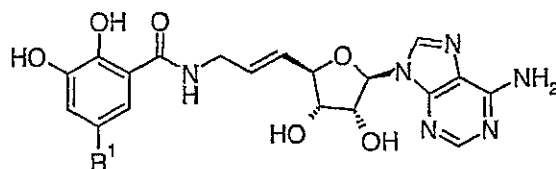


COMT inhibitors

The invention relates to purine derivatives of formula



I

wherein

- 5 R^1 is H, CN, halogen, $-COR^2$, $-S(O)_xR^2$, C_{1-12} -alkyl, C_{2-12} -alkenyl, C_{3-8} -cycloalkyl, a heterocyclyl group, an aryl group, a heteroaryl group, C_{3-8} -cycloalkyl- (C_{1-3}) -alkyl, a heterocyclyl- (C_{1-3}) -alkyl group, an aryl- (C_{1-3}) -alkyl or a heteroaryl- (C_{1-3}) -alkyl group; the alkyl, alkenyl, alkoxy, cycloalkyl, heterocyclyl group, aryl and
- 10 R^2 is $-N(R^3, R^3)$, C_{1-6} -alkyl, C_{3-8} -cycloalkyl, heterocyclyl, aryl, heteroaryl, C_{3-8} -cycloalkyl- (C_{1-3}) -alkyl, a heterocyclyl- (C_{1-3}) -alkyl group, an aryl- (C_{1-3}) -alkyl or a heteroaryl- (C_{1-3}) -alkyl group, the C_{1-6} -alkyl, C_{3-8} -cycloalkyl, heterocyclyl, aryl, heteroaryl may all be
- 15 R^3 and R^3 are independently hydrogen or (C_{1-3}) -alkyl;
- x is 0, 1 or 2;

and to the ester thereof which are hydrolyzable under physiological conditions and the pharmaceutically acceptable salts thereof.

- 20 Objects of the present invention are the compounds of formula I per se, the use of compounds of formula I and their pharmaceutically acceptable salts for the manufacture of medicaments for the treatment of diseases, related to the COMT inhibition, their manufacture, medicaments based on a compound in accordance with the invention and their production as well as the use of compounds of formula I in the control or
- 25 prevention of diseases such as depression, schizophrenia, Parkinson's disease, and to improve cognition.

POP/28.09.2004

The compounds of formula I possess valuable pharmacological properties. In particular, these compounds inhibit the enzyme catechol-O-methyltransferase (COMT), a magnesium-dependent enzyme which catalyzes the transfer of the methyl group of S-adenosylmethionine to a catechol substrate, whereby the corresponding methyl ethers are
5 formed. Suitable substrates which can be O-methylated by COMT and which can thus be deactivated are, for example, extraneuronal catecholamines and exogenously-administered therapeutically active substances having a catechol structure.

The compounds of formula I above can accordingly be used in the prevention or control of illnesses in which a deactivation of extraneuronal catecholamines by COMT plays a
10 role, for example, in the prevention or control of depressions. In this case the compounds of formula I above can be used as individual compounds or in combination with other therapeutically active substances which favorably influence the course of the illness. The compounds of formula I can, however, also be used as co-medications with other therapeutically active substances. In addition the compounds of formula I are COMT
15 inhibitors that lack the potential toxicity associated with nitrocatechol containing compounds (K. S. Smith, P. L. Smith, T. N. Heady, J. M. Trugman, W. D. Harman, T. L. Macdonald, Chem. Res. Toxicol. 2003, 16, 123-128; M. d'Ischia, C. Costantini, Bioorganic & Medicinal Chemistry 1995, 3, 923-927).

The compounds of formula I can also be used for the control of illnesses with
20 therapeutically active substances which have a catechol structure. The treatment of Parkinson's disease and of parkinsonism with L-dopa, a therapeutically active substance having the catechol structure, can be mentioned as an example. In such cases the compounds of formula I can be used in the form of a co-medication or as combination preparations.

25 Numerous documents describe the current knowledge on COMT- inhibition, for example - in the field of depression
Fava, M., J. F. Rosenbaum, A. R. Kolsky, J. E. Alpert, A. A. Nierenberg, M. Spillmann, C. Moore, P. Renshaw, T. Bottiglieri, G. Moroz, and G. Magni. Open study of the catechol-O-methyltransferase inhibitor tolcapone in major depressive disorder. J Clin
30 Psychopharmacol 1999, 19, 329.

- in the field of schizophrenia:

Weickert, C. S., and D. R. Weinberger. A candidate molecule approach to defining developmental pathology in schizophrenia. Schizophr Bull 1998, 24, 303.

- Weinberger, D. R., M. F. Egan, A. Bertolino, J. H. Callicott, V. S. Mattay, B. K. Lipska, K. F. Berman, and T. E. Goldberg. Prefrontal neurons and the genetics of schizophrenia. *Biol Psychiatry* 2001, 50, 825.
- Egan, M. F., T. E. Goldberg, B. S. Kolachana, J. H. Callicott, C. M. Mazzanti, R. E. Straub,
 5 D. Goldman, and D. R. Weinberger. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proc Natl Acad Sci U S A* 2001, 98, 6917
- in the field of Parkinson's Disease
- Two COMT inhibitors are marketed for improvement of levodopa therapy,
 Tasmar/Tolcapone
- 10 M. C. Kurth, C. H. Adler, M. St. Hilaire, C. Singer, C. Waters, P. LeWitt, D. A. Chernik, E. E. Dorflinger, K. Yoo,; Tolcapone improves motor function and reduces levodopa requirement in patients with Parkinson's disease experiencing motor fluctuations: A multicenter, double-blind, randomized, placebo-controlled trial. *Neurology*, 1997, 48, 81-87;
- 15 V. V. Myllylä, M. Jackson, J. P. Larsen, H. Baas, *Eur. J Neurol.*, 1997, 4, 333-341);
 Pfeiffer, Ronald F. Catechol-O-methyltransferase in Parkinson's disease. *Neurological Disease and Therapy* (2003), 59(Handbook of Parkinson's Disease (3rd Edition)), 437-451;
- and Entacapone
- 20 Gershanik, Oscar; Emre, Murat; Bernhard, Gudrun; Sauer, Dirk. Efficacy and safety of levodopa with entacapone in Parkinson's disease patients suboptimally controlled with levodopa alone, in daily clinical practice: an international, multicentre, open-label study. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 2003, 27(6), 963-971.
- in the field of cognition improvement
- 25 Lachman, H. M., D. F. Papolos, T. Saito, Y. M. Yu, C. L. Szumlanski, and R. M. Weinshilboum. Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. *Pharmacogenetics* 1996, 6, 243.
- Malhotra, A. K., L. J. Kestler, C. Mazzanti, J. A. Bates, T. Goldberg, and D. Goldman. A
 30 functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. *Am J Psychiatry* 2002, 159, 652.

The following definitions of the terms used in the present description shall apply irrespective whether these terms are used alone or in combination.

The term "C₁₋₁₂-alkyl" denotes a straight or branched chain hydrocarbon group with 1 to 12 carbon atoms, especially with 1 to 6 carbon atoms. Examples of such groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, tert.-pentyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl and 2-ethylbutyl; the alkyl groups may optionally be substituted by halogen, hydroxy, alkoxy, especially by halogen. Examples of such substituted alkyl groups are, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, trichloromethyl, hydroxymethyl, methoxymethyl, 2-methoxyethyl, and the like.

The term "C₁₋₁₂-alkoxy" represent an alkyl-O- group, where the alkyl part is as defined above.

The term "C₃₋₈-cycloalkyl" represents a saturated cyclic hydrocarbon such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; the cycloalkyl group may optionally be substituted by an alkyl group as defined above. Examples of such substituted groups are methylcyclopropyl, ethylcyclopropyl, methylcyclobutyl, methylcyclopentyl, methyl-2-cyclopentenyl, methyl-3-cyclopentenyl or methylcyclohexyl.

The term "heterocyclyl" represents 3- to 7-membered non-aromatic heterocyclic group containing 1 or 2 hetero atoms selected from nitrogen, oxygen and sulfur or sulfur oxidized to sulfones or sulfoxides. Examples of such groups are oxiranyl, azetidiny, oxetanyl, thietanyl, pyrrolidiny, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl and piperazinyl. Preferred heterocycles are piperidyl and morpholinyl. Such heterocyclic groups may optionally be substituted by alkyl or alkoxy.

The term "aryl" represents an mono- or bicyclic aromatic hydrocarbon group having 6 to 10 carbon atoms, examples of such groups are phenyl or naphthyl, a preferred aryl group is phenyl. These aryl groups may optionally be further substituted by one or several substituents chosen from halogen, alkyl or alkoxy groups as defined above. Examples of such substituted aryl groups are, 2, 3 or 4-fluorophenyl, 2, 3 or 4-bromophenyl, 2, 3 or 4-chlorophenyl, 2, 3 or 4-methylphenyl, 2,6- or 3,5-difluorophenyl, 2,6- or 3,5-dichlorophenyl, 2,6- or 3,5-dibromophenyl or 2,6- or 3,5-dimethylphenyl, and the like.

The term "heteroaryl group" represents 5- or 6- membered aromatic mono- or bicyclic heterocyclic group having 1 to 4 heteroatoms chosen from N, O and S. Examples of such aromatic heterocyclic groups include pyridyl, pyrimidinyl, pyridazinyl, pyrrolyl, furanyl, thiophenyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, thiazolyl, oxazolyl, 1,2,4-

oxadiazolyl, 1,2,3-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,4-triazolyl, 1,3,4-triazolyl, 1,2,3-triazolyl and tetrazolyl; examples of bicyclic heteroaryl groups are benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, 5 benzisothiazolyl, benzodioxolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolyl, quinazolinyl, quinoxalyl or phthalazinyl.

The "heteroaryl groups" may be further substituted by halogen or an alkyl group as defined above.

"Halogen" stand for fluorine, chlorine, bromine or iodine.

- 10 Preferred compounds of formula I are compounds wherein R^1 is a hydrogen, cyano, halogen, $-\text{COR}^2$, $-\text{S}(\text{O})_2\text{R}^2$, C_{1-6} -alkyl, C_{1-6} -alkyl substituted with halogen, C_{2-6} -alkenyl substituted with COR^2 , phenyl or phenyl substituted with C_{1-6} -alkyl or halogen, benzyl or benzyl substituted with C_{1-6} -alkyl, or heteroaryl such as pyridinyl, thiazolyl or benzthiazolyl and
- 15 wherein R^2 is C_{1-6} -alkyl, C_{1-6} -alkyl substituted with halogen or $-\text{N}(\text{R}^3, \text{R}^{3'})$ and R^3 and $\text{R}^{3'}$ are C_{1-3} -alkyl, furthermore wherein R^2 is phenyl or phenyl substituted with C_{1-6} -alkyl or halogen, cyclohexyl, or heteroaryl such as pyridinyl, thiazolyl or benzthiazolyl.

Preferred compounds are the compounds of formula I wherein R^1 is hydrogen cyano or halogen, such as for example

- 20 N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-benzamide (Example 1)
 N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-5-cyano-2,3-dihydroxy-benzamide (Example 3)
 N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-5-bromo-
 25 2,3-dihydroxy-benzamide (Example 2)
 N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-5-chloro-2,3-dihydroxy-benzamide (Example 7)

- Further preferred compounds are the compounds of formula I wherein R^1 is C_{1-6} -alkyl, C_{1-6} -alkyl substituted with halogen, C_{2-6} -alkenyl substituted with COR^2 , and wherein R^2 is
- 30 $-\text{NR}^3, \text{R}^{3'}$ and R^3 and $\text{R}^{3'}$ are C_{1-3} -alkyl, such as for example
 N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-isopropyl-benzamide (Example 17)
 N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-5-(2-dimethylcarbamoyl-vinyl)-2,3-dihydroxy-benzamide (Example 15)

N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-trifluoromethyl-benzamide (Example 16)

- A further group of preferred compounds of formula I are the compounds wherein R^1 is -COR² and R^2 is C₁₋₆-alkyl, C₁₋₆-alkyl substituted with halogen, -N(R³,R^{3'}) and R³ and R^{3'} are C₁₋₃₆-alkyl, such compounds are for example
- 5 N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-trifluoroacetyl-benzamide (Example 4)
- N3-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-4,5-dihydroxy-N1,N1-dimethyl-isophthalamide (Example 14)

- 10 A further group of preferred compounds of formula I are the compounds wherein R^1 is -COR², and wherein R^2 is phenyl, phenyl substituted with C₁₋₆-alkyl or halogen, C₃₋₈-cyclohexyl, or heteroaryl such as pyridinyl, thiazolyl or benzthiazolyl, for example
- N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-(4-methyl-benzoyl)-benzamide (Example 18)
- 15 N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-5-cyclohexanecarbonyl-2,3-dihydroxy-benzamide (Example 6)
- N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-(pyridine-4-carbonyl)-benzamide (Example 5)

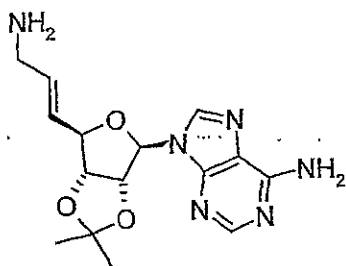
- A further preferred group of compounds are the compounds of formula I wherein R^1 is -S(O)₂R², and wherein R^2 is C₁₋₆-alkyl, C₁₋₆-alkyl substituted with halogen, -N(R³,R^{3'}) and R³ and R^{3'} are C₁₋₃-alkyl, furthermore wherein R^2 is phenyl, phenyl substituted with C₁₋₆-alkyl or halogen, cyclohexyl, or heteroaryl such as pyridinyl, thiazolyl or benzthiazolyl, for example
- 20 N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-(toluene-4-sulfonyl)-benzamide (Example 18)
- 25

- A further preferred group of compounds are the compounds of formula I wherein R^1 is phenyl or phenyl substituted with C₁₋₆-alkyl or halogen, pyridinyl, thiazolyl, benzthiazolyl, benzyl or benzyl substituted with C₁₋₆-alkyl, such as for example
- 4'-Fluoro-4,5-dihydroxy-biphenyl-3-carboxylic acid {3-[5-(6-amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-amide (Example 8)
- 30 N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-thiazol-2-yl-benzamide (Example 10)
- N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-pyridin-4-yl-benzamide (Example 12)

- 4,5-Dihydroxy-4'-methyl-biphenyl-3-carboxylic acid {3-[5-(6-amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-amide (Example 9)
- N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-5-benzothiazol-2-yl-2,3-dihydroxy-benzamide (Example 11)
- 5 N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-(4-methyl-benzyl)-benzamide (Example 13)

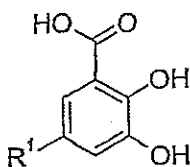
The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by process described below, which process comprises

- 10 a) reacting 9-[(3*aR*,4*R*,6*R*,6*aR*)-6-[(*E*)-3-aminoprop-1-enyl]-2,2-dimethylperhydro-furo[3,4-*d*][1,3]di-oxol-4-yl]-9H-purin-6-amine of formula II

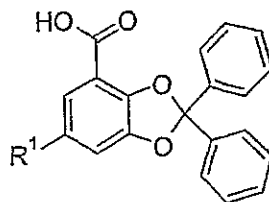


II

with a optionally protected 2,3-dihydroxy-benzoic acid derivative substituted by R¹ in position 5



IIIa



IIIb

15

wherein R¹ is as defined above

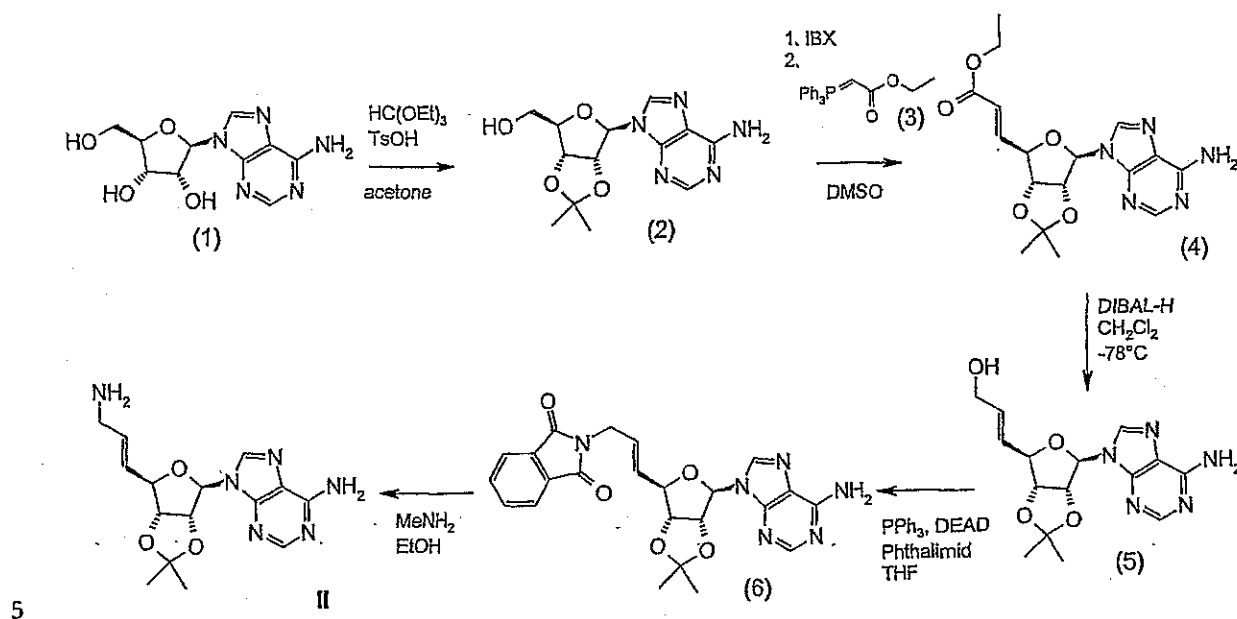
in the presence of (3-dimethylamino-propyl)-ethyl-carbodiimide (EDC), triethyl amine and *N*-hydroxy-succinimide (HOSu) in a suitable solvent such as dichloroethylene and

- 20 b) subsequent deprotection of the hydroxy groups where necessary with trifluoroacetic acid in an aqueous solution to form the compounds of formula I.

The amino-purin derivative of formula II can be prepared according to Scheme 1 starting from 2-(6-Amino-purin-9-yl)-5-hydroxymethyl-tetrahydro-furan-3,4-diol (1) which is

protected and subsequently reacted with (triphenyl-phosphanylidene)-acetic acid ethyl ester to the ester (4). The ester group in compound (4) is reduced to the alcohol (5) and transformed into the amide of formula II

Scheme 1

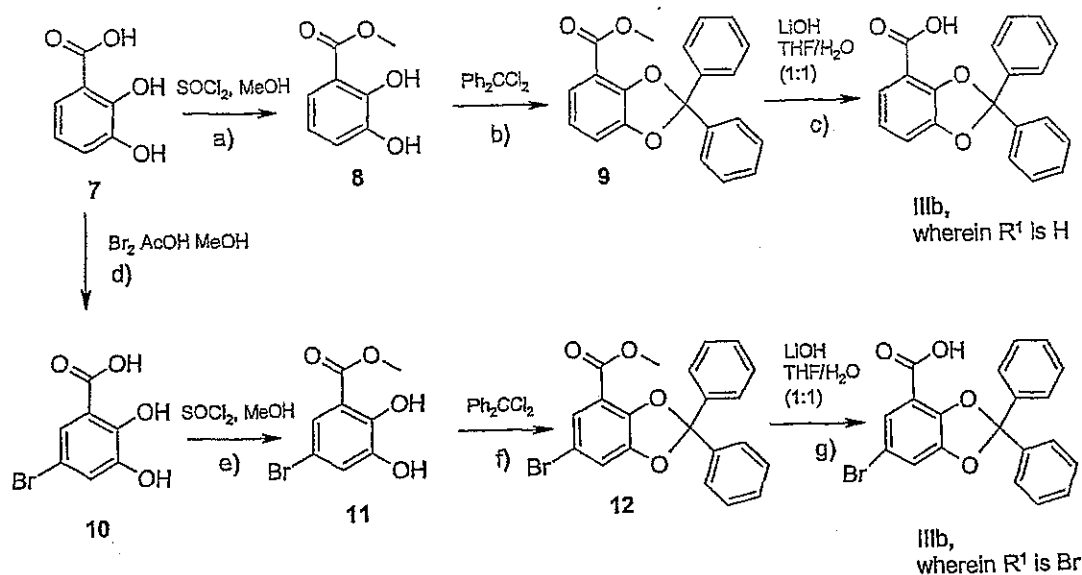


wherein TsOH stand for tosylchloride, IBX for 1-hydroxy-1,2-benziodoxol-3(1H)-1-oxide, DMSO for dimethylsulfoxide, PPh_3 for triphenylphosphine, DEAD for diethyl azodicarboxylate and THF for tetrahydrofuran, Angew. Chem. (2001) 113, 4164.

- 10 The optionally protected 2,3-dihydroxy-benzoic acid derivatives substituted by R^1 in position 5 (IIIa and IIIb) are prepared according to reaction schemes 2 to 6.

A method for the preparation of compounds of formula IIIb, wherein R^1 is hydrogen or bromine is given in scheme 2.

Scheme 2



step a) esterification of 2,3-dihydroxy-benzoic acid dissolved in a suitable solvent for example an alcohol such as methanol in the presence of thionylchloride to form the ester

5 (8);

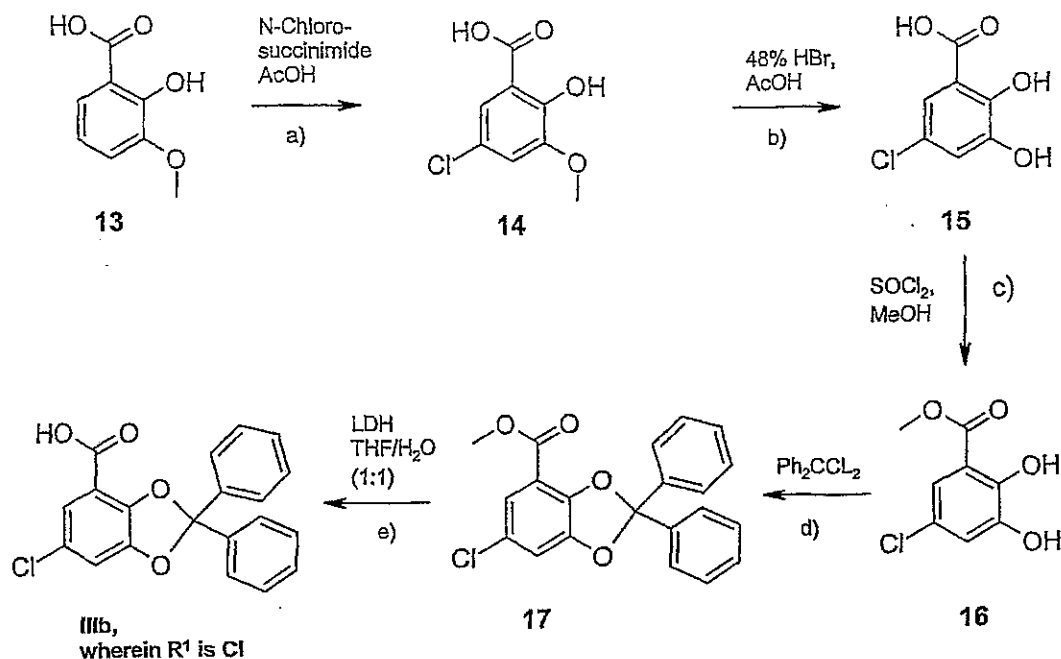
step b) protection of the ester (8) by ketalisation of the two hydroxy groups with a suitable ketone, e.g. with dichlorodiphenylmethane;

step c) hydrolysis of the ester group in the presence of a strong base such as LiOH.

step d) 2,3-dihydroxy-benzoic acid is brominated in acetic acid and in the following steps

10 e) to g) the carboxylic group is esterified to form the ester (11), the two hydroxy groups are protected to form the ketal (12) and the ester group is cleaved as described for steps a) to c).

The compounds of formula IIIb wherein R¹ is chlorine can be prepared as depicted in Scheme 3.



step a) 2-hydroxy-3-methoxybenzoic acid (13) is chlorinated for example with N-chlorosuccinimide in acetic acid to yield 5-chloro-2-hydroxy-3-methoxy benzoic acid (14);

- 5 step b) the methoxy group of compound (14) is reacted with hydrobromic acid in acetic acid to yield 5-chloro-2,3-dihydroxy benzoic acid (15);

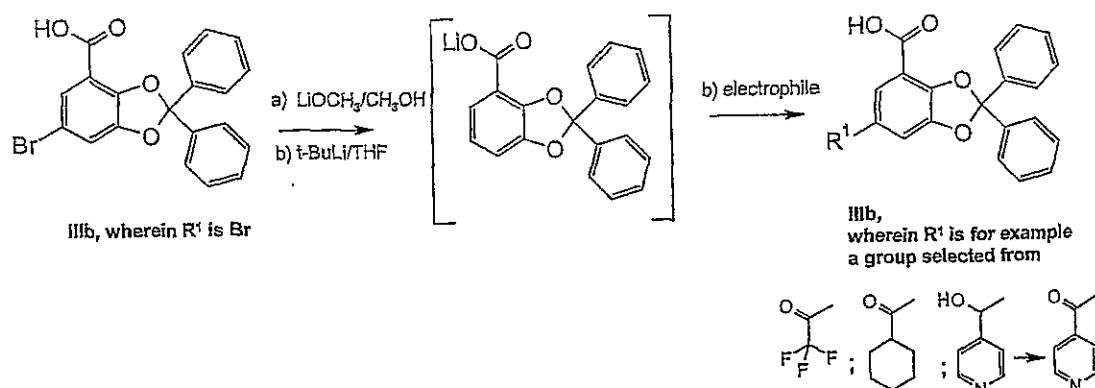
5-chloro-2,3-dihydroxy benzoic acid is then transformed into the protected compounds IIIb, wherein R¹ is chlorine by esterification of the carboxylic group, ketalisation of the two hydroxy groups and subsequent cleavage of the ester group (steps c) to e)) as

- 10 described above.

In Scheme 4 the preparation of derivatives of formula IIIb, wherein R¹ is -COR² and R² is trifluoromethyl, cyclohexyl or pyridin-4-yl. The protected 5-bromo-benzoic acid derivative (the compound of formula IIIb, wherein R¹ is bromine) is converted to its lithium salt. Lithium-halogen exchange and reaction with ethyl-trifluoroacetate,

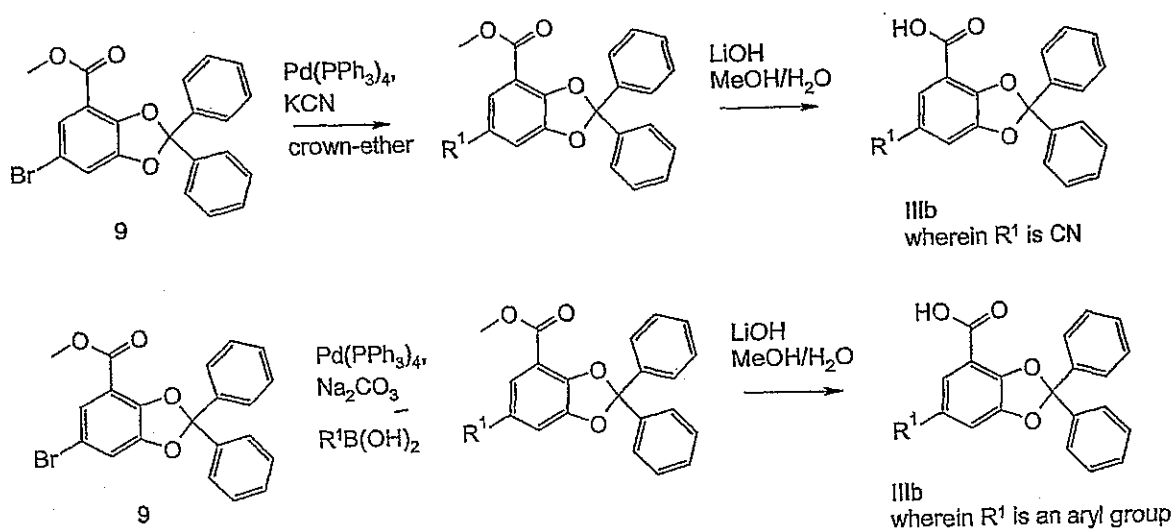
- 15 cyclohexane carboxylic acid methoxymethylamide, or pyridine-4-carbaldehyde followed by oxidation with IBX yielded the corresponding derivatives of formula IIIb.

Scheme 4



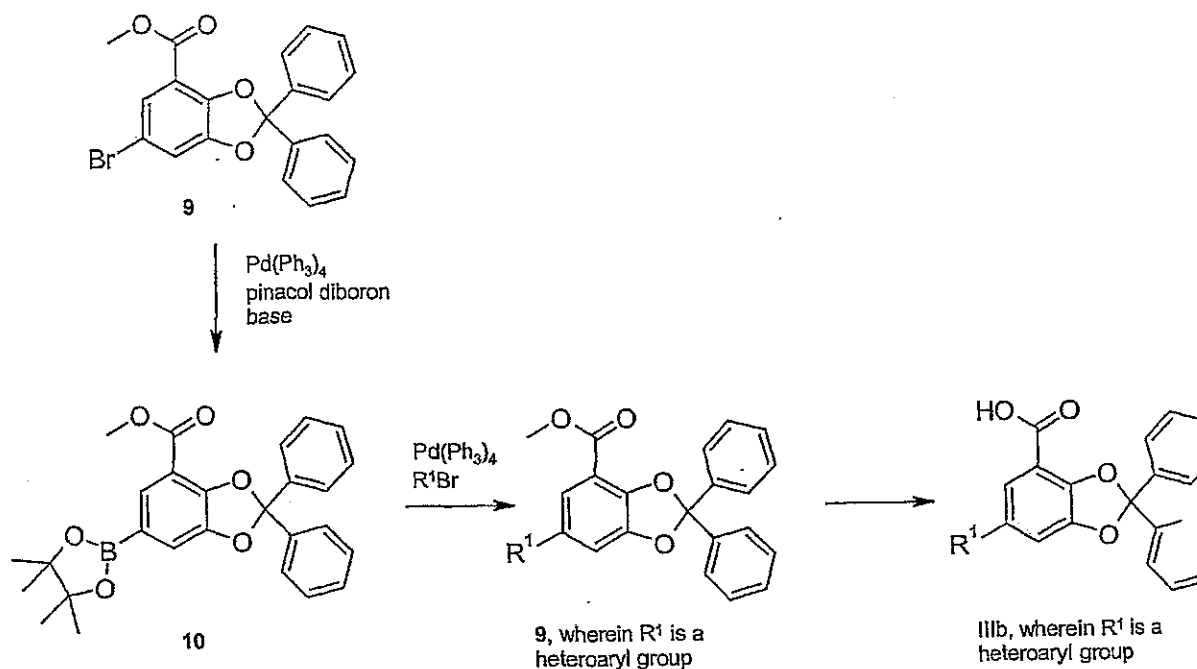
- In Scheme 5 the preparation of further derivatives of formula IIIb starting from protected 5-bromo benzoic acid ester (9) is shown. The nitrile is obtained by Pd catalysed cyanation. Arylsubstitutents were introduced using a Pd catalysed Suzuki-coupling with arylboronic acids.

Scheme 5



- 10 In Scheme 6 the preparation of several derivatives of formula IIIb starting from protected 5-bromo benzoic acid derivative (9) is shown. 5-Bromo benzoic acid ester (9) is first converted to the dioxaborolane (10) which is subsequently reacted with benzylbromides, bromo aryl or bromo heteroaryl compounds in a palladium catalysed Suzuki reaction to yield the corresponding derivatives IIIb.

Scheme 6



The various compounds which are used as starting materials are known or can be prepared according to known methods.

As mentioned earlier, the compounds of formula I inhibit the enzyme COMT. The inhibitory activity can be determined in vitro with COMT obtained from rat liver. Rat liver homogenate is incubated in the presence of a suitable substrate as described by Zürcher et al. in *J. Neurochem.* 1982, **38**, 191-195 and the COMT activity is measured.

The IC_{50} values (concentration of the inhibitor at which 50% activity of the enzyme is observed) were determined in a radiochemical assay described by Zürcher et al. (see above) and are listed in Table 1.

IC_{50} values were determined as follows: The inhibitors were dissolved in Me_2SO as 1.2 mM stock solution and further diluted with Me_2SO . The reactions were performed in standard polypropylene vials. 25 μl of the inhibitor in varying concentrations from 10^{-4} to 10^{-9} mol L^{-1} were mixed with 215 μl freshly prepared buffer-substrate mixture consisting of 170 μl potassium phosphate buffer (0.1 mol L^{-1} , pH 7.6), 10 μl MgCl_2 (0.1 mol L^{-1}), 10 μl dithiothreitol (0.065 mol L^{-1}) and 25 μl of tissue extract. The enzyme preparations were preincubated for 15 min at 37°C . The reaction was started by adding 30 μl substrate (benzene-1,2-diol, 0.025 mol L^{-1}), 10 μl [^3H]SAM (5.5 mmol L^{-1} , specific activity: 13.36 Bq mol $^{-1}$ (3.61 Ci mol $^{-1}$) and 20 μl deionized H_2O , reaching a final substrate

concentration of 2.5 mM and a final [^1H]/[^3H]SAM concentration of 183 μM . The reaction was stopped after incubating the vials in a water-bath at 37°C for 15 min by addition of 200 μl HOAc (5.7%) containing guaiacol (0.1 g L $^{-1}$). The reaction vessels were transferred into polyethylene scintillation vials and 3 ml of scintillation fluid (5 g butyl-PBD, dissolved in 200 ml toluene, made up to 1 L with *n*-hexane) was added. The vials were capped and more than 98% [^3H]guajacol formed was extracted into the organic phase by vigorous shaking for 3 min. The samples were counted in a Beckmann LS 6000 TA scintillation counter.

