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$FeCl_3$-catalysed C-N coupling reaction between cyclic ethers and heterocyclic amines

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ABSTRACT

A series of 2-hydroxypyrrolidine/piperidine derivatives (4a-h)/(4i-m) were prepared by reacting 2,3-dihydrofuran (2a)/3,4-dihydro-2*H*-pyran (2b) with various heterocyclic amines (3a-h), using $FeCl_3.6H_2O$ as catalyst. The synthesized compounds were characterized by various physic chemical techniques such as elemental analysis and spectral analysis viz, ^1H NMR, ^{13}C NMR and Mass.

1. Introduction

A myriad of pyrrolidine derivatives cover a great section of the medical chemistry drug armamentarium. Pyrrolidine and its derivatives are widely used in agrochemicals, photographic chemicals, corrosion inhibitors and curing agent for epoxy resins and as a catalyst in the manufacture of polyurethane [1-4]. It has been revealed from the literature that many biologically active alkaloids are found to possess pyrrolidine ring system [5,6]. Proline, hydroxyproline and higrine are amino acids which are the derivatives of pyrrolidine.

Dystonia, a rare disorder that causes abnormal muscle contraction, results in twisting postures of limbs, trunk or face [7-9]. Procyclidine is a drug, which is the derivative of pyrrolidine, used in the treatment of dystoniaand also used as anti-cholinergic drug [10]. The most wide spread usage of calcium channel blockers (CCB) is to decrease blood pressure. Bepridil is a derivative of pyrrolidine used as CCB drug [11,12]. It has been reported that hydroxy substituted pyrrolidines were used as anticancer drugs [13-15]. Influenza is an acute viral infection of the upper respiratory tract that can affect millions of people every year. Neuraminidase (NA) is one of the glycoproteins exposed on the influenza virus surface. The catalytic activity of NA is essential for influenza virus replication and infectivity. Pyrrolidine served as a scaffold for substituent's in potential NA inhibitors and used as anti-influenza drug [16-18].

Postpartum hemorrhage (PPH), the most common maternal morbidity in developed countries and a major cause of death worldwide. Blood loss exceeding 1000 mL is considered physiologically significant and can result in hemo-dynamic instability. Even with appropriate management, approximately three percent of vaginal deliveries will result in severe post-partum hemorrhage [19-22]. Carbetocin, an obstetric drug used to control postpartum hemorrhage and bleeding after giving birth, is a derivative of pyrrolidine [23-25]. Anisomycin, a derivative of pyrrolidine used as a compo-nent of Martin Lewis agar, an in-vitro diagnostic product [26,27]. Anisomycin can also sensitize metastatic epithelial cells to anoikis and reduce circulating tumor cell implantation in vivo. Vildagliptin, a derivative of pyrrolidine has been employed to reduce hyperglycemia in type 2 diabetes mellitus [28-30]. Further, this has been reported that the pyrrolidine derivatives employed as organo-catalysts for many chemical reactions [31-33].

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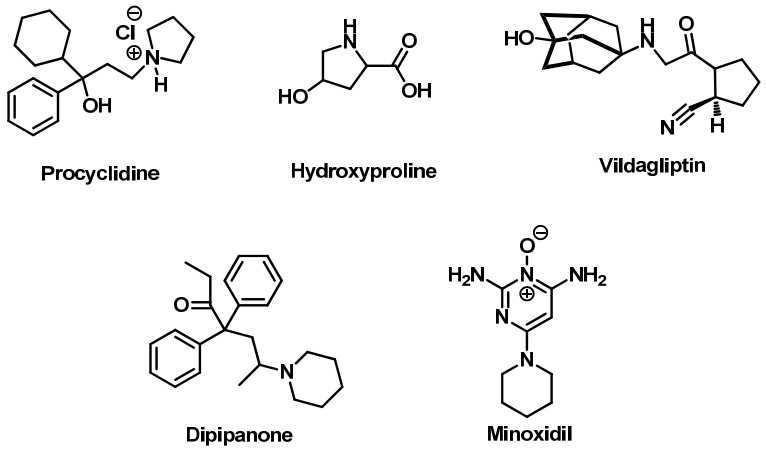


Figure 1. Pharmacologically relevant pyrrolidine and piperidine.

