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FACILE SYNTHESES OF FLUORINE-CONTAINING 4-METHOXY-PYRAZOLO[4,3-*c*]QUINOLINES AND 6-METHOXY-1,4-DIAZEPINO-[6,5-*c*]QUINOLINES

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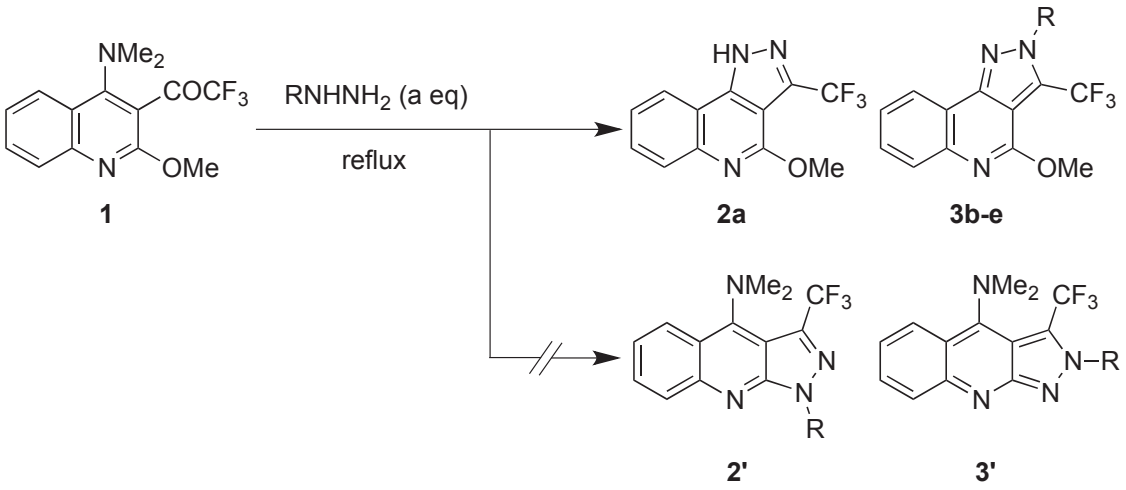
Abstract – *N*,*N*-Dimethyl-2-methoxy-3-trifluoroacetyl-4-quinolylamine underwent chemoselective aromatic nucleophilic *N*-*N* exchange reaction with hydrazines followed by cyclocondensation to afford the corresponding novel fluorine-containing 4-methoxy-1*H*- and 2*H*-pyrazolo[4,3-*c*]quinolines in good to high yields. Furthermore, the use of 1,2-ethylenediamine and 1,2-phenylenediamines gave the corresponding fluorine-containing 6-methoxy-1,4-diazepino[6,5-*c*]quinoline derivatives in good yields.

Pyrazolo[4,3-*c*]quinolines have been a target of great deal of a research because of their biological activities and pharmacological properties such as antiproliferative,[1,2] antitumor,[1,3] allergy inhibit,[2] anti-inflammatory,[2] antiparkinsonian,[4] antiglaucoma,[5] and anti-inflammatory activities.[5] 1,4-Diazepino[6,5-*c*]quinoline derivatives are also important heterocyclic systems demonstrating wide array of application for pharmacology such as nervous system[6] and neuroprotective agents,[6] and interesting biological activities such as anti-alzheimer,[6] antiproliferative,[6] antitumor,[6] antiviral,[6] antibacterial,[7] and HIV-1 reverse transcriptase inhibit activities.[8] Besides, considerable attention has been paid in recent years to the development of new methodologies for the syntheses of many kinds of fluorine-containing heterocycles, since these compounds are now widely recognized as important organic materials showing interesting biological activities for their potential use in medicinal and agricultural scientific fields.[9] For instance, it has been reported that fluorine-containing pyrazolo[4,3-*c*]quinolines have a potential use as analgesic and antipyretic drugs.[10] On the other hand, there has been no reported about fluorine-containing 1,4-diazepino[6,5-*c*]quinolines except for our previous report.[11] Thus, it would be very important to develop facile synthetic methods for novel fluorine-containing pyrazolo[4,3-*c*]quinolines and 1,4-diazepino[6,5-*c*]quinolines, which would be strongly expected to

present new bioactivities and functionalities.

