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Synthesis and Biological Evaluation of Small Molecule Inhibitors of BMPR1b

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A thesis submitted to the faculty of
Brigham Young University
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Master of Science

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ABSTRACT

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Methods for preparing an array of potential small molecule inhibitors of Bone Morphogenetic Protein Receptor 1b (BMPR1b) are described. Target molecules were prepared from two general classes: (1) N^9-aryl-N^6-ureidoadenines, and (2) dicarbamyl iodoacetamides. Recent data from the Peterson lab indicated that both classes might bind to BMPR1b and thus inhibit this key receptor. Docking studies performed using Sureflex Dock suggested the N^9-aryl-N^6-ureidoadenines would bind to the active site of BMPR1b. In addition antiproliferative activities of dicarbamyl iodoacetamides previously synthesized in the Peterson lab pointed to this moiety as an attractive target for structure activity relationship (SAR) development. Compounds were prepared in good to excellent yields and 40 derivatives were screened for antiproliferative activity. Of the N^9-aryl-N^6-ureidoadenine derivatives, N^9-phenyl-N^6-N-phenylureaadenine was most potent and exhibited selective activity against HeLa cells (IC50 = 11± 1 uM). Dicarbamyl iodoacetamide derivatives had similar activities compared to the previously reported compound (**JRS-150**).

Keywords: lung adenocarcinoma, small molecule inhibitors, bone morphogenetic protein receptor 1b.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Nucleosides have played an important role in the development of modern drugs as treatments for different diseases. Small modifications at specific locations in a nucleoside can drastically change its biological properties. This is a known and efficient technique employed in drug discovery. While these types of compounds can have different biological targets in an organism, it is imperative to developed a drug-candidate with high selectivity for a specific target. Protein kinases are appealing targets because they are known to play important roles in signaling and regulation of different processes in a cell. Thus, a modification or alteration of the properties of a protein kinase will have a direct effect in some process of a cell. Bone morphogenetic proteins belong to the transforming growth factor beta superfamily of cytokines.[1] These ligands form heterodimeric complexes of type I and type II bone morphogenetic receptors. The bone morphogenetic receptor 1b (BMPR1b) is a serine-threonine protein kinase and is part of a signaling pathway that regulates expression of Inhibitor of Differentiation 1 gene (Id1). Id1 along with three other known Id proteins (Id2, Id3, and Id4) belong to the helix-loop-helix (HLH) family of transcription factors. Id proteins lack a DNA binding domain and associate with other transcription factors preventing them from binding DNA or forming active heterodimers.[2] Overexpression of Id1 has been observed in more than twenty forms of cancer, including lung cancer cell lines as well as lung cancer tissues. Inactivation of Id1 has been shown to lead to apoptosis in ovarian,[3] prostate,[4] and breast cancers,[5] and has recently been shown to play a

crucial role in the development of lung cancer.[6] Nearly all currently available chemotherapies for cancer ultimately lead to resistant cell lines causing an unresponsive treatment, thus requiring that drug discovery efforts continue unabated. Inhibition of Id1 by targeting BMPR1b may provide an alternative approach for treatment of cancer patients. BMPR1b is a key target that has not yet been fully explored. Effective targeting of this newly identified receptor could offer potential treatment to cancer patients and a viable solution to the ever-evolving problem caused by drug resistance.[7]

A proposed model of BMRP1b regulation of Id1 is illustrated in Figure 1. This model consists of the following key features:[8]

(1) Bone morphogenetic protein 2 (BMP-2) in the cytosol binds BMPR2. Then, the type II receptor phosphorylates the type I receptor. This step initiates the cascade of events inside the cell.

(2) The activated receptors BMPR2/BMPR1b directly phosphorylate Smad1, Smad5, and Smad8 at serine residues in their C-terminus. Smad1, Smad5 and Smad8 are transcriptional factors, which function in the BMP signaling pathway.

(3) The phosphorylated form of Smad 1,5,and 8 hetero-oligomerize with Smad 4 forming a co-Smad complex. So far in mammals, this is the only co-Smad complex known to translocate to the nucleus.

(4) Inside the nucleus, Smads form complexes containing DNA binding factors to create stable binding and transcriptional activation of Id1.

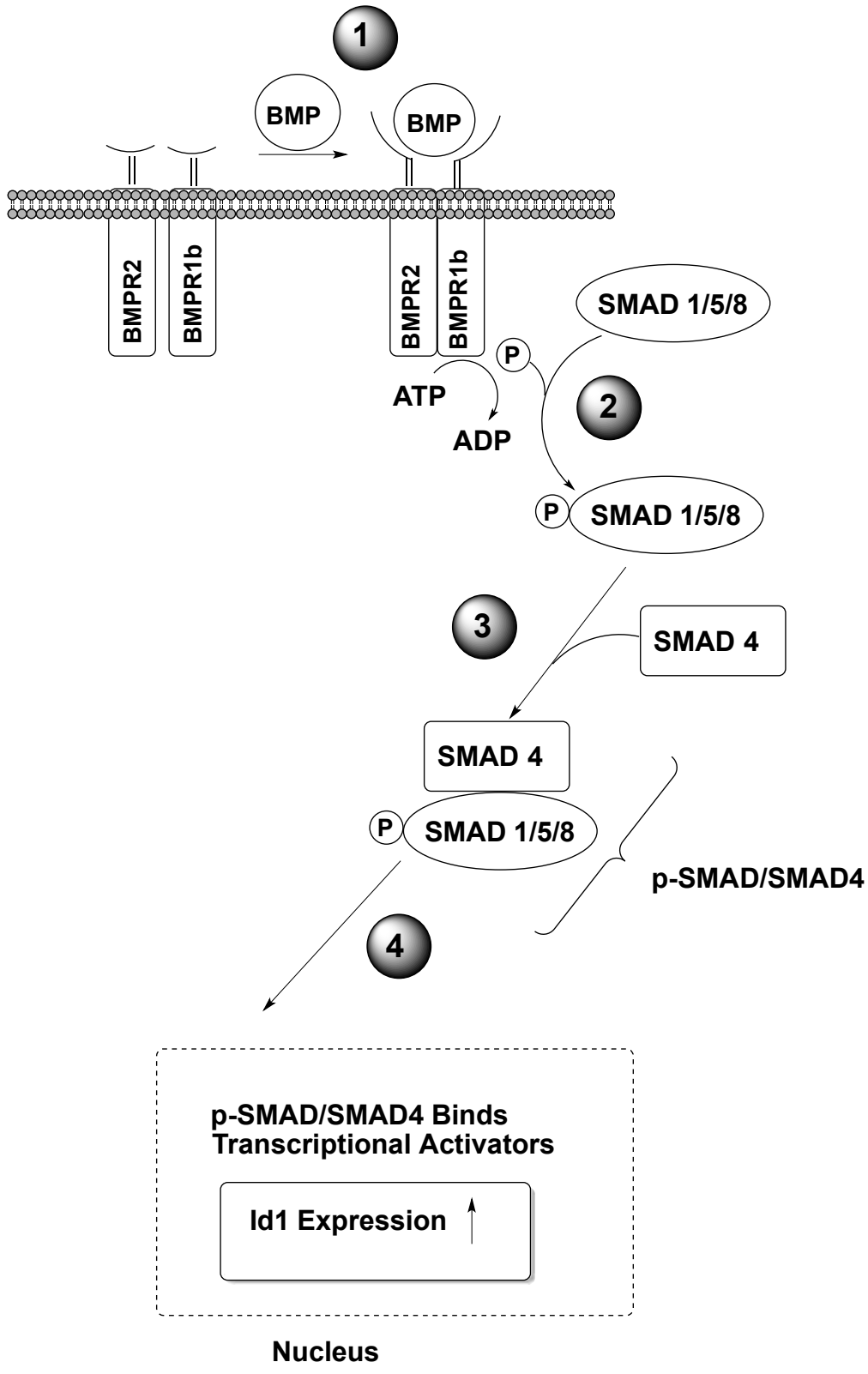


Figure 1. BMP signaling pathway

BACKGROUND

Recently, our lab discovered a compound **(JRS-150)** that exhibits potent and selective activity against lung adenocarcinoma *in vitro*. The IC_{50} value of this compound (Figure 2) was found to be 9.71 nM against a Non-Small Cell Lung Cancer cell line (NCI-H522) obtained from a NCI-60 cancer screen (Table 1).

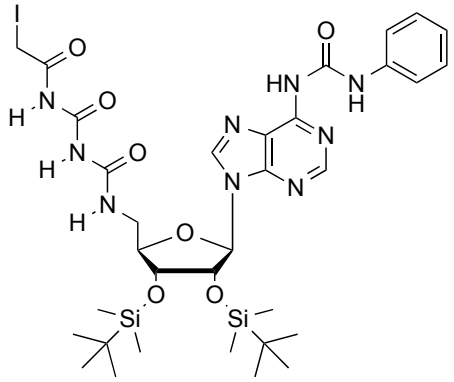
Table 1. IC_{50} values of **JRS-150** for Non-Small Cell Lung Cancer

			Log10 Concentration												
	Time		Mean Optical Densities					Percent Growth							
Panel/Cell Line	Zero	Ctrl	-8.3	-7.3	-6.3	-5.3	-4.3	-8.3	-7.3	-6.3	-5.3	-4.3	GI50	TGI	LC50
Non-Small Cell Lung Cancer															
A549/ATCC	0.405	1.568	1.636	1.314	1.198	0.746	0.264	106	78	68	29	-35	1.47E-6	1.43E-5	> 5.00E-5
EKVX	0.850	1.587	1.571	1.558	0.938	0.362	0.214	98	96	12	-57	-75	1.76E-7	7.42E-7	3.90E-6
HOP-62	0.354	0.753	0.741	0.780	0.232	0.074	0.120	97	107	-34	-79	-66	1.26E-7	2.85E-7	1.11E-6
NCI-H226	0.751	1.513	1.517	1.507	1.577	1.510	0.255	101	99	108	100	-66	9.96E-6	2.00E-5	4.00E-5
NCI-H23	0.522	1.391	1.359	1.266	0.767	0.358	0.143	96	86	28	-31	-73	2.08E-7	1.48E-6	1.41E-5
NCI-H460	0.267	2.320	2.353	2.291	2.313	0.959	0.212	102	99	100	34	-21	2.83E-6	2.09E-5	> 5.00E-5
NCI-H522	0.612	1.345	1.354	0.145	0.139	0.134	0.174	101	-76	-77	-78	-72	9.71E-9	1.86E-8	3.55E-8

Comparison of *in vitro* activity of **JRS-150** to *cis-platin* (CDDP) in the NCI-60 revealed that **JRS-150** is 100 times more potent and 25 more selective against non-small cell lung cancer cell lines in vitro. CDDP is known for its high potency and is widely used for treating different types of cancer. However it is also known for its high toxicity and numerous adverse side effects. It interferes with transcription and replication of DNA causing cytotoxicity which ultimately leads to apoptosis. Unfortunately, the lack of selectivity causes multiple side effects such as renal-

/neuro-toxicity or bone marrow-suppression and binding to other targets like proteins or enzymes, which may alter their mechanism of action.[9]

Most current cancer treatments exhibit similar problems,[10] thus there is an existing need for new ways to approach these ongoing problems.



JRS-150

Figure 2. Structure of **JRS-150**

Mechanism of action studies performed in our laboratory support the hypothesis that **JRS-150** could be binding to BMPR1b, thus inhibiting expression of Id1. For example, analogues of **JRS-150** (compounds **1**–**3**, Figures 3-4) have been studied in several in vitro assays that demonstrate that BMPR1b is an important target for this class of molecules. In one assay, compounds **1** and **2** were evaluated in a competitive binding inhibition assay of an ATP-binding site ligand for BMPR1b. This assay showed that compound **2** had a strong affinity for BMPR1b in this assay (K_d= 11.7 ± 0.5 μM).[11] This assay also implies that the two silyl protecting groups present in compound **1** interfered with its ability to inhibit BMPR1b. A second assay was performed to find a relationship between Id promoter activity and different concentrations of compound **3**

(Figure 4). Interestingly the presence of one silyl protecting group, as in compound **3**, did not interfere with its ability to inhibit Id1 transcription, as previously observed with compound **1** which has two silyl protecting groups. Compound **3** was shown by our collaborator Dr. Paul B. Yu (Harvard Medical School, Brigham and Women's Hospital) to inhibit transcriptional activation of Id1 in a whole-cell assay. Our current hypothesis is that compounds **1** and **3** are taken into cells via endocytosis, and that the TBS-protecting groups are hydrolyzed under the acidic conditions found inside the resulting lysosome.

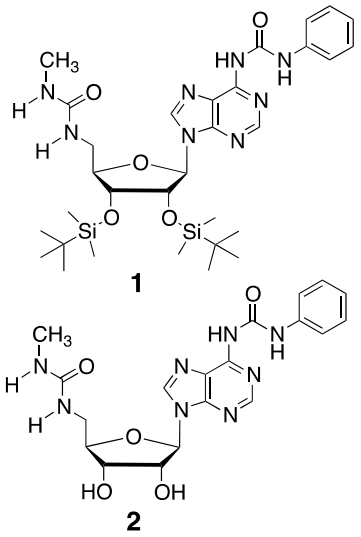


Figure 3. Analogues of **JRS-150** used in mechanism of action studies

Hydrolysis of the TBS groups from **1** and **3** would give the desilylated analogs intracellularly (i.e.; compound **2** and a de-silylated derivative of compound **3**, structure not shown). It is reasonable to expect that compound **3** undergoes hydrolysis within the lysosome due to the low pH typically observed in the lysosomal compartment.[12] The desilylated analogue would then

bind to BMPR1b and inhibit down-stream expression of Id1. Binding of compound **2** to BMPR1b in the above-mentioned competitive inhibition assay supports this hypothesis.

Based on the structural similarities between **JRS-150** and compounds **1** and **3**, we hypothesize that **JRS-150** may also inhibit expression of Id1.

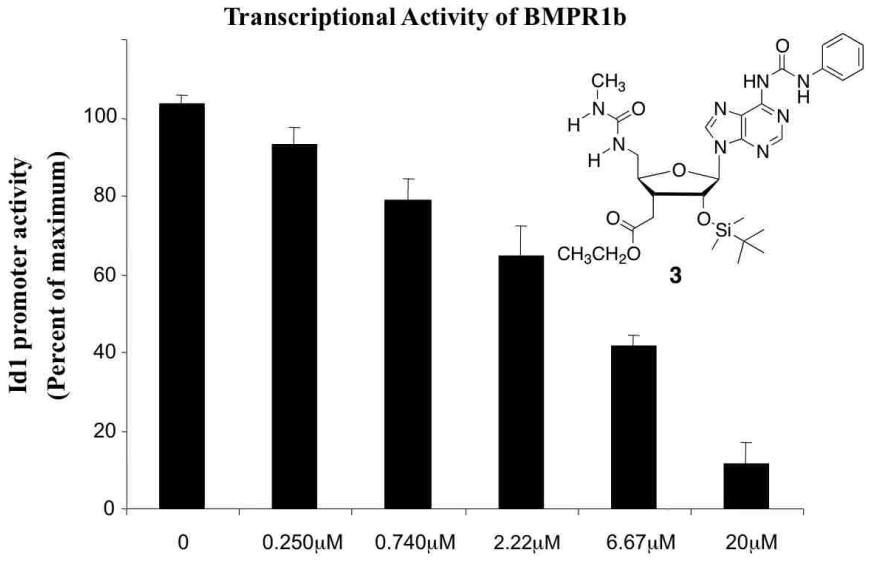


Figure 4. Id1 promoter activity in a multi-dose experiment

An additional structure activity relationship study (SAR) supported our conclusion that acid-sensitive functionality at the 2' and 3' positions are important. For example, compounds **1** and **4** (Figure 5) had nearly identical activities in an NCI-60 screen test.[13] In contrast, compounds **5** and **6** (which have considerably more acid-stable 2' and 3' protecting groups) were essentially inactive. Compounds **7**–**9**, which have protecting groups with intermediate acid-sensitivity, had

biological activities that were intermediate between those for compounds **1**/**4** and those for compounds **5**/**6** (Figure 5).

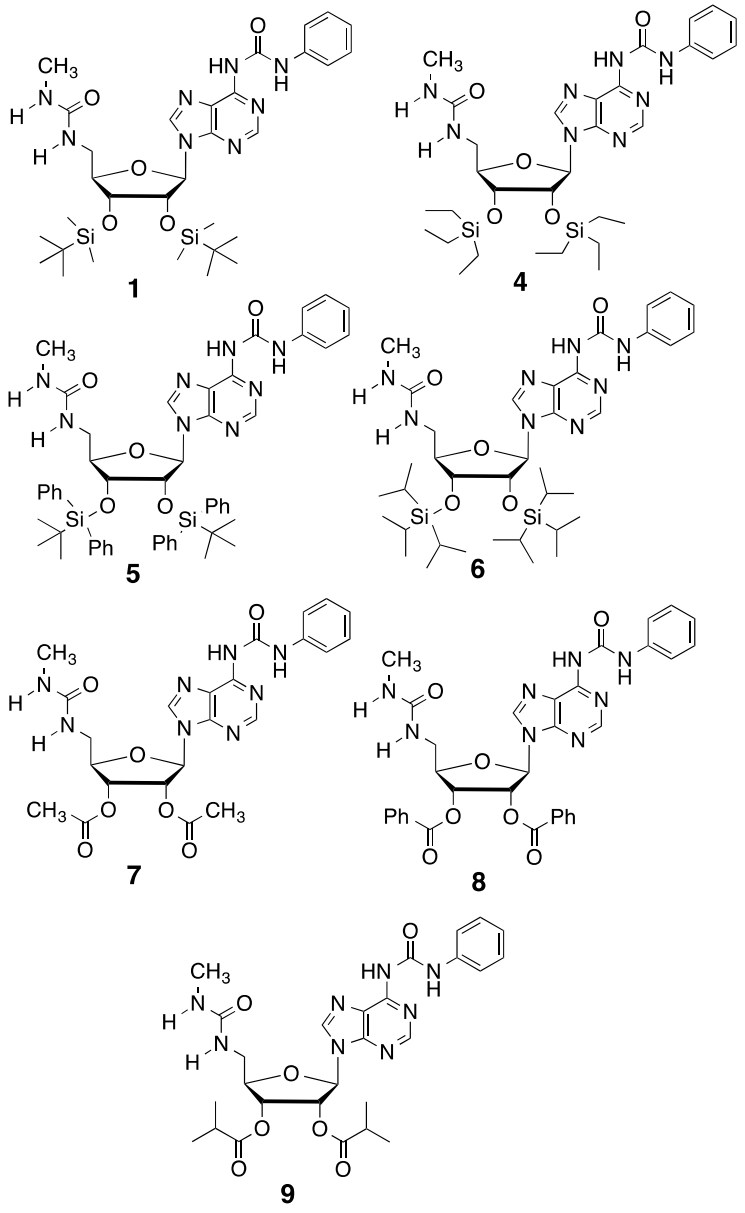


Figure 5. Compounds examined in structure activity relationship study demonstrating correlation between acid-sensitivity of 2'/3' protecting groups and antiproliferative activity

Using published crystallographic data for BMPR1b and Surflex Dock, a proven docking algorithm for predicting relevant binding interactions,[14] we predicted that **JRS-150** can bind to the ATP binding-site of BMPR1b. The lowest energy docking solution places the 5'-iodo group of **JRS-150** in close proximity to lysine residues (Lys 212 or 336) in the activation loop of BMPR1b. The lysine group could perform a nucleophilic attack on **JRS-150** thus covalently attaching it and irreversibly inhibiting the enzyme (Figure 6).

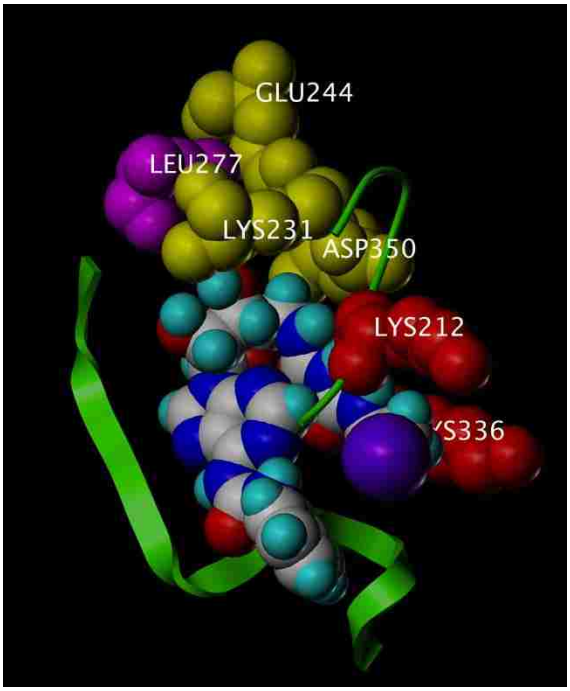


Figure 6. Lowest energy docking pose for **JRS-150** in active site of BMPR1b (pdb 3mdy)

Covalent inhibitors are a novel therapeutic approach with greater potency and selectivity, increased duration, and the ability to suppress mutation-associated drug resistance.[15]

Despite the high activity against lung adenocarcinoma and selectivity of **JRS-150**, it suffers from some drawbacks. Lipinski's rule of five provides guidelines to help predict the drug-like properties of chemical compounds.[16] They can be summarized as follow: a drug candidate should have no more than five hydrogen bond donors, no more than 10 hydrogen bond acceptors, a molecular weight under 500 g/mol, and a partition coefficient (log P) of lower than 5. Using these points we can identify some potential problems that may be associated with **JRS-150**. First, its molecular weight is greater than 500 g/mol. Second, the molecule is very hydrophobic. The partition coefficient log P indicates the ratio of concentration at equilibrium of a compound in two immiscible phases. A higher number indicates the compound is hydrophobic. In medicinal chemistry the distribution coefficient plays a major role in predicting the properties of a certain molecule. Orally absorbed drugs need to be lipophilic in order to pass through the different bilayers in the body to finally reach their targets. This also affects the rate a drug is metabolized helping determine how long it remains active in the body. Despite the fact that not every drug on the market follows Lipinski's rule of five, it does serve as a very useful guide for predicting the possible drug-like properties of a compound and helps with optimization of drug candidates. The fact that **JRS-150** fails to meet two of the Lipinski rules suggests that it may not be as bioavailable as needed. To overcome this problem we designed experiments to identify the structural features that could be kept constant while making necessary modifications in the non-required parts to reduce the molecular weight and hydrophobicity. The two goals of my research were therefore to (1) discover small molecule inhibitors of BMPR1b that obey Lipinski rules; and (2), determine structure activity relationship for **JRS-150** to understand the significance of the dicarbamyl iodoacetamide moiety and/or other functionality. For the first part of the study, over 100,000 different compounds were docked against the active site of BMPR1b using the

Surflex Dock docking algorithm. Several different sub-libraries were designed, using the basic template illustrated in Figure 7. This template has two places of variability, one at N^9 and one at N^6. From these libraries we selected a number of different compounds to be synthesized based on their binding scores and predicted synthetic difficulty.

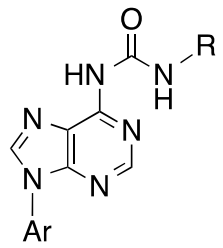


Figure 7. Basic template design for library molecules

To achieve our synthetic goals two different pathways were examined. The first series of compounds were synthesized using pathway A (Figure 8). Pathway A starts with a bis-Boc adenine made after the reaction of adenine with Boc anhydride followed by treatment of the resulting crude with sodium bicarbonate in methanol. The bis-Boc adenine is reacted with different commercially available boronic acids in a Cham-Lam cross coupling reaction; this key step generates diversity at the N^9 position. The initial idea was to remove both Boc groups and create an N^9 aryl adenine, which could then be treated with ethyl chloroformate to make the corresponding carbamate. However, mainly due to solubility problems, this planned method was discarded. An alternative idea was created in which one of the Boc groups is removed, then the resulting product is reacted with different amines. Pathway A is the result of the optimization of the Cham-Lam coupling, the selective deprotection of one Boc group, and the acylation to make different ureas. To perform a faster and more efficient SAR study at the N^9 position, an

alternative method (Pathway B) was designed (Figure 9). Pathway B allowed us to keep the N^6 position constant and to perform cross coupling at the N^9 position using a wide variety of commercially available boronic acids. Full details for these pathways along with the results from biological screening will be presented in the Results and Discussion section. The overall pathway employed for the SAR for the dicarbamyl iodoacetamide moiety is illustrated in Figure 10. Details for this pathway along with the results from biological screening will also be presented in the Results and Discussion section.

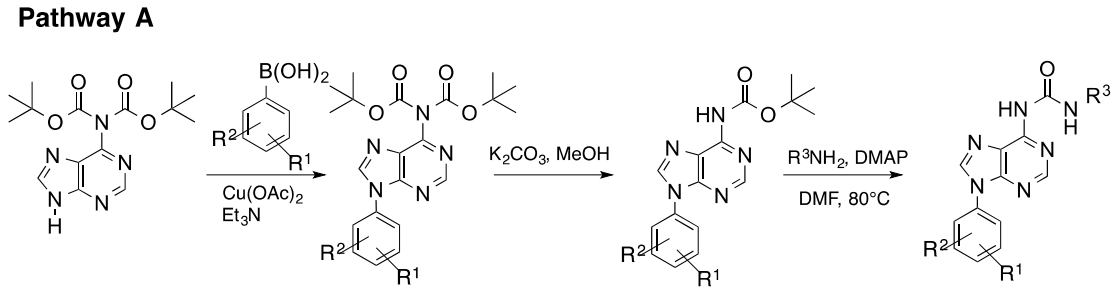


Figure 8. Outline of Pathway A employed in the synthesis of desired targets

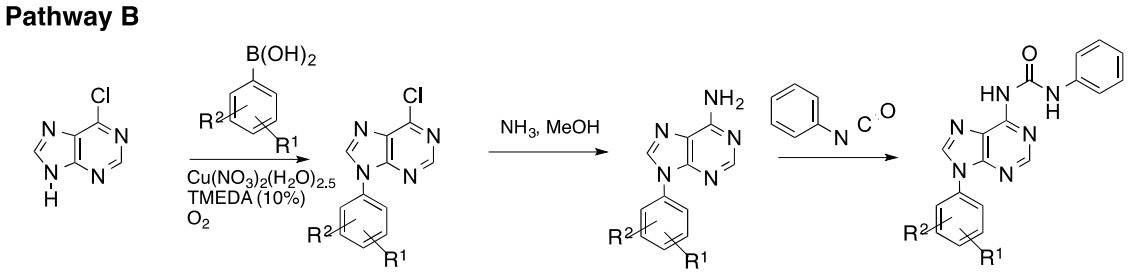


Figure 9. Outline of Pathway B employed in the synthesis of desired targets

Our interest in performing the SAR illustrated by compounds in Figure 10 was to determine the importance of the R group in conferring biological activity. Since amino acids play key roles in a number of biologically relevant processes and are known to interact with a number of receptors, we took as our first objective the goal of linking several amino esters to the dicarbamyl group (R = amino ester).

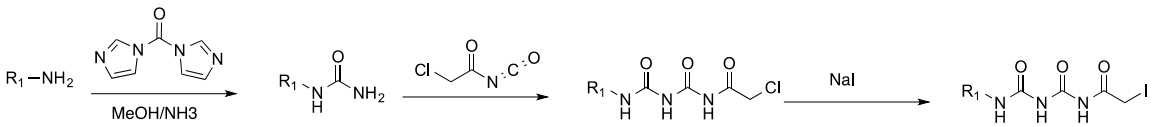


Figure 10. General outline for the synthesis of targets with a dicarbamyl iodoacetamide group

Using the outlined method in Figure 10 we planned to synthesize a wide variety of analogues containing this dicarbamyl iodoacetamide group. Results from the biological assays would help define the role this functional group plays in the biological activity of **JRS-150**.

RESULTS AND DISCUSSION

The main goal of the first part of my research was to synthesize libraries of small molecules that might mimic the activity of our lead compound (**JRS-150**), while at the same time more closely following Lipinski's rules. We initially chose to focus on pathway A for the preparation of these compounds. To illustrate the feasibility of this approach, we prepared model compound **12a** (Figure 11). Model compound **12a** is a key intermediate that could be converted to a variety of different products via simple displacement of the *tert*-butyloxy group by a nucleophilic amine. Treatment of compound **10** with phenylboronic acid in a Chan-Lam coupling gave compound **11a** (55%). The following step involved a selective deprotection of a single Boc group from compound **11a**. This step proved to be challenging because both Boc groups were susceptible to the deprotection, thus yielding the completely deprotected product (N^9-phenyladenine, structure not shown). When compound **11a** was treated with methanolic K_2CO_3 and stirred for approximately 2 hours at ambient temperature, optimum yields were obtained (33%). As might be expected, longer reaction times decreased the yield of the desired product and favored the completely deprotected byproduct. Shorter reactions times gave mixtures of the desired mono-Boc protected adenine **12a** and bis-Boc adenine **11a**.

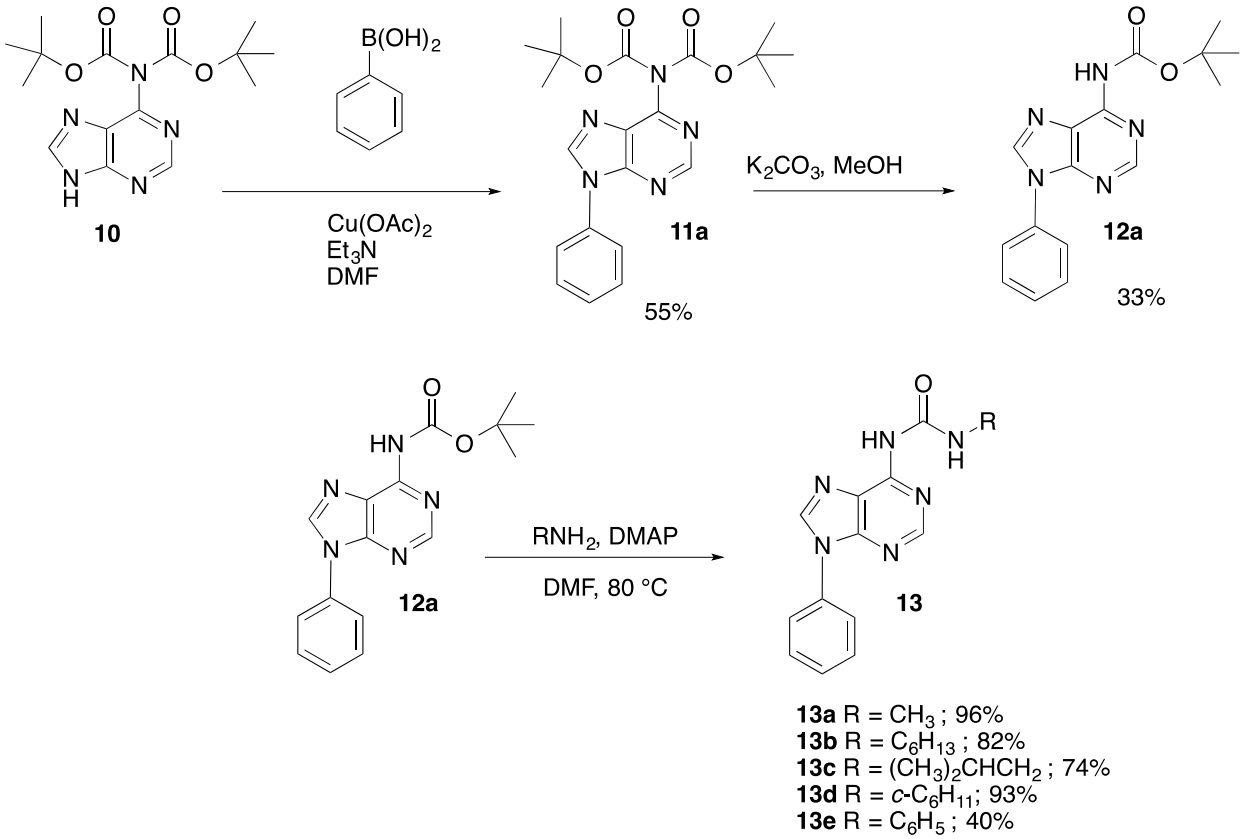


Figure 11. Outline of the synthesis of initial targets

Prior to our work, displacement of a *tert*-butyloxy group with primary amines to form ureas had been reported for only a limited number of substrates (none of them based on adenine), and relatively harsh and/or complicated reaction conditions were required to achieve this transformation.[17] We were thus delighted to find that using 4-dimethylaminopyridine (DMAP) as a catalyst, in the presence of 5 Å molecular sieves (MS) and excess amine in DMF at 80° C, we were able to obtain the desired final compounds (**13a**–**e**) in good yields. Alkyl amines tended to give isolated yields greater than 70% while aryl amines gave isolated yields lower than 50%. This phenomenon could be explained by considering the differences in reactivity of the nucleophilic nitrogen atoms. It is well known that aryl amines are less nucleophilic than alkyl

amines due to sterics and delocalization of the lone pair into the aromatic system. It was also interesting to note that of all of the alkyl amines studied in this reaction, the hindered isobutylamine gave the lowest yield. The successful synthesis of compounds **13** demonstrated the feasibility of pathway A and allowed us to optimize conditions to get the best yields possible for the rest of the analogues (Figure 12). Table 2 summarizes the results for the conversion of compounds **12a**–**e** to compounds **13**–**17**.

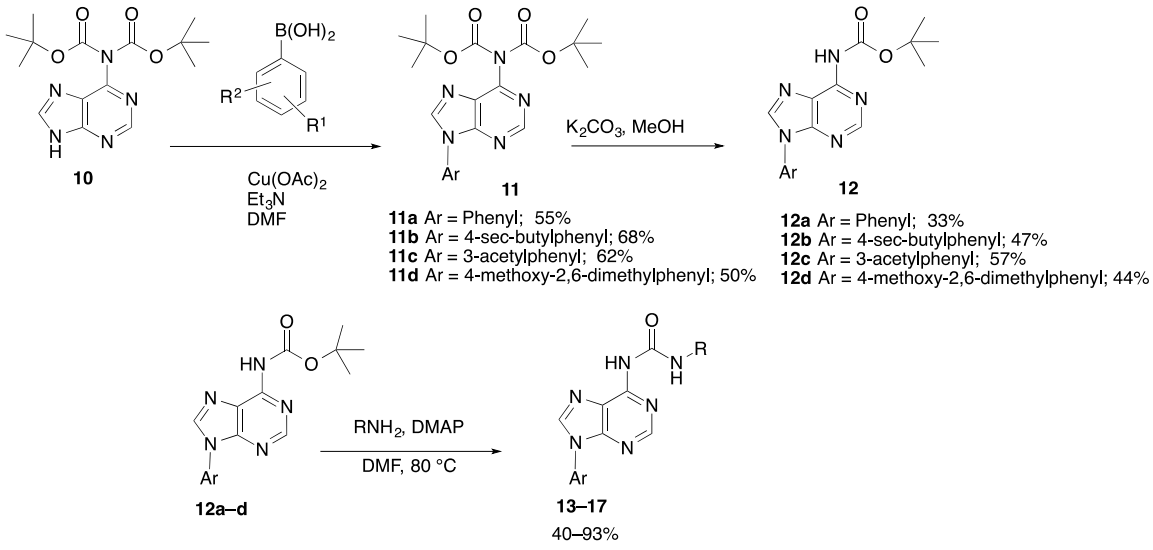
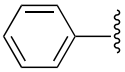
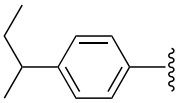
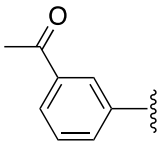
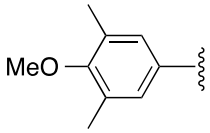
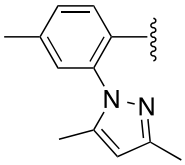


Figure 12. Synthetic approach to compounds **13–17**. R Groups detailed in Table 2

Due to the limitations associated with the Chan-Lam coupling step, most sterically hindered boronic acids do not react well under the conditions illustrated in Figure 12. For example coupling with (2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-methylphenyl)boronic acid required the use of a different set of conditions (Figure 13). After trying different solvents, catalysts and bases we discovered that the ideal conditions involved the use of $Cu(NO_3)_2$ and TMEDA in methanol.[18] Under these conditions we were able to achieve the coupling to give **12e** in 29% isolated yield

(Figure 13). The main problem we encountered in this reaction is dimerization of the boronic acid, which competes with the desired coupling at the N^9 position of the adenine.

Table 2. Yields for compounds **13-17**

Entry	Product	Ar	R	Yield (%)[a]
1	**13a**		CH_3	96
2	**13b**		C_6H_{13}	82
3	**13c**		$(CH_3)_2CHCH_2$	74
4	**13d**		c-C_6H_{11}	93
5	**13e**		C_6H_5	40
6	**14a**		CH_3	96
7	**14b**		C_6H_{13}	82
8	**14c**		$(CH_3)_2CHCH_2$	82
9	**14d**		c-C_6H_{11}	90
10	**15a**		CH_3	76
11	**15b**		C_6H_{13}	72
12	**15cl**		$(CH_3)_2CHCH_2$	85
13	**15d**		c-C_6H_{11}	76
14	**15e**		C_6H_5	27
15	**16a**		CH_3	82
16	**16b**		C_6H_{13}	66
17	**16c**		$(CH_3)_2CHCH_2$	97
18	**16d**		c-C_6H_{11}	86
19	**17a**		C_4H_9	74
20	**17b**		C_6H_{13}	93

[a]Isolated yields.

Continuous addition of the boronic acid during the reaction did not seem to have a noticeable improvement in the yield. On the other hand, it did increase the amount of the undesired dimer.

Selected analogues were submitted to the National Institute of Health (NIH) for the NCI-60 screen, which screens compounds against sixty different cancer cell lines.[19] Compounds were also screened against a smaller panel of cell lines (L1210, CEM, and HeLa) by our collaborators

at the Rega Institute for Medical Research in Leuven, Belgium. The results from these screens are illustrated in Table 3.

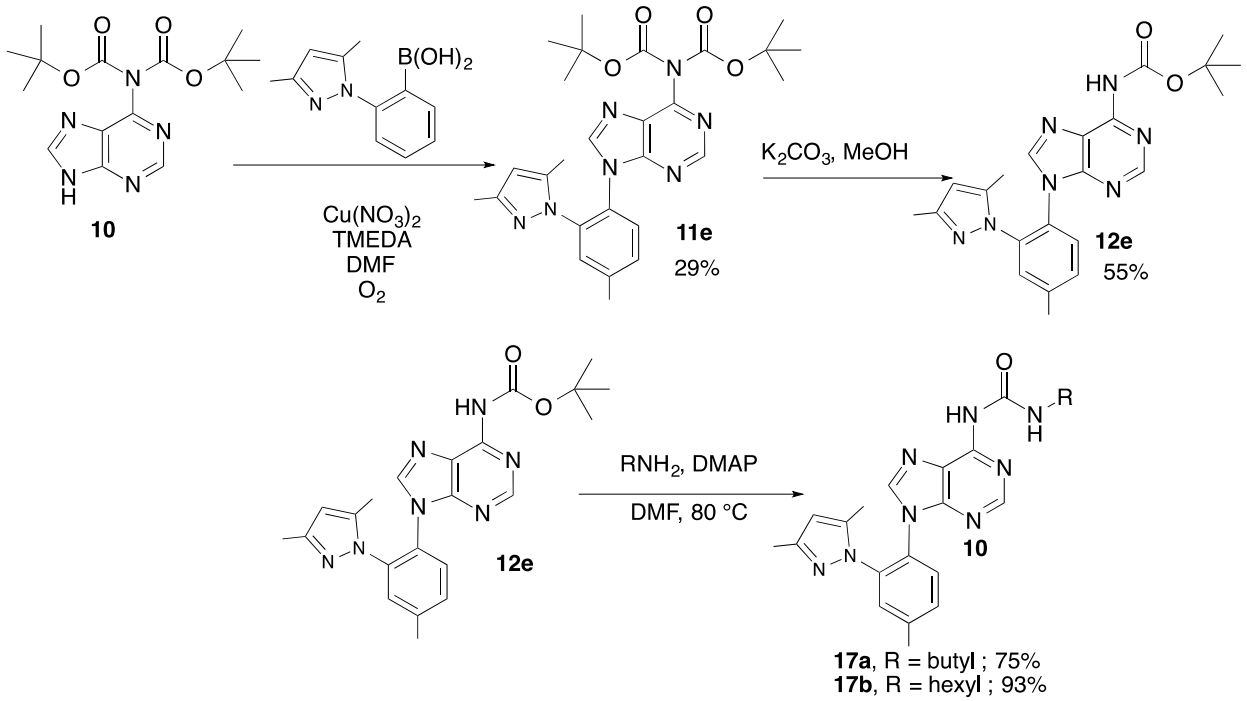


Figure 13. Efficient coupling of hindered aryl groups at the N^9 position

From the data in table 3 a few interesting trends appear. First, the most broadly active derivative is compound **17b**. IC_{50} values for this compound ranged from 15 – 27 uM against the cell lines tested. This is relevant because the docking study had predicted that derivatives with the 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-methylphenyl group at N^9 would be most active. This was encouraging because it suggested that the docking results could be used to reliably guide selection of more active candidates. Comparison of compounds **13d** and **13e** revealed another

Table 3. IC_{50} values for compounds **13-17** in L120, CEM and HeLa cell lines

Compound	IC_{50}* (μM)		
	L1210	CEM	HeLa
13a	> 250	> 250	222 ± 19
13b	> 100	> 100	> 100
13c	142 ± 24	156 ± 100	134 ± 25
13d	> 250	> 250	≥ 250
13e	75 ± 7	23 ± 7	11 ± 1
14a	nd	nd	nd
14b	> 250	> 250	> 250
14c	> 250	> 250	≥ 250
14d	24 ± 1	21 ± 1	36 ± 24
15a	nd	nd	nd
15b	> 250	> 250	> 250
15c	143 ± 106	191 ± 83	96 ± 3
15d	≥ 250	63 ± 4	105 ± 3
15e	78 ± 23	≥ 100	> 100
16a	216 ± 48	194 ± 79	88 ± 12
16b	60 ± 14	140 ± 10	135 ± 6
16c	> 250	> 250	> 250
16d	54 ± 18	167 ± 117	186 ± 91
17a	57 ± 13	47 ± 14	93 ± 18
17b	15 ± 10	27 ± 10	20 ± 4

*50% inhibitory concentration.

important conclusion from this study. Compound **13d** has a cyclohexyl urea at the N^6 position biological activity changed due to the presence of the phenyl urea in **13e**. This observation

formed the basis for the design of the next group of target compounds. Since compound **13e** was the most active compound overall, we decided to perform two structure activity relationship studies (SAR) that would allow us to optimize this lead structure. The first SAR focused on varying the boronic acids at N^9 while leaving the N^6 phenyl urea constant. The second SAR focused on using different aryl amines and heterocycles while leaving the N^9 phenyl constant.

