JOC The Journal of Organic Chemistry



Note

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*J. Org. Chem.*, **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b02269 • Publication Date (Web): 01 Dec 2017



## Just Accepted



ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

# One or two steps synthesis of *C-8* and *N-9* substituted purines.

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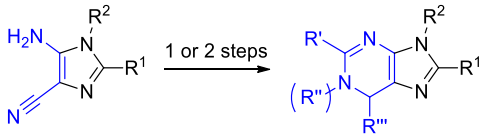
## ABSTRACT

A novel and original strategy to obtain rapidly a large diversity of *C*-8 and *N*-9 substituted purines was developed. The present procedure describes annulation reactions in one or two steps starting from 5-aminoimidazole-4-carbonitriles **1-8** in moderate to good yields. 8,9-disubstituted-6,9-dihydro-1*H*-purin-6-ones **9-14**, 6-amino-8,9-disubstituted-3,9-dihydro-2*H*-purin-2-ones **15-20**, 8,9-disubstituted-3,9-dihydro-2*H*-purin-2,6-diamines **21-24** and 6-imino-1-phenyl-8,9-disubstituted-6,9-dihydro-1*H*-purin-2-(3*H*)-ones **25-26** were synthesized in one step using formic acid, urea, guanidine carbonate and phenylisocyanate, respectively. Whereas 8,9-disubstituted-9*H*-purin-6-amines **27-31** and 6-imino-8,9-disubstituted-6,9-dihydro-1*H*-purin-1-amines **32-33** were obtained in two steps using formamide and hydrazine, respectively.

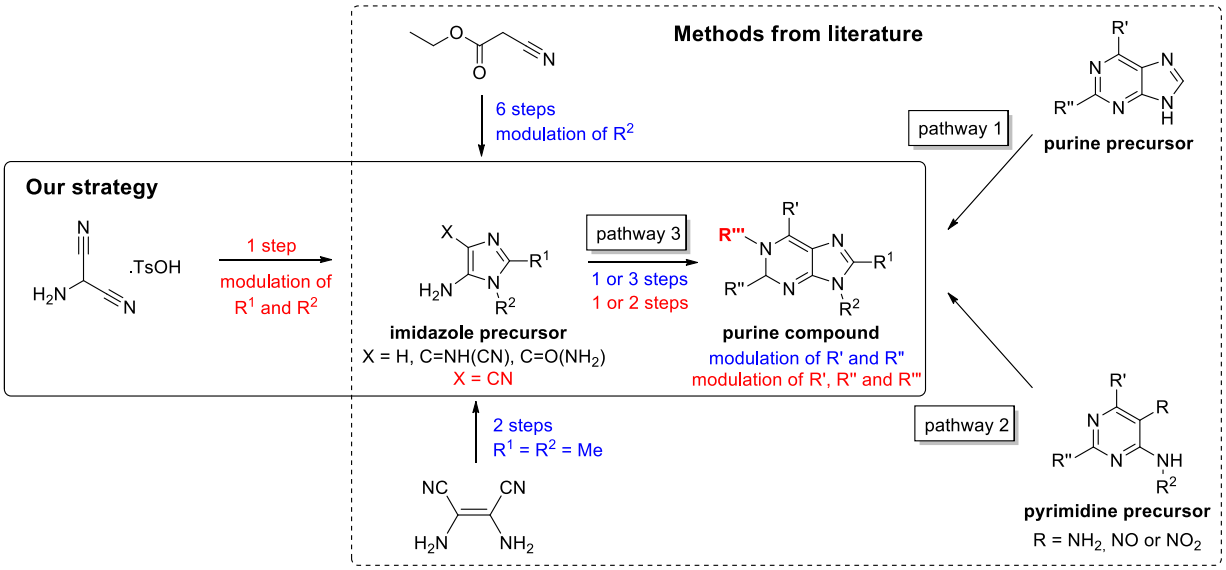



**25 examples**

Imidazo[4,5-*d*]pyrimidines better known as purines, are the most ubiquitous nitrogen containing heterocycles in nature. Among the greatest prominent examples are adenine and guanine in nucleic acids, uric acid or caffeine. Due to their implication in many biochemical pathways, purines fascinate pharmacochemists because of their great potential as biological tool and therapeutic agent. Purine-based compounds are currently used in the treatment of a wide range of diseases such as cancers (6-mercaptopurine, thioguanine), viral diseases (acyclovir, abacavir), neuropsychiatric disorders, neurodegenerative diseases, inflammatory diseases (theophylline, azathioprine, 6-mercaptopurine), tuberculosis or impotence.[1]

Hermann Emil Fischer achieved the first synthesis of imidazo[4,5-*d*]pyrimidine in 1898.[2] Since then, several synthetic routes to purine derivatives have been reported in literature.[3–7] For instance, 1,3,8-trisubstituted xanthines and 2,8-disubstituted adenines are obtained through cyclization of pyrimidine derivatives.[1] Another illustration are reactions like SNAr-type substitutions[8] or coupling reactions[9,10] on appropriately activated purines providing access to polyfunctionalized purines at positions 2, 6, 8 or 9. However, there have been very few publications describing 8,9-disubstituted purines to date. The few synthesis pathways that have been reported are generally limited by structural restrictions. Currently, three main approaches have been described (**Scheme 1**).

**Scheme 1. Synthetic routes to obtain 8,9-disubsituted purines: comparison of the described method to the reported methods**




The first one starts directly from purine structures (pathway 1).[9,11–14] Despite the good yields for the two steps, the first pathway cannot really be considered as a purine synthesis, strictly speaking, because no purine scaffold is build. This synthesis route uses either cross-coupling reactions (palladium,[11,12,14] iron,[9] metal-free using tBuOOtBu),[15] or lithiation reactions followed by an halogen trapping.[13] These strategies have the disadvantage to use harsh reaction conditions, to be toxic, expensive, not environmentally friendly, to generate regioselectivity problems, and thereby to be unsuitable for the development of pharmaceutical compounds.[16]

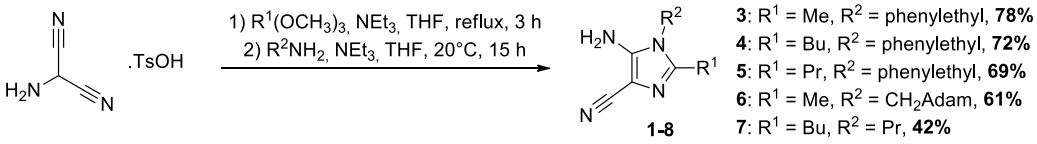
The second way starts from pyrimidines (pathway 2).[17–20] This well-established strategy provides 8,9-disubstituted purines either by the reaction of pyrimidine-4,5-diamines with orthoesters[19,20] or acyl chlorides,[17] or by refluxing 5-nitropyrimidin-4-amines in phenyl ether.[18] However, the structure of the synthesized purine (R' and R'') is limited to the nature of the starting pyrimidine.

Thus, the major drawback of the first two pathways is the restriction in the structure diversity of the resulting purines. To overcome this structural limitation and the problems encountered with pathways 1 and 2, construction of the six-membered ring can be achieved from imidazole derivatives (pathway 3).[21–23] Using this approach, various bicycles can be synthesized (e.g. 8,9-dimethyl-2-substituted-9*H*-purine-6-carboxamide, 8,9-dimethyl-2-substituted-9*H*-purine-6-carbonitrile, 2,6,9-trisubstituted-8-(substitutedthio)-9*H*-purine, 8,9-dimethyl-2-(trifluoromethyl)-5*H*-purin-6(9*H*)-one, 8,9-dimethyl-6,6-disubstituted-6,9-dihydro-1*H*-purin-2(3*H*)-one, 1*H*-purine-2,6(3*H*,7*H*)-dione, 1*H*-purin-6(9*H*)-one). Nevertheless, to the best of our knowledge, $R^1$ and $R^2$ are mostly limited to methyl groups.[21,23] Miscellaneous substituents can be introduced but it requires the previous synthesis of the starting imidazole in 6 steps (**Scheme 1**).[22] Therefore, the search for new rapid routes to 8,9-disubstituted purines remains a synthetic challenge.

Herein, we report a novel and efficient strategy to obtain a large diversity of *C*-8 and *N*-9 substituted purines in one or two steps from 5-amino-imidazole-4-carbonitriles. Because 5-amino-imidazole-4-carbonitriles contain a highly reactive β-enaminonitrile system, they can rapidly yield to new heterocycles.

