Tetrahedron 68 (2012) 1286–1298

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Synthesis of novel azanorbornylpurine derivatives

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ARTICLE INFO

*Article history:*
Received 28 July 2011
Received in revised form 25 October 2011
Accepted 14 November 2011
Available online 25 November 2011

Dedicated to the 75th anniversary of Professor Antonín Holý's birthday

*Keywords:*
Azanorbornane
Purines
Mitsunobu reaction
Coxsackievirus
Hepatitis C virus
Neuronal nicotinic acetylcholine receptor

ABSTRACT

Azanorbornylpurine derivatives were prepared by Mitsunobu reaction of appropriate hydroxyazanorbornane derivative with 6-chloropurine or construction of purine base at azanorbornylamines. The prepared target compounds were evaluated for antiviral activity and effect on neuronal and muscle nicotinic acetylcholine receptors.



## 1. Introduction

Human enteroviruses (HEV) belong to the Enterovirus (EV) genus of the family of the Picornaviridae. They are single stranded, positive sense non-envelop RNA virus with more than 80 serotypes. The genus can be subdivided into HEV-A, HEV-B, HEV-C, HEV-D. Coxsackieviruses B are representative members of the genus.[1] Although mild and self-limiting diseases are the major clinical features of CVB infection, CVB is a common etiological agent of myocarditis and aseptic meningitis.[2,3] Moreover, epidemiological data strongly suggest that enteroviruses, such as Coxsackievirus B4, are associated with type 1 diabetes.[4] Fatalities are often associated with neonatal myocarditis or hepatitis.[5,6] There are no drugs available for the treatment of infections with enteroviruses.[7] Such drugs are urgently needed for the treatment HEV infections.

Recently, we reported on the syntheses of novel potential Coxsackievirus inhibitors based on 6-chlorpurines substituted at position 9 with variously modified bicyclic scaffolds.[8] The impact of various substitutions of the purine moiety on the antiviral activity was also studied.[9] The most active compounds of these series were analogues **1** ($EC_{50}$ 0.81±0.20 μM, $CC_{50}$>50 μM) and **2** (0.66±0.35 μM, $CC_{50}$>50 μM) (Fig. 1).[8a]

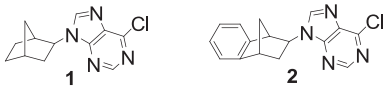

**Fig. 1.** Structure of compounds **1** and **2**.

This current study concerns the synthesis and antiviral evaluation of novel racemic purine analogues substituted at position 9 with 2-azanorbornane, 7-azanorbornane, and 7-azabenzonorbornane. These compounds exhibit a certain structural analogy to a very potent non-opioid analgesic—epibatidine (**3**, Fig. 2).

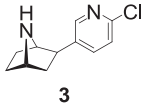

**Fig. 2.** Structure of epibatidine.

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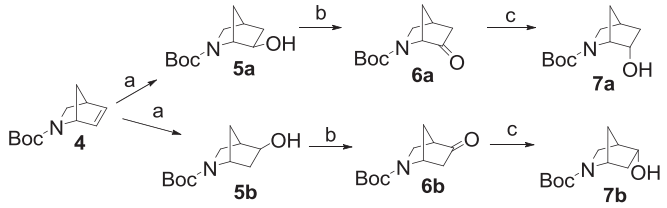
0040-4020/$ – see front matter © 2011 Published by Elsevier Ltd.
doi:10.1016/j.tet.2011.11.035

Epibatidine was isolated from the skin of the Ecuadorian frog *Epipedobates tricolor*,[10] and shortly afterward it was shown that its analgesic potency is about 200-fold higher than that of morphine. Epibatidine is a highly potent nicotinic acetylcholine receptor agonist.[11] Therefore, evaluation of this biological phenomenon of the target compounds is also subject of the paper.

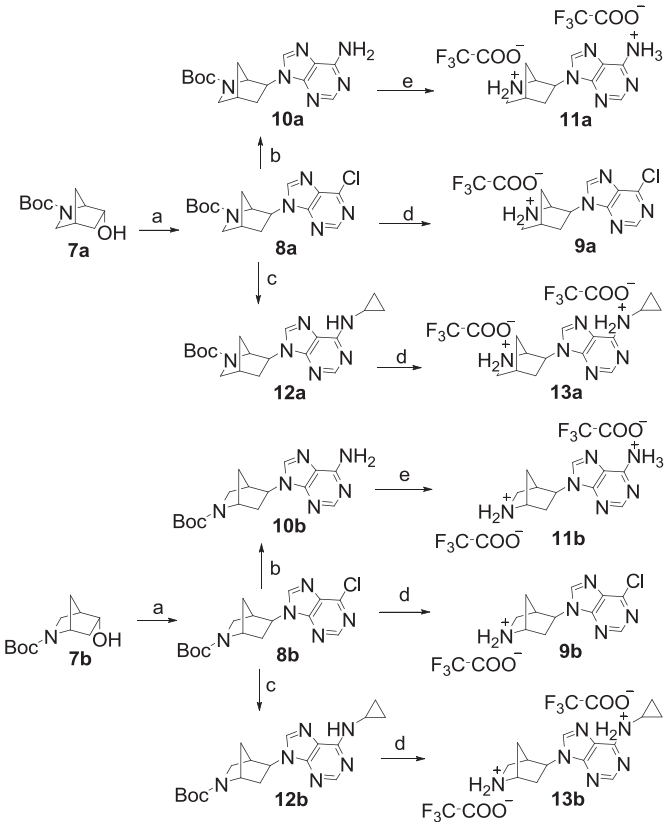
## 2. Results and discussion

Synthesis of the 2-azanorbornane derivatives started from protected 2-azanorbornene **4**[12] (Scheme 1). Hydroboration of **4** afforded a mixture of hydroxy derivatives **5a** and **5b** in moderate yields (18.5% and 24%, respectively). These alcohols were converted to ketones **6a** and **6b** with pyridinium dichromate in 49% and 92% yield, respectively. The key intermediates, alcohols **7a** and **7b**, were prepared by reduction of ketones **6a** and **6b** with sodium borohydride.



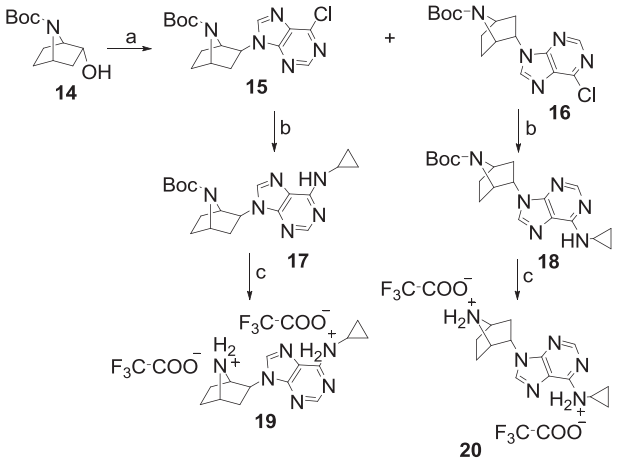
**Scheme 1.** Reagents and conditions: (a) 1. $BH_3$/THF, THF, 0 °C, 3 h, 2. $NaBO_3$, $H_2O$/THF, rt, overnight, 18.5% of **5a**, 24% of **5b**; (b) PDC, molecular sieves, $CH_2Cl_2$, rt, 96 h, 49% of **6a**, 92% of **6b**; (c) $NaBH_4$, $CH_3OH$, 0 °C, 40 min, 85% of **7a**, 98% of **7b**.

The Mitsunobu reaction[13] of **7a** and **7b** with 6-chloro-9*H*-purine afforded 6-chloropurine derivatives **8a** (72%) and **8b** (38%), respectively (Scheme 2). Ammonolysis of **8a** and **8b** with liquid ammonia at 75 °C gave adenine derivatives **10a** (91%) and **10b** (93%), respectively. Reaction of **8a** and **8b** with cyclopropylamine led to cyclopropylamine derivatives **12a** (89%) and **12b** (87%), respectively. Trifluoroacetic acid salts **9a**, **9b**, **11a**, **11b**, **13a**, and **13b** were obtained by treatment of *tert*-butylcarbonyl derivatives **8a**, **8b**, **10a**, **10b**, **12a**, and **12b**, respectively, with trifluoroacetic acid.



**Scheme 2.** Reagents and conditions: (a) 6-chloropurine, $PPh_3$, DIAD, THF, rt to reflux, 72% of **8a**, 38% of **8b**; (b) liquid $NH_3$, 70 °C, 48 h, 91% of **10a**, 93% of **10b**; (c) cyclopropylamine, rt, overnight, 89% of **12a**, 87% of **12b**; (d) TFA, $CH_2Cl_2$, rt, 3 h, 71% of **9a**, 77% of **9b**, 86% of **13a**, 86% of **13b**; (e) TFA, rt, 3 h, 88% of **11a**, 73% of **11b**.

Similarly, we tried to prepare of the 7-aza analogues by Mitsunobu reaction from alcohol **14**[14,15](Scheme 3). Unfortunately, this reaction led to an inseparable mixture of *exo* and *endo*-isomers **15** and **16**, probably due to the steric effect of the *tert*-butoxycarbonyl group. The mixture was treated with cyclopropylamine giving a mixture of cyclopropylamino derivatives **17** (21%) and **18** (23%), which were easily separated by chromatography on silica gel.

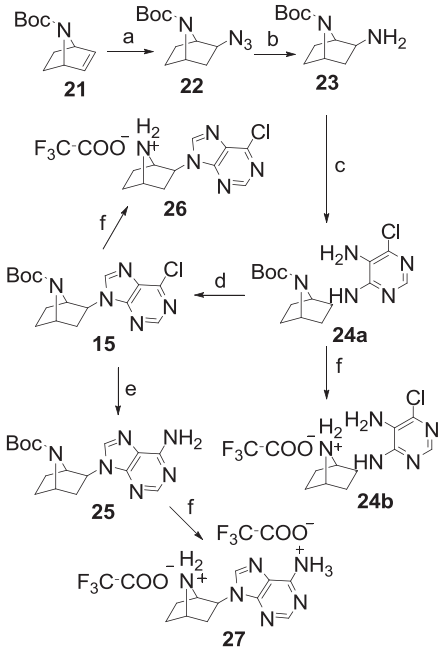


**Scheme 3.** Reagents and conditions: (a) 6-chloropurine, $PPh_3$, DIAD, THF, rt to reflux, 52.5% of the mixture **15** and **16**; (b) cyclopropylamine, rt, overnight, 21% of **17**, 23% of **18**; (c) TFA, $CH_2Cl_2$, rt, 3 h, 74% of **19**, 82% of **20**.

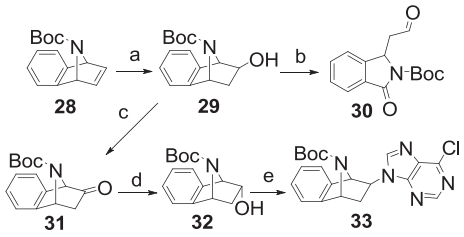
Since the Mitsunobu reaction of alcohol **14** led to a mixture of isomers, it was necessary to find a new route leading unambiguously to the target analogues with the *exo*-oriented purine base. We chose the mercuryazidation[16] of protected 7-azanorbornene **21**[17] for the introduction of the *exo*-amino function. Sodium borohydride reduction of the adduct of 7-azanorbornene **21** and mercuric azide gave azide **22** (85%), which was converted to amine **23** by hydrogenation using $Pd(OH)_2$ on activated charcoal as catalyst. The 6-chloropurine base was then constructed by a coupling of the amine **23** with 4,6-dichloropyrimidine-5-amine,[18] and the subsequent ring closure of the obtained pyrimidine derivative **24a** with diethoxymethyl acetate[19] (Scheme 4). This reagent was used in place of the commonly used triethyl orthoformate and mineral acid to avoid deprotection and side reactions. Ammonolysis of chloropurine analogue **15** furnished adenine derivative **25** (86%). Treatment of the *tert*-butylcarbonyl derivatives **15**, **17**, **18**, **24a**, and **25** with trifluoroacetic acid afforded salts of free bases **26**, **19**, **20**, **24b**, and **27**, respectively.

We recently found[8a] that compound **2**, with an annelated benzene ring, exhibits more pronounced antiviral activity then the norbornane analogue **1**, we decided to synthesize 7-azanorbornane analogues with an annelated benzene ring. The synthesis started from the easily accessible benzo derivative **28**[20] as shown in Scheme 5.

Hydroboration of **28** gave hydroxy derivative **29** (78.5%). Treatment of this compound with pyridinium dichromate furnished lactam **30**. This unexpected reaction could be explained by oxidation of the compound **29** in the bridgehead position, which proceeds simultaneously with oxidation of the hydroxy group. Nevertheless, Swern oxidation[21] of **29** gave ketone **31** (90%), which was treated with sodium borohydride affording *endo*-hydroxy derivative **32** (91%). Mitsunobu reaction of **32** with 6-chlorpurine led only to *exo*-isomer **33**, but in the very low yield (13%).

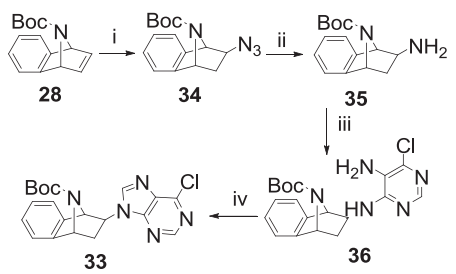


**Scheme 4.** Reagents and conditions: (a) 1. $NaN_3$, $Hg(CH_3COO)_2$, THF, 50 °C, 19 h, 2. KOH, $NaBH_4$, rt, 85%; (b) $Pd(OH)_2/C$, $H_2$, rt, overnight, 96%; (c) 4,6-dichloropyrimidin-5-amine, TEA, EtOH, 100 °C, 144 h, 77%; (d) $(EtO)_2CHOCOCH_3$, 110 °C, 120 h, 56%; (e) liquid $NH_3$, 70 °C, 48 h, 91%; (f) TFA, $CH_2Cl_2$, rt, 3 h, 91% of **24b**, 90% of **26**, 86% of **27**.

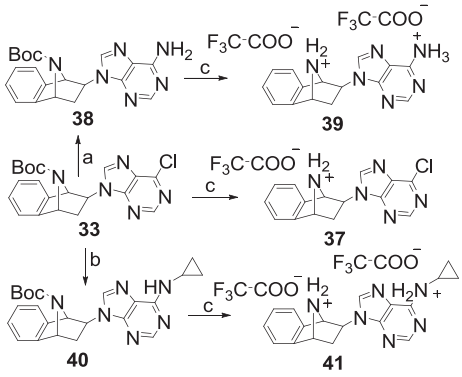


**Scheme 5.** Reagents and conditions: (a) 1. $BH_3$/THF, THF, 0 °C, 3 h, 2. $NaBO_3$, $H_2O$/THF, rt, overnight, 78.5%; (b) PDC, molecular sieves, $CH_2Cl_2$, rt, 96 h, 50%; (c) DMSO, $(CF_3CO)_2$, $CH_2Cl_2$, TEA, −65 °C, 90%; (d) $NaBH_4$, $CH_3OH$, 0 °C, 40 min, 91%; (e) 6-chloropurine, $PPh_3$, DIAD, toluene, rt to 108 °C, 13%.

As a consequence, we also choose mercuryazidation in this case as an alternative approach to the target compounds (Scheme 6). Mercuryazidation of **28** performed as in the case of the compound **21** afforded azide **34** (75%). The key amine **35** was obtained by hydrogenation. Reaction of **35** with 4,6-dichloropyrimidin-5-amine led to the pyrimidine derivative **36** (64%), which was treated with diethoxymethyl acetate giving 6-chloropurine analogue **33** (64%). Nucleophilic substitution of the chlorine atom in **33** afforded adenine and cyclopropylamino derivatives **38** (82%) and **40** (90%), respectively (Scheme 7). Trifluoroacetic salts of free bases **37**, **39**, and **41** were prepared by the treatment of protected compounds **33**, **38**, and **40**, respectively, with trifluoroacetic acid.

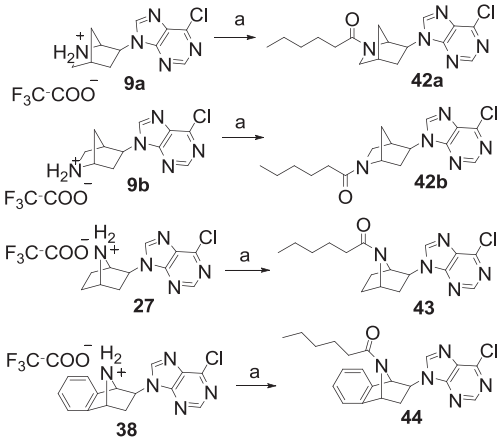


**Scheme 6.** Reagents and conditions: (i) (1) $NaN_3$, $Hg(CH_3COO)_2$, THF, 50 °C, 19 h, (2) KOH, $NaBH_4$, rt, 75%; (ii) $Pd(OH)_2/C$, $H_2$, rt, overnight, 76%; (iii) 4,6-dichloropyrimidin-5-amine, TEA, EtOH, 100 °C, 6 days, 64%; (iv) $(EtO)_2CHOCOCH_3$, 110 °C, 5 days, 64%.



