Synthesis of 2- and 5-(1,1-Dimethyl-1,2,5,6-tetrahydropyridinium-3-yl)oxadiazoline Iodides

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A series of 2- and 5-(1,1-dimethyl-1,2,5,6-tetrahydropyridinium-3-yl) oxadiazoline iodides, which might be used as M_1 muscarinic receptor agonists, was synthesized from nicotinaldehyde and nicotinhydrazine, respectively. Their structures were characterized by ^1H NMR, IR, MS spectra and elemental analysis.

Keywords tetrahydropyridine, oxadiazoline, muscarinic receptor agonist, synthesis

Introduction

Recently, the increasing demand for effective treatment of neurodegenerative diseases, particularly Alzheimer's disease (AD), is becoming more and more urgent. Among the researches in therapeutics for AD, many muscarinic compunds not only are beneficial in the treatment of AD symptoms, but also delay the progress of the diseases.[1] Arecoline (**1**) (Fig. 1), a naturally occurring alkaloid and unselective muscarinic receptor agonist, had been used for AD patients in early clinical trials, but it had been proved to be problematic due to its low clinical efficacy, lack of receptor subtype selectivity, and poor metabolic stability.[2] Many arecoline derivatives such as xanomeline (**2**)[3] and milameline (**3**)[4] have been synthesized in order to improve the pharmacological and pharmacokinetic properties.

Both oxadiazolines and tetrahydropyridines exhibit interesting biological activity in different animal disease models.[5] In order to search for potent and selective M_1 muscarinic receptor agonists for AD, we designed a series of tetrahydropyridinium derivatives with oxadiazoline moieties. They were synthesized through two routes respectively as shown in Schemes 1 and 2.

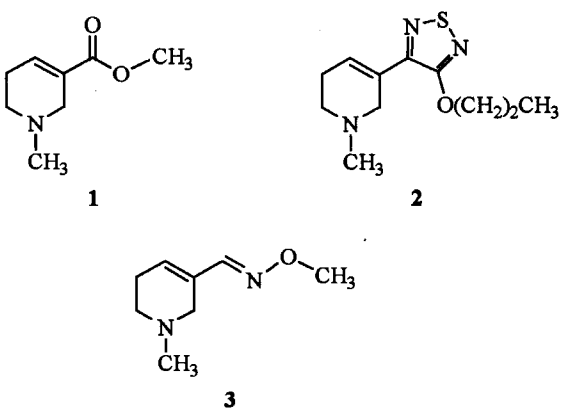

Fig. 1 Muscarinic receptor agonists.

Results and discussion

Under nitrogen atmosphere a solution of nicotinaldehyde (**4**) in an aqueous acetic acid was condensed with substituted aroylhydrazine (**5**) to give the corresponding hydrazone (**6**), which was quaternarized with 1.5 to 2 equivalents of methyl iodide in DMF at room temperature for 24 h to afford the pyridinium salt (**7**). The reduction of **7** with $NaBH_4$ in isopropanol and water at 80 ℃ gave corresponding tetrahydro-nicotinaldehyde hydrazone (**8**).

