Synthesis of Furanyl and Oxazolyl N-substituted Piperidine and Imidazoline Salts as Potential Agonists of M_1 Muscarinic Receptors

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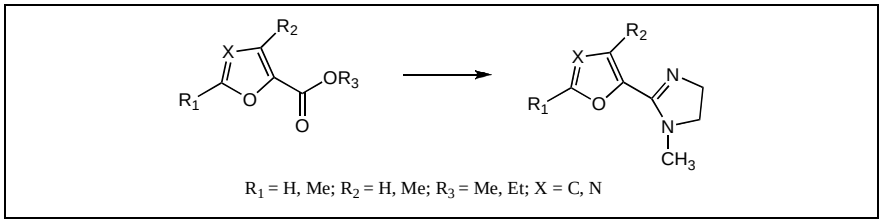

R_1 = H, Me; R_2 = H, Me; R_3 = Me, Et; X = C, N

Furanyl and oxazolyl N-substituted imidazoline salts were prepared by reacting furanyl and oxazolyl esters with ethylenediamine and trimethyl aluminum, followed by the addition of methyl iodide or hydrogen chloride. The piperidinium salts were prepared by treating furanyl and oxazolyl chlorides with piperidine base, followed by the addition of methyl iodide or hydrogen chloride.

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INTRODUCTION

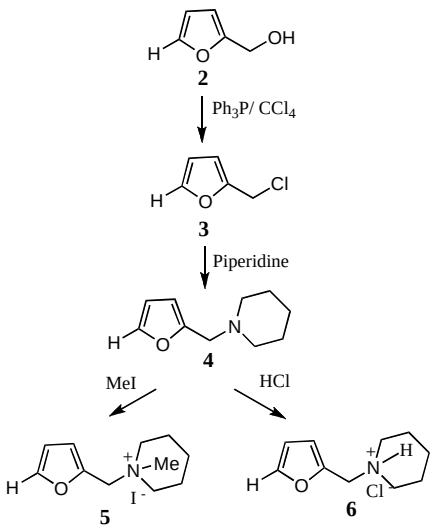
Potential M_1 muscarinic agonists have been synthesized in our laboratory based on Schulman's model of the muscarinic pharmacophore. Schulman's model [1] is based on detailed conformational analyses of known muscarinic agonists. Muscarinic agonists are currently therapeutic targets for the symptomatic treatment of Alzheimer's disease. The cholinergic hypothesis advanced by Schulman is based on the fact that, while neurons which express the M_2 muscarinic receptors are at risk of degenerating, the cortical neurons expressing the M_1 subtype which synapse with them are not altered. These M_1 receptors can become activated by selective agonists that could alleviate the symptom of Alzheimer's disease. Potent agonists should mimic the effects of acetylcholine in the brain by binding to the receptor site through a cationic head group, preferably a quaternary ammonium group. A second binding site on these agonists will make use of a region of negative electrostatic potential, preferably an ester or ether group, that can interact with a positive receptor residue through hydrogen bonding. Several pharmacological attributes for muscarinic activity are highly desirable for those potential agonists. Selective agonists can reduce side effects by having little effect on muscarinic M_2 receptors in cardiac and smooth muscles. These agonists must be able to penetrate the blood-brain barrier in order to reach the cortical neurons. Tertiary amines are reasonable candidates since they can be protonated and depronated at physiological pH and may cross the blood- brain barrier in their neutral forms. Tertiary amines are for *in vivo* testing while quaternary ammonium salts are for *in vitro* testing on CHO cell lines expressing muscarinic receptors. These quaternary salts can also be used pharmacologically as gastroprokinetic agents to increase gastrointestinal motility.

Over the last few years, many compounds [2] that conformed to Schulman's model were synthesized in our laboratory and tested for muscarinic activity. Unfortunately, biological test results from MDS Pharma services had revealed no significant muscarinic receptor affinity. However, recent work by Scapecchi [3] had shown that a compound with similar attributes could functionally be a M_2 partial agonist. In light of this new development, we decided to synthesize novel compounds containing piperidine and imidazoline moieties. Those compounds were tested and, again, no significant affinity was observed. The synthesis of these compounds is the main focus of this paper.