**Scheme 7.** Reagents and conditions: (a) liquid $NH_3$, 70 °C, 48 h, 82%; (b) cyclopropylamine, rt, overnight, 90%; (c) TFA, $CH_2Cl_2$, rt, 3 h, 90% of **37**, 94% of **39**, 84% of **41**.

Hexanoyl derivatives **42a**, **42b**, **43**, and **44** were also prepared for antiviral tests. They were obtained by the treatment of trifluoroacetic salts **9a**, **9b**, **27**, and **38**, respectively, with hexanoyl chloride in the presence of triethylamine and 4-(dimethylamino) pyridine (Scheme 8).



**Scheme 8.** Reagents and conditions: (a) hexanoyl chloride, THF, TEA, DMAP, rt, 2 h, 92% of **42a**, 82% of **42b**, 75% of **43**, and 87% of **44**.

The structures of the prepared compounds were confirmed by NMR spectroscopy. Complete assignment of all $^1H$ and $^{13}C$ resonances is based on a combination of $^1H$, $^{13}C$ APT, H,H COSY, H,C HSQC, and H,C HMBC experiments.

## 3. Conclusion

Novel racemic derivatives of 6-chloropurine, adenine, and 6-(cyclopropylamino)purine substituted with 2-azanorbornane, 7-azanorbornane, and 7-azabenzonorbornane were synthesized. *N*-Hexanoyl derivatives of the 6-chloropurine analogues were prepared as well. All target compounds were tested for anti-Coxsackievirus B3 (CVB3) and for their effect on the replication of the hepatitis C virus. None of the compounds exhibit substantial antiviral activity against either the Coxsackievirus or the HCV (Table 1). Compounds **9a**, **9b**, **24b**, **26**, and **37** were evaluated for potential activity as agonists of the α3β4 neuronal nicotinic acetylcholine receptor and the muscle nicotinic acetylcholine receptor. Compound **26** very weakly activated both receptors. On contrary, all the compounds inhibited the receptor activated with acetylcholine (Table 2).

**Table 1**
Antiviral evaluation against CVB3 in Vero cells and HCV in Huh cells

| Entry | Compound | CVB3 | | | HCV | |
|---|---|---|---|---|---|---|
| | | $EC_{50}$ (μM) | $EC_{90}$ (μM) | $CC_{50}$ (μM) | $EC_{50}$ (μM) | $EC_{90}$ (μM) |
| 1 | **8a** | 14 | ND[a] | 53 | 13 | >53 |
| 2 | **8b** | 13 | 28 | 50 | 7.3 | 25 |
| 3 | **9a** | >137 | >137 | 17 | 13 | ND |
| 4 | **9b** | >137 | >137 | 49 | 15 | ND |
| 5 | **10a** | >151 | >151 | >151 | 50 | >151 |
| 6 | **10b** | >151 | >151 | >151 | 77 | >151 |
| 7 | **11a** | >109 | >109 | >109 | >109 | >109 |
| 8 | **11b** | >109 | >109 | >109 | >109 | >109 |
| 9 | **12a** | >135 | >135 | >135 | >135 | >135 |
| 10 | **12b** | >135 | >135 | >135 | 67 | >135 |
| 11 | **13a** | >100 | >100 | >100 | >100 | >100 |
| 12 | **13b** | >100 | >100 | >303 | 116 | ND |
| 13 | **15** | 14 | >143 | 85 | 19 | 85 |
| 14 | **17** | >135 | >135 | >135 | >135 | >135 |
| 15 | **18** | >135 | >135 | >135 | <1.1 | <1.1 |
| 16 | **19** | >100 | >100 | >100 | >100 | >100 |
| 17 | **20** | >100 | >100 | >100 | >100 | >100 |
| 18 | **24a** | >147 | >147 | >147 | 1.2 | >147 |
| 19 | **24b** | >141 | >141 | >141 | >141 | >141 |
| 20 | **25** | >151 | >151 | >151 | >151 | >151 |
| 21 | **26** | >137 | >137 | 55 | 30 | 55 |
| 22 | **27** | >109 | >109 | >109 | >109 | >109 |
| 23 | **33** | 51 | 94 | 12 | 8.2 | >12 |
| 24 | **36** | >129 | >129 | >112 | 33 | 100 |
| 25 | **37** | 62 | >121 | 64 | 33 | >64 |
| 26 | **38** | >132 | >132 | >132 | >132 | >132 |
| 27 | **39** | >99 | >99 | >99 | >99 | >99 |
| 28 | **40** | >119 | >119 | >119 | 62 | ND |
| 29 | **41** | >91 | >91 | >91 | >91 | >91 |
| 30 | **42a** | 19 | ND | 71 | 32 | >71 |
| 31 | **42b** | 15 | ND | 86 | 20 | >86 |
| 32 | **43** | >144 | >144 | 104 | 19.2 | >104 |
| 33 | **44** | >126 | >126 | 12 | 10.2 | >12 |

[a] Not determined.

**Table 2**
Inhibition of the neuronal nicotinic acetylcholine receptor activated with acetylcholine[a]

| Entry | Compound | IC50 (μM) | $nH$[b] | $N$[c] |
|---|---|---|---|---|
| 1 | **9a** | 80±20 | 0.56±0.08 | 3 |
| 2 | **9b** | 230±30 | 0.75±0.1 | 3 |
| 3 | **24b** | 77±15 | 0.64±0.08 | 4 |
| 4 | **26** | 21.3±3 | 0.56±0.05 | 7 |
| 5 | **37** | 11.2±1.5 | 0.83±0.08 | 4 |

[a] At 10 μM concentration of acetylcholine.
[b] Hill coefficient.
[c] Cell number.

## 4. Experimental

### 4.1. General

Melting points were determined on a Büchi melting point B-540 apparatus. NMR spectra ($\delta$, ppm; $J$, Hz) were measured on Bruker Avance II-600 and/or Bruker Avance II-500 instruments (600.1 or 500.0 MHz for $^1$H and 150.9 or 125.7 MHz for $^{13}$C) in hexadeuterodimethyl sulfoxide and referenced to the solvent signal ($\delta$ 2.50 and 39.70, respectively). Mass spectra were measured on an LTQ Orbitrap XL (Thermo Fischer Scientific) using electrospray ionization (ESI) and a GCT Premier (Waters) using EI. The elemental analyses were obtained on a Perkin–Elmer CHN Analyzer 2400, Series II Sys (Perkin–Elmer) and X-ray fluorescence spectrometer SPECTRO iQ II (SPECTRO Analytical Instruments, Germany). Column chromatography and thin-layer chromatography (TLC) were performed using Silica gel 60 (Fluka) and Silufol Silica gel 60 $F_{254}$ foils (Merck), respectively. Solvents were evaporated at 2 kPa and bath temperature 30–60 °C. The compounds were dried at 13 Pa and 50 °C.

### 4.2. Hydroboration of a compound 4

A 1 M solution of borane in tetrahydrofuran (40 mmol) was added dropwise under argon to a stirred solution of unsaturated derivative **4**[12] (7.81 g, 40 mmol) in tetrahydrofuran (20 mL), which was cooled to 0 °C. The reaction mixture was stirred at 0 °C for 3 h. Excess borane was decomposed by addition of water (1 mL) and then a suspension of sodium perborate tetrahydrate (15.4 g, 100 mmol) in water (60 mL) was added in one portion. The reaction mixture was stirred at room temperature overnight and then diluted with ethyl acetate (250 mL). The organic layer was separated, washed with water (50 mL), dried over anhydrous $Na_2SO_4$ and evaporated. The residue was chromatographed on silica gel (500 g) in toluene/ethyl acetate (1:1). The separated compounds were crystallized from cyclohexane.

*4.2.1. tert-Butyl (1R*,4R*,6S*)-6-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate (**5a**).* Yield 1.58 g (18.5%) of a white powder. Mp 90–92 °C. IR ($CHCl_3$): 3609 (w), 3418 (br), 2982, 1679, 1478, 1417, 1399 (sh), 1368, 1078 cm$^{-1}$. $^1$H NMR: 4.85 (m, 1H, OH); 4.00 (s, 0.5H) and 3.97 (s, 0.5H, H-1); 3.78 (m, 1H, H-5); 3.06 (dd, 0.5H, $J$=9.9, 3.9) and 3.02 (dd, 0.5H, $J$=10.1, 3.9, H-3*exo*); 2.70 (m, 1H, H-3*endo*); 2.29 (br s, 1H, H-4); 1.82 (m, 1H, H-6*endo*); 1.67 (m, 1H, H-7b); 1.41 (m, 1H, H-7a); 1.37 (s, 4.5H) and 1.35 (s, 4.5H, $CH_3$); 1.30 (m, 1H, H-6*exo*). $^{13}$C NMR: 153.76 and 153.51 (C=O); 78.31 and 78.28 ($C(CH_3)_3$); 71.30 and 71.27 (C-5); 56.02 and 54.94 (C-1); 48.25 and 47.89 (C-3); 44.83 and 44.24 (C-4); 42.98 and 42.62 (C-6); 33.87 and 33.33 (C-7); 28.50 and 28.44 ($CH_3$) (mixture of two C/N rotamers 1:1). ESI MS, $m/z$ (%): 237.1 (14) [M+Na+1], 236.1 (100) [M+Na]. For $C_{11}H_{19}NO_3$ (213.28) calculated: 61.95% C, 8.98% H, 6.57% N; found: 62.02% C, 9.03% H, 6.51% N.

*4.2.2. tert-Butyl (1R*,4R*,5S*)-5-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate (**5b**).* Yield 2.03 g (24%) of a white powder. Mp 106.5–107.5 °C. IR ($CHCl_3$): 3612 (w), 3441 (br), 2981, 1681, 1478, 1416, 1392 (sh), 1367, 1159 cm$^{-1}$. $^1$H NMR: 4.94–4.98 (m, 1H, OH); 3.80 (s, 0.5H) and 3.75 (s, 0.5H, H-1); 3.67 (m, 1H, H-6); 3.02 (dt, 0.5H) and 2.97 (dt, 0.5H, $J$=9.2, 2.8, H-3*exo*); 2.67 (dm, 1H, $J$=9.2, H-3*endo*); 2.42 (m, 1H, H-4); 1.68 (m, 1H, H-5*endo*); 1.61 (m, 1H, H-7b); 1.41 (m, 1H, H-7a); 1.36 (s, 4.5H) and 1.39 (s, 4.5H, $CH_3$); 1.26 (m, 1H, H-5*exo*). $^{13}$C NMR: 153.80 and 153.52 (C=O); 78.36 and 78.33 ($C(CH_3)_3$); 71.45 and 71.09 (C-6); 61.11 and 60.13 (C-1); 51.68 and 51.27 (C-3); 39.50 and 39.38 (C-5); 35.69 and 35.13 (C-4); 33.41 and 32.87 (C-7); 28.41 and 28.36 ($CH_3$) (mixture of two C/N rotamers 1:1). ESI MS, $m/z$ (%): 237.1 (13) [M+Na+1], 236.1 (100) [M+Na]. For $C_{11}H_{19}NO_3$ (213.28) calculated: 61.95% C, 8.98% H, 6.57% N; found: 62.12% C, 9.02% H, 6.54% N.

### 4.3. Preparation of ketones 6a and 6b

A solution of alcohol **5a** or **5b** (2.13 g, 10 mmol) in dichloromethane (20 mL) was added to a suspension of powdered molecular sieves (5.5 g) and pyridinium dichromate (5.83 g, 15.5 mmol) in dichloromethane (60 mL). The reaction mixture was stirred at room temperature for 4 days. Solids were filtered off and washed with ethyl acetate. The filtrate was evaporated, and the residue was dissolved in ethyl acetate (100 mL), filtered and the filtrate evaporated. The residue was chromatographed on silica gel (150 g) in toluene/ethyl acetate (4:1).

*4.3.1. tert-Butyl (1R*,4S*)-6-oxo-2-azabicyclo[2.2.1]heptane-2-carboxylate (**6a**).* Yield 1.04 g (49%) of a white powder after crystallization from cyclohexane. Mp 85.5–86.5 °C. IR ($CHCl_3$): 2983, 1767, 1755, 1691, 1478, 1400, 1369, 1166, 1146 cm$^{-1}$. $^1$H NMR: 3.94 (br s, 0.6H) and 4.00 (br s, 0.4H, H-1); 3.32 (m, 1H, H-3*exo*); 3.06 (m, 1H, H-3*endo*); 2.76 (br s, 1H, H-4); 2.22 (ddd, 1H,

*J*=17.8, 4.8, 1.6, H-5*exo*); 1.96 (m, 1H, H-5*endo*); 1.71–1.84 (m, 2H, H-7); 1.37 (br s, 9H, $CH_3$). $^{13}$C NMR: 206.35 and 205.80 (C-6); 153.78 and 153.29 (COO); 79.36 ($C(CH_3)_3$); 62.35 and 61.31 (C-1); 50.69 and 50.25 (C-3); 41.32 (C-5); 35.98 and 35.43 (C-7); 34.64 and 34.00 (C-4); 28.25 ($CH_3$) (mixture of two C/N rotamers 2:3). ESI MS, *m*/*z* (%): 235.0 (12) [M+Na+H], 234.0 (100) [M+Na]. For $C_{11}H_{17}NO_3$ (211.26) calculated: 62.54% C, 8.11% H, 6.63% N; found: 62.69% C, 7.90% H, 6.50% N.

*4.3.2. tert-Butyl (1R*,4R*)-5-oxo-2-azabicyclo[2.2.1]heptane-2-carboxylate (**6b**).* Yield 1.94 g (92%) of a thick syrup. IR ($CHCl_3$): 2982, 1777, 1752, 1691, 1478, 1409, 1395 (sh), 1369, 1154 cm$^{-1}$. $^1$H NMR: 4.39 (br s, 0.5H) and 4.42 (br s, 0.5H, H-1); 3.37 (m, 1H, H-3*exo*); 3.11 (m, 1H, H-3*endo*); 2.81 (m, 1H, H-4); 2.27 (m, 1H, H-6*exo*); 2.04 (m, 1H, H-6*endo*); 1.91–2.01 (m, 2H, H-7); 1.40 (br s, 4.5H) and 1.38 (br s, 4.5H, $CH_3$). $^{13}$C NMR: 213.88 and 213.70 (C-6); 153.79 and 153.60 (COO); 79.14 ($C(CH_3)_3$); 56.40 and 55.41 (C-1); 50.56 and 49.88 (C-4); 47.64 and 47.31 (C-3); 45.42 and 45.70 (C-6); 37.14 and 36.67 (C-7); 28.34 ($CH_3$) (mixture of two C/N rotamers 1:1). ESI MS, *m*/*z* (%): 235.1 (13) [M+Na+H], 234.0 (100) [M+Na]. For $C_{11}H_{17}NO_3$ (211.26) calculated: 62.54% C, 8.11% H, 6.63% N; found: 62.46% C, 8.07% H, 6.56% N.

### 4.4. Reduction of ketones 6a and 6b

Sodium borohydride (303 mg, 8 mmol) was added to a stirred solution of ketone **6a** or **6b** (1.69 g, 8 mmol) in methanol (18 mL) at 0 °C. The mixture was stirred for 40 min at 0 °C and then a saturated aqueous solution of ammonium chloride (20 mL) was slowly added. The mixture was extracted with ethyl acetate (2×60 mL), the combined extracts were dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed on a silica gel column (100 g) in hexane/ethyl acetate (1:2).

*4.4.1. tert-Butyl (1R*,4S*,6S*)-6-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate (**7a**).* Yield 1.45 g (85%) of a white powder after crystallization from hexane. Mp 70.5–72.5 °C. IR ($CHCl_3$): 3574 (w), 3438 (br), 2981, 1678, 1477, 1418, 1394, 1368, 1156, 1070 (w) cm$^{-1}$. $^1$H NMR: 4.60 (d, 0.4H) and 4.57 (d, 0.6H, *J*=4.8, OH); 4.07 (m, 1H, H-6); 3.95 (m, 0.4H) and 3.87 (m, 0.6H, H-1); 3.21 (dt, 0.4H) and 3.15 (dt, 0.6H, *J*=9.2, 3.1, H-3*exo*); 2.92 (m, 1H, H-3*endo*); 2.34 (m, 1H, H-4); 1.90 (m, 1H, H-5*exo*); 1.35–1.50 (m, 11H, H-7 and $CH_3$); 0.80 (dt, 1H, *J*=12.7, 3.3, H-5*endo*). $^{13}$C NMR: 154.88 and 154.21 (COO); 77.71 and 77.66 ($C(CH_3)_3$); 72.38 and 72.31 (C-6); 60.76 and 59.83 (C-1); 52.89 and 52.29 (C-3); 37.41 and 36.78 (C-4); 37.21 and 37.10 (C-5); 35.53 and 35.99 (C-7); 28.50 and 27.96 ($CH_3$) (mixture of two C/N rotamers 2:3). ESI MS, *m*/*z* (%): 237.2 (11) [M+Na+H], 236.1 (100) [M+Na]. For $C_{11}H_{19}NO_3$ (213.28) calculated: 61.95% C, 8.98% H, 6.57% N; found: 62.05% C, 9.14% H, 6.53% N.

