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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antimalarial activity evaluation of some isoquine analogues

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Abstract The worldwide diffusion of resistance in malaria parasite, especially the *Plasmodium falciparum*, towards currently available drugs has become a major health and development challenges to human society. Isoquine, an isomeric analogue of amodiaquine, has been reported recently as a second generation lead compound for development of cost-effective and potentially safer alternative to amodiaquine which cause adverse effects including agranulocytosis and liver damage. In this study, a series of seven analogues of isoquine have been synthesized and subjected to in vitro antimalarial activity screening against the chloroquine sensitive 3D7 strain of *Plasmodium falciparum*. A simple two-step Mannich reaction was used to synthesize the compounds. All the seven compounds possessed little to moderate antimalarial activity. However, the analogues with aliphatic alcoholic amino group side chain having promising activity than the compounds with substituted aromatic ring side chain and compounds substituted with urea while analogues with heterocyclic ring side chain exhibits moderate antimalarial activity.

Keywords Antimalarial · Mannich reaction · Isoquine

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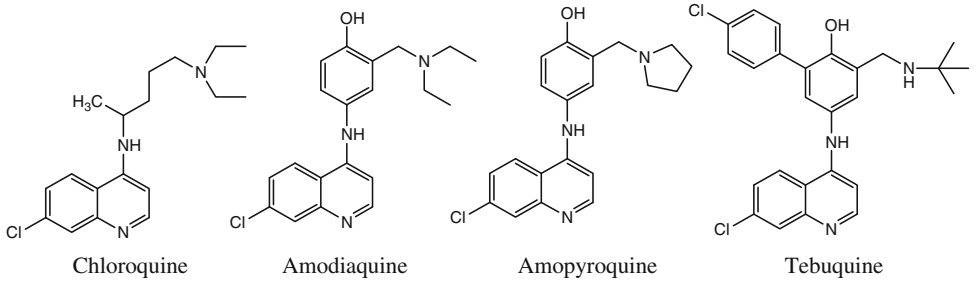
Introduction

Malaria is probably one of the oldest and most widespread diseases in the world, affecting the population living in tropical and subtropical areas. In human, malaria is caused by the four species of the protozoan parasite of the genus Plasmodium, namely *P. falciparum, P. vivax, P. malariae and P. ovale*. *P. falciparum* is the most dangerous of these malaria parasites causing heavy morbidity and mortality. Novel, effective, safe and inexpensive antimalarial agents are required for the management of malaria in the malaria endemic region. After its discovery in 1940 (Loeb *et al*., 1946), chloroquine (CQ) among the aminoquinolines has remained the drug of choice for the treatment of malaria.

Due to worldwide diffusion of resistance in *P. falciparum* to chloroquine, there is a urgent need to develop newer, potent and cost-effective antimalarial agents. In 1950s, amodiaquine (AQ), a Mannich base derivative, came into the market which was more effective than chloroquine (Nevill *et al*., 1994; Panali *et al*., 1994; Muller *et al*., 1996). However, the clinical use of amodiaquine has been restricted due to the hepatotoxicity and agranulocytosis caused by it (Douer *et al*., 1985; Neftel *et al*., 1986). The drug toxicity is believed to occur due to the formation of a metabolite quinoneimine which initiate hypersensitivity reaction. Subsequent research into the synthesis of Mannich base compounds led to the development of amopyroquine and Tebuquine which were found more active than chloroquine and amodiaquine though also caused chronic toxicity. Recently, isoquine, an isomeric analogue of amodiaquine, has been reported with potent antimalarial activity and a safer alternative to amodiaquine.



In the light of these observations, seven new isoquine analogues were synthesized involving Mannich reaction, where the diethylamino function of AQ was modified with primary or secondary amines (Table 1) to possess better antimalarial activity.

