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Synthesis and evaluation of the 2,4-diaminoquinazoline series as anti-tubercular agents

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ABSTRACT

The 2,4-diaminoquinazoline class of compounds has previously been identified as an effective inhibitor of *Mycobacterium tuberculosis* growth. We conducted an extensive evaluation of the series for its potential as a lead candidate for tuberculosis drug discovery. Three segments of the representative molecule *N*-(4-fluorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine were examined systematically to explore structure–activity relationships influencing potency. We determined that the benzylic amine at the 4-position, the piperidine at 2-position and the N-1 (but not N-3) are key activity determinants. The 3-deaza analog retained similar activity to the parent molecule. Biological activity was not dependent on iron or carbon source availability. We demonstrated through pharmacokinetic studies in rats that good in vivo compound exposure is achievable. A representative compound demonstrated bactericidal activity against both replicating and non-replicating *M. tuberculosis*. We isolated and sequenced *M. tuberculosis* mutants resistant to this compound and observed mutations in Rv3161c, a gene predicted to encode a dioxygenase, suggesting that the compound may act as a pro-drug.

1. Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, is an infectious disease for which there is still a great need for discovery and development of novel drugs to improve therapy.[1] In 2010 alone, the World Health Organization reported 8.8 million new cases and 1.4 million deaths from the disease.[2] In addition, billions of people harbor latent infections with no clinical symptoms, but with the potential to advance to active form. Current TB treatment requires a combination of four drugs, isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), ethambutol (ETH) for 2 months followed by an additional 4 months of INH and RIF. These drugs have been in use for many decades, contributing to a rise in the emergence of multidrug resistant (MDR) and extensively drug-resistant (XDR) strains of *M. tuberculosis*. New drugs are needed urgently to shorten the duration of therapy and to treat drug-resistant strains.

Diaminoquinazolines (DAQ) have been reported with activity against a diverse range of biological diseases including lupus, rheumatoid arthritis, malaria and hypertension.[3] The DAQ series is active against *M. tuberculosis*[4] and effective at preventing the growth of *M. tuberculosis*[5] with minimum inhibitory concentrations (MICs) reported in the range of 1.3–6.1 μg/mL. The DAQ series is less effective against other bacterial species, with weak activity against *Escherichia coli* and *Pseudomonas aeruginosa*, suggesting some element of selectivity.[6]

We were interested in the potential of the DAQ series as a starting point for drug discovery. We conducted an exploratory study to evaluate the potential of the series for progression as a drug lead molecule.

2. Results and discussion

To investigate the biological activity, and the pharmaceutical and pharmacokinetic (PK) properties of the DAQ class of compounds, we conducted a systematic structural modification of a

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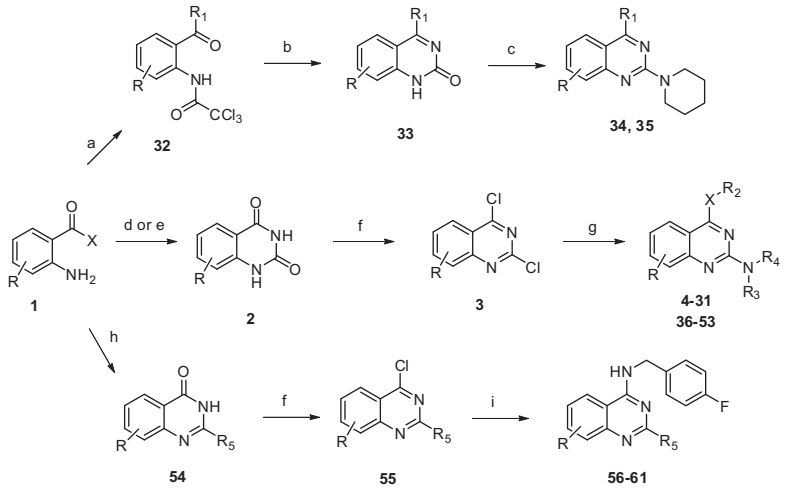
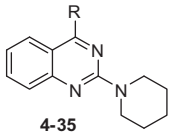
0968-0896/

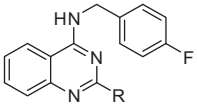


Scheme 1. Synthesis of 2,4-substituted quinazolines. Reagents and conditions: (a) X = R_1: Cl_3CCOCl, DMAP, CH_2Cl_2; (b) NH_4OAc, DMSO; (c) (i) $POCl_3$, (ii) Piperidine, *i*-PrOH, reflux; (d) X = OH: KOCN, NaOH; (e) X = NH_2: phosgene; (f) $POCl_3$, *NN*-dimethylaniline, reflux; (g) (i) nucleophile (R_2XH: X = O,S,NH), THF, room temperature, (ii) R_3R_4NH, *i*-PrOH, reflux; (h) X = OH: R_5CONH_2, HCO_2H (i) 4-fluorobenzylamine, THF, room temperature.

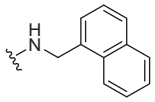
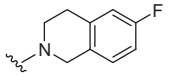
Table 1
Effect of C-2 and C-4 substitutions on biological potency of DAQ



4-35



7, 36-61

Compd	R-group	MIC	I	Compd	R-group	MIC	*I*
4	$PhCH_2HN$-	9.2	96	**34**	H-	469	<30
5	2-$FPhCH_2HN$-	nd	97	**35**	4-$FPhCH_2CH_2$-	nd	<30
6	3-$FPhCH_2HN$-	nd	98	**7**	Piperidin-1-yl	7.4	97
7	4-$FPhCH_2HN$-	7.4	97	**36**	4-(CH_3)piperidin-1-yl	nd	97
8	3-$MePhCH_2HN$-	nd	99	**37**	4-(OH)piperidin-1-yl	nd	<30
9	3-$IPhCH_2HN$-	nd	98	**38**	4-(NH_2)piperidin-1-yl	nd	<30
10	4-$MePhCH_2HN$-	nd	98	**39**	4-(NHMe)piperidin-1-yl	nd	33
11	4-$MeOPhCH_2HN$-	nd	97	**40**	4-(NMe2)piperidin-1-yl	nd	<30
12	4-OCF_3PhCH_2HN-	nd	95	**41**	4-(CO_2H)piperidin-1-yl	nd	<30
13	4-$ClPhCH_2HN$-	nd	99	**42**	3,5-(Me)piperidin-1-yl	nd	<30
14	4-CF_3PhCH_2HN-	6.6	99	**43**	4-(CH_2OH)piperidin-1-yl	nd	<30
15	4-NH_2PhCH_2HN-	nd	<30	**44**	4-($NHCH_2CO_2H$)piperidin-1-yl	nd	<30
16	2,4-$FPhCH_2HN$-	nd	97	**45**	2-(CH_2CO_2H)piperidin-1-yl	nd	<30
17	3,4-$FPhCH_2HN$-	nd	96	**46**	H_2N-	93	<30
18	2,4-$ClPhCH_2HN$-	nd	98	**47**	MeHN-	35	44
19	3,4-$ClPhCH_2HN$-	nd	98	**48**	Me_2N-	34	40
20	2,5-$ClPhCH_2HN$-	nd	97	**49**	Pyrrolidin-1-yl	31	97
21	3-Cl, 4-$MeOPhCH_2HN$-	nd	98	**50**	Isoindolin-2-yl	nd	78
22	4-$FPhCH_2O$-	296	<30	**51**	Piperazinyl	148	<30
23	4-$FPhCH_2S$-	282	<30	**52**	4-(4-Anilinyl)piperazin-1-yl	nd	94
24	MeHN-	206	<30	**53**	$(HOCH_2CH_2)_2HN$-	nd	<30
25	*i*PrHN-	25	37	**56**	(Piperidin-1-yl)CH_2HN-	29	<30
26	cyclohexylCH_2HN-	nd	99	**57**	H-	99	<30
27	4-$CF_3PhCH_2CH_2HN$-	5.7	97	**58**	Me-	94	<30
28		nd	97	**59**	F_3C-	nd	<30
29	4-FPhHN-	39	<30	**60**	Ph-	76	<30
30	Piperidin-1-yl	nd	<30	**61**	Cyclohexyl-	15	47
31		nd	94	Rifampicin[a]		0.013/0.004	100

Compounds were tested for inhibition of *M. tuberculosis* in liquid and on solid medium. The percent inhibition (*I*) of growth at 20 μM in liquid medium is reported. Compounds were considered inactive if %*I* <30 at 20 μM. Minimum inhibitory concentrations (MIC) were determined using the serial proportion method on solid agar.

[a] MIC reported for solid/liquid medium. nd = not determined.

lead compound, *N*-(4-fluorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (**7**). Analogs with key modifications to the piperidine residue at C-2, the 4-fluorobenzylamino residue at C-4 and the quinazoline core structure were synthesized to provide structure activity relationship (SAR) information. For each compound, the biological activity (growth inhibition) was tested against *M. tuberculosis* in liquid medium; for selected compounds activity was also tested on solid medium.

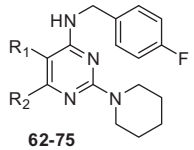
2.1. Exploration of C2 and C-4 substitutions

Several 2,4-diaminoquinazolines incorporating a single-point variation at C-2-position (**4**–**31**) or C-4-position (**36**–**53**) of the quinazoline template of the reference structure (**7**) were readily synthesized according to Scheme 1, by the nucleophilic aromatic substitution reaction on a key 2,4-dichloroquinazoline intermediate (**3**). The dichloroquinazolines were either purchased or prepared from commercial quinazoline-2,4(1*H*,3*H*)-dione (**2**) by chlorination with phosphorus oxychloride in *N*,*N*-dimethylaniline under reflux conditions. Where necessary, the quinazolinediones were prepared from corresponding anthranilamides (**1**) via condensation with phosgene. Regioselective substitution of C-4 chloride in **3** with the appropriate amine was accomplished at room temperature. Nucleophilic substitution at C-2 with the second amine proceeded smoothly at higher temperatures in isopropanol or tetrahydrofuran to give target compounds (**4**–**31**, **36**–**53**).[7] The C-4 ether, 4-(4-fluorobenzyloxy)-2-(piperidin-1-yl) quinazoline (**22**) and the thioether, 4-(4-fluorobenzylthio)-2-(piperidin-1-yl) quinazoline (**23**) were similarly prepared utilizing the corresponding sodium salt of benzyl alcohol or thiol as nucleophiles. Alternative routes were adapted to incorporate different alkyl and aryl substituents at these positions. The preparation of analogs **56**–**61**, bearing aliphatic or aromatic substituents at C-2 began with the condensation of anthranilamide with appropriate aldehydes, followed by chlorination of the resulting 2-substituted quinazolin-4(3*H*)-one (**54**) with phosphorus oxychloride to give key intermediates[8,9] (**55**), which were readily converted to the 4-amino analogs **56**–**61**. The synthesis of analogs **34** and **35** bearing alkyl group at C-4 were carried out using 2-aminophenones[10] (**1**, X = alkyl) as the starting point for similar condensation, chlorination and amination sequence of reactions.

The biological activity for each compound was determined by measuring inhibition of growth against a virulent strain of *M. tuberculosis* in liquid medium (Table 1–3). In liquid medium none of the compounds gave an MIC <20 μM, although most compounds had activity, that is, >30% inhibition of growth at 20 μM and could be ranked loosely based on this value. Several compounds were tested for MIC on solid medium; surprisingly MICs were lower than for liquid medium for several of the compounds (**4**, **7**, **14**, **27**), but a large variation was seen which was used to inform the SAR analysis.

Aromatic substituents on the benzylamino residue had very little or no influence on activity; analogs incorporating various substituents (F, Cl, Br, Me, OMe, NH_2, CF_3, OCF_3) (**5**–**21**) all showed comparable activities. However, the lipophilicity of the C-4 substituent seemed important as replacement of the benzyl with simple groups such as hydrogen (**34**), methyl (**24**) or an isopropyl (**25**) group, resulted in substantial reduction in the inhibitory activity. On the other hand, similar lipophilic groups like the non-aromatic cyclohexylmethyl (**26**) displayed good activity. The importance of the amino function at C-4 was examined by replacement with an ether (**22**), thioether (**23**) and methylene (**35**) units, all of which resulted in complete loss of activity. The activities of a secondary (tetrahydroisoquinoline, **31**) and primary C-4 amine analogs were comparable, precluding significance of any hydrogen-bonding contribution to activity. Homologation of the C-4 benzylamino group to a phenethylamino moiety (**27**) resulted in a very small improvement in the inhibitory activity. The aniline derivative (**29**) lacking any methylene spacer between the core and the lipophilic group was relatively less active.

Table 2
Effect of core replacement on biological potency



62-75

Compound	R1, R2	MIC	*I*
Rifampicin[a]		0.013/0.004	100
62	H, Me	83	<30
63	Me, H	83	<30
64	Me, Me	nd	<30
65	Benzyl, H	26	68
66	H, Benzyl	27	84
67		74	37
68		30	59
69		37	<30
70		73	nd
71		292	<30
72		nd	<30
73		nd	<30
74		nd	<30
75		nd	<30

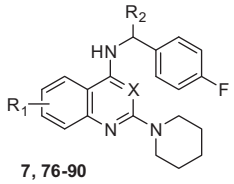
Compounds were tested for inhibition of *M. tuberculosis* in liquid and on solid medium. The percent inhibition (*I*) of growth at 20 μM in liquid medium is reported. Compounds were considered inactive if %*I* <30 at 20 μM. Minimum inhibitory concentrations (MIC) were determined using the serial proportion method on solid agar.

[a] MIC reported for solid/liquid medium. Nd = not determined.

2.2. Exploration of the core

We explored the core quinazoline structure through the synthesis of analogs outlined in Schemes 2–4. All azaquinazoline analogs (**67**–**69**) reported were easily prepared from their corresponding 2,4-dichlorides in good yields. We were, however, unable to prepare and isolate the 6-aza analog. Similarly, the thieno[2,3-*d*]pyrimidine (**70**, **71**), pyrrolo[2,3-*d*]pyrimidine (**72**, **73**) and purine (**74**, **75**) analogs were prepared from corresponding dihalides. Other quinazoline core replacement prepared include the quinoline analogs (**88**, **89**, **90**) which were similarly prepared from 2,4-dichloroquinoline. The synthesis of pyrazolo[1,5-*a*]pyrimidine (**94**) and triazolo[1.5-1]pyrimidine (**95**) analogs were achieved via a sequential diamination of their respective key dihalide (**93**)[11] intermediates as illustrated in Scheme 3.