*4.4.2. tert-Butyl (1R*,4R*,5R*)-5-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate (**7b**).* Yield 1.67 g (98%) of white crystals after crystallization from ethyl acetate/hexane. Mp 110.5–112.5 °C. IR ($CHCl_3$): 3616 (w), 3433 (br), 2981, 1628, 1478, 1417, 1395 (sh), 1367, 1160, 1072 cm$^{-1}$. $^1$H NMR: 4.89 (m, 1H, OH); 4.16 (m, 1H, H-5); 3.92 (m, 0.5H) and 3.89 (m, 0.5H, H-1); 3.50 (m, 1H, H-3*endo*); 2.97 (ddd, 0.5H, *J*=9.3, 3.5, 1.2) and 2.94 (ddd, 0.5H, *J*=9.4, 3.5, 1.2, H-3*exo*); 2.40 (m, 1H, H-4); 1.87 (m, 1H, H-6*exo*); 1.54 (m, 1H, H-7b); 1.42 (m, 1H, H-7a); 1.38 (s, 9H, $CH_3$); 1.09 m, 1H (H-6*endo*). $^{13}$C NMR: 153.56 and 153.42 (C=O); 78.06 and 78.09 ($C(CH_3)_3$); 68.62 and 68.59 (C-5); 57.20 and 56.19 (C-1); 44.65 and 44.30 (C-3); 43.39 and 42.86 (C-4); 40.20 and 39.81 (C-6); 36.57 and 36.07 (C-7); 28.50 ($CH_3$) (mixture of two C/N rotamers 1:1). ESI MS, *m*/*z* (%): 237.2 (12) [M+Na+H], 236.1 (100) [M+Na]. For $C_{11}H_{19}NO_3$ (213.28) calculated: 61.95% C, 8.98% H, 6.57% N; found: 61.96% C, 9.07% H, 6.52% N.

### 4.5. Mitsunobu reaction of 7a and 7b with 6-chloro-9*H*-purine

A solution of diisopropyl azodicarboxylate (1.18 mL, 6 mmol) in tetrahydrofuran (10 mL) was slowly added to a suspension of alcohol **7a** or **7b** (853 mg, 4 mmol), triphenylphosphine (2.10 g, 8 mmol) and 6-chloropurine (926 mg, 6 mmol) in tetrahydrofuran (30 mL). The reaction mixture was then heated to reflux for 6 h and evaporated. The residue was chromatographed on silica gel (500 g) in ethyl acetate/acetone/hexane (14:4:7).

*4.5.1. tert-Butyl (1R*,4R*,6R*)-6-(6-chloro-9H-purin-9-yl)-2-azabicyclo[2.2.1]heptane-2-carboxylate (**8a**).* Yield 1.01 g (72%) of a white powder after crystallization from ether. Mp 137–138.5 °C. IR ($CHCl_3$): 2986, 1690, 1591, 1563, 1480, 1440, 1409, 1368, 1339, 1155 cm$^{-1}$. $^1$H NMR: 8.89 (s, 0.6H) and 8.87 (s, 0.4H, H-8′); 8.80 (s, 0.4H) and 8.78 (s, 0.6H, H-2′); 4.69–4.77 (m, 1H, H-6); 4.49 (s, 0.4H) and 4.25 (s, 0.6H, H-1); 3.14–3.24 (m, 1H, H-3*exo*); 3.03 (br d, 0.6H) and 3.00 (br d, 0.4H, *J*=9.2, H-3*endo*); 2.72 (br s, 1H, H-4); 2.35–2.41 (m, 0.6H) and 2.18–2.24 (m, 1.4H, H-5); 1.89 (br d, 0.4H) and 1.84 (br d, 0.6H, *J*=10.8, H-7b); 1.65 (m, 1H, H-7a); 1.47 (s, 5.4H) and 1.42 (s, 3.6H, $CH_3$). $^{13}$C NMR: 153.66 and 153.39 (C=O); 152.24 and 152.15 (C-4′); 151.66 and 151.51 (C-2′); 149.28 (C-6′); 145.82 and 145.73 (C-8′); 131.41 and 131.34 (C-5′); 79.19 and 79.01 ($C(CH_3)_3$); 60.12 and 58.67 (C-1); 57.41 and 57.31 (C-6); 52.01 and 51.44 (C-3); 36.73 and 36.16 (C-4); 35.36 and 34.38 (C-5); 34.82 and 34.73 (C-7); 28.40 and 28.33 ($CH_3$) (mixture of two C/N rotamers 2:3). ESI MS, *m*/*z* (%): 374.1/372.1 (37/100) [M+Na], 352.0/349.9 (6/20) [M+1]. For $C_{16}H_{20}ClN_5O_2$ (349.82) calculated: 54.94% C, 5.76% H, 10.13% Cl, 20.02% N; found: 54.88% C, 5.86% H, 10.16% Cl, 19.85% N.

*4.5.2. tert-Butyl (1R*,4R*,5S*)-5-(6-chloro-9H-purin-9-yl)-2-azabicyclo[2.2.1]heptane-2-carboxylate (**8b**).* Yield 535 mg (38%) of a white powder after crystallization from acetone/ether. Mp 165–166 °C. IR ($CHCl_3$): 2985, 1689, 1591, 1563, 1484, 1480 (sh), 1438, 1395 (sh), 1368, 1342, 1159 cm$^{-1}$. $^1$H NMR: 8.85 (br s, 1H, H-8′); 8.78 (s, 1H, H-2′); 4.83 (m, 1H, H-5); 4.24 (br s, 0.5H) and 4.20 (br s, 0.5H, H-1); 3.29 (dd, 0.5H, *J*=10.0, 3.7) and 3.26 (dd, 0.5H, *J*=10.0, 3.7H-3*exo*); 3.15 (m, 1H, H-3*endo*); 2.95 (m, 0.5H) and 2.92 (m, 0.5H, H-4); 2.25–2.36 (m, 2H, H-6); 2.00 (m, 1H, H-7b); 1.72 (br d, 0.5H) and 1.68 (br d, 0.5H, *J*=10.7, H-7a); 1.414 (s, 4.5H) and 1.409 (s, 4.5H, $CH_3$). $^{13}$C NMR: 153.73 and 153.60 (C=O); 152.19 (C-4′); 151.59 (C-2′); 149.27 (C-6′); 145.92 and 145.88 (C-8′); 131.56 (C-5′); 78.85 and 78.80 ($C(CH_3)_3$); 56.87 (C-5); 56.61 and 55.60 (C-1); 50.72 and 50.29 (C-3); 43.08 and 42.34 (C-4); 39.15 and 38.65 (C-6); 35.54 and 35.04 (C-7); 28.44 ($CH_3$) (mixture of two C/N rotamers 1:1). ESI MS, *m*/*z* (%): 374.1/372.1 (33/100) [M+Na], 352.1/350.1 (27/77) [M+1]. For $C_{16}H_{20}ClN_5O_2$ (349.82) calculated: 54.94% C, 5.76% H, 10.13% Cl, 20.02% N; found: 54.87% C, 5.75% H, 10.25% Cl, 19.78% N.

### 4.6. Preparation of compounds 17 and 18

A solution of diisopropyl azodicarboxylate (1.2 mL, 6 mmol) in tetrahydrofuran (10 mL) was slowly added to a solution of alcohol **14**[14,15] (853 mg, 4 mmol), triphenylphosphine (1.57 g, 6 mmol) and 6-chloropurine (927 mg, 6 mmol) in THF (25 mL). The reaction mixture was then heated to reflux for 6 h and evaporated. Chromatography of the residue on silica gel (200 g) in toluene/ethyl acetate (1:1) gave 740 mg (50%) of a mixture of chloropurine derivatives **12** and **13**. The mixture was without isolation dissolved in cyclopropylamine (5 mL) and the solution was left standing at room temperature overnight and then evaporated. The residue was chromatographed on a silica gel column (100 g) in ethyl acetate/acetone/ethanol/water (112:8:3:2).

*4.6.1. tert-Butyl (1R*,2S*,4S*)-2-[6-(cyclopropylamino)-9H-purin-9-yl]-7-azabicyclo[2.2.1]heptane-7-carboxylate (**17**).* Yield 315 mg (21%) of a white powder after crystallization from ethanol/ether. Mp 217.5–218.5 decomp. IR ($CHCl_3$): 3428 (w), 3094 (vw), 2981, 1699, 1618, 1600 (sh), 1581, 1520 (w), 1476, 1394, 1370, 1354, 1156 $cm^{-1}$. $^1H$ NMR: 8.25 (br s, 1H, H-2′); 8.08 (s, 1H, H-8′); 7.92 (br s, 1H, NH); 4.68 (dd, 1H, *J*=8.4, 3.6, H-2); 4.28–4.32 (m, 2H, H-1 and H-4); 3.00 (br s, 1H, CH of cyclopropyl); 2.29 (m, 1H, H-3*exo*); 2.14 (dd, 1H, *J*=13.5, 8.4, H-3*endo*); 1.75 (m, 1H, H-6*exo*); 1.62–1.68 (m, 2H, H-5*exo* and H-6*endo*); 1.53 (m, 1H, H-5*endo*); 1.26 (br s, 9H, $CH_3$); 0.71 (m, 2H) and 0.60 (m, 2H, $CH_2$ of cyclopropyl); $^{13}C$ NMR: 155.74 (C-6′); 154.58 (COO); 152.49 (C-2′); 149.00 (C-4′); 138.04 (C-8′); 119.53 (C-5′); 79.47 (*C*($CH_3$)$_3$); 61.34 (C-1); 56.80 (C-2); 55.30 (C-4); 37.20 (C-3); 28.35 (C-5); 27.96 ($CH_3$); 26.07 (C-6); 6.58 ($CH_2$ of cyclopropyl). ESI MS, *m*/*z* (%): 393.3 (24) [M+Na], 372.3 (18) [M+2H], 371.3 (100) [M+H]. For $C_{19}H_{26}N_6O_2$ (370.46) calculated: 61.60% C, 7.07% H, 22.69% N; found: 61.55% C, 7.13% H, 22.56% N.

*4.6.2. tert-Butyl (1R*,2R*,4S*)-2-[6-(cyclopropylamino)-9H-purin-9-yl]-7-azabicyclo[2.2.1]heptane-7-carboxylate (**18**).* Yield 340 mg (23%) of a yellowish solid foam. IR ($CHCl_3$): 3428 (w), 3094 (vw), 2982, 1696, 1617, 1600 (sh), 1581, 1520 (w), 1476, 1393, 1369, 1354, 1154 $cm^{-1}$. $^1H$ NMR: 8.38 (s, 1H, H-8′); 8.26 (br s, 1H, H-2′); 7.95 (br s, 1H, NH); 4.82 (dtd, 1H, *J*=11.5, 4.8, 1.8, H-2); 4.53 (br t, 1H, *J*=4.8, H-1); 4.23 (br t, 1H, *J*=4.9, H-4); 2.99 (br s, 1H, CH of cyclopropyl); 2.36 (m, 1H, H-3*exo*); 2.24 (dd, 1H, *J*=13.1, 4.9, H-3*endo*); 1.78 (ddd, 1H, *J*=12.1, 8.9, 4.4, H-5*endo*); 1.69 (m, 1H, H-5*exo*); 1.48 (m, 1H, H-6*exo*); 1.42 (br s, 9H, $CH_3$); 1.11 (ddd, 1H, *J*=13.1, 9.0, 4.8, H-6*endo*); 0.72 (m, 2H) and 0.61 (m, 2H, $CH_2$ of cyclopropyl); $^{13}C$ NMR: 155.74 (C-6′); 154.96 (COO); 152.69 (C-2′); 149.70 (C-4′); 139.68 (C-8′); 119.79 (C-5′); 79.66 (*C*($CH_3$)$_3$); 59.10 (C-1); 57.00 (C-4); 54.86 (C-2); 32.26 (C-3); 29.10 (C-5); 28.11 ($CH_3$); 22.34 (C-6); 6.55 ($CH_2$ of cyclopropyl). ESI MS, *m*/*z* (%): 393.2 (11) [M+Na], 372.2 (24) [M+2H], 371.2 (100) [M+H]. For $C_{19}H_{26}N_6O_2$ (370.46) calculated: 61.60% C, 7.07% H, 22.69% N; found: 61.93% C, 7.04% H, 22.33% N.

### 4.7. Mercuryazidation of the olefins 21 and 28

Olefin **21**[17] or **28**[20] (5 mmol) was added to a stirred mixture of sodium azide (975 mg, 15 mmol), mercury(II) acetate (1.6 g, 5 mmol), tetrahydrofuran (5 mL), and water (5 mL) and the two-phase mixture was stirred at 50 °C for 19 h. After cooling, the mixture was diluted with 15% aqueous potassium hydroxide (5 mL) and treated with a solution of sodium borohydride (100 mg) in 15% aqueous potassium hydroxide (5 mL). Then ether (15 mL) was added, organic phase was separated and the aqueous phase was washed with ether (2×15 mL). The combined organic solutions were dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed on silica gel (100 g) in hexane/ethyl acetate (10:1).

*4.7.1. tert-Butyl (1R*,2S*,4S*)-2-azido-7-azabicyclo[2.2.1]heptane-7-carboxylate (**22**).* Yield 1.01 g (85%) of a yellowish oil. IR ($CHCl_3$): 2982, 2104, 1695 (br), 1478, 1393, 1368, 1160, 559 (w) $cm^{-1}$. $^1H$ NMR: 4.13 (m, 1H, H-4); 4.11 (m, 1H, H-1); 3.78 (br s, 1H, H-2); 1.83 (m, 1H, H-3*endo*); 1.67 (m, 1H, H-6*exo*); 1.48–1.57 (m, 2H, H-3*exo* and H-5*exo*); 1.28–1.40 (m, 2H, H-5*endo* and H-6*endo*); 1.39 (s, 9H, $CH_3$); $^{13}C$ NMR: 154.71 (COO); 79.20 (*C*($CH_3$)$_3$); 62.80 (C-2); 60.42 (C-1); 55.04 (C-4); 37.06 (C-3); 28.07 ($CH_3$); 27.84 (C-5); 25.55 (C-6); ESI MS, *m*/*z* (%): 262.3 (14) [M+Na+H], 261.3 (18) [M+Na]. For $C_{11}H_{18}N_4O_2$ (238.29) calculated: 55.44% C, 7.61% H, 23.51% N; found: 55.56% C, 7.62% H, 23.26% N.

*4.7.2. tert-Butyl (1R*,8R*,9S*)-9-azido-11-azatricyclo[6.2.1.0$^{2,7}$]undeca-2,4,6-triene-11-carboxylate (**34**).* Yield 1.075 g (75%) of a white powder after crystallization from heptane. Mp 68–69 °C. IR ($CHCl_3$): 2982, 2103, 1701, 1592 (vw), 1478 (w), 1461, 1395, 1369, 1168, 1155 $cm^{-1}$. $^1H$ NMR: 7.42 (m, 1H, H-6); 7.31 (m, 1H, H-3); 7.14–7.19 (m, 2H, H-4, H-5); 5.15 (br s, 1H, H-8); 5.11 (br d, 1H, *J*=4.1, H-1); 3.76 (br s, 1H, H-9); 1.70–1.93 (m, 2H, H-10); 1.33 (br s, 9H, $CH_3$). $^{13}C$ NMR: 154.49 (COO); 146.13 (C-2); 141.57 (C-7); 127.53 (C-4); 126.83 (C-5); 121.66 (C-3); 120.03 (C-6); 79.97 (*C*($CH_3$)$_3$); 65.68 (C-8); 61.62 (C-9); 59.94 (C-1); 35.11 (C-10); 28.07 ($CH_3$). ESI MS, *m*/*z* (%): 310.1 (25) [M+Na+H], 309.1 (100) [M+Na], 253.0 (86). For $C_{15}H_{18}N_4O_2$ (286.34) calculated: 62.92% C, 6.34% H, 19.57% N; found: 62.87% C, 6.35% H, 19.51% N.

### 4.8. Conversion of azides 22 and 34 to amines 23 and 35

Palladium hydroxide on carbon (20 wt %, 100 mg) was added to a solution of azide **22** or **34** (5 mmol) in methanol (15 mL), the mixture was stirred under hydrogen at room temperature overnight, filtered through Celite and evaporated. The residue was chromatographed on silica gel (100 g) in ethyl acetate/1,4-dioxane/ethanol/water/concd aqueous ammonia (18:3:2:1:1).

