

A general and efficient synthesis of 3,6-diazabicyclo[3.2.1]octanes

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Abstract—A convenient and efficient synthesis of *N*⁶-substituted 3,6-diazabicyclo[3.2.1]octanes (**6a–c**) has been achieved starting from suitably substituted lactams, which were converted to nitroenamines followed by reductive cyclization to afford 3,6-diazabicyclo[3.2.1]-octane-2-ones in good yields. These bicyclic lactams were then reduced to the corresponding 3,6-diazabicyclo[3.2.1]octanes and converted to the required *N*³,*N*⁶-disubstituted 3,6-diazabicyclo[3.2.1]octanes (**7a–h**), which were screened for α_1 -adrenoceptors antagonistic activities. © 2006 Elsevier Ltd. All rights reserved.

1. Introduction

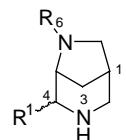
Lactams have been the subject of much study in this laboratory for creation of molecular diversity, a useful source of leads for potential bioactive agents/intermediates,^{1,2} through conversion to reactive intermediates such as lactim ethers, lactim thioethers and lactam acetals, which undergo facile reaction with both nucleophiles and electrophiles and also with bifunctional reagents. In our studies directed to the design of conformationally constrained prototypes incorporating the essential structural features of important pharmacophores,³ we were interested in the synthesis of 3,6-diazabicyclo[3.2.1]octanes (**6**). A literature survey revealed that 6-methyl-3,6-diazabicyclo[3.2.1]octane **6a** (Fig. 1) has been reported once as a conformationally rigid ethylenediamine systems from 2-azabicyclo[2.2.1]hept-5-ene via ozonolysis of the double bond to a dialdehyde followed by reductive amination using benzylamine.⁴ But this method has several limitations: (a) ozonolysis is not a very convenient reaction to carry out, (b) reductive amination was carried out in presence of sodium cyanoborohydride, which during

workup generate hydrogen cyanide gas, and (c) poor yields (18–40%). In this paper, we wish to report a convenient and efficient synthesis of 3,6-diazabicyclo[3.2.1]octanes from readily available 5-oxopyrrolidine-3-carboxylic acid methyl ester. This method also provides an easy access to the substitution at the N-3, N-6 and C-4 centre.

2. Results and discussion

A retrosynthetic analysis of compound **6** (Scheme 1) indicated the possibility of constructing 3,6-diazabicyclo[3.2.1]octanes ring through reductive cyclization of a nitroenamine of type II, which could in turn be obtained from lactam I, by activation of the amide group followed by condensation with nitroalkane.

1-Methyl-5-oxopyrrolidine-3-carboxylic acid methyl ester **1a** and 1-(2-methoxyphenyl)-5-oxopyrrolidine-3-carboxylic acid methyl ester **1b**, prepared from itaconic acid following



6a; R = Me, R¹ = H

6b; R = R¹ = Me

6c; R = 2-OMeC₆H₄, R¹ = H

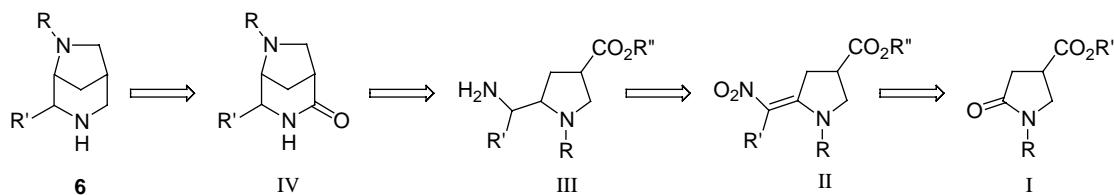
Figure 1.

Keywords: 3,6-Diazabicyclo[3.2.1]octanes; Lactams; Itaconic acid; Nitroenamine; Reductive cyclization; RBx 2258.

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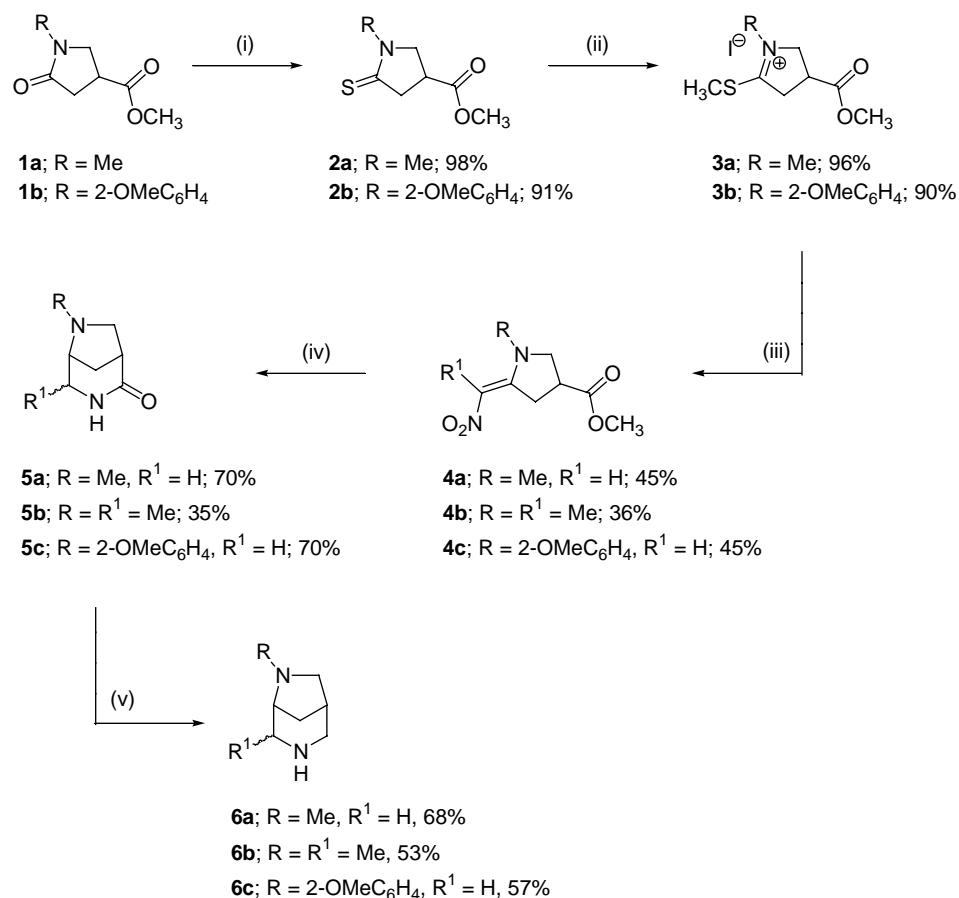


