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BURSA TECHNICAL UNIVERSITY
GRADUATE EDUCATION INSTITUTE

SYNTHESIS AND CHARACTERIZATION OF NEW 8-ARYL-1,3-DIMETHYLXANTHINE DERIVATIVES

MASTER'S THESIS

Hamsa Abdullah NAJEEB

Department of Chemistry

Master's Programme

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Thesis Advisor: Assoc. Prof. Dr. Gamze KOZ

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Hamsa Abdullah NAJEEB, a M.Sc. student of BTU Graduate Education Institute student ID 19296978016, successfully defended the thesis/dissertation entitled "SYNTHESIS AND CHARACTERIZATION OF NEW 8-ARYL-1,3-DIMETHYLXANTHINE DERIVATIVES", which she prepared after fulfilling the requirements specified in the associated legislations, before the jury whose signatures are below.

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Signature :

To The Memory of My Father, To My Family and Friends...

FOREWORD

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January 2023 Hamsa Abdullah NAJEEB

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ABBREVIATIONS

^{13}CNMR	: Carbon-13 Nuclear Magnetic Resonance.
^{1}HNMR	: Proton Nuclear Magnetic Resonance.
ACOH	: Acetic Acid.
d.p	: Decomposition point.
D_2O	: Deuterium Oxide.
DCM	: Dichloromethane
DME	: Dimethoxyethane Solvent.
DMSO	: Dimethyl Sulfoxide Solvent.
EtOH	: Ethanol.
FT-IR	: Fourier Transformation Infrared.
m.p	: Melting Point.
MeOH	: Methanol.
$Na_2S_2O_3$	: Sodium Thiosulfate.
NaOH	: Sodium Hydroxide.
ppm	: Parts Per Million.
TBDPSCl	: Tert-Butyl(chloro)diphenylsilane.
TLC	: Thin Layer Chromatography.
UV-Vis	: Ultraviolet-Visible.

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Yeni 8-Aril-1,3-dimetilksantin Türevlerinin Sentezi ve Karakterizasyonu

ÖZET

Ksantin, pürin bazları olarak bilinen gruba dahil aromatic heterosiklik bir bileşiktir. Kahve yaprakları ve çekirdeklerinde bulunan kafein, siyah ve yeşil çay yapraklarındaki teofilin ve teobroma, kakao ağacının tohumlarındaki teobromin gibi doğada pek çok türevi bulunmaktadır. İki önemli pürin türevi olan adenin ve guanin iskeletlerinin ksantin iskeleti ile benzerliği, ksantinin önemli bir terapötik molekül olduğunu göstermektedir. Bu nedenle son zamanlarda çeşitli hastalıkların tedavisi için ksantin türevlerinin kullanımı hedeflenmektedir. Ksantin moleküllerindeki sübstitüe grupların çeşitliliği, anti-Alzheimer ve anti-parkinsonizm, anti-kanser, anti-astım ve bronkodilatasyon, anti-depresan, anti-inflamatuar, anti-diyabetik, diüretik, anti-mikrobiyal, sirtuin inhibitörleri ve adenosin reseptör alt tiplerinin ligandları dahil olmak üzere birçok tedavide ilaç adayı olmasına önem verilmektedir. Moleküldeki C-8 pozisyonu, biyolojik aktivite üzerinde önemli bir etkiye sahiptir.

Bu tez çalışmasında, salisilaldehit, 5,6-diamino-1,3-dimetilurasil ile reaksiyona sokularak Schiff-bazları oluşturulmuştur. Elde edilen Schiff bazlarının, iyot kullanılarak gerçekleştirilen halka kapama reaksiyonu sonucu yeni 8-sübstitüe ksantin türevleri sentezlenmiştir.

Spektroskopik yöntemler kullanılarak sentezlenen 8-aril ksantin türevlerinin yapı tayini gerçekleştirilmiştir. Ksantin türevlerinin su ve organik çözücülerdeki sınırlı çözünürlüğü bu bileşiklerin tam karakterizasyonunun gerçekleştirilmesinde, özellikle ^{13}CNMR spektrumlarının eldesinde sorun teşkil etmiştir. 8-Aril ksantinlerin çözünürlüğünü arttırmak amacıyla deneysel çalışmalarda bulunulmuştur. Bu amaçla ksantin türevinin sodyum hidroksit ile reaksiyonu sonucu ksantin sodyum tuzlarının elde edilmesi planlanmıştır. Ksantin sodyum tuzlarının suda çözünür oldukları belirlenmiş ancak D_2O ile gerçekleştirilen NMR analizlerinden beklenen sonuç elde edilememiştir. Son olarak salisilaldehitin aromatik hidroksili üzerinden gerçekleştirilecek sililleme reaksiyonu ile ksantin türevlerinin organik çözücülerdeki çözünürlüğünün arttırılması hedeflenmiştir. Silillenmiş aldehitin, 5,6-diamino-1,3-dimetilurasil ile reaksiyonu sonucu silillenmiş Schiff-bazları elde edilmiştir. Son adım da ise halka kapama reaksiyonu ile diklorometan içinde çözünür silillenmiş ksantin ürünü elde edilmiştir.

Anahtar kelimeler: Ksantin, Salisilaldehit, 5,6-Diamino-1,3-dimetilurasil, 8-Aril-1,3-dimetilksantin.

SYNTHESIS AND CHARACTERIZATION OF NEW 8-ARYL-1,3-DIMETHYLXANTHINE DERIVATIVES

SUMMARY

Xanthine is a heterocyclic aromatic organic compound belongs to purine bases. It has many derivatives present in nature, such as caffeine in coffee leaves and beans, theophylline in black and green tea leaves, and theobromine in seeds of the Theobroma cocoa tree. Because of the similarity between the xanthine skeleton and the skeleton of two important purine derivatives, adenine and guanine, it is considered as an important therapeutic molecule. Thus, recently the treatments of various diseases are targeted by xanthine derivatives. The diversity of the substituted groups in xanthine molecules gives it importance to be a drug candidate in many treatments, including anti-parkinsonism and anti-Alzheimer's, anti-cancer, anti-asthmatic and bronchodilation, anti-diabetic, anti-depressant, anti-inflammatory, diuretic, anti-microbial, sirtuin inhibitors and ligands of adenosine receptor subtypes. C-8 position in the xanthine molecule have a significant impact on biological activity. So many prodrugs were designed through 8-substitution.

In this thesis, new 8-substituted xanthine derivatives were synthesized by reacting the corresponding aldehydes with 5,6-diamino-1,3-dimethyluracil to form Schiff bases and then performing the ring-closing reaction using iodine.

Spectroscopic methods were applied to confirm the structures of the synthesized xanthine derivatives. The poor solubility of these derivatives in water and common organic solvents limited the techniques used to characterize the products, especially the ^{13}CNMR analysis. Experimental attempts have been made to solve this solubility problem. Thus, the xanthine derivatives were reacted with sodium hydroxide to form xanthine sodium salts. The solubility of the products in water significantly improved and the product completely dissolved in water, but the expected results could not be obtained from NMR analysis which was performed in D_2O. Then we planned to improve the solubility of the products in common organic solvents by converting it to silyl derivatives. The silyl derived Schiff bases were obtained by reacting silylated salicylaldehyde derivative and 5,6-diamino-1,3-dimethyluracil. In the final step, silyl derived xanthine derivative, which was completely soluble in dichloromethane, was obtained.

Keywords: Xanthine, Salicylaldehyde, 5,6-Diamino-1,3-dimethyluracil, 8-Aryl-1,3-dimethylxanthine.

1. INTRODUCTION

Xanthines can be defined as nitrogen bases that belong to alkaloids. They are simply heterocyclic aromatic organic compounds (Kavi et al., 2014). The naturally occurring derivatives of xanthines like caffeine (the one that was isolated from coffee), theophylline (isolated from green and black tea leaves), and theobromine (isolated from the seeds of Theobroma cocoa) are very well-known compounds. The presence of these compounds is helpful for the plants to protect themselves against pathogens and predators.

Because of the similarity between the xanthine skeleton and the skeleton of two important purine basis adenine and guanine, xanthine is considered as a promising therapeutic molecule. It was used widely in pharmacy, also considered as a very important chemical class of adenosine receptor antagonists, thus various diseases are targeted by xanthine derivatives in recent years. For these reasons, the scientific communities, industries, and consumers increase their attention to these compounds, and they have generated considerable synthetic interest in preparing substituted xanthines (Singh et al., 2018).

Like the other molecules of this major group, xanthine derivatives show strong physiological effects on human beings and animals. It has been found that the various substituents at positions N-1, N-3, N-7 and C-8 have a significant impact on biological activity. Adenosine receptor subtypes A1 and A2a have been specifically targeted by powerful and selective antagonists that have methyl, ethyl, and propyl substitutions at position N-1, N-3 and C-8. A1 and A2B selective adenosine receptor antagonists belong to G protein-coupled family. The recent studies related to these receptors represent an important starting point to develop new drugs with high efficacy and selectivity in cardiovascular, neurological, inflammatory and cancer therapy. (Burbiel et al., 2006) (Trincavelli et al., 2010).

1.1 Xanthine Structure

Xanthine (1H-purine-2,6(3H,7H)-diones) is a nitrogen base of purines or alkaloids, it has $C_5H_4N_4O_2$ as a chemical formula and a 152.11g/mol as molecular weight. The molecular structure of xanthine belongs to heterocyclic compounds which contain two fused rings of six and five-membered, with nitrogen atoms at 1-, 3-, 7- and 9 positions. It has hydrogen substitution at positions N1, N3, and N7 and two ketone functional groups at positions C2 and C6 (Kapri, Pant, et al., 2022). As shown in (Figure 1.1).

The two hydrogen atoms that attached amino groups in positions 1 and 3 can be substituted to various functional groups to obtain drugs that can have different potency, efficacy, and pharmacology.

This variety of effective groups gives xanthines wide-range of substitutions, as mono substitution, there are five types (1-, 3-, 7-, 8- and 9-), di-substitutions (1,3-, 1,7-, 1,8-, 1,9-, 3,7-, 3,8-, 3,9- and 7, 8-), and as a tri-substitution (1,3,7-, 1,3,8-, 1,3,9). These substitutions can be attained easily except the N9 position because it has a low nucleophilicity. So the electrophiles can only attack in particular situations (Allwood et al., 2007)(Ranju Bansal, Gulshan Kumar, 2010)(Bandyopadhyay et al., 2012)(Lee et al., 2016).

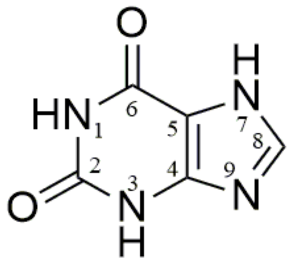

Figure 1.1 : The chemical structure of xanthine.

1.2 Natural Sources of Xanthines

Purines were isolated in 1776 by Von Scheele for the first time, then in about 1817 xanthine was discovered by the German chemist Emil Fisher. Xanthine derivatives were found in plants, animals, and microbes. Later in 1988 the “Xanthine” got its name. (Kavi et al., 2014)(Carter, 2012).

Caffeine, (1,3,7-trimethylxanthine) was extracted from the seeds and leaves of some fruit and plants. Coffee beans, cocoa beans, tea leaves, and kola nuts are the major sources of caffeine in nature. Furthermore, it was found in beans, fruit, and leaves of about 60 other plants and more. It acts as a natural pesticide. Caffeine has a history of use in medications as a nervous system stimulant. The studies on caffeine nowadays showed that it affects Parkinson's disease either on treatment or preventive measures, because of its ability to bind with adenosine A2A receptors and that gives motivation to synthesize 8-substituted xanthines, which is a key nucleus of several clinically available medications. Caffeine has the ability to stimulate the central nervous system (CNS) and it helps in getting rid of drowsiness and staying in mental alertness. It also helps to improve clear thinking (Sledz et al., 2015)(Monteiro et al., 2016)(Cappelletti et al., 2014)(Coelho et al., 2015).

Theophylline, (1,3-dimethylxanthine) Albrecht Kossel; a German biologist extracted theophylline from tea leaves in 1888. It can be found in black and green tea. Theophylline has been used for a very long time to treat asthma. It has uses in medication like a diuretic, smooth muscle relaxant, cardiac stimulator, bronchodilator, and central nervous system stimulator and stabilizer of the mast cells. Theophylline has been identified as a potent inhibitor for regulating the catalytic activity of alkaline phosphatase. It also shows antitumor, anti-inflammatory, and immunomodulatory activities (Foukas et al., 2002)(Spatafora et al., 1994)(Glogowski et al., 2002).

Theobromine, (3,7-dimethylxanthine), is extracted from Theobroma (a cacao tree) for the first time and it can be found in tea and coffee in small amounts. In addition, it presents as a human metabolite of caffeine. Theobromine is the reason behind mood improvement after consuming chocolate or cacao-containing products. Therapeutic uses of theobromine can be mentioned briefly as; it is used as a diuretic, vasodilator, antitumor agent, antitussive, antiangiogenic, and myocardial stimulant**.** After all, it is important to mention that the difficulties of using theophylline and theobromine in medication are their poor physical stability and very limited water solubility (Barcz et al., 2000)(Kakuyama (nee Iwazaki) & Sadzuka, 2005)(Usmani et al., 2005).

Paraxanthine, (1,7-dimethylxanthine) has an effect as a potent, antagonist of adenosine receptors A1, A2A, and A2B**.** As well, it shows lipolytic properties and causes an increase in the concentration of serum-free fatty acid when present in the blood. It increases the calcium ion concentration in muscle and the transportation of potassium ions into skeletal muscle tissue. (Hawke et al., 2000)(Orrú et al., 2013). The natural derivatives of xanthine are presented in (Figure 1.2).

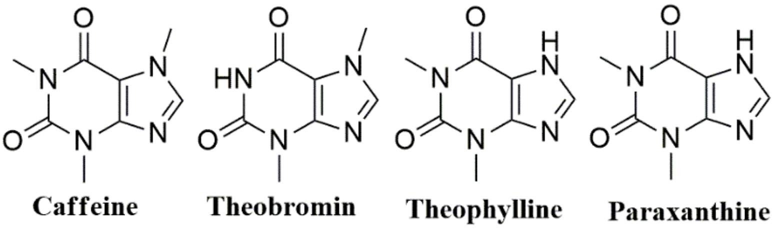

Figure 1.2 : The Structures of Naturally Occurring Xanthine Derivatives.

1.3 Applications of Xanthine Derivatives in Pharmacology

Xanthine lead has been used as a basic skeleton to design many medication candidates. These compounds showed various pharmacological activity in the respiratory tract, heart, smooth muscle cells, central nervous system (CNS), kidney, stomach, etc.

Furthermore, they are taking a part as an intermediate compound in guanosine monophosphate, guanosine diphosphate and guanosine triphosphate production in human cells. These are substituted by aromatic or heteroaromatic groups that have various biological activities including anti-Alzheimer's and parkinsonism, anti-cancer, anti-asthmatic, anti-diabetic, anti-depressant and anxiolytic, analgesic and anti-inflammatory, diuretic, etc (Janitschke et al., 2021)(Monteiro et al., 2016)(Pretze et al., 2020)(Khaliullin et al., 2020)(Constantin et al., 2019)(Flores et al., 2020).

The expected biological effects of the substitution in various positions of the xanthine scaffold are mentioned briefly in (Figure 1.3) (Singh et al., 2018).

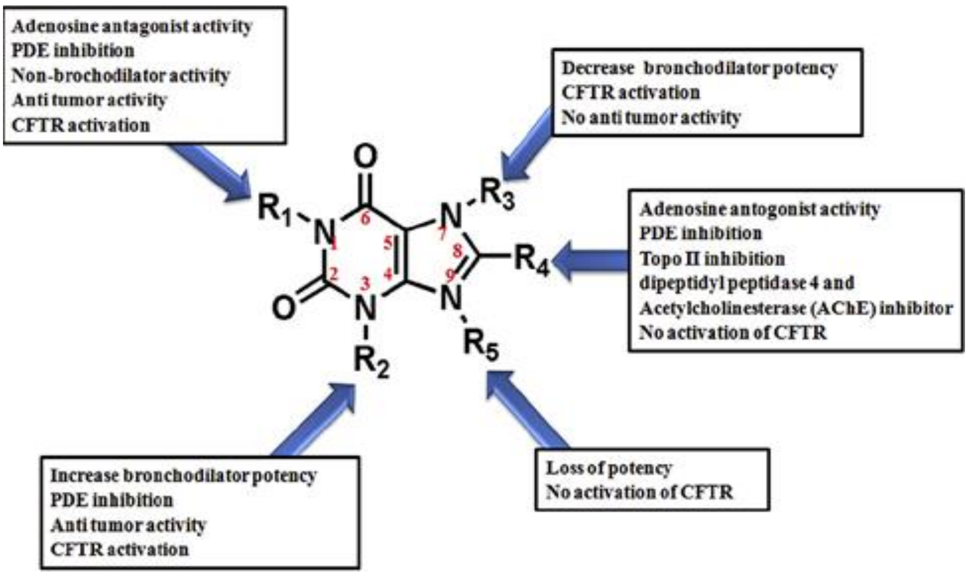

Figure 1.3 : Pharmaceutical significance of different substitutions of xanthine.

The xanthine scaffold was used in the synthesis of many drugs that are commonly marketed drugs nowadays (Kapri, Pant, et al., 2022), which are mentioned in (Figure 1.4).

