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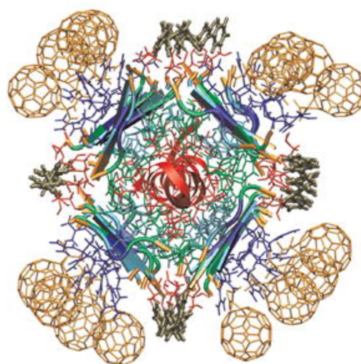

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Design and synthesis of quinolinones as methionyl-tRNA synthetase inhibitors

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Abstract—Five new structural analogues of substituted-1*H*-quinolinones (**19**, **20**, **23**, **24**, and **26**) have been synthesized and evaluated for *Staphylococcus aureus* methionyl-tRNA synthetase enzyme inhibitory activity. These compounds were also tested against pathogens of six *S. aureus*, two *Enterococcus faecalis*, and one *Enterococcus faecium*. Among all the synthesized quinolinones, compound **20** displayed significant inhibitory activities in the strains of *E. faecalis* and *E. faecium*.
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1. Introduction

Aminoacyl-tRNA synthetases (aaRSs) are a group of enzymes that precisely transfer amino acids from cellular pool to their corresponding tRNA cognates to form aminoacyl-tRNAs which serve as substrates for protein synthesis.[1] The transfer of a particular amino acid to tRNA under influence of aaRS occurs through formation of an active intermediate aminoacyladenylate (aa-AMP) by the reaction of the amino acid and ATP. The aa-AMP thus formed is attacked by either 2′-OH or 3′-OH of adenosine of tRNA to form ester with aminoacyl moiety. The catalytic activity of aaRSs is organism specific and it is different in pathogens and human beings. This difference in catalytic activity of aaRSs provides an opportunity to inhibit pathogens' aaRSs selectively without perturbing host aaRSs. Thus, aminoacyl-tRNA synthetases make an alternative drug target to develop antibacterial agents for the treatment of antibiotic-resistant bacterial strains such as methicillin, resistant *Staphylococcus aureus* (MRSA) and *Vancomycin resistant enterococci* (VRE).[2–4]

Aminoacyladenylate (aa-AMP) being highly active and susceptible to hydrolysis makes the possibility of synthesizing its stabilized analogues having potential inhibitory properties. In this respect various isosteres of linear chain attached to aa-AMP, such as alkylphosphate, ester, amide, hydroxamate, sulfamate,[5] sulfamide, *N*-alkoxysulfamide, and *N*-hydroxysulfamide have been prepared as replacement of the hydrolytically labile acylphosphate of the aminoacyladenylate. Inhibitors of aminoacyladenylate have been also synthesized by modifying hydroxyl groups of ribose present in aminoacyladenylate.[6]

Recently, a quinoline derivative[7] has been identified by high throughput screening of a library of compounds as a competitive inhibitor of methionyl-tRNA synthetase (MRS). Structure–activity relationship[7–10] study of the derivative led to the synthesis of **2** with IC_{50} value 16 nM against MRSA.

Keywords: Methionyl-tRNA synthetase inhibitor; Antibacterial agent; Quinolone.
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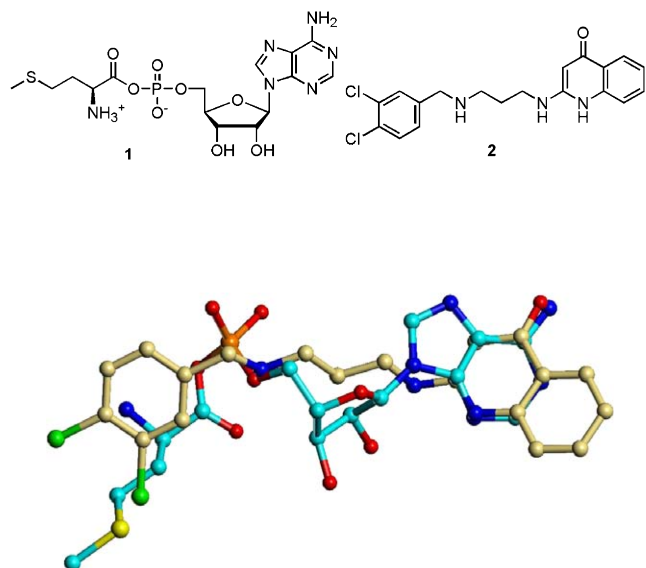


Figure 1. Pharmacophoric superimposition of compounds **1** and **2**.