Materials and methods

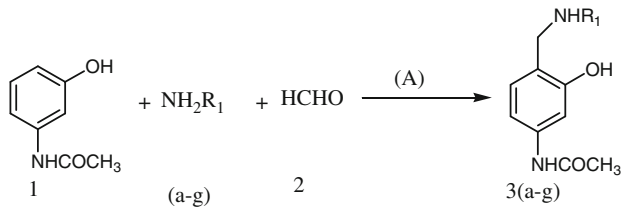
Chemistry

The desired compounds **3**(**a**–**g**) and **5**(**a**–**g**) were synthesized by the synthetic protocols as outlined in Schemes 1 and 2, respectively (Burckhalter *et al*., 1948); in these compounds, the 3′-diethylamino function of amodiaquine was replaced by a 4′-primary or secondary amino function. The synthesis of Mannich substituted amide derivatives **3**(**a**–**g**) was achieved by Mannich reaction of 3-hydroxyacetanilide (1) with different primary amines (**a**–**g**) shown in Table 2 (Blicke, 1942). Finally, new antimalarial compounds **5**(**a**–**g**) were synthesized by incorporating Mannich substituted amide derivatives **3**(**a**–**g**) with 4,7-dichloroquinoline (**4**). All the synthesized compounds were well characterized by FT-IR, mass, NMR and elemental analysis.

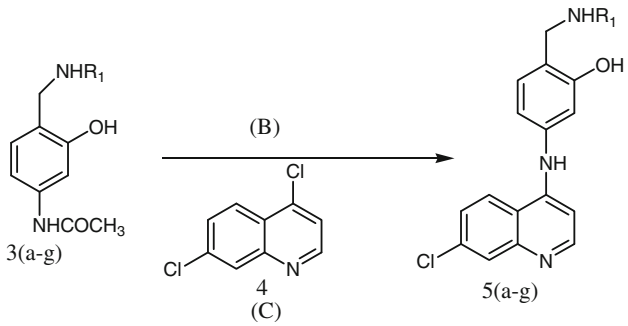
Table 1 Antimalarial activity profile of the synthesized compounds

Serial no.	Compound code	Dosage (μg/ml)	% (Dead rings + schizonts)[a]
1	**5a**	50	34
2	**5b**	50	25.5
3	**5c**	50	24
4	**5d**	50	36.5
5	**5e**	50	33
6	**5f**	50	28.5
7	**5g**	50	6.5
8	Chloroquine (standard)	0.4	68.5

[a] Mean of two replicates. Counted against 100 asexual parasites per replicate



Scheme 1 Reagents and conditions: (A) ethanol, reflux 24 h



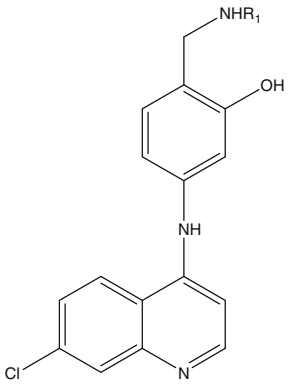
Scheme 2 Reagents and conditions: (B) ethanol/20% HCl reflux 6 h (C) ethanol, reflux 12 h

Pharmacology

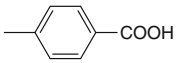
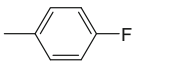
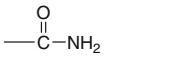
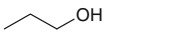
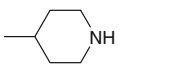
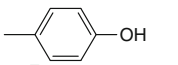
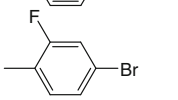
In vitro antimalarial efficacy test

The synthesized compounds were evaluated for in vitro antimalarial activity. Continuous culture of chloroquine sensitive strain of *P. falciparum* (3D7) was maintained in vitro in O^{+ve} human red blood cells diluted to 6% haematocrit in RPMI 1640 medium supplemented with 25 mmol HEPES, 1% D-glucose, 0.23% sodium bicarbonate, gentamycin (40 μg/ml), amphotericin-B (0.25 μg/ml) and 10% human AB+ serum. Incubations were done at 37°C and 5% CO_2 level in a modular incubator. D-Sorbitol synchronized 1% ring stage parasitaemia in 3% haematocrit was used for antimalarial assays using 96 well microtitre plate. A stock solution of 5 mg/ml of the test compound was prepared in DMSO, and subsequent dilutions were made with incomplete RPMI in duplicate. All test compounds were assayed at a fixed dose of 50 μg/ml. Each test well of the microtitre plate contained 20 μl of the compound and 180 μl of 1%