*4.8.1. tert-Butyl (1R*,2S*,4S*)-2-amino-7-azabicyclo[2.2.1]heptane-7-carboxylate (**23**).* Yield 1.02 g (96%) of a yellowish oil. IR ($CHCl_3$): 3372 (w), 2979, 1689 (br), 1477, 1392, 1368, 1173, 1144 $cm^{-1}$. $^1H$ NMR (70 °C): 4.03 (m, 1H, H-4); 3.74 (br d, 1H, *J*=4.7, H-1); 2.87 (m, 1H, H-2); 1.72 (dd, 1H, *J*=12.4, 7.7, H-3*endo*); 1.47–1.58 (m, 2H, H-5*exo* and H-6*exo*); 1.40 (s, 9H, $CH_3$); 1.23–1.31 (m, 2H, H-5*endo* and H-6*endo*); 1.18 (m, 1H, H-3*exo*). $^{13}C$ NMR (70 °C): 155.50 (COO); 78.29 (*C*($CH_3$)$_3$); 63.93 (C-1); 55.18 (C-4); 54.99 (C-2); 41.48 (C-3); 27.94 ($CH_3$); 27.76 (C-5); 25.54 (C-6). ESI MS, *m*/*z* (%): 235.2 (100) [M+Na], 213.2 (56%) [M+H]. For $C_{11}H_{20}N_2O_2$ (212.30) calculated: 62.23% C, 9.50% H, 13.20% N; found: 62.22% C, 9.52% H, 12.85% N.

*4.8.2. tert-Butyl (1R*,8R*,9S*)-9-amino-11-azatricyclo[6.2.1.0$^{2,7}$]undeca-2,4,6-triene-11-carboxylate (**35**).* Yield 989 mg (76%) of a white powder after crystallization from hexane. Mp 93–94.5 °C. IR ($CHCl_3$): 3376 (vw), 2981, 1693, 1590 (sh), 1478 (w), 1460, 1393, 1369, 1165 $cm^{-1}$. $^1H$ NMR: 7.29 (m, 1H, H-6); 7.25 (m, 1H, H-3); 7.08–7.12 (m, 2H, H-4 and H-5); 4.96 (br d, 1H, *J*=4.6, H-1); 4.65 (br s, 1H, H-8); 2.85 (m, 1H, H-9); 1.62 (br dd, 1H, *J*=12.0, 7.5, H-10*endo*); 1.47 (m, 1H, H-10*exo*); 1.28 (br s, 9H, $CH_3$). $^{13}C$ NMR: 155.95 (CON); 146.02 (C-2); 143.9 (C-7); 126.57 (C-4); 126.36 (C-5); 120.45 (C-6); 119.83 (C-3); 79.26 (*C*($CH_3$)$_3$); 69.90 (C-8); 61.00 (C-1); 53.70 (C-9); 38.07 (C-10); 28.10 ($CH_3$). ESI MS, *m*/*z* (%): 283.2 (100) [M+Na], 261.2 (78) [M+H]. For $C_{15}H_{20}N_2O_2$ (260.34) calculated: 69.20% C, 7.74% H, 10.76% N; found: 68.93% C, 7.61% H, 10.62% N.

### 4.9. Condensation of amines 23 and 35 with 4,6-dichloropyrimidin-5-amine

A solution of amine **23** or **35** (7 mmol), 4,6-dichloropyrimidin-5-amine (1.26 g, 7.7 mmol), and triethylamine (2.1 mL) in ethanol (21 mL) was heated in a pressure vessel at 100 °C for 6 days and, after cooling, was evaporated. The residue was crystallized from methanol and the mother liquor was chromatographed on a silica gel column (100 g) in chloroform/ethyl acetate (2:3).

*4.9.1. tert-Butyl (1R*,2S*,4S*)-2-[(5-amino-6-chloropyrimidin-4-yl) amino]-7-azabicyclo[2.2.1]heptane-7-carboxylate (**24**).* Yield 1.84 g (77%) of a white powder after crystallization from methanol. Mp 204–206 °C (decomp.). IR ($CHCl_3$): 3414 (w, br), 3348 (w, sh), 2982, 1691, 1697, 1620 (w), 1596, 1495, 1419, 1392, 1369, 1156 $cm^{-1}$. $^1H$ NMR: 7.76 (s, 1H, H-2′); 6.52 (br s, 1H, 9-NH); 5.17 (br s, 2H, $NH_2$); 4.14 (m, 1H, H-4); 4.09 (br m, 1H, H-1); 3.89 (m, 1H, H-2); 1.87 (dd, 1H, *J*=12.7, 8.2, H-3*endo*); 1.76 (m, 1H, H-3*exo*); 1.63 (m, 1H, H-6*exo*); 1.57 (m, 1H, H-5*exo*); 1.22–1.48 (m, 11H, H-5*endo*, H-6*endo* and $CH_3$). $^{13}C$ NMR: 155.40 (COO); 151.21 (C-4′); 145.54 (C-2′);

136.85 (C-6′); 123.95 (C-5′); 78.90 (*C*($CH_3$)$_3$); 60.43 (C-1); 55.01 (C-2); 55.00 (C-4); 37.50 (C-3); 28.33 (C-5); 28.08 ($CH_3$); 25.70 (C-6). ESI MS, *m*/*z* (%): 342.2/340.2 (36/100) [M+Na]. For $C_{15}H_{22}ClN_5O_2$ (339.83) calculated: 53.02% C, 6.53% H, 10.43% Cl, 20.61% N; found: 52.83% C, 6.56% H, 10.21% Cl, 20.32% N.

*4.9.2. tert-Butyl (1R*,8R*,9S*)-9-[(5-amino-6-chloropyrimidin-4-yl) amino]-11-azatricyclo[6.2.1.0$^{2,7}$]undeca-2,4,6-triene-11-carboxylate (**36**).* Yield 1.74 g (64%) of a white powder after crystallization from methanol. Mp 217–219 °C (decomp.). IR ($CHCl_3$): 3424 (w, sh), 3396 (w, br), 3348 (w, sh), 2983, 1702 (sh), 1686, 1575, 1492, 1461, 1418, 1393, 1369, 1155 cm$^{-1}$. $^1$H NMR: 7.84 (s, 1H, H-2′); 7.40 (m, 1H, H-6); 7.33 (m, 1H, H-3); 7.16–7.20 (m, 2H, H-4 and H-5); 6.92 (br s, 1H, 9-NH); 5.25 (br s, 2H, $NH_2$); 5.13 (m, 1H, H-1); 5.03 (br m, 1H, H-8); 3.89 (m, 1H, H-9); 2.11 (m, 1H, H-10*exo*); 1.81 (m, 1H, H-10*endo*); 1.22 (br s, 9H, $CH_3$). $^{13}$C NMR: 151.31 (C-4′); 146.08 (C-2); 145.62 (C-2′); 142.70 (C-7); 137.00 (C-6′); 127.11 (C-4); 126.67 (C-5); 124.17 (C-5′); 120.96 (C-6); 120.03 (C-3); 79.53 (*C*($CH_3$)$_3$); 65.86 (C-8); 60.30 (C-1); 53.50 (C-9); 34.20 (C-10); 27.99 ($CH_3$). ESI MS, *m*/*z* (%): 390.15/388.15 (45/100) [M+Na]. For $C_{19}H_{22}ClN_5O_2$ (387.87) calculated: 58.84% C, 5.72% H, 9.14% Cl, 18.06% N; found: 58.83% C, 5.55% H, 9.11% Cl, 17.87% N.

### 4.10. Chloropurine derivatives 15 and 33

A stirred suspension of pyrimidine derivative **24** or **36** (10 mmol) in diethoxymethyl acetate (30 mL) was slowly heated up to 110 °C under argon, and the obtained solution was heated at 110 °C for 5 days. Rising ethanol and ethyl acetate were continuously distilled off. The mixture was then evaporated. The residue was chromatographed on a silica gel column (300 g) in toluene/ethyl acetate (1:1).

*4.10.1. tert-Butyl (1R*,2S*,4S*)-2-(6-chloro-9H-purin-9-yl)-7-azabicyclo[2.2.1]heptane-7-carboxylate (**15**).* Yield 1.95 g (56%) of a white powder after crystallization from cyclohexane/ethanol. Mp 162–163 °C. IR ($CHCl_3$): 2984, 1702, 1589, 1564, 1485, 1427, 1395, 1370, 1340, 1158, 947 cm$^{-1}$. $^1$H NMR: 8.80 (s, 1H, H-2′); 8.66 (s, 1H, H-8′); 4.84 (dd, 1H, *J*=8.4, 3.5, H-2); 4.40 (br s, 1H, H-1); 4.33 (br t, 1H, *J*=4.6, H-4); 2.41 (m, 1H, H-3*exo*); 2.20 (dd, 1H, *J*=13.6, 8.4, H-3*endo*); 1.77 (m, 1H, H-6*exo*); 1.63–1.73 (m, 2H, H-5*exo* and H-6*endo*); 1.56 (m, 1H, H-5*endo*); 1.25 (br s, 9H, $CH_3$). $^{13}$C NMR: 154.54 (COO); 152.08 (C-4′); 151.60 (C-2′); 149.22 (C-6′); 145.04 (C-8′); 131.29 (C-5′); 79.55 (*C*($CH_3$)$_3$); 61.11 (C-1); 57.73 (C-2); 55.57 (C-4); 37.04 (C-3); 28.28 (C-5); 27.88 ($CH_3$); 25.88 (C-6). ESI MS, *m*/*z* (%): 374.1/372.1 (31/77) [M+Na], 352.1/350.1 (41/100) [M+H]. For $C_{16}H_{20}ClN_5O_2$ (349.82) calculated: 54.94% C, 5.76% H, 10.13% Cl, 20.02% N; found: 54.96% C, 5.59% H, 10.24% Cl, 19.87% N.

*4.10.2. tert-Butyl (1R*,8R*,9S*)-9-(6-chloro-9H-purin-9-yl)-11-azatricyclo[6.2.1.0$^{2,7}$]undeca-2,4,6-triene-11-carboxylate (**33**).* Yield 2.55 g (64%) of a white powder after crystallization from ethanol. Mp 190–191 °C. IR ($CHCl_3$): 1710, 1590, 1564, 1482, 1462, 1427, 1396, 1370, 1338, 1155, 945 cm$^{-1}$. $^1$H NMR: 8.84 (s, 2H, H-2′ and H-8′); 7.51 (m, 1H, H-6); 7.45 (m, 1H, H-3); 7.22–7.29 (m, 2H, H-4 and H-5); 5.40 (br s, 1H, H-8); 5.32 (br d, 1H, *J*=4.5, H-1); 4.74 (br dd, 1H, *J*=8.2, 3.4, H-9); 2.80 (dm, 1H, *J*=13.2, H-10*exo*); 2.12 (dd, 1H, *J*=13.2, 8.2, H-10*endo*); 1.17 (br s, 9H, $CH_3$). $^{13}$C NMR: 154.65 (CON); 152.44 (C-4′); 151.77 (C-2′); 149.30 (C-6′); 146.17 (C-2); 145.42 (C-8′); 141.80 (C-7); 131.32 (C-5′); 127.82 (C-4); 127.04 (C-5); 121.49 (C-6); 120.44 (C-3); 80.21 (*C*($CH_3$)$_3$); 66.36 (C-8); 60.74 (C-1); 55.90 (C-9); 34.90 (C-10); 27.79 ($CH_3$). ESI MS, *m*/*z* (%): 422.1/420.1 (38/98) [M+Na], 400.1/398.1 (37/100) [M+H], 322.1/320.1 (39/70) [M−Boc+H+Na], 300.1/298.1 (12/32) [M−Boc+2H]. For $C_{20}H_{20}ClN_5O_2$ (397.87) calculated: 60.38% C, 5.07% H, 8.91% Cl, 17.60% N; found: 60.11% C, 5.00% H, 9.14% Cl, 17.45% N.

*4.10.3. tert-Butyl (1R*,8R*,9S*)-9-hydroxy-11-azatricyclo[6.2.1.0$^{2,7}$]undeca-2,4,6-triene-11-carboxylate (**29**).* A 1 M solution of borane in tetrahydrofuran (30 mL) was added under argon to a solution of alkene **28**[20] (7.30 g, 30 mmol) in tetrahydrofuran (15 mL), which was cooled to 0 °C. The reaction mixture was stirred at 0 °C for 3 h. Excess borane was decomposed by addition of water and then a suspension of sodium perborate tetrahydrate (11 g) in water (45 mL) was added in one portion. The reaction mixture was stirred at room temperature overnight and then diluted with ethyl acetate (200 mL). The organic layer was separated, washed with water (50 mL), dried over anhydrous $Na_2SO_4$ and evaporated. Crystallization of the residue from ether gave 4.74 g (60.5%) of compound **29** as white crystals. Chromatography of the mother liquors on silica gel (100 g) in hexane/ethyl acetate (2:1) afforded 1.40 g (18%) of the same compound. Mp 109.5–111.5 °C (90–91 °C, Ref. 22). $^1$H NMR: 7.32 (m, 1H, H-6); 7.24 (m, 1H, H-3); 7.09–7.12 (m, 2H, H-4 and H-5); 5.22 (m, 1H, OH); 4.99 (m, 1H, H-1); 4.79 (m, 1H, H-8); 3.77 (br s, 1H, H-9); 1.65 (br s, 2H, H-10); 1.31 (br s, 9H, $CH_3$). $^{13}$C NMR: 155.42 (COO); 146.54 (C-2); 142.15 (C-7); 126.61 and 126.89 (C-4, C-5); 120.97 (C-6); 119.82 (C-3); 79.13 (*C*($CH_3$)$_3$); 72.31 (C-9); 69.10 (C-8); 59.81 (C-1); 37.57 (C-10); 28.15 ($CH_3$). ESI MS, *m*/*z* (%): 285.1 (20) [M+Na+H], 284.1 (100) [M+Na]. For $C_{15}H_{19}NO_3$ (261.32) calculated: 68.94% C, 7.33% H, 5.36% N; found: 68.94% C, 7.25% H, 5.32% N.

*4.10.4. tert-Butyl (3R*)-1-oxo-3-(2-oxoethyl)-1,3-dihydro-2H-isoindole-2-carboxylate (**30**).* A solution of alcohol **29** (1.31 g, 5 mmol) in dichloromethane (10 mL) was added to a suspension of powdered molecular sieves (2.60 g) and pyridinium dichromate (2.63 g, 7 mmol) in dichloromethane (30 mL). The reaction mixture was stirred at room temperature for 4 days. Solids were filtered off and washed with ethyl acetate. The filtrate was evaporated, the residue was dissolved in ethyl acetate (50 mL), filtered and the filtrate evaporated. Chromatography of the residue on silica gel (130 g) in hexane/ethyl acetate and subsequent crystallization from hexane/ethyl acetate gave 688 mg (50%) of aldehyde **30** as a pinkish powder, mp 88–89.5 °C. IR ($CHCl_3$): 2985, 2840 (w, sh), 2734 (vw), 1779, 1740, 1724, 1710 (sh), 1617 (w), 1600 (w), 1458 (w), 1395 (w), 1371, 1333, 1151 cm$^{-1}$. $^1$H NMR: 9.64 (t, 1H, *J*=1.7, CHO); 7.76 (m, 1H, H-7); 7.73 (m, 1H, H-5); 7.62 (m, 1H, H-4); 7.55 (m, 1H, H-6); 5.49 (t, 1H, *J*=5.3, H-3); 3.13–3.16 (m, 2H, 3-$CH_2$); 1.50 (s, 9H, $CH_3$). $^{13}$C NMR: 200.77 (CHO); 165.72 (C-1); 149.78 (COO); 145.21 (C-3a); 134.28 (C-5); 130.03 (C-7a); 129.05 (C-6); 124.24 (C-7); 123.52 (C-4); 82.79 (*C*($CH_3$)$_3$); 55.42 (C-3); 47.01 (3-$CH_2$); 27.86 ($CH_3$). For $C_{15}H_{17}NO_4$ (275.31) calculated: 65.44% C, 6.22% H, 5.09% N; found: 65.32% C, 6.14% H, 4.92% N.

*4.10.5. tert-Butyl (1R*,8R*)-9-oxo-11-azatricyclo[6.2.1.0$^{2,7}$]undeca-2,4,6-triene-11-carboxylate (**31**).* To a stirred solution of dimethyl sulfoxide (1.40 g, 18 mmol) in dichloromethane (9 mL), cooled to −65 °C, was dropwise added a solution of trifluoroacetic anhydride (1.95 mL, 14 mmol) in dichloromethane (6 mL) and, after 10 min, a solution of compound **29** (2.34 g, 9 mmol) in dichloromethane (6 mL). The mixture was stirred at −65 °C for 30 min, then triethylamine (7.5 mL) was added. The resulting mixture was stirred for 1 h while being allowed to slowly warm to room temperature, then diluted with dichloromethane (40 mL), washed with water (3×80 mL), dried over anhydrous sodium sulfate and evaporated. Chromatography of the residue on silica gel (150 g) in hexane/ethyl acetate (4:1) and subsequent crystallization from cyclohexane afforded 2.10 (90%) of ketone **31** as white crystals, mp 69–70.5 °C. IR ($CHCl_3$): 2983, 1765, 1705, 1592 (vw), 1477 (w), 1457 (w), 1407 (w), 1394, 1370, 1167 cm$^{-1}$. $^1$H NMR: 7.45 (br d, 1H, *J*=7.3, H-3); 7.51 (br d, 1H, *J*=7.2, H-6); 7.29 (td, 1H, *J*=7.4, 1.2, H-4); 7.24 (td, 1H, *J*=7.5, 1.2, H-5); 5.45 (dd, 1H, *J*=4.5, 1.3, H-1); 5.01 (br s, 1H, H-8); 2.60 (dd, 1H, *J*=16.9, 4.6, H-10*exo*); 2.02 (d, 1H, *J*=16.9, H-10*endo*); 1.34 (s, 9H, $CH_3$). $^{13}$C NMR: 205.77 (C-9); 154.82 (COO); 146.39 (C-2); 137.42 (C-

7); 128.68 (C-4); 127.71 (C-5); 123.13 (C-6); 121.36 (C-3); 80.98 ($C(CH_3)_3$); 69.09 (C-8); 61.09 (C-1); 39.19 (C-10); 27.94 ($CH_3$). ESI MS, *m/z* (%): 283.1 (17) [M+Na+H], 282.1 (100) [M+Na]. For $C_{15}H_{17}NO_3$ (259.31) calculated: 69.48% C, 6.61% H, 5.40% N; found: 69.28% C, 6.61% H, 5.56% N.

