

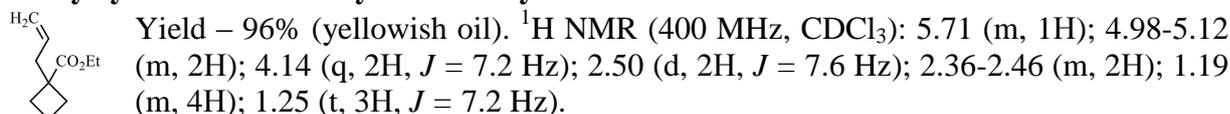
Synthesis of spiro-annulated pyroglutamides by the Ugi reaction

Vasiliy Yu. Stolyarenko, Anatoliy A. Evdokimov and Vladimir I. Shishkin

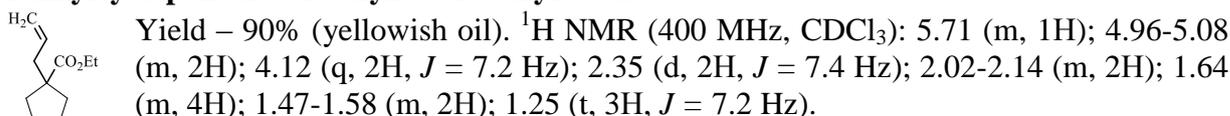
Experimental

Compounds **6-10** and **11-15** were obtained by allylation and oxidation procedures according to literature reference.¹⁷

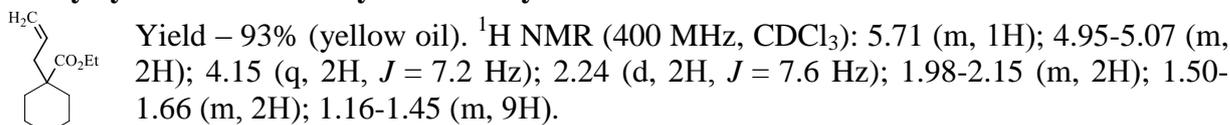
1-Allylcyclobutanecarboxylic acid ethyl ester **6**



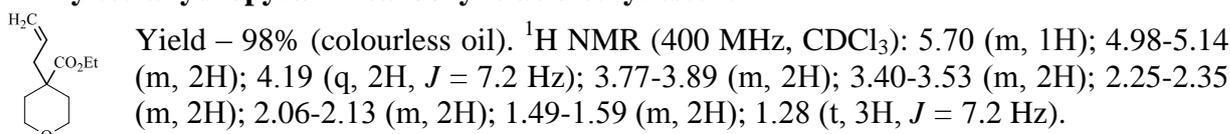
1-Allylcyclopentanecarboxylic acid ethyl ester **7**



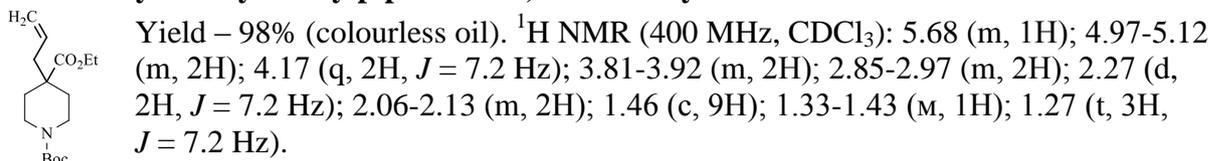
1-Allylcyclohexanecarboxylic acid ethyl ester **8**



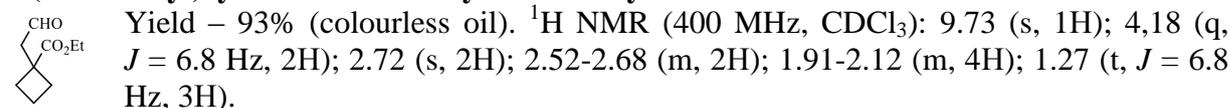
4-Allyltetrahydropyran-4-carboxylic acid ethyl ester **9**