Previously, we have found that *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine,[12] *N*,*N*-dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamine,[13] and *N*,*N*-dimethyl-3-trifluoroacetyl-4-quinolylamine[11] undergo *N*-*N* exchange reaction and the subsequent cyclization with various bifunctional *N*-nucleophiles to achieve the facile syntheses of naphthalene[12] and quinoline[11,13] fused heterocycles bearing trifluoromethyl groups. Recently, we have reported the aromatic nucleophilic substitution reaction of *N*,*N*-dimethyl-2-methoxy-3-trifluoroacetyl-4-quinolylamine (**1**) with various amines proceeded chemoselectively to give the corresponding dimethylamino-nucleophile exchanged products, 2-methoxy-3-trifluoroacetyl-4-quinolylamines without any formation of methoxy-nucleophile exchanged products in spite of the common knowledge that alkoxy group is better leaving group than amino group.[14] As an application of this chemoselective nucleophilic aromatic substitution (the *N*-*N* exchange reaction), we wish to report here the facile synthetic method for fluorine-containing 4-methoxy-1*H*- and 2*H*-pyrazolo[4,3-*c*]quinolines (**2, 3**) and 6-methoxy-1,4-diazepino[6,5-*c*]quinoline (**5**-**7**) by the reaction of **1** with bifunctional *N*-nucleophiles such as hydrazines and 1,2-diamines.

First, we examined the reaction of **1** with hydrazines (Scheme 1 and Table 1). Reaction of **1** with hydrazine monohydrate proceeded easily under reflux for 4 h in acetonitrile to afford the *N*-unsubstituted 4-methoxy-1*H*-pyrazolo[4,3-*c*]quinoline (**2a**) by *N*-*N* exchange reaction at the 4-position and cyclization in a quantitative yield (Entry 1). Neither *N*,*N*-dimethyl-3-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]-quinolin-4-amine (**2'**: R=H) nor *N*,*N*-dimethyl-3-(trifluoromethyl)-2*H*-pyrazolo[3,4-*b*]quinolin-4-amine (**3'**: R=H), which is formed by carrying out *O*-*N* exchange reaction at the 2-position, was obtained at all. A similar treatment of methylhydrazine gave exclusively the 2-methyl isomer (**3b**) in almost quantitative yield without any formation of the corresponding 1-methyl isomer (**2b**) (Entry 2).



Scheme 1

Table 1. Reaction of **1** with Hydrazines

Entry	R	a (eq)	Solvent	Time (h)	Product	Yield (%)[a]
1	H	1	MeCN	4	**2a**	100
2	Me	3	MeCN	4	**3b**	99
3	*t*-Bu[b]	10	PrCN	8	**3c**	82
4	Ph	5	MeCN	24	**3d**	87
5	*p*-$O_2NC_6H_4$	10	BuCN	24	**3e**	61

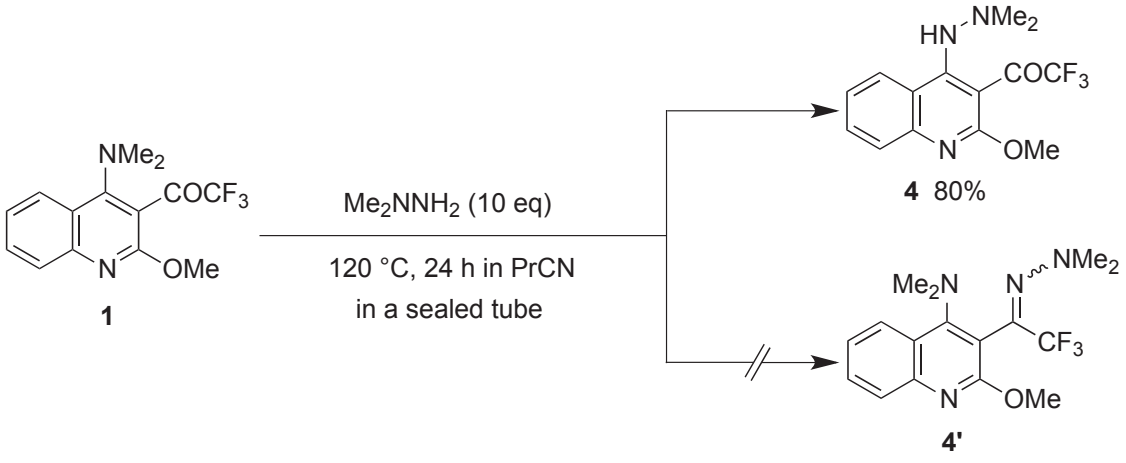
[a] Isolated yields.

