Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 5437–5440
Tetrahedron Letters

Facile synthesis of acyclic azanucleosides from *N*-pivaloyloxymethyl amides and sulfonamides: synthesis of aza-analogues of *Ganciclovir*

Mariola Koszytkowska-Stawińska and Wojciech Sas*

Warsaw University of Technology, Faculty of Chemistry, ul. Noakowskiego 3, 00-664 Warszawa, Poland

Received 16 February 2004; revised 4 May 2004; accepted 11 May 2004

Abstract—*N*-Pivaloyloxymethyl amides and sulfonamides, readily available from N-alkylation of both amides and sulfonamides with commercial chloromethyl pivaloate, were converted into acyclic azanucleosides via a one-pot base silylation/nucleoside coupling procedure.

Since some acyclic nucleosides are potent antiviral therapeutics, for example, acyclovir, ganciclovir, penciclovir (Fig. 1), their synthesis has attracted considerable attention.[1–3] Sugar mimics of these analogues typically possess oxygen (e.g., acyclovir and ganciclovir) or carbon (e.g., penciclovir) at the 2′-position and at least one hydroxy group (e.g., acyclovir). Acyclic analogues with a nitrogen atom at this position (termed acyclic azanucleosides) are also known, but there is much less work on their synthesis and biological properties, than on the corresponding oxa- and carbo-derivatives.[4–14] Most examples have been amino acid or peptide derivatives of pyrimidines, mostly 5-fluorouracil.[7–13] To our knowledge, the synthesis of aza-analogues of ganciclovir/penciclovir or acyclovir has not been described.

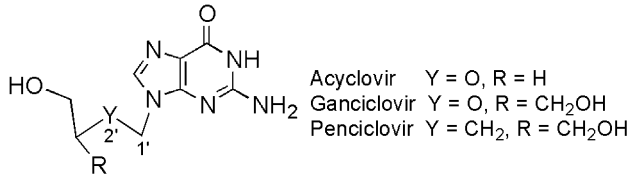


Figure 1.

Thus, our interest in the synthesis of cyclic azanucleosides has been extended recently to the synthesis of acyclic aza-derivatives **A** including aza-analogues **B** of ganciclovir (Fig. 2).[15]

The acyclic azanucleosides **A** (R≠H), which are not peptide or amino acid derivatives have been obtained by coupling silylated bases with *N*-alkoxymethyl amides[5] or *N*-chloromethyl sulfonamides.[6] We envisaged that *N*-pivaloyloxymethyl amides and sulfonamides would be more convenient starting materials for the synthesis of **A** and **B**, than those aforementioned, as they are easy to prepare (by alkylation of amides or sulfonamides with commercial chloromethyl pivaloate[16,17]), are stable and nontoxic.[18]

We first tested this approach to acyclic azanucleosides **3** using *N*-cyclohexyl-*N*-pivaloyloxymethyl-acetamide **2a** and methanesulfonamide **2b** (Scheme 1). Both **2a** and **2b** were obtained in 50% and 72% yield, respectively, from the N-alkylation of acetamide **1a** and sulfonamide **1b** with chloromethyl pivaloate in dry DMF in the presence

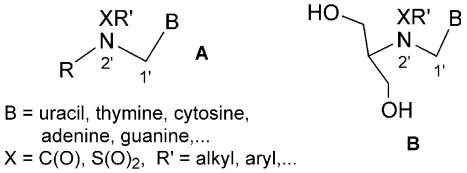
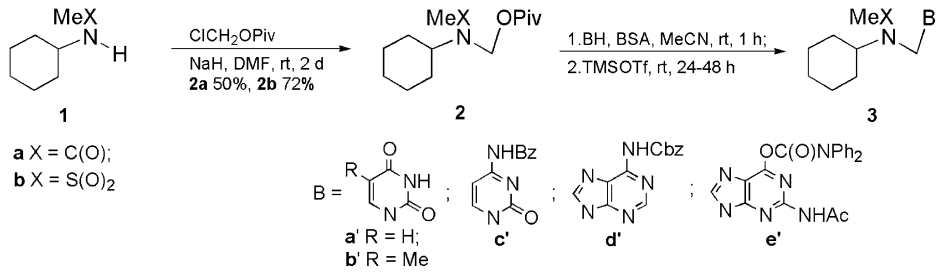


Figure 2.