In order to accomplish the first SAR, we needed to explore different approaches for installing the N^6-ureas since yields for the displacement of the *tert*-butyloxy group by aniline via pathway A are consistently poor (27 – 40%, Table 2, entries 5 and 14). The solution to the problem was to apply pathway B (Figure 14).

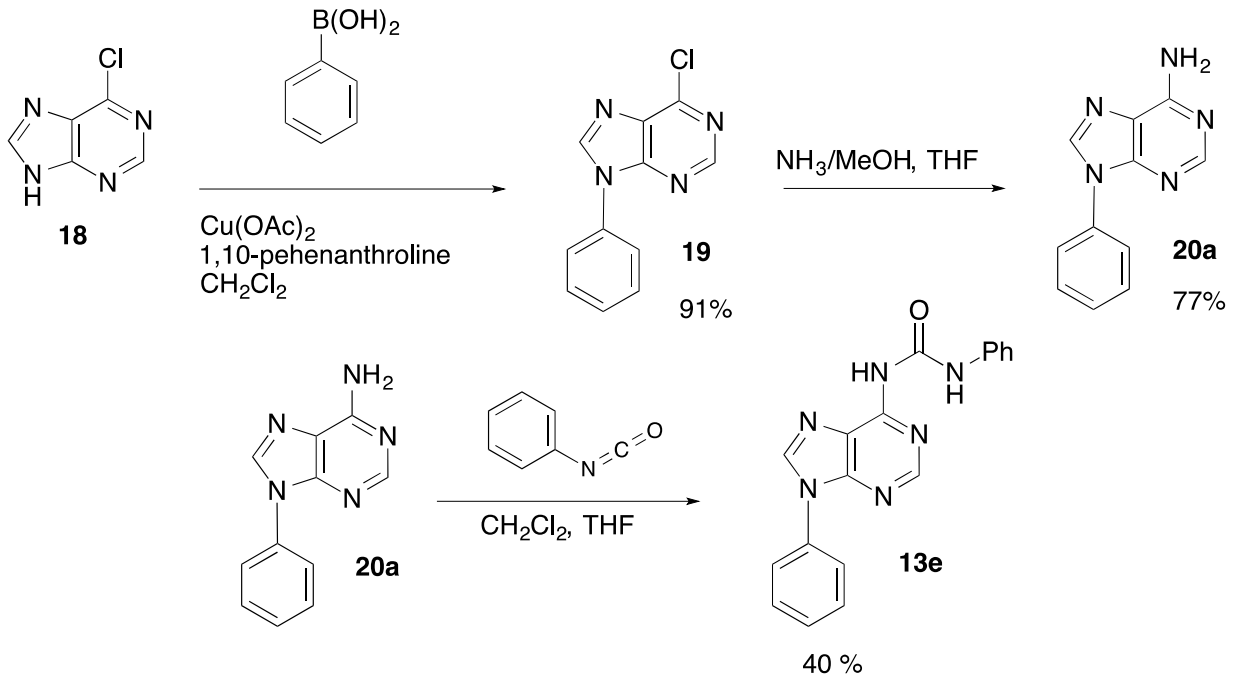
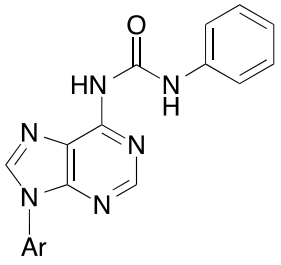


Figure 14. Model study showing efficiency of Pathway B

To demonstrate the feasibility of pathway B for ultimately preparing numerous derivatives varying only at N^9, compound **13e** was prepared as a model system (Figure 14). The first step involved coupling 6-chloropurine with a boronic acid via the Chan-Lam reaction using copper (II) acetate and 1,10-phenanthroline as a base. This step is the branch point for installing various aryl groups at N^9 to give a library of molecules with general structure **21** (Figure 15). Our goal was to make a library of at least 15 compounds with this general structure. Target compounds are illustrated in Figure 15.



21

21a	Ar = 4-*sec*-butylphenyl	**21i**	Ar = 2-Fluorophenyl
21b	Ar = 4-Methoxy-2,6-dimethylphenyl	**21j**	Ar = 3-Fluorophenyl
21c	Ar = 2-Methylphenyl	**21k**	Ar = 4-Fluoropheny
21d	Ar = 3-Methylphenyl	**21l**	Ar = 3-Pyridyl
21e	Ar = 4-Methylphenyl	**21m**	Ar = 4-Pyridyl
21f	Ar = 2-Chlorophenyl	**21n**	Ar = 1-Naphthyl
21g	Ar = 3-Chlorophenyl	**21o**	Ar = 1-Quinolinyl
21h	Ar = 4-Chlorophenyl	**21p**	Ar = 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-methylphenyl

Figure 15. Targets prepared via Pathway B

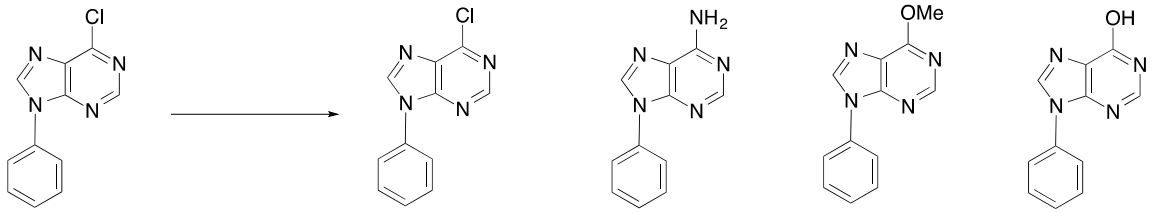
Chan Lam coupling of compound **18** with phenylboronic acid proceeded cleanly to give compound **19** in 91% yield (Figure 14). Displacement of the chlorine at the C-6 position using a saturated solution of ammonia in methanol required some optimization. The conditions we initially examined gave low yields due to the formation of several byproducts (chief of which was the C-6 methanol adduct). Ultimately it was found that byproduct formation could be

minimized by using ammonia in methanol:THF (1:1) (Table 4). The reaction required rigorously anhydrous conditions due to the ability of water to act as a nucleophile and displace the chlorine (which gave byproduct D) table 4 summaries the different conditions used to obtain the desired ammonolysis product.

Table 4. Different conditions employed for the ammonolysis of compound **19**

	Ratio of Products[a]			
Conditions	**A**	**B**	**C**	**D**
NH_3/MeOH	1	1	1	N/A
NH_3/MeOH, THF	N/A	9	1	N/A
NH_3/THF	1	1	1	N/A
Non-anhydrous	N/A	1	N/A	9

[a] Ratios determined by TLC



The final step in preparing compound **13e** involved treatment of compound **20** with phenylisocyanate to give to the desired product in 40% yield. Our yields for this last reaction

were impacted by the tendency of the isocyanate to react with residual moisture in the starting materials. In our hands, this moisture was impossible to completely remove, thus yields were somewhat lower than expected.

As mentioned earlier, the goal of the second SAR was to examine the effect of different aryl amines and heterocycles at N^6 while leaving the N^9 phenyl group constant. We planned to use pathway A to create a library of at least 15 compounds (**Figure 16**).

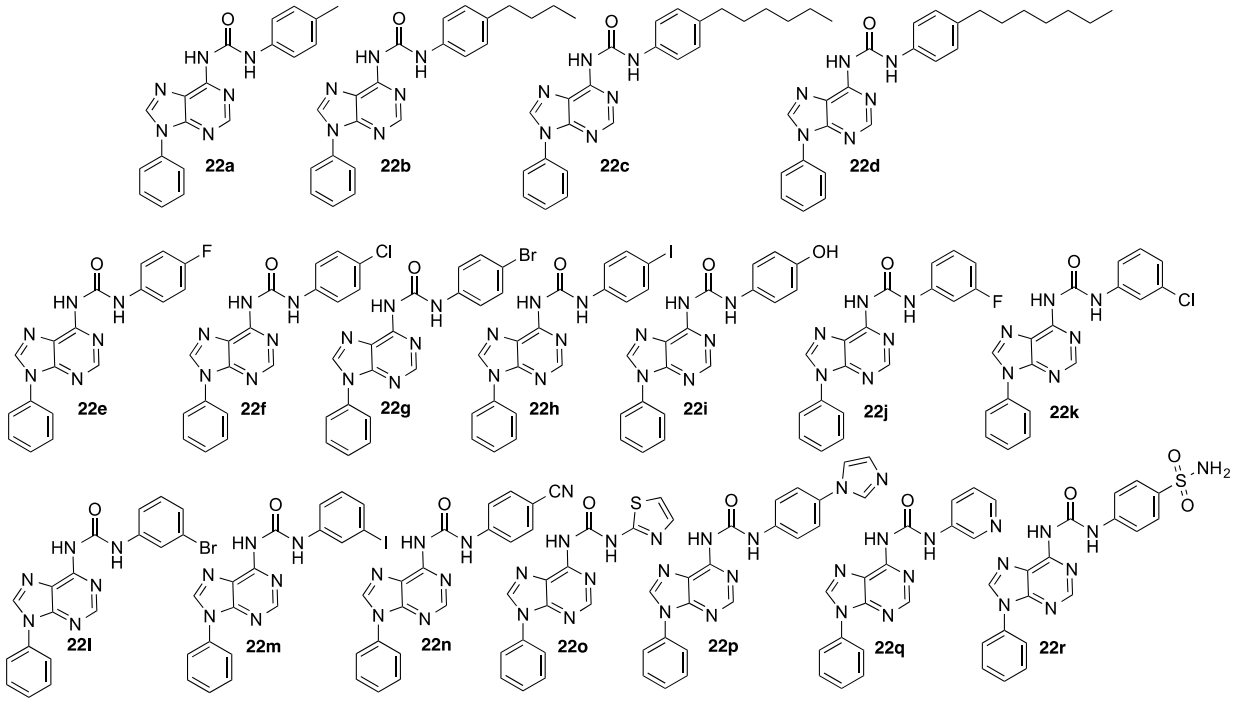


Figure 16. Targets **22a–r**

The analogues were designed with the following ideas in mind. Compounds **22a**–**d** were designed to test the steric tolerance of any binding pockets that might exist in the biological receptor for compound **13e**. Binding of aryl moieties in hydrophobic pockets has been reported

to be enhanced by alkyl substitution at the para-position in some potent bioactive compounds,[20] and derivatives **22a-d** were envisioned as being ideal for probing the possible existence of, and/or steric tolerance associated with, a hydrophobic binding pocket. Compounds **22e–h**, and **22j**–**m** were designed to probe the effect of halogens at either the meta or para positions. It is well known that halogen bonding can give substantial gains in binding affinities.[21] Compounds **22i**, and **22n–s** were designed to test the effects of a variety of hydrogen bond donor or acceptor groups at either the para position (**22i**, **22n**, or **22p**, or in the aromatic ring (**22o**). The results from biological screening of nine of these analogues are summarized in Table 5.

Table 5. IC_{50} values for compounds **22a-22i** for L1210, CEM, HeLa

Compound	IC_{50} (μM)		
	L1210	CEM	HeLa
13e	36 ± 3	60 ± 28	19 ± 3
22a	37 ± 3	46 ± 20	34 ± 1
22b	≥ 60	45 ± 16	≥ 60
22c	28 ± 2	45 ± 16	≥ 60
22d	≥ 60	48 ± 14	> 60
22e	> 60	≥ 60	> 60
22f	35 ± 5	38 ± 15	59 ± 2
22g	27 ± 3	35 ± 19	56 ± 6
22h	27 ± 0	41 ± 25	≥ 60
22i	> 60	≥ 60	> 60

From these data we can draw a few preliminary conclusions: (1) While a para-methyl group seems to be sell tolerated (**22a**), the increase in chain-length and hydrophobicity (**22b**–**d**) had an

overall negative effect on the biological activity; (2) polar groups at the para position (**22e** and **22i**) were not well tolerated; and (3) halogen substitution at the para position did not improve activity relative to the para-methyl derivative (**22a**), but was reasonably well-tolerated for chloro, bromo, and iodo derivatives (**22f**–**h**). These data suggest that there may be a hydrophobic pocket in the active site of the biological receptor(s) for these molecules and that this hydrophobic pocket is of limited size. The remaining analogues (**22j**–**p**) have also been synthesized but biological data is not available at the time of this writing.

An additional set of analogues which had a 4-aminobutyramide moiety attached at C^6 of the adenine nucleus were also indicated to be potential inhibitors of BMPR1b by the docking studies (Figure 17).

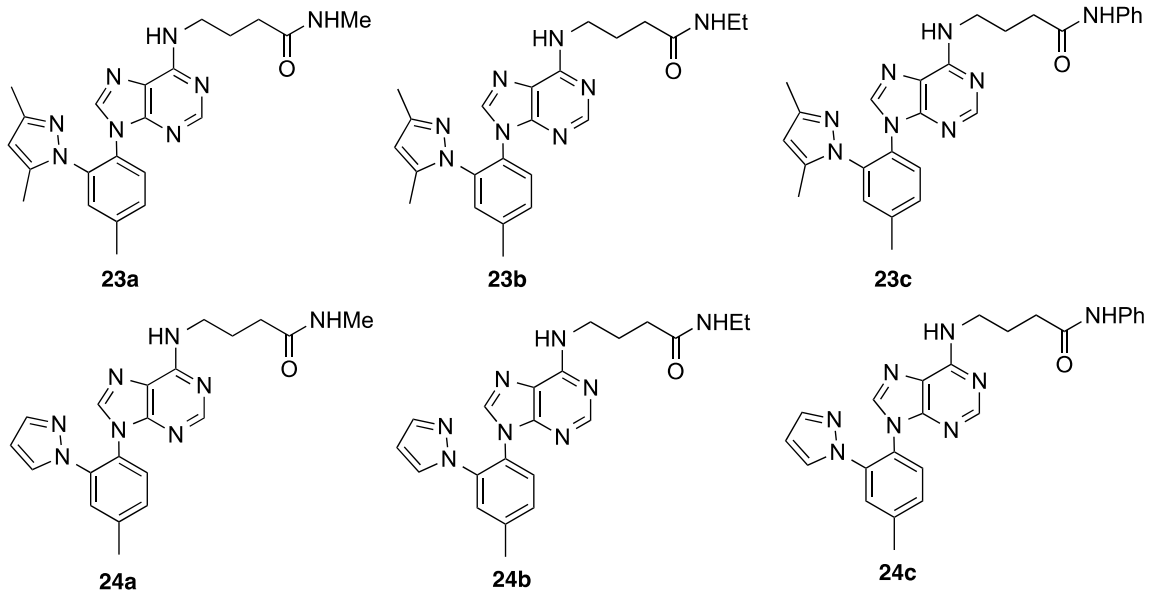


Figure 17. Potential targets containing a 4-aminobutyramide moeity at C^6

Since overall yields for the Cham-Lam coupling between **18** and (2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-methylphenyl)boronic acid had been low (Figure 13), we thought it wise to carry out model studies on more readily obtainable substrates. Hence compounds **27a–d** and **31a–c** were prepared from **19** and **28** (respectively) and screened for biological activity (Figure 18).

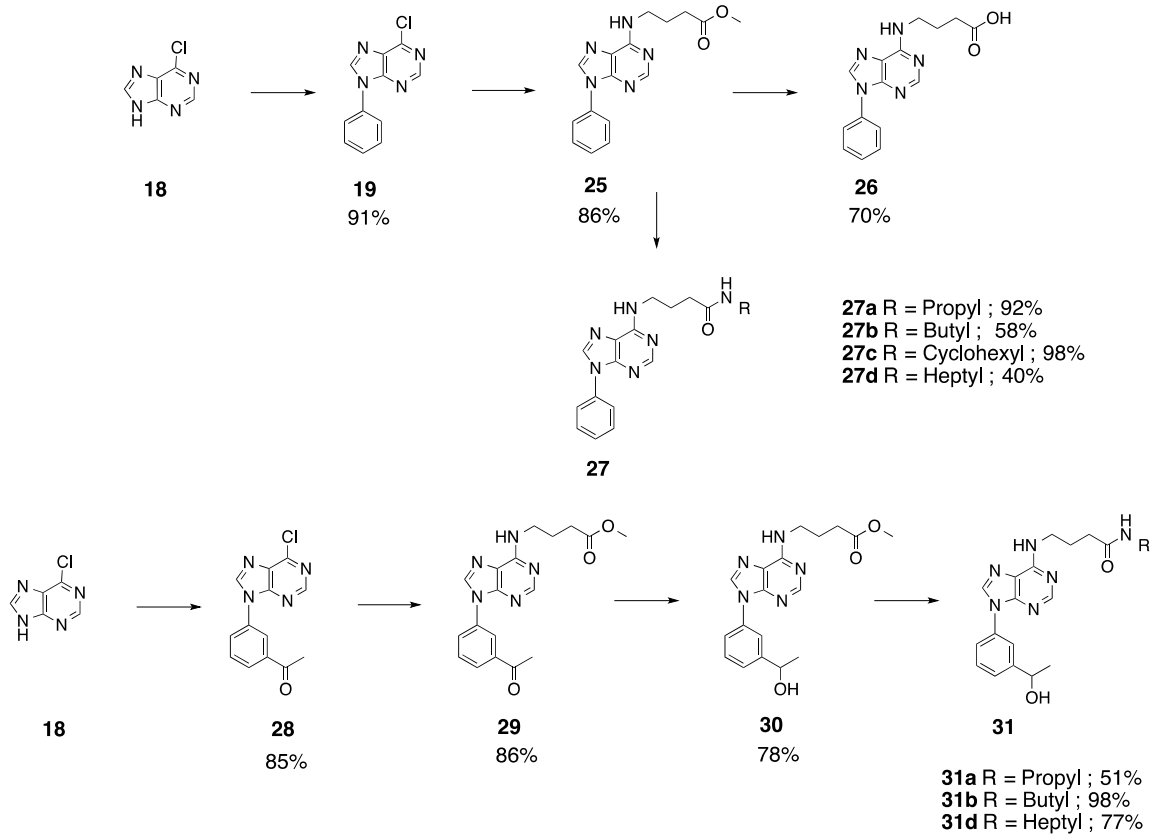
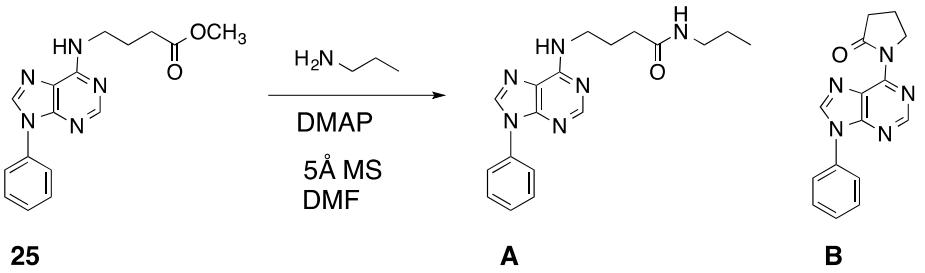


Figure 18. Outline for the synthesis of compounds **27a-d** and **31a-c**

The Chan-Lam coupling reactions proceeded smoothly as expected, giving compounds **19** and **28** in 91 and 85 % yields, respectively. The next step involved the use of methyl 4-aminobutyrate in a nucleophilic aromatic substitution reaction and gave **25** and **29** both in 86% yields. We decided to saponify compound **25** to give **26** since our first attempts at preparing

amides **27** and **31** from the corresponding esters gave products in low yields. (Compound **26** could then serve as a coupling partner for DCC promoted amide formation). Meanwhile, multiple additional conditions were screened for direct conversion of the esters to the amides. As illustrated in Figure 19, treatment of compound **25** with propylamine, DMAP, and 5 Å MS in DMF gave none of the desired product at temperatures as high as 100 °C. Heating at 110–120 °C gave a mixture of the undesired product (B) and unreacted starting material.



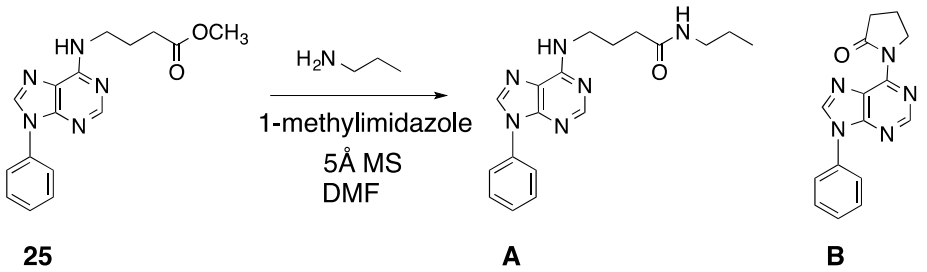
25 **A** **B**

Temperature (C°)	Results
70	No Rxn
80	No Rxn
90	No Rxn
100	No Rxn
110	**B** and **25**
120	**B** and **25**

Figure 19. Effect of temperature on the synthesis of **27a** using DMAP

Use of acylation catalysts 1-methylimidazole and 2-hydroxypyridine gave similar results (Figures 20 & 21). We were delighted to find that treatment of compound **25** with propylamine,

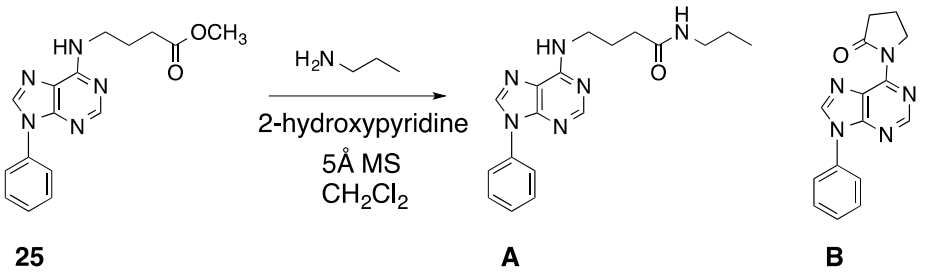
sodium methoxide, and p-nitrophenol, in toluene gave the desired product in excellent yield (Figure 22). This acylation method was used to prepare **27a**–**d** and **31a**–**c** (Figure 18). Data from the biological screening of these compounds are shown in Table 6.



25 **A** **B**

Temperature (C°)	Results
70	No Rxn
80	No Rxn
90	No Rxn
100	No Rxn
110	**B** and **25**
120	**B** and **25**

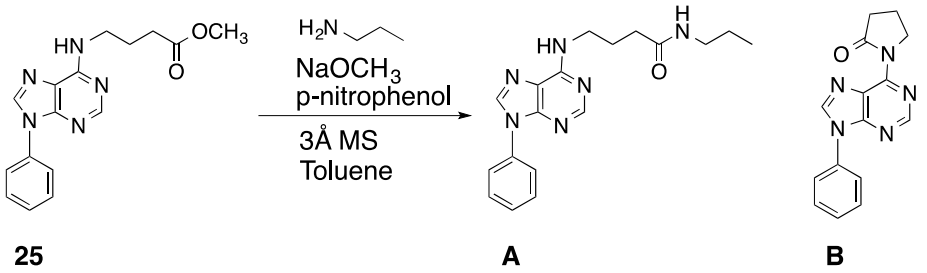
Figure 20. Effect of temperature on the synthesis of **27a** using 1-methylimidazole



25 **A** **B**

Temperature (C°)	Results
70	No Rxn
80	No Rxn
90	No Rxn
100	No Rxn
110	No Rxn
120	No Rxn

Figure 21. Effect of tempereature on the synthesis of **27a** using 2-hydroxypyridine



25 **A** **B**

Temperature (C°)	Results (Ratio)[a]
70	**A**: **25** (1:9)
80	**A**: **25** (1:4)
90	**A**: **25** (1:4)
100	**A**: **25** (1:1)
110	**A**: **25** (4:1)
120	**A**: **25** (9:1)
130	**A**: **25** (9:1)
140	**A**: **25** (9:1)

[a] Ratios were determined by TLC

Figure 22. Effect of temperature on the sythesis of **27a** using sodium methoxide and p-nitrotoluene

Table 6. IC_{50} data for compounds **27a-d**, **31a-31d** and **13b** on L1210, CEM and HeLa cell lines

Compound	IC_{50}* (μg/ml)		
	L1210	CEM	HeLa
27a	45 ± 7	35 ± 18	97 ± 4
27b	52 ± 17	40 ± 10	> 100
27c	26 ± 3	12 ± 3	30 ± 2
27d	19 ± 5	15 ± 7	36 ± 9
31a	39 ± 2	42 ± 1	50 ± 1
31b	30 ± 4	29 ± 0	43 ± 2
31d	8.9 ± 0.1	10 ± 1	20 ± 6
13b	> 100	> 100	> 100

*50% inhibitory concentration.

As mentioned earlier, the second main goal of my research was to synthesize analogues of **JRS-150** that contained the dicarbamyl iodoacetamide moiety in order to determine how critical this part of the molecule is to the observed biological activity. Our initial efforts in this area focused on the synthesis of only two analogues, compounds **32** and **33** (Figure 23). The synthesis of these targets is illustrated in Figures 24 and 25.

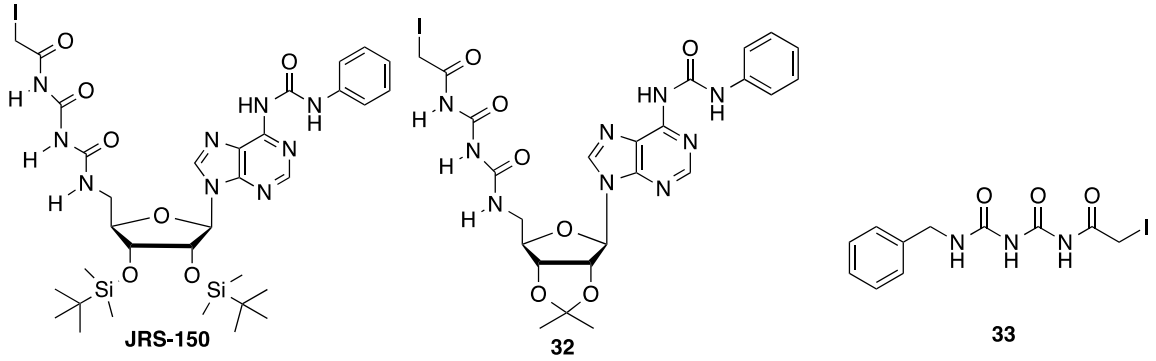


Figure 23. Analogues of **JRS-150**

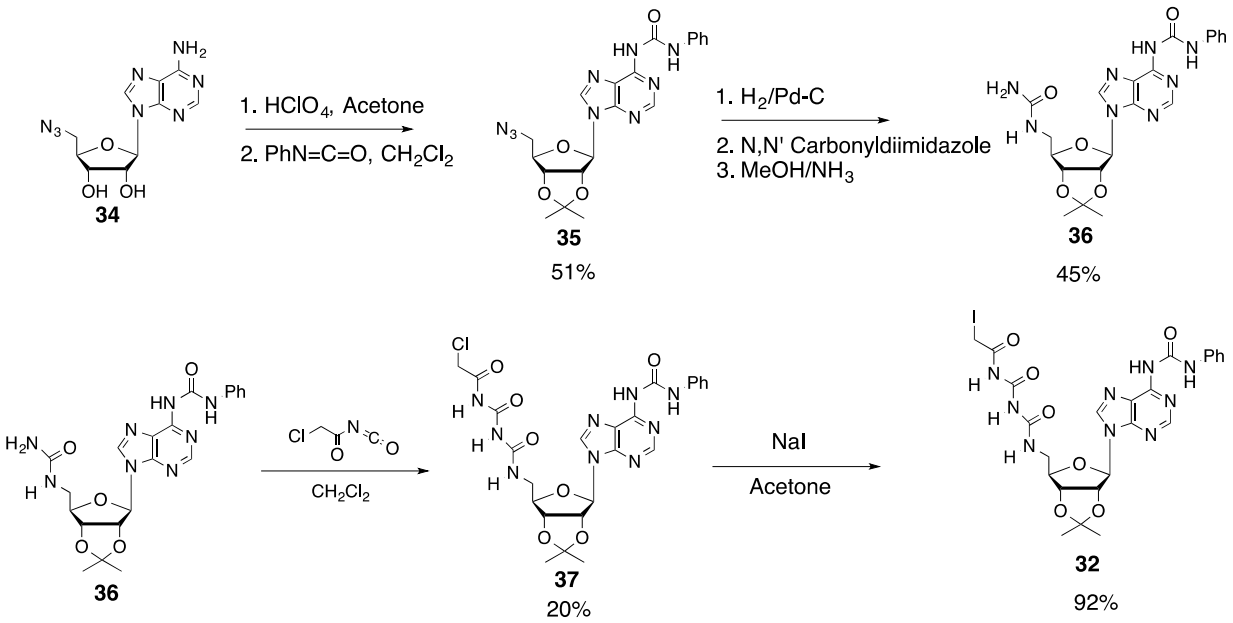


Figure 24. Outline for the synthesis of compound **32**

Compound **32** was prepared using fairly straightforward procedures (Figure 24).[22] Treatment of compound **34** with perchloric acid (cat.) and acetone gave the acetonide in nearly quantitative yield. Treatment of the crude acetonide with phenylisocyanate gave compound **35** in 51% yield after chromatography. Compound **35** could be converted to urea **36** via a three-step method as illustrated. Compound **36** was then treated with chloroacetylisocyanate to give **37**. Despite efforts to optimize this reaction, the yields were generally low. The final step involves a Finkelstein reaction using sodium iodide in acetone. The final product (**32**) was obtained in 92% isolated yield.

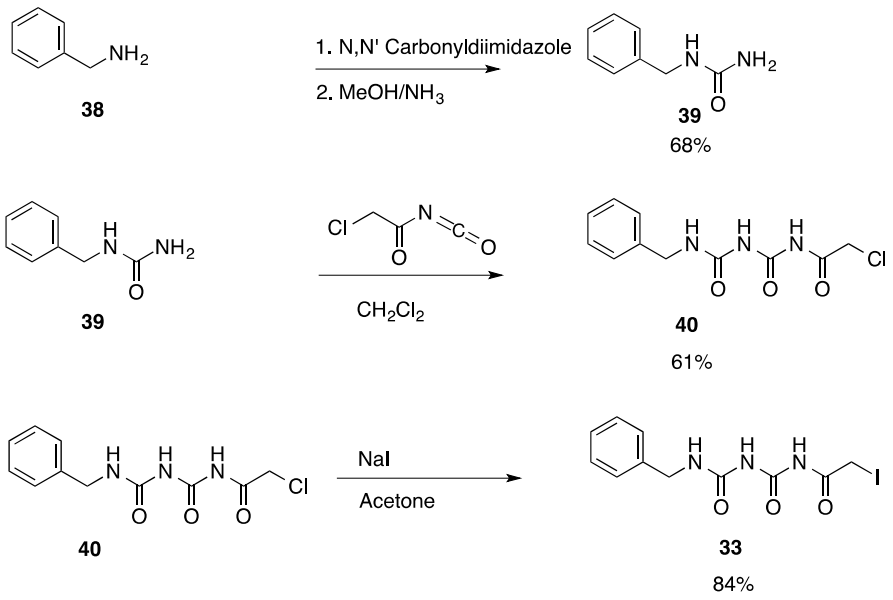


Figure 25. Outline for the synthesis of compound **33**

The synthesis of compound **33** was more straightforward and less time-consuming. There were only three steps in the synthesis of **33** and it was much more drug-like than either **JRS-150** or compound **32** (Figure 25).

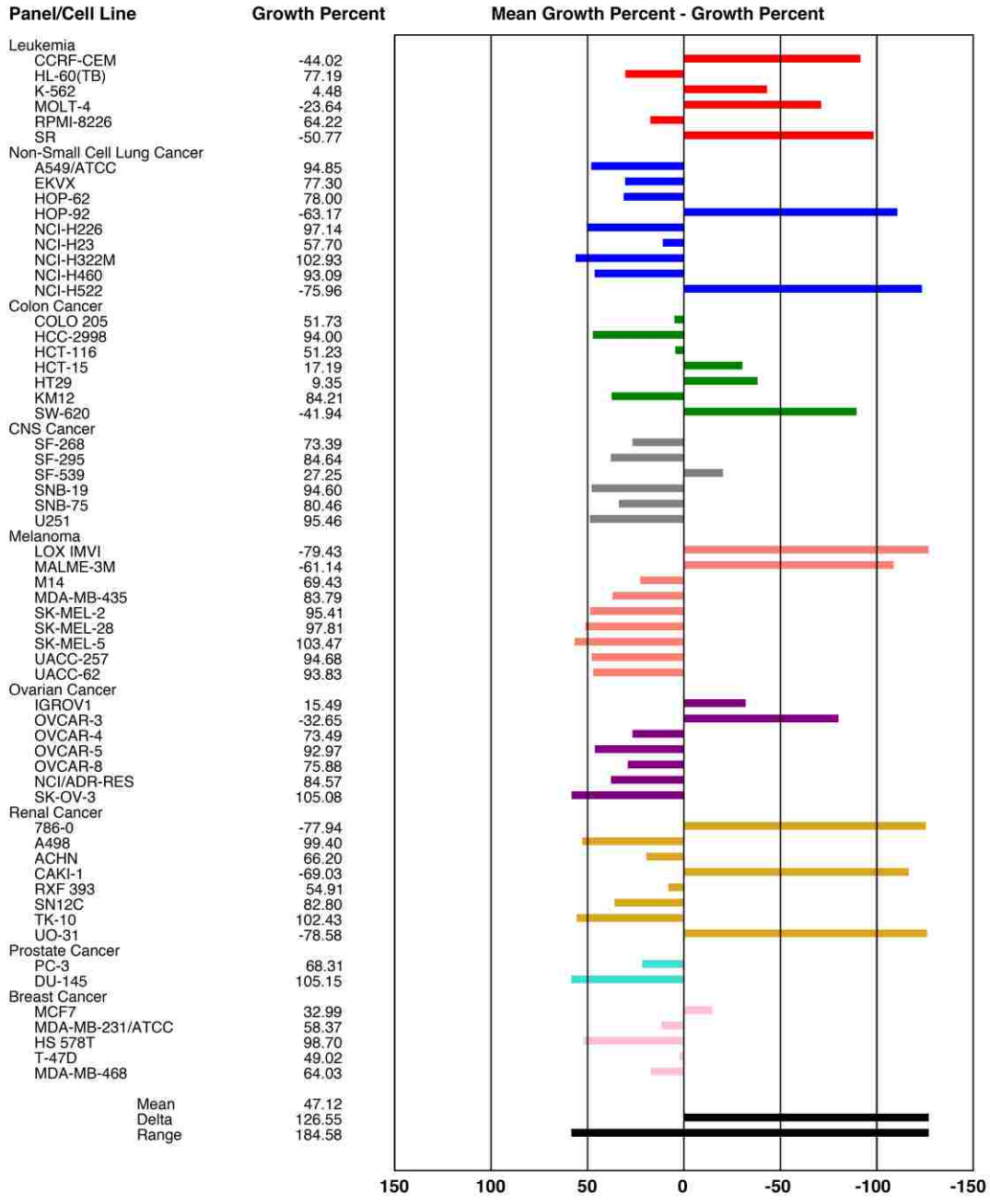
Commercially available benzylamine is stirred with N,N'-carbonyldiimidazole in dichloromethane for twenty four hours. The crude is then treated with a saturated solution of ammonia in methanol to give compound **39** in 68% isolated yield. This intermediate is then stirred for three days in dry dichloromethane with chloroacetylisocyanate to give compound **40** in 61% isolated yield. The final step involved treatment of **40** with sodium iodide in acetone to give **33** in 84% yield.

Compounds **32** and **33** were submitted to the NIH for the NCI-60 screen. Results obtained were very interesting and helped us guide selection of additional targets. Tables 7 and 8 summarize the

data obtained from compounds **32** and **33**, respectively. Table 9 summarize the data obtained from **JRS-150**.

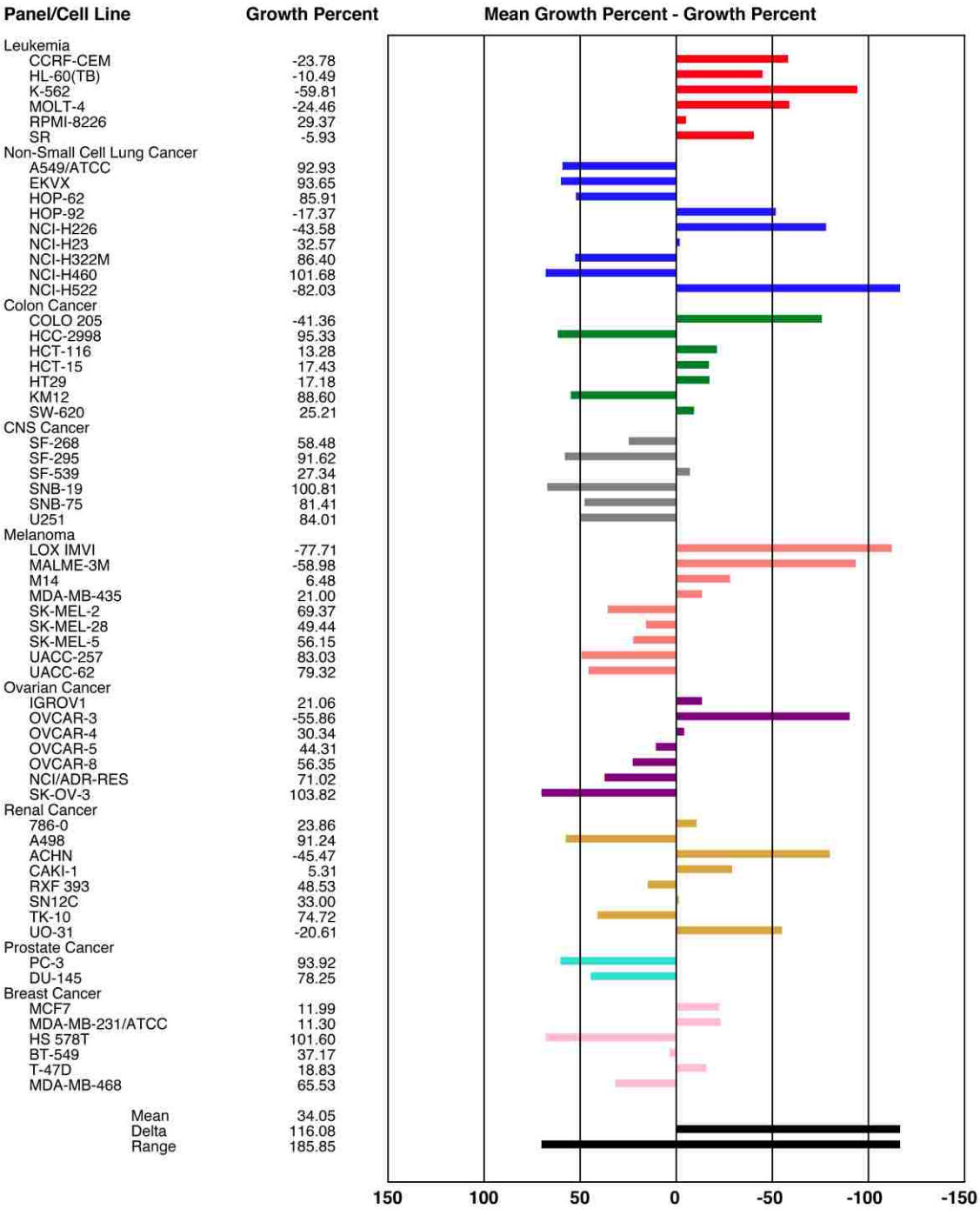
A quick visual inspection of these data reveal a few qualitative similarities. For example, all three compounds inhibited lung adenocarcinoma cell line NCI-H522 by about 80% relative to control. Melanoma cell lines LOX IMVI and MALME-3M were inhibited by all three compounds at a similar level. Several leukemia cell lines were potently inhibited, and ovarian cancer cell lines IGROV-1 and OVCAR-3 were selectively targeted. Compound **32** and **JRS-150** inhibited renal cancer cell line UO-31 by approximately 80%, but compound **33** inhibited this cell line to a lesser degree (20%). A COMPARE[23] analysis for compounds **33** and **JRS-150** revealed only a 0.5 correlation (Spearman's R, Table 10). This suggested to us that the structure of the moieties attached to the iodoacetamide dicarbamoyl moiety might play an important role in molecular recognition and that an SAR focused on the "non-iodoacetamide dicarbamoyl" functionality might reveal some novel activity. Toward this end the compounds in Figures 26 and 27 were prepared and evaluated.