[b] *tert*-Butylhydrazine hydrochloride was used in the presence of *i*-Pr_2NEt (10 eq).

tert-Butylhydrazine hydrochloride (10 eq) also reacted with **1** in the presence of *i*-Pr_2NEt (10 eq) under reflux temperature in butyronitrile to provide solely the 2*H*-pyrazoloquinoline (**3c**) in 82% yield (Entry 3). Likewise, arylhydrazines such as phenylhydrazine gave the corresponding 2-phenyl-2*H*-pyrazoloquinoline (**3d**) regioselectively in 87% yield (Entry 4). In the case of *p*-nitrophenylhydrazine showed lower reactivity than other hydrazines, the reaction was performed with a large amount of reagent (10 eq), under reflux in valeronitrile to provide the corresponding 2-aryl-2*H*-pyrazoloquinoline **3e** in 61% yield (Entry 5).

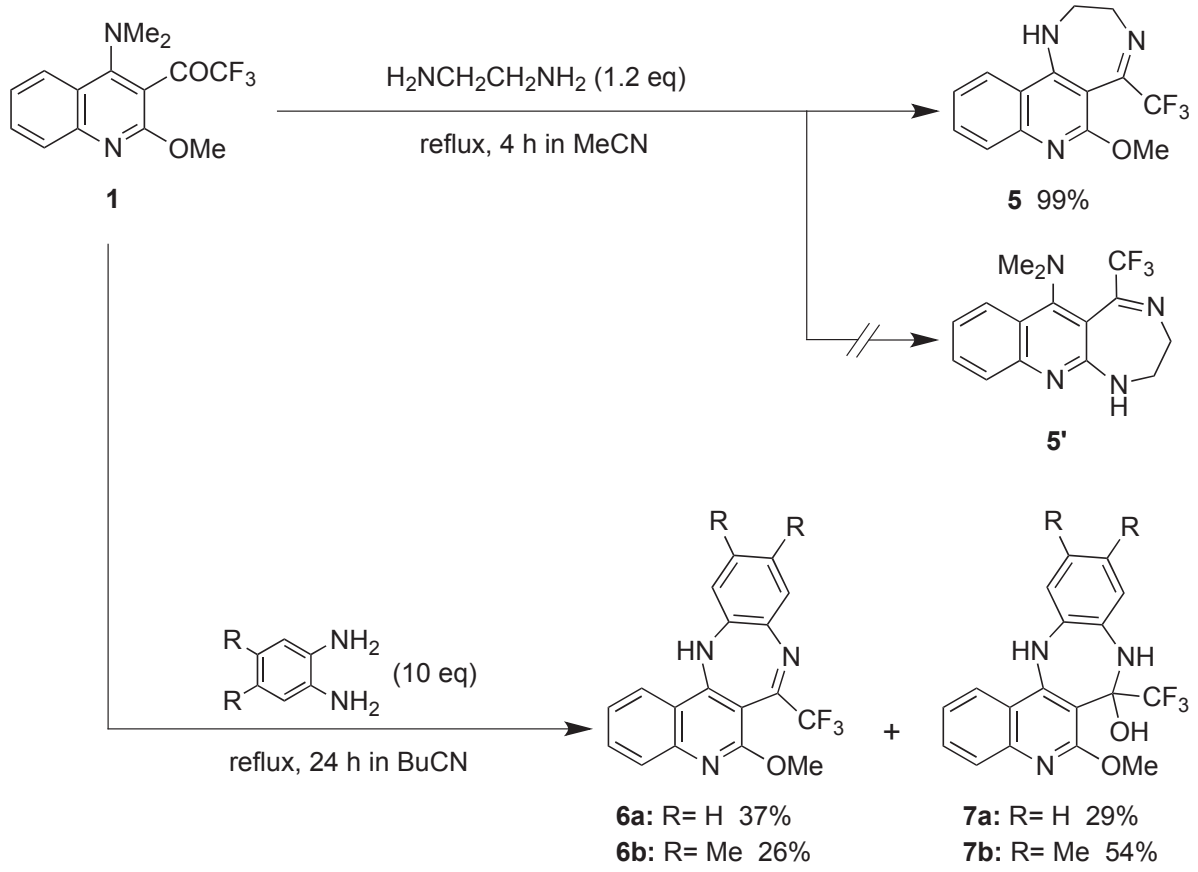
Next, the possibility that the reaction proceeds via the prior formation of a hydrazone at the trifluoroacetyl group followed by an intramolecular *N*-*N* exchange to give the cyclized product seems unlikely, since the reaction of **1** with *N*,*N*-dimethylhydrazine gave the *N*-*N* exchanged product **4** in high yield and the corresponding *N*,*N*-dimethylhydrazone **4'** could not be detected (Scheme 2).

