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Hybrid diarylbenzopyrimidine non-nucleoside reverse transcriptase inhibitors as promising new leads for improved anti-HIV-1 chemotherapy

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ABSTRACT

Molecular hybridization of the known anti-HIV-1 template DPC083 and etravirine based on docking model overlay has been generated a novel series of diarylbenzopyrimidine analogues (DABPs) (**5a–z**). These new hybrids were assessed for their activity against HIV in MT-4 cell cultures. Most of these compounds showed good activity against wild-type HIV-1 and mutant viruses. In particular, compound **5r** showed the most potent activity against wild-type HIV-1 with an EC_{50} value of 1.8 nM, and with a selectivity index up to 111,954. It also proved more active against mutant L100I, K103N, Y188L, and K103N + Y181C RT HIV-1 strains than efavirenz.

1. Introduction

Diarylpyrimidine analogues (DAPYs, **1**, Fig. 1), first discovered by Dr. Paul Janssen and his co-workers in 2001,[1] have attracted considerable attention due to their excellent activity and have led to the identification of highly potent compounds against both HIV-1 RT wild-type and mutant virus strains,[2–8] such as the marketed etravirine (**2**, Fig. 1).[1,9] Another emerging clinical candidate DPC083 (**3**, Fig. 1),[10,11] a more recent second-generation congener of the licensed NNRTI drug efavirenz (**4**, Fig. 1), are characterized by the improved profile of resilience to common resistance mutations. However, there is still a need for exploring additional novel chemical entities that present high potency and a broadened spectrum of activity toward a wide range of HIV-1 variants through molecular hybridization[12] of DPC083 with etravirine.

Our docking model of overlaying the lower-energy conformations of DPC083 and etravirine in the binding pocket of HIV-1 RT (Fig. 2) reveals that the hybrid molecules, derived from the fusion of the aromatic ring with the pyrimidine ring of etravirine (Fig. 3), share the features of DPC083 and etravirine. The steric and electronic similarities between DPC083 and etravirine suggested to us that they might overlap within the binding pocket and interact similarly with HIV-1 RT. On the basis of insights into the molecular modeling studies of these hybrid molecules with HIV-1 RT, a series of new diarylbenzopyrimidine hybrids **5** (DABPs) were synthesized and evaluated as novel NNRTIs.

2. Results and discussion

2.1. Chemistry

The synthetic route for the target compounds (**5a–z**) is outlined in Scheme 1. Treatment of the known intermediate 2,4-dichloroquinazolines **9a–b**, which was prepared from 2-aminobenzoic acid in a three-step sequence (reduction, cyclization, and chlorination),[13] with the corresponding phenols in the presence of anhydrous K_2CO_3 at 80 °C in EtOH provided the ethers (**10a–z**), which were converted into the desired target compounds **5a–z** in 32–68% yields upon treatment with 4-cyanoaniline at 190 °C for 2 h under solvent-free condition.

The structures of all these hybrids were determined by mass spectra, ^1H NMR, and ^{13}C NMR data. The structure of the representative compound **5o** in these series was further evaluated by X-ray analysis (Fig. 4).

2.2. Biology

The evaluation of the antiviral activity of the newly synthesized hybrids DABPs **5a–z** was based on the potency of inhibition of the

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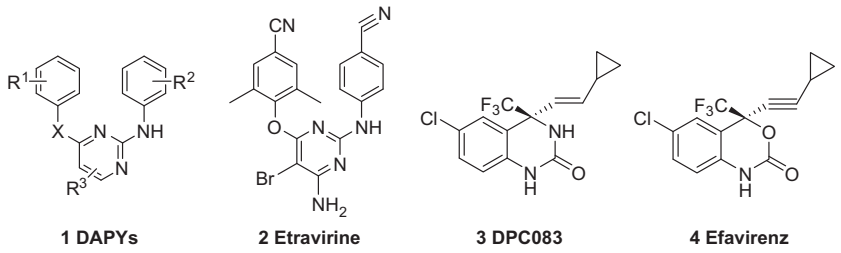


Figure 1. Chemical structures of DAPYs, etravirine, DPC083, and efavirenz.

replication of wild-type HIV-1 (IIIB) virus, the double mutant virus K103N + Y181C RT HIV-1 and HIV-2 strain ROD, respectively. Compounds **5r** and **5u** were further tested for their antiviral activity against a panel of important mutant virus strains (E138K, L100I, K103N, Y181C, and Y188L RT) and a double mutant virus strain (F227L + V106A). The concentrations required to achieve 50% protection from HIV cytopathicity in MT-4 cells were determined by the MTT method,[14,15] and are expressed as EC_{50} (nM or μM) values. The cytotoxic effects (CC_{50}, μM) were assayed in parallel with the antiretroviral activity. Three FDA approved drugs nevirapine (NEV), delavirdine (DEV), and efavirenz (EFV) were chosen as reference drugs. All results are presented in Table 1.

As seen from the results listed in Table 1, most of the tested compounds showed excellent activity against wild-type HIV-1 with a wide range of EC_{50} values ranging from 1331 to 1.8 nM. It is worth noting that compound **5r** was the most potent compound, with an EC_{50} value of 1.8 nM against wild-type HIV-1, which is much more effective than the reference compounds nevirapine (by 731-fold) and delavirdine (by 266-fold). More importantly, it also exhibited a very high selectivity index (111,954). Some other compounds, **5n**, **5t–w** and **5z** also showed high anti-HIV-1 potency (EC_{50} = 11, 8.7, 4.7, 7.5, 16, and 8.5 nM, respectively) and excellent selectivity indices (SI = 3215, 22,005, 46,947, 2969, 6771, and 13,832, respectively). These promising results appear to validate that the molecular hybridization of DPC083 with etravirine is beneficial to reinforce the van der Waals interaction between inhibitors and amino acid residues within the NNRTI binding pocket, thus enhancing their anti-HIV potency.

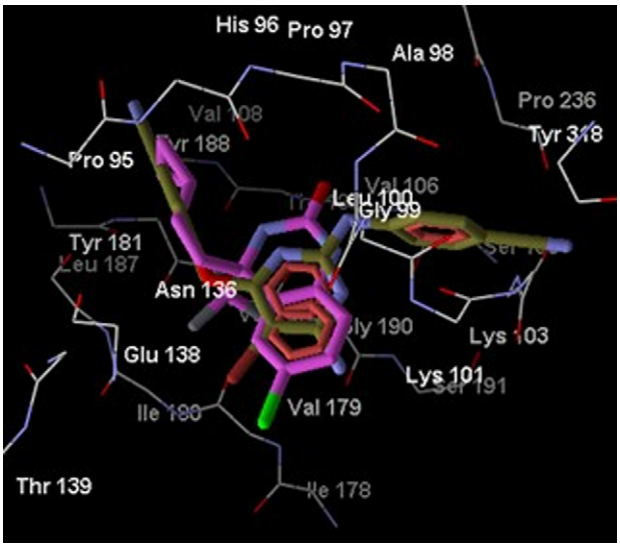


Figure 2. Superposition of lower-energy docking binding conformations of DPC083 (pink) and etravirine (gray) in the binding pocket of HIV-1 RT.

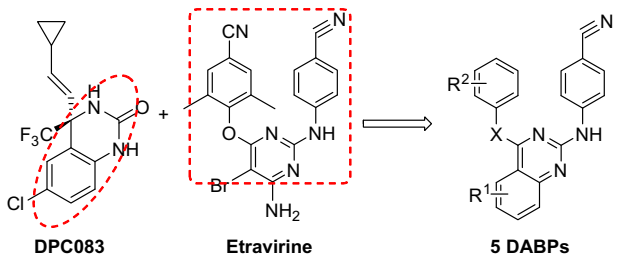


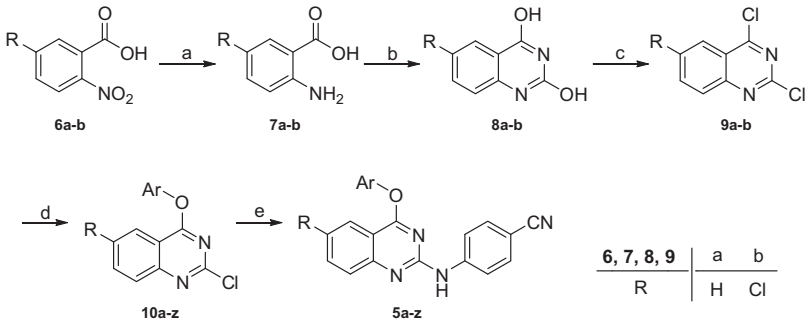
Figure 3. Molecular hybridization of DPC083 and etravirine to create the diarylbenzopyrimidines (DABPs) template **5**.

The activities against the double mutant strain K103N + Y181C of these compounds were also assessed. Compound **5r** turned out to be the most potent inhibitor with an EC_{50} of 0.06 μM, being about two times lower than that of efavirenz (0.11 μM). Compounds **5m**, **5o–p**, and **5u–v** also displayed high anti-HIV-1 activity against the double mutant virus strain (EC_{50} = 0.53, 0.35, 0.59, 0.2, and 0.29 μM, respectively), been more potent than nevirapine or delavirdine.

The potency of all title compounds to inhibit the replication of the HIV-2 ROD virus in MT-4 cells shown that some compounds also displayed micromolar activity. Compound **5p** was the most potent among these hybrids with an EC_{50} value 4.62 μM against HIV-2 ROD.