Table 3
Effect of core substitutions on biological potency



7, 76-90

Compound	R1	R2	X	MIC	*I*
Rifampicin				0.013/0.004[a]	100
7	H	H	N	7.4	97
76	5-F	H	N	nd	<30
77	8-NO_2	H	N	nd	<30
78	5-Cl	H	N	nd	<30
79	6-Cl	H	N	nd	49
80	7-Cl	H	N	nd	51
81	8-Cl	H	N	nd	<30
82	5-Me	H	N	nd	98
83	6-Me	H	N	nd	99
84	6-OMe	H	N	nd	97
85	7-OMe	H	N	nd	74
86	8-OMe	H	N	nd	83
87	6,7-OMe	H	N	25	92
88	H	H	C	nd	98
89	H	CH_2OH	C	nd	55
90	H	CO_2H	C	nd	<30
94	—	—	—	—	<30
95	—	—	—	—	<30
103	—	—	—	27.7/13.8[a]	98

Compounds were tested for inhibition of *M. tuberculosis* in liquid and on solid medium. The percent inhibition (*I*) of growth at 20 μM in liquid medium is reported. Compounds were considered inactive if %*I* <30 at 20 μM. Minimum inhibitory concentrations (MIC) were determined using the serial proportion method on solid agar.

[a] MIC reported for solid/liquid medium. nd = not determined.

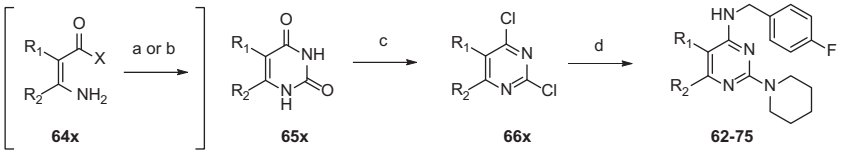
The potency of each compound was assessed by growth inhibition against a virulent strain of *M. tuberculosis* in agar and liquid medium (Table 2). Compounds had activity in both liquid and solid medium. Among the various C-2 substituents synthesized, piperidine remained a preferred residue (**7**) at this position. Pyrrolidine homologs (**49**, **50**) were also accommodated with no loss in activity. Piperazine substitution (**51**) resulted in complete loss of activity, but all activity was regained with an N-4′-aromatic substituted piperazine (**52**). Smaller, non-cyclic amines (**46**–**48**, **53**) showed greater than two-fold reduction in activity. Non-amine substitution such as alkyls or aryls (**56**–**61**) resulted in loss of activity with cyclohexyl analog (**61**) showing the least, a two-fold, reduction. We also investigated variously substituted piperidines (**36**–**45**) at the C-2 position for SAR exploration and for physicochemical property modulation. In general, substitution on the C-2 piperidine was detrimental to anti-TB activity.

The results also indicated that the benzo portion of this core is important to anti-TB activity. This was inferred from the very weak biological activity of core replacement analogs such as the substituted pyrimidine derivatives (**62**–**66**), thiophenopyrimidines (**70**–**71**), the diazaindoles (**72**–**73**) and purine analogs (**74**, **75**). A change to an azaquinazoline core (**67**–**69**) was tolerated but with relatively weaker activity compared to the parent quinazoline. To explore the role of the quinazoline ring nitrogens, we prepared and tested the analogous quinoline analogs (**88**–**90**). The retention of activity for this core indicated a non-essentiality of N-atom at N-3 position which prompted us to investigate other analogs based on this core. The pyrazolo[1,5-*a*]pyrimidine (**94**) and triazolo[1.5-1]pyrimidine (**95**) analogs, synthesized as representative extension of this core were essentially inactive but an imidazoquinoline derivative (**103**) displayed moderate activity.

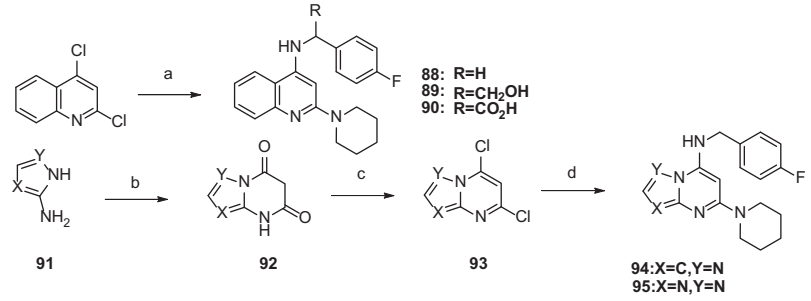
Substitutions at the C-5, C-6, C-7, and C-8 positions of the quinazoline core followed a general pattern in which electron-donating substituents (**82**–**87**) retained activity while electron-withdrawing groups had a negative impact (**76**–**81**).

2.3. Other analogs

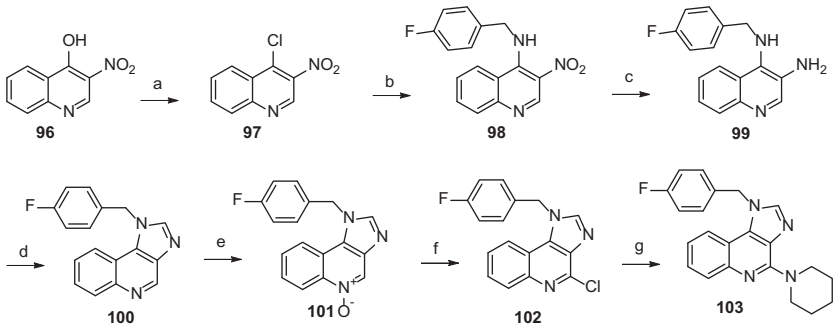
We prepared a number of scaffold analogs that incorporated changes at N-atom at position-3. The imidazoquinoline derivative (**103**) was prepared from commercial 3-nitroquinolin-4-ol (**96**) according to Scheme 4.[12] Chlorination of **96** with phosphorus oxychloride in *N*,*N*-dimethylformamide gave 3-nitro-4-chloroquinoline



Scheme 2. Synthesis of DAQ derivatives with variation in the benzo region. Reagents and conditions: (a) **64x**, X = OH: KOCN, NaOH; (b) **64x**, X = NH_2: phosgene; (c) $POCl_3$, *N*,*N*-dimethylaniline, reflux; (d) (i) 4-fluorobenzylamine, THF, room temperature, (ii) piperidine, *i*-PrOH, reflux.



Scheme 3. Synthesis of DAQ derivatives with variation in the core. Reagents and conditions: (a) (i) piperidine, 75 °C, (ii) benzylamine, $Pd_2(dba)_3$, BINAP, *t*-BuONa, toluene, reflux (b) $CH_2(CO_2Et)_2$, EtONa, EtOH, heat; (c) $POCl_3$, *NN*-dimethylaniline, reflux; (d) (i) a benzylamine, *n*-BuOH, Et_3N, 110 °C, (ii) piperidine, 180 °C.



Scheme 4. Synthesis of an imidazoquinoline derivative. Reagents and conditions: (a) $POCl_3$, DMF, heat; (b) 4-fluorobenzylamine, EtOH, Et_3N; (c) 5% Pt/C, H_2, ethyl acetate; (d) $HC(OEt)_3$, toluene, reflux; (e) CH_3CO_3H, CH_2Cl_2, heat; (f) $POCl_3$, CH_2Cl_2, reflux; (g) piperidine, DMF, Et_3N, reflux.

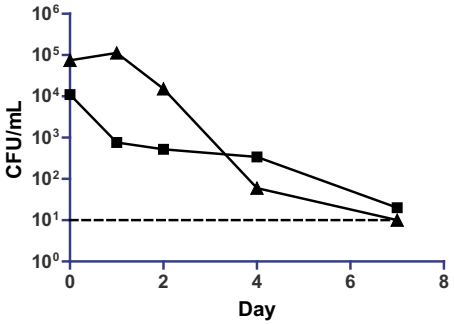


Figure 1. The representative DAQ exhibits bactericidal activity. Kill kinetics of *M. tuberculosis* by **14** in aerobically growing cells (squares) and under starvation conditions (triangles). For the aerobic kill curve, cells were inoculated to a starting OD_{590} of 0.01 into 7H9/OADC containing 124 μM of **14** and CFU/mL were enumerated at indicated time points. For the starvation-kill curve, cells were harvested at mid-log phase, re-suspended in phosphate buffered saline to an OD_{590} of 0.01 and maintained for 2 weeks at 37 °C. Compound **14** was added (124 μM) and CFU/mL determined at indicated time points following compound addition. The limit of detection was 10, as indicated by the dotted line.

(**97**) which was subsequently subjected to nucleophilic substitution of the chloride by 4-fluorobenzylamine to furnish *N*-(4-fluorobenzyl)-3-nitroquinolin-4-amine (**98**). Catalytic reduction of **98** led to the diamine derivative **99**, a precursor to the imidazoquinoline (**100**). The imidazoquinoline, prepared via condensation of **99** with refluxing triethyl orthoformate, was oxidized with peracetic acid to its N-oxide (**101**), and then chlorinated to provide the chloroimidazoquinoline (**102**). Finally, **102** was refluxed with piperidine in *N*,*N*-dimethylformamide to provide the target compound, 1-(4-fluorobenzyl)-4-(piperidin-1-yl)-1*H*-imidazo[4,5-*c*]quinoline (**103**).

2.4. The DAQ series show bactericidal activity

In order to probe the biological profile of the DAQ series, we conducted a number of additional microbiological assays. We selected compound **14** since it had relatively good activity in solid assays with an MIC of 6.6 μM. The most active compound (**14**) was tested for bactericidal activity in aerobic, replicating culture and under non-replicating conditions generated by nutrient starvation (Fig. 1). Interestingly, compound **14** was bactericidal against *M. tuberculosis* under both conditions. In aerobic culture a loss of 4

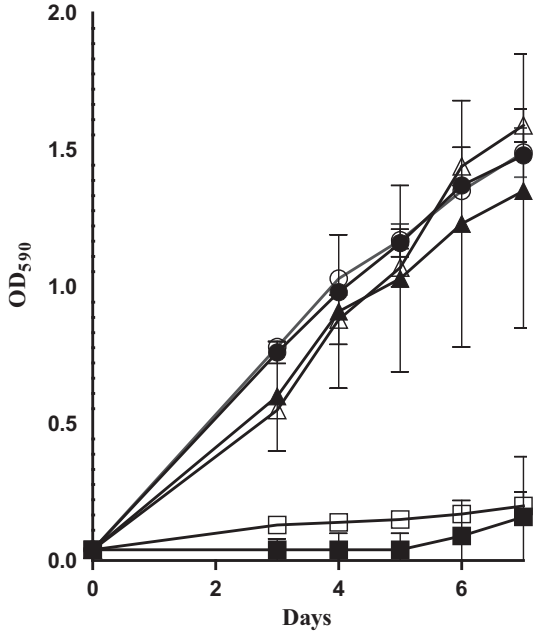


Figure 2. DAQ inhibit growth of *M. tuberculosis* under iron-excess conditions. Cells were inoculated to a starting OD_{590} of 0.04 into growth medium containing no compound **14** (circles), 28 mM compound **14** (triangles) and 56 mM compound **14** (squares). Growth was monitored in the presence (solid symbols) and absence (open symbols) of 40 mg/mL hemin supplementation.

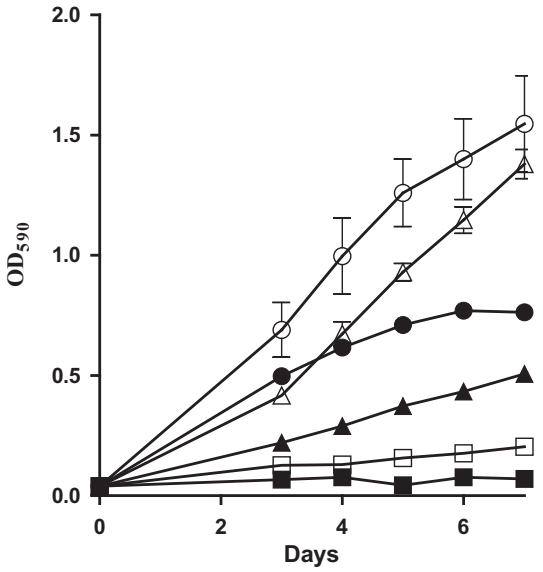


Figure 3. DAQ inhibition of *M. tuberculosis* is not dependent on carbon source. Cells were inoculated to a starting OD_{590} of 0.04 into growth medium containing no compound **14** (circles), 14 mM compound **14** (triangles) and 28 mM compound **14** (squares). Growth in medium containing palmitic acid (solid symbols) was compared to that containing OADC (open symbols) supplement.

Table 4
Pharmacokinetic parameters for DAQs following a single 10 mg/kg oral gavage dose in rats

Compd	MW	*C*Log*P* (day)	NV PSA	VDss (L/kg)	CL (mL/min/kg)	PO AUC (ng*hr/mL)	Bioavail (%*F*)
7	336.41	5.05	41.1	12.2 ± 2.7	115 ± 21	245 ± 66	16.7 ± 3.3
21	382.89	5.45	50.3	9.3 ± 1.0	133 ± 16	132 ± 20	10.3 ± 1.3
24	242.32	3.46	41.1	5.7 ± 0.6	179 ± 13	209 ± 134	21.8 ± 13.0
34	213.28	2.65	29	4.5 ± 0.2	153 ± 9	196 ± 82	17.6 ± 6.3
36	350.44	5.57	41.1	25.7 ± 18.3	179 ± 79	171 ± 32	21.7 ± 14.0
44	409.46	0.606	90.4	5.0 ± 1.2	99.2 ± 18.7	0.84 ± 0.89	0.05 ± 0.05
46	268.29	3.46	63.8	13.3 ± 0.2	154 ± 25	376 ± 48	34.0 ± 0.7
47	282.32	4.29	49.8	9.2 ± 1.0	95.3 ± 7.7	1610 ± 247	92.2 ± 18.9
48	296.35	4.38	41.1	8.1 ± 1.0	85.5 ± 11.6	1310 ± 339	65.9 ± 12.4
62	300.38	4.17	41.1	12.8 ± 0.9	131 ± 21	82 ± 16	6.4 ± 0.3
103	360.43	5.05	34	14.2 ± 6.2	201 ± 26	27.4 ± 6.5	3.4 ± 1.0

Compounds were administered to rats with a single oral dose of 10 mg/kg. Concentrations in plasma were determined at various time points over 24 h and pharmacokinetic parameters calculated using Watson (version 7.4; Thermo Fisher Scientific). Clearance (CL), volume of distribution (VDss), area-under-the-curve (PO AUC) and bioavailability (%F) are given. Molecular weight (MW); Calculated partition coefficient (*C*log*P*, daylight software); Topological polar surface area (TPSA, novartis software) are also given.

log viability was seen over 7d and similarly 3 logs of kill was seen over 7 days under starvation conditions.

2.5. Lack of iron chelating activity

The amine at the C4 position has the potential to form a chelating center with the N3 of the core, although it would be weak. Therefore, we considered the possibility that the compound might act via chelation of iron in cultures leading to an intracellular iron shortage. To test this possibility, we monitored growth in liquid in the presence of hemin to supply additional iron to the cells, since we already knew that hemin was transported into *M. tuberculosis*.[13] Under these conditions 56 μM of compound **14** was sufficient to prevent growth completely, regardless of hemin supplementation (Fig. 2). These data suggest that it is unlikely that the compound acts via iron chelation, in agreement with the structural features of **14** which are devoid of any signature chelation motifs.