Table 7. NCI-60 single dose data for compound **32**



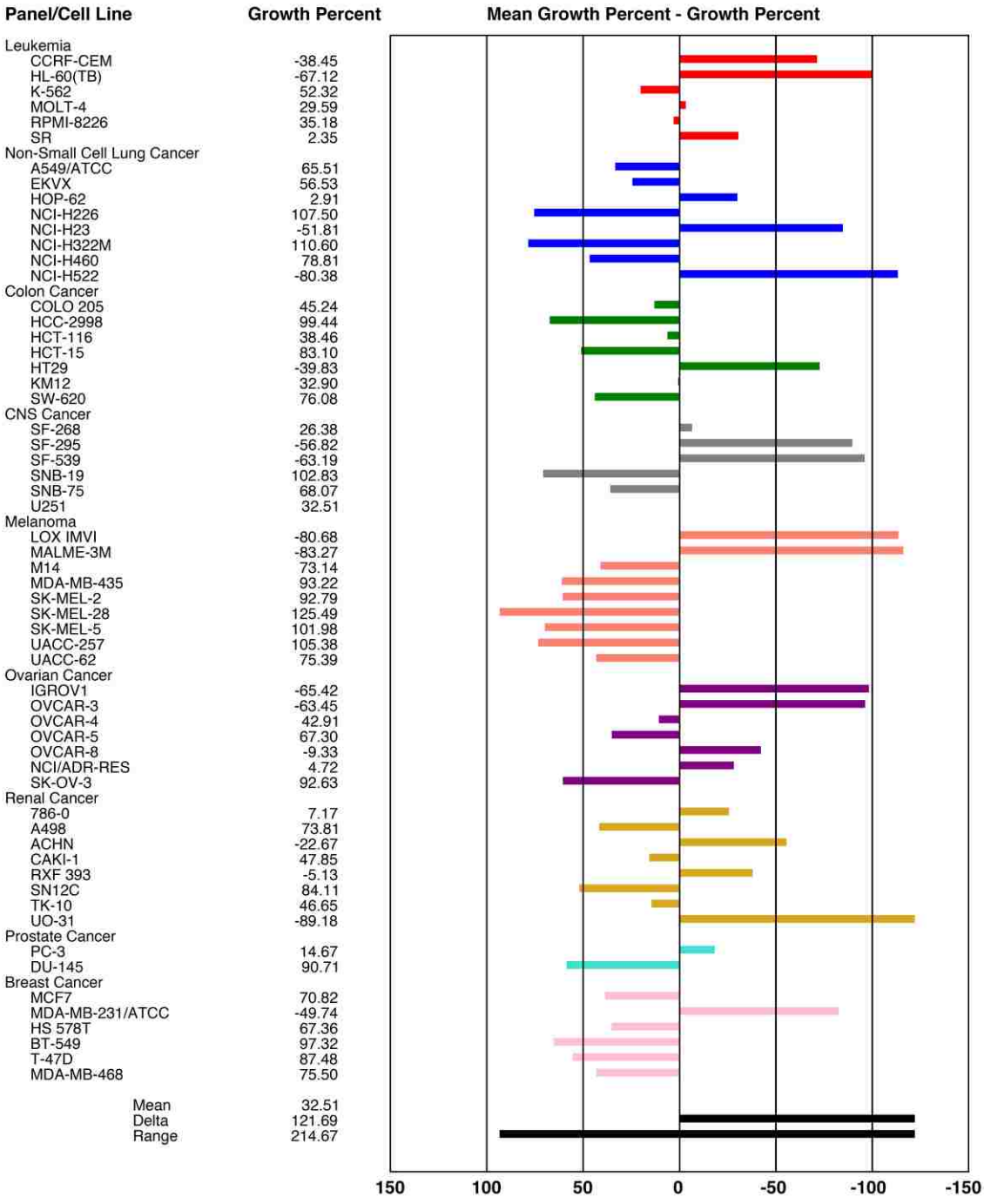
Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	-44.02
HL-60(TB)	77.19
K-562	4.48
MOLT-4	-23.64
RPMI-8226	64.22
SR	-50.77
Non-Small Cell Lung Cancer	
A549/ATCC	94.85
EKVX	77.30
HOP-62	78.00
HOP-92	-63.17
NCI-H226	97.14
NCI-H23	57.70
NCI-H322M	102.93
NCI-H460	93.09
NCI-H522	-75.96
Colon Cancer	
COLO 205	51.73
HCC-2998	94.00
HCT-116	51.23
HCT-15	17.19
HT29	9.35
KM12	84.21
SW-620	-41.94
CNS Cancer	
SF-268	73.39
SF-295	84.64
SF-539	27.25
SNB-19	94.60
SNB-75	80.46
U251	95.46
Melanoma	
LOX IMVI	-79.43
MALME-3M	-61.14
M14	69.43
MDA-MB-435	83.79
SK-MEL-2	95.41
SK-MEL-28	97.81
SK-MEL-5	103.47
UACC-257	94.68
UACC-62	93.83
Ovarian Cancer	
IGROV1	15.49
OVCAR-3	-32.65
OVCAR-4	73.49
OVCAR-5	92.97
OVCAR-8	75.88
NCI/ADR-RES	84.57
SK-OV-3	105.08
Renal Cancer	
786-0	-77.94
A498	99.40
ACHN	66.20
CAKI-1	-69.03
RXF 393	54.91
SN12C	82.80
TK-10	102.43
UO-31	-78.58
Prostate Cancer	
PC-3	68.31
DU-145	105.15
Breast Cancer	
MCF7	32.99
MDA-MB-231/ATCC	58.37
HS 578T	98.70
T-47D	49.02
MDA-MB-468	64.03
Mean	47.12
Delta	126.55
Range	184.58

Table 8. NCI-60 single dose data for compound **33**



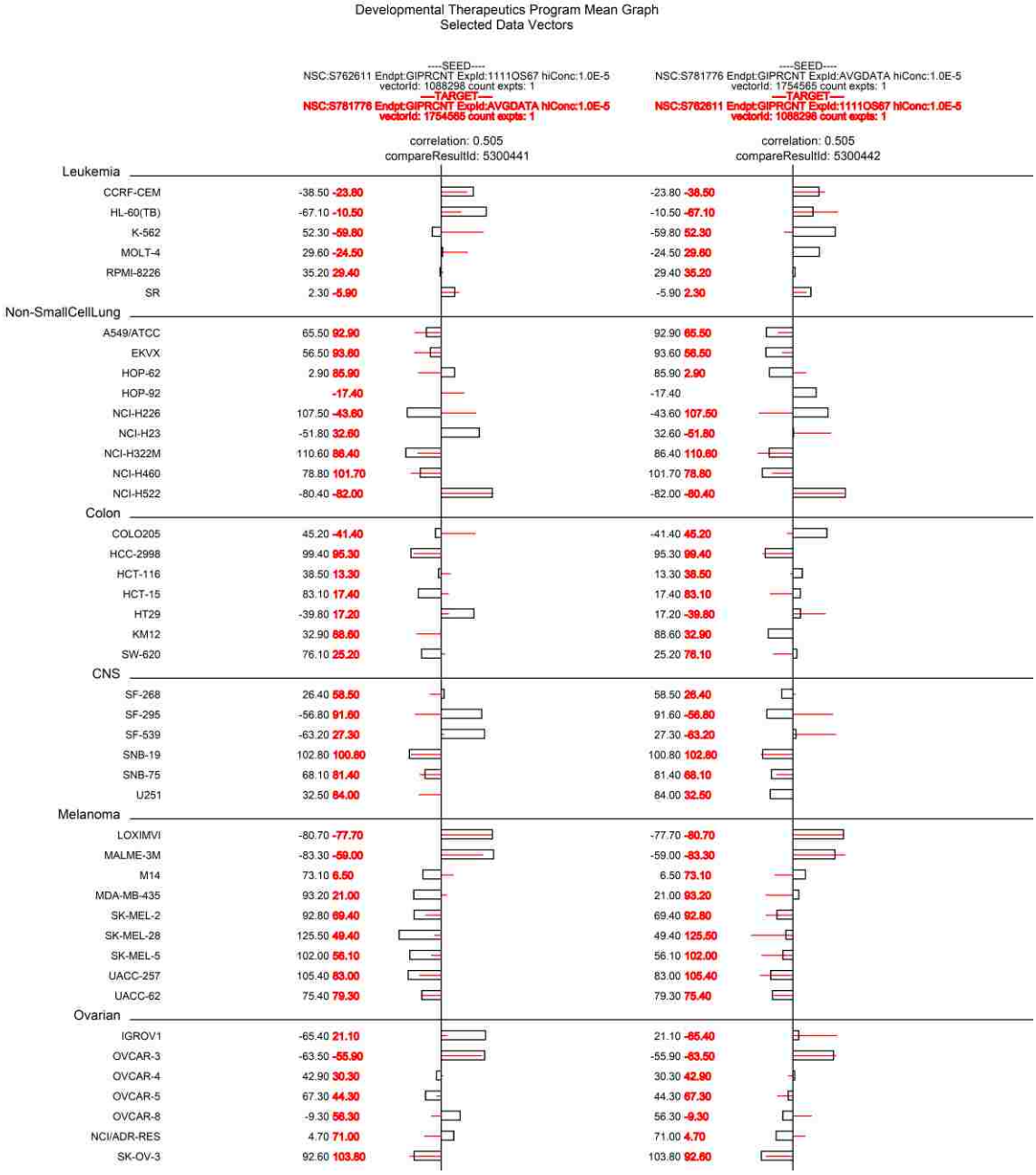
Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	-23.78
HL-60(TB)	-10.49
K-562	-59.81
MOLT-4	-24.46
RPMI-8226	29.37
SR	-5.93
Non-Small Cell Lung Cancer	
A549/ATCC	92.93
EKVX	93.65
HOP-62	85.91
HOP-92	-17.37
NCI-H226	-43.58
NCI-H23	32.57
NCI-H322M	86.40
NCI-H460	101.68
NCI-H522	-82.03
Colon Cancer	
COLO 205	-41.36
HCC-2998	95.33
HCT-116	13.28
HCT-15	17.43
HT29	17.18
KM12	88.60
SW-620	25.21
CNS Cancer	
SF-268	58.48
SF-295	91.62
SF-539	27.34
SNB-19	100.81
SNB-75	81.41
U251	84.01
Melanoma	
LOX IMVI	-77.71
MALME-3M	-58.98
M14	6.48
MDA-MB-435	21.00
SK-MEL-2	69.37
SK-MEL-28	49.44
SK-MEL-5	56.15
UACC-257	83.03
UACC-62	79.32
Ovarian Cancer	
IGROV1	21.06
OVCAR-3	-55.86
OVCAR-4	30.34
OVCAR-5	44.31
OVCAR-8	56.35
NCI/ADR-RES	71.02
SK-OV-3	103.82
Renal Cancer	
786-0	23.86
A498	91.24
ACHN	-45.47
CAKI-1	5.31
RXF 393	48.53
SN12C	33.00
TK-10	74.72
UO-31	-20.61
Prostate Cancer	
PC-3	93.92
DU-145	78.25
Breast Cancer	
MCF7	11.99
MDA-MB-231/ATCC	11.30
HS 578T	101.60
BT-549	37.17
T-47D	18.83
MDA-MB-468	65.53
Mean	34.05
Delta	116.08
Range	185.85

Table 9. NCI-60 single dose data for **JRS-150**



Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	-38.45
HL-60(TB)	-67.12
K-562	52.32
MOLT-4	29.59
RPMI-8226	35.18
SR	2.35
Non-Small Cell Lung Cancer	
A549/ATCC	65.51
EKVX	56.53
HOP-62	2.91
NCI-H226	107.50
NCI-H23	-51.81
NCI-H322M	110.60
NCI-H460	78.81
NCI-H522	-80.38
Colon Cancer	
COLO 205	45.24
HCC-2998	99.44
HCT-116	38.46
HCT-15	83.10
HT29	-39.83
KM12	32.90
SW-620	76.08
CNS Cancer	
SF-268	26.38
SF-295	-56.82
SF-539	-63.19
SNB-19	102.83
SNB-75	68.07
U251	32.51
Melanoma	
LOX IMVI	-80.68
MALME-3M	-83.27
M14	73.14
MDA-MB-435	93.22
SK-MEL-2	92.79
SK-MEL-28	125.49
SK-MEL-5	101.98
UACC-257	105.38
UACC-62	75.39
Ovarian Cancer	
IGROV1	-65.42
OVCAR-3	-63.45
OVCAR-4	42.91
OVCAR-5	67.30
OVCAR-8	-9.33
NCI/ADR-RES	4.72
SK-OV-3	92.63
Renal Cancer	
786-0	7.17
A498	73.81
ACHN	-22.67
CAKI-1	47.85
RXF 393	-5.13
SN12C	84.11
TK-10	46.65
UO-31	-89.18
Prostate Cancer	
PC-3	14.67
DU-145	90.71
Breast Cancer	
MCF7	70.82
MDA-MB-231/ATCC	-49.74
HS 578T	67.36
BT-549	97.32
T-47D	87.48
MDA-MB-468	75.50
Mean	32.51
Delta	121.69
Range	214.67

Table 10. Compare analysis of compound **33** (NSC:S781776) and **JRS-150** (NSC:S762611)



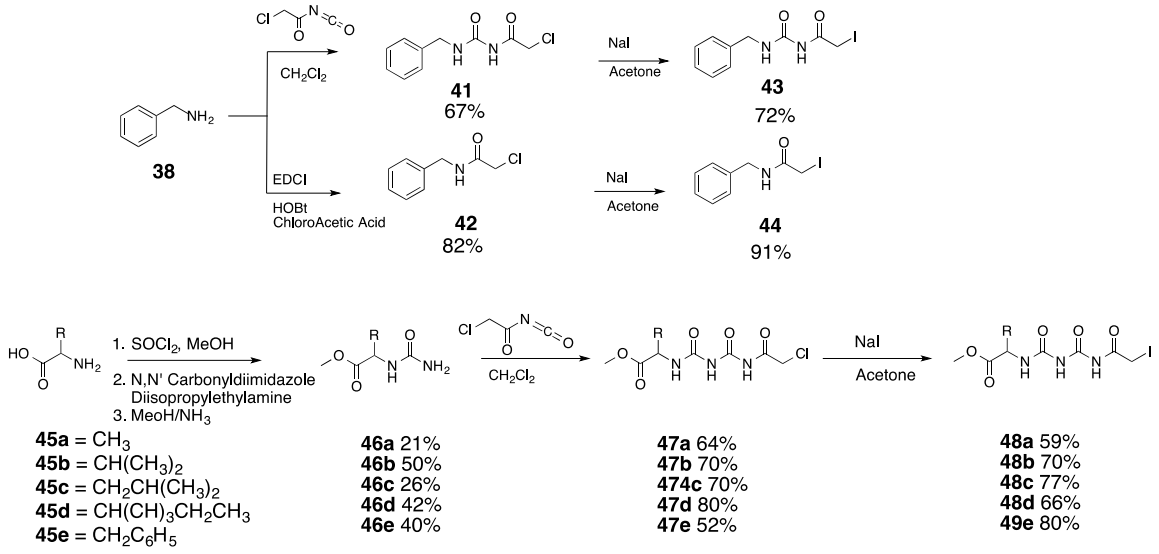


Figure 26. Synthesis of amino acid based analogues of compound **33**

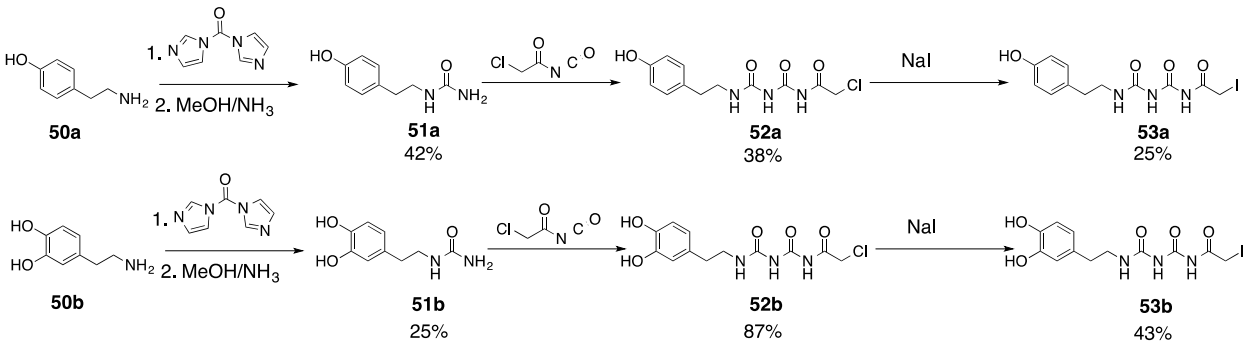


Figure 27. Synthesis of dopamine and tyramine analogues of compound **33**

For this study we decided to use some amino acids as well as dopamine and tyramine. Derivatives of some amino acids and both dopamine and tyramine have been used to make drugs. Also compounds **43** and **44** were synthesized in order to understand the importance of the size of the polycarbamyl chain. Analogues were sent to the NIH for the NCI-60 screen. Data from the screen test will be published as soon as it is available.

The main goal of my research was to create small molecule inhibitors of BMPR-1b using **JRS-150** as a starting point. Many of the compounds I synthesized have potent anticancer activities in vitro. Some of these compounds are more active than others, but all of the compounds help establish the SAR for these new compounds. These studies have given us vital information to improve the biological activity of our drug candidates and to design future experiments to further increasing their selectivity and inhibition properties.

CONCLUSIONS

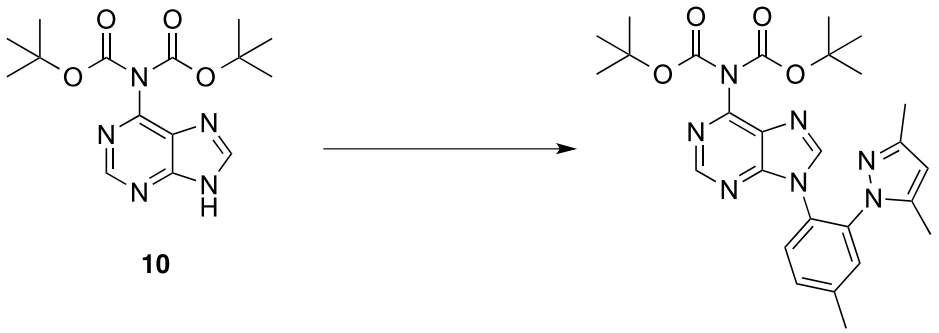
A series of N^9-aryl-N^6 ureidoadenine derivatives was prepared and tested for activities in antiproliferative assays against HeLa, L1210, CEM and the NCI 60 panel of human cancers. Two methods were developed to facilitate the exploration of groups at the N^6 and N^9 positions. From this study it was concluded that the phenyl ureas at the N^6 position show a positive effect on the biological activity of our compounds. Alkyl substitution at the para-position on the phenyl ureas showed a negative effect on the biological activities. Examination of different aryl groups at the N^9 position showed that the 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-methylphenyl group is the most active. It is important to mention that not all the compounds have been screened. Further conclusions will be made as soon as this data is available.

A second series containing a dicarbamoyl iodoacetamide group was made to explore the importance of that functional group on the biological activity of our compounds. Compounds were tested for activities in antiproliferative assays against HeLa, L1210, CEM and the NCI 60 panel of human cancers. Data obtained from this study strongly suggested that the dicarmaboyl iodoacetamide group plays a vital role in activity of our compounds. Nonetheless, additional studies are required to fully understand the mechanism of action.

EXPERIMENTAL SECTION

General Experimental

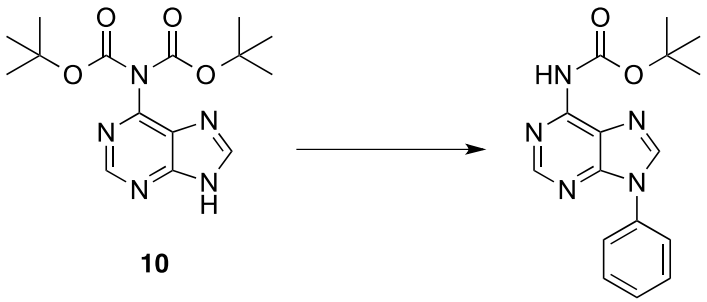
Flash Chromatography was carried out using 230-400 mesh silica gel. Preparative TLC was performed using Merck Kieselgel 60 F_{254} sheets. ^{1}H NMR spectra were obtained on either a Varian INOVA 300 MHz, a Varian INOVA 500 MHz or a Varian NMR-System 500 MHz spectrometer using internal references at δ 7.27 ($CDCl_3$), δ 2.50 (DMSO-*d6*) and δ 11.65, 2.04 (Acetic acid-*d4*). High resolution mass spectra were obtained using ESI techniques on an Agilent 6230 ToF or an Agilent 6210 ToF spectrometer. Commercially available reagents were used as supplied. All water sensitive reactions were performed in flame-dried flask under Nitrogen or Argon. Solvents used in the reactions were dried by passing through columns of activated alumina under Argon.



10 **11e**

N^6-bis-tert-butyloxycarbonyl-9-[2-(3,5-dimethylpyrazol-1-yl)-4-methylphenyl]-adenine (11e)

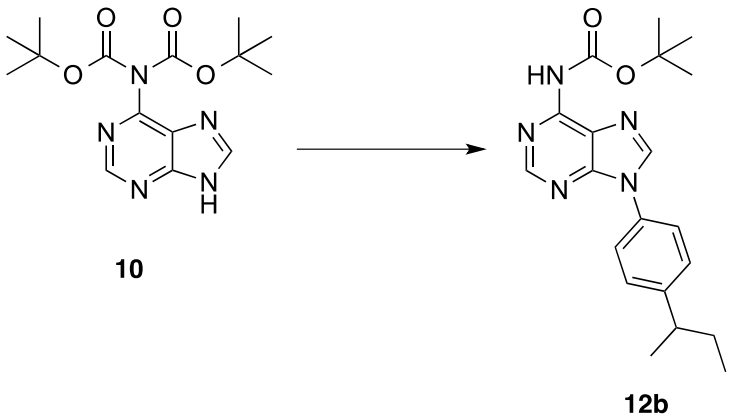
To a solution of **10** (60 mg, 0.18 mmol) and (2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-methylphenyl)boronic acid (81 mg, 0.35 mmol), in dry MeOH (3.0 mL) was added $Cu(NO_3)_2 \bullet 6H_2O$ (390 μL of 0.14 M solution in dry MeOH, 0.055 mmol) and TMEDA (390 μL of a 0.14 M solution in dry MeOH, 0.055 mmol). The resulting mixture was stirred for 24 h at ambient temperature under O_2. Volatiles were evaporated and the crude material was re-dissolved in CH_2Cl_2 and washed with saturated EDTA (aq). The organic layer was dried over Na_2SO_4 and volatiles were removed under reduced pressure. Flash chromatography (70% EtOAc/Hexanes) gave **11e** (27 mg, 0.052 mmol, 29%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.88 (s, 1H), 7.72 (s, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.45 (s, 1H), 5.77 (s, 1H), 2.53 (s, 3H), 2.24 (s, 3H), 1.69 (s, 3H), 1.46 (s, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.3, 152.7, 150.6, 150.3, 150.1, 144.8, 140.9, 140.7, 134.5, 130.9, 130.2, 128.44, 128.37, 127.0, 106.4, 83.8, 27.8, 21.1, 13.5, 10.8; HRMS [M+H] = 520.2677; $C_{27}H_{34}N_7O_4$ = 520.2672.



10 **12a**

N^6-*tert*-Butyloxycarbonyl-9-phenyladenine (12a)

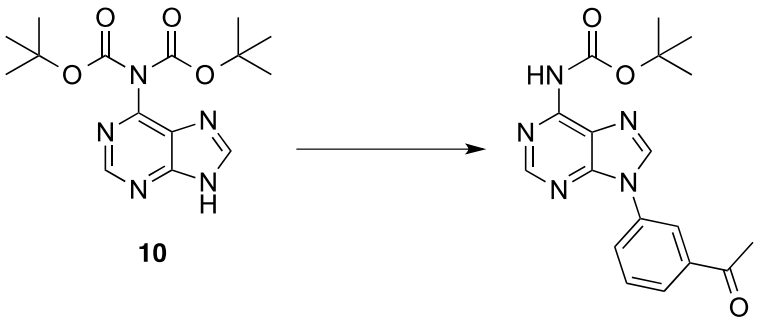
To a solution of **10** (100 mg, 0.30 mmol), phenylboronic acid (75 mg, 0.61mmol), and triethylamine (60 μL), in dry DMF (1.5 mL) was added copper (II) acetate (90 mg, 0.50 mmol) and 5Å molecular sieves (300 mg). The resulting mixture was stirred for 4 days at ambient temperature under air. Volatiles were evaporated and the crude material was re-dissolved in dry MeOH (3.0 mL). To this solution K_2CO_3 (100 mg, 0.72 mmol) was added and the mixture was stirred for 12 h at ambient temperature. Volatiles were evaporated and the crude was partitioned (CH_2Cl_2//H_2O). The organic layer was separated and dried over Na_2SO_4. Flash chromatography (70% EtOAc/Hexanes) gave **12a** (30 mg, 0.10 mmol, 33%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.84 (s, 1H), 8.24 (s, 1H), 8.15 (bs, 1H), 7.74 (d, *J* = 8.0, 2H), 7.62 (t, *J* = 7.5, 2H), 7.51 (t, *J* = 7.5, 1H), 1.60 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153. 7, 150.3, 149.7, 141.3, 134.3, 130.0, 128.6, 123.5, 82.4, 28.2; HRMS = [M+H] 312.1456; $C_{16}H_{18}N_5O_2$ = 312.1460.



10 **12b**

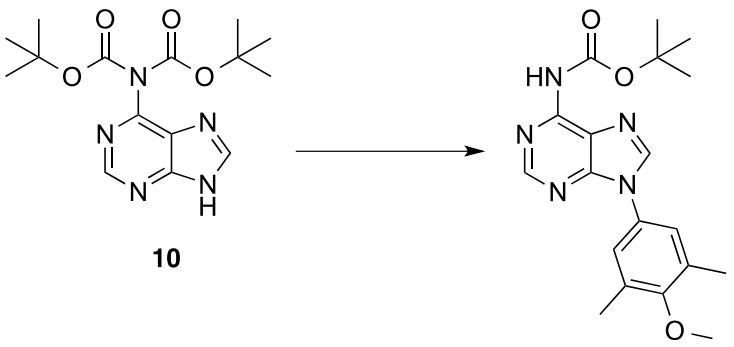
N^6-*tert*-Butyloxycarbonyl-9-(4-*sec*-butylphenyl)adenine (12b)

To a solution of **10** (100 mg, 0.30 mmol), 4-*sec*-butylphenylboronic acid (110 mg, 0.62 mmol), and triethylamine (60 μL) in dry DMF (1.5 mL) was added copper (II) acetate (90 mg, 0.50 mmol) and 5Å molecular sieves (300 mg). The resulting mixture was stirred for 4 days at ambient temperature under air. Volatiles were evaporated and the crude material was re-dissolved in dry MeOH (4.0 mL). To this solution K_2CO_3 (100 mg, 0.72 mmol) was added and the mixture was stirred for 12 h at ambient temperature. Volatiles were evaporated and the crude was partitioned (CH_2Cl_2//H_2O). The organic layer was separated and dried over Na_2SO_4. Flash chromatography (70% EtOAc/Hexanes) gave **12b** (50 mg, 0.14 mmol, 47%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.00 (s, 1H), 8.79 (s, 1H), 8.22 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 2.64 (sext, *J* = 7.0 Hz, 1H), 1.59 (pent, *J* = 7.3 Hz, 2H), 1.52 (s, 9H), 1.23 (d, *J* = 7.0 Hz, 3H), 0.81 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.5, 151.1, 150.5, 150.1, 148.4, 141.7, 131.9, 128.5, 123.5, 82.1, 41.4, 31.0, 28.1, 21.8, 12.2; HRMS [M+H] = 368.2093; $C_{20}H_{26}N_5O_2$ = 368.2087.



N^6-*tert*-Butyloxycarbonyl-9-(3-acetylphenyl)adenine (12c)

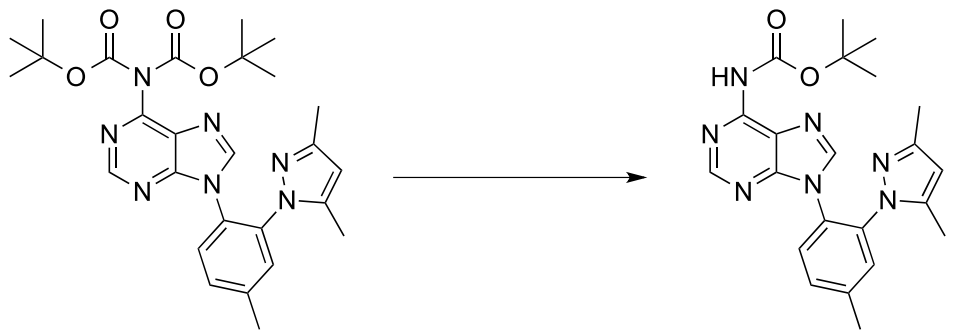
To a solution of **10** (100 mg, 0.30 mmol), 3-acetylphenylboronic acid (98 mg, 0.60 mmol), and triethylamine (60 μL) in dry DMF (1.5 mL) was added copper (II) acetate (90 mg, 0.50 mmol) and 5Å molecular sieves (350 mg). The resulting mixture was stirred for 4 days at ambient temperature under air. Volatiles were evaporated and the crude material was re-dissolved in dry MeOH (4.0 mL). To this solution K_2CO_3 (100 mg, 0.72 mmol) was added and the mixture was stirred for 12 h at ambient temperature. Volatiles were evaporated and the crude was partitioned (CH_2Cl_2/H_2O). The organic layer was separated and dried over Na_2SO_4. Flash chromatography (70% EtOAc/Hexanes) gave **12c** (60 mg, 0.17 mmol, 57%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.86 (s, 1H), 8.34 (t, *J* = 3.0 Hz, 1H), 8.32 (s, 1H), 8.12–8.05 (m, 3H), 7.77 (t, *J* = 13, 1H), 2.72 (s, 3H), 1.62 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.7, 153.9, 150.4, 149.6, 140.9, 138.7, 135.0, 130.4, 128.2, 127.7, 122.7, 122.2, 82.5, 28.2, 26.8; HRMS [M+H] = 354.1548; $C_{18}H_{20}N_5O_3$ = 354.1566.



10 **12d**

N^6-*tert*-Butyloxycarbonyl-9-(4-methoxy-3,5-dimethylphenyl)adenine (12d)

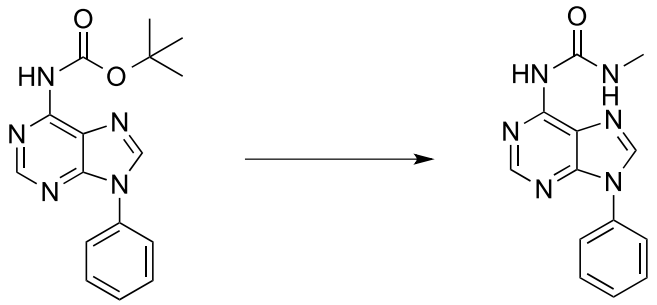
To a solution of **10** (100 mg, 0.30 mmol) and (4-methoxy-3,5-dimethylphenyl)boronic acid (108 mg, 0.60 mmol) in dry MeOH (5.0 mL) was added $Cu(NO_3)_2 \bullet 6H_2O$ (800 μL of 0.14 M solution in dry MeOH, 0.11 mmol) and TMEDA (800 μL of a 0.14 M solution in dry MeOH, 0.11 mmol). The resulting mixture was stirred for 24 h at ambient temperature under O_2. Volatiles were evaporated and the crude material was re-dissolved in CH_2Cl_2 and washed with saturated EDTA (aq). The organic layer was dried over Na_2SO_4 and volatiles were removed under reduced pressure. The crude material was dissolved in MeOH (4.0 mL). To this solution K_2CO_3 (100 mg, 0.72 mmol) was added and the mixture was stirred for 12 h at ambient temperature. Volatiles were evaporated and the crude was partitioned (CH_2Cl_2//H_2O). The organic layer was separated and dried over Na_2SO_4. Flash chromatography (70% EtOAc/Hexanes) gave **12d** (27 mg, 0.73 mmol, 24%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.82 (s, 1H), 8.24 (s, 1H), 8.15 (s, 1H), 7.30 (s, 2H), 3.77 (s, 3H), 2.38 (s, 6H), 1.58 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.2, 153.6, 150.2, 149.8, 141.7, 132.9, 129.5, 124.2, 82.3, 59.8, 28.2, 16.3; HRMS [M+H] = 370.1875; $C_{19}H_{24}N_5O_3$ = 370.1879.



11e **12e**

N^6-*tert*-Butyloxycarbonyl-9-[2-(3,5-dimethylpyrazol-1-yl)-4-methylphenyl]adenine (12e)

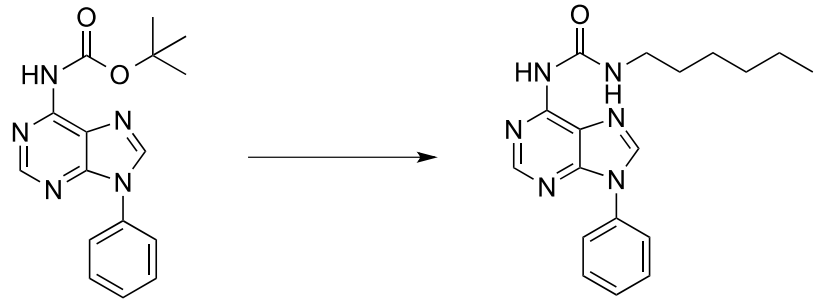
A solution of **11e** (50 mg, 0.096 mmol) in dry MeOH (4.0 mL) was treated with K_2CO_3 (120 mg, 0.87 mmol) and the mixture was stirred for 12 h at ambient temperature. Volatiles were evaporated and the crude was partitioned (CH_2Cl_2/H_2O). The organic layer was separated and dried over Na_2SO_4. Flash chromatography (70% EtOAc/Hexanes) gave **12e** (22 mg, 0.052 mmol, 55% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.74 (s, 1H), 8.06 (s, 1H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.52 (s, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.42 (s, 1H), 5.77 (s, 1H), 2.50 (s, 3H), 2.20 (s, 3H), 1.67 (s, 3H), 1.56 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.6, 150.1, 149.9, 149.6, 142.5, 141.1, 140.5, 134.4, 130.9, 130.1, 128.4, 126.9, 106.4, 82.3, 28.1, 21.1, 13.4, 10.7; HRMS [M+H] = 420.2155; $C_{22}H_{26}N_7O_2$ = 420.2148.



12a **13a**

N^6-(N-Methylcarbamyl)-9-phenyladenine (13a)

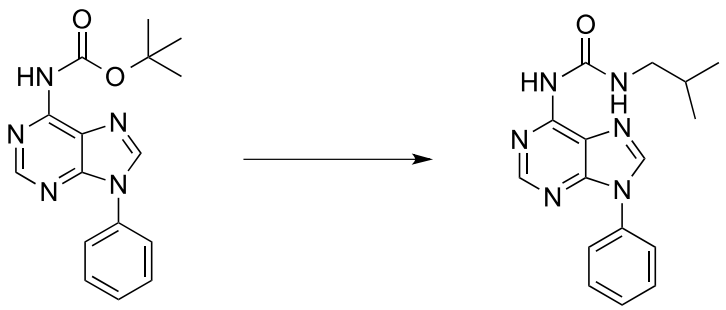
To a solution of methylamine (1.5 mL of 1.0 M in dry DMF/THF (1:1), 1.5 mmol), **12a** (22 mg, 0.07 mmol), and DMAP (12 mg, 0.10 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (350 mg). The mixture was stirred at room temperature for 2 h, then heated at 80°C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/ CH_2Cl_2) to give **13a** (18 mg, 0.067 mmol, 96% yield). ^{1}H NMR (7:1, $CDCl_3$: CD_3OD, 500 MHz) δ 9.43 (bs, 1H), 8.55 (s, 1H), 8.22 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 1H), 2.98 (d, *J* = 4.0 Hz, 3H); ^{13}C NMR (7:1, $CDCl_3$: CD_3OD, 125 MHz) δ 154.9, 151.8, 150.6, 150.1, 141.5, 134.0, 130.0, 128.8, 123.7, 120.4, 26.5, 26.4; HRMS [M+H] = 269.1172; $C_{13}H_{12}N_6O$ = 269.1151.



12a 13b

N^6-(N-Hexylcarbamyl)-9-phenyladenine (13b)

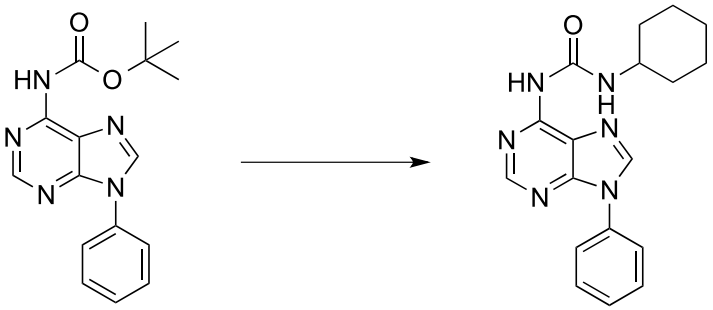
To a solution of hexylamine (0.5 mL of 0.5 M in dry DMF, 0.025 mmol), **12a** (7.5 mg, 0.024 mmol), and DMAP (3 mg, 0.024 mmol) in a flame-dried pressure tube was added dry DMF (0.5 mL) and 5Å molecular sieves (150 mg). The mixture was stirred at room temperature for 2 h, then heated at 80°C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/ CH_2Cl_2) to give **13b** (7 mg, 0.021 mmol, 86% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.50 (bs, 1H), 8.63 (s, 1H), 8.34 (s, 1H), 8.30 (bs, 1H), 7.73 (d, J = 7.8 Hz, 2H), 7.63 (t, J = 7.2 Hz, 2H), 7.52 (t, J = 7.2 Hz, 1H), 3.50–3.43 (m, 2H), 1.72–1.65 (m, 4H), 1.49–1.37 (m, 4H), 0.96 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.9, 151.8, 150.8, 141.7, 134.4, 130.0, 128.7, 123.7, 121.0, 40.3, 31.5, 29.8, 26.7, 22.6, 14.0; HRMS [M+H] = 339.1946; $C_{18}H_{23}N_6O$ = 339.1933.



12 13c

N^6-(N-Isobutylcarbamyl)-9-phenyladenine (13c)

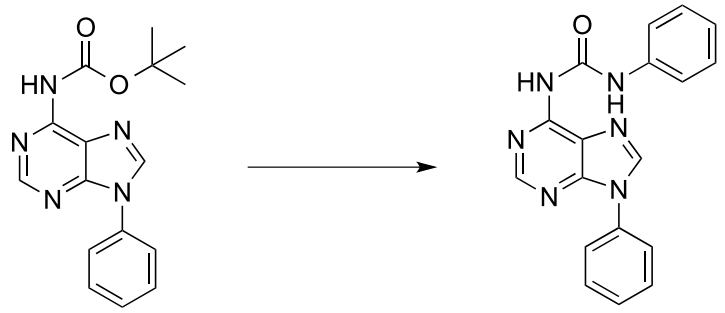
To a solution of isobutylamine (1.5 mL of 0.05 M in dry DMF, 0.08 mmol), **12a** (22 mg, 0.07 mmol), and DMAP (11 mg, 0.09 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (300 mg). The mixture was stirred at room temperature for 2 h, then heated at 80°C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/ CH_2Cl_2) to give **13c** (16 mg, 0.052 mmol, 74%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.62 (bs, 1H), 8.63 (bs, 1H), 8.61 (s, 1H), 8.43 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 2H), 7.51 (t, *J* = 7.5 Hz, 1H), 3.31 (t, *J* = 6.5 Hz, 2H), 1.98 (m, 1H), 1.04 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR δ ($CDCl_3$, 125 MHz) 154.1, 151.7, 150.9, 142.0, 134.4, 130.0, 128.6, 123.7, 120.8, 47.6, 28.7, 20.3; HMRS [M+H] = 311.1619; $C_{16}H_{19}N_6O$ = 311.1620.