Table 2 List of targeted compounds



5(a-g)

Compounds (**a–g**)	$-R_1$
a	
b	
c	
d	
e	
f	
g	

ring stage parasitaemia in 3% haematocrit. In addition, drug-free negative control to assess the parasite growth and chloroquine diphosphate, at predetermined 50% inhibitory concentration (IC_{50}) dose, as positive control to assess the integrity of the assay were also maintained in duplicate in the microtitre plate. After 40 h of incubation, the smears were prepared from each well, stained with 3% Giemsa and scanned under light microscope to ascertain % dead rings and trophozoites by examining a minimum of 200 asexual parasites (Smilkstein *et al*., 2004).

Results and discussion

Out of seven synthesized compounds **5**(**a**–**g**), six compounds **5**(**a**–**f**) exhibited good antimalarial activity, the best activity recorded by the compound (**5d**) with an aliphatic alcoholic amino group side chain. The compounds having *N*-substituted aromatic ring side chain (**5a**, **5b** and **5f**) showed much better activity than the *N*,*N* di substituted aromatic ring containing compound (**5g**). The compound (**5e**) with heterocyclic ring (piperazine) at the side chain showed moderate activity. However, none of the compounds showed activity comparable to chloroquine under the test conditions.

Conclusion

In conclusion, we have shown the potential 4-aminoquinoline containing substituted 4-aminophenol as antimalarial agents in vitro and thereby demonstrated a simple approach to the synthesis of analogues of existing antimalarial drugs. The efficiency of this approach is manifested in the preclusion of large sized libraries as the SAR libraries would already be enriched in antimalarial pharmacophores. Rationally, such a combination of antimalarial pharmacophores and other functionalities offer many attractive features for accelerating antimalarial drug discovery.

Experimental

4,7-Dichloroquinoline was obtained from M/s Mangalam Drug & Organics Ltd., Mumbai, as a gift sample. All the other chemicals used were of synthetic grade of Aldrich, Rankem or Merck without further purification and obtained from commercial suppliers. Analytical thin layer chromatography (TLC) was performed on aluminium sheets precoated with silica gel obtained from Merck. Visualization was accomplished by UV light (254 nm). UV spectrums were recorded on *Shimadzu UV-1700 UV–Visible* spectrophotometer. The C, H, N microanalyses of the synthesized compounds were recorded on *Perkin Elmer 2400 Series II* Analyzer. Infrared (IR) spectra were recorded on *Perkin Elmer Spectrum RX-I* spectrophotometers using KBr pellets. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on *Bruker Avance-II* 400 NMR Spectrometer. The mass spectra were recorded on *LC-MS Waters 4000 ZQ Mass* spectrometer. The antimalarial activity screenings of the synthesized compounds were done at Regional Medical Research Centre (ICMR), Dibrugarh.

General procedure for the synthesis of compounds **3**(**a**–**g**)

3-Hydroxyacetanilide (**1**) (5 g, 33.1 mmol) was added to 100-ml round-bottomed flask followed by ethanol (23.6 ml). One equivalent of different primary amines (**a**–**g**) shown in Table 2 (33.1 mmol) and aqueous

formaldehyde (**2**) (2.46 ml) was added, and the solution was allowed to heat under reflux for 24 h. After this reflux period, the solvent was removed under reduced pressure and the crude product was purified by silica gel flash column chromatography using 20–30% Methanol/dichloromethane as eluent. This gave the desired amide product **3**(**a**–**g**).

