Thesis for the Master's degree in chemistry

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Synthesis directed towards tricyclic heterocycles with DNA intercalating properties

60 study points

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ABSTRACT

4-Substituted pyrido[1,2-*e*]purines   (Figure 1) as anticancer agents have the ability to intercalate with DNA molecules and display improved cytotoxic activities especially towards the resistant cancer cell lines (MCF7R).[1-5] These compounds were originally synthesized from imidazopyridines via poor yielding synthetic routes.[1] Herein we discuss the development of more efficient strategies towards pyrido[1,2-*e*]purines.

Since pyrido[1,2-*e*]purines vary mostly by their 4-substituent,[1-5] we also wanted to develop more efficient strategy where the 4-substituent can be introduced in the last step (Figure 1).
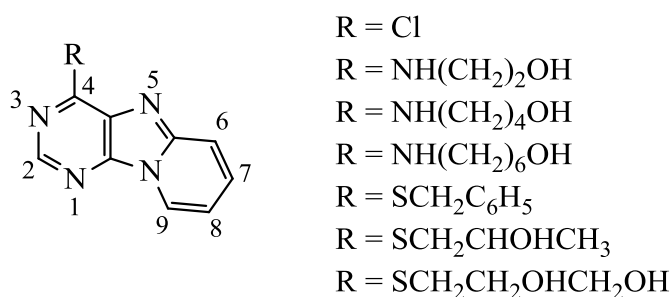
$R = Cl$
$R = NH(CH_2)_2OH$
$R = NH(CH_2)_4OH$
$R = NH(CH_2)_6OH$
$R = SCH_2C_6H_5$
$R = SCH_2CHOHCH_3$
$R = SCH_2CH_2OHCH_2OH$

Figure 1. 4-Substituted pyrido[1,2-*e*]purines as anticancer agents.[1-5]

ABBREVIATIONS

Ac	Acetyl
Ar	Aryl
Bu	Butyl
BuLi	Butyllithium
COSY	Correlation spectroscopy (NMR)
DCE	Dichloroethane
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DMA	Dimethylacetamide
DMF	*N,N*-dimethylformamide
DNA	Deoxyribonucleic acid
EI	Electron impact (MS)
EDG	Electron donating group
ESI	Electrosprayionisation (MS)
EtOAc	Ethyl acetate
EtOH	Ethanol
EWG	Electron withdrawing group
HMBC	Heteronuclear Multiple Bond Coherence
HMQC	Heteronuclear Multiple Quantum Coherence
HRMS	High Resolution Mass Spectra
HSQC	Heteronuclear Single Quantum Correlation (NMR)
IUPAC	International union of pure and applied chemistry
J	Coupling constant (NMR)
LDA	Lithium diisopropylamide

MD	Molecular dynamics calculation
MDR	Multi drug resistant (cancer cell lines)
Me	Methyl
MeOH	Methanol
MS	Mass Spectrometry
n.d.	Not determined
N3Et	Triethyl amine
NMR	Nuclear magnetic resonance spectroscopy
NOE	Nuclear Overhauser Effect (NMR)
NOESY	Nuclear Overhauser Effect Spectroscopy (NMR)
Ph	Phenyl
ppm	Parts per million
R	Hydrocarbon
RNA	Ribonucleic acid
rt	Room temperature
SAR	Structure activity relationship
SNAr	Nucleophillic Aromatic Substitution
t-**BuOk**	Potassium-tert-butoxide
TBAF	Tetra-*n*-butylammonium fluoride
THF	Tetrahydrofuran

1. Aim of the project

Synthesis of cytotoxic pyrido[1,2-*e*]purines was done before in literature through long poor yielding synthetic route starting with imidazopyridines (Scheme 1).[1]

R = NHCH$_3$, piperidinyl
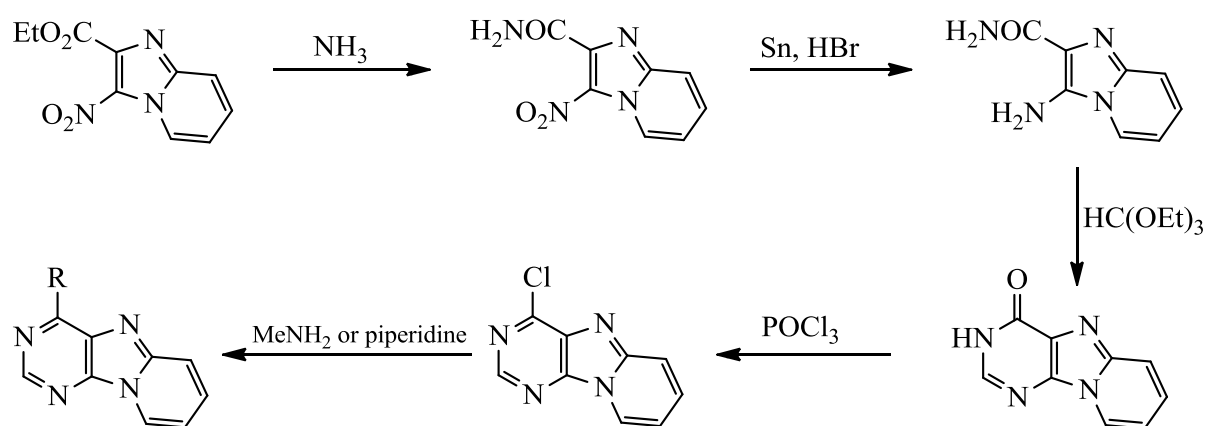
Scheme 1. Previous synthesis of pyrido[1,2-*e*]purines.[1]

Therefore, the aim of our project is to develop more efficient strategy towards the 4-substituted pyrido[1,2-*e*]purines starting from the commercially available 6-chloropurine depending mainly on N-allylation of purines and C-8 functioanlzation towards RCM reactions (Scheme 2).

R = Cl, piperidinyl
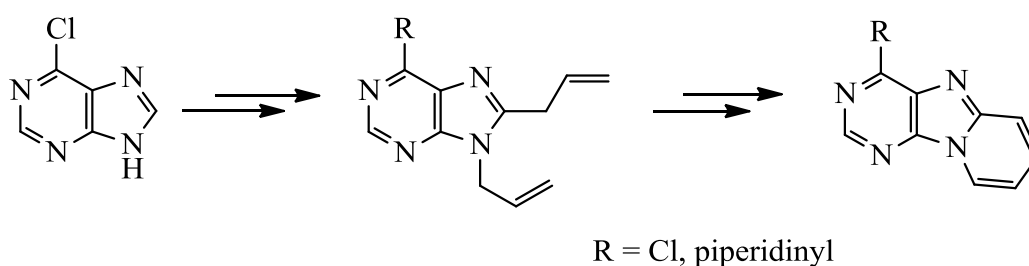
Scheme 2. The synthetic strategy of the project towards pyrido[1,2-*e*]purines.

2. Introduction

2.1 General

Purines **3** are heterocyclic aromatic compounds, consisting of a pyrimidine ring **1** fused to an imidazole ring **2** (Figure 2).[6] The name purine originates from the Latin word *purum* (pure) and *uricum* (urine). The name of this heterocycle was given by Emil Fischer as it was first synthesized from uric acid.[7]

Owing to their large abundance in natural products and biomolecules, the purine scaffold has received an enormous interest among biologists and chemists. The most important purine containing biomacromolecules are DNA and RNA.
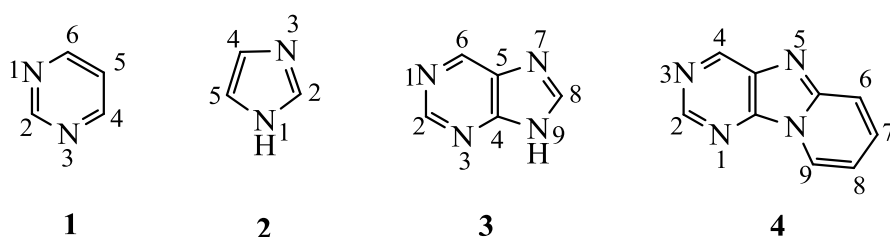
Figure 2. Numbering system for pyrimidine, imidazole, purine, and pyrido[1,2-*e*]purine.

While pyrido[1,2-*e*]purines **4** are consisted of the purine ring system fused to a benzene ring (Figure 2).

Several pyrido[1,2-*e*]purines are reported to exhibit inhibitory activity against certain cancer cell lines including activity against multi-drug resistant (MDR) cell lines.[1-5]

2.2 Biological significance of pyrido[1,2-*e*]purines.

In aggressive tumors, the nuclear DNA of malignant cells often replicates more quickly than the nuclear DNA of surrounding healthy tissues.[8] Interference in DNA replication of malignant cells inhibits tumor expansion, and reduces tumor mass if unsuccessful replication induces tumor cell death.[9] A substantial fraction of effective anticancer drugs bind nuclear DNA, either covalently or noncovalently, and interfere with replication.[10] The most prominent examples in general clinical use are the anthracycline antibiotics adriamycin and daunomycin, the anthracenedione mitoxandrone, and the antileukemic 9-anilinoacridineamsacrine.[11] However, both the development of acquired resistance and the severity of toxicity associated with antineoplasic agents have necessitated the continuing development of new drugs.

4-Subistituted pyrido[1,2-*e*]purines have been studied to show cytotoxic activity towards human certain cancer cell lines. The ability of the ring system of pyrido[1,2-*e*]purines to intercalate with synthetic oligonucleotides has established their antineoplastic activities.[1-5]

Cancer cells can develop mechanisms of resistance allows them to evade chemotherapy. The mechanisms of drug resistance are multifactorial: multidrug resistance (MDR) is the best known of all, since its molecular and genetic support has been identified.[12] MDR is associated with the expression of a membrane P-glycoprotein (PGP) which is an energy dependent efflux pump responsible for reducing intracellular drug concentration in resistant cells.[13,14]

The pyrido[1,2-*e*]purines were found to be active against MDR cell lines, MCF7R, which were shown to have increased resistance to doxorubicin. Consequently, drug activity is not affected by MDR resistance.

Therefore, in comparison with doxorubicin as anti-cancer drug, the cytotoxic activities of compounds **5**, **6**, **7**, and **8** (Figure 3) were investigated against the breast cancer cell lines MCF7 and the resistant MCF7R *in vitro* which showed a range of sensitivities towards them.[1]

5: R = H, R_1 = H, R_2 = CH_3
6: R = CH_3, R_1 = H, R_2 = CH_3
7: R = H, R_1, R_2 = -$(CH_2)_5$-
8: R = CH_3, R_1, R_2 = -$(CH_2)_5$-
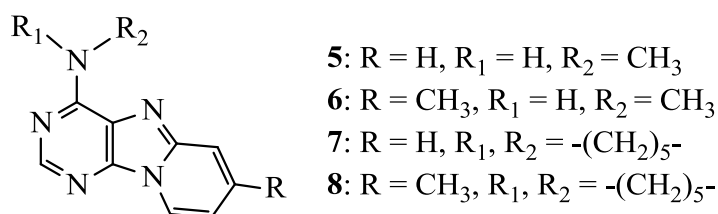
Figure 3.

The concentration inducing 50% inhibition of cell proliferation (IC_{50}) for doxorubicin was 7.5 x 10^{-7} M for the parental cell line MCF7 and 5 x 10^{-5} for the MCF7R cells. Therefore, MCF7R cell line was more resistant to doxorubicin than parental MCF7cells.

On the other hand, all breast cancer cell lines showed low growth activity when treated with median concentrations of compounds **5**, **6**, **7**, and **8**. The IC_{50} values for the sensitive parental cell lines MCF7 and the resistant cell lines MCF7R are illustrated in Table 1.

Table 1. IC$_{50}$ values of the investigated compounds.

	Doxorubicin	5	6	7	8
MCF7	7.5 x 10^{-7}	4.6 x 10^{-4}	7.2 x 10^{-4}	3.6 x 10^{-4}	1.6 x 10^{-4}
MCF7R	5 x 10^{-5}	6.7 x 10^{-4}	4.9 x 10^{-4}	1.8 x 10^{-4}	2.3 x 10^{-4}

The pyrido[1,2-*e*]purines reported here showed low activity on MCF7 parental cell lines, and interesting activity on MCF7R cell lines which proved to have increased resistance to doxorubicin.

Furthermore, alternating the 4-substiuent with other functional groups were attempted to increase the bioavailability of the drug candidates. Anticancer compounds **10** and **11** (Figure 4) were synthesized from compound **9** in order to, first, enhance biodisponibility by increasing the overall solubility in water, and second, enhance intercalating prosperities. To meet the first criterion, obtaining amphiphilic properties to enable these compounds to reach the intracellular target (i.e. DNA) by membrane transport, side chains of different lengths were used, providing different partition coefficients (1.3 (**10**)) and (2.38 (**11**)).[2]

9: R = Cl
10: R = NH(CH$_2$)$_4$OH
11: R = NH(CH$_2$)$_6$OH
12: R = SCH$_2$C$_6$H$_5$
13: R = SCH$_2$CHOHCH$_3$
14: R = SCH$_2$CH$_2$OHCH$_2$OH
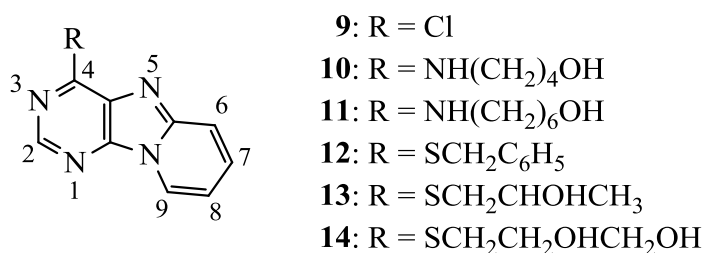
Figure 4.

According to ^{1}H, ^{31}P NMR, and molecular dynamics calculations (MD), the most hydrophobic compound **11**, exhibited only superficial interactions with the bilayers membrane due to micelle formation. While compound **10** could incorporate the external layer of the membrane and was more active *in vitro* against tumoral stems MCF7.

The two derivatives interacted quite differently with synthetic oligodeoxy nucleotide d(CGATCG)$_2$. Compound **11** exhibited weak intercalations with d(CGATCG)$_2$, only evocative of an external binding at the level of the G1C6 bases and is weakly mutagenic. Therefore, compound **11** does not fulfill the requirements for a drug with good anticancer activity. On the other hand, the interactions of compound **10** with DNA were quite different. A stable interaction of compound **10** in between the CG bases of the DNA fragment was observed. Thus compound **10** had proved to possess good intercalating properties and increasing interactions.

Moreover, the three pyrido[1,2-*e*]purines **12**, **13** , and **14** (Figure 4) of increasing hydrophilicity have been synthesized from 4-chloropyrido[1,2-*e*]purine **9** to be assessed as anticancer agents.[4] These drugs interact quite differently with a synthetic oligodeoxynucleotide d(CGATCG)$_2$. Compound **12** was very hydrophobic due to a phenyl residue in its side chain. Thus, it only showed limited interactions with the DNA minihelix without any evidence of intercalation. Compounds **13** and **14**, on the other hand, have one **13** or two **14** hydroxyl groups in their acyl chain and presented rather amphiphilic properties. The result was a similar intercalation of these derivatives (**13** and **14**) between C and G base pairs as revealed by intermolecular NOESY, ^{1}H, and ^{31}P chemical shift variations.

In order to resolve the structure of the complex formed between d(CGATCG)$_2$ and pyrido[1,2-*e*]purine dirivatives, 2-(pyrido[1,2-*e*]purin-4-yl)amino-ethanol **15** (Figure 5), a new antitumor drug under design, has been resolved using NMR spectroscopy and restrained molecular dynamic simulations.[5]
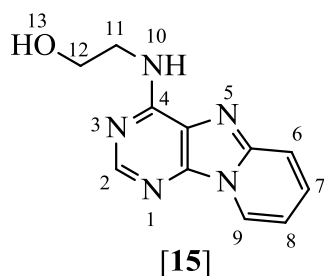

Figure 5.

Intercalation conformation of compound **15** and DNA showed that the aromatic moiety of the drug molecule **15** was weakly intercalated between the external GC base pairs (Figure 6), with the side chain of compound **15** lying in the minor groove of the hexamer. However, the drug/DNA affinity is enhanced by a hydrogen bond between the terminal hydroxyl group of the end of the intercalant side chain and the amide group of guanine G6.
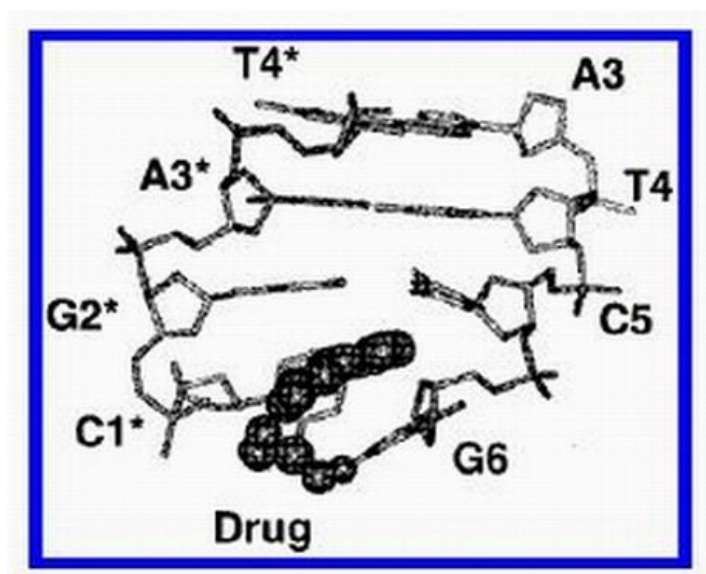
Figure 6.[5] Binding mode of the 2:1 complex of compound **15** with d(CGATCG)$_2$ represented by the closest structure of the NMR ensemble. View looking from the intercalation site into the minor groove of the oligomer. The bases labeled with an asterisk belong to one strand of DNA; the bases labeled without an asterisk belong to the complementary strand.

The preferential stacking of the pyridopurine derivative **15** on base G6 is stabilized by two alternative hydrogen bonding interactions (Figure 7). In most of the structures (38 out of 44), a hydrogen bond is possible between the extremity of the drug side chain (oxygen O13) and guanine G6 (amide proton H21 and nitrogen N2) (Figure 7A). The other hydrogen bond found in the second intercalation model involves the hydrogen H13, the oxygen O13 of the extremity of the drug side chain, and the nitrogen N3 of the guanine G6 (Figure 7B).

Of the two interaction models studied, only one model (Figure 7A), yielded a stable insertion of compound **15** inside DNA. While, hydrogen bond involving H13 and O13 of the extremity of the drug side chain and nitrogen N3 of guanine G6 appears far less stable (Figure 7B).
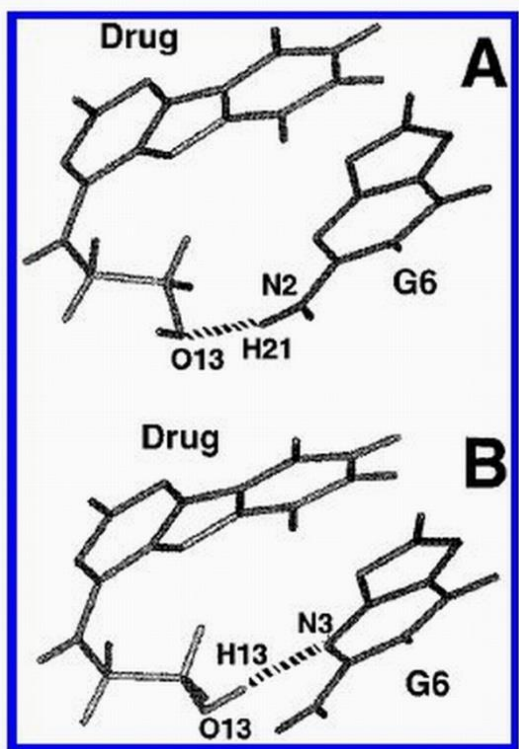
Figure 7.[5] Drug-base (G6) stacking interaction in the intercalation site. On the top is displayed the H-bond observed in 38 out of 44 intercalation structures. On the bottom is displayed the H-bond observed in 6 out of 44 intercalation structures.

Ab initio molecular simulation performed on the drug alone in a vacuum showed that the structure of compound **15** with minimum energy is planar up to carbon C11 of the tail. This structure is stabilized by a H-bond between H13 and N5. *Ab initio* optimized structures for both the lowest and second lowest energy structures show this same possibility of H-bond formation (Figure 8).
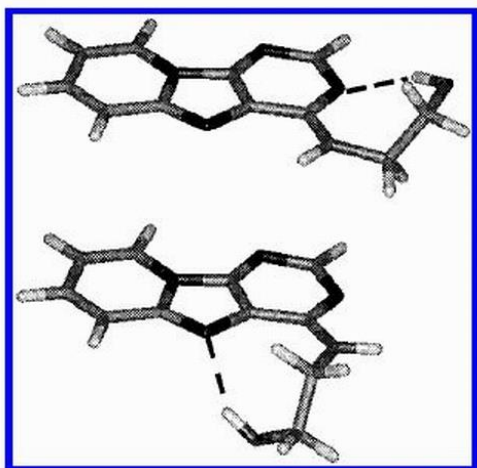
Figure 8. [5] *Ab initio* optimized structures of compound **15** in a vacuum. The lowest energy structure is displayed on the top of the figure. The second lowest energy structure is displayed on the bottom of the figure. Intramolecular H-bonds are displayed with dashed lines.

A normal view to the helix axis and looking into the minor groove of d(CGATCG)$_2$ of a representative structure of the NMR ensemble is presented in Figure 9A, and a view looking down the helix axis of the oligomer at the intercalation site is shown in Figure 9B. It can be seen that the pyridopurine derivative rings are not exactly perpendicular to the helix axis, with the drug stacking between the guanine G2 of one strand of the duplex and the guanine G6 of the other strand. The drug is not completely buried in the helical stack, but the stacking interaction seems to concern mainly the external ring of the drug comprising protons H6, H7, H8, and H9.
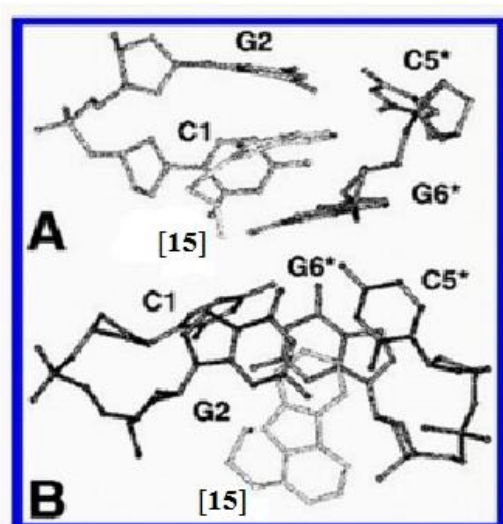
Figure 9. [5] Top view looking into the minor groove and normal to the helix axis of d(CGATCG)$_2$ at the intercalation site. Bottom view looking down the helix axis of d(CGATCG)$_2$ of a representative structure of the NMR structure ensemble. The bases labeled with an asterisk belong to one strand of DNA; the bases labeled without an asterisk belong to the complementary strand.

2.3 N-alkylation of purines

The significance of N-alkylation of purine core is not only about the biological impact, but also about advantages of removing or masking the acidic N-H proton in the synthetic routes.

Many factors affecting the position of the introduced alkyl group whether to be at N-9, N-7, or N-3 position, from which, the substituent in the C-6 position,[15] the used solvent,[16] and the concentration of the reaction mixture.[17]

2.3.1 Base-induced reaction

Base-induced reaction is the most conventional and well-recognized method for N-alkylation of purines. A general mechanism illustrating the role of the base and alkyl halide in the N-alkylation (Scheme 3).[18]
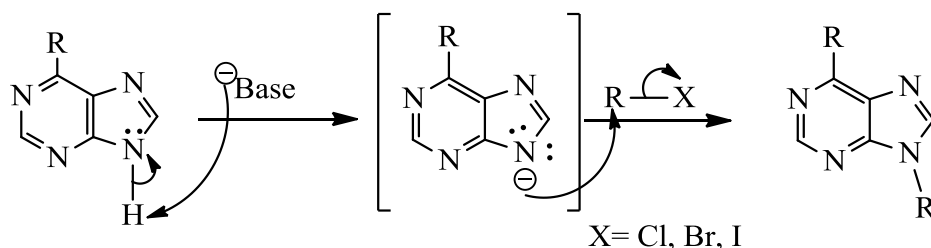
Scheme 3. General mechanism of base-induced N-alkylation of purines.

Several methods were reported for purines base-induced N-alkylation using different solvents, bases, temperatures, and reaction times. For example, N-methylation of 6-chloropurine **16** was done *via* four methods to obtain N-9 and N-7 isomers (Scheme 4). Using NaH as a base in method **A** requires neutralization at the end of the reaction. The main disadvantage of method **B** and **C** is the difficult elimination of the used solvent (DMSO) due to its high boiling point (190 °C). Heating is used in method **C** to accelerate the reaction and consequently decreasing the reaction time to 30 min than the usual time (16 - 24 h), but this required doing the reaction in a sealed tube. On the other hand, Method **D** was the most practical method due to its simplicity, ease of removal of DMF (boiling point = 150 °C), and the high yields where products **17** and **18** were isolated in yields 78% and 19% respectively.
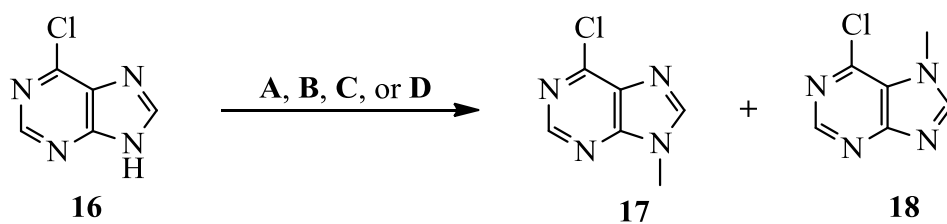
Scheme 4. Reactions and conditions: (**A**) NaH, MeI, DMF, rt, 16h;[19] (**B**) K$_2$CO$_3$, MeI, DMSO, rt, 24 h;[20] (**C**) K$_2$CO$_3$, MeI, DMSO, sealed tube, 55ºC, 30 min.[21] (**D**) K$_2$CO$_3$, MeI, DMF, rt, 16h.[21]

Method **D** which is commonly used, was employed for N-allylation of 6-chloropurine **16** by allyl bromide in the presence of K$_2$CO$_3$ as a base in DMF. N-9 and N-7 allylated isomers were obtained in a ratio (2.7:1) and isolated in yields 59% and 20% respectively (Scheme 5).[22]
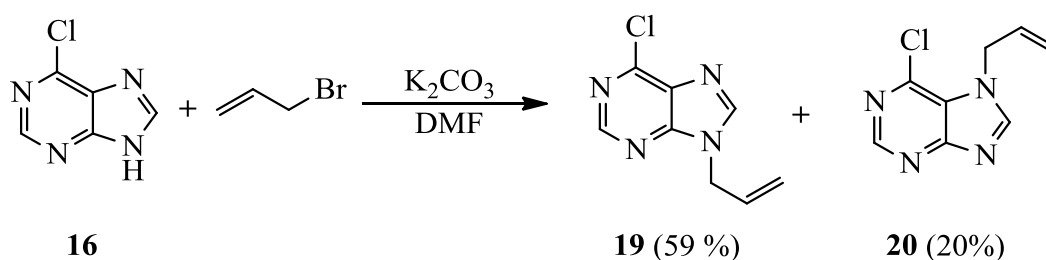
Scheme 5.

In order to examine the influence of the C-6 substituent on the resulting ratios between N-9 and N-7 alkylated compounds, alkylation using the same conditions for the base and solvent for compounds **21 a-k** employing various substituents on the 6-position was done (Scheme 6).[15]

The results were indicating that the obtained ratios between the N-9 and N-7 isomers are not attributed to the steric bulk or the electronic effect of 6-substituent on the purine ring. Further studies concluded that it is related to the partition coefficient (lipophilicity) parameter (π) of the introduced substituent. The relation between the lipophilicity of the 6-subsitiuent and tendency towards formation of N-9 isomer is directly proportional (Scheme 6).[15]

Scheme 6.
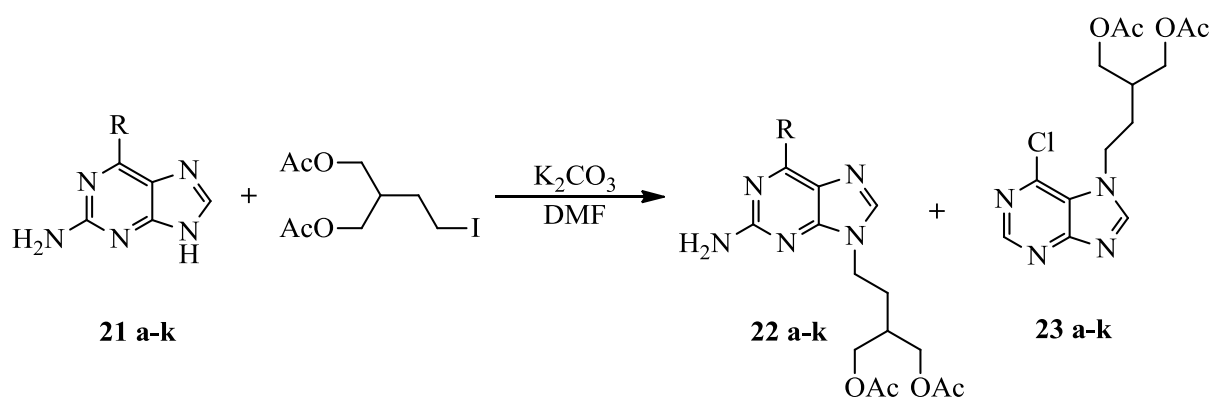
	R	N-9:N-7 ratio
a	OCH$_3$	1.8:1
b	F	3.4:1
c	H	4.0:1
d	SCH$_3$	3.8:1
e	Cl	5.5:1
f	CH$_3$	9.0:1

	R	N-9:N-7 ratio
g	Br	7.3:1
h	I	9.0:1
i	CH$_2$CH$_3$	16:1
j	CF$_3$	21:1
k	CH(CH$_3$)$_2$	25:1

On the other hand, allylation of compound **24** in the same conditions, gave the 9-allylpurine derivative **25** (35%) and the corresponding 3-allylpurine derivative **26** (58%) (Scheme 7).[23] The ratio of the allylated products **25** and **26** was analogous to the benzylated products prepared from 8-bromoadenine previousely.[24]
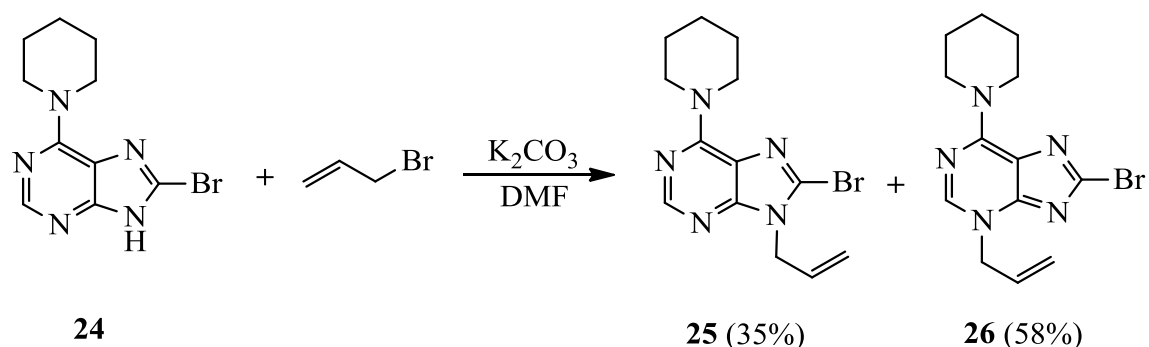
Scheme 7.

2.3.2 Mitsunobu reaction

A general protocol for N-alkylation of the 6-chloropurines by Mitsunobu reaction has been developed depending on functionalization of a range of various alcohols and diethylazodicarboxylate (DEAD).[25,26]

The mechanism of Mitsunobu reaction[18] involves a nucleophilic attack of the triphenylphosphine on DEAD to generate a phosphonium intermediate that binds to the alcohol oxygen, activating it as a leaving group. Substitution by the 9-purinyl anion completes the process (Scheme 8).
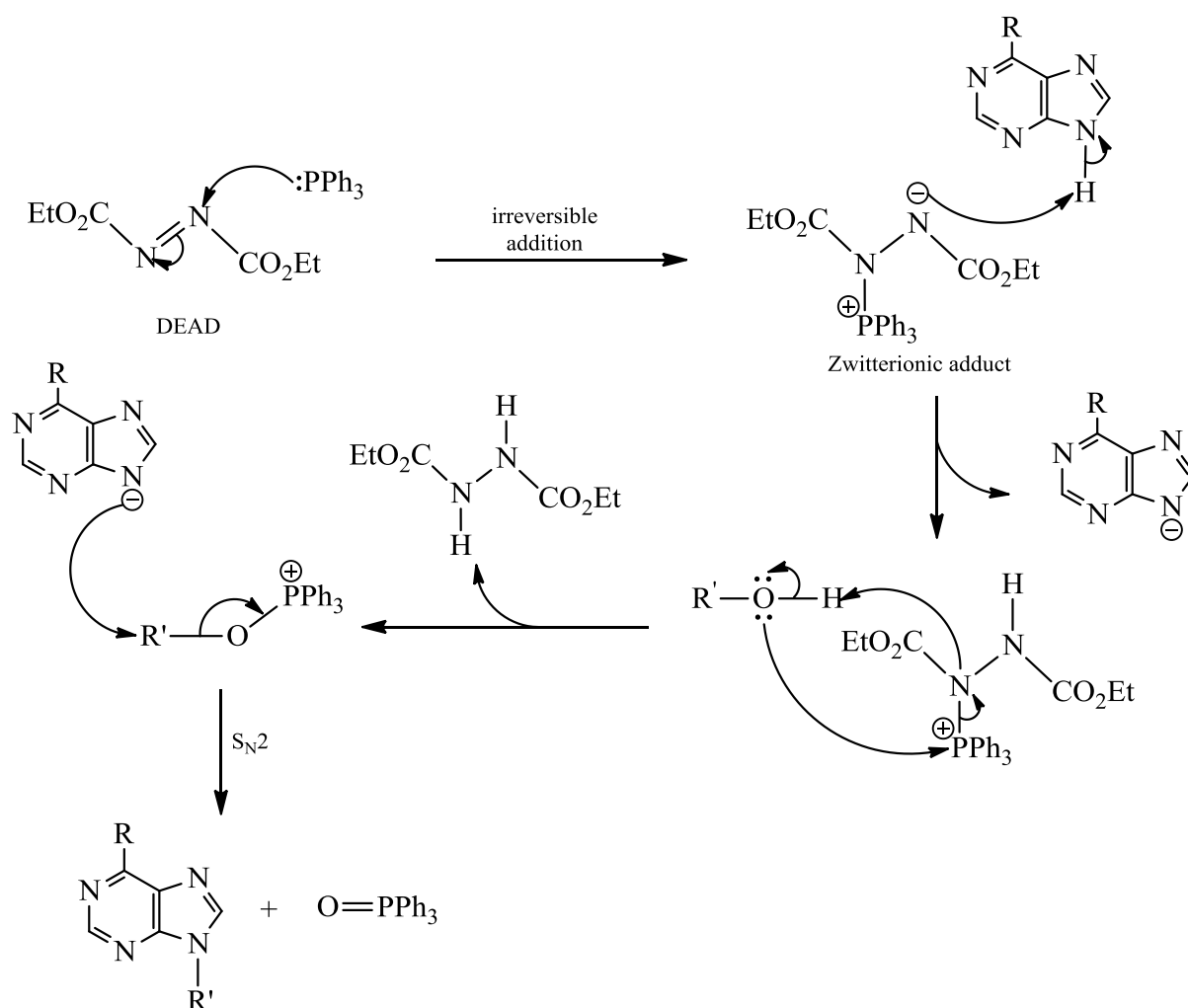
Scheme 8. General mechanism of the Mitsunobu reaction on purines.

Applying the Mitsunobu reaction on 6-chloropurine **16** using ethanol or benzyl alcohol has led to higher selectivity, compared to base-induced method, in favor of N-9 isomer (**27a** or **27b**) as the major product (yields 81%, 71%, respectively), while N-7 isomer (**28a** or **28b**) is

formed as the minor product (yields 14%, 25%, respectively) (Scheme 9).[26] The challenge in this kind of reactions is separating the desired products from triphenylphosphine oxide or bis(ethoxycarbonyl) hydrazine which makes it inconvenient for large scale syntheses.
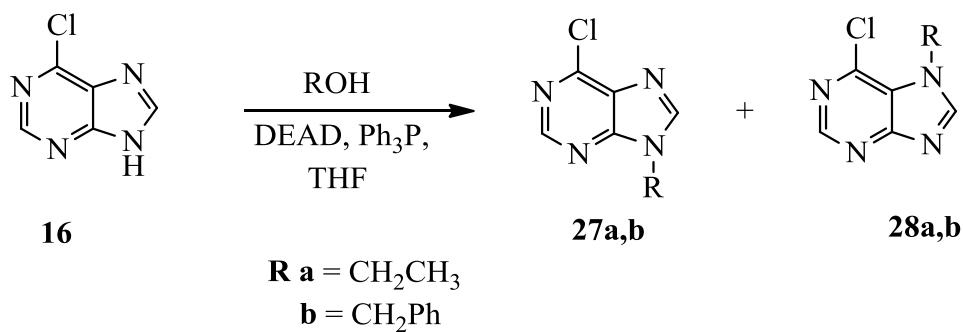
Scheme 9.

2.3.3 Phase-transfer catalysis

Aliquat 336 and TBAF are quaternary ammonium salts that are effectively employed in phase-transfer catalyzed alkylation. Compared to base-induced and Mitsunobu reactions, the major advantages of N-alkylation of 6-substitueted purines *via* phase-transfer catalysis are the short reaction time, simple work up, high yields, and the favourable substitution at N-9 position.[27]

An approach for a facilitated alkylation of pyrimidines and purines by TBAF was achieved for a short reaction time (1 h) giving high yields (85-99%). For instance, N9-methylation of adenine **29** gave an excellent yield (95%) of compound **30** (Scheme 10).[28]
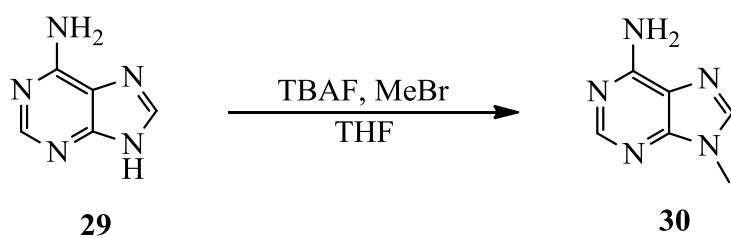
Scheme 10.

2.4 Amination of 6-halopurines

Amination of 6-halopurines usually go through nucleophilic aromatic substitution via addition-elimination mechanism where the electron withdrawing halide attached to the aromatic skeleton activates the ring towards nucleophilic attack. The loss of the halide comes fast because the ring becomes aromatic again. A proposed mechanism of amination of purines is illustrated in Scheme 11.[16]

Resonance-stabilized sigma complex
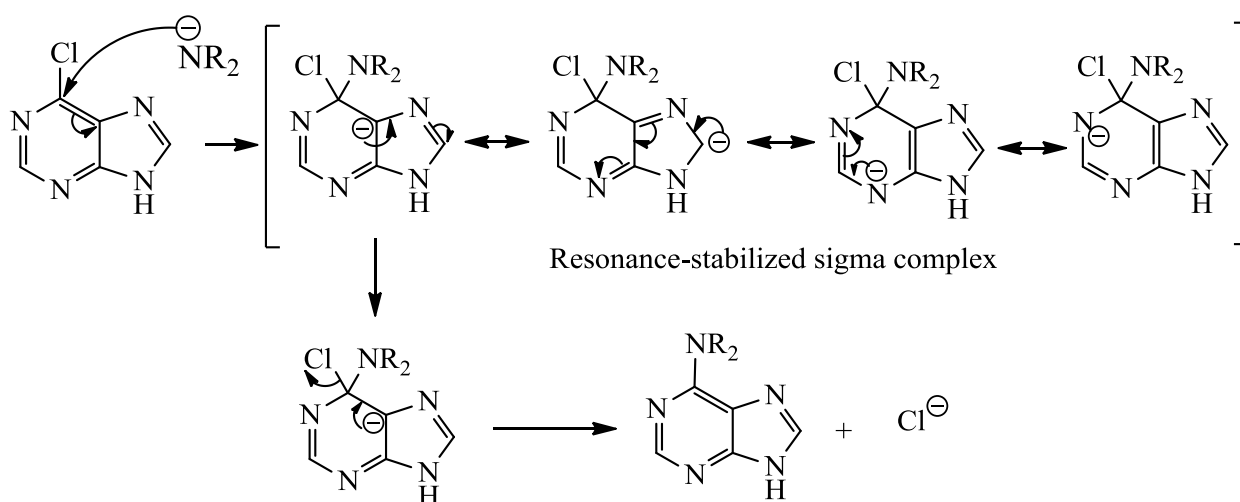
Scheme 11.

2.4.1 Heat-induced nucleophilic substitution

Reaction enhanced by heating is the most conventional method for amination of 6-halopurines and it is commonly used (Scheme 12 and Table 2).[29-31]
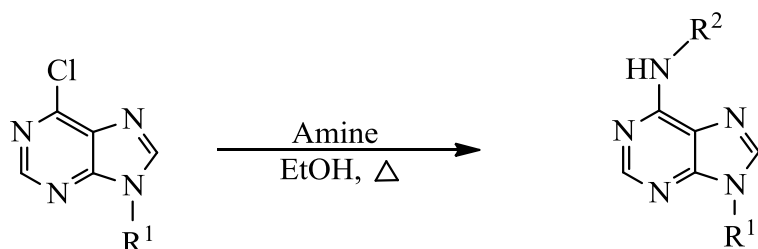
Scheme 12.

Table 2. Amination of 6-chloropurine derivatives with various amines.

Entry	R^1	R^2	Amine	Reaction time	Yield (%)
a	H	Et	$EtNH_2$	20 h	94
b	H	CH_2OHCH_3	$CH_3OHCH_2NH_2$	20 h	87
c	$(CH_2)_3OH$	H	NH_3	15 h	91

The adenine derivatives **33** and **34** were prepared by amination of compound **19** with piperidine **31** or morpholine **32** at 100 °C in H_2O. The conventional amination method of piperidinyl and morpholinyl derivatives **33** and **34** by refluxing in water gave good yields (95% and 91%, respectively) (Scheme 13).[32]
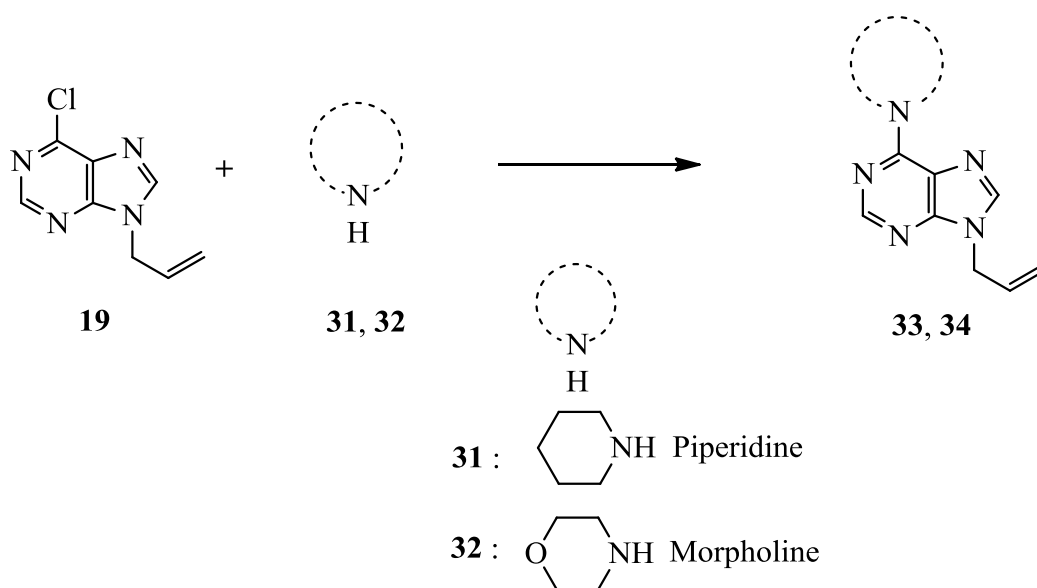
Schem 13. Reagents and conditions: H_2O, reflux, 24 h.

In case of simple 6-(piperidin-1-yl)purine analogues **35-38** which are lacking substituents in N-9 position, they were prepared by direct nucleophilic substitution of 6-chloropurine **16** using triethyl amine as a base and *n*-BuOH as a solvent instead of water due to the low polarity of N-9 unsubstituted purines and consequently the poor solubility in water even in the presence of the highly basic piperidine in the reaction (Scheme 14).[33]

16

35 R = H
36 R = CONH$_2$
37 R = CH$_2$NHBoc
38 R = NHBoc
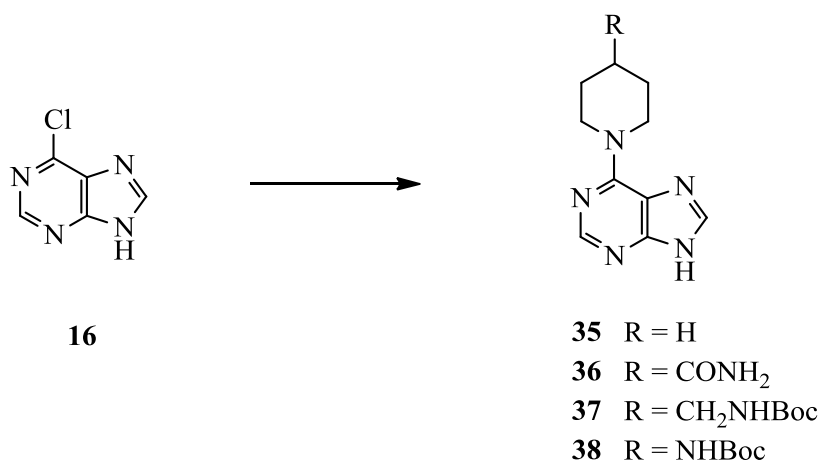
Scheme 14. Reagents and conditions: 4-substituted piperidine, Et$_3$N, *n*-BuOH, 100 °C

2.4.2 Microwave-promoted nucleophilic substitution

Microwave irradiation as a non-conventional energy source is a useful technique in organic chemistry. Many reactions have been demonstrated to result in higher yield and reduced reaction time under microwave irradiation compared with using the conventional heating method.[32-34]

Microwave promoting nucleophilic substitution reaction between a number of 6-chloropurine derivatives with piperidine, pyrrolidine, or hexamethyleneamine in water were employed (Scheme 15).[34]

This method has several advantages such as mild reaction conditions and short reaction times. Furthermore, most of the reactions involved are efficient, giving the desired compounds in higher purity and yield.
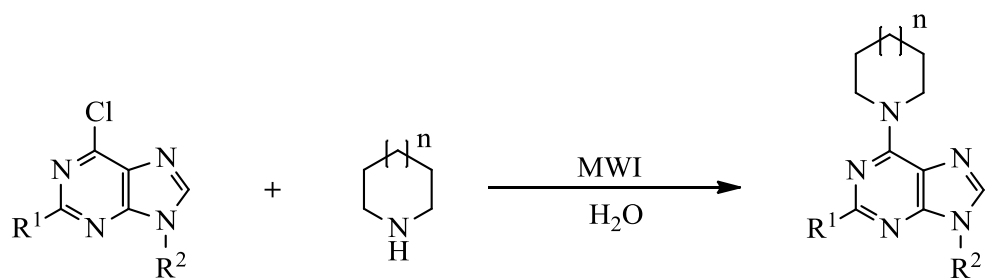
Scheme 15. Nucleophilic substitution reaction of 6-chlororopurines derivatives with piperidine, pyrrolidine or hexamethyleneamine.[34]

The products from 2,6-dichloropurine were obtained in higher yields compared with those from other 6-chloropurine analogues under the same reaction conditions. Moreover, when R^2 was cyanoethyl or allyl, the yields were higher compared with other substituted substrates.
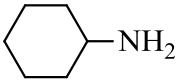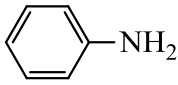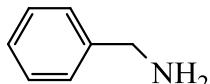
Using acyclovir analogue **39** as a substrate, a variety of nucleophilic aromatic substitutions were carried out using different amines as nucleophiles (Table 3).[35] Yields and reaction times under conventional conditions and under microwave irradiation were compared (Table 3). The standard protocol for microwave-assisted reactions involved 1.1 eq of the corresponding amine, 1.1 eq of diisopropylethylamine (DIPEA) and ethanol as the solvent (conditions A).

Alternatively, the reactions were carried out under conventional heating in an oil bath applying established conditions (conditions B and C) for nucleophilic aminations.[36] The microwave assisted reactions proceeded in all cases with higher yields (72% - 83%), and nearly complete conversions were already observed after short reaction times (10 min). In contrast, much longer reaction times (16 h) were needed to achieve satisfying conversions under the common conditions (conventional heating), which also led to generally lower yields (58% - 75%) (Scheme 16 and Table 3).
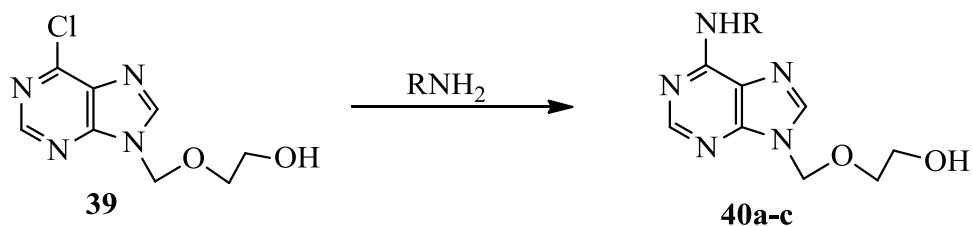
Scheme 16. Amination of acyclovir analogue.

Table 3. Amination of acyclovir analouge **39** with various amines.[35]

Entry	Amine	Conditions	Yield
a	⬡—NH$_2$	A	82 %
		B	69 %
		C	72 %
b	⬡—NH$_2$	A	77 %
		B	70 %
		C	71 %
c	⬡—CH$_2$NH$_2$	A	83 %
		B	75 %
		C	66 %

Conditions A: 1.1 eq. amine, 1.1 eq. DIPEA, EtOH, microwave (120 °C, 150 W), 10 min.

Conditions B: 1.1 eq. amine, 1.1 eq. DIPEA, BuOH, 75 °C, 16 h.

Conditions C: 5 eq. amine, EtOH, 75 °C, 16 h.

2.5   C-8 Halogenation of purines.

2.5.1 Direct Halogenation of 6-aminopurines.

Applying direct bromination on N-unsubstituted purines in order to obtain C-8 brominated purine derivatives was achieved smoothly using molecular bromine or NBS through several methods.[29,37,38]

The direct bromination of C-8 position of adenine **29** using Br$_2$ has been reported frequently giving 8-bromoadenine **41** in a high yield with various ways. Methods **a**,[29] **b**,[37] or **c**[37] led to 70% yield while method **d**[38] led to 83% yield (Scheme 17).
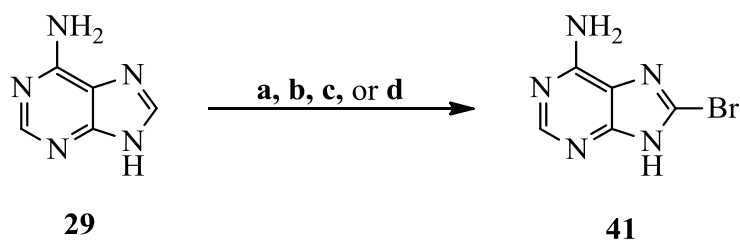
Scheme 17. Reagents and conditions: (a) Br$_2$, DMF, r.t., overnight;[29] (b) Br$_2$, DMF, 70 °C, 2 h;[37] (c) Br$_2$, r.t., overnight;[37] (d) Br$_2$, H$_2$O, r.t., overnight.[38]

On the other hand, by replacing the NH$_2$ group in adenine with a heterocyclic amine, the direct bromination of C-8 position was accomplished using the liquid bromine in a buffer solution of acetic acid and sodium acetate giving high yields (Scheme 18).[23]
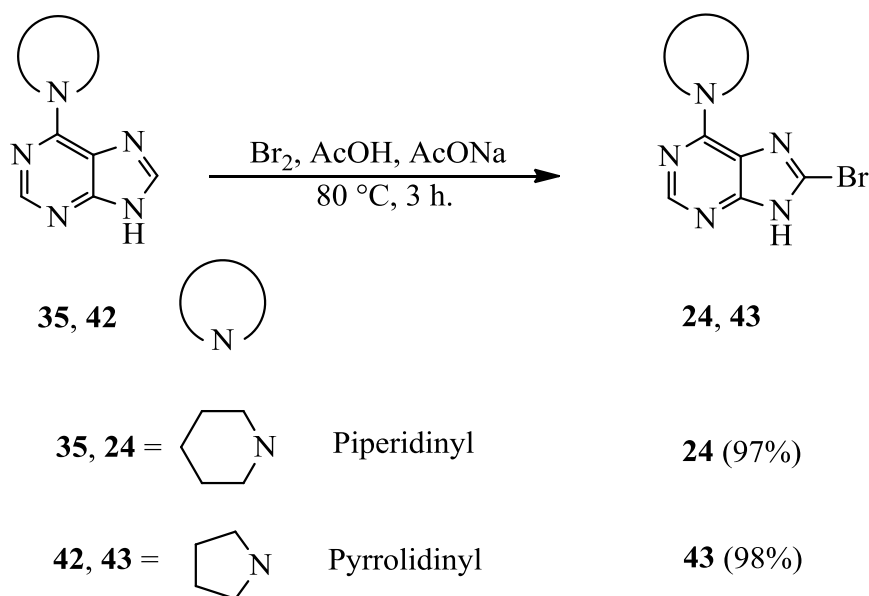
Scheme 18.

2.5.2 Lithiation / halogenation reactions.

Lithium diisopropylamide (LDA) is generated by reacting diisopropylamine with *n*-BuLi in THF at -78 °C under inert atmosphere (Scheme 19).[39]

LDA has proton-removing ability as a strong base but without any further functions like involving in a nucleophilic substitution due to its steric bulk which allows portons to be

attached to the basic nitrogen atom and preventing alkyl groups from doing so, thus it was termed as a non-nucleophilic base. It is a strong base commonly used for deprotonating the weakly acidic proton, H-8, in purines.
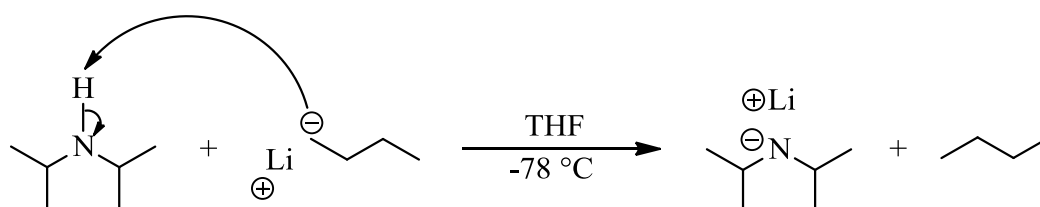
Scheme 19. Mechanism of formation of LDA

The reason behind using LDA for such reactions instead of other strong bases like hydroxides *e.g.* NaOH, KOH, is that such bases involve in a nucleophilic substitution reaction instead of deprotonation, displacing any good leaving group attached to the purine core to give the hydrolysed compounds.[40]

Furthermore, LDA is favoured over alkyllithiums such as *n*-BuLi and *t*-BuLi since they potentially participate in halogen exchange for attached halogens instead of deprotonation.[41]

C-8 lithiation of purines is done using LDA as a strong base to deprotonate C-8 position of purines to trap the 8-purinyl anion which attacks the elctrophile that acts as a halogen donor, in the haolgenation step afterwards, as illustrated in the mechanism (Scheme 20). This usually results in good yields.[42-53]
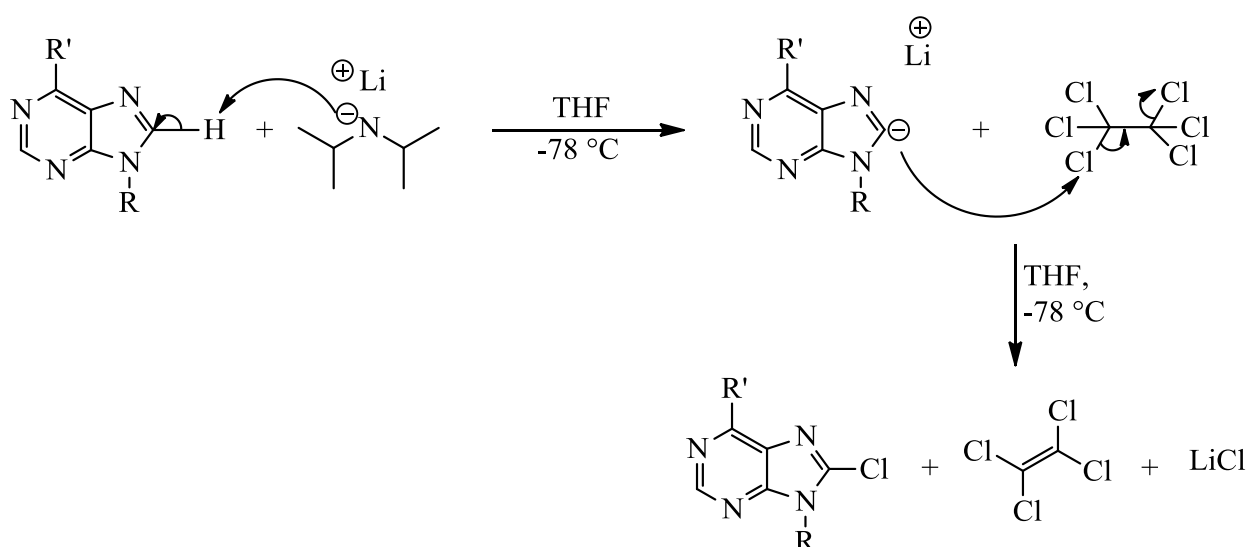
Scheme 20. General mechanism for lithiation-halogenation reactions.

A variety of different electrophilic sources can be utilized for the C-8 halogenation.[8,10] Molecular bromine, 1,2-dibromotetrachloroethane, or cyanogenbromide are used as bromine donors. Iodination can be done via molecular iodine. Besides, hexachloroethane is a good source for chlorine.

Effectively, C-8 position of 6-subistituted, 9-alkylated purines can be halogenated easily, in most cases, by applying lithiation followed by halogenation upon many derivatives of purine compounds which contain different substituents in 6- or 9-position using different electrophiles. That is usually achieved smoothly giving yields from moderate to high as illustrated (Scheme 21 and Table 4).[21,37,43,54]
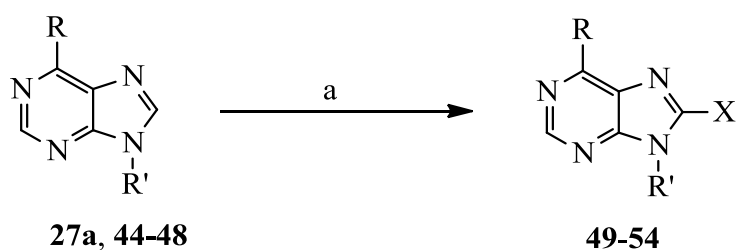
Scheme 21. (a) Reagents and conditions (see Table 4)

Table 4. Lithiation-halogenation of purines.

starting material	R	R'	Reaction conditions[a]	X	Product	Yield (%)
27a	Cl	CH_2CH_3	(1) LDA, (2) C_2Cl_6, THF, -78 °C	Cl	**49**[21]	74
44	NH_2	CH_2-c-hex	(1) LDA, (2) C_2Cl_6, THF, -78 °C	Cl	**50**[54]	68
45	NH_2	c-pent	(1) LDA, (2) C_2Cl_6, THF, -78 °C	Cl	**51**[54]	69
46	NH_2	Ph	(1) LDA, (2) C_2Cl_6, THF, -78 °C	Cl	**52**[54]	67
47	Cl	CH_2-Ph-p-F	(1) LDA, (2) $BrCCl_2CCl_2Br$, THF, -78 °C	Br	**53**[37]	55
48	Cl	CH_2-Ph-p-Me	(1) LDA, (2) $BrCCl_2CCl_2Br$, THF, -78 °C	Br	**54**[43]	76

2.6 Organomagnesium addition reactions on purines.

Allylmagnesium bromide reacts with 2,6-dihalopurine **55** giving derivatives **56** and **57** (Scheme 22).[55]

As a result of the addition of Grignard reagent to the 8-position of the purine nuclei, 2-magnesiated purine **57** is formed, which is stable and does not rearrange to the 8-derivative due to the presence of electron-donating substituents in the 6-position of purine nuclei. Smooth coupling of Grignard reagents with compound **55** is probably a result of the activation of iodine by the chlorine atom at the 2-position of the purine nuclei.
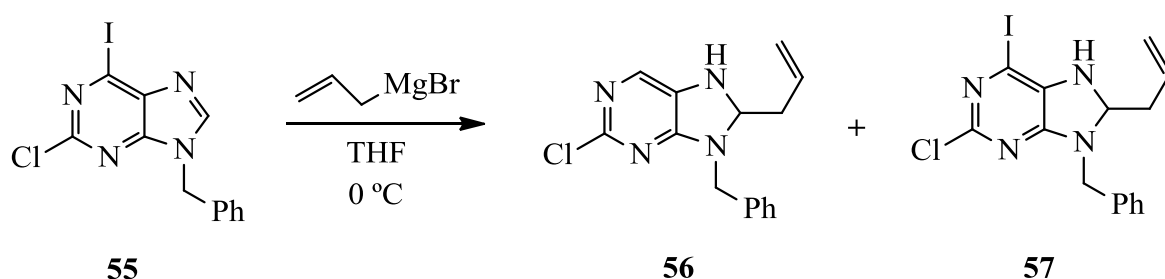
Scheme 22.

Stable adducts are formed when 1,3-, 1,7-, and 3,7-dibenzylpurin-2-one react with Grignard reagents and the reactions take place in the purine 6- or 8-position.[56]

When the 6-phenylpurinone **58** was treated with ethylmagnesium bromide, addition took place in only the 8-position to afford 8-ethyl adduct **59** which was oxidized during flash chromatography on silica gel to compound **60** (Scheme 23).This reaction demonstrates the large reactivity differences among dibenzylated purinones.
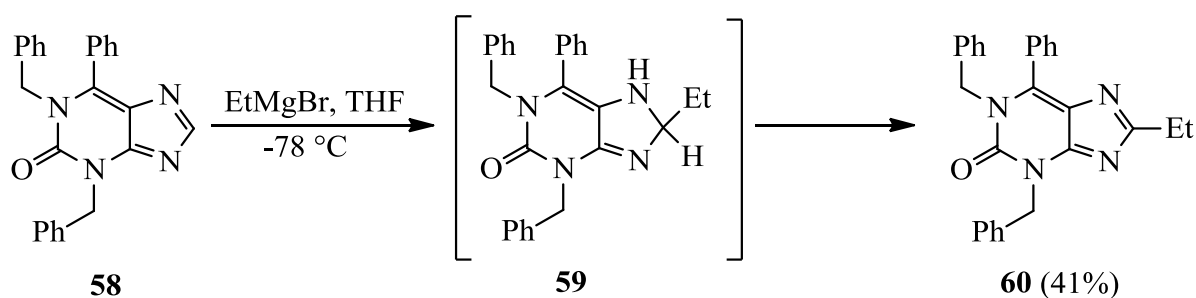
Scheme 23.

1,7-Dibenzyl-6-phenyl-2-purinone **61** reacted with ethylmagnesium bromide to afford 8-ethyl adduct **62** as the major product which was oxidized on silica gel during the chromatographic separation to compound **64**. In spite of steric hindrance, some addition of the nucleophile to the 6-position also took place, and compound **63** was formed (Scheme 24).[56]
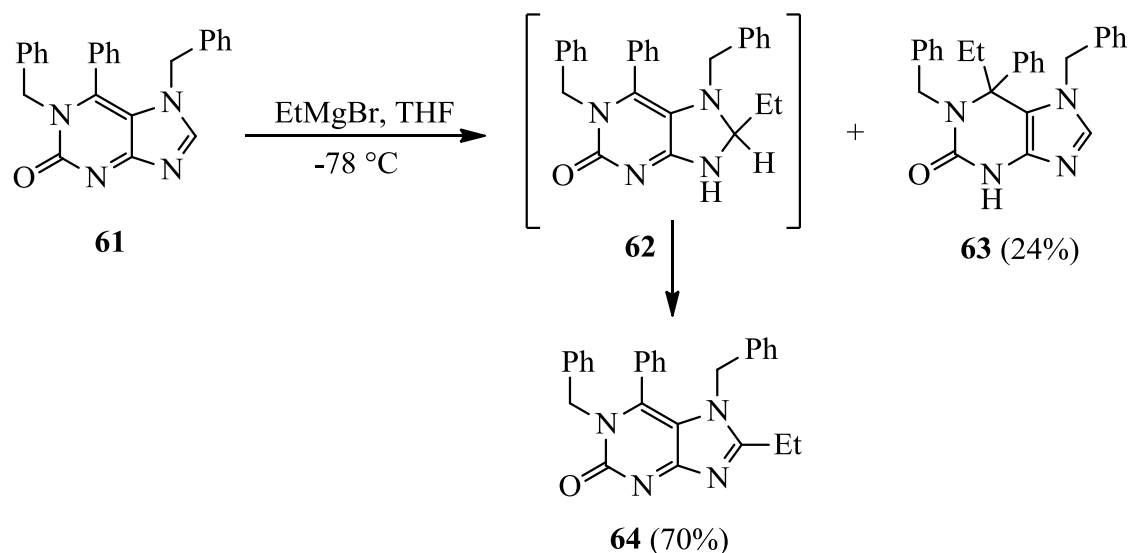
Scheme 24.

When 3,7-dibenzylated 2-purinone **65** was reacted with ethylmagnesium bromide, addition happened preferentially to the 6-position to give compound **66** as the major product while the 8-ethyl adduct **67** was formed as the minor isomer. The reaction gave a ca 7:2 mixture of the two regioisomers **66** and **67** (Scheme 25).[56]
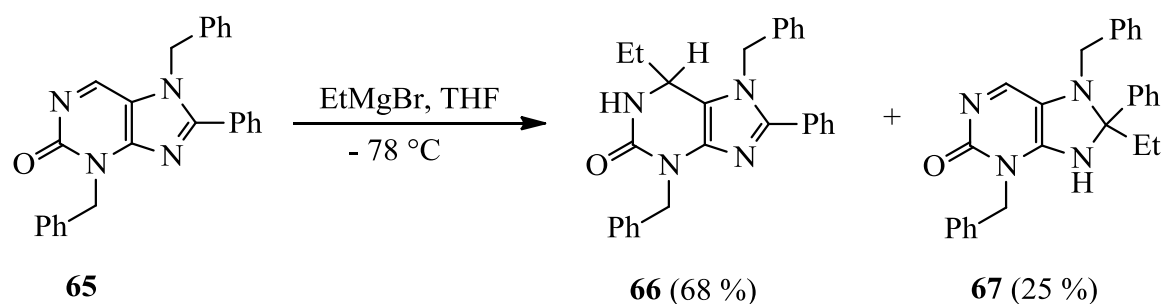
Scheme 25.

2.7 Organoindium addition reactions.

Indium element was discovered by Ferdinand Reich and Hieronymous Theodor Richter in Freiberg, 1863. It was named for the indigo blue line and used in metal alloys and electronics. It has two oxidation states (I) and (III).

The first example of an indium-mediated reaction was published by Rieke and co-worker in 1975.[57] To accomplish the reaction, they used especially activated indium metal prepared from indium chloride and potassium metal. This activated indium efficiently mediated the Reformatsky-type reaction of ethyl bromoacetate with carbonyl compounds (Scheme 26).
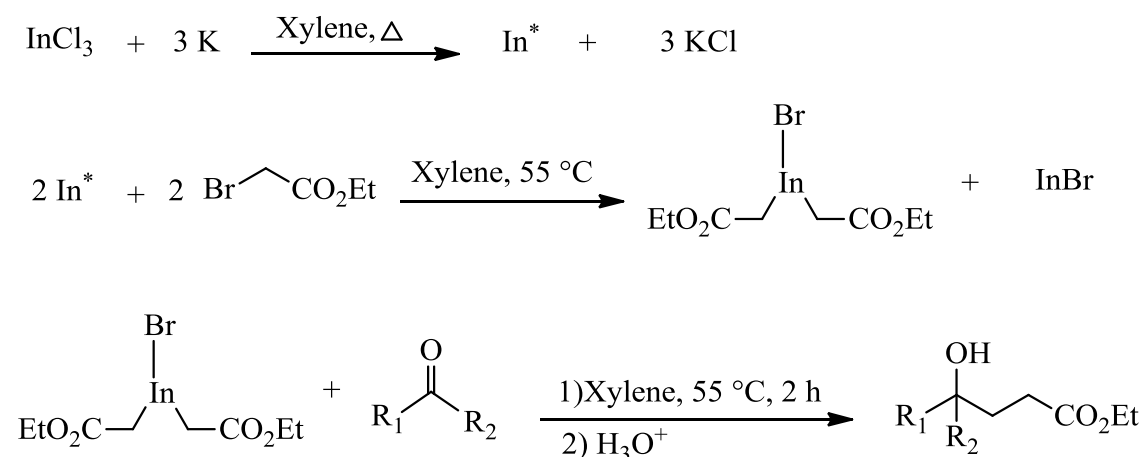
Scheme 26. Indium-mediated Reformatsky-type reaction

Since 1988 when Araki and Butsugan used indium for the Barbier-type addition of allyl bromide to carbonyl compounds (Scheme 27).[58] Synthetic use of indium metal has attracted considerable attention and a number of indium-mediated reactions have been reported.

