Thesis for the Master's degree in chemistry

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Synthetic Routes to Tetrahydrodiazepinopurines - The Heterocyclic Ring System Found in Asmarines

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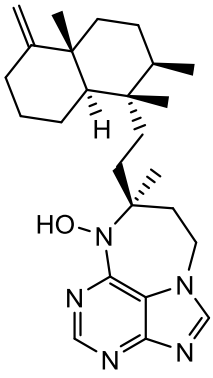
ABSTRACT

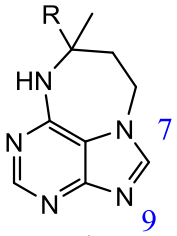
Asmarines, a group of cytotoxic compounds isolated from the marine sponge *Raspailia sp.* found in the Red Sea, has been a target of total synthesis since its discovery in the late 1990s.[1] At its core, Asmarines contain the tricyclic *tetrahydrodiazepinopurine* (THDAP) ring system **A** which has presented various synthetical challenges.

An initial route to THDAPs starting from a pyrimidine derivative was attempted. This method was found to be unsuitable for the synthesis THDAPs (Section 2.1)

One other possible synthetic route was also attempted starting from commercially available adenine, in which a major challenge is the selective alkylation of the *N-7* position over the preferred *N-9* position (Section 2.2). In this Project, a method for constructing *N-7* substituted adenine is presented. The new synthetic route did not go according to plan, but did produce an interesting hemiaminal ether, which can possibly be a useful intermediate in the total synthesis of asmarines.



Asmarine A



A

During the project, a novel methodology for the reduction of electron-poor Boc-protected purines to the corresponding 7,8-dihydropurines was discovered. These are important intermediates in the synthesis of potentially bioactive 7-substituted purines.[2,3]

ABBREVIATIONS

Aq. Aqueous

Bn Benzyl

Boc *tert*-Butoxycarbonyl

br broad (NMR)

C Carbon

Calc. Calculated

COSY Correlation spectroscopy

Δ heating

DBU 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCM Dichloromethane

DMAP 4-Dimethylaminopyridine

DMF Dimethylformamide

DMSO Dimethyl sulfoxide

EI Electron impact

Eq. Equivalents

Et al. et alii

EtOAc Ethyl acetate

GI_{50} growth inhibition that inhibits 50 %

h hour(s)

HMBC Heteronuclear multiple-bond correlation

HRMS High resolution mass spectrometry

HSQC Heteronuclear single-quantum coherence

Hz hertz

IC_{50} Inhibitory concentration that inhibits 50 %

J coupling constant (NMR)

LiHMDS Lithium hexamethyldisilazide

M multiplet (NMR)

M^+ molecular ion peak (MS)

Me Methyl

MeOH Methanol

MHz megahertz

MS Mass spectrometry

M.p. Melting point

m/z *mass to charge ratio*

n.r. *no reaction*

NMR Nuclear magnetic resonance

r. t. Room temperature

s Singlet (NMR)

sat. saturated

Temp. temperature

Tert tertiary

d dublet (NMR)

t Triplet (NMR)

TFA Triflouroacetic acid

THDAP tetrahydro-[1,4]diazepino[1,2,3-*gh*]purine

THF Tetrahydrofuran

TLC Thin layer chromatography

Table of Contents

1. INTRODUCTION

This section will provide a brief introduction to natural products and their current role in pharmaceuticals. Existing information available on asmarines will be summarized, such as their origin and biological activity as well as the synthetic endeavors that have been carried out in this area thus far.

1.1 NATURAL PRODUCTS

Nature is a vast source of biologically active compounds of great potential benefit.[4] They are called *natural products* and encompass all molecules that are produced by a living organism. The percentage of drugs approved by the FDA between 1981 and 2006 that was either a natural product or inspired by a natural product was roughly 52 %.[4] Only about 30 % were completely synthetic in origin. Of the 155 small molecule anti-cancer drugs approved, 47 % were natural products or natural product derivatives. These numbers reflect nature's important role as an inspiration for new pharmaceuticals.

A vast majority of nature's bioactive compounds are *secondary metabolites*. These are molecules that do not directly play a role in the development and reproduction of an organism, but provides some other evolutionary advantage to the organism, like fighting off microbes or repelling herbivores. These metabolites are important sources of new drugs as they already elicit powerful biological activity needed for these compounds to benefit the organism.

1.1.1 Traditional sources of natural products

Higher plants have been an important source of natural products since the isolation of morphine (Figure 1) from the poppy *papaver somniferum* in 1804.[5] Examples of important compounds that has been isolated from the plant kingdom include digoxin, quinine, quinidine, vincristine , vinblastine and atropine.[6] Taxol, isolated from the bark of the Pacific yew tree *Taxus brevifolia*, is a potent anticancer drug that became a huge commercial success for the treatment of ovarian-, breast- and some lung-cancers in the late 1990s.[7] In 2000, about one in four drugs prescribed worldwide originated from plants.[6]

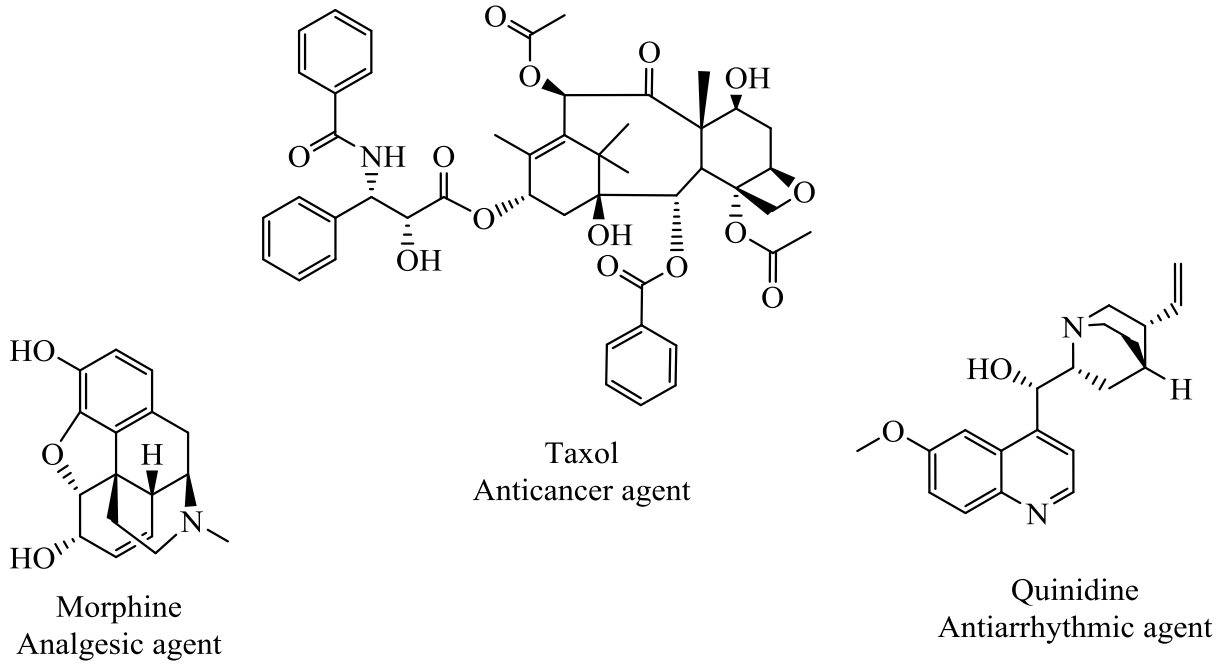


Figure 1. The structure of morphine, taxol and quinidine; natural products used as drugs.

The discovery of penicillin in 1929 spawned an era of exploration of microorganisms as a source of drugs.[5] Massive screening efforts were carried out after the Second World War looking for new antibiotics. Some of the most important drugs resulting from this screening include erythromycin, cephalosporin C and daunorubicin. Daunorubicin (Figure 2) served as a starting point for the synthesis of many other related compounds called *anthracyclines* including the important doxorubicin used in cancer chemotherapy. These compounds are some of the most effective antineoplastic compounds discovered with the widest spectrum of activity in human cancers.[8]

Animals also produce compounds with attractive pharmacological properties.[9-11] For instance, it was estimated that approximately 4 % of 800 evaluated arthropod extracts in the 1970s showed some degree of cytotoxicity.[12] Insects also provide a host of various chemical substances of interesting biological activity. Many of these substances are present in insects because of their extensive use of chemicals as a defense mechanism.[10] Venoms and toxin from snakes, spiders and frogs also contain potential lead compounds for novel therapeutics.[13,14] Epibatidine, a poisonous alkaloid present on the skin of certain species of poison dart frogs, was shown to possess analgesic properties 200 times more potent than morphine.[15] Although it is too poisonous to be used as a drug, it serves as a lead compound for the development of less toxic derivatives.[16]

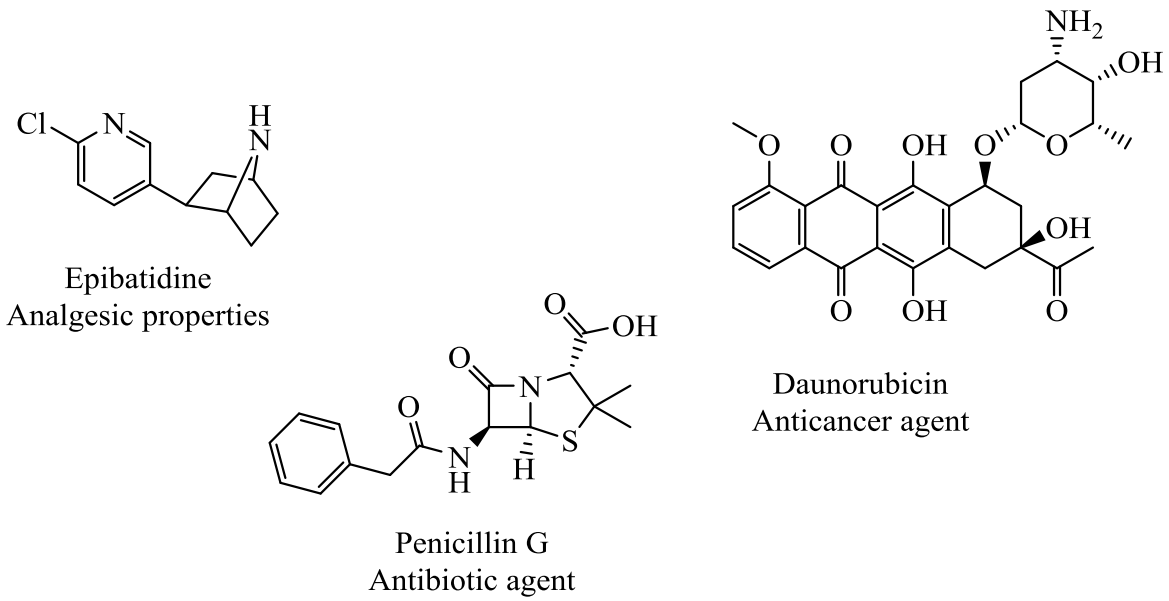


Figure 2. The structure of Epibatidine; penicillin G and Daunorubicin.

1.1.2 Marine sources of natural products

In recent years, there has been an upsurge in drug discovery of natural products and lead compounds from marine sources.[17] The most common such sources are the marine invertebrates which comprise around 60 % of all marine animal diversity.[18] These organisms are often soft-bodied, sedentary life-forms and hence often rely on chemical defense for survival. Since an aqueous environment quickly dilutes any chemical substances excreted by an organism, these molecules must possess potent biological activity in order to achieve its intended effect.[19] This creates an environment that is rich in potent bioactive compounds and marine organisms are thus attractive targets for the bioprospecting of potential drugs.[20,21]

Some of the earliest examples of natural products derived from marine sources are *spongothymidine* and *spongouridine* (Figure 3) isolated from the sea sponge *Cryptotethia crypta*.[22]

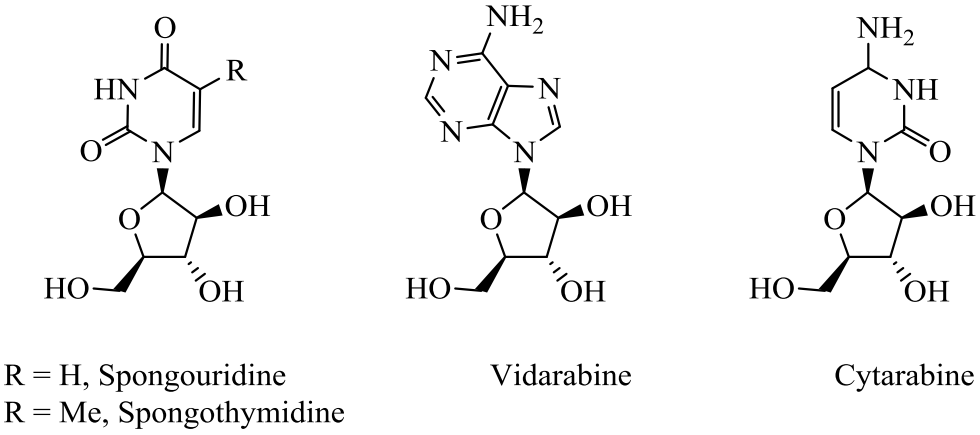


Figure 3. Structure of spongothymidine, spongouridine, vidarabine and cytarabine; compounds possessing antiviral activity.

These compounds were the inspiration for drugs such as *vidarabine* and *cytarabine* in clinical use today.[23] Vidarabine was initially planned to be an anticancer drug but was in the process discovered to possess significant antiviral activity.[24] Today, it is typically used in the treatment of diseases caused by herpes, pox- and rhabdoviruses.

The occurrence of cytotoxic activity in extracts of marine organisms far exceeds that of terrestrial samples.[20] Despite the abundance of potent, biologically active compounds found in marine ecosystems, very few clinically approved drugs of marine origin is found on the market. There are several reasons for this,[5] but perhaps the biggest reason is the lack of biomass available from wildstocks. The limited supply of material needed for drug development, severely hinders advancement in this area of drug discovery.[20]

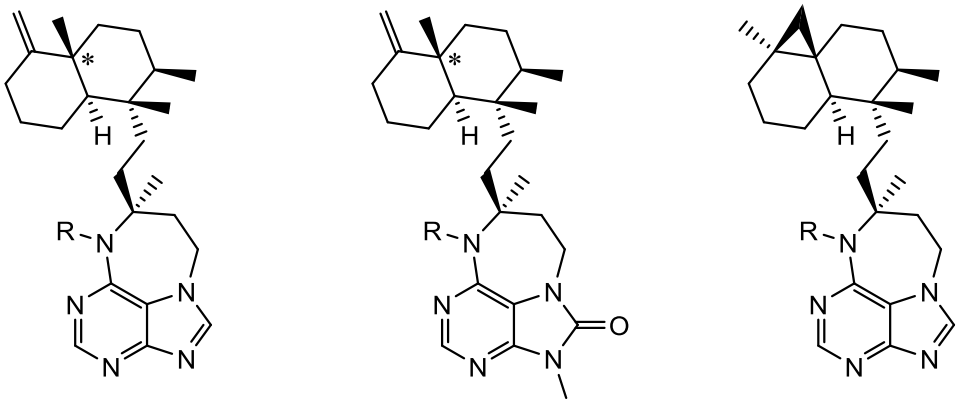
Bioprospecting of marine natural products is still a relatively new endeavor, but has already produced thousands of new compounds.[18] Due to the ocean's huge biodiversity, the number of discovered marine natural products as candidates for novel pharmaceutical agents is only expected to rise.

1.2 ASMARINES

Asmarines are a class marine alkaloids first reported isolated in 1998 from the sea sponge *Raspailia*.[25] Initial screening revealed they possess significant cytotoxicity against various types of cancer cells, including some important human cancer cell lines. The discovery of these compounds and their close similarity to *agelasines* and *agelasimines*, another set of marine alkaloids previously studied in our group shown to possess antimicrobial and antineoplastic activities,[26-31] has prompted research to try to synthesize these molecules. So far no total synthesis of any of the asmarine analogs has been reported in the literature.

1.2.1 Isolation, structure and biological activity

The discovery of the first asmarines was a result of a collaboration between researchers at the School of Chemistry with the Tel-Aviv University in Israel and the Oceanographic Research Institute (ORI) in the Republic of South Africa.[25] A sample of the marine sponge *Raspailia* (*Demospongiae, Poecilosclerida, Microcionina, Raspailiidae*) found in the Red Sea off the coast of Eritrea was collected and frozen on site. Chemical analysis of the freeze-dried sample, revealed three novel structurally related metabolites, named asmarine A – C. The same group reported three new asmarines (D – F) in 2000 and five more (G – K) in 2004 for a total of eleven compounds (Figure X).[32-34]



A R = OH
B R = OH, *-epi
G R = OMe
H R = H
K R = H, *-epi

C R = H, *-epi
D R = H,
E R = OMe
F R = OMe, *-epi

I R = OH
J R = H

Figure 4. The structures of all asmarines currently known.

Asmarines G and H was isolated from sponges near Shimoni in the Wasini Channel of southern Kenya while asmarines I, J and K appear in sponges in the waters near the Nosy Be Islands of Madagascar. Asmarines A and F are the only asmarines that have appeared in all of the three areas investigated.

Asmarines consist of a fused diterpene-heterocyclic structure. The diterpene-portion of the molecule resembles naturally occurring chelodane[35] and contains five stereocenters. Only one of the stereocenters (marked in Figure 4) has shown variation among the asmarine analogs. The heterocyclic part of the molecule is based on adenine. Conjugation of these two moieties is believed to be the biosynthetic origin of asmarines.[1]

Initial screening of asmarine A and B has revealed cytotoxicity against cell cultures of P-388 murine leukemia, A-549 human lung carcinoma, HT-29 human colon carcinoma and MEL-28 human melanoma.[25] The results of these studies are listed in Table 1.

Table 1. Anti-tumor activity of Asmarine A and B listed as IC_{50}-values in µM.

	P-388	**A-549**	**HT-29**	**MEL-28**
Asmarine A	1.18	1.18	1.18	1.18
Asmarine B	0.24	0.12	0.12	0.24

Asmarines A and B, together with several synthetic analogs, was later tested for cytotoxic activity against DU-145 prostate, IGROV-ET ovarian, SK-MEL-28 melanoma, A549 NSCL, PANC1 pancreas, HT29 colon and LOVO colon cancer cell lines (Table 2).[36]

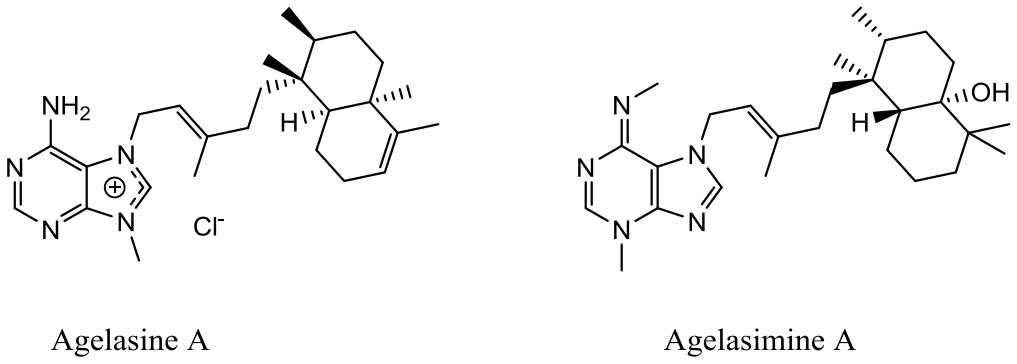
Table 2. GI_{50}-values of asmarine A and B against various cancer cell lines in µg/mL.

	Prostate	**Ovarian**	**Melanoma**	**NSCL**	**Pancreas**	**Colon**	
	DU-145	**IGROV-ET**	**SK-MEL-28**	**A549**	**PANC1**	**HT29**	**LOVO**
Asmarine A	2.7	0.7	2.7	4.1	1.1	0.4	1.0
Asmarine B	-	-	0.5	0.4	-	0.04	-

All synthetic analogs were found to be at least one order of magnitude less active than asmarine B. The importance of the hydroxyl-group in asmarine A and B for biological activity was also established; asmarine H shows no cytotoxic activity.

1.2.2 Related compounds

Two other subclasses of bioactive metabolites from marine sponges (*Agelas* sp., *Raspailia* sp.) are known: Agelasines and agelasimines. Far more is known about the biological activity of these compounds than for the related asmarines. Several synthetic analogs have been prepared and many of are even more potent than the naturally occurring compounds. Biological activities range from antibacterial,[26,27,29] antifungal,[3,26,27,31] antiprotozoal,[31,37,38] antineoplastic activity[3,28,31,39] to biofilm inhibition and antifouling properties.[40-42]



Agelasine A Agelasimine A

Figure 5. Structure of agelasine A and agelasimine A.

The close resemblance of agelasines and agelasimines to asmarines becomes evident from Figure 5. A key difference is the lack of the seven-membered ring seen in asmarines. Agelasines also contain an N-quaternary functionality.

1.3 PREVIOUS ATTEMPTS ON THE SYNTHESIS OF DIAZEPINOPURINE RING-SYSTEMS

So far, no asmarine has been prepared by total synthesis. Most of the chemistry reported on asmarine total synthesis has been on the heterocyclic-portion of the molecule. This 5-, 6-, 7-

membered tricyclic structure is referred to as THDAP (tetrahydro-[1,4]diazepino[1,2,3-*gh*]purine) (Figure 6).

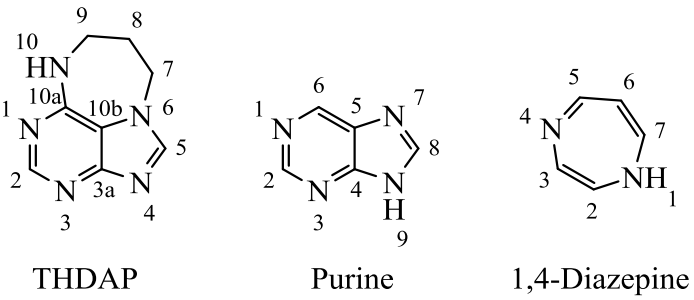


Figure 6. Numbering system for purine, diazepine and the THDAP core structure.

The main difficulty in synthesizing the THDAP ring-system lies in the construction of the seven-membered, diazepine-ring. The synthesis of THDAP and its derivatives can be divided into five strategies (*a*-*e*) based on which bond is formed in the ring-closing step of the diazepine ring (Figure 7).

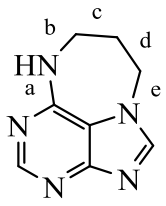
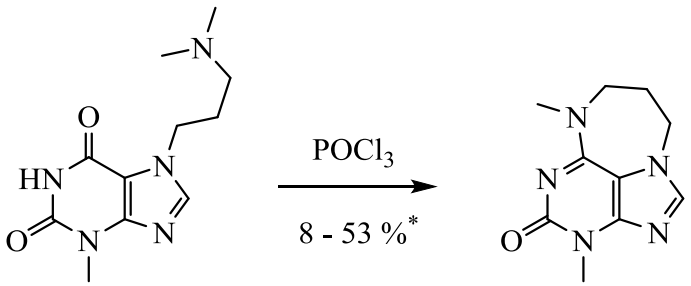


Figure 7. Bonds *a*-*e* refer to the five different strategies used to categorize the major synthetic routes to THDAP molecules.

This section will give an overview of previous attempts at constructing the THDAP ring-system.

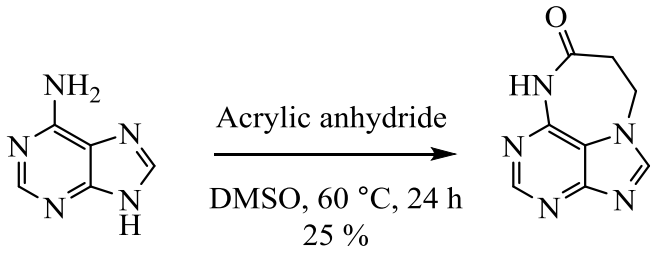
1.3.1 The first appearances of THDAPs in literature

The first example of the heterotricyclic diazepinopurine ring-system appearing in literature, was in 1977 by Glushkov et al.[43] While working on xanthine derivatives in the search for new spasmolytic drugs, they managed to ring-close an *N-7* alkylated 3-methylxanthine by treatment in neat phosphoryl chloride (Scheme 1).



Scheme 1. Ring-closing of an *N-7* alkylated 3-methylxanthine derivative using phosphoryl chloride. *Individual yields were not reported.

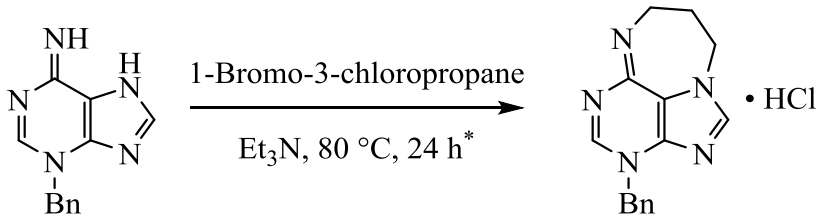
In 1985, Brahme and Smith reported synthesizing a THDAP from adenine by addition of acrylic anhydride in dry DMSO (Scheme 2).[44]



Scheme 2. Synthesis of 7,8-dihydro-[1,4]diazepino[1,2,3-gh]purin-9(10H)-one.[44]

1.3.2 Synthetic studies toward asmarines

The first synthesis of a THDAP system directed towards the total synthesis of asmarines, was performed by Kashman et al. (Scheme 3).[45]



Scheme 3. Synthesis of 3-benzyl THDAP as an HCl salt. * No yields reported.

In this case, the bulky benzyl group at N-3 steers further alkylations to take place at *N-7* rather than the now sterically crowded *N-9* position, thus making it possible to form the desired THDAP system.

The same group also proposed and tested two possible cyclizations to form the 10-hydroxy-THDAP system seen in most asmarines. The two routes involve either going through synthon S1, cyclizing on *N-7* (strategy *e*) or through synthon S2 cyclizing on N-6 (strategy *b*) (Figure 8).

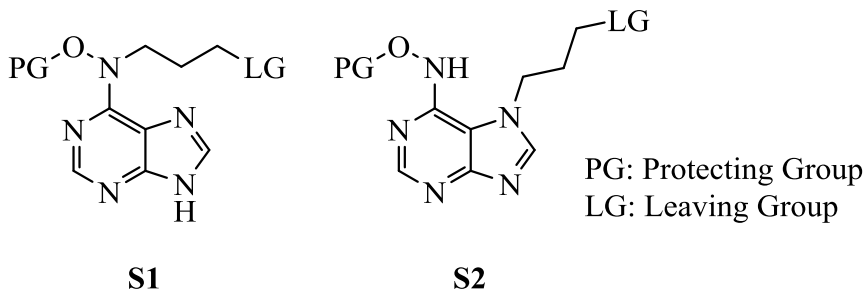
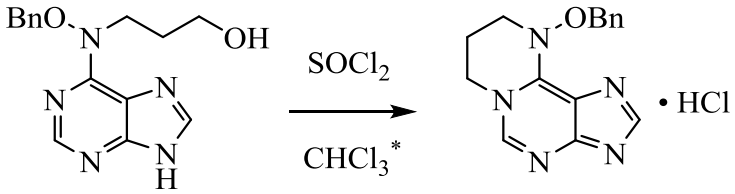


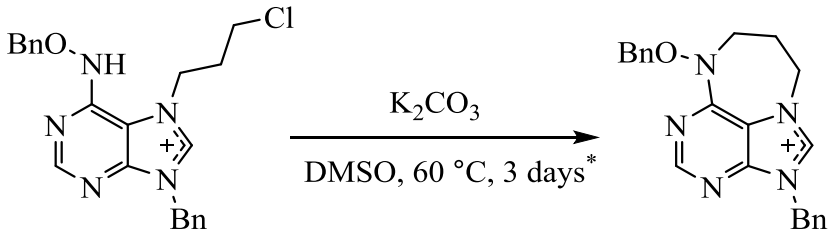
Figure 8. Two proposed synthons for the synthesis of 10-hydroxy-THDAP.[45]

The group's attempt at cyclizing through an S1-type molecule failed as cyclization took place on N-1 rather than on *N-7* (Scheme 4).



Scheme 4. Cyclization on N-1. *No yields reported.

On the other hand, ring-closure of an S2-type molecule has only one possible site of cyclization, namely N-6. Indeed this reaction produced the intended THDAP ring-system (Scheme 5).

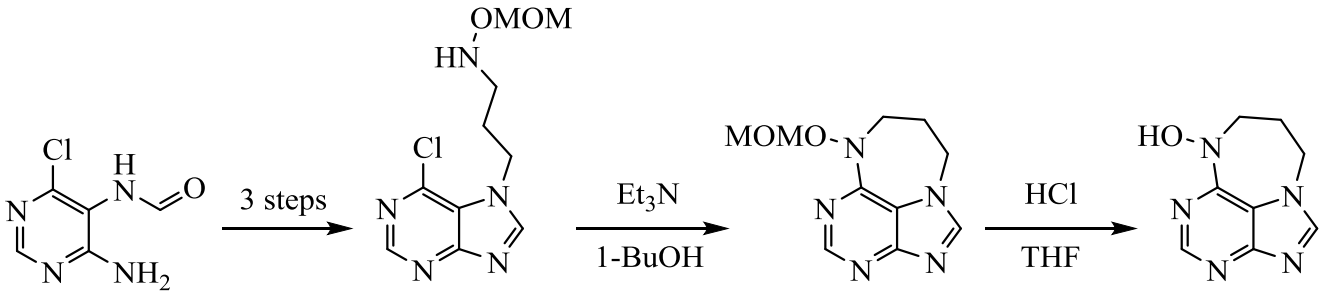


Scheme 5. Cyclization producing a possible 10-hydroxy-THDAP precursor using strategy b. * No yields reported.

However, a method to deprotect the di-benzylated THDAP system to produce the more interesting 10-hydroxy-THDAP was revealed to be problematic.[46]

Ohba et al. has reported methods to synthesize 10-hydroxy-THDAP, 4-methyl-5-oxo-THDAP and 10-methoxy-4-methyl-5-oxo-THDAP, the three major structural motifs for the tricyclic skeleton of asmarines.[47]

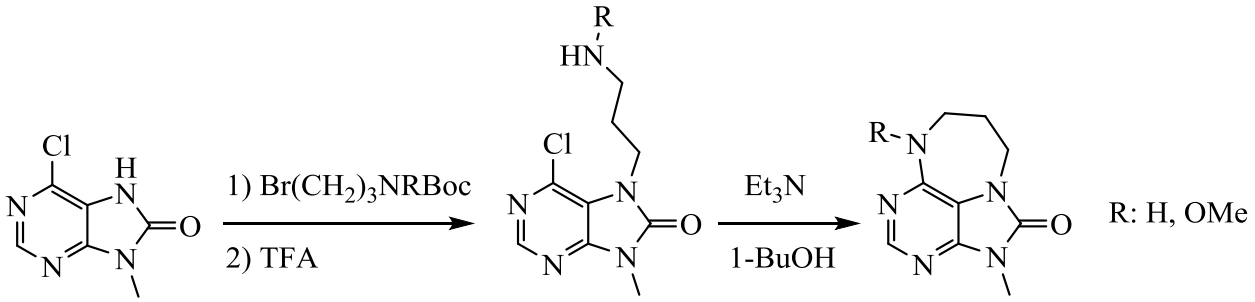
The synthesis of 10-hydroxy-THDAP was achieved by cyclization of a pyrimidine derivative (Scheme 6).



Scheme 6. First successful synthesis of 10-hydroxy-THDAP.[47]

The reasoning behind the use of this route is that direct alkylation of 6-chloropurine by alkyl halides or under Mitsunobu conditions is reported to occur preferentially on *N*-9.[48-57] By starting with 4-amino-6-chloro-5-formamidopyrimidine, the desired nitrogen can be alkylated under basic conditions and then cyclized to form the purine ring.

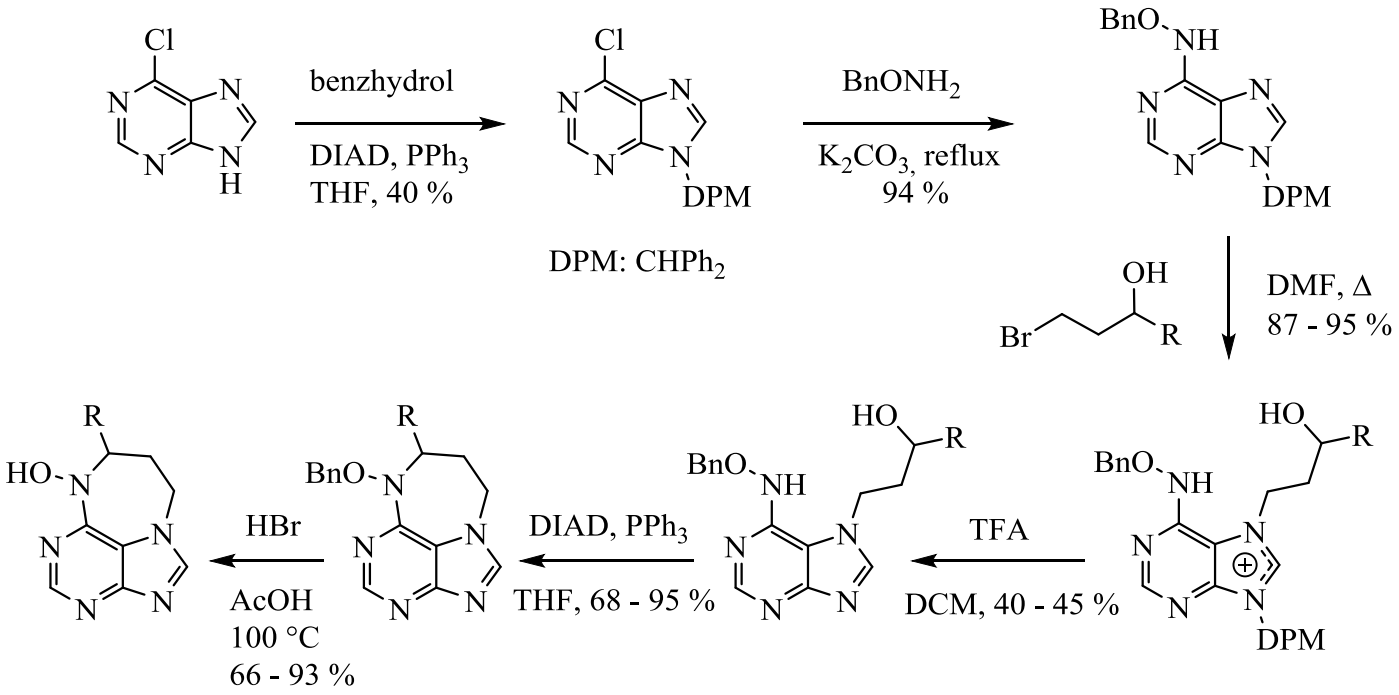
Strategy *a* has only been used to synthesize THDAP-systems unsubstituted in the diazepine-ring. It is, however, also the only method to have produced the 4-methyl-5-oxo-THDAP motif seen in asmarine C-F (Scheme 7).



Scheme 7. Ring-closing by nucleophilic aromatic substitution.

Strategy *b* is so far the only strategy successfully used to form C-9-substituted THDAPs.[46,58] Starting from 6-chloropurine, the *N*-9 position is protected and a nucleophilic aromatic

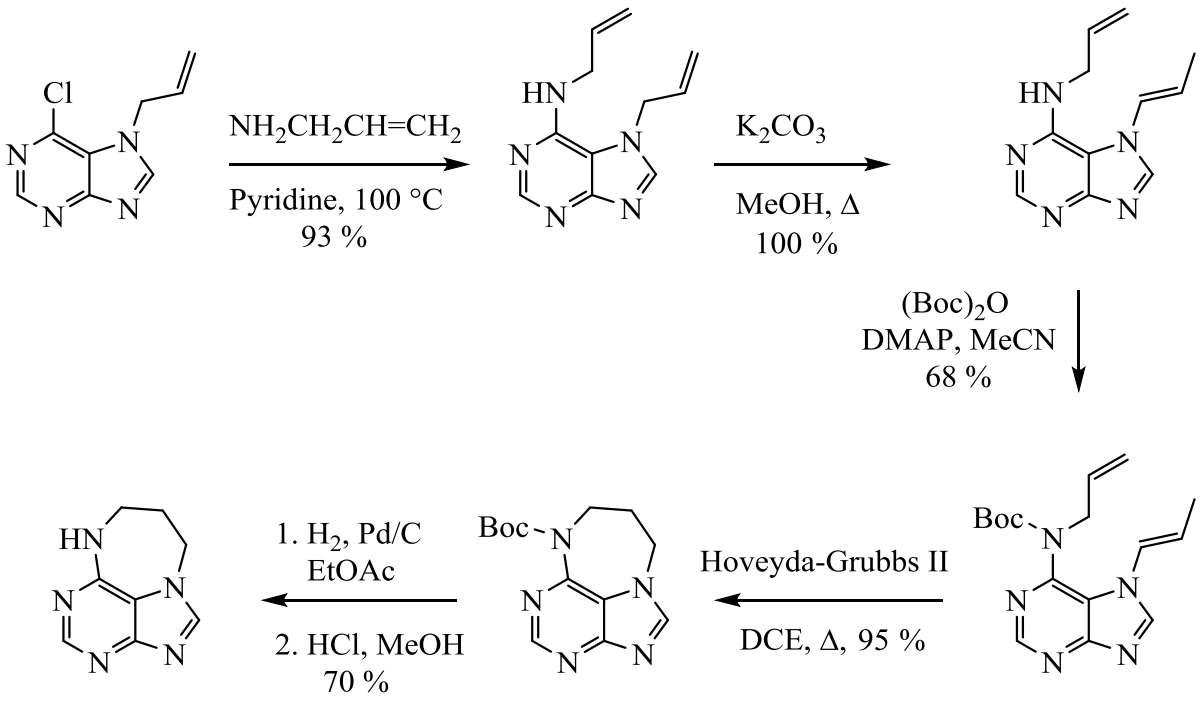
substitution introduces the hydroxylated nitrogen (Scheme 8). Subsequent alkylation at the *N-7* position carries the desired substituents and the right functionality to allow ring-closing under Mitsunobu conditions.



Scheme 8. Ring-closing using strategy *b* to afford C-9 substituted THDAPs.[46]

Limitations to this synthesis are low yields in the protection and deprotection step and the lack of stereochemical control in the ring-closing step.

Strategy *d* has previously been used in our group to synthesize THDAP by ring-closing metathesis (RCM).[59] Stereochemistry is not an issue in this route. Jähne et al. showed that selective *N-7*-allylation of 6-chloropurine can be achieved by using a Co-complex.[60] Using this reaction circumvented the need for *N-9*-protection. After introducing an allylamino-group in the 6-position, the double bond could selectively be rearranged to *N*-allyl-7-(1-propen-1-yl) purin-6-amine under basic conditions to allow seven-membered ring-formation after the RCM reaction (Scheme 9).



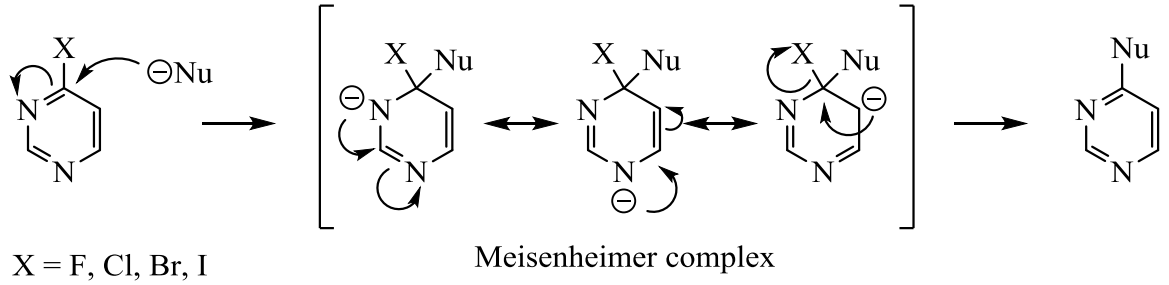
Scheme 9. Synthesis of THDAP by ring-closing metathesis.

1.4 Chemistry

This section will cover some aspects of the chemistry used in the master's project.

1.4.1 Nucelophilic aromatic substitution on purines and pyrimidines

The electron-poor nature of purines and pyrimidines means they are activated towards nucleophilic aromatic substitution reactions (S_NAr). Halogens in the 2-, 4- and 6-position of pyrimidines and the 2- and 6-position of purines provide excellent substrates for the introduction of a diverse number of substituents and are therefore common starting materials and intermediates in organic synthesis. Activation in these positions is a result of both inductive and mesomeric withdrawal of electrons by adjacent nitrogens as well as the inductive withdrawal of electrons by the halogen itself.[61] Polyhalogenated purines and pyrimidines will in most cases preferentially undergo substitution at the 4- and 6-position, although mixtures are common. The rate of reaction is largely determined by the electronegativity of the halogen. An increase in electronegativity will more strongly polarize the carbon-halogen-bond leaving carbon with a greater partial positive charge and thus more prone to nucleophilic attack. The leaving group-ability of the halogen has little to no impact on the reaction rate as the initial attack forming the *Meisenheimer complex* and breaking aromaticity is the rate-determining step (Scheme X). The aromaticity is restored in the second step when the leaving group is eliminated and is thus a fast reaction. This means that the halogen's order of reactivity for nucleophilic aromatic substitution is: F>Cl>Br>I, which is the opposite of regular S_n1 and S_n2-type reactions.[62]



Scheme 10. Reaction mechanism of nucleophilic aromatic substitution on pyrimidine.

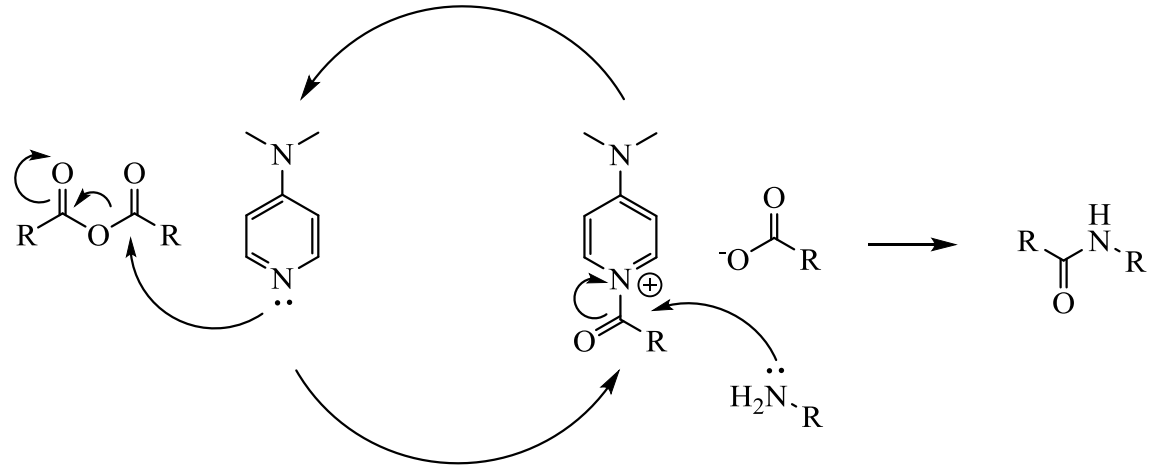
The presence of other substituents can greatly affect the propensity for nucleophilic aromatic substitution. As a general rule, electron-withdrawing groups will increase reaction rates, while electron-donating groups will decrease reaction rates. The presence of electron-withdrawing groups can inductively and mesomerically help stabilize the negative charge introduced by the nucleophile to lower the activation barrier of the rate-determining step. On the other hand, an electron-donating group will increase the aromatic stabilization of the reactant molecule and destabilize the negative charge increasing the activation barrier.

1.4.2 The tert-butoxycarbonyl (Boc) group – the role of DMAP

The *tert*-butoxycarbonyl (Boc) group is one of the most frequently used protecting group for amines in organic synthesis.[63] Conversion of amines to the corresponding *tert*-butyl carbamate drastically alters the reactivity of the amine allowing for other reactions to take place that would otherwise affect the amino-group. Boc-groups are usually stable under basic conditions, resistant to catalytic hydrogenolysis and inert toward most nucleophiles. It cleaves under moderate to strong acidic conditions, making it an ideal orthogonal partner to benzyl esters and other carbamates commonly used in peptide synthesis.[64]

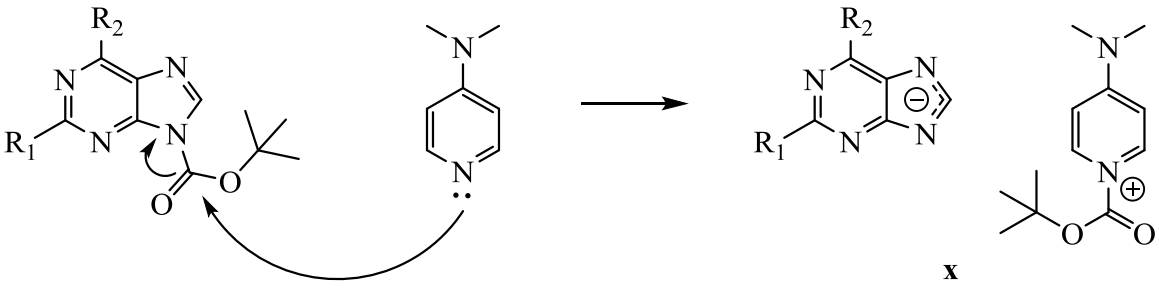
Boc-protection of amines is generally achieved by adding di-tert-butyl dicarbonate to the free amine in a suitable solvent with or without added bases such as triethylamine or diisopropylethylamine (DIPEA).[63] The addition of catalytic amounts of 4-dimethylaminopyridine (DMAP) will in many cases decrease reactions times and even allow for protection of groups that otherwise does not react. Sometimes addition of DMAP completely changes the outcome of the reaction.[65]

DMAP acts as a nucleophilic catalyst in acylation reactions.[66,67] The basis for the catalytic properties lies in its ability to form 1-acyl pyridinium salts (Scheme 11). These salts are often more reactive than the parent anhydride and thus facilitate acylation.



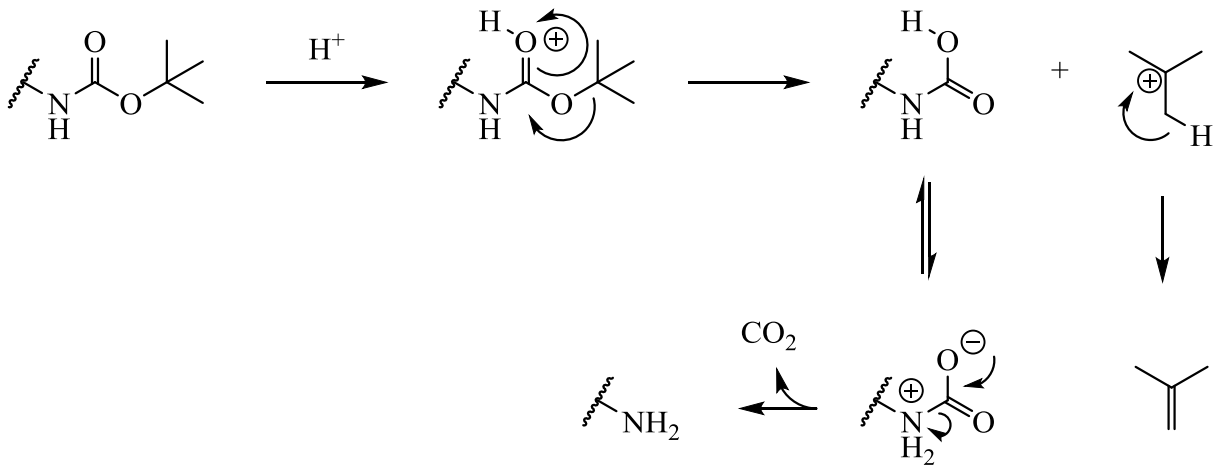
Scheme 11. Catalytic action of DMAP with anhydrides to produce reactive 1-acyl pyridinium salts.

Boc-protection of purine-derivatives will in most cases produce the *N-9* protected isomer.[68-70] It has been suggested that, in the presence of DMAP, these reactions are reversible and will initially produce mixtures of *N-7* and *N-9* protected isomers that over time resolves into the more thermodynamically stable product.[71] This would indicate the presence of an intermediate salt **x** (Scheme 12).



Scheme 12. Action of DMAP on Boc-protected purines.[71]

Deprotection of Boc-groups are usually achieved in neat trifluoroacetic acid (TFA) or mixtures of TFA in DCM.[63] Other common protocols are HCl in methanol or dioxane. The mechanism of deprotection is depicted in Scheme 13.[62]

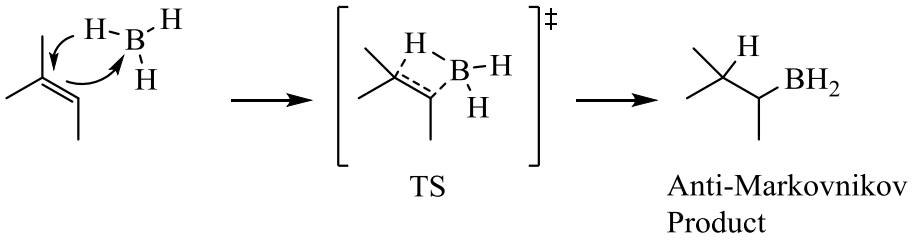


Scheme 13. Mechanism of Boc-deprotection.[62]

As shown in Scheme 13, *N-7* and *N-9* Boc-protected purines are prone to deprotection under non-acidic conditions. Even simple heating in nucleophilic solvents like methanol will deprotect Boc-protected adenine in the *N-9* position.[68] This effect can be attributed to the resonance-stabilized imidazolide ion formed in such nucleophilic deprotections.

1.4.3 Reductions using borane and sodium borohydride

Borane complexes like BH_3•THF and BH_3•DMS are reducing agents commonly used in hydroborations.[62] The reagent adds across double bonds in a concerted step most often producing the anti-Markovnikov product (Scheme X). The anti-Markovnikov product is formed because of steric interactions between the carbon substituents and boron.

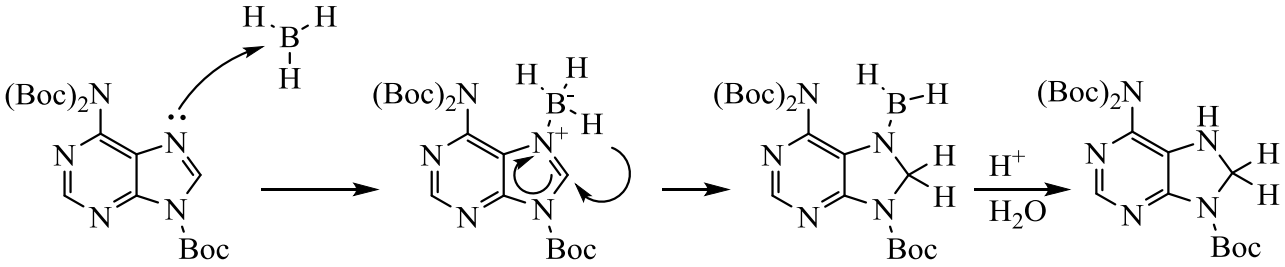


Scheme 14. Mechanism of borane addition over double bond.

The hydroborated product can serve as a useful intermediate for following chemical transformations. The product can be treated with aqueous acidic solutions to afford the reduced, non-functionalized product or, more commonly, treated with hydrogen peroxide to afford the

alcohol. The latter, two-step hydroboration/oxidation reaction is a powerful synthetic tool used to make alcohols from alkenes by *cis*-addition of water.[62]

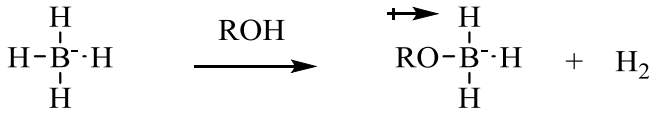
Limited information exists regarding the interaction of purines and boranes. Hirota et al. reduced inosine-derivatives to the corresponding 2,3-dihydroinosine.[72] The proposed mechanism involves complexation of borane to N-3 of the purine followed by hydride-delivery to the adjacent C-2. The proposed mechanism for the borane-reduction performed in this project is outlined in Scheme 15.



Scheme 15. Proposed mechanism of the borane-reduction used in this project.

Sodium borohydride is a widely used reducing agent in organic chemistry.[73] It is often chosen over other reducing agents for its safety and ease of handling. A major drawback is its relatively weak reducing strength, only capable of reducing the most reactive functional groups like imines, aldehydes, ketones and acyl chlorides.[74]

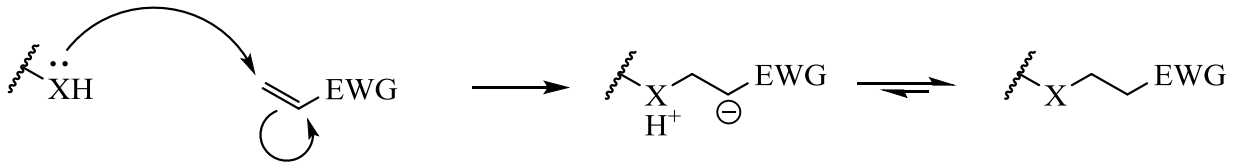
Sodium borohydride is a source of nucleophilic hydride-ions, the reactivity of which can be enhanced by the addition of methanol.[75,76] When alcohols react with sodium borohydride, various alkoxy hydroborates are produced. These intermediate species possess greater reducing capabilities than the original borohydride due to the electron-donating ability of the alkoxy group (Scheme X). The reaction will eventually lead to alkyl borate, quenching the reductive hydroborate intermediates.



Scheme 16. Reaction between simple alcohols and the borohydride ion. The electron-donating ability of the alkoxy-groups increases the nucleophilicity of the hydride-ions.

1.4.4 Michael addition

Michael addition allows for the introduction of alkyl chains with an electron-withdrawing group three carbons away from the nucleophile (Scheme 17). Typically the functional group is a carbonyl, but also other groups such as nitriles and nitro-groups are used. Although the traditional Michael addition is a conjugate addition of an α,β-unsaturated carbonyl compound to the enolate of a ketone or aldehyde, any nucleophile undergoing 1,4-addition will be referred to as a Michael-type reaction in this thesis.



Scheme 17. Mechanism of conjugate addition.

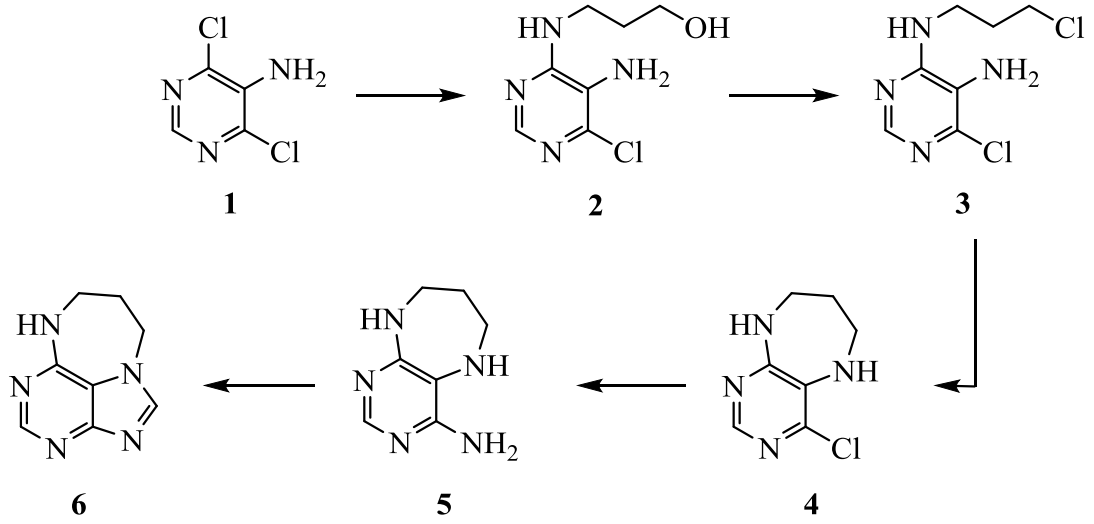
Conjugate addition is favorable with moderate to soft nucleophiles like amines, thiols and malonates.[62] This makes purines excellent substrates for Michael-type additions.[77-80]

2. SYNTHESIS

This section will cover all chemistry done in the Master's project.

2.1 Synthesis of THDAPs using strategy *e*

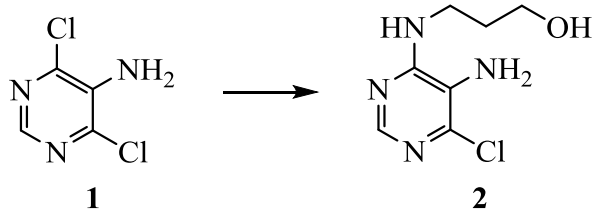
The proposed synthetic route is outlined in Scheme 18. This route was selected in order to test whether or not a pyrimidine-derivative would act differently than its purine analog in the cyclization step previously reported to occur on N-1.[45]



Scheme 18. Original synthetic route.

2.1.1 Synthesis of 3-((5-amino-6-chloropyrimidin-4-yl)amino)propan-1-ol (2)

5-amino-4,6-dichloropyrimidine **1** was reacted with 3-amino-1-propanol through a nucleophilic aromatic substitution to form 3-((5-amino-6-chloropyrimidin-4-yl)amino)propan-1-ol **2** (Scheme 19). The reaction is reported in the literature. [81,82]

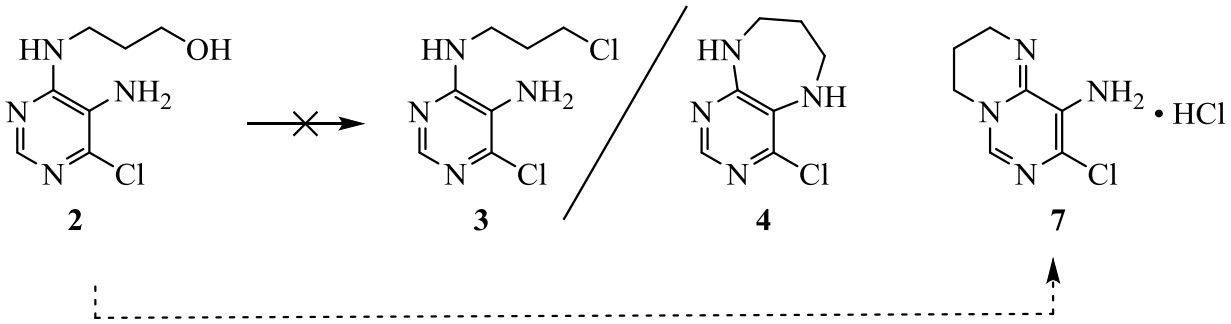


Scheme 19. Reagents and conditions: 3-Aminopropan-1-ol, 1,4-dioxane, 90 °C, 20 h.

Using an excess of 3-amino-1-propanol, the reaction shows complete conversion after about 20 hours at 90 °C. ^{1}H NMR- and TLC-analysis reveal the reaction produces a single product **2**. Yields usually lie between 50 – 65 % when purifying by recrystallization, somewhat less than the reported literature values of 80 – 81 %. Recrystallization from water, as reported in the literature,[81,82] affords the monohydrate not suitable for further chemistry without extensive drying. Purifying the product using flash column chromatography instead of recrystallization increases the yield to 92 % and avoids the need to remove water from the product.

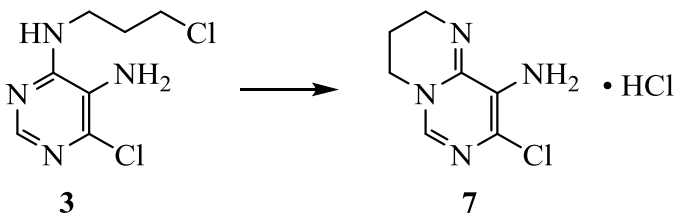
2.1.2 8-chloro-3,4-dihydro-2H-pyrimido[1,6-a]pyrimidin-9-amine hydrochloride (7)

Analogous to the scheme used by Kashman et al.[45], compound **2** was treated with thionyl chloride. Although a likely intermediate, compound **3** was not isolated as ring-closure occurred spontaneously. However, the intended product **4** was not observed. Instead, ring-closure took place on *N*-1 affording compound **7** as the hydrochloride salt (Scheme 20).



Scheme 20. Reagents and conditions: $SOCl_2$, THF, 1 hour at 0 °C then 1.5 hours at r.t.

Monitoring the reaction by TLC, full conversion is seen after 2 hours producing two main spots, one of which resides on the baseline eluting with DCM:MeOH (94:6). NMR analysis of the crude reaction mixture shows two products in a 2:1 ratio with compound **7** being the major. Upon standing, the minor compound gradually disappears over the course of a few days at room temperature in the NMR tube, leaving compound **7** as the sole product. MS analysis shows a peak corresponding to compound **3** (Scheme 21), which is the proposed reactive molecule producing compound **2** over time. Stirring the evaporated reaction mixture in THF at room temperature for three days produces product **7** in quantitative yields.



Scheme 21. Conditions: THF, r.t., 3 days.

When triethylamine is added to keep the pH level of the reaction solution more stable, no traces of compound **3** can be spotted either by MS, TLC or ^{1}H NMR analysis. This is likely due to a lower proportion of reactant molecules in a protonated state and thus more likely to act as nucleophiles (Figure 9).

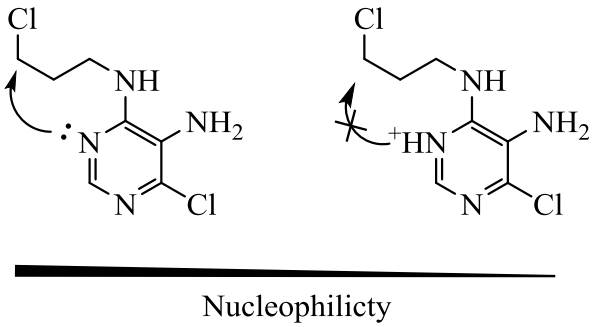
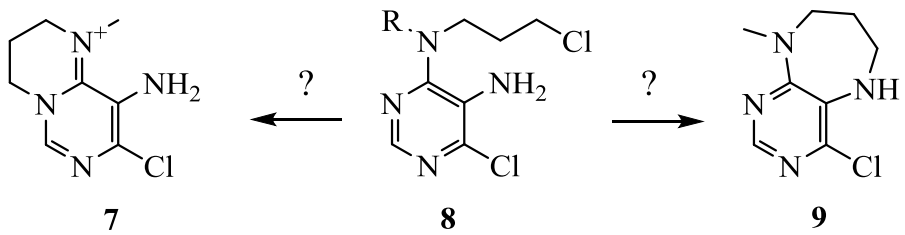


Figure 9. Protonation decreases the propensity of nucleophilic attack.

2.1.3 Substrate modification

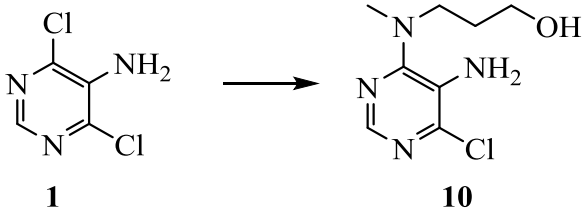
A similar reaction pathway was attempted, substituting 3-aminopropan-1-ol with 3-(methylamino)propan-1-ol to test the effect of the methyl group on the reaction outcome. Since ring-closure at the *N*-1 position in this case would produce a permanently charged product, it was anticipated that this would alter the dynamics of the reaction in such a way as to produce the neutral seven-membered ring-closed product instead (Scheme 22).



