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Graphical Abstract

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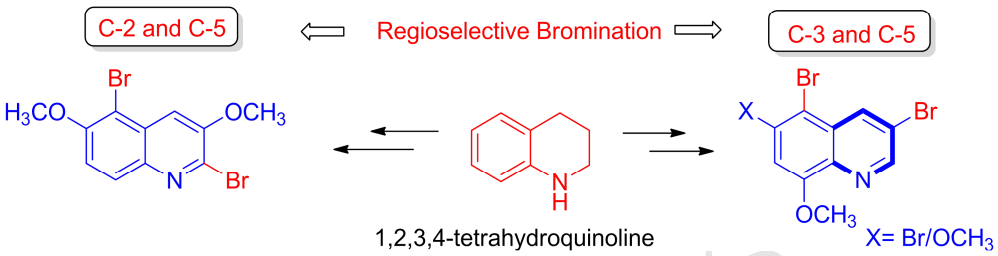

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Regioselective bromination: synthesis of brominated methoxyquinolines

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ABSTRACT

Simple synthetic methods are described for the synthesis of valuable polyfunctional brominated methoxyquinolines **10**-**13**, **20**-**21**, and **24**-**25**. Three regioselective routes are described for convenient preparation of brominated methoxyquinolines at the C-2, C-3, and C-5 positions with consecutive reaction steps under mild reaction conditions using molecular bromine. While bromination of 6-bromo-8-methoxy-1,2,3,4-tetrahydroquinoline (**8**) selectively gave 3,6-dibromo-8-methoxyquinoline (**10**) and 3,5,6-tribromo-8-methoxyquinoline (**11**), the reaction of 6,8-dimethoxy-1,2,3,4-tetrahydroquinoline (**9**) resulted in the formation of 3-bromo-6,8-dimethoxyqinoline (**12**) and tribromide **13**. On the other hand, direct bromination of 6-methoxy- **17** and 6,8-dimethoxyquinoline (**19**) gave 5-bromo derivatives **20** and **21**. However, the reaction 3,6-dimethoxyquinoline (**8**) resulted in dibromination to form 2,5-dibromoquinoline (**24**). This process selectively led to functionalization of the quinoline ring at both the C-2 and C-5 positions.

1. Introduction

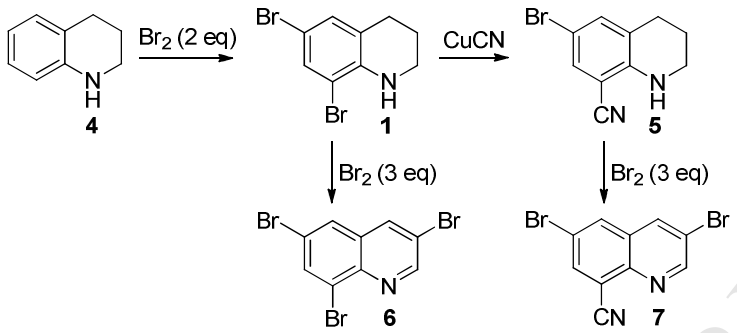
Developments in the synthesis of new quinoline derivatives are progressing and expanding hugely due to their pharmaceutical importance. Applications of quinoline derivatives have become widespread from anticancer drugs to almost every branch of medicinal chemistry.[1-3] A variety of heterocyclic ring systems for anticancer activity have been widely reported by a number of researchers to develop new approaches to a variety of heterocyclic ring systems, especially including 3-substituted quinoline derivatives.[3]

Several methods for the synthesis of haloquinolines have been reported, including direct halogenation, which always suffers from poor regioselectivity and overhalogenation,[4] but only a few methods for the regioselective synthesis of 3-haloquinolines are known.[5] The development of a new synthetic method for preparing halogen-containing quinolines would enable the synthesis of diverse quinoline frameworks because the halogen atom could enhance biological activity in many cases6 and could also be used for further functionalization in preparing other molecules.[7,8]

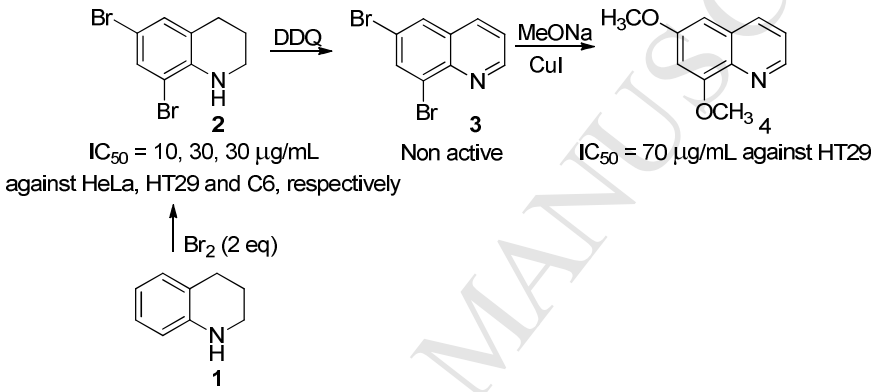
There has been enormous interest in developing efficient methods for the synthesis of quinoline derivatives considering their significant applications in the field of bioorganic, industrial, and synthetic organic chemistry. The Skraup, Friedländer, Doebner–von Miller, and Combes syntheses[8,9] of quinoline derivatives are important classical synthetic approaches. Almost all synthetic strategies are based on metal catalyzed cyclizations or acid catalyzed cycloadditions.[9] However, quinoline synthesis has important disadvantages, such as harsh reaction conditions and highly acidic media,[10] that make it tedious to isolate the product from the crude mixture. For instance, the Skraup procedure includes reactions of *meta*- or 3,4-disubstituted anilines normally giving a mixture of regioisomers difficult to isolate. Most of these methods are not fully satisfactory with respect to yield,[11–13] reaction conditions,[11,13] generality,[13,14] and practical use.[11,13] These synthetic problems have encouraged researchers to develop a practical efficient procedure for the synthesis of these important heterocycles.[15]

It is interesting that despite the considerable synthetic and biological interest in quinoline derivatives, very few general synthetic routes are available starting from quinoline or tetrahydroquinoline cores themselves. Recently, we have found that the bromination reaction of substituted 1,2,3,4-tetrahydroquinolines is a good starting point for functionalizing both rings. In our previous publications, brominated tetrahydroquinolines were transformed to their respective derivatives.[9,16] Bromination of 6-bromo-8-cyano-1,2,3,4-tetrahydroquinoline gave corresponding 3-brominated quinoline derivatives (Scheme 1).[16] This methodology uses neither metal catalyzed cyclizations nor acid catalyzed cycloadditions. The process constitutes a rapid and convenient method for obtaining selective brominated aromatic compounds as the sole products in high yields.