Our presumption that quinolone (**2**) inhibits catalytic activity of **1** by occupying binding site of methionyladenylate (**1**) led us to perform molecular modeling study of **1** and **2**. In the modeling principal pharmacophores of **2** were identified and compared with methionyladenylate (**1**). Positions of all five pharmacophoric groups of **2** were matched with those of methionyladenylate **1** in an energy-minimized conformation (Fig. 1).[11]

Carbonyl group, nitrogen atom of quinolone ring, and exocyclic nitrogen atom were superimposed with N_6-amino, N_3, and N_9-atoms of adenine ring of **1**, respectively. The other nitrogen atom of the linker and a chloro group of **2** superimposed with an oxygen and sulfur atoms of **1**. The RMS superposition of the pharmacophoric groups verified perfect correlation between **1** and **2**. Further, it is evident from Figure 1 that linear chain of compound **2** provides appropriate separation between quinolone and 3,4-dichlorobenzene ring but does not fully superimpose with ribose ring of **1**. The linker with a hydrophilic functionality such as hydroxy, methoxy, or hydroxymethyl might provide a better surrogate for ribose. This notion led us to design and synthesize **19**, **20**, **23**, **24**, and **26**.

2. Chemistry

The designed compounds **2**, **19**, **20**, **23**, **24**, and **26** have been synthesized by nucleophilic substitution reaction of aryloxyquinoline **5** with excess of either 1,3-diaminopropane or suitably substituted 1,3-diaminopropanes (**10**, **14**) followed by TFA-catalyzed hydrolysis of 4-methoxybenzyl group and reductive alkylation with 3,4-dichlorobenzaldehyde (Schemes 4–6). The quinoline **5** was previously prepared in two steps from aniline using literature procedure[12] (Scheme 1). Quinolone **6** has been isolated as minor product during the synthesis of **5** by the reaction of 2,4-dichloroquinoline (Scheme 1) and 4-methoxybenzylalcohol in presence of sodium hydride and catalyst 15-crown-5.

2-Methoxypropane-1,3-diamine (**10**) required for the synthesis of **20** was prepared in three steps from epichlorohydrin (**7**). A reaction of **7** and excess of dibenzylamine afforded 2-hydroxy-tetrabenzylpropane-1,3-diamine (**8**) which on methylation with sodium hydride and MeI furnished **9**. The compound **9** was debenzylated by stirring a mixture of **9** and $Pd(OH)_2$ in methanol at rt to produce **10**. The compound **10** was used as such without purification (Scheme 2).

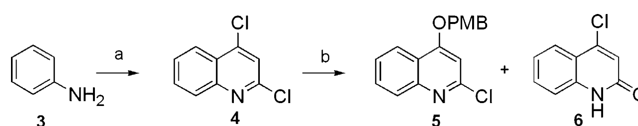
2,4-Diaminobutanol-1 (**14**) essential for synthesis of target compounds (**23**, **24**) was delineated from 2,4-diaminobutyric acid dihydrochloride (**11**) by different procedure as shown in Scheme 3. A reaction of **11** and benzylbromide in 1:1 mixture of NaOH and K_2CO_3 in aqueous methanol at reflux temperature provided **12** in good yield. Reduction of the ester **12** into corresponding alcohol **13** by $LiAlH_4$ in THF under reflux condition and subsequent debenzylation with $Pd(OH)_2$ yielded **14** which was used as such without purification. Synthesis of **23** and **24** relied on efficient isolation and characterization of their respective intermediates **21** and **22** in different yields. Stirring a mixture of **5** and **14** in 1:5 molar ratios in presence of K_2CO_3/DMSO at 80 °C for 48 h provided **21** in 41% and **22** in 8% yields.

3. Results and discussion

3.1. Methionyl-tRNA synthetase enzyme assay

All the synthesized compounds **2**, **19**, **20**, **23**, **24**, and **26** were evaluated for in vitro inhibitory activity against *S. aureus* methionyl-tRNA synthetase. The inhibitory activities of the compounds shown in Table 1 have been determined by measuring decrease in the generation of the aminoacyl product [^{35}S]methionyl *S. aureus*-tRNA,^{Met} in presence of different chemical concentrations as described.[6]

The reference compound **2** was found most active with IC_{50} value 1.09 nM under this condition. Introduction of a hydroxyl and methoxy group at C-2 in the linear chain of **2** provided relatively less potent compounds **19** and **20** by ca. 2-fold, respectively. Thus, C-2 position does not tolerate either H-bond donor or acceptor substituents. A compound **23** was then synthesized to explore C-3 position of the linker of compound **2** but this displayed almost same level of activity (IC_{50} = 2.85 nM). C-1 position of the linear chain of **2** was investigated by preparing compound **24** which showed around 9-fold decrease in



Scheme 1. Reagents and conditions: (a) Malonic acid, $POCl_3$, reflux, 55%; (b) (4-OMe)BnOH, 15-crown-5 ether, NaH, rt, 5:82%, 6:6%.