Scheme 22. Possible reaction directions after introduction of methyl-substituent.

2.1.4 Synthesis of 3-((5-amino-6-chloropyrimidin-4-yl)(methyl)amino)propan-1-ol (10)

3-((5-Amino-6-chloropyrimidin-4-yl)(methyl)amino)propan-1-ol (**10**) was prepared in the same manner as compound **2** (Scheme 23).

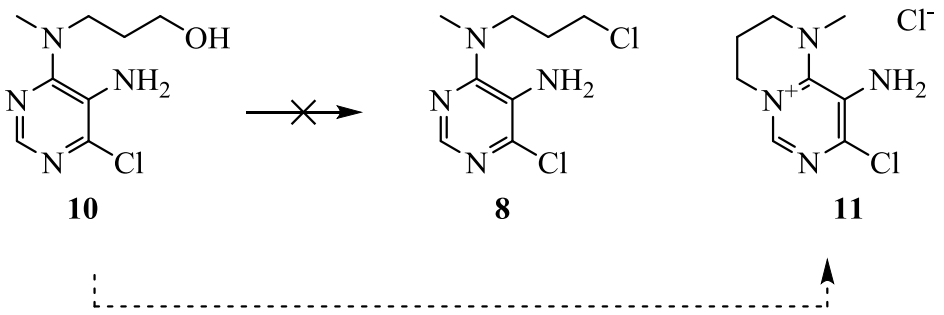


Scheme 23. Reagents and conditions: 3-Methylaminopropan-1-ol, 1,4-dioxane, 20 h., reflux.

Complete conversion is observed after 20 h by TLC-analysis, showing one big product spot along with other minor spots of higher polarity. The yield is excellent (96 %).

2.1.5 Synthesis of 9-amino-8-chloro-1-methyl-1,2,3,4-tetrahydropyrimido[1,6-a]pyrimidinium chloride (11)

Treating compound **10** with thionyl chloride, analogous to the reaction in Scheme 20, did not produce the desired seven-membered product **9**. Also this reaction afforded the *N*-1 ring-closed compound (Scheme 24).



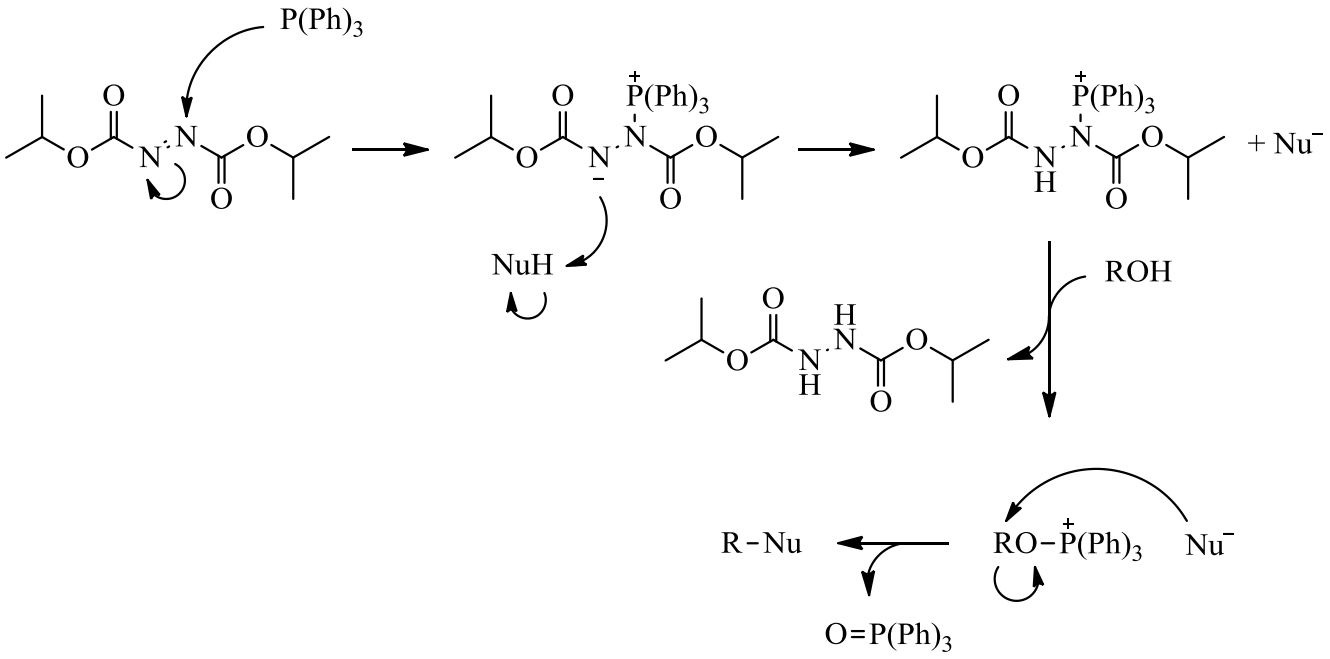
Scheme 24. Reagents and conditions: $SOCl_2$, THF, 90 min. at 0 °C then 1 h at r.t.

Yet again the crude NMR spectra showed a major product and a minor one (~14:1) disappearing over time. This time, the spectrum didn't clear up quite as cleanly as the reaction in scheme 21 upon standing. Purification of the salt was difficult.

2.1.6 Attempted ring-closure of 3-((5-amino-6-chloropyrimidin-4-yl)amino)propan-1-ol (2) under Mitsunobu conditions

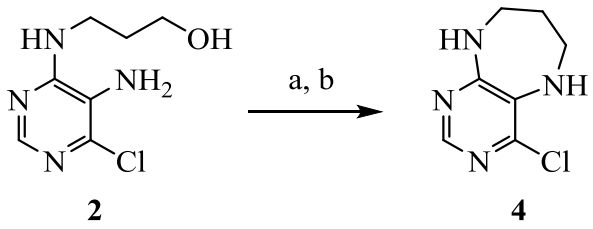
After the lack of success following the original scheme, where cyclization is brought about by a two-step process of leaving group transformation and subsequent alkylation, an attempt at uniting the two by virtue of the *Mitsunobu reaction* was made.

The Mitsunobu reaction has gained widespread popularity as an effective way to displace hydroxyl groups with a variety of nucleophiles.[83-85] The proposed mechanism is outlined in Scheme 25.



Scheme 25. Mechanism of the Mitsunobu reation.[83]

Compound **2** failed to produce any product under two common variations to the conditions of the Mitsunobu reaction (Scheme 26).



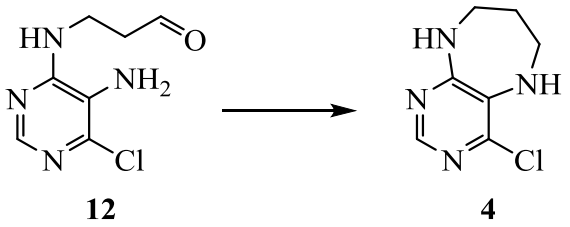
2 **4**

Scheme 26. Reagents and conditions: **a** – A solution of **2a** and triphenylphosphine (1.1 eq.) in THF was added slowly to a solution of DIAD (1.1 eq.) in THF at 0 °C over 35 min., warmed to r.t. and stirred for 3 h. **b** – A solution of **2a** in THF was added slowly to a pre-made solution of DIAD (1.1 eq.) and triphenylphosphine (1.6 eq.) in THF at 0 °C over 30 min., heated to reflux and stirred for 18 h.

In both instances (a and b of Scheme 26), only starting material could be observed by NMR analysis of the crude reaction mixture. An explanation for this lack of reactivity may be that the pK_a of the nucleophilic primary aryl nitrogen is not sufficiently low to allow deprotonation by the formed betaine (step 2, Scheme 25) thus preventing any further reaction. This limitation is well-known in the literature.[86,87]

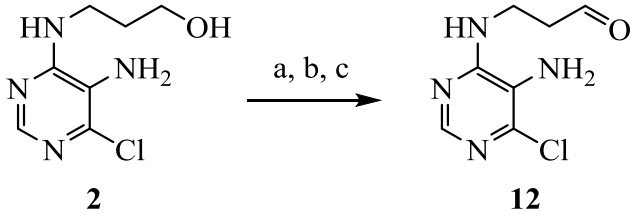
2.1.7 Attempted oxidations of 3-((5-amino-6-chloropyrimidin-4-yl)amino)propan-1-ol (2)

A few attempts at oxidizing compound **2** to the corresponding aldehyde **9** were made. The objective was to ring-close by reductive amination (Scheme 27).



Scheme 27. Ring-closure by reductive amination.

Three oxidation strategies were tried: Swern oxidation, Dess-Martin oxidation and oxidation using pyridinium chlorochromate (Scheme 28).

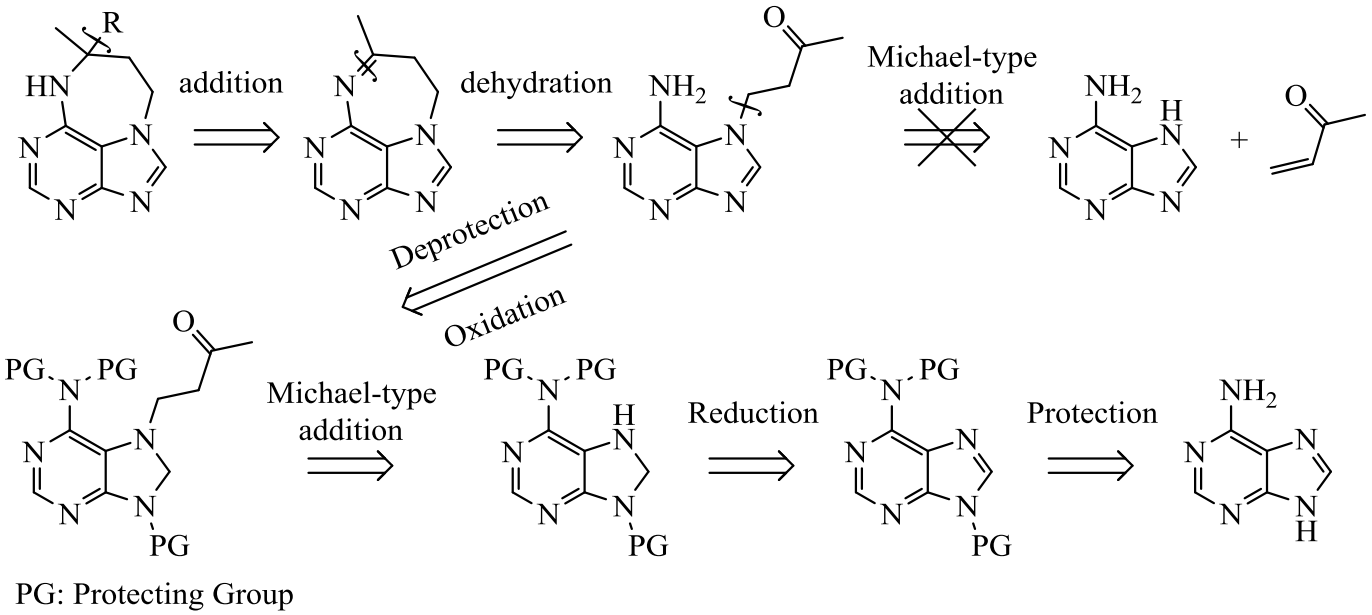


Scheme 28. Reagents and conditions: **a** – DMSO, oxalyl chloride, triethylamine, THF, 1.5 h. at -78 °C then 24 h. at r.t. **b** – Dess-Martin Periodinane, THF, 30 min. at 0 °C then 24 h. at r.t. **c** – Pyridinium chlorochromate, DCM/THF, 4 h. at r.t.

The Swern oxidation produced an array of unidentified products and no amount of the desired aldehyde **12** was observable in the crude reaction mixture by either NMR or MSanalysis. Other possible products such as the ring-closed imine analog of compound **4** or the ring-closed enamine analog of compound **7** were not found either. Common side-products of Swern oxidations are methylthiomethyl ethers resulting from a pummerer-type rearrangement of the ylide.[88,89] No such side-products were observed. Oxidation by Dess-Martin periodinane failed to produce any of the desired aldehyde **12**. Immediately after addition of the periodinane, a sudden change of color to a deep red was observed. TLC-analysis of the reaction showed a large array of highly polar compounds on or close to the baseline eluting with DCM in MeOH (9:1). Due to the large number of inseparable products, identification was difficult. Oxidation using pyridinium chlorochromate also produced a vast number of highly polar compounds difficult to analyze

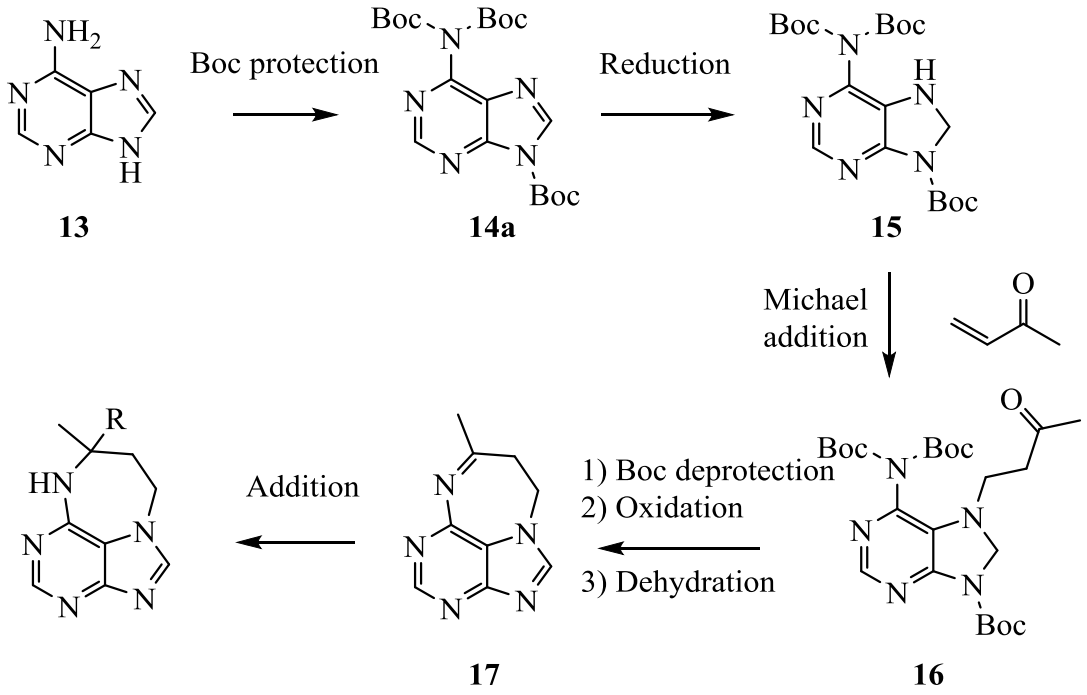
2.2 Synthesis of THDAPs using Strategy *b*

A different approach to the ring-closure of the diazepine ring was conceived starting from commercially available adenine (Scheme 30). Based on strategy *b* (Figure 7), the new synthetic route would ring-close by intramolecular imine-formation. The imine-functionality allows for nucleophilic addition on C-9 forming substituted 9-methyl-THDAPs as found in the asmarines. Having the C-9 carbon in the +II oxidation state not only allows for nucleophilic addition, but also means that the alkyl-chain can be introduced via a Michael-type addition on *N*-7.



Scheme 29. Retrosynthetic analysis of a strategy *b*-type synthetic route.

Adenine itself does not selectively produce *N*-7 alkylated products under Michael conditions as the *N*-9 isomers are favored.[44,90] This can be mitigated through the use of protecting groups. In order to retain a neutral *N*-9 protected, *N*-7 alkylated compound, a reduction/oxidation is required after protection/deprotection. This allows for easier purification of products as well as milder conditions and possibly improved selectivity during Michael addition due to the increased nucleophilicity of the *N*-7 nitrogen. The new synthetic route is outlined in Scheme 31.

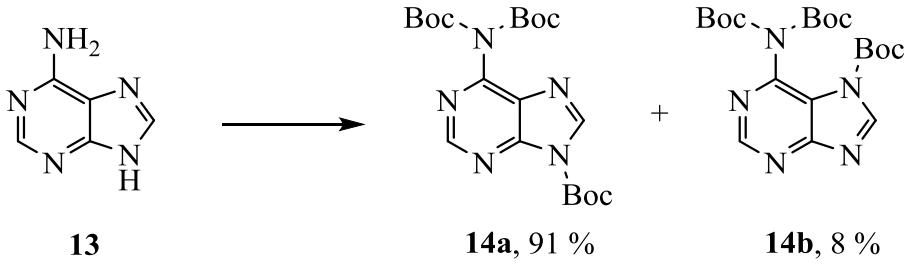


Scheme 30. Synthetic route based on strategy *b*.

The first step can be achieved following a literature procedure.[68] The reduction, Michael addition and subsequent deprotection/oxidation are based on procedures by Dvořák et al. used on similar substrates.[69]

2.2.1 Synthesis of tritert-butyl 9,10,10-adenineetricarboxylate (14a)

Tritert-butyl 9,10,10-adenineetricarboxylate **14a** was made by treating adenine **13** with di-tert-butyl dicarbonate in THF together with catalytic amounts of 4-dimethylaminopyridine (DMAP) (Scheme 32).

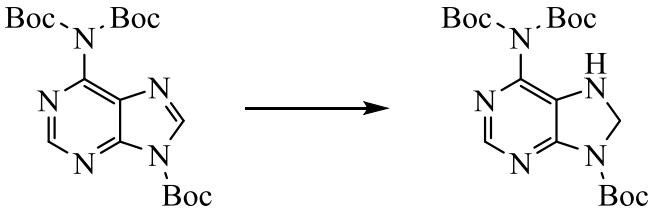


Scheme 31. Reagents and conditions: Di-*tert*-butyl dicarbonate, DMAP, THF, 22 h. at r.t.

The reaction was performed following the procedure reported by Dey and Garner.[68] The reaction time was increased from 8 to 22 hours as a second spot could be observed below the product-spot on TLC. The reaction was stopped after 22 hours at room temperature when the spot had reduced significantly in intensity. The yields (91 %) were near identical to the reported value (90 %). Additionally, 8 % of the *N*-7 substituted isomer **14b** was isolated. Formation of the *N*-7 isomer was not reported in the article by Dey and Garner, but is mentioned in an article by Ikonen and coworkers,[91] although not isolated by chromatographic means.

2.2.2 Synthesis of tert-butyl 6-(ditert-butoxycarbonylamino)-8,9-dihydropurine-9-carboxylate (15)

Compound **14a** was further reacted with a 1 molar borane tetrahydrofuran complex solution in THF reducing it to tert-butyl 6-(ditert-butoxycarbonylamino)-8,9-dihydropurine-9-carboxylate **15** (Scheme 33).



14a **15**, 78 %

Scheme 32. Reagents and conditions: BH_3•THF complex, THF, 2 h. at -78 °C then 18 h. at r.t.

The reaction was done using a modified procedure from Dvořák et al.[69] Yields are moderately high (78 %). ^{1}H NMR analysis of the crude reaction mixture indicates that the main impurity is starting material **14a**. Increasing the amount of reducing agent (from 1.4 eq. to 2.5 eq.) or the reaction time does not change the outcome. TLC analysis of the reaction mixture shows three large spots, two of which matches the product and starting material. Spotting the TLC-plate and letting it sit in open atmosphere for 15 min. before elution eliminates the third spot. The third spot is likely to be some sort of borane-adduct either of the starting material or the product. Leaving

the compound in solution at room temperature with access to air will slowly oxidize it back to compound **14a** (Figure 10).

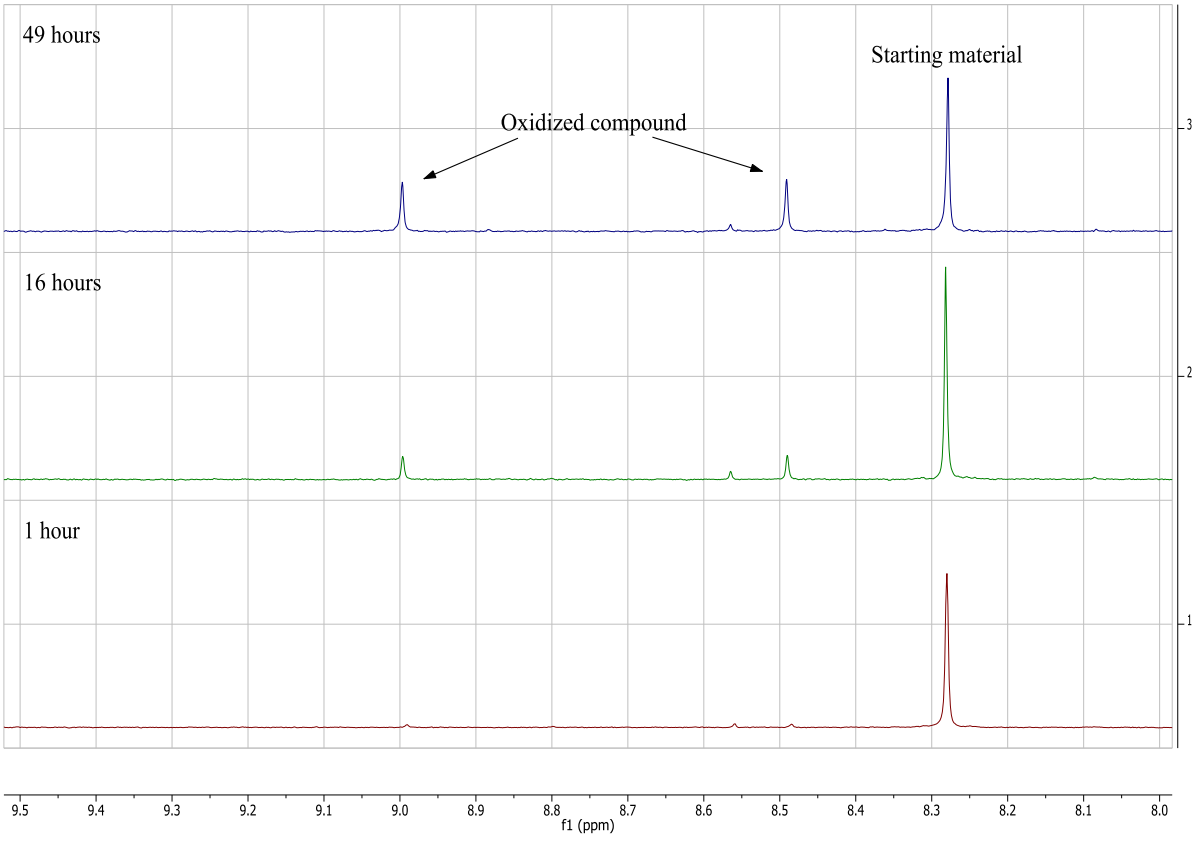
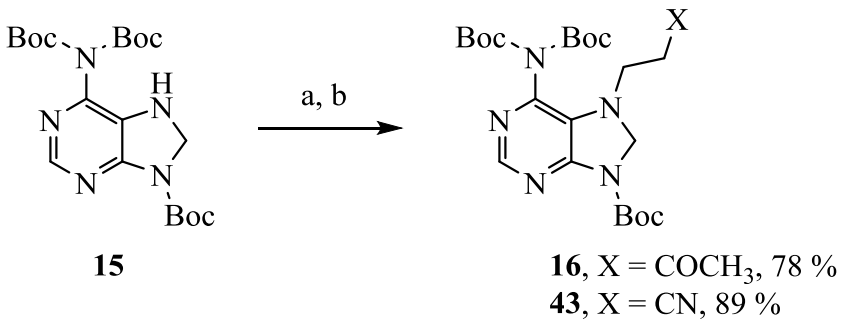


Figure 10. Figure showing the oxidation of compound **15** over 2 days.

2.2.3 Synthesis of tert-butyl 6-(ditert-butoxycarbonylamino)-7-(3-oxobutyl)-8,9-dihydropurine-9-carboxylate (16) and tert-butyl 7-(2-cyanoethyl)-6-(ditert-butoxycarbonylamino)-8,9-dihydropurine-9-carboxylate (43)

In addition to substrate **16** needed in the synthetic scheme, compound **43** was synthesized under similar conditions as a proof-of-concept.

Michael addition of **15** with but-3-en-2-one or acrylonitrile in acetonitrile produced the *N*-7 substituted tris boc-protected adenine **16** or **43** (Scheme 34).



Scheme 33. Reagents and conditions: **a** – (X = $COCH_3$), But-3-en-2-one, DBU, MeCN, 5 h at r.t. **b** – (X = CN), Acrylonitrile, DBU, MeCN, 5 hours at r.t.

These reaction conditions are also based on the procedure reported by Dvořák et al.[69] and in the case of compound **16**, modified by Urs Fabian Fritze.[92] Fritze found that slow addition of diluted but-3-en-2-one to a solution of **15** in acetonitrile together with 1.1 eq. of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was needed to obtain satisfactory yields of compound **16**. Moderately high yields of compound **16** (78 %) were obtained in this project. Unreacted starting material accounts for 7 mol% by ^{1}H NMR analysis of the crude reaction mixture with no other impurities present in sufficient amount. No further attempts to increase the yield were made.

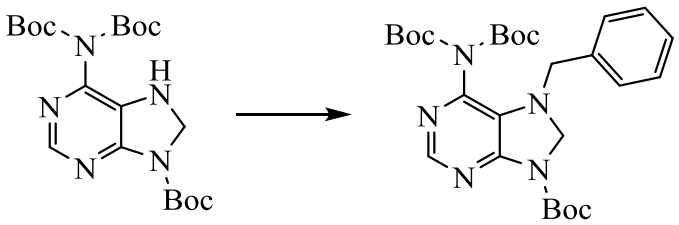
For compound **43**, it was found that slow addition of acrylonitrile was not necessary. The reaction proceeded cleanly to the product in high yields (89 %).

2.2.4 Synthesis of 9-methoxy-9-methyl-7,8,9,10-tetrahydro-[1,4]diazepino[1,2,3-gh]purinium 2,2,2-trifluoroacetate (18)

Early attempts to deprotect **16** using the standard procedure with trifluoroacetic acid in dichloromethane (1:1) produced a complicated mixture of products. Judging the outcome of the reaction from NMR-analysis of the crude reaction mixture was difficult and standard flash column chromatographic techniques on silica were problematic due to the highly polar nature of these compounds. To overcome this problem, a test-substrate carrying a non-reactive, lipophilic *N*-7 substituent was made to determine the appropriate reaction conditions for complete removal of all three Boc-groups using the least amount of potentially destructive acid. This made it possible to study the behavior of the Boc-groups under acidic conditions without any potential

interference of the *N*-7 oxo-butyl group. A lipophilic *N*-7 substituent in the test-system would simplify purification.

The test-system used was the *N*-7 benzylated analog **19** (Scheme 35)**.** Compound **19** was made from compound **15** by deprotonation with lithium hexamethyldisilazide (LiHMDS) in a mixture of THF and DMF at -78 °C followed by addition of benzyl bromide and subsequent warming to room temperature.

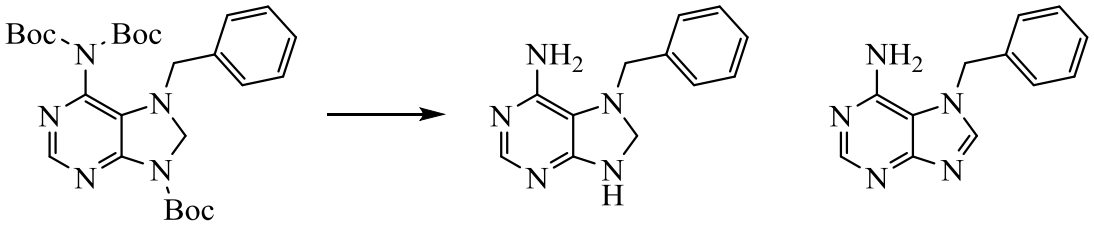


15 **19,** 85 %

Scheme 34. Reagents and conditions: LiHMDS, benzyl bromide, DMF/THF, 30 min. at -78 °C then 15 min. at r.t.

The procedure was taken from Dvořák et al.[69] and produced high yields (85 %) of the *N*-7 benzylated product **19**.

The deprotection of compound **19** with trifluoroacetic acid in dichloromethane afforded the oxidized compound 7-benzyladenine **21** (Scheme 36).

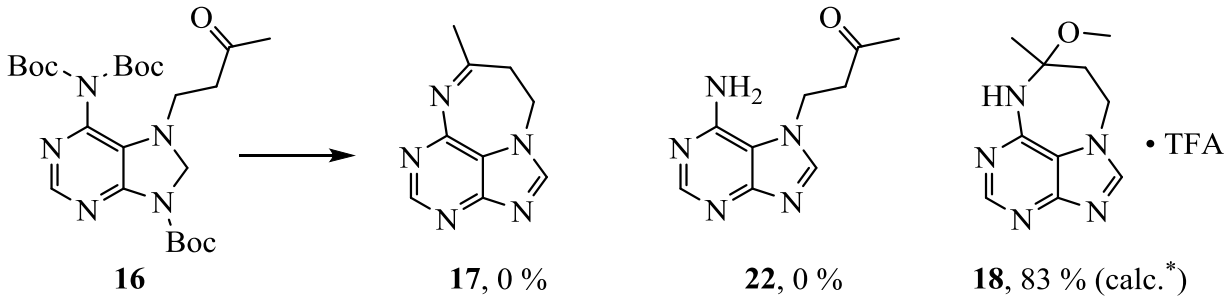


19 **20**, 0 % **21**, 84 %

Scheme 35. Reagents and conditions: **a** – DCM/TFA (5:1), 1 hour at r.t.

It was found that stirring the tris boc-protected substrate **19** in 17 % trifluoroacetic acid in dichloromethane for an hour at room temperature was enough to fully deprotect the compound. The 8,9-dihydropurine product **20** was not isolated. Instead, the oxidized compound **21** was obtained in high yields (84 %). Dihydropurines bearing electron-donating substituents in the 6-position are reportedly prone to oxidation.[93]

The Boc-deprotection of **16** was reattempted with the same acid-concentration as used in the test-system (Scheme 37). The reaction was performed under stringent anhydrous conditions together with freshly prepared molecular sieves in an attempt to produce the Schiff base **17** to increase lipophilicity and improve the chances of isolation.



16 **17**, 0 % **22**, 0 % **18**, 83 % (calc.*)

Scheme 36. Reagents and conditions: 1) DCM/TFA (5:1), Molecular sieves 3Å, 1 h at r.t. 2) MnO_2, DCM/THF, 5 h at r.t. 3) MeOH.

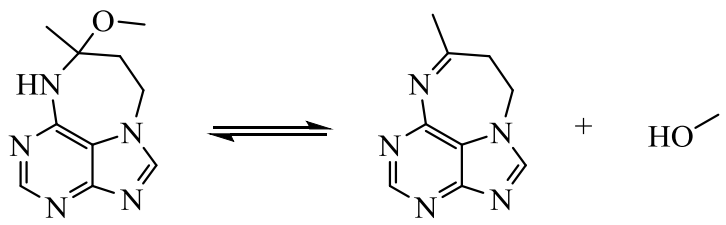
TLC analysis (DCM:MeOH – 9:1) of the crude reaction mixture produced two spots. Purification by flash column chromatography gave small amounts of compound **18** (18 %, calculated *) while no amount of imine **17** could be observed. It seemed that methanol from the eluent-system had added to the imine producing the hemiaminal ether **18** as a salt of trifluoroacetic acid.

NMR analysis of the separated second spot (by flash column chromatography on silica gel) showed that it contained several other compounds. Ketone **22** is likely to be one of these compounds. Experiments to convert compound **18** to ketone **22** by addition of water has been carried out, and NMR, MS and TLC analysis suggests compound **22** is produced but not as the sole product and separation by flash column chromatography was unsuccessful.

*Yields were calculated by taking the weight of isolated material and subtracting the amount of methanol present based on ^{1}H NMR analysis.

As no other methanol-free eluent-systems polar enough to move the produced compounds off the baseline (TLC) could be found, it was decided to add methanol to the crude in order to achieve full conversion to compound **18**.

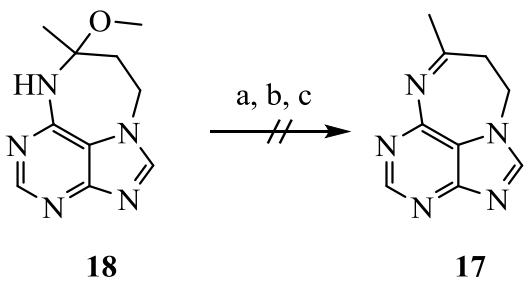
Compound **18** is, however, not very stable and decomposes into several unidentified compounds over the course of a couple of days even under inert atmosphere. It is also highly hygroscopic and even deliquescent. This poses a problem when handling the compound as the water it absorbs from the atmosphere decomposes it. However, it is stable as a solution in methanol, showing little degradation after several months. Only a calculated yield of 83 % (see previous footnote*) has been achieved as methanol is still present. Evaporating the methanol completely leaves the compound partially decomposed. Exchange of the 9-methoxy-group is seen when leaving the compound in deuterated methanol. This suggests the existence of an equilibrium between hemiaminal ether **x** and imine **x** which could explain the observed decomposition (Scheme 38).



18 **17**

Scheme 37. Possible equilibrium between hemiaminal ether (**18**) and imine (**17**).

Several attempts to convert hemiaminal ether **18** to imine **17** were unsuccessful (Scheme 39). Three attempts, exploiting the proposed equilibrium by using azeotropic distillation to remove methanol and drive the equilibrium to the right, was attempted. Since methanol is miscible in both toluene and dichloromethane a traditional distillation setup was used instead of the usual Dean-Stark apparatus. While heating with added molecular sieves 3Å, dry solvent was added at regular intervals.



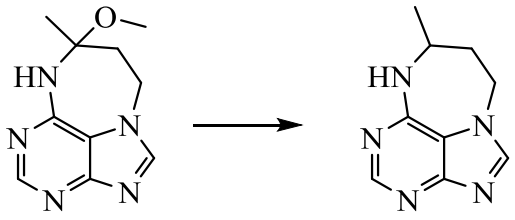
18 **17**

Scheme 38. Reagents and conditions: **a** – Toluene, molecular sieves 3Å, 8 hours at 75 °C. **b** – Dichloromethane, molecular sieves 3Å, 2 hours at 50 °C. **c** – 4-methylbenzenesulfonic acid, toluene, 12 hours at 80 °C.

Only partially decomposed starting material and no signs of a potential imine was observed (reaction a and b). An acid-catalyzed version of the azeotropic distillation was also attempted but resulted in severe decomposition to a wide array of unknown compounds.

2.2.5 Synthesis of 9-methyl-7,8,9,10-tetrahydro-[1,4]diazepino[1,2,3-gh]purine (23)

Even if compound **17** was not obtained, it was anticipated that the hemiaminal ether **18** could act as a *pseudoimine* and display some of the reactive properties one would expect of compound **17**. One such experiment was carried out by treating compound **18** with sodium borohydride in ethanol (Scheme 40).



18 **23**, 92 %

Scheme 39. Reagents and conditions: $NaBH_4$, EtOH, 24 hours at r.t.

Compound **23** was produced in very high yields (92 %). This asmarine analog has not been reported in the literature.

2.3 Sodium borohydride reductions in methanol

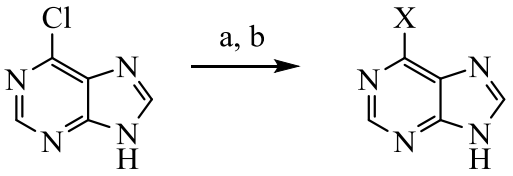
During work on the reduction of compound **14a** it was discovered that instead of the borane tetrahydrofuran complex solution used by Dvořák et al. in the reduction of Boc-protected 6-chloropurine and 6-iodopurine,[69] a simpler method using sodium borohydride in methanol could be employed.

Sodium borohydride has seen little use in the formation of 7,8-dihydropurines in the literature. Maki et al. reported reducing *N*-benzoyl-9-benzyladenine to the corresponding 7,8-dihydropurine by sodium borohydride in neat acetic acid.[94] Kelley and Linn[95] reduced 6-chloro-2-(trifluoromethy1)purine by sodium borohydride in refluxing THF while Pendergast and Hall[96] reduced several purines bearing electron-withdrawing substituents in the 6-position using sodium cyanoborohydride in dilute hydrochloric acid. The combination of sodium borohydride and methanol was used by Neiman in the reduction of 2,6-dichloro-7-methylpurine to the 8,9-dihydropurine.[97]

The use of sodium borohydride has some advantages over borane complexes such as BH_3•THF and BH_3•DMS. It is cheaper, easier to handle, less flammable and storable at room temperature without the need for stabilizers. Unlike the reported borane reactions, reductions using the sodium borohydride/methanol system can be carried out at room temperature in open atmosphere. Furthermore, all encountered side-products have been water-soluble and easily separable by simple extractions eliminating the need for chromatographic purification.

2.3.1 Synthesis of 6-methoxypurine (24) and 6-(piperidin-1-yl)purine (25)

6-Methoxypurine (**24**) and 6-(piperidin-1-yl)purine (**25**) was prepared by nucleophilic aromatic substitution of 6-chloropurine (Scheme 41).



24, X = OMe, 85 %
25, X = piperidin-1-yl, 95 %

Scheme 40. Reagents and conditions: **a** – (X = OMe), Na, MeOH, 24 hours at 65 °C. **b** – (X = piperidin-1-yl), Piperidine, *n*-BuOH, 18 hours at 100 °C.

Initial attempts to synthesize 6-methoxypurine **24** were done following literature procedures.[98,99] The different reaction conditions attempted are listed in Table 3.No product was observed from entry 1 and only minor amounts of product could be spotted in the crude reaction mixture of entry 2. Heating 6-chloropurine in a saturated solution of sodium methoxide in methanol prepared by adding sodium metal to methanol solved the problem (entry 3). The synthesis of compound **25** was achieved using a modified procedure by Caldwell et al.[100] with very high yields (95 %, entry 4).

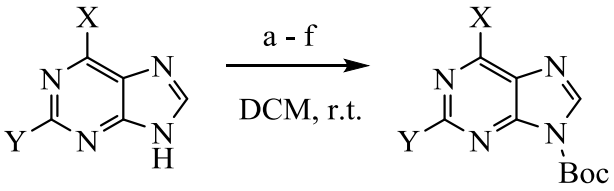
Table 3. Reagents, conditions and yields for the synthesis of 6-methoxypurine (**24**) and 6-(piperidin-1-yl)purine (**25**).

Entry	X	Solvent	Temperature (°C)	Reaction time (h)	Reagent	Yield (%)
1	OMe	DMF	[a]	[a]	NaOMe	-
2	OMe	MeOH	65	3	NaOMe	-
3	OMe	MeOH	65	24	Na	85 (**24**)
4	Piperidin-1-yl	*n*-BuOH	100	18	Piperidine	95 (**25**)

a – 5 min. at 90 °C (in microwave) then 30 min. at 120 °C (in microwave) then 3 days at 110 °C (oil bath).

2.3.2 Protection of substituted purines

All Boc-protections were carried out in DCM at room temperature using catalytic amounts of DMAP (Scheme 42).



X = Cl, Y = H — **26**, X = Cl, Y = H
X = I, Y = H — **27**, X = I, Y = H
24, X = OMe, Y = H — **28**, X = OMe, Y = H
25, X = piperidin-1-yl, Y = H — **29**, X = piperidin-1-yl, Y = H
X = Y = Cl — **30**, X = Y = Cl
X = Y = H — **31a**, X = Y = H

Scheme 41. Reagents and conditions: **a-f** – Table 4.

Table 4. Reagents, conditions and yields of the Boc-protection of substituted purines.

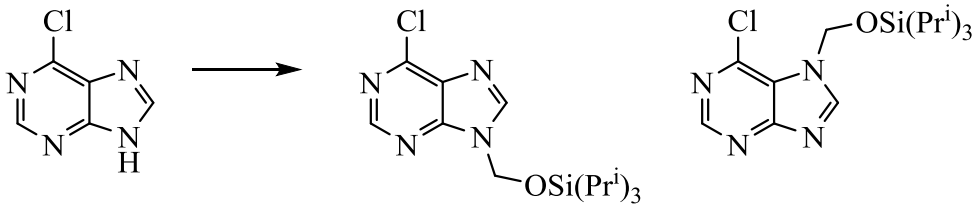
X	Y	Reaction time (h)	Eq. (Boc_2O)	DMAP (mol%)	Yield (%)
Cl	H	4	1.5	3.3	94 (**26**)
I	H	0.75	1.5	4.0	80 (**27**)
OMe	H	1	2.0	4.8	78 (**28**)
Piperidin-1-yl	H	0.5	2.5	4.9	93 (**29**)
Cl	Cl	2	2.0	5.0	87 (**30**)
H	H	2	2.0	5.5	84[a] (**31a** + **31b**)

a – Isolated as a mixture of *N*-9 (**31a**) and *N*-7 (**31b**) isomers (~1:3 respectively).

Yields are generally high (78 – 94 %). All compounds showed complete *N*-9 selectivity except for purine where it appears the *N*-7 Boc-protected compound (**31b**) is the thermodynamically favored product. However, the reaction was not completely *N*-7 selective in the reaction timeframe. Moreover, the *N*-7 protected compound displayed an R_f-value identical to that of the

N-9 protected isomer (**31a**) in all eluent-systems tested. As a result, a 1:3 mixture (**31a** to **31b**) was obtained after chromatographic purification on silica gel.

In addition to the Boc-protected analogs listed in Table 4 an *N*-9 substituted purine **32a** using a different protecting group was also prepared (Scheme 43). The silicon-based protecting was chosen as it can be cleaved under non-acidic conditions.[101]

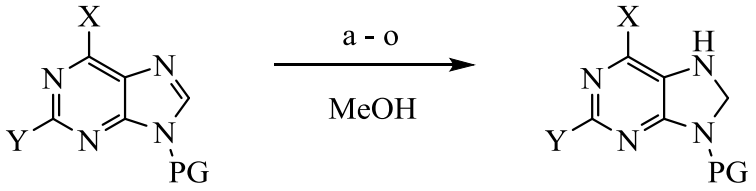


32a, 51 % **32b**, 36 %

Scheme 42. Reagents and conditions: $Si(Pr^i)_3OCH_2Cl$, Et_3N, DCM, 30 min. at r.t.

Unlike the Boc-protections, protection using (triisopropylsiloxy)methyl chloride displayed significantly reduced *N*-9 selectivity under these conditions giving a ratio of *N-9* to *N*-7 of roughly 7:5.

2.3.3 Reduction of N-9 protected purine analogs using sodium borohydride in methanol.



26, X = Cl, Y = H, PG = Boc
27, X = I, Y = H, PG = Boc
28, X = OMe, Y = H, PG = Boc
29, X = piperidin-1-yl, Y = H, PG = Boc
30, X = Y = Cl, PG = Boc
31a, X = Y = H, PG = Boc
32a, X = Cl, Y = H, PG = $CH_2OSi(Pr^i)_3$
33, X = Cl, Y = H, PG = THP

34, X = Cl, Y = H, PG = Boc
35, X = I, Y = H, PG = Boc
36, X = OMe, Y = H, PG = Boc
37, X = piperidin-1-yl, Y = H, PG = Boc
38, X = Y = Cl, PG = Boc
39a, X = Y = H, PG = Boc
40, X = Cl, Y = H, PG = $CH_2OSi(Pr^i)_3$
41, X = Cl, Y = H, PG = THP

Scheme 43. Reagents and conditions: **a-o** – Table 5.

The results from the reduction of protected purine substrates using the sodium borohydride/methanol-system (Scheme 44) are listed in Table 5.

Table 5. Products, conditions and yields for the $NaBH_4$/MeOH-reduction of protected purines.

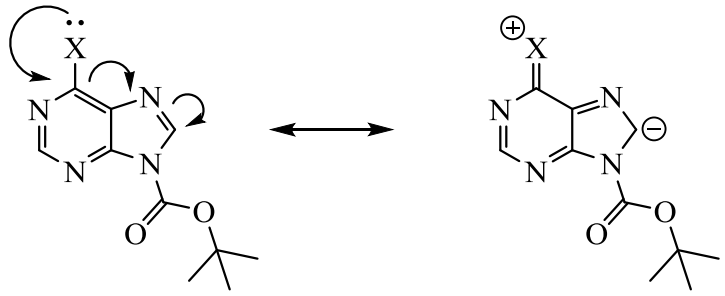
X	Y	PG	Eq. ($NaBH_4$)	Reaction time (min.)	Temperature	Yield (%)
Cl	H	Boc	2	15	r.t.	71
Cl	H	Boc	5	20	r.t.	85
I	H	Boc	2	20	r.t.	73
I	H	Boc	5	20	r.t.	76
$N(Boc)_2$	H	Boc	2	13	r.t.	81
$N(Boc)_2$	H	Boc	5	20	r.t.	84
OMe	H	Boc	2	30	r.t.	-
1-piperidinyl	H	Boc	2	20	r.t.	n.r.[a]
Cl	Cl	Boc	1.5	30	r.t.	63
H	H	Boc	2	20	r.t.	69[b]
Cl	H	THP	1.2	120	r.t.	n.r.
Cl	H	THP	2	40	65 °C	-
Cl	H	$CH_2OSi(Pr^i)_3$	2	300	r.t.	n.r.

a – No reaction. b – Isolated as a (1:3 mixture of *N*-9 to *N*-7).

Boc-protected purines carrying an electron-donating group in the 6-position (**x** and **x**) did not produce any of the desired 7,8-dihydropurines. Compound **28** was deprotected producing 6-methoxypurine **24** under the reaction conditions, while compound **29** failed to react at all. Purines protected by other groups than Boc (**32a** and **33**) also did not produce any reduced product.

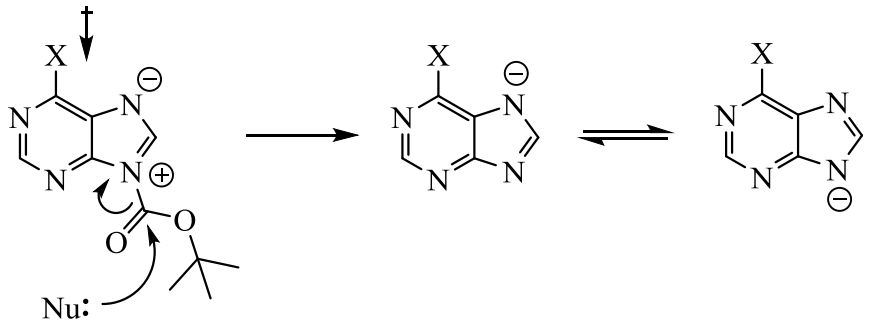
Boc-protected purines possessing either no or an electron-withdrawing substituent in the 6-position produce moderate to high yields of the corresponding *N*-9 protected 7,8-dihydropurine upon $NaBH_4$/MeOH-reduction. All compounds which underwent reduction also showed some degree of deprotection. Increasing the equivalents of sodium borohydride seems to have a small positive impact on the yields. Presumably, reduction is marginally the kinetic product.

The observed reactivity of the Boc-protected purines can be explained by considering the nature of the *C-6* substituent. Assuming the mechanism involves a nucleophilic attack on C-8, any electron-donating groups in the 6-position will contribute a partial negative charge on C-8 (Scheme 45).



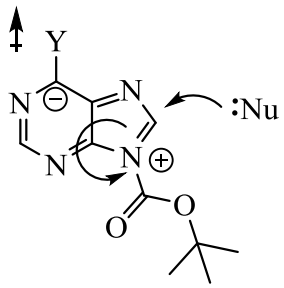
Scheme 44.

This positive mesomeric effect will repel nucleophilic attack on C-8. The stronger electron-donating ability of the dialkylamino group compared to the alkoxy-group can also explain the complete lack of reactivity of compound **29** while compound **28** showed deprotection of the Boc-group as deprotection would also involve a negative charge in the imidazole ring (Scheme 46).



Scheme 45.

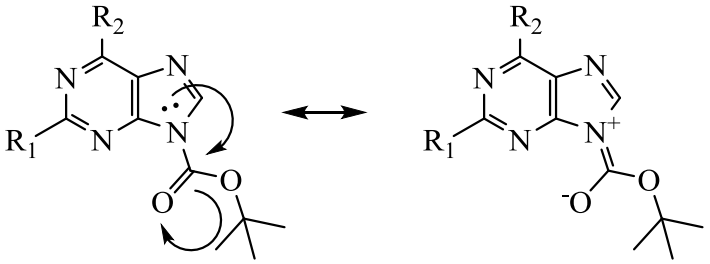
Contrariwise, an electron-withdrawing group in the *C-6* position will help stabilize negative charge in the pyrimidine ring making the imidazole ring comparably more electron-poor and disposed to nucleophilic attack (Scheme 47). These substrates are however still prone to nucleophilic deprotection.



Scheme 46.

The THP-protected compound **33** did not react at room temperature. Raising the temperature to force the reaction only resulted in nucleophilic aromatic substitution by the solvent furbishing 6-methoxy-9-(tetrahydropyran-2-yl)purine **42**. Expected to react the same way, compound **32a** was not tried reduced at elevated temperatures.

Scheme 48 explains how the Boc-group facilitates reduction. Its electron-withdrawing nature reduces the aromatic character of the imidazole ring, decreasing the energy needed to break aromaticity in order to afford the 7,8-dihydropurine.

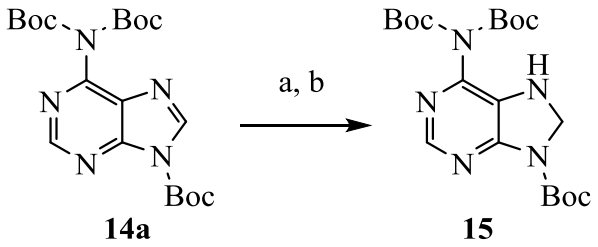


aromatic imidazole ring non-aromatic imidazole ring

Scheme 47.

2.3.4 Other solvents and reducing agents

Exchanging either the solvent or the reducing agent has a dramatic effect on the reaction (Scheme 49). Switching the solvent from methanol to THF significantly reduces the reaction rate and selectivity. The product is formed in the reaction, but only as a minor product along with several other partially deprotected isomers. The yield of reduced compound **15** was only 15 % from this reaction.



14a **15**

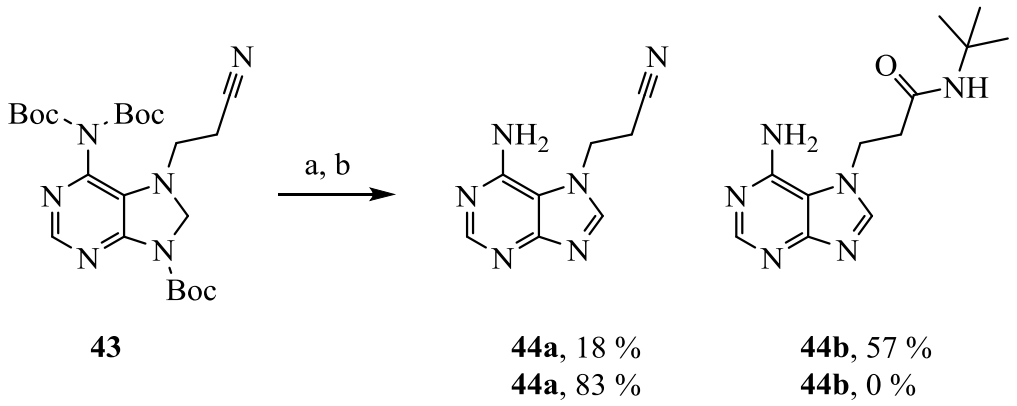
Scheme 48. Reagents and conditions: **a** – $NaBH_4$, THF, 2 days at r.t. **b** – $Na(CN)BH_3$, MeOH, 3 days at r.t. then 12 hours at reflux.

Keeping methanol as the solvent and replacing the reducing agent to the milder sodium cyanoborohydride, fails to induce any of the reaction at all. The apparent lack of reactivity using this reducing agent might be explained by the inability/reduced tendency of the cyanoborohydride ion to produce reactive intermediate alkoxy hydroborates species (Scheme 16) by virtue of the stabilizing electron-withdrawing nitrile group.

2.3.5 Synthesis of 3-(6-aminopurin-7-yl)propanenitrile (44a)

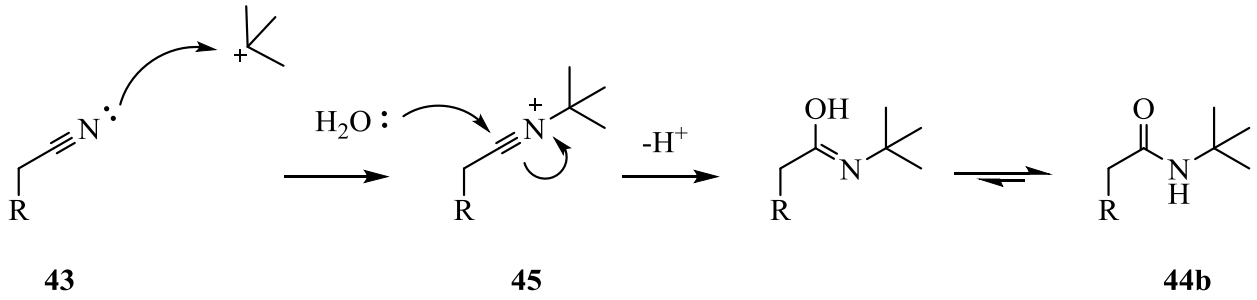
Continuing to explore the scope of the *N*-7 alkylation methodology used in this project, also compound **43** (synthesized in Section 2.2.3) was used as a substrate for the deprotection-conditions employed in Section 2.2.4.

Applying the same conditions as used in the deprotection of the tris-boc protected 7-benzyladenine **19**, the reaction produced two major spots on TLC (Scheme 50).



Scheme 49. Reagents and conditions: **a** – TFA, DCM, 20 hours at r.t. **b** – TFA, MeCN, DCM, 1 hour at r.t.

The product **44a** was indeed responsible for one of the spots seen by TLC-analysis of the reaction mixture. The other spot proved to be compound **44b**. A Ritter-type reaction had occurred,[102] converting the nitrile group into a *tert*-butyl amide. This happens as a result of the generated carbocations from the deprotection of the Boc-groups which attack the nitrogen in the nitrile group creating the electrophilic species **45** which converts to amide **44b** in the presence of water (Scheme 51).



Scheme 50. Mechanism of the Ritter reaction.

Although no water was present in the reaction mixture, exposure to atmospheric moisture was enough to convert the intermediate aminium-ion **45** to the corresponding amide **44b**.

Several reaction-conditions were tested in order to overcome this problem (Table 6). Typical carbocation scavengers like anisole, thioanisole and triethylsilane failed to affect the ratio of **44a** to **44b** much. One reaction was performed in water assuming that the carbocation would quickly be quenched producing *tert*-butanol. As anticipated, no amide **44b** was formed; however the reaction produced other unwanted compounds in addition to product **44a** failing to improve yields and complicating purification.

Table 6. Reagents, conditions and yields for the optimization of the synthesis of 3-(6-aminopurin-7-yl)propanenitrile **44a**.

Solvent	Reaction time (hours)	TFA concentration (vol%)	Additive	Yield, **44a** (%)	Yield, **44b** (%)	Yield, **43** (%)
DCM	2	17	-	-[a]	-[a]	-
DCM	20	44	-	18	57	-
DCM	20	10	-	46	32	-
DCM	24	24	Anisole	43	24	-
DCM	24	24	Thioanisole	22	17	-
DCM	24	24	Triethylsilane	50	31	-
THF	2	10[b]	H_2O	-[a]	-	-
MeCN	72	33	-	45	-	43
DCM	1	24	MeCN	83	-	-

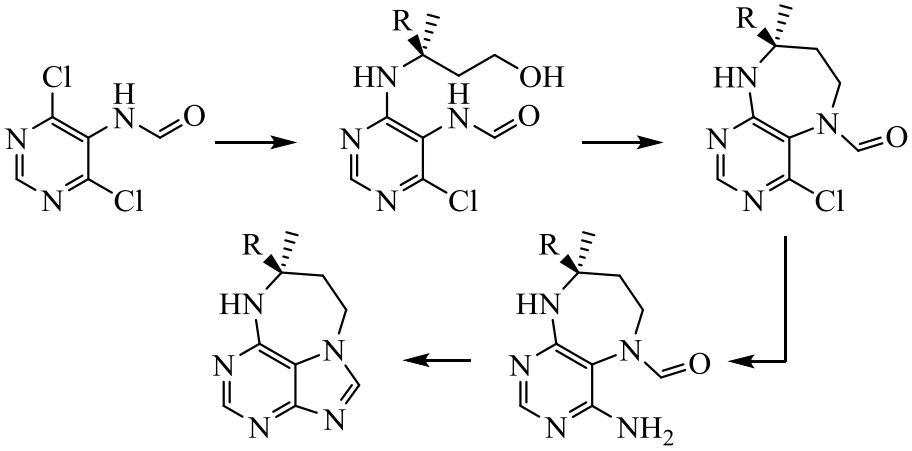
a – No yield due to impure fractions.

b – Hydrochloric acid was used instead of TFA.

It was found that formation of compound **44b** could be avoided by adding acetonitrile to the mixture producing high yields of nitrile **44a** (83 %). Presumably, a competition between the nitrile groups in the substrate and the acetonitrile for the Ritter-reaction minimized formation of compound **44b**. Running the reaction in acetonitrile as the only solvent severely impeded the rate of reaction.

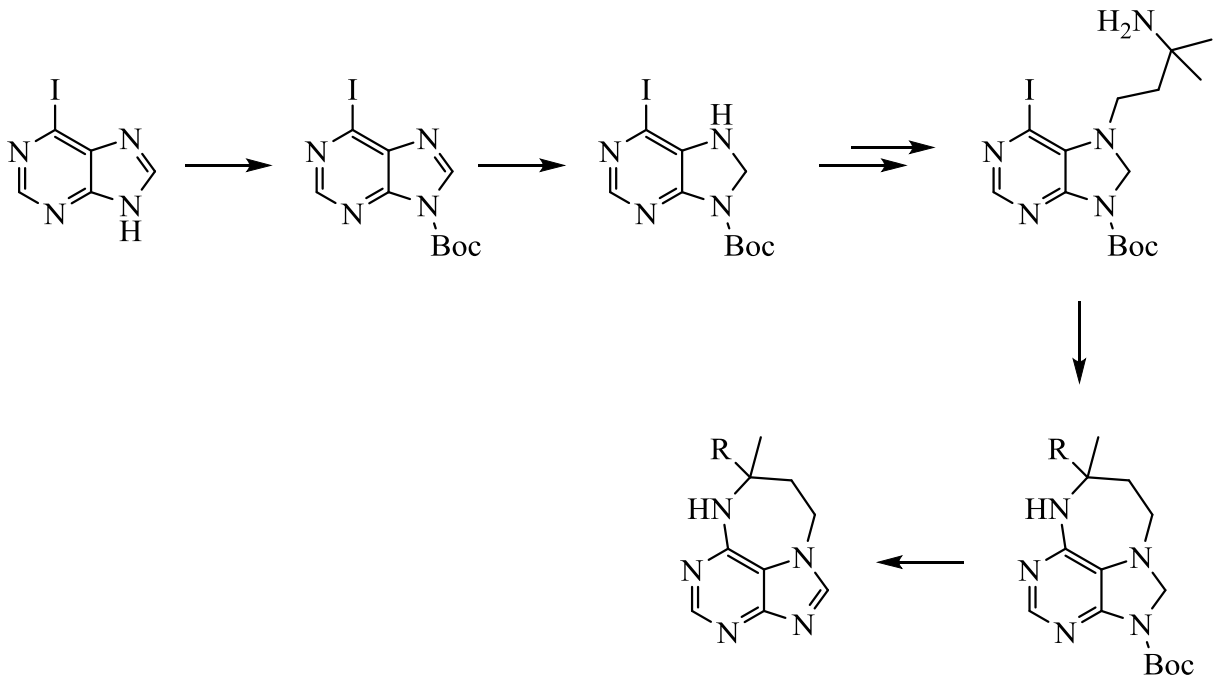
3. FURTHER RESEARCH

Difficulties encountered in the employment of strategy *e* in this project (Section 2.1), were largely due to either the lack of nucleophilicity or the lack of acidity of the 5-amino group in the pyrimidine ring. The latter issue can be mitigated by starting from a formamide instead of the free amino-group. This could allow for cyclization to occur under Mitsunobu conditions while simultaneously carrying functionality able to form the five-membered ring in later stages (Scheme 52).



Scheme 51. Possible synthetic route based on strategy *e* taking advantage of the acidity of the formamide group to achieve cyclization under Mitsunobu conditions.

Another interesting synthetic route worth investigating is the transition metal catalyzed cyclization under Buchwald-Hartwig conditions depicted in Scheme 52.



Scheme 52. Possible synthetic route based on strategy *a* by cross-coupling reaction.

4. CONCLUSION

It was demonstrated that cyclization of 6-substituted pyrimidine **2** under nucleophilic displacement of chloride preferentially occurs on *N*-1 affording the pyrimido[1,6-*a*]pyrimidine **7**. This is analogous to the reported results for the corresponding purine by Kashman et al.[45]

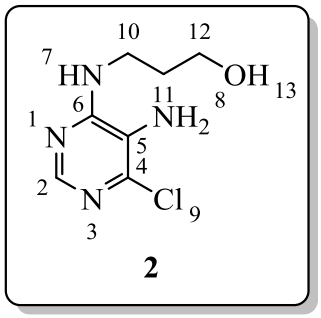
The formed hemiaminal ether **18** in strategy *b* (Section 2.2) is a possible interesting intermediate in the synthesis of substituted THDAPs. Its ability to undergo nucleophilic addition was demonstrated by the introduction of a hydride substituent. Whether other nucleophiles can act similarly remains to be seen.

A novel methodology for the reduction of electron-poor, *N*-9 Boc-protected purines forming important 7,8-dihydropurine intermediates was discovered employing the cheap and easy to handle reagent sodium borohydride under mild conditions. This is an important step in the synthesis of *N*-7 alkylated purines.

5. EXPERIMENTAL

^{1}H NMR spectra were recorded at 600 MHz with a Bruker AV600 instrument or a Bruker AVII600 instrument, at 500 MHz with a Bruker DRX500 instrument, at 400 MHz with a Bruker AVII400 instrument or at 200 MHz with a Bruker DPX200 instrument. The decoupled ^{13}C NMR spectra were recorded at 150, 125 or 100 MHz using the instruments mentioned above. All *J*-values are reported in Hertz. Mass spectra, under electron impact conditions, were recorded with a VG Prospec instrument at 70 eV ionizing voltage, and are presented as m/z (% rel. int.). HRMS-EI was performed with a double-focusing magnetic sector instrument mentioned above. Microwave experiments were carried out in sealed vessels in a synthesis reactor Monowave 300, Anton Paar GmbH, equipped with a Ruby thermometer and internal IR probe. Melting points were determined with a Büchi Melting Point B-545 apparatus and are uncorrected. Flash chromatography was performed on silica gel (Merck no. 09385). Dry DCM, THF, DMF and MeCN were obtained from solvent purification system, MB SPS-800 from MBraun, Garching, Germany. Hexanes were distilled before use. All other solvents and reagents were commercially available and used as received.