Dipipanone is a derivative of piperidine used as analgesic [34]. Narcolepsy is a chronic neurological disorder caused by the brain's inability to regulate sleep-wake cycles normally. People with narcolepsy often experience disturbed nocturnal sleep and an abnormal daytime sleep pattern. Methylphenidate, a derivative of piperidine used in the treatment of narcolepsy [35,36]. One of the derivatives of piperidine, ethylphenidate is a potent psychostimulant that act as both a dopamine reuptake inhibitor and norepinephrine reuptake inhibitor, meaning it effectively boosts the levels of the norepinephrine and dopamine neurotransmitters in the brain, by binding to, and partially blocking the transporter proteins that normally remove those monoamines from the synaptic cleft [37].

Osteoporosis is a progressive bone disease that is characterized by a decrease in bone mass and density and that leads to an increased risk of fracture. The form of osteoporosis is most common in women after menopause. Raloxifene is a derivative of piperidine used as a drug for the treatment of osteoporosis [38-40]. Androgenic alopecia is hair loss that occurs due to an underlying susceptibility of hair follicles to androgenic miniaturization. It is the common cause of hair loss and will affect upto 70% of men and 40% of women at some point in their lifetime. Minoxidil, a derivative of piperidine used to treat baldness and hair loss [41,42]. The structures of pharmacological important compounds possess pyrrolidine/ piperidine moieties are shown in Figure 1.

In the view of the above remarkable considerations, an attempt has been made to synthesize 2-hydroxypyrrolidine/ piperidine derivatives. Putta *et al.* have reported the synthesis and characterization of 2-hydroxypyrrolidine derivatives using cerium chloride as catalyst [43]. In the present study, we have made an attempt to synthesize 2-hydroxypyrrolidine and 2-hydroxypiperidine derivatives without catalyst and the results are not encouraging. Hence an alternate catalyst ($FeCl_3$. $6H_2O$) was employed to get the target products.

2. Experimental

2.1. Instrumentation

All the reagents were obtained from commercial suppliers and used without any further purification unless otherwise noted. Melting points were determined on an EZ-Melt automated melting point apparatus without corrections. All the reactions were carried out under the inert atmosphere of nitrogen. Analytical TLC was performed on pre-coated aluminum sheets of silica ($60F_{254}$) and visualized by short-wave UV light at λ 254 nm. Flash column chromatography was carried out on silica gel (230-400 mm) and semi-automated purification was carried out on a Biotage SP1 purification system, using SNAP cartridges. Solvent systems are reported by column volume (CV) with the solvent flow rate as stated.

Absorption maxima (ν_{max}) are quoted in wave numbers (cm^{-1}). ^1H NMR spectra were recorded on Bruker400 MHz using an internal deuterium lock. Chemical shifts are expressed in ppm, the following internal references were used $CDCl_3$ (H: 7.26 ppm), CD_3OD (H: 3.32 ppm) and DMSO-d_6 (H: 2.50 ppm). ^{13}C NMR spectra were recorded on 100 MHz using an internal deuterium lock. The following internal references were used: $CDCl_3$ (C: 77.0 ppm), CD_3OD (C: 49.0 ppm) and DMSO-d_6 (C: 39.5 ppm). LC/MS analyses were performed using ESI/APCI, with an ATLANTISC 18column (50×4.6 mm - 5 µm) and a flow rate of 1.2 mL/min. UV detection was at 215 nm. The elemental analysis was performed on vario MICRO CHNS analyzer.

2.2. Procedure for the synthesis of compounds 4a-m

To a solution of 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine (**3a**) (200 mg, 1.18 mmol) in acetonitrile (5 mL), 2,3-dihydrofuran (**2a**) (99 mg, 1.4 mmol) was added followed by ferric chloride hexahydrate ($FeCl_3.6H_2O$) (0.59 mmol) at 0°C. The reaction mixture was kept in an oil bath maintained at 60°C and stirred well for 30 min. Progress of the reaction was continuously monitored by LC/MS. The reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4 and concentrated by vacuum. The crude mass (**4a**) obtained was purified by column chromatography packed with 60/120 silica gel and eluted with 25-35% ethyl acetate in petroleum ether. The above procedure was employed for the preparation of remaining compounds **4b-m**.

