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Design, synthesis and biological evaluation of novel triazole, urea and thiourea derivatives of quinoline against *Mycobacterium tuberculosis* ☆

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ABSTRACT

A new series of 20 quinoline derivatives possessing triazolo, ureido and thioureido substituents have been synthesized and their antimycobacterial properties have been evaluated. Compounds **10**, **22** and **24** inhibited *Mycobacterium tuberculosis* H37Rv up to 96%, 98% and 94% respectively, at a fixed concentration of 6.25 μg/mL. Minimum inhibitory concentration of 3.125 μg/mL was obtained for compound **10** and **24**, while for compound **22** it was 6.25 μg/mL. Molecular docking calculations suggest critical hydrogen bonding and electrostatic interactions between polar functional groups (such as quinoline-nitrogen, urea-carbonyl and hydroxyl) of anti-mycobacterial (anti-TB) compounds and amino acids (Arg186 and Glu61) of ATP-synthase of *M. tuberculosis*, could be the probable reason for observed anti-mycobacterial action.

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1. Introduction

Tuberculosis is the leading cause of infectious disease mortality in the world.[1] Approximately 1.86 billion people, that is, 32%, of the world's population is infected[2] with *Mycobacterium tuberculosis* (MTB). World health organization (WHO) estimates about 8 million new active cases of tuberculosis (TB) per year and nearly 2 million deaths each year,[2,3] that is, 5000 people every day.[4] HIV positive patients are more susceptible to MTB with a 50-fold risk increase over HIV negative patients.[5,6] Similarly, the rate of progression of latent TB to active disease in HIV positive patients is higher than non-HIV infected individuals. An additional concern is the rise in multi drug resistance (MDR).[7–10] Increasing incidence of MTB strains resistant to one or more first line TB drugs such as isoniazid,[11] pyrazinamide[12] and rifampicin[13] has recently intensified the need to develop new and more efficient drugs for the treatment of mycobacterial infections.

We have previously reported the synthesis of novel quinoline derivatives[14] based on molecular dissection (NE and SE hemisphere modifications) of the diarylquinoline R207910 (DARQ, Fig. 1), which exhibited good antimycobacterial activity. DARQ is targeted to the proton pump of bacterial ATP synthase and have inhibited mycobacterial growth very effectively.[15] Our initial results showed that NE (hydroxyl and *N,N'* dimethyl amine) and SE (naphthyl) parts are critical for antimycobacterial activity of DARQ. Different amine substitutions at NE hemisphere have displayed good antimycobacterial activity.[14] Thus, continuing to develop the structure activity relationship (SAR), we herein report modification of the SW hemisphere of DARQ by systematically analyzing the C2 and C6 substituents of quinoline moiety (Fig. 1).

The bromide group at C6 position, *para* to the quinoline nitrogen, is chemically inactive, but could be involved in interactions with protein.[14] Replacing bromo group, with polar groups could lead to good anti-TB activity, hence we displaced it with polar

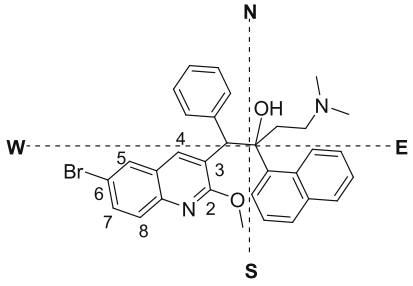

Figure 1. Four structural hemispheres of R207910 (DARQ).

Abbreviations: ATP, adenosine triphosphate; DMSO, dimethyl sulfoxide; TB, tuberculosis; WHO, World Health Organization; HIV, human immunodeficiency virus; DARQ, diarylquinoline; MTB, *Mycobacterium tuberculosis*; MDR, multi drug resistance; NE, north-east; SE, south-east; NW, north-west; SW, south-west; MIC, minimum inhibitory concentration; SAR, structure–activity relationship.

☆ All amino acid numbering corresponds to subunits A and C of *Mycobacterium tuberculosis* ATP synthase.

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groups such as ureas/thioureas and triazoles, which are also known to possess anti-mycobacterial activity.[16–20] A set of 5′-thiourea-substituted α-thymidine derivatives[16] and analogues of isoxyl thioureas[17] have shown good inhibitory activity on *Mycobacterium bovis* and *M. tuberculosis* strains. Several triazole-thiourea derivatives including fluorinated triazole pyrimidine carboxylic acid derivatives,[18,19] furanosyl-thiourea derivatives,[20] and uridinyl branched peptide ureas[21] have shown potential anti-TB therapeutic activity. With these changes synergistic effect against TB could also be expected. Secondly, we replaced the methoxy group at C2 with fluoro-aryloxy group having heterocyclic amine; which enabled us to identify the importance of C2 substituents. We expected at the outset that these modifications at C2 and C6 will alter the biological activity of the compounds and may help in developing structure–activity relationships.

2. Results

2.1. Chemistry

2.1.1. Synthesis of triazolines (10–13), ureas and thioureas (14–21)

The synthesis was started with reaction of 4-nitroaniline (**1**) with hydrocinnamoyl chloride to obtain the corresponding amide **2** in good yield (84%).[22] Treatment of the amide **2** with freshly prepared Vilsmier reagent[23] under cetyltrimethylammonium bromide condition[24] gave **3**. Nucleophilic displacement of chloro group at C2 in **3** with 1-(5-fluoro-2-hydroxy-phenyl)-ethanone[25] in dimethyl sulfoxide using potassium carbonate as a base gave the C2 aryloxy derivative **4** (25%). The reduction of the nitro group at C6 in **4** by hydrogenation using 10% palladium on charcoal gave amine **5** (86%). The amine **5** was converted to the corresponding azide **6** (56%) by diazotization with hydrochloric acid and sodium nitrite followed by displacement with sodium azide.[26] 'Click chemistry'[27] reaction was performed on azide **6** to obtain the corresponding 1,2,3-triazole derivative **7** (82%), which was subjected for reduction using sodium borohydride to give the alcohol **8** in good yield (91%). Conversion of the alcohol **8** to the chloride **9** (60%) was carried out by treatment with thionyl chloride, which was then nucleophilically substituted by a series of amines (R_2H) to give compounds **10**–**13** (19–60%, Scheme 1).

We initiated the synthesis of target compounds **22–29** from amine **5**. Amine **5** was treated with a series of isocyanates (R_3NCO) and isothiocyanates (R_3NCS) using pyridine as a base to give a series of ureas **14–17** and thioureas **18–21** in good yields (47–97%). These ureas and thioureas (**14**–**21**) were reduced by sodium borohydride to get target compounds **22–29** in moderate to good yields (40–99%).

2.1.2. Synthesis of amines 31–38

Synthesis of these target compounds was carried out as shown in Scheme 2. The synthesis started with bromination at the α-position[28] of the ketone moiety of the compound **4** to give **30** in excellent yield (95%). The nucleophilic substitution of the bromine in **30** with appropriate amines gave the series of compounds. These compounds were found to be unstable and therefore, they were used in the next step without further purification. Reduction of these compounds using sodium borohydride gave the corresponding amino alcohols **31**–**38** (10–30%).

2.2. Microbiology

All compounds **10**–**13**, **22–29**, **31**–**38** and drug references were dissolved in DMSO at a concentration of 6.25 μg/mL and stored at ~4 °C until used.

2.3. Antimycobacterial activity

Three different series of compounds **10**–**13**, **22**–**29** and **31**–**38** were synthesized and screened against *M. tuberculosis* H37Rv (ATCC 27294) in triplicate at the concentration of 6.25 μg/mL by BACTEC 460 radiometric methods.[29,30] Inhibitory effect of compounds is shown in Table 1. Good antimycobacterial activity was obtained for the compounds **10**, **22** and **24**. Graphs of growth index on the day basis for compounds **10**, **22** and **24** in comparison to isoniazid (Figs. 2 and 3) were plotted. For compounds **10** and **22**, Figure 2 reveals that the mycobacterial load never increased from day 1 to day 9. From graphs it is clear that the activity of compounds **10**, **22** and **24** is comparable to the standard drug isoniazid at concentration 6.25 μg/mL and under identical experimental conditions. The percentage (%) growth inhibition plot (Fig. 3) suggests that compounds **10**, **22** and **24** are able to inhibit the *M. tuberculosis* H37Rv 96% (±1.34), 98% (±1.30) and 94% (±2.06), respectively, compared to isoniazid (98.8%, Table S1).

Based on the primary growth inhibition activity, compounds **10**, **22**, **24** were selected to determine the minimum inhibitory concentration (MIC). The compounds were dissolved in DMSO and diluted twofold to obtain five serial dilutions (6.25, 3.125, 1.56, 0.78 and 0.39 μg/mL) of each compound. For compounds **10** and **24**, MIC was found to be 3.125 μg/mL and for compound **22** MIC was 6.25 μg/mL (Table 2).

2.4. Cytotoxicity

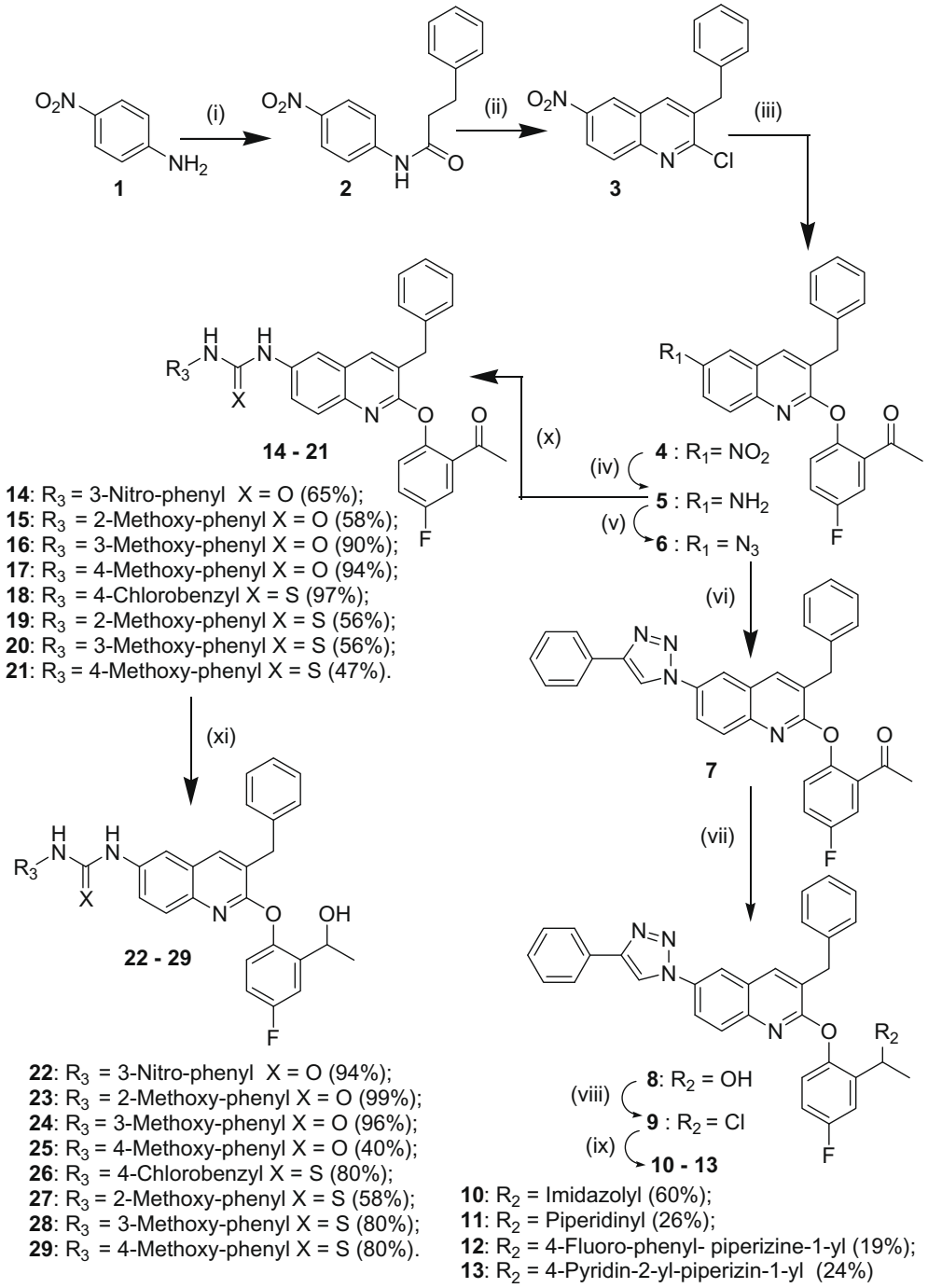
The most active compounds (**10**, **22** and **24**) of our data set were also subjected to cytotoxicity assay in two different concentrations at 1 and 10 μg/100μL. Table 3 lists the percentages of cell viability after 24 and 72 h of addition of compounds. Encouraging results were obtained to pursue further work.