Allylindium sesquiiodide
$(R_3In_2X_3)$

R^1 = alkyl, alkenyl, aryl
R^2 = H, alkyl
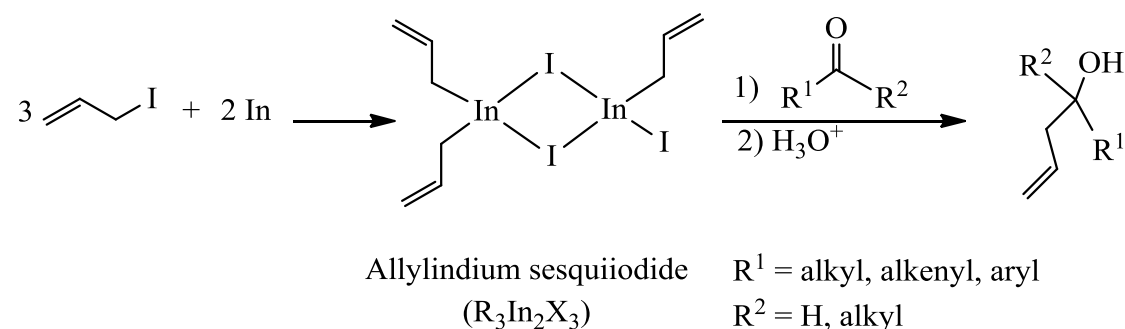
Scheme 27. Indium-mediated Barbier-type reaction.

Although the reactive organoindium intermediate is still a matter of debate, recent studies have revealed a lot about it.[59] After reacting indium metal with allyl bromide in THF, two major compounds were crystallized and separated to be identified as monoallylindium dibromide and diallylindium bromide (Scheme 28).[60]

In addition, other species may also be present in the solution, mass spectrometry has detected a variety of organoindium (III) species such as $InRX^{3-}$, $RXIn^{+}$, R_2In^{+}, X_2In^{+}, many of them are in equilibrium with each other.[61]

Monoallylindium dibromide   Diallylindium bromide
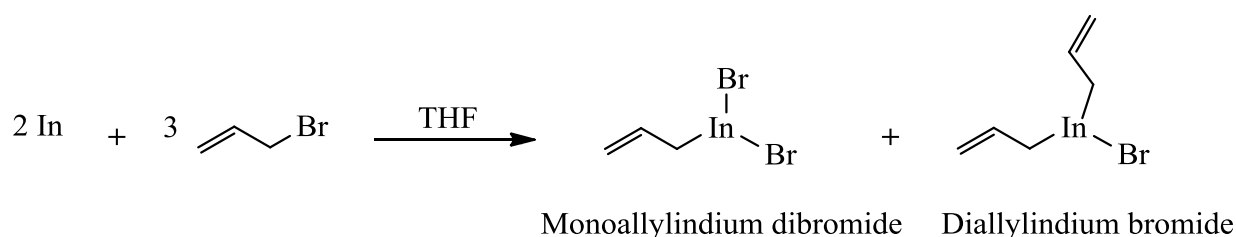
Scheme 28.

Organoindium species adds to carbonyl compounds more or less in the same way as organomagnesium species (Grignard reagents).[62] They also reacts with other functional groups[63,64] including electron deficient heterocycles.[65,66]

In fact, synthetic reactions in aqueous media evidence the advantages of indium reagents. For example, indium metal affects the allylation of aldehydes and ketones with allyl halides in water at room temperature without inert atmosphere (Scheme 29).[67]

X = I, Br, Cl
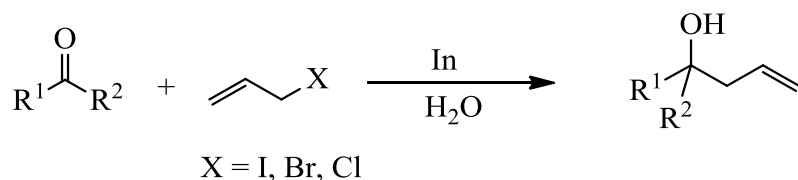
Scheme 29.

The reactions of allylindium reagents with C=N bond-containing compounds have been extensively investigated.[62,68] The C=N bonds in heterocyclic compounds, such as, pyridine,

quinoline, isoquinoline, and azirine did not, however, react with allylindium reagents under normal conditions.

Recently Hirashita and co-workers reported the reaction of allylindium reagents and azirines to produce allylaziridines in good yields (Scheme 30).[69]

Azirines are known to have a highly strained ring similar to cyclopropenes and are expected to be reactive substrates. The delivery of the allyl groups was well regulated by the substituents at the C-3 carbon of azirines.

The *cis*-allylation with respect to the substituent was realized with azirines bearing a hydroxymethyl or an acetoxymethyl group, due to the chelation with allylindium reagents, whereas, the trans-allylation was observed with azirines substituted by non-chelating groups, such as, methyl, phenyl, or ester groups owing to the steric repulsion.
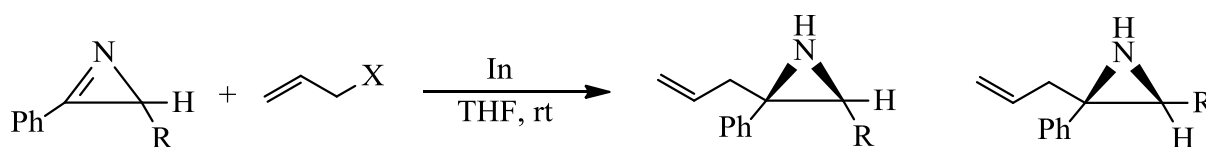
When R = CH$_2$OH, CH$_2$OAC, *cis* product is major
When R = Me, Ph, CO$_2$Et, *trans* product is major   (due to chelation with allylindium)

Scheme 30.

Yoon and co-workers reported an indium-mediated allylation of quinoline and isoquinoline activated by phenyl chloroformate in THF at room temperature and obtained the allyl dihydroquinoline and allyl dihydroisoquinoline in good yields (Scheme 31).[65]

(93% yield) over 2 steps

(89% yield) over 2 steps
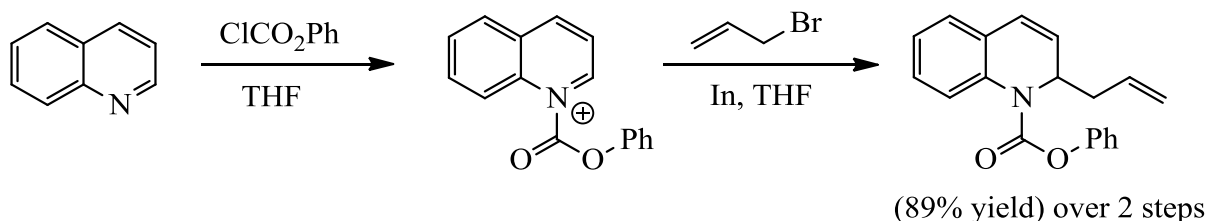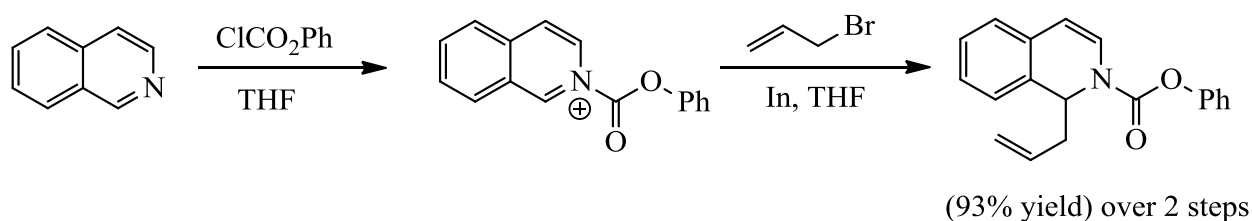
Scheme 31. Indium-mediated allylation of quinoline and isoquinoline activated by phenyl chloroformate.[65]

2.8 Olefin metathesis

The word Metathesis is derived from the Greek for "change position". Olefin metathesis is a metal-catalyzed transformation which involves the exchange of groups around double bonds. It is promoted by a metal carbene complex which acts on carbon-carbon double bonds and rearranges them via cleavage and reassembly through series of reversible [2+2] cycloadditions and cycloreversions.[70-74]

According to the mechanism proposed by Chauvin,[75] the coordination of an olefin to a metal carbene catalytic species leads to the reversible formation of a metallacyclobutane (Scheme 32). This intermediate then proceeds by cycloreversion yielding an olefin that has exchanged a carbon with the catalyst's alkylidene.
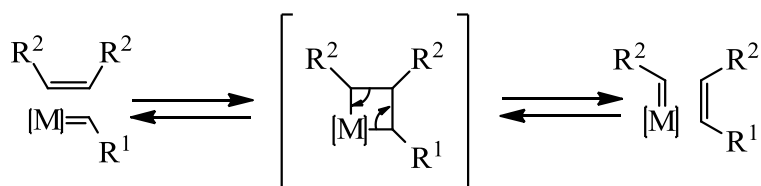
Scheme 32. General mechanism of olefin metathesis.

Several well-defined, single-species catalysts based on different transition metals such as titanium,[76] tungsten,[77-79] molybdenum,[77,80] rhenium,[81] osmium,[82] and ruthenium[83-85] have been evolved. The early transition metal catalysts are very active but also sensitive to many functional groups found in organic molecules, as well as moisture and air which significantly limits their synthetic applications.

Focusing on ruthenium-based catalysts (Figure 10), high reactivity of 2nd generation ruthenium catalysts, such as catalyst **69** and **70** enable them to react with electron-deficient α,β-unsaturated carbonyls, which are inert to catalyst **68**.[86,87]

68	**69**	**70**
Grubbs' 1st generation catalyst	Grubbs' 2nd generation catalyst	Hoveyda-Grubbs' 2nd generation catalyst
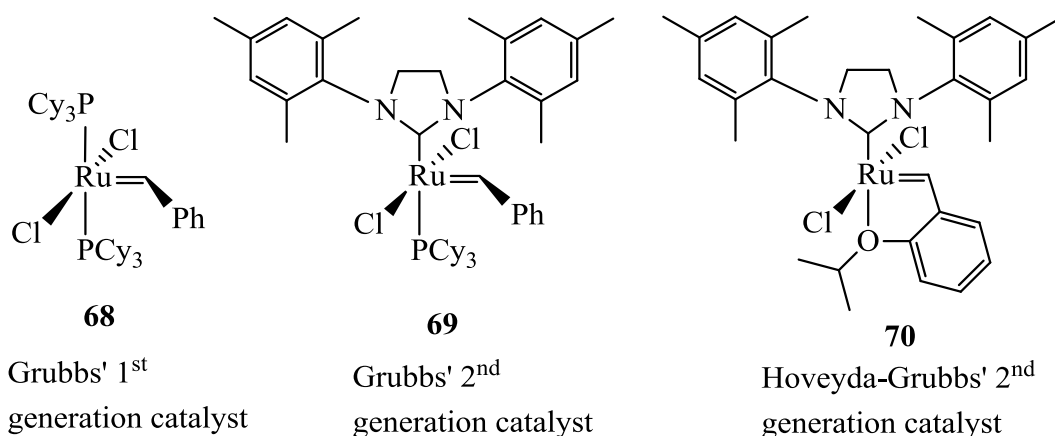
Figure 10.

While both catalysts **69** and **70** maintain excellent selectivity in most cases towards *Z*-isomers[88] for olefins typically of ruthenium catalysts, they have somewhat slower rates of initiation than the first generation catalysts.

2.8.1 Ring opening metathesis polymerization (ROMP)

Ring opening metathesis polymerization is a chain-growth type polymerization (Scheme 33) which relies on monomer ring strain and therefore, thermodynamically favored for strained ring systems, such as 3-, 4-, 8- and larger-membered compounds, thus, it can be efficiently controlled by catalyst loading.[89]
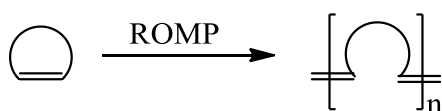
Scheme 33.

Block copolymers can be made by sequential addition of different monomers (a consequence of the "living" nature of the polymerization).

2.8.2 Acyclic diene metathesis (ADMET)

Acyclic diene metathesis is considered to be a step-growth[90] polycondensation-type polymerization reaction, which makes strictly linear chains from unconjugated dienes (Scheme 34).[91-95]

Scheme 34.

ADMET demands a very high monomer conversion rates to produce polymer chains of considerable size. Therefore, the more active 2nd generation catalysts such as **69** and **70** are usually better suited for ADMET than bisphosphine ones like catalyst **68** (Figure 10).[93]

2.8.3 Cross metathesis (CM)

Olefin cross-metathesis[96] can be described as the intermolecular mutual exchange of alkylidene (or carbene) fragments between two olefins promoted by metal-carbene complexes (Scheme 35). Thus, it is a convenient route to functionalized and higher olefins from simple alkene precursors.
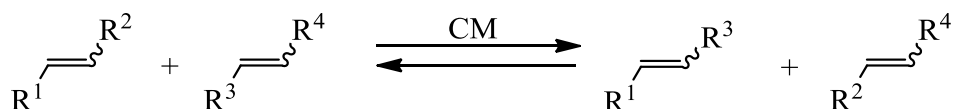
Scheme 35.

The major issues dominating cross metathesis process are the control of homodimerization of the resulting olefins in order to obtain useful yields. On the other hand, the ratios of *E/Z* which are hard to control and predict.

2.8.4 Ring closing metathesis (RCM)

Ring closing metathesis can be simply identified as an intramolecular metathesis of diene to form a cyclic olefin. The overall reaction mechanism involves a series of alternating [2+2] cycloadditions and cycloreversions between metal alkylidene and metallacyclobutane species (Scheme 36).[97]
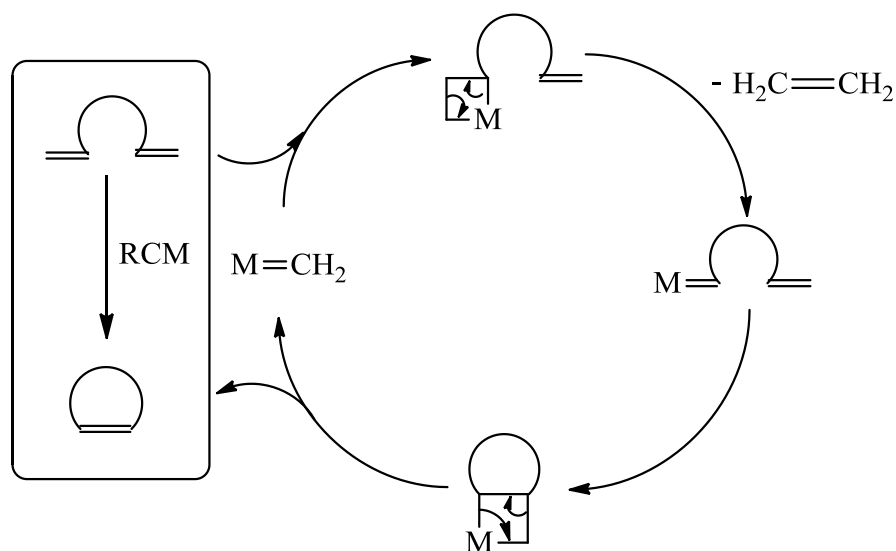
Scheme 36. General mechanism of ring closing metathesis.

By applying RCM on the 8,9-diallylpurine derivatives **71**, **72**, and **73** using Grubbs' 2nd generation catalyst **69** (19 mol %) in DCM at room temperature for 2 days, this gave 6,9-dihydropyrido[1,2-*e*]purine derivatives **74**, **75**, and **76** in high yields (Scheme 37).[23]
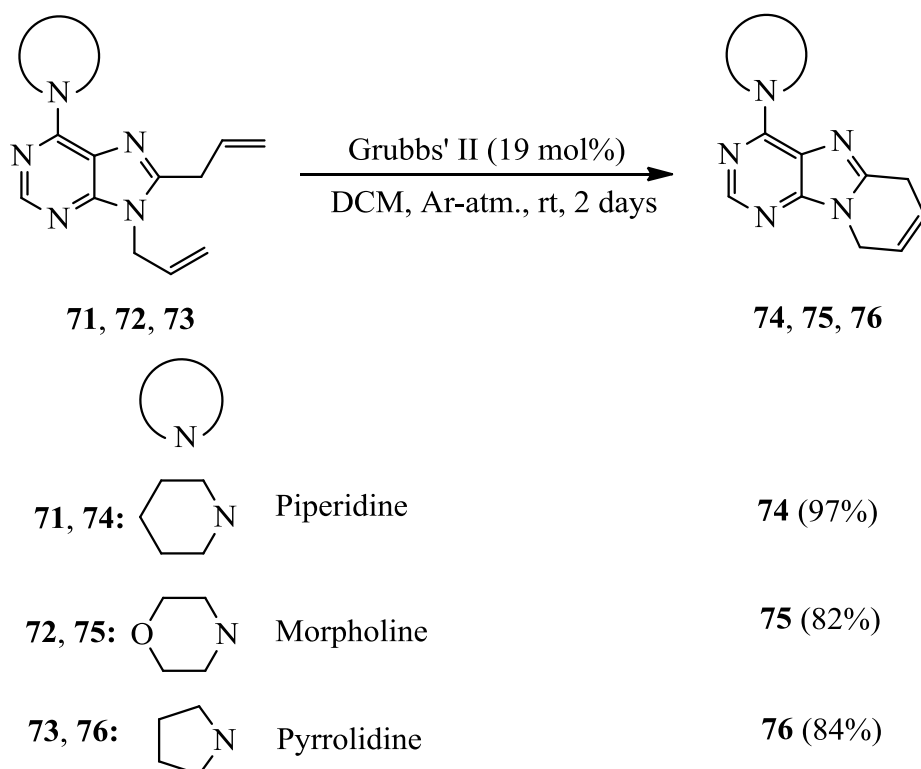
Scheme 37.

Another example for employing RCM on purine substrates, formation of an eight-membered ring on compounds **77a-d**. In the synthesis of azacyclooctenes by RCM, the yield is usually affected by the N-substituent.[98,99]

Only with the presence of the bulky *N*-Boc-group in compound **77d**, the reaction was carried out successfully either by Grubbs's II catalyst to give moderate yield (54%) or by the bisphosphine-free complex, Hovedya-Grubbs' II catalyst to give higher yield (73%) (Scheme 38).[100]

77a: X = NH
77b: X = NMe
77c: X = O
77d: X = NBoc

78
54% (Grubbs II)
73% (Hov.-Grubbs II)

Compounds **77a-c** (No Reaction)
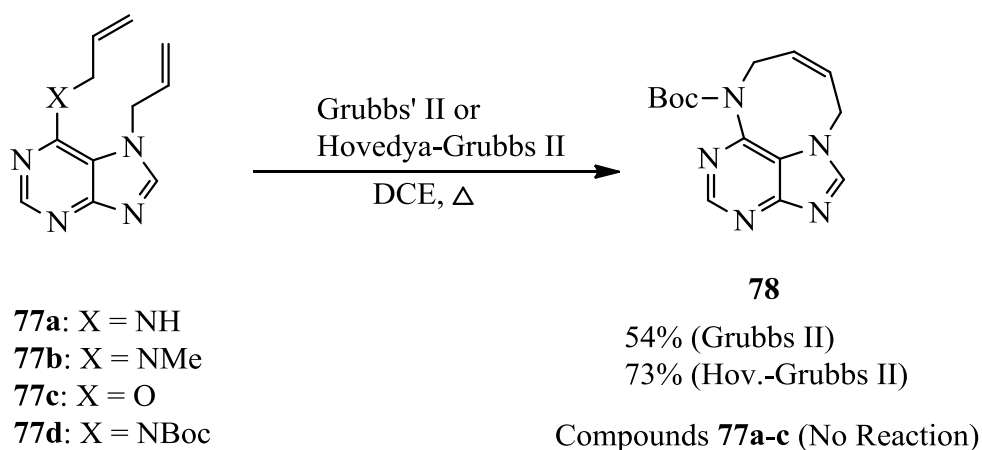
Scheme 38.

2.9   Oxidation (re-aromatization)

2.9.1 Oxidation of heterocyclic compounds *via* MnO$_2$

Selective oxidation for some functional groups in a molecule can be achieved via MnO$_2$ at room temperature, but heat is also used.[101] The oxidizing ability of MnO$_2$ increases sharply above 70 °C usually with loss of selectivity.[102] Manganese dioxide has the highest oxidizing activity in acidic media, moderate activity in neutral media, and close to zero activity in alkaline media.[103]

The main advantages of MnO$_2$ are the availability, low price, and the acceptable (with rare exceptions) degree and selectivity of the transformations even at room temperature.

Oxidation of substituents in heterocycles is a common benefit of MnO$_2$, but as a rule methyl groups in five-membered heterocycles are not oxidized by MnO$_2$.[104] However, 3-formyl-2-methyl-substituted **79a** and 2-formyl-3-methyl-substituted **79b** indoles are oxidized to the dialdehyde **80** on account evidently of the activating effect of the CHO group (Scheme 39).[104]
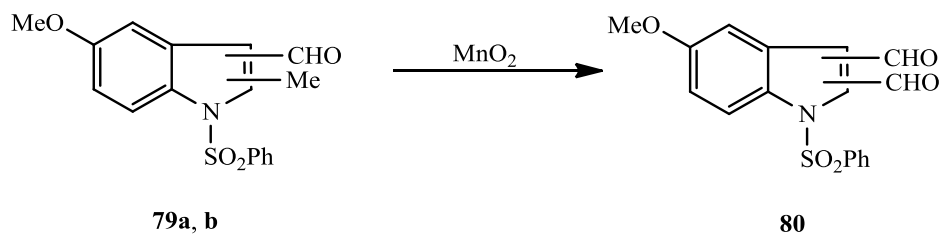
Scheme 39.

A large, constantly increasing, number of examples of the use of MnO$_2$ for the partial dehydrogenation or aromatization of heterocyclic compounds are known. Manganese dioxide is recognized as the most suitable dehydrogenizing agent for the synthesis of 2,4-di-acylfurans[105] and also N-benzyl- and N-acylpyrroles.[106,107] Thus, N-acylpyrroles **82** were obtained from N-acylpyrrolines **81** with yields of 78-91% (Scheme 40).[107]
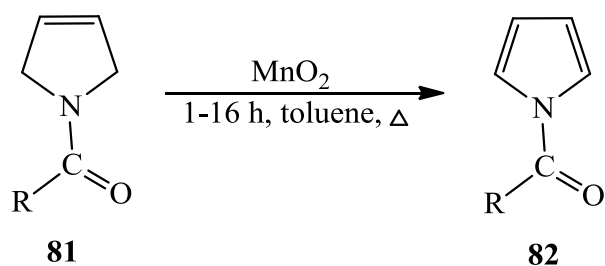
R = CH$_2$CH$_2$Ph, CH$_2$CH$_2$CH(OH)Me, CH$_2$CH(Me)COOCH$_2$Br

Scheme 40.

An example for the convenience of using MnO$_2$ as oxidising agent on purine derivatives, when the rearomatization of the adduct **83** was done via DDQ, the chromatographic separation of the polar purinone **58** and residual DDQH$_2$ was tedious. Thus, compound **58** was easily isolated in high yields when the adduct **83** was oxidized with MnO$_2$ in a polar solvent, DMSO or dichloromethane (Scheme 41).[56]
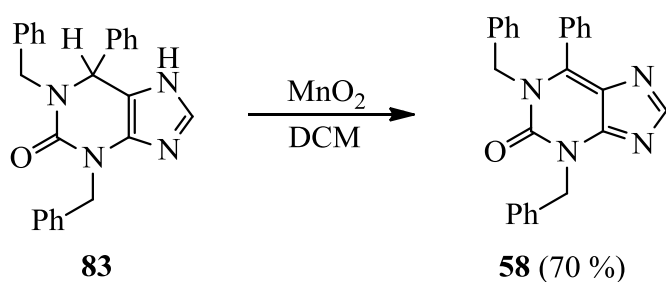
Scheme 41.

In the same way, compound **84** was easily oxidized to compound **85**, when treated with activated MnO$_2$ in dichloromethane (Scheme 42).[56]
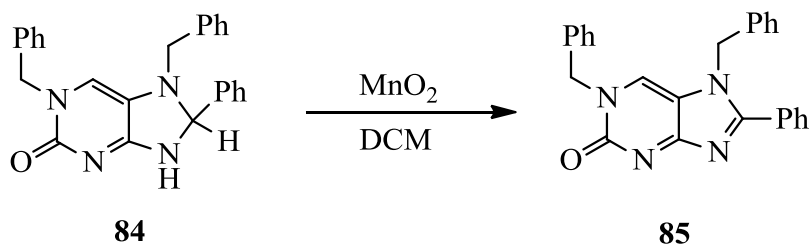
Scheme 42.

2.9.2 Oxidation of heterocyclic compounds *via* DDQ

Dichloro dicyano quinone (DDQ) has been investigated as a powerful oxidising agent for a wide range of reactions. DDQ reacts with water leading to possible hydrolysis of the cyanid-ion.[108]

Stability is generally increased in acidic conditions and at low temperatures. DDQ might decompose at temperatures above 200 °C giving HCN vapors. DDQ is very soluble in THF and ethyl acetate, moderately soluble in dichloromethane, toluene, dioxane, acetic acid, and insoluble in water (but reacts with).

It has been observed that the rate of the reaction with DDQ is accelerated in polar solvents and catalyzed by proton-donor species. The mechanism is supposed to be bimolecular. In the first rate-determining step, the formation of a charge-transfer complex occurs, according to the following scheme:[109]

$RH_2 + QH^+ \longrightarrow RH^+ + QH_2$, where Q : Quinone, R : reacting species, RH^+ : charge-transfer complex.

From the charge-transfer complex, two reactions are likely to happen:

- Elimination of a proton to give an insaturation on the molecule
- Wagner-Meerwein type rearrangement prior to the loss of proton may occur in specific cases.

For some other special reactions, a radical mechanism may be involved.

Dehydrogenation of hydrocarbons is based on an initial rate-determining transfer of hydride ion from the hydrocarbon to DDQ leading to hydroquinone derivative. The feasibility of the reaction depends upon the degree of stabilization of the transition-state carbocation. It has been observed that the presence of alkenes or aromatic moieties is sufficient to initiate hydrogen transfer in presence of DDQ, such as the synthesis of chromenes **87** by addition of an insaturation on chromanes **86** (Scheme 43).[110]
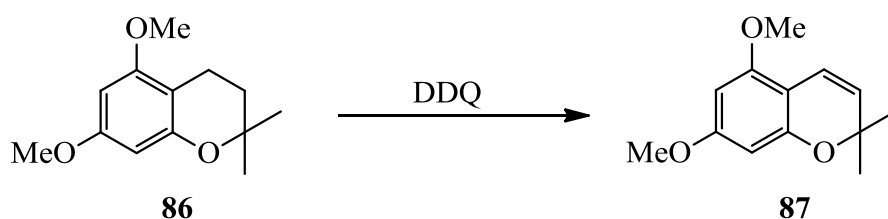
Scheme 43.

The regioselective dehydrogenation of steroids allows aromatization of specific cycles in the whole skeleton towards successful synthesis of the target molecules (Scheme 44).[111]
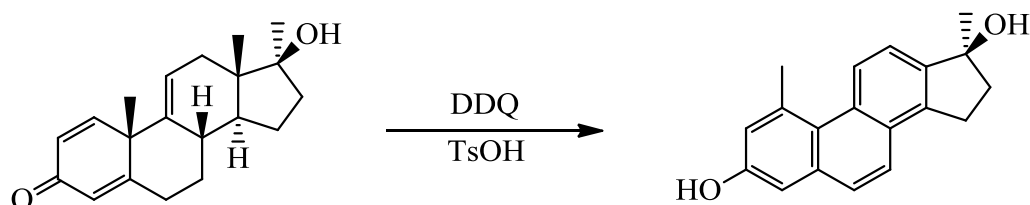
Scheme 44.

The dehydrogenation of hydroaromatic heterocycles is a powerful way to rearomatize heterocycles after they were functionalized through a nucleophilic addition.

For purine substrates, in many cases, DDQ is more advantageous over MnO_2 for the rearomatization. Adducts **88a-d** were oxidized smoothly by DDQ to give the compounds **89a-d**. Its chemical analogue Chloranil also afforded these oxidations, but on the other hand, activated MnO_2 failed to oxidize the alkyl adducts **88c** and **88d** (Scheme 45 and Table 5).[56]
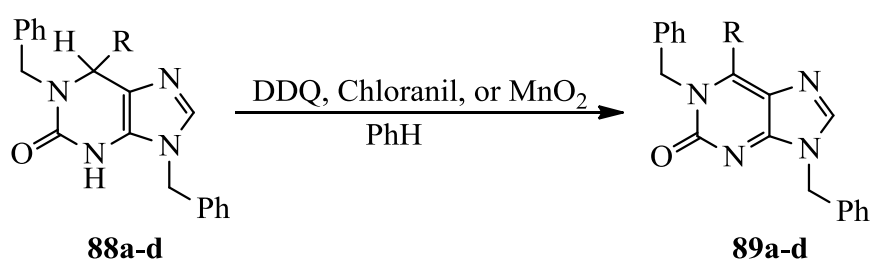
Scheme 45.

Table 5. Rearomatization of the adducts **88a-d** by several oxidants.[56]

Entry	R	Yield (%) **89a-d**		
		DDQ	Chloranil	MnO$_2$
a	Ph-	67	50	69
b	Ph-C≡C-	60	70	50
c	CH$_3$-	68	81	n.r.
d	(CH$_3$)$_2$CH-	52	55	n.r.

2.10 Overview of double-bond migration.

It is well-observed through many literature reactions,[21,100,112-114] that strong bases are affecting the terminal double bond of the allyl groups attached to the N-7 or N-9 in purines. That can be attributed to two factors, first, the ability of the strong base to deprotonate the allyl group and drive the migration, second, the tendency of the double bond to migrate towards the aromatic skeleton of purine forming a conjugated system which is more stable (Scheme 46).[21,112]
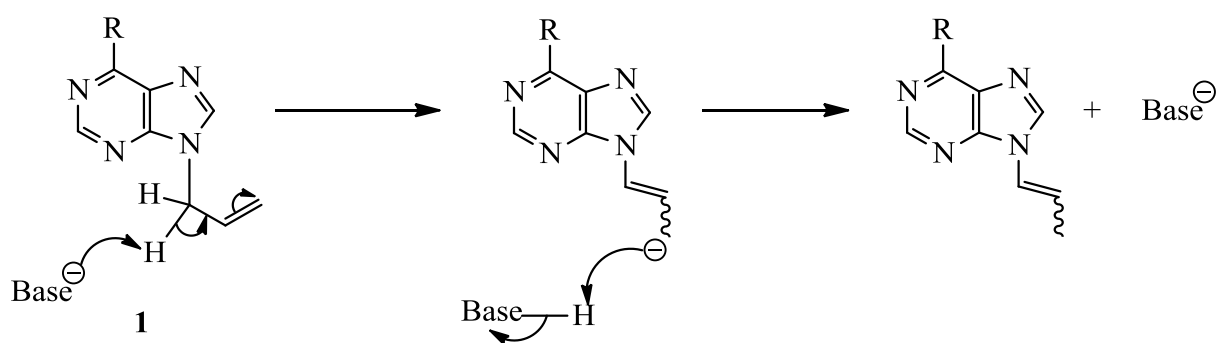
Scheme 46. General mechanism for base impact on N-allyl purines.

Protons of the allyl group attached to the purine ring undergo deprotonation under the influence of organolithium reagents, but not usually organomagnesium reagents, since they are strong bases that possess pKa values higher than the allyl group (pKa ≃ 38, in case of

CH$_2$=CH-CH$_2$-<u>H</u>)[113] which already decreased than normal due to linkage with the purine ring that lowers its basicity.

Potassium carbonate was chosen to enhance a selective migration for the double bond in the diallylpurine **90**. The reaction was done in refluxing acetonitrile to migrate the double bond in the N-7 allyl giving compound **91** in excellent yield (Scheme 47).[100]

In the case of compound **92**, the reaction was slower and required refluxing in *n*-butanol instead of acetonitrile but after all, the reaction was not completely selective and 10% of isomer **94** was obtained (Scheme 47).[100]
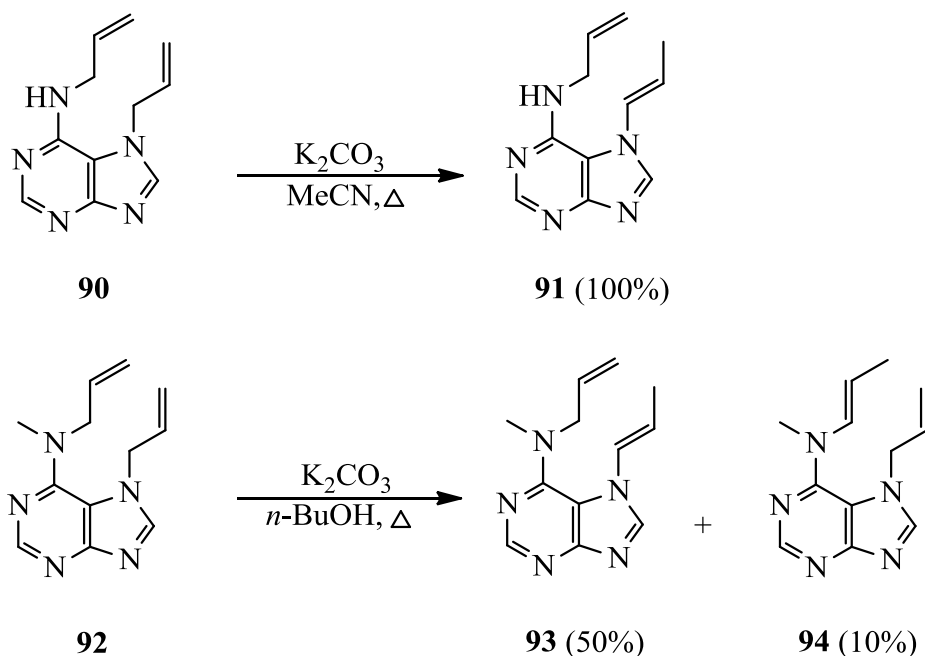
Scheme 47.

When both N-7 and N-9 allylated purines were subjected to bases such as K$_2$CO$_3$ or *t*-BuOk, rearrangement of the allyl group double bond occurred whether towards *E*- or *Z*-selectivity (Scheme 48).[114]
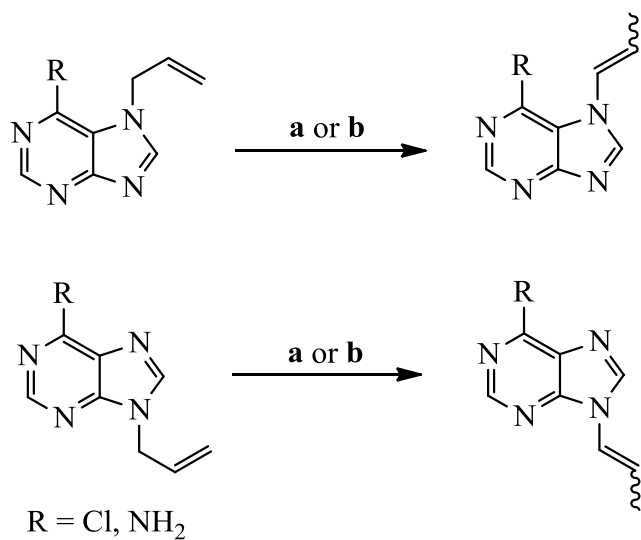
Scheme 48. Reagents and conditions (**a**) K_2CO_3, MeCN, Δ; (**b**) *t*-BuOK, DMSO, rt.

3. RESULTS AND DISCUSSION.
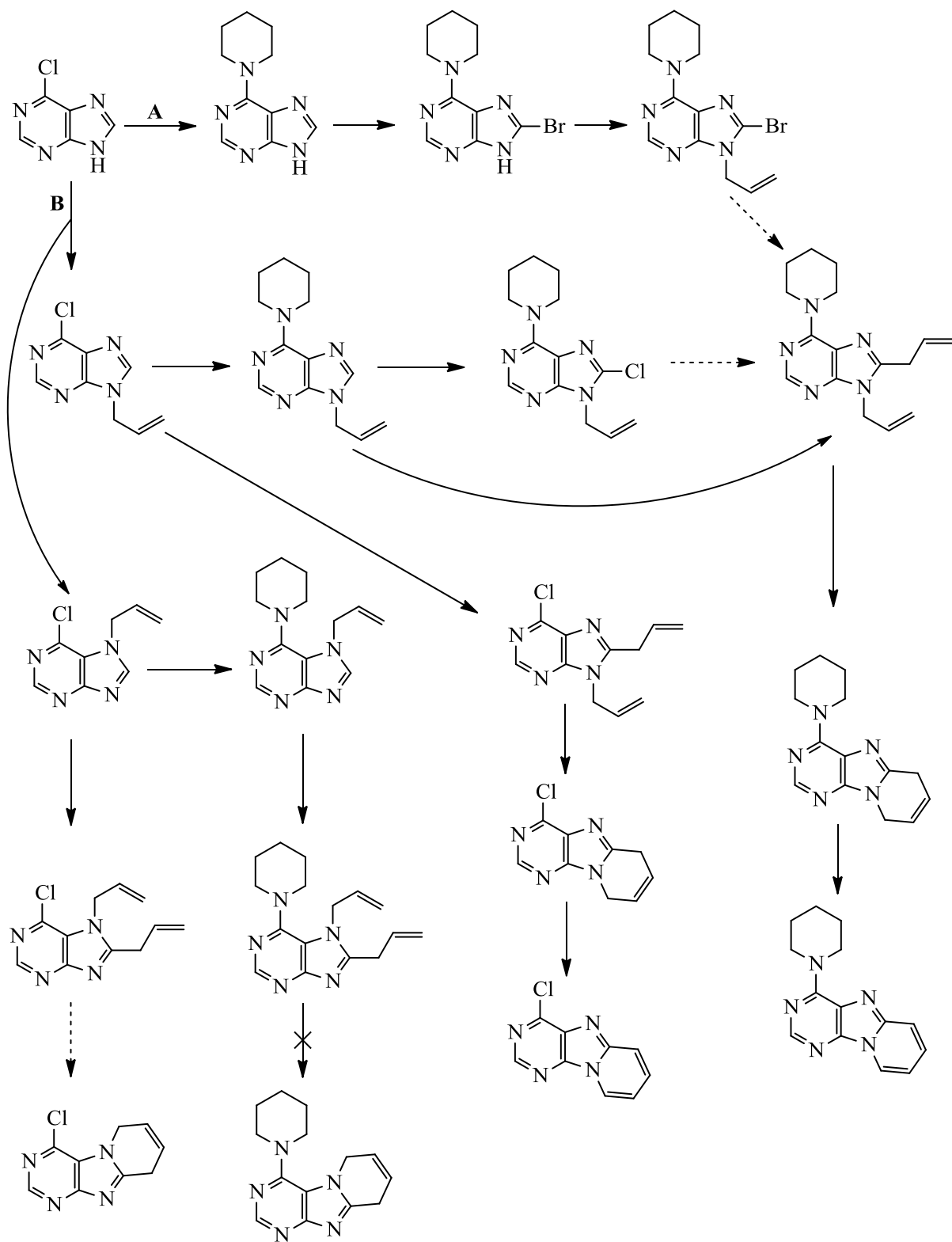
Scheme 49. General summary of the project synthetic routes.

A general summary for the work done in the project and the selected synthetic routes is illustrated in Scheme 49.

Two major routes were attempted towards the syntheses of the diallylpurines for RCM reactions. Route **A** involves mainly C-8 halogenation before N-allylation, while route **B** involves N-allylation before C-8 functionalization with other modifications introduced to improve this synthetic route which will be discussed in detail.

3.1 Synthesis directed towards diallylpurines for RCM reactions (route A)

The original route selected towards the syntheses of diallylpurines for RCM reactions involved C-8 bromiation followed by N-allylation as the key steps (Scheme 50).
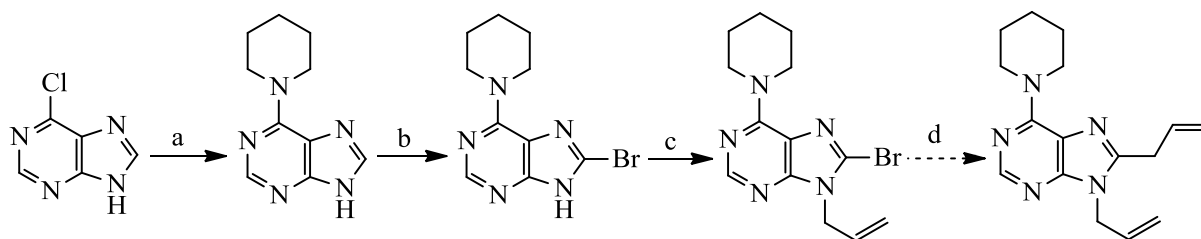
Scheme 50. Steps (a) C-6 amination, (b) C-8 bromination, (c) N-allylation, (d) C-8 allylation by Stille coupling.

3.1.1 Synthesis of 6-(piperidin-1-yl)-9*H*-purine (35).

6-(Piperidin-1-yl)-9*H*-purine **35** was prepared by direct nucleophilic substitution of 6-chloropurine **16** following a literature procedure.[33]

Amination of 6-chloropurine **16** with piperdine at 100 °C for 15 h was done in *n*-BuOH, using triethyl amine to increase the basicity of reaction medium, and consequently the solubility of 6-chloropurine (Scheme 51).
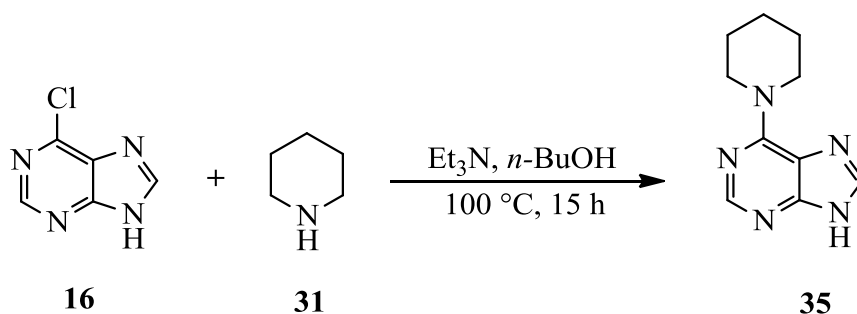
Scheme 51.

According to the literature procedure,[33] the crude product was triturated with MeOH once to give 56% yield but we succeeded to increase the yield significantly (87%) by triturating the crude product in MeOH three times. Moreover, the crude product did not require any further purification.

3.1.2 Synthesis of 8-bromo-6-(piperidin-1-yl)-9*H*-purine (24).

Bromination of compound **35** was reported previously in literature using bromine in a buffer solution of acetic acid and sodium acetate at 80 ^{O}C for 3 hours. After purification by flash chromatography the obtained yield was excellent (97%).[23]

Using solvents which are difficult to remove due to their high boiling points such as water is inconvenient. On the other hand, using the buffer solution demands chromatographic purification. Therefore, bromination of compound **35** was attempted to be improved using liquid bromine as a brominationg agent and solvent. The crude product was relatively pure, thus it only required to be washed with hot water, acetone, and diethyl ether to be purified more. Despite of the simplicity and convenience of this method, it afforded a lower yield (62%) (Scheme 52).
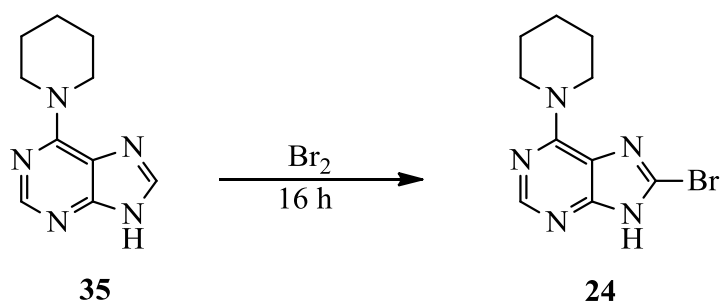
Scheme 52.

3.1.3 Synthesis of 9-allyl-8-bromo-6-(piperidin-1-yl)-9*H*-purine (25) and 3-allyl-8-bromo-6-(piperidin-1-yl)-3*H*-purine (26).

Following a literature procedure for this reaction,[23] 8-bromo-6-(piperidin-1-yl)-9*H*-purine **24** was N-allylated with allyl bromide in the presence of potassium carbonate and DMF as a solvent (Scheme 53).

24   **25**   **26**
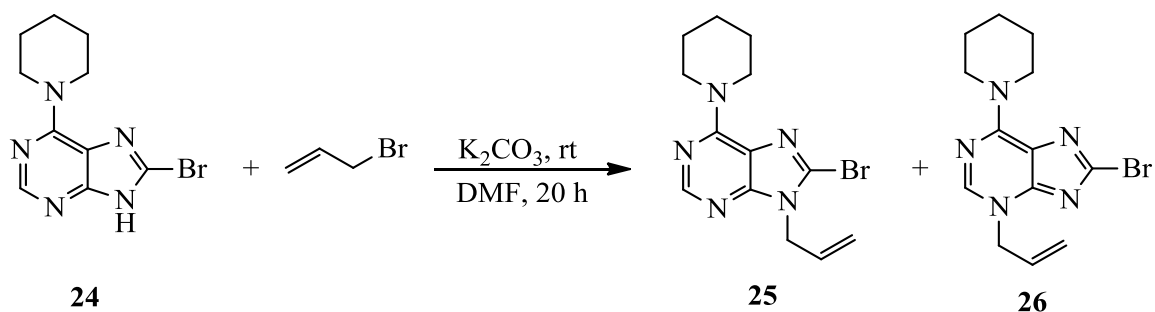
Scheme 53.

The N-9 allylated isomer was formed as the minor product and the N-3 allylated isomer as the major one. According to the ^{1}H NMR spectrum of the crude product, the isomer distribution was (N9/N3) 1 : 2.8. The products **25** and **26** were isolated in 21% (Lit.[23] 35%) and 69% (Lit.[23] 58%) yields, respectively, by flash chromatography.

The ratio of the allylated products **25** and **26** were analogous to the benzylated products prepared from 8-bromoadenine previously.[24]

The regioselctivity of compound **24** towards the N-3 alkyation could be explained comparable to adenine. Selective N-9 alkylation of adenine was often seen when the reaction is performed in the presence of base.[21] However, when 8-bromoadenine was N-alkylated under basic conditions, the selectivity towards N-9 was decreased and the 3-alkylated compound was obtained as the major isomer.[24] Therefore, it could be concluded that the presence of the bromide in the C-8 position had directed this reaction towards the N-3 alkylation due to its steric bulk.

The measured melting points for compounds **25** and **26** were 80-82 ℃ and 111-113 ℃, respectively, while the reported ones in literature are 65-66 ℃ and 82-83 ℃, respectively. This variation could be attributed to the less purity of the isolated products in our case.

HMBC NMR was employed to confirm the structure of compound **25**. Diagnostic long-range couplings of N(9)CH$_2$ with =CH$_2$, CH=, C-8, and C-4 were observed to indicate to the correct position of the allyl group (Table 6).

Table 6. Selected correlation from long range HMBC NMR spectrum for compound **25**.

X = coupling between carbon and proton

25
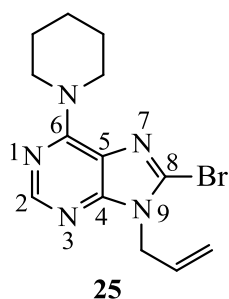
	3 x CH$_2$ in piperidinyl	N(9)CH$_2$	=CH$_{2a}$	=CH$_{2b}$	CH=	H-2
CH$_2$ in piperidinyl	X					
2 x CH$_2$ in piperidnyl	X					
N(9)CH$_2$			X	X	X	
2 x NCH$_2$ in piperidinyl	X					
=CH$_2$		X				
C-5						X
C-8		X				
CH=		X	X			
C-4		X				X
C-2						X
C-6						X

On the other hand, HMBC NMR of compound **26** refers to long-range couplings of N(3)CH$_2$ with =CH$_2$, CH=, C-2, and C-4 which indicates to the right position of the allyl group (Table 7).

Table 7. Selected correlation from long range HMBC NMR spectrum for compound **26.**

X = coupling between carbon and proton
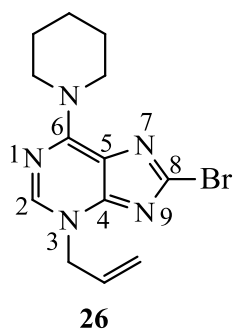
	3 x CH$_2$ in piperidinyl	N(3)CH$_2$	=CH$_2$	CH=	H-2
CH$_2$ in piperidinyl	X				
2 x CH$_2$ in piperidnyl	X				
NCH$_2$ in piperidinyl	X				
NCH$_2$ in piperidinyl	X				
N(3)CH$_2$			X	X	X
=CH$_2$		X			
C-5					X
CH=		X	X		
C-2		X			
C-6					X
C-4		X			X

26

Due to the low yield of 9-allyl-8-bromo-6-(piperidin-1-yl)-9*H*-purine **25** which is a key compound for further synthesis of the diallylpurine **71**, this strategy was stopped and C-8 allylation by Stille coupling was not performed. An alternative route (Chapter **3.2**) was attempted.

3.2 Synthesis directed towards diallylpurines for RCM reactions (route B).

The alternative route to synthesize the diallylpurines involves N-allylation before C-8 functionalization as the key steps (Scheme 54).

C-8 functionalization was attempted by various methods including lithiation / halogenation, organomagnesium, and organoindium addtions.
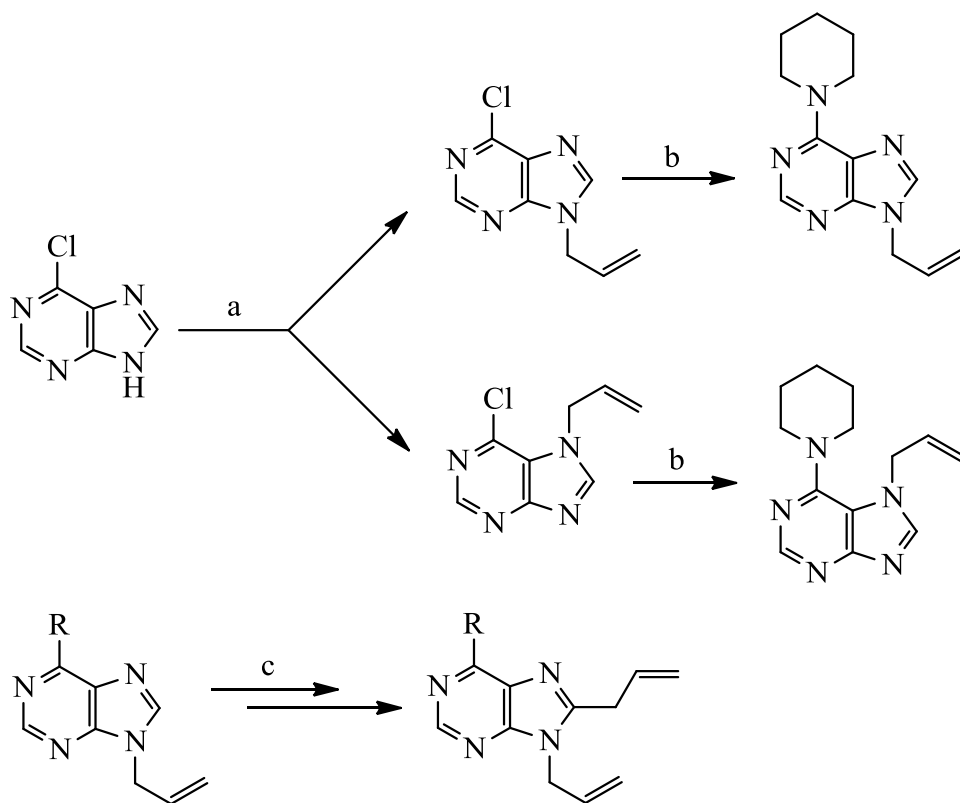
R = Cl, piperidinyl

Scheme 54. Steps (**a**) N-allylation, (**b**) C-6 amination, (**c**) lithiation/halogenation, Grignard addition, or organoindium addition.

3.2.1 Synthesis of 9-allyl-6-chloro-9*H*-purine (19) and 7-allyl-6-chloro-7*H*-purine (20).

6-Chloropurine **16** was N-allylated with allyl bromide in the presence of potassium carbonate. The reaction had run for 20 h in DMF at room temperature (Scheme 55).[22]
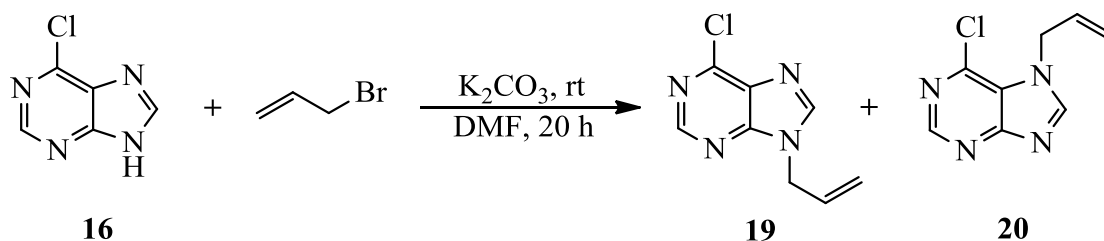
Scheme 55.

Both the N-9 and N-7 allylated isomers were formed with the latter as the minor isomer. The ^{1}H NMR spectrum of the crude product showed the isomer distribution of (N9/N7) to be 2.4 : 1, and the products **19** and **20** were isolated in 62% (Lit.[22] 59 %) and 21% (Lit.[22] 20%) yields, respectively, by flash chromatography.

3.2.2 Synthesis of 9-allyl-6-(piperidin-1-yl)-9*H*-purine (33).

Usually, most purine substrates are insoluble in water, thus the vast majority of purines reactions are done in organic media. Interestingly, amination of N-allylated 6-chloropurines by piperidine are done successfully in water as a non-toxic environmentally friendly solvent.

According to the literature, the synthesis of compound **33** was done in water by microwave irradation[34] (84% yield) as well as by heating-induced method[32] (95% yield).

We had achieved amination of 9-allyl-6-chloropurine **19** with piperidine as a heterocyclic amine. Reflux for 24 hours in H_2O at 100 °C gave 95% yield cleanly without further purifications (Scheme 56).
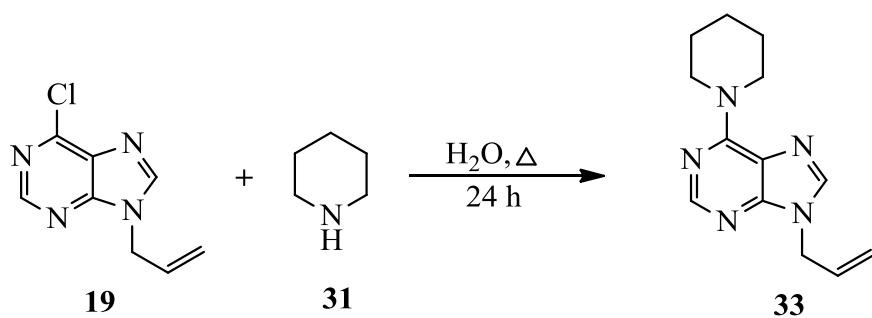
Scheme 56.

There was a mismatch of the measured melting point of compound **33** (80-82 °C) to what is reported in literature (54-56 °C).[34] This gap can only be attributed to a misprint or mismeasurement in literature since all other data and structure elucidation refer to the indicated compound.

3.2.3 Synthesis of 7-allyl-6-(piperidin-1-yl)-7*H*-purine (95).

Applying the previous procedure (Chapter **3.2.2**), amination of 7-allyl-6-chloropurine **20** by piperdine in H_2O for 24 h was achieved to obtain a pure product in a high yield (92%) without chromatographic purification (Scheme 57).
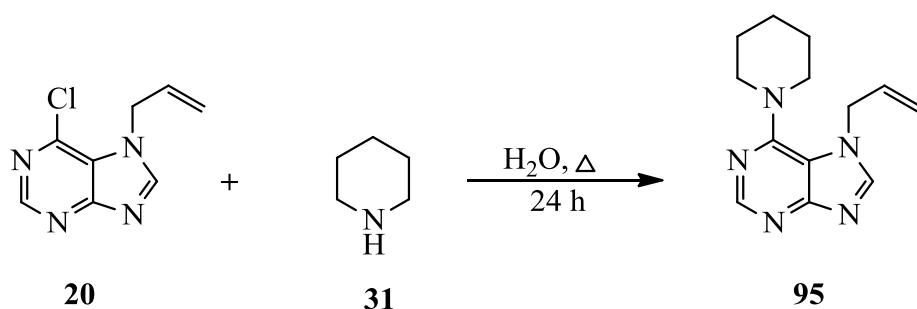
Scheme 57.

HMBC NMR was employed to confirm the structure of compound **95**. Long-range coupling was observed between the two symmetrical NCH_2 in piperidinyl ring and C-6, besides coupling of $N(7)CH_2$ with both C-5 and C-8 to indicate that compound **95** is the correct one (Table 8).

Table 8. Selected correlation from long range HMBC NMR spectrum for compound **95.**

X = coupling between carbon and proton

95
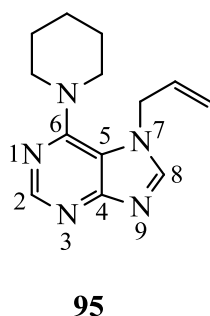
	2 x NCH$_2$ in piperidinyl	CH$_2$ in allyl	H-8	H-2
CH$_2$ in allyl			X	
2 x NCH$_2$ in piperidinyl	X			
C-5		X	X	X
C-8		X		
C-6	X		X	X
C-4			X	X

3.2.4 C-8 functionalization *via* lithiation

3.2.4.1 Synthesis of 9-allyl-8-chloro-6-(piperidin-1-yl)-9*H*-purine (96) and (*Z*)-8-chloro-6- (piperidin-1-yl)-9-(prop-1-en-1-yl)-9*H*-purine (97).

Lithiation of 9-allyl-6-(piperidin-1-yl)-9*H*-purine **33** by LDA prepared *in situ* followed by chlorination with hexachloroethane was achieved. The reaction afforded the 8-chloropurine **96** in a low yield (31%) and the 9-alkenylpurine **97** (22% yield), beside several other compounds which probably resulted from deprotonation / lithiation / chlorination of the allylic side chain, but they could not be isolated in pure form (Scheme 58).
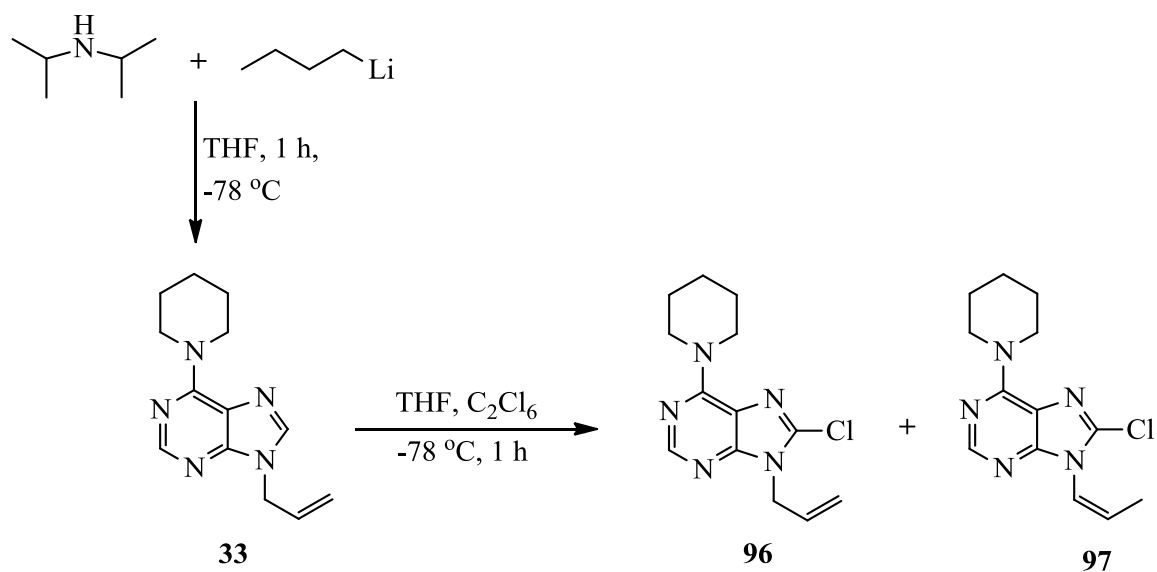
Scheme 58.

According to HMBC NMR of compound **96**, long-range correlations of NCH_2 in the allyl group with $=CH_2$, $=CH$, C-8, and C-4 had proved the correct structure (Table 9).

Table 9. Selected correlation from long range HMBC NMR spectrum for compound **96**.

X = strong coupling between carbon and proton.

x = weak coupling between carbon and proton.
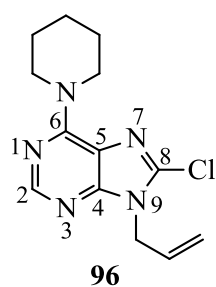
	CH_2 in allyl	$=CH_{2a}$ in allyl	$=CH_{2b}$ in allyl	$=CH$ in allyl	H-2
CH_2 in allyl		X	X	X	
$=CH_2$ in allyl	X				
C-5	x				X
$=CH$ in allyl	X	X			
C-8	X				
C-4	X				X
C-6					X

According to ^{1}H NMR spectrum for compound **97**, the coupling constant between the two protons around the double bond of the N-9 propenyl group equals 8.0 which is typical for *Z*-alkenes.[115]

On the other hand, HMBC NMR of product **97**, showed couplings of CH_3 with NCH=, CH=, and C-8 (Table 10).

Table 10. Selected correlation from long range HMBC NMR spectrum for compound **97.**

X = strong coupling between carbon and proton.

x = weak coupling between carbon and proton.
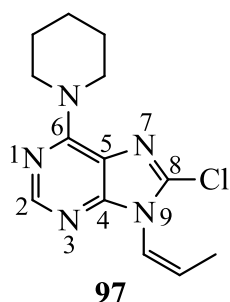
	CH_3	=CH in propenyl	NCH= in propenyl	H-2
CH_3		X	X	
=CH in propenyl	X			
C-5				X
NCH= in propenyl	X			
C-8	x			
C-4				X
C-6				X

3.2.4.2 Synthesis of 6,8-dichloro-9-ethyl-9*H*-purine (49).

In order to make sure that the problems encountered in the previous reaction (Chapter **3.2.4.1**) is attributed to the allyl group not to the LDA generation in the first step, lithiation of 6-chloro-9-ethyl-9*H*-purine **27a** was done, following a literature procedure,[21] using lithium diisopropylamide (LDA) which was prepared *in situ* by reacting a titrated *n*-BuLi with diisopropylamine in dry conditions at -78 °C under inert atmosphere using dry THF as a

solvent. Lithiation was followed by chlorination with hexachloroethane as a good electrophilic donor to afford compound **49** in 71% yield (Lit.[21] 74%) (Scheme 59).
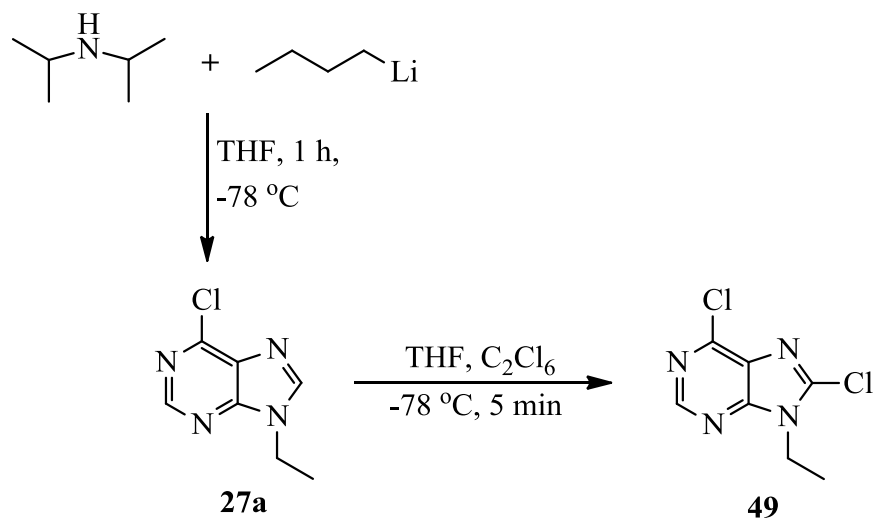
Scheme 59.

3.2.4.3 Synthesis of (*Z*)-6-(piperidin-1-yl)-9-(prop-1-en-1-yl)-9*H*-purine (98)

In order to explore the influence of LDA on N-9 allylated purine, compound **33** was subjected to freshly prepared LDA then quenched with NH$_4$Cl (aq). The obtained products were 37% of unaffected starting material **33** and 23% of N-propenylpurine **98** (Scheme 60).

It is well-observed through literature reactions on N-allylpurines that strong bases could induce the rearrangement of the N-allylic side chains.[21,100, 112,114] Thus, LDA could readily deprotonate the allyl chain and induce the double bond migration.
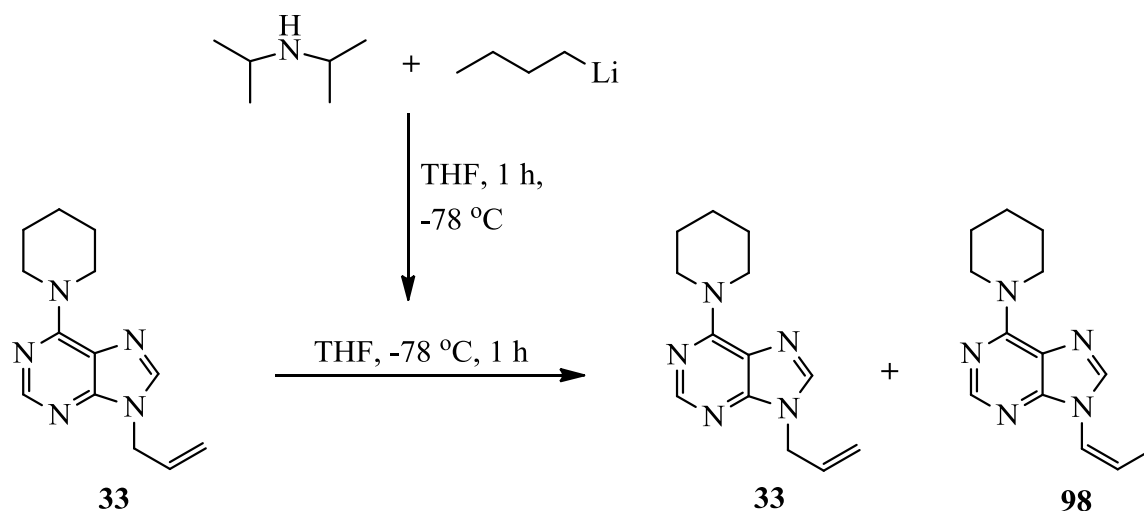
Scheme 60.

Rearrangement occurred in favor of the formation of compound **98** in complete selectivity towards *cis*-configuration. However the low yield of compound **98** may be attributed to the competition between lithiation at C-8 and the allyl group, subsequent allylic anions formed might revert again to the allylpurine **33** upon protonation.

According to the ^{1}H NMR spectrum of compound **98**, the vicinal coupling constant (^3J) between the two protons of NCH=CH equals 8.6 which is correspondent to *cis*- alkenes.[115]

Structure elucidation of compound **98** by HMBC NMR spectrum had shown diagnostic long-range coupling of the terminal CH_3 in the propenyl group with all of NCH=, CH=, C-8, and C-4 which confirm the structure of the product obtained (Table 11).

Table 11. Selected correlation from long range HMBC NMR spectrum for compound **98**.

X = strong coupling between carbon and proton.

x = weak coupling between carbon and proton.

98
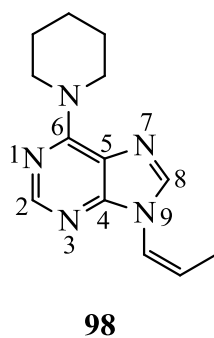
	CH_3	=CH in propenyl	NCH= in propenyl	H-8	H-2
CH_3		X	X		
C-5				X	X
NCH= in propenyl	X	X			
=CH in propenyl	X		X		
C-8	X	x	X		
C-4	X		x	X	X
C-6				x	X

3.2.4.4 Attempt to trap the C-lithiated purine with allyl bromide.

Lithation of 9-allyl-6-(piperidin-1-yl)-9*H*-purine **33** using LDA prepared *in situ* followed by allylation by allyl bromide did not succeed and 96% of the starting material was recovered again with nothing else formed according to TLC and the ^{1}H NMR spectrum (Scheme 61).
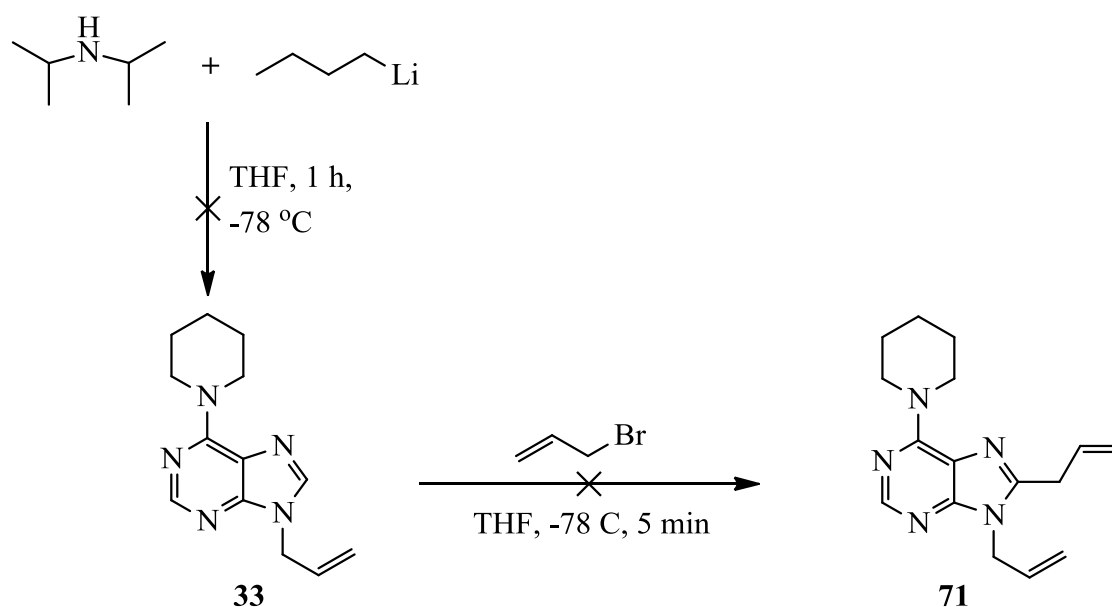
Scheme 61.

No double bond migration happened to the allyl group as it was confirmed in the previous reactions (Chapters **3.2.4.1** and **3.2.4.3**) and the starting material was recovered again in almost the same amount. Therefore, the failure of this reaction could be attributed to insufficient dry conditions used; hence the LDA was not generated in the first step.