This work presented herein is a continuation of our ongoing research and focuses on the synthesis of polyfunctional quinolines, starting from methoxy 1,2,3,4-tetrahydroquinoline, which provides an efficient synthesis of brominated derivatives at C-3 and C-5 (Scheme 1). We are also interested in investigation of the biological activity and structure–activity relationship (SAR) results because the synthesized quinoline derivatives exhibited promising anticancer activities and interesting SARs (Scheme 2).[9,17-20]



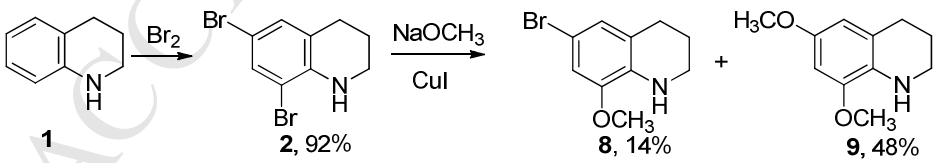
Scheme 1. Preparation of 3-bromo quinolines from tetrahydroquinolines.



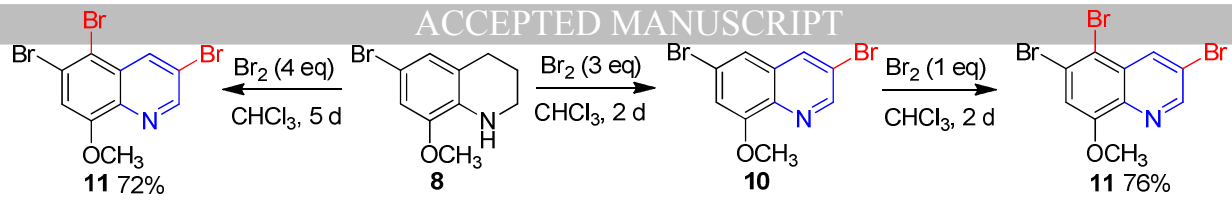
Scheme 2. Structure-Activity Relationship for compounds **2**, **3** and **4**.

2. Results and Discussion

The starting compounds were synthesized according to our procedures reported previously starting from 1,2,3,4-tetrahydroquinoline (**1**) (Scheme 3).[9,21-22] First we studied bromination of methoxy quinolines **8** and **9** with different equivalents of bromine. The product ratios and conversions are compiled in Scheme 4. While bromination of **8** with three equivalents of bromine afforded compound **10**, bromination with four equivalents of bromine gave tribromide **11** (Scheme 4).



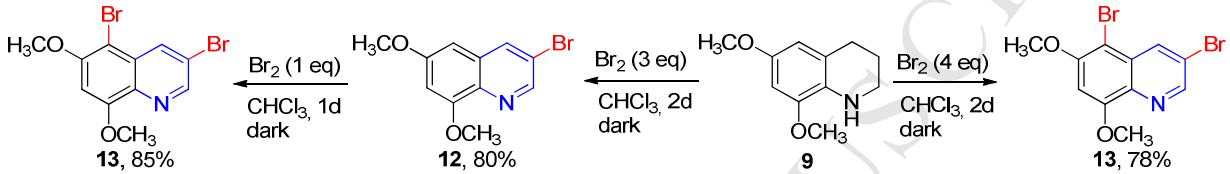
Scheme 3. Preparation of starting materials.



Entry	Br_2 (eq)	Product	Yield	Conversion
1	1	**10**	43%	50%
2	2	**10**	56%	68%
3	3	**10**	77%	100%
4	4	**11**	72%	100%

Scheme 4. Bromination reaction of 6-bromo-8-methoxy THQ **8** and synthesis of dibromide **10** and tribromide **11**.

Dimethoxide **9** was brominated with 3 equivalents of bromine, and the dibromide **12** was obtained as the sole product in high yield (80%) in reaction conditions similar to those of compound **8**. On the other hand, bromination of **9** with four equivalents of bromine gave dibromide **13** in 78% yield. The dibromide **13** was also achieved by the bromination of compound **12** using one equivalents of bromine in 85% yield (Scheme 5).



Scheme 5. Bromination of 6,8-dimethoxide **9**

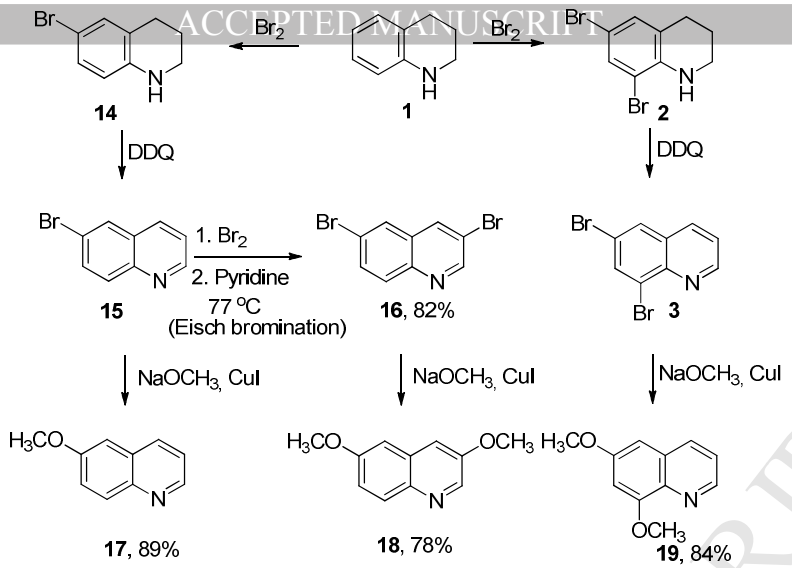
The ^{1}H NMR spectra of compounds **10**, **11**, **12**, and **13** exhibit simple aromatic signals, which are established easily by their vicinal coupling patterns. The ^{1}H NMR spectra of **10** consisted of four characteristic aryl signals with *meta* couplings (^4J = 1.6 Hz), indicating the positions of the bromine groups. The observation of *meta* couplings and a singlet signal (δ 4.1) in the ^{1}H NMR spectrum of **10** is consistent with the methoxy group at C-8 and two bromines bound to the C-3 and C-5 positions (Table 1). In the ^{13}C NMR spectrum of **10**, methoxy (δ_C 55.6) and aryl signals also support the suggested structure.

