Full Paper

New Purines with Antiplatelet Activity

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Four purine-2,6-diamines, **4a**, **b**, **5a**, **b**, nineteen *N*-(purin-2-yl)benzenecarboxamides **6a – q**, **7b**, and one *N*-(purin-2-yl)-2-furanecarboxamide **8** were prepared for the first time and tested for their inhibition of blood platelet aggregation. Six compounds, **6a**, **b**, **h**, **m**, **o**, **p**, inhibited the platelet aggregation induced by collagen with IC_{50} values between 3 and 10 μmol/L in the Born test. ADP, PAF, and adrenaline were used as specific aggregation inducers to examine the mechanism of the anti-aggregating activity. An astonishing pattern of activities in the nanomolar, with **6m**, **7b**, **8** and even subnanomolar range, with **6b**, was observed. Compound **6b** inhibited the platelet aggregation induced by ADP with an IC_{50} = 0.45 nM (**6m**: 3.5 nM; **8**: 30 nM). Compound **7b** showed an antagonism against the inducer adrenaline with an IC_{50} = 1.8 nM (**6o**: 20 nM; **8**: 30 nM). The strongest antagonism against PAF was observed with **7b** showing an IC_{50} = 1 nM (**6b**: 35 nM; **8**: 74 nM).

Keywords: *N*-(Purin-2-yl)benzenecarboxamides / Antiplatelet properties / Born test / PAF / ADP / Adrenaline antagonism

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Introduction

In a number of publications, we have shown that the substitution of heterocycles rich in nitrogen like indazoles [2], triazoles [3], oxadiazoles [4], imidazoles [5], or pyrimidocinnolines [6] with a carboxamide partial structure and additional hydrophobic and basic groups leads to a wide variety of compounds with antiplatelet activities in micromolar concentrations. In this paper, we wish to report a number of purine derivatives fulfilling these structural requirements and, consequently, were promising to show remarkable antiplatelet activities.

Results and discussion

Chemistry

The synthesis of the desired purinylbenzene-carboxamides **6** and **7** is summarised in Scheme 1. Starting material is the commercially available 6-chloro-9*H*-purine-2-amine **1**. The introduction of the hydrophobic moiety was achieved by reaction with benzylchloride in DMF/K_2CO_3 [7 – 9]. Whatever the reaction conditions are, a mixture of compounds **2** (~80%) and **3** (~20%) is obtained and can be separated by column chromatography (dichloromethane/ethanol 9.5:0.5). The assignment is made via ^{1}H-NMR data of H-8 (**2**: δ = 8.23 ppm; **3**: δ = 8.55 ppm) as well as the benzylic methylene group (**2**: δ = 5.29 ppm; **3**: δ = 5.56 ppm) and is based on known NMR-data [8, 9] for unambiguous syntheses [10 – 14]. The nucleophilic substitution of **2** or **3** by two diamines in 6-position gave the type **4** or type **5** compounds, respectively. As biological test results of the type **4** substances appeared to be superior to the corresponding type **5** compounds, only the first ones were transformed by suitable benzoic acid chlorides to the type **6** and **7** substances. One furanecarboxamide **8** (see Experimental) was prepared for comparison of aromatic **6**, **7** with heteroaromatic carboxamides.

Biology

The results of the Born test [4] with collagen as inducer of the platelet aggregation are compiled in Table 1. The starting material **1** (150 μM) and its benzyl derivatives **2**

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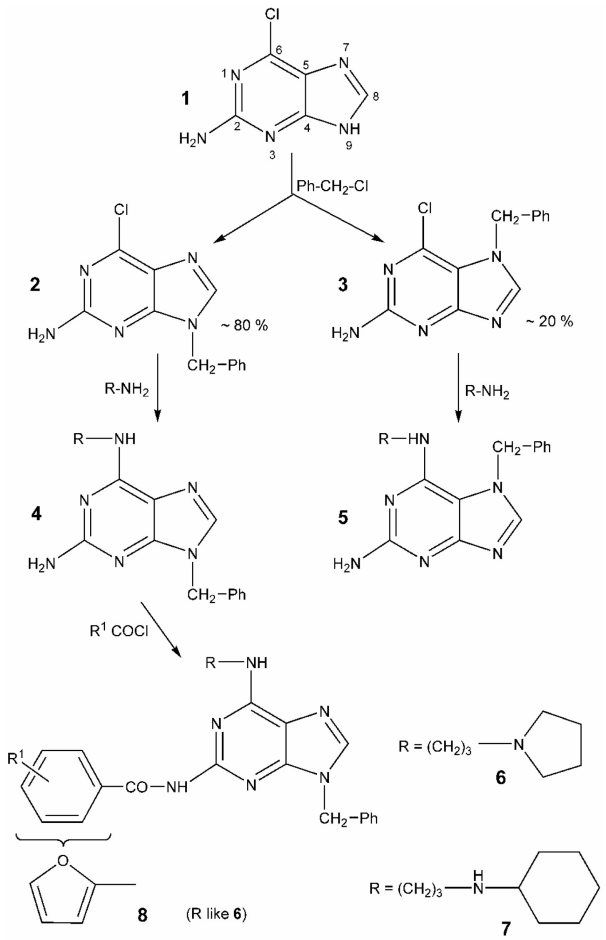


Scheme 1. Synthesis of *N*-(6-amino-purin-2-yl)-benzenecarboxamides **6** and **7**.

Table 1. *In vitro* antiplatelet activities (Born test).

Compound	R/R[1]	IC_{50} [μmol/L]
1	–	75
2	–	44
3	–	52
4a	$(CH_2)_3$-NH-cyclohexyl	11
4b	$(CH_2)_3$-1-pyrrolidinyl	150
5a	$(CH_2)_3$-NH-cyclohexyl	23
5b	$(CH_2)_3$-1-pyrrolidinyl	140
6a	4-$COOCH_3$	3
6b	3-CN	3
6c	4-OCH_3	19
6d	4-Cl	50
6e	3-(pyrrolidin-1-yl-sulfonyl)	19
6f	3-(morpholin-4-yl-sulfonyl)	19
6g	4-(morpholin-4yl-sulfonyl)	38
6h	3-(4-methylpiperazin-1-yl-sulfonyl)	10
6i	4-(pyrimidin-2-yl-piperazin-4-yl-sulfonyl)	35
6j	3-SO_2-NH-phenyl	40
6k	3-SO_2-N-$(C_2H_5)_2$	25
6l	3-SO_2-NH-$(CH_2)_2$-OCH_3	50
6m	4-SO_2-NH-$(CH_2)_2$-OCH_3	5
6n	3-SO_2-NH-$(CH_2)_3$-OCH_3	75
6o	4-SO_2-NH-$(CH_2)_3$-OCH_3	3
6p	3-SO_2-N$(CH_2$-CH_2-$OCH_3)_2$	10
6q	4-SO_2-N$(CH_2$-CH_2-$OCH_3)_2$	75
7b	3-CN	18
asa	–	175 ± 20

IC_{50} values using collagen as inducer are given (incubation time 20′). The standard deviation in this test is <10% (**asa**, acetylsalicylic acid). For **4a**, **4b**, **5a,** and **5b** the rest R (see Scheme 1) is given. For **6a–6q** and **7b** the rest R^1 is stated (compact Scheme 1).

(44 μM) and **3** (52 μM) showed small effects. A wide variety of amines including hydroxyalkylamines, hydroxyethoxyalkylamines, and furylmethylamines were used for the introduction of an additional substituent in 6-position. All compounds turned out to be inactive ($IC_{50} \gg 300$ μM) in the Born test (data not shown). According to previous experiences, now a number of diamines [2–6] were used for substituting the 6-position. The first trials with 3-(1-pyrrolidinyl)-propylamine led to the compounds **4b** (9-benzyl) and **5b** (7-benzyl) which showed a disappointingly small antiplatelet activity. As **4b** (IC_{50} = 150 mmol/L) and **5b** (IC_{50} = 140 mmol/L) are equipotent, further studies were performed with **4b** because it can be synthesised from **2** which, in turn, was synthesised from **1** in a 80% yield (**3**: 20%). At the end of his experiments, Steege [5] identified the cyclohexylaminopropylamine group as very potent concerning anti-aggregatory activities. Introduction of this amine in 6-position yielded **4a** (IC_{50} = 11 μmol) and **5a** (23 μmol/L), the most active species of type **4** and type **5** compounds.