Keywords: *N*-Pivaloyloxymethyl amides; *N*-Pivaloyloxymethyl sulfonamides; Acyclic azanucleosides.
* Corresponding author. Tel.: +48-22-628-0763; fax: +48-22-628-2741; e-mail: sas@ch.pw.edu.pl

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.05.042

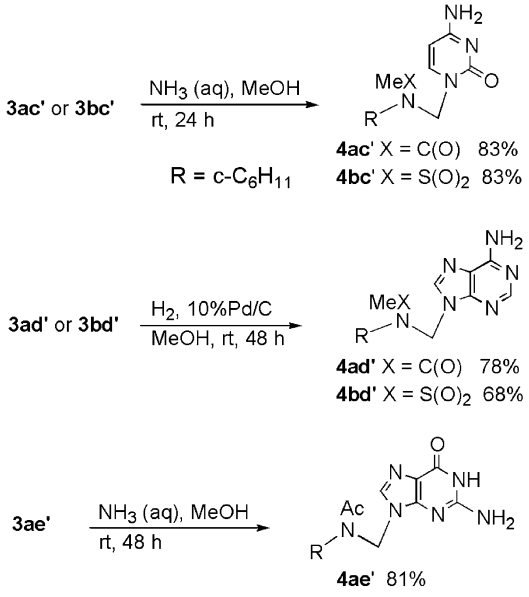


Scheme 1.

Table 1. Synthesis of nucleosides **3**

Entry	Base (BH)	Product **3**, X	Yield [%]
1	Uracil (U)	**aa′**, C(O)	51
2		**ba′**, $S(O)_2$	41
3	Thymine (**T**)	**ab′**, C(O)	70
4	N^4-Benzoylcytosine ($\mathbf{C}^{Bz}$)	**ac′**, C(O)	72[a]
5		**bc′**, $S(O)_2$	56
6	N^6-Cbz-adenine ($\mathbf{A}^{Cbz}$)	**ad′**, C(O)	58
7		**bd′**, $S(O)_2$	22
8	N^2-Acetyl-O^6-diphenyl-	**ae′**, C(O)	45
9	carbamoyl-guanine ($\mathbf{G}^{ADPC}$)	**be′**, $S(O)_2$	0

[a] The overall yield after deprotection.

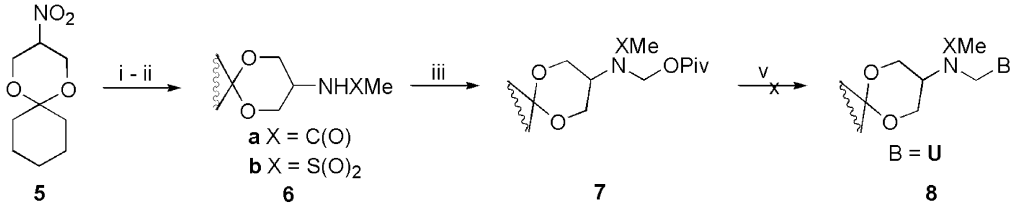


Scheme 2.

