to non-availability of the X4 tropic Indian subtype C strain, a representative strain available with NIHARRRP (subtype D) was used.

**Table 1.** Cytotoxicity and anti-HIV-1 activity of compounds against HIV-$1_{VB59}$ and HIV-$1_{UG070}$ using TZM-bl cell line

| Sr. No. | Compound | Cytotoxicity $CC_{50}$[b] (μM) | Anti-HIV-1 testing data | | | |
|---|---|---|---|---|---|---|
| | | | $IC_{50}$[a] HIV-$1_{VB59}$ (R5) (μM) | TI HIV-$1_{VB59}$ (R5) | $IC_{50}$[a] HIV-$1_{UG070}$ (X4) (μM) | TI HIV-$1_{UG070}$ (X4) |
| 1 | **16** | 77.95 | 121.61 | 0.64 | >100 | NA[c] |
| 2 | **17** | 122.23 | >130 | NA[c] | >130 | NA[c] |
| 3 | **18** | 79.15 | 126.90 | 0.62 | >100 | NA[c] |
| 4 | **19** | 92.13 | 114.95 | 0.80 | 115.00 | 0.80 |
| 5 | **20** | 113.76 | >130 | NA[c] | >130 | NA[c] |
| 6 | **21** | 56.10 | >130 | NA[c] | >130 | NA[c] |
| 7 | **22** | 103.10 | >130 | NA[c] | >100 | NA[c] |
| 8 | **27** | **98.24** | **24.13±13.11** | **4.07** | **12.68±3.81** | **7.75** |
| 9 | **28** | 11.48 | 10.38 | 1.11 | 10.80 | 1.06 |
| 10 | **29** | 20.60 | 100.73 | 0.20 | 154.79 | 0.13 |
| 11 | **30** | 127.78 | 123.88 | 1.08 | >130 | NA[c] |
| 12 | **31** | **53.61** | **3.35±0.87** | **16.00** | **2.57±0.71** | **20.82** |
| 13 | **32** | 79.15 | >130 | NA[c] | >100 | NA[c] |
| 14 | **33** | 236.71 | >300 | NA[c] | NT[d] | NT[d] |
| 15 | **34** | 413.44 | >600 | NA[c] | 61.98 | 6.67 |
| 16 | **35** | 694.62 | >900 | NA[c] | NT[d] | NT[d] |
| 17 | **36** | **413.38** | **45.09** | **9.17** | **135.32** | **3.05** |
| 18 | **37** | 37.81 | 36.93 | 1.02 | NT[d] | NT[d] |
| 19 | **38** | 75.22 | 35.89 | 2.10 | NT[d] | NT[d] |
| 20 | **39** | 133.74 | >135 | NA | NT[d] | NT[d] |
| 21 | **40** | 65.58 | >100 | NA[c] | NT[d] | NT[d] |
| 22 | **41** | 27.45 | 61.93 | 0.44 | NT[d] | NT[d] |
| 23 | **42** | 63.71 | >150 | NA[c] | 70.71 | 0.90 |
| 24 | **43** | 236.22 | >300 | NA[c] | NT[d] | NT[d] |
| 25 | **44** | 124.15 | 33.96 | 3.66 | 121.14 | 1.02 |
| 26 | **45** | 115.48 | 75.20 | 1.54 | 38.83 | 2.97 |
| 27 | **46** | 43.15 | 43.51 | 0.99 | 63.16 | 0.68 |
| 28 | **47** | 36.18 | 139.08 | 0.26 | NT[d] | NT[d] |
| 29 | **48** | 50.93 | 154.91 | 0.33 | NT[d] | NT[d] |
| 30 | **49** | 208.01 | 124.81 | 1.67 | 89.32 | 2.33 |
| 31 | **50** | 147.41 | 119.48 | 1.23 | 135.23 | 1.09 |
| 32 | **Azidothymidine** | 872.00 | 0.03 | 29066.67 | 0.027 | 32296.30 |

[a]$IC_{50}$ - Concentration showing 50% inhibition of HIV-1 replication in cell culture. [b]$CC_{50}$ - Concentration showing 50% cytotoxicity. The $IC_{50}$ values for compound **27** and **31**, are the mean ± SEM value of three individual experiments. [c]NA stands for not applicable. [d]NT stands for not tested.

Compounds **27**, **31** and **36** showed the highest TI values against both the HIV-1 strains *i.e.* HIV-$1_{VB59}$ and HIV-$1_{UG070}$ than rest of the compounds. Compounds with very low $CC_{50}$ values and very high $IC_{50}$ values against HIV-$1_{VB59}$ strain, were not studied for anti-HIV-1 activity against HIV-$1_{UG070}$. Amongst the three compounds, compound **31** showed lowest $IC_{50}$ values (3.35±0.87 and 2.57±0.71 μM) and highest TI values (16.00 and 20.82) against

both R5 tropic and X4 tropic HIV-1 strains *i.e.* HIV-$1_{VB59}$ and HIV-$1_{UG070}$ respectively. Hence, compound **31** was further tested for anti-HIV-1 activity in cell-free virus assays where the non-cytotoxic concentrations of compound were treated with virus (HIV-1) to allow the compound to inactivate the virus and to block the receptors on the target (TZM-bl) cells. In this experiment, dextran sulfate was used as a positive control (Table 2).

**Table 2.** Anti-HIV-1 activity of compound **31** against cell free HIV-$1_{VB59}$ and HIV-$1_{UG070}$ in TZM-bl cell line

| Sr. No. | Compound | Cytotoxicity $CC_{50}$[b] (µM) | Anti-HIV-1 testing data | | | |
|---|---|---|---|---|---|---|
| | | | $IC_{50}$[a] HIV-$1_{VB59}$ (R5) (µM) | TI HIV-$1_{VB59}$ (R5) | $IC_{50}$[a] HIV-$1_{UG070}$ (X4) (µM) | TI HIV-$1_{UG070}$ (X4) |
| 1 | **31** | 53.60 | 1.27±0.31 | 42.20 | 2.88±1.79 | 18.61 |
| 2 | **DS**[c] | 6095.47 | 4.10±0.21 | 1486.70 | 7.16±0.15 | 851.32 |

[a]$IC_{50}$ - Concentration showing 50% inhibition of HIV-1 replication in cell culture. [b]$CC_{50}$ - Concentration showing 50% cytotoxicity. The $CC_{50}$ values are the mean and $IC_{50}$ values are the mean ±SEM value of three individual experiments. [c]DS stands for dextran sulfate, used as positive control.

**Table 3.** Anti-HIV-1 activity of compounds **31** against HIV-$1_{VB51}$ in PBMCs

| Sr. No. | Compound | Cytotoxicity $CC_{50}$[b] (µM) | Cell-associated assay | | Cell-free assay | |
|---|---|---|---|---|---|---|
| | | | $IC_{50}$[a] (µM) | TI | $IC_{50}$[a] (µM) | TI |
| 1 | **31** | 9.56 | 5.49±2.17 | 1.74 | 0.81±0.62 | 11.80 |

[a]$IC_{50}$ - Concentration showing 50% inhibition of HIV-1 replication in cell culture. [b]$CC_{50}$ - Concentration showing 50% cytotoxicity. The $CC_{50}$ values are the mean and $IC_{50}$ values are the mean ±SEM value of three individual experiments.

Compound **31** showed activity against both R5 tropic and X4 tropic strains (HIV-$1_{VB59}$ and HIV-$1_{UG070}$, $IC_{50}$: 1.27±0.31 and 2.88±1.79 µM, respectively). Anti-HIV-1 activity of compound **31** was further confirmed against HIV-$1_{VB51}$ cell associated ($IC_{50}$ 5.49±2.17 µM) as well as cell free virus ($IC_{50}$ 0.81±0.62 µM) in primary cells like PBMCs (Table 3).

To determine the mechanism of action, viral entry inhibition (Table 4) and cell fusion inhibition (Table 5) assays were performed. In the viral entry inhibition assay, the non-cytotoxic concentrations of compound **31** were added to the TZM-bl cell line and incubated for 1 h. If the compound blocks the receptors on the target cells, it prevents HIV-1 from entering the cells and there is reduction in luminescence which confirms entry inhibition [9]. Compound **31** showed lower $IC_{50}$ (1.40±0.28 µM) and higher TI value (38.29) than the positive control (TAK-779: $IC_{50}$ 3.65±0.51 µM, TI 36.62) (Table 4).

**Table 4.** Entry inhibition activity of compound **31** using TZM-bl cell line

| Sr. No. | Compound | Cytotoxicity $CC_{50}$[b] (μM) | $IC_{50}$[a] (μM) | TI |
|---|---|---|---|---|
| 1 | **31** | 53.60 | 1.40±0.28 | 38.29 |
| 2 | **TAK-779** | 133.66 | 3.65±0.51 | 36.62 |

[a]$IC_{50}$ - Concentration showing 50% inhibition of HIV-1 replication in cell culture. [b]$CC_{50}$ - Concentration showing 50% cytotoxicity. The $CC_{50}$ values are the mean and $IC_{50}$ values are the mean±SEM value of three individual experiments. TAK-779 was used as positive control.

**Table 5.** Fusion inhibition activity of compound **31** using HL2/3 cell line and TZM-bl cell line

| Sr. No. | Compound | Cytotoxicity $CC_{50}$[b] (μM) | $IC_{50}$[a] (μM) | TI |
|---|---|---|---|---|
| 1 | **31** | 53.60 | 0.96±0.28 | 55.83 |
| 2 | **TAK-779** | 133.66 | 3.65±0.51 | 36.62 |

[a]$IC_{50}$ - Concentration showing 50% inhibition of HIV-1 replication in cell culture. [b]$CC_{50}$ - Concentration showing 50% cytotoxicity. The $CC_{50}$ values are the mean and $IC_{50}$ values are the mean±SEM value of three individual experiments. TAK-779 was used as positive control.