This preference in activity for **5a** and **5b** however changes, when, according to the rational stated in the introduction, the 2-amino group is reacted with various benzenecarboxylic acide chlorides to type **6** or type **7** compounds, respectively. Testing **6b** and **7b** against the platelet aggregation induced by collagen, an IC_{50} = 3 μM is observed for **6b**, while **7b** (IC_{50} = 18 μM) is less potent. Therefore, the experiments were continued with derivatives of **4b**, i.e. type **6** compounds.

Comparison of **6a–d** shows that the antiplatelet activity is generally enhanced by the aromatic carboxamide structure. This effect is sensitive to the kind of substitution in the aromatic ring. Compounds **6a** and **6b,** each with an IC_{50} = 3 mmol/L, show that electron-withdrawing substituents are more suitable than electron-donating ones (**6c**, **6d**). Compounds **6e–6q** were synthesised to investigate the effect of an additional sulfonamide moiety. Compared to the parent amine **4b**, this generally leads to more potent compounds. The series of compounds **6e–6i** comprises alicyclic sulfonamides which all

are active in the same order of magnitude. Comparison of **6f** and **6g** shows the influence of the position of the sulfonamide group in the aromatic ring. There is only a small difference with a slight advantage for the 3-position. Compounds **6k – q** are aliphatic sulfonamides. The *N*-(2-methoxyethyl) compound **6m** (IC_{50} = 5 μmol/L) and the *N*-(3-methoxypropyl)-compound **6o** (IC_{50} = 3 μmol/L) belong to the most active substances.

In secondary aliphatic sulfonamides, the 4-position appears favourable as the comparison of the pairs **6l**, **6m** and **6n**, **6o** suggests.

Tertiary sulfonamides show antiplatelet effects as well (see **6k**, **6p**, **6q**). Here, the 3-position seems favourable (IC_{50} = **6p**: 10 μmol/L, **6o**: 75 μmol/L). Even aromatic substitution is accepted (see **6f**).

To get an idea of the mechanism of action of the antiplatelet compounds, the Born test was performed with ADP, adrenaline, and Platelet Activating Factor (PAF) as inducers of the platelet aggregation. The results are summarised in Table 2.

Table 2. Inhibition of platelet aggregation induced with ADP, adrenaline, or PAF by selected type **6 – 8** purines.

Compound	Collagen	IC_{50} [μmol/L]		
		ADP	Adrenaline	PAF
6a	3	25	7.5	7
6b	3	0.00045	3.5	0.035
6h	10	43	14	1.4
6j	40	50	30	4
6m	5	0.0035	4.8	0.35
6o	3	6	0.02	0.4
6p	10	15	4	7
7b	18	6.5	0.0018	0.001
8	32	0.03	0.03	0.074
asa	175	–	–	–
NECA[a)]	–	–	1	–
phentolamine	–	–	2	–
apafant (WEB-2086)	–	–	–	0.6

Incubation time 20′, Standard deviation ≤ 10%.
[a)] NECA = 5-(**N**-**E**thyl**c**arboxamido)-**a**denosine.

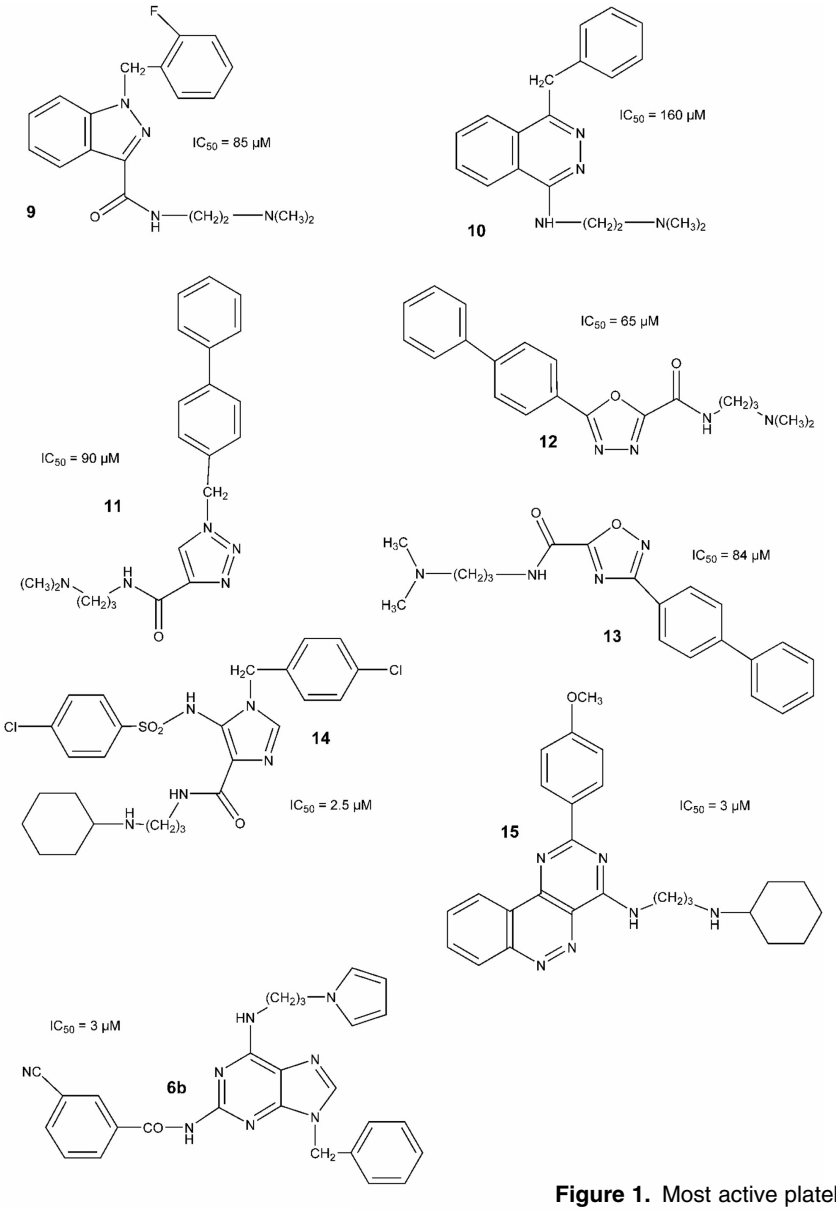
The selected compounds show a very differentiated pattern of antiplatelet activities. Comparing **6a** with **6b**, which differ only in the substituent R^1 (see Table 1), changing from an ester to a nitrile function a dramatic increase of the ADP antagonistic activity is observed (**6a**: 25 μM; **6b**: 0,45 nM). The difference comprises five orders of magnitude. Comparing **6b** with **7b** differing only slightly in the substituent in 6-position (**6b**: 1-pyrrolidinylpropyl; **7b**: cyclohexylaminopropyl) the ADP antagonism of **6b** is decreased by four orders of magnitude and shifted to adrenaline (IC_{50} = 1.8 nM) and PAF (IC_{50} = 1 nM) antagonism. Compound **6m** exhibits a rather specific ADP antagonism which is hundredfold stronger than the anti-PAF activity and thousandfold stronger than the effect on collagen- or adrenaline-induced platelet aggregation. Compounds **6h**, **6j**, and **6p** show comparable activity against all inducers in 1 – 50 μM concentrations. Compound **6o** is especially adrenaline-antagonistic. The 2-furyl-carboxamide derivative **8** shows that the benzene moiety can be replaced by a heteroaromatic one with IC_{50} values in the 30 – 74 nanomolar range against ADP, PAF, and adrenaline, while the antiplatelet effect against collagen stays in the usual micromolar concentration (IC_{50} = 32 μM).