of sodium hydride.[19] The derivatives **2** were transformed into **3** by an one pot-base silylation/nucleoside coupling procedure—a version in which *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and trimethylsilyl triflate (TMSOTf) were employed as the silylating agent and as the catalyst, respectively.[20,21] Thus, natural bases, unprotected (uracil and thymine) or protected (N^4-Bz-cytosine, N^6-Cbz-adenine[22] and N^2-Ac-O^6-diphenylcarbamoylguanine[23]), were treated with BSA in acetonitrile, then the corresponding **2** and TMSOTf were added successively and the resulting mixtures were allowed to stand at room temperature for 24 h to afford all the nucleosides **3** except **3be′** (Table 1).[24] An attempt to combine **3b** with $\mathbf{G}^{ADPC}$ in the presence of tin(IV) chloride also failed to yield **3be′**. The regiochemistry of the purine derivatives **3ad′**, **e′** and **3bd′** was derived from HMBC experiments; the correlation of H-1′ with C-8 and C-4, observed for all purine nucleosides, proved that the alkylation took place at *N*-*9*.

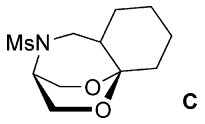
Generally, the *N*-acetyl derivatives **3a** were obtained in higher yield than the corresponding *N*-methanesulfonyl compounds **3b**. The protecting groups were routinely removed from the base moieties by treatment of **3** with methanolic ammonia (**3c′**,**e′**) or by palladium catalyzed hydrogenolysis (**3d′**) to afford nucleosides **4c′**–**e′** in high yields (Scheme 2).

Next this methodology was employed for a synthesis of the aza-analogues of ganciclovir **B**. We utilized as the starting material 2,2-pentamethylene-5-nitro-1,3-dioxane **5**,[25] which was used by us previously for the preparation of branched-chain azaisonucleosides.[26] The approach shown in Scheme 3 was tried initially, thus **5** was converted into *N*-pivaloyloxymethyl derivatives of acetamide **7a** and methanesulfonamide **7b** by the alkylation of the corresponding intermediates **6a** and **6b** with chloromethyl pivaloate as previously described; the yields of **7a** and **7b** were 50% and 70%, respectively.



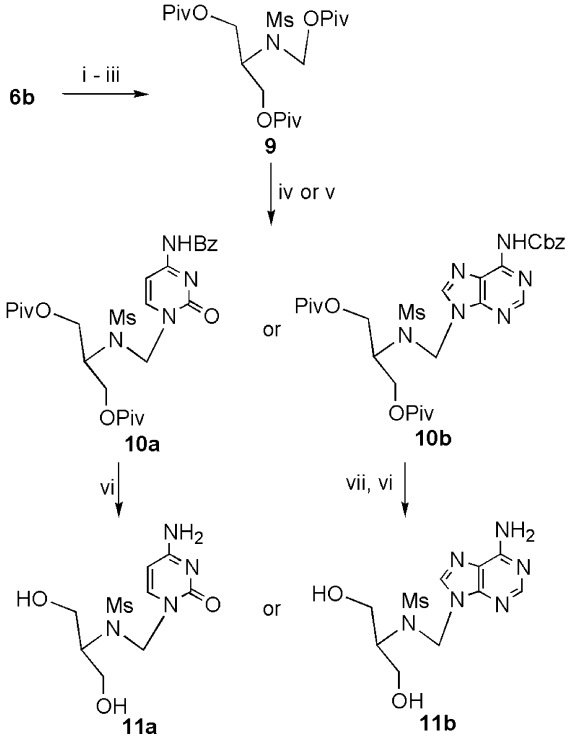
Scheme 3. Reagents and conditions: (i) H_2, 10%Pd/C, EtOH, rt, 60 bar, 1 d, quantitative; (ii) (a) Ac_2O, rt, 2 d, 80%; (b) $MeSO_2Cl$, pyridine, DCM, rt, 67%; (iii) $ClCH_2OPiv$, DMF, NaH, rt, 3 d, **7a** 50%, **7b** 70%; (iv) **U**, BSA TMSOTf, MeCN.