General procedure for the synthesis of compounds **5**(**a**–**g**)

Aqueous hydrochloric acid (20%, 25 ml) was added to a round-bottomed flask containing the amide **3**(**a**–**g**) (18.9 mmol), and solution heated under reflux for 6 h. The solvent was then removed in vacuum, and the resulting residue co-evaporated with ethanol to give the corresponding hydrochloride salt. 4,7-Dichloroquinoline (**4**) (4.12 g, 20.8 mmol) and ethanol (30 ml) were added, and the reaction was heated under reflux for 12 h until completion of the reaction (determined by TLC). Then the solvent was removed under reduced pressure. Then the product was purified by silica gel flash column chromatography using 20–80% MeOH/dichloromethane as eluent to yield the quinoline hydrochloride salt as a solid. To liberate the free base compound, this solid was dissolved in distilled water (18 ml), and the solution basified by careful addition of saturated sodium bicarbonate (added until no more precipitate formed). Dichloromethane was added (100 ml), and the free base was extracted into the organic layer. Subsequent drying and removal of solvent in vacuo afforded the desired product **5**(**a**–**g**).

Synthesis of 4-((4-(7-chloroquinolin-4-ylamino)-3-hydroxyphenyl) methylamino) benzoic acid (**5a**)

(% Yield: 60.56); mp: 214–216°C; R_f value: 0.85 (Propanol:Cyclohexane::1:3); UV(λ_{max}): 363.5 nm (DMSO); IR (KBr cm^{-1}) 3231, 3057, 3109, 1624, 1584, 1447, 1375, 1288, 1176, 1097, 852, 821; ^{1}H NMR (400 MHz, DMSOd6): δ 8.79 (d, 1H, J = 8.80 Hz, quinoline–H), δ 8.44 (d, 1H, J = 6.80 Hz, quinoline–H), δ 8.07 (d, 1H, J = 9.60 Hz, quinoline–H), δ 7.91 (d, 1H, J = 8.0 Hz, quinoline–H), δ 7.65 (d, 1H, J = 8.8 Hz, quinoline–H), δ 6.91 (d, 1H, J = 6.80 Hz, Ar–H), δ 6.42 (d, 1H, J = 8.0 Hz, Ar–H), δ 6.51 (s, 1H, OH), δ 6.63 (d, 1H, J = 6.8 Hz, Ar–H), 4.178 (t, 1H, Ar–NH), δ 2.36 (s, 2H, CH_2), δ 2.36 (s, 2H, amine); ^{13}C NMR (100 MHz, DMSOd6): δ 166.57, 153.41, 144.33,1 41.61, 140.04, 138.01, 130.86, 129.85, 128.48, 127.22, 126.29, 125.31, 123.99, 119.92, 119.10, 116.59, 112.52, 101.31, 60.80. Mass: 420.2 (m+); Anal Calcd for $C_{23}H_{18}ClN_3O_3$: C, 65.79; H, 4.32; N, 10.01. Found: C, 54.36; H, 4.92; N, 7.74.

Synthesis of 5-(7-chloroquinolin-4-ylamino)-2-((4-fluorophenylamino) methyl) phenol (**5b**)

