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Synthesis of Tetrahydropyridinyltriazolothiadiazines as Possible Muscarinic Agonists

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Abstract: 4-Amino-5-(pyridin-3-yl)-4*H*-1,2,4-triazole-3-thiol **1** were condensed with 2-bromo-1-(substituted phenyl)ethanone to give pyridinyltriazolothiadiazines **2a~c**, which were quaternarized with methyl iodide and oxidized with 30 % hydrogen peroxide to afford the corresponding methyl pyridinium salts **3a~c** and pyridine-1-oxides **4a~c**, respectively. The reduction of compounds **3** and **4** with $NaBH_4$ in methanol produced the target compounds 1-methyl-1, 2, 5, 6-tetrahydropyridin-3-yl)-6-aryl-*s*-triazolothiadiazines **5a~c** and 3-(1-hydroxyl-1, 2, 5, 6-tetrahydropyridin -3-yl)-6-aryl-*s*-triazolothiadiazines **6a~c**, respectively. The endothelium vascular relaxing activity of the target compounds was screened.

Keywords: Tetrahydropyridine, triazolothiadiazine, muscarinic agonist, vascular activity.

Recently, the increasing demand for effective treatment of cardiovascular diseases (CD), such as hypertension, heart failure, hypercholesterolemia, atherosclerosis, is becoming urgent task. The researches in therapeutics for CD focus on the modification of the classical muscarinic (M) receptor agonists, such arecoline as a naturally occurring alkaloid and unselective M receptor agonist, which could mediate endothelium-dependent vascular relaxation by releasing nitric oxide. Chemically, arecoline possess a 1,2,5,6-tetrahydropyridine ring and an unstable ester moiety, which has been replaced with the stable five-numbered heterocyclic rings in order to improve the pharmacological and pharmacokinetic properties[1,2]. Meanwhile, some arecoline derivatives containing oxadiazoline have been reported in our previous papers[3, 4]. We reported herein the synthesis of other new arecoline derivatives containing triazolothiadiazine ring in order to obtain potent vascular relaxing agonists, taking direct effect on endothelium target for acetylcholide[5] for the treatment of the above diseases (**Scheme 1**).

Synthesis of aryl substituted pyridinyltriazolothiadiazines **2a**~**e** were achieved from pyridinyltriazole **1** with the appropriate 2-bromo-1-(substituted phenyl)ethanones in refluxing ethnol in yields 78, 81, 67, 75, and 53 %, respectively. Subsequent quaternization of compounds **2a**~**e** with methyl iodide (3.0 eq.) in refluxing acetone for 24 hours and oxidation with 30 % hydrogen peroxide (1.5 eq.) in refluxing acetic acid for

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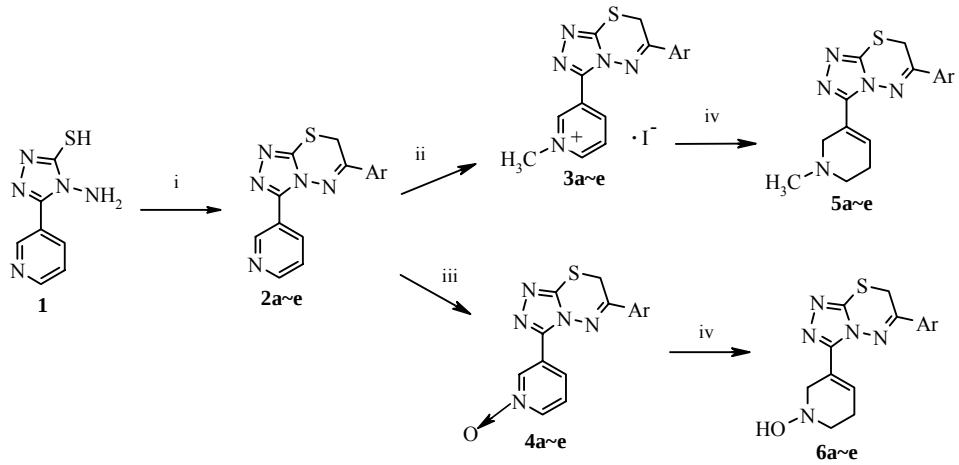
Scheme 1



Ar**:** **a**, C_6H_5; **b**, *p*-CH_3O-C_6H_4; **c**, *p*-CH_3-C_6H_4; **d**, *p*-Cl-C_6H_4; **e**, *p*-O_2N-C_6H_4