1-[5-(Trifluoromethyl)-1, 3, 4-thiadiazol-2-yl]pyrrolidin-2-ol (**4a**): Color: White solid. Yield: 30 mg, 90%. M.p.: 205.5-206.3 °C. ^1H NMR (400 MHz, DMSO-d_6, δ, ppm):9.21 (d, = 5.0 Hz, 1H, O*H*), 5.45-5.42 (q, *J* = 4.0 Hz, 1H, -C*H*-OH), 3.83-3.74 (m, *J* = 8.0 Hz, 2H, -N-CH_2), 2.15-2.09 (m, *J* = 3 Hz, 1H, O-CH-CH_2), 2.01-1.94 (m, *J* = 4 Hz, 3H, N-CH_2-CH_2+O-CH-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 172.09 (C-2), 120.79 (C-5), 118.09 (C-11), 87.16 (C-7), 67.45 (C-10), 32.04 (C-8), 23.81 (C-9). Anal. calcd. for $C_7H_8F_3N_3OS$: C, 35.15, H, 3.37, N, 17.57. Found: C, 35.49, H, 3.36, N, 17.68%. LC-MS (*m/z*): 240.2 (M+1).

1-(1,3,4-Thiadiazole-2-yl)pyrrolidine-2-ol (**4b**): Color: White crystalline solid. Yield: 25 mg, 92%. M.p.: 135-138 °C. ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 9.06 (d, *J* = 7.0 Hz 1H, -O*H*), 8.01 (s, 1H, -S-C*H*-N), 5.36-5.34 (dd, *J* = 6.0 Hz, 1H, -C*H*-*OH*), 3.80-3.70 (m, *J* = 8.0 Hz, 2H, -N-CH_2), 2.14-2.09 (m, *J* = 3.0 Hz, 1H, O-

CH-CH_2), 1.99-1.82 (m , J = 3.0 Hz, 3H, N-CH$_2$-CH_2+O-CH-CH_2). ^{13}C NMR (100 MHz, CDCl$_3$, δ, ppm): 183.45 (C-5), 159.13 (C-2), 86.52 (C-7), 67.46 (C-10), 32.36 (C-8), 24.01 (C-9). Anal. calcd. for $C_6H_9N_3OS$: C, 42.09, H, 5.30, N, 24.54. Found: C, 42.06, H, 5.10, N, 25.10%. LC-MS (*m/z*): 172.2 (M+1).

1-(1,2,4-Thiadiazol-5-yl)pyrrolidin-2-ol (**4c**): Color: White crystalline solid. Yield: 23 mg, 88 %. M.p.: 150-152 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 9.08 (d, J = 7.0 Hz, 1H, -OH), 8.01 (s, 1H, -N-CH-N), 5.37-5.33 (m, J = 3.0 Hz, 1H, -CHOH), 3.79-3.71 (m, J = 7.0 Hz, 2H, N-CH_2), 2.15-2.08 (m, J = 3.0 Hz, 1H, O-CH-CH_2), 2.00-1.90 (m, J = 2.0 Hz, 3H, N-CH$_2$-CH_2+O-CH-CH_2). ^{13}C NMR (100 MHz, CDCl$_3$, δ, ppm): 183.49 (C-5), 158.79 (C-3), 86.54 (C-7), 67.49 (C-10), 32.28 (C-8), 23.99 (C-9). Anal. calcd. for $C_6H_9N_3OS$: C, 42.09, H, 5.30, N, 24.54. Found: C, 42.06, H, 5.10, N, 25.10%. LC-MS (*m/z*): 172.2 (M+1).