However, attempts at coupling **7** with silylated **U** failed to give nucleoside **8**. In the presence of TMSOTf, *N*-pivaloyloxymethyl and 1,3-dioxane moieties interact and this resulted in the formation of a complex mixture from **7a** or the tricyclic derivative **C** from **7b**; **C** was obtained in 40% yield.[27]



C

Our further studies then concentrated on the synthesis of the *N*-methanesulfonyl aza-analogues (Scheme 4). This time, **6b** was converted into tripivaloyloxy derivative **9** via acidic hydrolysis, O-pivaloylation and N-alkylation with chloromethyl pivaloate. Compound **9** was coupled with silylated $\mathbf{C}^{Bz}$ in the presence of TMSOTf to give base protected nucleoside **10a** in 71% yield.[28] Since the condensation of **2b** with $\mathbf{A}^{Cbz}$ in the presence of TMSOTf gave the nucleoside **3bd′** in 22% yield only, for the preparation of **10b** tin(IV) chloride was employed as catalyst; **10b** was obtained in 44% yield.[28] The *N-9* regiochemistry of **10b** was proved by HMBC correlations. Treatment of **10a** with concentrated aqueous ammonia in methanol for 1 day at 70 °C in a sealed tube afforded the cytidine derivative **11a**.[29]



Scheme 4. Reagents and conditions: (i) MeOH, Dowex 50 (H^+), rt, 48 h, 67%; (ii) PivCl, pyridine, rt, 24 h, 42%; (iii) NaH, DMF, $ClCH_2OPiv$, rt, 72 h, 88%; (iv) $\mathbf{C}^{Bz}$, BSA, TMSOTf, MeCN rt, 24 h, 71%; (v) $\mathbf{A}^{Cbz}$, BSA, $SnCl_4$, MeCN, 24 h, 44%; (vi) NH_3 (aq), MeOH, sealed tube, 70 °C, 1 d, 83%; (vii) H_2 (balloon), 10% Pd/C, MeOH, rt, 1 d, then (vi), overall 73%.

The synthesis of **11b** was completed by palladium-catalyzed hydrogenolysis followed by reaction with ammonia to yield **11b** in 73% yield.[30]

In summary, we have shown that readily available *N*-pivaloyloxymethyl acetamide and methanesulfonamide can be effectively converted into acyclic azanucleosides by an one-pot base silylation/nucleoside coupling procedure. The presented procedure is relevant for the preparation of both pyrimidine and purine derivatives. We believe that our method might also be useful for the preparation of acyclic nucleosides possessing, at the 2′-position, not only nitrogen but also other heteroatoms, for example, oxygen. Further studies on the improvement and extension of the methodology for the synthesis of various acyclic nucleosides, mainly aza-analogues of guanine and unnatural bases, are in progress.