Table 1

Example		IC50 [nM]
comparative example	N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-nitro-benzamide	9
1	N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-benzamide	2600
2	N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-5-bromo-2,3-dihydroxy-benzamide	28
3	N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-5-cyano-2,3-dihydroxy-benzamide	29
4	N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-trifluoroacetyl-benzamide	39
5	N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-(pyridine-4-carbonyl)-benzamide	42

Example		IC ₅₀ [nM]
6	N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-5-cyclohexanecarbonyl-2,3-dihydroxy-benzamide	83
7	N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-5-chloro-2,3-dihydroxy-benzamide	44
8	4'-Fluoro-4,5-dihydroxy-biphenyl-3-carboxylic acid {3-[5-(6-amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-amide	21
9	4,5-Dihydroxy-4'-methyl-biphenyl-3-carboxylic acid {3-[5-(6-amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-amide	23
10	N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-thiazol-2-yl-benzamide	27
11	N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-5-benzothiazol-2-yl-2,3-dihydroxy-benzamide	29
12	N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-pyridin-4-yl-benzamide	23
13	N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-(4-methyl-benzyl)-benzamide	608
14	N3-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-4,5-dihydroxy-N1,N1-dimethyl-isophthalamide	2000

Example		IC50 [nM]
15	N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-5-(2-dimethyl-carbamoyl-vinyl)-2,3-dihydroxy-benzamide	97
16	N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-trifluoromethyl-benzamide	35
17	N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-isopropyl-benzamide	1370
18	N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-(toluene-4-sulfonyl)-benzamide	213
19	N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-(4-methyl-benzoyl)-benzamide	34

Medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier are also an object of the present invention, as is a process for their production, which comprises bringing one or more compounds of formula I and/or pharmaceutically acceptable acid addition salts and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically inert carriers.

The compounds of formula I, ester or ether derivatives thereof, and salts thereof can be used as medicaments, for example, in the form of pharmaceutical preparations for enteral or parenteral administration. The compounds of formula Ia can be administered, for example, perorally, for example in the form of tablets, coated tablets, dragees, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, for example, in the form of suppositories, or parenterally, for example, in the form of injection solutions.

The manufacture of the pharmaceutical preparations can be effected in a manner which is familiar to any person skilled in the art by bringing the compounds of formula I, optionally in combination with other therapeutically valuable substances, into a galenical

administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, the usual pharmaceutical adjuvants.

As carrier materials there are suitable not only inorganic carrier materials, but also organic carrier materials. Thus, for tablets, coated tablets, dragees and hard gelatine capsules there can be used as carrier materials, for example, lactose, maize starch or derivatives thereof, talc, stearic acid or its salts. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols. Depending on the nature of the active substances no carriers are, however, required in the case of soft gelatine capsules. Suitable carrier materials for the preparation of solutions and syrups are, for example, water, polyols, saccharose, invert sugar and glucose. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerine and vegetable oils. Suitable carrier materials for suppositories are, for example natural or hardened oils, waxes, fats and semi-liquid or liquid polyols.

As pharmaceutical adjuvants there come into consideration the usual preserving agents, solubilizers, stabilizing agents, wetting agents, emulsifying agents, flavor-improving agents such as sweetening agents and flavoring agents, coloring agents, salts for varying the osmotic pressure, buffers, coating agents and antioxidants.

The dosage of the compounds of formula I, or ester derivatives thereof and salts thereof can vary within wide limits depending on the illness to be treated, the age and the individual condition of the patient and on the mode of administration and will, of course, be fitted to the individual requirements in each particular case. For example in the improvement of the treatment of Parkinson's disease and of parkinsonism with or without L-dopa a daily dosage of 25 mg to about 1000 mg, especially about 100 mg to about 300 mg, comes into consideration. Depending on the dosage it is convenient to administer the daily dosage in several dosage units.

The pharmaceutical preparations in accordance with the invention conveniently contain about 25 mg to about 300 mg, preferably about 50 mg to about 150 mg, of a compound of formula I or of an ester derivative thereof which is hydrolyzable under physiological conditions or of a pharmaceutically acceptable salt thereof.

The Examples which follow will further illustrate the invention and contain detailed information concerning the preparation of compounds of formula I and the used starting materials.

Experimental

Materials and Methods

Solvents for extractions and chromatography were of technical grade and were distilled prior to usage. Reactions were performed using solvents of p.a. grade purchased from
5 *Fluka* or *J. T. Baker* or solvents of comparable quality. THF (tetrahydrofuran) was distilled from sodium benzophenone ketyl and CH_2Cl_2 from CaH_2 .

Thin layer chromatography was performed on aluminum-backed sheets coated with SiO_2 60 F₂₅₄ from *Macherey-Nagel* using UV-light (254 nm) for detection.

Column chromatography was performed using *Fluka* SiO_2 60, 40-63 mesh, at r.t. (room
10 temperature) and at a pressure of $1 \cdot 10^6$ to $4 \cdot 10^6$ Pa (0.1 - 0.4 bar)

Analytical HPLC was performed on a *Merck LiChrospher*® 100 RP-18 (250 x 4 mm, 5 μm , 100Å) column, using a linear gradient of CH_3CN in H_2O with 0.1% TFA (trifluoro acetic acid), 5 → 55% in 20 min, a flow of 1 mL / min, and UV-detection at 254 nm.

Preparative HPLC was performed on a *Merck LiChrosorb*® RP-18 (250 x 25 mm, 7 μm)
15 column, using a linear gradient of CH_3CN in H_2O with 0.1% TFA, a flow of 10 mL / min and UV-detection at 254 nm.

Melting points were determined on a *Büchi-510* apparatus and are uncorrected.

Infrared spectra were recorded on a *Perkin-Elmer 1600-FT* spectrometer.

NMR spectra (^1H and ^{13}C) were recorded at r.t. on *Varian-Mercury 300* or *Bruker AMX-*
20 *500* instruments.

Mass Spectra were recorded by the MS service of the Laboratorium für Organische Chemie at ETH Zürich using *IonSpec Ultima* (MALDI, with 2,5-dihydroxybenzoic acid or 2,4,6-trihydroxyacetophenone / diammonium citrate 2:1 as matrix) and *VG-TRIBID* (EI) spectrometers.

25 Elemental analyses were performed by the Mikrolabor of the Laboratorium für Organische Chemie at ETH Zürich.

General Procedures (GP)

General procedure 1 (GP1) for the synthesis of methyl 2,3-dihydroxybenzoate derivatives from the corresponding 2,3-dihydroxybenzoic acids

To a solution of the 2,3-dihydroxy-benzoic acid (1 eq.) in MeOH was slowly added SOCl_2 (3 eq.) via a syringe and the reaction mixture was then refluxed overnight. After evaporation of the solvent under reduced pressure the grayish solid was redissolved in EtOAc and washed twice with saturated K_2CO_3 solution, then saturated NaCl solution
5 before being dried over MgSO_4 and the solvent evaporated *in vacuo*. Drying under high vacuum yielded the product as a grayish solid.

General procedure (GP2) for the protection of catechols as diarylmethylketals

General procedure 2.1 (GP2.1) Protection as diphenylmethylketal.

Method A. A suspension of the corresponding methyl 2,3-dihydroxybenzoate (1 eq.) in
10 dichlorodiphenylmethane (1.5 eq.) was stirred at 160°C for 40 min. After cooling to 50°C , 30 mL MeOH was added to the viscous brown oil leading to the formation of a precipitate. The precipitate was filtered, washed with MeOH (3 x 20 mL) and dried under high vacuum to yield the desired compound as a colorless solid.

Method B. A suspension of the corresponding methyl 2,3-dihydroxybenzoate (1 eq.) in
15 3.7 mL dichlorodiphenylmethane (1.5 eq.) was stirred at 160°C for 40 min. After cooling, EtOAc was added to the viscous mixture and the solution was washed with saturated NaCl solution, dried over MgSO_4 and evaporated under reduced pressure. The crude product was purified using flash chromatography (silica gel, hexane / Et_2O 10:1) to yield the desired compound as a colorless solid.

20 *General procedure 2.2 (GP2.2) Protection as 4,4'-dimethoxy-diphenylmethylketal.*

4,4'-Dimethoxybenzophenone (1.5 eq.) and oxalyl chloride (8 eq.) were stirred at 60°C for 30 min., then the temperature was raised to 110°C to remove the excess oxalyl chloride and the corresponding methyl 2,3-dihydroxy-benzoate (1 eq.) was added to the reaction mixture. The dark red solution was stirred at 160°C for 40 min. After cooling,
25 EtOAc was added to the viscous mixture and the solution was washed with saturated NaCl solution, dried over MgSO_4 and evaporated under reduced pressure. The crude product was purified using flash chromatography (silica gel, hexane / Et_2O 10:1 or hexane / EtOAc 20:1).

General procedure 3 (GP3) for the synthesis of catechol carboxylic acids from the
30 *corresponding ester precursors*

The biphasic mixture of a solution of the methyl catechol carboxylate (1 eq.) in 5 mL THF and a solution of $\text{LiOH}\cdot\text{H}_2\text{O}$ (3 eq.) in 5 mL H_2O was refluxed for 3 h. After cooling to r.t. the reaction mixture was acidified by addition of 4 mL 10% AcOH – solution and poured into a separatory funnel containing 50 mL H_2O and 50 mL EtOAc. The layers

were separated and the aqueous layer was extracted twice with 20 mL EtOAc. The pooled organic fractions were washed twice with saturated NaCl-solution before being dried over MgSO_4 and evaporated *in vacuo* to yield the desired compound as a colorless solid.

5 *General procedure 4 (GP4)* for the synthesis of functionalized catechol carboxylic acids starting from 6-bromo-2,2-diphenyl-1,3-benzodioxole-4-carboxylic acid

Method A. To a suspension of 6-bromo-2,2-diphenyl-1,3-benzodioxole-4-carboxylic acid (1 eq.) in 3 mL MeOH, LiOMe (2 eq.) was added leading to the formation of a clear solution, which was stirred 20 min. at r.t. Following evaporation of the solvent under reduced pressure, the resulting white foam was dried overnight under vacuum. The
10 residue was then redissolved in 10 mL dry THF and cooled to -78°C . To this solution *t*-BuLi (1.5M solution in pentane, 2.5 eq.) was added dropwise via a syringe and the resulting dark yellow solution was stirred 30 min. at -78°C . The desired electrophile was added to the reaction mixture and the stirring continued 30 min. at low temperature. The cooling bath was removed and the reaction was stirred another 2 h at r.t., followed by
15 acidification with 10% AcOH-solution and extraction with EtOAc (2 x 30 mL). The organic fractions were pooled, dried over MgSO_4 and the solvent evaporated *in vacuo*. The crude product was purified using flash chromatography (silica gel, hexane/EtOAc/AcOH) to give the title compound as a yellowish to colorless solid.

Method B. To a solution of 6-bromo-2,2-diphenyl-1,3-benzodioxole-4-carboxylic acid (1
20 eq.) in 8 mL dry THF, LiH (2 eq.) was added. The reaction mixture was stirred 15 min. at r.t., then cooled to -78°C . To this solution *t*-BuLi (1.5M solution in pentane, 2.5 eq.) was added dropwise via a syringe and the resulting yellow solution was stirred 30 min. at -78°C . The desired electrophile was added to the reaction mixture and the stirring continued 30 min. at low temperature. The cooling bath was removed and the reaction
25 was stirred another 2 h at r.t., followed by acidification with 10% AcOH-solution and extraction with EtOAc (2 x 30 mL). The organic fractions were pooled, dried over MgSO_4 and the solvent evaporated *in vacuo*. The crude product was purified using flash chromatography (silica gel, hexane / EtOAc / AcOH) to give the desired compound as a colorless solid.

30 *General procedure 5 (GP5)* for the synthesis of biaryl catechol carboxylic esters via Suzuki reaction between methyl 6-bromo-2,2-diphenyl-1,3-benzodioxole-4-carboxylate and the corresponding aryl boronic acid

To a solution of methyl 6-bromo-2,2-diphenyl-1,3-benzodioxole-4-carboxylate (1 eq.) and $\text{Pd}(\text{PPh}_3)_4$ (0.05 eq.) in 10 mL toluene, a solution of the desired aryl boronic acid (4
35 eq.) in 1.5 mL EtOH and a solution of K_2CO_3 (6 eq.) in 1 mL H_2O were added. This

mixture was refluxed 2 h – 4 h. After cooling to r.t. the mixture was partitioned between EtOAc and H₂O. The organic layer was washed twice with saturated NaCl solution, dried over MgSO₄ and evaporated *in vacuo*. The crude product was further purified using flash chromatography (silica gel, hexane/EtOAc 20:1 → 5:1) to yield the desired compound as a colorless solid.

General procedure 6 (GP6) for the preparation of biaryl catechol carboxylic esters via one-pot arylboronate – Suzuki biaryl synthesis

To a solution of methyl 6-bromo-2,2-diphenyl-1,3-benzodioxole-4-carboxylate (1 eq.) in 20 mL dry toluene, Pd(PPh₃)₄ (0.05 eq.), bis(pinacolato)diboron (1.3 eq.) and KOAc (1.5 eq.) were added and the mixture refluxed for 4 h. After cooling to r.t. the reaction mixture was filtered over Celite, which was washed with an additional 30 mL of toluene. The combined toluene fractions were concentrated *in vacuo* to ca. 10-15 mL. To this yellowish solution Pd(PPh₃)₄ (0.05 eq.), 1.2 eq. of the desired arylbromide, e.g. 2-bromo-1,3-benzothiazole and a solution of K₂CO₃ (5 eq.) in 3 mL H₂O were added and the reaction was refluxed for 16 h. After cooling to r.t., the mixture was partitioned between H₂O and EtOAc and the organic fraction was washed twice with 20 mL saturated NaCl solution, before being dried over MgSO₄ and evaporated under reduced pressure. The crude product was further purified using flash column chromatography (silica gel, hexane/EtOAc 20:1 → 9:1) to yield the desired compound as a colorless solid.

General procedure 7 (GP7) for the amide coupling of catechol carboxylic acids and 9-{{(3aR,4R,6R,6aR)-6-[(E)-3-aminoprop-1-enyl]-2,2-dimethylperhydrofuro[3,4-d][1,3]dioxol-4-yl}-9H-purin-6-amine

To a solution of the catechol carboxylic acid (1 eq.) in 5 mL CH₂Cl₂, EDC·HCl (1-(dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride) (1.5 eq.) and N-hydroxy-succinimide (1.3 eq.) were added and the solution was stirred 2 h at r.t. After addition of 9-{{(3aR,4R,6R,6aR)-6-[(E)-3-aminoprop-1-enyl]-2,2-dimethylperhydrofuro[3,4-d][1,3]dioxol-4-yl}-9H-purin-6-amine (0.7 eq. – 1 eq.) and Et₃N (0.1 mL, 0.68 mmol) stirring was continued another 3 h, then the solution was poured into a separatory funnel containing CH₂Cl₂ and H₂O and the phases were separated. The aqueous phase was extracted with CH₂Cl₂ (3 x 15 mL), then the combined organic fractions were washed with saturated aqueous NaCl solution, dried over MgSO₄ and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (CH₂Cl₂ → CH₂Cl₂/MeOH = 20:1) to yield the desired compound as a colorless foam.

General procedure 8 (GP8) for the synthesis of target molecules by deprotection of the acetonide and the diarylmethylketal protecting groups

The protected precursor was treated with 3 mL of a mixture of TFA and H₂O (1:1) at r.t. for 20-60 min. The reaction mixture was then lyophilized. The crude product was

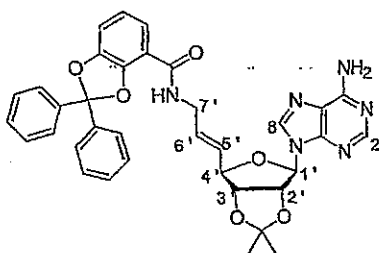
- 5 redissolved in 3 mL DMSO and purified using preparative HPLC chromatography. The product fractions were subsequently lyophilized to yield the desired compound as a fluffy solid.

Example 1

Preparation of N1-{(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-

- 10 dihydroxytetrahydrofuran-2-yl]prop-2-enyl}-2,3-dihydroxy-benzamide

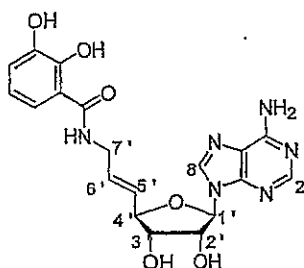
a) 2,2-Diphenyl-benzo[1,3]dioxole-4-carboxylic acid {3-[(3aR,4R,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-*d*][1,3]dioxol-4-yl]-prop-2-enyl}-amide



- 15 2,2-Diphenyl-1,3-benzodioxole-4-carboxylic acid (150 mg, 0.471 mmol, 1 eq.), EDC·HCl (136 mg, 0.71 mmol, 1.5 eq.), *N*-hydroxy-succinimide (65 mg, 0.565 mmol, 1.2 eq.), 9-[(3aR,4R,6R,6aR)-6-[(*E*)-3-aminoprop-1-enyl]-2,2-dimethylperhydrofuro[3,4-*d*][1,3]dioxol-4-yl]-9H-purin-6-amine (150 mg, 0.451 mmol, 1 eq.) and Et₃N (0.1 mL, 0.68 mmol) were reacted according to GP7.
- 20 Yield: 189 mg (67 %). Colorless foam. Mp.: 105°C. $[\alpha]_D^{20}$: -14.3 (*c*=1.0, MeOH). IR (KBr): 3424*m*; 3175*m*; 2987*w*; 1651*s*; 1532*s*; 1455*s*; 1373*m*; 1246*s*; 1082*s*; 867*m*; 748*m*. ¹H-NMR (300 MHz, CDCl₃): 1.37 (*s*, 3 H, CH₃-*exo*); 1.62 (*s*, 3 H, CH₃-*endo*); 4.05 (*m*, 2 H, H-C(7'), H-C(7'')); 4.69 (*m*, 1 H, H-C(4')); 4.95 (*dd*, *J* = 6.5, 3.7, 1 H, H-C(3')); 5.46 (*dd*, *J* = 6.5, 2.2, 1 H, H-C(2')); 5.61 (*bs*, 2 H, NH₂); 5.86 (*m*, 2 H, H-C(5'), H-C(6')); 6.08 (*d*, *J* = 2.2, 1 H, H-C(1')); 6.95 (*t*, *J* = 8.1, 1 H, H_{arom}, Cat.); 7.02 (*dd*, *J* = 8.1, 1.2, 1 H, H_{arom}, Cat.); 7.14 (*t*, *J* = 5.6, 1 H, NHCO); 7.35-7.39 (*m*, 6 H, H_{arom}, Ketal), 7.48-7.53 (*m*, 4 H, H_{arom}, Ketal); 7.58 (*dd*, *J* = 8.7, 1.2, H_{arom}, Cat.); 7.84 (*s*, 1 H, H-C(8)); 8.20 (*s*, 1 H, H-C(2)). ¹³C-NMR (75 MHz, CDCl₃): 25.5; 27.2; 40.7; 84.0; 84.5; 87.1; 90.2; 111.8; 114.6; 115.5; 118.1; 120.1; 122.0; 122.4; 126.3; 128.2; 128.3; 129.5; 130.6; 138.8; 139.6; 144.5; 147.0; 149.3; 153.0;

155.3; 163.2. HR-MS (MALDI): calcd. for $C_{35}H_{33}N_6O_6$ ($[M+H]^+$): 633.2461, found 633.2442.

b) N1-[(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-2,3-dihydroxy-benzamide



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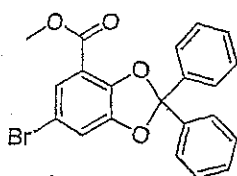
The protected precursor (120 mg, 0.19 mmol) was treated with 3.5 mL of a mixture of TFA and H_2O (5:2) at $0^\circ C$ for 60 min. The solvents were evaporated under reduced pressure, then the residue was dissolved in 5% NH_4OH in H_2O and extracted with $CHCl_3$ (3 x 15 mL). The aqueous phase was then evaporated under reduced pressure and
 10 coevaporated with H_2O (3 x 10 mL). The crude product was redissolved in 8 mL DMF and purified using HPLC chromatography to yield the title compound as a colorless solid.

Yield: 60 mg (74%). Mp.: $134^\circ C$ (dec.). $t_{R, analyt}$: 10.9 min. IR (KBr): 3424 *br, s*; 1641*s*; 1604*s*; 1460*w*; 1420*w*; 1340*w*; 1278*m*; 1129*w*; 1050*w*. 1H -NMR (500 MHz, $(CD_3)_2SO$):
 15 3.95 (*m*, 2 H, H-C(7'), H-C(7'')); 4.11 (*t*, $J = 4.8$, 1 H, H-C(4'')); 4.37 (*m*; 1 H, H-C(3'')); 4.65 (*t*, $J = 5.1$, 1 H, H-C(2'')); 5.82-5.93 (*m*, 2 H-C(5'), H-C(6'')); 5.93 (*d*, $J = 5.1$, 1 H, H-C(1'')); 6.69 (*t*, $J = 7.9$, 1 H, $H_{arom, Cat.}$); 6.92 (*dd*, $J = 7.9$, 1.1, 1 H, $H_{arom, Cat.}$); 7.31 (*dd*, $J = 7.9$, 1 H, $H_{arom, Cat.}$); 8.23 (*s*, 1 H, H-C(8)); 8.49 (*s*, 1 H, H-C(2)); 8.97 (*t*, $J = 5.4$, 1 H, H-NHCO); 12.64 (*bs*, 1H, OH). ^{13}C -NMR (125 MHz, $(CD_3)_2SO$): 40.1; 73.1; 73.9; 84.3; 87.8;
 20 115.0; 117.2; 118.0; 118.9; 119.1; 129.2; 129.6; 141.3; 146.2; 148.9; 149.0; 149.6; 153.2; 169.5. HR-MS (MALDI): calcd. for $C_{19}H_{21}N_6O_6$ ($[M+H]^+$): 429.1522, found 429.1513.

Example 2

Preparation of N1-[(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-bromo-2,3-dihydroxy-benzamide

25 a) Methyl 6-bromo-2,2-diphenyl-1,3-benzodioxole-4-carboxylate

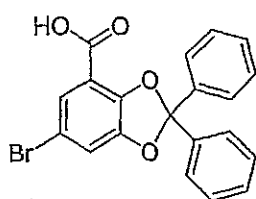


Methyl 5-bromo-2,3-dihydroxybenzoate (3 g, 12.87 mmol, 1 eq.) was reacted with dichlorodiphenylmethane (3.7 mL, 4.58 g, 19.31 mmol, 1.5 eq.) according to GP2, Method A.

Yield: 4 g (76 %). Colorless powder. Mp.: 146-148°C. IR (KBr): 3079 w ; 2950 w ; 1718 s

- 5 (CO); 1467 s ; 1355 s ; 1238 s ; 1204 s ; 1043 s ; 1013 s ; 944 m ; 867 m ; 780 s . $^1\text{H-NMR}$ (300 MHz, CDCl_3): 3.94 (s , 3 H, CH_3); 7.14 (d , $J = 1.9$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 7.38-7.41 (m , 6 H, $\text{H}_{\text{arom, Ketal}}$); 7.55-7.59 (m , 5 H, $\text{H}_{\text{arom, Cat.}}$, $\text{H}_{\text{arom, Ketal}}$). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 52.4; 112.6; 113.7; 115.6; 119.1; 125.0; 126.2; 128.3; 129.4; 139.0; 147.5; 149.1; 163.7. HR-MS (MALDI): calcd. for $\text{C}_{21}\text{H}_{16}\text{BrO}_4$ ($[\text{M}+\text{H}]^+$): 411.0231, found 411.0220.

- 10 b) 6-Bromo-2,2-diphenyl-1,3-benzodioxole-4-carboxylic acid

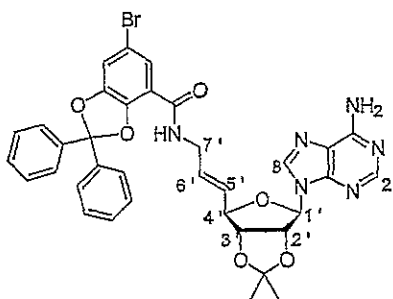


Methyl 6-bromo-2,2-diphenyl-1,3-benzodioxole-4-carboxylate (0.5 g, 1.216 mmol, 1 eq.) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (204 mg, 4.86 mmol, 4 eq.) were reacted according to GP3.

Yield: 437 mg (91%). Colorless solid. Mp.: 215°C. IR (KBr): 3063 m ; 2873 br, m ; 2538 m ;

- 15 1695 s (CO); 1598 w ; 1468 s ; 1406 m ; 1350 m ; 1287 s ; 1234 s ; 1202 s ; 1045 s ; 1023 s ; 949 m ; 858 m ; 784 m ; 698 s . $^1\text{H-NMR}$ (300 MHz, CDCl_3): 7.19 (d , $J = 2.1$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 7.40-7.42 (m , 6 H, $\text{H}_{\text{arom, Ketal}}$); 7.58-7.62 (m , 5 H, $\text{H}_{\text{arom, Cat.}}$, $\text{H}_{\text{arom, Ketal}}$). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 112.7; 112.8; 116.4; 119.5; 125.4; 126.3; 128.4; 129.5; 138.9; 148.3; 149.3; 167.9. HR-MS (MALDI): calcd. for $\text{C}_{20}\text{H}_{14}\text{BrO}_4$ ($[\text{M}+\text{H}]^+$): 397.0075, found 397.0078. Anal.
- 20 calcd. for $\text{C}_{20}\text{H}_{13}\text{BrO}_4$: C 60.47, H 3.30; found C 60.40, H 3.35.

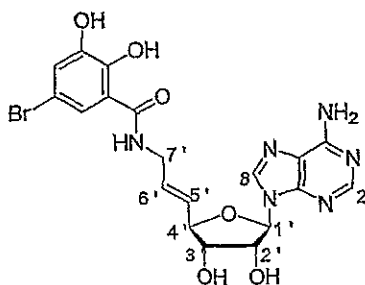
- c) 6-Bromo-2,2-diphenyl-benzo[1,3]dioxole-4-carboxylic acid {3-[(3aR,4R,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4- d][1,3]dioxol-4-yl]-prop-2-enyl}-amide



6-Bromo-2,2-diphenyl-1,3-benzodioxole-4-carboxylic acid (200 mg, 0.503 mmol, 1.4 eq.), EDC·HCl (145 mg, 0.755 mmol, 2.1 eq.), *N*-hydroxy-succinimide (76 mg, 0.654 mmol, 1.8 eq.), 9-((3*aR*,4*R*,6*R*,6*aR*)-6-[(*E*)-3-aminoprop-1-enyl]-2,2-dimethylperhydrofuro[3,4-*d*][1,3] di-oxol-4-yl)-9H-purin-6-amine (120 mg, 0.361 mmol, 1 eq.) and Et₃N (0.1 mL, 0.68 mmol) were reacted according to GP7.

Yield: 166 mg (65 %). Colorless foam. Mp.: 116°C. IR (KBr): 3424*m*; 3170 *br, w*; 2985*w*; 1636*s*; 1594*s*; 1531*m*; 1495*s*; 1423*w*; 1373*w*; 1236*s*; 1207*s*; 1156*w*; 1082*s*; 1016*m*; 867*w*; 778*w*; 698*m*. ¹H-NMR (300 MHz, CDCl₃): 1.38 (*s*, 3 H, CH₃-*exo*); 1.62 (*s*, 3 H, CH₃-*endo*); 4.04 (*m*, 2 H, H-C(7'), H-C(7'')); 4.69 (*m*, 1 H, H-C(4')); 4.95 (*dd*; *J* = 6.3, 3.6, 1 H, H-C(3'')); 5.45 (*dd*, *J* = 6.3, 2.3, 1 H, H-C(2'')); 5.84 (*m*, 2 H, H-C(5'), H-C(6'')); 5.96 (*bs*, 2 H, NH₂); 6.09 (*d*, *J* = 2.3, 1 H, H-C(1'')); 7.05 (*t*, *J* = 5.6, 1 H, NHCO); 7.15 (*d*, *J* = 2.0, 1 H, H_{arom}, Cat.); 7.35-7.40 (*m*, 6 H, H_{arom}, Ketal); 7.44-7.50 (*m*, 4 H, H-C(6), H_{arom}, Ketal); 7.72 (*d*, *J* = 2.0, 1 H, H_{arom}, Cat.); 7.87 (*s*, 1 H, H-C(8)); 8.20 (*s*, 1 H, H-C(2)). ¹³C-NMR (75 MHz, CDCl₃): 25.5; 27.3; 40.9; 84.1; 84.5; 87.1; 90.3; 114.0; 114.7; 115.2; 116.3; 119.5; 120.1; 125.0; 126.3; 128.4; 129.8; 130.5; 138.3; 140.1; 144.1; 148.1; 149.2; 151.7; 154.7; 162.0. HR-MS (MALDI): calcd. for C₃₅H₃₂BrN₆O₆ ([M+H]⁺): 711.1567, found 711.1553. Anal. calcd. for C₃₅H₃₁BrN₆O₆: C 59.08, H 4.39, N 11.81 found C 59.06, H 4.54, N 11.62.

d) N1-((*E*)-3-((3*aR*,4*R*,6*R*,6*aR*)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)prop-2-enyl)-5-bromo-2,3-dihydroxy-benzamide



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The protected precursor (50 mg, 0.07 mmol) was deprotected according to GP8.

Yield: 18 mg (52%). Colorless solid. *t*_{R, analyt.}: 13.4 min. Mp.: 123°C (dec.). IR (KBr): 3396 *br, m*; 1699*s*; 1637*m*; 1467*w*; 1426*w*; 1325*w*; 1203*s*; 1135*m*; 1050*w*. ¹H-NMR (500 MHz, CD₃OD): 4.03 (*m*, 2 H, H-C(7'), H-C(7'')); 4.23 (*t*, *J* = 5.0, 1 H, H-C(4')); 4.52 (*m*; 1 H, H-C(3'')); 4.72 (*t*, *J* = 4.8, 1 H, H-C(2'')); 5.92-5.94 (*m*, 2 H, H-C(5'), H-C(6'')); 6.06 (*d*, *J* = 4.8, H-C(1'')); 7.05 (*d*, *J* = 2.3, 1 H, H_{arom}, Cat.); 7.43 (*d*, *J* = 2.3, 1 H, H-C_{arom}, Cat.); 8.27 (*s*, 1 H, H-C(8)); 8.39 (*s*, 1 H, H-C(2)). ¹³C-NMR (125 MHz, CD₃OD): 41.6; 75.2; 75.6; 86.1; 90.6; 111.2; 118.2; 120.7; 121.3; 122.3; 130.3; 130.9; 143.4; 147.8; 148.8; 149.6; 150.2;

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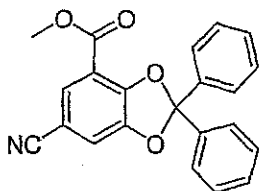
153.5; 169.9. HR-MS (MALDI): calcd. for $C_{19}H_{20}BrN_6O_6$ ($[M+H]^+$): 507.0628, found 507.0627.

Example 3

Preparation of N1-[(E)-3-[(3a*R*,4*R*,6*R*,6a*R*)-5-(6-amino-9H-purin-9-yl)-3,4-

5 dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-cyano-2,3-dihydroxy-benzamide

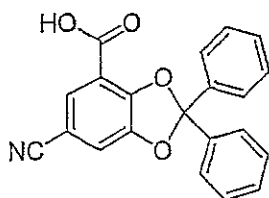
a) Methyl 6-cyano-2,2-diphenyl-1,3-benzodioxole-4-carboxylate



To a solution of methyl 6-bromo-2,2-diphenyl-1,3-benzodioxole-4-carboxylate (800 mg, 1.95 mmol, 1 eq.) in a mixture of 15 mL benzene and 5 mL DMF, $Pd(PPh_3)_4$ (225 mg, 0.195 mmol, 0.1 eq.), KCN (127 mg, 1.95 mmol, 1 eq.) and 18-crown-6 (415 mg, 1.56 mmol, 0.8 eq.) was added and the reaction mixture was stirred at 100°C overnight. Then, the reaction mixture was poured into a separatory funnel containing EtOAc and H_2O and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with H_2O , then saturated aqueous NaCl solution, dried over $MgSO_4$, and evaporated under reduced pressure. Flash chromatography on silica gel (hexane / EtOAc = 20:1 → 9:1) afforded the desired compound as a colorless solid.

Yield: 530 mg (76%). Mp.: 141°C. IR (KBr): 3051w; 2951w; 2228m (CN); 1713s (CO); 1470s; 1375m; 1264s; 1225s; 1045s; 917m; 786s. 1H -NMR (300 MHz, $CDCl_3$): 3.97 (s, 3 H, CH_3); 7.20 (d, $J = 1.9$, 1 H, $H_{arom, Cat.}$); 7.39-7.43 (m, 6 H, $H_{arom, Ketal}$); 7.55-7.58 (m, 4 H, $H_{arom, Ketal}$); 7.82 (d, $J = 1.9$, 1 H, $H_{arom, Cat.}$). ^{13}C -NMR (75 MHz, $CDCl_3$): 52.67; 104.8; 113.4; 113.9; 118.0; 120.4; 126.2; 128.4; 129.2; 129.7; 138.4; 148.9; 151.5; 163.1. HR-MS (MALDI): calcd. for $C_{22}H_{16}NO_4$ ($[M+H]^+$): 358.1079, found 358.1071.

b) 6-Cyano-2,2-diphenyl-1,3-benzodioxole-4-carboxylic acid

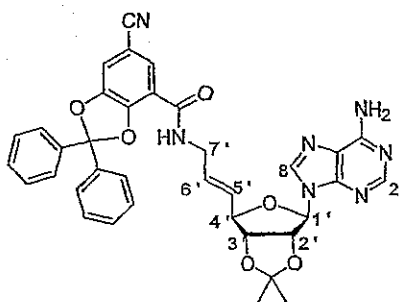


To a solution of methyl 6-cyano-2,2-diphenyl-1,3-benzodioxole-4-carboxylate (60 mg, 0.168 mmol, 1 eq.) in a mixture of 3 mL MeOH and 0.5 mL CH_2Cl_2 , a solution of

LiOH·H₂O (21 mg, 0.5 mmol, 3 eq.) in 3 mL H₂O was added. The reaction mixture was vigorously stirred 16 h at r.t., then acidified with 10% AcOH in H₂O and extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with saturated aqueous NaCl solution, dried over MgSO₄, and the solvents evaporated under reduced pressure to
 5 yield the desired compound as a colorless solid.