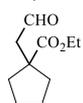


1-*tert*-Butyl 4-ethyl 4-allylpiperidine-1,4-dicarboxylate **10**

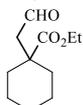


1-(2-Oxoethyl)cyclobutanecarboxylic acid ethyl ester **11**

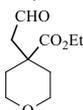


1-(2-Oxoethyl)cyclopentanecarboxylic acid ethyl ester 12

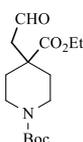
Yield – 93% (yellowish oil). ¹H NMR (400 MHz, CDCl₃): 9.73 (s, 1H); 4.15 (q, *J* = 7.0 Hz, 2H); 2.72 (s, 2H); 2.13-2.27 (m, 2H); 1.52-1.84 (m, 6H); 1.25 (t, *J* = 7.0 Hz, 3H).

1-(2-Oxoethyl)cyclohexanecarboxylic acid ethyl ester 13

Yield – 93% (yellow oil). ¹H NMR (400 MHz, CDCl₃): 9.73 (s, 1H); 4.18 (q, *J* = 7.0 Hz, 2H); 2.63 (s, 2H); 1.93-2.15 (m, 2H); 1.35-1.59 (m, 8H); 1.27 (t, *J* = 7.0 Hz, 3H).

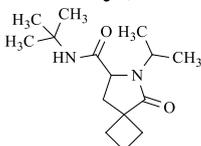
4-(2-Oxoethyl)tetrahydropyran-4-carboxylic acid ethyl ester 14

Yield – 93% (yellowish oil). ¹H NMR (400 MHz, CDCl₃): 9.74 (s, 1H); 4.23 (q, *J* = 7.2 Hz, 2H); 3.74-3.81 (m, 2H); 3.60-3.70 (m, 2H); 2.71 (s, 2H); 2.11-2.20 (m, 2H); 1.58-1.70 (m, 2H); 1.28 (t, *J* = 7.2 Hz, 3H).

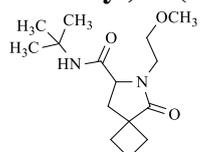
1-tert-Butyl 4-ethyl 4-(2-oxoethyl)piperidine-1,4-dicarboxylate 15

Yield – 93% (yellowish oil). ¹H NMR (400 MHz, CDCl₃): 9.73 (s, 1H); 5.68 (m, 1H); 4.97-5.12 (m, 2H); 4.17 (q, 2H, *J* = 7.2 Hz); 3.81-3.92 (m, 2H); 2.85-2.97 (m, 2H); 2.63 (s, 2H); 2.27 (d, 2H, *J* = 7.2 Hz); 2.06-2.13 (m, 2H); 1.46 (s, 9H); 1.33-1.43 (m, 1H); 1.27 (t, 3H, *J* = 7.2 Hz).

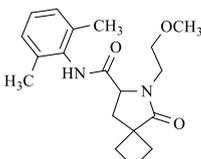
Spyrocyclic γ -lactames **21-25** were obtained by the **General procedure of hydrolysis/Ugi reaction**.

***N*-(tert-Butyl)-6-isopropyl-5-oxo-6-azaspiro[3.4]octane-7-carboxamide 21a**

Yield – 67%, white solid, mp 110-111°C. ¹H NMR (400 MHz, CDCl₃): 5.55 (s, 1H); 4.24 (q, 1H, *J* = 6.4 Hz); 3.84 (d, 1H, *J* = 8.0 Hz); 2.56 (m, 1H); 2.37 (m, 3H); 2.02 (m, 3H); 1.84 (m, 1H); 1.34 (s, 9H); 1.19 (d, 6H, *J* = 6.4 Hz). MS (ESI, *m/z*): 267.5 [M+H]⁺.