It has been suggested to extend the discussion on the comparison of the purine derivatives with other heterocycles having an identical substibution pattern e.g. indazoles **9** [2], triazoles **11** [3], oxadiazoles **12**, **13** [4], imidazoles **14** [5], pyrimidocinnolines [6], and phthalazines **10** [6a], which already have been investigated by our group. Unfortunately, such a set of data is not available because the kind of substituents was changed according to the test results or for synthetical reasons. Nevertheless, it might be attractive to compare the prerequisites for peak activities in the different classes of heterocycles. In general, it turns out that similar substitution patterns are observed with this respect. Figure 1 shows the most active aggregation inhibitors (inducer collagen) in each class of compounds. Suitable lipophilic moieties are phenylmethyl **10**, **6b**, substituted phenylmethyl **9**, **14**, biphenylmethyl **11**, biphenyl **12**, **13**, or simply 4-methoxyphenyl **15**. The link between the basic function and the heterocycle can be a carboxamide function, **9**, **11**, **12**, **13**, **14**, or simply an amino group, **6b**, **10**, **15**. The length of the connecting carbon chain consists of two (see **9**, **10**) or preferably three (see **6b**, **11**, **12**, **13**, **14**, **15**, 16) methylene groups. An additionally substituted benzenesulfonamido **14** or benzenecarboxamido group **6b** is well tolerated and leads to high activities.

Experimental

Chemistry

Mp. (uncorreted), Linström-Elementar analysis: Elementar vario EL. – NMR: Bruker DPX 400 (Bruker, Rheinstetten, Germany) EI-MS: CH-7A-Varian MAT (70 eV). – FAB-MS: CH-5-DF-MAT-Varian (Varian, Braunschweig, Germany). All compounds of type **4 – 8** were prepared for the first time. For assignment of NMR signals, following abbreviations are used: cyhex: cyclohexyl; pyr: pyridinyl; pyrr: pyrrolidinyl; SO_2pyrr: pyrrolidinylsulfonyl; suph: sulfonylphenyl; morph: morpholin; mepipera: methylpiperazinyl; pipera: piperazinyl; pyrim: pyrimidinyl; piperapyrim: pyrimidinylpiperazinyl



IC$_{50}$ values given for collagen as inducer.

Figure 1. Most active platelet aggregation inhibitors in each class of heterocycles.

*General procedure for the synthesis of type **4** and type **5** compounds (modified method of Kelley [14])*

Method A: Purine **2** or **3** (2 mmol) and 6 – 10 mmol of the amine are dissolved in 30 mL ethanol and kept at 60 °C. After 12 h, the progress of the reaction is controlled by TLC (dichloromethane/ethanol 1 : 1) and, if necessary, continued until no starting purine is left. Then, the solvent is removed *in vacuo*. The resulting yellow oil is mixed with 30 mL of water and kept for at least 1 day in the refrigerator (5°C). If crystals have formed they are sucked off and recrystallised from the solvent stated. Otherwise the mixture is extracted with dichloromethane several times. The combined organic phases are washed with water, dried with Na_2SO_4, filtered, and the solvent is removed *in vacuo*. The residue is dissolved in warm ethanol and water is added until turbidity occurs and then is kept in the refrigerator for crystallisations. If this is not the case, the purification is performed by column chromatography (CC) with silica gel.

Method B: Purine **2** or **3** (2 mmol) are mixed with 4 mL of the amine, heated to 100°C, and kept for 3 h at this temperature. After 1 h at the latest, a solution is obtained. After cooling to room temperature, 30 mL water is added and the mixture is kept in the refrigerator until crystals are formed. They are sucked off and recrystallised from ethanol/water.

*N^6-[3-Cyclohexylamino)propyl]-9-phenylmethyl-9H-purin-2,6-diamine **4a***

From 0.5 g (1.92 mmol) of **2** and 1.0 g (7.05 mmol) 3-(cyclohexylamino)propylamine (method A), 24 h. Crystals (ethanol/water), mp. 129°C, yield 0.6 g (82%). – Anal. $C_{21}H_{29}N_7$ (379.5). – IR (KBr): ν = 3343 cm^{-1}; 3205; 2927; 2853; 1655; 1600; 1489; 1452; 1402;

1342; 789; 726; 644. – ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 0.93 – 1.00 (m, 2H, cyhexH-3a,5a), 1.04 – 1.19 (m, 3H, cyhexH-3e,5e,4a), 1.53 (m, 1H, cyhexH-4e), 1.62 – 1.70 (m, 4H, $CH_2CH_2CH_2$ and cyhexH-2a,6a), 1.77 – 1.80 (m, 2H, cyhexH-2e,6e), 2.27 – 2.33 (m, 1H, cyhexH-1), 2.55 – 2.59 (t, *J* = 6.6 Hz, 2H, $NHCH_2CH_2CH_2$), 3.44 (brs, 2H, $NHCH_2CH_2$), 5.19 (s, 2H, CH_2Ph), 5.79 (brs, 2H, D$_2$O exchange, NH_2), 7.21 – 7.35 (m, 6H, 1H, D$_2$O exchange, ph and NH), 7.76 (s, 1H, purinH-8). – MS (EI, 50 °C): m/z (%) = 379 (8) [M$^{+\bullet}$], 282 (12) [M$^{+\bullet}$-NHcyhex+H], 267 (15) [M$^{+\bullet}$ – CH_2NHcyhex], 254 (33) [M$^{+\bullet}$ – CH_2CH_2NHcyhex+H], 241 (21) [M$^{+\bullet}$ – CH_2=$CHCH_2$NHcyhex+H], 91 (100) [$C_7H_7^+$], 56 (19), 41 (29), 30 (16) [CH_2=NH_2^+].

*9-Phenylmethyl-N^6-[3-((pyrrolidinyl)propyl]-9H-purin-2,6-diamine **4b***

From 0.5 g (1.92 mmol) of **2** and 0.9 g (7.03 mmol) 3-(pyrrolidinyl)propylamine (method A), 12 h. Crystals (ethanol/water), mp. 169 °C, yield 0.6 g (89%). – Anal. $C_{19}H_{25}N_7$ (351.5). – IR (KBr): ν = 3360 cm^{-1}; 3197; 2951; 2792; 1646; 1605; 1493; 1460; 1396; 1341; 1221; 1144; 787; 709; 646. – ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 1.68 – 1.77 (m, 6H, pyrrH-3,4 and $NHCH_2CH_2CH_2$), 2.44 – 2.47 (m, 6H, pyrrH-2,5 and $NHCH_2CH_2CH_2$), 3.44 (brs, 2H, $NHCH_2CH_2$), 5.19 (s, 2H, CH_2ph), 5.82 (brs, 2H, D$_2$O exchange, NH_2), 7.21-7.35 (m, 6H, 1H, D$_2$O exchange, ph and NH), 7.76 (s, 2H, purinH-8). – MS (EI, 110 °C): m/z (%) = 351 (32) [M$^{+\bullet}$], 267 (26) [M$^{+\bullet}$ – CH_2pyr], 254 (61) [M$^{+\bullet}$ – CH_2CH_2pyrr$^{+\bullet}$H], 241 (16), 240 (11) [M$^{+\bullet}$ – CH_2=$CHCH_2$pyrr], 226 (14), 163 (14), 111 (15) [$CH_2CH_2CH_2$pyrr$^{+\bullet}$ – H], 98 (15) [CH_2CH_2pyrr$^{+\bullet}$], 91 (86) [$C_7H_7^+$], 84 (100) [CH_2=pyrr$^+$], 42 (24).

