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Efficient synthesis of purines by inverse electron-demand Diels–Alder reactions of 1-substituted-1*H*-imidazol-5-amines with 1,3,5-triazines

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ABSTRACT

The reaction of 1,3,5-triazine and 2,4,6-tri(trifluoromethyl)-1,3,5-triazine with in situ generated 1-substituted 5-amino-1*H*-imidazoles led to a set of functionalized purines. The developed practical route could serve as a fundament for the preparation of related ADA inhibitors.

1. Introduction

Purines constitute a naturally widely spread heterocyclic core and play a devastatingly important role in life cycles of human, flora and fauna. The purine derivatives adenine and guanine are important subunits of the nucleic acids DNA and RNA. Moreover, their *N*-ribosyl substituted derivatives adenosine and guanosine are present in the human body and represent a class of important enzyme target moieties.[1]

Adenosine deaminase (or simply ADA) is a zinc metalloenzyme, which catalyzes the deamination of adenosine to inosine. Therefore, it plays a key role in the adenosine metabolism and in a number of physiological processes (e.g., the regulation of ion-channel activity, the inhibition of platelet aggregation and the inactivation of eosinophile migration). Moreover, it was shown, that ADA functional disorders affect on the differentiation and maturation of the lymphoid system leading to a severe combined immunodeficiency disease (SCID), due to the decreasing production of immunoglobulins.[2] Numerous recent studies have been directed towards ADA inhibition based on its exuberant reproduction which is observed in case of oncologic diseases,[3] tuberculosis,[4,8b] Parkinson's disease,[5] bacterial meningitis,[6] viral hepatitis[7] and auto immune diseases including sarcoidosis and rheumatoid arthritis.[8]

In recent years, mimicking the transition state of enzymes has become the dominating strategy for enzyme inhibition. Being structurally similar to the adenosine transition state, pentostatin, coformycin and their analogues show an almost irreversible binding with the ADA receptor[9] (Fig. 1). Pyrimidine derivatives, like ZEB or tetrahydrouridine, are promising inhibitors of cytidine deaminase[10] (Fig. 1). The commercially available drug nebularine is a bright example of an adenosine-like nucleoside, which mimics the ADA transition state through covalent hydration of an aglycone ring.[11]

The mechanism of enzymatic adenosine deamination, which leads to inosine formation,[12] is assumed to involve nucleophilic attack of water on position 6 of the purine ring followed by stereospecific hydroxyl group addition[13] (Scheme 1). In our concept, the enthalpy of covalent hydration of the adenosine-like transition state mimetic could be decreased by introducing an electron-withdrawing substituent into its heterocyclic core. As a promising candidate we have considered the CF_3-group, since it has proven to be isosterically close to the NH_2-functionality. This should additionally decrease the enthalpy of the activated complex with the enzyme leading to a more tightly binding to the receptor.

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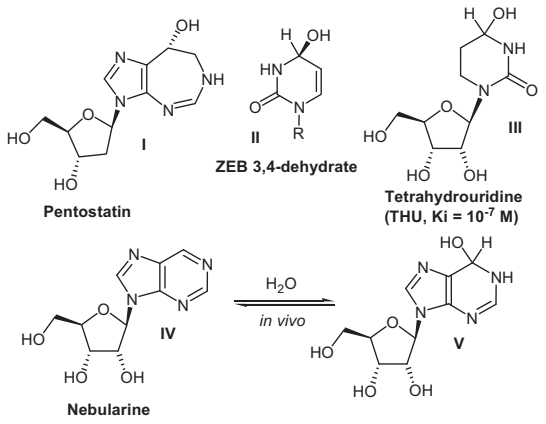
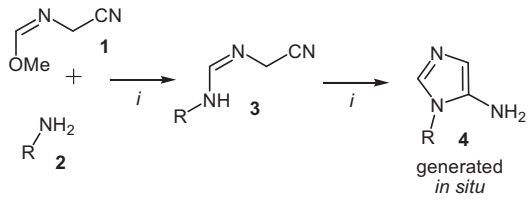


Fig. 1. Potent ADA and CDA inhibitors.



Scheme 1. Reagents and conditions: (i) CH_2Cl_2, under argon atmosphere, reflux, 2 h.

Continuing our research in the field of designing potential ADA inhibitors, we focused our attention on the development of a practical route to trifluoromethyl substituted purines as the aglycone moiety of the target structures. Bearing two strong electron-withdrawing groups at positions 2 and 6 of the purine ring, such synthones could easily interact with water in vivo under enzyme-catalyzed conditions, due to the higher electron deficiency in comparison with the non-fluorinated adenosine moiety. Therefore, they could be considered as highly efficient adenosine mimetics (Fig. 2).

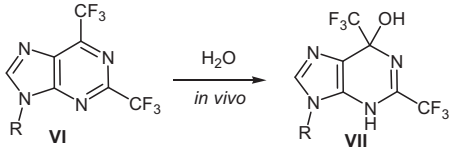


Fig. 2. 6-Acceptor-substituted 3*H*-imidazo[4,5-*b*]pyridines as new potential ADA inhibitors.

At the same time, it is well known from the literature that the attachment of fluorine-containing functional groups to biomolecules often results in the development of new physiologically active compounds.[14]

Recently, Iaroshenko's laboratory has developed a synthetic approach to several 2- or 6-CF_3-substituted purine isosteres and their correspondent nucleosides.[15]

From the other side, besides the goal of mechanism-based design of ADA-inhibitors mimicking a putative transition state of adenosine deamination in vivo, we have concentrated our attention on the investigation of the scope and limitations of the assembly of 9-substituted-2,6-bis(trifluoromethyl)-9*H*-purines using amines as the source of introducing the 9-substituent. We follow the inverse electron-demand Diels–Alder strategy starting from in situ generated 1-substituted-1*H*-imidazol-5-amines and 2,4,6-tris(trifluoromethyl)-1,3,5-triazine. Herein, the extension of the scope of this study is communicated.

2. Results and discussion

Carrying out a careful study of possible syntheses of 2,6-disubstituted purines, we have revealed a versatile route to six-membered heterocycles, based on the inverse electron-demand Diels–Alder cycloaddition, which has proven to be an efficient method for the synthesis of fused pyridines and pyrimidines. In this context, numerous studies directed to unknown cycloaddition reactions have been carried out. The reactions afforded a series of substances starting with various azadienes, such as 1,2-diazines,[16] 1,2,4-triazines,[17] 1,2,4,5-tetrazines[18] and 1,3,5-triazines.[19] Later on, the method was extended from the employment of substituted alkenes, cycloalkenes and naphthalenes as the dienophiles to the application of electron-rich aminoheterocycles, like 2-aminopyrroles,[20a] 5-amino-1*H*-pyrazoles,[20b,c] 1-substituted 5-amino-1*H*-imidazoles[21] and aminothiophenes[22] The described route provides an efficient pathway to the synthesis of 2,6-disubstituted purines.

Guided by our previous successful experience,[23] we have decided to use 1-substituted-5-amino-1*H*-imidazoles **4**, which were generated in situ following our developed procedure, as dienophiles in inverse electron-demand Diels–Alder reactions with the set of electron-deficient polyazines **5**–**7** (Fig. 3). Hereby we are communicating this later study.

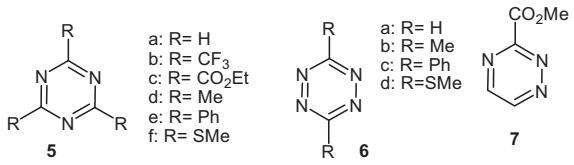
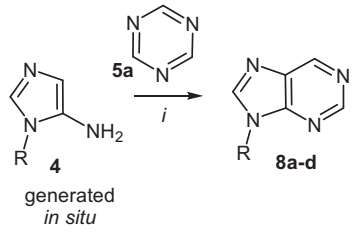


Fig. 3. Set of the azadienes tested.

The reaction of primary aliphatic amines with methyl-*N*-cyanomethyl-formimidate (**1**), via nucleophilic substitution and subsequent cyclization, resulted in the formation of the required substrates (Scheme 1). The reaction was carried out in dichloromethane under inert atmosphere. Our preliminary studies were focused on the interaction of the 5-amino-1*H*-imidazoles with unsubstituted 1,3,5-triazine **5a**.

The first attempts to obtain a simple 9-subtituted purine by addition of an equimolar amount of the corresponding azadiene **5a** to the reaction mixture with subsequent reflux for 5 h resulted in formation of the desired product in only 10% yield (Scheme 2). Posterior improvements of the procedure (the aminoheterocycle was generated in 20% excess and the reaction time was increased to 10 h, the addition of the triazine was conducted at 0 °C) resulted in an increased yield of **8** up to 40%, which is, however, still rather low. Our efforts, which resulted in the synthesis of a small number of 9-alkyl-purines **8** (Table 1), led to the conclusion that the chosen method is insufficient in case of 1,3,5-triazine.



Scheme 2. Reagents and conditions: (i) CH_2Cl_2, under argon atmosphere, reflux, 10 h.

Table 1
Yields of 9*H*-purines **8**

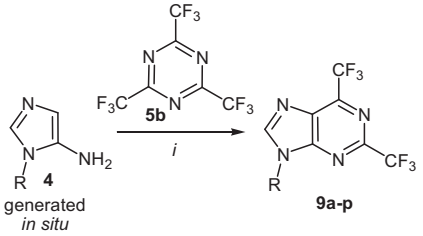
8	R	% (**8**)[a]
a	*t*-Bu	37
b	4-Methoxybenzyl	27
c	2-(Chloro)benzyl	43
d	2-(2-Chlorophenyl)ethyl	40

[a] Yields of isolated products.

At the same time triazine **5c** was reacted with **4** delivering, after protracting reflux for 7–10 h corresponding purine derivatives, which were detected by GC/MS. However reaction has been accompanied by the formation of mixture of many unidentified by-products as well as products of 1-substituted-5-amino-1*H*-imidazoles decomposition. As a result, we could not isolate products in pure form. In contrary, by using the derivatives **5d**–**f** we could not effort even a heterocyclization; addition of TMSO-triflate and some Lewis acids as well as using different solvents (CH_3CN, DMF and DMSO) and increasing temperature did not make any positive influence on the reaction.

In the following, we concentrated our attempts on the use of 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**5b**) as the reactant. Being by far more electron-deficient than its unsubstituted analogue, it represents a more promising substrate than parent 1,3,5-triazine **5a**. In fact, we have found that the application of **5b** concluded in high yields and short reaction times.

