

# Inhibition of Nucleoside Transport by New Analogues of 4-Nitrobenzylthioinosine: Replacement of the Ribose Moiety by Substituted Benzyl Groups

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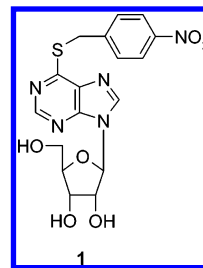
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4-Nitrobenzylthioinosine (NBTI, **1**) is a well-known inhibitor for the nucleoside transport protein ENT1. However, its highly polar nature is unfavorable for oral absorption and/or penetration into the CNS. In the search for compounds with lower polarity than NBTI we replaced its ribose moiety by substituted benzyl groups. Halogen, hydroxyl, (trifluoro)methyl(-oxy), nitro, and amine functionalities were among the substituents at the benzyl group. In general, substitution of the benzyl group resulted in a lower affinity for ENT1. Only 2-hydroxyl substitution showed a higher affinity. Most likely this is the result of hydrogen bonding. Substitution at the 2-position of the benzyl group with aryl groups was also addressed. Compared to parent compound carrying a 2-phenylbenzyl group, all synthesized analogues gave higher affinities. Introduction of fluoro, trifluoromethyl, methoxy, and hydroxyl groups at the phenyl group clearly showed that addition to the 4-position was preferable. Despite the highly different character of a ribose and a benzyl group,  $K_i$  values in the low nanomolar range were obtained for the benzyl-substituted derivatives. Compound **35**, LUF5919, and compound **60**, LUF5929, displayed the highest affinity ( $K_i = 39$  nM for both compounds), having a polar surface area of 101 Å<sup>2</sup> and 85 Å<sup>2</sup>, respectively.

## Introduction

Nucleoside transport proteins are specialized proteins that enable hydrophilic nucleosides such as adenosine to cross the cell membrane. These proteins are divided into two families: (1) the concentrative nucleoside transporters (CNT), which are Na<sup>+</sup>-dependent and drive the nucleoside flow against their concentration gradient, and (2) equilibrative nucleoside transporters (ENT), which drive the nucleoside flow following their concentration gradient.<sup>1–5</sup> Inhibition of the nucleoside transport proteins has been recognized as an important strategy for the treatment of several afflictions, including ischemic heart diseases, stroke, and host tissue protection in chemotherapy.<sup>5–7</sup>

The ENTs are subdivided into equilibrative sensitive (ENT1) and equilibrative insensitive (ENT2) proteins, based on their sensitivity toward inhibition by 4-nitrobenzylthioinosine (NBTI (**1**), Figure 1). Recently, two novel isoforms have been discovered, ENT3 and ENT4.<sup>2,3,8</sup> ENT1 is distributed in the dorsal horn of the spinal cord in close proximity to the adenosine A<sub>1</sub> receptor. Thus, inhibition of ENT1 will result in an increased extracellular concentration of adenosine, which in turn will lead to a more profound occupancy of the adenosine A<sub>1</sub> receptor through which adenosine exerts many of its physiological effects, e.g. counteracting pain.<sup>9,10</sup> NBTI (**1**) is a very active inhibitor of ENT1;



**Figure 1.** 4-Nitrobenzylthioinosine (NBTI, PSA = 154 Å<sup>2</sup>).

however, its high-polarity limits its possibilities for intestinal absorption or its use as a CNS drug.

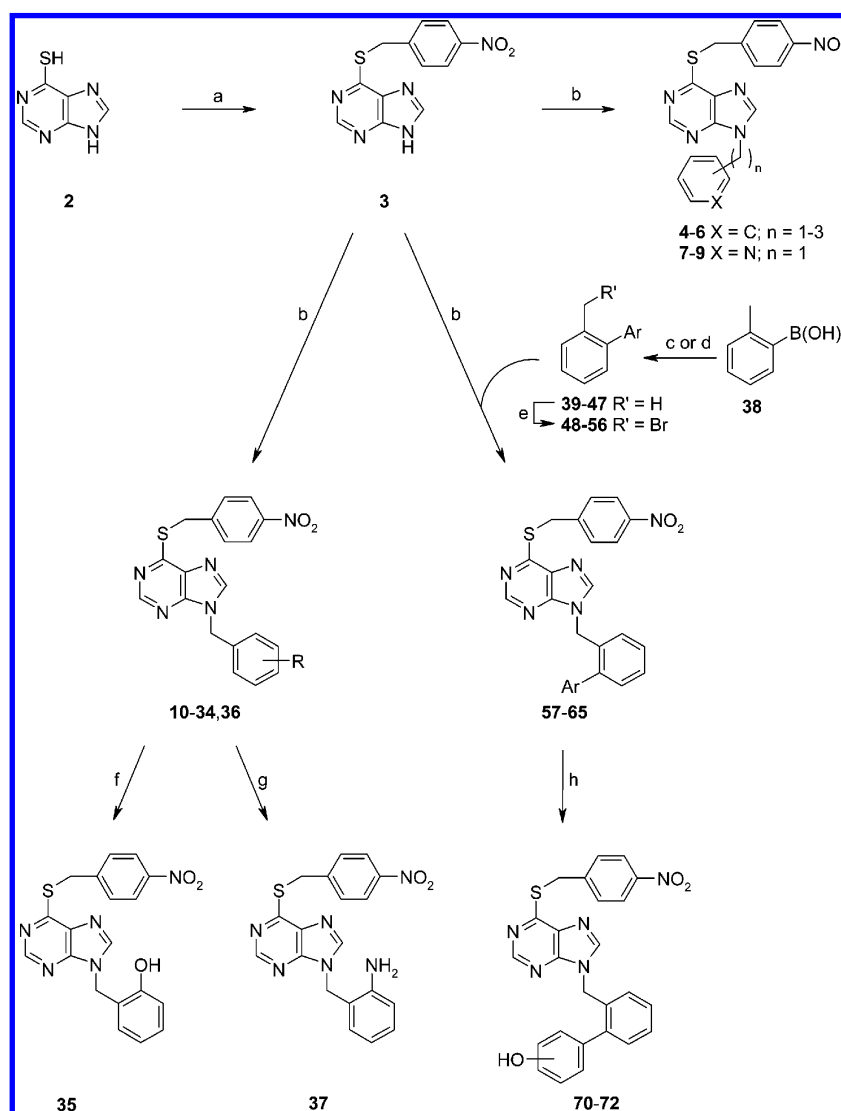
A parameter to predict intestinal absorption and/or brain permeation of compounds is the so-called polar surface area (PSA). The PSA is defined as the surface area of a molecule occupied by nitrogen and oxygen, and the hydrogen atoms that are attached to these atoms. In literature the upper limit for good intestinal absorption ranges from 120 Å<sup>2</sup> to 140 Å<sup>2</sup>.<sup>11–13</sup> For passage over the blood–brain barrier, the PSA value should be lower than 60–70 Å<sup>2</sup> or 90 Å<sup>2</sup>.<sup>12,14</sup> Variations in the given limits result from the differences in the methods used for the calculation of the PSA values.

Our present work aims at the synthesis of compounds that are significantly less polar than NBTI to improve their oral bioavailability and to increase their potential to cross the blood–brain barrier. Both the presence of the ribose and the nitro group contribute highly to this polarity. Much effort has been put in the search for a different substituent at the 6-thiol position but has so far not resulted in compounds that are less polar and still retain the high activity.<sup>15,16</sup> On the other hand

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Scheme 1<sup>a</sup>

<sup>a</sup> Reagents: (a) 4-nitrobenzyl bromide, K<sub>2</sub>CO<sub>3</sub>, DMF, rt, 4 h; (b) appropriate aryl bromide, NaH (1 equiv), DMF, rt, 16 h; (c) appropriate aryl bromide, toluene, EtOH, 2 M Na<sub>2</sub>CO<sub>3</sub> (aq), Pd(PPh<sub>3</sub>)<sub>4</sub> (cat.), 80 °C, 1–2 d; (d) appropriate aryl bromide, H<sub>2</sub>O, TBAB, Na<sub>2</sub>CO<sub>3</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub> (cat.),  $\mu$ W, 150 °C, 5–10 min; (e) NBS, benzoyl peroxide, CCl<sub>4</sub>, 80 °C, 40 h; (f) compound **25**, BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, –78° to rt, 5 h; (g) compound **29**, TFA, H<sub>2</sub>O, rt, 6 h; (h) compound **61**, **62**, or **63**, BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, –78° to rt, 5 h.

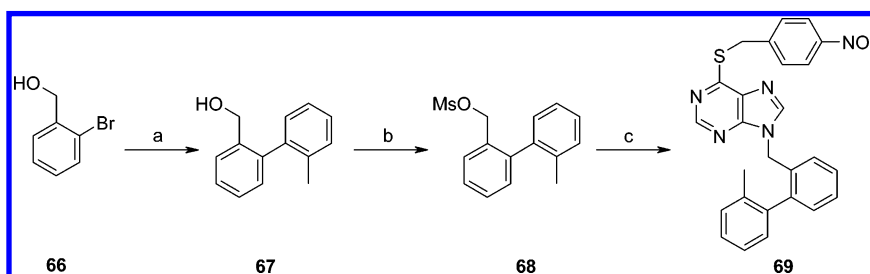
previous reports have shown that NBTI analogues without the ribose function are still able to inhibit the nucleoside transport protein.<sup>7</sup> Substitution of the ribose group also reduces the number of both hydrogen bond donors and acceptors, which is also important in terms of cell permeability and uptake into the CNS. Therefore, we chose to replace the ribose function. Here, we report on the synthesis and the affinities of NBTI analogues in which the ribose was substituted for a benzyl group. Also the influence of the distance between the aryl ring and the purine ring was investigated as well as the presence of a pyridyl function.

**Chemistry.** The novel NBTI analogues containing aryl functions instead of a ribose moiety were obtained as depicted in Scheme 1. First, commercially available mercaptopurine **2** was substituted at the 6-position with the 4-nitrobenzyl<sup>15</sup> group to give **3**. Substitution at N<sup>9</sup> with the aryl functions was performed by dissolving compound **3** in DMF, followed by addition of 1 equiv of sodium hydride and the appropriate aryl bromide.<sup>16</sup> To investigate the influence of the chain length between the purine and the phenyl group, compounds **4–6** were

prepared. The effect of a pyridyl ring was explored by the synthesis of **7–9**.

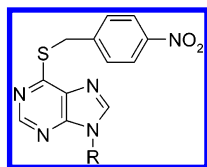
As benzyl substitution provided the most active compound (**4**), we subsequently investigated the influence of substitution of the benzyl function itself. Compounds **10–34** (Scheme 1) were synthesized directly from **3** using the substituted benzylic halide and sodium hydride in DMF as described for **4–9**. Boc-protected 2-aminobenzyl bromide used for the preparation of **29** was synthesized as described in the literature.<sup>17</sup> Hydroxyl-substituted **35** was obtained by demethylation of **25** using boron tribromide.<sup>18</sup> Compound **36** could be prepared directly from **3** using 3-hydroxybenzyl iodide. Removal of the Boc group of **29** with TFA afforded amine **37**.<sup>19</sup>

The result of compound **30** carrying a biphenyl group instead of a highly polar ribose urged us to further investigate aryl-substituted benzyl groups at the N<sup>9</sup>-position. These compounds were prepared by application of the Suzuki reaction.<sup>20</sup> 2-Tolylboronic acid (**38**) was reacted with the appropriate aryl bromide, using conventional or microwave-assisted heating to provide

Scheme 2<sup>a</sup>

<sup>a</sup> Reagents: (a) 2-tolylboronic acid (**38**), H<sub>2</sub>O, TBAB, Na<sub>2</sub>CO<sub>3</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub> (cat.),  $\mu$ W, 150 °C, 5–10 min; (b) MsCl, Et<sub>3</sub>N, MTBE, 0 °C–rt, 3 h; (c) compound **3**, NaH (1 equiv), DMF, rt, 16 h.