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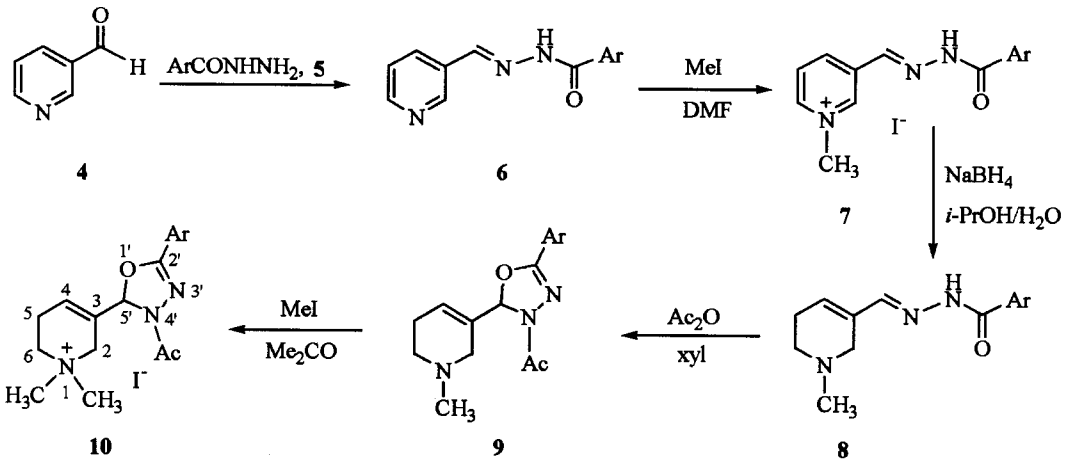
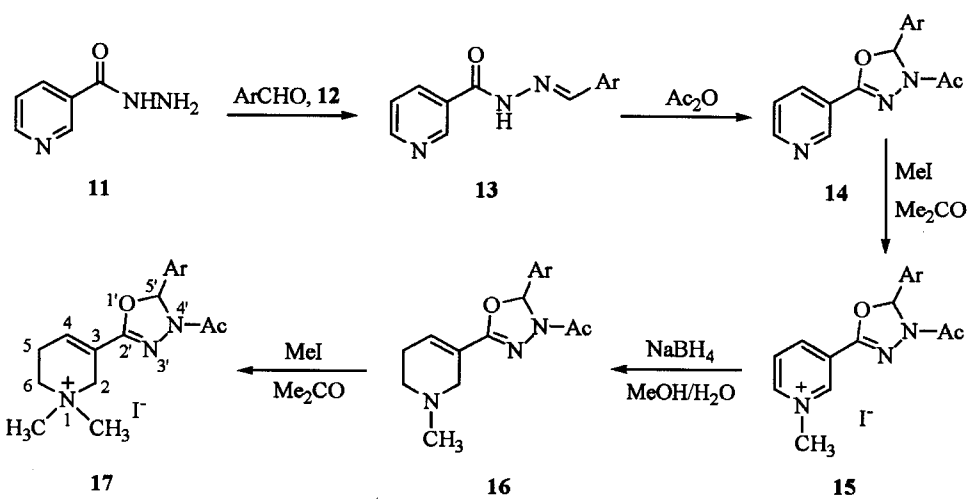
Received September 13, 2001; revised May 20, 2002; accepted June 27, 2002.
Project supported by the Major State Basic Research Development Program of China (No. 1998051112).

Scheme 1



Scheme 2



Cyclization of **8** in acetic anhydride and xylene yielded tetrahydro-pyridine oxadiazoline (**9**), which was subjected to quatenarization with MeI in acetone to give the desired compound (**10**) (Scheme 1).

The condensation of nicotinhydrazine (**11**) with arylaldehyde (**12**) yielded nicotinhydrazine arylaldehydehydrazone (**13**), which was cyclized in acetic anhydride to produce pyridine oxadiazoline (**14**). The treatment of **14** with MeI in acetone gave the corresponding salt (**15**). The reduction of **15** with $NaBH_4$ in methanol and water afforded tetrahydro-pyridine oxadiazoline (**16**), which was subsequently quaternarized with MeI in acetone to give the desired compound (**17**) (Scheme 2).

In the process of synthesizing theses compounds, we found that the products such as compound **17**, with the conjugation feature between tetrahydro-pyridine ring and oxadiazoline ring, could also be synthesized conveniently according to a similar procedure as shown in Scheme 1, but other products such as compound **10**, without conjugation between the two rings, can only be prepared by the method shown in Scheme 1.

Expermental

Melting points were determined with sealed capillary and uncorrected. IR spectra were recorded on a Nicolet Impact 410 spectrometer. ^1H NMR spectra were measured on a Bruker DR 500 spectrometer. Mass spectra were recorded on an HP 1100 instrument. Elemental analyses were carried out on a Carlo Erba 1106 instrument. The reagents and solvents were commercially available except where indicated.

General procedure for aroylhydrazine nicotinaldehyde hydrazone (**6**)

A mixture solution of aroylhydrazine (**5**) (15 mmol) and nicotinaldehyde (**4**) (15 mmol) in 1% aqueous acetic acid (150 mL) was stirred under nitrogen atmosphere for 3 h at room temperature. The resulting precipitate was filtered and recrystallized from DMF-H_2O to give **6**.

6a Ar = C_6H_5, yield 82%, m.p. 186—188 ℃; **6b** Ar = *p*-FC_6H_4, yield 87%, m.p. 205—206 ℃; **6c** Ar = *p*-ClC_6H_4, yield 91%, m.p. 198—200 ℃; **6d** Ar = *p*-$CH_3C_6H_4$, yield 72%, m.p. 209—211 ℃; **6e** Ar = *p*-$CH_3OC_6H_5$, yield 93%, m.p. 196—198 ℃; **6f** Ar = 3,4-$(OCH_2O)C_6H_3$, yield 95%, m.p. 218—220 ℃.