12a **13d**

N^6-(N-Cyclohexylcarbamyl)-9-phenyladenine (13d)

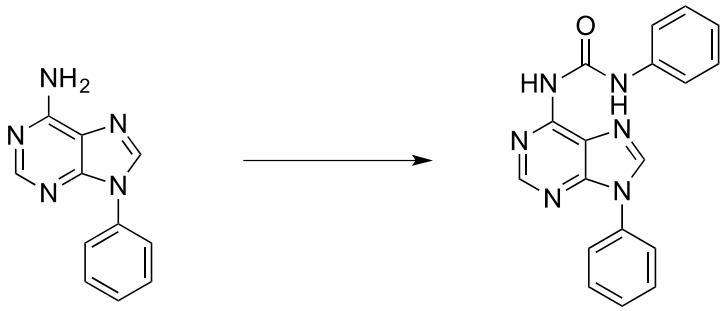
To a solution of cyclohexylamine (1.7 mL of 0.05 M in dry DMF, 0.09 mmol), **12a** (22 mg, 0.07 mmol), and DMAP (10 mg, 0.08 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (300 mg). The mixture was stirred at room temperature for 2 h, then heated at 80°C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/ CH_2Cl_2) to give **13d** (22 mg, 0.065 mmol, 93%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.50 (d, *J* = 7.0 Hz, 1H), 8.60 (s, 1H), 8.34 (bs, 2H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 1H), 3.87 (bs, 1H), 2.06–1.26 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.0, 151.9, 150.9, 141.7, 134.4, 130.0, 128.6, 123.7, 49.0, 33.2, 29.7, 25.7, 24.7. HRMS [M+H] = 337.1797; $C_{18}H_{20}N_6O$ = 337.1777.



12a 13e

N^6-(N-Phenylcarbamyl)-9-phenyladenine (13e)

To a solution of aniline (1.2 mL of 0.05 M in dry DMF, 0.06 mmol), **12a** (15 mg, 0.05 mmol), and DMAP (8 mg, 0.07 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (300 mg). The mixture was stirred at room temperature for 2 h, then heated at 80°C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/ CH_2Cl_2) to give **13e** (6 mg, 0.02 mmol, 40%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.83 (bs, 1H), 8.71 (s, 1H), 8.56 (bs, 1H), 8.40 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.64 (t, *J* = 8.0 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.16 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.6, 151.3, 150.5, 150.4, 142.2, 138.0, 134.2, 130.0, 129.1, 128.8, 124.0, 123.7, 120.9, 120.4; HRMS [M+H] = 331.1308; $C_{18}H_{15}N_6O$ = 331.1307.

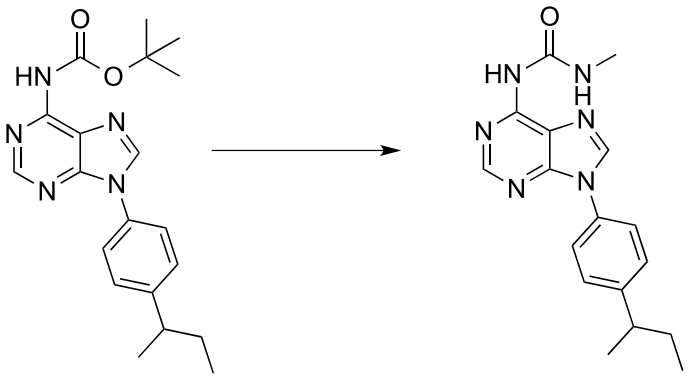


20 **13e**

N^6-(N-Phenylcarbamyl)-9-phenyladenine (13e)

A solution of phenylisocyanate (3.0 mL of 0.1 M in dry CH_2Cl_2, 3.0mmol), **20** (60 mg, 0.28 mmol), 3 mL of dry THF was stirred in a flame-dried round flask. The mixture was stirred for 12 h, then volatiles were evaporated using a stream of air. Crude material was redissolved in a minimal amount of 10% MeOH/CH_2Cl_2 and Flash column chromatographed (80% EtOAc/CH_2Cl_2) to give **13e** (56 mg, 0.17mmol, 60%).

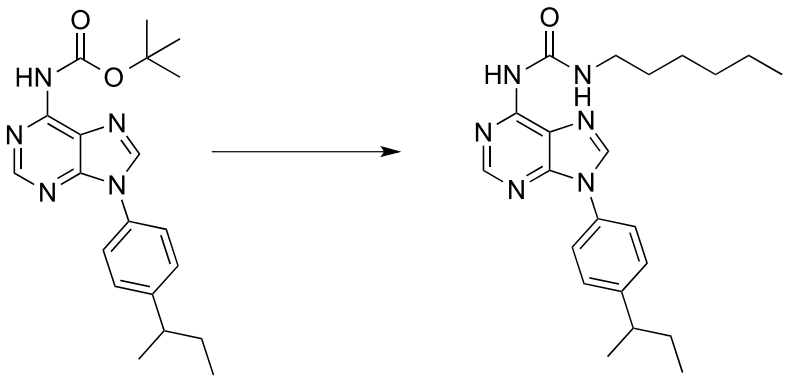
^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.83 (bs, 1H), 8.71 (s, 1H), 8.56 (bs, 1H), 8.40 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.64 (t, *J* = 8.0 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.16 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.6, 151.3, 150.5, 150.4, 142.2, 138.0, 134.2, 130.0, 129.1, 128.8, 124.0, 123.7, 120.9, 120.4; HRMS [M+H] = 331.1308; $C_{18}H_{15}N_6O$ = 331.1307.



12b **14a**

N^6-(N-Methylcarbamyl)-9-(4-sec-butylphenyl)adenine (14a)

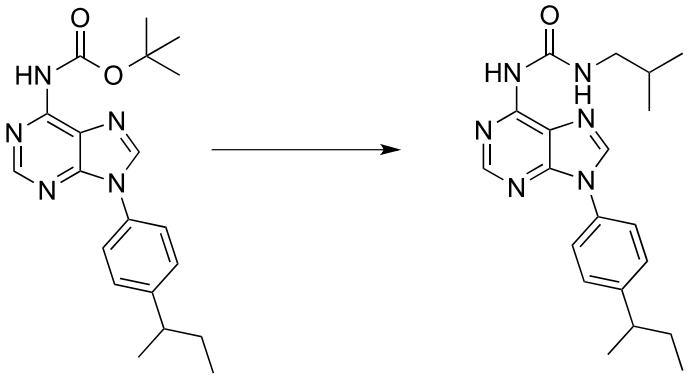
To a solution of methylamine (1.7 mL of 1.0 M in dry DMF/THF (1:1), 1.7 mmol), **12b** (25 mg, 0.068 mmol), and DMAP (12 mg, 0.10 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (350 mg). The mixture was stirred at room temperature for 2 h, then heated at 80°C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/ CH_2Cl_2) to give **14a** (18 mg, 0.056 mmol, 82%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.49 (bs, 1H), 8.79 (s, 1H), 8.60 (s, 1H), 8.44 (s, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 3.04 (d, *J* = 4.5 Hz, 3H), 2.71 (sext, *J* = 7.0 Hz, 1H), 1.66 (pent, *J* = 7.4 Hz, 2H), 1.29 (d, *J* = 7.0 Hz, 3H), 0.88 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.8, 151.6, 150.7, 150.3, 148.5, 142.4, 132.0, 128.6, 123.7, 120.7, 41.5, 31.1, 26.7, 21.8, 12.2. HRMS [M+H]= 325.1775; $C_{17}H_{21}N_6O$ = 325.1777.



12b **14b**

N^6-(N-Hexylcarbamyl)-9-(4-sec-butylphenyl)adenine (14b)

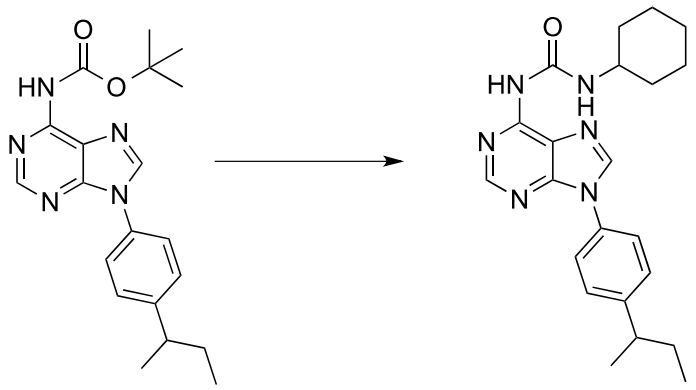
To a solution of hexylamine (1.5 mL of 0.05 M in dry DMF, 0.08 mmol), **12b** (23 mg, 0.062 mmol), and DMAP (12 mg, 0.10 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (350 mg). The mixture was stirred at room temperature for 2 h, then heated at 80°C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/ CH_2Cl_2) to give **14b** (20 mg, 0.051 mmol, 82%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.57 (t, *J* = 5.3 Hz, 1H), 8.75 (s, 1H), 8.60 (s, 1H), 8.44 (s, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 3.44 (q, *J* = 6.7 Hz, 2H), 2.71 (sext, *J* = 7.2 Hz, 1H), 1.70–1.63 (m, 4H), 1.45–1.42 (m, 2H), 1.36-1.32 (m, 4H), 1.29 (d, *J* = 7.0 Hz, 3H), 0.92-0.88 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.1, 151.6, 150.8, 150.3, 148.5, 142.4, 132.0, 128.6, 123.7, 120.7, 41.5, 40.2, 31.5, 31.1, 29.8, 26.7, 22.6, 21.9, 14.1, 12.2; HRMS [M+H]= 395.2569; $C_{22}H_{31}N_6O$ = 395.2559.



12b **14c**

N^6-(N-Isobutylcarbamyl)-9-(4-sec-butylphenyl)adenine (14c)

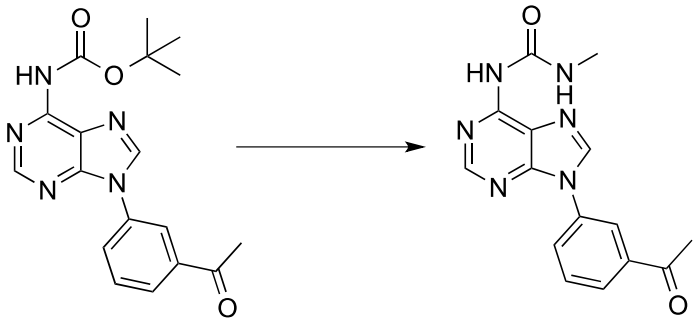
To a solution of isobutylamine (1.5 mL of 0.05 M in dry DMF, 0.08 mmol), **12b** (22 mg, 0.06 mmol), and DMAP (12 mg, 0.10 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (350 mg). The mixture was stirred at room temperature for 2 h, then heated at 80°C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/ CH_2Cl_2) to give **14c** (18 mg, 0.050 mmol, 83%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.64 (t, *J* = 5.5 Hz, 1H), 8.67 (s, 1H), 8.60 (s, 1H), 8.41 (s, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 3.29 (t, *J* = 6.3 Hz, 2H), 2.71 (sext, *J* = 7.0 Hz, 1H), 1.96 (sept, *J* = 6.8 Hz, 1H), 1.66 (pent, *J* = 7.3 Hz, 2H), 1.29 (d, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 6.5 Hz, 6H), 0.88 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.2, 151.7, 150.9, 150.3, 148.5, 142.3, 132.0, 128.6, 123.7, 120.7, 47.6, 41.5, 31.1, 28.7, 21.9, 20.3, 12.2; HRMS [M+H] = 367.2243; $C_{20}H_{27}N_6O$ = 367.2246.



12b **14d**

N^6-(N-Cyclohexylcarbamyl)-9-(4-sec-butylphenyl)adenine (14d)

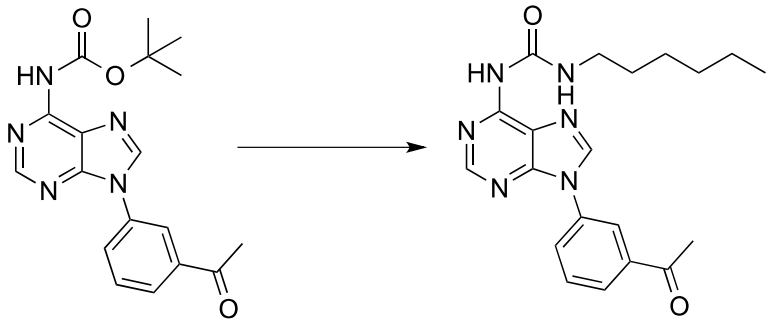
To a solution of cyclohexylamine (1.7 mL of 0.05 M in dry DMF, 0.09 mmol), **12b** (20 mg, 0.054 mmol), and DMAP (13 mg, 0.11 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (350 mg). The mixture was stirred at room temperature for 2 h, then heated at 80°C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/ CH_2Cl_2) to give **14d** (19 mg, 0.048 mmol, 90%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.53 (d, *J* = 7.5 Hz, 1H), 8.60 (s, 1H), 8.53 (s, 1H), 8.37 (s, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 3.88–3.87 (m, 1H), 2.71 (sext, *J* = 7.0 Hz, 1H), 2.06-2.04 (m, 2H), 1.83-1.76 (m, 2H), 1.66–1.63 (m, 3H), 1.47–1.42 (m, 4H), 1.31 (d, *J* = 7.0 Hz, 3H), 1.33–1.26 (m, 1H), 0.88 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.2, 151.7, 150.9, 150.2, 148.5, 142.1, 132.0, 128.6, 123.7, 120.7, 48.9, 41.5, 33.2, 31.1, 25.7, 24.7, 21.8, 12.2; HRMS [M+H] = 393.2402; $C_{22}H_{29}N_6O$ = 393.2403.



12c **15a**

N^6-(N-Methylcarbamyl)-9-(3-acetylphenyl)adenine (15a)

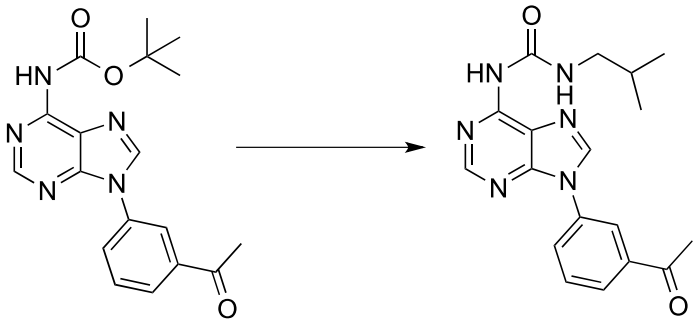
To a solution of methylamine (1.5 mL of 1.0 M in dry DMF/THF (1:1), 1.5 mmol), **12c** (27 mg, 0.076 mmol), and DMAP (13 mg, 0.11 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (350 mg). The mixture was stirred at room temperature for 2 h, then heated at 80°C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/ CH_2Cl_2) to give **15a** (18 mg, 0.058 mmol, 76%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.79 (1H), 9.26 (bs, 1H), 8.94 (s, 1H), 8.62 (s, 1H), 8.45 (s, 1H), 8.17 (d, J = 9.5 Hz, 1H), 8.07 (d, J = 7.5 Hz, 1H), 7.79 (t, J = 8.0 Hz, 1H), 2.84 (d, J = 4.5 Hz, 3H), 2.67 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 197.7, 154.5, 151.9, 151.0, 150.5, 142.8, 138.5, 135.4, 130.6, 128.3, 128.1, 123.2, 120.8, 110.0, 27.4, 26.8; HRMS [M+H] = 311.1282; $C_{15}H_{15}N_6O_2$ = 311.1256.



12c **15b**

N^6-(N-Hexylcarbamyl)-9-(3-acetylphenyl)adenine (15b)

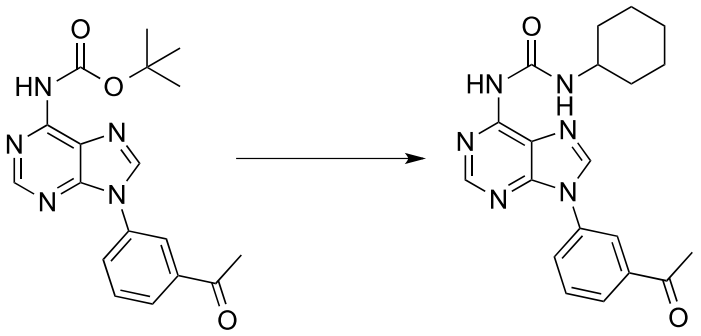
To a solution of hexylamine (1.5 mL of 0.05 M in dry DMF, 0.08 mmol), **12c** (22 mg, 0.07 mmol), and DMAP (12 mg, 0.10 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (350 mg). The mixture was stirred at room temperature for 2 h, then heated at 80°C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/ CH_2Cl_2) to give **15b** (19 mg, 0.065 mmol, 93%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.52 (bs, 1H), 8.67 (bs, 1H), 8,61 (s, 1H), 8.52 (s, 1H), 8.33 (bs, 1H), 8.07 (d, *J* = 7.5 Hz, 1H), 8.01 (d, *J* = 7.5 Hz, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 3.46 (q, *J* = 7.0 Hz, 2H), 2.70 (s, 3H), 1.69 (m, *J* = 7.5 Hz, 2H), 1.44-1.30 (m, 6H), 0.92 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.7, 154.0, 151.9, 151.0, 150.2, 141.8, 138.7, 135.0, 130.4, 128.2, 127.9, 123.1, 120.8, 40.3, 31.5, 29.8, 26.8, 26.7, 22.6, 14.05; HRMS [M+H] = 381.2055; $C_{20}H_{25}N_6O_2$ = 381.2039.



12c **15c**

N^6-(N-Isobutylcarbamyl)-9-(3-acetylphenyl)adenine (15c)

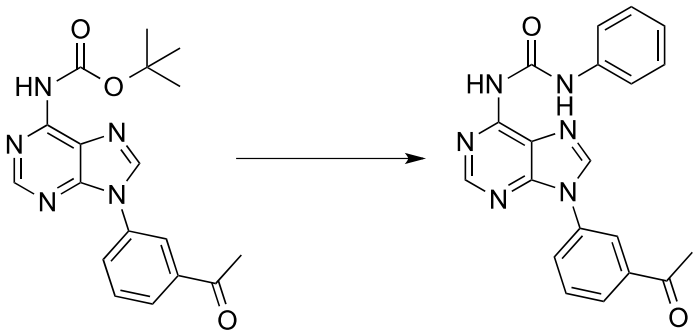
To a solution of isobutylamine (1.5 mL of 0.05 M in dry DMF, 0.08 mmol), **12c** (22 mg, 0.06 mmol), and DMAP (12 mg, 0.10 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (350 mg). The mixture was stirred at room temperature for 2 h, then heated at 80 °C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/ CH_2Cl_2) to give **15c** (18 mg, 0.05 mmol, 85%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.60 (bs, 1H), 8.66 (bs, 1H), 8.61 (s, 1H), 8.52 (s, 1H), 8.33 (bs, 1H), 8.07 (d, *J* = 7.5 Hz, 1H), 8.01 (d, *J* = 7.5 Hz, 1H), 7.74 (t, *J* = 7.5 Hz, 1H), 3.31 (t, *J* = 6.5 Hz, 2H), 1.98 (m, 1H) 1.04 (d, *J* = 6.5 Hz, 6H), 2.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.7, 154.0, 151.9, 151.0, 150.2, 141.8, 138.7, 135.0, 130.4, 128.2, 127. 9, 123.1, 120.8, 47.7, 28.7, 26. 8, 20.3; HRMS [M+H]= 353.1746; $C_{18}H_{20}N_6O_2$ = 353.1726.



12c 15d

N^6-(N-Cyclohexylcarbamyl)-9-(3-acetylphenyl)adenine (15d)

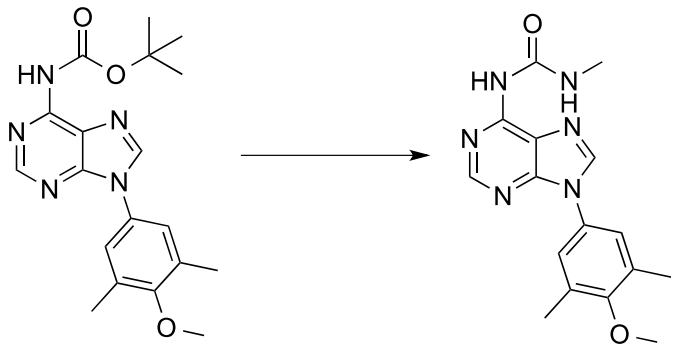
To a solution of cyclohexylamine (1.5 mL of 0.05 M in dry DMF, 0.08 mmol), **12c** (25 mg, 0.07 mmol), and DMAP (12 mg, 0.10 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (350 mg). The mixture was stirred at room temperature for 2 h, then heated at 80°C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/ CH_2Cl_2) to give **15d** (20 mg, 0.053 mmol, 76%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.53 (d, *J* = 7.5 Hz, 1H), 8.78 (s, 1H), 8.61 (s, 1H), 8.57 (s, 1H), 8.33 (t, *J* = 1.5 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 8.01 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 3.87 (t, *J* = 4.0 Hz, 1H), 2.70 (s, 3H), 2.06-1.25 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.6, 153.2, 151.9, 151.0, 150.2, 141.9, 138.7, 135.0, 130.4, 128.2, 127.9, 123.2, 120.8, 49.0, 33.2, 26.8, 24.7; HRMS [M+H] = 379.1886; $C_{20}H_{23}N_6O_2$ = 379.1882.



12c **15e**

N^6-(N-Phenylcarbamyl)-9-(3-acetylphenyl)adenine (15e)

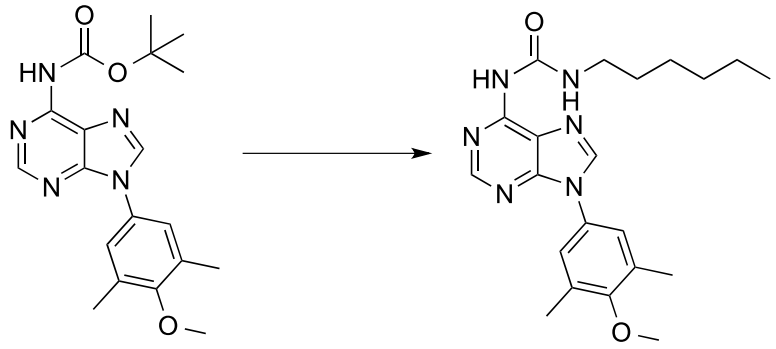
To a solution of aniline (2.4 mL of 0.05 M in dry DMF, 0.12 mmol), **12c** (40 mg, 0.11 mmol), and DMAP (27 mg, 0.22 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (300 mg). The mixture was stirred at room temperature for 2 h, then heated at 80°C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/ CH_2Cl_2) to give **15e** (12 mg, 0.03 mmol, 29%). ^{1}H NMR ($CDCl_3$+2drops of CD_3OD, 500 MHz) δ 8.67 (s, 1H), 8.32 (s, 1H), 8.28 (t, J = 1.8 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.96 (dd, J = 7.8, 1.3 Hz, 1H), 7.72 (t, J = 7.8, 1H), 7.60 (d, J = 7.5 Hz, 2H), 7.34 (t, J = 8.0 Hz, 2H), 7.10 (t, J = 7.3 Hz, 1H), 2.67 (s, 3H); ^{13}C NMR ($CDCl_3$+2drops of CD_3OD_3, 125 MHz) δ 151.9, 141.3, 130.5, 129.0, 128.5, 128.0, 124.1, 123.0, 120.3, 26.7; HRMS [M+H] = 373.1436; $C_{20}H_{17}N_6O_2$ = 373.1413.



12d **16a**

N^6-(N-Methylcarbamyl)-9-(4-methoxy-3,5-dimethylphenyl)adenine (16a)

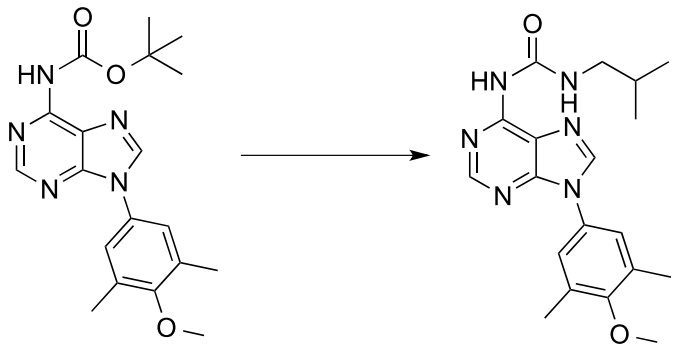
To a solution of methylamine (1.8 mL of 1.0 M in dry DMF:THF (1:1), 1.8 mmol), **12d** (18 mg, 0.049 mmol), and DMAP (13 mg, 0.11 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (350 mg). The mixture was stirred at room temperature for 2 h, then heated at 80°C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/ CH_2Cl_2) to give **16a** (13 mg, 0.040 mmol, 82%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.46 (bs, 1H), 8.66 (bs, 1H), 8.59 (s, 1H), 8.33 (bs, 1H), 7.20 (s, 2H), 3.79 (s, 3H), 3.04 (d, *J* = 3.0 Hz, 3H), 2.39 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.3, 154.8, 151.7, 150.7, 142.5, 132.9, 129.5, 124.4, 120.5, 59.8, 29.7, 26.7, 16.3; HRMS [M+H] = 327.1565; $C_{16}H_{19}N_6O_2$ = 327.1569.



12d **16b**

N^6-(N-Hexylcarbamyl)-9-(4-methoxy-3,5-dimethylphenyl)adenine (16b)

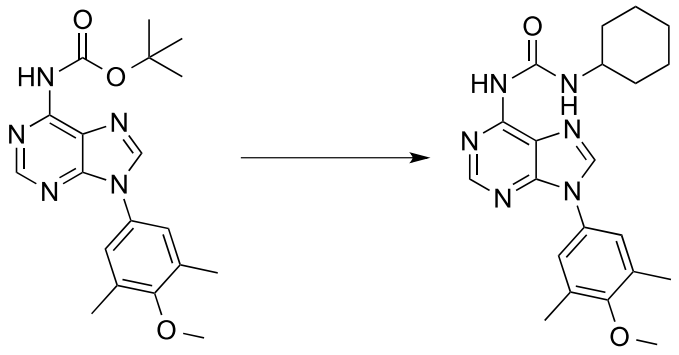
To a solution of hexylamine (1.8 mL of 0.05 M in dry DMF, 0.09 mmol), **12d** (13 mg, 0.035 mmol), and DMAP (13 mg, 0.11 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (350 mg). The mixture was stirred at room temperature for 2 h, then heated at 80°C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/ CH_2Cl_2) to give **16b** (9 mg, 0.023 mmol, 66%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.48 (bs, 1H), 8.59 (s, 1H), 8.24 (bs, 1H), 8.20 (s, 1H), 7.28 (s, 1H), 7.27 (s, 1H), 3.79 (s, 3H), 3.46 (quart, *J* = 6.5 Hz, 2H), 2.39 (s, 6H), 1.69 (pent, *J* = 7.5 Hz, 2H), 1.45–1.26 (m, 6H), 0.92 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.3, 153.9, 151.7, 150.7, 150.3, 142.0, 133.0, 129.5, 124.4, 120.6, 59.8, 40.3, 31.5, 29.8, 26.7, 22.6, 16.3, 14.0; HRMS [M+H] = 397.2347; $C_{21}H_{28}N_6O_2$ = 397.2352.



12d **16c**

N^6-(N-Isobutylcarbamyl)-9-(4-methoxy-3,5-dimethylphenyl)adenine (16c)

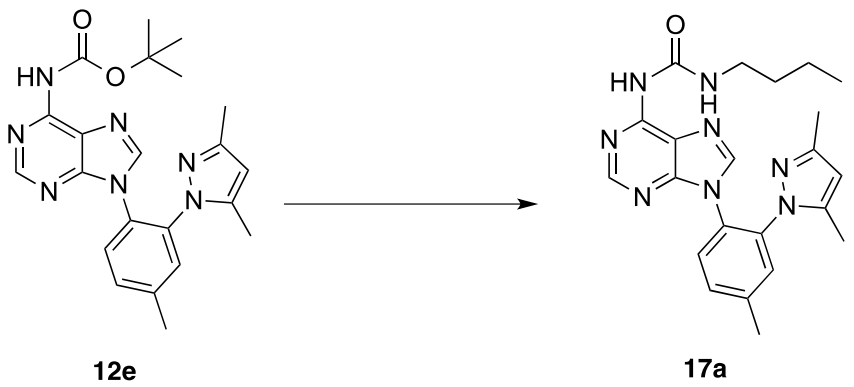
To a solution of isobutylamine (1.8 mL of 0.05 M in dry DMF, 0.09 mmol), **12d** (20 mg, 0.05 mmol), and DMAP (13 mg, 0.11 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (350 mg). The mixture was stirred at room temperature for 2 h, then heated at 80 °C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/ CH_2Cl_2) to give **16c** (18 mg, 0.048 mmol, 97%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.64 (bs, 1H), 8.69 (d, *J* = 5.0 Hz, 1H), 8.59 (t, *J* = 9.0 Hz, 1H), 8.34 (d, *J* = 7.0 Hz, 1H), 7.29 (t, *J* = 8.5 Hz, 2H), 3.79 (t, *J* = 9.0 Hz, 3H), 3.30 (m, *J* = 7.0 Hz, 2H), 2.39 (s, 6H), 1.97 (m, *J* = 5.0 Hz, 1H), 1.04 (m, *J* = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.3, 154.2, 151.6, 150.8, 150.4, 142.5, 139.9, 129.6, 124.5, 120.6, 59.8, 47.6, 28.7, 20.3, 16.3; HRMS [M+H] = 369.2035; $C_{19}H_{25}N_6O_2$ = 369.2039.



12d **16d**

N^6-(N-Cyclohexylcarbamyl)-9-(4-methoxy-3,5-dimethylphenyl)adenine (16d)

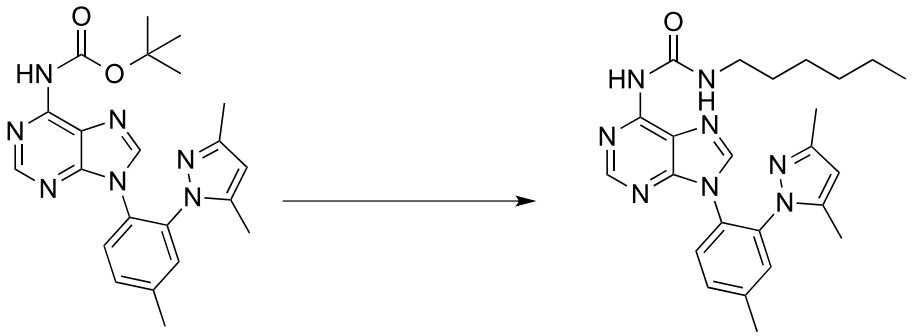
To a solution of cyclohexylamine (1.8 mL of 0.05 M in dry DMF, 0.09 mmol), **12d** (18 mg, 0.05 mmol), and DMAP (13 mg, 0.11 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (350 mg). The mixture was stirred at room temperature for 2 h, then heated at 80°C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/ CH_2Cl_2) to give **16d** (17 mg, 0.043 mmol, 86%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.50 (d, *J* = 7.5 Hz, 1H), 8.58 (s, 1H), 8.34 (bs, 1H), 8.24 (s, 1H), 7.28 (s, 1H), 3.87 (t, *J* = 4.5 Hz, 1H), 3.78 (s, 3H), 2.39 (s, 6H), 2.06 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.3, 153.1, 151.7, 150.8, 150.3, 142.1, 132.9, 129.5, 124.4, 120.6, 59.8, 49.0, 33.2, 33.1, 25.7, 25.4, 24.7, 16.3; HRMS [M+H] = 395.2189; $C_{21}H_{27}N_6O_2$ = 395.2195.



12e **17a**

N^6-(N-Butylcarbamyl)-9-[2-(3,5-dimethylpyrazol-1-yl)-4-methylphenyl]adenine (17a)

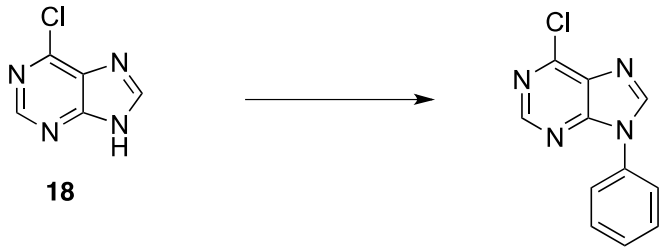
To a solution of butylamine (1.7 mL of 0.05 M in dry DMF, 0.09 mmol), **12e** (23 mg, 0.055 mmol), and DMAP (12 mg, 0.10 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (350 mg). The mixture was stirred at room temperature for 2 h, then heated at 80°C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/ CH_2Cl_2) to give **17a** (17 mg, 0.041 mmol, 75%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.36 (bs, 1H), 8.52 (s, 1H), 7.87 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.51 (s, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.42 (s, 1H), 5.80 (s, 1H), 3.43 (q, *J* = 6.5 Hz, 2H), 2.50 (s, 3H), 2.22 (s, 3H), 1.71 (s, 3H), 1.66 (pent, *J* = 7.4 Hz, 2H), 1.45 (pent, *J* = 7.4 Hz, 2H), 0.99 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.6, 151.8, 150.4, 150.2, 142.5, 140.9, 140.5, 134.5, 130.8, 130.1, 128.4, 126.9, 119.7, 106.4, 39.9, 31.9, 21.1, 20.2, 13.8, 13.5, 10.8; HRMS [M+H] = 419.2302; $C_{22}H_{27}N_8O$ = 419.2308.



12e **17b**

N^6-(N-Hexylcarbamyl)-9-[2-(3,5-dimethylpyrazol-1-yl)-4-methylphenyl]adenine (17b)

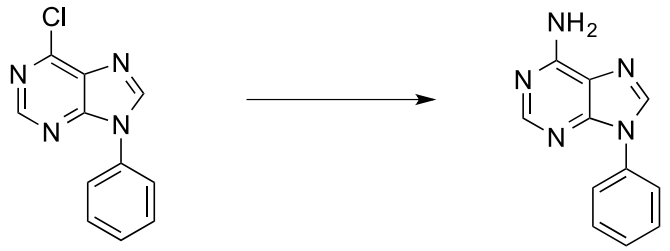
To a solution of hexylamine (1.8 mL of 0.05 M in dry DMF, 0.09 mmol), **12e** (25 mg, 0.06 mmol), and DMAP (14 mg, 0.11 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (350 mg). The mixture was stirred at room temperature for 2 h, then heated at 80°C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/ CH_2Cl_2) to give **17b** (25 mg, 0.056 mmol, 93%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.36 (s, 1H), 8.51 (s, 1H), 7.89 (s, 1H), 7.65 (d. *J* = 8.0 Hz, 1H), 7.52 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.42 (s, 1H), 5.79 (s, 1H), 3.43-3.39 (m, 2H), 2.50 (s, 3H), 2.21 (s, 3H), 1.71 (s, 3H), 1.67–1.62 (m, 2H), 1.41–1.25 (m, 6H), 0.90 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.1, 153.6, 151.8, 150.4, 150.2, 142.5, 140.9, 140.5, 134.4, 130.1, 128.4, 126.9, 119.7, 106.4, 40.2, 31.5, 29.8, 26.7, 22.6, 21.1, 14.0, 13.5, 10.8; HRMS [M+H] = 447.2621; $C_{24}H_{31}N_8O$ = 447.2621.



18 **19**

6-Chloro-9-phenylpurine (19)

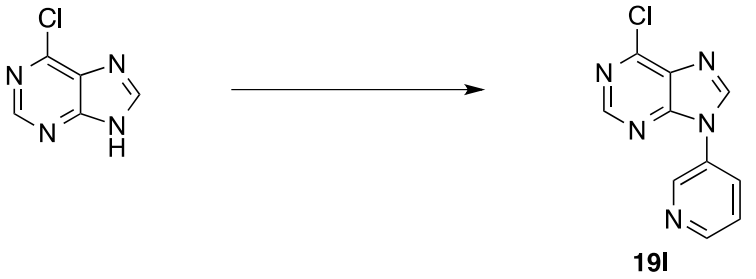
A solution of 6-chloropurine (100 mg, 0.65 mmol), phenylboronic acid (240 mg, 1.96mmol), copper (II) acetate (120 mg, 0.66 mmol), 1,10-phenanthroline (232 mg, 1.30 mmol), 5Å molecular sieves (1g) in CH_2Cl_2 (12 mL) was stirred at ambient temperature under reflux for four days. Crude was then filtered through celite using MeOH as an eluent. Volatiles were removed under reduced pressure and the crude mixture was dissolved in a minimal amount of CH_2Cl_2 and added to Flash column chromatography and eluted with 5% MeOH/CH_2Cl_2 to give **19** (129 mg, 0.56 mmol 86%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.86 (s, 1H), 8.44 (s, 1H), 7.75 (d, J = 7.8 Hz, 2H), 7.65 (t, J = 7.5 Hz, 2H), 7.56 (t, J = 7.2Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.7, 151.8, 151.5, 144.1, 133.9, 132.2, 130.1, 129.0, 123.7; HRMS [M+H] = 231.0418, $C_{11}H_8ClN_4$ = 231.0437.



19 **20a**

9-Phenyladenine (20a)

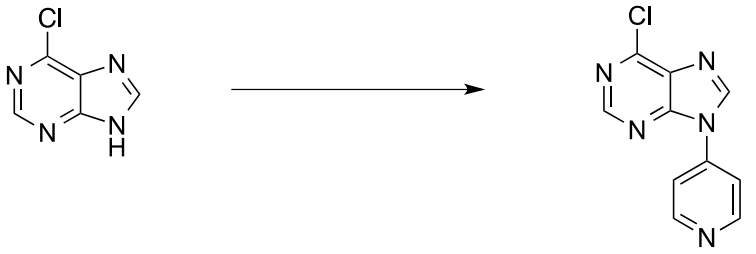
A solution of **19** (60 mg, 0.26 mmol) in THF and (1 mL) saturated solution of ammonia in methanol was stirred in a flame-dried pressure tube for two days at 65°C. Volatiles were evaporated and crude material was dissolved in a minimum amount of 10% MeOH/CH_2Cl_2 and Flash chromatographed in 10% MeOH/CH_2Cl_2 to give **20a** (36 mg, 0.17 mmol, 65%). ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.86 (s, 1H), 8.44 (s, 1H), 7.75 (d, *J*= 7.8Hz, 2H), 7.65 (t, *J*= 7.5hz, 2H), 7.56(t, *J*= 7.2Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.7, 151.8, 151.5, 144.1, 133.9, 132.2, 130.1, 129.0, 123.7; HRMS [M+H]= 231.0418; $C_{11}H_{10}N_5$= 212.0936



19l

6-Chloro-9-(3-pyridylpurine) (19l)

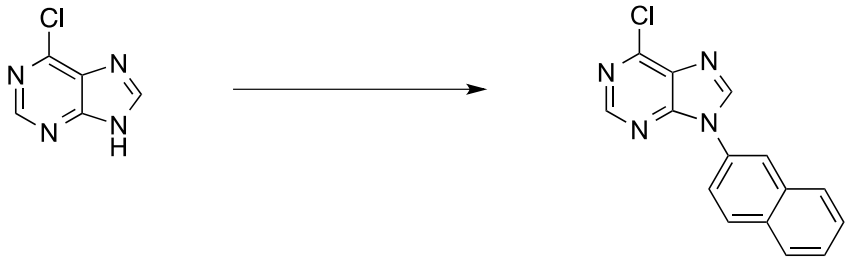
To a solution of 6-chlorpurine (60 mg, 0.39 mmol), 3-pyridylboronic acid (96 mg, 0.78 mmol), and triethylamine (60 μL) in dry DMF (1.5 mL) was added copper (II) acetate (71 mg, 0.39 mmol) and 5Å molecular sieves (350 mg). The resulting mixture was stirred for 4 days at ambient temperature under air. Volatiles were evaporated and the crude material was re-dissolved in CH_2Cl_2 and washed with saturated EDTA (aq). The organic layer was dried over Na_2SO_4 and volatiles were removed under reduced pressure. Flash chromatography (70% EtOAc/Hexanes) gave **19l** (20 mg, 0.086 mmol, 22%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.03 (s, 1H), 8.85 (s, 1H), 8.79 (d, J = 4.0 Hz, 1H), 8.46 (s, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.60 (dd, J = 8.3, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.0, 152.2, 151.5, 150.1, 144.3, 143.2, 131.0, 124.5; HRMS [M+H] = 232.0396; $C_{10}H_7ClN_5$ = 232.0390.