**Table 1.** <sup>a</sup>Affinities of Novel NBTI Analogues for the Nucleoside Transport Protein on Human Erythrocyte Membranes



compound	R	PSA (Å <sup>2</sup> ) <sup>b</sup>	K <sub>i</sub> (nM)
<b>4</b>	benzyl	86	135 (± 30)
<b>5</b>	ethylphenyl	86	2200 (± 600)
<b>6</b>	propylphenyl	86	488 (± 68)
<b>7</b>	pyridin-2'-ylmethyl	96	42% <sup>c</sup>
<b>8</b>	pyridin-3'-ylmethyl	99	2709 (± 1165)
<b>9</b>	pyridin-4'-ylmethyl	99	2165 (± 585)

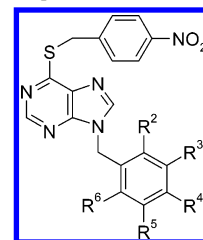
<sup>a</sup> Binding study: [<sup>3</sup>H]NBTI ( $K_D = 0.59$  nM) as radioligand and human erythrocyte membranes ( $n = 3$ ).  $K_i$  values are shown with SEM in parentheses. <sup>b</sup> See the Experimental Section for details on the calculation of the polar surface area (PSA). <sup>c</sup> Displacement at a concentration of 10  $\mu$ M.

biaryls **39–47** (Scheme 1). Next, the benzylic position was converted into the corresponding bromide (**48–56**) using NBS.<sup>21</sup> Coupling of the biaryl bromides to purine **3** provided compounds **57–65**. To avoid problems in the bromination reaction due to the presence of two methyl groups in 2,2'-dimethylbiphenyl, a different approach was used for the synthesis of **69**. 2-Tolylboronic acid (**38**) was attached to 2-bromobenzyl alcohol (**66**) by a Suzuki reaction, yielding **67** (Scheme 2). Mesylation of the benzylic alcohol function and subsequent coupling to **3** provided **69**. Hydroxyl-substituted **70–72** were obtained by demethylation of **61–63** following the same procedure as described for the synthesis of **35** (Scheme 1).<sup>18</sup>

**Biological Studies.** Compounds were tested in a radioligand binding assay using human erythrocyte membranes as the source of the nucleoside transport protein and [<sup>3</sup>H]NBTI as the radioligand ( $K_D$  value:  $0.59 \pm 0.07$  nM). Compounds that inhibited radioligand binding for 50% or more at a single concentration of 10  $\mu$ M were further analyzed over a range of concentrations. Their IC<sub>50</sub> values were converted to  $K_i$  values, which are represented in Tables 1–3.

**Calculation of the Polar Surface Area and Molecular Modeling.** The polar surface areas of the molecules were calculated using Spartan 5.0 for SGI,<sup>22</sup> in combination with an in-house developed application called PolSurf 1.0. The PSA of NBTI (**1**) calculated in this way was 154 Å<sup>2</sup>.<sup>23</sup> The contributions of the ribose function and the 4-nitrobenzyl group to the total PSA value of NBTI were 77 Å<sup>2</sup> and 45 Å<sup>2</sup>, respectively. The PSA values for all compounds together with the biological data are represented in Tables 1–3.

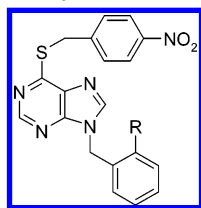
**Table 2.** <sup>a</sup>Affinities of Novel NBTI Analogues Carrying Substituted Benzyl Groups at the N<sup>9</sup>-Position



compd	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>	PSA (Å <sup>2</sup> ) <sup>b</sup>	K <sub>i</sub> (nM)
<b>4</b>	H	H	H	H	H	86	135 (± 30)
<b>10</b>	F	H	H	H	H	86	38% <sup>c</sup>
<b>11</b>	H	F	H	H	H	86	361 (± 108)
<b>12</b>	H	H	F	H	H	86	3340 (± 860)
<b>13</b>	F	F	H	H	H	86	32% <sup>c</sup>
<b>14</b>	F	H	F	H	H	86	4877 (± 1358)
<b>15</b>	F	H	H	F	H	86	1637 (± 1002)
<b>16</b>	F	H	H	H	F	86	32% <sup>c</sup>
<b>17</b>	H	F	F	H	H	86	653 (± 61)
<b>18</b>	H	F	H	F	H	86	1544 (± 89)
<b>19</b>	Cl	H	H	H	H	86	44% <sup>c</sup>
<b>20</b>	H	Cl	H	H	H	86	212 (± 62)
<b>21</b>	H	H	Cl	H	H	86	236 (± 36)
<b>22</b>	Cl	H	H	H	Cl	85	6% <sup>c</sup>
<b>23</b>	H	Cl	Cl	H	H	86	34% <sup>c</sup>
<b>24</b>	H	H	I	H	H	86	130 (± 21)
<b>25</b>	OMe	H	H	H	H	94	110 (± 16)
<b>26</b>	H	OMe	H	H	H	97	264 (± 43)
<b>27</b>	H	H	OMe	H	H	97	563 ± 91
<b>28</b>	H	OMe	H	OMe	H	108	47% <sup>c</sup>
<b>29</b>	NHBoc	H	H	H	H	122	422 (± 73)
<b>30</b>	Ph	H	H	H	H	86	281 (± 33)
<b>31</b>	H	CF <sub>3</sub>	H	H	H	86	2165 (± 221)
<b>32</b>	H	H	Me	H	H	86	711 (± 82)
<b>33</b>	H	H	NO <sub>2</sub>	H	H	129	200 (± 126)
<b>34</b>	H	H	OCF <sub>3</sub>	H	H	97	24% <sup>c</sup>
<b>35</b>	OH	H	H	H	H	101	39 (± 11)
<b>36</b>	H	OH	H	H	H	109	153 (± 33)
<b>37</b>	NH <sub>2</sub>	H	H	H	H	106	124 (± 8)

<sup>a</sup> Binding study: [<sup>3</sup>H]NBTI ( $K_D = 0.59$  nM) as radioligand and human erythrocyte membranes ( $n = 3$ ).  $K_i$  values are shown with SEM in parentheses. <sup>b</sup> See the Experimental Section for details on the calculation of the polar surface area (PSA). <sup>c</sup> Displacement at a concentration of 10  $\mu$ M.

The crystal structure of NBTI<sup>23</sup> (**1**) used for the illustrations in Figure 2 was retrieved from the Cambridge Structural Database<sup>24</sup> and imported into Spartan.<sup>25</sup> The structures of **35** and **36** were drawn and energy minimized in Spartan. The purine rings of NBTI and **35** or **36** were superimposed after which the benzyl ring was rotated to achieve an overlay between its hydroxyl function and either the 2'-, 3'-, or the 5'-OH of NBTI. The structures for NBTI and **35** with maximum overlay for the benzyl group and the ribose moiety are depicted in Figure 2.

**Table 3.** <sup>a</sup>Affinities of Biaryl-Substituted NBTI Analogues

compd	R	PSA (Å <sup>2</sup> ) <sup>b</sup>	K <sub>i</sub> (nM)
<b>30</b>	phenyl	86	281 (± 33)
<b>57</b>	2'-fluorophenyl	86	111 (± 8)
<b>58</b>	4'-fluorophenyl	85	93 (± 15)
<b>59</b>	3'-trifluoromethylphenyl	85	86 (± 11)
<b>60</b>	4'-trifluoromethylphenyl	85	39 (± 13)
<b>61</b>	2'-methoxyphenyl	96	225 (± 76)
<b>62</b>	3'-methoxyphenyl	96	221 (± 77)
<b>63</b>	4'-methoxyphenyl	96	104 (± 25)
<b>64</b>	2'-thiophene	86	129 (± 46)
<b>65</b>	3'-thiophene	86	89 (± 14)
<b>69</b>	2'-methylphenyl	85	126 (± 15)
<b>70</b>	2'-hydroxyphenyl	108	196 (± 78)
<b>71</b>	3'-hydroxyphenyl	109	196 (± 96)
<b>72</b>	4'-hydroxyphenyl	109	154 (± 58)

<sup>a</sup> Binding study: [<sup>3</sup>H]NBTI ( $K_D = 0.59$  nM) as radioligand and human erythrocyte membranes ( $n = 3$ ).  $K_i$  values are shown with SEM in parentheses. <sup>b</sup> See the Experimental Section for details on the calculation of the polar surface area (PSA).

## Results and Discussion

Parent compound **4** showed an affinity of 135 nM (Table 1). Elongation of the chain length between the purine and the phenyl ring (**5** and **6**) resulted in lower affinities. The presence of a pyridyl ring gave rise to much higher  $K_i$  values compared to benzyl-substituted **4**, independent of the position of the nitrogen atom. Compound **4** was also tested for its affinity for the adenosine receptor subtypes. It appeared to have little affinity for the human A<sub>1</sub>, A<sub>2A</sub>, and A<sub>3</sub> receptors (4%, 16%, and 37% radioligand displacement at 10 μM, respectively), indicating high selectivity for the nucleoside transport protein.

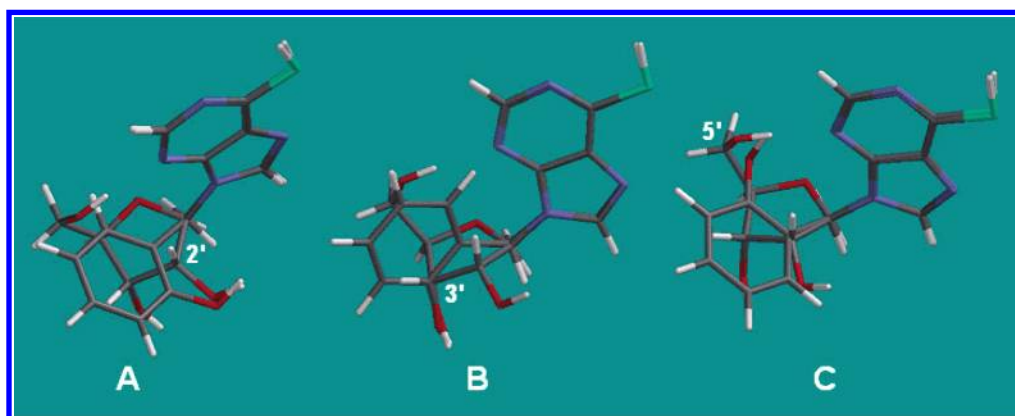
Next the effect of substitution of the *N*<sup>9</sup>-benzyl group was investigated. Therefore compounds **10–37** were prepared (Table 2). The presence of the strong electron-withdrawing fluoro group (**10–18**) decreased the affinity substantially. Fluoro substitution at the 3-position (**11**) gave the best affinity ( $K_i = 361$  nM), whereas 2-fluoro-substituted **10** proved the least favorable. A similar effect was observed for disubstituted compounds, such that all compounds carrying a fluoro at the 2-position

showed lower affinities than those (**17**, **18**) that did not. The same pattern was found for chloro-containing **19–23**. Substitution at the 3-position (**20**) or 4-position (**21**) gave the best  $K_i$  values, whereas 2-Cl derivative **19** was less active. Also, it seems that for mono-halogen-substituted compounds, the presence of a stronger electron-withdrawing halogen disfavors binding, since chlorinated **19–21** gave better results than fluorinated **10–12**. In line with the above 4-iodo substituted **24** proved better than both **12** (4-F) and **21** (4-Cl) and showed an affinity similar to that of **4**.