Scheme 1. Retrosynthetic approach to 3,6-diazabicyclo[3.2.1]octanes (**6**).

the procedure described in the literature,^{1d,5} were chosen as the starting material for the synthesis of 3,6-diazabicyclo[3.2.1]octanes (**6**). The lactam **1a** was treated with Lawesson's reagent to give the corresponding thiolactam **2a** in almost quantitative yields. The thiolactam **2a** was converted to methylthioimmonium iodide **3a** with excess methyl iodide in 96% yield, which on condensation with nitromethane in DMF and excess of triethylamine yielded the corresponding nitroenamine **4a** in 45% yield (Scheme 2). The nitroenamine **4a** appeared to be thermodynamically stable as the *E*-isomer as shown by NMR studies; irradiation of the olefinic proton resulted in 11% NOE enhancement for the *N*-methyl protons. Catalytic transfer hydrogenation of nitroenamine **4a** over 10% Pd–C in presence of ammonium formate in MeOH at reflux, resulted in reduction of both the double bond and the nitro group followed by in situ cyclization to furnish 6-methyl-3,6-diazabicyclo[3.2.1]octan-2-one **5a** in 70% yield. Finally, this bicyclic lactam

5a was subjected to LAH reduction in THF at reflux, which after chromatographic purification afforded 6-methyl-3,6-diazabicyclo[3.2.1]octane (**6a**) in 68% yield (Scheme 2). Analogously, the corresponding 4,6-dimethyl analogue **6b** and 6-(2-methoxyphenyl) analogue **6c** were synthesized in 53 and 57% yield, respectively, by using the appropriate lactams and nitroalkanes. Compound **6b** ($R^1 = CH_3$) was isolated as a mixture of diastereoisomers of unassigned relative configuration.

In the light of the likely benefits of restricted flexibility⁶ on the pharmacokinetic properties of bioactive agents, various 3-substituted 6-(2-methoxyphenyl)-3,6-diazabicyclo[3.2.1]octanes (**7a–h**) were prepared because of the structural analogy of 6-(2-methoxyphenyl)-3,6-diazabicyclo[3.2.1]octane nucleus (**6c**) with 1-(2-methoxyphenyl)piperazine the structural unit present in RBx 2258 (entry 9, Table 1), the analogue RBx 2258,⁷



Scheme 2. Reagents and conditions: (i) Lawesson's reagent, THF, rt, 3 h; (ii) CH₃I, PhMe or PhH, rt, 24 h; (iii) R¹CH₂NO₂, Et₃N, DMF, rt, 24 h; (iv) HCOONH₄, 10% Pd–C, MeOH, reflux, 7–10 h; (v) LAH, THF, reflux, 18 h.

which has shown good α_1 -adrenoceptor blocking activity and appear promising for the treatment of benign prostatic hyperplasia (BPH) is in phase II clinical trials.

Table 1. Preparation of 3-substituted 6-(2-methoxyphenyl)-3,6-diazabicyclo[3.2.1]octanes (**7a–h**)

Entry	Product	Yield (%) ^a	Reaction Scheme			
			Reagent	Condition		
1		78		Ref. 7		
2		70			$60\text{--}70^\circ\text{C}$	$15\text{--}18\text{ h}$
3		67		$60\text{--}70^\circ\text{C}$	$15\text{--}18\text{ h}$	
4		54		$60\text{--}70^\circ\text{C}$	$15\text{--}18\text{ h}$	
5		71		$60\text{--}70^\circ\text{C}$	$15\text{--}18\text{ h}$	
6		64		$60\text{--}70^\circ\text{C}$	$15\text{--}18\text{ h}$	
7		45		$60\text{--}70^\circ\text{C}$	$15\text{--}18\text{ h}$	
8		46		$60\text{--}70^\circ\text{C}$	$15\text{--}18\text{ h}$	
9		—		$60\text{--}70^\circ\text{C}$	$15\text{--}18\text{ h}$	

^a The yields are based on products isolated by column chromatography over silica gel.

The compounds **7a–h** (Table 1) were prepared starting from 1-(3-halopropyl)dicarboximides (**9**), which in turn were prepared by condensing various α,ω -dicarboximides (**8**) and 1-bromo-3-chloropropane according to the procedure described in literature.⁷ The compounds **9** were then condensed with 6-(2-methoxyphenyl)-3,6-diazabicyclo[3.2.1]octane (**6c**) in presence of K_2CO_3 in DMF at 60–70 °C to give 1-[6-(2-methoxyphenyl)-3,6-diazabicyclo[3.2.1]octan-3-yl]-3-[N -(α,ω -dicarboximido)]propanes **7a–h** in good yields (Table 1). Compounds **6b–c** and **7a–h** are hitherto unknown in the literature and their structures were confirmed on the basis of elemental and spectroscopic analysis.