The interaction between the 1-substituted-5-amino-1*H*-imidazole **4** with triazine **5b** resulted, in the first attempt, in the formation of the desired product **9a** in 54% yield after reflux for only for 2 h (Scheme 3). As the reaction was observed to be exothermic, consequently, the reaction mixture was cooled to 0 °C before the azadiene was added. This resulted in an increase of the yield (Table 2). Following these conditions, a number of 2,6-bis(trifluoromethyl) purines **9a**–**p** were prepared in excellent yields of 71–93%.



Scheme 3. Reagents and conditions: (i) CH_2Cl_2, under argon atmosphere, reflux, 2 h.

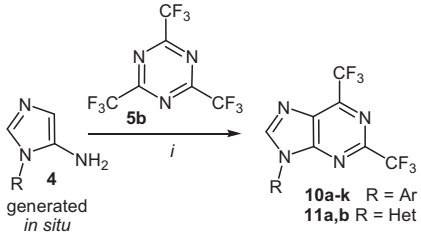
Table 2
Yields of 2,6-bis(trifluoromethyl)-9*H*-purines **9**

9	R	% (**9**)[a]
a	*t*-Bu	87
b	Allyl	68
c	*n*-Heptyl	68
d	Cyclopropyl	83
e	Cyclohexyl	90
f	*N*,*N*-Dimethyethyl	71
g	*N*,*N*-Diethyethyl	90
h	Morpholyl	48
i	3-Morpholinopropyl	90
j	4-Metylpiperazin-1-yl	73
k	Benzyl	75
l	(*S*)-1-Phenylethyl	75
m	Phenylethyl	68
n	2-Methoxyphenylethyl	77
o	3,4-Dimethoxyphenylethyl	93
p	Pyridin-4-yl-methyl	93

[a] Yields of isolated products.

Concerning azines **6** and methyl 1,2,4-triazine-3-carboxylate **7**, these compounds were not prone to react with **4** generate in situ. After 10 h reflux we have observed only starting azines in the reaction mixture without any traces of possible products. Afterwards **7** was completely recovered from reaction mixtures. It is known that 1,2,4,5-tetrazines are active azadienes in a inverse electron-demand Diels–Alder reaction. We have consider **6** as promising starting materials for the synthesis of an important from the pharmacological point of view 1-substituted-1*H*-imidazo[4,5-*d*] pyridazine heterocyclic scaffold. However, to our grate disappointment interaction of compounds **6a**–**d** with **4** experienced a failure.

It is important to be noted that the reaction could be applied only to aliphatic amines, since aromatic and heteroaromatic amines did not undergo, under our conditions, a reaction with **1**. Therefore, we were searching for suitable reaction conditions to succeed in the synthesis of purines bearing an aryl or heteroaryl moiety located at position 9 of the purine core. The addition of a catalytic amount of TMSO-triflate proved to be the crucial point to achieve the formation of the 5-amino-imidazole ring in the case of 9-aryl or heteroaryl derivatives. The subsequent reaction of the latter with triazine **5b** allowed the synthesis of 9-aryl-purines **10** as well as 9-heteroaryl-purines **11** (Scheme 4, Table 3).



Scheme 4. Reagents and conditions: (i) CH_2Cl_2, TMSOTf, under argon atmosphere, reflux, 10 h.

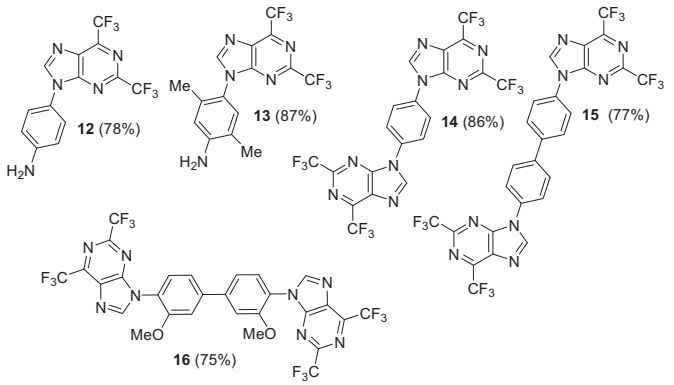
Table 3
Yields of 2,6-bis(trifluoromethyl)-9*H*-purines **10** and **11**

	R	%[a]
10a	3-Methoxyphenyl	70
10b	3,4-Dimethoxyphenyl	72
10c	3,5-Dimethoxyphenyl	78
10d	2,4-Dimethoxyphenyl	76
10e	3,4,5-Trimethoxyphenyl	65
10f	4-Ethoxyphenyl	62
10g	2,4,6-Trimethylphenyl	83
10h	3-Bromphenyl	67
10i	4-Bromphenyl	71
10j	2,6-Dibromo-4-methylphenyl	45
10k	4-*N*,*N*-Diethylphenyl	70
11a	Thiazol-2-yl	61
11b	Pyridin-2-yl	40

[a] Yields of isolated products.

We also studied the reaction of diamines with 1 and 2 equiv of **1** (dichloromethane, reflux, argon atmosphere), which resulted in the in situ formation of the correspondent 5-amino-imidazoles as well as the 5-amino-imidazoles linked by a bridge. These experiments show that the assembly of fluorinated purines **12**–**16** containing two domains, suitable for the application in the field of supramolecular chemistry, is possible. In the same time when the ratio amine to amidate was 1:1 we have observed exclusively the formation of products **12** and **13** (Scheme 5).

The constitution of the synthesized purines was mainly established by 1D and 2D NMR-methods. Moreover, we have independently established the structure of 2,6-bis(trifluoromethyl)-9*H*-purines **9i** and **9o** by X-ray single crystal structure analysis



Scheme 5. Purines obtained starting with aromatic diamines.

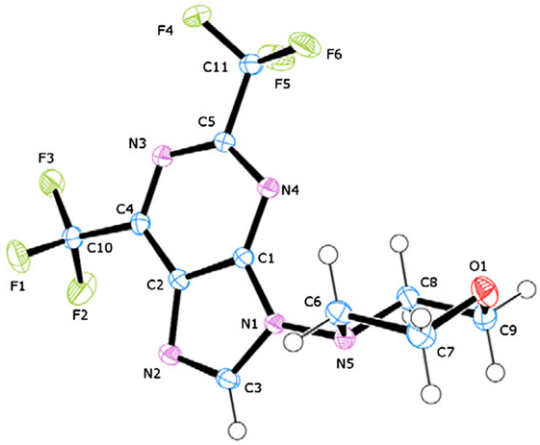


Fig. 4. Molecular structure of compound **9i**.

(Figs. 4 and 5).[24] In a case of be-purine **14** linked by phenyl ring we have also succeed to grow the crystal, which fully confirms its structure (Fig. 6).[24]

The product formation can be explained by a partially proven mechanism,[20b,21] which includes the formation of the zwitterion **B**, followed by a cascade of nucleophilic attack of nitrogen atom 4 on position 5 of the imidazole, C–N bond gap and cleavage of ammonia (intermediates **C**, **D**) resulting in purine formation. The formation of a charge transfer complex **A** as the initial step is theoretically possible (Scheme 6).

In conclusion, we have expanded the scope of 5-aminoimidazoles in inverse electron-demand Diels–Alder reaction and applied it for the synthesis of 9-functionalized purines and 2,6-bis(trifluoromethyl)purines. The procedure described provides a useful tool for the development of potential ADA

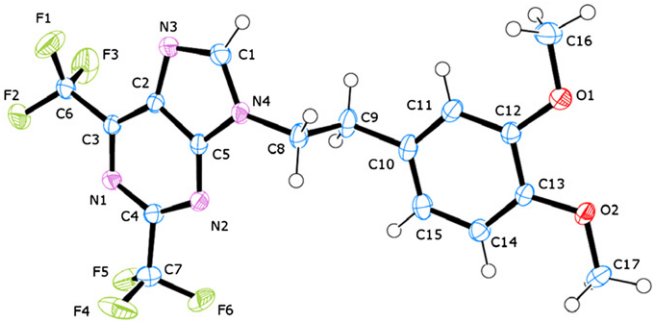


Fig. 5. Molecular structure of compound **9o**.

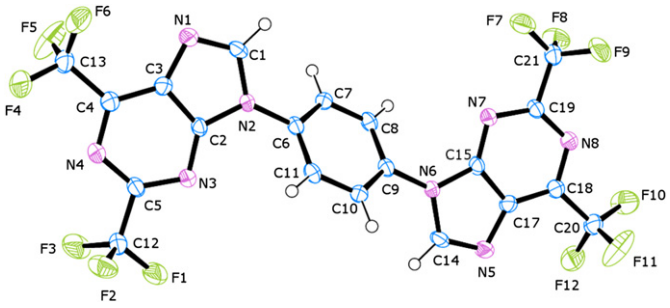
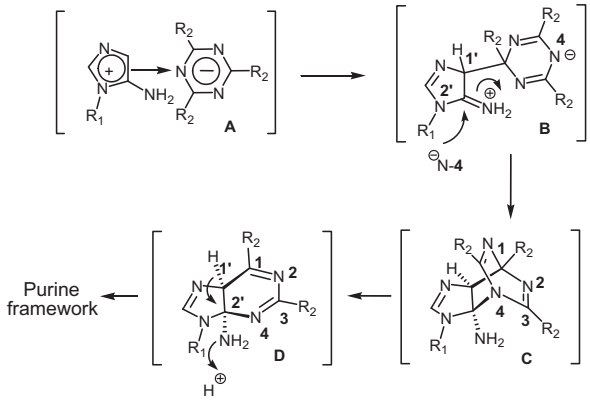


Fig. 6. Molecular structure of compound **14**.



Scheme 6. Putative mechanism.

inhibitors. The biological evaluation of the products prepared is currently under investigation.

3. Experimental section

3.1. General comments

Chemical yields refer to pure isolated substances. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker DPX-300 spectrometer. Chemical shifts of the ^{1}H and ^{13}C NMR are reported in parts per million using the solvent internal standard ($CDCl_3$ 7.26 ppm and 77.0 ppm, DMSO-d_6 2.49 ppm and 39.7 ppm). IR spectra were recorded on a Perkin–Elmer FT IR 1600 spectrometer for samples in KBr discs. Mass spectra were obtained on a Hewlett–Packard HP GC/MS 5890/5972 instrument (EI, 70 eV) by GC inlet or on an MX-1321 instrument (EI, 70 eV) by direct inlet. Elemental analyses were carried out at the Microanalytical laboratory of the University of Rostock Germany. Melting points are uncorrected. The solvents were purchased directly from ACROS and used without further purification. Analytical thin layer chromatography was performed on 0.20 mm 60 Å silica gel plates. Column chromatography was performed using 60 Å silica gel (60–200 mesh).