In contrast to what was found for the halogenated derivatives, methoxy substitution at the 2-position (**25**) showed a higher affinity (110 nM) than at the 3-position (**26**,  $K_i = 264$  nM), which in turn proved better than substitution at the 4-position (**27**,  $K_i = 563$  nM). Again disubstitution (**28**) proved less favorable.

The presence of a Boc-protected amino group (**29**) or a phenyl substituent (**30**) at the 2-position showed lower affinities than the 2-methoxy-substituted **25**, but considerably higher than the halogen-substituted compounds. In view of the size of an NHBoc group or of a phenyl ring, a large pocket seems to be present at the binding site. 3-Trifluoromethyl derivative **31** proved the least active of the 3-monosubstituted compounds, which might result from the highly electronegative nature of its substituent. 4-Methyl (**32**), 4-nitro (**33**), and 4-trifluoromethoxy (**34**) substitution provided lower affinities in comparison with unsubstituted **4**. 4-OCF<sub>3</sub> gave the poorest result of all 4-substituted compounds. 4-NO<sub>2</sub> substitution was equipotent to 4-Cl (**21**).

2-Hydroxy-substituted **35**, obtained by demethylation of **25**, gave the highest affinity of the tested compounds, with a  $K_i$  value of 39 nM. A possible explanation may be that the hydroxyl function of **35** interacts in a similar manner with ENT1 as one of the hydroxyl functions of the ribose moiety of NBTI (**1**). Overlaying the structures of NBTI<sup>23</sup> (**1**) and **35** showed that the hydroxyl function of **35** can be placed in close proximity to either the 2'-, the 3'-, and the 5'-hydroxyl function of NBTI. This superposition also shows that the volumes of both the ribose and the benzyl group are quite similar (150 Å<sup>3</sup> and 127 Å<sup>3</sup>, respectively, based on Spartan calculations). Six matching possibilities were found, two for each of the three hydroxyl functions of the ribose in which the ribose and the benzyl group either overlap or not. The cases in which the ribose and the benzyl overlapped are depicted in Figure 2. Most probable seems to be option



**Figure 2.** Overlaying structures of NBTI and compound **35**. See text for explanation. The nitrobenzyl group was omitted for reasons of clarity.<sup>25</sup>

B since it has been reported that the 3'-OH of NBTI is of major importance for high affinity.<sup>7</sup> Also, it has been demonstrated that the presence of either 2'- or 5'-deoxy ribose instead of an intact ribose moiety improved the affinity of adenosine derivatives, making options A and C less likely.<sup>26,27</sup> When we tried to superimpose NBTI<sup>23</sup> (**1**) and **36** no option was found in which the hydroxyl group of **36** coincided with one of the hydroxyl functions of the ribose moiety of NBTI. This might explain the lower affinity of 3-hydroxy-substituted **36** ( $K_i = 153$  nM) when compared to **35**.

An amino group at the 2-position (**37**) gave a 3-fold less potent compound in comparison to 2-hydroxy-substituted **35**, resulting in a similar affinity as parent compound **4**.

The relatively good affinity of **30** was further investigated by variation of the biphenyl group. Improved  $K_i$  values were found regardless of the nature of the substituent in comparison to **30** (Table 3). Substitution of the biaryl at the 2'- and 3'-position gave equipotent compounds whereas substitution at the 4'-position resulted in higher affinity. In contrast to the above, the presence of electron-withdrawing fluoro (**57**, **58**) and trifluoromethyl (**59**, **60**) improved the affinity in comparison to the unsubstituted biaryl compound **30**. Moreover, these compounds also showed better affinities than **4**. For compound **60**, a 7-fold improvement was found compared to unsubstituted **30**. Methoxy-substituted **61–63** also gave lower  $K_i$  values but to a lesser extent than **57–60**. Replacement of a phenyl ring by the smaller thiophene led to a 2- to 3-fold increased affinity, with a  $K_i$  value of 89 nM for 3'-thiophene-substituted **65**. 2'-Methyl substitution (**69**) showed 2-fold higher affinity than **30**. Hydroxy substitution (**70–72**) resulted in affinities comparable to those of the methoxy-substituted compounds.

With respect to the polar surface area, it is to be noted that all compounds have a much lower PSA value than NBTI.<sup>23</sup> In contrast to the latter, the synthesized ligands are within the range of the limits given for oral absorption. Moreover, taking into account the given maximum values for possible blood-brain barrier passage, most compounds may well be able to enter the CNS to some extent. In this respect, **60** is a particularly interesting compound with a PSA value of only 85 Å<sup>2</sup>, almost half of that of NBTI.

## Conclusions

In this study the search for less hydrophilic nucleoside transport inhibitors was addressed. Replacement of the ribose moiety of NBTI (**1**) by substituted benzyl functions was shown to greatly decrease the polarity. Most of the compounds presented have PSA values below 100 Å<sup>2</sup>. Generally, the biarylmethyl-substituted compounds proved to have higher affinities than the non-aryl-substituted benzyl compounds. Compound **35** carrying a 2-hydroxylbenzyl group at the  $N^9$ -position proved to be the most active compound for the first series ( $K_i = 39$  nM, PSA = 101 Å<sup>2</sup>). 4-Trifluoromethyl-substituted biphenylmethyl **60** showed the highest affinity for the  $N^9$ -biarylmethyl purines ( $K_i = 39$  nM, PSA = 85 Å<sup>2</sup>). Thus, despite the highly different character of a ribose and an (aryl)benzyl group,  $K_i$  values in the low nanomolar range were obtained. The substantial reduction

in polarity is likely to improve oral absorption and tissue distribution.

## Experimental Section

Column chromatography was performed on Baker Silica Gel (0.063–0.200 mm). For TLC analysis, Schleicher and Schuell F1500/LS 254 silica plates were used. Spots were visualized with ultraviolet light. <sup>1</sup>H NMR and <sup>13</sup>C NMR were recorded with a Bruker AC 200 spectrometer. Tetramethylsilane was used as internal standard;  $\delta$  in ppm,  $J$  in Hz. Melting points were determined with a Büchi melting point apparatus and are uncorrected. High-resolution mass spectroscopy was performed on a PE-Sciex API Qstar instrument. Microwave reactions were performed in an Emrys Optimizer.

The synthesis of compounds **10**, **11**, **13–19**, **22**, **24**, **28**, **30**, **34** has been published.<sup>28</sup> Boc-protected 2-aminobenzyl bromide for the formation of **29** was synthesized as described in the literature.<sup>17</sup>

**General Procedure A: Substitution at  $N^9$ .** To a well-stirred suspension of 40 mg of NaH (1 mmol, 60% dispersion in oil) in 4 mL of DMF was added 1 mmol of 6-(4-nitrobenzylsulfanyl)purine **3** (0.29 g). After stirring for 5 min, 1 mmol of the appropriate aryl halide was added and the reaction was left to stir overnight. After addition of 15 mL of water, the aqueous layer was extracted three times with 15 mL of EtOAc. The combined organic layers were dried (MgSO<sub>4</sub>), the solvent was evaporated, and the product was purified by column chromatography (eluent: mixtures of PE 40–60/EtOAc or CH<sub>2</sub>-Cl<sub>2</sub>/MeOH).

**General Procedure B: Demethylation of the Methoxy Groups.**<sup>18</sup> To a solution of 1 mmol of methoxybenzyl-substituted purine in 5 mL of dry CH<sub>2</sub>Cl<sub>2</sub> at –78 °C was added 3 mmol of BBr<sub>3</sub> (3 mL of a 1 M solution in CH<sub>2</sub>Cl<sub>2</sub>). The solution was allowed to slowly warm to rt. After stirring for 6 h, H<sub>2</sub>O and diethyl ether were added. The layers were separated, and the aqueous layer was extracted once more with diethyl ether. The combined layers were washed with brine and dried (MgSO<sub>4</sub>), and the solvent was evaporated. The product was purified by column chromatography (eluent: mixture of PE 40–60/EtOAc).

**General Procedure C: Coupling of Aromatic Rings by a Suzuki Reaction.**<sup>21</sup> To a solution of the aryl bromide (5 mmol) in 15 mL of toluene/EtOH (1/1, v/v) was added 0.17 g (0.14 mmol) of Pd(PPh<sub>3</sub>)<sub>4</sub>, and the mixture was stirred under nitrogen atmosphere. Then 2 M aqueous Na<sub>2</sub>CO<sub>3</sub> (7.5 mL) and 0.80 g (6 mmol) of 2-tolylboronic acid **38** were added. The mixture was refluxed at 80 °C for 1–2 days until reaction was completed (TLC). After cooling to rt, the product was extracted with EtOAc (2 × 25 mL). The organic layers were dried with MgSO<sub>4</sub>, filtered, and concentrated. Purification was performed by column chromatography using a mixture of PE 40–60/EtOAc.

**General Procedure D: Suzuki Reactions Performed in a Microwave.** The Suzuki reactions in the microwave were performed at 150 °C. TBAB (1 equiv), 2-tolylboronic acid **38** (1.2 equiv), Na<sub>2</sub>CO<sub>3</sub> (1.8 equiv), and H<sub>2</sub>O (2 mL) were added to the appropriate aryl bromide. Pd(PPh<sub>3</sub>)<sub>4</sub> was used as the catalyst. The reaction mixtures were extracted with EtOAc, dried (MgSO<sub>4</sub>), filtered, and concentrated. Products were purified by column chromatography using PE 40–60/EtOAc (99/1, v/v).

**General Procedure E: Bromination at the Benzylic Position.**<sup>21</sup> To a stirred solution of the appropriately substituted toluene in CCl<sub>4</sub> (10 mL per mmol) were added 0.95 equiv of NBS and benzoyl peroxide (5 mg per mmol). The reaction mixture was refluxed at 80 °C for about 40 h and then cooled to rt, filtered, and concentrated. The product was used without further purification.

**6-(4-Nitrobenzylsulfanyl)purine (**3**).** To 30 mmol of 6-mercaptapurine (**2**) in 25 mL of DMF were added 30 mmol of K<sub>2</sub>CO<sub>3</sub> and, after 5 min, 30 mmol of 4-nitrobenzyl bromide. After stirring for 4 h, 200 mL of H<sub>2</sub>O was added, the suspension filtered, the solid washed with EtOAc and CH<sub>2</sub>Cl<sub>2</sub> and dried in vacuo. Yield: 98%. White powder. Mp 239 °C

(decomp), lit.: 244–247 °C,<sup>29</sup> 262 °C.<sup>30</sup> <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  = 4.80 (s, 2H, CH<sub>2</sub>S), 7.76 (d, 2H, *J* = 8.8, CH arom), 8.18 (d, 2H, *J* = 8.8, CH arom), 8.48 (s, 1H, *H*-2), 8.74 (s, 1H, *H*-8). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>)  $\delta$  = 30.7, 123.5, 129.2, 130.2, 143.7, 146.5, 146.6, 150.5, 151.4, 156.5.

