Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthetic Strategies to 9-Substituted 8-Oxoadenines

Huey-San Melanie Siah [a] & Lise-Lotte Gundersen [a]

[a] Department of Chemistry, University of Oslo, Oslo, Norway

Accepted author version posted online: 05 Jun 2012.Version of record first published: 06 Mar 2013.

To cite this article: Huey-San Melanie Siah & Lise-Lotte Gundersen (2013): Synthetic Strategies to 9-Substituted 8-Oxoadenines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:11, 1469-1476

To link to this article: http://dx.doi.org/10.1080/00397911.2011.642051

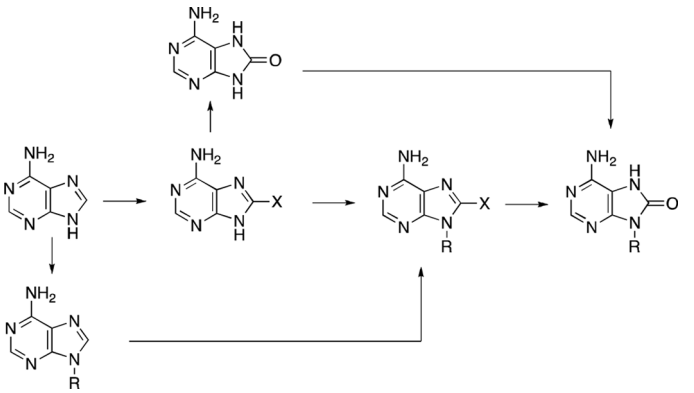
Synthetic Communications®, 43: 1469–1476, 2013

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.642051

SYNTHETIC STRATEGIES TO 9-SUBSTITUTED 8-OXOADENINES

Huey-San Melanie Siah and Lise-Lotte Gundersen
Department of Chemistry, University of Oslo, Oslo, Norway

GRAPHICAL ABSTRACT



Abstract *Three synthetic routes to 9-substituted 8-oxoadenines have been studied: bromination of adenine followed by N-9-alkylation/arylation and finally hydrolysis; bromination of adenine, hydrolysis, and N-functionalization as the last step; and N-9-alkylation of adenine, halogenation, and finally hydrolysis. As long as the N-9-functional group is compatible with conditions required for introduction of the halogen, the latter strategy was the most efficient. Also, a strategy starting from 5-amino-4,6-dichloropyrimidine was found to be a very good alternative for synthesis of 9-substituted 8-oxoadenines.*

Supplemental materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *to view the free supplemental file.*

Keywords Halogenation; hydrolysis; N-alkylation; 8-oxoadenine

INTRODUCTION

N-9-Substituted 8-oxoadenine derivatives may display a variety of biological properties including binding affinity to the corticotropin-releasing hormone receptor,[1] binding affinity to the benzodiazepine receptor,[2] antirhinovirus activity,[3] and interferon-inducing activity.[4–7] Further work on the interferon

Received November 4, 2011.