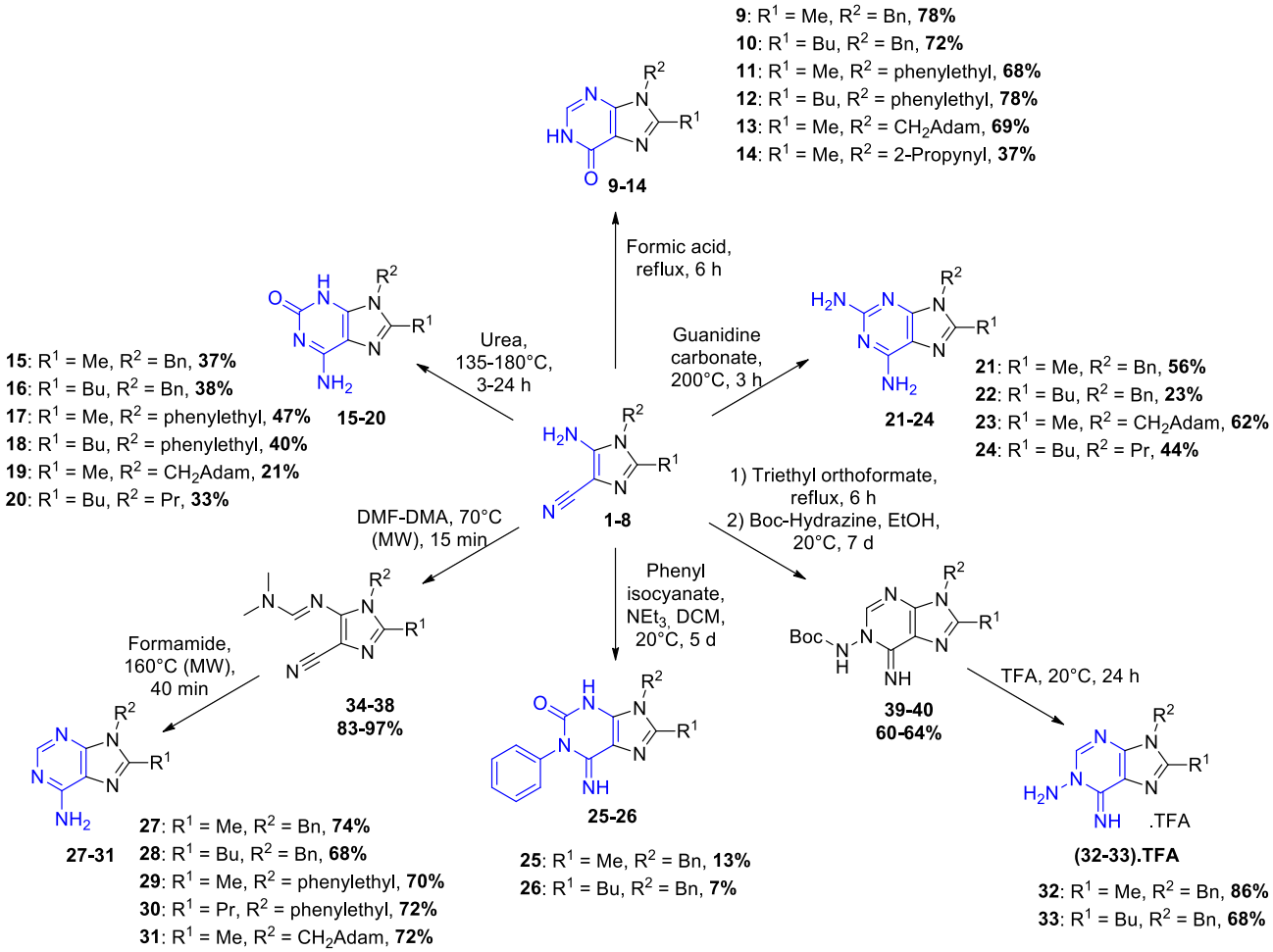
β-Enaminonitriles have been demonstrated as an important and versatile system to yield heterocycles rapidly. Thereby, association of an enaminonitrile system with an imidazole ring was applied to provide purines in few steps. Preliminary work was to synthesize *N*-1 and *C*-2 substituted 5-aminoimidazole-4-carbonitriles **1-8** as enaminonitrile system, through the multicomponent condensation reaction of aminomalononitrile, trimethylorthoester and primary amine in two steps (**Scheme 2**, 42-78%).[24] First, aminomalononitrile reacts with trimethylorthoester in THF at reflux for 3 h in the presence of triethylamine. Then, the reaction between the formed intermediate and a primary amine at 20 °C for 15 h affords the desired 5-aminoimidazole-4-carbonitriles **1-8** in good yields (42-78%).

**Scheme 2. Synthesis of 5-amino-imidazole-4-carbonitriles 1-8**




**1**: $R^1$ = Me, $R^2$ = Bn, **73%**
**2**: $R^1$ = Bu, $R^2$ = Bn, **66%**
**3**: $R^1$ = Me, $R^2$ = phenylethyl, **78%**
**4**: $R^1$ = Bu, $R^2$ = phenylethyl, **72%**
**5**: $R^1$ = Pr, $R^2$ = phenylethyl, **69%**
**6**: $R^1$ = Me, $R^2$ = $CH_2$Adam, **61%**
**7**: $R^1$ = Bu, $R^2$ = Pr, **42%**
**8**: $R^1$ = Me, $R^2$ = 2-Propynyl, **48%**

**Scheme 3. Synthesis of *C*-8 and *N*-9 substituted purines in one or two steps from 5-amino-imidazole-4-carbonitriles**




**9**: $R^1$ = Me, $R^2$ = Bn, **78%**
**10**: $R^1$ = Bu, $R^2$ = Bn, **72%**
**11**: $R^1$ = Me, $R^2$ = phenylethyl, **68%**
**12**: $R^1$ = Bu, $R^2$ = phenylethyl, **78%**
**13**: $R^1$ = Me, $R^2$ = $CH_2$Adam, **69%**
**14**: $R^1$ = Me, $R^2$ = 2-Propynyl, **37%**

**15**: $R^1$ = Me, $R^2$ = Bn, **37%**
**16**: $R^1$ = Bu, $R^2$ = Bn, **38%**
**17**: $R^1$ = Me, $R^2$ = phenylethyl, **47%**
**18**: $R^1$ = Bu, $R^2$ = phenylethyl, **40%**
**19**: $R^1$ = Me, $R^2$ = $CH_2$Adam, **21%**
**20**: $R^1$ = Bu, $R^2$ = Pr, **33%**

**21**: $R^1$ = Me, $R^2$ = Bn, **56%**
**22**: $R^1$ = Bu, $R^2$ = Bn, **23%**
**23**: $R^1$ = Me, $R^2$ = $CH_2$Adam, **62%**
**24**: $R^1$ = Bu, $R^2$ = Pr, **44%**

**27**: $R^1$ = Me, $R^2$ = Bn, **74%**
**28**: $R^1$ = Bu, $R^2$ = Bn, **68%**
**29**: $R^1$ = Me, $R^2$ = phenylethyl, **70%**
**30**: $R^1$ = Pr, $R^2$ = phenylethyl, **72%**
**31**: $R^1$ = Me, $R^2$ = $CH_2$Adam, **72%**

**25**: $R^1$ = Me, $R^2$ = Bn, **13%**
**26**: $R^1$ = Bu, $R^2$ = Bn, **7%**

**32**: $R^1$ = Me, $R^2$ = Bn, **86%**
**33**: $R^1$ = Bu, $R^2$ = Bn, **68%**

Starting from intermediates **1** to **8**, annulation of imidazoles to various purines was investigated. Three procedures were used including cyclisation with boiling formic acid,[25] or solvent-free cyclisation with urea[25,26] and guanidine carbonate[25] to provide 8,9-disubstituted-6,9-dihydro-1*H*-purin-6-ones (**9-14**, 37-78%), 6-amino-8,9-disubstituted-3,9-dihydro-2*H*-purin-2-ones (**15-20**, 21-47%), and 8,9-disubstituted-3,9-dihydro-2*H*-purin-2,6-diamines (**21-24**, 23-62%), respectively (**Scheme 3**). To improve the reaction yields for compounds **15-20**, we investigated the use of solvent and base.[27] Imidazole and urea were refluxed in ethanol with sodium ethanolate or in NMP for 4-6 h without success. Thus, we decided to boost the reaction using microwaves irradiation. The use of microwave energy is well known to afford better reaction yields and shorter reaction times than conventional heating.[28] Different irradiation conditions have been explored (temperature varying from 120 to 200 °C, power level from 140 to 300 W, open or closed vessel) without improving reaction yields.

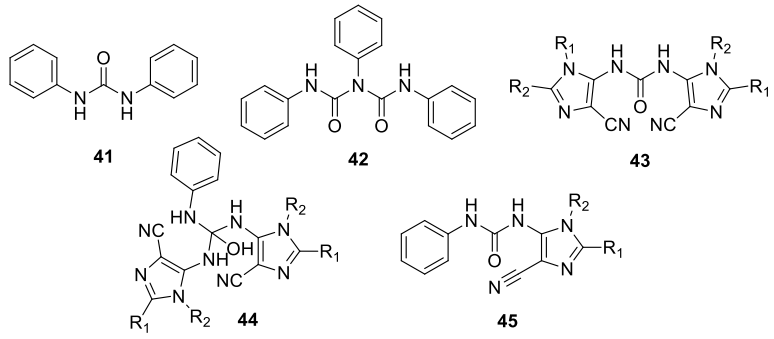
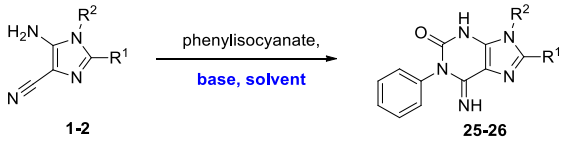



**Figure 1. Chemical structure of unexpected products 41-45**

Imidazole annulation provided also the synthesis of 6-imino-1-phenyl-8,9-disubstituted-6,9-dihydro-1*H*-purin-2-(3*H*)-ones (**25-26**) starting from 5-aminoimidazole-4-carbonitriles (**1-2**). To synthesize products **25-26**, imidazole **1** or **2** and phenylisocyanate (1 equiv.) were refluxed in pyridine for 24 h. Unfortunately, desired compounds **25-26** were not obtained.[29] Four products were detected on the LC-MS spectrum at *m/z* 212.1, 313.1, 450.2 and 543.3 (starting from compound **1**) and at *m/z* 212.1, 313.1, 534.3 and 627.3 (starting from compound **2**). We suggest that these 4 products correspond to 1,3-diphenylurea **41**, 1,3-diphenyl-1-(phenylcarbamoyl)urea **42**, product **43** and product **44**, respectively (**Figure 1**). Indeed, we assume that cyclization does not occurred and the open form 1-(4-cyano-1,2-disubstituted-3*H*-imidazol-5-yl)-3-phenylurea **45** of the desired product is formed instead. This open form may react with the starting imidazole left to give compound **43** and aniline. We assume that the released aniline react either with **43** to form **44**, or with 2 molecules of phenylisocyanate to give 1,3-diphenylurea **41** and 1,3-diphenyl-1-(phenylcarbamoyl)urea **42**, successively.