*N^6-[3-(Cyclohexylamino)propyl]-9-phenylmethyl-7H-purin-2,6-diamine **5a***

From 0.5 g (1.92 mmol) of **3** and 4 mL 3-(cyclohexylamino)propylamine (method B). Brownish bright crystals, mp. 149 °C, yield 0.5 g (69%). – Anal. $C_{21}H_{29}N_7$ (379.5). – IR (KBr) ν = 3457 cm^{-1}; 3390; 3294; 3147; 2927; 2853; 1600; 1574; 1483; 1451; 1384; 1293; 1234; 1235; 1189; 1123; 1031; 793; 731; 629. – ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 0.87 – 0.96 (m, 2H, cyhexH-3a,5a), 1.02 – 1.18 (m, 3H, cyhexH-3e,5e,4a), 1.49 – 1.55 (m, 3H, $CH_2CH_2CH_2$ and cyhexH-4e), 1.61 – 1.65 (m, 2H, cyhexH-2e,6e), 2.21 (m, 1H, cyhexH-1), 2.34 – 2.38 (t, *J* = 6.6 Hz, 2H, $NHCH_2CH_2CH_2$), 3.37 (m, 2H, $NHCH_2$), 5.55 (2 × s, 4H, 2H, D$_2$O exchange, CH_2ph and NH_2), 6.21 (t, *J* = 5.4 Hz, 1H, D$_2$O exchange, NH_2), 7.1 (d, *J* = 7.0 Hz, 2H, ph-H-2.6), 7.25 – 7.35 (m, 3H, phH-3,4,5), 8.03 (s, 1H, purinH-8). – MS (EI, 50 °C): m/z (%) = 379 (25) [M$^{+\bullet}$], 282 (33) [M$^{+\bullet}$ – NHcyhex+H], 267 (43) [M$^{+\bullet}$ – CH_2NHcyhex], 254 (100) [M$^{+\bullet}$ – CH_2CH_2NHcyhex+H), 241 (49) [M$^{+\bullet}$ – CH_2=$CHCH_2$NHcyhex+H], 177 (18), 91 (71) [$C_7H_7^+$], 56 (13), 41 (12), 30 (26) [CH_2=NH_2^+].

*7-Phenylmethyl-N^6-[3-(pyrrolidinyl)propyl]-7H-purin-2,6-diamine **5b***

From 0.5 g (1.92 mmol) of **3** and 4 mL 3-(pyrrolidinyl)propylamine (method B). Yellow crystals, mp. 156 °C, yield 0.6 g (89%). – Anal. $C_{19}H_{25}N_7$ (351.5). – IR (KBr): ν = 3339 cm^{-1}; 2959; 2826; 1615; 1574; 1480; 1445; 1392; 1371; 1293; 1207; 1150; 791; 728. – ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 1.54 – 1.59 (m, 2H, $NHCH_2CH_2CH_2$), 1.63 (m, 4H, pyrrH-3,4), 2.23 (t, J = 7.0 Hz, 2H, $NHCH_2CH_2CH_2$), 2.33 (brs, 4H, pyrrH-2,5), 3.33 – 3.36 (t, *J* = 6.6 Hz, 2H, after D$_2$O exchange, $NHCH_2$), 5.57 (2 × s, 4H, 2H, D$_2$O exchange, CH_2ph and NH_2), 6.14 (t, *J* = 5.3 Hz, 1H, D$_2$O exchange, NH), 7.11 (d, *J* = 7.1 Hz, 2H, phH-2,6), 7.26 – 7.35 (m, 3H, phH-3,4,5), 8.03 (s, 1H, purinH-8). – MS (EI, 180 °C): m/z (%) = 351 (35) [M$^{+\bullet}$], 268 (60) [M$^{+\bullet}$ – CH_2pyrr+H], 267 (47) [M$^{+\bullet}$ – CH_2pyrr], 254 (100) [M$^{+\bullet}$ – CH_2CH_2pyrr+H], 241 (17) [M$^{+\bullet}$ – CH_2=$CHCH_2$pyrr+H], 224 (15), 177 (35), 163 (14), 134 (21), 91 (75) [$C_7H_7^+$], 84 (74) [CH_2=pyrr$^{+\bullet}$], 65 (10) [$C_5H_5^+$], 42 (19).

*General procedure for the synthesis of type **6** N-(purin-2-yl)benzenecarboxamides [15, 16]*

To a solution of the appropriate benzoic acid (2.3 mmol) in 50 mL chloroform, 2 mL thionyl chloride was added at 75 °C. After 1 h, chloroform and thionyl chloride were removed *in vacuo*. The residue was dissolved in 30 mL pyridine at 100 °C and 0.4 g (1.14 mmol) of the type **4** purin added. The mixture was stirred for 30 – 60 min. After evaporation *in vacuo* the resulting brown syrup was dissolved in 50 mL chloroform and washed with NaOH (1N) three times. The organic phase was concentrated *in vacuo* and purified by column chromatography. For the synthesis of **6c**, **6d**, and **7b** the appropriate benzoyl chlorides were commercially available.

*4-[9-Phenylmethyl-6-(3-(pyrrolidinyl)propylamino)-9H-purin-2-ylaminocarbonyl]-benzoicacid methylester semihydrate **6a***

From 0.6 g (3.34 mmol) of terephthalic acid monomethylester and **4b**. Light brown crystals (SiO_2; CH_2Cl_2/MeOH saturated with NH_3 9 : 1), mp. 70 °C, yield 0.3 g (51%). – Anal. $C_{28}H_{32}N_7O_{3.5}$ (522.6). – ^{1}H-NMR/400 MHz ([D$_6$]DMSO: δ (ppm) = 1.65 (s, 4H, pyrr-3,4-H), 1.70 (m, 2H, $CH_2CH_2CH_2$), 2.40 (m, 6H, pyrr2,5-H and $NHCH_2CH_2CH_2$), 3.39 (brs, after D$_2$O exchange, 2H, $NHCH_2$), 3.89 (s, 3H, CH_3), 5.29 (s, 2H, CH_2ph), 7.26 – 7.35 (m, 5H, ph), 7.89 (s, 1H, D$_2$O exchange, NH), 7.93 – 7.97 (AA′BB′, *J* = 8.3 Hz, 2H, ph-3,5-H), 8.02 (AA′BB′, *J* = 8.4 Hz, 2H, ph-2,6-H), 8.13 (s, 1H, purin-8-H), 10.59 (s, 1H, D$_2$O exchange, CONH). – MS (70 eV, 250 °C): m/z (%) = 514 (3) [M$^{+\bullet}$], 417 (17) [M$^{+\bullet}$ – CH_2CH_2pyrr+H], 91 (56) [$C_7H_7^+$], 84 (100) [CH_2=pyrr$^+$], 57 (30), 42 (57).

*3-Cyano-N-[9-phenylmethyl-6-(3-(pyrrolidinyl)-propylamino)-9H-purin-2-yl]benzenecarboxamide semihydrate **6b***

From 0.5 g (3.4 mmol) of 3-cyanobenzoic acid and **4b**. Light brown crystals (SiO_2; CH_2Cl_2/EtOH saturated with NH_3 8 : 1), mp. 104 °C, yield 0.3 g (54%). – Anal. $C_{27}H_{29}N_8O_{1.5}$ (489.6). – ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 1.66 (s, 4H, pyrr3.4-H), 1.72 – 1.75 (m, 2H $CH_2CH_2CH_2$), 2.41 – 2.45 (m, 6H, pyrr2,5-H and $NHCH_2CH_2CH_2$), 3.42 (brs, 2H, after D$_2$O exchange, $NHCH_2$), 5.31 (s, 2H, CH_2ph), 7.27 – 7.36 (m, 5H, ph), 7.69 (dd, *J* = 7.8/7.8 Hz, 1H, ph5-H), 7.91 (s, 1H, D$_2$O exchange, NH), 8.01 (d, *J* = 7.7 Hz, 1H, ph4-H), 8.15 (m, 2H, ph6-H) and purin8-H), 8.31 (s, 1H, ph2-H), 10.64 (s, 1H, D$_2$O exchange, CONH). – MS (70 eV, 250 °C): m/z (%) = 480 (10) [M$^{+\bullet}$], 383 (77) [M$^{+\bullet}$ – CH_2CH_2pyrr], 91 (73) [$C_7H_7^+$], 84 (100) [CH_2=pyrr$^+$], 42 (17).