Furanyl N-substituted piperidine salts **5** and **6** (Scheme 1) were synthesize by reducing furfural **1** with sodium borohydride in basic solution to form the corresponding alcohol **2**. The alcohol was converted to furanyl chloride **3** with triphenyl phosphine in carbon tetrachloride. The chloride was then coupled with piperidine, through nucleophilic substitution, to form furanyl N-substituted piperidine base **4**. Methyl iodide or hydrogen chloride was added to the base to form the corresponding methyl iodide and hydrochloride salts **5** and **6**, respectively.

Oxazolyl N-substituted piperidine salts (Scheme 2) were prepared by reducing oxazolyl esters with lithium aluminum hydride (LAH) in anhydrous ether to yield alcohol **10**. The alcohol was then converted to oxazolyl

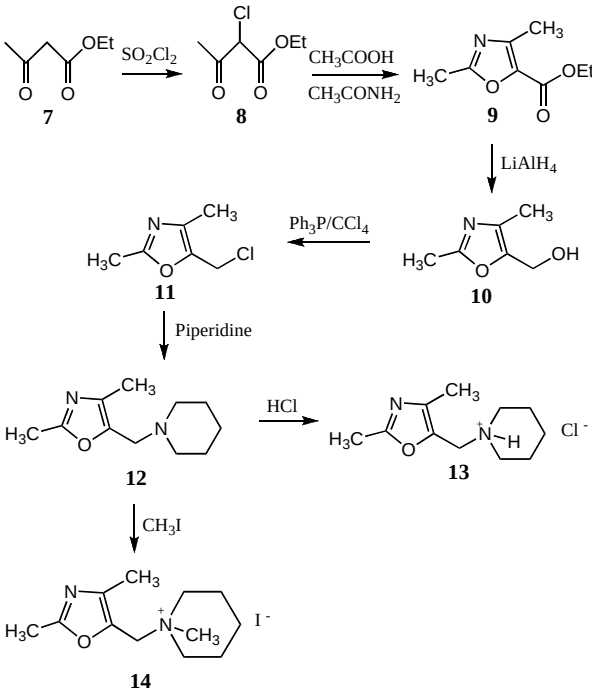
Scheme 1



chloride **11** with triphenyl phosphine in carbon tetrachloride. Piperidine was added to the chloride to yield oxazolyl N-substituted piperidine base **12**. The hydrochloride and methyl iodide salts were made from the base **13** and **14**, respectively.

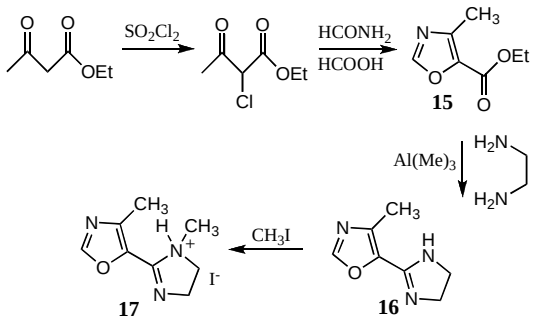
The oxazolyl N-substituted imidazoline salt (Scheme 3) was prepared by first condensing ethyl chloro acetoacetate **8** with formamide in acid solution to produce the oxazolyl ester **15**. The ester was then reacted with ethylene diamine and trimethyl aluminum in toluene [4] to form the

Scheme 2



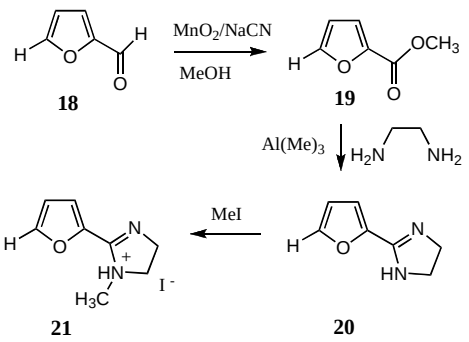
corresponding oxazolyl N-substituted imidazoline base **16**. The base was then converted to the methyl iodide salt **17**.