Ethyl-2-(2-hydroxypyrrolidin-1-yl)-1, 3-thiazole-4-carboxy late (**4d**): Color: White solid. Yield: 28 mg, 95%.M.p.: 78-80 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 8.49 (d, J = 8.0 Hz, 1H, -OH), 7.61 (s, 1H, -S-CH-C), 5.40-5.38 (q, J = 4.0 Hz, 1H, -CH-OH), 4.24-4.17 (q, J = 7.0 Hz, 2H, -O-CH_2), 3.75-3.71 (q, J = 7.0 Hz 2H, -N-CH_2), 2.14-2.08 (m, J = 4.0 Hz,1H, O-CH-CH_2) 1.99-1.92 (m, J = 5 Hz, 3H, N-CH$_2$-CH_2+O-CH-CH_2), 1.23 (t, J = 7 Hz, 3H, -CH_3). ^{13}C NMR (100 MHz, CDCl$_3$, δ, ppm): 167.82 (C-2), 161.50 (C-4), 142.88 (C-5), 117.61 (C-11), 88.37 (C-7), 66.94 (C-10) 61.05 (C-13), 32.27 (C-8), 24.29 (C-9), 14.27 (C-14). Anal. calcd. for $C_{10}H_{14}N_2O_3S$: C,49.57, H, 5.82, N, 11.56. Found: C, 48.87, H, 5.58, N, 11.66%. LC-MS (*m/z*): 241 (M+1).

2-(2-Hydroxypyrrolidin-1-yl)-N-(1-phenylethyl)-1, 3-thiazole-4-carboxamide (**4e**): Color: White solid. Yield: 20 mg, 80 %. M.p.: 135- 138 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 8.15 (d, J = 8.0 Hz, 1H, -OH), 7.35-7.27 (m, 6H, S-CH-C+Ar-H), 5.69 (s, 1H, -NH), 5.51-5.50 (m, 1H, -NH-CH-Ph), 5.07-5.03 (q, J = 7.0 Hz, 1H, -CH-OH), 3.74 (t, J = 6.0 Hz,2H, -N-CH_2), 2.14-2.10 (q, J = 6.0 Hz, 1H, O-CH-CH_2), 1.99-1.95 (q, J = 5.0 Hz, 1H, O-CH-CH_2), 1.85-1.79 (m, J = 6.0 Hz, 2H, -N-CH$_2$-CH_2) 1.49-1.47 (dd, J = 7.0 Hz, 3H, -CH_3). ^{13}C NMR (100 MHz, CDCl$_3$, δ, ppm): 167.21 (C-2), 166.81 (C-4), 160.47 (C-5), 145.66 (C-11), 143.13 (C-10), 48.49 (C-15), 32.26 (C-8), 24.44 (C-9), 21.84 (C-16). Anal. calcd. for $C_{16}H_{19}N_3O_2S$: C, 60.54, H, 6.03, N, 13.24. Found: C, 58.36, H, 5.86, N, 12.76%. LC-MS (*m/z*): 318.2 (M+1).

(2-(2-Hydroxypyrrolidin-1-yl)thiazol-4-yl) (piperidin-1-yl) methanone (**4f**): Color: White solid. Yield: 28 mg, 95 %. M.p.: 165- 168 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 8.35 (d, J = 8.0 Hz, 1H, -OH), 7.03 (s, 1H, S-CH-C), 5.40-5.37 (q, J = 4.0 Hz, 1H, -N-CH), 3.72 (t, J = 7.0 Hz, 2H, -N-CH_2), 3.54 (m, 4H, -N-CH_2piperidine ring), 2.12-2.06 (m, 2H, -O-CH-CH_2), 1.95-1.90 (m, 2H, -N-CH$_2$-CH$_2$CH_2 piperidine ring), 1.84-1.74 (m, 4H, -N-CH$_2$-CH_2piperidine ring), 1.58-1.47 (m, 2H, -O-CH$_2$-CH_2-). ^{13}C NMR (100 MHz, CDCl$_3$, δ, ppm): 167.26 (C-2), 163.45 (C-4), 146.38 (C-5), 111.97 (C-11), 86.50 (C-7), 67.08 (C-10), 48.13 (C-15), 43.60 (C-19), 32.27 (C-8), 26.56 (C-16), 25.59 (C-18), 4.50 (C-24), 23.42 (C-17). Anal. calcd. for$C_{13}H_{19}N_3O_2S$: C, 55.49, H, 6.81, N, 14.93. Found: C, 54.62, H, 6.68, N, 13.39%. LC-MS (*m/z*): 282.2 (M+1).