**Table 1. Effect of solvent, base and quantity of phenylisocyanate on the synthesis of 6-imino-1-phenyl-8,9-disubstituted-6,9-dihydro-1*H*-purin-2-(3*H*)-ones 25-26**

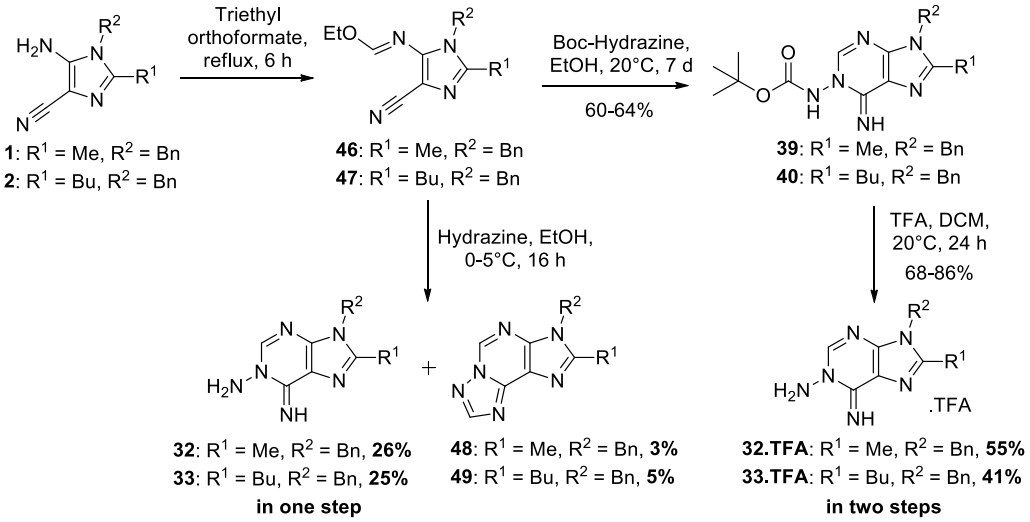



| Compound | Starting material | Phenylisocyanate | Solvent and base | Time | T °C | Yield % |
|---|---|---|---|---|---|---|
| **25 or 26** | - | 1 equiv | Pyridine | 24 h | reflux | 0 |
| **25** | - | 1 equiv | Pyridine (volume x 6) | 5 d | reflux | 0 |
| **25 or 26** | - | 1 equiv | DCM + TEA | 5 d | rt | 6-7 |
| **25** | slowly added during 12 h at -50 °C | 10 equiv | THF + TEA | 5 d | rt | 13 |

The formation of unexpected products prompted us to promote the intramolecular cyclisation over the intermolecular reaction by diluting 6 times the reaction medium without success (**Table 1**). Another procedure using dichloromethane with a few drops of triethylamine at room temperature for 5 days afforded the desired cyclized form with 6-7% yield (**Scheme 3**).[30] Encouraged by this promising result, 10 equivalents of phenylisocyanate were used and the starting imidazole was slowly added during 12 h at -50 °C. Furthermore, DCM was replaced by THF to circumvent the problem of starting material solubility in DCM at -50 °C. Under these conditions, reaction yield for 9-benzyl-6-imino-8-methyl-1-phenyl-6,9-dihydro-1*H*-purin-2-(3*H*)-one **25** was improved to 13% (**Table 1**).

In our attempts to form substituted purines, two additional procedures using the enaminonitrile cyclization strategy were carried out. 8,9-disubstituted-9*H*-purin-6-amines **27-31** and 6-imino-8,9-disubstituted-6,9-dihydro-1*H*-purin-1-amines **32-33** were obtained in two steps.[31] For compounds **27-31**, *N,N*-dimethylmethanimidamide intermediates **34-38** were first synthesized by the reaction of starting imidazoles **1-3**, **5-6** with *N,N*-dimethylformamide dimethyl acetal (DMF-DMA) at 70 °C under microwave irradiation (200 W) during 15 min in a sealed vessel (83-97%). Ammonia is generated *in situ* by microwave-assisted degradation of formamide and can thus perform a nucleophilic attack on intermediates **34-38** followed by intramolecular cyclization and tautomerization to lead to 9*H*-purin-6-amines **27-31** (68-74%, **Scheme 3**).

**Scheme 4. Synthesis of 6-imino-6,9-dihydro-1*H*-purin-1-amines 32-33**




The compounds **32-33** were synthesized from ethyl-*N*-(4-cyano-1*H*-imidazol-5-yl)formimidate intermediates **46-47**, previously obtained by reaction of starting imidazole (**1** or **2**) and an excess of triethylorthoformate.[32] Because these formimidate derivatives are easily hydrolyzable by water to the corresponding *N*-(4-cyano-1*H*-imidazol-5-yl)formimidic acids, they were involved in the next step without further purification. One equivalent of 99% hydrazine monohydrate was stirred with intermediates **46-47** for 3 h at 0-5 °C to give compounds **32-33** in moderate yields (25-26%). When an excess of 99% hydrazine monohydrate is used, iminoesters were reduced to starting imidazoles **1-2** by the preferential elimination of ethylformate hydrazone instead of the cyclization into 6-imino-8,9-disubstituted-6,9-dihydro-1*H*-purin-1-amines **32-33**. Despite the use of one equivalent of 99% hydrazine monohydrate, the formation of a side product was also observed. Indeed, residual triethylorthoformate from the first step reacts with the 6-imino-purin-1-amines **32-33** to give

2,3-disubstituted-3*H*-[1,2,4]triazolo[5,1-*i*]purines **48-49** (**Scheme 4**).[33] To prevent the formation of these tricyclic by-products, we decided to first synthesize Boc-protected compounds **39-40** (60-64%), whose *N*-protecting group was next cleaved with TFA (68-86%) to give 6-imino-1*H*-purin-1-amines **32-33** (**Scheme 4**). As compared with the first synthesis route, this *N*-protection based strategy led to a yield increase from 25-26% to 41-55%.

In conclusion, we described a new convenient and efficient strategy to synthesized 8,9-disubstituted purines. The advantage of our approach is to offer a large diversity of bicycles obtained in one or two steps from the common 5-aminoimidazole-4-carbonitrile such as hypoxanthine, isoguanine, adenine and 2-aminoadenine.

## EXPERIMENTAL SECTION

**General Information.** All commercial reagents and solvents were used without further purification. Analytical thin-layer chromatography was performed on pre-coated Polygram Sil G/UV254 plates (Macherey-Nagel®); the spots were located by UV (254 and 366 nm). Silica gel 60 230–400 mesh purchased from Merck® was used for column chromatography. Preparative HPLC were performed using an OmniSpher C18 column 10 µm particle size, dimensions 41 mm x 250 mm, on a Varian SD-1 prepstar equipped with a UV detector set at 254 nm. The following solvent system was used: eluent (A): 0.1% formic acid in $H_2O$, eluent (B) 100% $CH_3CN$ ; 10% eluent B for 5 min, then a gradient run to 70% eluent B over the next 20 min. The microwave reactions were performed using a CEM DiscoverSP, in sealed reaction vials, and the temperature was monitored using IR temperature sensor. All melting points were determined with a Büchi 535® capillary apparatus and remain uncorrected. $^1$H- and $^{13}$C-NMR spectra were obtained using a Bruker® 300 MHz or 500 MHz spectrometer, chemical shifts (δ) are expressed in ppm relative to tetramethylsilane used as an internal standard, J values are in hertz, and the splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; quint, quintet; sex, sextuplet; m, multiplet. All compounds were analyzed by HPLC-MS on a HPLC combined with a Surveyor MSQ (Thermo Electron®) equipped with an electrospray ionisation (ESI) or atmospheric pressure chemical ionization (APCI)-source. A Micromass (Waters, Manchester, UK) high resolution TOFMS with an ESI source was used to detect the analytes of interest in positive mode or negative mode. The TOF analyser was used in V mode at 9000 mass resolution. The purity of all compounds was determined by HPLC using a Chromazing column and a WATERS 600 pump chromatograph equipped with a WATERS 2487 dual absorption wavelength UV detector (λ = 254 nm and 366 nm). Retention time was obtained with flow rates of 1 mL/min. The acquisition time is 20 min.

**General Procedure for the Synthesis of 5-amino-1,2-disubstituted-1*H*-imidazole-4-carbonitriles (1-8).** To a solution of aminomalononitrile *p*-toluenesulfonate (5.9 mmol) in THF (30 mL) was added triethylamine (7.1 mmol). The mixture was stirred at room temperature for 30 min. To this solution was added the corresponding trimethyl orthoester (8.3 mmol) and the solution was refluxed for 3 h. After return to room temperature, triethylamine (7.1 mmol) and the corresponding primary amine (7.1 mmol) were added. The solution was stirred at room temperature for 15 h. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (30 mL), washed with saturated aqueous $Na_2CO_3$ (3 x 20 mL) and saturated aqueous NaCl (20 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure.

**5-Amino-1-benzyl-2-methyl-1*H*-imidazole-4-carbonitrile (1).** The crude residue was purified on silica gel chromatography eluting with 20% cyclohexane in ethyl acetate. Compound **1** (0.92 g, Y = 73%) was isolated as a beige solid ; mp = 172-174 °C. $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.39-7.32 (m, 3H), 7.07-7.04 (m, 2H), 4.99 (s, 2H), 4.12 (s, 2H), 2.27 (s,

3H). $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 145.5 (C), 141.1 (C), 134.2 (C), 129.5 (2CH), 128.6 (CH), 126.0 (2CH), 115.9 (C), 94.3 (C), 46.6 ($CH_2$), 13.57 ($CH_3$). LC-MS ($APCI^+$) *m/z* 213.1 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{12}H_{11}N_4$ 213.1135 ; found 213.1137.

**5-Amino-1-benzyl-2-butyl-1*H*-imidazole-4-carbonitrile (2).** The crude residue was purified on silica gel chromatography eluting with 50% cyclohexane in ethyl acetate. Compound **2** (0.99 g, Y = 66%) was isolated as a beige solid ; mp = 120-122 °C. $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.43-7.33 (m, 3H), 7.06-7.04 (m, 2H), 5.00 (s, 2H), 3.69 (s, 2H), 2.58 (t, 2H, *J* = 7.8 Hz), 1.60 (quint, 2H, *J* = 7.8 Hz), 1.35 (sex, 2H, *J* = 7.3 Hz), 0.90 (t, 3H, *J* = 7.3 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 145.3 (C), 144.8 (C), 134.4 (C), 129.5 (2CH), 128.5 (CH), 125.9 (2CH), 116.0 (C), 94.6 (C), 46.3 ($CH_2$), 29.4 ($CH_2$), 27.0 ($CH_2$), 22.3 ($CH_2$), 13.57 ($CH_3$). LC-MS ($APCI^+$) *m/z* 255.0 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{19}N_4$ 255.1606 ; found 255.1604.

**5-Amino-2-methyl-1-phenylethyl-1*H*-imidazole-4-carbonitrile (3).** The crude residue was purified on silica gel chromatography eluting with 20% cyclohexane in ethyl acetate. Compound **3** (1.04 g, Y = 78%) was isolated as a beige solid ; mp = 175-177 °C. $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.33-7.31 (m, 3H), 7.04-7.01 (m, 2H), 3.97 (t, 2H, *J* = 6.3 Hz), 3.19 (s, 2H), 2.96 (t, 2H, *J* = 6.3 Hz), 2.16 (s, 3H). $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 145.2 (C), 140.9 (C), 137.0 (C), 129.3 (2CH), 128.9 (2CH), 127.6 (CH), 116.0 (C), 94.7 (C), 45.1 ($CH_2$), 35.8 ($CH_2$), 13.3 ($CH_3$). LC-MS ($APCI^+$) *m/z* 227.1 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{13}H_{15}N_4$ 227.1291 ; found 227.1295.

