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Efficient synthesis of a new series of piperidine ring modified thiopene, furan, and pyridyl alcohol and methyl ether analogues of (±)-*threo*-methyl phenyl (piperidin-2-yl) acetate

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ABSTRACT

A series of novel piperidine ring modified thiopene, furan, and pyridyl alcohol and methyl ether analogues of (±)-*threo*-methyl phenyl (piperidin-2-yl) acetate was synthesized. This series of methyl phenyl (piperidin-2-yl) acetate analogues was developed by piperidine ring alkylation and reductive amination followed by lithium aluminum hydride reduction to give alcohol derivatives. Methylation of the alcohol analogues by extension of standard literature procedures gave the corresponding methyl ether derivatives. The chemical structure of these compounds was established based on MS, ^{1}H NMR and ^{13}C NMR spectra data, and CHN elemental analysis data. Several significant modifications in the literature methodologies were made in order to make the reaction more efficient, and good yields were generally obtained. © 2012 Trade Science Inc. - INDIA

KEYWORDS

Thiopene-based alcohol;
Ritalinol methyl ether;
Methyl phenyl (piperidin-2-yl) acetate;
Lithium aluminum hydride reduction;
Reductive amination.

INTRODUCTION

Methyl phenyl (piperidine-2-yl) acetate (Ritalin) has high potential for abuse and addiction due to its similarity pharmacologically to cocaine and amphetamine. The abuse of cocaine (and other stimulant drugs) is of the greatest concerns of the society today and has therefore become a focus of medical, social, and political leaders. Methyl phenyl (piperidin-2-yl) acetate was first synthesized in 1944 by Panizzon[1], and was identified as a stimulant in 1954[2]. A review on the synthesis of commercially pure ("R, 2'R)-(+) *threo*-methyl phenyl(piperidin-2-yl) acetate hydrochloride has been published[3]. The original method of Pannizzon[1] for the synthesis of methyl phenyl(piperidin-2-yl)acetate often gave mixtures of products which may require tedious chromatographic separations, resulting generally in a very low yield. A detailed review on piperidine analogs of cocaine, tropanes, and GBR 12935 compounds have been reported in the literature[4,5]. Furthermore, the synthesis of piperidine ring modified analogues of methylphenidate has been reported in the literature[5,6]. These analogues basically involve the replacement of the piperidine ring with other secondary amines with 5, 7, and 8-membered rings.

The chemical synthesis of a series of (±) *threo*-methyl phenyl (piperidin-2-yl) acetate analogs has been reported[4-14] in the literature, but not many reports on piperidine ring modified analogues utilizing methyl phenyl (piperidin-2-yl) acetate as the starting

point for the syntheses. In continuation of our drug development program, we have recently reported the chemical synthesis of a new series of piperidine ring modified (±)-*threo*-methyl phenyl (piperidin-2-yl) acetate analogues from methyl phenyl (piperidin-2-yl) acetate[15]. More recently, we have reported the synthesis of piperidine ring modified alcohol and methyl ether analogues of methyl phenyl (piperidin-2-yl) acetate by making several significant modifications to existing literature methodologies[16] in order to make the reaction more efficient and hence, produce compounds with improved yields[17]. In furtherance of our drug development efforts, we have investigated the use of other heteroaromatic systems (thiopene, furan and pyridyl) substitution on the piperidine nitrogen to synthesis a new series of alcohol and methyl ether analogues.

The synthesis of compounds *threo*-N-Benzylritalinol (1X, 100 % yield) and *threo*-N-Benzylritalinol Methyl Ether (2Y, 86 % yield) has been reported in the literature[14b]. However, there has never been any previous literature reports on the new series of compounds **(1a-1h)** (99 % yield) and **(2a-2h)** (93 % yield) reported in this manuscript. In our laboratory, the synthesis of both ritalinol and ritalinol methyl ether series was achieved by utilizing a different synthetic strategy than that reported in the literature[14b] and good yields were generally obtained. The rationale for this research is (a) to investigate the use of other heteroaromatic systems in the design of novel ligands, which may have some interest to the pharmaceutical industry as analogues of the drug Ritalin by embarking on the synthesis of a new series of piperidine ring modified thiopene, furan, and pyridyl alcohol and methyl ether analogues of (±)-*threo*-methyl phenyl (piperidin-2-yl) acetate. (b) to complete the series of compounds for SAR studies of the effect of both ester moiety and piperidine ring modifications on biological activity of these classes of compounds. Ultimately, these compounds should be useful in the synthesis of novel ligands for testing as pharmaceutical agents. We now wish to report the methodology for efficient synthesis of several new piperidine ring modified thiopene, furan, and pyridyl alcohol and methyl ether analogues of (±)-*threo*-methyl phenyl (piperidin-2-yl) acetate in good yields.