2-(2-Hydroxypyrrolidin-1-yl)-N-(propan-2-yl)-1, 3-thiazol-4-carboxamide (**4g**): Color: White solid. Yield: 28 mg, 95 %. M.p.: 157- 160 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 8.30 (s, 1H, -OH), 7.30 (s, 1H, S-CH-C), 5.38 (s, 1H, -NH), 4.03-3.98 (q, J = 6.0 Hz, 1H, -N-CH-OH), 3.64 (t, J = 7.0 Hz, 1H, -NH-CH), 3.65-3.62 (m, 2H, -N-CH_2), 2.00-1.90 (m, J = 2.0 Hz, 4H, O-CH-CH_2+-N-CH-CH_2), 1.14 (m, 6H, -CH_3-CH-CH_3). ^{13}C NMR (100 MHz, CDCl$_3$, δ, ppm): 167.37 (C-2), 161.02 (C-4), 146.17 (C-5), 112.70 (C-11), 84.69 (C-7), 69.19 (C-10), 41.19 (C-15), 30.88 (C-8), 24.51 (C-9), 23.05 (C-16), 22.80 (C-17). LC-MS (*m/z*): 256.2 (M+1).

N-(Butan-2-yl)-2-(2-hydroxypyrrolidin-1-yl)-1, 3-thiazole-4-carboxamide (**4h**): Color: White solid. Yield: 25 mg, 90 %. M.p.: 149- 151 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 8.33 (d, J = 8.0 Hz, 1H, -OH), 7.35 (s, J = 9.0 Hz, 1H, -S-CH-C), 7.29 (s, 1H, -NH-), 5.55-5.51 (m, 1H, -CH-OH), 3.87-3.85 (m, 1H, -NH-CH), 3.75- 3.72 (m, 2H, -N-CH_2), 2.14-2.08 (m, 1H, -O-CH-CH_2), 1.99-1.95 (m, 1H, -O-CH-CH_2), 1.85-1.77 (m, 2H, -N-CH$_2$-CH_2), 1.52-1.40 (m, 2H, CH$_3$-CH_2-), 1.13-1.09 (m, 3H, -CH-CH_3), 0.86 (m, 3H, -CH$_2$-CH_3). ^{13}C NMR (100 MHz, CDCl$_3$, δ, ppm): 167.10 (C-2), 160.72 (C-4), 145.99 (C-5), 112.96 (C-11), 86.22 (C-7), 67.08 (C-10), 46.39 (C-15), 32.29 (C-8), 29.68 (C-16), 24.46 (C-9), 20.40 (C-17), 10.38 (C-18). LC-MS (*m/z*): 270.2 (M+1).

1-(5-(Trifluoromethyl)-1, 3, 4-thiadiazol-2-yl)piperidin-2-ol (**4i**): Color: Off-white solid. Yield: 25mg, 85%. M.p.: 182.5-184.3 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 9.21 (d, J = 5.0 Hz, 1H, OH), 4.81- 4.77 (m, 1H, -CH-OH), 3.61-3.43 (q, J = 7.0 Hz, 2H, -N-CH_2), 1.82-1.76 (m, 2 H, O-CH-CH_2) 1.60-1.54 (m, 4 H, N-CH$_2$-CH_2+O-CH-CH2-CH_2). ^{13}C NMR (100 MHz, CDCl$_3$, δ, ppm):171.18 (C-2), 121.79 (C-5), 118.19 (C-12), 87.22 (C-7), 67.45 (C-11), 32.04 (C-8), 23.81 (C-10), 21.55 (C-9). Anal. calcd. for $C_8H_{10}F_3N_3OS$: C, 37.94; H, 3.98; N, 16.59. Found: C, 37.14; H, 3.86; N, 16.65%. LC-MS (*m/z*): 254.2 (M+1).

1-(1, 3, 4-Thiadiazol-2-yl)piperidin-2-ol (**4i**): Color: White solid. Yield: 24 mg, 87%. M.p.: 125-127 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 9.02 (d, J = 7.0 Hz 1H, -OH), 8.01 (s, 1H, -S-CH-N), 4.78- 4.74 (m, 1H, -CH-OH), 3.61-3.43 (q, J = 7.0 Hz, 2H, -N-CH_2), 1.82-1.75 (m, 2 H, O-CH-CH_2) 1.58-1.47 (m, 4 H, N-CH$_2$-CH_2+O-CH-CH2-CH_2). ^{13}C NMR (100 MHz, CDCl$_3$, δ, ppm): 183.45 (C-5), 159.13 (C-2), 86.52 (C-7), 67.46 (C-11), 32.36 (C-8), 24.01 (C-10), 21.05 (C-9). Anal. calcd. for $C_7H_{11}N_3OS$: C, 45.39, H, 5.99, N, 22.68. Found: C, 45.26, H, 5.82, N, 22.50%. LC-MS (*m/z*): 186.2 (M+1).

