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Versatile functionalization of electron rich-fused heterocyclic arenes via electrophilic aromatic addition reaction and their applications

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ABSTRACT

Divergent functionalized 8-methoxyquinaldines were synthesized via regioselective debromination, 1,3-bromine shift process, aromatization with treatment of a strong base, nucleophilic substitution reaction at the C7 position using amines and cyanide as a nucleophile in the absence of a metal source and a catalyst from an unusual electrophilic aromatic addition (Ad_EAr) reaction products **7** and **8**. In addition, quinaldine-7,8-dione was prepared by presence of CAN (ceric ammonium nitrate) in AcOH and H_2O for 10 min at room temperature from *N*-(alkylamino)-8-methoxyquinalidines. During the Ad_EAr reaction, new stereoselective dearomatized addition products were generated via discriminative reaction routes depending on the methoxy and bromine occupancy position. The Ad_EAr reaction not only allowed for the functionalization of electron rich-fused heterocyclic arenes, but also provided a new synthetic route to an alternative mechanism for electrophilic aromatic substitution reactions.

1. Introduction

Asymmetric dearomatization is one of the most important and efficient transformations of aromatic compounds that is wildly applied to the functionalization of aromatic molecules.[1] On the other hand, although there has been much focus on the development of general methods for asymmetric dearomatization and their transformations, asymmetric dearomatization reaction is not generally compatible with common reactions and limited applications to suitable arene compounds. As part of an ongoing study of 7-bromo-quinaldine-5,8-dione as a key intermediate in the synthesis of lavendamycin, an unusual electrophilic aromatic addition (Ad_EAr) reaction was encountered, which led only to the asymmetric dearomatized addition products under basic methanolic bromination.[2] During an electrophilic aromatic substitution reaction, if the addition of various nucleophiles to the σ-complex can be controlled, it might be possible to generate addition products with two stereocenters.[3] Although rapid aromatization is a general process after σ-complex carbocation formation due to the instability of the intermediate addition product isolation,[4] an exceptional nucleophilic addition reaction to a controlled σ-complex intermediate sometimes occurs, resulting in the synthesis of another addition products with multiple stereocenters and finally production of enantio- or diastereoselective compounds. A various range of methods has been reported to control the addition products, particularly asymmetric dearomatized compounds and maintain their stereochemistry, such as transition-metal catalyzed with nucleophiles,[5] five membered systems during electrophilic substitution,[6] nucleophilic dearomatizing (D_NAr) reaction of aromatic C—H systems,[7] and the known *ipso* attack at the substituted position.[8] These reactions could have tremendous opportunities in the synthesis of stable asymmetric addition products.

A preliminary study reported the isolation of stable addition products at an aromatic *H* substituent position during the electrophilic aromatic substitution of benzenoid compounds.[2] Considering our previous findings of Ad_EAr, it might be possible to control the stereoselective reaction and allow the further functionalization of fused aromatic systems as well as facile synthetic process to produce a substitution product from stable addition products that are synthetically difficult approaches using other methods. For example, the transition-metal catalyzed cross-coupling reaction between aryl halide and diverse amines was a general method to form C—N bonds of aryl amine structures.[9] Despite recent efforts to develop complementary amination methods to conventional

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approaches, there are no reports on the synthesis of 5-bromo-7-*N*-(alkylamino)-8-methoxyquinaldines by simple nucleophilic substitution reaction-aromatization from addition products without any types of metals or other additives towards electron rich-fused systems and the low reactive position of 8-methoxyquinaldine. When amination was performed of 4,7-dichloroquinoline using various amine sources on a microwave by nucleophilic substitution reaction, 4-amino-7-chloroquinolines were just only produced.[10] Furthermore, new stereoselective dearomatized addition products were controlled by either further electrophilic additive bromination to construct a bridged bromonium ion intermediate or discriminative resonance forms from σ-complexes depending on the respective methoxy and bromine occupancy position. Herein, we showed the preparation of various functionalized 8-methoxyquinaldines from the Ad_EAr addition products via diverse reaction routes and demonstrated an alternative synthetic route for electrophilic aromatic substitution reactions.

2. Results and discussion

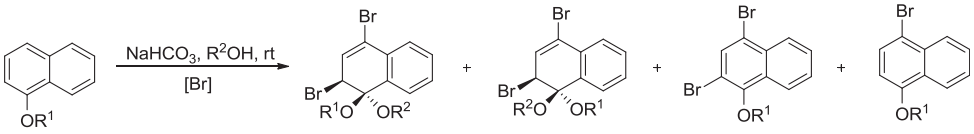
A previous study reported that quinoline and naphthalene containing either a pyridine moiety or not showed different reactivity for the Ad_EAr reaction. Initially, the base reactivity and bromine reagents were the determining factors in forming the addition products. Moreover, based on the different reactivity of quinoline and naphthalene, it was proposed that pyridine might play a role in sufficiently stabilizing the addition products for isolation and the role of pyridine in the Ad_EAr reaction was investigated (Table 1). 1-Methoxynaphthalene (**1a**) was carried out under the same reaction conditions except for pyridine (entries 1 and 2). Only the addition product **2a** was obtained in 91% yield when pyridine was added (entry 2), whereas in entry 1, without pyridine at room temperature, only substitution products such as 2,4-dibromo-1-methoxynaphthalene (**4a**) and 4-bromo-1-methoxynaphthalene (**5a**) were obtained in 33% and 17% yield, respectively. When **1a** was exchanged with 1-ethoxynaphthalene (**1b**) as the starting material under the same reaction conditions, only the addition product **3a** was obtained in the presence of pyridine (entry 3). Therefore, pyridine may play some role in producing the addition product. A pyridinium hydrobromide perbromide ($Py\cdot HBr_3$) containing pyridine moiety with bromine source was used because pyridine and bromine reagents are important factors in the Ad_EAr reaction (entries 4–6). The reaction with $Py\cdot HBr_3$ gave addition product in good yield (93%, entry 4). $Py\cdot HBr_3$ would be suitable as a brominating agent in future work because of its easy handling and operational simplicity. When the reaction was carried out in an EtOH system using **1a**, the bromoethoxylated adduct **2b** was obtained in moderate yield (73%) due to the steric hindrance to attack at the *ipso*-position of the methoxy group.