**9-Benzyl-6-(4-nitrobenzylsulfanyl)purine (4).** This compound was prepared according to general procedure A applying benzyl bromide. Yield: 37%. Yellowish solid. Mp 139 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 4.73 (s, 2H, CH<sub>2</sub>S), 5.41 (s, 2H, CH<sub>2</sub>N), 7.26–7.39 (m, 5H, CH arom), 7.66 (d, 2H, *J* = 8.8, CH arom), 7.95 (s, 1H, *H*-2), 8.15 (d, 2H, *J* = 8.8, CH arom), 8.77 (s, 1H, *H*-8). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  = 31.6, 47.3, 123.5, 127.7, 128.6, 129.0, 129.9, 130.9, 134.9, 142.8, 145.7, 146.9, 148.7, 151.8, 159.0. HRMS (ESI) *m/z* Found: 378.0981 [M + H]<sup>+</sup>, Calcd: 378.1024. Elem. anal. (C<sub>19</sub>H<sub>15</sub>N<sub>5</sub>O<sub>2</sub>S·0.1EtOAc) C, H, N, S.

**9-(2-Phenethyl)-6-(4-Nitrobenzylsulfanyl)purine (5).** This compound was prepared according to general procedure A applying (2-bromoethyl)benzene. Yield: 61%. White solid. Mp 137 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 3.17 (t, 2H, *J* = 6.9, CH<sub>2</sub>Ph), 4.49 (t, 2H, *J* = 6.9, CH<sub>2</sub>N), 4.71 (s, 2H, CH<sub>2</sub>S), 7.02–7.09 (m, 2H, CH arom), 7.23–7.32 (m, 3H, CH arom), 7.59 (s, 1H, *H*-2), 7.64 (d, 2H, *J* = 8.8, CH arom), 8.14 (d, 2H, *J* = 8.8, CH arom), 8.75 (s, 1H, *H*-8). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  = 31.6, 35.9, 45.4, 123.5, 127.0, 128.5, 128.7, 129.9, 131.0, 136.9, 143.0, 145.7, 146.9, 148.5, 151.6, 158.8. HRMS (ESI) *m/z* Found: 392.1190 [M + H]<sup>+</sup>, Calcd: 392.1181. Elem. anal. (C<sub>20</sub>H<sub>17</sub>N<sub>5</sub>O<sub>2</sub>S) C, H, N, S.

**6-(4-Nitrobenzylsulfanyl)-9-(3-phenylpropyl)purine (6).** This compound was prepared according to general procedure A applying (3-bromopropyl)benzene. Yield: 69%. White solid. Mp 130 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 2.27 (quint., 2H, *J* = 7.3, CH<sub>2</sub>CH<sub>2</sub>Ph), 2.67 (t, 2H, *J* = 7.3, CH<sub>2</sub>Ph), 4.26 (t, 2H, *J* = 7.3, CH<sub>2</sub>N), 4.72 (s, 2H, CH<sub>2</sub>S), 7.12–7.34 (m, 5H, CH arom), 7.64 (d, 2H, *J* = 9.1, CH arom), 7.92 (s, 1H, *H*-2), 8.15 (d, 2H, *J* = 9.1, CH arom), 8.74 (s, 1H, *H*-8). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  = 30.8, 31.4, 32.4, 43.3, 123.3, 126.1, 128.0, 128.3, 129.7, 130.9, 139.8, 142.9, 145.6, 146.7, 148.6, 151.4, 158.7. HRMS (ESI) *m/z* Found: 406.1292 [M + H]<sup>+</sup>, Calcd: 406.1337. Elem. anal. (C<sub>21</sub>H<sub>19</sub>N<sub>5</sub>O<sub>2</sub>S) C, H, N, S.

**6-(4-Nitrobenzylsulfanyl)-9-(pyridin-2-ylmethyl)purine (7).** This compound was prepared according to general procedure A applying 2-(bromomethyl)pyridine hydrobromide. Additional NaH (1 equiv) was added to the reaction mixture after 10 min. Yield: 32%. White solid. Mp 152 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 4.72 (s, 2H, CH<sub>2</sub>S), 5.53 (s, 2H, CH<sub>2</sub>N), 7.21–7.30 (m, 2H, CH arom), 7.62–7.71 (m, 3H, CH arom), 8.15 (d, 2H, *J* = 8.8, CH arom), 8.19 (s, 1H, *H*-2), 8.56 (ddd, 1H, *J* = 0.7, *J* = 1.5, *J* = 4.8, CH arom), 8.74 (s, 1H, *H*-8). <sup>13</sup>C NMR (CDCl<sub>3</sub>/MeOD)  $\delta$  = 31.0, 47.8, 122.0, 123.0, 129.5, 137.2, 143.7, 145.4, 146.3, 147.9, 148.9, 151.3, 153.7, 158.8. HRMS (ESI) *m/z* Found: 379.0989 [M + H]<sup>+</sup>, Calcd: 379.0971. Elem. Anal. found C 57.61, H 3.41, N 21.61, S 7.91, calcd for C<sub>18</sub>H<sub>14</sub>N<sub>6</sub>O<sub>2</sub>S C 57.13, H 3.73, N 22.21, S 8.47.

**6-(4-Nitrobenzylsulfanyl)-9-(pyridin-3-ylmethyl)purine (8).** This compound was prepared according to general procedure A applying 3-(bromomethyl)pyridine hydrobromide. Additional NaH (1 equiv) was added to the reaction mixture after 10 min. Yield: 29%. Yellowish solid. Mp 159–160 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 4.72 (s, 2H, CH<sub>2</sub>S), 5.44 (s, 2H, CH<sub>2</sub>N), 7.25–7.31 (m, 1H, CH arom), 7.55–7.68 (m, 3H, CH arom), 7.99 (s, 1H, *H*-2), 8.15 (d, 2H, *J* = 8.8, CH arom), 8.58–8.62 (m, 1H, CH arom), 8.65 (br s, 1H, CH arom), 8.76 (s, 1H, *H*-8). <sup>13</sup>C NMR (CDCl<sub>3</sub>/MeOD, 1/1)  $\delta$  = 31.1, 44.3, 123.0, 123.8, 129.5, 130.1, 131.3, 136.1, 143.0, 145.4, 146.5, 148.0, 148.1, 148.6, 151.5, 159.0. HRMS (ESI) *m/z* Found: 379.0948 [M + H]<sup>+</sup>, Calcd: 379.0971. Elem. Anal. found C 57.09, H 3.17, N 21.89, S 8.03, calcd for C<sub>18</sub>H<sub>14</sub>N<sub>6</sub>O<sub>2</sub>S C 57.13, H 3.73, N 22.21, S 8.47.

**6-(4-Nitrobenzylsulfanyl)-9-(pyridin-4-ylmethyl)purine (9).** This compound was prepared according to general procedure A applying 4-(bromomethyl)pyridine hydrobromide. Additional NaH (1 equiv) was added to the reaction mixture after 10 min. Yield: 40%. Yellow solid. Mp 187–188 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  = 4.80 (s, 2H, CH<sub>2</sub>S), 5.77 (s, 2H, CH<sub>2</sub>N), 7.21–7.24 (m, 2H, CH arom), 7.76 (d, 2H, *J* = 8.8, CH arom), 8.18 (d, 2H, *J* = 8.8, CH arom), 8.50–8.54 (m, 2H, CH arom),

8.65 (s, 1H, *H*-2), 8.76 (s, 1H, *H*-8). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>)  $\delta$  = 30.8, 45.6, 122.1, 123.6, 130.3, 131.0, 145.2, 145.2, 146.5, 148.7, 150.1, 151.7, 158.2. HRMS (ESI) *m/z* Found: 379.0950 [M + H]<sup>+</sup>, Calcd: 379.0971. Elem. anal. (C<sub>18</sub>H<sub>14</sub>N<sub>6</sub>O<sub>2</sub>S·0.15 CH<sub>2</sub>Cl<sub>2</sub>) C, H, N, S.

**9-(4-Fluorobenzyl)-6-(4-nitrobenzylsulfanyl)purine (12).** This compound was prepared according to general procedure A applying 4-fluorobenzyl bromide. Yield: 63%. Off-white solid. Mp 149 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 4.72 (s, 2H, CH<sub>2</sub>S), 5.38 (s, 2H, CH<sub>2</sub>N), 7.04 (t, 2H, *J* = 8.6, CH arom), 7.26–7.33 (m, 2H, CH arom), 7.65 (d, 2H, *J* = 8.8, CH arom), 7.95 (s, 1H, *H*-2), 8.16 (d, 2H, *J* = 8.8, CH arom), 8.76 (s, 1H, *H*-8). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  = 31.7, 46.6, 116.0 (d, *J* = 21), 123.6, 129.7 (d, *J* = 9), 129.9, 130.8 (d, *J* = 3), 131.0, 142.6, 145.7, 146.9, 148.7, 151.9, 159.0, 162.3 (d, *J* = 247). <sup>19</sup>F NMR (CDCl<sub>3</sub>)  $\delta$  = -35.4. HRMS (ESI) *m/z* Found: 396.0899 [M + H]<sup>+</sup>, Calcd: 396.0930. Elem. anal. (C<sub>19</sub>H<sub>14</sub>FN<sub>5</sub>O<sub>2</sub>S·0.1EtOAc) C, H, N, S.

**9-(3-Chlorobenzyl)-6-(4-nitrobenzylsulfanyl)purine (20).** This compound was prepared according to general procedure A applying 3-chlorobenzyl chloride. Yield: 56%. Yellow solid. Mp 139 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 4.72 (s, 2H, CH<sub>2</sub>S), 5.39 (s, 2H, CH<sub>2</sub>N), 7.18–7.31 (m, 4H, CH arom), 7.66 (d, 2H, *J* = 8.4, CH arom), 7.97 (s, 1H, *H*-2), 8.15 (d, 2H, *J* = 8.4, CH arom), 8.77 (s, 1H, *H*-8). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  = 31.7, 46.7, 123.6, 125.8, 127.8, 128.8, 129.9, 130.4, 135.0, 137.0, 139.1, 142.6, 147.0, 148.7, 155.5, 161.3. HRMS (ESI) *m/z* Found: 412.0606 [M + H]<sup>+</sup>, Calcd: 412.0635. Elem. anal. (C<sub>19</sub>H<sub>14</sub>ClN<sub>5</sub>O<sub>2</sub>S·0.25hexane) C, H, N, S.

**9-(4-Chlorobenzyl)-6-(4-nitrobenzylsulfanyl)purine (21).** This compound was prepared according to general procedure A applying 4-chlorobenzyl chloride. Yield: 61%. White solid. Mp 170 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 4.73 (s, 2H, CH<sub>2</sub>S), 5.39 (s, 2H, CH<sub>2</sub>N), 7.22 (d, 2H, *J* = 8.8, CH arom), 7.33 (d, 2H, *J* = 8.8, CH arom), 7.66 (d, 2H, *J* = 8.8, CH arom), 7.97 (s, 1H, *H*-2), 8.15 (d, 2H, *J* = 8.8, CH arom), 8.77 (s, 1H, *H*-8). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  = 31.7, 47.7, 123.6, 129.1, 129.2, 129.9, 130.9, 144.5, 134.6, 142.6, 145.5, 148.7, 152.0, 159.3. HRMS (ESI) *m/z* Found: 412.0629 [M + H]<sup>+</sup>, Calcd: 412.0635. Elem. anal. (C<sub>19</sub>H<sub>14</sub>ClN<sub>5</sub>O<sub>2</sub>S·0.2EtOAc) C, H, N, S.