2.5. Molecular docking

The intermolecular energy of protein-ligand complexes obtained from docking calculations for selected compounds are listed in Table 4. For the compounds **10–13,** intermolecular energy data is in coherence with the biological activity data, that is, intermolecular energies of active compounds (**10** and **11**) are considerably lower than less active compounds (**12** and **13**). For compounds **22–25, 27** and **29**, this was not the case. However, forcefield based interaction energy between protein and ligand was found to be lower for compounds **22**, **24** and **25** compared to **23**, **27** and **29** (Table 5). Electrostatic contribution of intermolecular energy was found critical for relatively more active compounds **31** and **33**, than compounds **36** and **37** (Table 4).

3. Discussion

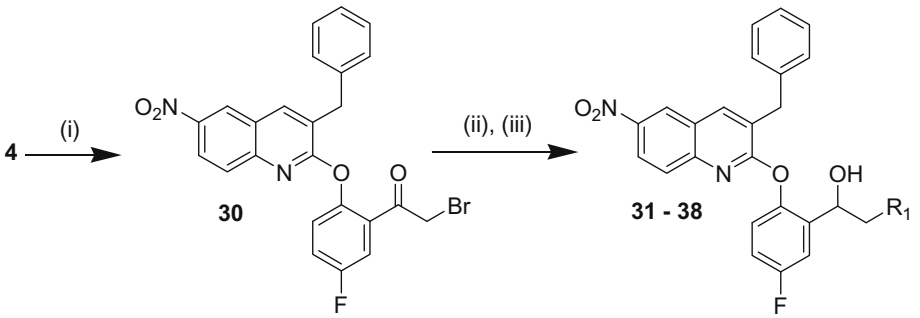
For compounds **10 –13,** the steric factor apparently plays an important role in the activity profile. As the steric bulk of the amines decreases, the antimycobacterial activity increases. For compounds **12** and **13**, the piperazine moiety with a 4-fluoro phenyl and a 2-pyridyl substituent, respectively, did not show any significant antimycobacterial activity. The reason could be steric factor as the polar atoms are buried between bulky non-polar aromatic parts. The replacement of aryl piperazine with smaller imidazole (**10**) and piperidine (**11**) has led to better inhibition profile. It is likely that compounds **10** and **11** with smaller substituents interact relatively better with the binding site. Among the series of ureas and thioureas, urea derivatives (**22**–**25**) have shown good activity compared to those of thioureas (**26**–**29**). The major difference in the anti-TB activity between the ureas (**22**–**25**) and thioureas (**26**–**29**) could be attributed to two major stereoelectronic



Scheme 1. Reagents and conditions: (i) hydrocinnamoyl chloride (1 equiv), Et_3N (1.5 equiv), dichloromethane, rt, 4 h; 84% (ii) DMF–$POCl_3$ (1:1), CTAB (0.3 mol %), acetonitrile, 80 °C, 16 h; 31% (iii) 1-(5-fluoro-2-hydroxy-phenyl)-ethanone (1.1 equiv), K_2CO_3 (1.2 equiv), DMSO, rt, 12 h; 25% (iv) H_2, Pd/C (10% w/w), ethyl acetate, rt, 4 h; 86% (v) $NaNO_2$ (1.4 equiv), 50% aq HCl, NaN_3 (2.8 equiv), NaOAc (5.6 equiv), water, 5 °C–rt, 1 h; 56% (vi) phenyl acetylene (1 equiv), CuI (1 equiv), diisopropylethylamine (3 equiv), acetonitrile, 0 °C, 10 min followed by rt, 4 h; 82% (vii) $NaBH_4$ (1 equiv), EtOH–THF (1:1), rt, 2 h; 91% (viii) $SOCl_2$ (1.3 equiv), acetonitrile, rt, 1 h; 60% (ix) R_2H (7.3 equiv), Et_3N (7.3 equiv), acetonitrile, reflux, sealed tube, 12 h; 19–60% (x) R_3NCX (1 equiv), pyridine (0.5 equiv), dichloromethane, rt, 12 h; 47–97% (xi) $NaBH_4$ (2.5 equiv), EtOH–THF (1:1), rt, 2 h; 40–99%.

factors: first, electronegativity of sulfur being less than that of oxygen, and therefore thioureas could not recruit required dipolar interaction for binding and, secondly, relative larger size of sulfur could alter the binding affinity of thioureas in the interacting site(s).

Compound **22** bearing an electron withdrawing group (NO_2) at *meta* position has shown very high activity (98% inhibition). Replacement of electron-withdrawing group (NO_2) with an electron donating group (OCH_3) in compound **24**, resulted in comparable activity and inhibition profile. However, in the case of compound **23** the inhibitory activity was completely abolished when the methoxy group was shifted from the *meta* to *ortho* position. Similarly, activity was found to be lower when methoxy group was moved to *para* position in compound **25**. The effect of substituent's position on the aromatic ring could be a key factor for its binding to the protein rather than the difference in func-



31: R_1 = Morpholinyl (15%); **32**: R_1 = Piperidinyl (15%);
33: R_1 = Imidazolyl (14%); **34**: R_1 = Pyrazolyl (16%);
35: R_1 = 3- (3-Methoxy-phenyl) pyrazolyl (27%);
36: R_1 = 3- (4-Methoxy-phenyl) pyrazolyl (30%);
37: R_1 = 3-(4-Trifluoromethyl phenyl)-pyrazolyl (15%);
38: R_1 = 3- (3-Chlorophenyl) pyrazolyl (10%)

Scheme 2. Reagents and conditions: (i) Br_2 (1.1 equiv), chloroform, rt, 15 h; 95% (ii) R_1H (2 equiv), DMF, rt, 15 min (for **31**–**33**), 48 h (for **34**–**38**); (iii) $NaBH_4$ (1.1 equiv), EtOH–THF (1:1), rt, 15 min, 10–30%.

Table 1
In vitro activity (% inhibition) of compounds **10**–**13**, **22**–**29** and **31**–**38** against *M. tuberculosis* H37Rv (at concentration 6.25 μg/mL)

Compd No.	% Inhibition[a]	Compd No.	% Inhibition[a]
10	96	**29**	27
11	81	**31**	29
12	20	**32**	20
13	29	**33**	58
22	98	**34**	53
23	8	**35**	7
24	94	**36**	5
25	25	**37**	6
26	37	**38**	0
27	14	Isoniazid	99
28	22		

[a] Values are means of triplicate.

tional group. The effect on the anti-TB activity of replacing urea and thiourea moiety with nitro group was also examined by synthesizing various heterocyclic secondary amines and substituted pyrazoles (**31**–**38**). Low inhibitory activity was observed when heterocyclic electron-rich amines (**33**, **34**) were replaced with saturated heterocyclic amine (**31**–**32**) or with substituted pyrazoles (**35**–**38**). Compounds **33** and **34** inhibited the growth of *M. tuberculosis* (58% and 53% inhibition respectively), suggesting that potency improvements could be achieved by extending the electron-rich aromatic structures, thus increasing the potential for hydrophobic interaction between the inhibitors and the target protein.

Figure 2 shows the day-wise growth index of *M. tuberculosis* H37Rv in the presence of compounds **10**, **22**, **24** and isoniazid under identical conditions. The growth index of compounds **10** and **24** for 11 days and of compound **22** for 9 days was used to examine the antimycobacterial activity of the compounds at 6.25 μg/mL concentration. This study clearly shows that there was no growth in *M. tuberculosis* (HRv37) up to 11 days, suggesting bactericidal nature of these compounds. Compound **22** demonstrates better activity profile than those of **10** and **24** as it can clear the mycobacterial growth within 4 days by maintaining >97% inhibition throughout the study. Figure 2 (inset) also reveals that compound **22** maintains consistent inhibition profile comparable to isoniazid, under identical experimental conditions.

3.1. Molecular docking

We have performed docking studies on selected ligand compounds from our data set. Compounds were docked to the previously discussed putative binding site of the ATP-synthase of *M. tuberculosis*.[31,14] The binding site comprises of some highly conserved polar and non-polar amino acid residues, including charged Arg186 (subunit A) and Glu61 (subunit C). We assume that these diarylquinoline based compounds, however, relatively large sized, binds in the same cavity located near the critical amino acid residues; Arg186 and Glu61. These compounds bind the protein in different structural orientations as well as with different binding affinities. We discuss here the energetics, structural analysis and possible mode of action of individual protein–ligand docking cases.

Because of the structural differences in compounds of our data set, we have classified them into three subclasses, that is, compounds: **10**–**13**, **22**–**29** and **31**–**38**. We have selected some active and less active compounds from each subclass and performed the docking calculations.

The compounds were docked according to the methodology described in the theoretical methods section (Supplementary data). The intermolecular energies of compounds **10** and **11** are considerably lower than **12** and **13**, in agreement with the antimycobacterial activity data (Table 4). The presence of bulky aromatic substituent in compounds **12** and **13** allows less effective binding in the site, resulting in high van der Waals energy (see below) (Table 4). Visual inspection of the docked complexes show that all four ligand molecules docked in a similar pose. The fluorophenyl-R_2 moiety in compounds **10** and **11** fits into the cavity made by Phe65, Tyr64 and Leu68; which are highly conserved residues of subunit C [see Fig. 4, Panel: 4(a)] and seems to form effective van der Waals interaction. This was not observed for compounds **12** and **13**, apparently due to their larger bulk, which could have led to their higher van der Waals energy. Furthermore, it was revealed that quinoline nitrogen and Arg186 could interact through a hydrogen bond: distance between quinoline–nitrogen and Arginine–nitrogen = 3.86 Å [Fig. 4, Panel: 4(a)]. This is in agreement with our previous study[14] where we have identified that the interactions between different functional groups of ligand and Arg186 could be a plausible reason for their activity. Similarly, this interaction could limit the flexibility of Arg186, which is apparently required for the efficient functioning of the enzyme.[32] On the contrary, such an interaction seems possible in all four docking cases, and thus does not allow us to discriminate between the active (**10** and **11**) and less active (**12** and **13**) compounds.