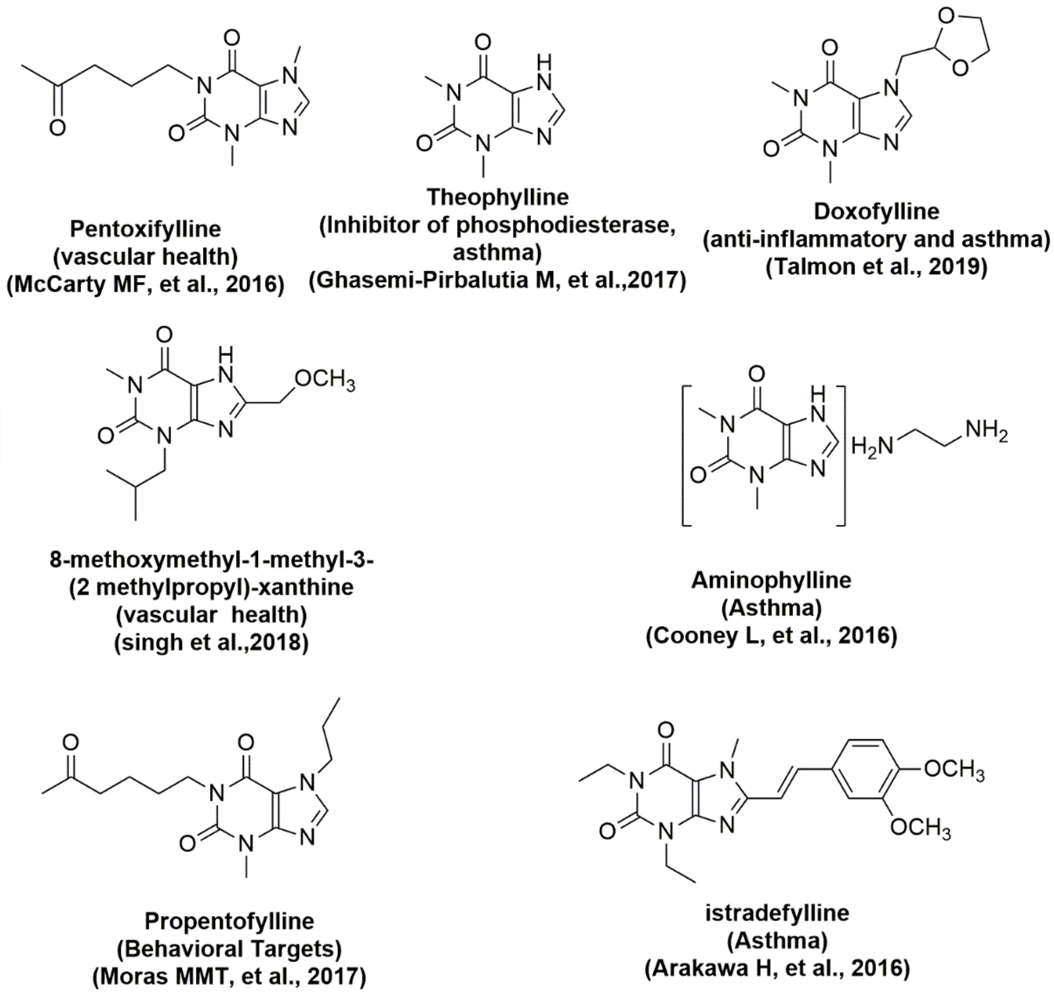

Figure 1.4 : Some of the Commonly Marketed Drugs of Xanthine Derivatives.

1.4 Literature Summary

Xanthine derivatives like caffeine, theophylline, and theobromine may have the ability to act as antitumor agents, for example, theophylline can reduce cell number in breast cancer cells (Crumpton et al., 2001).

Samar El-Kalyoubi et al. (2020) synthesized and characterized new 8-arylsubstituted xanthines by reacting 5,6-diaminouracil with aromatic aldehydes and they investigated their anticancer activity towards lung cancer A549 cell line (Figure 1.5).

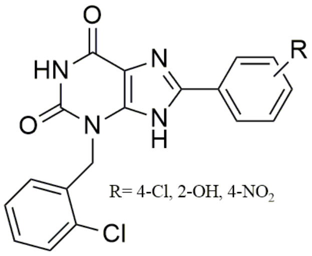

Figure 1.5 : The Structure of the Most Potent Molecule against Lung Cancer.

Hisham, et al. (2019) designed and synthesized a novel xanthine/NO donor of trisubstituted (1, 3, 8-) or disubstituted (1, 8-) xanthines. The further evaluation of these compounds in the human mammary gland epithelial cell line (MCF-10A) showed that oxime-containing compounds were more active as antiproliferative agents than their parent non-oxime derivatives; also, the hydroxyamino-phenethyl scaffold had a better activity than hydroxyamino-ethyl phenyl acetamide derivative (Figure 1.6).

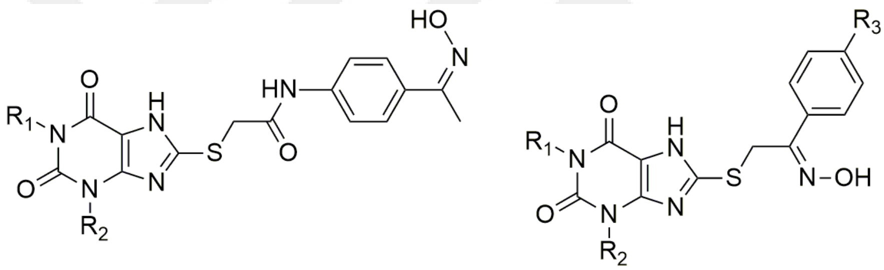

Figure 1.6 : The synthesized antiproliferative agents in the human mammary gland epithelial cell line.

M. Jiang, et al. (2019) synthesized new xanthines by linking various substituents to the sulfonamide residue to form the xanthinyl-8-yl-benzenesulphonamide derivatives. The tests of the synthesized compounds for adenosine receptors A_{2B}, a novel target for cancer immunotherapy showed high selectivity toward the A_2B receptor. The most promising compound as an A_2B antagonist was compound (PSB-1901). See (Figure 1.7).

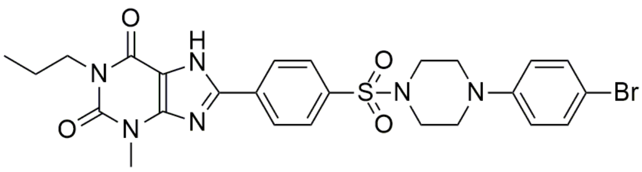

Figure 1.7 : Compound PSB-1901.

A_2A and A_2B adenosine antagonist receptors like caffeine and xanthine derivatives are candidate compounds used in Alzheimer’s disease therapy. (Kavi et al., 2014)

Koch, et al. (2018) synthesized 1,3-dialkyl-tetrahydropyrazino[2,1-f]purinediones as multi-target drugs which are able to block A1 and A2A adenosine receptors in human beings, as well as monoaminoxidase B (MAO-B) by substituting benzyl or phenethyl residues in position N8. See (Figure 1.8).

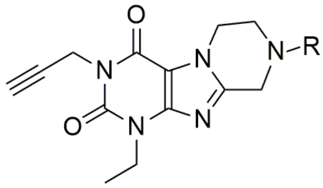

Figure 1.8 : Anti-Alzheimer's multi-target drug.

Harmse, et al. (2016) reported a series of xanthine analogs that could be used therapeutically in neurodegenerative disorders like Parkinson's or Alzheimer's disease (Figure 1.9).

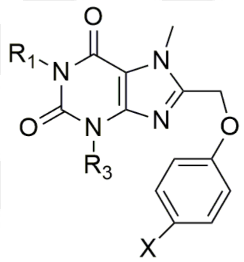

Figure 1.9 : Anti-Alzheimer's or Parkinson's drug candidate

Kuder, et al. (2020) designed and synthesized 20 new compounds and tested these derivatives as dual-target directed ligands as A2A antagonists and MAO-B inhibitors. The study concluded that the most potent dual-acting ligand from this series was the compound presented in (Figure 1.10).

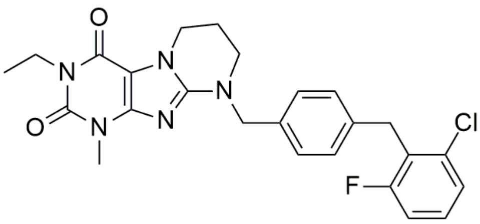

Figure 1.10 : Dual-acting molecule, A2A antagonists and MAO-B inhibitors.

Xanthine derivatives like methylxanthine, besides their anti-inflammatory effect, have the ability to inhibit phosphodiesterase thus these compounds are used in asthma treatments. (Barnes & Pauwels, 1994).

Theophylline has immunomodulatory, and anti-inflammatory effects besides bronchodilation but unlike Doxofylline theophylline has adverse effects involving cardiac and GIT which explains the poor compliance and high dropout rates reported with its uses. (Wood, et al., 1996).

Mohamed et al. (2017) reported research based on discovering 1-, 3-, 7- or 8-substituted bronchodilators that have higher efficacy compared to theophylline to treat asthma. Compound, 1-methyl-3-isobutyl-8-(4-benzohydrylpiperazinoethyl) xanthine S-9795 that was presented in (Figure 1.11) was found to be a promising prodrug in clinical trials of asthma treatment.

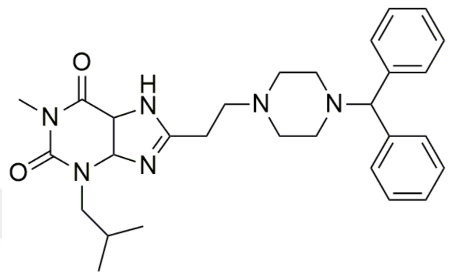

Figure 1.11 : S-9795 structure.

Basu, et al. (2017) synthesized new derivatives of xanthine as A2B adenosine receptor antagonists. Compounds in (Figure 1.12) was the most potent with a high binding affinity that can be promising in the treatment of asthma, and provide good pharmacotherapy properties by oral bioavailability of 27% and 65% respectively in rats.

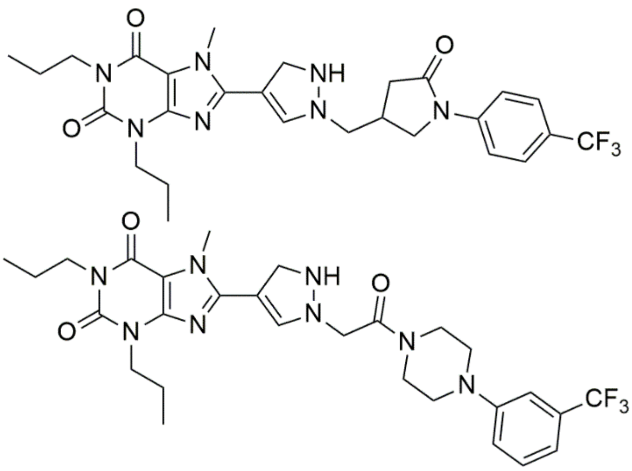

Figure 1.12 : Promising molecules in treatment of Asthma.

Xanthines like caffeine are used as antidepressants, anxiolytics, adenosine antagonist receptors and phosphodiesterase inhibitors (Daly, 2007).

Shabalina, et al. (2020) synthesized a new series of xanthines (8-amino-substituted-1-butyl-3-methylxanthines) showed anti-depressant activity. See (Figure 1.13).

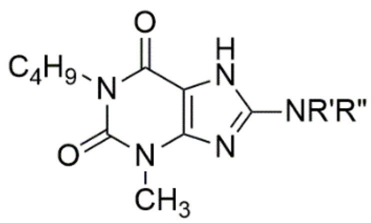

Figure 1.13 : The structure of the xanthine derivative with anti-depressant activity.

1.5 Synthesis of Xanthines

As natural xanthine derivatives are rare and economically expensive to be extracted on a large scale, and with the pharmaceutical needs for xanthine lead molecules to synthesize a number of other important xanthine derivatives, the necessity arose to synthesis these compounds in chemical ways. Chemical synthesis methods of xanthine derivatives can be considered a flexible way to avoid complicated extraction methods from medicinal plants. These methods are various like, classical condensation, ring-closing, and the use of natural xanthine derivatives as starting materials (Allwood et al., 2007)(Bandyopadhyay et al., 2012)(Lee et al., 2016)(Hayallah et al., 2002).

In general, the most common methods to synthesize xanthines are as in the following. *Traube method* is the oldest way to prepare xanthine derivatives by preparing 5,6-diaminouracil from N-substituted urea and then ring-closing. This method's main disadvantage is that the process is ponderous because of the ring closure mechanism. (Figure 1.14).

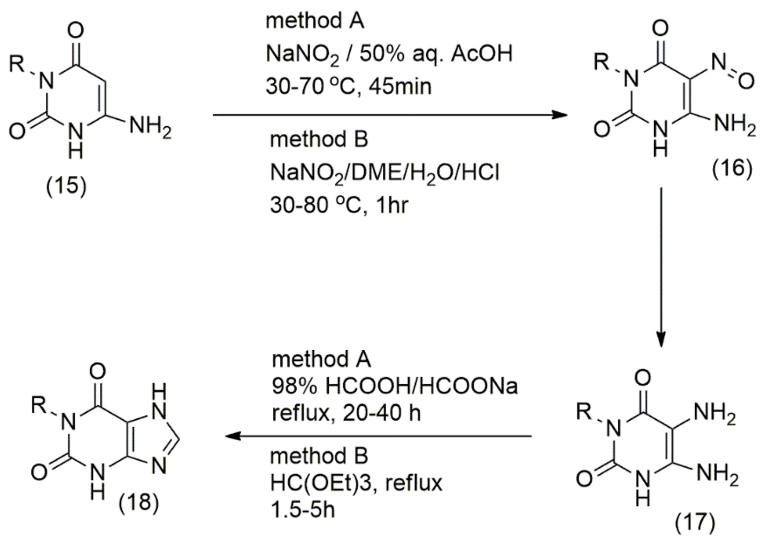

Figure 1.14 : Traube's method.

Xanthine-Anneleated Synthesis, in this method tricyclic xanthine derivatives are prepared by upgrading one more ring starting from bicyclic xanthine lead. This method gives new compounds with acceptable biological effects but is still tedious and not used widely. An example of this method is in (Figure 1.15).

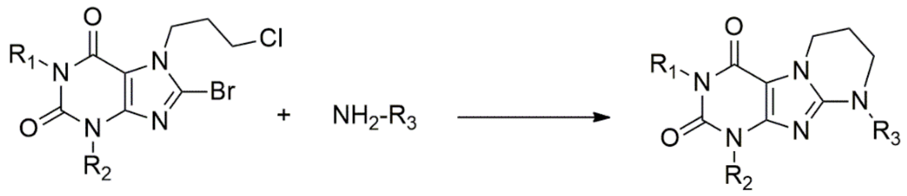

Figure 1.15 : Xanthine-Anneleated method.

One-Pot Synthesis, synthesis of xanthine derivatives by refluxing 5,6-diaminouracil with acetic anhydride in acetic acid. In this method, xanthines are obtained in a short time, good yields and without using toxic chemicals. (Figure 1.16).

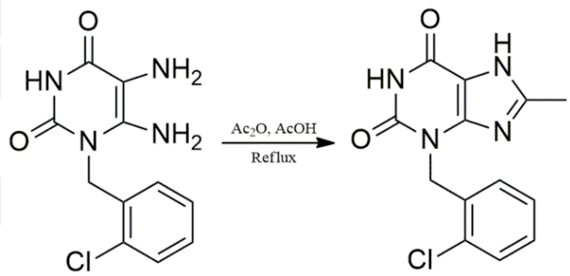

Figure 1.16 : One-Pot Synthesis.

Miscellaneous Synthesis, synthesis of 1-, 3-, 7- and 8- substituted xanthine derivatives starting from xanthine lead as a starting material (Kapri, Gupta, et al., 2022). See (Figure 1.17).

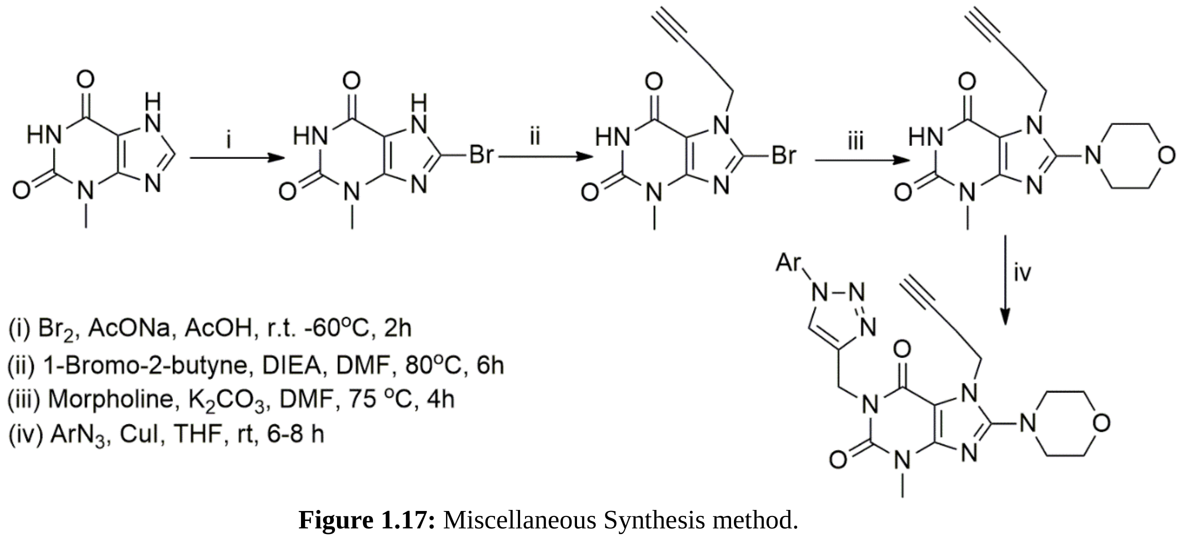

Figure 1.17: Miscellaneous Synthesis method.