Synthesis of 3-((5-amino-6-chloropyrimidin-4-yl)amino)propan-1-ol (2)



2

5-Amino-4,6-dichloropyrimidine (0.852 g, 5.20 mmol) and 3-amino-1-propanol (1.17 g, 15.6 mmol) were dissolved in 1,4-dioxane (10 ml) and stirred at 90 °C for 20 hours. The solvent was removed *in vacuo* and the resulting red/brown oil was purified by flash column chromatography (DCM:MeOH – 93:7) affording a pale yellow solid.

Yield 973 mg (92 %) (lit. 80 – 81 %).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.72 (s, 1H, 2), 6.77 (t, *J* = 5.2 Hz, 1H, 7), 5.00 (s, 2H, 8), 4.49 (t, *J* = 5.1 Hz, 1H, 13), 3.50-3.45 (m, 2H, 12), 3.45-3.40 (m, 2H, 10), 1.71 (p, *J* = 6.7 Hz, 2H, 11).

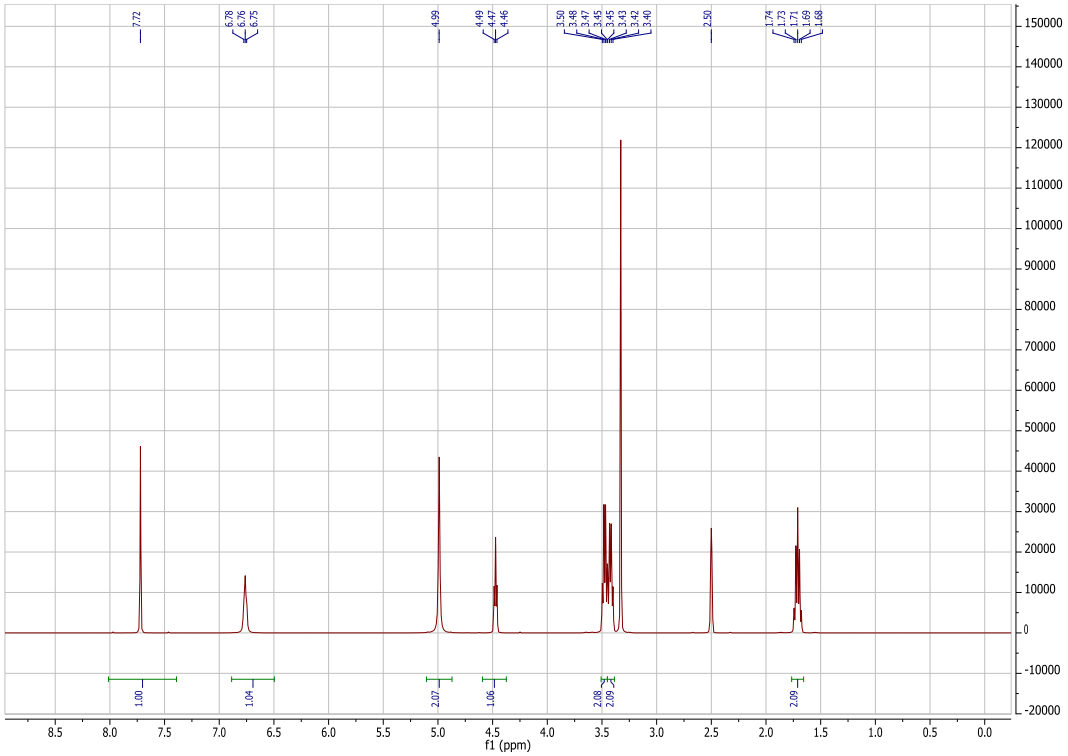
^{13}C NMR (DMSO-d_6, 100 MHz): δ 152.08 (6), 145.69 (2), 136.58 (4), 123.39 (5), 58.42 (12), 38.06 (10), 32.01 (11).

MS EI m/z (rel. %): 204/202 (20/60, M^+), 186/184 (3/11), 173/171 (24/72), 159/157 (45/100), 146/144 (15/47), 94 (28).

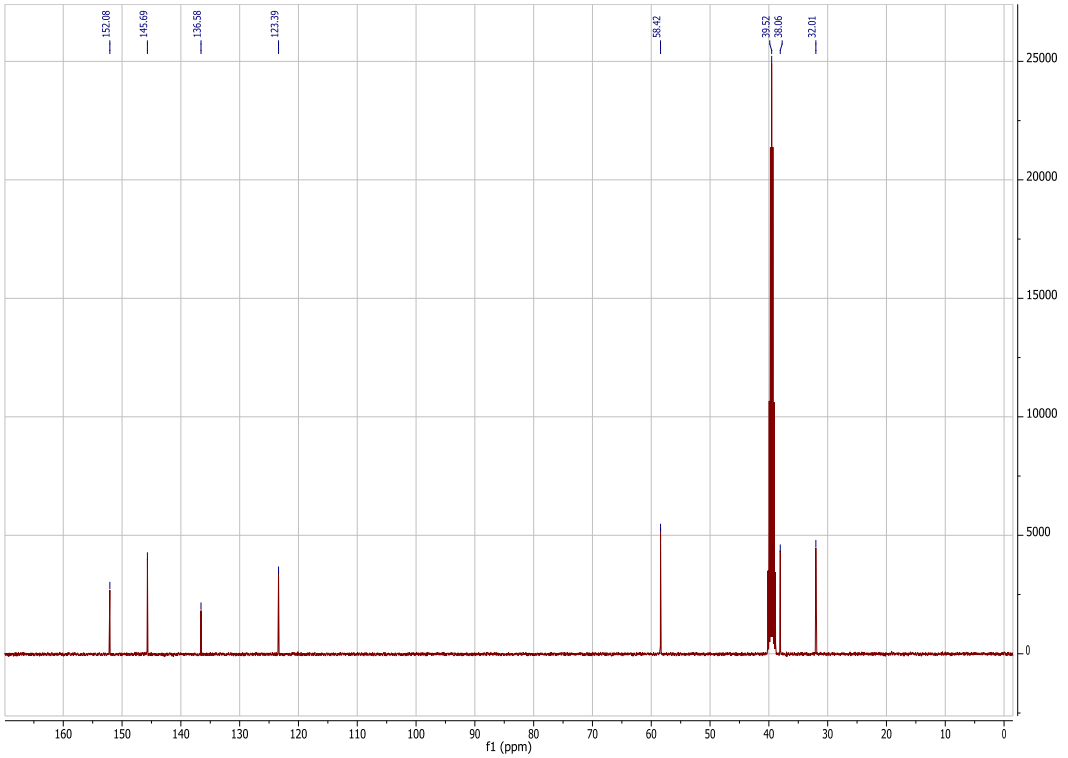
HR-MS Found 202.0626 calcd. for $C_7H_{11}ClN_4O$ 202.0621.

M.p., 106 °C, (86 – 87 °C as monohydrate (lit. 86 – 87 °C)).

Compound known in literature.[82]

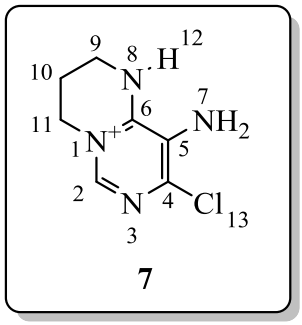


Spectrum 1. ^{1}H NMR (DMSO-d$_6$, 400 MHz) of 3-((5-amino-6-chloropyrimidin-4-yl)amino)propan-1-ol (**2**).



Spectrum 2. ^{13}C NMR (DMSO-d$_6$, 100 MHz) of 3-((5-amino-6-chloropyrimidin-4-yl)amino)propan-1-ol (**2**).

Synthesis of 8-chloro-3,4-dihydropyrimido[1,6-*a*]pyrimidin-9-amine hydrochloride (7)



7

3-((5-amino-6-chloropyrimidin-4-yl)amino)propan-1-ol (**2**) (400 mg, 1.97 mmol) was dissolved in THF (20 mL). Under an atmosphere of argon, the solution was cooled to 0 °C and thionyl chloride (430 µL, 5.92 mmol) was added dropwise through the septum over 5 min. The reaction mixture was stirred for 1 hour before it was allowed to warm to room temperature. The mixture was then stirred for an additional 1.5 hours at room temperature before the volatiles were removed *in vacuo*. The crude reaction mixture was dissolved in THF (30 mL) and MeOH (2 mL) and stirred at room temperature for three days before the volatiles were removed *in vacuo* affording 437 mg (quantitative) product as a brown powder.

^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.68 (bs, 1H, 12), 8.01 (s, 1H, 2), 6.55 (s, 2H, 7), 4.22 (t, *J* = 5.5 Hz, 2H, 11), 3.50 (t, *J* = 5.6 Hz, 2H, 9), 2.09 (m, 2H, 10).

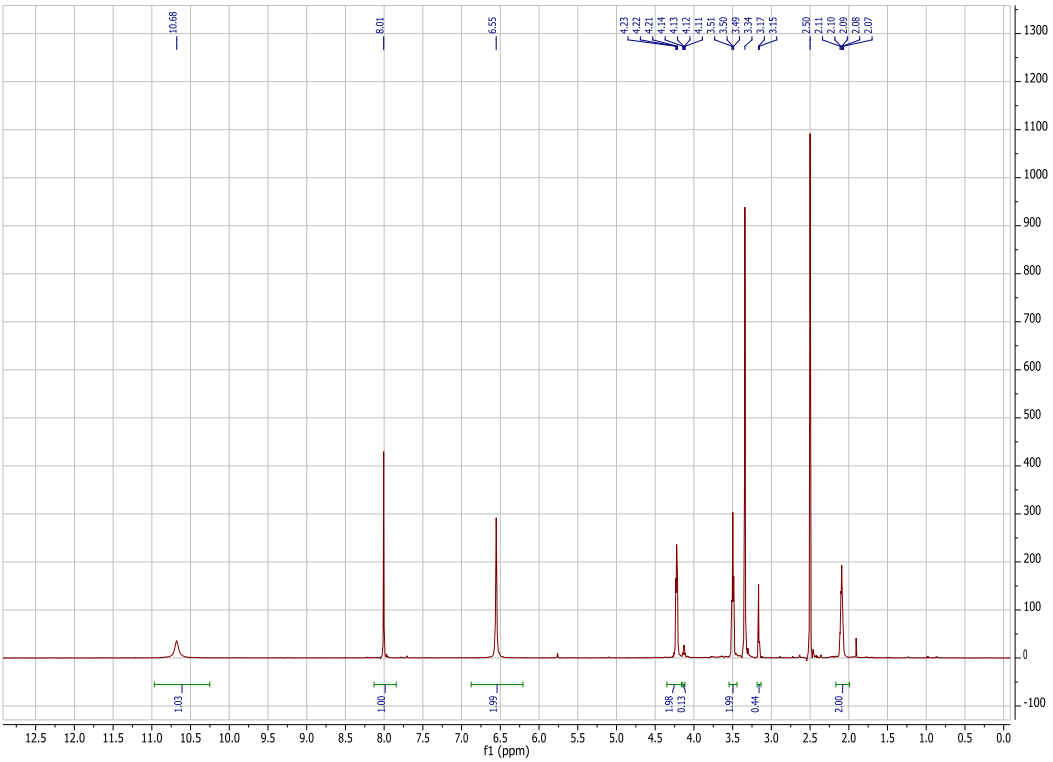
^{13}C NMR (DMSO-d_6, 125 MHz): δ 17.06 (10), 38.71 (9), 47.12 (11), 126.40 (5), 130.99 (4), 137.14 (2), 144.87 (6).

MS EI m/z (rel. %): 187/185 (9/71, M^+), 186/184 (23/81), 157 (100).

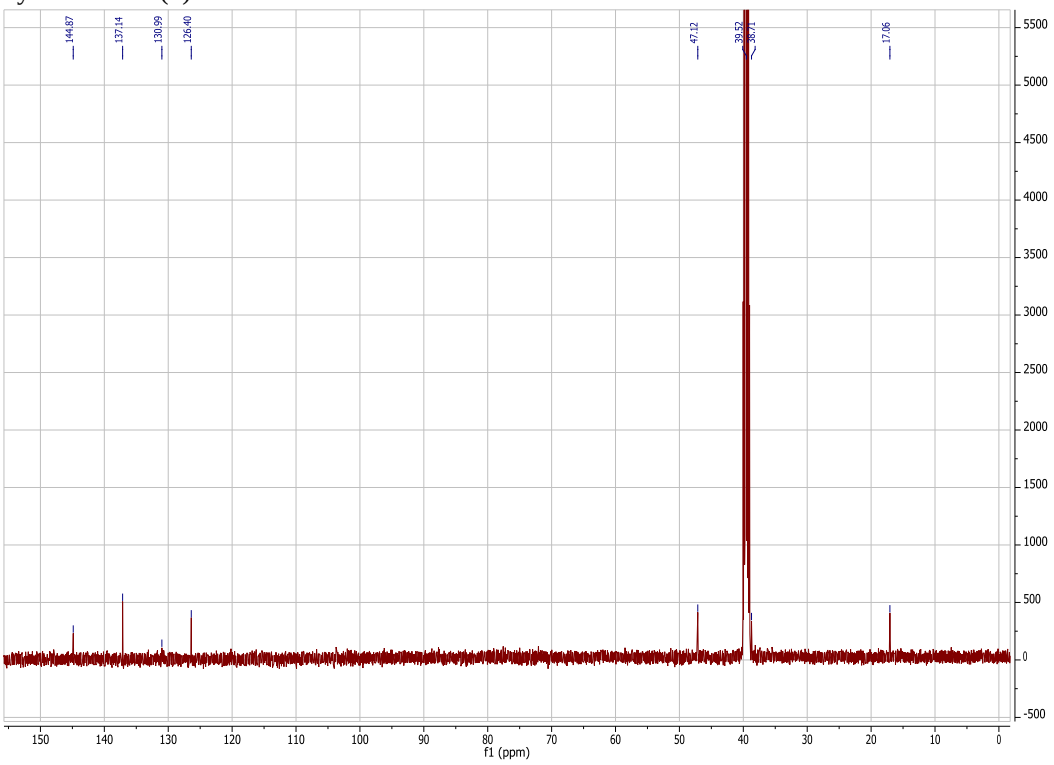
HR-MS Found 184.0515 calcd. for $C_7H_9ClN_4$ 184.0516.

M.p. 269 °C – 272 °C (dec.).

Compound not known in literature.

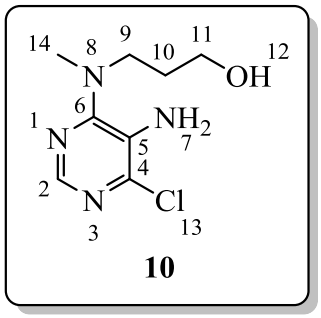


Spectrum 3. ^{1}H NMR (DMSO-d_6, 500 MHz) of 8-chloro-3,4-dihydropyrimido[1,6-*a*]pyrimidin-9-amine hydrochloride (**7**).



Spectrum 4. ^{13}C NMR (DMSO-d_6, 125 MHz) of 8-chloro-3,4-dihydropyrimido[1,6-*a*]pyrimidin-9-amine hydrochloride (**7**).

Synthesis of 3-((5-amino-6-chloropyrimidin-4-yl)(methyl)amino)propan-1-ol (10)



10

5-Amino-4,6-dichloropyrimidine (**1**) (351 mg, 2.14 mmol) and 3-methylamino-1-propanol (624 µL, 6.42 mmol) was dissolved in 1,4-dioxane (30 mL) and heated to reflux for 20 hours under argon atmosphere while stirring. The solvent was removed *in vacuo* and the crude reaction mixture was purified by flash column chromatography (DCM:MeOH 10:0 to 19:1 gradient) affording an off-white powder.

Yield 443.4 mg (96 %).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.90 (s, 1H, 2), 5.09 (bs, 2H, 7), 3.46 (t, 2H, 11), 3.33 (t, 2H, 9), 2.86 (s, 3H, 14), 1.70 (p, 2H, 10).

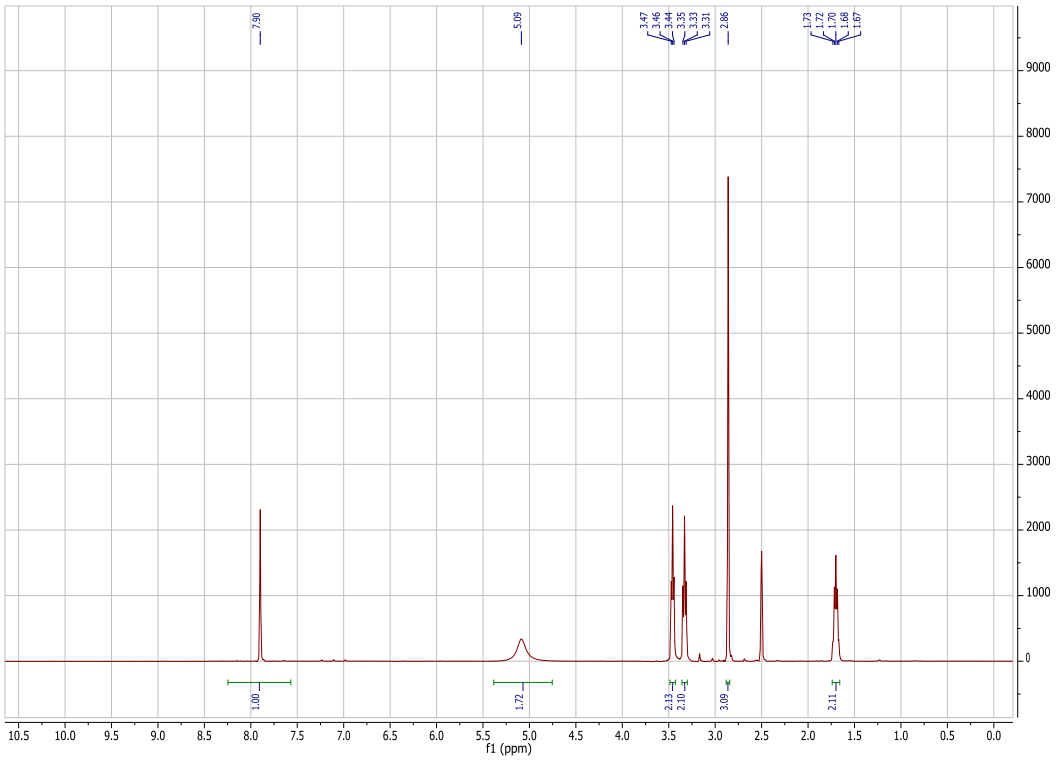
^{13}C NMR (DMSO-d_6, 100 MHz): δ 155.58 (6), 144.86 (2), 141.06 (4), 128.23 (5), 57.76 (11), 46.87 (9), 36.66 (14), 29.48 (10).

MS EI m/z (rel. %): 218/216 (10/30, M^+), 185 (13), 173/171 (32/100), 159 (12), 143 (9), 130 (5).

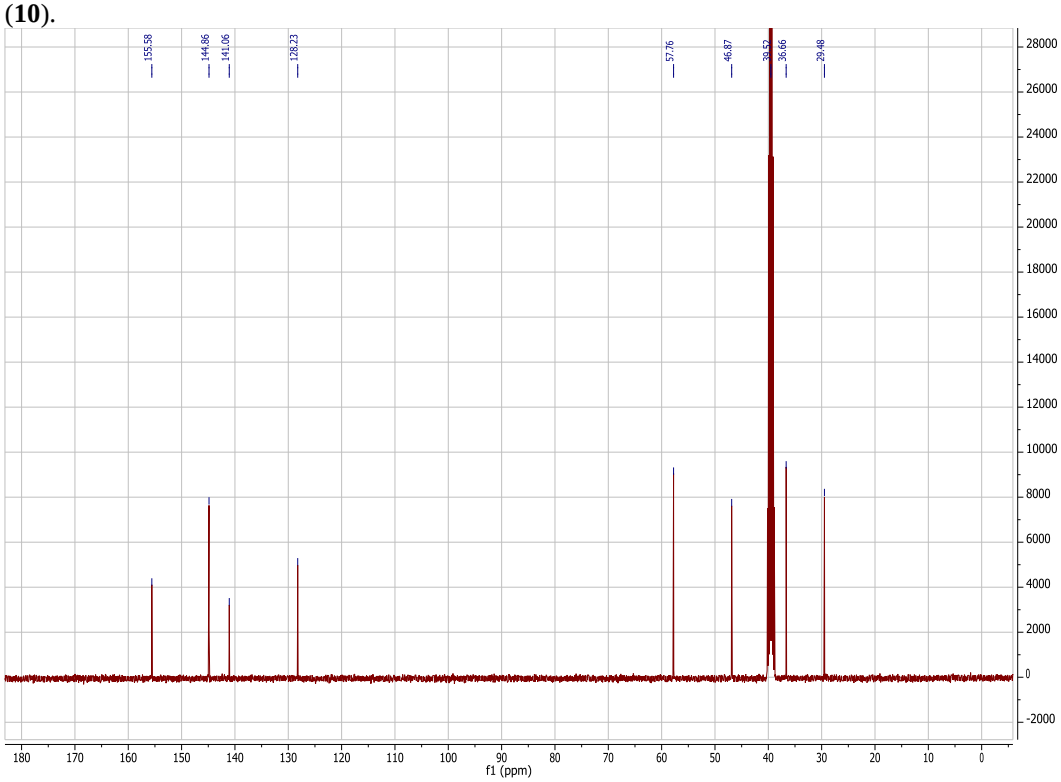
HR-MS Found 216.0771 calcd. for $C_8H_{13}ClN_4O$ 216.0778.

M.p. 69 °C – 70 °C.

Compound not known in literature.

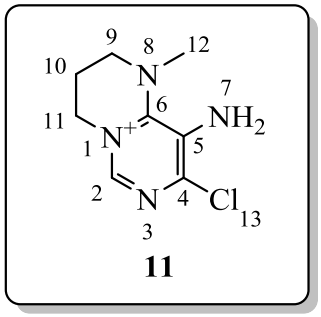


Spectrum 5. . ^{1}H NMR (DMSO-d_6, 400 MHz) of 3-((5-amino-6-chloropyrimidin-4-yl)(methyl)amino)propan-1-ol (**10**).



Spectrum 6. . ^{13}C NMR (DMSO-d_6, 100 MHz) of 3-((5-amino-6-chloropyrimidin-4-yl)(methyl)amino)propan-1-ol (**10**).

Synthesis of 9-amino-8-chloro-1-methyl-1,2,3,4-tetrahydropyrimido[1,6-*a*]pyrimidinium chloride (11)



11

3-((5-amino-6-chloropyrimidin-4-yl)(methyl)amino)propan-1-ol (**10**) (125 mg, 0.576 mmol) was dissolved in THF (30 mL), put under argon atmosphere and cooled to 0 °C. Thionyl chloride (42 µL, 0.60 mmol) was added dropwise to the solution over 5 min. The reaction mixture was stirred 90 min. at 0 °C before it was warmed to room temperature and stirred for an additional 1 hour. The volatiles were removed *in vacuo* affording 140 mg of a viscous brown oil of impure compound.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.24 (s, 1H, 2), 5.80 (bs, 2H, 7), 4.22 (t, *J* = 5.1 Hz, 2H, 11), 3.49 (t, *J* = 6.1 Hz, 2H, 9), 3.39 (s, 3H, 12), 2.18 (m, 2H, 10).

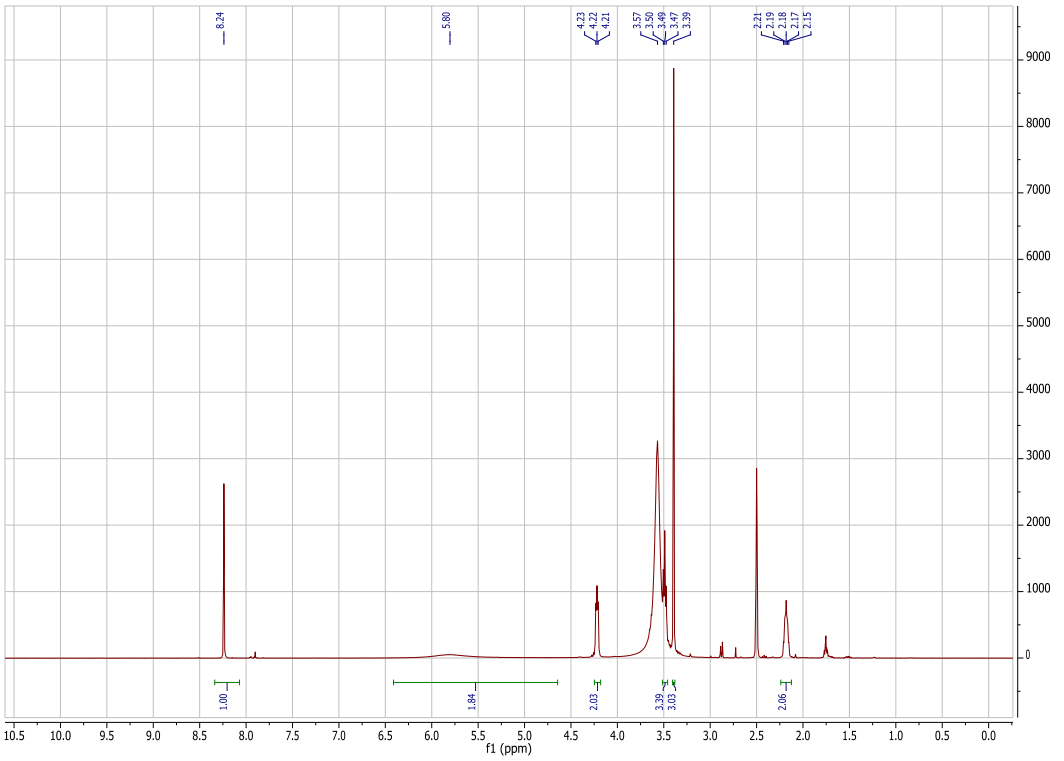
^{13}C NMR (DMSO-d_6, 100 MHz): δ 147.19 (6), 138.85 (2), 138.38 (4), 129.11 (5), 51.17 (9), 48.43 (11), 40.12 (12), 20.03 (10).

MS ESI m/z (rel. %): 199 (100, M^+).

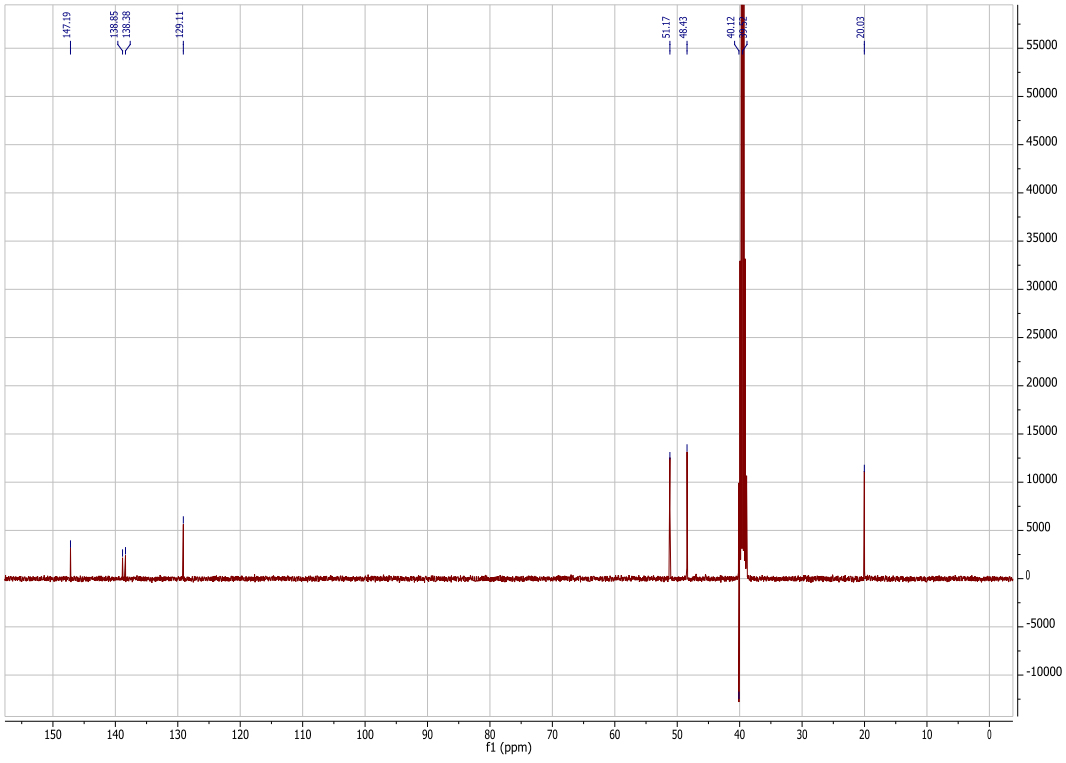
HR-MS Found 199,0754 calcd. for $C_8H_{12}ClN_4$ 199.0750.

M.p. >250 °C

Compound not known in literature.

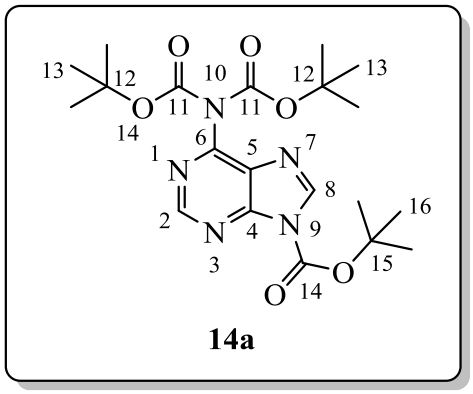


Spectrum 7. ^{1}H NMR (DMSO-d$_6$, 400 MHz) of 9-amino-8-chloro-1-methyl-1,2,3,4-tetrahydropyrimido[1,6-*a*]pyrimidinium chloride (**11**).



Spectrum 8. ^{13}C NMR - APT (DMSO-d$_6$, 100 MHz) of 9-amino-8-chloro-1-methyl-1,2,3,4-tetrahydropyrimido[1,6-*a*]pyrimidinium chloride (**11**).

Synthesis of *tritert*-butyl 9,10,10-adenineetricarboxylate (14a)



14a

Adenine (**13**) (1.36 g, 10.0 mmol) and 4-dimethylaminopyridine (122 mg, 0.996 mmol) was suspended in THF (50 mL). Di-*tert*-butyl dicarbonate (8.51 g, 39.0 mmol) was added to the suspension under an atmosphere of argon and the mixture was stirred at room temperature for 22 hours before the volatiles were removed *in vacuo* and the crude reaction mixture purified by flash column chromatography (hexanes:ethyl acetate – 7:3) affording a colorless solid.

Yield 3.98 g (91 %) (lit. 90 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.99 (s, 1H, 2), 8.48 (s, 1H, 8), 1.69 (s, 9H, 16), 1.41 (s, 18H, 13).

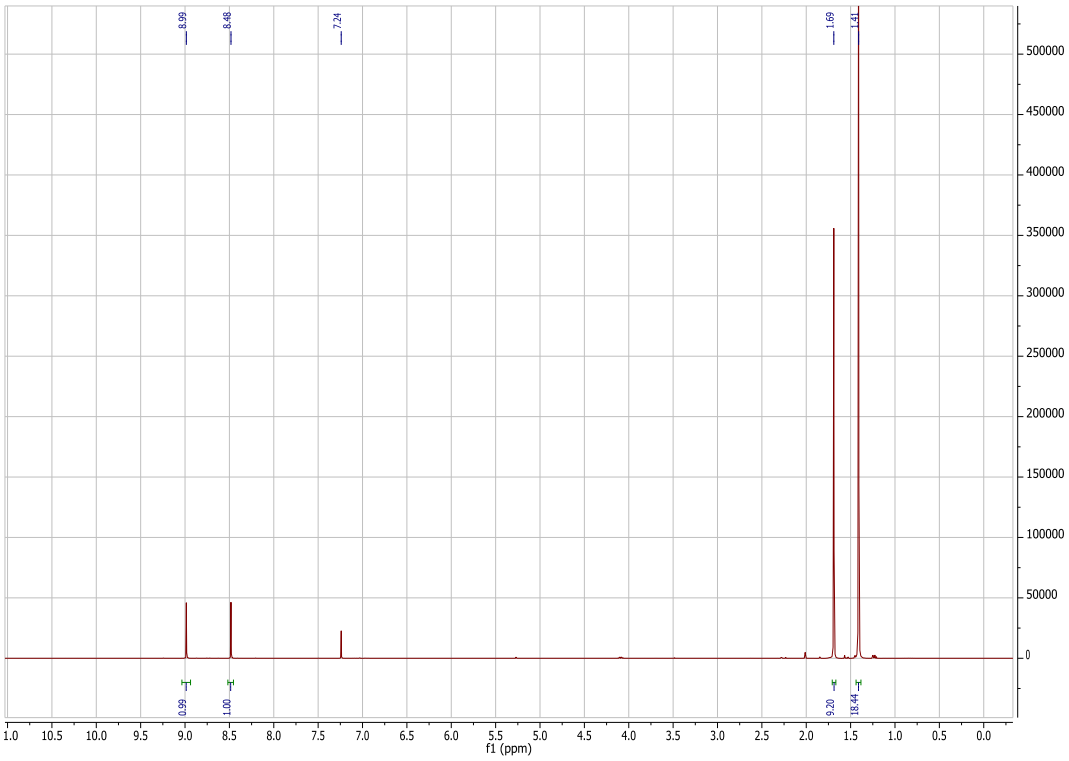
^{13}C NMR ($CDCl_3$, 125 MHz): δ 154.21 (2), 152.59 (4), 151.34 (6), 150.16 (11), 145.76 (14), 143.30 (8), 129.72 (5), 87.61 (15), 84.09 (12), 28.07 (16), 27.88 (13).

MS EI m/z (rel. %): 435 (1, M^+), 236 (3), 161 (46), 135 (88), 57 (60), 41 (100).

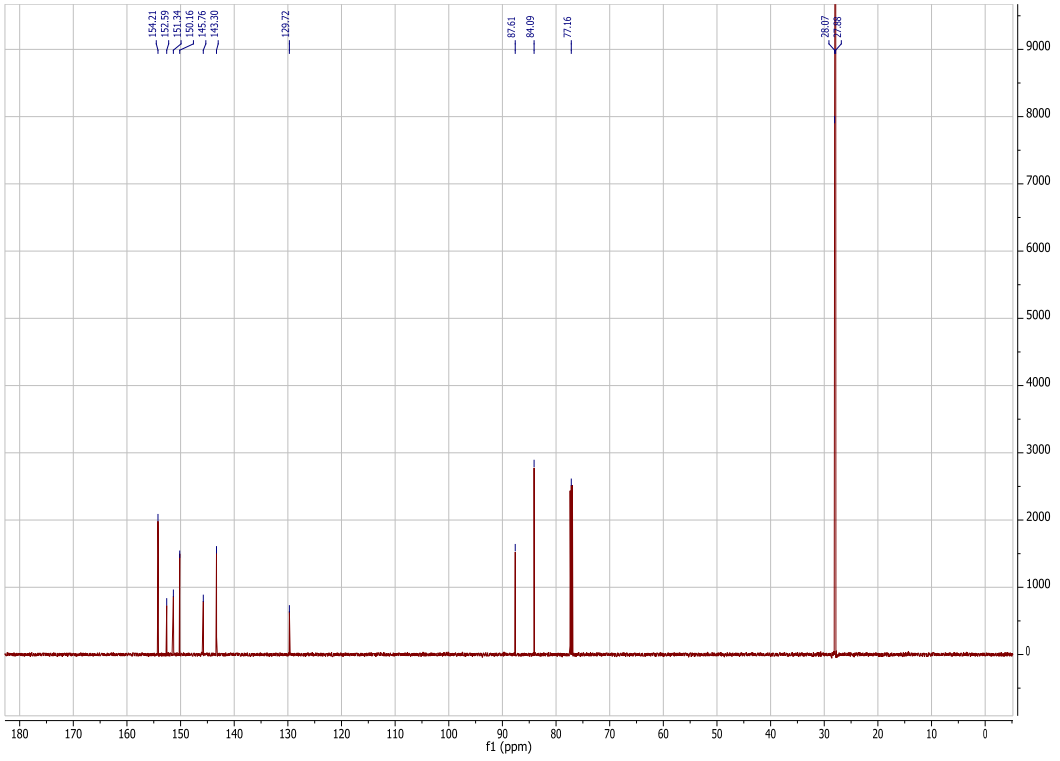
HR-MS Found 435.2121 calcd. for $C_{20}H_{29}N_5O_6$ 435.2118.

M.p. 54 – 55 °C (lit. 54 – 55 °C[68]).

Compound known in literature.[68]

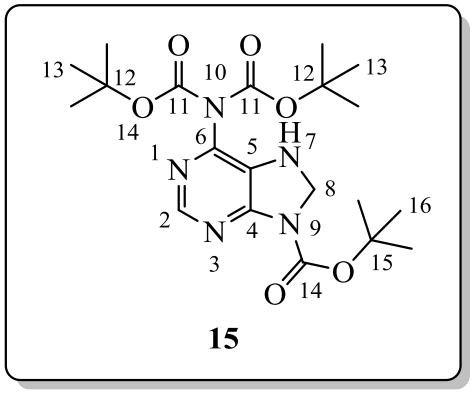


Spectrum 9. ^{1}H NMR ($CDCl_3$, 400 MHz) of *tritert*-butyl 9,10,10-adenineetricarboxylate (**14**).



Spectrum 10. ^{13}C NMR ($CDCl_3$, 150 MHz) of *tritert*-butyl 9,10,10-adenineetricarboxylate (**14**).

Synthesis of *tert*-butyl 6-(*ditert*-butoxycarbonylamino)-8,9-dihydropurine-9-carboxylate (15)



15

Reduction using borane-tetrahydrofuran complex:

Tritert-butyl-9,10,10-adenineetricarboxylate (**14**) (2.28 g, 5.21 mmol) was dissolved in THF (20 mL) and cooled to -78 °C on a dry ice/acetone bath under argon atmosphere. Borane tetrahydrofuran complex 1 M solution (7.30 mL, 7.30 mmol) was added through the septum and the mixture was stirred for 2 hours before it was warmed to room temperature and stirred for another 18 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride (20 mL) and stirred vigorously for 1 hour. The phases were separated and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by flash column chromatography (hexanes:ethyl acetate – 100:0 to 75:25 gradient) affording a colorless powder.

Yield 1.79 g (78 %).

Reduction using sodium borohydride in methanol:

Tritert-butyl-9,10,10-adenineetricarboxylate (**14**) (1.03 g, 2.37 mmol) was dissolved in MeOH (50 mL) and $NaBH_4$ (446 mg, 11.8 mmol) was added. The reaction was stirred for 20 min. before water (20 mL) was added and the mixture concentrated *in vacuo* until a white precipitate was formed. DCM (15 mL) and NaCl (0.5 g) was added and the phases were separated. The aqueous layer was extracted with DCM (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered and evaporated *in vacuo* to afford a colorless solid.

Yield 868 mg (84 %).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.26 (s, 1H, 2), 5.24 (s, 2H, 8), 4.15 (bs, 1H, 7), 1.54 (s, 9H, 16), 1.47 (s, 18H, 13).

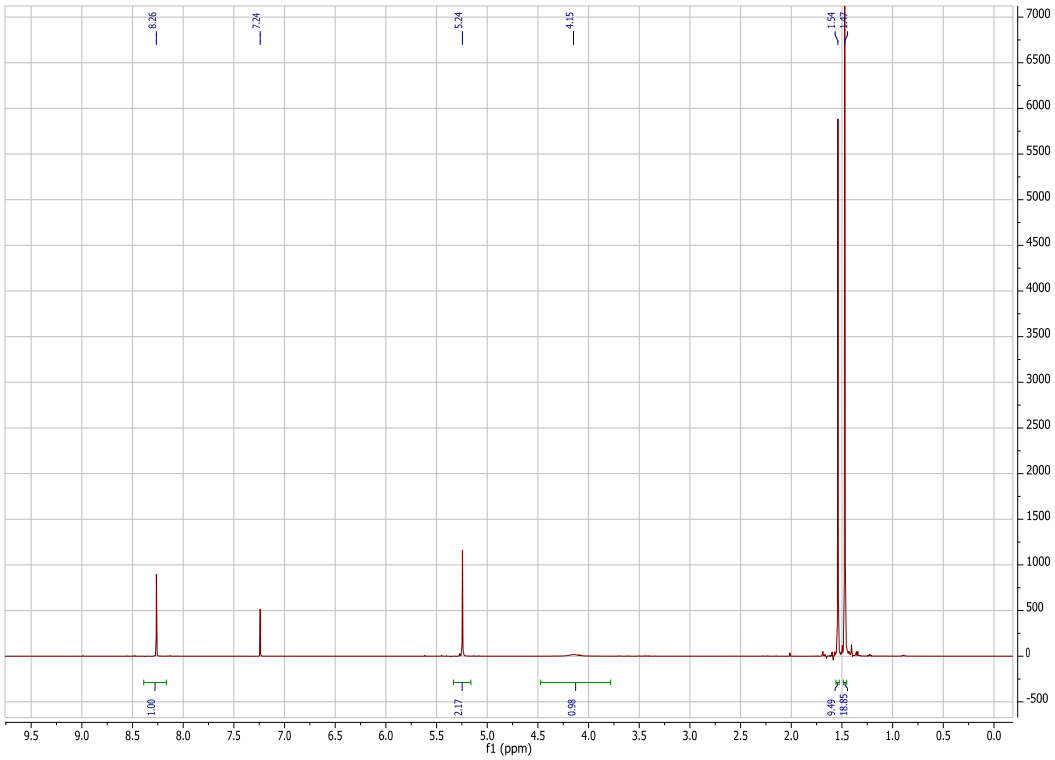
^{13}C NMR ($CDCl_3$, 150 MHz): 156.80 (4), 150.27 (11), 149.86 (2), 148.67 (14), 137.88 (6), 126.58 (5), 84.24 (12), 83.50 (15), 64.68 (8), 28.29 (16), 27.96 (13).

MS EI m/z (rel. %): 437 (7, M^+), 337 (11), 263 (7), 237 (15), 181 (38), 163 (85), 137 (40), 136 (38), 119 (8), 57 (100), 41 (45).

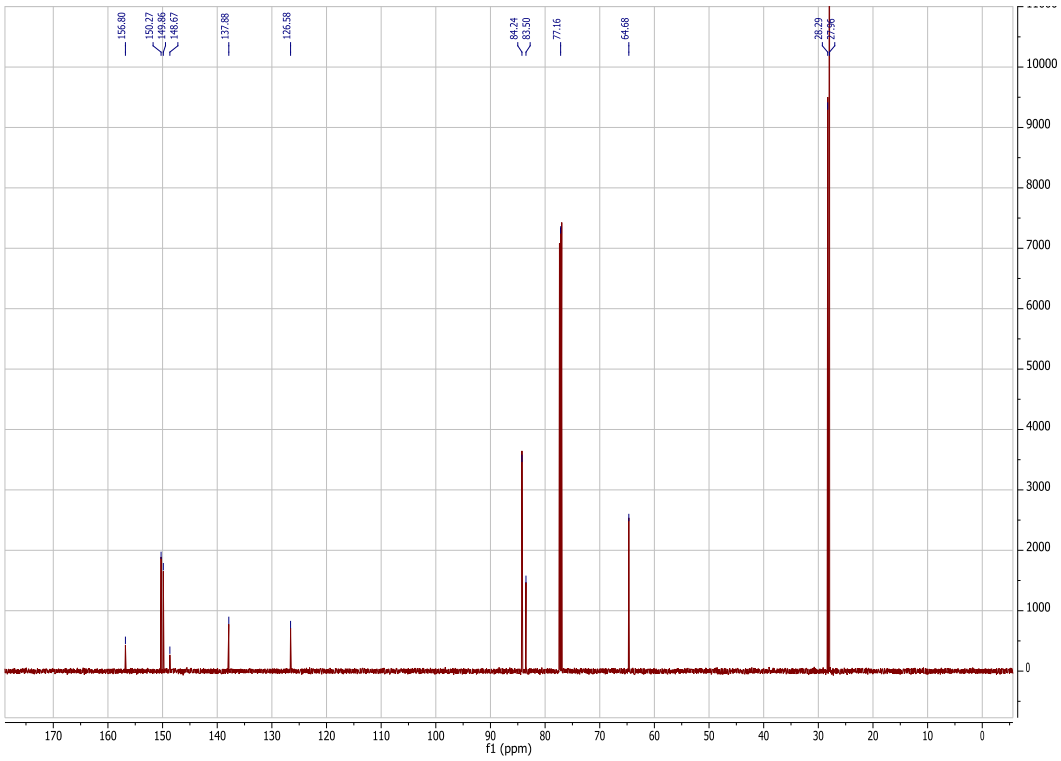
HR-MS Found 437.2269 calcd. for $C_{20}H_{31}N_5O_6$ 437.2274.

M.p. >250 °C (dec.)

Compound not known in literature.

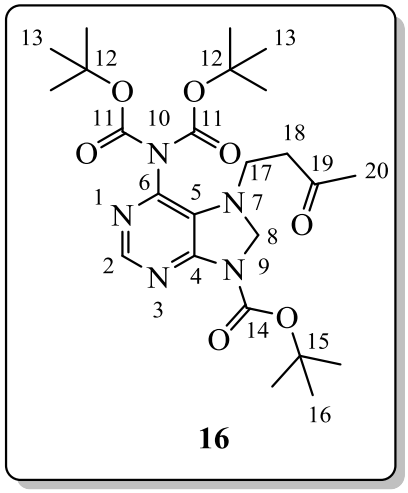


Spectrum 11. ^{1}H NMR ($CDCl_3$, 500 MHz) of *tert*-butyl 6-(*ditert*-butoxycarbonylamino)-8,9-dihydropurine-9-carboxylate (**15**).



Spectrum 12. ^{13}C NMR ($CDCl_3$, 150 MHz) of *tert*-butyl 6-(*ditert*-butoxycarbonylamino)-8,9-dihydropurine-9-carboxylate (**15**).

Synthesis of *tert*-butyl 6-(*ditert*-butoxycarbonylamino)-7-(3-oxobutyl)-8,9-dihydropurine-9-carboxylate (16)



16

tert-Butyl 6-(*ditert*-butoxycarbonylamino)-8,9-dihydropurine-9-carboxylate (**15**) (480 mg, 1.10 mmol) was dissolved in MeCN (30 mL) under an atmosphere of argon. 1,8-Diazabicyclo[5.4.0]undec-7-ene (180 µL, 1.21 mmol) was added through the septum. But-3-en-2-one (183 µL, 2.20 mmol) was dissolved in MeCN (3.5 mL) and added slowly to the reaction mixture with a syringe pump at 0.75 mL/h. After addition the volatiles were removed *in vacuo* and the resulting brown oil was purified by flash column chromatography (hexanes/ethyl acetate – 7:3 to 1:1 gradient) affording a colorless solid.

Yield 436 mg (78 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20 (s, 1H, 2), 5.15 (s, 2H, 8), 3.43 (t, *J* = 6.6 Hz, 2H, 17), 2.73 (t, *J* = 6.6 Hz, 2H, 18), 2.14 (s, 3H, 20), 1.55 (s, 9H, 16), 1.44 (s, 18H, 13).

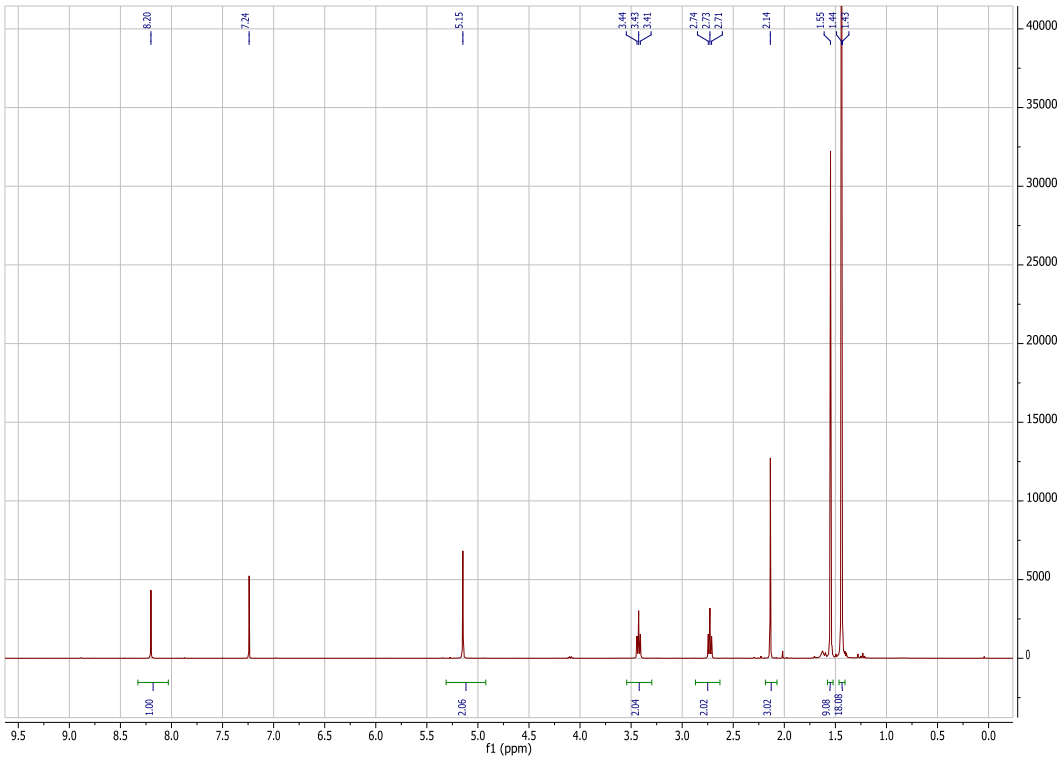
^{13}C NMR ($CDCl_3$, 150 MHz): δ 206.30 (19), 156.59 (4), 150.73 (14), 148.42 (2), 148.18 (11), 134.52 (6), 128.83 (5), 83.96 (12), 83.80 (15), 69.32 (8), 42.03 (17), 41.94 (18), 30.28 (20), 28.24 (16), 28.04 (13).

MS EI m/z (rel. %): 507 (7, M^+), 407 (11), 233 (69), 175 (53), 162 (33), 136(15), 119 (11), 57 (97), 41 (100).

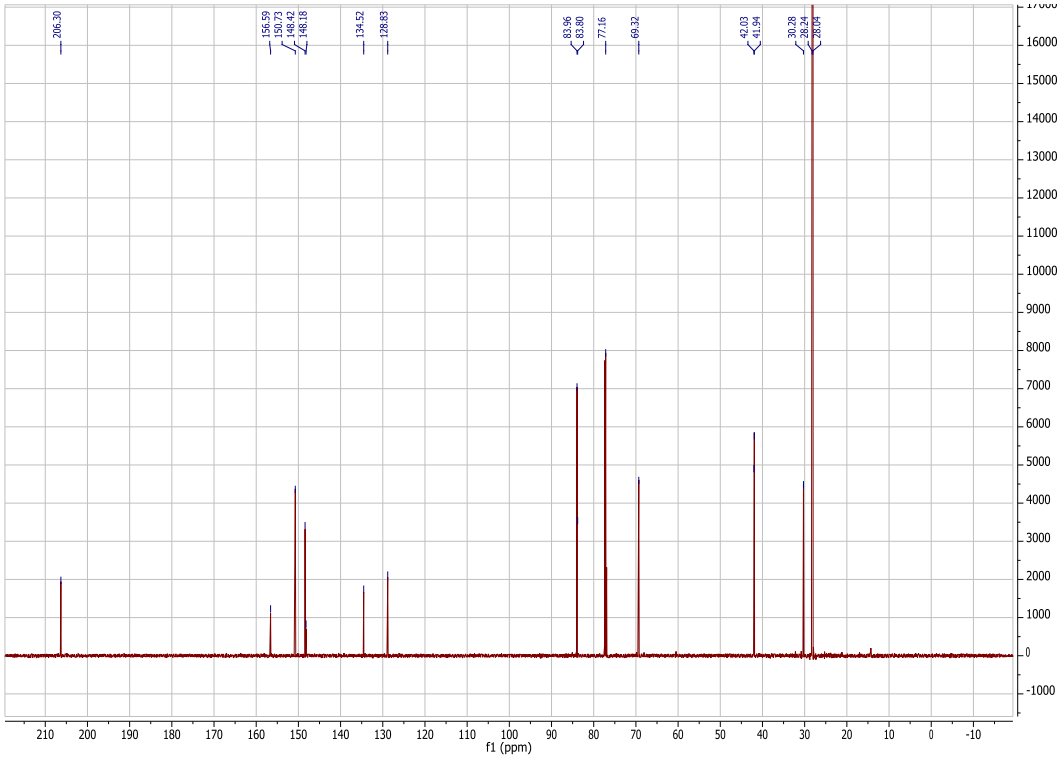
HR-MS Found 507.2686 calcd. for $C_{24}H_{37}N_5O_7$ 507.2693.

M.p. >133 °C (dec.).

Compound not known in literature.

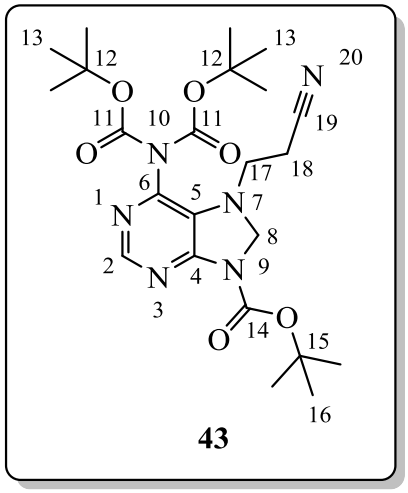


Spectrum 13. ^{1}H NMR ($CDCl_3$, 400 MHz) of *tert*-butyl 6-(*ditert*-butoxycarbonylamino)-7-(3-oxobutyl)-8,9-dihydropurine-9-carboxylate (**16**).



Spectrum 14. ^{13}C NMR ($CDCl_3$, 150 MHz) of *tert*-butyl 6-(*ditert*-butoxycarbonylamino)-7-(3-oxobutyl)-8,9-dihydropurine-9-carboxylate (**16**).

Synthesis of *tert*-butyl 7-(2-cyanoethyl)-6-(*ditert*-butoxycarbonylamino)-8,9-dihydropurine-9-carboxylate (43)



43

tert-Butyl 6-(*ditert*-butoxycarbonylamino)-8,9-dihydropurine-9-carboxylate (**15**) (853 mg, 1.94 mmol) was dissolved in MeCN (30 mL) under an atmosphere of argon. 1,8-Diazabicyclo[5.4.0]undec-7-ene (320 µL, 2.14 mmol) and acrylonitrile (255 µL, 3.89 mmol) was added to the reaction mixture. The reaction mixture was stirred for 5 hours before the volatiles were removed *in vacuo* and the resulting yellow oil purified by flash column chromatography (hexanes/ethyl acetate – 7:3) affording a colorless solid.

Yield 843 mg (89 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28 (s, 1H, 2), 5.27 (s, 2H, 8), 3.51 (t, *J* = 6.9 Hz, 2H, 17), 2.62 (t, *J* = 6.9 Hz, 2H, 18), 1.56 (s, 9H, 16), 1.45 (s, 18H, 13).

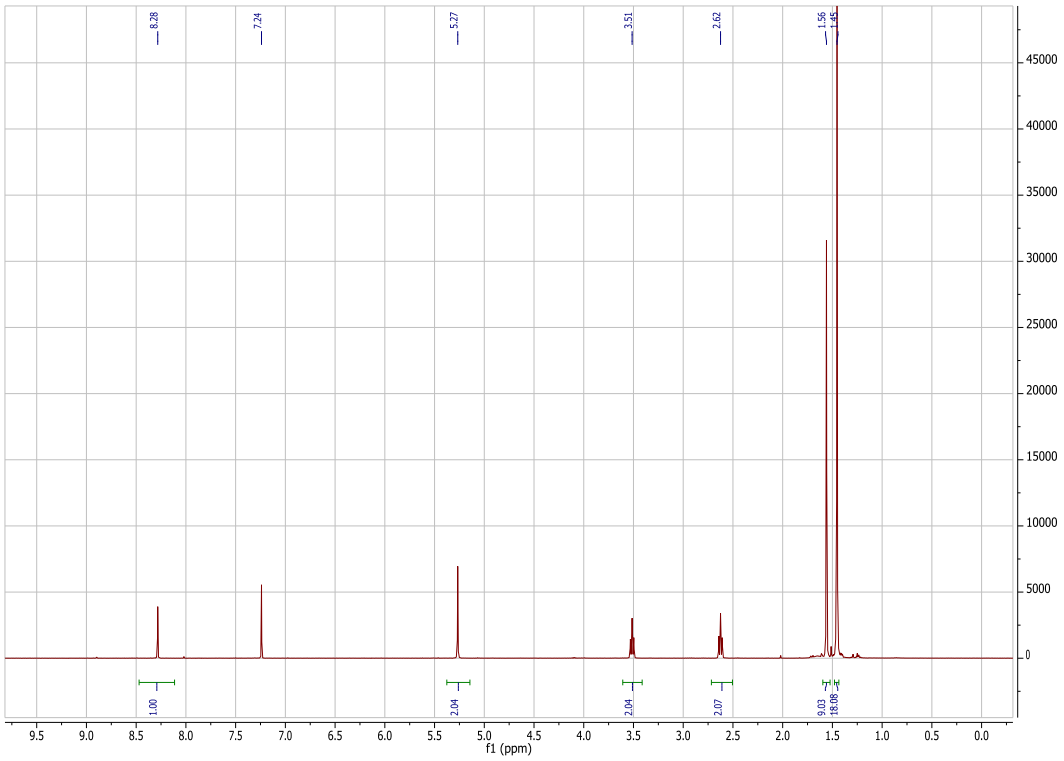
^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.54 (4), 150.61 (14), 149.72 (2), 148.01 (11), 135.74 (6), 127.79 (5), 117.39 (19), 84.56 (12), 84.32 (15), 69.07 (8), 44.32 (17), 28.25 (16), 28.04 (13), 16.97 (18).

MS EI m/z (rel. %): 490 (2, M^+), 390 (5), 216 (100), 215 (57), 190 (8), 176 (63), 174 (19), 161 (6), 119 (8).

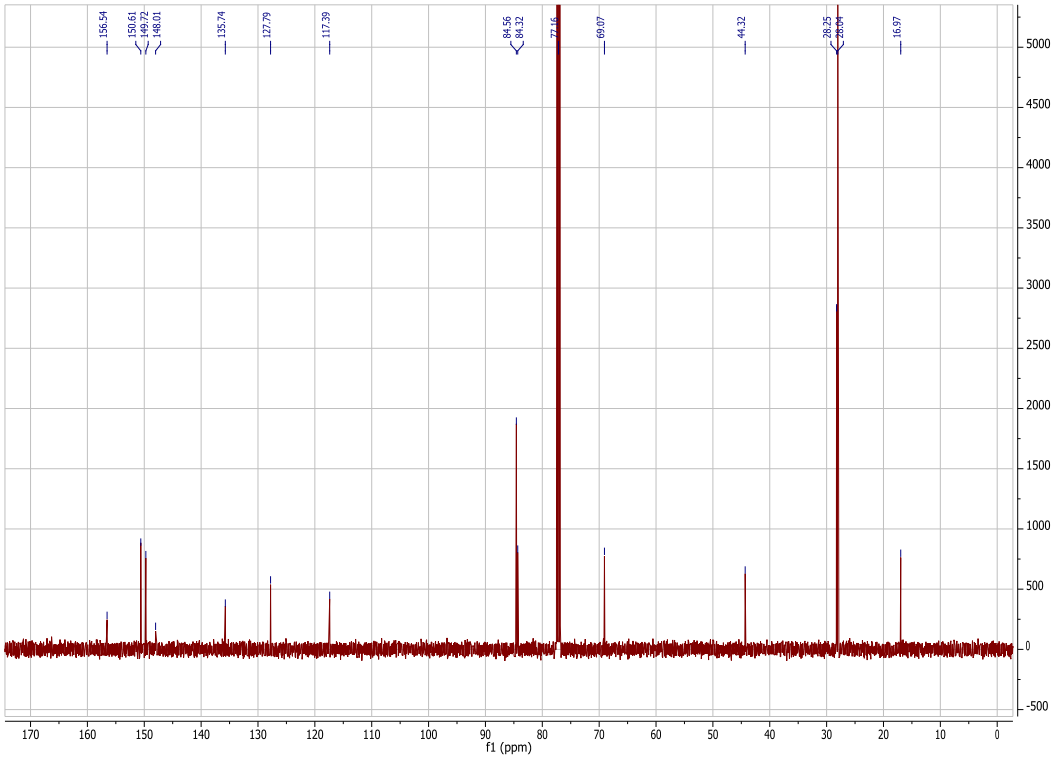
HR-MS Found 490.2555 calcd. for $C_{23}H_{34}N_6O_6$ 490.2540.

M.p. >134 °C (dec.).

Compound not known in literature.

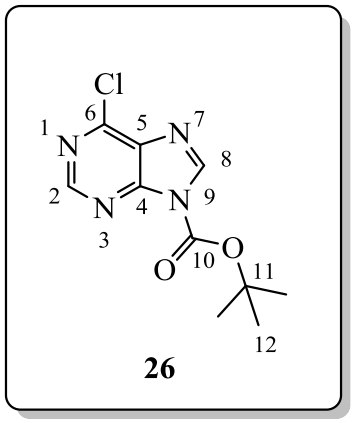


Spectrum 15. ^{1}H NMR ($CDCl_3$, 400 MHz) of *tert*-butyl 6-(*ditert*-butoxycarbonylamino)-7-(2-cyanoethtyl)-8,9-dihydropurine-9-carboxylate (**43**).



Spectrum 16. . ^{13}C NMR ($CDCl_3$, 125 MHz) of *tert*-butyl 6-(*ditert*-butoxycarbonylamino)-7-(3-cyanoethyl)-8,9-dihydropurine-9-carboxylate (**43**).

Synthesis of *tert*-butyl 6-chloropurine-9-carboxylate (26)



26

6-Chloropurine (502 mg, 3.25 mmol) and 4-dimethylaminopyridine (13.0 mg, 0.106 mmol) was suspended in DCM (6 mL). Di-*tert*-butyl dicarbonate (1.05 g, 4.82 mmol) was dissolved in DCM (4 mL) and added to the reaction flask. The mixture was stirred for 4 hours before the volatiles were removed *in vacuo.* The crude material was purified by flash column chromatography (hexanes:ethyl acetate – 8:2 to 65:35) affording a colorless solid.

Yield 777 mg (94 %).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.86 (s, 1H, 2), 8.52 (s, 2H, 8), 1.67 (s, 9H, 12).