Finally, we attempted to carry out the reaction of **1** with 1,2-diamines (Scheme 3). Reaction of **1** with 1,2-ethylenediamine proceeded successfully for 4 h in refluxing acetonitrile to give the desired



Scheme 2

6-methoxy-5-(trifluoromethyl)-2,3-dihydro-1*H*-[1,4]diazepino[6,5-*c*]quinoline (**5**) almost quantitatively without any formation of **5'** as a result of the *O-N* exchange reaction and the cyclization. Aromatic diamines such as 1,2-phenylenediamine (10 eq) reacted with **1** under more forced conditions (24 h in refluxing valeronitrile) to afford the corresponding diazepinoquinoline (**6a**) together with diazepinoquinolinol (**7a**), the precursor of **6a**. Reaction of **1** with 4,5-Dimethyl-1,2-phenylenediamine also proceeded to provide the corresponding diazepinoquinoline (**6b**) and diazepinoquinolinol (**7b**) in high combined yield.



Scheme 3

In summary, we succeeded in the reaction of **1** with various hydrazines and demonstrated a facile approach for the syntheses of 4-methoxy-1*H*- and 2*H*-pyrazolo[4,3-*c*]quinolines (**2**, **3**), which are not easily accessible by other methods, by chemoselective *N-N* exchange reaction and intramolecular cyclization. Furthermore, we also found that 6-methoxy-1,4-diazepino[6,5-*c*]quinoline derivatives (**5-7**) were easily prepared by the reaction of **1** with 1,2-diamines. It is worth of noting that these compounds (**2**, **3**, and **5-7**) have 2-methoxy group which enable further functionalization at this position. Evaluation of biological activities for all new compounds **2**, **3**, and **5-7** is now under way.

EXPERIMENTAL

^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra was obtained with a Bruker Avance 500 spectrometer; TMS was used as an internal standard. IR spectra were recorded on a PerkinElmer Spectrum ONE spectrophotometer. Microanalyses were obtained with a Yanaco CHN-Coder MT-5 analyzer. Melting points were determined on an electrothermal digital melting point apparatus and are uncorrected. Solvents such as MeCN, PrCN and BuCN were used after drying with 4Å molecular sieves. Other reagents were purchased as reagent grade and used without further purification. Column chromatography was carried out with Fuji Silysia Chemical PSQ100B as filler.

1*H*- and 2*H*-Pyrazolo[4,3-*c*]quinolines (2, 3): General Procedure

Using Hydrazine Monohydrate, Methyl-, Phenyl- and p-Nitrophenylhydrazines: To a solution of **1** (298 mg, 1 mmol) in MeCN or BuCN (4 mL) was added the appropriate hydrazine (1 mmol to 10 mmol) and the mixture was stirred under reflux for 4-24 h. Evaporation of the solvent in vacuo gave a crude mixture, which was subjected to column chromatography (silica gel, *n*-hexane-EtOAc, 50:1 to 5:1) to give the corresponding **2a**, **3b**, **3d** and **3e**.