1.6 8-Substituted Aryl Xanthine

Research of 8-substituted xanthines is attractive because substitution in this position gives these compounds more stability and prevents rapid oxidation of xanthines, as the common metabolic pathway for xanthines, is the oxidation in this position to uric acid. C-8 substitution has a noticeable increase in the pharmaceutical properties of these compounds. Where researchers have shown better potency and antiallergic properties with the combination of the substitution at C-8, N1, and N3 together, they are the most promising sites in the xanthine scaffold to generate derivatives that have selective potency to subtypes of adenosine receptors. Substituents like phenyl, styryl, aminoalkyl, or thioalkyl have the ability to increase the affinity of a certain type of receptor too (Nehlig, 2018)(van der Walt & Terre'Blanche, 2017)(Laddha et al., 2009). Caffeine and its 8-alkoxy-substituted derivatives have anti-bacterial properties against many human pathogens (Staphylococcus aureus, Klebsiella pneumonia and Pseudomonas aeruginosa)**.** It is generally prepared by reacting 5,6-diaminouracil derivatives and the required aldehydes or carboxylic acids and then ring closure reaction to form xanthine derivatives. In many cases, side reactions contain the formation of cyclic products, which are hard to be isolated, and this makes the purification of the desired product difficult and that's why there is always an interest to develop methods to get 8-substituted xanthines.

Theophylline and its 8-aryl substituted derivatives have enhanced potency, they were found to have a greater potency to binding to a-receptors for about 30 to 60 times than the non-substituted 8-position corresponding derivatives (Singh et al., 2018)(Reshetnikov et al., 2022).

1.7 Solubility

Due to the presence of lots of nonpolar aliphatic or aromatic residues in most of the synthesized xanthine derivatives, these compounds have low to moderate water solubility in general.

Another reason for low solubility is when the intramolecular bonds between N-H groups and inter-base hydrogen bonds and base stacking are strong enough it can hinder the solubility and that is what occurs in xanthine and its derivatives compared to purine (Singh et al., 2018)(Weyler et al., 2006).

Ideally, this problem can be solved by introducing a polar, ionizable substitution like sulfophenyl, carboxyl, and phosphoryl groups to the candidate compound and then converting it to a salt, which gives it high water solubility but also could cause loss of potency. If these compounds are prodrugs, their salts must have good stability in solvents but quickly degraded in vivo to cleave off and release the active compound by entering an enzymatic reaction. For example; Roland Sauer, et al synthesized water-soluble prodrugs by phosphorylating the prodrug xanthine derivative and then converting it to disodium salt. The study concluded that compound 9b has good stability in an aqueous solution of pH7 and rapidly cleaved to release the phosphoric group to the hydroxyl group by phosphatases (Faudone et al., 2021)(Sauer et al., 2000). As shown in (Figure 1.18).

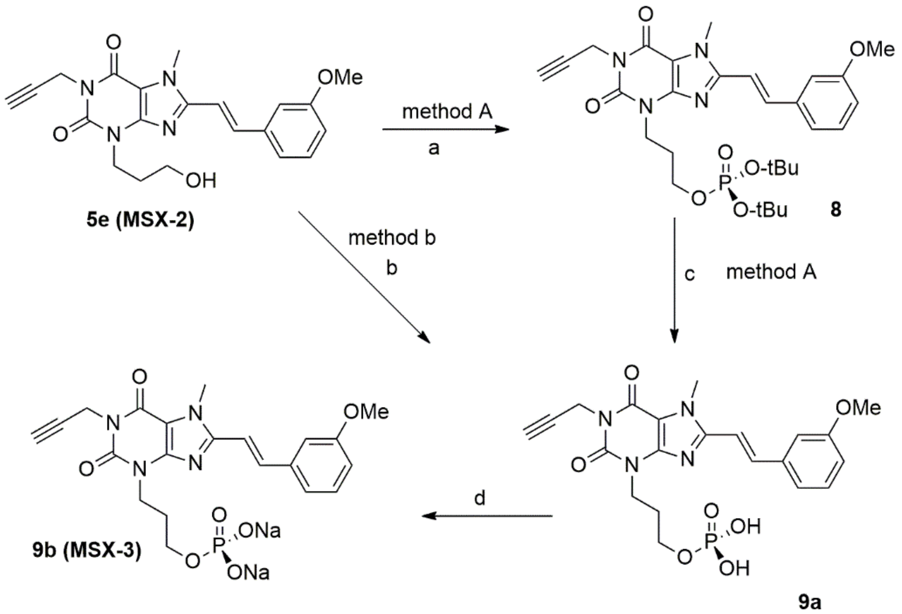

Figure 1.18: Increasing solubility by xanthine phosphorylation.

Alaa M. Hayallah, et al solve the problem of solubility by introducing polar groups like acidic or basic functional groups to the para position of 8-phenyl ring in (8-phenylxanthine) derivatives to increase the water solubility of these compounds (Hayallah et al., 2002).

Weyler et al., (2006) try to improve the water solubility of 3-(3-hydroxypropyl) substituted xanthine derivatives by preparing water-soluble derivatives as a prodrug like phosphoric or sulfuric acid, or amino acid esters as they were cleaved in vivo by esteras. See (Figure 1.19).

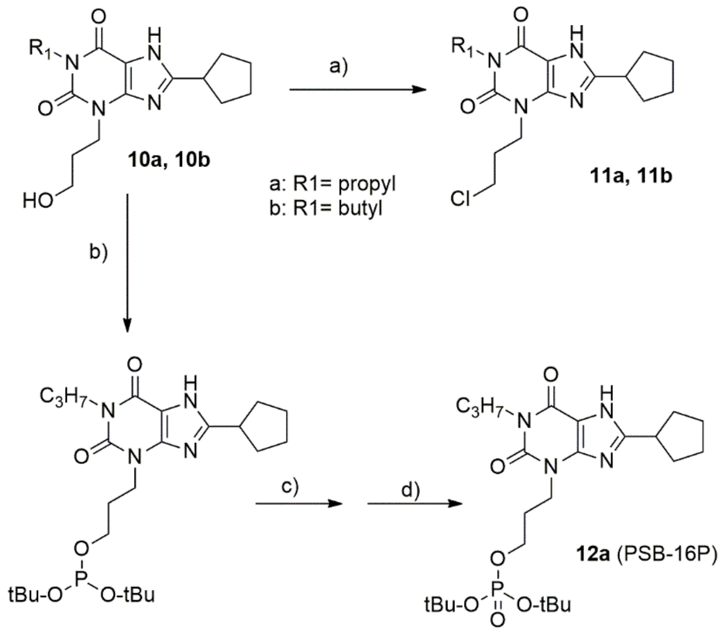

Figure 1.19 : Improving water solubility of 3-(3-hydroxypropyl) substituted xanthine derivatives.

2. EXPERIMENTAL PART

2.1 Materials and Instruments

All used chemicals were purchased from Sigma-Aldrich and Acros and used without any purification. The solvents were used as received from commercial suppliers. Melting points were recorded with electro thermal digital melting points apparatus. FT-IR spectra were recorded with NICOLET- IS50- FTIR. ^{1}H-NMR and ^{13}C-NMR spectra were carried out by 400 MHz Bruker NMR spectrometer at ambient temperature. Elemental analysis was carried out with LECO / TRUESPEC MİCRO. For thin layer chromatography, Silica gel F_{254} (Merck 5554) precoated plates were used.

2.2 Method

Iodine was used according to a known procedure (Ponnala & Prasad Sahu, 2006).
The corresponding Schiff-base (0.42 mmol) was added to a solution of iodine (0.46mmol 117mg) in DME (4ml) and stirred for 3 hours under reflux and left overnight at room temperature. The reaction progress was checked with thin layer chromatography (TLC). Then a saturated solution of $Na_2S_2O_3$ was added dropwise till the color of iodine completely disappeared. The precipitated product was filtered and washed several times with water then with hot MeOH and dried in a vacuum oven.

(a): 1,3-dimethyl-8-(2,3,4-trihydroxyphenyl)-1H-purine-2,6(3H,7H)-dione

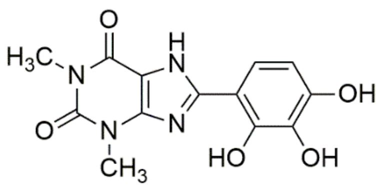

Figure 2.1 : The structure of molecule **(a)**.

Brown powder, 24% yield, m.p. >300^{o}C. FT-IR spectrum, ν, cm^{-1}: 3174, 1687, 1633, 1568, 1512, 1462, 1349, 1220, 1081, 1040, 981, 800, 754, 559. ^{1}H-NMR (400 MHz, DMSO-d_6) 13.58 (s, 1H), 11.65 (s, 1H), 9.55 (s, 1H), 8.53(s, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 6.40 (d, *J* = 7.2 Hz, 1H), 3.47 (s, 3H), 3.25 (s, 3H). Anal. calcd. for $C_{13}H_{12}N_4O_5$ %: C 51.32; H 3.98; N 18.41, found, %: C 43.15; H 3.11; N 16.81.

(b): 8-(2,3-dihydroxyphenyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione

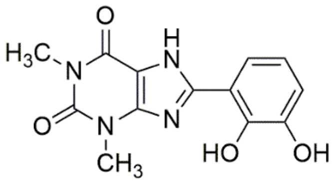

Figure 2.2 : The structure of molecule **(b)**.

White powder, 41% yield, d.p. =260°C. FT-IR spectrum, ν, cm^{-1}: 3457, 3088, 1697, 1650, 1563, 1526, 1467, 1409, 1382, 1371, 1278, 1224, 986, 757, 737, 502. ^{1}H-NMR (400MHz, DMSO-d_6) 13.94 (s, 1H), 11.72 (s, 1H), 9.27 (s, 1H), 7.54-6.77 (m, 3H), 3.49 (s, 3H), 3.28 (s, 3H). Anal. calcd. for $C_{13}H_{12}N_4O_4$ %: C 54.17; H 4.20; N 19.44, found, %: C 51.71; H 3.46; N 19.71.

(c): 8-(2-hydroxy-5-iodophenyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione

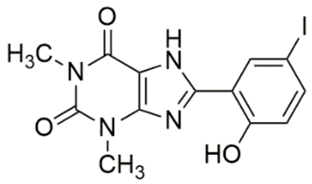

Figure 2.3 : The structure of molecule **(c)**.

White powder, 41%, m.p. >300 °C. FT-IR spectrum, ν, cm^{-1}: 3162, 2951, 1699, 1655, 1622, 1611, 1553, 1522, 1469, 1374, 1291, 1224, 980, 781, 754, 744. ^{1}H-NMR (400MHz, DMSO-d_6) 13.87 (s, 1H), 11.70 (s, 1H), 8.45 (d, *J* = 1.6 Hz, 1H), 7.65-7.63 (dd, *J* = 7.2, 1.6 Hz, 1H), 6.86 (d, *J* = 7.2 Hz, 1H), 3.50 (s, 3H), 3.27 (s, 3H). Anal. calcd. for $C_{13}H_{11}IN_4O_3$ %: C 39.22; H 2.78; N 14.07, found, %: C 39.63; H 2.33; N 13.681.

(d): 8-(2-hydroxy-4-methoxyphenyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione

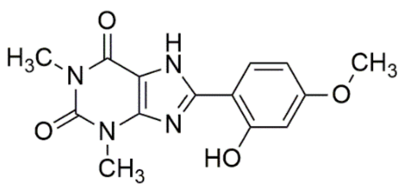

Figure 2.4 : The structure of molecule **(d)**.

White powder, 43% yield, d.p. =264 °C. FT-IR spectrum, ν, cm^{-1}: 3162, 2952, 1701, 1651, 1633, 1605, 1594, 1564, 1534, 1479, 1435, 1414, 1257, 1205, 960, 754, 747. ^{1}H-NMR (400MHz, DMSO-d_6) 13.64 (s, 1H), 11.79 (s, 1H), 8.00 (d, *J* = 7.2 Hz, 1H), 6.58-6.56 (dd, J = 7.2, 2.0 Hz, 1H), 6.54 (d, J = 2.0 Hz, 1H), 3.79 (s, 3H), 3.48 (s, 3H), 3.27 (s, 3H). Anal. calcd. for $C_{14}H_{14}N_4O_4$ %: C 55.63; H 4.67; N 18.53, found, %: C 56.95; H 4.80; N 18.10.

(e): 8-(2-hydroxy-3-methoxyphenyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione

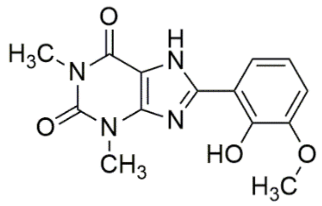

Figure 2.5 : The structure of molecule **(e)**.

White powder, 66% yield, d.p. =266^{o}C. FT-IR spectrum, ν, cm^{-1}: 3152, 2970, 1699, 1661, 1613, 1589, 1563, 1508, 1466, 1428, 1260, 1055, 794, 758, 740. ^{1}H-NMR (400MHz, DMSO-d_6) 13.88 (s, 1H), 11.64 (s, 1H), 7.68 (s, 1H), 7.08-6.91 (m, 2H), 3.82 (s, 3H), 3.50 (s, 3H), 3.28(s, 3H). Anal. calcd. for $C_{14}H_{14}N_4O_4$ %: C 55.63; H 4.67; N 18.53, found, %: C 56.06; H 4.51; N 18.02.

(f): 8-(2-((tert-butyldiphenylsilyl)oxy)-3-methoxyphenyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione

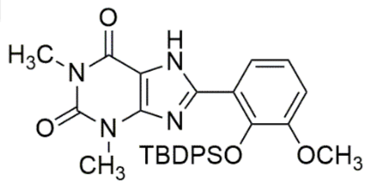

Figure 2.6 : The structure of molecule **(f)**.

A solution of *tert*-butyldiphenylsilylchloride (TBDPSCl) (0.6 mmol), salicylaldehyde (0.4 mmol) and imidazole (0.6 mmol) in 5ml DCM was stirred at room temperature. The reaction progress was checked with TLC. To complete the reaction, 4ml water was added and the crude was extracted with chloroform (3x4ml). The product was purified with column chromatography using ethyl acetate:hexane.

The xanthine precursor Schiff base was prepared by reacting silylated salicylaldehyde (0.32 mmol) with 5,6-diamino-1,3-dimethyluracil (0.3 mmol) in 5 ml EtOH in the presence of a few drops of acetic acid under reflux for 4 hours and left overnight at room temperature. The reaction progress was checked with TLC and the precipated product was filtered.

The silylated Schiff base (0.2 mmol) was added to a solution of iodine (0.22 mmol) in DME (3ml) and stirred for 3 hours under reflux. The reaction progress was checked with TLC. Then a saturated solution of $Na_2S_2O_3$ was added dropwise until the color of iodine completely disappeared. The product was obtained after purification by column chromatography as a white solid.

White powder, 51% yield, m.p. 81-83 ^oC. FT-IR spectrum, ν, cm^{-1}: 3137, 3071, 3046, 3015, 2999, 2959, 2893, 2854, 1694, 1647, 1601, 1582, 1558, 1515, 1478, 1267, 1113, 1063, 910, 739, 696. ^{1}H-NMR (400MHz, $CDCl_3$) 11.18 (s, 1H), 7.86 (d, J = 8.0 Hz 1H), 7.72-7.67 (m, 4H), 7.40-7.31 (m, 6H), 6.99 (t, J = 8.0 Hz, 1H), 6.6 (dd, J = 8.0, 1.6 Hz, 1H), 3.71 (s, 3H), 3.46 (s, 3H), 2.75 (s, 3H), 1.06 (s,9H).

3. RESULT AND DISCUSSION

In this research, xanthine derivatives have been synthesized in two steps. In the first step, corresponding Schiff bases have been prepared by reacting 5,6-diamino-1,3-dimethyluracil with substituted salicylaldehydes in presence of acetic acid. As the Schiff bases had been synthesized and characterized by our group before, we checked the melting points and FT-IR of the products to confirm the structures (Halic, A, M.Sc thesis, December 2020). The second step was the ring closing reaction of these Schiff bases to form the five-membered ring of xanthines. In our first attempts, we used 3-OCH_3 and 4-OCH_3 substituted Schiff bases and thionyl chloride ($SOCl_2$) to close the xanthine ring (Figure 3.1). Although the targeted molecules have been obtained in 2 hours, the isolation procedure was troublesome. As a result of its environmental risks, difficulty to get rid of thionyl chloride and the acidic workup procedure on a large scale led us to find another way to synthesize the target xanthines (Bansal R, et al. 2010).

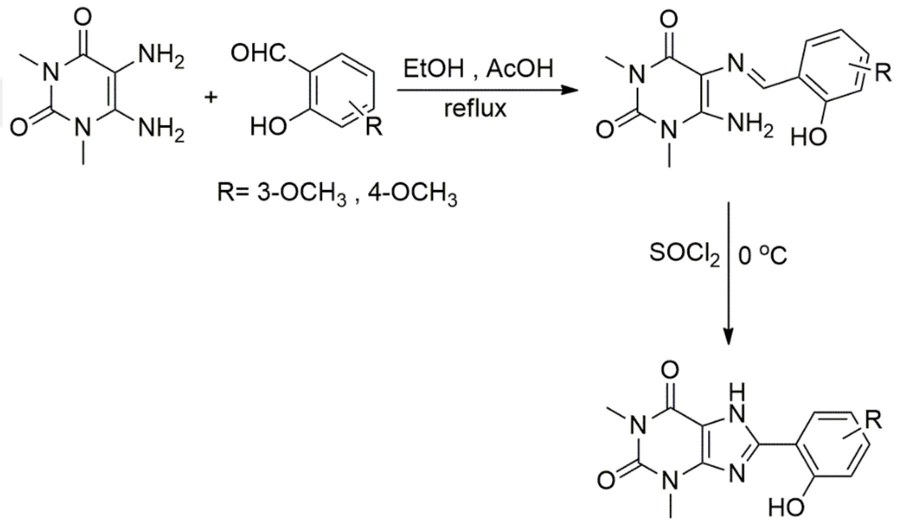

Figure 3.1: Xanthine synthesis using thionyl chloride.