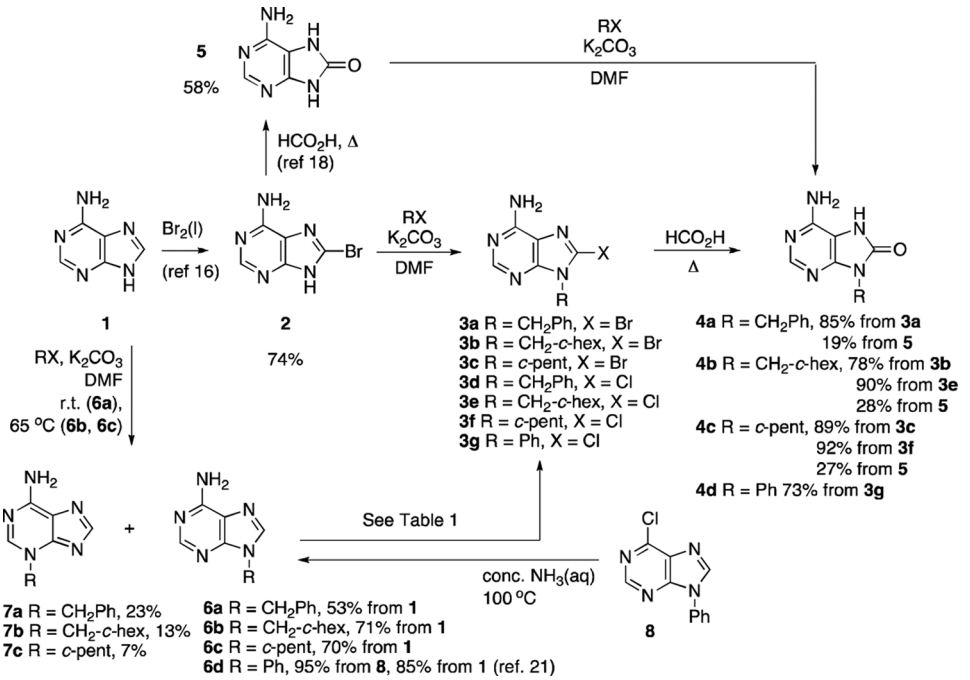
Address correspondence to Lise-Lotte Gundersen, Department of Chemistry, University of Oslo, P.O. Box 1033, Blindern, N-0314 Oslo, Norway. E-mail: l.l.gundersen@kjemi.uio.no

inducers suggested the TLR7 agonizing activity as the molecular basis of the biological action of 8-oxoadenine derivative,[8–9] and 8-oxoadenine derivatives as TLR7 agonists inducing dendritic cell maturation has also been reported.[10] 8-Oxoadenine derivatives are also found in nature.[11] Furthermore, 8-oxoadenine is found as an oxidized metabolite of DNA lesions,[12] and 8-oxoadenine derivatives may have potential in cancer therapy as inhibitors of DNA repair enzymes.

N-9-Substituted 8-oxoadenines may be synthesized with a ring-closing step starting from imidazole[4,5,13,14] or pyrimidine,[15] but adenine itself (or 6-chloropurine) may be regarded as a more convenient starting point. From adenine the following transformations must be included in the synthesis: Introduction of a functional group (for instance, halogen) at C-8, which can be hydrolyzed, and (selective) N-9-functionalization. The aim of the current study is to examine in which sequence the functionalization is most efficiently carried out.

RESULTS AND DISCUSSION

As target compounds 8-oxoadenines **4a**–**d** were selected (Scheme 1). The N-9-substituents were chosen so that the N-functionalization step would include alkylation with primary, secondary, and benzylic halide as well as N-arylation. Initially three synthetic sequences were evaluated: (1) bromination of adenine (**1**) followed by N-9-alkylation/arylation and finally hydrolysis; (2) bromination of adenine (**1**), hydrolysis, and N-functionalization as the last step; and (3) N-9-alkylation/arylation of adenine, halogenation, and finally hydrolysis.



Scheme 1.

Adenine (**1**) can easily be brominated at C-8 by a literature procedure.[16] However, we recently reported that benzylation of 8-bromoadenine (**2**) mainly afforded the N-3-benzylated isomer and that compound **3a** was isolated in only 15% yield.[17] Also, N-9-alkylation with (bromomethyl)cyclohexane was inefficient; compound **3b** was isolated in 13% yield (Table 1). Hence this synthetic route was abandoned.

8-Bromoadenine (**2**) was hydrolyzed to the 8-oxo analog **5** by treatment with formic acid.[18] Synthesis of targets compounds **4** by N-9-alkylation of compound **5** was an attractive strategy because all diversity is introduced in the last step, but unfortunately the yields of **4a**–**c** were only modest, mainly because also 7,9-dialkylated 8-oxopurines also were formed (but not isolated in pure form). N-9-Arylation of compound **5** was not attempted.