2.6. Carbon source dependency

Previously published data suggested that the DAQ series as a class of compounds had significantly lower MICs in liquid medium than those we found.[5] One of the major differences in the methodology for determining MIC was the carbon source in the growth medium, in our case the simple sugar glucose, as opposed to the fatty acid palmitate (hexadecanoate). Since the catabolic pathways for utilizing these carbon sources differ, it is possible this altered metabolism might be reflected in different MICs. We determined whether compound potency was carbon source-dependent using the same strain of *M. tuberculosis*. Growth was monitored in liquid medium and the MIC was determined on solid medium. No difference was seen, with the liquid MIC of 28 μM in both growth media, and the solid MIC of 16 μM (Fig. 3). Thus we discounted the possibility that the potency of the compound series is dependent on the carbon source.

2.7. Evaluation of pharmacokinetic properties in rats

To determine the in vivo exposure a set of twelve compounds was selected and evaluated for pharmacokinetic (PK) properties in rats (Table 4). The selection was guided by a multiparameter analysis of all compounds. Calculated compound properties taken into consideration included lipophilicity (*C*log*P*), distribution coefficient values at pH = 7.4 (*C*log*D*), molecular weight (MW), topological polar surface area (TPSA), number of hydrogen bond donors (HBD) and acidity/basicity parameter (pK_a).

Sprague-Dawley rats were administered a single dose of the test compound either iv at 1 mg/kg or orally at 10 mg/kg (Table 4). The volume of distribution was generally high for all compounds. Plasma clearance was rapid for all compounds and the absolute oral bioavailability was moderate (10–35%) for most compounds tested. However, two structurally similar analogs, **47** and **48**, were well-absorbed with bioavailability of 92% and 66% (%*F*), respectively. The carboxylate analog, **44**, registered the poorest oral exposure, presumably due to slow, passive permeability as a result of the high polarity conferred by the amino carboxylate and a drastically reduced lipophilicity (*C*log*P* = 0.6).

2.8. Resistant mutant isolation for target identification studies

Drug resistance in *M. tuberculosis* is largely mediated by chromosomal mutations. For example, mutations may modify the drug target, inactivate bacterial enzymes that activate pro-drugs, lead to decreased membrane permeability, or up-regulation of efflux pumps. To ascertain the mechanism(s) responsible for resistance to **14** we isolated spontaneous resistant mutants to this compound and analyzed 3 resistant mutants by whole genome sequencing. Resistant mutants were isolated which showed a four-fold shift towards resistance to compound **14**. We sequenced the entire genome in order to identify single nucleotide polymorphisms. In all three cases, mutations were observed in Rv3161c, a non-essential and poorly characterized gene predicted to encode a dioxygenase (Table 5). We observed an insertion of the transposable IS*6110* element and a 2 base pair deletion which should both result in gene inactivation. The third mutation results in the substitution of a cysteine residue at position 115 with tryptophan. This non-conservative amino acid substitution is also likely to inactivate the resultant protein product. Our findings are consistent with compound **14** functioning as a pro-drug in wild-type *M. tuberculosis*. Since Rv3161c is not essential, it seems unlikely this is the target. We propose that Rv3161c is able to modify the DAQ compounds and that the resulting metabolite is the active species. Inactivation of Rv3161c would thus lead to resistance.

Table 5
DAQ resistance results from mutations in the putative dioxygenase, Rv3161c

Strain	Compound **14** solid MIC (μM)	Rv3161c mutation
H37Rv	6.6	N/A
RM1	25	IS6110 at nt 801
RM2	25	GT deletion at 175–176
RM7	25	C115 W

Comparison of wild-type (H37RvLP) and 3 spontaneous resistant mutants to compound **14**. Solid MIC (mM) values to Compound **14** are indicated. Whole genome sequencing indicated that all three resistant strains contain mutations in Rv3161c as shown. RM: resistant mutant. N/A: not applicable. nt: nucleotide.

3. Conclusion

Based on previous reports of sub-micromolar MIC activity of the DAQ series in TB assays, the main goal of our work was to determine whether the series is a viable starting point for drug lead development. Surprisingly, we found the activity of the series in liquid medium was limited and anti-tubercular activity was weaker than previously reported. We hypothesized that this disparity was a result of variation in assay conditions, the most noticeable difference being a change in carbon source. However, we saw no improvement in anti-tubercular activity of these compounds when tested using palmitate as a carbon source. In previous work, cell viability was determined by metabolic activity (using Alamar blue), whereas we measured bacterial growth (by OD and fluorescence). This may be indicative of mode of action, since compounds might be able to reduce metabolic activity more efficiently than prevent growth.

However, good activity was seen on solid medium for these compounds where the MICs were lower than in liquid medium (even using the same carbon source, glucose). This was surprising, since in our experience MICs on solid medium are normally higher by several-fold. This may reflect a true difference in bacterial physiology or metabolism between the two states. Culture on solid medium may reflect better the physiological state of bacteria during infection, particularly in granulomas or in biofilms.

We conducted a systematic exploration of a diaminoquinazoline compound series for inhibitory activity against *M. tuberculosis*. SAR efforts around N-3 replacements led to a fused ring in the form of an imidazoquinoline (**103**) with an improvement in biological activity and an opportunity for SAR development on an alternate scaffold. PK evaluation indicated there is no obvious barrier to property optimization. Our data demonstrated that the DAQ series had an encouraging microbiological profile with bactericidal activity against replicating and non-replicating *M. tuberculosis*, suggesting that the target of the series is important for bacterial viability. Future work to identify the target could allow screening for alternative scaffolds with improved properties and biological activity. These properties may have implications in the application of these compounds as anti-TB agents. In addition, the DAQ series could be useful tools for probing cell death mechanisms and for target identification studies.

4. Experimental section

4.1. Determination of minimum inhibitory concentration (MIC)

M. tuberculosis H37Rv was grown in Middlebrook 7H9 medium containing 10% OADC (oleic acid, albumin, dextrose, catalase) supplement (Becton Dickinson) and 0.05% w/v Tween 80 (7H9-Tw-OADC). Liquid MICs were performed in 96-well plates as described.[14] Briefly, compounds were solubilized in DMSO and assayed using a 10-point two-fold serial dilution with the highest concentration of 20 μM. Bacterial growth was measured by OD after 5 days of incubation at 37 °C; growth curves were fitted to the Gompertz model. The MIC was defined as the minimum concentration required for complete growth inhibition. In order to generate an MIC, two points of complete inhibition were required; where MICs could not be calculated the % inhibition of growth at 20 μM was recorded. Inhibition of >30% was recorded as active, <30% was recorded as inactive. Data are from one run. The assay was validated according to NCGC guidelines with reproducibility between runs of <2-fold for MIC values.[14] MIC99 was determined on solid medium (Middlebrook 7H10 plus 10% v/v OADC) using the serial proportion method[15]: MIC was defined as the minimum concentration required to prevent 99% of growth.

4.2. Kill kinetics

For aerobic kill curves, cells were inoculated to a theoretical OD_{590} of 0.01 (theoretical) in 10 mL medium containing Compound **14**. For the starvation-kill determinations, 10 mL of culture was grown to mid-log phase, harvested by centrifugation for 10 min at 4000 rpm, and re-suspended in phosphate buffered saline. Cells were maintained as standing cultures at 37 °C for 2 weeks prior to the addition of compound to ensure that cells had adapted to the non-replicating state. Colony forming units were enumerated by plating dilutions of cells onto compound free plates at the indicated time points.

4.3. Growth curves

Growth curves were carried out in 16 mm diameter glass tubes with 2 mm stirrer bars containing 5 mL of 7H9-Tw-OADC medium plus 40 μg/mL hemin where required; 2 tubes were inoculated to a theoretical OD_{590} of 0.04. Cultures were incubated at 37 °C with stirring. For studies using palmitate as a carbon source, OADC and Tween 80 were omitted and medium was supplemented with 5 g/L BSA fraction V, 0.8 g/L NaCl, 0.05% v/v Tyloxapol and 0.25 mM palmitic acid.

4.4. Pharmacokinetics

Male Sprague-Dawley rats (250–350 g) were purchased from Harlan (Indianapolis, IN). The Institutional Animal Care and Use Committees at Covance and Harlan approved all animal procedures. Three rats were dosed per treatment group. Plasma samples were collected over 24 h in an intravenous/oral crossover study with a 1 day washout period between drug administrations. On day 0, compound was administered by intravenous bolus injection (1 mg/kg; 2 ml/kg, Captisol 20% w/v/$NaPO_4$ buffer 25 mM, pH2, q.s) and on day 1 by oral gavage (10 mg/kg; 10 mL/kg HEC 1% w/v/P80 0.25% v/v/AF 1510-US 0.05% v/v/DIW, q.s.). Arterial blood samples were collected at the following times after dose administration: 0 (oral arm only), 0.08 (intravenous arm only), 0.25, 0.5, 1, 2, 4, 8, 12, and 24 h.

Compound concentrations in plasma were quantified by LC-MS/MS. All samples were mixed with an organic internal standard solution to precipitate protein and centrifuged. The resulting supernatants were analyzed. Analytes were separated using a Betasil C18 (2.1 × 20 mm, 5 μm; Thermo Fisher Scientific, Waltham, MA) with gradient elution. All analytes were detected in positive ion mode reaction monitoring (Sciex API 4000 triple quadrupole mass spectrometer equipped with a TurboIonSpray interface; Applied Biosystems/MDS, Foster City, CA): The dynamic range of the assays was 1 to either 1250 or 5000 ng/mL for all analytes. Samples with analyte concentrations above the upper limit of quantification were diluted with matrix to within the assay range; concentrations below the lower limit of quantification (BQL) were reported as BQL. All bioanalytical assays met acceptance criteria for accuracy (<±30% relative error) and precision (<30% relative SD). Noncompartmental pharmacokinetic parameters were calculated using Watson (version 7.4; Thermo Fisher Scientific).

4.5. Resistant mutant isolation and characterization

Resistant mutants were isolated by plating 10^7, 10^8, or 10^9 bacteria onto agar plates containing 5X and 10X the solid MIC of compound. Resistant colonies were streaked onto plates containing compound and MICs were determined on solid medium to confirm resistance. Genomic DNA was prepared[16] and whole genome

sequencing performed[17]; mutations were confirmed by PCR and sequencing.

4.6. Compound synthesis

4.6.1. General methods

^{1}H and ^{13}C NMR spectral data were recorded in $CDCl_3$ or DMSO-d_6 on a 300 or 400 MHz Bruker NMR spectrometer. Column chromatography was conducted on silica gel (100–300 mesh). Reactions were monitored using thin-layer chromatography (TLC) on silica gel plates. HPLC analysis was conducted on an Agilent 1100 series LC system (Agilent ChemStation Rev.A.10.02; Phenomenex-Luna-C18, 4.8 mm × 150 mm, 5 μm, 1.0 mL/min, UV 254 nm, room temperature) with MeCN/H_2O (0.05% TFA or HCOOH buffer) gradient elution. HPLC-MS was performed on a Gilson 321 HPLC with detection performed by a Gilson 170 DAD and a Finnigan AQA mass spectrometer operating in electrospray ionisation mode using a Phenomenex Gemini C18 150 × 4.6 mm column. Purity was determined using a Waters Acquity UPLC system equipped with a BEH C18 1.7 μm 2.1 × 100 mm column.

4.6.1.1. Representative procedure I for preparation of 2,4-diaminoquinazolines 4–31, 36–53 and amino ethers 22, 23. To a stirred solution of substituted 2,4-dichloroquinazoline[9] (1 equiv) in THF were added an amine (1 equiv) and triethylamine (2 equiv). The reaction was allowed to stir at room temperature for 10–12 h and progress followed by TLC. The reaction mixture was quenched with addition of ice-water (40 mL) and extracted with CH_2Cl_2 (60 mL/g). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Crude products were purified by column chromatography on silica gel (100–200 mesh) to afford pure 2-chloro-4-aminoquinazoline intermediates.

To a stirred solution of 2-chloro-4-aminoquinazoline intermediate (1 equiv) in isopropyl alcohol was added an amine (2 equiv). The reaction mixture was heated in a sealed vial at 120 °C for 3–6 h and reaction monitored by TLC. The reaction mixture was quenched with addition of ice-water (40 mL) then extracted with ethyl acetate (60 mL/g). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Crude products were purified by column chromatography on silica gel (100–200 mesh) to afford pure products.

4.6.1.2. *N*-Benzyl-2-(piperidin-1-yl)quinazolin-4-amine (4). *N*-Benzyl-2-(piperidin-1-yl)quinazolin-4-amine (**4**) was purchased from Princeton Biomolecular.

4.6.1.3. *N*-(2-Fluorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (5). *N*-(2-Fluorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (**5**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 337.2 (M+1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.36–1.44 (4H, m), 1.53–1.61 (2H, m), 3.68–3.72 (4H, m), 4.71 (2H, d, J = 5.7 Hz), 7.05 (1H, ddd, J = 8.9 Hz, 6.9 Hz and 1.2 Hz), 7.09–7.31 (3H, m), 7.39 (1H, td, J = 7.7 Hz and 1.8 Hz), 7.49 (1H, ddd, J = 8.5 Hz, 6.9 Hz and 1.5 Hz), 8.02 (1H, dd, J = 8.2 Hz and 1.1 Hz), 8.50 (1H, t, J = 5.6 Hz).

4.6.1.4. *N*-(3-Fluorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (6). *N*-(3-Fluorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (**6**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 337.2 (M+1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.37–1.44 (4H, m), 1.53–1.61 (2H, m), 3.69–3.72 (4H, m), 4.67 (2H, d, J = 5.67 Hz), 7.08–7.00 (2H, m), 7.15–7.26 (3H, m), 7.31–7.38 (1H, m), 7.49 (1H, ddd, J = 8.4 Hz, 6.9 Hz and 1.4 Hz), 8.00 (1H, dd, J = 8.2 Hz and 1.0 Hz), 8.55 (1H, t, J = 5.9 Hz).

4.6.1.5. *N*-(4-Fluorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (7). *N*-(4-Fluorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (**7**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 337 (M+1); HRMS (ESMS) calcd for $C_{20}H_{21}FN_4$, 337.1823; found, 337.1824 (M+1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.45–1.70 (6H, m), 3.80 (4H, br s), 4.76 (2H , d, J = 5.6 Hz), 7.17 (2H, dt, J = 8.8 Hz, 1.2 Hz), 7.42–7.48 (3H, m), 7.68 (1H, d, J = 8.4 Hz), 7.81 (1H, t, J = 7.8 Hz), 8.27 (1H, d, J = 8.2 Hz).