**9-(3,4-Dichlorobenzyl)-6-(4-nitrobenzylsulfanyl)purine (23).** This compound was prepared according to general procedure A applying 3,4-dichlorobenzyl chloride. Yield: 67%. Off-white solid. Mp 171 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 4.74 (s, 2H, CH<sub>2</sub>S), 5.39 (s, 2H, CH<sub>2</sub>N), 7.15 (dd, 2H, *J* = 2.2, *J* = 8.0, CH arom), 7.41 (d, 1H, *J* = 2.2, CH arom), 7.43 (d, 1H, *J* = 8.0, CH arom), 7.66 (d, 2H, *J* = 8.8, CH arom), 8.06 (s, 1H, *H*-2), 8.16 (d, 2H, *J* = 8.8, CH arom), 8.77 (s, 1H, *H*-8). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>)  $\delta$  = 30.7, 45.5, 123.4, 128.1, 129.9, 130.1, 130.4, 130.7, 130.8, 131.3, 137.2, 144.8, 146.3, 146.4, 148.4, 151.5, 158.1. HRMS (ESI) *m/z* Found: 446.0233 [M + H]<sup>+</sup>, Calcd: 446.0245. Elem. anal. Calcd for C<sub>19</sub>H<sub>13</sub>Cl<sub>2</sub>N<sub>5</sub>O<sub>2</sub>S: C 51.13, H 0.94, N 15.69, S 7.18. Found: C 51.27, H 2.45, N 15.41, S 6.81.

**9-(2-Methoxybenzyl)-6-(4-nitrobenzylsulfanyl)purine (25).** This compound was prepared according to general procedure A applying 2-methoxybenzyl chloride. Yield: 52%. White solid. Mp 164 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 3.85 (s, 3H, CH<sub>3</sub>), 4.70 (s, 2H, CH<sub>2</sub>S), 5.39 (s, 2H, CH<sub>2</sub>N), 6.82–6.98 (m, 2H, CH arom), 7.33 (d, 2H, *J* = 7.3, CH arom), 7.63 (d, 2H, *J* = 8.8, CH arom), 8.05 (s, 1H, *H*-2), 8.12 (d, 2H, *J* = 8.8, CH arom), 8.74 (s, 1H, *H*-8). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  = 31.6, 42.9, 55.3, 110.5, 120.7, 123.0, 123.5, 129.9, 130.2, 130.4, 130.9, 143.7, 145.8, 146.7, 148.8, 151.6, 157.2, 158.5. HRMS (ESI) *m/z* Found: 408.1123 [M + H]<sup>+</sup>, Calcd: 408.1130. Elem. anal. (C<sub>20</sub>H<sub>17</sub>N<sub>5</sub>O<sub>3</sub>S) C, H, N, S.

**9-(3-Methoxybenzyl)-6-(4-nitrobenzylsulfanyl)purine (26).** This compound was prepared according to general procedure A applying 3-methoxybenzyl chloride. Yield: 52%. White solid. Mp 126 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 3.77 (s, 3H, CH<sub>3</sub>O), 4.72 (s, 2H, CH<sub>2</sub>S), 5.38 (s, 2H, CH<sub>2</sub>N), 6.78–6.92 (m, 3H, CH arom), 7.22–7.33 (m, 1H, CH arom), 7.65 (d, 2H, *J* = 8.8, CH arom), 7.95 (s, 1H, *H*-2), 8.15 (d, 2H, *J* = 8.8, CH arom), 8.77 (s, 1H, *H*-8). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  = 31.5, 47.1, 55.0, 113.4, 119.7, 123.4, 129.8, 130.0, 130.8, 136.7, 142.8,

145.6, 146.7, 148.6, 151.7, 158.8, 159.8. HRMS (ESI)  $m/z$  Found: 408.1124  $[M + H]^+$ , Calcd: 408.1130. Elem. anal. ( $C_{20}H_{17}N_5O_3S \cdot 0.05\text{hexane}$ ) C, H, N, S.

**9-(4-Methoxybenzyl)-6-(4-nitrobenzylsulfanyl)-purine (27).** This compound was prepared according to general procedure A applying 4-methoxybenzyl chloride. Yield: 59%. White solid. Mp 153 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 3.79 (s, 3H,  $\text{OCH}_3$ ), 4.72 (s, 2H,  $\text{CH}_2\text{S}$ ), 5.34 (s, 2H,  $\text{CH}_2\text{N}$ ), 6.87 (d, 2H,  $J$  = 8.8,  $\text{CH}$  arom), 7.25 (d, 2H,  $J$  = 8.8,  $\text{CH}$  arom), 7.65 (d, 2H,  $J$  = 8.8,  $\text{CH}$  arom), 7.93 (s, 1H,  $H-2$ ), 8.14 (d, 2H,  $J$  = 8.8,  $\text{CH}$  arom), 8.77 (s, 1H,  $H-8$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 31.6, 46.9, 55.1, 114.3, 123.5, 126.9, 129.3, 129.8, 131.0, 142.7, 145.7, 146.9, 148.6, 151.7, 158.8, 159.6. HRMS (ESI)  $m/z$  Found: 408.1123  $[M + H]^+$ , Calcd: 408.1130. Elem. anal. ( $C_{20}H_{17}N_5O_3S \cdot 0.15\text{hexane}$ ) C, H, N, S.

**9-(2'-tert-Butyloxocarbonylamino-6-(4-nitrobenzylsulfanyl)benzyl)purine (29).** This compound was prepared according to general procedure A applying Boc-protected 2'-amino-benzyl bromide.<sup>17</sup> Yield 27%. Off-white solid. Mp 77 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 1.56 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 4.71 (s, 2H,  $\text{CH}_2\text{S}$ ), 5.35 (s, 2H,  $\text{CH}_2\text{N}$ ), 7.08 (dt, 1H,  $J$  = 1.5,  $J$  = 7.7,  $\text{CH}$  arom), 7.27–7.38 (m, 2H,  $\text{CH}$  arom), 7.64 (d, 2H,  $J$  = 8.8,  $\text{CH}$  arom), 7.75 (d, 1H,  $J$  = 8.0,  $\text{CH}$  arom), 8.09 (s, 1H,  $H-2$ ), 8.15 (d, 1H,  $J$  = 8.8,  $\text{CH}$  arom), 8.72 (s, 1H,  $H-8$ ), 9.02 (br s, 1H,  $\text{NH}$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 28.2, 31.6, 44.2, 80.1, 123.6, 124.2, 124.6, 126.1, 129.9, 130.2, 137.0, 142.7, 145.5, 151.3, 153.8. Elem. anal. ( $\text{C}_{24}\text{H}_{24}\text{N}_6\text{O}_4\text{S} \cdot 0.4\text{CH}_2\text{Cl}_2$ ) C, H, N.

**6-(4-Nitrobenzylsulfanyl)-9-(3-trifluoromethylbenzyl)-purine (31).** This compound was prepared according to general procedure A applying 3-trifluoromethylbenzyl bromide. Yield: 56%. White solid. Mp 147 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 4.73 (s, 2H,  $\text{CH}_2\text{S}$ ), 5.48 (s, 2H,  $\text{CH}_2\text{N}$ ), 7.46–7.61 (m, 4H,  $\text{CH}$  arom), 7.61 (d, 2H,  $J$  = 8.8,  $\text{CH}$  arom), 7.99 (s, 1H,  $H-2$ ), 8.16 (d, 2H,  $J$  = 8.8,  $\text{CH}$  arom), 8.77 (s, 1H,  $H-8$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 31.6, 46.7, 123.5, 123.7 (q,  $J$  = 272), 124.4 (q,  $J$  = 4), 125.2 (q,  $J$  = 4), 129.6, 129.8, 130.8, 131.0, 131.2 (q,  $J$  = 33), 136.1, 142.6, 145.6, 146.8, 148.6, 151.9, 159.2.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 14.6. HRMS (ESI)  $m/z$  Found: 446.0923  $[M + H]^+$ , Calcd: 446.0899. Elem. anal. ( $\text{C}_{20}\text{H}_{14}\text{F}_3\text{N}_5\text{O}_2\text{S} \cdot 0.1\text{hexane}$ ) C, H, N, S.

**9-(4-Methylbenzyl)-6-(4-nitrobenzylsulfanyl)purine (32).** This compound was prepared according to general procedure A applying 4-methylbenzyl chloride. Yield: 61%. White solid. Mp 152 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 2.33 (s, 3H,  $\text{CH}_3$ ), 4.72 (s, 2H,  $\text{CH}_2\text{S}$ ), 5.36 (s, 2H,  $\text{CH}_2\text{N}$ ), 7.14 (d, 2H,  $J$  = 8.8,  $\text{CH}$  arom), 7.20 (d, 2H,  $J$  = 8.8,  $\text{CH}$  arom), 7.65 (d, 2H,  $J$  = 8.8,  $\text{CH}$  arom), 7.94 (s, 1H,  $H-2$ ), 8.14 (d, 2H,  $J$  = 8.8,  $\text{CH}$  arom), 8.77 (s, 1H,  $H-8$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 19.9, 31.7, 47.2, 123.6, 127.8, 129.7, 129.9, 131.0, 131.8, 138.5, 142.8, 145.7, 147.0, 148.8, 151.9, 157.9. HRMS (ESI)  $m/z$  Found: 392.1157  $[M + H]^+$ , Calcd: 392.1181. Elem. anal. ( $\text{C}_{20}\text{H}_{17}\text{N}_5\text{O}_2\text{S} \cdot 0.1\text{hexane}$ ) C, H, N, S.

**9-(4-Nitrobenzyl)-6-(4-nitrobenzylsulfanyl)purine (33).** This compound was prepared according to general procedure A applying 4-nitrobenzyl bromide. Yield: 40%. White solid. Mp 182 °C.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  = 4.81 (s, 2H,  $\text{CH}_2\text{S}$ ), 5.67 (s, 2H,  $\text{CH}_2\text{N}$ ), 7.57 (d, 2H,  $J$  = 8.8,  $\text{CH}$  arom), 7.77 (d, 2H,  $J$  = 8.8,  $\text{CH}$  arom), 8.16–8.23 (m, 4H,  $\text{CH}$  arom), 8.69 (s, 1H,  $H-2$ ), 8.77 (s, 1H,  $H-8$ ).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  = 30.8, 46.1, 123.6, 124.0, 128.7, 130.3, 143.9, 145.2, 146.5, 147.2, 148.6, 151.7, 158.3. HRMS (ESI)  $m/z$  Found: 423.0828  $[M + H]^+$ , Calcd: 423.0870. Elem. Anal. ( $\text{C}_{19}\text{H}_{14}\text{N}_6\text{O}_4\text{S} \cdot 0.1\text{CH}_2\text{Cl}_2$ ) C, H, N, S.

**9-(2-Hydroxybenzyl)-6-(4-nitrobenzylsulfanyl)-purine (35).** This compound was prepared from 25 according to general procedure B. Yield: 66%. White solid. Mp 201 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 4.74 (s, 2H,  $\text{CH}_2\text{S}$ ), 5.41 (s, 2H,  $\text{CH}_2\text{N}$ ), 6.75–6.88 (m, 2H,  $\text{CH}$  arom), 7.12–7.23 (m, 1H,  $\text{CH}$  arom), 7.33 (d, 1H,  $J$  = 8.0,  $\text{CH}$  arom), 7.69 (d, 2H,  $J$  = 8.8,  $\text{CH}$  arom), 8.15 (d, 2H,  $J$  = 8.8,  $\text{CH}$  arom), 8.28 (s, 1H,  $H-2$ ), 8.75 (s, 1H,  $H-8$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 30.6, 42.6, 115.2, 119.0, 122.1, 123.6, 129.4, 129.5, 130.2, 145.4, 146.5, 148.6, 151.4, 155.2, 157.7. HRMS (ESI)  $m/z$  Found: 394.0938  $[M + H]^+$ , Calcd: 394.0973. Elem. anal. ( $\text{C}_{19}\text{H}_{15}\text{N}_5\text{O}_3\text{S} \cdot 0.2\text{CH}_2\text{Cl}_2$ ) C, H, N, S.

