Thesis for a Master of Science Degree in Chemistry

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Functionalization of the Purine 8-Position via 8-Lithiated Species: Scopes and Limitations.

60 study points

DEPARTMENT OF CHEMISTRY

Faculty of Mathematical and Natural Sciences

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May 2009

ACKNOWLEDGEMENT

I am very grateful to the Norwegian Government for the Quota Scholarship Scheme of which I have been a beneficiary.

I am also very grateful to my supervisor, Prof. Lise-Lotte Gundersen, for giving me the opportunity to conduct my research in her group. In addition, I appreciate her kind guidance, advice, and suggestions towards the successful completion of this work.

I would also like to thank all lecturers who have taught me till date for the knowledge they imparted to me.

My sincere thanks also go to Dr Osamu Sekuguchi and Mr. Dirk Petersen for their assistance.

To my group members, I say thank you for the useful discussions we had as well as your support in various ways.

My appreciation also goes to my father and siblings for their support.

Finally to my friend, Josephine Selase Afiamefao, I say thank you for your love and support which has always been a source of urge to succeed.

ABSTRACT

In this study, 6-chloropurines with varied substituent in the 2 and 9 or 7 position were functionalized in the 8-position. This was done via lithiation and subsequent bromination to form 8-brominated purines.

It was observed that lithiation/bromination of N-9 benzylated purines bearing electron donating substituents on the phenyl ring gave good conversions and excellent yields of the expected 8-bromo purines. On the other hand, those bearing electron withdrawing groups on the phenyl ring gave poor conversions and yields of the expected 8-bromo purines. Aside the expected 8-bromo purines, dimers and aldehydes were observed as by-products of this reaction.

ABBREVIATIONS

Ac	Acetyl
Ar	Aryl group
BuLi	Butyllithium
cAMP	cyclic-Adenosine monophosphate
Compd.	Compound
DEPT	Distortionless enhancement by polarization transfer
DMF	Dimethylformamide
DNA	Deoxyribonucleic acid
E.g.	Example
EtOAc.	Ethyl acetate
Et al.	Et alia (and others)
Fig.	Figure
Hex.	Hexane
HMBC	Heteronuclear multiple bond correlation experiment
HMQC	Heteronuclear multiple-quantum coherance experiment
HSQC	Heteronuclear single quantum coherence
LDA	Lithium diisopropylamide
MIC	Minimum inhibitory concentration
M. p	Melting point
MS	Mass spectroscopy
NAD	Nicotinamide adenine dinucleotide
NMR	Nuclear magnetic resonance spectroscopy
Ph	Phenyl
RSM	Recovered starting material
RNA	Ribonucleic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran

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1.0 INTRODUCTION

Purines are one of the most common heterocycles in nature (Fig. 1). The ribonucleic acid (RNA) and the deoxyribonucleic acid (DNA) consist of two types of bases; the pyrimidine and the purine bases. These occur in the ratio of 1:1 making the percentage of purine bases (guanine and adenine) in RNA and DNA 50% of the total bases. The quantity of naturally occurring purines on earth is therefore enormous as RNA and DNA are very ubiquitous pair of substances associated with the living world.[1]

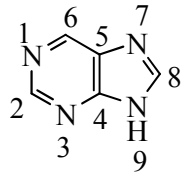

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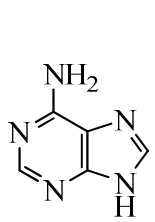
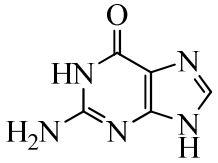
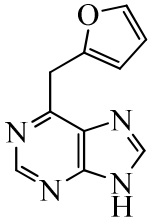
Figure 1. The purine ring and the accepted numbering system



2 (Adenine)



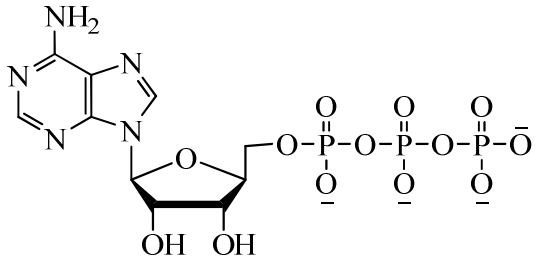
3 (Guanine)



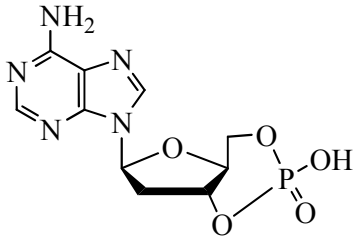
4 (Kinetin)

Figure 2. Structures of Adenine, Guanine and Kinetin

Purine derivatives are found in plants as growth hormones, examples are cytokinins. Cytokinins promote cell divisions in plants and an example is kinetin[1] (Fig. 2). Various other purine derivatives are involved in cellular machinery such as adenosine 5'–triphosphate (ATP, Fig. 3), used for the transport of chemical energy in the cell; adenosine 3',5'-cyclic monophosphate (cAMP, Fig. 3), which acts as a secondary messenger controlling the activation of protein kinase, the potassium level of the cell, as well as transcription and other metabolic process.[1] Purines are also constituents of flavin adenine dinucleotide (FAD) and nicotinamide adenine dinucleotide (NAD) which are involve in cellular reduction-oxidation processes.[1] They transfer electrons into the electron transport chain for ATP synthesis. Their presence in the above and other very important cellular molecules makes them very important structural components in many bioactive natural products as well as synthetic drugs (especially anti-cancer and antiviral drugs).



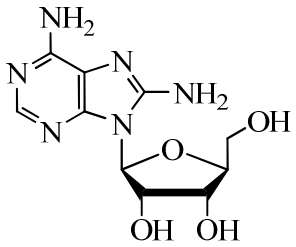
5 (ATP)



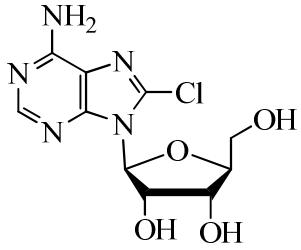
6 (cAMP)

Figure 3. Structures of ATP and cAMP.

Strides in the exploration of purine-based compounds have shown them as chemical-biological tools with potentials as therapeutic agents to treat an impressively broad spectrum of diseases. They are found to be interferon inducers, microtubule assembly inhibitors, antimycobacterials and phosphodiesterase inhibitors.[2] Among the potential antiviral and anticancer agents are 8-substituted purines bearing substituents in the 6- and 9-positions (6-, 8- and 9-substituted purines). Examples are 8-chloroadenosine (Fig. 4)[7,8] 8-mercaptoguanosine, [10] 8-amino-adenosine (Fig. 4) [11] 7,8-dihydro-8-oxoadenosine[12] and 8-amino-9-benzylguanine.[13] 8–substituted purine derivatives also have antimalarial potentials, examples are 8-amino-5'-deoxy-5'-chloroguanosine [3] and 8-amino-9-benzylguanine.[3] These potentials of 8-substituted purines as therapeutic agents make the exploration of purine chemistry in the 8-position very interesting.



7 (8-amino-adenosine)



8 (8-chloro-adenosine)

Figure 4. Structure of 8-amino adenosine and 8-chloro-adenosine potential anticancer substances

The purine ring can be functionalized at its various positions by introduction of a reactive

species into these positions via an appropriate route.[9] One of such reactive species is the halogens. The reactivity of halogens in the 2-, 6-, or 8-positions towards nucleophiles has made them one of the most indispensible intermediates for the synthesis and interconversion of purines.[1] 8-Halopurines are very good intermediates for the synthesis of 8-substituted purine derivatives, [14] therefore reactions that allow the direct introduction of halogens into the 8-position are essential since tedious starting materials syntheses are avoided.[4]

It has been shown that an efficient route to purine nucleosides modified at C-8 is lithiation followed by trapping with electrophilic species [1, 4, 5, 6] for example halogen donors for the synthesis of 8-halopurines. The halogen substituent can later be replaced by a nucleophile. 6-(2-Furyl)-8-methoxy-9-(methoxyphenyl)-9*H*-purine (Fig. 5) a potentially bioactive purine, active against *Mycobacterium tuberculosis* (showing 95% inhibition at 6.25μg/mL concentration) was reported synthesized by lithiation followed by a lithium-halogen exchange forming a halopurine. The halogen was later substituted by a methoxy group.[15]

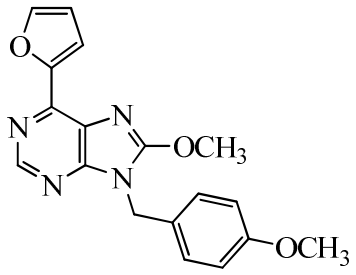


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Figure 5. The structure of 6-(2-Furyl)-8-methoxy-9-(methoxyphenyl)-9*H*-purine, an inhibitor of *Mycobacterium tuberculosis.*

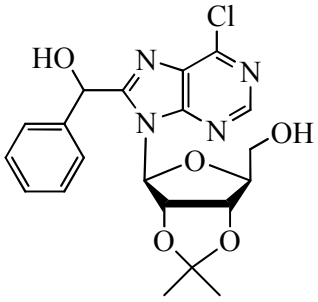

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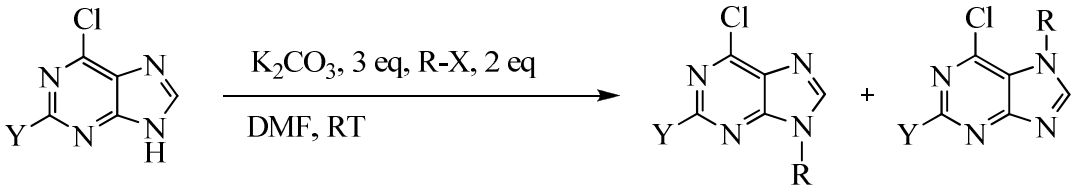
Figure 6. Structure of 8-phenylhydroxymethyl-6-chloro-9-(2,3-O-isopropylidene-β-D-ribofuranosyl).

Another purine synthesized via lithiation and subsequent reaction with an electrophile is 8-phenylhydroxymethyl-6-chloro-9-(2, 3-O-isopropylidene-β-D-ribofuranosyl) purine (Fig.3).[16]

However this method appeared not to be general. Substituents on the purine ring apparently affect the lithiation process since lithiation–halogenation of 6-chloro-9-benzylpurine failed.[17] Therefore the hypothesis for this study was that the stability of the intermediate "purinyl anion" is dependent on the identity of the N-9 or N-7 substituent.

1.1 *Objective of the project.*

The objective of this project was to undertake systematic study of the reaction sequence in Scheme 2, in order to explore the true scope and limitation of this methodology for the functionalization of the purine 8-position. This was to involve the variation of the substituents in the 2- and 9-positions Y and R respectively via the route in Scheme 1, followed by attempts to lithiate at 8-position thereby determining whether lithiation is/not possible for each substituent.

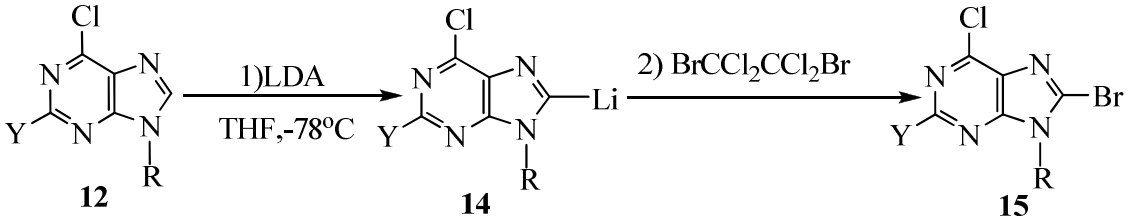


11 **12** **13**

Y: H, Cl, NO_2 X=Cl, Br

R: Various alkyl groups with different electronic and steric properties

Scheme 1



Y: H, Cl, NO_2

R: Various alkyl groups with different electronic and steric properties

Scheme 2

2.0 LITERATURE REVIEW

2.1 *Reactivity at the purine ring atoms*

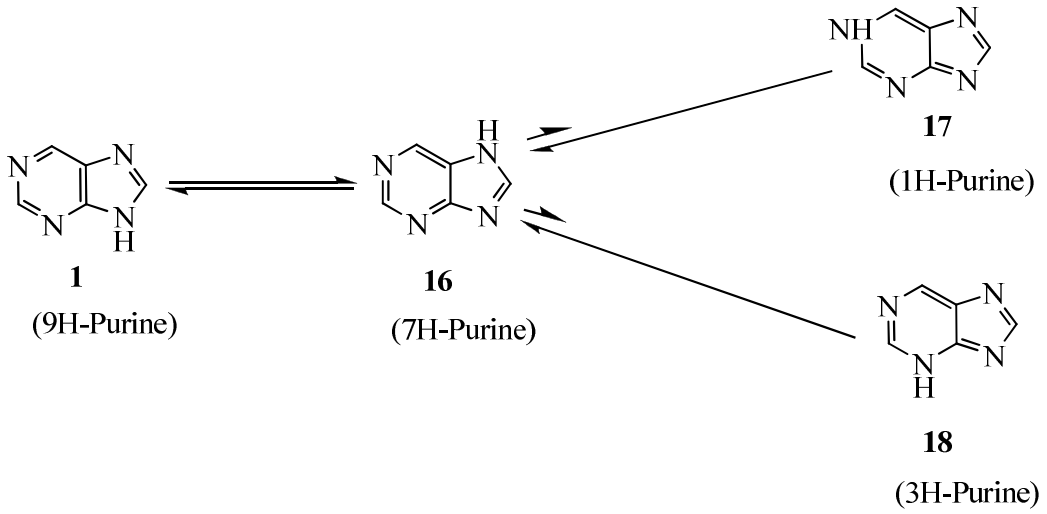
The purine is composed of the pyrimidine and the imidazole ring systems. The pyrimidine is a member of a class of molecules called the diazines. The unsubstituted diazines have six π-electrons distributed over a sigma framework of six atoms including two nitrogens. The two nitrogen heteroatoms in pyrimidines and the other diazines withdraw electron density from the ring carbons. The pyrimidine ring is therefore electron deficient. The imidazole ring on the other hand has six π-electrons spread over five atoms making it electron rich. Since the purine consist both of these ring systems, it is capable of undergoing both nucleophilic and electrophilic reaction at the ring atoms, but the products often depend on the state of polarization of the molecule.[14] The anionic forms of purines is readily attacked by electrophiles such as alkylating or glycosylating agents to produce N-substituted derivatives. In the neutral form the products may vary in some cases as in the case of vinylation, producing a mixture of N-9 and N-7 substituted products.[14] The reactivity of the N-9 or N-7 towards electrophiles therefore makes it imperative to always protect these positions in electrophilic reactions directed towards other ring atoms (e.g. C-8 position) so as to prevent undesirable products.

In addition to the ring nitrogen the adjacent carbon atoms also show degrees of electrophilic or nucleophilic character, the extent of which depends on the state of ionization of the molecule and the degree and type of substitution.[14] The purine-pyrimidine and -imidazole rings interact with electrons moving into the pyrimidine ring from the imidazole ring system. It can therefore undergo both nucleophilic and electrophilic attack on the carbons in the five member imidazole system but only nucleophilic reaction at the carbon in the six member pyrimidine system.[18] The large movement of negativity in purines from the π-electron excessive imidazole ring to the π-electron deficient pyrimidine ring results in the C-8 atom becoming the most electron deficient (electrophilic) in the unionized purine molecule[1, 14] thus the hydrogen attached at that position the most acidic after the N-9 hydrogen. This makes the C-8 position the first position of attack by a lithiating agent in 9-substituted purines. Also, the C-8 atom in purines may achieve sufficient electronegativity to permit attack by

electrophiles. This negativity is normally achieved with the presence of one or more electron-donating groups in the ring system.[14]

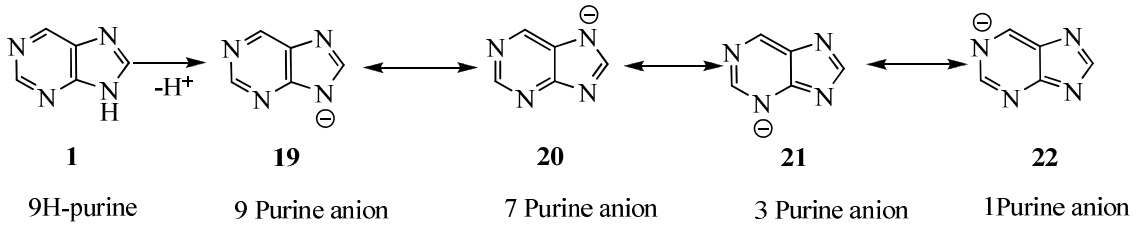
2.2 *N-Alkylation of purines*

The unsubstituted purine can exist as four possible tautomers (Scheme 3); but the ratio of these tautomers depends on the state of the purine. It exists as a 7H-tautomer in the crystalline state and 7H- and 9H-tautomers in approximately equal amounts in solution; while 1H- and 3H-tautomers are insignificant.[18]



Scheme 3[18]

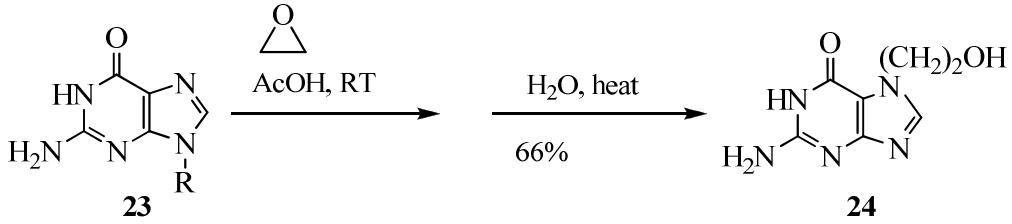
The purine nitrogen can react with electrophilic alkylating agents but this can be enhanced by using a base. The purine N-hydrogen is acidic and can be removed by a base forming a more reactive species. The anionic form can exist in any of the four resonance forms (Scheme 4).



Scheme 4

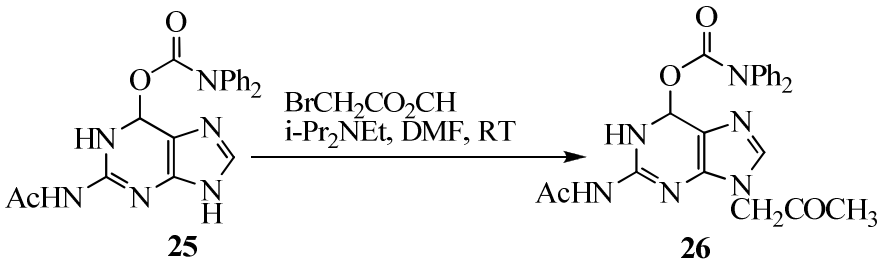
In principle therefore alkylation reaction can take place on any of the ring atoms. However the position of alkylation is affected by the substituent on the ring atom and the nature of the alkylating agent. Adenine for example gives mainly 3-alkylated products under neutral conditions but 7/9-substitution occur under basic conditions while adenosine derivatives usually give the 1-alkylated products presumably due to hindrance to the N-3 position.[18] These examples indicate that with an electron donating group in the six member ring, reactivity towards electrophiles is made possible and even enhanced in this ring. On the other hand with an electron withdrawing group in the six member ring for example the 6-chloropurines, reactivity is directed into the five member ring forming the N-7 and N-9 products the ratio of which depends on the alkylating agents. The major product in most cases is the N-9 substituted product. Benzyl halide alkylating agents give mainly the N-9 product as the major product for 6-chloropurine[18] presumably due to steric hindrance from the 6-chloro group in the formation of N-7 alkylated isomer. This to say the ratio of N-9 to the N-7 alkylated is greatly influenced by the size of the substituent in the 6-position.[18]

Regiospecific alkylation on the 7-position can be achieved via quaternisation of a 9-riboside followed by hydrolytic removal of the ribose residue as illustrated in Scheme 5.[18]



Scheme 5 [18]

In difficult situations where N-7/N-9 selectivity is poor, alkylation can be directed to the N-9 by using a bulky protecting group in the C-6 position (Scheme 6).[18] The protecting group can later be removed.

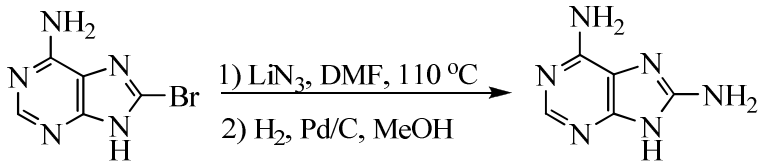


Scheme 6[18]

As mentioned earlier in this section, the N-H hydrogen of unsubstituted purines is acidic. This makes it important to protect this position in deprotonation reaction directed towards acidic carbon hydrogens. Alkylation agents such are benzyl groups and pyranyl group are therefore used as protection agents to protect this position from attack by basic reagents.

2.3 *Synthetic significance of halopurines*

Nucleophilic attack at the carbons in the purine ring is enhanced by replacing the hydrogen with a better leaving group example the halogens. The reaction of the 2-, 6- and 8-halopurines are very important in purine synthesis since they allow the introduction of other substituents (nucleophiles) into this position being good leaving groups. They are for example used in cross coupling reactions to introduce other substituents into the ring system.[17] By using halopurines relatively easy nucleophilic attack takes place at all the three positions with a wide range of nucleophiles (an example is shown in Scheme 7[19]) such as alkoxide, sulphides, amines, azide, cyanide, and melonate and related carbanions[18] also with hydrazine and compounds with active methyl groups.[14] This makes them very important reactive species in purine synthesis.



27 **28**

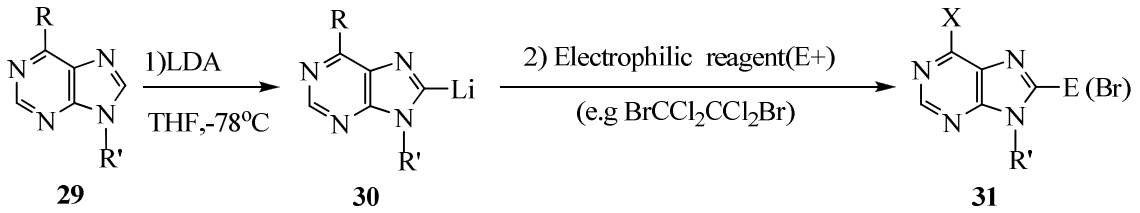
Scheme 7[19]

2.4 *8-halopurines*

Halopurines can be synthesized by direct halogenation. Direct halogenations at an unoccupied 8-position to synthesize 8-halopurines are widely used, particularly when the purine contains one or more electron–releasing groups.[1] Few reports of direct fluorination of the 8-position have been made while chlorination is difficult giving low yields.[1] Purines can be brominated at 8-position using bromine (which may occur via N-halopurinium salts and

later nucleophilic addition of bromide anion to the 8-position followed by elimination of hydrogen halide[18]) or N-bromoamides, but the outcome of the reactions are strongly dependent on the conditions employed as well as the lability of the starting material.[1, 4] For purine nucleoside starting materials, there could be cleavage of acid labile glycosidic bonds.[1] This form of bromination has been employed in the direct bromination of adenosine- and guanosine monophosphates.[24] Halopurines can also be prepared from oxy, amino, and thiopurine[1, 18] and 8-halopurines from purin-8-thiols.[1] Also 8-bromopurines can be synthesized by immobilizing purines on solid supports followed by bromination using a charge-transfer complex of the bromine with lutidine.[25]

However, there is always a need for an easier alternative and lithiation has been found to be an easy and efficient way of synthesizing 8-halopurines (an example is shown in Scheme 8) and other 8-substituted purines.[14, 4, 1, 5, 6]



29 **30** **31**

R=Cl, OH, NH_2
R'=2, 3, 5-tris-*O*-TBDMS-β-D-ribofuranosyl

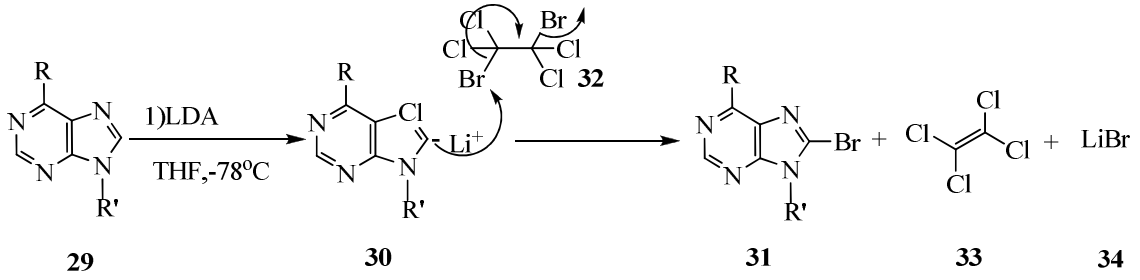
Scheme 8[14]

The presence of a halogen at the 8-position, as stated earlier, afford the possibility of introducing other groups into this position. This possibility was applied for 8-bromo purines by Havelková *et al*. in which various aryl groups were introduced into this position via Suzuki-Miyaura cross coupling method[26] and also by Čapek *et al*.[27] in the synthesis of purinyl-8-yl phenylalanines.[27] Similarly this functionality has been applied in the synthesis of an orally active purine-based inhibitor of the heat shock protein 90 (Hsp 90) via nucleophilic displacement of the bromo group.[28, 9] Hsp 90 is a molecular chaperone that maintains the proper conformation of its "client" proteins.[29, 30, 31, 32, 33] Chaperone Hsp 90 has been a target of interest in for the synthesis of drugs directed towards cancer because of its central regulatory role.[27] A prominent advantage that targeting of Hsp 90 offer is that it affords simultaneous depletion of multiple oncogenic proteins hence attacking several pathways necessary for cancer development and reducing the likelihood of the tumor acquiring

resistance to the Hsp 90 inhibitor.[34, 35] Another important advantage of Hsp 90 is that it occurs in an activated form in cancer cells and in a latent form in normal cells.[36, 37] 8-iodo purines have also been used to introduce various substituents into the 8-position.[38]

2.5 *Lithiation-based electrophilic substitution at the purine 8-position*

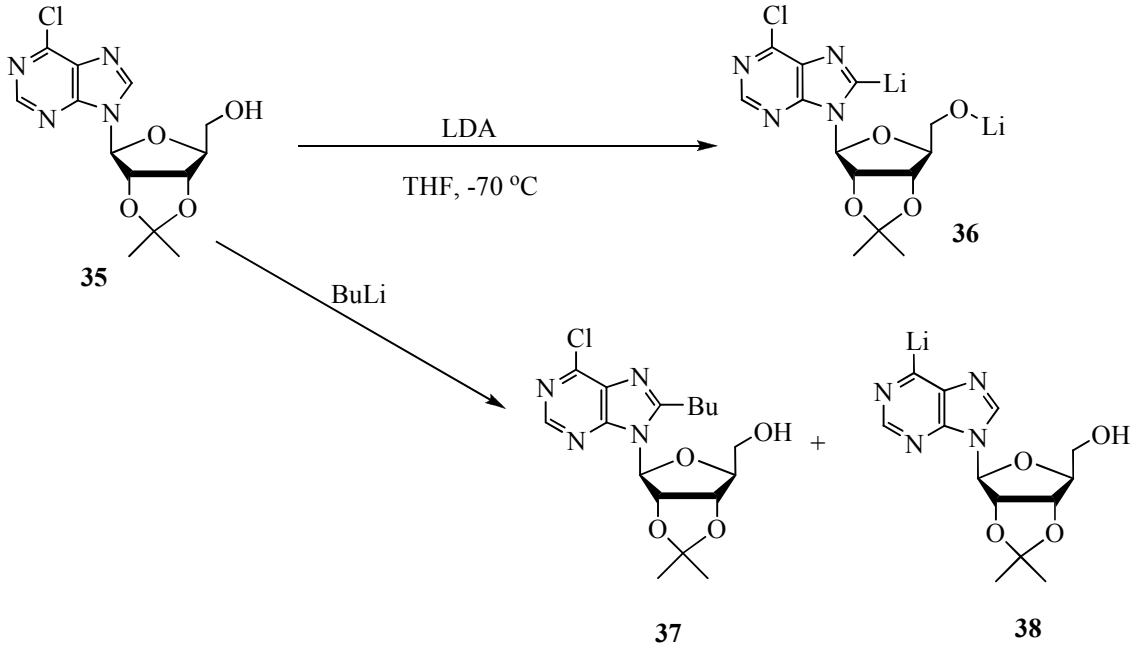
The purine 8-position (8-C-H) is not very reactive towards electrophiles but this reactivity can be improved by functionalization which involves an introduction of a more reactive species into this position. Functionalization can be done via lithiation. Lithiation results in the formation of "purinyl anion" which can react with electrophiles such as halogen donors (illustrated in Scheme 9). Lithiation-halogenation leads to the formation of another very reactive species, the 8-halopurines,[14, 1, 5, 6] which can further react with nucleophiles leading to the introduction of other groups in the 8-position. Also the lithiated products can react directly with an alkyl halides e.g. iodomethane to form an alkylated products.[1] The lithiation is mostly done using organonitrogen-lithium compounds.



Scheme 9

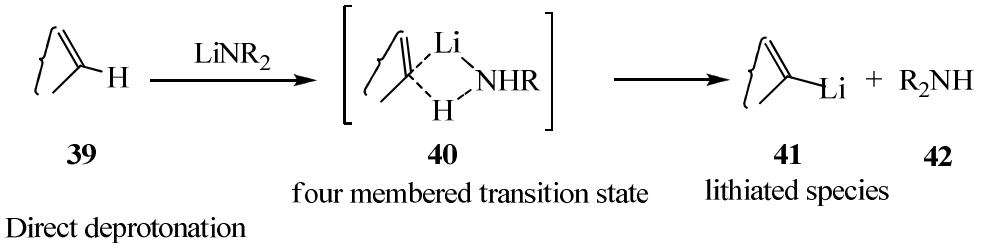
Organonitrogen-lithium compounds particularly lithium amides $(R_2NLi)_n$, are commonly used as strong bases in organic synthesis. The power of these species as reagents, especially where the organic groups (R) are bulky, relies mainly on their low nucleophilicity compared with C-Li bonded complexes (e.g. MeLi). These properties cause proton abstraction to be favoured over nucleophilic addition to an organic substance. Such deprotonation reaction can also be regio and/or enantiospecific.[39] One of such commonly used lithiation agents is lithium diisopropylamide (LDA). LDA has been indicated by Kato *et al.*[40] and Tanaka *et al.*[41] as a better lithiating agent compared with butyllithium for regioselective lithiation at position-8

(illustrated in Scheme 10). It can cause lithiation in position-8 even in the presence of a halogen (e.g. chlorine) in the 6-position. When butyllithium was used for the same reaction there was a nucleophilic addition of butyl to form 8-butylated purine and a lithium-halogen exchange forming a butyl chloride and a 6-lithiated purine.[16]



Scheme 10[16]

The exact mechanism of the metallation (lithiation) is not known, but it is thought to involve a four centre transition state (Scheme 11).[18] In the lithiation process although a "free anion" is never formed, the ease of lithiation correlates well with the C-hydrogen acidity and of course this, with the stability of the corresponding conjugate base (carbanion).[18]



Scheme 11[18]

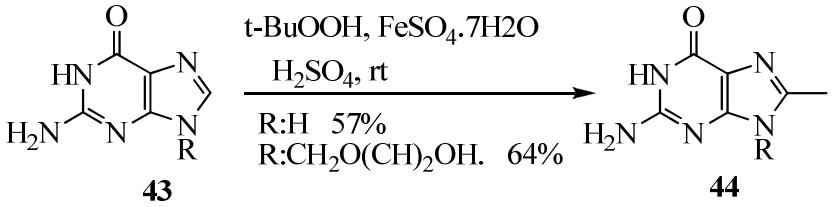
Due to the acidity of the N-9 and N-7 hydrogens, these positions need to be protected/blocked in lithiation reaction. When the 7/9 position are protected, lithiation (using strong base such as LDA) then takes place at C-8.[18] However this does not seem to be general since all attempts made by Nolsøe *et al*. to lithiate 6-chloro-9-benzylpurine failed.[17] Therefore it is speculated in this study that attached substituents in the imidazole ring depending on their nature can affect the C-hydrogen acidity in the ring either by inductive or mesomeric effect. A strong electron withdrawing group will better stabilize the carbanion formed thus making the corresponding C-hydrogen more acidic and therefore easy to lithiate. On the other hand a weak electron withdrawing group (or electron donating group) will stabilize weakly and thus making the corresponding C-hydrogen less acidic and therefore relatively difficult to lithiate. In the case of a strong electron withdrawing group though the lithiation process may be relatively easy the stabilization of the anionic species formed may make the species relatively unreactive compared to the species in the case of a weak electron withdrawing group. However it is important to have a substituent with electron releasing properties if after lithiation further electrophilic substitution is intended since that makes the carbon electron rich for attack by an electrophile. Substituents can also affect the ease lithiation through steric hindrance blocking the lithiating agent. Therefore the ease of lithiation of an acidic carbon with substituent in the ring depends on the size and the electronic properties of the substituents.

It has also been indicated that temperature and reaction time affects the regioselectivity of lithiation process. 6-iodo-9-(tetrahydropyran-2-yl)purine was found to undergo reaction with n-butyllithium in tetrahydrofuran (THF) to produce depending upon the time and temperature of the reaction, either 6-lithio or 8-lithio-9-(tetrahydropyran-2-yl)purine in predominance. It was indicated that shorter reaction time and lower temperature were necessary for the utilization of the 6-lithio derivatives, while longer reaction time and higher operating temperature favoured the equilibration to the 8-lithio isomer.[41]

2.6 ***Other methods for synthesizing 8-substituted purines***

8-Substituted purines can be synthesized through other methods. 8-alkylated purines can be synthesized via the reaction of the purines with free radicals or using Grignard reagents or through a complete ring synthesis using suitable starting materials.[1, 18] In the free radical

reaction, the purine is alkylated using alkyl hydro peroxides and the reaction is catalyzed by iron (II) ions. The reaction has been applied to guanine, hypoxanthine, and adenine as well as their nucleosides. A typical example is the 8-methylation of guanines (Scheme 12)[1].



Scheme 12[1]

They can be formed through purin-2-ones. Purin-2-ones are highly polarized compounds that can form adducts with nucleophiles therefore making them susceptible for the introduction of carbon substituents into their ring system at position 6 and 8 by the addition of organometallic (Grignard) reagents followed by rearromatization of the adduct. In this method even secondary alkyl can be easily introduced.[1] 8-Substituted purines can be synthesized by the reaction of 4,5-diaminopyrimidines with a suitable carboxylic acids or derivatives, the carboxyl carbon corresponding to carbon-8.[18, 14] Variety of 8-benzylpurines [42, 43] and trisubstituted purines[44, 45, 46, 47] have been synthesized using this method. The difficulty of this method is, the closure of the imidazole ring requires prolonged heating in acidic solution.[14]

8-substituted purines can also be prepared by using suitably substituted imidazole precursors e.g. 4(5)-aminoimidazole-5(4)-carboxylates.[1] This method has similar difficulty as the pyrimidine moiety.

2.7 *Significance of functionality in the 2 and 6-position of the purines used in the study*

In this project purines bearing chloro groups in the 6-position only or in both the 2- and 6- were first alkylated before bromination. The chloro group in the pymidine ring does not only enhance the alkylation in the imidazole ring but also provide extra functionality in the overall expected brominated product.[14] This functionality in the 6-chloro position has been exploited in the synthesis of potent inhibitors of 15-lipoxyenase(15-LO) via palladium coupling

reactions.[20, 21] The presence of chloro functionality in the 2- and 6-position has also been exploited in the synthesis of much more complex structures such as UK-371,104 which is an A2a agonist.[22] The 6-chloro group also afford the possibility of performing ring closing metathesis, by having the right substituents in the N-7 position in the synthesis, for example the synthesis of asmarines from the N-7 alkylated purines.[23]

2.8 ***Purine dimerization***.

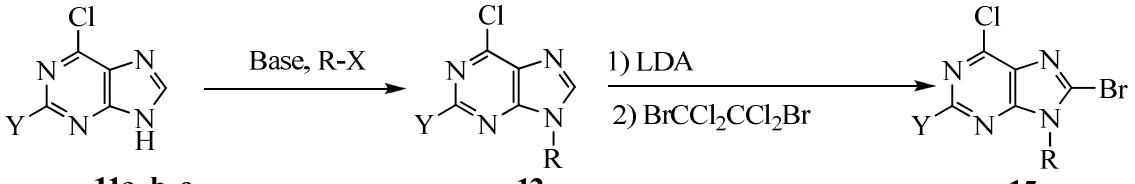
Purine dimerization was unprecedented in literature on synthesis until reports by Cerna *et al.*[48] of 8,8'-bispurines which they reported as by-products. However, there were reports of purine dimerization involving nucleosides, C-C 8,8'-dimers, which were reported as products of oxidative DNA damage.[49] Later there were reports of synthesis of C-C 6,8 dimers, 6, 8', 6', 8''-purine trimers and 6,8', 6', 8'', 6'', 8''-purine tetramers and Pd complex of corresponding cyclic tetramer synthesized via Negishi cross-coupling.[50] To the best of one's knowledge no practical preparative method nor biological evaluation of simple purine dimers connected directly by a C-C bond between the ring carbon atoms have been reported until work done by Tobrman *et al.*[50] which reported various purine dimers in good yields. So far purine dimerization has only been reported under coupling conditions. Purine dimers may be important molecules to investigate as purine bases are known to coordinate transition metals[51] hence the purine dimer may act as an interesting donor for metal ions.[50]

3.0 RESULTS AND DISCUSSION

The essence of this project was to introduce an extra functionality into the 8-position of N-alkylated 6-chloro-, 2,6-dichloro-, and 6-chloro-2-nitropurines. This was to be done via lithiation/bromination reactions. Attempts by Nolsøe *et al.*[17] to synthesize 9-benzyl-6-chloro-8-halopurines by lithiation/halogenation was not successful even though the method was successful for other compounds.[4] This gave an indication that the method may not be general. Hence it was speculated that the nature of the substituent in the N-9 or N-7 position can affect the lithiation-bromination process either by inductive and/or mesomeric effect or by sterical factors.

Attempts were therefore made to establish the scope and limitation of this process in functionalization of the purine 8-position. In order to achieve this, substituents in the N-9 or N-7 were varied. Substituents such as pyranyl; benzyl groups having electron donating groups such as methoxy, ethoxy and methyl groups; benzyl groups bearing electron withdrawing groups such as fluoro, chloro, methylfluro groups; alkyl groups such as ethyl and methylthiomethyl groups were used. In addition the substituents in the 2-position were varied. Substituents such as chloro and nitro groups were used in place of hydrogen. To investigate steric influences on the process, the position(s) of the substituent(s) on the phenyl ring in the case of the benzylated purines was(were) varied. In addition reactivity of isomers of the same compound were compared. This was done in the case of N-7 and N-9 benzylated purines to investigate if there is any special preference in the reaction of them.

The overall synthesis was in two steps as shown in Scheme 13 which is later illustrated clearly in Schemes 14-17 and 20-22. The first step involved the introduction of the N-substituent of interest and the second step was to introduce the bromo functionality into the 8-position.



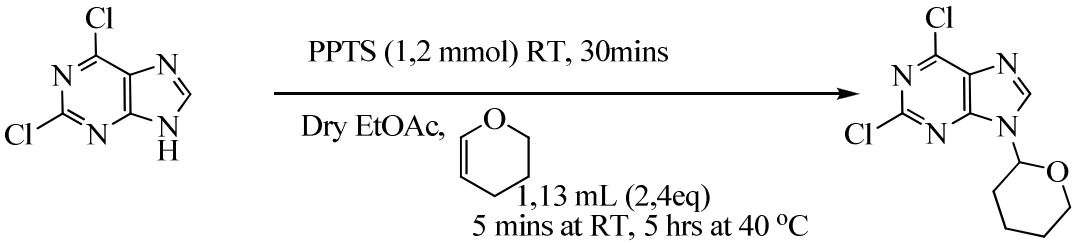
11a, b, c **12** **15**

X= Cl, Br **11a** Y=Cl, **11b** Y=H, **11c** Y=NO_2
R= Various alkyl groups with different electronic and steric properties

Scheme 13

3.1 *N-Alkylation of purines*

Compound **12a** was synthesized by reaction of the 2,6-dichloropurine with carbocation generated insitu[52] from 2,3-dihydropyrane (Scheme 14).[17, 52] In this reaction only the N-9 alkylated isomer was observed as product which was expected based on literature.[17, 53]

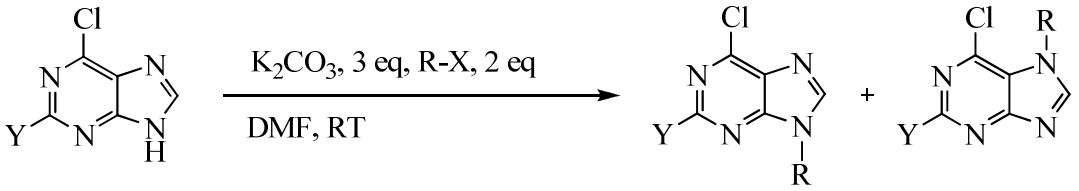


11a 76 %, **12a**

Scheme 14

The regioselectivity of this reaction has been extensively investigated by UV-VIS spectroscopy in previous reports.[52, 53, 54] Similar studies demonstrated that the reaction of 6-chloropurine and 2,6-dichloropurine with carbocations are selective for the N-9 isomer.[52, 53, 44].

Compounds **12b-h** and **13b-h** (Table 1) were synthesized by N-alkylation of the 6-chloropurines or the 2,6-dichloropurine under basic conditions using alkyl halides. These led to the N-9 alkylated purines as the major products and the N-7 alkylated purines as the minor products (Scheme 15 and Table 1).

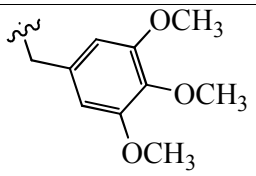
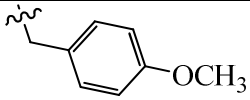
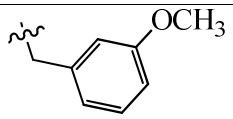
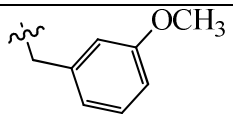
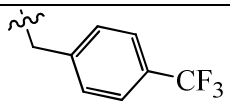
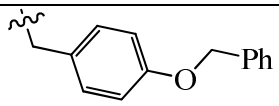


11a, b **12b-h** **13b-h**

11a Y=Cl
11b Y=H

Scheme 15

Table 1: Yield of N-9 and N-7 alkylated purines

Entry	Compd. **11**	X	R	Reaction time (h)[a]	N-9 Isomer Yield(%)[b] **12**	N-7 Isomer Yield(%)[b] **13**
1	**11b**	Cl		20	56, **12b**	23, **13b**
2	**11a**	Cl		20	59, **12c**	21, **13c**
3	**11b**	Cl		20	63, **12d**	21, **13d**
4	**11a**	Cl		20	54, **12e**	22, **13e**
5	**11b**	Br		21	50, **12f**	16, **13f**
6	**11b**	Cl		21	56, **12g**	27, **13g**
7	**11b**	Cl		24	40, **12h**	16, **13h**

[a]reaction time after addition benzyl halide or 2,3 dihydropyran. [b]yield of isolated product.

The synthesis process involved, as describe clearly in the experimental section, first heating of the purine with the base, K_2CO_3, in the solvent for 30 minutes. In this step, the base acts on the purine deprotonating the acidic proton on the N-7 or N-9 position leading to the N-7 and N-9 purine anion. The anion then attacks the highly electrophilic carbon, the benzylic carbon, on the benzyl halide kicking out the halogen leaving group then giving rise to the expected products.

6-Chloro-9-(methylthiomethyl)-9H-purine (**12h)** was synthesized by the general N-alkylation procedure and work up used for the synthesis of the other N-9 alkylated purines. Like the benzylation yielding **12c-g** this reaction also gave the two products N-9 and N-7 isomer **12h** and **13h** respectively. This method was much easier and better than the lengthy and more tedious procedure reported by Kelly *et al*.[55] giving the product in higher yield (40%) than the reported yield (10%).[55] Kelly *et al.*[55] described the procedure they used as follows: a mixture of 6-chloropurine (45 mmol), dimethylsulfoxide (100 mL), anhydrous potassium carbonate (58 mmol) and chloromethyl methyl sulphide (40.4 mmol) was stirred at ambient temperature for 6 days. The reaction mixture was poured into ice water (400 mL) and extracted with dichloromethane (4 x 100mL). The combined extracts were washed with water (6 x 50 mL), filtered through glass wool, and spin evapourated in vacuo. The residue was dissolved in dichloromethane and added to silica gel 60. The mixture was spin evaporated in vacuo and the residual solid was then purified by flash chromatography.

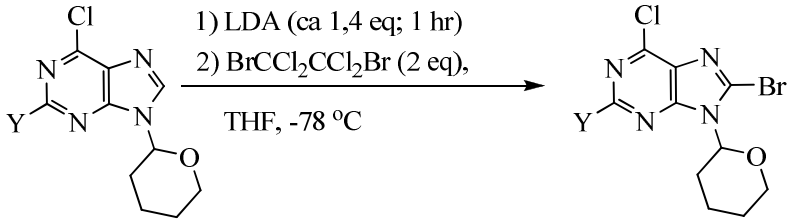
3.2 *Lithiation/bromination of purines*

The main objective of this project was to introduce extra functionality into the 8-position of selected purine substrates and investigate how the various substituents affect the lithiation-bromination process. To make this discussion clearer, this section has been grouped into five categories:

- Lithiation/bromination of 9-tetrahydropyranyl (THP)-purines.
- Lithiation/bromination of 9-benzylated purines 6-chloro- and 2,6-dichloropurines
- Lithiation/bromination of 9-benzylated 6-chloro-2-nitropurine.
- Lithiation/bromination of 7-benzylated purines 6-chloro- and 2,6-dichloropurines.
- Lithiation/bromination of 9-alkylated purines.

3.2.1 *Lithiation/bromination of 9-THP-purines*

Compounds **12a** and **12i** were lithiated at the position 8 via proton abstraction by lithium diisopropylamine (LDA is a non-nucleophilic base) forming “8-purinyl anion”, then brominated using 1,2-dibromotetrachloroethane (Scheme 16).



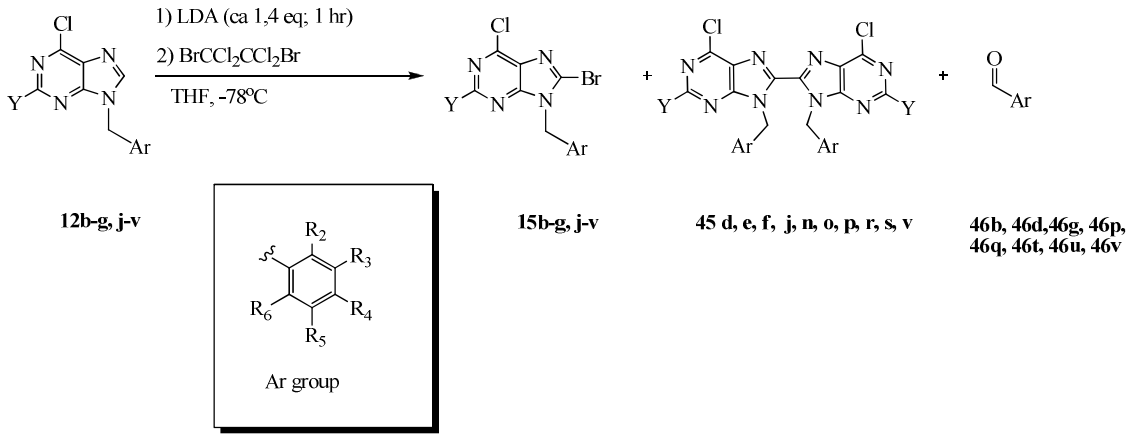
Scheme 16

This reaction yielded only the expected product. The difference in these compounds was the H-2 in the **12i** was substituted by a chloro group in **12a**. From the observations there was no major change in reactivity when the chloro group was substituted for the hydrogen. The only observed change is the reaction in the case of **12i** appeared to occur faster. However this cannot be said conclusively since this is based on TLC observation.

3.2.2 *Lithiation/bromination of 9-benzylated 6-chloro- and 2,6-dichloropurines (12b-h, j-v)*

N-9 benzylated purines, compounds ***12b-h, j-v***, bearing various substituents in varied positions on the phenyl rings were lithiated at their 8-positions via proton abstraction by the lithium diisopropylamine (a non-nucleophilic base) forming "8-purinyl anion", then brominated using 1,2-dibromotetrachloroethane (Scheme 17) forming the 8-bromo compounds ***15b-h, j-v***, Table 3. There was more than 80% conversion of starting material as judged by crude ^{1}H NMR spectra except in the cases of **12f**, **12j**, and **12o-v**. The expected products were observed in all cases. In addition to the expected products some by-products were isolated mainly dimers, **45d, e, f, j, n, o, p, r, s, v**, (Table 3).

In addition to isolated dimers, it has been observed that aldehydes such as isolated aldehyde **46b** in the case of **12b** were also formed for **12d**, **e**, **k**, **g**, **p**, **q**, **t**, **u**, **v** (Table 3), though not isolated for these substrates they were observed in their crude ^{1}H NMR spectra as indicated by the CHO hydrogen chemical shifts (Table 2).



Scheme 17

Table 2: The chemical shift (ppm) of CHO hydrogen of aldehydes, 46, from their crude ^{1}H NMR spectra.

Starting material, **12**	Chemical shift (ppm) of CHO hydrogens of aldehydes, **46**, in $CDCl_3$	Literature chemical shifts (ppm) of CHO hydrogens of observed aldehydes, **46,**
12b	9.86, **46b**	9.87 **46b**, in $CDCl_3$[56]
12d	9.92, **46d**	10.00, **46d**, in $CDCl_3$[57]
12e	9.97, **46d**	10.00, **46d**, in $CDCl_3$[57]
12g	9.89, **46g**	9.88, **46g**, in $CDCl_3$[58]
12k	9.97, **46k**	9.99, **46k**, $CDCl_3$[59]
12p	10.33, **46p**	10.30, **46p**, in DMSO[60]
12q	9.90, **46q**	9.99, **46q**, in $CDCl_3$ [60]
12t	10.44, **46t**	10.70, **46t**, in $CDCl_3$[61]
12u	10.15, **46u**	10.36, **46u**, in $CDCl_3$ [62]
12v	10.15, **46v**	10.30, **46v**, in $CDCl_3$-Acetone-d_6[63]
12x	9.81, **46x**	9.89, **46x** in $CDCl_3$[64]
13c	9.84, **46x**	9.89, **46x**, in $CDCl_3$ [64]
13o	9.99, **46o**	10.20, **46o**, in $CDCl_3$[61]

Table 3: Reaction time and yield of expected products and by-products

Entry	Compd. 12	Y	R_2	R_3	R_4	R_5	R_6	Reaction time (h)[a]	Yield (%)[b] 15	Yield (%)[b] 45	Yield (%)[b] 46	Yield (%), 12 RSM
8	**12b**	H	H	OCH_3	OCH_3	OCH_3	H	2.00	78, **15b**	-	8, **46b**	-
9	**12c**	Cl	H	H	OCH_3	H	H	2.5	80, **15c**	-	-	-
10	**12d**	H	H	OCH_3	H	H	H	2.75	25, **15d**	26, **45d**	1*, **46d**	-
11	**12e**	Cl	H	OCH_3	H	H	H	2.30	51, **15e**	8, **45e**	2*, **46d**	-
12	**12f**	H	H	H	CF_3	H	H	3.00	8[§], **15f**	7[§], **45f**	-	73, **12f**
13	**12g**	H	H	H	$OCH_2C_6H_5$	H	H	1.50	84, **15g**	-	1*, **46g**	-
14	**12j**	H	H	H	OCH_2CH_3	H	H	4.00	5[§], **15j**	2, **45j**	-	30, **12j**
15	**12k**	H	H	H	OCF_3	H	H	1.50	36, **15k**	-	-	-
16	**2l**	Cl	OCH_3	H	H	H	H	1.75	80, **15l**	-	-	-
17	**2m**	H	H	H	CH_3	H	H	1.25	76, **15m**	-	-	-

[a]reaction time after addition of $BrCCl_2CCl_2Br$. [b]yield of isolated product. Expt.:expected, pdts.:products, compd.:compound. [§] yield calculated from impure isolated product. *Calculated yield from crude ^1H NMR. RSM: recovered starting material

Table 3 continued

Entry	Compd. 12	Y	R_2	R_3	R_4	R_5	R_6	Reaction time (h)[a]	Yield (%)[b] 15	Yield (%)[b] 45	Yield (%)[b] 46	Yield (%), 12 RSM
18	**12n**	Cl	H	H	CH_3	H	H	2.00	75, **15n**	2[§], **45n**	-	-
19	**12o**	H	H	H	H	H	H	2.25	2[§], **15o**	11, **45o**	-	52, **12o**
20	**12p**	H	F	H	H	H	H	2.50	17[§], **15p**	3, **45p**	6*, **46p**	42, **12p**
21	**12q**	Cl	H	H	Cl	H	H	2.00	34, **15q**	-	11*, **46q**	26, **12q**
22	**12r**	H	H	H	F	H	H	2.25	19, **15r**	5, **45r**	-	16, **12r**
23	**12s**	H	H	Cl	H	H	H	2.50	15[§], **15s**	6, **45s**	-	19, **12s**
24	**12t**	H	Cl	H	H	H	H	2.00	9[§], **15t**	-	3*, **46t**	21, **12t**
25	**12u**	H	Cl	H	Cl	H	H	2.50	4[§], **15u**	-	0.1*, **46u**	71, **12u**
26	**12v**	H	F	H	H	H	F	2.50	7[§], **15v**	3[§], **45v**	8*, **46v**	50, **12v**
27	**12w**	H	H	Cl	Cl	H	H	2.00	19, **15w**	-	-	10, **12w**

[a]reaction time after addition of halogen donor $BrCCl_2CCl_2Br$. [b]yield of isolated product. Expt.:expected, pdts.:products, compd.:compound. *Calculated yield from crude ^1H NMR. [§] yield calculated from impure isolated product. RSM: recovered starting material

In general, it has been observed that, with the electron withdrawing groups (F, CF_3, and Cl) on the phenyl ring of the N-9 benzylated purines **12f**, **p-w** there were poor conversions and poor yields of the products. The N-9 benzylated purines **12b-e**, **g**, **k-i**, **m-n** with electron donating groups (alkoxy or methyl groups) showed much better conversions and yields of products. The reaction of **12j** however gave an unexpected (based on the trend stated above) poor conversion. This reaction was done only once so it could not be said conclusively that this observation annuls the stated trend.

Halogens are known to be electron withdrawing by inductive effect and electron donating by resonance effect however they are overall electron withdrawing. The alkoxy groups are known to be electron donating by resonance effect and withdrawing by inductive effect but they are overall electron donating while alkyl groups are electron donating by inductive effect.[65]

It has also been observed that the N-9 benzylated purines with the chloro group in the ortho position on the phenyl ring **12t** gave a much more complex mixture of products compared to the other halo-benzylated purines as judged by the ^{1}H NMR spectrum of the crude product. The product in this case as in the other cases was not obtained pure. Based on calculation using the ^{1}H NMR spectrum of the isolated product, there was a much lower yield of the expected product compared to the others. The ratio of product to starting material as judged by the crude ^{1}H NMR spectrum was 1.0:1.6 in the case of **12t**. While **12u (**which has the chloro group in the ortho and para positions) gave a much worse conversion with the ratio of product to starting material, as judged by the crude ^{1}H NMR spectrum, been 1.0:9.4. It could be conveniently speculated that the size of the chloro group is influencing the reaction in these cases. The chloro group could be "blocking" the 8-position of the purine because similarly with fluoro group (which is a much smaller group than) in the ortho position on the phenyl ring (compound **12p**) the expected product was observed in a much higher amount (the ratio of product to starting material as judge by the crude ^{1}H NMR spectrum was 1.8:1.0).

There was a much lower conversion when both ortho positions were occupied with the fluoro group (compound **12v)**. The ratio of product to starting material, as judged by the crude ^{1}H NMR spectrum, was 1.0:4.0. This could be explained by the possibility that in the case of **12p** the free rotation around the CH_2 bond offers the molecule the ability to orient the fluoro

group away from the target site for a longer time span. The site is only "blocked" after 360^{o} rotation. On the other hand, **12v** has both of the ortho positions occupied hence after every 180^{o} rotation the 8-position is "blocked". When the fluoro group was in the para position **12r** there was a slightly much better conversion compared to the ortho position. In this case the ratio of product to starting material, as judged by the crude ^{1}H NMR spectrum, was 2.0:1.0.

Aside steric factors which may have influence the reactivity in case of compound **12t**, other factors may have affected the reactivity in this case because compared to when the chloro group was in the meta position **12s** a much cleaner reaction was observed though there was poorer conversion (the ratio of product to starting material as judged by crude ^{1}H NMR was 1.0:5.5) in this case. The expected product was isolated in a higher yield. Comparing the case of **12p** (when the fluoro group was in the ortho position) and **12r** (when fluoro group was in the para position), there was a slightly much better conversion in the case of **12r**.

3.2.2.1 *Formation of dimer by-products; 45d, e, f, j, n, o, p, r, s, v, y*

In the case of **12d**, **e**, **f**, **j**, **n**, **o**, **p**, **r**, **s**, **v**, **y** dimer by-products **45d**, **e**, **f**, **j**, **n**, **o**, **p**, **r**, **s**, **v**, **y** were observed, as the reaction led to two different isolated products. The ^{1}H NMR spectrum of the crude product in the case of **12d** indicated the two products were formed in the ratio 1.0:1.0 corresponding to **12d**:**45d** while in the case of **12e** the ratio was 5.0:1.0 corresponding to **12e**:**45e**. The corresponding ratio of the dimers to expected products for the rest is given in Table 4.

It has been observed that generally the dimer by-products have the proton signal for the NCH_2 at a higher field compared to the 8-bromo compound **15** and the starting material **12** (Table 6). They generally have low solubility in $CDCl_3$ and precipitate off in test tube when out of the column. Formation of purine dimers under strongly basic conditions was also observed by Černa *et al.*[48] The formation of the purine dimers were thought to be formed via two possible pathways as illustrated in Scheme 18. The pathway 2 ways thought to be more likely hence it was investigated for the substrate **12e** (Table 5). Instead of addition of the electrophilic reagent in 10 minutes as the general procedure, the electrophilic reagent was added in 1 minute and 20 minutes. The expectation was if the reaction is by this pathway there would be more dimerization when the electrophile is added over a longer period and less if added over a shorter period.

Table 4: The ratio of the 8-bromo compounds (expected products), 15, to dimer by-products, 45, as judged by the ^{1}H NMR spectra for various starting materials, 12.

Compound, **12**	Ratio of expected product to dimer, (**15** : **45**)
12d	1.0 : 1.0
12e	5.0 : 1.0
12f	1.0 : 1.0
12j	1.0 : 1.3
12n	56 : 1.0
12o	1.0 : 2.8
12p	5.0 : 1.0
12r	4.0 : 1.0
12s	1.0 : 2.0
12v	1.0 : 1.2
12y	1.1: 1.0

A positive expected result was obtained when the electrophile was added over the 1 minute period. That is, only the 8-bromo compound **15e** was observed in an appreciable yield of 67%. While an addition over 20 minutes gave a much appreciable yield of the dimer product compared to the 10 minutes addition (Table 5), also a positive result.

Table 5: The effect of the time over which the electrophile was added on the reactivity of 12e.

Time over which the electrophile was added	Ratio of dimer to 8-bromo product	Comments
1 minutes	Only product observed	
10 minutes	5.0:1.0	
20 minutes	1.0:4.0.	Associated with decomposition

Hence there is indication that the time over which the electrophile was added affected the yield of the expected product and a strong indication that the dimerization may be occurring by pathway 2.

Other methods of investigating the dimerization pathways are possible but these were not carried out due to time constraint. One of such possible methods is; the reaction could be quenched before addition of the electrophile. In this case if dimerization occurs that would mean it is occurring by pathway 1.