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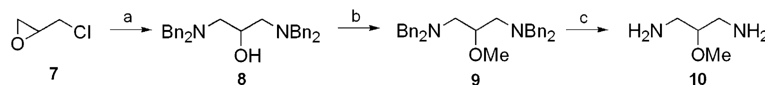
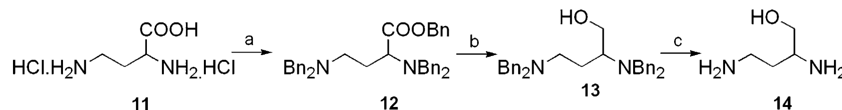


Scheme 2. Reagents and conditions: (a) Bn_2NH, 130 °C, 20 h, 85%; (b) MeI, NaH, rt, 6 h, 52%; (c) $Pd(OH)_2$, MeOH, rt, 24 h.



Scheme 3. Reagents and conditions: (a) BnBr, NaOH, K_2CO_3, MeOH–H_2O, reflux, 5 h, 88%; (b) $LiAlH_4$·THF, reflux, 6 h, 92%; (c) $Pd(OH)_2$, MeOH, rt, 24 h.

Table 1. In vitro inhibitory activities of the synthesized compounds against *S. aureus* methionyl-tRNA synthetase enzyme

Compound	Structure	IC_{50}[a] (nM)
2		1.09
19		2.32
20		2.48
23		2.85
24		18.6
26		4946

[a] Values represent means of three experiments.

potency. Replacement of 4-quinolone of **2** by 2-quinolone resulted a compound **26** with 5000 times less activity.

3.2. Antibacterial assay

Minimum inhibitory concentration (MIC) of the synthesized compounds shown in Table 2 was determined by a microdilution method with Mueller–Hinton Broth (MH, Difco Laboratories, Detroit, MI) for *staphylococci* and Brain Heart Infusion Broth (BHI, Difco) for *Enterococci* following the National Committee for Clinical Laboratory Standards (NCCLS).[13] Six bacterial strains of *S. aureus* (ATCC25923, ATCC6538P, ATCC10537, GIORGIO, SP-N2, and SMITH), one *Staphylococcus epidermidis* (ATCC12228), two *Enterococcus faecalis* (ATCC29212, ATCC19433), and one *Enterococcus faecium* (ATCC10541) were used for the assay. The stock solutions of test compounds were diluted to give a serial, 2-fold series yielding final chemical concentrations ranging from 64 to 0.03 μg/mL. The MIC was defined as the lowest concentration of the chemical that inhibited the development of visible bacterial growth after incubation for 16 h at 36 °C. Mupirocin and amoxicillin antibiotics were used as standard drug.

All the tested compounds were found less potent than both the standard antibiotic mupirocin and amoxicillin in all the strains of *S. aureus*. However, compounds **2**, **19**, and **20** displayed significant inhibitory activities against strains of *E. faecalis* and *E. faecium* but are less active than amoxicillin (Table 2). The compound **2** showed 64 times more inhibition against both the strains of *E. faecalis*, while 32-fold more inhibition against *E. faecium* strain than mupirocin. The compound **19** was found 4- and 8-fold more potent against strains of *E. faecalis* ATCC29212 and ATCC19433, respectively but only two times more active against *E. faecium* strain