19m

6-Chloro-9-(4-pyridyl)purine (19m)

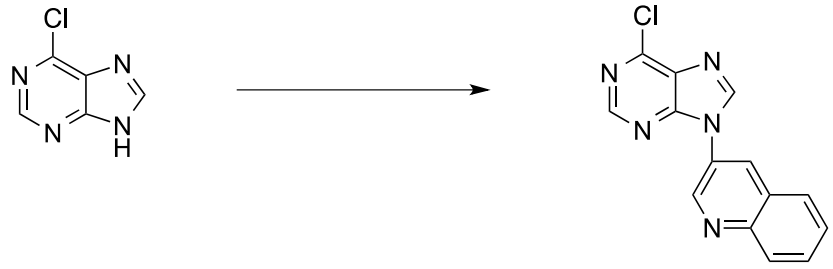
To a solution of 6-chloropurine (60 mg, 0.39 mmol), 3-pyridylboronic acid (96 mg, 0.78 mmol), and triethylamine (60 μL) in dry DMF (1.5 mL) was added copper (II) acetate (71 mg, 0.39 mmol) and 5Å molecular sieves (350 mg). The resulting mixture was stirred for 4 days at ambient temperature under air. Volatiles were evaporated and the crude material was re-dissolved in CH_2Cl_2 and washed with saturated EDTA (aq). The organic layer was dried over Na_2SO_4 and volatiles were removed under reduced pressure. Flash chromatography (70% EtOAc/Hexanes) gave **19m** (25 mg, 0.11 mmol, 28%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.86 (s, 1H), 8.86 (d, J = 6.0, 2H), 8.58 (s, 1H), 7.9 (d, J = 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.0, 152.2, 151.9, 151.2, 142.5, 141.2, 132.7, 116.1; HRMS [M+H] = 232.0391; $C_{27}H_{34}N_7O_4$ = 232.0390.



19n

6-Chloro-9-(2-napthyl)purine (19n)

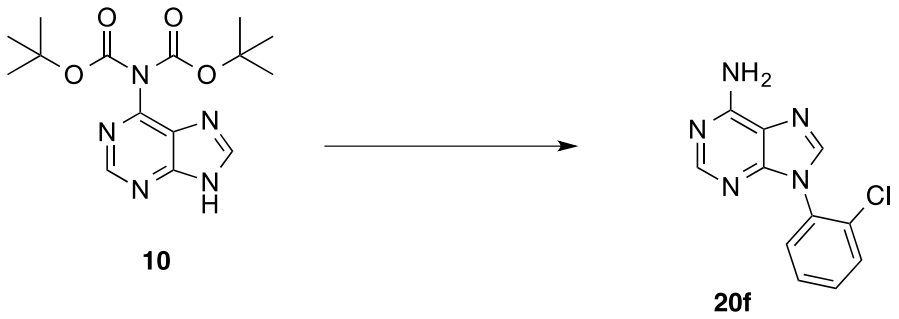
A solution of 6-chloropurine (60 mg, 0.39mmol), 2-naphthaleneboronic acid (134 mg, 0.78 mmol), copper (II) acetate (71 mg, 0.39 mmol), 1,10-phenanthroline (140.4 mg, 0.78 mmol), 5Å molecular sieves (250 mg) in CH_2Cl_2 (3 mL) was stirred at ambient temperature for four days. Crude material was then filtered through celite using MeOH as an eluent. Volatiles were removed under reduced pressure and the crude mixture was dissolved in a minimal amount of CH_2Cl_2 and added to a Flash column chromatography and eluted with 5% MeOH/CH_2Cl_2 to give **19n** (46 mg, 0.16 mmol 42%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.88 (s, 1H), 8.55 (s, 1H), 8.22 (d, *J* = 1.5 Hz, 1H), 8.11 (d, *J* = 9 Hz, 1H), 8.01-7.97 (m, 2H), 7.84 (dd, *J* = 8.9, 2.0 Hz, 1H), 7.68-7.63 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.8, 151.8, 144.4, 133.4, 132.8, 131.3, 130.4, 128.2, 128.0, 127.6, 127.4, 122.2, 121.3; HRMS [M+H] = 281.0598; $C_{15}H_{10}ClN_4O_4$ = 281.0594.



19q

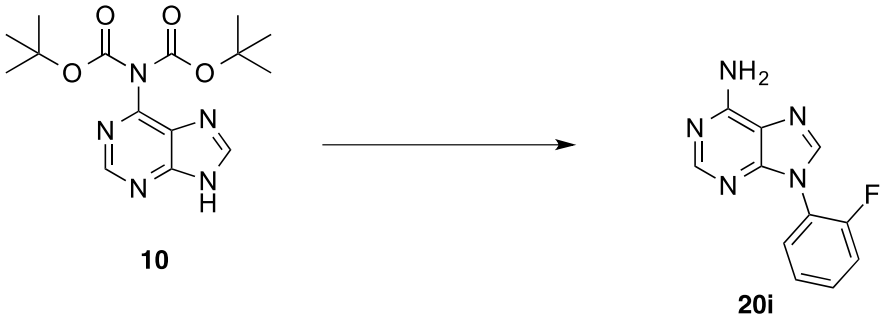
6-Chloro-9-(3-quinolinyl)purine (19q)

To a solution of 6-chloropurine (50 mg, 0.32 mmol), 3-quinolineboronic acid (112 mg, 0.64 mmol), and triethylamine (60 μL), in dry DMF (3.0 mL) was added copper (II) acetate (58 mg, 0.32 mmol) and 5Å molecular sieves (250 mg). The resulting mixture was stirred for 4 days at ambient temperature under air. Volatiles were evaporated and the crude was partitioned (CH_2Cl_2/H_2O). The organic layer was separated and dried over Na_2SO_4. Flash chromatography (70% EtOAc/Hexanes) gave **19q** (30 mg, 0.11 mmol, 33%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.40 (d, J = 2 Hz, 1H), 9.29 (s, 1H), 8.92 (d, J = 1.5 Hz, 1H), 8.91 (s, 1H), 8.14 (t, J = 8.3 Hz, 2H), 7.88 (t, J = 7.8 Hz, 1H), 7.75 (t, J = 7.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 152.9, 152.3, 150.2, 147.0, 146.9, 146.5, 131.9, 131.0, 130.3, 129.4, 128.9, 128.5, 128.3, 127.5; HRMS = [M+H] 282.0546; $C_{14}H_9ClN_5$ = 282.0547



9-(2-Chlorophenyl)adenine (20f)

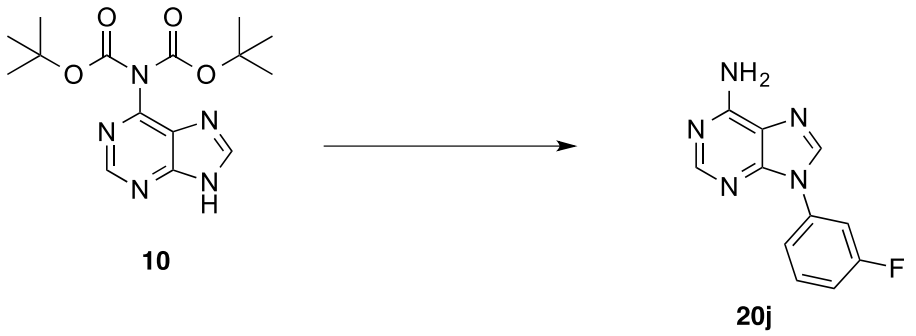
To a solution of **10** (60 mg, 0.18 mmol) and 2-chlorophenylboronic acid (56 mg, 0.36 mmol), in dry MeOH (3.0 mL) was added $Cu(NO_3)_2$ $(H_2O)_6$ (400 μL of 0.14 M solution in dry MeOH, 0.056 mmol) and TMEDA (400 μL of a 0.14 M solution in dry MeOH, 0.056 mmol). The resulting mixture was stirred for 24 h at ambient temperature under O_2. Volatiles were evaporated and the crude material was re-dissolved in CH_2Cl_2 and washed with saturated EDTA (aq). The organic layer was dried over Na_2SO_4 and volatiles were removed under reduced pressure. Crude product was re-dissolved in MeOH (3.0 mL) and Cs_2CO_3 (120 mg) was added. The resulting mixture was stirred for 1 hour at 80°C. Volatiles were evaporated under reduced pressure. Flash chromatography (10% MeOH/CH_2Cl_2) gave **20f** (10 mg, 0.04 mmol, 23%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.34 (s, 1H), 8.11 (bs, 1H), 7.76 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 7.5, 1H), 7.60 – 7.57 (m, 2H), 7.41 (bs, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 156.7, 153.6, 150.7, 141.1, 134.1, 132.5, 131.4, 131.2, 130.7, 130.5, 128.7; HRMS = [M+H] 246.0550; $C_{11}H_9ClN_5$ = 246.0546.



10 **20i**

9-(2-Fluorophenyl)adenine (20i)

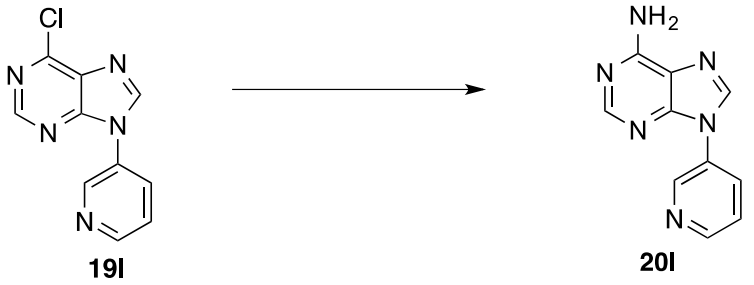
To a solution of **10** (60 mg, 0.18 mmol) and 2-fluorophenylboronic acid (50 mg, 0.36 mmol), in dry MeOH (3.0 mL) was added $Cu(NO_3)_2 \bullet 6H_2O$ (400 μL of 0.14 M solution in dry MeOH, 0.056 mmol) and TMEDA (400 μL of a 0.14 M solution in dry MeOH, 0.056 mmol). The resulting mixture was stirred for 24 h at ambient temperature under O_2. Volatiles were evaporated and the crude material was re-dissolved in CH_2Cl_2 and washed with saturated EDTA (aq). The organic layer was dried over Na_2SO_4 and volatiles were removed under reduced pressure. Crude product was re-dissolved in MeOH (3.0 mL) and Cs_2CO_3 (120 mL) was added. The resulting mixture was stirred for 1 hour at 80 °C. Volatiles were evaporated under reduced pressure. Flash chromatography (10% MeOH/CH_2Cl_2) gave **20i** (6 mg, 0.026 mmol, 14%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.41 (s, 1H), 8.16 (s, 1H), 7.76 (t, J = 7.5 Hz, 1H), 7.62 – 7.55 (m, 2H), 7.48 – 7.40 (m, 1H), 7.44 (bs, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 156.4 (d, J = 249 Hz), 156.7, 153.7, 150.4, 141.1 (d, J = 2 Hz), 131.1 (d, J = 7.5 Hz) 129.1, 125.6 (d, J = 4 Hz), 122.7 (d, J = 12 Hz), 118.8, 117.2 (d, J = 19 Hz); HRMS [M+H] = 230.0842; $C_{27}H_{34}N_7O_4$ = 230.0842



10 **20j**

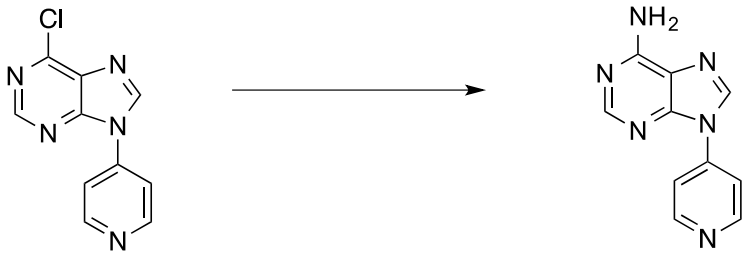
9-(3-Fluorophenyl)adenine (20j)

To a solution of **10** (60 mg, 0.18 mmol) and 3-fluorophenylboronic acid (50 mg, 0.36 mmol), in dry MeOH (3.0 mL) was added $Cu(NO_3)_2 \bullet 6H_2O$ (400 µL of 0.14 M solution in dry MeOH, 0.056 mmol) and TMEDA (400 µL of a 0.14 M solution in dry MeOH, 0.056 mmol). The resulting mixture was stirred for 24 h at ambient temperature under O_2. Volatiles were evaporated and the crude material was re-dissolved in CH_2Cl_2 and washed with saturated EDTA (aq). The organic layer was dried over Na_2SO_4 and volatiles were removed under reduced pressure. Crude product was re-dissolved in CH_2CL_2 (4.0 mL) and 4.0 M HCl solution in 1,4-dioxane (1.5 mL) was added. The resulting mixture was stirred for 30 minutes at room temperature. Volatiles were evaporated under reduced pressure. Flash chromatography (10% MeOH/CH_2Cl_2) gave **20j** (8 mg, 0.035 mmol, 19%). ^{1}H NMR (Acetic acid-d_4, 500 MHz) δ 8.59 (bs, 1H), 8.48 (bs, 1H), 7.66 – 7.64 (m, 3H), 7.31 (t, J = 3.3 Hz, 1H); ^{1}H NMR (CD_3OD, 500 MHz) δ 8.28 (s, 1H), 8.25 (s, 1H), 7.59 – 7.54 (m, 1H), 7.51 (d, J = 10.5 Hz, 2H), 7.19 (td, J = 8.5, 1.2 Hz, 1H); ^{13}C NMR (Acetic acid-d_4, 125 MHz) δ 162.9 (d, J = 246 Hz), 154.4, 150.3, 141.5, 135.2 (d, J = 11 Hz), 131.2 (d, J = 9 Hz), 119.9 (d, J = 3 Hz), 115.7 (d, J = 21 Hz), 111.8 (d, J = 26 Hz); ^{13}C NMR (CD_3OD:$CDCl_3$ (1:1), 125 MHz) δ 163.0 (d, J = 247 Hz), 156.0, 153.0, 149.2, 139.6, 135.6, 131.3 (d, J = 9 Hz), 119.1 (d, J = 3 Hz), 115.3 (d, J = 21 Hz), 111.2 (d, J = 25 Hz); HRMS [M+H] = 230.0848; $C_{11}H_9FN_5$ = 230.0842



9-(3-Pyridyl)adenine (20l)

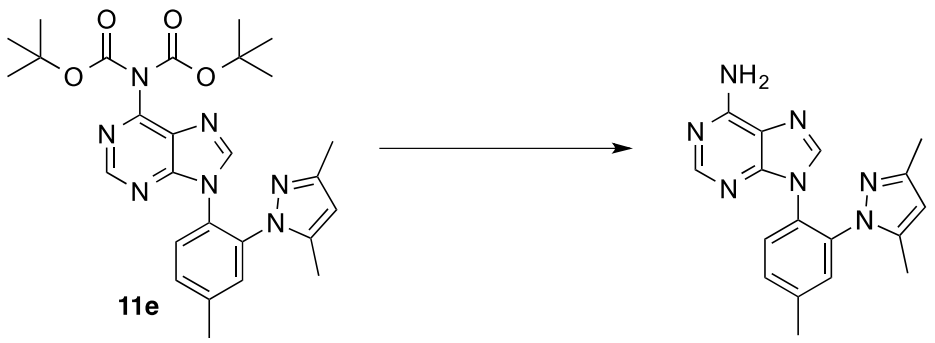
A solution of **19l** (20 mg, 0.087 mmol) in THF (1.5 mL) and saturated solution of ammonia in methanol (1.5 mL) was stirred in a flame-dried pressure tube for two days at 65°C. Volatiles were evaporated using a stream of air and crude product was re-dissolved in a minimum amount of 10% MeOH/CH_2Cl_2 and Flash chromatographed in 10% MeOH/CH_2Cl_2 to give **20l** (8 mg, 0.038 mmol, 44%). ^{1}H NMR (CD_3OD, 500 MHz) δ 9.01 (s, 1H), 8.67 (s, 1H), 8.41 (s, 1H), 8.28 (m, 2H), 7.65 (m, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 156.2, 153.4, 148.6, 143.9. 139.4, 132.0, 131.9, 124.7; HRMS [M+H] = 213.0889; $C_{10}H_9N_6$ = 213.0889.



19m **20m**

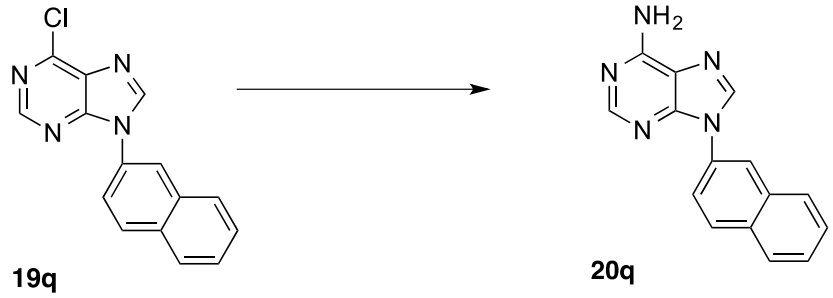
9-(4-Pyridyl)adenine (20m)

A solution of **19m** (25 mg, 0.11 mmol) in THF (1.5 mL) and saturated solution of ammonia in methanol (1.5 mL) was stirred in a flame-dried pressure tube for two days at 65 °C. Volatiles were evaporated using a stream of air and crude was re-dissolved in a minimum amount of 10% MeOH/CH_2Cl_2 and Flash chromatographed in 10% MeOH/ CH_2Cl_2 to give **20m** (22 mg, 0.10 mmol, 94%). ^{1}H NMR ($CDCl_3$:CD_3OD (1:1), 500 MHz) δ 8.72 (d, J = 3.0 Hz, 2H), 8.40 (s, 1H), 8.33 (s, 1H), 7.97 (d, J = 4.0 Hz, 2H) ; ^{13}C NMR ($CDCl_3$: CD_3OD (1:1), 125 MHz) δ 156.0, 153.7, 150.9, 149.4, 142.5, 138.3, 119.9, 116.5; HRMS [M+H] = 213.0897; $C_{10}H_9N_6$ = 213.0889.



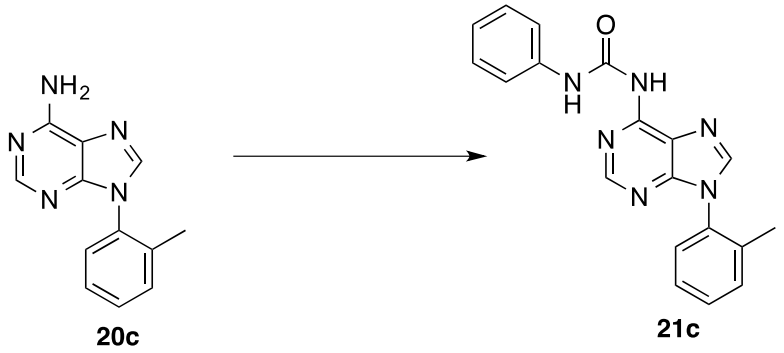
9-[2-(3,5-dimethylpyrazol-1-yl)-4-methylphenyl]adenine (20p)

To a solution of **11e** (60 mg, 0.12 mmol) in MeOH (3.0 mL) and Cs_2CO_3 (120 mg) was added. The resulting mixture was stirred for 12 hours at 65 °C. Volatiles were evaporated under reduced pressure. Flash chromatography (10% MeOH/CH_2Cl_2) gave **20p** (30 mg, 0.094 mmol, 78%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.07 (s, 1H), 7.67 (d, J = 8 Hz, 1H), 7.51 (d, J = 8 Hz, 1H), 7.45 (s, 1H), 7.43 (s, 1H), 7.27 (bs, 2H), 5.83 (s, 1H), 2.50 (s, 1.5H), 2.45 (s, 1.5H), 2.01 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 156.5, 153.5, 150.3, 148.6, 141.0, 140.3, 139.9, 134.9, 130.6, 129.8, 129.2, 128.3, 118.4, 106.2, 20.9, 13.6, 11.1; HRMS [M+H] = 320.1644; $C_{17}H_{17}N_7$ = 320.1624.



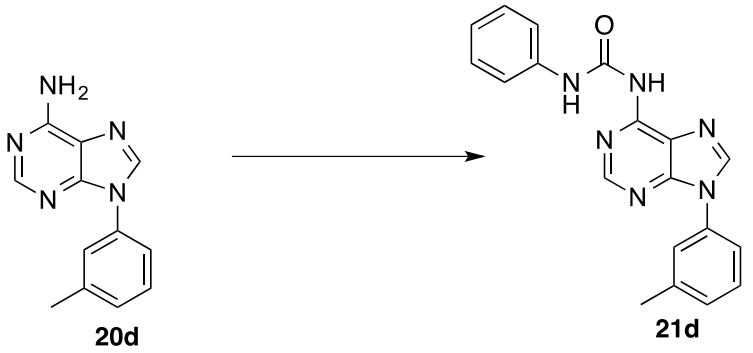
9-(2-Naphthyl)adenine (20q)

A solution of **19q** (30 mg, 0.10 mmol) in THF (1.5mL) and saturated solution of ammonia in methanol (1.5 mL) was stirred in a flame-dried pressure tube for two days at 65 °C. Volatiles were evaporated using a stream of air and crude was re-dissolved in a minimum amount of 10% MeOH/CH_2Cl_2 and Flash chromatographed in 10% MeOH/CH_2Cl_2 to give **20q** (22 mg, 0.084 mmol, 76%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.44 (d, J = 2.0 Hz, 1H), 8.91 (d, J = 2.0 Hz, 1H), 8.79 (s, 1H), 8.27 (s, 1H), 8.12 (t, J = 9.0 Hz, 2H), 7.84 (dd, J = 8.5, 7.0 Hz, 1H), 7.72 (t, J = 7.5 Hz, 1H), 7.51 (bs, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 156.9, 153.9, 149.9, 146.6, 146.3, 140.1, 130.5, 129.4, 129.3, 128.9, 128.8, 128.2, 127.7, 119.6; HRMS [M+H] = 263.1054; $C_{14}H_{11}N_6$ = 263.1045



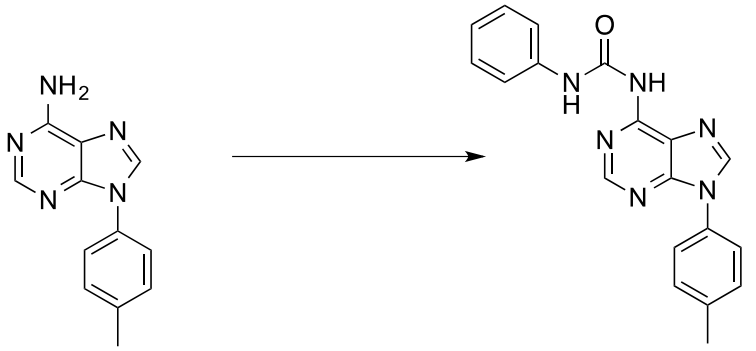
9-(2-Methylphenyl)-N^6-(N-phenylcarbamyl)adenine (21c)

A solution of phenylisocyanate (1.5 mL of 0.1 M in dry CH_2Cl_2, 0.15 mmol), and **20c** (21 mg, 0.093 mmol), in THF (1.5 mL) was stirred in a flame-dried flask. The mixture was stirred for 12 h, then volatiles were evaporated using a stream of air. Crude material was re-dissolved in a minimal amount of 10% MeOH/CH_2Cl_2 and Flash column chromatographed (80% EtOAc/CH_2Cl_2) to give **21c** (25 mg, 0.073 mmol, 78%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.9 (s, 1H), 10.3 (s, 1H), 8.64 (d, J = 6.5 Hz, 2H), 7.51 (d, J = 3.5 Hz, 2H), 7.49-7.44 (m, 2H), 7.36 (t, J = 8.0 Hz, 2H), 7.27 (t, J = 8.0 Hz, 1H), 7.09 (t, J = 7.3 Hz, 2H), 2.09 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 151.72, 151.69, 151.5, 150.6, 144.3, 140.2, 138.9, 135.4, 133.5, 131.6, 130.1, 129.4, 129.2, 128.4, 127.5, 123.7, 122.2, 120.3, 119.9, 118.6, 17.9; HRMS [M+H] = 345.1464; $C_{19}H_{17}N_6O$ = 345.1464



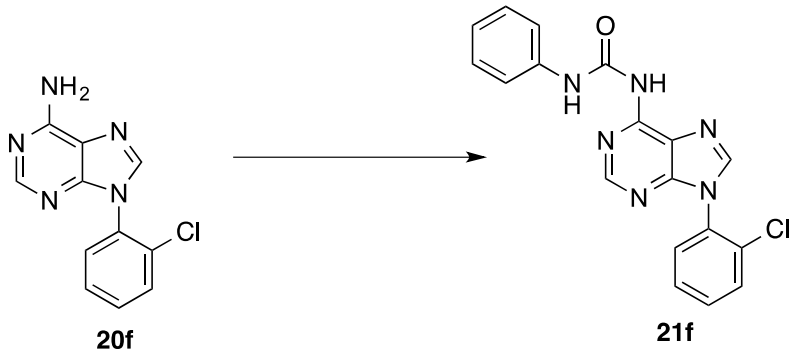
9-(3-Methylphenyl)-N^6-(N-phenylcarbamyl)adenine (21d)

A solution of phenylisocyanate (1.5 mL of 0.1 M in dry CH_2Cl_2, 0.15 mmol), and **20d** (10 mg, 0.044 mmol), 1.5 mL THF was stirred in a flame-dried round flask. The mixture was stirred for 12 h, then volatiles were evaporated using a stream of air. Crude material was re-dissolved in a minimal amount of 10% MeOH/CH_2Cl_2 and Flash column chromatographed (80% EtOAc/CH_2Cl_2) to give **21d** (3 mg, 0.009 mmol, 20%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.85 (s, 1H), 8.63 (s, 1H), 7.68 (d, J = 8.0 Hz, 2H), 7.61-7.59 (m, 3H), 7.52 (t, J = 7.8 Hz, 1H), 7.40-7.37 (m, 2H), 7.16 (t, J = 7.3 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 152.7, 151.6, 150.4, 150.1, 143.1, 140.1, 137.5, 133.9, 129.5, 128.9, 124.7, 124.2, 121.2, 120.5, 20.3; HRMS [M+H] = 345.1470; $C_{19}H_{17}N_6O$ = 345.1464



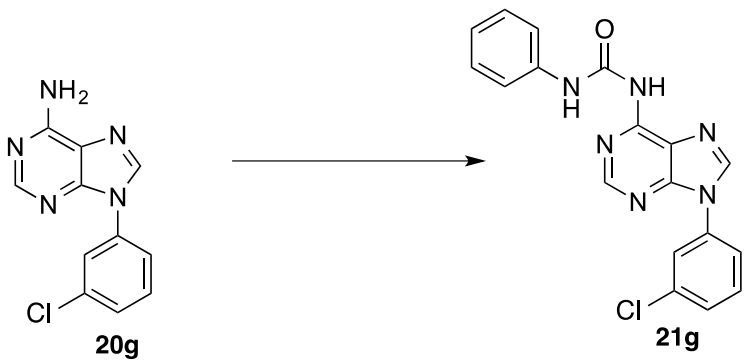
9-(4-Methylphenyl)-N^6-(N-phenylcarbamyl)adenine (21e)

A solution of phenylisocyanate (1.5 mL of 0.1 M in dry CH_2Cl_2, 0.15 mmol), and **20e** (22 mg, 0.098 mmol), 1.5 mL THF was stirred in a flame-dried round flask. The mixture was stirred for 12 h, then volatiles were evaporated using a stream of air. Crude material was re-dissolved in a minimal amount of 10% MeOH/CH_2Cl_2 and Flash column chromatographed (80% EtOAc/CH_2Cl_2) to give **21e** (28 mg, 0.081 mmol, 83%). ^{1}H NMR (DMSO-d_6:$CDCl_3$ (1:1); 500 MHz) δ 11.8 (s, 1H), 9.98 (s, 1H), 8.69 (s, 1H), 8.64 (s, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 7.5 Hz, 2H), 7.30 (t, J = 7.8 Hz, 2H), 7.03 (t, J = 7.3 Hz, 1H), 2.40 (s, 3H) ; ^{13}C NMR (DMSO-d_6:$CDCl_3$ (1:1); 125 MHz) δ 151.40, 151.37, 150.66, 150.62, 142.8, 138.8, 138.0, 132.3, 130.3, 129.1, 123.6, 123.5, 121.1, 119.9, 21.2; HRMS [M+H] = 345.1454; $C_{19}H_{17}N_6O$ = 345.1464.



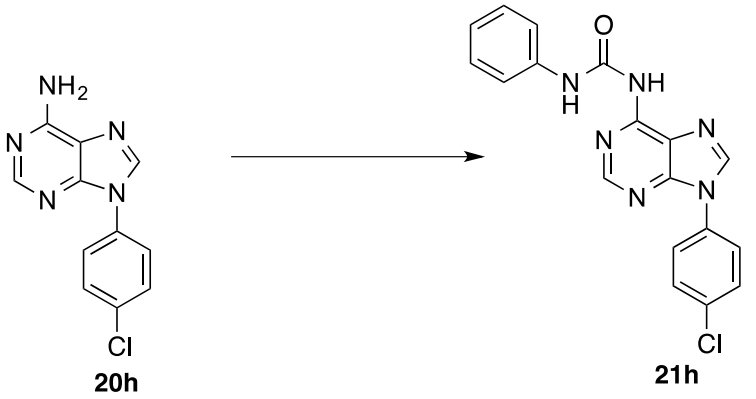
9-(2-Chlorophenyl)-N^6-(N-phenylcarbamyl)adenine (21f)

A solution of phenylisocyanate (1.5 mL of 0.1 M in dry CH_2Cl_2, 0.15mmol), and **20f** (10 mg, 0.040 mmol), in THF (1.5 mL) was stirred in a flame-dried round flask. The mixture was stirred for 12 h, then volatiles were evaporated using a stream of air. Crude material was re-dissolved in a minimal amount of 10% MeOH/CH_2Cl_2 and Flash column chromatographed (80% EtOAc/CH_2Cl_2) to give **21f** (7 mg, 0.019 mmol, 48%). ^{1}H NMR (Acetic acid-d_4, 500 MHz) δ 8.81 (s, 1H), 8.50 (s, 1H), 7.75 – 7.58 (m, 6H), 7.39 (t, J = 7.8 Hz, 2H), 7.16 (t, J = 7.3 Hz, 1H); ^{13}C NMR (Acetic acid-d_4, 125 MHz) δ 152.7, 151.8, 150.8, 150.5, 143.8, 137.5, 131.52, 131.49, 131.0, 130.6, 129.6, 128.84, 128.77, 128.1, 120.5, 119.3; HRMS [M+H] = 365.0922; $C_{18}H_{14}ClN_6O_4$ = 365.0918.



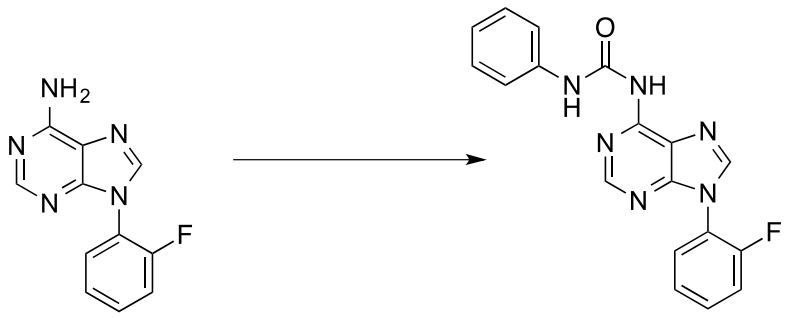
9-(3-Chlorophenyl)-N^6-(N-phenylcarbamyl)adenine (21g)

A solution of phenylisocyanate (1.5 mL of 0.1 M in dry CH_2Cl_2, 0.15 mmol), and **20g** (10 mg, 0.040 mmol), 1.5 mL THF was stirred in a flame-dried round flask. The mixture was stirred for 12 h, then volatiles were evaporated using a stream of air. Crude material was re-dissolved in a minimal amount of 10% MeOH/CH_2Cl_2 and Flash column chromatographed (80% EtOAc/CH_2Cl_2) to give **21g** (3 mg, 0.008 mmol, 21%). ^{1}H NMR (Acetic acid-d_4, 500 MHz) δ 8.85 (s, 1H), 8.69 (s, 1H), 7.97 (s, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 7.5 Hz, 2H), 7.64-7.58 (m, 2H), 7.39 (t, J = 7.8 Hz, 2H), 7.16 (t, J = 7.3 Hz, 1H); ^{13}C NMR (Acetic acid-d_4, 125 MHz) δ 152.7, 151.8, 142.7, 137.5, 135.2, 135.1, 131.0, 128.9, 128.8, 124.3, 124.2, 122.3, 120.5, 120.1; HRMS [M+H] = 365.0932; $C_{18}H_{14}ClN_6O$ = 365.0918.



9-(4-Chlorophenyl)-N^6-(N-phenylcarbamyl)adenine (21h)

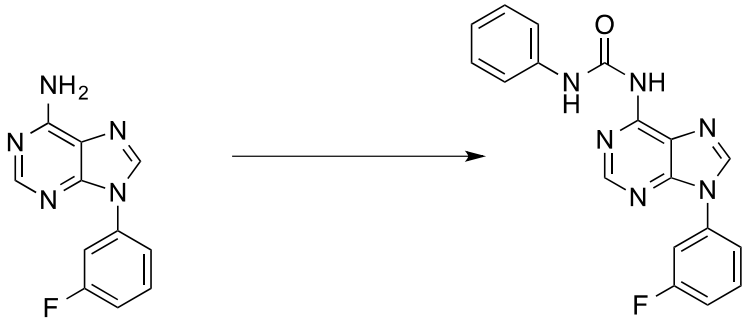
A solution of phenylisocyanate (1.5 mL of 0.1 M in dry CH_2Cl_2, 0.15mmol), and **20h** (22 mg, 0.089 mmol), in THF (1.5 mL) was stirred in a flame-dried flask. The mixture was stirred for 12 h, then volatiles were evaporated using a stream of air. Crude material was re-dissolved in a minimal amount of 10% MeOH/CH_2Cl_2 and Flash column chromatographed (80% EtOAc/CH_2Cl_2) to give **21h** (16 mg, 0.044 mmol, 49%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.8 (s, 1H), 10.3 (s, 1H), 8.92 (s, 1H), 8.75 (s, 1H), 7.98 (d, J = 8.5 Hz, 2H), 7.72 (d, J = 9.0 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H), 7.36 (t, J = 7.8 Hz, 2H), 7.09 (t, J = 7.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 151.9, 151.4, 150.7, 143.0, 138.9, 133.8, 132.8, 130.0, 129.4, 125.5, 123.7, 121.2, 119.9; HRMS [M+H] = 365.0920; $C_{18}H_{14}ClN_6O$ = 365.0918.



20i **21i**

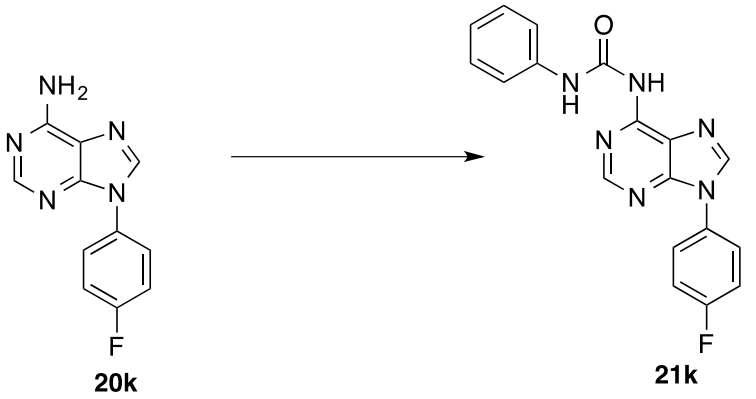
9-(2-Fluorophenyl)-N^6-(N-phenylcarbamyl)adenine (21i)

A solution of phenylisocyanate (1.5 mL of 0.1 M in dry CH_2Cl_2, 0.15 mmol), and **20i** (6 mg, 0.026 mmol), in THF (1.5 mL) was stirred in a flame-dried flask. The mixture was stirred for 12 h, then volatiles were evaporated using a stream of air. Crude material was re-dissolved in a minimal amount of 10% MeOH/CH_2Cl_2 and Flash column chromatographed (80% EtOAc/CH_2Cl_2) to give 21i (5 mg, 0.014 mmol, 55%). ^{1}H NMR (Acetic acid-d_4, 500 MHz) δ 8.82 (s, 1H), 8.55 (s, 1H), 7.80 (t, J = 7.3 Hz), 7.67 (d, J = 8.0 Hz, 2H), 7.67 – 7.62 (m, 1H), 7.50 – 7.45 (m, 2H), 7.39 (t, J = 8.0 Hz, 2H), 7.16 (t, J = 7.3 Hz, 1H); ^{13}C NMR (Acetic acid-d_4, 125 MHz) δ 156.5 (d, J = 250 Hz), 152.7, 151.8, 150.5 (d, J = 20.4 Hz), 143.8, 137.5, 131.4 (d, J = 7.6 Hz), 128.8, 128.3, 125.1 (d, J = 3.8 Hz), 124.2, 121.3 (d, J = 13 Hz), 120.5, 119.4, 116.9 (d, J = 19 Hz); HRMS [M+H] = 349.1218; $C_{18}H_{14}FN_6O$ = 349.1213



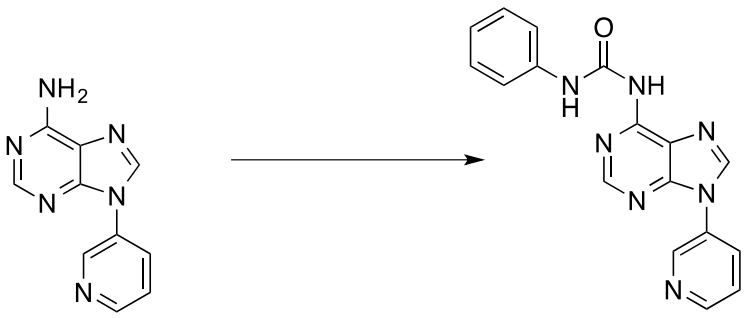
9-(3-Fluorophenyl)-N^6-(N-phenylcarbamyl)adenine (21j)

A solution of phenylisocyanate (1.5 mL of 0.1 M in dry CH_2Cl_2, 0.15 mmol), and **20j** (8 mg, 0.035 mmol), in THF (1.5 mL) was stirred in a flame-dried flask. The mixture was stirred for 12 h, then volatiles were evaporated using a stream of air. Crude material was re-dissolved in a minimal amount of 10% MeOH/CH_2Cl_2 and Flash column chromatographed (80% EtOAc/CH_2Cl_2) to give **21j** (5 mg, 0.014 mmol, 40%). ^{1}H NMR (Acetic acid-d_4, 500 MHz) δ 8.85 (s, 1H), 8.71 (s, 1H), 7.75 – 7.64 (m, 5H), 7.39 (t, J = 7.8 Hz, 2H), 7.32 (t, J = 7.8 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H); ^{13}C NMR (Acetic acid-d_4, 125 MHz) δ 162.9 (d, J = 246 Hz), 152.7, 151.7, 137.4, 131.3 (d, J = 9 Hz), 128.9, 124.3, 120.5, 119.6 (d, J = 3 Hz), 115.5 (d, J = 21 Hz), 111.5 (d, J = 26 Hz); HRMS [M+H] = 349.1214; $C_{18}H_{14}FN_6O$ = 349.1213.