The compounds **22**, **23**, **24**, **25**, **27** and **29** were also docked into the same putative binding site. The presence of planar amide moiety (urea) in some of the compounds results in the extended conformation of these compounds. Intermolecular energies as

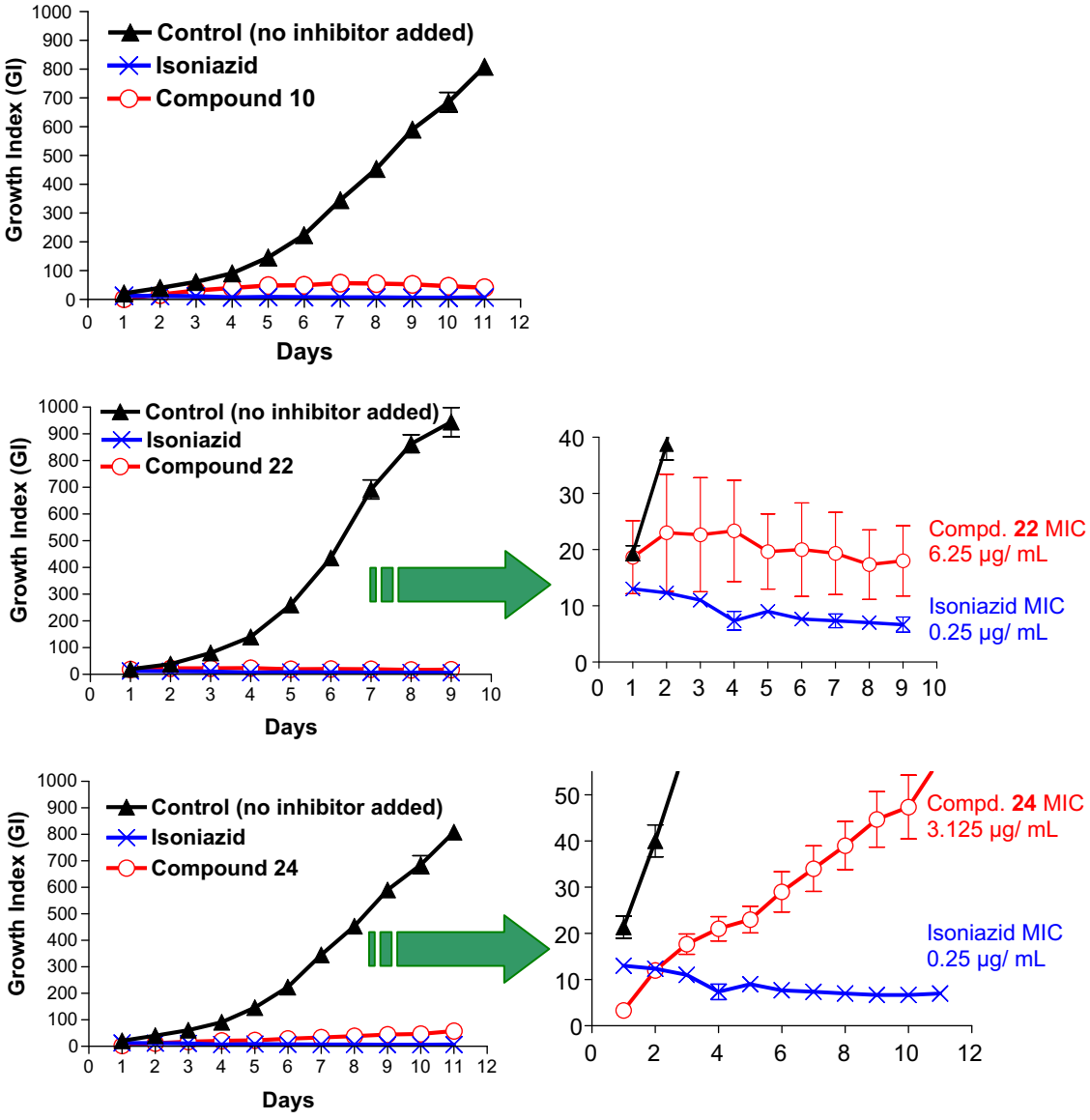


Figure 2. Day-wise growth index of MTB after single-dose administration at the day-one of infection.

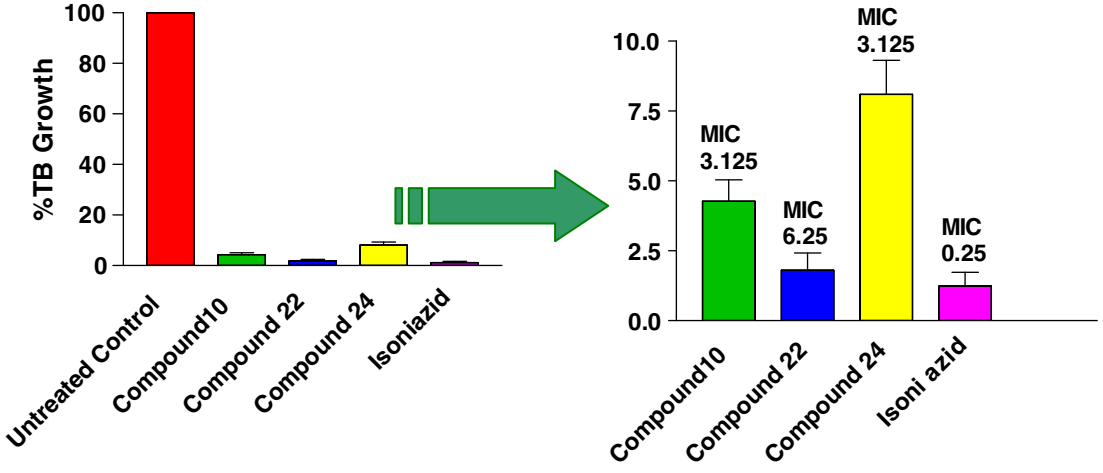


Figure 3. % TB growth under influence of untreated control, compounds (**10**, **22** and **24**) and Isoniazid.

Table 2
MIC of compounds against *M. tuberculosis* H37Rv

Compound	MIC (μg/mL)
10	3.125
22	6.25
24	3.125

Table 3
Cytotoxic effects of tested compounds on murine macrophage cells, 24 h and 72 h after treatment

Compound	10 μg/100 μL		1 μg/100 μL	
	24 h	72 h	24 h	72 h
10	88%	58%	100%	61%
22	87%	53%	91%	55%
24	79%	63%	100%	100%

Table 4
Intermolecular energies of docked complexes in kcal/mol

Compound number	IE[a]	vdW[b]	Elec[c]
10	−7.9	−7.78	−0.12
11	−8.5	−8.03	−0.47
12	−1.35	−1.02	−0.33
13	−5.61	−5.23	−0.38
22	−6.82	−7.23	0.41
23	−8.99	−8.98	−0.01
24	−8.88	−9.02	0.14
25	−9.5	−9.64	0.14
27	−11.78	−11.81	0.04
29	−10.01	−9.94	−0.07
31	−10.53	−9.39	−1.14
33	−9.65	−9.94	0.3
36	−10.57	−11.23	0.65
37	−11.95	−12.57	0.62

[a] IE: Intermolecular energy.
[b] vdw: van der Waals, hydrogen bond and desolvation energy.
[c] Elec: Electrostatic energy.

Table 5
Protein–ligand interaction energy for subclass compounds; **22**–**25**, **27** and **29** in kcal/mol

Compound number	vdW[a]	Elec[b]	Total[c]
22	−77.87	−48.37	−126.25
23	−74.71	−17.64	−92.36
24	−72.61	−23.18	−95.79
25	−71.27	−25.11	−96.39
27	−68.41	−0.935	−69.35
29	−70.01	−7.61	−77.63

[a] vdW: van der Waals energy.
[b] Elec: Electrostatic energy.
[c] Total: Total interaction energy.

obtained from docking calculations were in disagreement with the antimycobacterial biological data (Table 4). Thus, we performed energy minimization of docked complexes and calculated the protein–ligand interaction energies. Consequently, it was observed that compounds (**22**, **24** and **25**) have better interactions to protein compared to compounds **23**, **27** and **29** (Table 5). On visual inspection of the minimized complex of compound **22**, presence of two hydrogen bonds was revealed (distance between carboxyl oxygen of Glu61 of subunit C and hydroxyl of ligand = 2.55 Å; and carbonyl oxygen of Ala24 of subunit C and amide nitrogen of ligand = 2.89 Å) [Fig. 4, Panel: 4(b)]. Such an interaction could be responsible for the antimycobacterial activity of this compound. Glu61 is responsible for proton translocation in the enzyme,[32] interaction of a ligand with it could hamper proton transfer. The lowest energy docked conformation of similar compounds **23**, **24** and **25** were found slightly different. In the case of compounds **24** and **25**, hydrogen-bonding interaction was observed between carbonyl oxygen of urea moiety of the compound and protonated Glu61 (subunit C) (Graphical abstract). The *ortho*-methoxy substituted compound **23** did not reveal any hydrogen bonding interactions with protein upon energy minimization. Lowest energy docking pose of compound **27** was also found to be very different from the other subclass compounds and energetics on refinement suggests lacking electrostatic interactions is responsible for its relatively poorer activity. Examination of refined docked complex of compound **29** reveals no interactions with critical residues.

The biological activity of compounds **31**, **33**, **36** and **37** is relatively less variable, analogously intermolecular energies from docking calculations do not discriminate between active and less active compounds. However, the bulkier compounds **36** and **37** bind the protein with higher electrostatic energy (Table 4) and in relatively different poses compared to the active compounds **31** and **33**. Visual inspection of docked complexes of compounds **31** and **33** revealed similar poses of ligands in both the cases with the respective morpholine and imidazole/hydroxyl functional groups, and they were found to be in the vicinity of Arg186 [Fig. 4, Panel: 4(c)], such that H-bonding possibility cannot be completely denied.

Based on docking calculations, we propose that presence of different polar functional groups in diarylquinoline class of compounds would let them bind in different poses in the binding site. Interactions with the critical residues of subunit A and C, along with auxiliary interactions are responsible for biological activity.

4. Conclusion

As a part of our ongoing SAR for diarylquinoline class of compounds, we have identified functional groups that are critical for activity. On the basis of the preliminary biological results through in vitro BACTEC–460 method[29,30] compound **10**, **22** and **24** have shown a great potential to serve as promising candidates for further development of antimycobacterial agents with improved potency. Docking calculations and analysis have shed light on our knowledge of pharmacophoric contribution from different hemispheres of DARQ and their importance.

5. Experimental

5.1. General methods

All chemicals and reagents used were of reagent grade. Purification and drying of reagents and solvents was carried out according to literature procedure.[33] Thin layer chromatographic analyses were performed on E-Merck 60 F 254 precoated aluminum thin layer chromatographic plates. All air-sensitive reactions were carried out under nitrogen atmosphere. Melting points were determined on a Büchi melting point B-540 instrument and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Biospin 400 MHz spectrometer in the indicated solvents (TMS as an internal standard). The values of chemical shifts are expressed in ppm and the coupling constants (*J*) in hertz (Hz). Mass spectra were recorded in API 2000 LC/MS/MS system spectrometer and the IR spectra were recorded on Perkin Elmer FT-IR spectrometer.