To verify the Ad_EAr reaction, the bromomethoxylation of various methoxy-fused heterocyclic compounds were attempted under the same reaction conditions, as shown in Table 2. The Ad_EAr reaction of 5,8-dimethoxyquinaldine (**9**) produced two new addition products **10a** and **10b** (entry 1). Scheme 2 presents a plausible mechanism of this reaction. The Ad_EAr mechanism of **6** was already proposed, in which the bromine reactant forms a cationic intermediate (σ-complex), leading to nucleophilic addition and produced stable addition products (Scheme 1).[2] 5,8-Dihydro-5,5,8,8-tetramethoxyquinaldine (**10a**) was produced via a similar mechanism that allowed *ipso*-addition to the cationic intermediate and sequential replacement with methoxide at the benzylic bromine. This reaction was differentiated to the oxidative demethylation that produced 2-methylquinoline-5,8-dione from **9** using NBS under acid conditions.[11]

Another new stereoselective dearomatized addition product, (6*S*,7*S*)- and (6*R*,7*R*)-6,7-dibromo-5,5,8,8-tetramethoxy-5,6,7,8-tetrahydroquinaldine (**10b**), was produced from **10a** by a further reaction involving electrophilic additive bromination at the 6,7-alkene position to sequentially construct the bridged bromonium ion intermediate and allow the *anti*-addition of bromide. Structural characterization of **10b** was unambiguously confirmed by mass spectroscopy and single-crystal X-ray analysis (Fig. 1). The X-ray crystallographic data revealed the two bromines at C6 and C7 with *trans* stereochemistry.

5,8-Dimethoxylepidine (**11**) also gave a stable addition product **12a** and stereoselective dearomatized addition product **12b**, similar to **9** (entry 2). On the other hand, other similar compounds, 6-bromo-5,8-dimethoxyquinaldine (**13**) and 7-bromo-5,8-dimethoxyquinaldine (**15**), containing a bromine substituent at different positions, could proceed with only an addition reaction without further additive bromination (entries 3 and 4). With the C5 bromine substituent quinoline **17** (entry 5), addition product **7** was obtained in higher yield compared to 8-methoxyquinaldine (**6**). This suggests that the bromine substituent would be significantly affected by the Ad_EAr reaction. Alternatively, when another different position of bromine substituent quinoline, 7-bromo-8-methoxyquinaldine (**18**), was used, new addition product **19** containing three methoxy groups was acquired in 67% yield along with

Table 1
Ad_EAr of 1-methoxy (**1a**) and 1-ethoxy (**1b**) naphthalene under a range of conditions[a]

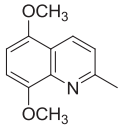
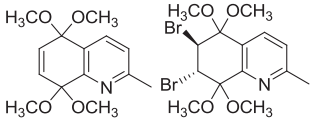
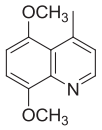
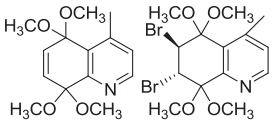
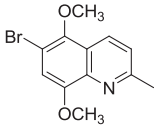
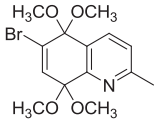
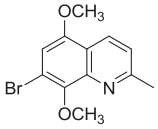
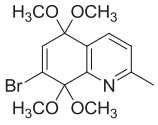
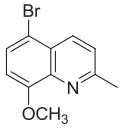
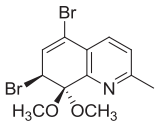
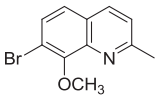
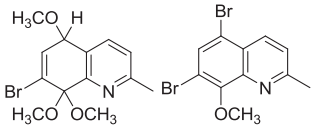
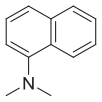
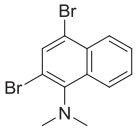


1a R^1 = Me, **1b** R^1 = Et; **2a** R^1 = Me, R^2 = Me; **2b** R^1 = Me, R^2 = Et; **3a** R^1 = Me, R^2 = Et; **4a** R^1 = Me; **4b** R^1 = Et; **5a** R^1 = Me; **5b** R^1 = Et

Entry	Substrate	Br source	Solvent	Yield (%)[b]		
				2 or **3**	**4**	**5**
1	**1a**	Br_2	MeOH	—	**4a** (33)	**5a** (17)
2	**1a**	Br_2/py	MeOH	**2a** (91)	—	—
3	**1b**	Br_2/py	MeOH	**3a** (90)	—	—
4	**1a**	$Py\cdot HBr_3$	MeOH	**2a** (93)	—	—
5	**1a**	$Py\cdot HBr_3$	EtOH	**2b** (73)		
6	**1b**	$Py\cdot HBr_3$	MeOH	**3a** (91)		

[a] Unless otherwise noted, all reactions were carried out on a 2.0 mmol reaction scale of 1-methoxy (**1a**) and 1-ethoxy (**1b**) naphthalene using 3.0 equiv of bromine for 15 min at room temperature.
[b] Isolated yields.

Table 2
Bromomethoxylation of various methoxy-fused heterocyclic compounds under the Ad_EAr[a]

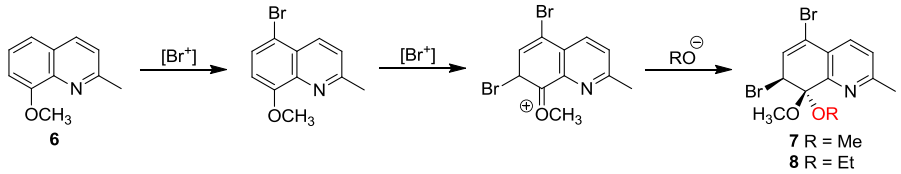
Entry	Substrate	Product[b]
1	 **9**	 **10a** (63) **10b** (30)
2	 **11**	 **12a** (81) **12b** (8)
3	 **13**	 **14** (63)
4	 **15**	 **16** (83)
5	 **17**	 **7** (90)
6	 **18**	 **19** (67) **20** (15)
7	 **21**	 **22** (42)

[a] All reactions were carried out under the same reaction conditions as shown in Scheme 1.
[b] Isolated yields.

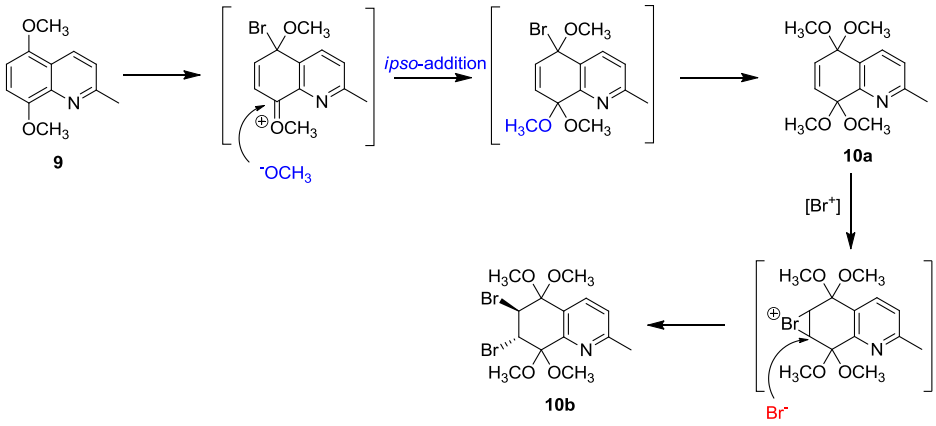
5,7-dibromo-8-methoxyquinaldine (**20**) (entry 6). Based on the proposed Ad_EAr mechanism, which generally involves a reaction with bromine molecules to produce a stable cationic intermediate followed by preferential methoxide nucleophile attack at the opposite side of the bromine group, the product had a discriminative resonance forms at each 5,6- or 6,7-alkene position from the respective σ-complex **17a** or **18a** depending on the bromine occupancy position (Scheme 3). The reaction was either just stabilized by the *ipso*-addition of methoxide into **17a** to produce **7** or regenerated toward easy access to both the allylic and benzylic position by nucleophilic addition reaction to produce **19** along with simultaneous deprotonation-aromatization to produce **20** from another addition intermediate **18b**. This means that a further addition reaction could be controlled to synthesize of another addition products from suitable compounds. The other aromatic compounds were also treated under the same reaction conditions but no addition product was observed (entry 7).