**9-(3-Hydroxybenzyl)-6-(4-nitrobenzylsulfanyl)-purine (36).** This compound was prepared according to

general procedure A applying 3-hydroxybenzyl iodide, which was prepared by stirring 3-hydroxybenzyl alcohol overnight in dioxane in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$  (1 equiv) and KI (1 equiv).<sup>31</sup> Yield: 56%. White solid. Mp 183–184 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3/\text{MeOD}$ , 3/1)  $\delta$  = 4.74 (s, 2H,  $\text{CH}_2\text{S}$ ), 5.37 (s, 2H,  $\text{CH}_2\text{N}$ ), 6.74–6.82 (m, 3H,  $\text{CH}$  arom), 7.18 (t, 1H,  $J$  = 8.0, 1H,  $\text{CH}$  arom), 7.45 (s, 1H,  $H-2$ ), 7.69 (d, 2H,  $J$  = 8.8,  $\text{CH}$  arom), 8.11 (s, 1H,  $H-8$ ), 8.16 (d, 2H,  $J$  = 8.8,  $\text{CH}$  arom).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 31.9, 47.1, 114.4, 115.3, 118.6, 123.3, 129.7, 129.9, 136.0, 143.2, 145.5, 146.7, 148.2, 151.5, 157.3. HRMS (ESI)  $m/z$  Found: 394.0926  $[M + H]^+$ , Calcd: 394.0974. Elem. anal. ( $\text{C}_{19}\text{H}_{15}\text{N}_5\text{O}_3\text{S} \cdot 0.1\text{EtOAc}$ ) C, H, N.

**9-(2-Aminobenzyl)-6-(4-nitrobenzylsulfanyl)purine (37).** Compound 29 (0.12 mmol) was dissolved in 2 mL of a mixture of TFA and  $\text{H}_2\text{O}$  (5/2, v/v) and stirred for 7 h at rt.<sup>19</sup> The solvents were evaporated, and the product was purified by column chromatography (eluent: EtOAc). Yield: 76%. Yellow solid. Mp 137 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 4.70 (s, 2H,  $\text{CH}_2\text{S}$ ), 5.48 (s, 2H,  $\text{CH}_2\text{N}$ ), 7.26–7.46 (m, 4H,  $\text{CH}$  arom), 7.59 (d, 2H,  $J$  = 8.8,  $\text{CH}$  arom), 8.15 (d, 2H,  $J$  = 8.8,  $\text{CH}$  arom), 8.36 (s, 1H,  $H-2$ ), 8.76 (s, 1H,  $H-8$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 31.8, 44.0, 113.7, 123.1, 123.5, 126.0, 127.6, 129.8, 131.0, 131.5, 133.0, 144.6, 151.1, 160.8. HRMS (ESI)  $m/z$  Found: 393.1082  $[M + H]^+$ , Calcd: 393.1128. Elem. anal. ( $\text{C}_{19}\text{H}_{16}\text{N}_6\text{O}_2\text{S} \cdot 0.2\text{EtOAc}$ ) C, H, N, S.

**2-Fluoro-2'-methylbiphenyl (39).** This compound was prepared according to general procedure D applying 2-bromofluorobenzene. Reaction time: 5 min. Yield: 68%. Colorless oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 2.20 (s, 3H,  $\text{CH}_3$ ), 7.11–7.34 (m, 8H,  $\text{CH}$  arom).

**4-Fluoro-2'-methylbiphenyl (40).** This compound was prepared according to general procedure D applying 4-bromofluorobenzene. Reaction time: 5 min. Yield: 73%. Colorless liquid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 2.24 (s, 3H,  $\text{CH}_3$ ), 7.04–7.12 (m, 2H,  $\text{CH}$  arom), 7.17–7.30 (m, 6H,  $\text{CH}$  arom).

**2'-Methyl-3-trifluoromethylbiphenyl (41).** This compound was prepared according to general procedure D applying 3-bromobenzotrifluoride. Reaction time: 5 min. Yield: 72%. Colorless oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 2.25 (s, 3H,  $\text{CH}_3$ ), 7.19–7.28 (m, 4H,  $\text{CH}$  arom), 7.48–7.59 (m, 4H,  $\text{CH}$  arom).

**2'-Methyl-4-trifluoromethylbiphenyl (42).** This compound was prepared according to general procedure D applying 4-bromobenzotrifluoride. Reaction time: 5 min. Yield: 88%. Colorless liquid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 2.25 (s, 3H,  $\text{CH}_3$ ), 7.22–7.28 (m, 4H,  $\text{CH}$  arom), 7.42 (d, 2H,  $J$  = 8.0,  $\text{CH}$  arom), 7.66 (d, 2H,  $J$  = 7.7,  $\text{CH}$  arom).

**2-Methoxy-2'-methylbiphenyl (43).** This compound was prepared according to general procedure C applying 2-bromoanisole. Yield: 32%. Colorless liquid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 2.13 (s, 3H,  $\text{CH}_3$ ), 3.72 (s, 3H,  $\text{OCH}_3$ ), 6.91–7.03 (m, 2H,  $\text{CH}$  arom), 7.11–7.36 (m, 6H,  $\text{CH}$  arom).

**3-Methoxy-2'-methylbiphenyl (44).** This compound was prepared according to general procedure C applying 3-bromoanisole. Yield: 74%. Colorless liquid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 2.26 (3s, 3H,  $\text{CH}_3$ ), 3.75 (s, 3H,  $\text{OCH}_3$ ), 6.86 (m, 3H,  $\text{CH}$  arom), 7.25 (m, 5H,  $\text{CH}$  arom).

**4-Methoxy-2'-methylbiphenyl (45).** This compound was prepared according to general procedure C applying 4-bromoanisole. Yield: 58% (95% pure), colorless liquid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 2.25 (s, 3H,  $\text{CH}_3$ ), 3.78 (s, 3H,  $\text{OCH}_3$ ), 6.91 (d, 2H,  $J$  = 8.8,  $\text{CH}$  arom), 7.19–7.24 (m, 6H,  $\text{CH}$  arom).

**2-(2'-Thiophene)-toluene (46).** This compound was prepared according to general procedure C applying 2-bromothiophene. Reaction time: 2 h. Yield: 69%. Blue-ish liquid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 2.51 (s, 3H,  $\text{CH}_3$ ), 7.12–7.17 (m, 2H,  $\text{CH}$  arom), 7.24–7.32 (m, 4H,  $\text{CH}$  arom), 7.38–7.40 (m, 1H,  $\text{CH}$  arom), 7.47–7.48 (m, 1H,  $\text{CH}$  arom).

**2-(3'-Thiophene)-toluene (47).** This compound was prepared according to general procedure C applying 3-bromothiophene. Reaction time: 2 h. Yield: 69%. Colorless liquid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 2.31 (s, 3H,  $\text{CH}_3$ ), 7.22 (m, 7H,  $\text{CH}$  arom).

**2'-Bromomethyl-2-fluorobiphenyl (48).** This compound was prepared from 39 according to general procedure E. Yellow oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 4.40 (s, 2H,  $\text{CH}_2\text{Br}$ ), 7.15–7.43 (m,

7H, CH<sub>arom</sub>), 7.52–7.57 (m, 1H, CH<sub>arom</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 31.7, 113.6, 115.5, 124.1, 127.9, 128.4, 128.6, 129.6, 129.8, 130.6, 130.9, 131.6, 197.6.

**2'-Bromomethyl-4-fluorobiphenyl (49).** This compound was prepared from **40** according to general procedure E. Yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 4.41 (s, 2H, CH<sub>2</sub>Br), 7.11–7.23 (m, 3H, m, CH<sub>arom</sub>), 7.32–7.51 (m, 5H, CH<sub>arom</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 32.0, 115.0, 115.4, 128.1, 128.6, 129.5, 130.5, 130.7, 130.9, 197.4.

**2-Bromomethyl-3'-trifluoromethylbiphenyl (50).** This compound was prepared from **41** according to general procedure E. Yellow oil. <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 31.5, 124.3, 125.9, 128.6, 128.8, 130.3, 131.1, 132.3, 135.2, 140.5, 140.9.

**2-Bromomethyl-4'-trifluoromethylbiphenyl (51).** This compound was prepared from **42** according to general procedure E. Yellow crystals. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 4.39 (s, 2H, CH<sub>2</sub>Br), 7.31–7.44 (m, 2H, CH<sub>arom</sub>), 7.50–7.59 (m, 4H, CH<sub>arom</sub>), 7.69–7.73 (d, 2H, J = 8.0, CH<sub>arom</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 31.6, 125.3, 128.7, 129.4, 130.2, 131.1.

**2-Bromomethyl-2'-methoxybiphenyl (52).** This compound was prepared from **43** according to general procedure E. Orange oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 3.70 (s, 3H, OCH<sub>3</sub>), 4.35 (AB, 2H, J = 9.9, CH<sub>2</sub>Br), 6.92–7.06 (m, 2H, CH<sub>arom</sub>), 7.17–7.36 (m, 5H, CH<sub>arom</sub>), 7.49–7.54 (m, 1H, CH<sub>arom</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 32.2, 55.3, 110.6, 120.5, 125.3, 127.2, 127.8, 128.1, 129.1, 130.1, 130.7, 131.1, 136.1, 156.2.

**2-Bromomethyl-3'-methoxybiphenyl (53).** This compound was prepared from **44** according to general procedure E. Colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 3.80 (s, 3H, CH<sub>3</sub>O), 4.43 (s, 2H, CH<sub>2</sub>Br), 6.89–7.03 (m, 3H, CH<sub>arom</sub>), 7.22–7.36 (m, 4H, CH<sub>arom</sub>), 7.46–7.49 (m, 1H, CH<sub>arom</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 32.2, 55.1, 114.1, 121.2, 125.5, 127.1, 127.9, 128.4, 129.2, 130.1, 130.8, 135.0, 141.4, 141.8.

**2-Bromomethyl-4'-methoxybiphenyl (54).** This compound was prepared from **45** according to general procedure E. Yellow liquid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 3.80 (s, 3H, CH<sub>3</sub>O), 4.43 (s, 2H, CH<sub>2</sub>Br), 6.95 (d, 2H, J = 8.4, CH<sub>arom</sub>), 7.20–7.38 (m, 5H, CH<sub>arom</sub>), 7.45–7.50 (m, 1H, CH<sub>arom</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 32.4, 55.1, 113.6, 115.6, 125.6, 126.8, 127.6, 128.4, 130.0, 130.9, 132.4, 135.2, 141.6, 158.9.

**2-(2'-Thiophene)benzyl Bromide (55).** This compound was prepared from **46** according to general procedure E. Colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 4.59 (s, 2H, CH<sub>2</sub>Br), 7.06–7.14 (m, 1H, CH<sub>arom</sub>), 7.30–7.47 (m, 5H, CH<sub>arom</sub>), 7.48–7.53 (m, 1H, CH<sub>arom</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 32.2, 125.8, 127.3, 127.6, 128.3, 128.4, 130.3, 130.5, 131.1.