5.1.1. *N*-(4-Nitro phenyl)-3-phenyl propionamide (2)

Hydrocinnamoyl chloride (21.5 ml, 144.9 mmol) was added to a mixture of 4-nitroanline (**1**, 21.0 g, 144.9 mmol) and triethylamine (30.0 g, 217.4 mmol) in dry dichloromethane (400 mL) at 0 °C and

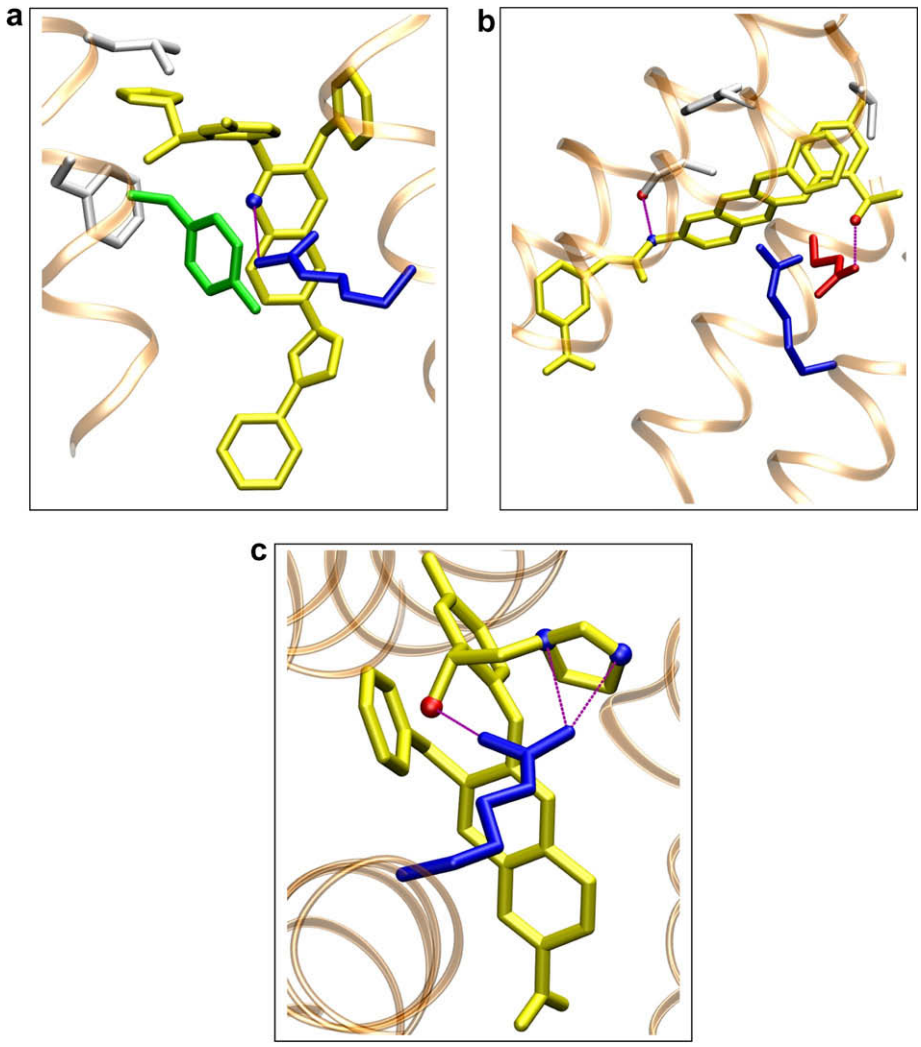


Figure 4. Docked compounds; **10** [Panel: 4(a)], **22** [Panel: 4(b)] and **31** [Panel: 4(c)] are shown in yellow licorice. Acidic, basic, polar and non-polar residues are shown in red, blue, green and white, respectively. Possible hydrogen bonding interactions are shown with purple lines. Transmembrane helices shown with orange ribbon representation. Nitrogen and Oxygen as blue and red spheres. Hydrogens are omitted for clarity.

mixture was stirred at room temperature for 12 h. The reaction was poured into ice-water and extracted with dichloromethane (500 mL). The organic layer was separated, washed with 10% aqueous solution of hydrochloric acid, saturated sodium bicarbonate solution, water and brine. Organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to give the crude product, which was triturated with diethyl ether to furnish the pure product **2** (33.0 g, 84%) as a yellow solid, mp 117–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.72 (t, J = 7.6 Hz, 2H), 3.05 (t, J = 7.5 Hz, 2H), 7.19–7.33 (m, 5H), 7.58–7.65 (m, 2H, 1H, D_2O-exchangeable), 8.15 (dd, J = 7.1, 1.8 Hz, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 31.1, 39.3, 119.0, 125.0, 126.5, 128.2, 128.6, 128.9, 140.0, 143.2, 143.7, 171.1. $[M+H]^+ = m/e$ 269.

5.1.2. 3-Benzyl-6-nitro-2-chloro-quinoline (3)

Phosphorus oxychloride (69 ml, 740 mmol) was added dropwise to *N,N*-dimethylformamide (57.0 ml, 736 mmol) at 5 °C, the mixture was allowed to warm up to room temperature and stirred for 20 min. The above reagent was added to a suspension of compound **2** (10.0 g, 37.03 mmol) and cetyltrimethylammonium bromide (CTAB, 0.04 g, 0.10 mmol) in acetonitrile (30 mL) at 5 °C. The reaction mixture was heated at 80 °C for 16 h, cooled to room temperature, poured into 400 ml of 3% hypo solution at 0 °C and extracted with dichloromethane. The organic layer was washed with water until the water extracts became neutral to pH paper. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (100–200 mesh, eluent: 3% ethyl acetate in hexane) to afford compound **3** (3.40 g, 31%) as a pale yellow crystalline solid, mp 159–161 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.26 (s, 2H), 7.21–7.28 (m, 2H), 7.29–7.35 (m, 1H), 7.36–7.43 (m, 2H), 7.89 (s, 1H), 8.11 (d, J = 9.3 Hz, 1H), 8.43 (dd, J = 9.1, 2.5 Hz, 1H), 8.65 (d, J = 2.4 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 39.0, 123.2, 123.8, 126.2, 127.1, 128.9, 129.2, 129.8, 135.8, 136.8, 139.1, 145.5, 148.2, 155.3. $[M+H]^+ = m/e$ 299.

5.1.3. 1-[2-(3-Benzyl-6-nitro-quinolin-2-yloxy)-5-fluoro-phenyl]-ethanone (4)

A mixture of **3** (2.0 g, 6.71 mmol), 1-(5-fluoro-2-hydroxy-phenyl)-ethanone (1.13 g, 7.38 mmol) and potassium carbonate (1.11 g, 8.05 mmol) in dry dimethylsulfoxide was stirred at room temperature for 12 h. The reaction was quenched by adding ice and extracted with ethyl acetate (100 mL × 3 times). The organic layer was washed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The

crude mixture was purified on column chromatography (silica gel 100–200 mesh, eluent: 10% ethyl acetate in hexane) to afford **4** (0.70 g, 25%) as a light green colored solid, mp 143–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 3H), 4.27 (s, 2H), 7.04 (dd, J = 8.9, 4.5 Hz, 1H), 7.22–7.40 (m, 6H), 7.54 (dd, J = 8.6, 3.1 Hz, 1H), 7.68 (d, J = 9.2 Hz, 1H), 7.95 (s, 1H), 8.29 (dd, J = 9.2, 2.5 Hz, 1H), 8.63 (d, J = 2.5 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 29.5, 36.3, 116.1, 116.4, 120.0, 120.2, 122.8, 123.6, 124.9, 125.4, 125.5, 126.9, 128.2, 128.5, 128.8, 129.3, 133.2, 133.3, 137.7, 139.5, 144.3, 147.3, 147.4, 147.8, 158.4, 160.8, 162.4, 196.7. $[M+H]^+$ = m/e 417.

5.1.4. 1-[2-(6-Amino-3-benzyl-quinolin-2-yloxy)-5-fluoro-phenyl]-ethanone (5)

A mixture of **4** (0.30 g, 0.72 mmol) and Pd/C (0.03 g, 10% w/w) in ethyl acetate (10 mL) was stirred under hydrogen balloon pressure at room temperature for 4 h. The mixture was filtered through celite and the filtrate was concentrated under reduced pressure. The buff colored solid obtained was triturated with hexane and dried to afford compound **5** (0.24 g, 86%) as light green colored solid, mp 89–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (s, 3H), 3.81 (bs, 2H, D_2O-exchangeable), 4.17 (s, 2H), 6.85 (d, J = 2.5 Hz, 1H), 6.92 (dd, J = 8.9, 4.5 Hz, 1H), 6.98 (dd, J = 8.9, 2.5 Hz, 1H), 7.12–7.18 (m, 1H), 7.20–7.33 (m, 5H), 7.46 (d, J = 8.9 Hz, 1H), 7.51 (dd, J = 8.9, 3.2 Hz, 1H), 7.68 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 30.0, 36.6, 107.9, 115.6, 115.8, 119.8, 120.0, 120.7, 124.7, 124.8, 125.6, 126.4, 127.5, 128.3, 128.50, 128.54, 129.1, 133.3, 133.4, 137.1, 139.0, 139.4, 143.6, 149.08, 149.10, 157.7, 157.8, 160.2, 197.6. $[M+H]^+$ = m/e 387.

5.1.5. 1-[2-(6-Azido-3-benzyl-quinolin-2-yloxy)-5-fluoro-phenyl]-ethanone (6)

To a solution of **5** (0.20 g, 0.6 mmol) in concentrated hydrochloric acid (0.3 mL) was added a solution of sodium nitrite (0.06 g, 0.84 mmol) in water (0.3 mL), while maintaining the temperature below 5 °C. The mixture was stirred for 5–10 min, this solution was added drop wise to a solution of sodium azide (0.11 g, 1.68 mmol) and sodium acetate (0.28 g, 3.36 mmol) in water (2 mL) and further stirred for 1 h at room temperature. The sticky solid was dissolved in dichloromethane (50 mL × 3 times). The organic layer was dried over anhydrous sodium sulfate, filtered, concentrated and dried under vacuum. The gray colored solid obtained was washed with diethyl ether to afford compound **6** (0.15 g, 56%), mp 127–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (s, 3H), 4.22 (s, 2H), 6.98 (dd, J = 8.9, 4.5 Hz, 1H), 7.17–7.22 (m, 2H), 7.25–7.36 (m, 5H), 7.52 (dd, J = 8.8, 3.2 Hz, 1H), 7.60 (d, J = 8.9 Hz, 1H), 7.78 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 29.8, 36.5, 115.0, 115.8, 116.0, 119.8, 120.1, 121.6, 125.1, 125.2, 126.70, 126.72, 126.8, 128.7, 129.1, 129.2, 133.5, 133.6, 136.8, 137.6, 138.4, 142.5, 148.23, 148.26, 158.1, 159.6, 160.6, 197.2. $[M+H]^+$ = m/e 413.

5.1.6. 1-{2-[3-Benzyl-6-(4-phenyl-[1,2,3]triazol-1-yl)-quinolin-2-yloxy]-5-fluoro-phenyl}-ethanone (7)

To a mixture of phenyl acetylene (0.04 g, 0.34 mmol), copper(I) iodide (0.06 g, 0.33 mmol) and diisopropylethylamine (0.13 g, 0.99 mmol), a solution of **6** (0.14 g, 0.33 mmol) in acetonitrile (5 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 5–10 min and then at room temperature for 4 h. The reaction was diluted with ethyl acetate (50 mL), filtered through Celite and treated with 10% hydrochloric acid solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The brownish solid obtained was triturated with diethyl ether to afford compound **7** (0.14 g, 82%), mp 181–183 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (s, 3H), 4.27 (s, 2H), 7.04 (dd, J = 8.8, 4.5 Hz, 1H), 7.20–7.40 (m, 7H), 7.46 (t, J = 7.4 Hz, 2H), 7.54 (dd, J = 8.7, 3.1 Hz, 1H), 7.78 (d, J = 9.0 Hz, 1H), 7.88–7.93 (m, 3H), 7.96 (dd, J = 9.0, 2.4 Hz, 1H), 8.12 (d, J = 2.3 Hz, 1H), 8.25 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 29.7, 36.5, 115.9, 116.2, 117.6, 117.7, 120.0, 120.2, 121.7, 125.3, 125.4, 125.8, 126.2, 126.8, 127.4, 128.5, 128.8, 128.9, 129.1, 129.3, 130.0, 133.50, 133.57, 133.6, 138.1, 138.6, 144.5, 147.88, 147.91, 148.5, 158.3, 160.7, 197.1. $[M+H]^+$ = m/e 515.

