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Synthesis and biological evaluation of novel spirocyclic β-lactams from reaction of pyrrolidine-2-carboxylic acid and benzyl amine

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ABSTRACT

A practical synthesis of spirocyclic 2-azetidinones or β–lactams (rotamers) starting from natural proline is described. α- Hydroxymethyl-N-Boc proline **(4)** has been converted via benzyl amide **(5)** and spiro-fused 2-azetidinones **(6)** into 2-(benzyl)-2,5-diaza-spiro[3.4] octan-1-one **(7)** on Boc deprotection. Which on further N-alkylations with various 2-chloromethyl pyridines to yield N-alkylated title compounds **(8a-e).** ^{1}H NMR and ^{13}C NMR clearly indicated that spiro- β -lactams are in rotamers.

KEYWORDS

Spiro- β -lactams;
α- Hydroxymethyl-N-Boc proline;
Synthetic intermediates.

INTRODUCTION

2-Azetidinones, commonly known as β-lactams, are the key structural motifs in the most widely used class of antibiotics, i.e. β-lactam antibiotics such as penicillins, cephalosporins, carbapenems, etc. Whether isolated from natural sources or synthesized chemically, penicillins and cephalosporins are marked by high efficacy and safe toxicological profiles and are still the most commonly used antibiotics the world over[1]. The resistance of pathogenic bacteria to β-lactam antibiotics has an important incidence in human infections. As a consequence, in the last few years many research groups have been actively involved in improving the microbiological activity of antibacterial agents, as well as finding β-lactamase inhibitors[2], and exploring new β-lactam containing ring systems. In particular, spirocyclic β-lactams have, at present, become the center of attraction as they exhibit cholesterol absorption inhibiting (CAI) activity[3,4], antiviral[5] and antibacterial properties[6], serve as efficient β-turn nucleators[7], behave as β-turn mimetics[8] and precursors of α,α-disubstituted β -amino acids[9]. Very recently, β-lactam antibiotics have been shown to offer neuroprotection by increasing glutamate transporters expression via gene activation[10]; in addition, the discoveries of new biologically active β-lactams such as cholesterol acyl transferase inhibitors[11–13], thrombin inhibitors[14], human cytomegalovirus protease inhibitors[15], matrix-metallo protease inhibitors[16], inhibitors of human leukocyte elastase (HLE)[17,18] and cysteine protease[19,20] and apoptosis inductors[21,22] have provided much needed motivation for continuous development of new β-lactam systems. Most synthetic efforts to form spiro-β-lactams utilize cycloaddition reactions. The cycloaddition usually uses ketene-imine[23]. Although, considerable synthetic progress has been made in the area of mono and bicyclic β-lactam antibiotics in recent years, the discovery and development of new antibacterial agents with enhanced bioactivity and greater stability toward β-lactamases still remains an important endeavor for medicinal chemists. Also, the widespread incidence of an-