However, this reaction was replaced with another convenient and more effective route to synthesize compound **71** without involving the double bond migration of the allylic side chain which is resulted from LDA impact, and the subsequent significant decrease in the obtained yield of the desired product.

3.2.5 C-8 allylation of 9-allylpurine by organomagnesium or organoindium addition reaction.

Since C-8 lithiation / halogenation / allylation route towards compound **71** was inconvenient due to influence of LDA on the N-9 allyl group and the low yield obtained for the desired product, direct allylation *via* organometallic reagent would be a real improvement.

To the best of our knowledge, direct C-8 allylation using an organometallic reagent was reported twice before in the literature, first, on 6-chloro-9-tetrahydropyranylpurine *via* Gilman reagent generated from allylmagnesium bromide and CuI,[116] second, on 9-benzyl-2-chloro-6-iodopurine by allylmagnesium bromide to give the corresponding 8-allyl-7,8-dihydropurine in 37% yield.[55]

Based on Grignard addition to carbonyl compounds,[18] a mechanism of the addition reaction *via* allylmagnesium bromide on C=N in purine is proposed (Scheme 62).
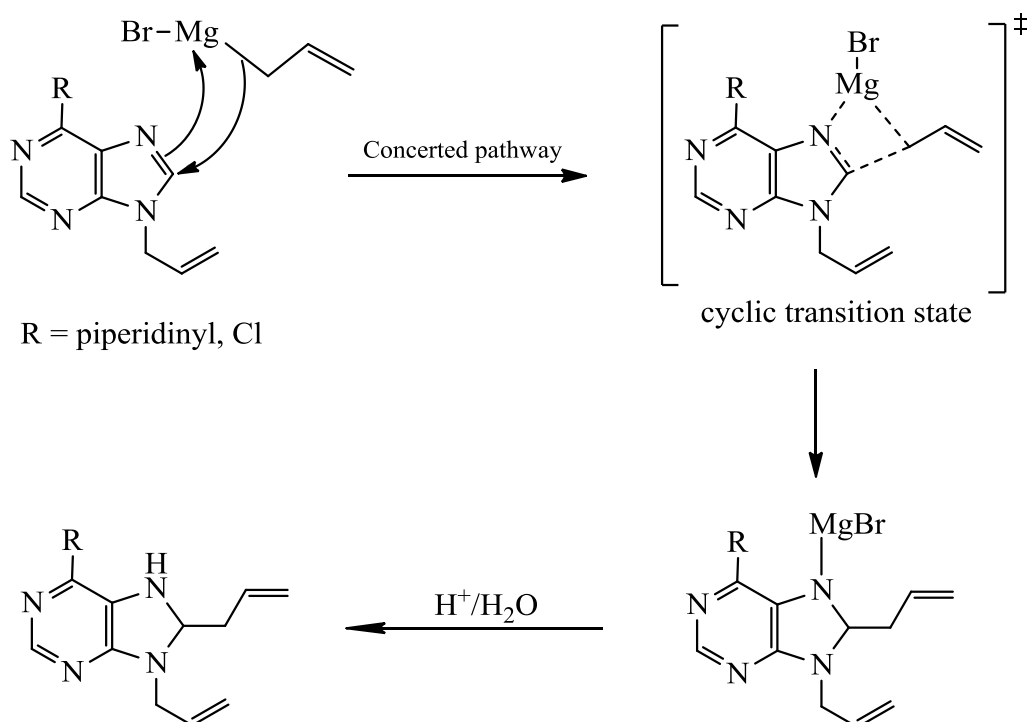
Scheme 62. Proposed general mechanism of Grignard addition on purines.

3.2.5.1 Synthesis of 8,9-diallyl-6-(piperidin-1-yl)-9*H*-purine (71)

Improving literature procedure for C-8 allylation of purines *via* Grignard reagent,[55] synthesis of compound **71** was carried out by allylmagnesium bromide on 9-allyl-6-(piperidin-1-yl)-9*H*-purine **33** at 0 °C in THF as a solvent (Scheme 63).
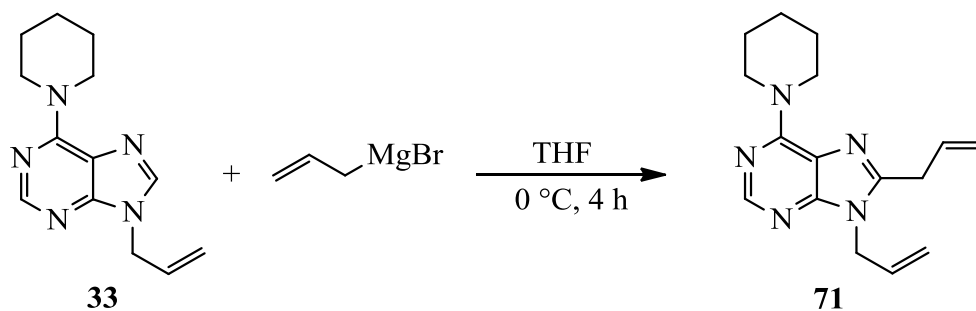
Scheme 63.

The anticipated product was the adduct compound **99** (Figure 11) according to the mechanism of Grignard addition, but fortunately, the rearomatized compound was obtained without using an oxidizing agent probably due to a quick self-oxidation by atmospheric oxygen during the work-up as well as the high tendency of this compound **99** towards the more stable aromatic form.
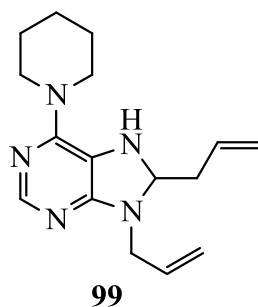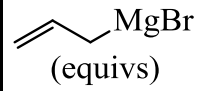
Figure 11.

Endeavoring for the optimization of this reaction, reaction times and amounts of allylmagnesium bromide were varied (Table 12). Running the reaction for 4 h with 3.00 equivs. of Grignard reagent had the optimal conversion (95%) and yield (89%) without any noticeable effect on N-9 allyl group or any potential double migration. Moreover, running the reaction with the same amount (3.00 equivs) for longer time (6 h) did not lead to any higher conversion (Table 12).

Table 12. Synthesis optimization of compound **71** *via* Grignard addition.

⌇MgBr (equivs)	Reaction time	Conversion (%)[a]	Yield (%)[b]
2.12	20 min	0	0
2.12	1 h	28	27
2.12	3 h	77	72
2.12	4 h	85	76
3.00	4 h	95	89
3.00	6 h	95	88

(a) According to ^{1}H NMR of the crude products.
(b) Yields of the isolated compounds.

3.2.5.2 Synthesis of 8,9-diallyl-6-chloro-9*H*-purine (100a)

Compound **100a** was synthesized *via* three methods depending mainly on employing organometallic coupling towards direct C-8 allylation (Scheme 64).
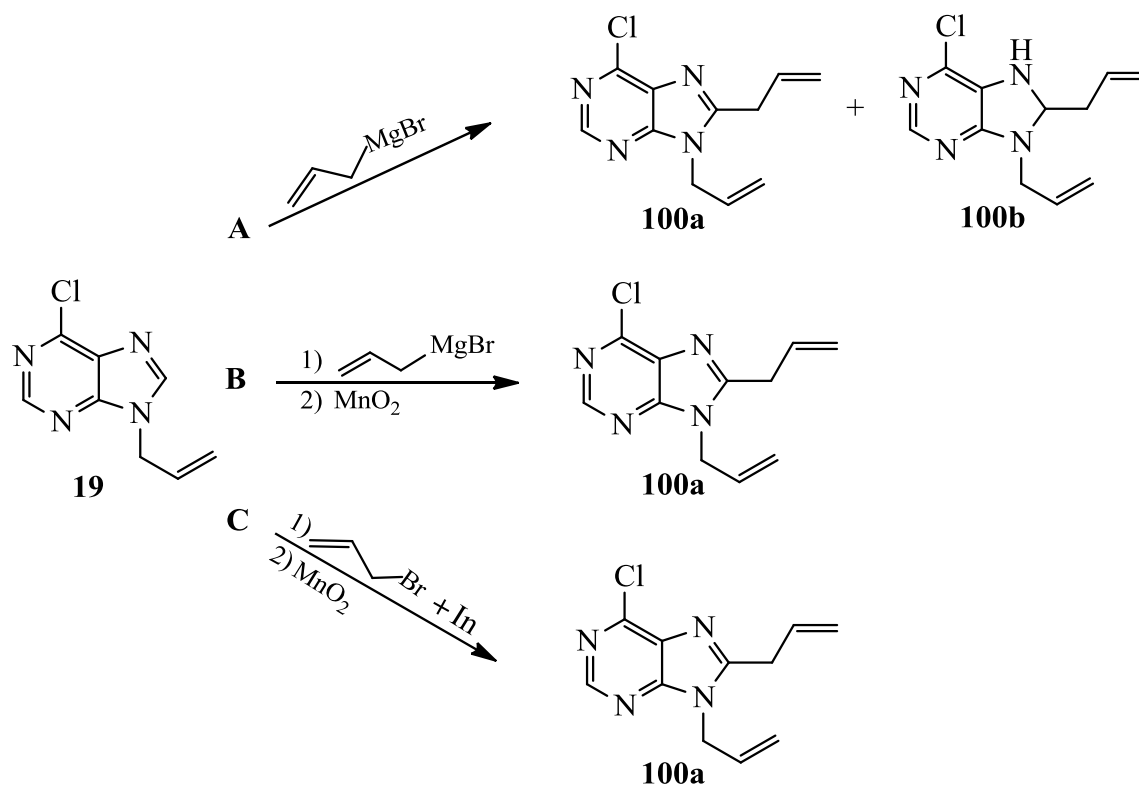
Scheme 64.

Method A.

Method **A** for C-8 allylation was carried out on 9-allyl-6-chloro-9*H*-purine **19** *via* Grignard reagent, allylmagnesium bromide, at 0 °C in THF as a solvent (Scheme 65).
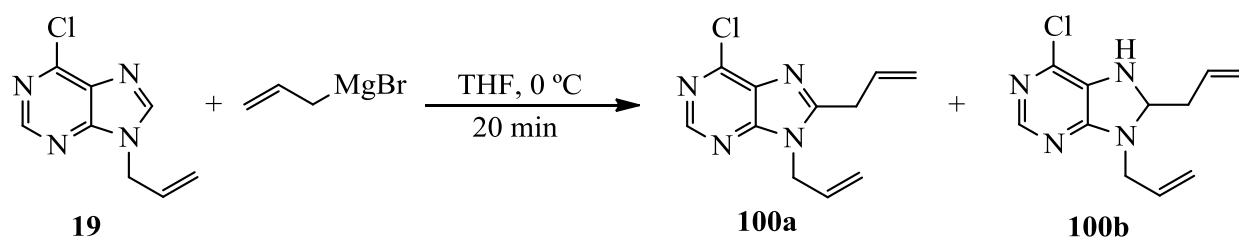
Scheme 65.

6-Chloropurine **19** showed to be more reactive towards Grignard addition compared to the 6-piperidinylpurine **33** (Chapter **3.2.5.1**), the reaction was run only for 20 min which is much shorter time compared to reaction time for synthesis of compound **71** previously (4 h) (Scheme 63).

Moreover, less amount of Grignard reagent was required (2.12 equivs) to get a high conversion (> 97%). In contrary to 6-piperidinylpurine **33**, 6-chloropurine **19** proved to form the adduct compound **100b** as the major product as well as the aromatized compound **100a** as the minor product. The two products were isolated by flash chromatography and that gave rise to compound **100a** (10% yield) and compound **100b** (74% yield).

According to HMBC NMR spectrum for compound **100a**, the diagnostic long-range couplings between CH_2 attached to C-8 with C-5 and C-6, and =CH in N-9 allyl with C-2 have established that the 8,9-diallylpurine **100a** is the correct compound (Table 13).

Table 13. ^{1}H-^{13}C correlations from long range HMBC NMR spectrum for compound **100a.** X = coupling between carbon and proton.

100a
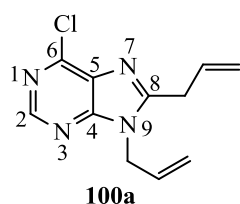
	N(9) CH_2	C(8) CH_2	=CH_{2a} in C(8) allyl	=CH_{2a} in N(9) allyl	=CH_{2b} in N(9) allyl	=CH_{2b} in C(8) allyl	=CH in C(8) allyl	=CH in N(9) allyl	H-2
N(9)CH_2				X	X			X	
C(8)CH_2			X			X	X		
=CH_2 in C(8) allyl		X							
=CH_2 in N(9) allyl	X								
C-5		X							X
CH= in N(9) allyl	X			X	X				
CH= in C(8) allyl		X	X			X			
C-4									X
C-2								X	
C-6		X							X
C-8	X	X						X	

Mass spectrometry (ESI) of adduct **100b** gave for the calculated value of $C_{11}H_{13}N_4Cl$ $[M+H]^+$ 237.0829 and the found value was 237.0901 which proves the presence of two extra protons than the aromatized compound **100a.**

HMBC NMR spectrum for compound **100b** had shown diagnostic long-range couplings of $N(9)CH_2$ with C-4 exclusively which does not appear with $C(8)CH_2$, strong coupling between C-8 with $=CH_2$ in C-8 allyl while it is weak with CH_2 in N-9 allyl, strong coupling of H-8 with $C(8)CH_2$, C-6, C-5, =CH in C-8 allyl, and C-4 besides a weak coupling with $N(9)CH_2$ (Table 14).

Table 14. ^{1}H-^{13}C correlations from long range HMBC NMR spectrum for compound **100b.**

X = strong coupling between carbon and proton.

x = weak coupling between carbon and proton.

100b
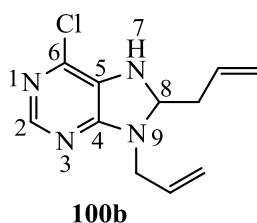
	$C(8)$ CH_2	NCH_2	$=CH_2$ in $C(8)$ allyl	$=CH_2$ in $N(9)$ allyl	H-8	2 x CH=	H-2
$C(8)CH_2$			X		X	X	
NCH_2				X	x	X	
C-8	X	X	X	x		X	
$=CH_2$ in N(9) allyl		X				x	
$=CH_2$ in C(8) allyl	X				X	x	
C-6					X		X
C-5					X		X
=CH in C(8) allyl	X		X		X		
=CH in N(9) allyl		X		X			
C-2							
C-4		X			X		X

Method B.

According to method **A** discussed, two compounds were obtained, the major was the adduct compound containing non-aromatized imidazole ring **100b** and the minor was the oxidized product with aromatized imidazole ring **100a**. The latter one is the desired compound for proceeding with cyclization. Thus, the crude product of the reaction was oxidized using activated manganese dioxide in DCM at room temperature to recover the aromaticity of imidazole ring in the purine skeleton of compound **100b**. The product was purified by flash chromatography to give 73% yield of compound **100a** (Scheme 66).
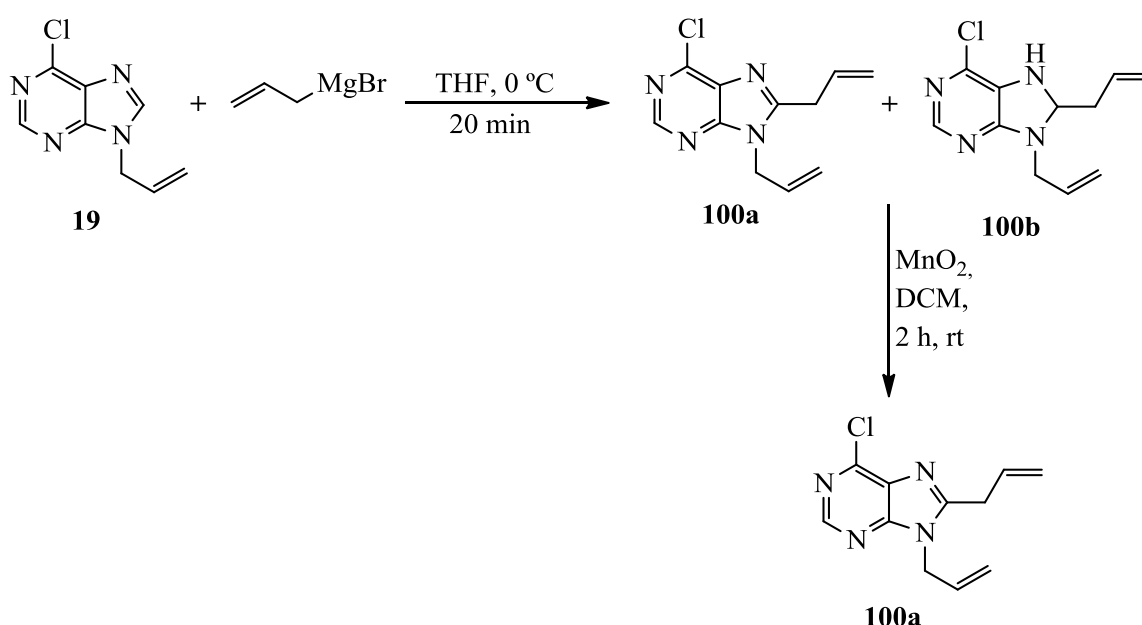
Scheme 66.

Method C.

Indium reacts more readily with electron-deficient heterocycles[62-66] than other metals, such as Mg, Pb, Bi, or Zn and does not require a promoter or flammable organic solvent to drive the reaction. Indium-mediated allylation have advantages over other carbon-carbon bond forming reactions because of their ability to be carried out in water, which is cheap and environmentally friendly. Therefore, these reactions represent green chemistry. Reactions yield a few by-products making it easy to purify the desired product.

In contrary of Gringard reagents, indium-mediated allylation provides a safer alternative since the reactive indium intermediate can be generated *in situ* from a mixture of indium metal, the desired allylic halide, and the electrophile. Therefore, no synthesis or handling of unstable Grignard reagents is required.

To the best of our knowledge, indium-mediated allylation has not been achieved on purine substrates before. Thus, it would be a novel route to attempt.

Based on organoindium addition to carbonyl compounds,[18] a mechanism of the addition reaction by monoallylindium dibromide on C=N in purine is proposed (Scheme 67).
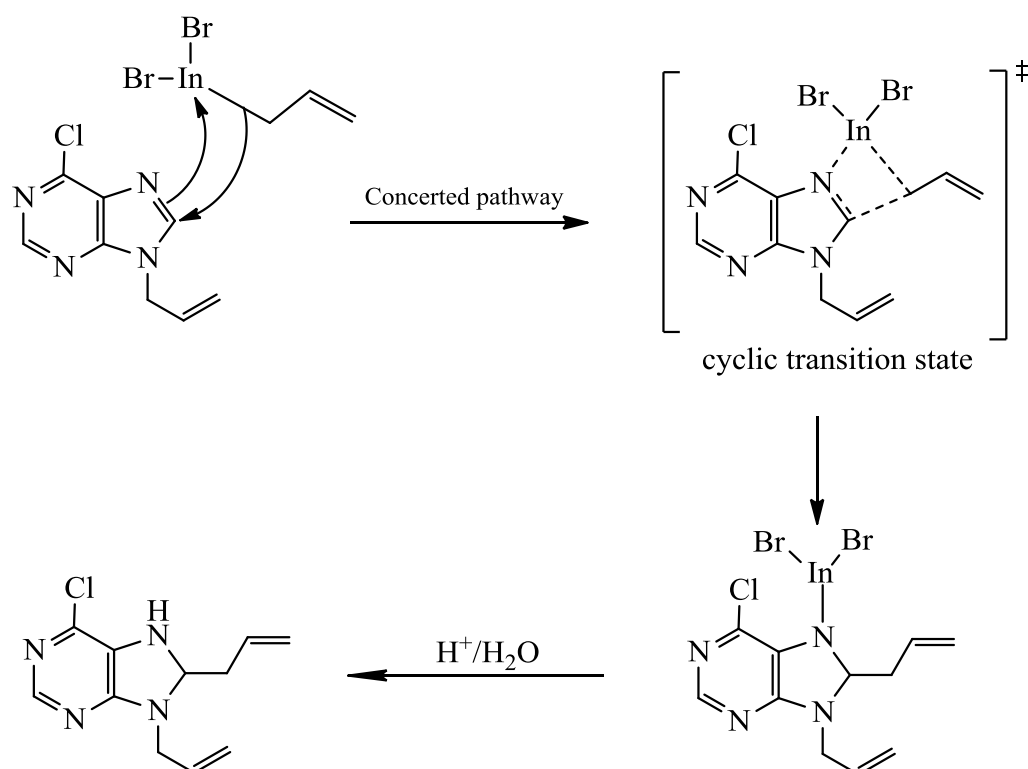
Scheme 67.

An attempt was done trying to react 9-allyl-6-chloropurin **19** with indium powder (8 equivs.) and allyl bromide (12 equivs.) in refluxing THF, but that gave an unidentified product probably because of the unsuitable reaction temperature for the organometallic addition reaction (Scheme 68 and Table 15).

Table 15. Attempts towards compound **100a**.

In (equivs.)	Allyl bromide (equivs.)	reaction conditions	Result
8	12	THF, △, 24 h	Unidentified product
8	12	THF, rt, 24 h	Target product

However, the reaction was accomplished successfully when it was run at room temperature for 24 h using the same amount of indium metal (8 equivs.) and allyl bromide (12 equivs.) to lead to 89% conversion affording mainly the adduct compound **100b** as the major product, according to the ^{1}H NMR of the crude product, which required oxidation to retrieve the aromaticity.

The oxidation was achieved by MnO_2 in DCM for 2 h at room temperature then the product was purified by flash chromatography to obtain 48% yield of the isolated product **100a** (Scheme 68).
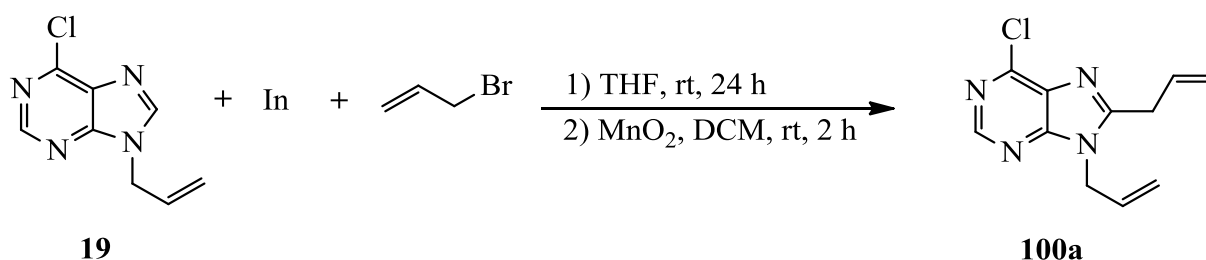
Scheme 68.

The reason behind the moderate yield obtained in spite of the good conversion is due to difficulties encountered in the work-up after the first step. A thick white emulsion was formed after quenching the reaction with NH_4Cl (aq.) which caused difficulties in the extraction and consequently loss in the product.

3.2.5.3 Attempts to synthesize 8,9-diallyl-6-(piperidin-1-yl)-9*H*-purine (71) by organoindium addition reaction.

Other attempts were done on 6-piperdinyl-9-allylpurine **33** with variations in indium amount (2 -10 equivs.), allyl bromide amount (3 - 15 equivs.), and reaction temperature (rt - reflux) but unfortunately that did not succeed (Scheme 69 and Table 16).
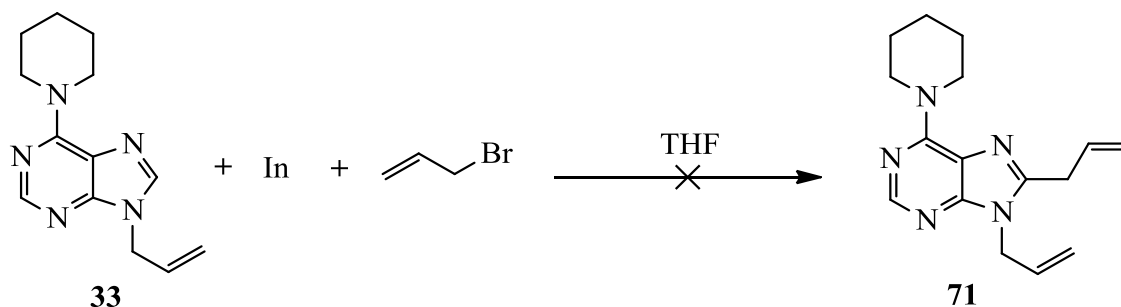
Scheme 69.

Table 16. Attempts towards compound **71**.

In (equivs.)	Allyl bromide (equivs.)	Reaction conditions	Result
2	3	THF, rt (2 h), 30 °C (0.5 h), 40 °C (1.5 h), 50 °C (17 h)	s.m.[a]
5	6	THF, rt (3 h), △ (16 h)	n.d.[b]
10	15	THF, rt, 48 h	n.d.[b]

a) Recoverd starting material

b) Unidentified product according to ^{1}H NMR of the crude products.

It is well-realized from Grignard addition previously and organoindium addition, that 6-chloro-9-allylpurine **19** is more reactive towards organometallic reagents than 6-piperdinyl-9-allylpurine **33**. Hence, the latter one has a promising scope for further studies, and moreover, improvements of the work-up for indium-mediated allylation.

3.2.6. C-8 allylation of 7-allylpurines by organomagnesium addition reaction.

3.2.6.1 Synthesis of 7,8-diallyl-6-(piperidin-1-yl)-7*H*-purine (103)

C-8 allylation of 7-allyl-6-piperidinylpurine **95** was attempted using various amounts of allylmagnesium bromide (1.00 - 3.00 equivs.) and reaction times (20 min - 6 h) at the same temperature (0 °C), but that mostly led to a mixture of the adduct compound **101** and another compound whose introduced C-8 allyl group has a migrated double bond **102** (Figure 12).
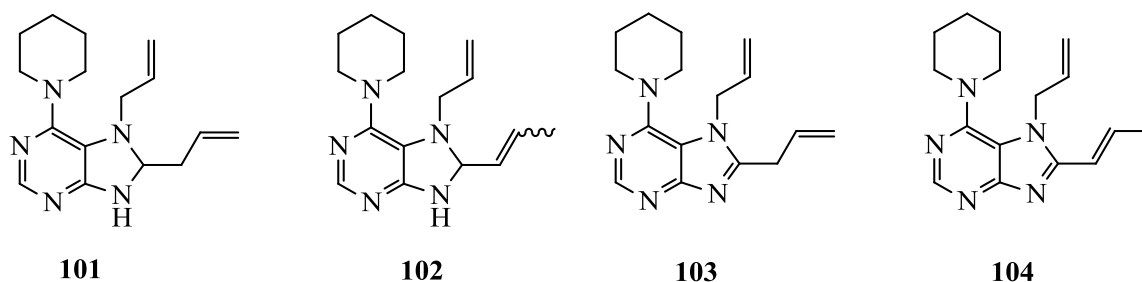
Figure 12.

Realizing that the adduct compound was formed by the Grignard addition, thus MnO_2 was added to the crude product from the first step to recover the aromaticity and isolate the desired product.

In some attempts, both compounds **103** and **104** were obtained as a mixture and could not be separated by flash chromatography (Table 17).

According to ^{1}H NMR, Compound **104** proved to have a *trans* C-8 propenyl group whose two protons around the double bond had a vicinal coupling constant (^3J) = 15.3 which is typical for *E*-alkenes.[115]

Although the corresponding N-9 allylated compound has previously required 3.00 equivs. of Grignard reagent for 4 h, but in this case (Scheme 70 and Table 17), the reaction was successfully controlled by using 2.00 equivs. of allylmagnesium bromide for only 40 min at 0 °C to afford 85% yield which indicates the reactivity of 7-allylpurines compared to 9-allyl purines.
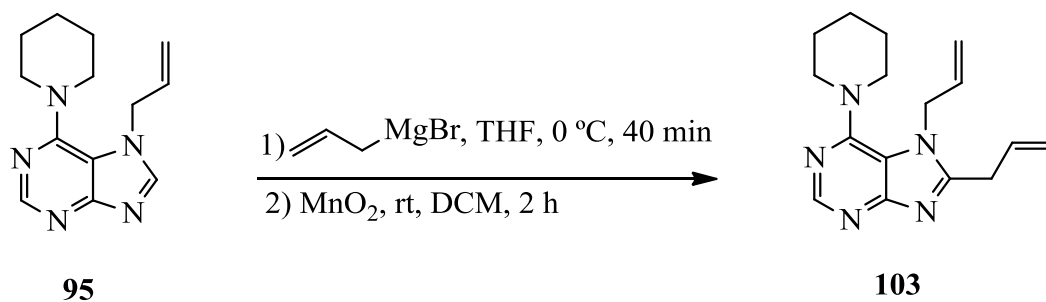
Scheme 70.

Table 17. Attempts to synthesize the 7,8-diallylpurine **103**.

1) ⟋⟍MgBr (equivs.)	Reaction time	2) MnO_2 (equivs.)[a]	Ratio (**103** : **104**)[b]
1.00	20 min	0	n.d.[c]
1.00	40 min	0	n.d.
1.00	2 h	0	n.d.
2.00	20 min	0	n.d.
2.00	40 min	0	n.d.
3.00	6 h	0	n.d.
2.12	3 h	5	86 : 14
2.51	2 h	5	77 : 23
2.00	40 min	5	100 : 0

a) MnO_2 added to the crude product after the first step.

b) According to ^{1}H NMR of the crude products.

c) Not determined (unidentified product).

In order to elucidate the structure of compound **103**, the HMBC NMR spectrum was employed to indicate diagnostic long-range couplings of $=CH_2$ in C-8 allyl group with C-8 while $=CH_2$ in N-7 allyl did not show this coupling with C-8, besides coupling between $=CH$ in C-8 ally with C-8 while $=CH$ in N-7 allyl did not show such coupling with C-8 which established that 7,8-diallyl **103** was obtained (Table 18).

Table 18. ^{1}H-^{13}C correlations from long range HMBC NMR spectrum for compound **103.**

X = strong coupling between carbon and proton.

x = weak coupling between carbon and proton.

103
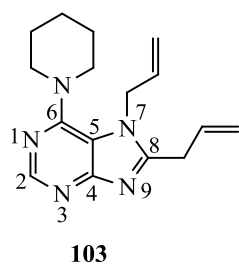
	C(8) CH₂	NCH₂	=CH₂ₐ in N(7) allyl	=CH₂ in C(8) allyl	=CH₂ᵦ in N(7) allyl	=CH in N(7)	=CH in C(8)	H-2
C(8)CH₂				X			X	
NCH₂		X	X		X	X		
C-5								X
=CH₂ in N(7) allyl		X						
=CH₂ in C(8) allyl	X							
=CH in C(8)	X			X				
=CH in N(7)		X						
C-6								X
C-8	X	X		x			X	
C-4								X

3.2.6.2. Synthesis of 7,8-diallyl-6-chloro-7*H*-purine (105a), (*E*)-7-allyl-6-chloro-8-(prop-1-en-1-yl)-7*H*-purine (105b), and (*E*)-3-(7-allyl-6-chloro-7*H*-purin-8-yl)acrylaldehyde (105c).

Several attempts were done for C-8 allylation of 7-allyl-6-chloropurine **20** using allylmagnesium bromide at 0 °C but it was obvious that the target compound **105a** was not stable enough towards Grignard reagent which affected the introduced allyl group and caused the double bond migration.

In order to control this kind of rearrangement, the reaction temperature was decreased to -20 °C using (1:3 NaCl / ice) bath and the reaction was run for only 5 min. Definitely, the rate of the double bond migration was decreased significantly but not completely. After the oxidation of the crude product with MnO$_2$ to rearomatize the adduct formed by Grignard addition, a

mixture of three compounds were obtained in a ratio (**105a/105b/105c**) (72%:20%:8%) but could not be isolated in a pure form due the intimate proximity of their TLC R_f values in different eluent systems (Scheme 71).
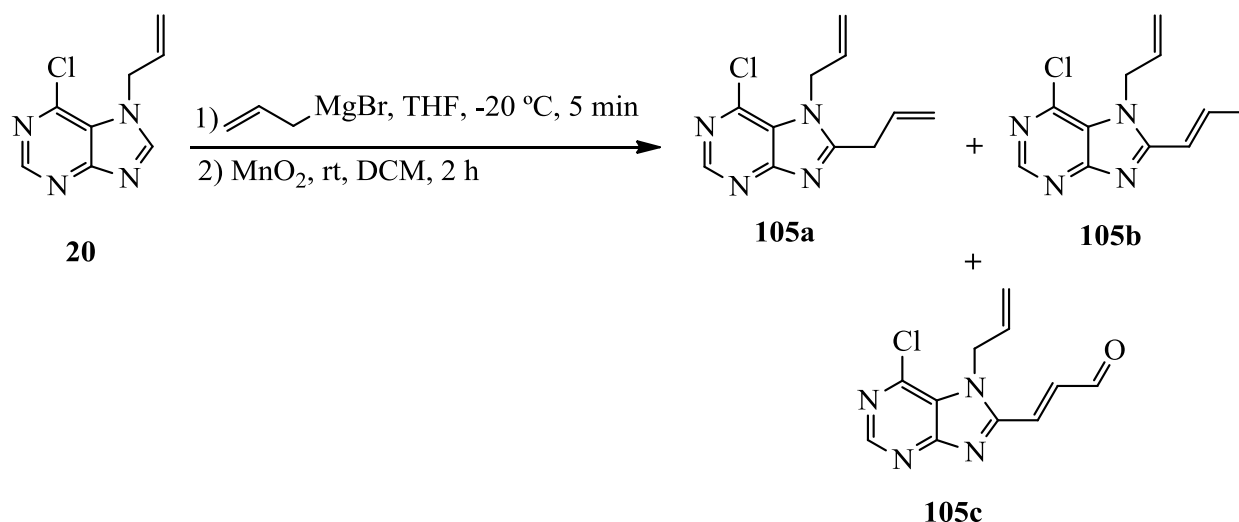
Scheme 71.

The possible reasons for aldehyde formation could be the oxidation of the terminal methyl group of C-8 propenyl in compound **105b** with MnO_2 to the aldehyde group, or the oxidation of the methyl group during the flash chromatography on the silica gel in the presence of the MnO_2.

It was reported in literature[104] that 3-formyl-2-methyl-substituted and 2-formyl-3-methyl-substituted indoles are oxidized to the dialdehyde upon treatment with MnO_2 which could explain the oxidative effect of MnO_2 on the terminal methyl group of compound **105b** in our case.

The desired diallylpurine **105a** could not be isolated in a pure form by flash chromatography, so we did not proceed with RCM reaction for this compound.

HMBC NMR spectrum for the diallylpurine **105a** refers to a long-range coupling of both NCH_2 and $C(8)CH_2$ with C-8 while exclusive coupling of NCH_2 with C-6 (Table 19).

Table 19. ^{1}H-^{13}C correlations from long range HMBC NMR spectrum for compound **105a.**

X = coupling between carbon and proton.

105a
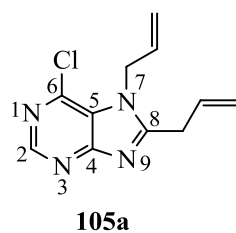
	C(8)CH$_2$	=CH$_{2a}$ in N(7)	N(7)CH$_2$	=CH$_2$ in C(8) allyl	=CH$_{2b}$ in N(7) allyl	CH= in N(7) allyl	CH= in C(8) allyl	H-2
C(8)CH$_2$				X			X	
N(7)CH$_2$		X			X	X		
=CH$_2$ in N(7) allyl			X					
=CH$_2$ in C(8) allyl	X							
C-6			X					X
CH= in C(8) allyl	X			X				
CH= in N(7) allyl		X	X		X			
C-4								X
C-8	X		X			X	X	
C-5								X

According to ^{1}H NMR, compound **105b** had a *trans*- propenyl group where its ^3J value = 15.2 while HMBC NMR indicated that the migration of the double bond had occurred in C-8 allyl group not N-7 allyl group where NCH$_2$ showed coupling with both of =CH2 and CH= in N-7 allyl group, besides C-6 exclusively, on the other hand, CH= in C-8 allyl group coupled with the terminal CH$_3$ and C-8 (Table 20).

Table 20. ^{1}H-^{13}C correlations from long range HMBC NMR spectrum for compound **105b.**

X = coupling between carbon and proton.
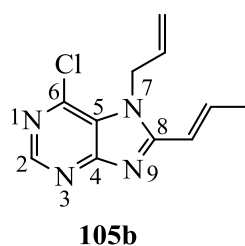
	CH$_3$ in C(8) propenyl	N(7)CH$_2$	=CH$_2$ in N(7) allyl	CH= in N(7) allyl	C(8)CH=	C(8)CH=C$\underline{H}$	H-2
CH$_3$ in C(8) propenyl					X	X	
N(7)CH$_2$				X			
C(8)CH=	X						
=CH$_2$ in N(7) allyl		X		X			
C-6		X					X
C(8)CH=C$\underline{H}$	X						
CH= in N(7) allyl		X	X				
C-8	X	X			X	X	
C-5				X			X

105b

Mass spectrometry (*ESI*) of the aldehyde **105c** gave for the calculated value of $C_{11}H_{11}N_4Cl$ [$M+H$]$^+$ 249.0465 and the found value was 249.0672 which indicates the formation of the aldehyde **105c.**

Furthermore, the propenyl aldehydic side chain of compound **105c** was the *trans-* isomer since its $^3J = 15.5$, according to ^{1}H NMR spectrum.

HMBC NMR confirmed the structure of compound **105c** where NCH$_2$ coupled with both CH= and =CH$_2$ in N-7 allyl group, while C(8)CH= had correlations with both C(8)CH=C$\underline{H}$ and CHO, on the other hand CHO coupled with C(8)CH=C$\underline{H}$ (Table 21).

Table 21. ^{1}H-^{13}C correlations from long range HMBC NMR spectrum for compound **105c.**

X = coupling between carbon and proton.
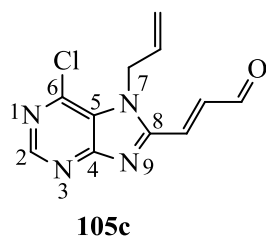
	N(7)CH$_2$	=CH$_2$ in N(7) allyl	CH= in N(7) allyl	C(8)CH=C$\underline{H}$	C(8)C$\underline{H}$=	H-2	CHO
N(7)CH$_2$		X	X				
=CH$_2$ in N(7) allyl	X						
CH= in N(7) allyl	X	X					
C(8)CH=C$\underline{H}$					X		X
C-8	X	X		X	X		
C-5	X	X				X	
CHO				X	X		

105c

3.2.6.3 Synthesis of 8-allyl-6-chloro-7-methyl-7*H*-purine (106a), (*E*)-6-chloro-7-methyl-8-(prop-1-en-1-yl)-7*H*-purine (106b), and (*E*)-3-(6-chloro-7-methyl-7*H*-purin-8-yl)acrylaldehyde (106c).

Besides the NMR structures elucidations that were done for the compounds of the previous reaction (Scheme 71), we wanted to make sure which allyl group (N-7 allyl or the introduced N-8 allyl) had undergone a double bond migration, and on the other hand, to reveal if the N-7 allyl was playing a role in driving the double bond migration (Scheme 71).

Thus, the same procedure in the previous reaction (Scheme 71) was used for C-8 allylation of compound **18** by allylmagnesium bromide at -20 °C for 20 min. There was still a ratio of the double bond rearrangement. The crude product was treated with MnO$_2$ to oxidize the formed adduct affording a mixture of three compounds (**106a/106b/106c**) (72:20:8) (Scheme 72).
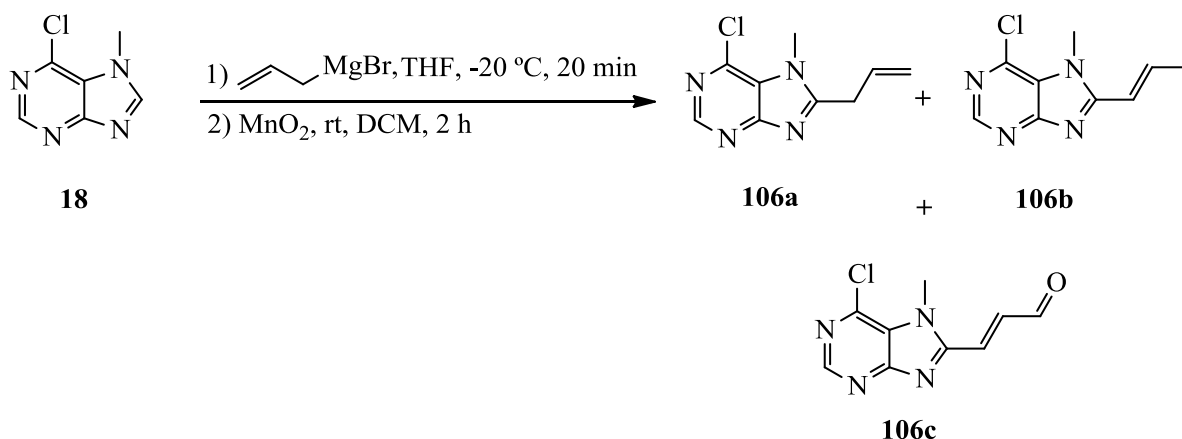
Scheme 72.

This reaction indicates that, in the previous case (Scheme 71), the double bond migration happened in the newly introduced C-8 allyl group, on the other hand, the N-7 allyl was not related directly to the double migration but definitely it has increased the instability of the molecule, thus reaction time was decreased to 5 min in the previous case compared to 20 min in this case.

Structure confirmation for the major compound **106a** by the HMBC NMR indicates to long range coupling of $=CH_2$ in C-8 allyl with $C(8)CH_2$ and $=CH$ in the allyl group, while NCH_3 correlates exclusively with C-6 (Table 22).

Table 22. ^1H-^{13}C correlations from long range HMBC NMR spectrum for compound **106a**.

X = strong coupling between carbon and proton.

x = weak coupling between carbon and proton.

	$C(8)CH_2$	$N(7)CH_3$	$=CH_{2a}$ in C(8) allyl	$=CH_{2b}$ in C(8) allyl	CH= in C(8) allyl	H-2
$C(8)\underline{C}H_2$			X	X	X	
$=CH_2$ in C(8) allyl	X					
C-5		X				X
CH= in C(8) allyl	X		X			
C-6		x				X
C-8	X	X			X	
C-4						X

79

Compound **106b** was formed as the *trans-* isomer exclusively where the vicinal coupling constant (^3J) between the two protons of C(8)CH=CH equaled 15.5, according to ^{1}H NMR spectrum.

Long-range HMBC NMR spectrum of compound **106b** refers to correlations of NCH$_3$ with C-5, C(8)CH=C$\underline{H}$ with C-8, besides coupling of the terminal CH$_3$ in the propenyl group with both C(8)CH=C$\underline{H}$ and C(8)CH (Table 23).

Table 23. ^{1}H-^{13}C correlations from long range HMBC NMR spectrum for compound **106b.** X = coupling between carbon and proton.
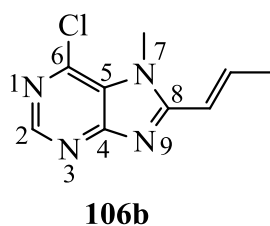
	CH$_3$ in C(8) propenyl	N(7)CH$_3$	C(8)CH=	C(8)CH=C$\underline{H}$	H-2
CH$_3$ in C(8) propenyl			X	X	
C(8)$\underline{C}$H=	X				
C-5		X			
C-6					X
C(8)CH=$\underline{C}$H	X				
C-8		X		X	
C-4					X

106b

Moreover, the aldehyde **106c** was formed probably because the oxidation of the terminal methyl group for compound **106b** by MnO$_2$ to the aldehyde group.

Mass spectrometry (*ESI*) of the aldehyde **106c** gave for the calculated value of C$_9$H$_7$N$_4$OCl $[M+H]^+$ 223.0308 and the found value was 223.0412 which indicates the formation of the aldehyde **106c.**

Compound **106c** formed had *trans-* configuration, according to the ^{1}H NMR, with 15.5 ^3J value between the both protons of C(8)CH=CH.

According to HMBC NMR spectrum of compound **106c**, the proton of the aldehyde group couples with C(8)CH=C$\underline{\text{H}}$ and on the other hand, C(8)C$\underline{\text{H}}$ couples with CHO which indicates to the correct compound (Table 24).

Table 24. ^{1}H-^{13}C correlations from long range HMBC NMR spectrum for compound **106c.**
X = coupling between carbon and proton.

106c
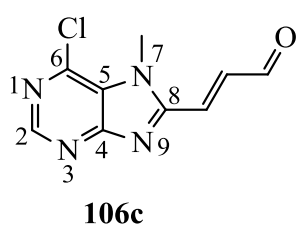
	N(7)CH$_3$	C(8)CH=C$\underline{\text{H}}$	C(8)CH=	H-2	CHO
C-5	X				
C(8)C$\underline{\text{H}}$=		X			
C(8)CH=C$\underline{\text{H}}$			X		X
C-6				X	
C-8	X	X	X		
C-4			X	X	
CHO			X		

3.3 Ring closing metathesis and aromatization of the ring formed.

Attempts to cyclize the diallylpurine derivatives **71** and **100a** were done using Grubbs' 2nd generation catalyst followed by rearomatization of the cyclized compounds by DDQ as an oxidizing agent to obtain the pyrido[1,2-*e*]purine derivatives.

3.3.1 Ring closing metathesis reactions

3.3.1.1 Synthesis of 4-(piperidin-1-yl)-6,9-dihydropyrido[1,2-*e*]purine (74).

Following a literature procedure,[23] ring closing metathesis was applied on 8,9-diallyl-6-(piperidin-1-yl)-9*H*-purine **71** using 19% Grubbs 2nd generation catalyst **69** (Figure 13) (four portions each after 2 h) in DCM for 48 h at room temperature (Scheme 73). Product **74** was

purified by flash chromatography to give 94% yield, slightly less than what is reported in literature (97%).[23]

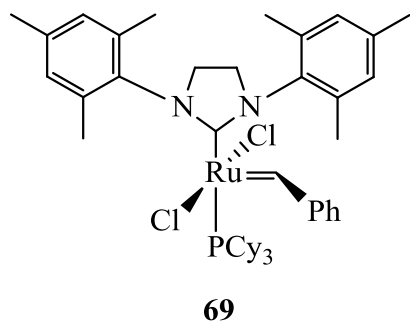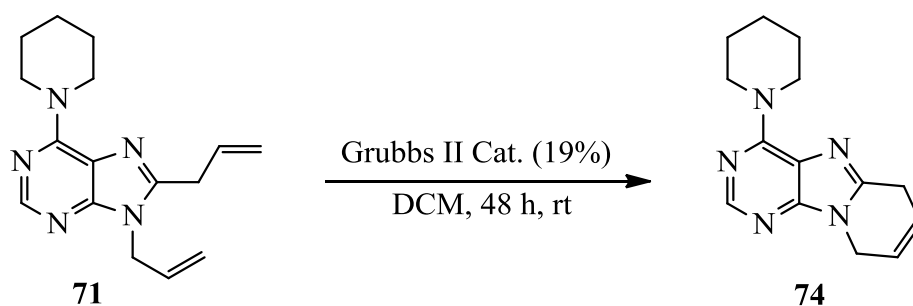**Figure 13.** Grubbs' 2nd generation catalyst.

Scheme 73.

Attempts were done to reduce the catalyst loading and run the reaction in refluxing DCE instead of DCM at room temperature to enhance the reaction by heating. 5% of catalyst for 48 h. led to a moderate yield, while 10% catalyst gave a fairly good yield. A comparison between the three methods that were used is summarized in Table 25.

Table 25. RCM of 8,9-diallyl-6-(piperidin-1-yl)-9*H*-purine **71.**

Conditions	Conversion[a] (%)	Yield[b] (%)
Grubbs II (19%),[c] DCM, rt, 48 h	>99	94[d]
Grubbs II (10%), DCE, △, 48 h	74	71
Grubbs II (5%), DCE, △, 48 h	44	40

(a) From the ^{1}H NMR spectra of the crude products.
(b) Yield of isolated compound.
(c) According to Ref. 23, the catalyst was added in four portions each after 2 h.
(d) Lit.[23] yield is 97%.

3.3.1.2 Synthesis of 4-chloro-6,9-dihydropyrido[1,2-*e*]purine (107).

When the literature procedure for RCM[23] was applied on the 6-chloropurine **100a** by Grubbs' 2nd generation catalyst **69** (added in four portions each after 2 h) in DCM for 48 h at room temperature, the conversion was incomplete (77%) and the obtained yield for the isolated cyclized compound **107** was 74%.

It was obvious that these conditions are not optimal for this substrate and 6-chloropurine **100a** is less reactive towards RCM at room temperature than piperidine derivative **71**. Thus, the reaction conditions were changed to refluxing DCE which has a higher boiling point than DCM. That led to a complete conversion only after 6 h affording an excellent yield (98%). Furthermore, the catalyst loading was decreased in several attempts; a complete conversion was obtained for at least 8% catalyst added in one portion (Scheme 74 and Table 26).
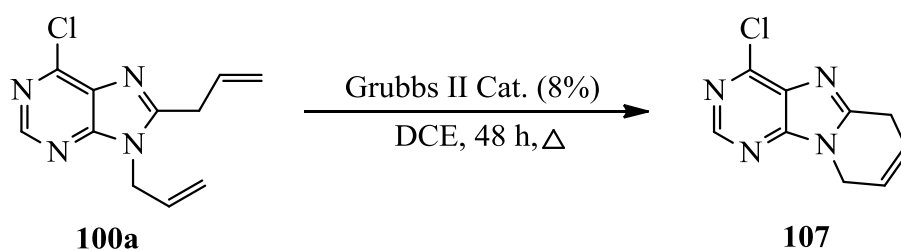

100a → **107**

Grubbs II Cat. (8%)
DCE, 48 h, △

Scheme 74.

Table 26. RCM optimization of compound **100a**.

Conditions	Conversion[a] (%)	Yield[b] (%)
Grubbs II (19%),[c] DCM, rt, 48 h	77	74
Grubbs II (19%),[d] DCE, △, 6 h	>99	98
Grubbs II (10%), DCE, △, 24 h	>99	95
Grubbs II (8%), DCE, △, 48 h	>99	97
Grubbs II (5%), DCE, △, 48 h	91	88

(a) From the ^{1}H NMR spectra of the crude products.
(b) Yield of isolated compound.
(c) The catalyst was added in four portions each after 2 h.
(d) The catalyst was added in four portions each after 1 h.

Table 27. [1]H-^{13}C correlations from long range HMBC NMR spectrum for compound **107.**

X = coupling between carbon and proton.

x = weak coupling between carbon and proton.

107
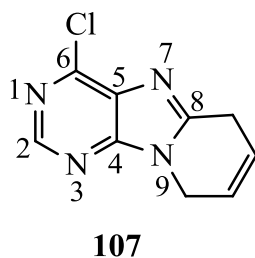
	C(8) CH$_2$	N(9)CH$_2$	CH=CH	H-2
C(8)CH$_2$		X	X	
N(9)CH$_2$	X		X	
=CH [C(8)]	X	X		
=CH [N(9)]	X	X		
C-5	X			X
C-6	x			X
C-4		X	X	X
C-8	X	X	X	

According to the HMBC NMR spectrum for compound **107**, diagnostic long-range couplings were observed for C(8)CH$_2$ with C-5 and weak coupling with C-6, besides coupling of N(9)CH$_2$ with C-4 which indicates to the correct compound **107** (Table 27).
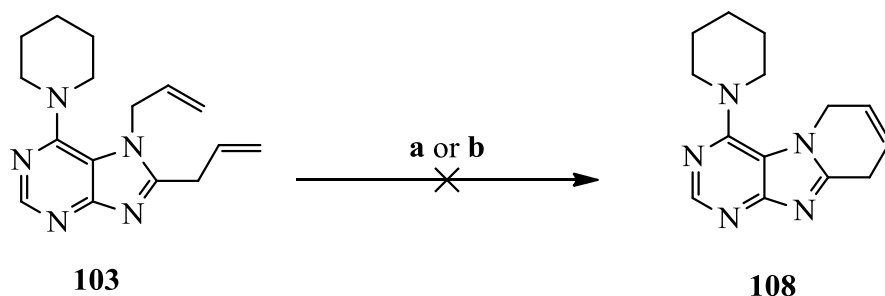
### 3.3.1.3 Attepmpts to cyclize 7,8-diallyl-6-(piperidin-1-yl)-7*H*-purine (103)

Attempts to cyclize the 7,8-diallyl compound **103** following the previous successful procedures for the corresponding 8,9-diallyl via Grubbs' 2nd generation catalyst failed (Scheme 75).

Scheme 75. Reagents and conditions: (**a**) Grubbs' II cat. (19%), DCM, rt, 48 h; (**b**) Grubbs' II cat. (14%), DCE, Δ, 48 h.

The reaction was tried in both DCM at room temperature and in refluxing DCE for 48h. In both cases the reaction did not proceed as it was expected. The crude product was attempted to be purified by flash chromatography. According to ^{1}H NMR of the resulted product, the starting material had been consumed but with no indication to the desired product **108**.

It is not understood exactly what happened for the starting material **103** but it was reported in literature[114] that a ruthenium catalyst (not RCM catalyst used in our case) could drive the double bond migration for both N-9 allyl and N-7 allyl of purines (Scheme 76). Thus, might be the starting material **103** had decomposed under the effect of the ruthenium catalyst which induced the double bond migration.
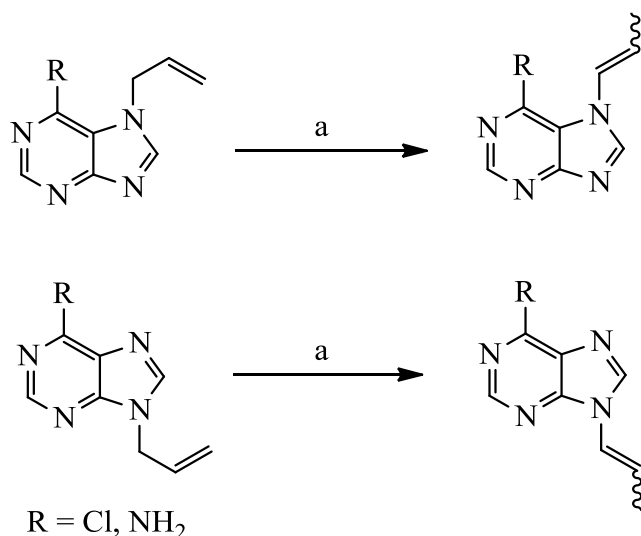
Scheme 76. Reagents and conditions: (**a**) Cat. RuClH(CO)(PPh$_3$)$_3$, xylenes, Δ.[114]

Moreover, we could realize from the Grignard additions done on 7-allylated purines that the formed 7,8-diallyl products are unstable in the presence of base and undergo double bond migration easily.

3.3.2 Oxidation of RCM products

3.3.2.1 Synthesis of 4-(piperidin-1-yl)pyrido[1,2-*e*]purine (7).

Compound **74** was oxidized by DDQ (2 equivs.) in DCM at room temperature to get a complete conversion, according to the crude product ^{1}H NMR and TLC, after 24 h. The product was purified by flash chromatography to afford the cytotoxic pyrido[1,2-*e*]purine **7**[1] in 87% yield (Scheme 77).
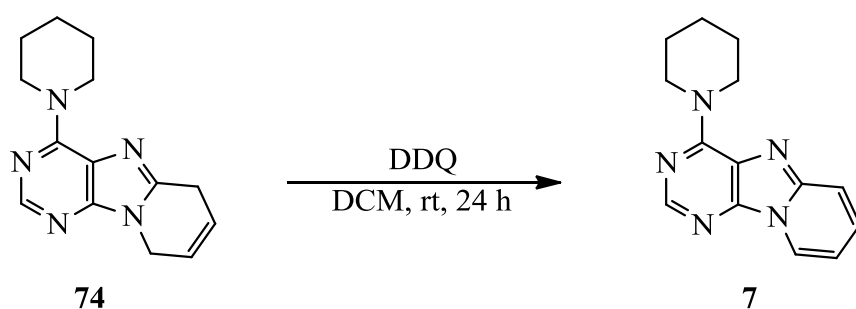
Scheme 77.

3.2.2.2 Synthesis of 4-chloropyrido[1,2-*e*]purine (9).

In contrast to piperidine **74**, DDQ-mediated oxidation of chloride-containing compound **107** in DCM at room temperature for 24 h did not lead to any conversion at all. Carrying out the reaction in refluxing DCE led to a complete conversion, according to the crude product ^{1}H NMR and TLC, after only 6 h. The product was purified by flash chromatography to afford 91% yield (Scheme 78).
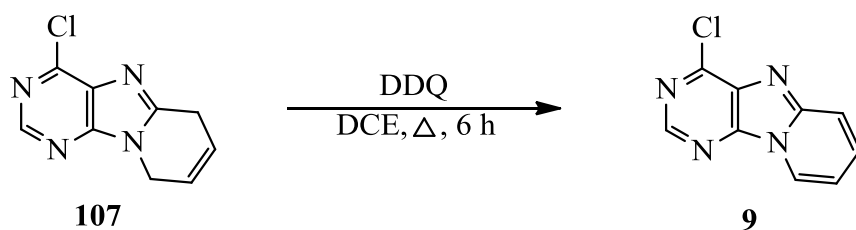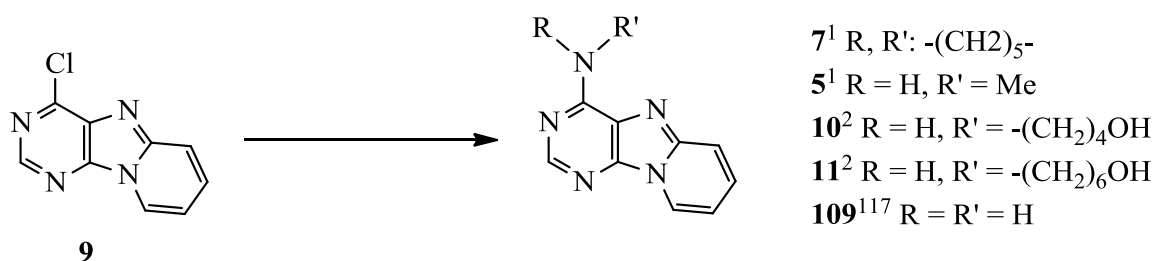

Scheme 78.

Oxidation of chloride-containing compound **107** proved that this substrate is less reactive in room temperature but remarkably affected by heating to give the desired product in shorter time compared to piperidine compound **74**.

The significance of this adopted synthetic route towards compound **9** starting with N-9 allylation, C-8 allylation, RCM, and finally the oxidation are, first, the high yields afforded, second, the pyrido[1,2-*e*]purines which has been studied as DNA intercalating agents vary mostly by their 4-substituent. Thus, the 4-substituent can be introduced in the last step.

Compound **9** was converted previously into DNA intercalators such as piperidine **7**[1] and other amines (Scheme 79).

7[1] R, R': -(CH2)$_5$-
5[1] R = H, R' = Me
10[2] R = H, R' = -(CH$_2$)$_4$OH
11[2] R = H, R' = -(CH$_2$)$_6$OH
109[117] R = R' = H

Scheme 79. Reagents and conditions: (References 1, 2, and 117).

4. CONCLUSION

In the synthesis towards 4-substituted pyrido[1,2-*e*]purines, the original route involving C-8 bromination of purine followed by N-allylation have shown to be inefficient route due to the low yield obtained for the desired N-9 allylated isomer.

On the other hand, the alternative route involving N-allylation of purine followed by C-8 functionalization has proved to be efficient way with some modifications. The major product of N-allylation was the desired N-9 allyl isomer.

In order to introduce the allyl group onto C-8 position, lithiation followed by chlorination was done. Unfortunately, LDA influenced the N-9 allyl group resulting in rearrangement of the double bond and consequently low yielding of the desired compound.

Attempting to employ organometallic reagent, to directly allylate C-8 position was a real improvement. It has proved to be an efficient and high yielding method to synthesize 8,9-diallylpurines which are key compounds for further syntheses of cytotoxic pyrido[1,2-*e*]purines.

Organometallic additions to synthesize 7,8-diallylpurines have shown to be inconvenient due to the double bond migration happened in the introduced allyl group in position-8.

Ring closing metathesis of 6-piperidinyl-8,9-diallylpurine was done at room temperature followed by oxidation with DDQ.

On the other hand, ring closing metathesis of 6-chloro-8,9-diallylpurine has proved to be more efficient at DCE refluxing temperature more than the room temperature. The RCM product was rearomatized by DDQ in a convenient way.

5. EXPERIMENTAL

The ^{1}H NMR spectra were acquired on a 400 MHz on a Bruker AVII 400 instrument or at 200 MHz on a Bruker Avance DPX 200 instrument and the ^{1}H decoupled. ^{13}C NMR spectra were recorded at 100 MHz using the Bruker AVII 400 spectrometer. Assignments of ^{1}H and ^{13}C resonances were based on HMBC and HSQC NMR. 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.). Electrospray MS spectra were recorded with a Bruker Apex 47e FT-ICR mass spectrometer. Dry THF and DCM were obtained from a solvent purification system, MB SPS-800 from MBraun, Garching, Germany. Melting points were determined on a Büchi Melting Point B-545 apparatus and are uncorrected.

Diisopropyl amine was distilled from calcium hydride and stored under N_2 over dry molecular sieves. *n*-BuLi was titrated against diphenylacetic acid and dry THF was used as a solvent.[118]
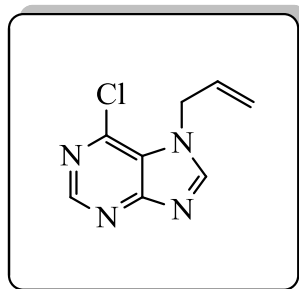
Allylmagnesium bromide was titrated against menthol as anhydrous protic reagent in the presence of 1,10-phenanthroline as a colour-indicator and dry THF was used as a solvent.[119]

All other reagents were commercially available and used as received.

9-Allyl-6-chloro-9*H*-purine (19) and 7-allyl-6-chloro-7*H*-purine (20)
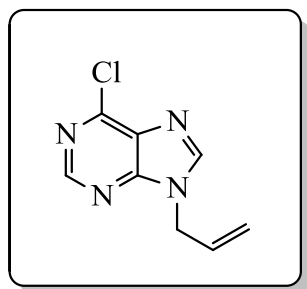
19

20

Potassium carbonate (4.15 g, 30.0 mmol) was added to a stirred solution of 6-chloropurine **16** (1.58 g, 10.2 mmol) in dry DMF (40 mL) at ambient temperature under N_2. After 20 min., allyl bromide (1.70 mL, 19.7 mmol) was added and the resulting mixture was stirred for 20 h, filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting first with 0.5 % MeOH in DCM followed by 1 % MeOH in DCM. This gave 1.24 g (62%) of 9-allyl-6-chloro-9*H*-purine **19** as a colourless solid and 430 mg (21%) of 7-allyl-6-chloro-9*H*-purine **20** as a yellow solid.
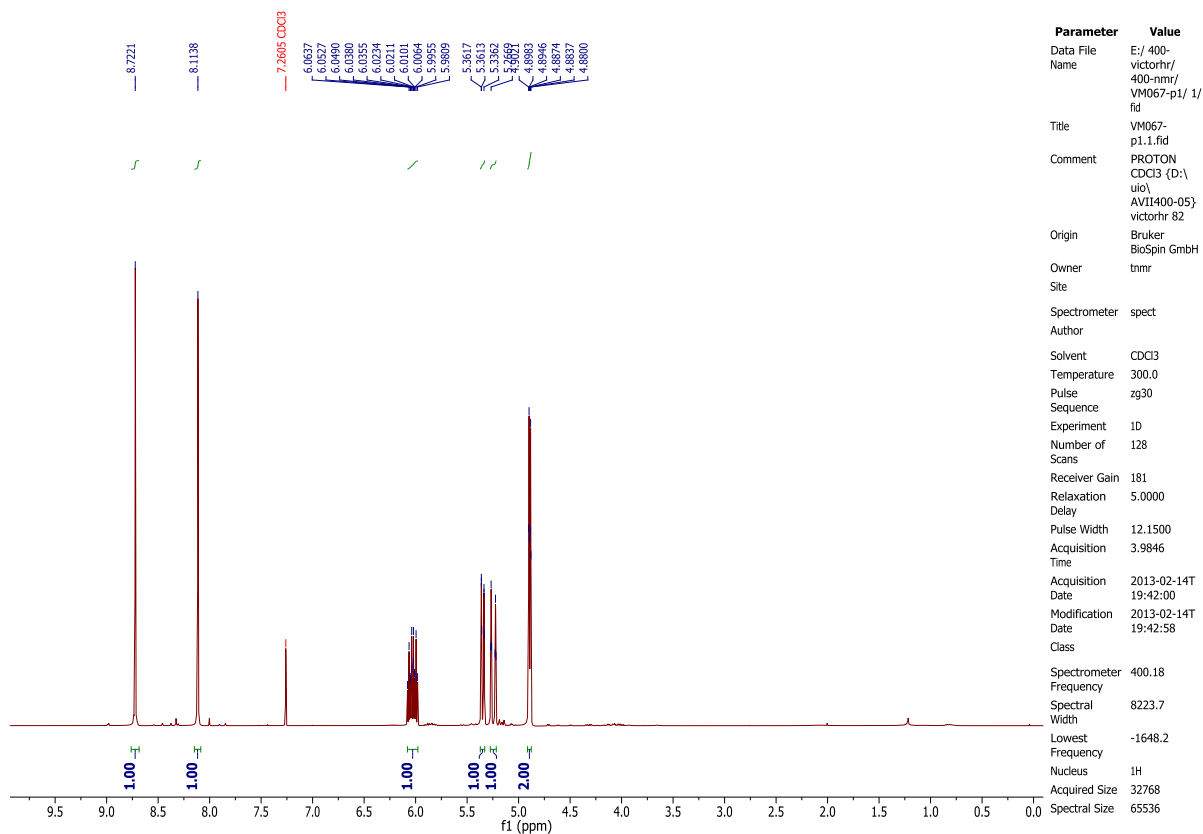
9-Allyl-6-chloro-9*H*-purine (**19**)

^{1}H NMR (CDCl$_3$, 400 MHz) δ 4.89 (dt, *J* = 5.7, 1.6 Hz, 2H, CH$_2$), 5.25 (dt, *J* = 17.0, 1.6 Hz, 1H, =CH$_{2a}$), 5.35 (dt, *J* = 10.2, 1.6 Hz, 1H, =CH$_{2b}$), 5.98-6.09 (m, 1H, =CH), 8.12 (s, 1H, H-8), 8.74 (s, 1H, H-2).

^{13}C NMR (CDCl$_3$, 400 MHz) δ 46.3 (CH$_2$), 120.0 (=CH$_2$), 130.9 (=CH), 131.6 (C-5), 144.9 (C-8), 151.1 (C-4), 151.7 (C-6), 152.1 (C-2).
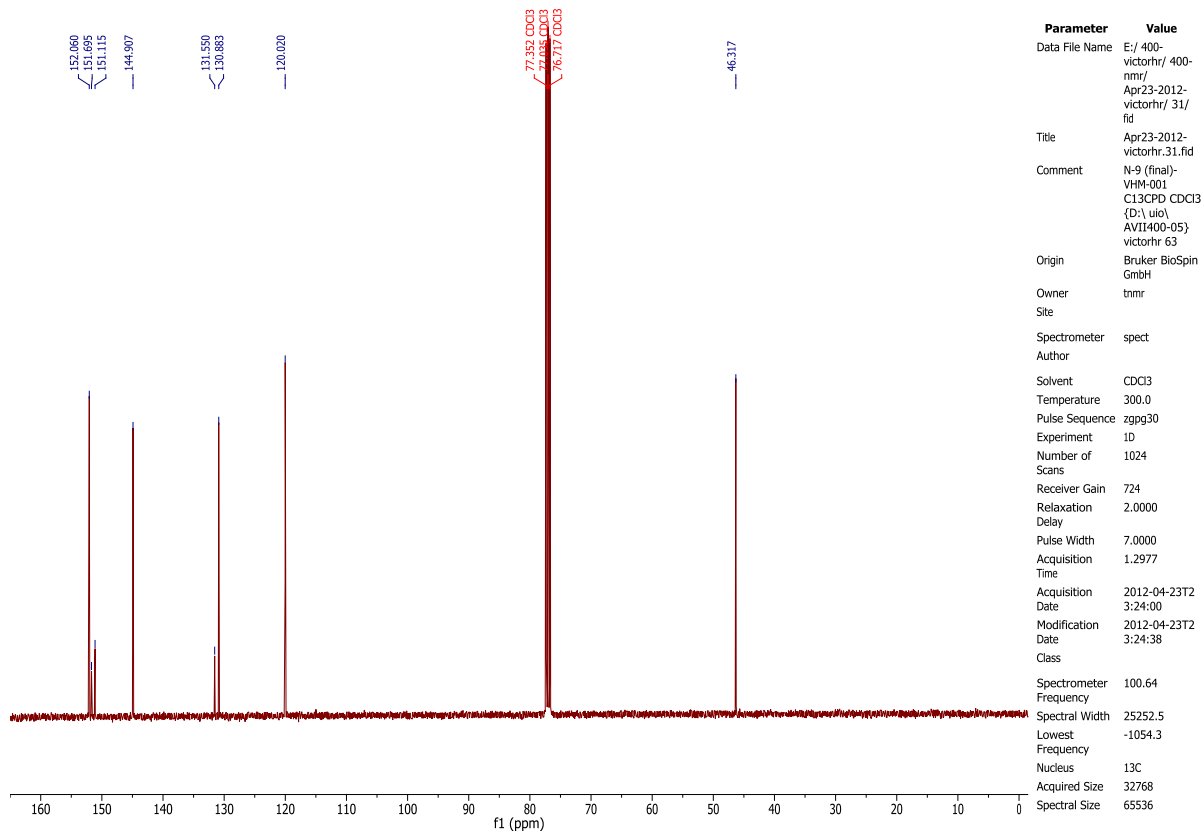
MS (EI). *m/z* (rel. %): 196/194 (28/87, *M*$^+$), 193 (100), 169 (8), 167 (27), 154 (12), 132 (10), 119 (6), 77 (6).

HR-MS. Found 194.0355 calculated for C$_8$H$_7$N$_4$Cl 194.0359.

M.p. 76-78 °C (Lit.[22] 79.6-80.1 °C)

Spectrum 1. ^{1}H NMR of 9-allyl-6-chloro-9*H*-purine (**19**).

Spectrum 2. ^{13}C NMR of 9-allyl-6-chloro-9*H*-purine (**19**).

7-Allyl-6-chloro-9*H*-purine (**20**)

1H NMR (CDCl3, 400 MHz) δ 5.08-5.17 (m, 3H, CH_2 and $=CH_{2a}$), 5.37 (d, *J*=10.2 Hz, 1H, $=CH_{2b}$), 6.01-6.15 (m, 1H, =CH), 8.22 (s, 1H, H-8), 8.87 (s, 1H, H-2).