EXPERIMENTAL

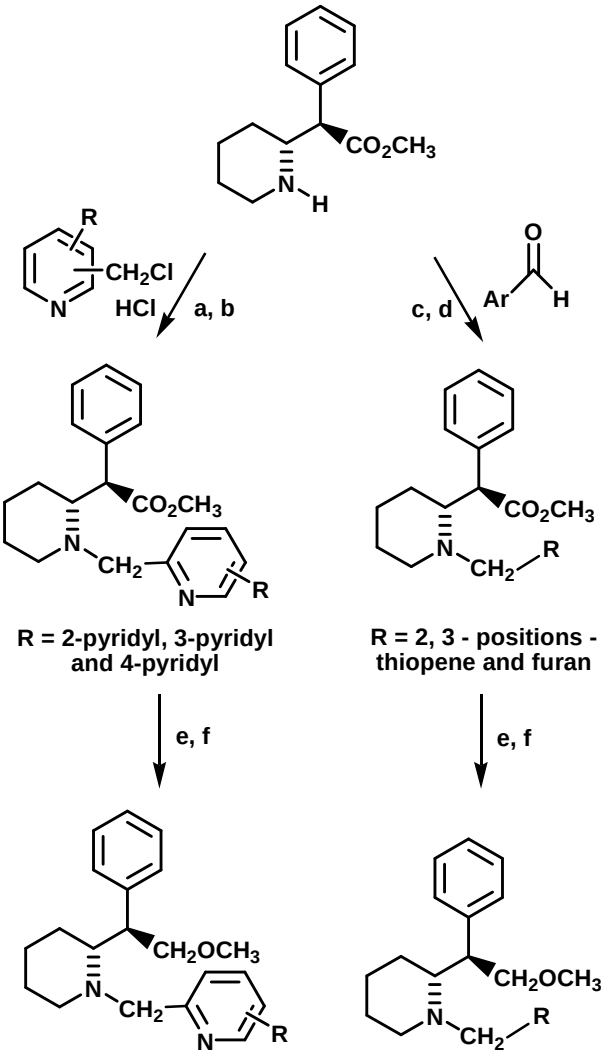
General

Compounds were synthesized utilizing reagents commercially available from Aldrich Chemical Co. and Fisher Scientific without further purification. Melting points (EtOAc-Hexane) were determined in open capillary tubes on a Mel-Temp melting point apparatus and are uncorrected. ^{1}H NMR (500 MHz, TMS) and ^{13}C NMR (100 MHz, TMS) spectra were obtained on a Bruker DSX-500 Spectrometer. Chemical shifts are quoted in parts per million from internal standard tetramethylsilane (TMS). All solvents and chemicals were of research grade and were obtained from Merck and Lancaster. The progress of the reaction was monitored by TLC. High-resolution mass spectra (EI, Cl, and FAB) were recorded on a VG Analytical 70-SE mass spectrometer equipped with an 11-250J data system. Elemental analyses were performed on a Perker-Elmer 2400 CHN analyzer instrument, and were within ± 0.4 % of calculated values.

Synthetic chemistry

The synthesis of methyl phenyl (piperidin-2-yl) acetate has previously been described in the literature, based on the alkylation of 2-bromopyridine with various phenylacetonitrile anions. The original method developed by Panizzon[1] was modified in a previous report[14]. The chemical synthesis of several piperidine ring modified analogues of methyl phenyl (piperidin-2-yl) acetate has recently been reported[15]. N-Alkylation of methyl phenyl (piperidin-2-yl) acetate with 2-chloro methylpyridine and 2-chloro-5-(chloromethyl) thiopene produced the N-(2-methylpyridyl) and N-methyl-(5-chlorothiopene) methyl ester derivatives, respectively[15]. Thiopene and furan methyl ester derivatives were synthesized[15] by reductive amination of methyl phenyl (piperidin-2-yl) acetate with their corresponding aldehydes utilizing sodium cyanoborohydride. The ester derivatives were subsequently reduced with lithium aluminum hydride in anhydrous solvents to give the corresponding alcohols generally in excellent yield. The effect of reaction solvents is a very important factor in regulating the reactivity. Methylation was smoothly achieved utilizing aprotic polar solvents (DMF: DMSO). Also, it

was observed that the best optimum condition was a 1:1 mixture of polar aprotic solvents in presence of methyl iodide as the alkylating agent and powdered potassium hydroxide as the base at a temperature of 0-5 °C. A summary of this method is described in Scheme 1.



Scheme 1 : General scheme for the synthesis of thiopene, furan and pyridyl ritalinol and ritalinol methyl ether analogues.

Reagents and conditions: (a) Potassium iodide (KI), acetone (b) powdered potassium carbonate (K_2CO_3), room temperature, 24 h (c) triethylamine (Et_3N), methanol (MeOH), molecular sieves (4A) (d) sodium cyanoborohydride ($NaBH_3CN$), room temperature, overnight (e) Lithium aluminum hydride (LAH), anhydrous diethyl ether (f) DMSO:DMF (1:1), hexane, powdered potassium hydroxide, methyl iodide, room temperature, 12 h.

(±)-*Threo*-N-(methyl-2-thiopene) methyl phenyl (piperidin-2-yl) ritalinol (1a)

(±)-*Threo*-N-(methyl-2-thiopene) methyl phenyl (piperidin-2-yl) acetate[15] (1.0 g, 3.32 mmol) was dissolved in anhydrous Et_2O (15 mL) and cooled in ice-bath for 15 minutes. A solution of $LiAlH_4$ in ether (1M) (0.252 g, 6.64 mmol) was added *via* syringe under a nitrogen atmosphere and the mixture stirred in ice-bath for an additional 5 minutes. The resulting mixture was heated under reflux for 2 h, and then cooled in ice-bath. Unreacted $LiAlH_4$ was quenched by careful addition of aqueous 10 % NaOH solution until gas evolution ceased. The reaction flask was subsequently rinsed with water and ether. The ether layer was separated and the aqueous layer extracted with ethyl acetate (3 x 50 mL). The ether/ethyl acetate extracts were combined, washed with water (2 x 50 mL), dried ($MgSO_4$), and evaporated *in vacuo* provided a yellow solid residue (0.600 g, 99.8 %). The hydrochloride salt was obtained by addition of 1M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness *in vacuo* and recrystallization (EtOAc-Hexane) provided 0.540 g (99 %) of **(1a)** as a yellow solid: mp 189-191 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.6-1.1 (m, 6H), 2.58-2.53 (m, 1H), 3.03-2.95 (m, 1H), 3.66-3.49 (m, 1H), 3.83 (t, 1H, J = 11.0 Hz), 3.97 (d, 1H, J=13.4 Hz), 3.84 (d, 1H, J=13.2 Hz), 4.00 (s, 2H), 4.2 (d, 1H, J=10.4 Hz), 6.9 (d, 1H, J = 13.2 Hz), 7.3 (dd, 2H,3.3, 11.0 Hz), 7.4-7.2 (m, 5H, aromatic-H), ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.59, 141.0, 138.6, 133.78, 129.2, 128.7, 128.03, 127.9, 126.8, 124.97, 57.2, 46.36, 45.2, 43.06, 26.56, 25.54, 25.53, 18.8. MS-FB+ (70 eV): m/z 302.43, calcd. for $C_{18}H_{24}NOS$ (MH+). Anal. Calcd for $C_{18}H_{23}NOS$: C 71.72, H 7.69, N 4.65. Found C 71.49, H 7.89, N 4.48.