Reagents and conditions: i, 2-bromo-1-(substituted phenyl)ethanones, EtOH, reflux; ii, CH_3I, acetone, reflux; iii, H_2O_2, Ac_2O, reflux; iv, $NaBH_4$, MeOH, H_2O, 0~60℃

3 hours afforded the corresponding methylpyridinium salts **3a**~**e** and pyridine-1-oxides **4a**~**e**, respectively. The reduction of compounds **3a**~**e** and **4a**~**e** with $NaBH_4$ (2.5 eq.) in methanol-water produced the tetrahydropyridine compounds 3-(1-methyl-1, 2, 5, 6-tetra-hydropyridin-3-yl)-6-aryl-*s*-triazolothiadiazines **5a**~**c** and 3-(1-hydroxyl-1, 2, 5, 6-tetrahy-pyridin-3-yl)-6-aryl-*s*-triazolothiadiazines **6a**~**c**, respectively. The *in vitro* preliminary biological tests showed that the vascular relaxation effects on isolated endothelial cells are 21, 28, 22, 11, 25 for compounds **5a**, **b**, **c**, **d**, **e** and 27, 33, 24, 10, 29 % for compounds **6a**, **b**, **c**, **d**, **e**, respectively. The vascular relaxing activity of the title compounds, except **5d** and **6d**, are comparable to that of arecoline (36.5 %).

The structures of the target compounds were confirmed by elemental analysis (EA), ^{1}H NMR, IR and MS[6].

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6. **5a**: yield 57%, mp 161~162℃. IR (KBr) *υ*: 3217, 1632, 1485, 1261 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ ppm)*:* 8.12~7.68 (m, 5H, Ph-H), 6.64 (d, 2H, H-4′, *J*=3.5 Hz,), 4.26 (s, 2H, CH_2), 3.45 (brs, 2H, H-2′), 2.66 (brs, 2H, H-6′), 2.55 (brs, 2H, H-5′), 2.43 (s, 3H, NCH_3); EIS-MS (70 eV) *m/z:*

312 (M+H). Anal. (Calcd. for $C_{16}H_{17}N_5S$): C 61.71, H 5.50, N 22.49; Found: C 61.84, H 5.48, N 22.64.

5b: yield 62%, mp 156~157℃. IR (KBr) ν: 3205, 1616, 1556, 1265 cm^{-1}; ^1H NMR (DMSO-d_6, δ ppm)*:* 8.04~7.53 (m, 4H, Ph-H), 6.53 (br, 2H, H-4′), 4.18 (s, 2H, CH_2), 3.87 (s, 3H, CH_3O), 3.38 (brs, 2H, H′-2), 2.82 (brs, 2H, H-6′), 2.57 (brs, 2H, H-5′), 2.44 (s, 3H, NCH_3); EIS-MS (70 eV) *m/z:* 342 (M+H). Anal. (Calcd. for $C_{17}H_{19}N_5OS$): C 59.80, H 5.61, N 20.51; Found: C 60.12, H 5.71, N 20.66.

5c: yield 43%, mp 141~142℃. IR (KBr) ν: 3054, 1614, 1563, 1260 cm^{-1}; ^1H NMR (DMSO-d_6, δ ppm)*:* 8.17~7.43 (m, 4H, Ph-H), 6.58 (d, 2H, *J*=3.2 Hz, H-4′), 4.24 (s, 2H, CH_2), 3.37 (brs, 2H, H-2′), 2.74 (brs, 2H, H-6′), 2.55 (brs, 2H, H-5′), 2.43 (s, 3H, NCH_3), 2.32 (s, 3H, CH_3); EIS-MS (70 eV) *m/z:* 326 (M+H). Anal. (Calcd. for $C_{17}H_{19}N_5S$): C 62.74, H 5.88, N 21.52; Found: C 62.88, H 5.67, N 21.48

5d: yield 22%, mp 160~162℃. IR (KBr) ν: 3007, 1607, 1465, 1268 cm^{-1}; ^1H NMR (DMSO-d_6, δ ppm): 8.20~7.38 (m, 4H, Ph-H), 6.54 (brs, 2H, H-4′), 4.24 (s, 2H, CH_2), 3.42 (brs, 2H, H-2′), 2.76 (brs, 2H, H-6′), 2.55 (brs, 2H, H-5′), 2.43 (s, 3H, NCH_3); EIS-MS (70 eV) *m/z:* 345 (M^+). Anal. (Calcd. for $C_{16}H_{16}ClN_5S$): C 55.56, H 4.66, N 20.25; Found: C 55.48, H 4.54, N 20.33.