Receptor binding assays were performed for native α_1 -adrenoreceptors. Rat submaxillary and liver membrane preparations were used to assess the affinity for $\alpha_{1\text{A}}$ and $\alpha_{1\text{B}}$ subtypes, respectively.⁸ Aliquots of membrane protein (100–200 μg) were incubated in a final volume of 250 μL assay buffer (50 mM Tris, 0.5 mM EDTA at pH 7.4) with 0.5 nM [³H]prazosin for 60 m at 28 °C. Reaction was stopped by rapid filtration on Millipore filters. Filters were dried and bound radioactivity counted. Non-specific binding was determined in the presence of 0.3 mM prazosin. Protein was assayed according to the method of protein estimation⁹ with minor modifications. All the newly synthesized analogues of RBx 2258 were screened for $\alpha_{1\text{A}}$ inhibition. However, none of these compounds have shown any remarkable activity.

3. Conclusion

In conclusion, a convenient and new approach for the synthesis of 3,6-diazabicyclo[3.2.1]octanes (**6**) has been accomplished. The key step of the synthesis involves catalytic hydrogenation, accompanied with spontaneous cyclization, of the nitroenamine **4**. These nitroenamine can be conveniently prepared in large quantities from readily available starting materials. In addition, various conformationally constrained analogues of RBx 2258 have been synthesized. However, derivatives of our novel 6-(2-methoxyphenyl)-3,6-diazabicyclo[3.2.1]octane ring systems have not shown any activity against α_1 -adrenoreceptors. The lack of activity against α_1 -adrenoceptors may be probably due to steric hindrance of the methylene bridge in the ligands–receptor interaction.

4. Experimental

4.1. General

Melting points were recorded on a Büchi B-540 melting point apparatus. Compounds were routinely checked for their purity on silica gel 60 F_{254} TLC plates and their spots were visualized by exposing them to iodine vapor, UV lamp or by spraying the plates with Dragendorff's or KMnO_4 reagents. IR spectra (ν_{max} in cm^{-1}) were recorded on Perkin Elmer Paragon-1000PC instrument and NMR (300 MHz) spectra were recorded on Bruker 300-DRX instrument as solutions using TMS as internal standard, and chemical shifts are expressed in δ units. Mass spectra were recorded

on API-3000 LCMS/MS using direct inlet system under positive ion electrospray ionization source. Elemental analyses were carried out with a Perkin Elmer 2400 analyzer and values found were within $\pm 0.4\%$ of theoretical values.

4.2. General method of lactam 1

4.2.1. 1-Methyl-5-oxopyrrolidine-3-carboxylic acid methyl ester (1a). This was prepared according to the literature method^{1d,5} starting from itaconic acid in 87% yield as a thick oil; ν_{max} (CH₂Cl₂) 1736, 1689 cm⁻¹; δ_{H} (CDCl₃) 2.67–2.71 (m, 2H), 2.87 (s, 3H), 3.26 (m, 1H), 3.56–3.76 (m, 2H), 3.76 (s, 3H); m/z 158 (M+1). Anal. Calcd for C₇H₁₁NO₃ (157.17): C, 53.49; H, 7.05; N, 8.91. Found: C, 53.52; H, 6.99; N, 9.05%.

4.2.2. 1-(2-Methoxyphenyl)-5-oxopyrrolidine-3-carboxylic acid methyl ester (1b). To a cooled (-5°C) solution of MeOH (100 mL), freshly distilled thionyl chloride (13.09 g, 0.11 mmol) was added dropwise over a period of 0.5 h, after addition was completed the resulting mixture stirred at the same temperature for 0.5 h. To this 1-(2-methoxyphenyl)-5-oxopyrrolidine-3-carboxylic acid^{5a} (23.5 g, 0.10 mmol) was added portion wise, at the same temperature, stirred for another 0.5 h and then temperature was allowed to rise to 25–30 °C and then stirred for 3 h. MeOH was removed completely under reduced pressure. The residue was dissolved in CHCl₃ (200 mL) and washed with 20% aq NaHCO₃ (3 \times 50 mL), water (1 \times 50 mL), brine (1 \times 25 mL), dried (Na₂SO₄) and filtered. The filtrate was concentrated under reduced pressure to give **1b** as white powder, yield 23.8 g (96%), mp 82–83 °C; ν_{max} (KBr) 3000, 2960, 1729, 1690, 1593, 1503, 1414 cm⁻¹; δ_{H} (CDCl₃) 2.74–2.94 (m, 2H), 3.35–3.46 (m, 1H), 3.77 (s, 3H), 3.85 (s, 3H), 3.94–3.97 (d, J =7.7 Hz, 2H), 6.94–7.00 (m, 2H), 7.24–7.30 (m, 2H); δ_{C} (CDCl₃) 174.4, 170.0, 153.9, 126.5, 125.0, 121.4, 121.0, 114.1, 56.3, 50.6, 42.5, 36.0, 31.1; m/z 250 (M+1). Anal. Calcd for C₁₃H₁₅NO₄ (249.26): C, 62.64; H, 6.07; N, 5.62. Found: C, 63.00; H, 6.13; N, 5.29%.

4.3. General method of thiolactam 2

4.3.1. 1-Methyl-5-thioxopyrrolidine-3-carboxylic acid methyl ester (2a). This was prepared according to the literature method^{1d} starting from **1a** in 98% yield as a thick oil; ν_{max} (CH₂Cl₂) 1736, 1210 cm⁻¹; δ_{H} (CDCl₃) 3.26 (s, 3H), 3.31–3.35 (m, 3H), 3.74 (s, 3H), 3.90–3.97 (m, 1H), 4.04–4.09 (m, 1H); m/z 174 (M+1). Anal. Calcd for C₇H₁₁NO₂S (173.23): C, 48.53; H, 6.40; N, 8.09. Found: C, 48.20; H, 6.55; N, 8.00%.