(±)-*Threo*-N-(methyl-3-thiopene) methyl phenyl (piperidin-2-yl) ritalinol (1b)

(±)-*Threo*-N-(methyl-3-thiopene) methyl phenyl (piperidin-2-yl) acetate[15] (1.0 g, 3.32 mmol) was dissolved in anhydrous Et_2O (15 mL) and cooled in ice-bath for 15 minutes. The mixture was reduced with $LiAlH_4$ in ether (1M) (0.252 g, 6.64 mmol) by a method virtually identical to that used to synthesize **(1a)**, provided a yellow solid residue (0.599 g, 99.4 %). The

hydrochloride salt was obtained by addition of 1M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness *in vacuo* and recrystallization (EtOAc-Hexane) provided 0.534 g (98 %) of **(1b)** as a yellow solid: mp 184-186 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.6-1.1 (m, 6H), 2.58-2.53 (m, 1H), 3.03-2.95 (m, 1H), 3.66-3.49 (m, 1H), 3.83 (t, 1H, J = 11.0 Hz), 3.95 (d, 1H, J=13.4 Hz), 3.87 (d, 1H, J=13.2 Hz), 4.01 (s, 2H), 4.3 (d, 1H, J=10.4 Hz), 7.1 (s, 1H, thiopene-H), 7.4-7.2 (m, 5H, aromatic-H), 7.50 (d, 1H, J = 8.2 Hz), 7.60 (d, 1H, J = 8.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.59, 141.0, 138.6, 133.78, 129.2, 128.7, 128.03, 127.9, 126.8, 124.97, 57.2, 46.36, 45.2, 43.06, 26.56, 25.54, 25.53, 18.8. MS-FB+ (70 eV): m/z 302.43, calcd. for $C_{18}H_{24}NOS$ (MH+). Anal. Calcd for $C_{18}H_{23}NOS$: C 71.72, H 7.69, N 4.65. Found C 71.54, H 7.54, N 4.81.

(±)-*Threo*-N-methyl-(5-chlorothiopene) methyl phenyl (piperidin-2-yl) ritalinol (1c)

(±)-*Threo*-N-methyl-(5-chlorothiopene) methyl phenyl (piperidin-2-yl) acetate[15] (1.0 g, 2.98 mmol) was dissolved in anhydrous Et_2O (15 mL) and cooled in ice-bath for 15 minutes. The mixture was reduced with $LiAlH_4$ in ether (1M) (0.226 g, 5.96 mmol) by a method virtually identical to that used to synthesize **(1a)** provided a brown solid residue (0.590 g, 98.9 %). The hydrochloride salt was obtained by addition of 1M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness *in vacuo* and recrystallization (EtOAc-Hexane) provided 0.531 g (97 %) of **(1c)** as a brown solid: mp 181-183 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.6-1.1 (m, 6H), 3.03-2.95 (m, 1H), 2.77-2.60 (m, 1H), 3.59-3.42 (m, 1H), 3.80 (t, 1H, J = 11.0 Hz), 3.94 (d, 1H, J= 13.2 Hz), 4.05 (s, 2H), 4.10 (d, 1H, J= 10.2 Hz), 6.77 (dd, 2H, J = 8.2, 9.9 Hz), 7.4-7.2 (m, 5H, aromatic-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.59, 141.0, 138.6, 133.78, 129.2, 128.7, 128.03, 127.9, 126.8, 124.97, 57.2, 46.36, 45.2, 43.06, 26.56, 25.54, 25.53, 18.8. MS-CI (70 eV): m/z 336.87 calcd. for $C_{18}H_{23}NOSCl$ (MH+). Anal. Calcd for $C_{18}H_{22}NOSCl$: C 64.37, H 6.60, N 4.17. Found C 64.67, H 6.76, N 3.99.

(±)-*Threo*-N-(methyl-2-furan) methyl phenyl (piperidin-2-yl) ritalinol (1d)

(±)-*Threo*-N-(-methyl-2-furan) methyl phenyl (piperidin-2-yl) acetate[15] (1.0 g, 3.50 mmol) was dissolved in anhydrous Et_2O (15 mL) and cooled in ice-bath for 15 minutes. The mixture was reduced with $LiAlH_4$ in ether (1M) (0.266 g, 7.01 mmol) by a method virtually identical to that used to synthesize **(1a)** provided a white solid residue (0.587 g, 98.8 %). The hydrochloride salt was obtained by addition of 1M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness *in vacuo* and recrystallization (EtOAc-Hexane) provided 0.522 g (98 %) of **(1d)** as a white solid: mp 179-181 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.6-1.1 (m, 6H), 2.58-2.53 (m,1H), 3.03-2.95 (m, 1H), 3.66-3.49 (m, 1H), 3.81 (t, 1H, J = 11.0 Hz), 3.98 (d, 1H, J= 13.4 Hz), 3.86 (d, 1H, J= 13.2 Hz), 4.08 (s, 2H), 4.3 (d, 1H, J=10.4 Hz), 6.4 (d, 1H, J = 13.1 Hz), 6.6 (d, 1H, J = 13.2 Hz), 7.4-7.2 (m, 5H, aromatic-H), 7.58 (d, 1H, J = 8.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.41, 144.82, 141.0, 138.6, 129.2, 128.7, 127.9, 126.8, 117.91, 111.89, 57.2, 46.36, 45.2, 43.06, 26.56, 25.54, 25.53, 18.6. MS-FB+ (70 eV): m/z 286.36, calcd. for $C_{18}H_{24}NO_2$ (MH+). Anal. Calcd for $C_{18}H_{23}NO_2$: C 75.76, H 8.12, 4.91. Found C 75.86, H 8.21, N 5.09.