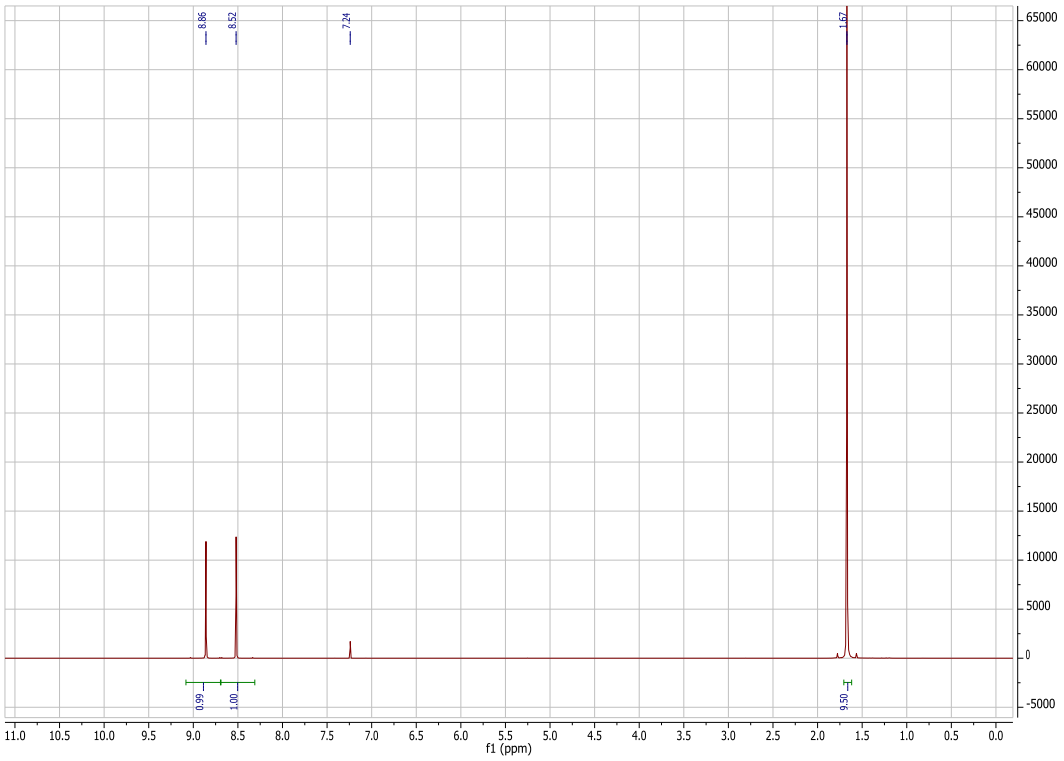
^{13}C NMR ($CDCl_3$, 150 MHz): δ 154.05, 152.11, 151.19, 145.45, 143.95, 132.56, 88.13, 77.16, 28.01.

MS EI m/z (rel. %): 254 (3, M^+), 239 (6), 181 (8), 157 (7), 156 (15 (, 155 (22), 154 (41), 119 (22), 57 (100).

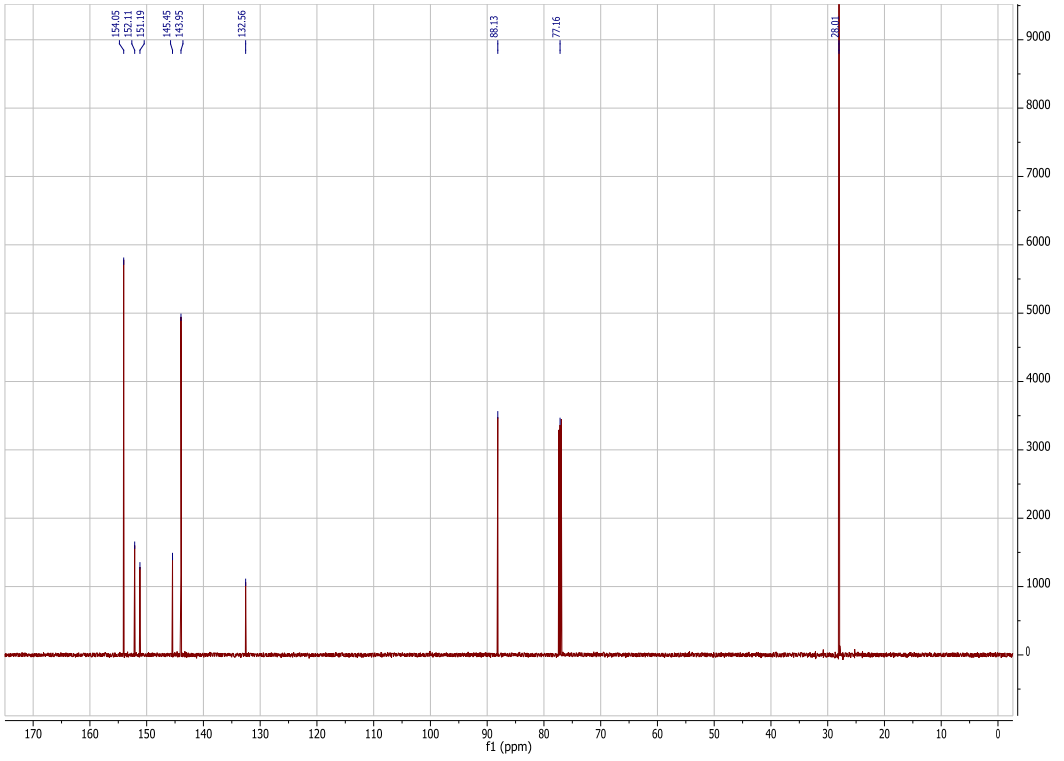
HR-MS Found 254.0573 calcd. for $C_{10}H_{11}ClN_4O_2$ 254.0571.

M.p. >110 °C (dec.).

Compound known in literature.[69]

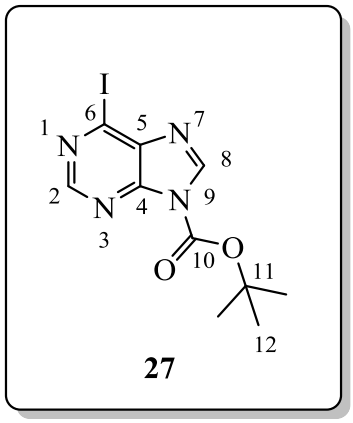


Spectrum 17. ^{1}H NMR ($CDCl_3$, 600 MHz) of *tert*-butyl 6-chloropurine-9-carboxylate (**26**).



Spectrum 18. ^{13}C NMR ($CDCl_3$, 150 MHz) of *tert*-butyl 6-chloropurine-9-carboxylate (**26**).

Synthesis of *tert*-butyl 6-iodopurine-9-carboxylate (27)



27

6-Iodopurine (127 mg, 0.518 mmol) was dissolved in DCM (10 mL) and 4-dimethylaminopyridine (2.5 mg, 0.0205 mmol) was added. Di-*tert*-butyl dicarbonate (167 mg, 0.767 mmol) was dissolved in DCM (5 mL) and added to the reaction flask. The mixture stirred for 45 minutes before removing the volatiles *in vacuo*. The residue was purified by flash column chromatography (hexanes:ethyl acetate – 75:25) affording a colorless solid.

Yield 144 mg (80 %).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.75 (s, 1H, 2), 8.53 (s, 2H, 8), 1.68 (s, 9H, 12).

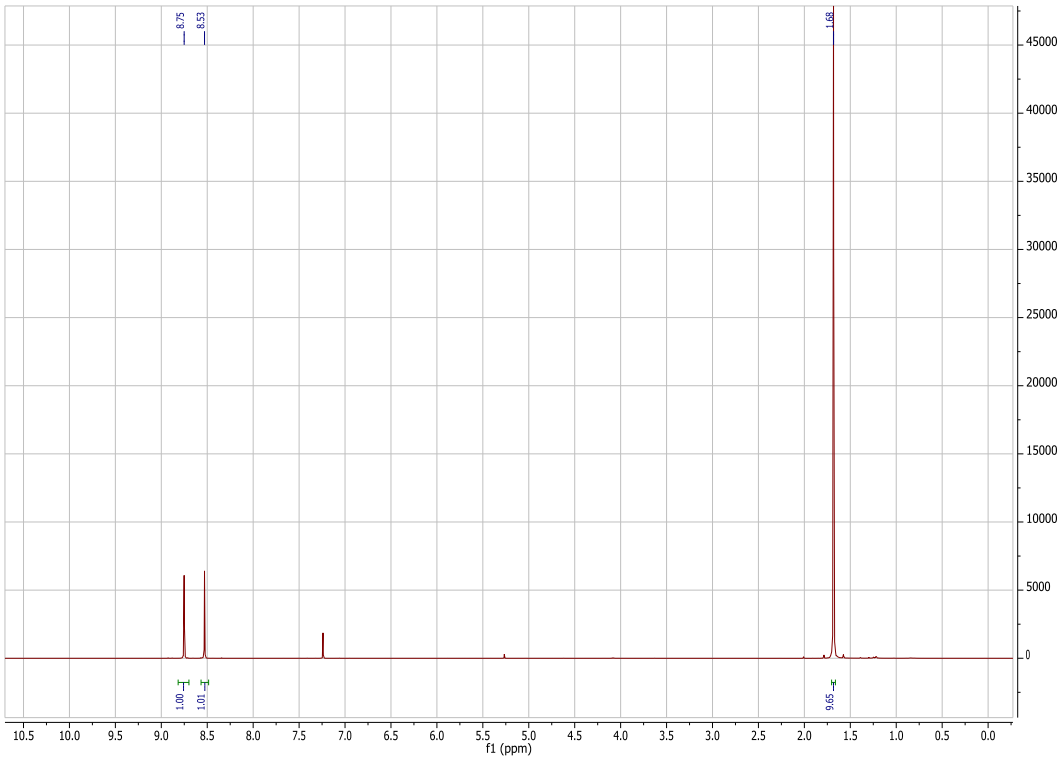
^{13}C NMR ($CDCl_3$, 150 MHz): δ 154.03 (2), 147.56 (4), 145.69 (10), 143.31 (8), 139.41 (5), 123.06 (6), 88.14 (11), 28.06 (12).

MS EI m/z (rel. %): 346 (7, M^+), 247 (15), 246 (85), 119 (100), 92 (16), 65 (19), 57 (60).

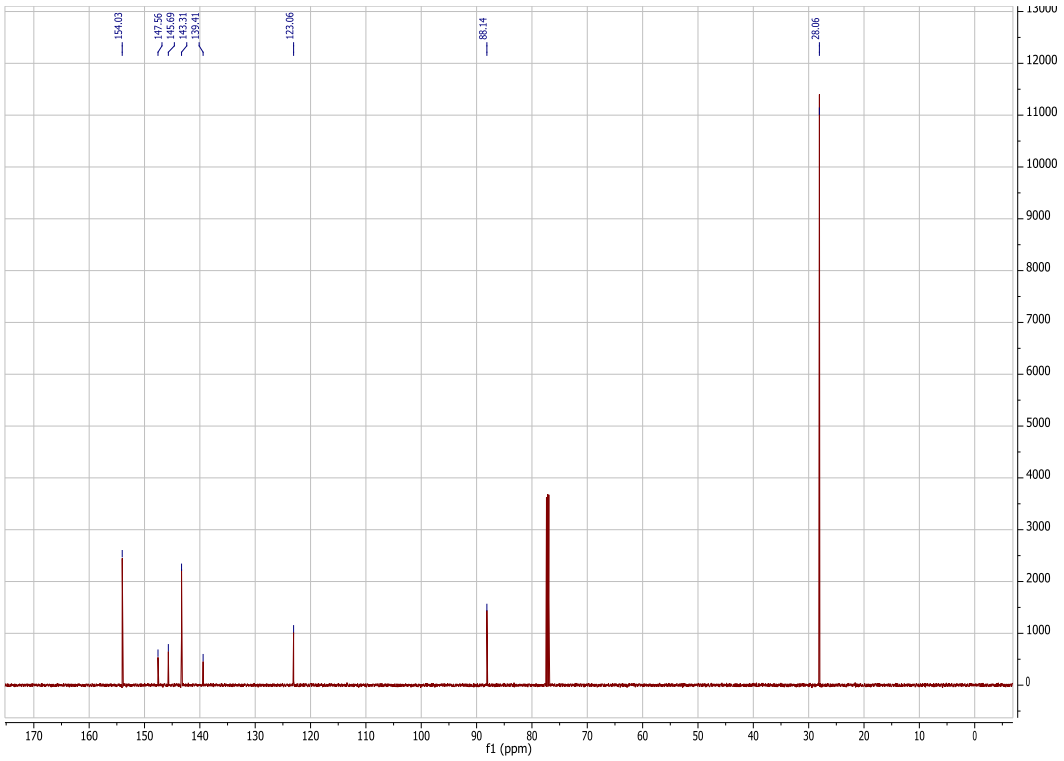
HR-MS Found 345.9938 calcd. for $C_{10}H_{11}IN_4O_2$ 345.9927.

M.p. >111 °C (dec.).

Compound known in literature.[69]

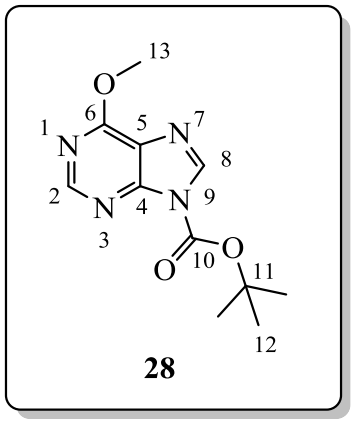


Spectrum 19. ^{1}H NMR ($CDCl_3$, 600 MHz) of *tert*-butyl 6-iodopurine-9-carboxylate (**27**).



Spectrum 20. ^{13}C NMR ($CDCl_3$, 150 MHz) of *tert*-butyl 6-iodopurine-9-carboxylate (**27**).

Synthesis of *tert*-butyl 6-methoxypurine-9-carboxylate (28)



28

6-Methoxypurine (151 mg, 1.01 mmol) and 4-dimethylaminopyridine (5.9 mg, 0.048 mmol) was suspended in DCM (10 mL). Di-*tert*-butyl dicarbonate (439 mg, 2.01 mmol) was dissolved in DCM (5 mL) and added to the reaction flask. The mixture was stirred for 1 hour before removing the volatiles *in vacuo*. The residue was purified by flash column chromatography (hexanes:ethyl acetate – 1:1) affording a colorless solid.

Yield 196 mg (78 %).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.67 (s, 1H, 2), 8.33 (s, 2H, 8), 4.17 (s, 3H, 13), 1.67 (s, 9H, 12).

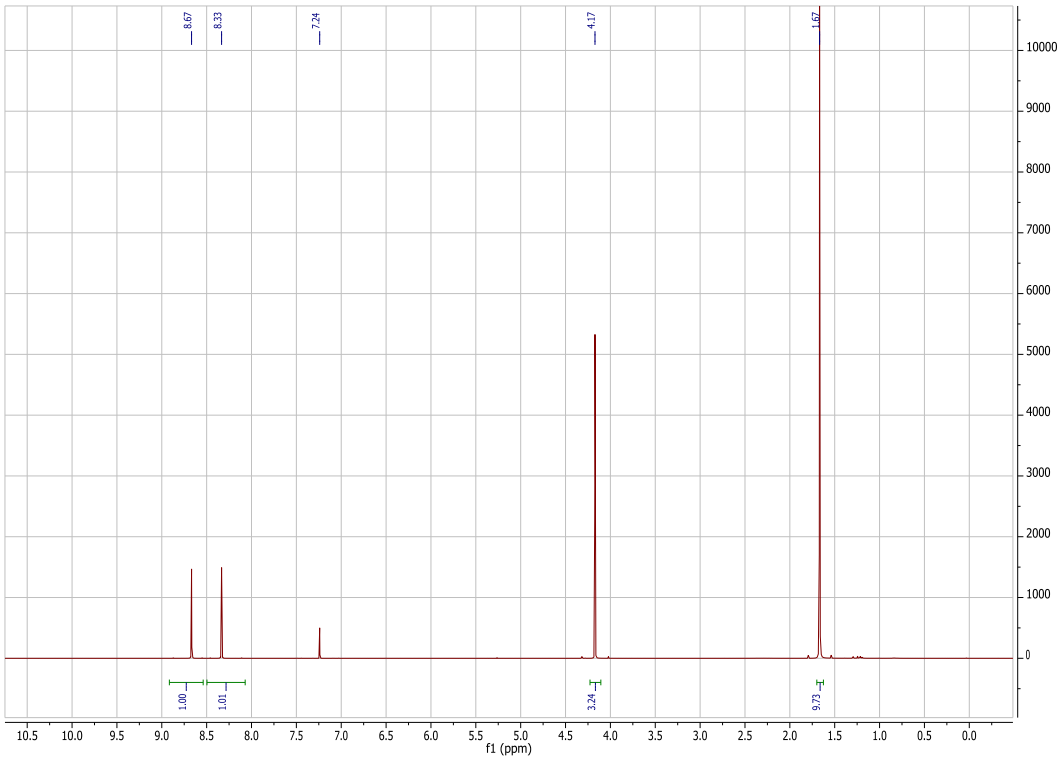
^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.49, 154.33, 151.55, 145.92, 141.13, 122.38, 87.18, 77.16, 54.59, 28.07.

MS EI m/z (rel. %): 250 (15, M^+), 235 (9), 177 (15), 151 (15), 150 (73), 149 (32), 121 (22), 120 (31), 93 (18), 57 (100).

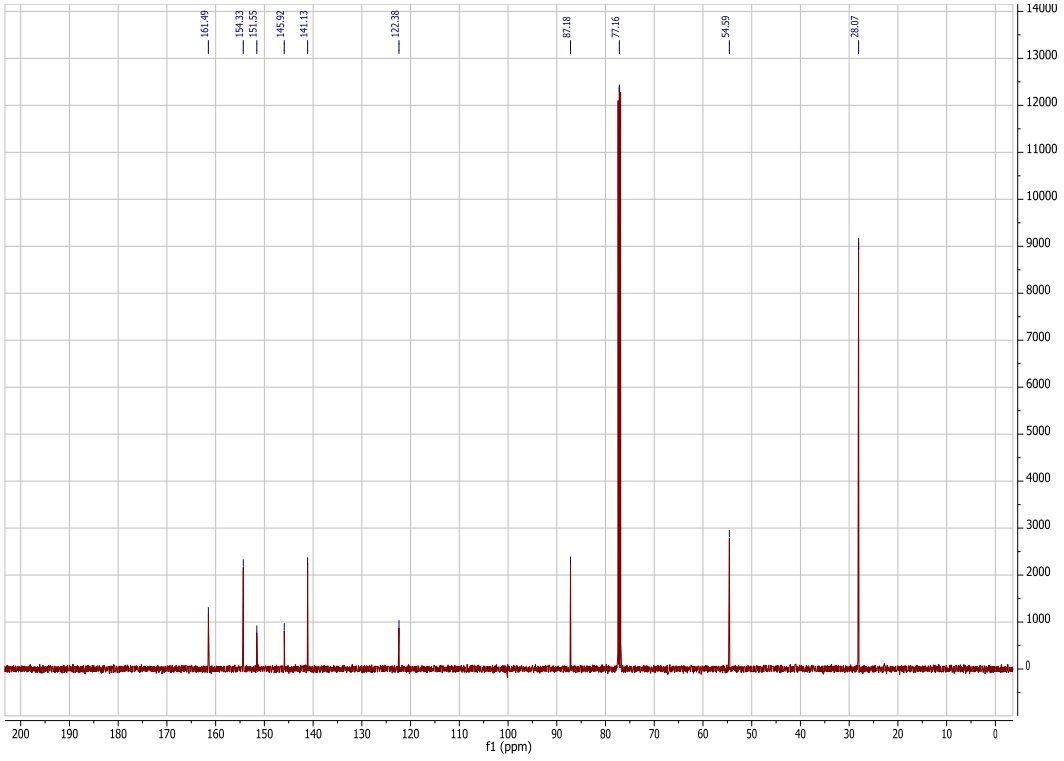
HR-MS Found 250.1071 calcd. for $C_{11}H_{14}N_4O_3$ 250.1066.

M.p. 94 – 95 °C.

Compound not known in literature.

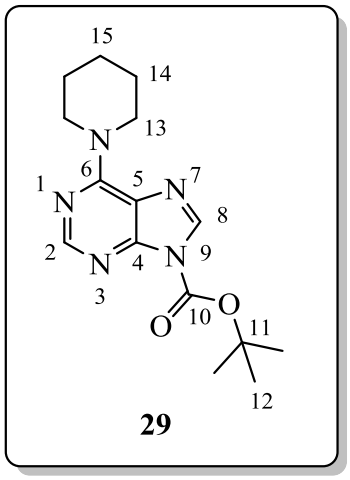


Spectrum 21. ^{1}H NMR ($CDCl_3$, 500 MHz) of *tert*-butyl 6-methoxypurine-9-carboxylate (**28**).



Spectrum 22. ^{13}C NMR ($CDCl_3$, 125 MHz) of *tert*-butyl 6-methoxypurine-9-carboxylate (**28**).

Synthesis of *tert*-butyl 6-(piperidin-1-yl)purine-9-carboxylate (29)



29

6-(Piperidin-1-yl)purine (165 mg, 0.809 mmol) and 4-dimethylaminopyridine (4.9 mg, 0.040 mmol) was suspended in DCM (10 mL). Di-*tert*-butyl dicarbonate (439 mg, 2.01 mmol) was dissolved in DCM (5 mL) and added to the reaction flask. The mixture stirred for 30 minutes before removing the volatiles *in vacuo*. The residue was purified by flash column chromatography (hexanes:ethyl acetate – 7:3) affording a colorless solid.

Yield 228 mg (93 %).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.43 (s, 1H, 2), 8.11 (s, 2H, 8), 4.19 (m, 4H, 13), 1.69 (m, 6H, 14), 1.65 (s, 9H, 12).

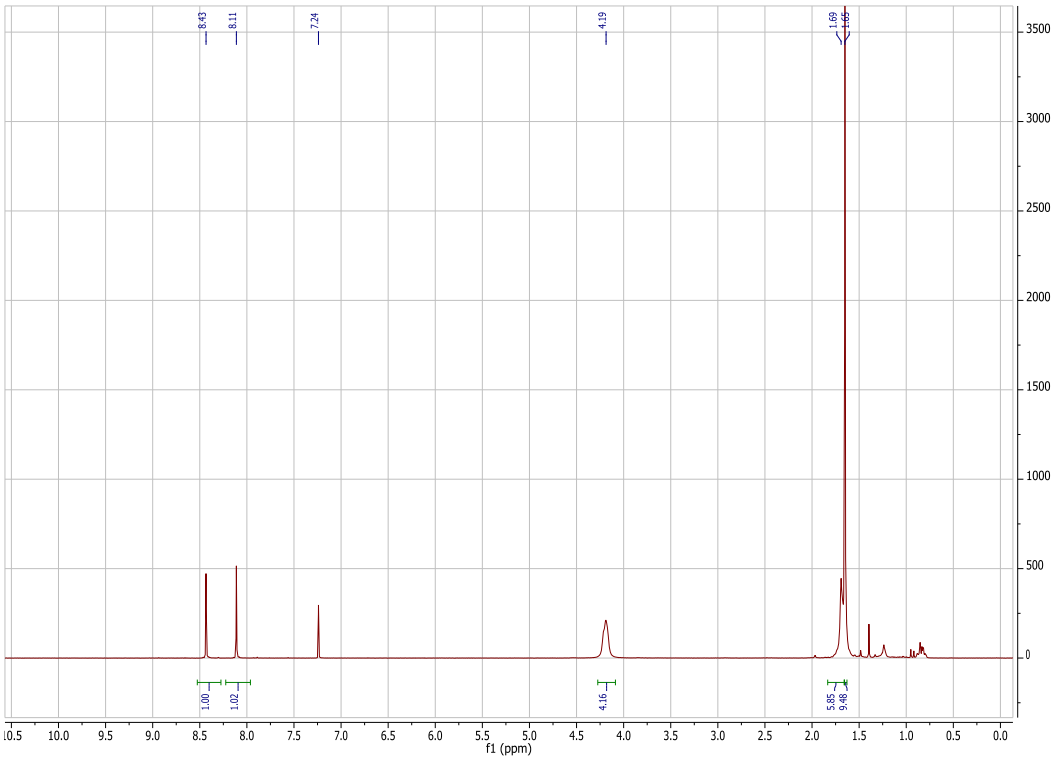
^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.54, 154.07, 151.02, 146.30 , 136.77, 120.32, 86.30 , 46.62, 28.12, 26.22, 24.91.

MS EI m/z (rel. %): 303 (10, M^+), 203 (100), 188 (14), 174 (72), 160 (30), 148 (31), 135 (20), 120 (29), 93 (16), 84 (13).

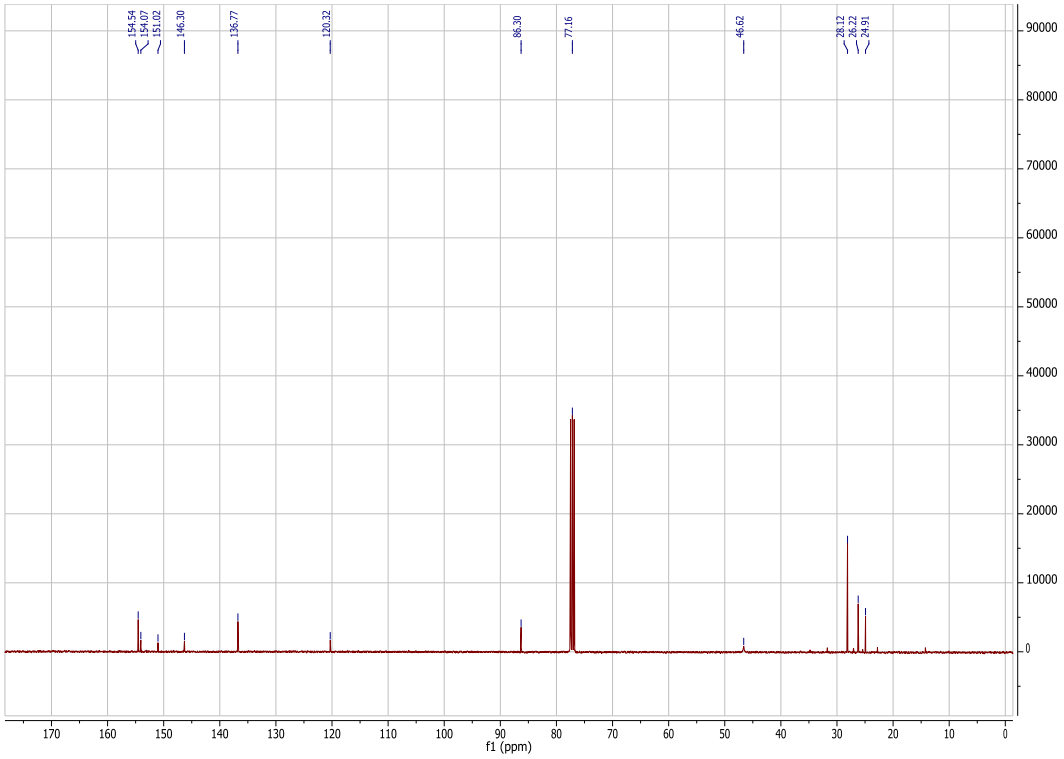
HR-MS Found 303.1687 calcd. for $C_{15}H_{21}N_5O_2$ 303.1695.

M.p. 73 – 74 °C.

Compound not known in literature.

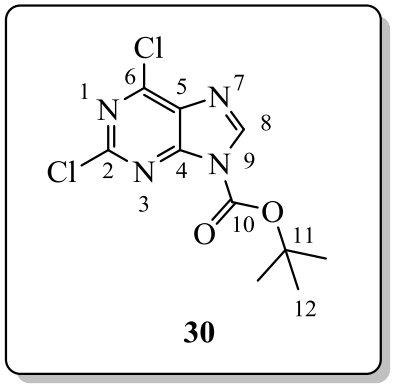


Spectrum 23. ^{1}H NMR ($CDCl_3$, 200 MHz) of *tert*-butyl 6-(piperidin-1-yl)purine-9-carboxylate (**29**).



Spectrum 24. ^{13}C NMR ($CDCl_3$, 100 MHz) of *tert*-butyl 6-(piperidin-1-yl)purine-9-carboxylate (**29**).

Synthesis of *tert*-butyl 2,6-dichloropurine-9-carboxylate (30)



30

2,6-Dichloropurine (252 mg, 1.33 mmol) and 4-dimethylaminopyridine (8.0 mg, 0.066 mmol) was suspended in DCM (10 mL). Di-*tert*-butyl dicarbonate (584 mg, 2.68 mmol) was dissolved in DCM (5 mL) and added to the reaction flask. The mixture stirred for 2 hours before removing the volatiles *in vacuo*. The residue was purified by flash column chromatography (hexanes:ethyl acetate – 8:2) affording a colorless solid.

Yield 336 mg (87 %).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.52 (s, 1H, 8), 1.69 (s, 9H, 12).

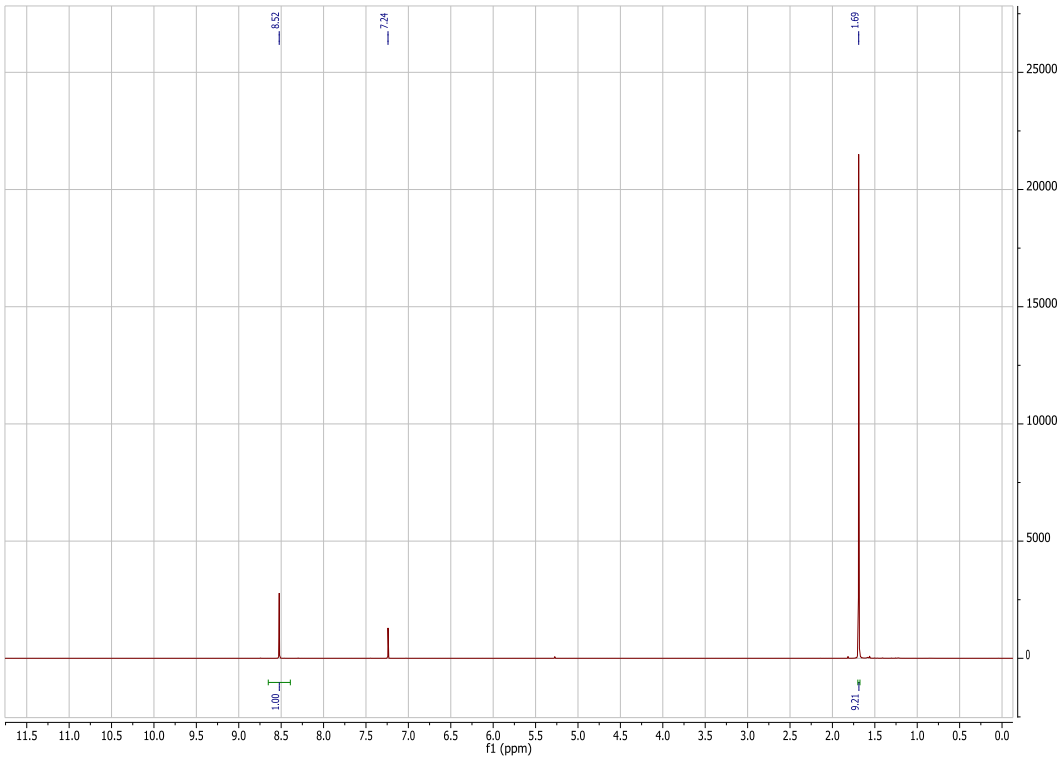
^{13}C NMR ($CDCl_3$, 125 MHz): δ 155.36 (10), 152.88 (2), 152.21 (4), 145.14 (6), 144.45 (8), 131.76 (5), 88.66 (11), 28.02 (12).

MS EI m/z (rel. %): 290/288 (1/2, $[M+2]^+/M^+$), 215 (6), 192 (6), 191 (10), 190 (38), 188 (57), 155 (7), 153 (22), 92 (7), 57 (100).

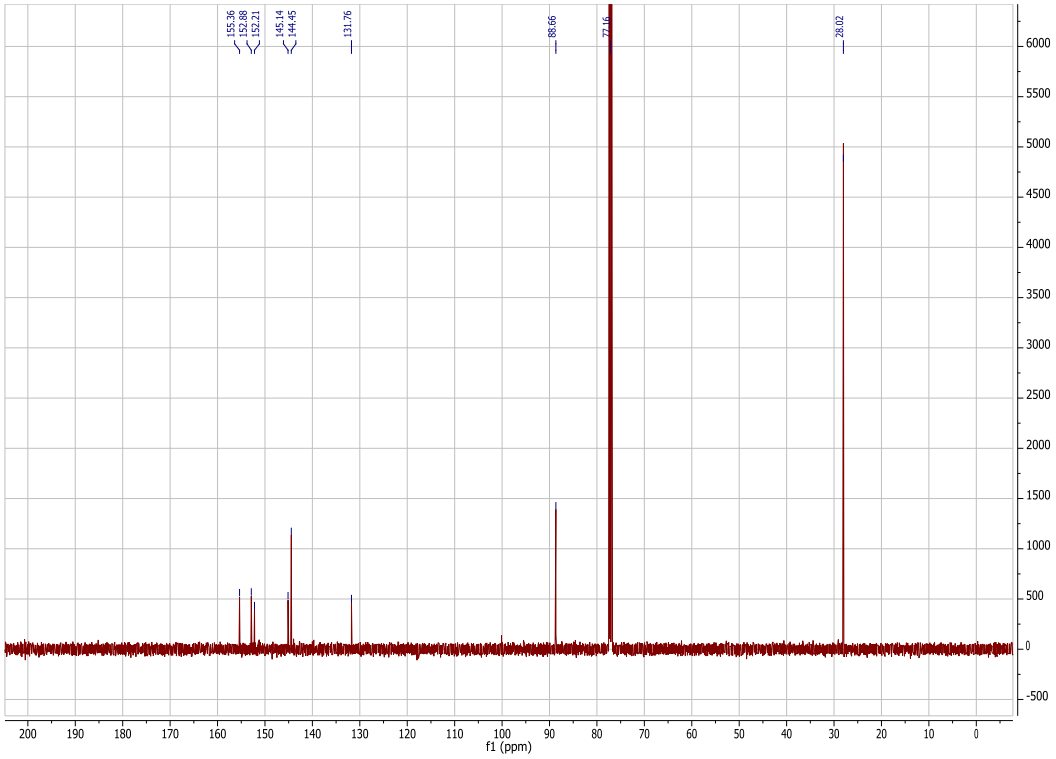
HR-MS Found 288.0191 calcd. for $C_{10}H_{10}Cl_2N_4O_2$ 288.0181.

M.p. X °C.

Compound not known in literature.

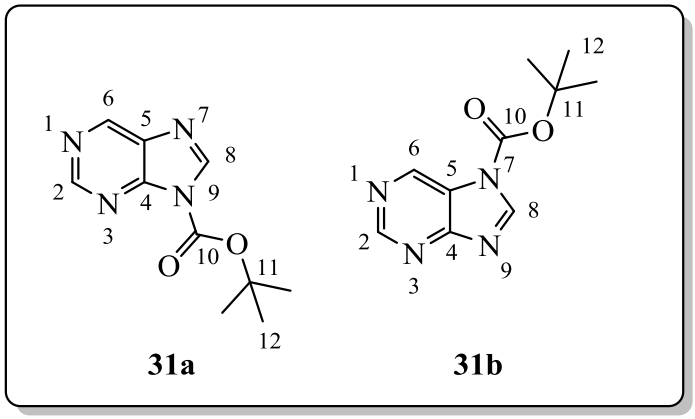


Spectrum 25. ^{1}H NMR ($CDCl_3$, 500 MHz) of *tert*-butyl 2,6-dichloropurine-9-carboxylate (**30**).



Spectrum 26. ^{13}C NMR ($CDCl_3$, 125 MHz) of *tert*-butyl 2,6-dichloropurine-9-carboxylate (**30**).

Synthesis of *tert*-butyl purine-9-carboxylate (31a) and *tert*-butyl purine-7-carboxylate (31b)



Purine (77 mg, 0.64 mmol) and 4-dimethylaminopyridine (4.3 mg, 0.035 mmol) was suspended in DCM (5 mL). Di-*tert*-butyl dicarbonate (281 mg, 1.29 mmol) was dissolved in DCM (3 mL) and added to the reaction flask. The mixture stirred for 2 hours before removing the volatiles *in vacuo*. The residue was purified by flash column chromatography (hexanes:ethyl acetate – 25:75) affording a colorless solid.

Yield 118 mg (84 %).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.33, 9.20, 9.18, 9.14, 8.74, 8.53, 7.24, 1.71, 1.70.

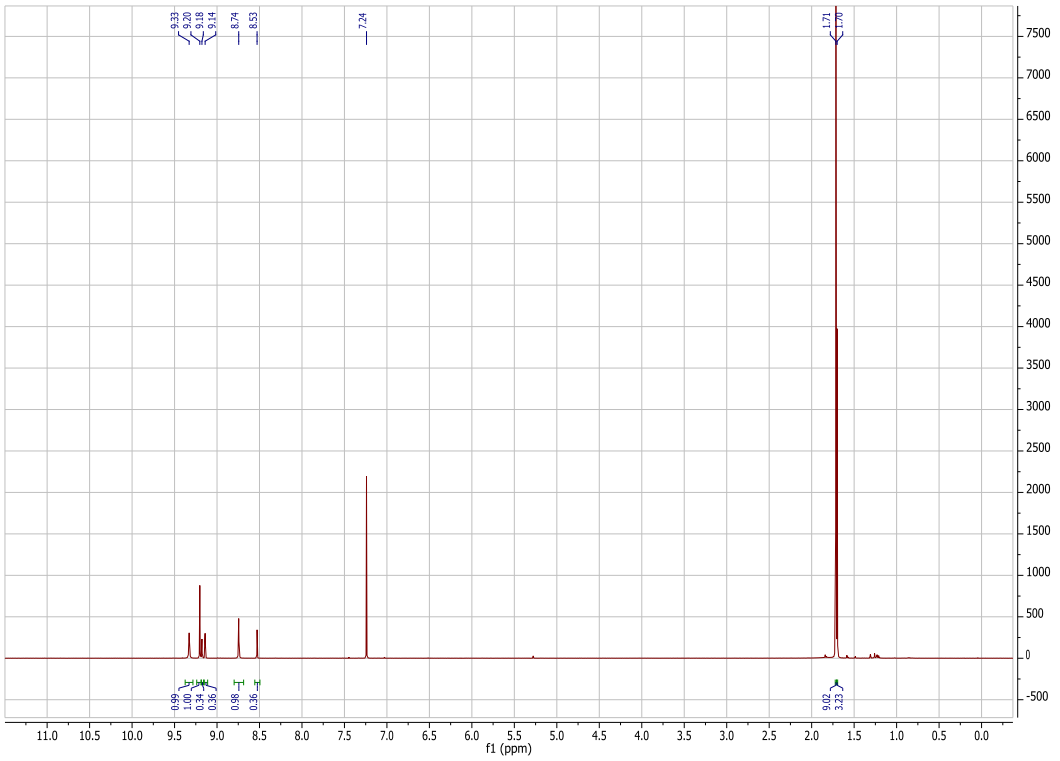
^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.62, 154.90, 154.65, 150.94, 149.44, 146.84, 146.55, 145.82, 144.04, 143.78, 134.87, 123.25, 88.08, 87.52, 77.16, 28.10, 28.07.

MS EI m/z (rel. %): 220 (11, M^+), 147 (10), 120 (84), 93 (17), 66 (23), 57 (100).

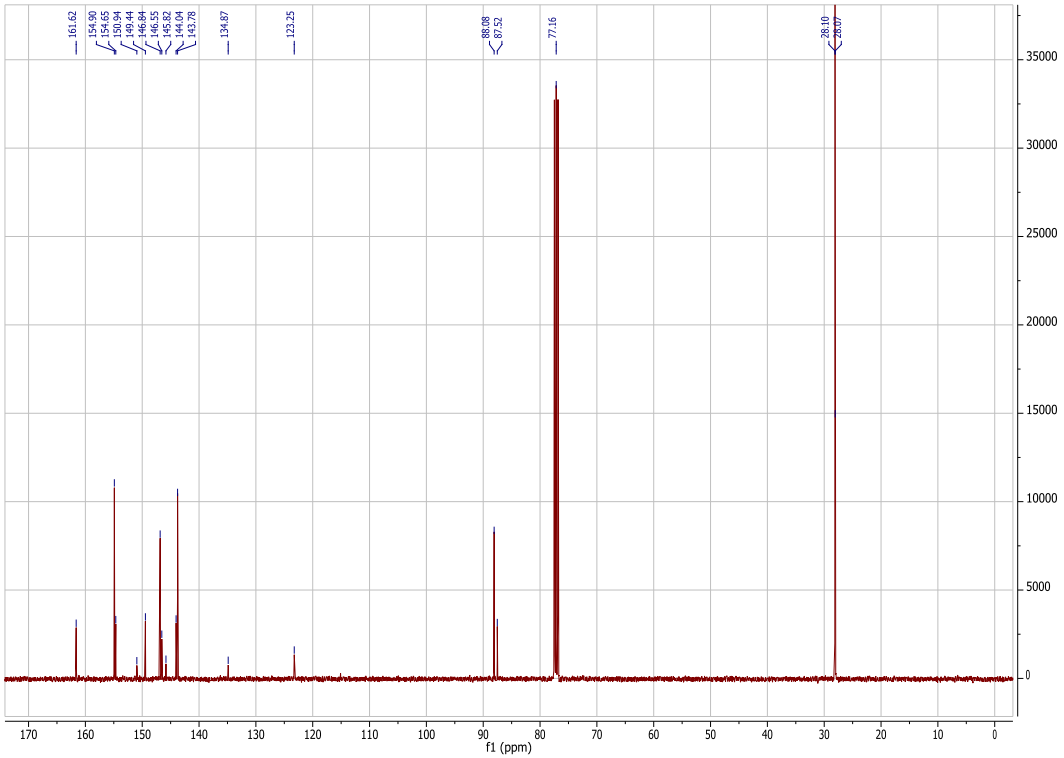
HR-MS Found 220,0956 calcd. for $C_{10}H_{12}N_4O_2$ 220.0960.

M.p. 145 °C.

Compounds not known in literature.

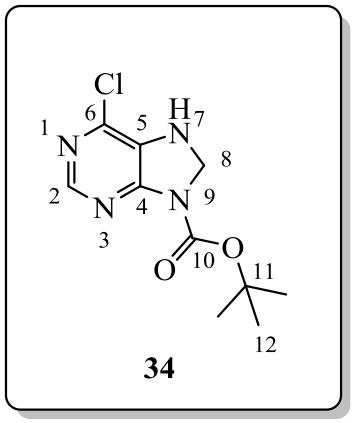


Spectrum 27. ^{1}H NMR ($CDCl_3$, 500 MHz) of *tert*-butyl purine-9-carboxylate (**x**) and *tert*-butyl purine-7-carboxylate (**31ab**).



Spectrum 28. ^{13}C NMR ($CDCl_3$, 100 MHz) of *tert*-butyl purine-9-carboxylate (**x**) and *tert*-butyl purine-7-carboxylate (**31ab**).

Synthesis of *tert*-butyl 6-chloro-7,8-dihydropurine-9-carboxylate (34)



34

tert-Butyl 6-chloropurine-9-carboxylate (**26**) (934 mg, 3.67 mmol) was dissolved in MeOH (50 mL) and set to vigorous stirring. Sodium borohydride (695 mg, 18.4 mmol) was added and the mixture stirred for 20 minutes before water (20 mL) was added. The mixture was concentrated *in vacuo* until a white precipitate was formed. DCM (15 mL) and sodium chloride (0.5 g) was added to the suspension, shaken and transferred to a separation funnel. The layers were separated and the water-phase extracted with DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated *in vacuo* to afford a colorless solid.

Yield 800 mg (85 %).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.16 (s, 1H, 2), 5.33 (s, 2H, 8), 3.85 (br s, 1H, 7), 1.55 (s, 9H, 12).

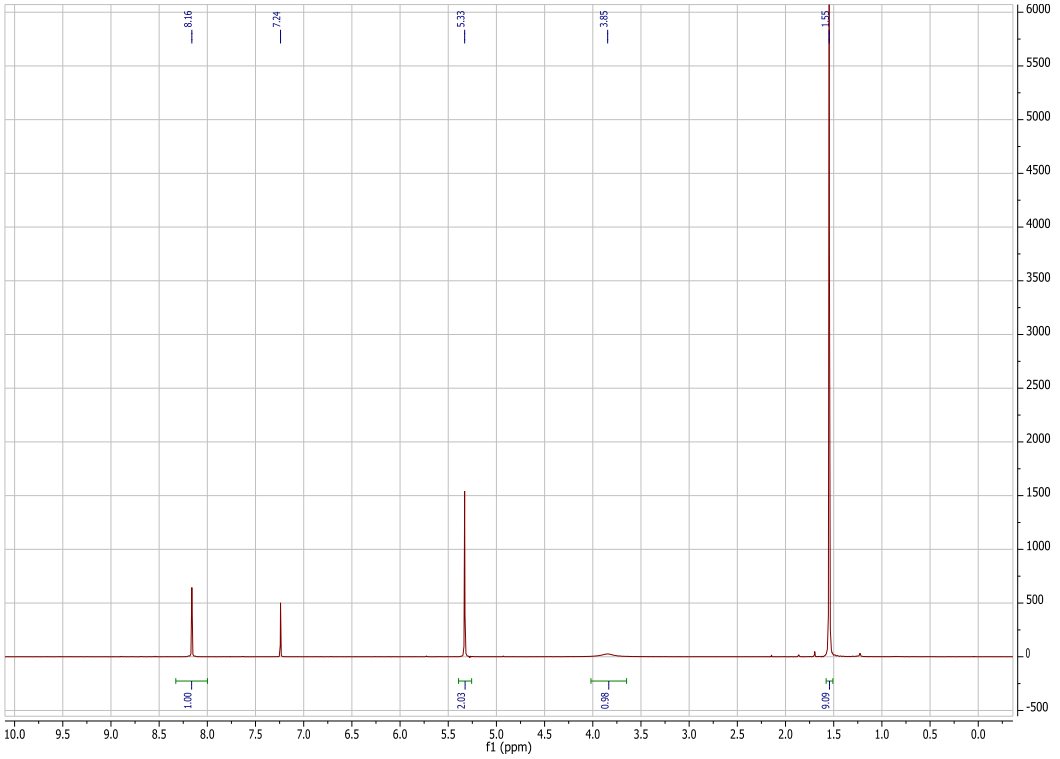
^{13}C NMR ($CDCl_3$, 150 MHz): δ 154.72 (4), 149.50 (2), 148.49 (10), 134.13 (6), 131.00 (5), 84.20 (11), 64.68 (8), 28.27 (12).

MS EI m/z (rel. %): 256 (7, M^+), 183 (7), 158/156 (17/60), 157/155 (35/100), 119 (48), 92 (7), 67 (6), 57 (70).

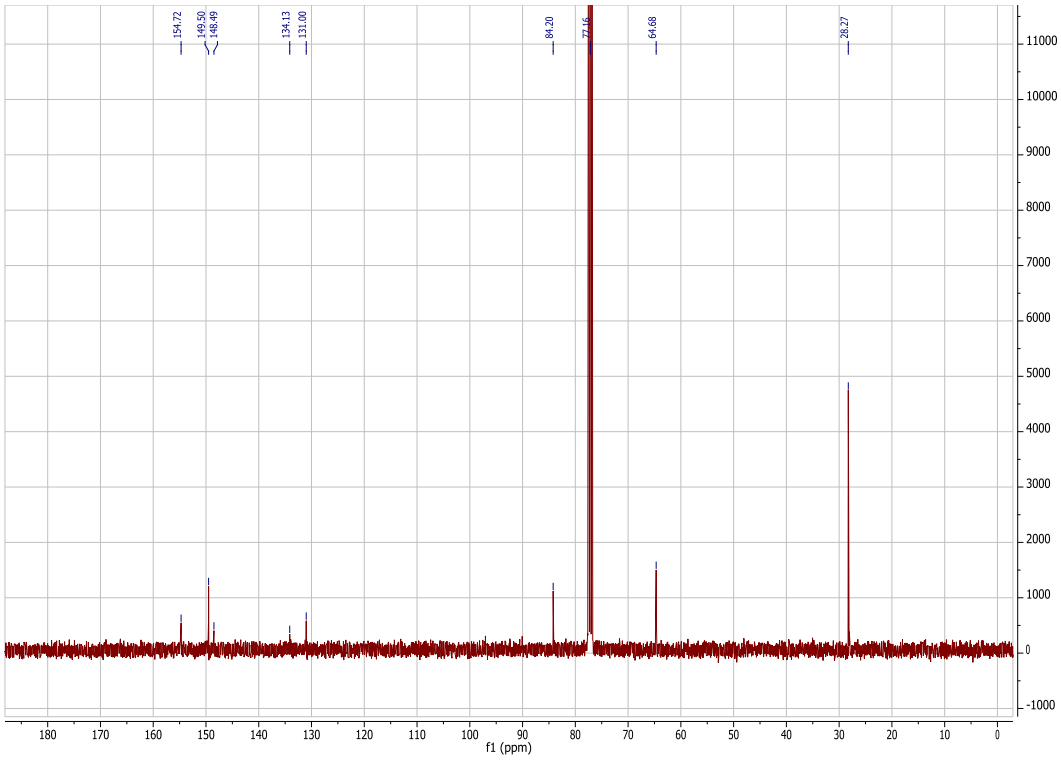
HR-MS Found 256.0726 calcd. for $C_{10}H_{13}ClN_4O_2$ 256.0727.

M.p. >185 °C (dec.) (lit. >185 °C (dec.)).

Compound known in literature.[69]

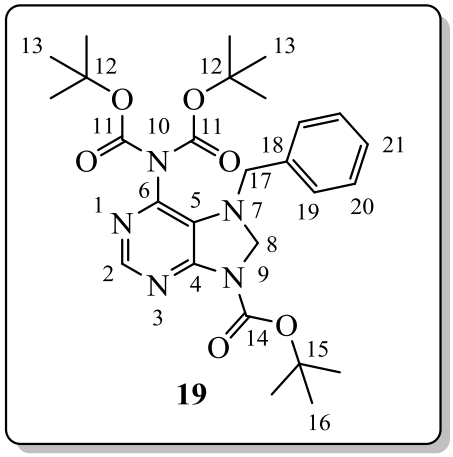


Spectrum 29. ^{1}H NMR ($CDCl_3$, 200 MHz) of *tert*-butyl 6-chloro-7,8-dihydropurine-9-carboxylate (**34**).



Spectrum 30. ^{13}C NMR ($CDCl_3$, 100 MHz) of *tert*-butyl purine-9-carboxylate (**34**).

Synthesis of *tert*-butyl 7-benzyl-6-(*ditert*-butoxycarbonylamino)-8,9-dihydropurine-9-carboxylate (19)



Lithium hexamethyldisilazide (615 µL, 1 M in THF, 0.615 mmol) was added over a period of 5 min to a stirring solution of compound **15** (256 mg, 0.585 mmol) in DMF (7 mL) and THF (3 mL) under argon-atmosphere at -78 °C. After stirring for 10 min., benzyl bromide (105 µL, 0.884 mmol) was added dropwise over a period of 5 min. After stirring for an additional 10 min., the mixture was allowed to warm to room temperature and stirred for 15 min. before sat. aq. NH_4Cl (8 mL) and EtOAc (15 mL) were added. The layers were separated and the water phase extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (2 x 6 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified by flash column chromatography (EtOAc:hexanes – 1:4) affording a colorless solid.

Yield 262 mg (85 %).

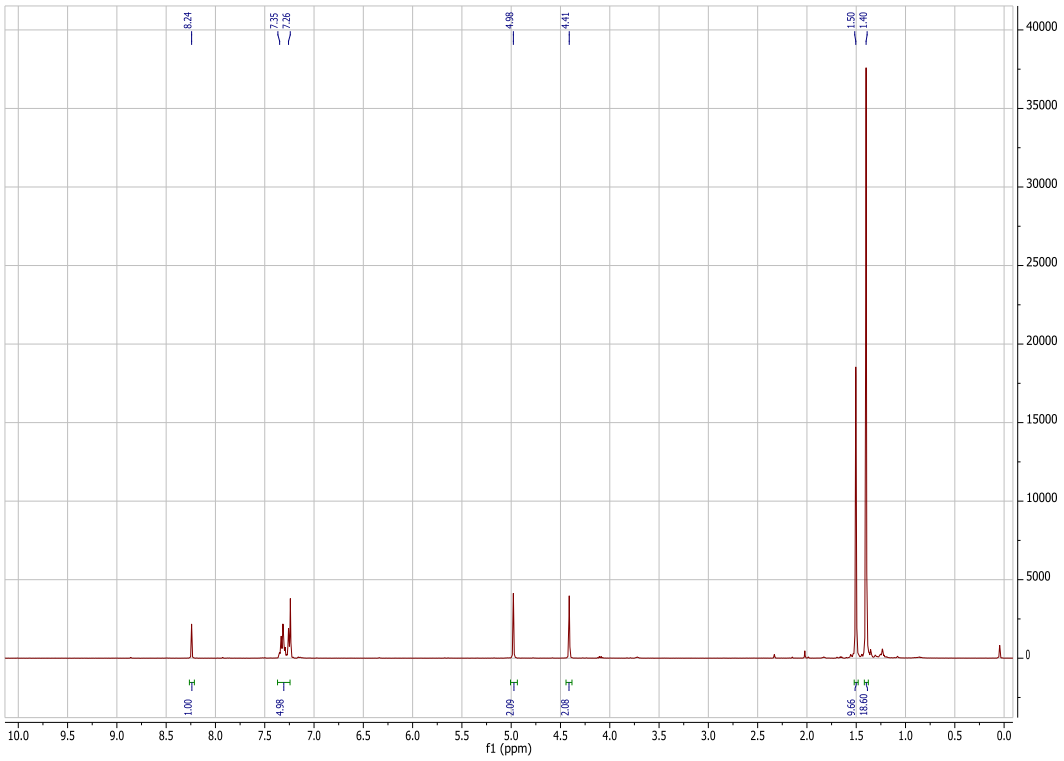
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (s, 1H, 2), 7.35-7.26 (m, 5H, 19/20/21), 4.98 (s, 2H, 8), 4.41 (s, 2H, 17), 1.50 (s, 9H, 16), 1.40 (s, 18H, 13).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.23 (4), 150.45 (11), 148.38 (14), 148.24 (2), 135.55 (18), 134.41 (6), 129.16 (5), 129.06 (20), 128.27 (21), 127.98 (19), 83.93 (12), 83.90 (15), 68.08 (8), 51.05 (17), 28.24 (16), 28.06 (13).

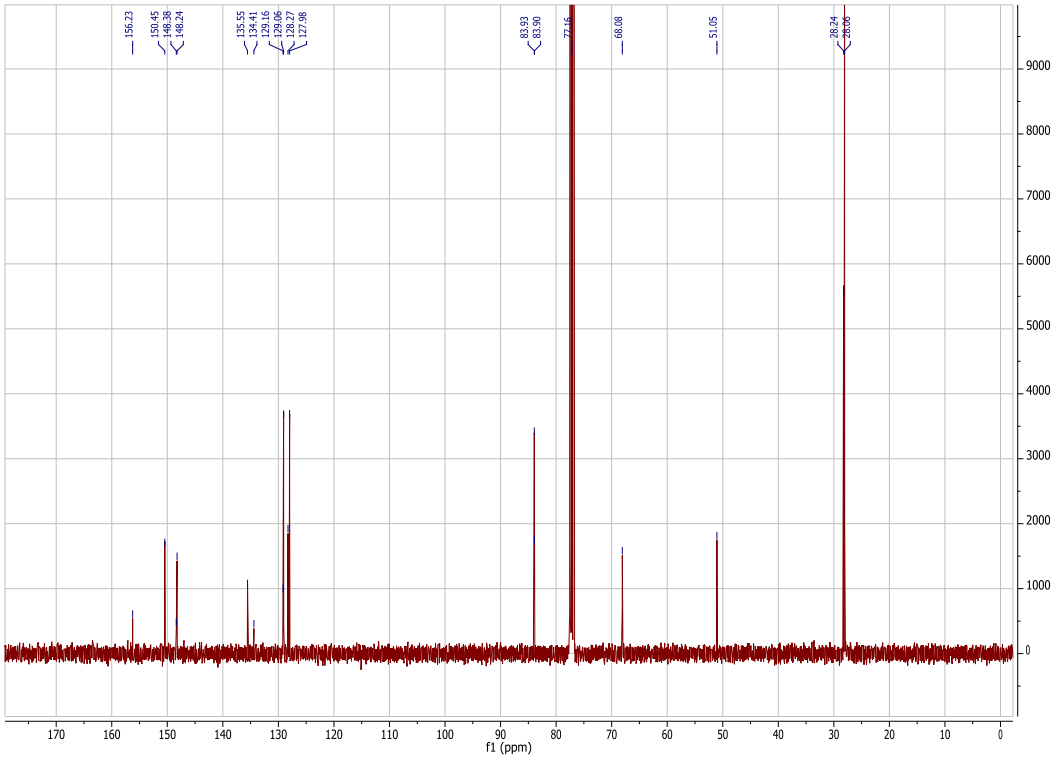
MS EI m/z (rel. %): 527 (2, M^+), 427 (3), 253 (34), 251 (39), 91 (100).

HR-MS Found 527.2733 calcd. for $C_{27}H_{37}N_5O_6$ 527.2744.

M.p. 49 – 50 °C. Compound not known in literature.

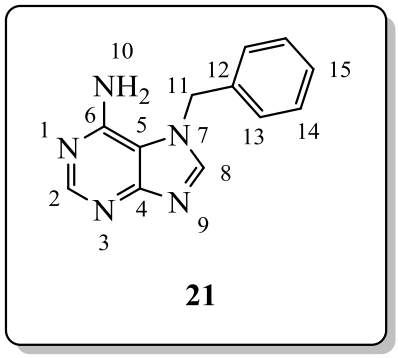


Spectrum 31. ^{1}H NMR ($CDCl_3$, 400 MHz) of *tert*-butyl 7-benzyl-6-(*ditert*-butoxycarbonylamino)-8,9-dihydropurine-9-carboxylate (**19**).



Spectrum 32. ^{13}C NMR ($CDCl_3$, 100 MHz) of *tert*-butyl 7-benzyl-6-(*ditert*-butoxycarbonylamino)-8,9-dihydropurine-9-carboxylate (**19**).

Synthesis of 7-benzylpurin-6-amine (21)



21

Tert-Butyl 7-benzyl-6-(*ditert*-butoxycarbonylamino)-8,9-dihydropurine-9-carboxylate (**19**) (185 mg, 0.351 mmol) was dissolved in DCM (5 mL) and the reaction flask flushed with argon. Trifluoroacetic acid (1.00 mL, 13.0 mmol) was added and the mixture was stirred for 1 hour before the volatiles were removed *in vacuo*. The crude product was purified by flash column chromatography (DCM:MeOH – 9:1) affording a grey solid.

Yield 67 mg (85 %).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.42 (s, 1H, 8), 8.18 (s, 1H, 2), 7.33 (t, *J* = 7.4 Hz, 2H, 14), 7.27 (t, *J* = 7.4 Hz, 1H, 15), 7.14 (d, *J* = 7.4 Hz, 2H, 13), 6.81 (s, 2H, 10), 5.68 (s, 2H, 11).

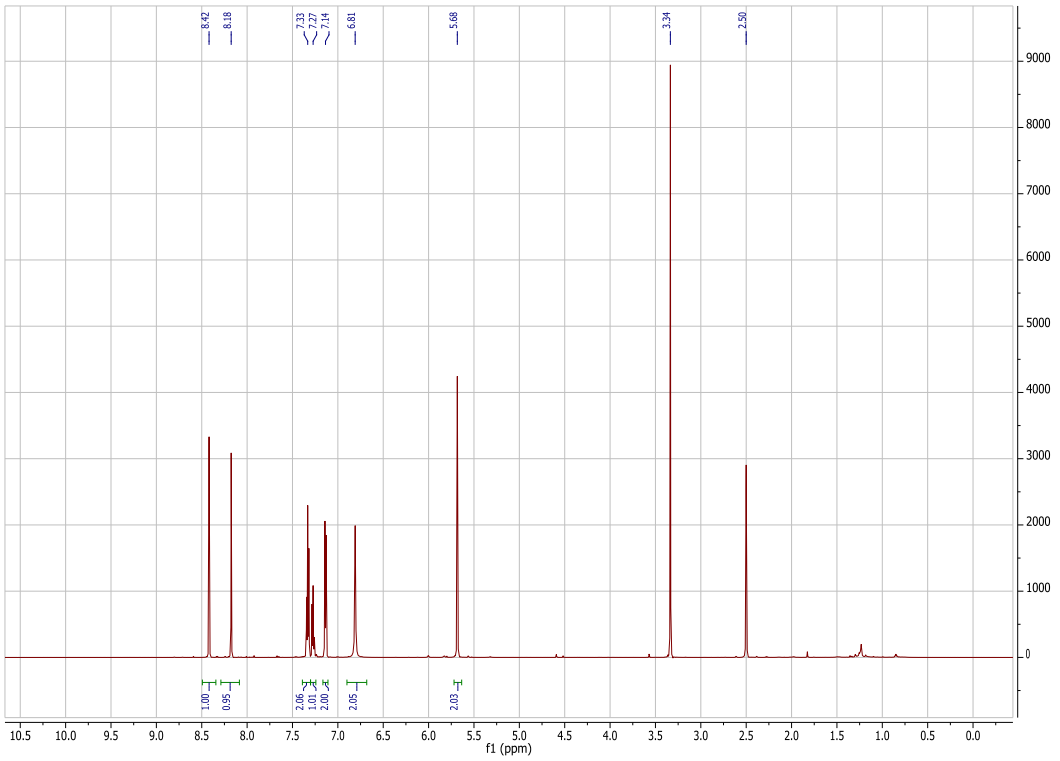
^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.18 (4), 152.39 (2), 151.45 (6), 146.34 (8), 137.47 (12), 128.78 (14), 127.79 (15), 126.63 (13), 110.78 (5), 49.01 (11).

MS ESI m/z (rel. %): 226 ($[M+H]^+$), 248 ($[M+Na]^+$).

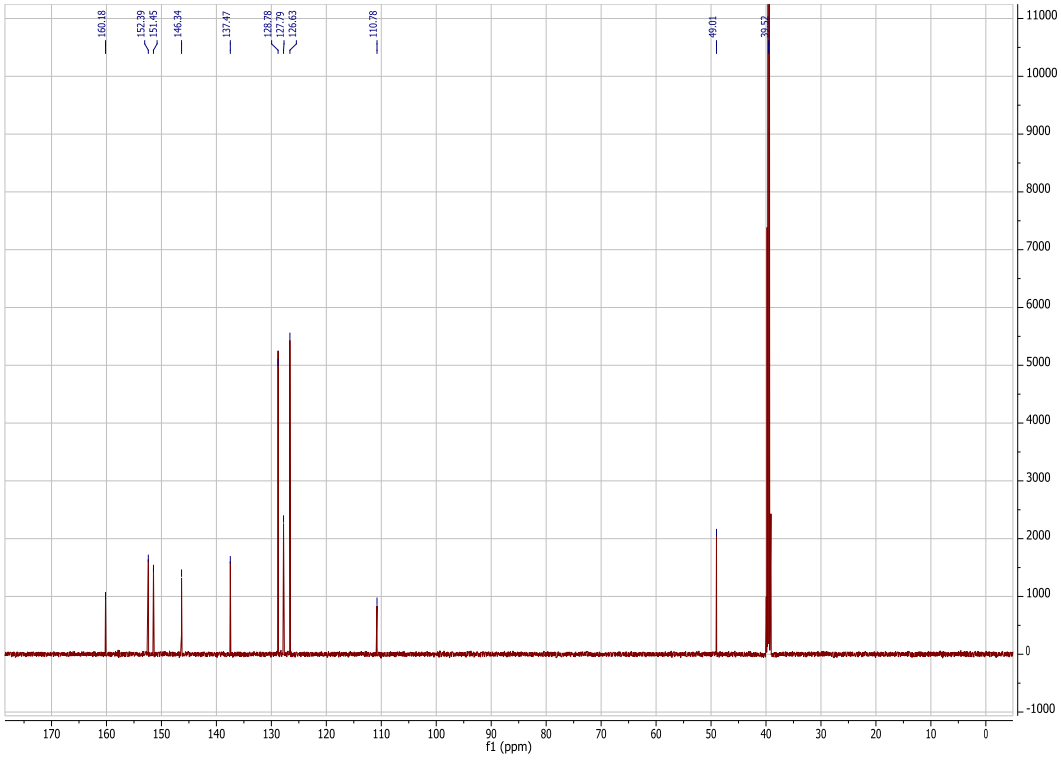
HR-MS Found 226.1089 calcd. for $C_{12}H_{12}N_5$ 226.1087.