13C NMR (CDCl3, 100 MHz) δ 49.2 (CH_2), 119.5 ($=CH_2$), 122.4 (C-5), 131.7 (=CH), 143.0 (C-6), 148.8 (C-8), 152.5 (C-2), 161.9 (C-4).

MS (EI). *m/z* (rel. %): 196/194 (35/100, M^+), 167 (10), 159 (8), 132 (19), 105 (6), 77 (5).

HR-MS: Found 194.0364 calculated for $C_8H_7N_4Cl$ 194.0359.

M.p. 89-91 °C (Lit.[22] 92.8-93 °C)
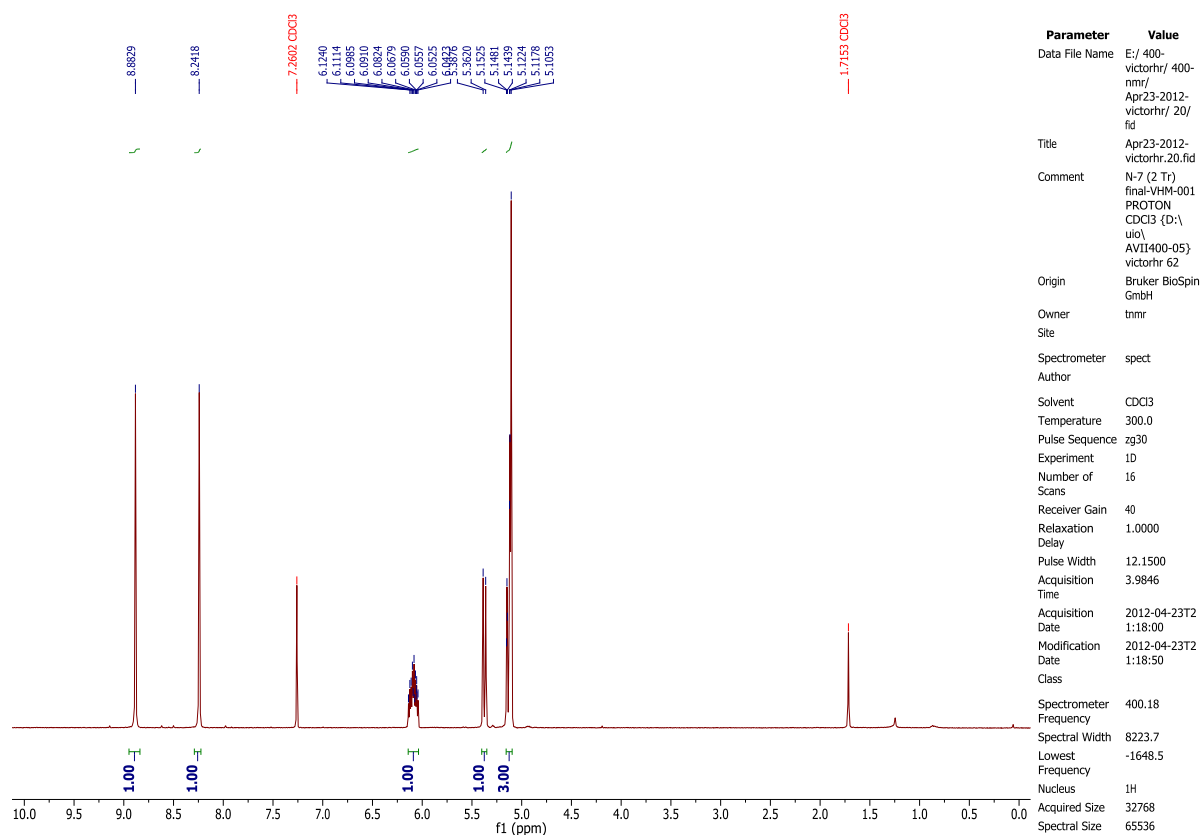
Spectrum 3. ^{1}H NMR of 7-allyl-6-chloro-9*H*-purine (**20**).

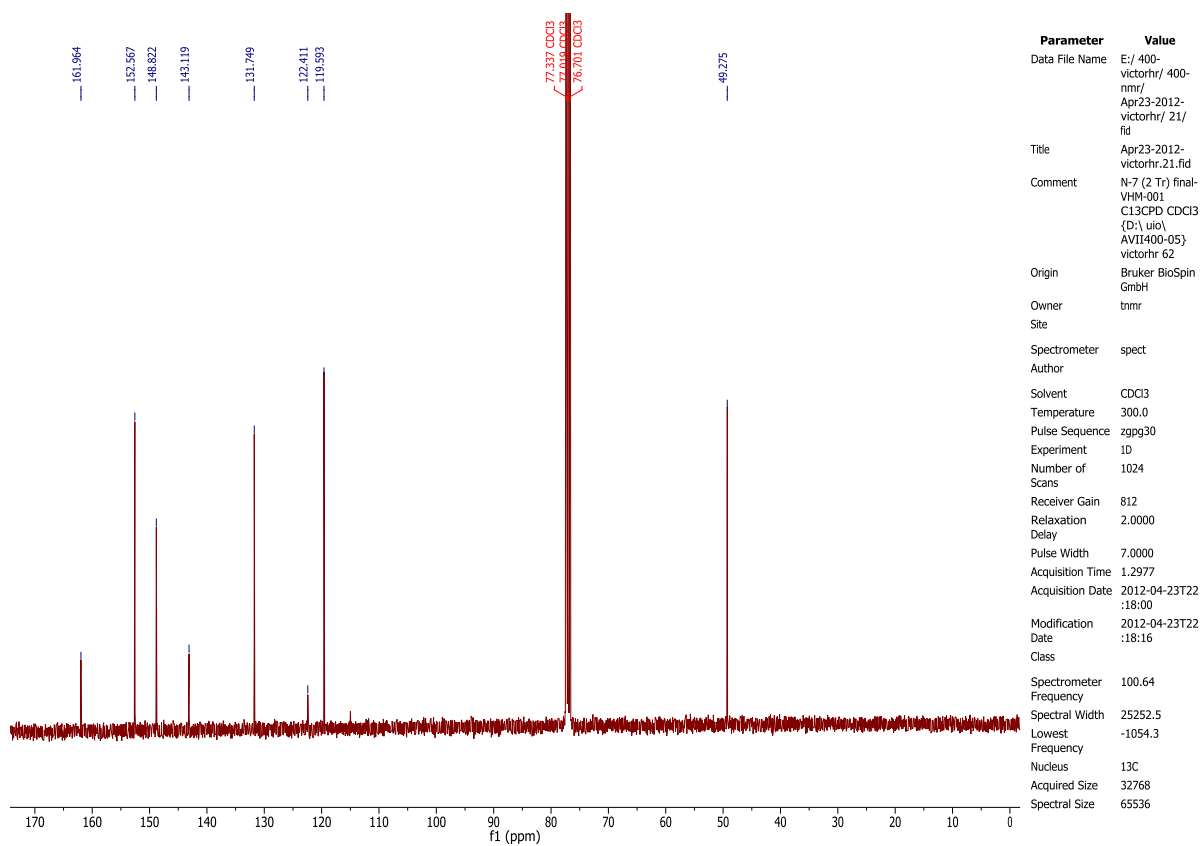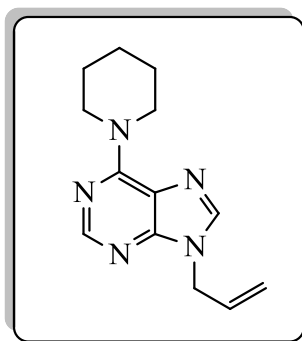**Spectrum 4.** ^{13}C NMR of 7-allyl-6-chloro-9*H*-purine (**20**).

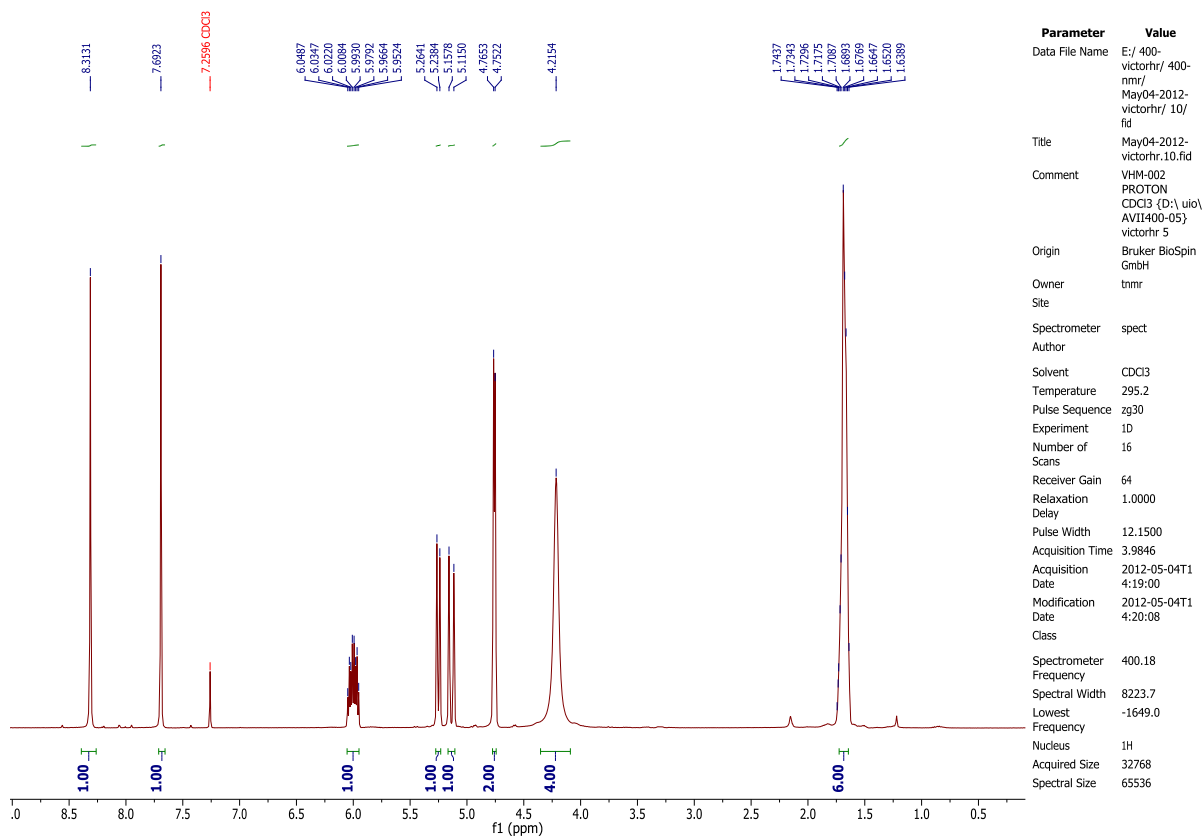**9-Allyl-6-(piperidin-1-yl)-9*H*-purine (33)**

33

A mixture of compound **19** (864 mg, 4.44 mmol) and piperidine (0.88 mL, 8.913 mmol) in H_2O (8 mL) was refluxed for 24 h. After cooling, the mixture was extracted with DCM (2 x 20 mL) and the organic layer was washed with H_2O (2 x 20 mL), dried with $MgSO_4$ and evaporated *in vacuo.* to give 1.023 g (95%) 9-allyl-6-(piperidin-1-yl)-9*H*-purine **33** as a colourless solid.

¹H NMR (CDCl₃, 400 MHz) δ 1.60-1.77 (m, 6H, 3 x CH_2 in piperidinyl), 4.21 (brs, 4H, 2 x CH_2 in piperidinyl), 4.76 (d, *J* = 5.6, 2H, CH_2 in allyl), 5.14 (d, *J* = 17.1 Hz, 1H, =CH_{2a}), 5.25 (d, *J* = 10.2 Hz, 1H, =CH_{2b}), 5.98-6.07 (m, 1H, =CH), 7.71 (s, 1H, H-2), 8.34 (s, 1H, H-8).

¹³C NMR (CDCl₃, 100 MHz) δ 24.8 (CH_2 in piperidinyl), 26.0 (2 x CH_2 in piperidinyl), 45.5 (CH_2 in allyl), 46.3 (2 x CH_2 in piperidinyl), 118.5 (=CH_2), 119.7 (=CH), 132.1 (C-8), 137.7 (C-4), 150.8 (C-2), 152.6 (C-6), 153.9 (C-5).

MS (EI). *m/z* (rel. %): 244/243 (20/100, M^+), 228 (11), 214 (51), 202 (27), 187 (24), 174 (22), 160 (19), 147 (8), 132 (6), 119 (10), 84 (11).

M.p. 80-82 $^{\circ}$C (Lit.[34] 54-56 $^{\circ}$C).

Spectrum 5. ^{1}H NMR of 9-allyl-6-(piperidin-1-yl)-9*H*-purine (**33**).
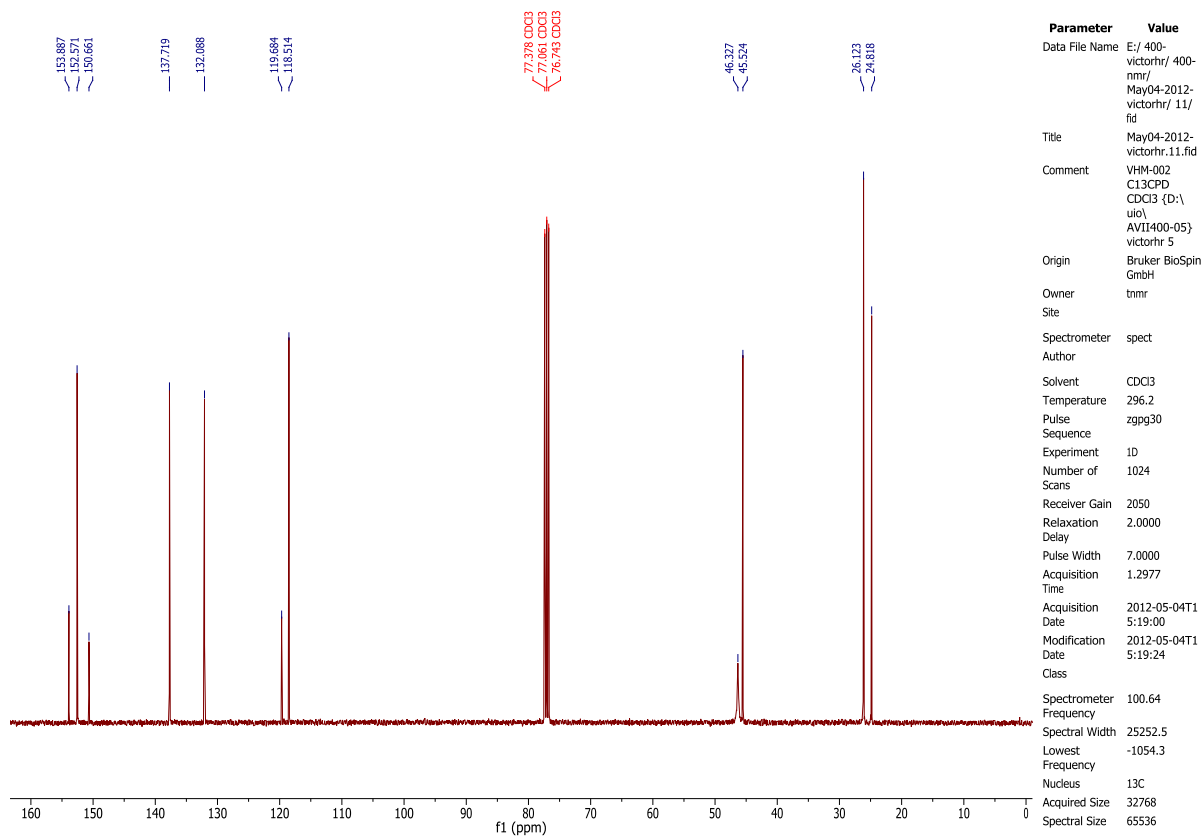
Spectrum 6. ^{13}C NMR of 9-allyl-6-(piperidin-1-yl)-9*H*-purine (**33**).
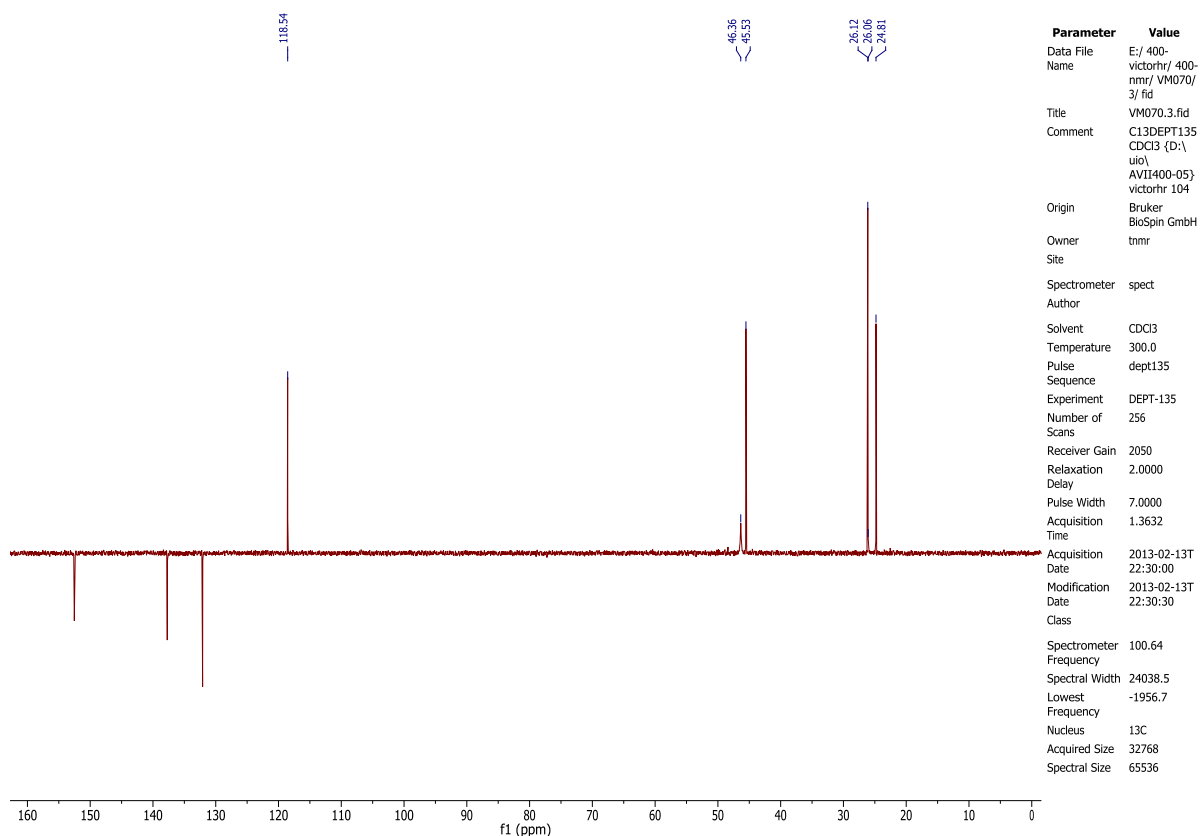
Spectrum 7. ^{13}C DEPT NMR of 9-allyl-6-(piperidin-1-yl)-9H-purine (**33**).
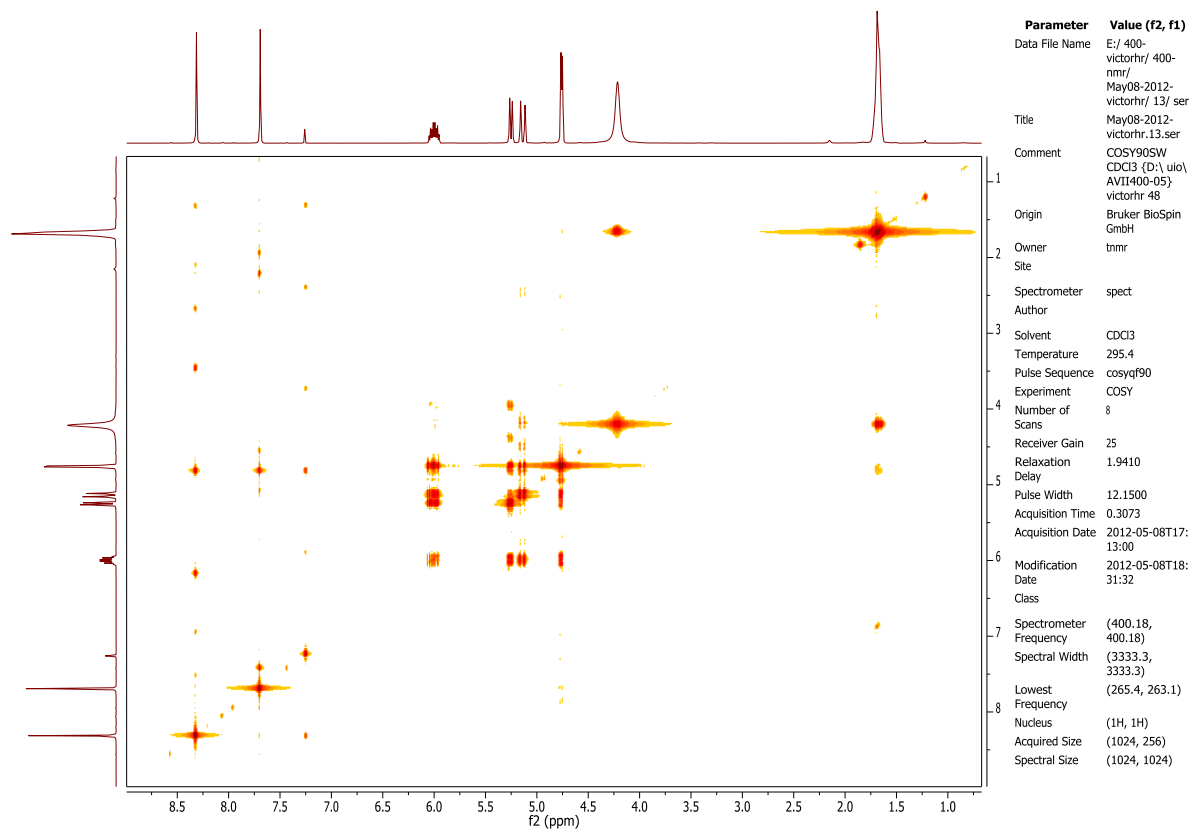
Spectrum 8. COSY NMR of 9-allyl-6-(piperidin-1-yl)-9H-purine (**33**).
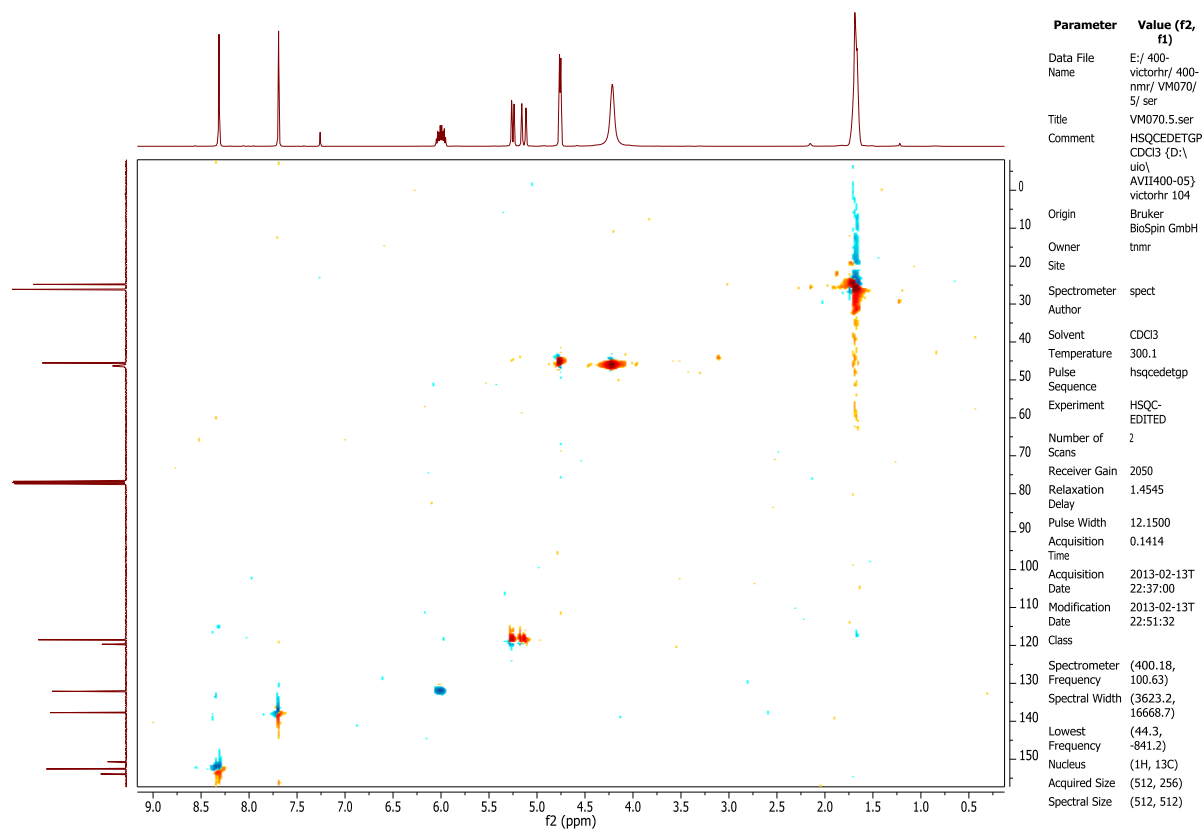
Spectrum 9. HSQC NMR of 9-allyl-6-(piperidin-1-yl)-9*H*-purine (**33**).
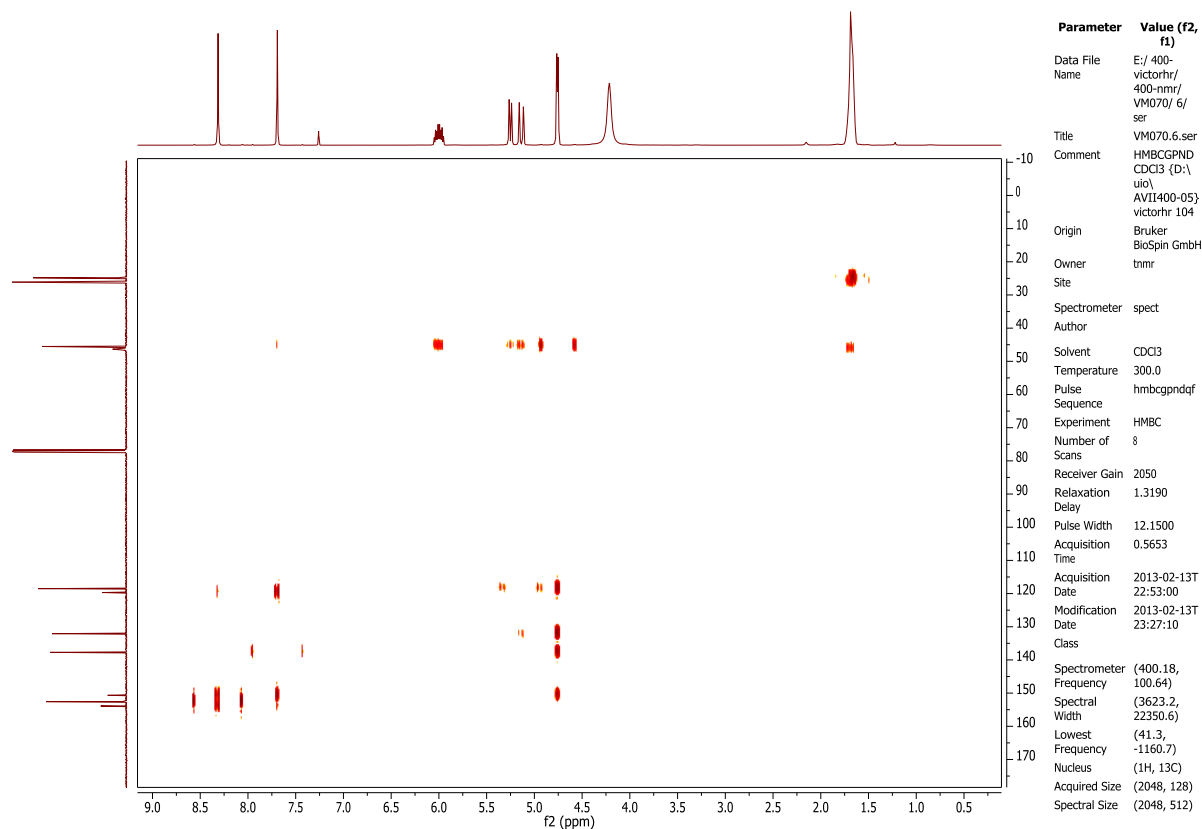
Spectrum 10. HMBC NMR of 9-allyl-6-(piperidin-1-yl)-9*H*-purine (**33**).

7-Allyl-6-(piperidin-1-yl)-7*H*-purine (95)
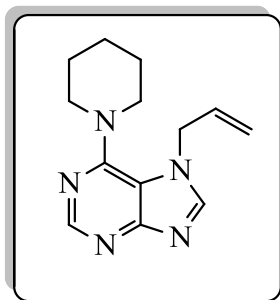
95

A mixture of compound **20** (410 mg, 2.10 mmol) and piperidine (0.42 mL, 4.20 mmol) in H$_2$O (5 mL) was refluxed for 24 h. After cooling, the mixture was extracted with DCM (2 x 15 mL) and the organic layer was washed with H$_2$O (2 x 15 mL), dried with MgSO$_4$ and evaporated *in vacuo.* to give 471 mg (92%) 7-allyl-6-(piperidin-1-yl)-9*H*-purine **95** as a colourless solid.

¹H NMR (CDCl$_3$, 400 MHz) δ 1.64-1.79 (m, 6H, 3 x CH$_2$ in piperidinyl), 3.28-3.37 (m, 4H, 2 x CH$_2$ in piperidinyl), 4.92 (d, *J* = 5.3 Hz, 2H, CH$_2$ in allyl), 5.23 (d, *J* = 17.2 Hz, 1H, =CH$_{2a}$), 5.35 (d, *J* = 10.3 Hz, 1H,=CH$_{2b}$), 5.98-6.05 (m, 1H, =CH), 8.04 (s, 1H, H-8), 8.67 (s, 1H, H-2).

¹³C NMR (CDCl$_3$, 100 MHz) δ 24.2 (CH$_2$ in piperidinyl), 25.5 (2 x CH$_2$ in piperidinyl), 48.5 (CH$_2$ in allyl), 51.2 (2 x NCH$_2$ in piperidinyl), 115.8 (C-5), 119.2 (=CH$_2$), 132.2 (=CH), 146.3 (C-8), 152.4 (C-2), 156.2 (C-6), 161.3 (C-4).

MS (EI). *m/z* (rel. %): 244/243 (22/93, *M*⁺), 228 (41), 214 (49), 159 (66), 84 (100).

HRMS. Found 243.1477 calculated for C$_{13}$H$_{17}$N$_5$ 243.1484.

M.p. 74-76 °C.
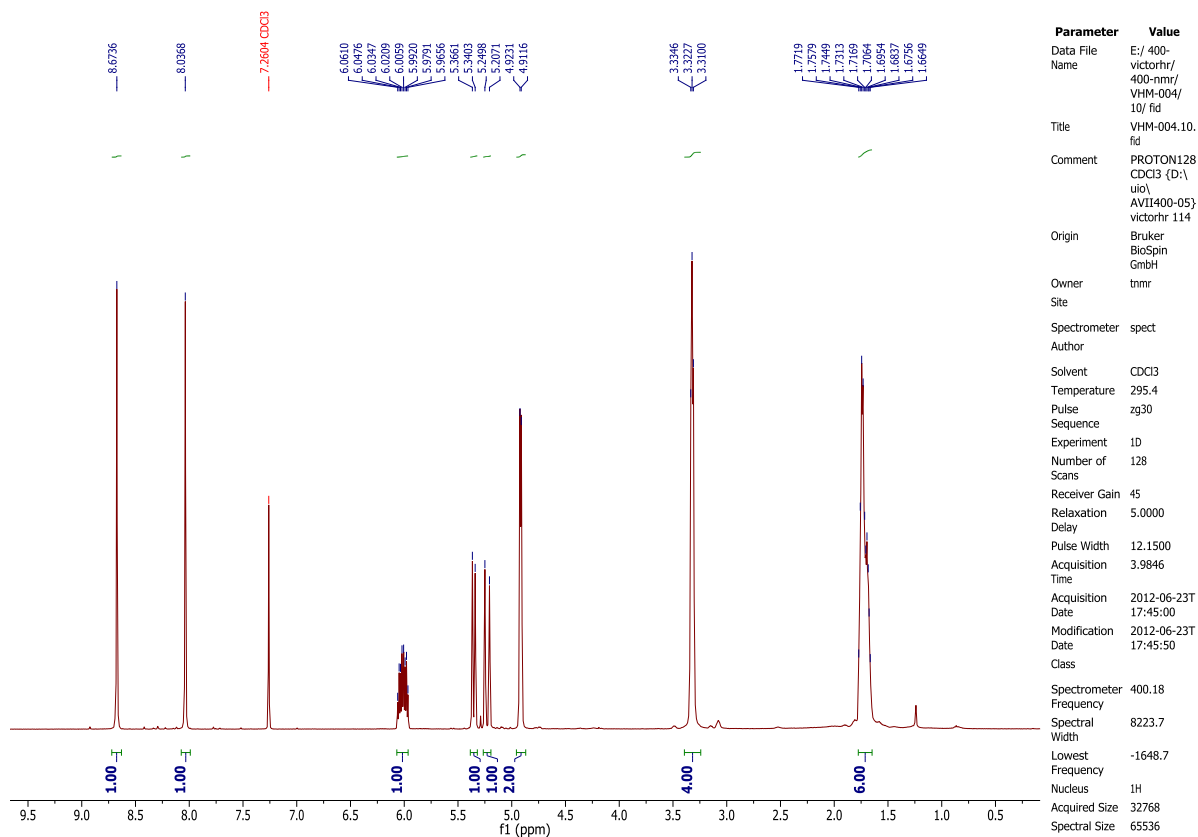
Spectrum 11. ^{1}H NMR of 7-allyl-6-(piperidin-1-yl)-7H-purine (**95**).
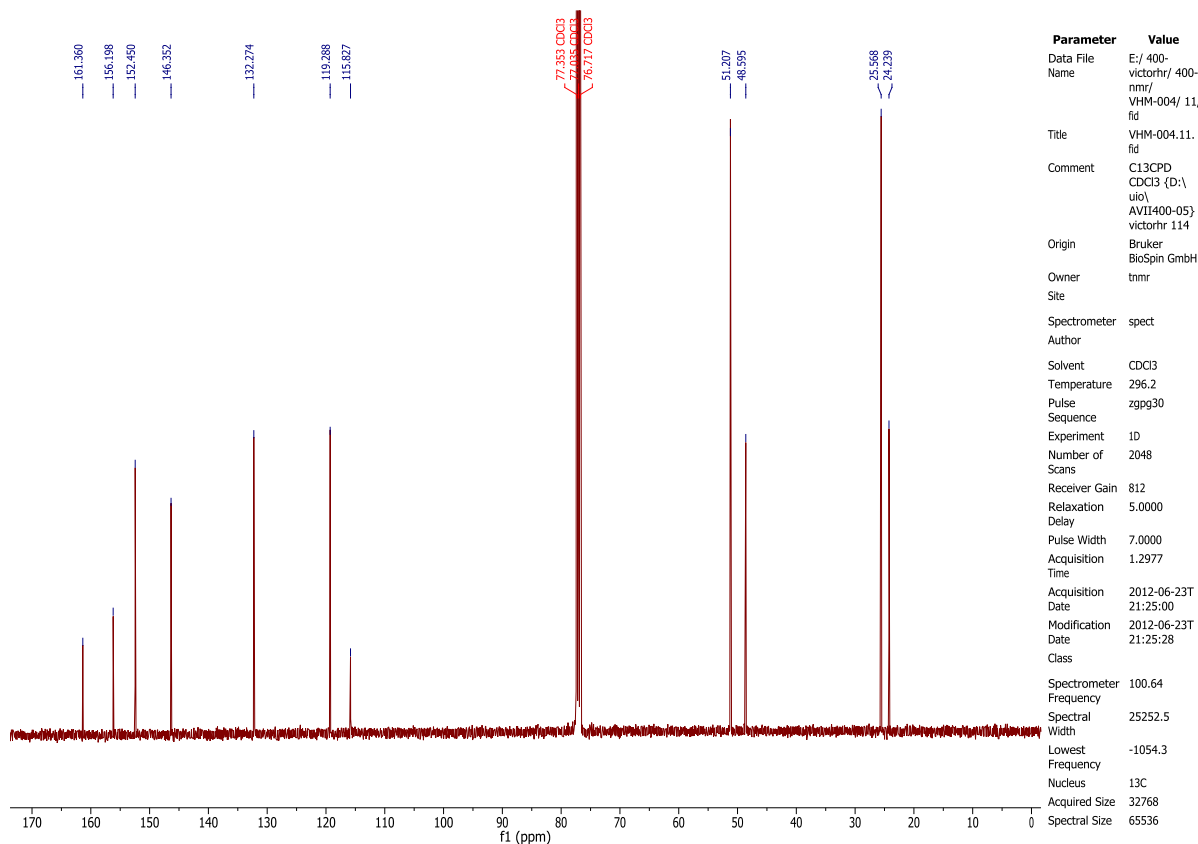
Spectrum 12. ^{13}C NMR of 7-allyl-6-(piperidin-1-yl)-7H-purine (**95**).
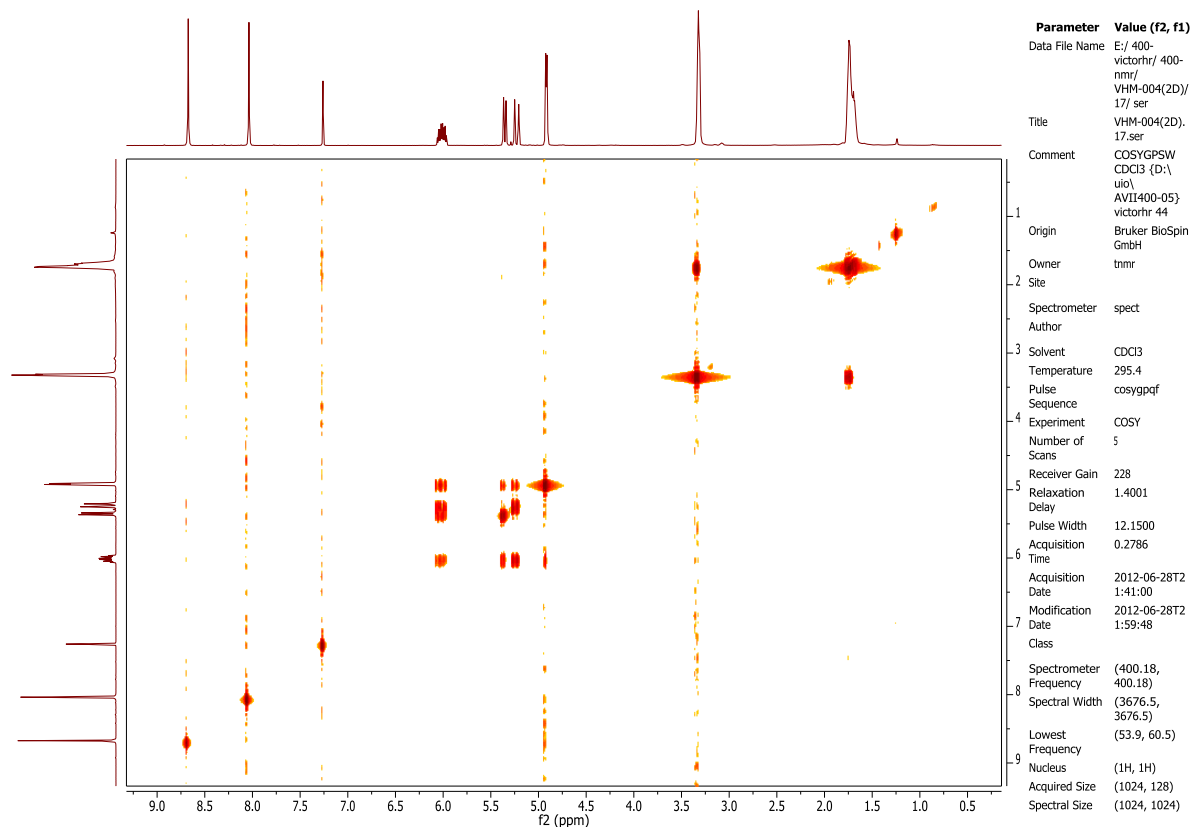
**Spectrum 13.** COSY NMR of 7-allyl-6-(piperidin-1-yl)-7*H*-purine (**95**).
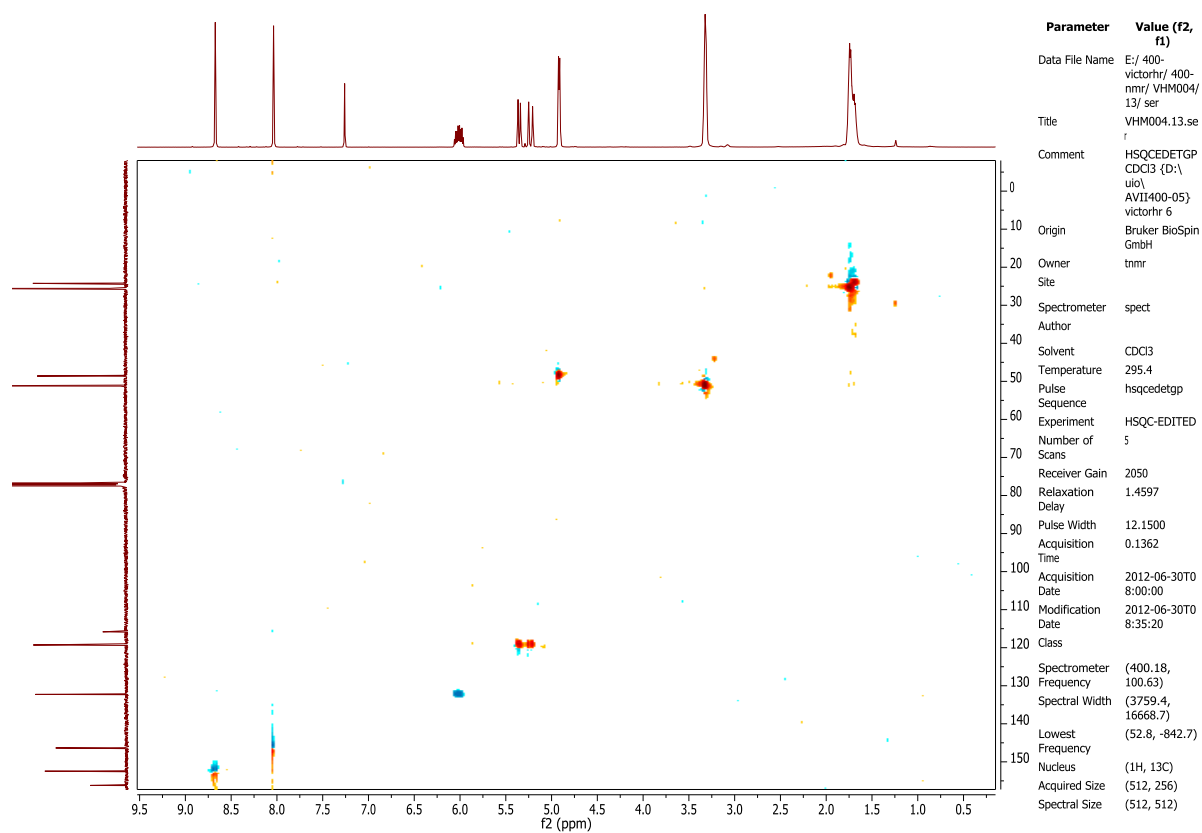
Spectrum 14. HSQC NMR of 7-allyl-6-(piperidin-1-yl)-7*H*-purine (**95**).
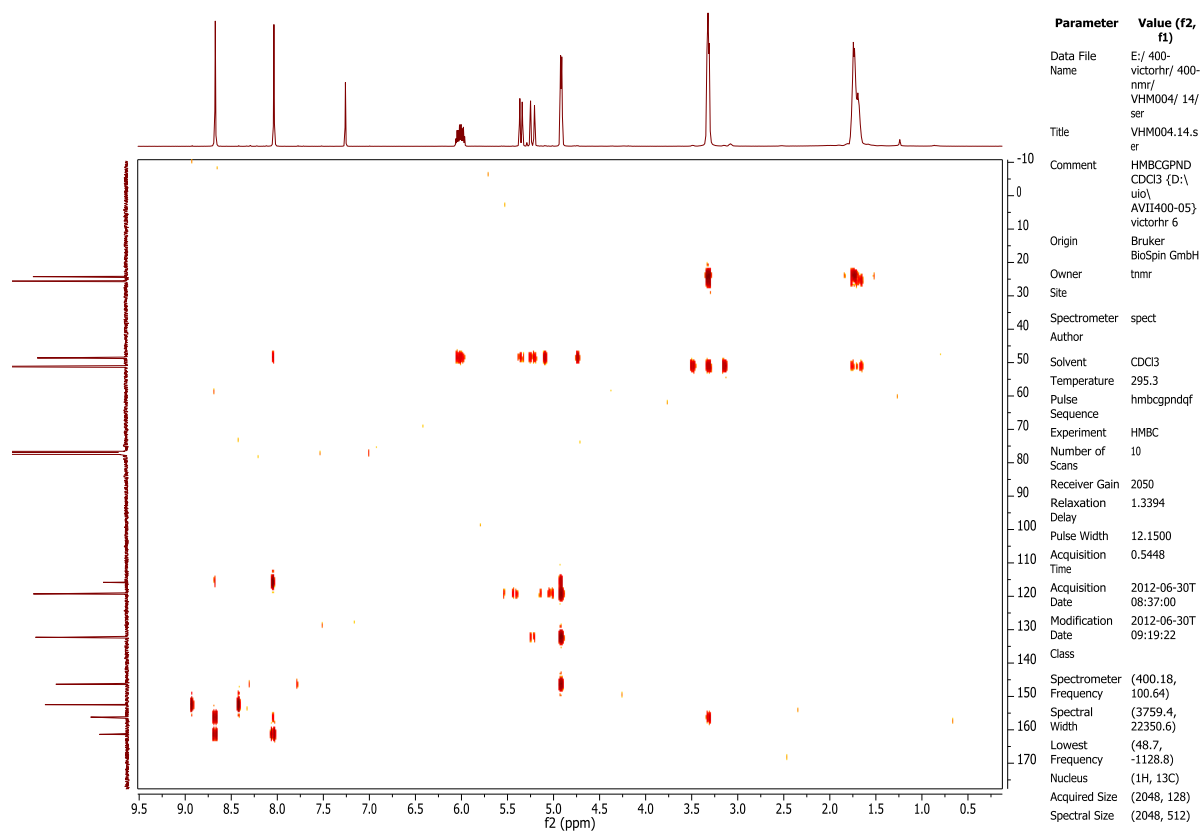
Spectrum 15. HMBC NMR of 7-allyl-6-(piperidin-1-yl)-7*H*-purine (**95**).

Parameter	Value (f2, f1)
Data File Name	E:/ 400-victorhr/ 400-nmr/ VHM004/ 14/ ser
Title	VHM004.14.ser
Comment	HMBCGPND CDCl3 {D:\ uio\ AVII400-05} victorhr 6
Origin	Bruker BioSpin GmbH
Owner	tnmr
Site	
Spectrometer	spect
Author	
Solvent	CDCl3
Temperature	295.3
Pulse Sequence	hmbcgpndqf
Experiment	HMBC
Number of Scans	10
Receiver Gain	2050
Relaxation Delay	1.3394
Pulse Width	12.1500
Acquisition Time	0.5448
Acquisition Date	2012-06-30T 08:37:00
Modification Date	2012-06-30T 09:19:22
Class	
Spectrometer Frequency	(400.18, 100.64)
Spectral Width	(3759.4, 22350.6)
Lowest Frequency	(48.7, -1128.8)
Nucleus	(1H, 13C)
Acquired Size	(2048, 128)
Spectral Size	(2048, 512)

6-(Piperidin-1-yl)-9*H*-purine (35)[33]

35

A solution of 6-chloropurine **16** (3.00 g, 19.40 mmol), piperidine (3.26 g, 38.4 mmol), and Et$_3$N (13.42 mL, 96.23 mmol) in *n*-BuOH (195 mL) was stirred at 100 ºC for 15 h. The mixture was cooled and concentrated on rotavapor to evaporate half of the amount of the solvent, and the white precipitate was triturated with MeOH (15 mL) three times. The white solid was collected and dried *in vacuo.* to give 3.44 g (87%) of 6-(piperidin-1-yl)-9*H*-purine **35** as a colourless solid.

^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.67-1.80 (m, 6H, 3 x CH$_2$), 4.29 (brs, 4H, 2 x CH$_2$), 7.95 (s, 1H, H-8), 8.37 (s, 1H, H-2), 13.89 (brs, 1H, NH).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 24.8 (CH$_2$), 26.1 (2 x CH$_2$), 46.4 (2 x NCH$_2$), 119.5 (C-5), 136.4 (C-8), 151.1 (C-4), 151.5 (C-2), 153.9 (C-6).

MS (EI). *m/z* (rel. %): 204/203 (12/100, *M*$^+$), 188 (15), 174 (78), 160 (31), 148 (33), 135 (22), 120 (30), 93 (18), 84 (16).

M.p. 275-277 ºC.
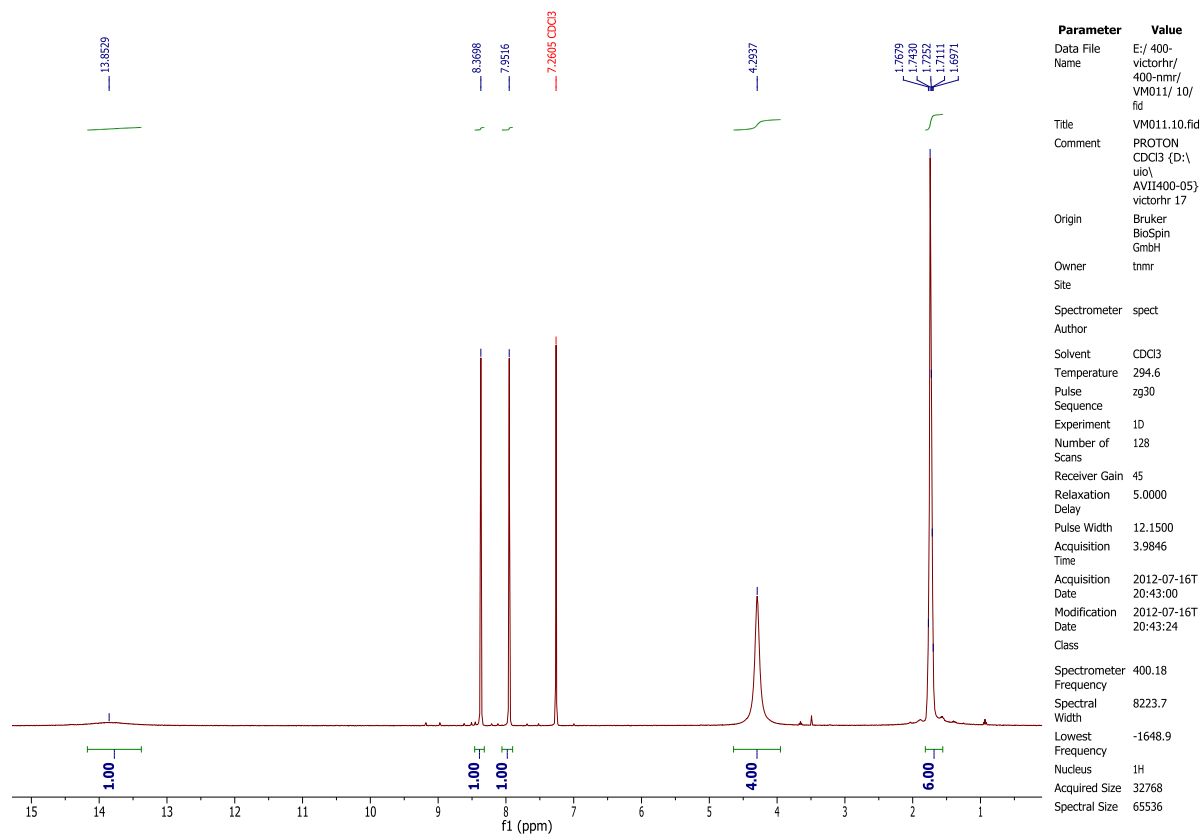
Spectrum 16. ^{1}H NMR of 6-(piperidin-1-yl)-9*H*-purine (**35**).
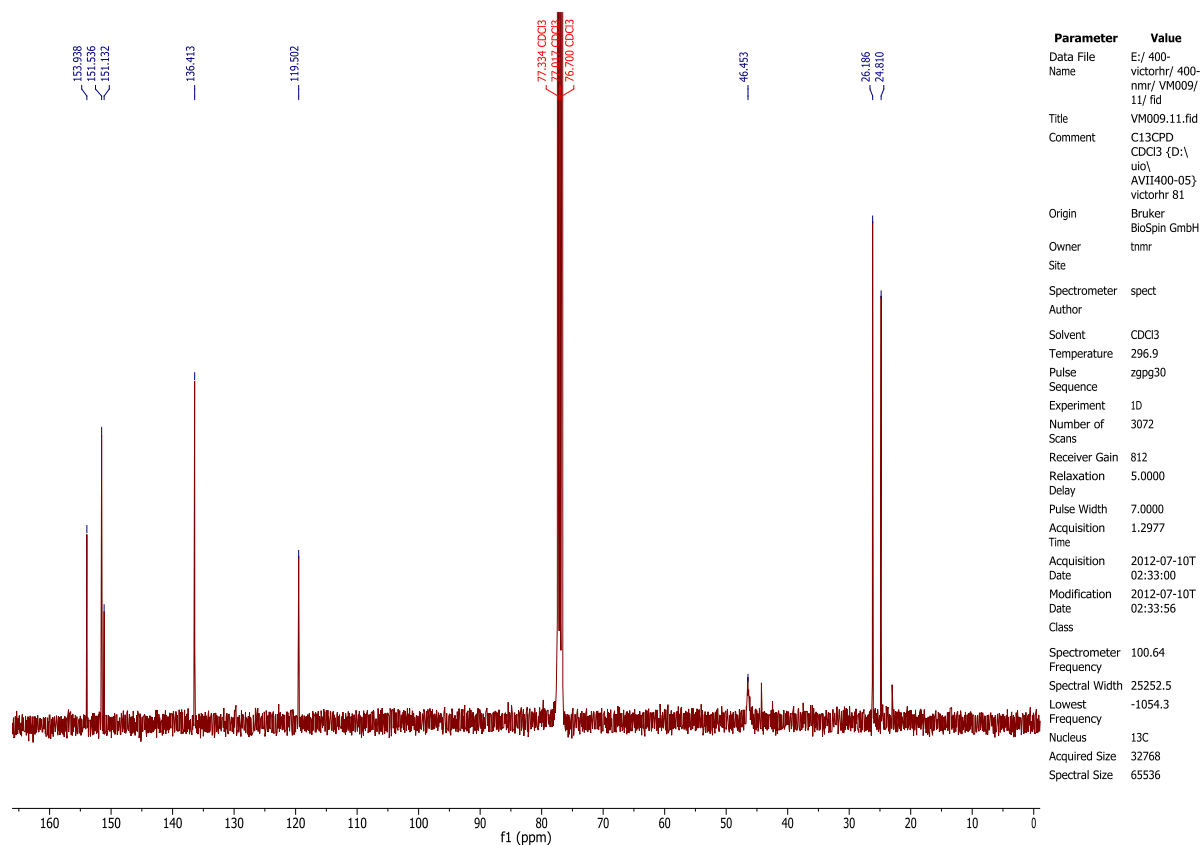
Spectrum 17. ^{13}C NMR of 6-(piperidin-1-yl)-9*H*-purine (**35**).

8-Bromo-6-(piperidin-1-yl)-9*H*-purine (24)[23]
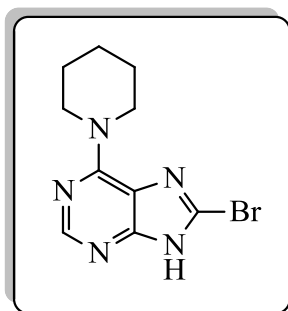
24

Compound **35** (116 mg, 0.57 mmol) and liquid bromine (0.22 mL, 4.28 mmol) were mixed and kept in a closed flask for 4 h, before the stopper was removed. The mixture was allowed to stand for 16 h., before the resulting solid was stirred in water (5 mL). Concentrated aqueous ammonia (10 mL) was added until dissolution and the solution neutralised with acetic acid. The precipitate was filtered, washed with water (5 mL), boiled in water (5 mL), and filtered while hot. Then, it was washed with water, acetone and ether, and dried *in vacuo*. to give 100 mg (62%) of 8-bromo-6-(piperidin-1-yl)-9*H*-purine **24** as a yellow solid.

¹H NMR (CDCl₃, 400 MHz) δ 1.71-1.73 (m, 6H, 3 x CH₂), 4.25 (brs, 4H, 2 x NCH₂), 8.25 (s, 1H, H-2),10.86 (brs, 2H, NH).

¹³C NMR (CDCl₃, 100 MHz) δ 24.6 (CH₂), 26.1 (2 x CH₂), 46.6 (2 x NCH₂), 121.3 (C-5), 125.6 (C-8), 148.1 (C-2), 152.0 (C-4), 152.2 (C-6).

MS (EI). *m/z* (rel. %): 283/281 (46/47, M^+), 254 (30), 252 (30), 228 (11), 226 (11), 202 (100), 174 (18), 147 (11).

HRMS. Found 281.0278 Calculated for $C_{10}H_{12}N_5Br$ 281.0276.

M.p. 212- 214 °C.
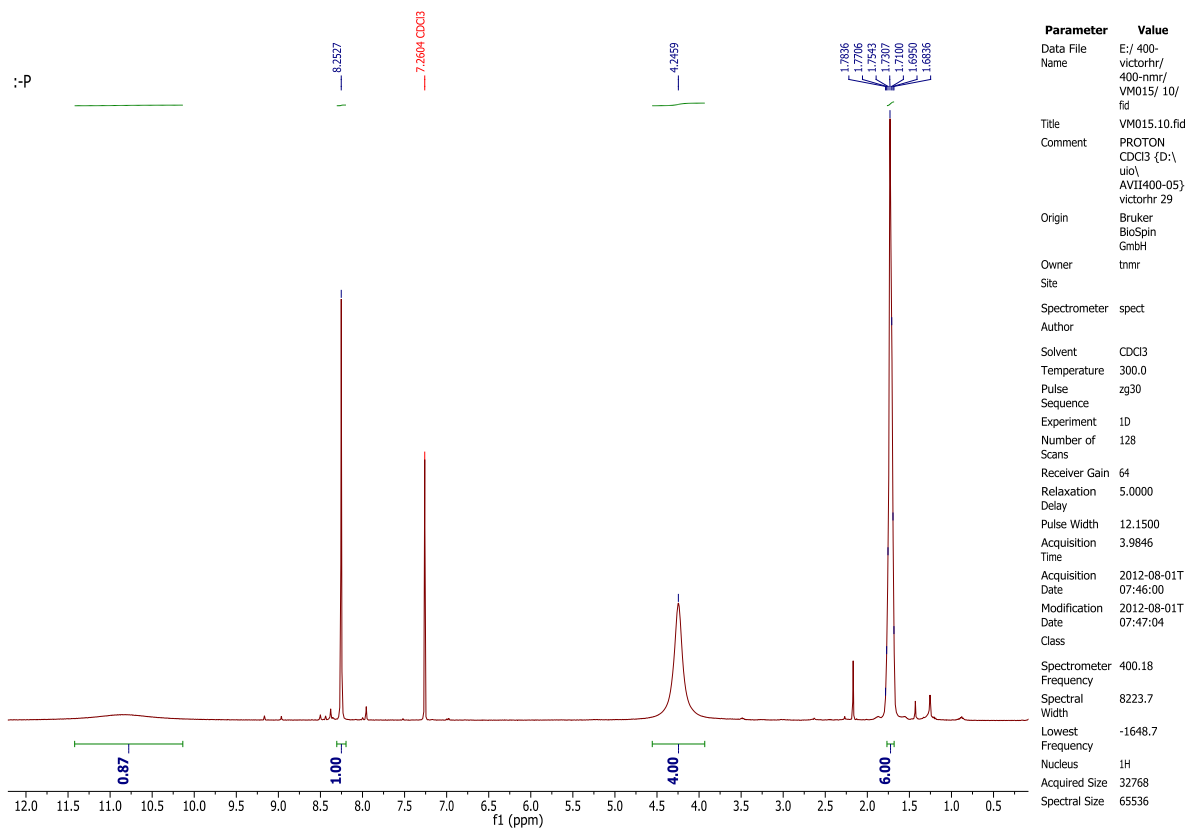
Spectrum 18. ^{1}H NMR of 8-bromo-6-(piperidin-1-yl)-9*H*-purine (**24**).

Spectrum 19. ^{13}C NMR of 8-bromo-6-(piperidin-1-yl)-9*H*-purine (**24**).