Compound **11** was unambiguously assigned on the basis of its ^{1}H NMR spectrum due to the three CH signals, which are one singlet (7.31 ppm, H-7) and two doublets with *meta* coupling ($J_{2,4}$ = 2.0 Hz) at δ_H 8.92 and 8.75, belonging to H-2 and H-4, respectively. The presence of six quaternary and three CH carbon atoms in the ^{13}C NMR spectrum confirms two bromine atoms at the C-3 and C-5 positions in the structure (Table 1).

The NMR spectroscopy clearly identified that the expected products **12** and **13** are formed. The ^{1}H NMR spectrum of 3,6-dibromide **12** exhibits four *meta* coupled aryl signals (δ_H 8.65 and 8.51, $^4J_{5,7}$ = 1.8 Hz; δ_H 7.02 and 6.56, $^4J_{2,4}$ = 2.0 Hz) appearing downfield in comparison with starting material **9**.[9] However, the ^{1}H NMR of **13** consists of two *meta* coupled doublets of H-4 (δ_H 8.68, $^4J_{2,4}$ = 2.0 Hz) and H-2 (δ_H 8.78), one singlet of H-7 (δ_H 6.89), and two methoxide signals (δ_H 4.08 and 4.14).

Table 1. ^{1}H-NMR data of brominated methoxy quinoline **10-13**.

Compounds	**Protons**							**Coupling constants (Hz)**
	H2	H3	H4	H5	H6	H7	H8	
10	8.91 d	-	8.21 d	7.51 d	-	7.16 d	-	$J_{2,4}$ = 1.6 Hz $J_{5,7}$ = 1.6 Hz 4.10 s, OCH_3
11	8.92 d	-	8.75 d	-	-	7.31 s	-	$J_{2,4}$ = 2 .0Hz 4.10 s, OCH_3
12	8.65 d	-	8.51 d	7.02 d	-	6.56 d		$J_{2,4}$ = 2.0 Hz $J_{5,7}$ = 1.8 Hz 4.00, 3.94 s, OCH_3
13	8.78 d	-	8.68 d	-	-	6.89 s		$J_{2,4}$ = 2.0 Hz 4.08, 4.14 s, OCH_3

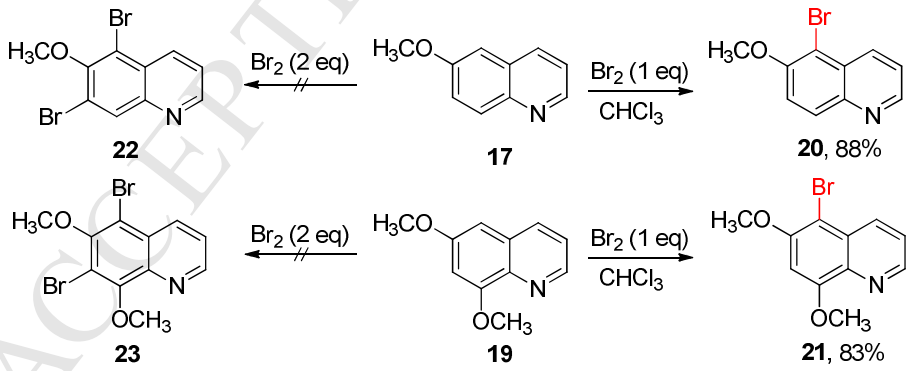


Scheme 6. Synthesis of starting compounds **17**-**19**

The synthesis of **11** and **13** from **10** and **12**, respectively, prompted us to study the bromination of methoxyquinolines **17**, **18**, and **19** (Schemes 7 and 8) to show whether the selectivity at the C-5 position can be generalized to other methoxy quinolones or not. For this purpose, 6-methoxy **17** and 6,8-dimethoxide **19** were prepared from corresponding the bromoquinolines[21] (**3, 15**) according to our previously reported methods (Scheme 6).[9] Additionally, we developed a new methodology for the formation of 3,6-dimethoxyquinoline (**18**) from its corresponding bromo derivative **16** (Scheme 6). In this context, dibromo derivative **16** was treated with sodium methoxide in DMF in the presence of copper iodide. Copper-assisted nucleophilic substitution afforded corresponding 3,6-dimethoxide **18** as the sole product in a yield of 78%. Kobayashi *et al.* (2003)[23] obtained 3,6-dimethoxide **18** using the Friedländer quinoline synthesis in a five-step cyclization of 1-isocyano-2-(2-lithio-2-methoxyethenyl)benzene. Therefore, our method seems shorter and more practical than the method in the literature.