N-Alkylation of adenine (**1**) gave the 9-substituted compounds **6a**–**c** as the major products, but in all cases some N-3-alkylated isomer **7** was formed. The N-9-selectivity, however, is much better compared to what was obtained in alkylations of 8-bromoadenine (**2**). The structural elucidation of compounds **6** and **7** were done by various two-dimensional (2D) NMR techniques, and as reported for 3-benzyl-8-bromoadenine before,[17] restricted rotation around the C–6–N[6] bond was also observed for **7a**–**c**. It is worth noting that benzylation (and other alkylations) of adenine (**1**) under essentially identical reaction conditions previously was reported to give the N-7-benzyladenine (and other N-7-alkylated adenines).[19] However, the reported spectral data strongly indicate that also in this case the N-3-alkylated adenine was the minor isomer.

We previously found that N-arylation of adenine was not successful with phenylboronic acid in the presence of phenanthroline and anhydrous copper(II) acetate in CH_2Cl_2,[20] but later others have published a modified procedure [$PhB(OH)_2$, $Cu(OAc)_2$, TMEDA, MeOH, H_2O] for efficient N-9-phenylation of adenine (**1**).[21] Phenyladenine is also easily available by N-arylation of 6-chloropurine[20] followed by aminolysis of compound **8**.

9-Alkyladenines **6a**–**c** could be brominated by N-bromosuccinimide (NBS) or Br_2 (Table 1) to give the 8-bromopurines **3a**–**3c** in reasonably good yields. We and others have shown that C-8 halogenation of purines often can be achieved in good yields when the parent purine is lithiated with lithium diisopropylamide (LDA) and

Table 1. C-8 halogenation of adenines

Starting material	Reaction conditions	Product	R	X	Yield[a] (%)
2	$PhCH_2Br$, K_2CO_3, DMF	**3a**	CH_2Ph	Br	15[b]
6a	NBS, DMF	**3a**	CH_2Ph	Br	42
2	*c*-hexCH_2Br, K_2CO_3, DMF	**3b**	CH_2-*c*-hex	Br	13
6b	Br_2, H_2O	**3b**	CH_2-*c*-hex	Br	66
6c	Br_2, H_2O	**3c**	*c*-pent	Br	67
6a	(1) LDA, (2) C_2Cl_6, THF, −78 °C	**3d**	CH_2Ph	Cl	—[b]
6b	(1) LDA, (2) C_2Cl_6, THF, −78 °C	**3e**	CH_2-*c*-hex	Cl	68
6c	(1) LDA, (2) C_2Cl_6, THF, −78 °C	**3f**	*c*-pent	Cl	69
6d	(1) LDA, (2) C_2Cl_6, THF, −78 °C	**3g**	Ph	Cl	67

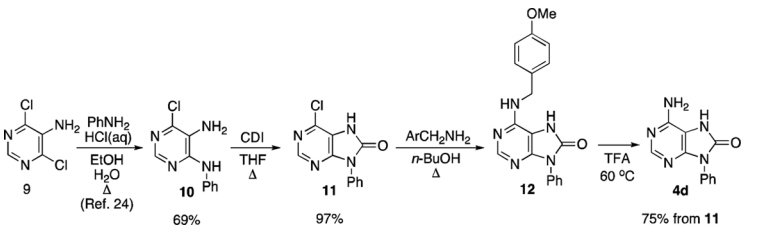
[a]Isolated yields
[b]Taken from Ref. 17.

trapped with a halogen donor.[22,23] Hence, we first treated the compounds **6** with LDA followed by $CBrCl_2CBrCl_2$. Extensive decomposition (and probably debenzylation) took place when 9-benzyladenine **6a** was reacted with LDA. Also, 9-benzyl-6-chloropurine, but not certain substituted benzylpurines, decomposes when treated with LDA.[23] The other purines **6** tolerated LDA well and gave the corresponding 8-bromopurines in good yield (data not shown) after trapping with $CBrCl_2CBrCl_2$. However, careful inspection of the NMR and MS spectra revealed that the product in fact was a mixture of the 8-bromo- and 8-chloropurine with the former as the major product. Hence we decided to trap lithiated purines **6b–d** with C_2Cl_6, and the 8-chloropurines **3e-g** were isolated in good yields (Table 1).