**2-(3'-Thiophene)benzyl Bromide (56).** This compound was prepared from **47** according to general procedure E. Brown oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 4.46 (s, 2H, CH<sub>2</sub>Br), 7.14–7.49 (m, 7H, CH<sub>arom</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 32.6, 122.5, 123.1, 124.8, 125.6, 125.7, 127.2, 127.9, 128.6, 128.6, 128.8, 129.7, 130.3, 131.1, 135.3, 136.6, 140.2.

**9-(2'-Fluorobiphenyl-2-ylmethyl)-6-(4-nitrobenzylsulfanyl)purine (57).** This compound was prepared from **48** according to general procedure A. Yield: 24%. White solid. Mp: 156 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 4.70 (s, 2H, CH<sub>2</sub>S), 5.36 (s, 2H, CH<sub>2</sub>N), 7.13–7.17 (m, 3H, CH<sub>arom</sub>), 7.26–7.43 (m, 5H, CH<sub>arom</sub>), 7.48 (s, 1H, H-2), 7.64 (d, 2H, J = 8.9, CH<sub>arom</sub>), 8.14 (d, 2H, J = 8.9, CH<sub>arom</sub>), 8.67 (s, 1H, H-8). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 31.7, 45.3, 115.8 (d, J = 23), 123.6, 124.5, 124.6, 128.7, 128.8 (d, J = 9), 128.7, 129.8, 130.0, 131.0, 131.2 (d, J = 3), 133.5, 135.3, 142.9, 145.7, 147.0, 148.9, 151.7, 158.7, 159.6 (d, J = 245). <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ = -37.4. HRMS (ESI) *m/z* found 472.1241 [M + H]<sup>+</sup>, calcd 472.1244. Elem. anal. (C<sub>25</sub>H<sub>18</sub>FN<sub>5</sub>O<sub>2</sub>S·0.1EtOAc) C, H, N, S.

**9-(4'-Fluorobiphenyl-2-ylmethyl)-6-(4-nitrobenzylsulfanyl)purine (58).** This compound was prepared from **49** according to general procedure A. Yield: 39%. Yellow solid. Mp: 109 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 4.70 (s, 2H, CH<sub>2</sub>S), 5.36 (s, 2H, CH<sub>2</sub>N), 7.00–7.09 (m, 2H, CH<sub>arom</sub>), 7.23–7.41 (m, 6H, CH<sub>arom</sub>), 7.48 (s, 1H, H-2), 7.64 (d, 2H, J = 8.8, CH<sub>arom</sub>), 8.15 (d, 2H, J = 8.8, CH<sub>arom</sub>), 8.68 (s, 1H, H-8). <sup>13</sup>C NMR (CDCl<sub>3</sub>) d = 31.6, 45.2, 115.4 (d, J = 21), 123.5, 128.2, 128.6, 129.1, 129.9, 130.3 (d, J = 9), 130.6, 132.4, 135.6, 140.9, 142.7,

145.7, 147.0, 148.7, 151.6, 158.7, 159.6 (d, J = 247). <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ = -36.9. HRMS (ESI) *m/z* found 472.1246 [M + H]<sup>+</sup>, calcd 472.1244. Elem. anal. (C<sub>25</sub>H<sub>18</sub>FN<sub>5</sub>O<sub>2</sub>S·0.1EtOAc) C, H, N, S.

**6-(4-Nitrobenzylsulfanyl)-9-(3'-trifluoromethylbiphenyl-2-ylmethyl)purine (59).** This compound was prepared from **50** according to general procedure A. Yield: 41%. Yellowish solid. Mp: 142 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 4.70 (s, 2H, CH<sub>2</sub>S), 5.35 (s, 2H, CH<sub>2</sub>S), 7.25–7.35 (m, 2H, CH<sub>arom</sub>), 7.38–7.53 (m, 6H, CH<sub>arom</sub>), 7.57 (s, 1H, H-2), 7.64 (d, 2H, J = 8.8, CH<sub>arom</sub>), 8.14 (d, 2H, J = 8.8, CH<sub>arom</sub>), 8.63 (s, 1H, H-8). <sup>13</sup>C NMR (CDCl<sub>3</sub>) d = 31.7, 45.2, 123.6, 123.7 (q, J = 272), 124.4 (q, J = 4), 125.4 (q, J = 4), 128.7, 128.9, 129.0, 129.1, 129.9, 130.6, 131.2, 131.9, 132.1, 132.4, 140.4, 140.5, 142.5, 145.7, 147.0, 148.6, 151.7, 159.0. <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ = 14.7. HRMS (ESI) *m/z* found 522.1224 [M + H]<sup>+</sup>, calcd 522.1212. Elem. anal. (C<sub>26</sub>H<sub>18</sub>F<sub>3</sub>N<sub>5</sub>O<sub>2</sub>S·0.1EtOAc) C, H, N, S.

**6-(4-Nitrobenzylsulfanyl)-9-(4'-trifluoromethylbiphenyl-2-ylmethyl)purine (60).** This compound was prepared from **51** according to general procedure A. Yield: 30%. Yellowish solid. Mp: 147 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 4.69 (s, 2H, CH<sub>2</sub>S), 5.35 (s, 2H, CH<sub>2</sub>N), 7.25–7.44 (m, 6H, CH<sub>arom</sub>), 7.53 (s, 1H, H-2), 7.57 (m, 2H, CH<sub>arom</sub>), 7.64 (d, 2H, J = 8.8, CH<sub>arom</sub>), 8.15 (d, 2H, J = 8.8, CH<sub>arom</sub>), 8.63 (s, 1H, H-8). <sup>13</sup>C NMR (CDCl<sub>3</sub>) d = 31.6, 45.2, 123.6, 123.9 (q, J = 272), 125.3 (q, J = 4), 128.7, 128.8, 129.1, 129.9, 130.4, 132.3, 140.5, 142.5, 143.3, 145.7, 147.0, 148.6, 151.7, 158.9. <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ = 14.7. HRMS (ESI) *m/z* found 522.1220 [M + H]<sup>+</sup>, calcd 522.1212. Elem. anal. (C<sub>26</sub>H<sub>18</sub>F<sub>3</sub>N<sub>5</sub>O<sub>2</sub>S·0.1EtOAc) C, H, N, S.

**9-(2'-Methoxybiphenyl-2-ylmethyl)-6-(4-nitrobenzylsulfanyl)purine (61).** This compound was prepared from **52** according to general procedure A. Yield: 45%. Yellow white solid. Mp: 103 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 3.69 (s, 3H, CH<sub>3</sub>O), 4.68 (s, 2H, CH<sub>2</sub>S), 5.35 (s, 2H, CH<sub>2</sub>N), 6.82–6.89 (m, 1H, CH<sub>arom</sub>), 6.92 (dd, 1H, J = 1.1, J = 7.3, CH<sub>arom</sub>), 7.03 (dd, 1H, J = 1.8, J = 7.3, CH<sub>arom</sub>), 7.20–7.25 (m, 2H, CH<sub>arom</sub>), 7.27–7.37 (m, 3H, CH<sub>arom</sub>), 7.42 (s, 1H, H-2), 7.62 (d, 2H, J = 8.8, CH<sub>arom</sub>), 8.11 (d, 2H, J = 8.8, CH<sub>arom</sub>), 8.65 (s, 1H, H-8). <sup>13</sup>C NMR (CDCl<sub>3</sub>) d = 31.6, 45.6, 55.3, 110.8, 120.8, 123.5, 127.9, 128.5, 128.9, 129.3, 129.9, 130.8, 130.9, 133.6, 138.5, 143.2, 145.8, 146.9, 148.8, 151.5, 156.0, 158.3. HRMS (ESI) *m/z* found 484.1401 [M + H]<sup>+</sup>, calcd 484.1443. Elem. anal. (C<sub>26</sub>H<sub>21</sub>N<sub>5</sub>O<sub>3</sub>S) C, H, N, S.

**9-(3'-Methoxybiphenyl-2-ylmethyl)-6-(4-nitrobenzylsulfanyl)purine (62).** This compound was prepared from **53** according to general procedure A. Yield: 37%. Yellow crystals. Mp: 121 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 3.77 (s, 3H, CH<sub>3</sub>O), 4.69 (s, 2H, CH<sub>2</sub>S), 5.40 (s, 2H, CH<sub>2</sub>N), 6.73–6.75 (m, 1H, CH<sub>arom</sub>), 6.79–6.86 (m, 2H, CH<sub>arom</sub>), 7.24–7.38 (m, 5H, CH<sub>arom</sub>), 7.46 (s, 1H, H-2), 7.64 (d, 2H, J = 9.1, CH<sub>arom</sub>), 8.14 (d, 2H, J = 8.8, CH<sub>arom</sub>), 8.67 (s, 1H, H-8). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 31.5, 45.1, 55.0, 112.9, 114.2, 120.9, 123.4, 127.9, 128.4, 129.0, 129.4, 129.7, 130.2, 132.2, 140.9, 141.7, 142.7, 145.6, 151.4, 159.4. HRMS (ESI) *m/z* found 484.1442 [M + H]<sup>+</sup>, calcd 484.1443. Elem. anal. (C<sub>26</sub>H<sub>21</sub>N<sub>5</sub>O<sub>3</sub>S·0.1EtOAc) C, H, N, S.

**9-(4'-Methoxybiphenyl-2-ylmethyl)-6-(4-nitrobenzylsulfanyl)purine (63).** This compound was prepared from **54** according to general procedure A. Yield: 37%. Yellow solid. Mp: 163 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 3.79 (s, 3H, CH<sub>3</sub>O), 4.68 (s, 2H, CH<sub>2</sub>S), 5.39 (s, 2H, CH<sub>2</sub>N), 6.90 (d, 2H, J = 8.8, CH<sub>arom</sub>), 7.16 (d, 2H, J = 8.8, CH<sub>arom</sub>), 7.26–7.31 (m, 4H, CH<sub>arom</sub>), 7.44 (s, 1H, H-2), 7.62 (d, 2H, J = 8.8, CH<sub>arom</sub>), 8.10 (d, 2H, J = 8.8, CH<sub>arom</sub>), 8.66 (s, 1H, H-8). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 31.6, 45.3, 55.2, 113.9, 123.5, 127.7, 128.6, 129.2, 129.9, 130.7, 132.0, 132.5, 141.7, 142.8, 145.7, 147.1, 148.8, 151.6, 159.1. HRMS (ESI) *m/z* found 484.1476 [M + H]<sup>+</sup>, calcd 484.1443. Elem. anal. (C<sub>26</sub>H<sub>21</sub>N<sub>5</sub>O<sub>3</sub>S·0.15CH<sub>2</sub>Cl<sub>2</sub>) C, H, N, S.