(% Yield: 78.50); mp: 130–132°C; R_f value: 0.73 (Propanol:Cyclohexane:: 4:6); UV (λ_{max}): 260 nm (DMSO); IR (KBr cm^{-1}): 3187, 3006, 2905, 1654, 1585, 1452, 1367, 1291, 1211, 1152, 1167, 965, 869, 823, 762; ^{1}H NMR (400 MHz, DMSOd6): δ 8.97 (d, 1H, J = 9.2 Hz, quinoline–H), δ 8.56 (d, 1H, J = 4 Hz, quinoline–H), δ 8.26 (s, 1H, quinoline–H), δ 8.10 (d, 1H, J = 12 Hz, quinoline–H), δ 7.99 (d, 1H, J = 8 Hz, quinoline–H), δ 7.92 (t, 1H, J = 8 Hz, quinoline–H), δ 7.75 (s, 1H, OH) δ 7.59 (t, 1H, J = 4.00 Hz, quinoline–H), δ 7.47 (m, 1H, J = 8 Hz, Ar–H), δ 6.78 (d, 1H, J = 6.8 Hz, Ar–H), δ 6.14 (d, 1H, J = 7.6 Hz, Ar–H), δ 6.05 (d, 1H, J = 7.2 Hz, Ar–H), δ 4.992 (m, 1H, J = 5.2 Hz, Ar–NH), δ 4.18 (s, 1H, OH), δ 2.55 (s, 2H, CH_2), δ 2.21 (m, 1H, amine); ^{13}C NMR (100 MHz, DMSOd6): δ 162.05, 159.62, 155.14, 143.25, 138.94, 138.35, 133.19, 127.94, 127.30, 126.23, 119.08, 116.89, 116.66, 115.81, 100.14, 40.04; Mass: 394.2 (m+); Anal Calcd for $C_{22}H_{17}ClFN_3O$: C, 67.09; H, 4.35; N, 10.67. Found: C, 53.50; H, 4.81; N, 8.31.

Synthesis of 1-((4-(7-chloroquinolin-4-ylamino)-2-hydroxyphenyl) methyl) urea (**5c**)

(% Yield: 64.09); mp: 122–124°C; R_f value: 0.86 (Ethyl acetate: Acetone:: 5:5); UV (λ_{max}): 265 nm (DMSO); IR (KBr cm^{-1}): 3221, 2897, 1846, 1751, 1685 1609, 1534, 1448, 1374, 1374, 1238, 1098, 856, 815; ^{1}H NMR (400 MHz DMSOd6): δ 8.60 (d, 1H, J = 8.8 Hz, quinoline–H), δ 8.51 (t, 1H, J = 8Hz, quinoline–H), δ 8.20 (d, 1H, J = 8.8 Hz, quinoline–H), δ 8.11 (d, 1H, J = 8.4 Hz, quinoline–H), δ 7.99 (d, 1H, J = 10.8 Hz, quinoline–H), δ 7.71 (m, 1H, J = 10.4 Hz, quinoline–H), δ 7.29 (d, 1H, J = 8.00 Hz, quinoline–H), δ 7.36 (d, 1H, J = 8.8 Hz, Ar–H), δ 7.12 (m, 1H, J = 8 Hz, Ar–H)), δ 7.07 (d, 1H, J = 4 Hz, Ar–H), δ 6.98 (d, 1H, J = 4 Hz, Ar–H), δ 6.87 (d, 1H, J = 7.2 Hz, Ar–H), δ 6.71 (m, 1H, J = 8 Hz, Ar–H), δ 6.30 (s, 1H, OH), δ 6.12 (d, 1H, J = 7.2 Hz, Ar–H), δ 5.55 (s, 1H, Ar–NH), δ 4.64 (s, 1H, Ar–OH), δ 3.99 (d, 2H, J = 6.4 Hz, CH_2), δ 2.56 (s, 1H, amine); ^{13}C NMR (100 MHz, DMSOd6): δ 158.35, 153.05, 139.96, 136.16, 135.26, 135.00, 131.29, 130.18, 127.39, 127.22, 127.13, 126.13, 125.89, 125.44, 124.92, 124.24, 123.43, 117.40, 113.72, 110.08, 109.20; Mass: 342.9 (m+); Anal Calcd for $C_{17}H_{15}ClN_4O_2$: C, 59.57; H, 4.41; N, 16.34. Found: C, 56.71; H, 5.31; N, 7.97.