4.3.2. 1-(2-Methoxyphenyl)-5-thioxopyrrolidine-3-carboxylic acid methyl ester (2b). To a solution of lactam **1b** (23.65 g, 95 mmol) in dry THF (100 mL) was added Lawesson's reagent (19.19 g, 47.5 mmol) portion wise under stirring at 25–30 °C and resulting reaction mixture stirred for 4–5 h at same temperature. THF was removed under reduced pressure to obtain a viscous residue, which was dissolved in EtOAc (200 mL), washed with 10% NaHCO₃ (5 \times 50 mL), brine (30 mL), dried (Na₂SO₄) and filtered. The filtrate was concentrated under reduced pressure to give the thiolactam **2b** as off white powder,

yield 22.91 g (91%), mp 92–93 °C; ν_{max} (CH₂Cl₂) 1738, 1585, 1210 cm⁻¹; δ_{H} (CDCl₃) 3.47–3.50 (m, 3H), 3.78 (s, 3H), 3.84 (s, 3H), 4.17–4.27 (m, 2H), 7.01–7.06 (m, 2H), 7.26–7.39 (m, 2H); δ_{C} (CDCl₃) 197.9, 174.4, 158.9, 126.5, 125.6, 125.0, 121.1, 114.5, 59.5, 56.0, 50.8, 48.5, 36.5; m/z 266 (M+1). Anal. Calcd for C₁₃H₁₅NO₃S (265.33): C, 58.85; H, 5.70; N, 5.28. Found: C, 59.03; H, 5.86; N, 5.02%.

4.4. General procedure for compounds 3

4.4.1. 3-Methoxycarbonyl-1-methyl-5-methylthio-3,4-dihydro-2H-pyrrolium iodide (3a). A solution of the thiolactam **2a** (17.3 g, 100 mmol) and methyl iodide (70.95 g, 500 mmol) was stirred at 25–30 °C for 2 h, the formation of a yellow precipitate indicates the formation of the methylthioimmonium iodide. The excess of methyl iodide was removed under reduced pressure, the residue taken up in dry benzene, stirred for 10 min, the solid, which separated out was filtered, washed well with dry benzene and dry ether and dried under vacuum over P₂O₅ to give **3a** as pale yellow solid, yield 30.24 g (96%), mp 104–106 °C; ν_{max} (KBr) 2363, 2344, 1735, 1617 cm⁻¹; δ_{H} (CDCl₃) 2.94 (s, 3H), 3.45 (s, 3H), 3.68–3.74 (m, 1H), 3.80 (s, 3H), 3.94–4.02 (m, 1H), 4.26 (dd, J =10.2 Hz, 1H), 4.45 (dd, J =4.5 Hz, 1H), 4.79 (t, J =11.1 Hz, 1H); m/z 189 (M+1). Anal. Calcd for C₈H₁₄INO₂S (315.17): C, 30.49; H, 4.48; N, 4.44. Found: C, 30.59; H, 4.56; N, 4.50%.

4.4.2. 3-Methoxycarbonyl-1-(2-methoxyphenyl)-5-methylthio-3,4-dihydro-2H-pyrrolium iodide (3b). This was obtained in 90% yield as creamish-white powder by reacting methyl iodide with thiolactam **2b** according to the procedure described for compound **3a**; mp 139–141 °C; ν_{max} (KBr) 2951, 1792, 1573, 1497 cm⁻¹; δ_{H} (CDCl₃) 2.84 (s, 3H), 3.66 (m, 1H), 3.82 (s, 3H), 3.90 (s, 3H), 4.28–4.29 (m, 1H), 4.58–4.68 (m, 1H), 4.72–4.80 (m, 2H), 7.04–7.15 (m, 2H), 7.48–7.54 (m, 2H); m/z 281 (M+1). Anal. Calcd for C₁₄H₁₈INO₂S (407.27): C, 41.29; H, 4.45; N, 3.44. Found: C, 41.05; H, 4.65; N, 3.03%.

4.5. General procedure for compounds 4

4.5.1. 1-Methyl-5-nitromethylene-pyrrolidine-3-carboxylic acid methyl ester (4a). To a stirred solution of **3a** (7.88 g, 25 mmol) in dry DMF (50 mL), dry Et₃N (2.78 g, 27.5 mmol) and distilled nitromethane (7.63 g, 125 mmol) were added under nitrogen atmosphere. The reaction mixture was stirred at 25–30 °C for 12 h. DMF and excess of nitromethane were removed under reduced pressure to give a crude product, which was purified by column chromatography over silica gel (230–400 mesh) using CHCl₃–MeOH (98/2) as eluent to afford nitroenamine **4a** as yellow solid, yield 2.27 g (45%), mp 76–78 °C; ν_{max} (KBr) 1733, 1590, 1359 cm⁻¹; δ_{H} (CDCl₃) 2.87 (s, 3H), 3.23–3.33 (m, 1H), 3.63–3.69 (m, 3H), 3.73 (s, 3H), 3.84–3.89 (m, 1H), 6.63 (s, 1H); δ_{C} (CDCl₃) 174.8, 161.5, 102.1, 57.5, 51.0, 46.1, 35.5, 33.5; m/z 201 (M+1). Anal. Calcd for C₈H₁₂N₂O₄ (200.19): C, 48.00; H, 6.04; N, 13.99. Found: C, 47.98; H, 6.22; N, 14.10%.

4.5.2. 1-Methyl-5-(1-nitroethylidene)-pyrrolidine-3-carboxylic acid methyl ester (4b). This was obtained in 36% yield as thick oil by reacting nitroethane with **3a**

according to the procedure described for compound **4a**; ν_{\max} (CH₂Cl₂) 1738, 1581, 1376 cm⁻¹; δ_{H} (CDCl₃) 2.31 (s, 3H), 3.14 (s, 3H), 3.18–3.28 (m, 1H), 3.57–3.60 (m, 3H), 3.72 (s, 3H), 3.77–3.88 (m, 1H); δ_{C} (CDCl₃) 174.9, 154.1, 111.5, 57.6, 50.6, 46.5, 35.8, 32.9, 10.8; m/z 215 (M+1). Anal. Calcd for C₉H₁₄N₂O₄ (214.22): C, 50.46; H, 6.59; N, 13.08. Found: C, 50.55; H, 6.51; N, 13.17%.