3.2. General procedure for the synthesis of purines 8–16

To a Schlenck flask, set with reflux, CH_2Cl_2 (2.5 mL), primary amine **2** (0.00345 mol) and methyl *N*-(cyanomethyl)-formimidate **1** (0.338 g, 0.00345 mol) were added under an argon atmosphere at rt. The reaction mixture was kept under reflux and after that, the mixture was cooled down to rt, and then to 0 °C on an ice bath. Afterwards corresponding triazine (0.00345 mol) was added, and the mixture continued to stir at the same temperature for 15–20 min and then refluxed. After the product formation is completed, the solvent was evaporated to dryness and the residue

was purified by column chromatography (EtOAc) to give purines. In a case of all aromatic and heteroaromatic amines, after the addition of triazine at 0 °C, catalytic amount of TMSOTf (about three drops) was added. For the synthesis of purines **8** the 20% excess of **4** was generated.

*3.2.1. 9-tert-Butyl-9H-purine (**8a**).* White solid isolated by column chromatography (heptane/EtOAc, 3:7); mp 114–116 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.80 (s, 9H, $3CH_3$), 8.14 (s, 1H, CH), 8.92 (s, 1H, CH), 9.09 (s, 1H, NC*H*N). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=28.91 ($3CH_3$), 57.8 (C), 135.2 (C), 142.9 (C), 148.6 (C), 151.5 (C), 151.6 (NC*H*N). MS (GC, 70eV): *m*/*z* (%)=176 (M^+, 49), 121 (100), 120 (39), 93 (11), 41 (11). HRMS (EI): calcd for $C_9H_{12}N_4$ (M^+) 176.10565, found 176.105568. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3268 (w), 3102 (w), 3075 (w), 3034 (w), 2976 (w), 2915 (w), 1867 (w), 1731 (w), 1681 (w), 1593 (m), 1568 (m), 1519 (w), 1492 (m), 1463 (w), 1398 (m), 1362 (m), 1344 (m), 1298 (m), 1253 (m), 1225 (m), 1179 (m), 1105 (m), 1031 (w), 961 (w), 911 (m), 841 (w), 792 (m), 641 (m), 621 (m), 549 (m).

*3.2.2. 9-(4-Methoxybenzyl)-9H-purine (**8b**).* White solid isolated by column chromatography (2-propanol/EtOAc, 3:2); mp 86–88 °C: ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.72 (s, 3H, CH_3), 5.31 (s, 2H, CH_2), 6.80–6.83 (d, 2H, ^3J=8.6 Hz, 2× CH_{Ar}), 7.20–7.22 (d, 2H, ^3J=8.6 Hz, $2CH_{Ar}$), 7.97(s, 1H, CH), 8.95 (s, 1H, CH), 9.07 (s, 1H, NC*H*N). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=46.8 (CH_3), 55.3 (CH_2), 114.5 (CH_{Ar}), 126.9 (C), 129.5 (CH_{Ar}), 134.0 (C), 144.9 (C), 148.6 (CH), 151.3 (C), 152.7 (CH), 159.8 (NC*H*N). MS (GC, 70eV): *m*/*z* (%)=240 (M^+, 80), 225 (10), 121 (100), 78 (12). HRMS (EI): calcd for $C_{13}H_{12}ON_4$ (M^+) 240.10056, found 240.100832. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2993 (w), 2953 (w), 2833 (w), 1900 (w), 1655 (m), 1613 (m), 1577 (s), 1513 (s), 1452 (m), 1438 (m), 1410 (m), 1374 (w), 1338 (m), 1302 (s), 1240 (s), 1175 (s), 1158 (s), 1103 (m), 1028 (s), 985 (w), 933 (m), 895 (m), 823 (m), 789 (s), 763 (s), 704 (m), 646 (s), 566 (s).

*3.2.3. 9-(2-Chlorobenzyl)-9H-purine (**8c**).* White solid isolated by column chromatography (heptane/EtOAc, 7:3); mp 102–104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.37 (s, 2H, CH_2), 7.02–7.25 (m, 4H, 4× CH_{Ar}), 7.97 (s, 1H, CH), 8.81 (s, 1H, CH), 8.95 (s, 1H, NC*H*N). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=44.8 (CH_2), 127.5 (CH), 130.0 (CH), 130.2 (CH), 130.5 (CH), 132.4 (C), 133.6 (C), 133.8 (C), 145.2 (CH), 148.6 (CH), 151.4 (C), 152.8 (NC*H*N). MS (GC, 70eV): *m*/*z* (%)=244 (M^+, 10), 209 (100), 125 (12). ESI (M+H^+): calcd for $C_{12}H_{10}ClN_4$ (M+H^+) 245.05885, found 245.05898. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3067 (w), 2986 (w), 2919 (w), 1657 (w), 1592 (m), 1580 (m), 1496 (m), 1427 (m), 1348 (m), 1340 (m), 1244 (w), 1162 (m), 1095 (w), 1039 (m), 943 (w), 896 (m), 813 (w), 788 (m), 751 (s), 690 (m), 635 (s), 556 (m).

*3.2.4. 9-(2-Chlorophenethyl)-9H-purine (**8d**).* Light yellow solid isolated by column chromatography (heptane/EtOAc, 10:1); mp 130–132 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.33 (t, 2H, ^3J=6.9 Hz, CH_2), 4.57 (t, 2H, ^3J=6.9 Hz, CH_2), 6.95 (dd, 1H, J=6.0, 3.0 Hz, CH_{Ar}), 7.04–7.10 (m, 1H, CH_{Ar}), 7.14–7.25 (m, 1H, CH_{Ar}), 7.35 (dd, 1H, J=9.0, 6.0 Hz, CH_{Ar}), 7.69 (s, 1H, CH), 8.98 (s, 1H, CH), 9.11 (s, 1H, NC*H*N). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=32.9 (CH_2), 42.3 (CH_2), 126.2 (CH), 127.8 (CH), 128.8 (CH), 130.0 (CH), 132.9 (C), 133.0 (C), 136.6 (C), 144.2 (CH), 147.6 (CH), 150.3 (C), 151.6 (NC*H*N). MS (GC, 70eV): *m*/*z* (%)= 258 (M^+, 10), 223 (100), 140 (11), 138 (33), 103 (10). ESI (M+H^+): calcd for $C_{13}H_{12}ClN_4$ (M+H^+) 259.0745, found 259.0749. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3080 (w), 3023 (w), 2928 (w), 1593 (w), 1578 (m), 1539 (w), 1497 (w), 1442 (w), 1408 (m), 1363 (w), 1345 (m), 1302 (m), 1260 (w), 1226 (m), 1199 (m), 1151 (w), 1102 (m), 1094 (m), 1050 (m), 1021 (w), 971 (w), 918 (w), 858 (w), 793 (m), 741 (m), 678 (m), 638 (m), 609 (w), 546 (m).

*3.2.5. 9-tert-Butyl-2,6-bis(trifluoromethyl)-9H-purine (**9a**).* Light yellow solid isolated by column chromatography (heptane/EtOAc, 7:3); mp 89–91 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.88 (s, 9H, $3CH_3$), 8.48 (s, 1H, NC*H*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.6, −66.0. ^{13}C NMR (300 MHz, $CDCl_3$): δ=28.9 ($3CH_3$), 59.6 (C), 119.5 (q, J=274.8 Hz, CCF_3), 120.3 (q, J=274.8 Hz, CCF_3), 132.3 (C), 145.6 (q, J=37.7 Hz, CCF_3), 147.5 (C), 148.7 (q, J=37.7 Hz, CCF_3), 154.2 (NC*H*N). MS (GC, 70eV): *m*/*z* (%)=312 (M^+, 51), 297 (11), 277 (18), 257 (100), 237 (47), 57 (65), 56 (28). 41 (26). HRMS (EI): calcd for $C_{11}H_{10}N_4F_6$ (M^+) 312.08042, found 312.080675. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2983 (w), 2941 (w), 2879 (w), 1792 (w), 1733 (w), 1667 (w), 1584 (w), 1485 (w), 1426 (w), 1397 (w), 1332 (w), 1284 (w), 1206 (w), 1139 (m), 1077 (w), 1031 (w), 951 (w), 889 (w), 819 (w), 738 (w), 663 (m), 614 (w), 549 (w).

*3.2.6. 9-Allyl-2,6-bis(trifluoromethyl)-9H-purine (**9b**).* Colourless oil isolated by column chromatography (heptane/EtOAc, 3:7); ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.03 (d, 2H, J=6.0 Hz, NCH_2CHCH_2), 5.34–5.44 (m, 2H, NCH_2CHCH_2), 6.00–6.13 (m, 1H, NCH_2CHCH_2), 8.46 (s, 1H, NC*H*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.6, −66.0. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=45.8 (CH_2), 118.4 (q, J=274.5 Hz, CCF_3), 119.3 (q, J=274.5 Hz, CCF_3), 120.2 ($2CH_2$), 129.0 (CH), 130.1 (C), 144.4 (q, J=38.4 Hz, CCF_3), 148.9 (q, J=38.4 Hz, CCF_3), 148.0 (C), 153.1 (NC*H*N). MS (GC, 70eV): *m*/*z* (%)=296 (M^+, 100), 295 (57), 277 (25), 276 (11), 275 (19), 269 (16), 268 (10), 256 (11), 249 (11), 237 (13), 69 (16), 41 (14). ESI: calcd for $C_{10}H_7N_4F_6$ (M+H^+) 297.0569, found 297.0573. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3092 (w), 2996 (w), 2933 (w), 1748 (w), 1647 (w), 1598 (w), 1504 (w), 1455 (w), 1403 (m), 1361 (w), 1304 (m), 1270 (s), 1219 (s), 1127 (s), 1056 (w), 990 (w), 962 (m), 915 (w), 888 (m), 819 (w), 757 (w), 736 (m), 661 (s), 640 (w), 549 (w).