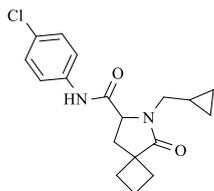
***N*-(tert-Butyl)-6-(2-methoxyethyl)-5-oxo-6-azaspiro[3.4]octane-7-carboxamide 21b**

Yield – 55%, white solid, mp 98-99°C. ¹H NMR (400 MHz, CDCl₃): 6.20 (s, 1H); 3.90 (dd, 1H, *J* = 8.8 Hz, *J* = 4.4 Hz); 3.69 (m, 1H); 3.54 (m, 2H); 3.41 (m, 1H); 3.35 (s, 3H); 2.45 (m, 3H); 2.30 (m, 1H); 1.96 (m, 4H); 1.34 (s, 9H). MS (ESI, *m/z*): 283.3 [M+H]⁺.

***N*-(2,6-Dimethylphenyl)-6-(2-methoxyethyl)-5-oxo-6-azaspiro[3.4]octane-7-carboxamide 21c**

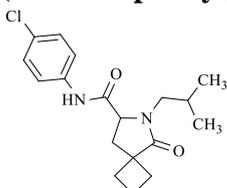
Yield – 73%, yellowish solid, mp 104-105°C. ¹H NMR (400 MHz, CDCl₃): 8.49 (s, 1H); 7.34 (s, 1H); 7.25 (d, 1H, *J* = 8.4 Hz); 7.08 (d, 1H, *J* = 8.4 Hz); 4.12 (dd, 1H, *J* = 10.0 Hz, *J* = 4.0 Hz); 3.82 (m, 1H); 3.56 (m, 3H); 3.39 (s, 3H); 2.50 (m, 4H); 2.24 (d, 6H, *J* = 10.0 Hz); 1.99 (m, 4H). MS (ESI, *m/z*): 331.5 [M+H]⁺.

***N*-(4-Chlorophenyl)-6-(cyclopropylmethyl)-5-oxo-6-azaspiro[3.4]octane-7-carboxamide 21d**



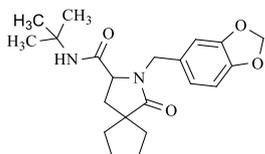
Yield – 72%, beige solid, mp 173-174°C. ¹H NMR (400 MHz, CDCl₃): 7.70 (s, 1H); 7.50 (d, 2H, *J* = 8.8 Hz); 7.31 (d, 2H, *J* = 8.8 Hz); 3.77 (dd, 1H, *J* = 9.2 Hz, 4.4 Hz); 3.56 (dd, 1H, *J* = 14.4 Hz, 6.4 Hz); 2.98 (dd, 1H, *J* = 14.4 Hz, 6.4 Hz); 2.60 (dd, 1H, *J* = 13.2 Hz, 4.0 Hz); 2.51 (m, 1H); 2.36 (dd, 1H, *J* = 13.2 Hz, 4.0 Hz); 2.11 (m, 1H); 1.96 (m, 2H); 0.91 (m, 3H); 0.54 (m, 2H); 0.25 (m, 2H). MS (ESI, *m/z*): 333.7 [M+H]⁺.

***N*-(4-Chlorophenyl)-6-isobutyl-5-oxo-6-azaspiro[3.4]octane-7-carboxamide 21e**



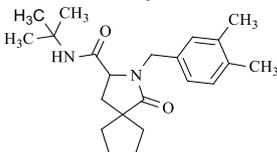
Yield – 83%, beige solid, mp 183-185°C. ¹H NMR (400 MHz, CDCl₃): 8.04 (s, 1H); 7.54 (d, 2H, *J* = 8.8 Hz); 7.30 (d, 2H, *J* = 8.8 Hz); 4.12 (dd, 1H, *J* = 4.0 Hz, 8.0 Hz); 3.62 (dd, 1H, *J* = 13.6 Hz, 8.8 Hz); 2.76 (dd, 1H, *J* = 13.6 Hz, 5.6 Hz); 2.57 (dd, 1H, *J* = 13.6 Hz, 8.8 Hz); 2.49 (m, 2H); 2.32 (dd, 1H, *J* = 13.6 Hz, 6.8 Hz); 2.00 (m, 5H); 0.92 (d, 3H, *J* = 6.8 Hz); 0.83 (d, 3H, *J* = 6.8 Hz). MS (ESI, *m/z*): 335.8 [M+H]⁺.