4.5.3. 1-(2-Methoxyphenyl)-5-nitromethylene-pyrrolidine-3-carboxylic acid methyl ester (4c). This was obtained in 45% yield as thick yellow oil by reacting nitromethane with **3b** according to the procedure described for compound **4a**; ν_{\max} (CH₂Cl₂) 2948, 1728, 1570, 1506, 1351 cm⁻¹; δ_{H} (CDCl₃) 3.40–3.50 (m, 1H), 3.79 (s, 3H), 3.84 (s, 3H), 3.85–3.92 (m, 3H), 4.03–4.23 (m, 1H), 6.38 (s, 1H), 6.99–7.04 (m, 2H), 7.35–7.40 (m, 2H); δ_{C} (CDCl₃) 174.6, 153.7, 145.5, 129.1, 117.7, 114.6, 113.5, 103.5, 57.5, 56.1, 50.7, 45.5, 29.9; m/z 293 (M+1). Anal. Calcd for C₁₄H₁₆N₂O₅ (292.29): C, 57.53; H, 5.52; N, 9.58. Found: C, 57.39; H, 5.65; N, 9.88%.

4.6. General procedure for compounds 5

4.6.1. 6-Methyl-3,6-diazabicyclo[3.2.1]octan-2-one (5a). To a solution of nitroenamine **4a** (3.0 g, 15.0 mmol) and ammonium formate (18.9 g, 300 mmol) in MeOH (80 mL) was added 10% Pd–C (2.25 g, wet) and the resulting reaction mixture was refluxed under stirring for 10 h. After completion of reaction, reaction mixture was cooled to 25–30 °C and filtered through Celite bed, washed with MeOH (2×5 mL) and the combined filtrate was concentrated under reduced pressure to afford crude product, which was dissolved in CHCl₃ (10 mL). To this 10% NH₃–CHCl₃ (10 mL) was added and stirred for 0.5 h at 25–30 °C, solid separated out was filtered off and filtrate was concentrated under reduced pressure to obtain an oily residue, which was purified by column chromatography over silica gel (100–200 mesh) using CHCl₃–MeOH (99.5/0.5)→(98/2) as eluent to afford bicyclic lactam **5a** as thick oil, yield 1.48 g (70%); ν_{\max} (CH₂Cl₂) 1682 cm⁻¹; δ_{H} (CDCl₃) 2.03–2.16 (m, 2H), 2.58 (s, 3H), 2.85 (br s, 1H), 3.01–3.11 (m, 2H), 3.36 (br s, 1H), 3.24 (d, J =11.5 Hz, 1H), 3.48 (d, J =11.2 Hz, 1H), 5.92 (br s, 1H); δ_{C} (CDCl₃) 179.9, 63.6, 51.8, 49.2, 39.5, 35.8, 30.6; m/z 141 (M+1). Anal. Calcd for C₇H₁₂N₂O (140.18): C, 59.98; H, 8.63; N, 19.98. Found: C, 59.73; H, 8.56; N, 19.80%.

4.6.2. 4,6-Dimethyl-3,6-diazabicyclo[3.2.1]octan-2-one (5b). This was obtained in 35% yield as thick oil from **4b** according to the procedure described for compound **5a**; ν_{\max} (CH₂Cl₂) 1680 cm⁻¹; δ_{H} (CDCl₃) 1.58 (d, J =6.3 Hz, 3H), 1.92 (br s, 3H), 2.49 (s, 3H), 2.79 (br s, 2H), 3.28–3.38 (m, 2H), 5.30 (br s, 1H); δ_{C} (CDCl₃) 179.8, 67.5, 52.2, 48.6, 39.5, 36.3, 27.9, 17.1; m/z 155 (M+1). Anal. Calcd for C₈H₁₄N₂O (154.21): C, 62.31; H, 9.15; N, 18.17. Found: C, 62.57; H, 8.99; N, 18.06%.

4.6.3. 6-(2-Methoxyphenyl)-3,6-diazabicyclo[3.2.1]-octan-2-one (5c). This was obtained in 70% yield as thick oil from **4c** according to the procedure described for compound **5a**; ν_{\max} (CH₂Cl₂) 1685 cm⁻¹; δ_{H} (CDCl₃) 2.04–2.11 (m, 2H), 2.97 (br s, 1H), 3.28–3.33 (m, 1H), 3.55–3.72 (m, 3H), 3.83 (s, 3H), 4.62 (br s, 1H), 5.40 (br s, 1H),

6.60–6.69 (m, 4H); δ_{C} (CDCl₃) 179.6, 146.7, 130.3, 121.5, 119.1, 115.0, 114.3, 63.5, 56.1, 51.9, 48.7, 39.0, 30.2; m/z 233 (M+1). Anal. Calcd for C₁₃H₁₆N₂O₂ (232.28): C, 67.22; H, 6.94; N, 12.06. Found: C, 67.25; H, 6.89; N, 11.96%.