Table 6: Comparison of the NCH_2 proton chemical shift of starting materials for the bromination reaction, 12, 8-bromo compounds (expected products), 15, and dimer by-products, 45.

Chemical shift (ppm) of NCH_2 of starting material, **12**	Chemical shift(ppm) of NCH_2 of 8-bromo compound, **15**	Chemical shift (ppm) of NCH_2 of Dimer, **45**
5.39, **12d**	5.47, **15d**	6.21, **45d**
5.31, **12e**	5.40, **15e**	6.14, **45e**
5.39, **12n**	5.42, **15n**	6.10, **45n**
5.36, **12j**	5.40, **15j**	6.14, **45j**
5.50, **12f**	5.52, **15f**	6.29, **45f**
5.36, **12o**	5.48, **15o**	6.24, **45o**
5.47, **12p**	5.55, **15p**	6.27, **45p**
5.42, **12r**	5.43, **15r**	6.20, **45r**
5.51 , **12s**	5.43, **15s**	6.19, **45s**
5.52, **12v**	5.56**, 15v**	6.34, **45v**
4.33, **12y**	4.36, **15y**	5.09, **45y**

Possible mechanisms of purine dimerization

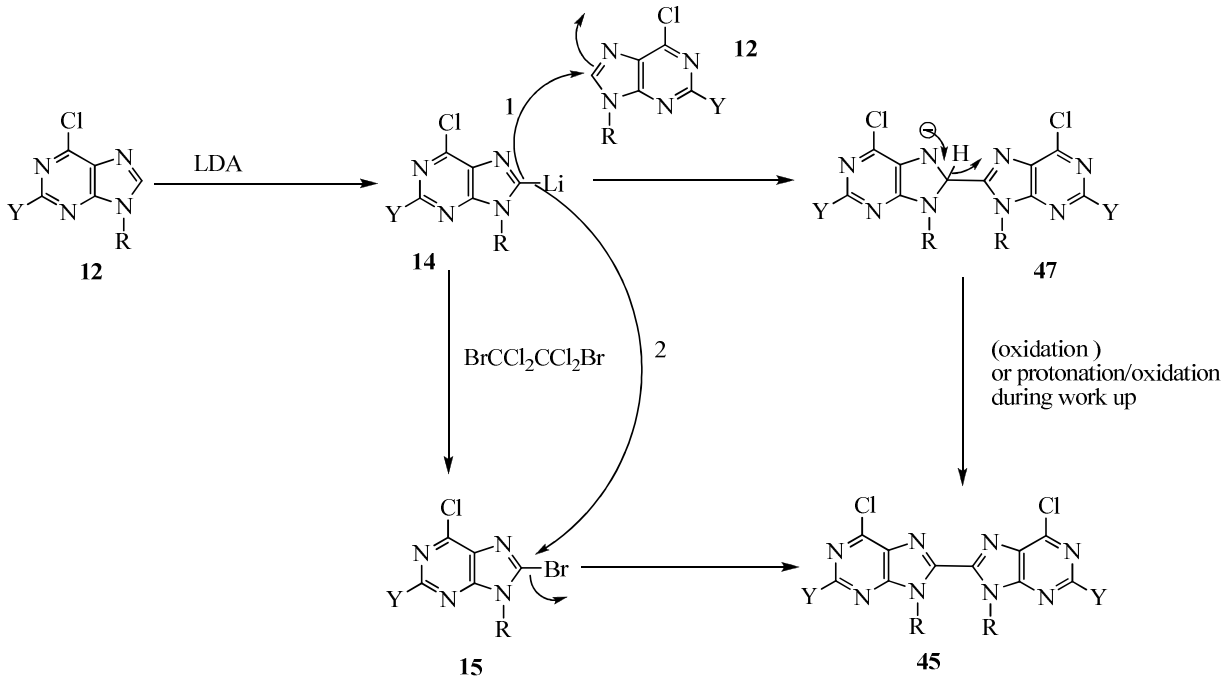
Pathway 1

The purine **12** is deprotonated at the carbon-8 position forming the lithiated species **14**. This species reacts with the starting material **12** forming compound **47**. The ionic species formed then oxidizes upon work up forming the dimer **45**.

Pathway 2

The purine **12** is deprotonated at the carbon-8 position forming the lithiated species **14**. This species reacts with the electrophile (1,2-dibromotetrachloroethane) forming compound **15**, the expected 8-bromo purine. Unreacted lithiated species then reacts with already formed 8-bromo species which now have a better leaving group in the 8-position, bromo group, forming the dimer **45**.

Possible mechanisms of purine dimerization



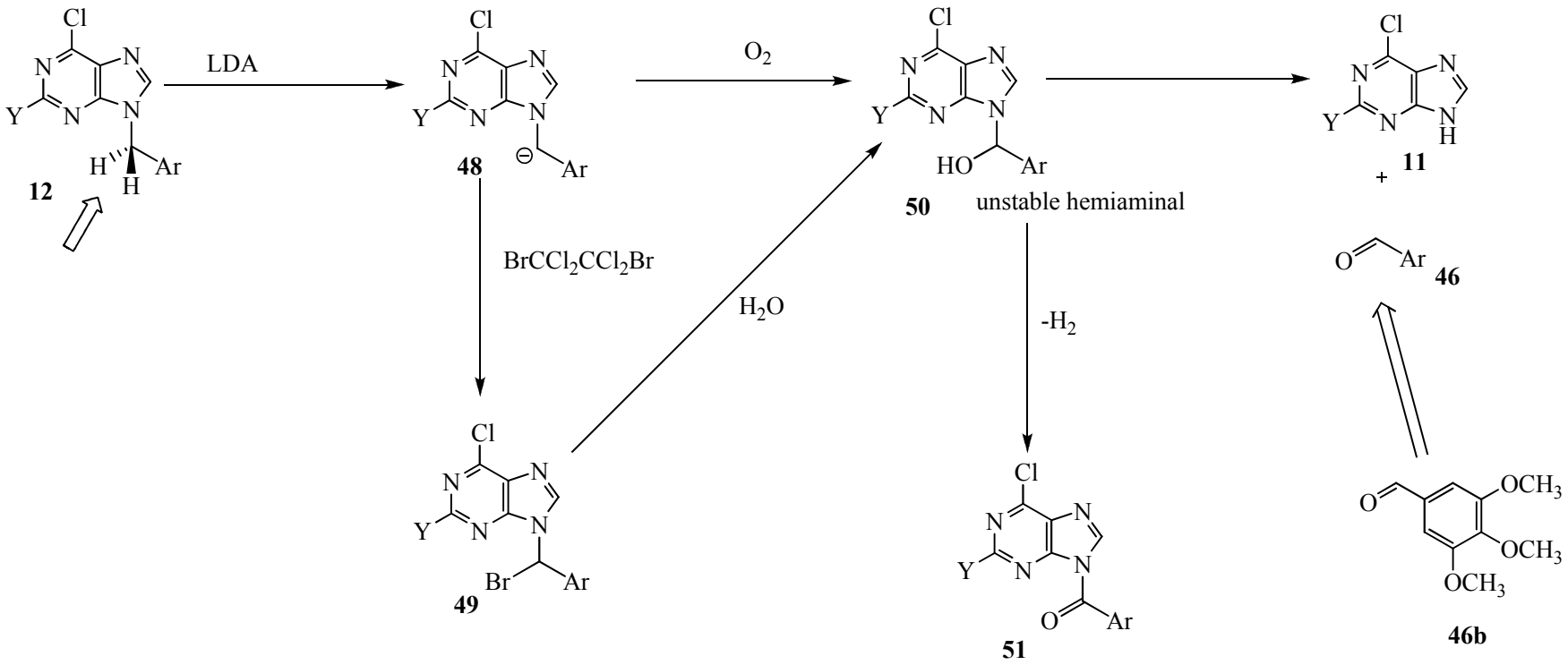
Scheme 18

3.2.2.2 Formation of aldehyde by-products

The aldehyde by-product **46b** might have resulted from de-benzylation of the starting material **12b** via the proposed mechanism in Scheme 19. De-benzylation of heterocycles under strong basic condition is not unprecedented since this has been reported for indoles.[66] It is proposed that starting material might have been de-benzylated following similar mechanism as reported for indoles[66] (Scheme 19). The two aromatic rings which bond to the NCH_2, pull the electron cloud to their ring systems rendering this position electron deficient and therefore make the protons acidic. In the presence of a strong base this carbon can be deprotonated forming a carbanion (compound **48)**. The NCH carbanion formed can attack the electrophilic reagent giving **49**. The compound **49** having a good leaving group, bromo group, can be attacked by a nucleophile since this position is already activated for nucleophilic attack because of the two aromatic groups attached. The nucleophile in this case can be water during work up forming the unstable hemiaminal **50**. Another possibility is the carbanion **48** could react with oxygen also forming **50**. The hemiaminal **50** being unstable can oxidize to the more stable ketone **51** or de-benzylate forming the unbenzylated purine **11** and the aldehyde **46** which is the product observed in our case.

These aldehyde by-products were also observed for other substrates **12 d**, **e**, **k**, **g**, **p**, **q**, **t**, **u**, **v**, **x**, and **13c**, **o** judged by their crude ^{1}H NMR but these were not isolated. Most of the substrates with halogen group(s) seem to form the aldehyde by-products. This is consistent to the fact the debenzylation is related to the acidity of the NCH_2 protons. With the halogen(s) which is/are electron withdrawing groups on the phenyl, the whole phenyl substituent is made more electron withdrawing and hence the NCH_2 protons more acidic. It has been observed that some of theses aldehydes have low boiling points for instance 2,6-difluorobenzaldehyde, **46v**, has a boiling point of 76-80 ^oC[62] and 4-(trifloromethoxy)benzaldehyde, **46k**, has a boiling point of 73-75 ^oC. In addition, 2,4-Dichlorobenzaldehyde, **46u**, is reported to rapidly decompose on standing in $CDCl_3$ at 0 ^oC.[61] Hence it is possible that the aldehydes may have been produced in the case of more other substrates than recorded in this report. The inability to isolate **46 d**, **e**, **k**, **g**, **p**, **q**, **t**, **u**, **v**, **x**, and **13c**, **o** may be due the possibility of them been lost by evaporation on the rotar vapour, or decomposition and the fact that some may as well have been produced in relatively lower amounts compared to **46b**. The same reasons may account for the inability to observe the aldehyde formation for other substrates used in this study though they might have been formed.

Possible mechanism of 46b formation (a mechanism for de-benzylation of N-9 substituted purines under basic conditions)

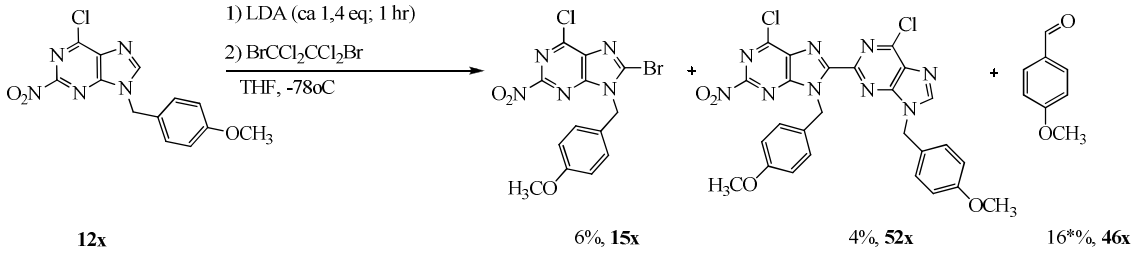


Scheme 19

3.2.3 Lithiation/bromination of 6-chloro-9-(4-methoxybenzyl)-2-nitro-9H-purine

The lithiation/bromination of this substrate seems not a good reaction. There was poor conversion of starting material to product giving a recovered yield of starting material 33% (Scheme 20). The reactivity of this substrate was comparable to that of the halobenzylated purines in which case there was poor conversion of starting material to product. This general observation points out that with strong electron withdrawing groups on the purine ring system the lithiation/bromination reaction is difficult. Unlike the normal 8,8' dimerization observed in the other cases described earlier, **12x** indicated an unusual by-product **52x** in which there was an 8 to 2' bonding between two molecules of the starting material. The by-product observed in this case indicated there was a reaction on the C-2 of the starting material in which the NO_2 group was displaced by a nucleophile (8-purinyl anion). Nitro groups acting as leaving groups in the 2-position of purines is not unprecedented. The 2-NO_2 of various purines have been displaced by various nucleophiles.[67, 15, 68] They have been shown to be displaced by nucleophiles such as amines and alcohols.[67, 15] Comparing reactivity of **12x** and **12c**; it is worth noting that aromatic nitro groups are much more labile (better leaving groups) than chloro groups.[69, 70] The nitro group is activated towards displacement by inductive effect from the 6-chloro group in its meta position.[69, 70] In addition to the **52x** the aldehyde by-product **46x** (the ^{1}H chemical shift value for the CHO hydrogen was 9.81 ppm, Table 2) was also observed in the crude ^{1}H NMR of **12x** in a much higher yield, compared to the other observed case describe earlier, which is consistent with the influence of the nitro group on the acidity of the NCH_2 hydrogen.

The structure of **52x** has not been fully confirmed hence is a suggested structure. It has not been fully confirmed due to poor data. The poor data is because of the low amount of substance. Some of the expected coupling to fully confirm this structure have been missing on HMBC hence the structure was elucidated mainly based the proton spectrum, ^{13}Carbon spectrum and HMQC; and based on possible products from the reaction in correspondence with the MS data. The data from HMBC was relatively poor hence not much contribution was from here but it was partly used in the elucidation.



Reaction time after addition of $BrCCl_2CCl_2Br$: 2.75hrs
Yield of recovered starting material, **12x**, 33%
*Yield calculated from Crude ^1H NMR

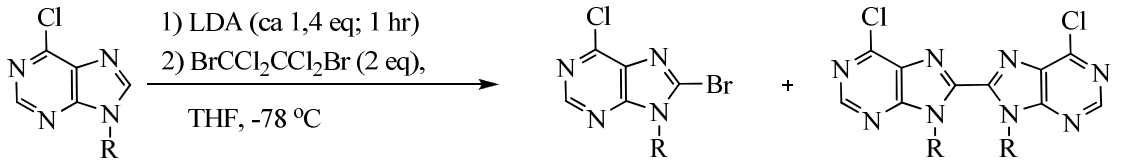
Scheme 20

3.2.4 Lithiation/bromination of N-9 alkylated-6-chloropurines

The lithiation/bromination of the two substrates **12h** and **12y** (Scheme 21) demonstrated moderate conversion to the expected product in the case of **12y** as judged by crude ^1H NMR spectrum while an excellent conversion was observed for **12h**. Comparing **12h** and **12y**, **12h** had almost 100% conversion of starting material as judge by crude ^1H NMR spectrum while **12y** had approximately 25% of starting material present in the crude product. The ratio of product to dimer from crude ^1H NMR spectrum for **12y** was 1.1:1.0. The major difference between these two substrates is, the alkyl chain in **12h** is longer than **12y** by having a sulphur atom in the chain. Also in **12h** the sulphur atom intercepts the CH_2 and the CH_3 group. Both sulphur and carbon have approximately the same electronegativity however sulphur is larger than carbon hence a longer carbon-sulphur bond compared to a carbon-carbon bond. These differences between the two substrates could not account for the difference in reactivity between the two substrates in which **12y** yielded two products while **12h** gave only one product.

Similar reaction on 6-chloro-9-methylpurine reported only one single product, which was 8-bromo-6-chloro-9-methyl purine in good yield (66%)[71], as in the case of **12h**. The difference between the method used for 6-chloro-9-methylpurine and our case is; the LDA generation in the case of 6-chloro-9-methylpurine was over 1 hour while in the case of both **12h** and **12y** the generation was in 30 minutes. The generation of LDA in 30 minutes may only result in

residuals of unconverted BuLi. There is however no observed effect of this on the reactivity in the case of neither **12y** nor **12h**.



12h R=CH_2SCH_3, RT=0.75 hrs
12y R=CH_2CH_3, RT=3.00 hrs

15h R=CH_2SCH_3 86%
15y R=CH_2CH_3 19%*

45y R=CH_2CH_3 18%

*Calculated yield from impure isolated compound
Yield recovered starting material **12y** 23%
RT= reaction time after addition of $BrCCl_2CCl_2Br$

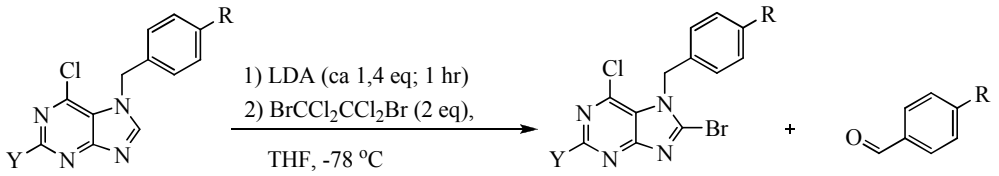
Scheme 21

3.2.5 Lithiation/bromination of N-7 benzylated 6-chloro- and 2,6-chloropurines

The lithiation-bromination of N-7 alkylated purines (Scheme 22) seem not to be a "clean reaction" based on the crude ^{1}H NMR spectrum the two compounds **13c** and **13o**. The expected products **53c** and **53o** were only isolated in moderate yields, Table 6. Studying the ^{1}H NMR, there was indication of the aldehyde by-product formations, (**46o** has ^{1}H chemical shift for the CHO hydrogen at 9.99 ppm, while **46c** at 9.84 ppm; Table 2), as observed in the case of N-9 benzylated purines. There was however no indication of dimer formation. Comparing compounds **12o** and **13o**, the dimer by-product was observed in the case of **12o** (**12o** is the N-9 isomer of **13o**) but not in the case of **13o**. The inability of **13o** to dimerize may be due to sterical reasons. Unlike **12o**, a dimer from **13o** may be sterically crowded in one side of the molecule. The chloro group in the 6-position may forces the N-7 benzyl group to orient towards the 8-position hence hindering any bulky group from been attached in the 8-position as would have been in the case of the dimer. In the case of the N-9 benzylated purines there is no such sterical hindrance hence the dimerization observed in this case.

Comparatively **13o** yielded more expected product (8-bromo purine) than the **12o** its N-9 isomer. On the other hand **13c** gave a lower yield of the expected product compared to **12c** its N-9 isomer. Hence no trend in the ease of lithiation/bromination could be observed in

comparison of reactions of the N-7 and N-9 isomers. However it is worth saying that, contrary to observation by Nolsøe *et al.*[17] 9-benzyl-6-chloro-9H-purine (**12o**) gave the expected 9-benzyl-8-bromo-6-chloro-9H-purine (**15o**) however in extremely poor yield.



13c Y=Cl, R=OCH_3, RT=2.25
13o Y=H, R=H, RT=2.30

53c Y=Cl, R=OCH_3, 41%
53o Y=H, R=H, 23%

46x Y=Cl, R=OCH_3, 5*%
46o Y=H, R=H, 3*%

RT= reaction time after addition of $BrCCl_2CCl_2Br$
*calculated yield by Crude ^1H NMR

Scheme 22

4.0 CONCLUSION

6-Chloropurines bearing varied substituent in the 2 and N-9 or N-7 position were lithiated and brominated in the 8-position. All the substrates investigated indicated the formation of the expected 8-bromo purine. For the N-9 benzylated purines, it was realized that with an electron donating group on the phenyl ring, the reactions gave good conversions and yields of the expected products. On the other hand, with electron withdrawing groups there were poorer conversions and yields of expected products. There were indications that in the case of the N-9 halo-benzylated purines the size and position(s) of the halogen group(s) on the phenyl ring affected the reactivity of the substrate and the overall yield of the expected product.

Also, in addition to the expected products, by-products such as dimers and aldehydes were observed.

5.0 SYNTHETIC SIGNIFICANCE OF WORK DONE IN THIS PROJECT.

In this project an extra functionality was introduced in the purine 8-position of 6-chloro and 2,6-dichloropurines. In order to do this various benzyl groups and tetrahydropyranyl groups (THP) were use to protect the amine functionality at the N-7 and N-9 positions. These groups can be removed and other groups substituted in these positions. Besides the use of tert-butoxycarbonyl, benzyloxycarbonyl, and triethoxycarbonyl groups; benzyl groups have also been used to protect amines.[72] Various methods are used in the removal of this benzyl groups which yield the expected amine. Methods such as: (1) catalytic transfer hydrogenolysis: in this method the tertiary amine is refluxed with an excess of the hydrogen donor (ammonium formate and hydrazine found to be more efficient donors than sodium formate and hydrazine) in alcoholic solvents for a few hours using catalytic amounts of 10% palladium on carbon.[73] The result is the secondary amine. (2) They can also be removed under oxidative conditions such as using BuOK and O_2 in DMSO or treatment with aqueous ceric ammonium nitrate (CAN).[72, 74] This procedure involves the deprotonation at the benzylic position and then oxidation of the formed hemiaminalate ion which being unstable goes to form the benzylaldehyde.[72] The pyranyl protecting group can removed using the more efficient method (more efficient than using 2.5 M HCl then water/trifluoroacetic acid in ratio of 1:1) which involves refluxing the substrate with 10 mol % of copper (II) chloride in ethanol/ water.[62]

The introductions of extra functionality onto the purine ring resulted in products with functionality in 2-, 6- and 8-positions (trihalopurines) and 6- and 8-positions (dihalopurines). This functionality offers us an ability to do more interesting chemistry in these positions. Halogen atoms in purines are known to be replaceable selectively using nitrogen and oxygen nucleophiles. In the case of N-7/N-9 alkylated purines the ease of displacement of the halogens is generally $8 \approx 6 > 2$.[75, 76, 77] Studies done have shown that the difference in reactivity of the 6-chloro-9-methylpurines and 8-chloro-9-methyl purines towards nucleophile is not very profound. Similar observations were made for the 6,8 dichloropurines. However there is profound difference in the reactivity of the 6-chloropurine and the 2-chloropurines.[78] Works done so far has been in situation where there is chlorine in these positions. Though calculations have shown that there is equal possibility for nucleophilic attack at either position 6 or 8 of the purine ring real experiment has not been conducted in situations with

varied halogens in this positions.[76] Selectivity between the 8- and 6-position can be enhance with varied reaction conditions and nature of nucleophile.[78] More interesting chemistry can be done with fine tuned reaction condition by selectively introducing nucleophiles into the 6- and/or 8- and/or 2-position of the purines synthesized. Using the benzylated purines synthesized steric factors could play a role in the selectivity between the 6- and 8-position. The 8-position more sterically hindered in the most of the purines synthesized and hence selectivity in this case would be dependent on the size of the nucleophile.[77, 79] It is to be noted that for 6,8 dichloropurines selectivity in nucleophilic reaction with small nucleophiles has been in favour of the 8-chloropurines.[77, 79]

Another chemistry that can be done with the synthesized 8-bromo purines is C-C coupling chemistry. In this case the selectivity has been demonstrated to be governed by the nature of the halogen. For 2,6 dichloro purines selectivity is for the 6-position exclusively and this was reversed by placing a better leaving group (Br or I) in the 2-position.[75] Similarly for 6,8 dichloropurines selectivity is favour of 6-position which is reversed by introduction of a better leaving group in the 8-position.[17] In view of this, reactions of di and trihalopurines, examples of which were synthesized in this project, are regioselective. This can be applied to the synthesis of di and trisubstituted purines bearing different substituents.[80] In this project a bromine group which is a better leaving group has been introduced in the 8-position hence defining the order of selectivity in the purines synthesized as 8>6>2. Hence for palladium catalyzed reaction on the purines synthesized, the order of reactivity would be 8>6>2.

6.0 EXPERIMENTAL

The ^{1}H NMR spectra were recorded a at 500 MHz with Bruker DRX 500, 300MHz with a Bruker DPX 300 MHz or at 200 MHz with Bruker DPX 200 instrument. The ^{13}C NMR spectra were recorded at 125, 75 or 50 MHz with a Bruker Avance DRX 500, DPX 300, and DPX 200 instrument respectively. Mass spectra were recorded, by electron ionization, at 70 eV ionizing voltage and are presented as *m*/*z* (% relative intensity). The chemical shifts (δ) are given in ppm. THF was obtained distilled from sodium / benzophenone or from solvent purifying system (Günter) and diisopropylamine from CaH_2. Compound **12i** was obtained synthesized by the method described by Robins *et al.*[25] while **12j-y** were obtained synthesized as previously described.[81] **12a-h** were synthesized as given below in general procedure. All other reagents were commercially available and used as received.

6.1 General procedure

This section is grouped into two the N-alkylation of the purines, section 6.1.1, and the Lithiation/bromination of purines, section 6.1.2.

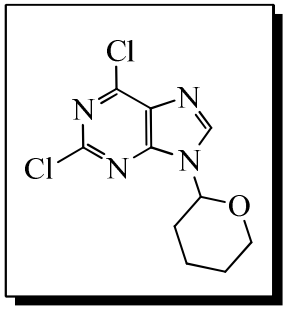
6.1.1 N-Alkylation of 6-chloro- and 2,6-dichloropurines

This section is divided into two as the procedure for introduction of the pyranyl group was different from that of the benzyl group and alkyl chain.

6.1.1.1 *Synthesis of 2,6-dichloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine (12a)*

2,6-Dichloropurine **11a** (955 mg, 5.05 mmol) was dissolved in dry EtOAc (50 mL). Pyridinium tosylate (299 mg, 1.2 mmol) was added and the mixture stirred at ambient temperature under nitrogen for 30 minutes. 2,3-Dihydropyrane (1.13 mL, 12 mmol) was added, and the mixture stirred for 5 minutes at ambient temperature followed by 5 hours at 40 ^{o}C. The mixture was cooled to ambient temperature, diluted with ethyl acetate (150 mL), washed with brine (2 x 70 mL), dried using $MgSO_4$ and evaporated. The residue was recrystallized from Hexane.

2,6-*Dichloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine* **(12a)**



12a

Purified by recrystalisation from hexane; Yield 1044mg (76%), colourless solid.

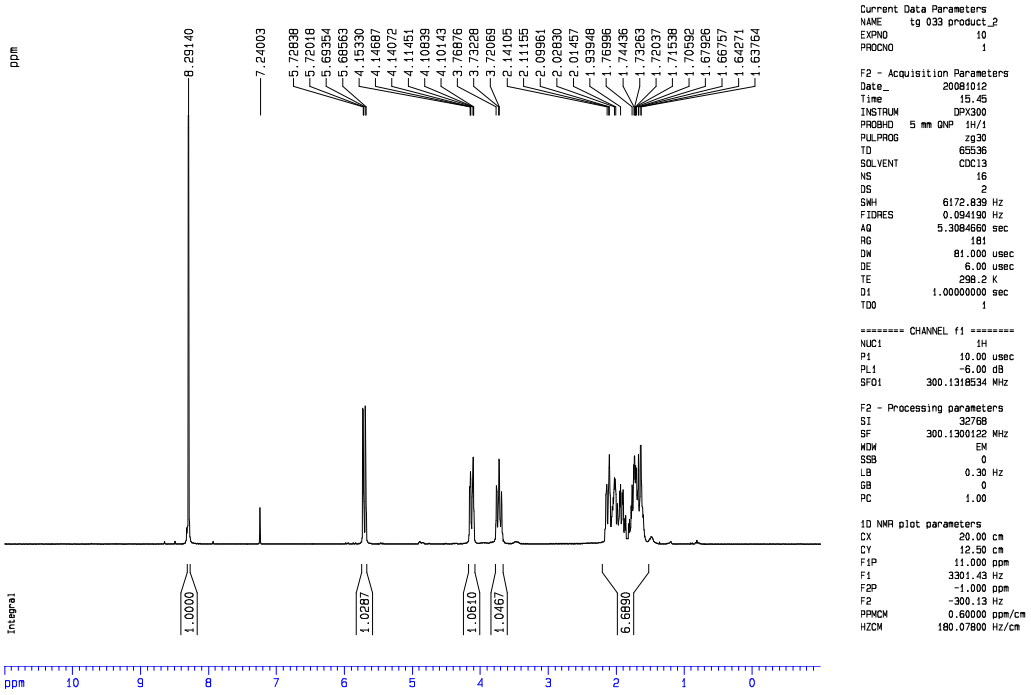
^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.67-2.17 (m, 6H, $3CH_2$), 3.75-3.80 (m, 1H), 4.14-4.19 (m, 1H), 5.72-5.76 (dd, 1H, J_1 10.4 Hz, J_2 2.4 Hz, H-2'), 8.30(s, 1H, H-8).

^{13}C NMR ($CDCl_3$, 75MHz) δ: 22.4 (C-5'), 24.6 (C-4'), 31.9 (C-6'), 68.9 (C-3'), 82.4 (C-1'), 130.7(C-5), 143.7 (C-8), 151.6 (C-4), 152.1(C-6), 152.9(C-2).

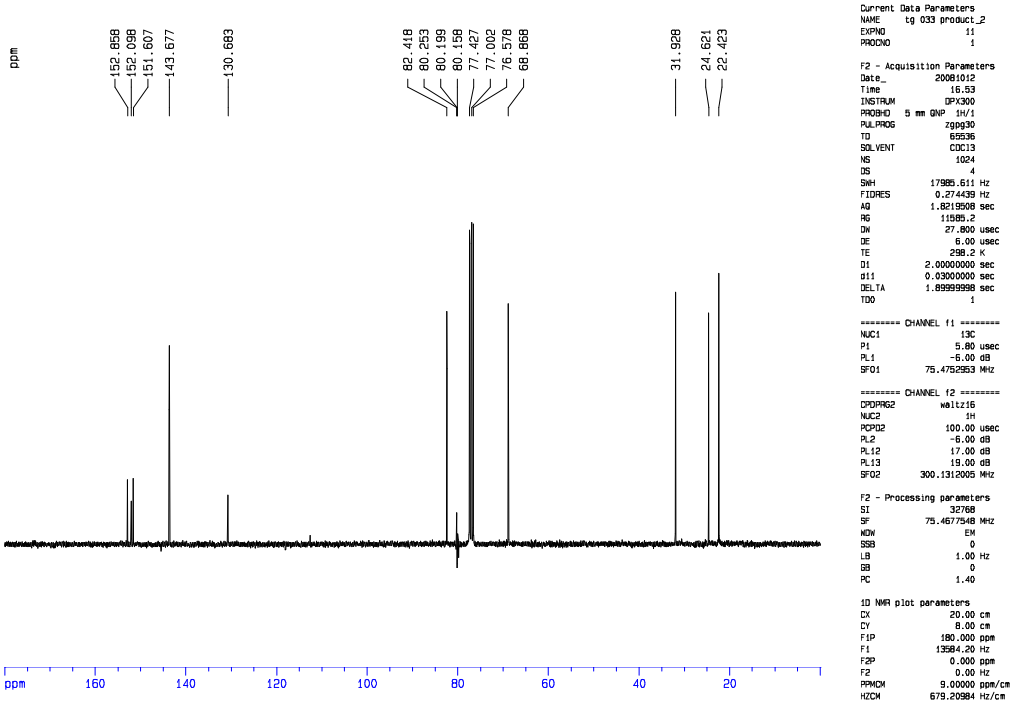
MS (EI). m/z (rel. %): 274/272 (3/4), 190/188 (6/9), 153 (7), 92 (3), 91 (1), 86 (7), 85 (100), 84 (8), 67 (13), 65 (2).

HR-MS. found 272.0227 calculated for $C_{10}H_{10}Cl_2N_4O$ 272.0232.

M. p. 117.5-118 ^{o}C (lit.119-120 ^{o}C). [82]



Spectrum 1. ^{1}H NMR of 2,6-*Dichloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine* (**12a**).

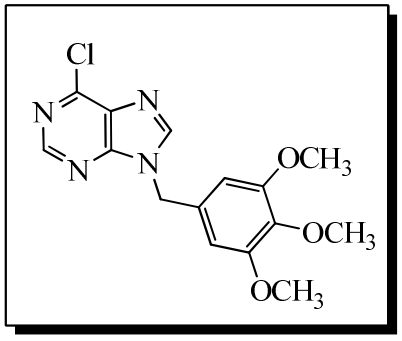


Spectrum 2. ^{13}C NMR of 2,6-*Dichloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine* (**12a**).

6.1.1.2 Synthesis of N-alkylated purines 12b-h, 13b-h

The synthesis was on a 5 mmol scale unless otherwise started. A mixture of 6-chloropurine **11b** or 2,6-dichloropurine **11a** (5.0 mmol) and potassium carbonate (2.07g, 15 mmol) in DMF (20 mL) was stirred at ambient temperature under nitrogen atmosphere for 30 minutes, after which the benzyl halide (10mmol) was added. After stirring for 20-24 hours the reaction mixture was filtered and evaporated in vacuo. The products were then isolated by flash chromatography on silica gel.[81] The 9-alkylated isomers, the expected products, **12b-h** were eluted first. The 7-alkylated isomers the by-products **13b-h** were eluted second.

6-Chloro-9-(3,4,5-trimethoxybenzyl)-9H-purine **(12b).**



12b

EtOAc-hexane (2:1), (3:1) then pure EtOAc. were used for flash chromatography; Yield 952mg (56%), colourless solid.

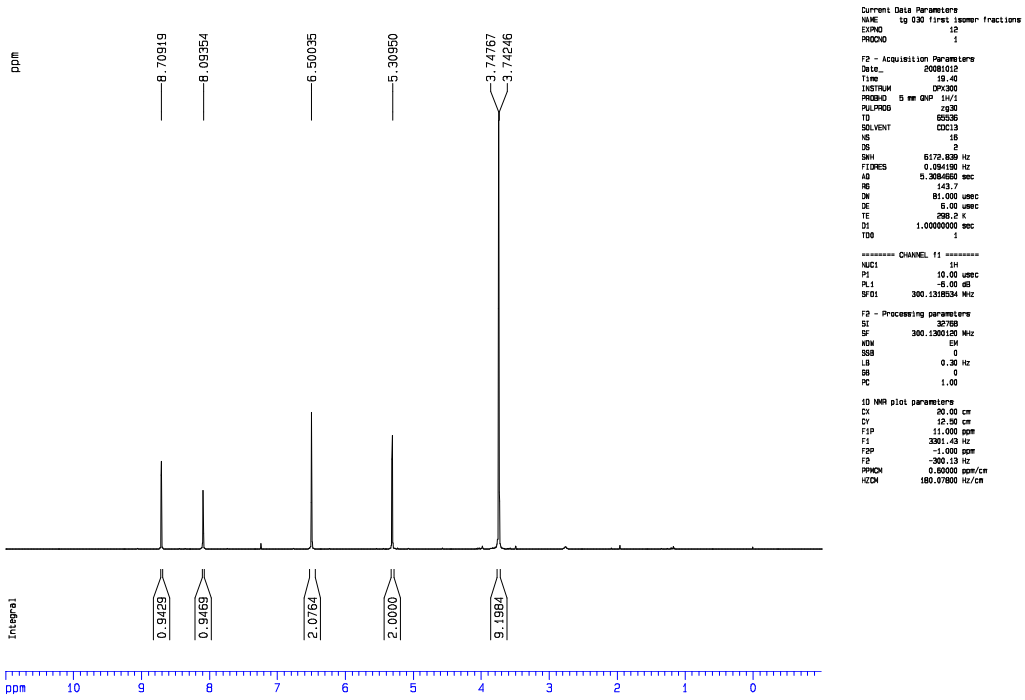
^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.75 (s, 9H, 3xOCH_3), 5.30 (s, 2H, CH_2), 6.50 (s, 2H, Ar), 8.09 (s, 1H, H-8), 8.71(s, 1H, H-2).

^{13}C NMR ($CDCl_3$, 75MHz) δ: 48,1 (CH_2), 56.1 (3'-OCH_3 and 5'-OCH_3), 60.7 (4'-OCH_3), 105.2 (C-2 and C-6 Ar), 129.8 (C-1 Ar), 131.3 (C-5), 138.2 (C-4), 144.9 (C-8), 150.9 (C-6), 151.7(C-6), 151.9(C-2), 153.6 (C-3 and C-5 Ar).

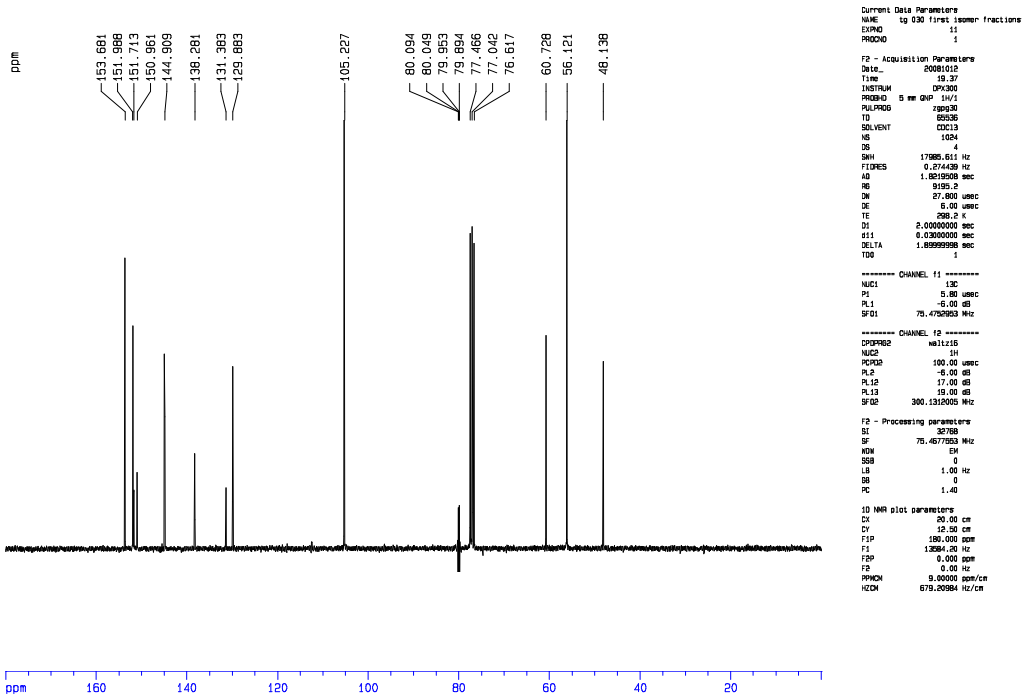
MS (EI). m/z (rel. %): 336/334 (34/99, M^+), 233 (7), 182(11), 181 (100), 151 (8), 136 (7), 79 (6), 78 (4), 65 (3).

HR-MS. found 334.0843 calculated for $C_{15}H_{15}ClN_4O_3$ 334.0833.

M. p. 115-116 °C (lit.115-116 °C).[81]

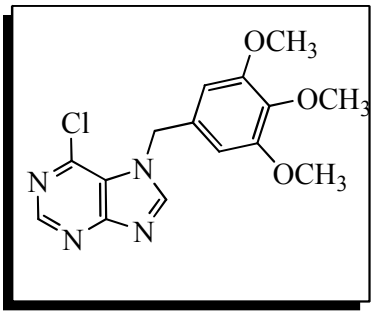


Spectrum 3. ^{1}H NMR of *6-Chloro-9-(3,4,5-trimethoxybenzyl)-9H-purine* (**12b**).



Spectrum 4. ^{13}C NMR of *6-Chloro-9-(3,4,5-trimethoxybenzyl)-9H-purine* (**12b**).

6-Chloro-7-(3,4,5-trimethoxybenzyl)-7H-purine **(13b)**.



13b

EtOAc-hexane (2:1), (3:1) then pure EtOAc. were used for flash chromatography; Yield 386mg (23%), colourless solid.

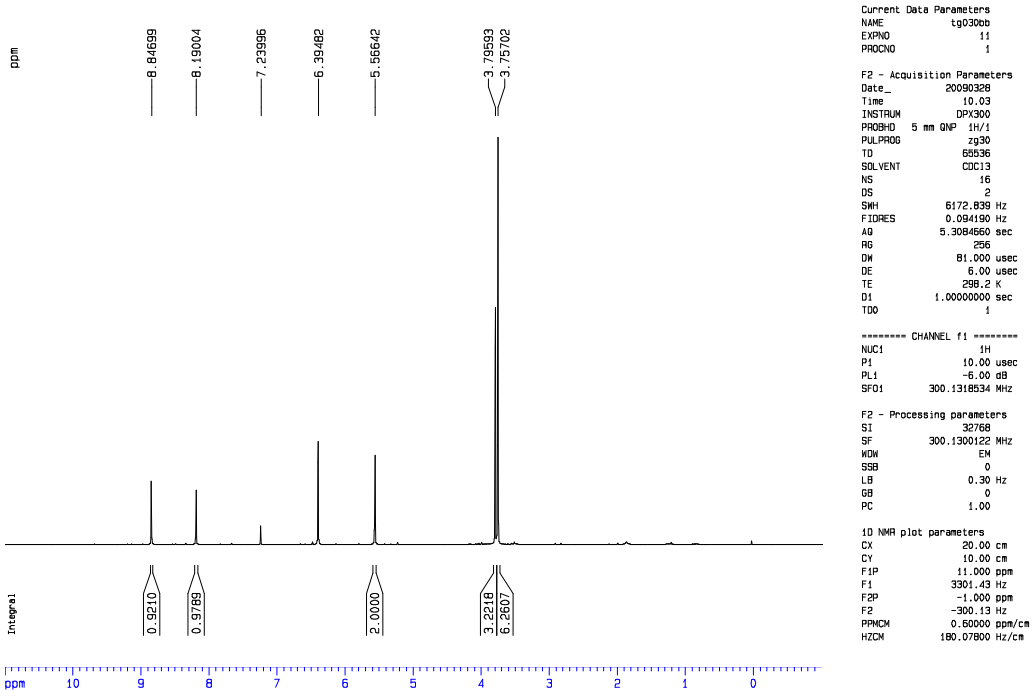
^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.76 (s, 6H, 2xOCH_3), 3.80 (s, 3H, OCH_3), 5.57 (s, 2H, CH_2), 6.39 (s, 2H, Ar), 8.19 (s, 1H, H-8), 8.85 (s, 1H, H-2).

^{13} C NMR ($CDCl_3$, 75MHz) δ: 51.0 (CH_2), 56.2 (3'-OCH_3 and 5'-OCH_3), 60.8 (4'-OCH_3), 104.6 (C-2 and C-6 Ar), 122.5 (C-5), 129.7 (C-1), 138.5 (C-4 Ar), 143.1 (C-4), 148.9 (C-8), 152.5 (C-2), 153.9 (C-3 and C-5 Ar), 162.0 (C-6).

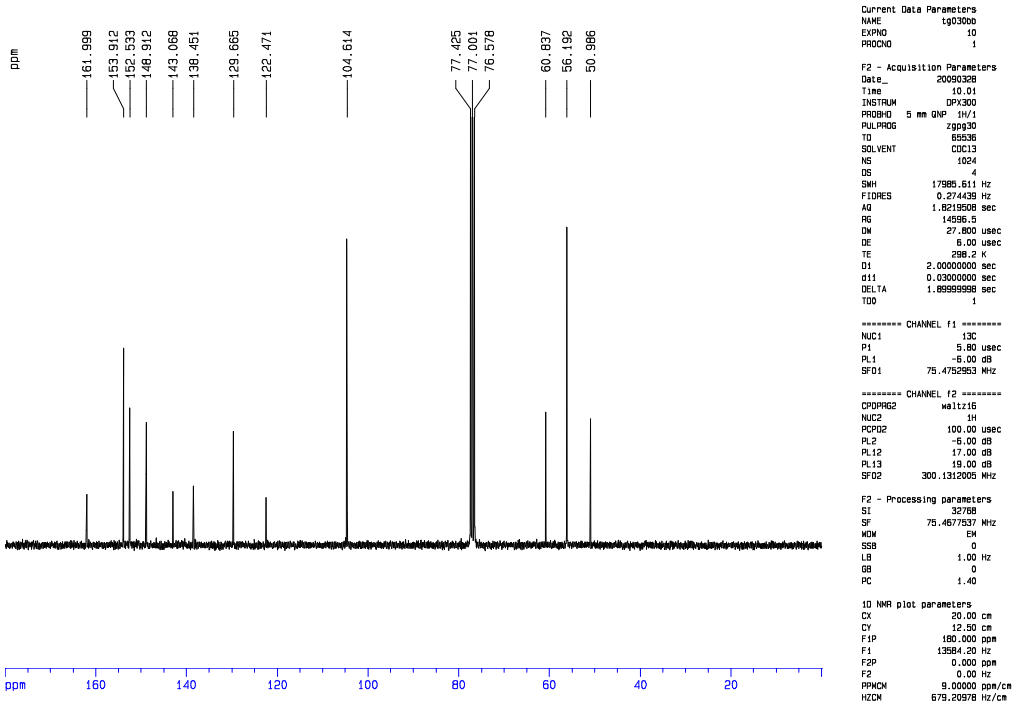
MS (EI). m/z (rel. %): 336/334 (35/73, M^+), 319 (6), 182 (20), 181 (100), 148 (8), 136 (7), 79 (3), 77 (4), 65 (2).

HR-MS. found 334.0830 calculated for $C_{15}H_{15}ClN_4O_3$ 334.0833

M. p. 122 °C (lit. 121-122 °C) .[81]

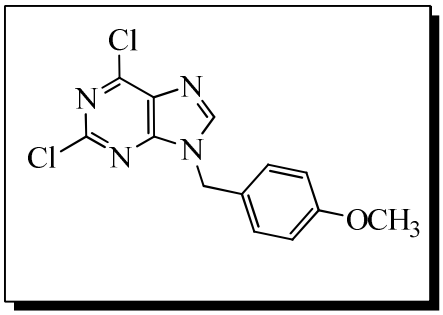


Spectrum 5. ^{1}H NMR of *6-Chloro-7-(3,4,5-trimethoxybenzyl)-7H-purine* (**13b**).



Spectrum 6. ^{13}C NMR of *6-Chloro-7-(3,4,5-trimethoxybenzyl)-7H-purine* (**13b**).

2,6-Dichloro-9-(4-methoxybenzyl)-9H-purine **(12c)**.



12c

EtOAc-Hexane 2:3 then pure EtOAc. were used for flash chromatography; Yield 910mg (59%) colourless solid.

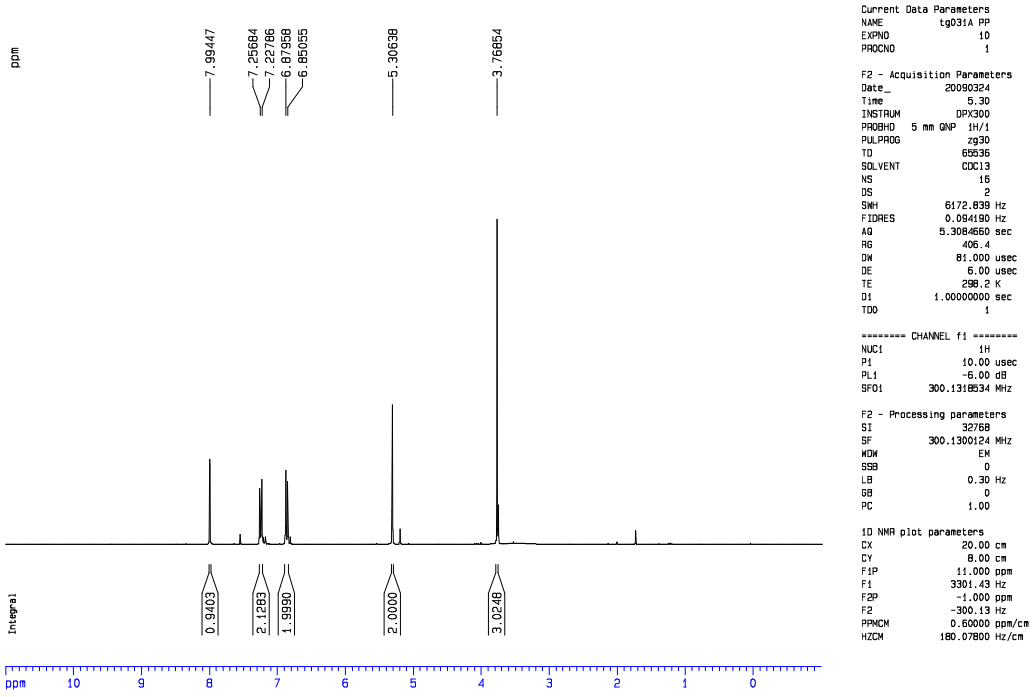
^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.79 (s, 3H, OCH_3), 5.32 (s, 2H, CH_2), 6.89 (d, J 8.7 Hz, 2H, Ar), 7.26(d, J 8.7 Hz, 2H, Ar), 7.99 (s, 1H, H-8).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 47.6 (CH_2), 55.3 (OCH_3), 114.6 (C-3 and C-5 Ar), 125.8 (C-1 Ar), 129.7 (C-2 and C-6 Ar), 130.7 (C-5), 145.5 (C-8), 151.7 (C-6), 152.9 (C-4), 153.0 (C-2), 160.0 (C-4 Ar).

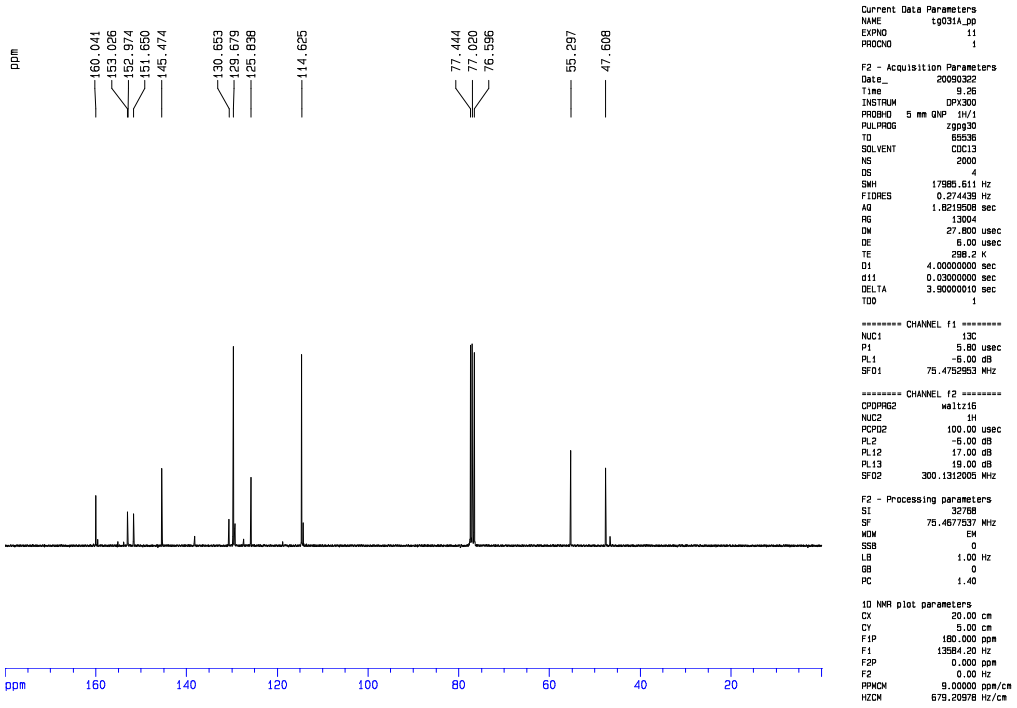
MS (EI). m/z (rel. %): 312/310/308 (4/22/31, M^+), 196 (2), 122 (19), 121 (100), 92 (1), 91 (6), 90 (2), 89 (3), 78 (12), 77 (9), 63 (2).

HR-MS. found 308.0234 calculated for $C_{13}H_{10}Cl_2N_4O$ 308.0232.

M. p. 127-128 °C (lit. 128-130 °C).[81]

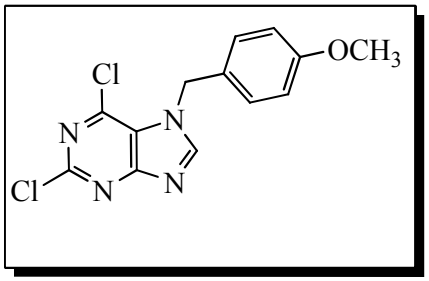


Spectrum 7. ^{1}H NMR of *2,6-Dichloro-9-(4-methoxybenzyl)-9H-purine* (**12c**).



Spectrum 8. ^{13}C NMR of *2,6-Dichloro-9-(4-methoxybenzyl)-9H-purine* (**12c**)

2,6-Dichloro-7-(4-methoxybenzyl)-7H-purine **(13c)**.



13c

EtOAc-Hexane 2:3 then pure EtOAc were used for flash chromatography; Yield 316mg (21%) colourless solid.

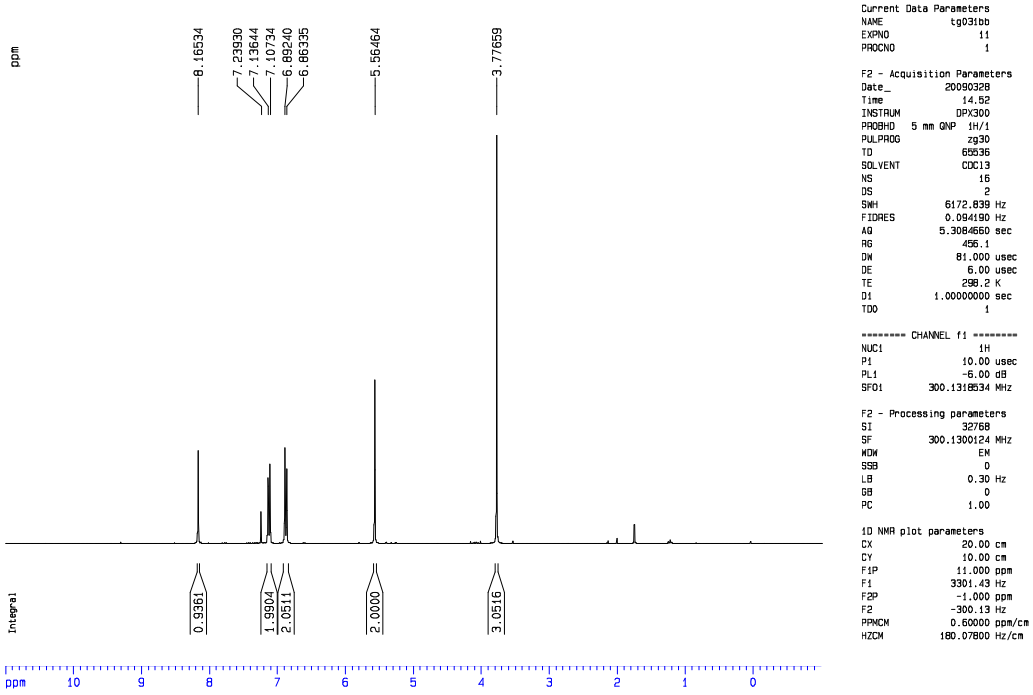
^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.78 (s, 3H, OCH_3), 5.56 (s, 2H, CH_2), 6.88 (d, J_1 8.7 Hz, 2H, Ar), 7.12 (d, J_1 8.7 Hz, 2H, Ar), 8.17 (s, 1H, H-8).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 50.6 (CH_2), 55.4 (OCH_3), 114.8 (C-3 and C-5 Ar), 121.7 (C-5 Ar), 125.7 (C-1 Ar), 128.9 (C-2 and C-6 Ar), 143.9 (C-4), 150.2 (C-8), 153.2 (C-2), 160.1 (C-4 Ar), 163.7 (C-6).

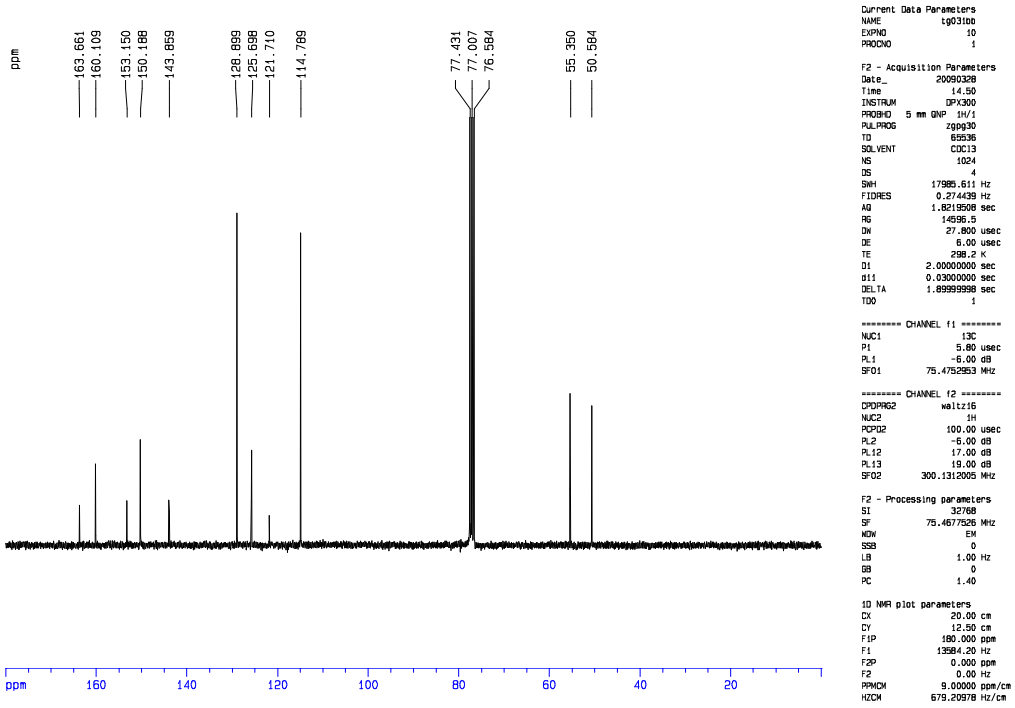
MS (EI). m/z (rel. %): 312/310/308 (2/13/19), 122 (16), 121 (100), 91 (5), 78 (9), 77 (8).

HR-MS. found 308.0233 calculated for $C_{13}H_{10}Cl_2N_4O$ 308.0232

M. p. 138-139 °C (lit. 146-148 °C).[81]

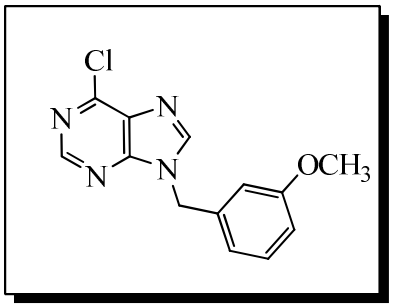


Spectrum 9. ^{1}H NMR of *2,6-Dichloro-7-(4-methoxybenzyl)-7H-purine* (**13c**).



Spectrum 10. ^{13}C NMR of *2,6-Dichloro-7-(4-methoxybenzyl)-7H-purine* (**13c**).

6-Chloro-9-(3-methoxybenzyl)-9H-purine (**12d**).



12d

EtOAc-Hexane 1:1 then pure EtOAc were used for flash chromatography; Yield 870mg (63%) colourless solid.