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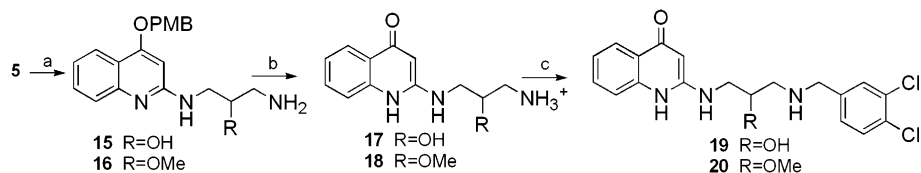
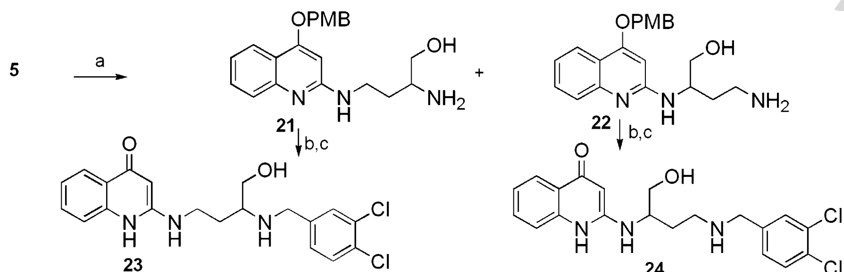
Table 2. In vitro minimum inhibitory concentration (MIC) of compounds against strains of *S. aureus*, *E. faecalis*, and *E. faecium*

Strains	**STD**[1]/**STD**[2]	**2**	**19**	**20**	**23**	**24**	**26**
S. aureus ATCC25923	0.12/0.25	32	>64	>64	>64	>64	32
S. aureus ATCC6538P	0.06/0.25	8	32	16	>64	>64	32
S. aureus ATCC10537	0.12/0.12	32	64	32	>64	>64	32
S. aureus GIORGIO	0.06/0.12	32	64	32	>64	>64	32
S. aureus SP-N2	0.25/>64	16	32	32	>64	>64	32
S. aureus Smith	0.12/0.25	16	64	32	>64	>64	32
S. epidermidis ATCC12228	0.12/8	16	64	32	>64	>64	32
E. faecalis ATCC29212	64/0.5	1	16	8	64	64	64
E. faecalis ATCC19433	64/0.5	1	8	4	32	64	32
E. faecium ATCC10541	16/2	0.5	8	2	32	64	64

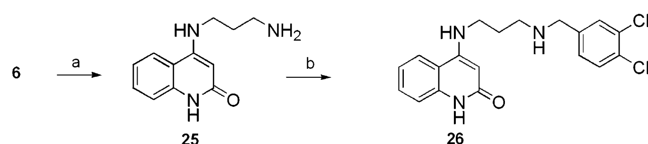
STD[1], Mupirocin; **STD**[2], Amoxicillin.



Scheme 4. Reagents and conditions: (a) $NH_2CH_2CH(OH)CH_2NH_2$ or **10**, K_2CO_3, DMSO, 80 °C, 48 h, **15**, 55%, **16**, 51%; (b) 20% TFA–DCM, rt, 2 h; (c) 3,4-Cl_2PhCHO, AcOH, MeONa, $NaCNBH_3$, MeOH, 50 °C, 6 h, **19**, 48%, **20**, 52%.



Scheme 5. Reagents and conditions: (a) **14**, K_2CO_3, DMSO, 80 °C, 48 h, **21**, 41%, **22**, 8%; (b) 20% TFA–DCM, rt, 2 h; (c) 3,4-Cl_2PhCHO, AcOH, MeONa, $NaCNBH_3$, MeOH, 50 °C, 6 h, **23**, 55%, **24**, 48%.



Scheme 6. Reagents and conditions: (a) $NH_2(CH_2)_3NH_2$, 110 °C, 48 h, 62%; (b) 3,4-Cl_2PhCHO, AcOH, MeONa, $NaCNBH_3$, MeOH, 50 °C, 6 h, 60%.

ATCC10541 than the standard mupirocin. Compound **20**, a methylated analogue of **19**, showed similar pattern of antibacterial properties but found 2-fold more active against *E. faecalis* and 4-fold more active against *E. faecium* than **19**. The increased inhibitory activity of compound **20** was probably due to less polarity and better bioavailability than **19**. The compounds **23** and **26** displayed similar antibacterial activity in all pathogens of *S. aureus* and *E. faecium*, while 2-fold more activity in *E. faecalis* ATCC19433 than mupirocin. Compound **24** did not show any significant activity.

4. Conclusion

The present study suggests that linear carbon chain present in the compound **2** seems to be appropriate and substitution of hydroxyl or hydroxymethyl group at any position in the chain is detrimental for the methionyl-tRNA synthetase inhibitory activity. However, non-polar substitution at C-2 position favors antibacterial activity. Further optimization of linear chain of **2** is under progress.