The fusion cell inhibition assay mimics gp120-CD4 mediated fusion using HL2/3 cells as effector cells and TZM-bl as indicator cells. HL2/3 expresses HIV Env on its surface and Tat protein in the cytoplasm. Upon fusion, Tat activates luciferase gene in TZM-bl cells and fused cells are measured with luciferase receptor gene. HL2/3 cells were added to the TZM-bl cell line and allowed to fuse. Subsequently, non-cytotoxic concentrations of the test compound were added to the fused cells to determine fusion inhibition [9]. If the drug inhibits fusion of HL2/3 with TZM-bl cells, there is reduction in luminescence which confirms fusion inhibition. The assay was standardized using TAK779, a known CCR5 co-receptor antagonist which was used as a control in the subsequent assays. Compound **31** also showed lower $IC_{50}$ (0.96±0.28 μM) and higher TI value (55.83) than the positive control (TAK-779: $IC_{50}$ 3.65±0.51 μM, TI 36.62) (Table 5).

Based on the above results, it can be concluded that $\alpha,\beta$-unsaturated amide derivatives at C-2 position of quinoline (**27-31**) showed good anti-HIV-1 potential, whereas, 2,3-disubstituted quinoline derivatives (**16-22**) and quinoline derivatives with 1,3,4-oxadiazole at C-2 position (**33-50**) were less active. In case of $\alpha,\beta$-unsaturated amide derivatives, unsubstituted anicillary phenyl ring (**27**) and *ortho* substituted ancillary phenyl ring with electron withdrawing fluoro group (**31**) showed low $IC_{50}$ values and with high selectivity for anti-

HIV-1 activity. Substitution at *para* position of ancillary phenyl ring (**28**, **29**, **30**) did not favour anti-HIV-1 activity as there is insignificant difference between $IC_{50}$ and $CC_{50}$ values. Modification of unsaturation of amide bridge, hampers anti-HIV-1 activity (compound **32** in comparison with **27**) as well as selectivity, as no change was observed in cytotoxicity values. In case of oxadiazoles derivatives, substitution at *para* position of ancillary phenyl ring with electron donating (e.g. $–OCH_3$, $–CH_3$) group led to better anti-HIV-1 activity with higher selectivity as compared to that with *ortho* and *meta* positions (compound **36** over **34** and **35,** compound **38** over **37**). Anti-HIV-1 activity order for oxadiazoles derivatives was obtained as $4–CF_3$ (**44**) > $4–CH_3$ (**38**) > $4–C(CH_3)_3$ (**46**) > $4–OCH_3$ (**36**) > $4–N(CH_3)_2$ (**45**), whereas, selectivity order was obtained as $4–OCH_3$ (**36**) > $4–CF_3$ (**44**) > $4–CH_3$ (**38**) > $4–N(CH_3)_2$ (**45**) > $4–C(CH_3)_3$ (**46**). Oxadiazole derivatives containing phenyl ring substituted with dimethoxy group (**39**) and trimethoxy group (**40**) did not show anti-HIV-1 activity. Oxadiazole derivatives containing fluoro substituted phenyl ring (**41**, **42**, **and 43**) did not show anti-HIV-1 activity. Heterocyclic substituted oxadiazoles (**47-50**) did not show anti-HIV-1 activity. Replacement of $\alpha,\beta$-unsaturated amide group with 1,3,4-oxadiazole ring hampers anti-HIV-1 activity (compounds **27**, **31,** in comparison with **33, 41**, respectively).

2.3. Molecular modeling

As the structures of newly synthesized compounds are different from previously reported quinoline compounds known to act by inhibiting HIV integrase enzyme, it was thought worthwhile to identify the binding mode of the most active compound **31** which showed activity in entry inhibition and fusion inhibition assays. The known entry inhibitors *i.e.* NBD556, BMS806, IC9564 (Figure 3) were selected for comparison in the molecular modelling study. The docked conformation of NBD556, as reported by Madani *et al.* was used for the validation of docking protocol [24]. The second highest energy binding conformer of NBD556 obtained by our docking protocol was showing similar interactions

(ASP368, VAL430, GLU370, TRP427, PHE382, TRP112) as shown by the conformer reported by Madani *et al.* (Figure 4). Binding interactions of reported inhibitors BMS806 and IC9564 were also compared with compound **31**. Conjugated double bond in compound **31** showed hydrophobic interaction with GLU370, ASN425 and TRP427 residues (Figure 4). GLU370 flank the PHE43 cavity and is involved in the resistance to NBD-556 [24]. Amide NH of compound **31** showed H-bonding interaction with the highly conserved residue MET426. The methoxy substituent on quinoline ring also showed H-bonding interaction with ASN425. As NBD-556-gp120 complex is stabilized by the aromatic-aromatic stacking interactions with the TRP427, PHE382, similar interactions are shown by the quinoline ring of compound **31** with TRP427 and PHE382 residues. VAL255, THR257 and MET475 which are in 4 Angstrom of the quinoline ring also stabilize the compound **31**- gp120 complex. Phenyl moiety of compound **31** showed hydrophobic interactions in the vestibule of the cavity with VAL430. Similar interaction is also shown by NBD556 and BMS806. Compound IC9564 showed a lower docking score and its binding profile was found to be different from NBD556, BMS806 and compound **31**. Docking score of NBD556, BMS806, IC9564 and compound **31** were -8.31, -8.17, -7.48 and -8.20, respectively.

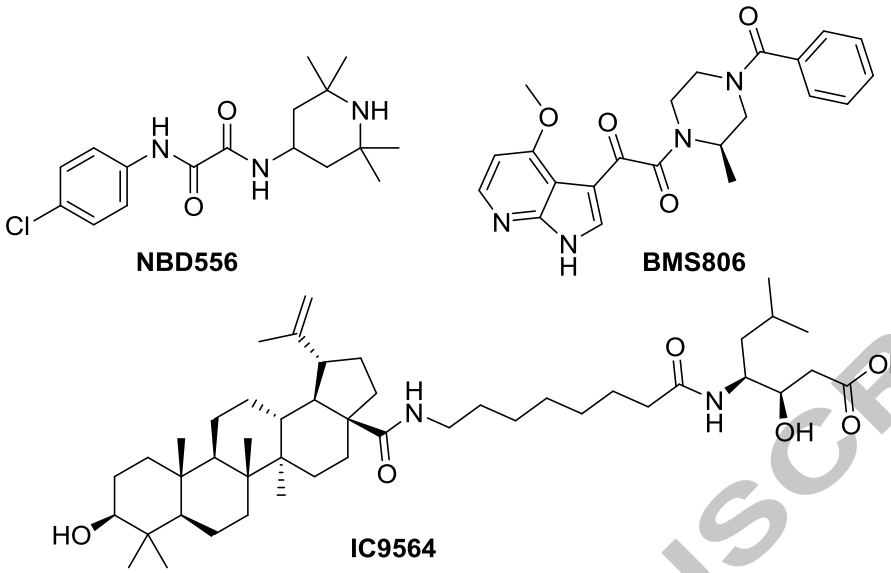



**Figure 3.** Reported gp120-CD4 interaction inhibitors.

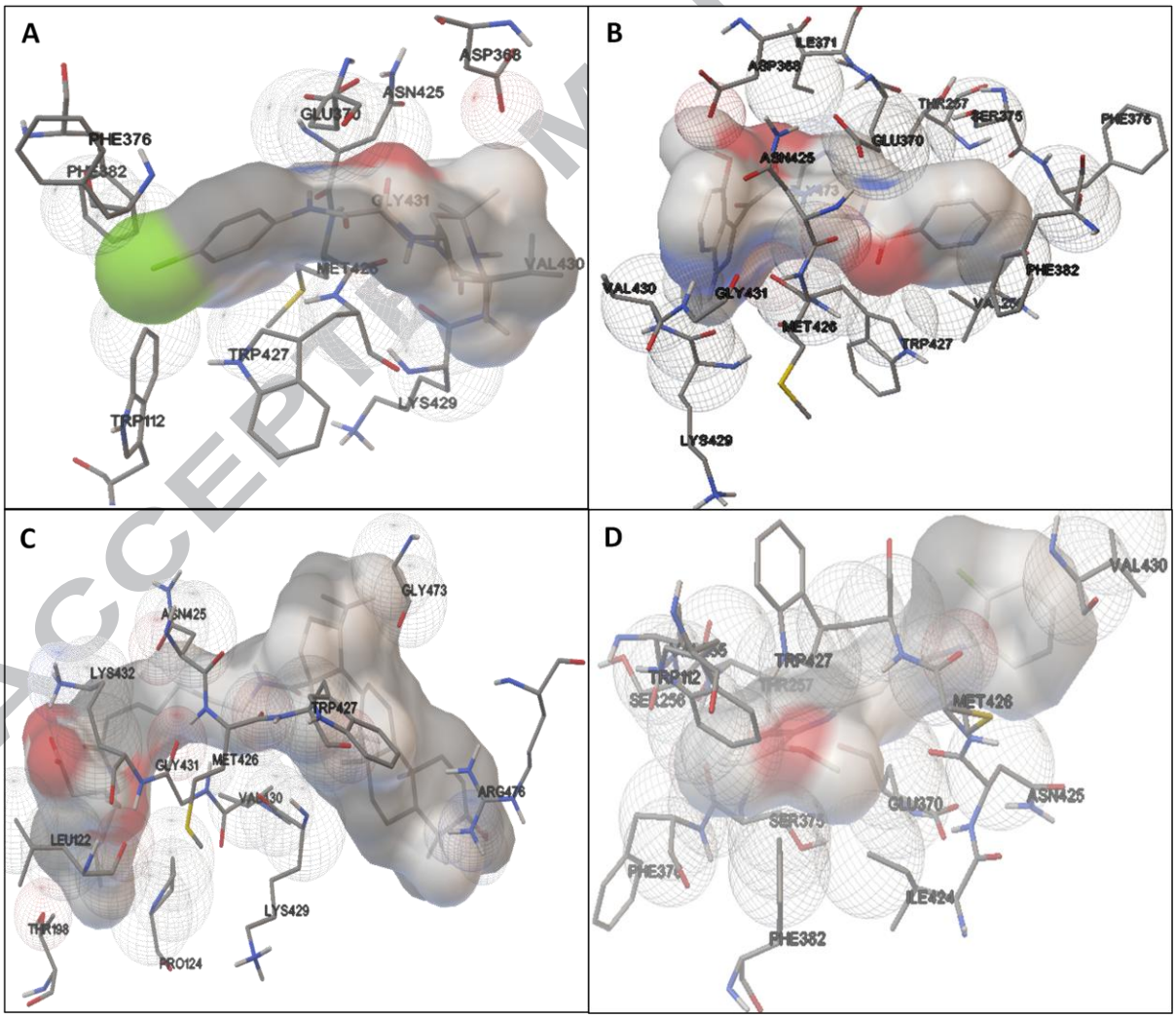



**Figure 4.** Binding pose of (A) NBD556, (B) BMS806, (C) IC9564 and (D) compound **31** with gp120 (AutoDock tool viewed).

