



Multicomponent approach to unique 1,4-diazepine-2-amines

Volodymyr Kysil^{a,*}, Alexander Khvat^a, Sergey Tsirulnikov^b, Sergey Tkachenko^a, Alexandre Ivachtchenko^a

^a ChemDiv, Inc., 6605 Nancy Ridge Dr., San Diego, CA 92121, USA

^b Chemical Diversity Research Institute, Khimki, Moscow Reg. 114401, Russia

ARTICLE INFO

Article history:

Received 20 February 2009

Revised 17 March 2009

Accepted 18 March 2009

Available online 25 March 2009

Keywords:

Isocyanide-based multicomponent reaction (IMCR)

1,4-Diazepine-2-amine

1,4-Diazepine ring synthesis

Trimethylchlorosilane (TMSCl)

Spiro-compounds

ABSTRACT

Isocyanide-based multicomponent reaction (IMCR) of 1,3-diaminopropane with carbonyl compounds has been developed as an efficient strategy for the synthesis of 1,4-diazepine-2-amines. Brønsted and Lewis acids are able to promote the reaction, and TMSCl has been found to be the most efficient among them. The IMCR is applicable to a variety of carbonyl compounds and isocyanides.

© 2009 Elsevier Ltd. All rights reserved.

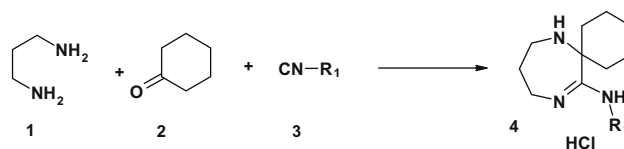
1,4-Diazepines are of considerable importance due to their wide spectrum of biological activity. For instance, substituted 1,4-diazepines have been reported as dipeptidyl peptidase IV inhibitors for treatment of type 2 diabetes¹, gelatinase type A (MMP-2) and type B (MMP-9) and collagenase 3 (MMP-13) inhibitors (potentially antiarthritic and oncolytic drugs),² HDM2 antagonists,³ caspase inhibitors,⁴ LFA-1/ICAM-1 interaction inhibitors (antipsoriatics),⁵ chymase inhibitors (agents for treatment of atopic dermatitis),⁶ integrin alphaLbeta2 (LFA-1) antagonists,⁷ 5-HT_{2C} agonists,⁸ melanocortin MC1 and MC4 receptor agonists.⁹ In addition, the nucleus of highly functionalized 1,4-diazepine is a key structural fragment of recently isolated *Streptomyces* sp. II novel lipo-nucleoside antibiotics caprazamycins.¹⁰ Moreover, according to Prous Science Integrity data,¹¹ several functionalized 1,4-diazepines are currently being developed in phase II clinical studies for treatment of several conditions: overactive bladder or urge urinary incontinence,¹² schizophrenia, obesity,¹³ nausea and vomiting.¹⁴ Therefore, 1,4-diazepines are an attractive synthetic target. Although many synthetic routes for 1,4-diazepine ring construction have been developed, novel flexible strategies for the synthesis of diverse hitherto unknown 1,4-diazepines should benefit both synthetic heterocyclic and medicinal chemistry.

During the past decade, isocyanide-based multicomponent reactions (IMCRs) gained significant interest within the scientific community as an efficient, convenient, time-saving, and atom-economical approach to a variety of drug-like small heterocyclic mol-

ecules.¹⁵ At the same time, only a few examples of the IMCR-based approaches for the synthesis of 1,4-diazepines have been reported.¹⁶

We have recently reported an unprecedented IMCR of ethylenediamine(s) with carbonyl compounds which leads to highly substituted pyrazine-2-amines.¹⁷ We assumed that this IMCR could be broadened to the synthesis of 1,4-diazepine-2-amines if 1,3-diamines are involved as starting diamines. The present Letter describes such extension as a part of scope evaluation of the mentioned IMCR. It should be noted, that while IMCRs of 1,2-diazanucleophiles including primary amines are under extensive elaboration for the last few years,^{18,19} only one example of seven-membered ring formation employing 5-(2-pyrrolidinyl)methyl-1H-tetrazole as a 1,3-diazanucleophile has been reported^{18d} to date.