Utilizing of applicable addition products, we showed a new facile synthetic approach for the preparation of 5-bromo-7-*N*-(alkylamino)-8-alkoxyquinaldines from the addition products **7** and **8** by simple a nucleophilic substitution reaction with subsequent aromatization, which is synthetically difficult by other methods[10] (Table 3). As the result of nucleophilic substitution/rearomatization sequence from unusual Ad_EAr products of 8-methoxyquinaldine, it makes easy and simple approach to the introduction of nitrogen nucleophile into *ortho*-position of the methoxy group. This is complementary to general process for the synthesis of various 5-bromo-7-*N*-(alkylamino)-8-alkoxyquinaldines and enable to synthesis of further functionalized quinaldine derivatives utilizing the remaining bromine group. It worked extremely well with various primary and secondary amines such as *n*-propyl, *n*-butyl, benzyl, 1-cyclohexyl, diethylamine, pyrrolidine, piperidine, and morpholine from electron rich-fused addition products by facile nucleophilic substitution without any metal sources and catalysts, affording to 5-bromo-7-*N*-(alkylamino)-8-alkoxyquinaldines in moderate yields (36–45%) along with deprotonated-rearomatization products. When the piperidination of **7** was examined at reflux on a Pyrex tube for 1 h in EtOH (Scheme 4), 5-bromo-8-methoxy-7-(piperidin-1-yl)quinaldine (**28**) was obtained in 35% yield with **20** and unexpected 8,8-dimethoxy-quinalidin-5-one (**31**) in 15% and 38% yield, respectively. This means that this reaction involves competition with substitution, elimination, and unusual reaction, which was suggested to involve a 1,3-bromine shift process mechanism by piperidine as a catalyst, followed by hydrolysis (Scheme 5). This hydrolysis may be faster than elimination and nucleophilic substitution. Considering nucleophilic substitution, it is unclear from the results if substitution is S_N1 or S_N2 process. To ascertain the reaction, another adduct, such as (*S*,*S*)- and (*R*,*R*)-5,7-dibromo-8-ethoxy-8-methoxy-7,8-dihydroquinaldine (**8**), was used (Scheme 6). The piperidination of **8** under the same reaction condition, resulted in not only substitution products, 5-bromo-8-ethoxy-7-(piperidin-1-yl)quinaldine (**32**) and **28**, but also different eliminated products, **20** and 5,7-dibromo-8-ethoxyquinaldine (**34**). Taking this result into account, the nucleophile acts as S_N1 and E1cb based on each different *N*-alkylated-8-alkoxyquinaldine and 5,7-dibromo-8-alkoxyquinaldine compounds. (*S*)- and (*R*)-8-Ethoxy-8-methoxy-quinaldin-5-one (**33**) was also obtained with the stereochemistry maintained at the C8 position in 27% yield, which was similar to that observed with **31**. In both cases, the enone compounds **31** and **33** were stable under nucleophilic conditions. The dialkoxy groups appear to prevent the access of the nucleophile to the *r*-position of the enone by the steric bulkiness and repulsion between the nonbonding electrons.

Other nucleophiles, cyanide, thiol, and fluoride, were applied under the same reaction conditions (Table 4). 5-Bromo-7-cyano-8-methoxyquinaldine (**35**) was obtained in 30% yield from **7** by one step nucleophilic substitution-aromatization at the 7-position with eliminated compound **20** (entry 1), similar results as Table 3. In the case of thiolation, thiol attacked at the bromine and there was no reaction center at the 7-position, resulting in a mono-brominated product **17** in 82% yield via selective debromination without



Scheme 1. Reaction mechanism of Ad_EAr reaction.



Scheme 2. Proposed mechanism of **10a** and **10b**.

a thiolated product (entry 2). To ascertain the selective debromination, another addition product, 6,8-dibromo-5,5-dimethoxy-5,6-dihydroquinaldine (**36**), was used and shown as the same reaction outcome (entry 3). Otherwise, in case of fluorination, no transformation to aromatic fluorine compound was observed and just only produced in eliminated product **20** due to fluoride totally acts as a base not nucleophile (Scheme 7).

For the synthesis of various *N*-alkylated substituted lavendamycin, oxidation from 5-bromo-7-*N*-(alkylamino)-8-methoxyquinaldines was carried out under a range of conditions, such as NBS,[11] $K_2Cr_2O_7$,[12] HNO_3,[13] and CAN (ceric ammonium nitrate)[14] under acidic condition. Unfortunately, only the starting material or decomposed compounds were observed except when CAN was used, in which 5-bromoquinaldine-7,8-dione (**38**), not 7-*N*-(alkylamino)-2-methylquinoline-5,8-dione, was obtained in 82% yield in the presence of CAN in AcOH and H_2O for 10 min at room temperature from **26** and **27** (Scheme 8). Although this route was not proper to facile synthesis of 7-*N*-(alkylamino)-2-methylquinoline-5,8-diones from 5-bromo-7-*N*-(alkylamino)-8-methoxyquinaldines, further modification of **25**, followed by debenzylation, acetylation and sequent oxidation, will provide an alternative processes for regioselective 7-*N*-(alkylamino)-2-methylquinoline-5,8-dione to the lavendamycin synthesis.[15]