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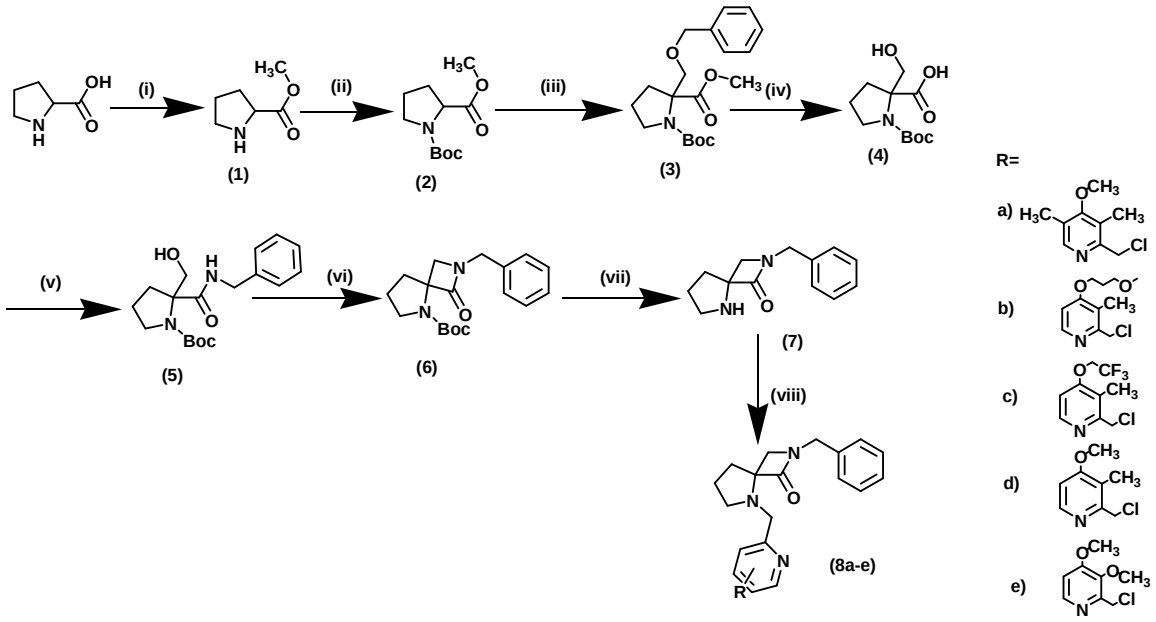
tibacterial resistance to β-lactam antibiotics caused by β-lactamase formation has provoked a growing interest in the development of effective β-lactamase inhibitors. In addition, the search for novel candidates with different biological activities still remains a field of much interest. The synthesis of β-lactams having a small fused ring is of interest since the large strain of the ring should substantially alter the reactivity of β-lactams. Several approaches for the synthesis of spiro-β -lactams have been described in literature. In this paper, we present the synthesis of spiro-β-lactam **(6)** and spiro-β-lactam derivatives **8(a-e)**, from 2-hydroxymethyl-4-hydroxybenzyl amide **(5)** with TPP/DEAD (scheme 1).

RESULTS AND DISCUSSION

All reagents used were commercial grade; melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on potassium bromide disks on a perkin-Elmer 383 spectrophotometer. ^{1}H NMR spectra were obtained on a varian 400 MHz instrument with TMS as internal standard and chemical shifts are expressed δ ppm solvent used id $CDCl_3$ & $DMSOd_6$ and mass spectrum on a Hewelett Packard mass spectrometer operating at 70ev, purity of the compounds were checked by TLC, which is performed with.E.Merck precoated silica gel plates (60F-254) with



Reagents and conditions: (i) MeOH/HCl/ 0 0C- RT(ii) TEA /(BOC)2O /THF (iii) NaH/ Benzyloxy methyl chloride 0 ^{0}C- RT- Rt (iv) 10%-Pd/C, LIOH,Water,THF, MeOH (v) HOBT,EDC,benzyl amine, Diisopropyl ethyl amine.(vi) Di tert butyl azadicarboxylate,TPP,Diethyl ether (vii) TFA (viii) Chloro comp,Potassium carbonate,DMF, at 70 ^{0}C.

Scheme 1 : Synthesis of The formation of spiro ß-lactam(8a-e) .

iodine as a developing agent. Acme, India silica gel, 60-120 and 230-400 mesh for column chromatography is used. All compounds are recrystalised in ethanol and ethylacetate.

Pyrrolidine-2-carboxylic acid methyl ester **(1)** was prepared by the reaction of pyrrolidine-2-carboxylic acid in methanolic hydrochloric acid, protection wih Boc anhydride to yields N-Boc protected pyrrolidine-2-carboxylic acid methyl ester **(2).** Which on deprotonated with NaH, followed by addition of benzyloxy methyl chloride, at 0^{0}C- RT afford the 2-benzyloxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester **(3)** with good yield, which on cleavage of ether linkage by using with 10%-Pd/C followed by hydrolysis with LiOH in THF:Water affords intermediate α- hydroxymethyl-N-bocproline **(4).** Further this has been converted into 2-benzylcarbamoyl-2-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester **(5)** by using with EDCI/ HOBt and benzyl amine. Formation of the β-lactam was accomplished by intramolecular Mitsunobu reaction with DEAD and PPh3,[23] furnishing the molecular scaffold 2-benzyl-1-oxo-2,5-diaza-spiro[3.4]octane-5-carboxylic acid tert-butyl ester **(6)**. Which on Boc deprotecton by using with TFA/DCM to afford the