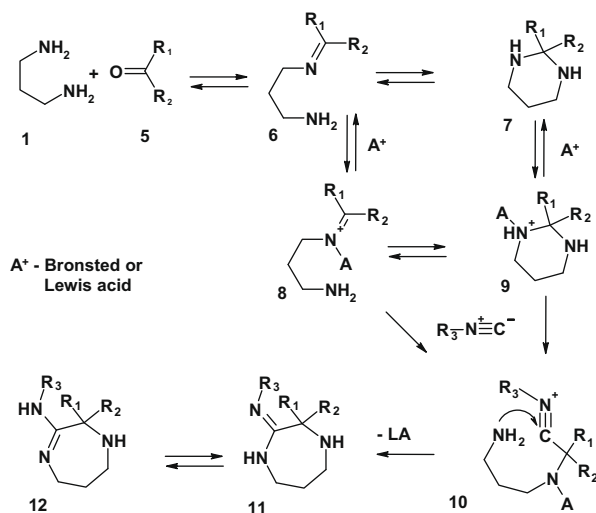
In our initial experiments, we evaluated conditions and potential promoters for the IMCR performance on a model reaction of 1,3-diaminopropane **1**, cyclohexanone **2**, and *tert*-butyl isocyanide **3a** (Scheme 1). Notably, acidic catalysis is usually required



Scheme 1. IMCR of 1,3-diaminopropane with cyclohexanone and various isocyanides.

* Corresponding author. Tel.: +1 858 794 4860; fax: +1 858 794 4931.

E-mail addresses: vkysil@chemdiv.com, vkysil@sbcglobal.net (V. Kysil).



Scheme 2. Proposed mechanistic scenario of the IMCR of 1,3-diaminopropane with carbonyl compounds.

for successful IMCRs. In the case of the most popular Passerini and Ugi IMCRs, carboxylic acid, which is one of the components of these reactions, plays the role of activating agent due to protonation of C=O or C=N bonds consequently for further reaction with isocyanide. Otherwise, Brønsted or Lewis acid activation is necessary, and the success of such reactions dramatically depends on the right choice of acid.¹⁹ Therefore, the following set of potential acidic promoters was selected on the basis of previously reported acid-catalyzed reactions of carbonyl and azomethine compounds with various π -C-nucleophiles including isocyanides: HCl, TsOH,^{18e,g} Sc(OTf)₃, Yb(OTf)₃,^{18a} TMSCl, TBSOTf, and TMSOTf.^{17,20}

According to LC–MS- (including UV- and ELSD-) monitoring of reaction mixtures, all evaluated additives demonstrated reactivity in the investigated MCR to a certain extent. However, formation of target product **4a** was accompanied by several high molecular weight by-products when these additives were used in catalytic amounts. This might be explained on the basis of a postulated mechanism of the IMCR (Scheme 2).

The mechanism entails condensation of starting carbonyl compound **5** and diamine **1** providing azomethine **6** or cyclic aminal **7** whose activation with acid A⁺ provides intermediates **8** and **9** that are able to react with isocyanide **3** to form cation **10**. Intramolecular attack in the cation **10** assures diazepine ring closure with the formation of imine **11** or its amino-tautomer **12**. Alternatively, highly reactive cation **10** can be trapped by any nucleophile existing in the reaction mixture including starting isocyanide²¹ or available amines that should lead to high molecular weight by-products. As a result of several additional experiments, we found that these side reactions could be minimized when TMSCl was used in equimolar ratio. This improved the reaction outcome in yield and purity of target compound

Table 1

Synthesis of 1,4-diazepine-2-amines by the IMCR of 1,3-diaminopropane and carbonyl compounds

Entry	Carbonyl compound	Isocyanide	Product	Yield (%)
1	Cyclohexanone 2	<i>tert</i> -Butyl isocyanide 3a	4a R = <i>t</i> -Bu	63
2	Cyclohexanone 2	Cyclopentyl isocyanide 3b	4b R = <i>cyclo</i> -C ₅	81
3	Cyclohexanone 2	Benzyl isocyanide 3c	4c R = Bn	79
4	Cyclohexanone 2	4-Chlorobenzyl isocyanide 3d	4d R = 4-ClC ₆ H ₄ CH ₂	91
5	Tetrahydro-4H-thiopyran-4-one 13a	Cyclohexyl isocyanide 3e	15a X = S	72
6	<i>N</i> -Boc-piperidone-4 13b	Cyclohexyl isocyanide 3e	15b X = <i>N</i> -Boc	62
7	4-Methoxybenzaldehyde 14a	Cyclohexyl isocyanide 3e	16a R = 4-MeOC ₆ H ₄	64
8	1-Methyl-pyrrole-2-carbaldehyde 14b	Cyclohexyl isocyanide 3e	16b R = 1-Methylpyrrol-2-yl	59

and allowed isolation of target material employing chromatography-free simple work-up and purification procedures.²²