1-(1,2,4-Thiadiazol-5-yl)piperidin-2-ol (**4k**): Color: White crystalline solid. Yield: 24 mg, 87 %. M.p.: 140-141 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 9.02 (d, J = 7.0 Hz, 1H, -OH), 8.11 (s, 1H, -N-CH-N), 4.80- 4.76 (m, 1H, -CH-OH), 3.61-3.43 (q, J = 7.0 Hz, 2H, -N-CH_2), 1.87-1.81 (m, 2 H, O-CH-CH_2) 1.71-1.67 (m, 4 H, N-CH$_2$-CH_2+O-CH-CH2-CH_2). ^{13}C NMR (100 MHz, CDCl$_3$, δ, ppm): 183.49 (C-5), 158.79 (C-3), 86.54 (C-7), 67.49 (C-11), 32.28 (C-8), 23.99 (C-10), 21.05 (C-9). Anal. calcd. for $C_7H_{11}N_3OS$: C, 45.39, H, 5.99, N, 22.68. Found: C, 45.20, H, 5.88, N, 22.82%. LC-MS (*m/z*): 186.2 (M+1).

Ethyl 2-(2-hydroxypiperidin-1-yl)thiazole-4-carboxylate (**4l**): Color: White solid. Yield: 32 mg, 93%. M.p.: 70-72 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 8.57 (d, J = 8.0 Hz, 1H, -OH), 7.62 (s, 1H, -S-CH-C), 4.78- 4.74 (m, 1H, -CH-OH), 4.24-4.19 (q, J = 7.0 Hz, 2H, -O-CH_2), 3.81-3.43 (q, J = 7.0 Hz, 2H, -N-CH_2), 1.82-1.75 (m, 2 H, O-CH-CH_2) 1.58-1.47 (m, 4 H, N-CH$_2$-CH_2+O-CH-CH2-CH_2), 1.46- 1.42 (t, J = 7 Hz, 3H, -CH_3). ^{13}CNMR (100 MHz, CDCl$_3$, δ, ppm): 167.48 (C-12), 161.51 (C-5), 142.79 (C-3), 117.72 (C-2), 83.38 (C-7), 64.99 (C-11) 61.08 (C-13), 30.73 (C-8), 24.87 (C-10), 21.55 (C-9), 14.28 (C-14). Anal. calcd. for $C_{11}H_{16}N_2O_3S$: C, 51.55, H, 6.29, N, 10.93. Found: C, 51.38, H, 6.38, N, 11.06%. LC-MS (*m/z*): 257.2 (M+1).

2-(2-Hydroxypiperidin-1-yl)-N-isopropylthiazole-4-carbox amide (**4m**): Color: White solid. Yield: 28 mg, 95 %. M.p.: 148-150 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 8.30 (s, 1H, -OH), 7.30 (s, 1H, S-CH-C), 5.38 (s, 1H, -NH), 4.03-3.98 (q, J = 6.0 Hz, 1H, -N-CH-OH), 3.64 (t, J = 7.0 Hz, 1H, -NH-CH), 3.65-3.62 (m, 2H, -N-CH_2), 2.00-1.90 (m, J = 2.0 Hz, 4H, O-CH-CH_2+-N-CH$_2$-CH_2), 1.58-1.47 (m, 2 H, O-CH-CH2-CH_2)1.14 (m, 6H, -CH_3-CH-CH_3). ^{13}C NMR (100 MHz, CDCl$_3$, δ, ppm): 167.37 (C-12), 161.02 (C-5), 146.17 (C-3), 112.70 (C-2), 84.69 (C-7), 69.19 (C-11), 41.19 (C-14), 30.88 (C-8), 24.51 (C-10), 23.05 (C-15), 22.80 (C-16), 21.07 (C-9). LC-MS (*m/z*): 270.2 (M+1).