Yield: 53 mg (92%). Mp.: 221°C. IR (KBr): 2925 m ; 2229 m ; 1696 s ; 1449 s ; 1267 s ; 1213 s ; 1048 s ; 949 m ; 922 m ; 756 m ; 694 s ; 641 m ; 617 w . ¹H-NMR (300 MHz, CDCl₃): 7.25 (d , J = 1.7, 1 H, H_{arom}, Cat.); 7.41 (m , 6 H, H_{arom}, Ketal); 7.58 (m , 4 H, H_{arom}, Ketal); 7.87 (d , J = 1.7, 1 H, H_{arom}, Cat.). ¹³C-NMR (75 MHz, CDCl₃): 105.0; 112.6; 114.4; 117.8; 120.7; 126.1; 128.5; 129.6; 129.8; 138.2; 149.0; 152.1; 167.1. HR-MS (MALDI): calcd. for C₂₁H₁₄NO₄ ([M+H]⁺): 344.0923, found 344.0910.

c) 6-Cyano-2,2-diphenyl-benzo[1,3]dioxole-4-carboxylic acid {3-[(3aR,4R,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4- d][1,3]dioxol-4-yl]-prop-2-enyl}-amide



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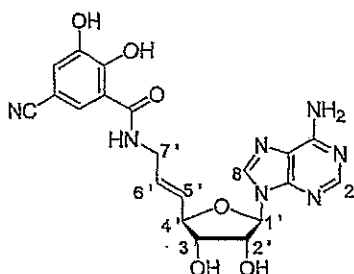
6-Cyano-2,2-diphenyl-1,3-benzodioxole-4-carboxylic acid (80 mg, 0.23 mmol, 1.5 eq.), EDC·HCl (73 mg, 0.38 mmol, 2.5 eq.), 9-[(3aR,4R,6R,6aR)-6-[(*E*)-3-aminoprop-1-enyl]-2,2-dimethylperhydrofuro[3,4- d][1,3]di-oxol-4-yl]-9H-purin-6-amine (50 mg, 0.15 mmol, 1 eq.) and Et₃N (0.05 mL, 0.34 mmol) were reacted according to GP7.

20 Yield: 67 mg (68%). Colorless foam. Mp.: 125°C. IR (KBr): 3428 s ; 3171 w ; 2986 w ; 2227 w ; 1635 s ; 1597 m ; 1528 m ; 1466 s ; 1374 m ; 1262 s ; 1209 s ; 1082 m ; 1017 m ; 867 w ; 762 w ; 699 m ; 641 w . ¹H-NMR (300 MHz, CDCl₃): 1.38 (s , 3 H, CH_{3-exo}); 1.62 (s , 3 H, CH_{3-endo}); 4.05 (m , 2 H, H-C(7'), H-C(7'')); 4.70 (m , 1 H, H-C(4')); 4.96 (dd , J = 6.3, 3.9, 1 H, H-C(3')); 5.46 (dd , J = 6.3, 2.0, 1 H, H-C(2')); 5.79 (bs , 2 H, NH₂); 5.83 (m , 2 H, H-C(5'), H-C(6')); 6.08 (d , J = 2.0, 1 H, H-C(1')); 7.00 (t , J = 5.7, 1 H, NHCO); 7.22 (d , J = 1.7, 1 H, H_{arom}, Cat.); 7.38-7.49 (m , 10 H, H_{arom}, Ketal); 7.86 (s , 1 H, H-C(8)); 7.99 (d , J = 1.7, H_{arom}, Cat.); 8.19 (s , 1 H, H-C(2)). ¹³C-NMR (75 MHz, CDCl₃): 25.5; 27.3; 41.0; 84.1; 84.5; 87.2; 90.3; 105.9; 113.7; 114.7; 116.1; 118.0; 120.2; 120.7; 126.3; 128.6; 128.8; 129.1; 130.1; 130.2;

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137.6; 140.0; 147.8; 148.0; 149.2; 152.3; 155.0; 161.2. HR-MS (MALDI): calcd. for $C_{36}H_{32}N_7O_6$ ($[M+H]^+$): 658.2414, found 658.2403.

d) N1-[(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-cyano-2,3-dihydroxy-benzamide



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The protected precursor (70 mg, 0.11 mmol) was deprotected according to GP8.

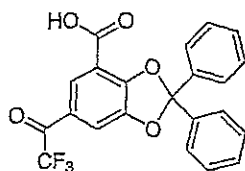
Yield: 20 mg (42%). $t_{R, \text{analyt.}}$: 9.0 min. IR (KBr): 3396 *br, s*; 2233 *w*; 1703 *s*; 1639 *s*; 1477 *w*; 1441 *w*; 1303 *m*; 1195 *s*; 1137 *m*; 1050 *w*. $^1\text{H-NMR}$ (500 MHz, CD_3OD): 4.06 (*d*, $J = 3.7$, 2 H, H-C(7'), H-C(7'')); 4.24 (*t*, $J = 4.9$, 1 H, H-C(4'')); 4.51 (*t*, $J = 4.9$, 1 H, H-C(3'')); 4.73 (*t*, $J = 4.6$, 1 H, H-C(2'')); 5.94 (*m*, 2 H, H-C(5'), H-C(6'')); 6.04 (*d*, $J = 4.6$, 1 H, H-C(1'')); 7.17 (*d*, $J = 1.8$, 1 H, $H_{\text{arom, Cat.}}$); 7.70 (*d*, $J = 1.8$, 1 H, $H_{\text{arom, Cat.}}$); 8.23 (*s*, 1 H, H-C(8)); 8.33 (*s*, 1 H, H-C(2)). $^{13}\text{C-NMR}$ (75 MHz, ($\text{CD}_3\text{OD} + 2$ drops of DMSO-d_6)): 41.7; 75.2; 75.4; 85.9; 90.2; 102.6; 117.3; 119.8; 120.5; 121.1; 124.2; 130.5; 130.6; 143.6; 146.3; 148.4; 149.9; 154.6; 169.3 (1 peak missing). HR-MS (MALDI): calcd. for $C_{20}H_{20}N_7O_6$ ($[M+H]^+$): 454.1475, found 454.1466.

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Example 4

Preparation of N1-[(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-(2,2,2-trifluoro-acetyl)-2,3-dihydroxy-benzamide

20 a) 2,2-Diphenyl-6-(trifluoroacetyl)-1,3-benzodioxole-4-carboxylic acid

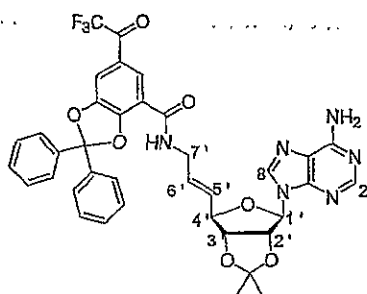


6-Bromo-2,2-diphenyl-1,3-benzodioxole-4-carboxylic acid (200 mg, 0.503 mmol, 1 eq.), LiOMe (40 mg, 1 mmol, 2 eq.) and ethyl trifluoroacetate (0.6 mL, 5.03 mmol, 10 eq.) as the electrophile were reacted according to GP4, Method A. The crude product was

purified using flash chromatography (silica gel, hexane/EtOAc/AcOH 77:20:3) to give the title compound as a yellowish solid.

- Yield: 79 mg (38%). Mp.: 187°C. IR (KBr): 2925 m ; 2555 m ; 1692 s ; 1635 m ; 1482 s ; 1254 s ; 1213 s ; 1131 s ; 1048 m ; 1013 m ; 987 m ; 945 m ; 802 m ; 760 s ; 699 s . $^1\text{H-NMR}$ (300 MHz, CDCl_3): 7.40-7.44 (m , 6 H, $\text{H}_{\text{arom, Ketal}}$); 7.59-7.62 (m , 4 H, $\text{H}_{\text{arom, Ketal}}$); 7.74 (d , $J = 1.2$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 8.35 (m , 1 H, $\text{H}_{\text{arom, Cat.}}$). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 111.7; 112.4; 116.5 (q , $J = 289$); 121.0; 124.0; 126.2; 128.5; 128.9; 129.8; 138.3; 149.6; 154.3; 167.7; 178.1 (q , $J = 35.2$). $^{19}\text{F-NMR}$ (282 MHz, CDCl_3): -70.72 (s). HR-MS (MALDI): calcd. for $\text{C}_{22}\text{H}_{14}\text{F}_3\text{O}_5$ ($[\text{M}+\text{H}]^+$): 415.0793, found 415.0784. Anal. calcd. for $\text{C}_{22}\text{H}_{13}\text{F}_3\text{O}_5$: C 63.77, H 3.16; found C 63.81, H 3.29.

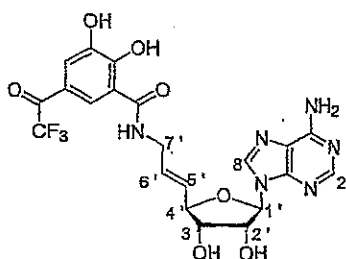
b) 2,2-Diphenyl-6-(2,2,2-trifluoro-acetyl)-benzo[1,3]dioxole-4-carboxylic acid {3-[(3a*R*,4*R*,6*R*,6a*R*)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4- d][1,3]dioxol-4-yl]-prop-2-enyl}-amide



- 15 GP7, starting from 2,2-diphenyl-6-(trifluoroacetyl)-1,3-benzodioxole-4-carboxylic acid (250 mg, 0.603 mmol, 1 eq.), EDC·HCl (175 mg, 0.91 mmol, 1.5 eq.), *N*-hydroxy-succinimide (90 mg, 0.784 mmol, 1.3 eq.) and 9-[(3a*R*,4*R*,6*R*,6a*R*)-6-[(*E*)-3-aminoprop-1-enyl]-2,2-dimethyl-perhydrofuro[3,4- d][1,3]di-oxol-4-yl]-9H-purin-6-amine (120 mg, 0.361 mmol, 0.6 eq.) provided the title compound as a colorless foam.
- 20 Yield: 174 mg (66%). Mp.: 108-110°C. IR (KBr): 3426 m ; 3199 m ; 2986 w ; 2227 w ; 1644 s ; 1599 m ; 1534 m ; 1476 m ; 1442 m ; 1378 w ; 1253 s ; 1207 s ; 1151 m ; 1082 m ; 1017 w ; 866 w ; 761 w ; 699 m ; 642 w . $^1\text{H-NMR}$ (300 MHz, CDCl_3): 1.38 (s , 3 H, $\text{CH}_3\text{-exo}$); 1.62 (s , 3 H, $\text{CH}_3\text{-endo}$); 4.07 (m , 2 H, H-C(7'), H-C(7'')); 4.68 (m , 1 H, H-C(4')); 4.97 (dd ; $J = 6.3, 3.6$, 1 H, H-C(3')); 5.47 (dd , $J = 6.3, 2.1$, 1 H, H-C(2')); 5.85 (m , 4 H, H-C(5'), H-C(6'), NH_2); 6.08 (d , $J = 2.1$, 1 H, H-C(1')); 7.03 (t , $J = 5.7$, 1 H, NHCO); 7.38-7.45 (m , 6 H, $\text{H}_{\text{arom, Ketal}}$); 7.47-7.52 (m , 4 H, $\text{H}_{\text{arom, Ketal}}$); 7.69 (d , $J = 1.7$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 7.86 (s , 1 H, H-C(8)); 8.21 (s , 1 H, H-C(2)); 8.43 (d , $J = 1.7$, $\text{H}_{\text{arom, Cat.}}$). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 25.5; 27.3; 41.1; 84.1; 84.5; 87.1; 90.2; 111.5; 114.7; 115.5; 116.6 (q , $J = 281$); 120.1; 120.9; 124.8; 126.3;

128.2; 128.6; 128.8; 130.2; 137.6; 137.7; 139.9; 148.4; 149.2; 150.2; 152.3; 155.0; 161.6; 178.5 (q , $J = 35.5$). ^{19}F -NMR (282 MHz, CDCl_3): -71.24 (s). HR-MS (MALDI): calcd. for $\text{C}_{37}\text{H}_{32}\text{F}_3\text{N}_6\text{O}_7$ ($[\text{M}+\text{H}]^+$): 729.2285, found 729.2291.

- c) N1-[(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-(2,2,2-trifluoro-acetyl)-2,3-dihydroxy-benzamide



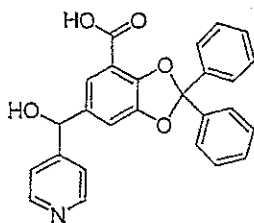
GP8, starting from the protected precursor (100 mg, 0.137 mmol) gave the desired product as a colorless solid.

- Yield: 40 mg (56%). $t_{\text{R, analyt.}}$: 11.1 min. IR (KBr): 3370 *br, s*; 1699 s ; 1640 s ; 1545 w ; 1439 w ; 1326 m ; 1283 m ; 1202 s ; 1142 s ; 1052 w ; 724 w . ^1H -NMR (500 MHz, CD_3OD): 4.05 (d , $J = 2.2$, 2 H, H-C(7'), H-C(7'')); 4.23 (t , $J = 5.0$, 1 H, H-C(4'')); 4.52 (m , 1 H, H-C(3'')); 4.72 (t , $J = 4.9$, 1 H, H-C(2'')); 5.94 (m , 2 H, H-C(5'), H-C(6'')); 6.05 (d , $J = 4.9$, 1 H, H-C(1'')); 7.18 (s , 1 H, H-C(8)); 7.57 (m , 1 H, $\text{H}_{\text{arom, Cat.}}$); 8.26 (d , $J = 4.2$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 8.38 (s , 1 H, H-C(2)). ^{13}C -NMR (125 MHz, CD_3OD): 41.6; 75.2; 75.6; 86.1; 90.5; 116.4; 119.2; 119.3; 120.7; 124.4 (q , $J = 286$); 126.4; 130.2; 131.1; 143.1; 147.2; 148.6; 150.3; 151.0; 154.0; 170.9 (1 peak missing). HR-MS (MALDI): calcd. for $\text{C}_{21}\text{H}_{20}\text{F}_3\text{N}_6\text{O}_7$ ($[\text{M}+\text{H}]^+$): 525.1346, found 525.1345.

Example 5

- Preparation of N1-[(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-(pyridine-4-carbonyl)-2,3-dihydroxy-benzamide

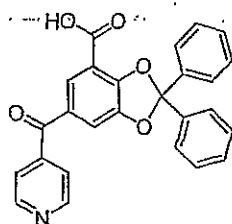
- a) 6-(Hydroxy-pyridin-4-yl-methyl)-2,2-diphenyl-1,3-benzodioxole-4-carboxylic acid



6-Bromo-2,2-diphenyl-1,3-benzodioxole-4-carboxylic acid (1 g, 2.52 mmol, 1 eq.), LiOMe (192 mg, 5.04 mmol, 2 eq.) and pyridine-4-carbaldehyde (0.48 mL, 5.03 mmol, 2 eq.) as the electrophile were reacted according to GP4, Method A. The crude product was purified using flash chromatography (silica gel, CH₂Cl₂/MeOH 92:8 → 80:20) to give the title compound as a yellow solid.

Yield 350 mg (33%). Mp.: 213-217°C (dec.). IR (KBr): 3381 *br, s*; 1565*s*; 1473*m*; 1410*s*; 1257*s*; 1205*s*; 1047*s*; 1026*m*; 948*w*; 806*w*; 777*m*; 698*m*; 642*m*. ¹H-NMR (300 MHz, (CD₃)₂SO): 5.63 (*s*, 1 H, H_{benz.}); 6.11 (*bs*, 1 H, OH); 7.04 (*s*, 1 H, H_{arom, Cat.}); 7.36 (*d*, *J* = 5.7, 2 H, H_{arom, Pyr.}); 7.40-7.42 (*m*, 7 H, H_{arom, Cat.}, H_{arom, Ketal}); 7.50-7.54 (*m*, 4 H, H_{arom, Ketal}); 8.46 (*d*, *J* = 5.7, 1 H, H_{arom, Pyr.}). ¹³C-NMR (75 MHz, (CD₃)₂SO): 62.6; 108.2; 116.1; 120.9; 121.4; 125.7; 128.2; 129.1; 137.3; 139.5; 139.6; 145.3; 147.0; 149.2; 153.6; 189.8. HR-MS (MALDI): calcd. for C₂₆H₂₀NO₅ ([M+H]⁺): 426.1341, found 426.1332.

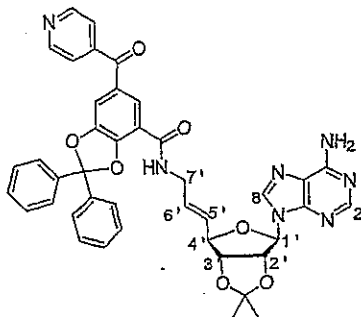
b) 2,2-Diphenyl-6-(pyridine-4-carbonyl)-1,3-benzodioxole-4-carboxylic acid



To a solution of 6-(hydroxy-pyridin-4-yl-methyl)-2,2-diphenyl-1,3-benzodioxole-4-carboxylic acid (128 mg, 0.324 mmol, 1 eq.) in a mixture of 10 mL acetone and 3 mL DMSO, IBX (273 mg, 0.973 mmol, 3 eq.) was added and the reaction mixture was stirred 3 h at 50°C. The mixture was partitioned between H₂O and EtOAc, and the organic layer was washed with saturated NaCl solution before being dried over MgSO₄ and evaporated under reduced pressure to yield the title compound as a yellowish solid.

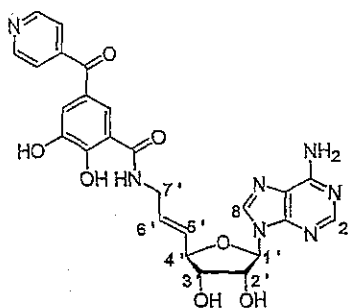
Yield: 130 mg (95%). Mp.: 256-257°C. IR (KBr): 3447 *br, w*; 3062*w*; 2426*w*; 1709*m*; 1669*m*; 1624*m*; 1475*m*; 1440*s*; 1408*w*; 1323*w*; 1270*s*; 1211*s*; 1048*s*; 1017*m*; 910*w*; 801*w*; 759*m*; 698*m*; 642*m*. ¹H-NMR (300 MHz, (CD₃)₂SO): 7.45-7.48 (*m*, 7 H, H_{arom, Cat.}, H_{arom, Ketal}); 7.54-7.58 (*m*, 6 H, H_{arom, Ketal}, H_{arom, Pyr.}); 7.73 (*s*, 1 H, H_{arom, Cat.}); 8.77 (*d*, *J* = 4.5, 2 H, H_{arom, Pyr.}). ¹³C-NMR (75 MHz, (CD₃)₂SO): 111.8; 112.9; 118.9; 122.4; 125.8; 127.9; 128.6; 129.5; 129.8; 138.2; 144.2; 148.4; 149.8; 151.1; 163.9; 192.1. HR-MS (MALDI): calcd. for C₂₆H₁₉NO₅ ([M+2H]⁺): 425.1263, found 425.1254.

c) 2,2-Diphenyl-6-(pyridine-4-carbonyl)-benzo[1,3]dioxole-4-carboxylic acid {3-[(3a*R*,4*R*,6*R*,6a*R*)-6-(6-amino-9*H*-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-*d*][1,3]dioxol-4-yl]-prop-2-enyl}-amide



- 5 2,2-Diphenyl-6-(pyridine-4-carbonyl)-1,3-benzodioxole-4-carboxylic acid (100 mg, 0.236 mmol, 1 eq.), EDC-HCl (68 mg, 0.354 mmol, 1.5 eq.), N-hydroxy-succinimid (36 mg, 0.307 mmol, 1.3 eq.), 9-[(3a*R*,4*R*,6*R*,6a*R*)-6-[(*E*)-3-aminoprop-1-enyl]-2,2-dimethylperhydrofuro [3,4-*d*][1,3]di-oxol-4-yl]-9*H*-purin-6-amine (72 mg, 0.215 mmol, 0.9 eq.) and Et₃N (0.1 mL, 0.68 mmol) were reacted according to GP7.
- 10 Yield: 98 mg (62%). Colorless foam. Mp.: 122-126°C. IR (KBr): 3427*m*; 1661*s*; 1596*m*; 1528*m*; 1472*m*; 1435*m*; 1374*w*; 1266*s*; 1208*s*; 1019*w*; 867*w*; 780*w*; 759*w*; 700*w*; 647*w*. ¹H-NMR (300 MHz, CDCl₃): 1.38 (*s*, 3 H, CH₃-*exo*); 1.62 (*s*, 3 H, CH₃-*endo*); 4.07 (*m*, 2 H, H-C(7'), H-C(7'')); 4.72 (*m*, 1 H, H-C(4'')); 4.93 (*dd*; *J* = 6.3, 3.6, 1 H, H-C(3'')); 5.40 (*dd*, *J* = 6.3, 2.0, 1 H, H-C(2'')); 5.83 (*m*, 2 H, H-C(5'), H-C(6'')); 6.10 (*d*, *J* = 2.0, 1 H, H-C(1'')); 6.55 (*bs*, 2 H, NH₂); 7.10 (*t*, *J* = 5.4, 1 H, NHCO); 7.39-7.45 (*m*, 6 H, H_{arom}, Ketal); 7.51-7.55 (*m*, 6 H, H-C_{arom}, Ketal, H_{arom}, pyridyl); 7.65 (*d*, *J* = 1.8, 1 H, H_{arom}, Cat.); 7.92 (*s*, 1 H, H-C(8)); 8.03 (*d*, *J* = 1.8, H_{arom}, Cat.); 8.29 (*s*, 1 H, H-C(2)); 8.79 (*dd*, *J* = 4.5, 1.8, 2 H, H_{arom}, pyridyl). ¹³C-NMR (75 MHz, CDCl₃): 25.5; 27.2; 41.0; 84.2; 84.4; 87.2; 90.4; 111.8; 114.6; 114.7; 120.0; 120.4; 122.6; 126.3; 128.0; 128.6; 130.1; 130.3; 130.8; 137.9; 138.0; 140.2; 144.3; 148.4; 148.9; 149.1; 150.3; 151.0; 154.4; 162.1; 193.0. HR-MS (MALDI): calcd. for C₄₁H₃₆N₇O₇ ([M+H]⁺): 738.2676, found 738.2677.
- 20

d) N1-[(*E*)-3-[(3a*R*,4*R*,6*R*,6a*R*)-5-(6-amino-9*H*-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-(pyridine-4-carbonyl)-2,3-dihydroxybenzamide



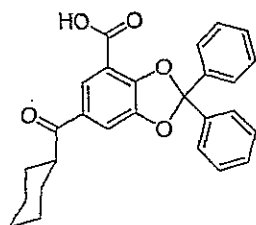
GP8, starting from the protected precursor (50 mg, 0.068 mmol) afforded the desired product as a yellowish solid.

Yield: 18 mg (50%). $t_{R, \text{analyt.}}$: 10.9 min. IR (KBr): 3385 *br, s*; 1678*s*; 1637*s*; 1432*w*; 1307*m*; 1201*s*; 1132*m*; 1051*w*; 835*w*; 723*w*. $^1\text{H-NMR}$ (500 MHz, CD_3OD): 3.94 (*d*, $J = 3.7$, 2 H, H-C(7'), H-C(7'')); 4.13 (*t*, $J = 5.3$, 1 H, H-C(4')); 4.39 (*t*, $J = 5.3$, 1 H, H-C(3')); 4.64 (*t*, $J = 4.8$, 1 H, H-C(2'')); 5.82 (*m*, 2 H, H-C(5'), H-C(6')); 5.93 (*d*, $J = 4.8$, 1 H, H-C(1')); 7.37 (*d*, $J = 2.1$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 7.57 (*dd*, $J = 4.6$, 1.6, 2 H, $\text{H}_{\text{arom, Pyr.}}$); 7.71 (*d*, $J = 2.1$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 8.12 (*s*, 1 H, H-C(8)); 8.22 (*s*, 1 H, H-C(2)); 8.65 (*dd*, $J = 4.6$, 1.6, 2 H, $\text{H}_{\text{arom, Pyr.}}$). $^{13}\text{C-NMR}$ (125 MHz, CD_3OD): 41.7; 75.1; 75.6; 85.9; 90.5; 116.7; 119.6; 120.7; 123.5; 124.5; 127.9; 130.5; 130.7; 142.5; 147.7; 148.1; 150.3; 150.4; 150.5; 155.1; 155.7; 170.2; 194.7. HR-MS (MALDI): calcd. for $\text{C}_{25}\text{H}_{24}\text{N}_7\text{O}_7$ ($[\text{M}+\text{H}]^+$): 534.1737, found 534.1729.

Example 6

Preparation of N1-[(E)-3-[(3a*R*,4*R*,6*R*,6a*R*)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-cyclohexanecarbonyl-2,3-dihydroxybenzamide

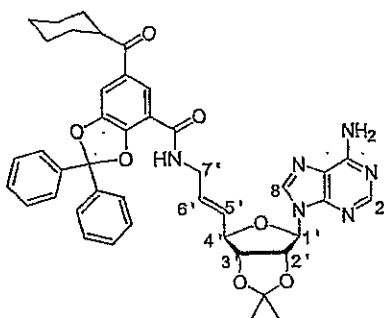
a) 6-Cyclohexanecarbonyl-2,2-diphenyl-1,3-benzodioxole-4-carboxylic acid



6-Bromo-2,2-diphenyl-1,3-benzodioxole-4-carboxylic acid (1.26 g, 3.16 mmol, 1 eq.), LiOMe (240 mg, 6.32 mmol, 2 eq.) and cyclohexanecarboxylic acid methoxy-methylamide (650 mg, 3.8 mmol, 1.2 eq.) as the electrophile were reacted according to GP4, Method A. The crude product was purified using flash chromatography (silica gel, hexane/Et₂O/AcOH 5:1:0.1) and subsequent recrystallization from CH_2Cl_2 / hexane to give the title compound as a yellowish solid.

Yield: 338 mg (25%). Mp.: 212-214°C. IR (KBr): 3062 w ; 2932 m ; 2854 m ; 1693 s ; 1628 w ; 1448 s ; 1250 s ; 1205 s ; 1155 m ; 1042 m ; 1020 m ; 988 m ; 948 m ; 875 w ; 752 m ; 695 s . $^1\text{H-NMR}$ (300 MHz, CDCl_3): 1.26-1.52 (m , 6 H, CH_2 ,cyclohexyl); 1.72-1.86 (m , 4H, CH_2 ,cyclohexyl); 3.24 (m , 1 H, CHCO); 7.38-7.45 (m , 6 H, $\text{H}_{\text{arom, Ketal}}$); 7.59-7.65 (m , 4 H, $\text{H}_{\text{arom, Ketal}}$); 7.70 (d , J = 1.7, 1 H, $\text{H}_{\text{arom, Cat.}}$); 8.16 (d , J = 1.7, 1 H, $\text{H}_{\text{arom, Cat.}}$). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 25.9; 26.0; 29.7; 45.4; 110.9; 112.1; 119.8; 125.4; 126.3; 128.4; 129.6; 130.7; 138.8; 149.3; 152.4; 168.8; 201.2. HR-MS (MALDI): calcd. for $\text{C}_{27}\text{H}_{25}\text{O}_5$ ($[\text{M}+\text{H}]^+$): 429.1702, found 429.1693.

b) 6-Cyclohexanecarbonyl-2,2-diphenyl-benzo[1,3]dioxole-4-carboxylic acid {3-
10 [(3aR,4R,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-
 d][1,3]dioxol-4-yl]-prop-2-enyl}-amide

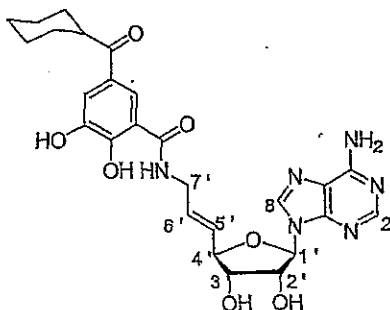


2,2-Diphenyl-6-cyclohexanecarbonyl-1,3-benzodioxole-4-carboxylic acid (197 mg, 0.46
mmol, 1 eq.), EDC-HCl (133 mg, 0.69 mmol, 1.5 eq.), *N*-hydroxy-succinimide (70 mg,
15 0.6 mmol, 1.3 eq.), 9-[(3aR,4R,6R,6aR)-6-[(*E*)-3-aminoprop-1-enyl]-2,2-
dimethylperhydrofuro [3,4- d][1,3]di-oxol-4-yl]-9H-purin-6-amine (130 mg, 0.391
mmol, 0.85 eq.) and Et_3N (0.1 mL, 0.68 mmol) were reacted according to GP7.

Yield: 145 mg (50%). Colorless foam. Mp.: 120-122°C. IR (KBr): 3428 br, m ; 2931 m ;
2853 w ; 1667 s ; 1636 s ; 1596 m ; 1529 m ; 1473 m ; 1433 m ; 1376 w ; 1252 s ; 1209 s ; 1154 w ; 1082 m ;
20 1049 m ; 1018 w ; 867 w ; 777 w ; 699 w . $^1\text{H-NMR}$ (300 MHz, CDCl_3): 1.24-1.52 (m , 9 H, CH_3 -
 exo , CH_2 ,cyclohexyl); 1.62 (s , 3 H, CH_3 - $endo$); 1.70-1.86 (m , 4 H, CH_2 ,cyclohexyl); 3.70 (m , 1 H,
 CHCO); 4.07 (m , 2 H, $\text{H-C}(7')$, $\text{H-C}(7'')$); 4.70 (m , 1 H, $\text{H-C}(4')$); 4.96 (dd ; J = 6.5, 3.9, 1
H, $\text{H-C}(3')$); 5.45 (dd , J = 6.5, 2.1, 1 H, $\text{H-C}(2')$); 5.86 (m , 2 H, $\text{H-C}(5')$, $\text{H-C}(6')$); 5.92
(bs , 2 H, NH_2); 6.09 (d , J = 2.1, 1 H, $\text{H-C}(1')$); 7.11 (t , J = 5.4, 1 H, NHCO); 7.36-7.41 (m ,
25 6 H, $\text{H}_{\text{arom, Ketal}}$); 7.48-7.52 (m , 4 H, $\text{H-C}_{\text{arom, Ketal}}$); 7.65 (d , J = 1.5, 1 H, $\text{H-C}_{\text{arom, Cat.}}$); 7.87
(s , 1 H, $\text{H-C}(8)$); 8.22 (s , 1 H, $\text{H-C}(2)$); 8.24 (d , J = 1.5, $\text{H-C}_{\text{arom, Cat.}}$). $^{13}\text{C-NMR}$ (75 MHz,
 CDCl_3): 25.4; 25.8; 26.0; 27.2; 29.6; 40.9; 45.3; 84.1; 84.4; 87.1; 90.2; 110.9; 114.4; 114.7;
119.7; 120.1; 124.6; 126.3; 128.4; 129.8; 130.4; 131.5; 138.1; 138.2; 139.9; 148.0; 148.1;

149.2; 152.0; 154.8; 162.5; 201.8. HR-MS (MALDI): calcd. for $C_{42}H_{43}N_6O_7$ ($[M+H]^+$): 743.3193, found 743.3195. Anal. calcd. for $C_{42}H_{42}N_6O_5$: C 67.91, H 5.70, N 11.31 found C 67.77, H 5.85, N 11.05.

- c) N1-{(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl}-5-cyclohexanecarbonyl-2,3-dihydroxy-benzamide



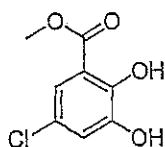
GP8, starting from the protected precursor (60 mg, 0.081 mmol) afforded the desired product as a colorless solid.

- Yield: 25 mg (59%). $t_{R, \text{analyt.}}$: 14.5 min (linear gradient of CH_3CN in H_2O with 0.1% TFA
 10 15 $\rightarrow$ 55% in 20 min.) IR (KBr): 3388 *br, s*; 2933 *m*; 1700 *s*; 1638 *s*; 1543 *w*; 1430 *w*; 1326 *m*; 1295 *m*; 1202 *s*; 1130 *m*; 1048 *w*; 837 *w*; 801 *w*; 724 *w*. 1H -NMR (500 MHz, CD_3OD): 1.23-1.29 (m, 1 H, 3.94 $CH_{2, \text{cyclohexyl}}$); 1.38-1.50 (m, 4 H, $CH_{2, \text{cyclohexyl}}$); 1.72-1.83 (m, 5 H, $CH_{2, \text{cyclohexyl}}$); 3.35 (t, $J = 1.6$, 1 H, $CHCO$); 4.08 (d, $J = 3.3$, 2 H, $H-C(7')$, $H-C(7'')$); 4.25 (t, $J = 5.0$, 1 H, $H-C(4')$); 4.52 (t, $J = 5.0$, 1 H, $H-C(3')$); 4.74 (t, $J = 4.7$, 1 H, $H-C(2')$);
 15 5.96 (m, 2 H, $H-C(5')$, $H-C(6')$); 6.04 (d, $J = 4.7$, 1 H, $H-C(1')$); 7.53 (d, $J = 2.0$, 1 H, $H_{\text{arom, Cat.}}$); 8.02 (d, $J = 2.0$, 1 H, $H_{\text{arom, Cat.}}$); 8.23 (s, 1 H, $H-C(8)$); 8.34 (s, 1 H, $H-C(2)$). ^{13}C -NMR (125 MHz, CD_3OD): 26.8; 27.1; 30.8; 41.7; 46.0; 75.1; 75.6; 86.0; 90.5; 116.4; 118.5; 120.7; 128.6; 130.5; 130.9; 142.8; 147.8; 149.7; 150.3; 154.7; 154.9; 170.7; 204.6. HR-MS (MALDI): calcd. for $C_{26}H_{31}N_6O_7$ ($[M+H]^+$): 539.2254, found 539.2244.

20 Example 7

Preparation of N1-{(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl}-5-chloro-2,3-dihydroxy-benzamide

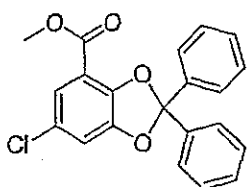
- a) Methyl 5-chloro-2,3-dihydroxy-benzoate



5-Chloro-2,3-dihydroxybenzoic acid (290 mg, 1.54 mmol, 1 eq.) and SOCl_2 (550 mg, 4.61 mmol, 3 eq.) were reacted according to GP1.

