

## Synthesis and Antibacterial Activity of Novel [3-(4-substitutedphenylamino)-8-azabicyclo [3.2.1] oct-8yl]-phenyl-methanone Derivatives

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**ABSTRACT.** The synthesis, as well as spectroscopic and biological studies of a novel class of [3-(4-substitutedphenylamino)-8-azabicyclo [3.2.1] oct-8yl]-phenyl-methanone derivatives are described. All the synthesized compounds were characterized by elemental analysis FTIR, <sup>1</sup>H-NMR, <sup>13</sup>C NMR, and Mass spectral data. All the synthesized compounds were exhibit *in vitro* antibacterial activity.

**Key words:** Azabicyclo-phenyl methanone, Antibacterial activity

### INTRODUCTION

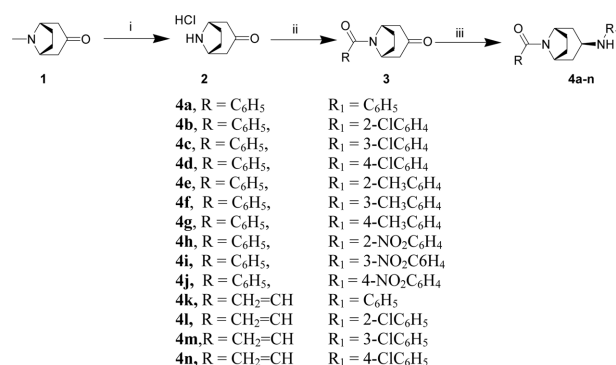
The synthesis and the use of conformationally rigid unnatural compounds have attracted the chemist's interest since long time.<sup>1,2</sup> It is commonly assumed that the restriction of the flexibility by structural modifications, such as the insertion of a cyclic scaffold, is an efficient tool to reduce the possible structural conformations of a molecule. The 8-azabicyclo[3.2.1]octane ring is a central structural element in a number of neuroactive compounds, including cocaine and atropine.<sup>3</sup> Because of their importance in synthetic and medicinal chemistry and in peptide research, conformationally rigid, alicyclic  $\beta$ -amino acids have been subject to considerable interest during the past 20 years.<sup>4</sup> *N*-Heterocyclic  $\beta$ -amino acids have also attracted attention in view of their biological properties and their applications in peptide synthesis.<sup>5</sup> Bicyclic  $\alpha$ - or  $\beta$ -amino acids in which the *N* atom of the amino function is part of the ring system are a class of compounds of appreciable importance. Thus, bicyclic  $\alpha$ -amino acids with the *N* atom in the ring system, such as 7-azabicyclo[2.2.1]heptane-1-carboxylic acid, its derivatives and compounds with an 8-azabicyclo[3.2.1]octane skeleton are conformationally restricted analogs of proline, hydroxyprolines and related proline derivatives.<sup>6,7</sup> 7-Azabicyclo[2.2.1]heptane-2-carboxylic acid  $\beta$ -amino acids key compounds in novel  $\beta$ -peptide syntheses<sup>8</sup> were recently reported to behave as conformationally restricted proline analogs, acting as efficient catalysts in organocatalytic aldol processes<sup>9</sup> Moreover, both bicyclic  $\alpha$ - and  $\beta$ -amino acids with the *N* atom in the ring system serve as key precursors for the syn-

thesis of medicinally valuable alkaloids such as anatoxin-*a*,<sup>10</sup> epibatidine, epiboxidine etc.<sup>11</sup> A number of pharmacologically active 3-azabicyclo[3.2.1]octanes have been reported as bioactive molecules,<sup>12</sup> the most important of them probably being those with an amino or carboxyl function in their structure. 3-Azabicyclo[3.2.1]octane  $\alpha$ -amino acids were recently synthesized in enantiomerically pure form.<sup>12a</sup> Because of the importance of the conformationally constrained alicyclic or heterocyclic  $\beta$ -amino acids, our work was directed toward the synthesis of novel [3-(4-substitutedphenylamino)-8-azabicyclo [3.2.1] oct-8yl]-phenyl-methanone derivatives.