4.6.1.6. *N*-(3-Methylbenzyl)-2-(piperidin-1-yl)quinazolin-4-amine hydrochloride (8). *N*-(3-Methylbenzyl)-2-(piperidin-1-yl)quinazolin-4-amine hydrochloride (**8**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 333.3 (M+1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.50–1.71 (6H, br m), 2.28 (3H, s), 3.78–3.87 (4H, br m), 4.73 (2H, d, J = 5.8 Hz), 7.05–7.11 (1H, d, J = 6.5 Hz), 7.16–7.26 (3H, br m), 7.44 (1H, td, J = 7.6 Hz and 1.5 Hz), 7.71–7.85 (2H, br m), 8.31 (1H d, J = 8.3 Hz).

4.6.1.7. *N*-(3-Iodobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (9). *N*-(3-Iodobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (**9**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 445.1 (M+1); HRMS (ESMS) calcd for $C_{20}H_{21}IN_4$, 445.0884; found, 445.0882 (M+1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.61–1.80 (6H, br m), 3.85–3.89 (4H, br m), 4.75 (2H, d, J = 5.7 Hz), 5.81–5.92 (1H, br s), 7.09 (2H, q, J = 7.8 Hz), 7.37 (1H, d, J = 7.2 Hz), 7.42–7.58 (3H, m), 7.63 (1H, d, J = 6.9 Hz), 7.79 (1H, s).

4.6.1.8. *N*-(4-Methylbenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (10). *N*-(4-Methylbenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (**10**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 333.2 (M+1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.39–1.49 (4H, m), 1.53–1.63 (2H, m), 2.25 (3H, s), 3.73 (4H, t, J = 5.3 Hz), 4.62 (2H, d, J = 5.8 Hz), 7.02 (1H, ddd, J = 8.1 Hz, 7.0 Hz and 1.2 Hz), 7.10 (2H, d, J = 7.8 Hz), 7.23 (1H, d, J = 7.9 Hz), 7.26 (2H, d, J = 8.1 Hz), 7.47 (1H, ddd, J = 8.2 Hz, 6.8 Hz and 1.3 Hz), 7.99 (1H, dd, J = 8.3 Hz and 1.1 Hz), 8.47 (1H, t, J = 6.3 Hz).

4.6.1.9. *N*-(4-Methoxybenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (11). *N*-(4-Methoxybenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (**11**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 349.2 (M+1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.40–1.50 (4H, m), 1.55–1.64 (2H, m), 3.70 (3H, s), 3.75 (4H, t, J = 5.3 Hz), 4.61 (2H, d, J = 5.9 Hz), 6.86 (2H, d, J = 8.7 Hz), 7.02 (1H, ddd, J = 8.1 Hz, 7.1 Hz and 1.1 Hz), 7.23 (1H, dd, J = 8.4 Hz and 0.8 Hz), 7.30 (2H, d, J = 8.7 Hz), 7.47 (1H, ddd, J = 8.3 Hz, 7.0 Hz and 1.2 Hz), 7.98 (1H, dd, J = 8.2 Hz and 1.1 Hz), 8.47 (1H, t, J = 5.8 Hz).

4.6.1.10. 2-(Piperidin-1-yl)-*N*-(4-(trifluoromethoxy)benzyl)quinazolin-4-amine (12). 2-(Piperidin-1-yl)-*N*-(4-(trifluoromethoxy) benzyl)quinazolin-4-amine (**12**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 403.1(M+1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.33–1.43 (4H, br m), 1.51–1.61 (2H, br s), 3.65–3.72 (4H, br m), 4.68 (2H, d, J = 5.8 Hz), 7.05 (1H, td, J = 7.6 Hz and 1.2 Hz), 7.22–7.33 (3H, br s), 7.45–7.52 (3H, br s), 8.00 (1H, d, J = 8.2 Hz), 8.56 (1H, br s).

4.6.1.11. *N*-(4-Chlorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (13). *N*-(4-Chlorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (**13**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 353.1 (M+1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.37–1.44 (4H, m), 1.54–1.61 (2H, m), 3.69 (4H, t, J = 5.3 Hz), 4.64 (2H, d, J = 5.7 Hz), 7.04 (1H, ddd, J = 8.0 Hz, 7.0 Hz and 1.0 Hz), 7.22–7.25 (1H, d, J = 7.6 Hz), 7.33–7.40 (4H, m), 7.48 (1H, ddd, J = 8.3 Hz, 7.0 Hz and 1.2 Hz), 7.98 (1H, d, J = 7.58 Hz), 8.54 (1H, t, J = 6.0 Hz).

4.6.1.12. 2-(Piperidin-1-yl)-*N*-(4-(trifluoromethyl)benzyl)quinazolin-4-amine (14). 2-(Piperidin-1-yl)-*N*-(4-(trifluoromethyl)benzyl)quinazolin-4-amine (**14**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 387 (M+1); HRMS (ESMS) calcd for $C_{21}H_{21}F_3N_4$, 387.1791; found, 387.1793 (M+1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.50–1.64 (6H, m), 3.74–3.77 (4H, m), 4.86 (2H, d, J = 5.5 Hz), 7.47 (1H, t, J = 7.6 Hz), 7.59–7.73 (5H, m), 7.83 (1H, t, J = 7.5 Hz), 8.28 (1H, d, J = 7.9 Hz).

4.6.1.13. *N*-(4-Aminobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (15). *N*-(4-Aminobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (**15**) was prepared from a nitro derivative according to the representative procedure I. The nitro group was further reduced to the desired aniline product. HRMS (ESMS) calcd for $C_{20}H_{23}N_5$, 334.2026; found, 334.2030 (M+1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59–1.67 (6H, m), 3.79–3.83 (4H, m), 4.68 (2H, d, J = 5.4 Hz), 6.83 (2H, d, J = 7.8 Hz), 7.23 (2H, d, J = 8.4 Hz), 7.45 (1H, t, J = 8.1 Hz), 7.67 (1H, d, J = 8.1 Hz) 7.80 (1H, t, J = 7.2 Hz) 8.26 (1H, d, J = 8.4 Hz), 9.95 (1H, m).

4.6.1.14. *N*-(2,4-Difluorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine hydrochloride (16). *N*-(2,4-Difluorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine hydrochloride (**16**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 355.3(M+1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.49–1.71 (6H, br m), 3.77–3.88 (4H, m), 4.77 (2H, d, J = 5.5 Hz), 7.02–7.12 (1H, td, J = 8.5 Hz and 2.5 Hz), 7.22–7.32 (1H, m), 7.40–7.58 (2H, m), 7.77–7.87 (2H, m), 8.36 (1H, d, J = 8.3 Hz), 10.09–10.17 (1H, br m), 11.97 (1H, br s).

4.6.1.15. *N*-(3,4-Difluorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine hydrochloride (17). *N*-(3,4-Difluorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine hydrochloride (**17**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 355.2 (M+1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.49–1.70 (6H, br m), 3.76–3.87 (4H, m), 4.75 (2H, d, J = 5.5 Hz), 7.22–7.30 (1H, m), 7.34–7.56 (3H, m), 7.76–7.85 (2H, m), 8.33 (1H, d, J = 8.1 Hz), 10.16 (1H, s), 11.80 (1H, br s).

4.6.1.16. *N*-(2,4-Dichlorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (18). *N*-(2,4-Dichlorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (**18**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: not found. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.30–1.42 (4H, br m), 1.49–1.60 (2H, br m), 3.59–3.69 (4H, br m), 4.71 (2H, d, J = 5.7), 7.07 (1H, td, J = 7.5 Hz and 1.2 Hz), 7.26 (1H, dd, J = 8.5 Hz and 0.8 Hz), 7.35 (2H, d, J = 1.2 Hz), 7.50 (1H, td, J = 7.7 Hz and 1.4 Hz), 7.61 (1H, t, J = 1.1 Hz), 8.03 (1H, dd, J = 8.3 Hz and 1.1 Hz), 8.57 (1H, t, J = 5.6 Hz).

4.6.1.17. *N*-(3,4-Dichlorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (19). *N*-(3,4-Dichlorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (**19**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 387.1(M+1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.45–1.34 (4H, br m), 1.52–1.62 (2H, br m), 3.64–3.73 (4H, br m), 4.63 (2H, d, J = 5.9), 7.05 (1H, td, J = 7.6 Hz and 1.1 Hz), 7.24 (1H, dd, J = 8.5 Hz and 0.9 Hz), 7.34 (1H, dd, J = 8.5 Hz and 2.0 Hz), 7.49 (1H, td, J = 7.6 Hz and 1.4 Hz), 7.56 (1H, d, J = 8.2 Hz), 7.62 (1H, d, J = 2.0 Hz), 7.97 (1H, dd, J = 8.2 Hz and 1.1 Hz), 8.57 (1H, t, J = 5.8 Hz).

4.6.1.18. *N*-(2,4-Dichlorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (20). *N*-(2,4-Dichlorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (**20**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: not found. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.30–1.42 (4H, br m), 1.49–1.60 (2H, br m), 3.59–3.69 (4H, br m), 4.71 (2H, d, J = 5.7 Hz), 7.07 (1H, td, J = 7.5 Hz and 1.2 Hz), 7.26 (1H, dd, J = 8.5 Hz and 0.8 Hz), 7.35 (2H, d, J = 1.2 Hz), 7.50 (1H, td, J = 7.7 Hz and 1.4 Hz), 7.61 (1H, t, J = 1.1 Hz), 8.03 (1H, dd, J = 8.3 Hz and 1.1 Hz), 8.57 (1H, t, J = 5.6 Hz).

4.6.1.19. *N*-(3-Chloro-4-methoxybenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (21). *N*-(3-Chloro-4-methoxybenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (**21**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 383.2 (M+1); HRMS (ESMS) calcd for $C_{21}H_{23}ClN_4O$, 383.1633; found, 383.1635 (M+1). LCMS: 99.3% purity. ^{1}H NMR: (300 MHz, $CDCl_3$): δ 1.40–1.50 (4 H, m), 1.55–1.64 (2 H, m), 3.75 (4 H, m), 3.80 (3 H, s), 4.60 (2 H, m), 7.02–7.11 (2 H, m), 7.23–7.31 (2 H, m), 7.40–7.51 (2 H, m), 7.91 (1H, d, J = 8.2 Hz), 8.10 (1H, s), 8.5–8.6 (1H, m).

4.6.1.20. 4-(4-Fluorobenzyloxy)-2-(piperidin-1-yl)quinazoline (22). 4-(4-Fluorobenzyloxy)-2-(piperidin-1-yl)quinazoline (**22**) was prepared according to the representative procedure I substituting (4-fluorophenyl)methanol for the amine in the initial reaction step. Yield: 118 mg, 44%. MS: ESI-MS, *m*/*z*: 338.19 (M+1); HRMS (ESMS) calcd for $C_{20}H_{20}FN_3O$, 338.1663; found, 338.1664 (M+1). LCMS: 99% purity. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 1.61–1.69 (6H, m), 3.86–3.90 (4H, m), 5.50 (2H, s), 7.03–7.13 (3H, m), 7.44–7.50 (3H, m), 7.58 (1H, t, J = 5.6 Hz), 7.91 (1H, d, J = 7.2 Hz).

4.6.1.21. 4-(4-Fluorobenzylthio)-2-(piperidin-1-yl)quinazoline (23). 4-(4-Fluorobenzylthio)-2-(piperidin-1-yl)quinazoline (**23**) was prepared according to the representative procedure I substituting (4-fluorophenyl)methanethiol for the amine in the initial reaction step. Yield 54 mg, 35%. MS: ESI-MS, *m*/*z*: 354.19 (M+1); HRMS (ESMS) calcd for $C_{20}H_{20}FN_3S$, 354.1435; found, 354.1437 (M+1). LCMS: 93.9% purity. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 1.60–1.75 (6H, m), 3.89–3.94 (4H, m), 4.51 (2H, s), 6.97–7.02 (2H, m), 7.05–7.12 (1H, m), 7.38–7.42 (2H, m), 7.45–7.50 (1H, m), 7.54–7.60 (1H, m), 7.77 (1H, dd, J = 7.6 Hz).

4.6.1.22. *N*-Methyl-2-(piperidin-1-yl)quinazolin-4-amine (24). *N*-Methyl-2-(piperidin-1-yl)quinazolin-4-amine (**24**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 243.16 (M+1); HRMS (ESMS) calcd for $C_{14}H_{18}N_4$, 243.1604; found, 243.1605 (M+1), LCMS: 99.4% purity. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 1.60–1.65 (6H, m), 3.14 (3H, d, J = 4.4 Hz) 3.85–3.92 (4H, m), 5.44–5.50 (1H, m), 6.99–7.05 (1H, m), 7.41–7.50 (3H, m).

4.6.1.23. *N*-Isobutyl-2-(piperidin-1-yl)quinazolin-4-amine (25). *N*-Isobutyl-2-(piperidin-1-yl)quinazolin-4-amine (**25**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 285 (M+1); HRMS (ESMS) calcd for $C_{17}H_{24}N_4$, 285.2074; found, 285.2077 (M+1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.67 (4H, br s), 2.06 (1H, septet, J = 6.7 Hz), 3.84 (4H, br s), 7.43 (1H, t, J = 7.6 Hz), 7.67 (1H, d, J = 8.0 Hz), 7.78 (1H, t, J = 7.4 Hz), 8.27 (1H d, J = 7.9 Hz), 9.48 (1H t, J = 5.2 Hz), 11.7 (1H, s).

4.6.1.24. *N*-(Cyclohexylmethyl)-2-(piperidin-1-yl)quinazolin-4-amine (26). *N*-(Cyclohexylmethyl)-2-(piperidin-1-yl)quinazolin-4-amine (**26**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 325.3 (M+1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.89–1.04 (2 H, m), 1.10–1.24 (3 H, m), 1.44–1.54 (4 H, m), 1.56–1.79 (8 H, m), 3.70 (3 H, s), 3.77 (4 H, t, J = 5.4), 7.00 (1H, ddd, J = 8.1, 6.9 and 1.2), 7.22 (1H, dd, J = 8.4 and 0.9), 7.45 (1H, ddd, J = 8.3, 6.9 and 1.4), 7.89 (1H, t, J = 5.6), 7.97 (1H, dd, J = 8.1 and 0.8).

4.6.1.25. 2-(Piperidin-1-yl)-*N*-(4-(trifluoromethyl)phenethyl)quinazolin-4-amine (27). 2-(Piperidin-1-yl)-*N*-(4-(trifluoromethyl)phenethyl)quinazolin-4-amine (**27**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 401.3 (M+1). ^{1}H

NMR (300 MHz, DMSO-d_6): δ 1.58–1.75 (6H, br m), 3.08 (2H, t, J = 6.9), 3.78–3.91 (6H, br m), 7.38–7.52 (3H, br s), 7.61–7.85 (4H, br m), 8.19 (1H, d, J = 8.3), 9.55 (1H, br s), 11.70 (1H, br s).