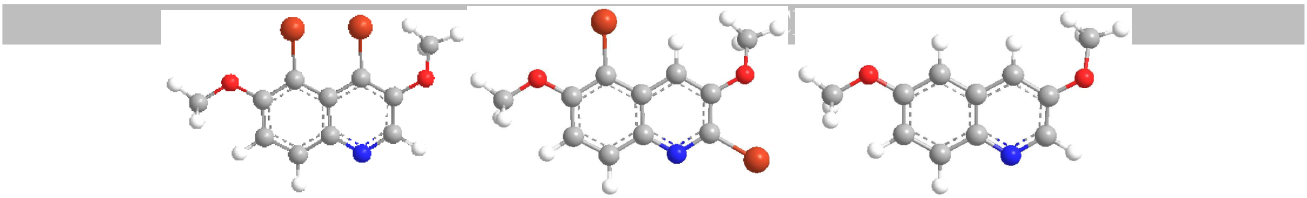
Bromination of 6-methoxy **17** and 6,8-dimethoxyquinoline **19** produced selectively the compounds **20** and **21** as the sole products (yields 88%, 83%, respectively). Compounds **17** and **18** were also treated with excess bromine (two or more equivalents), but no formation of dibrominated quinolines (**22** and **23**) was observed (Scheme 7).

5-Bromo-6-methoxyquinoline **20** was generated from 6-methoxyquinoline **17** by bromination in acetic acid in low yield (52%) as a patent procedure.[24] Another patent[25] described the same procedure, but was slightly modified and gave a lower yield (36%). Our synthetic procedure involves simple reaction conditions; for example, using a common solvent ($CHCl_3$ or CH_2Cl_2), in high yield (88%), at room temperature, with no extraction required.



Scheme 7. Bromination of methoxy quinolines (**3**, **13** and **14**) and preparation of 5-bromo quinolines (**22**-**24**).

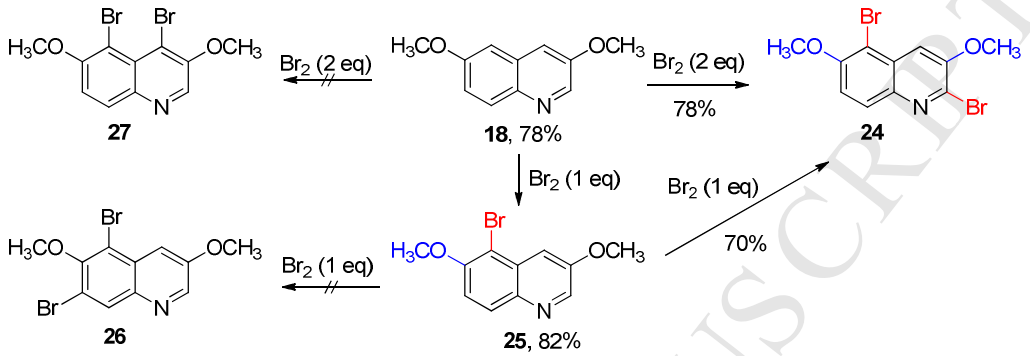
Bromination of dimethoxide **18** surprisingly resulted in dibromination, contrary to other methoxyquinolines (**17**, **19**). Direct bromination of dimethoxy **18** with 2 equivalents of bromine produced 2,5-dibromo-3,6-dimethoxy quinoline **24** in good yield (78%) (Scheme 8). Monobrominated compound **25** was also obtained after bromination with one equivalent of bromine in 82% yield. Actually, dibromination of **18** can lead to a multiplicity of isomers such as the formation of 4,5-, 2,5-, 5,7-, and 5,8-dibromoquinolines. No formation of other isomers may be attributed to the orientation of the methyl group in methoxy substituents of **18** (Scheme 8). This also explains the origin of selectivity in which bromination of 6-methoxy quinolines does not occur at the C-7 position. Furthermore, the fact that dibromide **24** was obtained, instead of dibromide **27**, can also be attributed to having enormous strain energy (46.83 kcal/mol) due to steric compression of the bromo groups in γ−gauche positions (Figure 1).



27 **24** **18**

Total energy: 46.83 kcal/mol (MM2) 23.46 kcal/mol (MM2) 15.58 kcal/mol (MM2)

Figure 1. 3D Structures of **18**, **27**, **24** and their total energies



Scheme 8. Bromination of dimethoxide **18** and preparation of dibromide **24**

Thus, we have developed a new way to obtain 2-substituted quinolines with a bromo group at C-2. Our studies on the preparation of C2-substituted quinoline derivatives are going on because quinolines substituted at C-2 on the quinoline scaffold have shown interesting anticancer activity in a number of anticancer assays.[26]

In the literature, studies on the bromination of methoxy quinolines using molecular bromine were reported. In one of the papers, the Eisch bromination of 7,8-dimethoxyquinoline resulted in the formation of a product mixture of 3-bromo-, 5-bromo, and 3,5-dibromo analogues in low yields.[26] It is well known that quinoline itself and bromoquinolines are not brominated with molecular bromine but rather, form an *N*-bromine complex.[8,16] The Eisch bromination[16,28] requires *N*-bromine complex formation in the first step. Trecourt *et al.* reported that treatment of 7,8-dimethoxyquinoline with bromine involved complex formation.[27] However, in our studies, we did not observe any complex formation during the bromination of methoxy quinolines under our reaction conditions.

In the ^{1}H NMR spectrum of **20**, the characteristic doublet for H-2 of the quinoline scaffold was observed at δ_H 8.81 ppm. Moreover, the protons of the benzene ring of **20** gave AB signal systems ($J_{8,7}$ = 9.2 Hz), assigning bromine to C-5. In the ^{1}H NMR spectrum of 5-bromo-6,8-dimethoxide **21**, four aromatic signals were observed. The doublets of H-2, H-3, and especially H-4 of **21** (δ_H 8.78, 7.47 and 8.46, respectively) appeared more downfield compared with its starting material **19**[9] (δ_H 8.57, 7.14, and 7.75, respectively). Furthermore, the signal of H-5 disappeared and the signal of H-7 was observed as a singlet signal at δ_H 6.86.