Scheme 3



The furanyl N-substituted imidazoline methyl iodide salt **21** (Scheme 4) was synthesized by converting furfural **18** to its corresponding methyl ester **19** with a mixture of manganese dioxide, sodium cyanide and methanol [5]. The ester was then treated with ethylene diamine and trimethyl aluminum in toluene to produce the base **20**. The base was converted to the methyl iodide salt **21**.

Scheme 4



EXPERIMENTAL

Reagents were purchased from Aldrich Chemical Company (St. Louis, MO) unless otherwise noted, and all starting liquid materials were distilled before use. NMR spectra were recorded on a Varian 300 MHz spectrometer. IR spectra were recorded on a Nicolet Impact 400D FT-IR and mass spectra on a Hewlett Packard 5972 Series MS interfaced with a Hewlett Packard 5890 Series II Plus GC. Elemental analyses were carried out by Galbraith Laboratories (Knoxville, TN) and all biological assays were conducted at MDS Pharma services (Taiwan). Melting points were determined on a MEL-TEMP II purchased from Laboratory Devices and are uncorrected.

Furfuryl chloride (3). A mixture of carbon tetrachloride (90 ml), furfuryl alcohol **2** (9.8 g, 0.100 mole) and triphenyl phosphine (34.09 g, 0.130 mole) was refluxed for one hour. The mixture was allowed to cool to room temperature, and 100 ml of

anhydrous pentane was added with stirring. The solution was filtered, and the precipitate washed a few times with a total of 50 ml of anhydrous pentane. The combined filtrate was then concentrated and distilled at 28-30°/4-5 mmHg to yield 6.65 g of liquid furfuryl chloride **3** (43.5%). ^{1}H nmr ($CDCl_3$): δ 4.9 (s, 2H), 6.6 (m, 2H), 7.7 (d, 1H).

1-(2-Furylmethyl)piperidine (4). A solution of 3.3 g of **3** (0.0283 mol) in acetonitrile was added to a mixture containing 2.4 g of piperidine (0.0283 mol), 2.0 g of anhydrous sodium carbonate and 15 ml of acetonitrile. After addition, the mixture was allowed to stir overnight, filtered, and concentrated to yield 4.3 g of fairly pasty and pure **4** (92%). ^{1}H nmr ($CDCl_3$): δ 1.4 (m, 2H), 1.6 (m, 4H), 2.4 (m, 4H), 3.5 (s, 2H), 6.2 (d, 1H), 6.3 (dd, 1H), 7.4 (d, 1H). MS: m/z 165 (M^+), 81 (base), 53.

1-(2-Furylmethyl)-1-methylpiperidinium iodide (5). To a solution containing 2.0 g (0.012 mol) of **4** dissolved in 10 ml of CH_2Cl_2 was added 2.0 g of methyl iodide (0.014 mol) with stirring. The solution was stirred overnight, and concentrated to yield 3.5 g of solid **5** (94%), m.p 163-165 °C. ^{1}H nmr ($CDCl_3$): δ 1.8 (m, 2H), 2.2 (m, 4H), 3.4 (s, 3H), 3.8 (m, 4H), 5.2 (s, 2H), 6.5 (d, 1H), 7.1 (dd, 1H), 7.6 (d, 1H). *Anal*. Calcd. For $C_{11}H_{18}NOI$: C 43.01 %, H 5.91 %, N 4.56 %, I 41.31 %. Found: C 43.31 %, H 5.95 %, N 4.57 %, I 43.36 %

1-(2-Furylmethyl)piperidinium chloride (6). Hydrogen chloride gas was passed through a solution containing 2.0 g (0.012 mol) of **4** dissolved in 10 ml of CH_2Cl_2 for about ten minutes. The solution was stirred overnight, and concentrated to yield 2.3 g of solid **6** (96%), m.p 105-107 °C. ^{1}H nmr (D_2O): δ 1.4-2.2 (m, 6H), 2.8-3.8 (m, 4H), 5.0 (s, 2H), 6.5 (d, 1H), 6.7 (dd, 1H), 7.6 (d, 1H). *Anal*. Calcd. $C_{10}H_{16}NOCl$: C 59.55 %, H 7.99 %, N 6.95 %, Cl 17.58%. Found: C 58.65 %, H 7.94 %, N 6.95 %, Cl 17.32 %.