### RESULTS AND DISCUSSIONS

In biological and chemical systems, one-pot reductive amination of aldehydes and ketones is an important transformation, which allows the direct conversion of carbonyl compounds into amines using simple operations.<sup>13</sup> The reductive aminations with NaBH<sub>3</sub>CN are successfully carried out using a five-fold excess of amine at pH 6-8.<sup>14</sup>

The synthetic pathway employed to prepare the title compounds is outlined in *Scheme 1*. [3-(4-substitutedphenylamino)-8-azabicyclo [3.2.1] oct-8yl]-phenyl-methanone derivatives were synthesized by the reaction of tropinone **1** with 1-chloroethyl chloroformate in presence of dichloromethane to get the compound **2** in the form of brownish white solid. The amine salt of compound **2** was dissolved in dry dichloromethane under nitrogen atmosphere and stirred for 15 minutes at room temperature. After 15 minutes Et<sub>3</sub>N was added and stirred for 10 minutes then dif-



**Scheme 1.** Synthesis of **4**, reagents and conditions: (i) MeCH(Cl)OCOCI/DCM or MeOH. (ii) RCOCl-Et<sub>3</sub>N/THF. (iii) R<sub>1</sub>NH<sub>2</sub>, NaBH<sub>3</sub>CN/MeOH-AcOH.

ferent acid chlorides were added and the reaction mixture was stirred at room temperature for over night to get compound **3**. Reduction of compound **3** with NaBH<sub>3</sub>CN in presence of MeOH, and in neat conditions in the presence of small amounts of AcOH to get title compounds **4a-n**. All the synthesized compounds were characterized on the basis of FTIR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR and Mass spectroscopic analysis. The IR spectral data of all compounds showed the characteristic peaks of NH stretching at 3325-3389 cm<sup>-1</sup>, aliphatic tertiary C-N stretching at 1354-1340 cm<sup>-1</sup>. The peaks at 3415 and 1523 cm<sup>-1</sup> indicating the presence of OH- and NO<sub>2</sub>- groups respectively were also observed in the corresponding synthesized compounds.

**Table 1.** Anti bacterial activity of the compounds **4a-n**

Compound	Antibacterial activity				
	<i>S. a</i>	<i>E. c</i>	<i>S. a</i>	<i>S. f</i>	<i>P. a</i>
<b>4a</b>	++	++	++	++	+++
<b>4b</b>	++	++	++	++	++
<b>4c</b>	+++	++++	+++	++	+
<b>4d</b>	+++	+++	++	+	++
<b>4e</b>	++++	++	+	+	+
<b>4f</b>	+++	++	++	++	++
<b>4g</b>	+++	++	+++	++	+++
<b>4h</b>	++	++	+	++	++
<b>4i</b>	++++	++	++	++	+++
<b>4j</b>	++	++	++	++	+++
<b>4k</b>	++	++	++	++	+++
<b>4l</b>	++	++	+++	++	+++
<b>4m</b>	++	++	++	++	+++
<b>4n</b>	++	++	++	++	++

50 µgm/mL = +++++, 100 µgm/mL = +++, 150 µgm/mL = ++, 200 µgm/mL = +, Not active upto 200 µgm/mL = - Ciprofloxacin, Cloxacillin & Gentamycin<sup>21</sup> is (+++++) at 50 µgm/mL. *S. a* = *Staphylococcus aureus*, *S. p* = *Salmonella paratyphi*, *E. c* = *Escherichia coli*, *S. f* = *Shigella flexneri*, *P. a* = *Pseudomonas auregenosa*.

### Antibacterial activity

The minimum inhibition concentration (MIC) was determined using the streak plate and cup plate method by measuring the zone of inhibition according to a standard procedure.<sup>14</sup> All the synthesized compounds were screened *in vitro* for their antibacterial activity against a variety of bacterial strains such as *Staphylococcus aureus*, *Salmonella paratyphi*, *Escherichia coli*, *Shigella flexneri*, *Pseudomonas auregenosa* (Table 1). The MIC of the compounds was defined, as the lowest concentration at which there was 80% inhibition of growth compared with the growth for a drug free control.<sup>15</sup> Standard inhibition of zone size for Ciprofloxacin, Cloxacillin and for Gentamycin<sup>15</sup> is (+++++) at 50 µgm/mL against all microbes.