The results listed in Table 1 revealed some important SAR information on the role of different substitutions in the DABPs. First of all, the nature of the Ar in the DABPs was investigated by preparing a series of Ar analogues of DABPs. Analogs that are mono-substituted on the Ar ring gave enhanced activity (**5b–j**) as compared with the unsubstituted compound **5a**, regardless of the electronic effect and steric bulk. In contrast to the anti-HIV potency of compounds **5b**, **5d**, and **5c** demonstrated a positional preference for *ortho* substitution in the Ar ring. The activity of the synthesized *ortho* and *para* congeners (**5b**, **5e–f** and **5d**, **5g–j**) revealed that the chloro and methyl provided similar activity in inhibiting wild-type HIV-1, whereas other substituents such as F, Br, and MeO led to decreased activity. Clearly, di- or tri-substitution significantly increased inhibitory activity against wild-type HIV-1 as well as double mutant virus K103N + Y181C as compared to the corresponding mono-substitution (**5n** > **5m** > **5b**, or **5l** > **5k** > **5f**). Maximum activity was observed with the compound **5r** with a 2,6-diMe-4-cyano phenyl group as the Ar group. Increasing the steric bulk of *ortho* disubstituents in the Ar ring resulted in a decreased antiviral activity (**5r** > **5t** > **5w** > **5y**, or **5u** > **5v**). These rules were in agreement with the previous results as disclosed by our group.[8] It is worth noting that introducing Cl at the 6-position of the quinazoline ring led to a slight decrease of the anti-HIV-1 potency (**5z** < **5r**).

Furthermore, promising compounds **5r** and **5u** were subsequently tested for their antiviral activity against a panel of important single mutant RT (E138K, L100I, K103N, Y181C, and Y188L) and



5, 10	R	Ar
a	H	C_6H_5
b	H	2-Me-C_6H_4
c	H	3-Me-C_6H_4
d	H	4-Me-C_6H_4
e	H	2-MeO-C_6H_4
f	H	2-Cl-C_6H_4
g	H	4-F-C_6H_4
h	H	4-Cl-C_6H_4
i	H	4-Br-C_6H_4

5, 10	R	Ar
j	H	p-MeO-C_6H_5
k	H	2,4-diCl-C_6H_3
l	H	2,4,6-triCl-C_6H_2
m	H	2,6-diMe-C_6H_3
n	H	2,4,6-triMe-C_6H_2
o	H	2,4-diBr-6-Me-C_6H_2
p	H	2,6-diBr-4-Me-C_6H_2
q	H	2,4,6-triBr-C_6H_2
r	H	4-CN-2,6-diMe-C_6H_2

5, 10	R	Ar
s	H	4-CN-2-MeO-C_6H_3
t	H	4-CN-2,6-diMeO-C_6H_2
u	H	2-Cl-4-CN-6-MeO-C_6H_2
v	H	2-Cl-4-CN-6-EtO-C_6H_2
w	H	4-CN-2,6-diEtO-C_6H_2
x	H	4-CN-2-MeO-6-PrO-C_6H_2
y	H	4-CN-2-EtO-6-PrO-C_6H_2
z	Cl	4-CN-2,6-diMe-C_6H_2

Scheme 1. Synthetic route to target compounds **5a–z**. Reagents and conditions: (a) Raney Ni, $NaBH_4$, 20 min, 30–40 °C; (b) urea, 180 °C, 3 h; (c) $POCl_3$, *N*,*N*-diethyl aniline, reflux, 2 h; (d) K_2CO_3, phenol derivatives, EtOH, 5 min, then **9**, 80 °C, 12 h; (e) 4-cyanoaniline, 180–190 °C, 2 h.

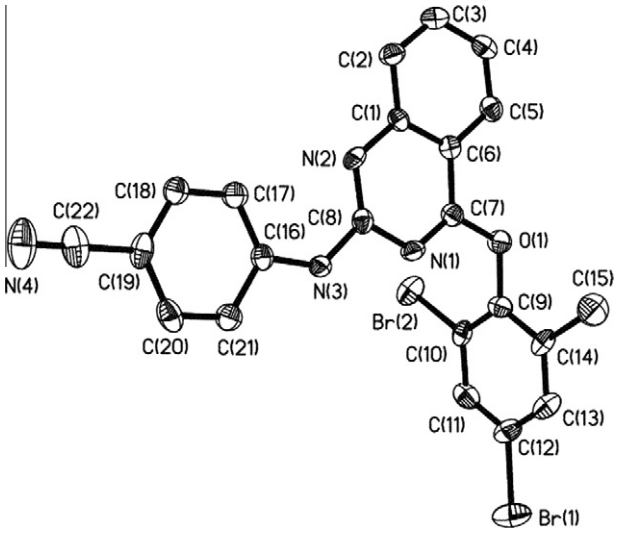


Figure 4. Crystal structure of compound **5o**.

double RT mutant strains (F227L + V106A and K103N + Y181C) (Table 2). It was found that these two compounds showed excellent activity against wild-type and mutant strains. Compound **5r** and efavirenz were equipotent inhibitors against the E138K, L100I, F227L + V106A RT mutant virus strains. Although the compound **5r** is approximately five times less potent than efavirenz against the Y181C RT HIV-1 mutant, for the K103N and Y188L single RT HIV-1 mutants, compound **5r** was 6–20-fold more potent than the clinically used efavirenz. Compound **5u** also kept potent activity against the K103N RT mutant virus strain. The re-assessed activities against wild-type and K103N + Y181C were in accordance with the above mentioned.

2.3. Molecular modeling calculations

Compound **5r**, as the representative of the hybrid molecules, was docked into the non-nucleoside binding site (NNBS) with Molegro Virtual Docker demo version[16] (Fig. 5) to investigate the binding mode of our hybrid compounds with NNBS of HIV-1 RT. The coordinates of the NNBS were taken from the crystal structure of the RT/4-(4-(mesitylamino)pyrimidin-2-ylamino)benzonitrile (**TMC120**) complex (pdb code: 1S6Q).[17] The model revealed that the analogue binds to HIV-1 RT in the horseshoe mode of action, like most of the DAPYs compounds do.[17] According to this mode of action, the NH group that is linking the quinazoline ring and 4-cyanophenyl group could create the hydrogen bonds with the amino acid residues Lys101 and Lys103. The left Ar ring interacts through π–π interactions with a hydrophobic pocket formed mainly by the side chains of aromatic amino acids Tyr181, Tyr188, Phe227, Tyr318, and Trp229. Secondly, this mode of binding of **5r** allows to keep the conformational flexibility which may compensate for the effects of resistance mutations. Finally, the fusing phenyl parts of the hybrid molecule enhanced the van der Waals interaction between **5r** and the adjacent amino acid residues (Glu138, Val179, Lys101, and Lys103) within the binding pocket of RT. All these interactions would favor the high binding affinity and increased activity against wild-type and mutant virus strains.

3. Conclusion

In summary, we designed and synthesized a novel series of diarylbenzopyrimidine analogues (DABPs) and evaluated their activity against HIV in MT-4 cells. The activities against HIV-1 indicated that the designed compounds showed potent antiviral activity with EC_{50} values in the low nanomolar range. DABPs derivatives with 2,6-dime-4-cyano phenyl group as Ar group (**5r**) showed the most potent activity against wild-type HIV-1 with an EC_{50} value of 1.8 nM, and with a selectivity index up to 111,954. Also, compound

Table 1
Anti-HIV-1 activity and cytotoxicity of compounds **5a–z** in MT-4 cells[a]

Compd	EC_{50}[b]			CC_{50}[c] (μM)	SI[d]
	WT (IIIB) (nM)	HIV-2 (μM)	K103N + Y181C (μM)		
5a	1331 ± 769	>369	>369	370	>279
5b	57 ± 20	>355	>355	355	>6211
5c	823 ± 340	>355	>355	355	>436
5d	105 ± 51	>86	>86	87 ± 69	831
5e	120 ± 103	>26	>149	150 ± 89	1265
5f	37 ± 5.3	>37	>37	38 ± 2.8	982
5g	590 ± 421	>351	>351	>351	>607
5h	190 ± 16	>197	>197	198 ± 9.2	1037
5i	264 ± 72	>214	>214	215 ± 35	810
5j	190 ± 49	>339	>339	340	>1794
5k	23 ± 8.8	>31	>31	32 ± 4	1412
5l	21 ± 9.3	>55	1.5 ± 1	56 ± 19	2626
5m	23 ± 13	⩾10	0.53 ± 0.27	35 ± 2	1511
5n	11 ± 0.8	>34	2.0 ± 0.9	>34 ± 1.4	3215
5o	19 ± 10	⩾14	0.35 ± 0.14	150 ± 18	7931
5p	20 ± 9.8	⩾4.6	0.59 ± 0.2	25 ± 2.3	1281
5q	28 ± 12	⩾8.6	0.93 ± 0.5	58 ± 21	2122
5r	1.8 ± 0.5	32	0.06 ± 0.02	203 ± 35	111,954
5s	33 ± 13	>140	>140	⩾140	⩽4195
5t	8.7 ± 3.3	>194	0.92 ± 0.19	194 ± 12	22,005
5u	4.7 ± 1.9	>219	0.16	220 ± 11	46,947
5v	7.5 ± 1.8	>21	0.29 ± 0.09	22 ± 4.4	2969
5w	16 ± 3.5	>108	>108	108 ± 8.3	6771
5x	13 ± 5.1	>5.2	>5.2	5.2 ± 0.8	408
5y	58 ± 9.3	>122	>122	123 ± 11	2084
5z	8.5 ± 2.1	>117	0.7	117 ± 6.2	13,832
NEV	1316 ± 827	—	⩾15	⩾15	>114
EFV	2.1 ± 1.3	—	0.11 ± 0.03	⩾6.3	>3082
DEV	479 ± 131	—	>43	>43	>92

[a] All data represent mean values for at least two separate experiments.
[b] EC_{50}: effective concentration of compound required to protect the cell against viral cytopathogenicity by 50% in MT-4 cells.
[c] CC_{50}: cytotoxic concentration of compound that reduces the normal uninfected MT-4 cell viability by 50%.
[d] SI: selectivity index: ratio CC_{50}/EC_{50}.