Yield: 250 mg (80%). Gray powder. IR (KBr): 3453s; 3096m; 2960m; 1700s; 1673s; 1471s; 1437s; 1316s; 1233s; 1202s; 1152s; 1013m; 932m; 863m; 788m; 723m. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 3.96 (s, 3 H, OCH_3); 5.73 (bs, 1 H, OH); 7.10 (d, $J = 2.1$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 7.35 (d, $J = 2.1$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 10.84 (s, 1 H, OH). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 52.8; 112.7; 119.7; 120.0; 124.1; 145.7; 147.6; 169.7. HR-MS (EI): calcd. for $\text{C}_8\text{H}_7\text{ClO}_4$ ($[\text{M}+\text{H}]^+$): 202.0033, found 201.9774.

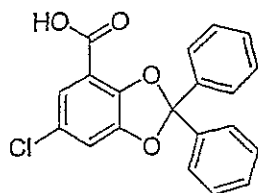
b) Methyl 6-chloro-2,2-diphenyl-1,3-benzodioxole-4-carboxylate



Methyl 5-chloro-2,3-dihydroxybenzoate (330 mg, 1.63 mmol, 1 eq.) and dichlorodiphenyl-methane (470 mg, 1.96 mmol, 1.2 eq.) were reacted according to GP2, Method B.

Yield: 310 mg (52%). Colorless solid. Mp.: 151-152°C. IR (KBr): 3086w; 2947w; 1719s (CO); 1595w; 1468s; 1445m; 1360m; 1277m; 1245s; 1202s; 1166m; 1042m; 1014m; 905w; 866w; 806m; 781m; 762m; 696m. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 3.94 (s, 3 H, CH_3); 7.00 (d, $J = 2.1$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 7.38-7.40 (m, 6 H, $\text{H}_{\text{arom, Ketal}}$, $\text{H}_{\text{arom, Cat.}}$); 7.56-7.59 (m, 4 H, $\text{H}_{\text{arom, Ketal}}$). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 52.6; 111.1; 113.3; 119.4; 122.3; 126.3; 126.6; 128.6; 129.7; 139.4; 147.4; 149.3; 164.2. HR-MS (MALDI): calcd. for $\text{C}_{21}\text{H}_{16}\text{ClO}_4$ ($[\text{M}+\text{H}]^+$): 367.0737, found 367.0731. Anal. calcd. for $\text{C}_{21}\text{H}_{15}\text{ClO}_4$: C 68.77, H 4.12, found C 68.64, H 4.29.

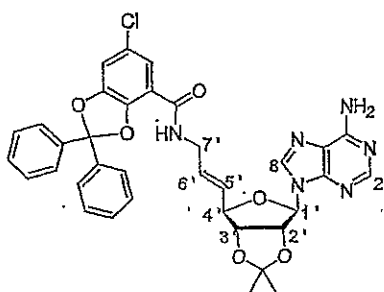
c) 6-Chloro-2,2-diphenyl-1,3-benzodioxole-4-carboxylic acid



Methyl 6-chloro-2,2-diphenyl-1,3-benzodioxole-4-carboxylate (150 mg, 0.408 mmol, 1 eq.) and $\text{LiOH} \cdot \text{H}_2\text{O}$ (52 mg, 1.23 mmol, 3 eq.) were reacted according to GP3.

Yield: 117 mg (82%). Colorless solid. Mp.: 206-207°C. IR (KBr): 3071 m ; 2868 m ; 2616 w ; 1704 s (CO); 1599 w ; 1469 s ; 1450 m ; 1407 w ; 1350 w ; 1284 m ; 1267 m ; 1238 s ; 1200 s ; 1044 m ; 1022 m ; 949 w ; 908 w ; 859 w ; 799 m ; 761 m ; 698 m ; 642 w . $^1\text{H-NMR}$ (300 MHz, CDCl_3): 7.05 (d , $J = 2.1$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 7.39-7.42 (m , 6 H, $\text{H}_{\text{arom, Ketal}}$); 7.46 (d , $J = 2.1$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 7.58-7.61 (m , 4 H, $\text{H}_{\text{arom, Ketal}}$). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 112.3; 114.1; 119.9; 122.6; 126.5; 126.6; 128.7; 129.8; 139.2; 148.1; 149.5; 168.5. HR-MS (MALDI): calcd. for $\text{C}_{20}\text{H}_{14}\text{ClO}_4$ ($[\text{M}+\text{H}]^+$): 353.0581, found 353.0576.

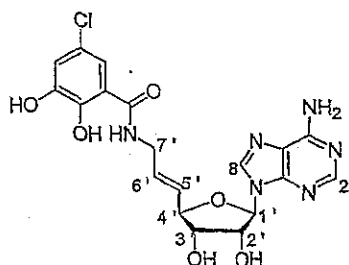
d) 6-Chloro-2,2-diphenyl-benzo[1,3]dioxole-4-carboxylic acid {3-[(3aR,4R,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4- d][1,3]dioxol-4-yl]-prop-2-enyl}-amide



6-Chloro-2,2-diphenyl-1,3-benzodioxole-4-carboxylic acid (90 mg, 0.255 mmol, 1 eq.), EDC-HCl (75 mg, 0.383 mmol, 1.5 eq.), *N*-hydroxy-succinimide (40 mg, 0.332 mmol, 1.3 eq.), 9-[(3aR,4R,6R,6aR)-6-[(*E*)-3-aminoprop-1-enyl]-2,2-dimethylperhydrofuro[3,4- d][1,3] di-oxol-4-yl]-9H-purin-6-amine (85 mg, 0.255 mmol, 1 eq.) and Et_3N (0.1 mL, 0.68 mmol) were reacted according to GP7.

Yield: 123 mg (73%). Colorless foam. Mp.: 111-113°C. IR (KBr): 3424 m ; 3176 m ; 2986 m ; 1638 s ; 1595 s ; 1530 m ; 1462 s ; 1374 m ; 1329 m ; 1240 s ; 1208 s ; 1156 w ; 1083 m ; 1047 m ; 1017 m ; 971 w ; 867 w ; 778 w ; 698 m . $^1\text{H-NMR}$ (300 MHz, CDCl_3): 1.37 (s , 3 H, $\text{CH}_3\text{-exo}$); 1.61 (s , 3 H, $\text{CH}_3\text{-endo}$); 4.04 (m , 2 H, H-C(7'), H-C(7'')); 4.69 (m , 1 H, H-C(4')); 4.94 (dd , $J = 6.3$, 3.6, 1 H, H-C(3')); 5.44 (dd , $J = 6.3$, 2.1, 1 H, H-C(2')); 5.83 (m , 2 H, H-C(5'), H-C(6')); 6.05 (bs , 2 H, NH_2); 6.08 (d , $J = 2.1$, 1 H, H-C(1')); 7.00 (d , $J = 2.1$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 7.06 (t , $J = 5.7$, 1 H, NHCO); 7.35-7.40 (m , 6 H, $\text{H}_{\text{arom, Ketal}}$); 7.44-7.50 (m , 4 H, H-C(6), $\text{H}_{\text{arom, Ketal}}$); 7.56 (d , $J = 2.1$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 7.87 (s , 1 H, H-C(8)); 8.19 (s , 1 H, H-C(2)). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 25.6; 27.4; 41.0; 84.4; 84.7; 87.4; 90.5; 112.8; 115.0; 116.1; 119.8; 120.2; 122.3; 126.6; 127.6; 128.6; 128.8; 130.2; 130.8; 138.7; 140.4; 143.9; 148.3; 149.5; 152.2; 155.1; 162.5. HR-MS (MALDI): calcd. for $\text{C}_{35}\text{H}_{32}\text{ClN}_6\text{O}_6$ ($[\text{M}+\text{H}]^+$): 667.2072, found 667.2065.

e) N1-[(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-chloro-2,3-dihydroxy-benzamide



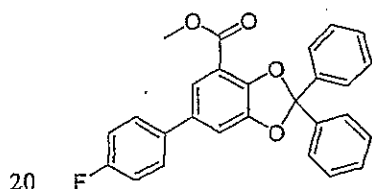
GP8, starting from the protected precursor (70 mg, 0.105 mmol) afforded the desired product as a colorless solid.

Yield: 35 mg (73%). $t_{R, \text{analyt.}}$: 13.1 min. IR (KBr): 3396 *br, s*; 1700s; 1636*m*; 1542*w*; 1469*w*; 1429*w*; 1326*w*; 1203s; 1135*m*; 1050*w*; 972*w*; 800*w*; 725*w*. $^1\text{H-NMR}$ (500 MHz, $(\text{CD}_3)_2\text{SO}$): 3.93 (*m*, 2 H, H-C(7'), H-C(7'')); 4.09 (*t*, $J = 4.9$, 1 H, H-C(4')); 4.35 (*m*; 1 H, H-C(3')); 4.64 (*t*, $J = 5.1$, 1 H, H-C(2')); 5.78-5.89 (*m*, 2 H, H-C(5'), H-C(6')); 5.91 (*d*, $J = 5.1$, H-C(1')); 6.92 (*d*, $J = 2.5$, 1 H, $H_{\text{arom, Cat.}}$); 7.41 (*d*, $J = 2.5$, 1 H, $H_{\text{arom, Cat.}}$); 8.12 (*bs*, 1 H, OH); 8.23 (*s*, 1 H, H-C(8)); 8.46 (*s*, 1 H, H-C(2)); 9.02 (*t*, $J = 5.4$, 1 H, H-NHCO); 12.62 (*bs*, 1 H, OH). $^{13}\text{C-NMR}$ (125 MHz, CD_3OD): 40.1; 73.0; 73.9; 84.3; 87.8; 115.7; 116.5; 118.3; 119.1; 121.7; 129.3; 129.4; 141.1; 147.6; 148.8; 148.9; 149.3; 153.4; 168.3. HR-MS (MALDI): calcd. for $\text{C}_{19}\text{H}_{20}\text{ClN}_6\text{O}_6$ ($[\text{M}+\text{H}]^+$): 463.1132, found 463.1133.

15 Example 8

Preparation of N1-[(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-(4-fluoro-phenyl)-2,3-dihydroxy-benzamide

a) Methyl 6-(4-fluoro-phenyl)-2,2-diphenyl-1,3-benzodioxole-4-carboxylate

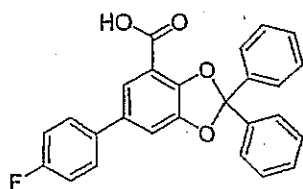


Methyl 6-bromo-2,2-diphenyl-1,3-benzodioxole-4-carboxylate (100 mg, 0.243 mmol, 1 eq.), $\text{Pd}(\text{PPh}_3)_4$ (15 mg, 0.012 mmol, 0.05 eq.), 4-fluorophenylboronic acid (135 mg, 0.972 mmol, 4 eq.) and K_2CO_3 (202g, 1.46 mmol, 6 eq.) were reacted according to GP5.

Yield: 80 mg (78%). Colorless solid. Mp.: 125-127°C. IR (KBr): 3061*m*; 2950*m*; 1723s (CO); 1634*w*; 1603*m*; 1517*m*; 1472s; 1364*m*; 1257s; 1215s; 1053s; 947*m*; 833s; 780*m*; 698s;

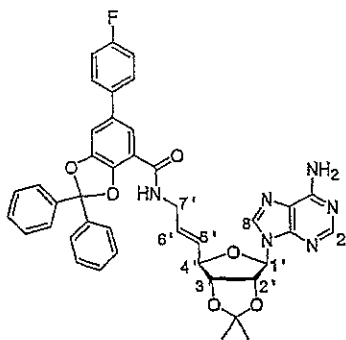
- 640m. ^1H -NMR (300 MHz, CDCl_3): 3.97 (s, 3 H, CH_3); 7.10 (tt, $J = 8.7, 2.0$, 2 H, $\text{H}_{\text{arom, p-F-phenyl}}$); 7.20 (d, $J = 2.0$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 7.39-7.42 (m, 6 H, $\text{H}_{\text{arom, Ketal}}$); 7.45-7.50 (m, 2 H, $\text{H}_{\text{arom, p-F-phenyl}}$); 7.59 (d, $J = 2.0$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 7.62-7.65 (m, 4 H, $\text{H}_{\text{arom, Ketal}}$). ^{13}C -NMR (75 MHz, CDCl_3): 52.2; 111.1; 112.7; 115.6 (d, $J = 21.2$); 118.4; 121.1; 126.3; 128.2; 128.3; 129.2; 134.0; 136.0; 139.4; 147.4; 148.8; 162.2 (d, $J = 244.7$); 164.8. ^{19}F -NMR (282 MHz, CDCl_3): -115.9 (tt, $J = 9.6, 5.4$). HR-MS (MALDI): calcd. for $\text{C}_{27}\text{H}_{19}\text{FO}_4$ ($[\text{M}]^+$): 426.1267, found 426.1258.

b) 6-(4-Fluoro-phenyl)-2,2-diphenyl-1,3-benzodioxole-4-carboxylic acid



- 10 Methyl 6-(4-fluoro-phenyl)-2,2-diphenyl-1,3-benzodioxole-4-carboxylate (250 mg, 0.586 mmol, 1 eq.) and $\text{LiOH} \cdot \text{H}_2\text{O}$ (74 mg, 1.76 mmol, 3 eq.) were reacted according to GP3.
- Yield: 214 mg (89%). Colorless solid. Mp.: 215-217°C. IR (KBr): 3032m; 2625w; 1687s (CO); 1635w; 1604m; 1519m; 1473s; 1422m; 1355w; 1281s; 1219s; 1179m; 1055s; 1022s; 948m; 918w; 832s; 784m; 756m; 699s; 641m. ^1H -NMR (300 MHz, CDCl_3): 7.10 (t, $J = 8.7$, 2 H, $\text{H}_{\text{arom, p-F-phenyl}}$); 7.26 (d, $J = 1.0$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 7.39-7.43 (m, 6 H, $\text{H}_{\text{arom, Ketal}}$); 7.46-7.51 (m, 2 H, $\text{H}_{\text{arom, p-F-phenyl}}$); 7.63-7.66 (m, 5 H, $\text{H}_{\text{arom, Ketal, H}_{\text{arom, Cat.}}}$). ^{13}C -NMR (75 MHz, CDCl_3): 111.7; 112.0; 115.7 (d, $J = 21.2$); 118.9; 121.6; 126.3; 128.3; 128.4; 129.4; 134.3; 135.9 (d, $J = 3.1$); 139.3; 148.1; 149.0; 162.3 (d, $J = 245.3$); 169.0. ^{19}F -NMR (282 MHz, CDCl_3): -115.7 (tt, $J = 8.5, 5.4$). HR-MS (MALDI): calcd. for $\text{C}_{27}\text{H}_{19}\text{FO}_4\text{Na}$ ($[\text{M}+\text{Na}]^+$): 435.1009, found 435.1000.

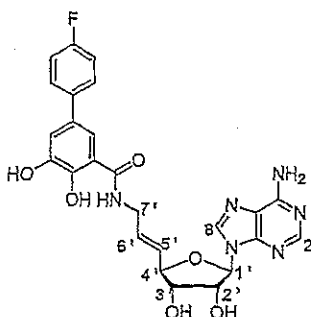
c) 6-(4-Fluoro-phenyl)-2,2-diphenyl-benzo[1,3]dioxole-4-carboxylic acid {3-[(3aR,4R,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxol-4-yl]-prop-2-enyl}-amide



6-(4-Fluoro-phenyl)-2,2-diphenyl-1,3-benzodioxole-4-carboxylic acid (130 mg, 0.315 mmol, 1 eq.), EDC·HCl (91 mg, 0.473 mmol, 1.5 eq.), *N*-hydroxy-succinimide (48 mg, 0.409 mmol, 1.3 eq.), 9-[(3*aR*,4*R*,6*R*,6*aR*)-6-[(*E*)-3-aminoprop-1-enyl]-2,2-dimethylperhydrofuro[3,4-*d*] [1,3]di-oxol-4-yl]-9H-purin-6-amine (90 mg, 0.271 mmol, 0.86 eq.) and Et₃N (0.1 mL, 0.68 mmol) were reacted according to GP7.

Yield: 130 mg (66%). Colorless foam. Mp.: 123-125°C. IR (KBr): 3425*m*; 3175*w*; 2987*w*; 1636*s*; 1598*m*; 1517*m*; 1469*s*; 1373*w*; 1274*m*; 1213*s*; 1158*w*; 1082*m*; 1052*m*; 1016*w*; 867*w*; 834*w*; 777*w*; 699*m*. ¹H-NMR (300 MHz, CDCl₃): 1.38 (*s*, 3 H, CH₃-*exo*); 1.62 (*s*, 3 H, CH₃-*endo*); 4.08 (*m*, 2 H, H-C(7'), H-C(7'')); 4.71 (*m*, 1 H, H-C(4')); 4.95 (*dd*; *J* = 6.6, 3.6, 1 H, H-C(3')); 5.44 (*dd*, *J* = 6.6, 2.3, 1 H, H-C(2')); 5.87 (*m*, 2 H, H-C(5'), H-C(6')); 5.93 (*bs*, 2 H, NH₂); 6.09 (*d*, *J* = 2.3, 1 H, H-C(1')); 7.10 (*tt*, *J* = 8.7, 2.1, 2 H, H_{arom}, *p*-F-phenyl); 7.12 (*t*, *J* = 5.6, 1 H, NHCO); 7.22 (*d*, *J* = 1.8, 1 H, H-C_{arom}, Cat.); 7.37-7.41 (*m*, 6 H, H_{arom}, Ketal); 7.47-7.56 (*m*, 6 H, H_{arom}, Ketal, H_{arom}, *p*-F-phenyl); 7.77 (*d*, *J* = 1.8, H_{arom}, Cat.); 7.87 (*s*, 1 H, H-C(8)); 8.19 (*s*, 1 H, H-C(2)). ¹³C-NMR (75 MHz, CDCl₃): 25.5; 27.3; 40.9; 84.1; 84.5; 87.1; 90.3; 110.6; 114.7; 115.3; 115.6 (*d*, *J* = 21.2); 118.8; 120.1; 121.0; 126.4; 128.2; 128.4; 128.5; 129.7; 130.7; 135.0; 136.1; 138.7; 139.9; 144.1; 147.8; 149.2; 152.0; 154.8; 162.3 (*d*, *J* = 244.7); 163.1. ¹⁹F-NMR (282 MHz, CDCl₃): -115.9 (*tt*, *J* = 8.5, 5.4). HR-MS (MALDI): calcd. for C₄₁H₃₅FN₆O₆Na ([M+Na]⁺): 749.2500, found 749.2501.

d) N1-[(*E*)-3-[(3*aR*,4*R*,6*R*,6*aR*)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-(4-fluoro-phenyl)-2,3-dihydroxybenzamide



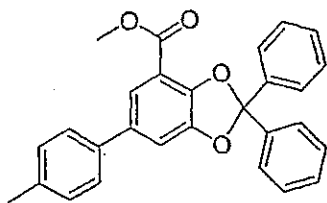
GP8, starting from the protected precursor (70 mg, 0.096 mmol) afforded the desired product as a colorless solid.

Yield: 28 mg (56%). $t_{R, \text{analyt.}}$: 17.8 min. IR (KBr): 3407 *br, s*; 1700*s*; 1641*m*; 1542*w*; 1479*w*; 1314*w*; 1204*s*; 1137*m*; 1050*w*; 835*w*; 801*w*; 725*w*. $^1\text{H-NMR}$ (500 MHz, CD_3OD): 4.07 (*m*, 2 H, H-C(7'), H-C(7'')); 4.24 (*t*, $J = 5.3$, 1 H, H-C(4')); 4.52 (*t*, $J = 5.3$, 1 H, H-C(3')); 4.73 (*t*, $J = 4.8$, 1 H, H-C(2')); 5.96 (*bd*, $J = 3.3$, 2 H, H-C(5'), H-C(6')); 6.05 (*d*, $J = 4.8$, 1 H, H-C(1')); 7.13 (*t*, $J = 8.8$, 2 H, $\text{H}_{\text{arom, p-F-phenyl}}$); 7.20 (*d*, $J = 2.0$, 1 H, $\text{H-C}_{\text{arom, Cat.}}$); 7.51 (*d*, $J = 2.0$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 7.58 (*dd*, $J = 8.8, 5.4$, 2 H, $\text{H}_{\text{arom, p-F-phenyl}}$); 8.23 (*s*, 1 H, H-C(8)); 8.37 (*s*, 1 H, H-C(2)). $^{13}\text{C-NMR}$ (125 MHz, CD_3OD): 41.7; 75.2; 75.6; 86.1; 90.5; 116.4 (*d*, $J = 21.3$); 117.0; 117.1; 118.2; 129.3; 129.4; 130.3; 131.0; 132.3; 138.1; 143.0; 147.8; 149.0; 152.6; 149.8; 163.6 (*d*, $J = 242.5$); 171.2. HR-MS (MALDI): calcd. for $\text{C}_{25}\text{H}_{24}\text{FN}_6\text{O}_6$ ($[\text{M}+\text{H}]^+$): 523.1741, found 523.1731.

Example 9

Preparation of N1-[(E)-3-[(3*aR*,4*R*,6*R*,6*aR*)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-*p*-tolyl-2,3-dihydroxy-benzamide

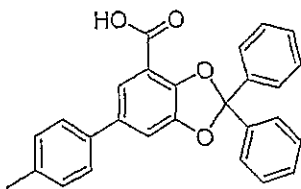
a) Methyl 2,2-diphenyl-6-*p*-tolyl-1,3-benzodioxole-4-carboxylate



Methyl 6-bromo-2,2-diphenyl-1,3-benzodioxole-4-carboxylate (500 mg, 1.215 mmol, 1 eq.) $\text{Pd}(\text{PPh}_3)_4$ (70 mg, 0.06 mmol, 0.05 eq.), *p*-tolylboronic acid (330 mg, 2.43 mmol, 2 eq.) and K_2CO_3 (1g, 7.29 mmol, 6 eq.) were reacted according to GP5.

Yield: 403 mg (79%). Colorless solid. Mp.: 159-160°C. IR (KBr): 3034*w*; 2941*w*; 1719*s*; 1470*s*; 1450*s*; 1429*m*; 1363*w*; 1255*s*; 1209*s*; 1161*m*; 1053*s*; 1028*s*; 944*w*; 817*m*; 775*m*; 702*s*; 640*m*. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 2.38 (*s*, 3 H, CH_3); 3.97 (*s*, 3 H, OCH_3); 7.22 (*d*, $J = 7.8$, 2 H, $\text{H}_{\text{arom, p-tolyl}}$); 7.26 (*d*, $J = 1.8$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 7.38-7.44 (*m*, 8 H, $\text{H}_{\text{arom, p-tolyl}}$ $\text{H}_{\text{arom, Ketal}}$); 7.62-7.66 (*m*, 5 H, $\text{H}_{\text{arom, Cat.}}$ $\text{H}_{\text{arom, Ketal}}$). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 21.2; 52.2; 111.1; 112.7; 118.2; 121.0; 126.3; 126.6; 128.2; 129.2; 129.4; 135.0; 136.9; 137.0; 139.6; 147.3; 148.7; 164.9. HR-MS (MALDI): calcd. for $\text{C}_{28}\text{H}_{22}\text{O}_4\text{Na}$ ($[\text{M}+\text{Na}]^+$): 445.1416, found 445.1406.

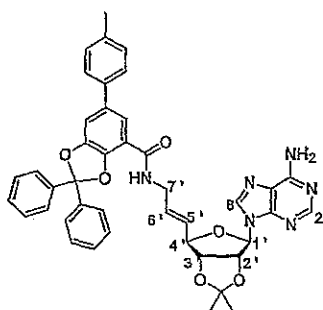
b) 2,2-Diphenyl-6-*p*-tolyl-1,3-benzodioxole-4-carboxylic acid



Methyl 2,2-diphenyl-6-*p*-tolyl-1,3-benzodioxole-4-carboxylate (280 mg, 0.662 mmol, 1 eq.) and LiOH·H₂O (84 mg, 2 mmol, 3 eq.) were reacted according to GP3.

Yield: 251 mg (93%). Colorless solid. Mp.: 223-224°C. IR (KBr): 3030*m*; 2624*m*; 1684*s* (CO); 1634*m*; 1602*w*; 1473*s*; 1421*m*; 1355*w*; 1282*s*; 1213*s*; 1055*s*; 1023*s*; 947*m*; 918*w*; 871*w*; 814*m*; 784*m*; 758*m*; 699*s*; 640*m*. ¹H-NMR (300 MHz, CDCl₃): 2.39 (*s*, 3 H, CH₃); 7.23 (*d*, *J* = 7.8, 2 H, H_{arom}, *p*-tolyl); 7.31 (*d*, *J* = 1.8, 1 H, H_{arom}, Cat.); 7.39-7.45 (*m*, 8 H, H_{arom}, Ketal; H_{arom}, *p*-tolyl); 7.64-7.67 (*m*, 4 H, H_{arom}, Ketal); 7.71 (*d*, *J* = 1.8, 1 H, H_{arom}, Cat.). ¹³C-NMR (75 MHz, CDCl₃): 21.1; 111.8; 112.0; 118.7; 121.5; 126.4; 126.7; 128.4; 129.4; 129.5; 135.3; 136.9; 137.2; 139.5; 148.0; 149.0; 169.4. HR-MS (MALDI): calcd. for C₂₇H₂₀O₄Na ([M+Na]⁺): 431.1259, found 431.1259.

c) 2,2-diphenyl-6-*p*-tolyl-benzo[1,3]dioxole-4-carboxylic acid {3-[(3*aR*,4*R*,6*R*,6*aR*)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-*d*][1,3]dioxol-4-yl]-prop-2-enyl}-amide



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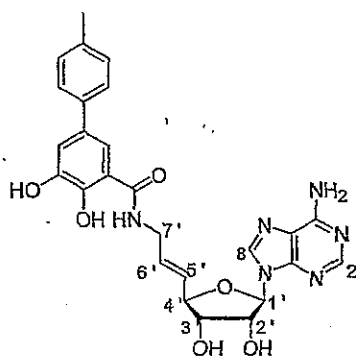
2,2-diphenyl-6-*p*-tolyl-1,3-benzodioxole-4-carboxylic acid (164 mg, 0.4 mmol, 1 eq.), EDC·HCl (115 mg, 0.6 mmol, 1.5 eq.), *N*-hydroxy-succinimide (60 mg, 0.52 mmol, 1.3 eq.), 9-[(3*aR*,4*R*,6*R*,6*aR*)-6-[(*E*)-3-aminoprop-1-enyl]-2,2-dimethylperhydrofuro[3,4-*d*][1,3]di-oxol-4-yl]-9H-purin-6-amine (90 mg, 0.271 mmol, 0.68 eq.) and Et₃N (0.1 mL, 0.68 mmol) were reacted according to GP7.

Yield: 111 mg (57%). Colorless foam. Mp.: 124-126°C. IR (KBr): 3423*m*; 3176*m*; 2986*w*; 1638*s*; 1597*s*; 1531*m*; 1469*s*; 1434*m*; 1373*w*; 1329*w*; 1276*s*; 1207*s*; 1156*w*; 1081*m*; 1052*s*; 1016*m*; 970*w*; 867*m*; 818*m*; 777*m*; 699*m*; 641*m*. ¹H-NMR (300 MHz, CDCl₃): 1.38 (*s*, 3 H, CH₃-_{exo}); 1.62 (*s*, 3 H, CH₃-_{endo}); 2.37 (*s*, 3 H, CH₃); 4.09 (*m*, 2 H, H-C(7'), H-C(7'')); 4.71 (*m*, 1 H, H-C(4')); 4.94 (*dd*; *J* = 6.5, 3.6, 1 H, H-C(3')); 5.42 (*dd*, *J* = 6.5, 2.6, 1 H, H-

25

C(2'')); 5.86 (*m*, 2 H, H-C(5'), H-C(6'')); 6.06 (*bs*, 2 H, NH₂); 6.09 (*d*, *J* = 2.6, 1 H, H-C(1'')); 7.17 (*t*, *J* = 5.6, 1 H, NHCO); 7.21 (*d*, *J* = 8.3, 2 H, H_{arom, p-tolyl}); 7.26 (*d*, *J* = 1.8, 1 H, H_{arom, Cat.}); 7.36-7.42 (*m*, 6 H, H_{arom, Ketal}); 7.46 (*d*, *J* = 8.3, 2 H, H_{arom, p-tolyl}); 7.51-7.56 (*m*, 4 H, H_{arom, Ketal}); 7.82 (*d*, *J* = 1.8, H-C_{arom, Cat.}); 7.88 (*s*, 1 H, H-C(8)); 8.19 (*s*, 1 H, H-C(2)). ¹³C-NMR (75 MHz, CDCl₃): 25.2; 25.5; 27.2; 40.8; 84.1; 84.4; 87.1; 90.3; 110.5; 114.7; 115.2; 118.6; 120.0; 120.8; 126.4; 126.6; 128.0; 128.3; 129.4; 129.6; 130.8; 135.9; 136.0; 137.0; 138.8; 140.0; 143.8; 147.7; 149.1; 151.5; 154.6; 163.2. HR-MS (MALDI): calcd. for C₄₂H₃₈N₆O₆Na ([M+Na]⁺): 745.2751, found 745.2750. Anal. calcd. for C₄₂H₃₈N₆O₆: C 69.79, H 5.30, N 11.63, found C 69.61, H 5.56, N 11.93.

- 10 d) N1-[(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-*p*-tolyl-2,3-dihydroxy-benzamide



GP8, starting from the protected precursor (70 mg, 0.097 mmol) afforded the desired product as a colorless solid.

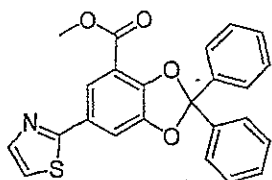
- 15 Yield: 28 mg (56%). *t_{R, analyt.}*: 18.3 min. IR (KBr): 3397 *br, s*; 1700*s*; 1640*m*; 1541*w*; 1478*w*; 1430*w*; 1319*w*; 1203*s*; 1137*m*; 1050*w*; 973*w*; 799*w*; 725*w*. ¹H-NMR (500 MHz, (CD₃)₂SO): 3.97 (*m*, 2 H, H-C(7'), H-C(7'')); 4.10 (*t*, *J* = 4.9, 1 H, H-C(4')); 4.37 (*t*, *J* = 4.9, 1 H, H-C(3'')); 4.64 (*t*, *J* = 5.1, 1 H, H-C(2'')); 5.83-5.90 (*m*, 2 H, H-C(5'), H-C(6'')); 5.91 (*d*, *J* = 5.1, H-C(1'')); 7.20 (*d*, *J* = 1.9, 1 H, H_{arom, Cat.}); 7.22 (*d*, *J* = 8.0, 1 H, H_{arom, p-tolyl}); 7.51 (*d*, *J* = 8.0, 1 H, H_{arom, p-tolyl}); 7.63 (*d*, *J* = 1.9, 1 H, H_{arom, Cat.}); 8.12 (*bs*, 1 H, OH); 8.23 (*s*, 1 H, H-C(8)); 8.47 (*s*, 1 H, H-C(2)); 9.16 (*t*, *J* = 5.5, 1 H, H-NHCO); 12.79 (*bs*, 1 H, OH). ¹³C-NMR (125 MHz, (CD₃)₂SO): 20.6; 40.1; 73.0; 73.9; 84.2; 87.7; 114.8; 114.9; 116.8; 119.0; 125.9; 129.3; 129.5; 130.1; 136.0; 136.7; 141.0; 146.5; 148.9; 149.2; 149.4; 153.5; 169.6. HR-MS (MALDI): calcd. for C₂₆H₂₆N₆O₆Na ([M+Na]⁺): 541.1812, found 541.1810.

Example 10

Preparation of N1-[(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-

dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-thiazol-2-yl-2,3-dihydroxy-benzamide

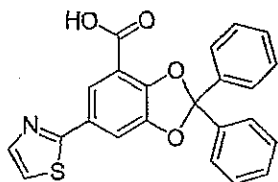
a) Methyl 2,2-diphenyl-6-thiazol-2-yl-1,3-benzodioxole-4-carboxylate



Methyl 6-bromo-2,2-diphenyl-1,3-benzodioxole-4-carboxylate (250 mg, 0.608 mmol, 1 eq.) Pd(PPh₃)₄ (70 mg, 0.06 mmol, 0.1 eq.), bis(pinacolato)diboron (200 mg, 0.79 mmol, 1.3 eq.) and KOAc (90 mg, 0.912 mmol, 1.5 eq.), then Pd(PPh₃)₄ (70 mg, 0.06 mmol, 0.1 eq.), 2-bromo-thiazole (110 mg, 0.67 mmol, 1.1 eq.) and K₂CO₃ (420 mg, 3.04 mmol, 5 eq.) were used according to GP6 to yield the title product as a colorless solid.

Yield: 166 mg (66%). Mp.: 154-155°C. IR (KBr): 3054w; 2947w; 1712s (CO); 1627w; 1497w; 1468s; 1447s; 1359m; 1321w; 1286m; 1254s; 1212s; 1047s; 1017s; 944w; 929w; 883w; 801m; 781m; 760m; 699s; 641m. ¹H-NMR (300 MHz, CDCl₃): 3.97 (s, 3 H, OCH₃); 7.28 (d, J = 3.2, 2 H, H_{arom}, thiazolyl); 7.37-7.42 (m, 6 H, H_{arom}, Ketal); 7.60-7.63 (m, 4 H, H_{arom}, Ketal); 7.71 (d, J = 2.3, 1 H, H_{arom}, Cat.); 7.81 (d, J = 3.2, 2 H, H_{arom}, thiazolyl); 8.01 (d, J = 2.3, 1 H, H_{arom}, Cat.). ¹³C-NMR (75 MHz, CDCl₃): 52.5; 110.4; 113.1; 118.9; 119.4; 122.2; 126.6; 127.8; 128.6; 129.7; 139.5; 143.5; 149.4; 149.9; 164.6; 167.4. HR-MS (MALDI): calcd. for C₂₄H₁₈NO₄S ([M+H]⁺): 416.0957, found 416.0947.