References and notes

1. El Ashry, E. S. H.; El Kilany, Y. *Adv. Heterocycl. Chem.* **1997**, *67*, 391–438, **1997**, *68*, 1–88; **1998**, *69*, 129–215.
2. Gao, H.; Mitra, A. K. *Synthesis* **2000**, 329–351.
3. Recent selected papers on acyclonucleoside synthesis: Guillarme, S.; Legoupy, S.; Bourgougnon, N.; Aubertin, A.-M.; Huet, F. *Tetrahedron* **2003**, *59*, 9635–9639; Zheng, Q.-H.; Wang, J.-Q.; Fei, X.; Hutchins, G. D. *Synthesis* **2003**, 2785–2794; Wang, J.-Q.; Zheng, Q.-H.; Fei, X.; Mock, B. H.; Hutchins, G. D. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3933–3938; Hernandez, A. I.; Balzarini, J.; Rodrigeuz-Barrios, F.; San-Felix, A.; Karlsson, A.; Gago, F.; Cumarasa, M. J.; Perez-Perez, M. *J. Bioorg. Med. Chem. Lett.* **2003**, *13*, 3027–3030; Amblard, F.; Nolan, S. P.; Gillaizeau, I.; Agrofoglio, L. A. *Tetrahedron Lett.* **2003**, *44*, 9177–9180; Salamończyk, G. M. *Tetrahedron Lett.* **2003**, *44*, 7449–7453; Gondela, A.; Walczak, K. *Tetrahedron Lett.* **2003**, *44*, 7291–7293; Meng, G.; Chen, F.-E.; De Clercq, E.; Balzarini, J.; Pannecouque, C. *Chem. Pharm. Bull.* **2003**, *51*, 779–789; Guillarme, S.; Legoupy, S.; Aubertin, A.-M.; Olicard, C.; Bourgougnon, N.; Huet, F. *Tetrahedron* **2003**, *59*, 2177–2184; Boesen, T.; Pedersen, D. S.; Nielsen, B. M.; Petersen, A. B.; Henriksen, V.; Dahl, B. M.; Dahl, O. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 847–850.
4. Montgomery, J. A.; Temple, C. *J. Am. Chem. Soc.* **1961**, *83*, 630–635.
5. Nishitani, T.; Horikawa, H.; Iwasaki, T.; Matsumoto, K.; Inoue, I.; Miyoshi, M. *J. Org. Chem.* **1982**, *47*, 1706–1712.
6. Sergeev, V. N.; Shapovalenko, E. P.; Baukov, Yu. I. *Zh. Obshch. Khim.* **1987**, *57*, 1316–1321.
7. Nishitani, T.; Iwasaki, T.; Mushika, Y.; Inoue, I.; Miyoshi, M. *Chem. Pharm. Bull.* **1980**, *28*, 1137–1141.
8. Seiyaku, T. Jp 58216169, 1983; *Chem. Abstr.* **1984**, *100*, 174851b.
9. Seiyaku, T. Jp 58213726, 1983; *Chem. Abstr.* **1984**, *100*, 174852c.
10. Kingsbury, W. D.; Boehm, J. C.; Mehta, R. J.; Grappel, S. F.; Gilvarg, C. *J. Med. Chem.* **1984**, *27*, 1447–1451.
11. Nichifor, M.; Schacht, E. H. *Tetrahedron* **1994**, *50*, 3747–3760.
12. Khutova, B. M.; Klyuchko, S. V.; Prikazchikova, L. P. *Khim. Geterotsikl. Soedin.* **1991**, 512–515.
13. Besova, E. A.; Goloshchapov, N. M.; Goloshchapova, E. N.; Michurina, A. E.; Shipov, A. G.; Baukov, Yu. I. *Zh. Obshch. Khim.* **1998**, *68*, 502–504.