## 3. Conclusion

In gist, thirty-one quinoline derivatives with different linkers to ancillary phenyl ring were synthesized and evaluated for their *in vitro* anti-HIV-1 activity against HIV-$1_{VB59}$ and HIV-$1_{UG070}$ primary isolates in TZM-bl cell lines. Compounds **27**, **31** and **36** showed highest TI values against both the HIV-1 strains. Anti-HIV-1 activity of compound **31** was also confirmed against HIV-$1_{VB51}$ in PBMCs. Further studies on compound **31** showed that the potential for anti-HIV-1 activity might be due to its entry inhibition ($IC_{50}$ 1.40±0.28 μM, TI 38.29) as well as fusion inhibition ($IC_{50}$ 0.96±0.28 μM, TI 55.83) potential. Compound **31** showed similar interaction profile with gp120 protein as shown by reported gp120 inhibitors **NBD556, BMS806** and **IC9564**. Compound **31** showed H-bond with the highly conserved residue MET426 and ASN425. In addition, conjugated double bond in compound **31** showed hydrophobic interaction with GLU370, ASN425 and TRP427 residues.

## 4. Experimental

### 4.1. General

All chemicals were purchased from Sigma-Aldrich, Merck, SD fine chemicals, Loba Chemie, Spectrochem and Central Drug House (CDH), *etc*. and used without further purification unless otherwise specified. Solvents purchased from commercial sources were of analytical grade. Solvents used for the chemical synthesis were dehydrated and distilled according to standard protocols. Compounds were purified either by crystallization or silica gel column chromatography (60-120, 230-400 # size, Merck, Germany), whereas TLC developments were performed on silica gel coated aluminium sheets (TLC Silica Gel 60 $F_{254}$, 0.2 mm thickness, Merck, Germany). Developed plates were visualized by UV light and derivatized using Dragendorff reagent.

Melting points of compounds were recorded on Veego Melting point apparatus (Mumbai, India). IR spectra were recorded on FTIR spectrometer (PerkinElmer, USA). $^{1}H$ and $^{13}C$ NMR spectra were recorded at 400 MHz and 100 MHz respectively on Bruker Avance III spectrometer (Bruker, Germany) using TMS as internal standard and the chemical shifts were reported in $\delta$ ppm. Mass spectra were recorded on Thermo LTQ-XL mass spectrometer (Thermo, USA). High-Resolution Mass Spectra were recorded on Maxis$^{TM}$ UHR-TOF (Bruker, Germany). The HPLC % purity of compounds were carried out on a reverse-phase C18 column (X-Bridge® Sun Fire, 4.6 X 250 mm; 5µ) connected to a Shimadzu HPLC system (Shimadzu Corporation, Kyoto, Japan) consisting of a model LC-20 AD fitted with a SIL-20 AC HT autosampler and SPD-M20A photodiode-array detector. A step gradient method was run using solvent A (water with 0.1 % formic acid) and solvent B (methanol) at a flow rate of 1.0 mL/min from 40-100 % of solvent B over 30 min, followed by washing with 100 % of solvent B for 10 min. The temperature of the column was set at 40 °C. Injection volume was 5 or 10 µL of sample solution (1 mg/mL). LC Solution software (Shimadzu) was

used both for data collection and integration. The chromatograms were recorded on range of 190-600 nm and observed at the respective $\lambda_{max}$ for percentage purity of compounds.

4.2. Synthesis of 2,3-disubstituted quinoline derivatives (**16-22**)

4.2.1. Synthesis of acetanilide (**14**)

Aniline (26.8 mmol) (**13**) was treated with acetic anhydride (32.1 mmol, 1.2 eq.) and stirred at 40 °C for 10 min to obtain acetanilide (m.p. 114-116 °C) (**14**). After completion of reaction, precipitates were formed, which were washed with water several times and then dried. The compound was identified by TLC with an authentic sample.

4.2.2. Synthesis of 2-chloro-quinoline-3-carbaldehyde (**15**)

Acetanilide (15.6 mmol, 1.0 eq) (**14**) was treated with $POCl_3$ (156.0 mmol, 10.0 eq.) and DMF (51.48 mmol, 3.3 eq.) at 80 °C for 8 h. The reaction mixture was cooled to room temperature (40 °C) and poured into crushed ice under stirring. Pale yellow precipitates were formed, which were washed with cold water several times and dried to give 2-chloro-quinoline-3-carbaldehyde (**15**).

*2-Chloro-quinoline-3-carbaldehyde (**15**):* yellow solid, yield 65%, m.p. 150-151 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 3043, 2872, 1722, 1684, 1567, 1489, 760, 748; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 10.55 (s, 1H), 8.74 (s, 1H), 8.06 (d, 1H, $J$ = 8.5 Hz), 7.98 (d, 1H, $J$ = 8.2 Hz), 7.88 (ddd, 1H, $J$ = 1.4, 7.0 and 8.4 Hz), 7.65 (td, 1H, $J$ = 1.0 and 7.6 Hz); $^{13}$C NMR ($CDCl_3$, 100MHz): $\delta$ 189.1, 150.1, 149.6, 140.3, 133.6, 129.7, 128.6, 128.1, 126.5, 126.4; ESI-MS found *m/z* 191.96 $[M+H]^+$ and 193.98 $[M+H+2]^+$.

4.2.3. General procedure for synthesis of 2,3-disubstituted quinoline derivative **(16-22)**

The synthesized 2-chloro-quinoline-3-carbaldehyde (1.05 mmol, 1.0 eq.), was treated with substituted anilines (2.63 mmol, 2.5 eq.) in presence of DMF at 75 °C to give 2,3-

disubstituted quinoline derivatives (**16-22**). The compounds were purified by column chromatography over silica gel (230-400#) using mixture of hexane and EtOAc (98:2) as eluent.

*4.2.3.1. (E)-N-phenyl-3-((phenylimino)methyl)quinolin-2-amine (**16**)*: yellow solid, yield 50%, m.p. 150-152 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 3264, 3055, 2924, 1622, 1592, 1546, 1497, 1405, 1236, 1162, 751; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 11.90 (s, 1H), 8.66 (s, 1H), 8.10 (s, 1H), 8.07 (dd, 2H, $J$ = 0.8 and 8.0 Hz), 7.83 (d, 1H, $J$ = 8.4 Hz), 7.68-7.62 (m, 2H), 7.47 (td, 2H, $J$ = 1.6, and 7.8 Hz), 7.39 (t, 2H, $J$ = 7.4 Hz), 7.34-7.24 (m, 4H), 7.06 (t, 1H, $J$ = 7.4 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 160.3, 152.2, 149.8, 148.3, 144.4, 140.7, 131.8, 129.5 (2 x C), 128.9 (2 x C), 128.2, 127.0, 126.9, 123.1, 122.9, 122.3, 121.2 (2 x C), 120.0 (2 x C), 117.2; HRESI-MS calcd. for $C_{22}H_{17}N_3$ $[M+H]^+$ 324.1501, found *m/z* 324.1504; anal. HPLC $t_R$ = 31.6 min, 95.5% at 296 nm.

*4.2.3.2. (E)-N-(4-methoxyphenyl)-3-(((4-methoxyphenyl)imino)methyl)quinolin-2-amine (**17**):* brown solid, yield 55 %, mp 147-149 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 3187, 3057, 3000, 2929, 1621, 1574, 1547, 1508, 1407, 1297, 1247, 1166, 1034, 827, 753; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 11.81 (s, 1H), 8.64 (s, 1H), 8.03 (s, 1H), 7.96 (dt, 2H, $J$ = 2.2, 3.4 and 9.0 Hz), 7.77 (d, 1H, $J$ = 8.3 Hz), 7.64-7.57 (m, 2H), 7.32 (dt, 2H, $J$ = 2.7 and 8.8 Hz), 7.22 (d, 1H, $J$ = 8.0 Hz), 6.98 (tt, 4H, $J$ = 2.7 and 9.0 Hz), 3.85 (s, 3H), 3.83 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 158.9, 158.0, 155.0, 152.3, 148.3, 143.7, 142.7, 134.1, 131.5, 128.1, 126.7, 122.9, 122.7, 122.4 (2 x C), 121.4 (2 x C), 117.3, 114.7 (2 x C), 114.1 (2 x C), 55.61, 55.58; HRESI-MS calcd. for $C_{24}H_{21}N_3O_2$ $[M+H]^+$: 384.1712, found *m/z* 384.1720; anal. HPLC $t_R$ = 25.4 min, >99.0% at 366 nm.

*4.2.3.3. (E)-N-(4-chlorophenyl)-3-(((4-chlorophenyl)imino)methyl)quinolin-2-amine (**18**):* yellow solid, yield 58%, m.p. 174-176 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 3054, 2923, 1621, 1591, 1568,

1546, 1488; $^{1}$H NMR ($CDCl_3$, 400 MHz): $\delta$ 11.77 (s, 1H), 8.64 (s, 1H), 8.14 (s, 1H), 8.00 (dt, 2H, $J$ = 3.1 and 8.9 Hz), 7.82 (d, 1H, $J$ = 8.3 Hz), 7.69-7.65 (m, 2H), 7.43 (dt, 2H, $J$ = 2.8 and 9.5 Hz), 7.35-7.25 (m, 5H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 160.6, 151.8, 148.2, 148.1, 144.8, 139.1, 132.7, 132.1, 129.6, 128.8, 128.2, 127.0, 126.9, 123.5, 123.0, 122.4, 121.1, 116.9; HRESI-MS calcd. for $C_{22}H_{15}Cl_2N_3$ $[M+H]^+$ and $[M+H+2]^+$: 392.0721, 394.0692 found *m/z* 392.0714, 394.0693; ESI-MS calcd. for $C_{22}H_{15}Cl_2N_3$ $[M]^+$ 391.06, found *m/z* 391.00; anal. HPLC $t_R$ = 35.1 min, 95.4% at 301 nm.