5.1.7. 1-{2-[3-Benzyl-6-(4-phenyl-[1,2,3]triazol-1-yl)-quinolin-2-yloxy]-5-fluoro-phenyl}-ethanol (8)

To a solution of **7** (0.06 g, 0.12 mmol) in ethanol–tetrahydrofuran (1:1, 10 mL) mixture, sodium borohydride (0.005 g, 0.12 mmol) was added at 0 °C and reaction was stirred at room temperature for 2 h. Reaction mixture was concentrated under reduced pressure. Reaction was quenched by adding water (2 mL), extracted with ethyl acetate (20 mL). Organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The sticky solid obtained was triturated with *n*-hexane and diethyl ether to obtain **8** (0.05 g, 91%) as a white solid, mp 102–103 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (d, J = 6.4 Hz, 3H), 2.73 (d, J = 2.2 Hz, 1H, D_2O-exchangeable), 4.29 (s, 2H), 4.80 (q, J = 6.5 Hz, 1H), 6.90 (dd, J = 8.0, 4.8 Hz, 1H), 6.98–7.04 (m, 1H), 7.31–7.42 (m, 7H), 7.49 (t, J = 7.3 Hz, 2H), 7.79 (d, J = 9.0 Hz, 1H), 7.91–8.00 (m, 4H), 8.17 (d, J = 2.3 Hz, 1H), 8.27 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 22.4, 36.7, 63.8, 113.1, 113.3, 115.0, 115.3, 117.6, 117.7, 121.7, 123.7, 123.8, 125.8, 126.1, 126.8, 127.3, 128.5, 128.7, 128.9, 129.0, 130.0, 133.5, 138.4, 138.7, 140.2, 140.3, 144.4, 145.8, 148.5, 159.2, 161.2, 161.6. $[M+H]^+$ = m/e 517.

5.1.8. 3-Benzyl-2-[2-(1-chloro-ethyl)-4-fluoro-phenoxy]-6-(4-phenyl-[1,2,3]triazol-1-yl)-quinoline (9)

To a solution of **8** (0.02 g, 0.03 mmol) in acetonitrile (1 mL), thionyl chloride (0.005 g, 0.04 mmol) was added at 0 °C and stirred at room temperature for 1 h. Reaction mixture was concentrated under reduced pressure, treated with water and extracted with ethyl acetate (25 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was triturated with *n*-hexane and dried to get compound **9** (0.01 g, 60%) as a white solid, mp 151–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60 (d, J = 6.7 Hz, 3H), 4.28 (s, 2H), 4.87 (q, J = 6.8 Hz, 1H), 7.01–7.09 (m, 2H), 7.27–7.41 (m, 7H), 7.46 (t, J = 7.7 Hz, 2H), 7.80 (d, J = 9.0 Hz, 1H), 7.89–7.98 (m, 4H), 8.14 (d, J = 2.3 Hz, 1H), 8.26 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 25.8, 36.7, 51.7, 114.1, 114.3, 115.7, 115.9, 117.6, 117.7, 121.7, 124.2, 124.3, 125.8, 126.2, 126.8, 127.2, 128.5, 128.7, 128.9, 129.0, 129.2, 130.1, 133.5, 137.2, 137.3, 138.4, 138.5, 144.6, 145.2, 145.3, 148.5, 158.8, 160.6, 161.3. $[M+H]^+$ = m/e 535, 537.

5.2. General procedure for the synthesis of compounds 10–13 (procedure A)

A mixture of compound **9** (1 equiv), appropriate secondary amine (R_2H, 1.5 equiv) and triethylamine (1.5 equiv) in acetonitrile (1 mL) was refluxed for 12 h. Reaction mixture was concentrated under reduced pressure. The mixture was diluted with water, extracted with ethyl acetate (25 mL × 2) and dried over anhydrous sodium sulfate. Organic layer was filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on neutral alumina to get pure compound (**10**–**13**).

5.2.1. 3-Benzyl-2-[4-fluoro-2-(1-imidazol-1-yl-ethyl)-phenoxy]-6-(4-phenyl-[1,2,3]triazol-1-yl)-quinoline (10)

Compound **9** (0.02 g, 0.03 mmol), imidazole (0.01 g, 0.22 mmol), triethylamine (0.02 g, 0.22 mmol) in acetonitrile (1 mL) gave compound **10** (0.01 g, 60%) according to procedure A (eluent 3% methanol in chloroform) as a white solid, mp 118–120 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.55 (d, J = 7.0 Hz, 3H), 4.31 (s, 2H), 5.14–

5.23 (m, 1H), 6.78 (s, 1H), 7.07 (s, 1H), 7.16–7.28 (m, 4H), 7.32–7.44 (m, 6H), 7.52 (t, J = 7.7 Hz, 2H), 7.77 (d, J = 9.0 Hz, 1H), 7.96 (d, J = 7.2 Hz, 2H), 8.19 (dd, J = 8.9, 2.4 Hz, 1H), 8.38 (s, 1H), 8.52 (d, J = 2.3 Hz, 1H), 9.44 (s, 1H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 20.4, 35.8, 49.7, 113.3, 113.5, 115.6, 115.9, 117.4, 119.6, 121.5, 124.9, 125.0, 125.2, 125.9, 126.4, 126.8, 128.2, 128.3, 128.4, 128.5, 128.8, 128.9, 130.1, 133.1, 136.6, 136.7, 138.9, 139.0, 143.7, 145.6, 145.7, 147.3, 158.2, 160.3, 160.6. $[M+H]^+$ = m/e 567.

5.2.2. 3-Benzyl-2-[4-fluoro-2-(1-piperidin-1-yl-ethyl)-phenoxy]-6-(4-phenyl-[1,2,3]triazol-1-yl)-quinoline (11)

Eluent: 15% ethylacetate in hexane, yield 26%. White solid, mp 215–216 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (d, J = 6.4 Hz, 3H), 1.20–1.30 (m, 2H), 1.33–1.45 (m, 4H), 2.12–2.25 (m, 4H), 3.18–3.25 (m, 1H), 4.26 (s, 2H), 6.95–7.02 (m, 2H), 7.26–7.41 (m, 7H), 7.46 (t, J = 7.7 Hz, 2H), 7.75 (d, J = 9.0 Hz, 1H), 7.88–7.95 (m, 4H), 8.11 (d, J = 2.3 Hz, 1H), 8.25 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.6, 24.4, 26.1, 36.6, 51.7, 58.2, 113.8, 114.1, 114.4, 114.6, 117.6, 117.8, 121.5, 123.9, 124.0, 125.8, 125.9, 126.7, 127.1, 128.5, 128.7, 128.9, 129.0, 129.1, 130.1, 133.2, 138.1, 138.6, 140.2, 140.3, 144.8, 146.7, 148.5, 159.1, 161.1, 161.5. $[M+H]^+$ = m/e 584.

5.2.3. 3-Benzyl-2-(4-fluoro-2-{1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-ethyl}-phenoxy)-6-(4-phenyl-[1,2,3]triazol-1-yl)-quinoline (12)

Eluent: 10% ethylacetate in hexane, yield 19%. White solid, mp 173–175 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (d, J = 6.5 Hz, 3H), 2.40–2.48 (m, 4H), 2.90–3.00 (m, 4H), 3.21–3.28 (m, 1H), 4.29 (d, J = 2.6 Hz, 2H), 6.75–6.81 (m, 2H), 6.92 (t, J = 8.7 Hz, 2H), 7.00–7.08 (m, 2H), 7.27–7.42 (m, 7H), 7.48 (t, J = 7.5 Hz, 2H), 7.77 (d, J = 9.0 Hz, 1H), 7.92–8.00 (m, 4H), 8.13 (d, J = 2.2 Hz, 1H), 8.27 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.8, 36.6, 50.2, 50.6, 57.7, 114.2, 114.3, 114.4, 114.5, 115.2, 115.5, 117.5, 117.60, 117.63, 117.8, 121.7, 124.2, 124.3, 125.8, 126.0, 126.7, 126.9, 128.5, 128.7, 128.9, 129.0, 130.0, 133.3, 138.3, 138.5, 139.6, 139.7, 144.7, 146.70, 146.73, 147.84, 147.86, 148.5, 155.8, 158.2, 159.2, 161.1, 161.6. $[M+H]^+$ = m/e 679.

5.2.4. 3-Benzyl-2-{4-fluoro-2-[1-(4-pyridin-2-yl-piperazin-1-yl)-ethyl]-phenoxy}-6-(4-phenyl-[1,2,3]triazol-1-yl)-quinoline (13)

Eluent: 12% ethylacetate in hexane, yield 24%. White solid, mp 153–154 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.05 (d, J = 6.5 Hz, 3H), 2.17–2.20 (m, 4H), 3.07 (q, J = 6.8 Hz, 1H), 3.25–3.28 (m, 4H), 4.28 (s, 2H), 6.56 (dd, J = 6.8, 4.9 Hz, 1H), 6.67 (d, J = 8.6 Hz, 1H), 7.17–7.19 (m, 3H), 7.28–7.53 (m, 9H), 7.77 (d, J = 9.0 Hz, 1H), 7.95 (d, J = 7.1 Hz, 2H), 8.03–8.04 (m, 1H), 8.17 (dd, J = 9.0, 2.4 Hz, 1H), 8.38 (s, 1H), 8.48 (d, J = 2.3 Hz, 1H), 9.41 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.8, 36.7, 45.2, 50.4, 57.8, 106.9, 113.1, 114.2, 114.3, 114.46, 114.55, 117.6, 117.8, 121.6, 124.2, 124.3, 125.8, 126.0, 126.7, 126.9, 128.5, 128.7, 128.9, 129.0, 130.1, 133.3, 137.3, 138.3, 138.5, 139.6, 139.7, 144.7, 146.70, 146.72, 147.8, 148.5, 159.2, 159.4, 161.1, 161.6. $[M+H]^+$ = m/e 662.

5.3. General procedure for the synthesis of compound 14–21 (procedure B)

To a solution of amine **5** (1 equiv) and pyridine (0.5 equiv) in dry dichloromethane, appropriate isocyanate (R_3NCO, 1 equiv) or isothiocyanate (R_3NCS, 1 equiv) in dry dichloromethane (10 mL) was added drop wise at 0 °C and stirred at room temperature for 12 h. Reaction mixture was concentrated under reduced pressure and diluted with 10% hydrochloric acid (15 mL). The reaction mixture was extracted with ethyl acetate (10 mL × 2). The organic layer was washed with water (10 mL × 2), brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The syrupy liquid obtained was triturated with *n*-hexane and *n*-pentane and dried under vacuum to afford N-substituted ureas **14–17** and thioureas **18–21**.

5.3.1. 1-[2-(2-Acetyl-4-fluoro-phenoxy)-3-benzyl-quinolin-6-yl]-3-(3-nitro-phenyl)-urea (14)

Yield 65%. Pale yellow solid, mp 201–202 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.20 (s, 3H), 4.20 (s, 2H), 7.14 (dd, J = 8.9, 4.3 Hz, 1H), 7.21–7.25 (m, 1H), 7.30–7.35 (m, 4H), 7.44–7.51 (m, 2H), 7.55–7.61 (m, 3H), 7.72 (d, J = 8.0 Hz, 1H), 7.83 (dd, J = 8.2, 1.2 Hz, 1H), 8.10 (d, J = 2.1 Hz, 1H), 8.61 (t, J = 2.0 Hz, 1H), 9.10 (s, 1H, D_2O-exchangeable), 9.32 (s, 1H, D_2O-exchangeable). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 29.4, 35.6, 112.1, 112.4, 113.8, 115.2, 115.5, 116.2, 116.6, 119.8, 120.1, 122.6, 124.2, 124.5, 125.5, 125.6, 126.2, 126.3, 127.0, 128.4, 128.8, 129.9, 133.4, 133.5, 136.1, 138.5, 139.2, 140.3, 140.9, 147.6, 148.0, 152.4, 157.3, 158.7, 159.8, 196.9. $[M+H]^+$ = m/e 551.