General procedure for aroylhydrazine N-methylnicotinaldehyde hydrazone iodide (**7**)

A mixture solution of **6** (10 mmol) and iodomethane (15 mmol) in DMF (15 mL) was stirred for 24 h at room temperature. The resulting precipitate was filtered and recrystallized from ethanol to afford quaternary salt (**7**).

7a Ar = C_6H_5, yield 72%, m.p. 216—218 ℃ (with dec.); **7b** Ar = *p*-FC_6H_4, yield 80%, m.p. 228—230 ℃ (with dec.); **7c** Ar = *p*-ClC_6H_4, yield 77%, m.p. 223—225 ℃ (with dec.); **7d** Ar = *p*-$CH_3C_6H_4$, yield 72%, m.p. 211—213 ℃ (with dec.); **7e** Ar = *p*-$CH_3OC_6H_5$, yield 81%, m.p. 198—200 ℃ (with dec.); **7f** Ar = 3,4-$(OCH_2O)C_6H_3$, yield 92%, m.p. 228—232 ℃ (with dec.).

General procedure for aroylhydrazine N-methyl tetrahydronicotinaldehyde hydrazone (**8**)

A stirred and cooled suspension of **7** (10 mmol) in isopropanol (50 mL) and water (50 mL) was treated portionwise with 1.0 g (25 mmol) of sodium borohydride, then stirred at 80 ℃ for 30 min. After removal of solvent, the residue was purified by chromatography on silica gel eluting with ethyl acetate/ethanol (3:1; *V*:*V*) to give the corresponding tetrahydropyridine hydrazone (**8**).

8a Ar = C_6H_5, pale yellow solid, yield 35%, m.p. 175—176 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.42—2.44 (m, 5H, 5-CH_2, NCH_3), 2.57 (t, J = 5.5 Hz, 2H, 6-CH_2), 3.35 (brs, 2H, 2-CH_2), 6.17 (s, 1H, 4-CH), 7.38—8.05 (m, 6H, PhH, N=CH), 8.94 (brs, 1H, CONH); IR (KBr) ν: 3225, 3201, 3047, 2995, 1645, 1567, 1178, 845 cm^{-1}; MS (EIS, 70 V) *m/z* (%): 243 (M^+, 100), 201 (4.7). Anal. calcd for $C_{14}H_{17}N_3O\cdot 1/3H_2O$: C 67.45, H 7.14, N 16.85; found C 67.60, H 7.22, N 16.75.

8b Ar = *p*-FC_6H_4, pale yellow solid, yield 32%, m.p. 184—186 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.43 (s, 5H, 5-CH_2, NCH_3), 2.57 (t, J = 5.5 Hz, 2H, 6-CH_2), 3.35 (brs, 2H, 2-CH_2), 6.19 (s, 1H, 4-CH), 7.14—7.86 (m, 5H, PhH, N=CH), 8.94 (brs, 1H, CONH); IR (KBr) ν: 3227, 3203, 3047, 2996, 1654, 1567, 1178, 867 cm^{-1}; MS (EIS, 70 V) *m/z* (%): 261 (M^+, 100), 260 (7.7), 239 (6.4), 219 (30). Anal. calcd for $C_{14}H_{16}N_3OF\cdot 1/2H_2O$: C 62.27, H 6.37, N 15.66; found C 62.50, H 6.37, N 15.55.

8c Ar = *p*-ClC_6H_4, pale yellow solid, yield 17%, m.p. 174—176 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.43 (s, 5H, 5-CH_2, NCH_3), 2.57 (t, J = 5.5 Hz, 2H, 6-CH_2), 3.48 (brs, 2H, 2-CH_2), 6.16 (s, 1H, 4-CH), 7.02—7.82 (m, 4H, PhH.), 8.10 (s, 1H, N=CH), 9.25 (brs, 1H, CONH); IR (KBr) ν: 3218, 3213, 3038, 2989, 1652, 1574, 1148, 837 cm^{-1}; MS (EIS, 70 V) *m/z* (%): 277(M^+, 100), 235 (4.7). Anal. calcd for $C_{14}H_{16}N_3OCl$: C 60.54, H 5.81, N 15.19; found C 60.55, H 6.08, N 15.23.