The other alternative method for the ring closure step was iodine mediated. Iodine is used as an oxidation agent to softly deprotonate the Schiff base and close the ring to form the targeted xanthine compounds as in (Figure 3.2). The yields of the reactions were higher than the yields obtained with the thionyl chloride procedure.

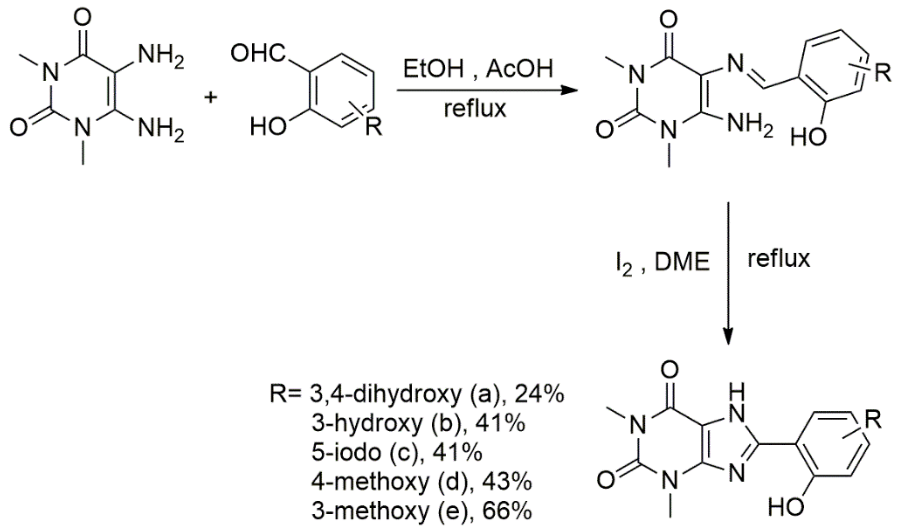

Figure 3.2: Xanthin synthesis using iodine.

The mechanism of ring closing reaction was explained in (Figure 3.3) (Ponnala & Prasad Sahu, 2006).

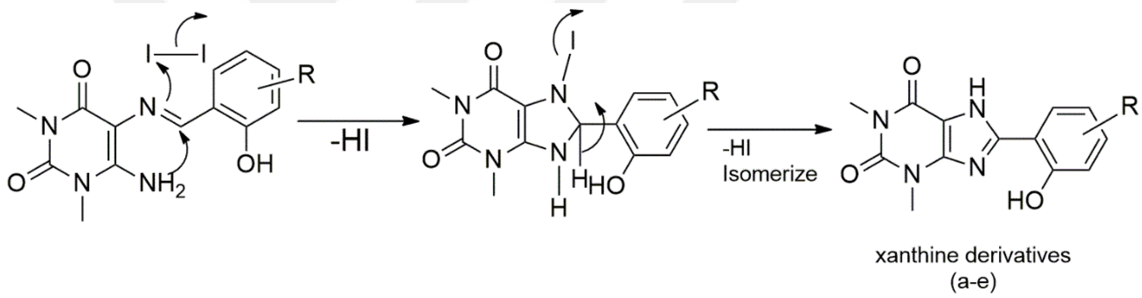

Figure 3.3 : Mechanism of the ring closure reaction.

We used Fourier-transform infrared spectroscopy (FT-IR), ^{1}HNMR and elemental analysis to characterize the compounds. The main problem for the characterization was the poor solubility of the xanthine structures. The solubility of the products was very limited in water, chloroform, pyridine and DMSO and as a result, it was not possible to perform high resolution mass spectrometry (HR-MS) analysis. Also, ^{13}CNMR analysis results were not satisfactory even after overnight NMR experiments.

FT-IR spectra of the starting Schiff bases and final xanthines were compared to prove the functional group transformations (Figure 3.4). The characteristic functional groups in the starting Schiff bases were imine (C=N) and primary amine (-NH_2) which were converted to a C=N double bond with a different chemical environment and -NH.

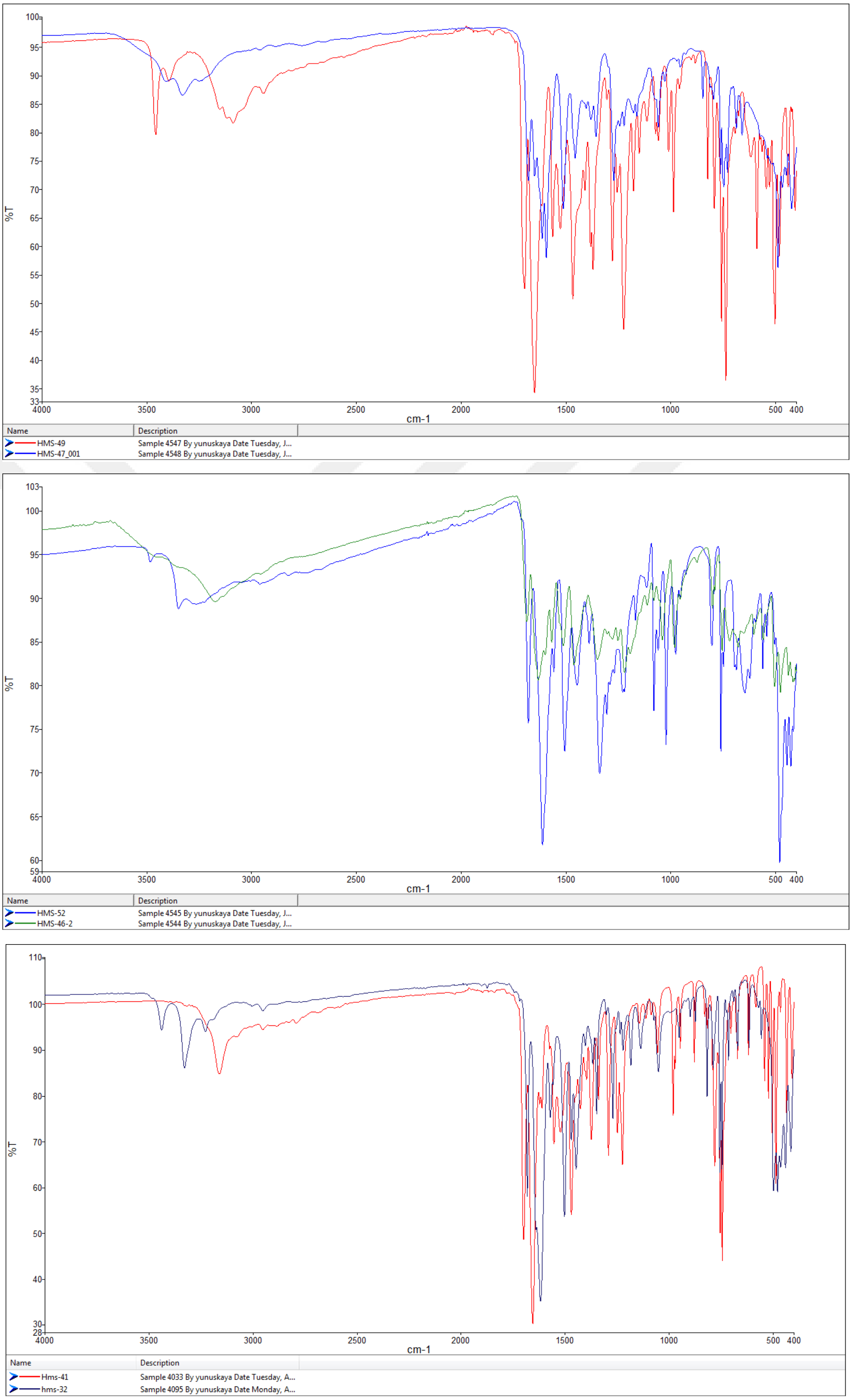

Figure 3.4: FT-IR Spectra of Schiff bases and xanthines (**a-e**).

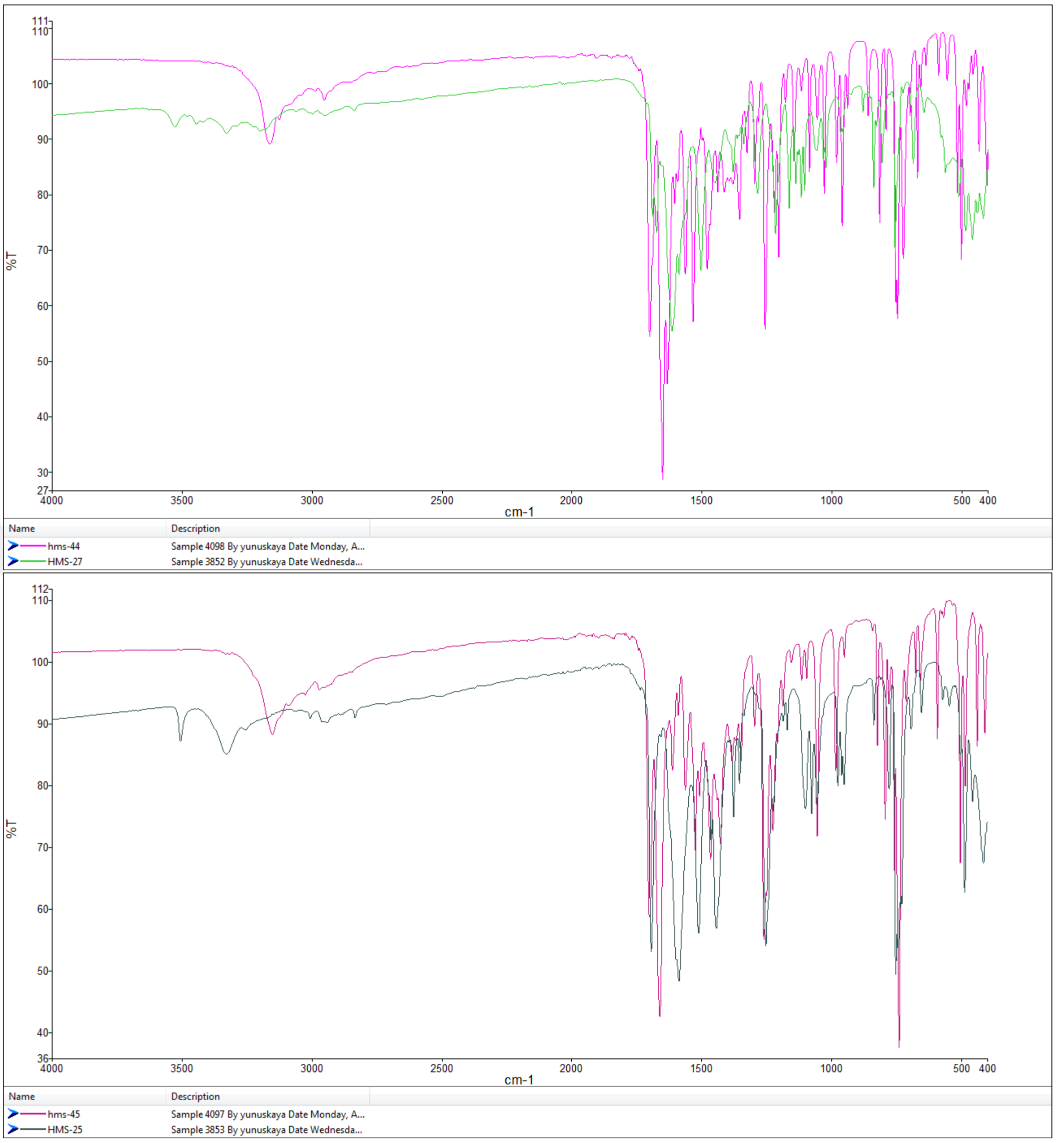

Figure 3.4: FT-IR Spectra of Schiff bases and xanthines **(a-e)** (continued).

The characteristic FT-IR peaks of the uracil carbonyl group and C=N double bond of the Schiff bases were observed around 1670-1680 cm^{-1} and 1611-1649 cm^{-1} respectively while the related peaks of xanthine structure were observed between 1701-1688 cm^{-1} and 1634-1661 cm^{-1}. For xanthine **a** and **b**, the characteristic peaks for amino and hydroxyl functional groups were observed between 3000-3300 cm^{-1}. On the other hand, in the spectra of **c**, **d** and **e**, the expected -OH and -NH peaks were not observed instead a strong -NH stretching similar to an amine salt were observed. This was attributed to the strong intramolecular or intermolecular (dimerization) hydrogen bonding between the aromatic hydroxyl group of the 8-aryl ring and the -NH group of the xanthine ring.

In ^{1}HNMR spectra of the target 8-arylxanthine derivatives, the characteristic aromatic OH (~13-10 ppm), xanthine NH (~13-10 ppm) and uracil N-CH_3 protons (~3 ppm) were observed as singlets and aromatic hydrogens were observed as multiplets between 7-8 ppm, as expected.

Elemental analysis data were compatible with the xanthine structures as presented in (Table 3.1).

Table 1.1: Elemental analysis results of xanthines.

Compound No	Elements	Calculated Content	Found %
a	%N	18.41	16.81
	%C	51.32	43.15
	%H	3.98	3.11
b	%N	19.44	19.71
	%C	54.17	51.71
	%H	4.20	3.46
c	%N	14.7	13.681
	%C	39.22	39.63
	%H	2.78	2.33
d	%N	18.53	18.10
	%C	55.63	56.95
	%H	4.67	4.80
e	%N	18.53	18.02
	%C	55.63	56.06
	%H	4.67	4.51

Finally, we tried to improve the water solubility of 8-arylxanthines not only for spectral analysis but also for future biological activity studies. Thus, we used NaOH to form the sodium salt of an 8-arylxanthine. The sodium salt of 5-methyl substituted xanthine, which had been prepared using thionyl chloride, was obtained as presented in (Figure 3.5). The product was easily dissolved in water but we could not obtain the expected ^{1}HNMR spectrum in D_2O.

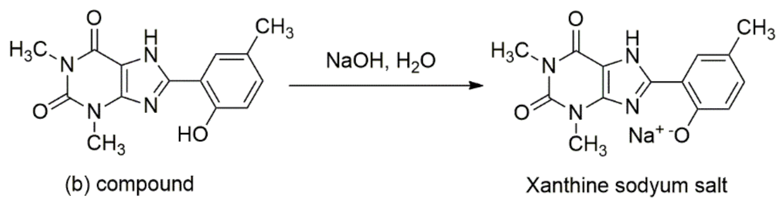

Figure 3.5 : Sodium salt of 5-methylxanthine.

We also tried to improve the solubility of 8-arylxanthines in organic solvents by silylation. The desired salicylaldehyde derivative has been silylated first using *tert*-butydiphenylsilylchloride (TBDPSCl) and then the silylated aldehyde in the next step was converted to silylated xanthine derivative (Figure 3.6). The product was obtained after purification by column chromatography as a white solid and easily dissolved in dichloromethane.

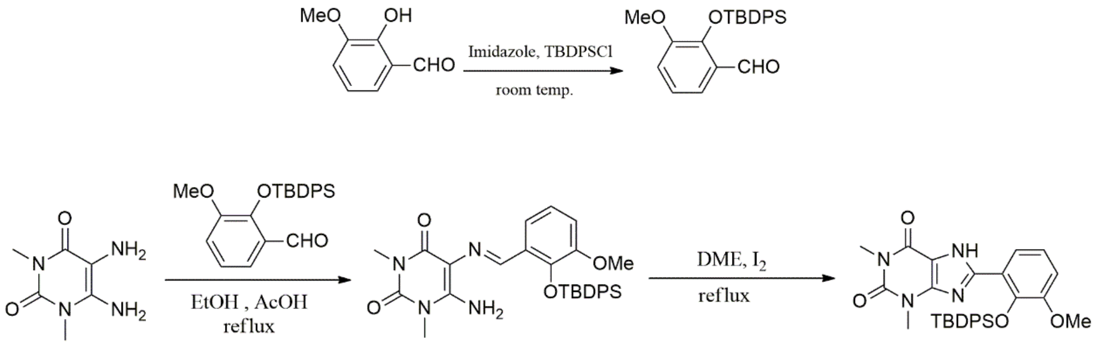

Figure 3.6 : The synthesis of silylated 8-arylxanthine compound **f**.

The structural characterization of silylated xanthine **f** had been proved by ^{1}H-NMR as seen in (Figure A.12). The characteristic xanthine NH (~11 ppm) and uracil N-CH_3 protons (~3 ppm) were observed as singlets and TBDPS's tert-butyl protons (~1 ppm) and aromatic hydrogens were observed as multiplets in between 7-8 ppm, as expected. FT-IR Spectra of silylated Schiff base and silylated xanthine was presented in (Figure 3.7).

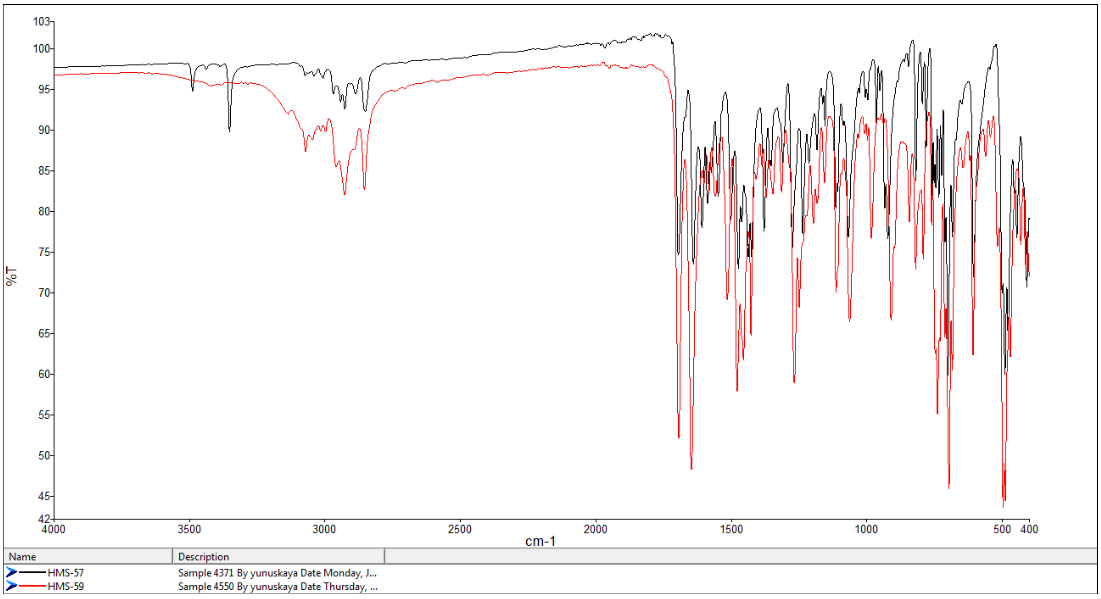

Figure 3.7 : FT-IR Spectra of silylated Schiff bases and silylated xanthine compound **f.**

Reference

Allwood, M. B., Cannan, B., van Aalten, D. M. F., & Eggleston, I. M. (2007). Efficient synthesis of 1,3,7-substituted xanthines by a safety-catch protection strategy. *Tetrahedron*, *63*(50), 12294–12302.