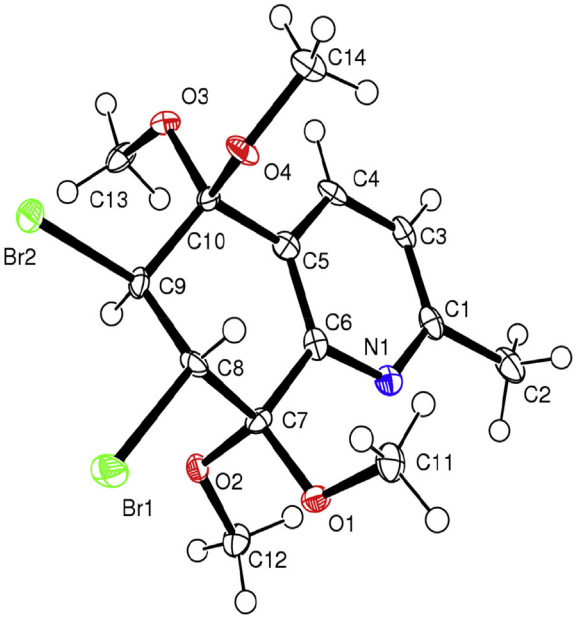
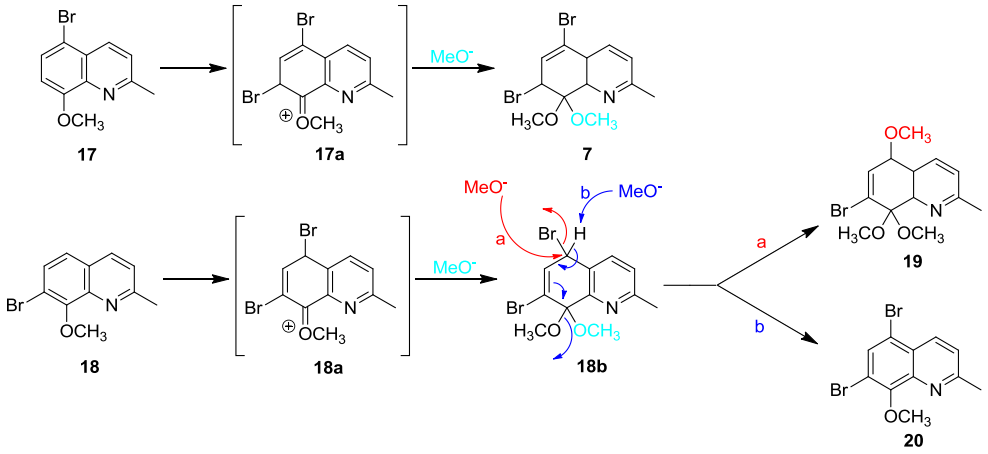


Fig. 1. X-ray structure of **10b**.

To synthesize the 8-alkoxyquinoline derivatives, strong base and an excess of reagent is generally needed, which are hazardous and generate a large amount of waste. On the other hand, treatment of **7** with NaOH in methanol gave **20** in almost quantitative yield. Moreover, compound **8** was eliminated by the treatment of NaOH in methanol to produce **34** and **20** in 63% and 29% yield, respectively (Scheme 9). Although the detail mechanism studies will be needed, this reaction presumably proceeds through the E1cb mechanism. After the formation of the carbanion at the C7 position, either the methoxide or ethoxide at the C8 position are eliminated.

3. Conclusion

The Ad_EAr reaction is an efficient methodology to isolate stable addition products and new stereoselective dearomatized addition products from electron rich-fused heterocyclic compounds as well as providing a range of functionalized 8-methxoxyquinaldine. In particular, depending on nucleophile characters, it provides a new facile synthetic route for preparation of the substituted, eliminated, and selective debrominated 5-bromo-8-alkoxyquinaldine at the C7 position as well as the enone compounds from Ad_EAr addition products, which the nucleophiles act as the simultaneous S_N1 reaction, E1cb reaction, and 1,3-bromine shift process via catalyst mechanism at aromatic systems during simple nucleophilic substitution reaction. This is complementary to general protocols for the synthesis of various *N*-(alkylamino)-substituted quinolines. The



Scheme 3. Mechanistic differences of the Ad_EAr reaction toward **17** and **18**.

Ad_EAr reaction not only allowed to versatile functionalization of electron rich-fused heterocyclic arenes, but also provided an alternative synthetic route for electrophilic aromatic substitution reactions.

4. Experimental section

4.1. Typical procedure for the electrophilic aromatic addition reaction

To the suspension of alkoxy compound (2.0 mmol) and $NaHCO_3$ (3.5 equiv or 1.75 equiv) in MeOH (6.0 mL) was added the solution of Py·HBr_3 (3.0 equiv or 1.5 equiv) in MeOH (1.5 mL) with stirring at room temperature. After 5 min, water (3 mL) was added and the reaction was stirred for another 5 min. Then, water (30 mL) and Na_2SO_3 (0.32 g) were added. The mixture was extracted with CH_2Cl_2 (20 mL×2) and the combined organic layers were washed by brine, and dried (Na_2SO_4). The residue was purified by flash column chromatography.

4.2. (*S*,*R*)- and (*R*,*S*)-2,4-Dibromo-1-ethoxy-1-methoxy-1,2-dihydronaphthalene (3a)

From **1b**: Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.81 (m, 1H), 7.70–7.67 (m, 1H), 7.46–7.42 (m, 2H), 6.65 (d, *J*=6.4 Hz, 1H), 4.83 (d, *J*=6.8 Hz, 1H), 3.75–3.67 (m, 2H), 2.89 (s, 3H), 1.38 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 132.3, 130.7, 129.2, 129.0, 128.8, 127.9, 127.1, 124.9, 98.1, 56.0, 51.0, 47.7, 14.9; MS (EI) 363 (M^+), 361 (M^+, 100), 359 (M^+). HRMS (EI) calcd for $C_{13}H_{14}Br_2O_2$ (M^+) 361.9340 found 361.9341.

4.3. 5,8-Dihydro-5,5,8,8-tetramethoxyquinaldine (10a)

From **9**: Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J*=8.4 Hz, 1H), 7.19 (d, *J*=8.0 Hz, 1H), 6.41 (d, *J*=10.8 Hz, 1H), 6.22 (d, *J*=10.8 Hz, 1H), 3.27 (s, 6H), 3.10 (s, 6H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 152.8, 134.8, 132.9, 130.6, 128.7, 123.8, 96.2, 93.5, 51.2 (2C), 51.0 (2C), 24.7; MS (EI) 265, 204 (M^+, 100), 188, 174, 160, 130, 117, 102. HRMS (EI) calcd for $C_{14}H_{19}NO_4$ (M^+) 265.1314 found 265.1309.

4.4. (6*S*,7*S*)- and (6*R*,7*R*)-6,7-Dibromo-5,5,8,8-tetramethoxy-5,6,7,8-tetrahydroquinaldine (10b)

From **9**: White solid; mp 124–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J*=8.0 Hz, 1H), 7.26 (d, *J*=8.4 Hz, 1H), 5.09 (d, *J*=10.0 Hz, 1H), 5.00 (d, *J*=10.0 Hz, 1H), 3.33 (s, 3H), 3.30 (s, 3H), 3.25 (s, 3H), 3.17 (s, 3H), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 151.1, 136.2, 125.5, 122.8, 98.5, 98.4, 56.2, 55.9, 51.6, 50.7, 49.8, 24.7; MS (FAB) 428 (M^++1), 426 (M^++1), 424 (M^++1), 394, 314, 266, 234 (100), 204, 188, 174, 106. HRMS (FAB) calcd for $C_{14}H_{20}Br_2NO_4$ (M^++1) 425.9739 found 425.9762.