*4.2.3.4. (E)-N-(4-fluorophenyl)-3-(((4-fluorophenyl)imino)methyl)quinolin-2-amine (**19**):* yellow solid, yield 61%, m.p. 157-159 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 3398, 1627, 1551, 1504, 1416, 1202, 1149, 1039, 829, 782; $^{1}$H NMR ($CDCl_3$, 400 MHz): $\delta$ 11.70 (s, 1H), 8.54 (s, 1H), 8.01 (s, 1H), 7.99-7.93 (m, 2H), 7.76 (d, 1H, $J$ = 8.8 Hz), 7.64-7.60 (m, 2H), 7.29-7.22 (m, 3H), 7.13 (tt, 2H, $J$ = 2.76 and 8.6 Hz), 7.06 (tt, 2H, $J$ = 2.9 and 8.7 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 161.8 (d, $J_{C\text{-}F}$ = 245.0 Hz), 160.0, 158.3 (d, $J_{C\text{-}F}$ = 239.0 Hz), 151.9, 148.2, 145.8 (d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 3.0 Hz), 144.5, 136.7 (d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 3.0 Hz), 131.9, 128.2, 126.8, 123.2, 122.9, 122.6 (d, 2 x C, $J_{C\text{-}C\text{-}C\text{-}F}$ = 8.0 Hz), 121.3 (d, 2 x C, $J_{C\text{-}C\text{-}C\text{-}F}$ = 7.0 Hz), 116.9, 116.3 (d, 2 x C, $J_{C\text{-}C\text{-}F}$ = 23.0 Hz), 115.3 (d, 2 x C, $J_{C\text{-}C\text{-}F}$ = 22.0 Hz); HRESI-MS calcd. for $C_{22}H_{15}F_2N_3$ $[M+H]^+$: 360.1312, found *m/z* 360.1313; anal. HPLC $t_R$ = 31.5 min, 98.3% at 292 nm.

*4.2.3.5. (E)-N-(4-methylphenyl)-3-(((4-methylphenyl)imino)methyl)quinolin-2-amine (**20**):* yellow solid, yield 40%, m.p. 152-154 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 2923, 2852, 1596, 1539, 1508, 1409, 1360, 1311, 1237, 1158, 816, 756; $^{1}$H NMR ($CDCl_3$, 400 MHz): $\delta$ 11.88 (s, 1H), 8.61 (s, 1H), 8.00 (s, 1H), 7.97 (d, 2H, $J$ = 8.4 Hz), 7.82 (d, 1H, $J$ = 8.8 Hz), 7.65-7.60 (m, 2H), 7.28-7.21 (m, 7H), 2.42 (s, 3H), 2.39 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 159.3, 152.3, 148.3, 147.2, 144.1, 138.2, 137.0, 131.7, 131.6, 130.1 (2 x C), 129.4 (2 x C), 128.2, 126.9,

122.9, 122.8, 121.1 (2 x C), 120.1 (2 x C), 117.3, 21.9, 21.0; HRESI-MS calcd. for $C_{24}H_{21}N_3$ $[M+H]^+$: 352.1814, found *m/z* 352.1815; anal. HPLC $t_R$ = 33.1 min, 97.4% at 299 nm.

*4.2.3.6. (E)-N-(3-fluorophenyl)-3-(((3-fluorophenyl)imino)methyl)quinolin-2-amine (**21**):* yellow solid, yield 42%, mp 150-152 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 3276, 2924, 1600, 1575, 1548, 1489, 1447, 1406, 1260, 1132, 1115, 953, 860, 771, 753; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 11.83 (s, 1H), 8.67 (s, 1H), 8.26 (dt, 1H, *J* = 2.2 and 11.9 Hz), 8.18 (s, 1H), 7.87 (d, 1H, *J* = 8.4 Hz), 7.72-7.67 (m, 2H), 7.49-7.40 (m, 2H), 7.35-7.27 (m, 2H), 7.12 (dd, 1H, *J* = 1.0 and 7.5 Hz), 7.07-7.00 (m, 2H), 6.74 (td, 1H, *J* = 1.8 and 8.3 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 163.4 (d, $J_{C-F}$ = 247.0 Hz), 163.3 (d, $J_{C-F}$ = 241.0 Hz), 161.3, 151.8, 151.4 (d, $J_{C-C-C-F}$ = 9.0 Hz), 148.3, 145.0, 142.1 (d, $J_{C-C-C-F}$ = 11.0 Hz), 132.3, 130.7 (d, $J_{C-C-C-F}$ = 9.1 Hz), 129.7 (d, $J_{C-C-C-F}$ = 9.5 Hz), 128.3, 127.1, 123.6, 123.0, 117.1 (d, $J_{C-C-C-C-F}$ = 2.9 Hz), 116.8, 115.20 (d, $J_{C-C-C-C-F}$ = 2.4 Hz), 113.8 (d, $J_{C-C-F}$ = 21.0 Hz), 108.8 (d, $J_{C-C-F}$ = 22.0 Hz), 108.3 (d, $J_{C-C-F}$ = 23.0 Hz), 107.1 (d, $J_{C-C-F}$ = 27.0 Hz); HRESI-MS calcd. for $C_{22}H_{15}F_2N_3$ $[M+H]^+$: 360.1312, found *m/z* 360.1311; anal. HPLC $t_R$ = 33.4 min, 98.2% at 298 nm.

*4.2.3.7. (E)-N-(3-bromophenyl)-3-(((3-bromophenyl)imino)methyl)quinolin-2-amine (**22**):* yellow solid, yield 54%, m.p. 156-158 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 3399, 2924, 1618, 1586, 1564, 1538, 1474, 1425, 1405, 1360, 1164, 992, 882, 768, 751, 680; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 11.69 (s, 1H), 8.64 (s, 1H), 8.46 (t, 1H, *J* = 1.9 Hz), 8.17 (s, 1H), 7.86 (d, 1H, *J* = 8.3 Hz), 7.82 (dd, 1H, *J* = 1.2 and 8.0 Hz), 7.72-7.67 (m, 2H), 7.48-7.45 (m, 2H), 7.37-7.31 (m, 2H), 7.27-7.25 (m, 1H) 7.23-7.16 (m, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 161.5, 151.7, 151.2, 148.2, 145.1, 141.8, 132.3, 130.8, 130.0, 129.8, 128.3, 127.1, 125.2, 123.9, 123.7, 123.2, 123.0, 122.7, 122.6, 120.3, 118.4, 116.8; HRESI-MS calcd for $C_{22}H_{15}Br_2N_3$ $[M+H]^+$, $[M+H+2]^+$, $[M+H+4]^+$: 479.9711, 481.9691, 483.9670 respectively and found *m/z* 479.9702, 481.9688 and 483.9669 respectively; anal. HPLC $t_R$ = 35.1 min, 94.6% at 298 nm.

4.3. Synthesis of 2-substituted quinoline derivatives (**27-32**, **33-50**)

4.3.1. Synthesis of 8-methoxy-2-methylquinoline (**24**)

Toluene (110 mL) was added dropwise to the mixture of *o*-anisidine **(23)** (81.2 mmol) in 6M HCl (190 mL) and stirred at 100 °C for 5 minutes. To it, crotonaldehyde (162.4 mmol, 2.0 eq) was added dropwise and reaction mixture was stirred at 110°C for 3 h to yield 8-methoxy-2-methylquinoline **(24)**. After completion of the reaction; the reaction mixture was cooled to room temperature and aqueous layer was separated and neutralized with aqueous NaOH solution followed by extraction with chloroform. Chloroform layer was concentrated to give crude reaction mixture. The crude product was purified by column chromatography over silica gel (60-120#) using chloroform as eluent.

*8-Methoxy-2-methylquinoline (**24**):* white solid, yield 61%, m.p. 123-125 °C; $^{1}$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.01 (d, 1H, $J$ = 8.4 Hz), 7.41-7.32 (m, 3H), 7.03 (dd, 1H, $J$ = 1.2 and 7.5 Hz), 4.08 (s, 3H), 2.80 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 158.2, 154.9, 139.8, 136.2, 127.7, 125.8, 122.7, 119.5, 107.7, 56.1, 25.8. ESI-MS found *m/z* 174.00 $[M+H]^+$.

4.3.2. Synthesis of 8-methoxyquinoline-2-carbaldehyde (**25**)

8-Methoxy-2-methylquinoline **(24)** (28.9 mmol) was reacted with $SeO_2$ (52.0 mmol, 1.8 eq) in anhydrous 1,4-dioxane (500 mL) at 110 °C for 2 h to give 8-methoxyquinoline-2-carboxaldehyde **(25)**. After completion of the reaction; the inorganic compounds were filtered off and poured into cold water and partitioned with chloroform. The chloroform layer was concentrated and the crude product obtained was purified by column chromatography over silica gel (60-120#) using chloroform as eluent.

*8-Methoxyquinoline-2-carbaldehyde (**25**):* yellow solid, yield 81%, m.p. 102-104 °C; $^{1}$H NMR ($CDCl_3$, 400 MHz): $\delta$ 10.32 (s, 1H), 8.29 (d, 1H, $J$ = 8.4 Hz), 8.08 (d, 1H, $J$ = 8.4 Hz), 7.63 (t, 1H, $J$ = 8.0 Hz), 7.48 (d, 1H, $J$ = 8.2 Hz), 7.16 (d, 1H, $J$ =7.8 Hz), 4.17 (s, 3H); $^{13}$C

NMR ($CDCl_3$, 100 MHz): $\delta$ 193.7, 156.1, 151.5, 139.9, 137.3, 131.4, 129.8, 119.6, 118.0, 108.6, 56.4; ESI-MS found *m/z* 187.98 $[M+H]^+$.

4.3.3. Synthesis of *(E)*-3-(8-methoxyquinolin-2-yl)acrylic acid (**26**)

8-Methoxyquinoline-2-carbaldehyde **(25)** (24.06 mmol) was reacted with malonic acid (36.1 mmol, 1.5 eq.) in pyridine (80 mL) at 70 °C for 2 h to yield *(E)*-3-(8-methoxyquinolin-2-yl)acrylic acid **(26)**. After completion of the reaction, the solution was poured into ice cold water and acidified with hydrochloric acid to pH~4. The reaction mixture was partitioned with chloroform. The chloroform layer was concentrated and crude product obtained was purified by column chromatography over silica gel (60-120#) using chloroform: methanol (95:5) as eluent.