*4-Methoxy-N-[9-phenylmethyl-6-(3-(pyrrolidinyl)propyl-amino)-9H-purin-2-yl]benzenecarboxamide **6c***

From 0.3 g (1.76 mmol) of 4-methoxybenzoyl chloride and **4b**. Light yellow crystals (SiO_2; CH_2Cl_2/EtOH saturated with NH_3 8 : 2), mp. 157 °C, yield 0.2 g (36%). – Anal. $C_{27}H_{31}N_7O_2$ (485.6). – ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 1.66 (s, 4H, pyrr3.4-H), 1.75 –

1.78 (tt, *J* = 6.8/6.8 Hz, 2H, $CH_2CH_2CH_2$), 2.45 (m, 6H, pyrr2,5-H and $NHCH_2CH_2CH_2$), 3.47 (s, 2H, $NHCH_2$), 3.83 (s, 3H, OCH_3), 5.32 (s, 2H, CH_2ph), 7.00 (AA'BB`, *J* = 8.8 Hz, 2H, ph3,5-H), 7.27 – 7.34 (m, 5H, ph), 7.87 (s, 1H, D_2O exchange, NH), 7.92 (AA′BB′, *J* = 8.8 Hz, 2H, ph2.6-H), 8.13 (s, 1H, purin8-H), 10.22 (s, 1H, D_2O exchange, CONH). – MS (70 eV, 50°C): m/z (%) = 485 (11) [$M^{+\bullet}$], 401 (21) [$M^{+\bullet}$ – CH_2pyrr], 388 (100) [$M^{+\bullet}$ – CH_2CH_2pyrr+H], 135 (38), 91 (14) [$C_7H_7^+$], 84 (25) [CH_2=pyrr$^+$], 42 (14), 36 (33).

4-Chloro-N-[9-phenylmethyl-6-(3-(pyrrolidinyl)-propylamino)-9H-purin-2-yl]benzenecarboxamide semihydrate ***6d***

From 0.5 g (2.86 mmol) of 4-chlorobenzoyl chloride and **4b**. Yellow crystals (SiO_2; CH_2Cl_2/MeOH saturated with NH_3 9:1), mp. 57°C, yield 0.2 g (36%). – Anal. $C_{26}H_{29}N_7O_{1.5}$ (499.0). – ^{1}H-NMR/400 MHz ([D_6]DMSO): δ (ppm) = 1.66 (s, 4H, pyrr3,4-H), 1.72 – 1.76 (m, 2H, $CH_2CH_2CH_2$), 2.41 – 2.46 (m, 6H, pyrr2,5-H and $NHCH_2CH_2CH_2$), 3.45 (brs, 2H, after D_2O exchange, $NHCH_2$), 5.31 (s, 2H, CH_2ph), 7.27 – 7.36 (m, 5H, ph), 7.53 (AA′BB′, *J* = 8.5 Hz, 2H, ph3,5-H), 7.90 (AA′BB′, *J* = 8.3 Hz, 2H, ph2,6-H), 8.14 (s, 1H, purin8-H), 10.47 (s, 1H, D_2O exchange, CONH). – MS (70 eV, 180°C): m/z (%) = 489 (10) [$M^{+\bullet}$], 396 (85), 91 (73) [$C_7H_7^+$], 84 (100) [CH_2=pyrr$^+$], 55 (14), 42 (21).

3-[Pyrrolidinylsulfonyl]-N-[9-phenylmethyl-6-(3-(pyrrolidinyl)propylamino)-9H-purin-2-yl]benzenecarboxamide ***6e***

From 0.8 g (3.13 mmol) of 4-[pyrrolidinylsulfonyl]benzoic acid and **4b**. Light yellow crystals (SiO_2; CH_2Cl_2/MeOH saturated with NH_3 9:1), mp. 85°C, yield 0.5 g (75%). – Anal. $C_{30}H_{36}N_8O_3S$ (588.7). – ^{1}H-NMR/400 MHz ([D_6]DMSO): δ (ppm) = 1.58 – 1,61 (m, 4H, pyrr3,4-H), 1.66 (s, 4H, pyrr3,4-H), 1.73 (m, 2H, $CH_2CH_2CH_2$), 2.44 (m, 6H, pyrr2,5-H and $NHCH_2CH_2CH_2$), 3.11 (s, 4H, SO_2pyrr2,5-H), 3.39 (brs, 2H, after D_2O exchange, $NHCH_2$), 5.31 (s, 2H, CH_2ph), 7.27 – 7.36 (m, 5H, ph), 7.73 – 7.77 (dd, *J* = 7.8/7.8 Hz, 1H, suph5-H), 7.93 – 7.98 (m, 2H, 1H, D_2O exchange, NH and suph4-H), 8.15 – 8.19 (m, 3H, suph2,6-H and purin8-H), 10.78 (s, 1H, D_2O exchange, CONH). – MS (70 eV, 80 °C): m/z (%) = 588 (11) [$M^{+\bullet}$], 504 (21), 491 (70) [$M^{+\bullet}CH_2$pyrr+H], 478 (17) [$M^{+\bullet}$ – CH_2=$CHCH_2$pyrr+H], 358 (19), 110 (22), 91 (100) [$C_7H_7^+$], 84 (96) [CH_2=pyrr$^+$], 70 (24), 42 (42).

3-[Morpholin-4-ylsulfonyl]-N-[9-phenylmethyl-6-(3-(pyrrolidinyl)propylamino)-9H-purin-2-yl]-benzenecarboxamide ***6f***

From 0.8 g (2.95 mmol) of 3-[morpholin-4-ylsulfonyl]benzoic acid and **4b**. Light yellow crystals (SiO_2; CH_2Cl_2/EtOH saturated with NH_3 8.5:1.5), mp. 85°C, yield 0.5 g (73%). – Anal. $C_{30}H_{36}N_8O_4S$ (604.7). – ^{1}H-NMR/400 MHz ([D_6]DMSO): δ (ppm) = 1.65 (s, 4H, pyrr3,4-H), 1.72 (m, 2H, $CH_2CH_2CH_2$), 2.41 – 2.46 (m, 6H, pyrr2,5-H and $NHCH_2CH_2CH_2$), 2.84 (s, 4H morph3,5-H), 3.41 (brs, 2H, after exchange, $NHCH_2$) 3.59 (s, 4H, morph2,6-H), 5.30 (s, 2H, CH_2ph), 7.26 – 7.36 (m, 5H, ph), 7.76-7.80 (dd, *J* = 7.8 Hz, 1H, suph5-H), 7.88-7.93 (m, 3H, 1H, D_2O exchange, NH and suph4-H), 8.10 – 8.21 (m, 3H, suph2,6-H) and purin8-H), 10.77 (s, 1H, D_2O exchange, CONH). – MS (70 eV, 210 °C): m/z (%) = 504 (11) [$M^{+\bullet}$], 520 (18), 507 (77) [$M^{+\bullet}$ – CH_2CH_2pyrr+H], 494 (11) [$M^{+\bullet}$ – CH_2=$CHCH_2$pyrr+H], 358 (14), 110 (21), 98 (16), 91 (64) [$C_7H_7^+$], 84 (100) [CH_2=pyrr$^+$], 56 (15), 42 (14), 28 (20).

4-[Morpholin-4-ylsulfonyl]-N-[9-phenylmethyl-6-(3-(pyrrolidinyl)propylamino)-9H-purin-2-yl]benzenecarboxamide ***6g***

From 0.8 g (2.95 mmol) of 4-[morpholin-4-ylsulfonyl]benzoic acid and **4b**. Light yellow crystals (SiO_2; CH_2Cl_2/EtOH saturated with NH_3 8.5:1.5), mp. 106°C, yield 0.4 g (58%). – Anal. $C_{30}H_{36}N_8O_4S$ (604.7). – ^{1}H-NMR/400 MHz ([D_6]DMSO): δ (ppm) = 1.65 (s, 4H, pyrr3,4-H), 1.70 – 1.74 (m, 2H, $CH_2CH_2CH_2$), 2.40 – 2.45 (m, 6H, pyrr2,5-H and $NHCH_2CH_2CH_2$), 2.90 (t, *J* = 4.5, 4H morph3,5-H), 3.37 (brs, 2H, after D_2O exchange, $NHCH_2$) 3.64 (t, *J* = 4.6 Hz, 4H, morph2,6-H), 5.29 (s, 2H, CH_2ph), 7.27 – 7.37 (m, 5H, ph), 7.82 (AA′BB′, *J* = 8.3 Hz, 2H, suph3,5-H), 7.91 (s, 1H, D_2O exchange, NH), 8.06 (AA′BB′, *J* = 7.7 Hz, 2H, suph2,6-H), 8.14 (s, 1H, purin8-H), 10.67 (s, 1H, D_2O exchange, CONH). – MS (70 eV, 250°C): m/z (%) = 604 (4) [$M^{+\bullet}$], 520 (12), 507 (48) [$M^{+\bullet}$ – CH_2CH_2pyrr+H], 494 (11) [$M^{+\bullet}$ – CH_2=$CHCH_2$pyrr+H], 110 (24), 91 (67) [$C_7H_7^+$], 84 (100) [CH_2=pyrr$^+$], 56 (21), 42 (20), 28 (19).