2-[(Benzo[d][1,3]dioxol-5-yl)methyl]-*N*-(*tert*-butyl)-1-oxo-2-azaspiro[4.4]nonane-3-carboxamide 22a



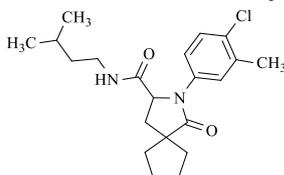
Yield – 69%, yellowish solid, mp 193-194°C. ¹H NMR (400 MHz, CDCl₃): 6.75 (m, 2H); 6.69 (m, 2H); 5.96 (s, 2H); 5.36 (s, 2H); 4.85 (d, 1H, *J* = 14.4 Hz); 3.98 (d, 1H, *J* = 14.4 Hz); 3.64 (dd, 1H, *J* = 8.8, 5.6 Hz); 2.19 (dd, 1H, *J* = 13.2, 8.4 Hz); 2.08 (m, 1H); 1.94 (dd, 1H, *J* = 12.4, 5.6 Hz); 1.84 (m, 2H); 1.64 (m, 5H); 1.31 (s, 9H). MS (ESI, *m/z*): 373.4 [M+H]⁺.

***N*-(*tert*-Butyl)-2-(3,4-dimethylbenzyl)-1-oxo-2-azaspiro[4.4]nonane-3-carboxamide 22b**



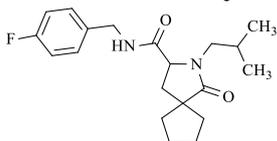
Yield – 72%, beige solid, mp 172-174°C. ¹H-NMR(400 MHz, CDCl₃): 7.09 (m, 1H); 6.97 (m, 1H); 5.33 (s, 1H); 4.84 (d, 1H, *J* = 14.4 Hz); 4.04 (d, 1H, *J* = 14.4 Hz); 3.63 (dd, 1H, *J* = 8.4, 5.6 Hz); 2.24 (s, 3H); 2.18 (dd, 1H, *J* = 13.2, 8.4 Hz); 2.02 (m, 3H); 1.85 (m, 1H); 1.64 (m, 3H); 1.47 (m, 1H); 1.27 (s, 9H). MS (ESI, *m/z*): 356.6 [M+H]⁺, 799 [2M+H]⁺.

2-(4-Chloro-3-methylphenyl)-*N*-isopentyl-1-oxo-2-azaspiro[4.4]nonane-3-carboxamide 22c

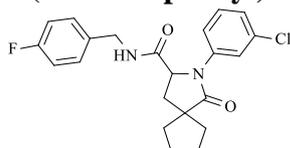


Yield – 70%, white solid, mp 141-143°C. ¹H NMR (400 MHz, CDCl₃): 7.51 (s, 1H); 7.32 (m, 2H); 5.60 (s, 1H); 4.58 (m, 1H); 3.27 (m, 1H); 3.17 (d, 3H, *J* = 5.2 Hz); 3.14 (m, 1H); 2.46 (dd, 1H, *J* = 12.8 Hz, 8.8 Hz); 2.37 (s, 3H); 2.12 (m, 2H); 2.01 (m, 1H); 1.86 (m, 2H); 1.68 (m, 6H); 1.20 (m, 2H). MS (ESI, *m/z*): 377.9 [M+H]⁺.