Table 2
Antiviral activity (nM) against wild-type HIV-1 LAI virus and a panel of single and double mutant strains of compounds **5r** and **5u**

Compd	LAI	E138K	L100I	K103N	Y181C	Y188L	F227L + V106A	K103N + Y181C
5r	2.3 ± 1	11	18 ± 1.5	⩽3.6	31 ± 20	36 ± 28	107 ± 92	56 ± 15
5u	5.4 ± 1.9	12 ± 1.6	110 ± 49	⩽5.4	49 ± 23.3	280 ± 210	467 ± 140	159
NEV	102 ± 64	162 ± 117	2030 ± 1241	6729 ± 1128	>15,037	>15,037	>15,037	>15,037
DEV	610 ± 174	566 ± 457	7952 ± 9547	6514 ± 8779	6253 ± 4749	6427 ± 458	9847 ± 7538	⩾43,573
EFV	2.2 ± 0.9	5.4 ± 0.3	32	66 ± 19	5.7 ± 0.6	222 ± 54	104 ± 107	85

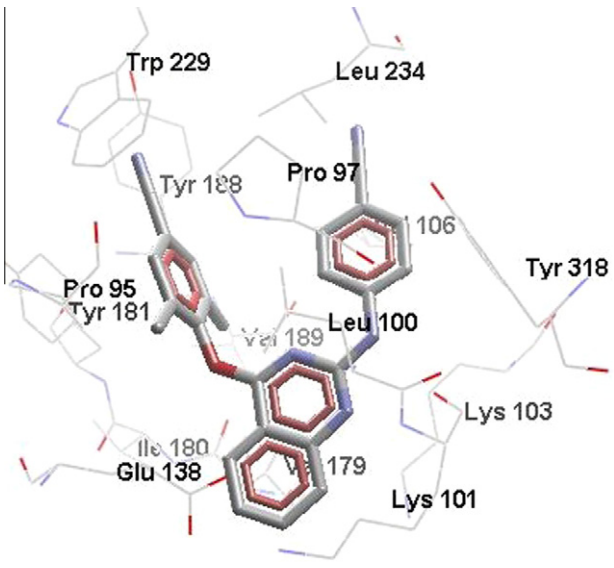


Figure 5. Model of **5r** docked into the HIV-1 RT non-nucleoside binding site.

5r showed excellent potency against the L100I, K103N, Y188L, and K103N + Y181C mutant strains with EC_{50} value 18, 3.6, 36, and 60 nM, respectively. The compound can serve as the basis for further modification in searching for more effective candidates for improved anti-HIV-1 chemotherapy.

4. Experimental section

4.1. Chemistry

Melting points were measured on a WRS-1 digital melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra on a Brucker AV 400 MHz spectrometer were recorded in $CDCl_3$ or DMSO-d_6. Chemical shifts are reported in δ (ppm) units relative to the internal standard tetramethylsilane (TMS). Mass spectra were obtained on an Agilent MS/5975 mass spectrometer. All chemicals and solvents used were of reagent grade and were purified and dried by standard methods before use. All air-sensitive reactions were run under a nitrogen atmosphere. All the reactions were monitored by TLC on pre-coated silica gel G plates at 254 nm under a UV lamp using ethyl acetate/hexane as eluents. Flash chromatography separations were obtained on silica gel (300–400 mesh).

4.2. General procedure for the synthesis of 7a–b[13a]

To a solution of 2-nitrobenzoic acid **6a–b** (100 mmol) in methanol (200 mL) Raney nickel (590 mg, 10 mol %) was added at room temperature. Thereafter, sodium borohydride (7.6 g, 200 mmol, 2 equiv) was slowly and carefully added in a few portions by keeping the temperature between 30 and 40 °C with external cooling. The reaction mixture was stirred for 20 min. The catalyst was filtered off, washed with methanol (30 mL), and immediately immersed in distilled water to prevent spontaneous combustion. The filtrate was evaporated to dryness and the residue was partitioned between water (200 mL) and dichloromethane (200 mL). After separation of the phases, water layer was additionally extracted with dichloromethane (3 × 60 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness to afford products which could be used in the next step without further purification.

4.3. General procedure for the synthesis of 8a–b[13b]

A flask containing urea (15.0 g, 0.25 mol) and 2-aminobenzoic acid **7a–b** (62.5 mmol) was heated at 180 °C. After being stirred for 3 h, the reaction mixture was cooled to 100 °C and an equal volume of water was added. The obtained suspension was left to stir for 10 min, after which it was cooled to room temperature. The precipitate was filtered off and recrystallized from DMF to obtain the title compounds.

4.4. General procedure for the synthesis of 9a–b[13b]

A mixture of 80 ml $POCl_3$, *N*,*N*-diethylaniline (300 mmol) and quinazoline-2,4-diol derivatives **8a–b** (150 mmol) was refluxed for 2 h. The cooling mixture poured into 250 mL ice-water and the mixture was stirred at room temperature. The resulting precipitate was filtered off and washed with 50 mL water, and dried to give products **9a–b** to be used in the next step without further purification.

4.5. General procedure for the synthesis of 10a–z[18]

Potassium carbonate (10 mmol) was added to a solution of phenol derivatives (2 mmol) in 20 mL of anhydrous EtOH and was stirred for 5 min. Then, 2,4-dichloroquinazolines **9a–b** (2 mmol) were then added. The reaction mixture was refluxed for 12 h. After completion, the reaction mixture was treated with cold water (200 mL), and the resulting precipitate was filtered off. The crude products **10a–z** were recrystallized from DMF.

4.5.1. 2-Chloro-4-phenoxyquinazoline (10a)

Yield: 87.5%. Mp 117.1–117.7 °C; ^{1}H NMR (DMSO-d_6) δ (ppm) 7.35–7.56 (m, 5H, Ar″*H*), 7.48 (t, 1H, *J* = 8.0 Hz, Ar*H*$_7$), 7.80 (d, 1H, *J* = 8.4 Hz, Ar*H*$_6$), 8.08 (t, 1H, *J* = 8.4 Hz, Ar*H*$_8$), 8.39 (d, 1H, *J* = 8.4 Hz, Ar*H*$_9$); MS (ESI) *m*/*z* 257 (M^++1).

4.5.2. 2-Chloro-4-(*o*-tolyloxy)quinazoline (10b)

Yield: 86.3%. Mp 110.9–111.3 °C (lit.[18] mp 128–130 °C). ^{1}H NMR (DMSO-d_6) δ (ppm) 2.15 (s, 3H, C*H*$_3$), 7.28–7.42 (m, 4H, Ar″*H*$_{3,4,5,6}$), 7.81–7.85 (m, 1H, Ar*H*$_7$), 7.95–7.97 (m, 1H, Ar*H*$_6$), 8.08–8.12 (m, 1H, Ar*H*$_8$), 8,43–8.45 (m, 1H, Ar*H*$_9$); MS (ESI) *m*/*z* 271 (M^++1).

4.5.3. 2-Chloro-4-(*m*-tolyloxy)quinazoline (10c)

Yield: 86.9%. Mp 134.2–134.6 °C (lit.[18] mp 139–141.5 °C). ^{1}H NMR (DMSO-d_6) δ (ppm) 2.37 (s, 3H, C*H*$_3$), 7.17–7.19 (m, 3H, Ar″*H*), 7.40 (t, 1H, *J* = 8.0 Hz, Ar″*H*), 7.79 (t, 1H, *J* = 8.0 Hz, Ar*H*$_7$), 7.93 (d, 1H, *J* = 8.4 Hz, Ar*H*$_6$), 8.06 (td, 1H, *J* = 7.2 Hz, *J*′ = 0.8 Hz, Ar*H*$_8$), 8.36 (d, 1H, *J* = 8.0 Hz, Ar*H*$_9$); MS (ESI) *m*/*z* 271 (M^++1).

4.5.4. 2-Chloro-4-(*p*-tolyloxy)quinazoline (10d)

Yield: 87.5%. Mp 148.4–149.0 °C (lit.[18] mp 154–156 °C). ^{1}H NMR (DMSO-d_6) δ (ppm) 2.38 (s, 3H, C*H*$_3$), 7.27 (d, 2H, *J* = 8.4 Hz, Ar″*H*$_{3,5}$), 7.32 (d, 2H, *J* = 8.4 Hz, Ar″*H*$_{2,6}$), 7.80 (t, 1H, *J* = 8.0 Hz, Ar*H*$_7$), 7.93 (d, 1H, *J* = 8.0 Hz, Ar*H*$_6$), 8.08 (td, 1H, *J* = 8.4 Hz, *J*′ = 1.2 Hz, Ar*H*$_8$), 8.38 (d, 1H, *J* = 8.0 Hz, Ar*H*$_9$); MS (ESI) *m*/*z* 271 (M^++1).

4.5.5. 2-Chloro-4-(2-methoxyphenoxy)quinazoline (10e)

Yield: 87.5%. Mp 117.1–117.7 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 7.35–7.56 (m, 5H, Ar″*H*), 7.48 (t, 1H, *J* = 8.0 Hz, Ar*H*$_7$), 7.80 (d, 1H, *J* = 8.4 Hz, Ar*H*$_6$), 8.08 (t, 1H, *J* = 8.4 Hz, Ar*H*$_8$), 8.39 (d, 1H, *J* = 8.4 Hz, Ar*H*$_9$); MS (ESI) *m*/*z* 287 (M^++1).

4.5.6. 2-Chloro-4-(2-chlorophenoxy)quinazoline (10f)

Yield: 68.4%. Mp 163.9–164.4 °C (lit.[18] mp 166–167 °C). ^{1}H NMR (DMSO-d_6) δ (ppm) 7.42–7.71 (m, 4H, Ar″*H*), 7.84 (t, 1H, *J* = 7.6 Hz, Ar*H*$_7$), 7.98 (d, 1H, *J* = 8.4 Hz, Ar*H*$_6$), 8.12 (t, 1H, *J* = 8.4 Hz, Ar*H*$_8$), 8.43 (d, 1H, *J* = 8.0 Hz, Ar*H*$_9$); MS (ESI) *m*/*z* 292 (M^++1).