Finally, the 8-haloadenines **3** were efficiently hydrolyzed to the 8-oxoadenines **4** in refluxing formic acid. The yields from the chloropurines were slightly greater than from the bromopurines.

Even though 8-oxo-9-phenyladenine (**4d**) could be synthesized efficiently as shown in Scheme 1, we also explored an alternative route. The commercially available dichloropyrimidine **9** was reacted with aniline according to a literature procedure,[24] and ring closing to the 8-oxopurine **11** in an excellent yield was achieved with carbonyldiimidazole (CDI) (Scheme 2). In contrast, a recent attempt to synthesize compound **11** by a one-step substitution–ring-closing reaction on the methyl carbamate of **9** failed.[15] We first treated the chloropurine **11** with concentrated NH_3 (aqueous), but even after 7 days at 130 °C, the conversion to the desired amine **4d** was only slightly more than 50%. The substitution was expected to be difficult because deprotonation (removal of the NH proton) was believed to take place before the substitution. Benzylamines are more nucleophilic than ammonia,[25] and we tried substitution on the chloropurine **11** with the electron-rich *p*-methoxybenzylamine. Conversion to the aminopurine **12** was almost quantitative, and crude **12** was reacted directly in the TFA-mediated debenzylation to give target compound **4d** in 75%yield over two steps. We envisage that many 9-substituted 8-oxoadenines will be available by the route depicted in Scheme 2 as long as the amine needed as nucleophile in the first step is available.

Three synthetic routes to 9-substituted 8-oxoadenines have been compared. As long as the N-9-functional group is compatible with conditions required for introduction of the halogen, N-9-alkylation/arylation followed by C-8-halogenation and finally hydrolysis is the most efficient route. Also a strategy starting from 5-amino-4,6-dichloropyrimidine was found to be a very good alternative for synthesis of 9-substituted 8-oxoadenines.



Scheme 2.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded at 600 MHz with a Bruker AV 600 instrument, at 400 MHz with a Bruker AVII 400 instrument, at 300 MHz with a Bruker Avance DPX 300 instrument, or at 200 MHz with a Bruker Avance DPX 200 instrument. The decoupled ^{13}C NMR spectra were recorded at 150, 100, or 75 MHz using instruments mentioned previously. Mass spectra under electron-impact conditions were recorded with a VG Prospec instrument at 70-eV ionizing voltage, and are presented as m/z (% rel. int.). Melting points were determined with a Büchi melting-point B-545 apparatus and are uncorrected. Dry dimethylformamide (DMF) and tetrahydrofuran (THF) were obtained from a solvent purification system, MB SPS-800, from MBraun, Garching, Germany. Diisopropylamine was distilled from CaH_2. All other reagents were commercially available and used as received. All flash chromatography was performed with silica gel from Merck, Darmstadt, Germany (Merck No. 09385). Compounds available by literature methods were 8-bromoadenine (**2**),[16] 9-benzyl-8-bromo-*9H*-purin-6-amine (**3a**) from compound **2**,[17] 8-oxoadenine (**5**),[18] 6-chloro-9-phenyl-9*H*-purine (**8**),[20] and 6-chloro-N^4-phenylpyrimidine-4,5-diamine (**10**).[24]

N-Alkylation of 8-Bromoadenine: 9-(Cyclohexylmethyl)-8-bromo-*9H*-purin-6-amine (3b)