deboc compound 2-benzyl-2,5-diaza-spiro[3.4]octan-1-one **(7).** Finally, the N-alkylated spiro-β-lactams compounds **(8a-e)** were prepared by alkylation of **(7)** with various 2-chloromethyl pyridines by using with K2CO3 as a base in DMF at 70 ^{0}C. All the compounds were characterized by ^{1}H NMR, ^{13}C NMR, Elemental analysis, Mass and melting points. By spectral data clearly indicated that spiro- β -lactams are in rotamers.

Antimicrobial evaluation

The N-alkylated spiro-β-lactams derivatives **(8a-e)** were evaluated for their in vitro growth antibacterial activity against different microbes. The bacterial strains used were Staphylococcus aureus, Streptococcus mutans and Bacillus subtilis (all Gram positive) and Ecsherichia coli, Salmonella typhi and Pseudomonas aeruginosa (all Gram negative) using the cup diffusion technique[24,25]. The compounds were dissolved in DMSO at a concentration of 1 mg/ml. sterile nutrient agar (oxoid) was incubated with the organisms tested. Each 100 ml of the medium received 1 ml of 24 h broth culture and 3 drops of the test compounds were placed separately in cups (8 mm diameter) cut in the agar. The plates were incubated at 37 ^{o}C for 24 h, DMSO as a blank showed no inhibition zone. A solution of 0.1% of penicillin G or streptomycin sulfate in DMSO was used as the standard for Gram-Positive and Gram-negative bacteria, respectively. The resulting inhibition zone diameters (I.Z) were measured in mm. For compounds, which exhibited reasonable inhibition zones (e• 20 mm), the MIC was determined. The organisms tested were grown in suitable broth media for 24 h at 37 ^{o}C.

Antibacterial activity						
	Gram-positive bacteria			Gram-negative bacteria		
Compound	S. aureus	S. mutans	B. subtilis	E. Coli	S. typhi	P. aeruginosa
8a	18	17	12	18	10	11
8b	17	18	13	11	9	13
8c	15	16	16	12	6	11
8d	16	18	17	15	13	12
8e	19	15	18	16	11	12
Penicillin G[a]	20	19	19	16	14	17

[a]Penicillin (10 µg/disc) used as positive reference; synthesized compounds (300 µg/disc)

The results of the biological evaluation indicate that all the compounds tested were moderate active than the reference standard Penicillin G. On the basis of these results the N-alkylated spiro-β-lactams derivatives **(8a-e)** seem to be more active against S.aureus, S.Mutans and B.subtilis (Gram-positive bacteria) than S.Typhi and P.aeruginosa (Gram-negative bacteria). Further studies under Evaluation.

EXPERIMENTAL

Pyrrolidine-2-carboxylic acid methyl ester (1)

To a solution of pyrrolidine-2-carboxylic acid (10g, 8.69 mmol) in methanol (75 ml) was treated with dry hydrogen chloride until homogeneous. The solution was heated to the reflux temperature for 3 h. The completion of reaction was monitored by TLC, the reaction mixture was cooled to RT, concentrated methanol in vacuo. Upon cooling, the product was crystallized from the solvent, collected by filtration, washed with acetone and ether, and dried under reduced pressure to yield pyrrolidine-2-carboxylic acid methyl ester **(1)** as white solid (11.0 g, 98%), mp 171–172 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.83 (s, 3H, O-CH3), 3.68 (t, 1H, J= 5.2 Hz), 2.98 (t, 2H, J= 5.3 Hz), 2.34 (s, 1H, NH), 2.10 (q, 2H), 1.68 (m, 2H); MS (EI): m/z (M+1) 130.3, Analysis (% Cal/fou) for C6H11NO2 C: 55.80/ 55.78, H: 8.58/ 8.63, N: 10.84/ 10.65.

Pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (2)

To a solution of the pyrrolidine-2-carboxylic acid methyl ester **(1)** (10.0g, 7.74 mmol) in THF (100 mL) was added TEA (11.75g, 11.61 mmol), followed by $(Boc)_2O$ (18.5g, 8.52 mmol). The resulting solution was stirred for 6 hours at room temperature. The reaction mixture was washed with brine, and the organic layer was dried (MgSO4) and concentrated. The resulting residue was purified by silica gel column to yield **(2)** as clear oil (16.5 g, 93%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.57 (t, 1H, J=7.6 Hz), 3.81 (s, 3H, O-CH3), 3.58 (t, 2H, J=5.4 Hz), 2.13 (m, 2H), 1.65 (m, 2H), 1.53 (s, 9H, 3CH3); MS (EI): m/z (M+1) 230.2, Analysis (% Cal/fou) for C11H19NO4, C: 57.62/ 57.73, H: 8.35/ 8.23, N: 6.11/ 6.05.

2-Benzyloxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (3)

To a solution of the pyrrolidine-1,2-dicarboxylic

acid 1-tert-butyl ester 2-methyl ester **(2)** (5.0g, 2.17 mmol) in THF (50 mL) was added sodium hydride (0.92 g, 60% dispersion in mineral oil, 4.26 mmol) portion wise at 0 °C, stirred for 15 min, benzyloxy methyl chloride (3.73, 2.38 mmol) in THF (50 mL) was added slowly drop wise over 20 min. The resultant solution was stirred at room temperature for 3 h. Water (100 mL) was added and the aqueous phase was extracted with ether (3 x 100 mL). The combined organic phase was washed with brine (100 mL), dried (MgSO4) and the solvent was removed under reduced pressure. Flash chromatography of the residue using hexane : ethyl acetate, (9:1) yielded **(3)** as a off-white solid, (7.2 g, 95%), mp 174–176 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (brs, 1H), 8.50 (brs,1H), 7.35-7.27(m,5H), 4.52-4.47(m,2H), 3.79 (d, J=9.5 Hz,1H), 3.56 (d, J=9.5 Hz, 1H), 3.31-3.27 (m, 1H), 2.50-2.01 (m, 1H), 1.43-1.36 (2s, 9H); ^{13}C NMR (200 MHz, $CDCl_3$): 185.6 (*COOH), 164.7 (*COO$^{t\text{-}Bu}$), 161.2, 142.4,130.2, 130.4, 137.4, 136.2, 135.2, 130.2,130.4, 128.3, 128.6, 81.1(O*CH2Ph),76.8 (*C(CH3)3), 52.6, 32.2 (3*CH3), 17.9; MS (EI): m/z (M+1) 350.4, Analysis (% Cal/fou) for C19H27NO5, C: 65.31/ 65.28, H: 7.79/ 7.63, N: 4.01/ 4.05.

2-Hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (4)