### EXPERIMENTAL

Melting points were recorded using a digital Gallenkamp (Sanyo) model MPD BM 3.5 apparatus and are uncorrected. <sup>1</sup>H and <sup>13</sup>C-NMR spectra were determined in deuterium chloroform solutions using a Bruker AM-300 spectrophotometer. FTIR spectra were recorded on an FTS 3000 MX spectrophotometer. Mass spectra (EI, 70eV) were obtained on a GC-MS instrument of Agilent technologies.

#### General procedure for the preparation of title compounds

Tropinone **1** (10 g, 0.071 mol) was dissolved in dry DCM (100 mL) under nitrogen atmosphere and stirred for 15 minutes. To this solution 1-chloroethylchloroformate (22.6 g, 0.158 mol) was added and the reaction mixture was refluxed for 4 h at 40 °C. After completion of reaction DCM was concentrated under vacuum and then dry MeOH (200 mL) was added to the residue and refluxed for over night at 65 °C. Concentrate MeOH under high vacuum till complete dryness. Filter off the brownish white solid under nitrogen atmosphere. The Compound was pure enough to go further for next step.

The compound **2** (5 g, 0.03 mol) was dissolved in dry DCM (150 mL) under nitrogen atmosphere and stirred for 15 minutes at rt. After 15 minutes Et<sub>3</sub>N (15 mL) was added and stirred for 10 minutes then RCOCl (4.3 g, 0.027 mol) was added and reaction mixture was stirred at rt for over night. Filter off the salt precipitated. The filtrate was taken in dry DCM and given saturated NaHCO<sub>3</sub> solution washings. Combined organic layers were concentrated under vacuum to get compound **3**. The Compound was purified by column chromatography using 20% Ethyl ace-

tate in Hexane.

Compound 3 (0.15g, 0.0005 mol) was dissolved in dry MeOH (5 mL) followed by the addition of Anhydrous MgSO<sub>4</sub> (300 mg) and R<sub>1</sub>NH<sub>2</sub> (0.064 g, 0.0006 mol). The reaction mass was stirred for 6 h. at rt. Then add NaBH<sub>3</sub>CN (0.134 g, 0.0021 mol) and Acetic acid (0.1 mL) and stir the reaction mixture at rt for over night. The reaction mixture was filtered and the filtrate was taken in DCM and given saturated NaHCO<sub>3</sub> solution washings. Combined organic layers were concentrated under vacuum. The compound was purified by column chromatography using 15% Ethyl acetate/Hexane to get pure compound 4a-n.

**[3-(3-phenylamino-8-aza-bicyclo [3.2.1] oct-8-yl)-phenyl-methanone 4a.** Yellow precipitate; yield: 68%; Rf: 0.45; IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3328, 3286, 3065, 2960, 890, 1725, 1652, 1596, 1340, 1143, 664; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  8.06-6.88 (m, 10H, Ar-H), 4.59 (brs, 1H, NH), 3.95 (m, 1H, CH), 2.56 (d,  $J=6.8$  MHz, 4H, CH<sub>2</sub>), 2.17 (t,  $J=6.4, 6.8$  MHz, 4H, CH<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  172.7, 149.5, 144.9, 132.3, 131.7, 129.3, 127.0, 121.2, 115.7, 52.6, 49.1, 43.0, 28.7; MS (ESI): m/z 306.42 (M<sup>+</sup>).

**[3-(2-chlorophenylamino)-8-aza-bicyclo [3.2.1] oct-8-yl]-phenyl-methanone 4b.** Yellow precipitates; yield: 59%; Rf: 0.45; IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3356, 3287, 3020, 2960, 2855, 1230, 1651, 1587, 1343, 1144, 668; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  8.00-6.95 (m, 9H, Ar-H), 4.65 (brs, 1H, NH), 3.84 (m, 1H, CH), 2.76 (d,  $J=6.2$  MHz, 4H, CH<sub>2</sub>), 2.13 (t,  $J=6.0, 6.4$  MHz, 2H, CH<sub>2</sub>), 1.86 (m, 4H, CH<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  172.7, 149.5, 144.9, 132.3, 131.7, 129.3, 127.0, 121.2, 115.7, 52.6, 49.1, 43.0, 28.7; MS (ESI): m/z 340.85 (M<sup>+</sup>).