In the ^{1}H NMR spectrum of monobrominated 3,6-dimethoxy compound **25**, protons of the benzene ring of **25** ($J_{8,7}$ = 8.7 Hz) gave AB signal systems, assigning bromine to C-5. Similarly, the ^{1}H NMR spectrum of **24** consisted of two doublet and one singlet signals as expected. It was seen that after bromination, the signal of H-2 disappeared, which is evidence for the existence of bromination of the C-2 position. Furthermore, the signals for aromatic protons H-7 and H-8 (δ_H 7.35 and 8.06 ppm, respectively; $J_{8,7}$ = 8.0 Hz) were shifted downfield when compared with signals of the starting material **18** (H-7 and H-8; δ_H 7.22 and 7.95 ppm, respectively) in Table 2. The signal of H-4 is a singlet at δ_H 7.73 ppm as expected. The characteristic methoxide signals (δ_C 55.1 and 55.7) and six quaternary carbons in the ^{13}C NMR spectra helped to confirm the structure of **24**.

Table 2. The ^{1}H-NMR values of methoxy quinoline derivatives **18-21** and **24-25**

Compounds	Proton							Coupling constants (Hz)
	H-2	H-3	H-4	H-5	H-6	H-7	H-8	
18	8.54 d	-	7.32 d	7.03 d	-	7.22 d	7.95 d	$J_{2,4}$ = 2.4 Hz $J_{8,7}$ = 9.2 Hz $J_{7,5}$ = 2.8 Hz 3.96, 3.94 s OMe
19	8.57 d	7.14 dd	7.75 d	6.50 d	-	6.4 d	-	$J_{2,3}$ = 4.0 Hz $J_{4,3}$ = 8.2 Hz $J_{5,7}$ = 1.6 Hz 3.68, 3.85 OMe
20	8.81 dd	7.46 dd	8.52 dd	-	-	7.51 d	8.10 d	$J_{2,3}$ = 3.2 Hz, $J_{4,3}$ = 8.8 Hz $J_{8,7}$ = 9.2 Hz 4.06 s OMe

21	8.78 d	7.47 dd	8.46 d	-	-	6.86 s	-	$J_{2,3}$ = 4 Hz, $J_{4,3}$ = 8.4 Hz 4.06 s OMe
24	-	-	7.73 s	-	-	7.35 d	8.06 d	$J_{8,7}$ = 8.0 Hz 4.02, 4.07 s OMe
25	8.60 d	-	7.52 d	-	-	7.32 d	8.00 d	$J_{2,4}$ = 2.2 Hz $J_{8,7}$ = 8.7 Hz 4.06, 3.96 s OMe

3. Conclusion

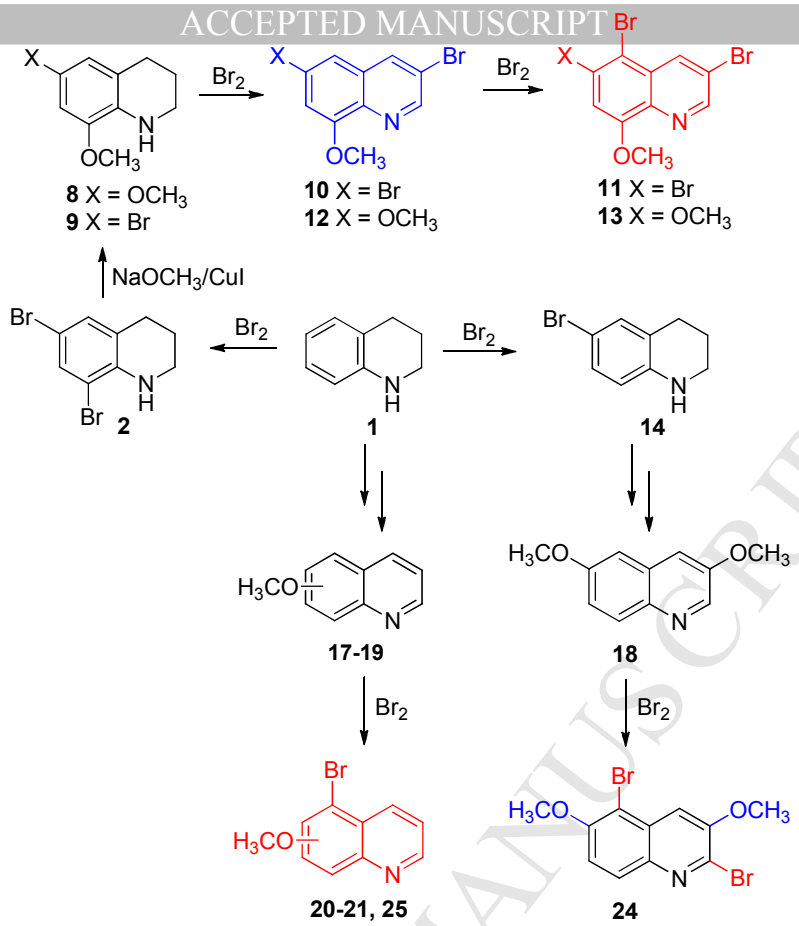
Two regioselective routes are described for the convenient preparation of 3- and 5-brominated methoxy quinolines. Quinoline cores are selectively functionalized at both the C-3 and C-5 positions under mild reaction conditions.

We found that methoxy 1,2,3,4-tetrahydroquinolines firstly were brominated at the C-3 and C-5 positions to give corresponding bromoquinolines. Bromination of 6-bromo-8-methoxy-1,2,3,4-tetrahydroquinoline (**9**) under different equivalents of molecular bromine selectively gave dibromo **10** and **11** using three and four equivalents of bromine, respectively. Similarly, bromination of 6,8-dimethoxy-1,2,3,4-tetrahydroquinoline (**8**) gave dibromo **12** (with three equivalents of Br_2) and tribromo **13** (with four equivalents of Br_2) methoxyquinolines. Selectivity at C-5 was also confirmed by separate bromination reactions of **17** and **19** to give 5-bromo **20** and **21** as the sole products in high yields.

In the literature, functionalized 3-substituted quinolines were prepared by the condensation of substituted anilines in the presence of some metals or Lewis acids used as catalyst.[28] Due to general protocols to obtain 3-functionalized quinoline derivatives based on cyclization or cycloaddition of substituted aniline or substituted benzene, the preparation of novel quinoline derivatives substituted at C-3 or other positions was restricted. On the other hand, the bromine group is a good starting point for not only nucleophilic/electrophilic substitution but also palladium catalyzed cross coupling reactions described in our ongoing research. We are currently working on the nitration of bromo and methoxy derivatives of quinolines subsequently their nucleophilic substitution and palladium catalyzed cross coupling reactions, especially Suzuki coupling with brominated tetrahydroquinolines and quinolines.