5.3.2. 1-[2-(2-Acetyl-4-fluoro-phenoxy)-3-benzyl-quinolin-6-yl]-3-(2-methoxy-phenyl)-urea (15)

Yield 58%. White solid, mp 242–243 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.19 (s, 3H), 3.88 (s, 3H), 4.20 (s, 2H), 6.90–6.96 (m, 2H), 7.03 (dd, J = 8.0, 1.3 Hz, 1H), 7.12 (dd, J = 9.0, 4.7 Hz, 1H), 7.30–7.35 (m, 4H), 7.42–7.55 (m, 3H), 7.59 (dd, J = 8.9, 3.1 Hz, 1H), 8.09 (d, J = 2.0 Hz, 1H), 8.14–8.17 (m, 2H), 8.30 (s, 1H, D_2O-exchangeable), 9.55 (s, 1H, D_2O-exchangeable). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 29.5, 35.6, 55.7, 110.6, 112.8, 115.2, 115.4, 118.2, 119.8, 120.1, 120.5, 121.8, 122.1, 125.4, 125.50, 125.53, 126.2, 126.4, 127.0, 128.38, 128.45, 128.8, 133.57, 133.63, 136.7, 138.4, 139.3, 140.0, 147.60, 147.62, 147.64, 152.3, 157.3, 158.5, 159.7, 197.0. $[M+H]^+$ = m/e 536.

5.3.3. 1-[2-(2-Acetyl-4-fluoro-phenoxy)-3-benzyl-quinolin-6-yl]-3-(3-methoxy-phenyl)-urea (16)

Yield 90%. White solid, mp 200–201 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.19 (s, 3H), 3.73 (s, 3H), 4.20 (s, 2H), 6.56 (dd, J = 7.8, 2.4 Hz, 1H), 6.94 (m, 1H), 7.12–7.18 (m, 2H), 7.20–7.28 (m, 2H), 7.29–7.39 (m, 4H), 7.43–7.52 (m, 2H), 7.55 (dd, J = 9.0, 2.3 Hz, 1H), 7.59 (dd, J = 9.0, 3.2 Hz, 1H), 8.06 (d, J = 2.1 Hz, 1H), 8.16 (s, 1H), 8.78 (s, 1H, D_2O-exchangeable), 8.90 (s, 1H, D_2O-exchangeable). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 29.5, 35.6, 54.8, 103.9, 107.1, 107.3, 110.5, 113.2, 115.2, 115.5, 119.8, 120.0, 122.4, 125.48, 125.53, 125.56, 126.2, 126.4, 127.0, 128.3, 128.9, 129.5, 133.57, 133.63, 136.6, 138.4, 139.2, 140.1, 140.8, 147.6, 152.4, 157.3, 158.5, 159.6, 159.7, 197.0. $[M+H]^+$ = m/e 536.

5.3.4. 1-[2-(2-Acetyl-4-fluoro-phenoxy)-3-benzyl-quinolin-6-yl]-3-(4-methoxy-phenyl)-urea (17)

Yield 94%. White solid, mp 220–221 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.19 (s, 3H), 3.72 (s, 3H), 4.20 (s, 2H), 6.87 (d, J = 9.0 Hz, 2H), 7.13 (dd, J = 8.0, 4.8 Hz, 1H), 7.20–7.25 (m, 1H), 7.26–7.40 (m, 6H), 7.41–7.49 (m, 2H), 7.53–7.60 (m, 2H), 8.04 (d, J = 2.1 Hz, 1H), 8.14 (s, 1H), 8.59 (s, 1H, D_2O-exchangeable), 8.85 (s, 1H, D_2O-exchangeable). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 29.5, 35.6, 55.1, 112.9, 113.9, 115.2, 115.4, 119.8, 120.0, 120.1, 122.4, 125.4, 125.9, 126.2, 126.4, 126.9, 128.4, 128.6, 128.8, 132.5, 133.5, 133.6, 136.8, 138.4, 139.3, 139.9, 147.64, 147.66, 152.7, 154.4, 157.3, 158.4, 159.7, 197.0 $[M+H]^+$ = m/e 536.

5.3.5. 1-[2-(2-Acetyl-4-fluoro-phenoxy)-3-benzyl-quinolin-6-yl]-3-(4-chloro-benzyl)-thiourea (18)

Yield 97%. White solid, mp 179–180 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.19 (s, 3H), 4.21 (s, 2H), 4.80 (d, J = 5.0 Hz, 2H), 7.13 (dd, J = 8.9, 4.6 Hz, 1H), 7.21–7.24 (m, 1H), 7.25–7.41 (m, 7H), 7.42–7.52 (m, 3H), 7.58–7.63 (m, 2H), 8.01 (s, 1H), 8.19 (s,

1H), 8.27 (br s, 1H, D_2O-exchangeable), 9.95 (br s, 1H, D_2O-exchangeable). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 29.4, 35.5, 45.1, 115.4, 115.6, 119.8, 119.9, 120.1, 125.48, 125.55, 125.9, 126.3, 126.8, 127.0, 128.4, 128.5, 128.78, 128.85, 129.0, 131.8, 133.5, 133.6, 135.9, 136.0, 138.7, 139.2, 141.5, 147.42, 147.44, 157.4, 159.3, 159.8, 181.3. $[M+H]^+ = m/e$ 570, 572.

5.3.6. 1-[2-(2-Acetyl-4-fluoro-phenoxy)-3-benzyl-quinolin-6-yl]-3-(2-methoxy-phenyl)-thiourea (19)

Yield 56%. Sticky solid. ^1H NMR (400 MHz, DMSO-d_6): δ 2.20 (s, 3H), 3.83 (s, 3H), 4.22 (s, 2H), 6.93 (t, J = 7.3 Hz, 1H), 7.06 (d, J = 7.4 Hz, 1H), 7.11–7.28 (m, 3H), 7.29–7.39 (m, 4H), 7.43–7.56 (m, 2H), 7.61 (dd, J = 9.0, 3.2 Hz, 1H), 7.67 (dd, J = 9.0, 2.2 Hz, 1H), 7.86 (d, J = 7.3 Hz, 1H), 8.08 (d, J = 2.0 Hz, 1H), 8.20 (s, 1H), 9.29 (s, 1H, D_2O-exchangeable), 10.10 (s, 1H, D_2O-exchangeable). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 29.4, 35.5, 55.6, 111.4, 115.3, 115.6, 119.7, 119.9, 120.0, 120.1, 125.5, 125.6, 125.8, 125.9, 126.2, 126.4, 127.0, 127.4, 128.4, 128.8, 133.5, 133.6, 136.2, 138.7, 139.2, 141.5, 147.4, 152.0, 157.4, 159.3, 159.8, 179.5, 197.0. $[M+H]^+ = m/e$ 552.

5.3.7. 1-[2-(2-Acetyl-4-fluoro-phenoxy)-3-benzyl-quinolin-6-yl]-3-(3-methoxy-phenyl)-thiourea (20)

Yield 56%. Off white solid. Mp 111–112 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 2.19 (s, 3H), 3.73 (s, 3H), 4.21 (s, 2H), 6.71 (dd, J = 8.2, 2.1 Hz, 1H), 7.03 (d, J = 7.8 Hz, 1H), 7.13 (dd, J = 8.9, 4.7 Hz, 1H), 7.17 (t, J = 1.9 Hz, 1H), 7.19–7.27 (m, 2H), 7.28–7.38 (m, 4H), 7.44–7.54 (m, 2H), 7.56–7.68 (m, 2H), 7.97 (d, J = 2.1 Hz, 1H), 8.21 (s, 1H), 9.90 (s, 1H, D_2O-exchangeable), 10.00 (s, 1H, D_2O-exchangeable). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 29.4, 35.5, 55.0, 109.2, 109.8, 111.1, 114.4, 115.3, 115.60, 115.65, 118.1, 119.9, 120.1, 120.2, 125.5, 125.8, 126.2, 126.4, 127.1, 128.4, 128.8, 129.2, 133.5, 133.6, 136.2, 138.7, 139.2, 140.4, 141.5, 147.4, 157.4, 159.2, 159.3, 159.8, 179.5, 196.9. $[M+H]^+ = m/e$ 552.

5.3.8. 1-[2-(2-Acetyl-4-fluoro-phenoxy)-3-benzyl-quinolin-6-yl]-3-(4-methoxy-phenyl)-thiourea (21)

Yield 47%. Light brown solid, mp 63–64 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 2.19 (s, 3H), 3.74 (s, 3H), 4.21 (s, 2H), 6.90 (d, J = 8.9 Hz, 2H), 7.13 (dd, J = 8.9, 4.7 Hz, 1H), 7.19–7.39 (m, 7H), 7.42–7.54 (m, 2H), 7.59–7.69 (m, 2H), 7.97 (d, J = 1.9 Hz, 1H), 8.20 (s, 1H), 9.72 (s, 1H, D_2O-exchangeable), 9.84 (s, 1H, D_2O-exchangeable). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 29.9, 36.0, 55.6, 114.1, 115.5. 115.8, 116.0, 120.4, 120.6, 122.6, 125.9, 126.0, 126.3, 126.5, 126.7, 126.9, 127.6, 127.8, 128.9, 129.3, 132.5, 134.0, 134.1, 136.8, 139.2, 139.7, 142.0, 147.91, 147.93, 157.0, 157.9, 159.0, 159.7, 160.3, 180.5, 197.4. $[M+H]^+ = m/e$ 552.

5.4. General procedure for the synthesis of compound 22–29 (procedure C)

To a solution of compounds **14–21** (1 equiv) in ethanol–tetrahydrofuran mixture (1:1, 4 mL), sodium borohydride (2.5 eq) was added at 0 °C and stirred at room temperature for 2 h. Reaction mixture was concentrated under reduced pressure, poured into ice water and extracted with ethyl acetate (50 mL × 2). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The sticky compounds were triturated with n-pentane to furnish pure compounds **22–29**.

5.4.1. 1-{3-Benzyl-2-[4-fluoro-2-(1-hydroxy-ethyl)-phenoxy]-quinolin-6-yl}-3-(3-nitro-phenyl)-urea (22)

Yield 94%. White solid, mp 217–219 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 1.04 (d, J = 6.3 Hz, 3H), 4.20 (s, 2H), 4.52–4.62 (m, 1H), 5.19 (d, J = 4.4 Hz, 1H, D_2O-exchangeable), 6.80–7.05 (m, 1H), 7.06–7.13 (m, 1H), 7.21–7.38 (m, 6H), 7.49 (d, J = 8.9 Hz, 1H), 7.54–7.63 (m, 2H), 7.73 (dd, J = 8.0, 1.7 Hz, 1H), 7.83 (dd, J = 8.0, 1.7 Hz,1H), 8.10 (d, J = 2.2 Hz, 1H), 8.20 (s, 1H), 8.61 (t, J = 2.1 Hz, 1H), 9.09 (s, 1H, D_2O-exchangeable), 9.32 (s, 1H, D_2O-exchangeable). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 24.6, 35.7, 62.8, 112.1, 112.3, 112.5, 113.7, 113.90, 113.94, 116.3, 122.5, 124.1, 124.2, 124.3, 125.2, 126.20, 126.22, 127.1, 128.4, 128.5, 130.0, 136.0, 138.5, 139.4, 140.5, 140.9, 142.1, 142.2, 145.2, 145.3, 148.1, 152.5, 158.1, 158.8, 160.5. $[M+H]^+ = m/e$ 553.