*4.10.6. tert-Butyl (1R*,8R*,9R*)-9-hydroxy-11-azatricyclo[6.2.1.0$^{2,7}$] undeca-2,4,6-triene-11-carboxylate (**32**).* Sodium borohydride (455 mg, 12 mmol) was added to a stirred solution of ketone **31** (3.11 g, 12 mmol) in methanol (30 mL) at 0 °C. The mixture was stirred for 40 min at 0 °C and then a saturated aqueous solution of ammonium chloride (30 mL) was slowly added. The mixture was extracted with ethyl acetate (2×100 mL), the combined extracts were dried over anhydrous sodium sulfate and evaporated. Chromatography of the residue on a silica gel column (150 g) in toluene/ethyl acetate (2:1) and subsequent crystallization from ethyl acetate/cyclohexane gave 2.85 g (91%) of hydroxy derivative **32** as a white powder, mp 134.5–136.5 °C. IR ($CHCl_3$): 3613 (w), 3573 (w), 2982, 1698, 1603 (vw), 1477 (w), 1460, 1393, 1369, 1168, 1050 cm$^{-1}$. $^1$H NMR: 7.29–7.32 (m, 2H, H-3, H-6); 7.13–7.18 (m, 2H, H-4, H-5); 4.94 (d, 1H, *J*=3.9, OH); 4.92 (br d, 1H, *J*=4.9, H-1); 4.82 (br d, 1H, *J*=4.6, H-8); 4.45 (m, 1H, H-9); 2.38 (ddd, 1H, *J*=12.0, 8.7, 4.9, H-10*exo*); 1.30 (br s, 9H, $CH_3$); 0.80 (dd, 1H, *J*=12.0, 3.0, H-10*endo*). $^{13}$C NMR: 154.79 (COO); 145.86 (C-2); 141.22 (C-7); 126.55 (C-4); 126.02 (C-5); 123.34 (C-6); 119.11 (C-3); 79.46 ($C(CH_3)_3$); 67.70 (C-9); 64.80 (C-8); 61.50 (C-1); 37.20 (C-10); 28.00 ($CH_3$). ESI MS, *m/z* (%): 284.1 (100) [M+Na], 244.4 (35). For $C_{15}H_{19}NO_3$ (261.32) calculated: 68.94% C, 7.33% H, 5.36% N; found: 68.69% C, 7.37% H, 5.28% N.

### 4.11. Mitsunobu reaction of alcohol 32 with 6-chloropurine

A solution of diisopropyl azodicarboxylate (1.48 mL, 7.5 mmoll) in toluene (5 mL) was slowly added to a suspension of alcohol **32** (1.31 g, 5 mmol), triphenylphosphine (2.10 g, 8 mmol), and 6-chloropurine (1.16 g, 6 mmol) in toluene (30 mL). The reaction mixture was stirred at room temperature for 2 h and then heated to 108 °C for 3 h and evaporated. Chromatography of the residue on a silica gel column (250 g) in hexane/ethyl acetate (2:1) and subsequent crystallization from methanol afforded 170 mg (8.5%) of compound, which was identical with 6-chloropurine derivative **33**.

### 4.12. General method for preparation of adenine analogues 10a, 10b, 25, and 38

A solution of chloropurine derivatives **8a**, **8b**, **15**, or **33** (2 mmol) in liquid ammonia (20 mL) was heated in an autoclave at 70 °C for 48 h and then ammonia was evaporated. The residue was crystallized from aqueous ethanol.

*4.12.1. tert-Butyl (1R*,4R*,6R*)-6-(6-amino-9H-purin-9-yl)-2-azabicyclo[2.2.1]heptane-2-carboxylate (**10a**).* Yield 602 mg (91%) of a white powder. Mp 223–225 °C, decomp. IR ($CHCl_3$): 3526 (w), 3414 (w), 2984, 1689, 1630, 1586, 1496 (w), 1473, 1412, 1395 (sh), 1368, 1334 (w), 1156 cm$^{-1}$. $^1$H NMR: 8.30 (s, 0.6H) and 8.28 (s, 0.4H, H-8′); 8.14 (s, 0.4H) and 8.13 (s, 0.6H, H-2′); 7.24 (br s, 2H, $NH_2$); 4.62 (m, 0.6H) and 4.57 (m, 0.4H, H-6); 4.37 (br s, 0.4H) and 4.14 (br s, 0.6H, H-1); 3.20 (dm, 0.4H) and 3.14 (dm, 0.6H, *J*=9.3, H-3*exo*); 3.00 (br d, 0.6H) and 2.97 (br d, 0.4H, *J*=9.3, H-3*endo*); 2.69 (br s, 1H, H-4); 2.29 (m, 0.6H) and 2.12–2.20 (m, 1.4H, 2× H-5); 1.93 (br d, 0.4H) and 1.88 (br d, 0.6H, *J*=10.5, H-7b); 1.61–1.65 (m, 1H, H-7a); 1.46 (br s, 4H) and 1.41 (br s, 5H, $CH_3$). $^{13}$C NMR: 156.26 (C-6′); 153.75 and 153.39 (C=O); 152.63 and 152.52 (C-2′); 149.86 and 149.70 (C-4′); 139.09 and 139.01 (C-8′); 119.22 and 119.15 (C-5′); 79.12 and 78.93 ($C(CH_3)_3$); 60.44 and 58.94 (C-1); 56.60 and 56.52 (C-6); 51.98 and 51.41 (C-3); 36.72 and 36.15 (C-4); 35.71, 34.78 and 34.66 (C-5, C-7); 28.42 and 28.28 ($CH_3$) (mixture of two C/N rotamers 2:3). ESI MS, *m/z* (%): 354.1 (20) [M+Na+H], 353.1 (100) [M+Na], 332.2 (13) [M+2H], 331.2 (73) [M+H]. For $C_{16}H_{22}N_6O_2$ (330.39) calculated: 58.17% C, 6.71% H, 25.44% N; found: 58.09% C, 6.71% H, 25.43%.

*4.12.2. tert-Butyl (1R*,4R*,5S*)-5-(6-amino-9H-purin-9-yl)-2-azabicyclo[2.2.1]heptane-2-carboxylate (**10b**).* Yield 612 mg (93%) of a white powder. Mp 227–228 °C, decomp. IR ($CHCl_3$): 3526 (w), 3414 (w), 2983, 1688, 1630, 1585, 1495 (w, sh), 1471, 1412, 1393 (sh), 1368, 1335 (w), 1156 cm$^{-1}$. $^1$H NMR: 8.28 (s, 0.5H) and 8.28 (s, 0.5H, H-8′); 8.14 (s, 1H, H-2′); 7.24 (br s, 2H, $NH_2$); 4.66 (m, 1H, H-5); 4.23 (br s, 0.5H) and 4.19 (br s, 0.5H, H-1); 3.26 (dd, 0.5H) and 3.23 (dd, 0.5H, *J*=10.0, 3.7, H-3*exo*); 3.12 (m, 1H, H-3*endo*); 2.80 (m, 0.5H) and 2.77 (m, 0.5H, H-4); 2.20–2.30 (m, 2H, H-6); 2.00 (m, 1H, H-7b); 1.68 (br d, 0.5H) and 1.64 (br d, 0.5H, *J*=10.4, H-7a); 1.413 (s, 4.5H) and 1.406 (s, 4.5H, $CH_3$). $^{13}$C NMR: 156.25 (C-6′); 153.76 and 153.61 (C=O); 152.57 (C-2′); 149.76 (C-4′); 139.15 and 139.11 (C-8′); 119.40 (C-5′); 78.78 and 78.73 ($C(CH_3)_3$); 56.62 and 55.60 (C-1); 55.86 (C-5); 50.86 and 50.42 (C-3); 43.39 and 42.66 (C-4); 39.05 and 38.55 (C-6); 35.43 and 34.91 (C-7); 28.46 and 28.43 ($CH_3$) (mixture of two C/N rotamers 1:1). ESI MS, *m/z* (%): 353.1 (10) [M+Na], 332.2 (20) [M+2H], 331.2 (100) [M+H]. For $C_{16}H_{22}N_6O_2$ (330.39) calculated: 58.17% C, 6.71% H, 25.44% N; found: 57.89% C, 6.68% H, 25.25% N.

*4.12.3. tert-Butyl (1R*,2S*,4S*)-2-(6-amino-9H-purin-9-yl)-7-azabicyclo[2.2.1]heptane-7-carboxylate (**25**).* Yield 601 mg (91%) of a white powder. Mp 221–222 °C, decomp. IR ($CHCl_3$): 3526 (w), 3414, 2928, 1699, 1630, 1568, 1473, 1413, 1393, 1369, 1322, 1155 cm$^{-1}$. $^1$H NMR: 8.15 (br s, 1H, H-2′); 8.08 (s, 1H, H-8′); 7.25 (br s, 2H, $NH_2$); 4.66 (dd, 1H, *J*=8.4, 3.6, H-2); 4.25–4.35 (m, 2H, H-1, H-4); 2.29 (m, 1H, H-3*exo*); 2.14 (dd, 1H, *J*=13.4, 8.4, H-3*endo*); 1.75 (m, 1H, H-6*exo*); 1.62–1.69 (m, 2H, H-5*exo*, H-6*endo*); 1.53 (m, 1H, H-5*endo*); 1.26 (br s, 9H, $CH_3$). $^{13}$C NMR: 156.21 (C-6′); 154.56 (COO); 152.57 (C-2′); 149.72 (C-4′); 138.18 (C-8′); 119.13 (C-5′); 79.44 ($C(CH_3)_3$); 61.31 (C-1); 55.43 (C-4); 56.9 (C-2); 37.2 (C-3); 28.32 (C-5); 27.95 ($CH_3$); 26.05 (C-6). ESI MS, *m/z* (%): 332.2 (17) [M+2H], 331.2 (100) [M+H]. For $C_{16}H_{22}N_6O_2$ (330.39) calculated: 58.17% C, 6.71% H, 25.44% N; found: 58.13% C, 6.78% H, 25.32% N.

*4.12.4. tert-Butyl (1R*,8R*,9S*)-9-(6-amino-9H-purin-9-yl)-11-azatricyclo[6.2.1.0$^{2,7}$]undeca-2,4,6-triene-11-carboxylate (**38**).* Yield 620 mg (82%) of white powder. Mp 205–207 °C. IR ($CHCl_3$): 3526 (w), 3414 (w), 2983, 1707, 1630, 1586, 1495 (w), 1471, 1413, 1394 (w), 1370, 1331, 1155 cm$^{-1}$. $^1$H NMR: 8.26 (s, 1H, H-8′); 8.19 (s, 1H, H-2′); 7.50 (m, 1H, H-6); 7.42 (m, 1H, H-3); 7.30 (br s, 2H, $NH_2$); 7.21–7.26 (m, 2H, H-4, H-5); 5.31 (br s, 1H, H-8); 5.29 (br d, 1H, *J*=4.5, H-1); 4.57 (br dd, 1H, *J*=8.1, 3.4, H-9); 2.67 (dm, 1H, *J*=12.7, H-10*exo*); 2.07 (dd, 1H, *J*=13.0, 8.1, H-10*endo*); 1.18 (br s, 9H, $CH_3$); $^{13}$C NMR: 156.24 (C-6′); 154.60 (CON); 152.76 (C-2′); 150.08 (C-4′); 146.15 (C-2); 142.12 (C-7); 138.61 (C-8′); 127.69 (C-4); 126.98 (C-5); 121.40 (C-6); 120.35 (C-3); 119.16 (C-5′); 80.09 ($C(CH_3)_3$); 66.56 (C-8); 60.30 (C-1); 54.90 (C-9); 34.50 (C-10); 27.84 ($CH_3$). ESI MS, *m/z* (%): 401.2 (76) [M+Na], 379.2 (100) [M+H]. For $C_{20}H_{22}N_6O_2$ (378.44) calculated: 63.48% C, 5.86% H, 22.21% N; found: 63.11% C, 5.89% H, 21.89% N.

### 4.13. General method for preparation of 6-(cyclopropylamino)-9*H*-purine analogues 12a, 12b, and 40

A solution of chloropurine derivative **8a**, **58b**, or **33** (1 mmol) in cyclopropylamine (3 mL) was allowed to stand at room temperature overnight and then evaporated. The residue was chromatographed on silica gel (30 g) in ethyl acetate/acetone/ethanol/water (150:10:4:3).

*4.13.1. tert-Butyl (1R*,4R*,5S*)-6-[6-(cyclopropylamino)-9H-purin-9-yl]-2-azabicyclo[2.2.1]heptane-2-carboxylate (**12a**).* Yield 330 mg (89%) of a white powder after crystallization from methanol/water.

Mp 213–214.5 °C. IR ($CHCl_3$): 3428, 3094 (w), 2982, 1688, 1617, 1600 (sh), 1581, 1519 (w), 1476, 1410, 1393 (sh), 1368, 1335, 1156 $cm^{-1}$. $^1H$ NMR: 8.30 (s, 0.6H) and 8.28 (s, 0.4H, H-8′); 8.23 (br s, 1H, H-2′); 7.91 (br s, 1H, NH); 4.64 (m, 0.6H) and 4.58 (m, 0.4H, H-6); 4.37 (br s, 0.4H) and 4.12 (br s, 0.6H, H-1); 3.20 (m, 0.4H) and 3.15 (m, 0.6H, H-3*exo*); 3.00 (br s, 1H, CH of cyclopropyl); 3.00 (br d, 0.6H) and 2.97 (br d, 0.4H, *J*=9.4, H-3*exo*); 2.69 (br s, 1H, H-4); 2.12–2.31 (m, 2H, H-5); 1.93 (br d, 0.4H) and 1.88 (br d, 0.6H, *J*=10.6, H-7b); 1.58–1.66 (m, 1H, H-7a); 1.46 (br s, 5H) and 1.41 (br s, 4H, $CH_3$); 0.60 (m, 2H) and 0.71 (m, 2H, $CH_2$ of cyclopropyl). $^{13}C$ NMR: 155.78 (C-6′); 153.72 and 153.35 (C=O); 152.52 and 152.42 (C-2′); 149.10 (C-4′); 138.89 and 138.81 (C-8′); 119.58 (C-5′); 79.09 and 78.91 (*C*$(CH_3)_3$); 60.45 and 58.92 (C-1); 56.51 (C-6); 51.97 and 51.37 (C-3); 36.71 and 36.14 (C-4); 35.68, 34.77, and 34.71 (C-5, C-7); 28.40 and 28.27 ($CH_3$); 24.00 (CH of cyclopropyl); 6.60 ($CH_2$ of cyclopropyl) (mixture of two C/N rotamers 2:3). ESI MS, *m*/*z* (%): 394.1 (23) [M+Na+H], 393.1 (100) [M+Na], 372.2 (17) [M+2], 371.2 (70) [M+1]. For $C_{19}H_{26}N_6O_2$ (370.46) calculated: 61.60% C, 7.07% H, 22.69% N; found: 61.65% C, 7.07% H, 22.44% N.