On the other hand, the reaction of 3,6-dimethoxyquinoline (**8**) with two equivalents of bromine resulted in dibromination (**24**) at C-5 and C-2. Thus, we not only opened up functionlization at C-3 and C-5 but also at the C-2 position of quinoline due to the bromine group. Therefore, simple synthetic methods were described for the valuable polyfunctional methoxyquinolines **10**, **11**, **13**, **18**, **20**, **21**, **24**, and **25**, which can be converted to corresponding substituted quinolines, otherwise difficult to obtain (Scheme 9).

We found that both the methoxy derivatives of 1,2,3,4-tetrahydroquinolines and methoxy quinolines were highly reactive towards bromination and investigations are ongoing regarding the generality and application of this approach to other substituted quinoline derivatives. The reactivity difference of bromine atoms on the heterocyclic ring facilitates the consecutive substitution, leading to the series of polysubstituted analogues. In summary, we have developed three selective routes for the synthesis of quinoline compounds containing bromine substituents at the C-2, C-3, and C-5 positions that along with other bromo methoxides could be important starting materials for the synthesis of polyfunctionalized quinoline derivatives (Scheme 9). The experimental methods are simple, require cheap starting materials (**1**, **2**, **14**), promise large-scale synthesis with high yields, and involve easy isolation of the final products.



Scheme 9. General overwiev of bromination methods for methoxy quinolines/ tetrahydroquinolines

4. Experimental section

General Methods. Thin layer chromatography was carried out on Merck silica F254 0.255 mm plates, and spots were visualized by UV at 254 nm. Flash column chromatography was performed using Merck 60 (70–230 mesh) silica gel. Melting points were determined on a Thomas-Hoover capillary melting point apparatus. Solvents were concentrated at reduced pressure. IR spectra were recorded on a Jasco 430 FT/IR instrument. Elemental analyses were recorded on an Elementar Vario MICRO Cube. NMR spectra were recorded on a Bruker spectrometer at 400 MHz for ^{1}H NMR and at 100 MHz for ^{13}C NMR.

*4.1. Synthesis of 3,6-dibromo-8-methoxyquinoline (**10**).* To a solution of 6-bromo-8-methoxy-1,2,3,4-tetrahydroquinoline (**8**, 241 mg, 1.0 mmol, 1 eq) in $CHCl_3$ (20 mL), was added a solution of bromine (527 mg, 3.3 mmol, 3.3 eq) in $CHCl_3$ (5 mL) over 10 min in the dark at rt. After completion of the reaction (bromine completely consumed, 2 days), the resulting mixture was washed with a solution of 5% aq $NaHCO_3$ (3 × 20 mL) and dried over Na_2SO_4. After evaporation of the solvent, the crude material (253 mg) was passed through a silica column eluting with AcOEt/hexane (1:3, 100 mL). The crude product was recrystalized in $CHCl_3$/hexane (1:3) to give 3,6-dibromo-8-methoxyquinoline (**10**). White powder solid (242 mg, 77% yield): mp 134-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, J_{24} = 1.6 Hz, 1H, H_2), 8.21 (d, J_{42} = 2.0 Hz, 1H, H_4), 7.51 (d, J_{57} = 1.6 Hz, 1H, H_5), 7.16 (d, J_{75} = 1.2 Hz, 1H, H_7), 4.10 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1 (q), 150.4, 137.1 (q), 136.1, 130.9 (q), 121.9 (q), 120.7, 119.2 (q), 112.2, 56.5 (OCH_3); IR (KBr, cm^{-1}) *v* 3047, 2925, 1727, 1592, 1558, 1482, 1371, 1346, 1255, 902, 858, 829, 788, 748; Anal. Calcd for $C_{10}H_7Br_2NO$: C, 37.89%; H, 2.23%; N, 4.42%. Found: C, 36.90%; H, 2.32%; N, 4.48%.

*4.2. Synthesis of 3,5,6-tribromo-8-methoxyquinoline (**11**).* The same procedure was applied in synthesis of **10** but 4.2 equivalents of bromine (671 mg, 4.2 mmol) was used in $CHCl_3$ (20 mL). The crude product was passed through a silica column eluting with $CHCl_3$/hexane (1:3) to give 3,5,6-tribromo-8-methoxyquinoline (**11**) in 72% yield (282 mg) as yellow powder solid.

3,5,6-Tribromo-8-methoxyquinoline (**11**) was synthesized by treating of 3,6-dibromo-8-methoxyquinoline (**10**) with 1 equivalent of bromine for 1 day at rt. The reaction procedure is similar to the above process. This reaction afforded 3,5,6-tribromo-8-methoxyquinoline (**11**). Yellow powder solid (282 mg, 76% yield): mp 164-166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, J_{24} = 2.0 Hz, 1H, H_2), 8.75 (d, J_{42} = 2.0 Hz, 1H, H_4), 7.31 (s, 1H, H_7), 4.10 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2 (q), 150.7, 138.0, 132.5 (q), 132.2 (q), 128.3 (q), 125.6 (q), 120.7 (q), 113.2, 56.6 (OCH_3); IR (KBr, cm^{-1}) *v* 2960, 2925, 2852, 2360, 2337, 1731, 1641, 1562, 1487, 1461, 1280, 1147, 1132, 1024, 943, 821, 765; Anal. Calcd for $C_{10}H_6Br_3NO$: C, 30.34%; H, 1.53%; N, 3.54%. Found: C, 30.40%; H, 1.49%; N, 3.77%.