Arakawa, H., Hamasaki, Y., Kohno, Y., Ebisawa, M., Kondo, N., Nishima, S., ... & Japanese Society of Allergology. (2017). Japanese guidelines for childhood asthma 2017. *Allergology International*, *66*(2), 190-204.

Bandyopadhyay, P., Agrawal, S. K., Sathe, M., Sharma, P., & Kaushik, M. P. (2012). A facile and rapid one-step synthesis of 8-substituted xanthine derivatives via tandem ring closure at room temperature. Tetrahedron, 68(20), 3822-3827.

Barcz, E., Sommer, E., Janik, P., Marianowski, L., & Skopinska-Rozewska, E. (2000). Adenosine receptor antagonism causes inhibition of angiogenic activity of human ovarian cancer cells. *Oncology Reports*, *7*(6), 1285–1376.

Barnes, P. J., & Pauwels, R. A. (1994). Theophylline in the management of asthma: Time for reappraisal? *European Respiratory Journal*, *7*(3), 579–591.

Basu, S., Barawkar, D. A., Ramdas, V., Waman, Y., Patel, M., Panmand, A., Kumar, S., Thorat, S., Bonagiri, R., Jadhav, D., Mukhopadhyay, P., Prasad, V., Reddy, B. S., Goswami, A., Chaturvedi, S., Menon, S., Quraishi, A., Ghosh, I., Dusange, S., … Mookhtiar, K. A. (2017). A2Badenosine receptor antagonists: Design, synthesis and biological evaluation of novel xanthine derivatives. *European Journal of Medicinal Chemistry*, *127*, 986–996.

Burbiel, J. C., Hockemeyer, J., & Müller, C. E. (2006). Microwave-assisted ring closure reactions: Synthesis of 8-substituted xanthine derivatives and related pyrimido- and diazepinopurinediones. *Beilstein Journal of Organic Chemistry*, *2*(1),20

Cappelletti, S., Daria, P., Sani, G., & Aromatario, M. (2015). Caffeine: Cognitive and Physical Performance Enhancer or Psychoactive Drug? *Current Neuropharmacology*, *13*(1), 71–88.

Carter, K. (2012). The History of Barbiturik Acid. 917, 5753.

Coelho, A., Fraichard, S., Le Goff, G., Faure, P., Artur, Y., Ferveur, J. F., & Heydel, J. M. (2015). Cytochrome P450-dependent metabolism of caffeine in Drosophila melanogaster. *PLoS ONE*, *10*(2), e0117328.

Constantin, S. M., Buron, F., Routier, S., Vasincu, I. M., Apotrosoaei, M., Lupaşcu, F., Confederat, L., Tuchilus, C., Constantin, M. T., Sava, A., & Profire, L. (2019). Formulation and characterization of new polymeric systems based on chitosan and xanthine derivatives with thiazolidin-4-one scaffold. *Materials*, *12*(4), 558.

Cooney, L., Sinha, I., & Hawcutt, D. (2016). Aminophylline dosage in asthma exacerbations in children: a systematic review. *PLoS One*, *11*(8), e0159965.

Crumpton, T. L., Seidler, F. J., & Slotkin, T. A. (2001). Generation of reactive oxygen species by xanthine derivatives in MDA-MB-231 human breast cancer cells. *Breast Cancer Research and Treatment*, *66*(2), 143–146.

Daly, J. W. (2007). Caffeine analogs: Biomedical impact. *Cellular and Molecular Life Sciences*, *64*(16), 2153–2169.

Harmse, R., Van der Walt, M. M., Petzer, J. P., & Terre'Blanche, G. (2016). Discovery of 1, 3-diethyl-7-methyl-8-(phenoxymethyl)-xanthine derivatives as novel adenosine A1 and A2A receptor antagonists. *Bioorganic & Medicinal Chemistry Letters*, *26*(24), 5951-5955.

El-Kalyoubi, S., & Agili, F. (2020). Synthesis, in silico prediction and in vitro evaluation of antitumor activities of novel pyrido[2,3-d]pyrimidine, xanthine and lumazine derivatives. *Molecules*, *25*(21), 5205.

Faudone, G., Arifi, S., & Merk, D. (2021). The Medicinal Chemistry of Caffeine. *Journal of Medicinal Chemistry*, *64*(11), 7156–7178.

Flores, S., Culichia, C. N., Villarreal, E. G., Savorgnan, F., Checchia, P. A., & Loomba, R. S. (2020). Xanthine Derivatives for Kidney Protection in the Critically Ill Pediatric Population: A Systematic Review. *Journal of Pediatric Intensive Care*, *09*(03), 155–161.

Foukas, L. C., Daniele, N., Ktori, C., Anderson, K. E., Jensen, J., & Shepherd, P. R. (2002). Direct effects of caffeine and theophylline on p110δ and other phosphoinositide 3-kinases: Differential effects on lipid kinase and protein kinase activities. *Journal of Biological Chemistry*, *277*(40), 37124–37130.

Ghasemi-Pirbaluti, M., Motaghi, E., Najafi, A., & Hosseini, M. J. (2017). The effect of theophylline on acetic acid induced ulcerative colitis in rats. Biomedicine & Pharmacotherapy, 90, 153-159.

Glogowski, J., Danforth, D. R., & Ciereszko, A. (2002). Inhibition of alkaline phosphatase activity of boar semen by pentoxifylline, caffeine, and theophylline. *Journal of Andrology*, *23*(6), 783–792.

HALIÇ, A. (2020). Synthesis, characterization and cytotoxic activity studies of new arilidene uracil derivatives (M.Sc, Thesis), Bursa Technical University, Faculty of Engineering and Natural Science Bursa.

Hawke, T. J., Allen, D. G., & Lindinger, M. I. (2000). Paraxanthine, a caffeine metabolite, dose dependently increases [Ca2+](i) in skeletal muscle. *Journal of Applied Physiology*, *89*(6), 2312–2317.

Hayallah, A. M., Sandoval-Ramírez, J., Reith, U., Schobert, U., Preiss, B., Schumacher, B., Daly, J. W., & Müller, C. E. (2002). 1,8-Disubstituted xanthine derivatives: Synthesis of potent A2B-selective adenosine receptor antagonists. *Journal of Medicinal Chemistry*, *45*(7), 1500–1510.

Hisham, M., Youssif, B. G. M., Osman, E. E. A., Hayallah, A. M., & Abdel-Aziz, M. (2019). Synthesis and biological evaluation of novel xanthine derivatives as potential apoptotic antitumor agents. *European Journal of Medicinal Chemistry*, *176*, 117–128.

Janitschke, D., Lauer, A. A., Bachmann, C. M., Grimm, H. S., Hartmann, T., & Grimm, M. O. W. (2021). Methylxanthines and neurodegenerative diseases: An update. *Nutrients*, *13*(3), 803.

Jiang, J., Seel, C. J., Temirak, A., Namasivayam, V., Arridu, A., Schabikowski, J., Baqi, Y., Hinz, S., Hockemeyer, J., & Müller, C. E. (2019). A2B Adenosine Receptor Antagonists with Picomolar Potency. *Journal of Medicinal Chemistry*, *62*(8), 4032–4055.

Kakuyama (nee Iwazaki), A., & Sadzuka, Y. (2005). Effect of Methylxanthine Derivatives on Doxorubicin Transport and Antitumor Activity. *Current Drug Metabolism*, *2*(4), 379–395.

Kapri, A., Gupta, N., & Nain, S. (2022). Recent Advances in the Synthesis of Xanthines: A Short Review. *Scientifica*, *2022*(July), 1–24.

Kapri, A., Pant, S., Gupta, N., & Nain, S. (2022). Recent Advances in the Biological Significance of Xanthine and its Derivatives: A Review. *Pharmaceutical Chemistry Journal*, *56*(4), 461–474.

Kavi, K. P. B., Bandopadhyay, R., & Suravajhala, P. (2014). Xanthine derivatives: a molecular modeling perspective. Agricultural Bioinformatics, 283-291.

Khaliullin, F. A., Mamatov, Z. K., Timirkhanova, G. A., Samorodov, A. V., & Bashirova, L. I. (2020). Synthesis, Antiaggregant, and Antioxidant Activity of 2-{[1-iso-butyl-3-methyl-7-(thietanyl-3)xanthine-8-yl]thio}acetic Acid Salts. *Pharmaceutical Chemistry Journal*, *54*, 891–896.

Koch, G. (2017). Medicinal Chemistry. *Chimia*, *71*(10), 643.

Koch, P., Brunschweiger, A., Namasivayam, V., Ullrich, S., Maruca, A., Lazzaretto, B., Küppers, P., Hinz, S., Hockemeyer, J., Wiese, M., Heer, J., Alcaro, S., Kiec-Kononowicz, K., & Müller, C. E. (2018). Probing substituents in the 1- and 3-position: Tetrahydropyrazino-annelated water-soluble xanthine derivatives as multi-target drugs with potent adenosine receptor antagonistic activity. *Frontiers in Chemistry*, *6*, 206.

Kuder, K. J., Załuski, M., Schabikowski, J., Latacz, G., Olejarz-Maciej, A., Jaśko, P., Doroz-Płonka, A., Brockmann, A., Müller, C. E., & Kieć-Kononowicz, K. (2020). Novel, Dual Target-Directed Annelated Xanthine Derivatives Acting on Adenosine Receptors and Monoamine Oxidase B. *ChemMedChem*, *15*(9), 772–786.

Laddha, S. S., Wadodkar, S. G., & Meghal, S. K. (2009). CAMP-dependent phosphodiesterase inhibition and SAR studies on novel 6,8-disubstituted 2-phenyl-3-(substituted benzothiazole-2-yl)-4[3H]-quinazolinone. *Medicinal Chemistry Research*, *18*, 268–276.

Lee, D., Lee, S., Liu, K. H., Bae, J. S., Baek, D. J., & Lee, T. (2016). Solid-Phase Synthesis of 1,3,7,8-Tetrasubstituted Xanthine Derivatives on Traceless Solid Support. *ACS Combinatorial Science*, *18*(1), 70–74.

McCarty, M. F., O'Keefe, J. H., & DiNicolantonio, J. J. (2016). Pentoxifylline for vascular health: a brief review of the literature. Open heart, 3(1), e000365.

Monteiro, J. P., Alves, M. G., Oliveira, P. F., & Silva, B. M. (2016). Structure-bioactivity relationships of methylxanthines: Trying to make sense of all the promises and the drawbacks. *Molecules*, *21*(8), 974.

Moraes, M. M., Galvao, M. C., Cabral, D., Coelho, C. P., Queiroz-Hazarbassanov, N., Martins, M. F., ... & Kirsten, T. B. (2017). Propentofylline prevents sickness behavior and depressive-like behavior induced by lipopolysaccharide in rats via neuroinflammatory pathway. *PLoS One*, *12*(1), e0169446.

Nehlig, A. (2018). Interindividual differences in caffeine metabolism and factors driving caffeine consumption. *Pharmacological Reviews*, *70*(2), 384–411.

Orrú, M., Guitart, X., Karcz-Kubicha, M., Solinas, M., Justinova, Z., Barodia, S. K., Zanoveli, J., Cortes, A., Lluis, C., Casado, V., Moeller, F. G., & Ferré, S. (2013). Psychostimulant pharmacological profile of paraxanthine, the main metabolite of caffeine in humans. *Neuropharmacology*, *67*, 476–484.

Ponnala, S., & Prasad Sahu, D. (2006). Iodine-mediated synthesis of 2-arylbenzoxazoles, 2-arylbenzimidazoles, and 1,3,5-trisubstituted pyrazoles. *Synthetic Communications*, *36*(15), 2189–2194.

Pretze, M., Neuber, C., Kinski, E., Belter, B., Köckerling, M., Caflisch, A., Steinbach, J., Pietzsch, J., & Mamat, C. (2020). Synthesis, radiolabelling and initial biological characterisation of 18F-labelled xanthine derivatives for PET imaging of Eph receptors. *Organic and Biomolecular Chemistry*, *18*(16), 3104–3116.

Bansal, R., Kumar, G., Gandhi, D., Yadav, R., Young, L. C., & Harvey, A. L. (2010). Synthesis of 8-(cyclopentyloxy) phenyl substituted xanthine derivatives as adenosine A2A ligands. *Arzneimittelforschung*, *60*(03), 131-136.

Reshetnikov, D. V., Burova, L. G., Rybalova, T. V., Bondareva, E. A., Patrushev, S. S., Evstropov, A. N., & Shults, E. E. (2022). Synthesis and Antibacterial Activity of Caffeine Derivatives Containing Amino-Acid Fragments. *Chemistry of Natural Compounds*, *58*(5), 908–915.

Sauer, R., Maurinsh, J., Reith, U., Fülle, F., Klotz, K. N., & Müller, C. E. (2000). Water-soluble phosphate prodrugs of 1-propargyl-8-styrylxanthine derivatives, A2(A)-selective adenosine receptor antagonists. *Journal of Medicinal Chemistry*, *43*(3), 440–448.

Shabalina, Y. V., Khaliullin, F. A., Nikitina, I. L., Miftakhova, A. F., & Sharafutdinov, R. M. (2020). Synthesis and Antidepressant Activity of 8-Amino-Substituted 1-Butyl-3-Methylxanthines Containing a Thietane Ring. *Pharmaceutical Chemistry Journal*, *53*, 1009–1012.

Singh, N., Shreshtha, A. K., Thakur, M. S., & Patra, S. (2018). Xanthine scaffold: scope and potential in drug development. *Heliyon*, *4*(10), e00829.

Sledz, W., Los, E., Paczek, A., Rischka, J., Motyka, A., Zoledowska, S., Piosik, J., & Lojkowska, E. (2015). Antibacterial activity of caffeine against plant pathogenic bacteria. *Acta Biochimica Polonica*, *62*(3), 605–612.

Spatafora, M., Chiappara, G., Merendino, A. M., D'Amico, D., Bellia, V., & Bonsignore, G. (1994). Theophylline suppresses the release of tumour necrosis factor-α by blood monocytes and alveolar macrophages. *European Respiratory Journal*, *7*(2), 223–228.

Talmon, M., Massara, E., Brunini, C., & Fresu, L. G. (2019). Comparison of anti-inflammatory mechanisms between doxofylline and theophylline in human monocytes. *Pulmonary Pharmacology & Therapeutics*, *59*, 101851.

Trincavelli, M. L., Daniele, S., & Martini, C. (2010). *Adenosine Receptors : What We Know and What We are Learn*ing. *Current topics in medicinal chemistry*, 10(9), 860-877.

Usmani, O. S., Belvisi, M. G., Patel, H. J., Crispino, N., Birrell, M. A., Korbonits, M., Korbonits, D., & Barnes, P. J. (2005). Theobromine inhibits sensory nerve activation and cough. *The FASEB Journal*, *19*(2), 1–16.

van der Walt, M. M., & Terre'Blanche, G. (2017). Selected C8 two-chain linkers enhance the adenosine A1/A2Areceptor affinity and selectivity of caffeine. *European Journal of Medicinal Chemistry*, *125*, 652–656.

Weyler, S., Fülle, F., Diekmann, M., Schumacher, B., Hinz, S., Klotz, K. N., & Müller, C. E. (2006). Improving potency, selectivity, and water

solubility of adenosine A 1 receptor antagonists: Xanthines modified at position 3 and related pyrimido[1,2,3-cd]purinediones. *ChemMedChem, Chemistry Enabling Drug Discovery*, *1*(8), 891–902.
Wood, A. J. J., Weinberger, M., & Hendeles, L. (1996). Theophylline in asthma. *N Engl J Med*, 334, 1380-1388.