M.p. >220 °C (dec.).

Compound known in literature.[103]

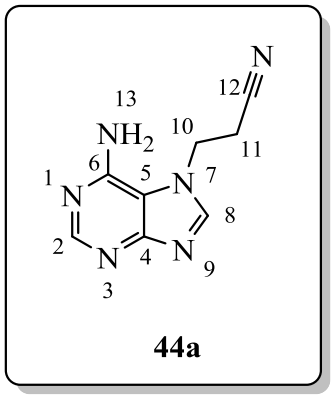


Spectrum 33. ^{1}H NMR (DMSO-d_6, 600 MHz) of 7-benzylpurin-6-amine (**21**).



Spectrum 34. ^{13}C NMR (DMSO-d_6, 150 MHz) of 7-benzylpurin-6-amine (**21**).

Synthesis of 3-(6-aminopurin-7-yl)propanenitrile (44a)



44a

tert-Butyl 7-(2-cyanoethyl)-6-(*ditert*-butoxycarbonylamino)-8,9-dihydropurine-9-carboxylate (**43**) (122 mg, 0.249 mmol) was dissolved in DCM (4.75 mL) and acetonitrile (0.25 mL) was added. Trifluoroacetic acid (1.2 mL) was added over a period of 1 min. under an atmosphere of argon. The mixture was stirred for 1 hour before adding acetonitrile (5 mL) and removing the volatiles *in vacuo*. The residue was purified by flash column chromatography (DCM:MeOH – 9:1) affording an off-white powder.

Yield 39 mg (83 %).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.32 (s, 1H, 8), 8.21 (s, 1H, 2), 7.01 (s, *J* = 6.6 Hz, 2H, 13), 4.70 (t, *J* = 6.6 Hz, 2H, 10), 2.99 (t, 2H, 11).

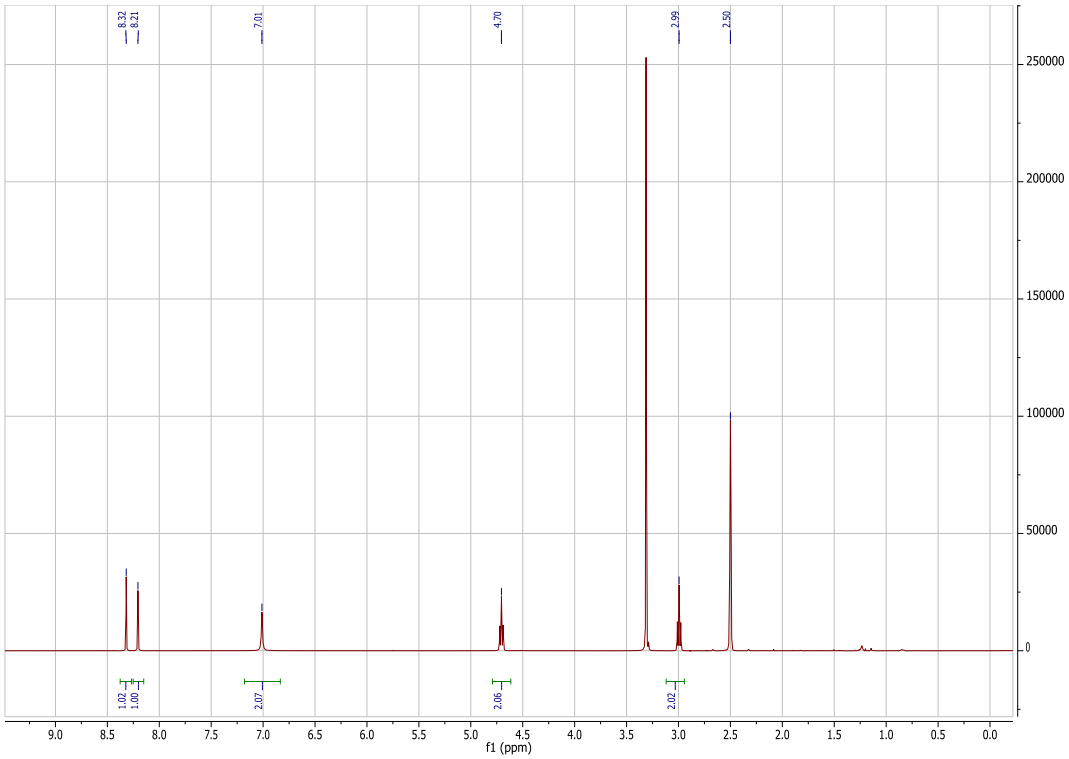
^{13}C NMR (DMSO-d_6, 100 MHz): δ 160.07 (4), 152.45 (2), 151.28 (6), 145.97 (8), 117.93 (12), 110.46 (5), 41.64 (10), 20.57 (11).

MS EI m/z (rel. %): 188 (3, M^+), 135 (10), 108 (24), 81 (4), 66 (1), 53 (25).

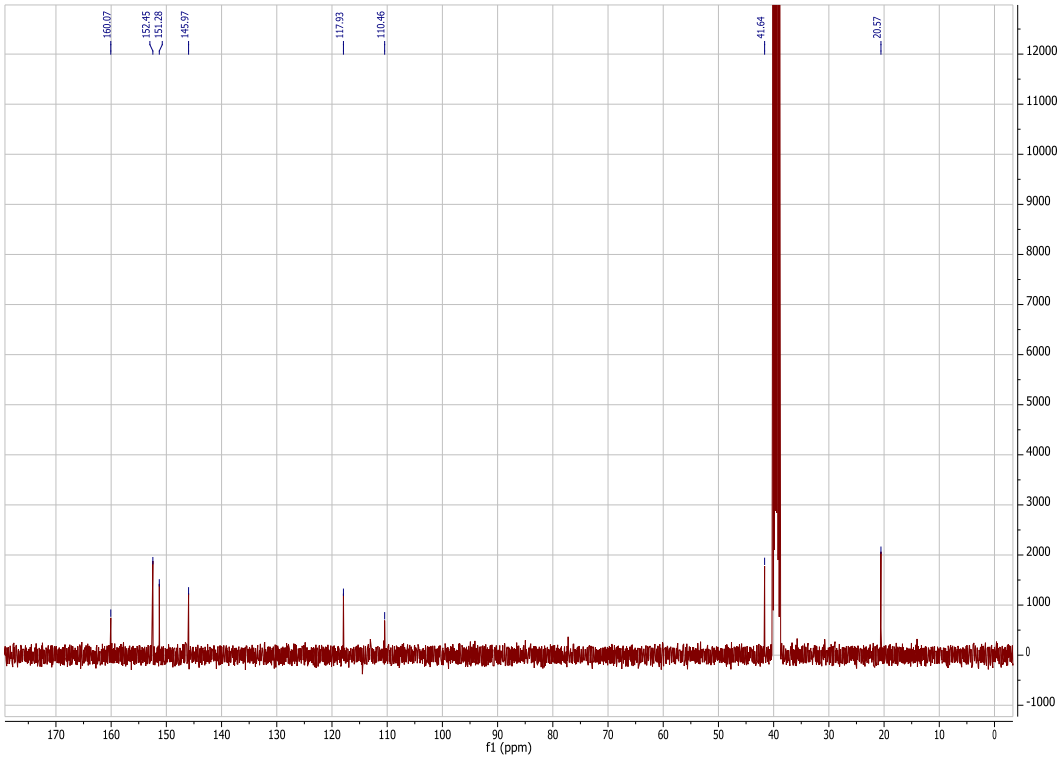
HR-MS Found 188.0813 calcd. for $C_8H_8N_6$ 188.0810.

M.p. >300 °C (lit. >300 °C).

Compound known in literature.[44]

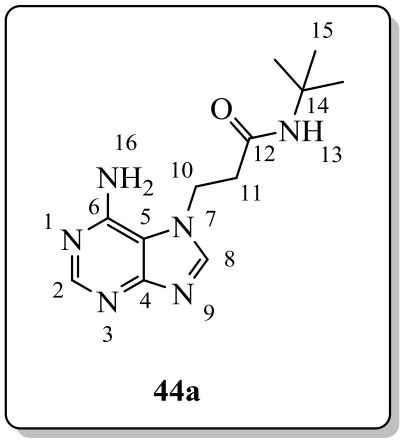


Spectrum 35. ^{1}H NMR (DMSO-d_6, 400 MHz) of 3-(6-aminopurin-7-yl)propanenitrile (**44a**).



Spectrum 36. ^{13}C NMR (DMSO-d_6, 100 MHz) of 3-(6-aminopurin-7-yl)propanenitrile (**44a**).

Synthesis of 3-(6-aminopurin-7-yl)-*N*-(*tert*-butyl)propanamide(44b)



44a

tert-Butyl 7-(2-cyanoethyl)-6-(*ditert*-butoxycarbonylamino)-8,9-dihydropurine-9-carboxylate (**43**) (248 mg, 0.505 mmol) was dissolved in DCM (5 mL). Trifluoroacetic acid (4.0 mL) was added over a period of 1 min. under an atmosphere of argon. The mixture was stirred for 20 hours before removing the volatiles *in vacuo*. The residue was purified by flash column chromatography (DCM:MeOH – 9:1) affording an off-white powder.

Yield 75 mg (57 %).

^{1}H NMR (MeOH-d_4, 600 MHz): δ 8.23 (s, 1H, 2), 8.18 (s, 1H, 8), 4.66 (t, *J* = 6.2 Hz, 2H, 10), 2.70 (t, *J* = 6.2 Hz, 2H, 11), 1.20 (s, 9H, 15).

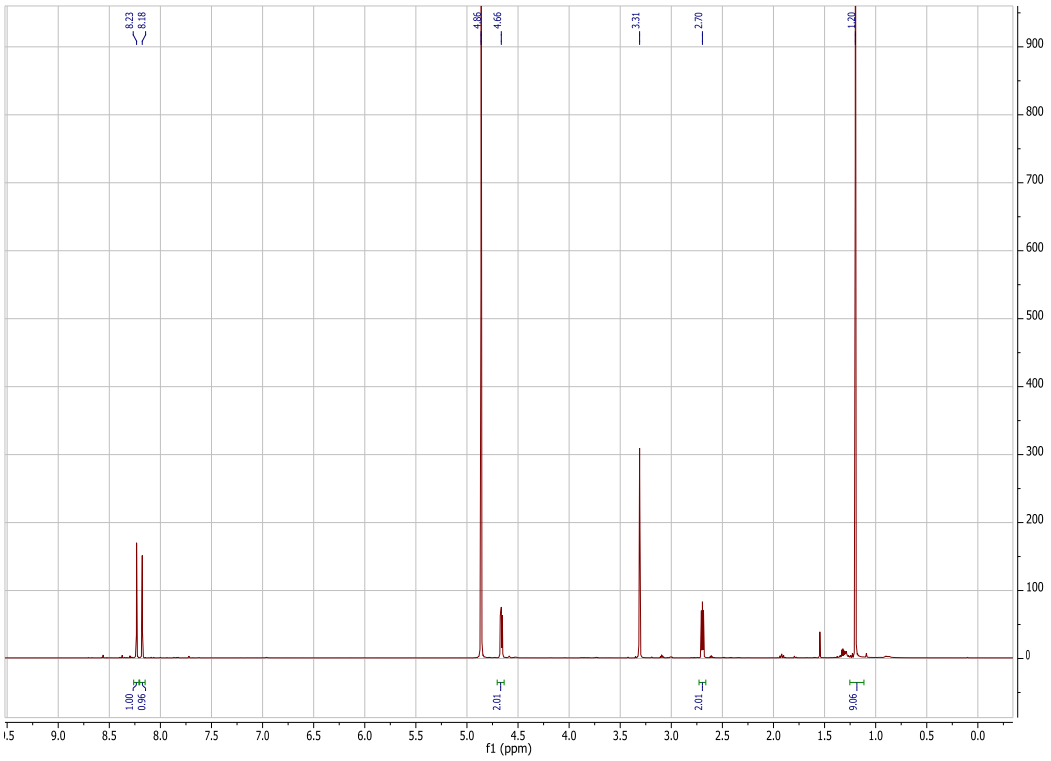
^{13}C NMR (MeOH-d_4, 150 MHz): δ 171.23 (12), 160.16 (4), 153.66 (6), 153.60 (2), 147.56 (8), 112.51 (5), 52.14 (14), 44.44 (10), 39.33 (11), 28.70 (15).

MS ESI m/z (rel. %): 547 ($[2M + Na]^+$), 285 ($[M+Na]^+$), 263 ($[M+H]^+$).

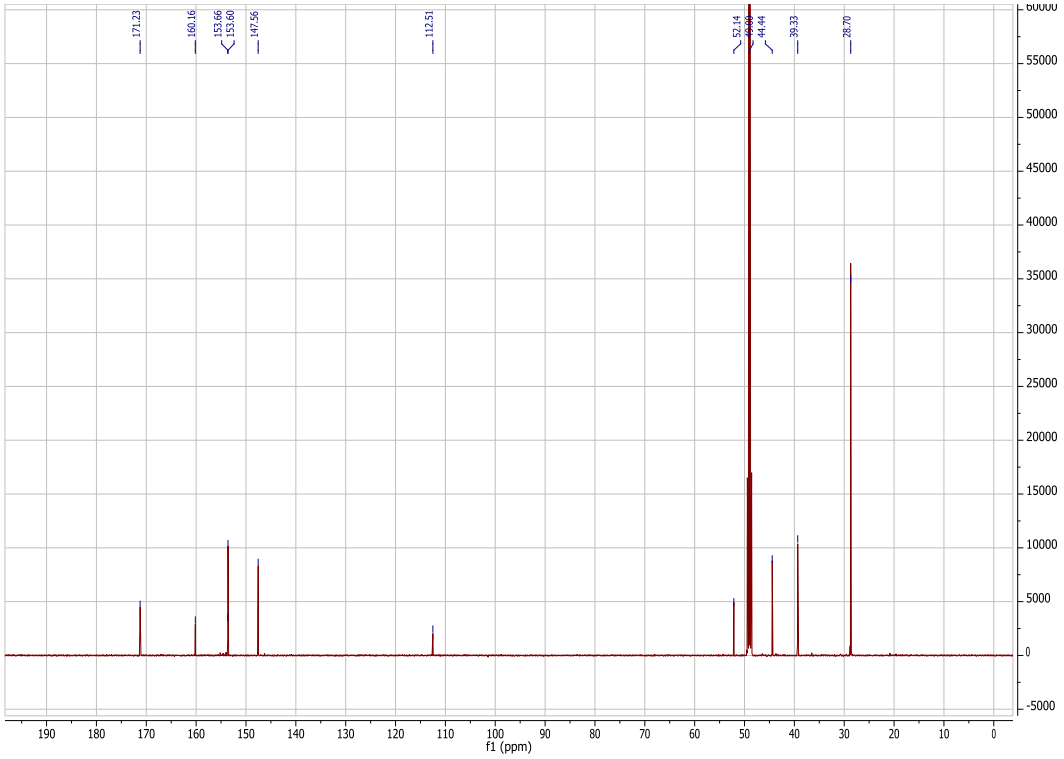
MS EI m/z (rel. %): 262 (100, M^+), 162 (25), 135 (88), 128 (12), 72 (41), 58 (26).

HR-MS Found 262.1548 calcd. for $C_{12}H_{18}N_6O$ 262.1542.

Compound not known in literature.

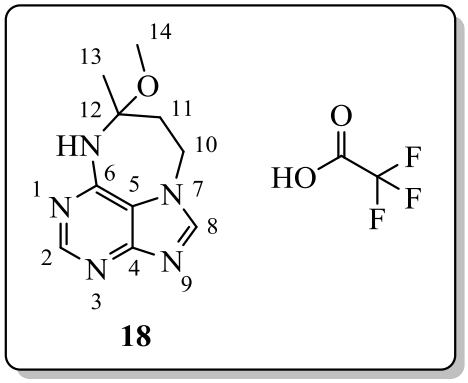


Spectrum 37. ^{1}H NMR (MeOH-d_4, 600 MHz) of 3-(6-amino-7H-purin-7-yl)-N-(tert-butyl)propanamide(**44b**).



Spectrum 38. ^{13}C NMR (MeOH-d_4, 150 MHz) of 3-(6-amino-7H-purin-7-yl)-N-(tert-butyl)propanamide(**44b**).

Synthesis of 9-methoxy-9-methyl-7,8,9,10-tetrahydro-[1,4]diazepino[1,2,3-*gh*]purinium 2,2,2-trifluoroacetate (18)



18

tert-Butyl 6-(*ditert*-butoxycarbonylamino)-7-(3-oxobutyl)-8,9-dihydropurine-9-carboxylate (**16**) (1.012 g, 1.995 mmol) was dissolved in DCM (10 mL), molecular sieves 3Å (5 g) was added. Trifluoroacetic acid (2 mL) was added dropwise through the septum over a period of 3 minutes under an atmosphere of argon and the reaction mixture was stirred for 1 hour. The volatiles were removed *in vacuo* and the crude oil was dissolved in THF (10 mL) and DCM (10 mL). Manganese(IV) oxide (347 mg, 3.99 mmol) was added under an atmosphere of argon. The reaction was stirred for 2 hours before the mixture was filtered through a pad of celite, concentrated to a yellow oil and purified by flash column chromatography (silica gel, DCM:MeOH – 91:9) affording an off-white hygroscopic powder.

Yield 556 mg (calc. 83 %[†])

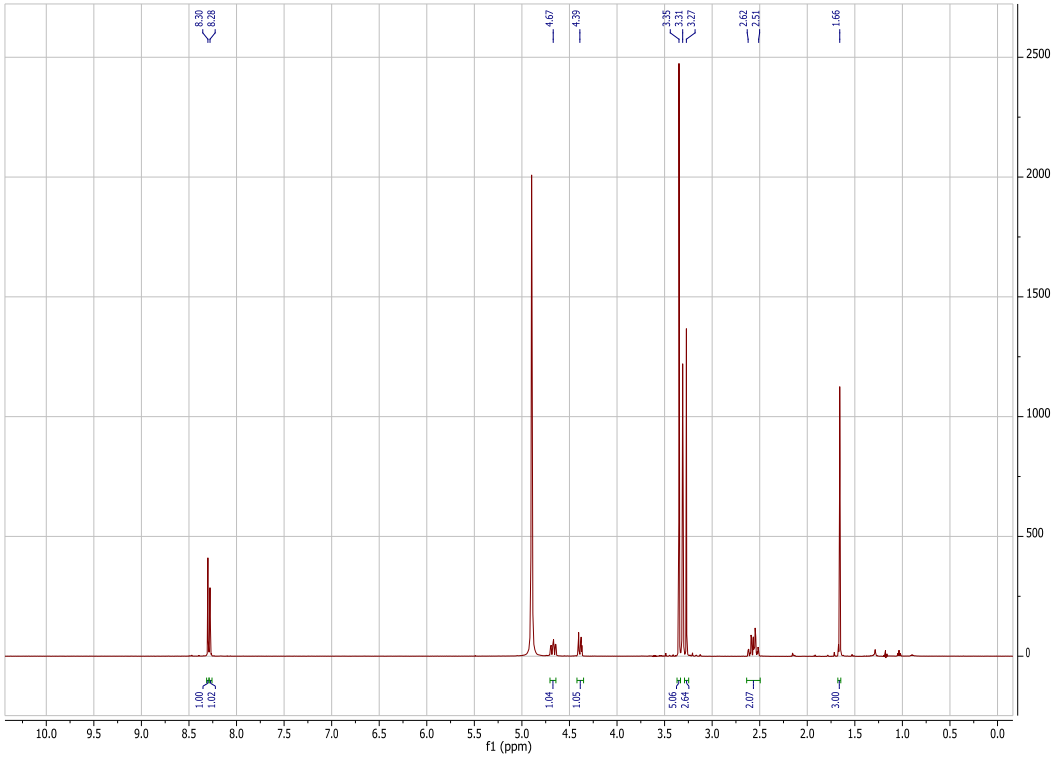
^{1}H NMR (MeOH-d_4, 500 MHz): δ 8.31 (s, 1H, 2), 8.29 (s, 1H, 8), 4.67 (td, *J* = 3.3 Hz, 13.0 Hz, 1H, 10), 4.39 (dt, *J* = 3.3 Hz, 13.0 Hz, 1H, 10), 3.27 (s, 3H, 14), 2.55 (m, 2H, 11), 1.66 (s, 3H, 13).

^{13}C NMR (MeOH-d_4, 125 MHz): δ 159.52 (4), 153.66 (2), 152.16 (6), 146.18 (8), 113.80 (5), 85.29 (12), 56.74 (14), 43.31 (10), 40.83 (11), 26.07 (13).
MS ESI m/z (rel. %): 461 (*[2M + Na]*$^{+}$), 220 (*[M + H]*$^{+}$).

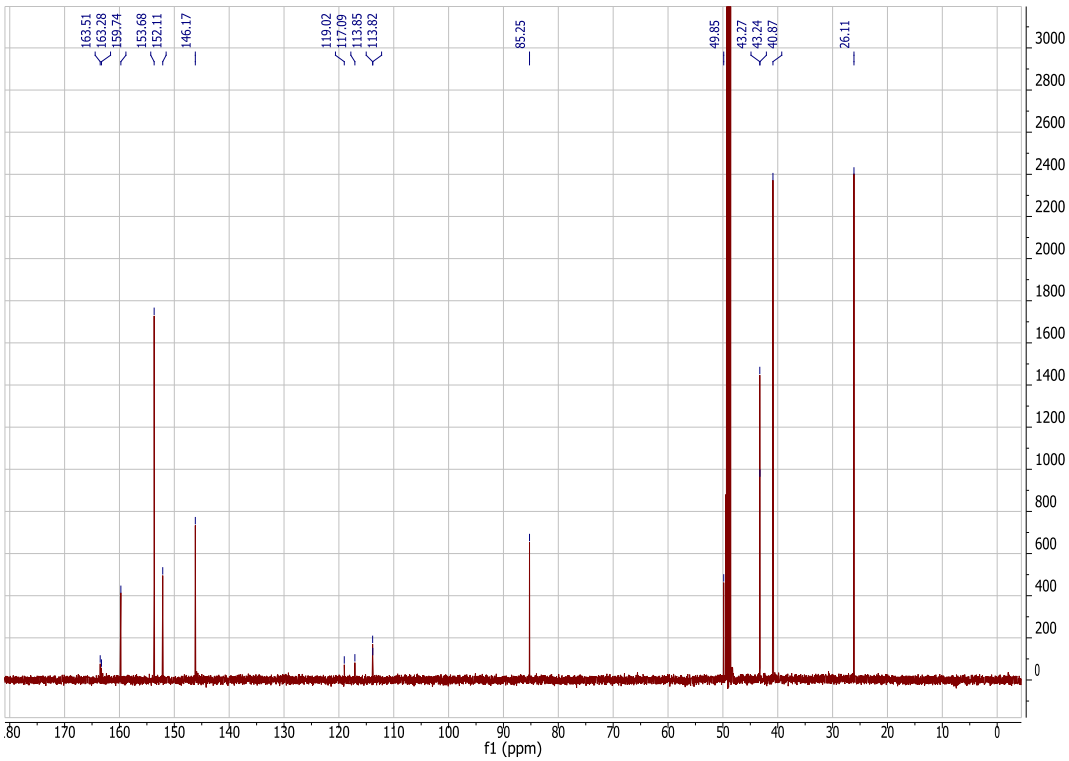
HR-MS Found 220.1196 calcd. for $C_{10}H_{14}N_5O$ 220.1193.

M.p. Deliquescent.
Compound not known in literature.

[†] Calculated by subtracting the amount of methanol present measured by ^{1}H NMR from the weight of the isolated material.

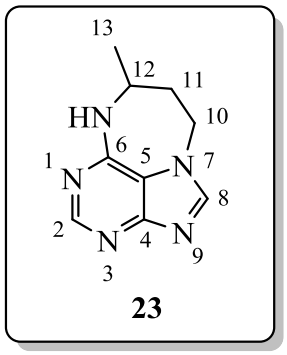


Spectrum 39. ^{1}H NMR (MeOH-d_4, 500 MHz) of 9-methoxy-9-methyl-7,8,9,10-tetrahydro-[1,4]diazepino[1,2,3-*gh*]purinium 2,2,2-trifluoroacetate (**18**).



Spectrum 40. ^{13}C NMR (MeOH-d_4, 150 MHz) of 9-methoxy-9-methyl-7,8,9,10-tetrahydro-[1,4]diazepino[1,2,3-*gh*]purinium 2,2,2-trifluoroacetate (**18**).

Synthesis of 9-methyl-7,8,9,10-tetrahydro-[1,4]diazepino[1,2,3-*gh*]purine (23)



23

9-Methoxy-9-methyl-7,8,9,10-tetrahydro-[1,4]diazepino[1,2,3-*gh*]purinium trifluoroacetate (**18**) (93 mg, 0.28 mmol) was dissolved in ethanol (10 mL), $NaBH_4$ (42 mg, 1.1 mmol) was added and the reaction stirred for 24 h. The volatiles were evaporated *in vacuo* and the crude material was purified by flash column chromatography (DCM:MeOH:Et_3N – 90:10:2) affording a colorless solid.

Yield 49 mg (92 %).

^{1}H NMR (MeOH-d_4, 200 MHz): δ 8.25 (s, 1H, 2), 8.22 (s, 1H, 8), 4.60 (m, 1H, 10), 4.66 – 4.55 (m, 1H, 10), 4.32 – 4.19 (m, 1H, 10), 3.88 – 3.73 (m, 2H, 12), 2.37 – 2.05 (m, 2H, 11). 1.46 (d, J = 6.6 Hz, 3H, 13).

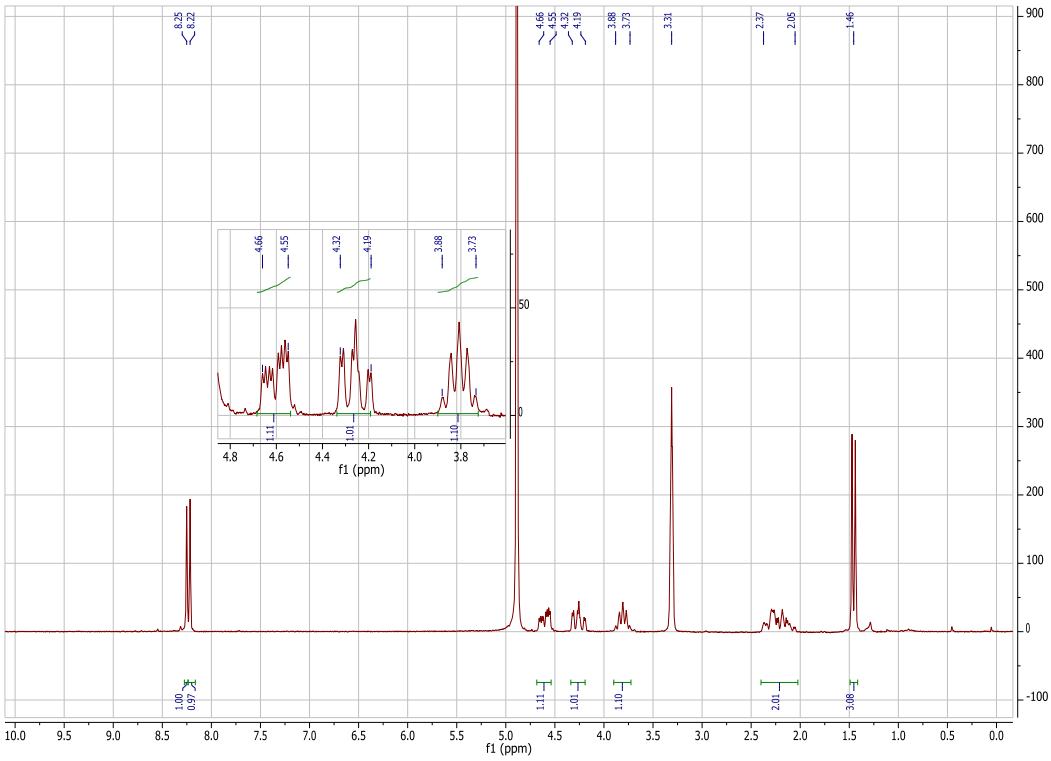
^{13}C NMR (MeOH-d_4, 150 MHz): δ 154.58 (4), 153.80 (6), 149.85 (2), 146.93 (8), 112.61 (5), 52.78 (12), 47.86 (10), 35.87 (11), 21.96 (13).

MS EI m/z (rel. %): 190 (8), 189 (80, M^+), 160 (4), 120 (19), 93 (3).

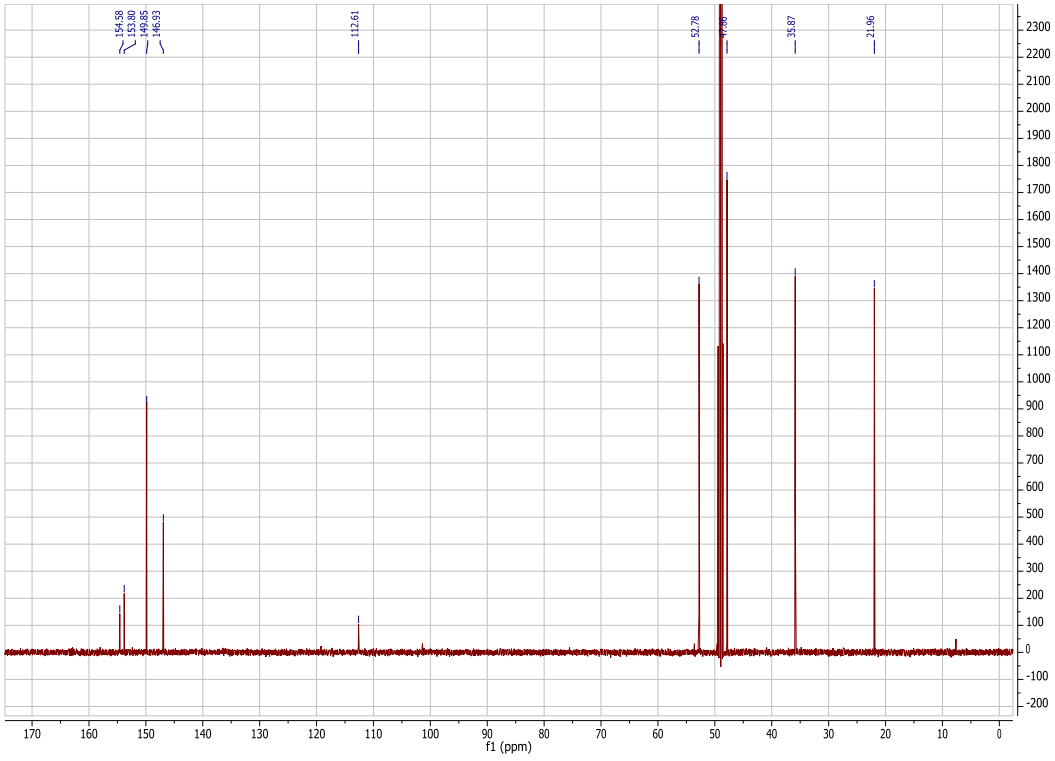
HR-MS Found 189.1019 calcd. for $C_9H_{11}N_5$ 189.1014.

M.p. >250 °C.

Compound not known in literature.

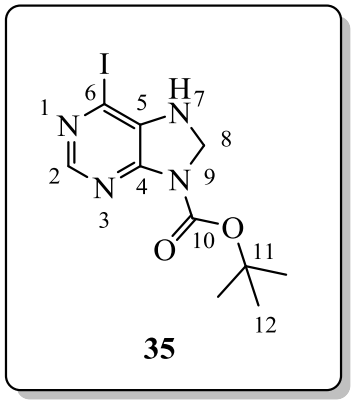


Spectrum 41. ^{1}H NMR (MeOH-d_4, 200 MHz) of 9-methyl-7,8,9,10-tetrahydro-[1,4]diazepino[1,2,3-*gh*]purine (**23**).



Spectrum 42. ^{13}C NMR (MeOH-d_4, 150 MHz) of 9-methyl-7,8,9,10-tetrahydro-[1,4]diazepino[1,2,3-*gh*]purine (**23**).

Synthesis of *tert*-butyl 6-iodo-7,8-dihydropurine-9-carboxylate (35)



35

tert-Butyl 6-iodopurine-9-carboxylate (**27**) (862 mg, 2.49 mmol) was dissolved in MeOH (50 mL). Sodium borohydride (475 mg, 12.6 mmol) was added and the mixture was stirred for 20 minutes before water (20 mL) was added. The mixture was concentrated *in vacuo* until a white precipitate was formed. DCM (15 mL) and sodium chloride (0.5 g) was added and the layers separated. The water-phase was extracted with DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated *in vacuo* to afford a colorless solid.

Yield 659 mg (76 %).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.04 (s, 1H, 2), 5.31 (s, 2H, 8), 4.04 (br s, 1H, 7), 1.54 (s, 9H, 12).

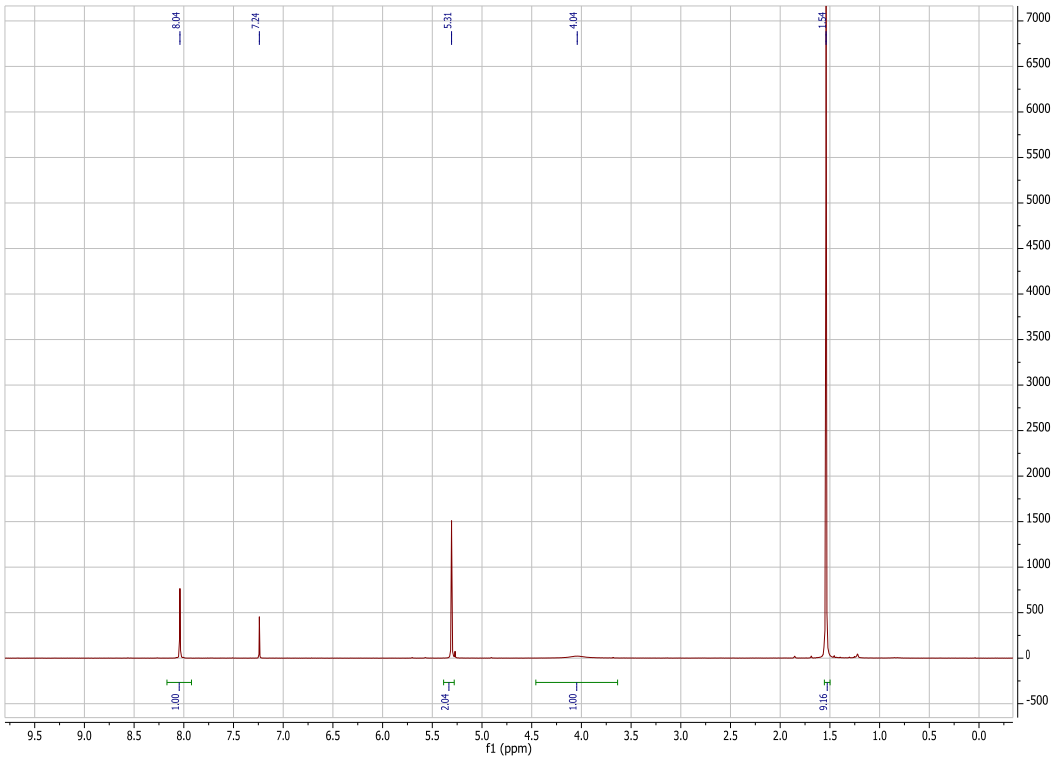
^{13}C NMR ($CDCl_3$, 150 MHz): δ 151.38 (4), 149.83 (2), 148.77 (10), 137.99 (5), 99.63 (6), 84.05 (11), 63.43 (8), 28.26 (12).

MS EI m/z (rel. %): 256 (7, M^+), 183 (7), 158/156 (17/60), 157/155 (35/100), 119 (48), 92 (7), 67 (6), 57 (70).

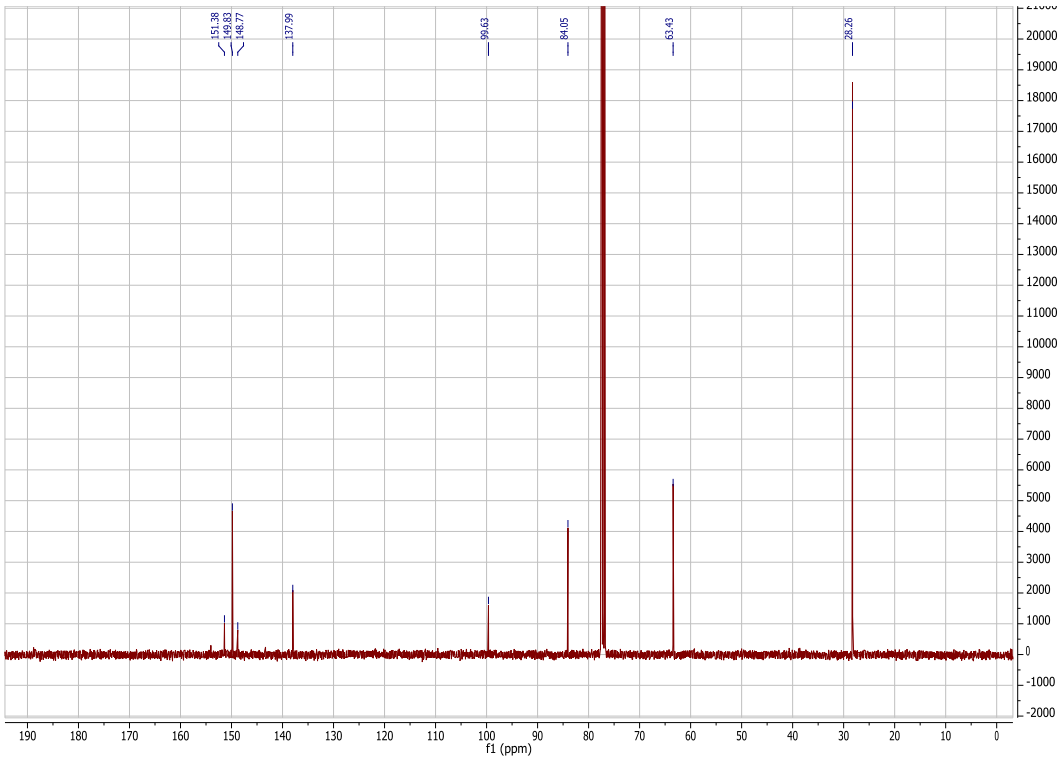
HR-MS Found 256.0726 calcd. for $C_{10}H_{13}ClN_4O_2$ 256.0727.

M.p. >164 °C (dec.) (lit. >165 °C (dec.)).

Compound known in literature.[69]

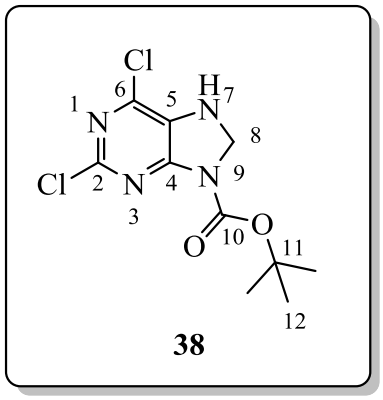


Spectrum 43. ^{1}H NMR ($CDCl_3$, 200 MHz) of *tert*-butyl 6-iodo-7,8-dihydropurine-9-carboxylate (**35**).



Spectrum 44. ^{13}C NMR ($CDCl_3$, 100 MHz) of *tert*-butyl 6-iodo-7,8-dihydropurine-9-carboxylate (**35**).

Synthesis of *tert*-butyl 2,6-dichloro-7,8-dihydropurine-9-carboxylate (38)



38

tert-butyl 2,6-dichloropurine-9-carboxylate (**30**) (101 mg, 0.349 mmol) was dissolved in MeOH (5 mL). Sodium borohydride (27 mg, 0.71 mmol) was quickly and the mixture was stirred for 20 minutes before water (5 mL) was added. The mixture was concentrated *in vacuo* until a white precipitate was formed. DCM (5 mL) and sodium chloride was added to the suspension. The layers were separated and the water-phase extracted with DCM (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated *in vacuo* to afford a colorless solid.

Yield 76 mg (75 %).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.37 (s, 2H, 8), 4.48 (br s, 1H, 7), 1.52 (s, 9H, 12).

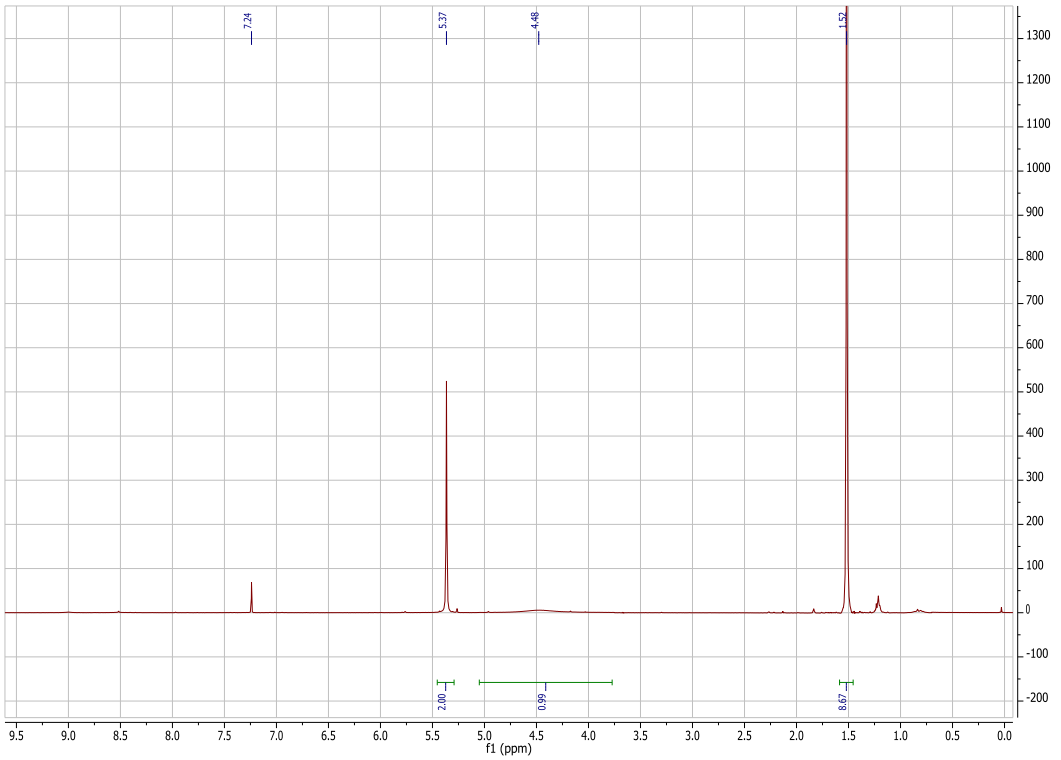
^{13}C NMR ($CDCl_3$, 150 MHz): δ 156.20, 149.14, 148.17, 134.10, 130.24, 84.59, 77.16, 65.49, 28.19.

MS EI m/z (rel. %): 290 (3, M^+), 190 (100).

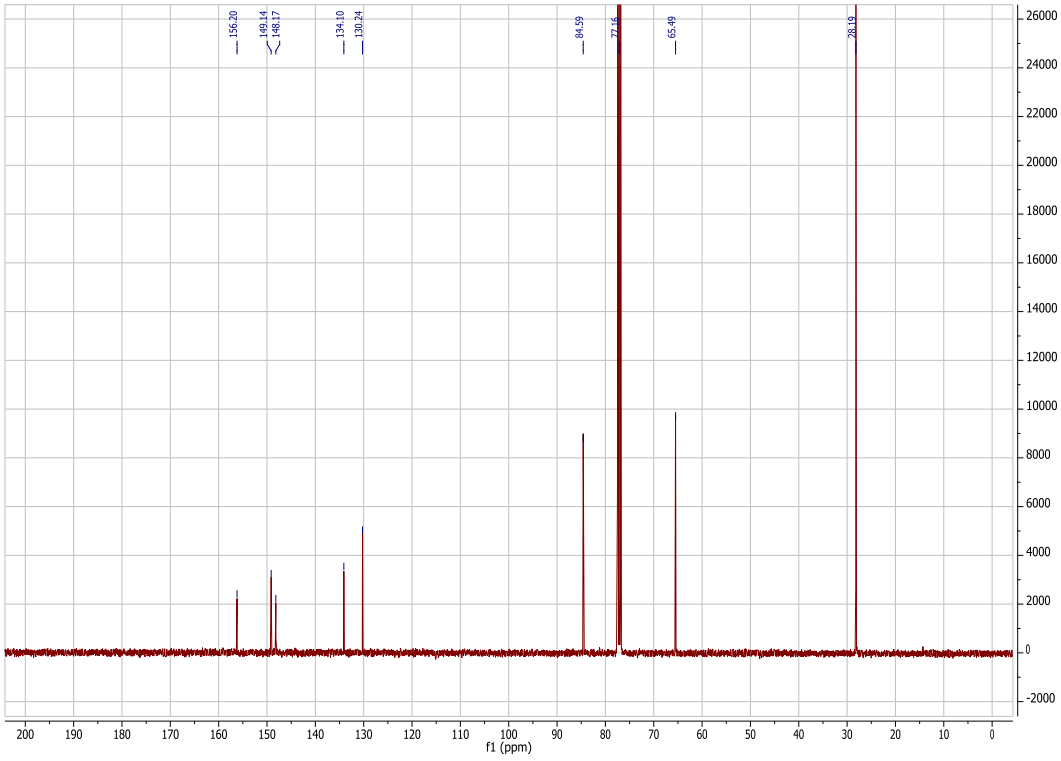
HR-MS Found 290.0330 calcd. for $C_{10}H_{12}Cl_2N_4O_2$ 290.0337.

M.p.: >165 °C (dec.)

Compound known in literature.[69]

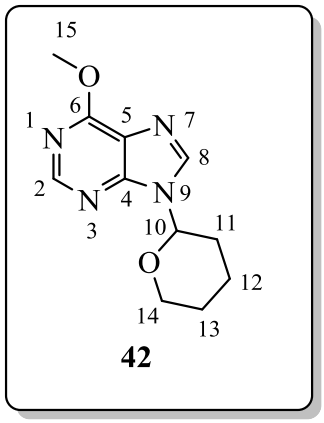


Spectrum 45. ^{1}H NMR ($CDCl_3$, 200 MHz) of *tert*-butyl 2,6-dichloro-7,8-dihydropurine-9-carboxylate (**38**).



Spectrum 46. ^{13}C NMR ($CDCl_3$, 100 MHz) of *tert*-butyl 2,6-dichloro-7,8-dihydropurine-9-carboxylate (**38**).

Synthesis of 6-methoxy-9-(tetrahydro-*2H*-pyran-2-yl)purine (42)



42

6-Chloro-9-(tetrahydro-*2H*-pyran-2-yl)purine (**33**) (52 mg, 0.22 mmol) was dissolved in methanol (5 mL) and heated to reflux. $NaBH_4$ (16 mg, 0.42 mmol) was added and the reaction was stirred for 40 min. The flask was cooled, volatiles removed *in vacuo* and the crude product purified was by flash column chromatography (DCM:MeOH – 97:3) affording a grey solid.

Yield 12 mg (23 %).

^{1}H NMR (MeOH-d_4, 600 MHz): δ 8.53 (s, 1H, 2), 8.12 (s, 1H, 8), 5.75 – 5.73 (m, 1H, 10), 4.17 (s, 3H, 150), 4.16 – 4.14 (m, 1H, 14), 3.78 – 3.74 (m, 1H, 14), 2.12 – 2.01 (m, 3H, 11/12), 1.80 – 1.69 (m, 2H, 12/13), 1.67 – 1.62 (m, 1H, 13).

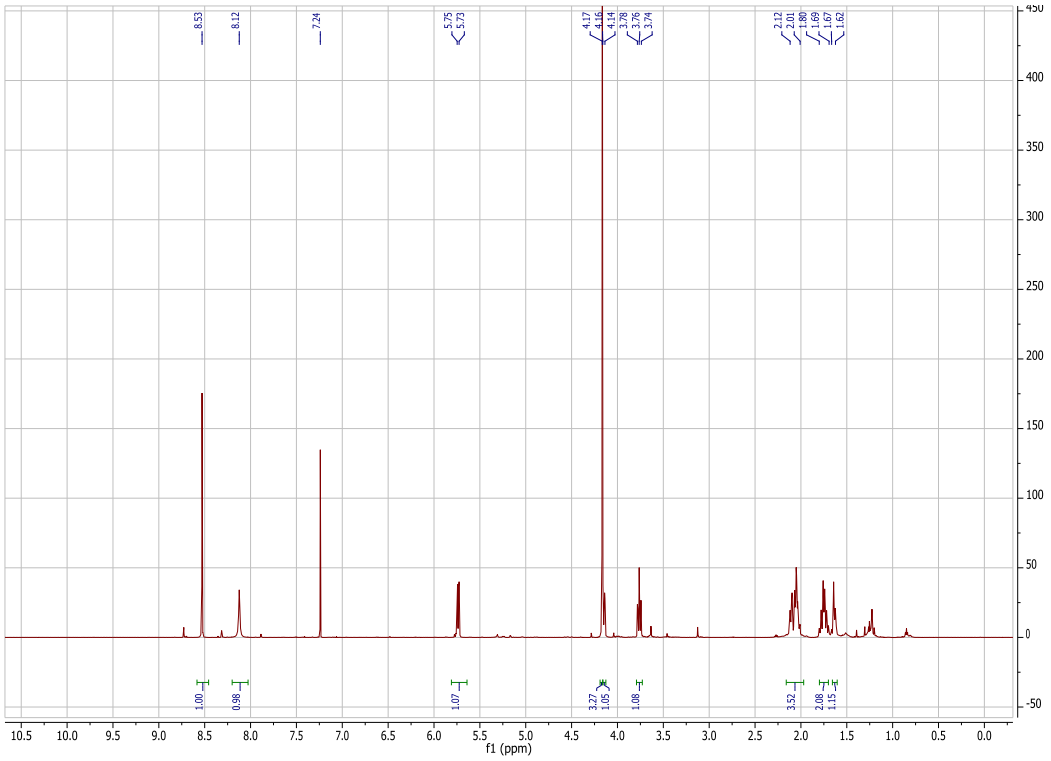
^{13}C NMR (MeOH-d_4, 150 MHz): δ 161.23 (6), 152.35 (2), 151.35 (4), 140.08 (8), 121.56 (5), 82.27 (10), 68.96 (14), 54.39 (15), 31.95 (11), 25.01 (13), 22.95 (12).

MS EI m/z (rel. %): 234 (27, M^+), 206 (15), 152 (7), 151 (100), 149 (14), 121 (10), 120 (19), 93 (12), 85 (62), 84 (33), 67 (15).

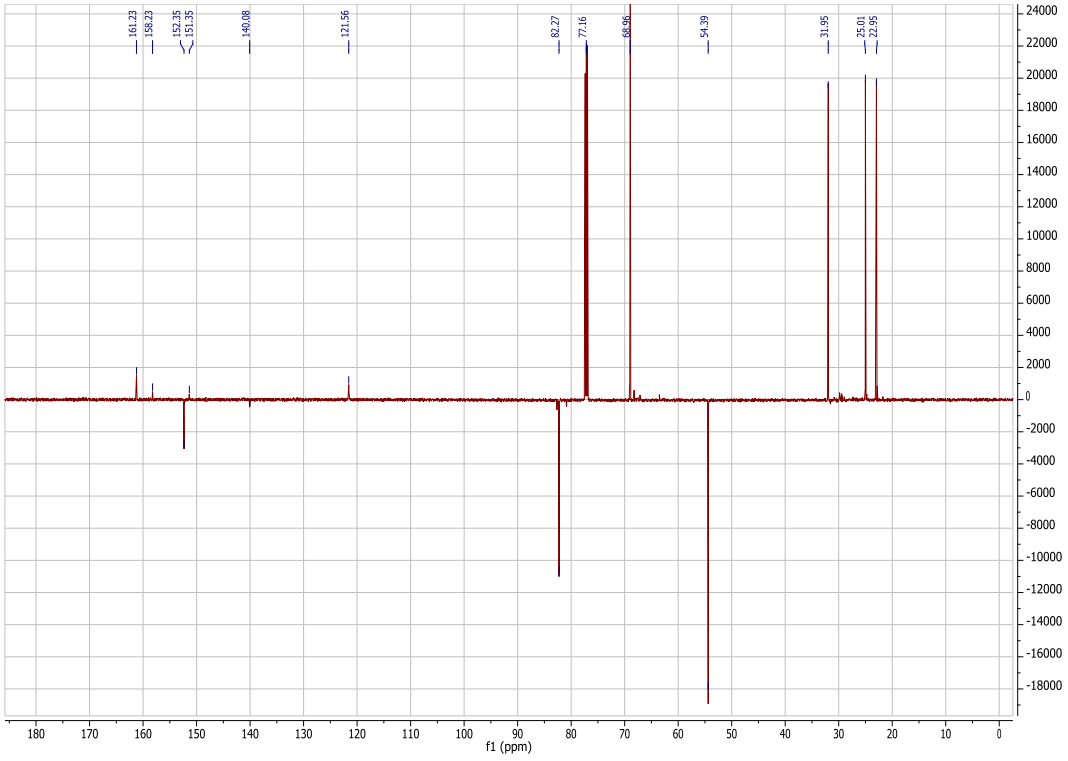
HR-MS Found 240.0771 calcd. for $C_{10}H_{13}ClN_4O$ 240.0778.

M.p. >250 °C.

Compound not known in literature.

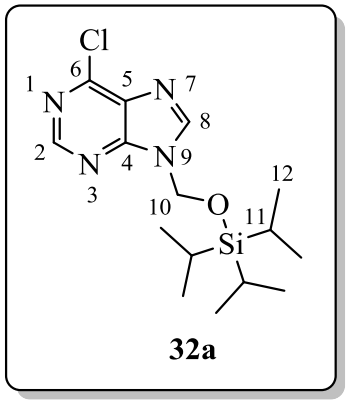


Spectrum 47. ^{1}H NMR ($CDCl_3$, 600 MHz) of 6-methoxy-9-(tetrahydro-*2H*-pyran-2-yl)purine (**42**).



Spectrum 48. ^{13}C NMR APT ($CDCl_3$, 150 MHz) of 6-methoxy-9-(tetrahydro-*2H*-pyran-2-yl)purine (**42**).

Synthesis of 6-chloro-9-(((triisopropylsilyl)oxy)methyl)purine (32a)



32a

6-Chloropurine (296 mg, 1.92 mmol) was suspended in DCM (6 mL) and triethylamine (295 µL, 2.12 mmol) was added. (Triisopropylsiloxy)methyl chloride (490 µL, 2.11 mmol) was added under an atmosphere of argon. The mixture was stirred for 30 minutes and the volatiles were removed *in vacuo*. The crude product was purified by flash column chromatography (hexanes:ethyl acetate – 7:3 to 3:7 gradient) affording a yellow solid.

Yield 332 mg (51 %).

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.74 (s, 1H, 2), 8.30 (s, 1H, 8), 5.89 (s, 2H, 10), 1.17 (sept, *J* = 7.5 Hz, 3H, 11), 1.03 (d, *J* = 7.5 Hz, 18H, 12).

^{13}C NMR ($CDCl_3$, 150 MHz): δ 152.33 (2), 151.31 (4), 151.24 (6), 144.79 (8), 131.63 (5), 68.34 (10), 17.88 (12), 11.98 (11).

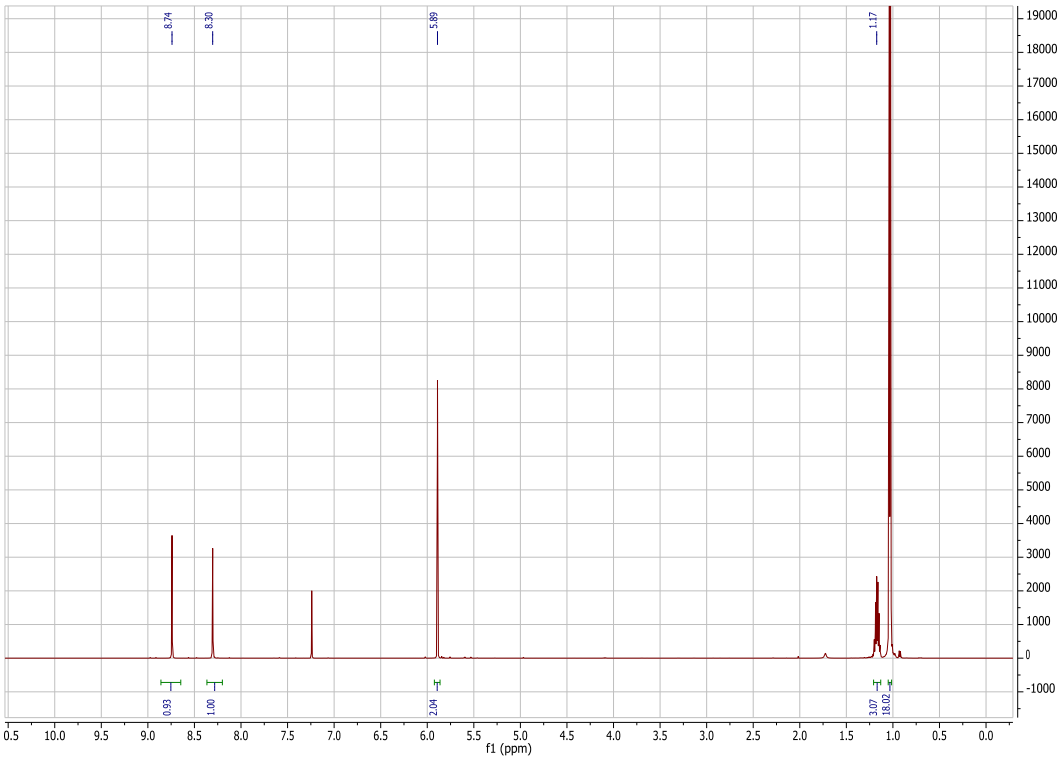
MS EI m/z (rel. %): 300 (6), 299 (37), 298 (19), 297 (100), 211 (7).

MS ESI m/z (rel. %): 341 ($[M+H]^+$).

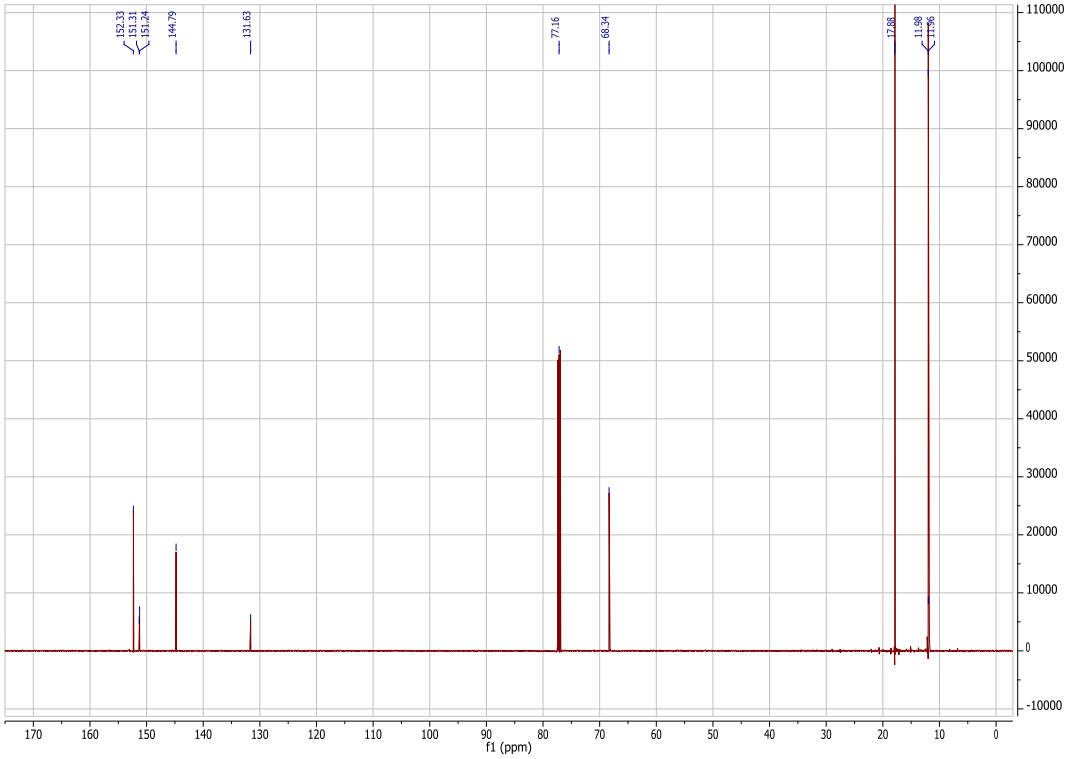
HR-MS Found 341.1555 calcd. for $C_{15}H_{26}ClN_4OSi$ 341.1559.

M.p. 71 – 72 °C.

Compound not known in literature.

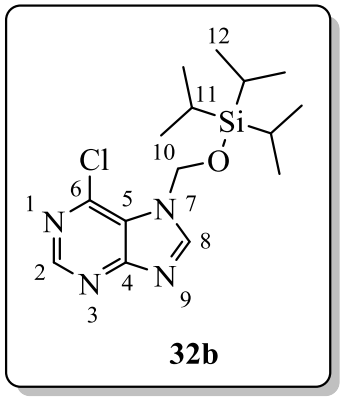


Spectrum 49. ^{1}H NMR ($CDCl_3$**,** 600 MHz) of 6-chloro-9-(((triisopropylsilyl)oxy)methyl)purine (**32a**).



Spectrum 50. ^{1}H NMR ($CDCl_3$, 150 MHz) of 6-chloro-9-(((triisopropylsilyl)oxy)methyl)purine (**32a**).

Synthesis of 6-chloro-7-(((triisopropylsilyl)oxy)methyl)purine (32b)



32b

6-Chloropurine (296 mg, 1.92 mmol) was suspended in DCM (6 mL) and triethylamine (295 µL, 2.12 mmol) was added. (Triisopropylsiloxy)methyl chloride (490 µL, 2.11 mmol) was added under an atmosphere of argon. The mixture was stirred for 30 minutes and the volatiles were removed *in vacuo*. The crude product was purified by flash column chromatography (hexanes:ethyl acetate – 7:3 to 3:7 gradient) affording a yellow solid.

Yield 235 mg (36 %).