**5-Amino-2-butyl-1-phenylethyl-1*H*-imidazole-4-carbonitrile (4).** The crude residue was purified on silica gel chromatography eluting with 40% cyclohexane in ethyl acetate. Compound **4** (1.14 g, Y = 72%) was isolated as a beige solid ; mp = 90-92 °C. $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.33-7.31 (m, 3H), 7.04-7.01 (m, 2H), 3.97 (t, 2H, *J* = 6.4 Hz), 3.15 (s, 2H), 2.96 (t, 2H, *J* = 6.4 Hz), 2.42 (t, 2H, *J* = 7.8 Hz), 1.74-1.64 (m, 2H), 1.40 (sex, 2H, *J* = 7.5 Hz), 0.94 (t, 3H, *J* = 7.5 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 145.3 (C), 144.7 (C), 137.1 (C), 129.2 (2CH), 128.9 (2CH), 127.6 (CH), 116.1 (C), 94.5 (C), 44.8 ($CH_2$), 36.0 ($CH_2$), 29.2 ($CH_2$), 26.7 ($CH_2$), 22.4 ($CH_2$), 13.7 ($CH_3$). LC-MS ($APCI^+$) *m/z* 269.1 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{21}N_4$ 269.1761 ; found 269.1761.

**5-Amino-1-phenylethyl-2-propyl-1*H*-imidazole-4-carbonitrile (5).** The crude residue was purified on silica gel chromatography eluting with 50% cyclohexane in ethyl acetate. Compound **5** (1.04 g, Y = 69%) was isolated as a beige solid ; mp = 112-114 °C. $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.32-7.30 (m, 3H), 7.04-7.01 (m, 2H), 3.97 (t, 2H, *J* = 6.4 Hz), 3.14 (s, 2H), 2.96 (t, 2H, *J* = 6.4 Hz), 2.40 (t, 2H, *J* = 6.1 Hz), 1.73 (sex, 2H, *J* = 7.6 Hz), 1.01 (t, 3H, *J* = 7.4 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 145.3 (C), 144.5 (C), 137.1 (C), 129.3 (2CH), 128.9 (2CH), 127.6 (CH), 116.0 (C), 94.5 (C), 44.7 ($CH_2$), 36.0 ($CH_2$), 28.9 ($CH_2$), 20.5 ($CH_2$), 13.9 ($CH_3$). LC-MS ($APCI^+$) *m/z* 255.2 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{19}N_4$ 255.1604 ; found 255.1607.

**5-Amino-1-(adamantan-1-ylmethyl)-2-methyl-1*H*-imidazole-4-carbonitrile (6).** The crude residue was purified on silica gel chromatography eluting with 50% cyclohexane in ethyl acetate. Compound **6** (1.3 g, Y = 61%) was isolated as a beige solid ; mp = 239-241 °C. $^1$H NMR (DMSO, 300 MHz) δ 5.93 (s, 2H), 3.50 (s, 2H), 2.15 (s, 3H), 1.92 (s, 3H), 1.65-1.51 (m, 12H). $^{13}$C NMR (DMSO, 75 MHz) δ 149.8 (C), 140.4 (C), 118.4 (C), 88.5 (C), 53.6 ($CH_2$), 40.2 (3 $CH_2$), 36.6 (3 $CH_2$), 36.4 (C), 28.0 (3 CH), 14.7 ($CH_3$). LC-MS (ESI) *m/z* 271.2 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{23}N_4$ 271.1917 ; found 271.1917.

**5-Amino-2-butyl-1-(propyl)-1*H*-imidazole-4-carbonitrile (7).** The crude residue was purified on silica gel chromatography eluting with 40% ethyl acetate in cyclohexane.

Compound **7** (510 mg, Y = 42%) was isolated as a beige solid ; mp = 102-104 °C. $^{1}$H NMR (DMSO, 300 MHz) δ δ 6.03 (s, 2H), 3.67 (t, 2H, *J* = 7.6 Hz), 2,46 (t, 2H), 1.62-1.47 (m, 4H), 1.39-1.26 (sex, 2H, *J* = 7.4 Hz), 0.90-0.81 (m, 6H). $^{13}$C NMR (DMSO, 75 MHz) δ 148.4 (C), 142.8 (C), 118.5 (C), 88.6 (C), 43.5 ($CH_2$), 29.2 ($CH_2$), 26.2 ($CH_2$), 22.5 ($CH_2$), 22.2 ($CH_2$), 14.2 ($CH_3$), 11.2 ($CH_3$). LC-MS (ESI) *m/z* 207.2 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{11}H_{19}N_4$ 207.1604 ; found 207.1614.

**5-Amino-2-methyl-1-(prop-2-yn-1-yl)-1*H*-imidazole-4-carbonitrile (8).** The crude residue was purified on silica gel chromatography eluting with 50% cyclohexane in ethyl acetate. Compound **8** (605 mg, Y = 48%) was isolated as a beige solid ; mp = 172-174 °C. $^{1}$H NMR (DMSO, 300 MHz) δ 6.21 (s, 2H), 4.68 (d, 2H, *J* = 2.5 Hz), 3.41 (t, 1H, *J* = 2.5 Hz), 2.20 (s, 3H). $^{13}$C NMR (DMSO, 75 MHz) δ 148.2 (C), 139.4 (C), 118.0 (C), 88.4 (C), 78.2 (C), 75.8 (CH), 32.0 ($CH_2$), 13.5 ($CH_3$). LC-MS (ESI) *m/z* 161.1 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_8H_9N_4$ 161.0822 ; found 161.0822.

**General Procedure for the Synthesis of 8,9-disubstituted-6,9-dihydro-1*H*-purin-6-ones (9-14).** 5-Amino-1,2-disubstituted-1*H*-imidazole-4-carbonitrile (**1-4**, **6** or **8**) (3.8 mmol) was dissolved in formic acid (3 mL) and the mixture was refluxed for 15 h. After return to room temperature, the mixture was poured into water (30 mL). The resulting precipitate was filtered and washed with water.

**9-Benzyl-8-methyl-6,9-dihydro-1*H*-purin-6-one (9).** The precipitate was recrystallized from DMF/$H_2O$ (1:1). Compound **9** (Y = 78%, 710 mg from 800 mg (3.8 mmol) of **1**) was isolated as a green solid ; mp > 250 °C. $^{1}$H NMR (DMSO, 300 MHz) δ 12.26 (s, 1H), 8.01 (s, 1H), 7.34-7.30 (m, 3H), 7.18-7.15 (m, 2H), 5.35 (s, 2H), 2.36 (s, 3H). $^{13}$C NMR (DMSO, 75 MHz) δ 156.7 (C), 149.8 (C), 148.4 (CH), 145.7 (C), 136.9 (C), 129.4 (2CH), 128.2 (CH), 127.4 (2CH), 123.1 (C), 45.7 ($CH_2$), 14.1 ($CH_3$). LC-MS ($APCI^+$) *m/z* 241.1 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{13}H_{13}N_4O$ 241.1084 ; found 241.1078.

**9-Benzyl-8-butyl-6,9-dihydro-1*H*-purin-6-one (10).** Compound **10** (Y = 72%, 640 mg from 800 mg (3.1 mmol) of **2**) was isolated as a beige solid ; mp = 222-224 °C. $^{1}$H NMR (DMSO, 300 MHz) δ 12.25 (s, 1H), 8.00 (s, 1H), 7.33-7.27 (m, 3H), 7.16-7.13 (m, 2H), 5.36 (s, 2H), 2.66 (t, 2H, *J* = 7.5 Hz), 1.56 (quint, 2H, *J* = 7.5 Hz), 1.29 (sex, 2H, *J* = 7.5 Hz), 0.80 (t, 3H, *J* = 7.1 Hz). $^{13}$C NMR (DMSO, 75 MHz) δ 156.8 (C), 151.6 (C), 149.7 (C), 145.6 (CH), 137.1 (C), 129.2 (2CH), 128.1 (CH), 127.2 (2CH), 123.2 (C), 45.5 ($CH_2$), 28.9 ($CH_2$), 26.7 ($CH_2$), 22.1 ($CH_2$), 14.1 ($CH_3$). LC-MS ($APCI^+$) *m/z* 283.1 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{16}H_{18}N_4ONa$ 305.1383 ; found 305.1376.

**8-Methyl-9-phenylethyl-6,9-dihydro-1*H*-purin-6-one (11).** Compound **11** (Y = 68%, 610 mg from 800 mg (3.5 mmol) of **3**) was isolated as a beige solid ; mp > 250 °C. $^{1}$H NMR (DMSO, 300 MHz) δ 12.18 (s, 1H), 7.97 (s, 1H), 7.28-7.18 (m, 3H), 7.08-7.04 (m, 2H), 4.29 (t, 2H, *J* = 7.0 Hz), 3.01 (t, 2H, *J* = 7.0 Hz), 2.11 (s, 3H). $^{13}$C NMR (DMSO, 75 MHz) δ 156.7 (C), 149.5 (C), 148.3 (C), 145.3 (CH), 138.3 (C), 129.3 (2CH), 128.9 (2CH), 127.1 (CH), 123.1 (C), 44.6 ($CH_2$), 35.6 ($CH_2$), 13.6 ($CH_3$). LC-MS ($APCI^+$) *m/z* 255.1 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{14}H_{15}N_4O$ 255.1240 ; found 255.1245.