To a solution of the 2-benzyloxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester **(3)** (5.0g, 1.43 mmol) in ethanol (50 mL) was added Pd-C (1.5g, 10%) portion wise at RT, under argon. The mixture was degassed and saturated with hydrogen. The reaction was stirred at room temperature under a hydrogen atmosphere (balloon) until completion by TLC. The catalyst was removed by filtration through celite with MeOH as the eluent, dried over $MgSO^4$, and concentrated in vacuo to yield crude product as off white solid. Then the crude product was taken in aq THF (1:1, 50 mL), was added LiOH monohydrate (0.68g, 2.86 mmol) at RT. The resultant solution was stirred at room temperature for 5 h. The reaction mixture was quenched with dilute HCl solution, extracted with ethyl acetate (3x100 mL). The combined organic phase was washed with brine (100 mL), dried (MgSO4) and the solvent was removed under reduced pressure. Purified by column chromatography using 60-120 mesh silica gel, eluted with hexane : ethyl acetate, (8: 2) yielded **(4)** as a off-white solid, (3.0 g, 85%), mp 135–137 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.80-12.29 (br s, 1H), 4.95-4.60 (brs, 1H), 3.95-3.83 (m, 1H), 3.62-3.59 (m, 1H), 3.32-3.25 (m, 1H), 2.36-2.17(m,1H),1.98-1.72 (m, 3H), 1.38-1.33 (2s, 9H) ; ^{13}C NMR (400 MHz, $CDCl_3$): 182.4 (*COOH), 158.7 (*COO$^{t\text{-}Bu}$), 82.3, 72.2 (*C(CH3)3), 62.6 (*CH2OH),45.4(*CH2N), 30.7(3*CH3), 27.4, 19.3; MS (EI): m/z (M+1) 246.3, Analysis (% Cal/fou) for C11H19NO5, C: 53.87/ 53.92, H: 7.81/ 7.83, N: 5.71/ 5.85.

2-Benzylcarbamoyl-2-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (5)

To a stirred solution of 2-hydroxymethyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester **(4)** (3.0g 1.22 mmol) in DMF (30 mL) was added HOBt (1.81g, 1.34 mmol), EDCI (1.89g, 1.22 mmol) under N2 atmosphere. The reaction mixture was stirred at room temp. For 15 mins. and then the solution of benzyl amine (1.43g, 1.34 mmol) in DMF (15ml) was added to this reaction mixture, was stirred overnight. Reaction was monitored using TLC. To this reaction mixture, 20 ml ethyl acetate was added. It was washed with 10% aqueous solution. of sodium bicarbonate. Two layers were separated properly, the ethyl acetate layer was washed with 10% HCl solution and two layers were separated. It was then washed with 10ml of brine solution. The ethyl acetate layer was dried over anhydrous sodium sulfate and evaporated in vacuum to give crude product. The residue was purified by column chromatography on silica gel (3:7 ethyl acetate/hexanes) give pure **(5)** as a white solid (3.8g, 93 % yield). mp 154–156 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (rotamers were observed) 10.94-10.84 (2s, 1H), 7.40-7.34 (m, 5H), 4.88-4.86 (m, 1H), 4.80-4.70 (m, 2H), 3.88-3.70 (m,2H), 3.50 (m,1H), 3.21 (m, 1H), 2.24 (m, 1H), 1.84-1.67 (m,3H), 1.39-1.34 (2s, 9H); ^{13}C NMR (200 MHz, $CDCl_3$) :183.1 (*CONH), 162.4 (*COO$^{t\text{-}Bu}$), 148.3, 132.4, 132.8, 133.2, 75.8*C(CH3)3),74.2, 65.6 (*CH2OH), 55.7 (3*CH2NH), 47.4, 33.2 (3CH3), 29.3,19.6; MS (EI): m/z (M+1) 335.3, Analysis (% Cal/fou) for C18H26N2O4, C: 64.65 / 64.71, H: 7.84 / 7.82, N: 8.38 / 8.25.

2-Benzyl-1-oxo-2,5-diaza-spiro[3.4]octane-5-carboxylic acid tert-butyl ester (6)