(±)-*Threo*-N-(methyl-3-furan) methyl phenyl (piperidin-2-yl) ritalinol (1e)

(±)-*Threo*-N-(-methyl-3-furan) methyl phenyl (piperidin-2-yl) acetate[15] (1.0 g, 3.50 mmol) was dissolved in anhydrous Et_2O (15 mL) and cooled in ice-bath for 15 minutes. The mixture was reduced with $LiAlH_4$ in ether (1M) (0.266 g, 7.01 mmol) by a method virtually identical to that used to synthesize **(1a)** provided a white solid residue (0.600 g, 99.7 %). The hydrochloride salt was obtained by addition of 1M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness *in vacuo* and recrystallization (EtOAc-Hexane) provided 0.539 g (99 %) of **(1e)** as a white solid: mp 193-195 °C; The hydrochloride salt was recrystallized from EtOAc-Hexane: mp 181-182 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.6-1.1 (m, 6H), 2.58-2.53 (m, 1H), 3.03-2.95 (m, 1H), 3.66-3.49 (m, 1H), 3.82 (t, 1H, J = 11.0 Hz), 3.96 (d, 1H, J=13.4 Hz), 3.85 (d, 1H, J=13.2 Hz), 4.03 (s, 2H), 4.1 (d, 1H, J=10.4 Hz), 6.4 (s, 1H, furan-H), 6.6 (d, 1H, J = 13.2 Hz), 7.4-

7.2 (m, 5H, aromatic-H), 7.50 (dd, 2H, 8.3, 9.9 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.41, 144.82, 141.0, 138.6, 129.2, 128.7, 127.9, 126.8, 117.91, 111.89, 57.2, 46.36, 45.2, 43.06, 26.56, 25.54, 25.53, 18.6. MS-FB+ (70 eV): m/z 286.36, calcd. for $C_{18}H_{24}NO_2$ (MH+). Anal. Calcd for $C_{18}H_{23}NO_2$: C 75.76, H 8.12, 4.91. Found C 75.45, H 7.93, N 5.02.

(±)-*Threo*-N-(2-methylpyridyl) methyl phenyl (piperidin-2-yl) ritalinol (1f)

(±)-*Threo*-N-(2-methylpyridyl) methyl phenyl (piperidin-2-yl) acetate[15] (1.0 g, 3.37 mmol) was dissolved in anhydrous Et_2O (15 mL) and cooled in ice-bath for 15 minutes. The mixture was reduced with $LiAlH_4$ in ether (1M) (0.256 g, 6.75 mmol) by a method virtually identical to that used to synthesize **(1a)** provided a brown solid residue (0.598 g, 98.2 %). Recrystallization of the dihydrochloride salt (EtOAc-Hexane) provided 0.550 g (96 %) of **(1f)** as a light brown solid: mp 165-168 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.6-1.1 (m, 6H), 2.58-2.53 (m, 1H), 3.03-2.95 (m, 1H), 3.66-3.49 (m, 1H), 3.82 (t, 1H, J = 11.0 Hz), 3.98 (d, 1H, J=13.4 Hz), 3.8 (d, 1H, J =13.2 Hz), 4.05 (s, 2H), 4.18 (d, 1H, J=10.4 Hz), 7.1 (t, 1H, J = 9.3 Hz), 7.3-7.2 (m, 9H, aromatic-H), 7.4 (d, 1H, J = 8.2 Hz), 7.8 (t, 1H, J = 9.3 Hz), 8.45 (d, 1H, J = 8.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.50, 152.00, 141.0, 138.70, 138.6, 135.26, 129.2, 128.7, 127.9, 126.8, 125.79, 57.2, 45.2, 43.06, 25.54, 25.53, 26.56, 46.36, 18.9. MS-FB+ (70 eV): m/z 297.39 calcd. for $C_{19}H_{25}N_2O$ (MH+). Anal. Calcd for $C_{19}H_{24}N_2O$: C 76.99, H 8.16, N 9.45. Found C 77.12, H 7.97, N 9.61

(±)-*Threo*-N-(3-methylpyridyl) methyl phenyl (piperidin-2-yl) ritalinol (1g)

(±)-*Threo*-N-(3-methylpyridyl) methyl phenyl (piperidin-2-yl) acetate[15] (1.0 g, 3.37 mmol) was dissolved in anhydrous Et_2O (15 mL) and cooled in ice-bath for 15 minutes. The mixture was reduced with $LiAlH_4$ in ether (1M) (0.256 g, 6.75 mmol) by a method virtually identical to that used to synthesize **(1a)** provided a brown solid residue (0.585 g, 95.8 %). Recrystallization of the dihydrochloride salt (EtOAc-Hexane) provided 0.532 g (94 %) of **(1g)** as a brown solid: mp 170-172 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ d 1.6-1.1 (m, 6H), 2.58-2.53 (m, 1H), 3.03-2.95 (m, 1H), 3.66-3.49 (m, 1H), 3.80 (t, 1H, J = 11.0 Hz), 3.96 (d, 1H, J=13.4 Hz), 3.8 (d, 1H, J =13.2 Hz), 4.07 (s, 2H), 4.2 (d, 1H, J=10.4 Hz), 7.3-7.2 (m, 9H, aromatic-H), 7.4 (s, 1H, pyridyl-H), 7.6 (d, 1H, j = 8.1 Hz), 8.5 (d, 2H, J = 8.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.50, 152.00, 141.0, 138.70, 138.6, 135.26, 129.2, 128.7, 127.9, 126.8, 125.79, 57.2, 45.2, 43.06, 25.54, 25.53, 26.56, 46.36, 18.9. MS-FB+ (70 eV): m/z 297.39 calcd. for $C_{19}H_{25}N_2O$ (MH+). Anal. Calcd for $C_{19}H_{24}N_2O$: C 76.99, H 8.16, N 9.45. Found C 77.31, H 8.35, N 9.29.