4.5.7. 2-Chloro-4-(4-fluorophenoxy)quinazoline (10g)

Yield: 68.4%. Mp 143.2–142.4 °C (lit.[18] mp 120–122 °C). ^{1}H NMR (DMSO-d_6) δ (ppm) 7.33–7.46 (m, 4H, Ar″*H*), 7.79 (t, 1H, *J* = 8.0 Hz, Ar*H*$_7$), 7.92 (d, 1H, *J* = 8.8 Hz, Ar*H*$_6$), 8.07 (t, 1H, *J* = 8.4 Hz, Ar*H*$_8$), 8.36 (d, 1H, *J* = 7.6 Hz, Ar*H*$_9$); MS (ESI) *m*/*z* 275 (M^++1).

4.5.8. 2-Chloro-4-(4-chlorophenoxy)quinazoline (10h)

Yield: 76.3%. Mp 158.6–160.2 °C (lit.[18] mp 145–147 °C). ^{1}H NMR (DMSO-d_6) δ (ppm) 7.47 (d, 2H, *J* = 6.8 Hz, Ar″*H*$_{3,5}$), 7.59 (d, 2H, *J* = 6.8 Hz, Ar″*H*$_{2,6}$), 7.80 (t, 1H, *J* = 8.0 Hz, Ar*H*$_6$), 7.95 (d, 1H, *J* = 8.4 Hz, Ar*H*$_7$), 8.09 (t, 1H, *J* = 8.0 Hz, Ar*H*$_8$), 8.37 (d, 1H, *J* = 8.4 Hz, Ar*H*$_9$); MS (ESI) *m*/*z* 292 (M^++1).

4.5.9. 4-(4-Bromophenoxy)-2-chloroquinazoline (10i)

Yield: 85.5%. Mp 160.1–160.2 °C (lit.[18] mp 161.5–163.5 °C). ^{1}H NMR (DMSO-d_6) δ (ppm) 7.41 (d, 2H, *J* = 6.8 Hz, Ar″*H*$_{2,6}$), 7.73 (d, 2H, *J* = 6.8 Hz, Ar″*H*$_{3,5}$), 7.81 (t, 1H, *J* = 8.4 Hz, Ar*H*$_7$), 7.95 (d, 1H, *J* = 8.8 Hz, Ar*H*$_6$), 8.09 (td, 2H, *J* = 8.4 Hz, *J*′ = 1.2 Hz, Ar*H*$_8$), 8.38 (d, 1H, *J* = 8.4 Hz, Ar*H*$_9$); MS (ESI) *m*/*z* 335 (M^++1).

4.5.10. 2-Chloro-4-(4-methoxyphenoxy)quinazoline (10j)

Yield: 89.0%. Mp 127.9–128.0 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 3.87 (s, 3H, C*H*$_3$O), 7.01 (d, 2H, *J* = 6.8 Hz, Ar″*H*$_{3,5}$), 7.22 (d, 2H, *J* = 6.8 Hz, Ar″*H*$_{2,6}$), 7.65–7.69 (m, 1H, Ar*H*$_7$), 7.93–7.95 (m, 2H, Ar*H*$_{6,8}$), 8.36 (d, 1H, *J* = 8.4 Hz, Ar*H*$_9$); MS (ESI) *m*/*z* 287 (M^++1).

4.5.11. 2-Chloro-4-(2,4-dichlorophenoxy)quinazoline (10k)

Yield: 74.2%. Mp 172.4–172.6 °C (lit.[18] mp 174.5–1175.5 °C). ^{1}H NMR (DMSO-d_6) δ (ppm) 7.59–7.88 (m, 4H, Ar″*H* + Ar*H*$_6$), 7.97 (d, 1H, *J* = 8.8 Hz, Ar*H*$_7$), 8.11 (t, 1H, *J* = 8.4 Hz, Ar*H*$_8$), 8.40 (d, 1H, *J* = 8.0 Hz, Ar*H*$_9$); MS (ESI) *m*/*z* 326 (M^++1).

4.5.12. 2-Chloro-4-(2,4,6-trichlorophenoxy)quinazoline (10l)

Yield: 88.9%. Mp 223.2–224.1 °C (lit.[18] mp 228–230 °C). ^{1}H NMR (DMSO-d_6) δ (ppm) 7.94 (dt, 1H, *J* = 6.8 Hz, *J*′ = 1.2 Hz, Ar*H*$_7$), 8.04 (s, 2H, Ar″*H*$_{3,5}$), 8.09 (d, 1H, *J* = 8.4 Hz, Ar*H*$_6$), 7.91 (dt, 1H, *J* = 6.8 Hz, *J*′ = 1.2 Hz, Ar*H*$_8$), 8.36 (dd, 1H, *J* = 8.4 Hz, *J*′ = 0.8 Hz, Ar*H*$_9$); MS (ESI) *m*/*z* 361 (M^++1).

4.5.13. 2-Chloro-4-(2,6-dimethylphenoxy)quinazoline (10m)

Yield: 87.3%. Mp 136.5–138.1 °C (lit.[18] mp 140–142 °C). ^{1}H NMR (DMSO-d_6) δ (ppm) 2.12 (s, 6H, 2C*H*$_3$), 7.22–7.26 (m, 3H, Ar″*H*), 7.87 (t, 1H, *J* = 8.0 Hz, Ar*H*$_7$), 8.00 (d, 1H, *J* = 8.8 Hz, Ar*H*$_6$), 8.13 (t, 1H, *J* = 7.2 Hz, Ar*H*$_8$), 8.50 (d, 1H, *J* = 8.0 Hz, Ar*H*$_9$); MS (ESI) *m*/*z* 285 (M^++1).

4.5.14. 2-Chloro-4-(mesityloxy)quinazoline (10n)

Yield: 66.9%. Mp 163.6–164.5 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 2.04 (s, 6H, 2CH_3), 2.30 (s, 3H, CH_3), 7.01 (s, 2H, Ar″$H_{3,5}$), 7.82 (t, 1H, J = 8.0 Hz, ArH_7), 7.96 (d, 1H, J = 8.4 Hz, ArH_6), 8.10 (t, 1H, J = 8.4 Hz, ArH_8), 8.46 (d, 1H, J = 8.0 Hz, ArH_9); MS (ESI) m/z 299 (M^++1).

4.5.15. 2-Chloro-4-(2,4-dibromo-6-methylphenoxy)quinazoline (10o)

Yield: 81.7%. Mp 205.2–205.5 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 2.21 (s, 3H, CH_3), 7.72–7.73 (m, 1H, Ar″H), 7.87 (t, 1H, J = 8.4 Hz, ArH_6), 7.89–7.90 (m, 1H, Ar″H), 8.01 (d, 1H, J = 8.0 Hz, ArH_7) 8.15 (td, 1H, J = 8.0 Hz, J' = 1.2 Hz, ArH_8), 8.46 (d, 1H, J = 7.6 Hz, ArH_9); MS (ESI) m/z 429 (M^++1).

4.5.16. 2-Chloro-4-(2,6-dibromo-4-methylphenoxy)quinazoline (10p)

Yield: 80.7%. Mp 194.6–195.6 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 2.39 (s, 3H, CH_3), 7.70 (s, 2H, Ar″H), 7.70–8.19 (m, 3H, Ar$H_{6,7,8}$), 8.47 (dd, 1H, J = 8.0 Hz, J' = 0.8 Hz, ArH_9); MS (ESI) m/z 429 (M^++1).

4.5.17. 2-Chloro-4-(2,4,6-tribromophenoxy)quinazoline (10q)

Yield: 77.9%. Mp 190.3–190.9 °C (lit.[18] mp 228–230 °C). ^{1}H NMR (DMSO-d_6) δ (ppm) 7.57–8.16 (m, 5H, Ar$H_{6,7,8}$ + Ar″H), 8.43 (d, 1H, J = 8.0 Hz, ArH_9); MS (ESI) m/z 494 (M^++1).

4.5.18. 4-(2-Chloroquinazolin-4-yloxy)-3,5-dimethylbenzonitrile (10r)

Yield: 85.6%. Mp 251.2–252.0 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 2.20 (s, 6H, 2CH_3), 7.71 (s, 2H, Ar″$H_{3,5}$), 7.86 (t, 1H, J = 7.6 Hz, ArH_7), 7.96 (d, 1H, J = 8.4 Hz, ArH_6), 8.12 (t, 1H, J = 8.0 Hz, ArH_8), 8.51 (d, 1H, J = 8.4 Hz, ArH_9); MS (ESI) m/z 310 (M^++1).

4.5.19. 4-(2-Chloroquinazolin-4-yloxy)-3-methoxybenzonitrile (10s)

Yield: 88.6%. Mp 240.1–240.8 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 3.84 (s, 3H, CH_3O), 7.31–8.00 (m, 6H, Ar$H_{6,7,8}$ + Ar″H), 8.39 (d, 1H, J = 8.0 Hz, ArH_9); MS (ESI) m/z 312 (M^++1).

4.5.20. 4-(2-Chloroquinazolin-4-yloxy)-3,5-dimethoxybenzonitrile (10t)

Yield: 80.2%. Mp 270.2–270.7 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 3.79 (s, 6H, 2CH_3O), 7.43 (s, 2H, Ar″$H_{3,5}$), 7.81 (t, 1H, J = 7.6 Hz, ArH_6), 7.96 (d, 1H, J = 8.4 Hz, ArH_7), 8.09 (t, 1H, J = 7.6 Hz, ArH_8), 8.37 (d, 1H, J = 8.4 Hz, ArH_9); MS (ESI) m/z 342 (M^++1).

4.5.21. 3-Chloro-4-(2-chloroquinazolin-4-yloxy)-5-methoxybenzonitrile (10u)

Yield: 74.4%. Mp 241.6–242.0 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 3.66 (s, 3H, CH_3O), 7.13–7.87 (m, 6H, ArH + Ar″$H_{3,5}$); MS (ESI) m/z 347 (M^++1).