*3.2.7. 2,6-Bis(trifluoromethyl)-9-heptyl-9H-purine (**9c**).* Light yellow oil isolated by column chromatography (heptane/EtOAc, 7:3); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.86 (t, 3H, J=6.7 Hz, CH_3), 1.24–1.36 (m, 8H, $4CH_2$), 1.92–2.02 (m, 8H, $4CH_2$), 4.40 (t, 4H, J=6.9 Hz, CH_2), 8.40 (s, 1H, NC*H*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.5, −66.0. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=13.9 (CH_3), 22.4, 26.5, 28.5, 29.7, 31.5, 44.7 (CH_2), 119.5 (q, J=276.1 Hz, CCF_3), 120.2 (q, J=276.2 Hz, CCF_3), 131.1 (C), 145.5 (q, J=38.0 Hz, CCF_3), 149.5 (C), 149.7 (q, J=38.0 Hz, CCF_3), 154.2 (NC*H*N). MS (GC, 70eV): *m*/*z* (%)=355 (15), 354 (M^+, 100), 353 (24), 335 (26), 334 (32), 326 (12), 325 (12), 312 (17), 311 (43), 298 (15), 297 (41), 292 (10), 285 (13), 283 (57), 270 (84), 269 (70), 257 (82), 256 (37), 250 (36), 249 (18), 237 (39), 69 (26), 55 (37), 41 (38), 29 (15). ESI: calcd for $C_{14}H_{17}N_4F_6$ (M+H^+) 355.13519, found 355.13492. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3089 (w), 2957 (w), 2860 (w), 1599 (w), 1505 (w), 1454 (w), 1404 (w), 1307 (m), 1271 (m), 1218 (s), 1140 (s), 1100 (m), 956 (m), 888 (m), 819 (w), 736 (m), 658 (m), 577 (w).

*3.2.8. 9-Cyclopropyl-2,6-bis(trifluoromethyl)-9H-purine (**9d**).* White crystalline isolated by column chromatography (heptane/EtOAc, 3:7); mp 86–88 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.23–1.36 (m, 4H, $2CH_2$), 3.58–3.65 (m, 1H, CH), 8.41 (s, 1H, NC*H*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.5, −66.0. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=6.2 ($2CH_2$), 26.1 (CH), 119.5 (q, J=277.0 Hz, CCF_3), 120.2 (q, J=277.0 Hz, CCF_3), 131.4 (C), 146.1 (q, J=38.2 Hz, CCF_3), 149.9 (q, J=38.2 Hz, CCF_3), 150.2 (C), 155.2 (NC*H*N). MS (GC, 70eV): *m*/*z* (%)= 296 (M^+, 100), 295 (46), 277 (29), 276 (18), 275 (21), 269 (21), 268 (30), 249 (21), 248 (24), 119 (10), 100 (10), 69 (28), 41 (12), 39 (12). HRMS (EI): calcd for $C_{10}H_6N_4F_6$ (M^+) 296.04912, found 296.049152. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3110 (w), 3078 (w), 1860 (w), 1598 (w), 1498 (w), 1450 (w), 1402 (m), 1371 (w), 1330 (m), 1276 (s), 1225 (s), 1186 (s), 1131 (s), 1067 (s), 1034 (m), 958 (s), 933 (m), 890 (m), 819 (m), 784 (w), 737 (s), 670 (m), 637 (s), 558 (w), 530 (w).

*3.2.9. 9-Cyclohexyl-2,6-bis(trifluoromethyl)-9H-purine (**9e**).* White solid isolated by column chromatography (heptane/EtOAc, 7:3); mp 88–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.32–2.02 (m, 8H, $4CH_2$), 2.20–2.25 (m, 2H, CH_2), 4.62–4.70 (m, 1H, CH), 8.46 (s, 1H, NC*H*N).

^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.4, −66.0. ^{13}C NMR (300 MHz, acetone-d_6): δ=20.6 (CH_2), 21.0 ($2CH_2$), 28.7 ($2CH_2$), 51.4 (CH), 115.2 (q, J=275.4 Hz, CCF_3), 116.1 (q, J=275.4 Hz, CCF_3), 127.0 (C), 140.9 (q, J=37.4 Hz, CCF_3), 143.5 (C), 145.0 (q, J=37.4 Hz, CCF_3), 149.4 (N*CH*N). MS (GC, 70eV): m/z (%)=338 (M^+, 23), 319 (10), 257 (100), 237 (28), 82 (14), 67 (25). ESI: calcd for $C_{13}H_{13}N_4F_6$ ($M+H^+$) 339.10389, found 339.10372. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3097 (w), 2957 (w), 2868 (w), 1597 (w), 1493 (w), 1450 (w), 1398 (w), 1350 (w), 1317 (w), 1280 (w), 1221 (w), 1131 (w), 1028 (w), 952 (w), 889 (w), 819 (w), 761 (w), 714 (w), 659 (w), 581 (w), 529 (w).

*3.2.10. 2-(2,6-Bis(trifluoromethyl)-9H-purin-9-yl)-N,N-dimethylethanamine (**9f**).* Light yellow oil isolated by column chromatography (2-propanol/EtOAc, 2:8); ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.30 (s, 6H, $2CH_3$), 2.77 (t, 4H, J=5.6 Hz, CH_2), 4.47 (t, 2H, J=5.6 Hz, CH_2), 8.61 (s, 1H, N*CH*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.5, −65.9. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=41.2 (CH_2), 44.0 ($2CH_3$), 57.0 (CH_2), 115.8 (q, J=276.7 Hz, CCF_3), 116.6 (q, J=276.6 Hz, CCF_3), 129.9 (C), 143.9 (q, J=38.2 Hz, CCF_3), 148.3 (q, J=38.2 Hz, CCF_3), 148.9 (C), 149.7 (N*CH*N). MS (GC, 70eV): m/z (%)=327 (M^+, 10), 71 (14), 59 (100), 42 (10). ESI: calcd for $C_{11}H_{12}N_5F_6$ ($M+H^+$) 328.09914, found 328.09995. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3090 (w), 2952 (w), 2866 (w), 2779 (w), 1598 (w), 1505 (w), 1454 (w), 1403 (w), 1301 (m), 1271 (s), 1217 (s), 1132 (m), 1059 (m), 971 (m), 929 (m), 888 (s), 818 (m), 736 (s), 655 (s), 575 (w).

*3.2.11. 2-(2,6-Bis(trifluoromethyl)-9H-purin-9-yl)-N,N-diethylethanamine (**9g**).* Yellow oil isolated by column chromatography (2-propanol/EtOAc, 2:8); ^{1}H NMR (300 MHz, DMSO): δ=0.75 (t, 6H, J=6.9 Hz, $2CH_3$), 2.41−2.51 (m, 4H, $2NCH_2CH_3$), 2.82 (t, 2H, J=5.9 Hz, NCH_2CH_3N), 4.46 (t, 2H, J=5.9 Hz, NCH_2CH_3N), 9.09 (s, 1H, N*CH*N). ^{19}F NMR (300 MHz, DMSO): δ= −67.4, −64.9. ^{13}C NMR (75.4 MHz, DMSO): δ=11.5 ($2CH_3$), 42.4 (NCH_2CH_3N), 46.1 (CH_2NCH_2), 51.0 (NCH_2CH_2N), 119.5 (q, J=275.0 Hz, CCF_3), 120.3 (q, J=275.0 Hz, CCF_3), 131.0 (C), 142.4 (q, J=37.1 Hz, CCF_3), 147.3 (q, J=37.1 Hz, CCF_3), 153.1 (C), 154.7 (N*CH*N). MS (GC, 70eV): m/z (%)=355 (M^+, 10), 340 (10), 86 (100). ESI: calcd for $C_{13}H_{16}N_5F_6$ ($M+H^+$) 356.13044, found 356.13129. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2973 (w), 2939 (w), 2819 (w), 1598 (w), 1598 (w), 1505 (m), 1452 (m), 1403 (m), 1363 (w), 1301 (m), 1269 (s), 1201 (s), 1134 (s), 1068 (m), 1010 (w), 965 (m), 933 (m), 888 (s), 818 (w), 736 (m), 678 (w), 638 (s), 573 (w).

*3.2.12. 2,6-Bis(trifluoromethyl)-9-morpholino-9H-purine (**9h**).* White crystalline isolated by column chromatography (heptane/EtOAc, 2:8); mp 105−107 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.64 (t, 4H, J=4.7 Hz, $2CH_2$), 3.94 (t, 4H, J=4.7 Hz, $2CH_2$), 8.48 (s, 1H, N*CH*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.5, −65.9. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=53.7 (CH_2), 65.7 (CH_2), 116.3 (q, J=272.0 Hz, CCF_3), 118.3 (q, J=272.0 Hz, CCF_3), 129.2 (C), 145.2 (q, J=38.5 Hz, CCF_3), 148.2 (q, J=38.4 Hz, CCF_3), 148.9, 151.9 (N*CH*N). MS (GC, 70eV): m/z (%)=341 (M^+, 10), 322 (39), 284 (54), 264 (27), 257 (29), 256 (49), 237 (23), 236 (78), 209 (14), 86 (12), 85 (97), 69 (32), 56 (25), 55 (100), 42 (11). ESI: calcd for $C_{11}H_{10}ON_5F_6$ ($M+H^+$) 342.07841, found 342.107838. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3112 (w), 2988 (w), 2918 (w), 2875 (w), 1824 (w), 1728 (w), 1593 (w), 1505 (w), 1469 (w), 1420 (w), 1386 (w), 1330 (w), 1301 (m), 1274 (m), 1229 (s), 1204 (s), 1138 (s), 1104 (s), 1045 (m), 967 (w), 946 (m), 899 (m), 845 (w), 817 (w), 743 (w), 727 (m), 659 (s), 636 (s), 567 (w), 528 (m).

*3.2.13. 2,6-Bis(trifluoromethyl)-9-(3-morpholinopropyl)-9H-purine (**9i**).* Yellow oil isolated by column chromatography (2-propanol/EtOAc, 3:7); ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.07−2.16 (p, 2H, CH_2CHCH_2), 2.30−237 (m, 6H, $3CH_2$), 3.62 (t, 4H, J=4.7 Hz, CH_2CHCH_2), 4.52 (t, 2H, J=6.4 Hz, CH_2), 8.46 (s, 1H, N*CH*N). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=26.1 (CH_2), 43.7 (CH_2), 54.2 ($2CH_2$), 56.1 (CH_2), 67.2 ($2CH_2$), 120.9 (q, J=274.8 Hz, CCF_3), 121.5 (q, J=274.8 Hz, CCF_3), 132.7 (C), 144.4 (q, ^2J=41.02 Hz, CCF_3), 149.2 (q, J=41.02 Hz, CCF_3), 153.3 (C), 156.1 (N*CH*N). ^{19}F NMR (300 MHz, $CDCl_3$): −68.5, −66.0. MS (GC, 70eV): m/z (%)=384 (10), 383 (M^+, 11), 340 (13), 100 (100), 56 (12). HRMS (EI): calcd for $C_{14}H_{15}ON_5F_6$ (M^+) 383.11753, found 383.118385. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3090 (w), 2958 (w), 2894 (w), 2817 (w), 1599 (w), 1506 (w), 1450 (w), 1404 (w), 1358 (w), 1306 (m), 1273 (m), 1219 (m), 1132 (s), 1068 (m), 1005 (w), 953 (m), 888 (m), 817 (w), 736 (m), 657 (m), 574 (w).