8d Ar = *p*-$CH_3C_6H_4$, pale yellow solid, yield 28%, m.p. 158—160 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.37 (s, 3H, $PhCH_3$), 2.44 (s, 5H, 5-CH_2, NCH_3), 2.57 (t, J = 5.5 Hz, 2H, 6-CH_2), 3.47 (brs, 2H, 2-CH_2), 6.16 (s, 1H, 4-CH), 7.02—8.06 (m, 5H, PhH, N=CH), 9.07 (brs, 1H, CONH); IR (KBr) ν: 3212, 3207, 3027, 2997, 1645, 1564, 1148, 854 cm^{-1}; MS (EIS, 70 V) *m/z* (%): 257 (M^+, 100), 216 (4.2), 215 (27). Anal. calcd for $C_{15}H_{19}N_3O\cdot 1/3H_2O$: C 68.44, H 7.48, N 15.97; found C 68.32, H 7.43, N 16.04.

8e Ar = *p*-$CH_3OC_6H_4$, pale yellow solid, yield 21%, m.p. 185—186 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.43 (s, 5H, 5-CH_2, NCH_3), 2.57 (t, J = 5.5 Hz, 2H, 6-CH_2), 3.34 (brs, 2H, 2-CH_2), 3.88 (s, 3H, CH_3), 6.16 (s, 1H, 4-CH), 7.00—8.00 (m, 5H, PhH, N=CH), 8.90 (brs, 1H, CONH); IR (KBr) ν: 3226, 3093, 3055, 2989, 1633, 1514, 1176, 848 cm^{-1}; MS (EIS, 70 V) *m/z* (%): 273

(M$^+$, 100), 231 (30.5), 135 (10.6). Anal. calcd for $C_{15}H_{19}N_3O_2 \cdot 1/3H_2O$: C 63.14, H 7.20, N 14.73; found C 63.15, H 7.48, N 14.51.

8f Ar = 3,4-(OCH_2O)C_6H_3, pale yellow solid, yield 31%, m.p. 186—188 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.43 (s, 5H, 5-CH_2, NCH_3), 2.57 (t, J = 5.5 Hz, 2H, 6-CH_2), 3.37 (brs, 2H, 2-CH_2), 5.88 (s, 2H, OCH_2O), 6.16 (s, 1H, 4-CH), 6.86—8.10 (m, 4H, PhH, N=CH), 9.05 (brs, 1H, CONH); IR (KBr) ν: 3318, 3206, 3052, 2967, 1634, 1574, 1150, 837 cm^{-1}; MS (EIS, 70 V) *m/z* (%): 287 (M$^+$, 100), 245 (23), 149 (6.86). Anal. calcd for $C_{15}H_{17}N_3O_3 \cdot 2/3H_2O$: C 60.19, H 6.17, N 14.03; found C 60.20, H 6.16, N 13.80.

General procedure for 5-(1, 1-*dimethyl*-1, 2, 5, 6-*tetrahydropyridinium*-3-*yl*) *oxadiazoline iodide* (**10**)

A mixture solution of **8** (10 mmol), acetic anhydride (8 mL) and xylene (8 mL) were refluxed for 30 min, then evaporated to dryness. The residue was dissolved in acetone (20 mL) followed by adding iodomethane (1 mL) and refluxed for 3 h. The resulting precipitate was filtered and recrystallized from ethanol to afford desired compound **10**.

10a Ar = C_6H_5, white solid, yield 65%, m.p. 218—220 ℃ (with dec.); ^{1}H NMR (D_2O, 500 MHz) δ: 2.54 (s, 3H, $COCH_3$), 2.86 (brs, 2H, 5-CH_2), 3.29 (s, 3H, NCH_3), 3.34 (s, 3H, NCH_3), 3.70 (t, J = 6 Hz, 2H, 6-CH_2), 4.12 (dd, J = 15.6, 16 Hz, 2H, 2-CH_2), 6.68 (brs, 1H, 4-CH), 6.86 (s, 1H, OCH=), 7.73—8.09 (m, 5H, PhH); IR (KBr) ν: 3025, 3005, 2932, 2915, 1667, 1634, 1442, 1194, 1059, 946, 688 cm^{-1}; MS (EIS, 70 V) *m/z* (%): 300[(M − 127)$^+$, 100]. Anal. calcd for $C_{17}H_{22}N_3O_2I$: C 47.79, H 5.19, N 9.83; found C 47.75, H 5.11, N 10.11.