*(E)-3-(8-methoxyquinolin-2-yl)acrylic acid (**26**):* off white solid, yield 65%, m.p. 196-197 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 3340, 2937, 2837, 1708, 1693, 1634, 1560, 1461, 1428, 1330, 1311, 1259, 1107, 985, 835, 758, 720; $^1H$ NMR ($CDCl_3$:$CD_3OD$, 400 MHz): $\delta$ 8.08 (d, 1H, *J* = 8.6 Hz), 7.87 (d, 1H, *J* = 16.0 Hz), 7.64 (d, 1H, *J* = 8.6 Hz), 7.40 (t, 1H, *J* = 8.0 Hz), 7.31 (dd, 1H, *J* = 8.2, 1.0 Hz), 7.00 (dd, 1H, *J* = 7.8, 0.7 Hz), 6.78 (d, 1H, *J* = 16.0 Hz), 4.00 (s, 3H); $^{13}C$ NMR ($CDCl_3$:$CD_3OD$, 100 MHz): $\delta$ 169.1, 155.3, 152.6, 144.3, 139.9, 136.9, 129.1, 127.7, 124.4, 120.1, 119.4, 108.4, 55.9; ESI-MS found *m/z* 230.01 $[M+H]^+$.

4.3.4. General procedure for synthesis of quinoline amides (**27-32**)

*(E)*-3-(8-methoxyquinolin-2-yl)acrylic acid **(26)** (0.87 mmol) upon reaction with different substituted anilines (3.0 mmol) in presence of *N,N'*-diisopropylcarbodiimide (DIC, 1.5 mmol) and 1-Hydroxybenzotriazole hydrate (HOBt, 1.5 mmol) using DMF as a solvent at 40 °C yields various 2-substituted quinoline derivatives **(27-32)**. The reaction was performed under nitrogen atmosphere. The compounds were purified by column chromatography over silica gel (230-400#) using mixture of hexane and EtOAc (60:40) as eluent. An exceptional result

was obtained with aniline, which yielded **32** in addition to **27**, due to Michael addition to the $\alpha,\beta$-unsaturated carbonyl group.

*4.3.4.1. (E)-N-phenyl-3-(8-methoxyquinolin-2-yl)acrylamide (**27**):* off white solid, yield 57%, m.p. 180-182 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 3271, 2926, 1667, 1599, 1549, 1499, 1463, 1443, 1329, 1260, 1111, 1041, 833, 751; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.08 (d, 1H, $J$ = 8.5 Hz), 8.03 (br s, 1H), 7.92 (d, 1H, $J$ = 15.4 Hz), 7.64 (d, 2H, $J$ = 7.9 Hz), 7.49 (d, 1H, $J$ = 8.4 Hz), 7.46 (t, 1H, $J$ = 7.9 Hz), 7.37 (dd, 1H, $J$ = 1.0 and 8.2 Hz), 7.33 (t, 2H, $J$ = 8.0 Hz), 7.27 (d, 1H, $J$ = 15.4 Hz), 7.11 (t, 1H, $J$ = 7.4 Hz), 7.06 (dd, 1H, $J$ = 0.8 and 7.7 Hz), 4.07 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 163.8, 155.4, 152.4, 141.0, 140.3, 138.2, 136.9, 129.3, 129.2 (2 x C), 127.5, 127.0, 124.6, 121.8, 120.0, 119.6 (2 x C), 108.4, 56.2; HRESI-MS calcd. for $C_{19}H_{16}N_2O_2$ $[M+H]^+$: 305.1290, found *m/z* 305.1278; anal. HPLC $t_R$ = 18.8 min, 99.8% at 278 nm.

*4.3.4.2. (E)-N-(4-methoxyphenyl)-3-(8-methoxyquinolin-2-yl)acrylamide (**28**):* off white solid, yield 69%, m.p. 186-188 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 3253, 2923, 1663, 1606, 1558, 1510, 1460, 1383, 1242, 1171, 1111, 1036, 826, 748, 517; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.10 (d, 1H, $J$ = 8.4 Hz), 7.89 (d, 1H, $J$ = 15.4 Hz), 7.81 (br s, 1H), 7.58 (d, 2H, $J$ = 8.9 Hz), 7.52 (d, 1H, $J$ = 8.5 Hz), 7.47 (t, 1H, $J$ = 8.0 Hz), 7.38 (d, 1H, $J$ = 7.7 Hz), 7.24 (d, 1H, $J$ = 14.8 Hz), 7.07 (d, 1H, $J$ = 7.6 Hz), 6.77 (dt, 2H, $J$ = 2.7 and 9.0 Hz), 4.09 (s, 3H), 3.79 (s, 3H); $^{13}$C NMR ($CDCl_3$, 400 MHz): $\delta$ 163.4, 156.5, 155.4, 152.4, 140.5, 140.2, 136.8, 131.2, 129.2, 127.4, 126.9, 121.7, 121.6 (2 x C), 119.5, 114.2 (2 x C), 108.3, 56.1, 55.5; HRESI-MS calcd. for $C_{20}H_{18}N_2O_3$ $[M+H]^+$: 335.1396, found *m/z* 335.1390; anal. HPLC $t_R$ = 18.4 min, 98.6% at 276 nm.

*4.3.4.3. (E)-N-(4-methylphenyl)-3-(8-methoxyquinolin-2-yl)acrylamide (**29**):* off white solid, yield 65%, m.p. 187-189 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 3341, 2968, 1614, 1464, 1385, 1362, 1325,

1246, 1169, 1130, 1111, 959, 866, 637; $^{1}$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.14 (d, 1H, *J* = 8.4 Hz), 7.89 (d, 1H, *J* = 15.4 Hz), 7.73 (br s, 1H), 7.57 (d, 1H, *J* = 8.5 Hz), 7.53 (d, 2H, *J* = 8.1 Hz), 7.48 (t, 1H, *J* = 7.9 Hz), 7.39 (dd, 1H, *J* = 1.0 and 8.2 Hz), 7.26 (d, 1H, *J* = 15.4 Hz), 7.15 (d, 2H, *J* = 8.2 Hz), 7.08 (dd, 1H, *J* = 0.8 and 7.6 Hz), 4.10 (s, 3H), 2.33 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 163.5, 155.4, 152.3, 140.6, 140.2, 136.9, 135.5, 134.2, 129.6 (2 x C), 129.3, 127.4, 126.9, 121.8, 119.9, 119.6 (2 x C), 108.3, 56.2, 20.9; HRESI-MS calcd. for $C_{20}H_{18}N_2O_2$ $[M+H]^+$: 319.1447, found *m/z* 319.1444; anal. HPLC $t_R$ = 21.1 min, >99.0% at 278 nm.

*4.3.4.4. (E)-N-(4-chlorophenyl)-3-(8-methoxyquinolin-2-yl)acrylamide (**30**):* yellow solid, yield 62%, m.p. 183-185 °C; IR (KBr): $\upsilon_{max}$ cm$^{-1}$ 3324, 3052, 1688, 1670, 1601, 1538, 1488, 1464, 1345, 1261, 1241, 1110, 1085, 1006, 823, 744, 717, 508; $^{1}$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.13 (br s, 1H), 8.10 (d, 1H, *J* = 8.5 Hz), 7.91 (d, 1H, *J* = 15.4 Hz), 7.57 (d, 2H, *J* = 8.7 Hz), 7.51 (d, 1H, *J* = 8.5 Hz), 7.47 (t, 1H, *J* = 8.0 Hz), 7.38 (dd, 1H, *J* = 8.2, 1.0 Hz), 7.29-7.26 (m, 3H), 7.07 (dd, 1H, *J* = 7.7, 0.4 Hz), 4.07 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 163.8, 155.4, 152.3, 141.3, 140.3, 137.0, 136.8, 129.5, 129.4, 129.2 (2 x C), 127.7, 126.5, 121.9, 121.2, 119.7 (2 x C), 108.5, 56.2; HRESI-MS calcd. for $C_{19}H_{15}ClN_2O_2$ $[M+H]^+$: 339.0900, found *m/z* 339.0890; anal. HPLC $t_R$ = 22.2 min, 98.5% at 278 nm.

*4.3.4.5. (E)-N-(2-fluorophenyl)-3-(8-methoxyquinolin-2-yl)acrylamide (**31**):* off white solid; yield 56%; m.p. 178-180 °C; IR (KBr): $\upsilon_{max}$ cm$^{-1}$ 3385, 3016, 2918, 1683, 1632, 1617, 1558, 1533, 1524, 1452, 1350, 1173, 1109, 990, 841, 752; $^{1}$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.51 (t, 1H, *J* = 7.9 Hz, H-5'), 8.18 (d, 1H, *J* = 8.5 Hz, H-4), 7.94 (d, 1H, *J* = 15.4 Hz, H-9), 7.78 (br s, 1H, N-H), 7.63 (d, 1H, *J* = 8.4 Hz, H-3), 7.50 (t, 1H, *J* = 7.9 Hz, H-6), 7.41 (dd, 1H, *J* = 1.0 and 8.2 Hz, 1H, H-5), 7.31 (d, 1H, *J* = 15.4 Hz, H-10), 7.20-7.06 (m, 4H, H-7, 3', 4' and 6'), 4.13 (s, 3H, 8-$OCH_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 163.5 (C-11), 155.4 (C-8), 152.4 (d,

$J_{C\text{-}F}$ = 242.0 Hz, C-2'), 152.0 (C-2), 141.5 (C-9), 140.3 (C-8a), 136.9 (C-4), 129.4 (C-4a), 127.6 (C-6), 126.6 (d, $J_{C\text{-}C\text{-}F}$ = 10.0 Hz, C-1'), 126.1 (C-10), 124.7 (d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 3.0 Hz, C-6'), 124.4 (d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 7.0 Hz, C-4'), 122.0 (C-3), 121.7 (C-5'), 119.5 (C-5), 114.8 (d, $J_{C\text{-}C\text{-}F}$ = 19.0 Hz, C-3'), 108.3 (C-7), 56.2 (8-$OCH_3$); HRESI-MS calcd. for $C_{19}H_{15}FN_2O_2$ $[M+H]^+$ 323.1196, found *m/z* 323.1195; anal. HPLC $t_R$ = 18.9 min, 98.5% at 279 nm.