4.5.22. 3-Chloro-4-(2-chloroquinazolin-4-yloxy)-5-ethoxybenzonitrile (10v)

Yield: 92.7%. Mp 185.2–187.6 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 1.00 (t, 3H, J = 7.2 Hz, CH_3), 4.13 (q, 2H, J = 7.2 Hz, CH_2O), 7.80–7.89 (m, 3H, ArH_7 + Ar″$H_{3,5}$), 7.99 (d, 1H, J = 8.4 Hz, ArH_6), 8,13 (t, 1H, J = 8.4 Hz, ArH_8), 8.41 (d, 1H, J = 8.0 Hz, ArH_9); MS (ESI) m/z 361 (M^++1).

4.5.23. 4-(2-Chloroquinazolin-4-yloxy)-3,5-diethoxybenzonitrile (10w)

Yield: 76.9%. Mp 191.3–192.0 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 1.06 (t, 6H, J = 7.2 Hz, 2CH_3), 4.09 (q, 4H, J = 7.2 Hz, 2CH_2O), 7.16 (s, 2H, Ar″$H_{3,5}$), 7.82 (t, 1H, J = 8.0 Hz, ArH_7), 7.97 (d, 2H, J = 8.4 Hz ArH_6), 8.11 (t, 1H, J = 8.4 Hz, ArH_8), 8.38 (d, 1H, J = 8.0 Hz, ArH_9); MS (ESI) m/z 370 (M^++1).

4.5.24. 4-(2-Chloroquinazolin-4-yloxy)-3-methoxy-5-propoxybenzonitrile (10x)

Yield: 73.9%. Mp 169.3–171.2 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 0.67 (t, 3H, J = 7.2 Hz, CH_3), 1.53 (m, 2H, CH_2), 3.89 (s, 3H, CH_3O), 4.05 (t, 2H, J = 7.2 Hz, CH_2O), 7.27–7.66 (m, 2H, Ar″H), 7.82 (t, 1H, J = 8.4 Hz, ArH_7), 7.94 (d, 1H, J = 8.4 Hz, ArH_6), 8.09 (t, 1H, J = 8.4 Hz, ArH_8), 8.43 (d, 1H, J = 8.4 Hz, ArH_9); MS (ESI) m/z 370 (M^++1).

4.5.25. 4-(2-Chloroquinazolin-4-yloxy)-3-ethoxy-5-propoxybenzonitrile (10y)

Yield: 82.3%. Mp 192.7–194.0 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 0.54 (t, 3H, J = 7.2 Hz, CH_3), 0.97–1.45 (m, 5H, CH_3 + CH_2), 3.96–4.14 (m, 4H, 2CH_2O), 7.39–8.38 (m, 6H, ArH + Ar″H); MS (ESI) m/z 384 (M^++1).

4.5.26. 4-(2,6-Dichloroquinazolin-4-yloxy)-3,5-dimethylbenzonitrile (10z)

Yield: 72.6%. Mp 267.4–269.2 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 2.13 (s, 6H, 2CH_3), 7.15–8.51 (m, 5H, ArH + Ar″H); MS (ESI) m/z 345 (M^++1).

4.6. General procedure for the synthesis of 5a–z

Compounds **10a–z** (10 mmol) and 4-cyanoaniline (35 mmol) were thoroughly mixed and the mixture was slowly heated to 180–190 °C and maintained at this temperature for about 2 h. After cooling and dissolving the mixture in DMF and subsequent decolorization with charcoal, the product was precipitated with water. The precipitate was filtered and further purified by silica column chromatography (AcOEt/petroleum ether = 1:3).

4.6.1. 4-(4-Phenoxyquinazolin-2-ylamino)benzonitrile (5a)

Yield 59.6%. Mp 230.7–231.9 °C; ^{1}H NMR (DMSO-d_6) δ 7.38–7.43 (m, 3H, Ar′$H_{2,6}$ + Ar″H_4), 7.48 (t, 1H, J = 7.6 Hz, ArH_7), 7.55–7.59 (m, 4H, Ar″$H_{2,3,5,6}$), 7.72 (d, 1H, J = 8.0 Hz, ArH_6), 7.87–7.91 (m, 3H, ArH_8 + Ar′$H_{3,5}$), 8,23 (d, 1H, J = 8.0 Hz, ArH_9), 10.04 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 102.3, 112.0, 118.5 (2C), 119.5, 122.2 (2C), 123.7, 124.2, 125.4, 126.0, 129.9 (2C), 132.6 (2C), 134.9, 144.8, 152.4, 152.6, 155.1, 167.2; MS (ESI) m/z 337 (M^+−1). Anal. Calcd for $C_{21}H_{14}N_4O$: C, 75.54; H, 4.17; N, 16.56. Found: C, 75.42; H, 4.28; N, 16.66.

4.6.2. 4-(4-(*o*-Tolyloxy)quinazolin-2-ylamino)benzonitrile (5b)

Yield 45.1%. Mp 197.3–197.4 °C; ^{1}H NMR (DMSO-d_6) δ 2.16 (s, 3H, CH_3), 7.30–7.44 (m, 4H, Ar″$H_{3,4,5,6}$), 7.49 (td, 1H, J = 7.6 Hz, J' = 1.2 Hz, ArH_7), 7.56 (d, 2H, J = 8.8 Hz, Ar′$H_{2,6}$), 7.72 (d, 1H, J = 8.4 Hz, ArH_6), 7.86 (d, 2H, J = 8.8 Hz, Ar′$H_{3,5}$), 7.90 (td, 1H, J = 7.6 Hz, J' = 1.2 Hz, ArH_8), 8.27 (dd, 1H, J = 8.0 Hz, J' = 0.8 Hz, ArH_9), 10.04 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 16.4, 102.8, 112.2, 118.9 (2C), 120.0, 122.9, 124.2, 124.8, 125.9, 126.7, 128.0, 130.7, 131.9, 133.1, 135.4 (2C), 145.4, 151.4, 153.1, 155.7, 167.2; MS (ESI) m/z 353 (M^++1). Anal. Calcd for $C_{22}H_{16}N_4O$: C, 74.98; H, 4.58; N, 15.90. Found: C, 75.06; H, 4.43; N, 15.99.

4.6.3. 4-(4-(*m*-Tolyloxy)quinazolin-2-ylamino)benzonitrile (5c)

Yield 68.3%. Mp 219.7–220.3 °C; ^{1}H NMR (DMSO-d_6) δ 2.39 (s, 3H, CH_3), 7.18–7.22 (m, 3H, Ar″$H_{2,4,6}$), 7.43 (d, 1H, J = 7.6 Hz, Ar″H_5), 7.48 (td, 1H, J = 8.0 Hz, J' = 1.2 Hz, ArH_7), 7.59 (d, 2H, J = 8.4 Hz, Ar′$H_{2,6}$), 7.72 (d, 1H, J = 8.4 Hz, ArH_6), 7.88 (td, 1H, J = 7.2 Hz, J' = 1.2 Hz, ArH_8), 7.93 (d, 2H, J = 8.4 Hz, Ar′$H_{3,5}$), 8.22 (dd, 1H, J = 8.4 Hz, J' = 1.2 Hz, ArH_9), 10.03 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 20.8, 102.3, 112.0, 118.4 (2C), 119.0, 119.4, 122.4, 123.6,

124.1, 125.3, 126.5, 129.5, 132.6 (2C), 134.8, 139.6, 144.8, 152.3, 152.5, 155.0, 167.1; MS (ESI) *m*/*z* 353 (M^++1). Anal. Calcd for $C_{22}H_{16}N_4O$: C, 74.98; H, 4.58; N, 15.90. Found: C, 75.18; H, 4.56; N, 15.82.

4.6.4. 4-(4-(*p*-Tolyloxy)quinazolin-2-ylamino)benzonitrile (5d)

Yield 56.6%. Mp 220.6–220.8 °C; ^{1}H NMR (DMSO-d_6) δ 2.39 (s, 3H, CH_3), 7.26 (d, 2H, J = 8.8 Hz, Ar′$H_{2,6}$), 7.33 (d, 2H, J = 8.4 Hz, Ar″$H_{3,5}$), 7.46 (t, 1H, J = 8.0 Hz, ArH_7), 7.58 (d, 2H, J = 8.4 Hz, Ar″$H_{2,6}$), 7.70 (d, 1H, J = 8.4 Hz, ArH_6), 7.87 (td, 1H, J = 8.0 Hz, J' = 1.6 Hz, ArH_8), 7.94 (d, 2H, J = 8.8 Hz, Ar′$H_{3,5}$), 8.20 (dd, 1H, J = 8.4 Hz, J' = 0.8 Hz, ArH_9), 9.98 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 20.5, 102.4, 112.1, 118.5 (2C), 119.5, 121.8 (2C), 123.7, 124.2, 125.4, 130.2 (2C), 132.6 (2C), 134.8, 135.1, 144.9, 150.1, 152.5, 155.1, 167.2; MS (ESI) *m*/*z* 351 (M^+−1). Anal. Calcd for $C_{22}H_{16}N_4O$: C, 74.98; H, 4.58; N, 15.90. Found: C, 75.11; H, 4.60; N, 15.81.