(±)-*Threo*-N-(4-methylpyridyl) methyl phenyl (piperidin-2-yl) ritalinol (1h)

(±)-*Threo*-N-(4-methylpyridyl) methyl phenyl (piperidin-2-yl) acetate[15] (1.0 g, 3.37 mmol) was dissolved in anhydrous Et_2O (15 mL) and cooled in ice-bath for 15 minutes. The mixture was reduced with $LiAlH_4$ in ether (1M) (0.256 g, 6.75 mmol) by a method virtually identical to that used to synthesize **(1a)** provided a brown solid residue (0.600 g, 98.9 %). Recrystallization of the dihydrochloride salt (EtOAc-Hexane) provided 0.528 g (97 %) of **(1h)** as a brown solid: mp 152-153 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.6-1.1 (m, 6H), 2.58-2.53 (m, 1H), 3.03-2.95 (m, 1H), 3.66-3.49 (m, 1H), 3.83 (t, 1H, J = 11.0 Hz), 3.97 (d, 1H, J=13.4 Hz), 3.81 (d, 1H, J =13.2 Hz), 4.02 (s, 2H), 4.2 (d, 1H, J=10.4 Hz), 7.3-7.2 (m, 9H, aromatic-H), 7.4 (d, 2H, J = 8.1 Hz), 8.5 (d, 2H, j = 8.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.50, 152.00, 141.0, 138.70, 138.6, 135.26, 129.2, 128.7, 127.9, 126.8, 125.79, 57.2, 45.2, 43.06, 25.54, 25.53, 26.56, 46.36, 18.9. MS-FB+ (70 eV): m/z 297.39 calcd. for $C_{19}H_{25}N_2O$ (MH+). Anal. Calcd for $C_{19}H_{24}N_2O$: C 76.99, H 8.16, N 9.45. Found C 76.84, H 8.05, N 9.36.

(±)-*Threo*-N-(methyl-2-thiopene) methyl phenyl (piperidin-2-yl) ritalinol methyl ether (2a)

(±)-*Threo*-N-(methyl-2-thiopene) methyl phenyl (piperidin-2-yl) ritalinol (0.500 g, 1.59 mmol) was dissolved in a mixture of DMSO and DMF (1:1). After cooling to 0-5 °C, powdered potassium hydroxide (0.133 g, 2.38 mmol) and methyl iodide (0.226 g, 0.099 ml, 1.59 mmol) were added and the reaction

mixture was stirred for 12 h. The progress of the reaction was monitored by TLC and HPLC which showed that up to 98-99 % of the methylated product was formed. After 12.0 h the organic hexane layer separated out and the DMSO: DMF layer was extracted with hexane (3 x 20 ml). Both hexane layers were combined and washed with water to remove the inorganic salts. Removal of solvents *in vacuo* provided a yellow solid residue (0.516 g, 92.7 %), HPLC purity = 96 %. The hydrochloride salt was obtained by addition of anhydrous 1M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness *in vacuo* and recrystallization (EtOAc-Hexane) provided **(2a)** (0.465 g, 92 %) of the methyl ether derivatives as a off-white crystal: mp 208-210 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.6-1.1 (m, 6H), 2.58-2.53 (m, 1H), 3.03-2. Hz), 4.01-3.95 (m, 2H), 4.2 (d, 1H, J=10.4 Hz), 6.9 (d, 1H, J = 13.2 Hz), 7.3 (dd, 2H, J = 6.0, 9.9 Hz), 7.4-7.2 (m, 5H, aromatic-H), ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.59, 142.4, 140.6, 133.78, 128.7, 128.6, 128.2, 128.03, 124.97, 58.9, 55.3, 47.4, 43.06, 25.54, 25.53, 26.56, 46.36, 20.0. MS-FB+ (70 eV): m/z 316.46, calcd. for $C_{19}H_{26}NOS$ (MH+). Anal. Calcd for $C_{19}H_{25}NOS$: C 72.34, H 7.99, N 4.44. Found C 71.99, H 8.15, N 4.66.

(±)-*Threo*-N-(methyl-3-thiopene) methyl phenyl (piperidin-2-yl) ritalinol methyl ether (2b)

(±)-*Threo*-N-(methyl-3-thiopene) methyl phenyl (piperidin-2-yl) ritalinol (0.500 g, 1.59 mmol) was dissolved in a mixture of DMSO and DMF (1:1). After cooling to 0-5 ^{o}C, powdered potassium hydroxide (0.133 g, 2.38 mmol) and methyl iodide (0.226 g, 0.099 ml, 1.59 mmol) by a method virtually identical to that used to synthesize **(2a)** provided a yellow solid residue (0.500 g, 91.7 %). The hydrochloride salt was obtained by addition of anhydrous 1M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness *in vacuo* and recrystallization (EtOAc-Hexane) provided **(2a)** (0.450 g, 90 %) of the methyl ether derivatives as a off-white crystal: mp 199-201 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.6-1.1 (m, 6H), 2.58-2.53 (m, 1H), 3.03-2.95 (m, 1H), 3.25 (s, 3H, OCH_3), 3.66-3.49 (m, 1H), 3.98 (d, 1H, J=13.4 Hz), 3.87 (d, 1H, J=13.2 Hz), 4.00-3.93 (m, 2H), 4.2 (d, 1H, J=10.4 Hz), 7.1 (s, 1H, thiopene-H), 7.4-7.2 (m, 5H, aromatic-H), 7.50 (d, 1H, J = 8.1 Hz), 7.60 (d, 1H J = 8.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.59, 142.4, 140.6, 133.78, 128.7, 128.6, 128.2, 128.03, 124.97, 58.9, 55.3, 47.4, 43.06, 25.54, 25.53, 26.56, 46.36, 20.0. MS-FB+ (70 eV): m/z 316.46, calcd. for $C_{19}H_{26}NOS$ (MH+). Anal. Calcd for $C_{19}H_{25}NOS$: C 72.34, H 7.99, N 4.44. Found C 72.25, H 7.87, N 4.59.