Using tert-Butylhydrazine Hydrochloride: To a solution of **1** (298 mg, 1 mmol) in PrCN (4 mL) were added *tert*-butylhydrazine hydrochloride (1246 mg, 10 mmol) and *i*-Pr_2NEt (1293 mg, 10 mmol), and the mixture was stirred under reflux for 8 h. The mixture was washed with 1N HCl (30 mL) and extracted with CH_2Cl_2 (50 mL), and the extracts were dried (Na_2SO_4). Evaporation of the solvent in vacuo gave the crude mixture, which was subjected to column chromatography (silica gel, *n*-hexane-EtOAc, 50:1) to give **3c**.

4-Methoxy-3-(trifluoromethyl)-1*H*-pyrazolo[4,3-*c*]quinoline (2a): mp 240-241 °C (*n*-hexane/EtOAc); IR (KBr): 3253, 1142, 1117 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 12.63-12.50 (br, 1H, NH), 8.01 (d, J = 7.7 Hz, 1H), 7.74 (d, J = 7.7 Hz, 1H), 7.62 (t, J = 7.7 Hz, 1H), 7.45 (t, J = 7.7 Hz, 1H), 4.11 (s, 3H); ^{13}C NMR ($CDCl_3$): 155.1, 145.1, 144.5, 135.6 (q, J_{CF} = 38.9 Hz), 129.9, 127.3, 124.6, 121.6, 121.3 (q, J_{CF} = 268.0 Hz), 113.3, 104.6, 53.2. Anal. Calcd for $C_{12}H_8F_3N_3O$: C, 53.94; H, 3.02; N, 15.73. Found: C, 54.11; H, 2.95; N, 15.63.

4-Methoxy-2-methyl-3-(trifluoromethyl)-2*H*-pyrazolo[4,3-*c*]quinoline (3b): mp 142-143 °C (*n*-hexane/EtOAc); IR (KBr): 1182, 1163, 1141 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.31 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 4.32 (s, 3H), 4.16 (s, 3H); ^{13}C NMR ($CDCl_3$): 155.1, 149.5, 143.9, 129.2, 127.4, 125.9 (q, J_{CF} = 41.4 Hz), 124.8, 121.7, 119.9 (q, J_{CF} = 270.2 Hz), 117.6, 107.9, 53.7, 40.8. Anal. Calcd for $C_{13}H_{10}F_3N_3O$: C, 55.52; H, 3.58; N, 14.94. Found: C, 55.60; H, 3.61; N, 14.83.

2-*tert*-Butyl-4-methoxy-3-(trifluoromethyl)-2*H*-pyrazolo[4,3-*c*]quinoline (3c): bp 165 °C/3 torr (oven temperature of Kugelrohr); IR (KBr): 1193, 1160, 1134 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.27 (d, J = 7.4 Hz,

1H), 7.69 (d, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.30 (t, *J* = 7.4 Hz, 1H), 4.06 (s, 3H), 1.74 (s, 9H); ^{13}C NMR ($CDCl_3$): 155.3, 147.3, 143.6, 128.9, 127.1, 125.6 (q, J_{CF} = 42.1 Hz), 124.6, 121.7, 120.1 (q, J_{CF} = 269.9 Hz), 118.0, 109.6, 66.4, 53.6, 30.7. Anal. Calcd for $C_{16}H_{16}F_3N_3O$: C, 59.44; H, 4.99; N, 13.00. Found: C, 59.59; H, 5.05; N, 12.80.

4-Methoxy-2-phenyl-3-(trifluoromethyl)-2*H*-pyrazolo[4,3-*c*]quinoline (3d): mp 159-160 °C (*n*-hexane/EtOAc); IR (KBr): 1190, 1136, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.43 (d, *J* = 7.7 Hz, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.59 (s, 5H, C_6H_5), 7.47 (t, *J* = 7.7 Hz, 1H), 4.23 (s, 3H); ^{13}C NMR ($CDCl_3$): 155.2, 150.4, 144.1, 139.8, 130.1, 129.6, 129.1, 127.4, 126.7 (q, J_{CF} = 41.2 Hz), 126.3, 124.9, 122.0, 119.4 (q, J_{CF} = 270.8 Hz), 117.5, 108.4, 53.8. Anal. Calcd for $C_{18}H_{12}F_3N_3O$: C, 62.97; H, 3.52; N, 12.24. Found: C, 63.00; H, 3.65; N, 12.08.