Parameter	Value
Data File Name	E:/ 400-victorhr/ 400-nmr/ VM015/ 15/ fid
Title	VM015.15.fid
Comment	C13DEPT135 CDCl3 {D:\ uio\ AVII400-05} victorhr 29
Origin	Bruker BioSpin GmbH
Owner	tnmr
Site	
Spectrometer	spect
Author	
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	dept135
Experiment	DEPT-135
Number of Scans	256
Receiver Gain	2050
Relaxation Delay	2.0000
Pulse Width	7.0000
Acquisition Time	1.3632
Acquisition Date	2012-08-02T 02:31:00
Modification Date	2012-08-02T 02:31:58
Class	
Spectrometer Frequency	100.64
Spectral Width	24038.5
Lowest Frequency	-1956.7
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

Spectrum 20. ^{13}C DEPT NMR of 8-bromo-6-(piperidin-1-yl)-9*H*-purine (**24**).
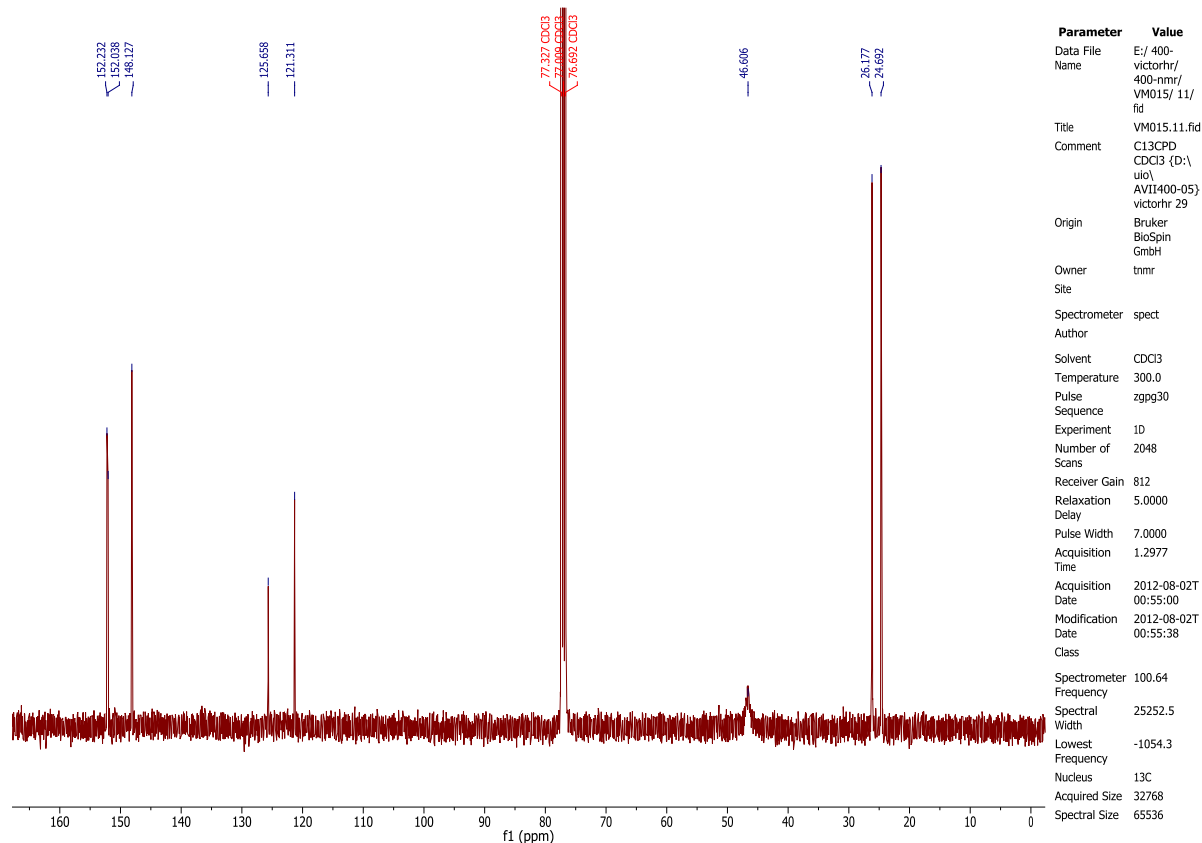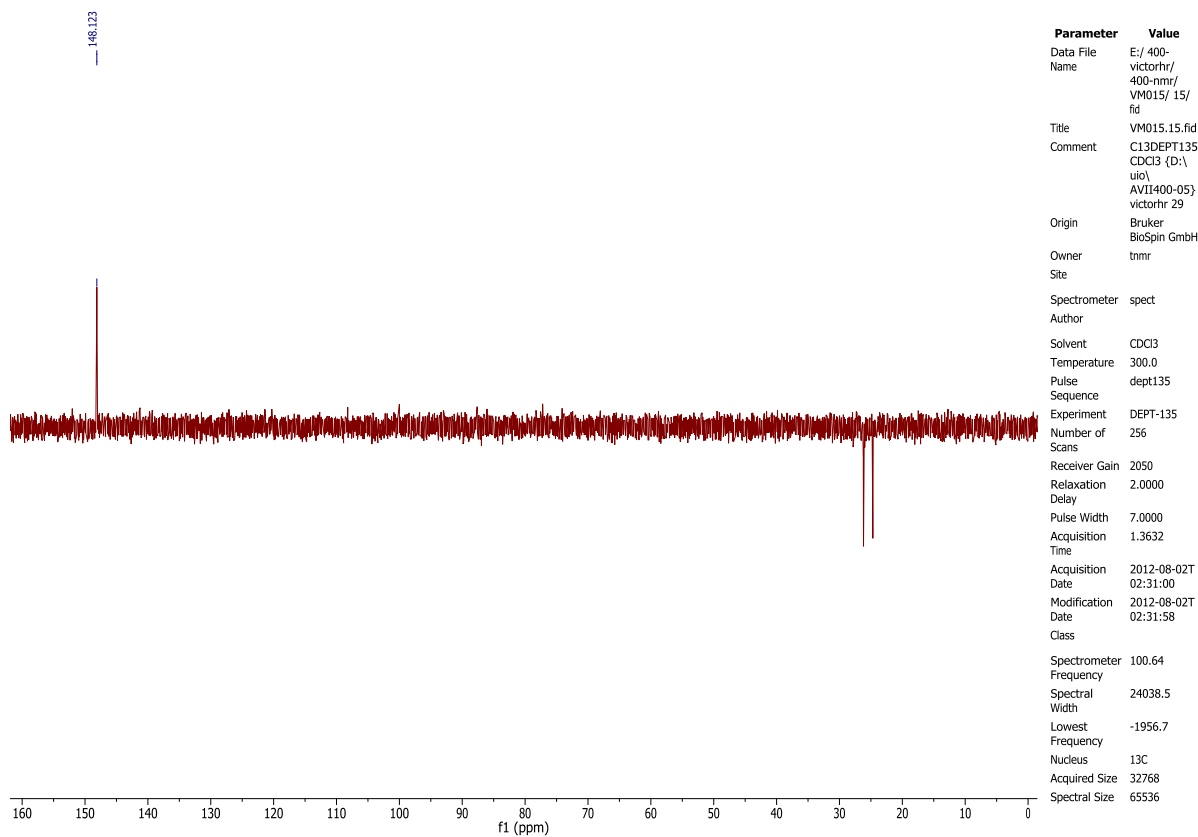

Parameter	Value (f2, f1)
Data File Name	E:/ 400-victorhr/ 400-nmr/ VM015/ 14/ ser
Title	VM015.14.ser
Comment	COSYGPSW CDCl3 {D:\ uio\ AVII400-05} victorhr 29
Origin	Bruker BioSpin GmbH
Owner	tnmr
Site	
Spectrometer	spect
Author	
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	cosygpqf
Experiment	COSY
Number of Scans	1
Receiver Gain	203
Relaxation Delay	1.4738
Pulse Width	12.1500
Acquisition Time	0.2049
Acquisition Date	2012-08-02T 02:11:00
Modification Date	2012-08-02T 02:15:32
Class	
Spectrometer Frequency	(400.18, 400.18)
Spectral Width	(5000.0, 5000.0)
Lowest Frequency	(127.6, 129.6)
Nucleus	(1H, 1H)
Acquired Size	(1024, 128)
Spectral Size	(1024, 1024)

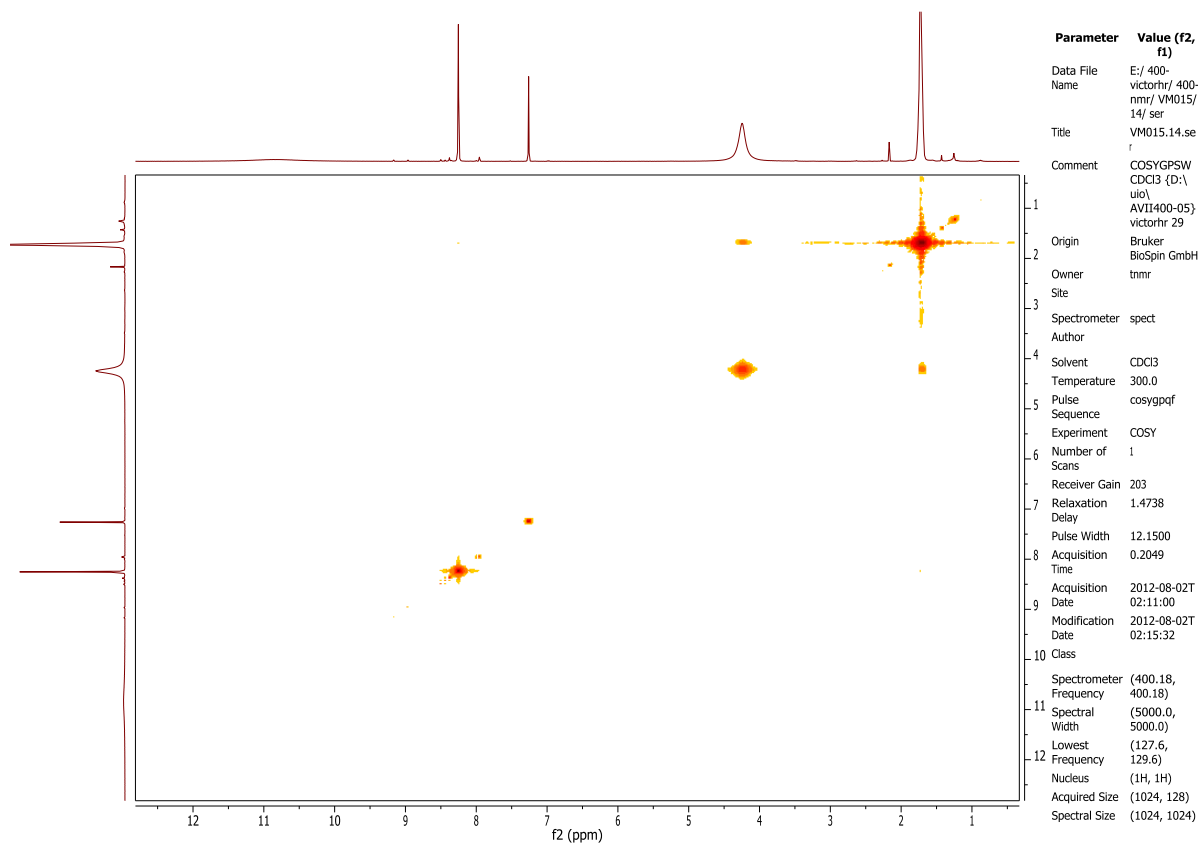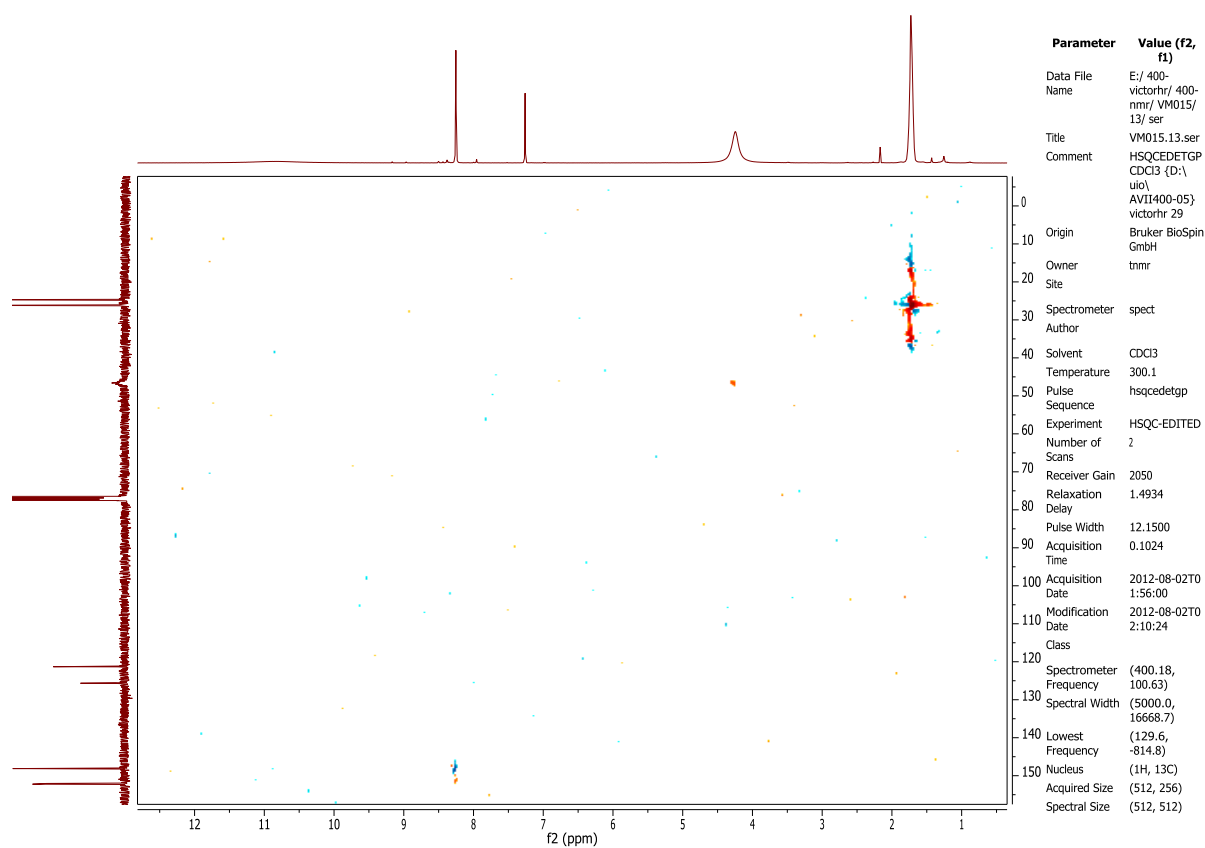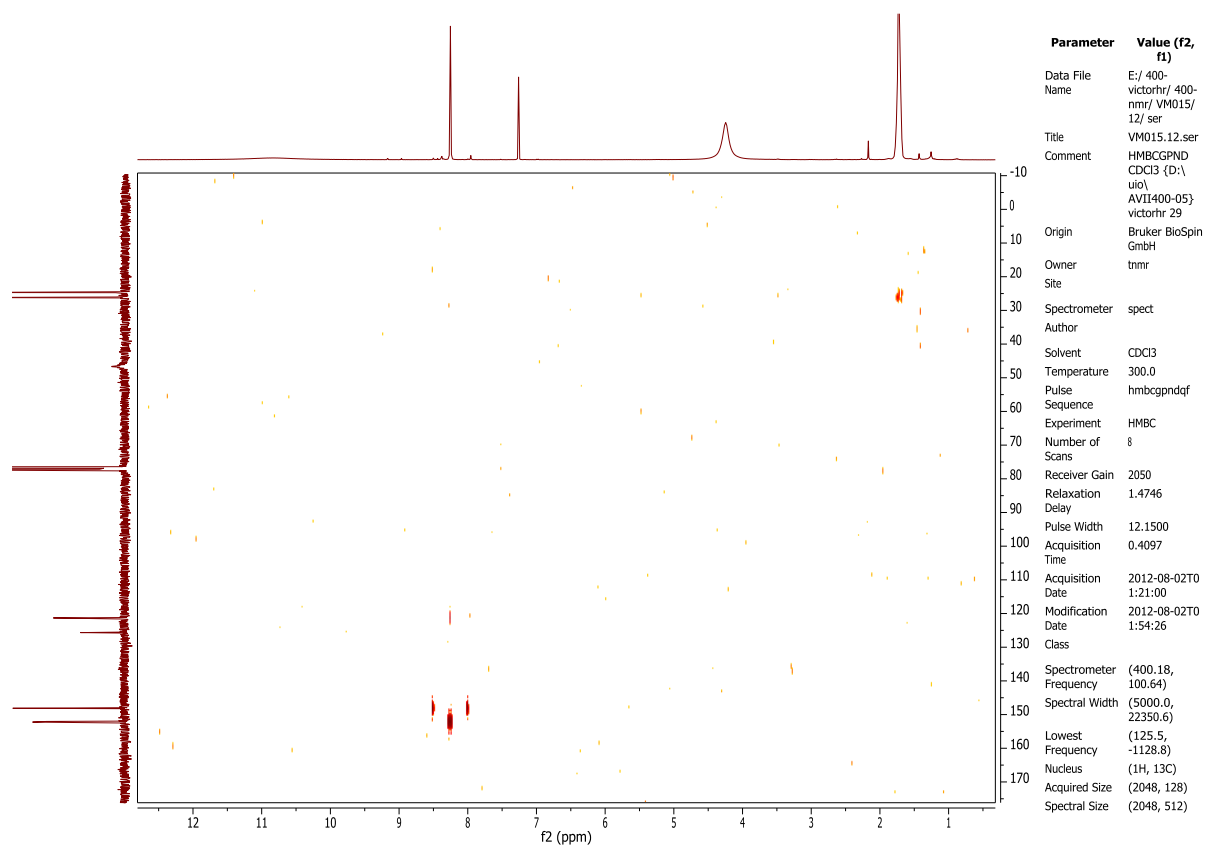**Spectrum 21.** COSY NMR of 8-bromo-6-(piperidin-1-yl)-9*H*-purine (**24**).
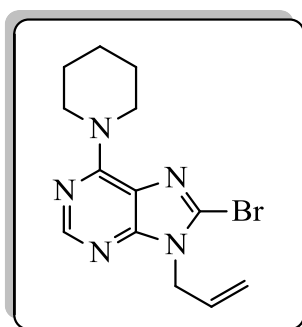
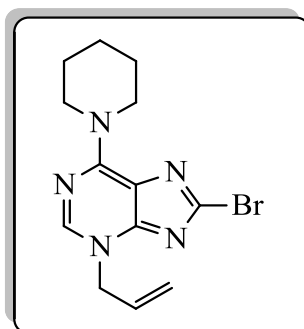**Spectrum 22.** HSQC NMR of 8-bromo-6-(piperidin-1-yl)-9*H*-purine (**24**).

Spectrum 23. HMBC NMR of 8-bromo-6-(piperidin-1-yl)-9*H*-purine (**24**).

9-Allyl-8-bromo-6-(piperidin-1-yl)-9*H*-purine (25) and 3-allyl-8-bromo-6-(piperidin-1-yl)-3*H*-purine (26).

25   26

Potassium carbonate (148 mg, 1.07 mmol) was added to a stirring solution of 8-bromo-6-(piperidin-1-yl)-9*H*-purine **24** (100 mg, 0.361 mmol) in dry DMF (6 mL) at ambient temperature under $N_{2\text{-atm}}$. After 20 min., allyl bromide (0.11 mL, 0.69 mmol) was added, the resulting mixture was stirred for 20 h., filtered and evaporated *in vacuo.* The isomers were separated by flash chromatography on silica gel using 0.5-2% MeOH / DCM as an eluent. This gave 24 mg (21%) of 9-allyl-8-bromo-6-(piperidin-1-yl)-9*H*-purine **25** as a colourless solid and 79 mg (69%) of 3-allyl-8-bromo-6-(piperidin-1-yl)-3*H*-purine **26** as a yellow solid.

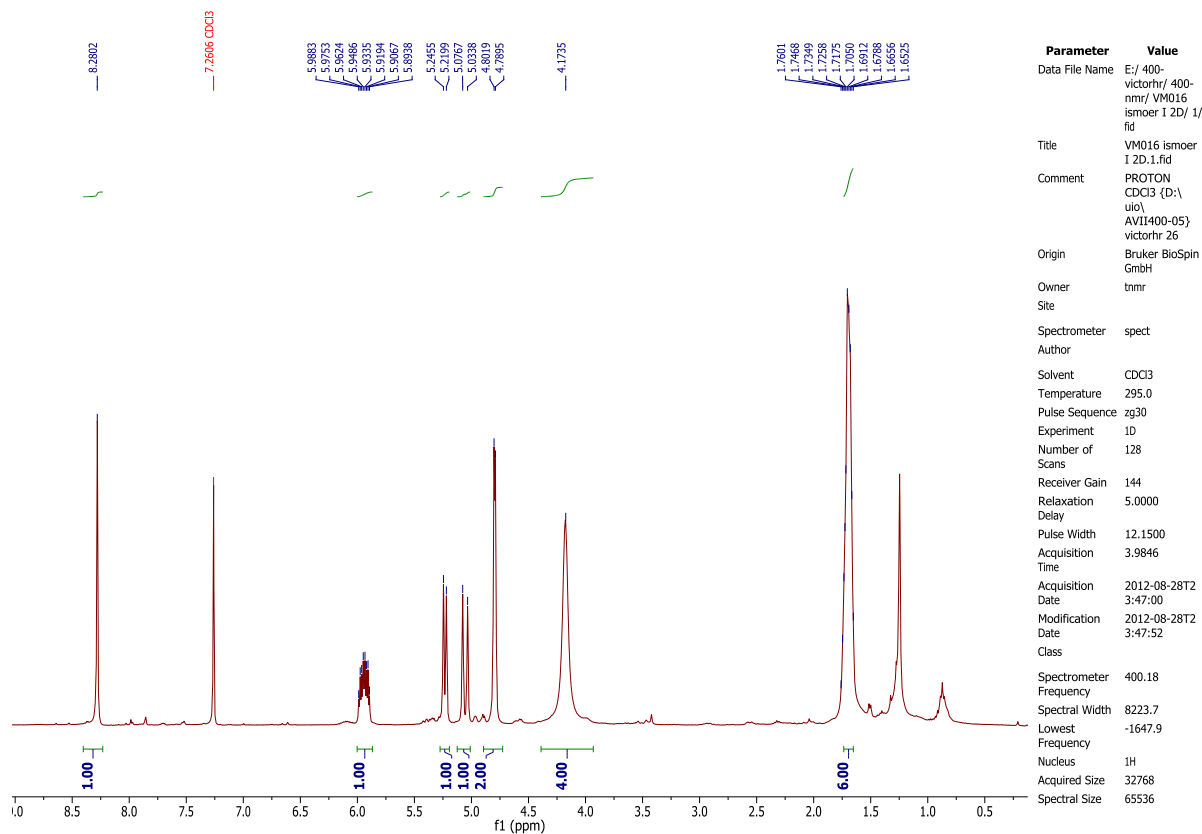9-Allyl-8-bromo-6-(piperidin-1-yl)-9*H*-purine (**25**)

¹H NMR (CDCl$_3$, 400 MHz) δ 1.61-1.78 (m, 6H, 3 x CH$_2$ in piperidine), 4.17 (brs, 4H, 2 x NCH$_2$ in piperidine), 4.79 (d, *J* = 5.2 Hz, 2H, CH$_2$ in allyl), 5.06 (d, *J* = 17.1 Hz, 1H, =CH$_{2a}$ in allyl), 5.23 (d, *J* = 10.5 Hz, 1H, =CH$_{2b}$ in allyl), 5.87-5.99 (m, 1H, =CH in allyl), 8.28 (s, 1H, H-2).

¹³C NMR (CDCl$_3$, 100 MHz) δ 23.7 (CH$_2$ in piperidinyl), 25.0 (2 x CH$_2$ in piperidinyl), 44.9 (CH$_2$ in allyl), 45.3 (2 x NCH$_2$ in piperidinyl), 117.0 (=CH$_2$ in allyl), 119.1 (C-5), 123.3 (C-8), 129.9 (=CH in allyl), 151.0 (C-4), 151.5 (C-2), 151.6 (C-6).

MS (EI). *m/z* (rel. %): 323/321 (58/59, *M*$^+$), 294 (22), 292 (22), 267 (15), 265 (15), 242 (100), 214 (10), 187 (8), 159 (5), 84 (15).

HRMS. Found 321.0583 calculated for C$_{13}$H$_{16}$N$_5$Br 321.0589.

M.p. 80-82 °C (Lit.[23] 65-66 °C).

Spectrum 24. ^{1}H NMR of 9-allyl-8-bromo-6-(piperidin-1-yl)-9H-purine (**25**).
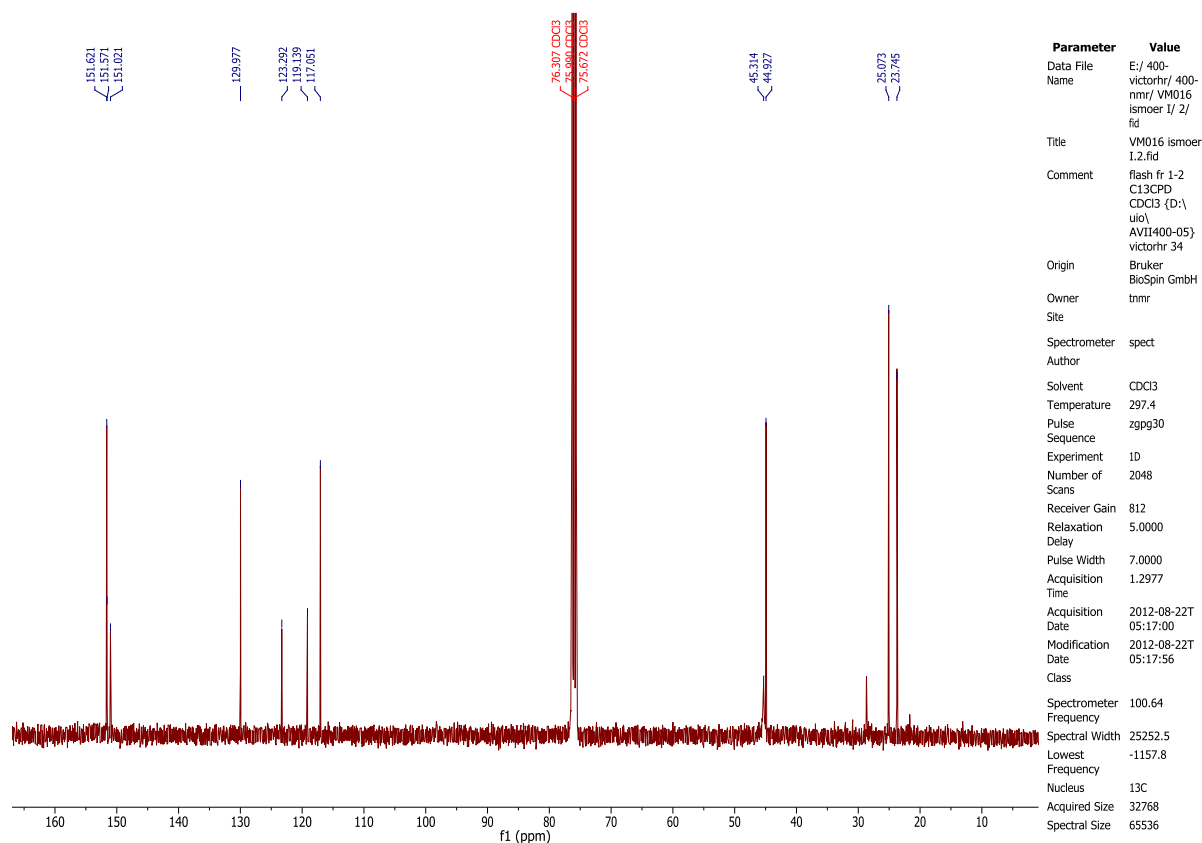
Spectrum 25. ^{13}C NMR of 9-allyl-8-bromo-6-(piperidin-1-yl)-9H-purine (**25**).
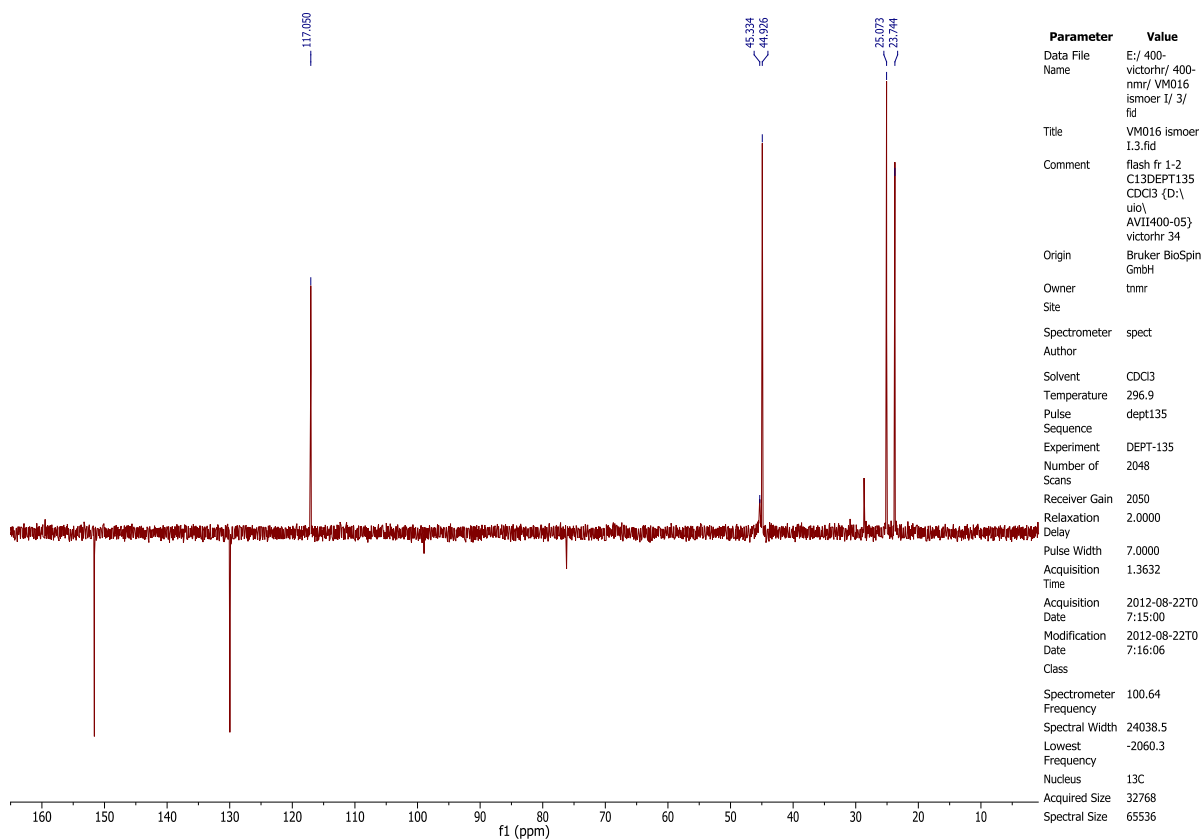
Spectrum 26. ^{13}C DEPT NMR of 9-allyl-8-bromo-6-(piperidin-1-yl)-9*H*-purine (**25**).
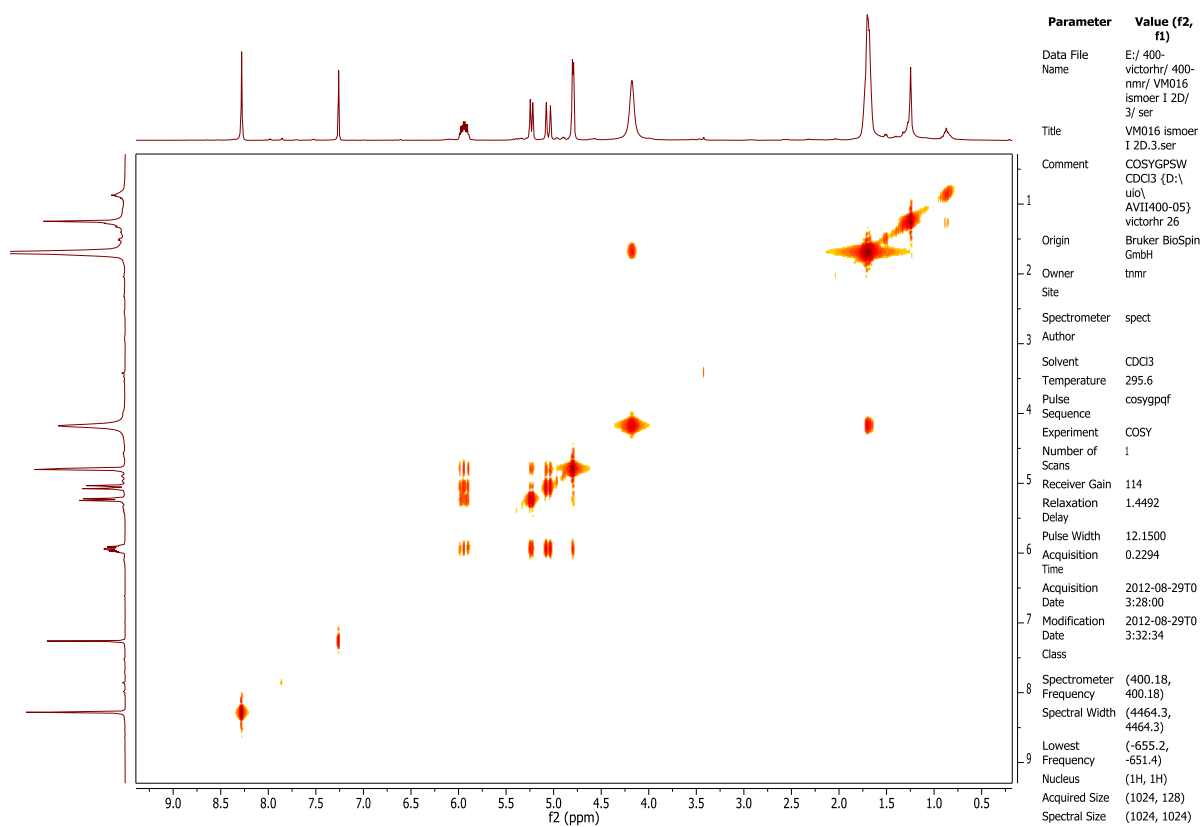
Spectrum 27. COSY NMR of 9-allyl-8-bromo-6-(piperidin-1-yl)-9*H*-purine (**25**).

Spectrum 28. HSQC NMR of 9-allyl-8-bromo-6-(piperidin-1-yl)-9*H*-purine (**25**).

Spectrum 29. HMBC NMR of 9-allyl-8-bromo-6-(piperidin-1-yl)-9*H*-purine (**25**).

3-Allyl-8-bromo-6-(piperidin-1-yl)-3*H*-purine (**26**)

¹H NMR (CDCl$_3$, 400 MHz) δ 1.68-1.74 (m, 6H, 3 x CH$_2$ in piperidinyl), 3.96 (brs, 2H, NCH$_2$ in piperidinyl), 4.57 (brs, 2H, NCH$_2$ in piperidinyl), 4.88 (d, *J* = 5.9 Hz, 2H, CH$_2$ in allyl), 5.24-5.41 (m, 2H, =CH$_2$ in allyl), 6.01-6.12 (m, 1H, =CH in allyl), 7.85 (s, 1H, H-2).

¹³C NMR (CDCl$_3$, 100 MHz) δ 23.5 (CH$_2$ in piperidinyl), 25.2 (2 x CH$_2$ in piperidinyl), 44.6 (NCH$_2$ in piperidinyl), 47.2 (NCH$_2$ in piperidinyl), 50.3 (CH$_2$ in allyl), 119.2 (=CH$_2$ in allyl), 121.2 (C-5), 129.8 (=CH in allyl), 138.5 (C-8), 139.6 (C-2), 149.2 (C-6), 149.7 (C-4).

MS (EI). *m/z* (rel. %): 323/321 (72/74, *M*$^+$), 294 (16), 292 (16), 282 (93), 280 (100), 254 (28), 252 (29), 240 (15), 238 (15), 199 (12), 197 (11), 118 (5).

HRMS. Found 321.0585 calculated for C$_{13}$H$_{16}$N$_5$Br 321.0589.

**M.p.** 111-113 ºC (Lit.[23] 82-83 ºC).
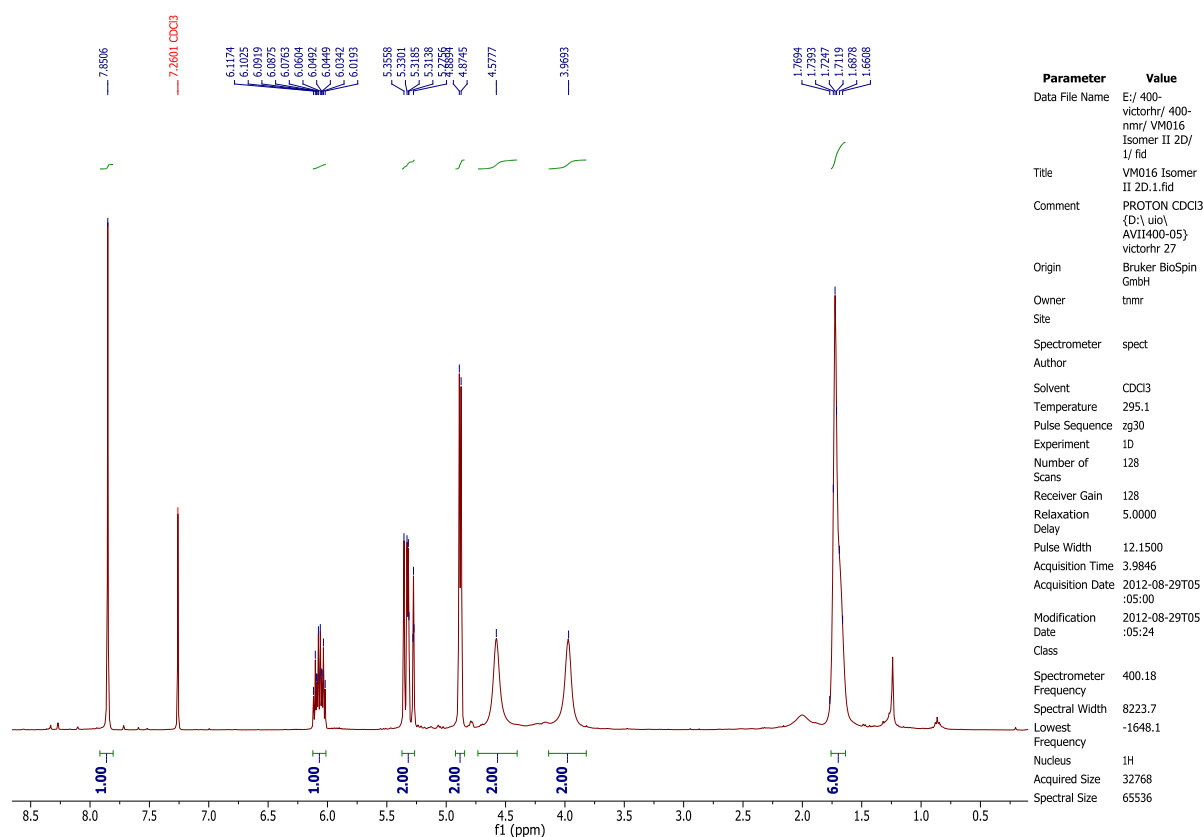
Spectrum 30. ¹H NMR of 3-allyl-8-bromo-6-(piperidin-1-yl)-3*H*-purine (**26**).
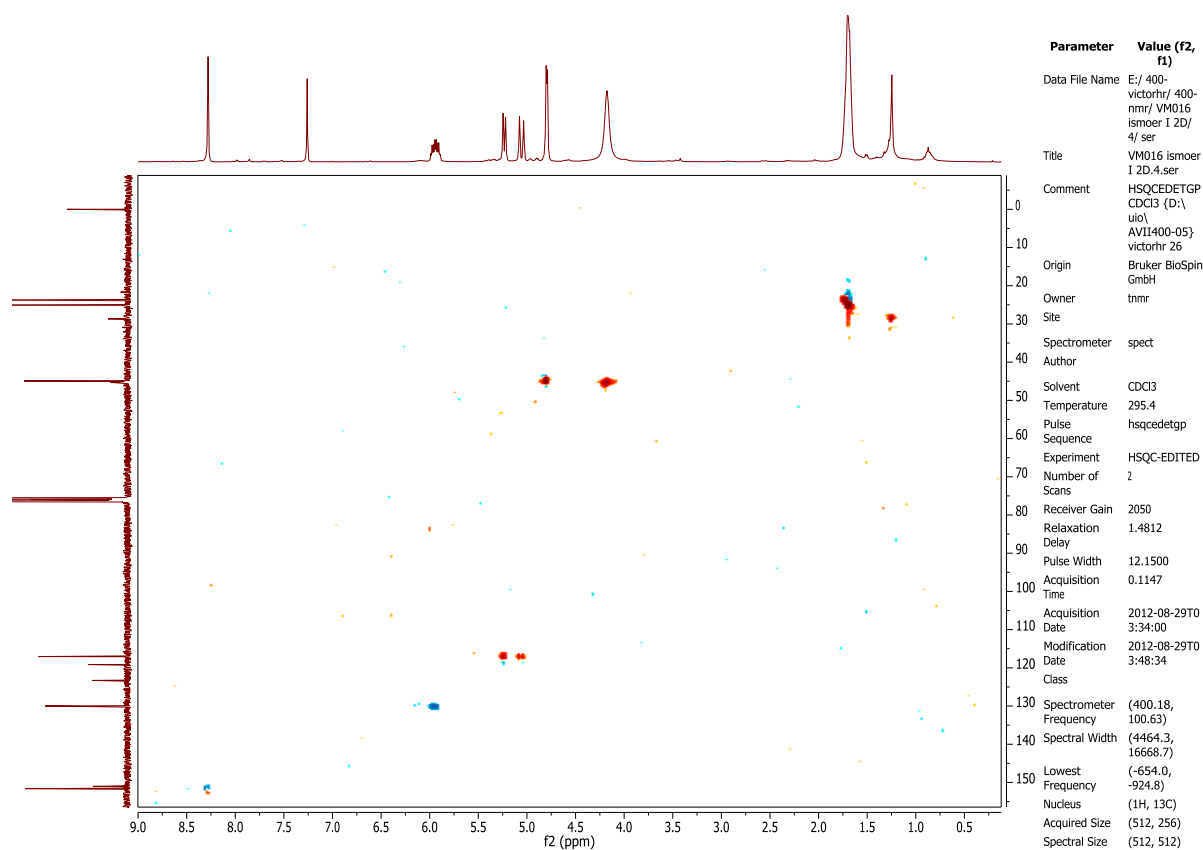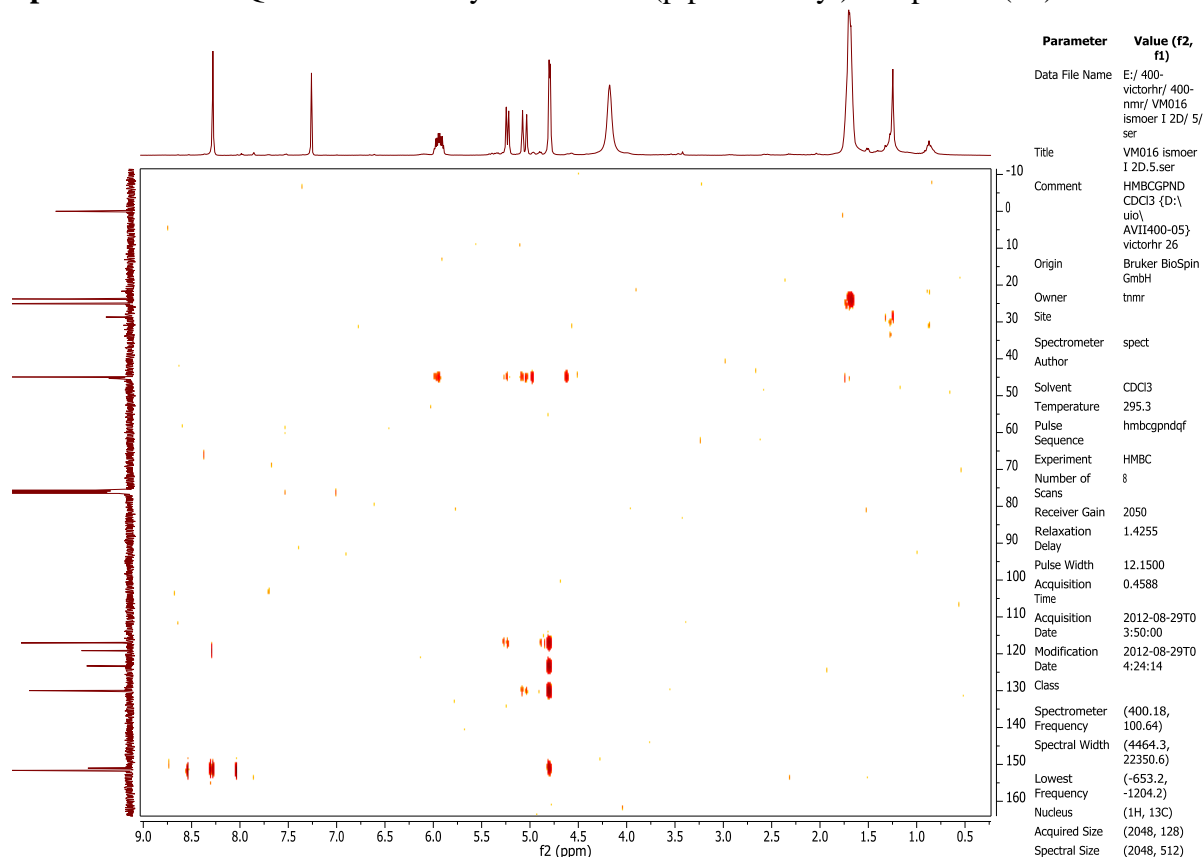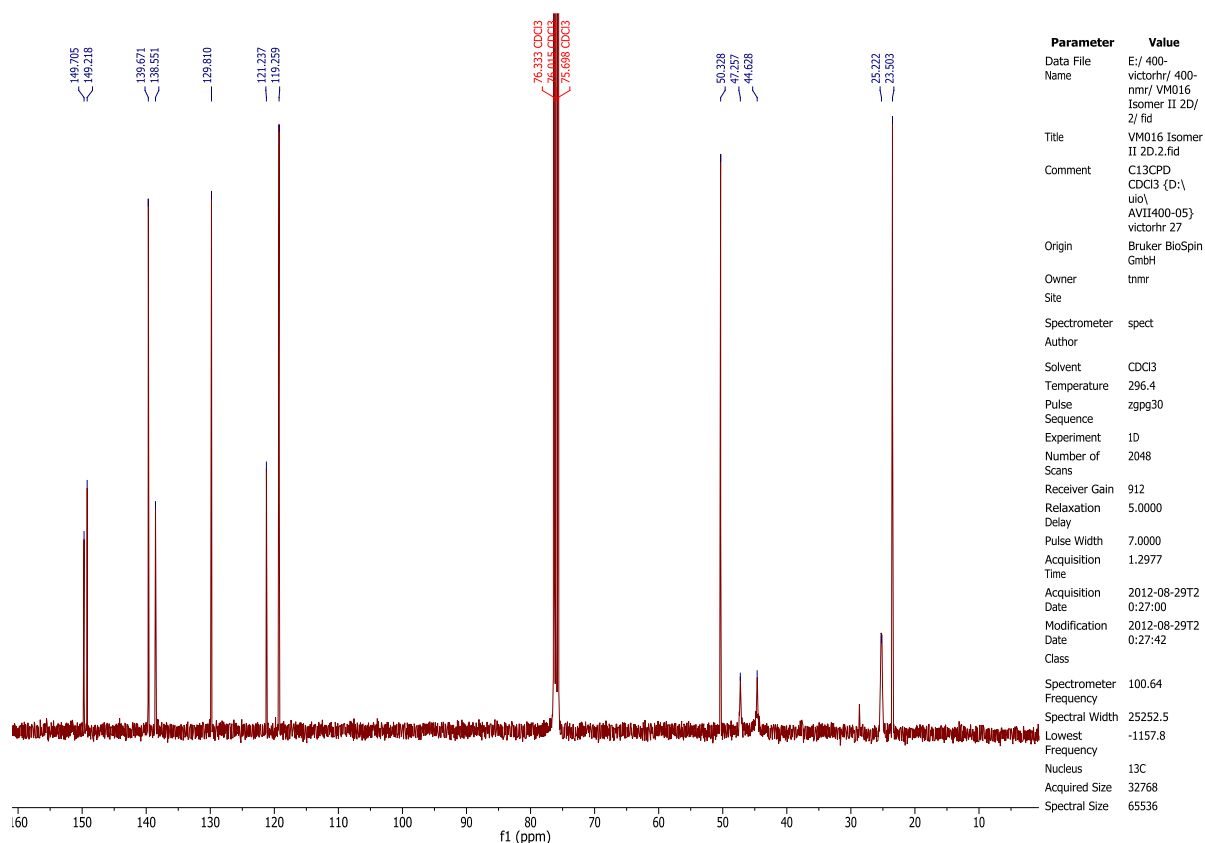
Spectrum 31. ^{13}C NMR of 3-allyl-8-bromo-6-(piperidin-1-yl)-3*H*-purine (**26**).
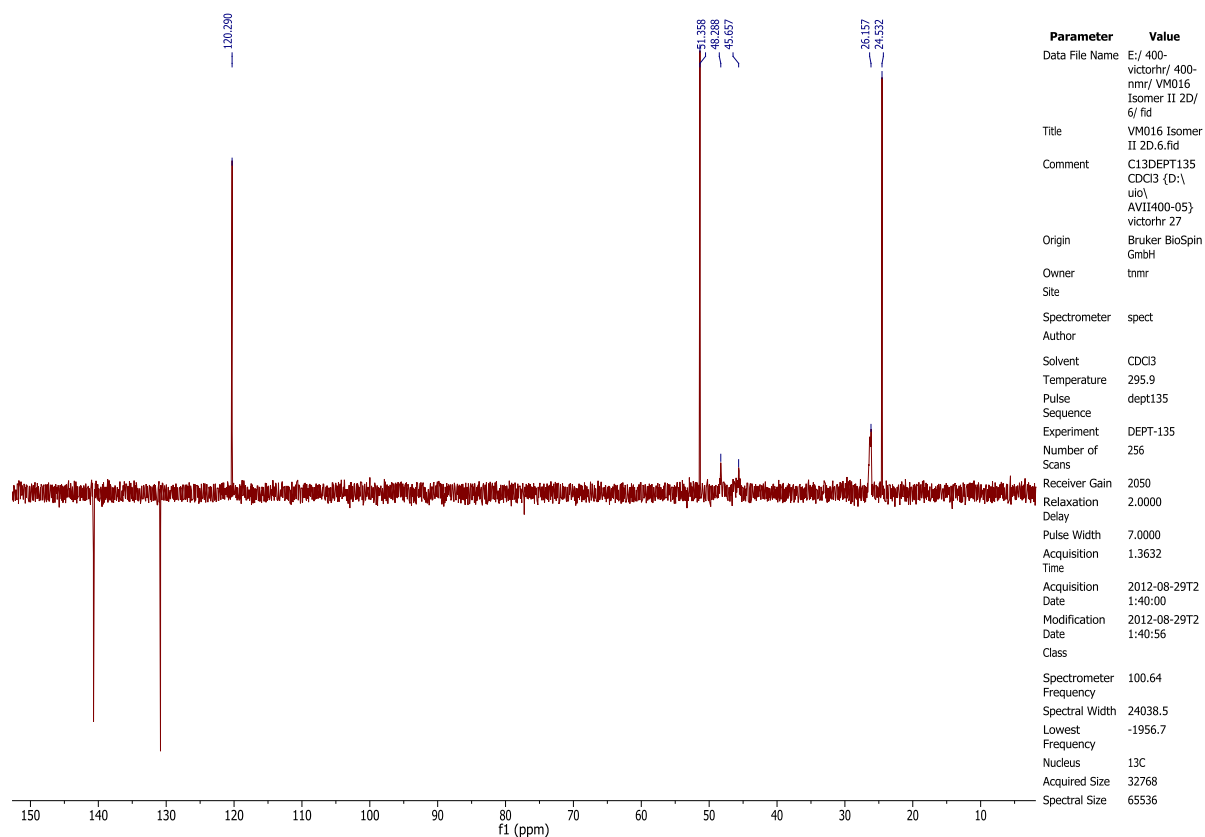
Spectrum 32. ^{13}C DEPT NMR of 3-allyl-8-bromo-6-(piperidin-1-yl)-3*H*-purine (**26**).
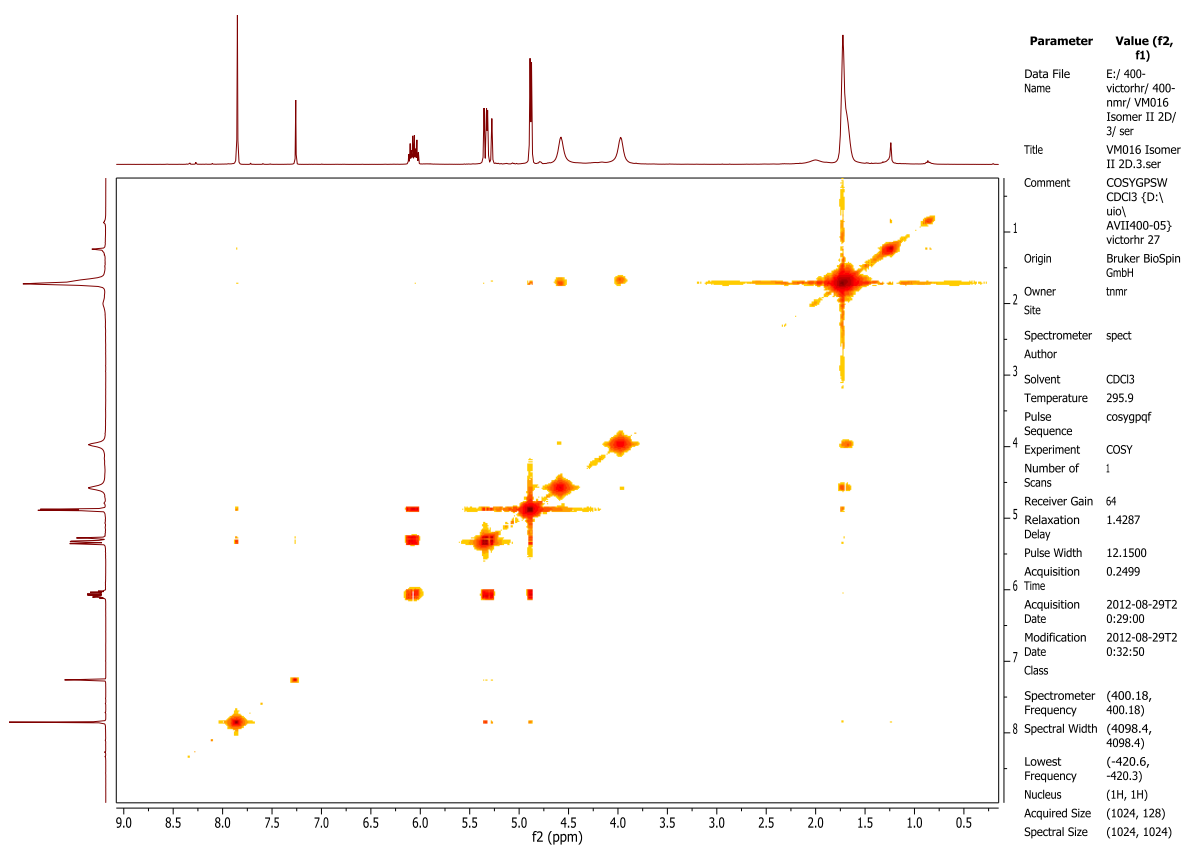
Spectrum 33. COSY NMR of 3-allyl-8-bromo-6-(piperidin-1-yl)-3*H*-purine (**26**).
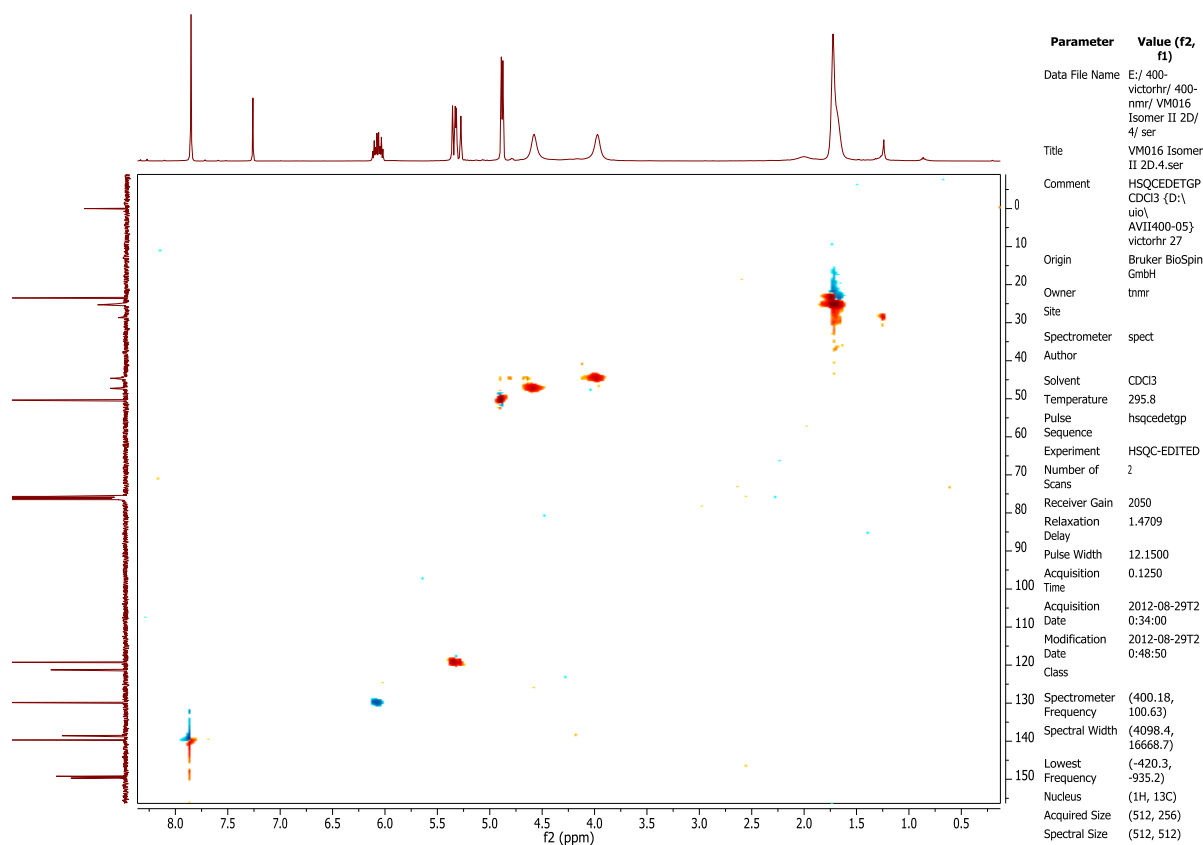
Spectrum 34. HSQC NMR of 3-allyl-8-bromo-6-(piperidin-1-yl)-3*H*-purine (**26**).

Spectrum 35. HMBC NMR of 3-allyl-8-bromo-6-(piperidin-1-yl)-3*H*-purine (**26**).

6,8-Dichloro-9-ethyl-9*H*-purine (49)
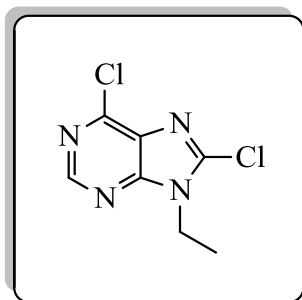
49

A solution of diisopropylamine (0.11 mL, 0.75 mmol) in dry THF (2 mL) was cooled to -78 ºC under N_2-atm. 1.03 M *n*-BuLi in hexane (0.68 mL, 0.70 mmol) was added dropwise over 10 min. and the mixture was stirred at -78 ºC under N_2-atm. for 1 h. 6-Chloro-9-ethyl-*9H*-purine **27a** (91 mg, 0.50 mmol) in dry THF (2 mL) was added dropwise over 10 min to the reaction mixture and stirred at -78ºC under N_2-atm. for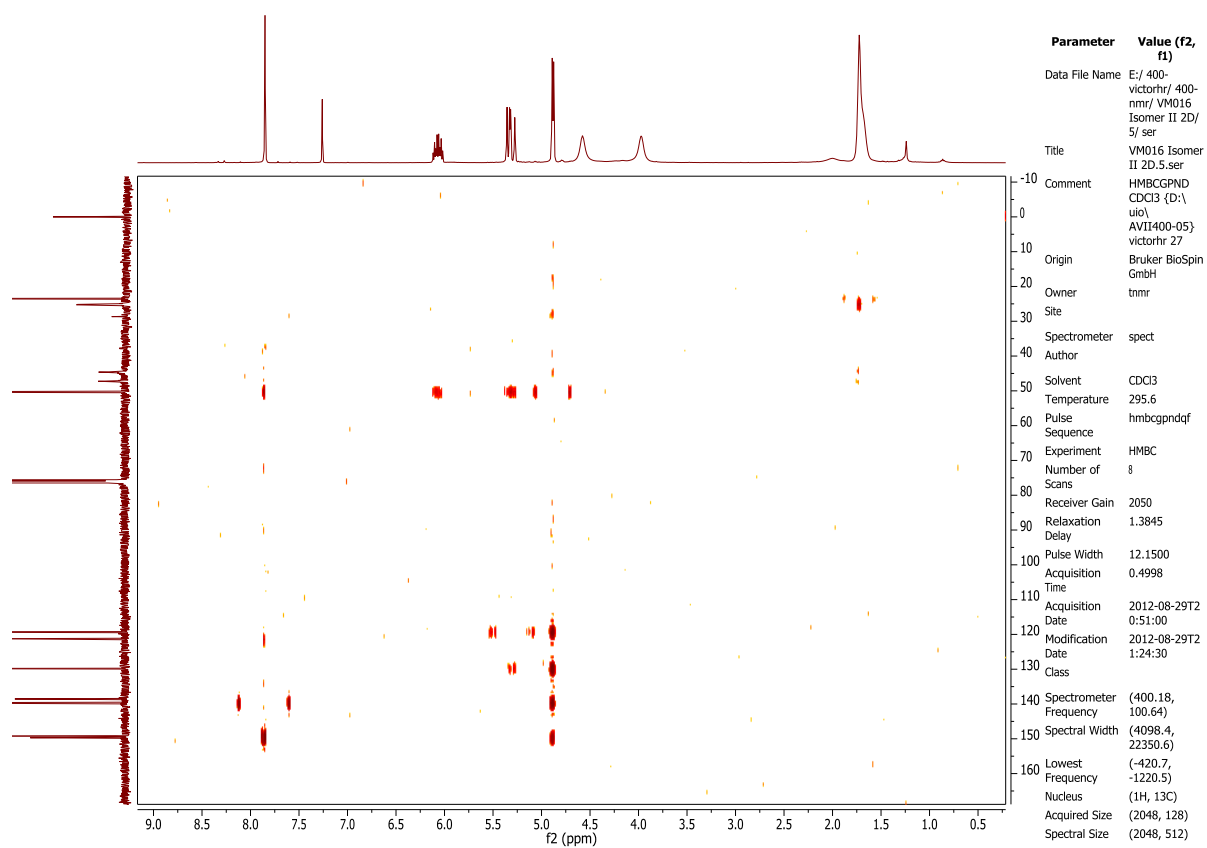 1 h. C_2Cl_6 (237 mg, 1.00 mmol) was dissolved in dry THF (1 mL) and added dropwise over 10 min. to the reaction mixture and stirred at -78ºC under N_2-atm. for 5 minutes. Sat. aq. NH_4Cl (15 mL) was added and the mixture was left to warm up to r.t., and extracted with EtOAc (2 x 25 ml). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified by flash chromatography eluting with 0-3% MeOH in DCM to give 81 mg (74%) of 6,8-dichloro-9-ethyl-9*H*-purine **49** as a yellow solid.

^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.49 (t, *J* = 7.3 Hz, 3H, CH$_3$), 4.38 (q, *J* = 7.3 Hz, 2H, CH$_2$), 8.73 (s, 1H, H-2).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 14.5 (CH$_3$), 39.4 (CH$_2$), 130.70 (C-5), 144.1 (C-8), 149.4 (C-6), 151.9 (C-2), 152.2 (C-4).

MS (EI). *m/z* (rel. %): 220/218 (5/31, *M*$^+$), 216 (48), 192 (11), 190 (67), 188 (100), 155 (8), 153(23), 127 (9).

HRMS. Found 215.9963 calculated for $C_7H_6N_4Cl_2$ 215.9970.

M.p. 90-92 ºC (Lit.[21] 91.4-91.9 ºC).

Parameter	Value
Data File Name	E:/ 400-victorhr/ 400-nmr/ VM027/ 1/ fid
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Owner	tnmr
Site	
Spectrometer	spect
Author	
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	128
Receiver Gain	322
Relaxation Delay	5.0000
Pulse Width	12.1500
Acquisition Time	3.9846
Acquisition Date	2012-09-16T1 5:41:00
Modification Date	2012-09-16T1 5:41:24
Class	
Spectrometer Frequency	400.18
Spectral Width	8223.7
Lowest Frequency	-1647.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

Spectrum 36. ^{1}H NMR of 6,8-dichloro-9-ethyl-9H-purine (**49**).

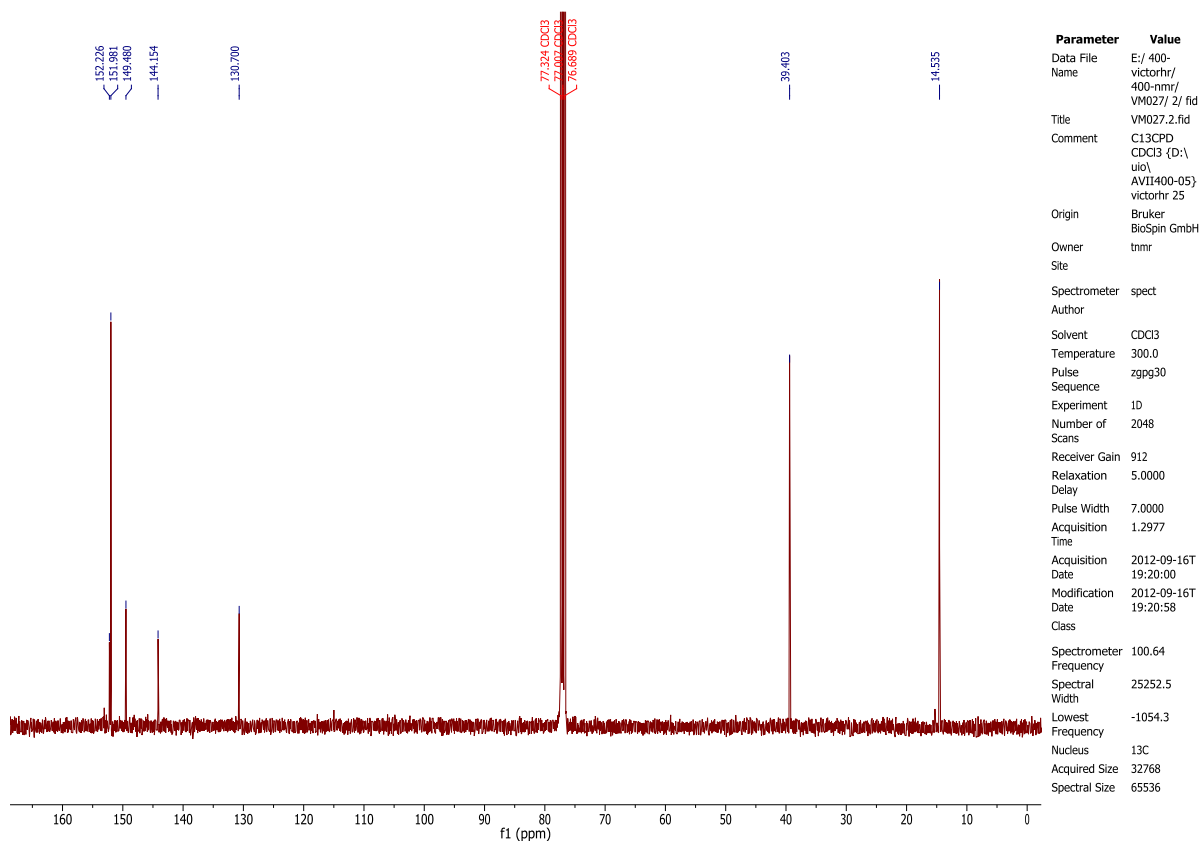| Parameter	Value
Data File Name	E:/ 400-victorhr/ 400-nmr/ VM027/ 2/ fid
Title	VM027.2.fid
Comment	C13CPD CDCl3 {D:\ uio\ AVII400-05} victorhr 25
Origin	Bruker BioSpin GmbH
Owner	tnmr
Site	
Spectrometer	spect
Author	
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	2048
Receiver Gain	912
Relaxation Delay	5.0000
Pulse Width	7.0000
Acquisition Time	1.2977
Acquisition Date	2012-09-16T 19:20:00
Modification Date	2012-09-16T 19:20:58
Class	
Spectrometer Frequency	100.64
Spectral Width	25252.5
Lowest Frequency	-1054.3
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

Spectrum 37. ^{13}C NMR of 6,8-dichloro-9-ethyl-9H-purine (**49**).
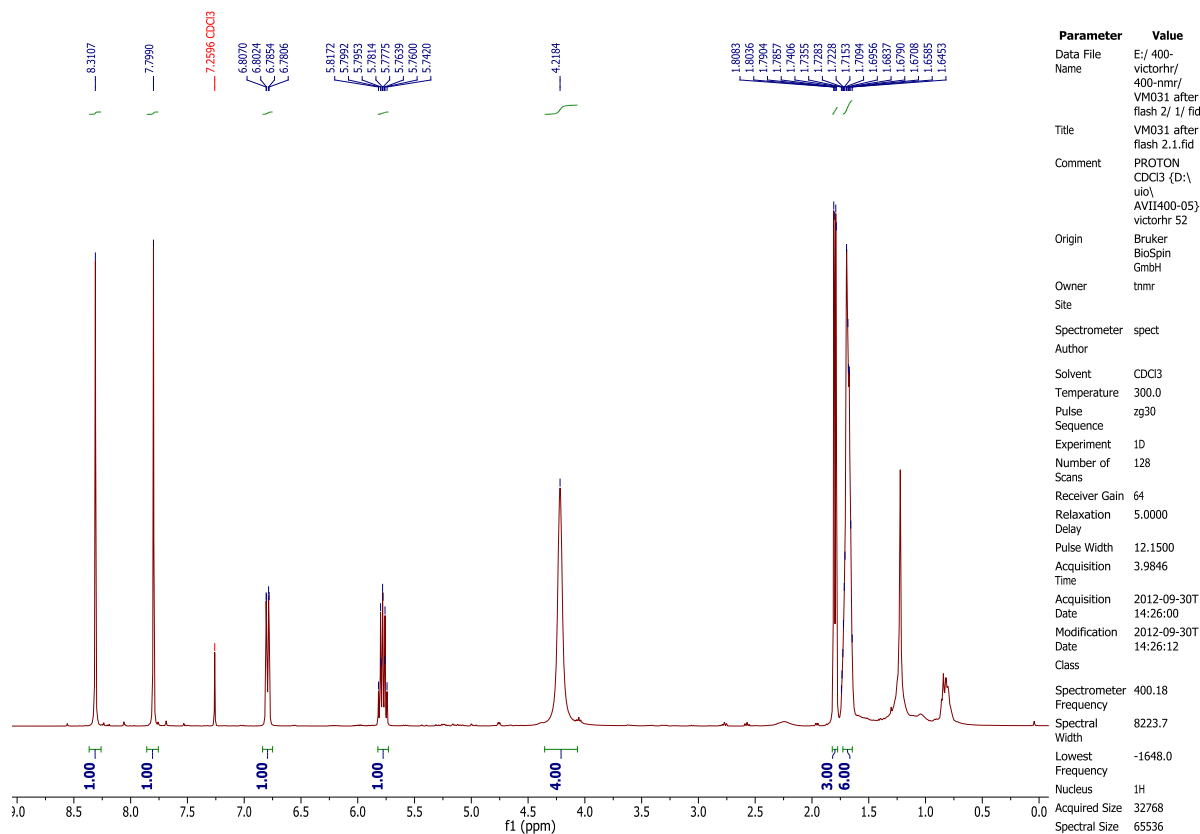
(Z)-6-(Piperidin-1-yl)-9-(prop-1-en-1-yl)-9H-purine (98)
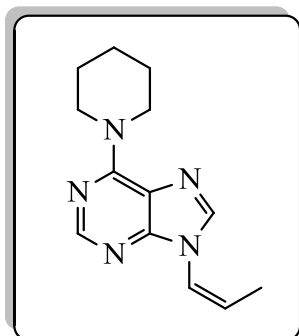
98

A solution of diisopropylamine (0.33 ml, 2.25 mmol) in dry THF (6 mL) was cooled to -78 ºC under N_2-atm. 1.03 M n-BuLi in hexane (2.04 mL, 2.10 mmol) was added dropwise over 10 min. and the mixture was stirred at -78 ºC under N_2-atm. for 1 h. 9-Allyl-6-(piperidin-1-yl)-9H-purine **33** (273 mg, 1.50 mmol) in dry THF (6 mL) was added dropwise over 10 min. to the reaction mixture and stirred at -78 ºC under N_2-atm. for 1 h. Sat. aq. NH_4Cl (45 mL) was added and the mixture was left to warm up to room temprature, and extracted with EtOAc (2 x 75 mL). The combined organic extracts were washed with brine (60 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The products were separated by flash chromatography eluting with 1:1 EtoAc:Hexane. This gave 101 mg (37%) of unaffected starting material **33** and 63 mg (23%) of *(Z)*-6-(piperidin-1-yl)-9-(prop-1-en-1-yl)-9H-purine **98** as a yellow oil.

¹H NMR (CDCl₃, 400 MHz) δ 1.58-1.76 (m, 6H, 3 x CH₂ in piperidinyl), 1.80 (dd, *J* = 7.2, 1.7 Hz, 3H, CH₃), 4.22 (brs, 4H, 2 x NCH₂ in piperidinyl), 5.72-5.82 (m, 1H, =CH in propenyl), 6.79 (dd, *J* = 8.6, 1.7 Hz, 1H, NCH= in propenyl), 7.80 (s, 1H, H-8), 8.31 (s, 1H, H-2).

¹³C NMR (CDCl3, 100 MHz) δ 12.8 (CH₃), 24.80 (CH₂ in piperdinyl), 26.1 (2 x CH₂ in piperdinyl), 46.3 (2 x NCH₂ in piperdinyl), 119.0 (C-5), 120.5 (NCH= in propenyl), 122.5 (=CH in propenyl), 137.1 (C-8), 150.7 (C-4), 152.8 (C-2), 153.8 (C-6).

MS (EI). *m/z* (rel. %): 244/243 (18/100, *M*⁺), 228 (10), 214 (56), 200 (24), 188 (27), 160 (17), 145 (15), 132 (5), 84 (15).

HRMS. Found 243.1482 calculated for $C_{13}H_{17}N_5$ 243.1484.

Spectrum 38. ^{1}H NMR of (*Z*)-6-(piperidin-1-yl)-9-(prop-1-en-1-yl)-9*H*-purine (**98**).
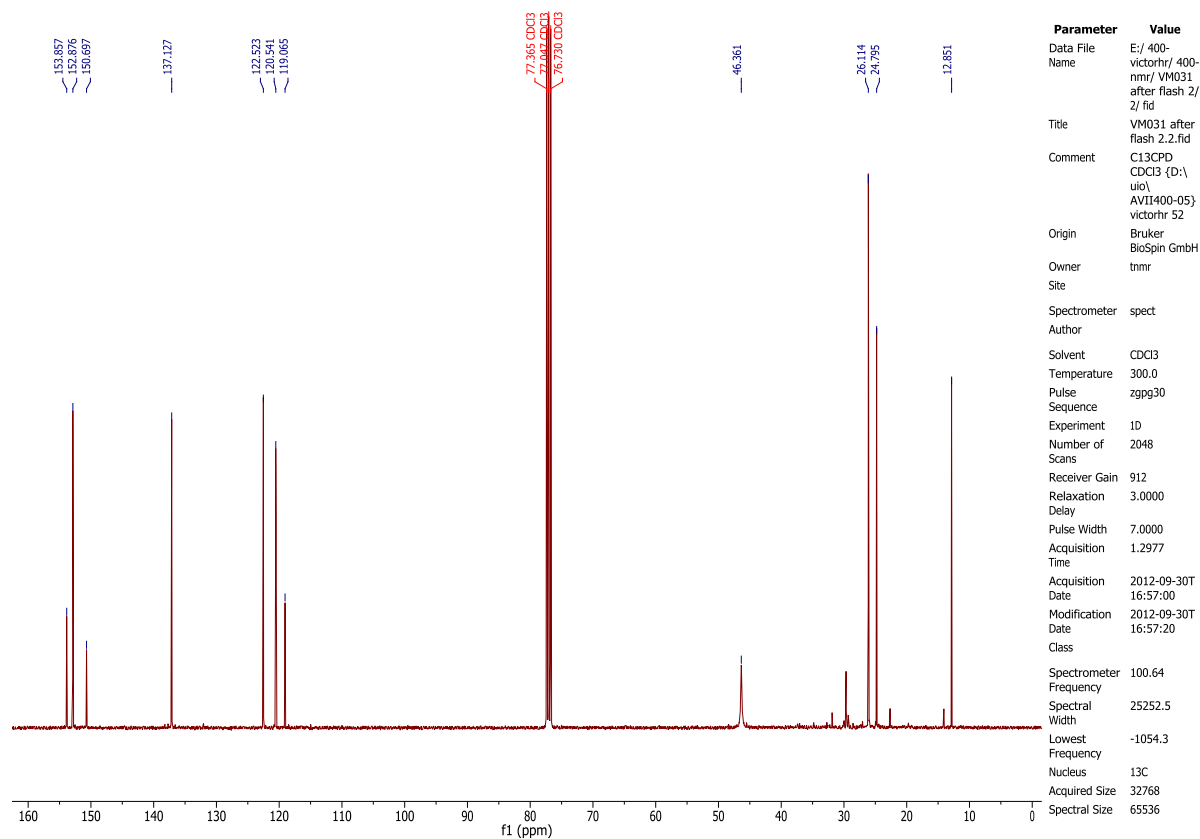
Spectrum 39. ^{13}C NMR of (*Z*)-6-(piperidin-1-yl)-9-(prop-1-en-1-yl)-9*H*-purine (**98**).