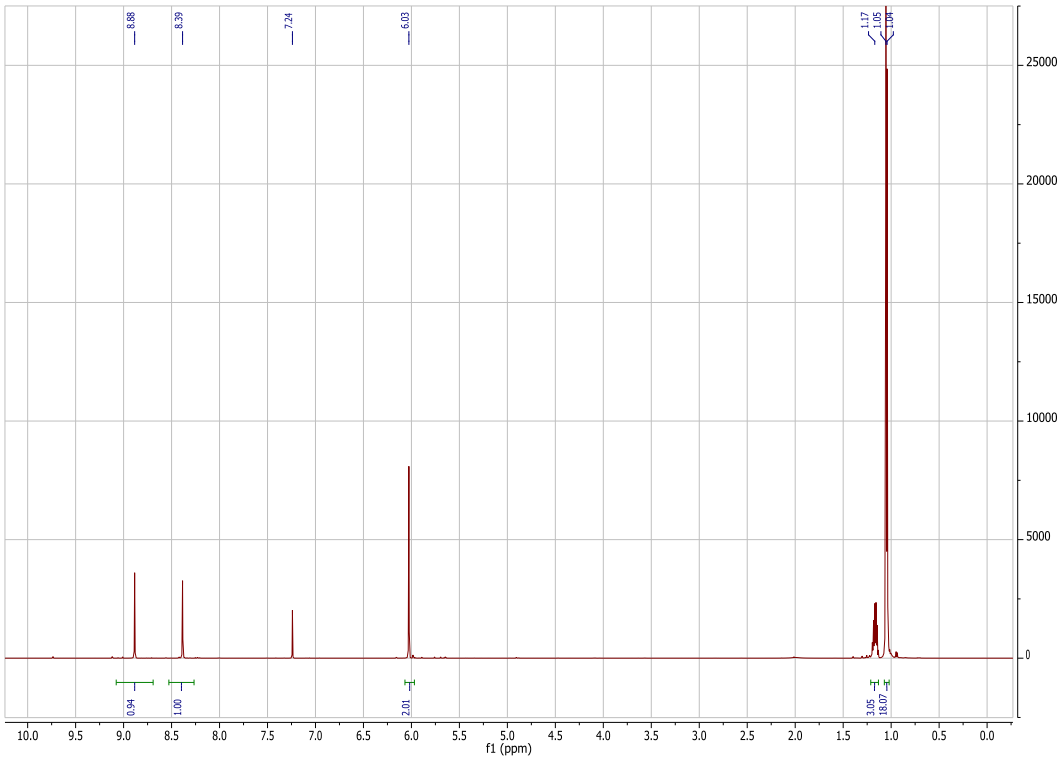
^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.88 (s, 1H, 2), 8.39 (s, 1H, 8), 6.03 (s, 2H, 10), 1.17 (sept, *J* = 7.5 Hz, 3H, 11), 1.04 (d, *J* = 7.5 Hz, 18H, 12).

^{13}C NMR ($CDCl_3$, 150 MHz): δ 162.47 (4), 152.89 (2), 148.29 (8), 143.40 (6), 122.07 (5), 71.20 (10), 17.90 (12), 12.03 (11).

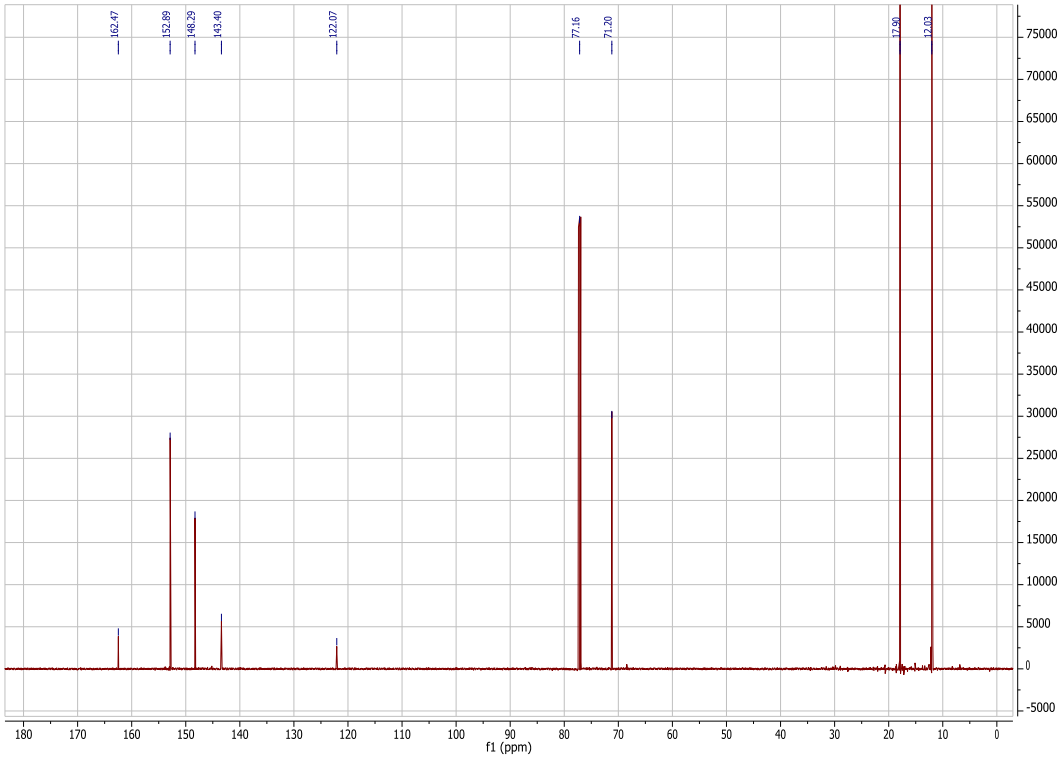
MS EI m/z (rel. %): 300 (8), 299 (33), 298 (22), 297 (100), 211 (11).

M.p. 88 – 89 °C.

Compound not known in literature.

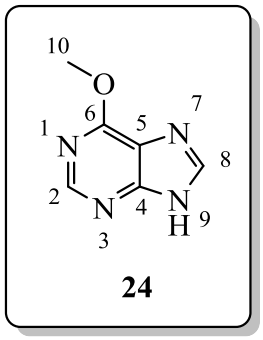


Spectrum 51. ^{1}H NMR ($CDCl_3$**,** 600 MHz) of 6-chloro-7-(((triisopropylsilyl)oxy)methyl)purine (**32b**).



Spectrum 52. ^{13}C NMR ($CDCl_3$**,** 150 MHz) of 6-chloro-7-(((triisopropylsilyl)oxy)methyl)purine (**32b**).

Synthesis of 6-methoxypurine (24)



24

Sodium (450 mg, 19.6 mmol) was added to methanol (8 mL) and allowed to react and dissolve. This solution was added to 6-chloropurine (300 mg, 1.94 mmol) and the suspension heated to 65 °C on an oil bath. The reaction was stirred for 24 hours before being cooled and acetic acid (0.5 mL) was added. The volatiles were removed *in vacuo* and the crude product purified by flash column chromatography (DCM:MeOH – 9:1) affording a colorless solid.

Yield 247 mg (85 %).

^{1}H NMR (DMSO-d_6, 200 MHz): δ 13.38 (br s, 1H, 9), 8.50 (s, 1H, 2), 8.37 (s, 1H, 8), 4.09 (s, 3H, 10, 2.50.

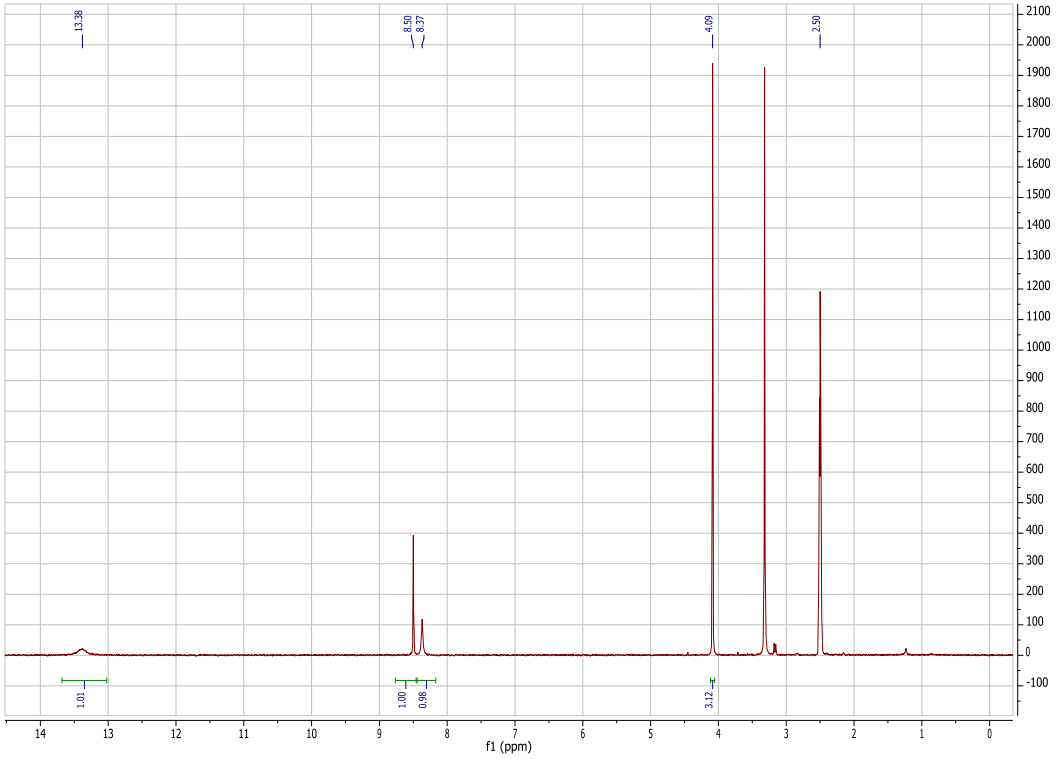
^{13}C NMR ($CDCl_3$, 150 MHz): δ 154.72 (4), 149.50 (2), 148.49 (10), 134.13 (6), 131.00 (5), 84.20 (11), 64.68 (8), 28.27 (12).

MS EI m/z (rel. %): 151 (8), 150 (100, M^+), 149 (60), 121 (36), 120 (38), 93 (47), 66 (21), 53 (9).

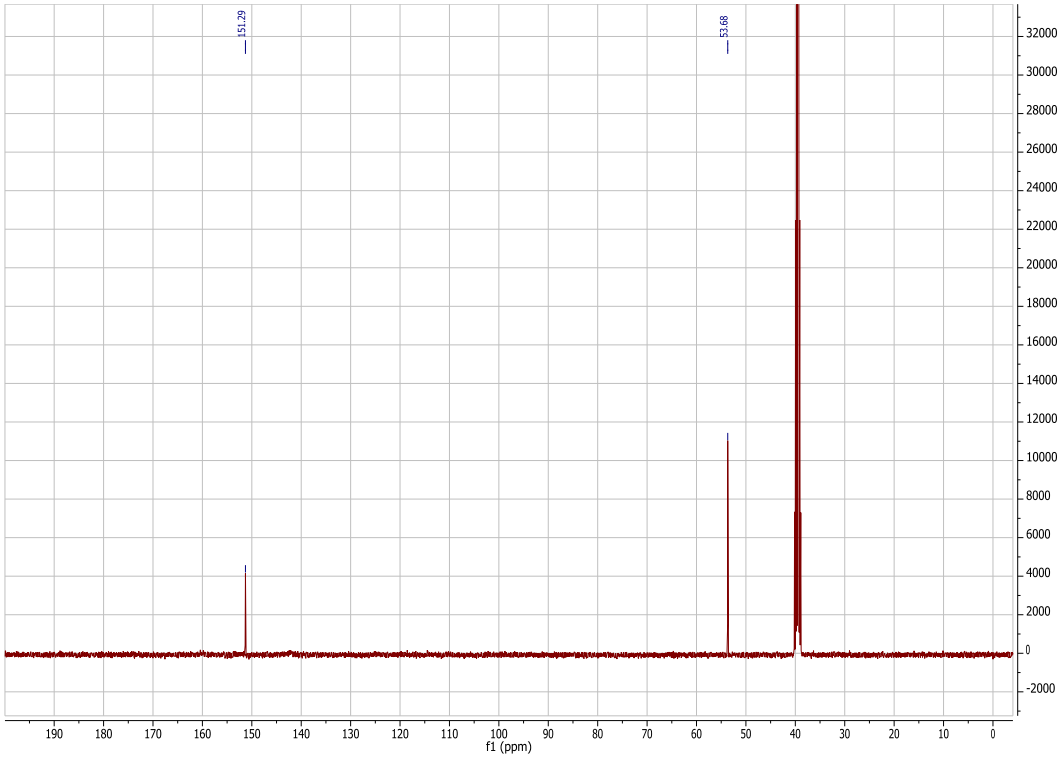
HR-MS Found 150.0547 calcd. for $C_6H_6N_4O$ 150.0542.

M.p. 190 – 191 °C (lit. 195 – 196 °C[98]).

Compound known in literature.[98,99]

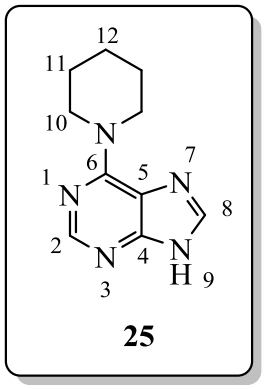


Spectrum 53. ^{1}H NMR (DMSO-d_6, 200 MHz) of 6-methoxypurine (**24**).



Spectrum 54. ^{13}C NMR (DMSO-d_6, 100 MHz) of 6-methoxypurine (**24**).

Synthesis of 6-(piperidin-1-yl)purine (25)



25

6-Chloropurine (344 mg, 2.23 mmol) was dissolved in 1-butanol (5 mL) and piperidine (1.10 mL, 11.1 mmol) was added. The solution was heated to 100 °C on an oil bath and stirred for 18 hours. The mixture was cooled and the volatiles were removed *in vacuo.* The crude product was purified by flash column chromatography (DCM:MeOH – 95:5) affording a yellow solid.

Yield 432 mg (95 %).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.94 (bs, 1H, 9), 8.17 (s, 1H, 2), 8.07 (s, 1H, 8), 4.19 (br s, 4H, 10), 1.71 – 1.65 (m, 2H, 12), 1.60 – 1.54 (m, 4H, 11).

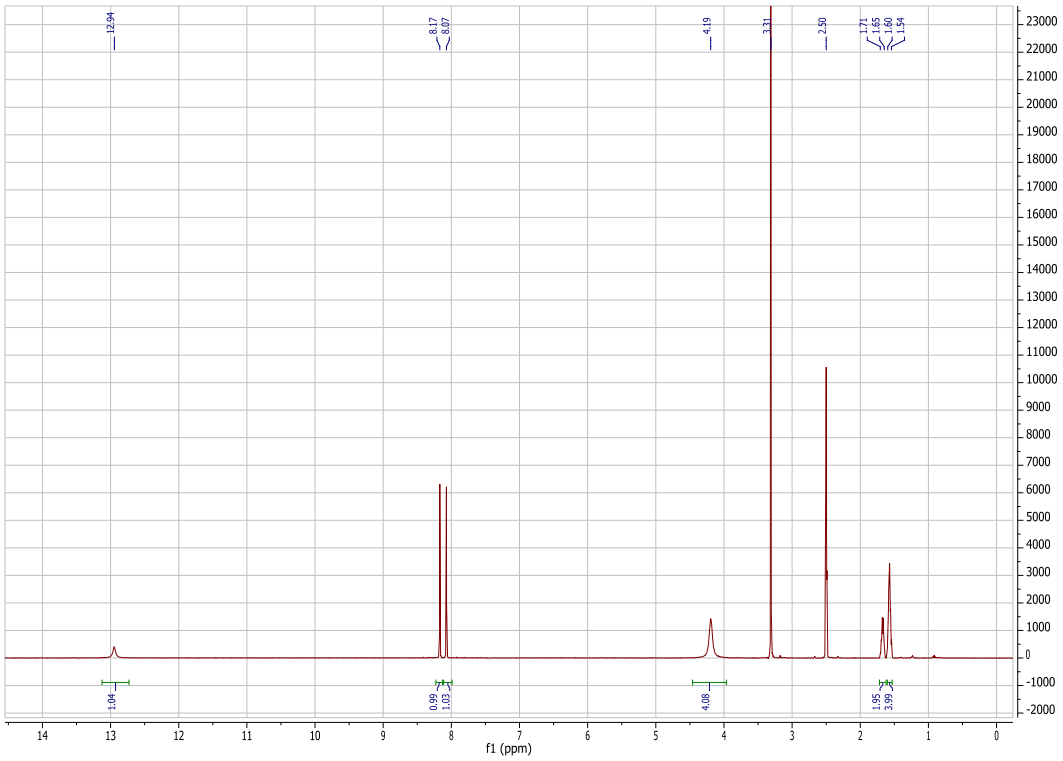
^{13}C NMR (DMSO-d_6, 100 MHz): δ 153.10 (6), 151.81 (2), 151.29 (4), 137.68 (8), 118.65 (5), 45.57 (10), 25.65 (11), 24.29 (12).

MS EI m/z (rel. %): 204 (11), 203 (100, M^+), 202 (20), 188 (15), 175 (12), 174 (83), 160 (33), 148 (34), 147 (31), 135 (24), 120 (30), 93 (20), 84 (14).

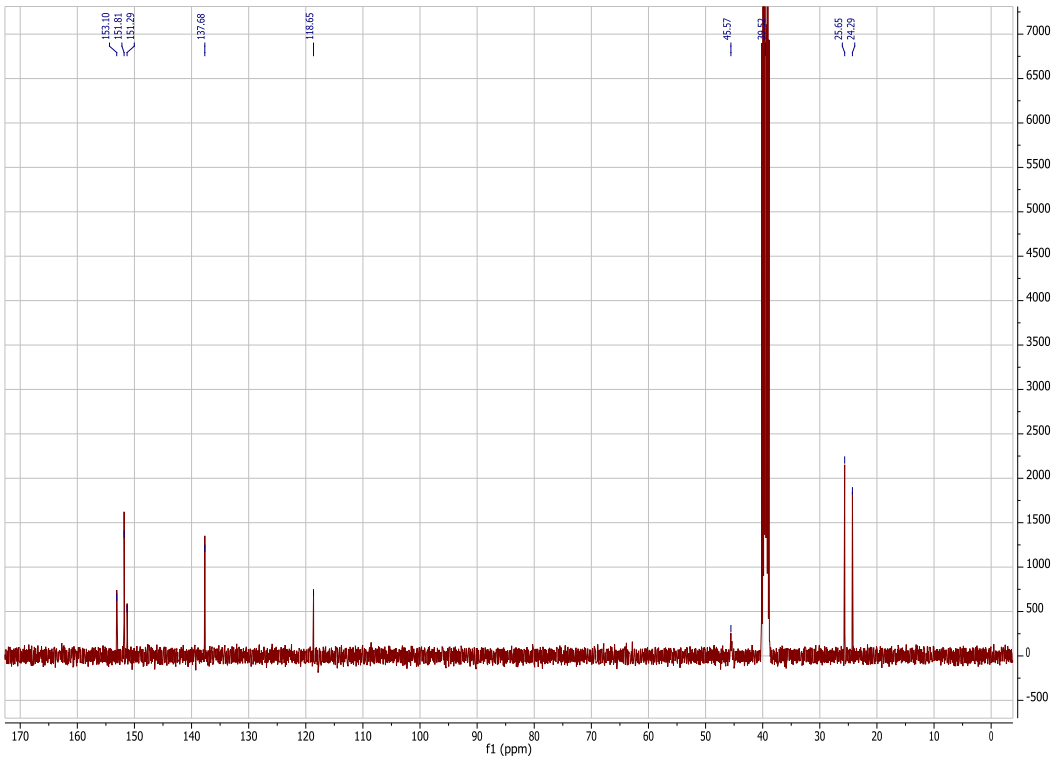
HR-MS Found 203.1169 calcd. for $C_{10}H_{13}N_5$ 203.1171.

M.p. 277 – 278 °C (lit. 277 – 278 °C[104]).

Compound known in literature.[104]

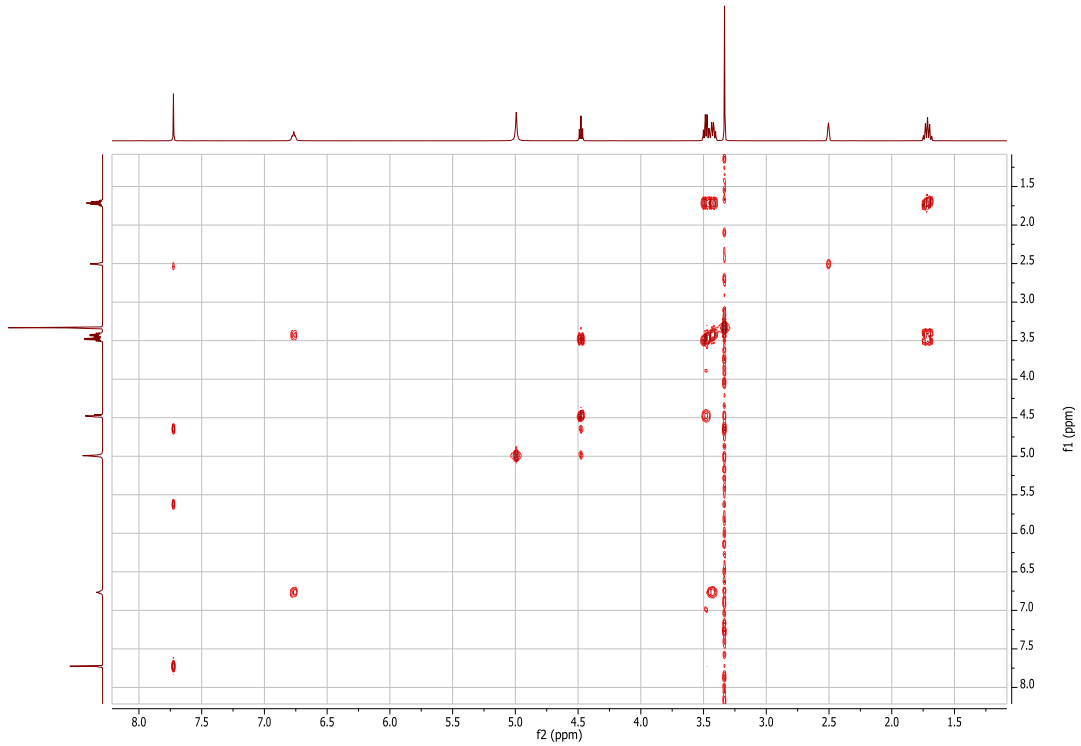


Spectrum 55. ^{1}H NMR (DMSO-d_6, 400 MHz) of 6-(piperidin-1-yl)purine (**25**).

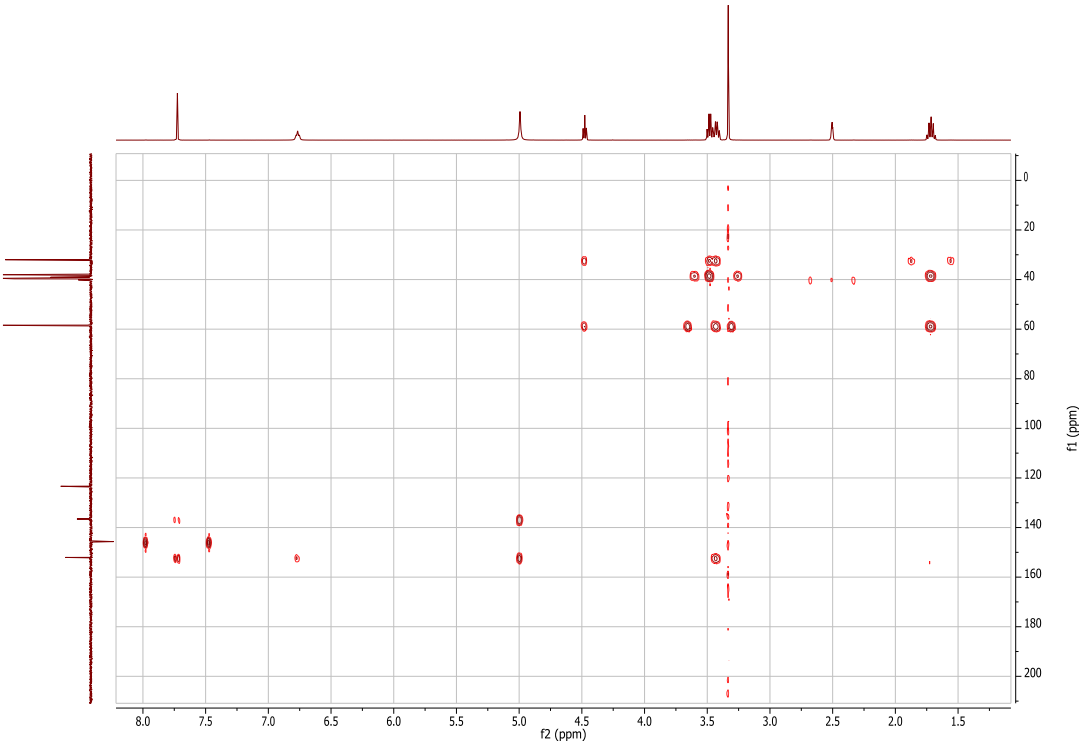


Spectrum 56. ^{13}C NMR (DMSO-d_6, 100 MHz) of 6-(piperidin-1-yl)purine (**25**).

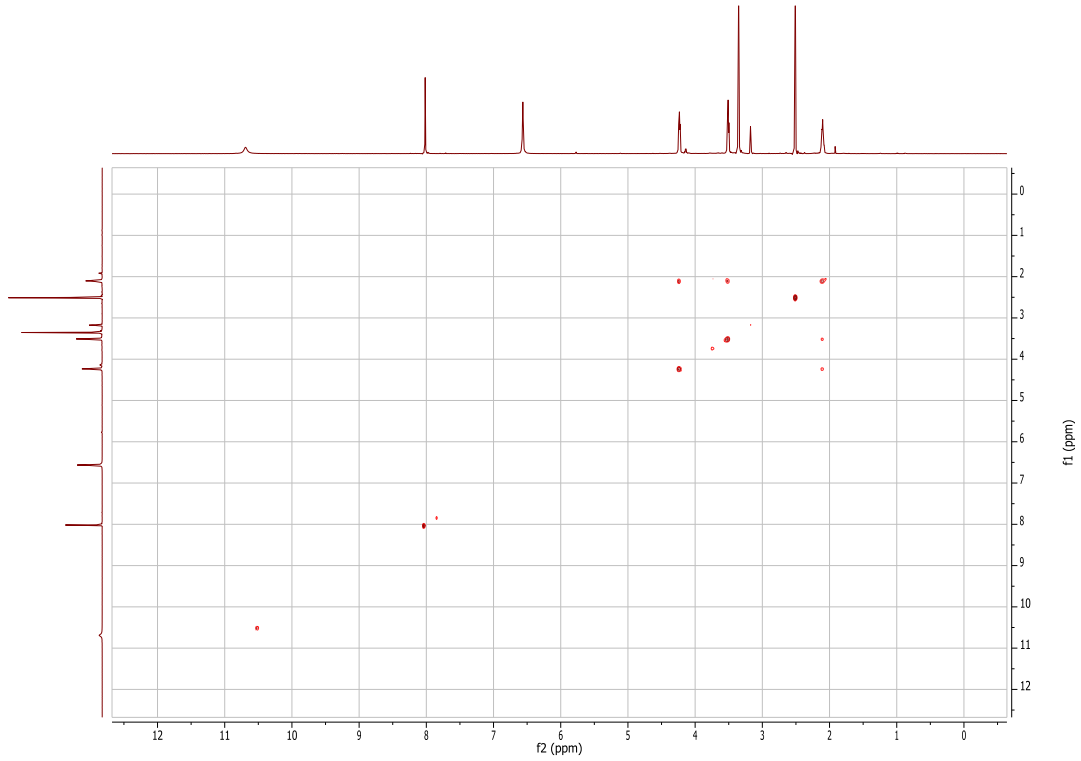
6. APPENDIX



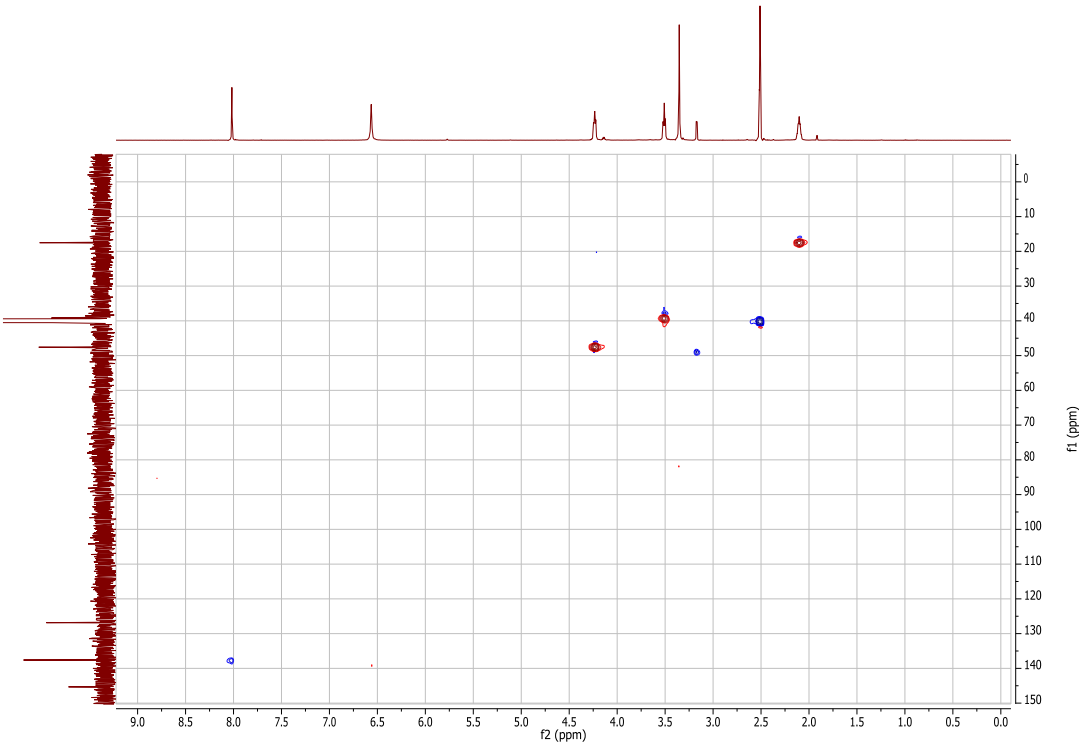
Spectrum 57. COSY (400 MHz, DMSO-d_6) of 3-((5-amino-6-chloropyrimidin-4-yl)amino)propan-1-ol (**2**).



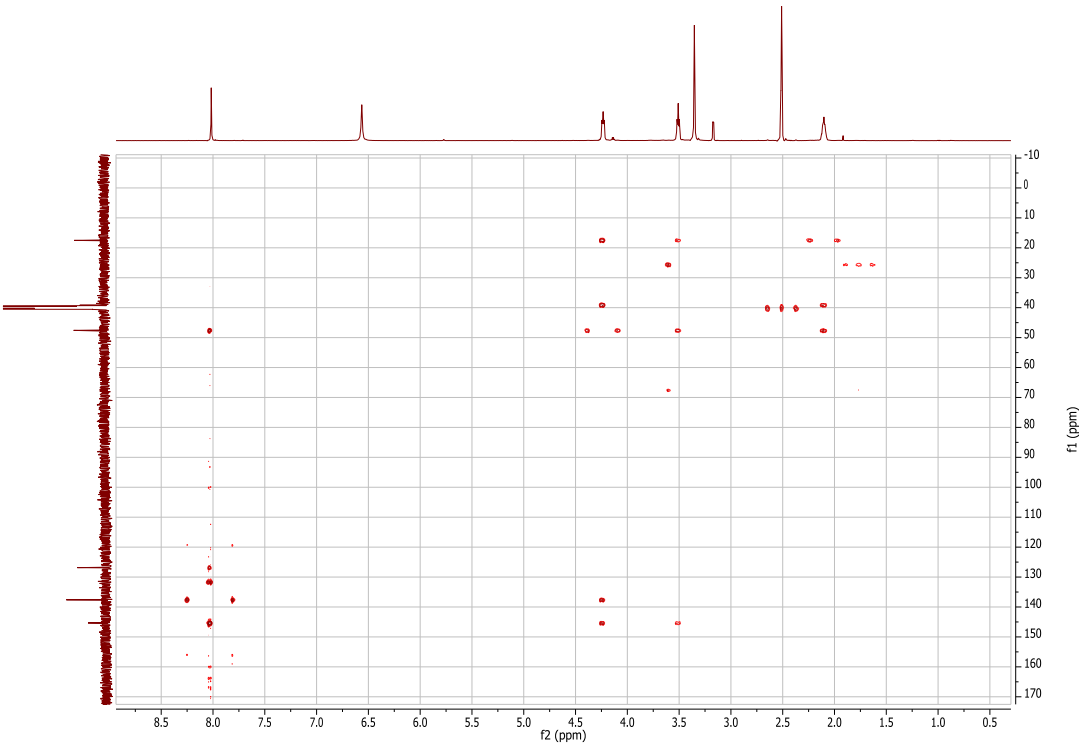
Spectrum 58. HMBC (400 MHz, DMSO-d_6) of 3-((5-amino-6-chloropyrimidin-4-yl)amino)propan-1-ol (**2**).



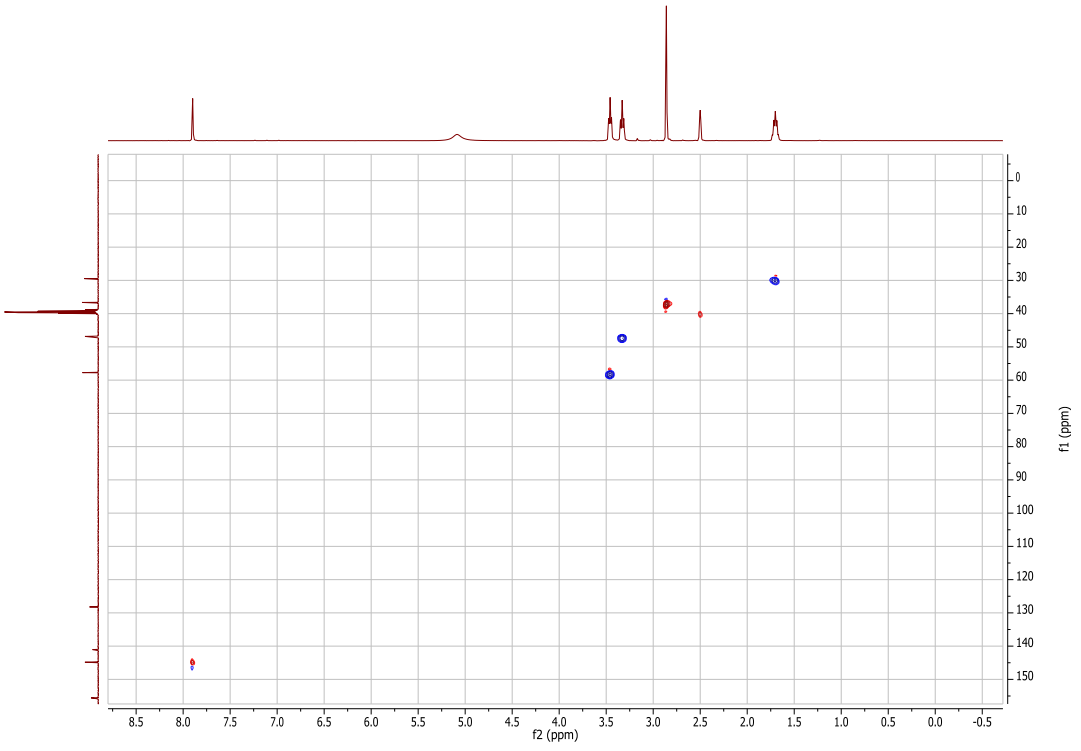
Spectrum 59. COSY (DMSO-d6, 500 MHz) of 8-chloro-3,4-dihydropyrimido[1,6-a]pyrimidin-9-amine hydrochloride (**7**).



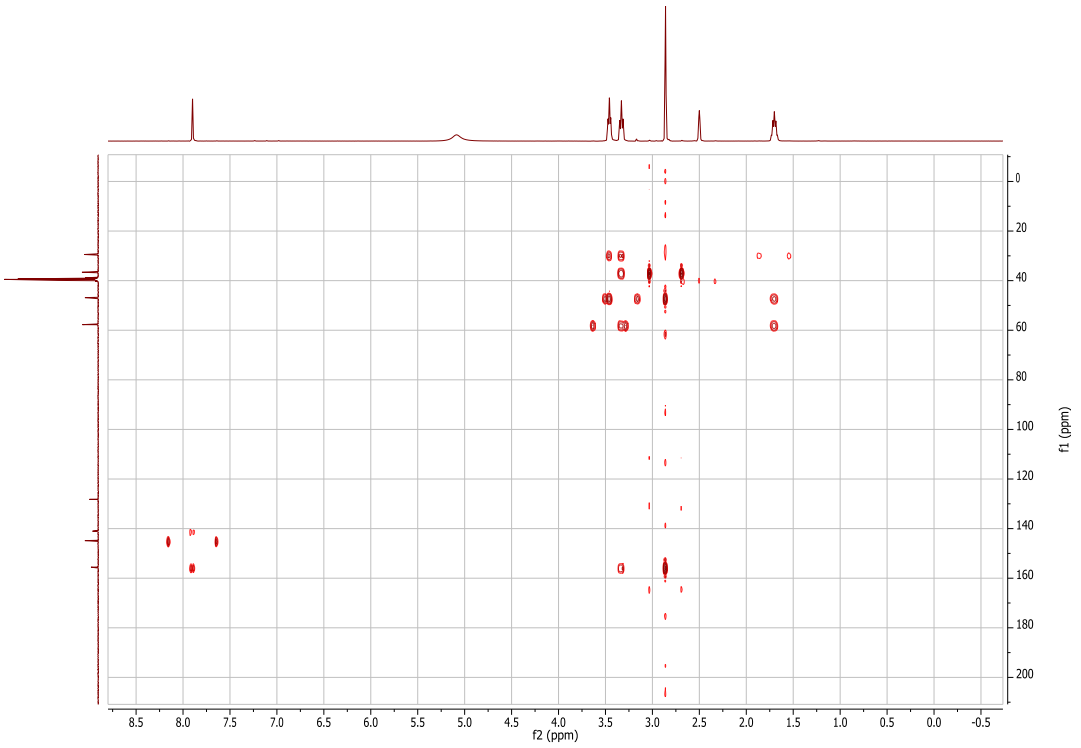
Spectrum 60. HSQC (DMSO-d6, 500 MHz) of 8-chloro-3,4-dihydropyrimido[1,6-a]pyrimidin-9-amine hydrochloride (**7**).



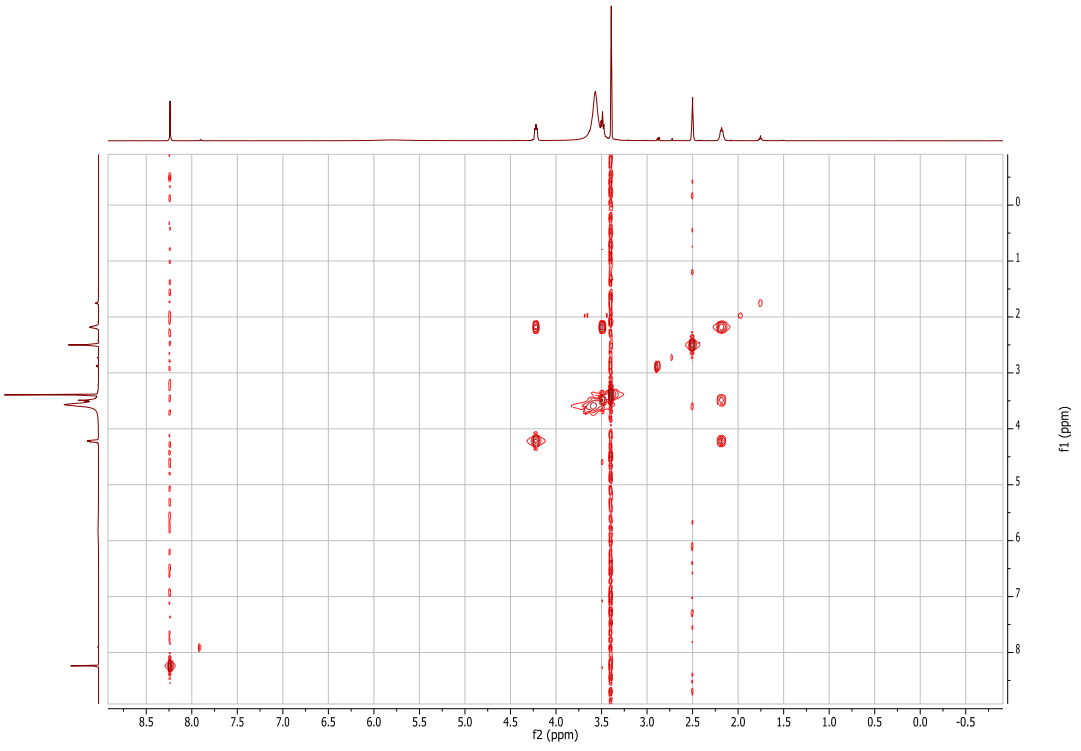
Spectrum 61. HMBC (DMSO-d6, 500 MHz) of 8-chloro-3,4-dihydropyrimido[1,6-a]pyrimidin-9-amine hydrochloride (**7**).



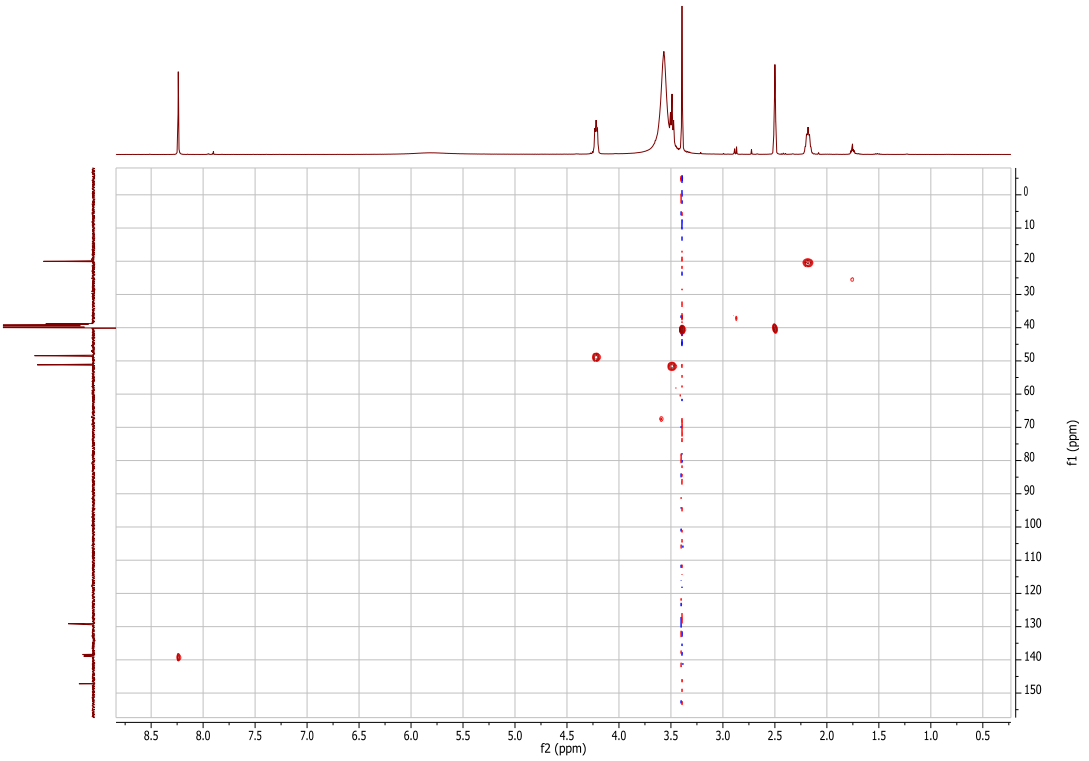
Spectrum 62 HSQC (DMSO-d_6, 400 MHz) of 3-((5-amino-6-chloropyrimidin-4-yl)(methyl)amino)propan-1-ol (**10**).



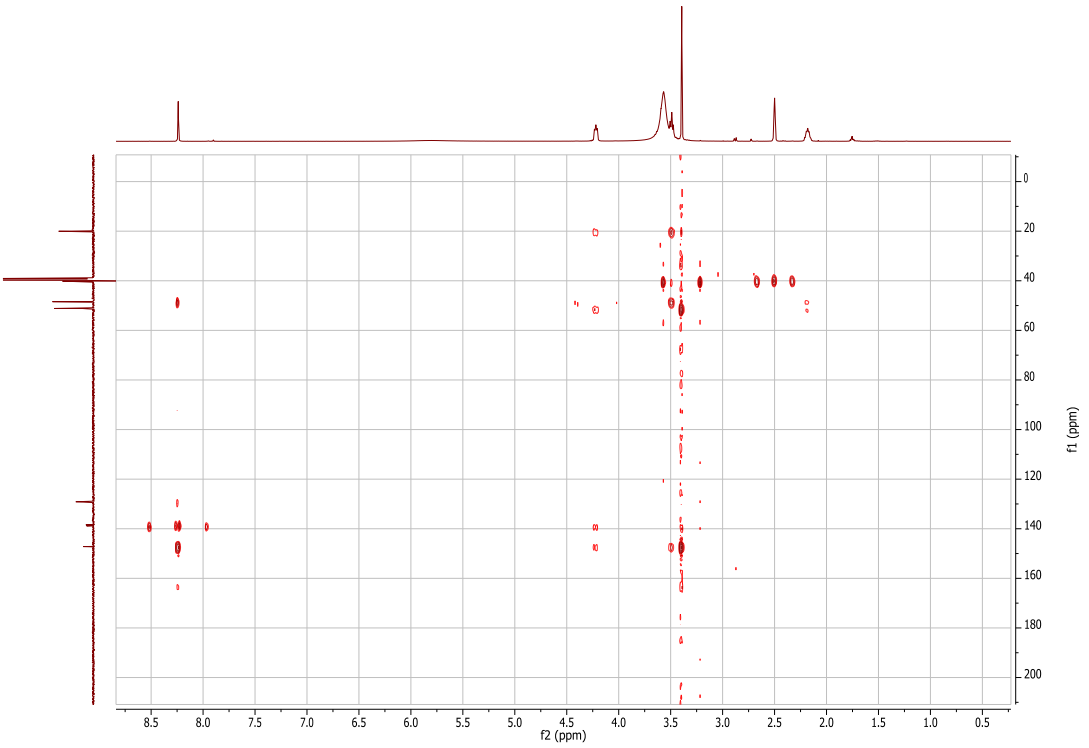
Spectrum 63 HMBC (DMSO-d_6, 400 MHz) of 3-((5-amino-6-chloropyrimidin-4-yl)(methyl)amino)propan-1-ol (**10**).



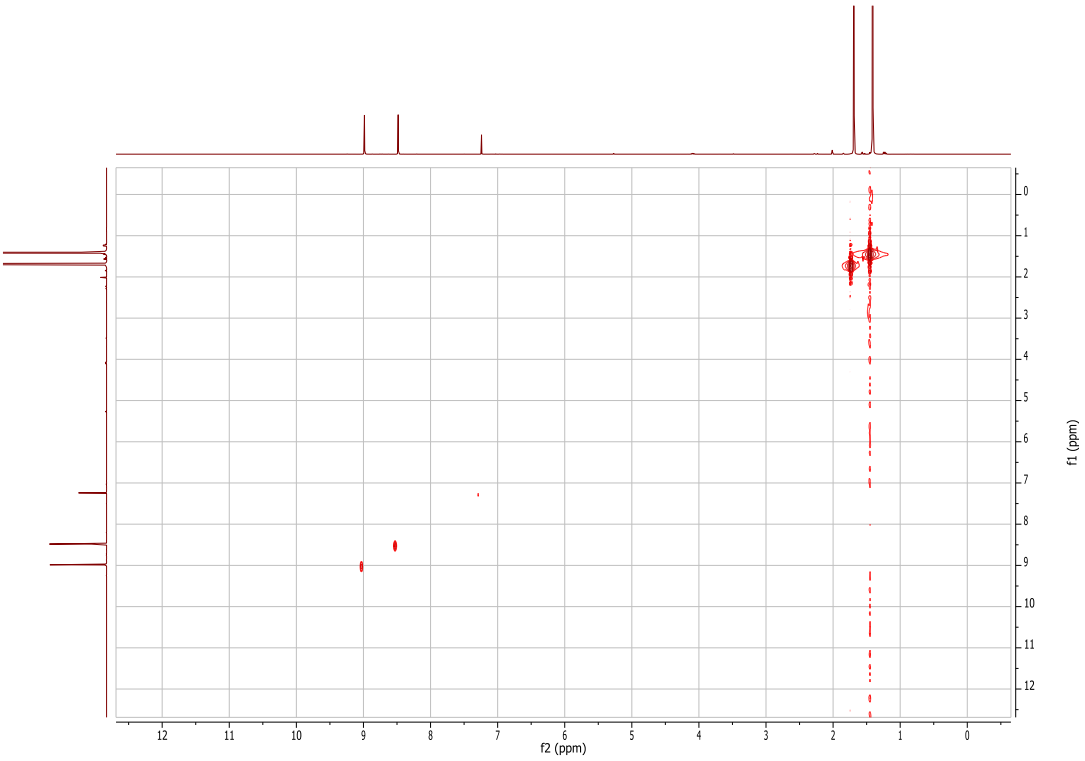
Spectrum 64 COSY (DMSO-d_6, 400 MHz) of 9-amino-8-chloro-1-methyl-1,2,3,4-tetrahydropyrimido[1,6-*a*]pyrimidinium chloride (**11**).



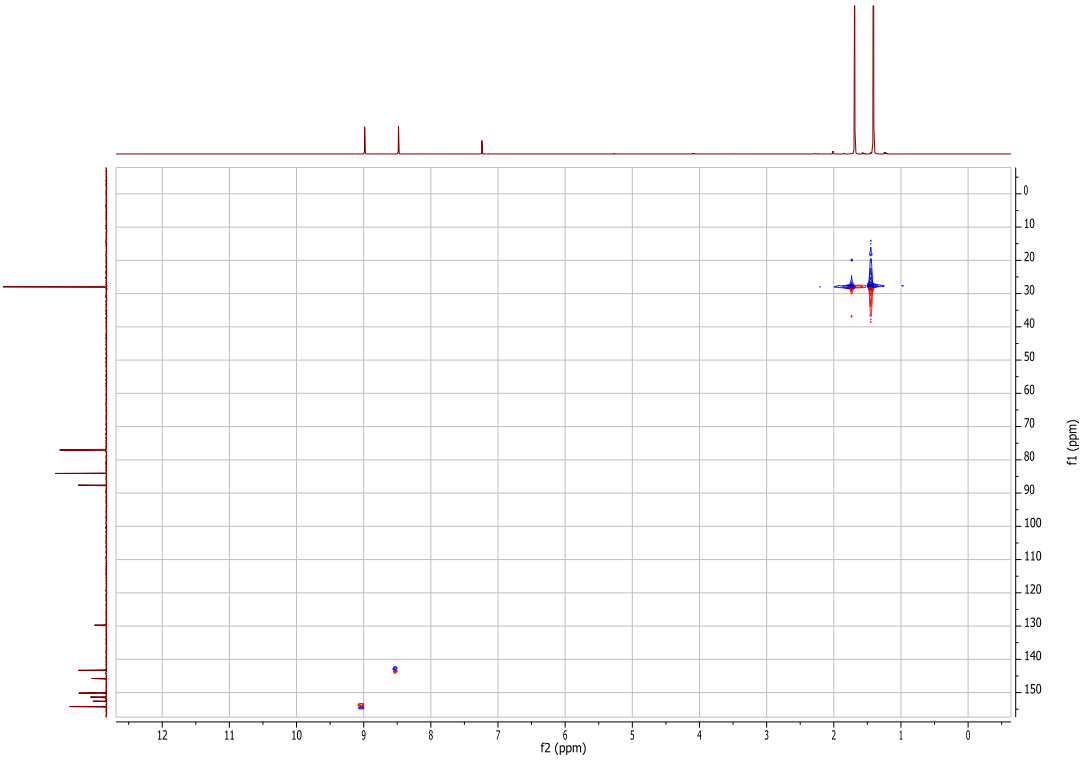
Spectrum 65 HSQC (DMSO-d_6, 400 MHz) of 9-amino-8-chloro-1-methyl-1,2,3,4-tetrahydropyrimido[1,6-*a*]pyrimidinium chloride (**11**).



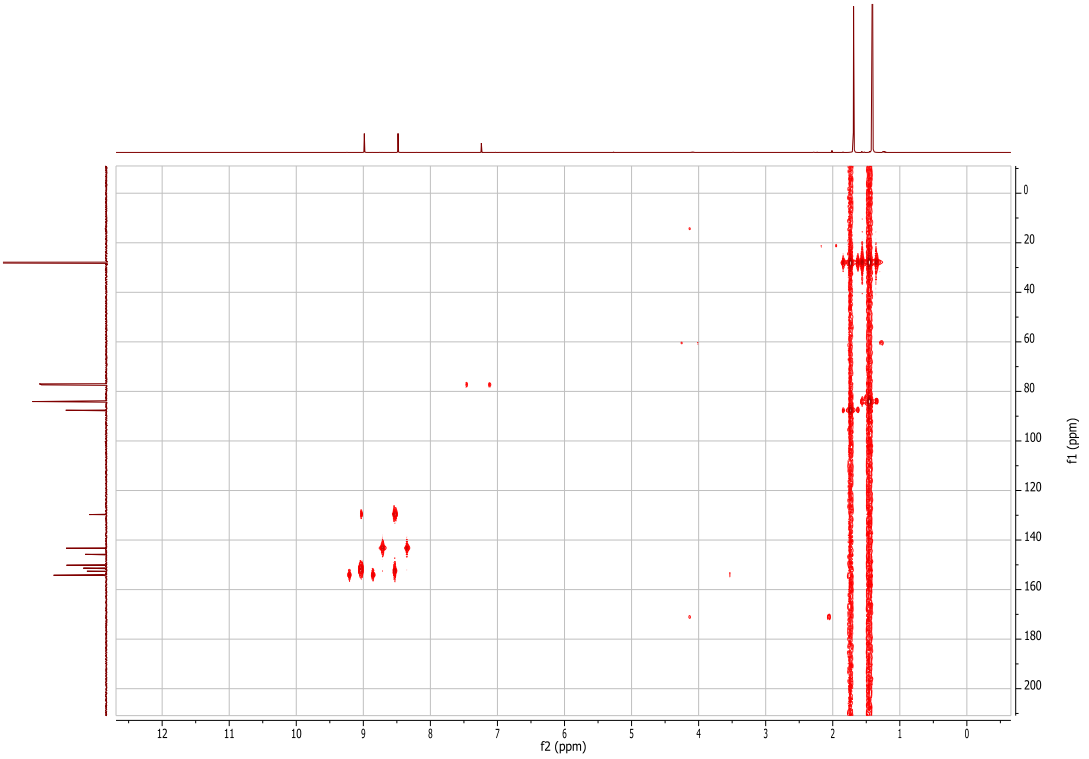
Spectrum 66 HMBC (DMSO-d_6, 400 MHz) of 9-amino-8-chloro-1-methyl-1,2,3,4-tetrahydropyrimido[1,6-*a*]pyrimidinium chloride (**11**).



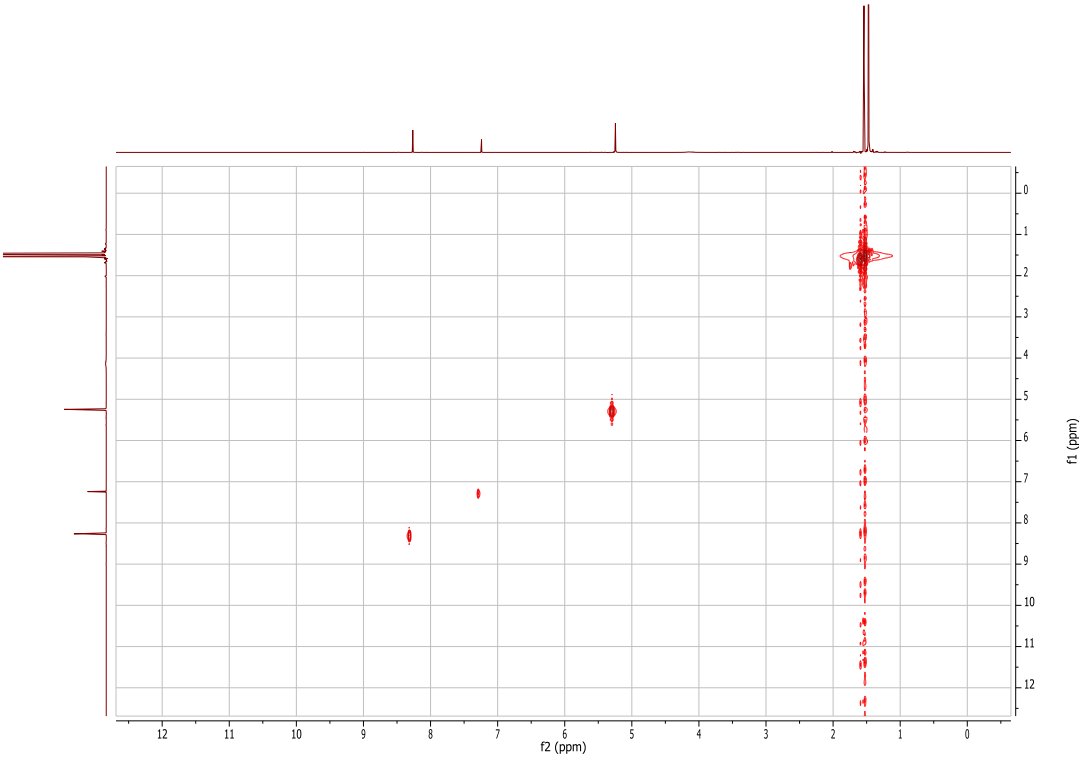
Spectrum 67 COSY ($CDCl_3$, 600 MHz) of *tritert*-butyl 9,10,10-adenineetricarboxylate (**14**).



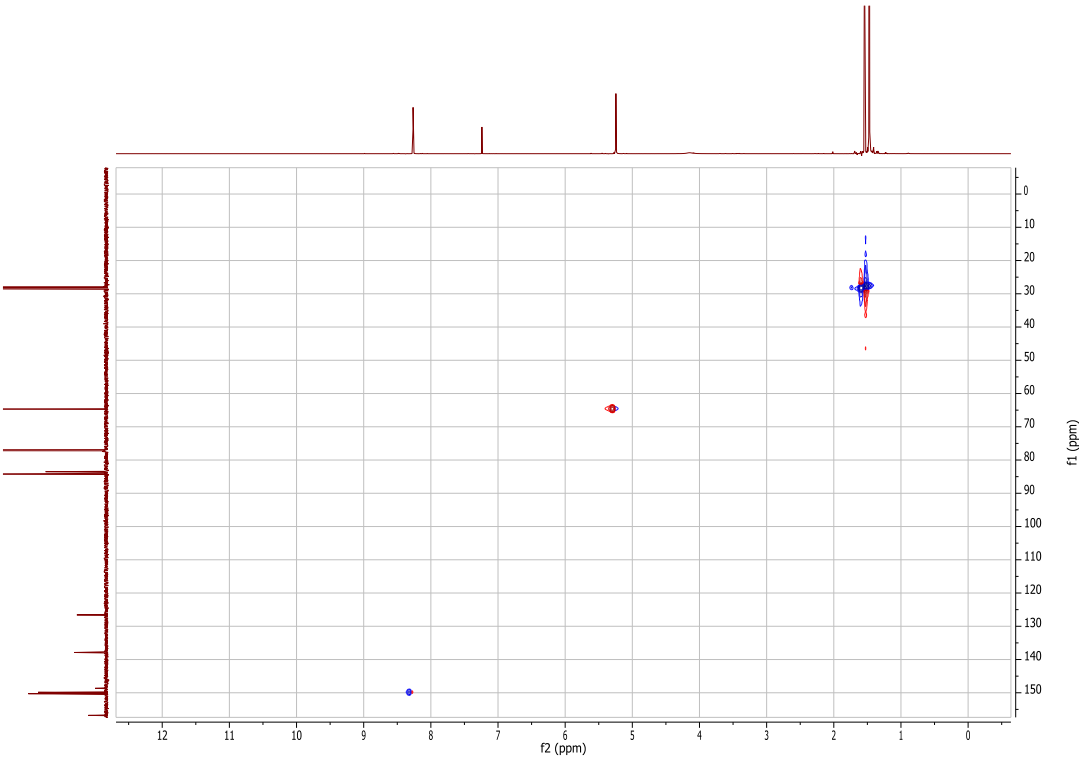
Spectrum 68 HSQC ($CDCl_3$, 600 MHz) of *tritert*-butyl 9,10,10-adenineetricarboxylate (**14**).



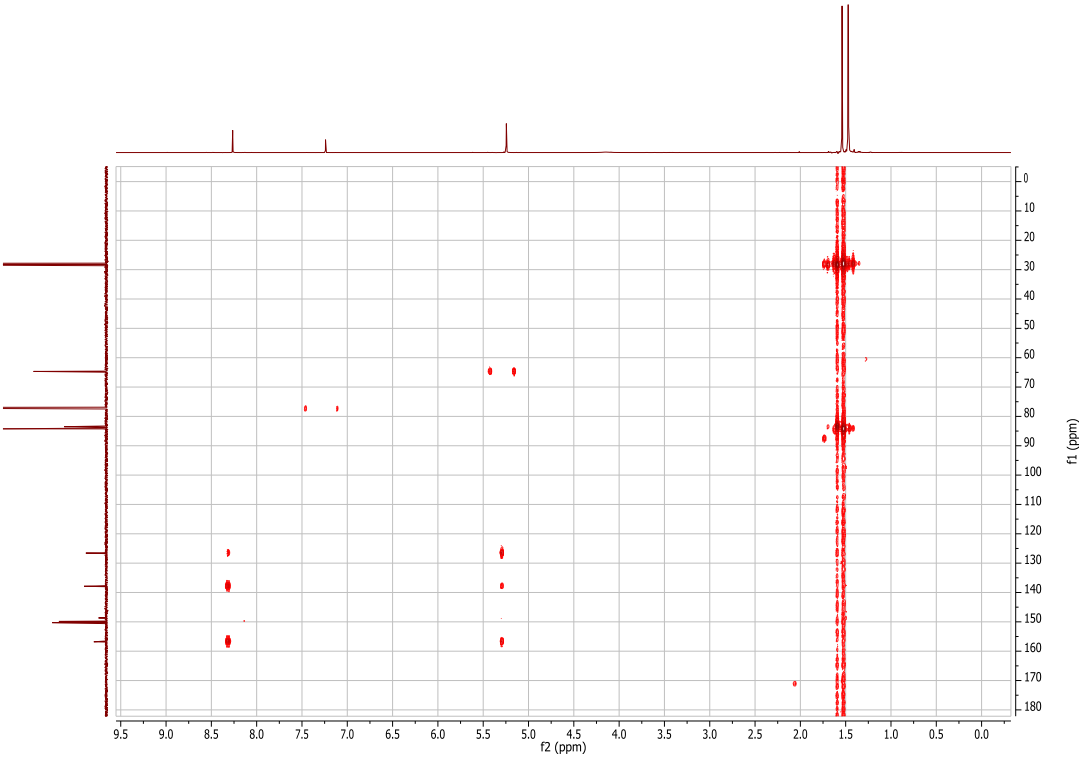
Spectrum 69 HSQC ($CDCl_3$, 600 MHz) of *tritert*-butyl 9,10,10-adenineetricarboxylate (**14**).