4.5. 5,8-Dihydro-5,5,8,8-tetramethoxyepidine (12a)

From **11**: Off white solid; mp 49–51 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J*=4.8 Hz, 1H), 7.10 (d, *J*=4.0 Hz, 1H), 6.46 (d, *J*=10.8 Hz, 1H), 6.12 (d, *J*=10.8 Hz, 1H), 3.30 (s, 6H), 3.10 (s, 6H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 149.8, 148.4, 131.9, 131.5, 129.3, 127.1, 98.4, 93.7, 51.1, 50.9, 20.1; MS (EI) 265 (M^+), 250, 204 (100), 188, 174, 160, 145, 130, 117, 102. HRMS (EI) calcd for $C_{14}H_{19}NO_4$ (M^+) 265.1314 found 265.1317.

4.6. 6-Bromo-5,8-dihydro-5,5,8,8-tetramethoxyquinaldine (14)

From **13**: Yellow solid; mp 85–87 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.89 (d, *J*=8.4 Hz, 1H), 7.30 (d, *J*=8.0 Hz, 1H), 7.00 (s, 1H), 3.41 (s, 6H), 3.00 (s, 6H), 2.68 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.3, 153.0, 137.1, 135.6, 128.3, 126.5, 124.5, 98.2, 95.0, 51.3, 24.7; MS (FAB) 346 (M^++1), 344 (M^++1), 312 (100), 282, 280. HRMS (FAB) calcd for $C_{14}H_{19}BrNO_4$ (M^++1) 344.0497, found 344.0498.

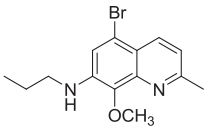
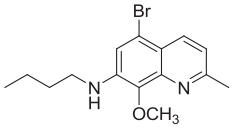
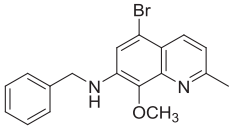
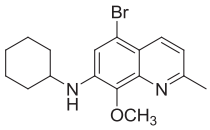
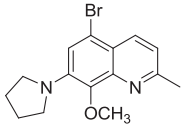
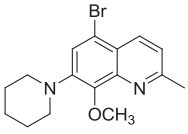
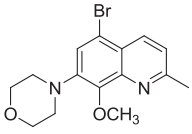
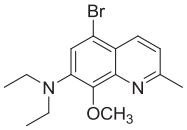
4.7. 7-Bromo-5,8-dihydro-5,5,8,8-tetramethoxyquinaldine (16)

From **15**: Red solid; mp 69–71 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.86 (d, *J*=8.0 Hz, 1H), 7.28 (d, *J*=8.0 Hz, 1H), 6.84 (s, 1H), 3.24 (s, 6H), 3.17 (s, 6H), 2.67 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.1, 150.7, 134.8, 134.7, 131.3, 129.6, 124.0, 96.8, 95.8, 51.7, 51.1, 24.6; MS (FAB) 346 (M^++1), 344 (M^++1), 312 (100), 282, 280. HRMS (FAB) calcd for $C_{14}H_{19}BrNO_4$ (M^++1) 344.0497, found 344.0495.

4.8. 7-Bromo-5,8-dihydro-5,8,8-trimethoxyquinaldine (19)

From **18**: Colorless liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.78 (d, *J*=8.2 Hz, 1H), 7.27 (d, *J*=8.0 Hz, 1H), 6.93 (d, *J*=3.6 Hz, 1H), 5.03 (d, *J*=3.6 Hz, 1H), 3.62 (s, 3H), 3.14 (s, 3H), 3.12 (s, 3H), 2.67 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.4, 149.6, 135.8, 135.2, 128.8, 128.5, 123.6, 96.3, 72.2, 53.2, 51.6, 51.3, 24.4; MS (EI) 316, 314 (M^+), 312, 300, 282, 255, 254 (100), 237, 224, 202, 188, 174, 172, 142, 130, 115, 102. HRMS (FAB) calcd for $C_{13}H_{17}BrNO_3$ (M^++1) 314.0392, found 314.0394.

Table 3
Nucleophilic substitution reaction at the 7-position with various primary and secondary amines from **7**[a]

Entry	Amines	Product[b]
1	*n*-Propylamine	 **23** (38)
2	*n*-Butylamine	 **24** (38)
3	Benzylamine	 **25** (45)
4	1-Cyclohexylamine	 **26** (36)
5	Pyrrolidine	 **27** (42)
6	Piperidine	 **28** (38)
7	Morpholine	 **29** (40)
8	Diethylamine	 **30** (36)

[a] All reactions were carried out on a 1.0 mmol reaction scale of **7** using 3.0 equiv of each amine at reflux for 1 h in dry THF (10 mL).
[b] Isolated yields.

4.9. General procedure for nucleophilic amination of addition product 7

A solution of **7** (0.363 g, 1.0 mmol) and corresponding amines (3.0 mmol) in dry THF (10 mL) was refluxed under nitrogen atmosphere for 1 h. After cooling, H_2O (30 mL) was added to the reaction mixture. The mixture was extracted with CH_2Cl_2 (2×50 mL), and the combined organic layer was washed with water and brine, and evaporated. The residue was purified by flash column chromatography.

4.10. 5-Bromo-8-methoxy-7-[*N*-(*n*-propyl)amino]quinaldine (23)

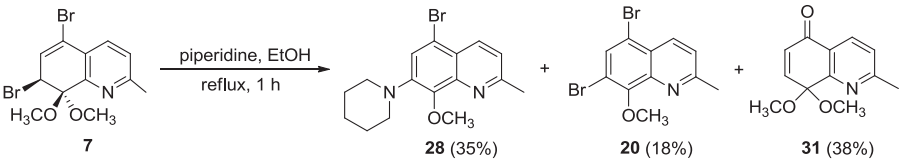
Yellow solid; mp 139–141 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.95 (d, J=8.6 Hz, 1H), 7.17 (d, J=8.4 Hz, 1H), 6.61 (s, 1H), 4.02 (s, 3H), 3.12 (t, J=7.2 Hz, 2H), 2.71 (s, 3H), 1.78–1.67 (m, 2H), 1.04 (t, J=7.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.8, 144.1, 143.2, 140.5, 129.2, 120.3, 117.8, 117.0, 107.3, 61.7, 46.0, 25.4, 22.4, 11.7; MS (EI) 310 (M^+), 308 (M^+, 100), 306 (M^+), 293, 279, 251, 223. HRMS (EI) calcd for $C_{14}H_{17}BrN_2O$ (M^+) 308.0524, found 308.0526.