10b Ar = *p*-FC_6H_4, white solid, yield 62%, m.p. 222—224 ℃ (with dec.); ^{1}H NMR (D_2O, 500 MHz) δ: 2.30 (s, 3H, $COCH_3$), 2.62 (brs, 2H, 5-CH_2), 3.04 (s, 3H, NCH_3), 3.10 (s, 3H, NCH_3), 3.46 (t, J=6 Hz, 2H, 6-CH_2), 3.92 (dd, J = 11.5, 10.5 Hz, 2H, 2-CH_2), 6.44 (brs, 1H, 4-CH), 6.64 (s, 1H, OCH=), 7.22 (t, J = 9 Hz, 2H, PhH), 7.88 (q, J=5.5 Hz, 2H, PhH); IR (KBr) ν: 3015, 3007, 2946, 2912, 1668, 1633, 1448, 1046, 943, 686 cm^{-1}; MS (EIS, 70 V) *m/z* (%): 318 [(M − 127)$^+$, 100]. Anal. calcd for $C_{17}H_{21}N_3O_2FI$: C 45.86, H 4.75, N 9.44; found C 45.65, H 4.55, N 9.70.

10c Ar = *p*-ClC_6H_4, white solid, yield 61%, m.p. 214—216 ℃ (with dec.); ^{1}H NMR (D_2O, 500 MHz) δ: 2.30 (s, 3H, OCH_3), 2.63 (brs, 2H, 5-CH_2), 3.05 (s, 3H, NCH_3), 3.12 (s, 3H, NCH_3), 3.46 (t, J=6, 6.5 Hz, 2H, 6-CH_2), 3.88 (dd, J = 16.5 Hz, 2H, 2-CH_2), 6.45 (brs, 1H, 4-CH), 6.65 (s, 1H, OCH=), 7.44—7.88 (m, 4H, PhH); IR (KBr) ν: 3035, 3007, 1662, 1633, 1476, 1015, 941 cm^{-1}; MS (EIS, 70 V) *m/z* (%): 344 [(M − 127)$^+$, 100]. Anal. calcd for $C_{17}H_{21}N_3O_2ClI$: C 44.23, H 4.61, N 9.10; found C 44.04, H 4.58, N 9.32.

10d Ar = *p*-$CH_3C_6H_4$, white solid, yield 71%, m.p. 221—223 ℃ (with dec.); ^{1}H NMR (D_2O, 500 MHz) δ: 2.14 (s, 3H, $PhCH_3$), 2.30 (s, 3H, $COCH_3$), 2.63 (brs, 2H, 5-CH_2), 3.03 (s, 3H, NCH_3), 3.09 (s, 3H, NCH_3), 3.46 (t, J = 6, 6.5 Hz, 2H, 6-CH_2), 3.86 (dd, J = 16 Hz, 2H, 2-CH_2), 6.42 (brs, 1H, 4-CH), 6.60 (s, 1H, OCH=), 7.32 (d, J = 8 Hz, 2H, PhH), 7.72 (d, J = 8 Hz, 2H, PhH); IR (KBr) ν: 3033, 2937, 1676, 1633, 1432, 1026, 945 cm^{-1}; MS (EIS, 70 V) *m/z* (%): 314 [(M − 127)$^+$, 100]. Anal. calcd for $C_{18}H_{24}N_3O_2I$: C 49.00, H 5.48, N 9.52; found C 48.76, H 5.32, N 9.73.

10e Ar = *p*-$CH_3OC_6H_4$, white solid, yield 63%, m.p. 217—219 ℃ (with dec.); ^{1}H NMR (D_2O, 500 MHz) δ: 2.36 (s, 3H, $COCH_3$), 2.69 (s, 2H, 5-CH_2), 3.11 (s, 3H, NCH_3), 3.17 (s, 3H, NCH_3), 3.52 (brs, 2H, 6-CH_2), 3.90—4.00 (m, 5H, 2-CH_2, OCH_3), 6.49 (s, 1H, 4-CH), 6.67 (s, 1H, OCH=), 7.13 (d, J = 7 Hz, 2H, PhH), 7.73 (d, J = 7 Hz, 2H, PhH); IR (KBr) ν: 3015, 2934, 1663, 1633, 1442, 1045, 954 cm^{-1}; MS (EIS, 70 V) *m/z* (%): 330 [(M − 127)$^+$, 100]. Anal. calcd for $C_{18}H_{24}N_3O_3I$: C 47.32, H 5.31, N 9.22; found C 47.15, H 5.31, N 9.43.