**8-Butyl-9-phenylethyl-6,9-dihydro-1*H*-purin-6-one (12).** Compound **12** (Y = 78%, 690 mg from 800 mg (3.0 mmol) of **4**) was isolated as a beige solid ; mp = 215-217 °C. $^{1}$H NMR (DMSO, 300 MHz) δ 12.18 (s, 1H), 7.98 (s, 1H), 7.25-7.20 (m, 3H), 7.06-7.03 (m, 2H), 4.29 (t, 2H, *J* = 7.4 Hz), 3.02 (t, 2H, *J* = 6.9 Hz), 2.36 (t, 2H, *J* = 7.6 Hz), 1.52 (quint, 2H, *J* = 7.3 Hz), 1.27 (sex, 2H, *J* = 7.6 Hz), 0.84 (t, 3H, *J* = 7.3 Hz). $^{13}$C NMR (DMSO, 75 MHz) δ 156.7 (C), 151.8 (C), 149.4 (C), 145.2 (CH), 138.3 (C), 129.3 (2CH), 128.9 (2CH), 127.1 (CH), 123.2 (C), 44.3 ($CH_2$), 35.7 ($CH_2$), 28.9 ($CH_2$), 26.2 ($CH_2$), 22.2 ($CH_2$), 14.1 ($CH_3$). LC-MS

(APCI$^+$) *m/z* 297.1 [M+H]$^+$. HRMS (ESI-TOF) *m/z* [M+H]$^+$ calcd for $C_{17}H_{21}N_4O$ 297.1710 ; found 297.1696.

**9-(Adamantan-1-ylmethyl)-8-methyl-6,9-dihydro-1*H*-purin-6-one (13).** Compound **13** (Y = 69%, 303 mg from 400 mg (1.5 mmol) of **6**) was isolated as a beige solid ; mp > 250 °C. $^1$H NMR (DMSO, 300 MHz) δ 12.20 (s, 1H), 7.95 (d, 1H, *J* = 2.6 Hz), 3.81 (s, 2H), 2.45 (s, 3H), 1.91 (s, 3H), 1.64-1.51 (m, 12H). $^{13}$C NMR (DMSO, 75 MHz) δ 156.6 (C), 150.5 (C), 149.2 (C), 144.8 (CH), 122.8 (C), 54.3 ($CH_2$), 40.7 (3 $CH_2$), 36.6 (3 $CH_2$), 36.0 (C), 28.0 (3 CH), 14.8 ($CH_3$). LC-MS (ESI) *m/z* 299.2 [M+H]$^+$. HRMS (ESI-TOF) *m/z* [M+H]$^+$ calcd for $C_{17}H_{24}N_4O$ 299.1866 ; found 299.1871.

**8-Butyl-9-(prop-2-yn-1-yl)-6,9-dihydro-1*H*-purin-6-one (14).** Compound **14** (Y = 37%, 129 mg from 300 mg (1.9 mmol) of **8**) was isolated as a beige solid ; mp > 250 °C. $^1$H NMR (DMSO, 300 MHz) δ 12.29 (s, 1H), 8.01 (s, 1H), 4.98 (d, 2H, *J* = 2.5 Hz), 3.45 (t, 1H, *J* = 2.5 Hz), 2.50 (s, 3H). $^{13}$C NMR (DMSO, 75 MHz) δ 156.5 (C), 149.0 (C), 148.1 (C), 145.7 (CH), 123.0 (C), 78.2 (C), 76.1 (CH), 31.9 ($CH_2$), 13.9 ($CH_3$). LC-MS (ESI) *m/z* 189.1 [M+H]$^+$. HRMS (ESI-TOF) *m/z* [M+H]$^+$ calcd for $C_9H_9N_4O$ 189.0771 ; found 189.0776.

**General Procedure for the Synthesis of 6-amino-8,9-disubstituted-3,9-dihydro-2*H*-purin-2-ones (15-20).** 5-Amino-1,2-disubstituted-1*H*-imidazole-4-carbonitrile **(1-4** or **6-7)** (3.8 mmol) and urea (7.6 mmol) were heated at 135-180 °C according to the starting imidazole melting point and the mixture was stirred 24 h. The temperature was lowered to 100-110 °C and water (10 mL) was added. The resulting mixture was stirred for 1 h. The resulting precipitate was filtered and washed with water and with dichloromethane.

**6-Amino-9-benzyl-8-methyl-3,9-dihydro-2*H*-purin-2-one (15).** The precipitate was purified on silica gel chromatography eluting with 15% methanol in dichloromethane. Compound **15** (Y = 37%, 360 mg from 800 mg (3.8 mmol) of **1**) was isolated as a beige solid ; mp > 250 °C. $^1$H NMR (DMSO, 300 MHz) δ 10.27 (s, 1H), 7.39-7.27 (m, 4H), 7.24-7.16 (m, 2H), 5.75 (s, 1H), 5.11 (s, 2H), 2.24 (s, 3H). $^{13}$C NMR (DMSO, 75 MHz) δ 155.9 (C), 150.6 (C), 150.5 (C), 146.8 (C), 137.0 (C), 128.7 (2CH), 127.4 (CH), 126.8 (2CH), 107.4 (C), 44.2 ($CH_2$), 13.7 ($CH_3$). LC-MS (APCI$^+$) *m/z* 256.1 [M+H]$^+$. HRMS (ESI-TOF) *m/z* [M+H]$^+$ calcd for $C_{13}H_{14}N_5O$ 256.1193 ; found 256.1197.

**6-Amino-9-benzyl-8-butyl-3,9-dihydro-2*H*-purin-2-one (16).** The precipitate was washed in hot ethanol. Compound **16** (Y = 38%, 220 mg from 500 mg (2.0 mmol) of **2**) was isolated as a beige solid ; mp > 250 °C. $^1$H NMR (DMSO, 300 MHz) δ 10.80 (s, 1H), 7.57 (s, 2H), 7.32-7.26 (m, 3H), 7.16-7.14 (m, 2H), 5.13 (s, 1H), 2.55 (t, 2H, *J* = 7.3 Hz), 1.50 (quint, 2H, *J* = 7.3 Hz), 1.25 (sex, 2H, *J* = 7.2 Hz), 0.78 (t, 3H, *J* = 7.0 Hz). $^{13}$C NMR (DMSO, 125 MHz) δ 158.1 (C), 156.3 (C), 153.0 (C), 150.2 (C), 137.3 (C), 128.7 (2CH), 127.4 (CH), 126.7 (2CH), 126.2 (C), 44.0 ($CH_2$), 28.7 ($CH_2$), 26.5 ($CH_2$), 21.7 ($CH_2$), 13.6 ($CH_3$). LC-MS (APCI$^+$) *m/z* 298.1 [M+H]$^+$. HRMS (ESI-TOF) *m/z* [M+H]$^+$ calcd for $C_{16}H_{18}N_5O$ 298.1662 ; found 296.1666.

**6-Amino-8-methyl-9-phenylethyl-3,9-dihydro-2*H*-purin-2-one (17).** The precipitate was washed in hot ethanol. Compound **17** (Y = 47%, 235 mg from 420 mg (1.9 mmol) of **3**) was isolated as a beige solid ; mp > 250 °C. $^1$H NMR (DMSO, 300 MHz) δ 10.49 (s, 1H), 7.36-7.22 (m, 5H), 7.20-7.11 (m, 2H), 4.06 (t, 2H, *J* = 7.0 Hz), 2.95 (t, 2H, *J* = 7.0 Hz), 1.98 (s, 3H). $^{13}$C NMR (DMSO, 125 MHz) δ 156.8 (C), 156.0 (C), 150.0 (C), 146.8 (C), 138.3 (C), 128.9 (2CH), 128.5 (2CH), 126.6 (CH), 107.3 (C), 43.2 ($CH_2$), 34.6 ($CH_2$), 13.12 ($CH_3$). LC-MS (ESI) *m/z* 270.1 [M+H]$^+$. HRMS (ESI-TOF) *m/z* [M+H]$^+$ calcd for $C_{14}H_{16}N_5O$ 270.1349 ; found 270.1335.

**6-Amino-8-butyl-9-phenylethyl-3,9-dihydro-2*H*-purin-2-one (18).** The precipitate was washed in hot acetonitrile. Compound **18** (Y = 40%, 185 mg from 400 mg (1.5 mmol) of **4**)

was isolated as a beige solid ; mp > 250 °C. $^{1}$H NMR (DMSO, 300 MHz) δ 10.59 (s, 1H), 7.41 (s, 2H), 7.30-7.19 (m, 3H), 7.12-7.10 (m, 2H), 4.06 (t, 2H, *J* = 7.0 Hz), 2.96 (t, 2H, *J* = 7.0 Hz), 2.27 (t, 2H, *J* = 7.5 Hz), 1.53-1.43 (quint, 2H, *J* = 7.6 Hz), 1.30-1.18 (sex, 2H, *J* = 7.4 Hz), 0.83 (t, 3H, *J* = 7.3 Hz). $^{13}$C NMR (DMSO, 75 MHz) δ 156.1 (C), 156.0 (C), 150.8 (C), 150.1 (C), 138.3 (C), 128.9 (2CH), 128.4 (2CH), 126.5 (CH), 107.7 (C), 43.1 ($CH_2$), 34.7 ($CH_2$), 28.6 ($CH_2$), 25.9 ($CH_2$), 21.8 ($CH_2$), 13.7 ($CH_3$). LC-MS (ESI) *m/z* 312.2 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M-H]^+$ calcd for $C_{17}H_{20}N_5O$ 312.1819 ; found 312.1823.

**6-Amino-9-(adamantan-1-ylmethyl)-8-methyl-3,9-dihydro-2*H*-purin-2-one (19).** The crude residue was isolated and purified on preparative HPLC. Compound **19** (Y = 21%, 96 mg from 400 mg (1.5 mmol) of **6**) was isolated as a beige solid ; mp > 250 °C. $^{1}$H NMR (DMSO, 300 MHz) δ 10.53 (s, 1H), 7.41 (s, 2H), 3.58 (s, 2H), 2.36 (s, 3H), 1.92 (s, 3H), 1.65-1.52 (m, 12H). $^{13}$C NMR (DMSO, 75 MHz) δ 156.4 (C), 151.4 (C), 151.0 (C), 148.0 (C), 108.2 (C), 53.4 ($CH_2$), 40.8 (3 $CH_2$), 36.7 (3 $CH_2$), 36.1 (C), 28.1 (3 CH), 14.9 ($CH_3$). LC-MS (ESI) *m/z* 314.2 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M-H]^-$ calcd for $C_{17}H_{22}N_5O$ 312.1819 ; found 312.1823.