*4.3. Synthesis of 3-bromo-6,8-dimethoxyquinoline (**12**).* To a solution of 6,8-dimethoxy-1,2,3,4-tetrahydroquinoline (**9**, 193 mg, 1.0 mmol, 1 eq) in $CHCl_3$ (15 mL), was added a solution of bromine (495 mg, 3.1 mmol, 3.1 eq) in $CHCl_3$ (5 mL) over 5 min in the dark at

rt. After completion of the reaction (bromine completely consumed, 3 days), the resulting mixture was washed with a solution of 5% aq $NaHCO_3$ (3 × 20 mL) and dried over Na_2SO_4. After evaporation of the solvent, the crude material (220 mg) was passed through a silica column eluting with AcOEt/hexane (1:3, 100 mL). The crude product was recrystalized in $CHCl_3$/hexane (1:3) to give 3-bromo-6,8-dimethoxyquinoline (**12**). White powder solid (213 mg, 80% yield): mp 124-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J_{24} = 2.0 Hz, 1H, H_2), 8.51 (d, J_{42} = 2.0 Hz, 1H, H_4), 7.02 (d, J_{57} = 1.8 Hz, 1H, H_5), 6.56 (d, J_{75} = 1.8 Hz, 1H, H_7), 4.00 (s, 3H OCH_3), 3.94 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3 (q), 152.6 (q), 138.3, 134.2, 131.3 (q), 128.0 (q), 122.3, 100.6, 98.3 (q), 56.8, 54.4 (OCH_3); IR (KBr, cm^{-1}) *v* 3016, 2973, 2792, 1741, 1638, 1454, 1422, 1361, 1342 1361, 1297, 1238, 1110, 983, 912, 828, 689; Anal. Calcd for $C_{11}H_{10}BrNO_2$: C, 49.28%; H, 3.76%; N, 5.22%. Found: C, 49.45%; H, 3.82%; N, 5.16%.

*4.4. Synthesis of 3,5-dibromo-6,8-dimethoxyquinoline (**13**).* The same procedure was applied in synthesis of **12** but 4.2 equivalents of bromine (671 mg, 4.2 mmol) in $CHCl_3$ (20 mL) was used and the reaction was carried on a period of 5 days at rt. The crude product was recrystalized in $CHCl_3$/hexane (1:3) to give 3,5-dibromo-6,8-dimethoxyquinoline (**13**) in 78% yield (269 mg) as white powder solid.

3,5-Dibromo-6,8-dimethoxyquinoline (**13**) was synthesized by treating of 3-bromo-6,8-dimethoxyquinoline (**12**) with 1 equivalents of bromine in $CHCl_3$ (20 mL) for 2 day at rt. The reaction procedure is similar to the above precess. This reaction was afforded 3,5-dibromo-6,8-dimethoxyquinoline (**13**) in 85% yield. White powder solid (269 mg, 85% yield): mp 133-135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, J_{24} = 2.0 Hz, 1H, H_2), 8.68 (d, J_{42} = 2.0 Hz, 1H, H_4), 6.89 (s, 1H, H_7), 4.10 (s, 3H, OCH_3), 4.14 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5 (q), 155.3 (q), 148.3, 135.8, 134.6 (q), 130.0 (q), 120.3 (q), 97.3, 97.1 (q), 57.1, 56.4 (OCH_3); IR (KBr, cm^{-1}) *v* 2956, 2923, 2852, 1731, 1608, 1554, 1482, 1461, 1367, 1311, 1207, 1138, 1090, 993, 923, 808, 777; Anal. Calcd for $C_{11}H_9Br_2NO_2$: C, 38.07%; H, 2.61%; N, 4.04%. Found: C, 37.40%; H, 2.42%; N, 4.09%.

*4.5. Synthesis of 3,6-dibromoquinoline (**16**).* In the reported procedure,[15,27] 3,6-dibromoquinoline was synthesized by Eisch bromination of 6-bromoquinoline in yield of 82%.

*4.6. Synthesis of 3,6-dimethoxyquinoline (**18**).* Freshly cut sodium (0.7 g, 30 mmol) was added to dry methanol (25 mL) under nitrogen gas atmosphere. When dissolution was complete, the warm solution was diluted with dry dimethylformamid by addition of vacuum dried cuprous iodide (1.0 g, 0.51 mmol). After dissolution, 3,6-dibromoquinoline (**16**) (450 mg, 1.05 mmol) into dry DMF (30 mL) was added. The reaction mixture was stirred magnetically under a nitrogen gas atmosphere at reflux (ca 150 °C) for 6 h. The reaction's progress was monitored by TLC until the starting material was all consumed. After cooling to rt, H_2O (25 mL) and $CHCl_3$ (50 mL) were added to the reaction mixture. The organic layers were separated, washed with H_2O (2 × 20 mL), and dried over Na_2SO_4. The solvent was removed and the crude product was passed through a short silica gel (3g) column eluting with AcOEt/hexane (1:3, 100 mL). After filtration and purification, the resultant product was 3,6-dimethoxyquinoline (**18**). Pale yellow powder solid (156 mg, 78% yield): mp 84-86 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J_{24} = 2.4 Hz, 1H, H_2), 7.95 (d, J_{87} = 9.2 Hz, 1H, H_8), 7.32 (d, J_{42} = 2.4 Hz, 1H, H_4), 7.22 (dd, J_{78} = 9.2 Hz, J_{75}= 2.8 Hz, 1H, H_7), 7.03 (d, J_{57} = 2.4 Hz, 1H, H_5), 3.96 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4 (q), 153.7 (q), 141.7, 139.4 (q), 130.6, 130.1 (q), 119.0, 111.8, 104.8, 55.5 (OCH_3), 55.4 (OCH_3). All data were identical to that reported in the literature.[22]