5. Experimental

5.1. Chemistry

All the chemical reagents used were either synthesized or commercially available. Melting points were determined on a Melting Point Büchi B-540 apparatus and are uncorrected. Silica gel column chromatography was performed on silica gel 230–400 mesh, Merck. Proton NMR spectra were recorded on a JEOL JNM-LA 300 at 300 MHz. Chemical shifts are reported in ppm units with Me_4Si as an internal reference standard. Infrared spectra were recorded on a Perkin-Elmer 1710 Series FTIR. Mass spectra were recorded on a VG Trio-2 GC–MS.

5.2. 1,3-Bis-dibenzylaminopropan-2-ol (8)

A mixture of **7** (1.0 mL) and dibenzylamine (10 mL) was stirred at 130 °C for 20 h. Excess of dibenzylamine was removed under vacuum and residue thus obtained was purified on silica gel using hexane/CH_2Cl_2 (9:1) as eluent. Colorless oil; yield 85%; IR (Neat) ν 3457 cm^{-1} (OH); MS(FAB) *m/z* 451 (MH^+, 100%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.41 (d, $J = 6.21$ Hz, 4H, CH_2), 3.44–3.65 (m, 8H, CH_2), 3.74–3.84 (m, 1H, CH), 7.20–7.31 (m, 20 H, ArH).

5.3. *N,N,N′,N′*-Tetrabenzyl-2-methoxypropane-1,3-diamine (9)

To a solution of **8** (2.0 g, 4.45 mmol) in dry DMF (10 mL), sodium hydride (0.12 g, 4.88 mmol) was added in portions and resulting suspension stirred at rt for 15 min. Methyl iodide (0.41 mL, 6.67 mmol) was added dropwise and stirred for 4 h at rt. The reaction mixture was poured into water (30 mL) and extracted with diethyl ether (15× 3 mL). Ether layers were combined, dried over $MgSO_4$, and evaporated under vacuum. Residue obtained was purified on silica gel column using hexane/CH_2Cl_2 (1:1) as eluent. White solid; mp 64–65 °C; yield 52%; MS(FAB) *m/z* 465 (MH^+, 100%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.36 (dd, $J = 13.38$, 5.90 Hz, 2H, CH_2), 2.54 (dd, $J = 13.38$, 5.90 Hz, 2H, CH_2), 3.32 (s, 3H, OCH_3), 3.38–3.67 (m, 9H, CH and CH_2), 7.22–7.31 (m, 20H, ArH).

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5.4. 2-Methoxypropane-1,3-diamine (10)

A mixture of **3** (2.0 g) and $Pd(OH)_2$ (2.0 g, 20%) in methanol (15 mL) was stirred under H_2 balloon for 24 h at rt. $Pd(OH)_2$ was filtered over a Celite pad, evaporated under reduced pressure to yield **10** which, used as such for next stage.

5.5. 2,4-Bis-dibenzylaminobutyric acid benzyl ester (12)

Benzyl bromide (6.8 mL, 57.59 mmol) was added to a solution of 2,4-diaminobutyric acid dihydrochloride **11** (2.0 g, 10.47 mmol) in a mixture of sodium hydroxide (1.24 g, 31.32 mmol) and K_2CO_3 (4.32 g, 31.32 mmol) in $MeOH/H_2O$ (15 mL/15 mL). The reaction mixture was refluxed for 6 h, cooled to rt, extracted with dichloromethane (20× 3 mL), evaporated, and purified on silica gel column using hexane/CH_2Cl_2 (1:1). Colorless oil; yield: 88%; IR (neat) ν 1727 cm^{-1} (CO); MS(EI) *m/z* 568 (M^+, 100%). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.82–2.05 (m, 2H, CH_2), 2.22–2.30 (m, 1H, NCH_2), 2.56–2.66 (m, 1H, NCH_2), 3.28 (d, J = 13.53 Hz, 2H, NCH_2), 3.39 (d, J = 13.53 Hz, 2H, NCH_2), 3.42 (d, J = 13.53 Hz, 2H, NCH_2), 3.46 (t, J = 7.14 Hz, 1H, CH), 3.79 (d, J = 13.53 Hz, 2H, CH_2), 4.98 (d, J = 12.27 Hz, 1H, OCH_2), 5.15 (d, J = 12.27 Hz, 1H, OCH_2), 7.16–7.39 (m, 25H, ArH).