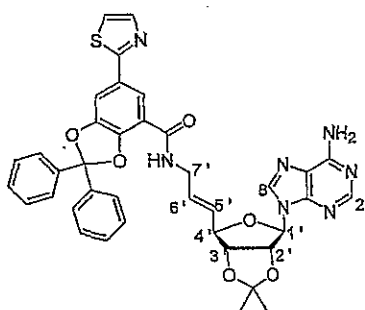
b) 2,2-diphenyl-6-thiazol-2-yl-1,3-benzodioxole-4-carboxylic acid



Methyl 2,2-diphenyl-6-thiazol-2-yl-1,3-benzodioxole-4-carboxylate (300 mg, 0.722 mmol, 1 eq.) and LiOH·H₂O (91 mg, 2.17 mmol, 3 eq.) were reacted according to GP3. Yield: 280 mg (96%). Colorless solid. Mp.: 226-227°C. IR (KBr): 3122w; 2924w; 1702m (CO); 1629w; 1477s; 1446s; 1319w; 1266s; 1235m; 1213s; 1133s; 1048m; 1018m; 948w; 909w; 851w; 792m; 762w; 720w; 699m; 641w. ¹H-NMR (300 MHz, (CD₃)₂SO): 7.46-7.50 (m, 6 H, H_{arom}, Ketal); 7.34-7.57 (m, 4 H, H_{arom}, Ketal); 7.76 (d, J = 3.0, 2 H, H_{arom}, thiazolyl); 7.78 (d, J = 1.8, 1 H, H_{arom}, Cat.); 7.89 (d, J = 3.0, 2 H, H_{arom}, thiazolyl); 7.92 (d, J = 1.8, 1 H, H_{arom}, Cat.). ¹³C-NMR (75 MHz, CDCl₃): 109.7; 113.8; 118.3; 120.4; 121.3; 125.9; 127.3; 128.7;

129.7; 138.7; 143.7; 148.4; 148.5; 164.4; 165.7. HR-MS (MALDI): calcd. for $C_{23}H_{16}NO_4S$ ($[M+H]^+$): 402.0800, found 402.0794.

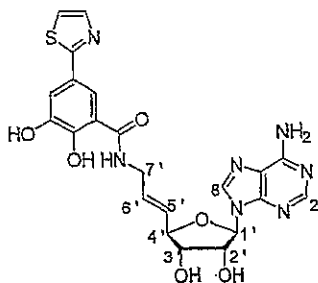
- c) 2,2-diphenyl-6-thiazol-2-yl-benzo[1,3]dioxole-4-carboxylic acid {3-
[(3a*R*,4*R*,6*R*,6a*R*)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-
5 *d*][1,3]dioxol-4-yl]-prop-2-enyl]-amide



- 2,2-diphenyl-6-thiazol-2-yl-1,3-benzodioxole-4-carboxylic acid (160 mg, 0.4 mmol, 1
eq.), EDC·HCl (115 mg, 0.6 mmol, 1.5 eq.), *N*-hydroxy-succinimide (60 mg, 0.52 mmol,
1.3 eq.), 9-[(3a*R*,4*R*,6*R*,6a*R*)-6-[(*E*)-3-aminoprop-1-enyl]-2,2-
10 dimethylperhydrofuro[3,4-*d*][1,3]di-oxol-4-yl]-9H-purin-6-amine (100 mg, 0.3 mmol,
0.75 eq.) and Et_3N (0.1 mL, 0.68 mmol) were reacted according to GP7.

- Yield: 158 mg (74%). Colorless foam. Mp.: 132°C. IR (KBr): 3424*m*; 3199*w*; 2987*w*;
1639*s*; 1598*m*; 1532*m*; 1471*m*; 1440*m*; 1374*w*; 1329*w*; 1263*m*; 1212*s*; 1156*w*; 1081*m*;
1050*m*; 1015*m*; 867*w*; 779*w*; 700*m*; 643*w*. 1H -NMR (300 MHz, $CDCl_3$): 1.39 (*s*, 3 H, CH_3 -
15 *exo*); 1.62 (*s*, 3 H, CH_3 -*endo*); 4.08 (*m*, 2 H, H-C(7'), H-C(7'')); 4.76 (*m*, 1 H, H-C(4')); 4.93
(*dd*; *J* = 6.2, 3.0, 1 H, H-C(3')); 5.42 (*dd*, *J* = 6.2, 2.0, 1 H, H-C(2')); 5.82 (*m*, 2 H, H-
C(5'), H-C(6')); 6.10 (*d*, *J* = 2.0, 1 H, H-C(1')); 6.63 (*bs*, 2 H, NH_2); 7.12 (*t*, *J* = 5.7, 1 H,
 $NHCO$); 7.30 (*d*, *J* = 3.5, 2 H, $H_{arom, thiazolyl}$); 7.37-7.43 (*m*, 6 H, $H_{arom, Ketal}$); 7.50-7.54
(*m*, 4 H, $H_{arom, Ketal}$); 7.73 (*d*, *J* = 1.7, 1 H, $H_{arom, Cat.}$); 7.81 (*d*, *J* = 3.5, 2 H, $H_{arom, thiazolyl}$);
20 7.92 (*s*, 1 H, H-C(8)); 8.14 (*d*, *J* = 1.7, $H_{arom, Cat.}$); 8.20 (*s*, 1 H, H-C(2)). ^{13}C -NMR (75
MHz, $CDCl_3$): 25.4; 27.1; 40.9; 84.3; 84.4; 87.3; 90.7; 109.7; 114.6; 115.4; 119.0; 119.3;
119.9; 121.9; 126.4; 127.9; 128.4; 128.6; 129.8; 130.8; 138.4; 140.5; 143.3; 145.9; 148.0;
148.9; 149.5; 153.8; 162.6; 167.2. HR-MS (MALDI): calcd. for $C_{38}H_{33}N_7O_6SNa$
($[M+Na]^+$): 738.2111, found 738.2095. Anal. calcd. for $C_{42}H_{38}N_6O_6$: C 63.76, H 4.65, N
25 13.70, found C 63.55, H 4.70, N 13.68.

- d) N1-[(*E*)-3-[(3a*R*,4*R*,6*R*,6a*R*)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydro-
furan-2-yl]prop-2-enyl]-5-thiazol-2-yl-2,3-dihydroxy-benzamide



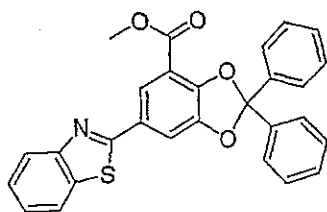
GP8, starting from the protected precursor (80 mg, 0.112 mmol) afforded the desired product as a colorless solid.

Yield: 43 mg (75%). $t_{R, \text{analyt.}}$: 13.1 min. IR (KBr): 3402 *br, s*; 1700*s*; 1642*m*; 1597*m*; 1552*w*; 1428*w*; 1318*w*; 1293*w*; 1200*s*; 1136*m*; 1050*w*; 837*w*; 800*w*; 723*m*. $^1\text{H-NMR}$ (500 MHz, $(\text{CD}_3)_2\text{SO}$): 3.97 (*m*, 2 H, H-C(7'), H-C(7'')); 4.10 (*t*, $J = 4.9$, 1 H, H-C(4'')); 4.37 (*dd*, $J = 5.0, 4.9$, 1 H, H-C(3'')); 4.63 (*t*, $J = 5.0$, 1 H, H-C(2'')); 5.82-5.91 (*m*, 2 H, H-C(5'), H-C(6'')); 5.92 (*d*, $J = 5.0$, H-C(1'')); 7.53 (*d*, $J = 1.7$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 7.68 (*d*, $J = 3.3$, 1 H, $\text{H}_{\text{arom, thiazolyl}}$); 7.83 (*d*, $J = 3.3$, 1 H, $\text{H}_{\text{arom, thiazolyl}}$); 7.92 (*d*, $J = 1.7$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 8.52 (*s*, 1 H, H-C(8)); 8.56 (*bs*, 1 H, OH); 9.27 (*t*, $J = 5.7$, 1 H, H-NHCO); 9.71 (*s*, 1 H, H-C(2)); 12.98 (*bs*, 1 H, OH). $^{13}\text{C-NMR}$ (125 MHz, $(\text{CD}_3)_2\text{SO}$): 40.1; 73.2; 73.9; 84.3; 87.8; 115.5; 115.8; 115.9; 119.0; 119.6; 123.8; 129.3; 129.6; 141.4; 143.4; 146.8; 148.4; 148.8; 151.5; 152.7; 167.0; 168.9. HR-MS (MALDI): calcd. for $\text{C}_{22}\text{H}_{21}\text{N}_7\text{O}_6\text{SNa}$ ($[\text{M}+\text{Na}]^+$): 534.1172, found 534.1173.

15 Example 11

Preparation of N1-[(*E*)-3-[(3*aR*,4*R*,6*R*,6*aR*)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-benzothiazol-2-yl-2,3-dihydroxybenzamide

a) Methyl 6-benzothiazol-2-yl-2,2-diphenyl-1,3-benzodioxole-4-carboxylate

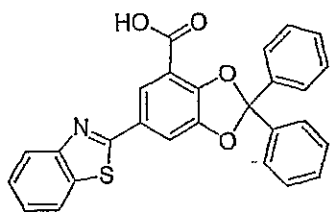


20

Methyl 6-bromo-2,2-diphenyl-1,3-benzodioxole-4-carboxylate (600 mg, 1.459 mmol, 1 eq.), $\text{Pd}(\text{PPh}_3)_4$ (85 mg, 0.073 mmol, 0.05 eq.), bis(pinacolato)diboron (480 mg, 1.9 mmol, 1.3 eq.) and KOAc (216 mg, 2.2 mmol, 1.5 eq.), then $\text{Pd}(\text{PPh}_3)_4$ (85 mg, 0.073 mmol, 0.05 eq.), 2-bromo-1,3-benzothiazole (375 mg, 1.75 mmol, 1.2 eq.) and K_2CO_3 (1 g, 7.3 mmol, 5 eq.) were used according to GP6 to yield the title product as a colorless solid.

Yield: 274 mg (41%). Mp.: 184-185°C. IR (KBr): 3055w; 2950w; 1718s; 1635w; 1502w; 1446s; 1368m; 1297m; 1239s; 1212s; 1163m; 1047s; 1015s; 945m; 921m; 874m; 795m; 776s; 759s; 723w; 701s; 640m. ¹H-NMR (300 MHz, CDCl₃): 4.00 (s, 3 H, OCH₃); 7.38-7.51 (m, 8 H, H_{arom}, benzothiazole, H_{arom}, Ketal); 7.62-7.64 (m, 4 H, H_{arom}, Ketal); 7.86 (d, J = 1.7, 1 H, H_{arom}, Cat.); 7.88 (d, J = 9.3, 1 H, H_{arom}, benzothiazole); 8.04 (d, J = 9.3, 1 H, H_{arom}, benzothiazole); 8.13 (d, J = 1.7, 1 H, H_{arom}, Cat.). ¹³C-NMR (75 MHz, CDCl₃): 52.4; 110.6; 112.8; 119.3; 121.5; 122.9; 123.2; 125.1; 126.3; 127.5; 128.3; 129.4; 134.8; 139.1; 149.1; 150.2; 153.7; 164.1; 166.5. HR-MS (MALDI): calcd. for C₂₈H₂₀NO₄S ([M+H]⁺): 466.1113, found 466.1113. Anal. calcd. for C₂₈H₁₉NO₄S: C 72.24, H 4.11, N 3.01, found C 72.15, H 4.03, N 3.19.

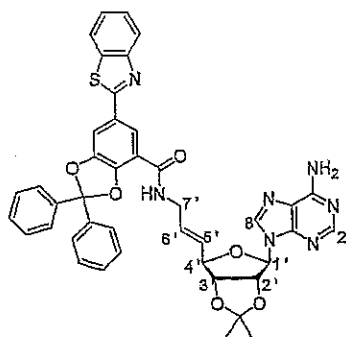
b) 2,2-diphenyl-6-benzothiazol-2-yl-1,3-benzodioxole-4-carboxylic acid



Methyl 2,2-diphenyl-6-benzothiazol-2-yl-1,3-benzodioxole-4-carboxylate (210 mg, 0.451 mmol, 1 eq.) and LiOH·H₂O (57 mg, 1.35 mmol, 3 eq.) were reacted according to GP3.

Yield: 201 mg (99%). Colorless solid. Mp.: 227°C. IR (KBr): 3437w; 2965w; 2610w; 1738m; 1688s; 1634w; 1460s; 1427m; 1360w; 1256s; 1237s; 1211s; 1047s; 1048m; 1015m; 999m; 928w; 878w; 788m; 760m; 726w; 699m; 641w. ¹H-NMR (300 MHz, CDCl₃): 7.36-7.44 (m, 7 H, H_{arom}, benzothiazole; H_{arom}, Ketal); 7.46-7.53 (m, 1 H, H_{arom}, benzothiazole); 7.53-7.67 (m, 4 H, H_{arom}, Ketal); 7.88 (d, J = 1.8, 1 H, H_{arom}, Cat.); 7.89 (d, J = 8.7, 1 H, H_{arom}, benzothiazole); 8.15 (d, J = 8.7, 1 H, H_{arom}, benzothiazole); 8.28 (d, J = 1.8, 1 H, H_{arom}, Cat.). ¹³C-NMR (75 MHz, CDCl₃): 111.4; 112.2; 119.7; 121.5; 123.1; 123.7; 125.2; 126.3; 126.4; 127.5; 128.3; 129.5; 134.6; 138.9; 149.3; 150.9; 153.6; 166.6; 167.8. HR-MS (MALDI): calcd. for C₂₇H₁₈NO₄S ([M+H]⁺): 452.0957, found 452.0955.

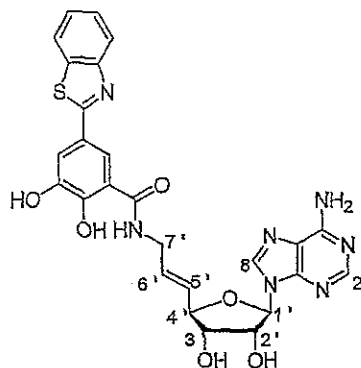
c) 6-Benzothiazol-2-yl-2,2-diphenyl-benzo[1,3]dioxole-4-carboxylic acid {3-[(3aR,4R,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxol-4-yl]-prop-2-enyl}-amide



2,2-diphenyl-6-benzothiazol-2-yl-1,3-benzodioxole-4-carboxylic acid (170 mg, 0.38 mmol, 1 eq.), EDC·HCl (110 mg, 0.565 mmol, 1.5 eq.), *N*-hydroxy-succinimide (57 mg, 0.49 mmol, 1.3 eq.), 9-[(3*aR*,4*R*,6*R*,6*aR*)-6-[(*E*)-3-aminoprop-1-enyl]-2,2-dimethylperhydrofuro[3,4-*d*][1,3]di-oxol-4-yl]-9H-purin-6-amine (100 mg, 0.3 mmol, 0.8 eq.) and Et₃N (0.1 mL, 0.68 mmol) were reacted according to GP7.

Yield: 151 mg (66%). Colorless foam. Mp.: 138-140°C. IR (KBr): 3424*m*; 2982*w*; 1635*s*; 1596*m*; 1533*m*; 1463*m*; 1436*s*; 1373*w*; 1259*m*; 1208*s*; 1155*w*; 1081*m*; 1048*m*; 1011*m*; 867*w*; 759*w*; 699*w*; 641*w*. ¹H-NMR (300 MHz, CDCl₃): 1.38 (s, 3 H, CH₃-*exo*); 1.62 (s, 3 H, CH₃-*endo*); 4.07 (*m*, 2 H, H-C(7'), H-C(7'')); 4.72 (*m*, 1 H, H-C(4'')); 4.95 (*dd*, *J* = 6.3, 3.6, 1 H, H-C(3'')); 5.44 (*dd*, *J* = 6.3, 2.3, 1 H, H-C(2'')); 5.85 (*m*, 2 H, H-C(5'), H-C(6'')); 6.09 (*d*, *J* = 2.3, 1 H, H-C(1'')); 6.17 (*bs*, 2 H, NH₂); 7.13 (*t*, *J* = 5.7, 1 H, NHCO); 7.34-7.49 (*m*, 8 H, H_{arom}, Ketal, H_{arom}, benzoth.); 7.49-7.55 (*m*, 4 H, H_{arom}, Ketal); 7.87 (s, 1 H, H-C(8)); 7.88 (*d*, *J* = 7.8, 2 H, H_{arom}, benzoth.); 7.91 (*d*, *J* = 1.9, 1 H, H_{arom}, Cat.); 7.81 (*d*, *J* = 7.8, 2 H, H_{arom}, benzoth.); 8.20 (s, 1 H, H-C(2)); 8.22 (*d*, *J* = 1.9, H_{arom}, Cat.). ¹³C-NMR (75 MHz, CDCl₃): 25.4; 27.2; 40.9; 84.1; 84.4; 87.2; 90.3; 110.1; 114.6; 115.4; 119.5; 120.0; 121.5; 122.9; 123.2; 125.1; 126.2; 126.4; 128.3; 128.4; 128.6; 129.8; 130.5; 135.0; 138.3; 140.0; 146.7; 148.1; 149.1; 151.5; 153.7; 154.7; 162.4; 166.7. HR-MS (MALDI): calcd. for C₄₂H₃₅N₇O₆Na ([M+Na]⁺): 788.2267, found 788.2266.

d) N1-[(*E*)-3-[(3*aR*,4*R*,6*R*,6*aR*)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-benzothiazol-2-yl-2,3-dihydroxybenzamide

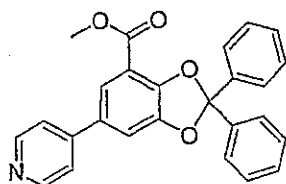


GP8, starting from the protected precursor (83 mg, 0.108 mmol) afforded the desired product as a yellowish solid.

Yield: 38 mg (64%). $t_{R, \text{analyt.}}$: 17.7 min. IR (KBr): 3377 *br, s*; 1685*s*; 1645*m*; 1544*w*; 1436*m*; 1303*m*; 1202*s*; 1137*m*; 834*w*; 800*w*; 759*w*; 724*w*. $^1\text{H-NMR}$ (500 MHz, $(\text{CD}_3)_2\text{SO}$): 4.01 (*m*, 2 H, H-C(7'), H-C(7'')); 4.13 (*t*, $J = 4.9$, 1 H, H-C(4')); 4.39 (*dd*, $J = 6.7, 4.9$, 1 H, H-C(3'')); 4.66 (*t*, $J = 5.0$, 1 H, H-C(2'')); 5.80-5.96 (*m*, 2 H, H-C(5'), H-C(6'')); 5.93 (*d*, $J = 5.0$, H-C(1')); 7.43 (*t*, $J = 8.0$, 1 H, $H_{\text{arom, benzoth.}}$); 7.53 (*t*, $J = 8.0$, 1 H, $H_{\text{arom, benzoth.}}$); 7.68 (*d*, $J = 2.0$, 1 H, $H_{\text{arom, Cat.}}$); 8.00 (*d*, $J = 8.0$, 1 H, $H_{\text{arom, benzoth.}}$); 8.09 (*d*, $J = 2.0$, 1 H, $H_{\text{arom, Cat.}}$); 8.12 (*d*, $J = 8.0$, 1 H, $H_{\text{arom, benzoth.}}$); 8.27 (*s*, 1 H, H-C(8)); 9.37 (*t*, $J = 5.3$, 1 H, H-NHCO); 9.86 (*s*, 1 H, H-C(2)); 13.19 (*bs*, 1 H, OH). $^{13}\text{C-NMR}$ (125 MHz, $(\text{CD}_3)_2\text{SO}$): 40.1; 73.0; 73.9; 84.2; 87.7; 115.4; 115.5; 116.4; 119.1; 122.3; 122.4; 123.3; 125.2; 126.6; 129.4; 129.5; 134.4; 141.0; 147.0; 149.0; 149.1; 152.6; 153.3; 153.5; 167.0; 168.7. HR-MS (MALDI): calcd. for $\text{C}_{26}\text{H}_{23}\text{N}_7\text{O}_6\text{SNa}$ ($[\text{M}+\text{Na}]^+$): 584.1328, found 584.1330.

15 Example 12

Preparation of N1-[(E)-3-[(3a*R*,4*R*,6*R*,6a*R*)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-pyridin-4-yl-2,3-dihydroxy-benzamide
a) Methyl 2,2-diphenyl-6-pyridin-4-yl-1,3-benzodioxole-4-carboxylate

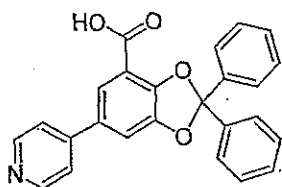


20 Methyl 6-bromo-2,2-diphenyl-1,3-benzodioxole-4-carboxylate (400 mg, 0.973 mmol, 1 eq.), $\text{Pd}(\text{PPh}_3)_4$ (100 mg, 0.087 mmol, 0.09 eq.), bis(pinacolato)diboron (320 mg, 1.26 mmol, 1.3 eq.) and KOAc (150 mg, 1.5 mmol, 1.5 eq.), then $\text{Pd}(\text{PPh}_3)_4$ (112 mg, 0.097 mmol, 0.1 eq.), 2-bromo-pyridine hydrochloride (265 mg, 1.36 mmol, 1.4 eq.) and

K₂CO₃ (680 mg, 4.9 mmol, 5 eq.) were used according to GP6 to yield the title product as a colorless solid.

Yield: 264 mg (67%). Mp.: 151-152°C. IR (KBr): 3030w; 2954w; 1718s; 1635w; 1594m; 1475s; 1439s; 1418m; 1325m; 1291m; 1269s; 1225s; 1180m; 1054s; 1038m; 1018m; 947w; 927w; 886w; 815m; 782m; 753w; 703m; 693m; 641m. ¹H-NMR (300 MHz, CDCl₃): 3.98 (s, 3 H, OCH₃); 7.31 (d, *J* = 1.8, 1 H, H_{arom, Cat.}); 7.39-7.41 (m, 6 H, H_{arom, Ketal}); 7.48 (dd, *J* = 4.7, 1.8, 1 H, H_{arom, pyridyl}); 7.61-7.64 (m, 4 H, H_{arom, Ketal}); 7.75 (d, *J* = 1.7, 1 H, H_{arom, Cat.}); 8.63 (dd, *J* = 4.7, 1.8, 1 H, H_{arom, pyridyl}). ¹³C-NMR (75 MHz, CDCl₃): 52.6; 110.9; 113.4; 119.4; 121.6; 122.3; 126.6; 128.6; 129.8; 131.7; 139.5; 148.0; 149.4; 149.7; 149.8
164.9. HR-MS (MALDI): calcd. for C₂₆H₂₀NO₄ ([M+H]⁺): 410.1392, found 410.1383.

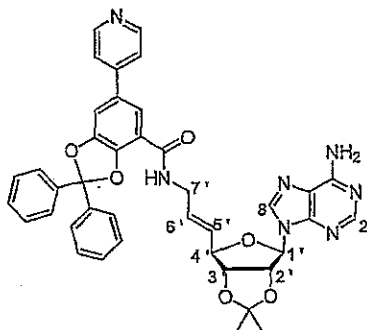
b) 2,2-diphenyl-6-pyridin-4-yl-1,3-benzodioxole-4-carboxylic acid



Methyl 2,2-diphenyl-6-pyridin-4-yl-1,3-benzodioxole-4-carboxylate (250 mg, 0.61 mmol, 1 eq.) and LiOH·H₂O (80 mg, 1.84 mmol, 3 eq.) were reacted according to GP3.

Yield: 220 mg (92%). Grayish solid. Mp.: 266°C (dec.). IR (KBr): 3446br, w; 3061w; 2447br, w; 1696m; 1632w; 1603m; 1469s; 1440m; 1373w; 1326w; 1273s; 1213s; 1182m; 1054s; 1015m; 949w; 921w; 906w; 832m; 789w; 777w; 765m; 701m; 640w. ¹H-NMR (300 MHz, (CD₃)₂SO): 7.46-7.48 (m, 6 H, H_{arom, Ketal}); 7.52-7.58 (m, 4 H, H_{arom, Ketal}); 7.67 (d, *J* = 4.4, 2 H, H_{arom, pyridyl}); 7.73 (m, 2 H, H_{arom, Cat.}); 8.59 (d, *J* = 4.4, 2 H, H_{arom, pyridyl}). ¹³C-NMR (75 MHz, CDCl₃): 110.7; 113.9; 117.9; 120.8; 121.6; 125.8; 128.6; 129.6; 131.1; 138.7; 145.6; 147.8; 148.5; 150.0; 164.6. HR-MS (MALDI): calcd. for C₂₅H₁₈NO₄ ([M+H]⁺): 396.1236, found 396.1234.

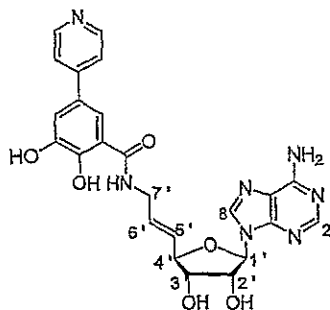
c) 2,2-Diphenyl-6-pyridin-4-yl-benzo[1,3]dioxole-4-carboxylic acid {3-[(3aR,4R,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxol-4-yl]-prop-2-enyl}-amide



- 5 The reaction of 2,2-diphenyl-6-pyridin-4-yl-1,3-benzodioxole-4-carboxylic acid (160 mg, 0.405 mmol, 1 eq.), EDC·HCl (117 mg, 0.608 mmol, 1.5 eq.), *N*-hydroxy-succinimide (61 mg, 0.527 mmol, 1.3 eq.), 9-[(3aR,4R,6R,6aR)-6-[(*E*)-3-aminoprop-1-enyl]-2,2-dimethyl-perhydrofuro[3,4-*d*][1,3]di-oxol-4-yl]-9H-purin-6-amine (100 mg, 0.3 mmol, 0.74 eq.) and Et₃N (0.1 mL, 0.68 mmol) was carried out in CH₂Cl₂ / DMF 1:1 according
10 to GP7.

Yield: 95 mg (45%). Yellowish foam. IR (neat, dropcast from CH₂Cl₂): 3321*br*, *w*; 2963*m*; 1696*m*; 1645*m*; 1597*m*; 1530*w*; 1468*s*; 1435*w*; 1374*w*; 1261*s*; 1213*s*; 1053*s*; 867*w*; 799*m*; 699*m*; 642*w*. ¹H-NMR (300 MHz, CDCl₃): 1.37 (*s*, 3 H, CH₃-*exo*); 1.61 (*s*, 3 H, CH₃-*endo*); 4.08 (*m*, 2 H, H-C(7'), H-C(7'')); 4.70 (*m*, 1 H, H-C(4')); 4.96 (*dd*; *J* = 6.3, 3.9, 1 H, H-C(3'')); 5.45 (*dd*, *J* = 6.3, 2.3, 1 H, H-C(2'')); 5.86 (*m*, 2 H, H-C(5'), H-C(6'')); 5.98 (*bs*, 2 H, NH₂); 6.08 (*d*, *J* = 2.3, 1 H, H-C(1'')); 7.16 (*t*, *J* = 5.7, 1 H, NHCO); 7.31 (*d*, *J* = 1.7, 1 H, H_{arom}, Cat.); 7.36-7.42 (*m*, 6 H, H_{arom}, Ketal); 7.47-7.55 (*m*, 6 H, H_{arom}, Ketal, H_{arom}, pyridyl); 7.86 (*s*, 1 H, H-C(8)); 7.92 (*d*, *J* = 1.7, 2 H, H_{arom}, Cat.); 8.18 (*s*, 1 H, H-C(2)); 8.61 (*d*, *J* = 6.3, H_{arom}, pyridyl). ¹³C-NMR (75 MHz, CDCl₃): 25.6; 27.4; 41.1; 84.3; 84.7; 87.4; 90.5; 110.4; 114.9; 116.0; 119.7; 120.4; 121.6; 122.0; 126.2; 126.7; 128.8; 130.2; 130.8; 132.8; 138.8; 140.1; 145.9; 147.6; 148.6; 149.6; 150.2; 153.0; 155.6; 163.1. HR-MS (MALDI): calcd. for C₄₀H₃₅N₇O₆Na ([M+Na]⁺): 732.2547, found 732.2549.

d) N1-{(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl}-5-pyridin-4-yl-2,3-dihydroxy-benzamide



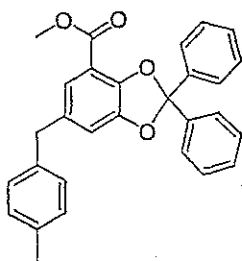
GP8, starting from the protected precursor (35 mg, 0.049 mmol) afforded the desired
5 product as a yellowish solid.

Yield: 15 mg (63%). Mp.: 133-137°C (dec.). $t_{R, \text{analyt.}}$: 10.6 min. IR (KBr): 3384 *br, s*; 1684*s*; 1633*m*; 1474*w*; 1431*m*; 1321*m*; 1202*s*; 1134*m*; 832*w*; 723*w*. $^1\text{H-NMR}$ (500 MHz, $(\text{CD}_3)_2\text{SO}$): 4.02 (*m*, 2 H, H-C(7'), H-C(7'')); 4.11 (*t*, $J = 4.8$, 1 H, H-C(4')); 4.37 (*m*; 1 H, H-C(3')); 4.67 (*t*, $J = 5.1$, 1 H, H-C(2')); 5.82-5.94 (*m*, 2 H, H-C(5'), H-C(6')); 5.91 (*d*, $J = 5.1$, H-C(1')); 7.52 (*d*, $J = 1.8$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 7.85 (*bs*, 1 H, OH); 8.01 (*d*, $J = 1.8$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 8.08 (*d*, $J = 5.2$, 1 H, $\text{H}_{\text{arom, pyridyl}}$); 8.17 (*s*, 1 H, H-C(8)); 8.42 (*s*, 1 H, H-C(2)); 8.79 (*d*, $J = 5.2$, 1 H, $\text{H}_{\text{arom, pyridyl}}$); 9.23 (*t*, $J = 5.5$, 1 H, H-NHCO); 9.69 (*bs*, 1 H, OH); 13.35 (*bs*, 1 H, OH). $^{13}\text{C-NMR}$ (125 MHz, $(\text{CD}_3)_2\text{SO}$): 40.1; 72.9; 73.9; 84.1; 87.7; 115.2; 117.0; 117.2; 119.1; 121.8; 124.8; 129.1; 129.6; 140.7; 144.9; 147.3; 149.0; 150.3; 152.6; 154.2; 169.2. HR-MS (MALDI): calcd. for $\text{C}_{24}\text{H}_{23}\text{N}_7\text{O}_6\text{Na}$ ($[\text{M}+\text{Na}]^+$): 528.1608, found 528.1607.

Example 13

Preparation of N1-{(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl}-5-(4-methyl-benzyl)-2,3-dihydroxy-
20 benzamide

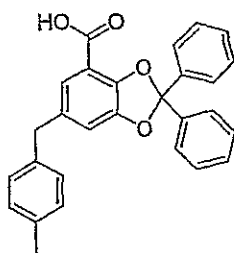
a) Methyl 2,2-diphenyl-6-(4-methyl-benzyl)-1,3-benzodioxole-4-carboxylate



Methyl 6-bromo-2,2-diphenyl-1,3-benzodioxole-4-carboxylate (200 mg, 1.486 mmol, 1 eq.), Pd(PPh₃)₄ (57 mg, 0.049 mmol, 0.1 eq.), bis(pinacolato)diboron (160 mg, 0.632 mmol, 1.3 eq.) and KOAc (72 mg, 0.73 mmol, 1.5 eq.), then Pd(PPh₃)₄ (57 mg, 0.049 mmol, 0.1 eq.), 1-bromomethyl-4-methyl-benzene (117 mg, 0.63 mmol, 1.3 eq.) and
 5 K₂CO₃ (336 mg, 2.43 mmol, 5 eq.) were reacted according to GP6 to yield the title product as a colorless, very slowly solidifying oil.

Yield: 197 mg (80%). IR (neat): 3030w; 2950w; 1722s; 1636w; 1603w; 1477s; 1449s; 1381w; 1251s; 1202s; 1047s; 1019m; 948w; 918w; 829w; 782m; 763m; 699m; 642m. ¹H-NMR (300 MHz, CDCl₃): 2.32 (s, 3 H, CH₃); 3.85 (s, 2H, CH₂); 3.93 (s, 3H, OCH₃); 6.83
 10 (d, J = 1.8, 1 H, H_{arom, Cat.}); 7.06 (d, J = 8.6, 2 H, H_{arom, p-Tol.}); 7.10 (d, J = 8.6, 1 H, H_{arom, p-Tol.}); 7.29 (d, J = 1.8, 1 H, H_{arom, Cat.}); 7.35-7.38 (m, 6 H, H_{arom, Ketal}); 7.57-7.60 (m, 4 H, H_{arom, Ketal}). ¹³C-NMR (75 MHz, CDCl₃): 21.0; 41.1; 52.0; 112.2; 113.1; 117.9; 122.3; 126.3; 128.2; 128.7; 129.1; 129.2; 134.9; 135.8; 137.5; 139.8; 146.6; 148.5; 165.2. HR-MS (MALDI): calcd. for C₂₉H₂₄O₄Na ([M+Na]⁺): 459.1572, found 459.1573.

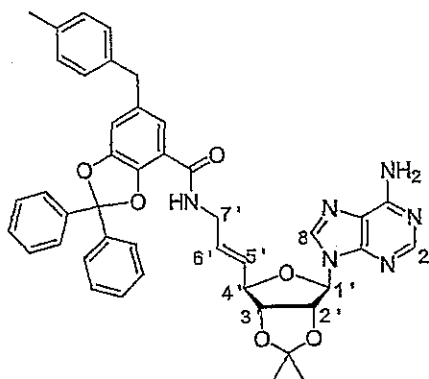
15 b) 2,2-diphenyl-6-(4-methyl-benzyl)-1,3-benzodioxole-4-carboxylic acid



Methyl 2,2-diphenyl-6-(4-methyl-benzyl)-1,3-benzodioxole-4-carboxylate (300 mg, 0.69 mmol, 1 eq.) and LiOH·H₂O (87 mg, 2.06 mmol, 3 eq.) were reacted according to GP3.