A mixture of 8-bromoadenine (**2**) (217 mg, 1.06 mmol) andK_2CO_3 (280 mg, 2.01 mmol) in dry DMF (5 mL) was stirred under N_2 at ambient temperature for 20 min. (Bromomethyl)cyclohexane (0.28 mL, 2.0 mmol) was added, and the mixture was stirred for 20 h. The mixture was filtered, and the solvent was evaporated in vacuo. The residue was purified by flash chromatography eluting with 0–10% MeOH in CH_2Cl_2; yield 43 mg (13%), mp 228–230 °C, colorless powdery crystals.^{1}H NMR (DMSO-d_6, 300 MHz) 8.11 (s, 1H, H-2), 7.35 (br s, 2H, NH_2), 3.94 (d, $J = 7.5$ Hz, 2H, NCH_2), 1.90 (ddd, $J = 10.6$, 7.3, 3.4 Hz, 1H, CH in *c*-hex), 1.78 – 1.36 (m, 5H, *c*-hex), 1.36 – 0.91 (m, 5H, *c*-hex); ^{13}C NMR (DMSO-d_6, 75 MHz) 154.7 (C-6), 152.8 (C-2), 151.0 (C-4), 126.6 (C-8), 118.9 (C-5), 49.5 (NCH_2), 37.3 (CH in *c*-hex), 30.0 (CH_2 in *c*-hex), 25.7 (CH_2 in *c*-hex), 25.1 (CH_2 in *c*-hex); MS EI m/z (rel. %) 311/309 (2/2, M^+), 231 (39), 230 (100), 227 (10), 215/213 (28/26), 148 (40). HRMS found 309.0587; calculated for $C_{12}H_{16}BrN_5$309.0589.

Direct Bromination of N-Substituted Adenine: 9-(Cyclohexylmethyl)-8-bromo-*9H*-purin-6-amine (3b)

A solution of bromine (0.20 mL, 3.9 mmol) and distilled water (15 mL) was added to a flask containing 9-(cyclohexylmethyl)adenine (**6b**) (146 mg, 0.631 mmol). The flask was fitted with a condenser and the resulting mixture was stirred at ambient temperature for 17 h. The flask was left open in the fumehood until most of the Br_2 was evaporated, and the solvent was removed in vacuo. The residue was purified by flash chromatography eluting with 0–100% EtOAc in hexane; yield 126 mg (66%).

General Procedure for Lithiation and Subsequent Chlorination of 9-Substituted Adenines 6

Lithium diisopropylamide (LDA) was generated from *n*-BuLi in hexanes and dry diisopropylamine by cooling diisopropylamine (ca. 2.6 mmol) in dry THF (5 mL) to −78 °C under Ar. *n*-BuLi in hexanes (ca. 2.5 mmol) was added dropwise, and the mixture was stirred for 1 h under these conditions. The appropriate 9-substituted adenine **6** (0.500 mmol) was dissolved in dry THF (10 mL) and added dropwise to the LDA solution. The mixture was stirred for 1 h before hexachloroethane (1.50 mmol) and dry THF (2 mL) were added dropwise, and the reaction was stirred for a further 4 h. The reaction was quenched with saturated aqueous NH_4Cl (0.5 mL) and warmed to ambient temperature. The mixture was transferred to a separatory funnel and saturated aqueous NH_4Cl (15 mL) was added. The phases were separated, and the water phase was extracted with EtOAc (3 × 15 mL). The organic phases were combined, washed with brine (15 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by flash chromatography, eluting with 0–100% EtOAc in hexane to give compounds **3e**–**3g**.

8-Chloro-9-(cyclohexylmethyl)-*9H*-purin-6-amine (3e)

Yield 90 mg (68%), mp 229–230 °C, colorless powdery crystals. ^{1}H NMR (DMSO-d_6, 400 MHz) 8.13 (s, 1H, H-2), 7.36 (s, 2H, NH_2), 3.96 (d, $J = 7.4$ Hz, 2H, NCH_2), 1.87 (ddd, $J = 10.9$, 7.4, 3.5 Hz, 1H, CH in *c*-hex), 1.75 – 1.30 (m, 5H, *c*-hex), 1.13 – 0.99 (m, 5H, *c*-hex); ^{13}C NMR (DMSO-d_6, 150 MHz) 154.8 (C-6), 152.9 (C-2), 150.6 (C-4), 136.8 (C-8), 117.4 (C-5), 48.7 (NCH_2), 37.1 (CH in *c*-hex), 29.9 (CH_2 in *c*-hex), 25.7 (CH_2 in *c*-hex), 25.0 (CH_2 in *c*-hex); MS EI *m*/*z* (rel. %) 267/265 (2/8, M^+), 230 (100), 185/183 (7/21), 184/182 (8/19), 171/169 (14/43), 148 (15), 142 (8). HRMS Found 265.1098, calculated for $C_{12}H_{16}ClN_5$ 265.1094.