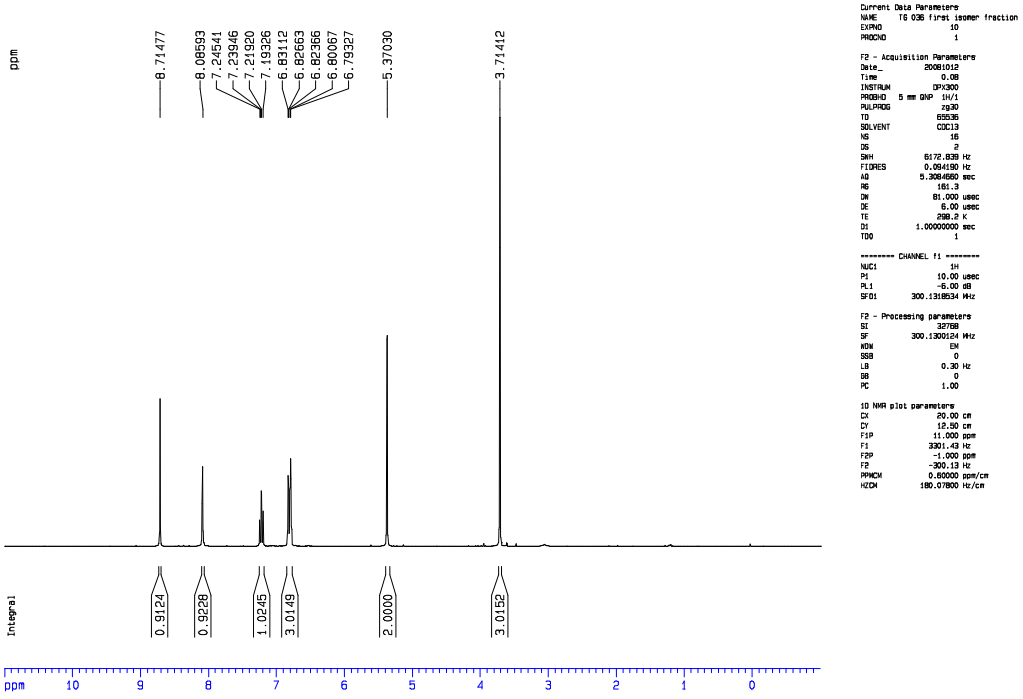
^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.75 (s, 3H, OCH_3), 5.39 (s, 2H, CH_2), 6.81-6.87 (m, 3H, Ar), 7.23-7.29 (m, 1H, Ar), 8.08 (s, 1H, H-8) 8.76 (s, 1H, H-2).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 47.7 (CH_2), 55.2 (OCH_3), 113.7 (C-4 Ar), 113.8 (C-2 Ar), 119.9 (C-6 Ar), 130.3 (C-5 Ar), 131.3m (C-5), 135.9 (C-1 Ar), 144.9 (C-8), 150.9 (C-6), 151.7 (C-4), 152.0 (C-2), 160.0 (C-3 Ar).

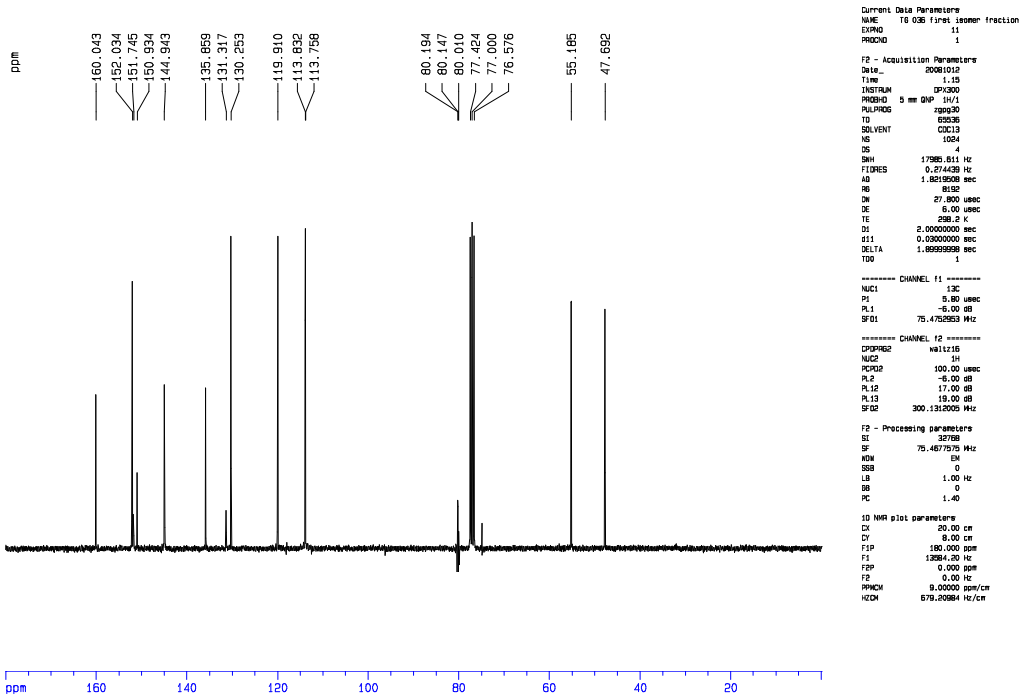
MS (EI). m/z (rel. %): 276/274 (21/66, M^+), 259 (10), 239 (6), 212 (8), 167 (11), 122 (9), 121 (100), 92 (6), 91 (40), 78 (42), 77 (25).

HR-MS. found 274.0619 calculated for $C_{13}H_{11}ClN_4O$ 274.0621

M. p. 105-106 °C (lit. 104-105 °C).[81]

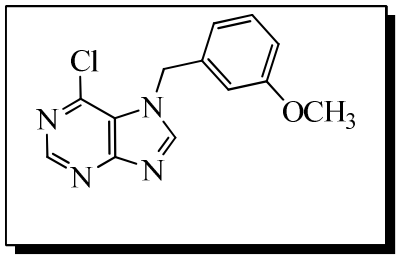


Spectrum 11. ^{1}H NMR of *6-Chloro-9-(3-methoxybenzyl)-9H-purine* (**12d**).



Spectrum 12. ^{13}C NMR of *6-Chloro-9-(3-methoxybenzyl)-9H-purine* (**12d**).

6-Chloro-7-(3-methoxybenzyl)-7H-purine **(13d)**.



13d

EtOAc-Hexane 1:1 then pure EtOAc were used for flash chromatography; Yield 293mg (21%) colourless solid.

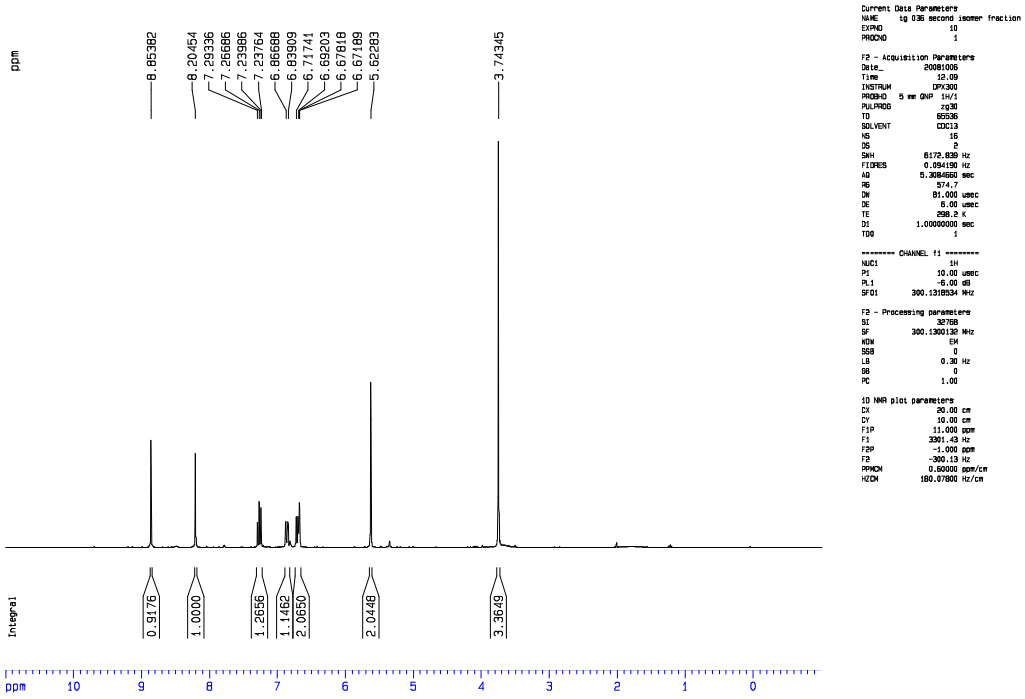
^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.74 (s, 3H, OCH_3), 5.62 (s, 2H, CH_2), 6.67-6.72 (m, 2H, Ar), 6.84-6.87 (m, 1H, Ar), 7.24-7.29 (m, 1H, Ar), 8.20 (s, 1H, H-8), 8.85 (s, 1H, H-2).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 50.6 (CH_2), 55.3 (OCH_3), 113.2 (C-4 Ar), 113.8 (C-2 Ar), 119.2 (C-6 Ar), 122.6 (C-5), 130.5 (C-5 Ar), 136.1 (C-1 Ar), 143.2 (C-4), 149.1 (C-8), 152.6 (C-2), 160.2 (C-6), 162.0 (C-3 Ar).

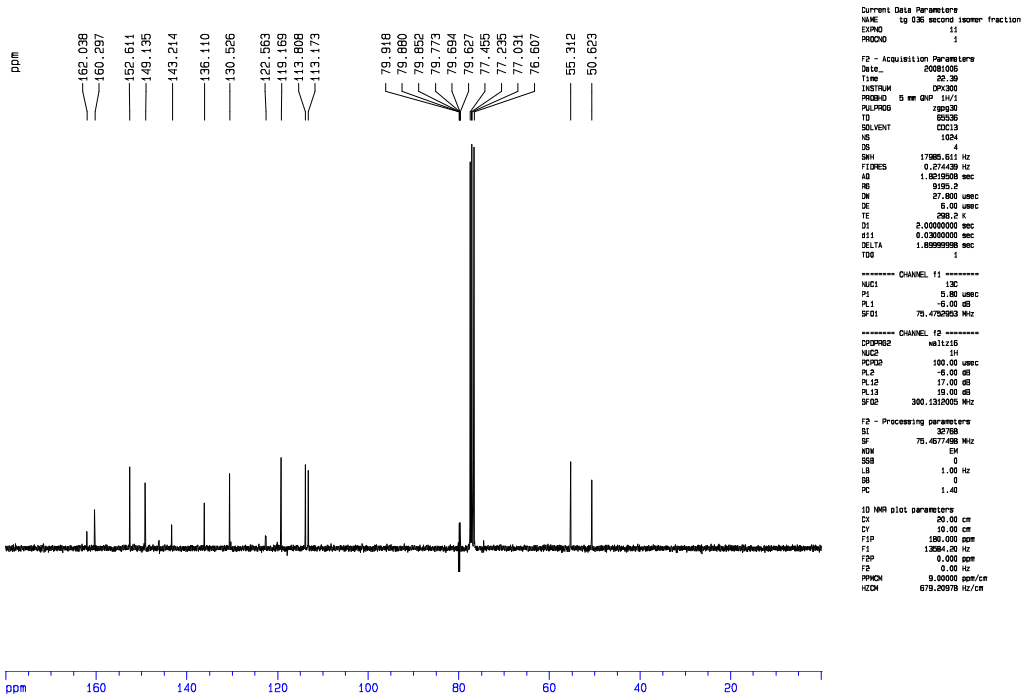
MS (EI). m/z (rel. %): 276/274 (31/67, M^+), 239 (22), 122 (16), 121 (100), 92 (3), 91 (28), 78 (17), 77 (11), 65 (9).

HR-MS. found 274.0619 calculated for $C_{13}H_{11}ClN_4O$ 274.0621

M. p. 150-152 °C (lit. 160-162 °C).[81]

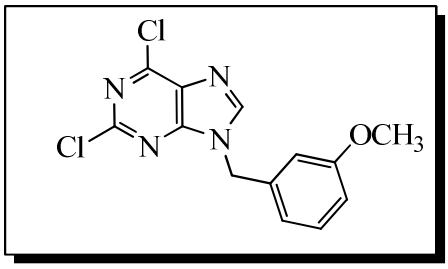


Spectrum 13. ^{1}H NMR of *6-Chloro-7-(3-methoxybenzyl)-7H-purine* (**13d**).



Spectrum 14. ^{13}C NMR of *6-Chloro-7-(3-methoxybenzyl)-7H-purine* (**13d**)

2,6-Dichloro-9-(3-methoxybenzyl)-9H-purine **(12e)**.



12e

EtOAc- hexane (1:2) then pure EtOAc were used for flash chromatography Yield 837mg (54%) colourless solid.

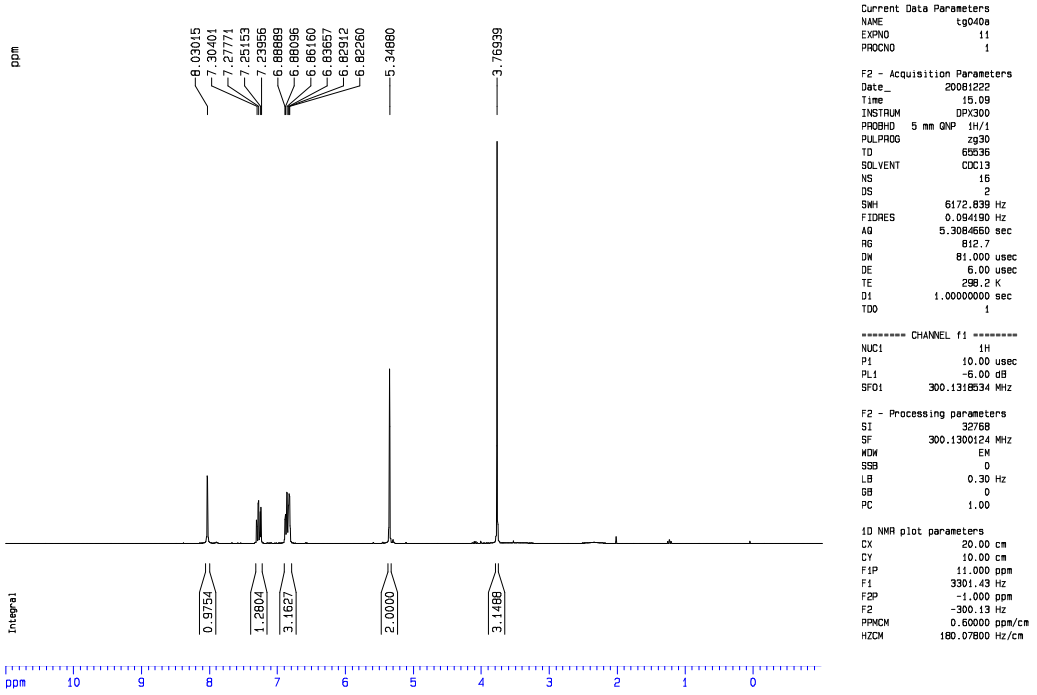
^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.77(s, 3H, OCH_3), 5.35(s, 2H, CH_2), 6.82-6.88(m, 3H, Ar), 7.25-7.28(m, 1H, Ar) 8.03 (s, 1H, H-8).

^{13}C NMR ($CDCl_3$, 75MHz): δ 48.0 (CH_2), 55.4 (OCH_3), 114.0 (C-2 Ar), 114.3 (C-4 Ar), 120.2 (C-6 Ar), 130.5 (C-5 Ar), 130.7 (C-5), 135.4 (C-1 Ar), 145.6 (C-8), 151.9 (C-4/C-6), 153.2 (C-2), 160.3 (C-3 Ar).

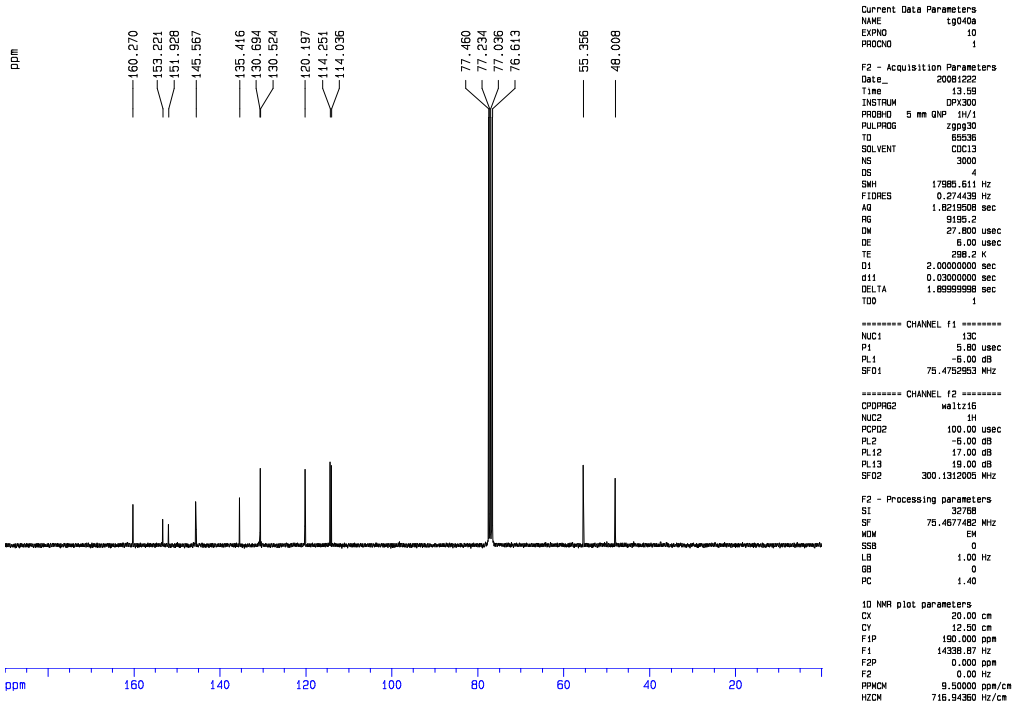
MS (EI). m/z (rel. %): 312/310/308 (6/36/57, M^+), 275/273 (3/9), 122 (9), 121 (100), 91 (21), 78 (12), 65 (6).

HR-MS. found 308.0227 calculated for $C_{13}H_{10}C_{l2}N_4O$ 308.0232.

M. p. 118-119 °C (lit. 119-121 °C).[81]

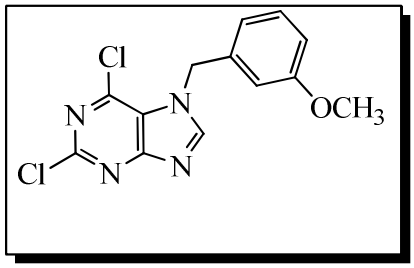


Spectrum 15. ^{1}H NMR of *2,6-Dichloro-9-(3-methoxybenzyl)-9H-purine* (**12e**).



Spectrum 16. ^{13}C NMR of *2,6-Dichloro-9-(3-methoxybenzyl)-9H-purine* (**12e**).

2,6-Dichloro-7-(3-methoxybenzyl)-7H-purine **(13e)**.



13e

EtOAc- hexane (1:2) then pure EtOAc were used for flash chromatography Yield 341mg (22%) off white solid.

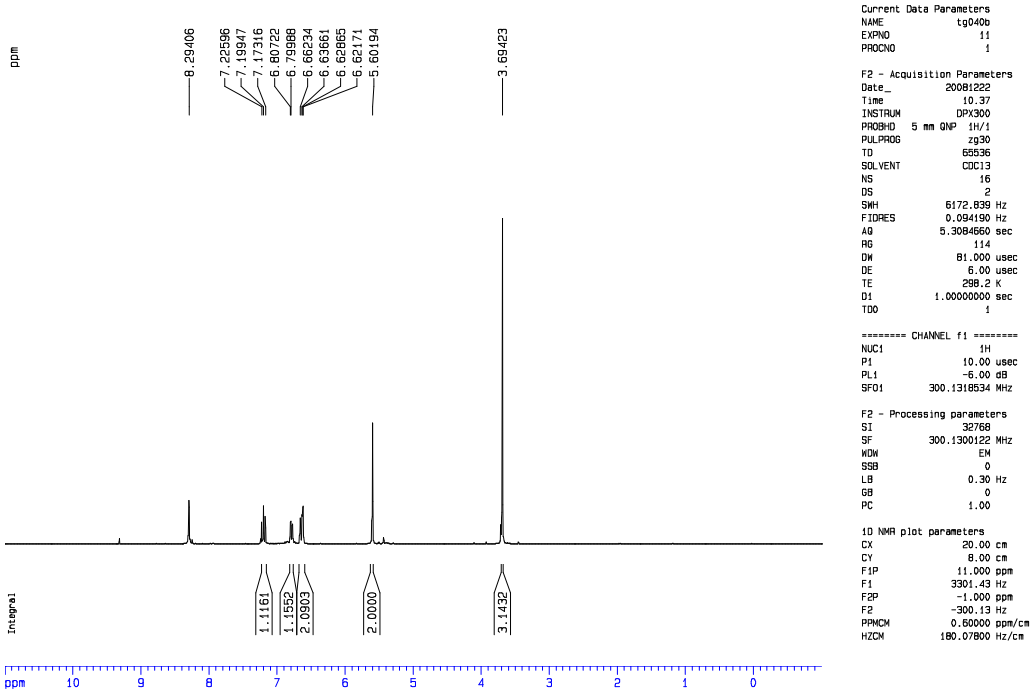
^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.69 (s, 3H, OCH_3), 5.60 (s, 2H, CH_2), 6.62-6.66(m, 2H, Ar), 6.77-6.81(dd, J_1=8.1 Hz, J_2 =2.2 Hz, 1H, Ar), 7.20(t, J_1=7.9Hz, 1H, Ar), 8.29(s, 1H, H-8)

^{13}C NMR ($CDCl_3$, 75MHz): δ 50.6 (CH_2), 55.2 (OCH_3), 113.0 (C-4 Ar), 113.6 (C-2 Ar), 119.0 (C-6 Ar), 130.3 (C-5 Ar), 135.7 (C-1 Ar), 143.8 (C-5), 150.6 (C-8 Ar), 152.8 (C-6/C-4), 160.0 (C-3 Ar), 163.4 (C-6).

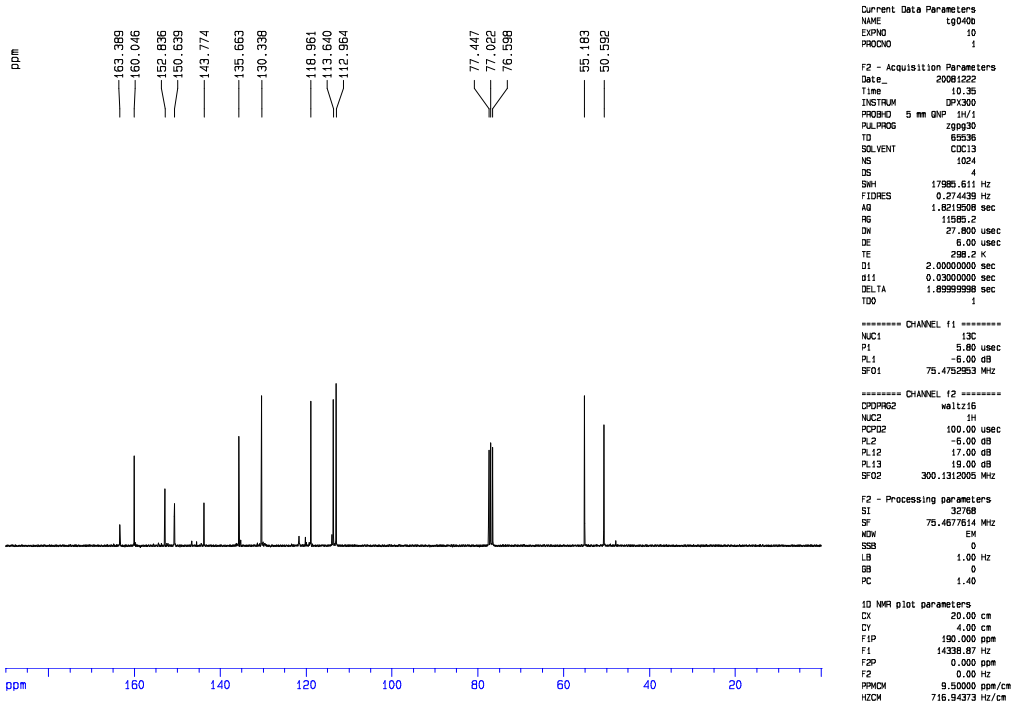
MS (EI). m/z (rel. %): 312/310/308 (5/30/44, M^+), 275/273 (3/11), 122 (13), 121 (100), 91 (20), 78 (11), 65(6).

HR-MS. found 308.0227 calculated for $C_{13}H_{10}C_{l2}N_4O$ 308.0232.

M. p. 110-112 °C (litt. 106-108 °C).[81]

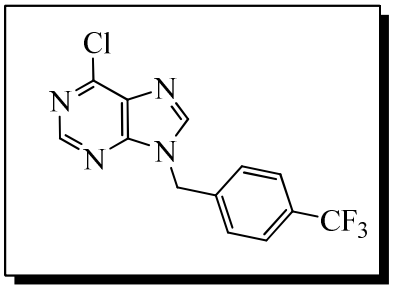


Spectrum 17. ^{1}H NMR of *2,6-Dichloro-7-(3-methoxybenzyl)-7H-purine* (**13e**).



Spectrum 18. ^{13}C NMR of *2,6-Dichloro-7-(3-methoxybenzyl)-7H-purine* (**13e**).

6-Chloro-9-(4-trifluoromethylbenzyl)-9H-purine (12f)



12f

EtOAc-Hexane 3:4 then pure EtOAc were used for flash chromatography; Yield 780mg (50%) white solid.

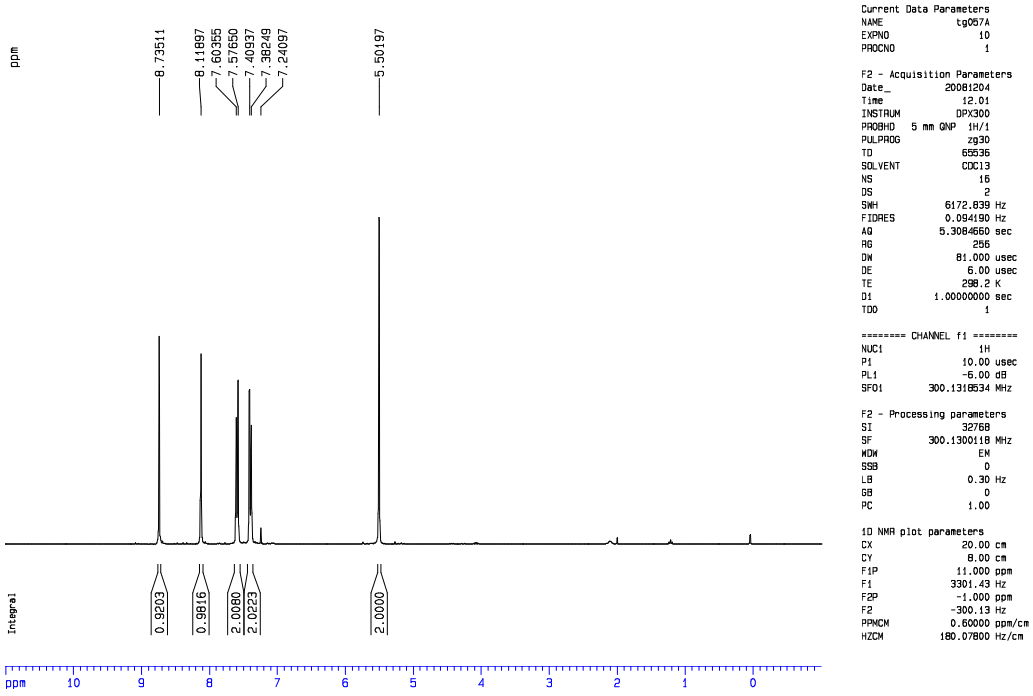
1H NMR (CDCl3, 300 MHz): δ 5.50 (s, 2H, CH2), 7.40 (d, J=8.1 Hz, 2H, Ar), 7.59(d, J= 8.1Hz, 1H, Ar), 8.12 (s, 1H, H-8) 8.74 (s, 1H, H-2)

13C NMR (CDCl3, 75 MHz): δ; 47.3 (CH_2), 123.5 (q, J=271.6 Hz, CF_3), 126.3 (C-3 and C-5), 128.1 (C-2 and C-6 Ar), 131.3 (C-4 Ar), 131.4 (C-5), 138.4 (C-1 Ar), 144.7 (C-8), 151.2 (C-6), 151.7 (C-4), 152.2 (C-2).

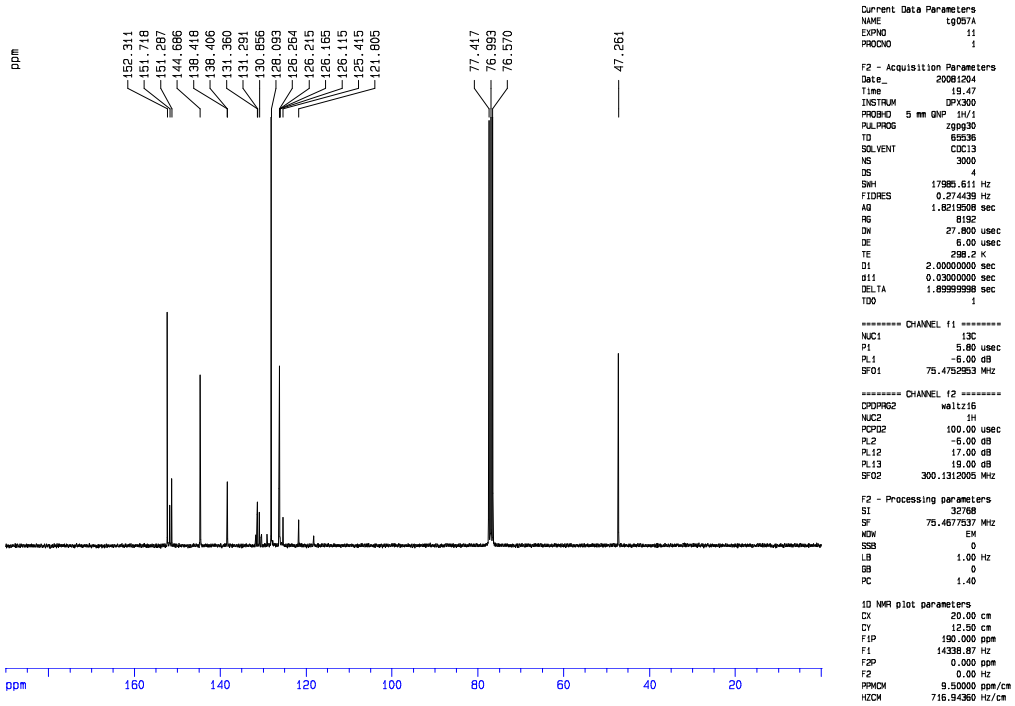
MS (EI). m/z (rel. %):314/312 (36/89, M^+), 311 (100), 250 (27), 167 (10), 159 (87), 119 (10), 109 (29), 77 (2), 65 (1).

HR-MS. found 312.0384 calculated for $C_{13}H_8ClF_3N_4$ 312.0390

M. p. 128-129 °C (lit. 130-132 °C).[81]

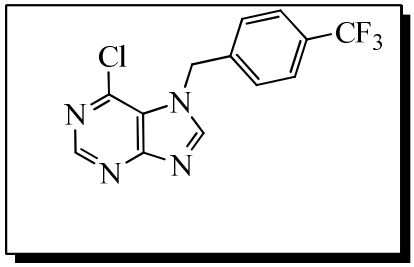


Spectrum 19. ^{1}H NMR of *6-Chloro-9-(4-trifluoromethylbenzyl)-9H-purine* (**12f**).



Spectrum 20. ^{13}C NMR of *6-Chloro-9-(4-trifluoromethylbenzyl)-9H-purine* (**12f**).

6-Chloro-7-(4-trifluoromethylbenzyl)-7H-purine **(13f)**.



13f

EtOAc-Hexane 3:4 then pure EtOAc were used for flash chromatography; Yield 257mg (16%) white solid.

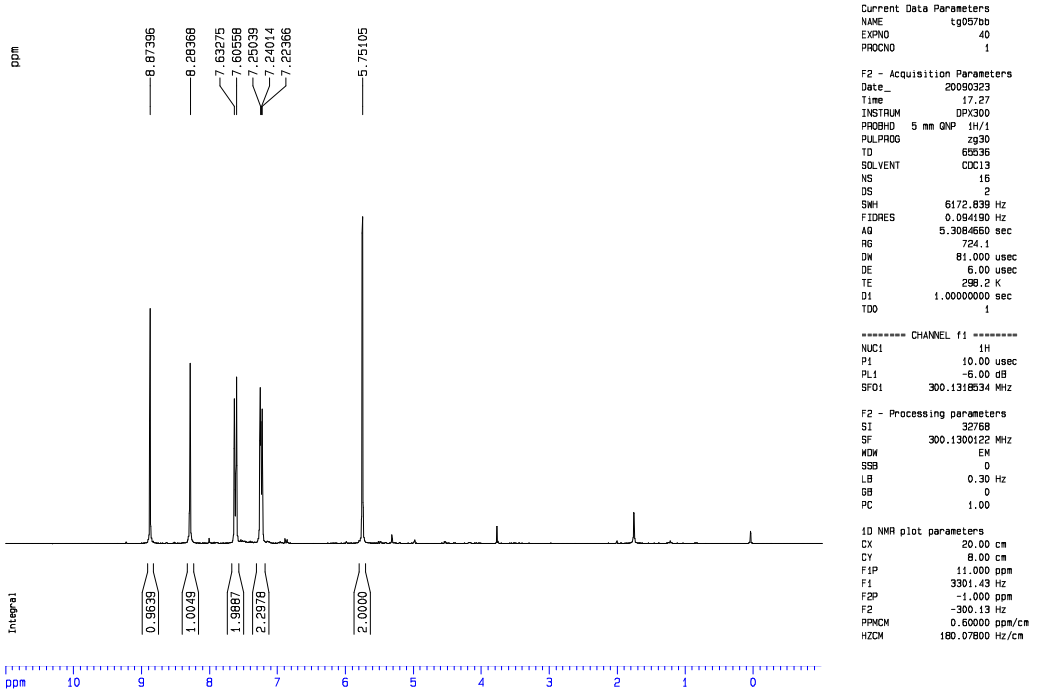
^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.80 (s, 2H, CH_2), 7.28 (d, J= 8.1 Hz, 2H, Ar), 7.65(d, J =8.1Hz, 1H, Ar), 8.40 (s, 1H, H-8) 8.90 (s, 1H, H-2)

^{13}C NMR ($CDCl_3$, 75 MHz): δ 49.9 (CH_2), 121.7 (q, J=270.7 Hz, CF_3), 126.2 (C-3 and C-5 Ar), 127.0 (C-2 and C-6 Ar), 130.6 (C-5), 131.1 (C-4 Ar), 131.5 (C-4), 138.9 (C-1 Ar), 143.3 (C-8),149.3 (C-4),152.6 (C-2), 161.9 (C-6).

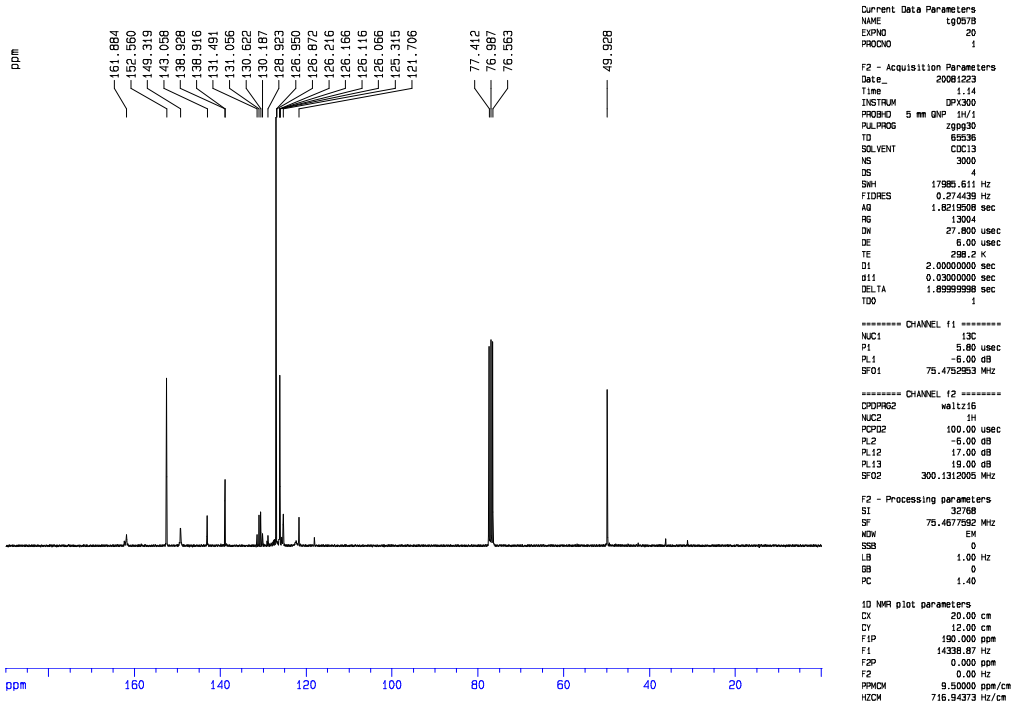
MS (EI). m/z (rel. %): 314/312 (40/78, M^+), 311 (33), 250 (5), 160 (19), 159 (100), 119 (10), 109 (33), 89 (5).

HR-MS. found 312.0386 calculated for $C_{13}H_8ClF_3N_4$ 312.0390

M. p. 129-130 °C (lit. 135-136 °C).[81]

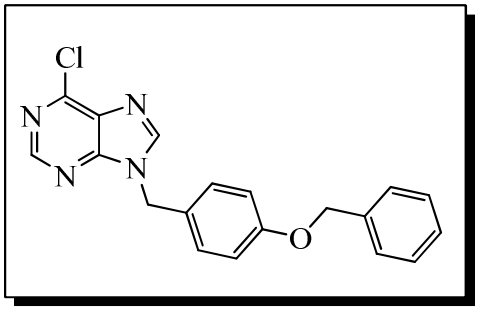


Spectrum 21. ^{1}H NMR of *6-Chloro-7-(4-trifluoromethylbenzyl)-7H-purine* (**13f**).



Spectrum 22. ^{13}C NMR of *6-Chloro-7-(4-trifluoromethylbenzyl)-7H-purine* (**13f**).

6-Chloro-9-(4-benzyloxybenzyl)-9H-purine **(12g)**.



12g

EtOAc-Hexane 2:1 was used for flash chromatography; Yield 489mg (56%) colourless solid.

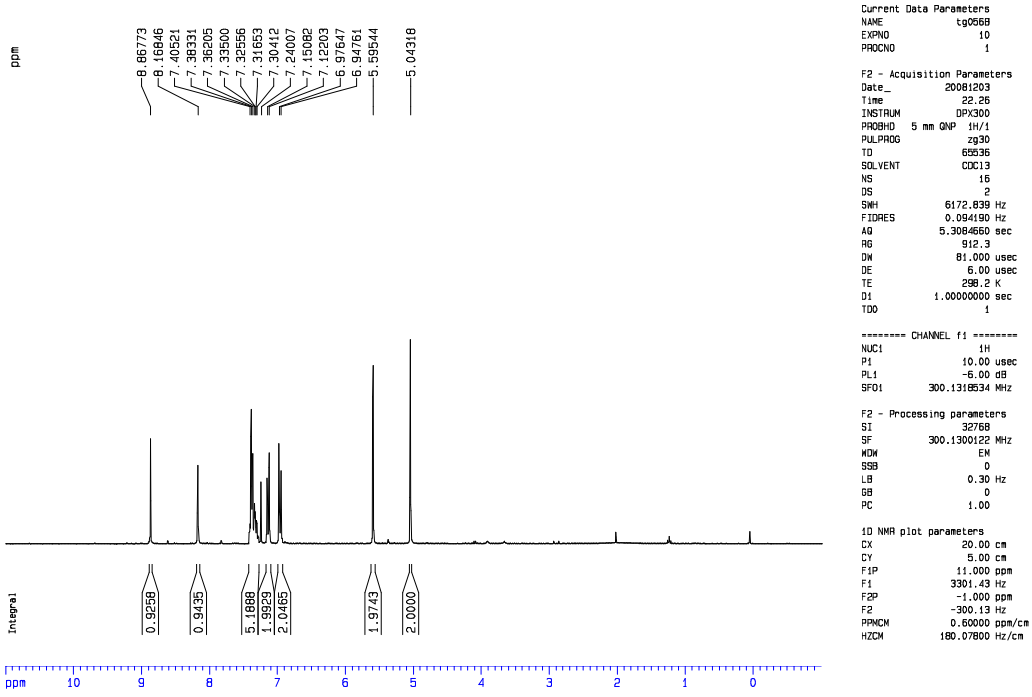
^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.07 (s, 2H, CH_2), 5.40 (s, 2H, CH_2), 6.97-7.44 (m, 9H, Ar), 8.09(s, 1H, H-8), 8.80 (s, 1H, H-2).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 47.5 (N-CH_2), 70.1 (O-CH_2), 115.6 (C-3' and C-5' Ar), 126.8 (C-2" and C-6" Ar), 127.4 (C-4" Ar), 128.1 (C-3" and C-5" Ar), 128.7 (C-2' and C-6' Ar), 129.6 (C-1' Ar), 131.6 (C-5), 136.5 (C-1" Ar), 144.9 (C-8), 151.1 (C-6), 151.8 (C-4), 152.2 (C-2), 159.2 (C-4' Ar).

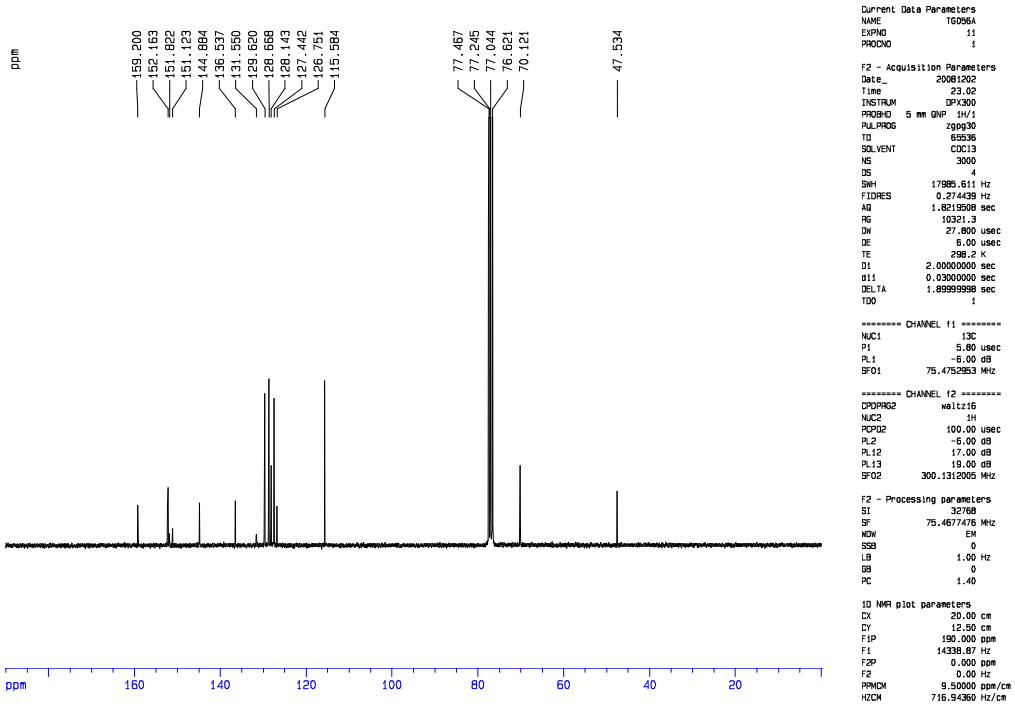
MS (EI). m/z (rel. %): 352/350 (16/42, M^+), 107 (2), 105 (2), 92 (13), 91 (100), 78 (5), 77 (3), 65 (9).

HR-MS. found 350.0939 calculated for $C_{19}H_{15}ClN_4O$ 350.0934

M. p. 129-130 °C (lit. 127-128 °C).[81]

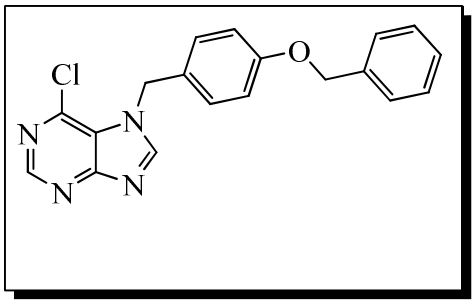


Spectrum 23. ^{1}H NMR of *6-Chloro-9-(4-benzyloxybenzyl)-9H-purine* (**12g**).



Spectrum 24. ^{13}C NMR of *6-Chloro-9-(4-benzyloxybenzyl)-9H-purine* (**12g**).

6-Chloro-7-(4-benzyloxybenzyl)-7H-purine **(13g).**



13g

EtOAc-Hexane 2:1 was used for flash chromatography; Yield 260mg (27%) colourless solid.

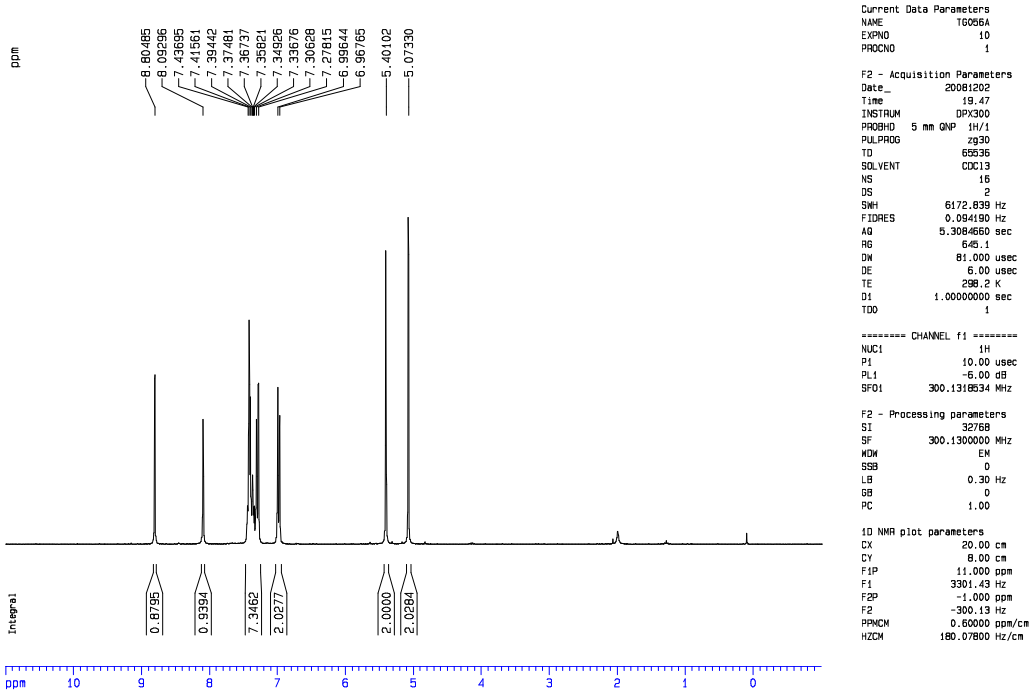
^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.03 (s, 2H, CH_2), 5.59 (s, 2H, CH_2), 6.95 (d, J=8.7 Hz, 2H, Ar), 7.13 (d, J=8.7 Hz, 2H, Ar), 7.35-7.37(m, 5H, Ar) 8.16(s, 1H, H-8) 8.87(s, 1H, H-2)

^{13}C NMR ($CDCl_3$, 75 MHz): δ 50.4 ($N\text{-}CH_2$), 70.1 (O-CH2), 115.7 (C-3' and C-5' Ar), 122.5 (C-5), 126.5 (C-2" and C-6" Ar), 127.4 (C-4" Ar), 128.1 (C-3" and C-5" Ar), 128.6 (C-2' and C-6' Ar), 128.9 (C-1' Ar), 136.4 (C-1" Ar), 143.2 (C-4), 148.7 (C-8), 152.7 (C-2), 159.2 (C-4' Ar), 161.9 (C-6).

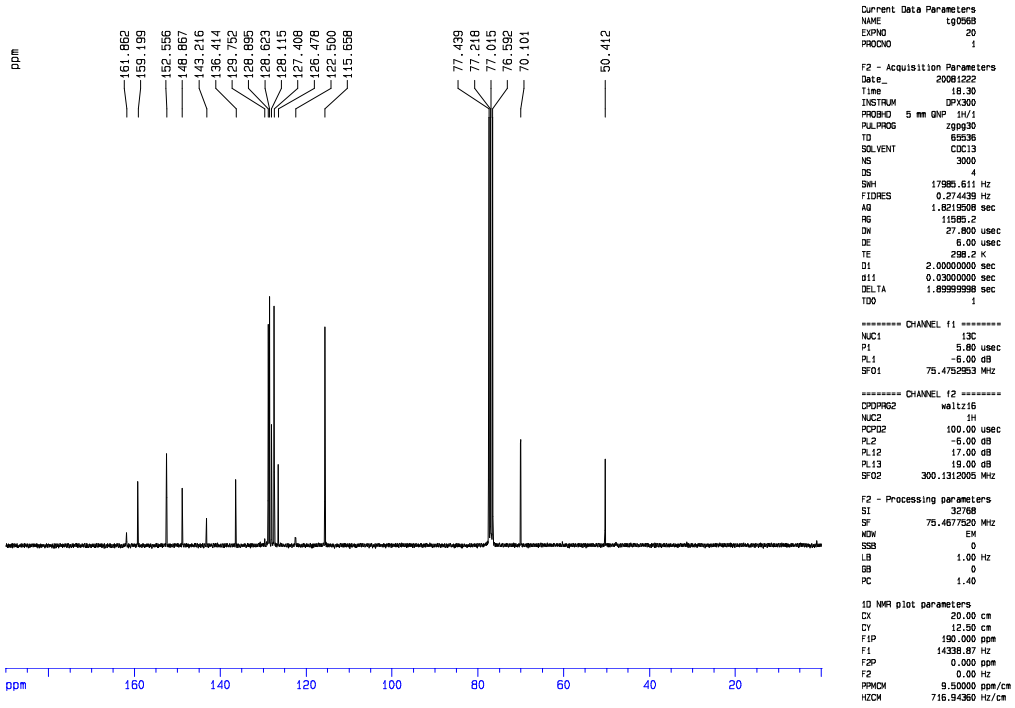
MS (EI). m/z (rel. %): 352/350 (10/30, M^+), 244 (6), 243 (7), 107 (1), 106 (1), 92 (8), 91 (100), 77 (2), 65 (8).

HR-MS. found 350.0942 calculated for $C_{19}H_{15}ClN_4O$ 350.0934.

M. p. 140-142 °C (lit. 142-143 °C).[81]

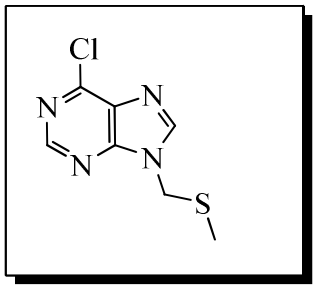


Spectrum 25. ^{1}H NMR of *6-Chloro-7-(4-benzyloxybenzyl)-7H-purine* (**13g**).



Spectrum 26. ^{13}C NMR of *6-Chloro-7-(4-benzyloxybenzyl)-7H-purine* (**13g**).

6-Chloro-9-(methylthiomethyl)-9H-purine **(12h)**



12h

EtOAc: Hex 1:1 and EtOAc. were used for flash chromatography; Yield 469 mg (43%) colourless solid.

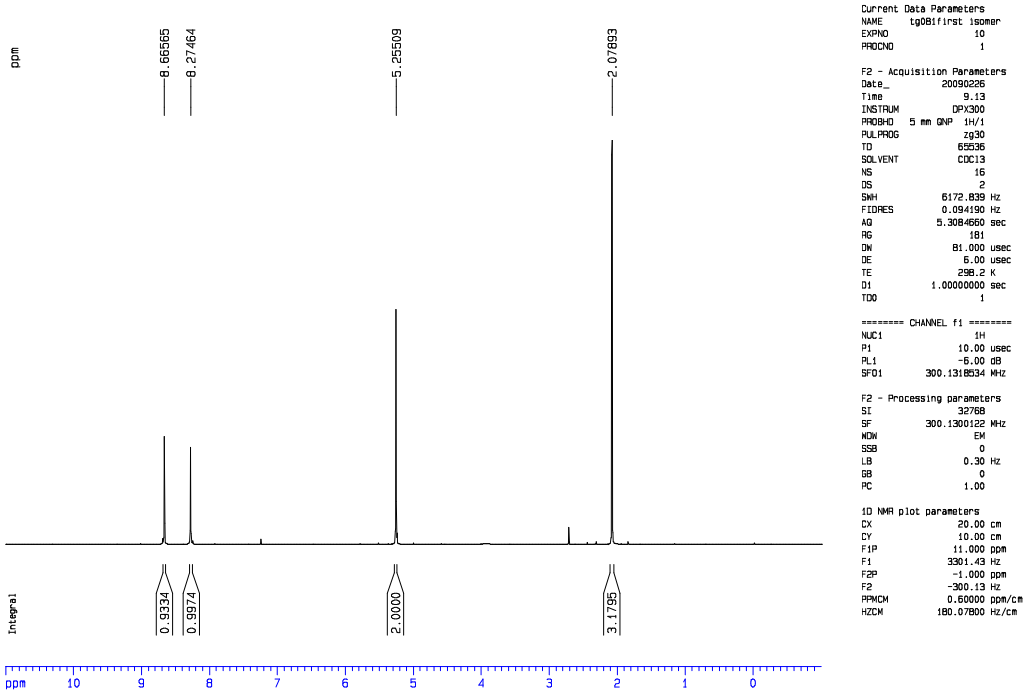
^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.08 (s, 3H, CH_3), 5.26 (s, 2H, CH_2), 8.27 (s, 1H, H-8), 8.67 (s, 1H, H-2).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.2 (CH_3), 46.8(CH_2), 131.3 (C-5), 144.7 (C-8), 151.0 (C-6), 151.7 (C-4), 152.0 (C-2).

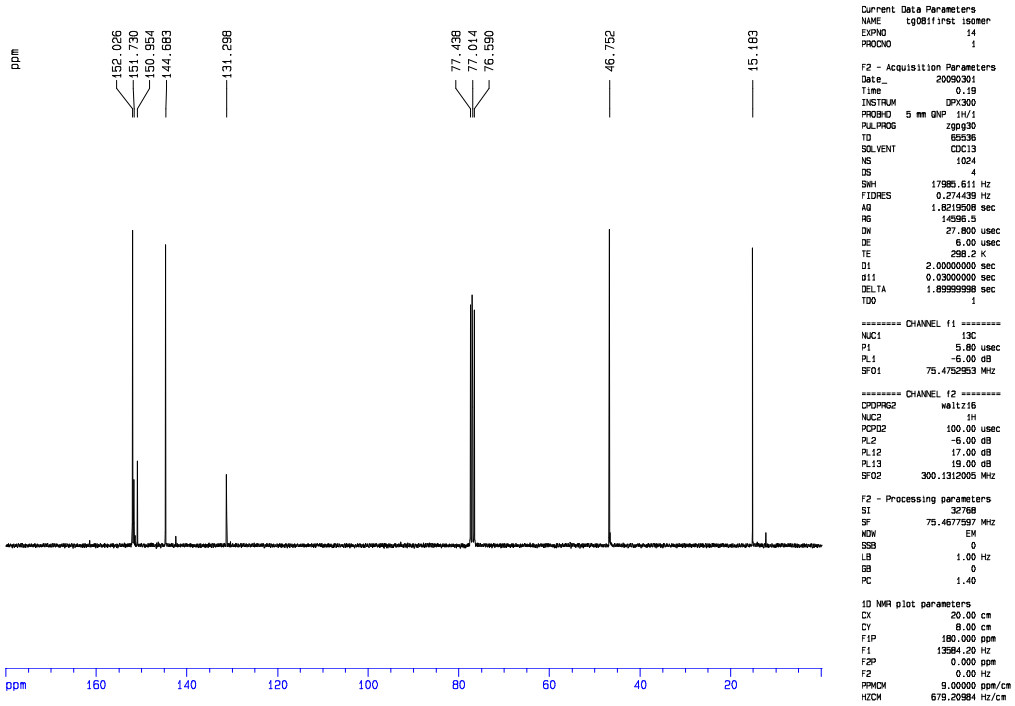
MS (EI). m/z (rel. %): 216/214 (7/20, M^+), 179 (3), 170/168 (33/100), 169/167 (25/52), 140 (6), 113 (5), 104 (15), 87 (4), 84 (6), 79 (13), 77 (20), 65 (39, 61 (85).

HR-MS. found 214.0074 calculated for $C_7H_7ClN_4S$ 214.0080

M. p. 84-85°C (literature value not found).

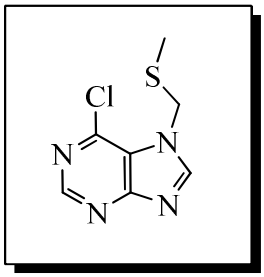


Spectrum 27. ^{1}H NMR of *6-Chloro-9-(methylthiomethyl)-9H-purine* (**12h**).



Spectrum 28. ^{13}C NMR of *6-Chloro-9-(methylthiomethyl)-9H-purine* (**12h**).

6-Chloro-7-(methylthiomethyl)-7H-purine **(13h)**



13h

EtOAc: Hex 1:1 and EtOAc. were used for flash chromatography; Yield 174 mg (16%) pale yellow solid.

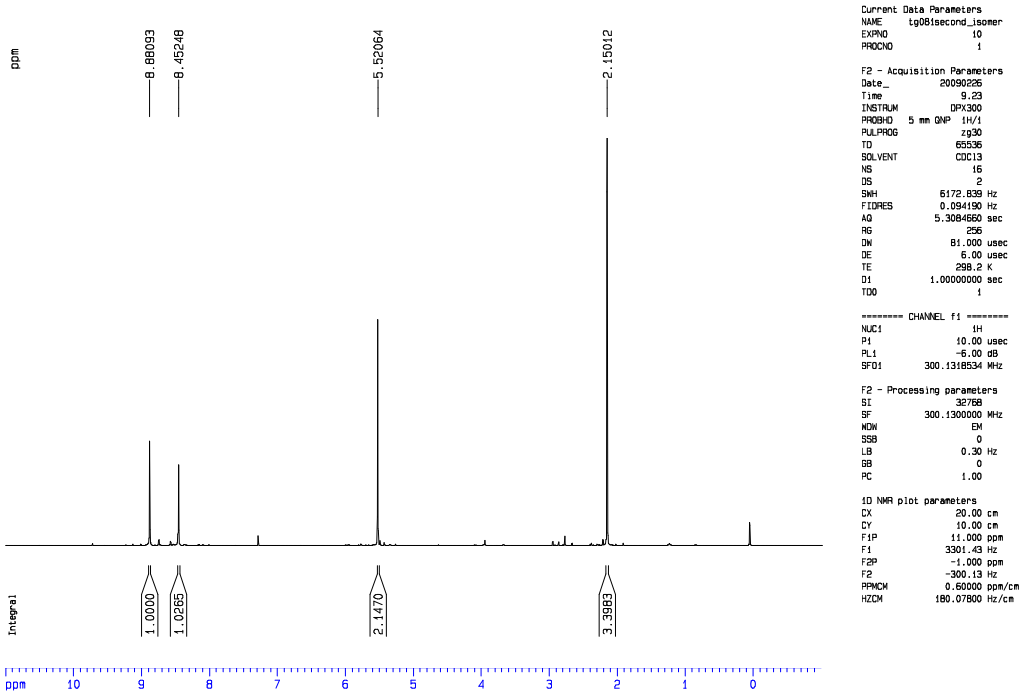
^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.15 (s, 3H, CH_3), 5.52 (s, 2H, CH_2), 8.45 (s, 1H, H-8), 8.88 (s, 1H, H-2).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.5 (CH_3), 50.5(CH_2), 122.0 (C-5), 143.4 (C-4), 148.5 (C-8), 152.7 C-2), 162.2 (C-6).