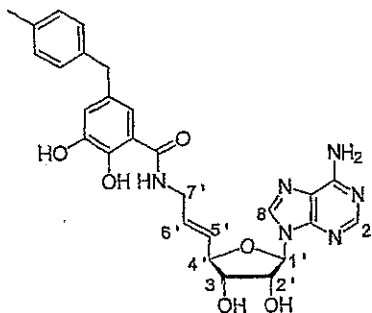
Yield: 287 mg (99%). Colorless solid. Mp.: 211-213°C. IR (KBr): 3434br, w; 2904w; 2571w; 1685m; 1638w; 1604w; 1479m; 1464m; 1304m; 1252m; 1209s; 1050m; 1027m; 947w; 921w; 828w; 784m; 750w; 797m; 641w. ¹H-NMR (300 MHz, CDCl₃): 2.32 (s, 3 H, CH₃); 3.86 (s, 2H, CH₂); 6.88 (d, J = 1.2, 1 H, H_{arom, Cat.}); 7.07 (d, J = 8.4, 2 H, H_{arom, p-Tol.}); 7.11 (d, J = 8.4, 1 H, H_{arom, p-Tol.}); 7.34-7.40 (m, 7 H, H_{arom, Cat.}, H_{arom, Ketal}); 7.58-7.62 (m, 4 H, H_{arom, Ketal}). ¹³C-NMR (75 MHz, CDCl₃): 21.0; 41.1; 111.3; 113.9; 118.4; 122.7; 126.4; 128.3; 128.7; 129.3; 135.2; 135.9; 137.4; 139.6; 147.3; 148.6; 169.7. HR-MS (MALDI):
 25 calcd. for C₂₈H₂₂O₄Na ([M+Na]⁺): 445.1416, found 445.1415.

c) 2,2-Diphenyl-6-(4-methyl-benzyl)-benzo[1,3]dioxole-4-carboxylic acid {3-[(3aR,4R,6R, 6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxol-4-yl]-prop-2-enyl}-amide



- 5 2,2-diphenyl-6-(4-methyl-benzyl)-1,3-benzodioxole-4-carboxylic acid (165 mg, 0.39 mmol, 1 eq.), EDC·HCl (115 mg, 0.59 mmol, 1.5 eq.), *N*-hydroxy-succinimide (57 mg, 0.49 mmol, 1.3 eq.), 9-[(3aR,4R,6R,6aR)-6-[(*E*)-3-aminoprop-1-enyl]-2,2-dimethylperhydrofuro[3,4-*d*][1,3] di-oxol-4-yl]-9H-purin-6-amine (100 mg, 0.3 mmol, 0.77 eq.) and Et₃N (0.1 mL, 0.68 mmol) were reacted according to GP7.
- 10 Yield: 172 mg (78%). Colorless foam. Mp.: 107-110°C. IR (KBr): 3426*m*; 3176*w*; 2986*w*; 1636*s*; 1597*s*; 1529*m*; 1474*s*; 1440*m*; 1374*w*; 1328*w*; 1254*s*; 1207*s*; 1156*w*; 1082*m*; 1049*m*; 1020*m*; 868*w*; 776*w*; 699*m*; 642*w*. ¹H-NMR (300 MHz, CDCl₃): 1.38 (*s*, 3 H, CH₃-*exo*); 1.62 (*s*, 3 H, CH₃-*endo*); 2.29 (*s*, 3 H, CH₃, *p*-Tol.); 3.87 (*s*, 2H, CH₂, *benzyl*); 4.05 (*m*, 2 H, H-C(7'), H-C(7'')); 4.71 (*m*, 1 H, H-C(4')); 4.91 (*dd*; *J* = 6.4, 3.6, 1 H, H-C(3')); 5.38 (*dd*, *J* = 6.4, 2.4, 1 H, H-C(2')); 5.83 (*m*, 2 H, H-C(5'), H-C(6')); 6.09 (*d*, *J* = 2.4, 1 H, H-C(1')); 6.40 (*bs*, 2 H, NH₂); 6.83 (*d*, *J* = 1.8, 1 H, H_{arom}, Cat.); 7.07 (*s*, 4 H, H_{arom}, *p*-tolyl); 7.14 (*t*, *J* = 5.7, 1 H, NHCO); 7.33-7.38 (*m*, 6 H, H_{arom}, Ketol); 7.45-7.49 (*m*, 5 H, H_{arom}, Ketol, H_{arom}, Cat.); 7.91 (*s*, 1 H, H-C(8)); 8.16 (*s*, 1 H, H-C(2)). ¹³C-NMR (75 MHz, CDCl₃): 21.1; 25.4; 27.2; 40.7; 41.3; 84.2; 84.4; 87.1; 90.4; 112.5; 114.7; 114.8; 118.2; 119.9; 122.1; 126.3; 127.7; 128.3; 128.6; 129.1; 129.5; 131.0; 135.7; 136.0; 137.5; 138.9; 140.5; 143.0; 147.3; 148.9; 149.8; 153.8; 163.4. HR-MS (MALDI): calcd. for C₄₃H₄₀N₆O₆Na ([M+Na]⁺): 759.2907, found 759.2909. Anal. calcd. for C₄₃H₄₀N₆O₆: C 70.09, H 5.47, N 11.41, found C 69.89, H 5.60, N 11.33.
- 15
- 20

d) N1-[(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-(4-methyl-benzyl)-2,3-dihydroxy-benzamide



- 5 GP8, starting from the protected precursor (90 mg, 0.122 mmol) afforded the desired product as a colorless solid.

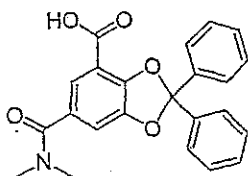
Yield: 63 mg (97%). $t_{R, \text{analyt.}}$: 15.8 min. IR (KBr): 3384 *br, s*; 1700*s*; 1640*m*; 1596*m*; 1534*w*; 1513*w*; 1484*w*; 1437*m*; 1324*m*; 1290*w*; 1205*s*; 1133*m*; 1048*w*; 972*w*; 836*w*; 799*w*; 725*w*.

- $^1\text{H-NMR}$ (500 MHz, CD_3OD): 2.25 (*s*, 3 H, ArCH_3); 3.79 (*s*, 2H, CH_2 , *benzyl*.); 4.03 (*m*, 2 H, H-C(7'), H-C(7'')); 4.22 (*t*, $J = 5.0$, 1 H, H-C(4')); 4.51 (*m*, 1 H, H-C(3')); 4.73 (*t*, $J = 4.9$, 1 H, H-C(2')); 5.93 (*m*, 2 H, H-C(5'), H-C(6')); 6.05 (*d*, $J = 4.9$, H-C(1')); 6.76 (*d*, $J = 2.1$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 7.04 (*s*, 4 H, $\text{H}_{\text{arom, p-Tol.}}$); 7.14 (*d*, $J = 2.1$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 8.17 (*s*, 1 H, H-C(8)); 8.39 (*s*, 1 H, H-C(2)). $^{13}\text{C-NMR}$ (75 MHz, CD_3OD): 21.1; 41.6; 41.9; 75.3; 75.7; 86.2; 90.7; 116.5; 118.8; 120.6; 120.8; 129.7; 130.1; 130.2; 131.2; 133.6; 136.7; 139.7; 143.5; 147.3; 147.6; 148.5; 150.2; 153.4; 171.3. HR-MS (MALDI): calcd. for $\text{C}_{27}\text{H}_{28}\text{N}_6\text{O}_6\text{Na}$ ($[\text{M}+\text{Na}]^+$): 555.1968, found 555.1957.

Example 14

Preparation of N1-[(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-dimethylcarbamoyl-2,3-dihydroxy-benzamide

a) 6-Dimethylcarbamoyl-2,2-diphenyl-1,3-benzodioxole-4-carboxylic acid

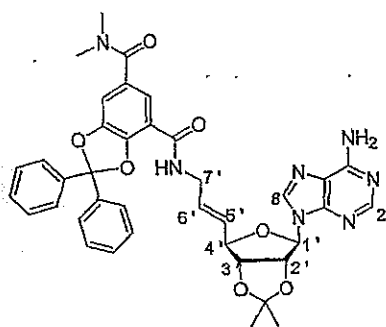


- 6-Bromo-2,2-diphenyl-1,3-benzodioxole-4-carboxylic acid (200 mg, 0.486 mmol), LiH (10 mg, 0.97 mmol, 2 eq.) and dimethylcarbamoylchloride (0.18 mL, 1.94 mmol, 4 eq.) as the electrophile were reacted according to GP4, Method B. The crude product was

purified using flash chromatography (silica gel, hexane/EtOAc/AcOH 67:30:3) to give the title compound as a colorless solid.

Yield: 40 mg (21%). Mp.: 207-208°C. IR (KBr): 3417w; 2935w; 1718s; 1635m; 1607s; 1448s; 1415m; 1247s; 1207s; 1075w; 1041s; 1023s; 949m; 881m; 788m; 765m; 701s; 643m.
 5 ¹H-NMR (300 MHz, CDCl₃): 3.06 (bs, 6 H, CH₃); 7.20 (d, *J* = 1.5, 1 H, H_{arom}, Cat.); 7.37-7.41 (m, 6 H, H_{arom}, Cat.); 7.56 (d, *J* = 1.5, 1 H, H_{arom}, Cat.); 7.58-7.62 (m, 4 H, H_{arom}, Ketal).
¹³C-NMR (75 MHz, CDCl₃): 35.8; 40.0; 111.2; 112.4; 119.3; 122.7; 126.4; 128.4; 129.4; 129.5; 139.1; 148.8; 149.8; 168.5; 170.1. HR-MS (MALDI): calcd. for C₂₃H₂₀NO₄ ([M+H]⁺): 390.1341, found 390.1340.

- 10 b) 6-Dimethylcarbamoyl-2,2-diphenyl-benzo[1,3]dioxole-4-carboxylic acid {3-[(3aR,4R,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxol-4-yl]-prop-2-enyl}-amide

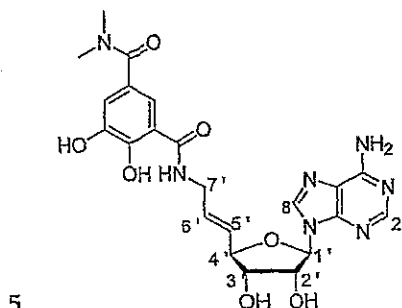


- 6-Dimethylcarbamol-2,2-diphenyl-1,3-benzodioxole-4-carboxylic acid (120 mg, 0.31 mmol, 1 eq.), EDC-HCl (90 mg, 0.46 mmol, 1.5 eq.), *N*-hydroxy-succinimide (46 mg, 0.4 mmol, 1.3 eq.), 9-[(3aR,4R,6R,6aR)-6-[(*E*)-3-aminoprop-1-enyl]-2,2-dimethylperhydrofuro[3,4-*d*][1,3] di-oxol-4-yl]-9H-purin-6-amine (93 mg, 0.28 mmol, 0.9 eq.) and Et₃N (0.1 mL, 0.68 mmol) were reacted according to GP7.

- Yield: 160 mg (81%). Colorless foam. IR (KBr): 3425m; 3193w; 2932w; 1639s; 1528m; 1471m; 1449m; 1396w; 1329w; 1263m; 1208s; 1157w; 1082m; 1048m; 1018m; 867w; 781w; 700m; 643w. ¹H-NMR (300 MHz, CDCl₃): 1.38 (s, 3 H, CH₃-exo); 1.61 (s, 3 H, CH₃-endo); 3.02 (bs, 3 H, N(CH₃)₂); 3.07 (bs, 3 H, N(CH₃)₂); 4.05 (m, 2 H, H-C(7'), H-C(7'')); 4.74 (dd, *J* = 7.2, 3.3, 1 H, H-C(4')); 4.91 (dd, *J* = 6.5, 3.3, 1 H, H-C(3')); 5.43 (dd, *J* = 6.5, 2.0, 1 H, H-C(2')); 5.79 (m, 2 H, H-C(5'), H-C(6')); 6.08 (d, *J* = 2.0, 1 H, H-C(1')); 6.18 (bs, 2 H, NH₂); 7.08 (t, *J* = 5.7, 1 H, NHCO); 7.16 (d, *J* = 1.8, 1 H, H_{arom}, Cat.); 7.35-7.42 (m, 6 H, H_{arom}, Ketal); 7.46-7.51 (m, 4 H, H_{arom}, Ketal); 7.69 (d, *J* = 1.8, 1 H, H_{arom}, Cat.); 7.82 (s, 1 H, H-C(8)); 8.17 (s, 1 H, H-C(2)). ¹³C-NMR (75 MHz, CDCl₃): 25.3; 27.0; 35.5; 39.8; 40.6; 84.4; 84.6; 87.5; 90.7; 111.2; 114.5; 114.6; 119.3; 120.1; 122.2; 126.4; 128.0; 128.5; 129.8;

130.3; 130.8; 138.5; 139.9; 145.6; 147.5; 149.1; 151.6; 154.8; 162.7; 170.3. HR-MS (MALDI): calcd. for $C_{38}H_{38}N_7O_7$ ($[M+H]^+$): 704.2833, found 704.2834.

c) N1-[(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-dimethylcarbamoyl-2,3-dihydroxy-benzamide



GP8, starting from the protected precursor (90 mg, 0.128 mmol) afforded the desired product as a colorless solid.

Yield: 54 mg (86%). $t_{R, \text{analyt.}}$: 7.3 min. IR (KBr): 3385 *br, s*; 1700*s*; 1605*s*; 1548*w*; 1509*w*; 1478*w*; 1416*w*; 1326*w*; 1296*m*; 1253*w*; 1202*s*; 1137*m*; 1048*w*; 972*w*; 838*w*; 801*w*; 725*w*.

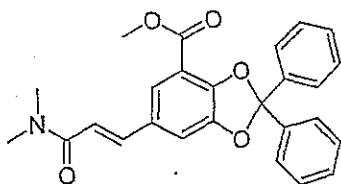
10 $^1\text{H-NMR}$ (500 MHz, CD_3OD): 2.96 (*bs*, 6 H, $\text{N}(\text{CH}_3)_2$); 3.95 (*m*, 2 H, $\text{H-C}(7')$, $\text{H-C}(7'')$); 4.14 (*t*, $J = 4.9$, 1 H, $\text{H-C}(4')$); 4.42 (*t*, $J = 4.9$, 1 H, $\text{H-C}(3')$); 4.66 (*t*, $J = 4.8$, 1 H, $\text{H-C}(2')$); 5.83 (*m*, 2 H, $\text{H-C}(5')$, $\text{H-C}(6')$); 5.96 (*d*, $J = 4.8$, $\text{H-C}(1')$); 6.92 (*d*, $J = 2.0$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 7.29 (*d*, $J = 2.0$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 8.15 (*s*, 1 H, $\text{H-C}(8)$); 8.31 (*s*, 1 H, $\text{H-C}(2)$).

15 $^{13}\text{C-NMR}$ (125 MHz, CD_3OD): 34.4; 38.8; 40.1; 73.7; 74.2; 84.8; 89.3; 115.1; 116.7; 116.8; 119.3; 126.0; 128.7; 129.4; 142.4; 145.4; 146.1; 148.6; 150.3; 151.5; 169.0; 171.8. HR-MS (MALDI): calcd. for $\text{C}_{22}\text{H}_{26}\text{N}_7\text{O}_7$ ($[M+H]^+$): 500.1894, found 500.1894.

Example 15

Preparation of N1-[(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-((E)-2-dimethylcarbamoyl-vinyl)-2,3-dihydroxy-benzamide

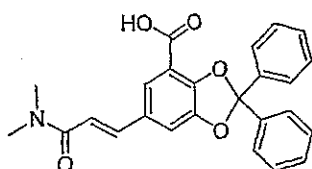
a) Methyl 6-((E)-2-dimethylcarbamoyl-vinyl)-2,2-diphenyl-1,3-benzodioxole-4-carboxylate



A solution of methyl 6-bromo-2,2-diphenyl-1,3-benzodioxole-4-carboxylate (130 mg, 0.32 mmol), *N,N*-dimethylacrylamide (47 mg, 0.47 mmol, 1.5 eq.), $P(OPh)_3$ (980 mg, 3.16 mmol, 10 eq.), Bu_4NBr (20 mg, 0.06 mmol, 0.2 eq.), Na_2CO_3 (40 mg, 0.38 mmol, 1.2 eq.) and $Pd(OAc)_2$ (10 mg, 0.03 mmol, 0.1 eq.) in 10 mL dimethylacetamide was stirred at 140°C for 72 h. After cooling to r.t. the mixture was partitioned between EtOAc and H_2O . The organic layer was washed twice with saturated NaCl solution, dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified using flash chromatography (silica gel, hexane/EtOAc 5:1 → 3:2) to yield the desired compound as a colorless, slowly solidifying viscous oil.

Yield: 60 mg (44%). IR (KBr): 3059w; 2927w; 1721s; 1652s; 1607m; 1481m; 1447s; 1396m; 1300m; 1256s; 1203s; 1046m; 1017m; 970w; 779w; 699m; 641w. 1H -NMR (300 MHz, $CDCl_3$): 3.11 (bs, 6 H, $N(CH_3)_2$); 3.96 (s, 3H, OCH_3); 6.75 (d, $J = 15.6$, 1H, $C(O)CH$); 7.20 (d, $J = 1.8$, 1 H, $H_{arom, Cat.}$); 7.36-7.41 (m, 6 H, $H_{arom, Ketal}$); 7.55-7.61 (m, 6 H, $H_{arom, Ketal}$, $H_{arom, Cat.}$, Ar-CH). ^{13}C -NMR (75 MHz, $CDCl_3$): 36.2; 37.7; 52.5; 110.5; 113.0; 116.8; 119.1; 124.1; 126.6; 128.6; 129.6; 129.7; 139.6; 141.5; 149.2; 149.5; 164.9; 166.7. HR-MS (MALDI): calcd. for $C_{26}H_{23}NO_5Na$ ($[M+Na]^+$): 452.1474, found 452.1473.

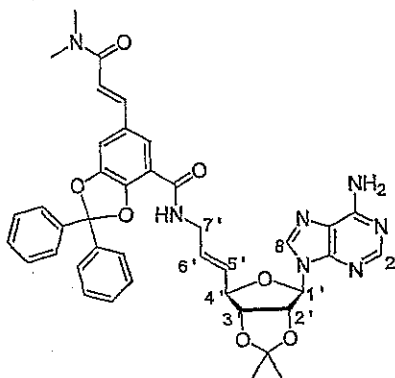
b) 6-((*E*)-2-Dimethylcarbamoyl-vinyl)-2,2-diphenyl-1,3-benzodioxole-4-carboxylic acid



Methyl 6-((*E*)-2-dimethylcarbamoyl-vinyl)-2,2-diphenyl-1,3-benzodioxole-4-carboxylate (170 mg, 0.4 mmol, 1 eq.) and $LiOH \cdot H_2O$ (50 mg, 1.19 mmol, 3 eq.) were reacted according to GP3.

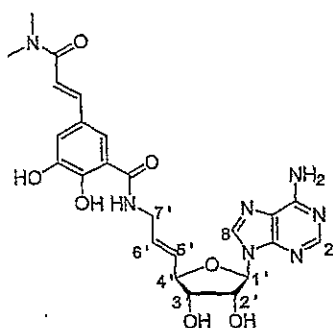
Yield: 126 mg (77%). Mp.: 230-231°C. IR (KBr): 3431w; 3058w; 1710s; 1653m; 1596m; 1467m; 1445m; 1404w; 1249s; 1212m; 1176m; 1050m; 1027w; 975w; 843w; 784w; 697w; 641w. 1H -NMR (300 MHz, $CDCl_3$): 3.07 (s, 3 H, $N(CH_3)_2$); 3.16 (s, 3 H, $N(CH_3)_2$); 6.75 (d, $J = 15.3$, 1H, $C(O)CH$); 7.24 (d, $J = 1.5$, 1 H, $H_{arom, Cat.}$); 7.35-7.40 (m, 6 H, $H_{arom, Ketal}$); 7.59-7.62 (m, 5 H, $H_{arom, Ketal}$, Ar-CH); 7.67 (d, $J = 1.5$, 1 H, $H_{arom, Cat.}$). ^{13}C -NMR (75 MHz, $CDCl_3$): 36.1; 37.5; 110.6; 112.3; 116.4; 119.2; 124.6; 126.3; 128.4; 129.4; 129.5; 139.2; 141.5; 149.1; 149.8; 166.8; 167.8. HR-MS (MALDI): calcd. for $C_{25}H_{22}NO_5$ ($[M+H]^+$): 416.1498, found 416.1498.

c) 6-((E)-2-Dimethylcarbamoyl-vinyl)-2,2-diphenyl-benzo[1,3]dioxole-4-carboxylic acid {3-[(3a*R*,4*R*,6*R*,6a*R*)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-*d*][1,3]dioxol-4-yl]-prop-2-enyl}-amide



- 5 6-((E)-2-Dimethylcarbamoyl-vinyl)-2,2-diphenyl-1,3-benzodioxole-4-carboxylic acid (90 mg, 0.22 mmol, 1 eq.), EDC·HCl (63 mg, 0.33 mmol, 1.5 eq.), *N*-hydroxy-succinimide (33 mg, 0.28 mmol, 1.3 eq.), 9-[(3a*R*,4*R*,6*R*,6a*R*)-6-[(*E*)-3-aminoprop-1-enyl]-2,2-dimethylperhydro-furo[3,4-*d*][1,3]di-oxol-4-yl]-9H-purin-6-amine (72 mg, 0.22 mmol, 1 eq.) and Et₃N (0.1 mL, 0.68 mmol) were reacted according to GP7.
- 10 Yield: 63 mg (40%). Colorless foam. IR (KBr): 3424*m*; 2931*w*; 1653*s*; 1598*s*; 1528*m*; 1474*m*; 1437*m*; 1374*w*; 1259*m*; 1207*m*; 1154*w*; 1081*m*; 1049*m*; 1019*m*; 973*w*; 867*w*; 776*w*; 699*w*; 642*w*. ¹H-NMR (300 MHz, CDCl₃): 1.37 (*s*, 3 H, CH₃-*exo*); 1.61 (*s*, 3 H, CH₃-*endo*); 3.05 (*s*, 3 H, N(CH₃)₂); 3.14 (*s*, 3 H, N(CH₃)₂); 4.05 (*m*, 2 H, H-C(7'), H-C(7'')); 4.69 (*m*, 1 H, H-C(4')); 4.96 (*dd*; *J* = 6.6, 3.9, 1 H, H-C(3')); 5.46 (*dd*, *J* = 6.6, 2.1, 1 H, H-C(2')); 5.70 (*bs*, 2 H, NH₂); 5.84 (*m*, 2 H, H-C(5'), H-C(6')); 6.08 (*d*, *J* = 2.1, 1 H, H-C(1')); 6.82 (*d*, *J* = 15.5, 1 H, C(O)CH); 7.07 (*t*, *J* = 6.0, 1 H, NHCO); 7.17 (*d*, *J* = 1.7, 1 H, H_{arom}, Cat.); 7.35-7.42 (*m*, 6 H, H_{arom}, Ketal); 7.47-7.52 (*m*, 4 H, H_{arom}, Ketal); 7.60 (*d*, *J* = 15.5, 1 H, Ar-CH); 7.80 (*d*, *J* = 1.7, 1 H, H_{arom}, Cat.); 7.84 (*s*, 1 H, H-C(8)); 8.19 (*s*, 1 H, H-C(2)). ¹³C-NMR (75 MHz, CDCl₃): 25.4; 27.1; 35.9; 37.4; 40.7; 84.1; 84.5; 87.2; 90.3; 110.6; 114.6; 115.4; 117.0; 119.2; 120.2; 122.8; 126.4; 128.5; 129.8; 130.3; 130.5; 138.5; 138.6; 139.8; 141.2; 145.6; 147.9; 149.4; 153.0; 155.3; 162.9; 166.5. HR-MS (MALDI): calcd. for C₄₀H₄₀N₇O₇ ([M+H]⁺): 730.2989, found 730.2993.
- 15
- 20

d) N1-[(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-((E)-2-dimethylcarbamoyl-vinyl)-2,3-dihydroxy-benzamide



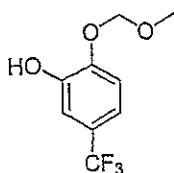
GP8, starting from the protected precursor (35 mg, 0.048 mmol) afforded the desired product as a colorless solid.

Yield: 12 mg (48%). $t_{R, \text{analyt.}}$: 9.7 min. IR (KBr): 3373 *br, s*; 1696s; 1642s; 1591s; 1499w; 1419w; 1307w; 1264w; 1201m; 1138w; 1052w; 977w; 840w; 800w; 723w; 642w. $^1\text{H-NMR}$ (500 MHz, CDCl_3): 3.05 (*s*, 3 H, $\text{N}(\text{CH}_3)_2$); 3.22 (*s*, 3 H, $\text{N}(\text{CH}_3)_2$); 4.07 (*m*, 2 H, H-C(7'), H-C(7'')); 4.24 (*t*, $J = 5.0$, 1 H, H-C(4')); 4.53 (*m*, 1 H, H-C(3'')); 4.74 (*t*, $J = 4.8$, 1 H, H-C(2'')); 5.95 (*m*, 2 H, H-C(5'), H-C(6')); 6.06 (*d*, $J = 4.8$, H-C(1')); 6.96 (*d*, $J = 15.4$, 1 H, C(O)CH); 7.25 (*d*, $J = 1.8$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 7.46 (*d*, $J = 15.4$, 1 H, Ar-CH); 7.53 (*d*, $J = 1.8$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 8.26 (*s*, 1 H, H-C(8)); 8.40 (*s*, 1 H, H-C(2)). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): 36.3; 37.9; 41.7; 75.3; 75.8; 86.2; 90.7; 116.5; 116.6; 117.9; 199.9; 120.8; 127.5; 130.4; 131.0; 143.5; 143.6; 147.5; 148.0; 150.2; 152.4; 153.3; 169.3; 171.0. HR-MS (MALDI): calcd. for $\text{C}_{24}\text{H}_{27}\text{N}_7\text{O}_7\text{Na}$ ($[\text{M}+\text{Na}]^+$): 548.1864, found 548.1859.

Example 16

Preparation of N1-[(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-trifluoromethyl-2,3-dihydroxy-benzamide

a) 2-Methoxymethoxy-5-trifluoromethyl-phenol

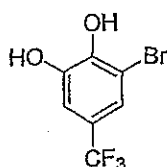


To a solution of 1-methoxymethoxy-4-trifluoromethyl-benzene (4.6 g, 22.31 mmol) in 60 mL dry THF cooled to -78°C , BuLi (21 mL of a 1.6 M sol. in hexane, 1.5 eq.) was added drop-wise via a syringe and the mixture was stirred at low temperature for 2 h, then the cooling bath was removed and the mixture was allowed to gradually warm to

0°C during 30 min. After cooling again to -78°C, B(OCH₃)₃ (3.95 g, 38 mmol, 1.7 eq.) was added to the reaction and the stirring was continued for another 1.5 h at -78°C, then the solution was allowed to warm to -10°C during 20 min. Re-cooling to -78°C was followed by addition of H₂O₂ (5.82 mL of a 30% solution in H₂O, 2 eq.) and NaOH_{aq} (5.8 mL of a 5 m aqueous solution, 1.3 eq.). This solution was stirred 16 h at r.t., then saturated NH₄Cl-solution was added and the mixture was extracted twice with 30 mL EtOAc. The pooled organic fractions were washed with saturated NaCl solution, dried over MgSO₄ and evaporated *in vacuo*. The crude product was purified using flash chromatography (silica gel, hexane / EtOAc 4:1) to yield the desired product as a yellowish oil.

Yield: 3.5 g (70%). IR (neat): 3426br, m; 2962m; 1709w; 1622m; 1516s; 1464m; 1330s; 1290s; 1162s; 1123s; 1085s; 982s; 914s; 879m; 816m; 762w; 658w; 618w. ¹H-NMR (300 MHz, CDCl₃): 3.52 (s, 3 H, OCH₃); 5.26 (s, 2H, OCH₂O); 5.97 (s, 1H, OH); 7.10-7.20 (m, 3 H, H_{arom}). ¹³C-NMR (75 MHz, CDCl₃): 56.6; 95.5; 112.4 (d, J = 3.6); 114.7; 117.5 (d, J = 3.6); 120.3 (q, J = 260); 125.0 (q, J = 32.8); 146.1; 146.7. ¹⁹F-NMR (282 MHz, CDCl₃): -62.4 (s). HR-MS (EI+): calcd. for C₉H₉F₃O₃ ([M]⁺): 222.0504, found 222.0501.

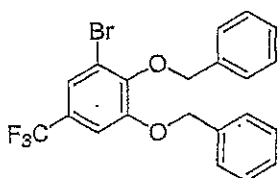
b) 3-Bromo-5-trifluoromethyl-benzene-1,2-diol



To a solution of 4-trifluoromethyl-benzene-1,2-diol (870 mg, 4.8 mmol) in 20 mL CCl₄, Br₂ (770 mg, 4.8 mmol, 1 eq.) was added and the mixture was stirred at 60°C for 10 h. The solvent was then removed *in vacuo* and the crude product was purified by flash chromatography (silica gel, hexane / EtOAc 4:1 → 3:2) to yield the desired product as a yellowish oil.

Yield: 910 mg (74%). ¹H-NMR (300 MHz, CDCl₃): 5.68 (bs, 1H, OH); 5.81 (bs, 1H, OH); 7.14 (dd, J = 2.3, 0.6, 1 H, H_{arom}); 7.32 (dd, J = 2.3, 0.6, 1 H, H_{arom}).

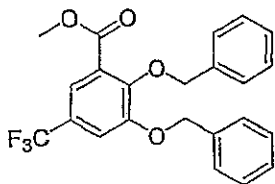
c) 1,2-Bis-benzyloxy-3-bromo-5-trifluoromethyl-benzene



To a solution of 3-bromo-5-trifluoromethyl-benzene-1,2-diol (510 mg, 1.98 mmol) in 10 mL acetone, K_2CO_3 (2.74 g, 19.84 mmol, 10 eq.) and benzyl bromide (1.02 g, 5.95 mmol, 3 eq.) were added and the solution was refluxed for 4 h. After cooling to r.t., H_2O and EtOAc were added to the mixture and the phases were separated. The organic fraction was washed with saturated NaCl solution, dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified using flash chromatography (silica gel, hexane / EtOAc 10:1) to yield the title compound as a colorless solid.

Yield: 750 mg (87%). Mp.: 79–80°C. IR (KBr): 3032w; 2935w; 2884w; 1576w; 1499w; 1485w; 1455w; 1424m; 1382w; 1335s; 1290m; 1230m; 1164s; 1120s; 1011m; 957m; 919w; 859w; 751m; 698m. 1H -NMR (300 MHz, $CDCl_3$): 5.09 (s, 2 H, OCH_2Ar); 5.15 (s, 2 H, OCH_2Ar); 5.97 (s, 1H, OH); 7.18 (d, $J = 1.5$, 1 H, $H_{arom, Cat.}$); 7.32–7.47 (m, 11 H, $H_{arom, Cat., H_{arom, Benzyl}}$). ^{13}C -NMR (75 MHz, $CDCl_3$): 71.5; 75.0; 110.3 (d, $J = 3.9$); 118.4; 122.5 (d, $J = 3.9$); 123.1 (q, $J = 271$); 127.0 (q, $J = 33.6$); 127.6; 128.2; 128.3; 128.4; 128.5; 128.6; 135.5; 136.3; 148.4; 152.8. ^{19}F -NMR (282 MHz, $CDCl_3$): -62.6 (s). HR-MS (MALDI): calcd. for $C_{21}H_{16}BrF_3O_2Na$ ($[M+Na]^+$): 459.0183, found 459.0169.

d) Methyl 2,3-bis-benzyloxy-5-trifluoromethyl-benzoate

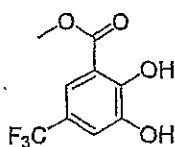


To a solution of 1,2-bis-benzyloxy-3-bromo-5-trifluoromethyl-benzene (750 mg, 1.76 mmol) in 10 mL dry THF cooled to -90°C, BuLi (3.3 mL of a 1.6 m solution in hexane, 5.28 mmol, 3 eq.) was slowly added via a syringe and the yellow solution was stirred at low temperature for 15 min. Methyl chloroformate (1.66 g, 17.6 mmol, 10 eq.) was then added to the solution and the reaction mixture was allowed to warm to r.t. where the stirring was continued for 1 h. The mixture was then poured into a separatory funnel containing H_2O and EtOAc and the phases were separated. The organic phase was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified using flash chromatography (silica gel, hexane / EtOAc 10:1) to yield the desired compound as a colorless solid.

Yield: 383 mg (52%). Mp.: 78–79°C. IR (KBr): 3033w; 2950w; 1733s; 1610w; 1486w; 1430m; 1363s; 1299m; 1250s; 1199m; 1151m; 1121s; 1045s; 956w; 935w; 909w; 867w; 750w; 698m. 1H -NMR (300 MHz, $CDCl_3$): 3.87 (s, 3H, OCH_3); 5.14 (s, 2 H, OCH_2Ar);

- 5.17 (s, 2 H, OCH₂Ar); 7.30-7.45 (m, 11 H, H_{arom}, Cat., H_{arom}, Benzyl.); 7.65 (dd, *J* = 1.8, 1.2, 1 H, H_{arom}, Cat.). ¹³C-NMR (75 MHz, CDCl₃): 52.5; 71.6; 75.8; 113.9 (*d*, *J* = 3.3); 118.0; 119.9 (*d*, *J* = 3.3); 123.4 (*q*, *J* = 270); 126.0 (*q*, *J* = 33.6); 127.0; 127.6; 128.1; 128.3; 128.4; 128.5; 128.6; 135.5; 136.6; 150.7; 153.0; 165.4. ¹⁹F-NMR (282 MHz, CDCl₃): -62.7 (s).
- 5 HR-MS (MALDI): calcd. for C₂₃H₁₉F₃O₂Na ([M+Na]⁺): 439.1133, found 439.1132. Anal. calcd. for C₂₃H₁₉O₄F₃: C 66.34, H 4.60 found C 66.16, H 4.78.

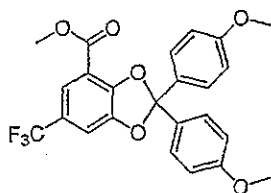
e) Methyl 2,3-dihydroxy-5-trifluoromethyl-benzoate



- To a solution of methyl 2,3-bis-benzyloxy-5-trifluoromethyl-benzoate (280 mg, 0.67 mmol) in 10 mL MeOH, Pd/C (10%, 30 mg) was added and the mixture was stirred 16 h under a H₂ atmosphere. The reaction mixture was then filtered through Celite and evaporated *in vacuo* to yield the title compound as a greyish solid.