**6-Amino-8-butyl-9-propyl-3,9-dihydro-2*H*-purin-2-one (20).** The crude residue was purified on silica gel chromatography eluting with 5% ammonia saturated methanol in dichloromethane and washed with ethanol. Compound **20** (Y = 33%, 80 mg from 200 mg (0.97 mmol) of **7**) was isolated as a beige solid ; mp > 250 °C. $^{1}$H NMR (DMSO, 300 MHz) δ 10.41 (s, 1H), 7.35 (s, 2H), 3.81 (m, 2H), 2.67 (t, 2H, *J* = 7.6 Hz), 1.68-1.63 (m, 4H), 1.42-1.34 (m, 2H), 0.93-0.85 (m, 6H). $^{13}$C NMR (DMSO, 75 MHz) δ 155.9 (C), 155.3 (C), 151.3 (C), 150.6 (C), 108.0 (C), 43.3 ($CH_2$), 29.4 ($CH_2$), 26.7 ($CH_2$), 22.8 ($CH_2$), 22.3 ($CH_2$), 14.2 ($CH_3$), 11.4 ($CH_3$). LC-MS (ESI) *m/z* 250.2 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{12}H_{20}N_5O$ 250.1662 ; found 250.1672.

**General Procedure for the Synthesis of 8,9-disubstituted-3,9-dihydro-2*H*-purin-2,6-diamines (21-24).** Imidazole (**1-2**, **6-7**) (1.4 mmol) and guanidine carbonate (2.8 mmol) were heated at 175 °C for 20 min. The temperature was raised to 200 °C and the mixture was stirred for 2 h. The reaction mixture was poured in hot water (20 mL) and the mixture was stirred for 10 min.

**9-Benzyl-8-methyl-3,9-dihydro-2*H*-purin-2,6-diamine (21).** After return to room temperature, the residue was extracted with ethyl acetate (3 x 15 mL). The organic layer was washed with saturated aqueous NaCl (3 x 15 mL), dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude residue was purified on silica gel chromatography eluting with 10% ethanol in ethyl acetate and washed with diethyl ether. Compound **21** (Y = 56%, 200 mg from 300 mg (1.4 mmol) of **1**) was isolated as a beige solid ; mp = 247-249 °C. $^{1}$H NMR (DMSO, 300 MHz) δ 7.32-7.25 (m, 3H), 7.14-7.12 (m, 2H), 6.60 (s, 2H), 5.73 (s, 2H), 5.17 (s, 2H), 2.27 (s, 3H). $^{13}$C NMR (DMSO, 75 MHz) δ 160.4 (C), 155.7 (C), 153.5 (C), 145.2 (C), 137.8 (C), 129.1 (2CH), 127.8 (CH), 127.1 (2CH), 112.2 (C), 44.7 ($CH_2$), 14.0 ($CH_3$). LC-MS (ESI) *m/z* 255.1 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{13}H_{15}N_6$ 255.1353 ; found 255.1346.

**9-Benzyl-8-butyl-3,9-dihydro-2*H*-purin-2,6-diamine (22).** After return to room temperature, the residue was extracted with ethyl acetate (3 x 15 mL). The organic layer was washed with saturated aqueous NaCl (3 x 15 mL), dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude residue was purified on silica gel chromatography eluting with 20% ethanol in ethyl acetate and washed with diethyl ether. Compound **22** (Y = 23%, 80 mg from 300 mg (1.2 mmol) of **2**) was isolated as a beige solid ; mp = 196-198 °C. $^{1}$H NMR (DMSO, 300 MHz) δ 7.34-7.22 (m, 3H), 7.12-7.09 (m, 2H), 6.58 (s, 2H), 5.72 (s, 2H), 5.19 (s, 2H), 2.28 (t, 2H, *J* = 7.7 Hz), 1.56-1. 46 (quint, 2H, *J* = 7.5 Hz), 1.31-1.19 (sex, 2H, *J* = 7.4 Hz), 0.78 (t, 3H, *J* = 7.3 Hz). $^{13}$C NMR (DMSO, 75 MHz) δ 160.4 (C), 155.8 (C), 153.5 (C),

148.7 (C), 138.0 (C), 129.1 (2CH), 127.8 (CH), 126.9 (2CH), 112.3 (C), 44.6 ($CH_2$), 29.46 ($CH_2$), 26.9 ($CH_2$), 22.2 ($CH_2$), 14.1 ($CH_3$). LC-MS (ESI) *m/z* 297.2 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{21}N_6$ 297.1822 ; found 297.1826.

**9-(Adamantan-1-ylmethyl)-8-methyl-3,9-dihydro-2*H*-purin-2,6-diamine (23).** After return to room temperature, the precipitate was filtered, washed with water and with dichloromethane. Then, the precipitate was purified on thick-layer chromatography eluting with 15% ethanol in ethyl acetate. Compound **23** (Y = 62%, 215 mg from 300 mg (1.1 mmol) of **6**) was isolated as a beige solid ; mp > 250 °C. $^1$H NMR (DMSO, 300 MHz) δ 12.20 (s, 1H), 7.95 (d, 1H, *J* = 2.6 Hz), 3.81 (s, 2H), 2.45 (s, 3H), 1.91 (s, 3H), 1.64-1.51 (m, 12H). $^{13}$C NMR (DMSO, 75 MHz) δ 160.0 (C), 155.5 (C), 154.4 (C), 146.0 (C), 122.3 (C), 53.5 ($CH_2$), 40.9 (3 $CH_2$), 36.7 (3 $CH_2$), 36.1 (C), 28.1 (3 CH), 14.8 ($CH_3$). LC-MS (ESI) *m/z* 313.3 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{25}N_6$ 313.2135 ; found 313.2143.

**8-Butyl-9-propyl-3,9-dihydro-2*H*-purin-2,6-diamine (24).** After return to room temperature, the precipitate was filtered, washed with water and the crude residue was purified on thick-layer chromatography eluting with 10% ethanol in ethyl acetate. Compound **24** (Y = 44%, 106 mg from 200 mg (0.97 mmol) of **7**) was isolated as a beige solid ; mp = 171-173 °C. $^1$H NMR (DMSO, 300 MHz) δ 6.45 (s, 2H), 5.64 (s, 2H), 3.85 (t, 2H, *J* = 7.4 Hz), 2,69 (t, 2H *J* = 7.6 Hz), 1.74-1.61 (m, 4H), 1.44-1.32 (sex, 2H, *J* = 7.4 Hz), 0.93-0.82 (m, 6H). $^{13}$C NMR (DMSO, 75 MHz) δ 160.1 (C), 155.6 (C), 153.2 (C), 148.6 (C), 112.4 (C), 43.3 ($CH_2$), 29.8 ($CH_2$), 26.7 ($CH_2$), 23.1 ($CH_2$), 22.3 ($CH_2$), 14.3 ($CH_3$), 11.5 ($CH_3$). LC-MS (ESI) *m/z* 249.2 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{12}H_{21}N_6$ 249.1822 ; found 249.1831.

**Synthesis of 9-benzyl-6-imino-8-methyl-1-phenyl-6,9-dihydro-1*H*-purin-2-(3*H*)-one (25).** 5-Amino-1-benzyl-2-methyl-1*H*-imidazole-4-carbonitrile **1** (0.9 mmol) was dissolved in THF (10 mL) containing triethylamine (0.45 mmol). This solution was slowly added dropwise in a solution of phenylisocyanate (9.4 mmol) in THF (5 mL). Then, the mixture was stirred at room temperature during 7 days. The solvent was evaporated and the residue was dissolved in DCM (10 mL). The organic layer was washed with saturated aqueous NaCl (3 x 10 mL), dried over $CaCl_2$ and was evaporated under reduced pressure. The crude residue was purified on silica gel chromatography eluting with 10% ethanol in ethyl acetate. Compound **25** (Y = 13%, 40 mg from 200 mg (0.9 mmol) of **1**) was isolated as a beige solid ; mp > 250 °C. $^1$H NMR (DMSO, 300 MHz) δ 7.55-7.23 (m, 12H), 5.13 (s, 2H), 2.29 (s, 3H). $^{13}$C NMR (DMSO, 125 MHz) δ 155.7 (C), 154.7 (C), 150.8 (C), 147.1 (C), 137.5 (C), 136.9 (C), 130.3 (2CH), 129.3 (2CH), 129.2 (2CH), 129.1 (CH), 128.0 (CH), 127.5 (2CH), 107.0 (C), 44.5 ($CH_2$), 14.2 ($CH_3$). LC-MS (ESI) *m/z* 332.1 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{18}N_5O$ 332.1506 ; found 332.1509.

**Synthesis of 9-benzyl-8-butyl-6-imino-1-phenyl-6,9-dihydro-1*H*-purin-2-(3*H*)-one (26).** 5-Amino-1-benzyl-2-butyl-1*H*-imidazole-4-carbonitrile **2** (0.4 mmol) was dissolved in DCM (5 mL) containing few drops of triethylamine. To this solution was added phenylisocyanate (0.5 mmol) and the mixture was stirred at room temperature during 12 days. The organic layer was washed with saturated aqueous NaCl (3 x 5 mL), dried over $CaCl_2$ and was evaporated under reduced pressure. The crude residue was purified on silica gel chromatography eluting with 10% ethanol in ethyl acetate. Compound **26** (Y = 7%,11 mg from 100 mg (0.4 mmol) of **2**) was isolated as a beige solid ; mp > 250 °C. $^1$H NMR (DMSO, 500 MHz) δ 7.54-7.24 (m, 12H), 5.17 (s, 2H), 2.61 (t, 2H, *J* = 7.5 Hz), 1.55-1.49 (quint, 2H, *J* = 7.5 Hz), 1.31-1.27 (m, 2H), 0.81 (t, 3H, *J* = 7.3 Hz). $^{13}$C NMR (DMSO, 125 MHz) δ 155.3 (C), 154.8 (C), 150.9 (C), 150.6 (C), 137.7 (C), 136.9 (C), 130.3 (2CH), 129.3 (2CH), 129.1 (3CH), 127.9 (CH), 127.3 (2CH), 106.7 (C), 44.4 ($CH_2$), 29.3 ($CH_2$), 27.0 ($CH_2$), 22.2 ($CH_2$), 14.1 ($CH_3$). LC-MS (ESI) *m/z* 374.2 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{24}N_5O$ 374.1934 ; found 374.1939.

**General Procedure for the Synthesis of *N'*-(4-cyano-1,2-disubstituted-1*H*-imidazol-5-yl)-*N,N*-dimethylmethanimidamides (34-38).** 5-Amino-1,2-disubstituted-1*H*-imidazole-4-carbonitrile **(1-3** or **5-6)** (1.7 mmol) was dissolved in *N,N*-dimethylformamide dimethylacetal (DMF-DMA, 3 mL) and the solution was irradiated at 70 °C (200 W) for 15 min in a sealed vessel. After return to room temperature, the mixture was poured into water (30 mL) and the residue was extracted with ethyl acetate (3 x 20 mL). The organic layer was washed with water (2 x 20 mL) and saturated aqueous NaCl (20 mL), dried over $MgSO_4$ and the solvent evaporated under reduced pressure.