N-Alkylation of 8-Oxoadenines: 6-Amino-9-(cyclohexylmethyl)-*7H*-purin-8(*9H*)-one (4b)

A mixture of 8-oxoadenine (**5**) (128 mg, 0.847 mmol) and K_2CO_3 (238 mg, 1.73 mmol) in dry DMF (5 mL) was stirred under N_2 at 50 °C for 20 min. (Bromomethyl)cyclohexane (0.14 mL, 1.013 mmol) was added, and the mixture was stirred at 70 °C for 24 h. The mixture was filtered, and the solvent was evaporated in vacuo. The residue was purified by flash chromatography (see method A); yield 51 mg (28%), mp 287–289 °C, colorless powdery crystals. ^{1}H NMR (DMSO-d_6, 300 MHz) 10.11 (s, 1H, NH), 8.00 (s, 1H, H-2), 6.39 (s, 2H, NH_2), 3.55 (d, $J = 7.3$ Hz, 2H, NCH_2), 1.80 (ddd, $J = 10.7$, 7.3, 3.4 Hz, 1H, CH in *c*-hex), 1.63 – 1.51 (m, 5H, *c*-hex), 1.32 – 0.74 (m, 5H, *c*-hex); ^{13}C NMR (DMSO-d_6, 75 MHz) 152.3 (C-8), 150.9 (C-2), 147.8 (C-4), 146.5 (C-6), 103.1 (C-5), 45.1 (NCH_2), 36.3 (CH in *c*-hex), 30.1 (CH_2 in *c*-hex), 25.9 (CH_2 in *c*-hex), 25.1 (CH_2 in *c*-hex); MS EI*m*/*z* (rel. %) 247 (48, M^+), 231 (49), 165 (53), 151 (100), 136 (31). HRMS found 247.1422, calculated for $C_{12}H_{17}N_5O$ 247.1433.

Hydrolysis of 8-Haloadenines: 6-Amino-9-(cyclohexylmethyl)-*7H*-purin-8(*9H*)-one (4b)

A mixture of 9-(cyclohexylmethyl)-8-bromoadenine (**3b**) (129 mg, 0.42 mmol) in concentrated HCO_2H (10 mL), or of 9-(cyclohexylmethyl)-8-chloroadenine (**3e**) (180 mg, 0.678 mmol) in concentrated HCO_2H (20 mL), was stirred at reflux for 16 h. The HCO_2H was co-evaporated with water (3×20 mL), and the residue was dried in vacuo. The product was purified by flash chromatography, eluting with 3–5% MeOH in CH_2Cl_2; yield 199 mg (78%) from **3b** and 151 mg (90%) from **3e**.

Synthesis of 8-Oxo-adenines from 6-Chloro-8-oxopurines: 6-Amino-9-phenyl-*7H*-purin-8(*9H*)-one (4d)

6-Chloro-9-phenyl-*7H*-purin-8(*9H*)-one (**11**) (249 mg, 1.01 mmol) and *para*-methoxybenzylamine (0.55 mL, 4.2 mmol) were refluxed in *n*-butanol (20 mL) for 24 h. The solvent was evaporated in vacuo, and the residue was purified by flash chromatography (see method A); yield 345 mg of crude compound **12**, which was heated in TFA (5 mL) at 60 °C for 2 h. The acid was evaporated in vacuo, and the residue was purified by flash chromatography eluting with 0–10% MeOH in CH_2Cl_2; yield 171 mg (75% from **3g**), mp 300 °C (dec.; lit.[14] > 300 °C), colorless powdery crystals. NMR and MS data were in good agreement with those reported before.[14]