To a stirred solution of 2-benzylcarbamoyl-2-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester **(5)** (2.00 g, 0.59 mmol), triphenylphosphine (1.72 g, 0.65 mmol) in THF (20 mL) under nitrogen at room temperature was added a solution of diethyl azodicarboxylate (1.53 g, 0.88 mmol) in THF (10 mL) dropwise for 5 min with a syringe. The reaction mixture was stirred for 3 h and concentrated by rotary evaporator. The residue was diluted with 10 mL of ether and placed in refrigerator. Precipitated triphenylphosphine oxide was filtered off and the residue was further concentrated and purified by column chromatography on silica gel. (30:70 ethyl acetate/hexanes) give pure **(6)** as a white solid (1.4g, 75 % yield). mp 144–146 ^{0}C; ^{1}H NMR (500 MHz, $CDCl_3$): (rotamers were observed) 7.26-7.18 (m, 2H), 7.12-7.02 (m, 2H), 5.61&5.53 (2s, 1H), 3.90 & 3.67 (2d, j=4Hz, 1H), 3.51-3.41 (m,2H), 3.23&3.20(2d, J=4Hz, 1H), 2.40-2.36 (m,1H), 2.17-2.14 (m, 1H), 1.98-1.95 (m, 1H), 1.85-1.81 (m, 1H), 1.53 (s, 9H); ^{13}C NMR (500 MHz, $CDCl_3$): 182.3 and 182.2 (*CON), 161.4 and 161.2(*$COO^{t\text{-}Bu}$),139.2 and 139.1, 131.8,131.6,1131.3, 75.4*C(CH3)3), 70.2, 61.6, 56.4, 52.9 (*CH2N), 47.8, 32.5 (3CH3),19.7; MS (EI): m/z (M+1) 317.4, Analysis (% Cal/fou) for C18H24N2O3, C: 68.33 / 68.41, H: 7.65 / 7.62, N: 8.85 / 8.89.

2-Benzyl-2,5-diaza-spiro[3.4]octan-1-one (7)

To a solution of 2-benzyl-1-oxo-2,5-diaza-spiro[3.4]octane-5-carboxylic acid tert-butyl ester **(6)** (2.00 g, 0.63 mmol) in dry CH_2Cl_2 (20 mL) was added trifluoroacetic acid (1.29 mL, 1.58 mmol) stirred at 25°C for 3 hours. CH2Cl2 was evaporated and replaced by anhydrous toluene which was then evaporated to azeotrope excess tifluoroacetic acid. This operation was repeated three times to yield off-white solid which was dried in vacuo. Purified by filter column using 60-120 mesh silica gel, eluted with hexane : ethyl acetate, (8: 2) yielded **(7)** as a white solid, (1.26 g, 92%), 1H NMR (400 MHz, CDCl3; δ (rotamers were observed) 8.12 and 8.10 (2s, 1H), 7.32-7.18 (m, 5H), 4.56 and 4.55 (2 s, 2.4 H), 4.25 and 4.27 (2 s, 2.6 H), 3.45 and 3.44 (2 s, 2H), 3.18 and 3.15 (d,d, 2H, J = 4.1 and 4.1 Hz), 2.02-1.92 (m, 2H), 1.62-1.51 (m, 2H); ^{13}C NMR (400 MHz, CDCl3; (rotamers were observed) 180.6 and 180.4 (*CON), 139.0 and 138.8, 132.4 and 132.5, 131.6 and 131.8, 129.3 and 129.4, 71.6 and 71.8, 58.4 and 58.2, 53.3 and 53.2, 48.9 and 48.4, 43.3 and 42.8, 35.3 and 34.2, 19.4 and 19.5; MS (EI): m/z (M+1) 217.3, Analysis (% Cal/fou) for C13H16N2O, C: 72.19/ 72.31, H: 7.46/7.52, N: 12.95/ 12.85.

2-Benzyl-5-(4-methoxy-3,5-dimethyl-pyridin-2-ylmethyl)-2,5-diaza-spiro[3.4]octan-1-one (8a)