***N'*-(1-Benzyl-4-cyano-2-methyl-1*H*-imidazol-5-yl)-*N,N*-dimethylmethanimidamide (34).** The crude residue was purified on silica gel chromatography eluting with 30% cyclohexane in ethyl acetate. Compound **34** (Y = 97%, 450 mg from 370 mg (1.7 mmol) of **1**) was isolated as a yellow oil. $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.21 (s, 1H), 7.34-7.29 (m, 3H), 7.11-7.08 (m, 2H), 5.03 (s, 2H), 3.08 (s, 3H), 3.00 (s, 3H), 2.19 (s, 3H). $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 155.0 (CH), 150.1 (C), 142.1 (C), 136.3 (C), 128.8 (2CH), 127.7 (CH), 126.8 (2CH), 118.3 (C), 93.1 (C), 45.7 ($CH_2$), 40.6 ($CH_3$), 34.3 ($CH_3$), 14.0 ($CH_3$). LC-MS (APCI$^+$) *m/z* 268.2 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{18}N_5$ 268.1557 ; found 268.1561.

***N'*-(1-Benzyl-2-butyl-4-cyano-1*H*-imidazol-5-yl)-*N,N*-dimethylmethanimidamide (35).** The crude residue was purified on silica gel chromatography eluting with 30% cyclohexane in ethyl acetate. Compound **35** (Y = 97%, 590 mg from 500 mg (2.0 mmol) of **2**) was isolated as a purple solid ; mp = 83-85 °C. $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.22 (s, 1H), 7.32-7.29 (m, 3H), 7.10-7.07 (m, 2H), 5.06 (s, 2H), 3.09 (s, 3H), 2.99 (s, 3H), 2.46 (t, 2H, *J* = 7.8 Hz), 1.63-1.53 (m, 2H), 1.30 (sex, 2H, *J* = 7.5 Hz), 0.85 (t, 3H, *J* = 7.3 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 155.0 (CH), 149.9 (C), 145.9 (C), 136.6 (C), 128.8 (2CH), 127.7 (CH), 126.6 (2CH), 118.2 (C), 93.2 (C), 45.5 ($CH_2$), 40.6 ($CH_3$), 34.3 ($CH_3$), 29.2 ($CH_2$), 27.3 ($CH_2$), 22.3 ($CH_2$), 13.7 ($CH_3$). LC-MS (APCI$^+$) *m/z* 310.1 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{18}H_{24}N_5$ 310.2026 ; found 310.2027.

***N'*-(4-Cyano-2-methyl-1-phenylethyl-1*H*-imidazol-5-yl)-*N,N*-dimethylmethanimidamide (36).** The crude residue was purified on silica gel chromatography eluting with 30% cyclohexane in ethyl acetate. Compound **36** (Y = 84%, 420 mg from 400 mg (1.8 mmol) of **3**) was isolated as a beige solid ; mp = 98-100 °C. $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.91 (s, 1H), 7.29-7.22 (m, 3H), 7.03-6.98 (m, 2H), 4.01 (t, 2H, *J* = 6.9 Hz), 3.04 (s, 3H), 3.01 (s, 3H), 2.92 (t, 2H, *J* = 6.9 Hz), 2.06 (s, 3H). $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 154.6 (CH), 150.0 (C), 141.7 (C), 137.8 (C), 128.9 (2CH), 128.6 (2CH), 126.7 (CH), 118.2 (C), 93.2 (C), 44.4 ($CH_2$), 40.5 ($CH_3$), 35.9 ($CH_2$), 34.2 ($CH_3$), 13.4 ($CH_3$). LC-MS (APCI$^+$) *m/z* 282.2 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{20}N_5$ 282.1713 ; found 282.1715.

***N'*-(4-Cyano-1-phenylethyl-2-propyl-1*H*-imidazol-5-yl)-*N,N*-dimethylmethanimidamide (37).** The crude residue was purified on silica gel chromatography eluting with 30% cyclohexane in ethyl acetate. Compound **37** (Y = 97%, 470 mg from 400 mg (1.6 mmol) of **5**) was isolated as an orange oil. $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.89 (s, 1H), 7.28-7.22 (m, 3H), 7.03-7.00 (m, 2H), 4.02 (t, 2H, *J* = 7.1 Hz), 3.04 (s, 3H), 3.01 (s, 3H), 2.92 (t, 2H, *J* = 7.1 Hz), 2.34 (t, 2H, *J* = 7.7 Hz), 1.67 (sex, 2H, *J* = 7.4 Hz), 0.94 (t, 3H, *J* = 7.4 Hz). $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.91 (s, 1H), 7.29-7.22 (m, 3H), 7.03-6.98 (m, 2H), 4.01 (t, 2H, *J* = 6.9 Hz), 3.04 (s, 3H), 3.01 (s, 3H), 2.92 (t, 2H, *J* = 6.9 Hz), 2.06 (s, 3H). $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 154.6 (CH), 150.0 (C), 145.2 (C), 137.9 (C), 128.9 (2CH), 128.6 (2CH), 126.6 (CH), 118.4 (C), 93.5 (C), 44.1 ($CH_2$), 40.5 ($CH_3$), 36.2 ($CH_2$), 34.2 ($CH_3$), 29.1 ($CH_2$), 20.7 ($CH_2$), 13.4 ($CH_3$). LC-MS (APCI$^+$) *m/z* 310.1 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{18}H_{24}N_5$ 310.2026 ; found 310.2028.

***N'*-(1-Adamantan-1-ylmethyl)-4-cyano-2-methyl-1*H*-imidazol-5-yl)-*N,N*-dimethylmethanimidamide (38).** For this compound, the mixture was poured into water (30 mL). The resulting precipitate was filtered and washed with water. Compound **38** (Y = 83%, 400 mg from 400 mg (1.5 mmol) of **6**) was isolated as a beige solid; mp = 198-200 °C. $^{1}$H NMR (DMSO, 300 MHz) ) δ 8.02 (s, 1H), 3.52 (s, 2H), 3.06 (s, 3H), 2.97 (s, 3H), 2.23 (s, 3H), 1.91 (s, 3H), 1.64-1.47 (m, 12H). $^{13}$C NMR (DMSO, 75 MHz) δ 155.5 (CH), 151.9 (C), 143.1 (C), 1118.9 (C), 93.2 (C), 53.9 ($CH_2$), 40.2 ($3CH_2$), 36.6 ($3CH_2$), 36.0 (C), 34.5 ($2CH_3$), 28.1 (3CH), 14.9 ($CH_3$). LC-MS (ESI) *m/z* 326,2 ($MH^+$). HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{28}N_5$ 326.2339 ; found 326.2347.

**General Procedure for the Synthesis of 8,9-disubstituted-9*H*-purin-6-amines (27-31):** *N'*-(4-Cyano-1,2-disubstituted-1*H*-imidazol-5-yl)-*N,N*-dimethylmethanimidamide **(34-38)** (1.5 mmol) was dissolved in formamide (3 mL). The solution was irradiated at 170 °C (200 W) for 30 min in a sealed vessel. After return to room temperature, the mixture was poured into water (30 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layer was extracted with 1N aqueous HCl (3 x 20 mL). Then, the aqueous layer was neutralized with 1N aqueous NaOH (20 mL) and was extracted with ethyl acetate (3 x 20 mL). The organic layer was washed with water (2 x 20 mL) and saturated aqueous NaCl (20 mL), dried over $MgSO_4$ and the solvent was evaporated under reduced pressure.

**9-Benzyl-8-methyl-9*H*-purin-6-amine (27).** The precipitate was purified on silica gel chromatography eluting with 10% ethanol in ethyl acetate and then, on thick-layer chromatography eluting with 10% ethanol in ethyl acetate. Compound **27** (Y = 74%, 270 mg from 410 mg (1.5 mmol) of **34**) was isolated as a beige solid ; mp = 238-240 °C. $^{1}$H NMR (DMSO, 300 MHz) δ 8.12 (s, 1H), 7.35-7.24 (m, 3H), 7.19-7.14 (m, 4H), 5.35 (s, 2H), 2.41 (s, 3H). $^{13}$C NMR (DMSO, 75 MHz) δ 155.5 (C), 152.4 (C), 151.2 (CH), 149.0 (C), 137.3 (C), 129.2 (2CH), 128.0 (CH), 127.4 (2CH), 118.0 (C), 45.3 ($CH_2$), 14.2 ($CH_3$). LC-MS ($APCI^+$) *m/z* 240.1 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{13}H_{14}N_5$ 240.1244 ; found 240.1249.

**9-Benzyl-8-butyl-9*H*-purin-6-amine (28).** The precipitate was recrystallized from acetonitrile. Compound **28** (Y = 68%, 309 mg from 500 mg (1.6 mmol) of **35**) was isolated as a beige solid ; mp = 134-136 °C. $^{1}$H NMR (DMSO, 300 MHz) δ 8.10 (s, 1H), 7.34-7.22 (m, 3H), 7.16-7.09 (m, 2H), 7.09 (s, 2H), 5.36 (s, 2H), 2.72 (t, 3H, *J* = 7.6 Hz), 1.57 (quint, 2H, *J* = 7.6 Hz), 1.27 (sex, 2H, *J* = 7.4 Hz), 0.80 (t, 3H, *J* = 7.3 Hz). $^{13}$C NMR (DMSO, 75 MHz) δ 155.5 (C), 152.4 (1C and 1CH), 151.2 (C), 137.5 (C), 129.2 (2CH), 128.0 (CH), 127.2 (2CH), 118.1 (C), 45.1 ($CH_2$), 29.3 ($CH_2$), 27.0 ($CH_2$), 22.2 ($CH_2$), 14.1 ($CH_3$). LC-MS ($APCI^+$) *m/z* 282.1 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{20}N_5$ 282.1713 ; found 282.1711.