(±)-*Threo*-N-methyl-(5-chlorothiopene) methyl phenyl (piperidin-2-yl) ritalinol methyl ether (2c)

(±)-*Threo*-N-methyl-(5-chlorothiopene) methyl phenyl (piperidin-2-yl) ritalinol (0.500 g, 1.43 mmol) was dissolved in a mixture of DMSO and DMF (1:1). After cooling to 0-5 ^{o}C, powdered potassium hydroxide (0.121 g, 2.14 mmol) and methyl iodide (0.203 g, 0.089 ml, 1.43 mmol) by a method virtually identical to that used to synthesize **(2a)** provided a brown solid residue (0.525 g, 94.1 %). The hydrochloride salt was obtained by addition of anhydrous 1M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness *in vacuo* and recrystallization (EtOAc-Hexane) provided **(2c)** (0.468 g, 93 %) of the methyl ether derivatives as a light brown crystal: mp 194-197 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.6-1.1 (m, 6H), 3.03-2.95 (m, 1H), 2.77-2.60 (m, 1H), 3.59-3.42 (m, 1H), 3.26 (s, 3H, OCH_3), 3.92 (d, 1H, J= 13.2 Hz), 4.02-3.96 (m, 2H), 4.10 (d, 1H, J= 10.2 Hz), 6.8 (dd 2H, 6.0, 9.9 Hz), 7.4-7.2 (m, 5H, aromatic-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.59, 142.4, 140.6, 133.78, 128.7, 128.6, 128.2, 128.03, 124.97, 58.9, 55.3, 47.4, 43.06, 25.54, 25.53, 26.56, 46.36, 20.0. MS-CI (70 eV): m/z 350.89 calcd. for $C_{19}H_{25}NOSCl$ (MH+). Anal. Calcd for $C_{19}H_{24}NOSCl$: C 65.22, H 6.91, N 4.00. Found C 65.54, H 7.03, N 3.88.

(±)-*Threo*-N-(methyl-2-furan) methyl phenyl (piperidin-2-yl) ritalinol methyl ether (2d)

(±)-*Threo*-N-(methyl-2-furan) methyl phenyl (piperidin-2-yl) ritalinol (0.500 g, 1.67 mmol) was dissolved in a mixture of DMSO and DMF (1:1). After cooling to 0-5 ^{o}C, powdered potassium hydroxide (0.141 g, 2.51 mmol) and methyl iodide (0.237 g, 0.104 ml, 1.67 mmol) by a method virtually identical to that used to synthesize **(2a)** provided a white solid

residue (0.495 g, 91.1 %). The hydrochloride salt was obtained by addition of anhydrous 1M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness *in vacuo* and recrystallization (EtOAc-Hexane) provided **(2d)** (0.456 g, 89 %) of the methyl ether derivatives as a white crystal: mp 192-194 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.6-1.1 (m, 6H), 2.58-2.53 (m,1H), 3.03-2.95 (m, 1H), 3.66-3.49 (m, 1H), 3.24 (s, 3H, OCH_3), 3.97 (d, 1H, J= 13.4 Hz), 3.85 (d, 1H, J= 13.2 Hz), 4.01-3.96 (m, 2H), 4.2 (d, 1H, J=10.4 Hz), 6.4 (d, 1H, J = 7.8 Hz), 6.6 (d, 1H, J = 7.8 Hz), 7.4-7.2 (m, 5H, aromatic-H), 7.58 (d, 1H, J = 8.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.41, 144.82, 142.4, 140.6, 128.7, 128.6, 128.2, 117.89, 111.89, 58.9, 55.3, 47.4, 43.06, 25.54, 25.53, 26.56, 46.36, 20.0. MS-FB+ (70 eV): m/z 300.38, calcd. for $C_{19}H_{26}NO_2$ (MH+). Anal. Calcd for $C_{19}H_{25}NO_2$: C 76.22, H 8.42, 4.68. Found C 76.09, H 8.33 N 4.99.

(±)-*Threo*-N-(methyl-3-furan) methyl phenyl (piperidin-2-yl) ritalinol methyl ether (2e)

(±)-*Threo*-N-(methyl-3-furan) methyl phenyl (piperidin-2-yl) ritalinol (0.500 g, 1.67 mmol) was dissolved in a mixture of DMSO and DMF (1:1). After cooling to 0-5 °C, powdered potassium hydroxide (0.141 g, 2.51 mmol) and methyl iodide (0.237 g, 0.104 ml, 1.67 mmol) by a method virtually identical to that used to synthesize **(2a)** provided a white solid residue (0.504 g, 92.0 %). The hydrochloride salt was obtained by addition of anhydrous 1M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness *in vacuo* and recrystallization (EtOAc-Hexane) provided **(2e)** (0.453 g, 90 %) of the methyl ether derivatives as a white crystal: mp 210-213 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.6-1.1 (m, 6H), 2.58-2.53 (m, 1H), 3.03-2.95 (m, 1H), 3.66-3.49 (m, 1H), 3.26 (s, 3H, OCH_3), 3.98 (d, 1H, J=13.4 Hz), 3.86 (d, 1H, J=13.2 Hz), 4.02-3.95 (m, 2H), 4.2 (d, 1H, J=10.4 Hz), 6.4 (s, 1H, furan-H), 6.6 (d, 1H, J = 7.8 Hz), 7.4-7.2 (m, 5H, aromatic-H), 7.50 (dd, 2H, J = 8.2, 9.9 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.41, 144.82, 142.4, 140.6, 128.7, 128.6, 128.2, 117.89, 111.89, 58.9, 55.3, 47.4, 43.06, 25.54, 25.53, 26.56, 46.36, 20.0. MS-FB+ (70 eV): m/z 300.38, calcd. for $C_{19}H_{26}NO_2$ (MH+). Anal. Calcd for $C_{19}H_{25}NO_2$: C 76.22, H 8.42, 4.68. Found C 75.94, H 8.61, N 4.78.