We further evaluated a small set of additional isocyanides **3b–d** in the IMCR of cyclohexanone and 1,3-diaminopropane under our discovered conditions (Scheme 1). In addition, two more ketones (namely tetrahydro-4H-thiopyran-4-one **13a** and *N*-Boc-piperidone-4 **13b**) and two aldehydes (*p*-methoxybenzaldehyde **14a** and 1-methyl-pyrrole-2-carbaldehyde **14b**) were allowed to react with 1,3-diaminopropane and cyclohexyl isocyanide with the hope of expanding the scope of this reaction (Scheme 3). We were pleased to find that all these reactions proceeded cleanly, providing target 1,4-diazepine-2-amines **4**, **15**, and **16** in good yields (Table 1, entries 1–8).

Spectral data for the synthesized compounds were found to be in a good agreement with proposed structures of 1,4-diazepine-2-amine monohydrochlorides.²³

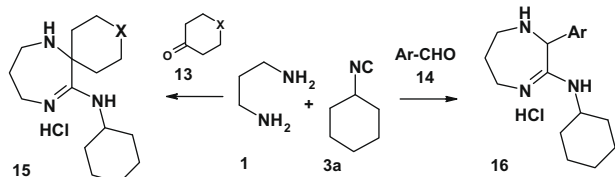
In conclusion, we have reported a novel strategy for the 1,4-diazepine ring construction based on MCR of 1,3-propanediamine, carbonyl compounds, and isocyanides, which allows the synthesis of hitherto unknown highly substituted 1,4-diazepine-2-amines including spiro-heterocycles. While scope of the IMCR is still under evaluation, it appears to be general with regard to carbonyl and isocyanide components. Further scope evaluation of the IMCR with respect to a variety of 1,3-diamines, carbonyl compounds, and isocyanides as well as applications of the IMCR are now under investigation in our laboratories.

Acknowledgment

The authors thank Dr. Frederick Lakner for critical reading and correction of this Letter.

References and notes

- (a) Biftu, T.; Feng, D.; Qian, X.; Liang, G. B.; Kieczkowski, G.; Eiermann, G.; He, H.; Leiting, B.; Lyons, K.; Petrov, A.; Sinha-Roy, R.; Zhang, B.; Scapin, G.; Patel, S.; Gao, Y. D.; Singh, S.; Wu, J.; Zhang, X.; Thornberry, N. A.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 49–52; (b) Liang, G. B.; Qian, X.; Feng, D.; Biftu, T.; Eiermann, G.; He, H.; Leiting, B.; Lyons, K.; Petrov, A.; Sinha-Roy, R.; Zhang, B.; Wu, J.; Zhang, X.; Thornberry, N. A.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1903–1907.
- (a) Zhang, Y. M.; Fan, X.; Yang, S. M.; Scannevin, R. H.; Burke, S. L.; Rhodes, K. J.; Jackson, P. F. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 405–408; (b) Zask, A.; Kaplan, J.; Du, X. M.; Sandanayaka, V.; Eudy, N.; Levin, J.; Jin, G.; Xu, J.; Cummons, T.; Barone, D.; Ayral-Kaloustian, S.; Skotnicki, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1641–1645.
- Raboisson, P.; Marugán, J. J.; Schubert, C.; Koblisch, H. K.; Lu, T.; Zhao, S.; Player, M. R.; Maroney, A. C.; Reed, R. L.; Huebert, N. D.; Lattanze, J.; Parks, D. J.; Cummings, M. D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1857–1861.



Scheme 3. IMCR of 1,3-diaminopropane with cyclohexyl isocyanide and various carbonyl compounds.