Synthesis of 5-(7-chloroquinolin-4-ylamino)-2-((2-hydroxyethylamino) methyl) phenol (**5d**)

(% Yield: 89.86); mp: 268–270°C; R_f value: 0.9 (Methanol: Dichloromethane:: 5:5); UV(λ_{max}): 259.5 nm (DMSO);

IR(KBr cm^{-1}): 3411, 3233, 2913, 2768, 1654, 1534, 1449, 1375, 1238, 1122, 908, 854, 816; ^{1}H NMR (400 MHz, DMSOd6): δ 8.69 (d, 1H, J = 4.8 Hz, quinoline–H), δ 8.49 (d, 1H, J = 8.8 Hz, quinoline–H), δ 8.43 (d, 1H, J = 5.2 Hz, quinoline–H), δ 8.09 (d, 1H, J = 8.8 Hz, quinoline–H), δ 8.04 (d, 1H, J = 8.4 Hz, quinoline–H), δ 7.90(t, 1H, J = 14.8 Hz, quinoline–H), δ 7.66 (s, 1H, OH), δ 7.55 (m, 1H, J = 10 Hz, Ar–H), δ 7.31 (d, 1H, J = 8.4 Hz, Ar–H), δ 7.21 (t, 1H, J = 8 Hz, quinoline–H), δ 6.99 (m, 1H, J = 4.8 Hz, Ar–H), δ 6.80 (d, 1H, J = 6.8 Hz, Ar–H), δ 6.63 (d, 1H, J=8 Hz, Ar–H), δ 6.5 (s, 1H, OH), δ 4.09 (s, 1H, Ar–OH), δ 4.01 (s, 1H, Ar–NH), δ 3.82 (s, 2H, CH_2), δ 2.84 (s, 1H, acetylene); ^{13}C NMR (100 MHz, DMSOd6): δ 158.30, 153.03, 150.16, 149.99, 147.39, 140.46, 138.29, 136.19, 134.72, 131.30, 130.13, 127.19, 126.12, 125.64, 119.29, 117.79, 113.59, 111.92, 110.84, 109.94, 109.17, 101.98, 67.34, 64.42, 57.36, 41.14; Mass: 343.0 (m+); Anal Calcd for $C_{18}H_{18}ClN_3O_2$: C, 62.88; H, 5.28; N, 12.22. Found: C, 51.32; H, 5.53; N, 8.30.

Synthesis of 5-(7-chloroquinolin-4-ylamino)-2-((piperidin-4-ylamino) methyl) phenol (**5e**)

(% Yield: 92.54); mp: 94–96°C; R_f value: 0.89 (Methanol: Dichloromethane:: 5:5); UV(λ_{max}): 335.0 nm (DMSO); IR (KBr cm^{-1}): 3246, 2800, 2700, 1654, 1560, 1438, 1376, 1274, 1210, 873, 822; ^{1}H NMR (400 MHz, DMSOd6): δ 8.72 (d, 1H, J = 4.4 Hz, quinoline–H), δ 8.07 (d, 1H, J = 9.6 Hz, quinoline–H), δ 7.99 (s, 1H, quinoline–H), δ 7.92 (d, 1H, J = 7.2 Hz, quinoline–H), δ 7.78 (d, 1H, J = 7.2 Hz, quinoline–H), δ 7.66 (s, 1H, OH), δ 7.56 (m, 1H, J = 8.4 Hz, quinoline–H), δ 7.30 (dd, 1H, J = 8, 8.8 Hz, Ar–H), δ 7.08 (d, 1H, J = 4.8 Hz, Ar–H), δ 6.96 (d, 1H, J = 14.4 Hz, Ar–H), δ 6.75 (s, 1H, OH), δ 6.07 (d, 1H, J = 7.2 Hz, Ar–H), δ 4.10 (s, 1H, Ar–NH), δ 3.32 (s, 2H, CH_2), δ 2.79 (s, 1H, amine), δ 2.66 (s, H, piperidine–H), δ 2.49 (s, H, piperidine–H); ^{13}C NMR (100 MHz, DMSOd6): δ 155.68, 151.71, 148.84, 140.05, 134.07, 127.42, 127.21, 126.20, 126.16, 123.54, 120.92, 117.41, 109.66, 109.17; Mass: 367.9 (m+); Anal Calcd for $C_{21}H_{23}ClN_4O$: C, 65.87; H, 6.05; N, 14.63. Found: C, 55.06; H, 4.44; N, 7.65.