5.4.2. 1-{3-Benzyl-2-[4-fluoro-2-(1-hydroxy-ethyl)-phenoxy]-quinolin-6-yl}-3-(2-methoxy-phenyl)-urea (23)

Yield 99%. Yellow solid, mp 216–219 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 1.04 (d, J = 6.3 Hz, 3H), 3.88 (s, 3H), 4.20 (s, 2H), 4.54–4.62 (m, 1H), 5.18 (d, J = 4.2 Hz, 1H, D_2O-exchangeable), 6.88–7.11 (m, 5H), 7.21–7.36 (m, 6H), 7.45–7.55 (m, 2H), 8.08 (d, J = 2.1 Hz, 1H), 8.12–8.20 (m, 2H), 8.29 (s, 1H, D_2O-exchangeable), 9.52 (s, 1H, D_2O-exchangeable). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 24.6, 35.7, 55.7, 62.7, 110.6, 112.2, 112.5, 112.9, 113.7, 113.9, 118.2, 120.5, 121.8, 122.0, 124.0, 124.1, 125.1, 126.1, 126.3, 127.1, 128.4, 128.5, 136.5, 138.4, 139.4, 140.2, 142.1, 142.2, 145.22, 145.24, 147.6, 152.3, 158.0, 158.6, 160.4. $[M+H]^+ = m/e$ 538.

5.4.3. 1-{3-Benzyl-2-[4-fluoro-2-(1-hydroxy-ethyl)-phenoxy]-quinolin-6-yl}-3-(3-methoxy-phenyl)-urea (24)

Yield 96%. White solid, mp 217–218 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 1.04 (d, J = 6.0 Hz, 3H), 3.73 (s, 3H), 4.20 (s, 2H), 4.52–4.65 (m, 1H), 5.19 (d, J = 3.9 Hz, 1H, D_2O-exchangeable), 6.55 (d, J = 7.6 Hz, 1H), 6.94 (d, J = 7.7 Hz, 1H), 6.98–7.13 (m, 2H), 7.14–7.39 (m, 8H), 7.47 (d, J = 9.0 Hz, 1H), 7.55 (d, J = 8.7 Hz, 1H), 8.06 (s, 1H), 8.17 (s, 1H), 8.81 (s, 1H, D_2O-exchangeable), 8.92 (s, 1H, D_2O-exchangeable). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 24.6, 35.7, 54.9, 62.8, 103.9, 107.3, 110.5, 112.3, 112.5, 113.3, 113.7, 113.9, 122.3, 124.1, 124.2, 125.2, 126.2, 126.3, 127.1, 128.4, 128.5, 129.5, 136.4, 138.4, 139.5, 140.3, 140.8, 142.1, 142.2, 145.3, 152.5, 158.1, 158.7, 159.6, 160.5. $[M+H]^+ = m/e$ 538.

5.4.4. 1-{3-Benzyl-2-[4-fluoro-2-(1-hydroxy-ethyl)-phenoxy]-quinolin-6-yl}-3-(4-methoxy-phenyl)-urea (25)

Yield 40%. White solid, mp 200–201 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 1.04 (d, J = 6.3 Hz, 3H), 3.72 (s, 3H), 4.20 (s, 2H), 4.52–4.62 (m, 1H), 5.20 (d, J = 4.3 Hz, 1H, D_2O-exchangeable), 6.88 (d, J = 8.9 Hz, 2H), 6.97–7.14 (m, 2H), 7.19–7.42 (m, 8H), 7.46 (d, J = 8.9 Hz, 1H), 7.55 (dd, J = 9.1, 2.0 Hz, 1H), 8.05 (s, 1H), 8.15 (s, 1H), 8.56 (s, 1H, D_2O-exchangeable), 8.82 (s, 1H, D_2O-exchangeable). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 25.1, 36.2, 55.6, 63.2, 112.7, 112.9, 113.5, 114.2, 114.4, 120.5, 122.7, 124.5, 124.6, 125.6, 126.6, 126.7, 127.5, 128.9, 129.0, 133.0, 137.1, 138.8, 139.9, 140.6, 142.6, 142.7, 145.73, 145.75, 153.2, 154.9, 158.5, 159.1, 160.9. $[M+H]^+ = m/e$ 538.

5.4.5. 1-{3-Benzyl-2-[4-fluoro-2-(1-hydroxy-ethyl)-phenoxy]-quinolin-6-yl}-3-(4-chloro-benzyl)-thiourea (26)

Yield 80%. White Solid, mp 183–184 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 1.02 (d, J = 6.3 Hz, 3H), 4.21 (s, 2H), 4.51–4.63 (m, 1H), 4.80 (d, J = 5.1 Hz, 2H), 5.18 (d, J = 4.3 Hz, 1H, D_2O-exchangeable), 7.00 (dd, J = 8.8, 5.0 Hz, 1H), 7.04–7.13 (m, 1H), 7.20–7.41 (m, 9H), 7.45 (d, J = 7.4 Hz, 1H), 7.49 (d, J = 8.9 Hz, 1H), 7.59 (dd, J = 8.9, 2.1 Hz, 1H), 8.02 (s, 1H), 8.21 (s, 1H), 8.30 (br s, 1H, D_2O-exchangeable), 10.00 (s, 1H, D_2O-exchangeable). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 24.6, 35.6, 45.0, 62.7, 112.3, 112.6, 113.8, 114.0, 119.7, 124.1, 124.2, 125.2, 125.8, 126.2, 126.6, 126.8, 127.0, 128.4, 128.5, 128.8, 129.0, 131.8, 135.8, 136.0, 138.7, 139.4, 141.7, 142.1, 142.2, 145.1, 145.2, 158.1, 159.4, 160.5, 181.3. $[M+H]^+ = m/e$ 572, 574.

5.4.6. 1-{3-Benzyl-2-[4-fluoro-2-(1-hydroxy-ethyl)-phenoxy]-quinolin-6-yl}-3-(2-methoxy-phenyl)-thiourea (27)

Yield 58%. Yellow solid, mp 164–168 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.03 (d, J = 6.3 Hz, 3H), 3.83 (s, 3H), 4.22 (s, 2H), 4.53–4.61 (m, 1H), 5.20 (d, J = 4.3 Hz, 1H, D_2O-exchangeable), 6.93 (t, J = 7.6 Hz, 1H), 7.02 (dd, J = 8.7, 4.9 Hz, 1H), 7.06–7.13 (m, 2H), 7.14–7.19 (m, 1H), 7.20–7.37 (m, 6H), 7.49 (d, J = 8.9 Hz, 1H), 7.66 (dd, J = 8.9, 1.9 Hz, 1H), 7.86 (d, J = 7.7 Hz, 1H), 8.08 (s, 1H), 8.22 (s, 1H), 9.29 (s, 1H, D_2O-exchangeable), 10.11 (s, 1H, D_2O-exchangeable). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 24.6, 35.6, 55.6, 62.7, 111.4, 112.3, 112.5, 113.7, 114.0, 119.7, 119.9, 124.0, 124.1, 125.1, 125.6, 125.9, 126.2, 126.5, 126.9, 127.5, 128.4, 128.5, 136.0, 138.7, 139.4, 141.8, 142.1, 142.2, 145.1, 151.9, 158.1, 159.4, 160.5, 179.5. $[M+H]^+$ = m/e 554.

5.4.7. 1-{3-Benzyl-2-[4-fluoro-2-(1-hydroxy-ethyl)-phenoxy]-quinolin-6-yl}-3-(3-methoxy-phenyl)-thiourea (28)

Yield 80%. Brown solid, mp 71–72 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.02 (d, J = 6.3 Hz, 3H), 3.73 (s, 3H), 4.21 (s, 2H), 4.52–4.59 (m, 1H), 5.19 (d, J = 4.3 Hz, 1H, D_2O-exchangeable), 6.71 (dd, J = 8.3, 2.0 Hz, 1H), 6.99–7.05 (m, 2H), 7.06–7.14 (m, 1H), 7.17–7.19 (m, 1H), 7.20–7.28 (m, 2H), 7.29–7.36 (m, 5H), 7.48 (d, J = 9.0 Hz, 1H), 7.63 (dd, J = 9.0, 2.3 Hz, 1H), 7.97 (d, J = 2.0 Hz, 1H), 8.23 (s, 1H), 9.91 (s, 1H, D_2O-exchangeable), 10.02 (s, 1H, D_2O-exchangeable). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 24.6, 35.6, 55.0, 62.7, 109.2, 109.8, 112.3, 112.5, 113.8, 114.0, 115.6, 120.2, 124.0, 124.1, 125.1, 125.7, 126.2, 126.5, 127.0, 128.4, 128.5, 129.2, 136.0, 138.7, 139.4, 140.4, 141.8, 142.1, 142.2, 145.13, 145.15, 158.1, 159.2, 159.4, 160.5, 179.5. $[M+H]^+$ = m/e 554.

5.4.8. 1-{3-Benzyl-2-[4-fluoro-2-(1-hydroxy-ethyl)-phenoxy]-quinolin-6-yl}-3-(4-methoxy-phenyl)-thiourea (29)

Yield 80%. Brown solid, mp 82–84 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.02 (d, J = 6.3 Hz, 3H), 3.74 (s, 3H), 4.21 (s, 2H), 4.52–4.60 (m. 1H), 5.19 (d, J = 4.4 Hz, 1H, D_2O-exchangeable), 6.91 (d, J = 8.9 Hz, 2H), 7.02 (dd, J = 8.8, 4.9 Hz, 1H), 7.07–7.14 (m, 1H), 7.22–7.24 (m, 1H), 7.27–7.38 (m, 7H), 7.48 (d, J = 8.9 Hz, 1H), 7.62 (dd, J = 9.0, 2.3 Hz, 1H), 7.97 (d, J = 2.2 Hz, 1H), 8.22 (s, 1H), 9.70 (s, 1H, D_2O-exchangeable), 9.83 (s, 1H, D_2O-exchangeable). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 24.6, 35.6, 55.1, 62.7, 112.3, 112.5, 113.6, 113.8, 114.0, 120.1, 124.0, 124.1, 125.1, 125.7, 126.1, 126.2, 126.5, 127.0, 128.4, 128.5, 132.0, 136.2, 138.70, 138.75, 139.4, 141.8, 142.1, 142.2, 145.1, 145.2, 156.6, 158.1, 159.4, 160.5, 180.0. $[M+H]^+$ = m/e 554.

5.4.9. 1-[2-(3-Benzyl-6-nitro-quinolin-2-yloxy)-phenyl]-2-bromo-ethanone (30)

Bromine (0.284 mL, 5.55 mmol) was added to a solution of compound **4** (2.10 g, 5.04 mmol) in chloroform (105 mL) at 0 °C and stirred at room temperature for 15 h. The reaction mixture was quenched with ice-cold water. The separated organic layer was washed with saturated sodium bicarbonate solution, water, brine and dried over anhydrous sodium sulfate. The organic layer was concentrated under vacuum. The crude product was triturated with hexane to furnish the product **30** (2.20 g, 88%) as an off white solid, mp 119–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.09 (s, 2H), 4.30 (s, 2H), 7.07 (dd, J = 8.9, 4.4 Hz, 1H), 7.22–7.44 (m, 6H), 7.60 (dd, J = 8.5, 3.0 Hz, 1H), 7.73 (d, J = 9.2 Hz, 1H), 8.05 (s, 1H), 8.33 (dd, J = 9.2, 2.3 Hz, 1H), 8.68 (d, J = 2.1 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 34.2, 36.5, 116.7, 117.0, 120.9, 121.2, 123.0, 123.6, 125.1, 125.3, 125.4, 127.1, 128.1, 128.7, 128.9, 129.1, 130.5, 130.6, 137.6, 140.0, 144.6, 147.6, 147.7, 147.8, 158.4, 160.8, 162.1, 190.11, 190.12. $[M+H]^+$ = m/e 495, 497.

5.5. General procedure for the synthesis of compounds 31–38 (procedure D)

Compound **30** was dissolved in dry DMF, followed by the addition of corresponding amine (R_1H) and stirred at room temperature to get amine derivatives. These amine derivatives were dissolved in ethanol–tetrahydrofuran mixture (1:1, 10 mL) and sodium borohydride (1.1 equiv) was added at 0 °C and stirred at room temperature for 15 min. Reaction mixture was concentrated under reduced pressure, poured into ice water and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (100–200 mesh) eluting with hexane–ethyl acetate to give the pure compounds (**31**–**38**).