4. Mondragon, L.; Orzaez, M.; Sanclimens, G.; Moure, A.; Arminan, A.; Sepulveda, P.; Messeguer, A.; Vicent, M. J.; Perez-Paya, E. *J. Med. Chem.* **2008**, *51*, 521–529.
5. Oberhauser, B.; Scholz, D. WO 2006111371, 2006.
6. Maruoka, H.; Muto, T.; Tanaka, T.; Imajo, S.; Tomimori, Y.; Fukuda, Y.; Nakatsuka, T. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3435–3439.
7. (a) Wattanasin, S.; Kallen, J.; Myers, S.; Guo, Q.; Sabio, M.; Ehrhardt, C.; Albert, R.; Hommel, U.; Weckbecker, G.; Welzenbach, K.; Weitz-Schmidt, G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1217–1220; (b) Wattanasin, S.; Albert, R.; Ehrhardt, C.; Roche, D.; Sabio, M.; Hommel, U.; Welzenbach, K.; Weitz-Schmidt, G. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 499–502.
8. (a) Ahmad, S.; Ngu, K. WO 2006086464, 2006; (b) Ahmad, S.; Ngu, K.; Miller, K.; Wu, G.; Hung, C.-P.; Malmstrom, S.; Zhang, G.; Otanyi, E.; Keim, W. J.; Cullen, M. J.; Rohrbach, K. W.; Thomas, M.; Gan, J.; Narayanan, R.; Pelleymounter, M. A.; Robl, J. 232nd ACS Natl. Meet. (September 10–14, San Francisco), 2006, Abst. MEDI 408.
9. Szewczyk, J. R.; Speake, J. D.; Sammond, D. M.; Sherrill, R. G. WO 2005118573, 2005.
10. Igarashi, M.; Takahashi, Y.; Shitara, T.; Nakamura, H.; Naganawa, H.; Miyake, T.; Akamatsu, Y. *J. Antibiot.* **2005**, *58*, 327–337.
11. <http://integrity.prous.com/integrity/servelet/xmlxsl>.
12. (a) Dvorak, C. A.; Fisher, L. E.; Green, K. L.; Stabler, R. S.; Maag, H.; Prince, A.; Repke, D. B.; Harris, R. N. III WO 2001090081, 2001; (b) Cefalu, J. S.; Harris, R.; Maag, H.; Nunn, P. A.; Ford, A.; Hedge, S.; Wyllie, M. G. *J. Urol.* **2007**, *177*, Abst. 424.
13. Ramamoorthy, S. P. WO 2003091250, 2003.
14. (a) Harada, H.; Morie, T.; Kato, S. *Chem. Pharm. Bull.* **1998**, *46*, 1160–1164; (b) Yoshida, N. *J. Pharmacol. Exp. Ther.* **1992**, *260*, 1159–1165; (c) Yoshida, N.; Omoya, H.; Kato, S.; Ito, T. *Eur. J. Pharmacol.* **1992**, *216*, 435–440.
15. For recent reviews covering IMCRs and their applications see: (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89; (b) Akritopoulou-Zanze, I.; Djuric, S. W. *Heterocycles* **2007**, *73*, 125–147; (c) Akritopoulou-Zanze, I. *Curr. Opin. Chem. Biol.* **2008**, *12*, 324–331; (d) Hulme, C. In *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley-VCH, Verlag GmbH & Co.KGaA: Weinheim, 2005; pp 311–341; (e) Hulme, C.; Gore, V. *Current Med. Chem.* **2003**, *10*, 51–80; (f) Doemling, A. In *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley-VCH, Verlag GmbH & Co.KGaA: Weinheim, 2005; pp 76–94; (g) Marcaccini, S.; Torroba, T. In *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley-VCH, Verlag GmbH & Co.KGaA: Weinheim, 2005; pp 33–75; (h) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133–1144; (i) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899–907; (j) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210; (k) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463–472.
16. For examples of 1,4-diazepines synthesis employing IMCR based strategies see: (a) Banfi, L.; Basso, A.; Guanti, G.; Kielland, N.; Repetto, C.; Riva, R. *J. Org. Chem.* **2007**, *72*, 2151–2160; (b) Shaabani, A.; Maleki, A.; Mofakham, H.; Moghimi-Rad, J. *J. Org. Chem.* **2008**, *73*, 3925–3927; (c) Zychilinski, A. V.; Ugi, I. *Heterocycles* **1998**, *49*, 29–32; (d) Rossen, K.; Sager, J.; DiMichele, L. M. *Tetrahedron Lett.* **1997**, *38*, 3183–3186.