3. Results and discussion

In this study, a series of 2-hydroxypyrrolidine and piperidine derivatives were synthesized by reacting different heterocyclic amine (**3a**-**h**) and 2,3-dihydrofuran (**2a**) using $FeCl_3.6H_2O$ as catalyst. Heterocyclic amines (**3a**-**h**) and compound **2a** reacted leads to 2-hydroxypyrrolidine derivatives (**4a**-**h**) through the formation of oxonium ion. The formation of oxonium ion in the first step occurs through the binding of oxygen atom of compound **2a** with the catalyst.

Table 1. Effect of solvents on reaction compound **2a** with **3a**.

Entry	Solvents	% Yield of compound 4a [a]
1	Toluene	22
2	NMP	NR
3	DMF	Traces
4	THF	NR
5	1,4-Dioxane	30
6	Acetonitrile	90

[a] Reaction conditions: catalyst (0.5 equiv.), **3a** (1 equiv.), **2a** (1.2 equiv.), 60 °C (2-3 h), solvents (10 vol.), NR = No result.

Table 2. Effect of temperature on reaction compound **2a** with **3a**.

Entry	Temp. (°C)	% Yield of compound 4a [a]
1	RT	NR
2	40	NR
3	50	Traces
4	60	90
5	70	40
6	80	Dec.
7	100	Dec.

[a] Reaction conditions: **3a** (1 equiv.), **2a** (1.2 equiv.), catalyst (0.2 equiv.), (2-3 h), solvents (acetonitrile 10 vol.). NR = No result.

Table 3. Effect of catalyst on reaction compound **2a** with **3a**.

Entry	Catalyst	% Yield of compound 4a [a]
1	$HgCl_2$	NR
2	$CeCl_3.7H_2O$	75
3	$InCl_3$	NE
4	SmI_2	NR
5	$HgCl_2$	NE
6	$FeCl_3.6H_2O$	90
7	$SnCl_2$	40

[a] Reaction conditions: **3a** (1 equiv.), **2a** (1.2 equiv.), catalyst (0.2 equiv.), 60 °C (2-3 h), solvents (10 vol.). NE = Not expected, NR = No result.

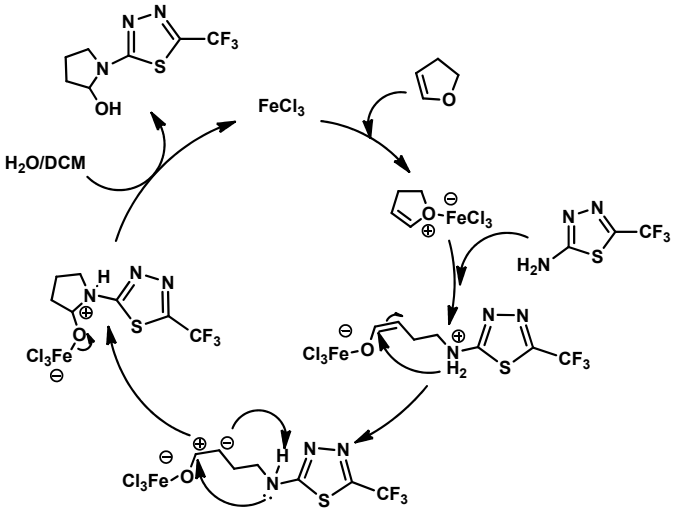


Figure 2. Mechanism of the cyclisation.