9-(4-Fluorophenyl)-N^6-(N-phenylcarbamyl)adenine (21k)

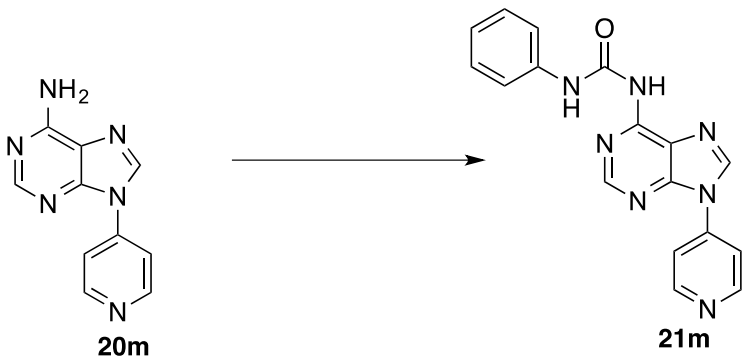
A solution of phenylisocyanate (1.5 mL of 0.1 M in dry CH_2Cl_2, 0.15 mmol), and **20k** (22 mg, 0.096 mmol), in THF (1.5 mL) was stirred in a flame-dried flask. The mixture was stirred for 12 h, then volatiles were evaporated using a stream of air. Crude material was re-dissolved in a minimal amount of 10% MeOH/CH_2Cl_2 and Flash column chromatographed (80% EtOAc/CH_2Cl_2) to give **21k** (16 mg, 0.046 mmol, 48%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.8 (s, 1H), 10.31 (s, 1H), 8.89 (s, 1H), 8.75 (s, 1H), 7.97 (dd, J = 15.0, 8.0 Hz, 2H), 7.66 (d, J = 7.8 Hz, 2H), 7.52 (t, J = 8.8, 2H), 7.38 (t, J = 8.0 Hz, 2H), 7.11 (t, J = Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 161.8 (d, J = 244 Hz), 151.8, 151.4, 150.9, 150.7, 143.3, 138.9, 131.2 (d, J = 3 Hz), 129.4, 126.4 (d, J = 9 Hz), 123.7, 121.0, 119.9, 116.9 (d, J = 23 Hz); HRMS [M+H] = 349.1214; $C_{18}H_{14}FN_6O$ = 349.1213



20l **21l**

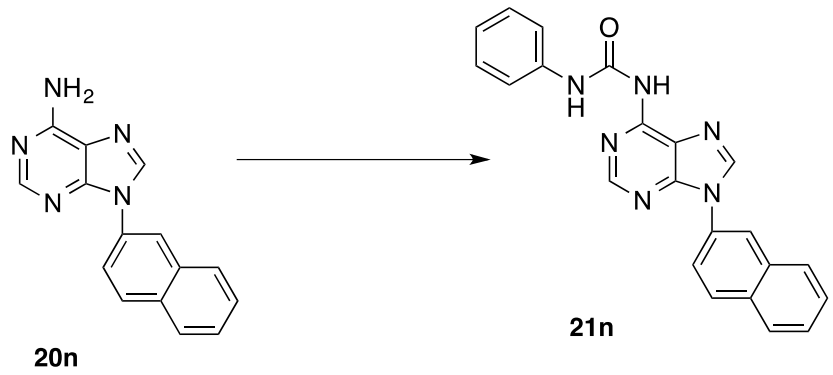
N^6-(N-Phenylcarbamyl)-9-(3-pyridyl)adenine (21l)

A solution of phenylisocyanate (1.5 mL of 0.1 M in dry CH_2Cl_2, 0.15mmol), and **20l** (8 mg, 0.038 mmol), in THF (1.5 mL) was stirred in a flame-dried flask. The mixture was stirred for 12 h, then volatiles were evaporated using a stream of air. Crude material was re-dissolved in a minimal amount of 10% MeOH/CH_2Cl_2 and Flash column chromatographed (80% EtOAc/CH_2Cl_2) to give **21l** (7 mg, 0.021 mmol, 56%). ^{1}H NMR (Acetic acid-d_4, 500 MHz) δ 9.24 (d, J = 2.0 Hz, 1H), 8.86 (d, J = 6.5 Hz, 2H), 8.85 (s, 1H), 8.79 (s, 1H), 8.50 (d, J = 8.5 Hz, 1H), 7.83 (dd, J = 8.0, 5.0 Hz, 1H), 7.67 (d, J = 6.0 Hz, 2H), 7.39 (t, J = 8.0 Hz, 2H), 7.16 (t, J = 7.5 Hz, 1H); ^{13}C NMR (Acetic acid-d_4, 125 MHz) δ 152.7, 152.0, 150.5, 147.8, 143.1, 142.5, 137.4, 133.6, 132.0, 128.9, 125.2, 124.3, 120.5, 120.1; HRMS [M+H] = 332.1265 ; $C_{17}H_{14}N_7O$ = 332.1260



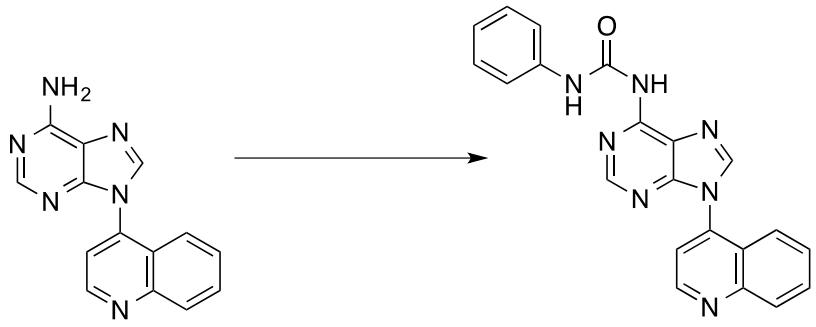
N^6-(N-Phenylcarbamyl)-9-(4-pyridyl)adenine (21m)

A solution of phenylisocyanate (1.5 mL of 0.1 M in dry CH_2Cl_2, 0.15 mmol), and **20m** (22 mg, 0.10 mmol), in THF (1.5 mL) was stirred in a flame-dried flask. The mixture was stirred for 12 h, then volatiles were evaporated using a stream of air. Crude material was re-dissolved in a minimal amount of 10% MeOH/CH_2Cl_2 and Flash column chromatographed (80% EtOAc/CH_2Cl_2) to give **21m** (12 mg, 0.036 mmol, 36%). ^{1}H NMR (Acetic acid-d^4, 500 MHz) δ 9.00 (d, J = 7.0 Hz, 2H), 8.99 (s, 1H), 8.90 (s, 1H), 8.44 (d, J = 6.5 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 7.40 (t, J = 8.0 Hz, 2H), 7.17 (t, J = 7.3 Hz, 1H); ^{13}C NMR (Acetic acid-d_4, 125 MHz) δ 152.7, 152.2, 150.6, 150.5, 148.4, 144.4, 141.8, 137.4, 128.9, 124.4, 120.9, 120.5, 117.3; HRMS [M+H] = 332.1260 ; $C_{17}H_{14}N_7O$ = 332.1260



9-(2-Napthyl)-N^6-(N-phenylcarbamyl)adenine (21n)

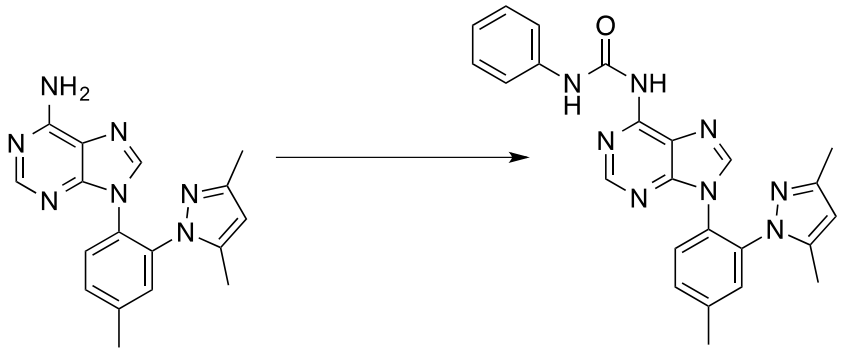
A solution of phenylisocyanate (2.2 mL of 0.1 M in dry CH_2Cl_2, 0.22 mmol), and **20n** (10 mg, 0.038 mmol), in THF (2.2 mL) was stirred in a flame-dried flask. The mixture was stirred for 12 h, then volatiles were evaporated using a stream of air. Crude material was re-dissolved in a minimal amount of CH_2Cl_2 and Flash column chromatographed (60% EtOAc/CH_2Cl_2) to give **21n** (8 mg, 0.021 mmol, 55%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.77 (bs, 1H), 8.74 (s, 1H), 8.39 (s, 1H), 8.20 (s, 1H), 8.17 (s, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.98 (t, *J* = 7.5 Hz, 2H), 7.84 (dd, *J* = 8.8, 1.8 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.63 (t, *J* = 3.8 Hz, 2H), 7.41-7.37 (m, 2H), 7.17-7.14 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.7, 151.1, 150.3, 141.9, 137.9, 133.4, 132.8, 131.6, 130.3, 129.4, 129.1, 128.2, 128.0, 127.5, 127.3, 124.5, 124.1, 122.2, 121.5, 121.3, 120.4; HRMS [M+H] = 381.1472 ; $C_{22}H_{17}N_6O$ = 381.1464



20o **21o**

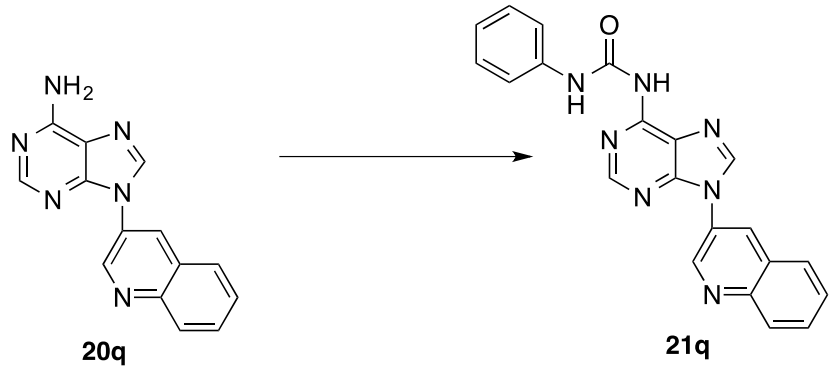
N^6-(N-Phenylcarbamyl)-9-(4-quinolinyl)adenine (20o)

A solution of phenylisocyanate (1.5 mL of 0.1 M in dry CH_2Cl_2, 0.15 mmol), and **20o** (2 mg, 0.008 mmol) was stirred in a flame-dried flask. The mixture was stirred for 12 h, then volatiles were evaporated using a stream of air. Crude material was re-dissolved in a minimal amount of 10% MeOH/CH_2Cl_2 and Flash column chromatographed (80% EtOAc/CH_2Cl_2) to give **21o** (2 mg, 0.005 mmol, 69%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.8 (bs, 1H, 105. (bs, 1H), 9.16 (d, J = 4.5 Hz, 1H), 8.84 (bs, 1H), 8.62 (bs, 1H), 8.24 (d, J = 9.0 Hz, 1H), 7.91 (d, J = 7.3 Hz, 1H), 7.86 (d, J = 5.0 Hz, 1H), 7.68 – 7.60 (m, 4H), 7.36 (t, J = 7.8 Hz, 2H), 7.08 (t, J = 7.3 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 152.1, 151.4, 149.4, 138.9, 131.1, 129.9, 129.4, 128.5, 124.1, 123.6, 120.3, 119.8; HRMS [M+H] = 382.1391; $C_{27}H_{34}N_7O_4$ = 382.1416



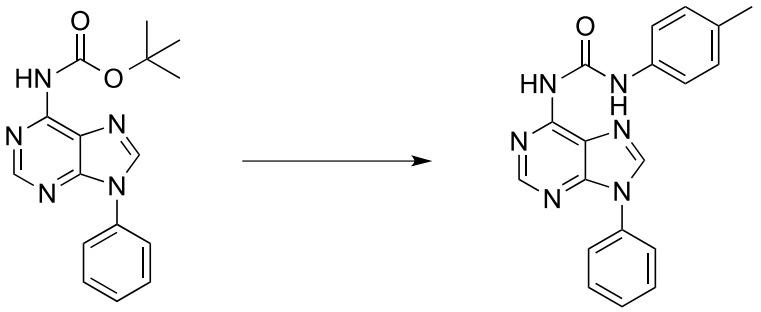
N^6-(N-Phenylcarbamyl)-9-[2-(3,5-dimethylpyrazol-1-yl)-4-methylphenyl]-adenine (21p)

A solution of phenylisocyanate (2.5 mL of 0.1 M in dry CH_2Cl_2, 0.25 mmol), and **20p** (30 mg, 0.094 mmol), in THF (2.5 mL) was stirred in a flame-dried flask. The mixture was stirred for 12 h, then volatiles were evaporated using a stream of air. Crude material was re-dissolved in a minimal amount of CH_2Cl_2 and Flash column chromatographed (80% EtOAc/CH_2Cl_2) to give **21p** (21 mg, 0.048 mmol, 51%). ^{1}H NMR (Acetic acid-d_4, 300 MHz) δ 8.73 (s, 1H), 8.12 (s, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.62 (m, 3H), 7.60 (s, 1H), 7.39 (t, J = 7.8 Hz, 2H), 7.16 (t, J = 7.4 Hz, 1H), 5.89 (bs, 1H), 2.58 (s, 3H), 2.17 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (Acetic acid-d_4, 75 MHz) δ 152.6, 151.5, 150.7, 150.2, 150.1, 143.9, 142.3, 141.4, 137.5, 134.0, 131.1, 129.7, 128.8, 128.2, 128.1, 124.2, 120.5, 119.0, 106.3, 20.1, 11.7, 10.0; HRMS [M+H] = 439.2030; $C_{27}H_{34}N_7O_4$ = 439.1995.



N^6-(N-Phenylcarbamyl)-9-(3-quinolinyl)adenine (21q)

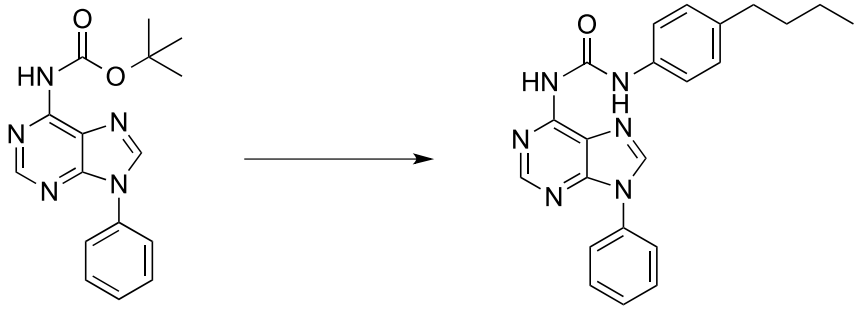
A solution of phenylisocyanate (2.5 mL of 0.1 M in dry CH_2Cl_2, 0.25 mmol), and **20q** (22 mg, 0.08 mmol), in THF (2.5 mL) was stirred in a flame-dried flask. The mixture was stirred for 12 h, then volatiles were evaporated using a stream of air. Crude material was re-dissolved in a minimal amount of CH_2Cl_2 and Flash column chromatographed (5 – 10% MeOH/CH_2Cl_2) to give **21q** (7 mg, 0.018 mmol, 23%). ^{1}H NMR (Acetic acid-d_4: $CDCl_3$ (10:1), 500 MHz) δ 9.43 (d, J = 2.5 Hz, 1H), 8.84 (d, J = 2.0 Hz, 1H), 8.82 (s, 1H), 8.75 (s, 1H), 8.32 (d, J = 8.5 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.92 (t, J = 7.3 Hz, 1H), 7.77 (t, J = 7.5 Hz, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.38 (t, J = 7.8 Hz, 2H), 7.15 (t, J = 7.3 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 152.0, 150.6, 146.0, 145.0, 142.3, 137.4, 131.7, 131.4, 128.9, 128.5, 128.4, 128.1, 127.84, 127.1, 124.3, 120.5; HRMS [M+H] = 382.1422; $C_{21}H_{16}N_7O$ = 382.1416.



12a **22a**

N^6-(N-(4-Methylphenylcarbamyl)-9-phenyladenine (22a)

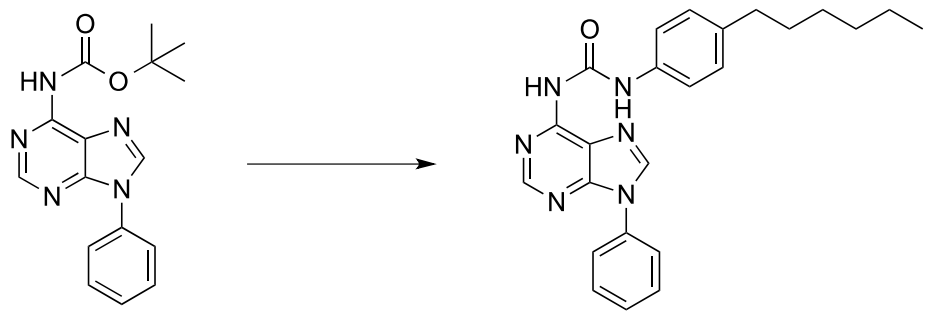
To a solution of 4-methylaniline (1.2 mL of 0.05 M in dry DMF, 0.06 mmol), **12a** (18 mg, 0.06 mmol), and DMAP (12 mg, 0.1 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (350 mg). The mixture was stirred at room temperature for 2 h, then heated at 80 °C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/CH_2Cl_2) to give **22a** (5 mg, 0.02 mmol, 33%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.7 (s, 1H), 8.71 (s, 1H), 8.31 (s, 1H), 8.29 (bs, 1H), 7.73 (d, *J* = 7.5 Hz, 2H), 7.63 (d, *J* = 7.8 Hz, 2H), 7.56-7.51 (m, 3H), 7.15 (d, *J* = 8.0 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.7, 151.2, 150.4, 141.8, 135.3, 134.2, 133.6, 130.1, 129.6, 128.8, 123.7, 120.4, 20.9; HRMS [M+H] = 345.1471; $C_{19}H_{17}N_6O$ = 345.1464.



12a **22b**

N^6-(N-(4-Butylphenylcarbamyl)-9-phenyladenine (22b)

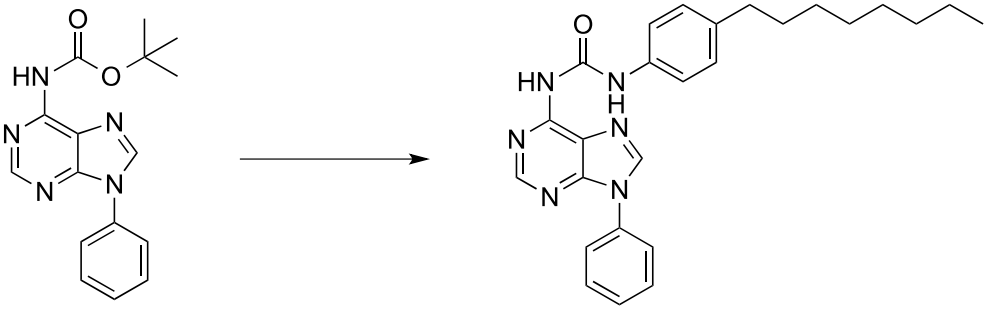
To a solution of 4-butylaniline (1.8 mL of 0.05 M in dry DMF, 0.09 mmol), **12a** (22 mg, 0.07 mmol), and DMAP (12 mg, 0.1 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (350 mg). The mixture was stirred at room temperature for 2 h, then heated at 80 °C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/CH_2Cl_2) to give **22a** (4 mg, 0.01 mmol, 15%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.71 (s, 1H), 8.70 (s, 1H), 8.46 (s, 1H), 8.37 (s, 1H), 7.73 (d, *J* = 7.5 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.56 (t, *J* = 8.0 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 2.62 (t, *J* = 7.5 Hz, 2H), 1.63-1.60 (m, 2H), 1.40-1.35 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.6, 151.3, 150.4, 142.0, 138.8, 135.4, 134.3, 130.0, 128.9, 128.8, 123.7, 120.9, 120.5, 35.1, 33.7, 22.3, 14.0; HRMS [M+H] = 387.1940; $C_{22}H_{22}N_6O$ = 387.1933.



12a **22c**

N^6-(N-(4-Hexylphenylcarbamyl)-9-phenyladenine (22c)

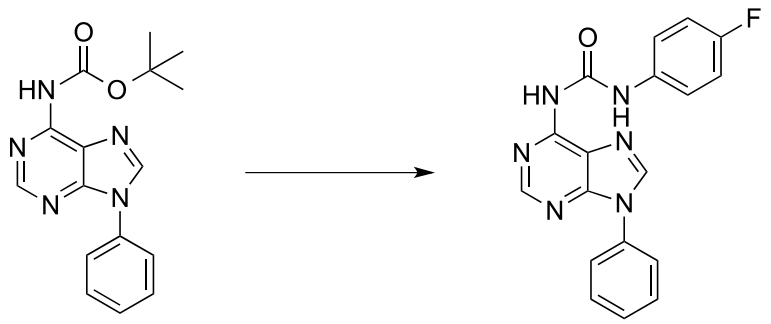
To a solution of 4-hexylaniline (1.8 mL of 0.05 M in dry DMF, 0.09 mmol), **12a** (17 mg, 0.05 mmol), and DMAP (12 mg, 0.1 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (350 mg). The mixture was stirred at room temperature for 2 h, then heated at 80 °C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/CH_2Cl_2) to give **22c** (6 mg, 0.01 mmol, 25%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.73 (s, 1H), 8.70 (s, 1H), 8.59 (s, 1H), 8.41 (s, 1H), 7.73 (d, *J* = 7.5 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 2.61 (t, *J* = 7.8 Hz, 2H), 1.63-1.60 (m, 2H), 1.40-1.35 (m, 6H), 0.90 (apparent "t", 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.6, 151.4, 150.4, 142.2, 138.8, 135.4, 134.3, 130.0, 128.9, 128.8, 123.7, 120.9, 120.5, 35.4, 31.8, 31.6, 28.9, 22.6, 14.1; HRMS [M+H] = 415.2238; $C_{24}H_{26}N_6O$ = 415.2246.



12a **22d**

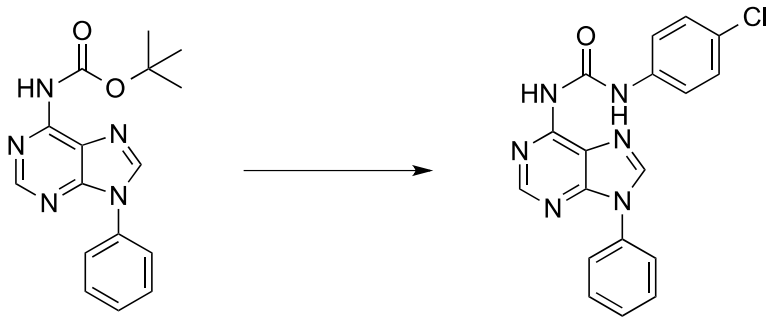
N^6-(N-(4-Butylphenylcarbamyl)-9-phenyladenine (22d)

To a solution of 4-octylaniline (1.8 mL of 0.05 M in dry DMF, 0.09 mmol), **12a** (14 mg, 0.04 mmol), and DMAP (12 mg, 0.1 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (350 mg). The mixture was stirred at room temperature for 2 h, then heated at 80°C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/CH_2Cl_2) to give **22d** (10 mg, 0.02 mmol, 50%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.80 (s, 1H), 8.70 (s, 1H), 8.68 (s, 1H), 8.43 (s, 1H), 7.73 (d, *J* = 7.5 Hz, 2H), 7.62 (t, *J* = 7.8 Hz, 2H), 7.62 (t, *J* = 7.8 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 2.60 (t, *J* = 7.5 Hz, 2H); 1.70-1.60 (m, 2H), 1.32-1.27 (m, 10H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.6, 151.4, 150.5, 142.2, 138.8, 135.4, 134.3, 130.0, 128.9, 128.7, 123.8, 120.9, 35.4, 31.9, 31.6, 29.7, 29.5, 29.30, 29.28, 22.7, 14.1; HRMS [M+H] = 443.2559; $C_{26}H_{31}N_6O$ = 443.2559.



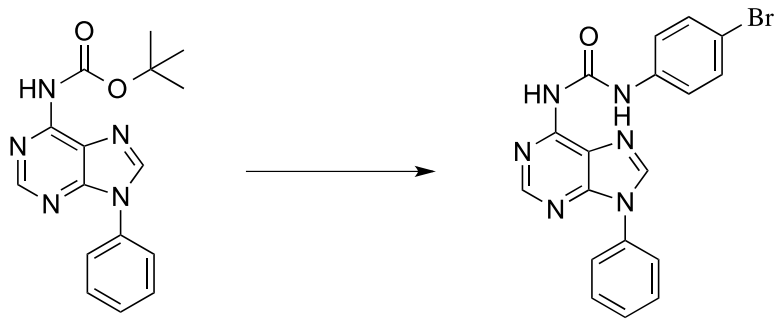
N^6-(N-(4-Fluorophenylcarbamyl)-9-phenyladenine (22e)

To a solution of 4-fluorolaniline (1.8 mL of 0.05 M in dry DMF, 0.09 mmol), **12a** (27 mg, 0.09 mmol), and DMAP (12 mg, 0.1 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (350 mg). The mixture was stirred at room temperature for 2 h, then heated at 80 °C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/CH_2Cl_2) to give **22e** (5 mg, 0.01 mmol, 11%). ^{1}H NMR (Acetic Acid-d_4:$CDCl_3$ (1:1), 500 MHz at 70°C) δ 8.75 (s, 1H), 8.46 (s, 1H), 7.77 (d, J = 7.5 Hz, 2H), 7.62 (Bd, J = 7.5 Hz, 4H), 7.55 (t, J = 7.5 Hz, 1H), 7.09 (t, J = 8.5 Hz, 2H); ^{13}C NMR (Acetic Acid-d_4:$CDCl_3$ (1:1), 125 MHz at 70°C) δ160.60, 158.66, 152.51, 151.66, 150.50, 150.42, 142.45, 134.15, 133.58, 129.72, 128.76, 123.9, 122.46, 122.40, 115.47, 115.29; HRMS [M+H] = 349.1215; $C_{18}H_{14}FN_6O$ = 349.1213.



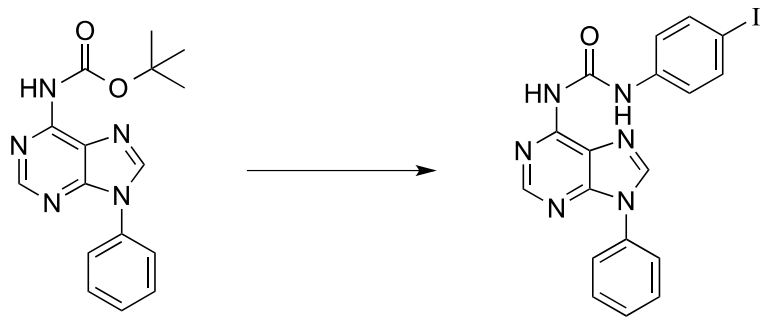
N^6-(N-(4-Chlorophenylcarbamyl)-9-phenyladenine (22f)

To a solution of 4-chloroaniline (1.8 mL of 0.05 M in dry DMF, 0.09 mmol), **12a** (18 mg, 0.06 mmol), and DMAP (12 mg, 0.1 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (350 mg). The mixture was stirred at room temperature for 2 h, then heated at 80 °C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/CH_2Cl_2) to give **22f** (6 mg, 0.02 mmol, 33%). ^{1}H NMR (Acetic Acid-d_4:$CDCl_3$(1:10), 500 MHz) δ 8.78 (s, 1H), 8.51 (s, 1H), 7.76 (d, J = 8Hz, 2H), 7.65 (t, J = 8.5 Hz, 4H), 7.56 (t, J = 7.5 Hz, 1H), 7.35 (d, J = 8.5 Hz); ^{13}C NMR (Acetic Acid-d_4:$CDCl_3$ (1:1), 125 MHz) δ 152.5, 151.7, 150.3, 142.6, 136.2, 133.9, 129.9, 129.1, 128.9, 124.0, 121.7, 120.2; HRMS [M+H] = 365.0923; $C_{18}H_{14}ClN_6O$ = 365.0918.



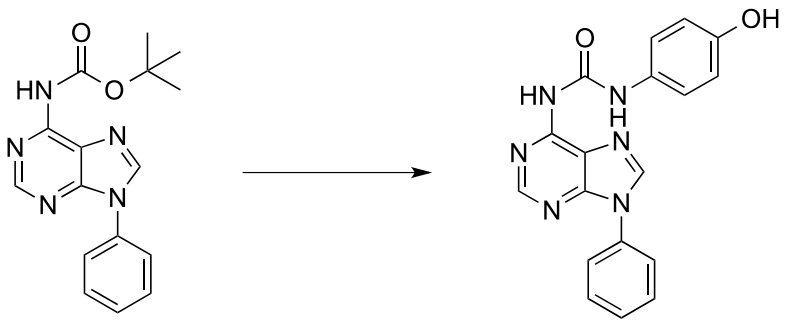
N^6-(N-(4-Bromophenylcarbamyl)-9-phenyladenine (22g)

To a solution of 4-bromoaniline (1.8 mL of 0.05 M in dry DMF, 0.09 mmol), **12a** (21 mg, 0.07 mmol), and DMAP (12 mg, 0.1 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (350 mg). The mixture was stirred at room temperature for 2 h, then heated at 80 °C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/CH_2Cl_2) to give **22g** (6 mg, 0.01 mmol, 14%). ^{1}H NMR (CD_3OD, 500 MHz) δ 8.67 (s, 1H), 8.34 (s, 1H), 7.69 (d, *J* = 7.5 Hz, 2H), 7.60 (t, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 9.0 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.5, 150.3, 142.0, 138.0, 136.8, 131.9, 131.7, 130.0, 129.0, 123.8, 121.9, 120.5, 116.6, 115.0, 110.0; HRMS [M+H] = 409.0417; $C_{18}H_{14}BrN_6O$ = 409.0417.



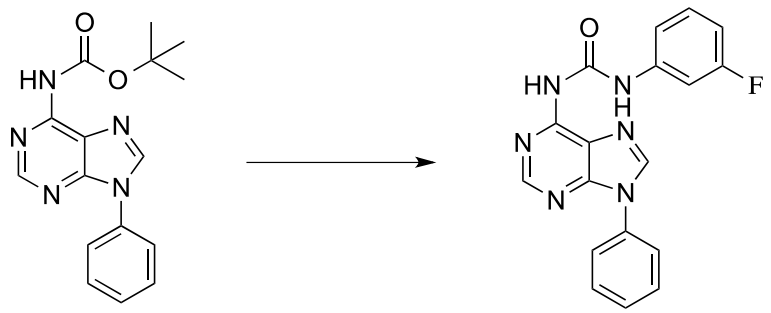
N^6-(N-(4-Iodophenylcarbamyl)-9-phenyladenine (22h)

To a solution of 4-iodoaniline (1.8 mL of 0.05 M in dry DMF, 0.09 mmol), **12a** (17 mg, 0.05 mmol), and DMAP (12 mg, 0.1 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (350 mg). The mixture was stirred at room temperature for 2 h, then heated at 80 °C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/CH_2Cl_2) to give **22h** (6 mg, 0.01 mmol, 20%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.80 (s, 1H), 8.71 (s, 1H), 8.30 (s, 1H), 8.21 (s, 1H), 7.72 (d, *J* = 7.5 Hz, 2H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.63 (t, *J* = 7.8 Hz, 2H), 7.53 (t, *J* = 7.0 Hz, 1H), 7.47 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.6, 150.9, 150.5, 150.1, 141.9, 137.9, 137.8, 134.1, 130.1, 128.9, 123.7, 122.1, 120.9; HRMS [M+H] = 457.0268; $C_{18}H_{14}IN_6O$ = 457.0274.



N^6-(N-(4-Hydroxyphenylcarbamyl)-9-phenyladenine (22i)

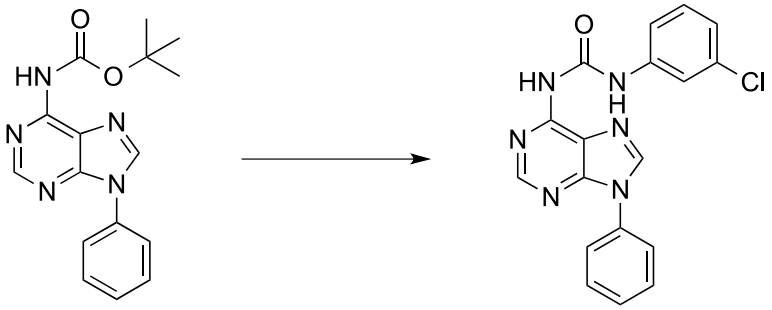
To a solution of 3-hydroxyaniline (1.8 mL of 0.05 M in dry DMF, 0.09 mmol), **12a** (25 mg, 0.08 mmol), and DMAP (12 mg, 0.1 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (250 mg). The mixture was stirred at room temperature for 2 h, then heated at 80°C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/CH_2Cl_2) to give **22i** (6 mg, 0.02 mmol, 25%). ^{1}H NMR (CD_3OD, 500 MHz) δ 8.63 (s, 1H), 8.27 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.58 (t, *J* = 7.8 Hz, 2H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.37 (t, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (Acetic Acid-d_4, $CDCl_3$ (1:1), 125 MHz at 70°C) δ 153.33, 152.76, 151.70, 150.53, 150.42, 142.37, 134.20, 129.93, 129.1, 128.71, 123.99, 122.74, 120.36; HRMS [M+H] = 347.1255; $C_{18}H_{15}N_6O_2$ = 347.1257.



12a 22j

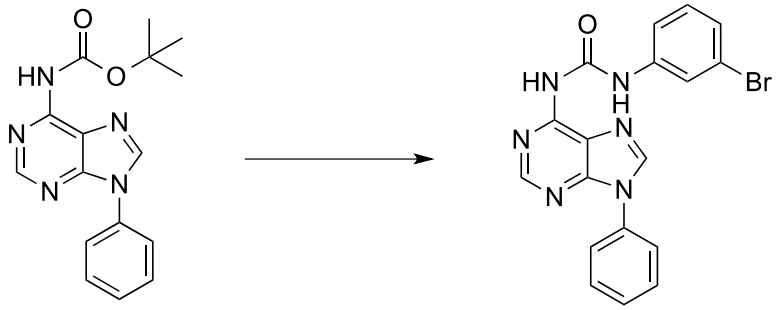
N^6-(N-(3-Fluorophenylcarbamyl)-9-phenyladenine (22j)

To a solution of 3-fluoroaniline (1.8 mL of 0.05 M in dry DMF, 0.09 mmol), **12a** (25 mg, 0.08 mmol), and DMAP (12 mg, 0.1 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (250 mg). The mixture was stirred at room temperature for 2 h, then heated at 80 °C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/CH_2Cl_2) to give **22j** (6 mg, 0.02 mmol, 25%). ^{1}H NMR (Acetic acid-d_4, 500 MHz) δ 8.85 (s, 1H), 8.67 (bs, 1H), 7.83 (d, J = 7.5 Hz, 1H), 7.66 (t, J = 7.8 Hz, 3H), 7.62-7.56 (m, 3H), 6.89 (t, J = 8.0 Hz, 1H); HRMS [M+H] = 349.1204; $C_{18}H_{14}FN_6O$ = 349.1213.



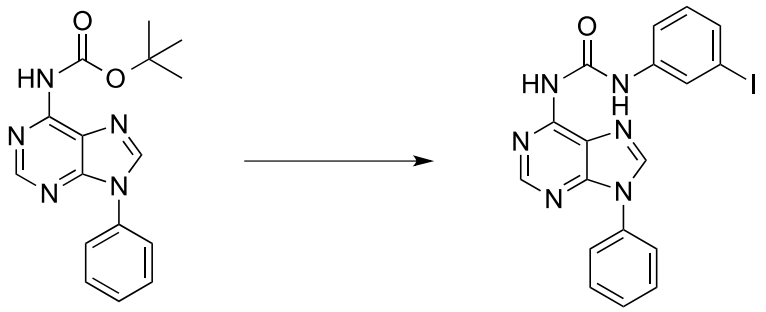
N^6-(N-(3-Chlorophenylcarbamyl)-9-phenyladenine (22k)

To a solution of 3-chloroaniline (1.8 mL of 0.05 M in dry DMF, 0.09 mmol), **12a** (20 mg, 0.06 mmol), and DMAP (12 mg, 0.1 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (250 mg). The mixture was stirred at room temperature for 2 h, then heated at 80 °C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/CH_2Cl_2) to give **22k** (15 mg, 0.04 mmol, 67%). ^{1}H NMR (Acetic acid-d_4, $CDCl_3$ (4:1), 500 MHz) δ 8.81 (s, 1H), 8.58 (bs, 1H), 7.80-7.77 (m, 3H), 7.64 (t, J = 7.8 Hz, 2H), 7.58-7.54 (m, 2H), 7.32 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H); ^{13}C NMR (Acetic acid-d_4, $CDCl_3$ (4:1), 125 MHz) δ 152.6, 151.7, 150.3, 142.8, 138.9, 134.4, 133.9, 130.0, 129.8, 128.9, 124.1, 123.9, 120.2, 118.4; HRMS [M+H] = 365.0912; $C_{18}H_{14}ClN_6O$ = 365.0918.



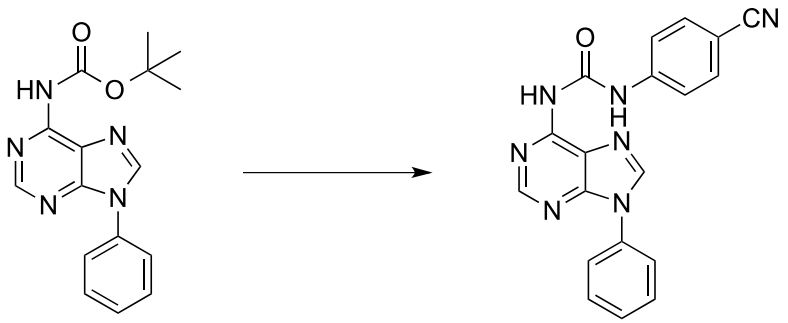
N^6-(N-(3-Bromophenylcarbamyl)-9-phenyladenine (22l)

To a solution of 3-bromoaniline (1.8 mL of 0.05 M in dry DMF, 0.09 mmol), **12a** (15 mg, 0.05 mmol), and DMAP (12 mg, 0.1 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (250 mg). The mixture was stirred at room temperature for 2 h, then heated at 80 °C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/CH_2Cl_2) to give **22l** (10 mg, 0.02 mmol, 40%). ^{1}H NMR (Acetic acid-d_4, $CDCl_3$ (4:1), 500 MHz) δ 8.79 (s, 1H), 8.51 (bs, 1H), 7.90 (s, 1H), 7.75 (d, J = 7.5 Hz, 2H), 7.65-7.61 (m, 3H), 7.56-7.54 (m, 1H), 7.27-7.24 (m, 2H); ^{13}C NMR (Acetic acid-d_4, $CDCl_3$ (4:1), 125 MHz) δ 151.7, 130.3, 129.9, 129.0, 128.9, 127.0, 124.0, 123.2, 122.4, 118.9; HRMS [M+H] = 409.0418; $C_{18}H_{14}BrN_6O$ = 409.0413.



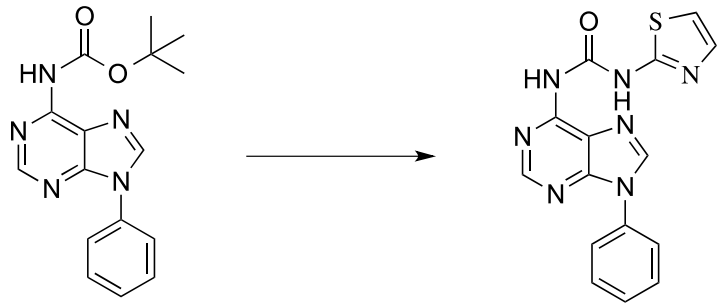
N^6-(N-(3-Iodophenylcarbamyl)-9-phenyladenine (22m)

To a solution of 3-iodoaniline (1.8 mL of 0.05 M in dry DMF, 0.09 mmol), **12a** (20 mg, 0.06 mmol), and DMAP (14 mg, 0.11 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (250 mg). The mixture was stirred at room temperature for 2 h, then heated at 80 °C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/CH_2Cl_2) to give **22m** (21 mg, 0.05 mmol, 83%). ^{1}H NMR (Acetic acid-d_4, $CDCl_3$ (4:1), 500 MHz) δ 8.80 (s, 1H), 8.56 (bs, 1H), 8.07 (s, 1H), 7.73 (d, J = 7.5 Hz, 2H), 7.69-7.62 (m, 3H), 7.55 (t, J = 7.5 Hz, 1H), 7.49 (d, J = 9.5 Hz, 1H), 7.11 (t, J = 8.0 Hz, 1H); ^{13}C NMR (Acetic acid-d_4, $CDCl_3$ (4:1), 125 MHz) δ 151.7, 138.9, 133.1, 130.4, 129.8, 128.9, 124.1, 119.6; HRMS [M+H] = 457.0284; $C_{18}H_{14}IN_6O$ = 457.0274.



N^6-(N-(4-Cyanophenylcarbamyl)-9-phenyladenine (22n)

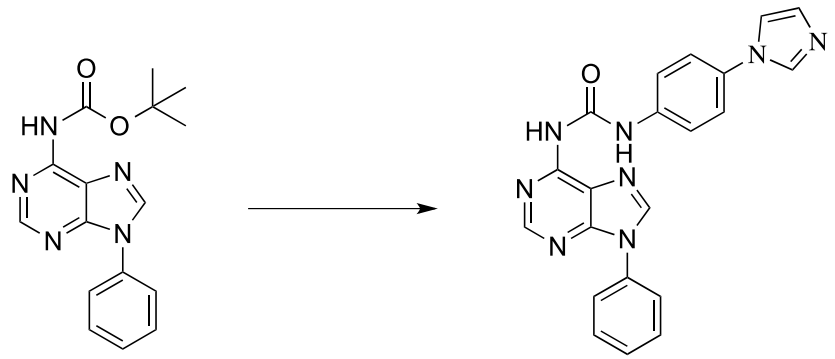
To a solution of 4-aminobenzonitrile (1.8 mL of 0.05 M in dry DMF, 0.09 mmol), **12a** (18 mg, 0.06 mmol), and DMAP (12 mg, 0.1 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (250 mg). The mixture was stirred at room temperature for 2 h, then heated at 80 °C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/CH_2Cl_2) to give **22n** (9 mg, 0.03 mmol, 50%). ^{1}H NMR (Acetic acid-d_4, $CDCl_3$ (4:1), 500 MHz) δ 8.81 (s, 1H), 8.56 (bs, 1H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 7.5 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.64 (t, *J* = 7.8 Hz, 2H), 7.59-7.56 (m, 1H); ^{13}C NMR (Acetic Acid-d_4, $CDCl_3$ (1:1), 500 MHz at 70°C) δ 151. 6, 150.2, 142.0, 134.1, 133.1, 133.1, 133.0, 129.8, 129.7, 128.9, 128.8, 124.2, 124.0, 120.2, 119.0, 118.4, 107.1; HRMS [M+H] = 356.1268; $C_{19}H_{14}N_7O$ = 356.1260.