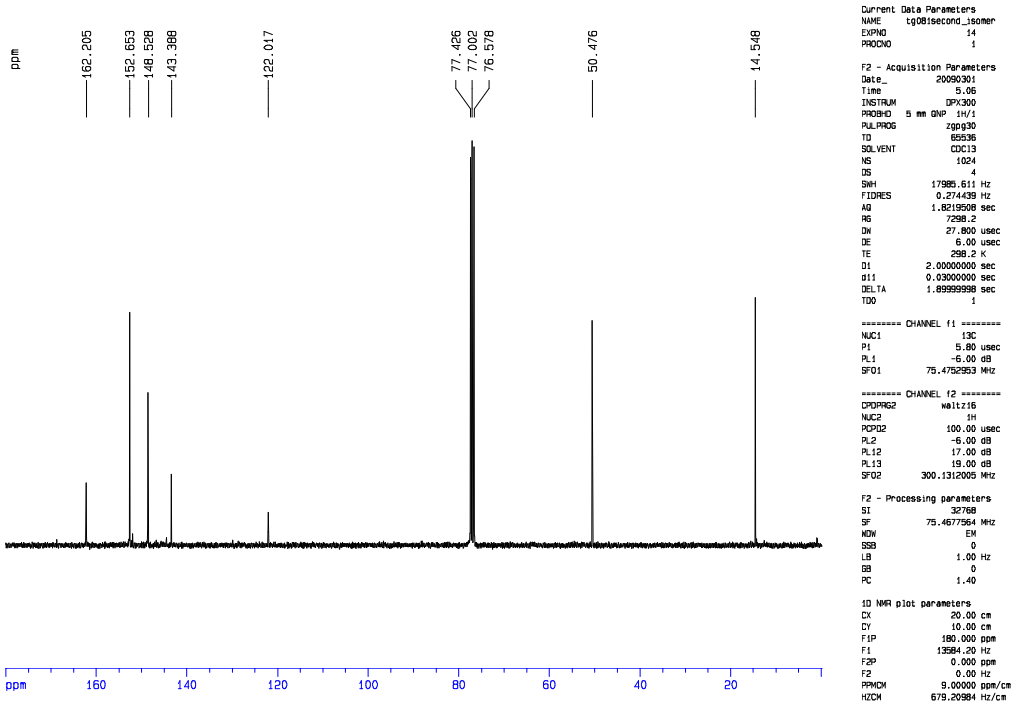
MS (EI). m/z (rel. %): 216/214 (21/55, M^+), 179 (2), 170/168 (6/19), 169/167 (34/100), 142 (8), 140 (24), 119 (6), 113 (9), 105(1), 104 (5), 87 (2), 86 (11), 79 (4), 77 (8), 65 (2), 61 (80).

HR-MS. found 214.0075 calculated for $C_7H_7ClN_4S$ 214.0080.

M. p. 120-121 ^{o}C (literature value not found).



Spectrum 29. ^{1}H NMR of *6-Chloro-7-(methylthiomethyl)-7H-purine* (**13h**).



Spectrum 30. ^{13}C NMR of *6-Chloro-7-(methylthiomethyl)-7H-purine* (**13h**).

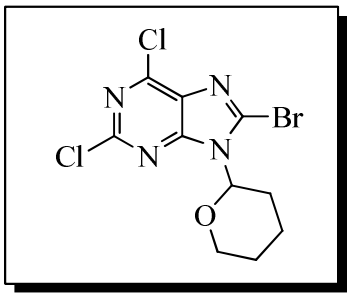
6.1.2 Synthesis of 8-bromo purines (15, 53) via lithiation/bromination

Generally the synthesis was on a 0.5 mmol scale unless otherwise started. A solution of purine, **12** or **13** (0.5 mmol) in THF (2.0 mL) was added dropwise over 10 minutes to a stirred solution of LDA (ca 0.5M in THF, amount of LDA 1.4 mL). After stirring for 1 hour, a solution of $BrCCl_2CCl_2Br$ (326 mg, 1 mmol) in THF (1.0 mL) was added dropwise over 10 minutes. The resulting mixture was stirred at -78 ^{o}C under N_2 for the time given in the Table 2 before quenching using saturated aqueous NH_4Cl (15 mL). The mixture was warmed to ambient temperature and extracted using ethyl acetate (3x25 mL). The extract was washed with NaCl (20 mL) then dried further with $MgSO_4$. The extract was evaporated *in vacuo* and the crude product was purified by flash chromatography on silica gel.

The LDA was prepared in situ from butyllithium (0.7 mmol) and diisopropylamine (0.75 mmol),) by addition of the butyllithium dropwise over 5 minutes to a stirred solution of

diisopropylamine under N_2 at -78 ^oC and mixture left to stir for a period of 30 minutes (and 1hour in the case of **12x**).

8-Bromo-2,6-dichloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine **(15a).**



15a

Hexane followed by EtOAc- hexane (1:6) and (1:3) were used for flash chromatography. Yield 141mg (80%), pale yellow.

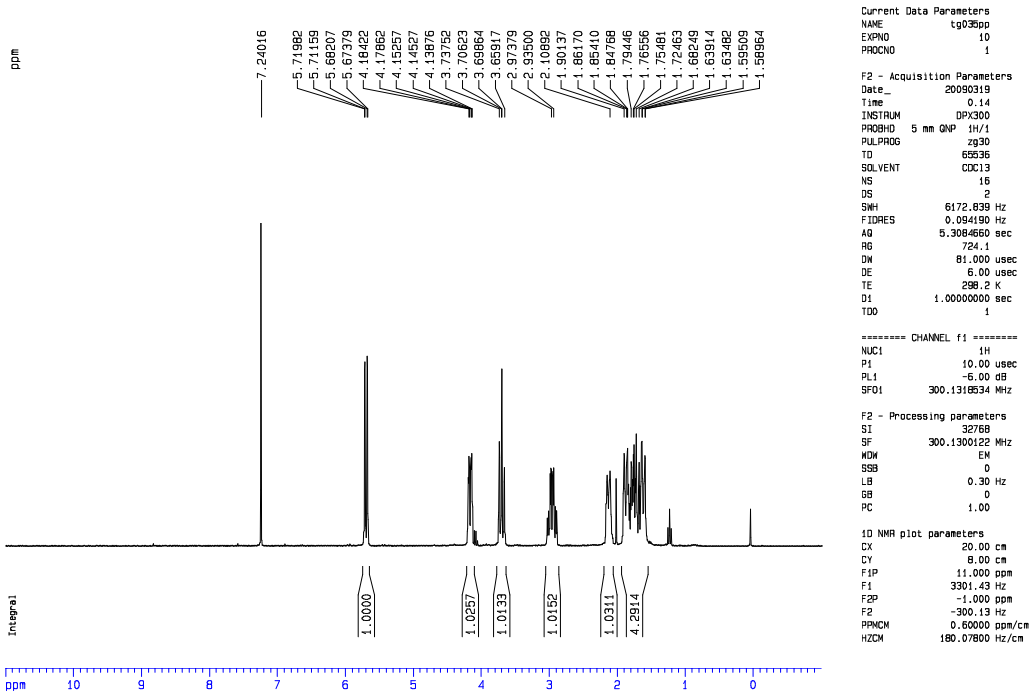
^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.59-1.90 (m, 5H, $3CH_2$), 2.92-2.96 (m, 1H), 3.69-3.73 (m, 1H), 4.14-4.19 (m, 1H), 5.68-5.72 (dd, 1H, J_1 11.3 Hz, J_2 2.4 Hz, H-2).

^{13}C NMR ($CDCl_3$, 75MHz): δ 23.1 (C-5 pyranyl), 24.5 (C-4 pyranyl), 28.6 (C-6 pyranyl), 69.3 (C-3 pyranyl), 85.3 (C-1 pyranyl), 130.9 (C-8), 133.8 (C-5), 150.3 (C-6), 152.9 (C-4), 153.6 (C-2).

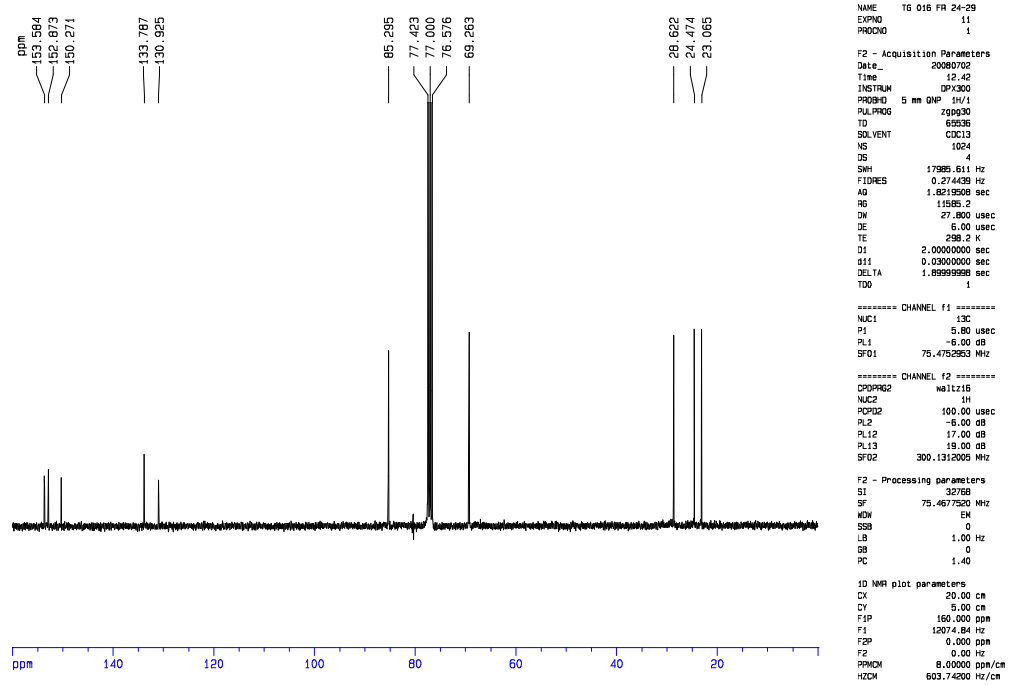
MS (EI). m/z (rel. %): 354/352/350 (0.2/0.5/0.3, M^+), 270/268/266 (10/23/14), 233 (8), 231(6), 85(100), 67(11), 57(18), 53(6), 43(13),39 (9), 29(25)

HR-MS: found 349.9329, calculated for $C_{10}H_9BrCl_2N_4O$ 349.9337.

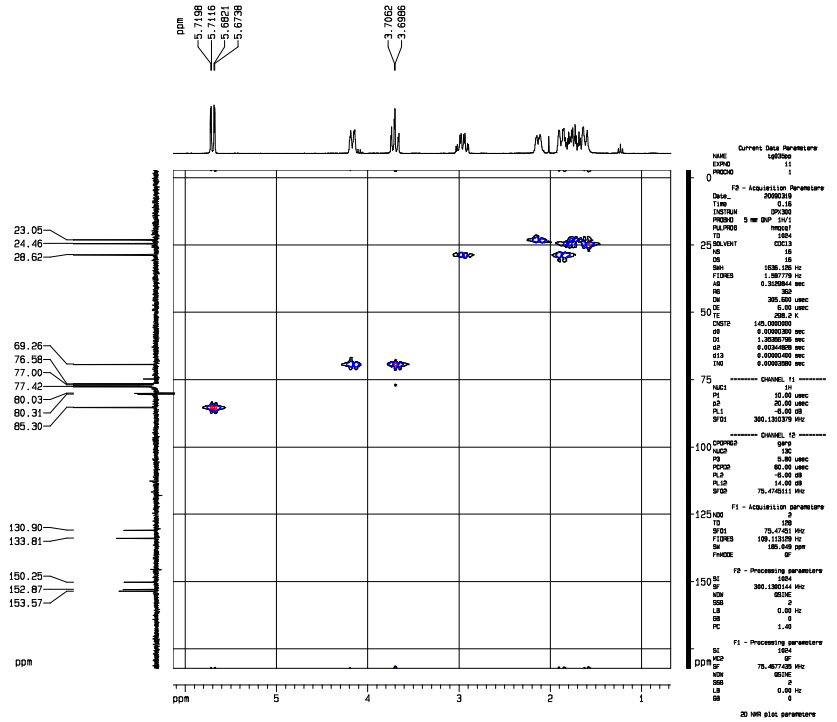
M.p.: 130 ^oC.



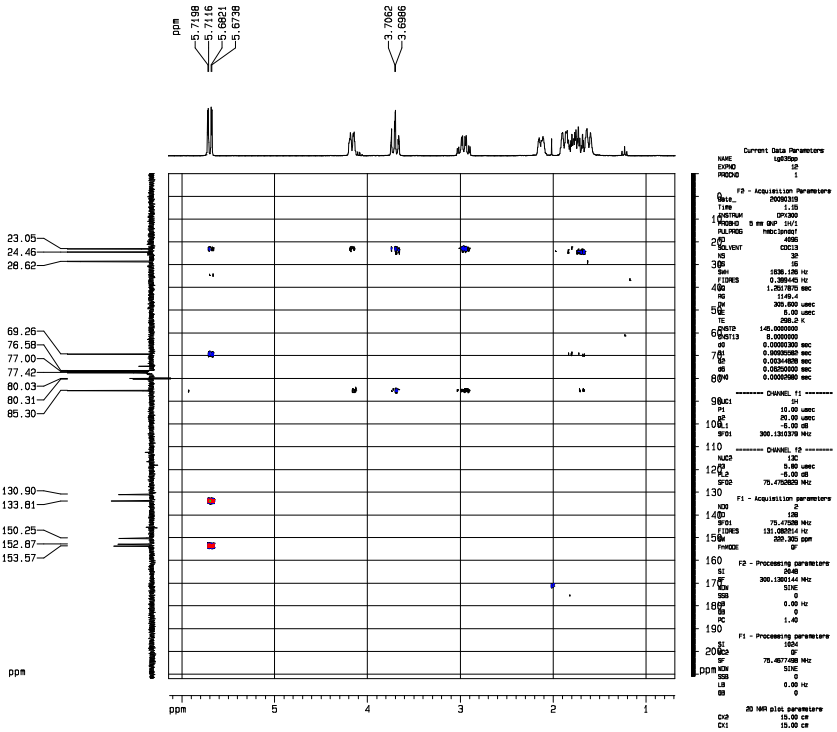
Spectrum 31. ^{1}H NMR of *8-Bromo-2, 6-dichloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine* (**15a**).



Spectrum 32. ^{13}C NMR of *8-Bromo-2, 6-dichloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine* (**15a**).

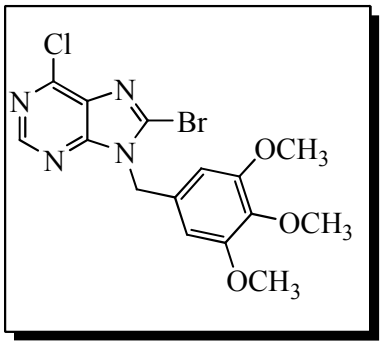


Spectrum 33. HMQC of *8-Bromo-2, 6-dichloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine* (**15a**).



Spectrum 34. HMBC of *8-Bromo-2, 6-dichloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine* (**15a**).

8-Bromo-6-chloro-9-(3,4,5-trimethoxybenzyl)-9H-purine **(15b)**.



15b

Hexane followed by EtOAc- hexane (1:3) and (1:1) were used for flash chromatography; Yield 160 mg (78%) off white solid.

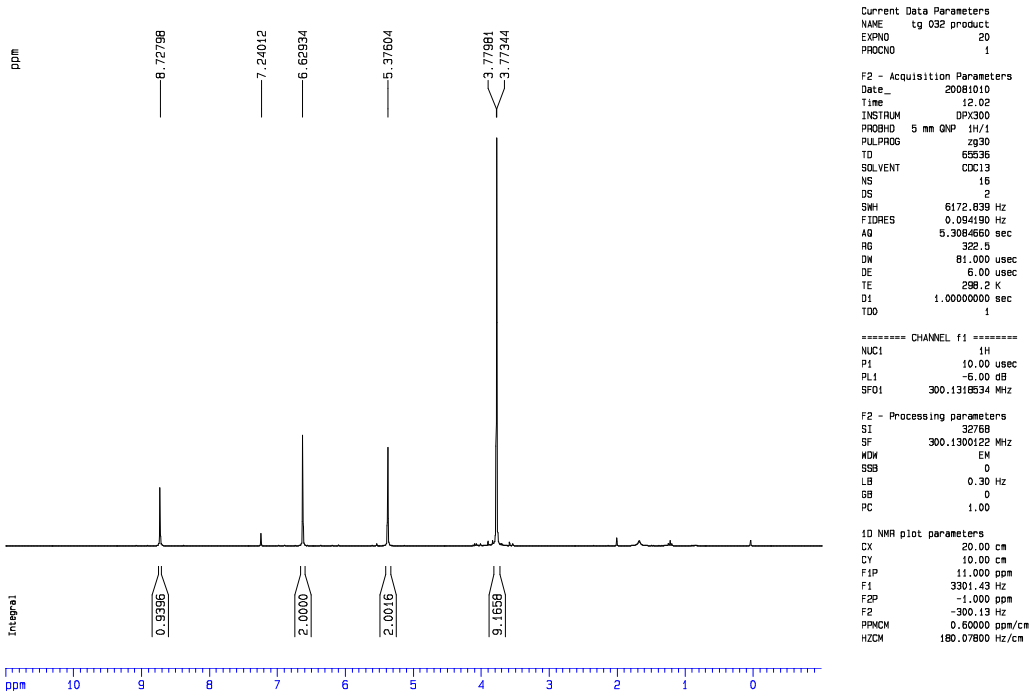
^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.77(s, 9H, 3x OCH_3), 5.37(s,2H, CH_2), 6.62(s, 2H, Ar), 8.72(s, 1H, H-2)

^{13}C NMR ($CDCl_3$, 75 MHz): δ 48.6 (CH_2), 56.1 (3'- OCH_3 and 5'- OCH_3), 60.8 (4'- OCH_3), 105.5 (C-2 and C-6 Ar), 129.5 (C-1 Ar), 131.8 (C-8), 134.1 (C-5), 138.3 (C-4 Ar), 149.6 (C-4), 152.1 (C-2), 152.8 (C-6), 153.5 (C-3 and C-5 Ar).

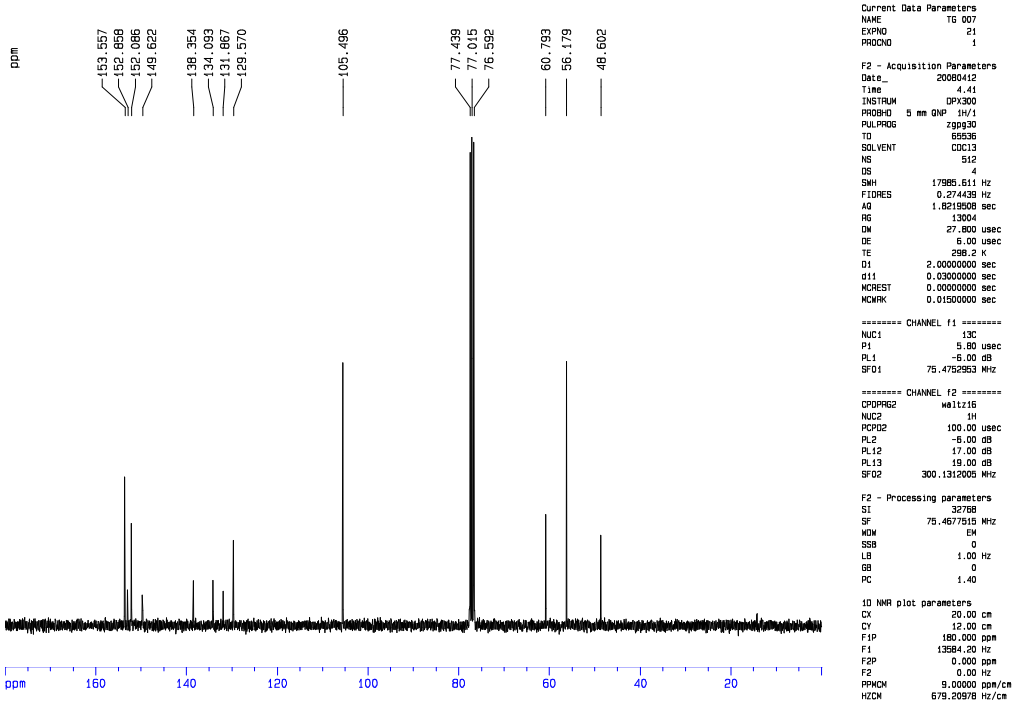
MS (EI). m/z (rel. %): 416/ 414/ 412(10/40/30, M^+), 399(6), 335/333 (8/23), 182(11), 181 (100), 148(6), 136(7), 77(6), 31(0.3).

HR-MS: found 411.9918, calculated for $C_{15}H_{14}BrClN_4O_3$ 411.9938.

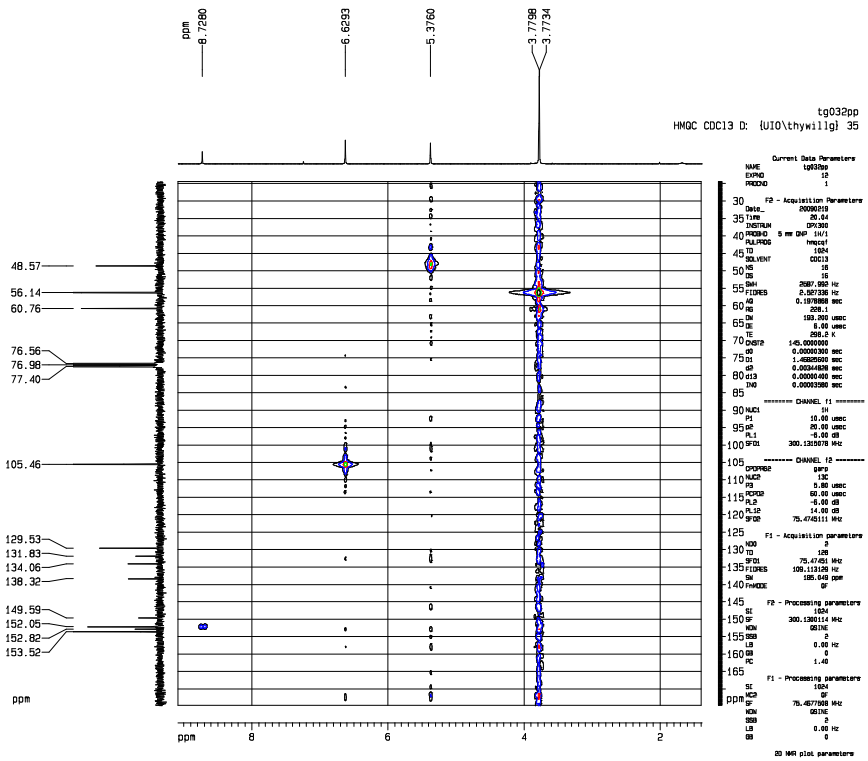
M.p.: 145-148 ^oC.



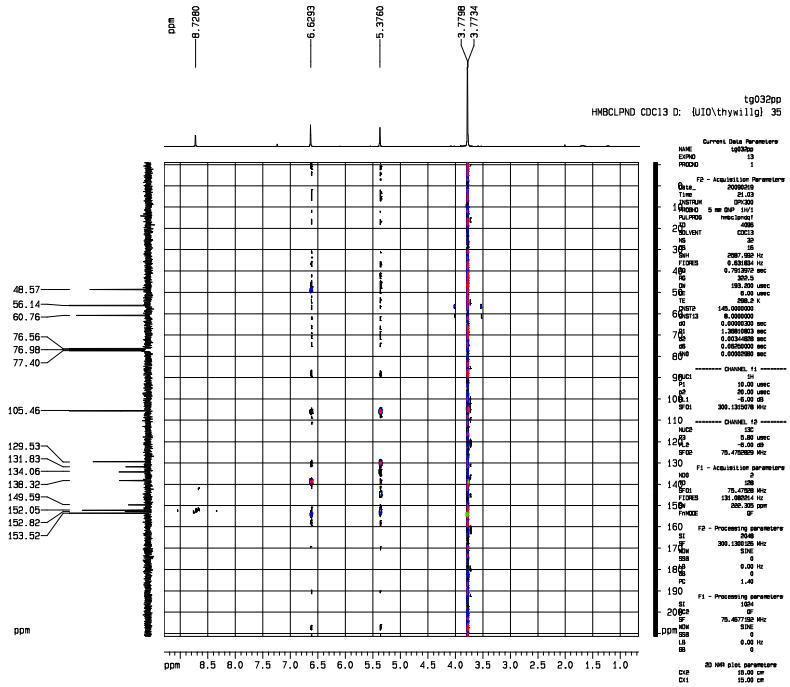
Spectrum 35. [1]H NMR of *8-Bromo-6-chloro-9-(3,4,5-trimethoxybenzyl)-9H-purine* (**15b**).



Spectrum 36. [13]C NMR of *8-Bromo-6-chloro-9-(3,4,5-trimethoxybenzyl)-9H-purine* (**15b**).

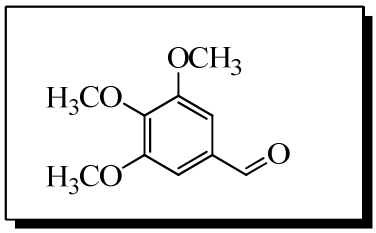


Spectrum 37. HMQC of *8-Bromo-6-chloro-9-(3,4,5-trimethoxybenzyl)-9H-purine* (**15b**).



Spectrum 38. HMBC of *8-Bromo-6-chloro-9-(3,4,5-trimethoxybenzyl)-9H-purine* (**15b**).

***3,4,5-Trimethoxybenzaldehyde* (46b).**



46b

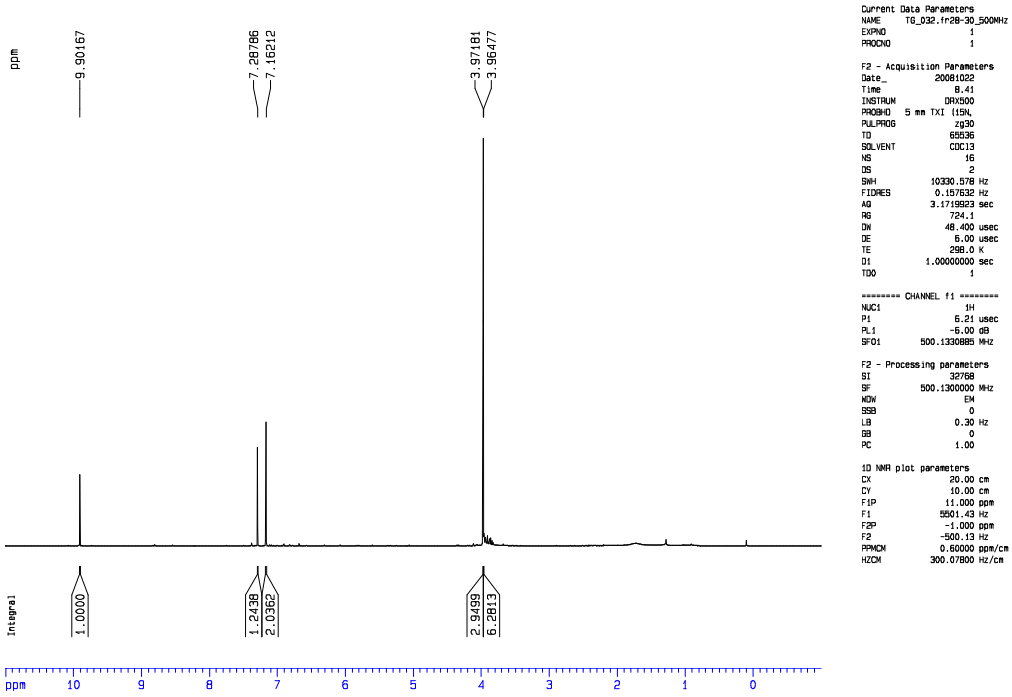
Hexane followed by EtOAc- hexane (1:3) and (1:1) were used for flash chromatography; Yield 8mg (8%) brown solid.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.92(s, 9H, 3x OCH_3), 7.1(s, 2H, Ar), 9.9(s, 1H, CHO)

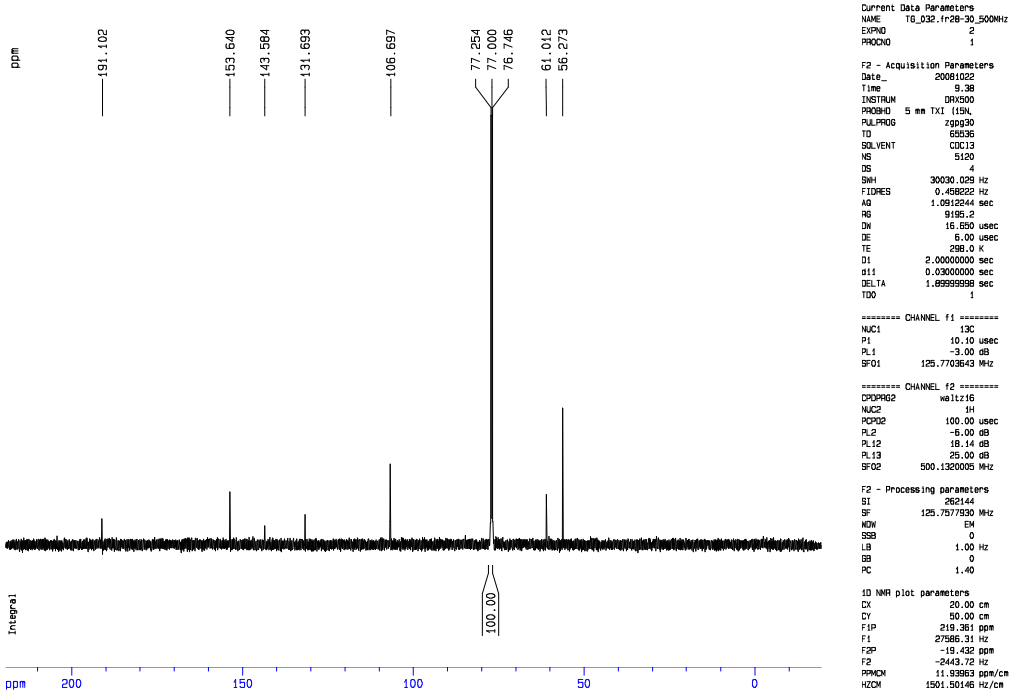
^{13}C NMR ($CDCl_3$, 125 MHz): δ 56.3(3,5-OCH_3) 61.0(4- OCH_3), 106.7(C-6, C-2), 131.7(C-1), 143.6(C-4), 153.6(C-3, C-5), 191.1(CHO).

MS (EI). m/z (rel. %): 196(100, M^+) 181(45), 153(6), 131(5), 125(21), 110(13), 125(21), 110(13), 95(9), 93(8), 77(5), 69(20).

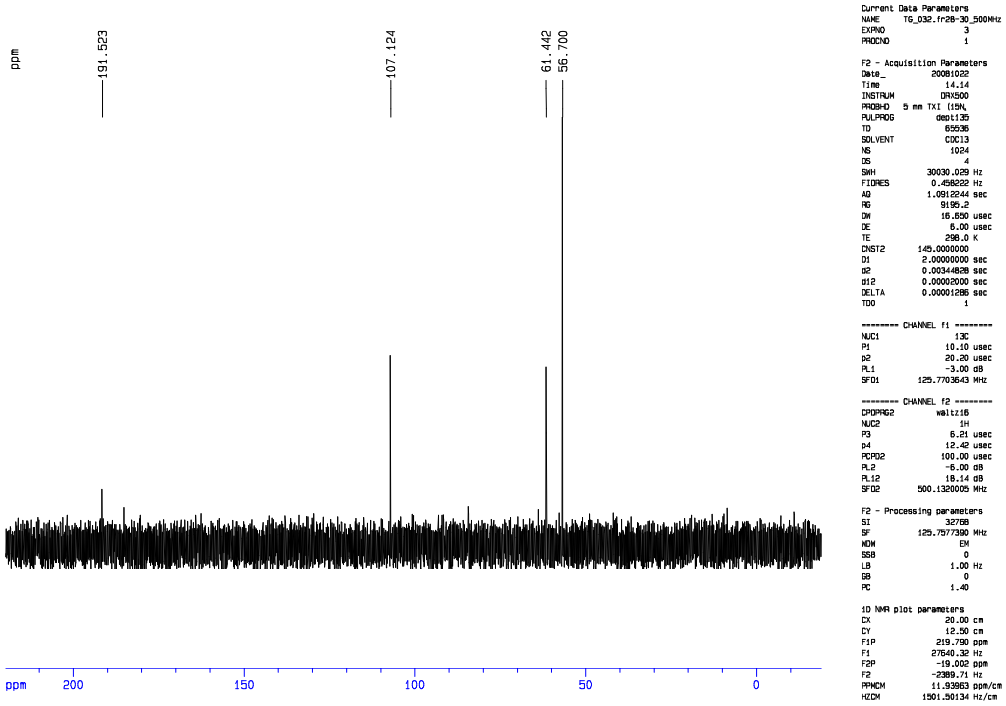
HR-MS: found 196.0743, calculated for $C_{10}H_{12}O_4$ 196.0736.



Spectrum 39. ^{1}H NMR of *3,4,5-Trimethoxybenzaldehyde* (**46b**).

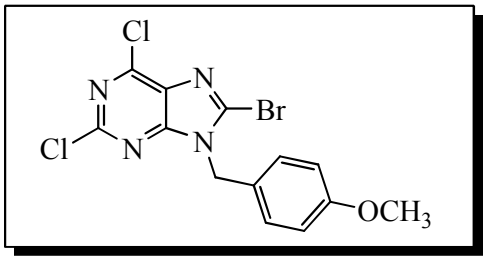


Spectrum 40. ^{13}C NMR of *3,4,5-Trimethoxybenzaldehyde* (**46b**).



Spectrum 41. DEPT 135 of *3,4,5-Trimethoxybenzaldehyde* (**46b**).

8-Bromo-2,6-dichloro-9-(4-methoxybenzyl)-9H-purine **(15c)**.



15c

Hexane followed by EtOAc- hexane (1:6) and (1:2) were used for flash chromatography Yield 154mg (80%) light yellow solid.

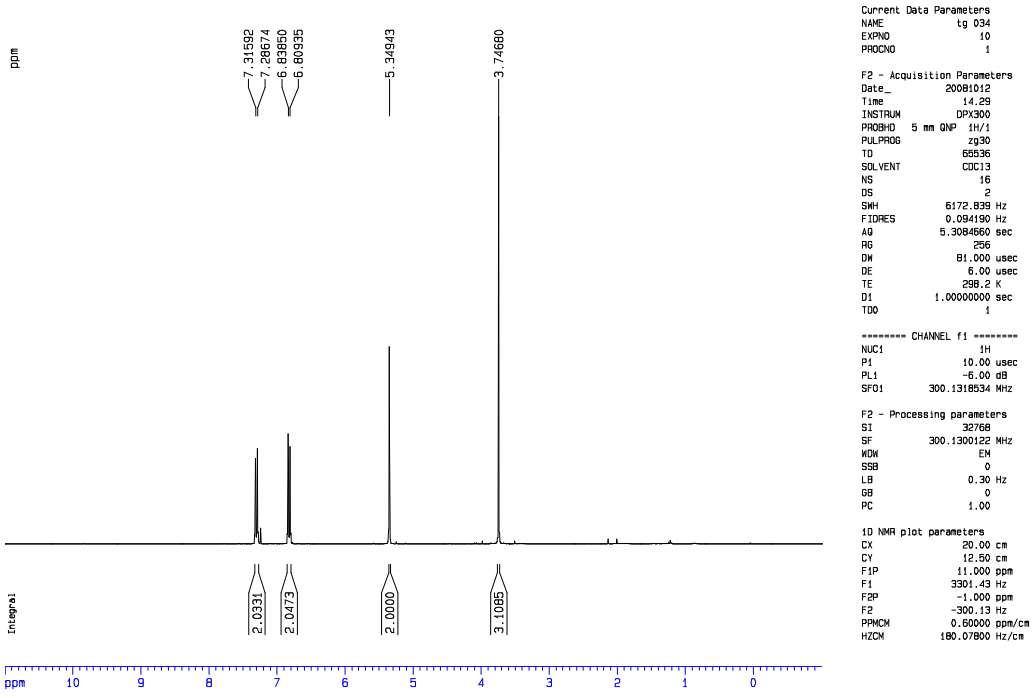
^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.75(s, 3H, OCH_3), 5.35(s, 2H, CH_2), 6.82 (d, J_1 8.8 Hz, 2H, Ar), 7.30 (d, J_1 8.8Hz, 2H, Ar).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 48.1 (CH_2), 55.3 (OCH_3), 114.4 (C-3 and C-5 Ar), 125.7 (C-1 Ar) , 129.7 (C-2 and C6 Ar), 130.8 (C-8), 134.6 (C-5), 150.1 (C-6), 153.1 (C-4), 153.9 (C-2), 159.9 (C-4 Ar).

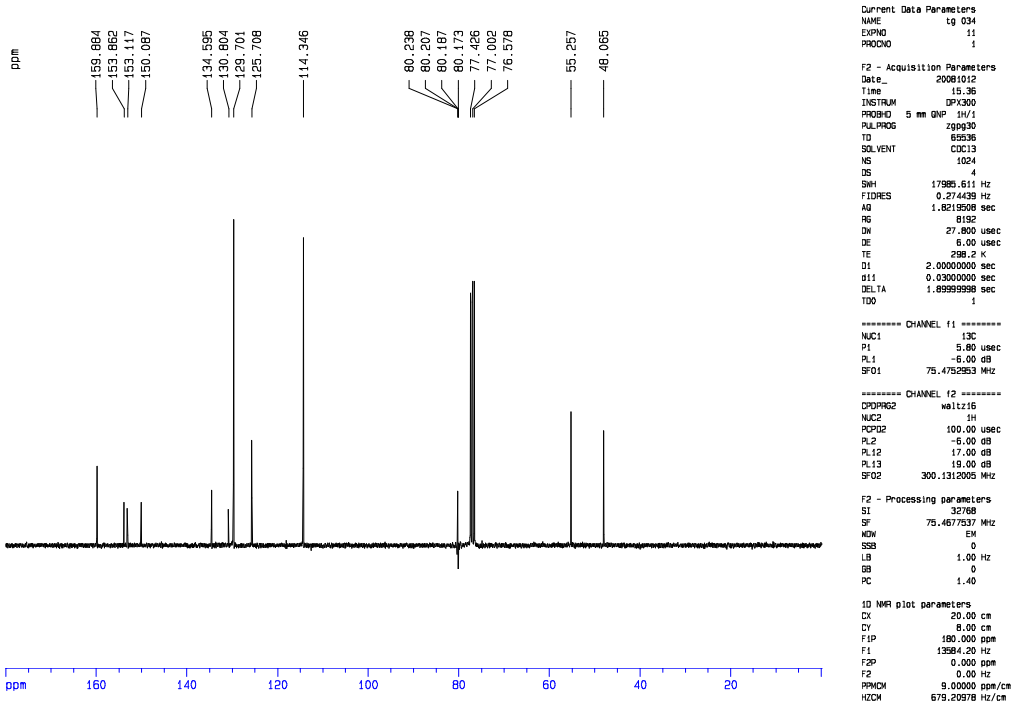
MS (EI). m/z (rel. %): 390/388/386 (3/7/4), 309(1), 305(0.1), 193(0.4), 122(11), 121(100), 78(8), 77(7), 65(2).

HR-MS: found 385.9334, calculated for $C_{13}H_9BrCl_2N_4O$ 385.9337.

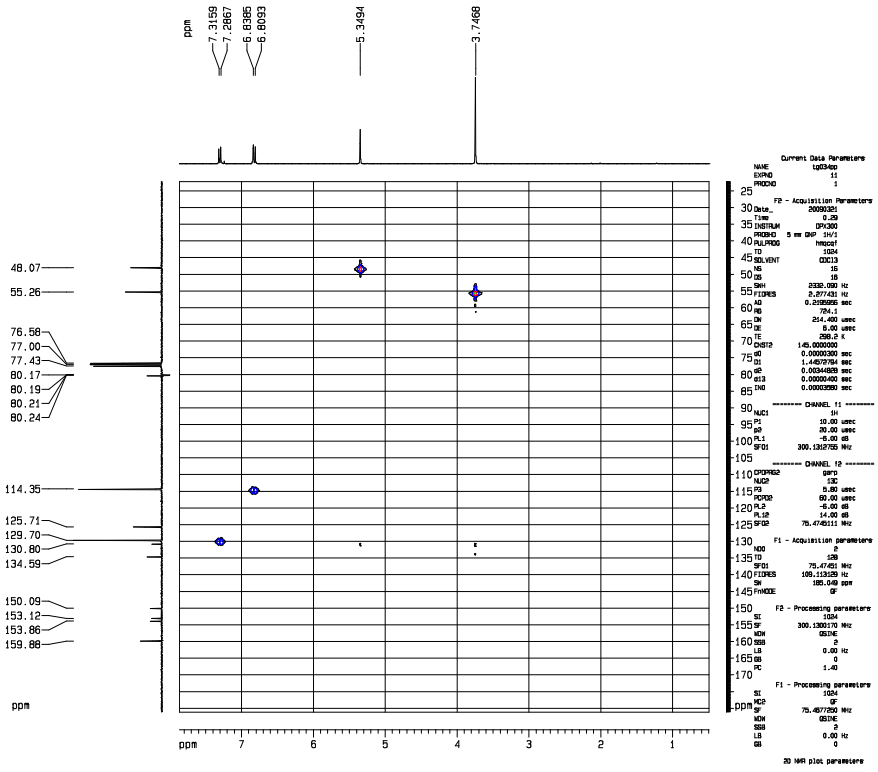
M.p.: 143-145 ^{o}C.



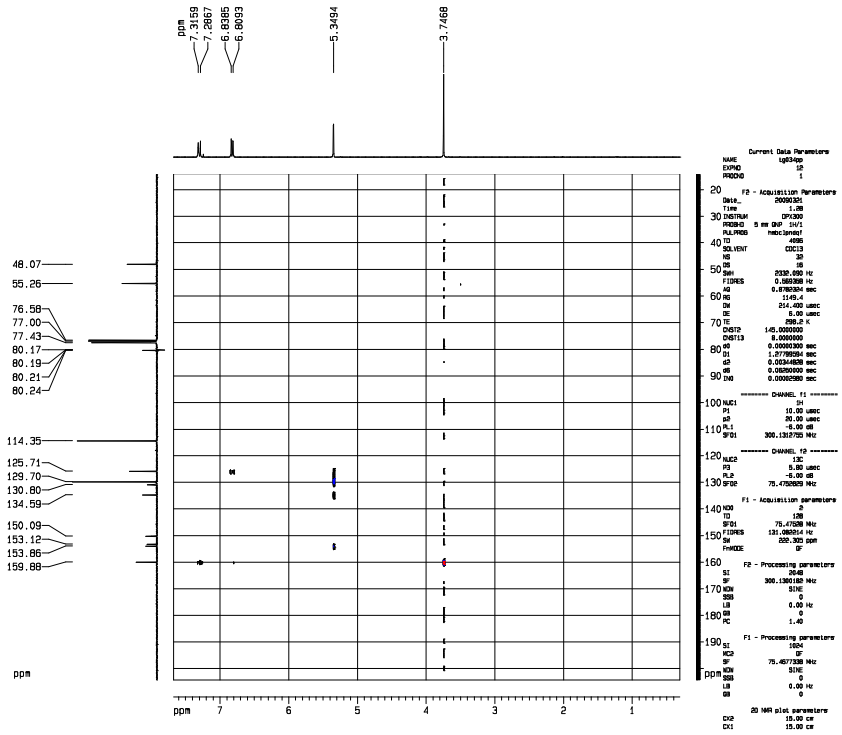
Spectrum 42 . ^{1}H NMR of *8-Bromo-2,6-dichloro-9-(4-methoxybenzyl)-9H-purine* (**15c**).



Spectrum 43. ^{13}C NMR of *8-Bromo-2,6-dichloro-9-(4-methoxybenzyl)-9H-purine* (**15c**).

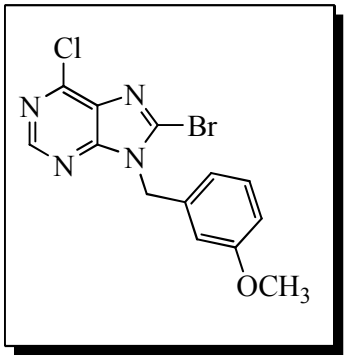


Spectrum 44. HMQC of *8-Bromo-2,6-dichloro-9-(4-methoxybenzyl)-9H-purine* (**15c**).



Spectrum 45. HMBC of *8-Bromo-2,6-dichloro-9-(4-methoxybenzyl)-9H-purine* (**15c**).

8-Bromo-6-chloro-9-(3-methoxybenzyl)-9H-purine **(15d)**.



15d

Hexane followed by EtOAc- hexane (1:6) and (1:3) were used for flash chromatography Yield 44mg (25%) pale yellow solid.

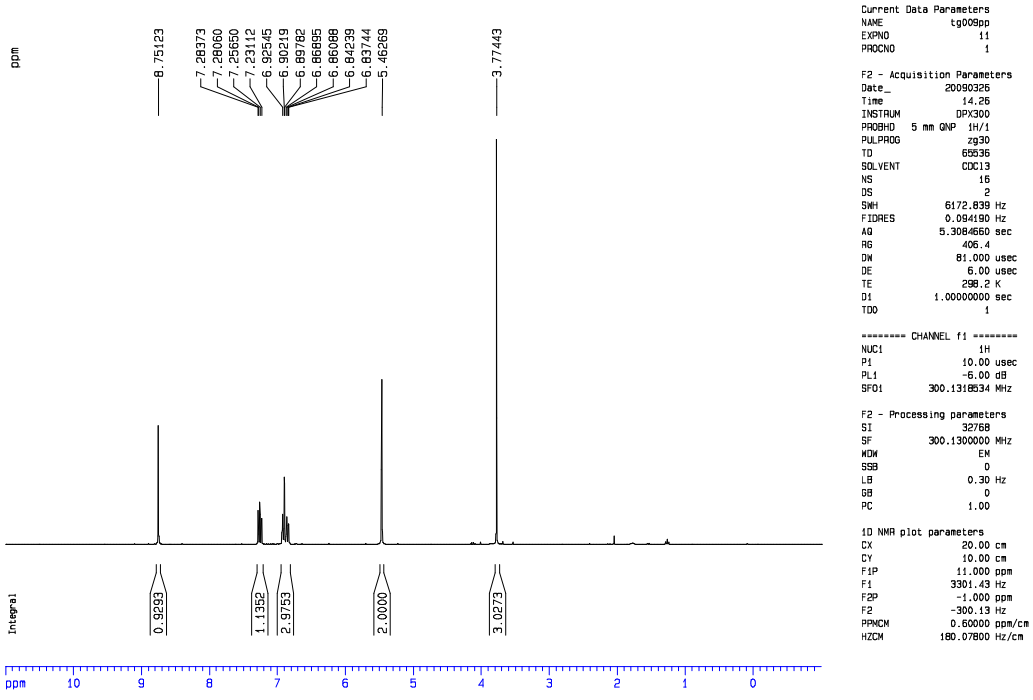
^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.78(s, 3H), 5.47(s, 2H), 6.91-6.84 (m, 2H), 6.93(s, 1H), 7.29-7.27(m, 1H), 8.76(s, 1H).

^{13}C NMR ($CDCl_3$, 75MHz): δ 48.2 (CH_2), 55.2 (OCH_3), 113.6 (C-4 Ar), 113.9 (C-2 Ar), 120.0 (C-6 Ar), 130.1 (C-5 Ar), 131.8 (C-5), 134.2 (C-8), 135.5 (C-1 Ar), 149.5 (C-4), 152.1 (C-2), 152.9 (C-6), 159.9 (C-3 Ar).

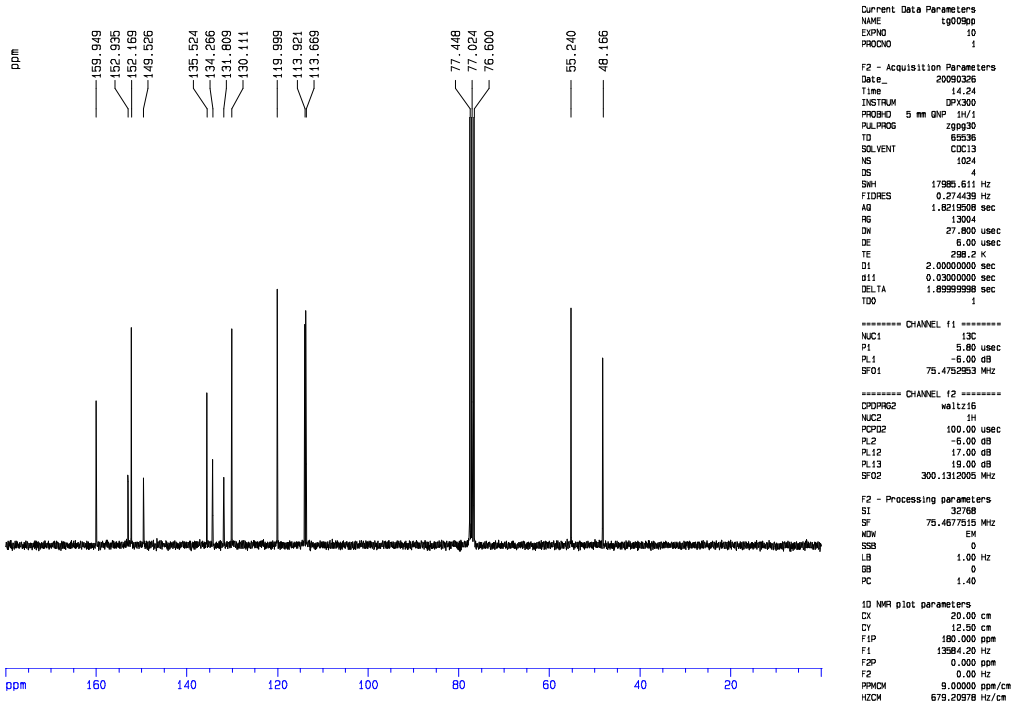
MS (EI). m/z (rel. %): 356/354/352 (8/30/24, M^+), 275(34), 274 (17), 273(100), 122(6) 121(68), 91(16), 78(9), 65(5).

HR-MS: found 351.9718 calculated for $C_{13}H_{10}BrClN_4O$ 351.9727.

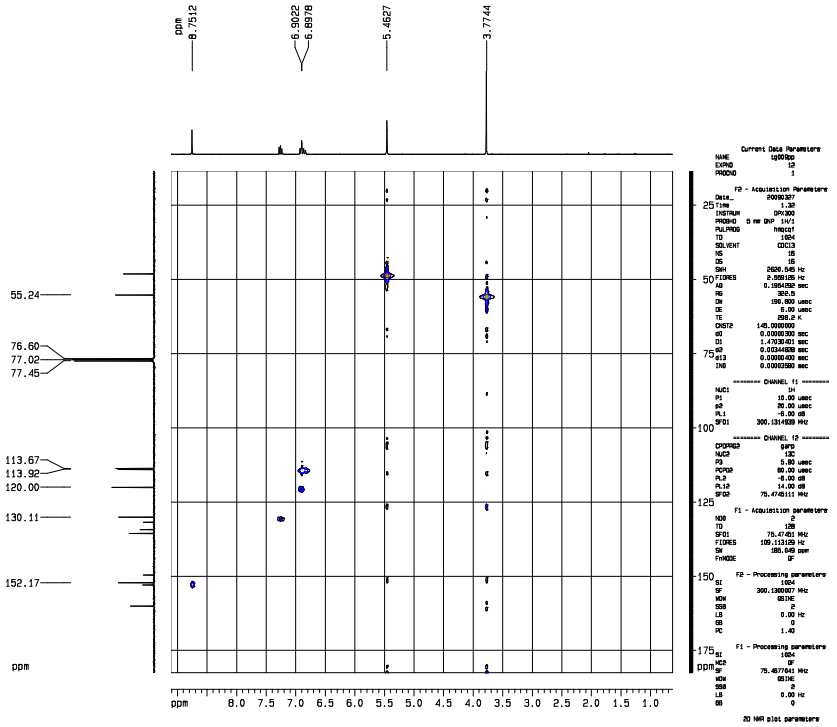
M.p.: 103-106 ^oC.



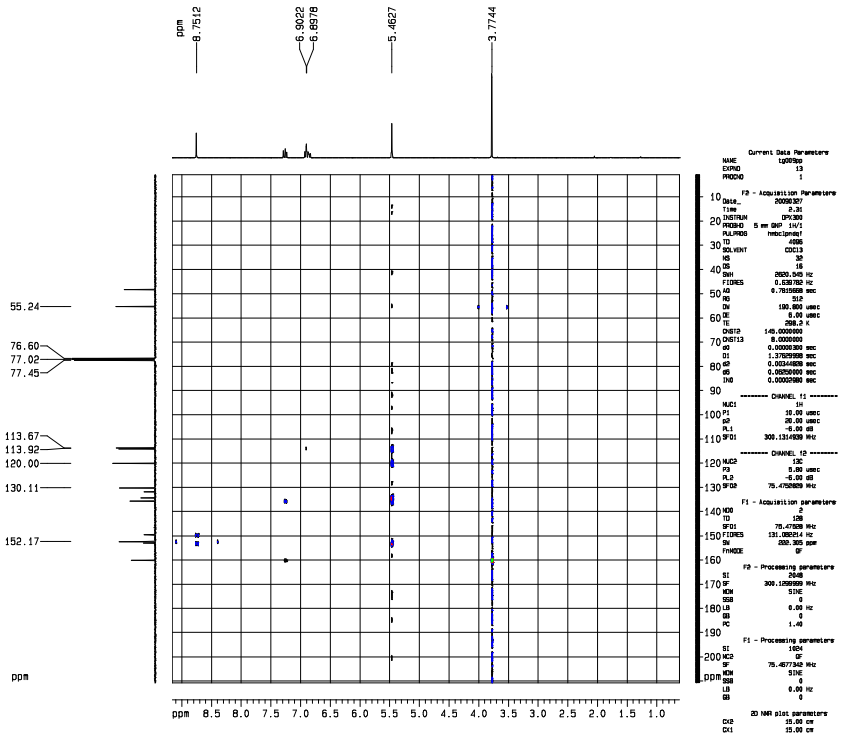
Spectrum 46 ^{1}H NMR of *8-Bromo-6-chloro-9-(3-methoxybenzyl)-9H-purine* (**15d**).



Spectrum 47. ^{13}C NMR of *8-Bromo-6-chloro-9-(3-methoxybenzyl)-9H-purine* (**15d**).

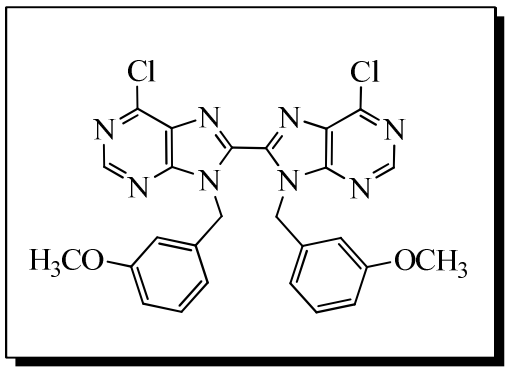


Spectrum 48. HMQC of *8-Bromo-6-chloro-9-(3-methoxybenzyl)-9H-purine* (**15d**).



Spectrum 49. HMBC of *8-Bromo-6-chloro-9-(3-methoxybenzyl)-9H-purine* (**15d**).

8,8'-bis[6-Chloro-9-(3-methoxybenzyl)-9H-purine] **(45d)**



45d

Hexane followed by EtOAc- hexane (1:6) and (1:2) were used for flash chromatography. Yield 35.3mg (26%) white.

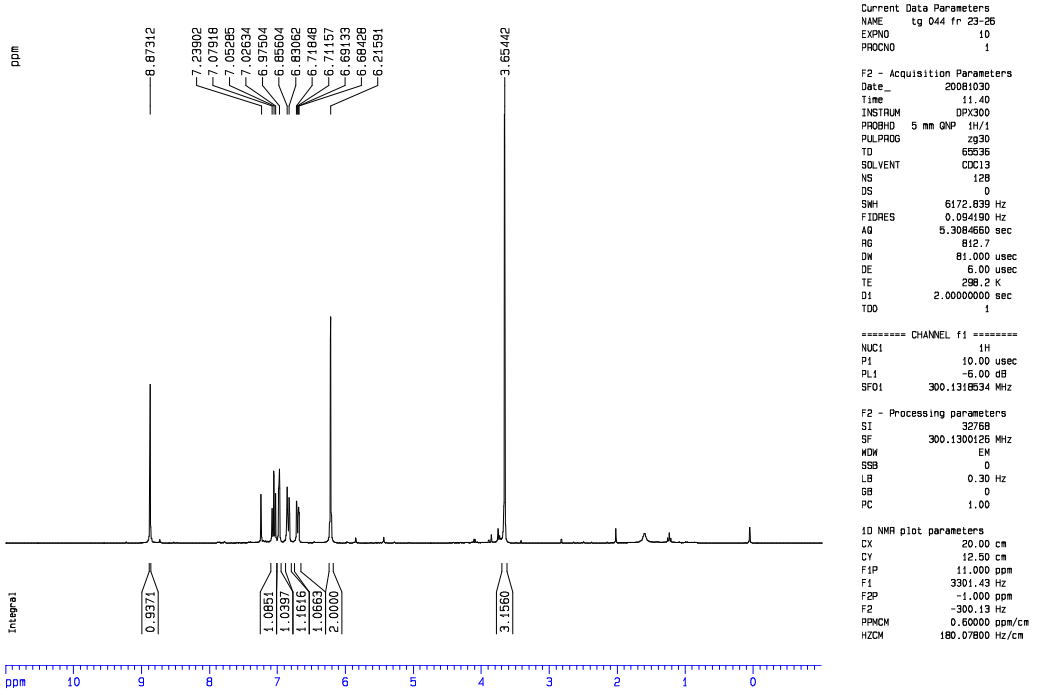
^{1}H NMR (CDCl3, 300 MHz): δ 3.65(s, 6H, 2x OCH_3), 6.21(s, 4H, 2xCH_2), 6.68-6.72(dd, 2H, J_1 8.1Hz, J_2 2.1Hz, Ar), 6.84.(d, J_1=7.6, 2H, Ar), 7.05(t, 2H, J_1=7.9 Hz, Ar), 8.9(s, 2H, 2xH-2).

13C NMR (CDCl3, 75MHz) δ 48.4 (CH_2), 55.1 (OCH_3), 113.6 (C-6 Ar), 114.0 (C-2 Ar), 120.4 (C-4 Ar), 129.6 (C-5 Ar), 130.8 (C-5), 137.2 (C-1 Ar), 143.3 (C-8), 152.2 (C-6), 153.1 (C-4), 153.4 (C-4), 159.6 (C-3 Ar) .

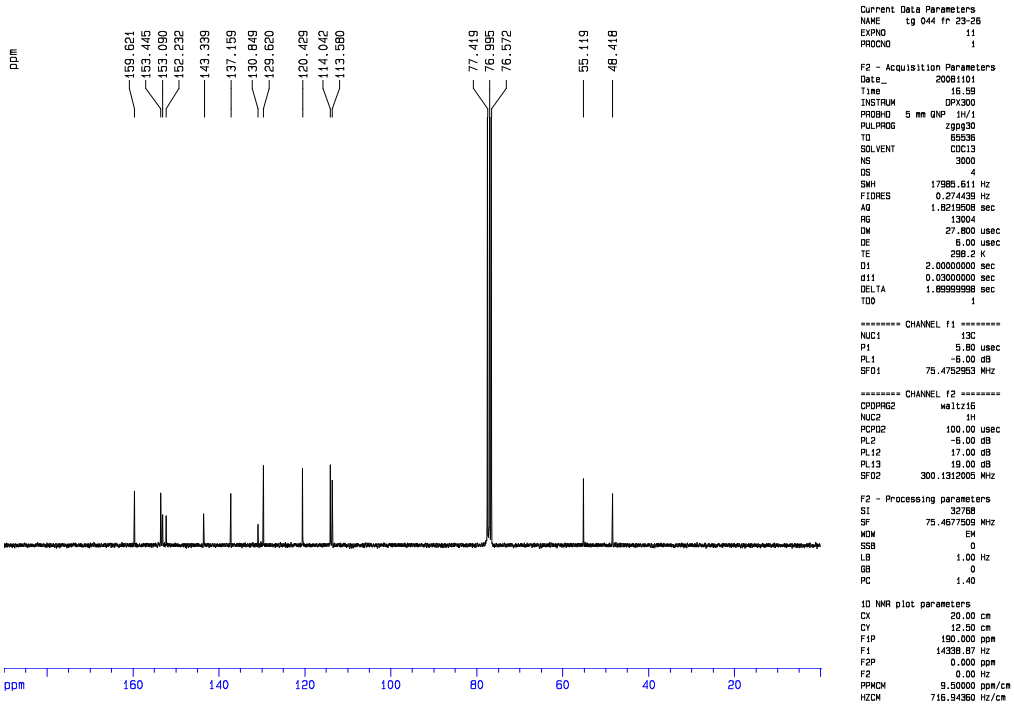
MS (EI). m/z (rel. %): 550/548/546 (5/36/53), M^+), 429/427/425(11/66/100), 426(22), 240(31), 121(93), 122(9), 92(3), 91(34), 78(16), 77(12), 65(8), 51(1).