**6-(4-Nitrobenzylsulfanyl)-9-[2-(2'-thiophene)benzyl]purine (64).** This compound was prepared from **55** according to general procedure A. Yield: 36%. Off-white foam. Mp: 62 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ = 4.70 (s, 2H, CH<sub>2</sub>S), 5.52 (s, 2H, CH<sub>2</sub>N), 7.01 (dd, 1H, J = 1.3, J = 3.5, CH<sub>arom</sub>), 7.08 (dd, 1H, J = 3.5, J = 5.1, CH<sub>arom</sub>), 7.24–7.48 (m, 5H, CH<sub>arom</sub>), 7.51 (s, 1H, H-2), 7.64 (d, 2H, J = 8.8, CH<sub>arom</sub>), 8.14 (d, 2H,

$J = 8.8$ , CH arom), 8.72 (s, 1H, H-8).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta = 31.5, 45.3, 123.4, 126.2, 127.0, 127.3, 128.5, 128.6, 129.2, 129.7, 130.7, 131.5, 133.0, 134.0, 140.2, 143.6, 145.5, 146.8, 148.6, 151.6, 158.7$ . HRMS (ESI)  $m/z$  found 460.0941  $[\text{M} + \text{H}]^+$ , calcd 460.0901. Elem. anal. ( $\text{C}_{23}\text{H}_{17}\text{N}_5\text{O}_2\text{S}_2 \cdot 0.1\text{CH}_2\text{Cl}_2$ ) C, H, N

**6-(4-Nitrobenzylsulfanyl)-9-[2-(3'-thiophene)benzyl]-purine (65).** This compound was prepared from **56** according to general procedure A. Yield: 44%. Yellow solid. Mp: 134 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta = 4.69$  (s, 2H,  $\text{CH}_2\text{S}$ ), 5.43 (s, 2H,  $\text{CH}_2\text{N}$ ), 7.06 (d, 1H,  $J = 4.8$ , CH arom), 7.18 (d, 1H,  $J = 4.4$ , CH arom), 7.28–7.39 (m, 5H, CH arom), 7.45 (s, 1H, H-2), 7.63 (d, 2H,  $J = 8.6$ , CH arom), 8.12 (d, 2H,  $J = 8.6$ , CH arom), 8.69 (s, 1H, H-8).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta = 31.5, 45.3, 123.2, 123.4, 126.2, 128.0, 128.2, 128.5, 129.1, 129.7, 130.5, 132.5, 136.5, 139.8, 142.6, 145.6, 148.6, 151.5$ . HRMS (ESI)  $m/z$  found 460.0929  $[\text{M} + \text{H}]^+$ , calcd 460.0901. Elem. anal. ( $\text{C}_{23}\text{H}_{17}\text{N}_5\text{O}_2\text{S}_2$ ) C, H, N.

**2-(2'-Methylphenyl)benzyl alcohol (67).** This compound was prepared according to general procedure D applying 2-bromobenzyl alcohol (**66**). Reaction time: 10 min. Catalyst:  $\text{Pd}(\text{OAc})_2$ . Yield: 53%. White solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta = 2.05$  (s, 3H,  $\text{CH}_3$ ), 4.40 (s, 2H,  $\text{CH}_2\text{OH}$ ), 7.11–7.29 (m, 5H, CH arom), 7.32–7.39 (m, 2H, CH arom), 7.52–7.55 (m, 1H, CH arom).

**2-(2'-Methylphenyl)benzyl mesylate (68).** A solution of 0.45 mmol of **67** in dry MTBE (2 mL) was cooled on an ice bath. 1.1 equiv of  $\text{MsCl}$  and 1.2 equiv of triethylamine were added. After addition of triethylamine the ice bath was removed and the mixture was stirred for 3 h at rt. Brine (1 mL) was added and the mixture was extracted with MTBE. The organic layers were dried ( $\text{MgSO}_4$ ) and concentrated. The crude product was used without further purification. Yield: 73%. Colorless liquid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta = 2.06$  (s, 3H,  $\text{PhCH}_3$ ), 2.64 (s, 3H,  $\text{SO}_2\text{CH}_3$ ), 4.96 (AB, 2H,  $J = 10.8$ ,  $\text{CH}_2\text{OMs}$ ), 7.11–7.30 (m, 5H, CH arom), 7.40–7.45 (m, 2H, CH arom), 7.51–7.57 (m, 1H, CH arom).

**9-(2'-Methylbiphenyl-2-ylmethyl)-6-(4-nitrobenzylsulfanyl)purine (69).** This compound was prepared from **68** according to general procedure A. Yield: 53%. Yellowish solid. Mp: 132 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta = 1.96$  (s, 3H,  $\text{PhCH}_3$ ), 4.69 (s, 2H,  $\text{CH}_2\text{S}$ ), 5.17 (AB, 2H,  $J = 15.0$ ,  $\text{CH}_2\text{N}$ ), 7.64 (d, 2H,  $J = 8.9$ , CH arom), 8.14 (d, 2H,  $J = 8.9$ , CH arom), 8.65 (s, 1H, H-8).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta = 19.8, 31.6, 45.5, 123.6, 125.9, 127.9, 128.0, 128.6, 129.1, 129.4, 129.9, 130.2, 130.4, 130.8, 132.6, 135.7, 139.0, 141.3, 142.9, 145.8, 147.0, 148.7, 151.6, 158.6$ . HRMS (ESI)  $m/z$  found 468.1470  $[\text{M} + \text{H}]^+$ , calcd 468.1494. Elem. anal. ( $\text{C}_{26}\text{H}_{21}\text{N}_5\text{O}_2\text{S} \cdot 0.1\text{EtOAc}$ ) C, H, N, S.

**9-(2'-Hydroxybiphenyl-2-ylmethyl)-6-(4-nitrobenzylsulfanyl)purine (70).** This compound was prepared from **61** according to general procedure B. Yield: 20%. White solid. Mp: 164 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta = 4.65$  (s, 2H,  $\text{CH}_2\text{S}$ ), 5.29 (s, 2H,  $\text{CH}_2\text{N}$ ), 6.90–7.00 (m, 2H, CH arom), 7.08 (dd, 1H,  $J = 1.5$ ,  $J = 7.7$ , CH arom), 7.19–7.40 (m, 5H, CH arom), 7.59 (d, 2H,  $J = 8.8$ , CH arom), 7.74 (s, 1H, H-2), 8.12 (d, 2H,  $J = 8.8$ , CH arom), 8.63 (s, 1H, H-8).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta = 31.6, 45.7, 116.7, 120.7, 123.6, 126.7, 128.6, 128.8, 128.9, 129.6, 129.9, 130.8, 131.3, 133.6, 137.7, 143.6, 145.6, 147.0, 148.4, 151.6, 153.0$ . HRMS (ESI)  $m/z$  found 470.1272  $[\text{M} + \text{H}]^+$ , calcd 470.1287. Elem. anal. ( $\text{C}_{25}\text{H}_{19}\text{N}_5\text{O}_3\text{S} \cdot 0.5\text{EtOAc}$ ) C, H, N, S. C: calcd. 63.14; found 62.34.

**9-(3'-Hydroxybiphenyl-2-ylmethyl)-6-(4-nitrobenzylsulfanyl)purine (71).** This compound was prepared from **62** according to general procedure B. Yield: 22%. White solid. Mp: 206 °C.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta = 4.78$  (s, 2H,  $\text{CH}_2\text{S}$ ), 5.44 (s, 2H,  $\text{CH}_2\text{N}$ ), 6.72–6.80 (m, 3H, CH arom), 6.98 (d, 1H,  $J = 6.6$ , CH arom), 7.18–7.37 (m, 4H, CH arom), 7.75 (d, 2H,  $J = 8.8$ , CH arom), 8.11 (s, 1H, H-2), 8.17 (d, 2H,  $J = 8.8$ , CH arom), 8.68 (s, 1H, H-8), 9.60 (br, s, 1H,  $\text{PhOH}$ ).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ )  $\delta = 30.7, 45.0, 114.4, 115.8, 119.5, 123.6, 127.6, 127.8, 128.0, 129.5, 129.9, 130.2, 133.1, 141.0, 141.0, 144.9, 146.5, 148.6, 151.4, 157.4, 157.8$ . HRMS (ESI)  $m/z$  found 470.1258  $[\text{M} + \text{H}]^+$ , calcd 470.1281. Elem. anal. ( $\text{C}_{25}\text{H}_{19}\text{N}_5\text{O}_3\text{S} \cdot 0.1\text{CH}_2\text{Cl}_2$ ) C, H, N, S.

**9-(4'-Hydroxybiphenyl-2-ylmethyl)-6-(4-nitrobenzylsulfanyl)purine (72)** This compound was prepared from **63** according to general procedure B. Yield: 43%. White solid. Mp: 194 °C.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta = 4.78$  (s, 2H,  $\text{CH}_2\text{S}$ ), 5.45 (s, 2H,  $\text{CH}_2\text{N}$ ), 6.84 (d, 2H,  $J = 8.8$ , CH arom), 6.95 (d, 1H,  $J = 7.7$ , CH arom), 7.18–7.38 (m, 5H, CH arom), 7.74 (d, 2H,  $J = 8.8$ , CH arom), 8.08 (s, 1H, H-2), 8.17 (d, 2H,  $J = 8.8$ , CH arom), 8.68 (s, 1H, H-8), 9.60 (s, 1H,  $\text{PhOH}$ ).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ )  $\delta = 30.7, 45.1, 115.3, 123.5, 127.3, 127.6, 127.9, 130.2, 130.3, 133.2, 141.0, 144.8, 146.4, 148.5, 151.4, 156.8, 157.8$ . HRMS (ESI)  $m/z$  found 470.1271  $[\text{M} + \text{H}]^+$ , calcd 470.1281. Elem. anal. ( $\text{C}_{25}\text{H}_{19}\text{N}_5\text{O}_3\text{S} \cdot 0.1\text{CH}_2\text{Cl}_2$ ) C, H, N.

**Erythrocytes and Membrane Preparation.** Whole human blood (Blood Bank, Leiden University Medical Center) was stirred in lysis buffer (1/2 v/v, 10 mM  $\text{MgCl}_2$  in 10 mM Tris-HCl, pH 8.0 at 25 °C) for 1 h. After homogenization, it was centrifuged for 50 min at 19 000 rpm. The supernatant was removed, and the pellet was dissolved in ice-cold water and centrifuged again for 50 min. This procedure was repeated two more times. After removal of the last supernatant, 25 mL of buffer (50 mM Tris-HCl, pH 7.4 at 25 °C) was added to the final pink pellet. This suspension was homogenized and the ghosts were collected. Aliquots were stored at –80 °C until further use.

**$^3\text{H}$ NBTI Binding Assay.** Saturation and displacement equilibrium NBTI binding to membranes prepared from human erythrocytes (ghosts) was determined at 25 °C based on a method previously described.<sup>32</sup>

**Calculation of the Polar Surface Area and Molecular Modeling.** The polar surface areas of the molecules were calculated using Spartan 5.0 for SGI,<sup>22</sup> in combination with an in-house developed application called PolSurf 1.0 [A copy of PolSurf and its (C) source code can be obtained from the corresponding author]. First Spartan was used to build the molecule, to optimize its 3D-structure by molecular mechanics (Merck force field) followed by semiempirical AM1 single point energy calculation. In all cases default settings were used. The electrostatic potentials were calculated over the entire accessible surface of the molecules (roughly equal to the van der Waals contact surface). Subsequently PolSurf was applied to convert the raw data from the Spartan "input" and "proparg" files into the polar surface area of the molecule.

The crystal structure of NBTI<sup>23</sup> (**1**, CSD code: NBTINS10) used for the illustrations in Figure 2 was retrieved from the Cambridge Structural Database<sup>24</sup> using ConQuest.<sup>33</sup> The structures of **35** and **36** were drawn and energy minimized (equilibrium geometry, semiempirical, AM1) in PC Spartan Pro.<sup>25</sup> Next, the 4-nitrobenzyl groups of NBTI, **35**, and **36** were omitted for reasons of clarity. In PC Spartan Pro, the purine rings of NBTI and **35** or **36** were matched after which the benzyl ring was rotated over the  $\text{Ph}-\text{CH}_2$ , the  $\text{PhCH}_2$ –purine and the  $\text{Ph}-\text{OH}$  bond to achieve an overlay between its hydroxyl function and either the 2', 3', or 5'-OH of NBTI. The structure of NBTI was left untouched.

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