*4.3.4.6. N-phenyl-3-(8-methoxyquinolin-2-yl)-3-(phenylamino)propanamide (**32**):* off white solid, yield 21%, mp 158-160 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 3300, 3056, 2960 ,2932, 1667, 1601, 1524, 1501, 1470, 1441, 1428, 1380, 1322, 1258, 1107, 995, 874, 832, 755, 718, 694; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 9.79 (s, 1H), 8.07 (d, 1H, *J* = 8.4 Hz), 7.55 (d, 2H, *J* = 7.6 Hz), 7.45 (t, 1H, *J* = 8.0 Hz), 7.40-7.35 (m, 2H), 7.28 (t, 2H, *J* = 7.9 Hz), 7.16-7.04 (m, 4H), 6.73 (t, 1H, *J* = 7.3 Hz), 6.67 (d, 2H, *J* = 7.7 Hz), 6.41 (br s, 1H), 4.32 (t, 1H, *J* = 6.1 Hz), 4.11 (s, 3H), 3.61 (1H, dd, *J* = 15.0, 5.2 Hz), 3.49 (1H, dd, *J* = 15.0, 7.2 Hz); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 171.5, 157.5, 154.9, 147.0, 139.1, 138.0, 137.3, 129.4 (2 x C), 128.9 (2 x C), 128.1, 126.7, 124.2, 122.5, 120.1 (2 x C), 119.6, 118.8, 114.1 (2 x C), 108.3, 59.1, 56.0, 40.3; HRESI-MS calcd. for $C_{25}H_{23}N_3O_2$ $[M+H]^+$: 398.1869, $[M+Na]^+$: 420.1688, found *m/z* 398.1877, 420.1694, respectively; anal. HPLC $t_R$ = 22.0 min, >99.0% at 245 nm.

4.3.5. General procedure for synthesis of quinoline oxadiazoles (**33-50**)

8-Methoxyquinoline-2-carbaldehyde **(25**, 0.534 mmol**)** was refluxed with various substituted acylhydrazines (0.587 mmol, 1.1 eq) in ethanol (5-10 mL) to get acyl hydrazides of 8-hydroxyquinoline. After completion of reaction, quinoline acyl hydrazides were found as precipitates on cooling to -15 °C. Precipitates were washed with cold ethanol and dried under vacuum. These acyl hydrazides were used directly for one pot synthesis of 2,5-disubstituted-1,3,4-oxadiazole using iodine/$K_2CO_3$ catalysed oxidative cyclization. To the acyl hydrazides (1.0 eq) in DMSO (5-10 mL), $K_2CO_3$ (3.0 eq) and iodine (1.2 eq) were added in sequence and

refluxed at 110 °C. After the completion, the reaction mixture was cooled and saturated solution of sodium thiosulfate was added. The precipitates were collected and dried under high vacuum to get the respective compounds (**33-50**).

*4.3.5.1. 2-(8-Methoxyquinolin-2-yl)-5-phenyl-1,3,4-oxadiazole (**33**):* light yellow solid; yield 50%; m.p. 157-158 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 3066, 2996, 2835, 1604, 1563, 1540, 1505, 1478, 1460, 1450, 1429, 1373, 1327, 1269, 1118, 1103, 992, 834, 755, 738, 707, 691; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.45 (d, 1H, $J$ = 8.6 Hz), 8.34 (d, 1H, $J$ = 8.6 Hz), 8.31 (dt, 2H, $J$ = 1.7 and 6.1 Hz), 7.61-7.52 (m, 4H), 7.48 (dd, 1H, $J$ = 0.9 and 8.2 Hz) 7.15 (dd, 1H, $J$ = 1.0 and 7.8 Hz), 4.16 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 166.1, 164.4, 155.8, 142.4, 140.0, 137.6, 132.2, 130.1, 129.1 (2 x C), 129.0, 127.7 (2 x C), 123.7, 120.7, 119.6, 108.8, 56.3; HRESI-MS calcd. for $C_{18}H_{13}N_3O_2$ $[M+Na]^+$ 326.0905, found *m/z* 326.0898; anal. HPLC $t_R$ = 21.3 min, 99.0% at 280 nm.

*4.3.5.2. 2-(8-Methoxyquinolin-2-yl)-5-(2-methoxyphenyl)-1,3,4-oxadiazole (**34**):* light brown solid; yield 71%; m.p. 149-150 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 3004, 2931, 2837, 1605, 1506, 1495, 1463, 1428, 1377, 1327, 1285, 1259, 1115, 1100, 1060, 1023, 840, 753; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.45 (d, 1H, $J$ = 8.6 Hz), 8.32 (d, 1H, $J$ = 8.6 Hz), 8.18 (dd, 1H, $J$ = 1.5 and 7.6 Hz), 7.60-7.52 (m, 2H), 7.47 (d, 1H, $J$ = 8.1 Hz) 7.15-7.09 (m, 3H), 4.14 (s, 3H), 4.04 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 164.6, 163.9, 158.4, 155.8, 142.6, 140.0, 137.4, 133.4, 131.1, 130.0, 128.8, 120.74, 120.71, 119.6, 112.9, 112.0, 108.7, 56.3, 56.2; HRESI-MS calcd. for $C_{19}H_{15}N_3O_3$ $[M+Na]^+$ 356.1011, found *m/z* 356.0998; anal. HPLC $t_R$ = 20.2 min, 97.9% at 280 nm.

*4.3.5.3. 2-(8-Methoxyquinolin-2-yl)-5-(3-methoxyphenyl)-1,3,4-oxadiazole (**35**):* white solid; yield 66%; m.p. 162-163 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 2915, 2853, 1593, 1547, 1463, 1236, 1104, 993, 834, 756, 742, 684; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.45 (d, 1H, $J$ = 8.6 Hz), 8.34 (d,

1H, *J* = 8.6 Hz), 7.90 (dt, 1H, *J* = 1.1 and 7.7 Hz), 7.82-7.81 (m, 1H), 7.57 (t, 1H, *J* = 8.0 Hz), 7.50-7.44 (m, 2H), 7.15 (d, 1H, *J* = 7.7 Hz), 7.12 (ddd, 1H, *J* = 0.7, 2.6 and 8.3 Hz), 4.16 (s, 3H), 3.93 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 166.1, 164.4, 160.1, 155.8, 142.5, 140.0, 137.6, 130.2, 130.1, 129.0, 124.8, 120.8, 120.3, 119.7, 118.9, 112.0, 108.8, 56.3, 55.8; HRESI-MS calcd. for $C_{19}H_{15}N_3O_3$ $[M+Na]^+$ 356.1011, found *m/z* 356.1003; anal. HPLC $t_R$ = 22.7 min, >99.0% at 280 nm.

*4.3.5.4. 2-(8-Methoxyquinolin-2-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (**36**):* off white solid; yield 87%; m.p. 202-203 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 2923, 2841, 1616, 1568, 1498, 1460, 1432, 1376, 1308, 1262, 1176, 1121, 1086, 1027, 991, 830, 749; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.44 (d, 1H, *J* = 8.6 Hz), 8.33 (d, 1H, *J* = 8.6 Hz), 8.26-8.23 (m, 2H), 7.59 (t, 1H, *J* = 8.0 Hz), 7.48 (dd, 1H, *J* = 1.0 and 8.2 Hz), 7.15 (dd, 1H, *J* = 0.9 and 7.8 Hz), 7.05 (dt, 2H, *J* = 2.4 and 9.0 Hz), 4.16 (s, 3H), 3.91 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 166.1, 164.0, 162.8, 156.0, 142.6, 140.0, 137.5, 130.0, 129.6 (2 x C), 128.8, 120.7, 119.7, 116.3, 114.6 (2 x C), 108.8, 56.3, 55.6; HRESI-MS calcd. for $C_{19}H_{15}N_3O_3$ $[M+Na]^+$ 356.1011, found *m/z* 356.1007; anal. HPLC $t_R$ = 22.0 min, 96.1% at 280 nm.

*4.3.5.6. 2-(8-Methoxyquinolin-2-yl)-5-(3-methylphenyl)-1,3,4-oxadiazole (**37**):* light brown solid; yield 66%; m.p. 148-149 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 2920, 1977, 1613, 1600, 1565, 1539, 1506, 1456, 1374, 1323, 1259, 1116, 1105, 989, 977, 844, 749, 716, 686; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.46 (d, 1H, *J* = 8.6 Hz), 8.34 (d, 1H, *J* = 8.6 Hz), 8.14 (s, 1H), 8.11 (d, 1H, *J* = 7.6 Hz) 7.60 (t, 1H, *J* = 8.0 Hz), 7.49 (d, 1H, *J* = 7.9 Hz), 7.44 (t, 1H, *J* = 7.6 Hz), 7.38 (d, 1H, *J* = 7.6 Hz), 7.16 (d, 1H, *J* = 7.6 Hz), 4.16 (s, 3H), 2.47 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 166.2, 164.3, 155.8, 142.5, 140.0, 139.0, 137.6, 133.0, 130.1, 129.0, 128.9, 128.2, 124.9, 123.5, 120.7, 119.6, 108.7, 56.3, 21.4; HRESI-MS calcd. for $C_{19}H_{15}N_3O_2$ $[M+Na]^+$ 340.1062, found *m/z* 340.1056; anal. HPLC $t_R$ = 23.9 min, 99.4% at 280 nm.