17. Kysil, V.; Tkachenko, S.; Khvat, A.; Williams, C.; Tsirulnikov, S.; Churakova, M.; Ivachtchenko, A. *Tetrahedron Lett.* **2007**, *48*, 6239–6244.
18. Besides our report,¹⁷ see also: (a) Keung, W.; Bakir, F.; Patron, A. P.; Rogers, D.; Priest, Ch. D.; Darmohusodo, V. *Tetrahedron Lett.* **2004**, *45*, 733–737; (b) Carballeas, S.; Espinosa, J. F. *Org. Lett.* **2005**, *7*, 2329–2331; (c) Illgen, K.; Nerdinger, S.; Behnke, D.; Friedrich, C. *Org. Lett.* **2005**, *7*, 2517–2518; (d) Franckevičius, V.; Longbottom, D. A.; Turner, R. M.; Ley, S. V. *Synthesis* **2006**, *19*, 3215–3223; (e) Shaabani, A.; Maleki, A.; Moghimi-Rad, J. *J. Org. Chem.* **2007**, *72*, 6309–6311; (f) Krasavin, M.; Parchinsky, V. *Synlett* **2008**, 645–648; (g) Shaabani, A.; Maleki, A.; Mofakham, H.; Khavasi, H. R. *J. Comb. Chem.* **2008**, *10*, 323–326; (h) Heravi, M. M.; Baghernejad, B.; Oskooie, H. A. *Tetrahedron Lett.* **2009**, *50*, 767–769; (i) Krasavin, M.; Shkavrov, S.; Parchinsky, V.; Bukhryakov, K. *J. Org. Chem.* **2009**, *74*, 2627–2629.
19. For the most recent comprehensive review concerning less conventional versus 'classic' Ugi IMCR interactions between isocyanides and iminium species following by trapping (including intramolecular) of nitrilium cation by N-, C-, O-, and S-nucleophiles see: El Kaim, L.; Grimaud, L. *Tetrahedron* **2009**, *65*, 2153–2171.
20. For selected examples of silicon Lewis acid catalyzed reactions see: (a) Xia, Q.; Ganem, B. *Org. Lett.* **2002**, *4*, 1631–1634; (b) Denmark, S. E.; Fan, Y. *J. Org. Chem.* **2005**, *70*, 9667–9776; (c) Dilman, A. D.; Ioffe, S. L. *Chem. Rev.* **2003**, *103*, 733–772; (d) Krasavin, M.; Tsirulnikov, S.; Nikulnikov, M.; Kysil, V.; Ivachtchenko, A. *Tetrahedron Lett.* **2008**, *49*, 5241–5243.
21. For representative examples of isocyanide double addition/insertion, see: (a) Tobisu, M.; Ito, S.; Kitajima, A.; Chatani, N. *Org. Lett.* **2008**, *10*, 5223–5225; (b) Tobisu, M.; Kitajima, A.; Yoshioka, S.; Hyodo, I.; Oshita, M.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 11431–11437; (c) Winkler, J. D.; Asselin, S. M. *Org. Lett.* **2006**, *8*, 3975–3977; (d) Nair, V.; Menon, R. S.; Deepthi, A.; Devi, B. R.; Bijju, A. T. *Tetrahedron Lett.* **2005**, *46*, 1337–1339; (e) Oshita, M.; Yamashita, K.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 761–766; (f) Yoshioka, S.; Oshita, M.; Tobisu, M.; Chatani, N. *Org. Lett.* **2005**, *7*, 3697–3699; (g) Chatani, N.; Oshita, M.; Tobisu, M.; Ishii, Y.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 7812–7813; (h) Bez, G.; Zhao, C.-G. *Org. Lett.* **2003**, *5*, 4991–4993; (i) Xia, Q.; Ganem, B. *Synthesis* **2002**, *14*, 1969–1972; (j) Koziowski, A. P.; Park, P. U. *J. Org. Chem.* **1984**, *49*, 1674–1676.
22. General procedure for the MCR of 1,3-diaminopropane, carbonyl compounds, and isocyanides. A mixture of carbonyl compound (0.5 mmol), 1,3-diaminopropane (0.5 mmol), and methanol (1 mL) was stirred in a 10 mL capped tube for 3 h at 45–50 °C. Solutions of TMSCl (500 µL of 1 M, 0.5 mmol) in acetonitrile and isocyanide (500 µL of 1 M, 0.5 mmol) in methanol were added into the reaction mixture, which was stirred at 50–60 °C for 4 h and then at 40–50 °C until completion of the reaction (based on LC–MS/ELSD-monitoring; reactions usually required stirring for 20–24 h). Volatiles were evaporated under reduced pressure and the residue was treated with dry EtOAc, kept in an ultrasonic bath until completion of precipitate formation, then centrifuged. Precipitate was washed twice with EtOAc, acetonitrile, and Et₂O with centrifugation each time, and dried under reduced pressure. The procedure usually provided pure monohydrochlorides of target materials.