APPENDICE

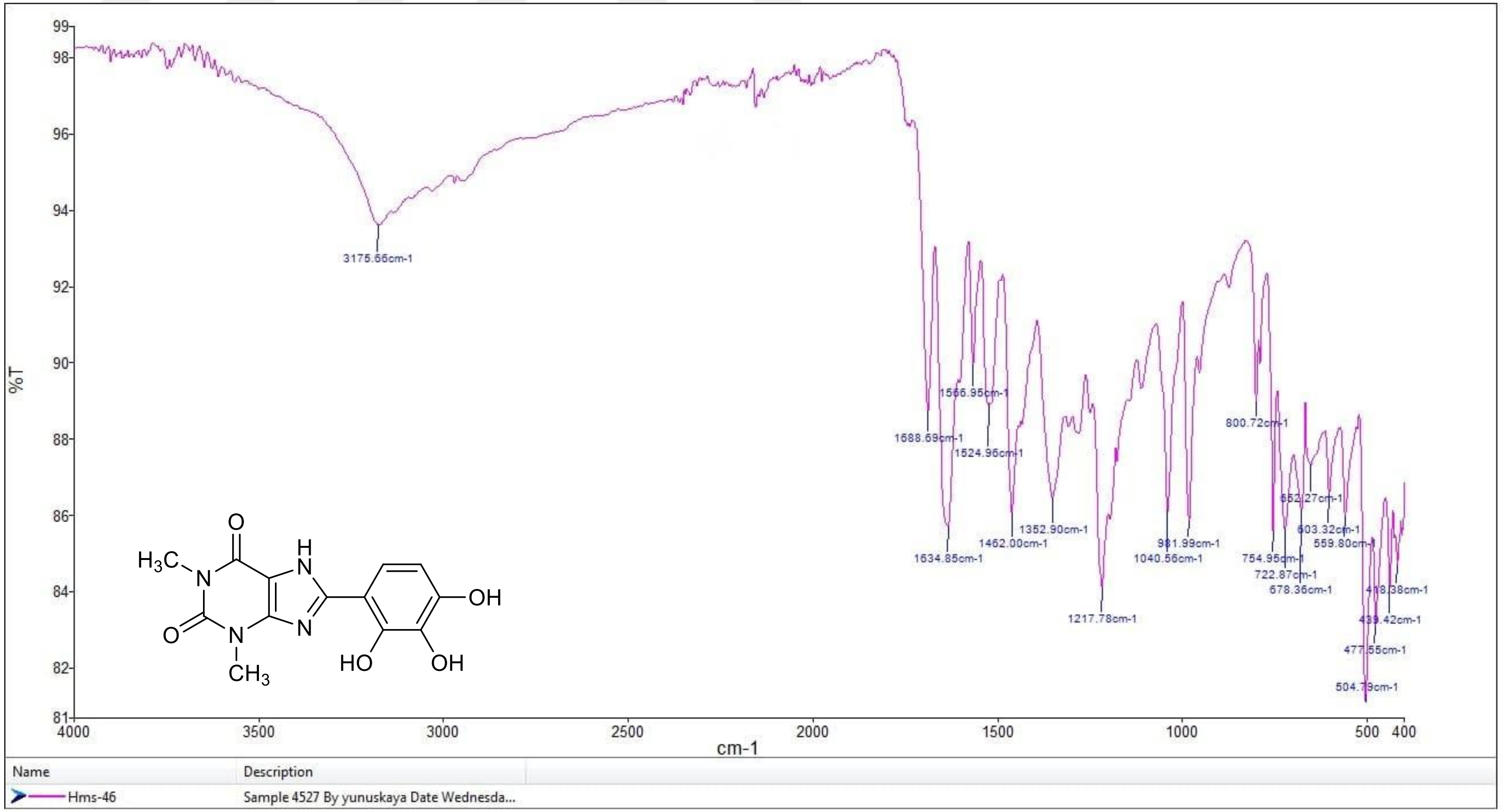

Figure A.1: FT-IR spectrum of compound **(a).**

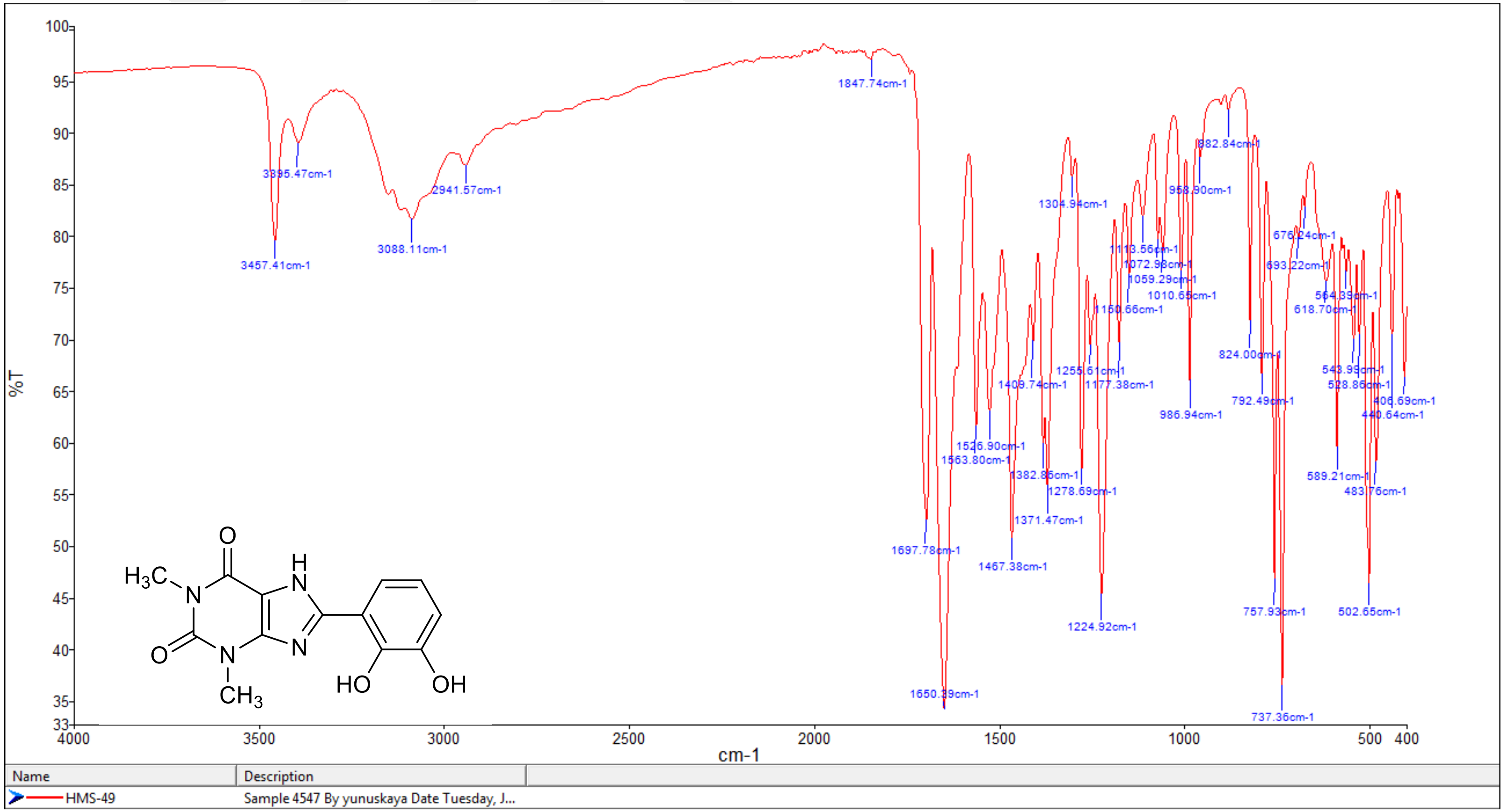

Figure A.2: FT-IR spectrum of compound **(b)**.

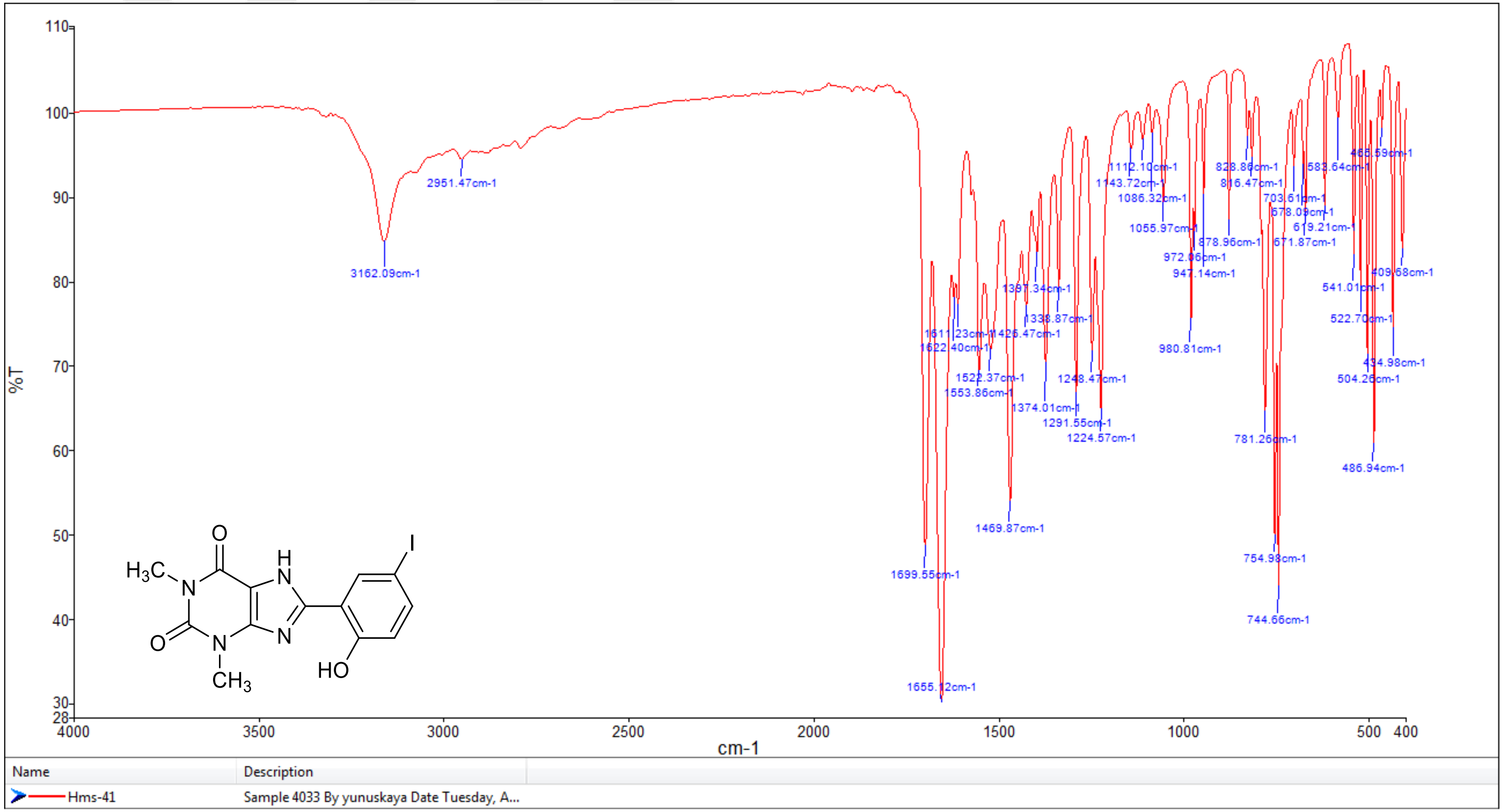

Figure A.3: FT-IR spectrum of compound **(c)**.

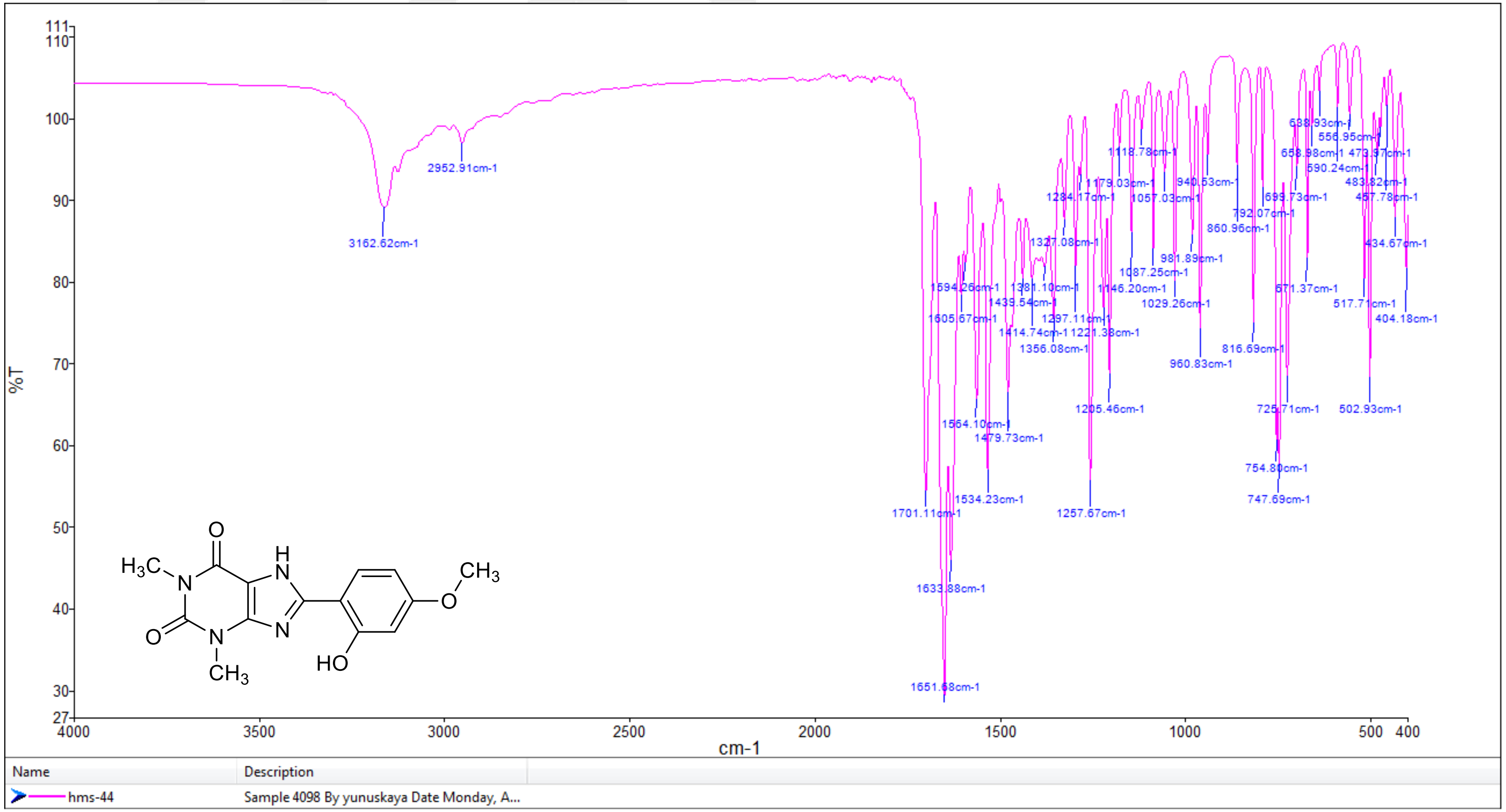

Figure A.4: FT-IR spectrum of compound **(d)**.

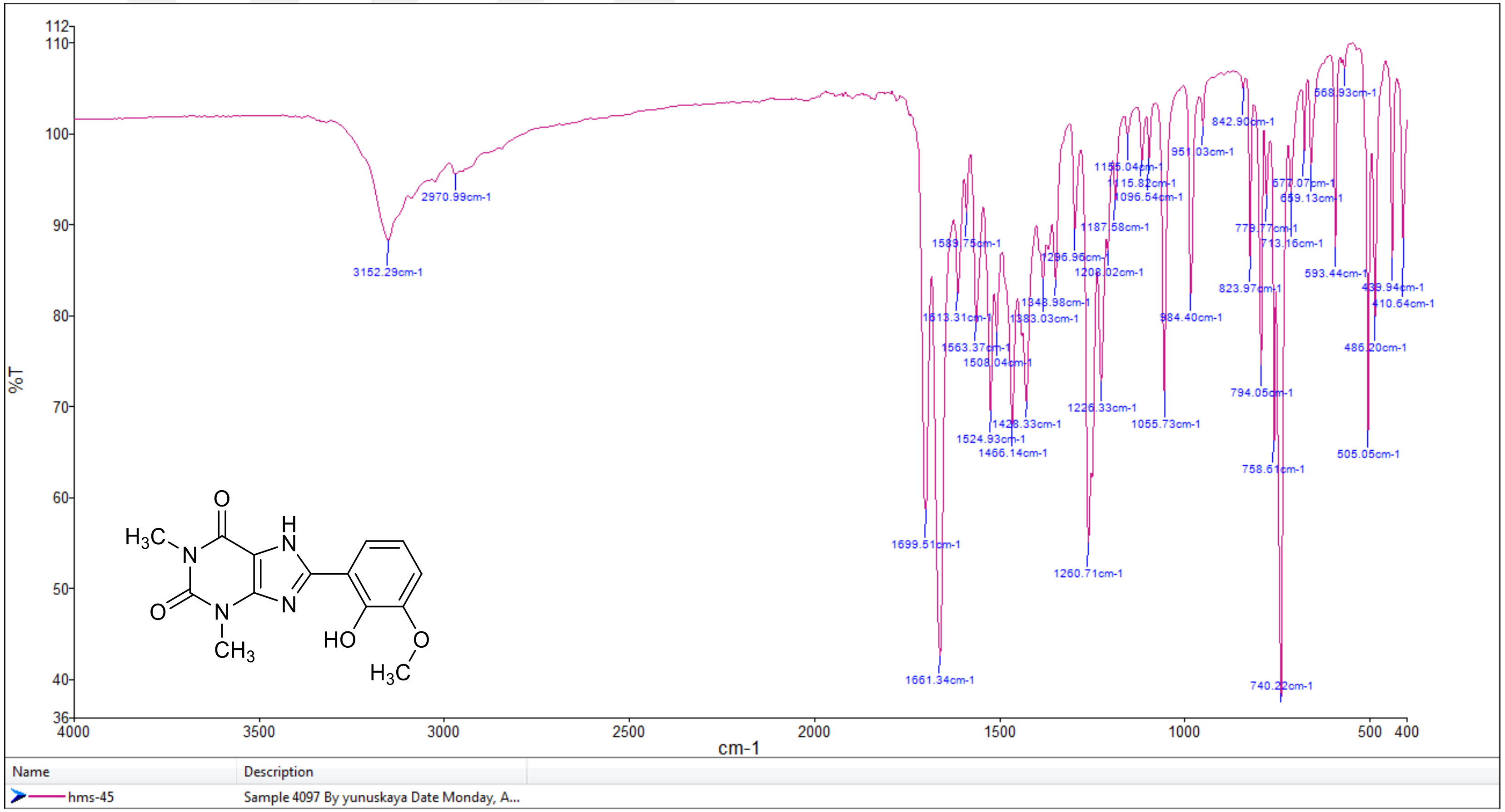

Figure A.5: FT-IR spectrum of compound **(e)**.