*4.7. Synthesis of 5-bromo-6-methoxyquinoline (**20**).* To a solution of 6-methoxyquinoline (**17**, 160 mg, 1.0 mmol, 1 eq) in CH_2Cl_2 (15 mL) was added a solution of bromine (176 mg, 1.1 mmol, 1.1 eq) in CH_2Cl_2 (15 mL) over 10 min in the dark at rt. After completion of the reaction (bromine completely consumed, 2 days), the resulting mixture was washed with a solution of 5% aq $NaHCO_3$ (3 × 20 mL) and dried over Na_2SO_4. After evaporation of the solvent, the crude material (215 mg) was passed through a silica column eluting with AcOEt/hexane (1:4, 150 mL). The crude product was recrystalized in $CHCl_3$/hexane (1:4) to give 5-bromo-6-methoxyquinoline (**20**). Brown cubic crystal (208 mg, 88% yield): mp 79-81 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (d, J_{23} = 3.2 Hz, 1H, H_2), 8.52 (d, J_{43} = 8.8 Hz, 1H, H_4), 8.10 (d, J_{87} = 9.2 Hz, 1H, H_8), 7.51 (d, J_{78} = 9.2 Hz, 1H, H_7), 7.46 (dd, J_{32} = 4.0 Hz, J_{34} = 8.4 Hz, 1H, H_3), 4.06 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 148.8, 144.3, 134.5, 130.3, 128.6, 122.4, 116.5, 107.4, 57.1 (-OCH_3); IR (KBr, cm^{-1}) *v* 2925, 1612, 1587, 1552, 1496, 1321, 1261, 1064, 964, 897, 822, 806, 584; Anal. Calcd for $C_{10}H_8BrNO$: C, 50.45%; H, 3.39%; N, 5.88%. Found: C, 50.40%; H, 3.32%; N, 5.98%.

*4.8. Synthesis of 5-bromo-6,8-dimethoxyquinoline (**21**).* To a solution of 6,8-dimethoxyquinoline (**19**, 190 mg, 1.0 mmol, 1 eq) in $CHCl_3$ (15 mL) was added a solution of bromine (176 mg, 1.1 mmol, 1.1 eq) in $CHCl_3$ (15 mL) over 10 min in the dark at rt. After completion of the reaction (bromine completely consumed, 2 days), the resulting mixture was washed with a solution of 5% aq $NaHCO_3$ (3 × 20 mL) and dried over Na_2SO_4. After evaporation of the solvent, the crude material (230 mg) was passed through a silica column eluting with AcOEt/hexane (1:4, 150 mL). The crude product was recrystalized in $CHCl_3$/hexane (1:4) to give 5-bromo-6,8-dimethoxyquinoline (**21**). Brown powder solid (221 mg, 83%yield): mp 58-59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, J_{23} = 4.0 Hz, 1H, H_2), 8.49 (d, J_{43} = 8.4 Hz, 1H, H_4), 7.48 (dd, J_{32} = 4.0 Hz, J_{34} = 8.4 Hz, 1H, H_3), 6.86 (s, 1H, H_7), 4.12 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2 (q), 154.3 (q), 136.5 (q), 128.8 (q), 97.8 (q), 147.4, 134.4, 123.1, 97.0, 57.2 (OCH_3), 56.2 (OCH_3); IR (KBr, cm^{-1}) *v* 2931, 2848, 1722, 1610, 1587, 1500, 1471, 1365, 1247, 1213, 1124, 1084, 898, 809, 781; Anal. Calcd for $C_{11}H_{10}BrNO_2$: C, 49.28%; H, 3.76%; N, 5.22%. Found: C, 49.25%; H, 3.74%, N, 5.15%.

*4.9. Synthesis of 2,5-dibromo-3,6-dimethoxyquinoline (**24**).* To a solution of 3,6-dimethoxyquinoline (**18**) (190 mg, 1.0 mmol, 1 eq) in CH_2Cl_2 (15 mL), was added a solution of bromine (352 mg, 2.2 mmol, 2.2 eq) in $CHCl_3$ (5 mL) over 10 min in the dark at rt. After completion of the reaction (bromine completely consumed, 3 days), the resulting mixture was washed with a solution of 5% aq $NaHCO_3$ (3 × 25 mL) and dried over Na_2SO_4. After evaporation of the solvent, the crude material (280 mg) was passed through a silica column eluting with AcOEt/hexane (1:3, 100 mL) The crude product was recrystalized in $CHCl_3$/hexane (1:4) to give 2,5-dibromo-3,6-dimethoxyquinoline (**24**). White powder solid (269 mg, 78% yield): mp 138-140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J_{87} = 8.0 Hz, 1H, H_8), 7.73 (s, 1H, H_4), 7.35 (d, J_{78} = 8.0 Hz, 1H, H_7), 4.07 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6 (q), 154.3 (q), 140.4 (q), 130.7, 130.2 (q), 129.0 (q), 125.6, 107.4, 99.8 (q), 55.7 (OCH_3), 55.1 (OCH_3); IR (KBr, cm^{-1}) *v* 2928, 1618, 993; Anal. Calcd for $C_{11}H_9Br_2NO_2$: C, 38.07%; H, 2.61%; N, 4.04%. Found: C, 38.40%; H, 2.42%; N, 4.13%.

*4.10. Synthesis of 5-bromo-3,6-dimethoxyquinoline (**25**).* The same procedure was applied in the synthesis of **24** but 1.1 equivalent of bromine (176 mg, 1.1 mmol) was used and the reaction was carried on a period of 2 days at rt. The crude product was recrystalized in $CHCl_3$/hexane (1:4) to give 5-bromo-3,6-dimethoxyquinoline (**25**). White powder solid (219 mg, yield 82%): mp 117-119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J_{24} = 2.2 Hz, 1H, H_2), 8.00 (d, J_{87} = 8.7 Hz, 1H, H_8), 7.52 (d, J_{42} = 2.2 Hz, 1H, H_4), 7.32 (dd, J_{78} = 8.7 Hz, 1H, H_7), 4.06 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2 (q), 153.9 (q), 140.6 (q), 139.4 (q), 130.6, 125.6 (q), 122.4, 110.3, 104.8, 55.8 (OCH_3), 55.2 (OCH_3); IR (KBr, cm^{-1}) *v* 2965, 1603, 1023; Anal. Calcd for $C_{11}H_{10}BrNO_2$: C, 49.28%; H, 3.76%; N, 5.22%. Found: C, 49.13%; H, 3.82%; N, 5.29%.

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