N-Alkylation of Adenine: 9-(Cyclohexylmethyl)-*9H*-purin-6-amine (6b) and 3-(Cyclohexylmethyl)-*3H*-purin-6-amine (7b)

A mixture of adenine (**1**) (135 mg, 1.00 mmol) and K_2CO_3 (314 mg, 2.28 mmol) in dry DMF (5 mL) was stirred under N_2 at 65 °C for 30 min. (Bromomethyl)cyclohexane (0.21 mL, 1.5 mmol) was added and the mixture was stirred for 72 h. The mixture was filtered, and the solvent was evaporated in vacuo. The residue was purified by flash chromatography, eluting with 0–10% MeOH in CH_2Cl_2; yield 720 mg (70%) of **6b** and 30 mg (13%) of **7b**.

9-(Cyclohexylmethyl)-9H-purin-6-amine (6b). Mp 224–226 °C, colorless powdery crystals. ^{1}H NMR,[26] ^{13}C NMR,[27] and MS[27] data were in good agreement with those reported before.

3-(Cyclohexylmethyl)-3H-purin-6-amine (7b). Mp 220–252 °C, colorless powdery crystals. ^{1}H NMR (DMSO-d_6, 600 MHz) 8.29 (s, 1H, H-2), 7.98 (br s, 1H, H_A in NH_2), 7.92 (br s, 1H, H_B in NH_2), 7.77 (s, 1H, H-8), 4.12 (d, $J = 7.4$ Hz, Hz, 2H, NCH_2), 2.01 (dtt, $J = 15.0$, 7.5, 3.8 Hz, CH in *c*-hex), 1.63 – 1.45 (m, 5H, *c*-hex), 1.10 – 0.97 (m, 5H, *c*-hex); ^{13}C NMR (DMSO-d_6, 150 MHz) 155.0 (C-6), 152.3 (C-2), 149.8 (C-4), 143.9 (C-8), 120.2 (C-5), 55.1 (NCH_2), 36.4 (CH in *c*-hex), 29.8 (CH_2 in *c*-hex), 25.9 (CH_2 in *c*-hex), 25.1 (CH_2 in *c*-hex); MS EI$m/z$ (rel. %) 231 (72, M^+), 188 (12), 149 (100), 148 (76), 136 (22), 135 (80), 108 (15). HRMS found 231.1479; calculated for $C_{12}H_{17}N_5$ 231.1484.

ACKNOWLEDGMENT

The Norwegian Research Council is gratefully acknowledged for partial financing of the Bruker Avance instruments used in this study.