To a solution of 2-benzyl-2,5-diaza-spiro[3.4]octan-1-one **(7)** (1.00 g, 0.46 mmol) in dry DMF (50 mL) was added potassium carbonate (1.27 g, 0.92 mmol) followed by 2-chloromethyl-4-methoxy-3,5-dimethyl-pyridine (0.93 g, 0.50 mmol) stirred at 70°C for 6 hours. The completion of reaction was monitored by TLC, the reaction mixture was cooled to RT, poured in ice-cold water and extracted with diethyl ether (3x20 mL), dried (MgSO4) and the solvent was removed under reduced pressure. Purified by column chromatography using 60-120 mesh silica gel, eluted with hexane : ethyl acetate, (8: 2) yielded **(8a)** as a white solid, (1.2 g, 71%), 1H NMR (400 MHz, CDCl3; δ (rotamers were observed) 8.47 and 8.48 (2s, 1H), 7.36-7.22 (m, 5H), 4.25 and 4.24 (2s, 2H), 4.15 and 4.12 (2s, 2H), 3.95 and 3.94 (2 s, 3H), 3.48 and 3.45 (d,d, 2H, J = 4.4 and 4.4 Hz), 2.19 and 2.17 (2s, 6H), 2.12-2.04 (m, 2H), 2.02-1.97 (m, 2H), 1.88-1.77 (m, 2H); ^{13}C NMR (400 MHz, CDCl3; (rotamers were observed) 182.5 and 182.4 (*CON), 169.0 and 168.6, (*C-OCH3), 163.4, 152.3, 138.4 and 138.5, 133.6 and 133.8, 128.3 and 128.4, 119.6 and 119.8(*C-CH3),114.2(*C-CH3), 73.6 and 73.8, 54.4 and 53.0, 52.3 and 52.2, 47.9 and 48.1, 43.0 and 42.6, 35.1 and 34.0, 19.1 and 19.2,14.5 and 14.6, 10.8 and 10.6, 6.7 and 6.4; MS (EI): m/z (M+1) 366.3, Analysis (% Cal/fou) for C22H27N3O2, C: 72.30/ 72.71, H: 7.45/ 7.82, N: 11.50/ 11.45.

2-Benzyl-5-[4-(3-methoxy-propoxy)-3-methyl-pyridin-2-ylmethyl]-2,5-diaza-spiro[3.4] octan-1-one (8b)

Off-white solid (76% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (rotamers were observed) 8.44 and 8.42

(2s, 1H), 7.38-7.23 (m, 6H), 4.23 and 4.20 (2 s, 2.0 H), 4.16-3.94 (m, 4H), 3.92 (t, J = 4.3, 2H), 3.75 and 3.74 (2s, 3H,OCH3), 3.48 and 3.42 (d,d, 2H, J = 4.3 and 4.3 Hz), 2.64 and 2.63 (2s, 3H), 2.52-2.48 (m, 2H), 2.12-2.02 (m, 4H), 1.82-1.71 (m, 2H); ^{13}C NMR (400 MHz, CDCl3; (rotamers were observed) 182.8 and 182.6 (*CON), 169.3 and 168.9 (*C-OCH3), 164.6, 156.5, 139.2,138.4, 135.6 and 135.8, 128.8 and 128.6, 119.3, 118.8 (*C-CH3),115.2 (*C-CH3), 78.6,76.8, 58.4 and 58.0, 52.3 and 52.2, 47.6, 47.0, 43.0 and 42.8, 35.8,34.3, 19.6 and 19.5,14.6 and 14.4, 10.7 and 10.6, 6.8 and 6.5; MS (EI): m/z (M+1) 410.6, Analysis (% Cal/fou) for C24H31N3O3, C: 70.39/ 70.28, H: 7.63/7.56, N: 10.26/ 10.23.

2-Benzyl-5-[3-methyl-4-(2,2,2-trifluoro-ethoxy)-pyridin-2-ylmethyl]-2,5-diaza-spiro[3.4] octan-1-one (8c)