4.6.1.26. *N*-(Naphthalen-1-ylmethyl)-2-(piperidin-1-yl)quinazolin-4-amine (28). *N*-(Naphthalen-1-ylmethyl)-2-(piperidin-1-yl)quinazolin-4-amine (**28**) was prepared according to the representative procedure I. MS: ESI-MS, m/z: MH^+ 369.3(M+1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.34–1.44 (4 H, m), 1.51–1.60 (2 H, m), 3.69 (4 H, t, J = 5.4), 5.16 (2 H, d, J = 5.4), 7.02 (1H, ddd, J = 8.1, 7.0 and 1.1), 7.24 (1H, dd, J = 8.4 and 0.8), 7.43–7.58 (5 H, m), 7.83 (1H, d, J = 8.1), 7.91–7.96 (1H, m), 8.05 (1H, d, J = 7.3), 8.30 (1H, dd, J = 7.1 and 2.2), 8.30 (1H, dd, J = 7.1 and 2.2), 8.49 (1H, t, J = 5.2).

4.6.1.27. *N*-(4-Fluorophenyl)-2-(piperidin-1-yl)quinazolin-4-amine (29). *N*-(4-Fluorophenyl)-2-(piperidin-1-yl)quinazolin-4-amine (**29**) was prepared according to the representative procedure I. Yield: 100 mg, 27%. MS: ESI-MS, m/z: 323.14 (M+1); HRMS (ESMS) calcd for $C_{19}H_{19}FN_4$, 323.1667; found, 323.1669 (M+1). UPLC: 98.5% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.46–1.53 (4H, m), 1.58–1.64 (2H, m), 3.70–3.77 (4H, m), 7.14 (1H, t, J = 7.6 Hz), 7.22 (2H, t, J = 8.8 Hz), 7.33 (1H, d, 8.4 Hz), 7.56 (1H, t , J = 7.2 Hz), 7.75–7.82 (2H, m), 8.24 (1H, d, J = 8 Hz), 9.52 (1H, s).

4.6.1.28. 2,4-Di(piperidin-1-yl)quinazoline (30). 2,4-Di(piperidin-1-yl)quinazoline (**30**) was prepared according to the representative procedure I. MS: ESI-MS, m/z: 297.2 (M+1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.72 – 1.45 (m, 12H), 3.57–3.51 (m, 4H), 3.78 (br t, J = 5.2 Hz, 4H), 7.06 (t, J = 7.2 Hz, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.68 (d, J = 8.2 Hz, 1H).

4.6.1.29. 4-(6-Fluoro-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-(piperidin-1-yl)quinazoline (31). 4-(6-Fluoro-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-(piperidin-1-yl)quinazoline (**31**) was prepared according to the representative procedure I. Yield: 42 mg, 45%. MS: ESI-MS, m/z: 363.13 (M+1); HRMS (ESMS) calcd for $C_{22}H_{23}FN_4$, 363.1980; found, 363.1980 (M+1). UPLC: 97.7% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.47–1.55 (4H, m), 1.58–1.63 (2H, m), 3.08 (2H, t, J = 5.6 Hz), 3.77–3.82 (4H, m), 3.87 (2H, t, J = 5.6 Hz), 4.77 (2H, s), 7.02 (1H, t, J = 8.4 Hz), 7.04–7.12 (2H, m), 7.29 (1H, t, J = 6 Hz), 7.36 (1H, d, J = 8.4 Hz), 7.54 (1H, t, J = 7.6 Hz), 7.82 (1H, d, J = 8 Hz).

4.6.1.30. 2-(Piperidin-1-yl)quinazoline (34). A solution of quinazolin-2(1*H*)-one (1 g, 6.7 mmol) in $POCl_3$ (15 mL) was heated in a sealed tube at 100 °C overnight. The reaction progress was followed by TLC. Reaction mixture was concentrated under reduced pressure and co-distilled with toluene. The resulting residue was dissolved in ethyl acetate (60 mL) and washed with aqueous $NaHCO_3$ (30 mL) and brine solution (30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Crude product was then purified by column chromatography on (100–200 mesh) silica gel using ethyl acetate in hexane to give 2-chloroquinazoline (0.79 g, 71.8%).

To a stirred solution of 2-chloroquinazoline (70 mg, 0.43 mmol) in MeCN was added piperidine (181 mg, 2.1 mmol) and K_2CO_3 (312 mg, 2.26 mmol) then heated in a sealed tube at 90 °C overnight. The reaction was monitored by TLC. The reaction was quenched with addition of ice-water (30 mL), concentrated to remove the MeCN then extracted with CH_2Cl_2 (2 × 30 mL). The organic extract was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Crude product was purified by column chromatography on (100–200 mesh) silica gel using ethyl acetate in hexane to afford 2-(piperidin-1-yl)quinazoline (85 mg, 94%). MS: ESI-MS, m/z: 214.46 (M+1), LCMS: 99.4% purity. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 1.74–1.87 (6H, m), 3.69–3.77 (4H, m), 7.43 (1H, t, J = 7.6 Hz), 7.71 (1H, t, J = 8 Hz), 7.86 (2H, d, J = 8.8 Hz), 8.71 (1H, s).

4.6.1.31. 4-(4-Fluorophenethyl)-2-(piperidin-1-yl)quinazoline (35). 4-(4-Fluorophenethyl)-2-(piperidin-1-yl)quinazoline (**35**) was similarly prepared from 4-(4-fluorophenethyl)quinazolin-2(3*H*)-one[9,10] following the procedure described for synthesis of **34**. MS: ESI-MS, m/z: 336.31 (M+1), LCMS: 95.8% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.51–1.57 (4H, m), 1.61–1.69 (2H, m), 3.13 (2H, t, J = 8 Hz), 3.44 (2H, t, J = 8 Hz), 3.82–3.90 (4H, m), 7.08 (2H, t, J = 8.8 Hz), 7.18(1H, t, J = 7.2 Hz), 7.31–7.35 (2H, m), 7.44 (1H, d, J = 8.4 Hz), 7.64 (1H, t, J = 6.8 Hz), 7.99 (1H, d, J = 8 Hz).

4.6.1.32. *N*-(4-Fluorobenzyl)-2-(4-methylpiperidin-1-yl)quinazolin-4-amine (36). *N*-(4-Fluorobenzyl)-2-(4-methylpiperidin-1-yl) quinazolin-4-amine (**36**) was prepared according to the representative procedure I. MS: ESI-MS, m/z: 351.23 (M+1); HRMS (ESMS) calcd for $C_{21}H_{23}FN_4$, 351.1980; found, 351.1981 (M+1). LCMS: 99.3% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 0.88 (3H, d, J = 6 Hz),0.94 (2H, t, J = 9.2 Hz), 1.52–1.60 (3H, m), 2.73 (2H, t, J = 11.2 Hz), 4.64 (2H, d, J = 6 Hz), 4.67–4.71 (2H, m), 7.03 (1H, dd, J = 8 Hz), 7.09–7.14 (2H, m), 7.23 (1H, d, J = 8.4 Hz), 7.38–7.41 (2H, m), 7.48 (1H, dd, J = 5.6 Hz), 7.98 (1H, d, J = 7.2 Hz), 8.51 (1H, t, J = 6 Hz, NH).

4.6.1.33. 1-(4-(4-Fluorobenzylamino)quinazolin-2-yl)piperidin-4-ol (37). 1-(4-(4-Fluorobenzylamino)quinazolin-2-yl)piperidin-4-ol (**37**) was prepared according to the representative procedure I. MS: ESI-MS, m/z: 353.21 (M+1); HRMS (ESMS) calcd for $C_{20}H_{21}FN_4O$, 353.1772; found, 353.1777 (M+1). LCMS: 99.4% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.19–1.24 (2H, m), 1.67–1.70 (2H, t), 3.12 (2H, t, J = 10 Hz), 3.62–3.66 (1H, m), 4.31–4.34 (2H, m), 4.61–4.65 (3H, m), 7.04 (1H, t, J = 7.6 Hz), 7.12 (2H, t, J = 8.8 Hz), 7.24 (1H, d, J = 8.4 Hz), 7.38–7.41 (2H, m), 7.48 (1H, t, J = 7.2 Hz), 7.99 (1H, d, J = 8 Hz), 8.54 (1H, t, NH).

4.6.1.34. 2-(4-Aminopiperidin-1-yl)-*N*-(4-fluorobenzyl)quinazolin-4-amine (38). 2-(4-Aminopiperidin-1-yl)-*N*-(4-fluorobenzyl) quinazolin-4-amine (**38**) was prepared according to the representative procedure I. MS: ESI-MS, m/z: 352.29 (M+1), LCMS: 98.2% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.02–1.15 (2H, m), 1.65–1.71 (2H, m), 2.70–2.75 (1H, m), 2.84–2.93 (2H, m), 4.54–4.57 (2H, m), 4.64 (2H, d, J = 5.6 Hz), 7.03 (1H, t, J = 7.6 Hz), 7.11(2H, t, J = 8.8 Hz), 7.23 (1H, d, J = 8 Hz), 7.38–7.42 (2H, m), 7.47 (1H, t, J = 7.6 Hz), 7.99 (1H, d, J = 8 Hz), 8.54(1H, t, J = 6 Hz).

4.6.1.35. *N*-(4-Fluorobenzyl)-2-(4-(methylamino)piperidin-1-yl) quinazolin-4-amine (39). *N*-(4-Fluorobenzyl)-2-(4-(methylamino) piperidin-1-yl)quinazolin-4-amine (**39**) was prepared according to the representative procedure I. MS: ESI-MS, m/z: 366.35 (M+1), LCMS: 96.6% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.00–1.08 (2H, m) 1.61–1.65 (1H, m), 1.74–1.77 (2H, m), 2.26 (3H, s), 2.92 (2H, t, J = 10.8 Hz), 4.51–4.54 (2H, m), 4.63 (2H, d, J = 5.6 Hz), 7.04 (1H, t, J = 8 Hz), 7.12 (2H, t, J = 8.8 Hz), 7.24 (1H, d, J = 8.4 Hz), 7.38–7.42 (2H, m), 7.48(1H, t, J = 6.8 Hz), 7.99 (1H, d, J = 8 Hz), 8.52 (1H, t, J = 6 Hz).

4.6.1.36. 2-(4-(Dimethylamino)piperidin-1-yl)-*N*-(4-fluorobenzyl)quinazolin-4-amine (40). 2-(4-(Dimethylamino)piperidin-1-yl)-*N*-(4-fluorobenzyl)quinazolin-4-amine (**40**) was prepared according to the representative procedure I. MS: ESI-MS, m/z: 380.23 (M+1), LCMS: 97.2% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.10–1.18 (2H, m), 1.71 (2H, d, J = 11.2 Hz), 2.14 (6H, s), 2.30–2.32 (1H, m), 2.75 (2H, t, J = 8 Hz), 4.65 (2H, d, J = 5.6 Hz), 4.69–4.72 (2H, m), 7.05 (1H, t, J = 7.2 Hz), 7.12 (2H, t, J = 8.8 Hz),

7.24 (1H, d, J = 8.4 Hz), 7.38–7.41 (2H, m),7.48 (1H, t, J = 7.2 Hz), 8.00 (1H, d, J = 8.4 Hz), 8.55 (1H, t, J = 5.6 Hz).

4.6.1.37. 1-(4-(4-Fluorobenzylamino)quinazolin-2-yl)piperidine-4-carboxylic acid (41). 1-(4-(4-Fluorobenzylamino)quinazolin-2-yl)piperidine-4-carboxylic acid (**41**) was prepared according to the representative procedure I. MS: ESI-MS, m/z: 381.21 (M+1), LCMS: 98% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.35–1.43 (2H, m), 1.79–1.81 (2H, t), 2.42–2.46 (1H, m), 2.98 (2H, t, J = 11.2 Hz), 4.52–4.55 (2H, m), 4.65 (2H, d, J = 5.2 Hz), 7.12(3H, t, J = 8.8 Hz), 7.31 (1H, d, J = 7.6 Hz), 7.39–7.42 (2H, m), 7.53 (1H, t, 7.2 Hz), 8.04 (1H, d, J = 8 Hz), 8.74 (1H, br s), 11.94 (1H, br s).

4.6.1.38. 2-(3, 5-Dimethylpiperidin-1-yl)-*N*-(4-fluorobenzyl)quinazolin-4-amine (42). 2-(3,5-Dimethylpiperidin-1-yl)-*N*-(4-fluorobenzyl)quinazolin-4-amine (**42**) was prepared according to the representative procedure I. MS: ESI-MS, m/z: 365.28 (M+1), LCMS: 93.1% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 0.68–0.74 (1H, m), 0.84 (6H, d, J = 6.8 Hz), 1.33–1.48 (2H, m), 1.72 (1H, d, J = 8.4 Hz), 2.13–2.29 (2H, m), 4.63 (2H, d, J = 5.2 Hz), 4.71 (2H, d, J = 11.6 Hz), 7.07 (1H, t, J = 7.2 Hz), 7.13–7.18 (2H, m), 7.24 (1H, d, J = 8.4 Hz), 7.38–7.41 (2H, m), 7.49 (1H, t, J = 7.2 Hz), 7.99 (1H, d, J = 7.6 Hz), 8.54 (1H, t, J = 5.6 Hz, NH).

4.6.1.39. (1-(4-(4-Fluorobenzylamino)quinazolin-2-yl)piperidin-4-yl)methanol (43). (1-(4-(4-Fluorobenzylamino)quinazolin-2-yl)piperidin-4-yl)methanol (**43**) was prepared according to the representative procedure I. MS: ESI-MS, m/z: 367.26 (M+1), LCMS: 99% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 0.93–1.01 (2H, m), 1.60–1.66 (2H, m), 2.75 (2H, t, J = 12.8 Hz), 3.23 (2H, t, J = 5.6 Hz), 4.43 (1H, t, J = 5.2 Hz), 4.65 (2H, d, J = 5.6 Hz), 4.70–4.73 (2H, m), 7.05 (1H, dd, J = 7.2 Hz), 7.12 (2H, t, 8.8 Hz), 7.26 (1H, d, J = 8 Hz) 7.38–7.42 (2H, m), 7.49 (1H, dd, J = 7.6 Hz), 8.00 (1H, d, J = 8 Hz), 8.58 (1H, br s).