*3.2.14. 2,6-Bis(trifluoromethyl)-9-(4-methylpiperazin-1-yl)-9H-purine (**9j**).* White crystalline isolated by column chromatography (heptane/EtOAc, 10:1); mp 174−176 °C. ^{1}H NMR (300 MHz, DMSO): δ=2.29 (s, 3H, CH_3), 2.51 (t, 4H, J=61.8 Hz, $2CH_2$), 3.50 (s, 4H, $2CH_2$), 9.37 (s, 1H, N*CH*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −67.1, −64.7. ^{13}C NMR (100.6 MHz, acetone-d_6): δ=45.9 (CH_3), 55.0 ($2CH_2$), 55.6 ($2CH_2$), 118.0 (q, J=275.1 Hz, CCF_3), 118.8 (q, J=275.1 Hz, CCF_3), 131.6 (C), 145.1 (q, J=73.2 Hz, CCF_3), 148.8 (q, J=37.2 Hz, CCF_3), 152.2 (C), 154.6 (N*CH*N). MS (GC, 70eV): m/z (%)=354 (M^+, 14), 99 (100), 98 (16), 70 (14), 69 (12), 56 (35), 42 (20). HRMS (EI): calcd for $C_{12}H_{12}N_6F_6$ (M^+) 354.10222, found 354.102311. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3119 (w), 2941 (w), 2858 (w), 2809 (w), 1589 (w), 1484 (w), 1421 (w), 1337 (w), 1298 (w), 1232 (w), 1140 (w), 1086 (w), 1009 (w), 949 (w), 898 (w), 818 (w), 744 (w), 659 (w), 608 (w), 551 (w).

*3.2.15. 9-Benzyl-2,6-bis(trifluoromethyl)-9H-purine (**9k**).* White crystalline isolated by column chromatography (heptane/EtOAc, 1:1); mp, 116−118 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.55 (s, 2H, CH_2), 7.38−7.40 (m, 5H, CH_{Ar}), 8.37 (s, 1H, N*CH*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.5, −65.9. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=48.3 (CH_2), 119.5 (q, J=276.5 Hz, CCF_3), 120.2 (q, J=276.5 Hz, CCF_3), 128.3 (2CH), 129.3 (CH), 129.5 (2CH), 131.1 (C), 133.6 (C), 145.7 (q, J=38.9 Hz, CCF_3), 149.3 (C), 150.0 (q, J=38.9 Hz, CCF_3), 154.1 (N*CH*N). MS (GC, 70eV): m/z (%)=346 (M^+, 100), 345 (47), 327 (16), 326 (25), 91 (98), 65 (14). HRMS (EI): calcd for $C_{14}H_8N_4F_6$ (M^+) 346.06477, found 346.064317. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3087 (w), 3043 (w), 2991 (w), 2917 (w), 2873 (w), 1600 (w), 1553 (w), 1502 (w), 1452 (w), 1398 (w), 1349 (w), 1299 (w), 1268 (m), 1203 (m), 1132 (s), 1075 (m), 1003 (w), 965 (m), 923 (w), 888 (m), 818 (w), 729 (s), 657 (m), 599 (w), 545 (w).

*3.2.16. 2,6-Bis(trifluoromethyl)-9-((S)-1-phenylethyl)-9H-purine (**9l**).* Yellow oil isolated by column chromatography (heptane/EtOAc, 2:8); ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.03 (d, 3H, J=7.5 Hz, CH_3), 6.06 (q, 1H, J=7.5 Hz, CH), 7.31−7.36 (m, 5H, CH_{Ar}), 8.33 (s, 1H, N*CH*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.5, −65.9. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=19.2 (CH_3), 54.5 (CH), 118.5 (q, J=276.0 Hz, CCF_3), 119.2 (q, J=276.0 Hz, CCF_3), 125.8 ($2CH_{Ar}$), 128.1 (C), 128.3 ($2CH_{Ar}$), 130.3 (CH_{Ar}), 137.0 (CH_{Ar}), 144.5 (q, J=38.4 Hz, CCF_3), 147.0 (C), 148.1 (q, J=38.4 Hz, CCF_3), 152.2 (N*CH*N). MS (GC, 70eV): m/z (%)=360 (M^+, 37), 345 (13), 105 (100), 77 (16). ESI: calcd for $C_{15}H_{11}N_4F_6$ ($M+H^+$) 361.08824, found 361.08796. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3112 (w), 3069 (w), 2989 (w), 2943 (w), 1717 (w), 1652 (w), 1595 (m), 1493 (m), 1453 (m), 1402 (m), 1315 (m), 1273 (s), 1218 (s), 1136 (s), 1090 (s), 1028 (w), 990 (w), 945 (s), 888 (s), 818 (w), 761 (w), 724 (m), 700 (w), 658 (s), 615 (w), 575 (w).

*3.2.17. 2,6-Bis(trifluoromethyl)-9-phenethyl-9H-purine (**9m**).* White solid isolated by column chromatography (heptane/EtOAc, 8:2); mp 70−72 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.20 (t, 2H, 6.8 Hz, CH_2), 4.64 (t, 2H, J=6.8 Hz. CH_2), 7.08 (dd, 1H, J=9.0, 6.0 Hz, CH_{Ar}), 7.18−7.28 (m, 4H, $4CH_{Ar}$), 7.95(s, 1H, N*CH*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.5, −65.9. ^{13}C NMR (300 MHz, $CDCl_3$): δ=36.1 (CH_2), 46.6 (CH_2), 120.8 (q, J=273.9 Hz, CCF_3), 121.5 (q, J=273.9 Hz, CCF_3), 127.7 (CH), 129.4 (2CH), 129.6 (2CH), 132.4 (C), 144.6 (q, J=37.5 Hz, CCF_3), 149.3 (q, J=37.5 Hz, CCF_3), 155.7 (N*CH*N). MS (GC, 70eV): m/z (%)=360 (M^+, 11) 141 (10), 121 (100), 105 (10), 104 (100), 91 (27).

ESI: calcd for $C_{15}H_{11}N_4F_6$ ($M+H^+$) 361.08824, found 361.08803. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3130 (w), 3091 (w), 3032 (w), 2998 (w), 2946 (w), 2859 (w), 1984 (w), 1955 (w), 1801 (w), 1739 (w), 1680 (w), 1599 (w), 1504 (w), 1452 (w), 1400 (w), 1357 (w), 1302 (w), 1271 (m), 1208 (s), 1199 (s), 1168 (m), 1130 (s), 1080 (m), 1010 (m), 962 (m), 905 (w), 886 (m), 817 (w), 766 (w), 723 (m), 676 (m), 640 (s), 586 (w), 546 (w).

*3.2.18. 9-(2-Methoxyphenethyl)-2,6-bis(trifluoromethyl)-9H-purine (**9n**).* White crystalline isolated by column chromatography (heptane/EtOAc, 10:1); mp 144–126 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.19 (t, 2H, J=6.4 Hz, NCH_2CH_2), 3.62 (s, 3H, CH_3), 4.65 (t, 2H, J=6.5 Hz, NCH_2CH_2), 6.75–6.88 (m, 3H, $3CH_{Ar}$), 7.16–7.21 (m, 1H, CH_{Ar}), 7.98 (s, 1H, N*CH*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.5, −65.9. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=31.2 (OCH_3), 44.8 (NCH_2CH_2), 55.0 (NCH_2CH_2), 110.5 (C), 119.5 (q, J=273.6 Hz, CCF_3), 120.3 (q, J=273.6 Hz, CCF_3), 120.9 (C), 124.6 (CH), 129.2 (CH), 130.6 (CH), 130.9 (CH), 145.1 (q, J=36.0 Hz, CCF_3), 149.6 (q, J=36.0 Hz, CCF_3), 149.9 (C), 154.5 (C), 157.3 (N*CH*N). MS (GC, 70eV): m/z (%)=392 (10), 390 (M^+, 16), 371 (14), 135 (12), 134 (100), 121 (15), 119 (58), 91 (62), 62 (10). ESI: calcd for $C_{16}H_{13}ON_4F_6$ ($M+H^+$) 391.09881, found 391.0995. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3068 (w), 2975 (w), 2841 (w), 1791 (w), 1717 (w), 1673 (w), 1601 (w), 1509 (w), 1455 (w), 1403 (w), 1369 (w), 1303 (w), 1265 (m), 1209 (m), 1167 (m), 1120 (m), 1053 (w), 1018 (w), 959 (w), 912 (w), 858 (w), 803 (w), 757 (m), 686 (w), 636 (m), 577 (w).

*3.2.19. 9-(3,4-Dimethoxyphenethyl)-2,6-bis(trifluoromethyl)-9H-purine (**9o**).* White solid isolated by column chromatography (heptane/EtOAc, 3:7); mp 145–147 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.14 (t, 2H, J=6.9 Hz, CH_2), 3.76 (s, 3H, CH_3), 3.81 (s, 3H, CH_3), 4.63 (t, 2H, J=6.9 Hz, CH_2), 6.50–6.52 (m, 2H, $2CH_{Ar}$), 6.72 (d, 1H, J=8.7 Hz, CH_{Ar}), 8.00 (s, 1H, N*CH*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.5, −65.9. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=35.6 (OCH_3), 46.2 (OCH_3), 55.8 (CH_2), 111.5 (CH), 119.2 (q, J=276.0 Hz, CCF_3), 119.8 (q, J=276.0 Hz, CCF_3), 120.8 (CH), 128.5 (CH), 130.9 (C), 145.4 (q, J=38.8 Hz, CCF_3), 148.4 (C), 149.5 (q, J=38.4 Hz, CCF_3), 148.4 (C), 149.4 (C), 14.6 (C), 154.0 (N*CH*N). MS (GC, 70eV): m/z (%)=420 (M^+, 23), 165 (11), 164 (100), 151 (32), 149 (15). ESI: calcd for $C_{17}H_{15}O_2N_4F_6$ ($M+H^+$) 421.10937, found 421.10979. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3113 (w), 3089 (w), 3006 (w), 2948 (w), 2849 (w), 1597 (w), 1514 (w), 1469 (w), 1404 (w), 1367 (w), 1307 (w), 1252 (w), 1224 (m), 1190 (w), 1131 (m), 1021 (w), 959 (w), 889 (s), 856 (w), 818 (w), 777 (w), 735 (w), 697 (w), 657 (w), 625 (w), 599 (w), 537 (w).