Ethyl chloroacetoacetate [6] (8). Ethyl acetoacetate **7** (130 g, 1 mol) was placed in a 500 mL 3-necked flask fitted with a dropping funnel, mechanical stirrer and a gas-absorption trap. Sulfuryl chloride (135 g, 1 mol) was then added dropwise with external cooling (ice-bath) for 2 hours. The solution was allowed to stand overnight and the remaining SO_2 and HCl were removed by evaporation. The resulting solution was then distilled using a Vigreux column at 25 mmHg, and the fraction boiling between 95-100 °C was collected to afford 95 g of liquid ethyl chloroacetoacetate **8** (64%); literature values: bp 85-89 °C/17 mmHg, (93-97%). ^{1}H nmr ($CDCl_3$): δ 1.1-1.5 (t, 3H), 2.4 (s, 3H), 4.1-4.5 (q, 2H), 4.8 (s, 1H).

Ethyl-2,4-dimethyl-1,3-oxazole-5-carboxylate (9). A mixture of ethyl chloroacetoacetate **8** (66.1 g, 0.40 mol), acetamide (47.4g, 0.80 mol) and glacial acetic acid (146 g) was refluxed for 22 hours. The residual dark solution was cooled in an ice-bath and made alkaline with 6 *N* sodium hydroxide. The mixture was extracted with ether and the combined extracts were dried over sodium sulfate. After filtration, the ether was removed and the remaining black residue (60 g) was distilled under reduced pressure to give 37.6 g of a colorless liquid. The distillate was shaken with 50 mL of cold 50% concentrated sulfuric acid. Two layers were formed, the upper one unreacted ethyl chloroacetoacetate and the lower sulfuric acid containing the oxazole. The sulfuric acid layer was diluted with cold water and made alkaline with 6 *N* KOH. The solution was then extracted with ether, and the combined ether extracts were dried over magnesium sulfate. The solution was concentrated and the residue distilled between 60-62 °C/4-5 mmHg to afford 30 g of the solid ester **9** (25%). ^{1}H nmr ($CDCl_3$): δ 1.2-1.6 (t, 3H), 2.4 (s, 3H), 2.5 (s,3H), 4.3-4.7 (q, 2H), 8.0 (s, 1H); ir (CCl_4): 1720 (C=O), 1610, 1560, 1440 cm^{-1}.

(2,4-Dimethyloxazol-5-yl)methanol (10). To 50 mL of anhydrous ether at -10 °C under nitrogen were added simultaneously, with mechanical stirring, a solution of the ester **9** (13.0 g, 70 mmol) in 15 mL of anhydrous ether and a solution of LAH (3.47 g, 90 mmol) in 56 mL of anhydrous ether. After 2.5 hours (including one hour for initial dropwise addition), ethyl acetate (11 mL) was added slowly. The solution was allowed to warm to room temperature, and excess LAH was destroyed with 95% ethanol. The reaction mixture was hydrolyzed with tartaric acid (19 g in water) and then made alkaline with 6 *N* NaOH. The solution was saturated with K_2CO_3, and the two layers were separated. The aqueous layer was extracted with benzene, and the benzene solution was dried over $MgSO_4$; the ether layer was also dried over $MgSO_4$. Both layers were concentrated, and the residues combined and distilled; the fraction boiling at 95 °C/ 3-4 mmHg afforded 7.3 g of solid alcohol **10** (80%). ^{1}H nmr ($CDCl_3$): δ 2.1 (s, 3H), 2.5 (s, 3H), 3.0-3.5 (bs, 2H), 4.6 (s, 2H); ir (CCl_4): 3600-3200 (OH), 1640, 1570, 1440 cm-^{1}. *Anal*. Calcd. for $C_6H_9NO_2$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.75; H, 6.98; N, 11.15.