5.6. 2,4-Bis-dibenzylaminobutan-1-ol (13)

A solution of **12** (3.0 g, 5.28 mmol) in THF (10 mL) was added slowly to a stirred suspension of $LiAlH_4$ in THF (20 mL). The reaction mixture was refluxed overnight, cooled, and added NaOH (15% aq) to quench the $LiAlH_4$, again refluxed for 30 min, cooled to rt, and filtered the solid precipitate. The filtrate was dried over $MgSO_4$, evaporated under vacuum, and purified on silica gel column using CH_2Cl_2/MeOH (49:1) as eluent. Colorless oil; yield 92%; IR (neat) ν 3430 cm^{-1} (OH); MS(FAB) *m/z* 465 (MH^+, 100%); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.36–1.46 (m, 1H, CH_2), 1.89–2.0 (m, 1H, CH_2), 2.30–2.47 (m, 2H, NCH_2). 2.71–2.74 (m, 1H, CH), 3.27 (d, J = 5.67 Hz, 2H, CH_2OH), 3.34 (d, J = 13.38 Hz, 2H, NCH_2), 3.48 (d, J = 13.38 Hz, 2H, NCH_2), 3.62 (d, J = 13.38 Hz, 2H, NCH_2), 3.72 (d, J = 13.38 Hz, 2H, NCH_2), 7.17–7.37 (m, 20H, ArH).

5.7. 2,4-Diaminobutan-1-ol (14)

A mixture of **13**, (2.0 g) and $Pd(OH)_2$ (2.0 g, 20%) was stirred in methanol for 24 h at rt. $Pd(OH)_2$ was filtered, methanol evaporated, and used as such for next stage.

5.8. General procedure for preparation of 4-Aryl-2-substituted aminoquinoline (15, 16, 21, 22)

A mixture of **9** (150 mg, 0.50 mmol) and 2-hydroxy-1,3-diaminopropane (225 mg, 2.5 mmol) was stirred in DMSO (15 mL) at 80 °C in presence of potassium carbonate (83 mg, 0.6 mmol) for 48 h. The reaction mixture was poured into distilled water (50 mL) and extracted with ethyl acetate (25× 3 mL), dried over sodium sulfate, and evaporated. The solid obtained was purified on silica gel column using $CH_2Cl_2/MeOH/NH_3$ sol (90:10:0.5) as eluent. Similarly, **16**, **21**, and **22** were prepared by the reaction of **5** with **10** and **14**, respectively.

5.8.1. 1-Amino-3-[4-(4-methoxybenzyloxy)-quinolin-2-yl-amino]-propan-2-ol (15). White solid; mp 133–135 °C; yield 55%; IR (KBr) ν 3336 cm^{-1} (OH); MS(FAB) *m/z* 354 (MH^+, 30%). ^1H NMR ($CDCl_3$, 300 MHz) δ 3.48–3.59 (m, 2H, NCH_2), 3.64–3.69 (m, 2H, NCH_2), 3.73–3.76 (m, 1H, CH), 3.88 (s, 3H, OCH_3), 5.09 (s, 2H, OCH_2), 6.37 (s, 1H, ArH), 9.94 (d, J = 8.70 Hz, 2H, ArH), 7.15–7.20 (m, 1H, ArH), 7.38 (d, J = 8.70 Hz, 2H, ArH), 7.48–7.53 (m, 1H, ArH), 7.58–7.61 (m, 1H, ArH), 7.96–7.99 (m, 1H, ArH).

5.8.2. 2-Methoxy-*N*′-[4-(4-methoxybenzyloxy)-quinolin-2-yl]propane-1,3-diamine (16). White solid; mp 125–127 °C; yield 51%; MS(FAB) *m/z* 368 (MH^+, 100%). ^1H NMR ($CDCl_3$, 300 MHz) δ 2.85–2.90 (m, 1H, CH), 3.46–3.48 (m, 2H, NCH_2), 3.45 (s, 3H, OCH_3), 3.70–3.75 (m, 2H, NCH_2), 3.84 (s, 3H, OCH_3), 5.13 (s, 2H, CH_2), 6.11 (s, 1H, ArH), 6.95 (d, J = 8.58 Hz, 2H, ArH), 7.15–7.20 (m, 1H, ArH), 7.40 (d, J = 8.58 Hz, 2H, ArH), 7.48–7.54 (m, 1H, ArH), 7.58–7.61 (m, 1H, ArH), 7.97–7.99 (m, 1H, ArH).