*3.2.20. 2,6-Bis(trifluoromethyl)-9-((pyridin-4-yl)methyl)-9H-purine (**9p**).* White crystalline isolated by column chromatography (heptane/EtOAc, 10:1); mp 126–128 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.58 (s, 2H, CH_2), 7.20 (d, 2H, J=6.1 Hz, $2CH_{Ar}$), 8.44 (s, 1H, N*CH*N), 8.63 (d, 2H, J=6.1 Hz, $2CH_{Ar}$). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.6, −65.9. ^{13}C NMR (100.6 MHz, acetone-d_6): δ=47.3 (CH_2), 120.7 (q, J=275.1 Hz, CCF_3), 121.5 (q, J=2775.1 Hz, CCF_3), 123.2 (C), 145.0 (q, J=37.6 Hz, CCF_3), 144.9 (C), 149.7 (q, J=37.6 Hz, CCF_3), 151.4 (C), 153.1 (C), 156.0 (N*CH*N). MS (GC, 70eV): m/z (%)=347 (M^+, 100), 346 (57), 328 (22), 327 (22), 326 (41), 307 (15), 278 (26), 183 (12), 92 (26), 69 (11), 65 (17). ESI: calcd for $C_{13}H_7N_5F_6$ ($M+H^+$) 348.06784, found 348.06797. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3087 (w), 3043 (w), 2983 (w), 1599 (w), 1505 (w), 1455 (w), 1416 (w), 1368 (w), 1307 (m), 1271 (m), 1230 (w), 1199 (m), 1120 (m), 1067 (w), 977 (m), 942 (w), 890 (m), 818 (w), 794 (m), 734 (w), 695 (m), 658 (m), 639 (m), 568 (w).

*3.2.21. 2,6-Bis(trifluoromethyl)-9-(3-methoxyphenyl)-9H-purine (**10a**).* White solid isolated by column chromatography (heptane/EtOAc, 10:1); mp 145–147 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.90 (s, 3H, OCH_3), 7.06–7.09 (m, 1H, CH_{Ar}), 7.25–7.28 (m, 1H, CH_{Ar}), 7.32 (t, 1H, J=2.2 Hz, CH_{Ar}), 7.53 (t, 1H, J=8.1 Hz, CH_{Ar}), 8.68 (s, 1H, N*CH*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.6, −65.9. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=55.7 (OCH_3), 109.6 (CH_{Ar}), 115.0 (CH_{Ar}), 115.3 (CH_{Ar}), 119.4 (q, J=276.4 Hz, CCF_3), 120.1 (q, J=276.4 Hz, CCF_3), 131.1 (CH_{Ar}), 131.7 (C), 134.0 (C), 146.3 (q, J=38.5 Hz, CCF_3), 148.4 (C), 150.3 (q, J=38.5 Hz, CCF_3), 153.6 (C), 160.9 (N*CH*N). MS (GC, 70eV): m/z (%)=362 (M^+, 100), 361 (25), 343 (11), 341 (32), 332 (12), 331 (10), 313 (13), 312 (16). HRMS (EI): calcd for $C_{14}H_8N_4F_6$ (M^+) 362.05968, found 362.058868. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3119 (w), 3021 (w), 2952 (w), 2845 (w), 1610 (w), 1555 (w), 1504 (w), 1450 (w), 1400 (w), 1335 (w), 1276 (w), 1212 (m), 1186 (w), 1136 (m), 1051 (w), 995 (w), 949 (m), 890 (w), 836 (w), 775 (m), 738 (w), 683 (w), 637 (w), 598 (w), 545 (w).

*3.2.22. 2,6-Bis(trifluoromethyl)-9-(3,4-dimethoxyphenyl)-9H-purine (**10b**).* White solid isolated by column chromatography (heptane/EtOAc, 7:3); mp 136–138 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.95 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 7.03 (d, 1H, J=8.3 Hz, CH_{Ar}), 7.18 (dd, 1H, J=8.2, 8.6 Hz, CH_{Ar}), 7.27 (d, 1H, J=2.6 Hz, CH_{Ar}), 8.64 (s, 1H, N*CH*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.6, −65.9. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=56.2 ($2OCH_3$), 107.5 (CH_{Ar}), 111.6 (CH_{Ar}),115.9 (CH_{Ar}), 119.2 (q, J=275.7 Hz, CCF_3), 120.3 (q, J=275.7 Hz, CCF_3), 125.8 (C), 131.5 (C), 146.2 (q, J=35.5 Hz, CCF_3), 148.7 (C), 150.0 (2C), 150.9 (q, J=35.5 Hz, CCF_3), 153.6 (N*CH*N). MS (GC, 70eV): m/z (%)=393 (17), 392 (M^+, 100), 377 (16), 349 (21), 329 (24). ESI: calcd for $C_{15}H_{11}O_2N_4F_6$ ($M+H^+$) 393.07837, found 393.07837. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3140 (w), 2961 (w), 2840 (w), 1603 (w), 1523 (w), 1469 (w), 1403 (w), 1334 (w), 1276 (w), 1212 (m), 1176 (m), 1141 (s), 1012 (m), 954 (m), 891 (w), 858 (m), 794 (m), 739 (m), 669 (w), 603 (w), 527 (w).

*3.2.23. 2,6-Bis(trifluoromethyl)-9-(3,5-dimethoxyphenyl)-9H-purine (**10c**).* White crystalline isolated by column chromatography (heptane/EtOAc, 10:1); mp 150–152 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.86 (s, 6H, $2OCH_3$), 6.58 (t, 1H, J=2.1 Hz, CH_{Ar}), 6.87 (d, 2H, J=2.8 Hz, $2CH_{Ar}$), 8.67 (s, 1H, N*CH*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.6, −65.9. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=55.7 ($2OCH_3$), 100.9 (CH_{Ar}), 101.9 ($2CH_{Ar}$), 119.3 (q, J=275.6 Hz, CCF_3), 120.1 (q, J=275.6 Hz, CCF_3), 131.7 (C), 134.4 (C), 146.3 (q, J=38.1 Hz, CCF_3), 148.4 (C), 150.4 (q, J=38.1 Hz, CCF_3), 153.5 (N*CH*N), 161.8 (2C). MS (GC, 70eV): m/z (%)=393 (M^+, 40), 392 (100), 391 (52), 373 (23), 371 (39), 362 (11), 361 (11), 343 (46), 341 (28), 313 (10), 312 (12), 69 (11). HRMS (EI): calcd for $C_{15}H_{10}ON_4F_6$ (M^+) 392.07025, found 392.070024. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3118 (w), 3024 (w), 2971 (w), 2845 (w), 1613 (w), 1585 (w), 1503 (w), 1461 (w), 1404 (w), 1356 (m), 1275 (m), 1235 (w), 1137 (m), 1076 (m), 1024 (w), 958 (m), 891 (w), 833 (m), 784 (w), 714 (w), 663 (w), 604 (w), 570 (w).

*3.2.24. 2,6-Bis(trifluoromethyl)-9-(2,4-dimethoxyphenyl)-9H-purine (**10d**).* White solid isolated by column chromatography (heptane/EtOAc, 7:3); mp 143–145 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.79 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.66–6.70 (m, 2H, J=2.5, 6.6 Hz, $2CH_{Ar}$), 7.44 (d, 1H, J=9.1 Hz, CH_{Ar}), 8.54 (s, 1H, N*CH*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.5, −65.9. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=55.8 (OCH_3), 55.9 (OCH_3), 100.4 (CH_{Ar}), 105.1 (CH_{Ar}),114.2 (C), 118.5 (q, J=276.3 Hz, CCF_3), 121.3 (q, J=276.3 Hz, CCF_3), 128.1 (CH_{Ar}), 130.8 (C), 145.5 (q, J=37.7 Hz, CCF_3), 150.1 (q, J=37.7 Hz, CCF_3), 151.1 (C), 154.6 (C), 162.1 (N*CH*N). MS (GC, 70eV): m/z (%)=393 (17), 392 (M^+, 100), 373 (12), 363 (14), 362 (10), 347 (17), 323 (11), 319 (10). ESI: calcd for $C_{15}H_{11}O_2N_4F_6$ ($M+H^+$) 393.07807, found 393.0788. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3079 (w), 2945 (w), 1595 (w), 1523 (w), 1453 (w), 1403 (w), 1342 (w), 1304 (w), 1237 (w), 1208 (m), 1190 (m), 1134 (s), 1041 (m), 1025 (m), 938 (m), 887 (w), 816 (m), 739 (w), 672 (m), 646 (m), 587 (w), 534 (w), 468 (w), 412 (w).

*3.2.25. 2,6-Bis(trifluoromethyl)-9-(3,4,5-trimethoxyphenyl)-9H-purine (**10e**).* White solid isolated by column chromatography (heptane/EtOAc, 7:3); mp 118–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$):

δ=3.92 (s, 9H, $3CH_3$), 6.92 (s, 2H, $2CH_{Ar}$), 8.66 (s, 1H, NC*H*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.7, −65.9. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=55.5 ($2CH_3$), 60.0 (OCH_3), 96.7 (C), 100.4 ($2CH_{Ar}$), 118.5 (q, *J*=278.5 Hz, CCF_3), 119.3 (q, *J*=278.5 Hz, CCF_3), 127.4 (C), 130.6 (C), 137.9 (C), 145.3 (q, *J*=36.5 Hz, CCF_3), 147.5 (C), 149.4 (q, *J*=36.5 Hz, CCF_3), 152.6 (C), 153.2 (NC*H*N). MS (GC, 70eV): *m*/*z* (%)=423 (17), 422 (M^+, 100), 408 (11), 407 (61), 379 (37), 93 (10). ESI: calcd for $C_{16}H_{13}OBrN_4F_6$ ($M+H^+$) 423.08864, found 423.08828. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3402 (w), 3112 (w), 2945 (w), 1687 (w), 1586 (w), 1451 (w), 1357 (w), 1232 (m), 1184 (w), 1121 (s), 1070 (m), 989 (m), 918 (w), 855 (w), 795 (w), 739 (w), 660 (w), 8596 (w), 520 (w), 463 (w), 408 (w).