5e: yield 12%, mp 182~184℃. IR (KBr) ν: 2996, 1603, 1552, 1260 cm^{-1}; ^1H NMR (DMSO-d_6, δ ppm)*:* 8.32~7.74 (m, 4H, Ph-H), 6.65 (br, 2H, H-4′), 4.26 (s, 2H, CH_2), 3.38 (brs, 2H, H-2′), 2.76 (brs, 2H, H-6′), 2.55 (brs, 2H, H-5′), 2.38 (s, 3H, NCH_3); EIS-MS (70 eV) *m/z:* 357 (M+H). Anal. (Calcd. for $C_{16}H_{16}N_6O_2S$): C 53.92, H 5.88, N 21.52; Found: C54.07, H 5.78, N 21.74.

6a: yield 72%, mp 174~176℃. IR (KBr) ν: 3345, 1617, 1557, 1264 cm^{-1}; ^1H NMR (DMSO-d_6, δ ppm)*:* 8.16~7.82 (m, 5H, Ph-H), 6.81 (d, 2H, *J*=3.2 Hz, H-4′), 4.08 (s, 2H, CH_2), 3.37 (brs, 2H, H-2′), 2.86~2.66 (m, 3H, H-6′ and OH), 2.53 (brs, 2H, H-5′); EIS-MS (70 eV) *m/z:* 314 (M+H). Anal. (Calcd. for $C_{15}H_{15}N_5OS$): C 57.49, H 4.82, N 22.35; Found: C 57.61, H 4.55, N 22.31.

6b: yield 63%, mp 168~170℃. IR (KBr) ν: 3362, 1624, 1602, 1265 cm^{-1}; ^1H NMR (DMSO-d_6, δ ppm)*:* 8.04~7.63 (m, 4H, Ph-H), 6.72 (d, 2H, *J*=3.6 Hz, H-4′), 4.12 (s, 2H, CH_2), 3.96 (s, 3H, CH_3O), 3.37 (brs, 2H, H-2′), 2.84~2.72 (m, 3H, H-6′ and OH), 2.55 (brs, 2H, H-5′); EIS-MS (70ev) *m/z:* 344 (M+H). Anal. (Calcd. for $C_{16}H_{17}N_5O_2S$): C 55.96, H 4.99, N 20.39; Found: C 56.12, H 4.87, N 20.43.

6c: yield 48%, mp 152~153℃. IR (KBr) ν: 3417, 1606, 1585, 1266 cm^{-1}; ^1H NMR (DMSO-d_6, δ ppm)*:* 7.87~7.34 (m, 4H, Ph-H), 6.68 (d, 2H, *J*=3.6 Hz, H-4′), 4.17 (s, 2H, CH_2), 3.35 (brs, 2H, H-2′), 3.15~2.74 (m, 3H, H-6′ and OH), 2.55 (brs, 2H, H-5′), 2.43 (s, 3H, CH_3); EIS-MS (70 eV) *m/z:* 328 (M+H). Anal. (Calcd. for $C_{16}H_{17}N_5OS$): C 58.70, H 5.23, N 21.39; Found: C 58.82, H 5.26, N 21.44.

6d: yield 35%, mp 160~162℃. IR (KBr) ν: 3437, 1624, 1557, 1265 cm^{-1}; ^1H NMR (DMSO-d_6, δ ppm)*:* 8.26~7.53 (m, 4H, Ph-H), 7.03 (d, *J*=3.5 Hz, 2H, H-4′), 4.21 (s, 2H, CH_2), 3.35 (brs, 2H, H-2′), 2.87~2.68 (m, 3H, H-6′ and OH), 2.53 (brs, 2H, H-5′); EIS-MS (70 eV) *m/z:* 348 (M+H). Anal. (Calcd. for $C_{15}H_{14}ClN_5OS$): C 51.80, H 4.06, N 20.13; Found: C 51.88, H 4.32, N 20.32.

6e: yield 17%, mp 188~190℃. IR (KBr) ν: 3345, 1617, 1485, 1264 cm^{-1}; ^1H NMR (DMSO-d_6, δ ppm)*:* 8.17~7.82 (m, 4H, Ph-H), 6.74 (d, 2H, *J*=3 Hz, H-4′), 4.15 (s, 2H, CH_2), 3.43 (brs, 2H, H-2′), 2.85~2.63 (m, 3H, H-6′ and OH), 2.55 (brs, H, H-5′); EIS-MS (70 eV) *m/z:* 359 (M+H). Anal. (Calcd. for $C_{15}H_{14}N_5O_3S$): C 50.27, H 3.94, N 23.45; Found: C50.41, H 4.12.48, N 23.60.

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