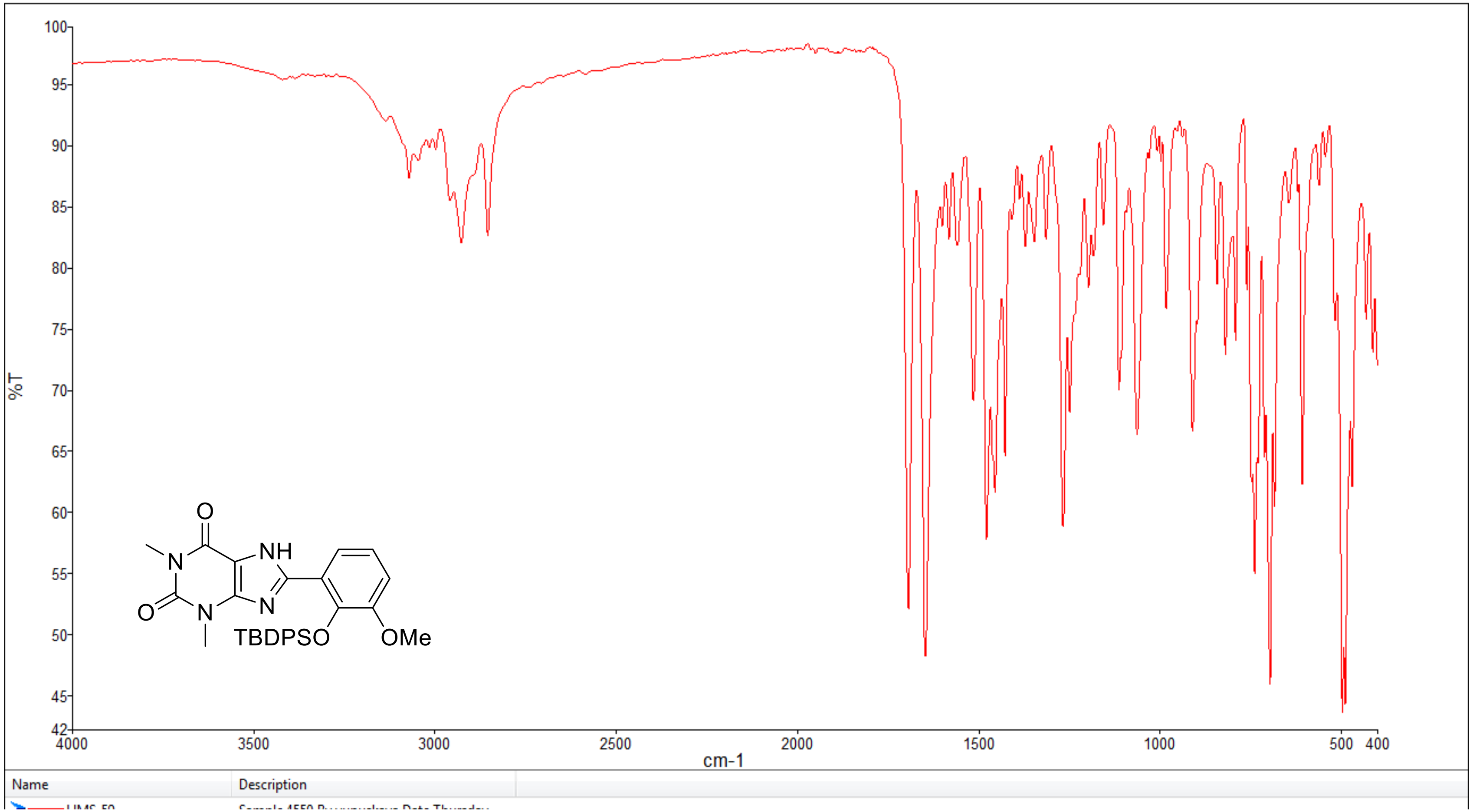

Figure A.6: FT-IR spectrum of compound **(f)**.

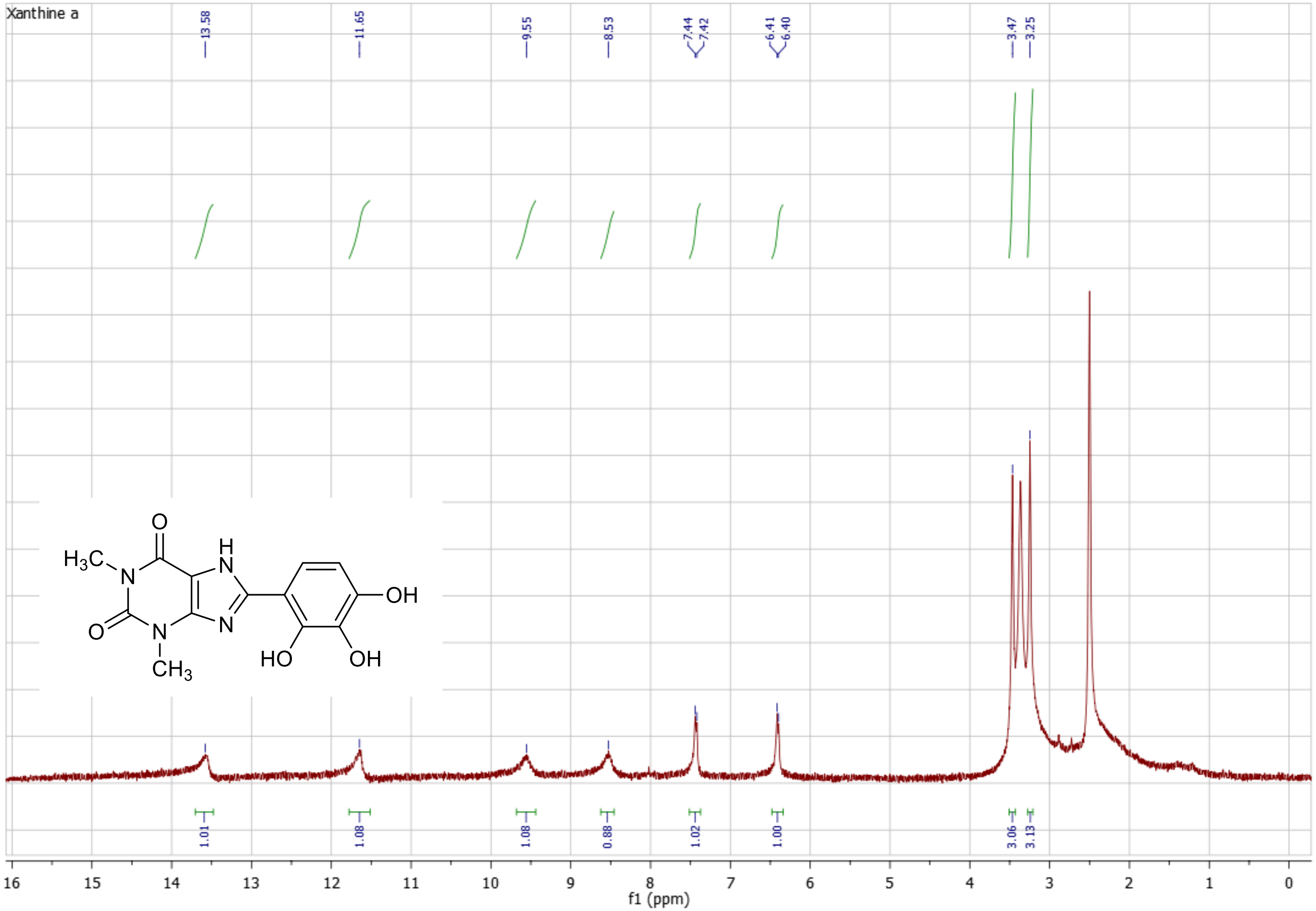

Figure A.7: ^{1}H-NMR spectrum of compound **(a).**

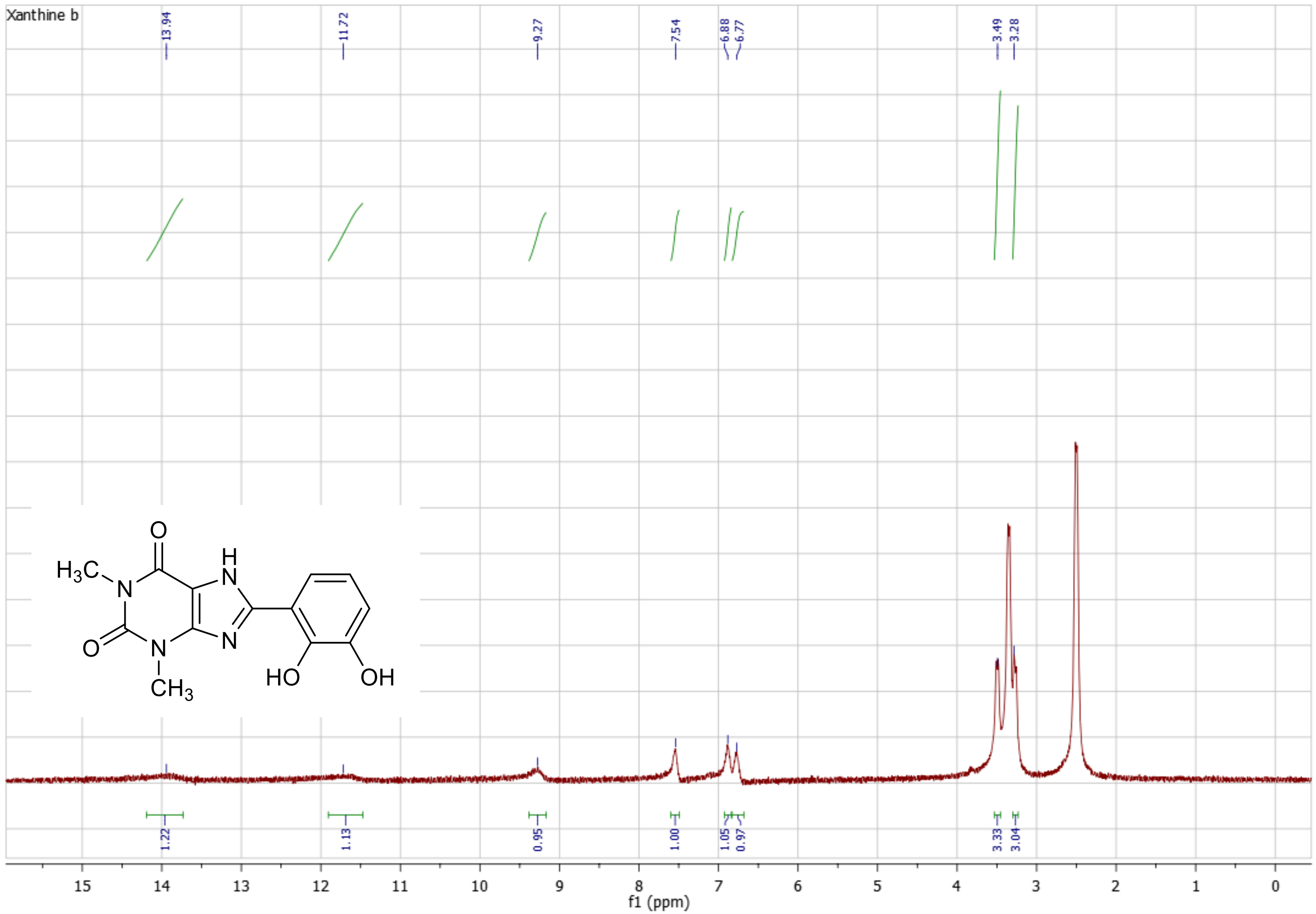

Figure A.8: ^{1}H-NMR spectrum of compound **(b)**.

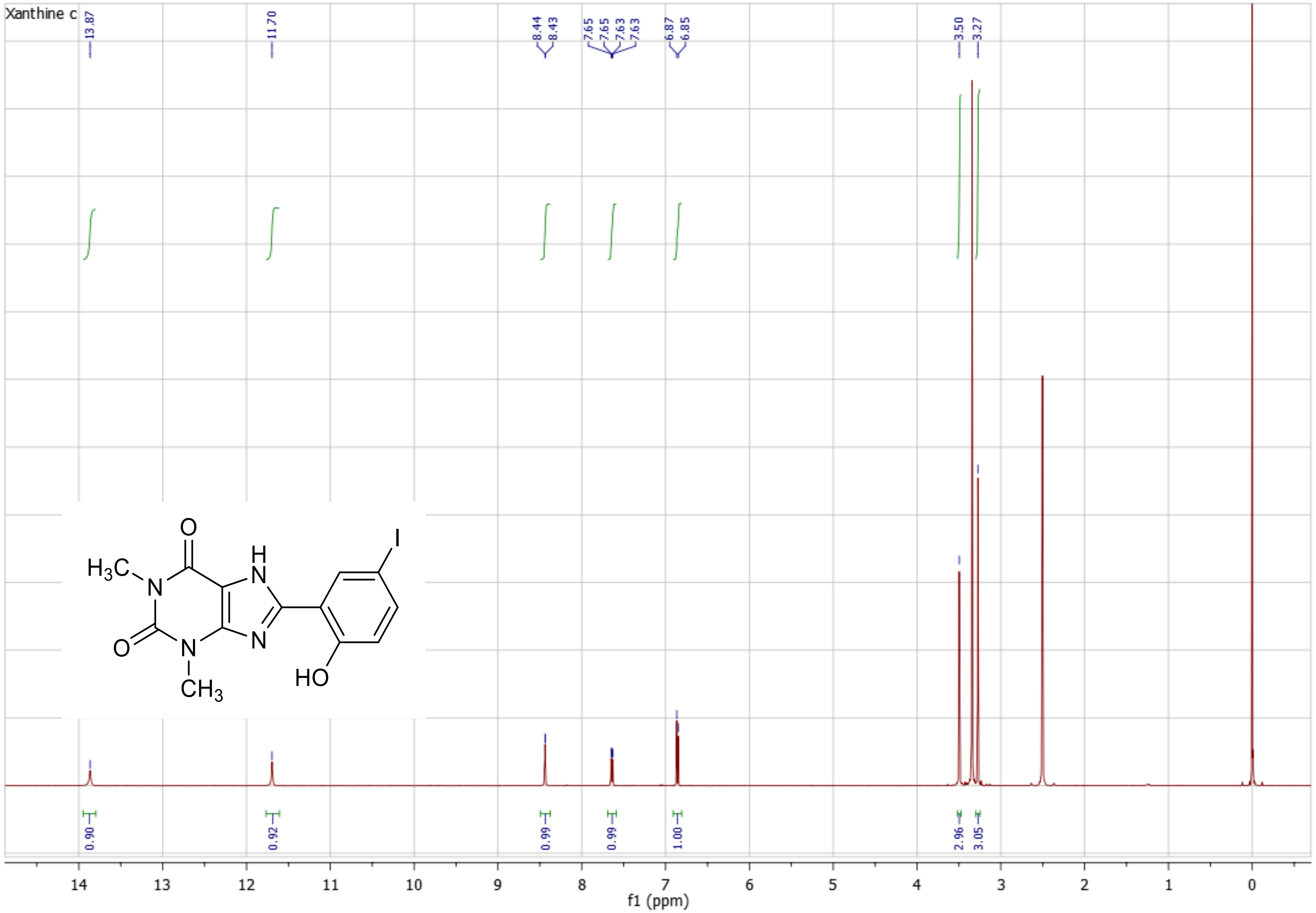

Figure A.9: ^{1}H-NMR spectrum of compound **(c).**

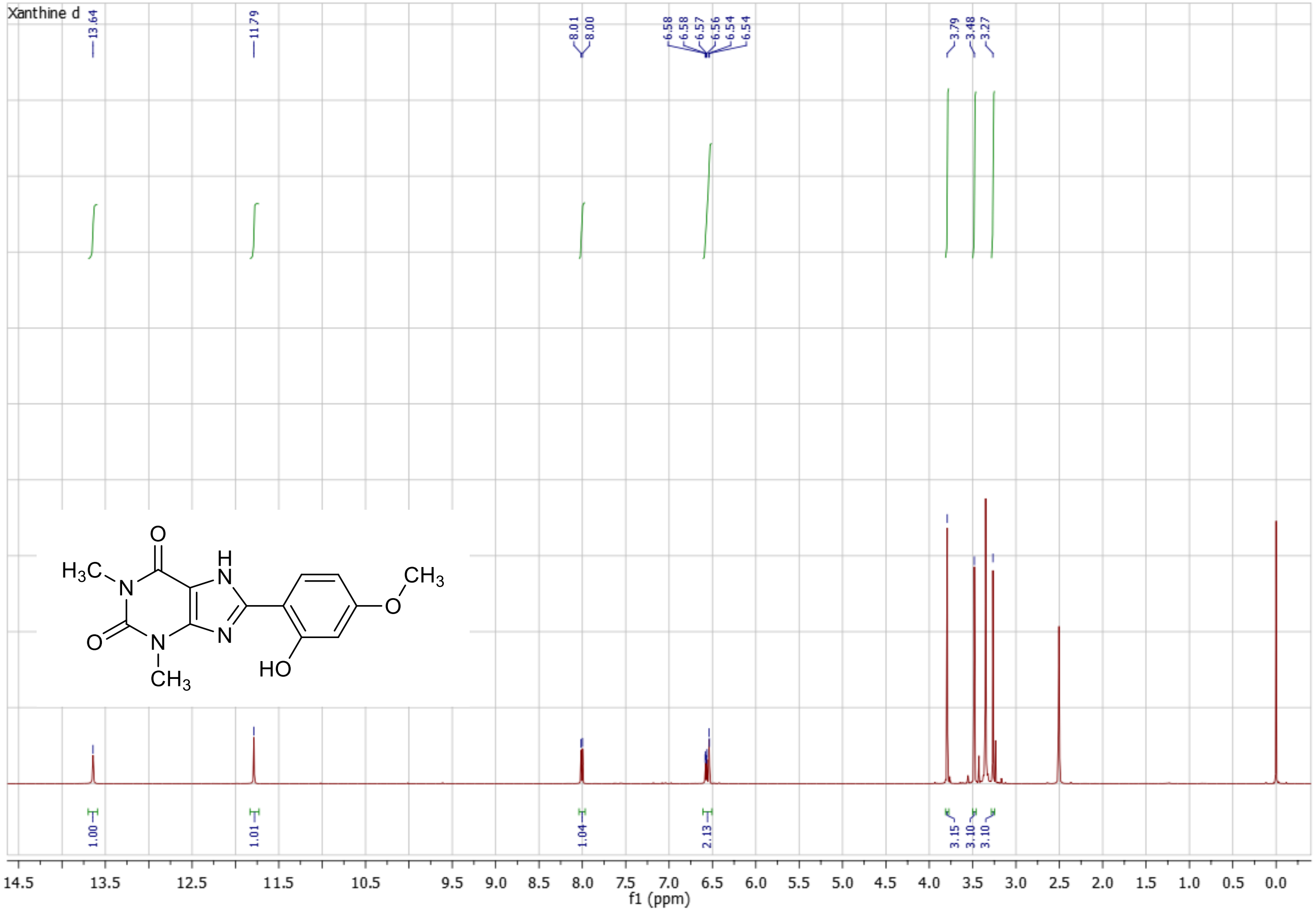

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Figure A.10: ^{1}H-NMR spectrum of compound **(d).**