4.7. General procedure for compounds 6

4.7.1. 6-Methyl-3,6-diazabicyclo[3.2.1]octane (6a). To a stirred suspension of pulverized lithium aluminum hydride (2.96 g, 78 mmol) in dry THF (5 mL), a solution of bicyclic lactam **5a** (2.73 g, 19.5 mmol) in dry THF (10 mL) was added under N₂ atmosphere at 25–30 °C and the resulting reaction mixture was refluxed under stirring for 18 h. After completion of reaction, reaction mixture was cooled to –5 °C and cautiously decomposed with water (15 mL). After stirring for 1 h at 25–30 °C, the reaction mass was filtered, washed with THF, the filtrate was collected and dried over Na₂SO₄, and filtered. The solvent was evaporated to yield crude product, which was purified by column chromatography over silica gel (100–120 mesh) using CHCl₃–MeOH (95/5) as eluent to afford 1.68 g (68%) of 6-methyl-3,6-diazabicyclo[3.2.1]octane (**6a**) as a pale yellow oil; ν_{\max} (CH₂Cl₂) 2908, 2805, 1490 cm⁻¹; δ_{H} (CDCl₃) 1.65–1.78 (m, 2H), 1.85–1.95 (m, 1H), 2.20–2.25 (m, 2H), 2.31 (s, 3H), 2.58–2.70 (m, 1H), 2.75–2.90 (m, 4H); δ_{C} (CDCl₃) 64.5, 54.3, 52.7, 51.5, 37.8, 36.9, 33.1; m/z 127 (M+1). Anal. Calcd for C₇H₁₄N₂ (126.20): C, 66.62; H, 11.18; N, 22.20. Found: C, 66.75; H, 11.22; N, 21.95%.

4.7.2. 4,6-Dimethyl-3,6-diazabicyclo[3.2.1]octane (6b). This was obtained in 53% yield as thick oil from bicyclic lactam **5b** according to the procedure described for compound **6a**; ν_{\max} (CH₂Cl₂) 2890, 2800, 1495 cm⁻¹; δ_{H} (CDCl₃) 1.38 (d, J =7.2 Hz, 3H), 1.95 (br s, 3H), 2.18–2.22 (m, 2H), 2.30 (s, 3H), 2.45–2.50 (m, 1H), 2.70–2.85 (m, 2H), 3.22–3.30 (m, 1H); δ_{C} (CDCl₃) 69.2, 54.8, 52.7, 49.2, 38.1, 36.7, 31.4, 18.6; m/z 141 (M+1). Anal. Calcd for C₈H₁₆N₂ (140.23): C, 68.52; H, 11.50; N, 19.98. Found: C, 68.25; H, 11.38; N, 20.10%.

4.7.3. 6-(2-Methoxyphenyl)-3,6-diazabicyclo[3.2.1]-octane (6c). This was obtained in 57% yield as pale yellow oil from bicyclic lactam **5c** according to the procedure described for compound **6a**; ν_{\max} (CH₂Cl₂) 2900, 2815, 1498 cm⁻¹; δ_{H} (CDCl₃) 1.78–1.82 (m, 2H), 1.94–1.99 (m, 1H), 2.30 (br s, 1H), 2.62–2.67 (d, J =9.6 Hz, 1H), 2.79–2.93 (dd, J =9.9 Hz, 2H), 3.29–3.32 (d, J =9.6 Hz, 1H), 3.60–3.65 (q, J =4.8 Hz, 1H), 3.78 (s, 3H), 4.21–4.24 (t, J =5.4 Hz, 1H), 6.67–6.73 (m, 2H), 6.82–6.88 (m, 2H); δ_{C} (CDCl₃) 146.5, 130.3, 121.9, 119.3, 115.6, 114.2, 63.6, 56.2, 53.9, 51.5, 50.0, 35.3, 31.9; m/z 219 (M+1). Anal. Calcd for C₁₃H₁₈N₂O (218.29): C, 71.53; H, 8.31; N, 12.83. Found: C, 71.68; H, 8.11; N, 12.80%.

4.8. General procedure for compounds 7

4.8.1. 1-[3-[6-(2-Methoxyphenyl)-3,6-diazabicyclo-[3.2.1]oct-3-yl]propyl]piperidine-2,6-dione (7a). A mixture of 1-(3-chloropropyl)piperidine-2,6-dione (0.834 g, 4.4 mmol), 6-(2-methoxyphenyl)-3,6-diazabicyclo[3.2.1]octane (**6c**, 0.863 g, 3.96 mmol, 0.9 equiv), K₂CO₃ (0.303 g, 2.2 mmol, 0.5 equiv) and KI (0.146 g, 0.88 mmol, 0.2 equiv) in DMF (15 mL) was heated at 60–70 °C under stirring for

18 h. After cooling the reaction mixture to ambient temperature, water (75 mL) was added and extracted with CH_2Cl_2 (2×50 mL). The combined organic phase was washed with water (2×50 mL) and dried (Na_2SO_4), filtered and concentrated under reduced pressure to give crude product, which was purified by column chromatography over silica gel (100–120 mesh) using CHCl_3 – MeOH (99/1) → (97/3) as eluent to afford **7a** as thick oil, yield 1.15 g (78%); ν_{max} (CH_2Cl_2) 2945, 1771, 1710, 1594, 1503, 1395 cm^{-1} ; δ_{H} (CDCl_3) 1.52–1.55 (m, 2H), 1.84–1.96 (m, 4H), 2.00–2.08 (br d, 1H), 2.32–2.41 (br d, 4H), 2.57 (t, $J=6.3$ Hz, 4H), 2.95 (d, $J=9.3$ Hz, 2H), 3.45–3.54 (m, 3H), 3.74 (d, $J=7.5$ Hz, 1H), 3.78 (s, 3H), 4.39 (br s, 1H), 6.61–6.84 (m, 4H); δ_{C} (CDCl_3) 172.6, 146.5, 130.3, 121.6, 119.0, 115.1, 114.4, 61.5, 56.2, 54.7, 53.7, 51.3, 38.9, 33.7, 32.8, 32.0, 28.6, 18.1; m/z 372 (M+1). Anal. Calcd for $\text{C}_{21}\text{H}_{29}\text{N}_3\text{O}_3$ (371.47): C, 67.90; H, 7.87; N, 11.31. Found: C, 68.03; H, 8.01; N, 11.38%.