119
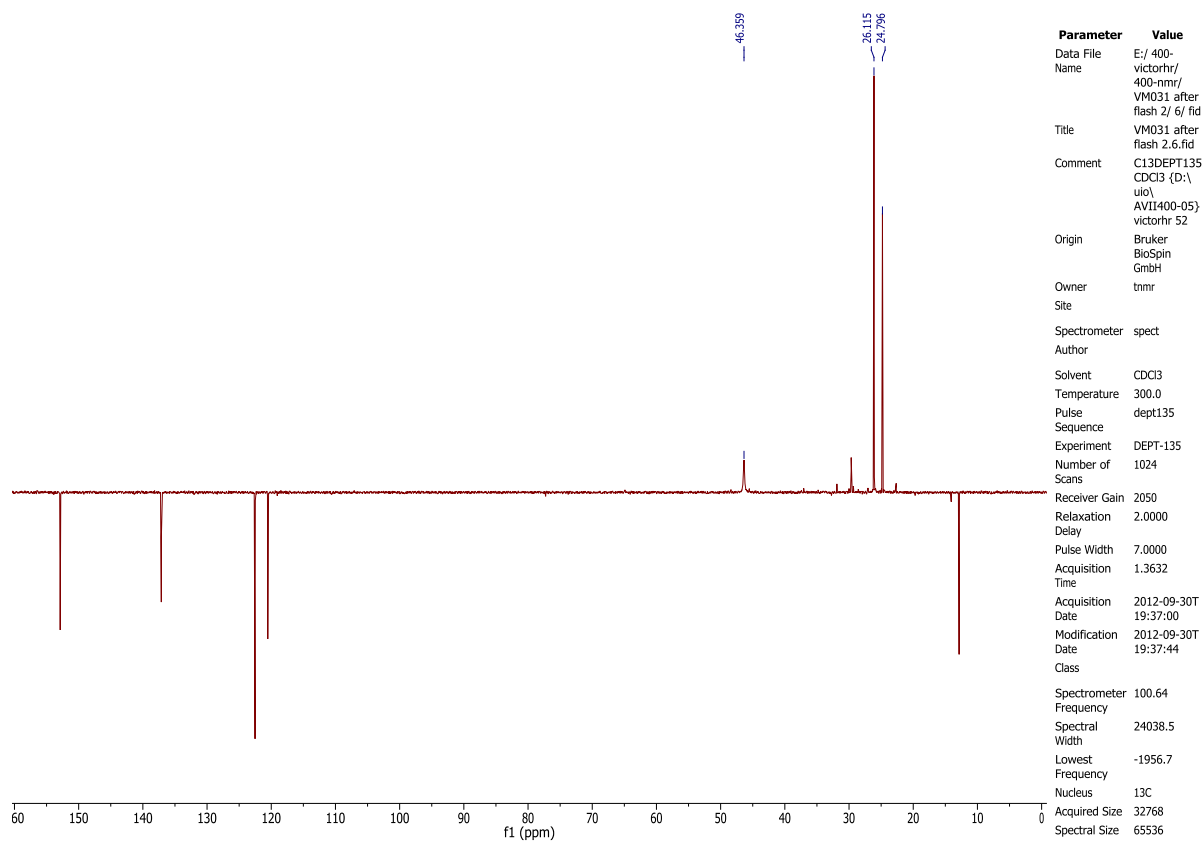
Spectrum 40. ^{13}C DEPT NMR of (*Z*)-6-(piperidin-1-yl)-9-(prop-1-en-1-yl)-9*H*-purine (**98**).

Spectrum 41. COSY NMR of (*Z*)-6-(piperidin-1-yl)-9-(prop-1-en-1-yl)-9*H*-purine (**98**).

Spectrum 42. HSQC NMR of (*Z*)-6-(piperidin-1-yl)-9-(prop-1-en-1-yl)-9*H*-purine (**98**).

Spectrum 43. HMBC NMR of (*Z*)-6-(piperidin-1-yl)-9-(prop-1-en-1-yl)-9*H*-purine (**98**).

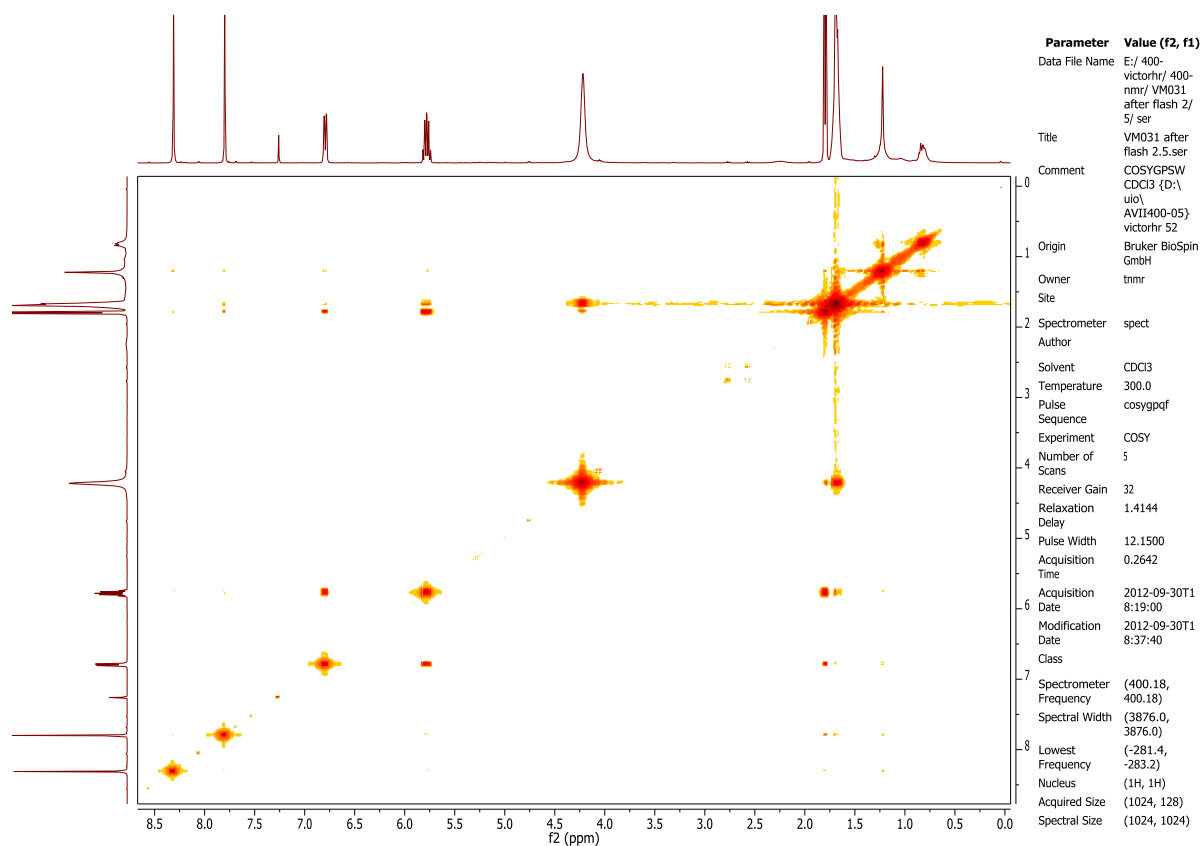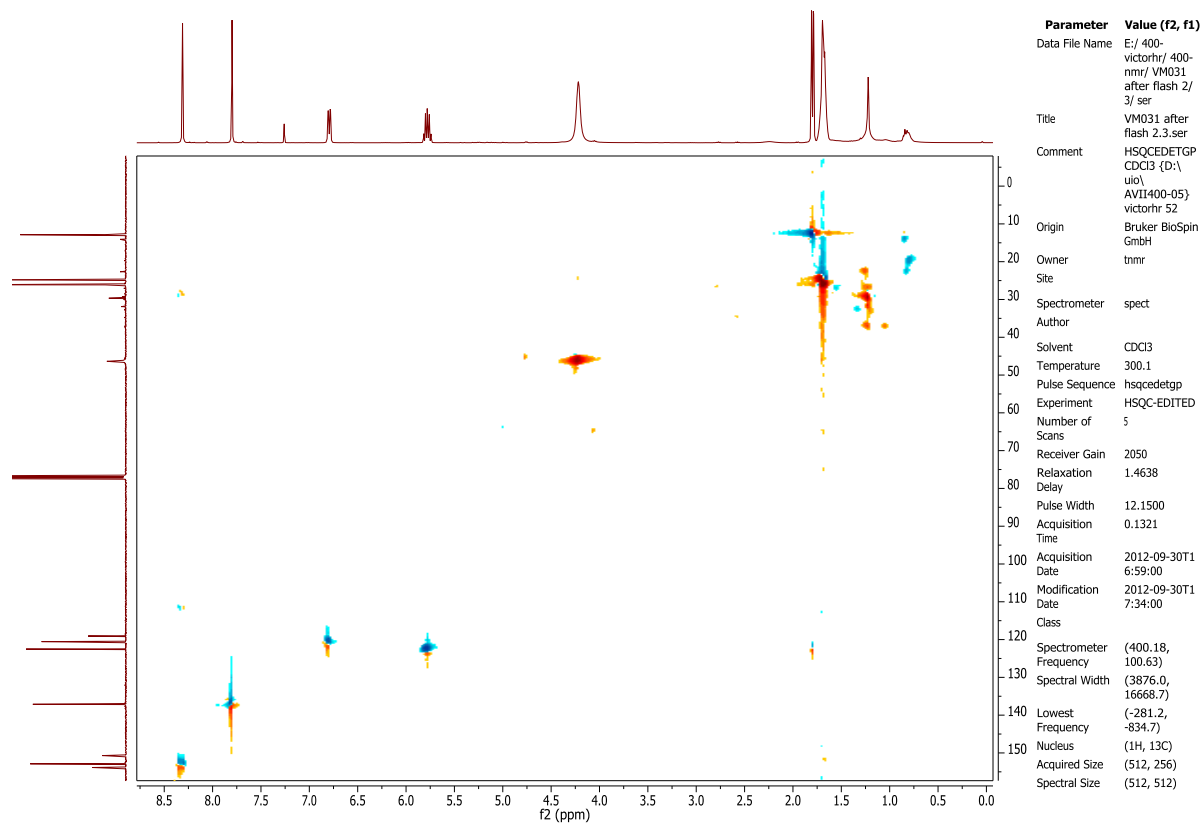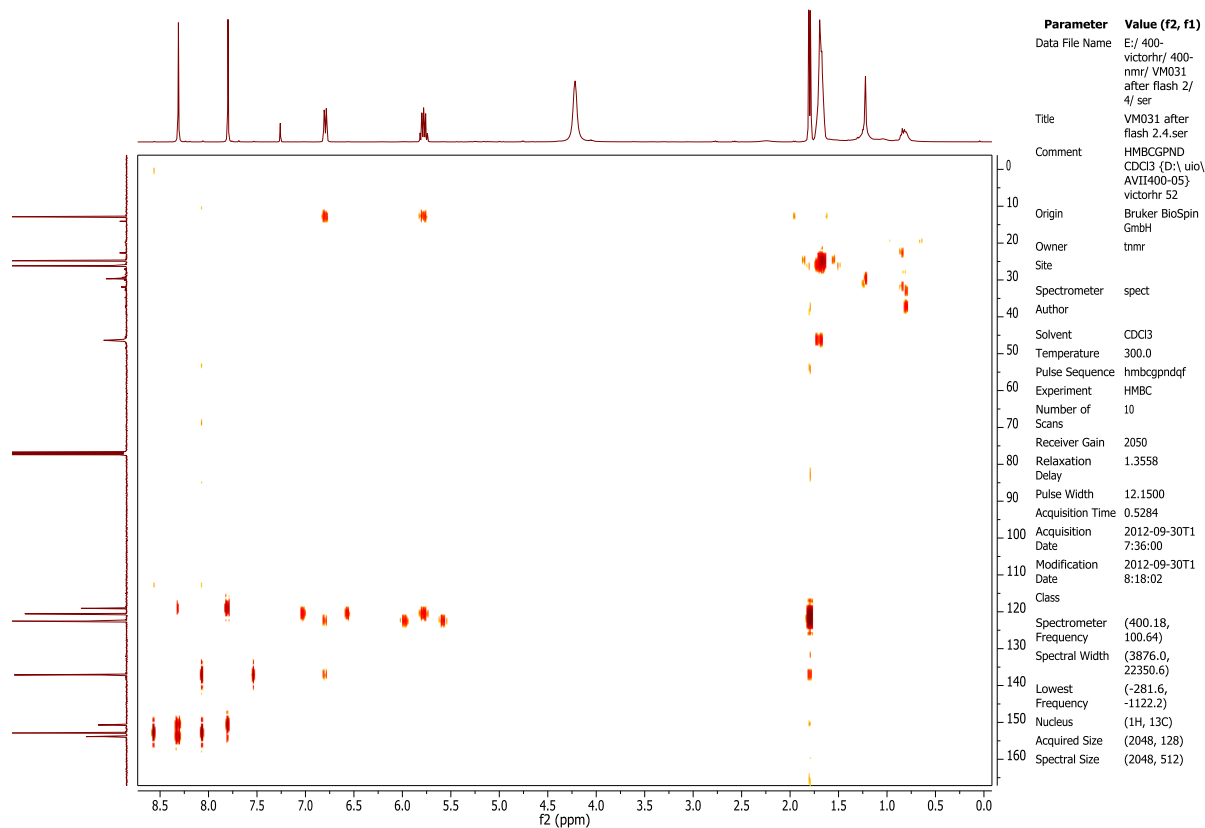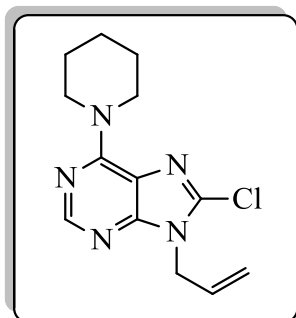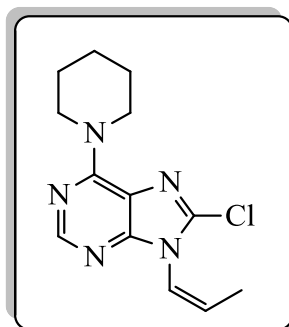**9-Allyl-8-chloro-6-(piperidin-1-yl)-9*H*-purine (96) and (*Z*)-8-chloro-6-(piperidin-1-yl)-9-(prop-1-en-1-yl)-9*H*-purine (97)**

96   **97**

A solution of diisopropylamine (0.44 mL, 3.0 mmol) in dry THF (8 mL) was cooled to -78 ºC under N_2-atm. 1.03 M *n*-BuLi in hexane (2.72 mL, 2.80 mmol) was added dropwise over 10 min. and the mixture was stirred at -78ºC under N_2-atm. for 1 h. 9-Allyl-6-(piperidin-1-yl)-9*H*-purine **33** (364 mg, 2.00 mmol) in dry THF (8 mL) was added dropwise over 10 min. to the reaction mixture and stirred at -78 ºC under N_2-atm. for 1 h. C_2Cl_6 (948 mg, 4.00 mmol) was dissolved in dry THF (4 mL) and added dropwise over 10 min to the reaction mixture and stirred at -78 ºC under N_2-atm. for 5 min. Sat. aq. NH_4Cl (60 mL) was added, the mixture was left to warm up to room temrature and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine (80 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The products were separated by flash chromatography eluting with 15% EtoAc in hexane. This gave 130 mg (31%) of 9-allyl-8-chloro-6-(piperidin-1-yl)-9*H*-purine **96** as a colourless solid and 90 mg (22%) of (*Z*)-8-chloro-6-(piperidin-1-yl)-9-(prop-1-en-1-yl)-9*H*-purine **97** as a yellow solid.

9-Allyl-8-chloro-6-(piperidin-1-yl)-9*H*-purine (**96**)

^{1}H NMR (CDCl$_3$, 200 MHz) δ 1.56-1.69 (m, 6H, 3 x CH$_2$ in piperidinyl), 4.16 (brs, 4H, 2x NCH$_2$ in piperidinyl), 4.73 (dt, *J* = 5.3, 1.6 Hz, 2H, CH$_2$ in allyl), 5.08 (d, *J* = 17.1, 1H, =CH$_{2a}$ in allyl), 5.18 (d, *J* = 10.4, 1H, =CH$_{2b}$ in allyl), 5.87-6.00 (m, 1H,=CH in allyl), 8.24 (s, 1H, H-2).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 24.7 (CH$_2$ in piperidinyl), 26.0 (2 x CH$_2$ in piperidinyl), 45.0 (CH$_2$ in allyl), 46.3 (2 x NCH$_2$ in piperdinyl), 118.1 (=CH$_2$ in allyl), 118.5 (C-5), 130.8 (=CH in allyl), 135.4 (C-8), 151.6 (C-4), 152.5 (C-2), 152.6 (C-6).

MS (EI). *m/z* (rel. %): 279/277 (33/100, *M*$^+$), 262 (12), 248 (57), 236 (38), 222 (25), 208 (24), 194 (21), 153 (9).

HRMS. Found 277.1090 calculated for C$_7$H$_6$Cl$_2$N$_4$ 277.1094.

M.p. 81-83 ºC.
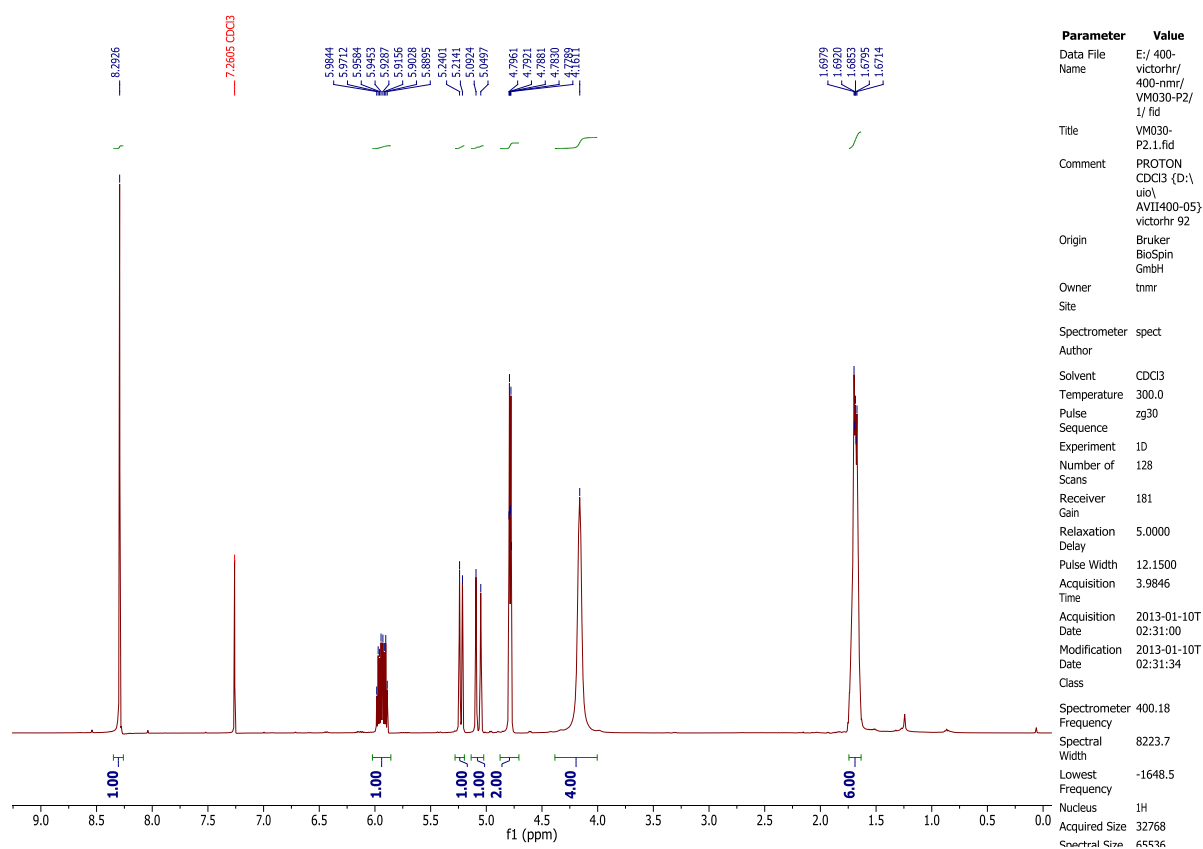
Spectrum 44. ^{1}H NMR of 9-allyl-8-chloro-6-(piperidin-1-yl)-9*H*-purine (**96**).
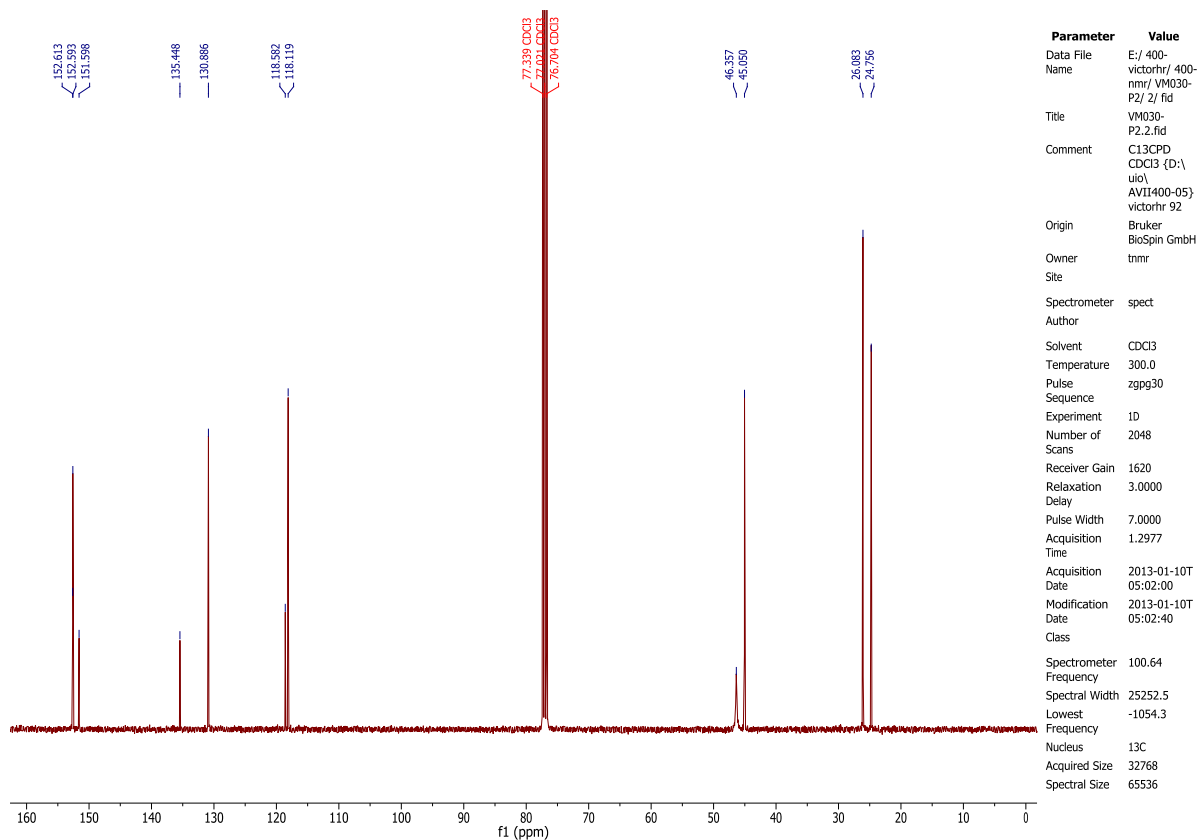
Spectrum 45. ^{13}C NMR of 9-allyl-8-chloro-6-(piperidin-1-yl)-9*H*-purine (**96**).
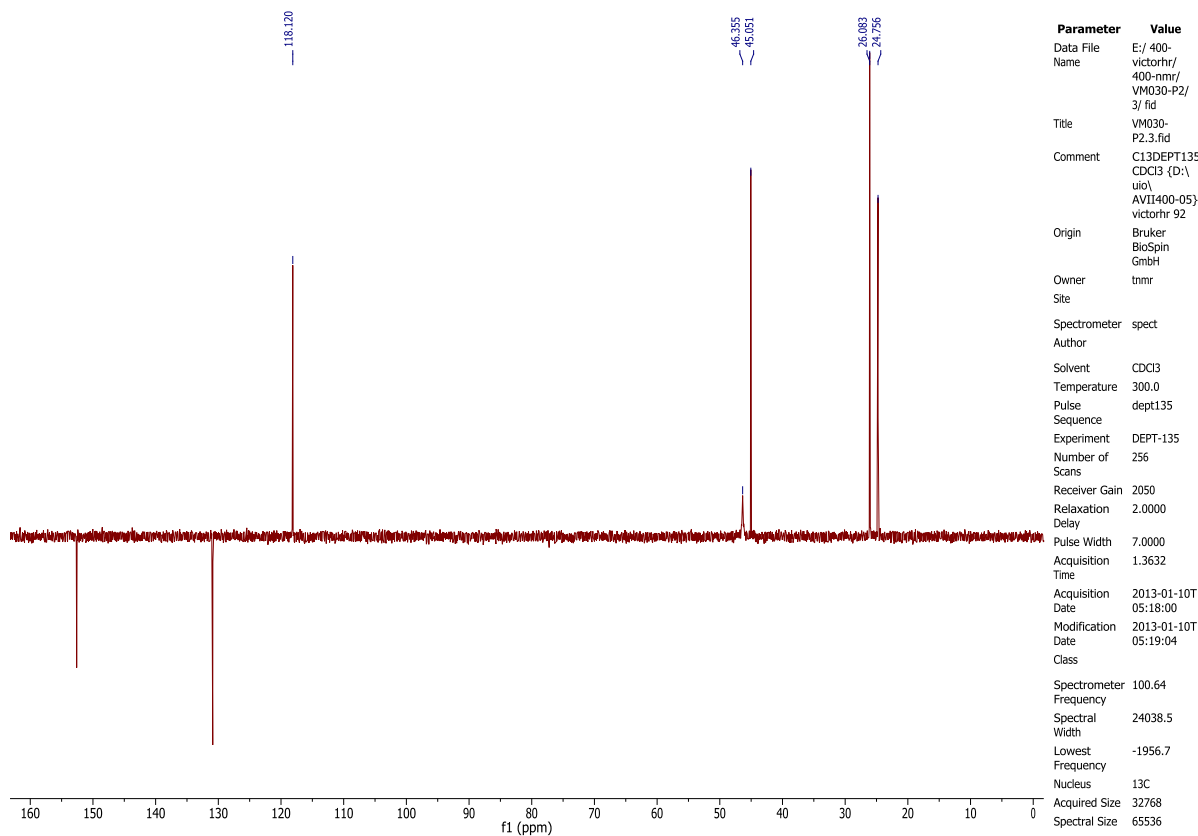
Spectrum 46. ^{13}C DEPT NMR of 9-allyl-8-chloro-6-(piperidin-1-yl)-9*H*-purine (**96**).
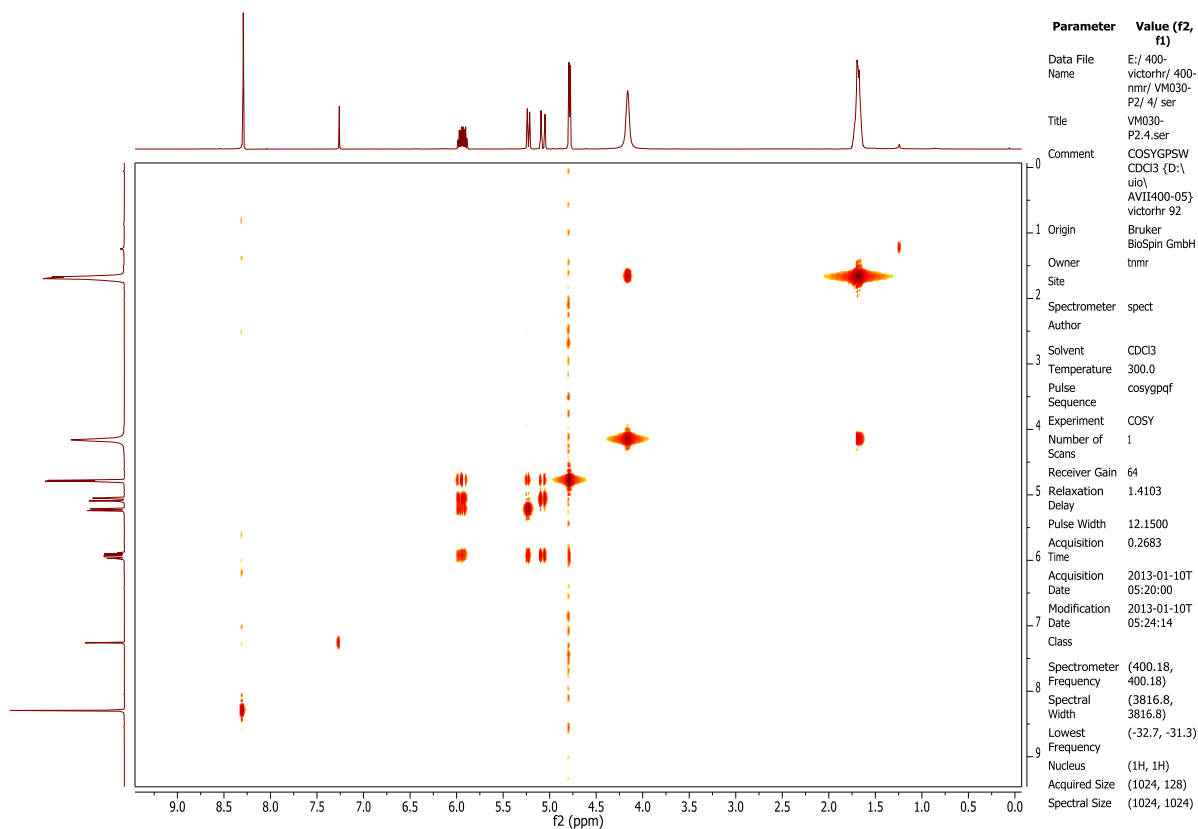
Spectrum 47. COSY NMR of 9-allyl-8-chloro-6-(piperidin-1-yl)-9*H*-purine (**96**).
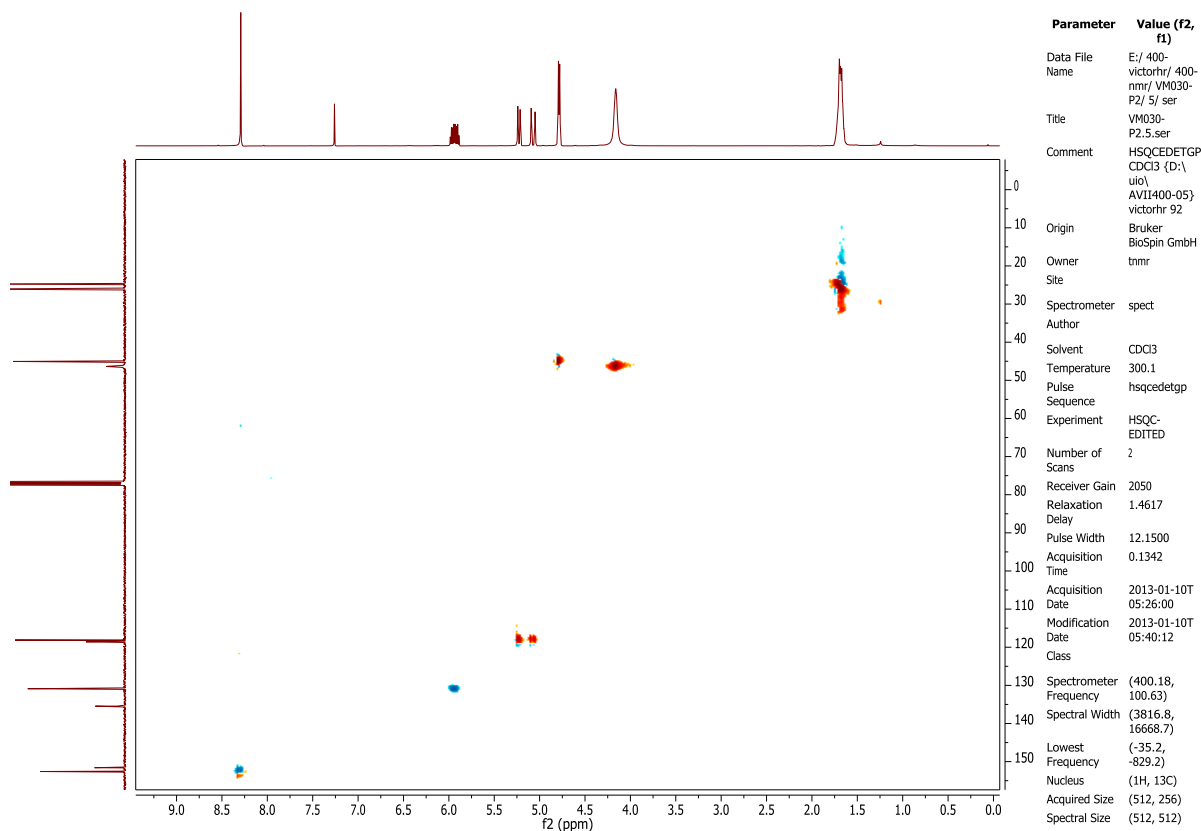
Spectrum 48. HSQC NMR of 9-allyl-8-chloro-6-(piperidin-1-yl)-9*H*-purine (**96**).
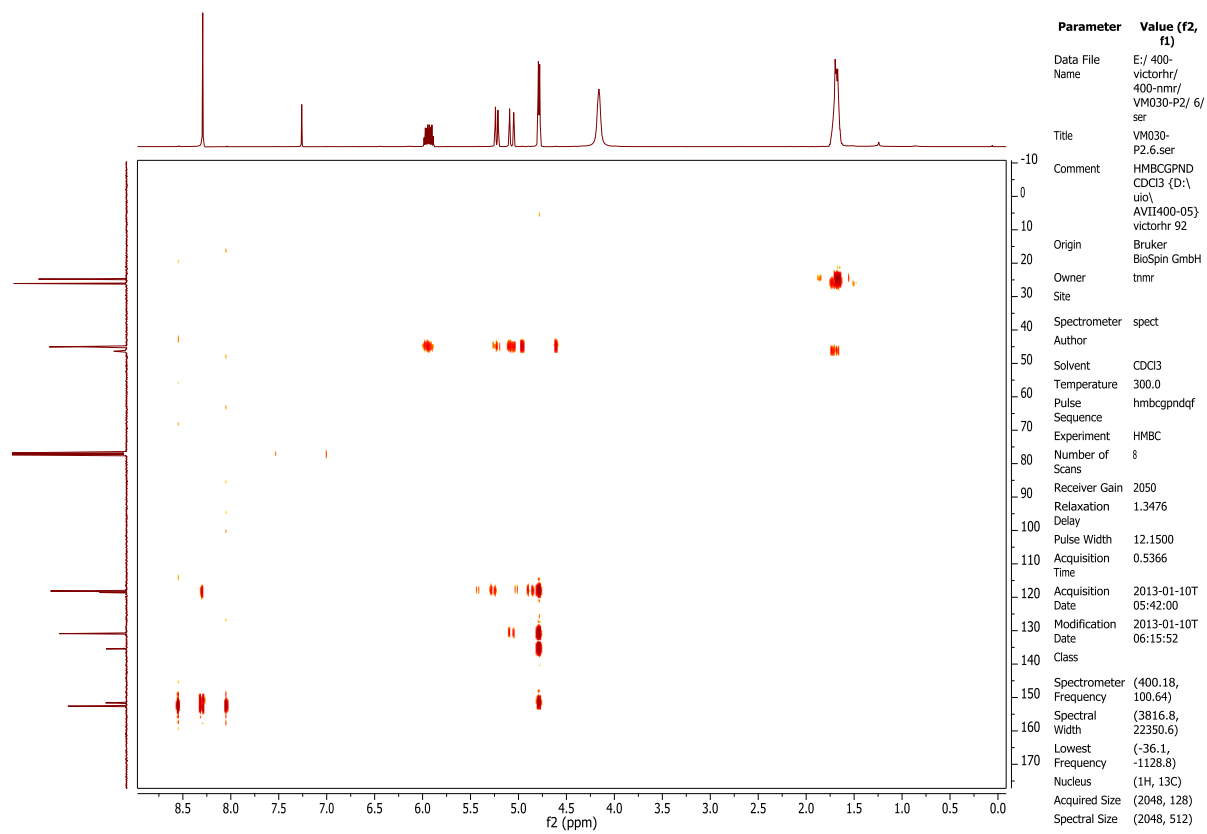
Spectrum 49. HMBC NMR of 9-allyl-8-chloro-6-(piperidin-1-yl)-9*H*-purine (**96**).

<u>(*Z*)-8-Chloro-6-(piperidin-1-yl)-9-(prop-1-en-1-yl)-9*H*-purine (**97**)</u>

^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.68 (dd, *J* = 7.0, 1.8 Hz, 3H, CH$_3$), 1.66-1.77 (m, 6H, 3×CH$_2$ in piperidinyl), 4.17 (brs, 4H, 2×NCH$_2$ in piperidinyl), 6.09-6.18 (m, 1H, =CH in propenyl), 6.49 (dd, *J* = 8.0, 1.8 Hz, 1H, NCH= in propenyl), 8.30 (s, 1H, H-2).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 13.2 (CH$_3$), 24.7 (CH$_2$ in piperidinyl), 26.1 (2×CH$_2$ in piperidinyl), 46.4 (2×NCH$_2$ in piperidinyl), 118.5 (=CH in propenyl), 119.5 (C-5), 131.4 (NCH= in propenyl), 135.2 (C-8), 152.1 (C-4), 152.6 (C-2), 152.8 (C-6).

MS (EI). *m/z* (rel. %): 279/277 (32/100, *M*$^+$), 262 (11), 248 (59), 234 (21), 221 (27), 208 (14), 194 (18), 179 (10).

HRMS. Found 277.1091 calculated for C$_{13}$H$_{16}$N$_5$Cl 277.1094.

M.p. 69-71 °C.
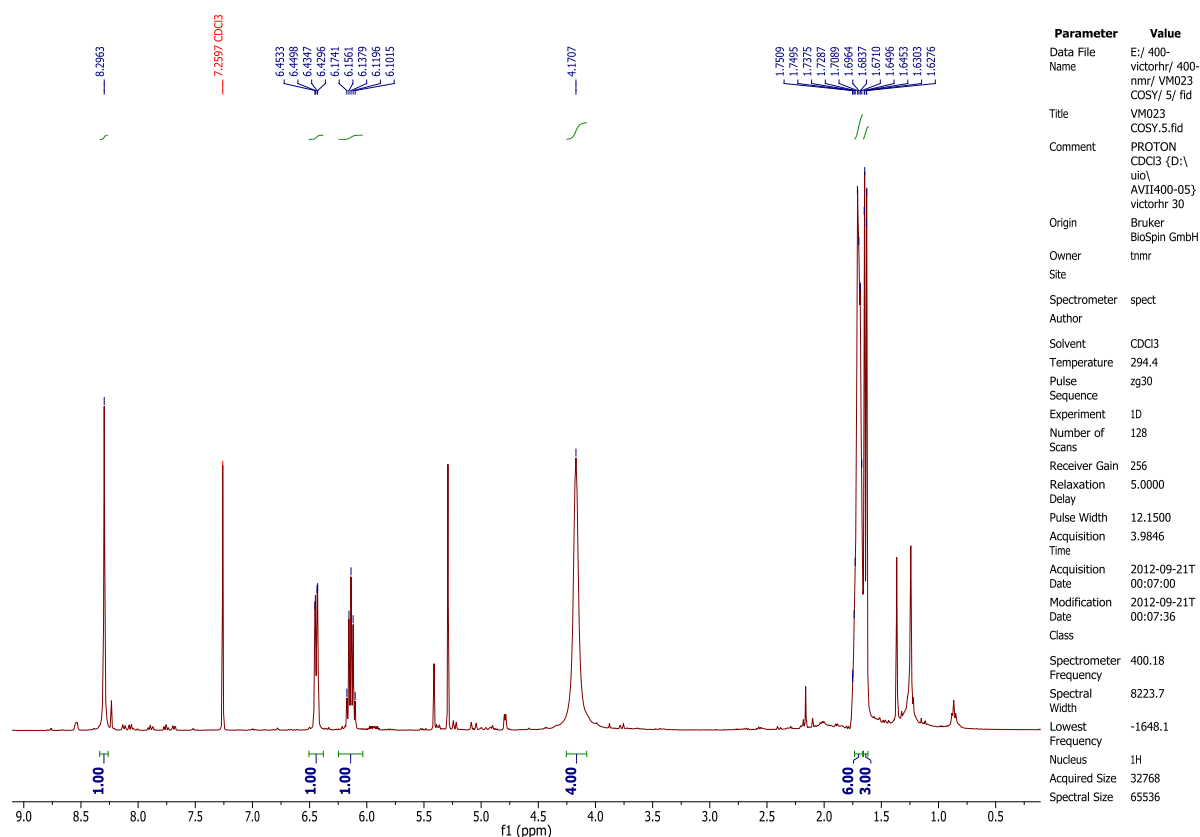
Spectrum 50. ^{1}H NMR of (*Z*)-8-chloro-6-(piperidin-1-yl)-9-(prop-1-en-1-yl)-9*H*-purine (**97**).
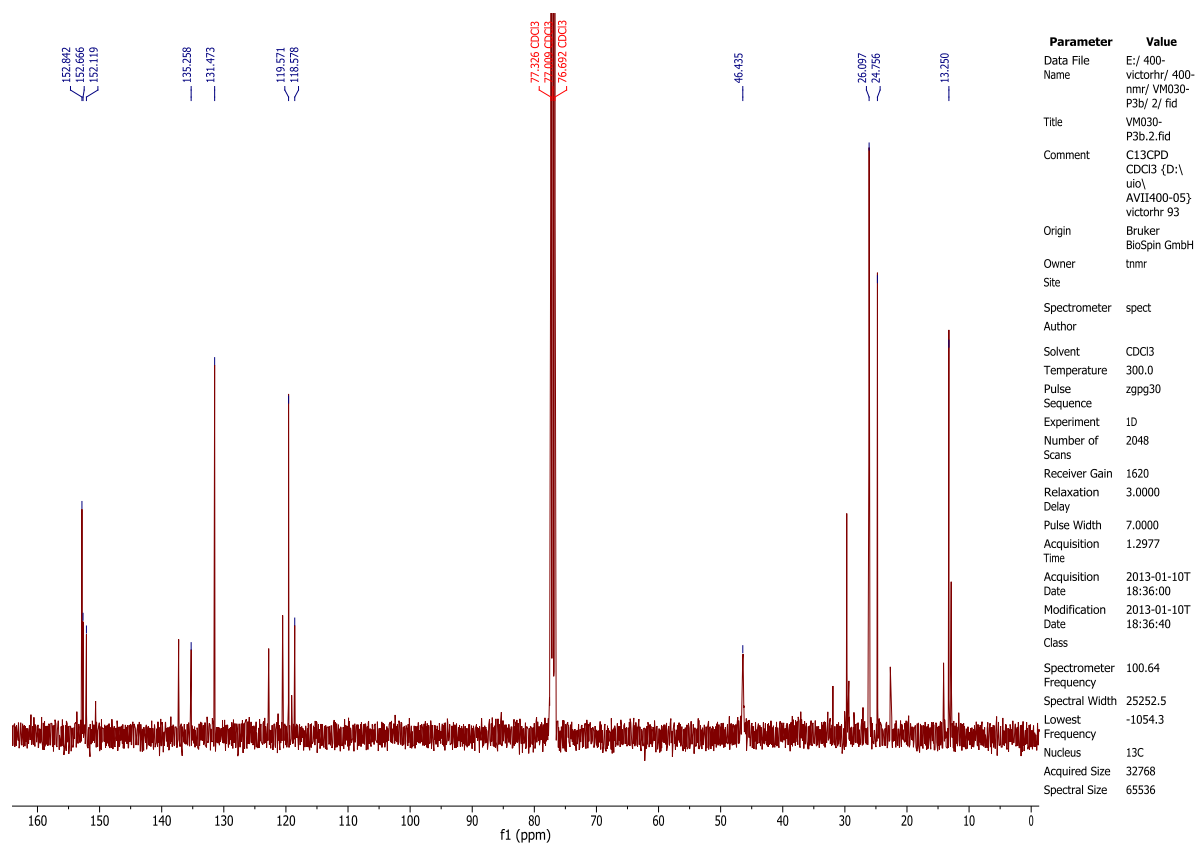
Spectrum 51. ^{13}C NMR of (*Z*)-8-chloro-6-(piperidin-1-yl)-9-(prop-1-en-1-yl)-9*H*-purine (**97**).
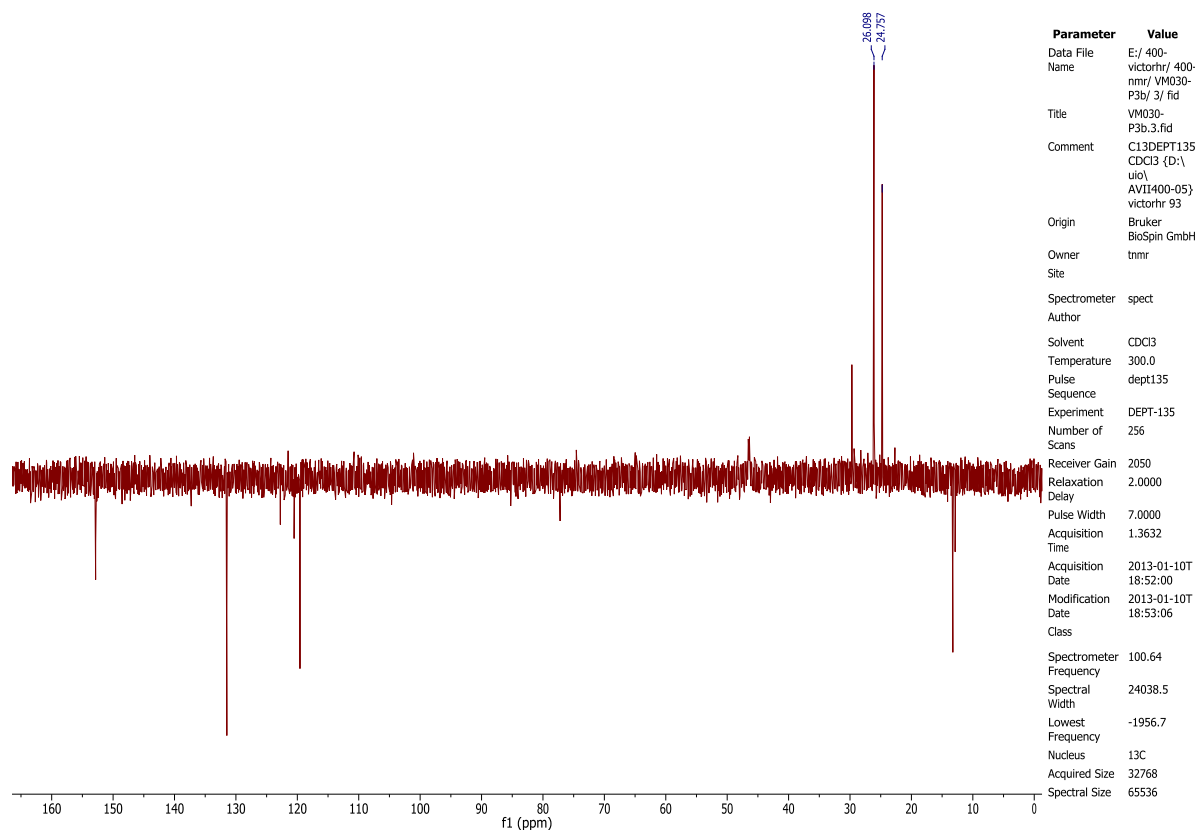
Spectrum 52. ^{13}C DEPT NMR of (*Z*)-8-chloro-6-(piperidin-1-yl)-9-(prop-1-en-1-yl)-9*H*-purine (**97**).
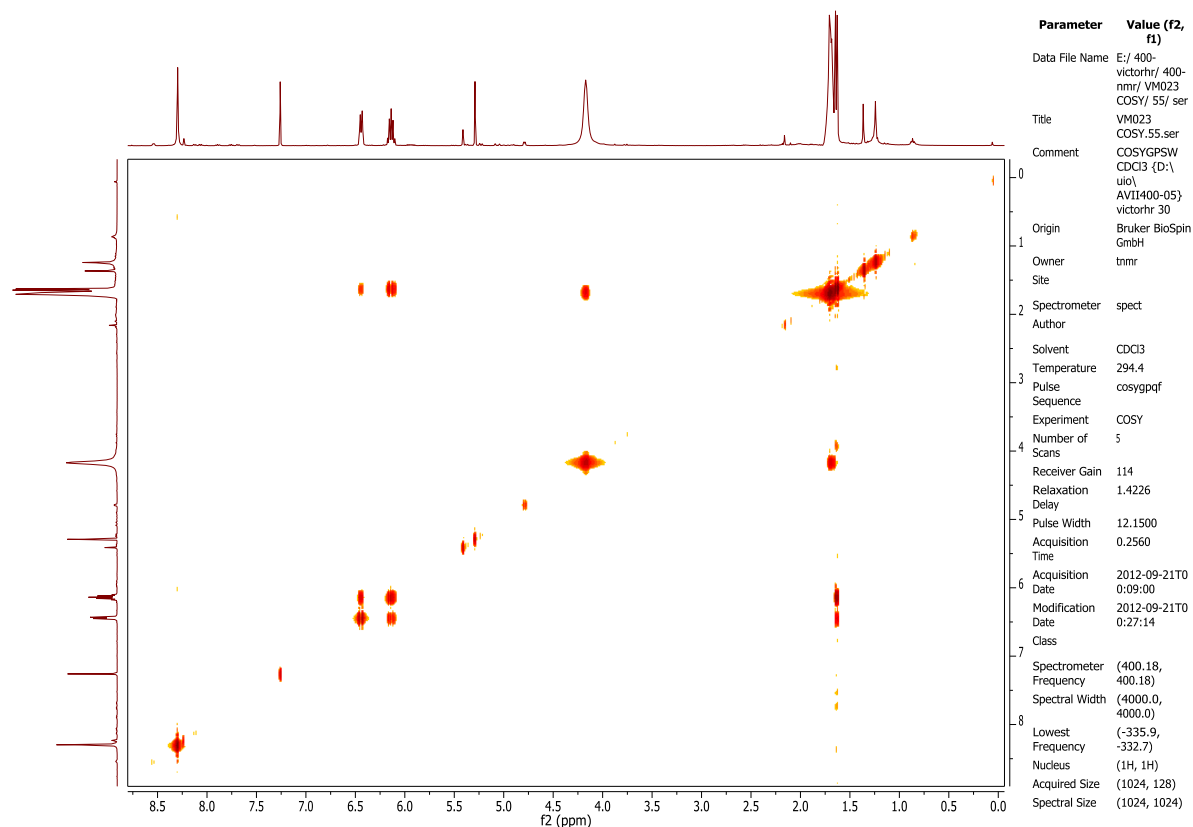
Spectrum 53. COSY NMR of (*Z*)-8-chloro-6-(piperidin-1-yl)-9-(prop-1-en-1-yl)-9*H*-purine (**97**).
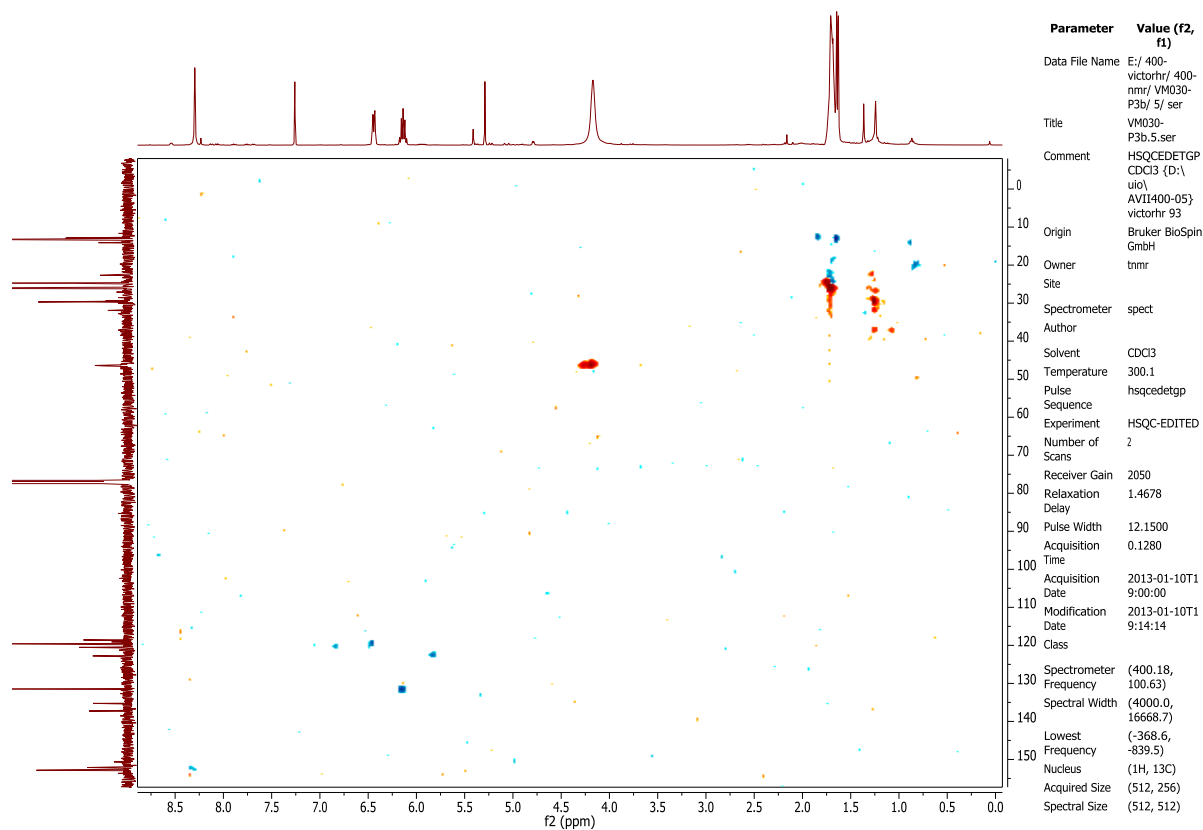
Spectrum 54. HSQC NMR of (*Z*)-8-chloro-6-(piperidin-1-yl)-9-(prop-1-en-1-yl)-9*H*-purine (**97**).

Parameter	Value (f2, f1)
Data File Name	E:/ 400-victorhr/ 400-nmr/ VM030-P3b/ 6/ ser
Title	VM030-P3b.6.ser
Comment	HMBCGPND CDCl3 {D:\ uio\ AVII400-05} victorhr 93
Origin	Bruker BioSpin GmbH
Owner	tnmr
Site	
Spectrometer	spect
Author	
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	hmbcgpndqf
Experiment	HMBC
Number of Scans	8
Receiver Gain	2050
Relaxation Delay	1.3722
Pulse Width	12.1500
Acquisition Time	0.5121
Acquisition Date	2013-01-10T19:16:00
Modification Date	2013-01-10T19:49:54
Class	
Spectrometer Frequency	(400.18, 100.64)
Spectral Width	(4000.0, 22350.6)
Lowest Frequency	(-376.5, -1121.3)
Nucleus	(1H, 13C)
Acquired Size	(2048, 128)
Spectral Size	(2048, 512)

Spectrum 55. HMBC NMR of (*Z*)-8-chloro-6-(piperidin-1-yl)-9-(prop-1-en-1-yl)-9*H*-purine (**97**).

8,9-Diallyl-6-(piperidin-1-yl)-9H-purine (71)[23]
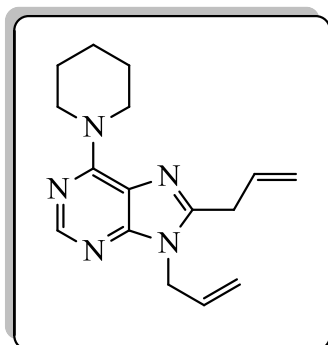
71

Allylmagnesium bromide (2.02 mL, 1.35 mmol, 0.67 M solution in diethyl ether) was added to a solution of compound **33** (109 mg, 0.448 mmol) in THF (5 mL) at 0 ℃ under N_2-atm and the resulting mixture was stirred at 0 ℃ for 4 h. Sat. aq. NH_4Cl (10 mL) was added, the phases were separated and the water layer was extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The product was purified by flash chromatography eluting with acetone-EtOAc-hexane (1:1:8) to give 113 mg (89%) of 8,9-diallyl-6-(piperidin-1-yl)-9H-purine **71** as a yellow oil.

^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.55-1.75 (m, 6H, 3×CH$_2$ in piperidinyl), 3.56 (d, J = 6.2, 2H, C(8)CH$_2$), 4.18 (brs, 4H, 2×NCH$_2$ in piperidinyl), 4.72 (d, J = 5.0, 2H, N(9)CH$_2$), 4.89 (d, J = 17.2 Hz, 1H, =CH$_{2a}$ in C(8) allyl), 5.04-5.22 (m, 3H, =CH$_{2b}$ in C(8) allyl and =CH$_2$ in N(9) allyl), 5.80-6.07 (m, 2H, 2×CH= in C(8) allyl and N(9) allyl), 8.25 (s, 1H, H-2).

^{13}C NMR (CDCl3, 100 MHz) δ 24.8 (CH$_2$ in piperidinyl), 26.0 (2×CH$_2$ in piperidinyl), 32.41 (C(8)CH$_2$), 44.17 (N(9)CH$_2$), 46.29 (2×NCH$_2$ in piperidinyl), 116.99 (=CH$_2$ in C(8) allyl), 117.67 (=CH$_2$ in N(9) allyl), 118.88 (C-5), 132.19 (CH= in N(9) allyl), 132.58 (CH= in C(8) allyl), 147.67 (C-8), 151.81 (C-4), 151.84 (C-2), 153.31 (C-6).

MS (EI). *m/z* (rel. %): 284/283 (21/100, M^+), 254 (38), 242 (37), 227 (33), 214 (22), 200 (18), 187 (10), 159 (9).

HRMS. Found 283.1792 calculated for $C_{16}H_{21}N_5$ 283.1797.
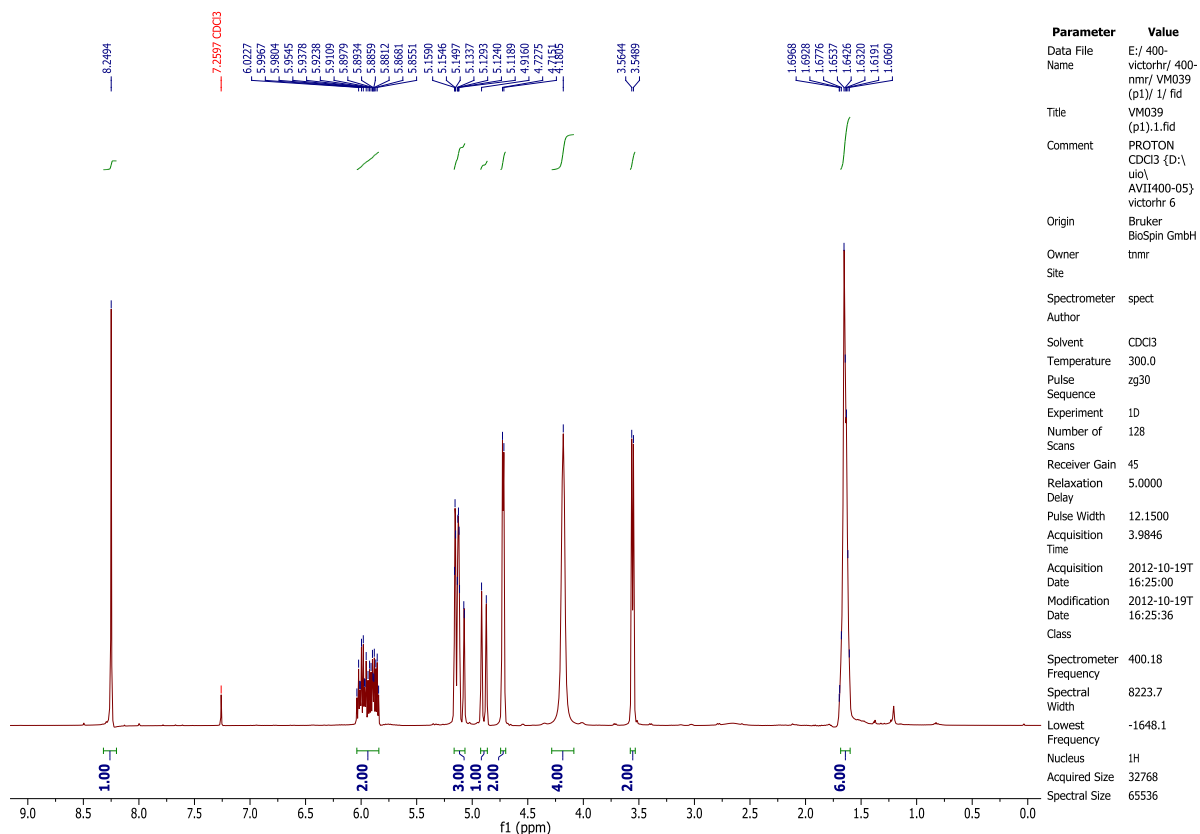
Spectrum 56. ^{1}H NMR of 8,9-diallyl-6-(piperidin-1-yl)-9*H*-purine (**71**).
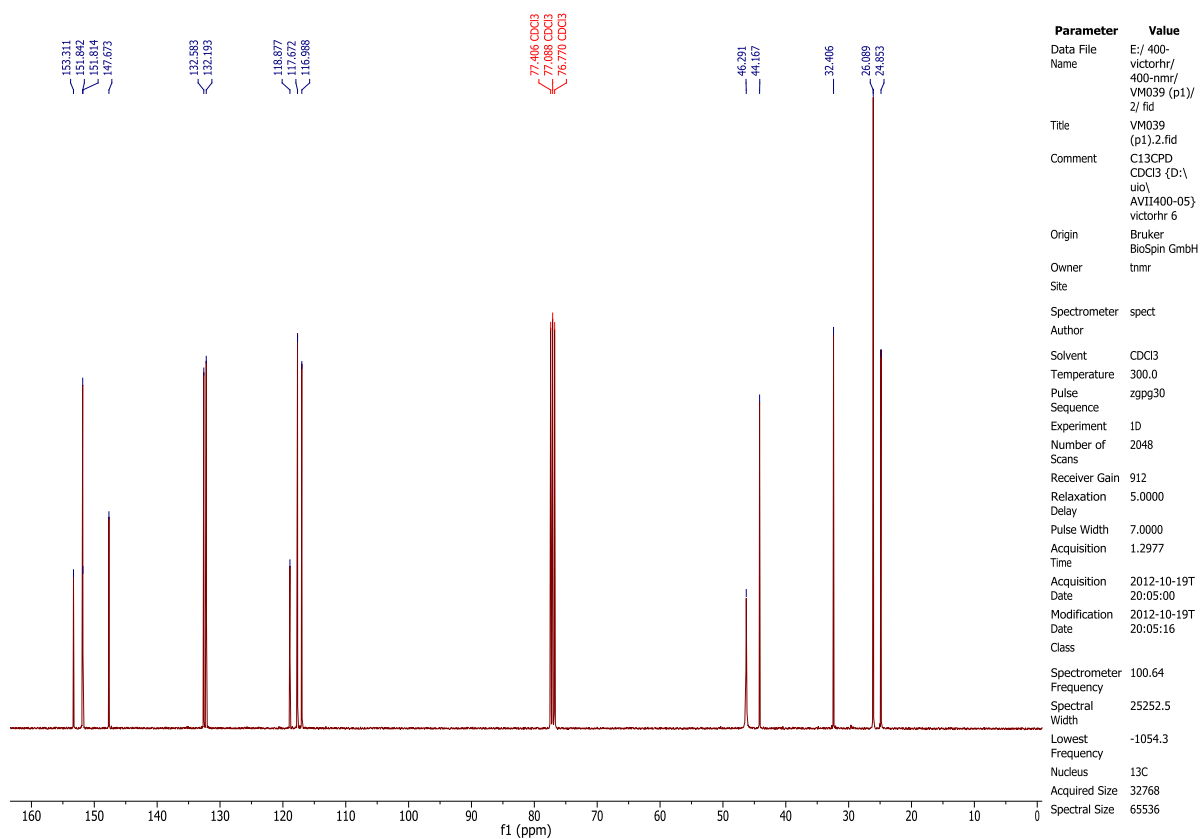
Spectrum 57. ^{13}C NMR of 8,9-diallyl-6-(piperidin-1-yl)-9*H*-purine (**71**).

4-(Piperidin-1-yl)-6,9-dihydropyrido[1,2-*e*]purine (74)
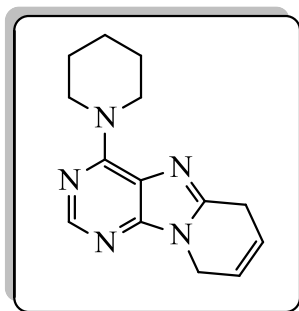
74

Grubbs' 2nd generation catalyst [26 mg (in 4 parts each after 2 h), 0.030 mmol] was added to a solution of compound **71** (45 mg, 0.15 mmol) in dry DCM (25 mL) after removing the air by a pump and filling with argon (three cycles) and the solution was stirred at room temprature for 48 h. After the evaporation of the solvent the residue was purified by column chromatography [silica gel, hexane – ethyl acetate (2:1)] to give 38 mg (94%) of 4-(piperidin-1-yl)-6,9-dihydropyrido[1,2-*e*]purine **74** as a yellow solid.

¹H NMR (CDCl$_3$, 400 MHz) δ 1.55-1.75 (m, 6H, 3×CH$_2$ in piperidine), 3.54-3.65 (m, 2H, C(8)CH$_2$), 4.18 (brs, 4H, 2×NCH$_2$ in piperidine), 4.63-4.71 (m, 2H, N(9)CH$_2$), 5.94-6.08 (m, 2H, CH=CH), 8.32 (s, 1H, H-2).

¹³C NMR (CDCl3, 100 MHz) δ 24.8 (CH$_2$ in piperdine), 25.5(C(8)CH$_2$), 26.1 (2 ×CH$_2$ in piperidine), 42.0 (N(9)CH$_2$), 46.3 (2×NCH$_2$ in piperdine), 119.3 (C-5), 119.9 (CH=), 122.1 (CH=), 143.8 (C-8), 150.6 (C-4), 151.5 (C-2), 153.2 (C-6).

MS (EI). *m/z* (rel. %): 256/255 (15/100, *M*[+]), 226 (51), 212 (27), 200 (27), 199 (34), 187 (15), 172 (19), 145 (17), 84 (9).

HRMS. Found 255.1480 calculated for C$_{14}$H$_{17}$N$_5$ 255.1484.

M.p. 110-112 ℃ (Lit.[23] 113-115 ℃).
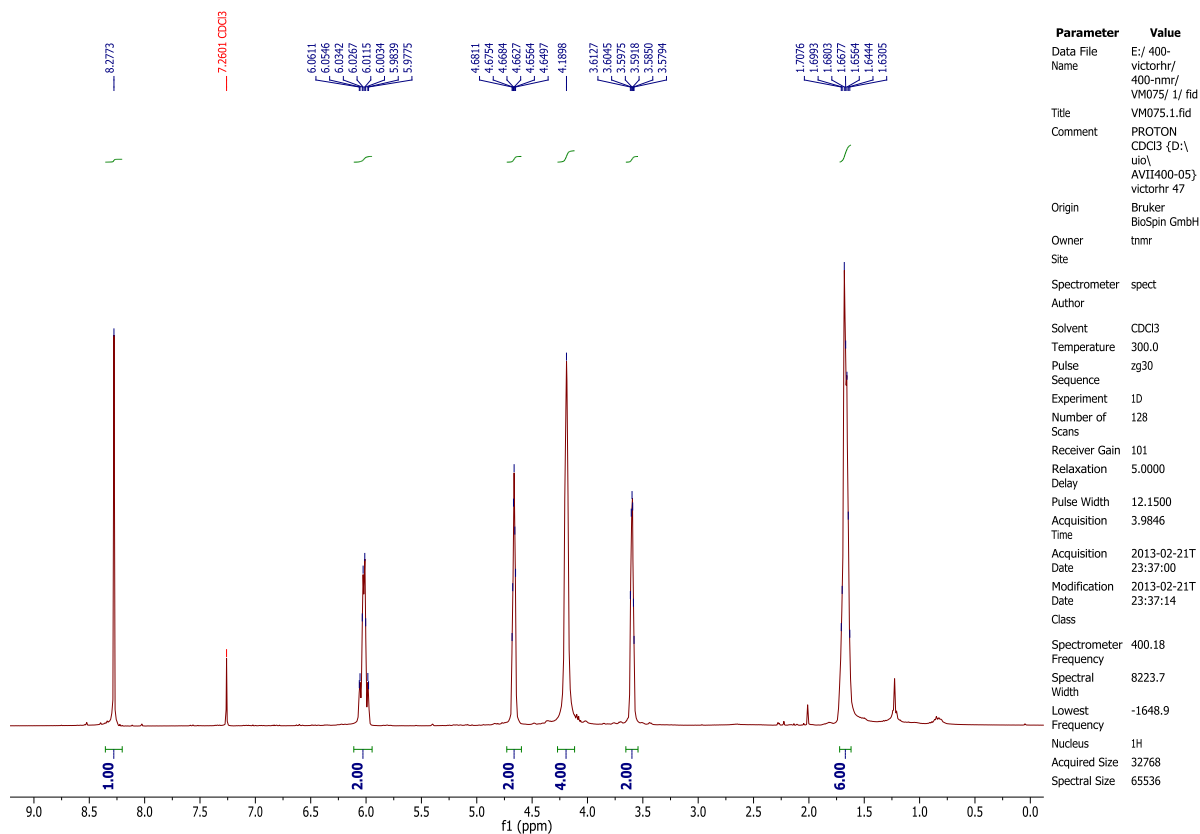
Spectrum 58. ^{1}H NMR of 4-(piperidin-1-yl)-6,9-dihydropyrido[1,2-*e*]purine (**74**).
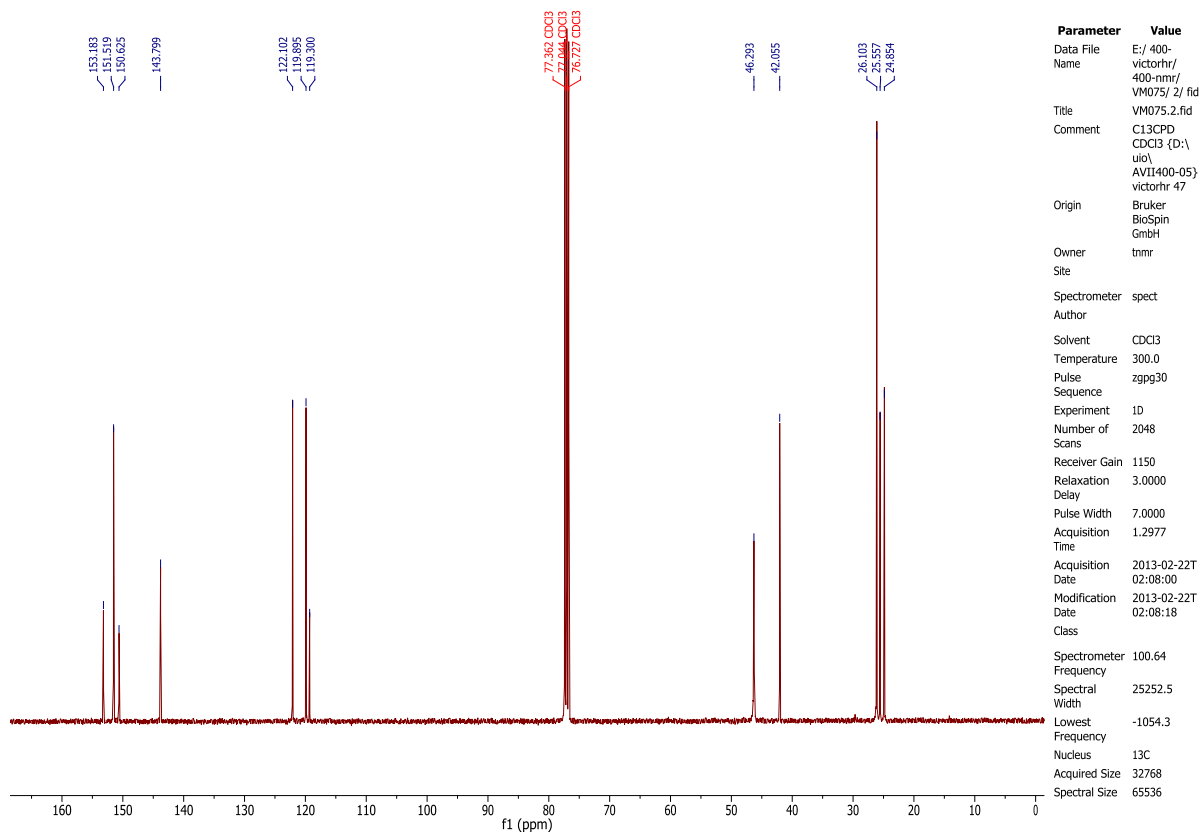
Spectrum 59. ^{13}C NMR of 4-(piperidin-1-yl)-6,9-dihydropyrido[1,2-*e*]purine (**74**).