14. Madec-Lougerstay, R.; Florent, J.-C.; Monneret, C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1369–1376.
15. We named nucleosides **B** as aza-analogues of ganciclovir due to the structural similarity of sugar mimics **B** and parent ganciclovir, independently of the kind of base.
16. Iley, J.; Moreira, R.; Rosa, E. *J. Chem. Soc., Perkin Trans. 2* **1991**, 563–570.
17. Lopes, F.; Moreira, R.; Iley, J. *Bioorg. Med. Chem.* **2000**, *8*, 707–716.
18. The pivaloyloxymethyl group is met frequently in many prodrugs; for example, see: Refs. 16,17; Calheiros, T.; Iley, J.; Lopes, F.; Moreira, R. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 937–940; Anastasi, C.; Quéléver, G.; Burlet, S.; Garino, C.; Souard, F.; Krus, J.-L. *Curr. Med. Chem.* **2003**, *10*, 1825–1843; Calogeropoulou, T.; Detsi, A.; Lekkas, E.; Koufaki, M. *Curr. Med. Top. Chem.* **2003**, *3*, 1467–1495.
19. All new compounds were fully characterized by HRMS, IR, ^{1}H and ^{13}C NMR spectroscopy.
20. Vorbüggen, H.; Ruh-Pohlenz, C. *Handbook of Nucleoside Synthesis*; John Wiley: New York, 2001; pp 29–33 and 110–140.
21. Böhringer, M.; Roth, H.-J.; Hunziker, J.; Göbel, M.; Krishnan, R.; Giger, A.; Schweizer, B.; Schreiber, J.; Leumann, C.; Eschenmoser, A. *Helv. Chim. Acta* **1992**, *75*, 1416–1477; Wright, G. E.; Dudycz, L. W. *J. Med. Chem.* **1984**, *27*, 175–181; Tarköy, M.; Bolli, M.; Schweizer, B.; Leumann, C. *Helv. Chim. Acta* **1993**, *76*, 481–510; Augustyns, K.; Rozenski, J.; Van Aerschot, A.; Janssen, G.; Herdewijn, P. *J. Org. Chem.* **1993**, *58*, 2977–2982; Shöning, K.-V.; Scholz, P.; Wu, X.; Guntha, S.; Delgado, G.; Krishnamurthy, R.; Eschenmoser, A. *Helv. Chim. Acta* **2002**, *85*, 4111–4153.
22. Thomson, S. A.; Josey, J. A.; Cadilla, R.; Gaul, M. D.; Hassman, C. F.; Luzzio, M. J.; Pipe, A. J.; Reed, K. L.; Ricca, D. J.; Wiethe, R. W.; Noble, S. A. *Tetrahedron* **1995**, *51*, 6179–6194.
23. Zou, R.; Robins, M. J. *Can. J. Chem.* **1987**, *65*, 1436–1437; Robins, M. J.; Zou, R.; Guo, Z.; Wnuk, S. F. *J. Org. Chem.* **1996**, *61*, 9207–9212; Dalpozzo, R.; DeNino, A.; Maiuolo, L.; Procopio, A.; De Munno, G.; Sindona, G. *Tetrahedron* **2001**, *57*, 4035–4038.
24. General procedure for synthesis of azaacyclic nucleosides **3**: A mixture of the pyrimidine base (2.0 mmol) and BSA (4.0 mmol, 1.0 cm^3) in dry acetonitrile (10 cm^3) was stirred at room temperature under an argon atmosphere for 1 h, then a solution of **2** (1.0 mmol) in acetonitrile (1 cm^3) and TMSOTf (1.66 mmol) were added successively. For the synthesis of purine nucleosides **3d′**,**e′** the molar ratio of base/BSA/**2**/TMSOTf was 2/5.7/1.0/1.66, respectively. The reaction mixture was left for 24 h at room temperature, then $CHCl_3$ (50 cm^3) and a saturated solution of sodium carbonate (1 cm^3) were added successively. The mixture was stirred for 1 h, then filtered through a Celite pad. The organic phase was separated, washed with water, brine and dried with anhydrous magnesium sulfate. The crude nucleosides were purified by flash chromatography (SiO_2, 200-400 mesh, various mixtures of $CHCl_3$/acetone or $CHCl_3$/MeOH were used as eluting solvents) or by crystallization (**3ab′**) to yield the corresponding nucleoside **3**. Crude **3ac′** was submitted to deprotection with conc. NH_3 (aq) in methanol.