10f Ar = 3, 4-(OCH_2O)C_6H_3, white solid, yield 72%, m.p. 232—234 ℃ (with dec.); ^{1}H NMR (D_2O, 500 MHz) δ: 2.30 (s, 3H, $COCH_3$), 2.62 (brs, 2H, 5-CH_2), 3.05 (s, 3H, NCH_3), 3.11 (s, 3H, NCH_3), 3.46 (brs, 2H, 6-CH_2), 3.86 (dd, J = 16 Hz, 2H, 2-CH_2), 6.06 (s, 2H, OCH_2O), 6.43

(brs, 1H, 4-CH), 6.63 (s, 1H, OCH=), 6.99 (d, J = 8.5 Hz, 1H, PhH), 7.36 (s, 1H, PhH), 7.56 (d, J = 8.5 Hz, 1H, PhH); IR (KBr) ν: 3023, 2935, 1667, 1628, 1453, 1024, 931 cm^{-1}; MS (EIS, 70 V) m/z (%): 344 [(M − 127)$^+$, 100]. Anal calcd for $C_{18}H_{22}N_3O_4I$: C 45.87, H 4.71, N 8.92; found C 45.67, H 4.94, N 9.02.

General procedure for 2-(1-*methyl pyridinium*-3-*yl*) *oxadiazoline iodide* (**15**)

Nicotinhydrazine arylaldehyde hydrazone[7] (**13**) (10 mmol) in acetic anhydride (10 mL) was refluxed for 1 h to give salts **15** using the work up procedure described for **10**.

15a Ar = C_6H_5, yellow solid, yield 75%, m.p. 175—176 ℃ (with dec.); ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.37 (s, 3H, $COCH_3$), 4.53 (s, 3H, $=N^+$-CH_3), 6.73 (s, 1H, OCH=), 7.32—7.76 (m, 5H, PhH), 8.15—9.87 (m, 4H, pyridyl-H); IR (KBr) ν: 3052, 3008, 2964, 1657, 1623, 1457, 1327, 1037, 777, 680 cm^{-1}; MS (EIS, 70 V) m/z (%): 282 [(M − 127)$^+$, 100]. Anal. calcd for $C_{16}H_{16}N_3O_2I$: C 46.69, H 3.94, N 10.27; found C 46.84, H 4.02, N 10.53.

15b Ar = p-FC_6H_4, yellow solid, yield 74%, m.p. 190—192 ℃ (with dec.); 1H NMR (DMSO-d_6, 500 MHz) δ: 2.37 (s, 3H, $COCH_3$), 4.50 (s, 3H, $=N^+CH_3$), 6.65 (s, 1H, OCH=), 7.36—7.86 (m, 4H, PhH), 8.15—9.87 (m, 4H, pyridyl-H); IR (KBr) ν: 3067, 3015, 2973, 1664, 1637, 1457, 1318, 1057, 786, 685 cm^{-1}; MS (EIS, 70 V) m/z (%): 300 [(M − 127)$^+$, 100]. Anal. calcd for $C_{16}H_{15}N_3O_2FI$: C 44.98, H 3.54, N 9.84; found C 45.06, H 3.37, N 10.08.

15c Ar = p-ClC_6H_4, yellow solid, yield 68%, m.p. 185—187 ℃ (with dec.); ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.37 (s, 3H, $COCH_3$), 4.47 (s, 3H, $=N^+$-CH_3), 6.65 (s, 1H, OCH=), 7.32—7.76 (m, 4H, PhH), 8.15—9.87 (m, 4H, pyridyl-H); IR (KBr) ν: 065, 3015, 2955, 1663, 1636, 1447, 1324, 1037, 778, 676 cm^{-1}; MS (EIS, 70 V) m/z (%): 316 [(M − 127)$^+$, 100]. Anal. calcd for $C_{16}H_{15}N_3O_2ClI$: C 43.31, H 3.41, N 9.47; found C 43.46, H 3.47, N 9.52.

15d Ar = p-$CH_3C_6H_4$, yellow solid, yield 66%, m.p. 172—173 ℃ (with dec.); ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.32 (s, 3H, $PhCH_3$), 2.43 (s, 3H, $COCH_3$), 4.47 (s, 3H, $=N^+CH_3$), 6.58 (s, 1H, OCH=), 7.08—7.65 (m, 4H, PhH), 8.17—9.87 (m, 4H, pyridyl-H); IR (KBr) ν: 3037, 3004, 2983, 1663, 1631, 1443, 1035, 776, 683 cm^{-1}; MS (EIS, 70 V) m/z (%): 296 [(M − 127)$^+$, 100]. Anal. calcd for $C_{17}H_{18}N_3O_2I$: C 48.24, H 4.29, N 9.93; found C 48.16, H 4.32, N 10.14.