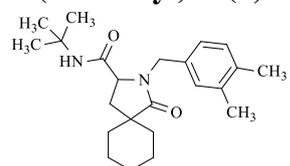
***N*-(4-Fluorobenzyl)-2-isobutyl-1-oxo-2-azaspiro[4.4]nonane-3-carboxamide 22d**



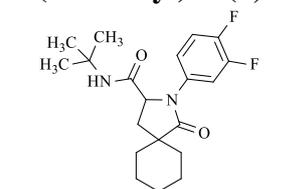
Yield – 68%, white solid, mp 123-125°C. ¹H NMR (400 MHz, CDCl₃): 7.25 (m, 2H); 7.03 (m, 2H); 6.16 (s, 1H); 4.44 (d, 2H, *J* = 6.2 Hz); 4.06 (dd, 1H, *J* = 8.8 Hz, 5.4 Hz); 3.59 (dd, 1H, *J* = 13.4 Hz, 9.4 Hz); 2.64 (dd, 1H, *J* = 13.4 Hz, 5.4 Hz); 2.31 (dd, 1H, *J* = 13.4 Hz, 9.4 Hz); 1.94 (m, 4H); 1.80 (m, 2H); 1.58-1.71 (m, 3H); 1.53 (m, 1H); 1.44 (m, 1H); 0.88 (d, 3H, *J* = 6.4 Hz); 0.81 (d, 3H, *J* = 6.2 Hz). MS (ESI, *m/z*): 345.5 [M+H]⁺.

2-(3-Chlorophenyl)-N-(4-fluorobenzyl)-1-oxo-2-azaspiro[4.4]nonane-3-carboxamide 22e

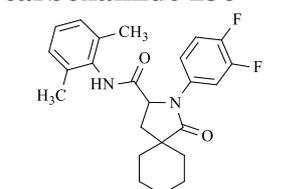
Yield – 71%, beige solid, mp >200°C. ¹H NMR (400 MHz, CDCl₃): 7.66 (s, 2H); 7.39 (d, 1H, *J* = 9.1 Hz); 7.28 (m, 5H); 7.17 (d, 2H, *J* = 7.9 Hz); 6.93 (m, 8H); 5.99 (s, 1H); 4.64 (dd, 1H, *J* = 8.5, 5.8 Hz); 4.35 (m, 2H); 2.49 (dd, 1H, *J* = 13.0, 8.5 Hz); 2.13 (dd, 1H, *J* = 13.0, 5.8 Hz); 2.02 (m, 2H); 1.86 (m, 2H); 1.66 (m, 5H). MS (ESI, *m/z*): 401.9 [M+H]⁺.

N-(tert-Butyl)-2-(3,4-dimethylbenzyl)-1-oxo-2-azaspiro[4.5]decane-3-carboxamide 23a

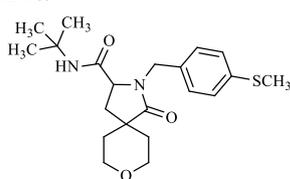
Yield – 82%, yellowish solid, mp >200°C. ¹H NMR (400 MHz, CDCl₃): 7.02 (m, 2H); 6.94 (s, 1H); 5.77 (d, 1H, *J* = 14.8 Hz); 5.27 (s, 1H); 4.52 (d, 1H, *J* = 14.8 Hz); 3.51 (m, 1H); 2.28 (s, 3H); 2.21 (s, 3H); 1.78 (m, 6H); 1.54 (m, 1H); 1.31 (s, 9H). MS (ESI, *m/z*): 367.1 [M+H]⁺.

N-(tert-Butyl)-2-(3,4-difluorophenyl)-1-oxo-2-azaspiro[4.5]decane-3-carboxamide 23b

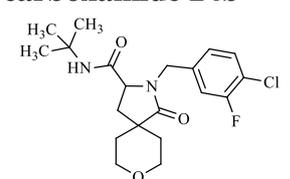
Yield – 92%, white solid, mp >200°C. ¹H NMR (400 MHz, CDCl₃): 7.64 (m, 1H); 7.15 (m, 2H); 5.35 (s, 1H); 4.39 (dd, 1H, *J* = 8.8 Hz, 6.4 Hz); 2.52 (dd, 1H, *J* = 13.6 Hz, 8.8 Hz); 2.01 (dd, 1H, *J* = 13.6 Hz, 6.4 Hz); 1.70 (m, 6H); 1.49 (m, 1H); 1.36 (m, 3H); 1.22 (s, 9H). MS (ESI, *m/z*): 365.6 [M+H]⁺.