4.6.5. 4-(4-(2-Methoxyphenoxy)quinazolin-2-ylamino)benzonitrile (5e)

Yield 52.9%. Mp 220.0–220.5 °C; ^{1}H NMR (DMSO-d_6) δ 3.73 (s, 3H, CH_3O), 7.10 (td, 1H, J = 7.6 Hz, J' = 1.6 Hz, Ar″H_6), 7.30 (dd, 1H, J = 8.4 Hz, J' = 1.2 Hz, Ar″H_3), 7.35–7.41 (m, 2H, Ar″$H_{4,5}$), 7.47 (td, 1H, J = 8.0 Hz, J' = 0.8 Hz, ArH_7), 7.56 (d, 2H, J = 8.8 Hz, Ar′$H_{2,6}$), 7.71 (d, 1H, J = 8.4 Hz, ArH_6), 7.84 (d, 2H, J = 8.8 Hz, Ar′$H_{3,5}$), 7.89 (td, 1H, J = 8.4 Hz, J' = 1.2 Hz, ArH_8), 8.22 (d, 1H, J = 8.4 Hz, ArH_9), 10.06 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 55.8, 102.3, 111.6, 113.4, 118.3 (2C), 119.5, 121.0, 123.1, 123.8, 124.2, 125.4, 127.2, 132.6 (2C), 134.9, 140.9, 144.9, 151.1, 152.6, 155.2, 166.8; MS (ESI) *m*/*z* 367 (M^+−1). Anal. Calcd for $C_{22}H_{16}N_4O_2$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.77; H, 4.27; N, 15.12.

4.6.6. 4-(4-(2-Chlorophenoxy)quinazolin-2-ylamino)benzonitrile (5f)

Yield 51.8%. Mp 190.9–192.3 °C; ^{1}H NMR (DMSO-d_6) δ 7.44–7.61 (m, 6H, ArH_7 + Ar′$H_{2,6}$ + Ar″$H_{4,5,6}$), 7.69–7.90 (m, 5H, Ar$H_{6,8}$ + Ar′$H_{3,5}$ + Ar″H_3), 8.24 (d, 1H, J = 8.4 Hz, ArH_9), 10.08 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 102.6, 111.5, 118.5 (2C), 119.5, 123.7, 124.5, 124.7, 125.5, 126.2, 127.9, 128.9, 130.6, 132.7 (2C), 135.3, 144.8, 148.3, 152.8, 155.0, 166.4; MS (ESI) *m*/*z* 373 (M^+−1). Anal. Calcd for $C_{21}H_{13}N_4OCl$: C, 67.66; H, 3.51; N, 15.03; Cl, 9.51. Found: C, 67.81; H, 3.44; N, 14.97; Cl, 9.58.

4.6.7. 4-(4-(4-Fluorophenoxy)quinazolin-2-ylamino)benzonitrile (5g)

Yield 55.6%. Mp 214.2–214.7 °C; ^{1}H NMR (DMSO-d_6) δ 7.37–7.39 (m, 2H, Ar′$H_{2,6}$), 7.44–7.48 (m, 3H, ArH_7 + Ar″$H_{3,5}$), 7.60 (d, 2H, J = 8.4 Hz, Ar″$H_{2,6}$), 7.70 (d, 1H, J = 8.4 Hz, ArH_6), 7.85–7.93 (m, 3H, ArH_8 + Ar′$H_{3,5}$), 8,20 (d, 1H, J = 8.0 Hz, ArH_9), 9.93 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 102.9, 112.5, 116.8 (2C), 117.1, 119.0 (2C), 120.0, 124.2, 124.5, 124.7 (2C), 125.9, 133.2 (2C), 135.4, 145.3, 148.9, 153.1, 155.5, 167.7; MS (ESI) *m*/*z* 357 (M^+−1). Anal. Calcd for $C_{21}H_{13}N_4OF$: C, 70.78; H, 3.68; N, 15.72; F, 5.33. Found: C, 70.72; H, 3.83; N, 15.77; F, 5.21.

4.6.8. 4-(4-(4-Chlorophenoxy)quinazolin-2-ylamino)benzonitrile (5h)

Yield 55.9%. Mp 252.3–252.7 °C; ^{1}H NMR (DMSO-d_6) δ 7.44–7.48 (m, 3H, ArH_7 + Ar′$H_{2,6}$), 7.58–7.61 (m, 4H, Ar′$H_{3,5}$ + Ar″$H_{3,5}$), 7.71 (d, 1H, J = 8.4 Hz, ArH_6), 7.87 (dt, 1H, J = 7.2 Hz, J' = 1.6 Hz, ArH_8), 7.93 (d, 2H, J = 8.4 Hz, Ar″$H_{2,6}$), 8,19 (d, 1H, J = 8.0 Hz, ArH_9), 9.99 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 102.5, 112.0, 118.6 (2C), 119.6, 123.8, 124.3 (2C), 124.4, 125.5, 129.8 (2C), 130.2, 132.7 (2C), 135.0, 144.9, 151.2, 152.6, 154.9, 167.1; MS (ESI) *m*/*z* 373 (M^+−1). Anal. Calcd for $C_{21}H_{13}N_4OCl$: C, 67.66; H, 3.51; N, 15.03; Cl, 9.51. Found: C, 67.62; H, 3.49; N, 15.06; Cl, 9.62.

4.6.9. 4-(4-(4-Bromophenoxy)quinazolin-2-ylamino)benzonitrile (5i)

Yield 55.0%. Mp 267.3–267.6 °C; ^{1}H NMR (DMSO-d_6) δ 7.41 (d, 2H, J = 6.8 Hz, Ar′$H_{2,6}$), 7.47 (t, 1H, J = 7.2 Hz, ArH_7), 7,61 (d, 2H, J = 8.8 Hz, Ar″$H_{2,6}$), 7.71–7.75 (m, 3H, ArH_6 + Ar′$H_{3,5}$), 7.88 (td, 1H, J = 8.4 Hz, J' = 1.2 Hz, ArH_8), 7.94 (d, 2H, J = 8.4 Hz, Ar″$H_{3,5}$), 8.21 (d, 1H, J = 8.4 Hz, ArH_9), 10.02 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 103.0, 112.5, 118.8 (2C), 119.0 (2C), 120.0, 124.2, 124.8, 125.2 (2C), 126.0, 133.1, 133.2 (2C), 135.5, 145.3, 152.2, 153.1, 155.4, 167.4; MS (ESI) *m*/*z* 417 (M^++1). Anal. Calcd for $C_{21}H_{13}N_4OBr$: C, 60.45; H, 3.14; N, 13.43; Br, 19.15. Found: C, 60.66; H, 3.02; N, 13.40; Br, 19.22.

4.6.10. 4-(4-(4-Methoxyphenoxy)quinazolin-2-ylamino)benzonitrile (5j)

Yield 59.1%. Mp 218.2–218.4 °C; ^{1}H NMR (DMSO-d_6) δ 3.83 (s, 3H, CH_3O), 7.08 (d, 2H, J = 6.8 Hz, Ar″$H_{3,5}$), 7.32 (d, 2H, J = 6.8 Hz, Ar″$H_{2,6}$), 7.47 (td, 1H, J = 8.0 Hz, J' = 0.8 Hz, ArH_7), 7.59 (d, 2H, J = 8.8 Hz, Ar′$H_{2,6}$), 7.71 (d, 1H, J = 8.4 Hz, ArH_6), 7.87 (td, 1H, J = 8.4 Hz, J' = 1.2 Hz, ArH_8), 7.95 (d, 2H, J = 8.4 Hz, Ar′$H_{3,5}$), 8.21 (dd, 1H, J = 8.4 Hz, J' = 1.2 Hz, ArH_9), 9.99 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 56.0, 102.9, 112.6, 115.3 (2C), 119.0 (2C), 120.1, 123.5 (2C), 124.2, 124.7, 125.9, 133.2, 135.3 (2C), 145.4, 146.2, 153.0, 155.6, 157.6, 167.9; MS (ESI) *m*/*z* 369 (M^++1). Anal. Calcd for $C_{22}H_{16}N_4O_2$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.79; H, 4.46; N, 15.03.

4.6.11. 4-(4-(2,4-Dichlorophenoxy)quinazolin-2-ylamino)benzonitrile (5k)

Yield 56.6%. Mp 213.1–214.0 °C; ^{1}H NMR (DMSO-d_6) δ 7.49 (t, 1H, J = 7.6 Hz, Ar″H_7), 7.60–7.66 (m, 4H, ArH_6 + Ar′$H_{2,6}$ + Ar″H_5), 7.73 (d, 1H, J = 8.8 Hz, ArH_6), 7.88–7.91 (m, 4H, ArH_8 + Ar′$H_{3,5}$ + Ar″H_3), 8.22 (d, 1H, J = 8.0 Hz, ArH_9), 10.06 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 103.2, 111.8, 119.0 (2C), 120.0, 124.1, 125.0, 126.0, 126.6, 128.0, 129.4, 130.5, 131.7, 133.2 (2C), 135.8, 145.1, 147.8, 153.2, 155.2, 166.6; MS (ESI) *m*/*z* 407 (M^++1). Anal. Calcd for $C_{21}H_{12}N_4OCl_2$: C, 61.93; H, 2.97; N, 13.76; Cl, 17.41. Found: C, 61.78; H, 3.12; N, 13.88; Cl, 17.25.

4.6.12. 4-(4-(2,4,6-Trichlorophenoxy)quinazolin-2-ylamino)-benzonitrile (5l)

Yield 56.4%. Mp 252.4–253.1 °C; ^{1}H NMR (DMSO-d_6) δ 7.34 (s, 1H, N*H*), 7.53–7.56 (m, 3H, ArH_7 + Ar″$H_{3,5}$), 7.60 (d, 2H, J = 7.2 Hz, Ar′$H_{2,6}$), 7.80 (d, 2H, J = 8.8 Hz, Ar′$H_{3,5}$), 7.86 (d, 1H, J = 8.0 Hz, ArH_6), 7.91 (dt, 1H, J = 6.8 Hz, J' = 1.2 Hz, ArH_8), 8.36 (dd, 1H, J = 8.0 Hz, J' = 0.8 Hz, ArH_9); ^{13}C NMR (DMSO-d_6) δ 104.2, 111.4, 117.8 (2C), 118.8 (2C), 119.0, 123.4, 124.3, 125.7, 129.7 (2C), 131.7, 132.7 (2C), 134.7, 143.1, 144.1, 152.9, 153.9, 165.2; MS (ESI) *m*/*z* 441 (M^+−1). Anal. Calcd for $C_{21}H_{11}N_4OCl_3$: C, 57.10; H, 2.51; N, 12.68; Cl, 24.08. Found: C, 57.02; H, 2.78; N, 12.86; Cl, 23.89.