5.5.1. 1-[2-(3-Benzyl-6-nitro-quinolin-2-yloxy)-5-fluoro-phenyl]-2-morpholin-4-yl-ethanol (31)

Yield 15%. White solid, mp 59–60 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.12–2.27 (m, 2H), 2.30–2.39 (m, 2H), 2.48 (d, J = 6.2 Hz, 2H), 3.57–3.65 (m, 4H), 4.18–4.28 (m, 2H), 4.73 (br s, 1H, D_2O-exchangeable), 4.85 (t, J = 6.5 Hz, 1H), 6.93–7.04 (m, 2H), 7.22–7.38 (m, 5H), 7.41 (dd, J = 9.3, 2.8 Hz, 1H), 7.70 (d, J = 9.2 Hz, 1H), 8.02 (s, 1H), 8.29 (dd, J = 9.2, 2.5 Hz, 1H), 8.64 (d, J = 2.3 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 36.5, 53.0, 63.1, 64.6, 66.1, 113.8, 114.0, 115.2, 115.4, 122.9, 123.6, 123.7, 123.8, 124.8, 127.0, 127.9, 128.5, 128.9, 129.1, 136.1, 136.2, 137.8, 139.5, 144.3, 145.4, 145.5, 148.0, 159.3, 161.7, 162.4. $[M+H]^+$ = m/e 504.

5.5.2. 1-[2-(3-Benzyl-6-nitro-quinolin-2-yloxy)-5-fluoro-phenyl]-2-piperidin-1-yl-ethanol (32)

Yield 15%. Off-white solid, mp 67–68 °C. ^{1}H NMR^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20–1.45 (m, 4H), 1.57–1.78 (m, 4H), 2.50–2.70 (m, 2H), 2.78–2.92 (m, 2H), 4.24 (s, 2H), 5.18 (d, J = 7.1 Hz, 1H), 6.89 (dd, J = 8.9, 4.6 Hz, 1H), 6.97–7.10 (m, 1H), 7.28–7.42 (m, 5H), 7.47 (dd, J = 9.1, 3.1 Hz, 1H), 7.71 (d, J = 9.1 Hz, 1H), 8.07 (s, 1H), 8.32 (dd, J = 9.1, 2.5 Hz, 1H), 8.68 (d, J = 2.5 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 22.0, 22.9, 36.5, 54.2, 62.6, 64.0, 114.1, 114.3, 115.8, 116.0, 123.0, 123.5, 123.6, 123.7, 124.9, 127.1, 128.2, 128.4, 128.9, 129.1, 135.2, 135.3, 137.9, 139.8, 144.5, 145.3, 145.4, 147.9, 159.3, 161.7, 162.5. $[M+H]^+$ = m/e 502.

5.5.3. 1-[2-(3-Benzyl-6-nitro-quinolin-2-yloxy)-5-fluoro-phenyl]-2-imidazol-1-yl-ethanol (33)

Yield 14%. Light-green solid, mp 196–197 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.75 (dd, J = 13.8, 7.1 Hz, 1H), 3.91 (dd, J = 14.2, 2.6 Hz, 1H), 4.31 (s, 2H), 4.65–4.73 (m, 1H), 5.83 (d, J = 4.1 Hz, 1H, D_2O-exchangeable), 6.64 (s, 1H), 6.71 (s, 1H), 7.04 (dd, J = 9.6, 3.0 Hz, 1H), 7.12 (dd, J = 8.8, 4.9 Hz, 1H), 7.15–7.23 (m, 2H), 7.24–7.28 (m, 1H), 7.31–7.38 (m, 4H), 7.74 (d, J = 9.2 Hz, 1H), 8.32 (dd, J = 9.2, 2.6 Hz, 1H), 8.61 (s, 1H), 8.99 (d, J = 2.5 Hz, 1H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 35.6, 51.7, 66.3, 113.5, 113.8, 115.1, 115.3, 119.8, 122.9, 124.1, 124.2, 124.9, 126.5, 127.5, 127.6, 128.0, 128.6, 128.7, 136.7, 136.8, 137.4, 138.6, 140.7, 143.9, 145.21, 145.23, 147.4, 158.2, 160.6, 162.4, 172.0. $[M+H]^+$ = m/e 485.

5.5.4. 1-[2-(3-Benzyl-6-nitro-quinolin-2-yloxy)-5-fluoro-phenyl]-2-pyrazol-1-yl-ethanol (34)

Yield 16%. Green solid, mp 99–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.94 (dd, J = 13.9, 6.9 Hz, 1H), 4.18 (dd, J = 13.8, 2.5 Hz, 1H), 4.27 (s, 2H), 4.50 (d, J = 4.6 Hz, 1H, D_2O-exchangeable), 4.87–4.95 (m, 1H), 6.13 (t, J = 2.1 Hz, 1H), 6.92 (d, J = 2.1 Hz, 1H), 6.94–7.05 (m, 2H), 7.12 (dd, J = 9.2, 2.9 Hz, 1H), 7.23–7.37 (m, 5H), 7.49 (d, J = 1.7 Hz, 1H), 7.74 (d, J = 9.1 Hz, 1H), 8.02 (s, 1H), 8.33 (dd, J = 9.2, 2.5 Hz, 1H), 8.67 (d, J = 2.5 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 36.6, 56.5, 68.2, 105.3, 113.9, 114.1, 115.4,

115.6, 123.0, 123.6, 123.8, 123.9, 124.9, 127.0, 128.0, 128.4, 128.8, 128.9, 130.3, 135.3, 135.4, 137.8, 139.7, 139.9, 144.4, 145.2, 145.3, 147.9, 159.1, 161.5, 162.5. $[M+H]^+ = m/e$ 485.

5.5.5. 1-[2-(3-Benzyl-6-nitro-quinolin-2-yloxy)-5-fluoro-phenyl]-2-[3-(3-methoxy-phenyl)-pyrazol-1-yl]-ethanol (35)

Yield 27%. White solid, mp 174–175 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.70 (s, 3H), 4.12 (dd, J = 13.8, 8.4 Hz, 1H), 4.27–4.45 (m, 3H), 5.00–5.07 (m, 1H), 5.82 (d, J = 4.8 Hz, 1H, D_2O-exchangeable), 6.55 (d, J = 2.1 Hz, 1H), 6.80 (dd, J = 8.2, 2.3 Hz, 1H), 7.02 (s, 1H), 7.10 (d, J = 7.5 Hz, 1H), 7.15–7.30 (m, 6H), 7.33 (d, J = 6.9 Hz, 2H), 7.41 (dd, J = 9.5, 2.9 Hz, 1H), 7.53 (d, J = 2.1 Hz, 1H), 7.70 (d, J = 9.1 Hz, 1H), 8.27 (dd, J = 9.2, 2.5 Hz, 1H), 8.44 (s, 1H), 8.90 (d, J = 2.4 Hz, 1H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 35.5, 54.8, 57.7, 66.6, 102.2, 110.2, 112.5, 113.6, 113.8, 115.0, 115.2, 117.2, 122.6, 124.1, 124.4, 124.5, 124.8, 126.4, 127.5, 128.1, 128.5, 128.8, 129.3, 132.3, 134.5, 137.3, 137.4, 138.3, 140.2, 143.7, 145.0, 145.1, 147.3, 149.7, 158.4, 159.3, 160.8, 161.9. $[M+H]^+ = m/e$ 591.

5.5.6. 1-[2-(3-Benzyl-6-nitro-quinolin-2-yloxy)-5-fluoro-phenyl]-2-[3-(4-methoxy-phenyl)-pyrazol-1-yl]-ethanol (36)

Yield 30%. Yellow solid, mp 172–173 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (s, 3H), 3.95 (dd, J = 13.8, 7.0 Hz, 1H), 4.17 (dd, J = 13.9, 2.5 Hz, 1H), 4.27 (s, 2H), 4.66 (d, J = 4.3 Hz, 1H, D_2O-exchangeable), 4.91–4.98 (m, 1H), 6.32 (d, J = 2.2 Hz, 1H), 6.87–6.95 (m, 3H), 7.00–7.07 (m, 2H), 7.18–7.35 (m, 6H), 7.62 (d, J = 8.7 Hz, 2H), 7.74 (d, J = 9.2 Hz, 1H), 7.99 (s, 1H), 8.32 (dd, J = 9.2, 2.5 Hz, 1H), 8.65 (d, J = 2.4 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 36.6, 55.3, 56.7, 68.2, 101.9, 113.9, 114.2, 115.4, 115.6, 123.0, 123.7, 123.8, 123.9, 124.9, 125.6, 126.7, 127.0, 128.0, 128.4, 128.9, 129.0, 131.6, 135.3, 135.4, 137.8, 139.7, 144.4, 145.2, 145.3, 148.0, 151.9, 159.2, 159.4, 161.6, 162.5. $[M+H]^+ = m/e$ 591.

5.5.7. 1-[2-(3-Benzyl-6-nitro-quinolin-2-yloxy)-5-fluoro-phenyl]-2-[3-(4-trifluoromethyl-phenyl)-pyrazol-1-yl]-ethanol (37)

Yield 15%. Off-white solid, mp 167–168 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.00 (dd, J = 13.9, 7.2 Hz, 1H), 4.24 (dd, J = 13.9, 2.7 Hz, 1H), 4.28 (s, 2H), 4.95–5.03 (m, 1H), 6.46 (d, J = 2.2 Hz, 1H), 6.98–7.08 (m, 3H), 7.18–7.34 (m, 6H), 7.59 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 9.2 Hz, 1H), 7.78 (d, J = 8.1 Hz, 2H), 8.00 (s, 1H), 8.31 (dd, J = 9.2, 2.5 Hz, 1H), 8.65 (d, J = 2.5 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 36.6, 57.1, 68.1, 103.1, 113.8, 114.1, 115.6, 115.8, 123.0, 123.8, 124.0, 124.1, 124.9, 125.5, 125.6, 127.0, 128.0, 128.4, 128.9, 129.0, 132.1, 135.1, 135.2, 136.2, 137.8, 139.7, 144.4, 145.2, 145.3, 147.9, 150.6, 159.2, 161.6, 162.5. $[M+H]^+ = m/e$ 629.

5.5.8. 1-[2-(3-Benzyl-6-nitro-quinolin-2-yloxy)-5-fluoro-phenyl]-2-[3-(3-chloro-phenyl)-pyrazol-1-yl]-ethanol (38)

Yield 10%. Yellow solid, mp 140–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.00 (dd, J = 14.3, 9.0 Hz, 1H), 4.14 (d, J = 4.3 Hz, 1H, D_2O-exchangeable), 4.23 (dd, J = 13.9, 2.5 Hz, 1H), 4.31 (s, 2H), 4.91–5.00 (m, 1H), 6.42 (d, J = 2.3 Hz, 1H), 6.98–7.10 (m, 3H), 7.21–7.35 (m, 8H), 7.57 (dd, J = 6.7, 1.8 Hz, 1H), 7.68 (s, 1H), 7.76 (d, J = 9.2 Hz, 1H), 8.05 (s, 1H), 8.35 (dd, J = 9.1, 2.5 Hz, 1H), 8.70 (d, J = 2.4 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 36.6, 57.0, 68.1, 102.7, 113.8, 114.1, 115.5, 115.8, 123.0, 123.5, 123.7, 124.0, 124.1, 124.9, 125.4, 126.9, 127.7, 128.0, 128.4, 128.8, 129.0, 129.8, 131.9, 134.5, 134.6, 135.2, 135.3, 137.8, 139.7, 144.4, 145.2, 145.3, 147.9, 150.6, 159.2, 161.6, 162.4. $[M+H]^+ = m/e$ 595, 597.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2009.04.069.

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