*4.13.2. tert-Butyl (1R*,4R*,5S*)-5-[(6-cyclopropylamino)-9H-purin-9-yl]-2-azabicyclo[2.2.1]heptane-2-carboxylate (**12b**).* Yield 321 mg (87%) of a white powder after crystallization from ether. Mp 173–174 °C. IR ($CHCl_3$): 3428 (w), 3094 (w), 2983, 1688, 1618, 1600, 1581 (w), 1520 (w), 1476, 1413, 1395 (sh), 1368, 1335 (w), 1158 $cm^{-1}$. $^1H$ NMR: 8.29 (s, 0.5H) and 8.28 (s, 0.5H, H-8′); 8.24 (br s, 1H, H-2′); 7.91 (br s, 1H, NH); 4.68 (m, 1H, H-5); 4.22 (br s, 0.5H) and 4.19 (br s, 0.5H, H-1); 3.26 (dd, 0.5H) and 3.23 (dd, 0.5H, *J*=10.0, 3.7, H-3*exo*); 3.12 (m, 1H, H-3*endo*); 2.99 (br s, 1H, CH of cyclopropyl); 2.80 (m, 0.5H) and 2.76 (m, 0.5H, H-4); 2.20–2.30 (m, 2H, H-6); 1.99 (m, 1H, H-7b); 1.68 (br d, 0.5H) and 1.64 (br d, 0.5H, *J*=10.5, H-7a); 1.413 (s, 4.5H) and 1.406 (s, 4.5H, $CH_3$); 0.71 (m, 2H) and 0.59 (m, 2H, $CH_2$ of cyclopropyl); $^{13}C$ NMR: 155.82 (C-6′); 153.74 and 153.60 (C=O); 152.46 (C-2′); 149.12 (C-4′); 138.95 and 138.91 (C-8′); 119.79 (C-5′); 78.76 and 78.72 (*C*$(CH_3)_3$); 55.84 (C-5); 56.62 and 55.60 (C-1); 50.84 and 50.41 (C-3); 43.38 and 42.64 (C-4); 39.07 and 38.56 (C-6); 35.42 and 34.89 (C-7); 28.45 and 28.42 ($CH_3$); 24.0 (CH of cyclopropyl); 6.61 ($CH_2$ of cyclopropyl) (mixture of two C/N rotamers 1:1). ESI MS, *m*/*z* (%): 393.1 (14) [M+Na], 372.2 (20) [M+2], 371.2 (100) [M+1]. For $C_{19}H_{26}N_6O_2$ (370.46) calculated: 61.60% C, 7.07% H, 22.69% N; found: 61.55% C, 7.08% H, 22.62% N.

*4.13.3. tert-Butyl (1R*,8R*,9S*)-9-[6-(cyclopropylamino)-9H-purin-9-yl]-11-azatricyclo[6.2.1.0$^{2,7}$]undeca-2,4,6-triene-11-carboxylate (**40**).* Yield 377 mg (90%) of a white powder after crystallization from ether. Mp 180.5–181.5 °C. IR ($CHCl_3$): 3428 (w), 3093 (w), 2982, 1707, 1618, 1599 (sh), 1582 (w), 1519 (w), 1475, 1458, 1394 (w), 1370, 1352, 1155 $cm^{-1}$. $^1H$ NMR: 8.29 (s, 1H, H-2′); 8.26 (s, 1H, H-8′); 7.96 (br s, 1H, NH); 7.50 (m, 1H, H-6); 7.43 (m, 1H, H-3); 7.21–7.27 (m, 2H, H-4, H-5); 5.31 (br s, 1H, H-8); 5.29 (br d, 1H, *J*=4.5, H-1); 4.59 (br dd, 1H, *J*=8.1, 3.4, H-9); 3.05 (br s, 1H, CH of cyclopropyl); 2.68 (dm, 1H, *J*=12.7, H-10*exo*); 2.07 (dd, 1H, *J*=13.0, 8.2, H-10*endo*); 1.18 (br s, 9H, $CH_3$); 0.73 (m, 2H) and 0.62 (m, 2H, $CH_2$ of cyclopropyl); $^{13}C$ NMR: 156.01 (C-6′); 154.80 (CON); 152.89 (C-2′); 149.60 (C-4′); 146.37 (C-2); 142.36 (C-7); 138.64 (C-8′); 127.92 (C-4); 127.21 (C-5); 121.63 (C-6); 120.58 (C-3); 119.77 (C-5′); 80.33 (*C*$(CH_3)_3$); 66.79 (C-8); 60.82 (C-1); 55.50 (C-9); 35.20 (C-10); 28.06 ($CH_3$); 6.83 ($CH_2$ of cyclopropyl). ESI MS, *m*/*z* (%): 441.3 (35) [M+Na], 419.3 (100) [M+H]. For $C_{23}H_{26}N_6O_2$ (418.50) calculated: 66.01% C, 6.26% H, 20.08% N; found: 65.69% C, 6.31% H, 19.79% N.

### 4.14. General method for preparation of trifluoroacetic acid salts 11a, 11b

A solution of protected chloropurine derivative **10a** or **10b** (330 mg, 1 mmol) in trifluoroacetic acid (3 mL) was allowed to stand at room temperature 3 h, then evaporated, codistilled with absolute ethanol (3×5 mL). The residue was crystallized from ethanol.

*4.14.1. 9-[(1R*,4S*,6R*)-2-Azabicyclo[2.2.1]hept-6-yl]-9H-purin-6-amine bis trifluoroacetic acid salt (**11a**).* Yield 405 mg (88%) of a white powder. Mp 202–203 °C, decomp. IR (KBr): 3252 (br), 3221 (br), 2969 (br), 2757 (br), 2682 (br), 2550 (br), 2469 (br), 2019 (w), 1954 (w, br), 1901 (w), 1712, 1665, 1634, 1561 (w), 1511, 1432, 1404, 1329, 1198, 1182, 1140, 833, 798, 723 $cm^{-1}$. $^1H$ NMR: 9.51 (br s, 1H), 9.00 (br s, 1H) and 8.56 (br s, 2H, NH); 8.54 (s, 1H, H-8); 8.41 (s, 1H, H-2); 5.02 (ddd, 1H, *J*=8.4, 5.2, 1.6, H-6′); 4.29 (br s, 1H, H-1′); 3.12 (m, 1H, H-3′*exo*); 3.02 (m, 1H, H-3′*endo*); 2.84 (br s, 1H, H-4′); 2.33 (m, 1H, H-5′*exo*); 2.27 (ddd, 1H, *J*=13.3, 8.4, 1.7, H-5′*endo*); 2.16 (dm, 1H, *J*=11.8, H-7′b); 1.74 (dm, 1H, *J*=11.9, H-7′a). $^{13}C$ NMR: 159.11 (q, *J*=33.4, C=O); 153.10 (C-6); 149.21 (C-4); 148.37 (C-2); 140.87 (C-8); 118.93 (C-5); 116.81 (q, *J*=295.8, $CF_3$); 59.71 (C-1′); 34.37 (C-7′); 35.05 (C-5′); 53.28 (C-6′); 48.92 (C-3′); 35.21 (C-4′). ESI MS, *m*/*z* (%): 232.2 (14) [M+2H], 231.2 (100) [M+H]. For $C_{15}H_{16}F_6N_6O_4$ (458.32) calculated: 39.31% C, 3.52% H, 18.34% N; found: 39.14% C, 3.48% H, 18.17% N.

*4.14.2. 9-[(1R*,4R*,5S*)-2-Azabicyclo[2.2.1]hept-5-yl]-9H-purin-6-amine bis trifluoroacetic acid salt (**11b**).* Yield 335 mg (73%) of a white powder. Mp 242 °C, decomp. IR (KBr): 3250 (sh), 3200 (sh), 2969 (br), 2758 (br), 2692, 2567, 2548, 2022 (w, br), 1958 (w, br), 1903 (w, br), 1717, 1667, 1631, 1556 (w), 1505, 1429, 1405, 1349, 1196, 1179, 1148, 836, 831, 798, 722 $cm^{-1}$. $^1H$ NMR: 9.11 (br s, 1H), 8.74 (br s, 1H) and 8.67 (br s, 1H, NH); 8.56 (s, 1H, H-8); 8.40 (s, 1H, H-2); 4.77 (br dd, 1H, *J*=8.4, 4.0, H-5′); 4.21 (br s, 1H, H-1′); 3.15–3.24 (m, 2H, H-3′); 3.03 (m, 1H, H-4′); 2.52 (ddd, 1H, *J*=15.1, 8.6, 2.9, H-6′*endo*); 2.38 (dm, 1H, *J*=15.2, H-6′*exo*); 2.13 (dm, 1H, *J*=11.8, H-7′b); 1.75 (dm, 1H, *J*=11.8, H-7′a). $^{13}C$ NMR: 159.18 (q, *J*=33.1, COO); 152.75 (C-6); 149.09 (C-4); 147.81 (C-2); 141.10 (C-8); 119.05 (C-5); 116.88 (q, *J*=296.2, $CF_3$); 56.79 (C-1′); 55.30 (C-5′); 47.21 (C-3′); 41.20 (C-4′); 34.18 and 34.22 (C-6′, C-7′). ESI MS, *m*/*z* (%): 232.2 (14) [M+2H], 231.2 (100) [M+H]. For $C_{15}H_{16}F_6N_6O_4$ (458.32) calculated: 39.31% C, 3.52% H, 18.34% N; found: 39.16% C, 3.59% H, 18.15% N.

### 4.15. General method for preparation of trifluoroacetic acid salts 9a, 9b, 13a, 13b, 19, 20, 24b, 26, 27, 37, 39, and 41

Trifluoroacetic acid (0.8 mL) was added to a stirred solution of protected derivative **8a**, **8b**, **12a**, **12b**, **17**, **18**, **15**, **24a**, **25**, **33**, **38**, or **40** (0.5 mmol) in dichloromethane (2.5 mL). The mixture was stirred at room temperature for 3 h and then evaporated. The residue was codistilled with absolute ethanol (2×4 mL) and crystallized from ethanol, ethanol/ether or ether.

*4.15.1. 9-[(1R*,4S*,6R*)-2-Azabicyclo[2.2.1]hept-6-yl]-6-chloro-9H-purine trifluoroacetic acid salt (**9a**).* Yield 129 mg (71%) of a white powder after crystallization from ethanol. Mp 172–173 °C, decomp. IR (KBr): 3129, 2971 (br), 2742 (w, br), 2664 (w, br), 2537 (w, br), 2455 (w, br), 1666, 1591, 1564, 1496 (w), 1441, 1427, 1398, 1345, 1212, 1193, 1177, 1138, 1125, 835, 799, 723 $cm^{-1}$. $^1H$ NMR: 9.25 (br s, 2H, NH); 8.86 (s, 1H, H-8); 8.83 (s, 1H, H-2); 5.12 (ddd, 1H, *J*=8.6, 5.2, 1.3, H-6′); 4.37 (br s, 1H, H-1′); 3.13 (dm, 1H, *J*=10.7, H-3′*exo*); 3.04 (dd, 1H, *J*=10.7, 1.5, H-3′*endo*); 2.86 (br s, 1H, H-4′); 2.41 (m, 1H, H-5′*exo*); 2.30 (ddd, 1H, *J*=13.7, 8.7, 2.2, H-5′*endo*); 2.18 (dm, 1H, *J*=11.9, H-7′b); 1.75 (dm, 1H, *J*=11.9, H-7′a). $^{13}C$ NMR: 158.56 (q, *J*=31.2, C=O); 152.20 (C-4); 151.68 (C-2); 149.34 (C-6); 145.76 (C-8); 131.39 (C-5); 59.51 (C-1′); 34.45 (C-7′); 53.70 (C-6′); 48.95 (C-3′); 35.19 (C-4′); 34.89 (C-5′). ESI MS, *m*/*z* (%): 252.1/250.1 (32/100) [M−$CF_3COOH$+1]. For $C_{13}H_{13}ClF_3N_5O_2$ (363.73) calculated: 42.93% C, 3.60% H, 9.75% Cl, 19.25% N; found: 42.76% C, 3.67% H, 9.88% Cl, 18.99% N.

*4.15.2. 9-[(1R*,4R*,5S*)-2-Azabicyclo[2.2.1]hept-5-yl]-6-chloro-9H-purine trifluoroacetic acid salt (**9b**).* Yield 140 mg (77%) of white powder after crystallization from ethanol. Mp 181.5–183 °C, decomp. IR (KBr): 3117, 3017 (br), 2791 (w, br), 2721 (w, br), 2547 (w, br), 1695, 1685, 1590, 1565, 1486 (w), 1443, 1418, 1392, 1345, 1200, 1181, 1125, 835, 789, 723 $cm^{-1}$. $^1H$ NMR: 9.12 (br s, 1H) and 8.75 (br s, 1H, NH); 8.87 (s, 1H, H-8); 8.79 (s, 1H, H-2); 4.86 (ddd, 1H, *J*=8.4, 4.2, 1.0, H-5); 4.23 (m, 1H, H-1′); 3.17–3.25 (m, 2H, H-3′); 3.12 (br d, 1H, *J*=3.6H, H-4′); 2.55 (ddd, 1H, *J*=15.1, 8.4, 2.7, H-6′*endo*); 2.44 (br dt, 1H, *J*=15.1, 3.7, H-6′*exo*); 2.17 (dm, 1H, *J*=11.8, H-7′b); 1.76 (dm, 1H, *J*=11.8, H-7′a). $^{13}C$ NMR: 158.75 (q, *J*=31.4, C=O); 152.17 (C-4); 151.61 (C-2); 149.32 (C-6); 145.85 (C-8); 131.56 (C-5); 117.41 (q, *J*=298.9, $CF_3$); 56.80 (C-1′); 55.77 (C-5′); 47.21 (C-3′); 40.97 (C-4′); 34.31 (C-7′); 34.10 (C-6′). ESI MS, *m*/*z* (%): 252.2/250.2 (30/100) [M−$CF_3COOH$+1]. For $C_{13}H_{13}ClF_3N_5O_2$ (363.73) calculated: 42.93% C, 3.60% H, 9.75% Cl, 19.25% N; found: 42.72% C, 3.73% H, 9.85% Cl, 18.99% N.

*4.15.3. 9-[(1R*,4S*,6R*)-2-Azabicyclo[2.2.1]hept-6-yl]-N-cyclopropyl-9H-purin-6-amine bis trifluoroacetic acid salt (**13a**).* Yield 215 mg (86%) of a white powder after crystallization from ethanol/ether. Mp 192–193.5 °C, decomp. IR (KBr): 3228 (sh), 3114, 3011–2965 (br), 2913 (br), 2749 (br), 2547 (br), 2472 (br), 1700, 1684, 1665, 1592, 1527, 1428, 1410, 1359, 1344, 1202, 1189 (sh), 1179 (sh), 1130, 834, 799, 722 $cm^{-1}$. $^1H$ NMR: 9.54 (br s, 1H) and 9.03 (br s, 2H, NH); 8.50 (s, 1H, H-8); 8.43 (br s, 1H, H-2); 5.02 (ddd, 1H, *J*=8.3, 5.3, 1.3, H-6′); 4.28 (m, 1H, H-1′); 3.13 (m, 1H, H-3′*exo*); 3.02 (m, 1H, H-3′*endo*); 2.93 (br s, 1H, CH of cyclopropyl); 2.84 (br s, 1H, H-4′); 2.33 (m, 1H, H-5′*exo*); 2.27 (ddd, 1H, *J*=13.3, 8.5, 1.8, H-5′*endo*); 2.15 (dm, 1H, *J*=11.8, H-7′b); 1.74 (dm, 1H, *J*=11.9, H-7′a); 0.82 (m, 2H) and 0.68 (m, 2H, $CH_2$ of cyclopropyl); $^{13}C$ NMR: 158.85 (q, *J*=31.2, C=O); 153.37 (C-6); 149.49 (C-2); 148.44 (C-4); 140.30 (C-8); 119.34 (C-5); 116.73 (q, *J*=295.5, $CF_3$); 59.73 (C-1′); 53.20 (C-6′); 48.93 (C-3′); 35.23 (C-4′); 35.08 (C-5′); 34.40 (C-7′); 23.89 (CH of cyclopropyl); 6.87 ($CH_2$ of cyclopropyl). ESI MS, *m*/*z* (%): 271.1 (100) [M+H], 176.2 (26) [6-(cyclopropylamino)purine+H]. For $C_{18}H_{20}F_6N_6O_4$ (498.39) calculated: 43.38% C, 4.05% H, 16.86% N; found: 43.20% C, 4.09% H, 16.73% N.

*4.15.4. 9-[(1R*,4R*,5S*)-2-Azabicyclo[2.2.1]hept-5-yl]-N-cyclopropyl-9H-purin-6-amine bis trifluoroacetic acid salt (**13b**).* Yield 214 mg (86%) of a white powder after crystallization from ethanol/ether. Mp 190–191.5 °C, decomp. IR (KBr): 3223 (br), 3111, 2967 (br), 2760 (br), 2552, 1984 (w, br), 1926 (w), 1875 (w), 1697, 1677, 1654, 1593, 1522, 1432, 1417, 1408, 1362, 1343, 1203, 1185, 1175, 1133, 836, 828, 799, 721 $cm^{-1}$. $^1H$ NMR: 9.19 (br s, 2H) and 8.79 (br s, 1H, NH); 8.51 (s, 1H, H-8); 8.41 (br s, 1H, H-2); 4.77 (br dd, 1H, *J*=8.4, 4.2, H-5′); 4.21 (br s, 1H, H-1′); 3.14–3.24 (m, 2H, H-3′); 3.01 (m, 1H, H-4′); 2.92 (br s, 1H, CH of cyclopropyl); 2.52 (ddd, 1H, *J*=15.1, 8.7, 2.6, H-6′*endo*); 2.38 (dm, 1H, *J*=15.1, H-6′*exo*); 2.13 (dm, 1H, *J*=11.8, H-7′b); 1.74 (dm, 1H, *J*=11.8, H-7′a); 0.82 (m, 2H) and 0.69 (m, 2H, $CH_2$ of cyclopropyl). $^{13}C$ NMR: 158.80 (q, *J*=33.5, COO); 153.2 (C-6); 149.23 (C-2); 148.48 (C-4); 140.51 (C-8); 119.47 (C-5); 116.78 (q, *J*=296.0, $CF_3$); 56.80 (C-1′); 55.18 (C-5′); 47.23 (C-3′); 41.23 (C-4′); 34.18 (C-6′, C-7′); 23.69 (CH of cyclopropyl); 6.91 ($CH_2$ of cyclopropyl). ESI MS, *m*/*z* (%): 272.2 (17) [M−2 $CF_3COOH$+2H], 271.2 (100) [M−2 $CF_3COOH$+H], 176.2 (9) [6-(cyclopropylamino)purine]. For $C_{18}H_{20}F_6N_6O_4$ (498.39) calculated: 43.38% C, 4.05% H, 16.86% N; found: 43.27% C, 3.96% H, 16.68% N.