3-[(4-Methyl)-piperazinylsulfonyl]-N-[9-phenylmethyl-6-(3-(pyrrolidinyl)propylamino)-9H-purin-2-yl]benzenecarboxamide ***6h***

From 0.6 g (2.11 mmol) of 3-[(4-methyl)piperazinylsulfonyl]benzoic acid and **4b**. Light yellow crystals (SiO_2; CH_2Cl_2/EtOH saturated with NH_3 8.5:1.5), mp. 81°C, yield 0.3 g (43%). – Anal. $C_{31}H_{39}N_9O_3S$ (617.8). – ^{1}H-NMR/400 MHz ([D_6]DMSO): δ (ppm) = 1.65 (s, 4H, pyrr3,4-H), 1.72 (m, 2H, $CH_2CH_2CH_2$), 2.12 (s, 3H, CH_3), 2.32 (s, 4H, mepipera3,5-H), 2.41 – 2.46 (m, 6H, pyrr2,5-H and $NHCH_2CH_2CH_2$), 2.86 (s, 4H, mepipera2,6-H), 3.43 (brs, 2H, after D_2O exchange, $NHCH_2$), 5.29 (s, 2H, CH_2ph), 7.26 – 7.36 (m, 5H, ph), 7.74-7.78 (dd, *J* = 7.8 Hz, 1H, suph5-H), 7.87 – 7.92 (m, 2H, 1H, D_2O exchange, NH and suph4-H), 8.09 – 8.19 (m, 3H, suph2,6-H and purin8-H), 10.77 (s, 1H, D_2O exchange, CONH). – MS (70 eV, 210°C): m/z (%) = 617 (1) [$M^{+\bullet}$], 254 (16). 99 (45), 91 (32) [$C_7H_7^+$], 84 (100) [CH_2pyrr$^+$], 56 (19), 42 (17).

3-[4-Pyrimidin-2-yl)-piperazinylsulfonyl]-N-[9-phenylmethyl-6-(3-(pyrrolidinyl)propylamino)-9H-purin-2-yl]benzenecarboxamide ***6i***

From 0.9 g (2.58 mmol) of 3-[4-pyrimidin-2-yl)piperazinylsulfonyl]benzoic acid and **4b**. Brown crystals (SiO_2; CH_2Cl_2/EtOH saturated with NH_3 8: 2), mp. 98°C, yield 0.3 g (39%). – Anal. $C_{34}H_{39}N_{11}O_3S$ (681.8). – ^{1}H-NMR/400 MHz ([D_6]DMSO): δ (ppm) = 1.63 (s, 4H, pyrr3,4-H), 1.72 (m, 2H, $CH_2CH_2CH_2$), 2.40 – 2.45 (s, 6H, pyrr2,5-H and $NHCH_2CH_2CH_2$), 2.96 (m, 4H, pipera3,5-H), 3.43 (brs, 2H, after D_2O exchange, $NHCH_2$), 3.81 (s, 4H, mepipera2,6-H), 5.29 (s, 2H, CH_2ph), 6.64 (dd, *J* = 4.8 Hz, 1H, pyrim5-H), 7.26 – 7.34 (m, 5H, ph), 7.72 – 7.76 (dd, *J* = 7.8 Hz, 1H, suph5-H), 7.90 (m, 2H, 1H, after D_2O exchange, NH and suph4-H), 8.14 – 8.18 (m, 3H, suph2,6-H) and purin8-H), 8.33 (d, *J* = 4.7 Hz, 2H, pyrim4,6-H), 10.75 (s, 1H, D_2O exchange, CONH). – MS (70 eV, 60°C): m/z (%) = 681 (1) [$M^{+\bullet}$], 254 (30), 163 (66) [piperapyrim$^{+\bullet}$] 91 (43) [$C_7H_7^+$], 84 (100) [CH_2pyrr$^+$], 56 (28), 42 (17), 28 (20).

3-[N-(Phenylmethyl)aminosulfonyl]-N-[9-phenylmethyl-6-(3-(pyrrolidinyl)propylamino)-9H-purin-2-yl]benzenecarboxamide ***6j***

From 0.6 g (2.1 mmol) of 3-[4-phenylmethyl)aminosulfonyl]benzoic acid and **4b**. Light brown crystals (SiO_2; CH_2Cl_2/EtOH saturated with NH_3 9: 1), mp. 104°C, yield 0.2 g (42%). – Anal.

$C_{33}H_{36}N_8O_3S$ (624.8). – ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 1.65 (s, 4H, pyrr3,4-H), 1.68 – 1.72 (m, 2H, $CH_2CH_2CH_2$), 2.39 – 2.45 (m, 6H, pyrr2,5-H and $NHCH_2CH_2CH_2$), 3.41 (brs, 2H, after D_2O exchange, $NHCH_2$), 3.96 (s, 2H, $NHCH_2$ph), 5.31 (s, 2H, CH_2ph), 7.21-7.36 (m, 10H, 2xph), 7.68 (dd, *J* = 7.8 Hz, 1H, suph5-H), 7.94 (d, *J* = 8.0 Hz, 1H, suph4-H), 8.10 (d, *J* = 7.7 Hz, 1H, suph6-H), 8.14 (s, 1H, purin8-H), 8.26 (s, 1H, suph2-H), 10.66 (s, 1H, D_2O exchange, CONH). – MS (70 eV, 80°C): m/z (%) = 624 (1) [M$^{+\bullet}$], 527 (28) [M$^{+\bullet}$ – CH_2CH_2pyrr+H], 91 (91) [$C_7H_7^+$], 84 (100) [CH_2=pyrr$^+$], 28 (25).

3-[N,N-Diethylaminosulfonyl]-N-[9-phenylmethyl-6-(3-(pyrrolidinyl)propylamino)-9H-purin-2-yl]benzenecarboxamide ***6k***

From 0.5 g (1.94 mmol) of 3-[N,N-diethylaminosulfonyl]benzoic acid and **4b**. Light yellow crystals (SiO_2; CH_2Cl_2/EtOH saturated with NH_3 8.5:1.5), mp. 65°C, yield 0.5 g (75%). – Anal. $C_{30}H_{38}N_8O_3S$ (590.8). – ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 1.02 (t, *J* = 7.1 Hz, 6H, 2 × CH_3), 1.65 (s, 4H, pyrr3,4-H), 1.72 (m, 2H, $CH_2CH_2CH_2$), 2.40 – 2.44 (m, 6H, pyrr2,5-H and $NHCH_2CH_2CH_2$), 3.10 – 3.15 (q, *J* = 6.9 Hz, 4H, $SO_2N(CH_2CH_3)_2$), 3.39 (brs, 2H, after D_2O exchange, $NHCH_2$), 5.30 (s, 2H, CH_2ph), 7.29 – 7.36 (m, 5H, ph), 7.69 – 7.73 (dd, *J* = 7.8/7.8 Hz, 1H, suph5-H), 7.95 (d, *J* = 7.7 Hz, 2H, 1H after D_2O exchange, suph4-H), 8.14 (m, 3H, suph2,6-H and purin8-H), 10.75 (s, 1H, D_2O exchange, CONH). – MS ([+]-FAB, DMSO/m-NO_2-C_6H_4OH): m/z (%) = 591 (45) [M$^{+\bullet}$+H], 110 (46), 105 (22), 91 (69) [$C_7H_7^+$], 84 (100) [CH_2=pyrr$^+$], 55 (16).