*3.2.26. 9-(4-Ethoxyphenyl)-2,6-bis(trifluoromethyl)-9H-purine (**10f**).* White solid isolated by column chromatography (heptane/EtOAc, 10:1); mp 144–146 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=1.47 (t, 3H, *J*=7.1 Hz, CH_3), 4.12 (q, 2H, *J*=7.1 Hz, CH_2), 7.10 (d, 2H, *J*=8.8 Hz, CH_{Ar}), 7.58 (d, 2H, *J*=8.8 Hz, CH_{Ar}), 8.61 (s, 1H, NC*H*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.5, −65.9. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=14.7 (OCH_3), 64.1 (CH_2), 115.5 (CH_{Ar}), 119.4 (q, *J*=276.9 Hz, CCF_3), 120.1 (q, *J*=276.9 Hz, CCF_3), 125.2 ($2CH_{Ar}$), 125.4 (C), 131.5 (C), 146 (q, *J*=39.5 Hz, CCF_3), 150.2 (C), 150.4 (q, *J*=39.5 Hz, CCF_3), 153.7 (C), 159.8 (NC*H*N). MS (GC, 70eV): *m*/*z* (%)=376 (M^+, 55), 349 (15), 348 (100), 347 (21). HRMS (EI): calcd for $C_{15}H_{10}ON_4F_6$ (M^+) 376.07533, found 376.075150. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3143 (w), 3089 (w), 3029 (w), 2965 (w), 2884 (w), 1947 (w), 1778 (w), 1612 (w), 1521 (m), 1465 (w), 1406 (w), 1349 (w), 1303 (w), 1244 (m), 1205 (m), 1170 (m), 1142 (s), 1038 (m), 1004 (w), 933 (m), 886 (m), 848 (m), 803 (m), 738 (m), 678 (m), 626 (m), 531 (m).

*3.2.27. 2,6-Bis(trifluoromethyl)-9-mesityl-9H-purine (**10g**).* White solid isolated by column chromatography (heptane/EtOAc, 7:3); mp 134–136 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=1.94 (s, 6H, $2CH_3$), 2.40 (s, 3H, CH_3), 7.09 (s, 2H, $2CH_{Ar}$), 8.36 (s, 1H, NC*H*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.4, −65.8. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=17.7 ($2CH_3$), 21.3 (CH_3), 119.4 (q, *J*=276.6 Hz, CCF_3), 120.3 (q, *J*=276.6 Hz, CCF_3), 128.3 (C), 128.3 (CH_{Ar}), 135.4 (C), 141.2 (C), 146.0 (q, *J*=39.2 Hz, CCF_3), 150.3 (C), 150.6 (q, *J*=39.2 Hz, CCF_3), 154.5 (NC*H*N). MS (GC, 70eV): *m*/*z* (%)=375 (57), 374 (M^+, 100), 373 (20), 355 (15), 353 (12), 305 (16), 279 (42), 210 (29). ESI: calcd for $C_{16}H_{13}N_4F_6$ ($M+H^+$) 375.10389, found 375.10455. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3116 (w), 2962 (w), 2863 (w), 1740 (w), 1608 (w), 1498 (w), 1452 (w), 1397 (w), 1332 (w), 1275 (m), 1237 (m), 1189 (m), 1135 (s), 1007 (m), 958 (w), 886 (m), 819 (w), 742 (m), 714 (w), 664 (m), 586 (w), 545 (w).

*3.2.28. 9-(3-Bromophenyl)-2,6-bis(trifluoromethyl)-9H-purine (**10h**).* White solid isolated by column chromatography (heptane/EtOAc, 8:2); mp 117–119 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=7.53 (t, 1H, *J*=8.3 Hz, CH_{Ar}), 7.69–7.75 (m, 2H, $2CH_{Ar}$), 7.89 (t, 1H, *J*=1.9 Hz, CH_{Ar}), 8.67 (s, 1H. NC*H*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.6, −65.9. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=119.4 (q, *J*=275.6 Hz, CCF_3), 120.1 (q, *J*=275.6 Hz, CCF_3), 122.3 (CH_{Ar}), 123.7 (C), 126.6 (CH_{Ar}), 130.3 (C), 132.8 (CH_{Ar}), 134.1 (C), 146.6 (q, *J*=39.3 Hz, CCF_3), 148 (2C), 150.7 (q, *J*=39.3 Hz, CCF_3), 153.5 (NC*H*N). MS (GC, 70eV): *m*/*z* (%)= 412 (M^+, 97), 411 (29), 410 (100), 409 (13), 331 (13), 69 (14). HRMS (EI): calcd for $C_{13}H_5N_4BrF_6$ (M^+) 411.95758, found 411.957617. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3147 (w), 3112 (w), 1587 (w), 1497 (w), 1454 (w), 1401 (w), 1344 (w), 1278 (w), 1213 (w), 1130 (w), 1021 (w), 935 (w), 889 (w), 851 (w), 796 (w), 677 (w), 625 (w), 558 (w), 528 (w).

*3.2.29. 9-(4-Bromophenyl)-2,6-bis(trifluoromethyl)-9H-purine (**10i**).* White solid isolated by column chromatography (heptane/EtOAc, 10:1); mp 168–170 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=7.62–7.65 (m, 2H, *J*=8.8 Hz, $2CH_{Ar}$), 7.77–7.80 (m, 2H, *J*=8.8 Hz, $2CH_{Ar}$), 8.67 (s, 1H, NC*H*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.6, −65.9. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=119.4 (q, *J*=276.0 Hz, CCF_3), 120.0 (q, *J*=276.0 Hz, CCF_3), 123.6 (C), 125 ($2CH_{Ar}$), 131.7 (C), 132.0 (C), 133.6 ($2CH_{Ar}$), 146.5 (q, *J*=38.8 Hz, CCF_3), 148.0 (C), 150.6 (q, *J*=38.8 Hz, CCF_3), 153.6 (NC*H*N). MS (GC, 70eV): *m*/*z* (%)=412 (99), 411 (M^+, 33), 410 (100), 409 (18). ESI: calcd for $C_{13}H_6BrN_4F_6$ ($M+H^+$) 412.9655, found 412.96591. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3144 (w), 3072 (w), 2992 (w), 1601 (w), 1552 (w), 1504 (w), 1452 (w), 1402 (w), 1344 (w), 1281 (w), 1221 (w), 1177 (w), 1139 (w), 1077 (w), 1010 (w), 931 (w), 886 (w), 842 (w), 740 (w), 695 (w), 660 (w), 614 (w), 530 (w).

*3.2.30. 9-(2,6-Dibromo-4-methylphenyl)-2,6-bis(trifluoromethyl)-9H-purine (**10j**).* White crystalline isolated by column chromatography (heptane/EtOAc, 8:2); mp 109–112 °C. ^1H NMR (250 MHz, $CDCl_3$): δ=2.41 (s, 3H, CH_3), 7.55 (s, 2H, $2CH_{Ar}$), 8.33 (s, 1H, NC*H*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.5, −65.8. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=21.0 (CH_3), 119.3 (q, *J*=273.7 Hz, CCF_3), 120.2 (q, *J*=273.7 Hz, CCF_3), 123.0 (2C), 128.5 (C), 130.6 (C), 133.6 ($2CH_{Ar}$), 144.7 (C), 146.2 (q, *J*=37.8 Hz, CCF_3), 149.5 (C), 150.5 (q, *J*=37.8 Hz, CCF_3), 153.9 (NC*H*N). MS (GC, 70eV): *m*/*z* (%)=506 (11), 505 (M^+, 10), 426 (16), 425 (97), 424 (17), 423 (100), 343 (16). ESI: calcd for $C_{14}H_6Br_2N_4F_6$ ($M+H^+$) 506.88972, found 506.88895. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3208 (w), 3113 (w), 2922 (w), 2849 (w), 1740 (w), 1658 (w), 1595 (w), 1545 (w), 1501 (w), 1451 (w), 1399 (w), 1336 (w), 1275 (w), 1201 (m), 1135 (m), 1085 (w), 1001 (w), 940 (m), 891 (w), 817 (w), 749 (w), 664 (m), 583 (w), 540 (w).

*3.2.31. 4-(2,6-Bis(trifluoromethyl)-9H-purin-9-yl)-N,N-diethylbenzenamine (**10k**).* Light green solid isolated by column chromatography (heptane/EtOAc, 7:3); mp 146–147 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=1.22 (t, 3H, *J*=6.5 Hz, $2CH_3$), 3.43 (q, 4H, *J*=7.2 Hz, $2CH_2$), 6.80 (d, 2H, *J*=9.8 Hz, $2CH_{Ar}$), 7.44 (d, 2H, *J*=9.8 Hz, $2CH_{Ar}$), 8.57 (s, 1H, NC*H*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.4, −65.9. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=12.4 ($2CH_3$), 44.8 ($2CH_2$), 111.9 (C), 119.4 (q, *J*=276.5 Hz, CCF_3), 120.3 (q, *J*=276.5 Hz, CCF_3), 125.2 ($2CH_{Ar}$), 131.4 (C), 145.9 (q, *J*=39.5 Hz, CCF_3), 148.3 (C), 149.9 (C), 150.2 (q, *J*=39.5 Hz, CCF_3), 153.9 (NC*H*N). MS (GC, 70eV): *m*/*z* (%)=403 (M^+, 35), 389 (19), 388 (100), 360 (25). HRMS (EI): calcd for $C_{17}H_{15}ON_5F_6$ (M^+) 403.12262, found 403.121853. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3128 (w), 2974 (w), 2903 (w), 2872 (w), 1609 (w), 1564 (w), 1524 (m), 1468 (w), 1399 (w), 1340 (w), 1275 (m), 1190 (m), 1130 (s), 1076 (w), 1023 (m), 935 (m), 886 (m), 815 (m), 742 (m), 708 (w), 661 (m), 628 (m), 551 (w).

*3.2.32. 2,6-Bis(trifluoromethyl)-9-(thiazol-2-yl)-9H-purine (**11a**).* White solid isolated by column chromatography (2-propanol/EtOAc, 3:7); mp 135–137 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=7.49 (d, 1H, *J*=3.5 Hz, CH_{Ar}), 7.75 (d, 1H, *J*=3.5 Hz, CH_{Ar}), 9.35 (s, 1H, NC*H*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.7, −65.9. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=119.2 (q, *J*=276.5 Hz, CCF_3), 119.1 (C), 119.8 (q, *J*=276.5 Hz, CCF_3), 131.9 (C), 139.7 (CH_{Ar}), 146.4 (C), 146.7 (q, *J*=35.9 Hz, CCF_3), 151.5 (q, *J*=35.9 Hz, CCF_3), 151.7 (C), 152.4 (NC*H*N). MS (GC, 70eV): *m*/*z* (%)=339 (M^+, 100), 320 (10), 58 (11). HRMS (EI): calcd for $C_{10}H_3SN_4F_6$ (M^+) 339.00079, found 339.001667. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3128 (w), 2922 (w), 2852 (w), 1818 (w), 1731 (w), 1652 (w), 1593 (w), 1526 (w), 1487 (w), 1445 (m), 1400 (w), 1308 (w), 1275 (w), 1229 (w), 1139 (m), 1052 (w), 1006 (w), 920 (w), 887 (w), 813 (w), 739 (w), 685 (w), 624 (w), 568 (w).