4.6.1.40. 2-(1-(4-(4-Fluorobenzylamino)quinazolin-2-yl)piperidin-4-yl-amino)acetic acid (44). 2-(1-(4-(4-Fluorobenzylamino) quinazolin-2-yl)piperidin-4-yl-amino)acetic acid (**44**) was prepared according to the representative procedure I. MS: ESI-MS, m/z: 410.28 (M+1); HRMS (ESMS) calcd for $C_{22}H_{24}FN_5O_2$, 410.1987; found, 410.1984 (M+1). LCMS: 95.9% purity. ^{1}H NMR: (400 MHz, DMSO-D_2O): δ 1.42–1.51 (2H, m), 2.05–2.12 (2H, m), 3.07 (2H, t, J = 13.2 Hz), 3.30–3.41 (1H, m) 3.49 (2H, s), 4.56 (2H , br s), 4.70 (2H, s), 7.12 (2H, t, J = 8.8 Hz), 7.41 (3H, t, J = 6.8 Hz), 7.58 (1H, d, J = 8.4 Hz) 7.77 (1H, t, J = 7.6 Hz), 8.14(1H, d, J = 7.6 Hz).

4.6.1.41. 2-(1-(4-((4-Fluorobenzyl)amino)quinazolin-2-yl)piperidin-2-yl)acetic acid (45). 2-(1-(4-((4-Fluorobenzyl)amino)quinazolin-2-yl)piperidin-2-yl)acetic acid (**45**) was prepared according to the representative procedure I. MS: ESI-MS, m/z: 395.23 (M+1), LCMS: 95.8% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.27–1.41 (1H, m), 1.55–1.71 (5H, m), 2.66–2.72 (1H, m), 2.99 (1H, br s), 3.37–3,40 (1H, m), 4.52 (1H, br s), 4.71 (2H, d, J = 5.6 Hz), 5.28 (1H, br s), 7.13 (2H, t, J = 8.8 Hz), 7.27 (1H , br s), 7.42–7.46 (2H, m), 7.48–7.52 (1H, m), 7.64–7.71 (1H, m), 8.15 (1H, d, J = 8 Hz), 9.34 (1H, br s), 12.12 (1H, br s).

4.6.1.42. N^4-(4-Fluorobenzyl)quinazoline-2,4-diamine (46). N^4-(4-Fluorobenzyl)quinazoline-2,4-diamine (**46**) was prepared according to the representative procedure I. MS: ESI-MS, m/z: 269 (M+1); HRMS (ESMS) calcd for $C_{15}H_{13}FN_4$, 269.1197; found, 269.1197 (M+1). UPLC: 99.4% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 4.76 (2H, d, J = 5.2 Hz), 7.16 (2H, t, J = 8.4 Hz), 7.30 (1H, t, J = 7.2 Hz), 7.38 (2H, d , J = 8 Hz), 7.43–7.47 (3H, m), 7.70 (1H, t, J = 7.6 Hz), 8.23 (1H, d, J = 8.4 Hz), 9.56 (1H, t, NH).

4.6.1.43. N^4-(4-Fluorobenzyl)-N^2-methylquinazoline-2,4-diamine (47). N^4-(4-Fluorobenzyl)-N^2-methylquinazoline-2,4-diamine (**47**) was prepared according to the representative procedure I. Yield: 60 mg, 65%. MS: ESI-MS, m/z: 283.21 (M+1); HRMS (ESMS) calcd for $C_{16}H_{15}FN_4$, 283.1354; found, 283.1354 (M+1). LCMS: 98.7% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 2.89–3.07 (3H, m), 4.71–4.79(2H, m), 7.17 (2H, t, J = 8.8 Hz), 7.41–7.47 (4H, m), 7.79 (2H, t, J = 8 Hz), 7.89 (1H, br s), 8.33 (1H, br s).

4.6.1.44. N^4-(4-Fluorobenzyl)-N^2,N^2-dimethylquinazoline-2,4-diamine (48). N^4-(4-Fluorobenzyl)-N^2,N^2-dimethylquinazoline-2,4-diamine (**48**) was prepared according to the representative procedure I. Yield: 46 mg, 53%. MS: ESI-MS, m/z: 297.22 (M+1); HRMS (ESMS) calcd for $C_{17}H_{17}FN_4$, 297.1510; found, 297.1514 (M+1). LCMS: 99.6% purity. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 3.23 (6H, s), 4.79 (2H, d, J = 5.6 Hz), 5.72 (1H, br s), 7.00–7.05 (3H, m), 7.35–7.38 (2H, m), 7.44–7.49 (3H, m).

4.6.1.45. *N*-(4-Fluorobenzyl)-2-(pyrrolidin-1-yl)quinazolin-4-amine (49). *N*-(4-Fluorobenzyl)-2-(pyrrolidin-1-yl)quinazolin-4-amine (**49**) was prepared according to the representative procedure I. Yield: 55 mg, 50%. MS: ESI-MS, m/z: 323.27 (M+1), LCMS: 99.3% purity. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 1.94–1.97 (4H, m), 3.63–3.66 (4H, m), 4.78–4.79 (2H, d, J = 5.6 Hz), 5.73 (1H, t, NH), 6.99–7.04 (3H, m), 7.35–7.39 (2H, m), 7.45 (1H, d, J = 8 Hz), 7.47–7.52 (2H, m).

4.6.1.46. *N*-(4-Fluorobenzyl)-2-(isoindolin-2-yl)quinazolin-4-amine hydrochloride (50). *N*-(4-Fluorobenzyl)-2-(isoindolin-2-yl)quinazolin-4-amine hydrochloride (**50**) was prepared according to the representative procedure I. MS: ESI-MS, m/z: 371.1(M+1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.89 (2H, d, J = 5.7 Hz), 5.04 (4H, d, J = 5.2 Hz), 7.22 (2H, t, J = 9.0 Hz), 7.37–7.61 (7H, br m), 7.83–7.91 (2H, br m), 8.39 (1H, d, J = 8.2 Hz), 10.23 (1H, br s), 12.08 (1H, br s).

4.6.1.47. *N*-(4-Fluorobenzyl)-2-(piperazin-1-yl)quinazolin-4-amine (51). *N*-(4-Fluorobenzyl)-2-(piperazin-1-yl)quinazolin-4-amine (**51**) was prepared according to the representative procedure I. MS: ESI-MS, m/z: 338.15 (M+1); HRMS (ESMS) calcd for $C_{19}H_{20}FN_5$, 338.1776; found, 338.1778 (M+1). UPLC: 96% purity. ^{1}H NMR: (400 MHz, CD_3OD): δ 2.81–2.88 (4H, m), 3.78–3.83 (4H, m), 4.74 (2H, d), 7.00–7.05 (2H, m), 7.13 (1H, t, J = 6.8 Hz), 7.37–7.40 (3H, m), 7.52–7.56 (1H, m), 7.88–7.91 (1H, m).

4.6.1.48. 2,2′-(4-(4-Fluorobenzylamino)quinazolin-2-ylazanediyl) diethanol (53). 2,2′-(4-(4-Fluorobenzylamino)quinazolin-2-ylazanediyl)diethanol (**53**) was prepared according to the representative procedure I. MS: ESI-MS, m/z: 357.19 (M+1), LCMS: 99.5% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 3.50–3.64 (8H, m), 4.65 (2H, d, J = 5.2 Hz), 7.15–7.05 (3H, m), 7.24–7.31 (1H, m), 7.38–7.41 (2H, m), 7.51 (1H, d, J = 10.4 Hz), 8.01–8.04 (1H, m), 8.62–8.60 (1H, d, J = 8.8 Hz).

4.6.2. Representative procedure II for the synthesis of 56–61

4.6.2.1. Synthesis of *N*-(4-fluorobenzyl)-2-phenylquinazolin-4-amine (60). To a stirred solution of 2-aminobenzamide (4 g, 29.4 mmol) in THF (100 mL) was slowly added benzoyl chloride (12.4 g, 88.2 mmol). The reaction mixture was stirred at rt for 1 h and concentrated under reduced pressure and the residue washed with hexane then recrystallized from a mixture of acetone and hexane, to afforded *N*-(2-carbamoylphenyl)benzamide (0.990 g, 15% yield).

To a stirred solution of 2(-(2-carbamoylphenyl)benzamide) (0.12 g, 0.5 mmol) in toluene (10 mL) was added NaOMe (0.067 g, 1.25 mmol) and refluxed at 110 °C for 5 h. The reaction progress

was followed by TLC. The reaction mixture is treated with saturated solution of NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 2-phenylquinazolin-4(3*H*)-one (85 mg, 77%). The 2-phenylquinazolin-4(3*H*)-one) (80 mg, 0.4 mmol) was taken up in $POCl_3$ (4 mL) and heated in a sealed tube at 120 °C for 3 h. The reaction mixture was concentrated under reduced pressure and co-distilled with toluene. The residue was dissolved in ethyl acetate (50 mL) and washed with aqueous $NaHCO_3$ (30 mL) and with brine (30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Crude product was purified by column chromatography on (100–200 mesh) silica gel using ethyl acetate in hexane to give 4-chloro-2-phenylquinazoline (40 mg, 46%). Reaction of this chloroquinazoline with (4-fluorophenyl)methanamine (41 mg, 0.33 mmol) according to representative procedure I afforded the final product, *N*-(4-fluorobenzyl)-2-phenylquinazolin-4-amine (45 mg, 73%). MS: ESI-MS, *m*/*z*: 330.09 (M+1), UPLC: 99.3% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 4.90 (2H, d, J = 4.8 Hz), 7.13–7.15 (2H, m), 7.45–7.53 (6H, m), 7.76–7.79 (2H, m), 8.29 (1H, d, J = 8 Hz), 8.42–8.45 (2H, m), 8.93 (1H, t, J = 5.6 Hz).

4.6.2.2. *N*-(4-Fluorobenzyl)-2-(piperidin-1-ylmethyl)quinazolin-4-amine (56). *N*-(4-Fluorobenzyl)-2-(piperidin-1-ylmethyl)quinazolin-4-amine (**56**) was prepared starting from 2-aminobenzamide and 2-(piperidin-1-yl)acetyl chloride according to representative procedure II described for synthesis of **60**. MS: ESI-MS, *m*/*z*: 351.37 (M+1), LCMS: 95.7% purity. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.25–1.34 (2H, m), 1.38–1.47 (4H, m), 2.39–2.45 (4H, m), 3.48 (2H, s), 4.74(2H, d, J = 5.6 Hz), 7.11 (2H, t, J = 8.8 Hz), 7.40–7.50 (3H, m), 7.65 (1H, d, J = 8 Hz), 7.73 (1H, t, J = 7.6 Hz), 8.22 (1H, d, J = 8 Hz), 8.76 (1H, t, J = 5.2 Hz).

4.6.2.3. *N*-(4-Fluorobenzyl)quinazolin-4-amine (57). *N*-(4-Fluorobenzyl)quinazolin-4-amine (**57**) was prepared starting from condensation of 2-aminobenzonitrile with 1,1-dimethoxy-*N*,*N*-dimethylmethanamine as the initial step to representative procedure II described for synthesis of **60**. MS: ESI-MS, *m*/*z*: 254.16 (M+1); HRMS (ESMS) calcd for $C_{15}H_{12}FN_3$, 254.1088; found, 254.1091 (M+1). LCMS: 99.6% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 4.77 (2H, d, J = 5.6 Hz) 7.13 (2H, t, J = 8.8 Hz), 7.38–7.42 (2H, m), 7.54 (1H, t, J = 7.2 Hz), 7.70 (1H, d, J = 8.4 Hz), 7.79 (1H, t, J = 7.2 Hz), 8.29 (1H, d, J = 8 Hz), 8.47 (1H, s), 8.93 (1H, br s).

4.6.2.4. *N*-(4-Fluorobenzyl)-2-methylquinazolin-4-amine (58). *N*-(4-Fluorobenzyl)-2-methylquinazolin-4-amine (**58**) was prepared starting from 2-aminobenzamide and acetylchloride according to representative procedure II described for synthesis of **60**. MS: ESI-MS, *m*/*z*: 268.21 (M+1); HRMS (ESMS) calcd for $C_{16}H_{14}FN_3$, 268.1245; found, 268.1247 (M+1). LCMS: 99.5% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 2.43 (3H, s), 4.75 (2H, d, J = 5.6 Hz), 7.12–7.17 (2H, m), 7.40–7.45 (3H, m), 7.59 (1H, d, J = 8.4 Hz), 7.69–7.73 (1H, m), 8.21 (1H, d, J = 8 Hz), 8.68 (1H, t, 6 Hz).

4.6.2.5. *N*-(4-Fluorobenzyl)-2-(trifluoromethyl)quinazolin-4-amine (59). *N*-(4-Fluorobenzyl)-2-(trifluoromethyl)quinazolin-4-amine (**59**) was prepared by amination of 4-chloro-2-(trifluoromethyl) quinazoline according to representative procedure I. MS: ESI-MS, *m*/*z*: 322.10 (M+1); HRMS (ESMS) calcd for $C_{16}H_{11}F_4N_3$, 322.0962; found, 322.0964 (M+1). LCMS: 99.5% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 4.77 (2H, s), 6.22 (1H, br s) 7.04 (3H, m), 7.41 (1H, dd, , J = 5.4 Hz and 3.0 Hz), 7.57 (1H, t, J = 7.2 Hz), 7.74–7.85 (2H, m), 7.98 (1H, d, J = 8.4 Hz).

4.6.2.6. 2-Cyclohexyl-*N*-(4-fluorobenzyl)quinazolin-4-amine (61). 2-Cyclohexyl-*N*-(4-fluorobenzyl)quinazolin-4-amine (**61**) was prepared starting from 2-aminobenzamide and cyclohexanecarbonyl chloride according to representative procedure II described for synthesis of **60**. MS: ESI-MS, *m*/*z*: 336.27 (M+1); HRMS (ESMS) calcd for $C_{21}H_{22}FN_3$, 336.1871; found, 336.1871 (M+1). LCMS: 98.7% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.51–1.87 (10H, m), 2.56–2.63 (1H, m), 4.75 (2H, d, J = 5.2 Hz), 7.13 (2H, t, 8.8 Hz), 7.39–7.45 (3H, m), 7.60 (1H, d, J = 7.6 Hz), 7.70 (1H, t, J = 7.2 Hz), 8.19 (1H, d, J = 8 Hz), 8.68 (1H, t, J = 6 Hz).

4.6.3. Representative procedure III for the synthesis of 62–66

4.6.3.1. 5-Benzyl-*N*-(4-fluorobenzyl)-2-(piperidin-1-yl)pyrimidin-4-amine (65). A solution of 5-benzylpyrimidine-2,4(1*H*,3*H*)-dione (0.5 g, 2.0 mmol) in $POCl_3$ (3 mL) in a sealed tube was stirred at 100 °C for 3 h, monitoring progress by TLC. The reaction mixture was concentrated under reduced pressure and co-distilled with toluene. The residue was dissolved in ethyl acetate (50 mL) and washed with aqueous $NaHCO_3$ (30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure, to afford 5-benzyl-2,4-dichloropyrimidine (0.4 g, 68% yield).