4.11. 5-Bromo-7-[*N*-(*n*-butyl)amino]-8-methoxyquinaldine (24)

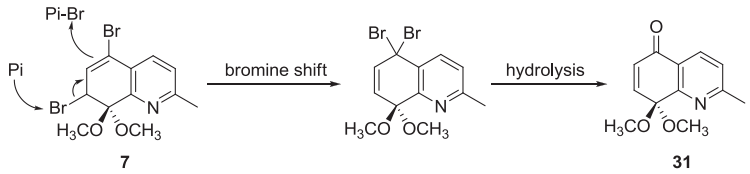
Greenish solid; mp 121–123 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.96 (d, J=8.8 Hz, 1H), 7.19 (d, J=8.4 Hz, 1H), 6.62 (s, 1H), 4.13 (br s, 1H), 4.02 (s, 3H), 3.16 (t, J=7.0 Hz, 2H), 2.72 (s, 3H), 1.74–1.64 (m, 2H), 1.53–1.42 (m, 2H), 0.98 (t, J=7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.9, 144.1, 143.2, 140.5, 129.2, 120.4, 117.9, 117.1, 107.3, 61.7, 43.9, 31.3, 25.4, 20.4, 13.9; MS (EI) 324 (M^+), 322 (M^+, 100), 320 (M^+), 307, 293, 279, 265, 251, 223. HRMS (EI) calcd for $C_{15}H_{19}BrN_2O$ (M^+) 322.0681 found 322.0677.

4.12. 7-(*N*-Benzylamino)-5-bromo-8-methoxyquinaldine (25)

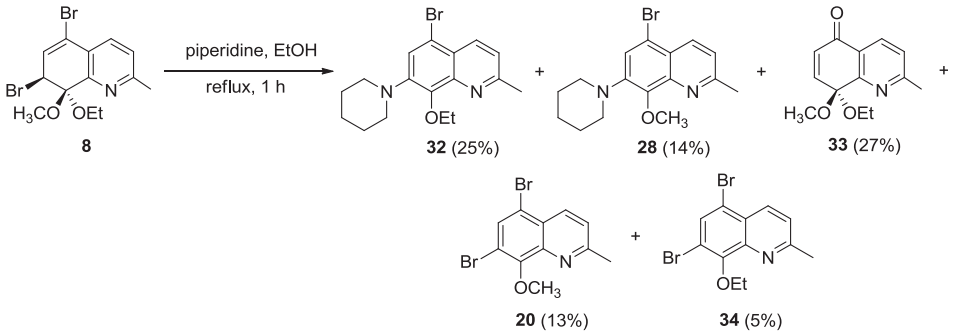
White solid; mp 133–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J=8.8 Hz, 1H), 7.49–7.32 (m, 5H), 7.20 (d, J=8.4 Hz, 1H), 6.71 (s, 1H), 4.38 (s, 2H), 4.04 (s, 3H), 2.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 144.7, 143.2, 140.1, 138.1, 129.3, 128.8 (2C), 127.9 (2C), 127.7, 120.5, 117.7, 117.2, 107.9, 61.7, 48.7, 25.4; MS (EI) 359, 357 (M^+), 355, 327, 325, 265 (100), 238, 236, 186, 185, 155, 117. Anal. Calcd for $C_{18}H_{17}BrN_2O$: C, 60.52; H, 4.80; N, 7.84. Found: C, 60.28; H, 5.19; N, 7.80.



Scheme 4. Piperidination of **7** at the 7-position by nucleophilic substitution.

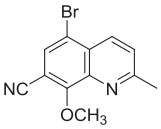
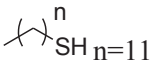
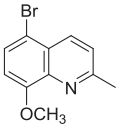
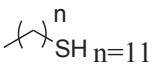
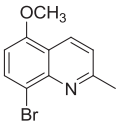


Scheme 5. Proposed plausible mechanism of 8,8-dimethoxy-quinalidin-5-one (**31**).



Scheme 6. Piperidination of **8** at the C7 position by nucleophilic substitution.

Table 4
Nucleophilic substitution reaction at the 7-position with KCN and 1-dodecanethiol from **7**[a]

Entry	Nucleophile	Product[b]
1	KCN	 **35** (30)
2		 **17** (82)
3[c]		 **37** (83)

[a] The reactions were carried out under the same reaction conditions as shown in Table 3.
[b] Isolated yields.
[c] The reaction was carried out on a 1.0 mmol reaction scale of 6,8-dibromo-5,5-dimethoxy-5,6-dihydroquinaldine (**36**) under the same reaction conditions.

4.13. 5-Bromo-7-(*N*-cyclohexylamino)-8-methoxyquinaldine (26)

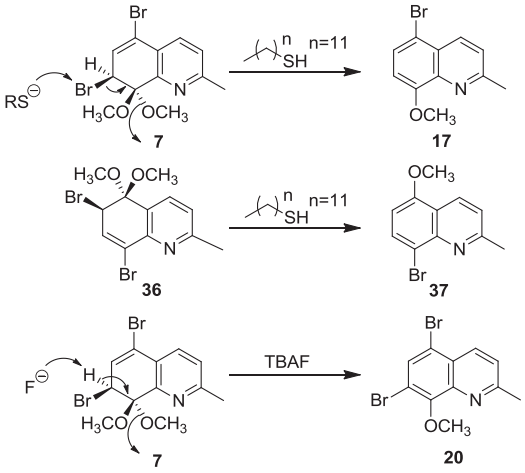
Brown solid; mp 132–134 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.94 (d, J=8.4 Hz, 1H), 7.16 (d, J=8.8 Hz, 1H), 6.64 (s, 1H), 4.01 (s, 3H), 3.37–3.28 (m, 1H), 2.71 (s, 3H), 2.13–2.07 (m, 2H), 1.83–1.64 (m, 3H), 1.50–1.13 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.8, 143.8, 143.4, 139.3, 129.2, 120.2, 117.8, 117.1, 107.7, 61.7, 51.8, 33.0, 25.8, 25.4, 24.8; MS (EI) 350 (M^+), 348 (M^+, 100), 333, 319, 305, 277, 265, 251, 237, 186. HRMS (EI) calcd for $C_{17}H_{21}BrN_2O$ (M^+) 348.0837, found 348.0835.

4.14. 5-Bromo-8-methoxy-7-(pyrrolidin-1-yl)quinaldine (27)

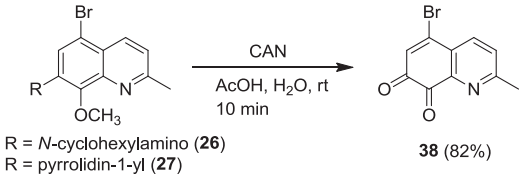
Brown liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.33 (d, J=8.8 Hz, 1H), 7.19 (d, J=8.8 Hz, 1H), 6.96 (s, 1H), 4.05 (s, 3H), 3.31–3.25 (m, 4H), 2.73 (s, 3H), 2.01–1.95 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.6, 146.9, 144.3, 143.4, 133.8, 121.6, 120.1, 116.8, 114.3, 61.7, 52.9, 25.3, 24.9; MS (EI) 324 (M^+), 322 (M^+, 100), 320, 291, 265, 237, 211. HRMS (EI) calcd for $C_{15}H_{17}BrN_2O$ (M^+) 320.0524, found 320.0529.