*4.3.5.7. 2-(8-Methoxyquinolin-2-yl)-5-(4-methylphenyl)-1,3,4-oxadiazole (**38**):* off white solid; yield 81%; m.p. 180-181 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 3039, 2961, 2914, 2838, 1613, 1565, 1539, 1495, 1462, 1439, 1428, 1375, 1327, 1259, 1117, 1099, 1084, 994, 839, 753, 743, 716; $^{1}$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.44 (d, 1H, *J* = 8.6 Hz), 8.33 (d, 1H, *J* = 8.6 Hz), 8.19 (dt, 2H, *J* = 1.6 and 8.2 Hz), 7.58 (t, 1H, *J* = 8.0 Hz), 7.47 (dd, 1H, *J* = 1.0 and 8.24 Hz), 7.35 (d, 2H, *J* = 8.0 Hz), 7.15 (dd, 1H, *J* = 0.9 and 7.8 Hz), 4.16 (s, 3H), 2.45 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 166.3, 164.1, 155.8, 142.8, 142.6, 140.0, 137.6, 130.0, 129.8 (2 x C), 128.9, 127.7 (2 x C), 121.0, 120.7, 119.6, 108.8, 56.3, 21.8; HRESI-MS calcd. for $C_{19}H_{15}N_3O_2$ $[M+Na]^+$ 340.1062, found *m/z* 340.1052; anal. HPLC $t_R$ = 23.5 min, 98.5% at 280 nm.

*4.3.5.8. 2-(8-Methoxyquinolin-2-yl)-5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazole (**39**):* light brown solid; yield 83%; m.p. 163-164 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 2924, 2834, 1606, 1595, 1567, 1499, 1464, 1431, 1373, 1323, 1282, 1264, 1252, 1235, 1117, 862, 830, 745, 720; $^{1}$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.46 (d, 1H, *J* = 8.6 Hz), 8.34 (d, 1H, *J* = 8.6 Hz), 7.92 (dd, 1H, *J* = 1.8 and 8.4 Hz), 7.77 (d, 1H, *J* = 1.8 Hz), 7.59 (t, 1H, *J* = 8.0 Hz), 7.48 (d, 1H, *J* = 8.1 Hz), 7.15 (d, 1H, *J* = 7.7 Hz ), 7.01 (d, 1H, *J* = 8.5 Hz ), 4.16 (s, 3H), 4.02 (s, 3H), 3.99 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 166.1, 164.1, 155.7, 152.5, 149.4, 142.6, 139.9, 137.6, 130.0, 128.9, 121.6, 120.8, 119.7, 116.3, 111.2, 110.1, 108.8, 56.4, 56.3, 56.2; HRESI-MS calcd. for $C_{20}H_{17}N_3O_4$ $[M+Na]^+$ 386.1117, found *m/z* 386.1116; anal. HPLC $t_R$ = 20.7 min, 97.6% at 280 nm.

*4.3.5.9. 2-(8-Methoxyquinolin-2-yl)-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole (**40**):* off white solid; yield 77%; m.p. 183-184 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 2812, 1687, 1598, 1500, 1421, 1400, 1334, 1039. $^{1}$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.46 (d, 1H, *J* = 8.6 Hz), 8.34 (d, 1H, *J* = 8.6 Hz), 7.60 (t, 1H, *J* = 8.0 Hz), 7.51 (s, 2H), 7.48 (dd, 1H, *J* = 0.7 and 8.2 Hz), 7.15 (dd,

1H, *J* = 0.7 and 7.8 Hz), 4.15 (s, 3H), 3.99 (s, 6H), 3.94 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 166.1, 164.3, 155.7, 153.8 (2 x C), 142.5, 141.5, 139.9, 137.7, 130.1, 129.0, 120.9, 119.7, 118.8, 108.8, 105.0 (2 x C), 61.2, 56.7 (2 x C), 56.3; HRESI-MS calcd. for $C_{21}H_{19}N_3O_5$ $[M+Na]^+$ 416.1222, found *m/z* 416.1213; anal. HPLC $t_R$ = 21.9 min, >99.0% at 280 nm.

*4.3.5.10. 2-(8-Methoxyquinolin-2-yl)-5-(2-fluorophenyl)-1,3,4-oxadiazole (**41**):* yellow solid; yield 76%; m.p. 169-170 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 3076, 3026, 2963, 2932, 1618, 1588, 1574, 1493, 1456, 1379, 1323, 1252, 1223, 1105, 1083, 1029, 990, 840, 820, 762, 743, 717, 695; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.44 (d, 1H, *J* = 8.6 Hz), 8.34 (d, 1H, *J* = 8.6 Hz), 8.27 (td, 1H, *J* = 1.7 and 7.4 Hz), 7.61-7.55 (m, 2H), 7.48 (dd,1H, *J* = 1.0 and 8.2 Hz), 7.36-7.28 (m, 2H), 7.15 (dd, 1H, *J* = 0.7 and 7.7 Hz), 4.15 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 164.4, 162.6 (d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 6.0 Hz), 160.5 (d, $J_{C\text{-}F}$ = 258.0 Hz), 155.9, 142.2, 140.1, 137.6, 133.9 (d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 8.0 Hz), 130.4, 130.10, 129.0, 124.7 (d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 4.0 Hz), 120.7, 119.6, 117.2 (d, $J_{C\text{-}C\text{-}F}$ = 21.0 Hz), 112.4 (d, $J_{C\text{-}C\text{-}F}$ = 11.0 Hz), 108.8, 56.3; HRESI-MS calcd. for $C_{18}H_{12}FN_3O_2$ $[M+Na]^+$ 344.0811, found *m/z* 344.0807; anal. HPLC $t_R$ = 20.3 min, >99.0% at 280 nm.

*4.3.5.11. 2-(8-Methoxyquinolin-2-yl)-5-(3-fluorophenyl)-1,3,4-oxadiazole (**42**):* yellow solid; yield 76%; m.p. 199-200 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 3043, 1615, 1591, 1567, 1543, 1507, 1486, 1464, 1421, 1375, 1262, 1190, 1160, 1115, 1101, 1065, 996, 866, 835, 810, 748, 718; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.44 (d, 1H, *J* = 8.6 Hz), 8.35 (d, 1H, *J* = 8.6 Hz), 8.10 (dt, 1H, *J* = 1.2 and 7.8 Hz), 8.01 (ddd, 1H, *J* = 1.6, 2.4 and 9.2 Hz), 7.60 (t, 1H, *J* = 8.0 Hz), 7.54 (td, 1H, *J* = 5.6 and 8.1 Hz), 7.49 (dd, 1H, *J* = 0.9 and 8.3 Hz), 7.28 (tdd, 1H, *J* = 0.8, 2.6 and 8.3 Hz), 7.16 (dd, 1H, *J* = 0.8 and 7.7 Hz), 4.16 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 165.1 (d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 4.0 Hz), 164.6, 163.0 (d, $J_{C\text{-}F}$ = 246.0 Hz), 155.8, 142.2, 140.0, 137.7, 130.9 (d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 8.0 Hz ), 130.1, 129.1, 125.6 (d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 8.0 Hz), 123.5 (d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 4.0 Hz),

120.8, 119.7, 119.2 (d, $J_{C\text{-}C\text{-}F}$ = 21.0 Hz), 114.7 (d, $J_{C\text{-}C\text{-}F}$ = 25.0 Hz), 108.9, 56.3; HRESI-MS calcd. for $C_{18}H_{12}FN_3O_2$ $[M+Na]^+$ 344.0811, found *m/z* 344.0808; anal. HPLC $t_R$ = 22.4 min, 99.3% at 280 nm.

*4.3.5.12. 2-(8-Methoxyquinolin-2-yl)-5-(4-fluorophenyl)-1,3,4-oxadiazole (**43**):* brown solid; yield 71%; m.p. 182-183 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 2918, 1610, 1492, 1460, 1430, 1374, 1328, 1259, 1230, 1117, 1102, 837, 757, 745, 718; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 8.45 (d, 1H, *J* = 8.6 Hz), 8.35 (d, 1H, *J* = 8.6 Hz), 8.33-8.30 (m, 2H), 7.60 (t, 1H, *J* = 8.0 Hz), 7.49 (d, 1H, *J* = 7.9 Hz), 7.25 (t, 2H, *J* = 8.6 Hz), 7.16 (d, 1H, *J* = 7.6 Hz ), 4.16 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 165.2 (d, $J_{C\text{-}F}$ = 252.0 Hz), 165.3, 164.4, 155.7 (2 x C), 142.3, 140.0, 137.6, 130.0 (d, 2 x C, $J_{C\text{-}C\text{-}C\text{-}F}$ = 9.0 Hz), 129.0, 120.7, 120.0 (d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 3.0 Hz), 119.7, 116.5 (d, 2 x C, $J_{C\text{-}C\text{-}F}$ = 22.0 Hz), 108.8, 56.3; HRESI-MS calcd. for $C_{18}H_{12}FN_3O_2$ $[M+Na]^+$ 344.0811, found *m/z* 344.0808; anal. HPLC $t_R$ = 22.1 min, 98.1% at 280 nm.

*4.3.5.13. 2-(8-Methoxyquinolin-2-yl)-5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazole (**44**):* lemon yellow solid; yield 74%; m.p. 225-226 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 3075, 2974, 2951, 2848, 1913, 1603, 1539, 1506, 1463, 1435, 1418, 1375, 1327, 1260, 1166, 1128, 1111, 1085, 1065, 866, 839, 752, 704; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 8.47-8.42 (m, 3H), 8.36 (d, 1H, *J* = 8.6 Hz), 7.82 (d, 2H, *J* = 8.4 Hz), 7.62 (t, 1H, *J* = 8.0 Hz), 7.50 (dd, 1H, *J* = 1.0 and 8.0 Hz), 7.17 (dd, 1H, *J* = 1.1 and 8.0 Hz), 4.17 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 164.86, 164.83, 155.8, 142.1, 140.0, 137.7, 133.7 (q, $J_{C\text{-}C\text{-}F}$ = 33.0 Hz), 130.2, 129.2, 128.0 (2XC), 127.0, 126.15 (q, 2XC, $J_{C\text{-}C\text{-}C\text{-}F}$ = 4.0 Hz), 123.7 (q, $J_{C\text{-}F}$ = 271.0 Hz), 120.8, 119.7, 108.9, 56.3; HRESI-MS calcd. for $C_{19}H_{12}FN_3O_2$ $[M+Na]^+$ 394.0779, found *m/z* 394.0779; anal. HPLC $t_R$ = 25.3 min, 99.1% at 280 nm.