REFERENCES

1. Beck, J. P.; Arvanitis, A. G.; Curry, M. A.; Rescinito, J. T.; Fitzgerald, L. W.; Gilligan, P. J.; Zaczek, R.; Trainor, G. L. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 967–972.
2. Kelley, J. L.; McLean, E. W.; Linn, J. A.; Krochmal, M. P.; Ferris, R. M.; Howard, J. L. *J. Med. Chem.* **1990**, *33*, 196–202.
3. Kelley, J. L.; Linn, J. A.; Selway, J. W. T. *J. Med. Chem.* **1991**, *34*, 157–160.
4. Hirota, K.; Kazaoka, K.; Niimoto, I.; Kumihara, H.; Sajiki, H.; Isobe, Y.; Takaku, H.; Tobe, M.; Ogita, H.; Kurimoto, A.; Kawakami, H. *J. Med. Chem.* **2002**, *45*, 5419–5422.
5. Kazaoka, K.; Sajiki, H.; Hirota, K. *Chem. Pharm. Bull.* **2003**, *51*, 608–611.
6. Hirota, K.; Kazaoka, K.; Sajiki, H. *Bioorg. Med. Chem.* **2003**, *11*, 2715–2722.
7. Kurimoto, A.; Ogino, T.; Ichii, S.; Isobe, Y.; Tobe, M.; Ogita, H.; Takaku, H.; Sajiki, H.; Hirota, K.; Kawakami, H. *Bioorg. Med. Chem.* **2003**, *11*, 5501–5508.
8. Jin, G.; Wu, C. C. N.; Tawatao, R. I.; Chan, M.; Carson, D. A.; Cottam, H. B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4559–4563.
9. Kurimoto, A.; Hashimoto, K.; Nakamura, T.; Norimura, K.; Ogita, H.; Takaku, H.; Bonnert, R.; McInally, T.; Wada, H.; Isobe, Y. *J. Med. Chem.* **2010**, *53*, 2964–2972.
10. Weterings, J. J.; Khan, S.; van der Heden van Noort, G. J.; Melief, C. J. M.; Overkleeft, H. S.; van der Burg, S. H.; Ossendorp, F.; van der Marel, G. A.; Filippov, D. V. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2249–2251.
11. See, for instance, Itaya, T.; Hozumi, Y.; Kanai, T.; Ohta, T. *Chem. Pharm. Bull*. **1999**, *47*, 1297–1300, and references cited therein.
12. Kamiya, H.; Miura, H.; Murata-Kamiya, N.; Ishikawa, H.; Sakaguchi, T.; Inoue, H.; Sasaki, T.; Masutani, C.; Hanaoka, F.; Nishimura, S.; Ohtsuka, E. *Nucleic Acids Res.* **1995**, *23*, 2893–2899.
13. Hirota, K.; Kazaoka, K.; Niimoto, I.; Sajiki, H. *Heterocycles* **2001**, *55*, 2279–2282.
14. Hirota, K.; Kazaoka, K.; Niimoto, I.; Sajiki, H. *Org. Biomol. Chem.* **2003**, *1*, 1354–1365.
15. Zhong, Q.-F.; Sun, L.-P. *Tetrahedron* **2010**, *66*, 5107–5111.
16. Meszarosova, K.; Holy, A.; Masojidkova, M. *Collect. Czech. Chem. Commun.* **2000**, *65*, 1109–1125.
17. Siah, H. -S. M.; Gundersen, L.-L.; Gørbitz, C. H.. *J. Heterocycl. Chem*. in press (doi: 10.1002/jhet733).
18. Borrmann, T.; Abdelrahman, A.; Volpini, R.; Lambertucci, C.; Alksnis, E.; Gorzalka, S.; Knospe, M.; Schiedel, A. C.; Cristalli, G.; Mueller, C. E. *J. Med. Chem.* **2009**, *52*, 5974–5989.
19. Lambertucci, C.; Antonini, I.; Buccioni, M.; Ben, D. D.; Kachare, D. D.; Volpini, R.; Klotz, K.-N.; Cristalli, G. *Bioorg. Med. Chem.* **2009**, *17*, 2812–2822.
20. Bakkestuen, A. K.; Gundersen, L.-L. *Tetrahedron Lett.* **2003**, *44*, 3359–3362.
21. Yue, Y.; Zheng, Z.-G.; Wu, B.; Xia, C.-Q.; Yu, X.-Q. *Eur. J. Org. Chem*. **2005**, 5154–5157.
22. Nolsøe, J. M. J.; Gundersen, L.-L.; Rise, F. *Synth. Commun.* **1998**, *28*, 4303–4315.
23. Gamadeku, T.; Gundersen, L.-L. *Synth. Commun*. **2010**, *40*, 2723–2735, and references cited therein.
24. Greenberg, S. M.; Ross, L. O.; Robins, R. K. *J. Org. Chem.* **1959**, *24*, 1314–1317.
25. Brotzel, F.; Chu, Y. C.; Mayr, H. *J. Org. Chem.* **2007**, *72*, 3679–3688.
26. Chou, P.-T.; Chen, Y.-C.; Wei, C.-Y.; Chen, W.-S. *J. Am. Chem. Soc.* **2000**, *122*, 9322–9323.
27. Schmidt, K. S.; Sigel, R. K. O.; Filippov, D. V.; van der Marel, G.; Lippert, B.; Reedijk, J. *New. J. Chem.* **2000**, *24*, 195–197.