HR-MS: found 546.1080 calculated for $C_{26}H_{20}Cl_2N_8O_2$ 546.1086.

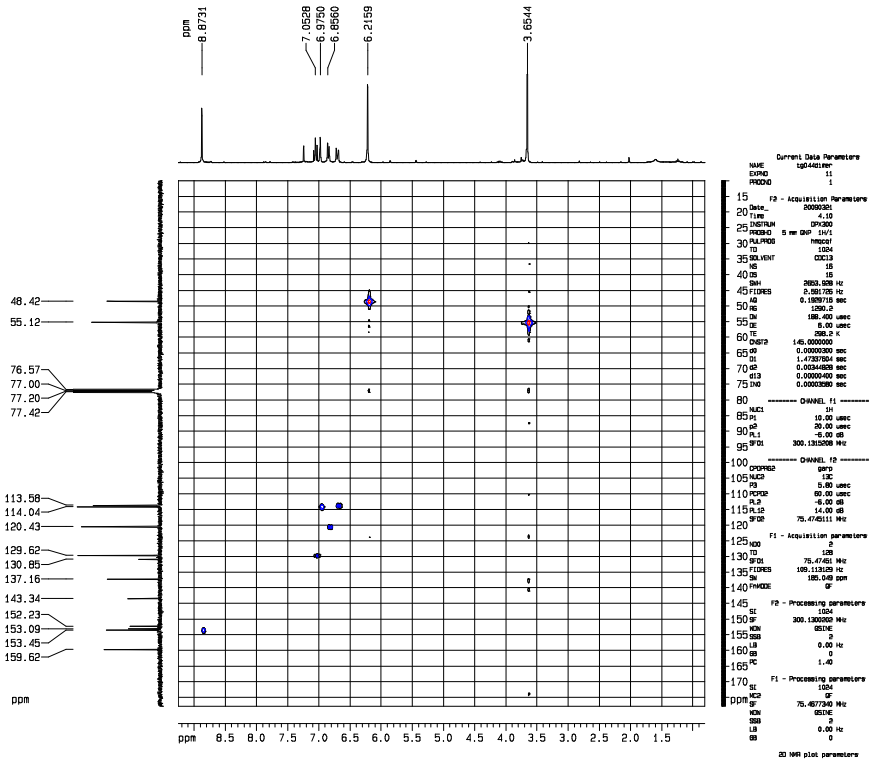
M.p.: 218-220^{o}C.



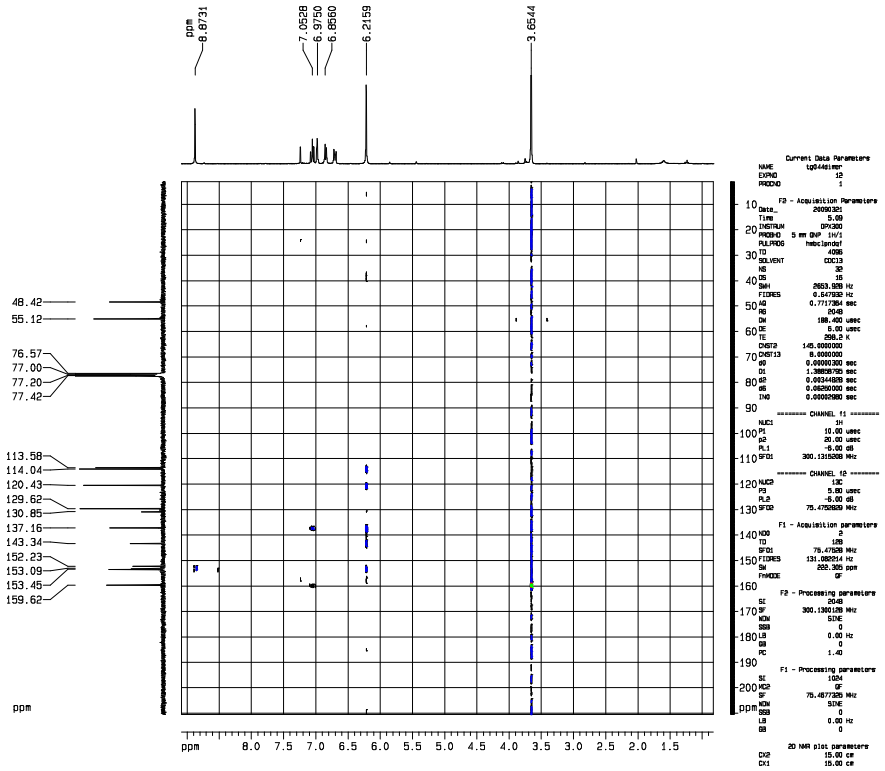
Spectrum 50. ^{1}H NMR of *8,8'-bis[6-Chloro-9-(3-methoxybenzyl)-9H-purine]* (**45d**).



Spectrum 51. ^{13}C NMR of *8,8'-bis[6-Chloro-9-(3-methoxybenzyl)-9H-purine]* (**45d**).

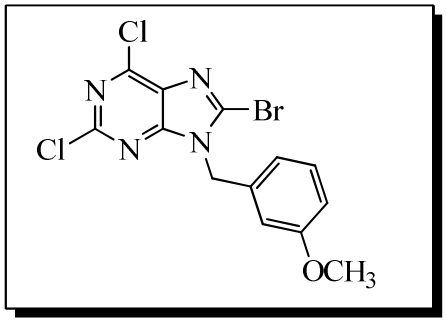


Spectrum 52. HMQC of *8,8'-bis[6-Chloro-9-(3-methoxybenzyl)-9H-purine]* (**45d**).



Spectrum 53. HMQC of *8,8'-bis[6-Chloro-9-(3-methoxybenzyl)-9H-purine]* (**45d**)

8-Bromo-2,6-dichloro-9-(3-methoxybenzyl)-9H-purine **(15e)**



15e

Hexane followed by EtOAc- hexane (1:6) and (1:2) were used for flash chromatography. Yield 108mg (56%) pale yellow solid.

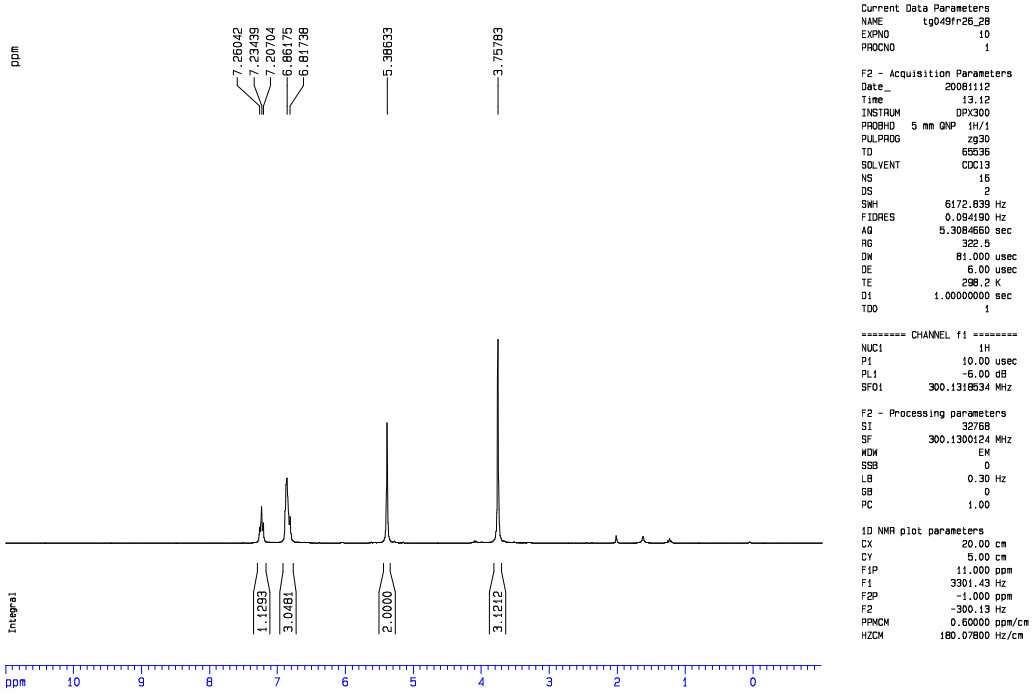
^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.76(s, 3H, OCH_3), 5.40(s, 2H, CH_2), 6.81-6.87(m,3H, Ar), 7.27(t,1H, J_1 8.0 Hz, Ar).

^{13}C NMR ($CDCl_3$, 75MHz): δ 48.4 (CH_2), 55.3 (OCH_3), 113.9 (C-2 Ar), 114.0 (C-4 Ar), 120.0 (C-6 Ar), 130.2 (C-5 Ar), 130.7 (C-8), 134.7 (C-5), 135.0 (C-1 Ar), 150.2 (C-6), 153.2 (C-4), 154.0 (C-2), 160.0 (C-3 Ar).

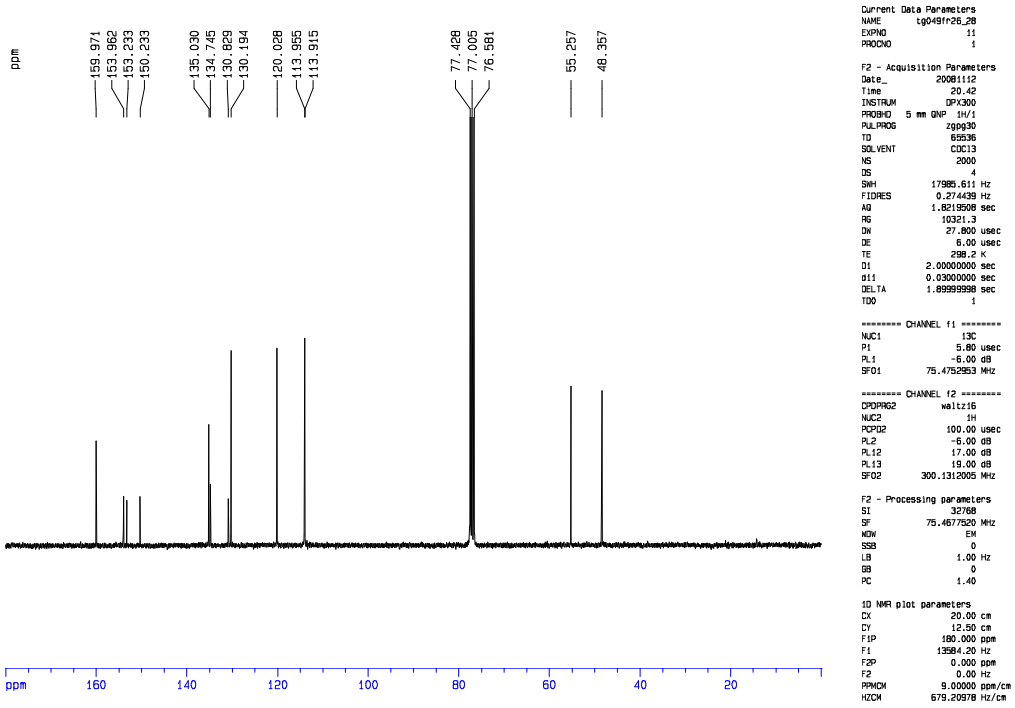
MS (EI). m/z (rel. %): 390/388/386 (11/23/14, M^+), 307(67), 122(9), 121(100), 91(19), 78(11), 65(6), 65(6).

HR-MS: found 385.9338 calculated for $C_{13}H_9BrCl_2N_4O$. 385.9337

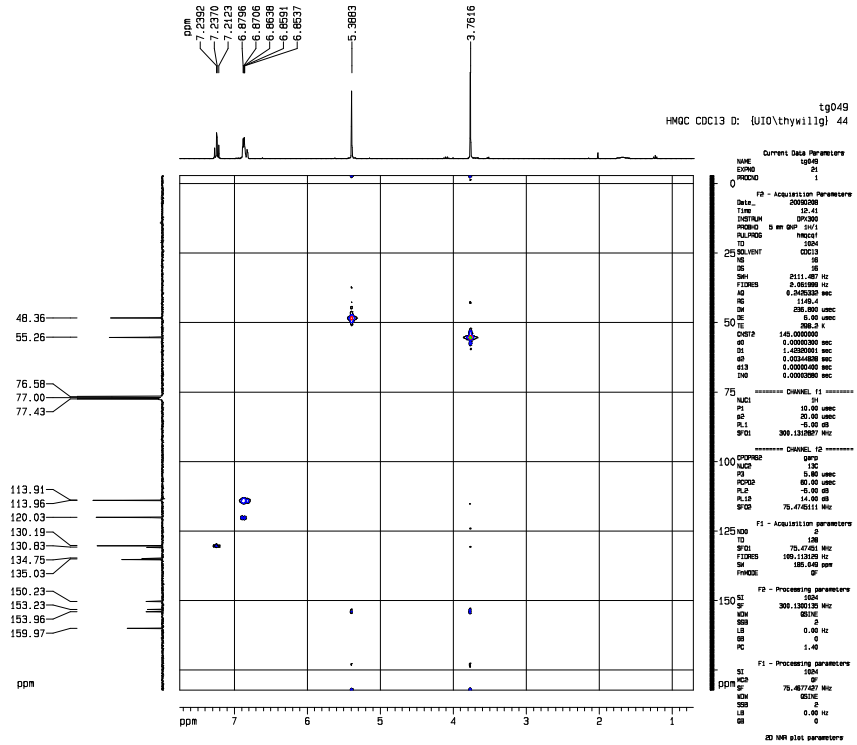
M.p.: 144-147 °C.



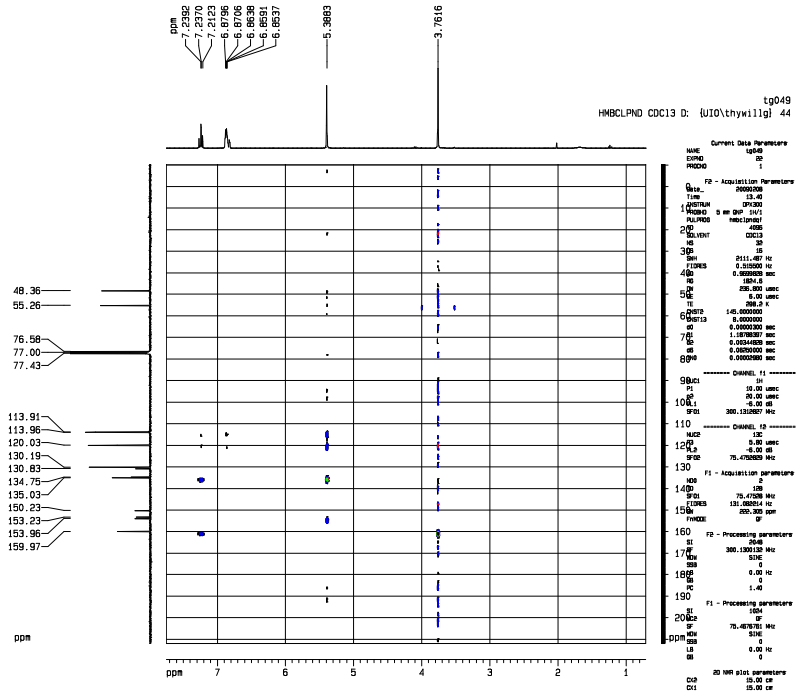
Spectrum 54. ^{1}H NMR of *8-Bromo-2,6-dichloro-9-(3-methoxybenzyl)-9H-purine* (**15e**).



Spectrum 55. ^{13}C NMR of *8-Bromo-2,6-dichloro-9-(3-methoxybenzyl)-9H-purine* (**15e**).

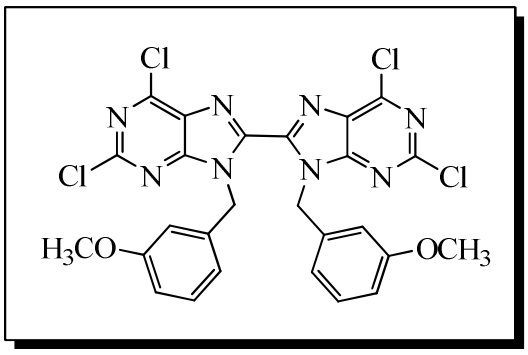


Spectrum 56. HMQC of *8-Bromo-2,6-dichloro-9-(3-methoxybenzyl)-9H-purine* (**15e**).



Spectrum 57. HMBC of *8-Bromo-2,6-dichloro-9-(3-methoxybenzyl)-9H-purine* (**15e**).

***8,8'-bis[2,6-dichloro-9-(3-methoxybenzyl)-9Hpurine]* (45e).**



45e

Hexane followed by EtOAc-hexane (1:6) and (1:2) were used for flash chromatography Yield 12.5mg (8%) colourless solid.

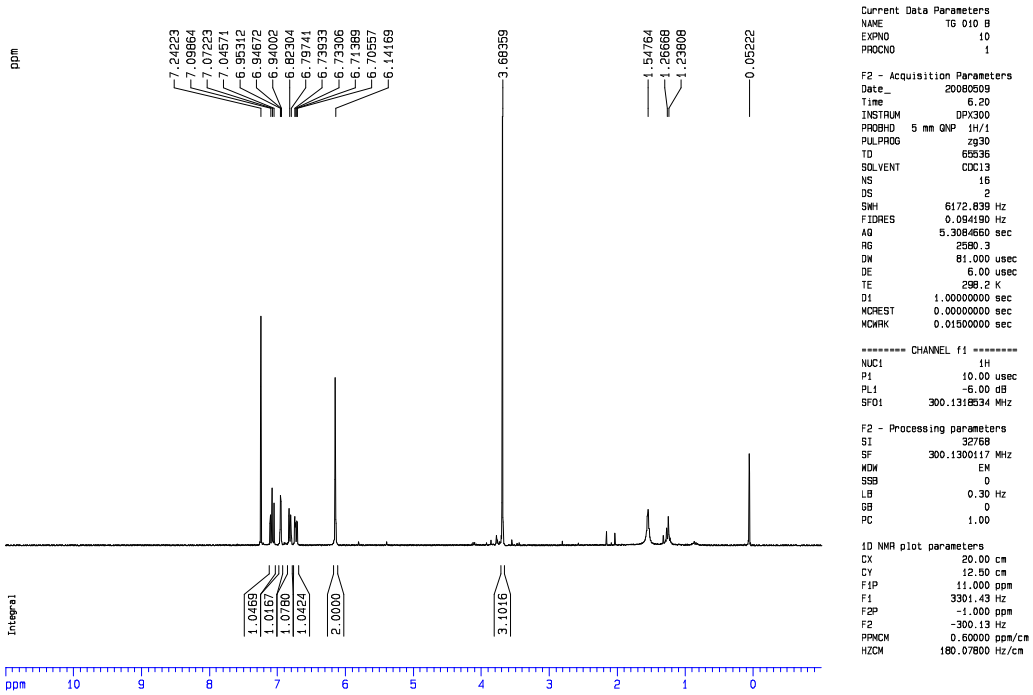
^{1}H NMR (CDCl3, 300 MHz): δ 3.68 (s, 6H, 2x OCH_3) , 6.14 (s, 4H, CH_2), 6.72 (dd, 4H, J_1 8.2Hz, J_2 2.0Hz, Ar), 6.82 (s, 2H, Ar), 7.07(t, 2H, J_1 8.0 Hz, Ar).

13C NMR (CDCl3, 75MHz) δ 48.8 (CH_2), 55.2 (OCH_3), 113.8 (C-6 Ar), 114.1 (C-2 Ar), 120.4 (C-4), 129.8 (C-4 Ar), 130.0 (C-5), 136.7 (C-1 Ar), 143.6 (C-8), 153.1 (C-6), 154.3 (C-6), 154.8 (C-4), 159.7 (C-3 Ar).

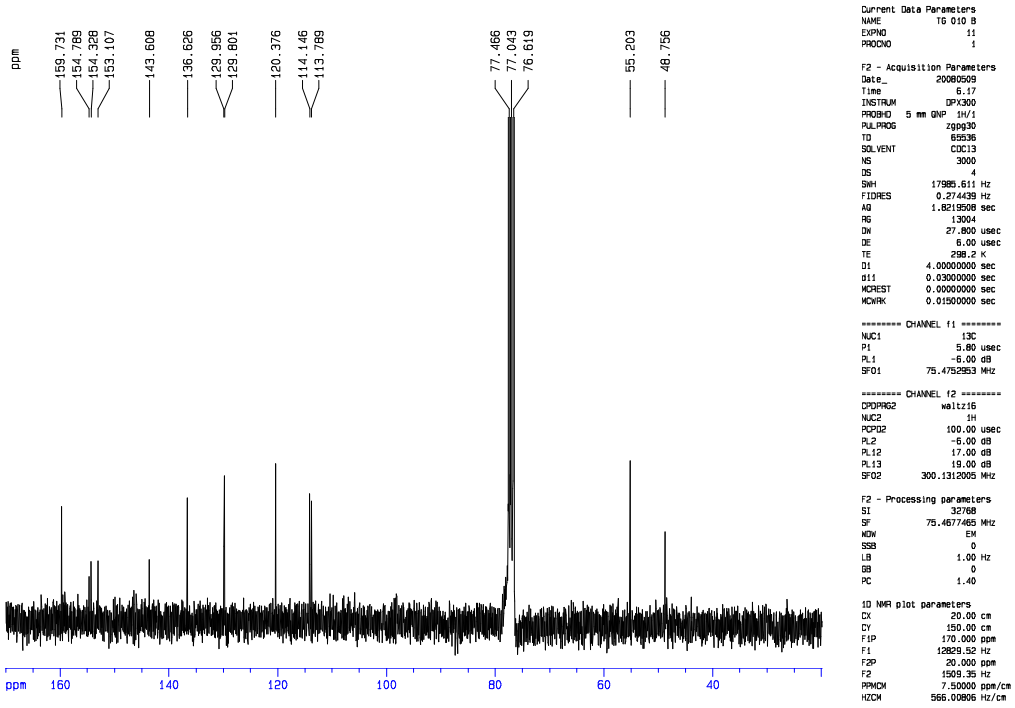
MS (EI). m/z(rel. %): 618/616/614 (7/13/10, M+), 497/495/493(15/34/26), 388(6), 309/307(16/26) 240(36), 121(100), 91(22), 78(12), 65(6), 39(3).

HR-MS: found 614.0323 calculated for $C_{26}H_{18}Cl_4N_8O_2$ 614.0307.

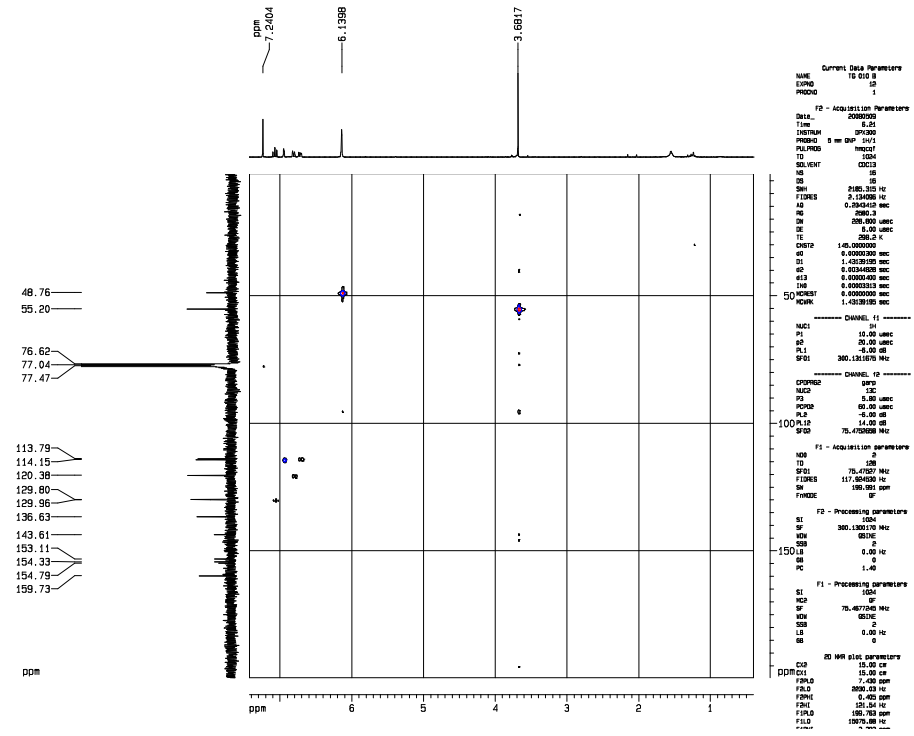
M.p.: 251-254°C.



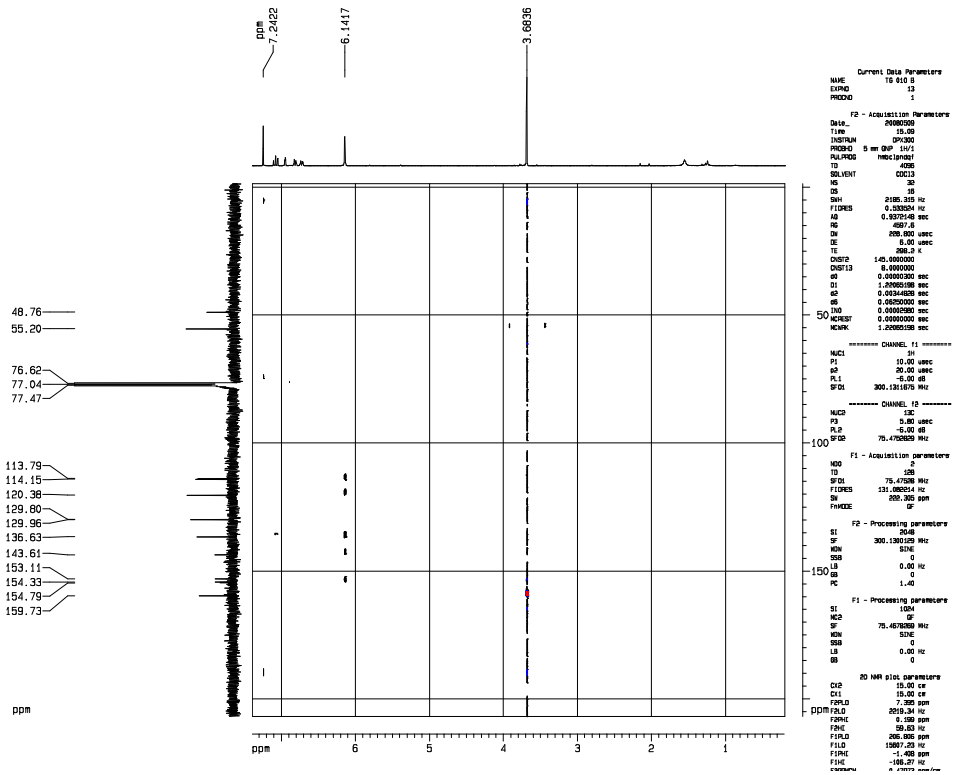
Spectrum 58. [1] H NMR of *8,8'-bis[2,6-dichloro-9-(3-methoxybenzyl)-9Hpurine]* (**45e**)



Spectrum 59. ^{13}C NMR of *8,8'-bis[2,6-dichloro-9-(3-methoxybenzyl)-9Hpurine]* (**45e**)

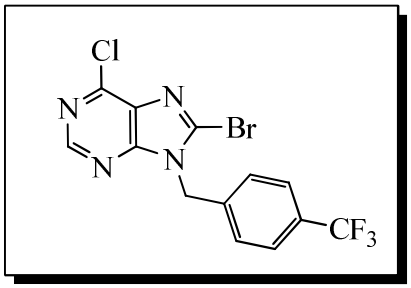


Spectrum 60. HMQC of *8,8'-bis[2,6-dichloro-9-(3-methoxybenzyl)-9Hpurine]* (**45e**)



Spectrum 61. HMBC of *8,8'-bis[2,6-dichloro-9-(3-methoxybenzyl)-9Hpurine]* (**45e**)

8-Bromo-6-chloro-9-(4-(trifluoromethylbenzyl)-9H-purine **(15f)**



15f

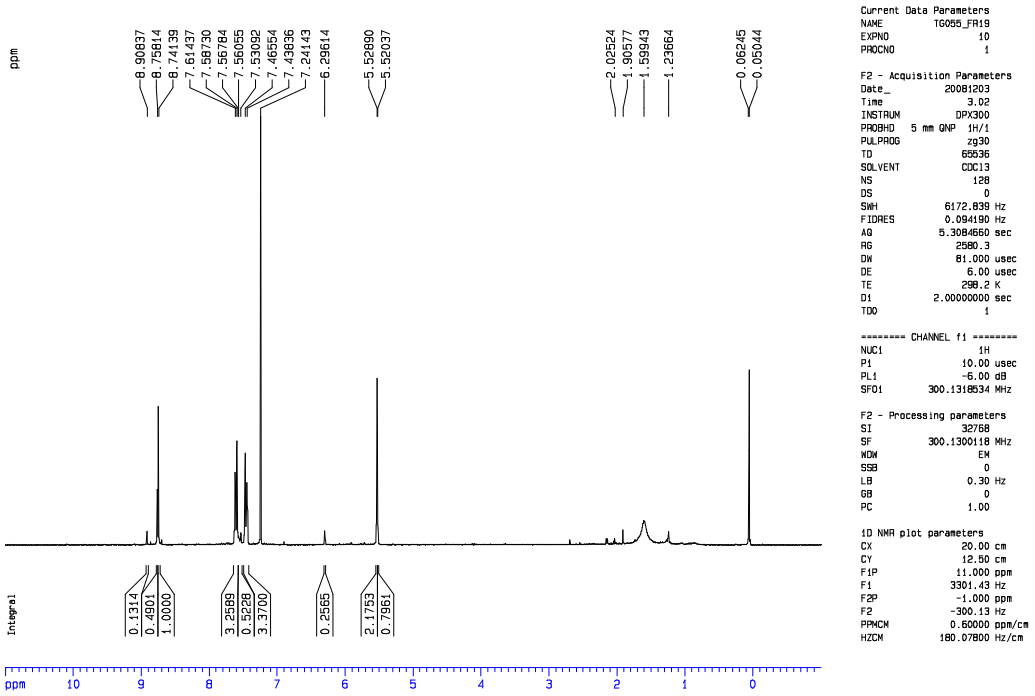
Hexane followed by EtOAc-hexane (1:2) and (1:1) were used for flash chromatography; Yield 16mg (ca 8%),

^{1}H NMR ($CDCl_3$, 300 MHz) 5.52 (s, 2H, CH_2), 7.45(d, J=8.1Hz, 2H, Ar) 7.60 (d, J=8.1Hz, 2H, Ar), 8.74 (s, 1H, H-2)

MS (EI). m/z (rel. %): 392/390 (31/24), 389 (8), 313/311 (25/73), 160 (9), 159 (100), 119 (7), 109 (24).

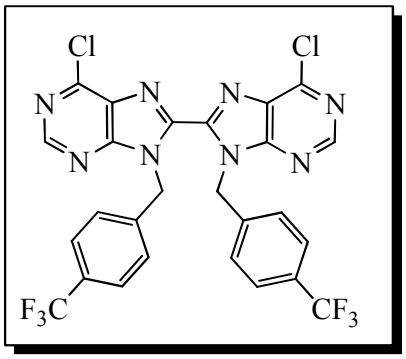
HR-MS: found 389.9484 calculated for $C_{13}H_7BrClF_3N_4$ 389.9495.

M. p. 173-175°C.



Spectrum 62. ^{1}H of *8-Bromo-6-chloro-9-(4-(trifluoromethylbenzyl)-9H-purine* (**15f**).

8,8'-bis[6-chloro-9-(4-(trifluoromethylbenzyl)-9H-purine] **(45f)**



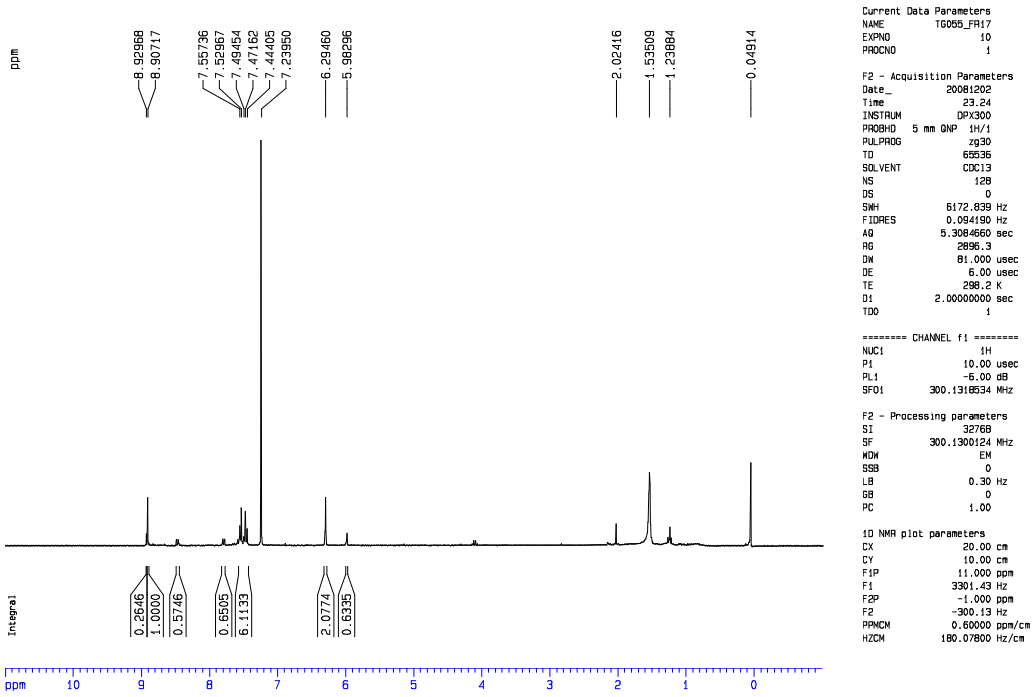
45f

Hexane followed by EtOAc-hexane (1:2) and (1:1) were used for flash chromatography; Yield 7mg (ca 4%),

^{1}H NMR ($CDCl_3$, 300 MHz): 6.29 (s, 4H, 2xCH_2), 7.46(d, J=8.3Hz, 4H, Ar) 7.54(d, J=8.3Hz, 4H, Ar), 8.91 (s, 2H, 2xH-2)

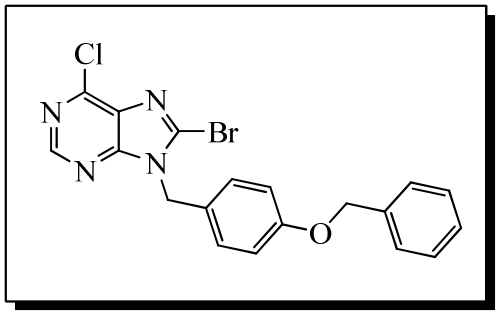
MS (EI). m/z (rel. %): 624/622 (36/54), 465/463 (65/100), 159(26), 121 (5), 109 (9).

HR-MS: found 622.0609 calculated for $C_{26}H_{14}Cl_2F_6N_8$ 622.0623.



Spectrum 63. ^{1}H of *8,8'-bis[6-chloro-9-(4-(trifluoromethylbenzyl)-9H-purine]* (**45f**)

8-Bromo-6-chloro-9-(4-benzyloxybenzyl)-9H-purine **(15g)**.



15g

Hexane followed by EtOAc- hexane (1:6) and (1:2) were used for flash chromatography; Yield 182mg (84%) pale yellow solid.

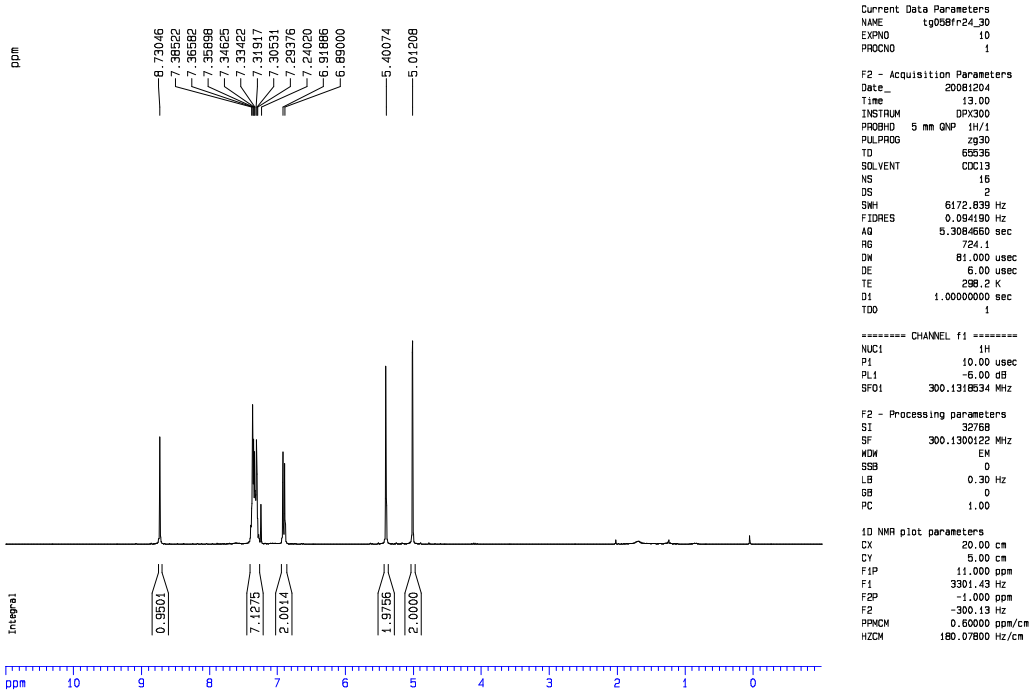
^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.01 (s, 2H, CH_2), 5.40 (s, 2H, CH_2), 6.89-7.39 (m, 9H, Ar), 8.73 (s, 1H, H-2).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 47.9 (N-CH_2), 70.0 (O-CH_2), 115.3 (C-3' and C-5' Ar), 126.5 (C-8), 127.4 (C-2" and C-6" Ar), 128.1 (C-4" Ar), 128.6 (C-3" and C-5" Ar), 129.7 (C-2' and C-6' Ar), 131.9 (C-1' Ar), 134.2 (C-5), 136.6 (C-1" Ar), 149.5 (C-4), 152.1 (C-2), 152.9 (C-6), 159.0 (C-4' Ar).

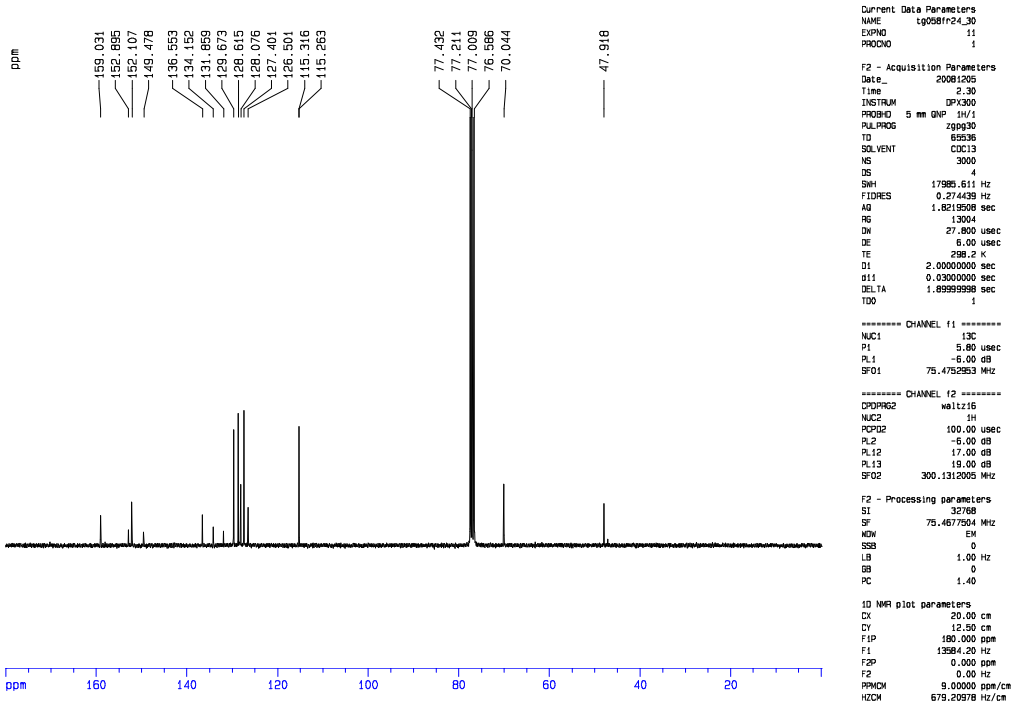
MS (EI). m/z (rel. %): 432/430/428 (2/8/6), 386/384 (2/4), 339 (1), 229(1), 120(1), 105(1), 106(1), 92(11), 91(100), 90(2), 89(2), 52(2), 51(2).

HR-MS: found 428.0030 calculated for $C_{19}H_{14}BrClN_4O$ 428.0040.

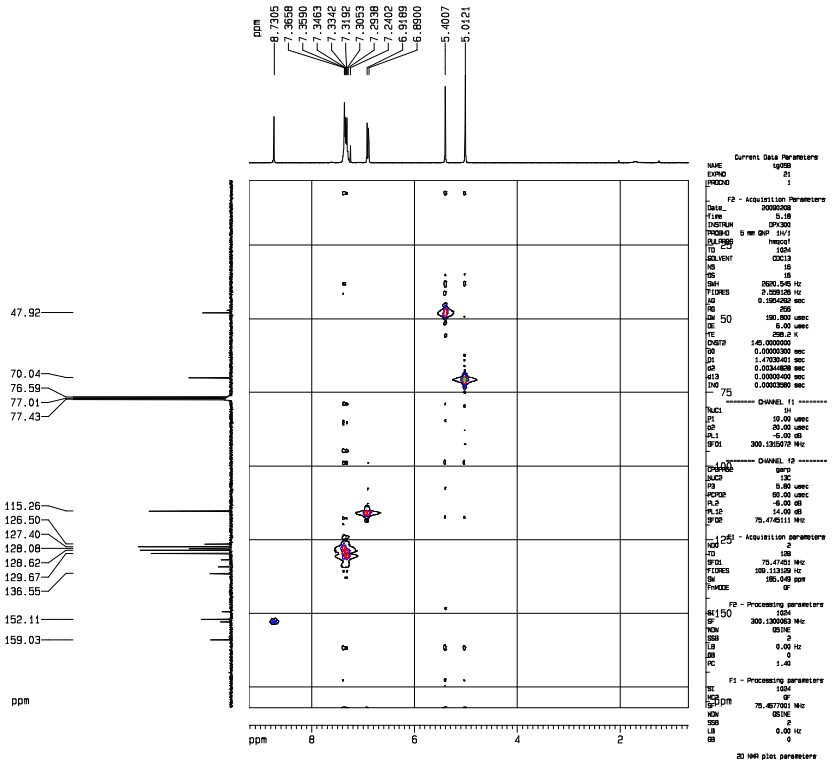
M. p.: 103-105°C.



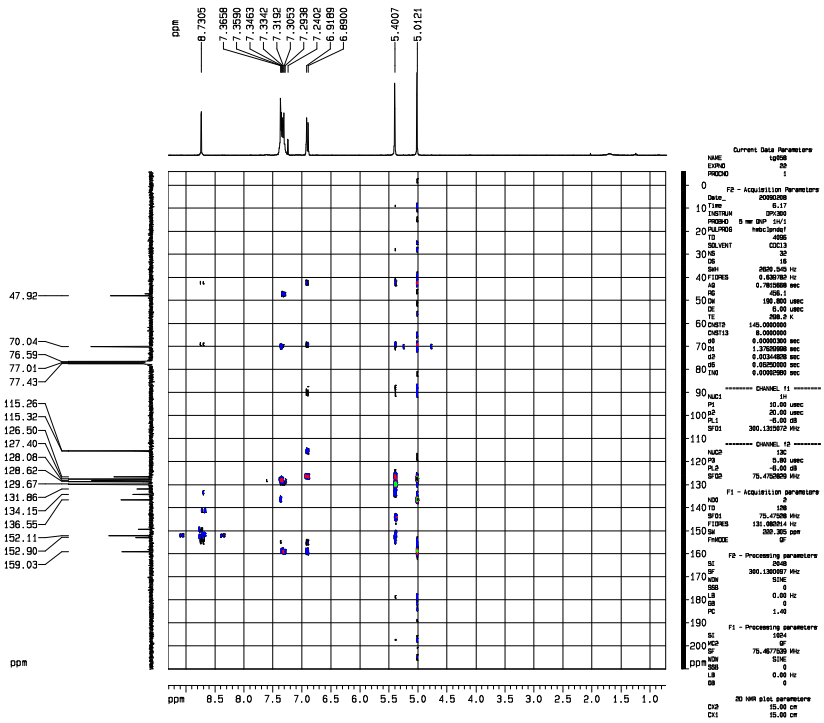
Spectrum 64. ^{1}H NMR of *8-Bromo-6-chloro-9-(4-benzyloxybenzyl)-9H-purine* (**15g**).



Spectrum 65. ^{13}C NMR of *8-Bromo-6-chloro-9-(4-benzyloxybenzyl)-9H-purine* (**15g**).

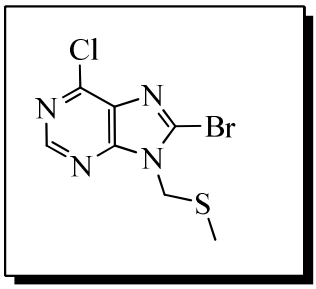


Spectrum 66. HMQC of *8-Bromo-6-chloro-9-(4-benzyloxybenzyl)-9H-purine* (**15g**).



Spectrum 67. HMBC of *8-Bromo-6-chloro-9-(4-benzyloxybenzyl)-9H-purine* (**15g**).

***8-Bromo-6-chloro-9-(methylthiomethyl)-9H-purine* (15h)**



15h

Hexane followed by EtOAc- hexane (1:2) were used for flash chromatography Yield 126mg (86%) off white solid.

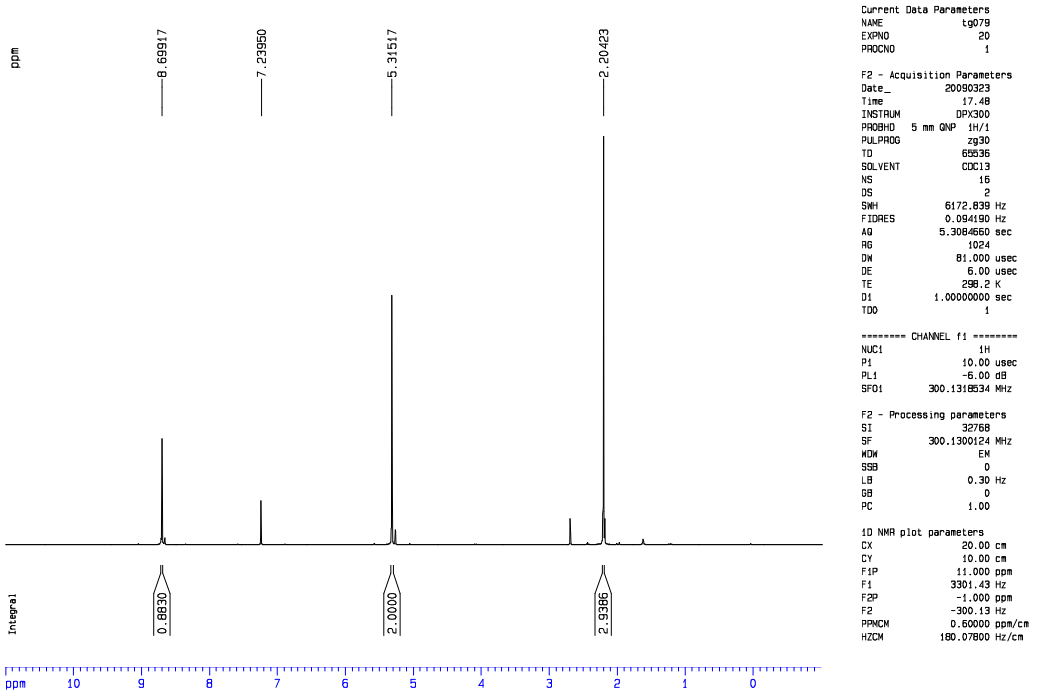
^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.20 (s, 3H, CH_3), 5.32 (s, 2H, CH_2), 8.70 (s, 1H, H-2).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.7 (CH_3), 47.9 (CH_2), 131.7 (C-5), 133.8 (C-8), 149 (C-6), 152.2 (C-2), 152.9 (C-4).

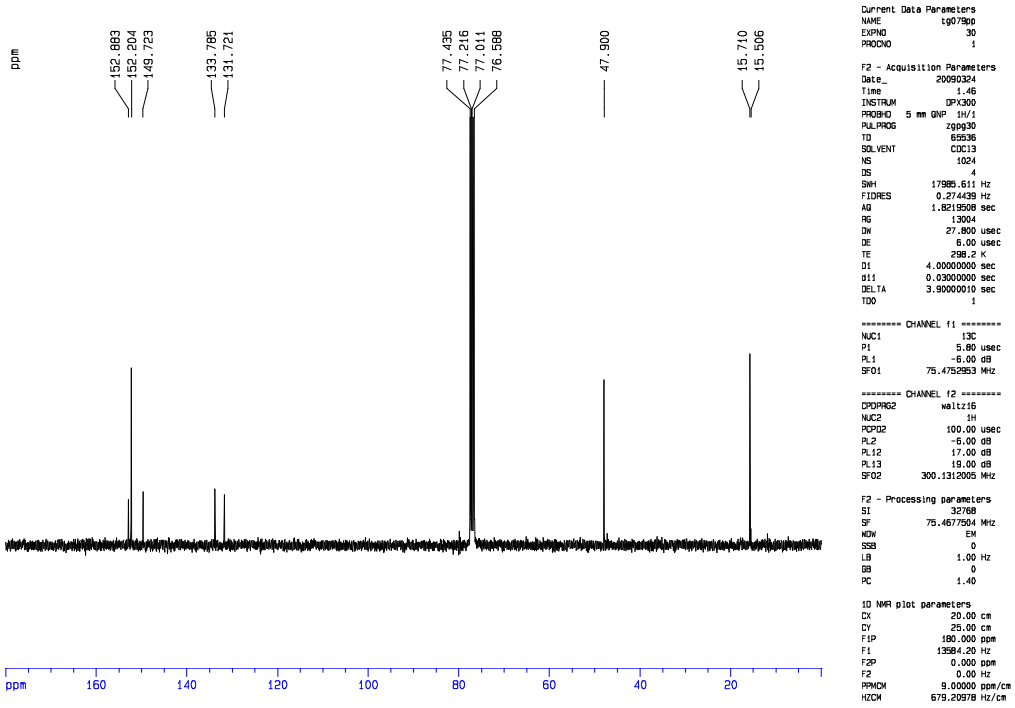
MS (EI). m/z (rel. %): 296/294 (2/6), 250/248 (10/39), 249/247 (6/13), 213 (11), 169/167 (6/17), 86 (6), 85(6) 77(16), 61 (100).

HR-MS: found 291. 9187 calculated $C_7H_6BrClN_4S$ 291.9185

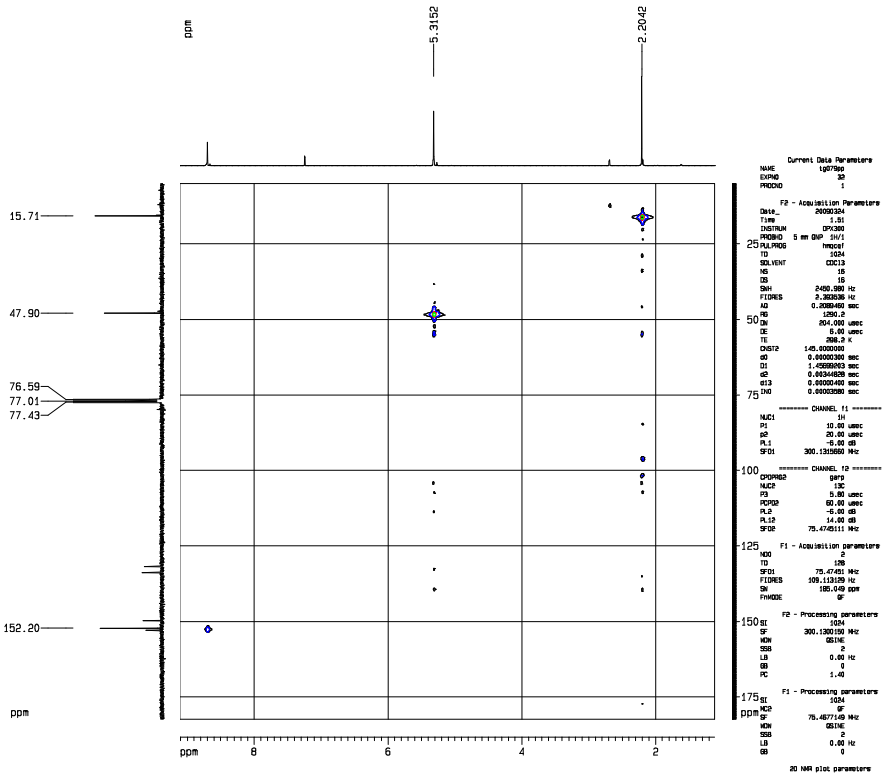
M.p.: 108-110 °C.



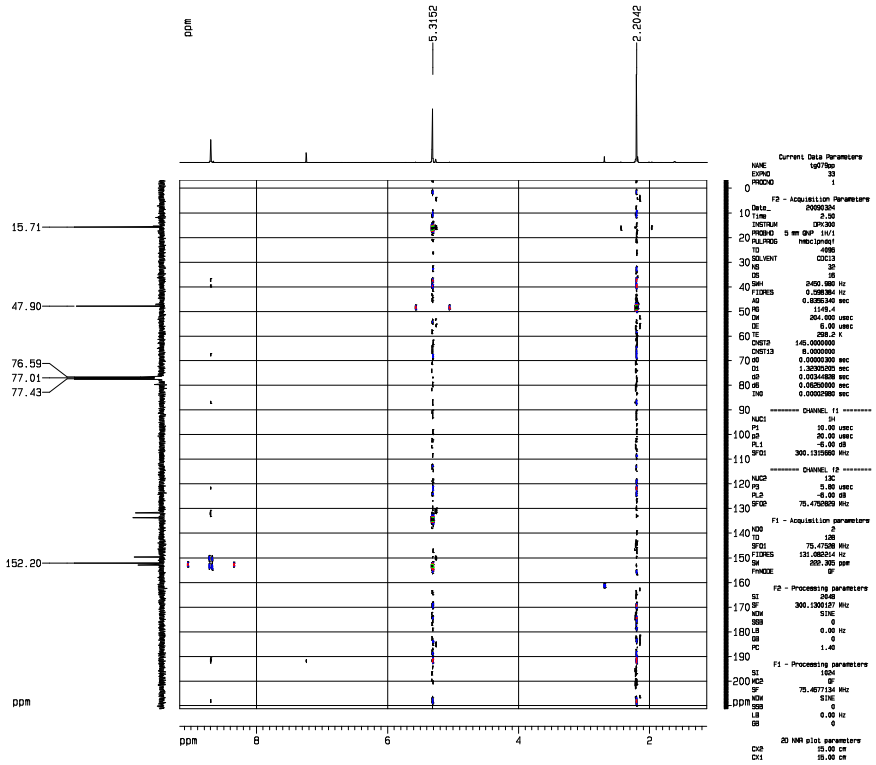
Spectrum 68. ^{1}H NMR of *8-Bromo-6-chloro-9-(methylthiomethyl)-9H-purine* (**15h**).



Spectrum 69. ^{13}C NMR **of** *8-Bromo-6-chloro-9-(methylthiomethyl)-9H-purine* (**15h**).

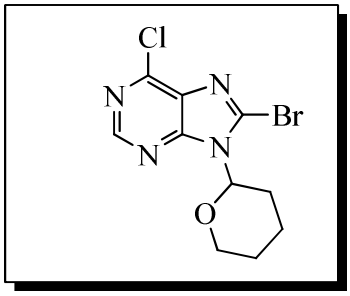


Spectrum 70. HMQC of *8-Bromo-6-chloro-9-(methylthiomethyl)-9H-purine* (**15h**).



Spectrum 71. HMBC of *8-Bromo-6-chloro-9-(methylthiomethyl)-9H-purine* (**15h**).

***8-Bromo-6-chloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine* (15i).**



15i

Hexane followed by hexane-EtOAc (6:1) and (3:1) were used for flash chromatography. Yield 139 mg (91%) off white solid.

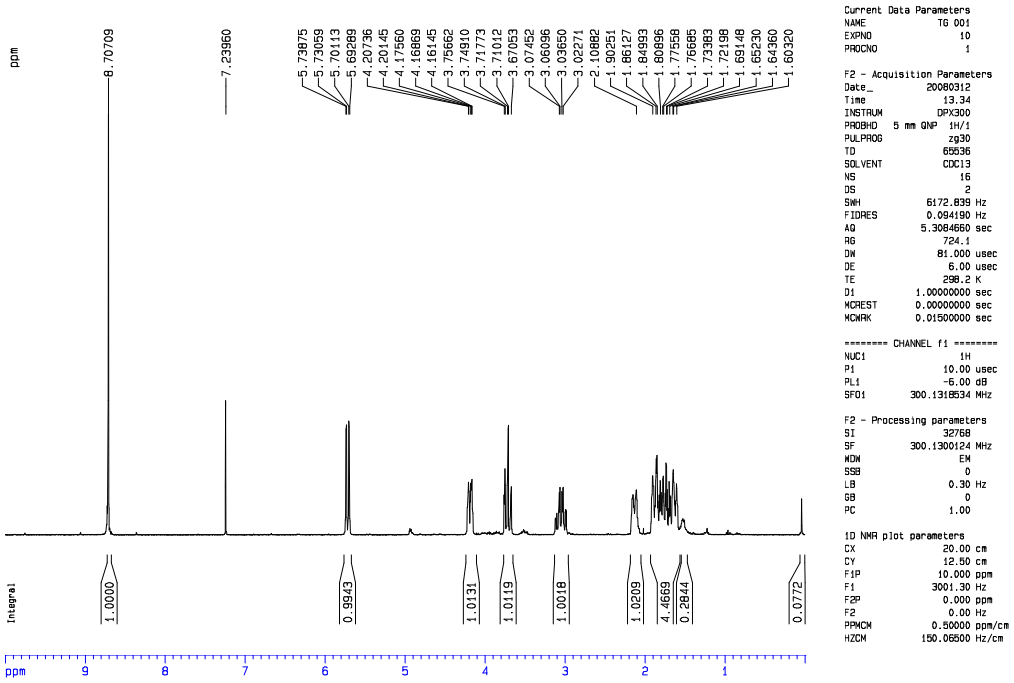
^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.60-1.76 (m, 4H), 1.80-1.90(m, 1H), 3.01-3.01(m, 1H), 3.66-3.74(m, 1H), 4.15-4.20(m, 1H), 5.71(dd, 1H, J_1 11.3 Hz, J_2 2.4Hz), 8.70(s, 1H).

^{13}C NMR ($CDCl_3$, 75MHz): δ 23.2 (C-5 pyranyl), 24.6 (C-4 pyranyl), 28.7 (C-6 pyranyl), 69.3 (C-3 pyranyl), 85.6 (C-1 pyranyl), 132.0 (C-8), 133.5 (C-5), 149.7 (C-4), 151.8 (C-2), 152.6 (C-6).