3-[N-(2-Methoxyethyl)aminosulfonyl]-N-[9-phenylmethyl-6-(3-(pyrrolidinyl)propylamino)-9H-purin-2-yl]benzenecarboxamide semihydrate ***6l***

From 0.8 g (3.09 mmol) of 3-[*N*-(2-methoxyethyl)aminosulfonyl]-benzoic acid and **4b**. Light brown crystals (SiO_2; CH_2Cl_2/EtOH saturated with NH_3 8:2), mp. 73°C, yield 0.1 g (15%). – Anal. $C_{29}H_{37}N_8O_{4.5}S$ (601.7). – ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 1.65 (s, 4H, pyrr3,4-H), 1.74 (m, 2H, $CH_2CH_2CH_2$), 2.41 – 2.46 (m, 6H, pyrr2,5-H and $NHCH_2CH_2CH_2$), 2.88 – 2.91 (t, *J* = 5.6 Hz, 2H, $NHCH_2CH_2OCH_3$), 3.14 (s, 3H, OCH_3), 3.27 (t, *J* = 5.6 Hz, 2H, after D_2O exchange, $NHCH_2CH_2OCH_3$), 3.41 (brs, 2H $NHCH_2$), 5.31 (s, 2H, CH_2ph), 7.27 – 7.36 (m, 5H, ph), 7.67 – 7.71 (dd, *J* = 7.8 Hz, 1H, suph5-H), 7.91 – 7.96 (m, 2H, 1H after D_2O exchange, suph4-H), 8.10 – 8.15 (m, 2H, suph6-H and purin8-H), 8.25 (s, 1H, suph2-H), 10.68 (s, 1H, D_2O exchange, CONH). – MS (70 eV, 130°C): m/z (%) = 592 (6) [M$^{+\bullet}$], 495 (48) [M$^{+\bullet}$ – CH_2CH_2pyrr+H], 254 (18), 91 (59) [$C_7H_7^+$], 84 (100) [CH_2=pyrr$^+$], 42 (17), 28 (16).

4-[N-(2-Methoxyethyl)aminosulfonyl]-N-[9-phenylmethyl-6-(3-(pyrrolidinyl)propylamino)-9H-purin-2-yl]benzenecarboxamide ***6m***

From 0.8 g (3.09 mmol) of 4-[N-(2-methoxyethyl)aminosulfonyl]-benzoic acid and **4b**. Light brown crystals (SiO_2; CH_2Cl_2/EtOH saturated with NH_3 8: 2), mp. 73°C, yield 0.1 g (15%). – Anal. $C_{29}H_{36}N_8O_4S$ (592.7). – ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 1.66 (s, 4H, pyrr3,4-H), 1.73 (m, 2H, $CH_2CH_2CH_2$), 2.44 (m, 6H, pyrr2,5-H and $NHCH_2CH_2CH_2$), 2.88 – 2.91 (dt, *J* = 5.5/5.5 Hz, 2H, $NHCH_2CH_2OCH_3$), 3.15 (s, 3H, OCH_3), 3.30 – 3.33 (t, *J* = 5.4 Hz, 2H, after D_2O exchange, $NHCH_2CH_2OCH_3$), 3.40 (brs, 2H, after D_2O exchange, $NHCH_2$), 5.33 (s, 2H, CH_2ph), 7.31 – 7.36 (m, 5H, ph), 7.86 – 7.91 (m, 4H, 2H, after D_2O exchange, suph3,5-H and 2xNH), 8.02 (AA′BB′, J = 8.1 Hz, 2H, suph2,6-H), 8.14 (s, 1H, purin8-H), 10.63 (brs, 1H, D_2O exchange, CONH). – MS (70 eV, 180°C): m/z (%) = 592 (2) [M$^{+\bullet}$], 495 (28) [M$^{+\bullet}$ – CH_2CH_2pyrr+H], 351 (20), 267 (18), 254 (31), 91 (72) [$C_7H_7^+$], 84 (100) [CH_2=pyrr$^+$], 42 (20), 28 (52).

3-[N-(3-Methoxypropyl)aminosulfonyl]-N-[9-phenylmethyl-6-(3-(pyrrolidinyl)propylamino)-9H-purin-2-yl]benzenecarboxamide ***6n***

From 0.8 g (2.93 mmol) of 3-[*N*-(3-methoxypropyl)aminosulfonyl]-benzoic acid and **4b**. Light yellow crystals (SiO_2; CH_2Cl_2/EtOH saturated with NH_3 8:2), mp. 67°C, yield 0.3 g (43%). – Anal. $C_{30}H_{38}N_8O_4S$ (606.8). – ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 1.54 – 1.61 (tt, *J* = 6.9/6.9 Hz, 2H, $CH_2CH_2CH_2OCH_3$), 1.66 (s, 4H, pyrr3,4-H), 1.74 (m 2H, $CH_2CH_2CH_2$), 2.42 – 2.47 (m, 6H, pyrr2,5-H and $NHCH_2CH_2CH_2$), 2.88 – 2.91 (dt, *J* = 6.6/6.6 Hz, 2H, $NHCH_2CH_2OCH_3$), 3.15 (s, 3H, OCH_3), 3.24 – 3.27 (t, *J* = 6.2 Hz, 2H, after D_2O exchange, $NHCH_2CH_2OCH_3$), 3.41 (brs, 2H, after D_2O exchange, $NHCH_2$), 5.31 (s, 2H, CH_2ph), 7.27 – 7.37 (m, 5H, ph), 7.68 – 7.72 (m, 2H, 1H after D_2O exchange, suph5-H and NH), 7.91 – 7.95 (m, 2H, 1H, after D_2O exchange, suph4-H), 8.11 – 8.15 (m, 2H, suph6-H and purin8-H), 8.24 (s, 1H, suph2-H), 10.69 (s, 1H, after D_2O exchange, CONH). – MS (70 eV, 100°C): m/z (%) = 606 (3) [M$^{+\bullet}$], 509 (27) [M$^{+\bullet}$ – CH_2CH_2pyrr+H], 254 (21), 91 (70),) [$C_7H_7^+$], 84 (100) [CH_2=pyrr$^+$], 42 (21), 30 (26), 28 (25).

4-[N-(3-Methoxypropyl)aminosulfonyl]-N-[9-phenylmethyl-6-(3-(pyrrolidinyl)propylamino)-9H-purin-2-yl]benzenecarboxamide semihydrate ***6o***

From 0.8 g (2.93 mmol) of 4-[*N*-(3-methoxypropyl)aminosulfonyl]-benzoic acid. Yellow crystals (SiO_2; CH_2Cl_2/EtOH saturated with NH_3 8:2), mp. 83°C, yield 0.2 g (28%). – Anal. $C_{30}H_{39}N_8O_{4.5}S$ (615.8). – ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 1.56 – 1.61 (tt, *J* = 6.8/6.8 Hz, 2H, $CH_2CH_2CH_2OCH_3$), 1.66 (s, 4H, pyrr2,4-H), 1.72 (m 2H, $CH_2CH_2CH_2$), 2.43 – 2.47 (m, 6H, pyrr2,5-H and $NHCH_2$ CH_2CH_2), 2.79 – 2.84 (dt, *J* = 6.7/6.7 Hz, 2H, $NHCH_2CH_2OCH_3$), 3.15 (s, 3H, OCH_3), 3.27-3.32 (t, *J* = 6.1 Hz, 2H, after D_2O exchange, $NHCH_2CH_2CH_2OCH_3$), 3.42 (s, 2H, after D_2O exchange, $NHCH_2$), 5.30 (s, 2H, CH_2ph), 7.28 – 7.37 (m, 5H, ph), 7.74 – 7.77 (t, *J* = 5.8 Hz, 1H, D_2O exchange, NH), 7.85 (AA′BB′, *J* = 8.4 Hz, 2H, suph3,5-H), 7.92 (s, 1H, D_2O exchange, NH), 8.02 (AA'BB`, *J* = 8.1 Hz, 2H, suph2,6-H), 8.15 (s, 1H, purin8-H), 10.64 (s, 1H, D_2O exchange, CONH). – MS (70 eV, 40°C): m/z (%) = 606 (3) [M$^{+\bullet}$], 509 (24) [M$^{+\bullet}$ – CH_2CH_2pyrr+H], 351 (30), 267 (24), 254 (50), 91 (81) [$C_7H_7^+$], 84 (100) [CH_2=pyrr$^+$], 42 (22).