12a 22o

N^6-(N-(Thiophen-2-yl)carbamyl)-9-phenyladenine (22o)

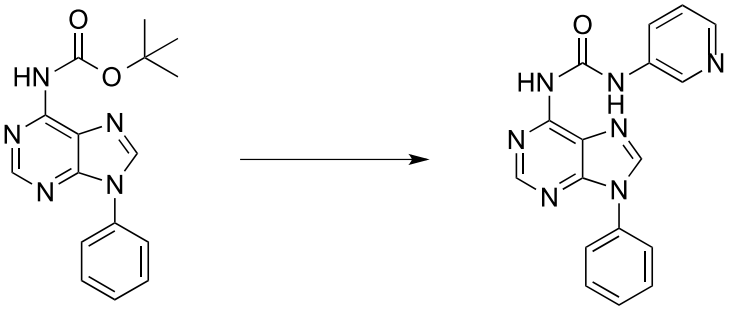
To a solution of 2-aminothiophene (1.8 mL of 0.05 M in dry DMF, 0.09 mmol), **12a** (20 mg, 0.06 mmol), and DMAP (12 mg, 0.1 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (250 mg). The mixture was stirred at room temperature for 2 h, then heated at 80 °C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/CH_2Cl_2) to give **22o** (5 mg, 0.02 mmol, 33%). ^{1}H NMR (Acetic acid-d_4, 500 MHz) δ 8.87 (s, 1H), 8.71 (s, 1H), 7.85 (d, J = 8.0 Hz, 2H), 7.67 (t, J = 7.8 Hz, 2H), 7.60-7.56 (m, 2H), 7.17 (d, J = 3.5 Hz, 1H); ^{13}C NMR (Acetic acid-d_4, 125 MHz) δ 159.7, 151.7, 151.6, 150.6, 149.5, 143.3, 136.2, 133.9, 129.7, 128.9, 124.1, 114.0; HRMS [M+H] = 338.0822; $C_{15}H_{12}N_7OS$ = 338.0824.



12a 22p

N^6-(N-(4-(Imidazol-1-yl)phenylcarbamyl)-9-phenyladenine (22p)

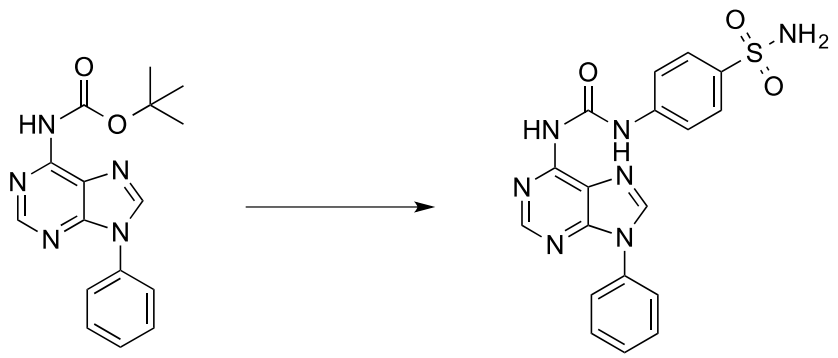
To a solution of 4-(imidazol-1-yl)aniline (1.8 mL of 0.05 M in dry DMF, 0.09 mmol), **12a** (20 mg, 0.06 mmol), and DMAP (12 mg, 0.1 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (250 mg). The mixture was stirred at room temperature for 2 h, then heated at 80 °C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/CH_2Cl_2) to give **22p** (7 mg, 0.02 mmol, 33%). ^{1}H NMR (Acetic acid-d_4, 500 MHz) δ 9.19 (s, 1H), 8.86 (s, 1H), 8.69 (s, 1H), 7.97 (d, J = 9.0 Hz, 2H), 7.84 (s, 1H), 7.83 (d, J = 7.5 Hz, 2H), 7.77 (s, 1H), 7.73 (d, J = 9.0 Hz, 2H), 7.66 (t, J = 7.0 Hz, 2H), 7.58 (t, J = 7.0 Hz, 1H); ^{13}C NMR (Acetic acid-d_4, 125 MHz) δ 152.5, 151.7, 150.3, 150.1, 143.2, 139.3, 134.1, 133.9, 130.9, 129.8, 128.9, 124.2, 123.0, 121.6, 121.3, 120.5, 119.9; HRMS [M+H] = 397.1528; $C_{21}H_{17}N_8O$ = 397.1525.



12a 22q

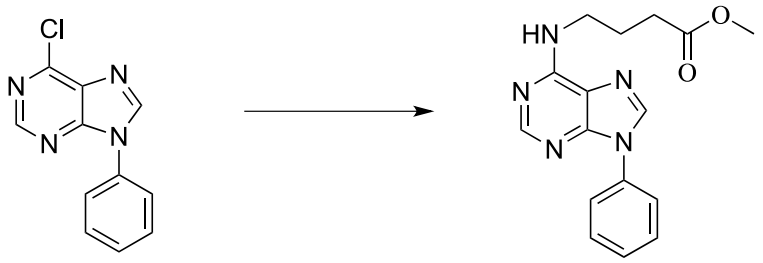
N^6-(N-(Pyridin-3-yl)carbamyl)-9-phenyladenine (22q)

To a solution of 4-aminotpyridine (1.2 mL of 0.05 M in dry DMF, 0.06 mmol), **12a** (15 mg, 0.05 mmol), and DMAP (8 mg, 0.07 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (300 mg). The mixture was stirred at room temperature for 2 h, then heated at 80 °C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/CH_2Cl_2) to give **22q** (6 mg, 0.02 mmol, 40%). ^{1}H NMR (Acetic acid-d_4, 500 MHz) δ 9.17 (s, 1H), 8.89 (s, 1H), 8.72 (s, 1H), 8.70 (s, 1H), 8.59 (d, J = 4.5 Hz, 1H), 7.84 (d, J = 7.5 Hz, 2H), 7.82-7.80 (m, 1H), 7.67 (t, J = 7.8 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H); ^{13}C NMR (Acetic acid-d_4, 125 MHz) δ 152.5, 151.7, 150.5, 149.9, 143.3, 139.5, 136.3, 133.9, 132.5, 129.8, 129.0, 126.0, 124.2; HRMS [M+H] = 332.1261; $C_{17}H_{14}N_7O$ = 332.1260.



N^6-(N-(4-Sulphonylaminophenyl)carbamyl)-9-phenyladenine (22r)

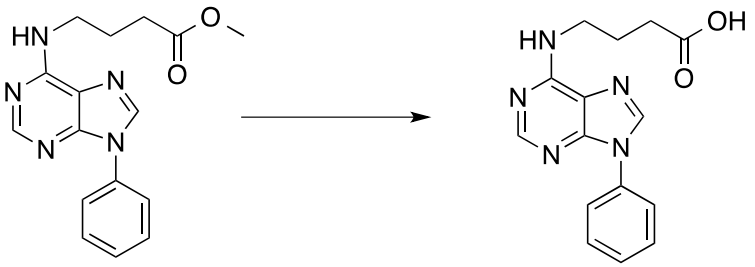
To a solution of sulphanilamide (1.8 mL of 0.05 M in dry DMF, 0.09 mmol), **12a** (18 mg, 0.06 mmol), and DMAP (12 mg, 0.1 mmol) in a flame-dried pressure tube was added 5Å molecular sieves (250 mg). The mixture was stirred at room temperature for 2 h, then heated at 80 °C for 48 h. Volatiles were evaporated and the crude material was Flash chromatographed (5% MeOH/CH_2Cl_2) to give **22r** (12 mg, 0.03 mmol, 50%). ^{1}H NMR (Acetic acid-d_4:$CDCl_3$ (4:1), 500 MHz) δ 8.82 (s, 1H), 8.54 (s, 1H), 7.92 (d, J = 9.0 Hz, 2H), 7.83 (d, J = 8.5 Hz, 2H), 7.77 (d, J = 7.5 Hz, 2H), 7.64 (t, J = 7.8 Hz, 2H), 7.56 (t, J = 7.0 Hz, 1H); ^{13}C NMR (Acetic acid-d_4:$CDCl_3$ (4:1), 125 MHz) δ 151.7, 150.2, 137.4, 133.8, 129.9, 129.0, 128.8, 127.5, 124.0, 119.8, 110.0; HRMS [M+H] = 410.1036; $C_{18}H_{16}N_7O_3S$ = 410.1035.



19 **25**

9-Phenyl-N^6-(methyl 4-butanoyl)adenine (25)

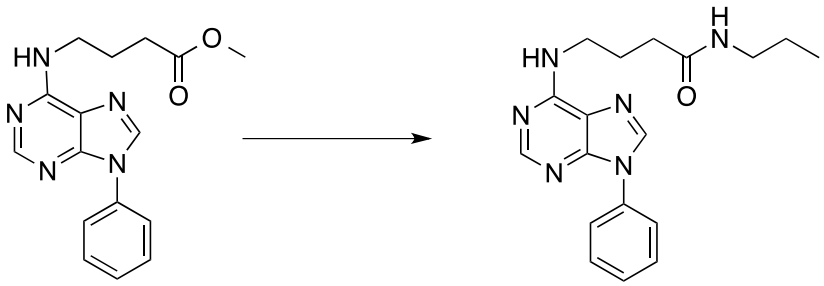
A solution of **19** (50 mg, 0.22 mmol), methyl 4-aminobutyrate (133 mg, 1.14 mmol), 5Å molecular sieves (250 mg) in dry MeOH (1 mL) was stirred at 70 °C in a pressure tube for three days. Volatiles were removed under reduced pressure and crude material was added directly to a Flash column chromatography and eluted with 5% MeOH/CH_2Cl_2 to give **25** (59 mg 0.19 mmol, 86%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.44 (s, 1H), 8.03 (s, 1H), 7.69 (d, J = 6.5 Hz, 2H), 7.56 (t, J = 7.8 Hz, 2H), 7.44 (t, J = 7.5Hz, 1H), 6.02 (bs, 1H), 3.75 (bs, 2H), 3.68 (s, 3H), 2.48 (t, J = 7.3 Hz, 2H), 2.07 (pent, J = 7.0 Hz, 2H), 1.90 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.7, 155.2, 153.8, 138.8, 134.9, 129.9, 128.1, 123.5, 51.7, 40.0, 31.4, 25.0; HRMS [M+H] = 312.1464; $C_{16}H_{18}N_5O_2$ = 312.1460.



25 **26**

N^6-(4-Butanoyl)-9-phenyladenine (26)

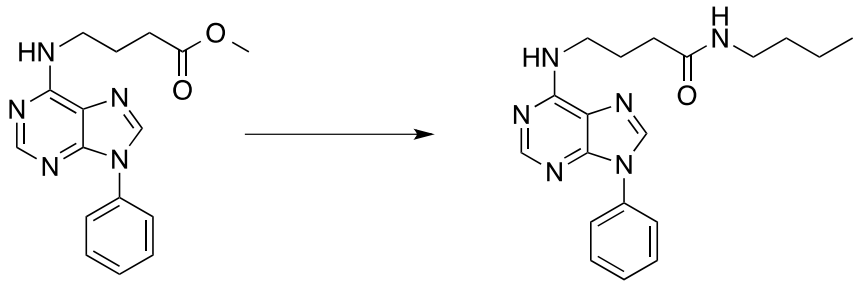
A solution of **25** (40 mg, 0.13 mmol) in 1N NaOH (480 µl) and dry MeOH (2 mL) was stirred for at ambient temperature for 4 hours. Volatiles were removed under reduce pressure. Crude material was re-dissolved in minimal amount of water and neutralize to pH 7 using carbon dioxide. Water was removed using a stream of air and crude was re-dissolved in 10% MeOH/CH_2Cl_2 and added to a Flash column chromatography and eluted with 10% MeOH/CH_2Cl_2 to give compound 26 (34 mg, 0.11 mmol 85%). HRMS [M+H] = 298.1324, $C_{15}H_{16}N_5O_2$ = 298.1304



25 **27a**

N^6-(N-Ethyl-4-butanamidyl)-9-phenyladenine (27a)

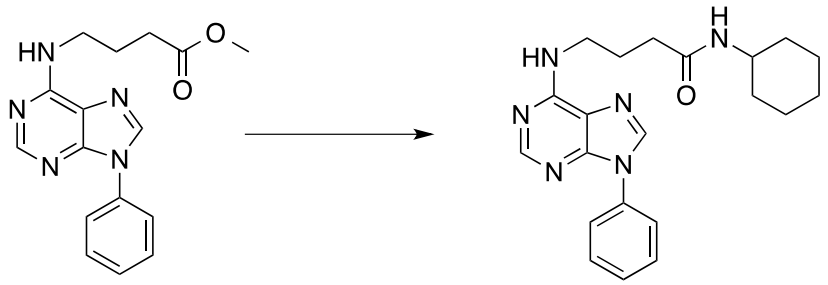
A solution of **25** (10 mg, 0.032 mmol), NaOMe (1.7 mg, 0.031mmol), p-nitrophenol (2.2 mg, 0.016 mmol), 3Å molecular sieves (100 mg) in dry toluene (1.0 mL) and propyl amine (1mL) was stirred at ambient temperature in a pressure tube for one day. The solution was then stirred in a pressure tube at 130 °C for one day. Volatiles were evaporated and crude material was re-dissolved in a minimal amount of CH_2CL_2 then added to Flash column chromatography and eluted with 5%-7.5% MeOH/CH_2Cl_2 to give **27a** (10 mg, 0.030 mmol 94%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.60 (s, 1H), 8.29 (bs, 1H), 7.97 (bs, 1H), 7.90 (d, J = 7.8 Hz, 2H), 7.82 (t, J = 7.5 Hz, 1H), 7.61 (t, J = 7.7 Hz, 2H), 7.47 (t, J = 1Hz, 1H), 3.52 (bs, 2H), 3.00 (q, J = 6.5 Hz, 2H), 2.16 (t, J = 7.5 Hz, 2H), 1.85 (pent, J = 7.1 Hz, 2H), 1.40 (sext, J = 7.2Hz, 2H), 0.84 (t, J = 7.4 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 172.1, 155.3, 153.6, 149.0, 139.9, 135.6, 130.0, 127.9, 123.4, 120.0, 33.5, 25.9, 22.9, 11.9; HRMS [M+H] = 339.1942, $C_{18}H_{23}N_6O$ = 339.1933.



25 27b

N^6-(N-Butyl-4-butanamidyl)-9-phenyladenine (27b)

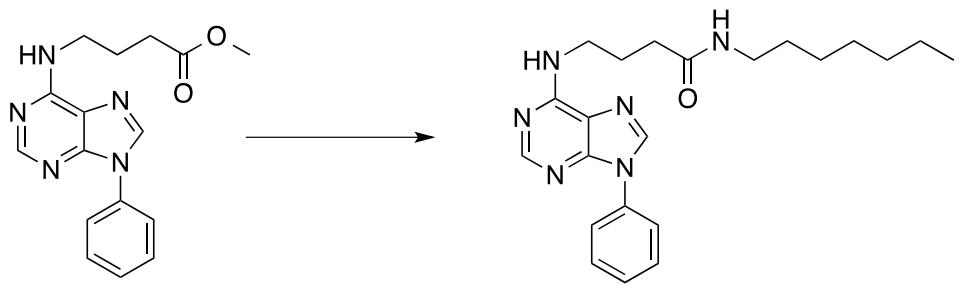
A solution of **25** (20 mg, 0.064 mmol), NaOMe (3.4 mg, 0.062 mmol) p-nitrophenol (4.4 mg, 0.032 mmol), 3Å molecular sieves (150 mg) in dry toluene (1.0 mL) and butyl amine (1.0 mL) was stirred at ambient temperature in a pressure tube for one day. The solution was then stirred in a pressure tube at 130 °C for one day. Volatiles were evaporated and crude material was re-dissolved in a minimal amount of CH_2CL_2 then added directly to Flash column chromatography and eluted with 5% MeOH/CH_2Cl_2 to give **27b** (12 mg, 0.034 mmol, 53%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.44 (bs, 1H), 8.06 (bs, 1H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.58 (t, *J* = 7.8 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 1H), 6.42 (bs, 1H), 6.24 (bs, 1H), 3.76 (bs, 2H), 3.29 (q, *J* = 6.7 Hz, 2H), 2.35 (t, *J* = 6.8 Hz, 2H), 2.06 (pent, *J* = 6.8 Hz, 2H), 1.51 (pent, *J* = 7.4 Hz, 2H), 1.37 (sext, *J* = 7.4 Hz, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.4, 155.4, 153.6, 138.9, 134.9, 129.9, 128.2, 123.5, 39.4, 33.8, 31.7, 29.7, 26.0, 20.2, 13.8. HRMS [M+H] = 353.2095, $C_{19}H_{25}N_6O$ = 253.2090.



25 27c

N^6-(N-Cyclohexyl-4-butanamidyl)-9-phenyladenine (27c)

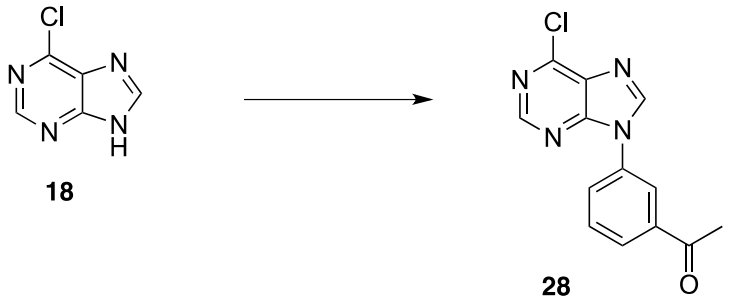
A solution of **25** (10 mg, 0.032 mmol), NaOMe (1.7 mg, 0.031 mmol) p-nitrophenol (2.2 mg, 0.016 mmol), 3Å molecular sieves (100 mg) in dry toluene (1.0 mL) and cyclohexyl amine (1.0 mL) was stirred at ambient temperature in a pressure tube for one day. The solution was then stirred in a pressure tube at 130 °C for 1day. Crude was added directly to Flash column chromatography and eluted with 5% MeOH/CH_2Cl_2 to give **27c** (8 mg, 0.021 mmol, 66%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.58 (s, 1H), 8.27 (s, 1H), 7.95 (bs, 1H), 7.88 (d, J = 7.5 Hz, 2H), 7.68 (d, J = 8.0 Hz, 2H), 7.58 (t, J = 8.0 Hz, 2H), 7.44 (t, J = 7.5 Hz, 1H), 3.51-3.47 (m, 3H), 2.11 (t, J = 6.5 Hz, 2H), 1.82 (t, J = 7.3 Hz, 2H), 1.71-1.63 (m, 4H), 1.58-1.50 (m, 1H), 1.24-1.13 (m, 2H), 1.10-1.08 (m, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 171.2, 155.3, 153.6, 148.8, 139.8, 135.6, 130.0, 127.9, 123.4, 120.13, 47.8, 33.5, 33.0, 26.0, 25.7, 25.1. HRMS [M+H] = 379.2224, $C_{21}H_{27}N_6O$ = 379.2246.



25 27d

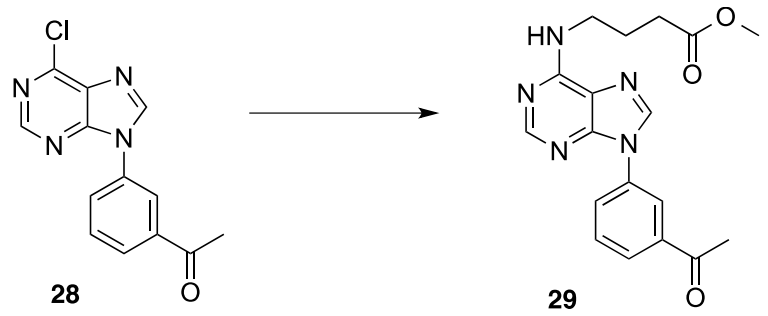
N^6-(N-Heptyl-4-butanamidyl)-9-phenyladenine (27d)

A solution of **25** (20 mg, 0.064 mmol), NaOMe (3.4 mg, 0.062mmol) p-nitrophenol (4.4 mg, 0.032 mmol), 3Å molecular sieves (150 mg) in dry toluene (1.0 mL) and heptylamine (1.0 mL) was stirred at ambient temperature in a pressure tube for one day. The solution was then stirred in a pressure tube at 130 °C for one day. Crude material was added directly to Flash chromatography column and eluted with 5% MeOH/CH_2Cl_2 to give **27d** (12 mg, 0.030 mmol, 48%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.43 (s, 1H), 8.06 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.57 (t, *J* = 7.8 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 1H), 6.44 (bs, 1H), 6.32 (bs, 1H), 3.75 (bs, 2H), 3.28 (q, *J* = 6.7 Hz, 2H), 2.33 (t, *J* = 6.5 Hz, 2H), 2.06 (pent, *J* = 6.5 Hz, 2H), 1.52 (sext, *J* = 7.0 Hz, 2H), 1.31-1.26 (m, 8H), 0.91 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.4, 155.4, 153.6, 138.9, 134.8, 129.9, 128.2, 123.5, 39.7, 33.8, 31.8, 29.7, 29.0, 27.0, 26.0, 22.6, 14.1; HRMS [M+H] = 395.2573, $C_{22}H_{31}N_6O$ = 395.2559.



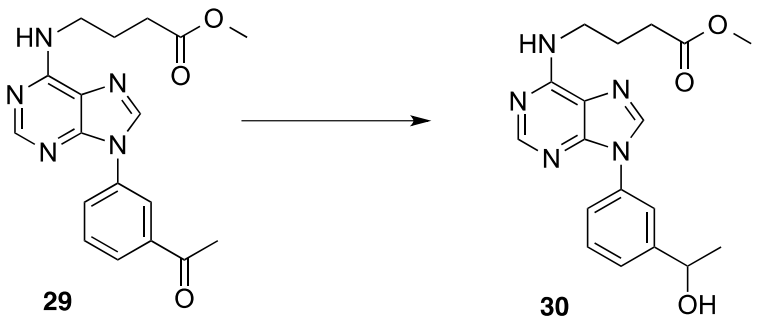
9-(3-Acetylphenyl)-6-chloropurine (28)

A solution of 6-chloropurine (100 mg, 0.65 mmol), m-acetylphenylboronic acid (240 mg, 1.46mmol), copper (II) acetate (120 mg, 0.66 mmol), 1,10-phenanthroline (232 mg, 1.30 mmol), 5Å molecular sieves (1.0 g) in CH_2Cl_2 (12 mL) was stirred at ambient temperature under reflux for four days. Crude product was then filtered through celite using MeOH as an eluent. Volatiles were removed under reduced pressure and the crude mixture was dissolved in a minimal amount of CH_2Cl_2 and added to a Flash chromatography column and eluted with 5% MeOH/CH_2Cl_2 to give **28** (129 mg, 0.47 mmol, 73%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.86 (s, 1H), 8.51 (s, 1H), 8.34 (s, 1H), 8.11 (d, J = 7.8 Hz, 1H), 8.03 (d, J = 8.1 Hz, 1H), 7.77 (t, J = 8.0 Hz, 1H), 2.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.5, 152.9, 152.0, 151.4, 143.7, 138.8, 134.6, 132.2, 130.6, 128.7, 127.7, 122.9, 26.8. HMRS [M+H] = 273.0518, $C_{13}H_9ClN_4O$ = 273.0543.



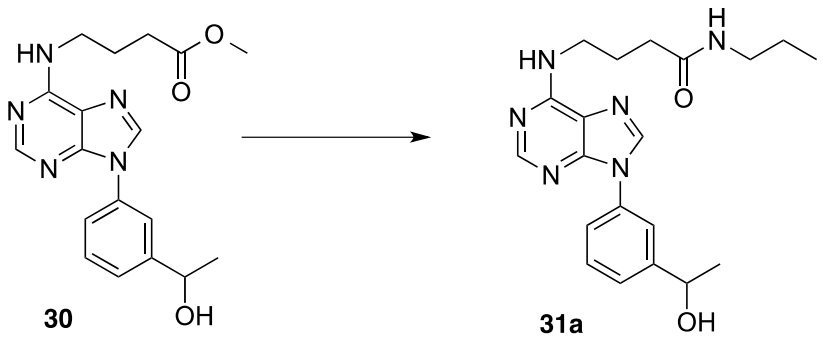
9-(3-Acetylphenyl)-N^6-(methyl 4-butanoyl)adenine (29)

A solution of **28** (50 mg, 0.18 mmol), methyl 4-aminobutyrate (133 mg, 1.14 mmol), 5Å molecular sieves (100 mg) in Et_3N (120 µl) and dry MeOH (1.0 mL) was stirred at 70 °C in a microwave for 3.5 hours. Volatiles were removed under reduced pressure and crude was added directly to a Flash chromatography column and eluted with 5% MeOH/CH_2Cl_2 to give **29** (55 mg, 0.16 mmol, 86%). ^{1}H NMR ($CDCl_3$: CD_3OD (2:1); 300 MHz) δ 8.34 (s, 1H), 8.28 (s, 1H), 8.22 (s, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.73 (t, *J* = 7.8 Hz, 1H), 4.50 (s, 2H), 3.69 (s, 3H), 3.34 (bs, 1H), 2.70 (s, 3H), 2.51 (t, *J* =7.5 Hz, 2H), 2.06 (pent, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$: CD_3OD (2:1); 125 MHz) δ 197.8, 174.2, 155.1, 153.6, 138.95, 138.90, 138.4, 135.0, 130.2, 130.1, 128.2, 123.3, 119.7, 51.6, 51.5, 39.8, 26.44, 26.39, 24.6. HRMS [M+H] = 354.1531, $C_{18}H_{20}N_5O_3$ = 354.1566.



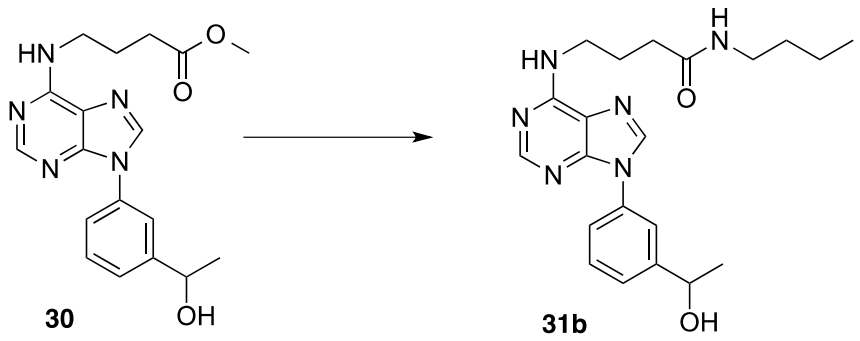
9-(3-(Ethanol-1-yl)phenyl)-N^6-(methyl 4-butanoyl)adenine (30)

A solution of **29** (86 mg, 0.24 mmol), $NaBH_4$ (45.4 mg, 1.2 mmol) in dry MeOH (4.0 mL) and dry CH_2Cl_2 (1.0 mL) was stirred at ambient temperature for 6 hours. The solution was quenched with water and MeOH and CH_2Cl_2 were removed under reduced pressure. The organic layer was extracted with CH_2Cl_2, which was later dried over sodium sulfate and filtered through filter paper. Crude product was added directly to a Flash chromatography column and eluted with 5% MeOH/CH_2Cl_2 to give **30** (68 mg, 0.19 mmol, 79%) ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.35 (bs, 1H), 8.01 (bs, 1H), 7.68 (s, 1H), 7.54 (d, *J*= 7.5 Hz, 1H), 7.48 (t, *J* = 8.3 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 6.37 (bs, 1H), 4.97 (q, *J* = 6.5 Hz, 1H), 3.95 (s, 1H), 3.70 (bs, 2H), 3.66 (s, 3H), 2.46 (t, *J* = 7.3 Hz, 2H), 2.04 (pent, *J* = 7.0 Hz, 2H), 1.52 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ173.7, 155.2, 153.7, 148.4, 138.9, 134.9, 129.8, 125.2, 122.4, 120.7, 69.5, 51.7, 40.0, 31.4, 25.3, 24.9; HRMS [M+H] = 356.1713, $C_{18}H_{22}N_5O_3$ = 356.1723.



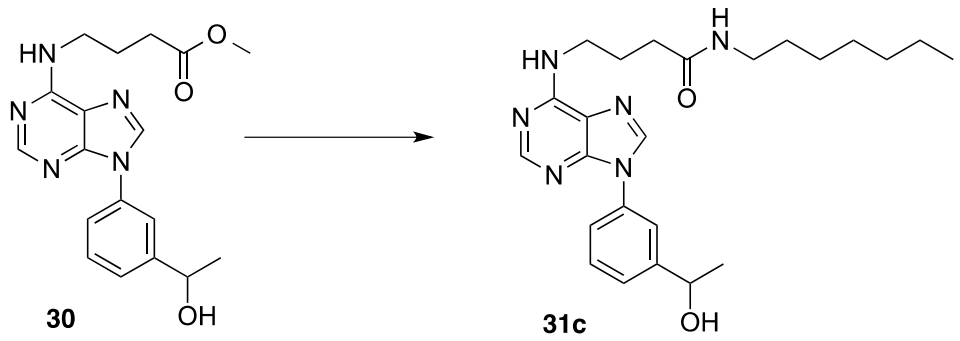
9-(3-(1-Ethanol-1-yl)phenyl)-N^6-(N-propyl-4-butanamidyl)adenine (31a)

A solution of **30** (20 mg, 0.056 mmol), NaOMe (3.4 mg, 0.062 mmol) p-nitrophenol (4.4 mg, 0.032 mmol), 3Å molecular sieves (150 mg) in dry toluene (1.0 mL) and propylamine (1.0 mL) was stirred at ambient temperature in a pressure tube for one day. The solution was then stirred in a pressure tube at 130 °C for one day. Crude product was added directly to a Flash chromatography column and eluted with 5%-7.5% MeOH/CH_2Cl_2 to give **31a** (15 mg, 0.039 mmol, 70%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.37 (bs, 1H), 8.02 (bs, 1H), 7.72 (bs, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 6.49 (bs, 1H), 6.44 (bs, 1H), 5.01 (q, *J* = 6.5 Hz, 1H), 3.73 (bs, 2H), 3.23 (q, *J* = 6.7 Hz, 2H), 2.32 (t, *J* = 6.8 Hz, 2H), 1.56-1.50 (m, 5H), 0.93 (t, *J* = 7.3 Hz, 3H), 2.0 (pent, *J* = 6.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.5, 155.3, 153.6, 148.3, 138.9, 134.9, 129.9, 125.3, 122.4, 120.6, 69.7, 41.4, 33.8, 29.7, 26.0, 25.4, 22.9, 11.5. HMRS [M+H] = 383. 2194, $C_{20}H_{27}N_6O_2$ = 383.2195.



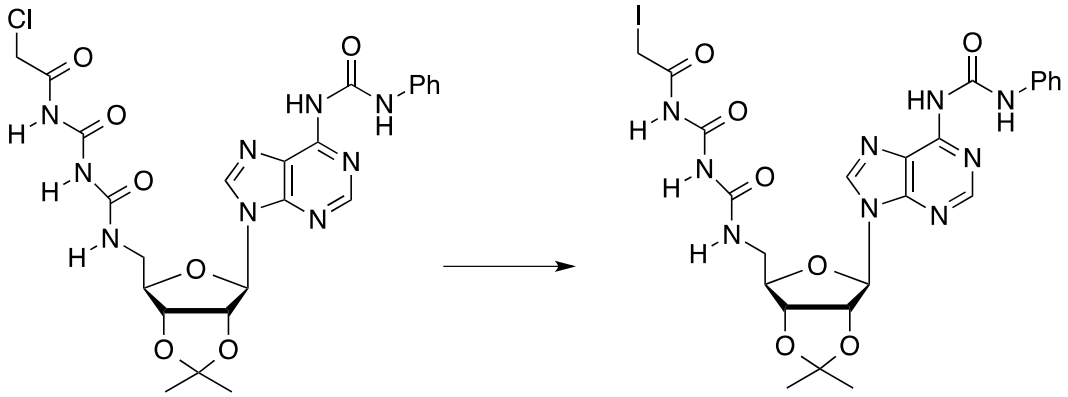
N^6-(N-Butyl-4-butanamidyl)-9-(3-(ethanol-1-yl)phenyl)adenine (31b)

A solution of **30** (20 mg, 0.056 mmol), NaOMe (3.4 mg, 0.062 mmol) p-nitrophenol (4.4 mg, 0.032 mmol), 3Å molecular sieves (150 mg) in dry toluene (1.0 mL) and butylamine (1.0 mL) was stirred at ambient temperature in a pressure tube for one day. The solution was then stirred in a pressure tube at 130 °C for one day. Crude product was added directly to a Flash chromatography column and eluted with 5%-7.5% MeOH/CH_2Cl_2 to give **31b** (22 mg, 0.055 mmol, 98%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.35 (bs, 1H), 8.04 (bs, 1H), 7.71 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 6.51 (bs, 2H), 5.0 (q, *J* = 6.3 Hz, 1H), 3.71 (bs, 2H), 3.26 (q, *J* = 6.7 Hz, 2H), 2.30 (t, *J* = 6.8 Hz, 2H), 2.03 (t, *J* = 6.5 Hz, 2H), 1.54 (d, *J* = 6.5 Hz, 3H), 1.51-1.46 (m, 2H), 1.38-1.30 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.5, 155.3, 153.6, 148.4, 139.0, 134.9, 129.9, 125.3, 122.4, 120.6, 69.6, 39.4, 33.8, 31.7, 26.0, 25.4, 20.2, 13.8; HMRS [M+H] = 397.2335, $C_{21}H_{29}N_6O_2$ = 397.2352.



9-(3-(Ethanol-1-yl)phenyl)-N^6-(N-heptyl-4-butanamidyl)adenine (31c)

A solution of **30** (20 mg, 0.056 mmol), NaOMe (3.4 mg, 0.062 mmol) p-nitrophenol (4.4 mg, 0.032 mmol), 3Å molecular sieves (150 mg) in dry toluene (1.0 mL) and heptylamine (1.0 mL) was stirred at ambient temperature in a pressure tube for one day. The solution was then stirred in a pressure tube at 130 °C for one day. Crude product was added directly to Flash column chromatography and eluted with 5%-7.5% MeOH/CH_2Cl_2 to give **31c** (19 mg, 0.043 mmol, 77%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.35 (bs, 1H), 8.04 (bs, 1H), 7.71 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.51(t, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 6.52 (bs, 1H), 5.00 (q, *J* = 6.3 Hz, 1H), 3.71(bs, 2H), 3.25 (q, *J* = 6.7 Hz, 2H), 2.30 (t, *J* = 7.0 Hz, 2H), 2.02 (pent, *J* = 6.8 Hz, 2H), 1.54 (d, *J* = 6.5 Hz, 3H), 1.52-1.47 (m, 2H), 1.29-1.25 (m, 8H), 0.86 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.5, 155.3, 153.6, 148.4, 139.0, 134.9, 129.9, 125.3, 122.4, 120.6, 69.6, 39.7, 33.8, 31.7, 29.6, 29.0, 27.0, 26.0, 25.4, 22.6, 14.1; HRMS [M+H]= 439.2798, $C_{24}H_{35}N_6O_2$ = 439.2821.



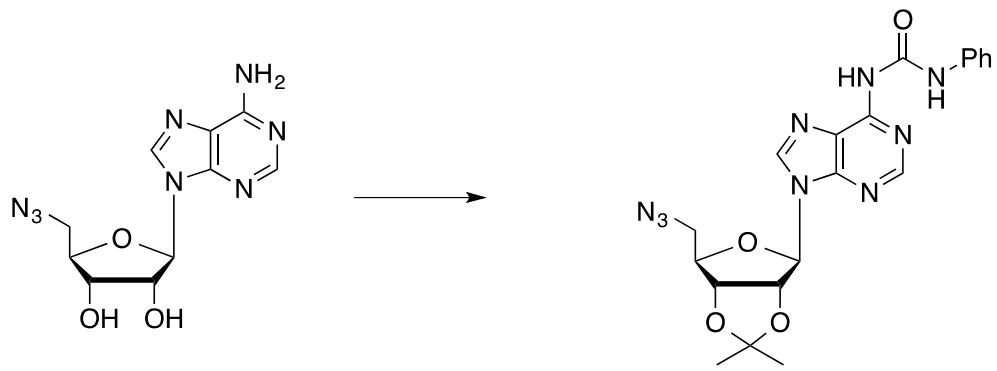
5'-N-[(Iodoacetyl)aminocarbonyl)aminocarbonyl]amino-5'-deoxy-2',3'-bis-*O*-isopropylidene-N^6-(N-phenylureido)adenosine (32)

A solution of **37** (9.5 mg, 0.016 mmol), sodium iodide (9.74 mg, 0.065 mmol) in acetone (4.0 mL) was stirred at 50 °C for 2 hrs. Volatiles were removed under reduced pressure and crude product was added straight to a Flash column chromatography and eluted with 5% MeOH/CH_2Cl_2 to give product **32** (10 mg, 0.015 mmol) in 94% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.12 (bs, 1H), 12.07 (bs, 1H), 10.30 (bs, 1H), 9.83 (bs, 1H), 8.53 (s, 1H), 8.41 (d, *J* = 7.5 Hz, 1H), 7.66 (s, 1H), 7.34 (d, *J* = 7.8 Hz, 2H), 7.08 (t, *J* = 7.8 Hz, 2H), 6.97 (t, *J* = 7.2 Hz, 1H), 6.03 (d, *J* = 3.0 Hz, 1H), 5.84 (dd, *J* = 6.5, 1.7 Hz, 1H), 5.35 (t, *J* = 6.3 Hz, 1H), 4.42 (dd, *J* = 14.6, 10.1 Hz, 1H), 4.34 (d, *J* = 5.1 Hz, 1H), 3.97 (d, *J* = 9.6 Hz, 1H), 3.88 (d, *J* = 9.6 Hz, 1H), 3.53 (d, *J* = 9.6 Hz, 1H), 1.66 (s, 3H), 1.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.7, 153.6, 153.2, 153.1, 150.24, 150.19, 149.7, 143.0, 137.0, 128.6, 124.0, 121.5, 120.7, 115.0, 89.9, 85.9, 82.9, 79.7, 39.9, 27.6, 25.6, -3.2; HRMS [M+H] = 680.1044, $C_{24}H_{27}N_9IO_7$ = 680.1078.

40 33

N-[(Iodoacetyl)aminocarbonyl)aminocarbonyl]benzylamine (33)

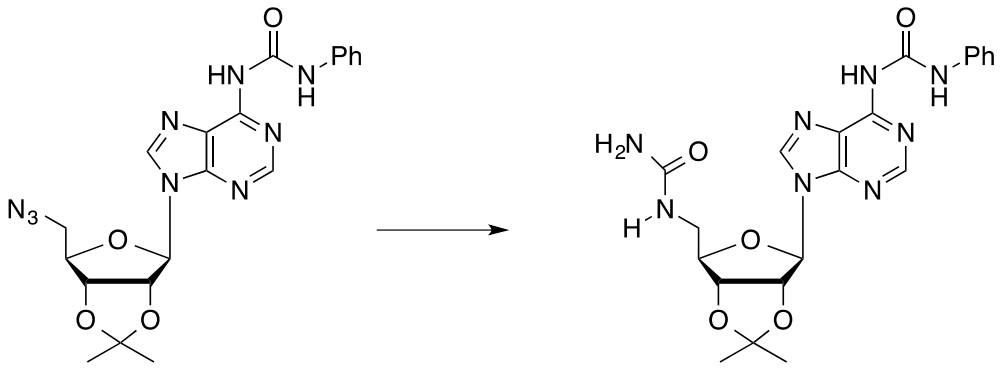
A solution of compound **40** (44 mg, 0.16 mmol), sodium iodide (96 mg, 0.64 mmol) in acetone (4.0 mL) was stirred at 50 °C for 1.5 hrs. Volatiles were evaporated and crude was added directly to a Flash column chromatography and eluted with 5% MeOH/CH_2Cl_2 to give **33** (50 mg, 0.14 mmol, 88%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.20 (s, 1H), 10.02 (s, 1H), 8.36 (bs, 1H), 7.35-7.26 (m, 5H), 4.39 (d, J = 6.0 Hz, 2H), 3.90 (s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 172.0, 152.6, 152.0, 139.5, 128.9, 127.7, 127.4, 43.3, 0.01; HRMS [M+H] = 361.9984, $C_{11}H_{13}IN_3O_3$ = 362.0002.