4.8.2. 2-[3-[6-(2-Methoxyphenyl)-3,6-diazabicyclo-[3.2.1]oct-3-yl]propyl]isoindole-1,3-dione (7b). This was obtained in 70% yield as thick oil by reacting 2-(3-chloropropyl)isoindole-1,3-dione with **6c** according to the procedure described for compound **7a**; ν_{max} (CH_2Cl_2) 2947, 1777, 1698, 1503, 1450 cm^{-1} ; δ_{H} (CDCl_3) 1.67–1.71 (m, 2H), 1.95–1.99 (br d, 2H), 2.15 (d, $J=10.2$ Hz, 2H), 2.35 (t, $J=6.6$ Hz, 2H), 2.41 (d, $J=3.9$ Hz, 1H), 2.88–3.12 (m, 2H), 3.42 (d, $J=6.3$ Hz, 1H), 3.46 (t, $J=5.1$ Hz, 2H), 3.68–3.70 (m, 1H), 3.78 (s, 3H), 4.39 (d, $J=3.9$ Hz, 1H), 6.60–6.75 (m, 1H), 6.78–6.81 (m, 3H), 7.65–7.69 (m, 2H), 7.70–7.80 (m, 2H); δ_{C} (CDCl_3) 167.2, 148.2, 133.4, 133.0, 131.1, 128.4, 122.9, 120.1, 116.2, 115.5, 62.8, 57.6, 57.0, 55.7, 54.9, 52.5, 40.2, 33.9, 33.2, 30.1; m/z 406 (M+1). Anal. Calcd for $\text{C}_{24}\text{H}_{27}\text{N}_3\text{O}_3$ (405.49): C, 71.09; H, 6.71; N, 10.36. Found: C, 70.94; H, 6.80; N, 10.13%.

4.8.3. 2-[3-[6-(2-Methoxyphenyl)-3,6-diazabicyclo-[3.2.1]oct-3-yl]propyl]-3a,4,7,7a-tetrahydroisoindole-1,3-dione (7c). This was obtained in 67% yield as thick oil by reacting 2-(3-chloropropyl)-3a,4,7,7a-tetrahydroisoindole-1,3-dione with **6c** according to the procedure described for compound **7a**; ν_{max} (CH_2Cl_2) 3976, 3396, 2949, 1722, 1671, 1590, 1505, 1350 cm^{-1} ; δ_{H} (CDCl_3) 1.51–1.59 (m, 4H), 1.65–1.70 (m, 2H), 1.94 (d, $J=9.9$ Hz, 2H), 2.13 (dd, $J=10.5$ Hz, 2H), 2.26 (t, $J=6.6$ Hz, 2H), 2.39 (br s, 1H), 2.52–2.57 (m, 1H), 2.92–2.93 (m, 1H), 2.97 (t, $J=6.6$ Hz, 2H), 3.18–3.25 (m, 2H), 3.45–3.47 (t, $J=6.3$ Hz, 2H), 3.78 (s, 3H), 4.39 (br s, 1H), 5.83–5.84 (d, $J=2.4$ Hz, 2H), 6.61–6.84 (m, 4H); δ_{C} (CDCl_3): δ 179.1, 147.8, 132.8, 131.4, 123.0, 120.1, 115.2, 114.9, 63.1, 57.6, 57.1, 55.8, 54.8, 52.5, 44.1, 40.1, 33.2, 33.0, 29.8, 28.0; m/z 410 (M+1). Anal. Calcd for $\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_3$ (409.52): C, 70.39; H, 7.63; N, 10.26. Found: C, 70.49; H, 7.68; N, 10.30%.

4.8.4. 4-Ethyl-1-[3-[6-(2-methoxyphenyl)-3,6-diazabicyclo[3.2.1]oct-3-yl]propyl]-4-methyl-piperidine-2,6-dione (7d). This was obtained in 54% yield as thick oil by reacting 1-(3-chloropropyl)-4-ethyl-4-methylpiperidine-2,6-dione with **6c** according to the procedure described for compound **7a**; ν_{max} (CH_2Cl_2) 3970, 3394, 2943, 1724, 1673, 1592, 1510 cm^{-1} ; δ_{H} (CDCl_3) 0.83–0.88 (t, $J=7.5$ Hz, 3H), 0.95 (s, 3H), 1.25–1.33 (m, 2H), 1.52–1.67 (m, 4H), 1.97 (d, $J=10.8$ Hz, 2H), 2.12 (br s, 1H), 2.30–2.34 (t, $J=7.2$ Hz, 2H), 2.42 (s, 4H), 2.88–3.12 (m, 2H), 3.46–

3.57 (m, 3H), 3.79 (br s, 4H), 4.40 (t, $J=4.2$ Hz, 1H), 6.61–6.84 (m, 4H); δ_{C} (CDCl_3) 174.2, 148.2, 131.4, 123.3, 120.0, 116.2, 115.5, 63.3, 57.8, 57.1, 56.2, 55.0, 52.3, 45.6, 40.1, 34.0, 33.4, 33.0, 30.1, 25.3, 22.4, 10.5; m/z 414 (M+1). Anal. Calcd for $\text{C}_{24}\text{H}_{35}\text{N}_3\text{O}_3$ (413.55): C, 69.70; H, 8.53; N, 10.16. Found: C, 70.01; H, 8.68; N, 10.01%.