3-[N,N-bis-(2-Methoxyethyl)aminosulfonyl]-N-[9-phenylmethyl-6-(3-(pyrrolidinyl)propylamino)-9H-purin-2-yl]-benzenecarboxamide ***6p***

From 0.6 g (1.89 mmol) of 3-[*N*,*N*-bis(3-methoxyethyl)aminosulfonyl]benzoic acid and **4b**. Crystals (SiO_2; CH_2Cl_2/EtOH saturated with NH_3 8,5:1,5), mp. 67°C, yield 0.4 g (54%). – Anal. $C_{32}H_{42}N_8O_5S$ (650.8). – ^{1}H-NMR/400 MHz ([D$_6$]DMSO): δ (ppm) = 1.85 (s, 4H, pyrr3,4-H), 1.94 (m, 2H, $CH_2CH_2CH_2$), 2.64 (m, 6H, pyrr2,5-H and $NHCH_2CH_2CH_2$), 3.37 (s, 6H, 2 × OCH_3), 3.30 – 3.33 (m, 4H, after D_2O exchange, $N(CH_2CH_2OCH_3)_2$), 3.40 – 3.43 (m, 6H, after D_2O exchange, $NHCH_2$ and $N(CH_2CH_2OCH_3)_2$), 5.50 (s, 2H, CH_2ph), 7.46 – 7.53 (m, 5H, ph), 7.88 – 7.92 (dd, *J* = 7.8/7.8 Hz, 1H, suph5-H), 8.11 (s, 1H, D_2O exchange, NH), 8.18 (d, *J* = 7.9 Hz, 1H, suph4-H), 8.34 (m, 2H, suph6-H and purin 8-H), 8.43 (s, 1H, suph2-H), 10.94 (s, 1H, D_2O exchange, CONH). – MS (70 eV, 80°C): m/z

(%) = 650 (5) [$M^{+\bullet}$], 553 (40) [$M^{+\bullet} - CH_2CH_2$pyrr+H], 254 (17), 91 (89), [$C_7H_7^+$], 84 (100) [CH_2=pyrr$^+$], 42 (25), 28 (49).

4-[N,N-bis-(2-Methoxyethyl)aminosulfonyl]-N-[9-phenylmethyl-6-(3-(pyrrolidinyl)propylamino)-9H-purin-2-yl]-benzenecarboxamide semihydrate ***6q***

From 0.8 g (2.52 mmol) of 4-[*N*,*N*-bis(2-methoxyethyl)aminosulfonyl]benzoic acid and **4b**. Light brown crystals (SiO_2; CH_2Cl_2/EtOH saturated with NH_3 8 : 2), mp. 75°C, yield 0.3 g (40%). – Anal. $C_{32}H_{43}N_8O_{5.5}S$ (659.8). – ^{1}H-NMR/400 MHz ([D_6]DMSO): δ (ppm) = 1.70 (s, 4H, pyrr3,4-H), 1.76 – 1.80 (m, 2H, $CH_2CH_2CH_2$), 2.57 (m, 6H, pyrr2,5-H and $NHCH_2CH_2CH_2$), 3.19 (s, 6H, 2 × OCH_3), 3.38 (m, 4H, after D_2O exchange, $N(CH_2CH_2OCH_3)_2$), 3.44 (m, 6H, after D_2O exchange, $NHCH_2$ and $N(CH_2CH_2OCH_3)_2$), 5.31 (s, 2H, CH_2ph), 7.27 – 7.37 (m, 5H, ph), 7.89 – 7.93 (m, 3H, 2H after D_2O exchange, suph3,5-H and NH), 8.04 (AA′BB′, *J* = 8.3 Hz, 2H, suph2,6-H), 8.16 (s, 1H, purin8-H), 10.69 (s, 1H, D_2O exchange, CONH). – MS (70 eV, 80°C): m/z (%) = 650 (19) [$M^{+\bullet}$], 553 (50) [$M^{+\bullet} - CH_2CH_2$pyrr+H], 272 (27), 254 (14), 91 (57) [$C_7H_7^+$], 84 (100) [CH_2=pyrr$^+$], 56 (28), 42 (25), 28 (30).

N-[6-[3-Cyclohexylamino)-propylamino]-9-phenylmethyl-9H-purin-2-yl]-3-cyanobenzenecarboxamide hydrate ***7b***

From 0.16 g (0.97 mmol) of 3-cyanobenzoic acid and 0.19 g (0.5 mmol) and **4a**. Light yellow crystals (SiO_2; CH_2Cl_2/EtOH saturated with NH_3 7.5 : 1), mp. 108°C, yield 0.20 g (76%). – Anal. $C_{29}H_{32}N_8O.H_2O$ (508.6). – ^{1}H-NMR/400 MHz ([D_6]DMSO): δ (ppm) = 1.0 – 1.2 (m, 5H, cyhex-H2a,3a,4a,5a,6a), 1.55 (m, 1H, cyhex-H4e), 1.63 (m, 2H, cyhex-H3e,5e), 1.75 (m, 2H, $-CH_2$-CH_2-CH_2), 1.83 (m, 2H, cyhex-H2e,6e), 2.41 (m, 1H, cyhex-H1a), 2.65 (dt, *J* = 6/6 Hz, 2-H, $-CH_2$-NH-cyhex), 3.35 (brs, 2H, NH, D_2O exchange), 3.5 (brs, 2H, CH_2-NH-purin), 5.33 (s, 2H, CH_2-ph), 7.3 (m, 5H, ph), 7.7 (dd, *J* = 8/8 Hz, 1H, H-5), 8.03 (d, *J* = 8 Hz, 1H, H-4), 8.17 (m, 2H, H-2,6), 8.32 (s, 1H, purinH-8). – MS (EI, 190°C): m/z (%) = 508 (9) [$M^{+\bullet}$], 383 (61), 370 (42), 242 (44), 130 (51), 112 (33), 91 (100).

N-[9-Phenylmethyl-6-[3-(pyrrolidinyl)propylamino]-9H-purin-2-yl]furane-2-carboxamide-semihydrate ***8***

From 0.4 g (3.08 mmol) of furane-2-carboxylicacid chloride and 0.4 g (1.14 mmol) and **4b**. Light brown crystals (SiO_2; CH_2Cl_2/EtOH saturated with NH_3 8 : 2), mp. 65°C, yield 0.1 g (19%). – Anal. $C_{24}H_{28}N_7O_{2.5}$ (454.5). – IR (KBr): δ = 3421 cm^{-1}; 2958; 2797; 1693; 1620; 1517; 1464; 1384; 1260; 1165; 724. ^{1}H-NMR/400 MHz ([D_6]DMSO): δ (ppm) = 1.68 (brs, 4H, pyrrH-3,4), 1.75 – 1.82 (tt, *J* = 7.0/7.0 Hz, 2H, $CH_2CH_2CH_2$), 2.45 (m, 6H, pyrrH-2,5 and $NHCH_2CH_2CH_2$), 3.50 (brs, 2H, $NHCH_2$), 5.32 (s, 2H, CH_2ph), 6.67 (m, 1H, furaneH-4), 7.28 – 7.35 (m, 5H, ph), 7.42 (d, *J* = 3.4 Hz, 1H, furaneH-5), 7.90 (s, 1H, furaneH-3), 7.93 (brs, 1H, D_2O exchange, NH), 8.15 (s, 1H, purinH-8), 10.10 (s, 1H, D_2O exchange, CONH). – MS (EI, 40°C): m/z (%) = 445 (14) [$M^{+\bullet}$], 361 (25) [$M^{+\bullet} - CH_2$pyrr], 348 (100) [$M^{+\bullet} - CH_2CH_2$pyrr+H], 91 (40) [$C_7H_7^+$], 84 (34) [CH_2=pyrr$^+$], 28 (28).

Biology

The Born test was carried out as reported in detail recently in this journal [4].

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