5-Chloromethyl-2,4-dimethyloxazole (11). A mixture of the alcohol **10** (6.0 g, 0.047 mol), anhydrous carbon tetrachloride (45 mL) and triphenyl phosphine (17.04 g, 0.065 mol) was refluxed for 2 hours. The reaction mixture was allowed to cool to room temperature and then diluted with 100 mL of dry pentane. The mixture was filtered and the filtrate concentrated to one-fourth of its original volume. The concentrated product was distilled to yield 3.73 g of the liquid chloride **11** (54.6%) which was collected at 53-54 °C/2-3 mmHg. ^{1}H nmr ($CDCl_3$): δ 2.1 (s, 3H), 2.4 (s, 3H), 4.5 (s, 2H).

1-[(2,4-Dimethyloxazol-5-yl)methyl]piperidine (12). 3.39 g of **11** (0.0235 mol) in acetonitrile was added slowly to a mixture containing 2.0 g of piperidine (0.0235 mol), 2.0 g of anhydrous sodium carbonate and 15 ml of acetonitrile. After addition, the mixture was allowed to stir overnight, filtered, concentrated to yield 3.66 g of fairly pasty and pure **12** (80%). ^{1}H nmr ($CDCl_3$): δ 1.35-1.68 (m, 6H), 2.05 (s, 3H), 2.35 (s, 3H), 3.0-3.2 (m, 4H), 3.38 (s, 2H). MS: m/z 194 (M^+), 110 (base) 84, 42.

1-[(2,4-Dimethyloxazol-5-yl)methyl]piperidinium chloride (13). Hydrogen chloride gas was bubbled through a solution containing 1.12 g of **12** (0.00577 mol) and 10 mL of dichloromethane for about 10 minutes. The solution was concentrated and the residue recrystallized from acetonitrile to yield 1.05 g of solid **13** (79%), mp 226-227 °C. ^{1}H nmr ($CDCl_3$): δ 1.2-1.8 (m, 6H), 2.0 (s, 3H), 2.3 (s, 3H), 2.6-3.0 (m, 2H), 3.2-3.5 (m, 2H), 4.2 (s, 2H). *Anal*. Calcd. For $C_{11}H_{19}N_2OCl$: C 57.26 %, H 8.30 %, N 12.14 %, Cl 15.37 %. Found: C 57.26 %, H 8.40 %, N 12.20 %, Cl 15.00 %.

1-[(2,4-Dimethyloxazol-5-yl)methyl]-1-methyl piperidinium iodide (14). Excess methyl iodide was added to 0.5 g (0.00258 mol) of **12** dissolved in 10 mL of acetonitrile. The reaction mixture was stirred overnight, concentrated and the residue recrystallized from *tert*-butyl alcohol/methanol to yield 0.52 g (60%) of solid **14**, mp 163 -164 °C. ^{1}H nmr (D_2O): δ 1.4-1.8 (m, 6H), 2.0 (s, 3H), 2.4 (s, 3H), 3.0-3.4 (m, 4H), 3.6 (m, 3H), 4.6 (s, 2H). *Anal*. Calcd. For $C_{12}H_{21}N_2OI$: C 42.87 %, H 6.295 %, N 8.332 %, I 37.74 %. Found: C 42.28 %, H 6.50 %, N 8.13 %, I 37.30 %.