134

4-(Piperidin-1-yl)pyrido[1,2-*e*]purine (7)
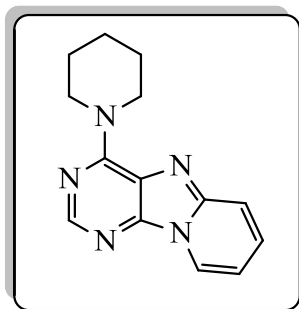
7

DDQ (209 mg, 0.920 mmol) was added to a solution of compound **74** (117 mg, 0.460 mmol) in dry DCM (40 mL) at room temperature and the resulting mixture was stirred for 24 h and evaporated *in vacuo*. The product was purified by flash chromatography on silica gel eluting with EtOAc-hexane (1:1) to give 102 mg (87%) of 4-(piperidin-1-yl)pyrido[1,2-*e*]purine **7** as a colourless solid.

^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.67-1.81 (m, 6H, 3×CH$_2$), 4.20-4.52 (s, 4H, 2×NCH$_2$), 6.83-6.89 (m, 1H, N(9)CH=C$\underline{H}$), 7.34-7.40 (m, 1H, C(8)CH=C$\underline{H}$), 7.61 (d, *J* = 9.3 Hz, 1H, C(8)CH), 8.43 (s, 1H, H-2), 8.57 (d, *J* = 6.7 Hz, 1H, N(9)CH).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 24.8 (CH$_2$), 26.2 (2×CH$_2$), 46.7 (2×NCH$_2$), 111.4 (N(9)CH=$\underline{C}$H), 118.3 (C(8)$\underline{C}$H), 122.1 (C-5), 124.1 (N(9)$\underline{C}$H), 129.2 (C(8)CH=$\underline{C}$H), 143.9 (C-8), 144.7 (C-4), 150.3 (C-2), 154.2 (C-6).

MS (EI). *m/z* (rel. %): 254/253 (17/100, *M*$^+$), 224 (35), 210 (32), 198 (22), 197 (34), 185 (21), 170 (23), 143 (34), 84 (11), 78 (22).

HRMS. Found 253.1322 calculated for C$_{14}$H$_{15}$N$_5$ 253.1327.

M.p. 125-127 ^{o}C (Lit.[1] 124-126 ^{o}C).

Spectrum 60. ^{1}H NMR of 4-(piperidin-1-yl)pyrido[1,2-*e*]purine (**7**).

Spectrum 61. ^{13}C NMR of 4-(piperidin-1-yl)pyrido[1,2-*e*]purine (**7**).

8,9-Diallyl-6-chloro-9*H*-purine (100a) and 8,9-diallyl-6-chloro-8,9-dihydro-7*H*-purine (100b)

Method A:
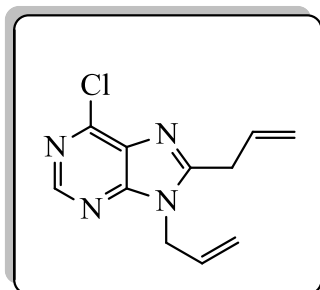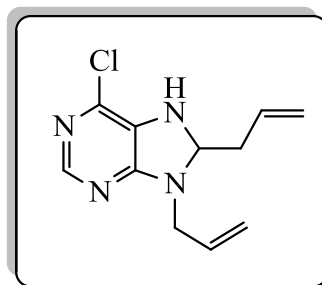
100a   **100b**

Allylmagnesium bromide (1.42 mL, 0.95 mmol of 0.67 M solution in diethyl ether) was added to a solution of compound **19** (88 mg, 0.45 mmol) in THF (5 mL) at 0 ºC under N_2-atm, and the resulting mixture was stirred at 0 ºC for 20 min. Sat. aq. NH_4Cl (10 mL) was added, the phases were separated and the water layer was extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The products were isloated by flash chromatography on silica gel eluting with acetone-EtOAc-hexane (1:1:8) to afford 11 mg (10%) of 8,9-diallyl-6-chloro-9*H*-purine **100a** as a yellow oil and 237 mg (74%) of 8,9-diallyl-6-chloro-8,9-dihydro-7*H*-purine **100b** as a yellow oil.

8,9-Diallyl-6-chloro-9*H*-purine (**100a**)

¹H NMR (CDCl$_3$, 400 MHz) 3.69 (d, *J* = 6.2, 2H, C(8)CH$_2$), 4.83 (d, *J* = 5.3, 2H, N(9)CH$_2$), 4.96 (d, *J* = 17.1 Hz, 1H, =CH$_{2a}$ in C(8) allyl), 5.15 (d, *J* = 17.1 Hz, 1H, =CH$_{2a}$ in N(9) allyl) 5.21 (d, *J* = 10.2 Hz, 2H, =CH$_{2b}$ in N(9) allyl and =CH$_{2b}$ in C(8) allyl), 5.84-6.06 (m, 2H, 2×CH=), 8.60 (s, 1H, H-2).

¹³C NMR (CDCl$_3$, 100 MHz) δ 32.7 (C(8)CH$_2$), 44.9 (N(9)CH$_2$), 118.2 (=CH$_2$ in C(8) allyl), 119.1 (=CH$_2$ in N(9) allyl), 130.8 (C-5), 130.9 (CH= in N(9) allyl), 131.0 (CH= in C(8) allyl), 149.2 (C-4), 151.3 (C-2), 152.9 (C-6), 156.1 (C-8).

MS (EI). *m/z* (rel. %): 236/234 (24/73, *M*⁺), 233 (100), 219 (9), 207 (21), 193 (43), 168 (6), 157 (12).

HRMS. Found 234.0672 calculated for C$_{11}$H$_{11}$N$_4$Cl 234.0672
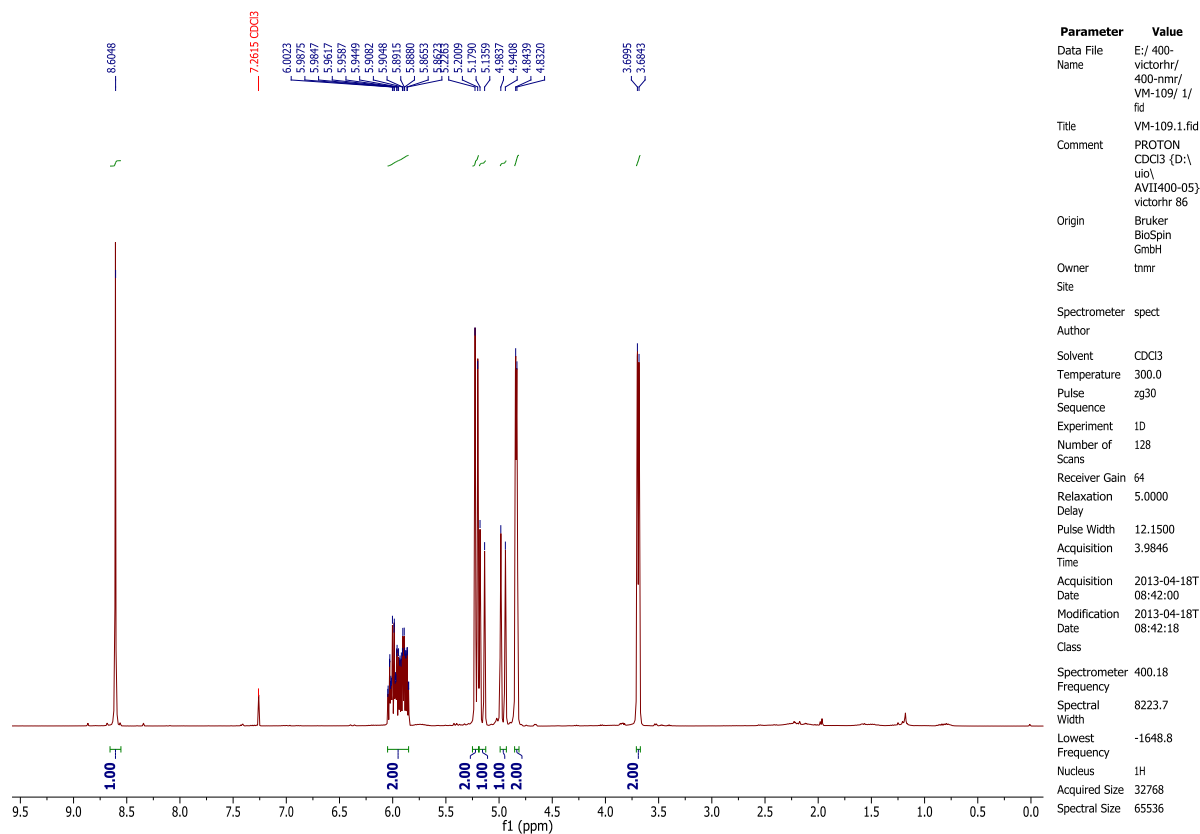
Spectrum 62. ¹H NMR of 8,9-diallyl-6-chloro-9*H*-purine (**100a**).

Spectrum 63. ¹³C NMR of 8,9-diallyl-6-chloro-9*H*-purine (**100a**).

Spectrum 64. ^{13}C DEPT NMR of 8,9-diallyl-6-chloro-9*H*-purine (**100a**).

Spectrum 65. ^{13}C APT NMR of 8,9-diallyl-6-chloro-9*H*-purine (**100a**).

Spectrum 66. COSY NMR of 8,9-diallyl-6-chloro-9*H*-purine (**100a**).

Parameter	Value (f2, f1)
Data File Name	E:/ 400-victorhr/ 400-nmr/ VM049 after flash/ 4/ ser
Title	VM049 after flash.4.ser
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Origin	Bruker BioSpin GmbH
Owner	tnmr
Site	
Spectrometer	spect
Author	
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	cosygpqf
Experiment	COSY
Number of Scans	1
Receiver Gain	32
Relaxation Delay	1.4103
Pulse Width	12.1500
Acquisition Time	0.2683
Acquisition Date	2012-11-18T 08:11:00
Modification Date	2012-11-18T 08:15:44
Class	
Spectrometer Frequency	(400.18, 400.18)
Spectral Width	(3816.8, 3816.8)
Lowest Frequency	(-37.5, -40.9)
Nucleus	(1H, 1H)
Acquired Size	(1024, 128)
Spectral Size	(1024, 1024)

Spectrum 67. HSQC NMR of 8,9-diallyl-6-chloro-9*H*-purine (**100a**).

Parameter	Value (f2, f1)
Data File Name	E:/ 400-victorhr/ 400-nmr/ VM049 after flash/ 6/ ser
Title	VM049 after flash.6.ser
Comment	HSQCEDETGP CDCl3 {D:\ uio\ AVII400-05} victorhr 99
Origin	Bruker BioSpin GmbH
Owner	tnmr
Site	
Spectrometer	spect
Author	
Solvent	CDCl3
Temperature	300.1
Pulse Sequence	hsqcedetgp
Experiment	HSQC-EDITED
Number of Scans	2
Receiver Gain	2050
Relaxation Delay	1.4617
Pulse Width	12.1500
Acquisition Time	0.1342
Acquisition Date	2012-11-18T0 8:53:00
Modification Date	2012-11-18T0 9:07:24
Class	
Spectrometer Frequency	(400.18, 100.63)
Spectral Width	(3816.8, 16668.7)
Lowest Frequency	(-38.9, -829.2)
Nucleus	(1H, 13C)
Acquired Size	(512, 256)
Spectral Size	(512, 512)

Parameter	Value (f2, f1)
Data File Name	E:/ 400-victorhr/ 400-nmr/ VM049 after flash/ 5/ ser
Title	VM049 after flash.5.ser
Comment	HMBCGPND CDCl3 {D:\ uio\ AVII400-05} victorhr 99
Origin	Bruker BioSpin GmbH
Owner	tnmr
Site	
Spectrometer	spect
Author	
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	hmbcgpndqf
Experiment	HMBC
Number of Scans	8
Receiver Gain	2050
Relaxation Delay	1.3476
Pulse Width	12.1500
Acquisition Time	0.5366
Acquisition Date	2012-11-18T0 8:18:00
Modification Date	2012-11-18T0 8:51:26
Class	
Spectrometer Frequency	(400.18, 100.64)
Spectral Width	(3816.8, 22350.6)
Lowest Frequency	(-38.5, -1128.8)
Nucleus	(1H, 13C)
Acquired Size	(2048, 128)
Spectral Size	(2048, 512)

Spectrum 68. HMBC NMR of 8,9-diallyl-6-chloro-9H-purine (**100a**).

<u>8,9-Diallyl-6-chloro-8,9-dihydro-7*H*-purine (**100b**)</u>

¹H NMR (CDCl₃, 400 MHz) δ 2.39-2.47 (m, 1H, C(8)CH$_{2a}$), 2.56-2.63 (m, 1H, C(8)CH$_{2b}$), 3.80 (ddt, *J* = 16.1, 6.9, 1.3 Hz, 1H, NCH$_{2a}$), 4.26 (ddt, *J* = 16.1, 4.9, 1.7 Hz, 1H, NCH$_{2b}$), 4.31 (brs, 1H, NH), 5.14-5.31 (m, 4H, 2×CH$_2$=), 5.40 (dt, *J* = 6.7, 2.6 Hz, 1H, H-8), 5.67-5.86 (m, 2H, 2×CH=), 7.81 (s, 1H, H-2).

¹³C NMR (CDCl₃, 100 MHz) δ 39.7 (CH$_2$), 44.6 (NCH$_2$), 76.1 (C-8), 118.6 (=CH$_2$ in N(9) allyl), 120.4 (=CH$_2$ in C(8) allyl), 127.8 (C-6), 129.3 (C-5), 130.5 (CH= in C(8) allyl), 131.6 (CH= in N(9) allyl), 149.5 (C-2), 159.1 (C-4).

MS (EI). *m/z* (rel. %): 238/236 (21/6, *M*⁺), 237 (100), 201 (14), 195 (59), 160 (7).

MS (ESI). 237.0901 [M+H]⁺ calculated for C$_{11}$H$_{13}$N$_4$Cl 237.0829.

Parameter	Value
Data File Name	E:/ 400-victorhr/ 400-nmr/ VM048 after flash (p2)/ 1/ fid
Title	VM048 after flash (p2).1.fid
Comment	PROTON CDCl3 {D:\ uio\ AVII400-05} victorhr 98
Origin	Bruker BioSpin GmbH
Owner	tnmr
Site	
Spectrometer	spect
Author	
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	128
Receiver Gain	81
Relaxation Delay	5.0000
Pulse Width	12.1500
Acquisition Time	3.9846
Acquisition Date	2012-11-18T0 1:13:00
Modification Date	2012-11-18T0 1:13:34
Class	
Spectrometer Frequency	400.18
Spectral Width	8223.7
Lowest Frequency	-1647.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

Spectrum 69. ¹H NMR of 8,9-diallyl-6-chloro-8,9-dihydro-7*H*-purine (**100b**).
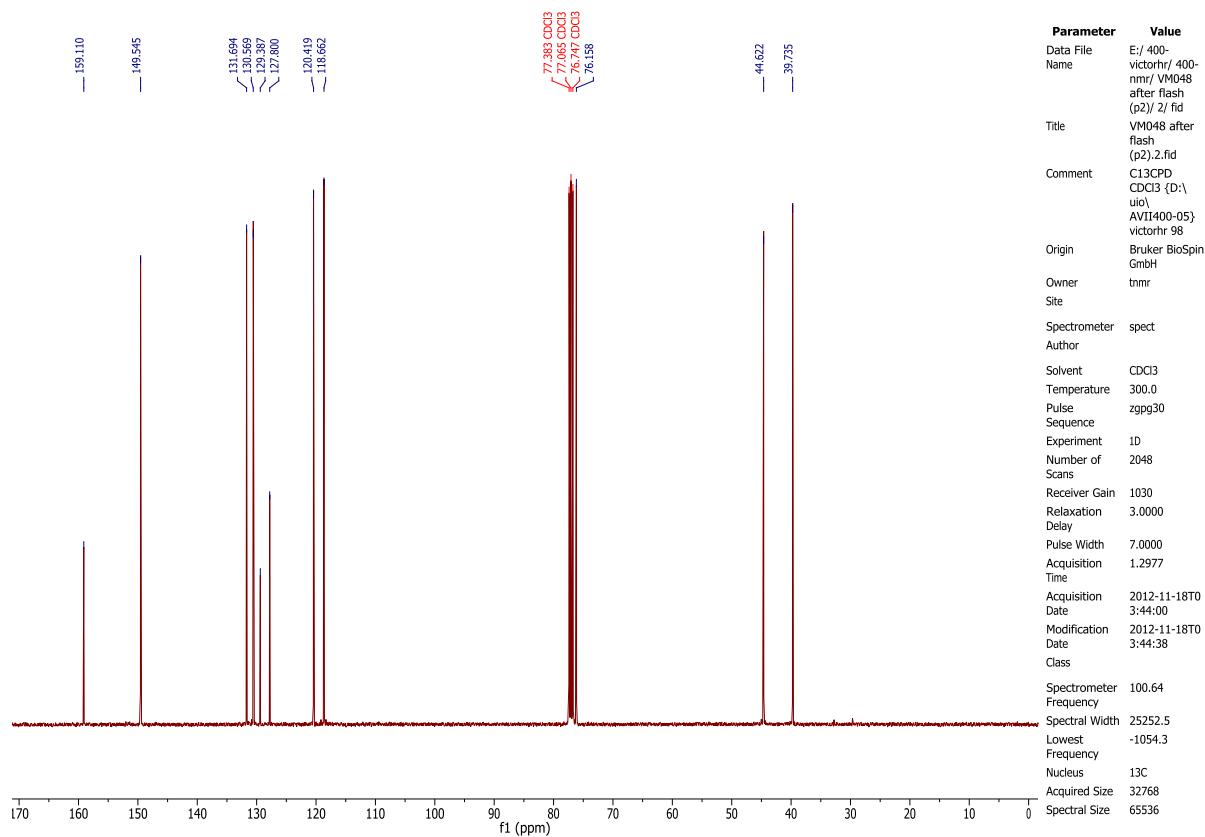
Spectrum 70. ^{13}C NMR of 8,9-diallyl-6-chloro-8,9-dihydro-7*H*-purine (**100b**).

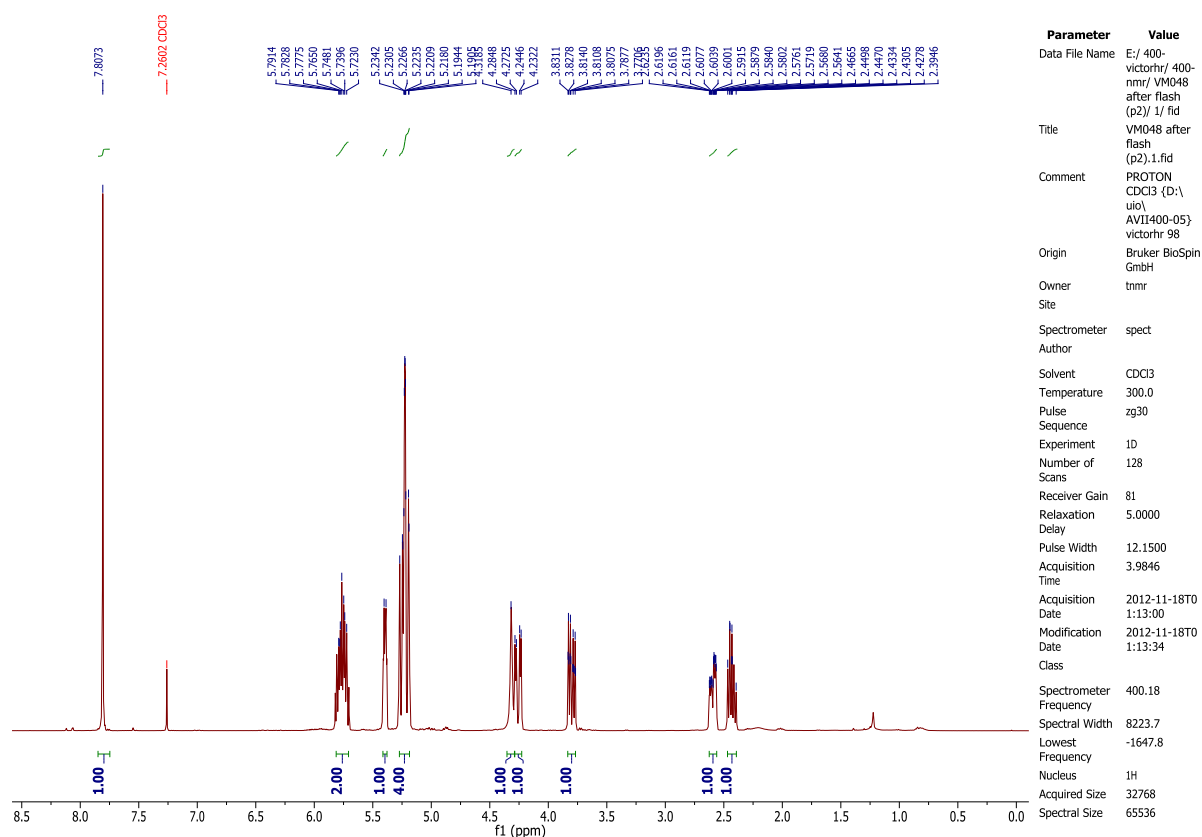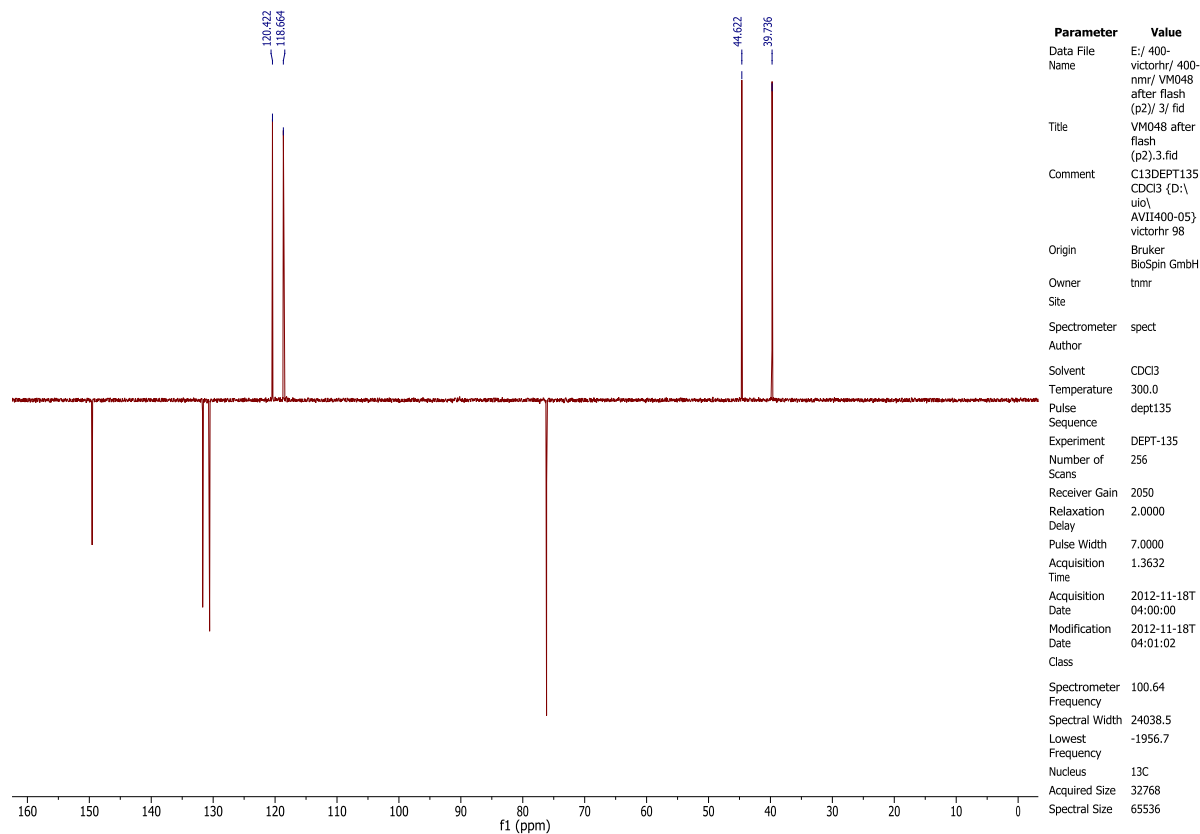**Spectrum 71.** ^{13}C DEPT NMR of 8,9-diallyl-6-chloro-8,9-dihydro-7*H*-purine (**100b**).

Spectrum 72. COSY NMR of 8,9-diallyl-6-chloro-8,9-dihydro-7*H*-purine (**100b**).
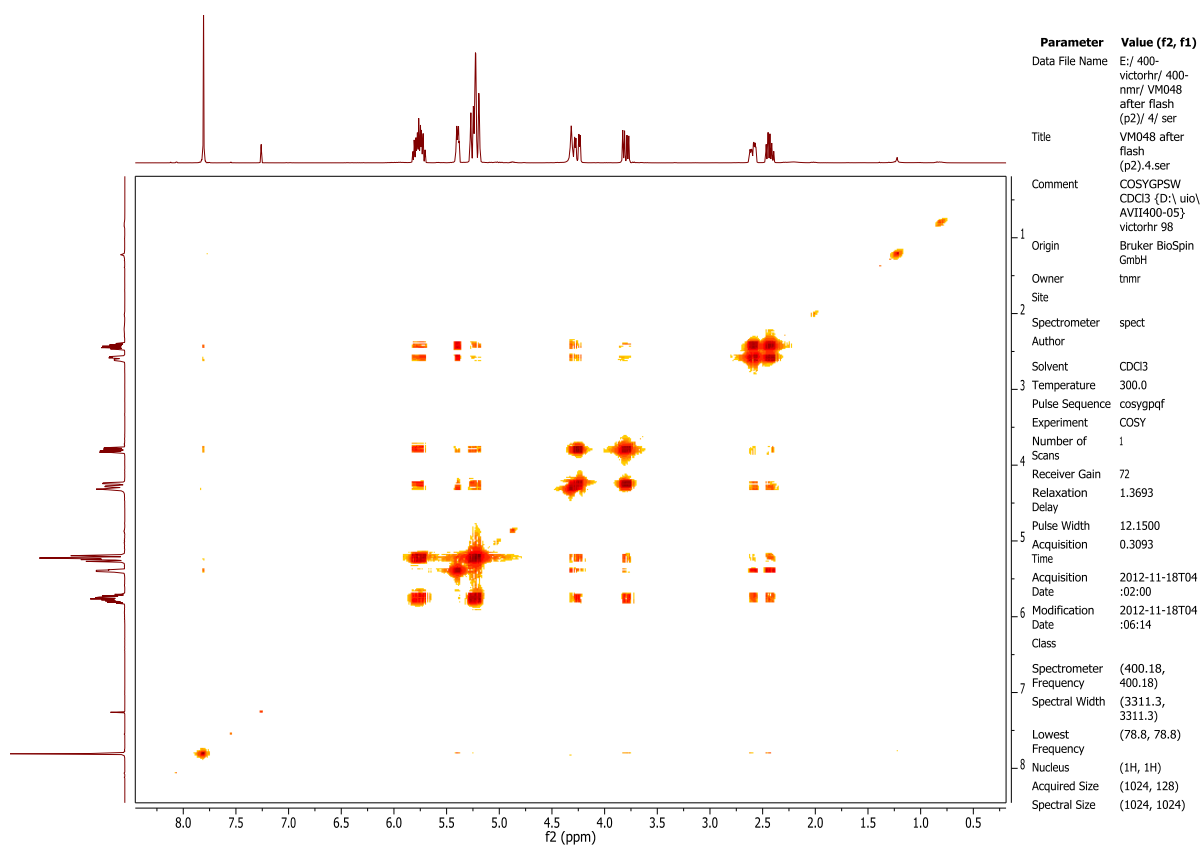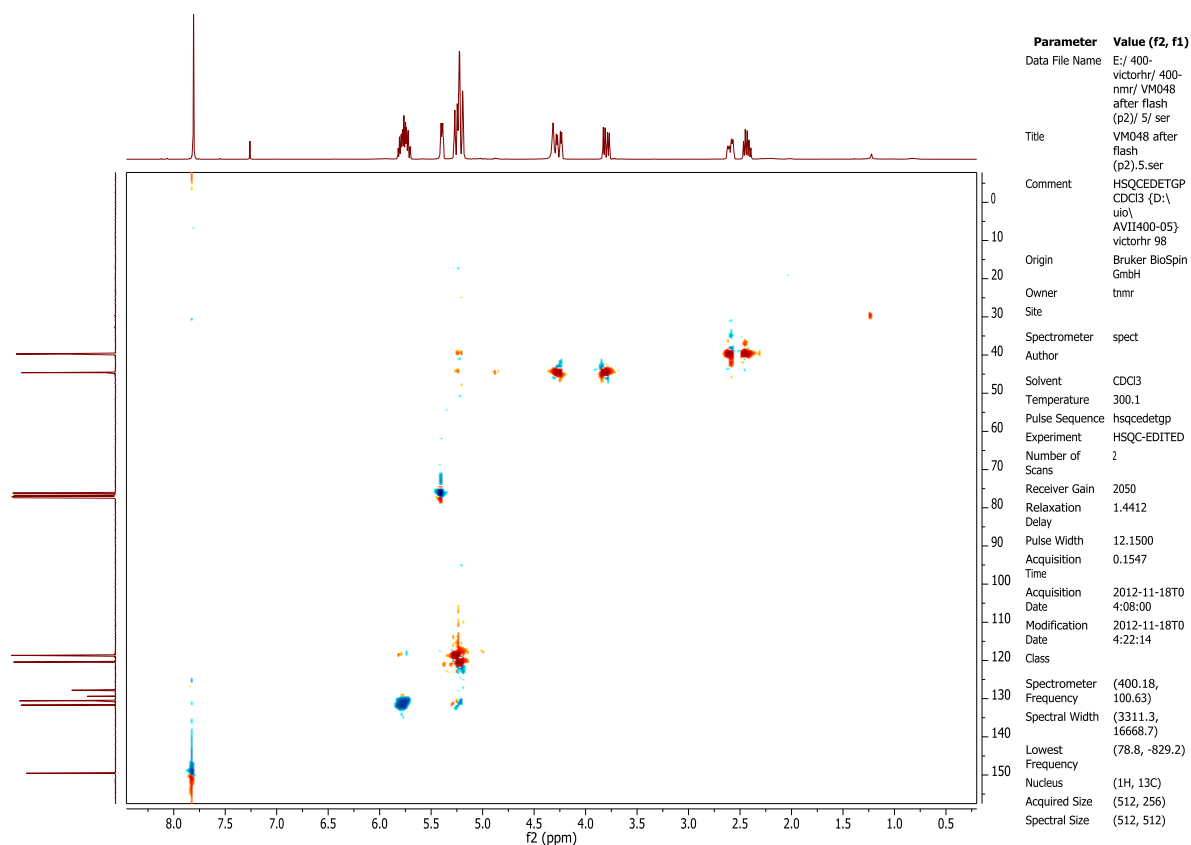

Spectrum 73. HSQC NMR of 8,9-diallyl-6-chloro-8,9-dihydro-7*H*-purine (**100b**).

Spectrum 74. HMBC NMR of 8,9-diallyl-6-chloro-8,9-dihydro-7*H*-purine (**100b**).
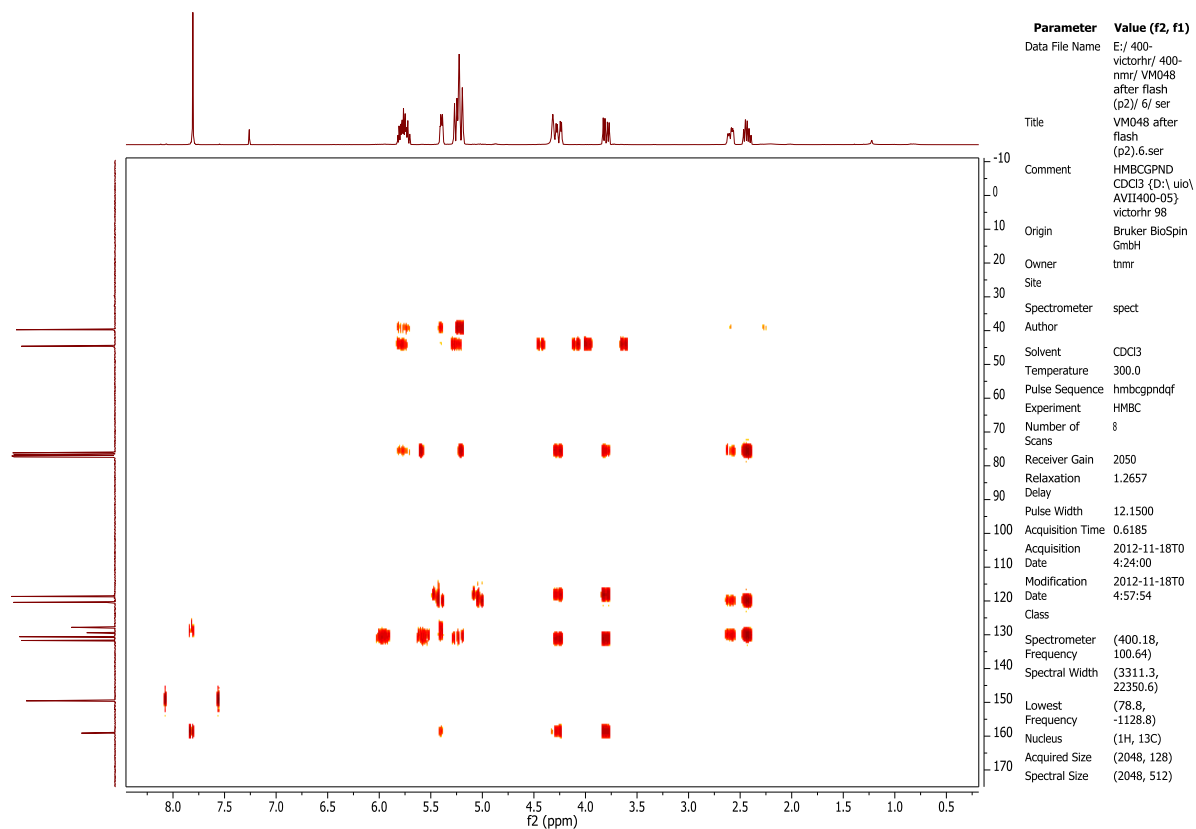
Method B:

Allylmagnesium bromide (1.42 mL, 0.951 mmol of 0.67 M solution in diethyl ether) was added to a solution of compound **19** (88 mg, 0.45 mmol) in THF (5 mL) at 0 °C under N_2-atm, and the resulting mixture was stirred at 0 °C for 20 min. Sat. aq. NH_4Cl (10 mL) was added, the phases were separated and the water layer was extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was dissolved in dry DCM (3 mL), MnO_2 (196 mg, 2.25 mmol) was added and the mixture was stirred at r.t. for 2 h and evaporated *in vacuo*. The product was purified by flash chromatography on silica gel eluting with acetone-EtOAc-hexane (1:1:8) to give 76 mg (73%) of 8,9-diallyl-6-chloro-9*H*-purine **100a** as a yellow oil.

Method C:

Compound **19** (292 mg, 1.50 mmol) and indium powder (1.378 g, 12.00 mmol) were stirred in dry THF (9 mL). Allyl bromide (1.56 mL, 18.034 mmol) was added and the reaction was stirred at room temperature, saturated aqueous solution of NH_4Cl (18 mL) was added, the phases were separated and the water layer was extracted with ethyl acetate (2 × 18 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was dissolved in dry DCM (9 mL), MnO_2 (653 mg, 7.50 mmol) was added and the resulting mixture was stirred at room tepmerature for 2 h. The crude product was purified by flash chromatography on silica gel eluting with EtOAc-hexane (1:1) to give 170 mg (48%) of 8,9-diallyl-6-chloro-9*H*-purine **100a** as a yellow oil.

4-Chloro-6,9-dihydropyrido[1,2-*e*]purine (107).
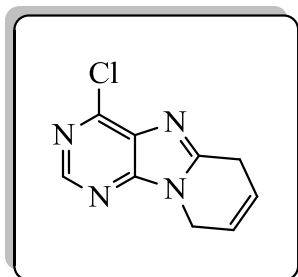
107

Grubbs' 2nd generation catalyst (63 mg, 0.074 mmol) was added to a solution of compound **100a** (218 mg, 0.920 mmol) in dry DCE (50 mL) after removing the air by a pump and filling with argon (three cycles) and the solution was refluxed for 48 h. After evaporation of the solvent *in vacuo* the residue was purified by flash chromatography eluting with EtOAc-hexane (1:1) to give 187 mg (97%) of 4-chloro-6,9-dihydropyrido[1,2-*e*]purine **107** as a colourless solid.

¹H NMR (CDCl₃, 400 MHz) δ 3.76-3.80 (m, 2H, C(8)CH₂), 4.78-4.87 (m, 2H, NCH₂), 6.18-6.04 (m, 2H, CH=CH), 8.69 (s, 1H, H-2).

¹³C NMR (CDCl₃, 100 MHz) δ 25.8 (C(8)$\underline{C}$H₂), 42.6 (NCH₂), 119.4 (CH=), 121.7 (CH=), 131.2 (C-5), 149.1 (C-6), 151.0 (C-2), 151.9 (C-4), 152.1 (C-8).

MS (EI). *m/z* (rel. %) 208/206 (38/100, *M*⁺), 207 (31), 205 (54), 169 (32), 153 (11), 155 (4), 85 (5), 78 (8).

HRMS. Found 206.0362 calculated for C₉ H₇N₄Cl 206.0359.

M.p. 160-162 ºC
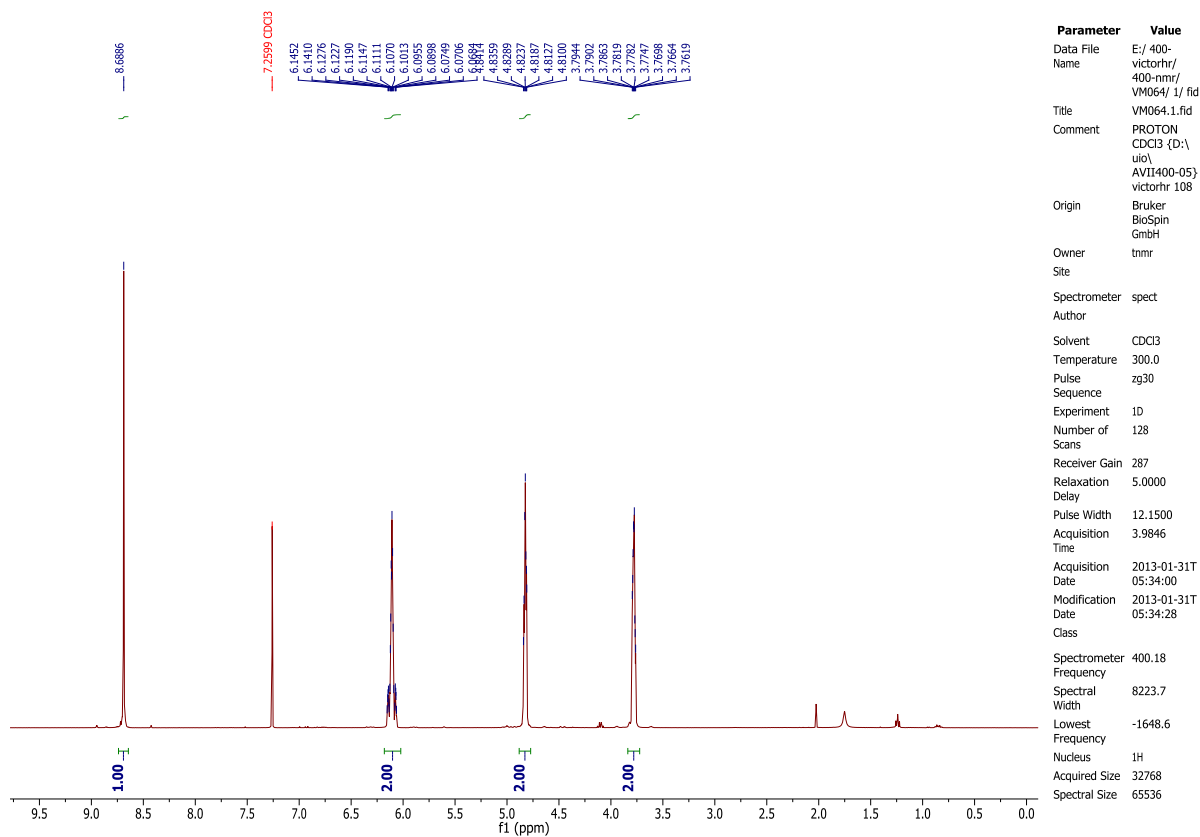
Spectrum 75. ^{1}H NMR of 4-chloro-6,9-dihydropyrido[1,2-*e*]purine (**107**).
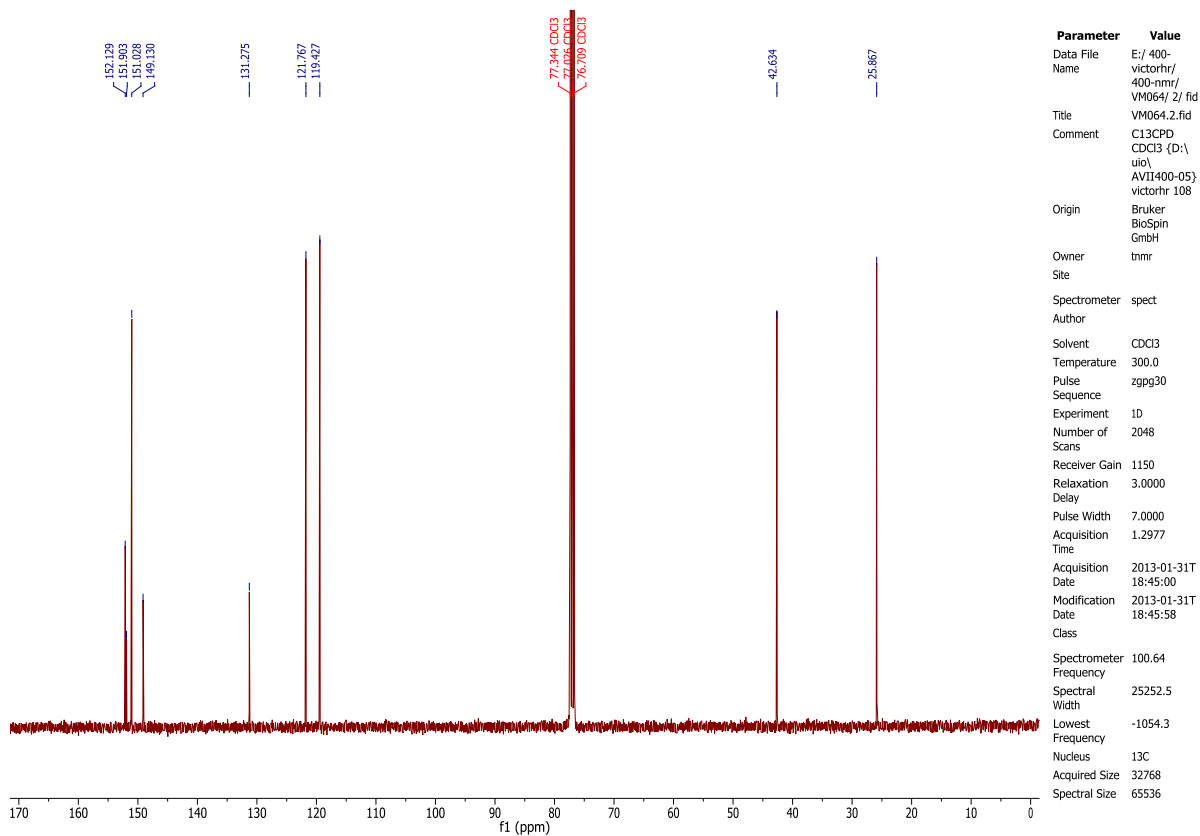
Spectrum 76. ^{13}C NMR of 4-chloro-6,9-dihydropyrido[1,2-*e*]purine (**107**).
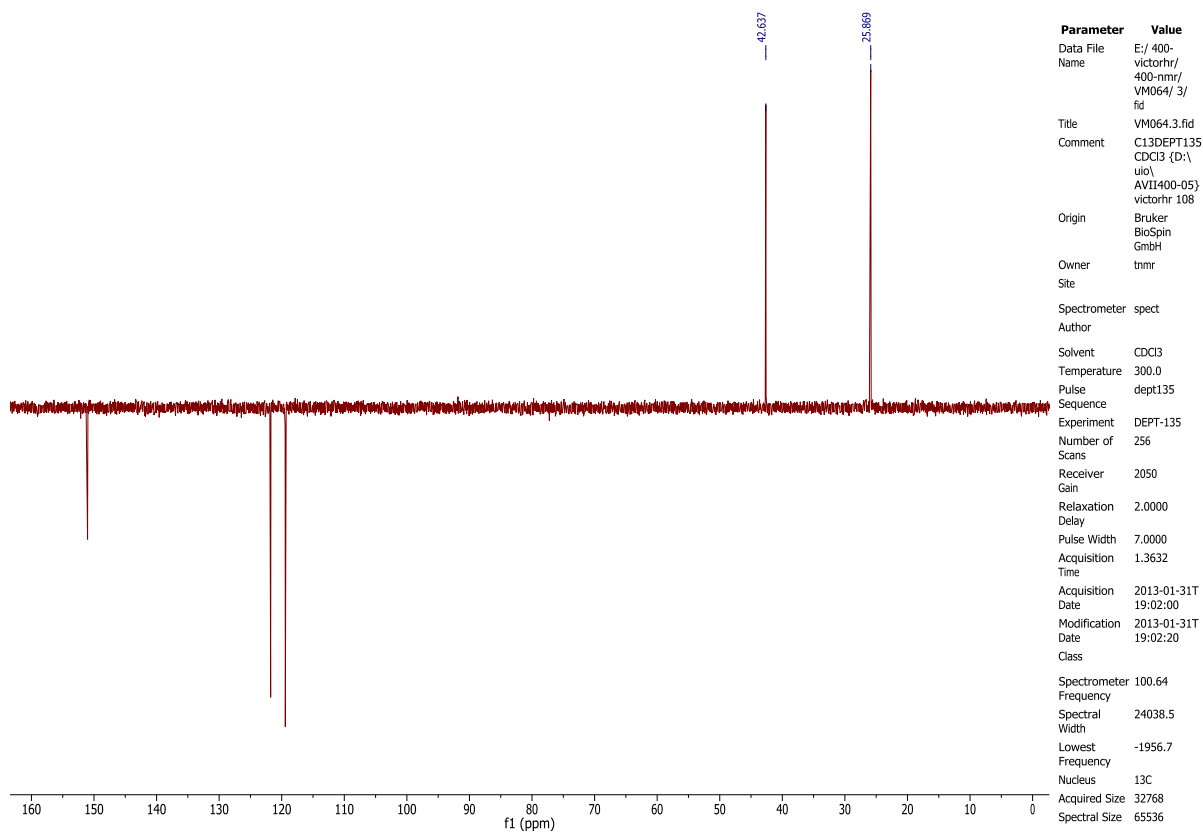
Spectrum 77. ^{13}C DEPT NMR of 4-chloro-6,9-dihydropyrido[1,2-*e*]purine (**107**).
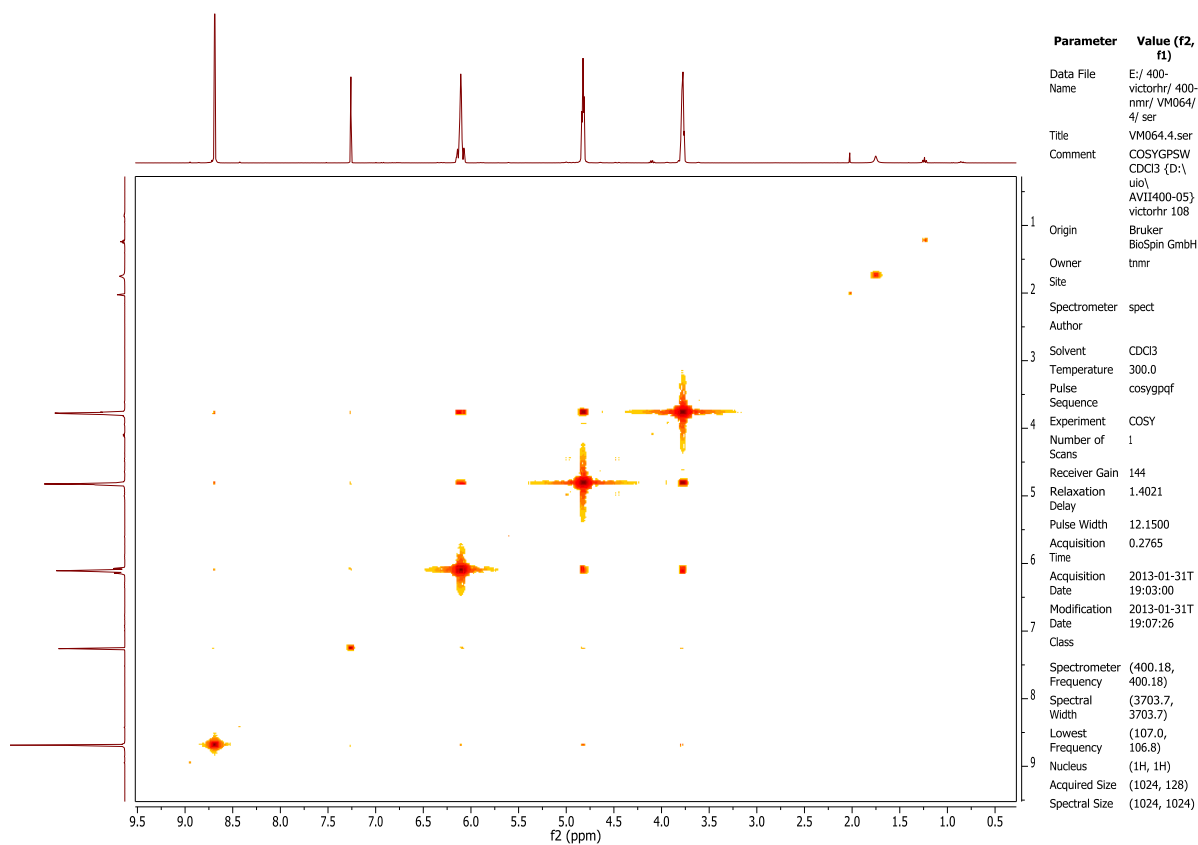
Spectrum 78. COSY NMR of 4-chloro-6,9-dihydropyrido[1,2-*e*]purine (**107**).
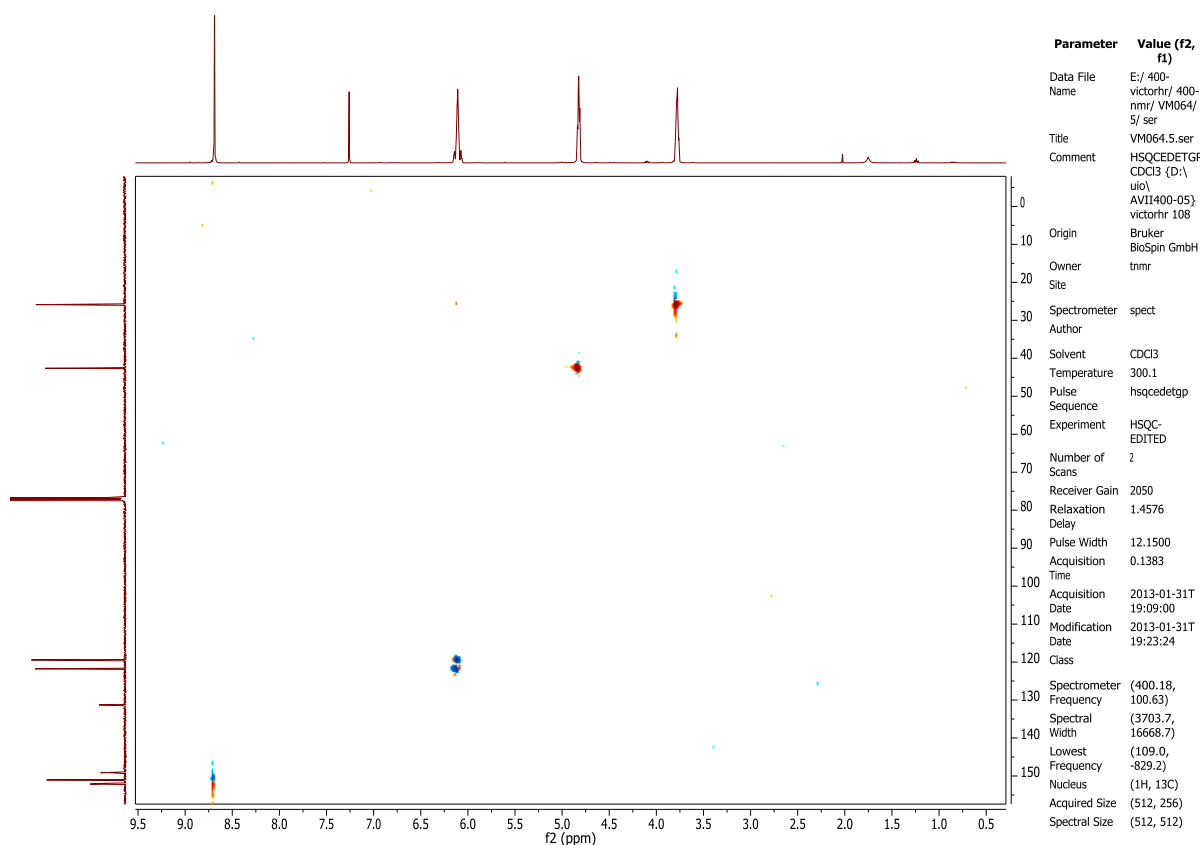
Spectrum 79. HSQC NMR of 4-chloro-6,9-dihydropyrido[1,2-*e*]purine (**107**).
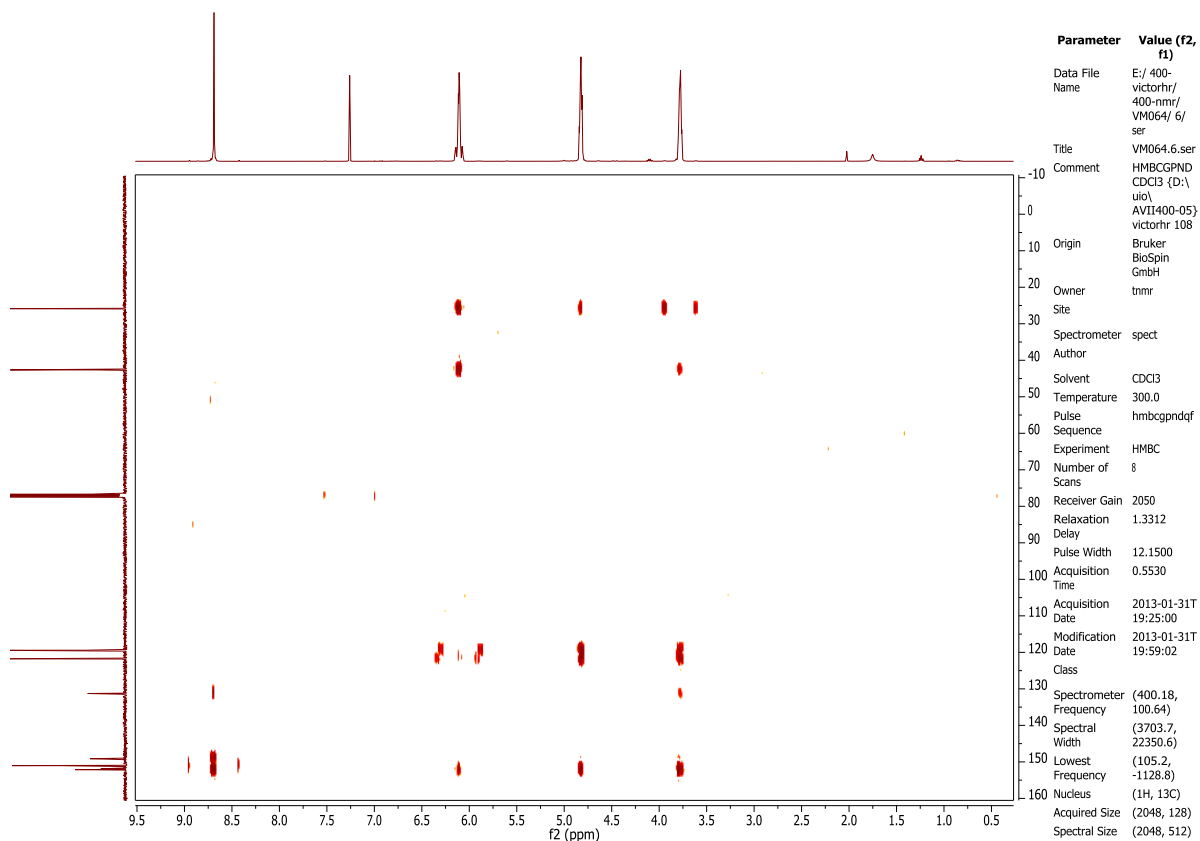
Spectrum 80. HMBC NMR of 4-chloro-6,9-dihydropyrido[1,2-*e*]purine (**107**).

4-Chloropyrido[1,2-*e*]purine (9)
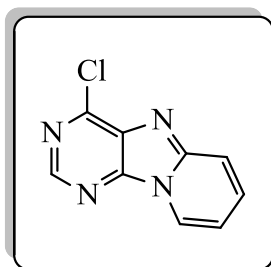
9

DDQ (411 mg, 1.80 mmol) was added to a solution of compound **107** (187 mg, 0.900 mmol) in dry DCE (45 mL) and the resulting mixture was refluxed for 24 h. After evaporation of the solvent *in vacuo* the residue was purified by flash chromatography on silica gel eluting with EtOAc-hexane (1:1) to give 170 mg (91%) of 4-chloropyrido[1,2-*e*]purine **9** as a colourless solid.

^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.02-7.09 (m, 1H, NCH=C<u>H</u>), 7.62-7.69 (m, 1H, C(8)CH=C<u>H</u>), 7.80 (d, *J* = 9.3 Hz, 1H, C(8)C<u>H</u>), 8.74 (d, *J* = 6.8 Hz, 1H, NC<u>H</u>), 8.85 (s, 1H, H-2).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 112.8 (NCH=<u>C</u>H), 119.0 (C(8)<u>C</u>H), 125.1(NCH), 132.74 (C-5), 133.2 (C(8)CH=<u>C</u>H), 146.3 (C-4), 149.0 (C-8), 149.1 (C-2), 151.0 (C-6).

**MS (EI).** *m/z* (rel. %): 206/204 (35/100, *M*$^+$), 179 (2), 177 (7), 169 (41), 142 (5), 78 (20).

HRMS. Found 204.0201 calculated for C$_9$H$_5$N$_4$Cl 204.0203.

M.p. 247-249 ^{o}C (Lit.[1] 250 ^{o}C).

Parameter	Value
Data File Name	E:/ 400-victorhr/ 400-nmr/ VM074/ 1/ fid
Title	VM074.1.fid
Comment	PROTON CDCl3 {D:\ uio\ AVII400-05} victorhr 46
Origin	Bruker BioSpin GmbH
Owner	tnmr
Site	
Spectrometer Author	spect
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zg30
Experiment	1D
Number of Scans	128
Receiver Gain	322
Relaxation Delay	5.0000
Pulse Width	12.1500
Acquisition Time	3.9846
Acquisition Date	2013-02-21T 19:24:00
Modification Date	2013-02-21T 19:24:30
Class	
Spectrometer Frequency	400.18
Spectral Width	8223.7
Lowest Frequency	-1648.6
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

Spectrum 81. ^{1}H NMR of 4-chloropyrido[1,2-*e*]purine (**9**).

Parameter	Value
Data File Name	E:/ 400-victorhr/ 400-nmr/ VM074/ 2/ fid
Title	VM074.2.fid
Comment	C13CPD CDCl3 {D:\ uio\ AVII400-05} victorhr 46
Origin	Bruker BioSpin GmbH
Owner	tnmr
Site	
Spectrometer Author	spect
Solvent	CDCl3
Temperature	300.0
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	2048
Receiver Gain	1150
Relaxation Delay	3.0000
Pulse Width	7.0000
Acquisition Time	1.2977
Acquisition Date	2013-02-21T 21:55:00
Modification Date	2013-02-21T 21:55:34
Class	
Spectrometer Frequency	100.64
Spectral Width	25252.5
Lowest Frequency	-1054.3
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

Spectrum 82. ^{13}C NMR of 4-chloropyrido[1,2-*e*]purine (**9**).

7,8-Diallyl-6-(piperidin-1-yl)-7*H*-purine (103)
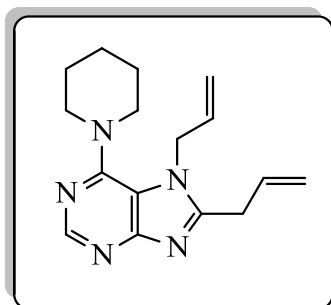

103

Allylmagnesium bromide (3.67 mL, 2.458 mmol of 0.67 M solution in diethylether) was added to a solution of compound **95** (300 mg, 1.23 mmol) in THF (15mL) at 0 ºC under N_2-atm, and the resulted mixture was stirred at 0 ºC for 40 min. Sat. aq. NH_4Cl (30 mL) was added, the phases were separated and the water layer was extracted with ethyl acetate (2x30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was dissolved in dry DCM (60 mL), MnO_2 (535 mg, 6.15 mmol) was added and the mixture was stirred at room temperature for 2 h and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with EtOAc-hexane (1:1) to give 296 mg (85%) of 7,8-diallyl-6-(piperidin-1-yl)-7*H*-purine **103** as a yellow oil.

^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.44-1.63 (m, 6H, 3×CH$_2$ in piperidinyl), 3.02-3.17 (m, 4H, 2×NCH$_2$ in piperidinyl), 3.52 (dt, *J* = 6.4, 1.6 Hz, 2H, C(8)CH$_2$), 4.76-4.87 (m, 3H, N(7)CH$_2$ and =CH$_{2a}$ in N(7) allyl), 4.97-5.08 (m, 2H, =CH$_2$ in C(8) allyl), 5.13 (d, *J* = 10.5 Hz, 1H, =CH$_{2b}$ in N(7) allyl), 5.76-5.99 (m, 2H, =CH in N(7) allyl and =CH in C(8) allyl), 8.48 (s, 1H, H-2).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 24.0 (CH2 in piperidinyl), 25.4 (2×CH2 in piperidinyl), 32.4 (C(8)CH2), 46.6 (N(7)CH2), 51.2 (2×NCH2 in piperidinyl), 116.9 (C-5), 117.3 (=CH$_2$ in N(7) allyl), 118.1 (=CH$_2$ in C(8) allyl), 131.7 (=CH in C(8) allyl), 132.3 (=CH in N(7) allyl), 151.9 (C-2), 155.5 (C-6), 157.4 (C-8), 160.5 (C-4).

MS (EI). *m/z* (rel. %): 284/283 (26/94, *M*$^+$), 268 (47), 254 (58), 242 (65), 240 (24), 227 (18), 200 (95), 199 (97), 174 (26), 84 (100).

HRMS. Found 283.1789 calculated for C$_{16}$H$_{21}$N$_5$ 283.1797.
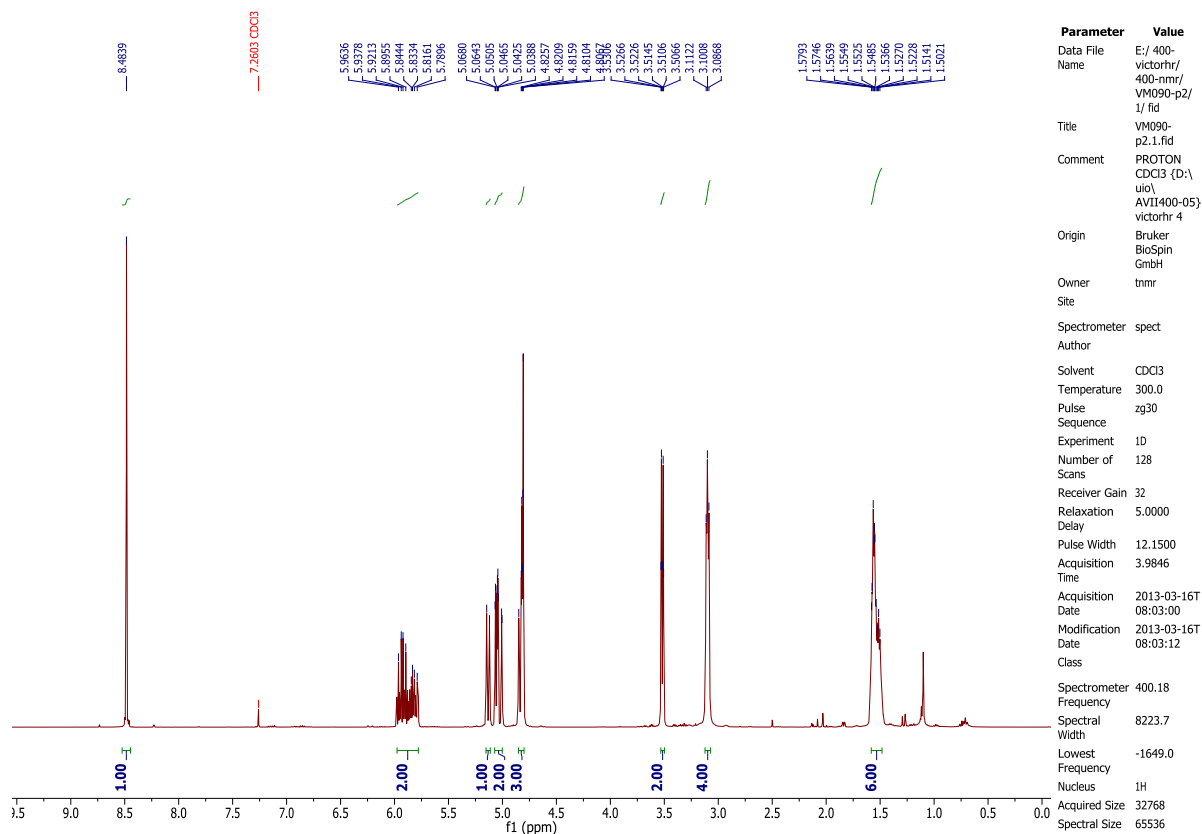
Spectrum 83. ^{1}H NMR of 7,8-diallyl-6-(piperidin-1-yl)-7H-purine (**103**).
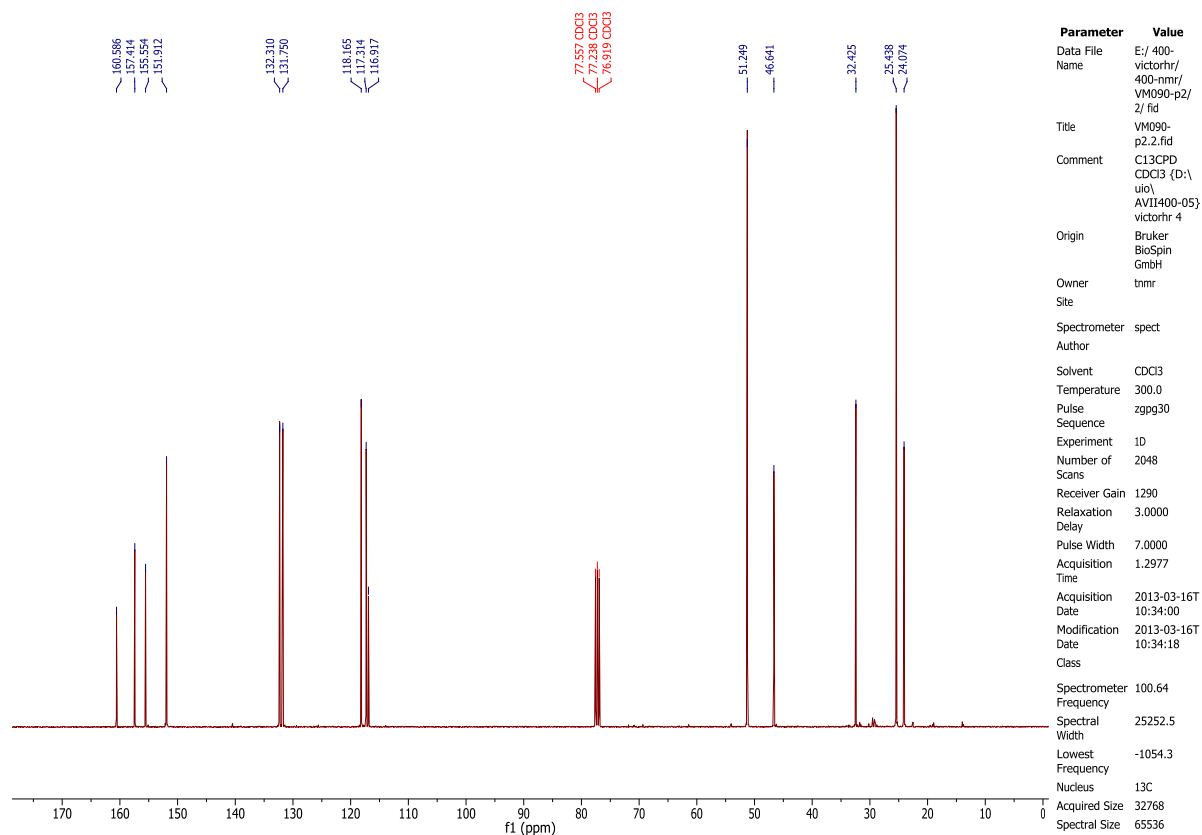
Spectrum 84. ^{13}C NMR of 7,8-diallyl-6-(piperidin-1-yl)-7H-purine (**103**).