**[3-(3-chlorophenylamino)-8-aza-bicyclo [3.2.1] oct-8-yl]-phenyl-methanone 4c.** White solid, Mp: 139-141 °C; yield: 59%; Rf: 0.47; IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3358, 3289, 3022, 2961, 2852, 1728, 1650, 1589, 1342, 1145, 669; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  8.05-6.82 (m, 9H, Ar-H), 4.69 (brs, 1H, NH), 3.82 (m, 1H, 2CH), 2.82 (d,  $J=6.6$  MHz, 4H, CH<sub>2</sub>), 2.18 (t,  $J=6.2, 6.8$  MHz, 2H, CH<sub>2</sub>), 1.76 (m, 4H, CH<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  174.1, 147.9, 143.9, 131.7, 130.7, 129.0, 127.6, 122.2, 114.6, 51.5, 47.1, 44.8, 27.4; MS (ESI): m/z 340.85 (M<sup>+</sup>).

**[3-(4-chlorophenylamino)-8-aza-bicyclo [3.2.1] oct-8-yl]-phenyl-methanone 4d.** Dark yellow solid, Mp: 192-194 °C; yield: 69%; Rf: 0.45; IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3363, 3294, 3018, 2963, 2859, 1733, 1652, 1580, 1348, 1147, 653; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  8.00-6.75 (m, 9H, Ar-H), 4.59 (brs, 1H, NH), 3.89 (m, 1H, 2CH), 2.85 (d,  $J=6.4$  MHz, 4H, CH<sub>2</sub>), 2.25 (t,  $J=6.1, 6.6$  MHz, 2H, CH<sub>2</sub>), 1.8 (m, 4H, CH<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  174.3,

147.0, 143.9, 132.0, 130.9, 129.2, 127.7, 122.3, 114.8, 51.0, 47.8, 44.5, 26.9; MS (ESI): m/z 340.85 (M<sup>+</sup>).

**(3-*o*-tolylamino-8-aza-bicyclo [3.2.1] oct-8-yl)-phenyl-methanone 4e.** Yellow powder; yield: 39%; IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3397, 3268, 3060, 2950, 2862, 1721, 1651, 1590, 1326, 1145; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  8.00-6.67 (m, 9H, Ar-H), 4.48 (brs, 1H, NH), 3.63 (m, 1H, 2CH), 2.86 (s, 3H, CH<sub>3</sub>), 2.54 (m, 4H, CH<sub>2</sub>), 2.16 (t,  $J=6.4$  MHz, 2H, CH<sub>2</sub>), 1.74 (m, 4H, CH<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  172.1, 145.9, 142.0, 132.9, 131.2, 129.4, 127.5, 123.8, 114.0, 51.5, 47.8, 44.1, 27.0, 14.5; MS (ESI): m/z 320.62 (M<sup>+</sup>).

**(3-*m*-tolylamino-8-aza-bicyclo [3.2.1] oct-8-yl)-phenyl-methanone 4f.** Brownish-black solid; yield: 49%; IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3345, 3275, 3085, 2925, 2840, 1720, 1640, 1589, 1350, 1152; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  8.05-6.70 (m, 9H, Ar-H), 4.45 (brs, 1H, NH), 3.69 (m, 1H, 2CH), 2.81 (s, 3H, CH<sub>3</sub>), 2.53 (m, 4H, CH<sub>2</sub>), 2.12 (t,  $J=6.4, 6.6$  MHz, 2H, CH<sub>2</sub>), 1.75 (m, 4H, CH<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  172.8, 145.2, 141.9, 133.0, 131.7, 129.3, 127.9, 124.0, 114.8, 52.8, 41.6, 44.8, 27.3, 13.9; MS (ESI): m/z 320.62 (M<sup>+</sup>).