(±)-*Threo*-N-(2-methylpyridyl) methyl phenyl (piperidin-2-yl) ritalinol methyl ether (2f)

(±)-*Threo*-N-(2-methylpyridyl) methyl phenyl (piperidin-2-yl) ritalinol (0.500 g, 1.61 mmol) was dissolved in a mixture of DMSO and DMF (1:1). After cooling to 0-5 °C, powdered potassium hydroxide (0.136 g, 2.42 mmol) and methyl iodide (0.229 g, 0.100 ml, 1.61 mmol) by a method virtually identical to that used to synthesize **(2a)** provided a brown solid residue (0.489 g, 89.6 %). The dihydrochloride salt was obtained by addition of anhydrous 1M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness *in vacuo* and recrystallization (EtOAc-Hexane) provided **(2f)** (0.450 g, 88 %) of the methyl ether derivatives as a light brown crystal: mp 185-187 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.6-1.1 (m, 6H), 2.58-2.53 (m, 1H), 3.03-2.95 (m, 1H), 3.66-3.49 (m, 1H), 3.28 (s, 3H, OCH_3), 3.97 (d, 1H, J=13.4 Hz), 3.80 (d, 1H, J =13.2 Hz), 4.01-3.94 (m, 2H), 4.18 (d, 1H, J=10.4 Hz), 7.1 (t, 1H, J = 9.3 Hz), 7.3-7.2 (m, 9H, aromatic-H), 7.4 (d, 1H, J = 8.2 Hz), 7.8 (t, 1H, J = 9.3 Hz), 8.45 (d, 1H, J = 8.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.50, 152.00, 142.4, 140.6, 138.70, 135.26, 128.7, 128.6, 128.2, 125.79, 58.9, 55.3, 47.4, 43.06, 25.54, 25.53, 26.56, 46.36, 20.0. MS-FB+ 70 eV): m/z 311.24 calcd. for $C_{20}H_{27}N_2O$ (MH+). Anal. Calcd for $C_{20}H_{26}N_2O$: C 77.43, H 8.45, N 9.03. Found C 77.24, H 8.56, N 9.17.

(±)-*Threo*-N-(3-methylpyridyl) methyl phenyl (piperidin-2-yl) ritalinol methyl ether (2g)

(±)-*Threo*-N-(3-methylpyridyl) methyl phenyl (piperidin-2-yl) ritalinol (0.500 g, 1.61 mmol) was dissolved in a mixture of DMSO and DMF (1:1). After cooling to 0-5 °C, powdered potassium hydroxide (0.136 g, 2.42 mmol) and methyl iodide (0.229 g, 0.100 ml, 1.61 mmol) by a method virtually identical to that used to synthesize **(2a)** provided a brown solid residue (0.509 g, 92.9 %). The dihydrochloride salt was obtained by addition of anhydrous 1M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness *in vacuo* and recrystallization (EtOAc-Hexane) provided **(2g)** (0.463 g, 92 %) of the methyl ether derivatives as a light brown crystal: mp 188-

191°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.6-1.1 (m, 6H), 2.58-2.53 (m, 1H), 3.03-2.95 (m, 1H), 3.66-3.49 (m, 1H), 3.28 (s, 3H, OCH_3), 3.97 (d, 1H, J=13.4 Hz), 3.8 (d, 1H, J =13.2 Hz), 4.02-3.96 (m, 2H), 4.2 (d, 1H, J=10.4 Hz), 7.3-7.2 (m, 9H, aromatic-H), 7.4 (s, 1H, pyridyl-H), 7.6 (d, 1H, J = 8.2 Hz), 8.5 (d, 2H, J = 8.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.50, 152.00, 142.4, 140.6, 138.70, 135.26, 128.7, 128.6, 128.2, 125.79, 58.9, 55.3, 47.4, 43.06, 25.54, 25.53, 26.56, 46.36, 20.0. MS-FB+ (70 eV): m/z 311.24 calcd. for $C_{20}H_{27}N_2O$ (MH+). Anal. Calcd for $C_{20}H_{26}N_2O$: C 77.43, H 8.45, N 9.03. Found C 77.59, H 8.27, N 8.84.

(±)-*Threo*-N-(4-methylpyridyl) methyl phenyl (piperidin-2-yl) ritalinol methyl ether (2h)

(±)-*Threo*-N-(4-methylpyridyl) methyl phenyl (piperidin-2-yl) ritalinol (0.500 g, 1.61 mmol) was dissolved in a mixture of DMSO and DMF (1:1). After cooling to 0-5 °C, powdered potassium hydroxide (0.136 g, 2.42 mmol) and methyl iodide (0.229 g, 0.100 ml, 1.61 mmol) by a method virtually identical to that used to synthesize **(2a)** provided a brown solid residue (0.522 g, 94.2 %). The dihydrochloride salt was obtained by addition of anhydrous 1M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness *in vacuo* and recrystallization (EtOAc-Hexane) provided **(2h)** (0.478 g, 93 %) of the methyl ether derivatives as a light brown crystal: mp 171-173 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.6-1.1 (m, 6H), 2.58-2.53 (m, 1H), 3.03-2.95 (m, 1H), 3.66-3.49 (m, 1H), 3.83 (t, 1H, J = 11.0 Hz), 3.96 (d, 1H, J=13.4 Hz), 3.8 (d, 1H, J =13.2 Hz), 4.02 (s, 2H), 4.2 (d, 1H, J=10.4 Hz), 7.3-7.2 (m, 9H, aromatic-H), 7.4 (d, 2H, J = 8.1 Hz), 8.5 (d, 2H, J = 8.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.50, 152.00, 142.4, 140.6, 138.70, 135.26, 128.7, 128.6, 128.2, 125.79, 58.9, 55.3, 47.4, 43.06, 25.54, 25.53, 26.56, 46.36, 20.0. MS-FB+ (70 eV): m/z 311.24 calcd. for $C_{20}H_{27}N_2O$ (MH+). Anal. Calcd for $C_{20}H_{26}N_2O$: C 77.43, H 8.45, N 9.03. Found C 77.34, H 8.36, N 8.94.