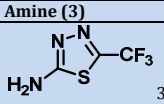
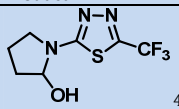
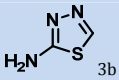
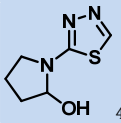
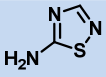
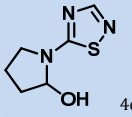
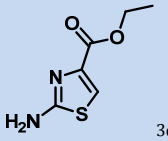
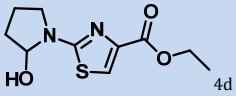
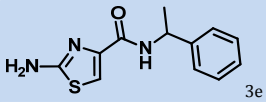
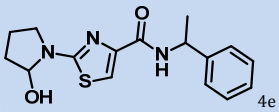
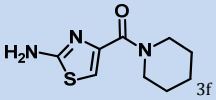
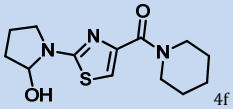
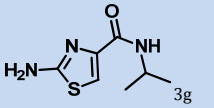
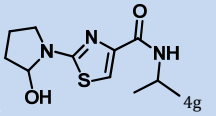
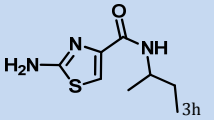
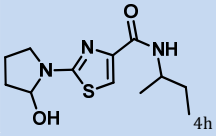
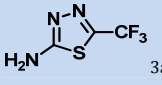
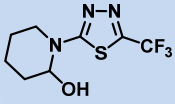
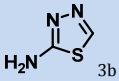
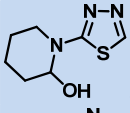
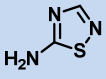
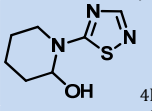
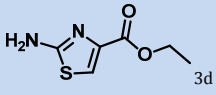
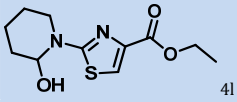
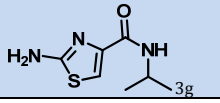
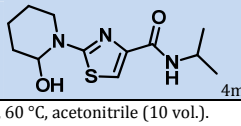
The oxonium ion thus formed was undergone cleavage by the approach of amino group at the 5thposition of compound **2a** leads to ring opening in the step 2. In the step 3 ring closure occurs through *N*-atom of compound **3a** followed by hydrolysis yielded the product (Figure 2). In the present study, C-N linkage made through $FeCl_3.6H_2O$ catalyst with excellent yield. $FeCl_3.6H_2O$ showed the remarkable catalytic activity than $CeCl_3.7H_2O$ which has been reported earlier. Furthermore a series of piperidine derivatives (**4i-m**) were synthesized by treating 3,4-dihydro-2*H*-pyran (**2b**) and various heterocyclic amines (**3a-3d** and **3g**).

Our initial attempt is to synthesize 1-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)pyrrolidin-2-olusing5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine and 2,3-dihydrofuran in the presence of cerium(III)chloride heptahydrate as catalyst and acetonitrile as solvent. In this condition, we observed the formation of required product but the yields are very less in the case of some of the primary amine. We changed the solvents (Table 1) and temperature (Table 2), but results are not much encouraging. Next, we focused the use of different catalyst. We screened a series of catalysts Table 3. From the Table 3, it is observed that ferric chloride hexahydrate catalyst resulted better yield than the others. Thus, our optimal conditions were 1 equiv. of primary amine 1.2 equiv. of 2,3-dihydrofuran, 0.2 equiv. of catalyst and acetonitrile as solvent. The structures of the compounds **4a-m** are shown in Table 4.

4. Conclusion

We have reported a series of 2-hydroxypyrrolidine and piperidine derivatives. Elemental analysis and melting point determination of the synthesized compound were reported.

Table 4. List of products and their corresponding reactants.

Entry	Reactant 1 (2)	Amine (3)	Product	Isolated yield (%) [a]
1	2a	 3a	 4a	9
2	2a	 3b	 4b	92
3	2a	 3c	 4c	88
4	2a	 3d	 4d	95
5	2a	 3e	 4e	80
6	2a	 3f	 4f	95
7	2a	 3g	 4g	92
8	2a	 3h	 4h	90
9	2b	 3a	 4i	88
10	2b	 3b	 4j	92
11	2b	 3c	 4k	92
12	2b	 3d	 4l	87
13	2b	 3g	 4m	90

[a] Reaction conditions: $FeCl_3.6H_2O$ (0.2 equiv.), **3a** (1 equiv.), **2a** (1.2 equiv.), 2-3 h, 60 °C, acetonitrile (10 vol.).

Spectral analyses of the compound were found to match with the proposed structure. Among the various solvent and catalyst used acetonitrile and $FeCl_3$. $6H_2O$ were found to be effective solvent and catalyst respectively. It is revealed from the reaction conditions, the product formation favours at 60 °C. The compounds thus synthesized using this methodology can be useful in the field of medicinal chemistry. The biological evaluation and Structure Activity Relationship studies of the newly synthesized compounds will be done in due course and communicated shortly.

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