**(3-*p*-tolylamino-8-aza-bicyclo [3.2.1] oct-8-yl)-phenyl-methanone 4g.** Solid; yield: 73%; IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3358, 3269, 3081, 2927, 2842, 1717, 1648, 1587, 1353, 1153; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  8.01-6.74 (m, 9H, Ar-H), 4.48 (brs, 1H, NH), 3.60 (m, 1H, 2CH), 2.88 (s, 3H, CH<sub>3</sub>), 2.54 (m, 4H, CH<sub>2</sub>), 2.19 (t,  $J=6.2, 6.8$  MHz, 2H, CH<sub>2</sub>), 1.70 (m, 4H, CH<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  172.0, 144.9, 142.0, 132.8, 131.4, 129.8, 128.9, 124.2, 115.1, 53.4, 42.8, 45.0, 27.7, 13.7; MS (ESI): m/z 320.62 (M<sup>+</sup>).

**[3-(2-nitrophenylamino)-8-aza-bicyclo [3.2.1] oct-8-yl]-phenyl-methanone 4h.** Yellow powder; yield: 49%; IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3428, 3358, 3296, 3117, 2952, 2864, 1729, 1663, 1587, 1358, 1149; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  8.16-6.95 (m, 9H, Ar-H), 4.75 (brs, 1H, NH), 3.95 (m, 1H, 2CH), 2.88 (m, 4H, CH<sub>2</sub>), 2.23 (t,  $J=6.4, 6.9$  MHz, 2H, CH<sub>2</sub>), 1.85 (m, 4H, CH<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  172.9, 145.4, 143.7, 142.8, 133.4, 132.0, 130.8, 128.1, 126.7, 118.4, 54.5, 43.7, 41.6, 28.2. C<sub>20</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>; MS (ESI): m/z 351.42 (M<sup>+</sup>).

**[3-(3-nitrophenylamino)-8-aza-bicyclo [3.2.1] oct-8-yl]-phenyl-methanone 4i.** Dark brown powder; yield: 58%; IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3415, 3386, 3245, 3110, 2955, 2860, 1735, 1663, 1584, 1354, 1146; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  8.10-6.99 (m, 9H, Ar-H), 4.78 (brs, 1H, NH), 3.99 (m, 1H, 2CH), 2.82 (m, 4H, CH<sub>2</sub>), 2.35 (t,  $J=5.8, 6.2$  MHz, 2H, CH<sub>2</sub>), 1.46 (m, 4H, CH<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  172.2, 145.2, 142.6, 141.9, 133.5, 132.2, 130.8, 128.6, 126.7, 118.4, 54.7, 43.2, 41.5, 28.5; MS (ESI): m/z 351.42 (M<sup>+</sup>).

**[3-(4-nitrophenylamino)-8-aza-bicyclo [3.2.1] oct-8-yl]-phenyl-methanone 4j.** Oil; yield: 86%; IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3415, 3359, 3284, 3118, 2951, 2869, 1730, 1664, 1582, 1358, 1143;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  8.15-6.94 (m, 9H, Ar-H), 4.72 (brs, 1H, NH), 3.97 (m, 1H, 2CH), 2.84 (m, 4H,  $\text{CH}_2$ ), 2.30 (t,  $J = 6.4, 6.6$  MHz, 2H,  $\text{CH}_2$ ), 1.51 (m, 4H,  $\text{CH}_2$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  172.7, 145.2, 142.7, 140.4, 133.6, 132.8, 130.2, 128.4, 126.4, 117.9, 53.9, 43.4, 41.8, 28.4; MS (ESI):  $m/z$  351.42 ( $\text{M}^+$ ).