- Yield: 148 mg (99%). IR (KBr): 3462m; 3132w; 2961w; 1676m; 1494m; 1447m; 1338s; 1245s; 1199m; 1120s; 1014w; 936w; 887w; 793m; 679m. ¹H-NMR (300 MHz, CD₃OD): 3.97 (s, 3H, OCH₃); 7.17 (s, 1 H, H_{arom}, Cat); 7.58 (s, 1 H, H_{arom}, Cat). ¹³C-NMR (75 MHz, CD₃OD): 53.2; 113.6; 116.9; 118.0; 121.8 (*q*, *J* = 32.8); 125.3 (*q*, *J* = 268); 148.6; 154.6; 170.9. ¹⁹F-NMR (282 MHz, CD₃OD): -62.0 (s). HR-MS (MALDI): calcd. for C₈H₃F₃O₃ ([M-CH₃OH]⁺): 204.0034, found 204.0024.

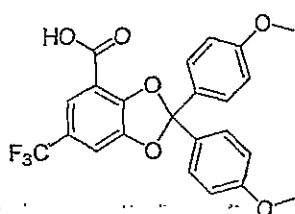
- f) Methyl 2,2-Bis-(4-methoxy-phenyl)-6-trifluoromethyl-1,3-benzodioxole-4-carboxylate



- 4,4'-Dimethoxybenzophenone (213 mg, 0.88 mmol, 1.5 eq.), oxalyl chloride (900 mg, 7.1 mmol, 8 eq.) and methyl 2,3-dihydroxy-5-trifluoromethyl-benzoate (130 mg, 0.59 mmol, 1 eq.) were reacted according to GP2.2. The crude product was purified using flash chromatography (silica gel, hexane / Et₂O 10:1) to yield the title compound as a yellowish, very viscous oil.

Yield: 170 mg (63%). IR (neat): 3003w; 2956w; 2839w; 1727s; 1642w; 1612s; 1585w; 1514s; 1486m; 1445s; 1324s; 1268s; 1234s; 1175s; 1123m; 1042s; 1005m; 935w; 832m; 783w; 674w. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 3.81 (s, 6H, ArOCH_3); 3.95 (s, 3H, C(O)OCH_3); 6.90 (dd, $J = 6.7, 2.3$, 4 H, $\text{H}_{\text{arom, Ketal}}$); 7.18 (d, $J = 1.5$, 1 H, $\text{H}_{\text{arom, Cat}}$); 7.47 (dd, $J = 6.7, 2.3$, 4 H, $\text{H}_{\text{arom, Ketal}}$); 7.74 (d, $J = 1.5$, 1 H, $\text{H}_{\text{arom, Cat}}$). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 52.4; 55.4; 108.6 (d, $J = 3.1$); 112.3; 113.7; 120.2; 120.8 (d, $J = 4.3$); 123.5 (q, $J = 270$); 123.6 (q, $J = 33.4$); 128.0; 131.0; 148.9; 150.7; 160.4; 163.8. $^{19}\text{F-NMR}$ (282 MHz, CDCl_3): -61.8 (s). HR-MS (MALDI): calcd. for $\text{C}_{24}\text{H}_{20}\text{F}_3\text{O}_6$ ($[\text{M}+\text{H}]^+$): 461.1212, found 461.1202. Anal. calcd. for $\text{C}_{24}\text{H}_{19}\text{O}_6\text{F}_3$: C 62.61, H 4.16 found C 62.52, H 4.26.

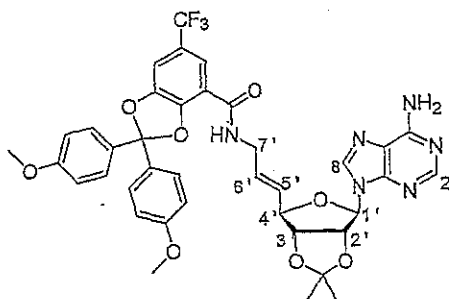
10 g) 2,2-Bis-(4-methoxy-phenyl)-6-trifluoromethyl-1,3-benzodioxole-4-carboxylic acid



Methyl 2,2-bis-(4-methoxy-phenyl)-6-trifluoromethyl-1,3-benzodioxole-4-carboxylate (60 mg, 0.13 mmol, 1 eq.) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (28 mg, 0.65 mmol, 5 eq.) were reacted according to GP3.

15 Yield: 53 mg (91%). Mp.: IR (KBr): 3441br, w; 2936w; 2837w; 1687w; 1611s; 1513s; 1442m; 1364m; 1312s; 1253s; 1175s; 1121m; 1031s; 1005m; 952w; 931w; 831m; 676w. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 3.79 (s, 6H, ArOCH_3); 6.94 (dd, $J = 6.9, 2.1$, 4 H, $\text{H}_{\text{arom, Ketal}}$); 7.30 (d, $J = 1.5$, 1 H, $\text{H}_{\text{arom, Cat}}$); 7.46 (dd, $J = 6.9, 2.1$, 4 H, $\text{H}_{\text{arom, Ketal}}$); 7.70 (d, $J = 1.5$, 1 H, $\text{H}_{\text{arom, Cat}}$). $^{19}\text{F-NMR}$ (282 MHz, CDCl_3): -63.7 (s). HR-MS (MALDI): calcd. for $\text{C}_{24}\text{H}_{20}\text{F}_3\text{O}_6$ ($[\text{M}+\text{H}]^+$): 447.1055, found 447.1059.

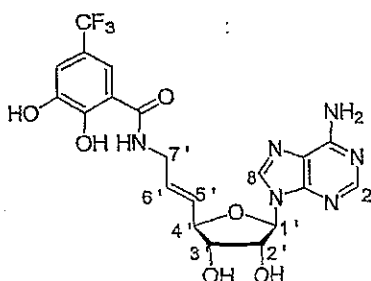
h) 2,2-Bis-(4-methoxy-phenyl)-6-trifluoromethyl-benzo[1,3]dioxole-4-carboxylic acid {3-[(3aR,4R,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-d][1,3]dioxol-4-yl]-prop-2-enyl}-amide



2,2-Bis-(4-methoxy-phenyl)-6-trifluoromethyl-1,3-benzodioxole-4-carboxylic acid (90 mg, 0.2 mmol, 1 eq.), EDC·HCl (58 mg, 0.3 mmol, 1.5 eq.), *N*-hydroxy-succinimide (31 mg, 0.26 mmol, 1.3 eq.), 9-[(3*aR*,4*R*,6*R*,6*aR*)-6-[(*E*)-3-aminoprop-1-enyl]-2,2-dimethylperhydrofuro [3,4-*d*][1,3]di-oxol-4-yl]-9H-purin-6-amine (70 mg, 0.2 mmol, 1 eq.) and Et₃N (0.1 mL, 0.68 mmol) were reacted according to GP7.

Yield: 119 mg (77%). Colorless foam. Mp.: 114-118°C. IR (KBr): 3426*m*; 3178*w*; 2935*w*; 2837*w*; 1640*s*; 1607*s*; 1514*m*; 1443*w*; 1375*w*; 1317*s*; 1254*s*; 1210*m*; 1175*s*; 1121*m*; 1025*m*; 1004*w*; 867*w*; 732*m*. ¹H-NMR (300 MHz, CDCl₃): 1.38 (*s*, 3 H, CH₃-*exo*); 1.62 (*s*, 3 H, CH₃-*endo*); 3.81 (*s*, 6 H, OCH₃); 4.04 (*m*, 2 H, H-C(7'), H-C(7'')); 4.68 (*m*, 1 H, H-C(4')); 4.95 (*dd*, *J* = 6.6, 3.6, 1 H, H-C(3')); 5.45 (*dd*, *J* = 6.6, 2.1, 1 H, H-C(2')); 5.81 (*m*, 4 H, H-C(5'), H-C(6'), NH₂); 6.08 (*d*, *J* = 2.1, 1 H, H-C(1')); 6.88-6.92 (*m*, 4 H, H_{arom}, Ketal); 7.09 (*t*, *J* = 5.7, 1 H, NHCO); 7.19 (*d*, *J* = 2.1, 1 H, H_{arom}, Cat.); 7.36-7.42 (*m*, 4 H, H_{arom}, Ketal); 7.85 (*s*, 1 H, H-C(8)); 7.91 (*d*, *J* = 2.1, 1 H, H_{arom}, Cat.); 8.22 (*s*, 1 H, H-C(2)). ¹³C-NMR (75 MHz, CDCl₃): 25.4; 27.2; 40.9; 55.4; 84.1; 84.5; 87.1; 90.2; 108.3; 113.7; 114.6; 115.1; 120.1; 120.6; 120.7; 123.54 (*q*, *J* = 270); 124.6 (*q*, *J* = 33.5); 128.1; 128.5; 130.1; 130.3; 139.8; 147.2; 147.9; 149.2; 152.3; 155.1; 160.7; 162.0. ¹⁹F-NMR (282 MHz, CDCl₃): -61.7 (*s*). HR-MS (MALDI): calcd. for C₃₈H₃₆F₃N₆O₈ ([M+H]⁺): 761.2547, found 759.2535.

i) N1-[(*E*)-3-[(3*aR*,4*R*,6*R*,6*aR*)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-trifluoromethyl-2,3-dihydroxybenzamide



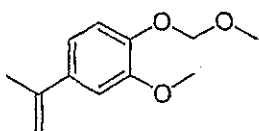
GP8, starting from the protected precursor (75 mg, 0.1 mmol) afforded the desired product as a colorless solid.

Yield: 48 mg (99%). *t*_{R, analyt.}: 14.7 min. IR (KBr): 3409 *br, s*; 1670*s*; 1649*m*; 1607*m*; 1545*w*; 1398*w*; 1327*m*; 1194*m*; 1124*m*; 1049*w*; 801*w*; 725*w*. ¹H-NMR (500 MHz,): 4.06 (*m*, 2 H, H-C(7'), H-C(7'')); 4.24 (*t*, *J* = 5.1, 1 H, H-C(4')); 4.52 (*m*, 1 H, H-C(3')); 4.71 (*t*, *J* = 4.8, 1 H, H-C(2')); 5.95 (*m*, 2 H, H-C(5'), H-C(6')); 6.06 (*d*, *J* = 4.8, H-C(1')); 7.15 (*d*, *J* = 1.2, 1 H, H_{arom}, Cat.); 7.64 (*d*, *J* = 1.2, 1 H, H_{arom}, Cat.); 8.29 (*s*, 1 H, H-C(8)); 8.39 (*s*, 1 H, H-C(2)). ¹³C-NMR (125 MHz,): 41.8; 75.3; 75.6; 86.1; 90.6; 115.5 (*q*, *J* = 2.5); 116.4 (*q*, *J* =

5.0); 116.9; 120.8; 121.9 (*q*, *J* = 32.5); 125.7 (*q*, *J* = 269); 130.5; 130.9; 143.4; 147.8; 148.3; 150.3; 153.3; 153.6; 170.1. ¹⁹F-NMR (282 MHz, CDCl₃): -61.6 (*s*). HR-MS (MALDI): calcd. for C₂₀H₂₀F₃N₆O₆ ([M+H]⁺): 497.1396, found 497.1401.

Example 17

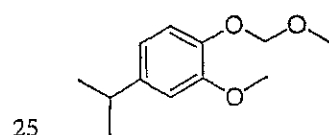
- 5 Preparation of N1-{(E)-3-[(3a*R*,4*R*,6*R*,6a*R*)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl}-5-isopropyl-2,3-dihydroxy-benzamide
a) 4-Isopropenyl-2-methoxy-1-methoxymethoxy-benzene



- A suspension of methyltriphenylphosphonium bromide (1.1 g, 3.09 mmol, 1.3 eq.) in 5
10 mL dry THF cooled to -80°C was slowly treated with BuLi (1.94 mL of a 1.6 m solution in hexane, 1.3 eq.). To this yellow suspension a solution of 1-(3-methoxy-4-methoxymethoxy-phenyl)-ethanone (500 mg, 2.38 mmol, 1 eq.) in 5 mL dry THF was added and the reaction mixture was allowed to warm to r.t. where stirring was continued for 12 h. The suspension was filtered and the solvent was evaporated *in vacuo*. The crude
15 product was purified using flash chromatography (silica gel, hexane /EtOAc 6:1) to yield the desired product as a color-less oil.

- Yield: 424 mg (86%). IR (neat): 3085w; 2952m; 2827w; 1627w; 1602w; 1580m; 1513s; 1463m; 1413m; 1300m; 1248s; 1224m; 1157s; 1139s; 1077s; 997s; 922m; 885m; 855m; 817w; 765w. ¹H-NMR (300 MHz, CDCl₃): 2.14 (*s*, 3 H, CH₃); 3.52 (*s*, 3 H, Ar-OCH₃);
20 3.91 (*s*, 3 H, OCH₃); 5.03 (*qu*, *J* = 1.5, 1 H, CH₂); 5.23 (*s*, 2 H, OCH₂O); 5.29 (*qu*, *J* = 1.5, 1 H, CH₂); 6.98-7.03 (*m*, 2 H, H_{arom}); 7.11 (*d*, *J* = 8.4; 1 H, H_{arom}). ¹³C-NMR (75 MHz, CDCl₃): 21.9; 55.8; 56.2; 95.4; 109.2; 111.4; 115.9; 118.1; 135.9; 142.9; 146.0; 149.3. HR-MS (EI⁺): calcd. for C₁₂H₁₆O₃ ([M]⁺): 208.1099, found 208.1097.

- b) 4-Isopropyl-2-methoxy-1-methoxymethoxy-benzene

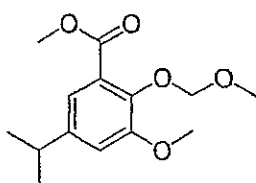


25 To a solution of 4-isopropenyl-2-methoxy-1-methoxymethoxy-benzene (3.5 g, 16.81 mmol) in 20 mL MeOH, Pd/C (10%, 350 mg) was added and the mixture was stirred 16 h under a H₂ atmosphere. The reaction mixture was then filtered through Celite and

evaporated *in vacuo* and briefly dried under vacuum to yield the title compound as a colorless oil.

Yield: 3.31 g (94%). IR (neat): 2959s; 2827w; 1592w; 1516s; 1464s; 1419m; 1297w; 1266s; 1228s; 1198m; 1156s; 1079s; 1037w; 1004s; 923m; 852w; 815w; 763w; 653w. ¹H-NMR (300 MHz, CDCl₃): 1.24 (d, J = 7.0, 6 H, CH₃); 2.86 (sep, J = 7.0, 1 H, CH); 3.52 (s, 3 H, Ar-OCH₃); 3.88 (s, 3 H, OCH₃); 5.20 (s, 2 H, OCH₂O); 6.73-6.78 (m, 2 H, H_{arom}); 7.07 (d, J = 8.1; 1 H, H_{arom}). ¹³C-NMR (75 MHz, CDCl₃): 24.1; 33.8; 55.8; 56.1; 95.6; 110.3; 116.5; 118.2; 143.5; 144.4; 149.5. HR-MS (EI+): calcd. for C₁₂H₁₈O₃ ([M]⁺): 210.1256, found 210.1246.

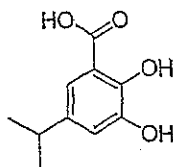
10 c) Methyl 5-Isopropyl-3-methoxy-2-methoxymethoxy-benzoate



To a solution of 4-isopropyl-2-methoxy-1-methoxymethoxy-benzene (2.0 g, 9.51 mmol) in 35 mL dry THF cooled to 0°C, BuLi (9 mL of a 1.6 M solution in hexane, 1.5 eq.) was added dropwise via a syringe and the reaction mixture was stirred 2.5 h at 0°C. This solution was then slowly added to a solution of methyl chloroformate (9g, 95.1 mmol, 10 eq.) in 10 mL dry THF at 0°C. The mixture was stirred 12 h at r.t. Saturated KHCO₃ solution and EtOAc were then added to the solution and the phases were separated. The organic layer was washed twice with saturated NaCl solution, dried over MgSO₄ and evaporated *in vacuo*. The crude product was purified using flash chromatography (silica gel, hexane EtOAc 9:1 → 6:1) to yield the title compound as a yellowish oil.

Yield: 1.3 g (51%). IR (neat): 2960m; 2841w; 1769m; 1729s; 1586w; 1487m; 1464m; 1439m; 1339m; 1263s; 1207s; 1157m; 1063s; 961s; 860w; 797w; 656w. ¹H-NMR (300 MHz, CDCl₃): 1.24 (d, J = 6.9, 6 H, CH₃); 2.88 (sep, J = 6.9, 1 H, CH); 3.57 (s, 3 H, Ar-OCH₃); 3.86 (s, 3 H, OCH₃); 3.90 (s, 3 H, C(O)OCH₃); 5.10 (s, 2 H, OCH₂O); 6.91 (d, J = 2.1, 1 H, H_{arom}); 7.18 (d, J = 2.1; 1 H, H_{arom}). ¹³C-NMR (75 MHz, CDCl₃): 24.0; 34.0; 52.2; 56.2; 75.4; 99.4; 114.4; 119.8; 126.0; 143.3; 144.9; 152.8; 166.8. HR-MS (EI+): calcd. for C₁₄H₂₀O₅ ([M]⁺): 268.1311, found 268.1300.

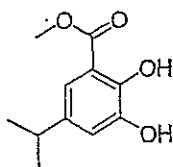
d) 2,3-Dihydroxy-5-isopropyl-benzoic acid



To a solution of methyl 5-Isopropyl-3-methoxy-2-methoxymethoxy-benzoate in 5 mL dry CH_2Cl_2 cooled to -80°C , BBr_3 (3.4 mL of a 1 M solution in CH_2Cl_2) was added dropwise via a syringe. The mixture was then stirred 30 min. at -70°C , then the cooling bath was removed and the stirring continued at r.t. for 1 h. The reaction was quenched by addition of H_2O and the resulting mixture was extracted twice with 30 mL CH_2Cl_2 . The combined organic fractions were dried over MgSO_4 and evaporated *in vacuo* to yield a brown solid. This material was redissolved in 1 mL AcOH to which 2.5 mL HBr (33% in AcOH) was added. The mixture was stirred at 120°C for 5 h, then H_2O was slowly added and the mixture was extracted with EtOAc . The organic layer was washed twice with saturated NaCl solution, dried over MgSO_4 and evaporated *in vacuo* to yield the desired product as a brown solid.

Yield: 45 mg (41%). Mp.: $151-152^\circ\text{C}$. IR (KBr): 3311m; 2958s; 1675s; 1613w; 1483s; 1384w; 1276s; 1161s; 986w; 872w; 796w; 778w; 728w; 703w. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 1.22 (d, $J = 7.1$, 6 H, CH_3); 2.84 (sep, $J = 7.1$, 1 H, CH); 5.64 (bs, 1 H, OH); 7.09 (d, $J = 2.4$, 1 H, H_{arom}); 7.30 (d, $J = 2.4$; 1 H, H_{arom}); 10.29 (s, 1 H, OH). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 23.9; 33.5; 110.8; 118.7; 119.7; 140.5; 144.8; 147.4; 174.8. HR-MS (EI+): calcd. for $\text{C}_{10}\text{H}_{10}\text{O}_3$ ($[\text{M}-\text{H}_2\text{O}]^+$): 278.0630, found 278.0623.

e) Methyl 2,3-dihydroxy-5-isopropyl-benzoate

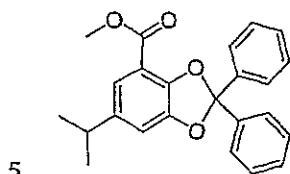


2,3-Dihydroxy-5-isopropyl-benzoic acid (140 mg, 0.71 mmol, 1 eq.) and SOCl_2 (430 mg, 3.6 mmol, 5 eq.) were reacted according to GP1.

Yield: 125 mg (83%). Grayish solid. Mp.: $66-67^\circ\text{C}$. IR (KBr): 3425s; 2955m; 1688s; 1485s; 1438s; 1338s; 1276s; 1231m; 1159m; 1112w; 1018m; 964w; 893w; 785m; 693w; 641w. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 1.21 (d, $J = 6.9$, 6 H, CH_3); 2.82 (sep, $J = 6.9$, 1 H, CH); 3.95 (s, 3 H, OCH_3); 5.61 (s, 1 H, OH); 7.02 (d, $J = 2.0$, 1 H, H_{arom}); 7.21 (d, $J = 2.0$, 1 H, H_{arom});

10.69 (s, 1 H, OH). ^{13}C -NMR (75 MHz, CDCl_3): 23.9; 33.5; 52.3; 111.8; 117.7; 118.4; 140.1; 144.7; 146.9; 170.8. HR-MS (EI+): calcd. for $\text{C}_{11}\text{H}_{14}\text{O}_4$ ($[\text{M}]^+$): 210.0892, found 210.0892.

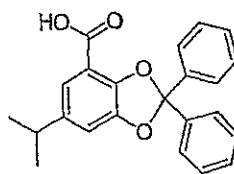
f) Methyl 6-isopropyl-2,2-diphenyl-1,3-benzodioxole-4-carboxylate



Methyl 2,3-dihydroxy-5-isopropyl-benzoate (85 mg, 0.4 mmol, 1 eq.) and dichlorodiphenyl-methane (125 mg, 0.53 mmol, 1.3 eq.) were reacted according to GP2, Method B.

Yield: 112 mg (74%). Colorless solid. Mp.: 108-110°C. IR (KBr): 2959w; 1714s; 1478s; 1447s; 1385w; 1285m; 1045m; 1017m; 915w; 868w; 807m; 782m; 701s; 641m. ^1H -NMR (300 MHz, CDCl_3): 1.21 (d, $J = 6.8$, 6 H, CH_3); 2.85 (sep, $J = 6.8$, 1 H, CH); 3.94 (s, 3 H, OCH_3); 6.92 (d, $J = 1.9$, 1 H, $\text{H}_{\text{arom, Cat}}$); 7.26 (d, $J = 1.9$, 1 H, H_{arom}); 7.35-7.41 (m, 6 H, $\text{H}_{\text{arom, Ketal}}$); 7.60-7.65 (m, 4 H, $\text{H}_{\text{arom, Ketal}}$). ^{13}C -NMR (75 MHz, CDCl_3): 24.0; 33.9; 52.0; 111.0; 112.1; 117.7; 119.9; 126.4; 128.2; 129.2; 140.0; 142.5; 146.3; 148.3; 165.4. HR-MS (MALDI): calcd. for $\text{C}_{24}\text{H}_{22}\text{O}_4\text{Na}$ ($[\text{M}+\text{Na}]^+$): 397.1416, found 397.1414.

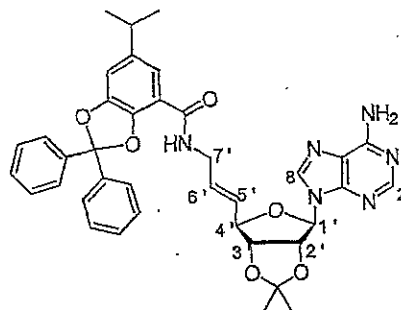
g) 6-Isopropyl-2,2-diphenyl-1,3-benzodioxole-4-carboxylic acid



Methyl 6-isopropyl-2,2-diphenyl-1,3-benzodioxole-4-carboxylate (100 mg, 0.267 mmol, 1 eq.) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (45 mg, 1.07 mmol, 4 eq.) were reacted according to GP3.

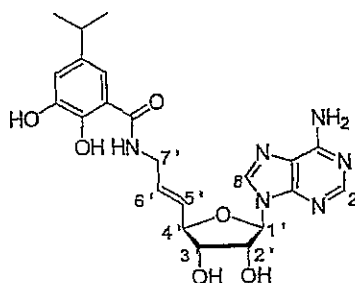
Yield: 91 mg (95%). Colorless solid. IR (KBr): 2958m; 2630w; 1683s; 1478s; 1450s; 1254s; 1207s; 1044m; 1023m; 947w; 864w; 760w; 697m; 641w. ^1H -NMR (300 MHz, CDCl_3): 1.21 (d, $J = 6.9$, 6 H, CH_3); 2.86 (sep, $J = 6.9$, 1 H, CH); 6.97 (d, $J = 1.8$, 1 H, $\text{H}_{\text{arom, Cat}}$); 7.31 (d, $J = 1.8$, 1 H, H_{arom}); 7.35-7.42 (m, 6 H, $\text{H}_{\text{arom, Ketal}}$); 7.61-7.64 (m, 4 H, $\text{H}_{\text{arom, Ketal}}$). ^{13}C -NMR (75 MHz, CDCl_3): 24.0; 33.8; 111.2; 111.9; 118.2; 120.3; 126.4; 128.3; 129.3; 139.8; 142.7; 146.9; 148.4; 169.6. HR-MS (MALDI): calcd. for $\text{C}_{23}\text{H}_{20}\text{O}_4\text{Na}$ ($[\text{M}+\text{Na}]^+$): 383.1259, found 383.1250.

h) 2,2-Diphenyl-6-isopropyl-benzo[1,3]dioxole-4-carboxylic acid {3-[(3aR,4R,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-*d*][1,3]dioxol-4-yl]-prop-2-enyl}-amide



- 5 6-Isopropyl-2,2-diphenyl-1,3-benzodioxole-4-carboxylic acid (80 mg, 0.22 mmol, 1 eq.), EDC·HCl (64 mg, 0.33 mmol, 1.5 eq.), *N*-hydroxy-succinimide (34 mg, 0.29 mmol, 1.3 eq.), 9-[(3aR,4R,6R,6aR)-6-[(*E*)-3-aminoprop-1-enyl]-2,2-dimethylperhydrofuro[3,4-*d*][1,3]di-oxol-4-yl]-9H-purin-6-amine (81 mg, 0.24 mmol, 1.1 eq.) and Et₃N (0.1 mL, 0.68 mmol) were reacted according to GP7.
- 10 Yield: 89 mg (57%). Colorless foam. IR (KBr): 3424*m*; 3179*w*; 2960*w*; 1645*s*; 1598*s*; 1530*m*; 1475*s*; 1449*m*; 1330*w*; 1255*s*; 1208*s*; 1156*w*; 1081*m*; 1047*m*; 1018*m*; 949*w*; 867*w*; 779*w*; 699*w*; 642*w*. ¹H-NMR (300 MHz, CDCl₃): 1.21 (*d*, *J* = 6.9, 6 H, CH₃); 1.37 (*s*, 3 H, CH₃-*exo*); 1.62 (*s*, 3 H, CH₃-*endo*); 2.88 (*sep*, *J* = 6.9, 1 H, CH); 4.05 (*m*, 2 H, H-C(7'), H-C(7'')); 4.68 (*m*, 1 H, H-C(4')); 4.93 (*dd*, *J* = 6.6, 3.9, 1 H, H-C(3'')); 5.44 (*dd*, *J* = 6.6, 2.4, 1 H, H-C(2'')); 5.79 (*bs*, 2 H, NH₂); 5.86 (*m*, 2 H, H-C(5'), H-C(6')); 6.08 (*d*, *J* = 2.4, 1 H, H-C(1')); 6.92 (*d*, *J* = 1.5, 1 H, H_{arom}, Cat.); 7.14 (*t*, *J* = 5.4, 1 H, NHCO); 7.35-7.39 (*m*, 6 H, H_{arom}, Ketal); 7.43 (*d*, *J* = 1.5, 1 H, H_{arom}, Cat.); 7.48-7.53 (*m*, 4 H, H_{arom}, Ketal); 7.86 (*s*, 1 H, H-C(8)); 8.23 (*s*, 1 H, H-C(2)). ¹³C-NMR (75 MHz, CDCl₃): 24.1; 25.5; 27.2; 34.1; 40.7; 84.0; 84.4; 87.0; 90.1; 110.3; 114.7; 118.0; 119.7; 120.1; 126.3; 128.0; 128.3; 128.4; 129.5; 130.8; 139.1; 139.8; 142.7; 143.4; 147.1; 149.3; 152.5; 155.0; 163.5. HR-MS (MALDI):
- 20 calcd. for C₃₈H₃₉N₆O₆ ([M+H]⁺): 675.2931, found 675.2947.

- i) N1-[(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-isopropyl-2,3-dihydroxy-benzamide



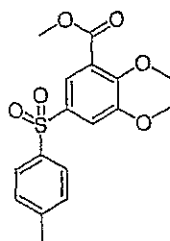
- GP8, starting from the protected precursor (50 mg, 0.074 mmol) afforded the desired product as a grayish solid.

Yield: 29 mg (85%). $t_{R, \text{analyt.}}$: 12.2 min. IR (KBr): 3378 br , s ; 2962 m ; 1700 s ; 1641 m ; 1594 m ; 1542 m ; 1484 w ; 1430 w ; 1323 w ; 1201 s ; 1137 m ; 1049 w ; 970 w ; 836 w ; 800 w ; 724 w ; 642 w . 1H -NMR (500 MHz, CD_3OD): 1.21 (d , $J = 6.8$, 6 H, CH_3); 2.79 (sep , $J = 6.8$, 1 H, CH); 4.03 (m , 2 H, H-C(7'), H-C(7'')); 4.23 (t , $J = 4.9$, 1 H, H-C(4')); 4.51 (m , 1 H, H-C(3')); 4.73 (t , $J = 4.8$, 1 H, H-C(2'')); 5.94 (m , 2 H, H-C(5'), H-C(6')); 6.03 (d , $J = 4.8$, H-C(1')); 6.85 (d , $J = 2.0$, 1 H, $H_{\text{arom, Cat.}}$); 7.12 (d , $J = 2.0$, 1 H, $H_{\text{arom, Cat.}}$); 8.22 (s , 1 H, H-C(8)); 8.37 (s , 1 H, H-C(2)). ^{13}C -NMR (125 MHz, CD_3OD): 24.5; 35.0; 41.6; 75.2; 75.6; 86.1; 90.6; 116.2; 116.3; 118.2; 120.8; 130.2; 131.2; 140.7; 143.2; 147.1; 148.2; 148.7; 150.3; 154.1; 171.5. HR-MS (MALDI): calcd. for $C_{22}H_{27}N_6O_6$ ($[M+H]^+$): 471.1992, found 471.1981.

15 Example 18

Preparation of N1-[(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-(toluene-4-sulfonyl)-2,3-dihydroxy-benzamide

- a) Methyl 2,3-dimethoxy-5-(toluene-4-sulfonyl)-benzoate

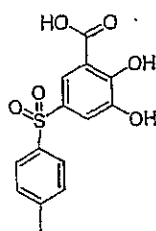


To a solution of methyl 5-iodo-2,3-dimethoxy-benzoate (2.25 g, 7.0 mmol) in 20 mL DMF, sodium *p*-toluenesulfinate hydrate (2.21 g, 11.26 mmol, 1.6 eq.) and CuI (2.22 g, 11.6 mmol, 1.66 eq.) were added and light green solution was stirred at 110°C for 14 h. H_2O and EtOAc were then added to the mixture and the phases were separated. The

organic layer was washed with saturated NaCl solution, dried over MgSO_4 and evaporated under reduced pressure. The crude product was purified using flash chromatography (silica gel, hexane / EtOAc 8:2 $\rightarrow$ 3:2) to yield the desired product as a colorless solid.

- 5 Yield. 1.41 g (58%). Mp.: 114°C . IR (KBr): 3081w; 2945w; 1731s; 1594w; 1482m; 1426w; 1317s; 1273s; 1146s; 1104m; 994w; 872w; 811w; 713w; 665m; 585m; 535w. ^1H -NMR (300 MHz, CDCl_3): 2.40 (s, 3 H, ArCH_3); 3.90 (s, 3 H, ArOCH_3); 3.92 (s, 3 H, ArOCH_3); 3.92 (s, 3 H, C(O)OCH_3); 7.31 (d, $J = 8.1$, 2 H, $\text{H}_{\text{arom, p-Tol.}}$); 7.54 (d, $J = 2.1$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 7.82 (d, $J = 8.1$, 2 H, $\text{H}_{\text{arom, p-Tol.}}$); 7.87 (d, $J = 2.1$; 1 H, $\text{H}_{\text{arom, Cat.}}$). ^{13}C -NMR (75 MHz, CDCl_3): 21.7; 52.6; 56.5; 61.7; 113.4; 122.0; 126.4; 127.5; 129.9; 136.8; 138.2; 144.2; 152.7; 153.8; 164.9. HR-MS (MALDI): calcd. for $\text{C}_{17}\text{H}_{18}\text{O}_6\text{SNa}$ ($[\text{M}+\text{Na}]^+$): 373.0722, found 373.0714. Anal. calcd. for $\text{C}_{17}\text{H}_{18}\text{O}_6\text{S}$: C 58.27, H 5.18, found C 58.38, H 5.36.

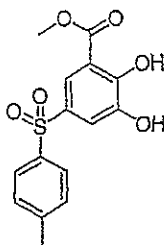
b) 2,3-Dihydroxy-5-(toluene-4-sulfonyl)-benzoic acid



- 15 Methyl 2,3-dimethoxy-5-(toluene-4-sulfonyl)-benzoate (1.3 g, 4.036 mmol) was dissolved in 5 mL AcOH to which HBr (15 mL of a 33% solution in AcOH) and Bu_4NBr (1.1 g, 3.4 mmol, 0.85 eq.) were added. The reaction mixture was stirred at 140°C for 20 h, then H_2O was slowly added and the mixture was extracted with EtOAc. The organic layer was washed twice with saturated NaCl solution, dried over MgSO_4 and evaporated *in vacuo*. The crude product was purified using flash chromatography (silica gel, hexane / EtOAc / AcOH 3:2:0.2 $\rightarrow$ 1:3:0.2) to yield the desired product as an orange solid.

- Yield: 560 mg (45 %). Mp.: $223\text{--}225^\circ\text{C}$ (dec.). IR (KBr): 3165br, m; 1692m; 1597w; 1467m; 1403w; 1282s; 1214w; 1141s; 1094m; 967w; 893w; 799w; 743w; 709m; 665m. ^1H -NMR (300 MHz, DMSO-d_6): 2.35 (s, 3 H, ArCH_3); 4.42 (bs, 1 H, OH); 7.28 (d, $J = 2.1$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 7.39 (d, $J = 8.1$, 2 H, $\text{H}_{\text{arom, p-Tol.}}$); 7.75 (m, 3 H, $\text{H}_{\text{arom, Cat.}}$, $\text{H}_{\text{arom, p-Tol.}}$); 9.86 (bs, 1 H, OH). ^{13}C -NMR (75 MHz, DMSO-d_6): 21.0; 114.7; 115.6; 120.0; 126.8; 128.7; 130.0; 138.9; 143.6; 147.1; 156.4; 170.5. HR-MS (MALDI): calcd. for $\text{C}_{14}\text{H}_{12}\text{O}_6\text{SNa}$ ($[\text{M}+\text{Na}]^+$): 331.0252, found 331.0246.