5.8.3. 2-Amino-4-[4-(4-methoxybenzyloxy)quinolin-2-yl-amino]butan-1-ol (21). White solid; mp 134–135 °C; yield 41%; IR (KBr) ν 3340 cm^{-1} (OH); MS(EI): *m/z* 367 (M^+, 100%). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.62–1.83 (m, 2H, CH_2), 2.95–2.99 (m, 1H, CH), 3.48–3.63 (m, 2H, OCH_2), 3.73–3.80 (m, 2H, CH_2), 3.84 (s, 3H, OCH_3), 5.12 (s, 2H, OCH_2), 5.98 (s, 1H, ArH), 6.96 (d, J = 8.60 Hz, 2H, ArH), 7.13–7.18 (m, 1H, ArH), 7.40 (d, J = 8.60 Hz, 2H, ArH), 7.43–7.53 (m, 1H, ArH), 7.61–7.64 (m, 1H, ArH), 7.98 (m, 1H, ArH).

5.8.4. 4-Amino-2-[4-(4-methoxybenzyloxy)quinolin-2-yl-amino] butan-1-ol (22). White solid; mp 155–156 °C; yield 8%; IR(KBr) ν 3337 cm^{-1} (OH); MS(EI): *m/z* 367 (M^+, 100%). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.65–1.66 (m, 2H, CH_2), 2.97–2.99 (m, 2H, NCH_2), 3.72–3.79 (m, 3H, CH and OCH_2), 3.83 (s, 3H, OCH_3), 5.09 (s, 2H, OCH_2), 6.10 (s, 1H, ArH), 6.94 (d, J = 8.60 Hz, 2H, ArH), 7.11–7.16 (m, 1H, ArH), 7.38 (d, J = 8.60 Hz, 2H, ArH), 7.44–7.49 (m, 1H, ArH), 7.53–7.56 (m, 1H, ArH), 7.94 (m,1H, ArH).

5.9. 4-(3-Aminopropylamino)-1*H*-quinolin-2-one (25)

A mixture of **6** (150 mg, 0.837 mmol) and 1,3-diaminopropane (2 mL, 23.9 mmol) was stirred at 110 °C for 48 h under nitrogen atmosphere. 1,3-Diaminopropane was evaporated under vacuum, the crude product was purified on silica gel column using CH_2Cl_2/MeOH/NH_3 soln (9:1:0.5) as eluent. Colorless oil; yield 62%; MS(FAB) *m/z* 218 (MH^+, 100%). ^1H NMR (CD_3OD, 300 MHz) δ 1.84–1.94 (m, 2H, CH_2), 2.79 (t, J = 7.2 Hz, 2H, NCH_2), 3.35 (t, J = 6.9 Hz, 2H, NCH_2), 5.54 (s, 1H, ArH), 7.19–7.24 (m, 1H, ArH), 7.31 (dd, J = 8.1, 0.6 Hz, 1H, ArH), 7.48–7.54 (m, 1H, ArH), 7.88 (dd, J = 8.4, 0.9 Hz, 1H, ArH).

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5.10. 3-(4-Oxo-1,4-dihydroquinolin-2-ylamino)-substituted-propylammonium (17,18)

These compounds were obtained by TFA-catalyzed hydrolysis of their corresponding 4-methoxybenzyloxybenzyloxy derivatives **15** and **16**, respectively. The compounds **17**, **18** were subjected to reductive alkylation with 3,4-dichlorobenzaldehyde without purification. Similarly **21** and **22** were hydrolyzed and used to synthesize target compounds **23** and **24**, respectively.

5.11. 2-[3-(3,4-Dichlorobenzylamino)-substituted propylamino]1*H*-quinolin-4-one (19, 20, 23, 24, 26)

General procedure

To a solution of **17** (100 mg, 0.43 mmol) in methanol (5 mL), acetic acid was added (0.1 mL) followed by 0.5 M MeONa (1 mL, 0.43 mmol) at rt (20 °C). The reaction mixture was stirred for 15 min at rt (20 °C) then 3,4-dichlorobenzaldehyde (75 mg, 0.43 mmol) added and stirred at 50 °C for 1 h. $NaCNBH_3$ (40 mg, 0.64 mmol) solution in MeOH (5 mL) was added, again stirred for 6 h at 50 °C. Methanol was evaporated and crude product purified by Silica gel column using CH_2Cl_2/MeOH/NH_3 sol (95:5:0.5) as eluent.