154
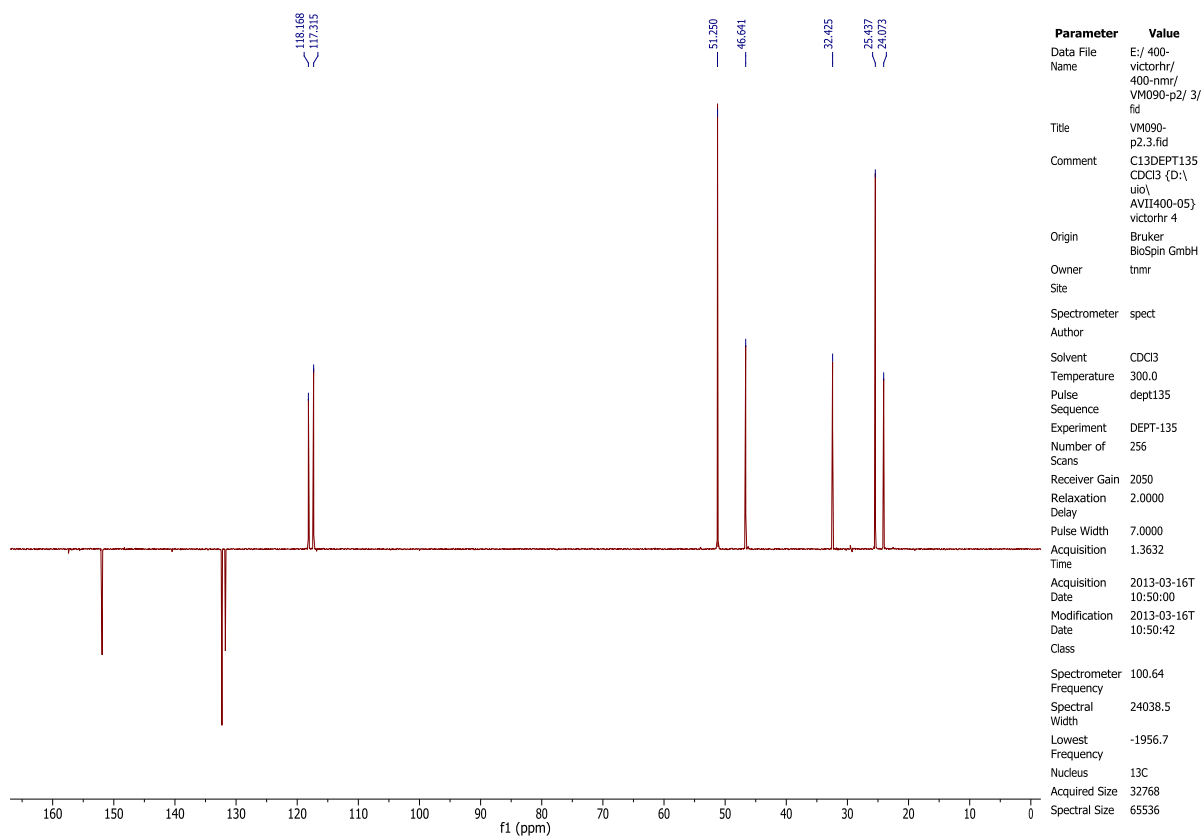
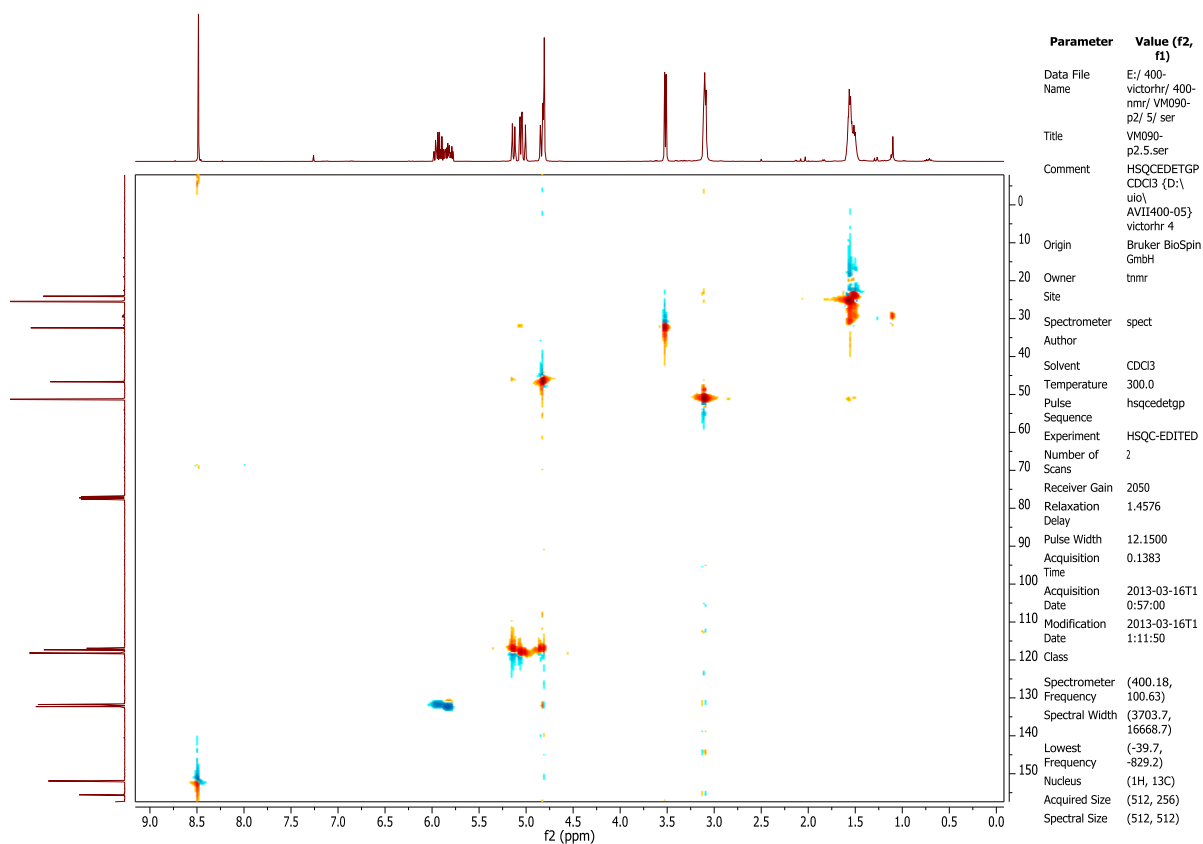**Spectrum 85.** ^{13}C DEPT NMR of 7,8-diallyl-6-(piperidin-1-yl)-7*H*-purine (**103**).

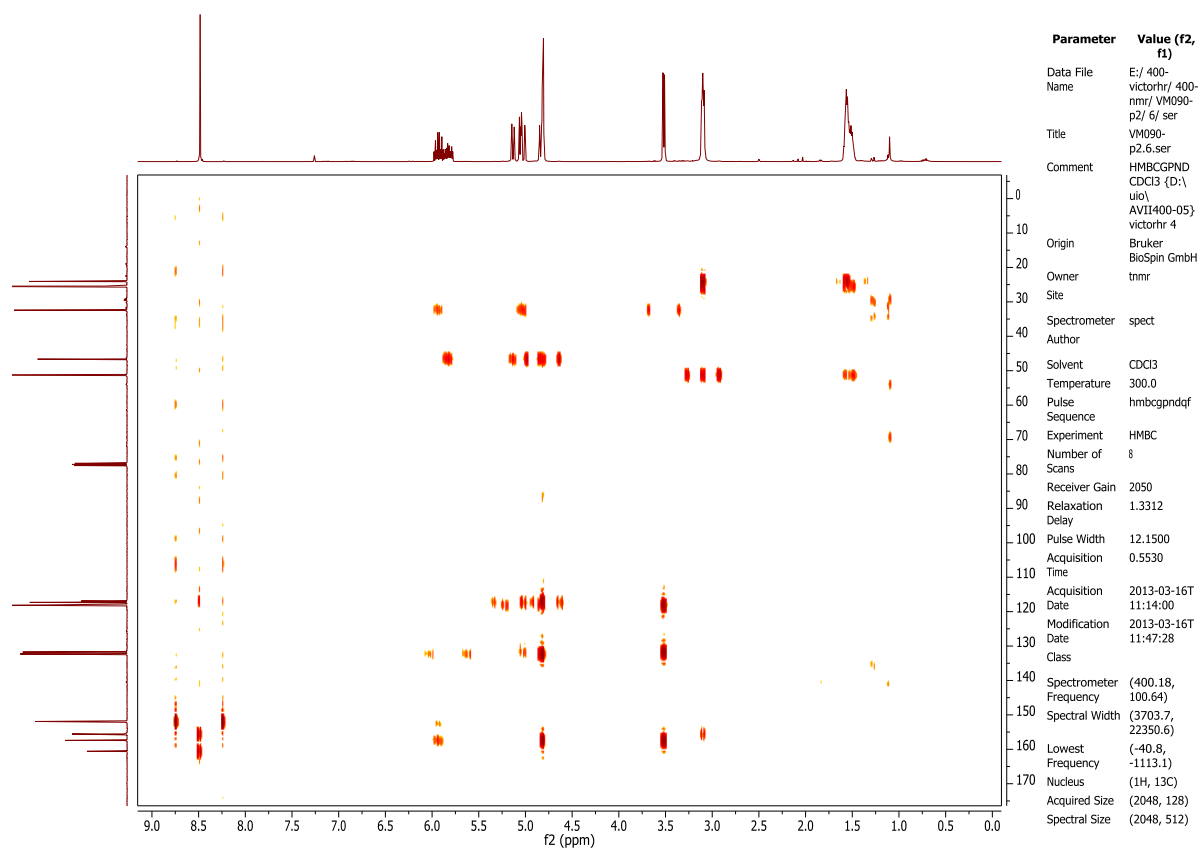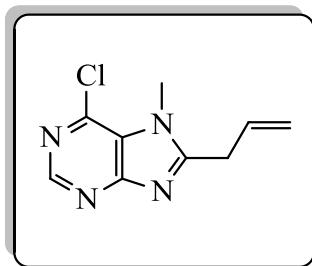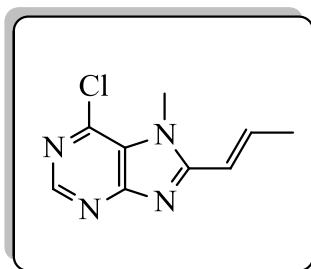**Spectrum 86.** HSQC NMR of 7,8-diallyl-6-(piperidin-1-yl)-7*H*-purine (**103**).

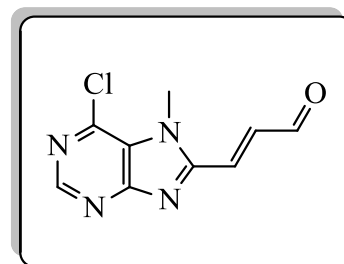**Spectrum 87.** HMBC NMR of 7,8-diallyl-6-(piperidin-1-yl)-7*H*-purine (**103**).

8-Allyl-6-chloro-7-methyl-7*H*-purine (106a), (*E*)-6-chloro-7-methyl-8-(prop-1-en-1-yl)-7*H*-purine (106b), and (*E*)-3-(6-chloro-7-methyl-7*H*-purin-8-yl)acrylaldehyde (106c).

106a   **106b**   **106c**

Allylmagnesium bromide (3.52 mL, 2.358 mmol of 0.67 M solution in diethyl ether) was added to a solution of compound **18** (200 mg, 1.18 mmol) in THF (15 mL) at -20 ℃ (1:3 NaCl/ice bath) under N_2-atm, and the resulting mixture was stirred at this temperature for 20 min. Sat. aq. NH_4Cl (30 mL) was added, the phases were separated and the water layer was extracted with ethyl acetate (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The crude product was dissolved in dry DCM (60 mL), MnO_2 (513 mg, 5.90 mmol) was added and the mixture was stirred at room temperature for 2 h. MnO_2 was filtered off, and the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with EtOAc-hexane (1:1) to give 216 mg of a yellow oil composed of a mixture of 8-allyl-6-chloro-7-methyl-7*H*-purine **106a** (85%), (*E*)-6-chloro-7-methyl-8-(prop-1-en-1-yl)-7*H*-purine **106b** (9%), and (*E*)-3-(6-chloro-7-methyl-7*H*-purin-8-yl)acrylaldehyde **106c** (6%).

<u>8-Allyl-6-chloro-7-methyl-7*H*-purine (**106a**)</u>

¹H NMR (CDCl₃, 400 MHz) δ 3.78 (d, *J* = 6.3 Hz, 2H, CH₂), 4.05 (s, 3H, CH₃), 5.11 (dd, *J* = 17.2, 1.3 Hz, 1H, =CH₂ₐ), 5.20 (dd, *J* = 10.2, 1.3 Hz, 1H, =CH₂ᵦ), 5.98-6.12 (m, 1H, CH=), 8.79 (s, 1H, H-2).

¹³C NMR (CDCl₃, 100 MHz) δ 32.4 (CH₃), 32.5 (CH₂), 119.2 (=CH₂), 123.7 (C-5), 130.5 (=CH), 141.8 (C-6), 152.1 (C-2), 159.8 (C-8), 161.0 (C-4).

MS (EI). *m/z* (rel. %): 210/208 (20/60, *M*⁺), 207 (100), 193 (11), 182 (11), 167 (9), 100 (11), 79 (5).

MS (ESI). 209.0618 [M+H]⁺ calculated for C₉H₉N₄Cl 209.0516.

<u>(*E*)-6-Chloro-7-methyl-8-(prop-1-en-1-yl)-7*H*-purine (**106b**)</u>

¹H NMR (CDCl₃, 400 MHz) δ 2.07 (d, *J* = 7.0 Hz, 1H, CH₃ in C(8) propenyl), 4.08 (s, 3H, NCH₃), 6.50 (d, *J* = 15.5 Hz, 1H, C(8)CH), 7.45 (m, 1H, C(8)CH=C<u>H</u>), 8.75 (s, 1H, H-2).

¹³C NMR (CDCl₃, 100 MHz) δ 19.3 (CH₃ in C(8) propenyl), 31.9 (NCH₃), 115.4 (C(8)<u>C</u>H), 123.6 (C-5), 141.6 (C-6), 143.9 (C(8)CH=<u>C</u>H), 152.3 (C-2), 157.2 (C-8), 161.0 (C-4).

MS (EI). *m/z* (rel. %): 210/208 (20/60, *M*⁺), 207 (100), 195 (24), 193 (70), 182 (7), 167 (8), 100 (14), 79 (6).

MS (ESI). 209.0618 [M+H]⁺ calculated for C₉H₉N₄Cl 209.0516.

<u>(*E*)-3-(6-Chloro-7-methyl-7*H*-purin-8-yl)acrylaldehyde (**106c**)</u>

¹H NMR (CDCl₃, 400 MHz) δ 4.00 (s, 1H, CH₃), 7.42 (dd, *J* = 15.5, 7.0 Hz, 1H, C(8)CH=C<u>H</u>), 7.59 (d, *J* = 15.5 Hz, 1H, C(8)CH), 8.74 (s, 1H, H-2), 9.81 (d, *J* = 7.0 Hz, 1H, CHO).

¹³C NMR (CDCl₃, 100 MHz) δ 32.7 (CH₃), 124.4 (C-5), 132.0 (C(8)<u>C</u>H), 138.2 (C(8)CH=<u>C</u>H), 143.4(C-6), 152.9 (C-2), 153.6 (C-8), 163.4 (C-4), 191.6 (CHO).

MS (EI). *m/z* (rel. %): 224/222 (5/16, *M*⁺), 208 (58), 207 (100), 195 (24), 193 (70), 182 (7), 167 (8), 100 (14), 79 (6).

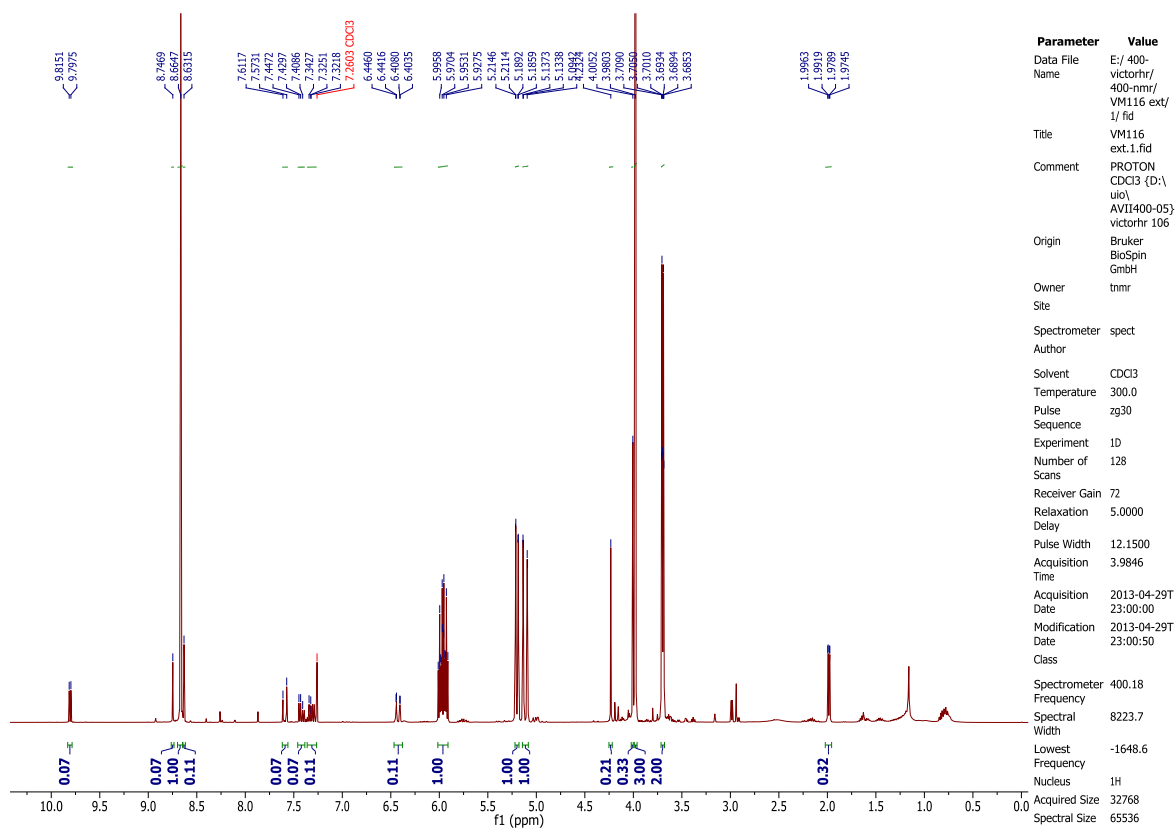**MS (ESI).** 223.0412 [M+H]⁺ calculated for C₉H₇N₄OCl 223.0308.

Spectrum 88. ^{1}H NMR of a mixture of 8-allyl-6-chloro-7-methyl-7*H*-purine (**106a**), (*E*)-6-chloro-7-methyl-8-(prop-1-en-1-yl)-7*H*-purine (**106b**), and (*E*)-3-(6-chloro-7-methyl-7*H*-purin-8-yl)acrylaldehyde (**106c**).
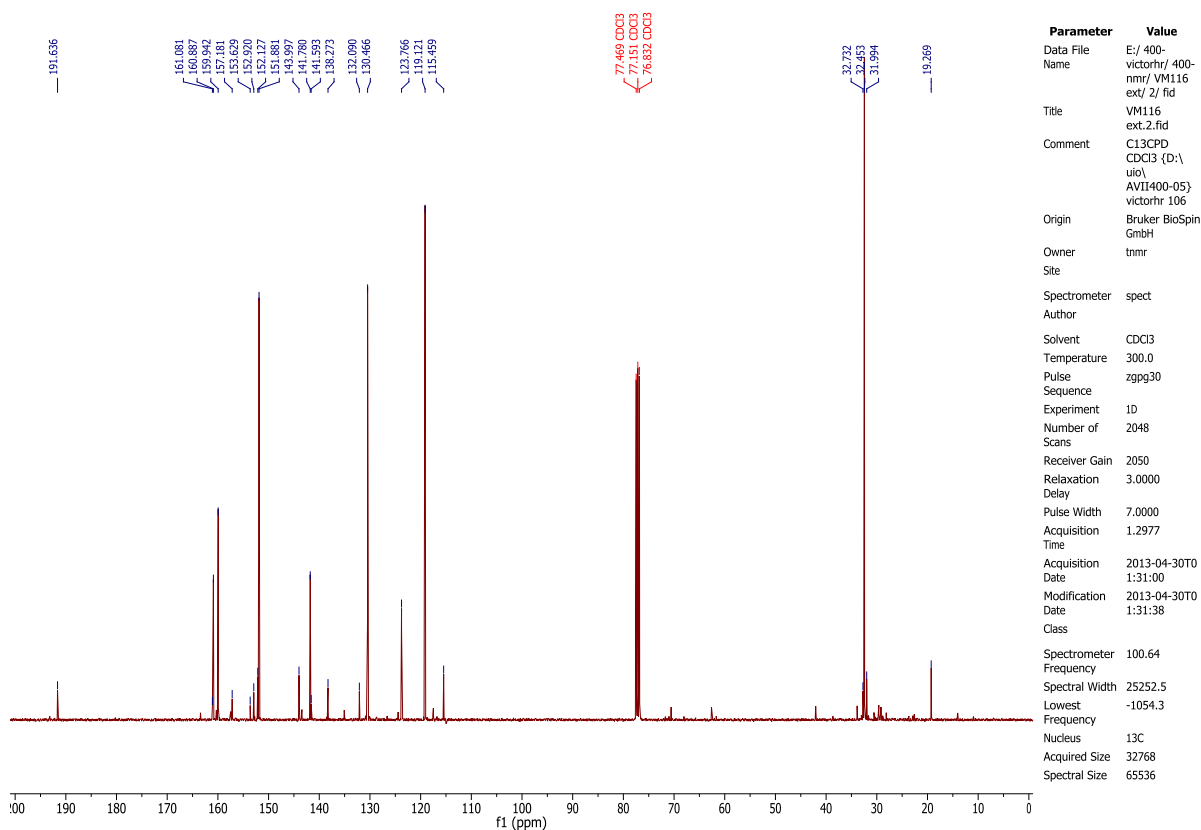
Spectrum 89. ^{13}C NMR of a mixture of 8-allyl-6-chloro-7-methyl-7*H*-purine (**106a**), (*E*)-6-chloro-7-methyl-8-(prop-1-en-1-yl)-7*H*-purine (**106b**), and (*E*)-3-(6-chloro-7-methyl-7*H*-purin-8-yl)acrylaldehyde (**106c**).
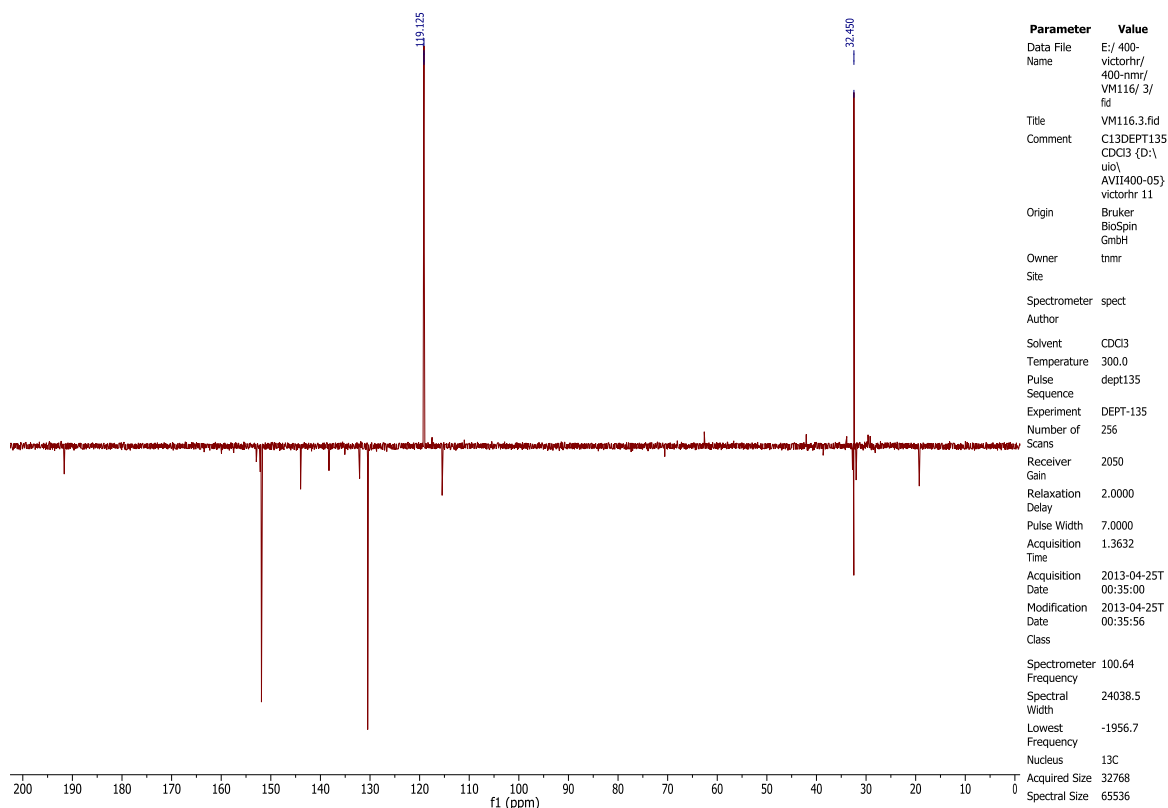
Spectrum 90. ^{13}C DEPT NMR of a mixture of 8-allyl-6-chloro-7-methyl-7*H*-purine (**106a**), (*E*)-6-chloro-7-methyl-8-(prop-1-en-1-yl)-7*H*-purine (**106b**), and (*E*)-3-(6-chloro-7-methyl-7*H*-purin-8-yl)acrylaldehyde (**106c**).

Spectrum 91. ^{13}C APT NMR of a mixture of 8-allyl-6-chloro-7-methyl-7*H*-purine (**106a**), (*E*)-6-chloro-7-methyl-8-(prop-1-en-1-yl)-7*H*-purine (**106b**), and (*E*)-3-(6-chloro-7-methyl-7*H*-purin-8-yl)acrylaldehyde (**106c**).

Spectrum 92. COSY NMR of a mixture of 8-allyl-6-chloro-7-methyl-7*H*-purine (**106a**), (*E*)-6-chloro-7-methyl-8-(prop-1-en-1-yl)-7*H*-purine (**106b**), and (*E*)-3-(6-chloro-7-methyl-7*H*-purin-8-yl)acrylaldehyde (**106c**).

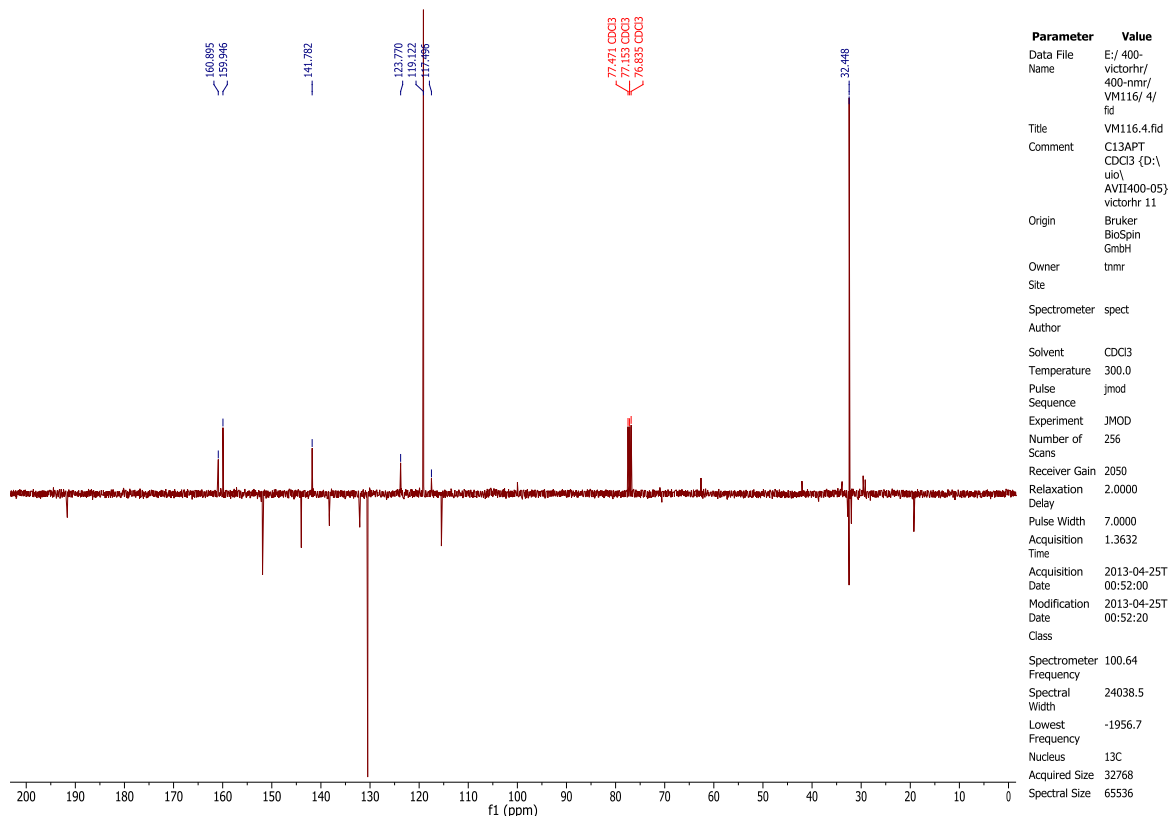**Spectrum 93.** HSQC NMR of a mixture of 8-allyl-6-chloro-7-methyl-7*H*-purine (**106a**), (*E*)-6-chloro-7-methyl-8-(prop-1-en-1-yl)-7*H*-purine (**106b**), and (*E*)-3-(6-chloro-7-methyl-7*H*-purin-8-yl)acrylaldehyde (**106c**).

Spectrum 94. HMBC NMR of a mixture of 8-allyl-6-chloro-7-methyl-7*H*-purine (**106a**), (*E*)-6-chloro-7-methyl-8-(prop-1-en-1-yl)-7*H*-purine (**106b**), and (*E*)-3-(6-chloro-7-methyl-7*H*-purin-8-yl)acrylaldehyde (**106c**).
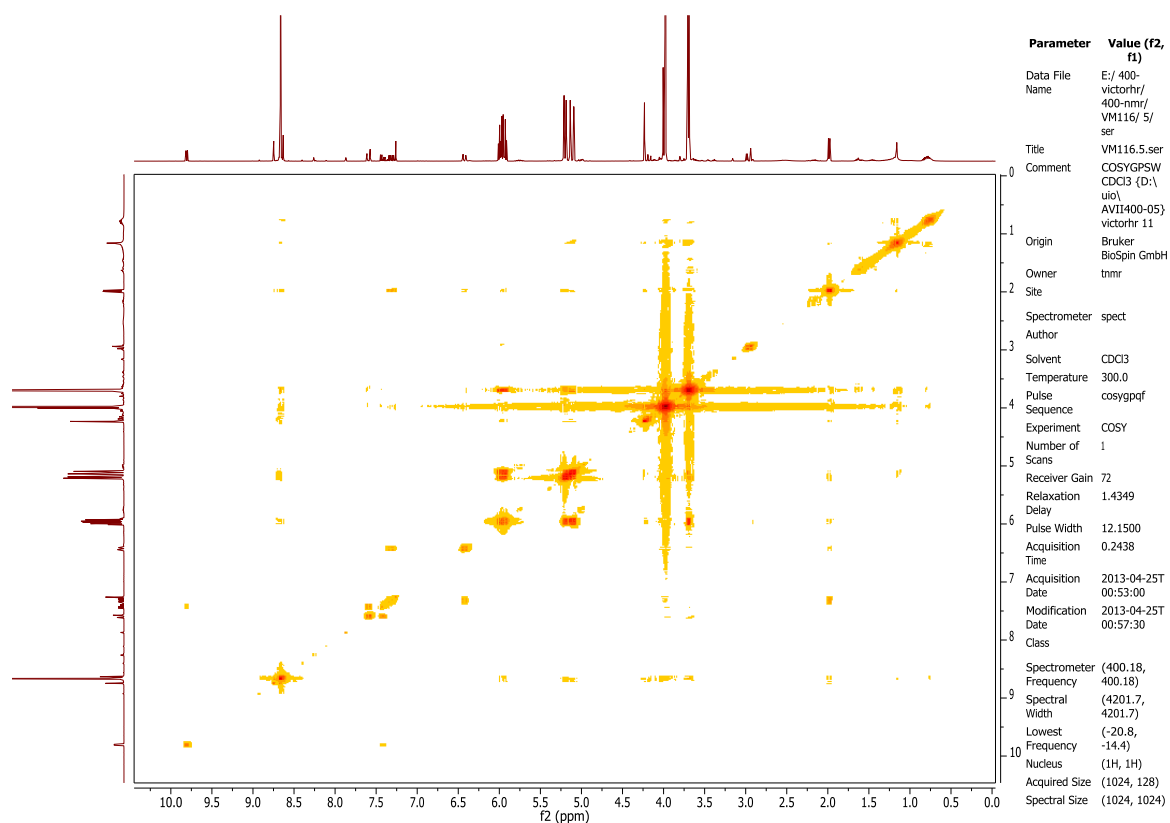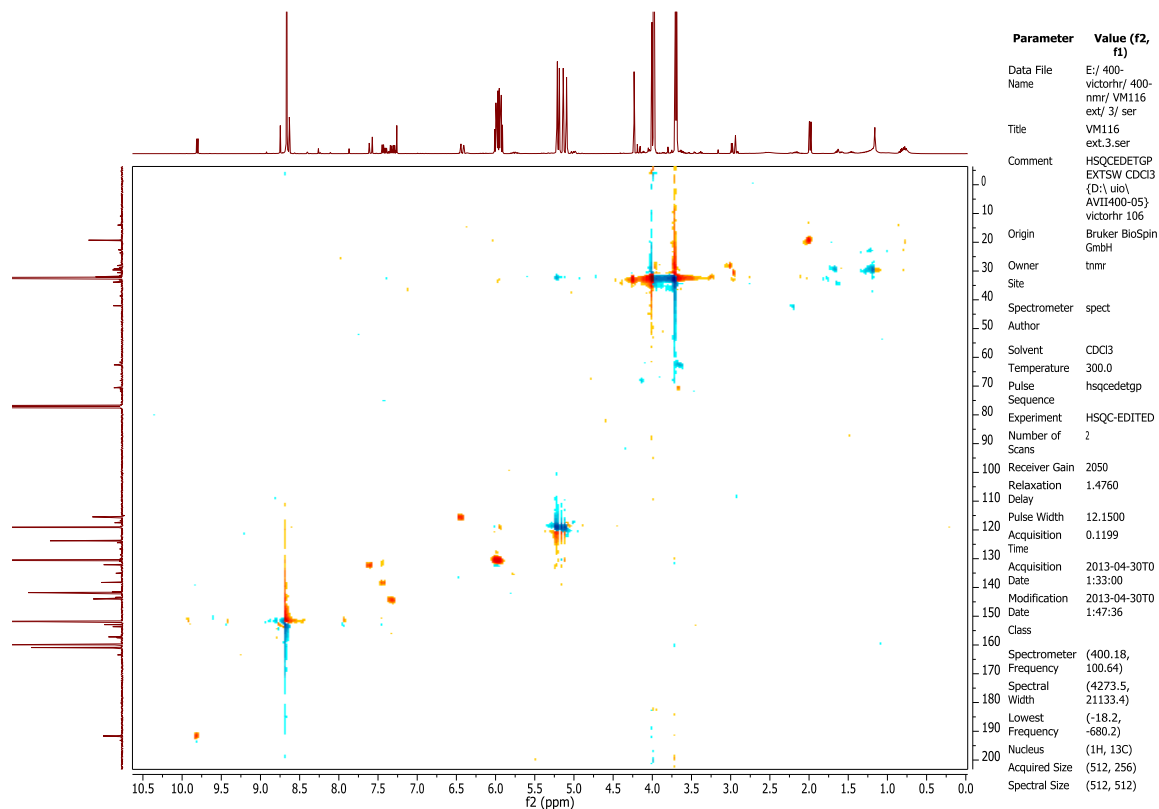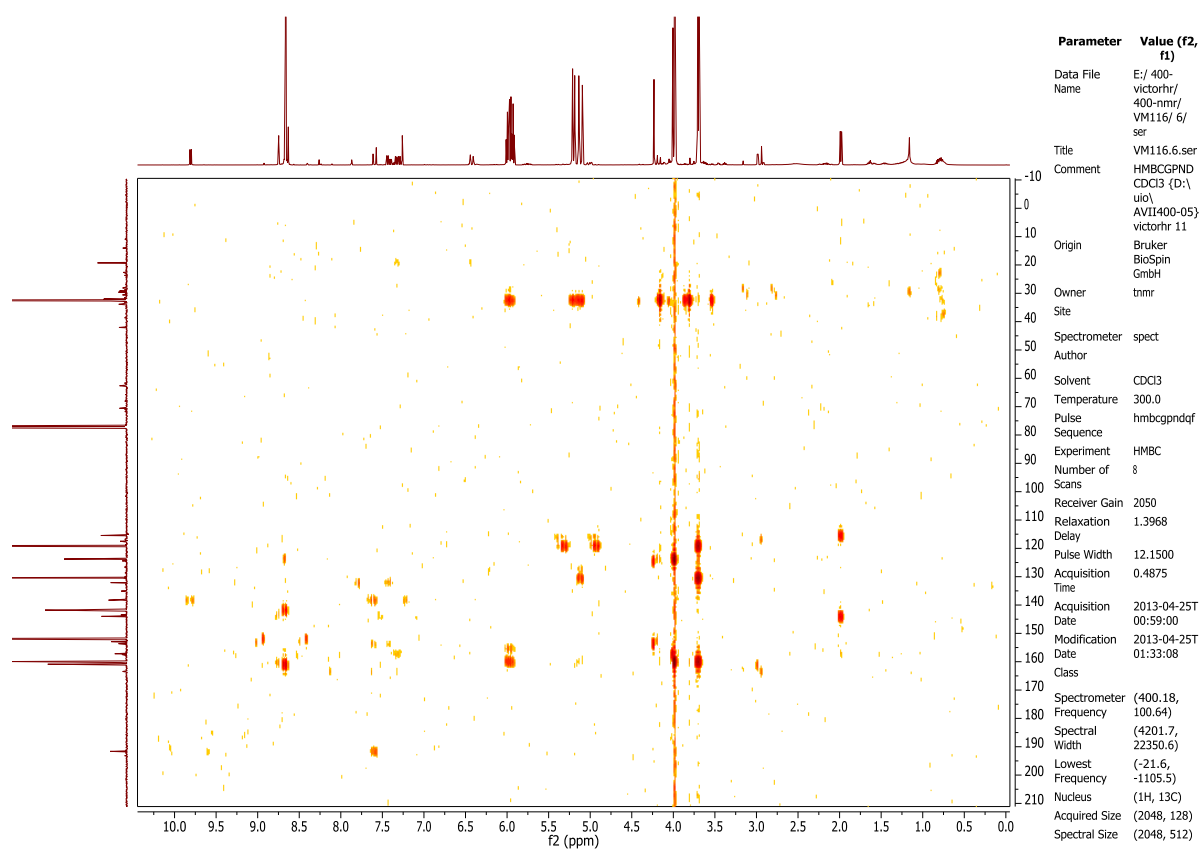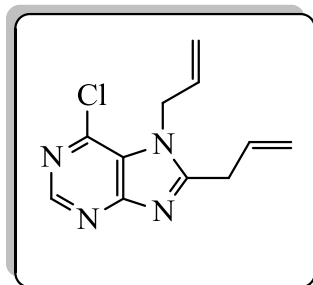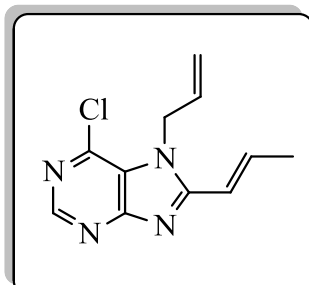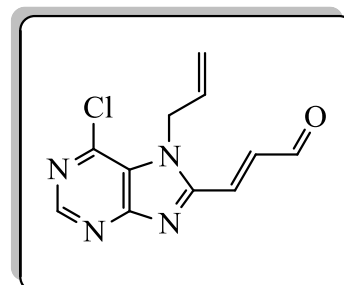
7,8-Diallyl-6-chloro-7*H***-purine (105a), (***E***)-7-allyl-6-chloro-8-(prop-1-en-1-yl)-7***H***-purine (105b), and (***E***)-3-(7-allyl-6-chloro-7***H***-purin-8-yl)acrylaldehyde (105c).**

105a

105b

105c

Allylmagnesium bromide (3.06 mL, 2.04 mmol of 0.67 M solution in diethylether) was added to a solution of compound **20** (200 mg, 1.02 mmol) in THF (10 mL) at -20 ℃ (1:3 NaCl/ice bath) under N_2-atm, and the resulting mixture was stirred at this temperature for 5 min. Sat. aq. NH_4Cl (20 mL) was added, the phases were separated and the water layer was extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The crude product was dissolved in dry DCM (40 mL), MnO_2 (447 mg, 5.10 mmol) was added and the mixture was stirred at room temperature for 2 h. MnO_2 was filtered off, and the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with EtOAc-hexane (1:1) to give 195 mg of a yellow oil composed of a mixture of 7,8-diallyl-6-chloro-7*H*-purine **105a** (72%), (*E*)-7-allyl-6-chloro-8-(prop-1-en-1-yl)-7*H*-purine **105b** (20%), and (*E*)-3-(7-allyl-6-chloro-7*H*-purin-8-yl) acrylald- ehyde **105c** (8%).

7,8-Diallyl-6-chloro-7*H*-purine (**105a**)

¹H NMR (CDCl₃, 400 MHz) δ 3.72 (dt, *J* = 6.4, 1.6 Hz, 1H, C(8)CH₂), 4.85 (dt, *J* = 17.1, 1.8 Hz, 1H, =CH₂a in N(7) allyl), 5.07 (dt, *J* = 4.7, 1.8 Hz, 1H, NCH₂), 5.18-5.30 (m, 3H, =CH₂ in C(8) allyl and =CH₂b in N(7) allyl), 5.94-6.14 (m, 2H, CH= in C(8) allyl and CH= in N(7) allyl), 8.80 (s, 1H, H-2).

¹³C NMR (CDCl₃, 100 MHz) δ 32.3 (C(8)CH₂), 47.0 (NCH₂), 117.8 (=CH₂ in N(7) allyl), 119.2 (=CH₂ in C(8) allyl), 123.2 (C-6), 130.7 (CH= in C(8) allyl), 131.8 (CH= in N(7) allyl), 141.7 (C-4), 152.2 (C-2), 160.0 (C-8), 161.1 (C-5).

MS (EI). *m/z* (rel. %): 236/234 (31/90, M^+), 233 (100), 219 (18), 207 (20), 168 (6), 157 (24), 130 (7), 103 (5).

MS (ESI). 235.0751 $[M+H]^+$ calculated for $C_{11}H_{11}N_4Cl$ 235.0672.

(*E*)-7-Allyl-6-chloro-8-(prop-1-en-1-yl)-7*H*-purine (**105b**)

^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.05 (dd, *J* = 7.0, 1.8 Hz, 1H, CH$_3$), 5.01-5.04 (m, 1H, NCH$_2$), 5.07-5.11 (m, 2H, =CH$_2$), 5.98-6.01 (m, 1H, CH= in N(7) allyl), 6.41 (dd, *J* = 15.2, 1.8 Hz, 1H, C(8)CH), 7.40-7.53 (m, 1H, C(8)CH=C<u>H</u>), 8.76 (s, 1H, H-2).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 19.3 (CH$_3$), 46.5 (NCH$_2$), 115.4 (C(8)CH), 117.5 (=CH$_2$ in N(7) allyl), 123.0 (C-6), 144.1 (C(8)CH=<u>C</u>H), 131.8 (CH= in N(7) allyl), 141.4 (C-4), 152.3(C-2), 157.2 (C-8), 161.3 (C-5).

MS (EI). *m/z* (rel. %): 236/234 (30/90, M^+), 233 (100), 219 (18), 195 (26), 193 (80), 157 (24), 130 (6), 103 (5).

MS (ESI). 235.0751 $[M+H]^+$ calculated for $C_{11}H_{11}N_4Cl$ 235.0672.

(*E*)-3-(7-Allyl-6-chloro-7*H*-purin-8-yl)acrylaldehyde (**105c**)

^{1}H NMR (CDCl$_3$, 400 MHz) δ 4.84 (dt, *J* = 12.3, 2.0 Hz, 2H, NCH$_2$), 5.24 (dt, *J* = 10.5, 1.8 Hz, 2H, =CH$_2$), 6.01-6.06 (m, 2H, CH= in N(7) allyl), 7.42 (dd, *J* = 15.5, 6.8 Hz, 1H, C(8)CH=C<u>H</u>), 7.50 (d, *J* = 15.5 Hz, 1H, C(8)CH), 8.76 (s, 1H, H-2), 9.77 (d, *J* = 6.8 Hz, 1H, CHO).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 47.1 (NCH$_2$), 118.1 (=CH$_2$), 132.2 (CH= in N(7) allyl), 138.3 (C(8)CH=<u>C</u>H), 141.4 (C-6), 151.3 (C(8)CH), 153.7 (C-8), 157.1 (C-2), 160.5 (C-4), 161.1 (C-5), 191.6 (CHO).

MS (EI). *m/z* (rel. %): 250/248 (10/33, M^+), 234 (80), 219 (100), 205 (41), 193 (75), 157 (24), 130 (6).

MS (ESI). 249.0672 $[M+H]^+$ calculated for $C_{11}H_{11}N_4Cl$ 249.0465.
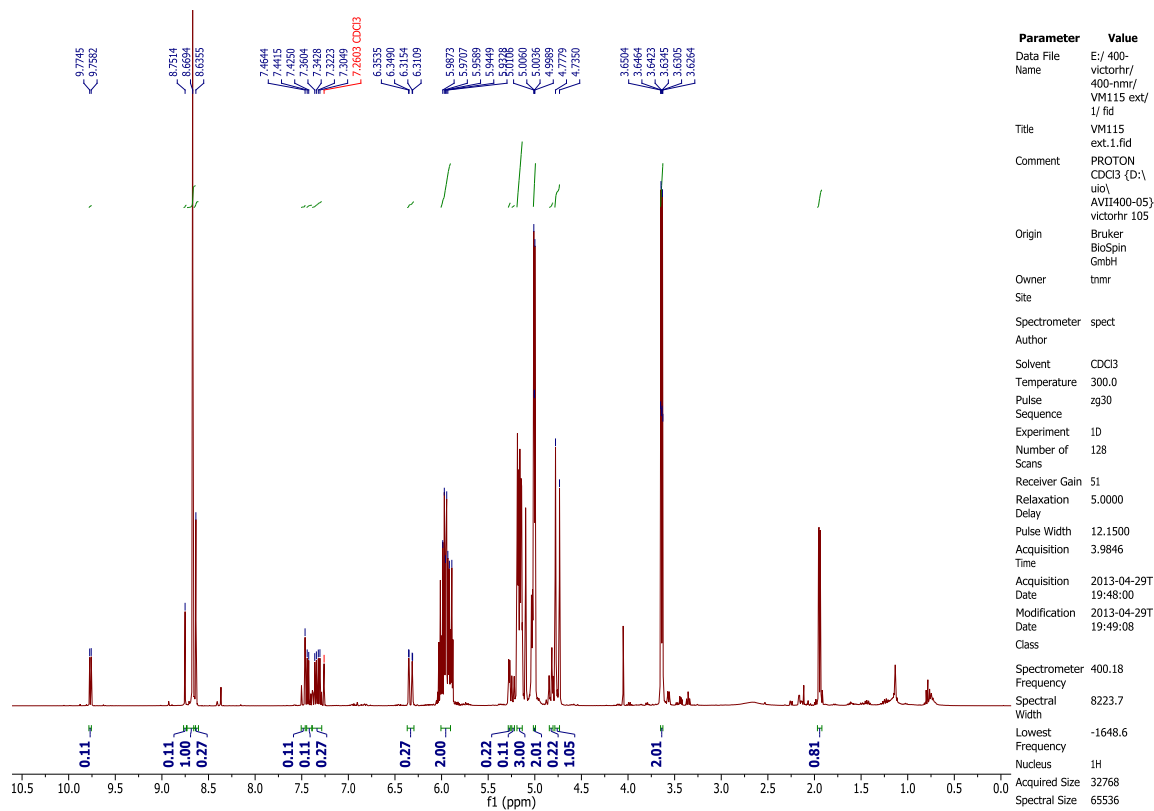
Spectrum 95. ¹H NMR of a mixture of 7,8-diallyl-6-chloro-7*H*-purine (**105a**), (*E*)-7-allyl-6-chloro-8-(prop-1-en-1-yl)-7*H*-purine (**105b**), and (*E*)-3-(7-allyl-6-chloro-7*H*-purin-8-yl)acrylaldehyde (**105c**).
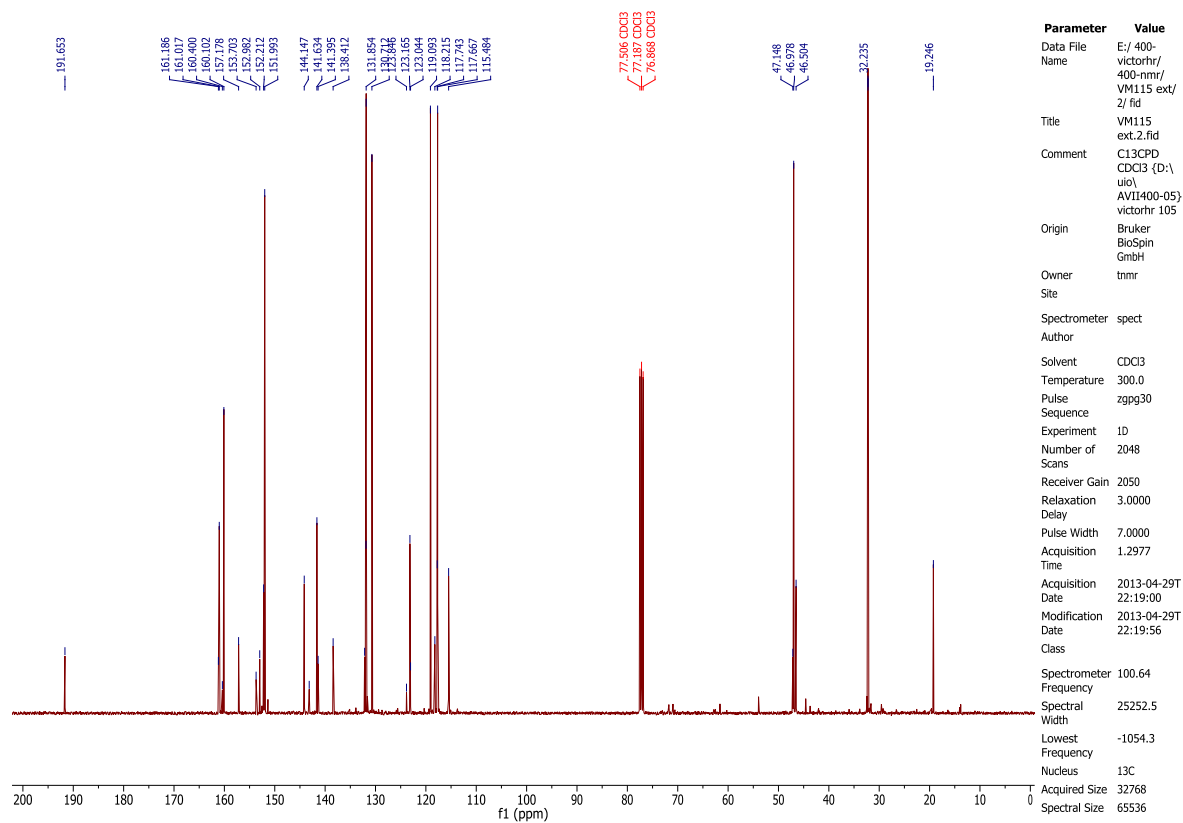
Spectrum 96. ¹³C NMR of a mixture of 7,8-diallyl-6-chloro-7*H*-purine (**105a**), (*E*)-7-allyl-6-chloro-8-(prop-1-en-1-yl)-7*H*-purine (**105b**), and (*E*)-3-(7-allyl-6-chloro-7*H*-purin-8-yl)acrylaldehyde (**105c**).
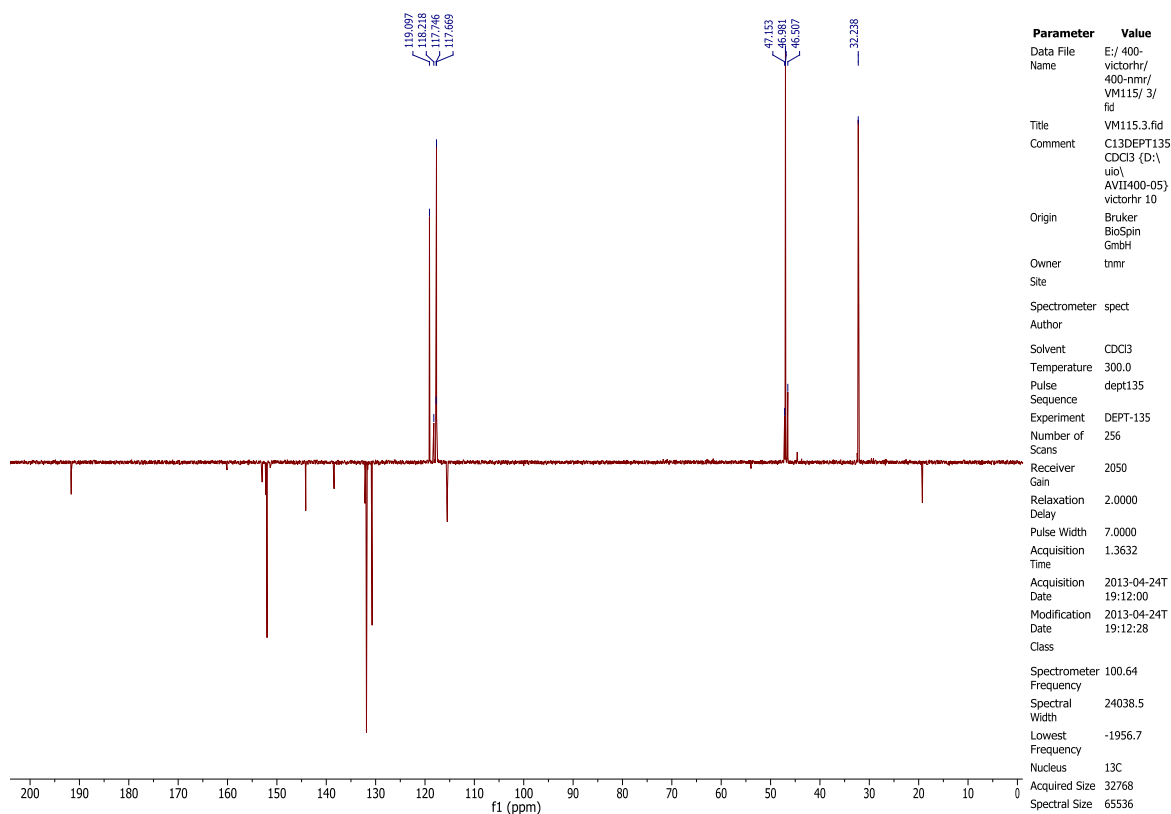
Spectrum 97. ^{13}C DEPT NMR of a mixture of 7,8-diallyl-6-chloro-7*H*-purine (**105a**), (*E*)-7-allyl-6-chloro-8-(prop-1-en-1-yl)-7*H*-purine (**105b**), and (*E*)-3-(7-allyl-6-chloro-7*H*-purin-8-yl)acrylaldehyde (**105c**).
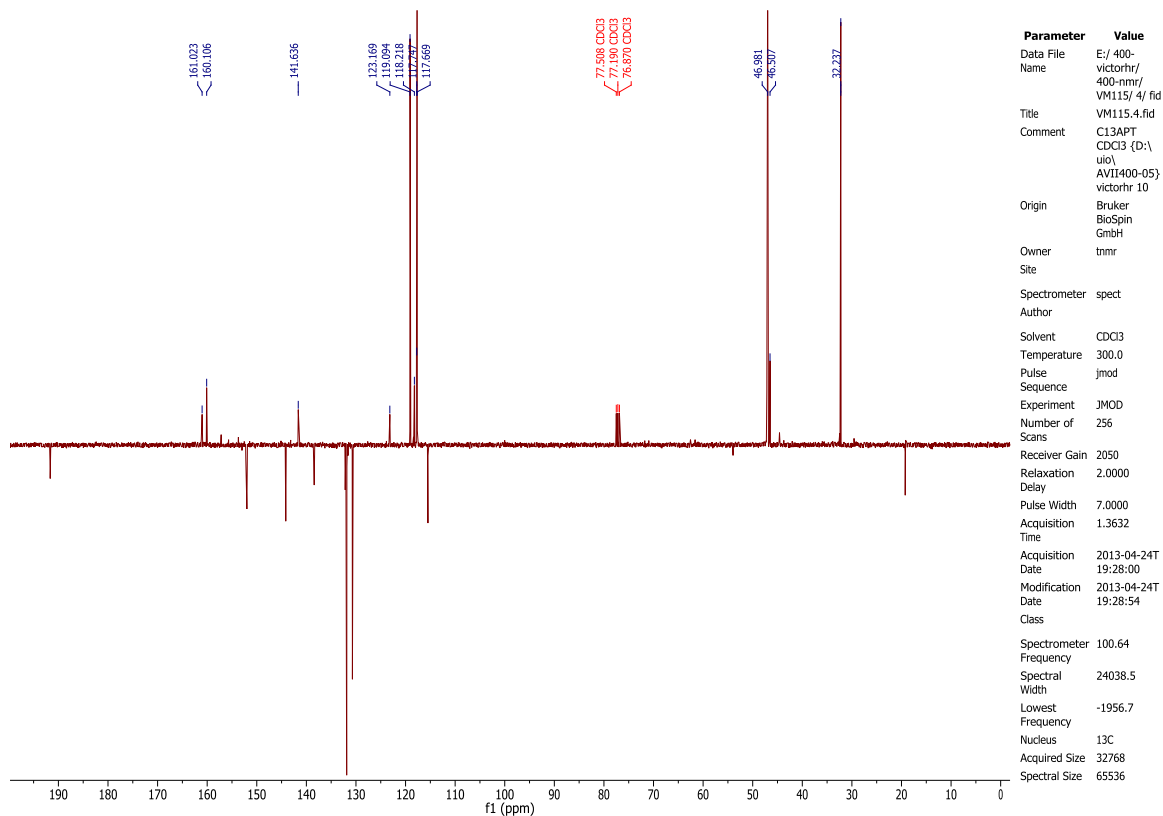
Spectrum 98. ^{13}C APT NMR of a mixture of 7,8-diallyl-6-chloro-7*H*-purine (**105a**), (*E*)-7-allyl-6-chloro-8-(prop-1-en-1-yl)-7*H*-purine (**105b**), and (*E*)-3-(7-allyl-6-chloro-7*H*-purin-8-yl)acrylaldehyde (**105c**).
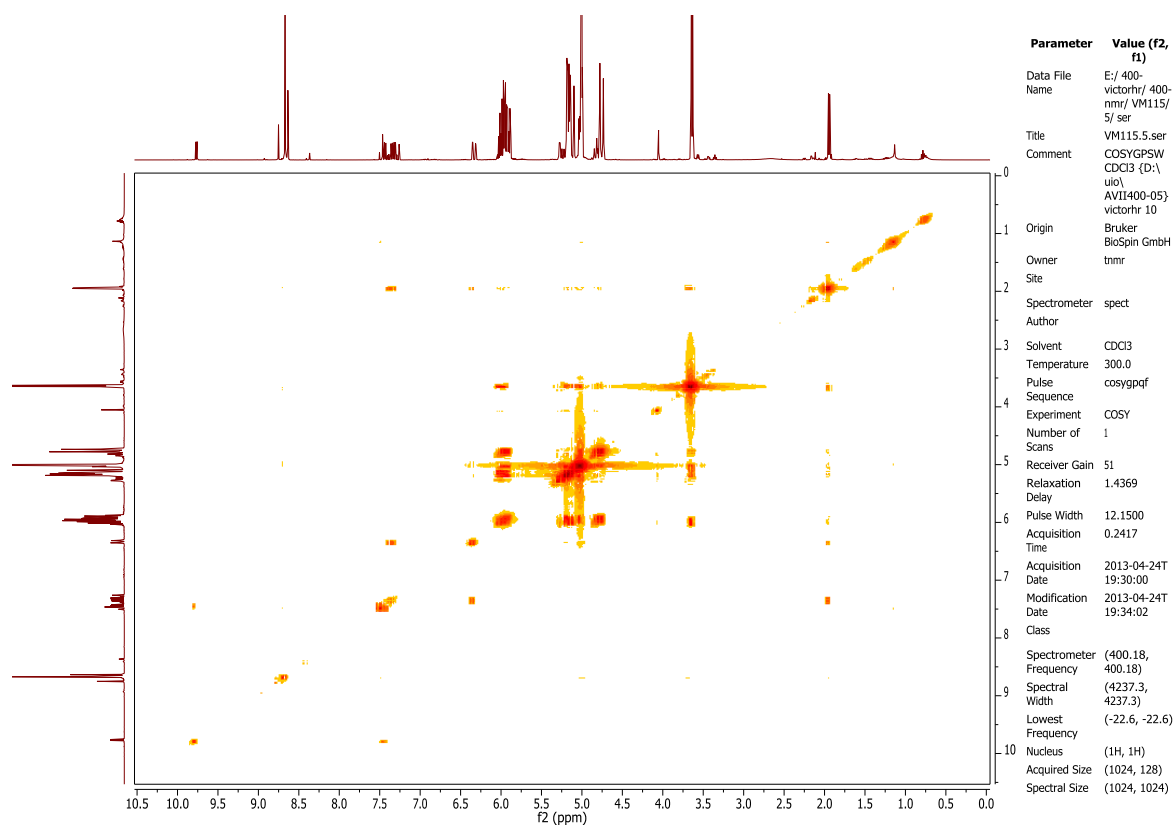
Spectrum 99. COSY NMR of a mixture of 7,8-diallyl-6-chloro-7*H*-purine (**105a**), (*E*)-7-allyl-6-chloro-8-(prop-1-en-1-yl)-7*H*-purine (**105b**), and (*E*)-3-(7-allyl-6-chloro-7*H*-purin-8-yl)acrylaldehyde (**105c**).

Spectrum 100. HSQC NMR of a mixture of 7,8-diallyl-6-chloro-7*H*-purine (**105a**), (*E*)-7-allyl-6-chloro-8-(prop-1-en-1-yl)-7*H*-purine (**105b**), and (*E*)-3-(7-allyl-6-chloro-7*H*-purin-8-yl)acrylaldehyde (**105c**).

Spectrum 101. HMBC NMR of a mixture of 7,8-diallyl-6-chloro-7*H*-purine (**105a**), (*E*)-7-allyl-6-chloro-8-(prop-1-en-1-yl)-7*H*-purine (**105b**), and (*E*)-3-(7-allyl-6-chloro-7*H*-purin-8-yl)acrylaldehyde (**105c**).
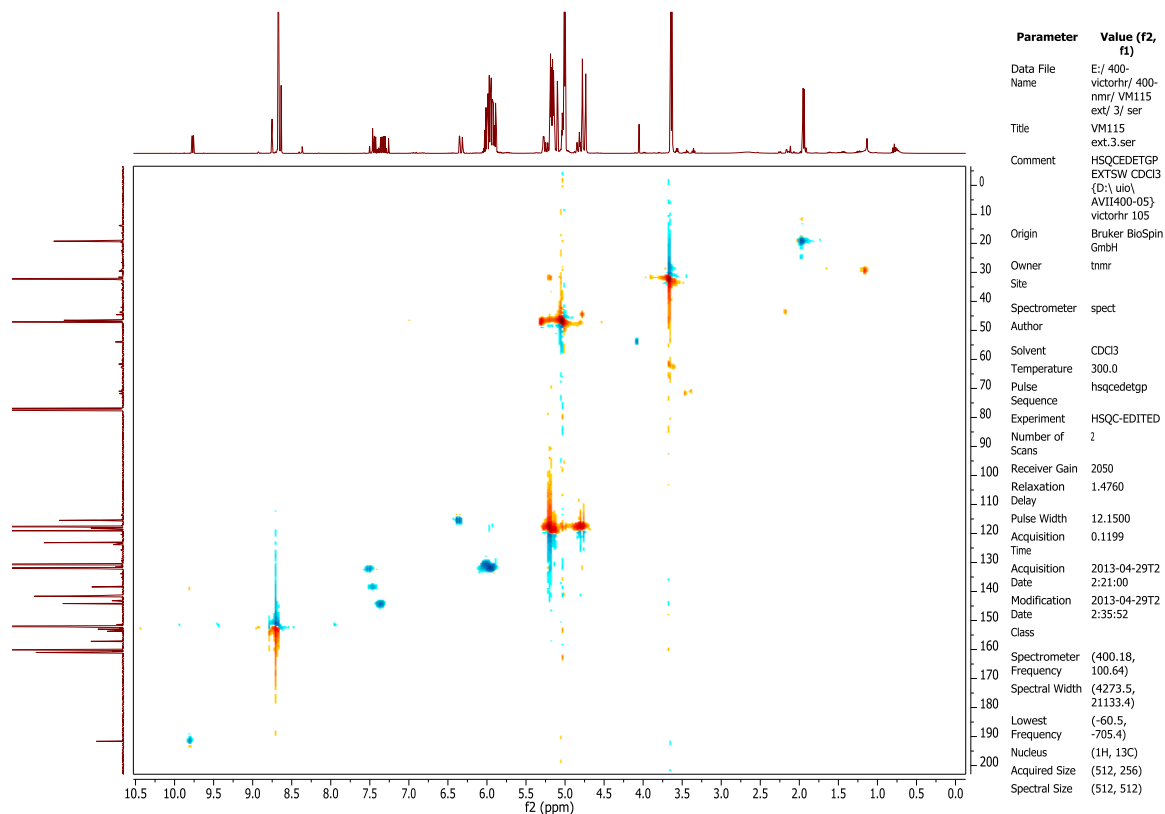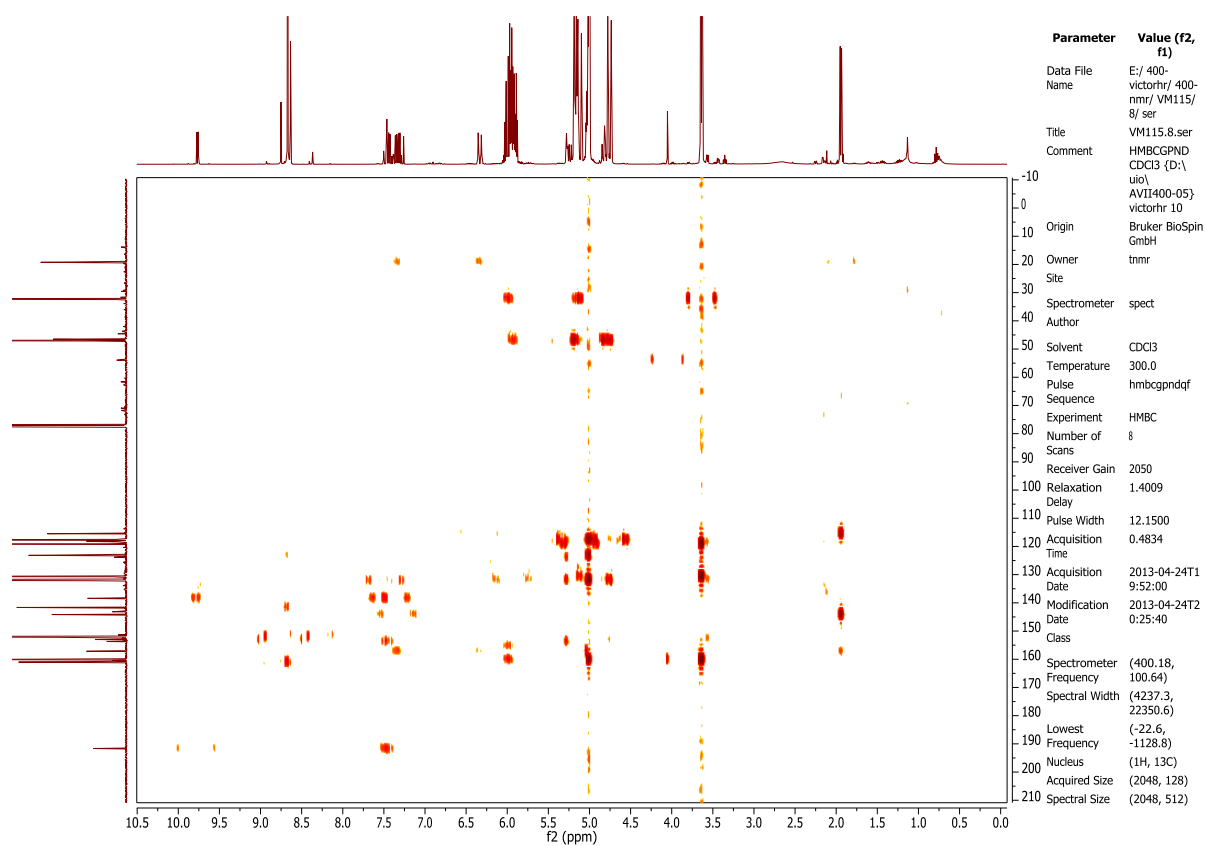
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