4.6.13. 4-(4-(2,6-Dimethylphenoxy)quinazolin-2-ylamino)-benzonitrile (5m)

Yield 62.9%. Mp 159.2–160.9 °C; ^{1}H NMR (DMSO-d_6) δ 2.11 (s, 6H, 2CH_3), 7.21–7.24 (m, 3H, Ar′$H_{2,6}$ + Ar″H_4), 7.58–7.61 (m, 4H, Ar′$H_{3,5}$ + Ar″$H_{3,5}$), 7.49 (t, 1H, J = 7.2 Hz, ArH_7), 7.54 (d, 1H, J = 8.8 Hz, Ar″$H_{3,5}$), 7.73 (d, 1H, J = 8.4 Hz, ArH_6), 7.84 (d, 2H, J = 8.0 Hz, Ar′$H_{3,5}$), 7.89 (t, 1H, J = 8.0 Hz, ArH_8), 8.30 (d, 1H, J = 7.6 Hz, ArH_9), 10.08 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 16.1 (2C), 102.5, 111.4, 118.5 (2C), 119.5, 123.8, 124.4, 125.4, 126.0, 128.9 (2C), 132.0 (2C), 132.7 (2C), 135.1, 144.9, 149.6, 152.5, 155.3, 166.1; MS (ESI) *m*/*z* 367 (M^+−1). Anal. Calcd for $C_{23}H_{18}N_4O$: C, 75.39; H, 4.95; N, 15.29. Found: C, 75.21; H, 5.12; N, 15.33.

4.6.14. 4-(4-(Mesityloxy)quinazolin-2-ylamino)benzonitrile (5n)

Yield 50.7%. Mp 206.9–207.9 °C; ^{1}H NMR (DMSO-d_6) δ 2.07 (s, 6H, 2CH_3), 2.33 (s, 3H, CH_3), 7.04 (s, 2H, Ar″$H_{3,5}$), 7.50 (t, 1H, J = 8.0 Hz, ArH_7), 7.57 (d, 2H, J = 8.8 Hz, Ar′$H_{2,6}$), 7.74 (d, 1H, J = 8.4 Hz, ArH_6), 7.88–7.93 (m, 3H, ArH_8 + Ar′$H_{3,5}$), 8.29 (dd, 1H, J = 8.0 Hz, J' = 0.8 Hz, ArH_9), 10.08 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 15.4 (2C), 19.8, 102.0, 110.9, 118.1 (2C), 118.9, 123.2, 123.8, 124.7, 128.8 (2C), 129.2 (2C), 132.1 (2C), 134.4, 134.5, 144.2, 146.8, 151.9, 154.7, 165.6; MS (ESI) m/z 381 (M^++1). Anal. Calcd for $C_{24}H_{20}N_4O$: C, 75.77; H, 5.30; N, 14.73. Found: C, 75.63; H, 5.45; N, 14.89.

4.6.15. 4-(4-(2,4-Dibromo-6-methylphenoxy)quinazolin-2-ylamino)benzonitrile (5o)

Yield 49.4%. Mp 218.6–220.2 °C; ^{1}H NMR (DMSO-d_6) δ 2.20 (s, 3H, CH_3), 7.51 (t, 1H, J = 7.6 Hz, ArH_7), 7.61 (d, 2H, J = 8.8 Hz, Ar′$H_{2,6}$), 7.73–7.76 (m, 2H, ArH_6 + Ar″H_5), 7.88–7.94 (m, 4H, ArH_8 + Ar′$H_{3,5}$ + Ar″H_3), 8.27 (d, 1H, J = 8.0 Hz, ArH_9), 10.09 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 16.3, 102.6, 111.2, 117.6, 118.5 (2C), 118.9, 119.5, 123.6, 124.5, 125.6, 132.7, 132.8 (2C), 133.3, 135.3, 135.5, 144.7, 147.6, 152.8, 154.9, 165.2; MS (ESI) m/z 511 (M^++1). Anal. Calcd for $C_{22}H_{14}N_4OBr_2$: C, 51.79; H, 2.77; N, 10.98; Br, 31.32. Found: C, 51.62; H, 2.95; N, 11.09; Br, 31.28.

4.6.16. 4-(4-(2,6-Dibromo-4-methylphenoxy)quinazolin-2-ylamino)benzonitrile (5p)

Yield 50.8%. Mp 249.1–249.6 °C; ^{1}H NMR (DMSO-d_6) δ 2.41 (s, 3H, CH_3), 7.53 (t, 1H, J = 8.0 Hz, ArH_7), 7.62 (d, 2H, J = 8.8 Hz, Ar′$H_{2,6}$), 7.72 (s, 2H, Ar″$H_{3,5}$), 7.76 (d, 1H, J = 8.4 Hz, ArH_6), 7.90–7.96 (m, 3H, ArH_8 + Ar′$H_{3,5}$), 8.27 (dd, 1H, J = 8.0 Hz, J' = 0.8 Hz, ArH_9), 10.14 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 19.3, 102.2, 110.6, 116.5 (2C), 117.9 (2C), 119.4, 123.0, 124.1, 125.0, 132.2 (2C), 132.7 (2C), 134.8, 139.0, 144.0, 144.1, 152.4, 154.3, 164.6; MS (ESI) m/z 511 (M^++1). Anal. Calcd for $C_{22}H_{14}N_4OBr_2$: C, 51.79; H, 2.77; N, 10.98; Br, 31.32. Found: C, 51.77; H, 2.91; N, 10.87; Br, 31.45.

4.6.17. 4-(4-(2,4,6-Tribromophenoxy)quinazolin-2-ylamino)-benzonitrile (5q)

Yield 52.2%. Mp 261.0–261.2 °C; ^{1}H NMR (DMSO-d_6) δ 7.54 (t, 1H, J = 7.2 Hz, ArH_7), 7.64 (d, 2H, J = 8.4 Hz, Ar′$H_{2,6}$), 7.78 (d, 1H, J = 8.4 Hz, ArH_6), 7.90–7.97 (m, 3H, ArH_8 + Ar′$H_{3,5}$), 8.21 (s, 2H, Ar″$H_{3,5}$), 8.27 (dd, 1H, J = 8.0 Hz, ArH_9), 10.16 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm) 102.8, 110.9, 118.5 (2C), 118.8 (2C), 119.4, 120.0, 123.5, 124.8, 125.6, 132.7 (2C), 135.1 (2C), 135.6, 144.5, 146.7, 152.9, 154.6, 164.8; MS (ESI) m/z 573 (M^++1). Anal. Calcd for $C_{21}H_{11}N_4OBr_3$: C, 43.86; H, 1.93; N, 9.47; Br, 41.69. Found: C, 43.58; H, 1.99; N, 9.87; Br, 41.72.

4.6.18. 4-(2-(4-Cyanophenylamino)quinazolin-4-yloxy)-3,5-dimethylbenzonitrile (5r)

Yield 44.7%. Mp 291.2–292.1 °C; ^{1}H NMR (DMSO-d_6) δ 2.07 (s, 6H, 2CH_3), 2.33 (s, 3H, CH_3), 7.04 (s, 2H, Ar″$H_{3,5}$), 7.50 (t, 1H, J = 8.0 Hz, ArH_7), 7.57 (d, 2H, J = 8.8 Hz, Ar′$H_{2,6}$), 7.74 (d, 1H, J = 8.4 Hz, ArH_6), 7.88–7.93 (m, 3H, ArH_8 + Ar′$H_{3,5}$), 8.29 (dd, 1H, J = 8.0 Hz, J' = 0.8 Hz, ArH_9), 10.08 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 15.4 (2C), 19.8, 102.0, 110.9, 118.1 (2C), 118.9, 123.2, 123.8, 124.7, 128.8 (2C), 129.2 (2C), 132.1 (2C), 134.4, 134.5, 144.2, 146.8, 151.9, 154.7, 165.6; MS (ESI) m/z 381 (M^++1). Anal. Calcd for $C_{24}H_{17}N_5O$: C, 73.64; H, 4.38; N, 17.89. Found: C, 73.43; H, 4.32; N, 17.98.

4.6.19. 4-(2-(4-Cyanophenylamino)quinazolin-4-yloxy)-3-methoxybenzonitrile (5s)

Yield 54.6%. Mp 251.7–252.4 °C; ^{1}H NMR (DMSO-d_6) δ 3.80 (s, 3H, CH_3O), 7.49 (t, 1H, J = 8.0 Hz, ArH_7), 7.61–7.64 (m, 4H, Ar′$H_{2,6}$ + Ar″$H_{3,5}$), 7.73 (d, 1H, J = 8.4 Hz, ArH_6), 7.84 (s, 1H, Ar″H_3), 7.86–7.90 (m, 3H, ArH_8 + Ar′$H_{3,5}$), 8.21 (d, 1H, J = 8.0 Hz, ArH_9), 10.06 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 56.6, 102.5, 109.8, 111.4, 117.0, 118.4 (2C), 118.5, 118.6, 119.5, 123.7, 124.4, 125.5, 125.9, 132.7 (2C), 135.1, 144.7, 144.9, 151.7, 152.6, 154.9, 166.3; MS (ESI) m/z 394 (M^++1). Anal. Calcd for $C_{23}H_{15}N_5O_2$: C, 70.22; H, 3.84; N, 17.80. Found: C, 70.29; H, 3.73; N, 17.93.