23. Data for the representative examples of synthesized compounds:
N-(*tert*-Butyl)-7,11-diazaspiro[5.6]dodec-11-en-12-amine hydrochloride **4a**. ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 8.06 (br t, *J* = 4.5 Hz, 1H); 7.41 (br s, 1H); 3.75–3.79 (m, 2H); 2.82 (br t, *J* = 6.0 Hz, 1H); 2.72–2.80 (m, 2H); 1.81–1.91 (m, 2H); 1.67–1.76 (m, 4H); 1.29–1.64 (m, 6H); 1.40 (s, 9H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) 172.9; 61.7; 54.1; 42.5; 32.3; 29.9; 28.4; 28.3; 24.1; 21.0. HRMS (ESI-TOF): calcd for C₁₄H₂₇N₃ (M+H⁺) 238.2278, found 238.2285.
N-Benzyl-7,11-diazaspiro[5.6]dodec-11-en-12-amine hydrochloride **4c**. ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 9.41 (br t, *J* = 5.7 Hz, 1H); 9.06 (br t, 1H); 7.24–7.38 (m, 5H); 4.56 (d, *J* = 5.7 Hz, 2H); 3.50–3.57 (m, 2H); 2.87 (br t, *J* = 6.1 Hz, 1H); 2.76–2.83 (m, 2H); 1.40–1.92 (m, 11H); 1.21–1.33 (m, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) 173.9; 136.2; 128.9; 127.9; 127.5; 61.1; 44.8; 41.9; 32.8; 30.0; 24.6; 20.9. HRMS (ESI-TOF): calcd for C₁₇H₂₅N₃ (M+H⁺) 272.2121, found 272.2125.
N-Cyclohexyl-3-thia-7,11-diazaspiro[5.6]dodec-11-en-12-amine hydrochloride **15a**. ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 9.22 (br s, 1H); 8.22 (br d, *J* = 8.0 Hz, 1H); 3.70–3.75 (m, 1H); 3.55–3.63 (m, 2H); 2.97–3.08 (m, 3H); 2.74–2.82 (m, 2H); 2.25–2.34 (m, 2H); 2.07–2.17 (m, 2H); 1.96–2.04 (m, 2H); 1.52–1.79 (m, 7H); 1.23–1.41 (m, 4H); 0.98–1.11 (m, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) 171.3; 60.5; 51.7; 41.1; 38.9; 33.2; 31.3; 29.7; 25.2; 24.8; 22.3. HRMS (ESI-TOF): calcd for C₁₅H₂₇N₃S (M+H⁺) 282.1998, found 282.1995.
tert-Butyl 12-(cyclohexylamino)-3,7,11-triazaspiro-[5.6]dodec-11-ene-3-carboxylate hydrochloride **15b**. ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 9.24 (br m, 1H); 8.01 (br d, *J* = 7.8 Hz, 1H); 3.64–3.85 (m, 3H); 3.57–3.63 (m, 2H); 2.88–3.10 (m, 3H); 2.75–2.85 (m, 2H); 1.50–1.94 (m, 11H); 1.37 (s, 9H); 1.18–1.36 (m, 4H); 0.98–1.11 (m, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) 171.1; 154.2; 79.2; 59.4; 51.8; 41.6; 32.1; 31.3; 29.9; 28.6; 25.2; 24.8. HRMS (ESI-TOF): calcd for C₂₀H₃₆N₄O₂ (M+H⁺) 365.2911, found 365.2913.
N-Cyclohexyl-2-(1-methyl-1H-pyrrol-2-yl)-2,5,6,7-tetrahydro-1H-1,4-diazepin-3-amine hydrochloride **16b**. ¹H NMR (400 MHz, DMSO-*d*₆): δ (ppm) 9.58 (br s, 1H); 9.31 (br d, *J* = 6.3 Hz, 1H); 6.78–6.80 (m, 1H); 5.93–5.96 (m, 1H); 5.83–5.85 (m, 1H); 5.30 (d, *J* = 2.5 Hz, 1H); 3.64–3.78 (m, 1H); 3.60 (s, 3H); 3.42–3.58 (m, 2H); 3.23–3.31 (m, 1H); 2.77–2.87 (m, 1H); 2.32–2.43 (m, 1H); 1.79–1.89 (m, 2H); 1.47–1.73 (m, 5H); 1.24–1.38 (m, 3H); 1.04–1.17 (m, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ (ppm) 167.5; 124.7; 124.6; 109.3; 106.9; 57.4; 51.1; 44.2; 43.3; 34.5; 31.5; 31.2; 30.6; 25.2; 24.5; 24.4. HRMS (ESI-TOF): calcd for C₁₆H₂₆N₄ (M+H⁺) 275.2230, found 275.2231.