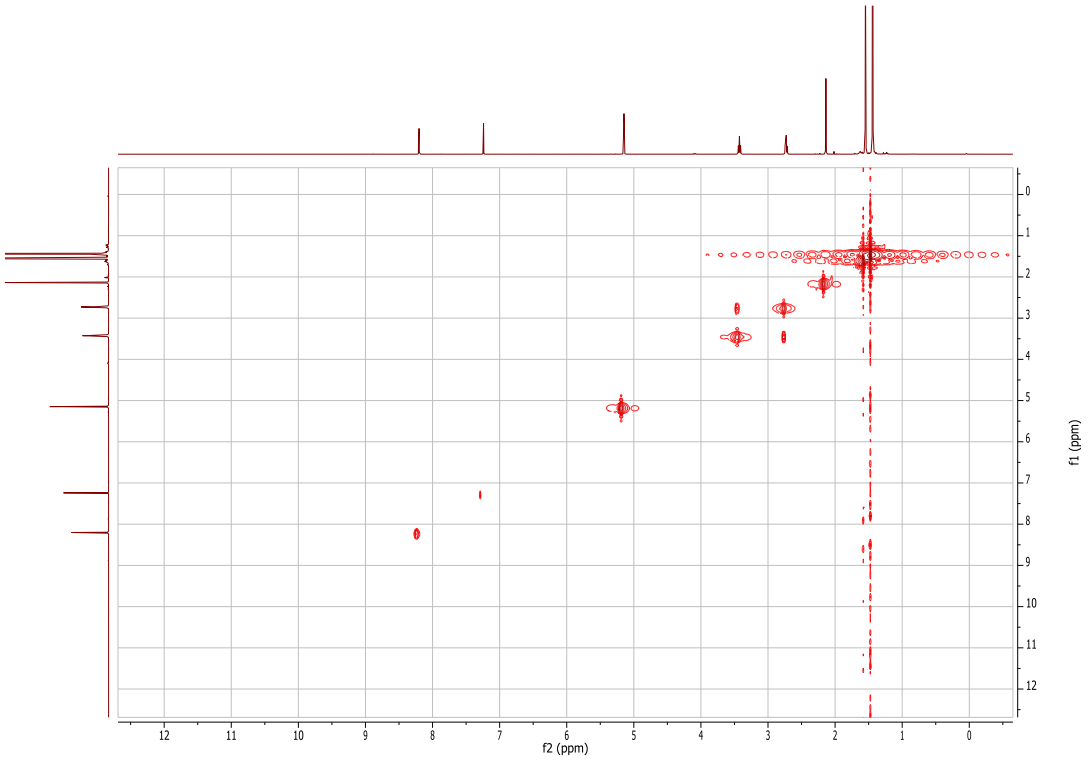
Spectrum 70 COSY ($CDCl_3$, 600 MHz) of *tert*-butyl 6-(*ditert*-butoxycarbonylamino)-8,9-dihydropurine-9-carboxylate (**15**).



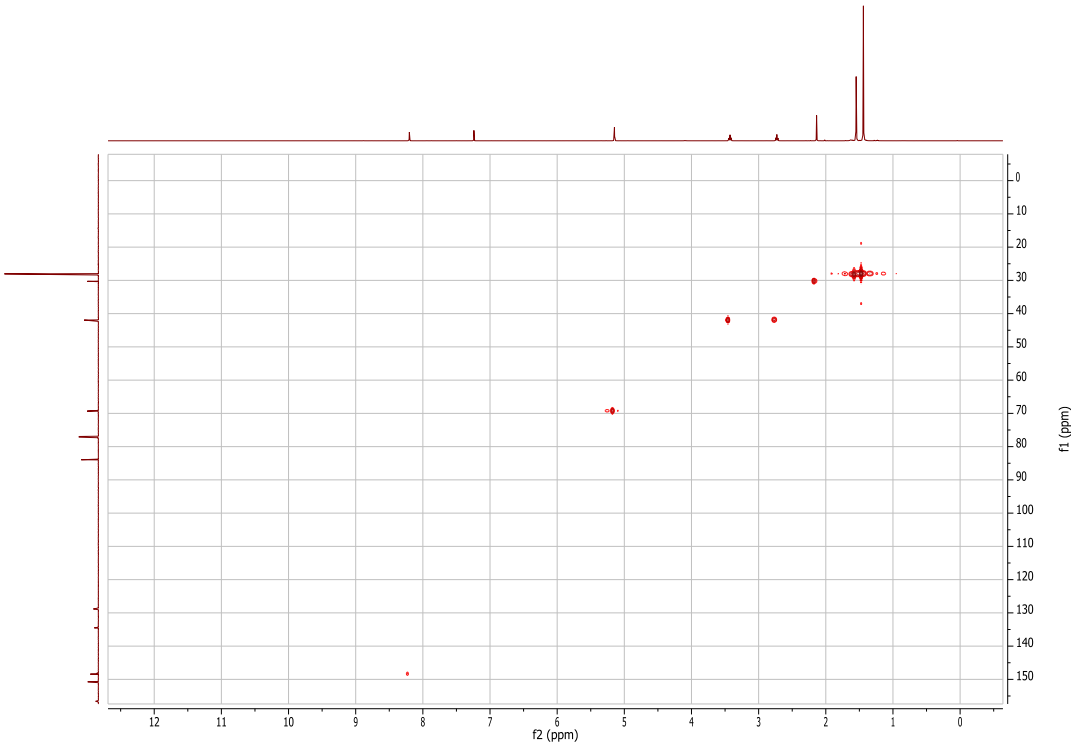
Spectrum 71 HSQC ($CDCl_3$, 600 MHz) of *tert*-butyl 6-(*ditert*-butoxycarbonylamino)-8,9-dihydropurine-9-carboxylate (**15**).



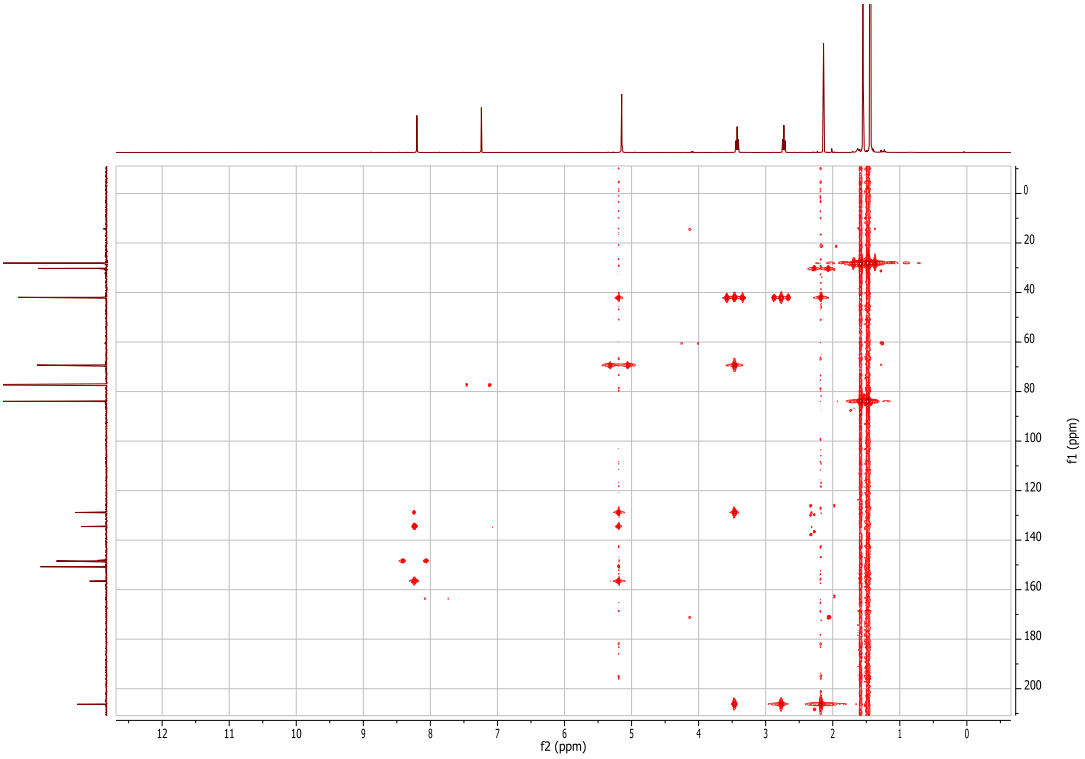
Spectrum 72 HMBC ($CDCl_3$, 600 MHz) of *tert*-butyl 6-(*ditert*-butoxycarbonylamino)-8,9-dihydropurine-9-carboxylate (**15**).



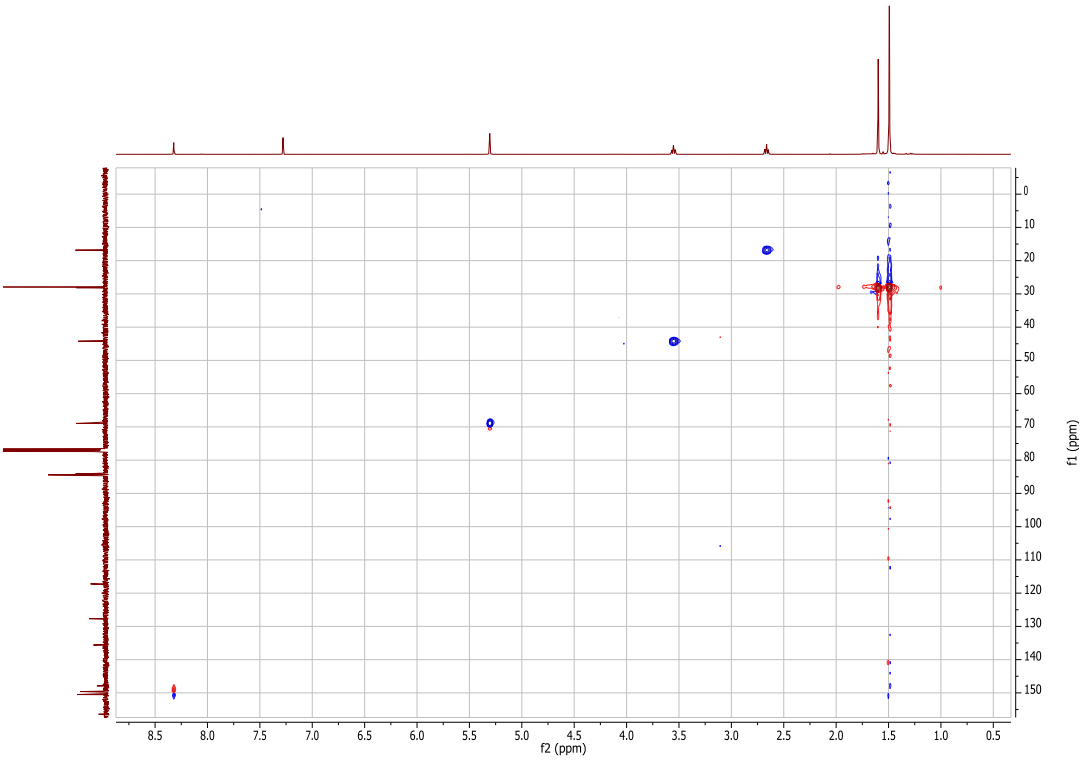
Spectrum 73 COSY ($CDCl_3$, 600 MHz) of *tert*-butyl 6-(*ditert*-butoxycarbonylamino)-7-(3-oxobutyl)-8,9-dihydropurine-9-carboxylate (**16**).



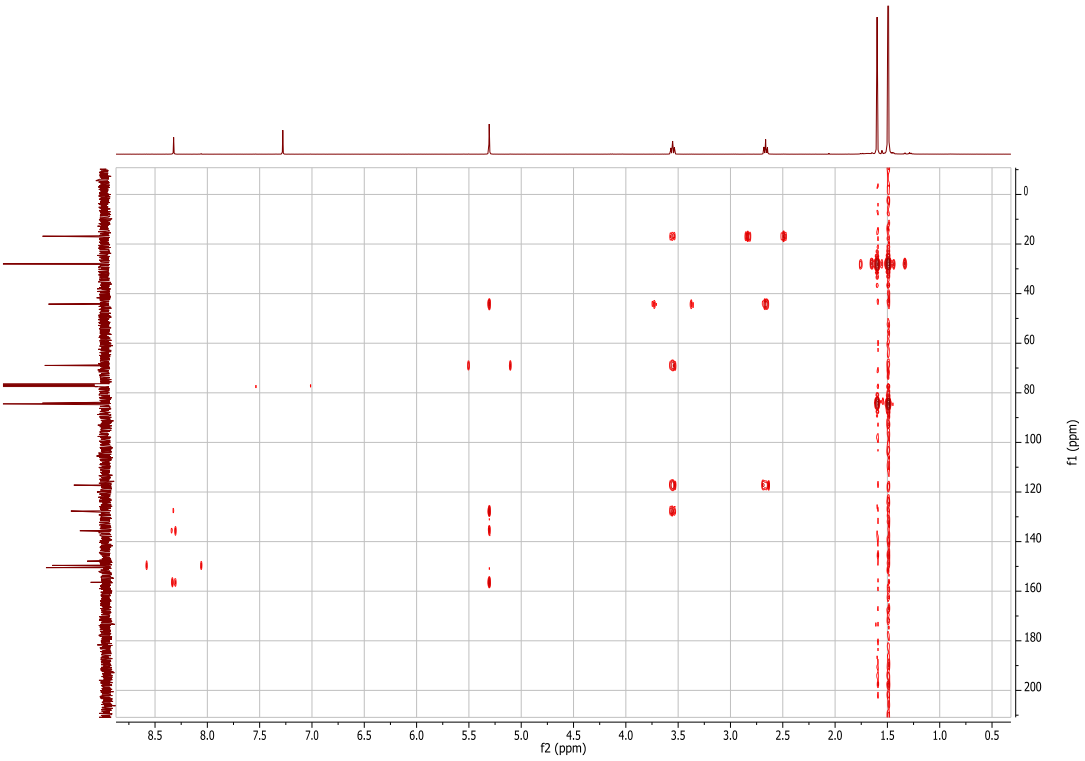
Spectrum 74 HSQC ($CDCl_3$, 600 MHz) of *tert*-butyl 6-(*ditert*-butoxycarbonylamino)-7-(3-oxobutyl)-8,9-dihydropurine-9-carboxylate (**16**).



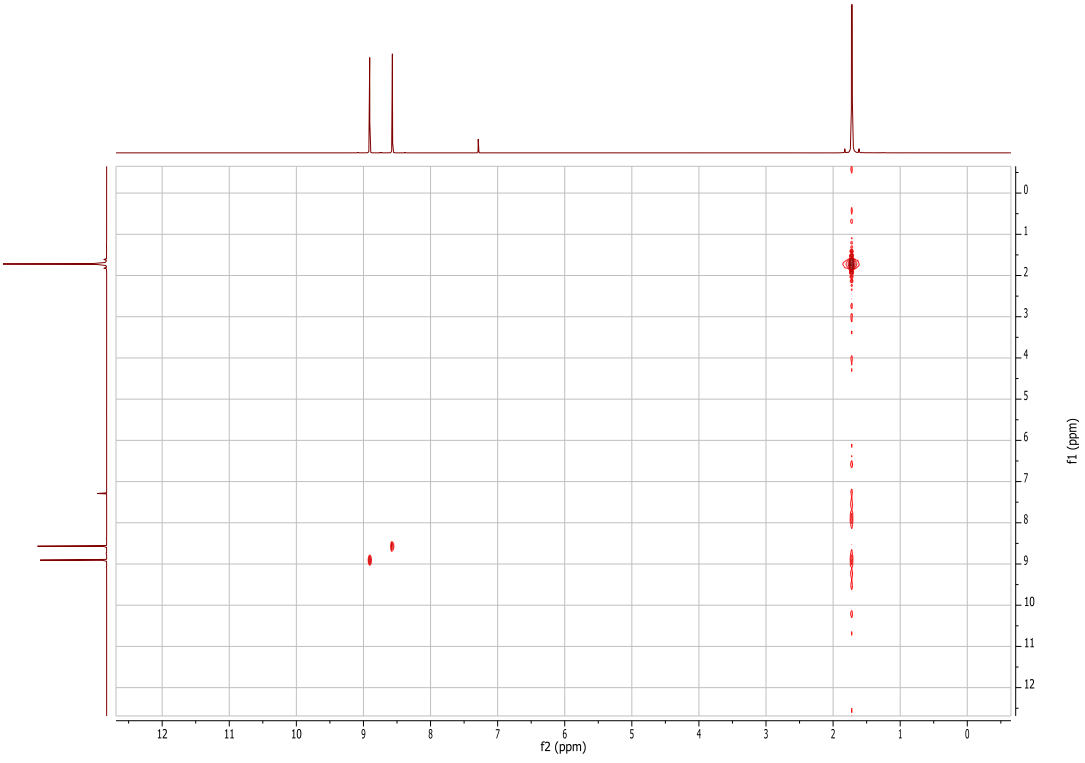
Spectrum 75 HSQC ($CDCl_3$, 600 MHz) of *tert*-butyl 6-(*ditert*-butoxycarbonylamino)-7-(3-oxobutyl)-8,9-dihydropurine-9-carboxylate (**16**).



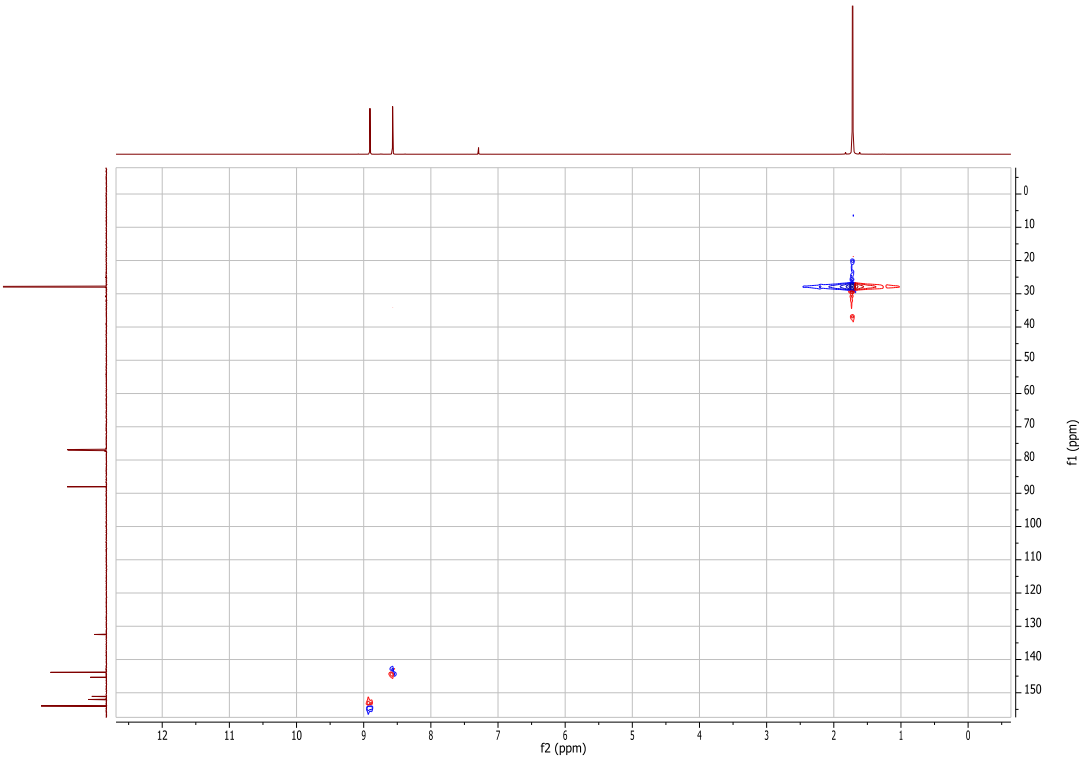
Spectrum 76 HSQC ($CDCl_3$, 400 MHz) of *tert*-butyl 7-(2-cyanoethyl)-6-(ditert-butoxycarbonylamino)-8,9-dihydropurine-9-carboxylate (**43**).



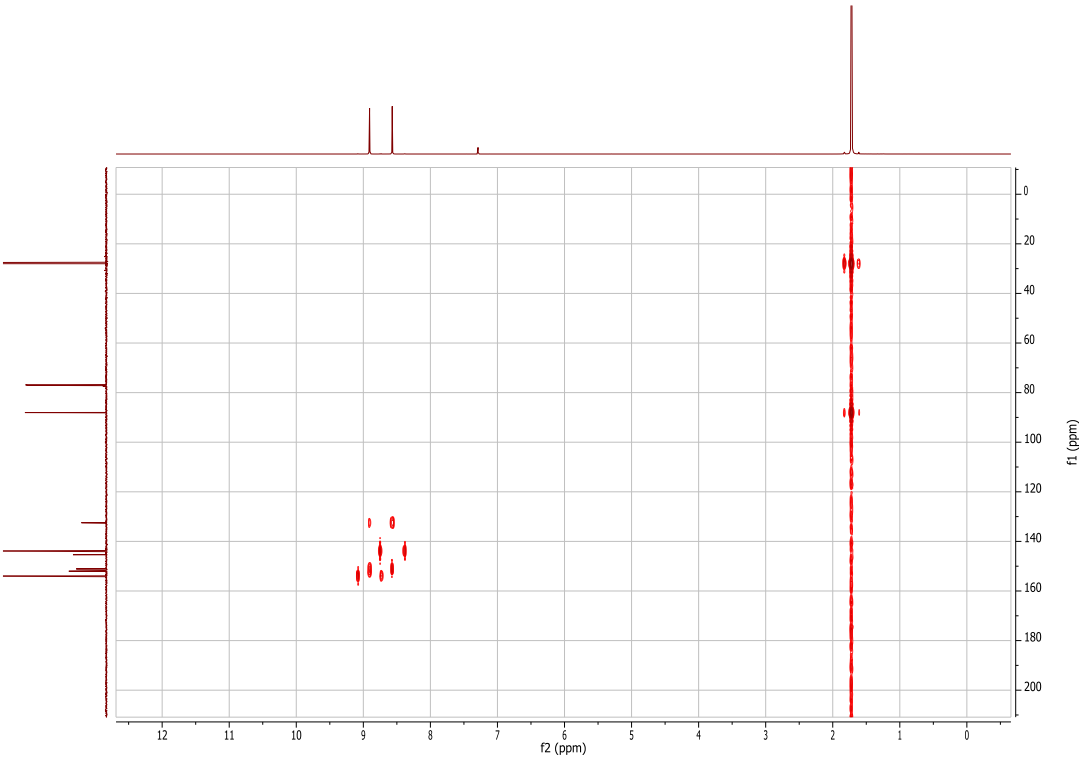
Spectrum 77 HMBC ($CDCl_3$, 400 MHz) of *tert*-butyl 7-(2-cyanoethyl)-6-(ditert-butoxycarbonylamino)-8,9-dihydropurine-9-carboxylate (**43**).



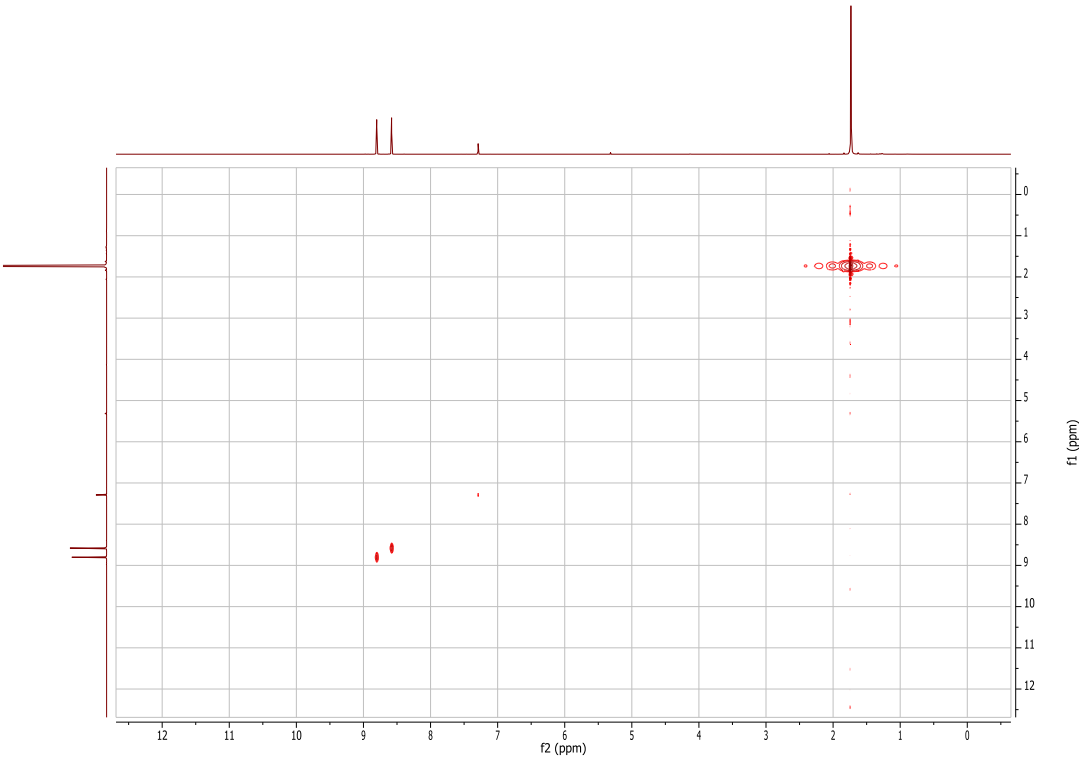
Spectrum 78 COSY ($CDCl_3$, 600 MHz) of *tert*-butyl 6-chloropurine-9-carboxylate (**26**).



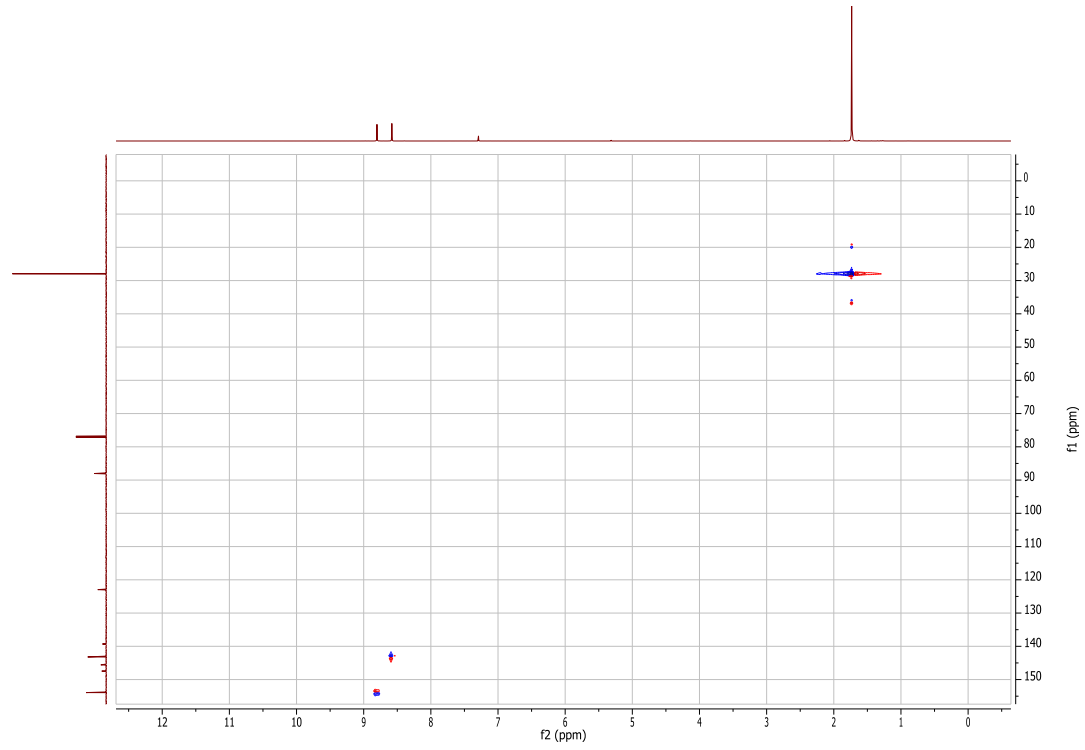
Spectrum 79 HSQC ($CDCl_3$, 600 MHz) of *tert*-butyl 6-chloropurine-9-carboxylate (**26**).



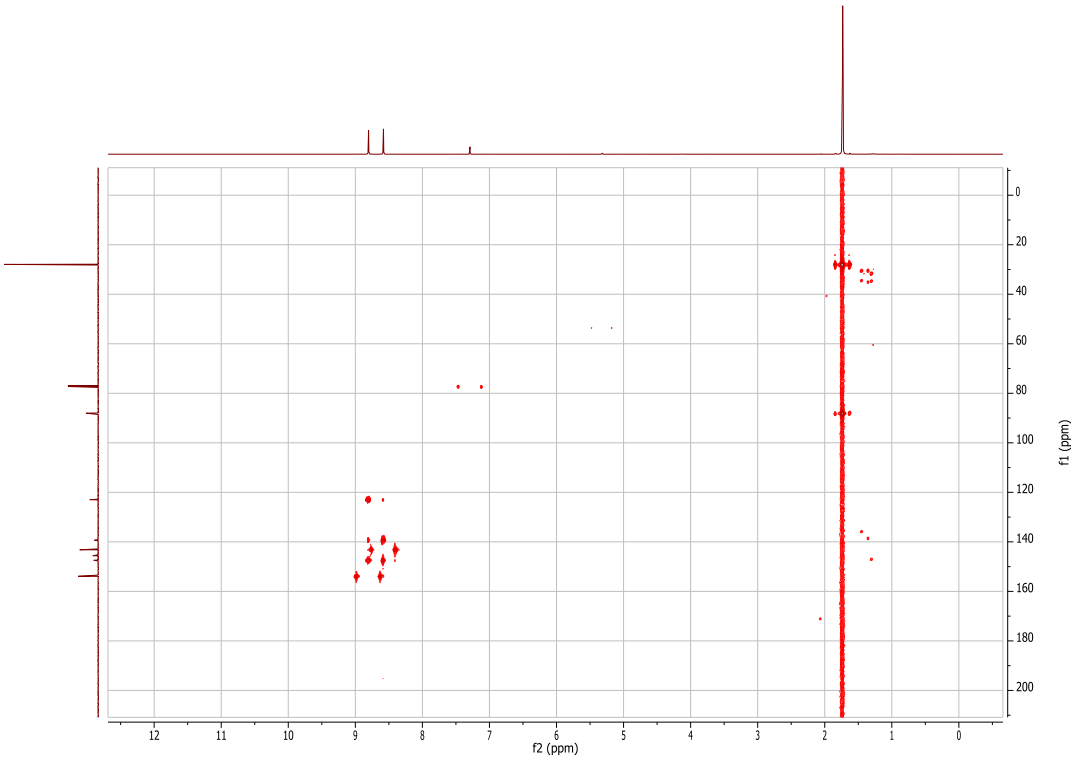
Spectrum 80 HMBC ($CDCl_3$, 600 MHz) of *tert*-butyl 6-chloropurine-9-carboxylate (**26**).



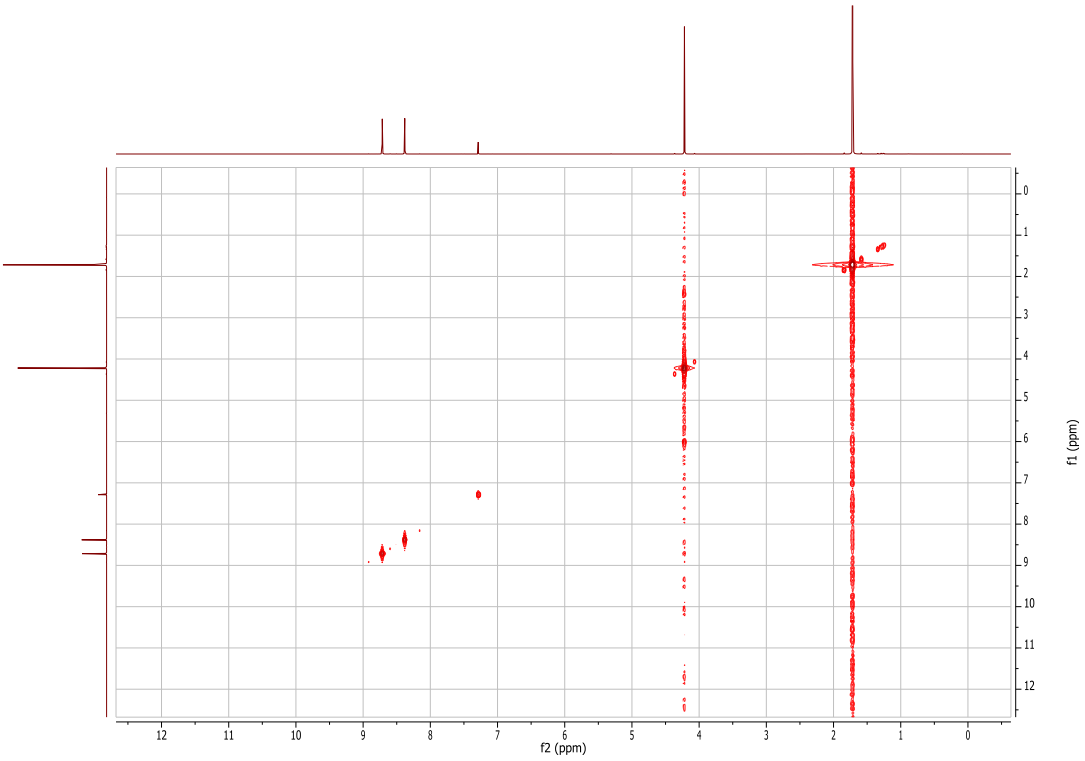
Spectrum 81 COSY ($CDCl_3$, 600 MHz) of *tert*-butyl 6-iodopurine-9-carboxylate (**27**).



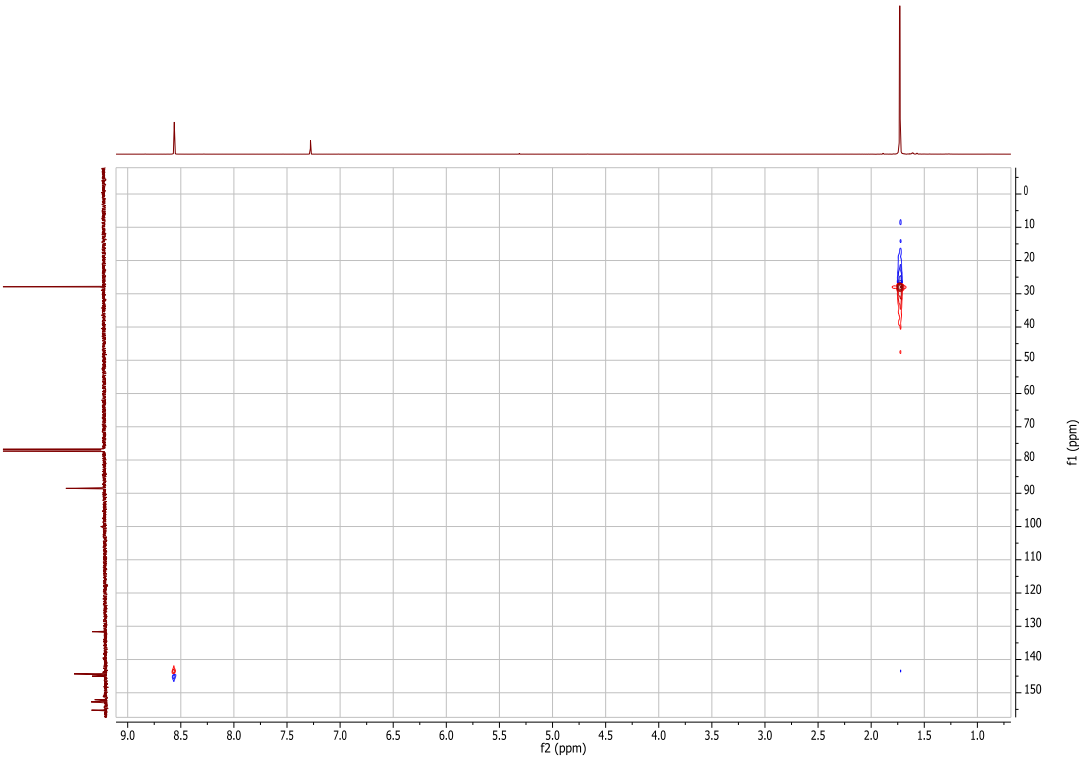
Spectrum 82 HSQC ($CDCl_3$, 600 MHz) of *tert*-butyl 6-iodopurine-9-carboxylate (**27**).



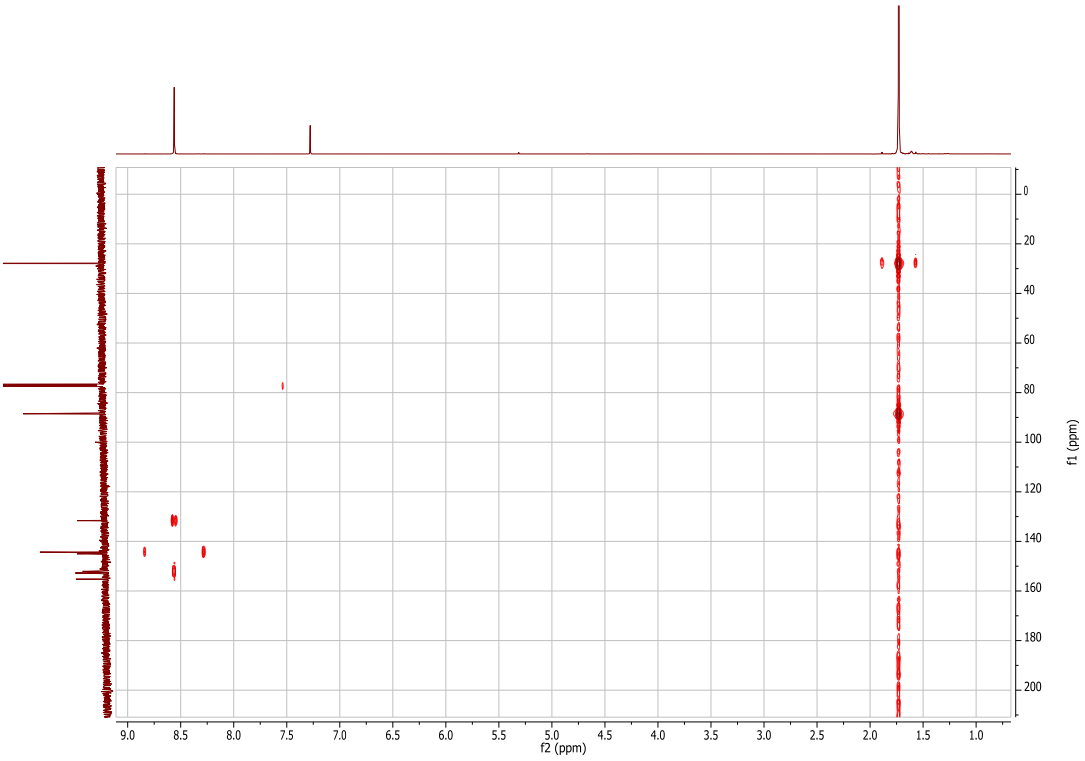
Spectrum 83 HSQC ($CDCl_3$, 600 MHz) of *tert*-butyl 6-iodopurine-9-carboxylate (**27**).



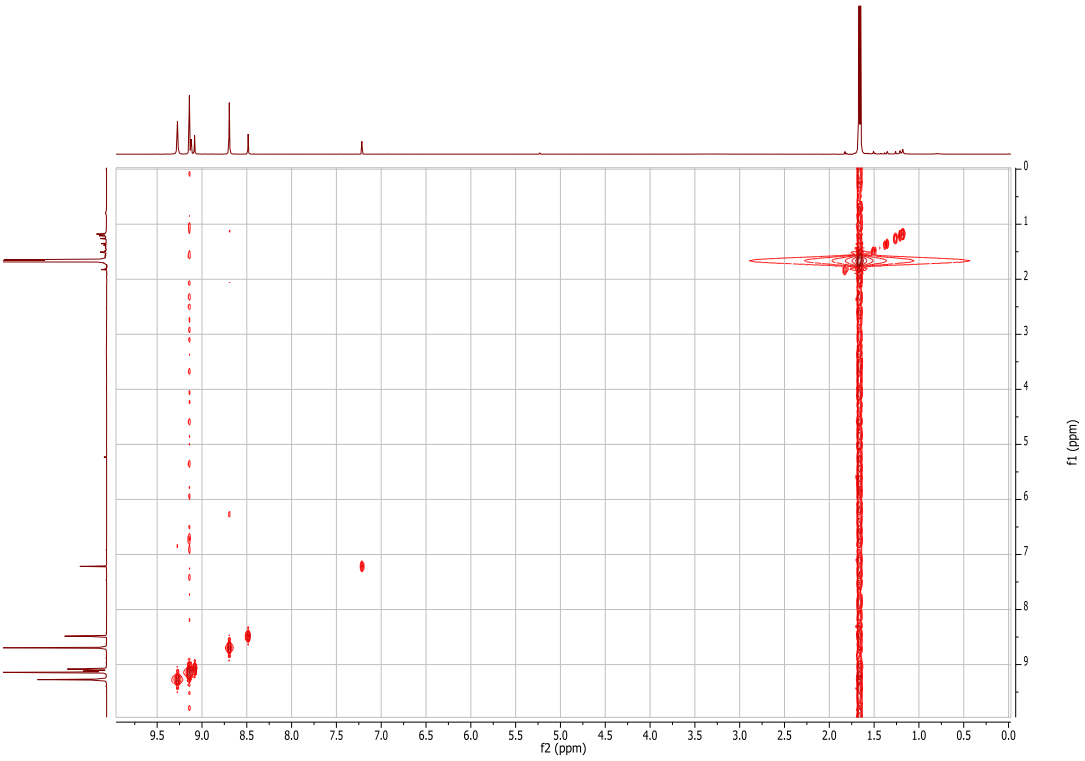
Spectrum 84 NMR ($CDCl_3$, 500 MHz) of *tert*-butyl 6-methoxypurine-9-carboxylate(**28**).



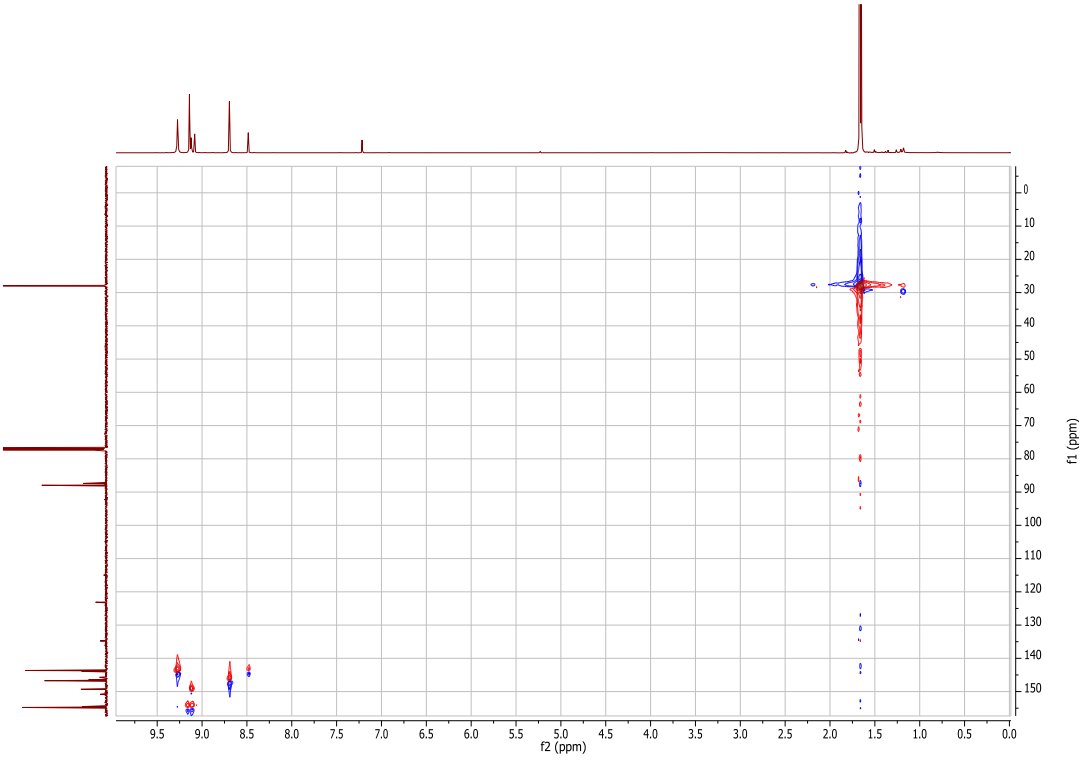
Spectrum 85 HSQC (CDCl3, 400 MHz) of tert-butyl 2,6-dichloropurine-9-carboxylate (**30**).



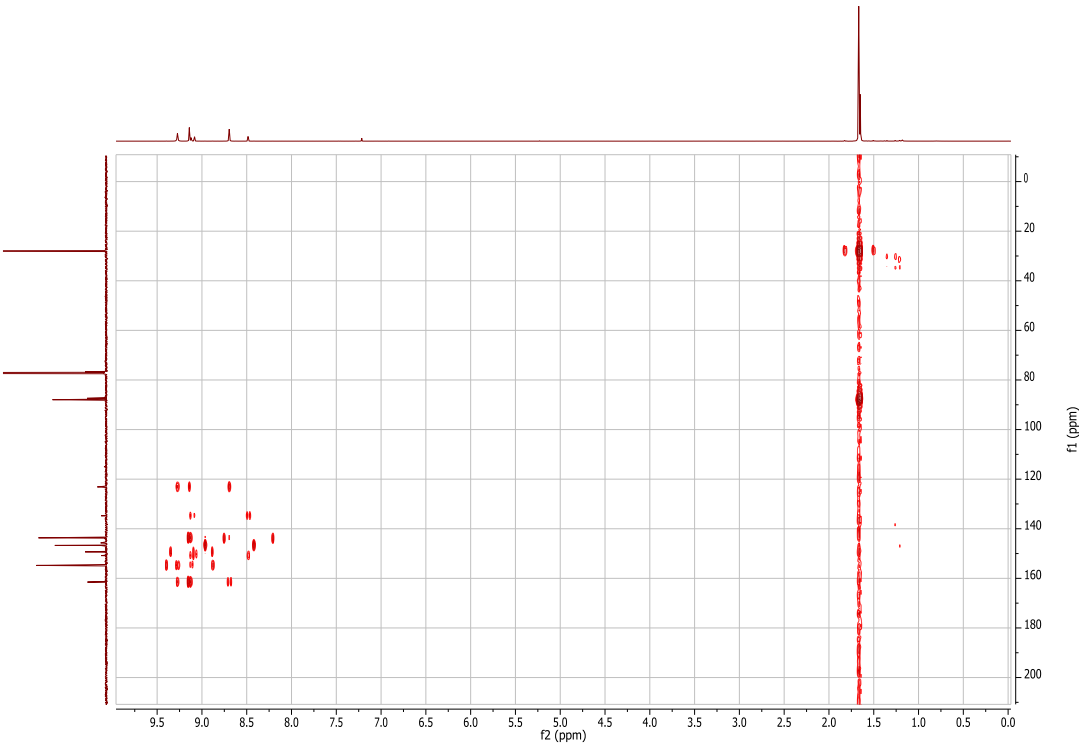
Spectrum 86 HMBC (CDCl3, 400 MHz) of tert-butyl 2,6-dichloropurine-9-carboxylate (**30**).



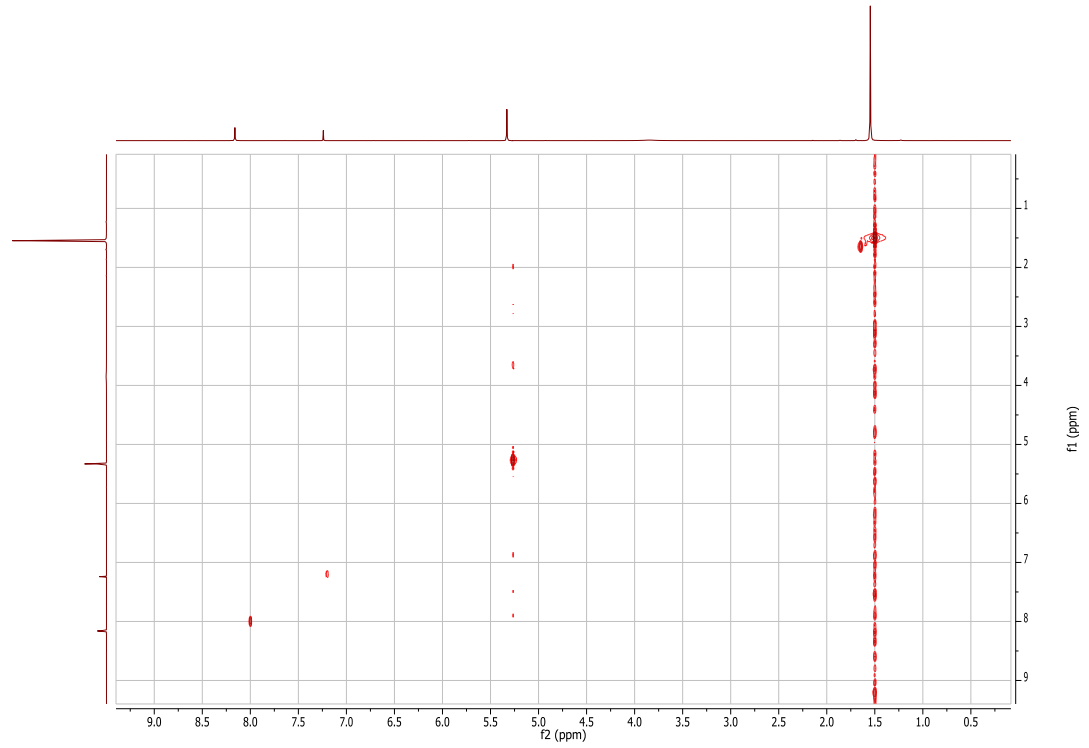
Spectrum 87 COSY ($CDCl_3$, 400 MHz) of *tert*-butyl purine-9-carboxylate (**31a**) and *tert*-butyl purine-7-carboxylate (**31b**).



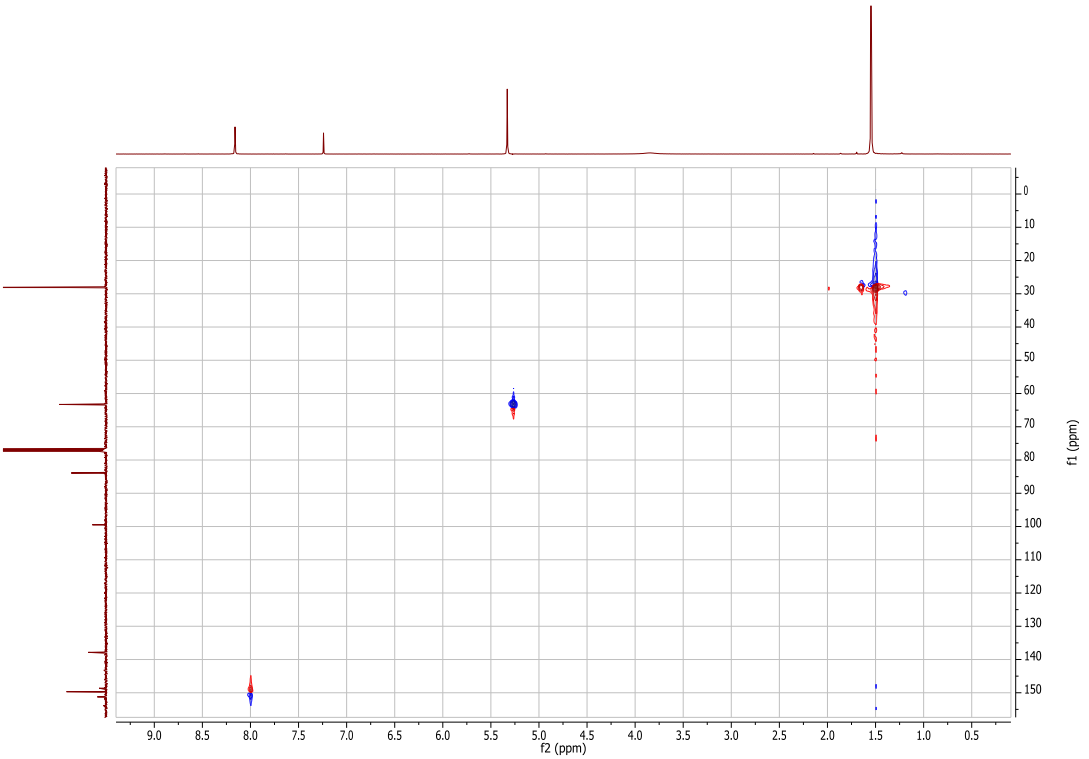
Spectrum 88 HSQC ($CDCl_3$, 400 MHz) of *tert*-butyl purine-9-carboxylate (**31a**) and *tert*-butyl purine-7-carboxylate (**31b**).



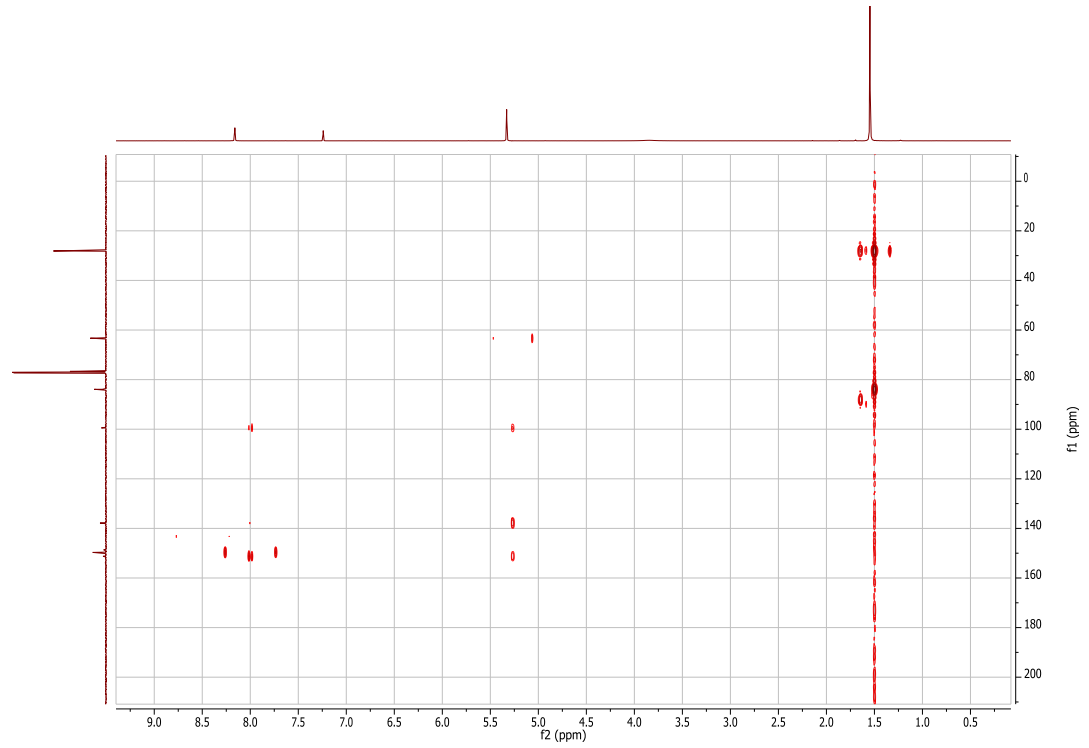
Spectrum 89 HMBC ($CDCl_3$, 400 MHz) of *tert*-butyl purine-9-carboxylate (**31a**) and *tert*-butyl purine-7-carboxylate (**31b**).



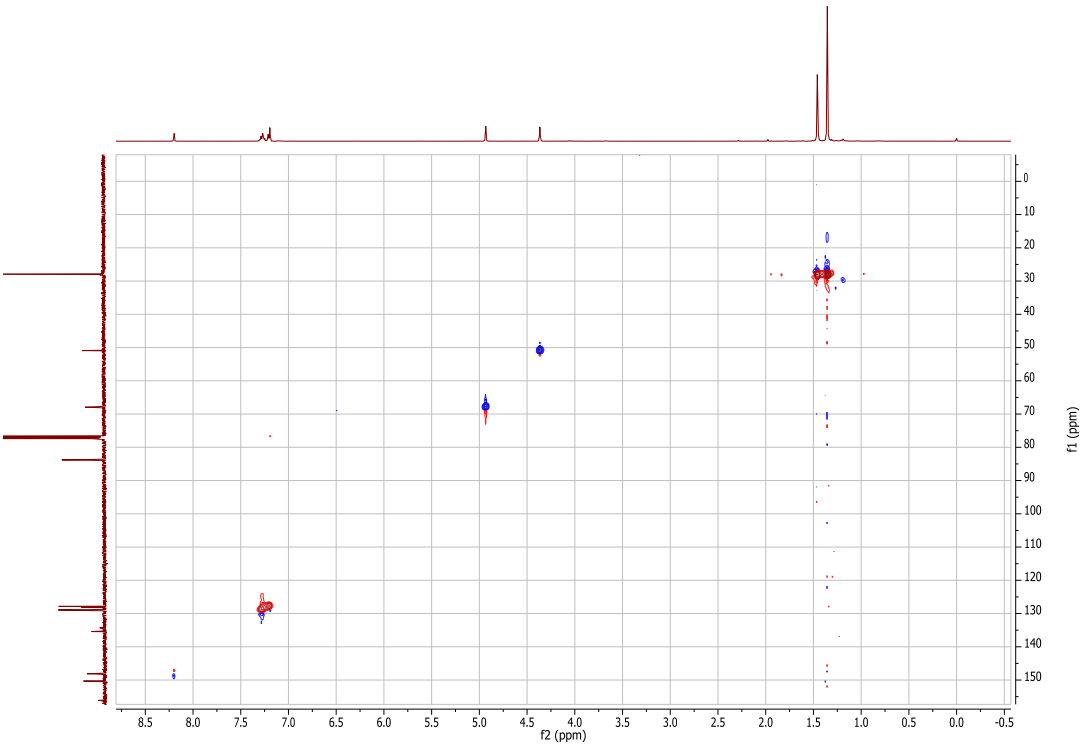
Spectrum 90 COSY ($CDCl_3$, 400 MHz) of *tert*-butyl 6-chloro-7,8-dihydropurine-9-carboxylate (**34**).



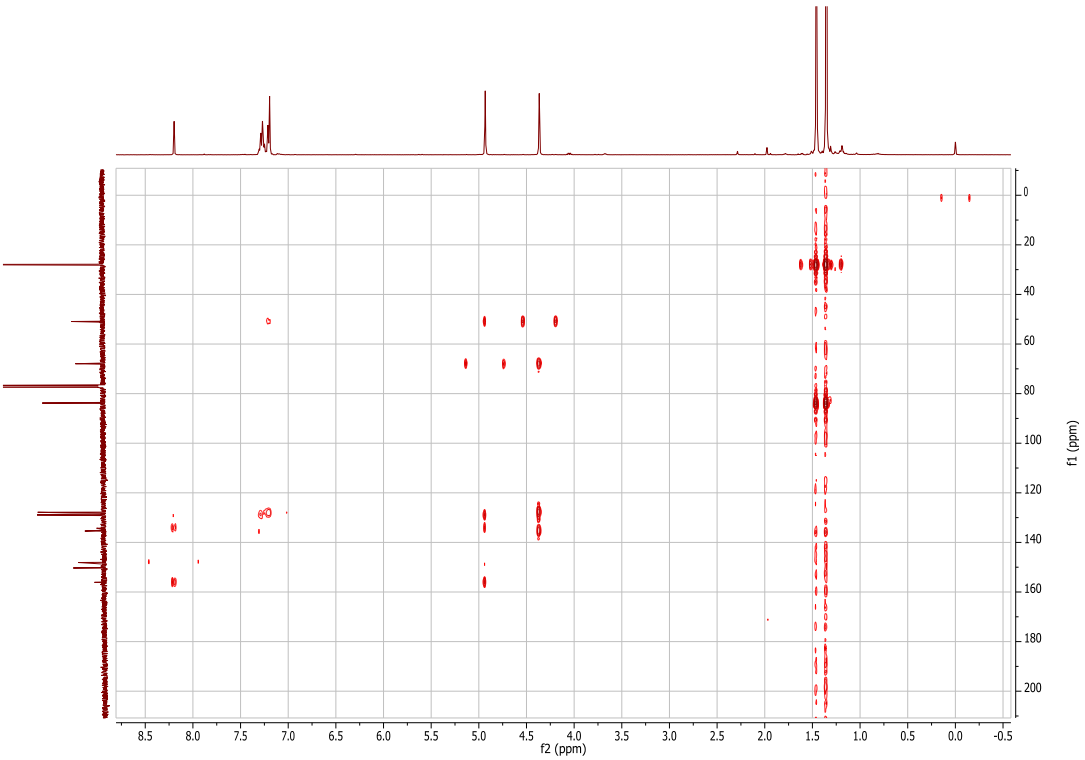
Spectrum 91 HSQC ($CDCl_3$, 400 MHz) of *tert*-butyl 6-chloro-7,8-dihydropurine-9-carboxylate (**34**).