5-(4,5-Dihydro-1*H*-imidazol-2-yl)-4-methyloxazole [4] (16). To a solution of ethylene diamine (0.0557 mol) in 65 mL of

toluene was added dropwise, with cooling, a 2 *M* solution of $Al(CH_3)_3$ (0.0557 mol) in toluene. A solution of 5.00 grams of ester **15** (0.032 mol) in 20 mL of toluene was added at 0 °C, and the mixture was refluxed for 15 hours. The mixture was concentrated to leave a residue. Water was added and the residue was extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Column chromatography over silica gel with 10:1 CH_2Cl_2/MeOH afforded solid **16**, 1.9 g (39.6 %), m.p. 105-108 °C. ^{1}H nmr ($CDCl_3$): δ 2.5 (s, 3H), 3.5 (m, 2H), 4.0 (m, 2H), 5.0 (s, 1H), 7.8 (s, 1H). MS: m/z 151 (M^+), 122, 95, 82, 53.

4-Methyl-5-(1-methyl-4,5-dihydro-1*H*-imidazol-2-yl) oxazole hydroiodide (17). To 1.0 g (0.0066 mol) of the base **16** was added 0.95 g (0.0067 mol) of CH_3I. The mixture was stirred overnight at room temperature. The residue was dried under vacuum and re-crystallized from acetonitrile to afford 1.25 g of the salt **17** (65%), mp 209-210 °C. ^{1}H NMR (D_2O): δ 2.2 (s, 3H), 3.9 (s, 3H), 8.25 (s, 1H). ^{1}H nmr (CD_3OD): δ 2.2 (s, 3H), 4.2 (s, 3H), 5.0 (m, 4H), 8.6 (s, 1H). *Anal.* Calcd. For $C_8H_{12}N_3OI$: C 32.78 %, H 4.126 %, N 14.34 %, I 43.29 %. Found: C 31.00 %, H 3.71%, N 14.70 %, I 46.10 %.

Methyl-2-furoate [5] (19). To a mixture containing 7.35 g NaCN (0.15 mol), 13.05 g of activated MnO_2, 10 mL of glacial acetic acid and 25 mL of anhydrous methanol was added 10.8 g of furfural (0.11 mol). The reaction mixture was allowed to stir overnight and gravity filtered to remove the manganese oxide. The filtrate was concentrated and chromatographed on silica gel (70-270 mesh) using a 1:1 mixture of hexane/dichloromethane to yield 4.0 g of solid **19** (28.9%), R_f (hexane/dichloromethane) 0.34. ^{1}H nmr ($CDCl_3$): δ 3.9 (s, 3H), 6.5 (dd, 1H), 7.2 (d, 1H), 7.6 (d, 1H).

2-(2-Furyl)-4,5-dihydro-1*H*-imidazole (20). To a solution of ethylene diamine (0.019 mol) in 20 mL of toluene was added dropwise, with cooling, a 2 *M* solution of $Al(CH_3)_3$ (0.019 mol) in toluene. A solution of 1.3 g of ester **19** (0.0103 mol) in 7 mL of toluene was added at 0 °C, and the mixture was refluxed for 10 hours. The mixture was concentrated to leave a pasty residue. Water was added and the residue was extracted with dichloromethane. The organic layers were dried over $MgSO_4$ and evaporated. Column chromatography over silica gel with 10:1 CH_2Cl_2/MeOH afforded 0.75 g (54%) of a pasty compound **20**. ^{1}H nmr ($CDCl_3$) 3.8 (m, 2H), 4.1 (m, 2H), 6.6 (m, 1H), 7.2 (d, 1H), 7.7 (d, 1H). MS: m/z 136 (M^+), 107, 79, 32.

2-(2-Furyl)-1-methyl-4,5-dihydro-1*H*-imidazole hydroiodide (21). To 0.50 g (0.0037 mol) of the base **20** was added 0.70 g (0.005 mol) of CH_3I. The mixture was stirred overnight at room temperature. The residue was dried under vacuum and re-crystallized from acetonitrile to afford 0.75 g of the salt **21** (73%). *Anal.* Calcd. For $C_8H_{11}N_2OI$: C 34.54 %, H 4.0 %, N 10.08 %, I 45.63 %. Found: C 34.20 %, H 3.91%, N 10.06 %, I 46.00 %.

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