**8-Methyl-9-phenylethyl-9*H*-purin-6-amine (29).** The precipitate was purified on thick-layer chromatography eluting with 8% methanol in dichloromethane. Compound **29** (Y = 70%, 189 mg from 300 mg (1.1 mmol) of **36**) was isolated as a beige solid ; mp = 197-199 °C. $^{1}$H NMR (DMSO, 300 MHz) δ 8.10 (s, 1H), 7.25-7.29 (m, 3H), 7.07-7.05 (m, 2H), 7.00 (s, 2H), 4.28 (t, 2H, *J* = 7.0 Hz), 3.02 (t, 2H, *J* = 7.0 Hz), 2.13 (s, 3H). $^{13}$C NMR (DMSO, 75 MHz) δ 155.3 (C), 152.1 (C), 150.9 (CH), 148.9 (C), 138.6 (C), 129.3 (2CH), 128.9 (2CH), 127.0 (CH), 118.1 (C), 44.1 ($CH_2$), 35.4 ($CH_2$), 13.6 ($CH_3$). LC-MS ($APCI^+$) *m/z* 254.0 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{14}H_{16}N_5$ 254.1400 ; found 254.1406.

**9-Phenylethyl-8-propyl-9*H*-purin-6-amine (30).** The precipitate was purified on thick-layer chromatography eluting with 10% ethanol in ethyl acetate. Compound **30** (Y = 72%, 295 mg from 450 mg (1.45 mmol) of **37**) was isolated as a beige solid ; mp > 250 °C. $^{1}$H NMR (DMSO, 300 MHz) δ 8.11 (s, 1H), 7.28-7.19 (m, 3H), 7.08-7.02 (m, 4H), 4.30 (t, 2H, *J* = 7.0 Hz), 3.04 (t, 2H, *J* = 7.0 Hz), 2.43 (t, 2H, *J* = 7.5 Hz), 1.59 (sex, 2H, *J* = 7.4 Hz), 0.85 (t, 3H, *J*

= 7.4 Hz). $^{13}$C NMR (DMSO, 75 MHz) δ 155.4 (C), 152.1 (1C et 1CH), 150.9 (C), 138.6 (C), 129.3 (2CH), 128.9 (2CH), 127.0 (CH), 118.2 (C), 43.9 ($CH_2$), 35.5 ($CH_2$), 28.7 ($CH_2$), 20.5 ($CH_2$), 14.2 ($CH_3$). LC-MS (APCI$^+$) *m/z* 282.1 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{20}N_5$ 282.1713 ; found 282.1720.

**9-(Adamantan-1-ylmethyl)-8-methyl-9*H*-purin-6-amine (31).** The precipitate was purified on silica gel chromatography eluting with 10% ethanol in ethyl acetate. Compound 31 (Y = 72%, 100 mg from 150 mg (0.46 mmol) of **38**) was isolated as white solid ; mp > 250 °C. $^1$H NMR (DMSO, 300 MHz) 8.05 (s, 1H), 7.00 (s, 2H), 3.80 (s, 2H), 2.49 (s, 3H), 1.91 (s, 3H), 1.64-1.53 (m, 12H). $^{13}$C NMR (DMSO, 75 MHz) δ 155.4 (C), 152.2 (C), 151.1 (CH), 149.8 (C), 118.0 (C), 54.0 ($CH_2$), 40.8 ($3CH_2$), 36.6 ($3CH_2$), 36.1 (C), 28.1 (3CH), 14.9 ($CH_3$). LC-MS (ESI) *m/z* 298.2 ($MH^+$). HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{17}H_{24}N_5$ 298.2026 ; found 298.2034.

**General Procedure for the Synthesis of *N*-(6-imino-8,9-disubstituted-6,9-dihydro-1*H*-purin-1-yl)(tert-butoxy)formamides (39-40).** 5-Amino-1,2-disubstituted-1*H*-imidazole-4-carbonitrile (**1-2**) (3.3 mmol) was dissolved in triethyl orthoformate (8 mL). The mixture was refluxed for 6 h. After return to room temperature, the mixture was evaporated under reduced pressure and dissolved in cold ethanol (5 mL). The *tert*-butyl carbazate (9.9 mmol) was added at 0-5 °C. The mixture was stirred at room temperature for 7 days. Then, the reaction mixture was poured in water (50 mL). The resulting precipitate was filtered, washed with water and purified on silica gel chromatography eluting with 10% ethanol in ethyl acetate.

***N*-(9-Benzyl-6-imino-8-methyl-6,9-dihydro-1*H*-purin-1-yl)(tert-butoxy)formamide (39).** Compound **39** (Y = 64%, 750 mg from 700 mg (3.3 mmol) of **1**) was isolated as a beige solid ; mp = 229-231 °C. $^1$H NMR (DMSO, 300 MHz) δ 8.58 (m, 1H), 7.38-7.19 (m, 6H), 5.37 (s, 2H), 2.42 (s, 3H), 1.40 (s, 9H). LC-MS (ESI) m/z 299.1 $[M-tBu+2H]^+$ and 355.2 $[M+H]^+$.

***N*-(9-Benzyl-8-butyl-6-imino-6,9-dihydro-1*H*-purin-1-yl)(tert-butoxy)formamide (40).** Compound **40** (Y = 60%, 285 mg from 300 mg (1.2 mmol) of **2**) was isolated as a light orange solid ; mp = 199-201 °C. $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.59 (s, 1H), 8.14 (s, 1H), 7.37-7.28 (m, 3H), 7.18-7.15 (m, 2H), 5.38 (s, 2H), 2.72 (t, 2H, *J* = 7.5 Hz), 1.60-1.50 (quint, 2H, *J* = 7,5 Hz), 1.40 (s, 9H), 1.34-1.24 (sex, 2H, *J* = 7,4 Hz), 0.79 (t, 3H, *J* =7.4 Hz). LC-MS (ESI) *m/z* 341.2 $[M-tBu+2H]^+$ and 397.2 $[M+H]^+$.

**General Procedure for the Synthesis of *N*-(6-imino-8,9-disubstituted-6,9-dihydro-1*H*-purin-1-aminium-2,2,2-trifluoroacetates (32-33).** *N*-(6-Imino-8,9-disubstituted-6,9-dihydro-1*H*-purin-1-yl)(tert-butoxy)formamide (**39-40**) (2.1 mmol) was dissolved in dichloromethane (15 mL) and trifluoroacetic acid (2.5 mL) was added. The mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in diethyl ether (3 mL). The resulting precipitate was filtered, washed with diethyl ether.

**9-Benzyl-6-imino-8-methyl-6,9-dihydro-1*H*-purin-1-aminium-2,2,2-trifluoroacetate (32).** Compound **32** (Y = 86%, 650 mg from 730 mg (2.1 mmol) of **39**) was isolated as a beige solid ; mp 195-197 °C. $^1$H NMR (DMSO, 300 MHz) δ 9.93 (s, 1H, OH, TFA), 9.05 (s, 1H), 8.61 (s, 1H), 7.39-7.31 (m, 3H), 7.23-7.21 (m, 2H), 6.56 (s, 2H), 5.47 (s, 2H), 2.52 (s, 3H). $^{13}$C NMR (DMSO, 75 MHz) δ 153.0 (C), 150.7 (C), 148.4 (CH), 147.1 (C), 135.5 (C), 128.9 (2CH), 128.0 (CH), 127.1 (2CH), 117.1 (C), 45.6 ($CH_2$), 14.0 ($CH_3$). LC-MS (ESI) *m/z* 255.1 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{13}H_{15}N_6^+$ 255.1353 ; found 255.1346.

**9-Benzyl-8-butyl-6-imino-6,9-dihydro-1*H*-purin-1-aminium-2,2,2-trifluoroacetate (33).** Compound **33** (Y = 68%, 105 mg from 150 mg (0.4 mmol) of **40**) was isolated as a beige solid ; mp 213-215 °C. $^1$H NMR (DMSO, 300 MHz) δ 9.89 (s, 1H, OH,TFA), 9.04 (s, 1H), 8.61

(s, 1H), 7.35-7.32 (m, 3H), 7.20-7.17 (m, 2H), 6.55 (s, 2H), 5.49 (s, 2H), 2.83 (t, 2H, *J* = 7.6 Hz), 1.63-1.53 (quint, 2H, *J* = 7.6 Hz), 1.35-1.23 (sex, 2H, *J* = 7.4 Hz), 0.80 (t, 3H, *J* = 7.4 Hz). $^{13}$C NMR (DMSO, 75 MHz) δ 155.4 (C), 151.3 (C), 148.3 (CH), 146.4 (C), 136.0 (C), 128.9 (2CH), 128.0 (CH), 126.9 (2CH), 117.8 (C), 45.5 ($CH_2$), 28.7 ($CH_2$), 26.7 ($CH_2$), 21.7 ($CH_2$), 13.6 ($CH_3$). LC-MS (ESI) *m/z* 297.2 $[M+H]^+$. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{21}N_6^+$ 297.1743 ; found 297.1750.

**3-Benzyl-2-methyl-3*H*-[1,2,4]triazolo[5,1-*i*]purine (48).**
Compound **48** (Y = 5%, 11 mg from 180 mg (0.8 mmol) of **1**) was isolated as a beige solid ; $^1$H NMR (DMSO, 300 MHz) δ 9.64 (s, 1H), 9.04 (s, 1H), 8.60 (s, 1H), 7.33-7.31 (m, 3H), 7.23-7.21 (m, 2H), 5.58 (s, 2H), 2.55 (s, 3H). LC-MS (ESI) *m/z* 265.1 $[M+H]^+$.

**3-Benzyl-2-butyl-3*H*-[1,2,4]triazolo[5,1-*i*]purine (49).**
Compound **49** (Y = 3%, 10 mg from 300 mg (1.2 mmol) of **2**) was isolated as a beige solid $^1$H NMR (DMSO, 300 MHz) δ 9.63 (s, 1H), 8.61 (s, 1H), 7.35-7.24 (m, 3H), 7.20-7.17 (m, 2H), 5.60 (s, 2H), 2.85 (t, 2H, *J* = 7.6 Hz), 1.65 (quint, 2H, *J* = 7.5 Hz), 1.31 (sex, 2H, *J* = 7.4 Hz), 0.82 (t, 3H, *J* = 7.3 Hz). LC-MS (ESI) *m/z* 307.2 $[M+H]^+$.

## ASSOCIATED CONTENT

### Supporting information

Copies of $^1$H and $^{13}$C NMR spectra for all new compounds (PDF).

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### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGEMENTS

We gratefully acknowledge the “Ecole Doctorale Biologie-Santé de Lille” for doctoral research allowance to Mélanie Bollier and the financial support of StartAIRR. The authors thank Dr. Audrey Hottin for assistance during the preparation of the manuscript.

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