*4.15.5. 9-[(1R*,2S*,4S*)-7-Azabicyclo[2.2.1]hept-2-yl]-N-cyclopropyl-9H-purin-6-amine bis trifluoroacetic acid salt (**19**).* Yield 184 mg (74%) of a white powder after crystallization from ethanol/ether. Mp 167–169 °C. IR (KBr): 3233 (br), 3097, 3017 (br), 2892 (br), 2861 (br), 2735 (br), 2559, 1998 (w, br), 1930 (w, br), 1886 (w, br), 1702, 1684 (br), 1602 (sh), 1559, 1516, 1430, 1411, 1362, 1200 (br), 1177, 1138 (br), 828, 799, 722 $cm^{-1}$. $^1H$ NMR: 9.73 (br s, 1H), 9.48 (br s, 1H) and 8.67 (br s, 1H, NH); 8.36 (br s, 1H, H-2); 8.26 (s, 1H, H-8); 4.99 (br dd, 1H, *J*=9.0, 4.6, H-2′); 4.60 (br d, 1H, *J*=4.6, H-1′); 4.46 (br t, 1H, *J*=4.5, H-4′); 2.98 (br s, 1H, CH of cyclopropyl); 2.48 (dd, 1H, *J*=14.0, 9.2, H-3′*endo*); 2.28 (dm, 1H, *J*=14.0, H-3′*exo*); 1.71–2.00 (m, 4H, H-5′, H-6′); 0.78 (m, 2H) and 0.66 (m, 2H, $CH_2$ of cyclopropyl); $^{13}C$ NMR: 158.55 (q, *J*=34.1, COO); 154.80 (C-6); 150.51 (C-2); 147.50 (C-4); 141.07 (C-8); 119.90 (C-5); 116.49 (q, *J*=294.9, $CF_3$); 62.14 (C-1′); 57.87 (C-4′); 56.40 (C-2′); 36.49 (C-3′); 25.61 (C-5′); 24.57 (C-6′); 6.54 ($CH_2$ of cyclopropyl). ESI MS, *m*/*z* (%): 272.3 (27) [M+2H], 271.3 (100) [M+H]. For $C_{18}H_{20}F_6N_6O_4$ (498.39) calculated: 43.38% C, 4.05% H, 16.86% N; found: 43.21% C, 3.92% H, 16.66% N.

*4.15.6. 9-[(1R*,2R*,4S*)-7-Azabicyclo[2.2.1]hept-2-yl]-N-cyclopropyl-9H-purin-6-amine bis trifloroacetic acid salt (**20**).* Yield 204 mg (82%) of a white powder after crystallization from ethanol/ether. Mp 183–185 °C. IR (KBr): 3222, 3182 (br), 3012 (br), 3103, 2903 (br), 2719 (br), 2582 (br), 1978 (w, br), 1930 (w, br), 1690 (br), 1672–1654 (br), 1592, 1522, 1433, 1412, 1359, 1128 (br), 837, 800, 721 $cm^{-1}$. $^1H$ NMR: 9.47 (br s, 1H), 9.40 (br s, 1H) and 8.95 (br s, 1H, NH); 8.58 (s, 1H, H-8); 8.41 (br s, 1H, H-2); 5.14 (m, 1H, H-2′); 4.59 (t, 1H, *J*=4.7, H-1′); 4.39 (m, 1H, H-4′); 2.95 (br s, 1H, CH of cyclopropyl); 2.50–2.54 (m, 2H, H-3′); 2.04 (ddd, 1H, *J*=12.7, 9.7, 4.6, H-5′*endo*); 1.92 (m, 1H, H-5′*exo*); 1.74 (m, 1H, H-6′*exo*); 1.35 ddd, 1H, *J*=13.8, 9.6, 4.7, (H-6′*endo*); 0.81 (m, 2H) and 0.69 (m, 2H, $CH_2$ of cyclopropyl). $^{13}C$ NMR: 158.70 (q, *J*=34.0, COO); 153.6 (C-6); 150.02 (C-2); 149.1 (C-4); 140.9 (C-8); 119.55 (C-5); 116.24 (q, *J*=295.2, $CF_3$); 59.69 (C-1′); 58.51 (C-4′); 53.19 (C-2′); 29.96 (C-3′); 26.45 (C-5′); 23.6 (CH of cyclopropyl); 20.48 (C-6′); 6.79 ($CH_2$ of cyclopropyl). ESI MS, *m*/*z* (%): 272.2 (18) [M+2H], 271.2 (100) [M+H]. For $C_{18}H_{20}F_6N_6O_4$ (498.39) calculated: 43.38% C, 4.05% H, 16.86% N; found: 43.09% C, 3.92% H, 16.59% N.

*4.15.7. (1R*,2S*,4S*)-2-[(5-Amino-6-chloropyrimidin-4-yl)amino]-7-azabicyclo[2.2.1]heptane trifluoroacetic acid salt (**24b**).* Yield 161 mg (91%) of a white powder after crystallization from ethanol/ether. Mp 166.5–168 °C. IR (KBr): 3417, 3343, 3253, 2972 (br), 2868, 2690, 2569, 1671 (br), 1604, 1580 (br), 1495, 1462, 1434, 1420, 1381, 1211, 1187, 1174, 1148, 1129, 838, 834, 801, 722 $cm^{-1}$. $^1H$ NMR: 9.00 (br s, 1H) and 8.76 (br s, 1H, NH); 7.81 (s, 1H, H-2); 6.81 (br d, 1H, *J*=5.2, 4-NH); 5.11 (br s, 2H, $NH_2$); 4.22 (m, 1H, H-4′); 4.17 (m, 1H, H-1′); 4.10 (m, 1H, H-2′); 2.21 (dd, 1H, *J*=13.6, 8.5, H-3′*endo*); 1.93 (dm, 1H, *J*=13.5, H-3′*exo*); 1.78–1.88 (m, 2H, H-5′*exo*, H-6′*exo*); 1.71 (m, 1H, H-6′*endo*); 1.62 (m, 1H, H-5′*endo*). $^{13}C$ NMR: 158.82 (q, *J*=31.3, COO); 151.31 (C-4); 145.64 (C-2); 137.56 (C-6); 124.49 (C-5); 117.30 (q, *J*=298.8, $CF_3$); 62.18 (C-1′); 57.06 (C-4′); 53.02 (C-2′); 35.63 (C-3′); 25.77 (C-5′); 23.71 (C-6′). ESI MS, *m*/*z* (%): 242.1/240.1 (35/100) [M+H]. For $C_{12}H_{15}ClF_3N_5O_2$ (353.73) calculated: 40.75% C, 4.27% H, 10.02% Cl, 19.80% N; found: 40.77% C, 4.32% H, 10.05% Cl, 19.64% N.

*4.15.8. 9-[(1R*,2S*,4S*)-7-Azabicyclo[2.2.1]hept-2-yl]-6-chloro-9H-purine trifluoroacetic acid salt (**26**).* Yield 164 mg (90%) of a white powder after crystallization from ethanol. Mp 153–156 °C decomp. IR (KBr): 3105, 3071, 2972, 2901 (br), 2725, 2674, 2542 (br), 1691, 1640, 1632 (sh), 1595, 1566, 1558, 1496 (w), 1428, 1417, 1400, 1343, 1203, 1181, 1123, 834, 794, 722 $cm^{-1}$. $^1H$ NMR: 9.34 (br s, 2H, NH); 8.83 (s, 1H, H-8); 8.82 (s, 1H, H-2); 5.06 (br dd, 1H, *J*=9.0, 4.9, H-2′); 4.82 (br d, 1H, *J*=4.8, H-1′); 4.41 (br t, 1H, *J*=4.5, H-4′); 2.55 (dd, 1H, *J*=14.1, 9.0, H-3′*endo*); 2.45 (m, 1H, H-3′*exo*); 1.73–2.03 (m, 4H, H-5′, H-6′). $^{13}C$ NMR: 151.86 (C-4); 151.36 (C-2); 149.41 (C-6); 146.60 (C-8); 131.77 (C-5); 61.62 (C-1′); 57.76 (C-4′); 56.53 (C-2′); 36.08 (C-3′); 25.42 (C-5′); 24.77 (C-6′). ESI MS, *m*/*z* (%): 252.1/250.1 (38/100) [M+H], 157.0/155.0 (11/33) [6-chloropurine+H]. For $C_{13}H_{13}ClF_3N_5O_2$ (363.73) calculated: 42.93% C, 3.60% H, 9.75% Cl, 19.25% N; found: 43.02% C, 3.64% H, 9.61% Cl, 19.27% N.

*4.15.9. 9-[(1R*,2S*,4S*)-7-Azabicyclo[2.2.1]hept-2-yl]-9H-purin-6-amine bis trifluoroacetic acid salt (**27**).* Yield 197 mg (86%) of a white powder after crystallization from ethanol. Mp 207–208 °C decomp. IR (KBr): 3262 (br), 3138, 2983–2934 (br), 2736, 2682, 2568, 1992 (w, br), 1939 (w, br), 1859 (w), 1708 (br), 1668 (br), 1616, 1549, 1503, 1437, 1410, 1392, 1354, 1331, 1212, 1197, 1183, 1138, 1127, 834, 805, 721 $cm^{-1}$. $^1H$ NMR: 9.58 (br s, 1H) and 9.50 (br s, 1H, NH); 8.33 (s, 1H, H-8); 8.32 (br s, 1H, H-2); 8.28 (br s, 2H, $NH_2$); 4.98 (dd, 1H, *J*=9.0, 4.7, H-2′); 4.63 (br d, 1H, *J*=4.7, H-1′); 4.44 (br t, 1H, *J*=4.5, H-4′); 2.49 (dd, 1H, *J*=14.0, 9.1, H-3′*endo*); 2.30 (dm, 1H, *J*=13.9, H-3′*exo*); 1.72–2.00 (m, 4H, H-5′, H-6′); $^{13}C$ NMR: 158.82 (q, *J*=33.8, COO); 154.40 (C-6); 149.40 (C-2); 148.37 (C-4); 141.59 (C-8); 119.39 (C-5); 116.63 (q, *J*=295.5, $CF_3$); 62.08 (C-1′); 57.85 (C-4′); 56.38 (C-2′); 36.48 (C-3′); 25.57 (C-5′); 24.63 (C-6′). ESI MS, *m*/*z* (%): 232.1 (14) [M+2H], 231.1 (100) [M+H]. For $C_{15}H_{16}F_6N_6O_4$ (458.32) calculated: 39.31% C, 3.52% H, 18.34% N; found: 39.36% C, 3.48% H, 18.10% N.

*4.15.10. (1R*,8R*,9S*)-9-(6-chloro-9H-purin-9-yl)-11-azatricyclo [6.2.1.0$^{2,7}$]undeca-2,4,6-triene trifluoroacetic acid salt (**37**).* Yield 185 mg (90%) of a white powder after crystallization from ethanol/ether. Mp 132.5–134.5 °C decomp. (hydrate). IR (KBr): 2964 (br), 2881 (br), 2629 (br), 2556 (br), 2513 (br), 1680 (br), 1591, 1569, 1497, 1419, 1401, 1339, 1201, 1171 (br), 1132, 837, 800, 720 $cm^{-1}$. $^1H$ NMR: 8.90 (s, 1H, H-8′); 8.86 (s, 1H, H-2′); 7.65 (m, 1H, H-6); 7.59 (m, 1H, H-3); 7.42–7.49 (m, 2H, H-4, H-5); 5.93 (br s, 1H, H-8); 5.55 (br d, 1H, *J*=4.3, H-1); 4.95 (dd, 1H, *J*=8.6, 4.3, H-9); 2.82 (dt, 1H, *J*=13.8, 4.4, H-10*exo*); 2.45 (dd, 1H, *J*=13.8, 8.7, H-10*endo*). $^{13}C$ NMR: 158.25 (q, *J*=32.2, COO); 152.01 (C-4′); 151.38 (C-2′); 149.54 (C-6′); 147.32 (C-8′); 140.42 (C-2); 137.69 (C-7); 131.88 (C-5′); 129.57 (C-4); 128.92 (C-5); 122.63 (C-6); 122.15 (C-3); 64.95 (C-8); 61.29 (C-1); 55.53 (C-9); 32.34 (C-10). ESI MS, *m*/*z* (%): 300.1/298.1 (18/51) [M+H], 283.1/281.1 (34/100) [M−$NH_3$+H]. For $C_{17}H_{13}ClF_3N_5O_2\cdot H_2O$ (429.79) calculated: 47.51% C, 3.52% H, 8.25% Cl, 16.30% N; found: 47.53% C, 3.48% H, 7.99% Cl, 16.12% N.

*4.15.11. 9-[(1R*,8R*,9S*)-11-Azatricyclo[6.2.1.0$^{2,7}$]undeca-2,4,6-trien-9-yl]-9H-purin-6-amine bis trifluoroacetic acid salt (**39**).* Yield 238 mg (94%) of a white powder after crystallization from ethanol/ether. Mp 196–197 °C decomp. IR (KBr): 3200 (br, sh), 3149, 3018 (br), 2759 (br), 2649 (br), 2553 (br), 2046 (w), 1981 (w), 1944 (w), 1705 (sh), 1688 (br), 1615, 1509, 1435, 1418, 1358, 1203 (br), 1174, 1144, 835, 799, 722 $cm^{-1}$. $^1H$ NMR: 10.31 (br s, 2H, NH); 8.37 (s 1H, H-8); 8.35 (s, 1H, H-2); 8.28 (br s, 2H, NH); 7.63 (m, 1H, H-6′); 7.58 (m, 1H, H-3′); 7.42–7.47 (m, 2H, H-4′, H-5′); 5.74 (br s, 1H, H-8′); 5.58 (br d, 1H, *J*=4.3, H-1′); 4.93 (dd, 1H, *J*=8.7, 4.2, H-9′); 2.64 (dt, 1H, *J*=13.8, 4.4, H-10′*exo*); 2.39 (dd, 1H, *J*=13.7, 8.8, H-10′*endo*). $^{13}C$ NMR: 158.75 (q, *J*=34.0, COO); 154.91 (C-6); 149.92 (C-2); 148.40 (C-4); 142.15 (C-8); 140.50 (C-2′); 137.82 (C-7′); 129.53 (C-4′); 128.87 (C-5′); 122.73 (C-6′); 122.11 (C-3′); 119.52 (C-5); 116.59 (q, *J*=295.9, $CF_3$); 65.44 (C-8′); 61.43 (C-1′); 55.30 (C-9′); 32.70 (C-10′). ESI MS, *m*/*z* (%): 280.1 (20) [M+2H], 279.1 (100) [M+H]. For $C_{19}H_{16}F_6N_6O_4$ (506.37) calculated: 45.07% C, 3.19% H, 16.60% N; found: 45.02% C, 3.18% H, 16.35% N.

*4.15.12. 9-[(1R*,8R*,9S*)-11-Azatricyclo[6.2.1.0$^{2,7}$]undeca-2,4,6-trien-9-yl]-N-cyclopropyl-9H-purin-6-amine bis trifluoroacetic acid salt (**41**).* Yield 229 mg (84%) of a white powder after crystallization from ether. Mp 146.5–148 °C. IR (KBr): 3228 (w, br), 3023, 2855 (br), 2757 (br), 2643 (br), 2532 (br), 1997 (w), 1930 (w), 1887 (w), 1686 (br), 1619, 1601 (sh), 1556 (w), 1513 (w), 1424, 1408, 1358, 1201, 1180, 1140, 833, 798, 722 $cm^{-1}$. $^1H$ NMR: 8.61 (br s, 1H) and 10.34 (br s, 2H, NH); 8.39 (br s, 1H, H-2); 8.27 (s, 1H, H-8); 7.63 (m, 1H, H-6′); 7.58 (m, 1H, H-3′); 7.42–7.47 (m, 2H, H-4′, H-5′); 5.69 (br s, 1H, H-8′); 5.59 (br d, 1H, *J*=4.3, H-1′); 4.95 (dd, 1H, *J*=8.7, 4.2, H-9′); 3.01 (br s, 1H, CH of cyclopropyl); 2.62 (dt, 1H, *J*=13.7, 4.4, H-10′*exo*); 2.38 (dd, 1H, *J*=13.7, 8.8, H-10′*endo*); 0.79 (m, 2H) and 0.67 (m, 2H, $CH_2$ of cyclopropyl). $^{13}C$ NMR: 155.22 (C-6); 158.50 (q, *J*=34.5, COO); 150.98 (C-2); 147.40 (C-4); 141.60 (C-8); 140.52 (C-2′); 137.85 (C-7′); 129.50 (C-4′); 128.85 (C-5′); 122.75 (C-6′); 122.09 (C-3′); 120.07 (C-5); 116.43 (q, *J*=294.3, $CF_3$); 65.52 (C-8′); 61.48 (C-1′); 55.29 (C-9′); 32.66 (C-10′); 6.52 ($CH_2$ of cyclopropyl). ESI MS, *m*/*z* (%): 320.3 (76) [M+2H], 319.3 (100) [M+H]. For $C_{22}H_{20}F_6N_6O_4$ (546.43) calculated: 48.36% C, 3.69% H, 15.38% N; found: 48.21% C, 3.57% H, 15.22% N.