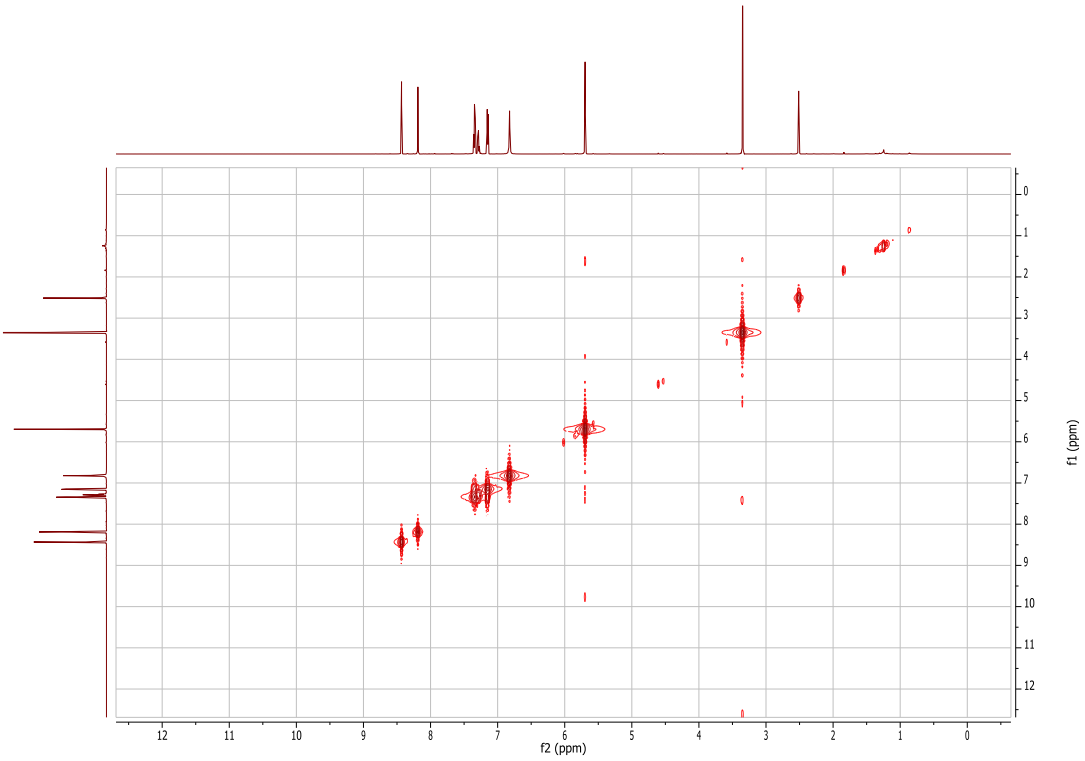
Spectrum 92 HMBC ($CDCl_3$, 400 MHz) of *tert*-butyl 6-chloro-7,8-dihydropurine-9-carboxylate (**34**).



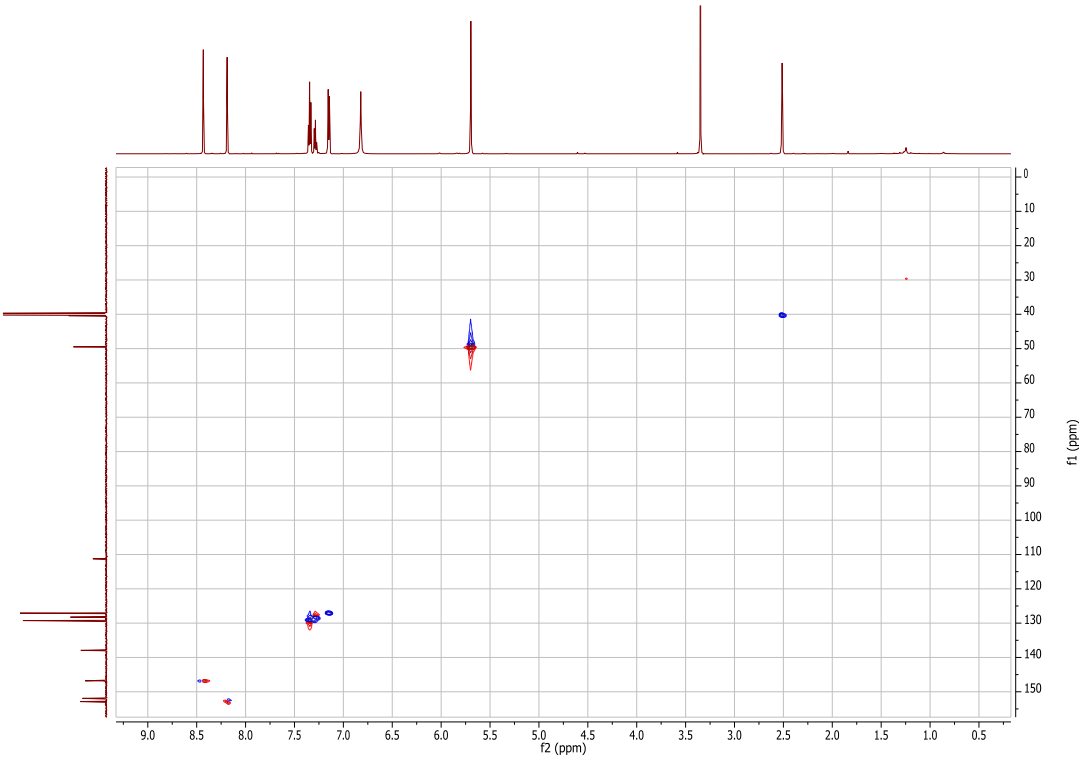
Spectrum 93 HSQC ($CDCl_3$, 400 MHz) of *tert*-butyl 7-benzyl-6-(*ditert*-butoxycarbonylamino)-8,9-dihydropurine-9-carboxylate (**19**).



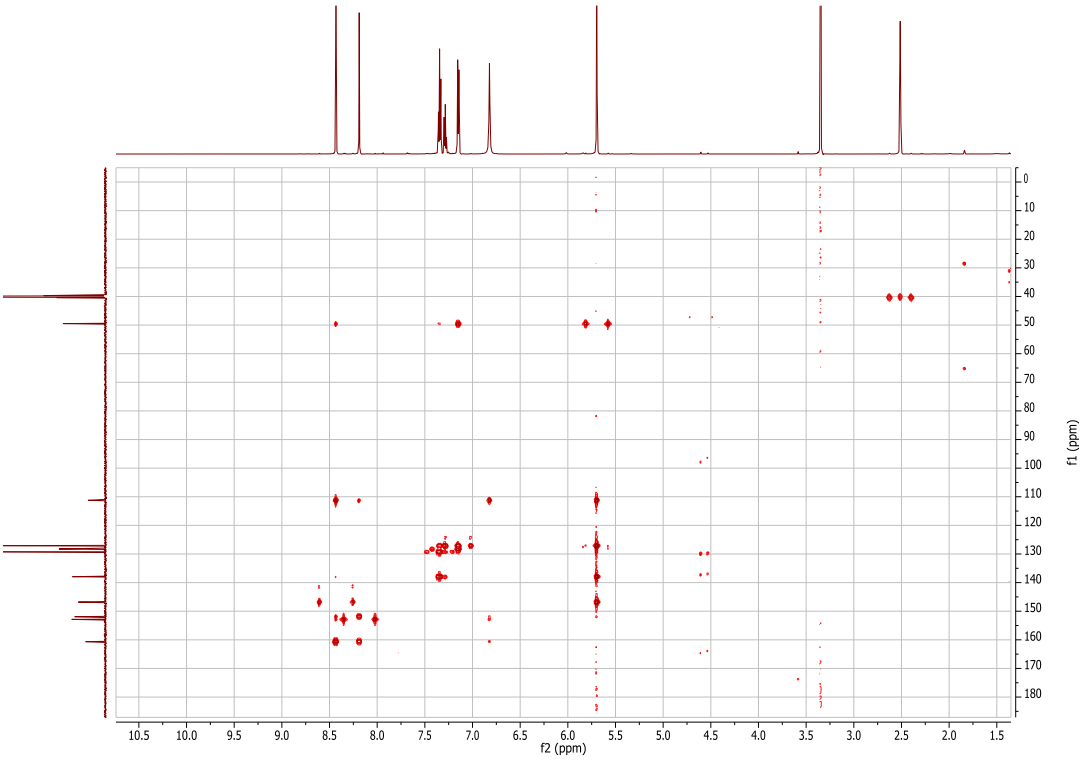
Spectrum 94 HMBC ($CDCl_3$, 400 MHz) of *tert*-butyl 7-benzyl-6-(*ditert*-butoxycarbonylamino)-8,9-dihydropurine-9-carboxylate (**19**).



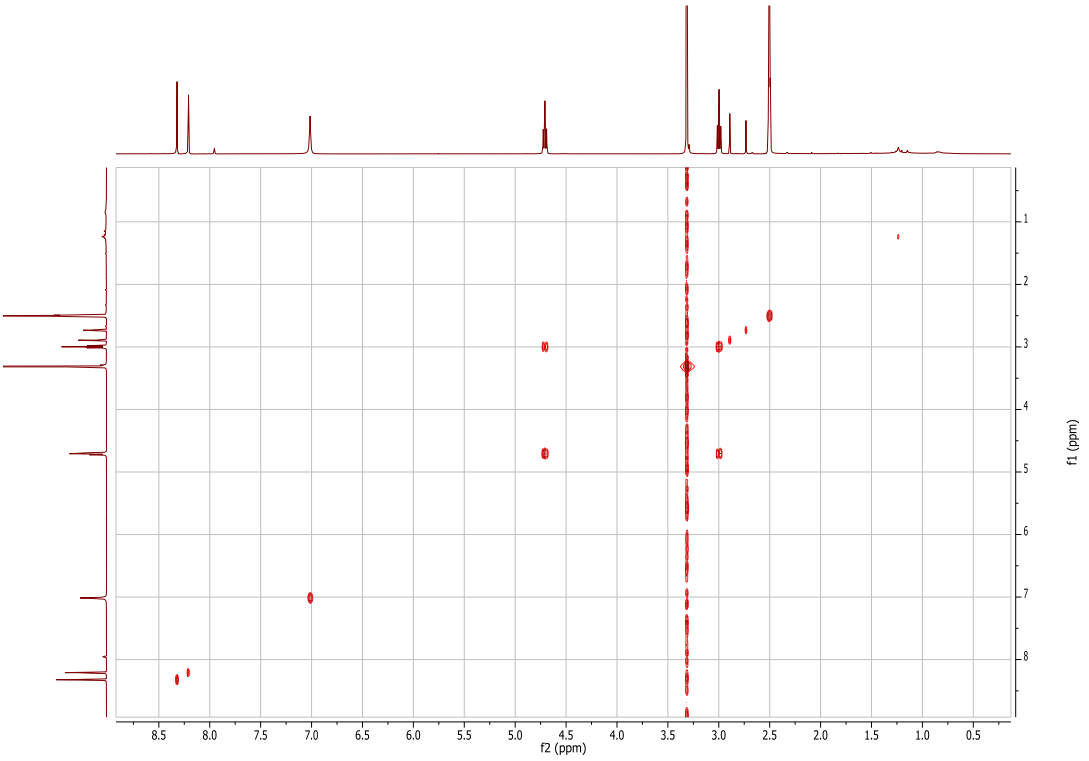
Spectrum 95 COSY (DMSO-d_6, 600 MHz) of 7-benzylpurin-6-amine (**21**).



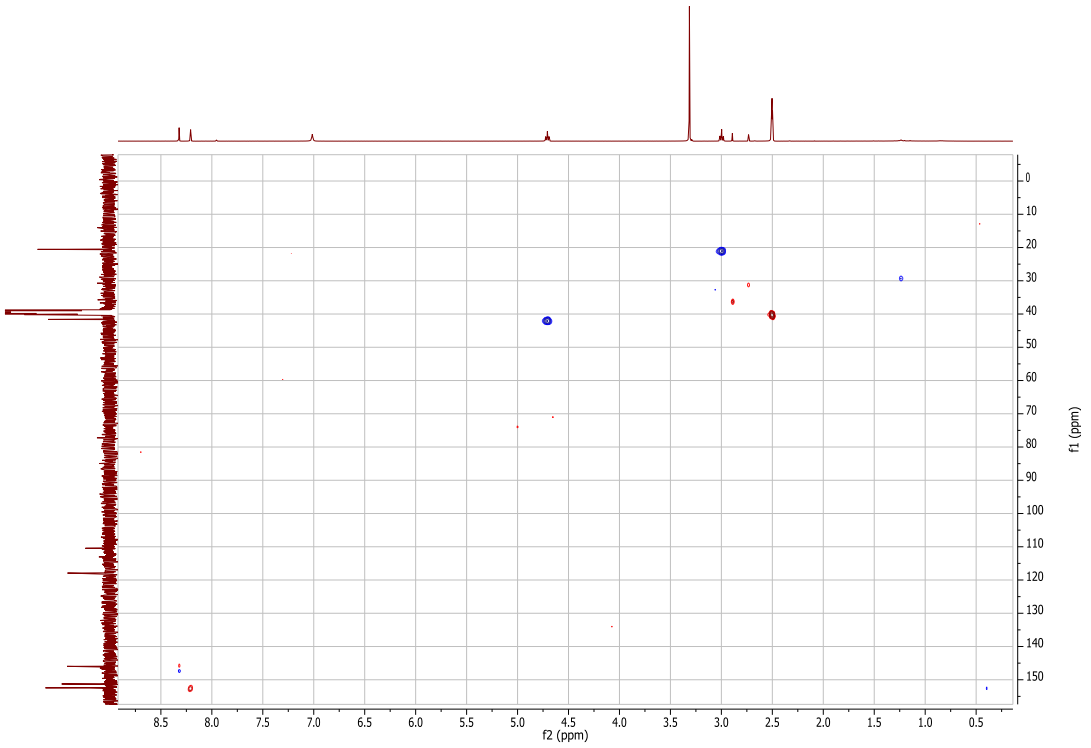
Spectrum 96 HSQC (DMSO-d_6, 600 MHz) of 7-benzylpurin-6-amine (**21**).



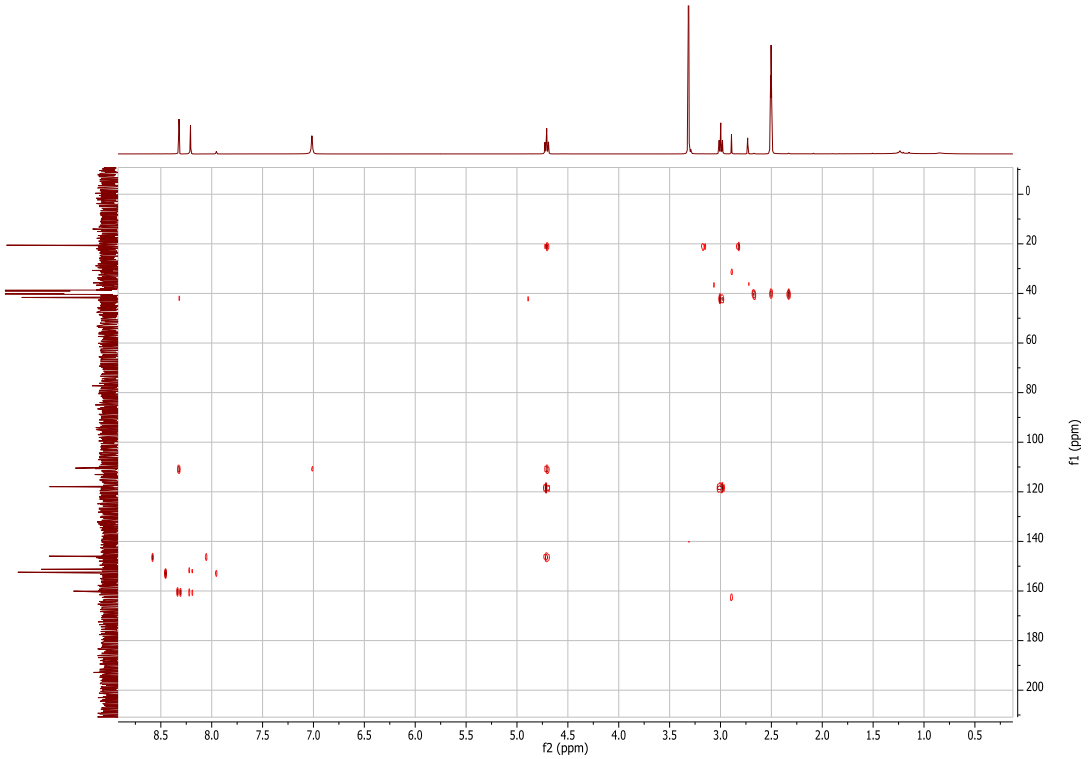
Spectrum 97 HMBC (DMSO-d_6, 600 MHz) of 7-benzylpurin-6-amine (**21**).



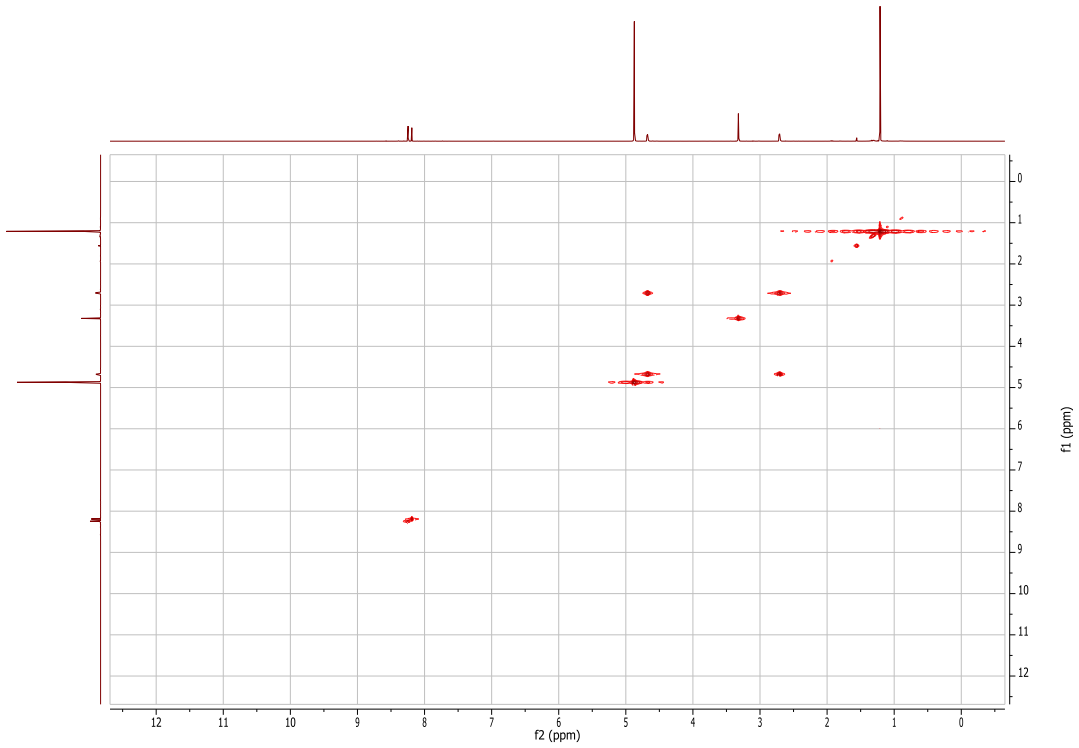
Spectrum 98 COSY (DMSO-d_6, 400 MHz) of 3-(6-aminopurin-7-yl)propanenitrile (**44a**).



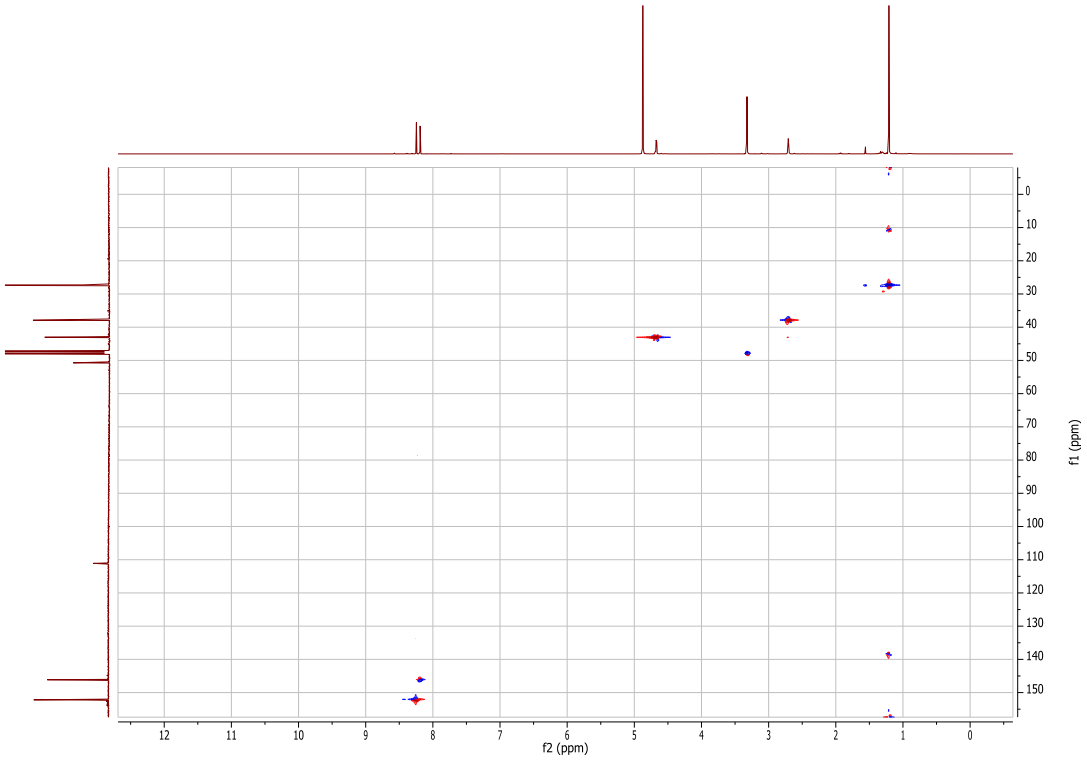
Spectrum 99 HSQC (DMSO-d_6, 400 MHz) of 3-(6-aminopurin-7-yl)propanenitrile (**44a**).



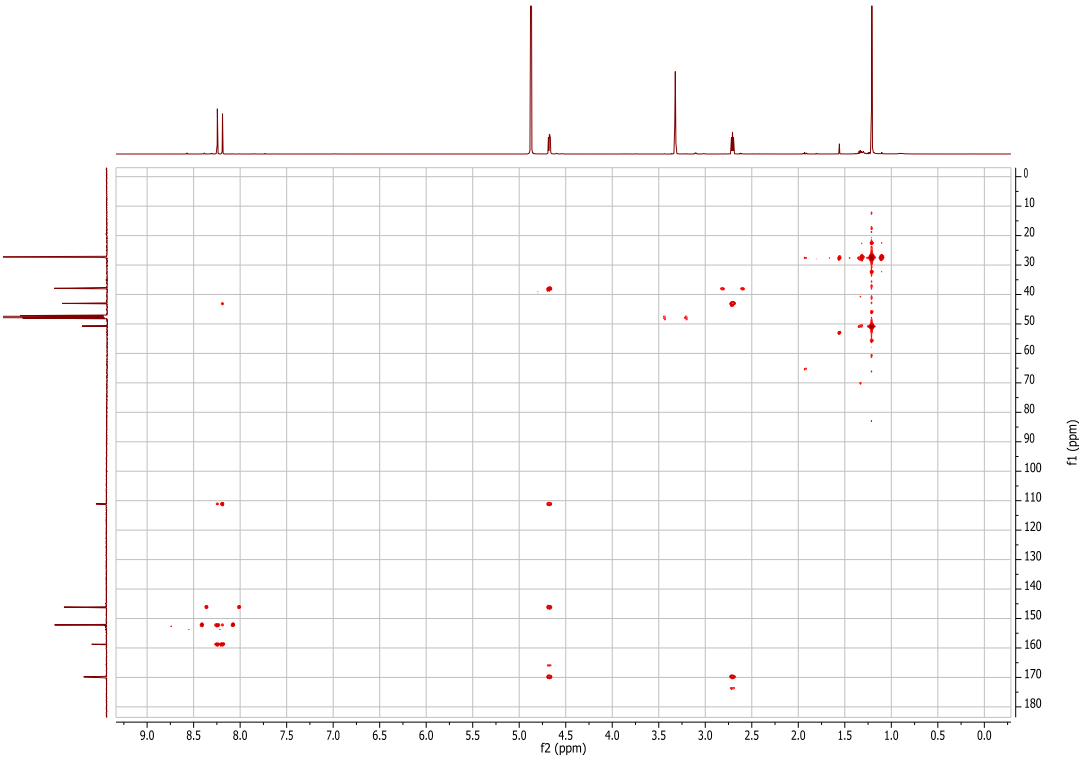
Spectrum 100 HMBC (DMSO-d_6, 400 MHz) of 3-(6-aminopurin-7-yl)propanenitrile (**44a**).



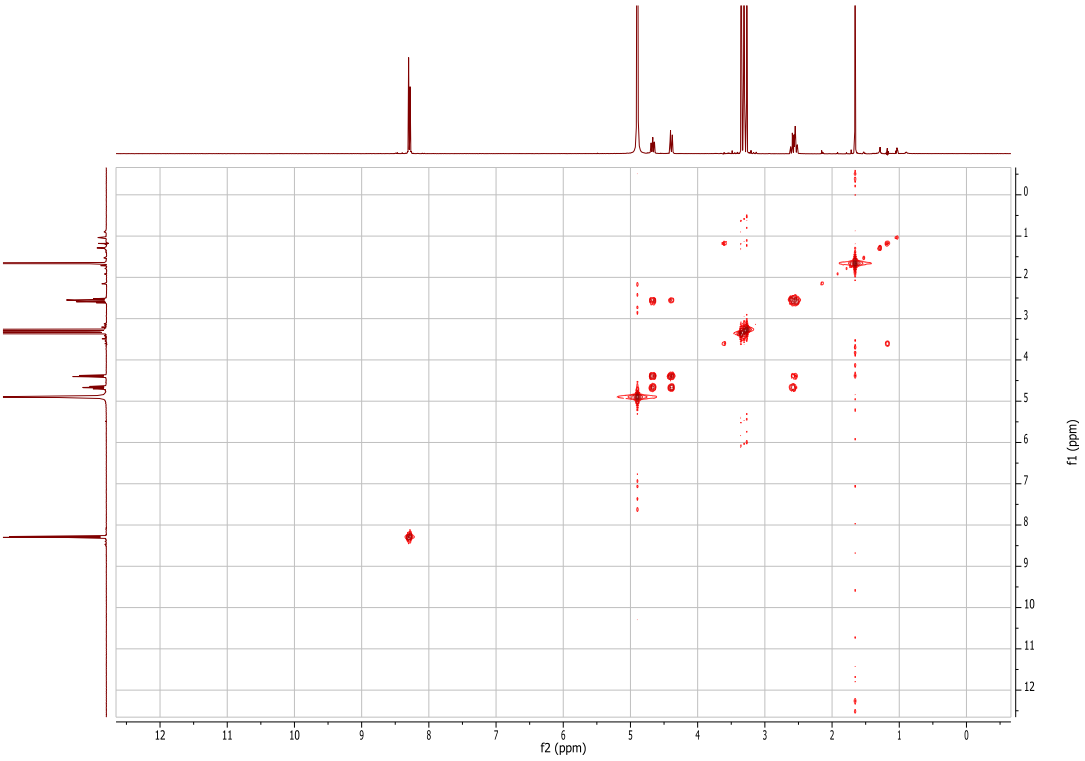
Spectrum 101 COSY (MeOH-d_4, 600 MHz) of 3-(6-amino-7H-purin-7-yl)-N-(tert-butyl)propanamide(**44b**).



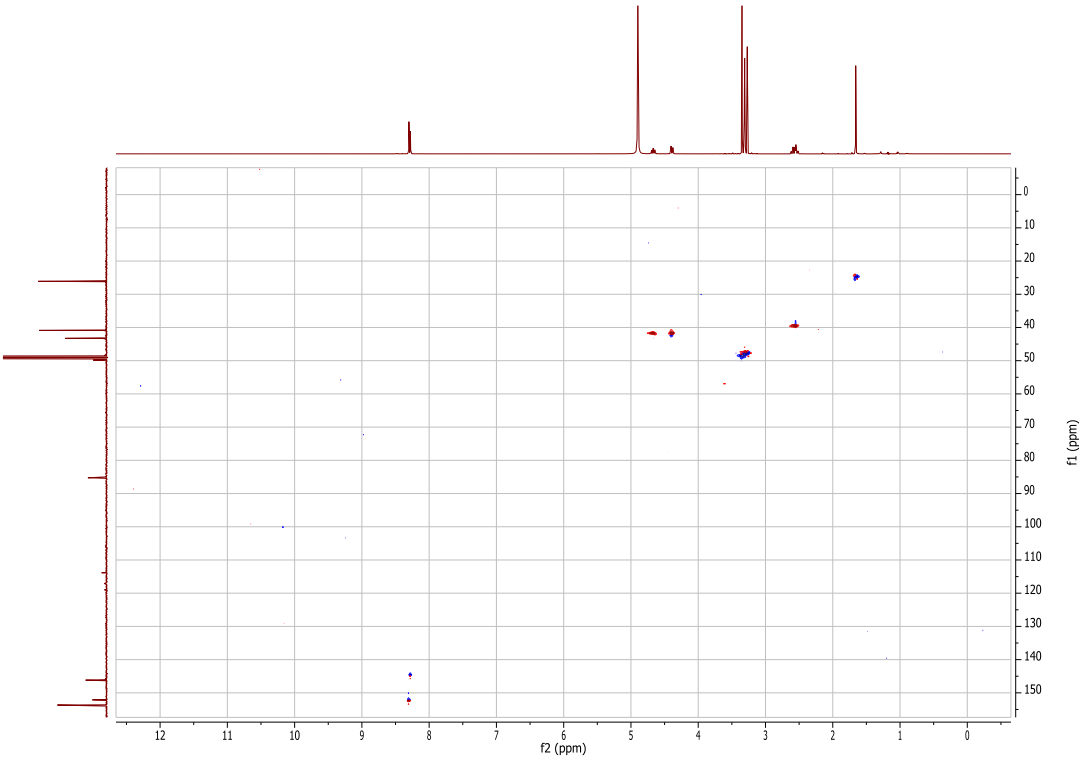
Spectrum 102 HSQC (MeOH-d_4, 600 MHz) of 3-(6-amino-7H-purin-7-yl)-N-(tert-butyl)propanamide(**44b**).



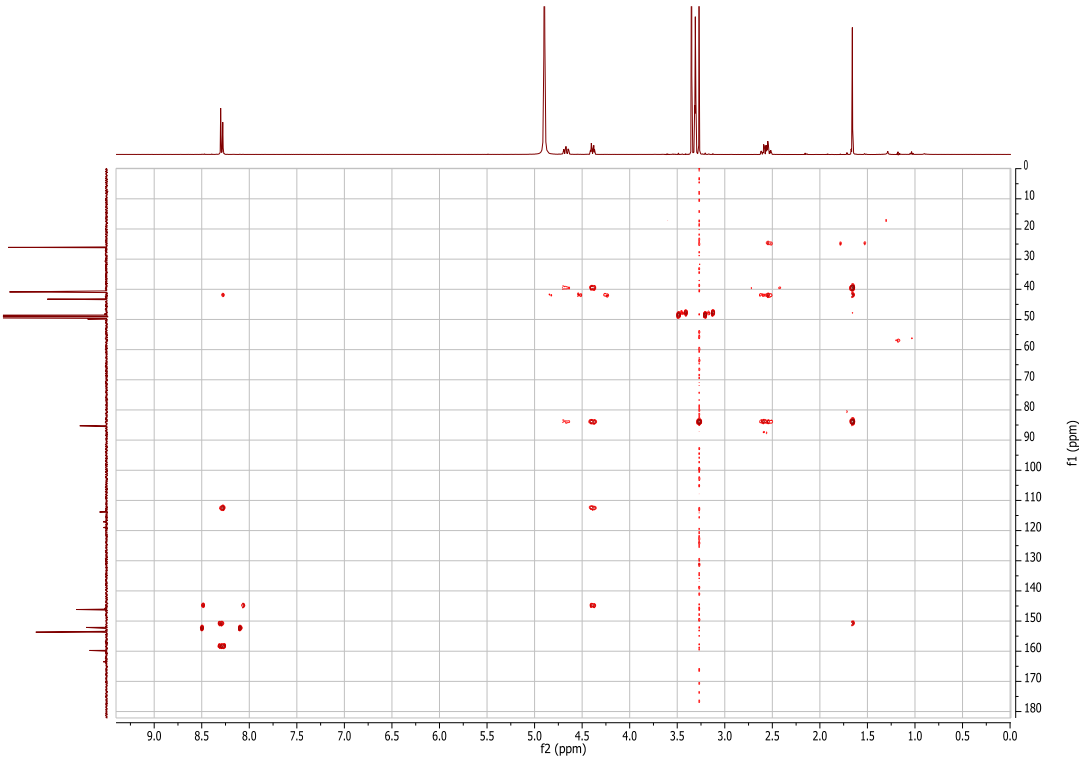
Spectrum 103 HMBC (MeOH-d_4, 600 MHz) of 3-(6-amino-7H-purin-7-yl)-N-(tert-butyl)propanamide(**44b**).



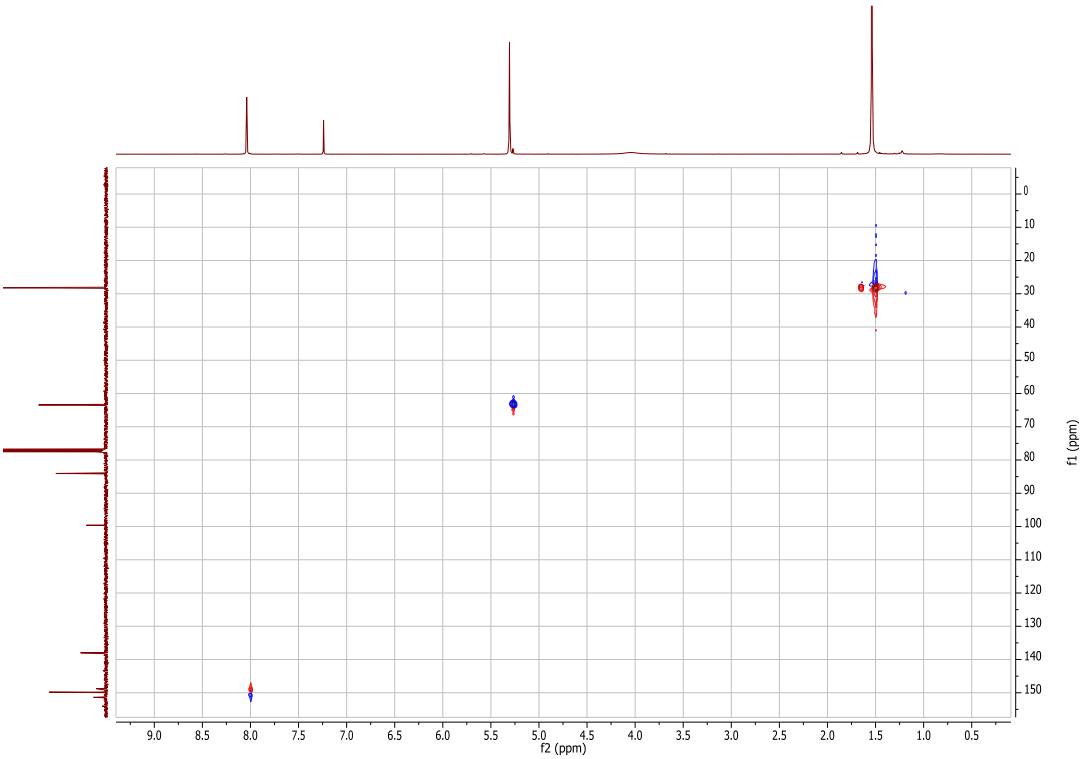
Spectrum 104 COSY (MeOH-d_4, 500 MHz) of 9-methoxy-9-methyl-7,8,9,10-tetrahydro-[1,4]diazepino[1,2,3-*gh*]purinium 2,2,2-trifluoroacetate (**18**).



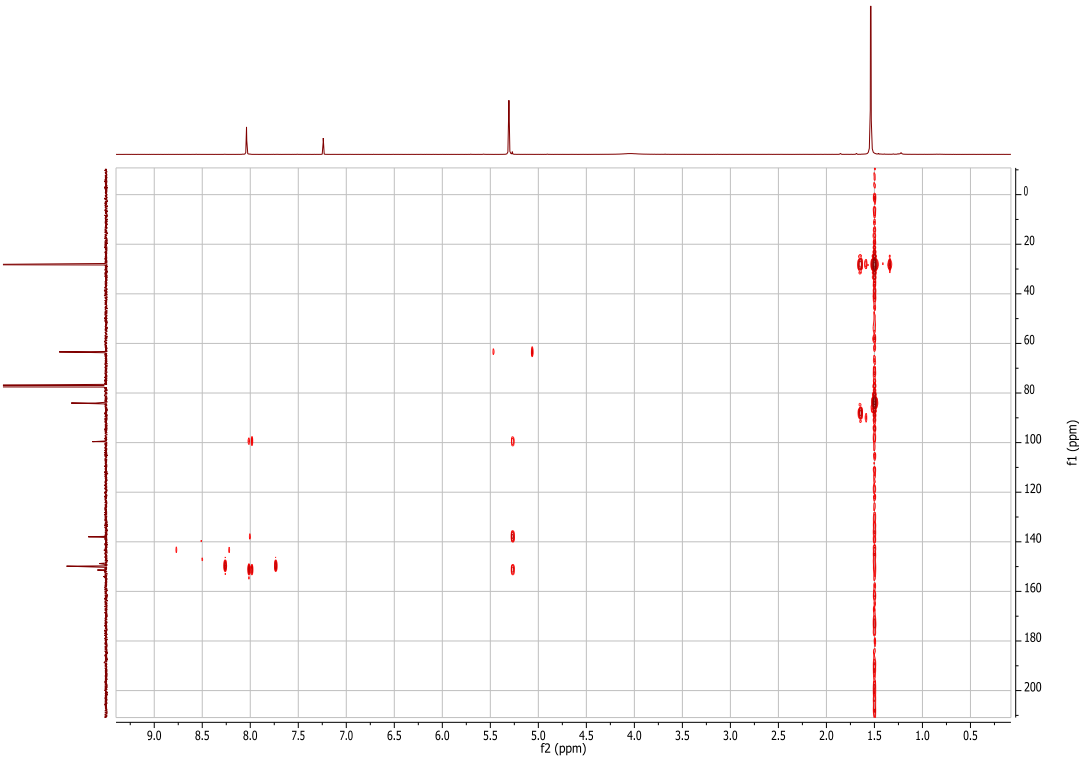
Spectrum 105 HSQC (MeOH-d_4, 500 MHz) of 9-methoxy-9-methyl-7,8,9,10-tetrahydro-[1,4]diazepino[1,2,3-*gh*]purinium 2,2,2-trifluoroacetate (**18**).



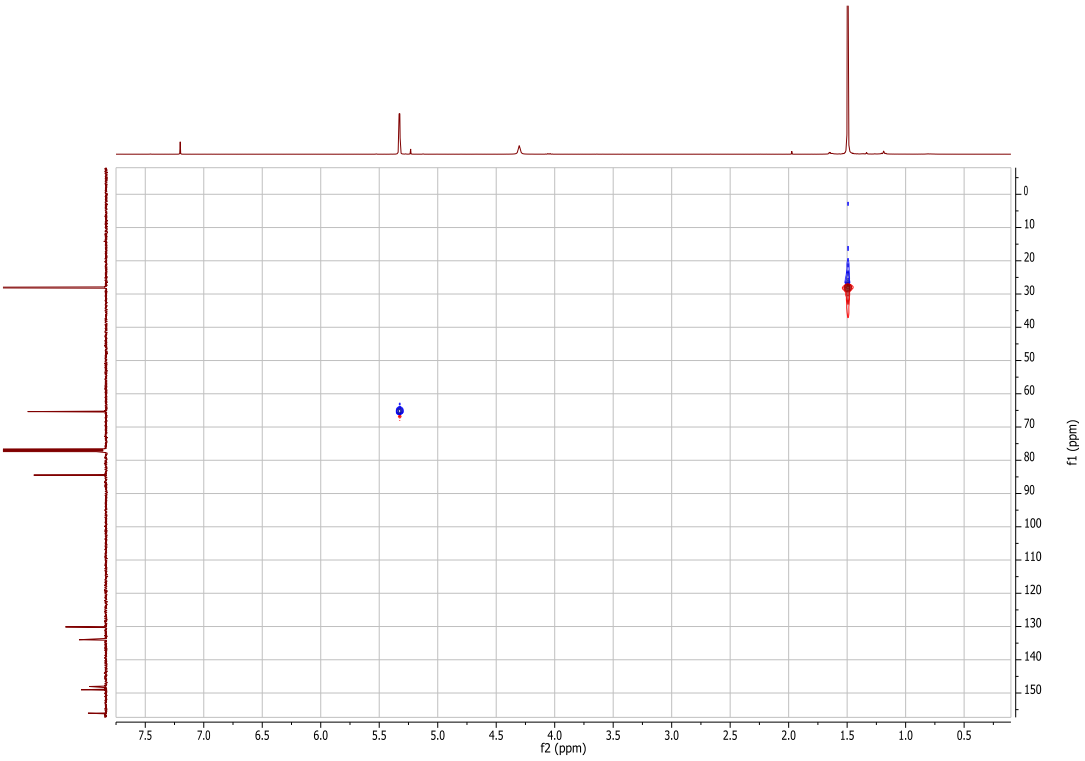
Spectrum 106 HMBC (MeOH-d_4, 500 MHz) of 9-methoxy-9-methyl-7,8,9,10-tetrahydro-[1,4]diazepino[1,2,3-*gh*]purinium 2,2,2-trifluoroacetate (**18**).



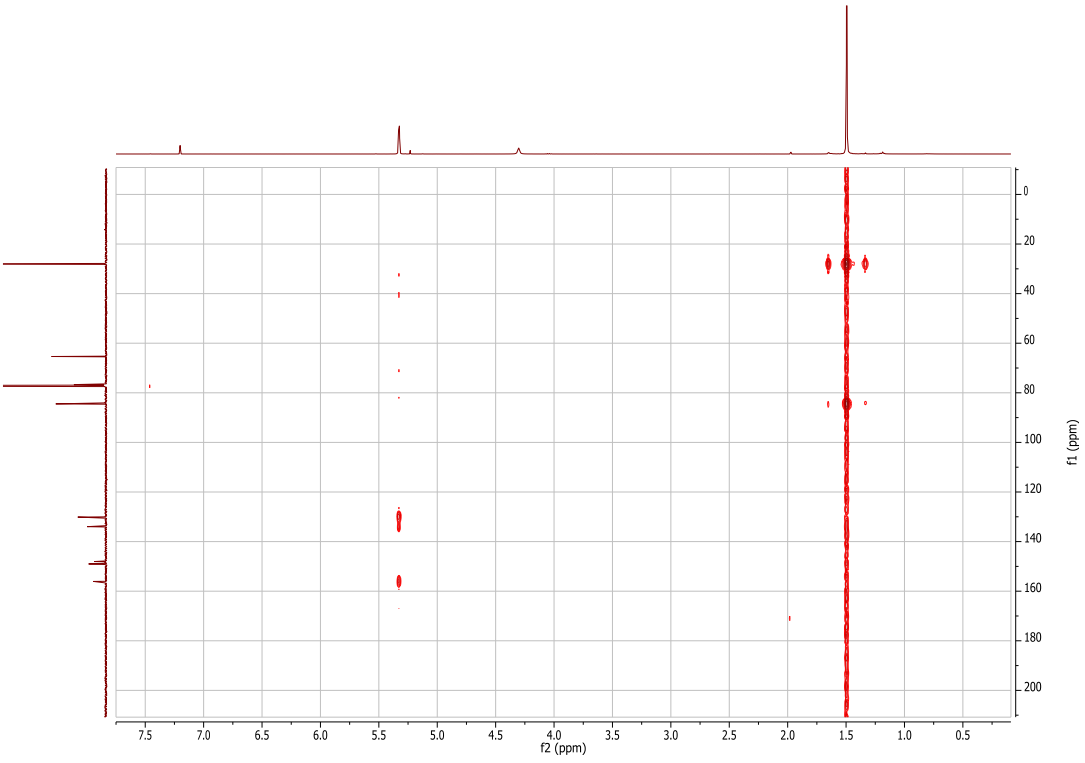
Spectrum 107 HSQC ($CDCl_3$, 400 MHz) of *tert*-butyl 6-iodo-7,8-dihydropurine-9-carboxylate (**35**).



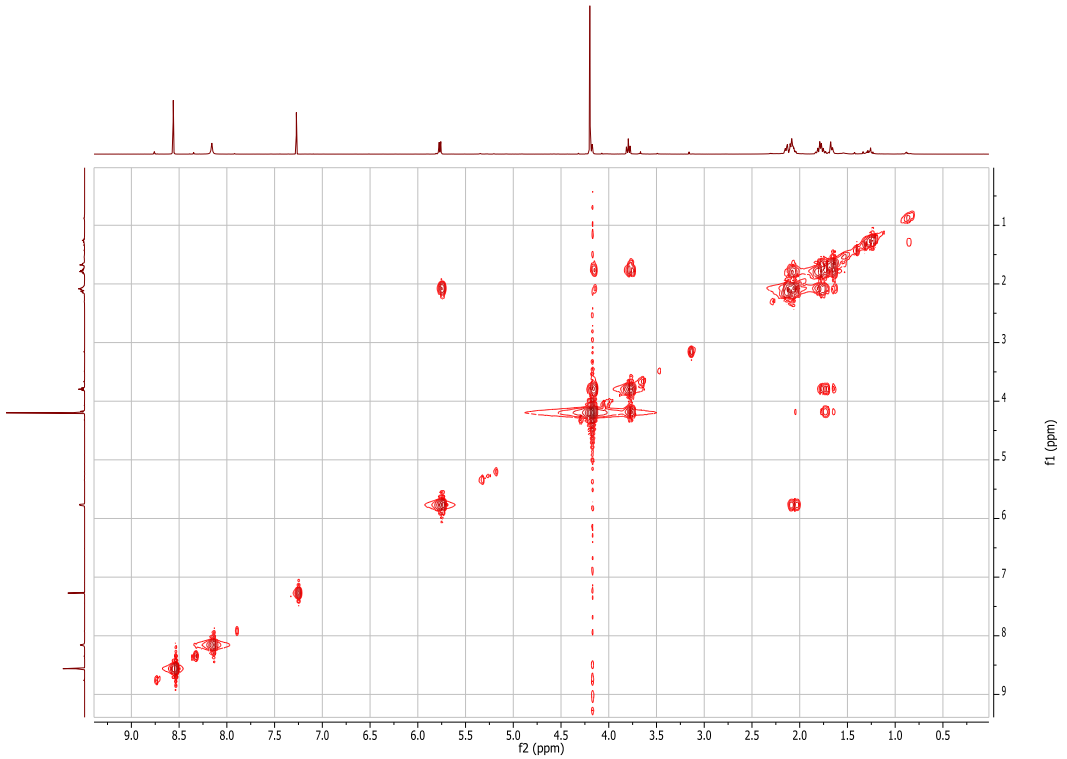
Spectrum 108 HSQC ($CDCl_3$, 400 MHz) of *tert*-butyl 6-iodo-7,8-dihydropurine-9-carboxylate (**35**).



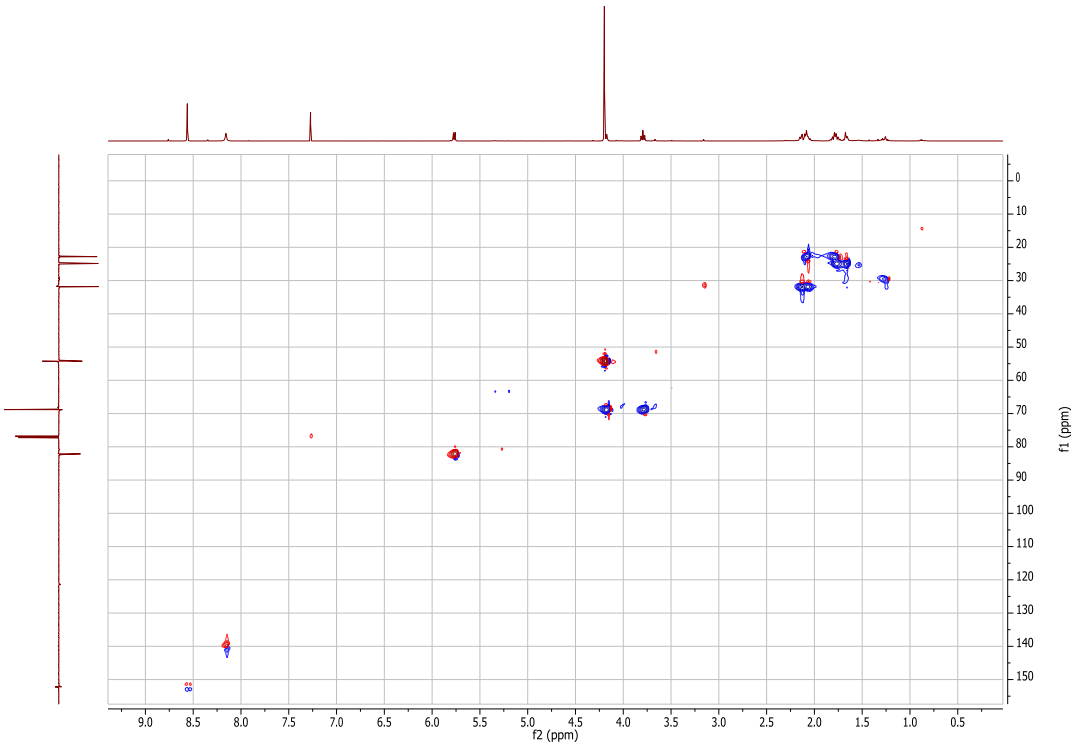
Spectrum 109 HSQC ($CDCl_3$, 400 MHz) of *tert*-butyl 2,6-dichloro-7,8-dihydropurine-9-carboxylate (**38**).



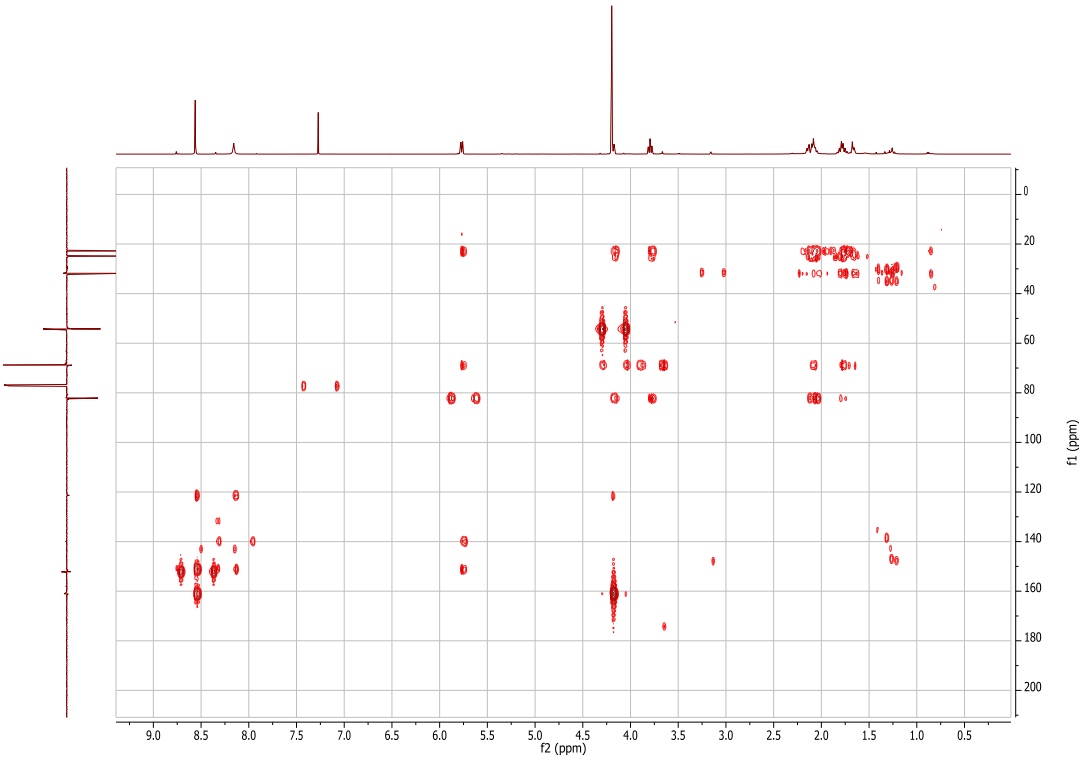
Spectrum 110 HMBC ($CDCl_3$, 400 MHz) of *tert*-butyl 2,6-dichloro-7,8-dihydropurine-9-carboxylate (**38**).



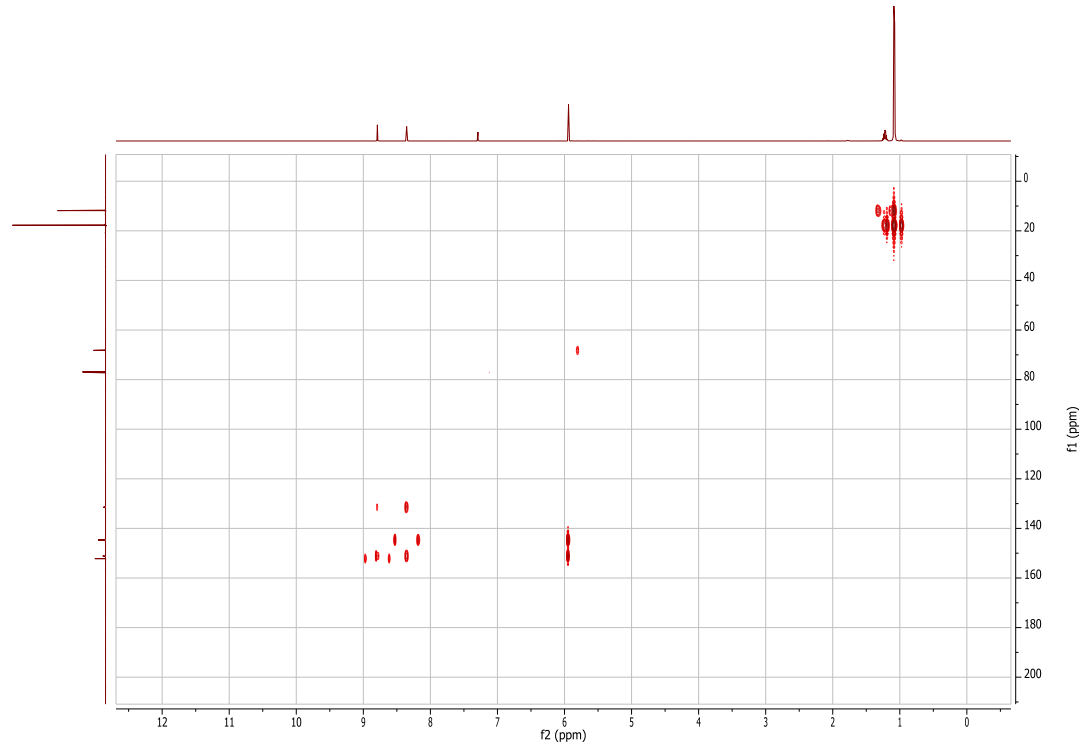
Spectrum 111 COSY ($CDCl_3$, 600 MHz) of 6-methoxy-9-(tetrahydro-*2H*-pyran-2-yl)purine (**42**).



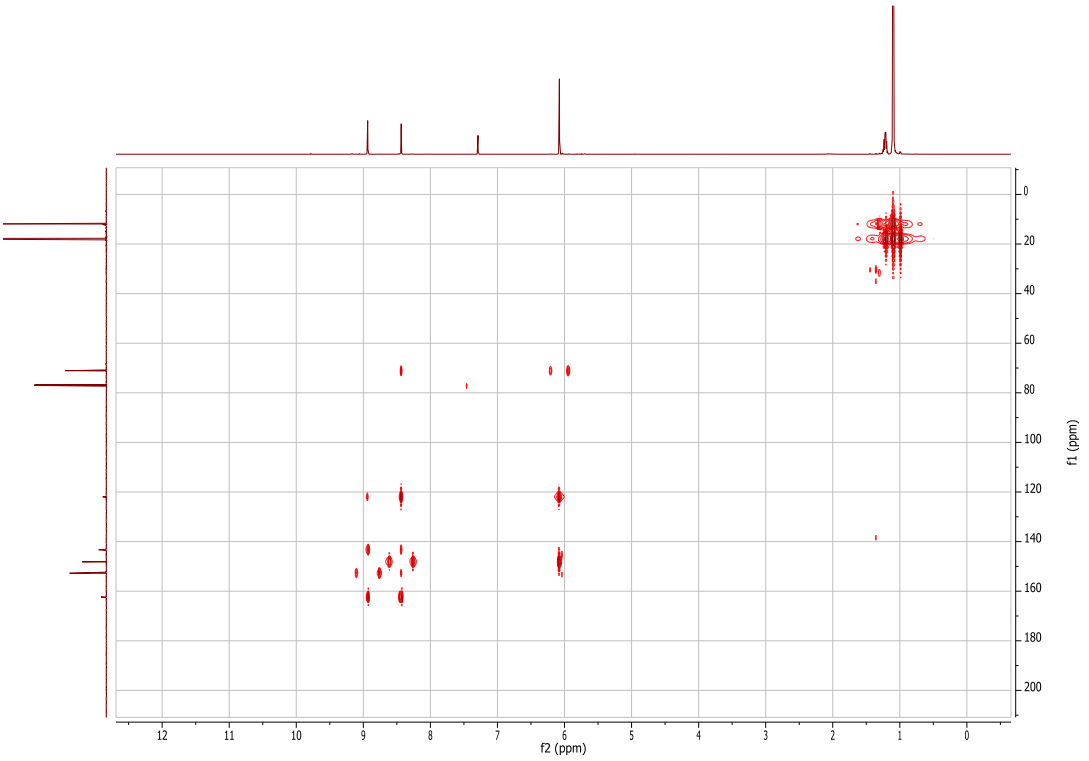
Spectrum 112 HSQC ($CDCl_3$, 600 MHz) of 6-methoxy-9-(tetrahydro-*2H*-pyran-2-yl)purine (**42**).



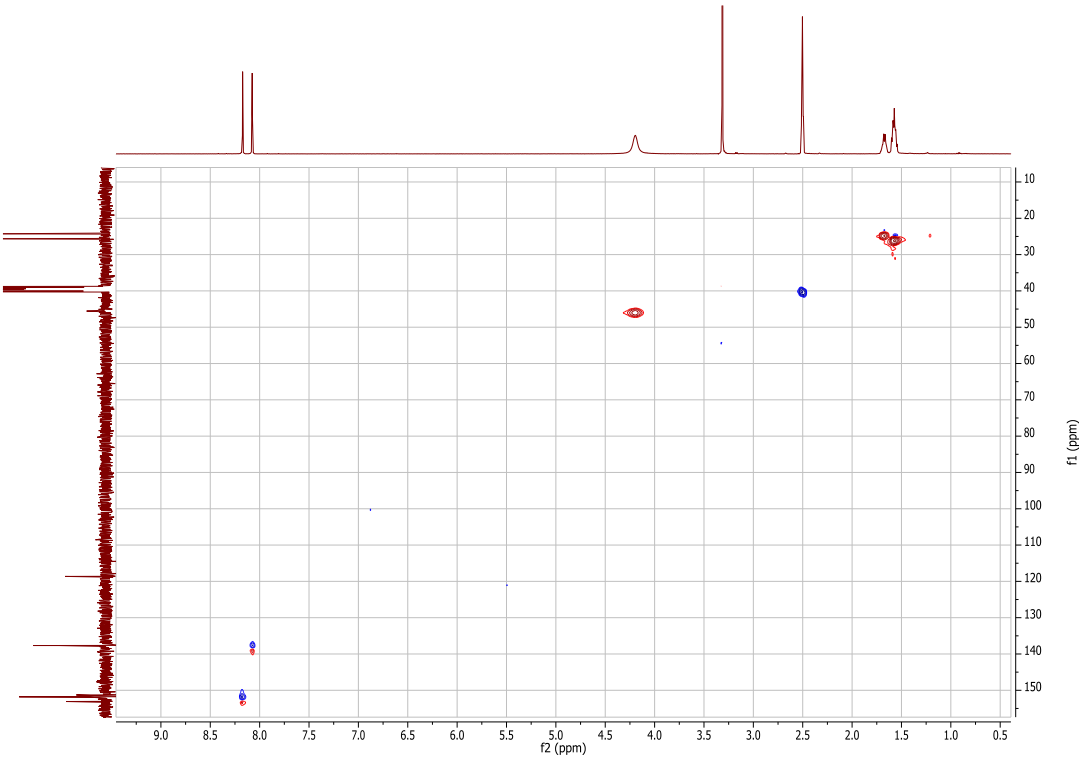
Spectrum 113 HMBC ($CDCl_3$, 600 MHz) of 6-methoxy-9-(tetrahydro-*2H*-pyran-2-yl)purine (**42**).



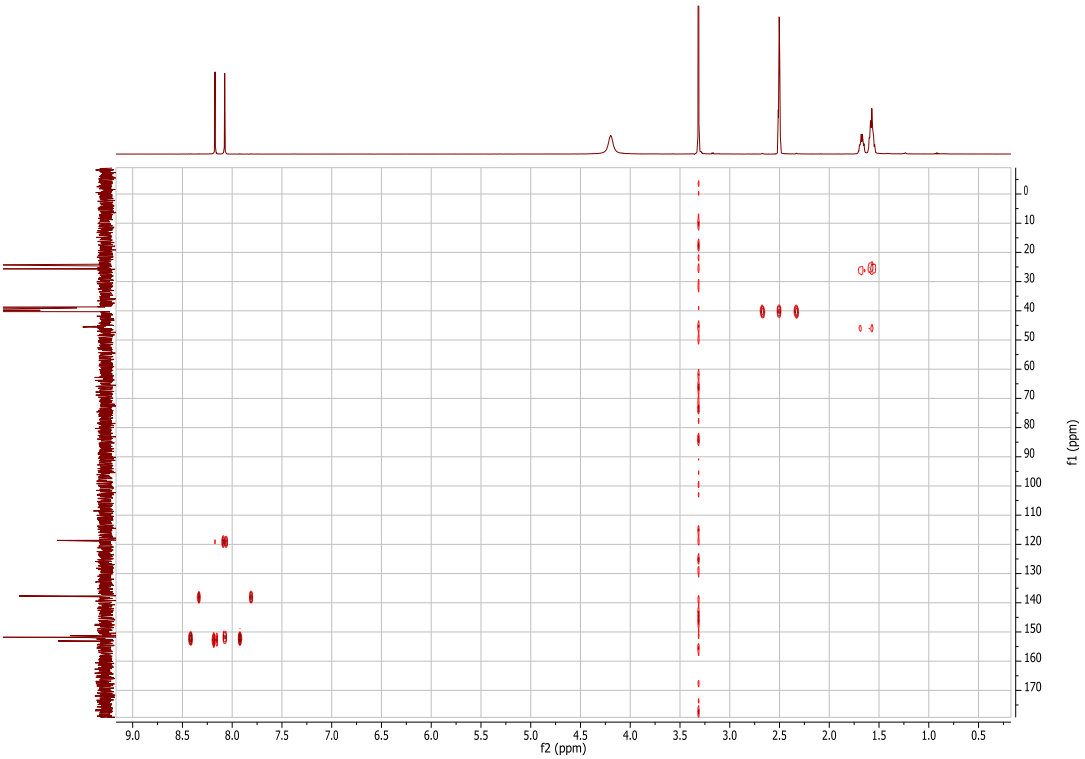
Spectrum 114 HMBC ($CDCl_3$**,** 600 MHz) of 6-chloro-9-(((triisopropylsilyl)oxy)methyl)purine (**32a**).



Spectrum 115 HMBC ($CDCl_3$, 600 MHz) of 6-chloro-9-(((triisopropylsilyl)oxy)methyl)purine (**32b**).



Spectrum 116 HSQC (DMSO-d_6, 400 MHz) of 6-(piperidin-1-yl)purine (**25**).



Spectrum 117 HSQC (DMSO-d_6, 400 MHz) of 6-(piperidin-1-yl)purine (**25**).

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