To a pre-cooled solution of 5-benzyl-2,4-dichloropyrimidine (0.4 g, 1.6 mmol) in THF (20 mL) in two-neck round-bottomed flask was added (4-fluorophenyl)methanamine (0.315 g, 2.5 mmol) drop wise then stirred for 20 min at rt under nitrogen atmosphere. The reaction was monitored by TLC. The mixture was concentrated under reduced pressure and the crude compound dissolved in ethyl acetate and washed with $NaHCO_3$ and brine solution. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Crude product was purified by column chromatography on (60–120 mesh) silica gel using 20% ethyl acetate in hexane to give 5-benzyl-2-chloro-*N*-(4-fluorobenzyl)pyrimidin-4-amine (0.24 g, 43%).

5-Benzyl-2-chloro-*N*-(4-fluorobenzyl)pyrimidin-4-amine (0.2 g, 0.6 mmol) in MeCN (10 mL) was treated with piperidine (0.155 g, 1.8 mmol) and K_2CO_3 (0.337 g, 2.7 mmol) then heated at 90 °C in a sealed tube for 16 h. The reaction mixture was quenched with water (50 mL), concentrated to remove MeCN then extracted with ethyl acetate (2 × 30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Crude product was purified by column chromatography on (60–120 mesh) silica gel using ethyl acetate in hexane to give pure 5-Benzyl-*N*-(4-fluorobenzyl)-2-(piperidin-1-yl)pyrimidin-4-amine (**65**) (0.140 g, 61% yield). MS: ESI-MS, *m*/*z*: 377.29 (M+1); HRMS (ESMS) calcd for $C_{23}H_{25}FN_4$, 377.2136; found, 377.2140 (M+1). LCMS: 97.8% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.33–1.42 (4H, m), 1.48–1.54 (2H, m), 3.53–3.58 (4H, m), 3.67 (2H, s), 4.45 (2H, d, J = 5.6 Hz), 7.03–7.07 (3H, m), 7.17–7.22 (5H, m), 7.26–7.29 (2H, m), 7.56 (1H, s).

4.6.3.2. *N*-(4-Fluorobenzyl)-6-methyl-2-(piperidin-1-yl)pyrimidin-4-amine (62). *N*-(4-Fluorobenzyl)-6-methyl-2-(piperidin-1-yl) pyrimidin-4-amine (**62**) was prepared from 2,4-dichloro-6-methylpyrimidine according to representative procedure III described for synthesis of **65**. Yield: 200 mg, 76%. MS: ESI-MS, *m*/*z*: 301.20 (M+1); HRMS (ESMS) calcd for $C_{17}H_{21}FN_4$, 301.1823; found, 301.1825 (M+1). LCMS: 98.6% purity. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 1.50–1.65 (6H, m), 2.18 (3H, s), 3.69–3.75 (4H, m), 4.47 (2H, d, J = 5.6 Hz), 4.74 (1H, br s), 5.51 (1H, s), 6.95–7.03 (2H, m), 7.25–7.30 (2H, m).

4.6.3.3. *N*-(4-Fluorobenzyl)-5-methyl-2-(piperidin-1-yl)pyrimidin-4-amine (63). *N*-(4-Fluorobenzyl)-5-methyl-2-(piperidin-1-yl) pyrimidin-4-amine (**63**) was prepared from 2,4-dichloro-5-methylpyrimidine according to representative procedure III described for synthesis of **65**. Yield: 35 mg, 51%. MS: ESI-MS, *m*/*z*: 301.22 (M+1); HRMS (ESMS) calcd for $C_{17}H_{21}FN_4$, 301.1823; found, 301.1823 (M+1). LCMS: 95.4% purity. ^{1}H NMR: (400 MHz, $CDCl_3$):

δ 1.54–1.59 (4H, m), 1.67–1.73 (2H, m), 1.90 (3H, s), 3.63–3.69 (4H, m), 4.63 (3H, s), 6.98–7.03 (2H, m), 7.29–7.33 (2H, m), 7.69 (1H, s).

4.6.3.4. *N*-(4-Fluorobenzyl)-5,6-dimethyl-2-(piperidin-1-yl)pyrimidin-4-amine (64). *N*-(4-Fluorobenzyl)-5,6-dimethyl-2-(piperidin-1-yl)pyrimidin-4-amine (**64**) was prepared from 2,4-dichloro-5,6-dimethylpyrimidine according to representative procedure III described for synthesis of **65**. Yield: 30 mg, 45%. MS: ESI-MS, *m*/*z*: 315.26 (M+1); HRMS (ESMS) calcd for $C_{18}H_{23}FN_4$, 315.1980; found, 315.1981 (M+1). LCMS: 98.6% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.33–1.39 (4H, m), 1.48–1.53 (2H, m), 1.88 (3H, s), 2.09 (3H, s), 3.51–3.56 (4H, m), 4.45 (2H, d, *J* = 5.6 Hz), 6.95 (1H, t, *J* = 6 Hz), 7.03–7.13 (2H, m), 7.29–7.35 (2H, m).

4.6.3.5. 6-Benzyl-*N*-(4-fluorobenzyl)-2-(piperidin-1-yl)pyrimidin-4-amine (66). 6-Benzyl-*N*-(4-fluorobenzyl)-2-(piperidin-1-yl)pyrimidin-4-amine (**66**) was prepared from 6-benzylpyrimidine-2,4(1*H*,3*H*)-dione according to representative procedure III described for synthesis of **65**. MS: ESI-MS, *m*/*z*: 377.3 (M+1); HRMS (ESMS) calcd for $C_{23}H_{25}FN_4$, 377.2136; found, 377.21368 (M+1), LCMS: 98.3% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.37–1.43 (4H, m), 1.52–1.61 (2H, m), 3.57–3.65 (6H, m), 4.35–4.39 (2H, m), 5.50 (1H, s), 7.09–7.11 (2H, m), 7.18–7.20 (1H, m), 7.23–7.30 (6H, m), 7.35 (1H, t, NH).

4.6.3.6. *N*-(4-Fluorobenzyl)-2-(piperidin-1-yl)pyrido[2,3-*d*]pyrimidin-4-amine (67). *N*-(4-Fluorobenzyl)-2-(piperidin-1-yl)pyrido[2,3-*d*]pyrimidin-4-amine (**67**) was prepared from 2-aminonicotinic acid via a pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione intermediate according to representative procedure III described for synthesis of **65**. MS: ESI-MS, *m*/*z*: 338.29 (M+1); HRMS (ESMS) calcd for $C_{19}H_{20}FN_5$, 338.1776; found, 338.1778 (M+1). LCMS: 99% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.39–1.50 (4H, m), 1.57–1.63 (2H, m), 3.71–3.80 (4H, m), 4.61–4.65 (2H, m), 7.01–7.07 (1H, m), 7.13 (2H, t, 8 Hz), 7.37–7.43 (2H, m), 8.39 (1H, d, *J* = 7.6 Hz), 8.59–8.65 (1H, m), 8.80 (1H, br s).

4.6.3.7. *N*-(4-Fluorobenzyl)-2-(piperidin-1-yl)pyrido[3,4-*d*]pyrimidin-4-amine (68). *N*-(4-Fluorobenzyl)-2-(piperidin-1-yl)pyrido[3,4-*d*]pyrimidin-4-amine (**68**) was prepared from 3-aminoisonicotinic acid via a pyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione intermediate according to representative procedure III described for synthesis of **65**. MS: ESI-MS, *m*/*z*: 338.40 (M+1); HRMS (ESMS) calcd for $C_{19}H_{20}FN_5$, 338.1776; found, 338.1778 (M+1). LCMS: 96.6% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.41–1.47 (4H, m), 1.52–1.61 (2H, m), 3.70–3.77 (4H, m), 4.66 (2H, d, *J* = 4.4 Hz), 7.13 (2H, t, 8.8 Hz), 7.37–7.43 (2H, m), 7.85(1H, d, *J* = 5.6 Hz), 8.15 (1H, d, *J* = 5.2 Hz), 8.61 (1H, s), 8.82 (1H, t, NH).

4.6.3.8. *N*-(4-Fluorobenzyl)-2-(piperidin-1-yl)pyrido[3,2-*d*]pyrimidin-4-amine (69). *N*-(4-Fluorobenzyl)-2-(piperidin-1-yl)pyrido[3,2-*d*]pyrimidin-4-amine (**69**) was prepared from 3-aminopicolinic acid via a pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione intermediate according to representative procedure III described for synthesis of **65**. MS: ESI-MS, *m*/*z*: 338.27 (M+1); HRMS (ESMS) calcd for $C_{19}H_{20}FN_5$, 338.1776; found, 338.1779 (M+1). LCMS: 99.3% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.42–1.50 (4H, m), 1.53–1.60 (2H, m), 3.72–3.77 (4H, m), 4.61 (2H, d, *J* = 6 Hz), 7.11 (2H, t, *J* = 8.8 Hz), 7.41–7.44 (2H, m), 7.50–7.53 (1H, m), 7.60 (1H, d, *J* = 8.4 Hz), 8.32 (1H, d, *J* = 4 Hz), 8.73 (1H, t, *J* = 6 Hz).

4.6.3.9. *N*-(4-Fluorobenzyl)-2-(piperidin-1-yl)thieno[2,3-*d*]pyrimidin-4-amine (70). *N*-(4-Fluorobenzyl)-2-(piperidin-1-yl)thieno[2,3-*d*]pyrimidin-4-amine (**70**) was prepared from 2-aminothiophene-3-carboxylic acid via a thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione intermediate according to representative procedure III described for synthesis of **65**. MS: ESI-MS, *m*/*z*: 343.26 (M+1), LCMS: 99.1% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.38–1.44 (4H, m), 1.54–1.57 (2H, m), 3.62–3.68 (4H, m), 4.60 (2H, d, *J* = 5.6 Hz), 6.96 (1H, d, *J* = 6 Hz), 7.13 (2H, t, *J* = 8.4 Hz), 7.33–7.42 (3H, m), 8.17 (1H, t, *J* = 5.6 Hz).

4.6.3.10. *N*-(4-Fluorobenzyl)-2-(piperidin-1-yl)thieno[3,2-*d*]pyrimidin-4-amine (71). *N*-(4-Fluorobenzyl)-2-(piperidin-1-yl)thieno[3,2-*d*]pyrimidin-4-amine (**71**) was prepared from 3-aminothiophene-2-carboxylic acid via a thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione intermediate according to representative procedure III described for synthesis of **65**. MS: ESI-MS, *m*/*z*: 343.22 (M+1); HRMS (ESMS) calcd for $C_{18}H_{19}FN_4S$, 343.1387; found, 343.1393 (M+1). LCMS: 98.2% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.39–1.45 (4H, m), 1.54–1.59 (2H, m), 3.62–3.69 (4H, m), 4.59 (2H, d, *J* = 5.6 Hz), 7.04 (1H, d, *J* = 5.2 Hz), 7.12 (2H, t, *J* = 9.2 Hz), 7.36–7.40 (2H, m), 7.87 (1H, d, *J* = 5.2 Hz), 8.08 (1H, br s).

4.6.3.11. *N*-(4-Fluorobenzyl)-2-(piperidin-1-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (72). *N*-(4-Fluorobenzyl)-2-(piperidin-1-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**72**) was prepared from 1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione according to representative procedure III described for synthesis of **65**. MS: ESI-MS, *m*/*z*: 326.17 (M+1), LCMS: 99.5% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.39–1.45 (4H, m), 1.52–1.58 (2H, m), 3.59–3.64 (4H, m), 4.58 (2H, d, *J* = 5.2 Hz), 6.31 (1H, s), 6.66 (1H, s), 7.11 (2H, t, *J* = 8.8 Hz), 7.37 (2H, t, *J* = 6 Hz), 7.66 (1H, br s), 10.77 (1H, s).

4.6.3.12. *N*-(4-Fluorobenzyl)-7-methyl-2-(piperidin-1-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (73). *N*-(4-Fluorobenzyl)-7-methyl-2-(piperidin-1-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**73**) was prepared by a standard methylation of *N*-(4-fluorobenzyl)-2-(piperidin-1-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (**72**) with methyl iodide in K_2CO_3 and MeCN. MS: ESI-MS, *m*/*z*: 340.20 (M+1), LCMS: 98.8% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.44–1.48 (4H, m), 1.53–1.57 (2H, m), 3.51 (3H, s), 3.64–3.67 (4H, m), 4.59 (2H, d, *J* = 6 Hz), 6.33 (1H, d, *J* = 3.6 Hz), 6.70 (1H, d, *J* = 3.6 Hz), 7.10 (2H, t, *J* = 8.8 Hz), 7.35–7.38 (2H, m), 7.65 (1H, t, *J* = 6 Hz).

4.6.3.13. *N*-(4-Fluorobenzyl)-2-(piperidin-1-yl)-9*H*-purin-6-amine (74). *N*-(4-Fluorobenzyl)-2-(piperidin-1-yl)-9*H*-purin-6-amine (**74**) was prepared from 2,6-dichloro-9*H*-purine according to representative procedure I. MS: ESI-MS, *m*/*z*: 327.28 (M+1), LCMS: 99.9% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.40–1.47 (4H, m), 1.52–1.58 (2H, m), 3.61–3.67 (4H, m), 4.55 (2H, s), 7.07–7.15 (2H, m), 7.37–7.40 (2H, m), 7.68 (1H, s), 7.93 (1H, br s), 12.18 (1H, s).

4.6.3.14. *N*-(4-Fluorobenzyl)-9-methyl-2-(piperidin-1-yl)-9*H*-purin-6-amine (75). *N*-(4-Fluorobenzyl)-9-methyl-2-(piperidin-1-yl)-9*H*-purin-6-amine (**75**) was prepared by direct methylation of *N*-(4-fluorobenzyl)-2-(piperidin-1-yl)-9*H*-purin-6-amine (**74**) with methyl iodine in K_2CO_3/MeCN. MS: ESI-MS, *m*/*z*: 341.18 (M+1), LCMS: 99.4% purity.^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.40–1.49 (4H, m), 1.53–1.59 (2H, m), 3.54 (3H, s), 3.62–3.69 (4H, m), 4.55 (2H, br s), 7.07–7.11 (2H, m), 7.35–7.39 (2H, m),7.69(1H, s), 7.87 (1H, br s).

4.6.3.15. 5-Fluoro-*N*-(4-fluorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (76). 5-Fluoro-*N*-(4-fluorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (**76**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 355.23 (M+1), LCMS: 99.8% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.38–1.42 (4H, m), 1.52–1.61 (2H, m), 3.67–3.71 (4H, m), 4.63 (2H, d, *J* = 5.6 Hz),

6.80(1H, dd, *J* = 4.4 Hz), 7.04 (1H, d, *J* = 8.4 Hz), 7.08–7.13 (2H, m), 7.37–7.46 (3H, m), 8.00–8.09 (1H, m).