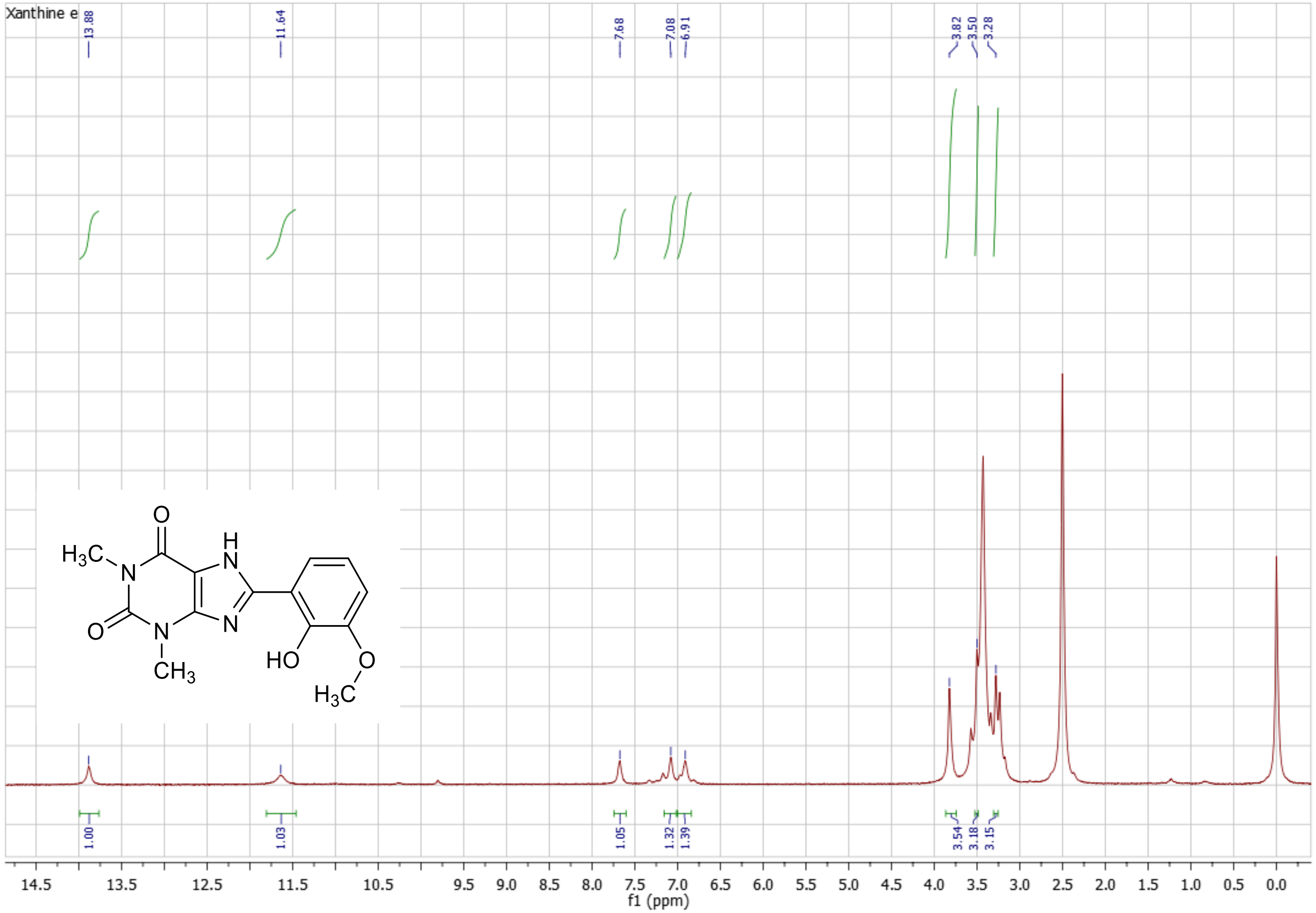


Figure A.11: ^{1}H-NMR spectrum of compound **(e)**.

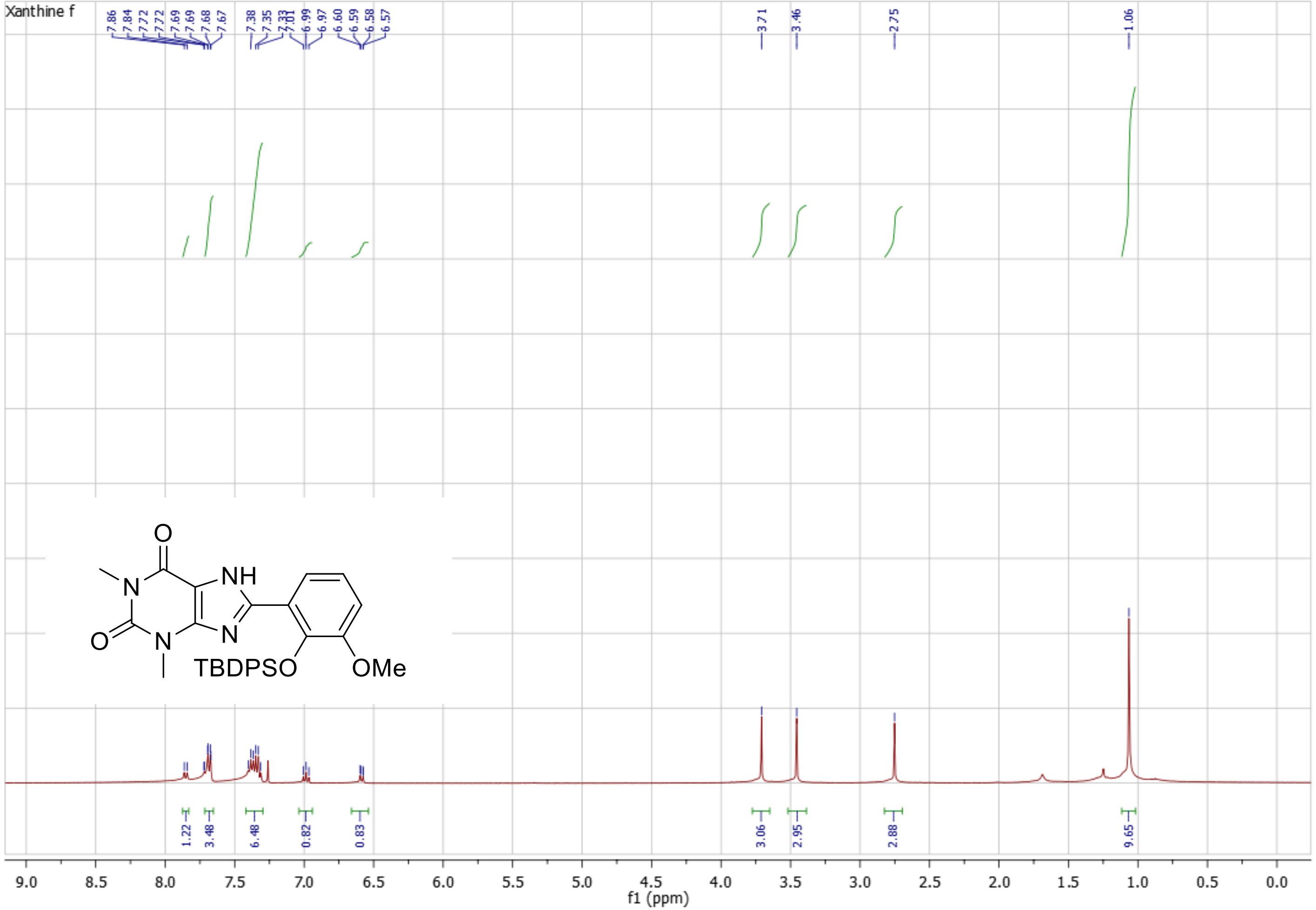
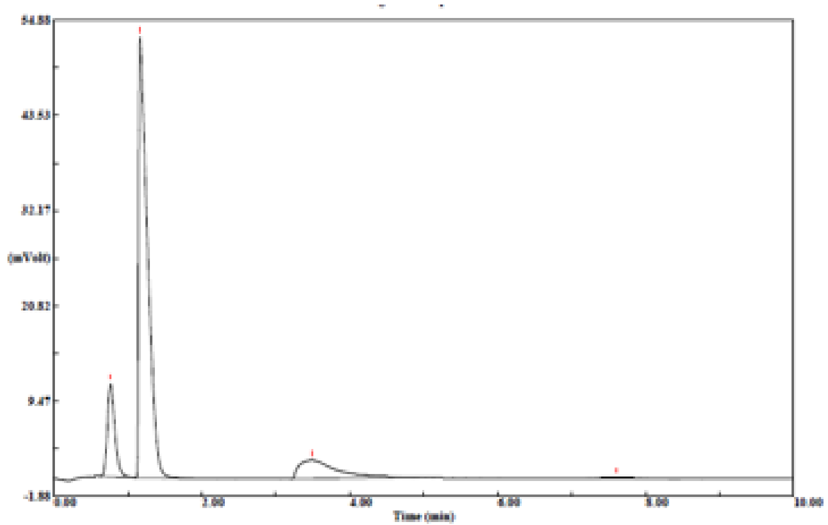
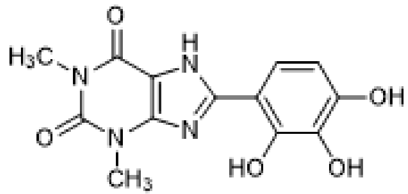


Figure A.12: ^{1}H-NMR spectrum of compound **(f).**

(a) 1,3-dimethyl-8-(2,3,4-trihydroxyphenyl)-1H-purine-2,6(3H,7H)-dione





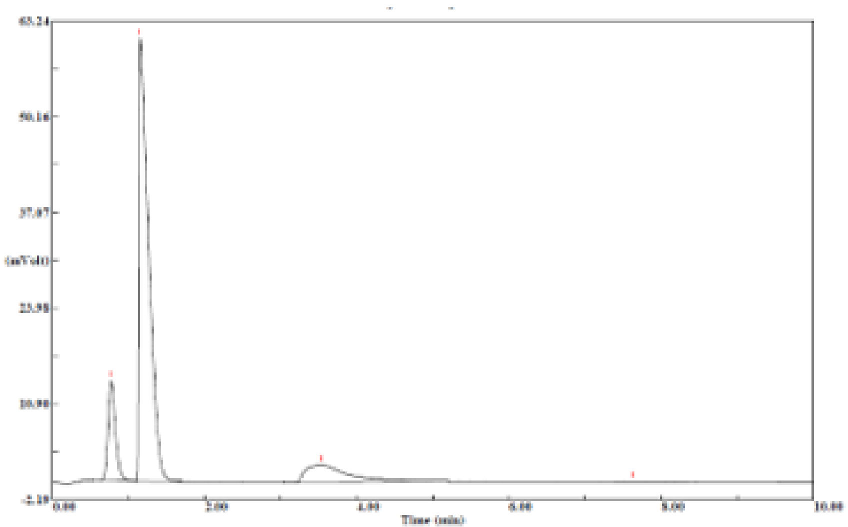
(a)

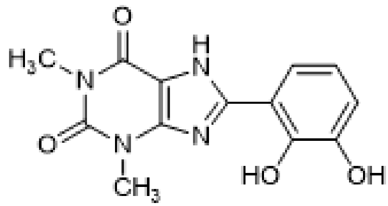
$C_{13}H_{12}N_4O_5$

Elements	Calculated	Found
%N	18.41	16.81
%C	51.32	43.15
%H	3.98	3.11

Figure A.13: Elemental analysis of compound **(a)**.

(b) 8-(2,3-dihydroxyphenyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione





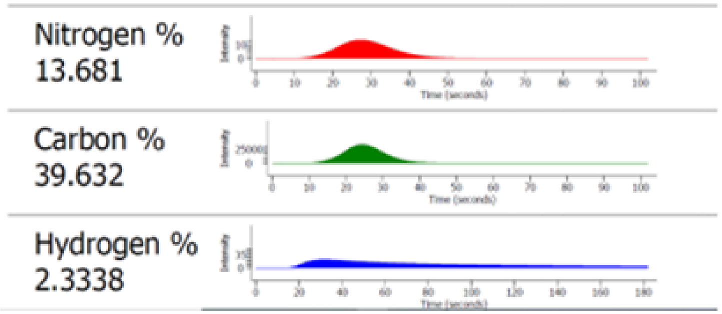
(b)

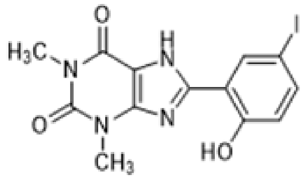
$C_{13}H_{12}N_4O_4$

Elements	Calculated	Found
%N	19.44	19.71
%C	54.17	51.71
%H	4.20	3.46

Figure A.14: Elemental analysis of compound **(b).**

(c) 8-(2-hydroxy-5-iodophenyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione





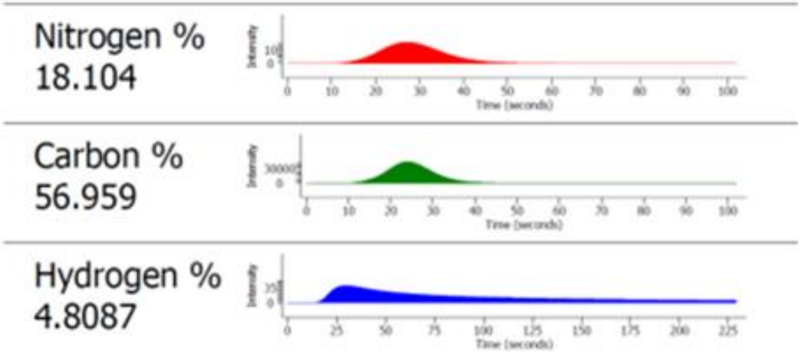
(c)

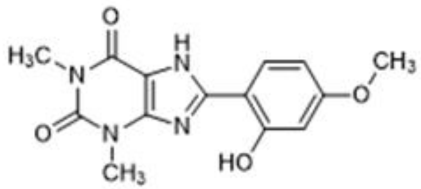
$C_{13}H_{11}IN_4O_3$

Elements	Calculated	Found
%N	14.07	13.681
%C	39.22	39.63
%H	2.78	2.33

Figure A.15: Elemental analysis of compound **(c).**

(d) 8-(2-hydroxy-4-methoxyphenyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione





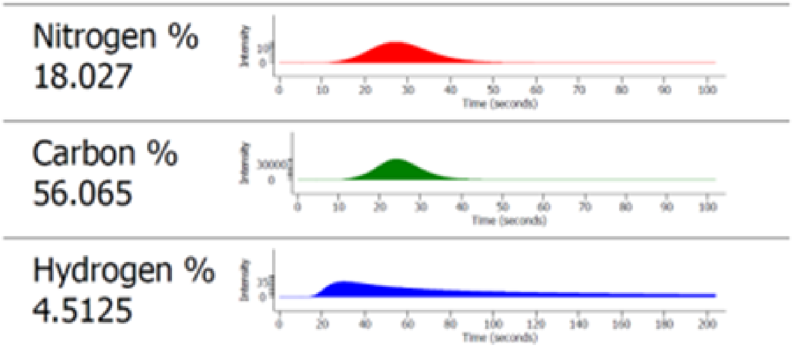
(d)

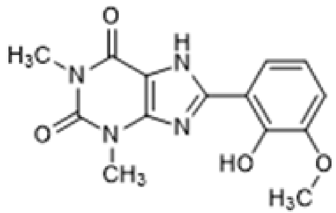
$C_{14}H_{14}N_4O_4$

Elements	Calculated	Found
%N	18.53	18.10
%C	55.63	56.95
%H	4.67	4.80

Figure A.16: Elemental analysis of compound **(d)**.

(e) 8-(2-hydroxy-3-methoxyphenyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione





(e)

$C_{14}H_{14}N_4O_4$

Elements	Calculated	Found
%N	18.53	18.02
%C	55.63	56.06
%H	4.67	4.51

Figure A.17: Elemental analysis of compound **(e).**

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