**1-(3-phenylamino-8-aza-bicyclo [3.2.1] oct-8-yl)-propanone 4k.** White solid, yield: 79%; IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3389, 3257, 3015, 2907, 1718, 1655, 1348, 1145, 1093, 987, 689;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  7.86-7.28 (m, 5H, Ar-H), 6.89 (t, 1H,  $J = 6.7, 6.9$  MHz), 6.56 (d, 1H,  $J = 6.4$  MHz,  $=\text{CH}_2$ ), 5.96 (d, 1H,  $J = 6.5$  MHz,  $=\text{CH}_2$ ), 4.15 (brs, 1H, NH), 3.65 (m, 1H, 2CH), 2.75 (m, 4H,  $\text{CH}_2$ ), 2.36 (t,  $J = 6.7, 6.9$  MHz, 2H,  $\text{CH}_2$ ), 1.58 (m, 4H,  $\text{CH}_2$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  170.9, 146.3, 132.8, 131.2, 130.9, 118.4, 113.3, 53.1, 49.7, 41.5, 27.8; MS (ESI):  $m/z$  256.58 ( $\text{M}^+$ ).

**1-[3-(2-chlorophenylamino)-8-aza-bicyclo [3.2.1] oct-8-yl]-propanone 4l.** White solid, yield: 75%; IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3384, 3252, 3017, 2917, 1716, 1653, 1349, 1147, 1099, 980, 688;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  7.78-7.16 (m, 4H, Ar-H), 6.99 (t, 1H,  $J = 6.2, 6.4$  MHz), 6.64 (d, 1H,  $J = 6.8$  MHz,  $=\text{CH}_2$ ), 5.99 (d, 1H,  $J = 6.2$  MHz,  $=\text{CH}_2$ ), 4.19 (brs, 1H, NH), 3.69 (m, 1H, 2CH), 2.78 (m, 4H,  $\text{CH}_2$ ), 2.34 (t,  $J = 6.5, 6.8$  MHz, 2H,  $\text{CH}_2$ ), 1.75 (m, 4H,  $\text{CH}_2$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  171.4, 146.0, 133.5, 132.6, 131.8, 118.4, 115.3, 53.4, 49.5, 42.0, 26.9; MS (ESI):  $m/z$  290.86 ( $\text{M}^+$ ).

**1-[3-(3-chlorophenylamino)-8-aza-bicyclo [3.2.1] oct-8-yl]-propanone 4m.** White solid, yield: 59%; IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3387, 3249, 3019, 2912, 1717, 1650, 1348, 1145, 1080, 989, 689;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  7.71-7.18 (m, 4H, Ar-H), 6.98 (t, 1H,  $J = 6.5, 6.8$  MHz), 6.69 (d, 1H,  $J = 6.9$  MHz,  $=\text{CH}_2$ ), 5.95 (d, 1H,  $J = 6.6$  MHz,  $=\text{CH}_2$ ), 4.24 (brs, 1H, NH), 3.75 (m, 1H, 2CH), 2.72 (m, 4H,  $\text{CH}_2$ ), 2.37 (t,  $J = 6.0, 6.4$  MHz, 2H,  $\text{CH}_2$ ), 1.82 (m, 4H,  $\text{CH}_2$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  171.0, 145.8, 133.7, 132.6, 130.1, 117.3, 115.7, 53.8, 49.4, 42.8, 26.1; MS (ESI):  $m/z$  290.86 ( $\text{M}^+$ ).

**1-[3-(4-chlorophenylamino)-8-aza-bicyclo [3.2.1] oct-8-yl]-propanone 4n.** White solid, yield: 84%; IR (KBr,  $\nu/\text{cm}^{-1}$ ): 3374, 3252, 3024, 2919, 1725, 1663, 1351, 1143, 1084, 981, 687;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  7.75-7.17 (m, 4H, Ar-H), 6.92 (t, 1H,  $J = 6.0, 6.7$  MHz), 6.65 (d, 1H,  $J = 6.2$  MHz,  $=\text{CH}_2$ ), 5.94 (d, 1H,  $J = 6.8$  MHz,  $=\text{CH}_2$ ), 4.26 (brs, 1H, NH), 3.70 (m, 1H, 2CH), 2.78 (m, 4H,  $\text{CH}_2$ ), 2.31 (t,  $J = 6.5, 6.8$  MHz, 2H,  $\text{CH}_2$ ), 1.72 (m, 4H,  $\text{CH}_2$ );

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  171.5, 146.0, 133.8, 132.1, 130.6, 117.9, 114.7, 54.0, 49.8, 42.1, 26.6; MS (ESI):  $m/z$  290.86 ( $\text{M}^+$ ).

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