15e Ar = p-$CH_3OC_6H_4$, yellow solid, yield 53%, m.p. 187—186 ℃ (with dec.); ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.35 (s, 3H, $COCH_3$), 3.98 (s, 3H, OCH_3), 4.50 (s, 3H, $=N^+CH_3$), 6.62 (s, 1H, OCH=), 7.25—7.78 (m, 4H, PhH), 8.10—9.83 (m, 4H, pyridyl-H); IR (KBr) ν: 3026, 3003, 2954, 1661, 1633, 1457, 1320, 1073, 785, 692 cm^{-1}; MS (EIS, 70 V) m/z (%): 312 [(M − 127)$^+$, 100]. Anal. calcd for $C_{17}H_{18}N_3O_3I$: C 46.48, H 4.13, N 9.57; found C 46.54, H 4.32, N 9.67.

15f Ar = 3,4-(OCH_2O)C_6H_3, yellow solid, yield 70%, m.p. 218—220 ℃ (with dec.); ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.37 (s, 3H, $COCH_3$), 4.50 (s, 3H, $=N^+CH_3$), 6.03 (s, 3H, OCH_2O), 6.65 (s, 1H, OCH=), 7.05—7.77(m, 4H, PhH), 8.15—9.81 (m, 4H, pyridyl-H); IR (KBr) ν: 3056, 3015, 2953, 1664, 1634, 1465, 1077, 785, 693 cm^{-1}; MS (EIS, 70 V) m/z (%): 323 [(M − 127)$^+$, 100]. Anal. calcd for $C_{17}H_{16}N_3O_4I$: C 45.35, H 2.91, N 9.33; found C 45.16, H 3.07, N 9.48.

General procedure for 2-(1,1-*dimethyl*-1,2,5,6-*tetrahydropyridinium-yl*) *oxadiazoline iodide* (**17**)

To a stirred suspension of **15** (5 mmol) in methanol (25 mL) and water (25 mL), sodium borohydride (0.46 g, 12.5 mmol) was added portionwise at 0 ℃ over 2 h. The reaction mixture was stirred at 0 ℃ for 1 h. After removal of solvent under reduced pressure, the residue was dissolved in 3% aqueous acetic acid (50 mL), and filtered. The filtrate was made basic (pH 8) with saturated sodium hydrogen carbonate, extracted with ether, washed with brine, and dried over anhydrous magnesium sulfate. Methyl iodide (0.5 mL, 7.5 mmol) was added to the filtrate and the reaction mixture was left overnight. The precipitate was filtered and recrystallized from ethanol to give the title compound **17**.

17a Ar = C_6H_5, white solid, yield 23%, m. p. 208—210 ℃ (with dec.); ^{1}H NMR (D_2O, 500 MHz) δ: 2.23 (s, 3H, $COCH_3$), 2.70 (brs, 2H, 5-CH_2), 3.15 [s, 6H, $^+N(CH_3)_2$], 3.48 (brs, 2H, 6-CH_2), 4.17 (brs, 2H, 2-CH_2), 6.80—7.10 (m, 7H, 4-CH, OCH =, PhH); IR (KBr) ν: 3022, 3018, 2997, 2950, 1664, 1634, 1409, 1042, 1027 cm^{-1}; MS (EIS, 70 V) *m/z* (%): 300 [(M − 127)$^+$, 100]. Anal. calcd for $C_{17}H_{22}N_3O_2I\cdot 1/3H_2O$: C 47.12, H 5.27, N 9.70; found C 47.32, H 5.35, N 9.86.

17b Ar = *p*-FC_6H_4, white solid, yield 25%, m.p. 222—223 ℃ (with dec.); ^{1}H NMR (D_2O, 500 MHz) δ: 2.23 (s, 3H, $COCH_3$), 2.76 (brs, 2H, 5-CH_2), 3.16 [s, 6H, $^+N(CH_3)_2$], 3.54 (brs, 2H, 6-CH_2), 4.21 (s, 2H, 2-CH_2), 6.82—7.14 (m, 6H, 4-CH, OCH =, PhH); IR (KBr) ν: 3076, 3056, 2996, 2950, 1658, 1624, 1328, 1072 cm^{-1}; MS (EIS, 70 V) *m/z* (%): 318 [(M − 127)$^+$, 100]. Anal. calcd for $C_{17}H_{21}N_3O_2FI\cdot 1/3H_2O$: C 45.24, H 4.84, N 9.31; found C 45.13, H 5.12, N 9.46.