4-Methoxy-2-(4-nitrophenyl)-3-(trifluoromethyl)-2*H*-pyrazolo[4,3-*c*]quinoline (3e): mp 208-209 °C (*n*-hexane/EtOAc); IR (KBr): 1196, 1142 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.45 (d, *J* = 8.5 Hz, 2H), 8.38 (d, *J* = 7.7 Hz, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 4.23 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$): 154.7, 150.9, 148.2, 144.3, 144.0, 129.9, 127.4, 127.2, 126.7 (q, J_{CF} = 41.2 Hz), 125.0, 124.4, 121.9, 119.1 (q, J_{CF} = 271.0 Hz), 116.9, 109.0, 53.8. Anal. Calcd for $C_{18}H_{11}F_3N_4O_3$: C, 55.68; H, 2.86; N, 14.43. Found: C, 55.61; H, 3.08; N, 14.28.

Synthesis of 1-(4-(2,2-Dimethylhydrazinyl)-2-methoxyquinolin-3-yl)-2,2,2-trifluoroethanone (4)

A solution of *N*,*N*-dimethylhydrazine (601 mg, 10 mmol) and **1** (298 mg, 1 mmol) in PrCN (4 mL) was heated in a sealed tube at 120 °C for 24 h. After removal of the solvent, the crude mixture was subjected to column chromatography (silica gel, *n*-hexane-EtOAc, 5:1) to give **4**. **4:** mp 136-137 °C (*n*-hexane/EtOAc); IR (KBr): 3311, 1685, 1200, 1142 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.66 (d, *J* = 8.1 Hz, 1H), 7.54-7.45 (m, 2H), 7.14 (t, *J* = 8.1 Hz, 1H), 6.23-6.12 (br, 1H), 3.90 (s, 3H), 2.73-2.10 (br, 6H); ^{13}C NMR ($CDCl_3$): 180.5 (q, J_{CF} = 37.3 Hz), 159.9, 151.2, 147.3, 130.8, 127.9, 123.6, 120.7, 116.7 (q, J_{CF} = 290.3 Hz), 114.6, 98.4, 53.6, 47.0, 45.7. Anal. Calcd for $C_{14}H_{14}F_3N_3O_2$: C, 53.67; H, 4.50; N, 13.41. Found: C, 53.89; H, 4.56; N, 13.11.

1,4-Diazepino[6,5-*c*]quinolines (5-7): General Procedure

Using 1,2-Ethylenediamine: To a solution of **1** (298 mg, 1 mmol) in MeCN (4 mL) was added 1,2-ethylenediamine (72 mg, 1.2 mmol) and the mixture was stirred under reflux for 4 h. Evaporation of the solvent in vacuo gave the crude mixture, which was subjected to column chromatography (silica gel, *n*-hexane-EtOAc, 1:1) to give **5**.

Using 1,2-Phenylenediamines: To a solution of **1** (298 mg, 1 mmol) in BuCN (1 mL) was added the appropriate 1,2-phenylenediamine (10 mmol) and the mixture was stirred at reflux temperature for 24 h. The solvent was evaporated under reduced pressure, and CH_2Cl_2 (50 mL) was added to the residue. The solution was washed with 1N HCl (50 mL) and then with H_2O (50 mL), and the organic layer was

separated and dried (Na_2SO_4). The solvent was evaporated in vacuo to give the crude mixture. In the case of the reaction with 1,2-phenylenediamine, the crude mixture was subjected to column chromatography (silica gel, *n*-hexane-EtOAc, 20:1 to 5:1) to give **6a** and **7a**. In the case of the reaction with 4,5-dimethyl-1,2-phenylenediamine, the crude mixture was subjected to column chromatography (silica gel, *n*-hexane-EtOAc, 20:1 to 10:1) to give **6b** and **7b**.