4.6.3.16. *N*-(4-Fluorobenzyl)-8-nitro-2-(piperidin-1-yl)quinazolin-4-amine (77). *N*-(4-Fluorobenzyl)-8-nitro-2-(piperidin-1-yl) quinazolin-4-amine (**77**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 382.41 (M+1), LCMS: 96.7% purity. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 1.53–1.59 (4H, m), 1.65–1.73 (2H, m), 3.87–3.95 (4H, m), 4.75 (2H, d, *J* = 5.2 Hz), 5.77 (1H, t, NH),6.94 (1H, t, *J* = 8 Hz), 7.03 (2H, t, *J* = 8.8 Hz), 7.35–7.41 (2H, m), 7.60 (1H, d, *J* = 7.6 Hz), 7.90 (1H, dd, *J* = 7.2 Hz).

4.6.3.17. 5-Chloro-*N*-(4-fluorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (78). 5-Chloro-*N*-(4-fluorobenzyl)-2-(piperidin-1-yl) quinazolin-4-amine (**78**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 371.23 (M+1), LCMS: 99.7% purity. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 1.52–1.58 (4H, m) 1.62–1.64 (2H, m), 3.78–3.80 (4H, m), 4.73 (2H, d, *J* = 5.2 Hz), 6.97 (1H, dd, *J* = 4.4 Hz), 7.00–7.05 (2H, m), 7.27–7.34 (2H, m), 7.36–7.38 (2H, m), 7.77 (1H, t, NH).

4.6.3.18. 6-Chloro-*N*-(4-fluorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (79). 6-Chloro-*N*-(4-fluorobenzyl)-2-(piperidin-1-yl) quinazolin-4-amine (**79**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 371.20 (M+1), LCMS: 99.9% purity. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 1.54–1.61 (4H, m), 1.62–1.66 (2H, m), 3.82–3.85 (4H, m), 4.74 (2H, d, *J* = 5.6 Hz), 5.59 (1H, t, NH), 7.01–7.06 (2H, m), 7.34–7.38 (3H, m), 7.40 (2H, br s).

4.6.3.19. 7-Chloro-*N*-(4-fluorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (80). 7-Chloro-*N*-(4-fluorobenzyl)-2-(piperidin-1-yl) quinazolin-4-amine (**80**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 371.23 (M+1), LCMS: 99.3% purity. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 1.51–1.61 (4H, m), 1.62–1.67 (2H, m), 3.83–3.86 (4H, m), 4.74 (2H, d, *J* = 5.6 Hz), 5.63(1H, br s, NH), 6.94 (1H, dd, *J* = 6.8 Hz) , 7.00–7.05 (2H, m), 7.33–7.37 (3H, m), 7.43 (1H, d, *J* = 2 Hz).

4.6.3.20. 8-Chloro-*N*-(4-fluorobenzyl)-2-(piperidin-1-yl)quinazolin-4-amine (81). 8-Chloro-*N*-(4-fluorobenzyl)-2-(piperidin-1-yl) quinazolin-4-amine (**81**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 371.23 (M+1), LCMS: 99.8% purity. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 1.56–1.61 (4H, m), 1.64–1.67 (2H, m), 3.89–3.91 (4H, m), 4.76 (2H, d, *J* = 5.2 Hz), 5.70 (1H, br s, NH), 6.90 (1H, t, *J* = 8 Hz), 7.03 (2H, m), 7.33–7.37 (3H, m), 7.61 (1H, d, *J* = 6.8 Hz).

4.6.3.21. *N*-(4-Fluorobenzyl)-5-methyl-2-(piperidin-1-yl)quinazolin-4-amine (82). *N*-(4-Fluorobenzyl)-5-methyl-2-(piperidin-1-yl)quinazolin-4-amine (**82**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 351.26 (M+1), LCMS: 98.9% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.31–1.42 (4H, m), 1.52–1.61 (2H, m), 2.79 (3H, s), 3.63–3.71 (4H, m), 4.65 (2H, d, *J* = 5.2 Hz), 6.81 (1H, d, *J* = 7.2 Hz), 7.07–7.13 (3H, m), 7.28–7.35 (2H, m), 7.39–7.43 (2H, m).

4.6.3.22. *N*-(4-Fluorobenzyl)-6-methyl-2-(piperidin-1-yl)quinazolin-4-amine (83). *N*-(4-Fluorobenzyl)-6-methyl-2-(piperidin-1-yl)quinazolin-4-amine (**83**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 351.21 (M+1); HRMS (ESMS) calcd for $C_{21}H_{23}FN_4$, 351.1980; found, 351.1983 (M+1). LCMS: 99.1% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.39–1.46 (4H, m) 1.55–1.61 (2H, m), 2.33 (3H, s), 3.66–3.72 (4H, m), 4.63 (2H, d, *J* = 5.6 Hz), 7.09–7.14 (2H, m), 7.16 (1H, d, *J* = 8.8 Hz), 7.32 (1H, d, *J* = 8.4 Hz), 7.38–7.41 (2H, m), 7.80 (1H, s), 8.41 (1H, t, *J* = 5.6 Hz).

4.6.3.23. *N*-(4-Fuorobenzyl)-6-methoxy-2-(piperidin-1-yl)quinazolin-4-amine (84). *N*-(4-Fuorobenzyl)-6-methoxy-2-(piperidin-1-yl)quinazolin-4-amine (**84**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 367.27 (M+1), LCMS: 97.1% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.39–1.42 (4H, m), 1.55–1.62 (2H, m), 3.67–3.71 (4H, m), 3.79 (3H, s), 4.66 (2H, d, *J* = 5.6 Hz), 7.10–7.17 (3H, m), 7.21 (1H, d, *J* = 8.8 Hz), 7.39–7.42 (2H, m), 7.49–7.50 (1H, d, *J* = 2.8 Hz), 8.41 (1H, t, *J* = 5.6 Hz, NH).

4.6.3.24. *N*-(4-Fluorobenzyl)-7-methoxy-2-(piperidin-1-yl)quinazolin-4-amine (85). *N*-(4-Fluorobenzyl)-7-methoxy-2-(piperidin-1-yl)quinazolin-4-amine (**85**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 367.27 (M+1), LCMS: 99.9% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.39–1.49 (4H, m), 1.53–1.61 (2H, m), 3.70–3.73 (4H, m), 3.8 (3H, s), 4.63 (2H, d, J= 5.6 Hz), 6.95 (1H, t, *J* = 7.6 Hz), 7.01 (1H, d, *J* = 6.8 Hz), 7.09–7.14 (2H, m), 7.37–7.40 (2H, m), 7.55 (1H, d, *J* = 6.8 Hz), 8.42 (1H, dd, *J* = 6 Hz, NH).

4.6.3.25. *N*-(4-Fluorobenzyl)-8-methoxy-2-(piperidin-1-yl)quinazolin-4-amine (86). *N*-(4-Fluorobenzyl)-8-methoxy-2-(piperidin-1-yl)quinazolin-4-amine (**86**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 367.25 (M+1), LCMS: 99.9% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.47–1.49 (4H, m), 1.52–1.61 (2H, m), 3.65–3.73 (4H, m), 3.81 (3H, s), 4.62 (2H, d, *J* = 6 Hz), 6.93–7.01 (2H, m), 7.09–7.15 (2H, m), 7.37–7.40 (2H, m), 7.55 (1H, dd, *J* = 6.8 Hz) 8.42 (1H, t , *J* = 5.6 Hz, NH).

N-(4-Fluorobenzyl)-6,7-dimethoxy-2-(piperidin-1-yl)quinazolin-4-amine hydrochloride (**87**) was prepared according to the representative procedure I. MS: ESI-MS, *m*/*z*: 397.2 (M+1); LCMS: 98.6% purity. ^{1}H NMR(400 MHz, DMSO-d_6): δ 1.70–1.49 (6H, br m), 3.81–3.73 (4H, br m), 3.86 (3H, s), 3.89 (3H, s), 4.75 (2H, d, *J* = 5.6 Hz), 7.18 (2H, t, *J* = 8.9 Hz), 7.32 (1H, s), 7.49–7.40 (2H, br m), 7.81 (1H, s), 9.84 (1H, br s), 11.73 (1H, br s).

4.6.3.26. *N*-(4-Fluorobenzyl)-2-(piperidin-1-yl)quinolin-4-amine (88). A mixture of 2,4-dichloroquinoline (0.3 g, 1.5 mmol) and piperidine (3 mL) was heated at 75 °C in a sealed vial for 1.5 h. The mixture was then concentrated under reduced pressure, dissolved in ethyl acetate (40 mL) and washed with water (20 mL) and with brine (20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate in hexane to give 4-chloro-2-(piperidin-1-yl)quinoline (0.207 g, 55.3%). To a solution of this product (0.15 g, 0.6 mmol) and (4-fluorophenyl)methanamine (91.2 mg, 0.7 mmol) in toluene (5 mL) was added $Pd_2(dba)_3$ (27.8 mg, 0.03 mmol), BINAP (37 mg, 0.06 mmol) and *t*-BuONa (116.8 mg, 1.21 mmol) under nitrogen atmosphere. The reaction mixture was refluxed for 16 h then filtered through a pad of Celite, rinsing with ethyl acetate. The filtrate was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography to afford product (62 mg, 30.3% yield). MS: ESI-MS, *m*/*z*: 336.19 (M+1), LCMS: 99.1% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.41–1.44 (4H, m), 1.52–1.57 (2H, m), 3.46–3.53 (4H, m), 4.50 (2H, d, *J* = 5.6 Hz), 5.86 (1H, s), 7.05–7.16 (3H, m), 7.37 (2H, t, *J* = 8 Hz), 7.41–7.45 (3H, m), 7.98 (1H, d, *J* = 8.4 Hz).

4.6.3.27. 2-(4-Fluorophenyl)-2-(2-(piperidin-1-yl)quinolin-4-ylamino)ethanol (89). 2-(4-Fluorophenyl)-2-(2-(piperidin-1-yl)quinolin-4-ylamino)ethanol (**89**) was prepared according to procedure described for **88** above but employing 2-amino-2-(4-fluorophenyl)ethanol for amination. MS: ESI-MS, *m*/*z*: 366.22 (M+1), LCMS: 99.1% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.35–1.42 (4H, m), 1.50–1.55 (2H, m), 3.37–3.49 (4H, m), 3.67–3.73 (1H, m), 3.78–3.84 (1H, m), 4.67 (1H, t, J = 6.4 Hz), 5.09 (1H, t, J = 6 Hz), 5.74 (1H, s), 6.78 (1H, d, J = 6 Hz), 7.10–7.15 (3H, m), 7.35–7.42 (2H, m), 7.48–7.50 (2H, m), 8.10 (1H, d, J = 8 Hz).

4.6.3.28. 2-(4-Fluorophenyl)-2-(2-(piperidin-1-yl)quinolin-4-ylamino)acetic acid (90). 2-(4-Fluorophenyl)-2-(2-(piperidin-1-yl) quinolin-4-ylamino)acetic acid (**90**) was prepared according to procedure described for **88** above but employing 2-amino-2-(4-fluorophenyl)acetic acid for amination. MS: ESI-MS, *m*/*z*: 380.18 (M+1), LCMS: 99.7% purity. ^{1}H NMR: (400 MHz, DMSO-d_6+TFA): δ 1.56–1.59 (4H, m), 1.61–1.64 (2H, m), 3.62–3.68 (4H, m), 5.91 (1H, d, J = 7.2 Hz), 5.97 (1H, s), 7.18 (2H, t, J = 8.8 Hz), 7.43 (1H, t, J = 7.6 Hz), 7.63–7.68 (2H, m), 7.71 (1H, d, J = 7.2 Hz), 7.81 (1H, d, J = 8.4 Hz), 8.27 (1H, d, J = 7.2 Hz,), 8.37 (1H, d, J = 8 Hz), 11.52 (1H, s).

4.6.3.29. *N*-(4-Fluorobenzyl)-5-(piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidin-7-amine (94). *N*-(4-Fluorobenzyl)-5-(piperidin-1-yl) pyrazolo[1,5-*a*]pyrimidin-7-amine (**94**) was prepared from 5,7-dichloropyrazolo[1,5-*a*]pyrimidine (93: X = C, Y = N)[11] according to representative procedure I with 110 °C and 180 °C as respective temperature conditions for each reaction step. MS: ESI-MS, *m*/*z*: 326.24 (M+1); HRMS (ESMS) calcd for $C_{18}H_{20}FN_5$, 326.1776; found, 326.1779 (M+1). LCMS: 99.7% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.42–1.46 (4H, m), 1.54–1.57 (2H, m), 3.46–3.50 (4H, m), 4.53 (2H, d, J = 6.4 Hz), 5.50 (1H, s), 5.87 (1H, d, J = 1.6 Hz), 7.14 (2H, t, J = 8.8 Hz), 7.44–7.47(2H, m), 7.77 (1H, d, J = 1.6 Hz), 7.96 (1H, t, J = 6.4 Hz).

4.6.3.30. *N*-(4-Fluorobenzyl)-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (95). *N*-(4-Fluorobenzyl)-5-(piperidin-1-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (**95**) was prepared from 5,7-dichloro-[1,2,4]triazolo[1,5-*a*]pyrimidine (**93**: X = N, Y = N)[11] according to representative procedure I with 110 °C and 180 °C as respective temperature conditions for each reaction step. MS: ESI-MS, *m*/*z*: 327.28 (M+1); HRMS (ESMS) calcd for $C_{17}H_{19}FN_6$, 327.1728; found, 327.1730 (M+1). LCMS: 98.7% purity. ^{1}H NMR: (400 MHz, DMSO-d_6): δ 1.43–1.47 (4H, m), 1.54–1.59 (2H, m), 3.54–3.58 (4H, m), 4.55 (2H, d, J = 6 Hz), 5.63 (1H, s), 7.15 (2H, t, 8.4 Hz), 7.44–7.47 (2H, m), 8.08 (1H, s), 8.21 (1H, t, J = 6 Hz).

4.6.3.31. 1-(4-Fluorobenzyl)-4-(piperidin-1-yl)-1*H*-imidazo[4,5-*c*]quinoline (103). 1-(4-Fluorobenzyl)-4-(piperidin-1-yl)-1*H*-imidazo[4,5-*c*]quinoline (**103**) was prepared from 3-nitroquinolin-4-ol (96) in 25 mg quantity according to literature[12] procedure. MS: ESI-MS, *m*/*z*: 361.20 (M+1); HRMS (ESMS) calcd for $C_{22}H_{21}FN_4$, 361.1823; found, 361.1825 (M+1). LCMS: 98.9% purity. ^{1}H NMR: (300 MHz, DMSO-d_6): δ 1.73–1.86 (6H, m), 4.33–4.48 (4H, m), 6.01 (2H, s), 7.17–7.21 (2H, m), 7.21–7.23 (2H, m), 7.40 (1H, t, J = 7.9 Hz), 7.66 (1H, t, J = 7.9 Hz), 8.0 (1H, d, J = 8.3 Hz), 8.08 (1H, d, J = 8.3 Hz), 8.69 (1H, s).

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