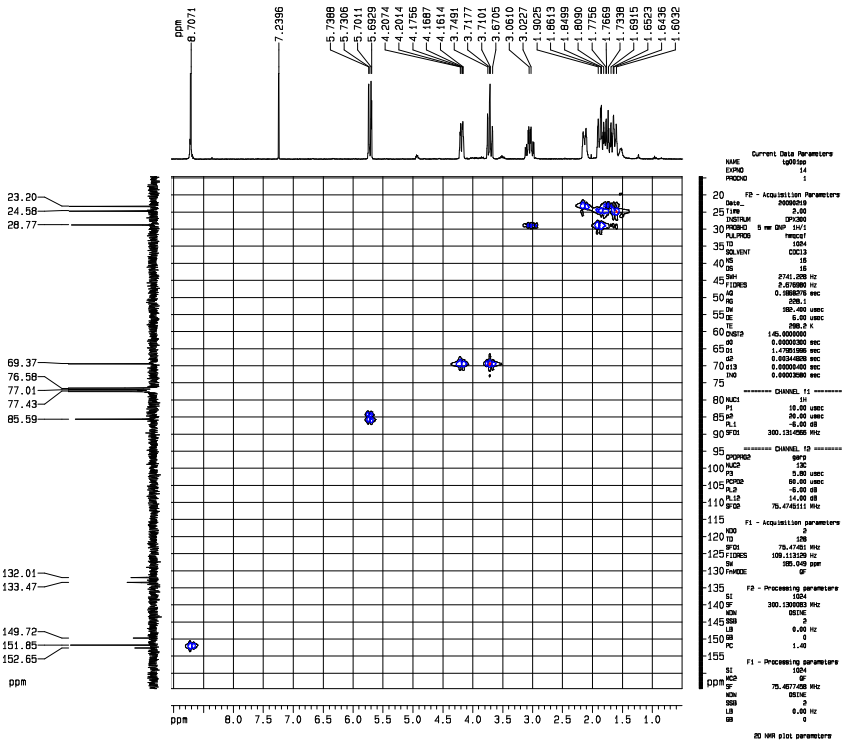
MS (EI). m/z (rel. %)**:** 318/316 (2/2, M^+), 278 /276/274 (18/9/1), 236/234/232 (11/42/33),190/188 (16/24), 155 (16), 153 (47), 118 (8), 91 (11), 85(100), 67 (13), 65 (12).

HR-MS. found 315.9736 calculated for $C_{10}H_{10}BrClN_4O$ 315.9727

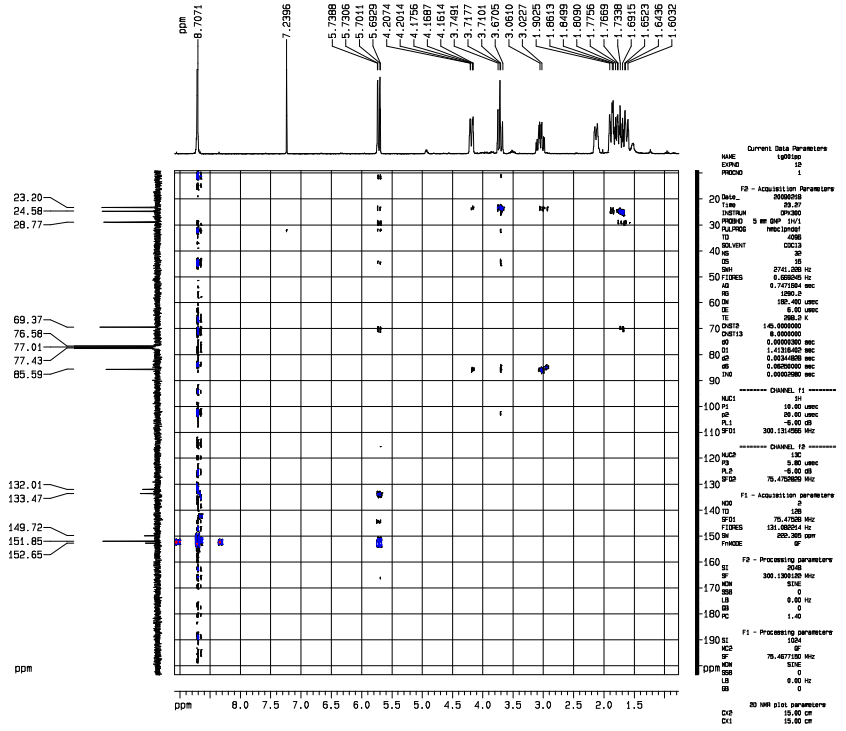
M. p.: 103-105°C. (lit.101-103 °C).[17]



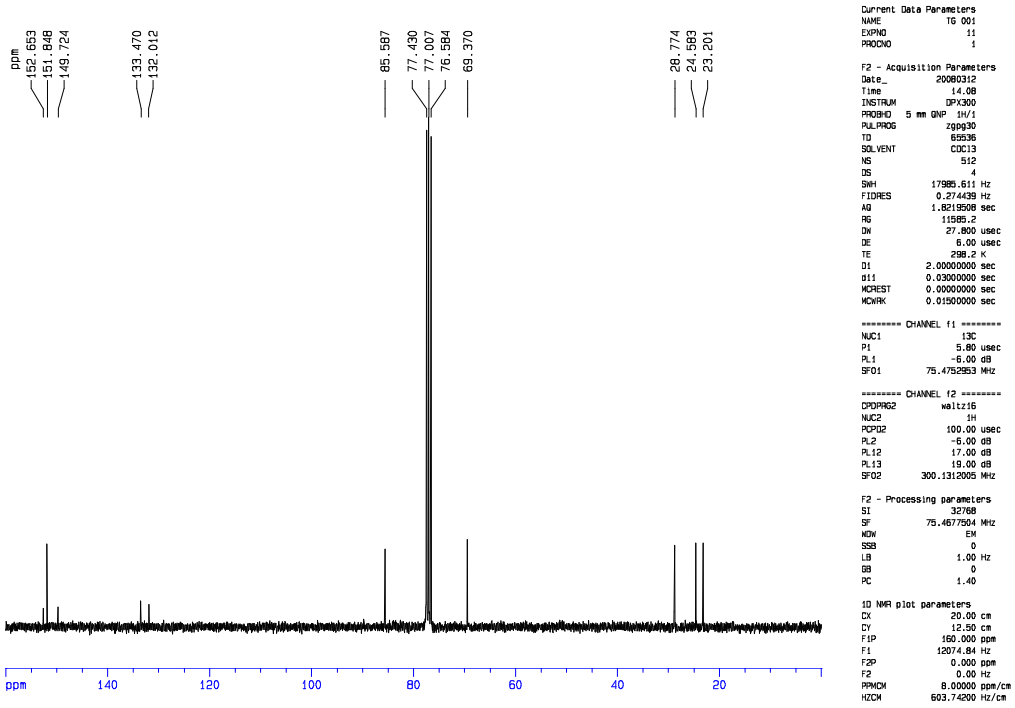
Spectrum 72.[1]H NMR of *8-Bromo-6-dichloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine* (**15i**).



Spectrum 73. ^{13}C NMR of *8-Bromo-6-dichloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine* (**15i**).

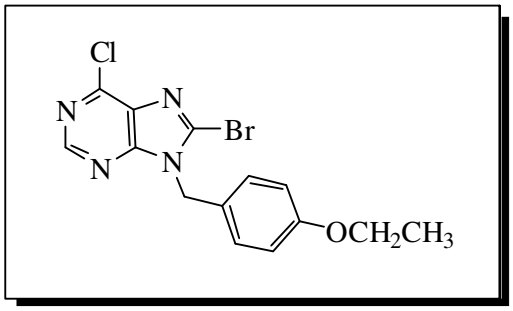


Spectrum 74. HMQC of *8-Bromo-6-dichloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine* (**15i**).



Spectrum 75. HMBC of *8-Bromo-6-dichloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine* (**15i**).

8-Bromo-6-chloro-9-(4-ethoxybenzyl)-9H-purine **(15j)**



15j

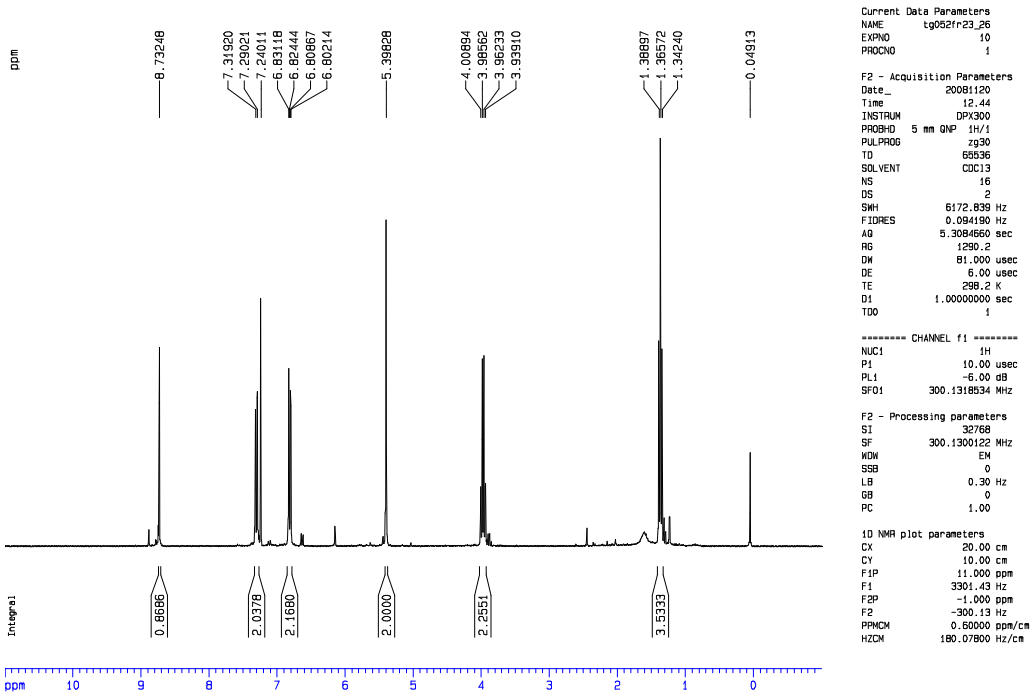
Hexane followed by EtOAc-Hex 1:4, EtOAc-Hex 1:2, EtOAc were used for flash chromatography. Yield 7mg (2%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.37 (t, J=7 Hz, 3H, CH_3), 3.97 (q, J=7 Hz, 2H, O-CH_2), 5.40 (2H, N-CH_2), 6.82 (d, J=8.7 Hz, 2H, Ar), 7.30 (d, J=8.7Hz, 2H, Ar), 8.73 (s, H-2)

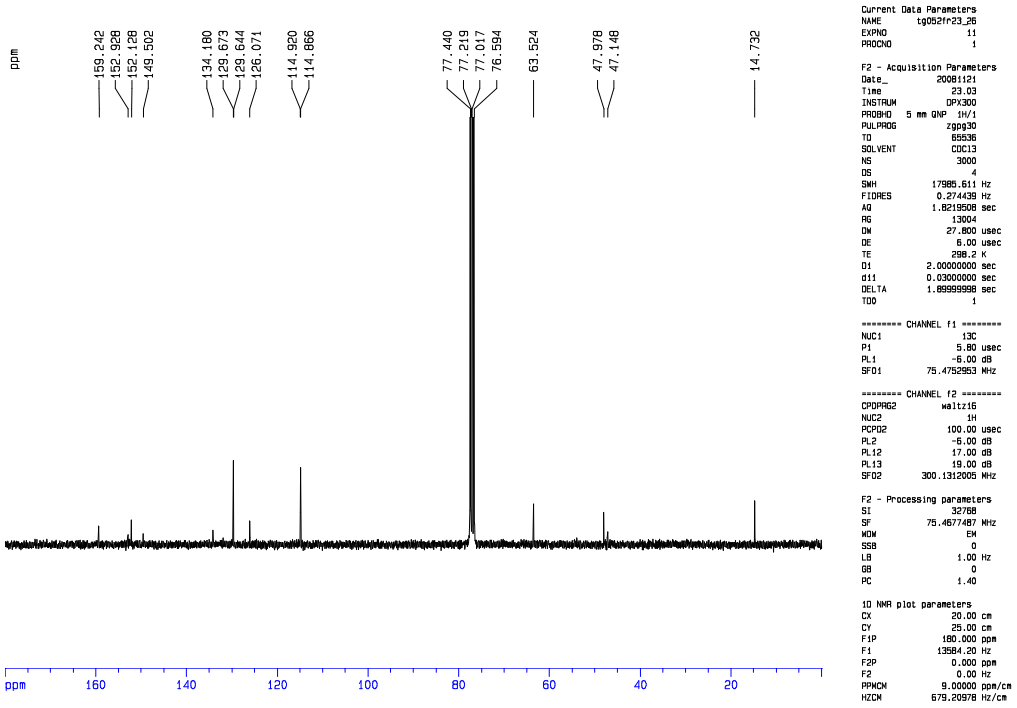
^{13}C NMR ($CDCl_3$, 75MHz): δ 14.7 (CH_3), 48.0 (CH_2), 63.5 (OCH_2), 114.9 (C-3 and C-5 Ar), 129.1 (C-1 Ar), 129.6 (C-2 and C-6 Ar), 129.7(C-5), 134.2 (C-8), 149.5(C-4), 152.1(C-2), 152.9 (C-6) ,159.2 (C-4 Ar).

MS (EI). m/z (rel. %): 370/368/366 (4/17/13), 288/287 (3/13), 136(10), 135 (100), 107 (63), 77 (10).

HR-MS: found 365.9895 calculated for $C_{14}H_{12}BrClN_4O$ 365.9883

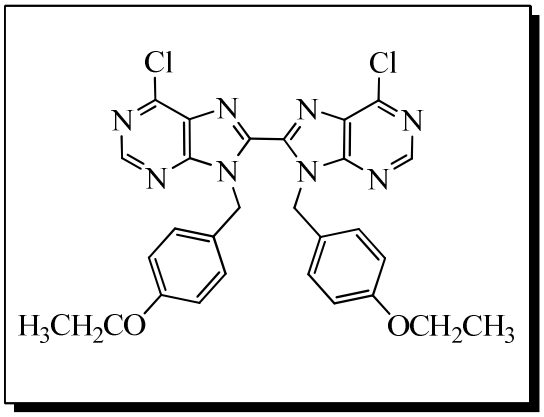


Spectrum 76. ^{1}H NMR of *8-Bromo-6-chloro-9-(4-ethoxybenzyl)-9H-purine* (**15j**)



Spectrum 77. ^{13}C NMR of *8-Bromo-6-chloro-9-(4-ethoxybenzyl)-9H-purine* (**15j**)

8, 8'-(6-chloro-9-(4-ethoxybenzyl)-9H-bispurine **(45j)**



45j

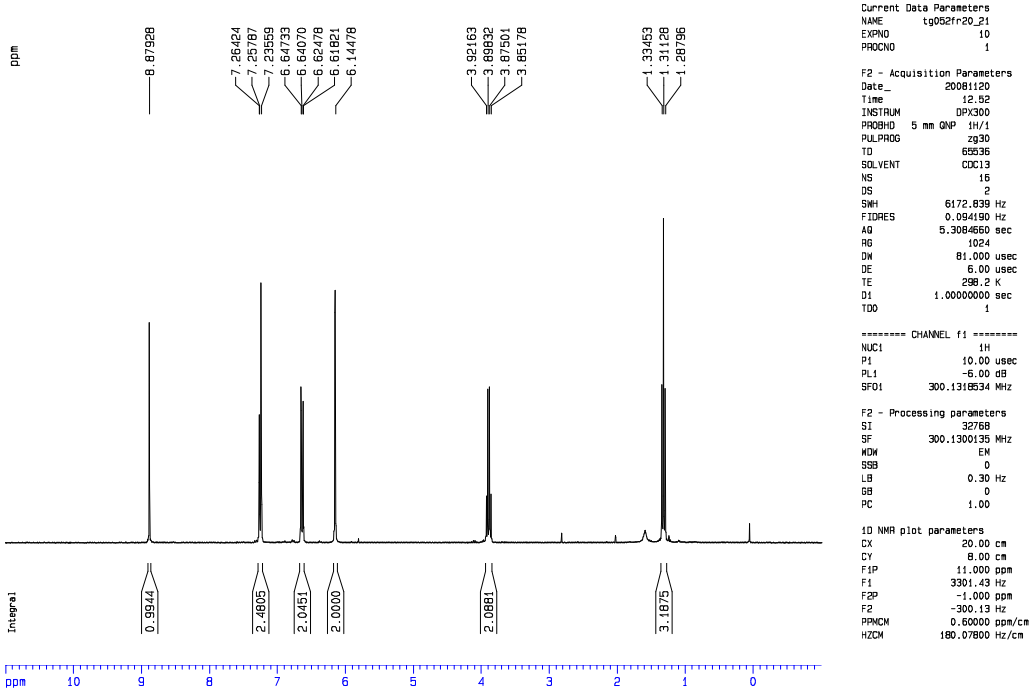
Hexane followed by EtOAc-Hex 1:4, EtOAc-Hex 1:2, EtOAc were used for flash chromatography. Yield 7mg (5%), colourless solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.31 (t, J=7.0, 6H, 2xCH_3), 3.88(q, J=7.0, 4H, 2xO-CH_2), 6.14(s, 4H, 2xN-CH_2), 6.63 (d, J= 8.7Hz 4H, Ar), 7.26(d, J= 8.7 Hz, 4H, Ar). 8.88 (s, 2H, 2xH-2).

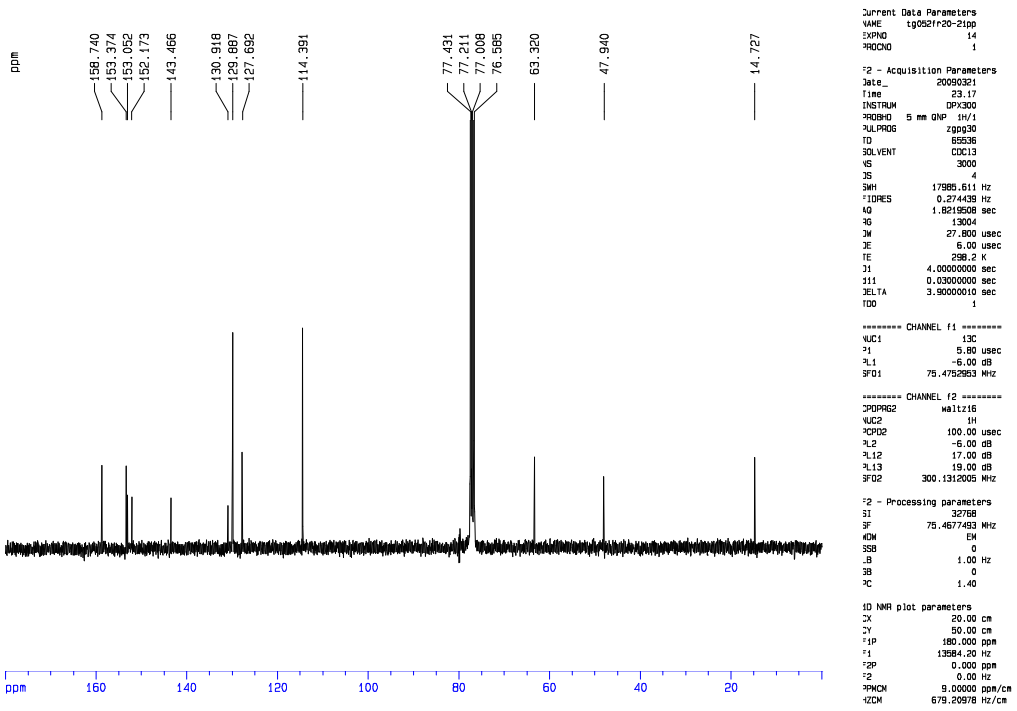
^{13}C NMR ($CDCl_3$, 75MHz): δ 14.7 (CH_3), 47.9 (N-CH_2), 63.3 (O-CH_2), 114.4 (C-3 and C-5 Ar), 127.7 (C-1 Ar), 129.9 (C-2 and C-6 Ar), 130.9 (C-5), 143.5 (C-8), 152.2 (C-4), 153.1 (C-6), 153.4 (C-2), 158.8 (C-4 Ar).

MS (EI). m/z (rel. %): 578/576/574 (0.4/4/6), 441/439 (28/41), 413/411 (6/9), 269/268 (13/68), 135 (100), 108 (7), 107 (91), 77 (11).

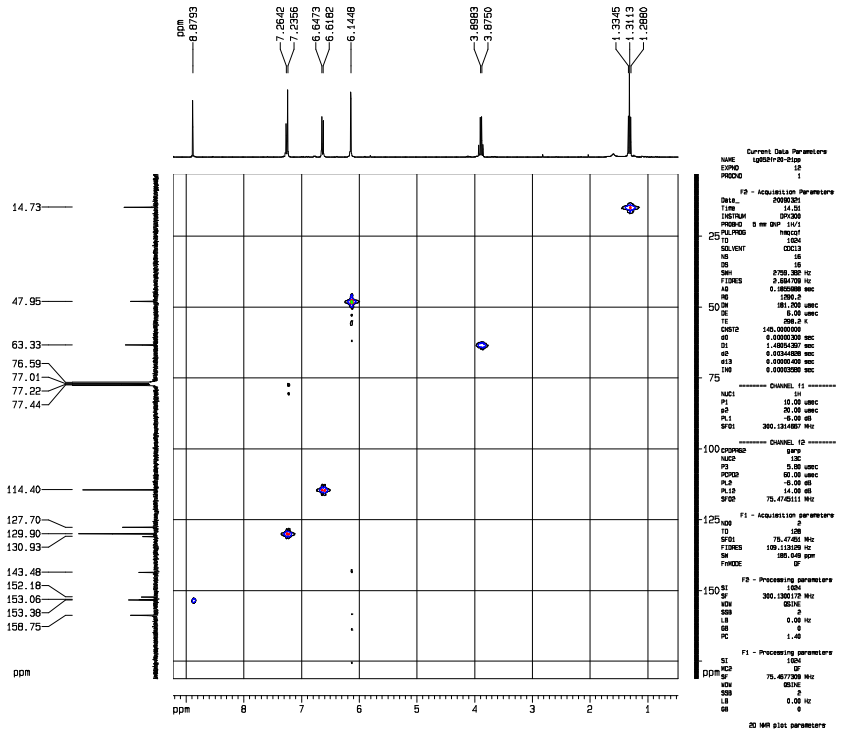
HR-MS: found 574.1384 calculated for $C_{28}H_{24}Cl_2N_8O_2$ 574.1399.



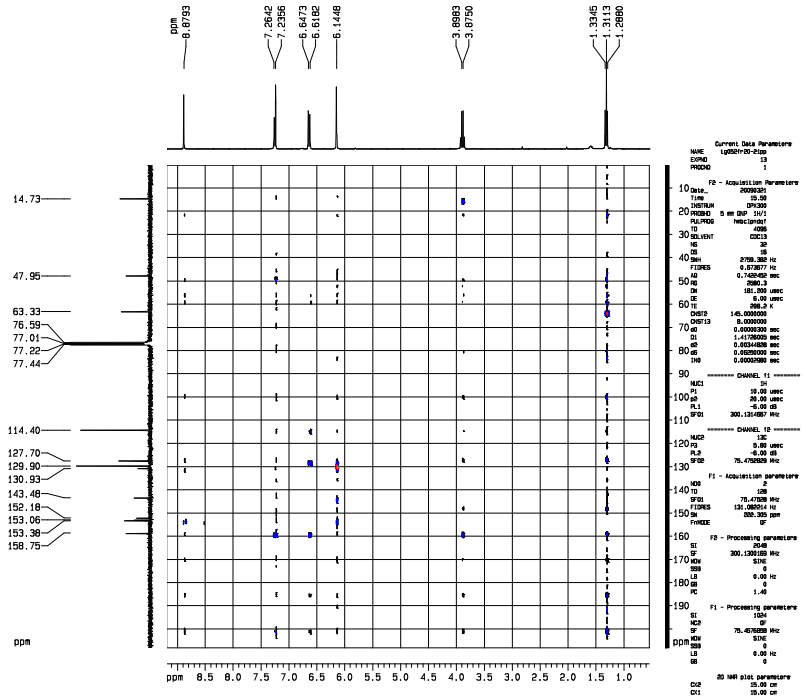
Spectrum 78. ^{1}H NMR of *8,8'-bis[6-chloro-9-(4-ethoxybenzyl)-9H-purine]* (**45j**).



Spectrum 79. ^{13}C NMR of *8,8'-bis[6-chloro-9-(4-ethoxybenzyl)-9H-purine]* (**45j**).

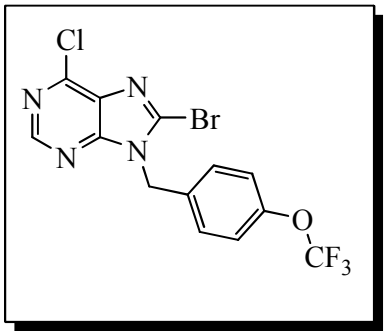


Spectrum 80. HMQC of *8,8'-bis[6-chloro-9-(4-ethoxybenzyl)-9H-purine]* (**45j**).



Spectrum 81. HMBC of *8,8'-bis[6-chloro-9-(4-ethoxybenzyl)-9H-purine]* (**45j**).

8-Bromo-6-chloro-9-(4-trifluoromethyoxybenzyl)-9H-purine **(15k)**.



15k

Hexane followed by EtOAc-hexane (1:8) and (1:2) were used for flash chromatography; scale 0.25mmol, Yield 36mg (36%) brown solid.

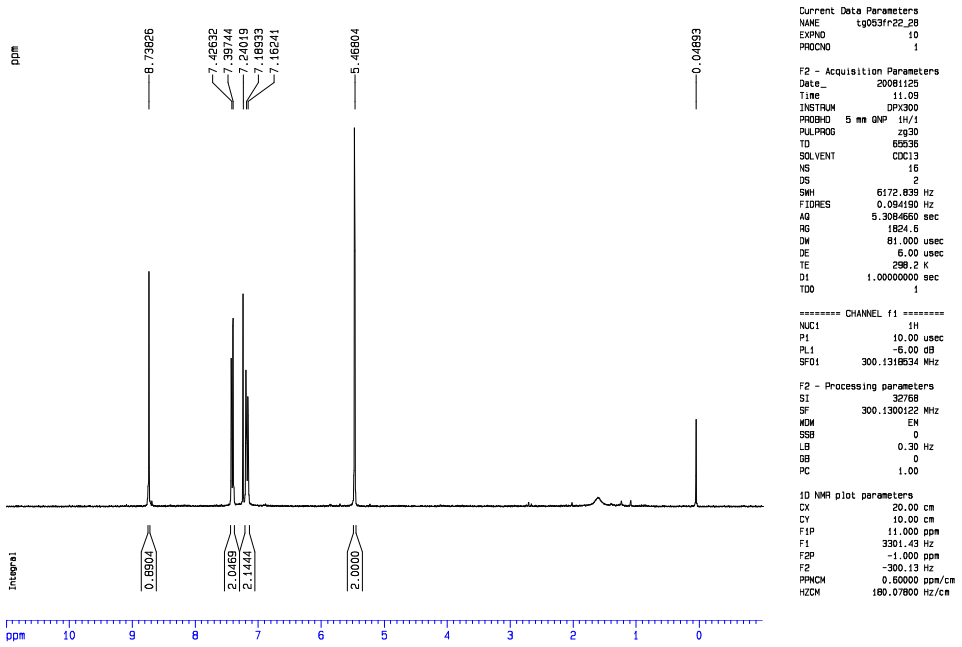
^{1}H NMR ($CDCl_3$, 300 MHz); δ 5.47 (s, 2H, CH_2), 7.16 -7.43(m, 2H, Ar), 8.74 (s, 1H, H-2)

^{13}C NMR ($CDCl_3$, 50MHz): δ 47.6 (CH_2), 121.5 (C-3 and C-5 Ar), 129.7 (C-2, C-6 Ar, and CF3), 131.9 (C-8), 132.7 (C-1 Ar), 133.9 (C-5), 149.4 (C-6), 149.8 (C-4 Ar), 152.3 C-2 Ar), 152.9 (C-4).

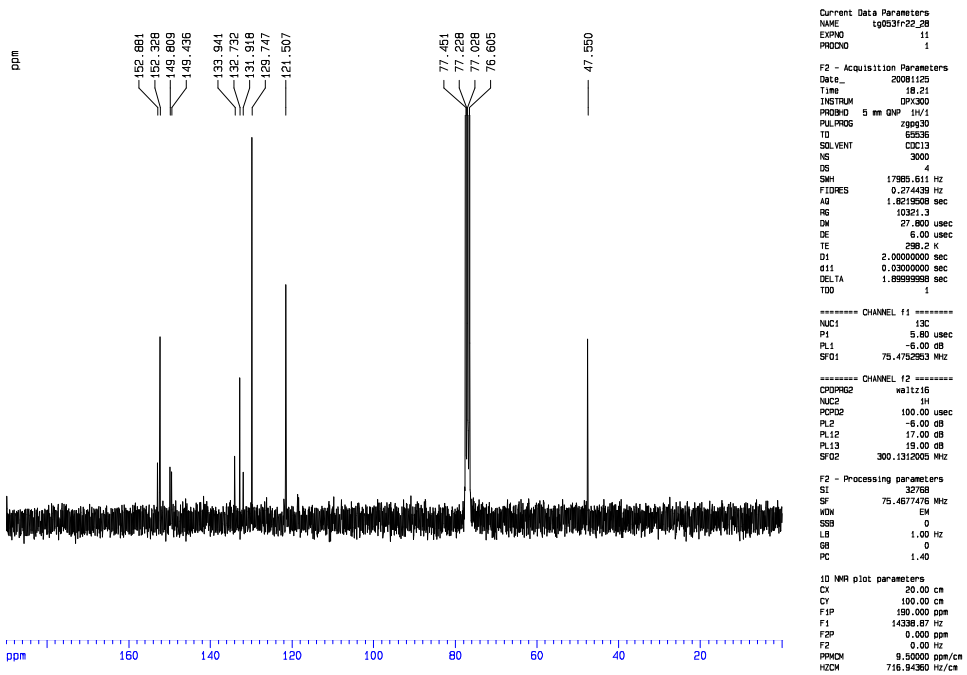
MS (EI). m/z rel. %): 410/408/406 (4/17/13), 329/327 (8/24), 176 (9), 175 (100), 109 (8), 78 (6), 69 (9).

HR-MS: found 405.9436 calculated for $C_{13}H_7BrClF_3N_4O$ 405.9444.

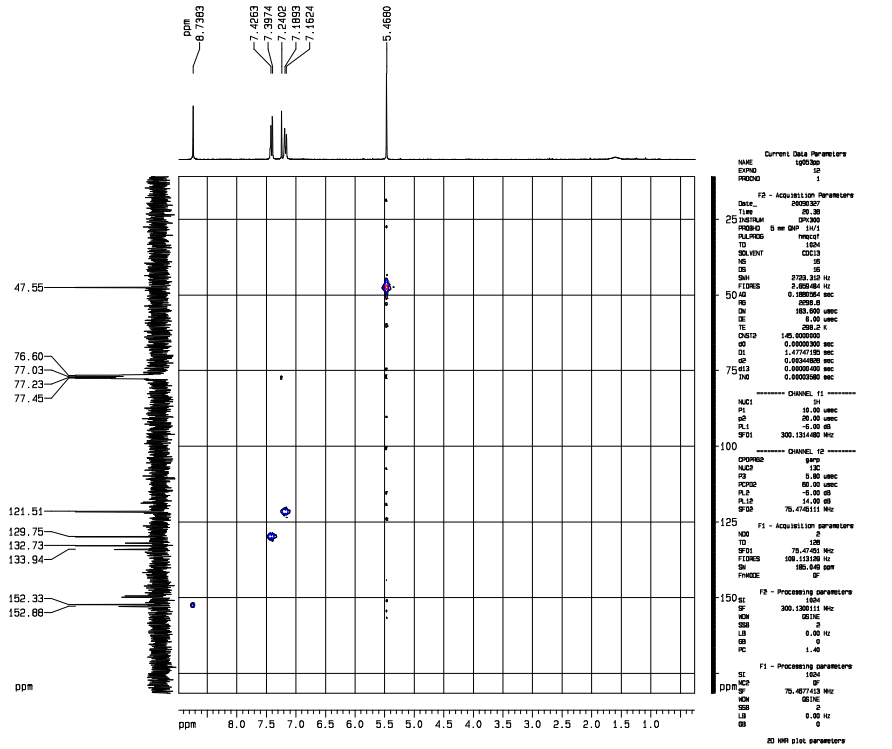
M. p.: 117-119°C.



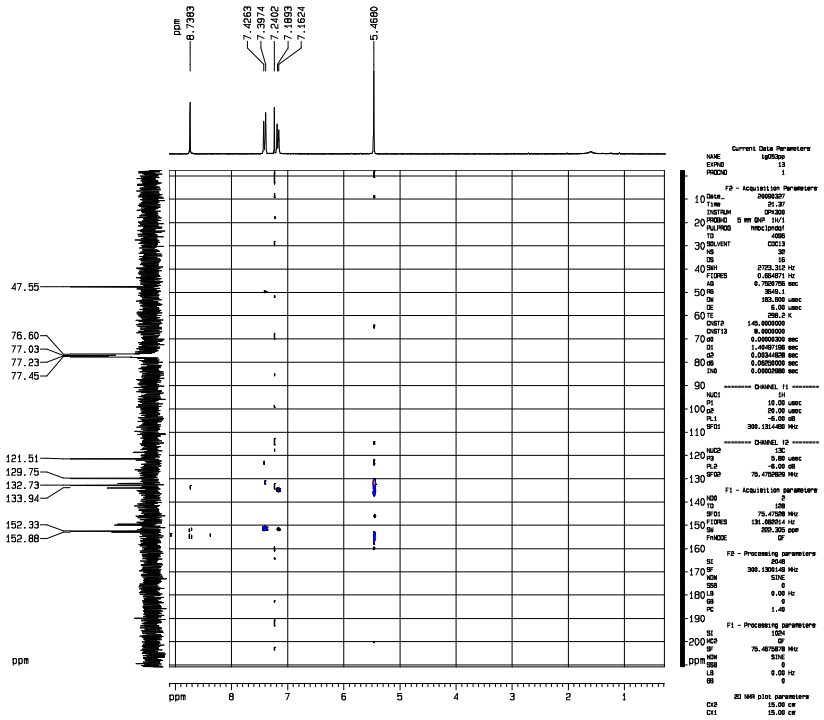
Spectrum 82. ^{1}H NMR of *8-Bromo-6-chloro-9-(4-trifluoromethyoxybenzyl)-9H-purine* (**15k**).



Spectrum 83. ^{13}C NMR of *8-Bromo-6-chloro-9-(4-trifluoromethyoxybenzyl)-9H-purine* (**15k**).

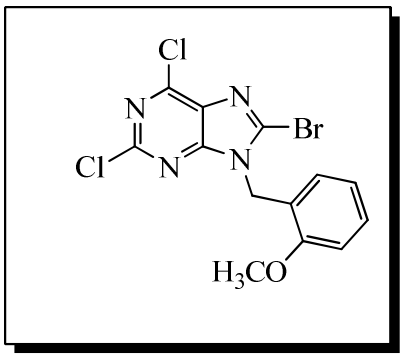


Spectrum 84. HMQC of *8-Bromo-6-chloro-9-(4-trifluoromethyoxybenzyl)-9H-purine* (**15k**).



Spectrum 85. HMBC of *8-Bromo-6-chloro-9-(4-trifluoromethyoxybenzyl)-9H-purine* (**15k**).

***8-Bromo-2, 6-dichloro-9-(2-methoxybenzyl)-9H-purine* (15l).**



15l

Hexane followed by EtOAc- hexane (1:2) were used for flash chromatography Yield 154mg (80%) pale yellow solid.

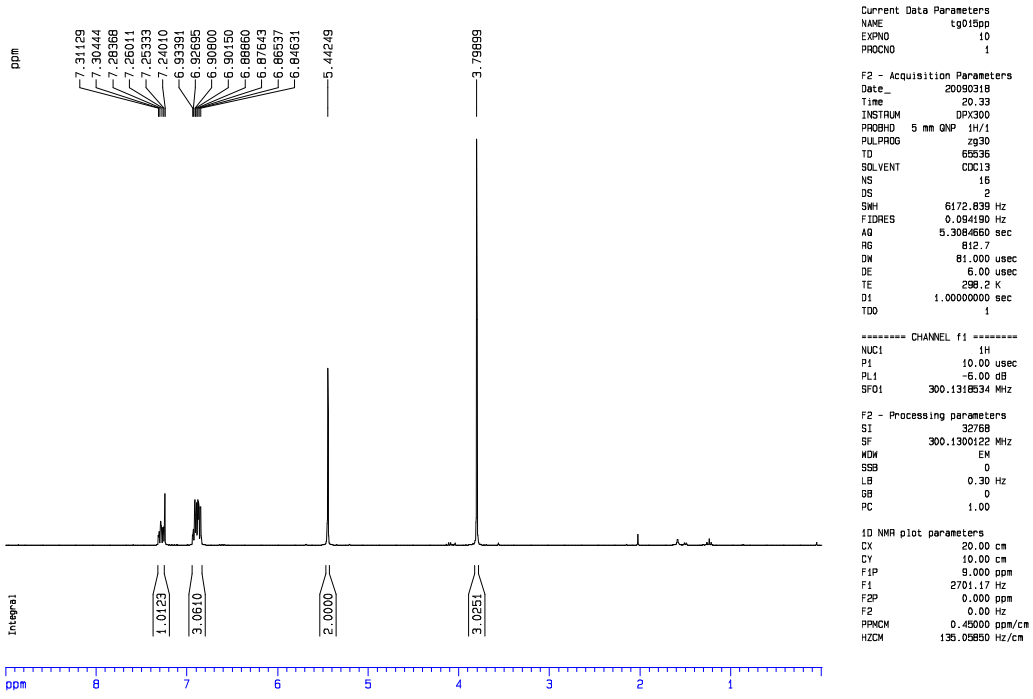
^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.80(s, 3H, OCH_3), 5.45(s, 2H, CH_2), 6.83-6.95(m, 3H, Ar), 7.25-7.32 (m, 1H, Ar).

^{13}C NMR ($CDCl_3$, 50MHz): δ 44.5 (CH_2), 55.2 (OCH_3), 110.5 (C-3 Ar), 120.5 (C-5 Ar), 121.5 (C-1 Ar), 128.7 (C-6 Ar), 129.9 (C-4 Ar), 130.8 (C-8), 135.5 (C-5), 149.9 (C-6), 152.9 (C-4), 154.3 (C-2), 156.9 (C-2 Ar).

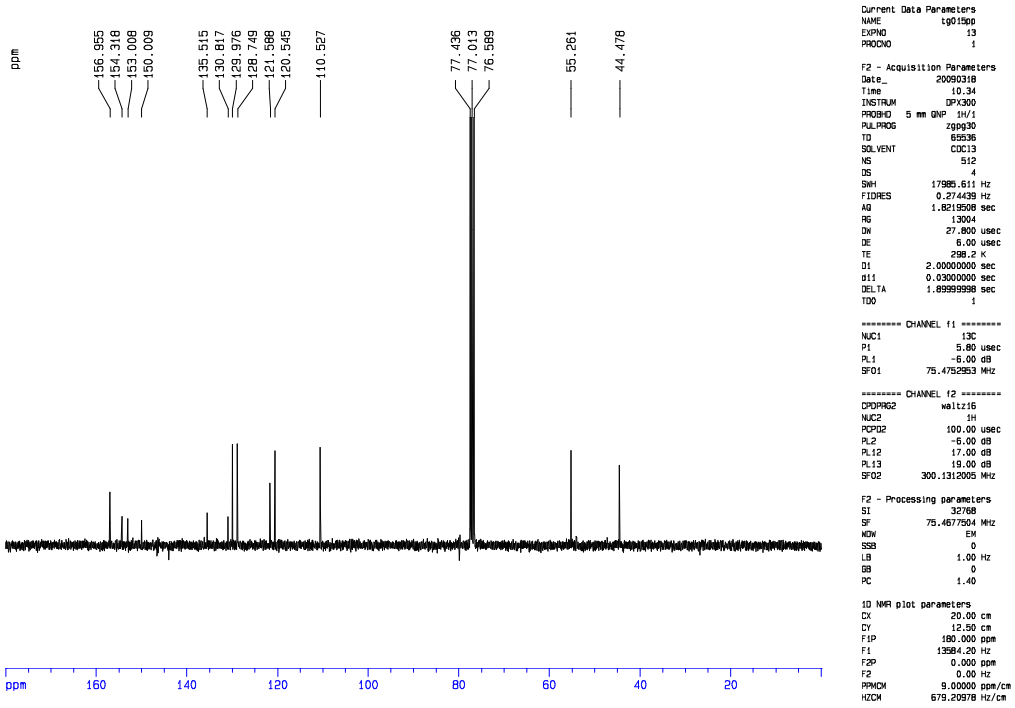
MS (EI). m/z(rel. %): 390/388/386 (5/ 11/ 6, M+), 309/307 (23/35), 122(9), 121(100), 91(48), 65(6), 51(3), 39(2).

HR-MS: found 385.9335 calculated for $C_{13}H_9BrCl_2N_4O$. 385.9337.

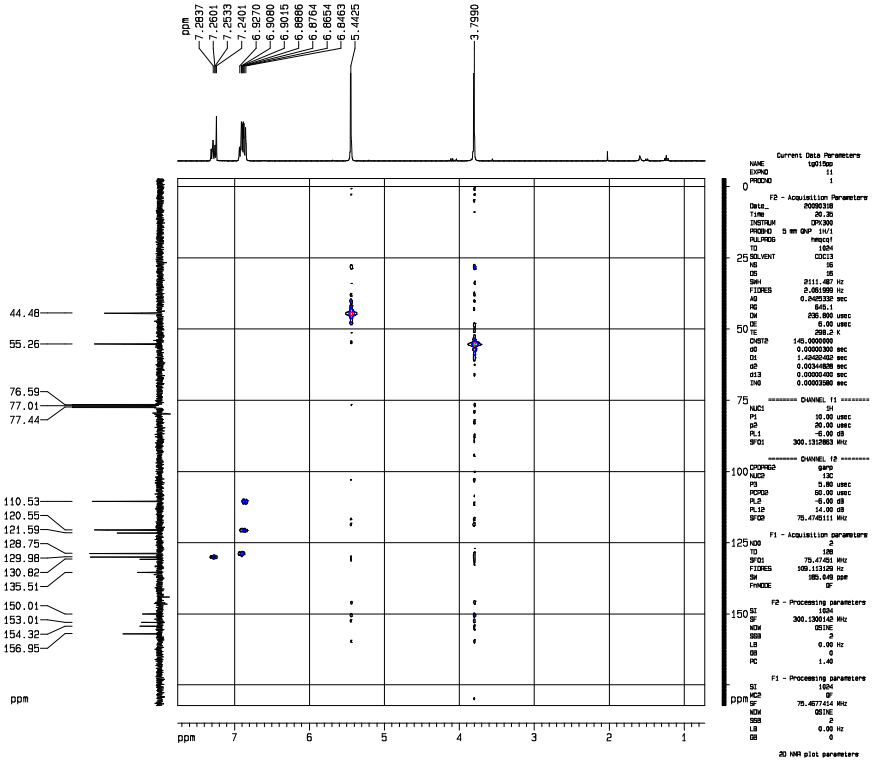
M.p.: 190-192°C.



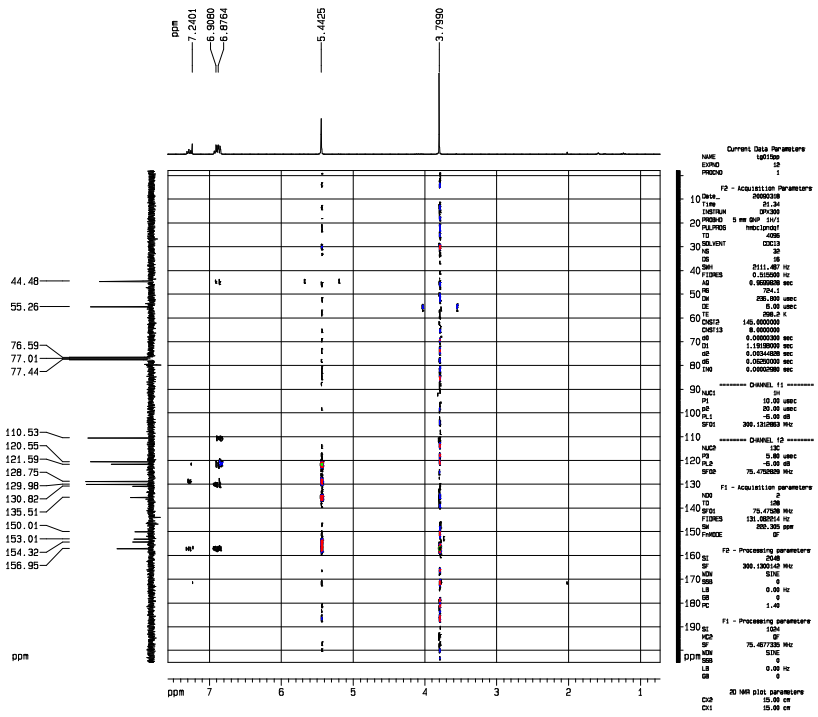
Spectrum 86. ^{1}H NMR of *8-Bromo-2,6-dichloro-9-(2-methoxybenzyl)-9H-purine* (**15l**).



Spectrum 87. ^{13}C NMR of *8-Bromo-2,6-dichloro-9-(2-methoxybenzyl)-9H-purine* (**15l**)**.**

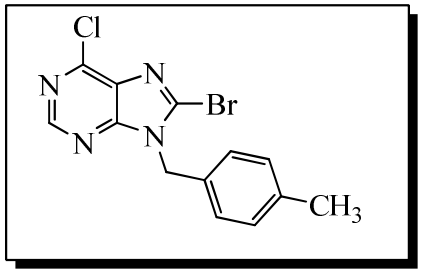


Spectrum 88. HMQC of *8-Bromo-2,6-dichloro-9-(2-methoxybenzyl)-9H-purine* (**15l**).



Spectrum 89. HMBC of *8-Bromo-2,6-dichloro-9-(2-methoxybenzyl)-9H-purine* (**15l**).

8-Bromo-6-chloro-9-(4-methylbenzyl)-9H-purine (**15m**).



15m

Hexane followed by EtOAc- hexane (1:8) and (1:4) were used for flash chromatography; Yield 127mg (76%), pale brown solid.

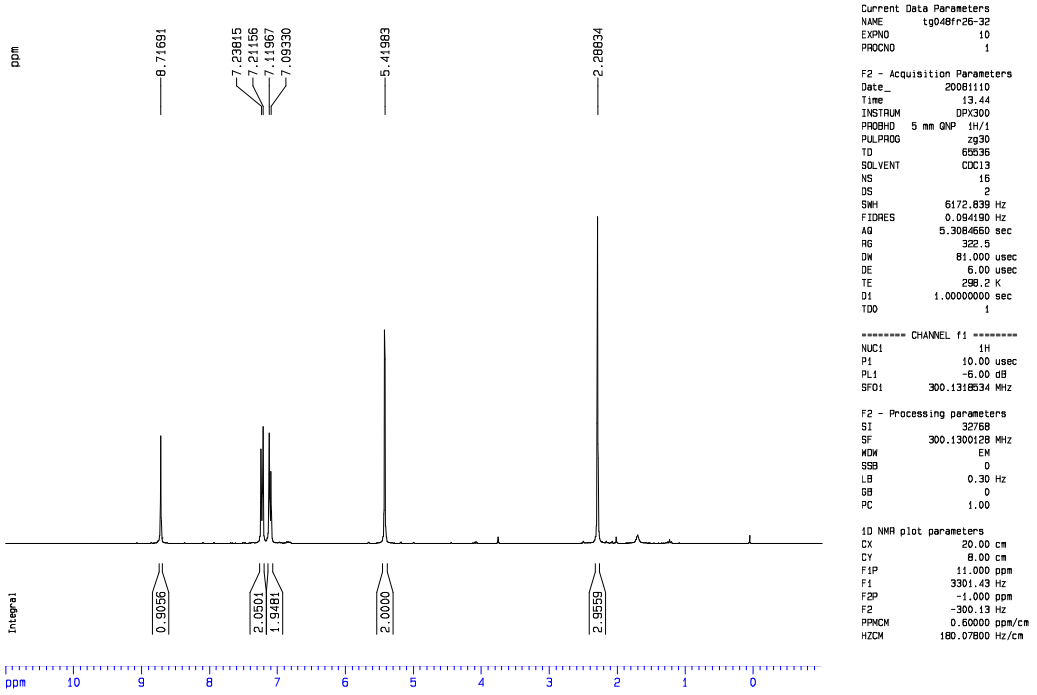
^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.29 (s, 3H, CH_3), 5.42 (s, 2H, CH_2), 7.11 (d, J=7.9Hz, 2H, Ar), 7.22(d, J=7.9Hz, 2H, Ar), 8.72(s, 1H).

^{13}C NMR ($CDCl_3$, 75MHz): δ 21.1 (CH_3), 48.1 (CH_2), 127.9 (C-2 and C-6 Ar), 129.6 (C-3 and C-5 Ar), 131.1 (C-8), 131.8 (C-5), 134.2 (C-4 Ar), 138.6 (C-1 Ar), 149.4 (C-4), 152.1 (C-2), 152.9 (C-6).

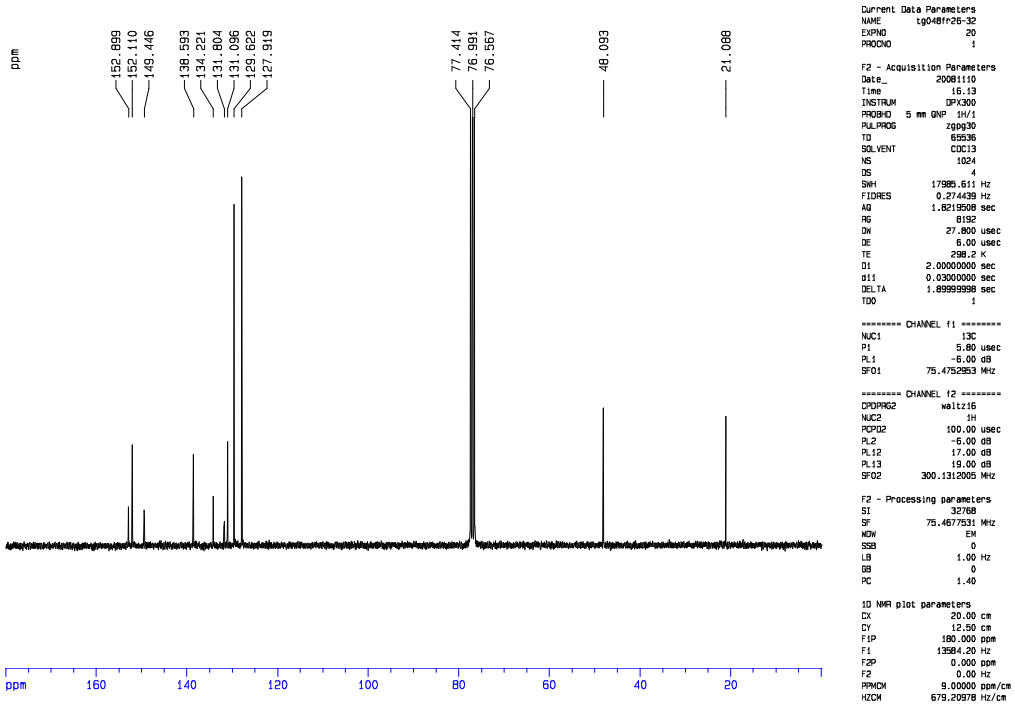
MS (EI). m/z (rel. %): 340/338/336(3/11/8), 259/257(5/16), 106(9), 105(100), 104(5), 77(18), 65(5), 51(5), 53(6), 39(5), 27(4).

HR-MS: found 335.9775 calculated for $C_{13}H_{10}BrClN_4$ 335.9777.

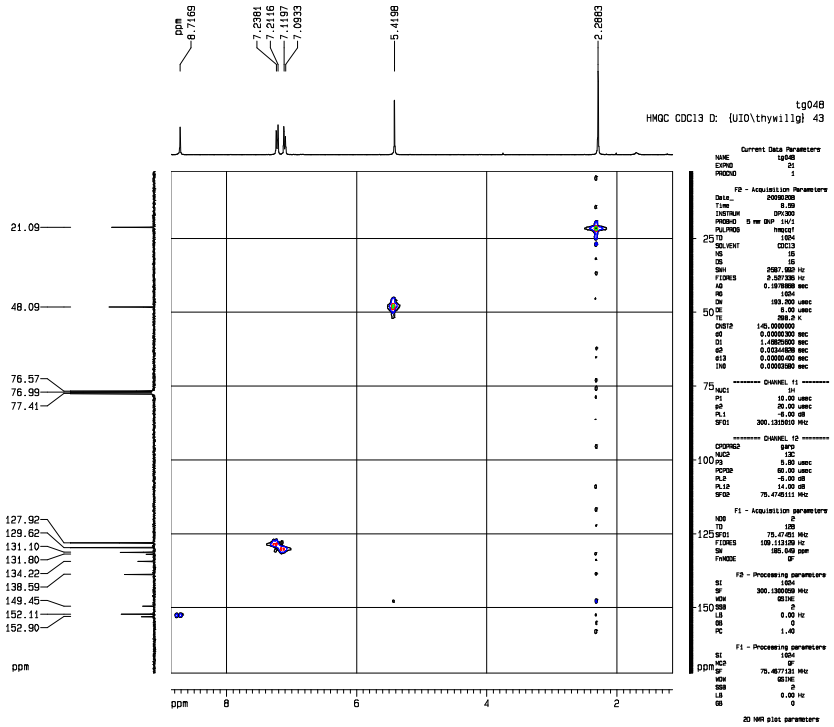
M. p.: 131-132°C.



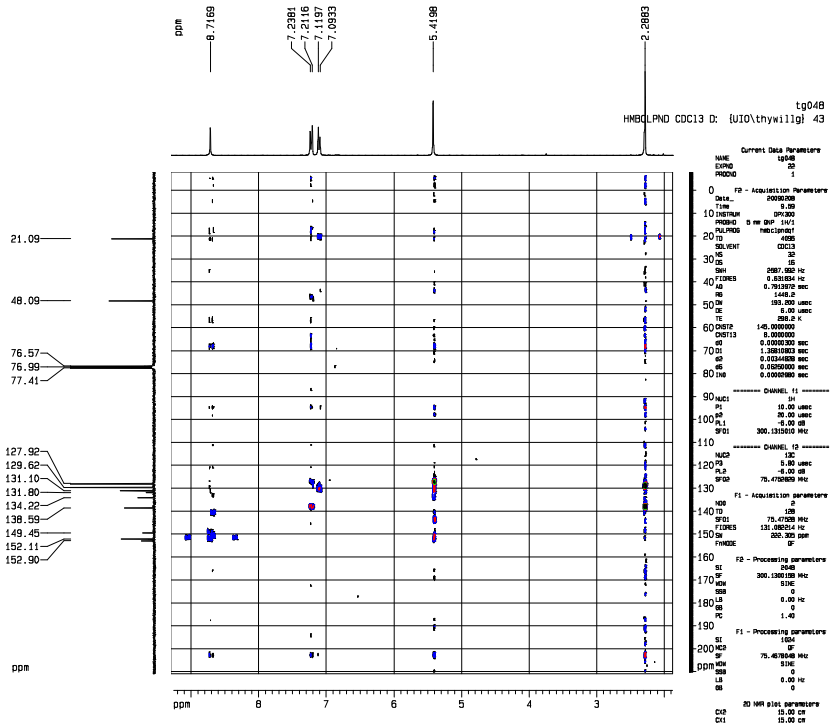
Spectrum 90. ^{1}H NMR of *8-Bromo-6-chloro-9-(4-methylbenzyl)-9H-purine* (**15m**).



Spectrum 91. ^{13}C NMR of *8-Bromo-6-chloro-9-(4-methylbenzyl)-9H-purine* (**15m**).

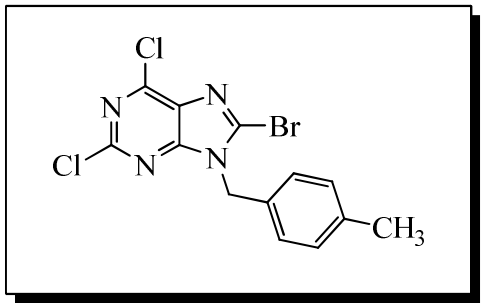


Spectrum 92. HMQC of *8-Bromo-6-chloro-9-(4-methylbenzyl)-9H-purine* (**15m**).



Spectrum 93. HMBC of *8-Bromo-6-chloro-9-(4-methylbenzyl)-9H-purine* (**15m**).

8-Bromo-2,6-dichloro-9-(4-methylbenzyl)-9H-purine **(15n)**.



15n

Hexane followed by EtOAc- hexane (1:6) and (1:3) were used for flash chromatography; Yield 129mg (75%) yellow solid.

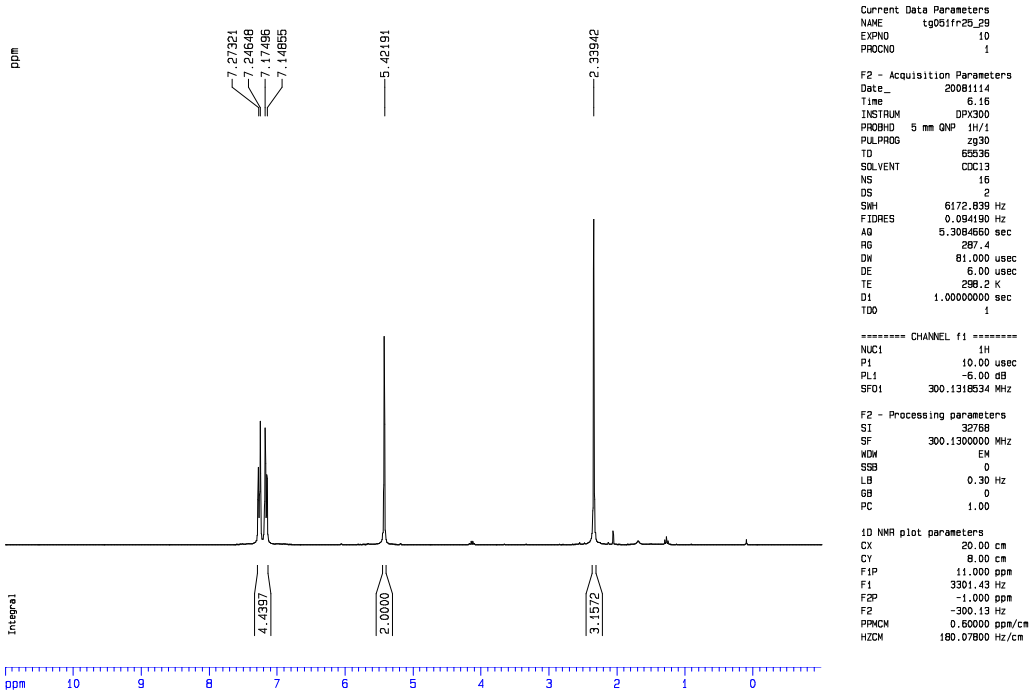
^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.34 (s, 3H, CH_3), 5.42 (s, 2H, CH_2), 7.16(d, J= 8.0Hz 2H, Ar), 7.25(d, J= 8.0 Hz, 2H, Ar).

^{13}C NMR ($CDCl_3$, 75MHz): δ 21.1 (CH_3), 48.3 (CH_2), 128.0 (C-2 and C-4 Ar), 129.7(C-3 and C-5 Ar), 130.6 (C-8), 130.8 (C-5), 134.7 (C-1 Ar), 138.8 (C-4 Ar), 150.1 (C-6), 153.2 (C-4), 153.9 (C-2).