6-Methoxy-5-(trifluoromethyl)-2,3-dihydro-1*H*-[1,4]diazepino[6,5-*c*]quinoline (5): mp 131-132 °C (*n*-hexane/EtOAc); IR (KBr): 3374, 1148 cm^{-1}; ^1H NMR (CD_3CN): δ 7.77 (d, J = 7.5 Hz, 1H), 7.63-7.58 (m, 2H), 7.32 (t, J = 7.5 Hz, 1H), 4.20 (br, 2H), 3.98 (s, 3H), 3.79 (br, 2H); ^{13}C NMR (CD_3CN): 162.2 (q, J_{CF} = 32.8 Hz), 161.8, 152.3, 147.7, 131.9, 128.5, 124.7, 121.9, 121.0 (q, J_{CF} = 278.6 Hz), 118.7, 93.1, 53.6, 52.0, 50.7. Anal. Calcd for $C_{14}H_{12}F_3N_3O$: C, 56.95; H, 4.10; N, 14.23. Found: C, 56.94; H, 4.03; N, 14.23.

6-Methoxy-7-Trifluoromethyl-13*H*-quino[4,3-*b*][1,5]benzodiazepine (6a): mp 179-180 °C (*n*-hexane/ EtOAc); IR (KBr): 3269, 1219, 1200, 1167 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.00 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.63 (t, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.44-7.34 (m, 3H), 5.84 (s, 1H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$): 163.5, 155.4 (q, J_{CF} = 37.3 Hz), 149.7, 147.4, 131.6, 130.9, 129.9, 128.0, 127.7, 127.4, 127.2, 123.6, 123.0, 119.5, 117.3, 115.5 (q, J_{CF} = 288.7 Hz), 91.9, 53.2. Anal. Calcd for $C_{18}H_{12}F_3N_3O$: C, 62.97; H, 3.52; N, 12.24. Found: C, 62.48; H, 4.00; N, 12.21.

6-Methoxy-10,11-dimethyl-7-trifluoromethyl-13*H*-quino[4,3-*b*][1,5]benzodiazepine (6b): mp 200-201 °C (*n*-hexane/ EtOAc); IR (KBr): 3328, 1191, 1151 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.79 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.68 (t, J = 8.2 Hz, 1H), 7.43 (t, J = 8.2 Hz, 1H), 7.08 (s, 1H), 6.55 (s, 1H), 5.89 (br s, 1H), 4.04 (s, 3H), 2.19 (s, 3H), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$): 164.2, 159.9, 158.9 (q, J_{CF} = 33.5 Hz), 147.9, 138.1, 137.9, 137.8, 134.1, 131.6, 129.4, 128.2, 124.4, 122.5, 119.6, 119.4 (q, J_{CF} = 280.0 Hz), 118.1, 104.0, 53.5, 19.1, 18.8. Anal. Calcd for $C_{20}H_{16}F_3N_3O$: C, 64.69; H, 4.34; N, 11.32. Found: C, 64.76; H, 4.47; N, 11.13.

6-Methoxy-7-Trifluoromethyl-8*H*-13*H*-quino[4,3-*b*][1,5]benzodiazepine-7-ol (7a): mp 171-172 °C (*n*-hexane/ EtOAc); IR (KBr): 3305, 1184, 1156 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.46-8.36 (br, 1H), 8.06 (d, J = 7.5 Hz, 1H), 7.85 (t, J = 7.5 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.48-7.31 (m, 4H), 6.46 (br s, 1H), 5.89 (s, 1H), 3.99 (s, 3H). Anal. Calcd for $C_{18}H_{14}F_3N_3O_2$: C, 59.83; H, 3.91; N, 11.63. Found: C, 59.62; H, 3.97; N, 11.67.

6-Methoxy-10,11-Dimethyl-7-trifluoromethyl-8*H*-13*H*-quino[4,3-*b*][1,5]benzodiazepine-7-ol (7b): mp 177-178 °C (*n*-hexane/ EtOAc); IR (KBr): 3353, 1209, 1171 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.35-8.23 (br, 1H), 7.87-7.77 (m, 3H), 7.65 (t, J = 7.4 Hz, 1H), 7.41 (t, J = 7.4 Hz, 1H), 7.16 (s, 1H), 6.38 (s, 1H), 5.85 (s, 1H), 3.99 (s, 3H), 2.32 (s, 3H), 2.26 (s, 3H). Anal. Calcd for $C_{20}H_{18}F_3N_3O_2$: C, 61.69; H, 4.66; N, 10.79. Found: C, 61.64; H, 4.72; N, 10.74.

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