4.6.20. 4-(2-(4-Cyanophenylamino)quinazolin-4-yloxy)-3,5-dimethoxybenzonitrile (5t)

Yield 55.1%. Mp 285.3–285.7 °C; ^{1}H NMR (DMSO-d_6) δ 3.85 (s, 6H, 2CH_3O), 7.51–7.54 (m, 3H, ArH_7 + Ar″$H_{3,5}$), 7.66 (d, 2H, J = 8.8 Hz, Ar′$H_{2,6}$), 7.77 (d, 1H, J = 8.8 Hz, ArH_6), 7.89–7.96 (m, 3H, ArH_8 + Ar′$H_{3,5}$), 8.24 (d, 1H, J = 8.0 Hz, ArH_9), 10.12 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 55.9 (2C), 102.6, 109.3, 110.0 (2C), 111.2, 118.4 (2C), 118.7, 119.6, 123.8, 124.5, 125.9, 132.8 (2C), 133.6, 135.2, 144.8, 152.7 (2C), 152.8, 155.1, 165.9; MS (ESI) m/z 424 (M^+−1). Anal. Calcd for $C_{24}H_{17}N_5O_3$: C, 68.08; H, 4.05; N, 16.54. Found: C, 68.19; H, 3.96; N, 16.45.

4.6.21. 3-Chloro-4-(2-(4-cyanophenylamino)quinazolin-4-yloxy)-5-methoxybenzonitrile (5u)

Yield 42.0%. Mp 267.2–269.5 °C; ^{1}H NMR (DMSO-d_6) δ 3.83 (s, 3H, CH_3O), 7.51 (t, 1H, J = 7.6 Hz, ArH_7), 7.64 (d, 2H, J = 8.8 Hz, Ar′$H_{2,6}$), 7.75 (d, 1H, J = 8.4 Hz, ArH_6), 7.88–7.94 (m, 5H, ArH_8 + Ar′$H_{3,5}$ + Ar″$H_{3,5}$), 8.22 (d, 1H, J = 8.0 Hz, ArH_9), 10.11 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 57.3, 102.8, 110.5, 110.8, 116.3, 117.4, 118.5 (2C), 119.2, 123.6, 124.8, 125.6, 125.8, 128.5, 132.8 (2C), 135.5, 142.3, 144.6, 152.9, 153.2, 154.7, 165.2; MS (ESI) m/z 428 (M^+−1). Anal. Calcd for $C_{23}H_{14}N_5O_2Cl$: C, 64.57; H, 3.30; N, 16.37; Cl, 8.29. Found: C, 64.47; H, 3.39; N, 16.44; Cl, 8.39.

4.6.22. 3-Chloro-4-(2-(4-cyanophenylamino)quinazolin-4-yloxy)-5-ethoxybenzonitrile (5v)

Yield 38.5%. Mp 262.2–263.7 °C; ^{1}H NMR (DMSO-d_6) δ 1.02 (t, 3H, J = 7.2 Hz, CH_3), 4.12 (q, 2H, J = 7.2 Hz, CH_2O), 7.49 (t, 1H, J = 7.2 Hz, ArH_7), 7.62 (d, 2H, J = 8.8 Hz, Ar′$H_{2,6}$), 7.74 (d, 1H, J = 8.4 Hz, ArH_6), 7.84–7.93 (m, 5H, ArH_8 + Ar′$H_{3,5}$ + Ar″$H_{3,5}$), 8.21 (d, 1H, J = 8.0 Hz, ArH_9), 10.10 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 14.5, 65.9, 103.2, 110.8, 111.3, 117.5, 117.8, 118.9 (2C), 119.6, 124.0, 125.2, 126.0, 126.2, 128.8, 133.2 (2C), 135.9, 142.4, 145.0, 152.7, 153.3, 155.2, 165.8; MS (ESI) m/z 442 (M^+−1). Anal. Calcd for $C_{24}H_{16}N_5O_2Cl$: C, 65.24; H, 3.65; N, 15.85; Cl, 8.02. Found: C, 65.35; H, 3.53; N, 15.76; Cl, 8.19.

4.6.23. 4-(2-(4-Cyanophenylamino)quinazolin-4-yloxy)-3,5-diethoxybenzonitrile (5w)

Yield 50.9%. Mp 217.2–217.7 °C; ^{1}H NMR (DMSO-d_6) δ 1.06 (t, 6H, J = 7.2 Hz, 2CH_3), 4.08 (q, 4H, J = 7.2 Hz, 2CH_2O), 7.43 (s, 2H, Ar″$H_{3,5}$), 7.48 (t, 1H, J = 8.0 Hz, ArH_7), 7.60 (d, 2H, J = 8.8 Hz, Ar′$H_{2,6}$), 7.76 (d, 1H, J = 8.8 Hz, ArH_6), 7.85–7.91 (m, 3H, ArH_8 + Ar′$H_{3,5}$), 8.20 (d, 1H, J = 8.8 Hz, ArH_9), 10.07 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 14.3 (2C), 65.0 (2C), 102.5, 109.1, 110.9 (2C), 111.3, 118.4 (2C), 118.7, 119.5, 123.7, 124.5, 125.5, 132.7 (2C), 134.6, 135.1, 144.8, 151.9 (2C), 152.7, 155.0, 166.1; MS (ESI) m/z 452 (M^+−1). Anal. Calcd for $C_{26}H_{21}N_5O_3$: C, 69.17; H, 4.69; N, 15.51. Found: C, 69.22; H, 4.85; N, 15.32.

4.6.24. 4-(2-(4-Cyanophenylamino)quinazolin-4-yloxy)-3-methoxy-5-propoxybenzonitrile (5x)

Yield 32.5%. Mp 196.8–198.4 °C; ^{1}H NMR (DMSO-d_6) δ 0.53 (t, 3H, J = 7.2 Hz, CH_3), 1.35–1.45 (m, 2H, CH_2), 3.78 (t, 2H, J = 7.2 Hz, CH_2O), 3.81 (s, 3H, CH_3O), 7.44–7.49 (m, 3H, ArH_7 + Ar′$H_{2,6}$), 7.59 (s, 1H, Ar″H_3), 7.61 (s, 1H, Ar″H_5), 7.71 (d, 1H, J = 8.4 Hz, ArH_6), 7.83–7.90 (m, 3H, ArH_8 + Ar′$H_{3,5}$), 8.19 (d, 1H, J = 8.4 Hz, ArH_9), 10.07 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 10.3, 22.1, 57.2, 71.0,

103.0, 109.7, 110.3, 111.4, 111.7, 118.8 (2C), 119.1, 120.0, 124.1, 124.9, 126.0, 133.2 (2C), 134.5, 135.6, 145.3, 152.4, 153.2, 153.3, 155.5, 166.5; MS (ESI) m/z 452 (M^+-1). Anal. Calcd for $C_{26}H_{21}N_5O_3$: C, 69.17; H, 4.69; N, 15.51. Found: C, 69.29; H, 4.81; N, 15.32.

4.6.25. 4-(2-(4-Cyanophenylamino)quinazolin-4-yloxy)-3-ethoxy-5-propoxybenzonitrile (5y)

Yield 54.5%. Mp 179.9–181.2 °C; ^{1}H NMR (DMSO-d_6) δ 0.54 (t, 3H, J = 7.2 Hz, CH_3), 1.08–1.12 (m, 3H, CH_3), 1.39–1.43 (m, 2H, CH_2), 3.98–4.13 (m, 4H, 2CH_2O), 7.39–8.20 (m, 10H, Ar$H_{6,7,8,9}$ + Ar′$H_{2,3,5,6}$ + Ar″$H_{3,5}$), 10.04 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 9.8, 14.3, 21.7, 22.1, 66.0, 71.7, 102.6, 109.1, 110.9, 111.3, 118.4 (2C), 118.9, 119.5, 123.7, 124.4, 125.5, 133.7 (2C), 134.5, 135.1, 144.8, 151.9, 152.0, 152.7, 156.1, 166.1; MS (ESI) m/z 466 (M^+-1). Anal. Calcd for $C_{27}H_{23}N_5O_3$: C, 69.66; H, 4.98; N, 15.04. Found: C, 69.78; H, 5.07; N, 14.87.

4.6.26. 4-(6-Chloro-2-(4-cyanophenylamino)quinazolin-4-yloxy)-3,5-dimethylbenzonitrile (5z)

Yield 49.6%. Mp 293.5–294.9 °C; ^{1}H NMR (DMSO-d_6) δ 2.15 (s, 6H, 2CH_3), 7.59 (d, 2H, J = 8.4 Hz, Ar′$H_{2,6}$), 7.74 (d, 1H, J = 8.4 Hz, ArH_8), 7.78 (s, 2H, Ar″$H_{3,5}$), 7.82–7.91 (m, 3H, ArH_8 + Ar′$H_{3,5}$), 8.28 (d, 1H, J = 2.4 Hz, ArH_6), 10.10 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 16.3 (2C), 103.4, 109.5, 112.4, 119.0 (2C), 119.1, 119.9, 123.0, 128.3, 128.7, 133.1 (2C), 133.2 (2C), 133.3 (2C), 136.0, 144.9, 151.9, 153.6, 155.7, 165.1; MS (ESI) m/z 426 (M^+-1). Anal. Calcd for $C_{24}H_{16}N_5OCl$: C, 67.69; H, 3.79; N, 16.44; Cl, 8.32. Found: C, 67.88; H, 3.72; N, 16.32; Cl, 8.45.

4.7. Antiviral assay

The anti-HIV activity and cytotoxicity of the compounds were evaluated against wild-type HIV-1 strain IIIB in MT-4 cell cultures using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method.[14] Briefly, virus stocks were titrated in MT-4 cells and expressed as the 50% cell culture infective dose ($CCID_{50}$). MT-4 cells were suspended in culture medium at 1×10^5 cells/mL and infected with HIV at a multiplicity of infection of 0.02. Immediately after viral infection, 100 μL of the cell suspension was placed in each well of a flat-bottomed microtiter tray containing various concentrations of the test compounds. The test compounds were dissolved in DMSO at 50 mM or higher. After 4 days of incubation at 37 °C, the number of viable cells was determined using the MTT method. Compounds were tested in parallel for cytotoxic effects in uninfected MT-4 cells. The selection and characterization of mutant virus strains have been performed previously.

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