Synthesis of 4-((4-(7-chloroquinolin-4-ylamino)-2-hydroxyphenyl)methyl amino) phenol (**5f**)

(% Yield: 58.75); mp: 192-194°C; R_f value: 0.78 (Propanol: Cyclohexane:: 5:5); UV(λ_{max}): 357.5 nm (DMSO); IR(KBr cm^{-1}): 3393, 3130, 2889, 1685, 1542, 1449, 1375, 1242, 976, 908, 819; ^{1}H NMR (400 MHz, DMSOd6): δ 8.32 (dd, 1H, J = 13.2, 14 Hz, quinoline–H), δ 8.13 (d, 1H, J = 4.8 Hz, quinoline–H), δ 7.82 (d, 1H, J = 8.8 Hz, quinoline–H), δ 7.67 (s, 1H, OH), δ 7.56 (d, 1H, J = 7.2 Hz, quinoline–H), δ 7.31 (d, 1H, J = 8.4, quinoline–H), δ 7.17 (d, 1H, J = 8 Hz, Ar–H), δ 6.94 (m, 1H, J = 8.8 Hz, Ar–H), δ 6.71 (dd, 1H, J = 5.2, 8.4 Hz, Ar–H), δ 6.58 (d, 1H, J = 9.2 Hz, Ar–H), δ 6.39 (d, 1H, J = 7.6 Hz, Ar–H), δ 5.83 (d, 1H, J = 6.8 Hz, Ar–OH), δ 5.77 (d, 1H, J = 7.2 Hz, CH_2); ^{13}C NMR (100 MHz, DMSOd6): δ 158.32, 155.41, 151.03, 150.77, 149.93, 148.61, 140.83, 134.22, 130.01, 127.19, 126.69, 126.34, 124.98, 124.79, 123.38, 118.09, 117.84, 117.43, 117.21, 116.07, 113.30, 111.55, 109.68, 109.17,101.17, 100.25, 40.01; Mass: 392.1 (m+); Anal Calcd for $C_{21}H_{16}ClN_3O_2$: C, 66.76; H, 4.27; N, 11.12. Found: C, 55.46; H, 4.48; N, 7.78.

Synthesis of 2-((4-bromo-2-fluorophenylamino) methyl)-5-(7-chloroquinolin-4-ylamino) phenol (**5g**)

(% Yield: 61.26); mp: 258-260°C; R_f value: 0.86(Dichloromethane: Methanol:: 5:5); UV(λ_{max}): 342.5 nm (DMSO); IR(KBr cm^{-1}): 3568, 3205, 2957, 2874, 1654, 1560, 1458, 1363, 1206, 1075, 1010, 873, 815, 764, 572; ^{1}H NMR (400 MHz, DMSOd6): δ 8.18 (d, 1H, J = 8.8 Hz, quinoline–H), δ 8.05 (d, 1H, J = 9.6 Hz, quinoline–H), δ 7.93 (d, 1H, J = 7.2 Hz, quinoline–H), δ 7.63 (d, 1H, J = 8.8 Hz, quinoline–H), δ 7.47 (m, 1H, J = 7.2 Hz, quinoline–H), δ 7.33 (d, 1H, J = 8.4 Hz, Ar–H), δ 7.24 (s, 1H, OH), δ 7.16 (d, 1H, J = 5.2 Hz, Ar–H), δ 7.11 (s, 1H, OH), δ 6.07 (d, 1H, J = 7.2 Hz, Ar–H), δ 4.36 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSOd6): δ 140.56, 132.76, 132.72, 129.19, 129.14, 129.11, 128.68, 128.57, 128.53, 127.74, 127.38, 124.64, 124.02, 119.99, 119.73, 117.90, 65.70; Mass: 475.5 (m+); Anal Calcd for $C_{22}H_{16}BrClFN_3O$: C, 55.89; H, 3.41; N, 8.89. Found: C, 49.86; H, 5.02; N 2.85.

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Conflict of interest Authors declare no conflict of interest.

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