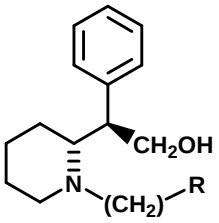
RESULTS AND DISCUSSION

The piperidine ring nitrogen was alkylated. The alkylated compound was subsequently reduced with lithium aluminum hydride to give the alcohol derivatives **(1a-1h)**, and the alcohol methylated in suitable solvents to give the methyl ether **(2a-2h)** analogues are summarized in the TABLE 1. From the results, these compounds were synthesized in high yields (90 % and above), and pure crystals of each compound were obtained. Several solvents were attempted for the alkylation process. When solvents such as dimethylformamide (DMF) and hexamethylphosphoramide (HMPA) were utilized in the alkylation process under a nitrogen atmosphere, there was no trace of alkylation. Also, dimethylsulfoxide (DMSO) and ethanol (EtOH) were employed under a nitrogen atmosphere, but both of these solvents gave a little trace of alkylation and the ^{1}H NMR data was not consistent with the expected structures for the alkylated product. Furthermore, when ethanol was used as the solvent for the alkylation reaction, it resulted in a trans-esterification product with little trace of alkylation. In general, acetone, methanol and methylene chloride were found to be the best solvent of choice because the products were obtained in relatively pure form (single spot on TLC). Furthermore, it was observed that methylation of the alcohol with methyl iodide proceeded efficiently in a mixture of polar aprotic solvents. A mixture of was used in the recrystallization process which resulted in pure crystals of the desired target compounds. The chemical structure of these compounds was established based on the MS, ^{1}H NMR and ^{13}C NMR spectra data. All compounds synthesized in this study gave satisfactory elemental analysis data, and were within ± 0.4 of calculated values.

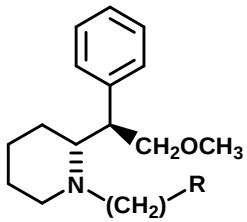
Directions for future research

Compounds synthesized and reported in this study are dl- threo-methyl phenyl (piperidin-2-yl) acetate analogues, consistent with previous literature reports. In continuation of our drug development efforts, we have recently embarked on the resolution of this racemic mixture into individual pure *d*- and *l*-enantiomers for pharmacological evaluation of biological activity; based on a previous report[18] that only the *d*-enantiomers significantly potentiated the pressor responses to intravenous norepinephrine. A manuscript based on the synthesis and biological activity of these pure enantiomers is currently in progress for submission to the Journal of Medicinal Chemistry.

TABLE 1 : Physical and analytical data of thiopene, furan and pyridyl alcohol and methyl ether analogues of methyl phenyl (piperidin-2-yl) acetate.



(1)



(2)

Comp. No.	R	M.p (°C)	Yield (%)	Molecular Formula (M)	Elemental analysis (%) (Calc./found)		
					C	H	N
1a	2-thiopene	189-191	99	$C_{18}H_{23}NOS$	71.72	7.69	4.65
				(301.423)	71.49	7.89	4.48
1b	3-thiopene	184-186	98	$C_{18}H_{23}NOS$	71.72	7.69	4.65
				(301.423)	71.54	7.54	4.81
1c	5-chlorothiopene	181-183	97	$C_{18}H_{22}NOSCl$	64.37	6.60	4.17
				(335.865)	64.67	6.76	3.99
1d	2-furan	179-181	98	$C_{18}H_{23}NO_2$	75.76	8.12	4.91
				(285.351)	75.86	8.21	5.09
1e	3-furan	193-195	99	$C_{18}H_{23}NO_2$	75.76	8.12	4.91
				(285.351)	75.45	7.93	5.02
1f	2-pyridyl	165-168	96	$C_{19}H_{24}N_2O$	76.99	8.16	9.45
				(296.380)	77.12	7.97	9.61
1g	3-pyridyl	170-172	94	$C_{19}H_{24}N_2O$	76.99	8.16	9.45
				(296.380)	77.31	8.35	9.29
1h	4-pyridyl	151-153	97	$C_{19}H_{24}N_2O$	76.99	8.16	9.45
				(296.380)	76.84	8.05	9.36
2a	2-thiopene	208-210	92	$C_{19}H_{25}NOS$	72.34	7.99	4.44
				(315.449)	71.99	8.15	4.66
2b	3-thiopene	199-201	90	$C_{19}H_{25}NOS$	72.34	7.99	4.44
				(315.449)	72.25	7.87	4.59
2c	5-chlorothiopene	194-197	93	$C_{19}H_{24}NOSCl$	65.22	6.91	4.00
				(349.892)	65.54	7.03	3.88
2d	2-furan	192-194	89	$C_{19}H_{25}NO_2$	76.22	8.42	4.68
				(299.373)	76.09	8.33	4.99
2e	3-furanl	210-213	90	$C_{19}H_{25}NO_2$	76.22	8.42	4.68
				(299.373)	75.94	8.61	4.78
2f	2-pyridyl	185-187	88	$C_{20}H_{26}N_2O$	77.43	8.45	9.03
				(310.233)	77.24	8.56	9.17
2g	3-pyridyl	188-191	92	$C_{20}H_{26}N_2O$	77.43	8.45	9.03
2h	4-pyridyl	171-173	93	(310.233)	77.59	8.27	8.84
1X	phenyl	Free base	100	$C_{20}H_{26}N_2O$	77.43	8.45	9.03
2Y	phenyl	Free base	86	(310.233)	77.34	8.36	8.94

Full Paper

CONCLUSIONS

In conclusion, a mixture of methyl phenyl (piperidin-2-yl) acetate, appropriate 2-chloro methylpyridine derivatives, and aromatic aldehydes (thiopene and furan, respectively) were reacted in suitable solvents and reaction conditions gave the corresponding piperidine ring modified methyl ester derivatives. Subsequent reduction of the methyl ester derivatives by treatment with lithium aluminum hydride (LAH) in anhydrous diethyl ether gave the corresponding alcohol derivatives. Thereafter, the alcohol was reacted with methyl iodide and powdered potassium hydroxide in a mixture of polar aprotic solvents (DMSO:DMF in a 1:1 ratio) at a temperature of 0-5 ^{o}C to provide the corresponding methyl ether analogues. An aqueous workup procedure gave the desired target compounds in good yield. This route may serve as an excellent synthetic methodology for efficient synthesis of several new piperidine ring modified thiopene, furan, and pyridyl alcohol and methyl ether analogues of (±)-*threo*-methyl phenyl (piperidin-2-yl) acetate in good yields.

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