Off-white solid (72% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (rotamers were observed) 8.43 and 8.42 (2s, 1H), 7.36-7.28 (m, 5H),7.12 (t, 1H, J = 4.3), 4.32-4.18 (m, 4H), 3.92 and 3.90 (d,d, 2H, J = 4.5 and 4.4 Hz), 3.76 and 3.74 (2s, 2H), 2.44 and 2.42 (2s, 3H), 2.48-2.32 (m, 2H), 2.22-2.11 (m, 4H); ^{13}C NMR (400 MHz, CDCl3; (rotamers were observed) 179.8 and 179.6 (*CON), 166.3 and 166.4, 161.3, 159.5, 149.2,138.4 and 138.5, 135.4 and 135.5, 129.3 and 129.4, 119.3, 118.4 (*C-CH3),115.2 (*CF3), 79.6,79.8, (*CH2CF3),59.6 and 59.4, 54.3 and 54.2, 48.6, 48.2, 43.2 and 42.7, 35.7,34.4, 19.7 and 19.5,14.8 and 14.7, 10.6 and 10.5, 6.9 and 6.4; MS (EI): m/z (M+1) 420.3, Analysis (% Cal/fou) for C22H24F3N3O2, C: 63.00/ 63.08, H: 5.77/5.76, N: 10.02/ 9.98.

2-Benzyl-5-(4-methoxy-3-methyl-pyridin-2-ylmethyl)-2,5-diaza-spiro[3.4]octan-1-one (8d)

Off-white solid (68% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (rotamers were observed) 8.53 and 8.52 (dd, 1H, J = 4.2 and 4.2 Hz), 7.38-7.19 (m, 6H), 4.32 and 4.30 (2s, 2H), 4.08 and 4.02 (2 s, 2H), 3.98 and 3.97 (2s, 3H), 3.82 and 3.81 (2 s, 2H), 2.84 and 2.82 (2s, 3H), 2.49-2.36 (m, 2H), 1.89-1.73 (m, 4H); ^{13}C NMR (400 MHz, CDCl3; (rotamers were observed) 181.3 and 181.1 (*CON), 168.4 and 168.2, 163.3, 160.5, 150.2,148.4 and 148.5, 136.4 and 136.5, 128.4 and 128.5, 121.3, 120.4 and 120.5 (*C-CH3),110.2, 78.8,79.0,58.6 and 58.4, 55.3 and 55.2, 49.6, 48.8, 43.6 and 43.4, 35.8,34.2, 19.4 and 19.2,16.4 and 16.5, 6.4 and 6.2; MS (EI): m/z (M+1) 352.3, Analysis (% Cal/fou) for C21H25N3O2, C: 71.77/ 71.78, H: 7.17/ 7.16, N: 11.96/ 11.93.

2-Benzyl-5-(3,4-dimethoxy-pyridin-2-ylmethyl)-2,5-diaza-spiro[3.4]octan-1-one (8e)

Off-white solid (70% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (rotamers were observed) 8.53 and 8.54 (dd, 1H, J = 4.2 and 4.2 Hz), 7.37-7.18 (m, 6H), 4.38 and 4.28 (m, 2H), 4.05 and 4.01 (2 s, 2H), 3.93 and 3.91 (2s, 6H), 3.46 and 3.42 (2s, 2H), 1.86-1.74 (m, 4H); ^{13}C NMR (400 MHz, CDCl3; (rotamers were observed) 180.7 and 180.5 (*CON), 167.6 and 167.5, 163.5, 160.4, 153.2,147.4 and 147.6(*C-OCH3),137.4 and 137.5(*C-OCH3),129.4 and 129.5, 122.4, 121.7 and 121.6, 111.2, 77.4,74.0,58.6 and 58.4(2-O*CH3),55.3 and 52.2, 48.6, 47.8, 42.6 and 42.4, 35.8,34.2, 19.8 and 19.6,16.6 and 16.5, 6.4 and 6.1; MS (EI): m/z (M+1) 368.3, Analysis (% Cal/fou) for C21H25N3O3, C: 68.64/ 68.74, H: 6.86/ 6.96, N: 11.44/ 11.53.

CONCLUSIONS

This article describes for the synthesis and characterization of some novel spiro-β-lactam **(6)** and N-aryl spiro-β-lactam derivatives **8(a-e)**, from 2-hydroxymethyl-4-hydroxybenzyl amide **(5)** with TPP/ DEAD effectively. These N-aryl-spirocyclic β–lactams were in rotamers and characterized by ^{1}H NMR, ^{13}C NMR and Elemental analysis.

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