4.15. 5-Bromo-8-methoxy-7-(piperidin-1-yl)quinaldine (28)

White solid; mp 102–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J=8.4 Hz, 1H), 7.18 (d, J=8.4 Hz, 1H), 7.04 (s, 1H), 4.02 (s, 3H), 2.88 (br s, 4H), 2.69 (s, 3H), 1.76–1.70 (m, 4H), 1.56 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 148.6, 147.5, 143.5, 132.9, 122.9, 121.3, 118.4, 116.4, 61.8, 54.8, 26.4, 25.5, 24.3; MS (EI) 337 (M^+), 335 (M^+), 333 (M^+), 319 (100), 305, 303, 277, 265, 251, 237, 225, 210, 195, 169, 155, 142, 128, 115, 101. HRMS (EI) calcd for $C_{16}H_{19}BrN_2O$ (M^+) 334.0681 found 334.0684.



Scheme 7. Different reaction pattern of nucleophilic substitution using thiol and fluoride from **7** and **36**.



Scheme 8. Synthesis of 5-bromoquinaldine-7,8-dione (**38**).

4.16. 5-Bromo-8-methoxy-7-(morpholin-4-yl)quinaldine (29)

Brown solid; mp 90–93 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.31 (d, J=8.8 Hz, 1H), 7.25 (d, J=8.4 Hz, 1H), 7.13 (s, 1H), 4.07 (s, 3H), 3.93–3.88 (m, 4H), 3.01–2.96 (m, 4H), 2.73 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.2, 149.4, 145.7, 143.5, 132.5, 122.7, 121.5, 118.8, 116.3, 67.1, 61.8, 53.6, 25.4; MS (EI) 338 (M^+), 336 (M^+, 100), 334 (M^+), 321, 307, 279, 249. HRMS (EI) calcd for $C_{15}H_{17}BrN_2O_2$ (M^+) 336.0473, found 336.0470.

4.17. 5-Bromo-7-(*N*,*N*-diethylamino)-8-methoxyquinaldine (30)

Yellow solid; mp 70–72 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.49 (d, J=8.8 Hz, 1H), 7.30 (d, J=8.8 Hz, 1H), 7.26 (s, 1H), 4.16 (s, 3H), 3.15 (q, J=7.1 Hz, 4H), 2.80 (s, 3H), 1.06 (t, J=7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.9, 149.1, 144.4, 143.4, 133.3, 125.3, 121.9, 121.4, 116.1, 61.8, 48.2, 25.4, 12.2; MS (EI) 324 (M^+), 322 (M^+), 320 (M^+), 307 (100), 293, 279, 249. HRMS (EI) calcd for $C_{15}H_{19}BrN_2O$ (M^+) 322.0681, found 322.0678.

4.18. 8,8-Dimethoxy-quinalidin-5-one (31)

Brown solid; mp 56–58 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J=8.0 Hz, 1H), 7.36 (d, J=8.0 Hz, 1H), 7.15 (d, J=10.4 Hz, 1H), 6.64 (d, J=10.4 Hz, 1H), 3.40 (s, 6H), 2.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.9, 162.7, 155.7, 144.1, 133.8, 129.9, 124.0, 123.4, 92.6, 50.8, 24.6; MS (FAB) 220 (M^++1), 188 (100), 154, 136. HRMS (FAB) calcd for $C_{12}H_{14}NO_3$ (M^++1) 220.0974, found 220.0978.

4.19. 5-Bromo-8-ethoxy-7-(piperidin-1-yl)quinaldine (32)

Yellow solid; mp 75–77 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.30 (d, J=8.4 Hz, 1H), 7.24 (d, J=8.6 Hz, 1H), 7.12 (s, 1H), 4.37 (q, J=6.9 Hz, 2H), 2.95 (br s, 4H), 2.74 (s, 3H), 1.85–1.75 (m, 4H), 1.64 (br s, 2H), 1.52 (t, J=7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.6, 148.0, 147.1, 143.6, 132.8, 122.8, 121.1, 118.4, 116.7, 70.4, 54.7, 26.4, 25.5, 24.3, 15.7; MS (EI) 350 (M^+), 348 (M^+), 319 (100), 305, 265, 251, 237, 220. HRMS (EI) calcd for $C_{17}H_{21}BrN_2O$ (M^+) 348.0837, found 348.0840.

4.20. (*S*)- and (*R*)-8-Ethoxy-8-methoxy-quinaldin-5-one (33)

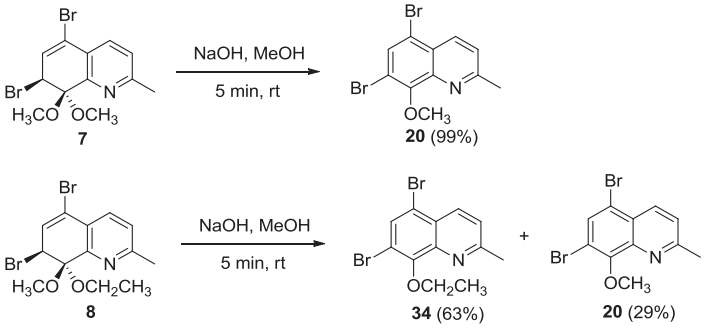
Brown liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.17 (d, J=8.0 Hz, 1H), 7.25 (d, J=8.2 Hz, 1H), 7.02 (d, J=10.6 Hz, 1H), 6.50 (d, J=10.6 Hz, 1H), 3.68–3.53 (m, 1H), 3.49–3.33 (m, 1H), 3.30 (s, 3H), 2.65 (s, 3H), 1.13 (t, J=7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 183.9, 163.6, 156.7, 145.4, 134.4, 130.6, 124.8, 124.1, 93.2, 59.4, 51.3, 25.1, 15.3; MS (FAB) 234 (M^++1), 188 (100), 174, 154, 136. HRMS (FAB) calcd for $C_{13}H_{16}NO_3$ (M^++1) 234.1130, found 234.1126.

4.21. 5,7-Dibromo-8-ethoxyquinaldine (34)

White solid; mp 75–77 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.30 (d, J=8.4 Hz, 1H), 7.88 (s, 1H), 7.36 (d, J=8.8 Hz, 1H), 4.44 (q, J=7.1 Hz, 2H), 2.77 (s, 3H), 1.53 (t, J=6.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.7, 152.3, 143.4, 135.8, 132.4, 126.3, 123.2, 116.5, 115.8, 71.0, 25.4, 15.7; MS (EI) 346 (M^+), 344 (M^+, 100), 342 (M^+), 330 (100), 328, 301, 289, 236, 220. HRMS (EI) calcd for $C_{12}H_{11}Br_2NO$ (M^+) 344.9187, found 344.9181. CAS No. 1383949-12-9.