*3.2.33. 2,6-Bis(trifluoromethyl)-9-(pyridin-2-yl)-9H-purine (**11b**).* White crystalline isolated by column chromatography (2-propanol/EtOAc, 2:8); mp 60–62 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=7.42–7.46 (m, 1H, CH_{Ar}), 8.02–8.08 (m, 1H, CH_{Ar}), 8.67 (dt, 1H, *J*=1.05, 8.18 Hz, CH_{Ar}), 8.65 (s, 1H, NC*H*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.6, −65.9. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=115.4 (CH_{Ar}), 119.4 (q, *J*=276.4 Hz, CCF_3), 120.1 (q, *J*=276.4 Hz, CCF_3), 123.8

(CH_{Ar}), 132.9 (C), 139.7 (CH_{Ar}), 145.5 (q, J=36.9 Hz, CCF_3), 147.0 (C), 148.0 (C), 149.0 (CH_{Ar}), 151.2 (q, J=36.9 Hz, CCF_3), 152.8 (N*CH*N). MS (GC, 70eV): m/z (%)=334 (10), 333 (M^+, 100), 314 (16), 307 (21), 306 (66), 288 (13), 264 (14), 237 (26), 211 (17), 191 (11), 169 (13), 78 (26), 69 (19), 63 (10). HRMS (EI): calcd for $C_{10}H_3SN_4F_6$ (M^+) 334.00078, found 334.001655. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3187 (w), 2923 (w), 2852 (m), 2771 (w), 1687 (s), 1588 (s), 1460 (m), 1436 (s), 1294 (s), 1203 (m), 1142 (s), 1000 (s), 854 (m), 771 (s), 702 (s), 627 (s), 522 (s), 474 (s), 407 (m).

*3.2.34. 4-(2,6-Bis(trifluoromethyl)-9H-purin-9-yl)benzenamine (**12**).* Yellow solid isolated by column chromatography (heptane/EtOAc, 7:3); mp 175–177 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.22 (br s, 2H, NH_2), 6.87 (m, 2H, J=8.6 Hz, $2CH_{Ar}$), 7.42 (m, 2H, J=8.6 Hz, $2CH_{Ar}$), 8.58 (s, 1H, N*CH*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.9, −65.9. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=119.0 ($2CH_{Ar}$), 124.6 (q, J=276.1 Hz, CCF_3), 125.8 (q, J=276.1 Hz, CCF_3), 130.9 ($2CH_{Ar}$), 136.9 (C), 147.9 (q, J=43.3 Hz, CCF_3), 152.9 (q, J=43.3 Hz, CCF_3), 155.1 (C), 157.3 (C), 159.7 (N*CH*N). MS (GC, 70eV): m/z (%)=347 (M^+, 100). ESI: calcd for $C_{13}H_8N_5F_6$ ($M+H^+$) 348.06784, found 348.06879. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3404 (w), 2078 (w), 1981 (w), 1626 (w), 1521 (w), 1456 (w), 1405 (w), 1338 (w), 1276 (w), 1243 (w), 1217 (w), 1177 (w), 1134 (w), 1022 (w), 1005 (w), 936 (w), 888 (w), 835 (w), 739 (w), 628 (w), 532 (w), 481 (w), 423 (w).

*3.2.35. 4-(2,6-Bis(trifluoromethyl)-9H-purin-9-yl)-2,5-dimethylbenzenamine (**13**).* White solid isolated by column chromatography (heptane/EtOAc, 7:3); mp 185–188 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.98 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 4.12 (br s, 2H, NH_2), 6.70 (s, 1H, CH_{Ar}), 6.96 (s, 1H, CH_{Ar}), 8.41 (s, 1H, N*CH*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.4, −65.9. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=16.8 (CH_3), 17.5 (CH_3), 116.8 (CH_{Ar}), 119.1 (q, J=277.7 Hz, CCF_3), 120.1 (q, J=277.7 Hz, CCF_3), 120.9 (C), 121.6 (C), 122.5 (C), 128.9 (CH_{Ar}), 130.5 (q, J=32.2 Hz, CCF_3), 130.8 (C), 133.6 (C), 139.7 (q, J=32.2 Hz, CCF_3), 146.4 (C), 150.6 (C), 154.4 (N*CH*N). MS (GC, 70eV): m/z (%)=376 (18), 375 (M^+, 100), 374 (12). ESI: calcd for $C_{15}H_{12}N_5F_6$ ($M+H^+$) 376.09914, found 376.09982. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3445 (w), 3341 (w), 1684 (w), 1632 (w), 1592 (w), 1516 (w), 1451 (w), 1399 (w), 1308 (w), 1276 (m), 1234 (m), 1198 (m), 1133 (m), 1036 (w), 975 (w), 928 (w), 888 (m), 819 (w), 739 (m), 661 (m), 578 (w), 524 (w), 455 (w), 414 (w).

*3.2.36. 9-(4-(2,6-Bis(trifluoromethyl)-9H-purin-9-yl)phenyl)-2,6-bis(trifluoromethyl)-9H-purine (**14**).* Yellow oil isolated by column chromatography (heptane/EtOAc, 7:3); ^{1}H NMR (300 MHz, acetone-d_6): δ=8.46 (s, 4H, $4CH_{Ar}$), 9.54 (s, 2H, N*CH*N). ^{19}F NMR (300 MHz, acetone-d_6): δ= −63.9, −61.3. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=120.6 (q, J=273.0 Hz, CCF_3), 121.8 (q, J=273.0 Hz, CCF_3), 126.7 ($4CH_{Ar}$), 133.4 (C), 135.0 (2C), 145.4 (q, J=38.8 Hz, CCF_3), 150.1 (q, J=38.8 Hz, CCF_3), 151.5 (C), 155.6 (N*CH*N). MS (GC, 70eV): m/z (%)=586 (M^+, 100), 567 (10). HRMS (EI): calcd for $C_{20}H_6N_8F_{12}$ (M^+) 586.05183, found 586.051343. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3107 (w), 1599 (w), 1595 (w), 1456 (w), 1405 (w), 1332 (w), 1275 (m), 1207 (m), 1136 (s), 1026 (m), 934 (m), 886 (m), 843 (m), 801 (w), 737 (w), 662 (w), 638 (w), 570 (w), 547 (w), 514 (w), 446 (w), 399 (w).

*3.2.37. 9-(4-(2,6-Bis(trifluoromethyl)-9H-purin-9-yl)biphenyl)-2,6-bis(trifluoromethyl)-9H-purine (**15**).* Yellow solid isolated by column chromatography (heptane/EtOAc, 6:4); mp 292–294 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.02 (s, 8H, $8CH_{Ar}$), 9.22 (s, 1H, N*CH*N). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=120.8 (q, J=275.4 Hz, CCF_3), 121.8 (q, J=275.4 Hz, CCF_3), 125.3 (C), 125.8 ($4CH_{Ar}$), 129.5 ($4CH_{Ar}$), 133.4 (C), 134.4 (C) 141.3 (C), 145.4 (q, J=35.4 Hz, CCF_3), 150.1 (q, J=35.4 Hz, CCF_3), 151.5 (2N*CH*N), 153.0 (C), 155.5 (C). MS (GC, 70eV): m/z (%)= 662 (M^+, 100), 661 (11), 643 (11), 595 (10), 594 (17), 295 (47), 276 (13), 275 (31), 43 (13). HRMS (EI): calcd for $C_{26}H_{10}N_8F_{12}$ (M^+) 662.08313, found 662.081757. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3334 (m), 3295 (m), 2901 (w), 1641 (w), 1425 (w), 1370 (w), 1335 (w), 1204 (w), 1159 (w), 1105 (w), 1029 (m), 896 (w), 873 (w), 555 (m).

*3.2.38. 9-(4-(4-(2,6-Bis(trifluoromethyl)-9H-purin-9-yl)-3-methoxyphenyl)-2-methoxyphenyl)-2,6-bis(trifluoromethyl)-9H-purine (**16**).* White solid isolated by column chromatography (heptane/EtOAc, 7:3); Mp 280–285 °C. ^{1}H NMR (300 MHz, acetone-d_6): δ=3.91 (s, 6H, $2OCH_3$), 7.52 (d, 1H, J=1.8 Hz, CH_{Ar}), 7.99 (d, 1H, J=1.8 Hz, CH_{Ar}), 7.60 (d, 2H, J=1.8 Hz, $2CH_{Ar}$), 7.75 (s, 1H, CH_{Ar}), 7.78 (s, 1H, CH_{Ar}), 9.02 (s, 1H, N*CH*N). ^{19}F NMR (300 MHz, $CDCl_3$): δ= −68.4, −65.9. ^{13}C NMR (100.6 MHz, acetone-d_6): δ=56.9 (s, 6H, $2OCH_3$), 112.9 (s, 2H, $2CH_{Ar}$), 120.8 (q, J=277.5 Hz, $2CCF_3$), 120.9 (s, 2H, $2CH_{Ar}$), 121.6 (q, J=277.5 Hz, $2CCF_3$), 122.3 (2C), 129.2 ($2CH_{Ar}$), 132.4 (2C), 144.2 (2C), 145.1 (q, J=36.6 Hz, $2CCF_3$), 150.1 (q, J=36.6 Hz, CCF_3), 153.2 (2C), 155.3 (2N*CH*N), 156.2 (C). MS (GC, 70eV): m/z (%)=772 (M^+, 100), 703 (15), 693 (17), 654 (10), 653 (15), 69 (10). HRMS (EI): calcd for $C_{28}H_{14}O_2N_8F_{12}$ (M^+) 722.10426, found 722.103828. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3120 (w), 2976 (w), 2914 (w), 2843 (w), 1596 (w), 1511 (w), 1469 (w), 1407 (w), 1337 (w), 1303 (w), 1251 (w), 1209 (w), 1157 (w), 1131 (w), 1065 (w), 1015 (w), 934 (w), 888 (w), 853 (w), 812 (w), 741 (w), 693 (w), 658 (w), 626 (w), 570 (w), 536 (w).

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24. Crystallographic data (excluding structure factors) for the structures **9i**, **9n**, **9o**, **10k**, **14** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 832486-832490, can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223) 336033; e-mail: deposit@ccdc.cam.ac.uk, or via www.ccdc.cam.ac.uk/data_request/cif.