5.11.1. 2-[3-(3,4-Dichlorobenzylamino)-2-hydroxypropylamino]-1*H*-quinolin-4-one (19). White solid; mp 220–222 °C; yield 48%; MS(FAB) *m/z* 393 (MH^+, 100%). ^1H NMR (CD_3OD, 300 MHz) δ 2.67–2.80 (m, 2H, NCH_2), 3.33–3.57 (m, 2H, NCH_2), 3.85 (s, 2H, CH_2), 3.92–3.99 (m, 1H, CHOH), 5.67 (s, 1H, ArH), 7.21–7.31 (m, 3H, ArH), 7.44 (d, J = 8.4 Hz, 1H, ArH), 7.49–7.56 (m, 2H, ArH), 8.06 (dd, J = 8.1, 1.2 Hz, 1H, ArH).

5.11.2. 2-[3-(3,4-Dichlorobenzylamino)-2-methoxypropylamino]-1*H*-quinolin-4-one (20). White Solid; mp 180–182 °C; yield 52%; MS(FAB) *m/z* 407 (MH^+, 100%). ^1H NMR (CD_3OD, 300 MHz) δ 2.72 (d, J = 5.13 Hz, 2H, NCH_2), 3.43 (s, 3H, OCH_3); 3.49–3.61 (m, 3H, CH), 3.74–3.84 (m, 2H, CH_2), 5.68 (s, 1H, ArH), 7.22–7.32 (m, 3H, ArH), 7.43 (d, J = 8.22 Hz, 1H, ArH), 7.49–7.54 (m, 2H, ArH), 8.06 (dd, J = 8.22, 1.2 Hz, 1H, ArH).

5.11.3. 2-[3-(3,4-Dichlorobenzylamino)-4-hydroxybutylamino]-1*H*-quinolin-4-one (23). White solid; mp 223–224 °C; yield 55%; IR (KBr) ν 3427 cm^{-1} (OH); MS(FAB) *m/z* 407 (MH^+, 100%). ^1H NMR (CD_3OD, 300 MHz) δ 1.77–1.83 (m, 2H, CH_2), 2.69–277 (m, 1H, CH), 3.34–3.46 (m, 2H, OCH_2), 3.54–3.69 (m, 2H, NCH_2), 3.74–3.85 (m, 2H, CH_2), 5.62 (s, 1H, ArH), 7.21–7.28 (m, 3H, ArH),7.37 (d, 1H, J = 8.20 Hz, ArH), 7.46–7.54 (m, 2H, ArH), 8.06 (dd, 1H, J = 8.1, 1.2 Hz, ArH).

5.11.4. 2-[3-(3,4-Dichlorobenzylamino)-1-hydroxymethylpropylamino]-1*H*-quinolin-4-one (24). White solid; mp 210–212 °C; yield 48%; IR (KBr) ν 3430 cm^{-1} (OH); MS(FAB) *m/z* 407 (MH^+, 100%). ^1H NMR (CD_3OD, 300 MHz) δ 1.77–1.83 (m, 2H, CH_2), 2.69–2.77 (m, 1H, CH), 3.34–3.46 (m, 2H, OCH_2), 3.54–3.69 (m, 2H, NCH_2), 3.74–3.85 (m, 2H, CH_2), 5.62 (s, 1H, ArH), 7.21–7.28 (m, 3H, ArH),7.37 (d, 1H, J = 8.20 Hz, ArH), 7.46–7.54 (m, 2H, ArH), 8.06 (dd, 1H, J = 8.1, 1.2 Hz, ArH).

5.11.5. 4-[3-(3,4-Dichlorobenzylamino)propylamino]-1*H*-quinolin-2-one (26). White Solid; mp 197–199 °C; yield 60%; MS(FAB) *m/z* 376 (MH^+, 100%). ^1H NMR (CD_3OD, 300 MHz) 1.89–2.00 (m, 2H, CH_2), 2.73 (t, J = 6.9 Hz, 2H, NCH_2), 3.34 (t, J = 7.2 Hz, 2H, NCH_2), 3.74 (s, 2H, CH_2), 5.51 (s, 1H, ArH), 7.12–7.7.18 (m, 1H, ArH), 7.24 (dd, J = 8.2, 2.0 Hz, 1H, ArH), 7.30 (dd, J = 8.4, 0.9 Hz, 1H, ArH), 7.41 (d, J = 8.1, 0.9 Hz, 1H, ArH), 7.47–7.52 (m, 2H, ArH), 7.76 (dd, J = 8.1, 0.9 Hz, 1H, ArH).

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