17c Ar = *p*-ClC_6H_4, white solid, yield 15%, m.p. 214—216 ℃ (with dec.); ^{1}H NMR (D_2O, 500 MHz) δ: 2.21 (s, 3H, $COCH_3$), 2.67 (brs, 2H, 5-CH_2), 3.24 [s, 6H, $^+N(CH_3)_2$], 3.56 (brs, 2H, 6-CH_2), 4.17 (s, 2H, 2-CH_2), 6.82—7.20 (m, 6H, 4-CH, OCH =, PhH); IR (KBr) ν: 3056, 3047, 2989, 1654, 1624, 1337, 1087 cm^{-1}; MS (EIS, 70 V) *m/z* (%): 334 [(M − 127)$^+$, 100]. Anal. calcd for $C_{17}H_{21}N_3O_2ClI$: C 44.02, H 4.404, N 9.67; found C 44.21, H 4.65, N 9.82.

17d Ar = *p*-$CH_3C_6H_4$, white solid, yield 17%, m. p. 211—212 ℃ (with dec.); ^{1}H NMR (D_2O, 500 MHz) δ: 2.23 (s, 3H, $COCH_3$), 2.43 (s, 3H, $PhCH_3$), 2.72 (brs, 2H, 5-CH_2), 3.15 [s, 6H, $^+N(CH_3)_2$], 3.56 (brs, 2H, 6-CH_2), 4.23 (s, 2H, 2-CH_2), 7.02—7.32 (m, 5H, 4-CH, OCH =, PhH); IR (KBr) ν: 3053, 3027, 2994, 1658, 1645, 1327, 1089 cm^{-1}; MS (EIS, 70 V) *m/z* (%): 314 [(M − 127)$^+$, 100]. Anal. calcd for $C_{18}H_{24}N_3O_2I$: C 48.99, H 45.48, N 9.52; found C 48.81, H 5.65, N 9.76.

17e Ar = *p*-$CH_3OC_6H_4$, white solid, yield 20%, m. p. 217—218 ℃ (with dec.); ^{1}H NMR (D_2O, 500 MHz) δ: 2.23 (s, 3H, $COCH_3$), 2.57 (brs, 2H, 5-CH_2), 3.16 [s, 6H, $^+N(CH_3)_2$], 3.47 (brs, 2H, 6-CH_2), 3.96—4.21 (m, 5H, OCH_3, 2-CH_2), 6.70 (s, 1H, 4-CH), 6.86 (s, 1H, OCH =), 7.02—7.35 (m, 4H, PhH); IR (KBr) ν: 3062, 3033, 2997, 1657, 1642, 1327, 1077 cm^{-1}; MS (EIS, 70 V) *m/z* (%): 330 [(M − 127)$^+$, 100]. Anal. calcd for $C_{18}H_{24}N_3O_3I\cdot 2/3H_2O$: C 46.07, H 5.44, N 8.95; found C 46.17, H 5.60, N 9.11.

17f Ar = 3,4-(OCH_2O)C_6H_3, white solid, yield 22%, m.p. 228—230 ℃ (with dec.); ^{1}H NMR (D_2O, 500 MHz) δ: 2.23 (s, 3H, $COCH_3$), 2.70 (brs, 2H, 5-CH_2), 3.17 [s, 6H, $^+N(CH_3)_2$], 3.51 (brs, 2H, 6-CH_2), 4.21 (s, 2H, 2-CH_2), 5.94 (s, 2H, OCH_2O), 6.77—7.00 (m, 5H, 4-CH, OCH =, PhH); IR (KBr) ν: 3072, 3053, 2997, 1663, 1644, 1327, 1057 cm^{-1}; MS (EIS, 70 V) *m/z* (%): 344 [(M − 127)$^+$, 100]. Anal. calcd for $C_{18}H_{22}N_3O_4I\cdot 2/3H_2O$: C 44.73, H 4.87, N 8.69; found C 44.86, H 5.02, N 8.72.

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(E0109135 LU, Y. J.; HUANG, W. Q.)