4.8.5. 5-Chloro-2-[3-[6-(2-methoxyphenyl)-3,6-diazabicyclo[3.2.1]oct-3-yl]propyl]-6-nitro-isoindole-1,3-dione (7e). This was obtained in 71% yield as thick oil by reacting 5-chloro-2-(3-chloropropyl)-6-nitro-isoindole-1,3-dione with **6c** according to the procedure described for compound **7a**; ν_{max} (CH_2Cl_2) 3447, 2944, 1767, 1708, 1627, 1592, 1520 cm^{-1} ; δ_{H} (CDCl_3) 1.94 (d, $J=10.6$ Hz, 1H), 2.06–2.13 (m, 3H), 2.58 (br s, 1H), 2.88–2.95 (m, 1H), 3.11 (d, $J=9.3$ Hz, 1H), 3.26 (t, $J=13.2$ Hz, 2H), 3.46–3.60 (m, 4H), 3.77 (t, $J=6.6$ Hz, 2H), 3.88 (s, 3H), 4.43–4.44 (m, 1H), 6.62–6.64 (m, 1H), 6.73–6.84 (m, 2H), 6.89–6.91 (m, 1H), 7.57 (s, 1H), 8.09 (s, 1H); δ_{C} (CDCl_3) 167.5, 154.3, 148.5, 141.6, 133.4, 132.3, 131.2, 129.7, 125.2, 122.7, 120.0, 116.4, 115.5, 63.1, 57.4, 57.0, 55.7, 54.9, 52.4, 40.5, 33.9, 33.1, 29.9; m/z 485 (M+1). Anal. Calcd for $\text{C}_{24}\text{H}_{25}\text{ClN}_4\text{O}_5$ (484.93): C, 59.44; H, 5.20; N, 11.55. Found: C, 59.51; H, 5.22; N, 11.50%.

4.8.6. 1-[3-[6-(2-Methoxyphenyl)-3,6-diazabicyclo[3.2.1]oct-3-yl]propyl]pyrrolidine-2,5-dione hydrochloride (7f). This was obtained by reacting 1-(3-chloropropyl)-pyrrolidine-2,5-dione with **6c** according to the procedure described for compound **7a**, which was converted to corresponding hydrochloride salt by treating with 1 equiv ethanolic-HCl, 64% yield, mp 114–116 °C; ν_{max} (KBr) 3428, 2958, 1769, 1694, 1593, 1502 cm^{-1} ; δ_{H} (D_2O) 1.96–2.07 (m, 2H), 2.77 (s, 4H), 2.83 (br s, 1H), 3.18 (t, $J=7.8$ Hz, 2H), 3.26 (br d, $J=12.0$ Hz, 2H), 3.51–3.54 (m, 4H), 3.84 (br s, 4H), 3.90 (s, 3H), 4.30 (br s, 1H), 6.97–7.07 (m, 4H); δ_{C} (D_2O) 175.5, 148.2, 132.4, 122.7, 120.6, 117.3, 116.1, 63.6, 58.5, 57.9, 55.7, 55.2, 52.3, 40.6, 34.2, 33.6, 30.8, 28.8; m/z 358 (M+1). Anal. Calcd for $\text{C}_{20}\text{H}_{27}\text{N}_3\text{O}_3 \cdot \text{HCl}$ (393.91): C, 60.98; H, 7.16; N, 10.67. Found: C, 60.61; H, 7.52; N, 10.35%.

4.8.7. 2-[3-[6-(2-Methoxyphenyl)-3,6-diazabicyclo[3.2.1]oct-3-yl]propyl]-1,1-dioxo-1,2-dihydro-1-benzo[d]isothiazol-3-one (7g). This was obtained in 45% yield as thick oil by reacting 2-(3-chloropropyl)-1,1-dioxo-1,2-dihydro-1-benzo[d]isothiazol-3-one with **6c** according to the procedure described for compound **7a**; ν_{max} (CHCl_3) 3417, 2915, 1731, 1594, 1502, 1457, 1332 cm^{-1} ; δ_{H} (CDCl_3) 1.94 (br s, 2H), 2.31 (t, $J=6.9$ Hz, 2H), 2.84 (br s, 1H), 3.08 (d, $J=6.6$ Hz, 1H), 3.30–3.39 (m, 5H) 3.64–3.68 (m, 2H), 3.75–3.80 (m, 5H), 4.26 (br s, 1H), 6.90–6.95 (m, 4H), 7.84–8.11 (m, 4H); δ_{C} (CDCl_3) 170.2, 148.2, 139.9, 134.5, 132.8, 131.5, 132.1, 129.4, 126.8, 123.5, 121.3, 116.8, 115.6, 63.5, 57.3, 57.0, 55.8, 54.9, 53.0, 38.9, 33.8, 33.0, 30.1; m/z 442 (M+1). Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}_4\text{S}$ (441.54): C, 62.56; H, 6.16; N, 9.52. Found: C, 62.25; H, 5.99; N, 9.50%.

4.8.8. 1-[3-[6-(2-Methoxyphenyl)-3,6-diazabicyclo[3.2.1]oct-3-yl]propyl]-4,4-dimethylpiperidine-2,6-dione (7h). This was obtained in 46% yield as thick oil by reacting 1-(3-chloropropyl)-4,4-dimethylpiperidine-2,6-dione with

6c according to the procedure described for compound **7a**; ν_{max} (CHCl₃) 2954, 2764, 1723, 1672, 1594, 1503, 1358 cm⁻¹; δ_{H} (CDCl₃) 1.01 (s, 6H), 1.51–1.63 (m, 5H), 1.97 (d, J =10.2 Hz, 1H), 2.10 (d, J =9.9 Hz, 1H), 2.32 (t, J =6.9 Hz, 2H), 2.43 (s, 4H), 2.91–3.01 (m, 2H), 3.52 (t, J =7.5 Hz, 2H), 3.73 (d, J =9.3 Hz, 2H), 3.78 (s, 3H), 4.39 (br s, 1H), 6.16–6.81 (m, 4H); δ_{C} (CDCl₃) 174.8, 148.2, 131.6, 123.1, 121.5, 116.8, 115.5, 63.3, 57.8, 57.0, 55.7, 55.1, 52.7, 48.0, 39.9, 34.2, 33.6, 30.3, 27.7, 19.8; *m/z* 400 (M+1). Anal. Calcd for C₂₃H₃₃N₃O₃ (399.53): C, 69.14; H, 8.33; N, 10.52. Found: C, 69.22; H, 8.50; N, 10.53%.

4.8.9. 1-(3-Halopropyl)dicarboximides (9). These were prepared according to the literature procedure⁷ by condensing various commercially available α,ω -dicarboximides (**8**) and 1-bromo-3-chloropropane.

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