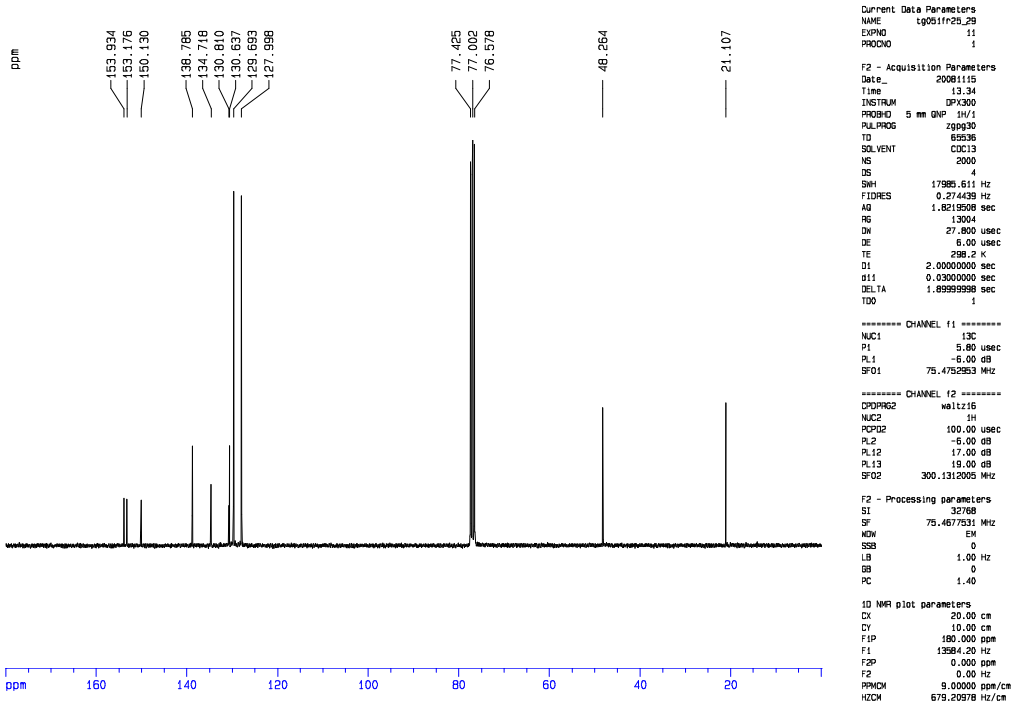
MS (EI). m/z (rel. %): 374/372/370 (M^+, 5/11/7), 293/291(3/5),185(2), 184(1), 105(100), 106(10), 103(6), 79(7), 77(10).

HR-MS: found 369.9393 calculated for $C_{13}H_9BrCl_2N_4$ 369.9388

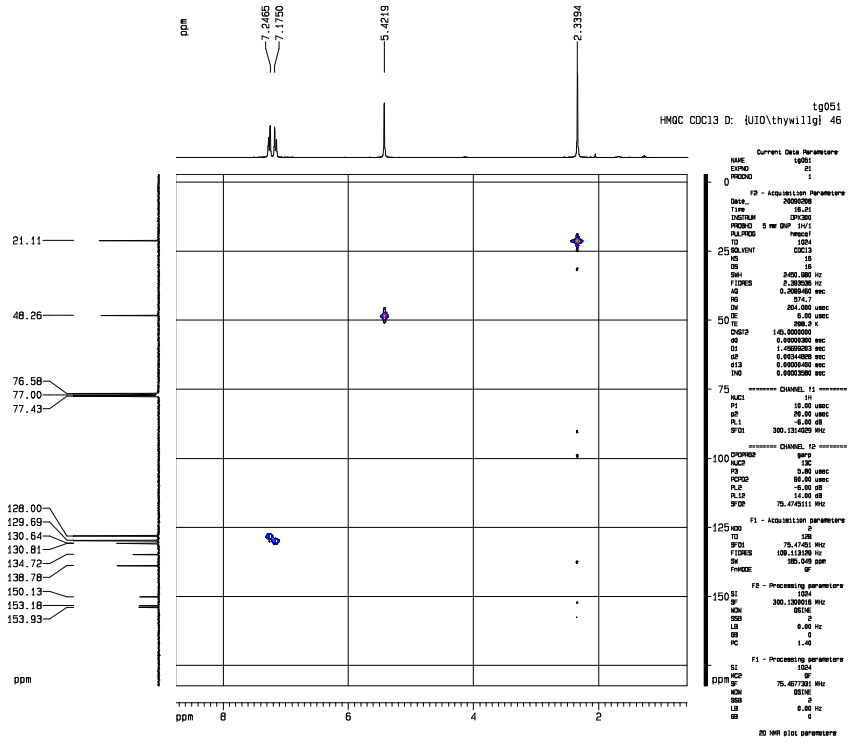
M. p.: 178-179 ^oC.



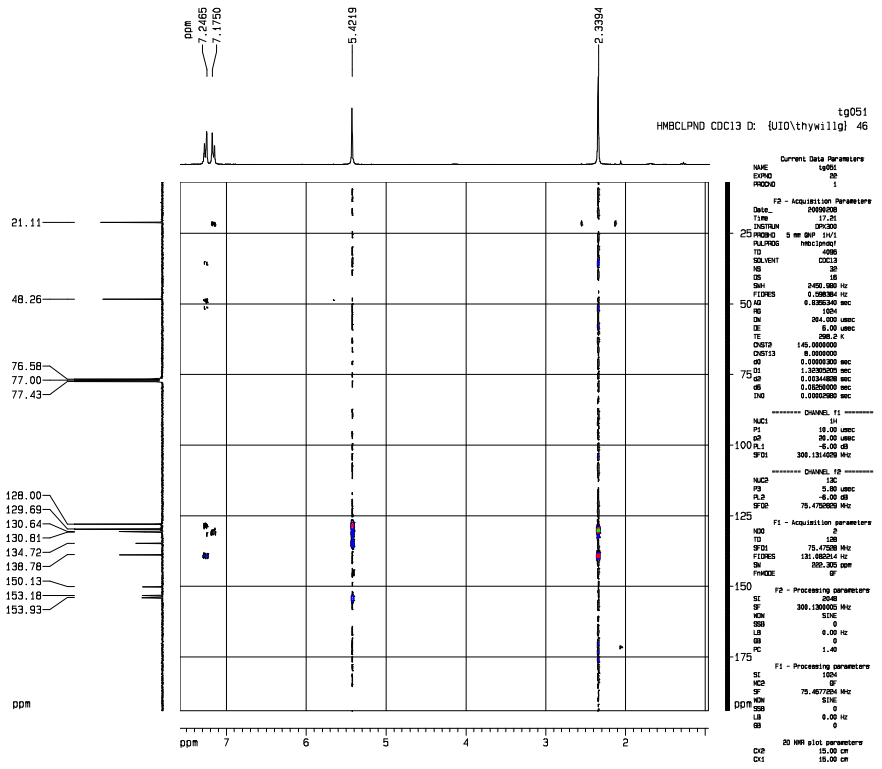
Spectrum 94. [1] H NMR of *8-Bromo-2,6-dichloro-9-(4-methylbenzyl)-9H-purine* (**15n**).



Spectrum 95. ^{13}C NMR of *8-Bromo-2,6-dichloro-9-(4-methylbenzyl)-9H-purine* (**15n**).

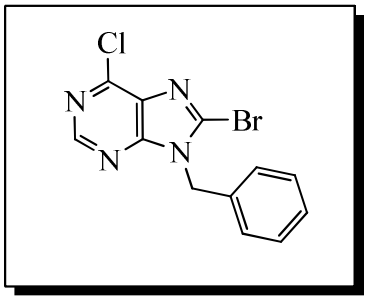


Spectrum 96. HMQC of *8-Bromo-2,6-dichloro-9-(4-methylbenzyl)-9H-purine* (**15n**).



Spectrum 97. HMBC of *8-Bromo-2,6-dichloro-9-(4-methylbenzyl)-9H-purine* (**15n**).

9-Benzyl-8-bromo-6-chloro-9H-purine **(15o)**



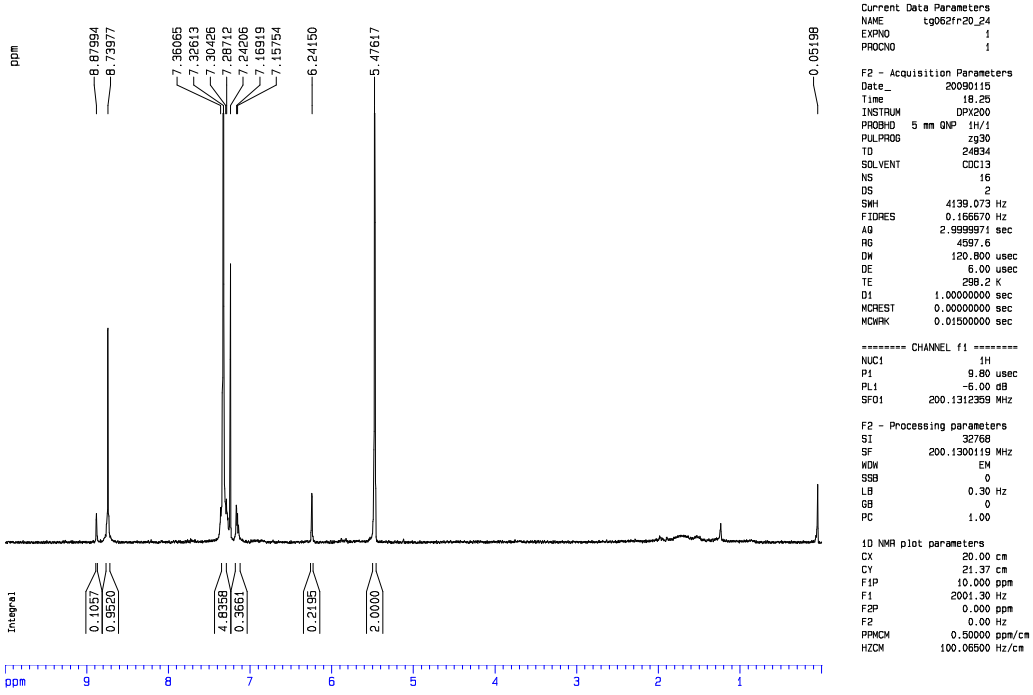
15o

Hexane followed by EtOAc-hexane (1:5) and (1:2) were used for flash chromatography. Yield 4mg (ca 2%), impure compound.

^{1}H NMR ($CDCl_3$, 300 MHz): 5.47 (s, 2H, CH_2), 7.29-7.36 (m, 5H, Ar), 8.74 (s, 1H, H-2)

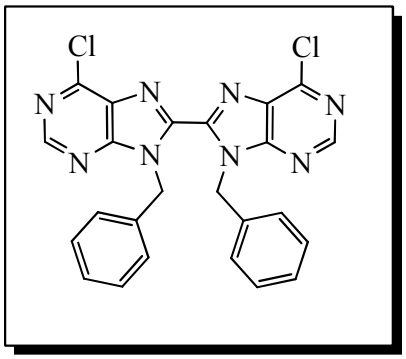
MS (EI). m/z (rel. %): 324/322 (9/7), 287 (6), 280 (5), 278 (8), 245 (6), 243 (18), 216(5), 92 (9), 91 (100), 90 (2), 65 (17).

HR-MS: found 321.9621 calculated for $C_{12}H_8BrClN_4$ 321.9616.



Spectrum 98. ^{1}H NMR of *9-Benzyl-8-bromo-6-chloro-9H-purine* (**15o**)

***8,8'-bis[9-benzyl-6-chloro)-9H-purine]* (45o)**



45o

Hexane followed by EtOAc: Hex, EtOAc: Hex were used for flash chromatography. Yield 14mg (11%), off white solid.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.24 (s, 4H, 2xCH_2), 7.13-7.17 (m, 6H, Ar), 7.28-7.30 (m, 4H, Ar), 8.88 (s, 2H, 2xH-2)

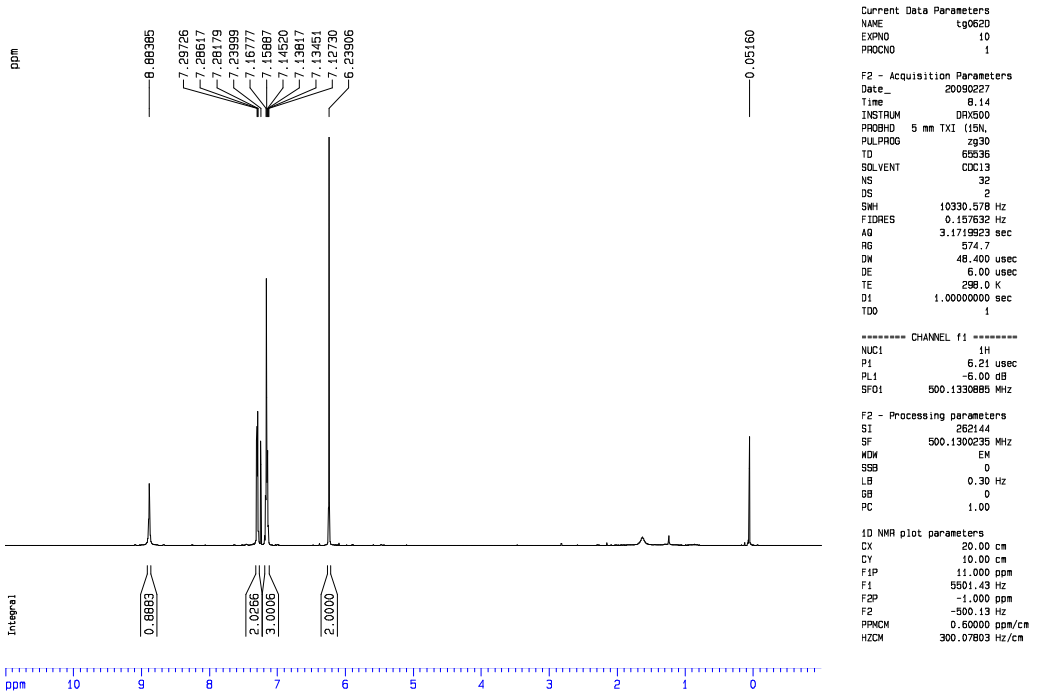
^{13}C NMR ($CDCl_3$, 125MHz): δ 48.4 (CH_2), 128.1 (C-4 Ar), 128.3(C-2 and C-6 Ar), 128.6 (C-3 and C-5 Ar), 135.7 (C-1 Ar), 143.4 (C-8), 153.1 (C-2)

*C-6 and C-4 and C-5 not observe.

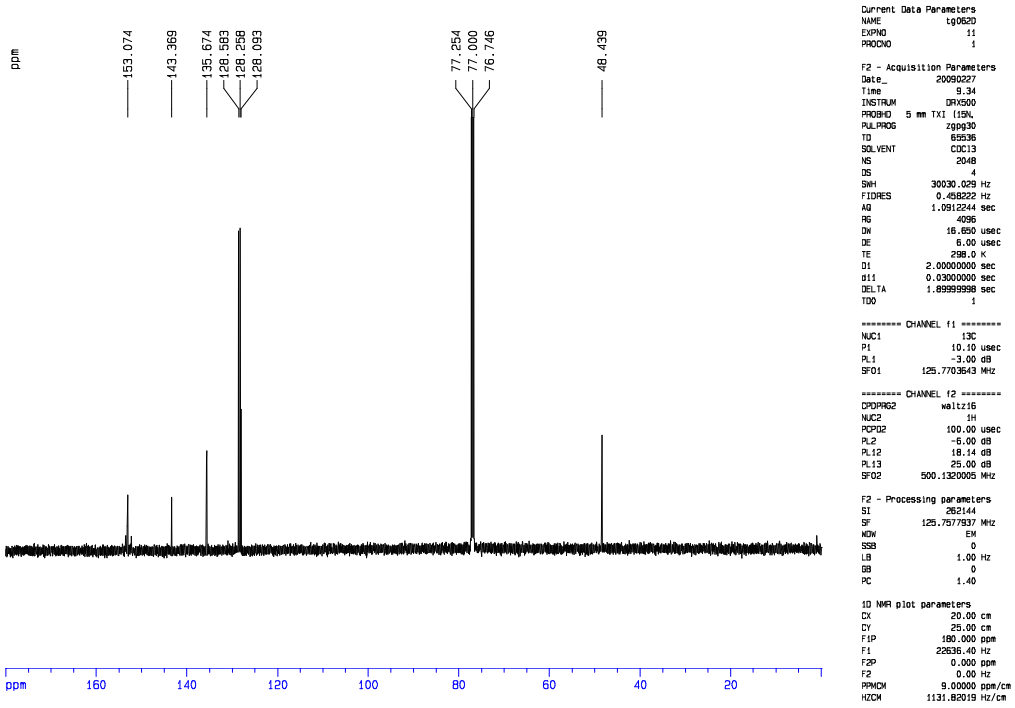
MS (EI). m/z (rel. %): 488/486 (30/44), 397/395 (66/100), 396 (22), 180 (19), 153 (6), 128 (6), 104 (3), 92 (7), 91 (93), 65 (18).

HR-MS: found 486.0880 calculated for $C_{24}H_{16}Cl_2N_8$ 486.0875

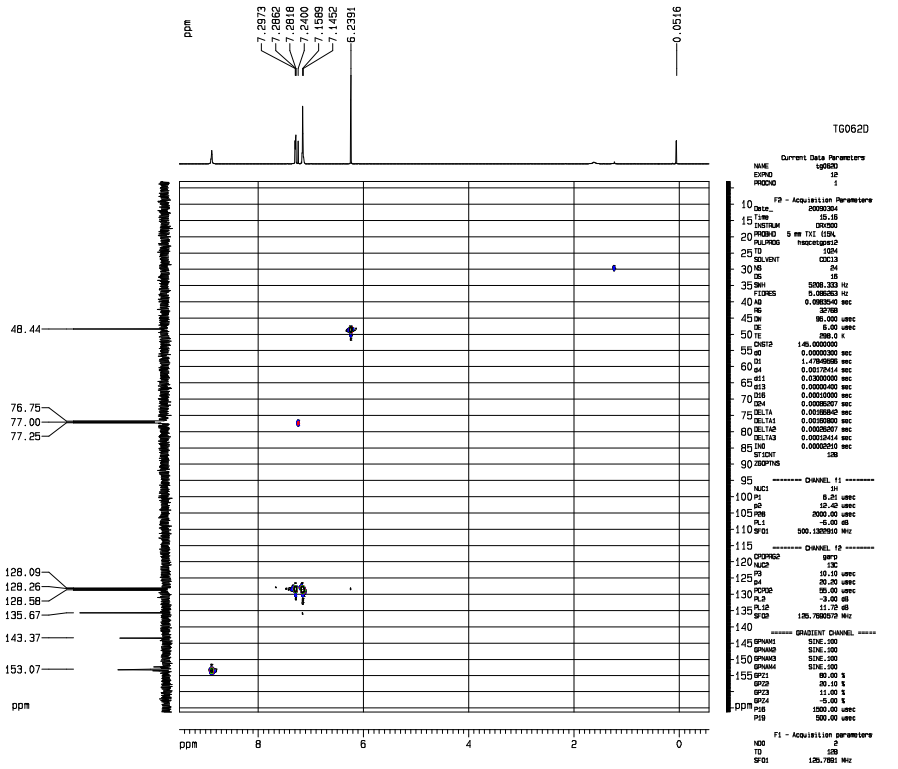
M. p.: 228-230^{o}C.



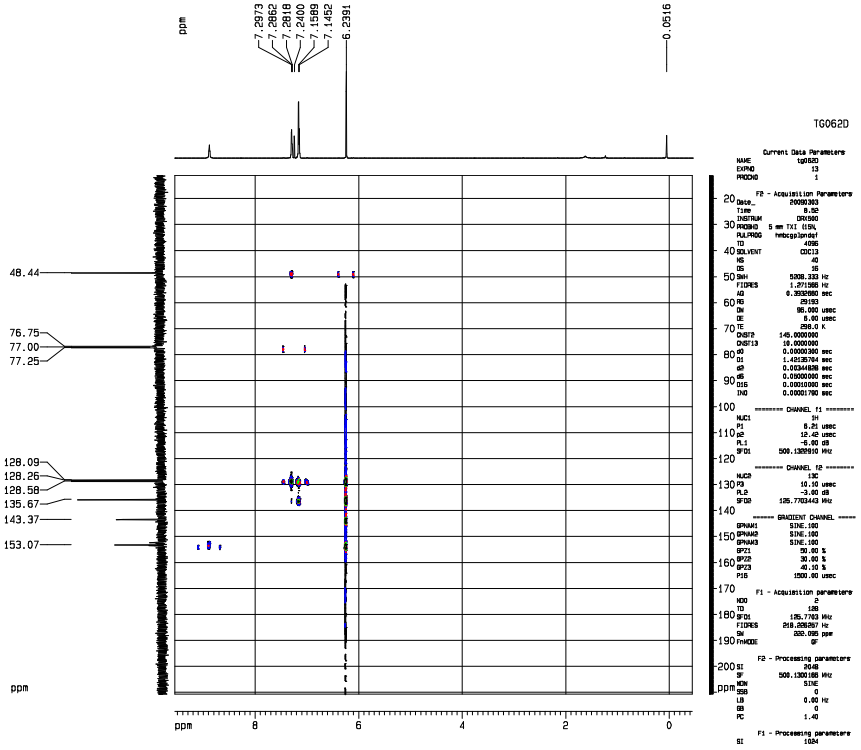
Spectrum 99. [1] H NMR of *8,8'-bis[9-benzyl-6-chloro)-9H-purine]* (**45o**).



Spectrum 100. ^{13}C NMR of *8,8'-bis[9-benzyl-6-chloro)-9H-purine]* (**45o**).

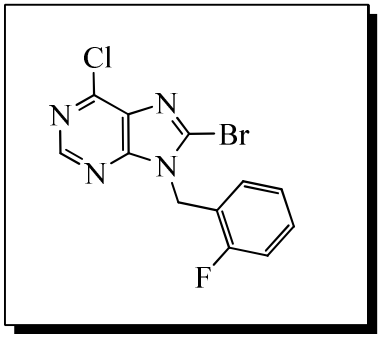


Spectrum 101. HSQC of *8,8'-bis[9-benzyl-6-chloro)-9H-purine]* (**45o**).



Spectrum 102. HMBC of *8,8'-bis[9-benzyl-6-chloro)-9H-purine]* (**45o**).

8-Bromo-6-chloro-9-(2-fluorobenzyl)-9H-purine **(15p)**



15p

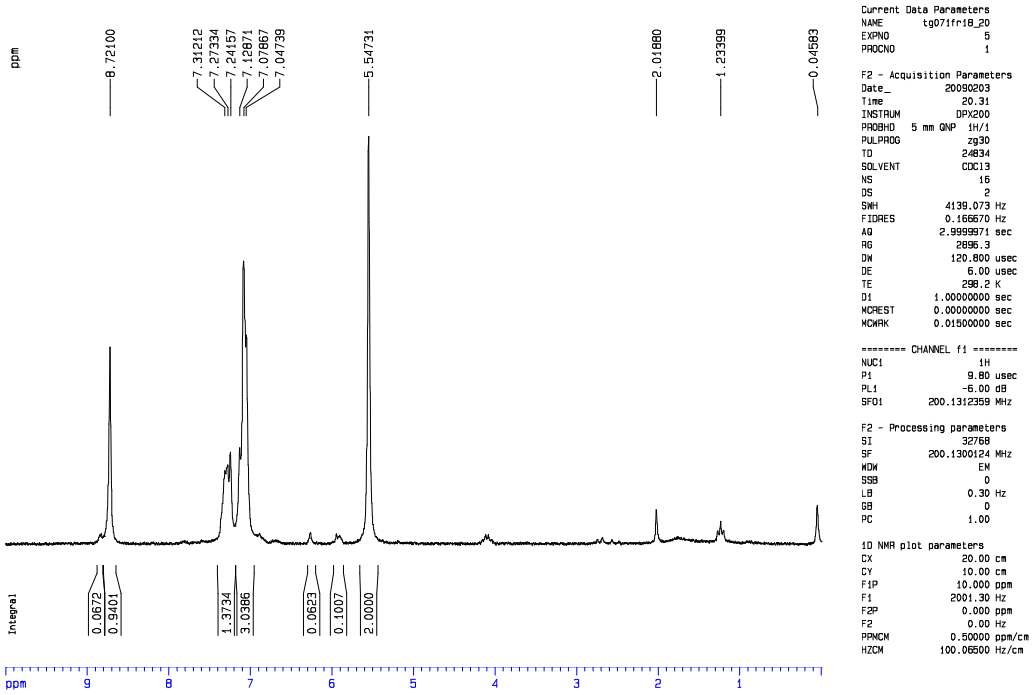
Hexane followed by EtOAc-hexane (1:2) and EtOAc. were used for flash chromatography; Yield 32mg (ca 17%), pale yellow.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.55 (s, 2H, CH2), 7.04-7.08 (m, 3H, Ar), 7.27-7.31 (m, 1H, Ar), 8.72 (s, 1H, H-2).

MS (EI). m/z (rel. %): 342/340 (22/17), 263/261 (10/29), 110 (9), 109(100), 83 (15)

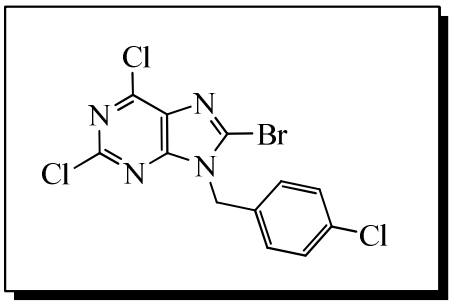
HR-MS: found 339.9537 calculated $C_{12}H_7BrClFN_4$ 339.9527.

M. p. 133-134°C.



Spectrum 103. ^{1}H **NMR** of *8-Bromo-6-chloro-9-(2-fluorobenzyl)-9H-purine* (**15p**).

8-Bromo-2,6-dichloro-9-(4-chlorobenzyl)-9H-purine **(15q)**



15q

Hexane followed by EtOAc-hexane (1:8), EtOAc-hexane (1:2) and EtOAc. were used for flash chromatography; Yield 64mg (34%), brown solid.

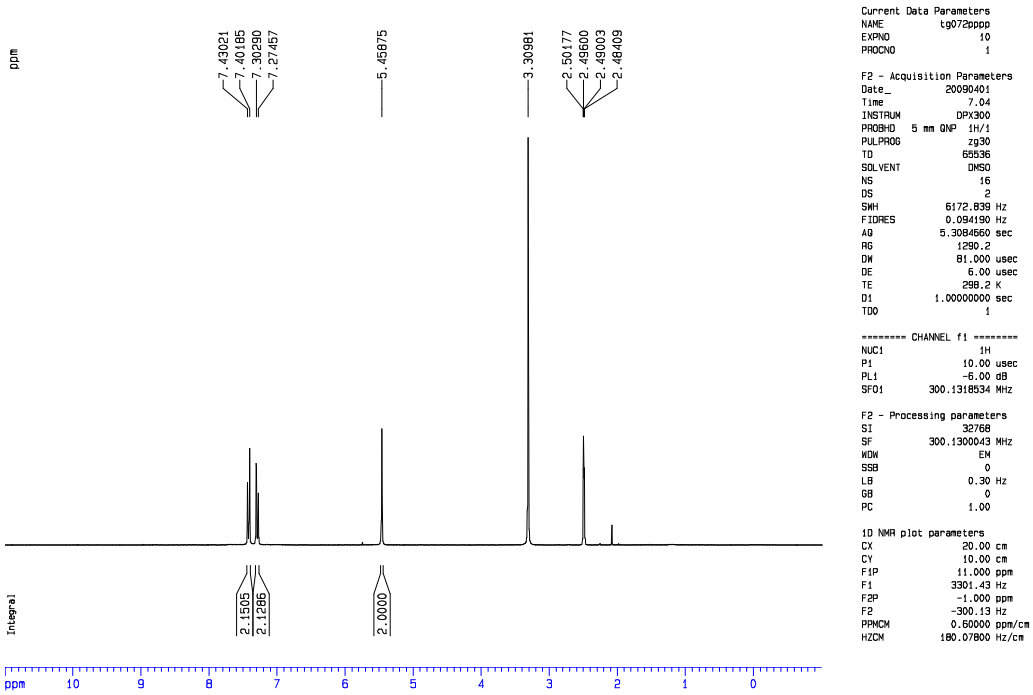
^{1}H NMR (DMSO, 300 MHz): δ 5.46 (s, 2H, CH_2), 7.29 (d, J=8.5Hz, 2H, Ar), 7.42 (d, J=8.5Hz, 2H, Ar).

^{13}C NMR (DMSO, 50MHz): 47.0 (CH_2), 128.7 (C-3 and C-5, Ar), 129.1 (C-2 and C-6, Ar), 130.8 (C-4 Ar), 132.7 (C-8), 133.6 (C-1, Ar), 136.3 (C-5), 148.2 (C-6), 151.4 (C-2), 154.4 (C-4).

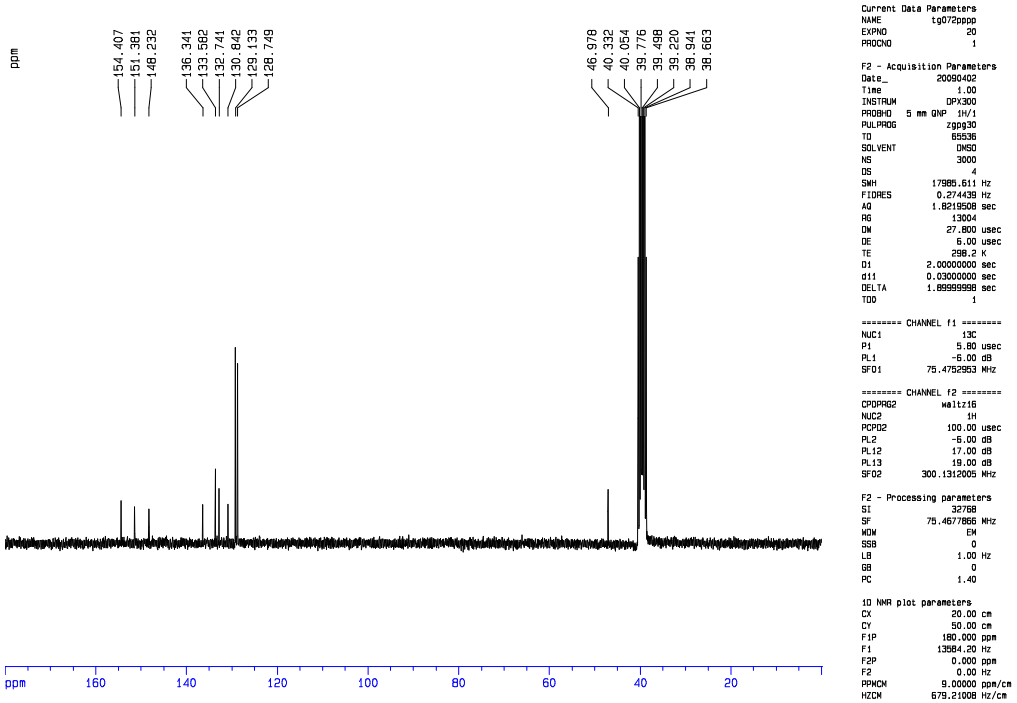
MS (EI). m/z (rel. %): 394/392/390 (11/17/9), 313/311 (10/11), 127 (42), 125 (100), 99 (5), 89 (14).

HR-MS: found 389.8832 calculated for $C_{12}H_6BrCl_3N_4$ 389.8841.

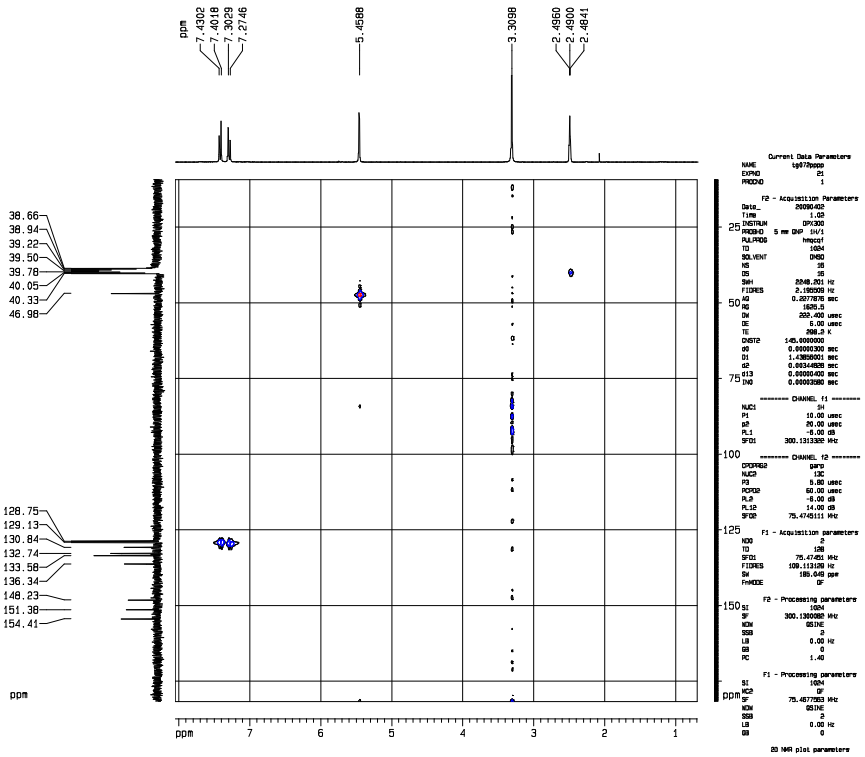
M. p. 203-205 ^oC.



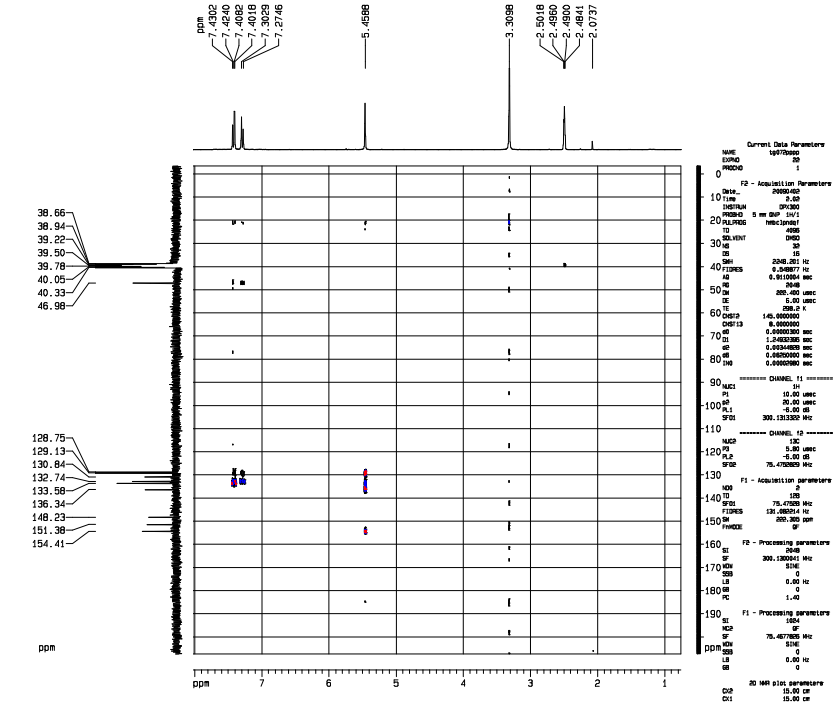
Spectrum 104. ^{1}H **NMR** of *8-Bromo-2,6-dichloro-9-(4-chlorobenzyl)-9H-purine* (**15q**).



Spectrum 105. ^{13}C **NMR** of *8-Bromo-2,6-dichloro-9-(4-chlorobenzyl)-9H-purine* (**15q**).

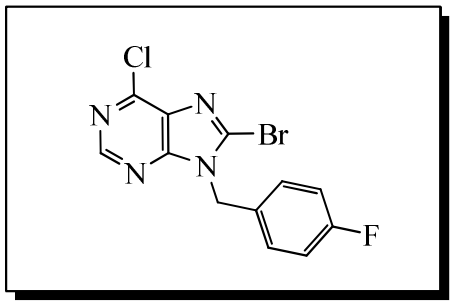


Spectrum 106. HMQC of *8-Bromo-2,6-dichloro-9-(4-chlorobenzyl)-9H-purine* (**15q**).



Spectrum 107. HMBC of *8-Bromo-2,6-dichloro-9-(4-chlorobenzyl)-9H-purine* (**15q**).

8-Bromo-6-chloro-9-(4-fluorobenzyl)-9H-purine **(15r)**



15r

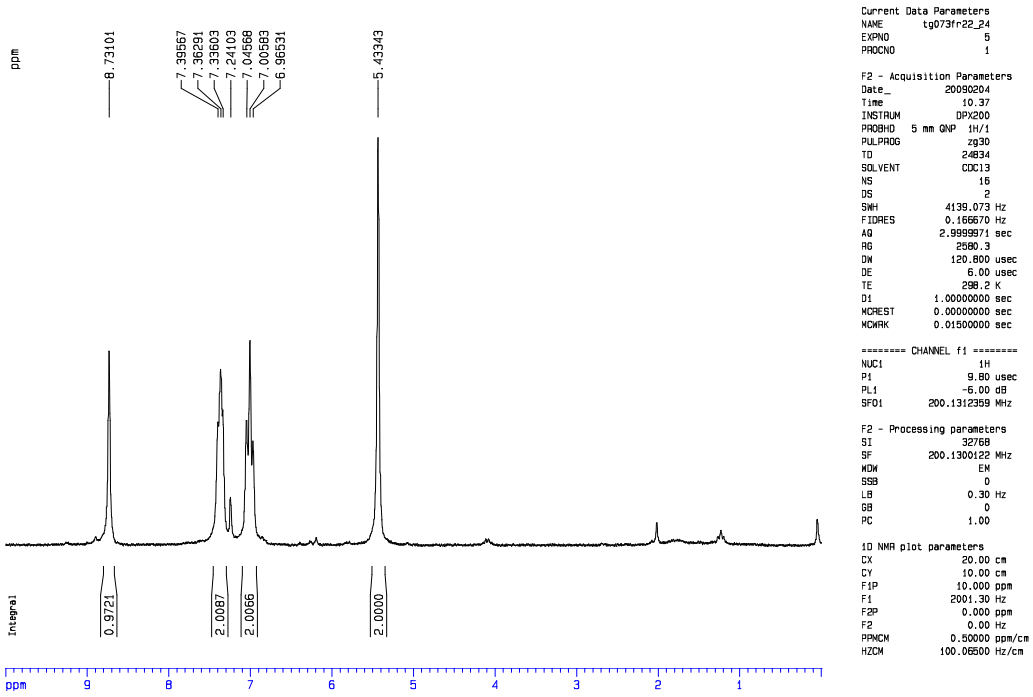
Hexane followed by EtOAc-hexane (2:3) and EtOAc were used for flash chromatography; Yield ca 21mg (19%), pale yellow solid.

^{1}H NMR ($CDCl_3$, 200 MHz); 5.43 (s, 2H, CH_2), 6.96-7.40 (4H, Ar), 8.73 (s, 1H, H-2)

MS (EI). m/z (rel. %): 342/340 (17/13), 263/261 (9/28), 110(10), 109 (100), 107 (4), 83 (13).

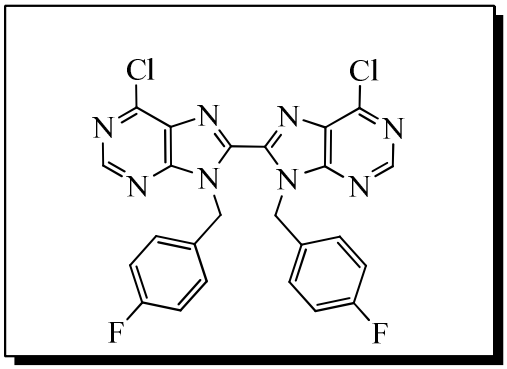
HR-MS: found 339.9528 calculated for $C_{12}H_7BrClFN_4$ 339.9527.

M. p. 143-144^{o}C.



Spectrum 108. ^{1}H NMR of *8-Bromo-6-chloro-9-(2-fluorobenzyl)-9H-purine* (**15r**).

8,8'-bis[6-chloro-9-(4-fluorobenzyl)-9H-purine] **(45r)**



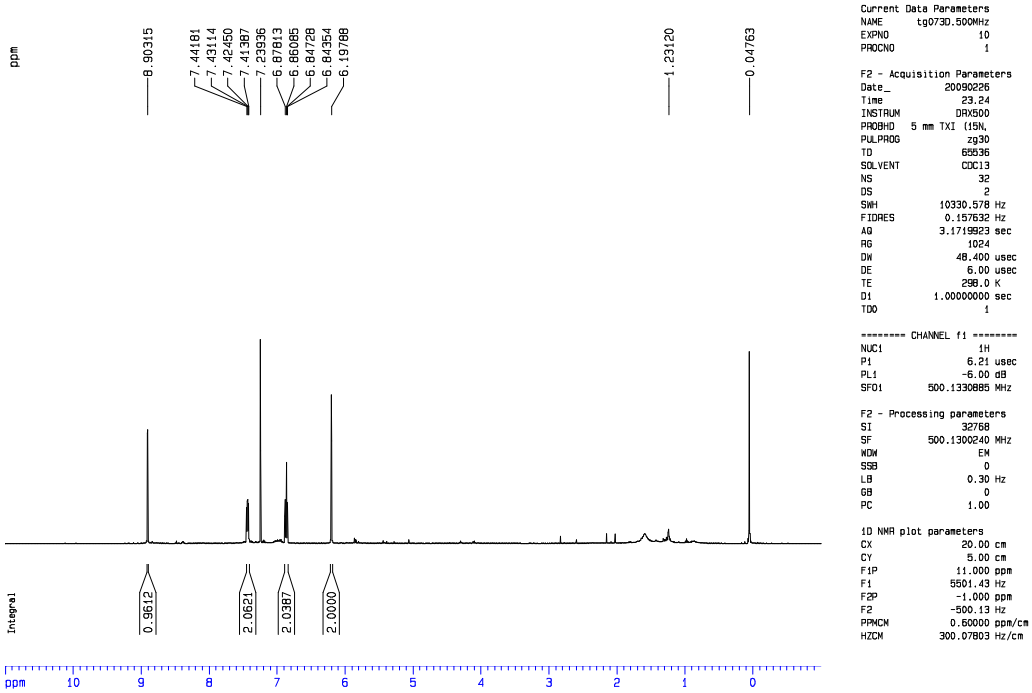
45r

Hexane followed by EtOAc: Hex 2:3 and EtOAc were used for flash chromatography; Yield 6mg (5%). Colourless solid.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.20 (s, 4H, 2xCH_2), 6.84-6.88 (dd, J_1=5.2 Hz and J_2=3.2 Hz, 6H, Ar), 7.41-7.44 (dd, J_1=5.2 Hz and J_2=3.2 Hz, 4H, Ar), 8.90 (s, 2H, 2x H-2)

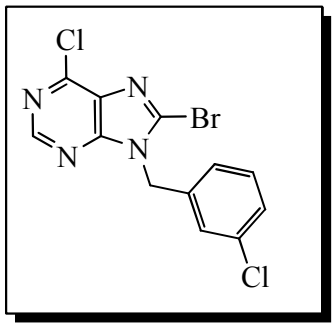
MS (EI). m/z (rel. %): 524/522 (20/29), 417/415/413 (9/50/75), 216 (7), 110 (8), 109 (100), 107 (5), 83 (13).

HR-MS: found 522.0700 calculated $C_{24}H_{14}Cl_2F_2N_8$ 522.0687.



Spectrum 109. ^{1}H NMR of *8,8'-bis[6-chloro-9-(4-fluorobenzyl)-9H-purine]* (**45r**).

8-Bromo-6-chloro-9-(3-chlorobenzyl)-9H-purine **(15s)**



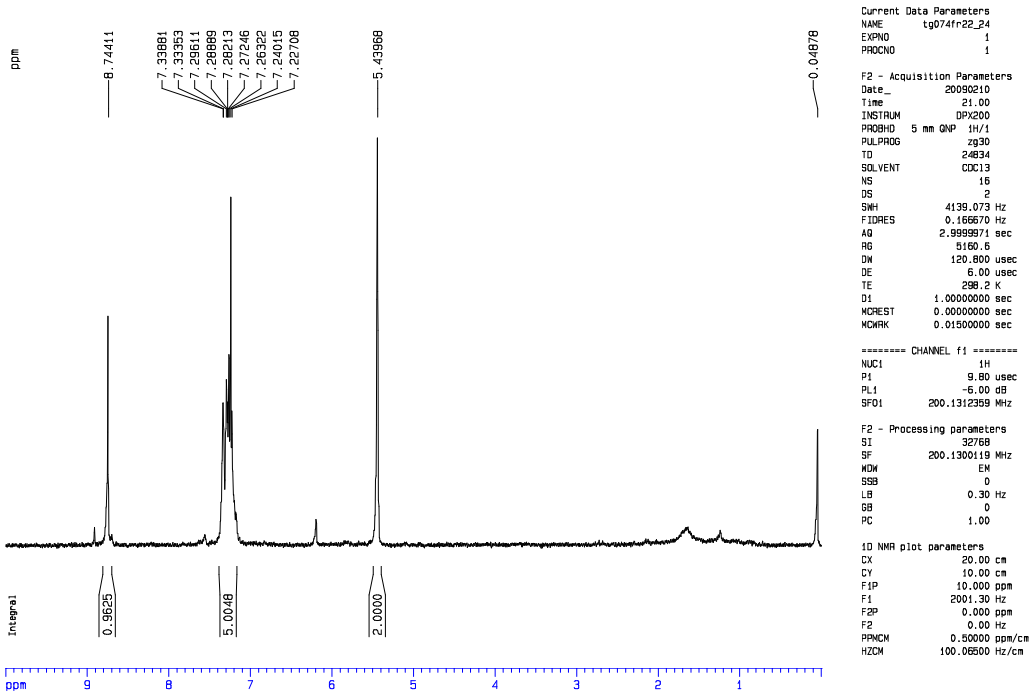
15s

Hexane followed by EtOAc-hexane (1:2) and EtAOc were used for flash chromatography; Yield ca 26mg (15%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.44 (CH_2), 7.23-7.34 (m, 4H, Ar), 8.74 (s, 1H, H-2)

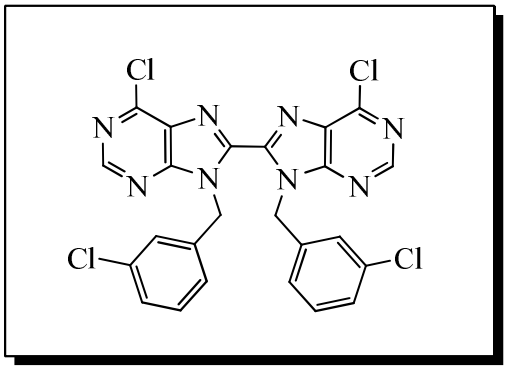
MS (EI). m/z (rel. %): 360/358/356 (9/20/12), 281 (6), 279/277 (34/52), 161 (5), 127 (35), 125 (100), 99 (9), 89 (22), 63 (8).

HR-MS: found 355.9227 calculated $C_{12}H_7BrCl_2N_4$ 355.9231.



Spectrum 110. ^{1}H NMR of *8-Bromo-6-chloro-9-(3-chlorobenzyl)-9H-purine* (**15s**).

8,8'-bis[6-chloro-9-(3-chlorobenzyl)-9H-purine] **(45s)**



45s

Hexane followed by EtOAc-hexane (1:2) and EtAOc were used for flash chromatography; Yield ca 8mg (6%), colourless solid.

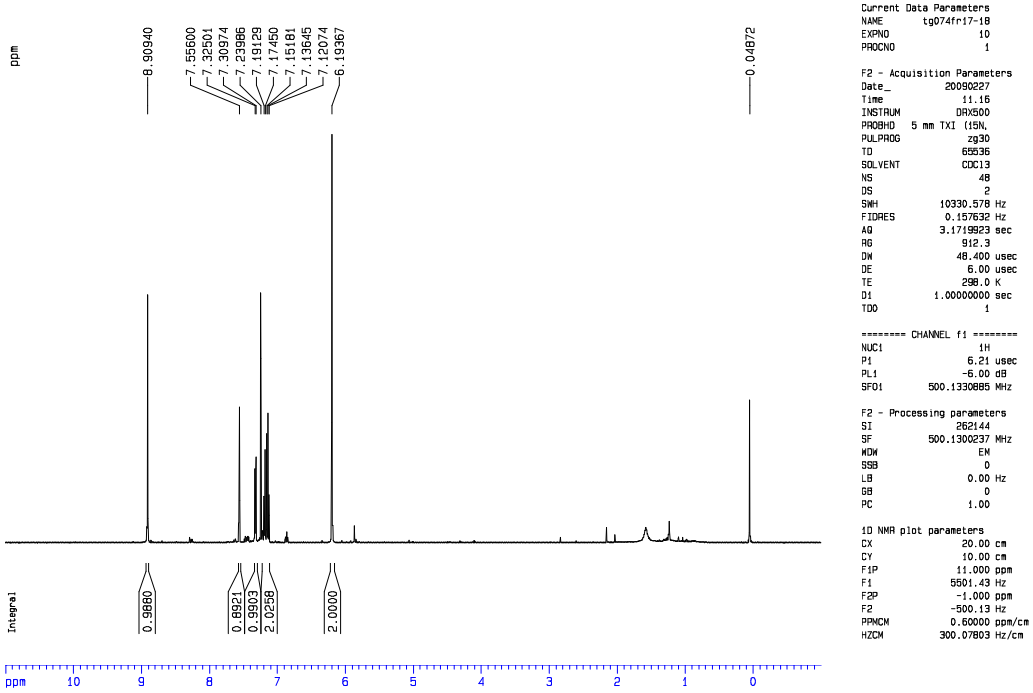
^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.19 (s, 2H, CH_2), 7.12-7.19 (m, 2H, Ar), 7.18 (d, J=8.4Hz, 1H, Ar), 7.56 (s, 1H, Ar), 8.91 (s, 1H, H-2).

^{13}C NMR ($CDCl_3$, 125MHz): δ 48.1 (CH_2), 126.7 (C-6, Ar), 128.5 (C-4, Ar), 129.0 (C-2, Ar), 129.9 (C-5 Ar), 130.9 (C-5), 134.4 (C-4, Ar), 137.5 (C-1, Ar), 143 (C-8), 152.6 (C-4), 153.1 (C-6), 153.7 (C-2).

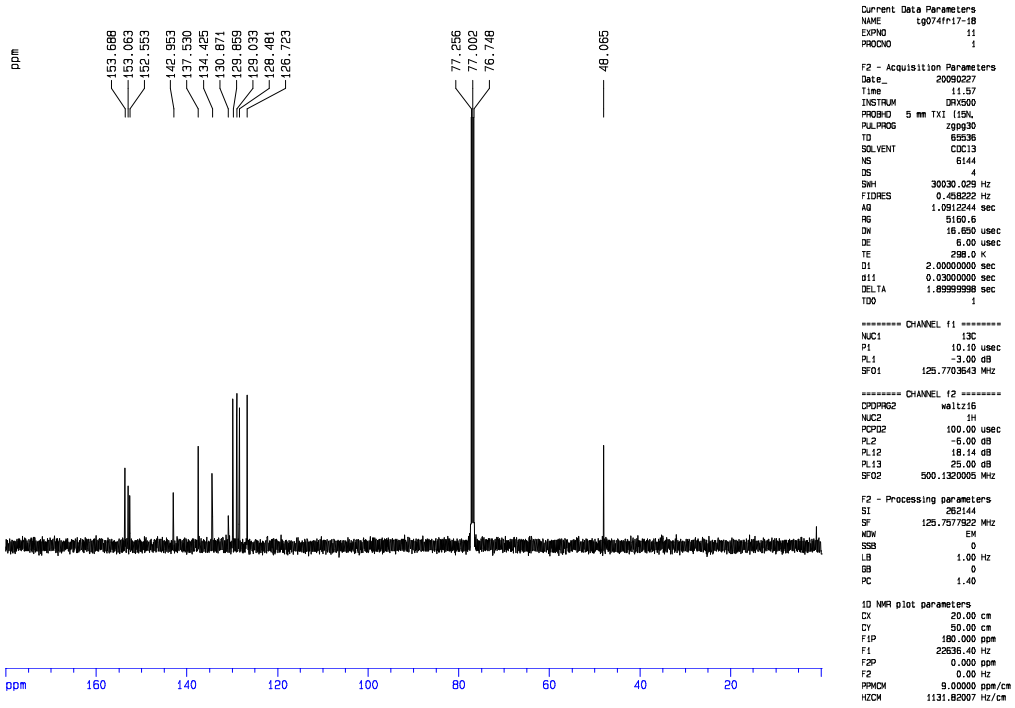
MS (EI). m/z (rel. %): 558/556/554 (20/40/30), 475 (5), 433 (32), 432 (20), 431 (97), 430 (21), 429 (100), 187 (6), 180 (9), 127 (28), 125 (79), 99 (9), 89 (27).

HR-MS: found 554.0084 calculated $C_{24}H_{14}Cl_4N_8$ 554.0096.

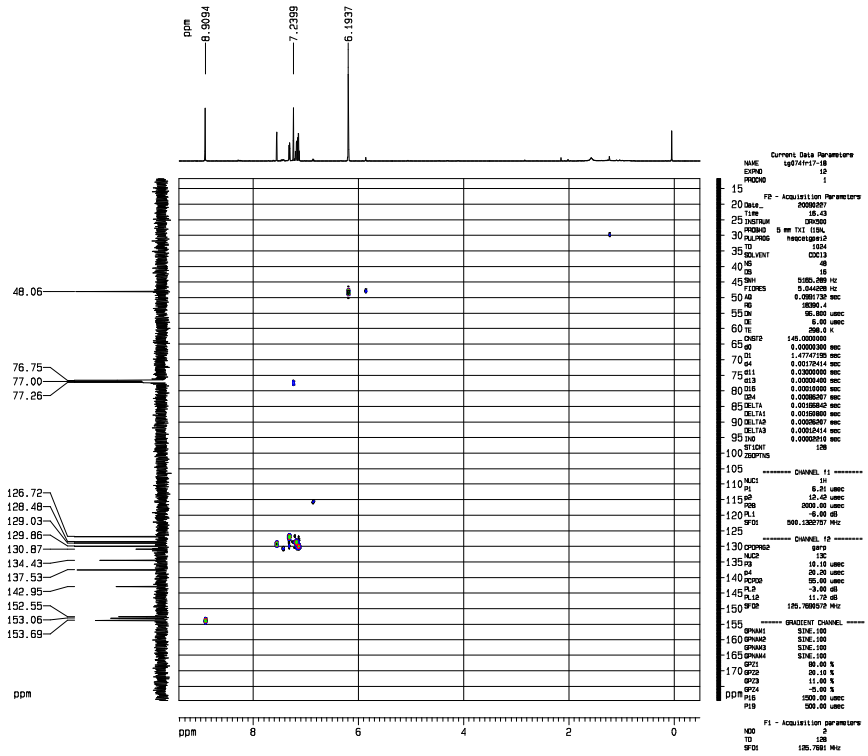
M. p. 245-246^{o}C.



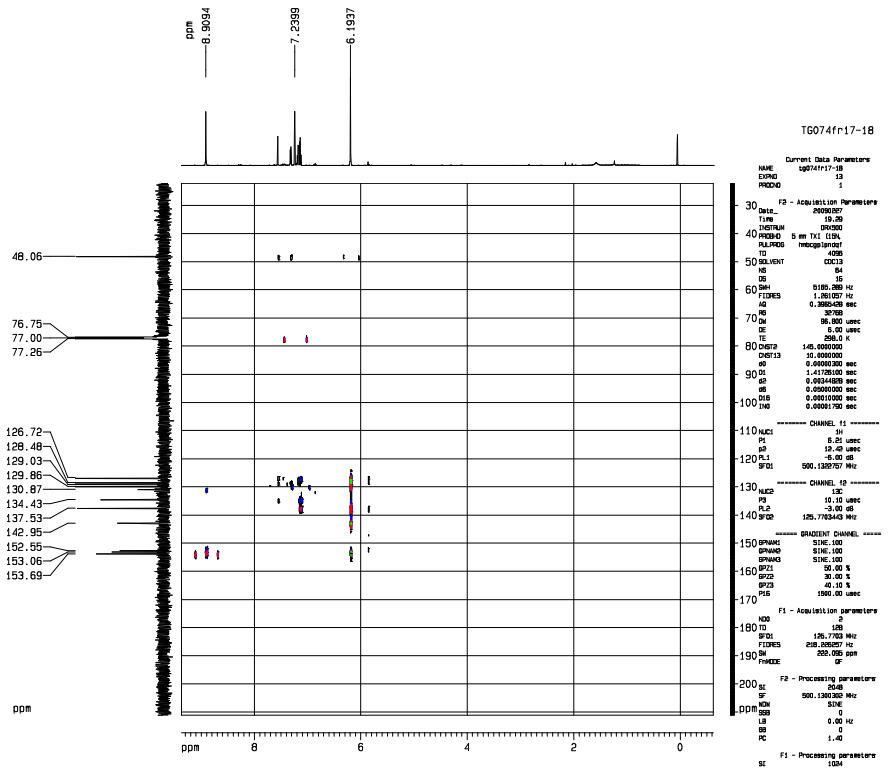
Spectrum 111. ^{1}H NMR of *8,8'-bis[6-chloro-9-(3-chlorobenzyl)-9H-purine]* (**45s**).



Spectrum 112. ^{13}C NMR of *8,8'-bis[6-chloro-9-(3-chlorobenzyl)-9H-purine]* (**45s**).

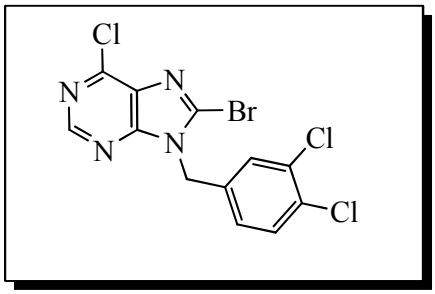


Spectrum 113. HMBC of *8,8'-bis[6-chloro-9-(3-chlorobenzyl)-9H-purine]* (**45s**).



Spectrum 114. HMBC of *8,8'-bis[6-chloro-9-(3-chlorobenzyl)-9H-purine]* (**45s**).

8-Bromo-6-chloro-9-(3, 4-dichlorobenzyl)-9H-purine **(15w)**



15w

Hexane followed by EtOAc: Hex 1:8, EtOAc: Hex 1:4 were used for flash chromatography; Yield 37mg (19%) brown solid.

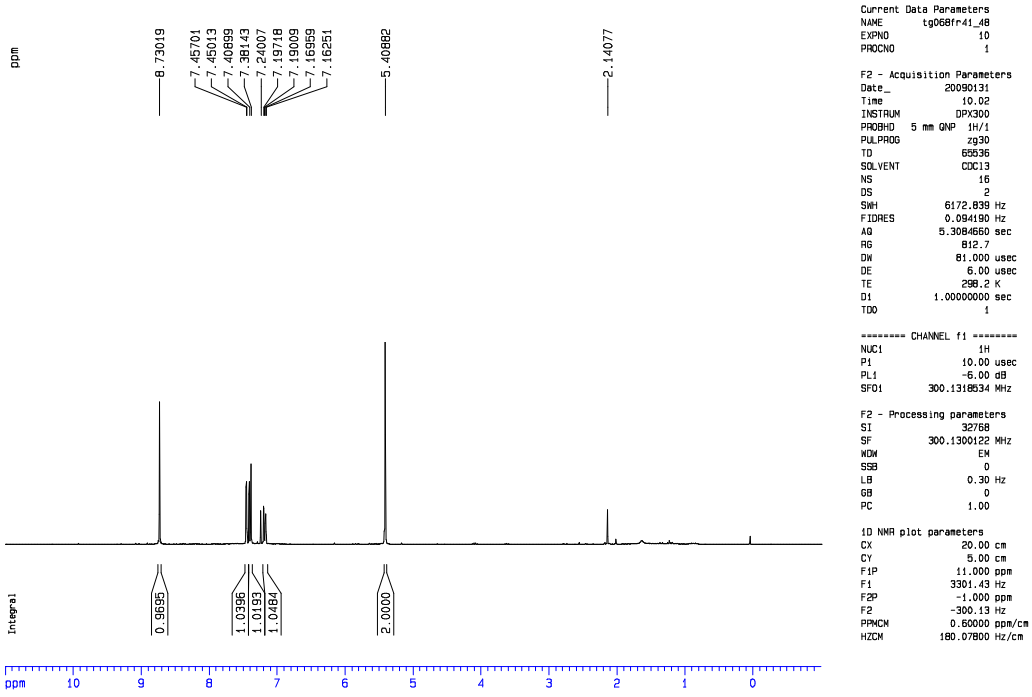
^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.41 (s, 2H, CH_2), 7.18 (dd, J_1=2.1 Hz and J_2=8.3 Hz, 1H, Ar), 7.40 (d, J= 8.3 Hz, 1H, Ar), 7.45 (d, J=2.1 Hz, 1H, Ar), 8.73 (s, 1H, H-2).