2-(3,4-Difluorophenyl)-N-(2,6-dimethylphenyl)-1-oxo-2-azaspiro[4.5]decane-3-carboxamide 23c

Yield – 87%, beige solid, mp >200°C. ¹H NMR (400 MHz, CDCl₃): 7.72 (s, 1H); 7.19 (m, 1H); 7.10 (m, 1H); 7.02 (m, 2H); 6.96 (s, 1H); 4.78 (t, 1H, *J* = 7.2 Hz); 2.74 (dd, 1H, *J* = 12.6 Hz, 9.4 Hz); 2.20 (dd, 1H, *J* = 12.6 Hz, 5.6 Hz); 1.93 (s, 6H); 1.76 (m, 5H); 1.57 (m, 2H); 1.40 (m, 3H). MS (ESI, *m/z*): 314.4 [M+H]⁺.

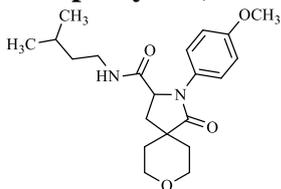
N-(tert-Butyl)-2-(4-methylthiobenzyl)-1-oxo-8-oxa-2-azaspiro[4.5]decane-3-carboxamide 24a

Yield – 82%, beige solid, mp 198-200°C. ¹H NMR (400 MHz, CDCl₃): 7.21 (d, 1H, *J* = 8.2 Hz); 7.13 (d, 1H, *J* = 8.2 Hz); 5.30 (s, 1H); 5.01 (d, 1H, *J* = 14.6 Hz); 4.00 (m, 1H, *J* = 11.7, 3.9 Hz); 3.90 (d, 1H, *J* = 14.7 Hz); 3.59 (dd, 1H, *J* = 8.6, 6.2 Hz); 3.50 (m, 1H); 2.48 (s, 1H); 2.28 (dd, 1H, *J* = 13.1, 8.5 Hz); 2.16 (m, 1H); 1.99 (m, 1H); 1.49 (m, 1H); 1.32 (s, 4H); 1.22 (m, 1H). MS (ESI, *m/z*): 391.6 [M+H]⁺.

N-(tert-Butyl)-2-(4-chloro-3-fluorobenzyl)-1-oxo-8-oxa-2-azaspiro[4.5]decane-3-carboxamide 24b

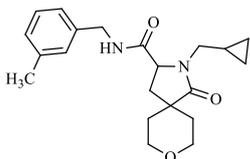
Yield – 78%. beige solid, mp 193-194°C. ¹H NMR (400 MHz, CDCl₃): 7.25 (d, 1H, *J* = 6.4 Hz); 7.07-7.15 (m, 2H); 5.30 (s, 1H); 4.99 (d, 1H, *J* = 14.7 Hz); 4.01 (m, 2H); 3.91 (d, 1H, *J* = 14.8 Hz); 3.59 (dd, 1H, *J* = 8.4, 6.1 Hz); 3.50 (m, 2H); 2.30 (dd, 1H, *J* = 13.1, 8.5 Hz); 2.15 (m, 1H); 1.99 (m, 2H); 1.51 (d, 1H, *J* = 12.2 Hz); 1.34 (s, 9H); 1.23 (m, 2H). MS (ESI, *m/z*): 397.9 [M+H]⁺.