4.22. 5-Bromo-7-cyano-8-methoxyquinaldine (35)

Yellow solid; mp 145–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J=8.4 Hz, 1H), 7.97 (s, 1H), 7.43 (d, J=8.8 Hz, 1H), 4.25 (s, 3H), 2.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 157.6, 142.0, 135.9, 133.7, 127.3, 124.4, 115.8, 115.0, 105.5, 63.0, 25.7; MS (EI) 277 (M^+), 275 (M^+), 249, 247, 167, 153, 140, 113. Anal. Calcd for $C_{13}H_9BrN_2O$: C, 52.01; H, 3.27; N, 10.11. Found: C, 52.32; H, 3.22; N, 10.43.



Scheme 9. Interconversion to 5,7-dibromo-8-alkoxyquinaldines (**20** and **34**) under basic methanolic conditions.

4.23. 5-Bromoquinaldine-7,8-dione (38)

A solution of ceric ammonium nitrate (500 mg, 0.9 mmol) in H_2O (3.0 mL) was slowly added to 5-bromo-7-(*N*-cyclohexylamino)-8-methoxyquinaldine (**26**, 105 mg, 0.3 mmol) or 5-bromo-8-methoxy-7-(pyrrolidin-1-yl)quinaldine (**27**, 100 mg, 0.3 mmol) in acetic acid (3.0 mL). After 10 min, water was added to the reaction mixture. The mixture was extracted with EtOAc (2×30 mL), and the combined organic layer was washed with water and brine, and evaporated. The residue was purified by flash column chromatography (30% EtOAc/Hx), yielding **38** (64 mg, 82%) as a brown solid. Mp 123–126 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.27 (d, J=8.0 Hz, 1H), 7.56 (d, J=8.6 Hz, 1H), 7.53 (s, 1H), 2.77 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 181.9, 176.2, 165.4, 146.2, 140.4, 139.4, 134.9, 128.0, 126.8, 29.6, 25.3; MS (EI) 252 (M^+), 250 (M^+), 144, 116 (100), 91. HRMS (EI) calcd for $C_{10}H_6BrNO_2$ (M^+) 250.9582 found 250.9583.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2016.07.010.

References and notes

1. (a) Yang, Z.-P.; Wu, Q.-F.; You, S.-L. *Angew. Chem., Int. Ed.* **2014**, *53*, 6986; (b) Nemoto, T.; Zhao, Z.; Yokosaka, T.; Suzuki, Y.; Wu, R.; Hamada, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 2217; (c) Zhuo, C.-X.; Zhang, W.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 12662; (d) Dohi, T.; Maruyama, A.; Takenaga, N.; Senami, K.; Minamitsuji, Y.; Fujioka, H.; Caemmerer, S. B.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3787.
2. Choi, H. Y.; Srisook, E.; Jang, K. S.; Chi, D. Y. *J. Org. Chem.* **2005**, *70*, 1222.
3. (a) Hebel, D.; Rozen, S. *J. Org. Chem.* **1991**, *56*, 6298; (b) Strand, J. W.; Kovacic, P. *J. Am. Chem. Soc.* **1973**, *95*, 2977; (c) Kovacic, P.; Levisky, J. A. *J. Am. Chem. Soc.* **1966**, *88*, 1000; (d) Jang, K. S.; Shin, H. Y.; Chi, D. Y. *Tetrahedron* **2008**, *64*, 5666.
4. Lenoir, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 854.
5. (a) Lautens, M.; Fagnou, K.; Rovis, T. *J. Am. Chem. Soc.* **2000**, *122*, 5650; (b) Lautens, M.; Schmid, G. A.; Chau, A. *J. Org. Chem.* **2002**, *67*, 8043; (c) Wu, M.-S.; Jeganmohan, M.; Cheng, C.-H. *J. Org. Chem.* **2005**, *70*, 9545; (d) Cho, Y. H.; Zunic, V.; Senboku, H.; Olsen, M.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 6837.
6. (a) Michels, J. G.; Hayes, K. J. *J. Am. Chem. Soc.* **1958**, *80*, 1114; (b) Kolb, V. M.; Darling, S. D.; Koster, D. F.; Meyers, C. Y. *J. Org. Chem.* **1984**, *49*, 1636.
7. Lopez-Ortiz, F.; Iglesias, M. J.; Fernandez, I.; Andujar-Sanchez, C. M.; Ruiz-Gomez, G. *Chem. Rev.* **2007**, *107*, 1580.
8. (a) Fischer, A.; Ramsay, J. N. *J. Am. Chem. Soc.* **1974**, *96*, 1614; (b) Hahn, R. C.; Strack, D. L. *J. Am. Chem. Soc.* **1974**, *96*, 4335.
9. (a) Wang, T.; Magnin, D. R.; Hamann, L. G. *Org. Lett.* **2003**, *5*, 897; (b) Loeppky, R. N.; Cui, W. *Tetrahedron* **2001**, *57*, 2953; (c) Margolis, B. J.; Long, K. A.; Laird, D. L. T.; Craig Ruble, J.; Pulley, S. R. *J. Org. Chem.* **2007**, *72*, 2232; (d) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240; (e) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722; (f) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046; (g) Lakshman, M. K.; Keeler, J. C.; Hilmer, J. H.; Martin, J. Q. *J. Am. Chem. Soc.* **1999**, *121*, 6090; (h) De Riccardis, F.; Bonala, R. R.; Johnson, F. *J. Am. Chem. Soc.* **1999**, *121*, 10453; (i) Elmquist, C. E.; Stover, J. S.; Wang, Z.; Rizzo, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 11189; (j) Dai, Q.; Ran, C.; Harvey, R. G. *Org. Lett.* **2005**, *7*, 999.
10. Melato, S.; Coghi, P.; Basilico, N.; Prosperi, D.; Monti, D. *Eur. J. Org. Chem.* **2007**, 6118.
11. Kim, D. W.; Choi, H. Y.; Lee, K. J.; Chi, D. Y. *Org. Lett.* **2001**, *3*, 445.
12. (a) Behforouz, M.; Cai, W.; Stocksdale, M. G.; Lucas, J. S.; Jung, J. Y.; Briere, D.; Wang, A.; Katen, K. S.; Behforouz, N. C. *J. Med. Chem.* **2003**, *46*, 5773; (b) Seradj, H.; Cai, W.; Erasga, N. O.; Chenault, D. V.; Knuckles, K. A.; Ragains, J. R.; Behforouz, M. *Org. Lett.* **2004**, *6*, 473.
13. Choi, H. Y.; Chi, D. Y. *Tetrahedron* **2004**, *60*, 4945.
14. (a) Hargreaves, R. H. J.; David, C. L.; Whitesell, L. J.; LaBarbera, D. V.; Jamil, A.; Chapuis, J. C.; Skibo, E. B. *J. Med. Chem.* **2008**, *51*, 2492; (b) Naruta, Y.; Nagai, N.; Arita, Y.; Maruyama, K. *J. Org. Chem.* **1987**, *52*, 3956.
15. Keyari, C. M.; Kearns, A. K.; Duncan, N. S.; Eickholt, E. A.; Abbott, G.; Beall, H. D.; Diaz, P. *J. Med. Chem.* **2013**, *56*, 3806.