25. Koszytkowska-Stawińska, M.; Sas, W. *J. Chem. Res. (S)* **1996**, 162–163.
26. Mironiuk-Puchalska, E.; Kołaczkowska, E.; Sas, W. *Tetrahedron Lett.* **2002**, *43*, 8351–8354.
27. The derivative **C** was formed when **7b** was treated with TMSOTf itself, $BF_3{\cdot}OEt_2$, or $AlCl_3$ in MeCN. The explanation for how **C** arises will be reported in a full paper.
28. Nucleoside **10a** was obtained by the procedure employed for the synthesis of **3ac′**.[23] **10b** was obtained in similar way as **3bd′** but TMSOTf was replaced by tin(IV) chloride. **10a** (flash chromatography: CH_2Cl_2/MeOH, 98/2, v/v; 71%, foam). δ_H (200 MHz, $CDCl_3$): 1.18 (s, 18H), 3.06 (s, 3H), 4.32 (m, 5H), 5.49 (s, 2H), 7.55 (m, 4H), 7.90 (m, 2H), 8.17 (d, $^{3}J = 7.6$, 1H), 8.78 (bs, 1H); δ_C (50 MHz, $CDCl_3$): 27.26, 38.89, 41.85, 56.67, 58.42, 62.04, 97.77, 127.74, 129.22, 132.94, 133.51, 148.41, 155.75, 163.00, 178.05; IR (KBr), ν (cm^{-1}): 3308, 2976, 2932, 1732, 1696, 1676, 1556, 1484, 1340, 1312, 1276, 1252, 1148; HRMS (ESI, MeOH): 565.2327 calcd for $C_{26}H_{37}N_4O_8S$ $(M+H)^+$, found 565.2346. **10b** (flash chromatography $CHCl_3$/acetone, 98/2, v/v, 44%, foam) δ_H (200 MHz, $CDCl_3$): 1.08 (m, 18H), 2.96 (s, 3H), 4.27 (m, 5H), 5.28 (s, 2H), 5.75 (s, 2H), 7.45 (m, 5H), 8.43 (s, 1H), 8.74 (s, 1H), 9.26 (bs, 1H); δ_C (50 MHz, $CDCl_3$): 27.07, 38.72, 41.98, 52.05, 56.08, 61.93, 67.83, 121.36, 128.51, 128.62, 135.46, 143.54, 149.87, 151.02, 151.16, 153.17, 177.84; IR (KBr), ν (cm^{-1}): 2976, 1732, 1616, 1588, 1472, 1340, 1284, 1212, 1148; HRMS (ESI, MeOH): 641.2364 calcd for $C_{28}H_{38}N_6O_8NaS$ $(M+Na)^+$, found 641.2380.
29. Heating **10a** with conc. NH_3 (aq) and MeOH in a sealed tube at 70 °C for 24 h afforded after solvent removal, a residue, which was purified by flash chromatography (acetone/MeOH/NH_3 (aq), 6/1/0.4, v/v/v) giving **11a** (mp 212–222 °C dec.). δ_H (200 MHz, DMSO-d_6): 3.06 (s, 3H), 3.44 (m, 4H), 3.79 (m, 1H), 4.90 (m, 2H), 5.19 (s, 2H), 5.76 (d, $^{3}J = 7.4$, 1H), 7.22 (2H, br s, 2H), 7.63 (d, $^{3}J = 7.4$, 1H); δ_C (50 MHz, DMSO-d_6): 39.94, 55.49, 59.57, 62.04, 94.60, 143.88, 155.63, 165.81; IR (KBr), ν (cm^{-1}): 3504, 3428, 3348, 3140, 1680, 1616, 1512, 1320, 1148; HRMS (ESI, MeOH): 293.0914 calcd for $C_9H_{17}N_4O_5S$ $(M+H)^+$, found 293.0925.
30. Compound **10b** was hydrogenated in MeOH in the presence of 10% Pd/C under ambient pressure at room temperature for 2 d, then treated with ammonia as above to yield after flash chromatography **11b** ($CHCl_3$/MeOH, 9:1, v/v, 73%, mp 240–242 °C). δ_H (200 MHz, DMSO-d_6): 3.10 (s, 3H), 3.47 (m, 4H), 3.82 (m, 1H), 5.00 (t, $^{3}J = 5.4$, 2H), 5.65 (s, 2H), 7.36 (bs, 2H), 8.13 (s, 1H), 8.19 (s, 1H); δ_C (50 MHz, DMSO-d_6): 39.97, 51.47, 59.50, 61.93, 118.34, 140.29, 149.05, 152.67, 156.08; IR (KBr), ν (cm^{-1}): 3324, 3160, 1664, 1600, 1332, 1152; HRMS (ESI, MeOH): 317.1027 calcd for $C_{10}H_{17}N_6O_4S$ $(M+H)^+$, found 317.1042.