^{13}C NMR ($CDCl_3$, 75MHz): δ 47.1 (CH_2), 127.3 (C-6 Ar), 130.0 (C-5 Ar), 131.1 (C-2 Ar), 131.8 (C-4 Ar), 133.2 (C-5) 133.3 (C-8), 133.7 (C-3 Ar), 134.0 (C-1 Ar), 149.8 (C-4), 152.3 (C-2), 152.8 (C-6).

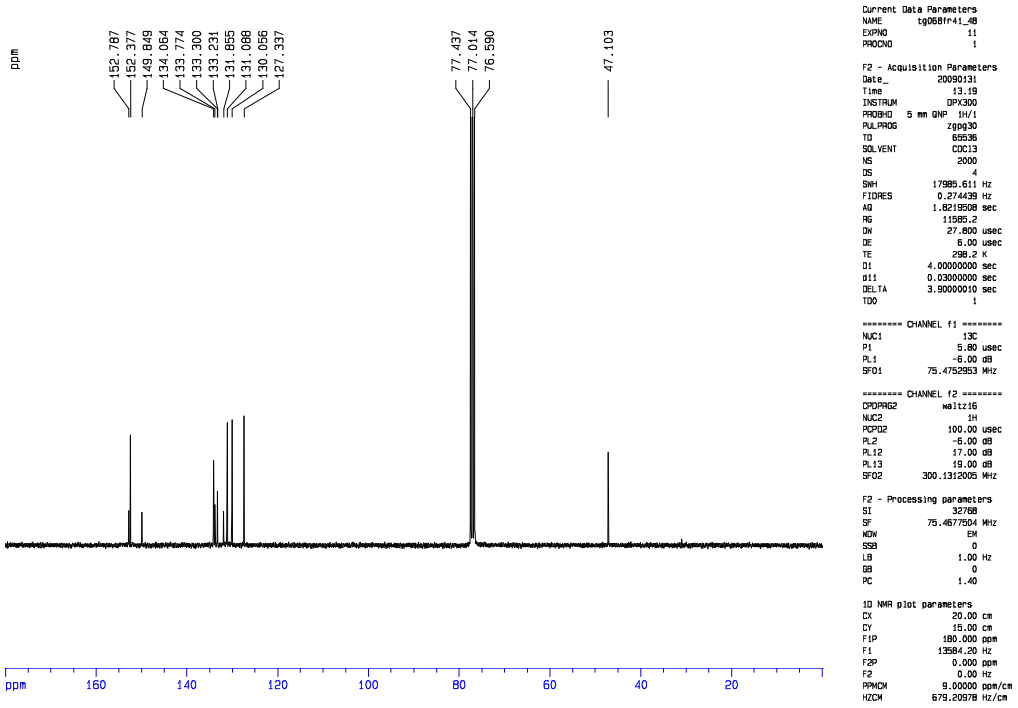
MS (EI). m/z (rel. %): 394/392/390 (18/27/14), 315/313/311 (15/45/47), 163/161/159 (11/65/100), 124 (8), 123 (16), 89 (15), 63 (7).

HR-MS: found 389.8834 calculated for $C_{12}H_6BrCl_3N_4$ 389.8841.

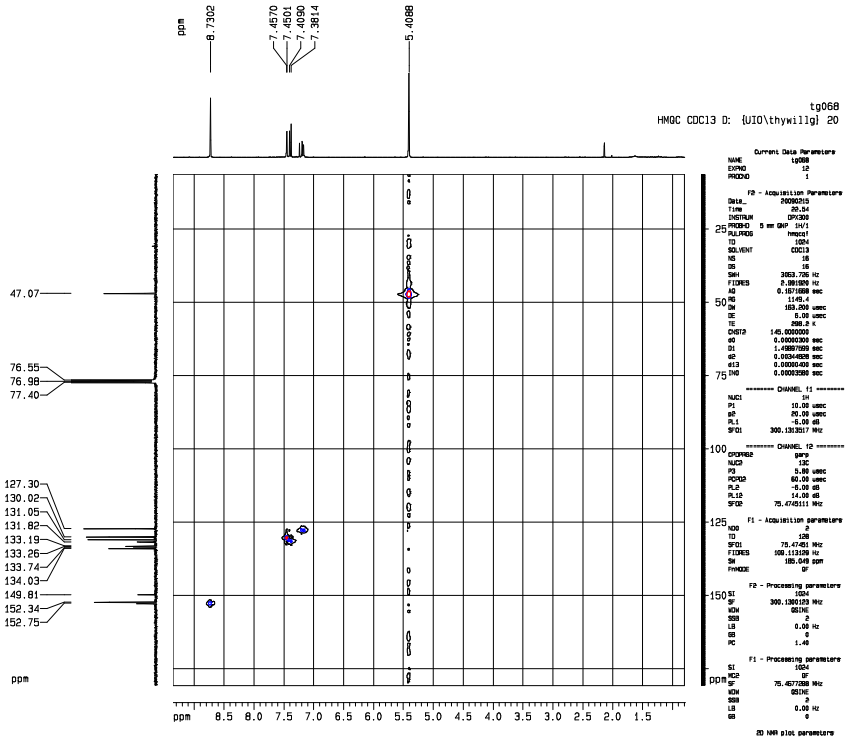
M. p.: 138-140°C



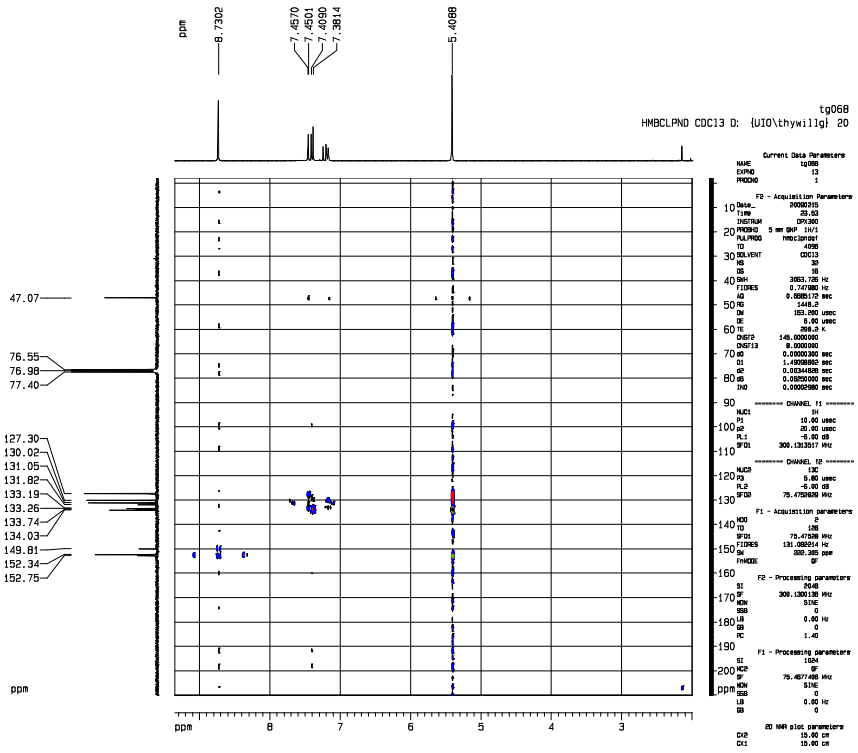
Spectrum 115. ^{1}H NMR of *8-bromo-6-chloro-9-(3, 4-dichlorobenzyl)-9H-purine* (**15w**).



Spectrum 116. ^{13}C NMR of *8-bromo-6-chloro-9-(3, 4-dichlorobenzyl)-9H-purine* (**15w**).

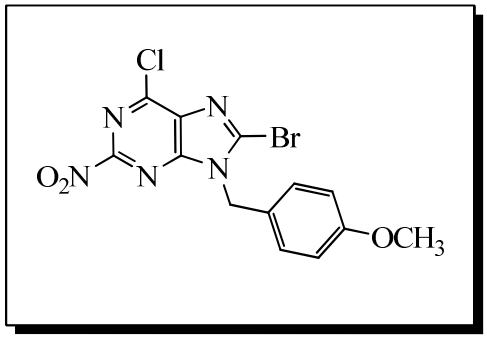


Spectrum 117. HMQC of *8-bromo-6-chloro-9-(3, 4-dichlorobenzyl)-9H-purine* (**15w**).



Spectrum 118. HMBC of *8-bromo-6-chloro-9-(3, 4-dichlorobenzyl)-9H-purine* (**15w**).

8-Bromo-6-chloro-9-(4-methoxybenzyl)-2-nitro-9H-purine **(15x)**



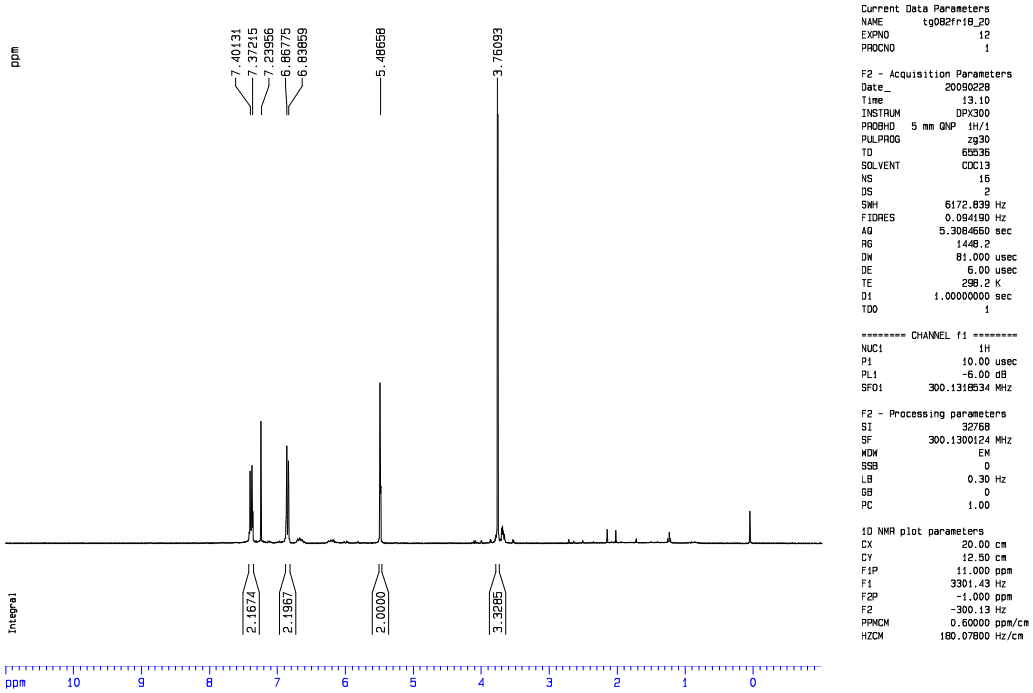
15x

Hexane followed by EtOAc-hexane (1:1) and EtOAc were used for flash chromatography; Yield ca 12mg (6%), yellow solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.76 (s, 3H, OCH_3), 5.49 (s, 2H, CH_2), 6.85 (d, J=8.7Hz, 2H, Ar), 7.39 (d, J=8.7Hz, 2H, Ar).

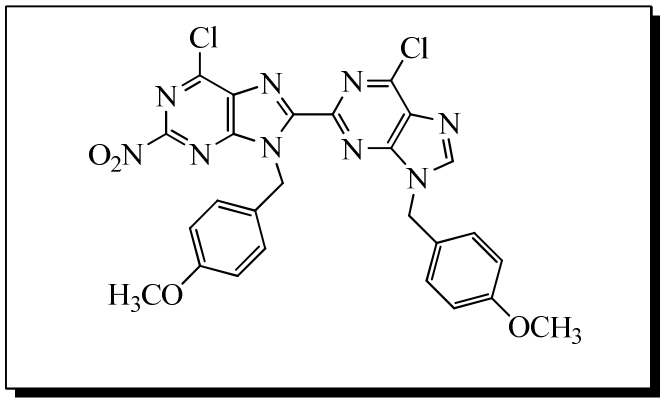
MS (EI). m/z (rel. %): 399/397 (11/9), 122 (12), 121 (100), 91 (5), 90 (2), 78 (8), 77 (8), 65 (2).

HR-MS: found 396.9575 calculated for $C_{13}H_9BrClN_5O_3$ 396.9577.



Spectrum 119. [1] H of *8-Bromo-6-chloro-9-(4-methoxybenzyl)-2-nitro-9H-purine* (**15x**).

***6-Chloro-8-(6'-chloro-9'-(4'-methoxybenzyl)-9'H-puri-2'-nyl)-9H-(4-methoxybenzyl)-2-nitro-9H-purine* (52x)**



52x

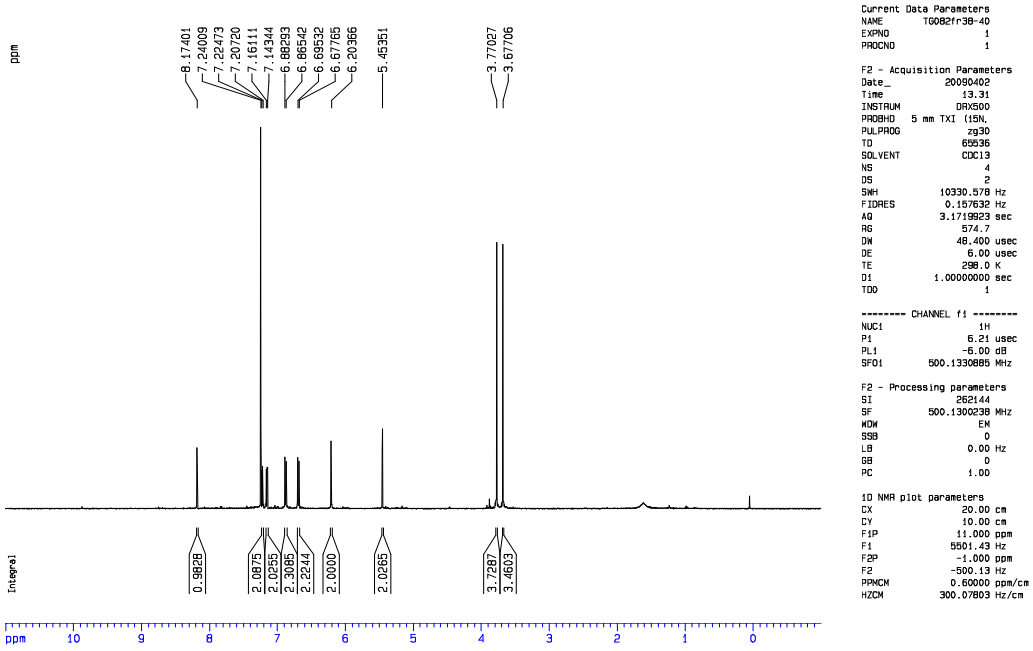
Hexane followed by EtOAc-hexane (1:1) and EtOAc were used for flash chromatography; Yield 6mg (4%), yellow solid.

^{1}H NMR ($CDCl_3$, 500MHz): δ 3.68 (s, 3H, OCH_3'), 3.77(s, 3H, OCH_3), 5.45 (s, 2H, CH_2'), 6.20 (s, 2H, CH_2), 6.69 (d, J=8.8Hz, 2H, Ar), 6.87 (d, J=8.8 Hz, 2H, Ar), 7.15(d, J=8.8Hz, 2H, Ar), 7.22(d, J=8.8Hz, 2H, Ar), 8.17(s, 1H, H-8').

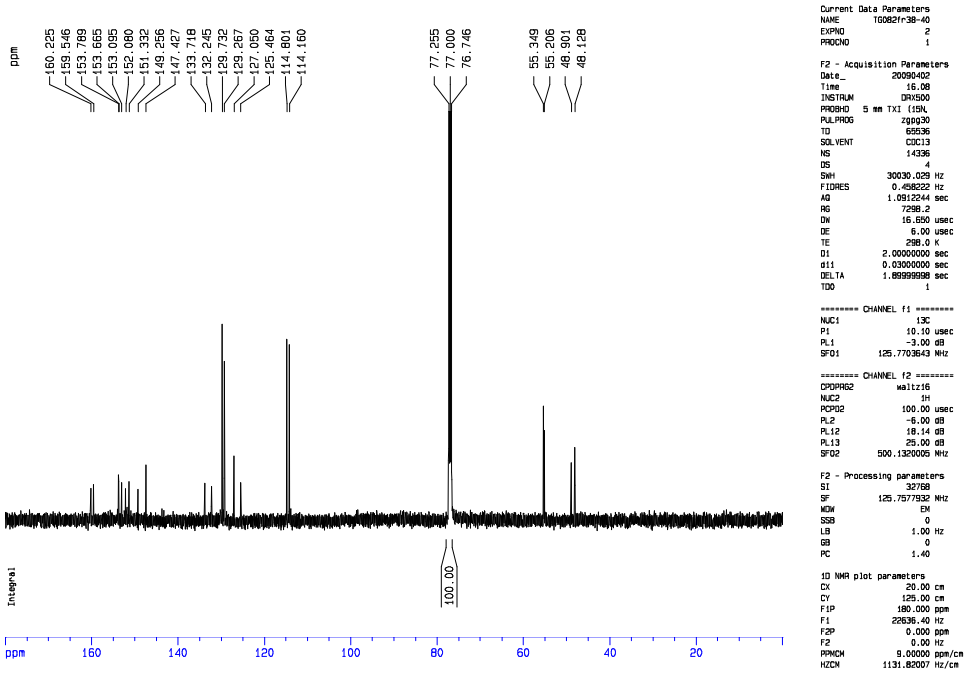
^{13}C NMR ($CDCl_3$, 125MHz): δ 48.1 (CH_2'), 48.9 (CH_2), 55.2 (OCH_3'), 55.3 (OCH_3), 114.2 (C-3' and C-5' Ar), 114.8 (C-3 and C-5, Ar), 125.5 (C-1' , Ar), 127.1 (C-1, Ar), 129.3 (C-2' and C-6', Ar), 129.7 (C-2 and C-6, Ar), 132.2 (C-5', Ar), 132.7 (C-5, Ar), 147.4 (C-8'), 149 (C-6'), 151.3 (C-6'), 152.1(C-2'), 153.1 (C-8 and/ or C-2), 153.7 (C-4), 153.8 (C-6), 159.5 (C-4' Ar), 160.2 (C-4 Ar).

MS (EI). m/z (rel. %): 593/591 (5/9), 121 (9), 121 (100), 77 (9).

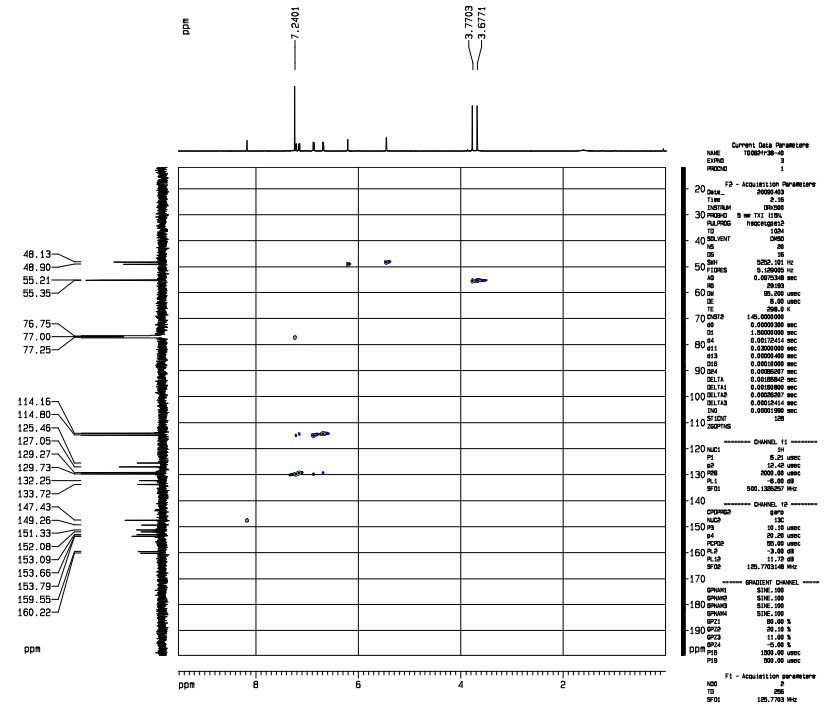
HR-MS: found 591.0955 calculated for $C_{26}H_{19}Cl_2N_9O_4$ 591.0937.



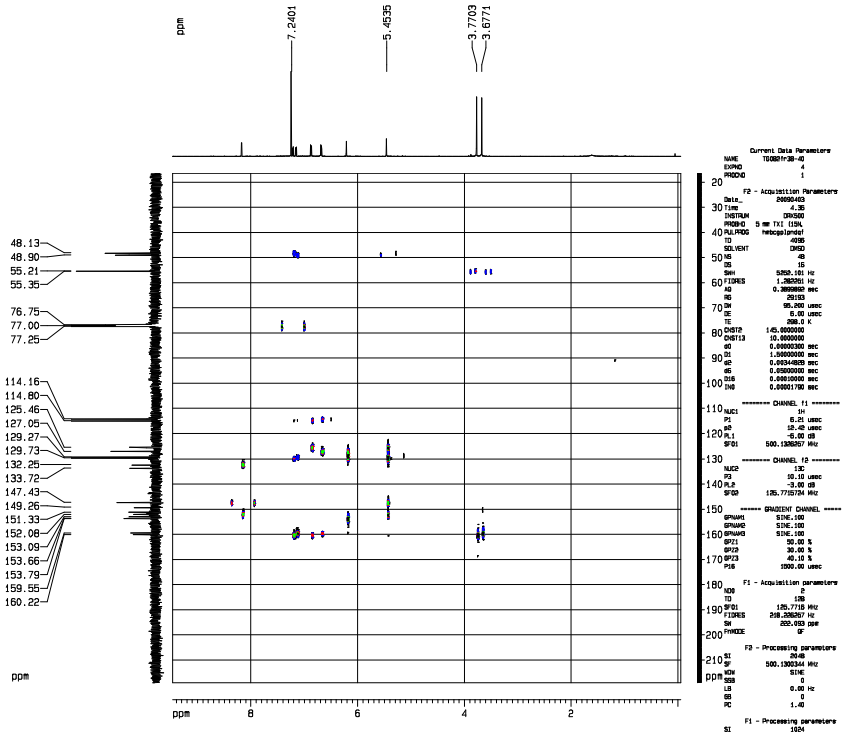
Spectrum 120. ^{1}H NMR of *6-Chloro-8-(6'-chloro-9'-(4'-methoxybenzyl)-9'H-puri-2'-nyl)-9H-(4-methoxybenzyl)-2-nitro-9H-purine* (**52x**)



Spectrum 121. ^{13}C NMR of *6-Chloro-8-(6'-chloro-9'-(4'-methoxybenzyl)-9'H-puri-2'-nyl)-9H-(4-methoxybenzyl)-2-nitro-9H-purine* (**52x**).

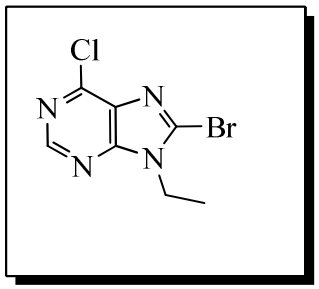


Spectrum 122. HSQC of *6-Chloro-8-(6'-chloro-9'-(4'-methoxybenzyl)-9'H-puri-2'-nyl)-9H-(4-methoxybenzyl)-2-nitro-9H-purine* (**52x**).



Spectrum 123. HMBC *6-Chloro-8-(6'-chloro-9'-(4'-methoxybenzyl)-9'H-puri-2'-nyl)-9H-(4-methoxybenzyl)-2-nitro-9H-purine* (**52x**).

8-Bromo-6-chloro-9-ethyl-9H-purine **(15y)**



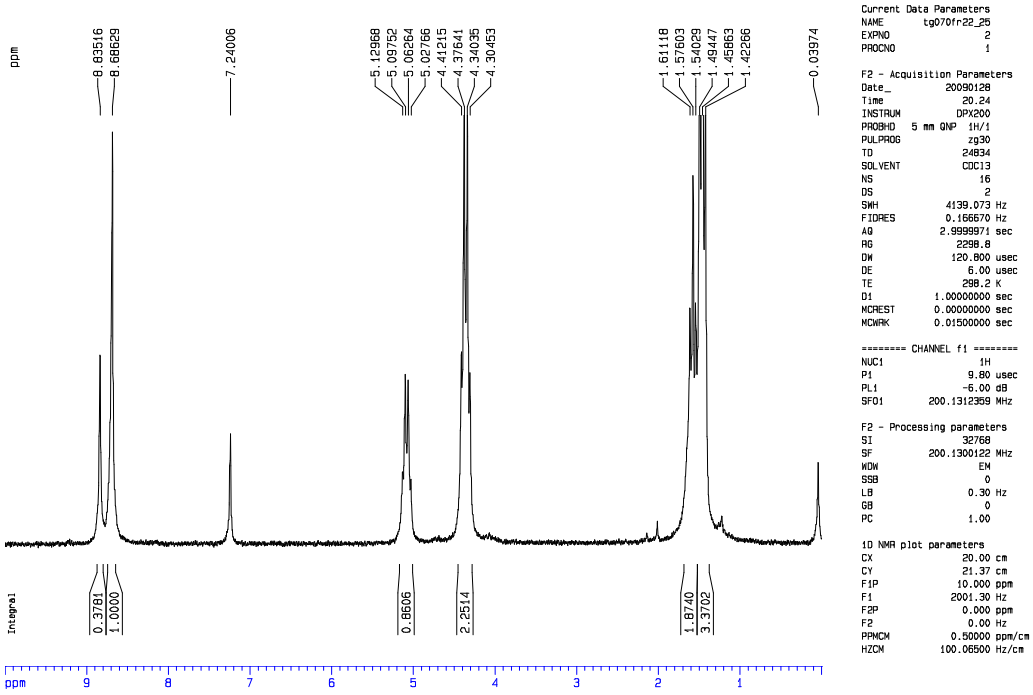
15y

Hexane followed by EtOAc-hexane (1:8), EtOAc-hexane (1:1) and EtOAc were used for flash chromatography; Yield ca 25mg (19%) impure (contaminated by the dimer by-product).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.46 (t, J=7.2Hz, 3H, CH_3), 4.36 (q, J=7.2Hz, 2H, CH_2), 8.69 (s, 1H, H-2).

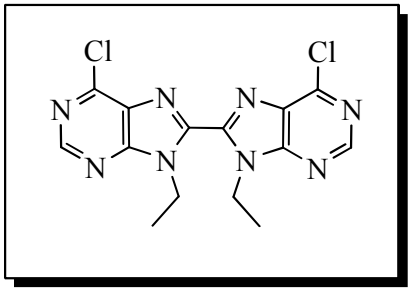
MS (EI). m/z (rel. %): 262/260 (39/30), 236(24) 234/232 (100/78), 190 (12), 188 (18), 181 (14), 153 (9), 127 (10), 118 (7), 91 (7), 77 (10), 64 (6).

HR-MS: found 259.9463 calculated $C_7H_6BrClN_4$ 259.9464.



Spectrum 124 .[1]H NMR of *8-Bromo-6-chloro-9-ethyl-9H-purine* (**15y**) with impurity of *8,8'-Bis[(6-chloro-9-ethyl)-9H-purine]* (**45y**)

8,8'-Bis[(6-chloro-9-ethyl)-9H-purine] (**45y**)



45y

Hexane followed by EtOAc-hexane (1:8), EtOAc-hexane (1:1) and EtOAc were used for flash chromatography; Yield 17mg (18%).Pale yellow solid.

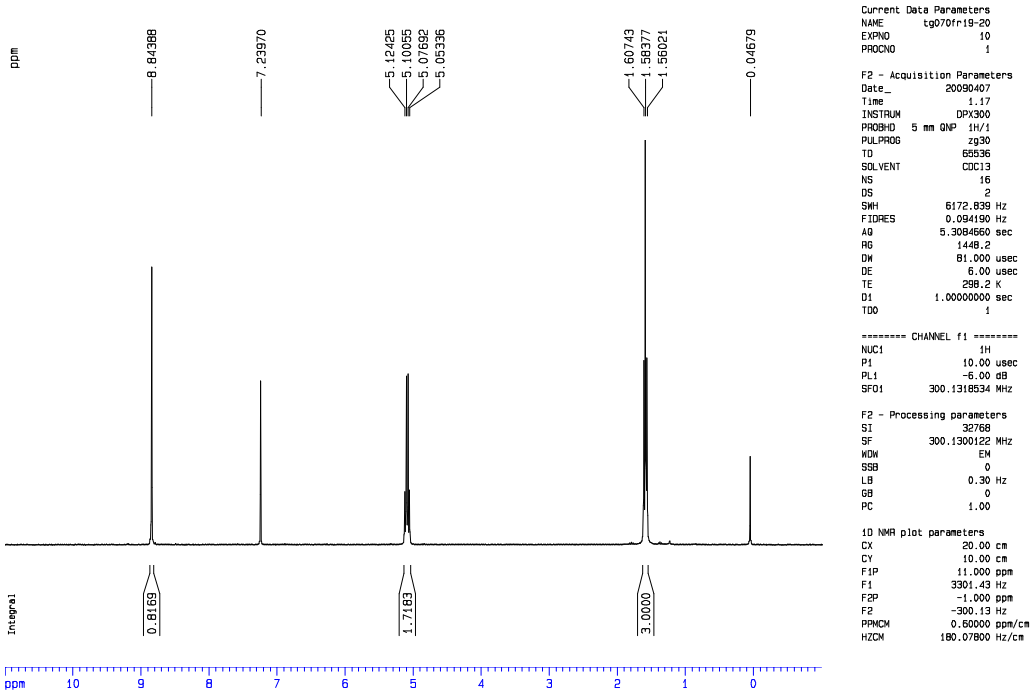
^{1}H NMR ($CDCl_3$, 300 MHz):. δ 1.58 (t, J=7.0Hz, 6H, 2xCH_3), 5.09 (q, J=7.0Hz, 4H, 2xCH_2), 8.84 (s, 2H, 2xH-2).

^{13}C NMR ($CDCl_3$, 300 MHz): δ 15.3 (CH_3), 41.2 (CH_2), 131.3 (C-5), 143.4 (C-8), 152.2 (C-6), 152.7 (C-4), 153.1 (C-2)

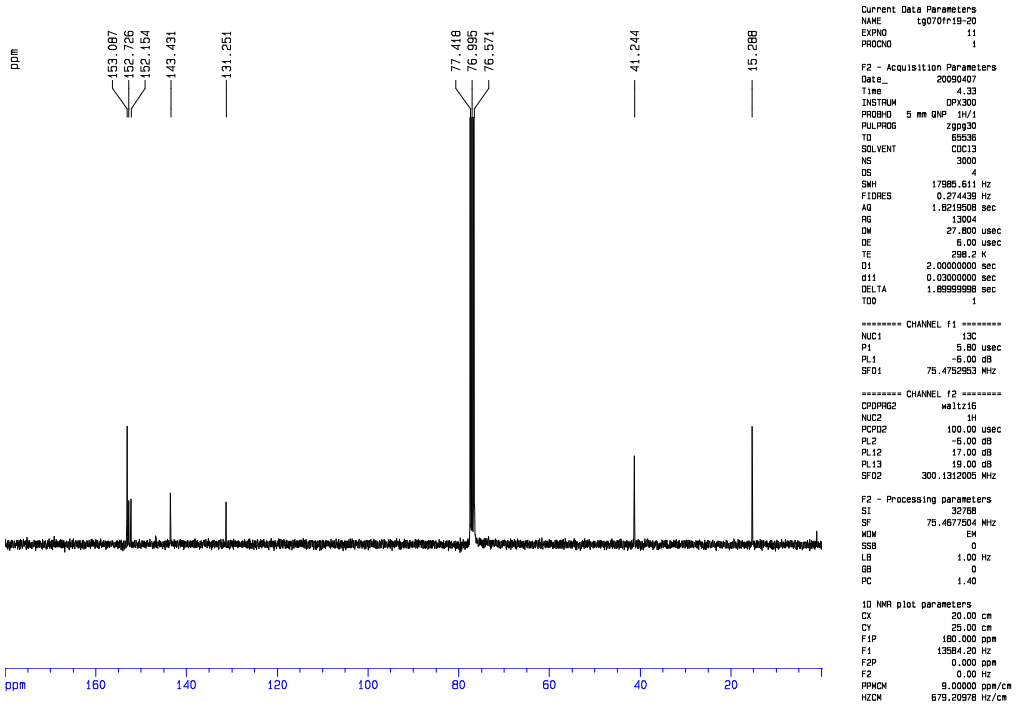
MS (EI). m/z (rel. %): 364/362 (60/39), 347 (7), 335/333 (68/100), 309 (8), 308 (11), 307 (13), 273 (6), 271 816), 235 (6), 180 (11),167 (5), 154 (9), 144 (12), 119 (5), 100 (2), 92 (4) 91 (2), 85(2).

HR-MS: found 362.0554 calculated $C_{14}H_{12}Cl_2N_8$ 362.0562.

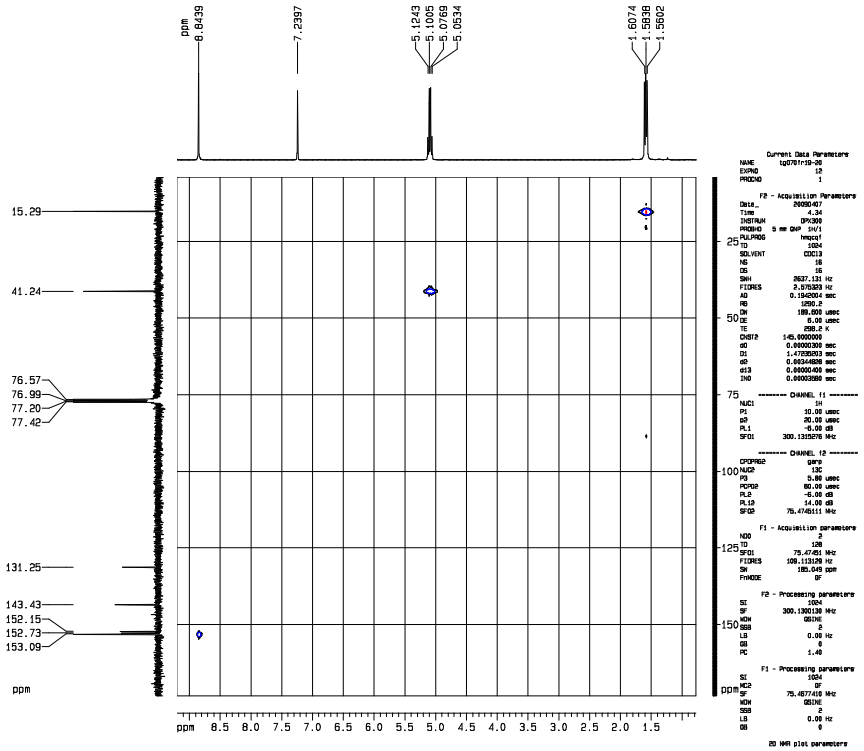
M. p. 256-257^{o}C.



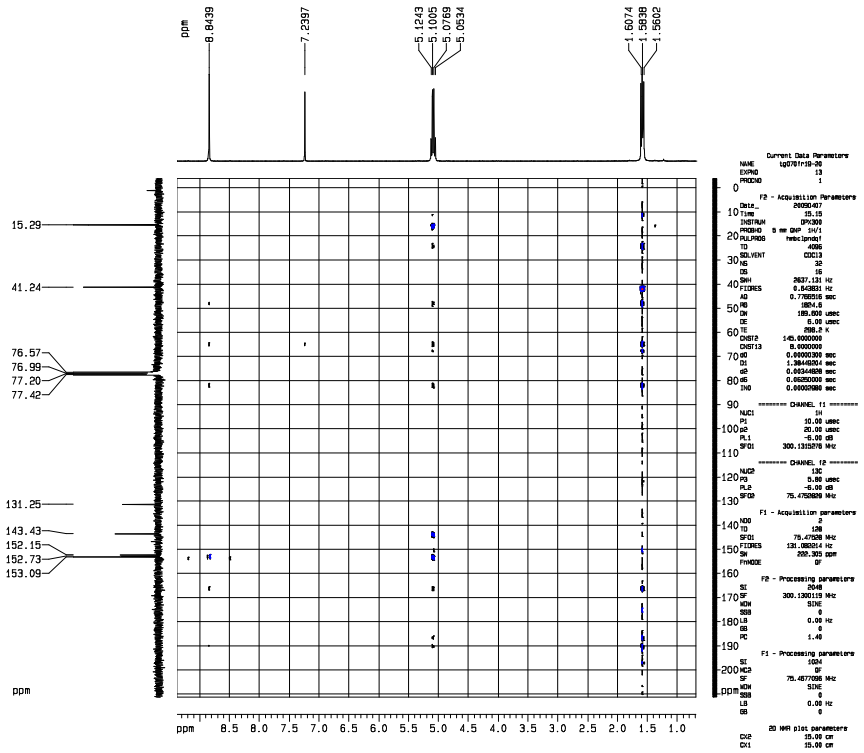
Spectrum 125. ^{1}H NMR of *8,8'-Bis[(6-chloro-9-ethyl)-9H-purine]* (**45y**).



Spectrum 126. ^{13}C NMR of *8,8'-Bis[(6-chloro-9-ethyl)-9H-purine]* (**45y**).

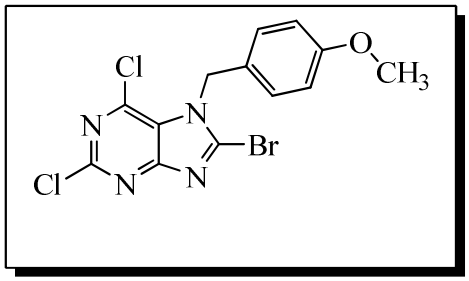


Spectrum 127. HMQC of *8,8'-Bis[(6-chloro-9-ethyl)-9H-purine]* (**45y**).



Spectrum 128. HMBC of *8,8'-Bis[(6-chloro-9-ethyl)-9H-purine]* (**45y**)

8-Bromo-2,6-dichloro-7-(4-methoxybenzyl)-7H-purine (**53c**).



53c

Hexane followed by EtOAc- hexane (1:4) and (1:1) were used for flash chromatography; Yield 80mg (41%) orange solid.

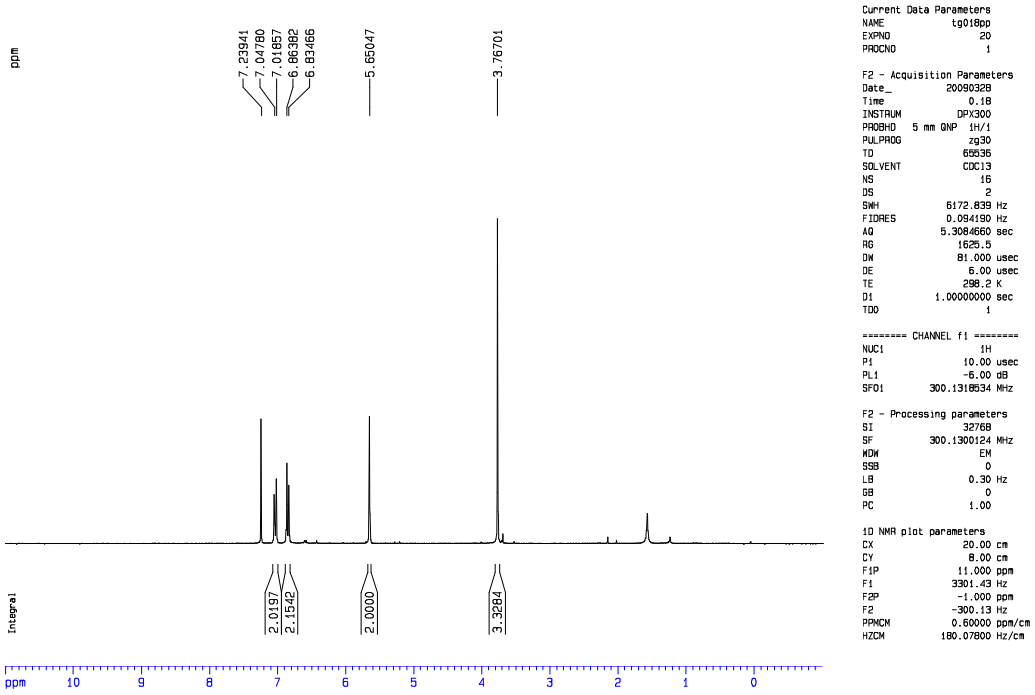
^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.77 (s, 3H, OCH_3), 5.65 (s, 2H, CH_2), 6.85(d, J= 8.6Hz, 2H, Ar), 7.03(d, J= 8.6Hz, 2H, Ar)

^{13}C NMR ($CDCl_3$, 75 MHz): δ 50.2 (CH_2), 55.3 (OCH_3), 114.5 (C-3 and C-5, Ar), 123.5 (C-5), 126.0 (C-1, Ar), 127.9 (C-2 and C-6, Ar), 141.4 (C-8), 142.6 (C-4), 153.6 (C-6), 159.7 (C-4, Ar), 162.3 (C-2 Ar).

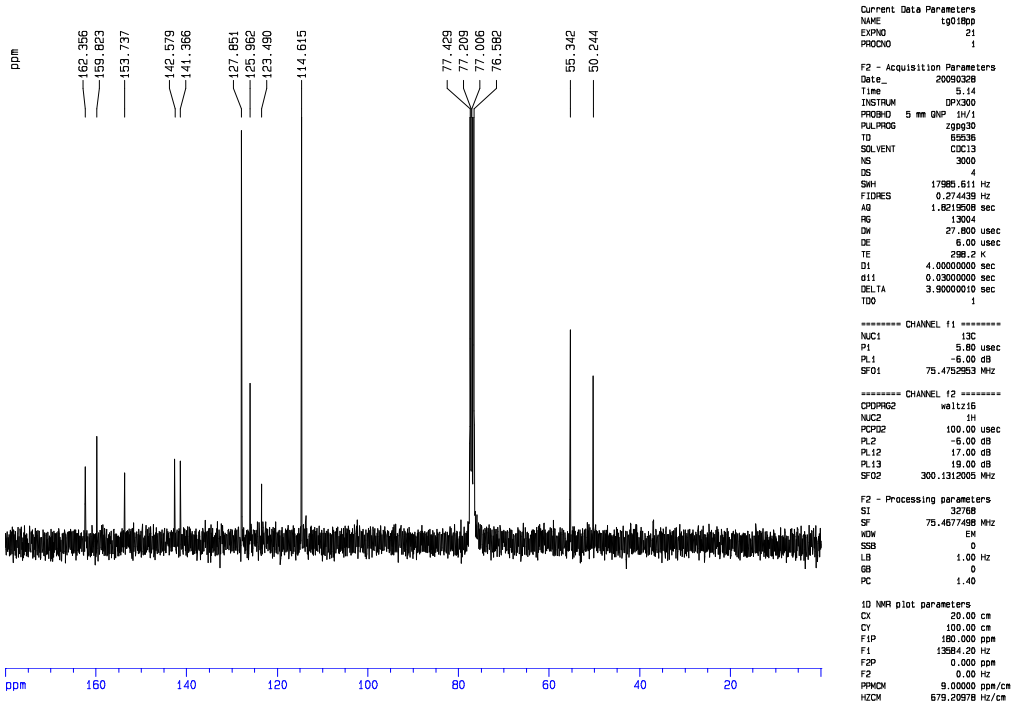
MS (EI). m/z (rel. %): 390/388/386 (3/6/3), 344/342 (5/6), 270/268/266 (3/6/4), 122 (17), 121(100), 91(5), 78 (11), 77(8), 65 (3).

HR-MS: found 385.9340 calculated $C_{13}H_9BrCl_2N_4O$ 385.9337

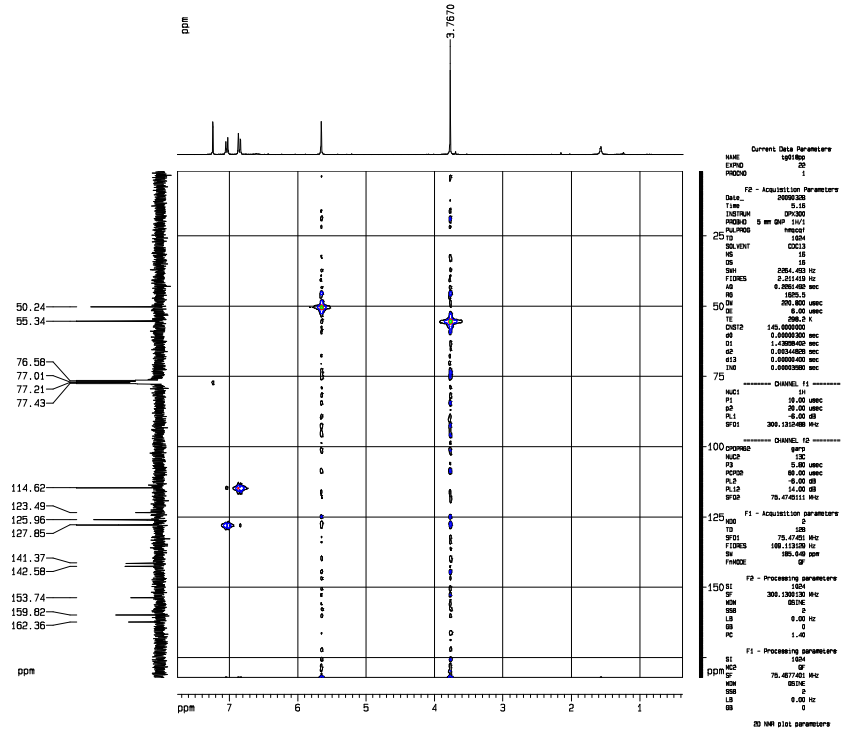
M. p.: 142-144°C.



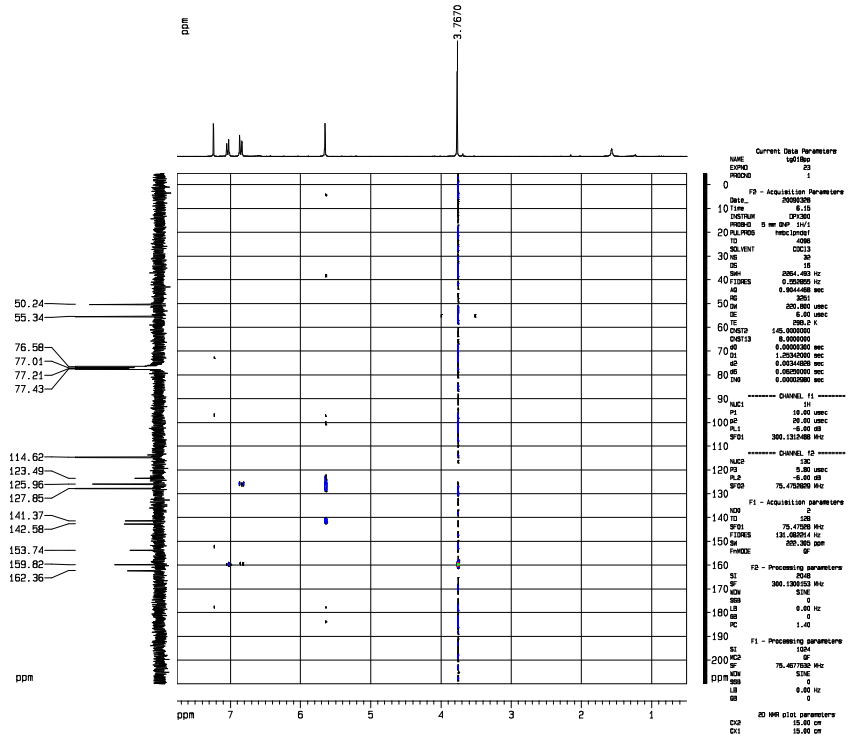
Spectrum 129.[1] H NMR of *8-Bromo-2,6-dichloro-7-(4-methoxybenzyl)-7H-purine* (**53c**).



Spectrum 130. ^{13}C NMR of *8-Bromo-2,6-dichloro-7-(4-methoxybenzyl)-7H-purine* (**53c**).

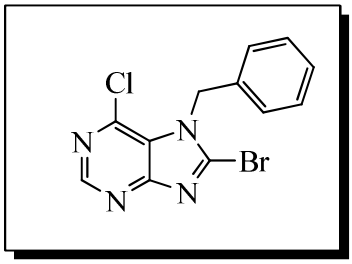


Spectrum 131. HMQC of *8-Bromo-2,6-dichloro-7-(4-methoxybenzyl)-7H-purine* (**53c**).



Spectrum 132. HMQC of *8-Bromo-2,6-dichloro-7-(4-methoxybenzyl)-7H-purine* (**53c**).

8-Bromo-6-chloro-7-(benzyl)-7H-purine **(53o)**.



53o

Hexane followed by EtOAc- hexane (1:3) and (1:1) were used for flash chromatography; scale 2mmol.Yield 148mg (23%), brown solid.

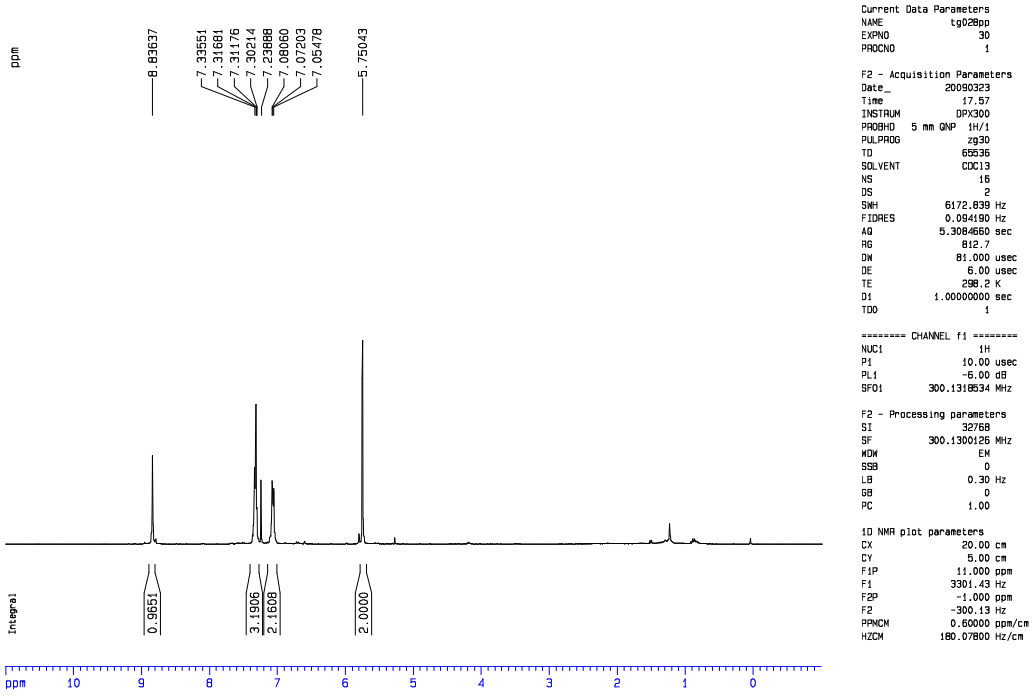
^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.75 (s, 2H, CH_2), 7.05-7.34 (m, 5H, Ar), 8.84 (s, 1H, H-2)

^{13}C NMR ($CDCl_3$, 50MHz): δ 50.5 (CH_2), 126.2 (C-8), 126.3 (C-2 and C-6 Ar), 128.5 (C-4 Ar), 129.2 (C-3 and C-5 Ar), 134.4 (C-1 Ar), 140.1 (C-5), 142.0 (C-4), 152.9 (C-2), 161.0 (C-6).

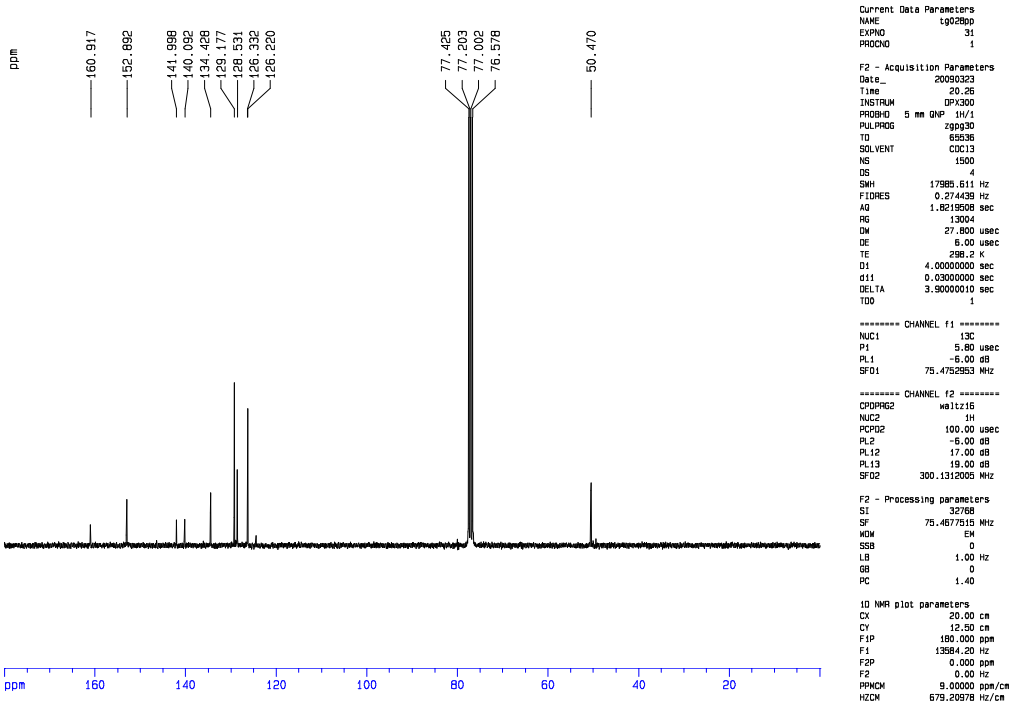
MS (EI). m/z (rel. %): 326/324/322 (3/14/11), 280/278(8/12), 245(3), 243 (9), 216(2), 153(1), 104(1), 91(100), 90(1), 89(3), 77(2) 51(3)39(4), 38(1).

HR-MS: found 321.9618 calculated $C_{12}H_8BrClN_4$ 321.9621

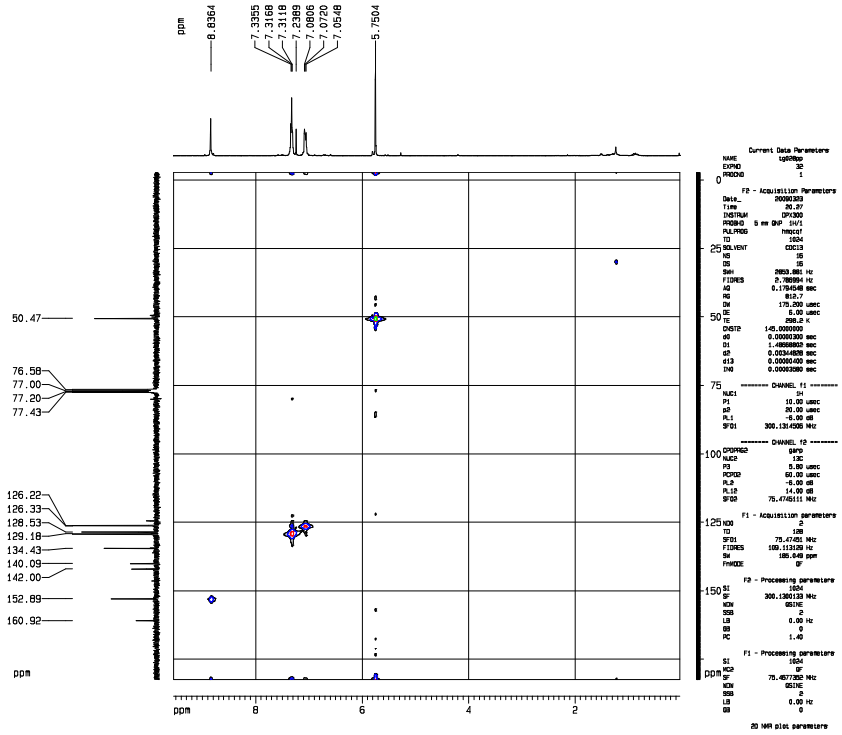
M. p.: 108-110°C.



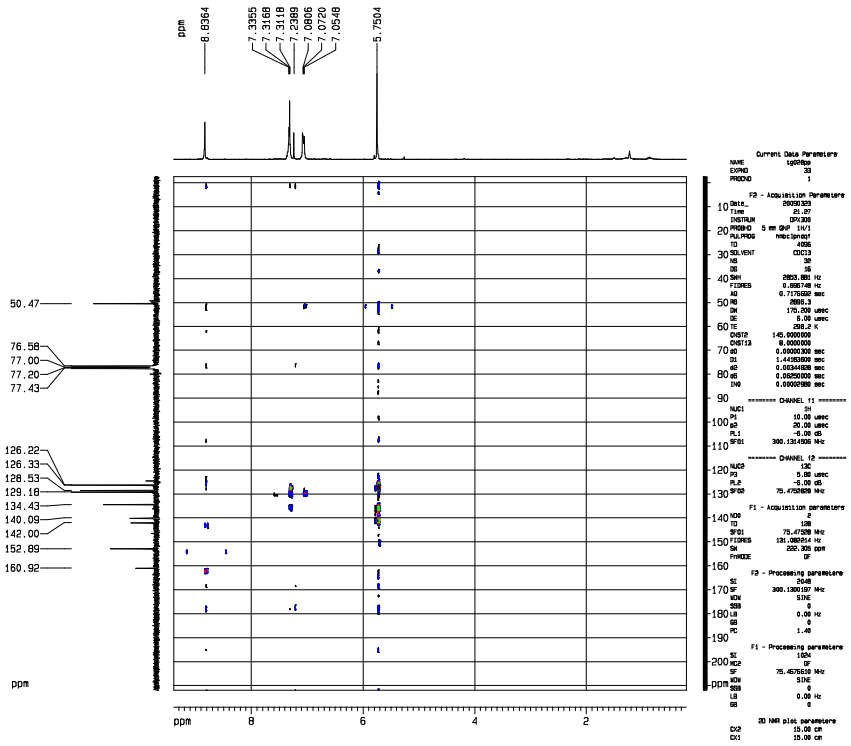
Spectrum 133. ^{1}H NMR of *8-Bromo-6-chloro-7-(benzyl)-7H-purine* (**53o**).



Spectrum 134. ^{13}C NMR of *8-Bromo-6-chloro-7-(benzyl)-7H-purine* (**53o**).



Spectrum 135. HMQC of *8-Bromo-6-chloro-7-(benzyl)-7H-purine* (**53o**).



Spectrum 136. HMBC of *8-Bromo-6-chloro-7-(benzyl)-7H-purine* (**53o**).

7.0 REFERENCES

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