***N*-Isopentyl-2-(4-methoxyphenyl)-1-oxo-8-oxa-2-azaspiro[4.5]decane-3-carboxamide 24c**



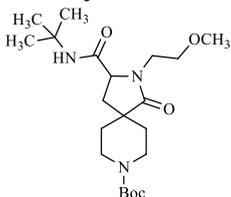
Yield – 67%. White solid, mp 138-140°C. ¹H NMR (400 MHz, CDCl₃): 7.43 (d, 2H, *J* = 9.0 Hz); 6.92 (d, 2H, *J* = 9.1 Hz); 5.50-5.69 (m, 1H); 4.59 (dd, 1H, *J* = 8.9, 5.6 Hz); 4.02 (m, 2H); 3.81 (s, 3H); 3.56 (m, 2H); 3.25 (m, 1H); 3.13 (m, 1H); 2.57 (dd, 1H, *J* = 13.1, 8.8 Hz); 2.20 (m, 2H); 2.06 (m, 1H); 1.53 (m, 1H); 1.43 (m, 1H); 1.20 (m, 3H); 0.79 (d, 6H, *J* = 6.1 Hz). MS (ESI, *m/z*): 375.6 [M+H]⁺.

2-(Cyclopropylmethyl)-*N*-(3-methylbenzyl)-1-oxo-8-oxa-2-azaspiro[4.5]decane-3-carboxamide 24d



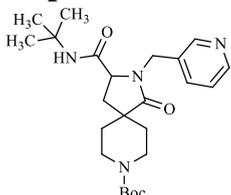
Yield – 68%, white solid, mp 114-115°C. ¹H NMR (400 MHz, CDCl₃): 7.24 (m, 1H); 7.13 (m, 1H); 7.05 (m, 2H); 6.18 (s, 1H); 4.52 (m, 1H); 3.94 (m, 2H); 3.48 (m, 2H); 3.43 (m, 2H); 2.65 (dd, 2H, *J* = 14.4 Hz, 8.0 Hz); 2.44 (dd, 2H, *J* = 13.2 Hz, 9.2 Hz); 2.35 (s, 3H); 2.02 (m, 3H); 1.55 (m, 1H); 1.29 (m, 3H); 0.86 (m, 1H); 0.54 (m, 1H); 0.45 (m, 1H); 0.23 (m, 1H); 0.14 (m, 1H). MS (ESI, *m/z*): 357.7 [M+H]⁺.

***tert*-Butyl 3-(*N*-*tert*-butylcarbamoyl)-2-(2-methoxyethyl)-1-oxo-2,8-diazaspiro[4.5]decane-8-carboxylate 25a**



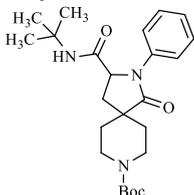
Yield – 59%, white solid, mp 192-193°C. ¹H NMR (400 MHz, CDCl₃): .32 (s, 1H); 4.00 (m, 2H); 3.78 (m, 1H); 3.69 (m, 1H); 3.51 (m, 1H); 3.20 (m, 1H); 2.96 (m, 2H); 2.23 (m, 1H); 2.05 (m, 1H); 1.92 (m, 1H); 1.87 (m, 1H); 1.54 (m, 1H); 1.46 (s, 9H); 1.37 (s, 1H). MS (ESI, *m/z*): 412.8 [M+H]⁺.

***tert*-Butyl 3-(*N*-*tert*-butylcarbamoyl)-1-oxo-2-(pyridin-3-ylmethyl)-2,8-diazaspiro[4.5]decane-8-carboxylate 25b**



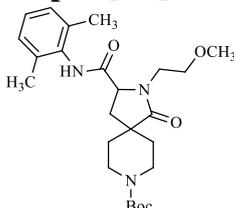
Yield – 73%, beige solid, mp >200°C. ¹H NMR (400 MHz, CDCl₃): 8.59 (m, 2H); 7.78 (m, 1H); 7.41 (m, 1H); 5.76 (m, 1H); 5.00 (d, 1H, *J* = 15.2 Hz); 4.10 (m, 1H); 3.98 (m, 2H); 3.78 (m, 1H); 2.90 (m, 2H); 2.23 (m, 1H); 1.98 (m, 1H); 1.81 (m, 1H); 1.60 (m, 1H); 1.46 (s, 9H); 1.32 (s, 9H). MS (ESI, *m/z*): 445.7 [M+H]⁺.