*4.3.5.13. 2-(8-Methoxyquinolin-2-yl)-5-(N,N-dimethylaniline-4-yl)-1,3,4-oxadiazole (**45**):* brown solid; yield 65%; m.p. 206-207 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 3216, 2921, 2361, 1615, 1500,

1459, 1431, 1364, 1258, 1196, 1056, 988, 837, 820, 759, 747, 716; $^{1}$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.42 (d, 1H, *J* = 8.6 Hz), 8.30 (d, 1H, *J* = 8.6 Hz), 8.14 (d, 2H, *J* = 9.0 Hz), 7.56 (t, 1H, *J* = 8.0 Hz), 7.45 (d, 1H, *J* = 7.7 Hz), 7.13 (d, 1H, *J* = 7.6 Hz), 6.76 (d, 2H, *J* = 9.0 Hz), 4.14 (s, 3H), 3.07 (s, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 166.8, 163.4, 155.7, 152.7, 142.9, 139.9, 137.4, 129.9, 129.2 (2 x C), 128.6, 120.7, 119.6, 111.5 (2 x C), 110.6, 108.6, 56.2, 40.2 (2 x C); HRESI-MS calcd. for $C_{20}H_{18}N_4O_2$ $[M+Na]^+$ 369.1327; found *m/z* 369.1321; anal. HPLC $t_R$ = 23.6 min, 97.1% at 266 nm.

*4.3.5.14. 2-(8-Methoxyquinolin-2-yl)-5-(4-(tert-butyl)phenyl)-1,3,4-oxadiazole (**46**):* white solid; yield 93%; m.p. 185-186 °C; IR (KBr): $\upsilon_{max}$ cm$^{-1}$ 3063, 2951, 2867, 1615, 1492, 1463, 1268, 1109, 992, 843, 757, 563; $^{1}$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.45 (d, 1H, *J* = 8.6 Hz), 8.33 (d, 1H, *J* = 8.6 Hz), 8.23 (dt, 2H, *J* = 1.9 and 8.6 Hz ), 7.61-7.55 (m, 3H), 7.48 (dd, 1H, *J* = 0.9 and 8.2 Hz), 7.16 (dd, 1H, *J* = 0.8 and 7.8 Hz), 4.16 (s, 3H), 1.38 (s, 9H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 166.2, 164.2, 155.8 (2 x C), 142.6, 140.0, 137.6, 130.0, 128.9, 127.6 (2 x C), 126.1 (2 x C), 120.9, 120.8, 119.7, 108.8, 56.3, 35.3, 31.3 (3 x C); HRESI-MS calcd. for $C_{22}H_{21}N_3O_2$ $[M+H]^+$ 360.1712, $[M+Na]^+$ 382.1531, found *m/z* 360.1701, 382.1520 respectively; anal. HPLC $t_R$ = 27.9 min, >99.0% at 280 nm.

*4.3.5.15. 2-(8-Methoxyquinolin-2-yl)-5-(furan-2-yl)-1,3,4-oxadiazole (**47**):* white solid; yield 92%; m.p. 258-259 °C; IR (KBr): $\upsilon_{max}$ cm$^{-1}$ 2937, 2812, 2352, 1635, 1548, 1506, 1464, 1383, 1326, 1261, 1122, 1105, 998, 865, 840, 748, 720; $^{1}$H NMR ($CD_3OD$, 400 MHz): $\delta$ 8.50 (d, 1H, *J* = 8.6 Hz), 8.32 (d, 1H, *J* = 8.6 Hz), 7.92 (d, 1H, *J* = 1.2 Hz), 7.65 (t, 1H, *J* = 8.0 Hz), 7.58-7.53 (m, 2H), 7.31 (d, 1H, *J* = 7.6 Hz), 6.79 (dd, 1H, *J* = 1.6 and 3.5 Hz), 4.13 (s, 3H); $^{13}$C NMR ($CD_3OD$, 100 MHz): $\delta$ 164.8, 160.0, 156.8, 148.4, 142.5, 140.9, 140.1, 139.2, 131.5, 130.5, 121.3, 120.8, 117.0, 113.7, 110.5, 56.7; HRESI-MS calcd. for $C_{16}H_{11}N_3O_3$

$[M+Na]^+$ 316.0698, $[2M+Na]^+$ 609.1499, found *m/z* 316.0698, 609.1487 respectively; found *m/z* 369.1321; anal. HPLC $t_R$ = 17.0 min, 98.3% at 280 nm.

*4.3.5.16. 2-(8-Methoxyquinolin-2-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole (**48**):* yellow solid; yield 78%; m.p. 191-192 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 3061, 2840, 1981, 1614, 1596, 1572, 1504, 1409, 1375, 1261, 1116, 1086, 837, 749; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 9.54 (d, 1H, *J* = 1.1 Hz), 8.82 (dd, 1H, *J* = 1.7 and 5.3 Hz), 8.58 (dt, 1H, *J* = 1.9 and 8.1 Hz), 8.46 (d, 1H, *J* = 8.6 Hz), 8.37 (d, 1H, *J* = 8.6 Hz), 7.61 (t, 1H, *J* = 8.0 Hz), 7.51 (td, 2H, *J* = 1.0 and 8.1 Hz), 7.17 (dd, 1H, *J* = 0.7 and 7.8 Hz), 4.17 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 164.8, 164.0, 155.8, 152.8, 148.6, 142.0, 140.0, 137.7, 134.8, 130.2, 129.2, 123.9, 120.7, 120.3, 119.7, 108.9, 56.3; HRESI-MS calcd. for $C_{17}H_{12}N_4O_2$ $[M+Na]^+$ 327.0858, $[2M+Na]^+$ 631.1818, found *m/z* 327.0857, 631.1811, respectively; anal. HPLC $t_R$ = 15.7 min, >99.0% at 280 nm.

*4.3.5.17. 2-(8-Methoxyquinolin-2-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazole (**49**):* yellow solid; yield 57%; m.p. 193-194 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 3784, 3037, 1606, 1573, 1460, 1373, 1331, 1103, 988, 843, 750, 701; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 8.87 (dd, 2H, *J* = 1.5 and 4.6 Hz), 8.46 (d, 1H, *J* = 8.6 Hz), 8.37 (d, 1H, *J* = 8.6 Hz), 8.15 (dd, 2H, *J* = 1.6 and 4.5 Hz), 7.63 (t, 1H, *J* = 8.0 Hz), 7.51 (dd, 1H, *J* = 0.9 and 8.2 Hz), 7.18 (dd, 1H, *J* = 0.9 and 7.8 Hz), 4.17 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 165.1, 164.2, 155.8, 151.0 (2 x C), 141.9, 140.0, 137.8, 130.9, 130.2, 129.3, 121.0 (2 x C), 120.8, 119.7, 108.9, 56.3; HRESI-MS calcd. for $C_{17}H_{12}N_4O_2$ $[M+Na]^+$ 327.0858, found *m/z* 327.0856; anal. HPLC $t_R$ = 15.8 min, >99.0% at 280 nm.

*4.3.5.18. 2-(8-Methoxyquinolin-2-yl)-5-(benzo[d][1,3]dioxol-5-yl)-1,3,4-oxadiazole (**50**):* white solid; yield 87%; m.p. 206-207 °C; IR (KBr): $\upsilon_{max}$ $cm^{-1}$ 3056, 2954, 2836, 1616, 1606, 1571, 1561, 1545, 1491, 1461, 1429, 1348, 1262, 1238, 1109, 1032, 869, 839, 752, 742; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 8.43 (d, 1H, *J* = 8.6 Hz), 8.33 (d, 1H, *J* = 8.6 Hz), 7.87 (dd, 1H, *J*

= 1.7 and 8.2 Hz), 7.74 (d, 1H, *J* = 1.6 Hz), 7.59 (t, 1H, *J* = 8.0 Hz), 7.48 (dd, 1H, *J* = 1.0 and 8.2 Hz), 7.15 (dd, 1H, *J* = 0.8 and 7.8 Hz), 6.96 (d, 1H, *J* = 8.2 Hz), 6.09 (s, 2H), 4.15 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 165.9, 164.0, 155.8, 151.1, 148.4, 142.5, 140.0, 137.5, 130.0, 128.9, 123.1, 120.7, 119.6, 117.6, 108.9, 108.8, 107.7, 102.0, 56.3; HRESI-MS calcd. for $C_{19}H_{13}N_3O_4$ $[M\text{-}CH_2O+Na]^+$ 340.0698, $[M+Na]^+$ 370.0804, found *m/z* 340.1052, 370.0794, respectively; anal. HPLC $t_R$ = 21.6 min, 99.7% at 280 nm.

4.4. *In vitro* anti-HIV-1 activity of the synthesized compounds

All the synthesized quinoline compounds were evaluated for *in vitro* anti-HIV-1 activity as per the protocol reported earlier by our group [9].

4.5. Molecular modelling

The X-ray crystal structure of the CD4-bound gp120 (PDB code 1G9M) was used in the modeling [25]. Protein structure was prepared according to the method reported by Kong *et al.* [26]. In brief, the antibody (light and heavy chains), CD4 and heteroatoms including water molecules were removed using PyMOL [27]. Non-polar hydrogens were merged and Kollman charges were added using AutoDockTools [28]. A grid box of dimension [x,y,z] 101 × 101 × 101 with grid spacing of 0.375 nm, centered around the average coordinates of Cα atoms of TRP427 and GLY474 was used for the grid map generation. Docking was performed using AutoDock 4.0 [28] with Lamarckian genetic algorithm (LGA) to search for the globally optimized conformation. All other options were kept at default value for preparing docking parameter file. The 3D structure of inhibitors *i.e.* **NBD556, BMS806** and **IC9564** were taken from PubChem [29]. The structure of compound **31** was made using ChemDraw. The structures of ligands were minimized using conjugate gradient AMMP incorporated in VEGA ZZ [30]. The interaction study was done using AutoDockTools.

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**Supplementary data**

Supplementary data associated with this article can be found in the online version.

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Highlights:

- Thirty-one substituted quinolines were synthesized exploring C-2 and C-3 positions
- Synthesized compounds included imines, amides and 1,3,4-oxadiazoles of quinoline
- All the compounds were evaluated for anti-HIV-1 potential
- **31** showed activity against HIV-$1_{VB59}$ ($IC_{50}$ 3.35 μM) and HIV-$1_{UG070}$ ($IC_{50}$ 2.57 μM)
- **31** showed entry inhibition ($IC_{50}$ 1.40 μM) and cell fusion inhibition ($IC_{50}$ 0.96 μM)

Graphical abstract