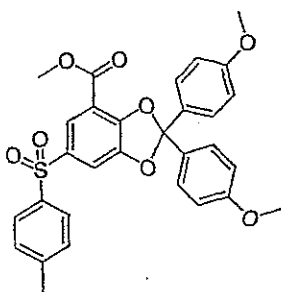
c) Methyl 2,3-dihydroxy-5-(toluene-4-sulfonyl)-benzoate



2,3-Dihydroxy-5-(toluene-4-sulfonyl)-benzoic acid (410 mg, 1.33 mmol, 1 eq.) and SOCl_2 (790 mg, 6.65 mmol, 5 eq.) were reacted according to GP1.

- 5 Yield: 321 mg (75%). Orange solid. Mp.: 168-170°C (dec.). IR (KBr): 3362br, m; 2956w; 1695s; 1596m; 1494m; 1447m; 1284s; 1243s; 1146s; 1094s; 1018m; 937w; 883m; 810m; 736w; 700w; 666s. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 2.39 (s, 3 H, ArCH_3); 4.00 (s, 3 H, OCH_3); 5.91 (bs, 1 H, OH); 7.29 (d, $J = 7.8$, 2 H, $\text{H}_{\text{arom, p-Tol.}}$); 7.55 (d, $J = 1.2$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 7.83 (d, $J = 7.8$, 2 H, $\text{H}_{\text{arom, p-Tol.}}$); 8.05 (d, $J = 1.2$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 11.43 (bs, 1 H, OH). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 21.7; 53.1; 112.2; 117.8; 120.9; 127.4; 129.8; 132.8; 138.5; 144.1; 145.6; 152.5; 169.6. HR-MS (MALDI): calcd. for $\text{C}_{15}\text{H}_{14}\text{O}_6\text{SNa}$ ($[\text{M}+\text{Na}]^+$): 345.0409, found 345.0402.
- 10

d) Methyl 2,2-bis-(4-methoxy-phenyl)-6-(toluene-4-sulfonyl)-1,3-benzodioxole-4-carboxylate



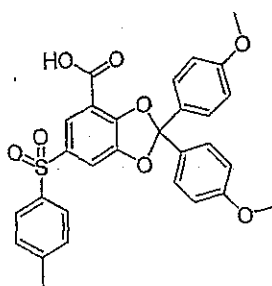
15

- 4,4'-Dimethoxybenzophenone (225 mg, 0.93 mmol, 1.5 eq.), oxalyl chloride (944 mg, 7.44 mmol, 8 eq.) and methyl 2,3-dihydroxy-5-(toluene-4-sulfonyl)-benzoate (200 mg, 0.62 mmol, 1 eq.) were reacted according to GP2.2. The crude product was purified using flash chromatography (silica gel, hexane / EtOAc 20:1 $\rightarrow$ 9:1) to yield the title compound
- 20 as a colorless solid.

Yield: 260 mg (77%). Mp.: 79-82°C. IR (KBr): 2951w; 2832w; 1727m; 1610m; 1512m; 1464s; 1320m; 1285m; 1248s; 1210m; 1175s; 1150s; 1090m; 1042m; 1004w; 885w; 832w; 739w; 663w; 616w. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 2.39 (s, 3 H, ArCH_3); 3.80 (s, 6 H, ArOCH_3); 3.93 (s, 3 H, C(O)OCH_3); 6.88 (dt, $J = 8.7, 2.5$, 4 H, $\text{H}_{\text{arom, Ketal}}$); 7.29 (d, $J =$

- 8.1, 2 H, $H_{\text{arom, p-Tol.}}$); 7.43 (*m*, 5 H, $H_{\text{arom, Cat.}}$, $H_{\text{arom, Ketal}}$); 7.81 (*d*, $J = 8.7$, 2 H, $H_{\text{arom, p-Tol.}}$); 8.09 (*d*, $J = 1.8$, 1 H, $H_{\text{arom, Cat.}}$). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 21.7; 52.5; 55.4; 110.1; 112.5; 113.6; 120.9; 124.0; 127.5; 127.9; 129.9; 130.7; 134.9; 138.4; 144.1; 149.2; 151.9; 160.4; 163.4. HR-MS (MALDI): calcd. for $\text{C}_{30}\text{H}_{27}\text{O}_8\text{S}$ ($[\text{M}+\text{H}]^+$): 547.1427, found 547.1428. Anal. calcd. for $\text{C}_{30}\text{H}_{26}\text{O}_8\text{S}$: C 65.65, H 4.87, found C 65.92, H 4.79.

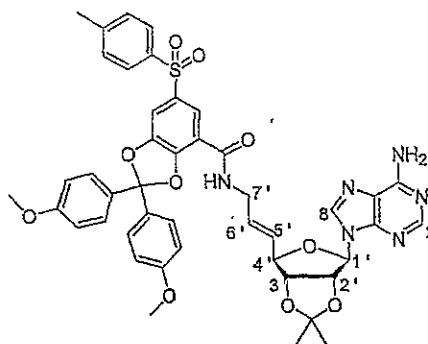
e) 2,2-Bis-(4-methoxy-phenyl)-6-(toluene-4-sulfonyl)-1,3-benzodioxole-4-carboxylic acid



- Methyl 2,2-bis-(4-methoxy-phenyl)-6-(toluene-4-sulfonyl)-1,3-benzodioxole-4-carboxylate (205 mg, 0.375 mmol, 1 eq.) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (79 mg, 1.88 mmol, 5 eq.) were reacted following GP3.

- Yield: 197 mg (99%). Colorless solid. IR (KBr): 3423*br, w*; 2961*w*; 2837*w*; 1649*w*; 1611*m*; 1514*m*; 1443*m*; 1313*s*; 1254*s*; 1175*s*; 1119*m*; 1030*s*; 931*w*; 903*w*; 832*m*; 675*w*. $^1\text{H-NMR}$ (300 MHz, CD_3OD): 2.32 (*s*, 3 H, ArCH_3); 3.73 (*s*, 6 H, ArOCH_3); 6.85 (*d*, $J = 8.7$, 4 H, $H_{\text{arom, Ketal}}$); 7.27 (*d*, $J = 8.1$, 2 H, $H_{\text{arom, p-Tol.}}$); 7.38 (*d*, $J = 8.7$, 4 H, $H_{\text{arom, Ketal}}$); 7.43 (*d*, $J = 1.8$, 1 H, $H_{\text{arom, Cat.}}$); 7.74 (*d*, $J = 8.1$, 2 H, $H_{\text{arom, p-Tol.}}$); 8.03 (*d*, $J = 1.8$, 1 H, $H_{\text{arom, Cat.}}$). $^{13}\text{C-NMR}$ (75 MHz, CD_3OD): 21.5; 55.8; 110.1; 114.0; 114.5; 125.4; 128.1; 128.4; 129.1; 130.8; 131.0; 132.0; 133.2; 135.9; 139.1; 145.7; 150.5; 162.0. HR-MS (MALDI): calcd. for $\text{C}_{29}\text{H}_{25}\text{O}_8\text{S}$ ($[\text{M}+\text{H}]^+$): 533.1270, found 533.1274.

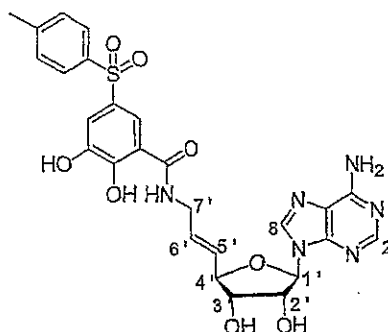
- f) 2,2-Bis-(4-methoxy-phenyl)-6-(toluene-4-sulfonyl)-benzo[1,3]dioxole-4-carboxylic acid {3-[(3*aR*,4*R*,6*R*,6*aR*)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyl-tetrahydro-furo[3,4-*d*][1,3]dioxol-4-yl]-prop-2-enyl}-amide



2,2-Bis-(4-methoxy-phenyl)-6-(toluene-4-sulfonyl)-1,3-benzodioxole-4-carboxylic acid (160 mg, 0.3 mmol, 1 eq.), EDC-HCl (86 mg, 0.45 mmol, 1.5 eq.), *N*-hydroxy-succinimide (46 mg, 0.39 mmol, 1.3 eq.), 9-[(3*aR*,4*R*,6*R*,6*aR*)-6-[(*E*)-3-aminoprop-1-enyl]-2,2-dimethylperhydro-furo[3,4-*d*][1,3]di-oxol-4-yl]-9H-purin-6-amine (100 mg, 0.31 mmol, 1 eq.) and Et₃N (0.1 mL, 0.68 mmol) were reacted according to GP7.

Yield: 146 mg (62%). Colorless foam. Mp.: 124-128°C. IR (KBr): 3424*m*; 2930*w*; 1640*s*; 1638*s*; 1607*s*; 1514*s*; 1458*s*; 1374*w*; 1315*m*; 1249*s*; 1209*m*; 1175*s*; 1184*s*; 1090*s*; 1004*m*; 833*m*; 664*m*; 616*w*. ¹H-NMR (300 MHz, CDCl₃): 1.38 (s, 3 H, CH₃-*exo*); 1.61 (s, 3 H, CH₃-*endo*); 2.38 (s, 3 H, ArCH₃); 3.80 (s, 6 H, OCH₃); 4.01 (*m*, 2 H, H-C(7'), H-C(7'')); 4.69 (*m*, 1 H, H-C(4')); 4.94 (*dd*, *J* = 6.5, 3.6, 1 H, H-C(3')); 5.45 (*dd*, *J* = 6.5, 2.1, 1 H, H-C(2'')); 5.77 (*m*, 2 H, H-C(5'), H-C(6')); 5.83 (*bs*, 2 H, NH₂); 6.09 (*d*, *J* = 2.1, 1 H, H-C(1'')); 6.88 (*dt*, *J* = 8.7, 1.8, 4 H, H_{arom}, Ketal); 6.99 (*t*, *J* = 5.7, 1 H, NHCO); 7.27 (*d*, *J* = 7.8, 2 H, H_{arom}, *p*-Tol.); 7.31-7.38 (*m*, 4 H, H_{arom}, Ketal); 7.48 (*d*, *J* = 1.8, 1 H, H_{arom}, Cat.); 7.83 (*d*, *J* = 7.8, 2 H, H_{arom}, *p*-Tol.); 7.84 (s, 1 H, H-C(8)); 8.21 (s, 1 H, H-C(2)); 8.22 (*d*, *J* = 1.8, 1 H, H_{arom}, Cat.). ¹³C-NMR (75 MHz, CDCl₃): 21.7; 25.4; 27.2; 40.9; 55.4; 84.2; 84.5; 87.2; 90.3; 109.8; 113.7; 114.5; 115.4; 120.1; 121.2; 124.0; 127.7; 128.1; 128.5; 129.8; 130.2; 136.1; 138.2; 139.8; 144.1; 148.1; 148.3; 149.2; 152.4; 155.0; 160.7; 161.6. HR-MS (MALDI): calcd. for C₄₄H₄₃N₆O₁₀S ([M+H]⁺): 847.2761, found 847.2747. Anal. calcd. for C₄₄H₄₂N₆O₁₀S: C 62.40, H 5.00, N 9.92 found C 62.16, H 5.21, N 9.81.

g) N1-[(*E*)-3-[(3*aR*,4*R*,6*R*,6*aR*)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl]-5-(toluene-4-sulfonyl)-2,3-dihydroxybenzamide

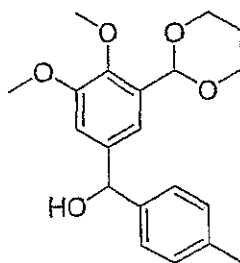


GP8, starting from the protected precursor (90 mg, 0.106 mmol) afforded the desired product as a colorless solid.

Yield: 61 mg (98%). $t_{R, \text{analyt.}}$: 13.9 min. IR (KBr): 3375 br , s ; 1695 s ; 1639 m ; 1597 m ; 1548 w ; 1467 w ; 1430 w ; 1286 m ; 1201 s ; 1144 s ; 1098 w ; 1051 w ; 973 w ; 799 w ; 723 w ; 666 m . 1H -NMR (500 MHz, CD_3OD): 2.37 (s , 3 H, CH_3); 4.05 (m , 2 H, H-C(7'), H-C(7'')); 4.23 (t , $J = 4.9$, 1 H, H-C(4'')); 4.51 (t , $J = 4.9$, 1 H, H-C(3'')); 4.72 (t , $J = 4.8$, 1 H, H-C(2'')); 5.94 (m , 2 H, H-C(5'), H-C(6'')); 6.05 (d , $J = 4.8$, H-C(1'')); 7.33 (d , $J = 8.2$, $H_{\text{arom, p-Tol}}$); 7.35 (d , $J = 2.2$, 1 H, $H_{\text{arom, Cat.}}$); 7.78 (d , $J = 8.2$, $H_{\text{arom, p-Tol}}$); 7.95 (d , $J = 2.2$, 1 H, $H_{\text{arom, Cat.}}$); 8.25 (s , 1 H, H-C(8)); 8.38 (s , 1 H, H-C(2)). ^{13}C -NMR (125 MHz, CD_3OD): 21.51; 41.8; 75.3; 75.6; 86.1; 90.7; 117.0; 117.2; 119.5; 120.8; 128.5; 130.5; 130.8; 131.1; 133.0; 140.5; 143.5; 145.7; 147.7; 148.6; 150.2; 153.5; 154.7; 169.8. HR-MS (MALDI): calcd. for $C_{26}H_{27}N_6O_6S$ ($[M+H]^+$): 583.1611, found 583.1600.

Example 19

- 15 Preparation of N1-[(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxy-tetrahydrofuran-2-yl]prop-2-enyl]-5-(4-methyl-benzoyl)-2,3-dihydroxy-benzamide
a) (3-[1,3]Dioxan-2-yl-4,5-dimethoxy-phenyl)-*p*-tolyl-methanol



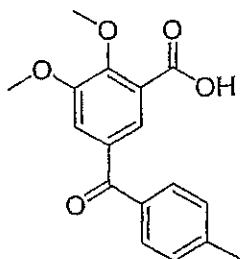
- To a solution of 2-(5-Bromo-2,3-dimethoxy-phenyl)-[1,3]dioxane (2 g, 6.6 mmol) in 13 mL dry THF cooled to $-78^\circ C$, t -BuLi (1.5M solution in pentane, 2.5 eq.) was added dropwise via a syringe and the resulting dark red suspension was stirred 30 min. at $-78^\circ C$. *p*-Tolualdehyde (1.2 g, 10 mmol, 1.5 eq.) was added dropwise to the mixture and the resulting clear solution was stirred 30 min at $-78^\circ C$, then 30 min at $0^\circ C$. H_2O (25 mL)

was slowly added and the resulting solution was extracted with EtOAc (3 x 25 mL). The pooled organic fractions were dried over MgSO₄ and evaporated *in vacuo*. The crude product was purified using flash chromatography (silica gel, hexane/EtOAc 3:2) to yield the desired compound as a colorless solid.

- 5 (Takamitsu Hosoya, Eiji Takashiro, Takashi Matsumoto, Keisuke Suzuki, *J. Am. Chem. Soc.* 1994, 116, 1004-1015).

Yield: 2.13 g (94%). Mp.: 83-84°C. IR (KBr): 3464*br*, s; 2964*m*; 2851*m*; 1596*w*; 1490*s*; 1380*s*; 1317*s*; 1241*s*; 1140*s*; 1079*s*; 999*s*; 896*m*; 824*w*; 772*m*. ¹H-NMR (300 MHz, CDCl₃): 1.43 (*bd*, *J* = 13.8, 1 H, CH₂); 2.23 (*m*, 1 H, CH₂); 2.32 (*s*, 3 H, Ar-CH₃); 3.80 (*s*, 3 H, OCH₃); 3.83 (*s*, 3 H, OCH₃); 4.01 (*tt*, *J* = 12.0, 2.7, 2 H, OCH₂); 4.24 (*m*, 2 H, OCH₂); 5.76 (*bs*, 1 H, O-CH(Ar)-O); 5.83 (*s*, 1 H, Ar-CH(OH)-Ar); 6.91 (*d*, *J* = 1.8, 2 H, H_{arom}); 7.12 (*d*, *J* = 8.1; 1 H, H_{arom, p-Tol}); 7.25 (*m*, 3 H, H_{arom}, H_{arom, p-Tol}). ¹³C-NMR (75 MHz, CDCl₃): 21.2; 25.9; 55.9; 61.4; 67.5; 75.9; 97.2; 110.8; 116.6; 126.4; 129.0; 132.1; 136.9; 140.1; 140.5; 145.8; 152.4. HR-MS (MALDI): calcd. for C₂₀H₂₄O₅Na ([M+Na]⁺): 367.1521, found 367.1513. Anal. calcd. for C₂₀H₂₄O₅: C 69.75, H 7.02, found C 69.81, H 7.15.

b) 2,3-Dimethoxy-5-(4-methyl-benzoyl)-benzoic acid

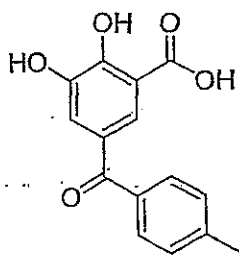


- To a solution of (3-[1,3]Dioxan-2-yl-4,5-dimethoxy-phenyl)-*p*-tolyl-methanol (2.13 g, 6.18 mmol) in 75 mL THF, 56 mL 8N H₂SO₄ was added and the resulting solution was stirred 2 h at 50°C. After addition of 50 mL saturated NaCl-solution the mixture was extracted with EtOAc (3 x 50 mL). The pooled organic fractions were washed with saturated NaHCO₃-solution (50 mL), then saturated NaCl-solution (50 mL) before being dried over MgSO₄ and evaporated under reduced pressure to yield the desired product as a colorless oil. This crude product (2 g) was added to a mixture of 45 mL *t*-BuOH, 24 mL of a 1.25M K₂HPO₄-solution and 37 mL of a 1M KMnO₄-solution and stirred 45 min. at 60°C. The mixture was partitioned between 100 mL saturated NaCl-solution and 100 mL CHCl₃ and the aqueous phase was extracted with CHCl₃ (3 x 100 mL). The pooled organic fractions were extracted with 2N NaOH-solution (3 x 100 mL), then the combined aqueous fractions were acidified with conc. HCl and extracted with CHCl₃ (4 x

100 mL). The organic fractions were pooled, dried over MgSO_4 and evaporated *in vacuo* to yield the title compound as a colorless solid.

Yield: 1.54 g (83%). Mp.: 135-136°C. IR (KBr): 2945 br , s ; 2620 m ; 1684 s ; 1598 s ; 1487 s ; 1442 s ; 1405 s ; 1339 s ; 1277 s ; 1129 s ; 1069 s ; 995 s ; 909 m ; 847 m ; 753 s . $^1\text{H-NMR}$ (300 MHz, CDCl_3): 2.45 (s , 3 H, Ar-CH_3); 4.01 (s , 3 H, OCH_3); 4.19 (s , 3 H, OCH_3); 7.30 (d , $J = 8.1$, 2 H, $\text{H}_{\text{arom, p-Tol.}}$); 7.69 (d , $J = 8.1$; 1 H, $\text{H}_{\text{arom, p-Tol.}}$); 7.72 (d , $J = 2.1$; 1 H, H_{arom}); 8.06 (d , $J = 2.1$; 1 H, H_{arom}). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 21.8; 56.4; 62.4; 117.4; 121.7; 126.3; 129.1; 130.0; 133.9; 134.0; 143.6; 151.5; 152.5; 165.6; 194.3. HR-MS (MALDI): calcd. for $\text{C}_{17}\text{H}_{17}\text{O}_5$ ($[\text{M}+\text{H}]^+$): 301.1076, found 301.1072.

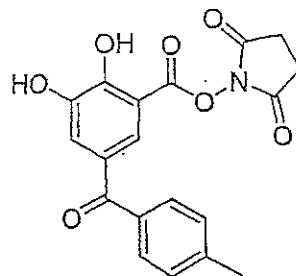
10 c) 2,3-Dihydroxy-5-(4-methyl-benzoyl)-benzoic acid



2,3-Dimethoxy-5-(4-methyl-benzoyl)-benzoic acid (300 mg, 1 mmol) was treated with a mixture of 6 mL 48% HBr and 3 mL AcOH and the mixture was stirred 14 h at 140°C. After cooling to r.t., the product was precipitated by addition of H_2O (60 mL). The precipitate was collected by filtration, washed with 60 mL H_2O and dried under reduced pressure.

Yield: 264 mg (97%). Mp.: 95-97°C (dec.). IR (KBr): 3417 br , s ; 2566 m ; 1680 s ; 1609 s ; 1566 w ; 1432 s ; 1295 s ; 1253 s ; 1179 s ; 1123 m ; 862 m ; 801 m ; 753 s . $^1\text{H-NMR}$ (300 MHz, CD_3OD): 2.44 (s , 3 H, Ar-CH_3); 7.33 (d , $J = 8.1$, 2 H, $\text{H}_{\text{arom, p-Tol.}}$); 7.47 (d , $J = 2.2$; 1 H, H_{arom}); 7.62 (d , $J = 8.1$; 1 H, $\text{H}_{\text{arom, p-Tol.}}$); 7.79 (d , $J = 2.2$; 1 H, H_{arom}). $^{13}\text{C-NMR}$ (75 MHz, CD_3OD): 21.6; 113.4; 121.5; 125.5; 129.4; 129.9; 130.7; 136.1; 144.3; 147.2; 155.8; 173.1; 196.5. HR-MS (MALDI): calcd. for $\text{C}_{15}\text{H}_{11}\text{O}_5$ ($[\text{M}+\text{H}]^+$): 271.0607, found 271.0610.

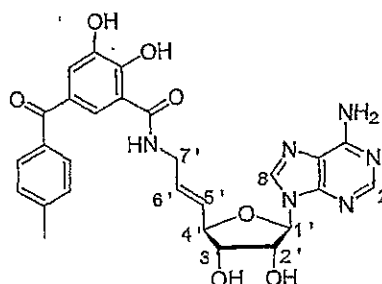
d) 2,3-Dihydroxy-5-(4-methyl-benzoyl)-benzoic acid 2,5-dioxo-pyrrolidin-1-yl ester



To a solution of 2,3-dihydroxy-5-(4-methyl-benzoyl)-benzoic acid (214 mg, 0.79 mmol) in 10 mL dry THF cooled to 0°C, N-hydroxysuccinimide (136 mg, 1.18 mmol, 1.5 eq.) and N-cyclohexylcarbodiimide, N^o-methyl polystyrene HL (Novabiochem) (1.9 eq./g, 832 mg, 2 eq.) were added and the solution was stirred 14 h while the cooling bath slowly warmed up to r.t. The solution was filtered and the filtrate was evaporated under reduced pressure. The crude product was recrystallised from H₂O to yield the desired product as a brownish solid.

Yield: 233 mg (80%). Mp.: 93-95°C (dec.). IR (KBr): 3341 $_{br}$, s; 2949 $_{m}$; 1738 $_{s}$; 1653 $_{m}$; 1606 $_{m}$; 1482 $_{w}$; 1368 $_{m}$; 1323 $_{m}$; 1203 $_{s}$; 1068 $_{s}$; 914 $_{w}$; 755 $_{w}$; 645 $_{w}$. ¹H-NMR (300 MHz, CD₃OD): 2.42 (s, 3 H, Ar-CH₃); 2.87 (s, 4 H, CH₂-CH₂); 7.33 (d, J = 8.0, 2 H, H_{arom, p-Tol.}); 7.57 (d, J = 1.7; 1 H, H_{arom}); 7.65 (d, J = 8.0; 1 H, H_{arom, p-Tol.}); 7.87 (d, J = 1.7; 1 H, H_{arom}). ¹³C-NMR (75 MHz, CD₃OD): 21.4; 26.4; 110.3; 121.9; 125.2; 129.8; 130.0; 130.6; 135.7; 144.3; 147.6; 154.6; 163.6; 171.2; 195.6. HR-MS (MALDI): calcd. for C₁₉H₁₆NO₇ ([M+H]⁺): 370.0927, found 370.0918.

e) N1-{(E)-3-[(3aR,4R,6R,6aR)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]prop-2-enyl}-5-(4-methyl-benzoyl)-2,3-dihydroxy-benzamide



To a solution of 2,3-dihydroxy-5-(4-methyl-benzoyl)-benzoic acid 2,5-dioxo-pyrrolidin-1-yl ester (100 mg, 0.27 mmol) in DMF (4 mL), (2R,3S,4R,5R)-2-((E)-3-Amino-propenyl)-5-(6-amino-purin-9-yl)-tetrahydro-furan-3,4-diol (79 mg, 0.27 mmol, 1 eq.) and Et₃N (113 μ L, 0.81 mmol, 3 eq.) were added and the solution was stirred 18 h at r.t. The crude product was purified using HPLC (RP C18, linear gradient of CH₃CN in H₂O

with 0.1% TFA, 5 → 100% in 20 min, flow of 1 mL / min (analytical), UV-detection at 254 nm) to yield the title compound as a colorless solid.

Yield: 54 mg (37%). $t_{R, \text{analyt.}}$: 13.6 min. IR (KBr): 3378 *br, s*; 1642*s*; 1604*s*; 1427*m*; 1296*s*; 1120*m*; 1043*w*; 753*w*. $^1\text{H-NMR}$ (500 MHz, CD_3OD): 2.32 (*s*, 3 H, CH_3), 3.94 (*m*, 2 H, H-C(7'), H-C(7'')); 4.13 (*t*, $J = 5.0$, 1 H, H-C(4')); 4.41 (*m*, 1 H, H-C(3')); 4.63 (*t*, $J = 4.8$, 1 H, H-C(2')); 5.83 (*m*, 2 H, H-C(5'), H-C(6')); 5.95 (*d*, $J = 4.8$, 1 H, H-C(1')); 7.22 (*d*, $J = 8.2$, 1 H, $\text{H}_{\text{arom, Cat, p-Tol.}}$); 7.28 (*d*, $J = 2$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 7.54 (*d*, $J = 8.2$, 1 H, $\text{H}_{\text{arom, Cat, p-Tol.}}$); 7.70 (*d*, $J = 2$, 1 H, $\text{H}_{\text{arom, Cat.}}$); 8.18 (*s*, 1 H, H-C(8)); 8.28 (*s*, 1 H, H-C(2)). $^{13}\text{C-NMR}$ (125 MHz, CD_3OD): 21.6; 41.6; 75.2; 75.6; 86.1; 90.6; 116.4; 120.3; 120.7; 122.7; 129.7; 130.1; 130.3; 130.9; 131.1; 136.4; 143.3; 144.5; 147.5; 148.0; 150.2; 153.6; 154.4; 170.4; 197.1. HR-MS (MALDI): calcd. for $\text{C}_{27}\text{H}_{27}\text{N}_6\text{O}_7$ ($[\text{M}+\text{H}]^+$): 547.1941, found 547.1934.

Tablet Formulation (Wet Granulation)

Item	Ingredients	mg/tablet	
		25 mg	100 mg
15	1. Compound of formula I	25	100
	2. Lactose Anhydrous DTG	105	30
	3. Sta-Rx 1500	6	6
	4. Microcrystalline Cellulose	30	30
	5. Magnesium Stearate	1	1
20	Total	167	167

Manufacturing Procedure

1. Mix items 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granules at 50°C.
3. Pass the granules through suitable milling equipment.
- 25 4. Add item 5 and mix for three minutes; compress on a suitable press.

Capsule Formulation

Item	Ingredients	mg/capsule	
		25 mg	100 mg
30	1. Compound of formula I	25	100
	2. Hydrus Lactose	123	148
	3. Corn Starch	35	40
	4. Talc	15	10

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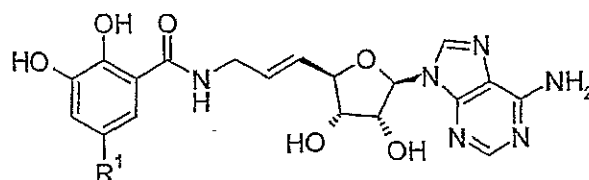
5.	Magnesium Stearate	2	2
	Total	200	300

Manufacturing Procedure

- 5 1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.

Claims

1. Compounds of formula



I

5 wherein

R^1 is H, CN, halogen, $-COR^2$, $-S(O)_xR^2$, C_{1-12} -alkyl, C_{2-12} -alkenyl, C_{3-8} -cycloalkyl, a heterocyclyl group, an aryl group, a heteroaryl group, C_{3-8} -cycloalkyl- (C_{1-3}) -alkyl, a heterocyclyl- (C_{1-3}) -alkyl group, an aryl- (C_{1-3}) -alkyl or a heteroaryl- (C_{1-3}) -alkyl group; the
 10 alkyl, alkenyl, alkoxy, cycloalkyl, heterocyclyl group, aryl and heteroaryl groups may all be optionally substituted;

R^2 is $-N(R^3, R^{3'})$, C_{1-6} -alkyl, C_{3-8} -cycloalkyl, heterocyclyl, aryl, heteroaryl, C_{3-8} -cycloalkyl- (C_{1-3}) -alkyl, a heterocyclyl- (C_{1-3}) -alkyl group, an aryl- (C_{1-3}) -alkyl or a heteroaryl- (C_{1-3}) -alkyl group, the
 15 C_{1-6} -alkyl, C_{3-8} -cycloalkyl, heterocyclyl, aryl, heteroaryl may all be optionally substituted;

R^3 and $R^{3'}$ are independently hydrogen or (C_{1-3}) -alkyl

x is 0, 1 or 2;

and the ester thereof which are hydrolyzable under physiological conditions and the
 20 pharmaceutically acceptable salts thereof.

2. Compounds according to claim 1, wherein R^1 is a hydrogen, cyano, halogen, $-COR^2$, $-S(O)_2R^2$, C_{1-6} -alkyl, C_{1-6} -alkyl substituted with halogen, C_{2-6} -alkenyl substituted with COR^2 , phenyl or phenyl substituted with C_{1-6} -alkyl or halogen, benzyl or benzyl substituted with C_{1-6} -alkyl, or heteroaryl such as pyridinyl, thiazolyl or benzthiazolyl and
 25 wherein R^2 is C_{1-6} -alkyl, C_{1-6} -alkyl substituted with halogen or $-N(R^3, R^{3'})$ and R^3 and $R^{3'}$ are C_{1-3} -alkyl, furthermore wherein R^2 is phenyl or phenyl substituted with C_{1-6} -alkyl or halogen, cyclohexyl, or heteroaryl such as pyridinyl, thiazolyl or benzthiazolyl.

3. The compounds according to claim 1 or 2 wherein R^1 is hydrogen cyano or halogen.

4. The compounds according to claims 1 or 2, wherein R^1 is C_{1-6} -alkyl, C_{1-6} -alkyl substituted with halogen, C_{2-6} -alkenyl substituted with COR^2 , and wherein R^2 is $-NR^3, R^3$ and R^3 and R^3 are C_{1-3} -alkyl.

5. The compounds according to claim 4

5 N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-isopropyl-benzamide

N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-5-(2-dimethylcarbamoyl-vinyl)-2,3-dihydroxy-benzamide

10 N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-trifluoromethyl-benzamide

6. The compounds according to claims 1 or 2 wherein R^1 is $-COR^2$ and R^2 is C_{1-6} -alkyl, C_{1-6} -alkyl substituted with halogen, $-N(R^3, R^3)$ and R^3 and R^3 are C_{1-36} -alkyl.

7. The compounds according to claim 5

15 N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-trifluoroacetyl-benzamide

N3-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-4,5-dihydroxy-N1,N1-dimethyl-isophthalamide

20 8. The compounds according to claims 1 or 2 wherein R^1 is $-COR^2$, and wherein R^2 is phenyl, phenyl substituted with C_{1-6} -alkyl or halogen, C_{3-8} -cyclohexyl, or heteroaryl such as pyridinyl, thiazolyl or benzthiazolyl.

9. The compounds according to claim 8

N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-(4-methyl-benzoyl)-benzamide

25 N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-5-cyclohexanecarbonyl-2,3-dihydroxy-benzamide

N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-(pyridine-4-carbonyl)-benzamide

10. The compounds according to claims 1 or 2 wherein R^1 is $-S(O)_2R^2$, and wherein R^2 is C_{1-6} -alkyl, C_{1-6} -alkyl substituted with halogen, $-N(R^3, R^{3'})$ and R^3 and $R^{3'}$ are C_{1-3} -alkyl, furthermore wherein R^2 is phenyl, phenyl substituted with C_{1-6} -alkyl or halogen, cyclohexyl, or heteroaryl such as pyridinyl, thiazolyl or benzthiazolyl.
- 5 11. The compound according to claim 10, N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-(toluene-4-sulfonyl)-benzamide
12. The compounds according to claim 1 or 2 wherein R^1 is phenyl or phenyl substituted with C_{1-6} -alkyl or halogen, pyridinyl, thiazolyl, benzthiazolyl, benzyl or benzyl
10 substituted with C_{1-6} -alkyl.
13. The compounds according to claim 12
- 4'-Fluoro-4,5-dihydroxy-biphenyl-3-carboxylic acid {3-[5-(6-amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-amide
- N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-
15 dihydroxy-5-thiazol-2-yl-benzamide
- N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-pyridin-4-yl-benzamide
- 4,5-Dihydroxy-4'-methyl-biphenyl-3-carboxylic acid {3-[5-(6-amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-amide
- 20 N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-5-benzothiazol-2-yl-2,3-dihydroxy-benzamide
- N-{3-[5-(6-Amino-purin-9-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl]-allyl}-2,3-dihydroxy-5-(4-methyl-benzyl)-benzamide
14. A medicament containing one or more compounds as claimed in anyone of claims
25 1 to 13 and pharmaceutically acceptable excipients.
15. A medicament according to claim 14 for the treatment of diseases related to the COMT inhibition.
16. A medicament according to claim 15 wherein the disease is depression or Parkinson's disease.

17. A medicament according to claim 14 to improve cognition.

18. The use of compounds according to anyone of claims 1 to 13 for the manufacture of a medicament for the prevention and treatment of diseases related to the COMT inhibition such as depression, Parkinson's disease, or to improve cognition.