***tert*-Butyl 3-(*N*-*tert*-butylcarbamoyl)-1-oxo-2-phenyl-2,8-diazaspiro[4.5]decane-8-carboxylate 25c**



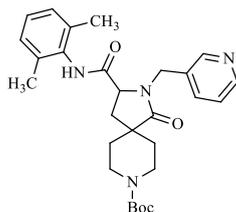
Yield – 62%, beige solid, mp >200°C. ¹H NMR (400 MHz, CDCl₃): 7.50 (d, 2H, *J* = 8.0 Hz); 7.40 (t, 2H, *J* = 8.4 Hz); 7.22 (t, 1H, *J* = 7.2 Hz); 5.38 (s, 1H); 4.53 (m, 1H); 4.04 (m, 2H); 3.03 (m, 2H); 2.52 (m, 1H); 2.13 (m, 1H); 2.04 (m, 1H); 1.89 (m, 1H); 1.65 (m, 2H); 1.58 (m, 1H); 1.48 (s, 9H); 1.16 (s, 1H). MS (ESI, *m/z*): 430.8 [M+H]⁺.

***tert*-Butyl 3-[*N*-(2,6-dimethylphenyl)carbamoyl]-2-(2-methoxyethyl)-1-oxo-2,8-diazaspiro[4.5]decane-8-carboxylate 25d**



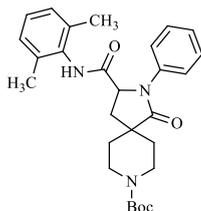
Yield – 78%, white solid, mp 86-87°C. ¹H NMR (400 MHz, CDCl₃): 8.07 (s, 1H); 7.11 (m, 3H); 4.57 (m, 1H); 4.40 (m, 1H); 4.01 (m, 2H); 3.86 (m, 2H); 3.42 (m, 1H); 3.34 (s, 3H); 3.00 (m, 2H); 2.41 (m, 1H); 2.23 (s, 6H); 2.18 (m, 1H); 1.97 (m, 1H); 1.85 (m, 1H); 1.59 (m, 1H); 1.47 (s, 9H). MS (ESI, *m/z*): 460.7 [M+H]⁺.

***tert*-Butyl 3-[*N*-(2,6-dimethylphenyl)carbamoyl]-1-oxo-2-(3-pyridylmethyl)-2,8-diazaspiro[4.5]decane-8-carboxylate 25e**



Yield – 89%, yellowish solid, mp 144-145°C. ¹H NMR (400 MHz, CDCl₃): 8.56 (s, 1H); 7.70 (d, 1H, *J* = 6.8 Hz); 7.53 (s, 1H); 7.37 (s, 1H); 7.12 (m, 3H); 5.26 (d, 1H, *J* = 15.6 Hz); 4.16 (m, 1H); 4.00 (m, 2H); 2.99 (m, 2H); 2.36 (m, 1H); 2.22 (s, 6H); 2.12 (m, 1H); 2.02 (m, 1H); 1.85 (m, 1H); 1.64 (m, 1H); 1.47 (s, 9H); 1.33 (m, 1H). MS (ESI, *m/z*): 493.8 [M+H]⁺.

***tert*-Butyl 3-[*N*-(2,6-dimethylphenyl)carbamoyl]-1-oxo-2-phenyl-2,8-diazaspiro[4.5]decane-8-carboxylate 25f**



Yield – 75%, beige solid, mp >200°C (dec). ¹H NMR (400 MHz, CDCl₃): 7.94 (m, 1H); 7.62 (d, 2H, *J* = 7.6 Hz); 7.44 (t, 2H, *J* = 8.0 Hz); 7.25 (t, 1H, *J* = 7.6 Hz); 7.06 (m, 2H); 6.98 (d, 2H, *J* = 7.6 Hz); 4.05 (m, 2H); 3.07 (m, 2H); 2.71 (m, 1H); 2.24 (m, 1H); 2.11 (m, 1H); 1.91 (m, 1H); 1.84 (s, 6H); 1.68 (m, 1H); 1.54 (m, 1H); 1.49 (s, 9H). MS (ESI, *m/z*): 478.6 [M+H]⁺.