### 4.16. General method for preparation of hexanoyl derivatives 42a, 2b, 43, and 44

To a stirred suspension of compound **9a**, **9b**, **27**, or **38** (182 mg, 0.5 mmol) in tetrahydrofuran (2.5 mL) were added hexanoyl chloride (1.05 mL, 0.75 mmol) and then dropwise a solution of triethylamine (2.1 mL, 1.5 mmol) and 4-dimethylaminopyridine (31 mg, 0.25 mmol) in tetrahydrofuran (1.5 mL). The mixture was stirred 2 h at room temperature and then methanol (0.1 mL) was added. The precipitate was filtered off, washed with tetrahydrofuran and collected filtrates were evaporated. The residue was chromatographed on silica gel in ethyl acetate/acetone/ethanol/water (150:10:4:3).

### 4.17. 1-[(1*R**,4*R**,6*R**)-6-(6-Chloro-9*H*-purin-9-yl)-2-azabicyclo[2.2.1]hept-2-yl]hexan-1-one (42a)

Yield 160 mg (92%) of a white solid foam. IR ($CHCl_3$): 2932, 2875, 2861, 1633, 1509, 1564, 1483, 1439, 1428, 1398, 1342 $cm^{-1}$. $^1H$ NMR: 8.91 (s, 0.6H) and 8.87 (s, 0.4H, H-8′); 8.772 (s, 0.4H) and 8.769 (s, 0.6H, H-2′); 4.75–4.79 (m, 1H, H-1, H-6); 4.67 (m, 0.4H, H-6); 4.52 (br s, 0.6H, H-1); 3.39 (m, 0.4H), 3.19 (m, 1H) and 3.08 (m, 0.6H, H-3); 2.79 (m, 0.4H) and 2.75 (m, 0.6H, H-4); 2.39–2.55 (m, 2H) and 2.12–2.30 (m, 2H, H-5, H-1″); 1.96 (dm, 0.4H) and 1.85 (dm, 0.6H, *J*=10.7, H-7b); 1.47–1.68 (m, 3H, H-7a, H-2″); 1.22–1.34 (m, 4H, H-3″, H-4″); 0.84–0.88 (m, 3H, H-5″). $^{13}C$ NMR: 170.60 and 170.44 (CON); 152.41 and 152.11 (C-4′); 151.61 and 151.53 (C-2′); 149.28 (C-6′); 145.80 and 145.67 (C-8′); 131.60 and 131.30 (C-5′); 60.30 (C-1); 58.14 (C-6); 57.64 (C-1); 56.95 (C-6); 51.87 and 51.25 (C-3); 36.97 and 35.71 (C-4); 35.67, 35.37, 34.42, 33.95, and 33.24 (C-5, C-7, C-1″); 31.33 and 31.27 (C-3″); 24.62 and 24.13 (C-2″); 22.28 and 22.19 (C-4″); 14.19 (C-5″) (mixture of two C/N rotamers 2:3). ESI MS, *m*/*z* (%): 372.2/370.2 (34/100) [M+Na], 350.2/348.2 (24/79) [M+H]. For $C_{17}H_{22}ClN_5O$ (347.85) calculated: 58.70% C, 6.38% H, 10.19% Cl, 20.13% N; found: 58. 39% C, 6.33% H, 9.91% Cl, 19.85% N.

### 4.18. 1-[(1*R**,4*R**,5*S**)-5-(6-Chloro-9*H*-purin-9-yl)-2-azabicyclo[2.2.1]hept-2-yl]hexan-1-one (42b)

Yield 142 mg (82%) of a brownish thick syrup. IR ($CHCl_3$): 2933, 1626, 1587, 1569, 1455 (br), 1371, 1339 $cm^{-1}$. $^1H$ NMR: 8.871 (s, 0.5H) and 8.867 (s, 0.5H, H-8′); 8.79 (s, 0.5H) and 8.78 (s, 0.5H, H-2′); 4.89 (m, 0.5H) and 4.80 (m, 0.5H, H-5); 4.55 (br s, 0.5H) and 4.45 (br s, 0.5H, H-1); 3.47 (dd, 0.5H, *J*=9.5, 3.8, H-3*exo*); 3.37 (m, 0.5H, H-3*endo*); 3.29 (dd, 0.5H, *J*=11.1, 3.8, H-3*exo*); 3.19 (dd, 0.5H, *J*=11.0, 1.7, H-3*endo*); 2.98 (m, 1H, H-4); 2.08–2.38 (m, 4H, H-1″, H-6); 2.09 (m, 0.5H) and 1.99 (dm, 0.5H, *J*=10.5, H-7b); 1.74 (dm, 0.5H) and 1.65 (dm, 0.5H, *J*=10.7, H-7a); 1.47–1.54 (m, 2H, H-2″); 1.22–1.32 (m, 4H, H-3″, H-4″); 0.86 (t, 3H, *J*=7.0, H-5″). $^{13}C$ NMR: 170.09 and 169.92 (C=O); 152.19 and 152.17 (C-4′); 151.56 and 151.54 (C-2′); 149.23 (C-6′); 145.91 and 145.78 (C-8′); 131.53 and 131.49 (C-5′); 56.96 (C-1); 56.88 and 56.58 (C-5); 54.35 (C-1); 50.53 and 49.94 (C-3); 43.25 and 41.93 (C-4); 38.48 (C-1″); 36.14 and 34.52 (C-7); 33.69 and 33.17 (C-6); 31.25 (C-3″); 24.56 and 24.14 (C-2″); 22.24 (C-4″); 14.14 (C-5″) (mixture of two C/N rotamers 1:1). ESI MS, *m*/*z* (%): 372.2/370.2 (34/100) [M+Na], 350.2/348.2 (29/82) [M+1]. For $C_{17}H_{22}ClN_5O$ (347.85) calculated: 58.70% C, 6.38% H, 10.19% Cl, 20.13% N; found: 58.47% C, 6.45% H, 10.36% Cl, 19.85% N.

### 4.19. 1-[(1*R**,2*S**,4*S**)-2-(6-Chloro-9*H*-purin-9-yl)-7-azabicyclo [2.2.1]hept-7-yl]hexan-1-one (43)

Yield 130 mg (75%) of a white powder after crystallization from cyclohexane. Mp 99.5–101.5 °C. IR ($CHCl_3$): 2930, 2874, 2858, 1639, 1588, 1565, 1485, 1440, 1417, 1398, 1340, 947 $cm^{-1}$. $^1H$ NMR: 8.80 (s, 0.4H) and 8.78 (s, 0.6H, H-2); 8.63 (s, 0.4H) and 8.56 (s, 0.6H, H-8); 4.96 (m, 0.4H) and 4.88 (m, 0.6H, H-2′); 4.50–4.66 (m, 2H, H-1′, H-4′); 2.16–2.45 (m, 3H) and 1.95 (m, 1H, H-2″, H-3′); 1.44–1.77 (m, 5H, H-3″b, H-5′, H-6′); 1.00–1.30 (m, 5H, H-3″a, H-4″, H-5″); 0.84 (br t, 1.8H) and 0.75 (br t, 1.2H, *J*=6.8, H-6″). $^{13}C$ NMR: 170.96 and 170.02 (C-1″); 152.06 and 151.84 (C-4); 151.61 (C-2); 149.19 (C-6); 145.13 and 144.95 (C-8); 131.28 and 131.20 (C-5); 61.23 and 57.88 (C-1′); 58.06 and 56.99 (C-2′); 55.22 and 52.64 (C-4′); 38.91 and 36.27 (C-3′); 33.19 (C-2″); 31.11 and 30.87 (C-4″); 29.42 and 27.75 (C-5′); 26.94 and 25.46 (C-6′); 24.52 (C-3″); 22.13 and 21.96 (C-5″); 14.07 and 13.93 (C-6″) (mixture of two C/N rotamers 2:3). ESI MS, *m*/*z* (%): 372.2/370.2 (28/75) [M+Na], 350.2/348.2 (36/100) [M+H]. For $C_{17}H_{22}ClN_5O$ (347.85) calculated: 58.70% C, 6.38% H, 10.19% Cl, 20.13% N; found: 58.59% C, 6.59% H, 10.36% Cl, 19.89% N.

### 4.20. 1-[(1*R**,8*R**,9*S**)-9-(6-Chloro-9*H*-purin-9-yl)-11-azatricyclo[6.2.1.0$^{2,7}$]undeca-2,4,6-trien-11-yl]hexan-1-one (44)

Yield 172 mg (87%) of a white powder after crystallization from cyclohexane. Mp 139–140 °C. IR ($CHCl_3$): 2931, 2874 (w), 2862 (w), 1655 (br), 1590, 1564, 1485, 1462, 1439, 1398, 1340, 946 $cm^{-1}$. $^1H$ NMR: 8.84 (s, 0.5H), 8.83 (s, 0.5H), 8.80 (s, 0.5H) and 8.73 (s, 0.5H, H-2′, H-8′); 7.43–7.51 (m, 2H, H-3, H-6); 7.22–7.28 (m, 2H, H-4, H-5); 5.63–5.69 (m, 2H, H-1, H-8); 4.86 (dd, 0.5H, *J*=8.2, 3.3) and 4.77 (dd, 0.5H, *J*=8.1, 3.1, H-9); 2.78 (m, 1H, H-10*exo*); 2.47 (m, 0.5H) and 2.26 (m, 0.5H, H-2″b); 2.20 (dd, 0.5H, *J*=13.1, 8.2) and 2.12 (dd, 0.5H, *J*=13.2, 8.3, H-10*endo*); 2.00 (m, 0.5H) and 1.91 (m, 0.5H, H-2″a); 1.41 (m, 1H, H-3″b); 1.12–1.24 (m, 3H, H-3″a, H-4″b, H-5″b); 1.06 (m, 1H, H-5″a); 0.97 (m, 1H, H-4″a); 0.79 (t, 1.5H) and 0.71 (t, 1.5H, *J*=7.3, H-6″). $^{13}C$ NMR: 171.62 and 170.36 (C-1″); 152.44 and 152.29 (C-4′); 151.78 (C-2′); 149.30 (C-6′); 147.08 and 146.25 (C-2); 145.54 and 145.24 (C-8′); 142.31 and 141.84 (C-7); 121.61, 121.10, 120.58, and 120.05 (C-3, C-6); 131.39 and 131.28 (C-5′); 127.83 and 127.78 (C-4); 127.04 and 127.01 (C-5); 66.19, 63.31, 60.11, and 57.99 (C-1, C-8); 56.73 and 55.31 (C-9); 36.83 and 34.03 (C-10); 33.66 and 33.54 (C-2″); 31.01 and 30.76 (C-4″); 24.21 and 24.16 (C-3″); 22.08 and 21.93 (C-5″); 14.04 and 13.90 (C-6″) (mixture of two C/N rotamers 1:1). ESI MS, *m*/*z* (%): 420.1/418.1 (24/100) [M+Na]. For $C_{21}H_{22}ClN_5O$ (395.89) calculated: 63.71% C, 5.60% H, 8.96% Cl, 17.69% N; found: 63.65% C, 5.58% H, 8.86% Cl, 17.65% N.

### 4.21. Antiviral assay

Anti-coxsackievirus activities and cytotoxicity in Vero cells were determined by the same methodologies as described previously.[8a]

The selective antiviral effect of the compounds was evaluated according to the following procedure: Huh 5.2 cells containing the hepatitis C virus genotype 1b I389luc-ubi-neo/NS3-3′/5.1 replicon[23] were sub-cultured in DMEM supplemented with 10% FCS, 1% non-essential amino acids, 1% penicillin/streptomycin and 2% Geneticin at a ratio of 1:3 to 1:4, and grown for 3 to 4 days in 75 $cm^2$ tissue culture flasks. One day before addition of the compound, cells were harvested and seeded in assay medium (DMEM, 10% FCS, 1% non-essential amino acids, 1% penicillin/streptomycin) at a density of 6500 cells/well (100 μl/well) in 96-well tissue culture microtiter plates for evaluation of antimetabolic effect and CulturPlate (Perkin–Elmer) for evaluation of antiviral effect. The microtiter plates were incubated overnight (37 °C, 5% CO2, 95–99% relative humidity), yielding a non-confluent cell monolayer.

The evaluation of antimetabolic as well as antiviral effect of each compound was performed in parallel. Four-step, 1 to 5 compound dilution series were prepared. Following assay setup, the microtiter plates were incubated for 72 h (37 °C, 5% CO2, 95–99% relative humidity). For the evaluation of antimetabolic effects, the assay medium was aspirated, replaced with 75 μl of a 5% MTS solution in phenol red-free medium and incubated for 1.5 h (37 °C, 5% CO2, 95–99% relative humidity). Absorbance was measured at a wavelength of 498 nm (Safire$^2$, Tecan), and optical densities (OD values) were converted to percentage of untreated controls.

For the evaluation of antiviral effects, assay medium was aspirated and the cell monolayers were washed with PBS. The wash buffer was aspirated, and 25 μl of Glo Lysis Buffer (Promega) was added allowing for the lysis to proceed for 5 min at room temperature. Subsequently, 50 μl of Luciferase Assay System (Promega) was added, and the luciferase luminescence signal was quantified immediately (1000 ms integration time/well, Safire$^2$, Tecan). Relative luminescence units were converted into percentage of untreated controls.

The EC50 and EC90 (values calculated from the dose–response curve) represent the concentrations at which 50% and 90% inhibition, respectively, of viral replication is achieved. The CC50 (value calculated from the dose–response curve) represents the concentration at which the metabolic activity of the cells is reduced by 50% as compared to untreated cells.

A concentration of compound is considered to elicit a genuine antiviral effect in the HCV replicon system when the anti-replicon effect is well above the 70% threshold at concentrations where no antimetabolic activity is observed.

### 4.22. Detection of functional interaction with nicotinic acetylcholine receptors

The experiments were performed on TE 671 cells and COS cells by the whole-cell patch-clamp method using an Axopatch 200A amplifier (Axon Instruments, Foster City, CA). TE 671 cells and COS cells were cultivated in a minimal essential medium (Gibco), which was supplemented with 10% of fetal calf serum (from Sigma Chemical, St. Louis, MO). Nicotine (100 μM) was added to cultivation medium of TE 671 cells 2 to 3 days before measurement to increase nicotinic receptors expression.[24] Cells were held at −40 mV during recordings.

Fire-polished glass micropipettes with an outer diameter of approx. 3 μm were filled with a solution of the following composition (in mM): CsF 110, CsCl 30, $MgCl_2$ 7, $Na_2ATP$ 5, EGTA 2, HEPES/CsOH 10, pH 7.4. The resulting resistances of the microelectrodes were 3–5 MΩ. The cell bath solution contained (in mM): NaCl 160, KCl 2.5, $CaCl_2$ 1, $MgCl_2$ 2, HEPES/NaOH 10, glucose 10, pH 7.3. Solutions of drugs were applied using a rapid perfusion system[25] consisting of an array of 12 parallel quartz-glass tubes each approximately 400 μm in diameter. The tubes were positioned and the flow of different solutions was switched on under microcomputer control.[25,26] A complete change of the solution around the cell could be carried out in 20–60 ms. For signal recording and evaluation of data, an Axon Instruments Digidata 1440A digitizer and pCLAMP10 software package (Axon Instruments, Foster City, CA) were used. Data were low-pass filtered at 1 kHz and digitized at 2 kHz. The inhibitory effects were estimated by preapplication and coapplication of compounds with 10 μM of acetylcholine.

### Acknowledgements

The authors are indebted to Ms. Jaroslava Sklenářová, Mr. Stijn Delmotte, Ms. Mieke Flamant, Mr. Tom Bellon, and Ms. Annelies De Ceulaer for excellent technical assistance and to the staff of the Analytical Laboratory of the Institute for elemental analyses. This

study, a part of the research project Z4 055 0506 and Z5 011 0509, was supported by Grant Agency of the Czech Republic (grant No. 202/09/0806), the Ministry of Education, Youth and Sports of the Czech Republic (Centre for New Antivirals and Antineoplastics # 1M0508 and Center of Neuroscience # LC554), and Gilead Sciences, Inc. (Foster City, CA, U.S.A.).

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