34 **35**

5'-Azido-5'-deoxy-2',3'-bis-*O*-isopropylidene-N^6-(N-phenylureido)adenosine (35)

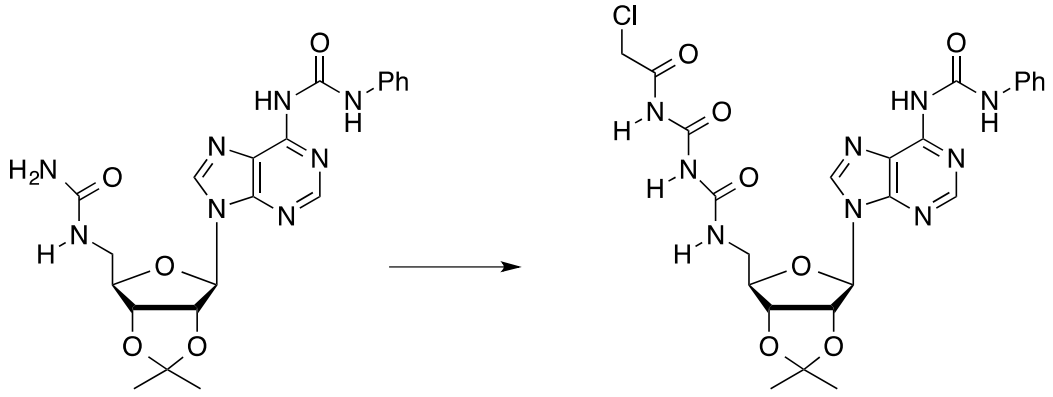
A solution of **34** (100 mg, 0.34 mmol), perchloric acid (100 µl) in acetone (100 mL) was stirred for 3 hours at room temperature. Sodium carbonate was then added (250 mg) and the solution was stirred for 30 minutes. Crude product was filtered and volatiles were removed under reduced pressure. Benzene was used to remove excess water. Crude material was stirred with 0.1M of phenylisocyante in CH_2Cl_2 (7.2 mL) for 3 days at room temperature. Volatiles were removed under reduced pressure and crude product was added directly to a Flash column chromatography and eluted with 60% Ethyl Acetate/Hexane mixture to give **35** (70 mg, 0.016 mmol) in 47% yield.



35 **36**

5'-N-(Carbamoyl)amino-5'-deoxy-2',3'-bis-*O*-isopropylidene-N^6-(N-phenylureido)adenosine (36)

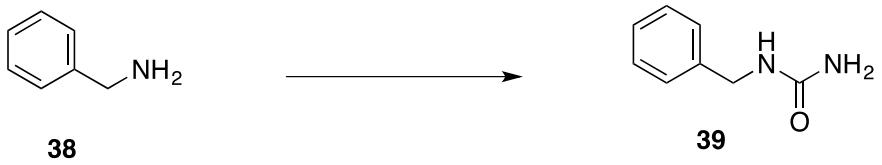
A solution of compound **35** (35 mg, 0.078 mmol), palladium on carbon (25 mg) in Ethyl Acetate (7.0 mL) was stirred for 24 hours. Crude product was filtered through celite using MeOH as an eluent. Volatiles were removed under reduced pressure. Crude material and 0.05M of carbonyldiimdazole in CH_2Cl_2 (6.0 mL) were stirred at ambient temperature overnight. Then, MeOH/NH_3 (1.5 mL) was added and stirred at ambient temperature for 24 hours. Volatiles were removed under reduced pressure and crude material was added directly to a Flash column chromatography and eluted with 2.5%-7.5% MeOH/CH_2Cl_2 to give **36** (16 mg, 0.035 mmol) in a 45% yield. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.75 (s, 1H), 10.22 (s, 1H), 8.71 (s, 1H), 8.65 (s, 1H), 7.62 (d, J = 7.5 Hz, 2H), 7.36 (t, J = 8.0 Hz, 2H), 7.08 (t, J = 7.5 Hz, 1H), 6.24 (d, J = 2.5 Hz, 1H), 6.14 (t, J = 6.0 Hz, 1H), 5.51 (bs, 2H), 5.48 (dd, J = 6.5, 2.5 Hz, 1H), 4.96 (dd, J = 6.5, 3.0 Hz, 1H), 4.16 (td, J = 6.3, 3.2 Hz, 1H), 3.30-3.25 (m, 1H), 3.18-3.14 (m, 1H), 1.54 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 159.0, 151.5, 151.3, 150.6, 150.5, 143.1, 138.9, 129.4, 123.7, 121.1, 119.9, 113.9, 89.7, 85.9, 83.7, 83.6, 82.15, 82.07, 41.7, 27.4, 25.7; HRMS [M+H]= 469.1968, $C_{21}H_{25}N_8O_5$ = 469.1948.



36 **37**

5'-N-[(Chloroacetyl)aminocarbonyl)aminocarbonyl]amino-5'-deoxy-2',3'-bis-*O*-isopropylidene-N^6-(N-phenylureido)adenosine (37)

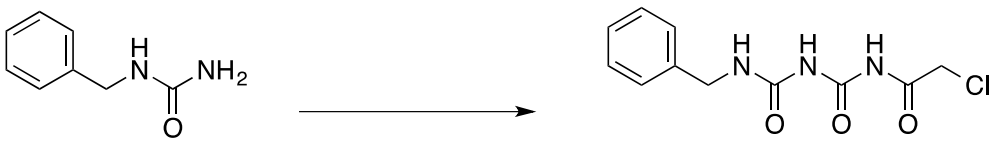
A solution of **36** (21 mg, 0.045 mmol) in 0.1M chloroacetylisocyanate in CH_2Cl_2 (1.5 mL) was stirred at ambient temperature for three days Volatiles were removed and crude material was added directly to a Flash column chromatography and eluted with 2%-3% MeOH/CH_2Cl_2 to give **37** (9.5 mg, 0.16 mmol) in 36% yield. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.8 (s, 1H), 11.1 (s, 1H), 10.2 (s, 1H), 9.80 (s, 1H), 8.68 (s, 1H), 8.64 (s, 1H), 7.90 (bs, 1H), 7.62 (d, J = 7.5 Hz, 2H), 7.35 (t, J = 7.3 Hz, 2H), 7.08 (t, J = 7.3 Hz, 1H), 6.28 (d, J = 2.5 Hz, 1H), 5.50 (dd, J = 6.3, 2.3 Hz, 1H), 5.05 (dd, J = 6.3, 3.8 Hz, 1H), 4.41 (s, 2H), 4.29-4.28 (m, 1H), 3.46 (t, J = 6.0 Hz, 2H), 1.54 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 169.1, 168.3, 152.9, 151.5, 151.4, 150.6, 143.2, 138.9, 129.4, 123.7, 121.0, 119.9, 114.0, 89.33, 89.22, 85.08, 83.8, 83.7, 81.8, 44.1, 43.1, 41.4, 27.5, 25.8; HRMS [M+H] = 588.1740, $C_{24}H_{27}ClN_9O_7$ = 588.1722.



38 39

N-Carbamylbenzylamine (39)

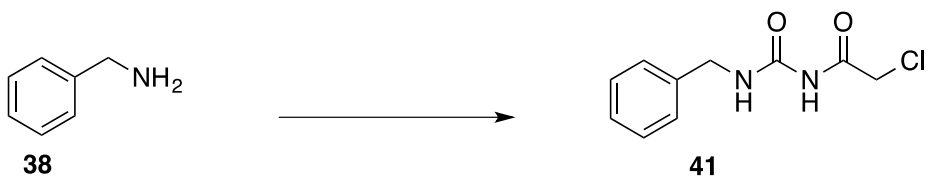
A solution of benzylamine (200 µl, 1.8 mmol) and 2.0 mmol of N,N'-carbonyldiimidazole (324 mg, 2.0 mmol) in CH_2Cl_2 (80 mL) was stirred at ambient temperature for one day. NH_3/MeOH (4.0 mL) was added to the reaction mixture and let it stir for one day. Volatiles were evaporated and crude material was added to a Flash column chromatography and eluted with 2.5%-7.5% MeOH/CH_2Cl_2 to give **39** (190 mg, 1.3 mmol, 72%). ^{1}H NMR (CD_3OD, 500 MHz) δ 7.33-7.22 (m, 5H), 4.30 (s, 2H); ^{13}C NMR (CD_3OD, 125 MHz) δ 160.7, 139.7, 128.1, 126.8, 126.6, 43.3; HRMS [M+H] = 151.0871, $C_8H_{11}N_2O$ = 151.0871.



39 **40**

N-[(Chloroacetyl)aminocarbonyl)aminocarbonyl]benzylamine (40)

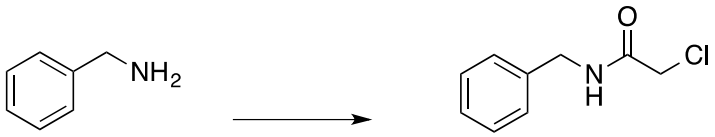
A solution of **39** (37 mg, 0.25 mmol), chloroacetylisocyanate (69 μl, 0.81 mmol) in CH_2Cl_2 (8.0 mL) was stirred at ambient temperature for three days. Volatiles were evaporated and the crude mixture was added directly to a Flash column chromatography and eluted with 4% MeOH/CH_2Cl_2 to give **40** (44 mg, 0.16 mmol, 64%). ^{1}H NMR (CD_3OD, 500 MHz) δ 7.34-7.33 (m, 5H), 4.47 (s, 2H, major conformer), 4.26 (s, 2H, major conformer); ^{13}C NMR (CD_3OD, 125 MHz) δ 168.3, 156.7, 155.3, 138.7, 128.2, 126.91, 126.89, 42.81, 40.04; HRMS [M+H] = 270.0634, $C_{11}H_{13}ClN_3O_3$ = 270.0645.



38 41

N-(Chloroacetyl)aminocarbonyl)benzylamine (41)

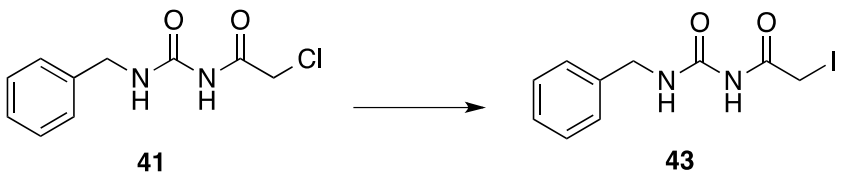
A solution of benzylamine (26 µl, 0.24 mmol), chloroacetylisocyanate (0.47 mmol) in CH_2Cl_2 (4.7 mL) was stirred at ambient temperature for three days. Volatiles were removed and crude was added straight to a Flash chromatography column and eluted with 5% MeOH/CH_2Cl_2 to give **41** (37 mg, 0.16 mmol, 67%) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.99 (bs, 1H), 8.55 (bs, 1H), 7.41-.29 (m, 5H), 4.55 (d, *J* = 5.7 Hz, 2H), 4.13 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.5, 152.5, 137.6, 128.8, 127.7, 127.6, 43.9, 42.4. HRMS [M+H] = 227.0584, $C_{10}H_{12}ClN_2O_2$ = 227.0587.



38 **42**

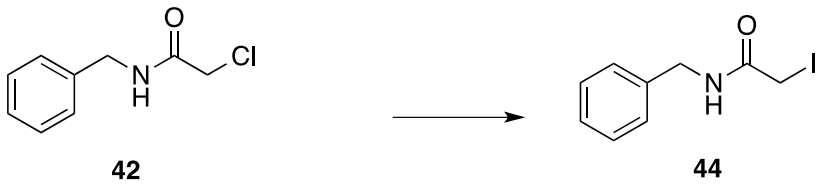
N-(Chloroacetyl)benzylamine (42)

A solution of benzylamine (100 µl, 0.92 mmol), chloroacetic acid (71 mg, 0.75 mmol), EDCI (173 mg 0.90 mmol), HOBT (101 mg, 0.75 mmol) in CH_2Cl_2 was stirred at ambient temperature under Argon for one day. Volatiles were removed and crude product was added directly to a Flash chromatography column and eluted with 40% EtOAc/Hex to **42** (100 mg, 0.55 mmol, 72%) ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.75 (bs, 1H), 7.37-7.24 (m, 5H), 4.32 (d, J = 6.0 Hz, 2H), 4.14 (s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 166.5, 139.3, 128.8, 127.8, 127.4, 43.1, 42.9; HRMS [M+H] = 184.0522, $C_9H_{10}ClNO$ = 184.0529.



N-(Iodoacetyl)aminocarbonyl)benzylamine (43)

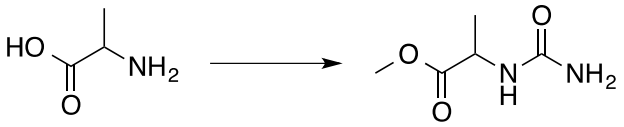
A solution of **41** (30 mg, 0.13 mmol), sodium iodide (80 mg, 0.53 mmol) in acetone (4.0 mL) was stirred at 50 °C for 2hrs. Volatiles were evaporated and crude product was added directly to a Flash column chromatography and eluted with 5% MeOH/CH_2Cl_2 to give **43** (26 mg, 0.08 mmol, 62%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.66 (bs, 1H), 8.59 (bs, 1H), 7.37-7.24 (m, 5H), 4.38 (d, J = 6.0 Hz, 2H), 3.82 (s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 171.0, 153.5, 139.6, 128.9, 128.8, 127.7, 127.4, 43.1, 0.36; HRMS [M+H] = 318.9930; $C_{10}H_{11}IN_2O_2$ = 318.9943.



42 **44**

N-(Iodacetyl)benzylamine (44)

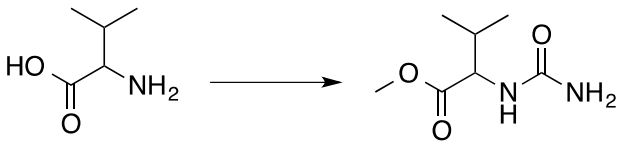
A solution of **42** (50 mg, 0.27 mmol), sodium iodide (162 mg, 1.1 mmol) in acetone (6.0 mL) was stirred at 50 °C for 2 hrs. Volatiles were evaporated and crude product was added directly to a Flash chromatography column and eluted with 5% MeOH/ CH_2Cl_2 to give **44** (68 mg, 0.25 mmol, 93%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.75 (s, 1H), 7.37-7.26 (m, 5H), 4.29 (d, J = 6.0 Hz, 2H), 3.71 (s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 168.2, 139.5, 128.8, 127.7, 127.4, 42.9, 1.15; HRMS [M+H] = 275.9876; $C_9H_{11}INO$ = 275.9885.



45a **46a**

Methyl N-Carbamylalaninate (46a)

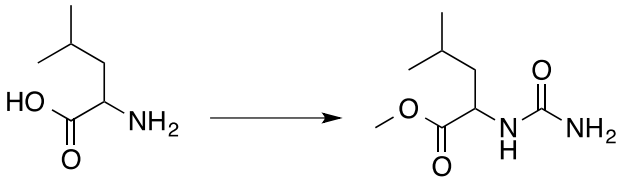
A solution of alanine (120 mg, 1.3 mmol) in thionyl chloride (400 µl) and dry MeOH (4.0 mL) was stirred at ambient temperature overnight. Volatiles were removed under reduced pressure. A solution of the crude material, diisopropylethylamine (400 µl, 2.30 mmol), carbonyldiimadazole (400 mg, 2.47 mmol) in CH_2Cl_2 (4.0 mL) was stirred at ambient temperature for 24 hours. Then, MeOH/NH_3 (4.0 mL) was added and the mixture was stirred at ambient temperature for 24 hours. Volatiles were removed under reduced pressure and crude product was added directly to a Flash chromatography column and eluted with 2.5% MeOH/CH_2Cl_2 to give compound **46a** (42 mg, 0.29 mmol, 22%) ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.21 (d, *J* = 7.5 Hz, 1H), 5.23 (bs, 2H), 4.41 (pent, *J* = 7.3 Hz, 1H), 3.72 (s, 3H), 1.36 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.2, 159.0, 52.4, 48.7, 18.5; HRMS [M+H] = 147.0770; $C_5H_{11}N_2O_3$ = 147.0770.



45b **46b**

Methyl N-Carbamylvalinate (46b)

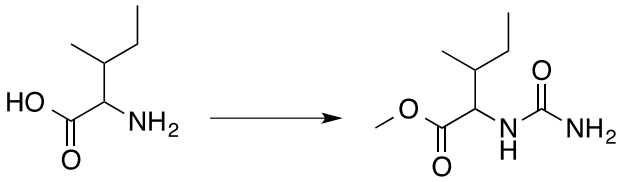
A solution of valine (30 mg, 0.26 mmol) in thionyl chloride (100 µl) and dry MeOH (1.0 mL) was stirred at ambient temperature overnight. Volatiles were removed under reduced pressure. A solution of the crude material, diisopropylethylamine (100 µl, 0.57 mmol), carbonyldiimadazole (100 mg, 0.62 mmol) in CH_2Cl_2 (1.0 mL) was stirred at ambient temperature for 24 hours. MeOH/NH_3 (1.0 mL) was added and stirred at ambient temperature for 24 hours. Volatiles were removed under reduced pressure and crude material was added directly to a Flash chromatography column and eluted with 2.5% MeOH/CH_2Cl_2 to give compound **46b** (22 mg, 0.13 mmol, 50%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.06 (d, *J* = 10.0 Hz, 1H), 5.02 (bs, 2H), 4.26 (dd, *J* = 8.8, 4.8 Hz, 1H), 3.72 (s, 3H), 2.12 (oct, *J* = 7.0 Hz, 1H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.3, 159.0, 58.0, 52.1, 31.3, 19.0, 17.7; HRMS [M+H] = 175.1090; $C_7H_{15}N_2O_3$ = 175.1083.



45c **46c**

Methyl N-Carbamylleucinate (46c)

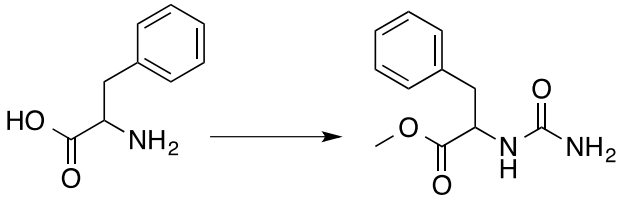
A solution of leucine (120 mg, 0.92 mmol) in thionyl chloride (400 µl) and dry MeOH (4.0 mL) was stirred at ambient temperature overnight. Volatiles were removed under reduced pressure. A solution of the crude material, diisopropylethylamine (400 µl, 2.30 mmol), carbonyldiimadazole (400 mg, 2.47 mmol) in CH_2Cl_2 (4.0 mL) was stirred at ambient temperature for 24 hours. Then, MeOH/NH_3 (4.0 mL) was added and the mixture was stirred at ambient temperature for 24 hours. Volatiles were removed under reduced pressure and crude was added directly to a Flash chromatography column and eluted with 2.5% MeOH/CH_2Cl_2 to give compound **46c** (44 mg, 0.23 mmol, 25%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.86 (d, J = 8.4 Hz, 1H), 4.96 (bs, 2H), 4.48 (ddd, J = 14.1, 8.7, 5.4 Hz, 1H), 3.75 (s, 3H), 1.76-1.49 (m, 3H), 0.96 (d, J = 2.4 Hz, 3H), 0.95 (d, J = 2.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.4, 158.7, 52.3, 51.6, 41.8, 24.8, 22.9, 21.9; HRMS [M+H] = 189.1236; $C_8H_{17}N_2O_3$ = 189.1239.



45d **46d**

Methyl N-Carbamylisoleucinate (46d)

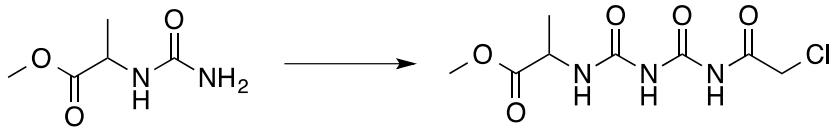
A solution of isoleucine (30 mg, 0.23 mmol) in thionyl chloride (100 µl) and dry MeOH (1.0 mL) was stirred at ambient temperature overnight. Volatiles were removed under reduced pressure. A solution of the crude material, diisopropylethylamine (100 µl, 0.57 mmol), carbonyldiimadazole (100 mg, 0.62 mmol) in CH_2Cl_2 (1.0 mL) was stirred at ambient temperature for 24 hours. MeOH/NH_3 (1.0 mL) was added and the mixture was stirred at ambient temperature for 24 hours. Volatiles were removed under reduced pressure and crude product was added directly to a Flash chromatography column and eluted with 2.5% MeOH/CH_2Cl_2 to give compound **46d** (19 mg, 0.10 mmol, 43%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.92 (d, *J* = 8.5 Hz, 1H), 4.93 (bs, 2H), 4.44 (dd, *J* = 7.5, 5.0 Hz, 1H), 3.72 (s, 3H), 1.88-1.84 (m, 1H), 1.43-1.39 (m, 1H), 1.19-1.15 (m, 1H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.3, 158.7, 57.4, 52.1, 38.1, 25.0, 15.5, 11.6; HRMS [M+H] = 189.1242; $C_8H_{17}N_2O_3$ = 189.1239.



45e **46e**

Methyl N-Carbamylphenylalaninate (46e)

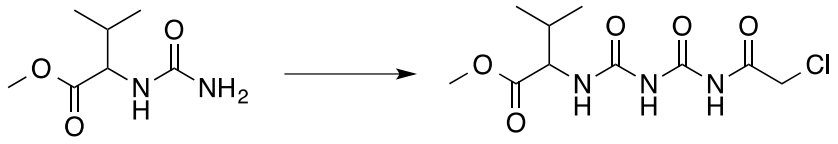
A solution of phenylalanine (120 mg, 0.73 mmol) in thionyl chloride (400 µl) and dry MeOH (4.0 mL) was stirred at ambient temperature overnight. Volatiles were removed under reduced pressure. A solution of the crude material, diisopropylethylamine (250 ul, 1.43 mmol), carbonyldiimadazole (236 mg, 1.45 mmol) in CH_2Cl_2 (4.0 mL) was stirred at ambient temperature for 24 hours. MeOH/NH_3 (2.0 mL) was added and the mixture was stirred at ambient temperature for 24 hours. Volatiles were removed under reduced pressure and crude product was added directly to a Flash chromatography column and eluted with 2.5% MeOH/CH_2Cl_2 to give compound **46e** (44 mg, 0.20 mmol, 27%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (t, *J* = 7.3 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1 H), 7.12 (d, *J* = 7.5 Hz, 2H), 6.11 (d, *J* = 8.5 Hz, 1H), 4.98 (s, 2H), 4.72-4.68 (m, 1H), 3.67 (s, 3H), 3.67 (s, 3H), 3.05 (dd, *J* = 14.0, 5.5 Hz, 1H), 2.96 (dd, *J* = 13.5, 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.8, 173.8, 158.7, 158.0 (minor), 136.4, 135.5, 129.3, 128.8, 128.5, 126.9, 59.9 (minor), 54.1, 52.3, 38.5, 37.7 (minor); HRMS [M+H] = 223.1104, $C_{11}H_{15}N_2O_3$ = 223.1083



46a **47a**

Methyl N-[(Chloroacetyl)aminocarbonyl)aminocarbonyl]alaninate (47a)

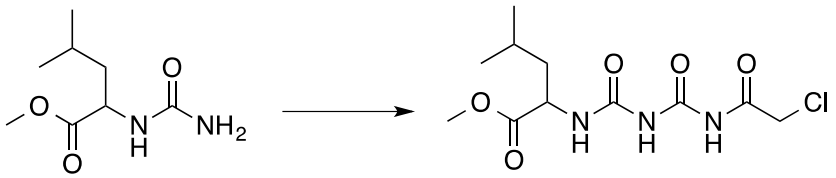
A solution of **46a** (42 mg, 0.29 mmol) in 0.1M chloroacetylisocyanate in CH_2Cl_2 (4.5 mL) was stirred at ambient temperature for 3 days. Volatiles were removed and the crude mixture was added directly to a Flash chromatography column and eluted with 2%-3% MeOH/CH_2Cl_2 to give **47a** (49 mg, 0.18 mmol) in 64% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.10 (bs, 1H), 8.84 (bs, 1H), 8.41 (bs, 1H), 4.59 (pent, J = 7.2 Hz, 1H), 4.22 (s, 2H), 3.80 (s, 3H), 1.52 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.0, 167.4, 151.3, 151.0, 52.6, 48.9, 42.4, 18.3; HRMS [M+H] = 266.0587; $C_8H_{13}ClN_3O_5$ = 266.0574.



46b **47b**

Methyl N-[(Chloroacetyl)aminocarbonyl)aminocarbonyl]valinate (47b)

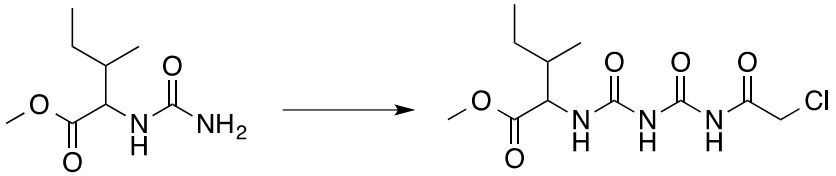
A solution of **46b** (22 mg, 0.13 mmol) in 0.1M chloroacetylisocyanate in CH_2Cl_2 (3.0 mL) was stirred at ambient temperature for three days. Volatiles were removed and crude product was added directly to a Flash chromatography column and eluted with 2%-3% MeOH/CH_2Cl_2 to give **47b** (26 mg, 0.09 mmol) in a 70% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.1 (bs, 1H), 8.98 (bs, 1H), 8.43 (bs, 1H), 4.49 (dd, *J* = 8.3, 4.8 Hz, 1H), 4.21 (d, *J* = 16.5 Hz, 1H), 4.18 (d, *J* = 16.5 Hz, 1H), 3.76 (s, 3H), 2.28-2.24 (m, 1H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.0, 167.5, 151.9, 151.3, 58.3, 52.3, 42.4, 30.9, 19.1, 17.7; HRMS [M+H]= 294.0890; $C_{10}H_{17}ClN_3O_5$ = 294.0857.



46c **47c**

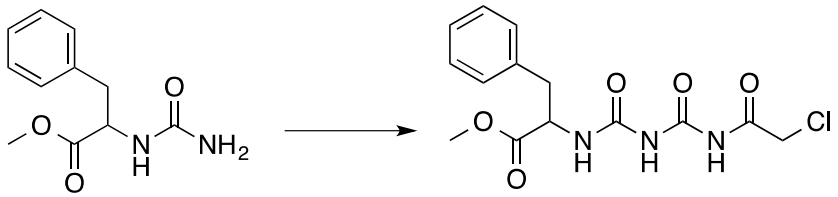
Methyl N-[(Chloroacetyl)aminocarbonyl)aminocarbonyl]leucinate (47c)

A solution of **46c** (44 mg, 0.23 mmol) in 0.1M chloroacetylisocyanate in CH_2Cl_2 (3.6 mL) was stirred at ambient temperature for 3 days. Volatiles were removed and the crude product was added directly to a Flash chromatography column and eluted with 2%-3% MeOH/CH_2Cl_2 to give **47c** (46 mg, 0.15 mmol) in 65% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.11 (bs, 1H), 8.93 (bs, 1H), 8.28 (bs, 1H), 4.60-4.57 (m, 1H), 4.21 (s, 2H), 3.78 (s, 3H), 1.76-1.66 (m, 3H), 0.98 (d, *J* = 5.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 173.1, 167.5, 151.7, 151.2, 52.5, 51.7, 42.4, 41.1, 24.9, 22.9, 21.8; HRMS [M+H] = 308.1018; $C_{11}H_{19}ClN_3O_5$ = 308.1013.



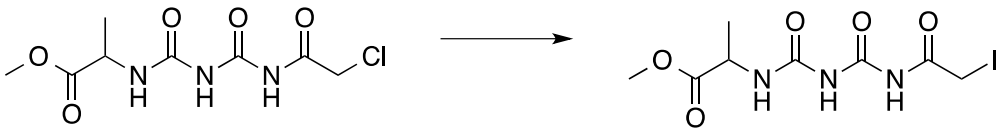
Methyl N-[(Chloroacetyl)aminocarbonyl)aminocarbonyl]isoleucinate (47d)

A solution of **46d** (17 mg, 0.09 mmol) in 0.05M chloroacetylisocyanate in CH_2Cl_2 (3.5 mL) was stirred at ambient temperature for 3 days. Volatiles were removed and crude was added straight to a Flash chromatography column and eluted with 2%-3% MeOH/CH_2Cl_2 to give **47d** (22 mg, 0.07 mmol) in 78% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.11 (bs, 1H), 8.96 (bs, 1H), 8.44 (bs, 1H), 4.55 (dd, *J* = 8.4, 4.8 Hz, 1H), 4.22 (s, 2H), 3.78 (s, 3H), 2.04-1.99 (m, 1H), 1.54-1.45 (m, 1H), 1.29-1.24 (m, 1H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.961 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.0, 167.4, 151.8, 151.3, 57.6, 52.3, 42.4, 37.6, 25.1, 15.7, 11.6; HRMS [M+H] = 308.1010; $C_{11}H_{18}IN_3O_5$ = 308.1013.



Methyl N-[(Chloroacetyl)aminocarbonyl)aminocarbonyl]isoleucinate (47e)

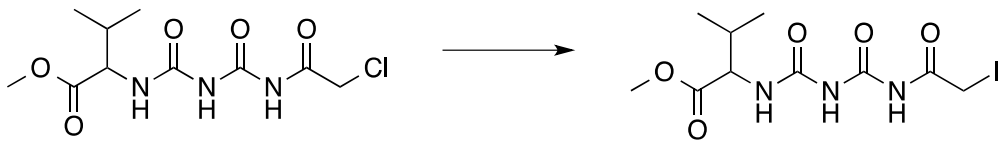
A solution of **46e** (60 mg, 0.27 mmol) in 0.1M chloroacetylisocyanate in CH_2Cl_2 (3.0 mL) was stirred at ambient temperature for 3 days. Volatiles were removed and the crude product was added directly to a Flash chromatography column and eluted with 2%-3% MeOH/CH_2Cl_2 to give **47e** (45 mg, 0.13 mmol) in 48% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.10 (bs, 1H), 9.10 (bs, 1H), 8.40 (bs, 1H), 7.31-7.15 (m, 5H), 4.82 (dd, *J* = 13.0, 7.0 Hz, 1H), 4.09 (s, 2H), 3.74 (s, 3H), 3.21 (dd, *J* = 13.8, 5.3 Hz, 1H), 3.12 (dd, *J* = 13.8, 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.7, 167.6, 151.6, 151.3, 135.7, 129.3, 128.6, 127.2, 54.3, 52.5, 42.4, 37.9; HRMS [M+H] = 342.0866; $C_{14}H_{17}ClN_3O_5$ = 342.0857.



47a 48a

Methyl N-[(Iodoacetyl)aminocarbonyl)aminocarbonyl]alaninate (48a)

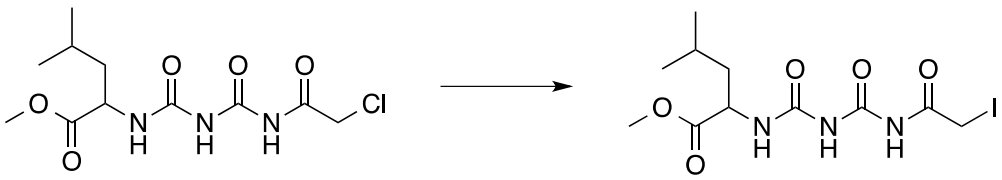
A solution of compound **47a** (10 mg, 0.04 mmol), sodium iodide (24 mg, 0.16 mmol) in acetone (2.0 mL) was stirred at 50 °C for 2 hrs. Volatiles were removed under reduced pressure and crude product was added directly to a Flash chromatography column and eluted with 5% MeOH/CH_2Cl_2 to give **48a** (8 mg, 0.02 mmol) in 50% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.2 (bs, 1H), 9.84 (bs, 1H), 8.53 (bs, 1H), 4.57 (pent, *J* = 6.5 Hz, 1H), 3.91 (d, *J* = 10.5 Hz, 1H), 3.86 (d, *J* = 10.5 Hz, 1H), 3.78 (s, 3H), 1.50 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.3, 169.9, 152.8, 151.4, 52.7, 48.9, 18.4, -3.2; HRMS [M+H] = 357.9902; $C_8H_{13}IN_3O_5$ = 357.9900.



47b 48b

Methyl N-[(Iodoacetyl)aminocarbonyl)aminocarbonyl]valinate (48b)

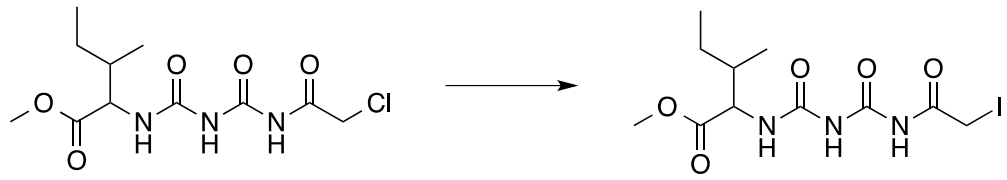
A solution of compound **47b** (26 mg, 0.09 mmol), sodium iodide (54 mg, 0.36 mmol) in acetone (1.0 mL) was stirred at 50 °C for 2 hrs. Volatiles were removed under reduced pressure and crude product was added directly to a Flash chromatography column and eluted with 5% MeOH/CH_2Cl to give **48b** (22 mg, 0.06 mmol) in 67% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.21 (bs, 1H), 9.70 (bs, 1H), 9.48 (bs, 1H), 4.51 (dd, *J* = 8.5, 5.0 Hz, 1H), 3.90 (d, *J* = 10.5 Hz, 1H), 3.77 (s, 3H), 3.74 (d, *J* = 10.5 Hz, 1H), 2.28-2.26 (m, 1H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.3, 169.8, 152.9, 151.9, 58.3, 52.3, 31.1, 19.1, 17.8, -3.39; HRMS [M+H] = 386.0245; $C_{10}H_{17}IN_3O_5$ = 386.0213.



47c 48c

Methyl N-[(Iodoacetyl)aminocarbonyl)aminocarbonyl]valinate (48c)

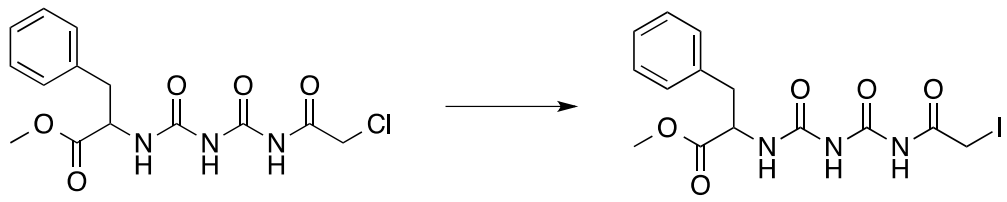
A solution of compound **47c** (20 mg, 0.07 mmol), sodium iodide (39 mg, 0.26 mmol) in acetone (4.0 mL) was stirred at 50 °C for 2 hrs. Volatiles were removed under reduced pressure and crude product was added directly to a Flash chromatography column and eluted with 5% MeOH/CH_2Cl_2 to give **48c** (20 mg, 0.05 mmol) in 72% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.18 (bs, 1H), 9.46 (bs, 1H), 8.34 (bs, 1H), 4.61-4.59 (m, 1H), 3.90 (d, *J* = 10.5 Hz, 1H), 3.84 (d, *J* = 10.5 Hz, 1H), 3.79 (s, 3H), 1.78-1.69 (m, 3H), 0.99 (d, *J* = 5.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.5, 169.6, 152.5, 151.7, 52.6, 51.7, 41.2, 24.9, 22.9, 21.8, -3.43; HRMS [M+H] = 400.0373; $C_{11}H_{18}IN_3O_5$ = 400.0369.



47d 48d

Methyl N-[(Iodoacetyl)aminocarbonyl)aminocarbonyl]isoleucinate (48d)

A solution of compound **47d** (22 mg, 0.07 mmol), sodium iodide (41 mg, 0.27 mmol) in acetone (1.0 mL) was stirred at 50 °C for 2 hrs. Volatiles were removed under reduced pressure and crude product was added directly to a Flash chromatography column and eluted with 5% MeOH/CH_2Cl_2 to give product **48d** (19 mg, 0.047 mmol) in 68% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.2 (bs, 1H), 9.66 (bs, 1H), 8.50 (bs, 1H), 4.55 (dd, *J* = 8.3, 4.8 Hz, 1H), 3.89 (d, *J* = 10.3 Hz, 1H), 3.84 (d, *J* = 10.3 Hz, 1H), 3.77 (s, 3H), 2.01-1.99 (m, 1H), 1.49-1.47 (m, 1H), 1.26-1.22 (m, 2H), 0.98-0.95 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.3, 169.7, 152.9, 151.7, 57.6, 52.3, 37.7, 25.2, 15.7, 11.6, -3.4. HRMS [M+H] = 400.0364; $C_{11}H_{18}IN_3O_5$ = 400.0369.



47e **48e**

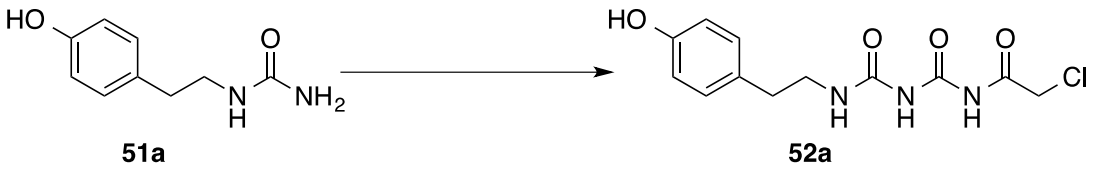
Methyl N-[(Iodoacetyl)aminocarbonyl)aminocarbonyl]phenylalaninate (48e)

A solution of compound **47e** (45 mg, 0.13 mmol), sodium iodide (97 mg, 0.65 mmol) in acetone (1.0 mL) was stirred at 50 °C for 2 hrs. Volatiles were removed under reduced pressure and crude product was added directly to a Flash chromatography column and eluted with 5% MeOH/CH_2Cl_2 to give product **48e** (48 mg, 0.11 mmol) in 85% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.2 (bs, 1H), 9.75 (bs, 1H), 8.49 (bs, 1H), 7.34-7.17 (m, 5H), 4.87 (dd, *J* = 21.5, 10.5 Hz, 1H), 3.77 (s, 3H), 3.79-3.69 (m, 2H), 3.26 (dd, *J* = 23.0, 9.0 Hz, 1H), 3.17 (dd, *J* = 23.3, 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.8, 169.9, 152.8, 151.5, 135.8, 129.4, 128.7, 127.2, 54.4, 52.6, 37.9, -3.25; HRMS [M+H] = 434.0200, $C_{14}H_{17}IN_3O_5$ = 434.0213

50a **51a**

1-(4-hydrophenethyl)urea (51a)

A solution of tyramine (80 mg, 0.58 mmol), carbonyldiimadazole (114 mg, 0.70 mmol) in dry MeOH (4.0 mL) and dry THF (4.0 mL) was stirred at ambient temperature overnight. $MeOH/NH_3$ (4.0 mL) was added and the mixture was stirred at ambient temperature for 24 hours. Volatiles were removed under reduced pressure and crude product was added directly to a Flash chromatography column and eluted with 10% $MeOH/CH_2Cl_2$ to give compound **51a** (63 mg, 0.35 mmol, 60%). ^1H NMR (CD_3OD, 500 MHz) δ 7.04 (d, J = 8.5 Hz, 2H), 6.72 (d, J = 8.5 Hz, 2H), 3.28 (t, J = 7.0 Hz, 2H), 2.67 (t, J = 7.3 Hz, 2H); ^{13}C NMR (CD_3OD, 125 MHz) δ 160.8, 155.4, 130.0, 129.4, 114.8, 41.4, 35.1; HRMS [M+H] = 181.0996; $C_9H_{13}IN_2O_2$ = 181.0997.



51a **52a**

2-chloro-N-(((40hydroxyphenethyl)carbamoyl)acetamide (52a)

A solution of **51a** (63 mg, 0.35 mmol) in 0.1 M chloroacetylisocyanate in CH_2Cl_2 (4.2 mL) was stirred at ambient temperature for 3 days. Volatiles were removed and the crude mixture was chromatographed on a preparatory TLC using 10% MeOH/CH_2Cl_2 to give **52a** (40 mg, 0.13 mmol) in 37% yield. ^{1}H NMR (CD_3OD, 500 MHz) δ 7.05 (d, J = 8.0 Hz, 2H), 6.72 (d, J = 8.0 Hz, 2H), 4.24 (s, 2H), 3.45 (t, J = 7.3 Hz, 2H), 2.75 (t, J = 7.3 Hz, 2H); ^{13}C NMR (CD_3OD, 125 MHz) δ 169.0, 155.6, 153.3, 151.6, 129.6, 129.5, 129.4, 114.9, 42.3, 41.3, 40.9, 40.1, 34.6, 34.4; HRMS [M+H] = 300.0732; $C_{12}H_{15}ClN_3O_4$ =300.0751.

52a **53a**

N-(((4-hydroxyphenethyl)carbamoyl)carbamoyl)-2-iodoacetamide (53a)

A solution of compound **52a** (40 mg, 0.13 mmol) and sodium iodide (80 mg, 0.53 mmol) in acetone (5.0 mL) was stirred at 50 °C for 2 hrs. Volatiles were removed under reduced pressure and crude product was added directly to a Flash chromatography column and eluted with 5% MeOH/CH_2Cl_2 to give **53a** (10 mg, 0.03 mmol) in 23% yield. ^{1}H NMR (CD_3OD, 500 MHz) δ 7.05 (d, *J* = 8.0 Hz, 2H), 6.72 (d, *J* = 8.0 Hz, 2H), 3.85 (s, 2H), 3.45 (t, *J* = 7.3 Hz, 2H), 2.75 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR (CD_3OD, 125 MHz) δ 171.5, 155.6, 153.3, 151.9, 129.5, 129.4, 114.9, 41.3, 40.9, 34.6, 34.4, 29.3, -4.37; HRMS [M+H] = 392.0118; $C_{12}H_{15}IN_3O_4$ =392.0107.

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