



# “SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY EVALUATION OF 4-AMINOQUINOLINE 1, 2, 4-TRIAZOLE DERIVATIVES”

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## ABSTRACT

Xanthenes' derivative is nitrogen containing heterocyclic aromatic compounds. Various heterocyclic compounds have show stimulation of cardiac muscle, enhanced diuresis, stimulation of CNS and finally a soothing relaxation of Bronchi and the coronary arteries. Literatures in the recent past reveal that some theophylline derivative possesses antibacterial and enhance Antitussive and Bronchodilator activity.

The synthesis of substituted 1,3-Dimethylxanthine derivative consist of the following steps which are as follows.

Step-I: **Synthesis of the 7-(undec-10-ene)theophylline**

Step-II: **Synthesis of the 8-(7-Chloroquinoline)-7-(undec-10-ene)theophylline**

Step-III: **Synthesis of 7-(7-Chloroquinoline)theophylline**

All the synthesized compounds by the above described method result in products with good yields. IR, <sup>1</sup>H NMR and Mass spectroscopic analysis conformed the structures of new synthesized compounds. The newly synthesized compounds were screened for their Bronchodilator activities by using Theophylline as standard and are found to be effective Bronchodilator agent.

## 1. INTRODUCTION

### 1.1 About Medicinal Chemistry:

Drugs- natural and synthetic alike- are chemicals used for medicinal purposes. They interact with complex chemical systems of humans or animals. Medicinal chemistry is concerned with this interaction, focusing on the organic and biochemical reactions of drug substances with their targets. This is one aspect of drug chemistry. Other important aspects are the synthesis and analysis of drug substances (Wilson and Gisvold's, 1998).

Medicinal chemistry concerns the discovery, development, the identification and the interpretation of the mode of action of biologically active compounds at the molecular levels. Emphasis is put on drugs but the interest of medicinal chemist are not restricted to drugs but include bioactive compounds in general. Medicinal chemistry is also concerned with the study, identification and synthesis of metabolic product of drugs and related compounds (Wermuth Camille Georges, 2009).

Medicinal chemistry is science whose roots lie in all branches of chemistry and biology. It concerns essentially the understanding and explanation of the mechanisms of the actions of drugs. On this basis it attempts to establish relationships between chemical structure and biological activity and to link biodynamic behavior to the chemical reactivity and physical properties of therapeutic agent. Medicinal chemistry also involves the isolation, characterization and synthesis of compounds that can be used in medicine for prevention, treatment and cure of disease. Medicinal chemistry thus provides the chemical basis for the interdisciplinary field of therapeutics (Burger Alfred, 1970).

The main objective of medicinal chemistry is the design and the production of compounds that can be used as medicine for the prevention, treatment and cure of human or animal diseases. Medicinal chemistry includes the following stages : First stage new active drugs are identified and prepared from natural sources. They are known as lead molecules. Second stage is optimization of lead structure to improve potency, selectivity and lessen toxicity. Third stage is development stage involves optimization of synthetic route for bulk production and modification of pharmacokinetic and pharmaceutical properties of active substance to render it chemically useful (Singh Harikishan, 2008) To provide an understanding of the principle of medicinal chemistry, it is necessary to co side the physicochemical properties used to develop new pharmacologically active compounds and their mechanism of activities of metabolism including possible biological activities of stereochemistry in drug design (Lemke Thomas L, 2010). The discipline of medicinal chemistry is devoted to the discovery development of new agents for treating diseases. Most of this activity is directed to new natural or synthetic organic compounds. Inorganic compounds continue to be

important in therapy eg- trace elements in nutritional therapy, antacids and radio pharmaceuticals, but organic molecules with increasingly specific pharmacological activities are clearly dominant. Development of organic compound has grown beyond traditional synthetic methods (Wilson and Gisvold's, 1998).

In the pharmaceutical industry, medicinal chemistry is at the heart of finding new medicines. The objectives of medicinal chemistry are as easily formulated as they are difficult to achieve. Find, develop and improve drug substances that cure or elevate diseases and understand the causative and accompanying chemical processes (Wermuth Georges Camille, 2009).

## **1.2 About Heterocyclic compounds:**

A cyclic organic compound containing all carbon atoms in ring formation is referred to as a carboxylic compound. If at least one atom other than carbon, forms a part of the ring system then it is designated as a heterocyclic compound. Nitrogen, oxygen and sulfur are the most common heteroatom's (Jamali, 2014).

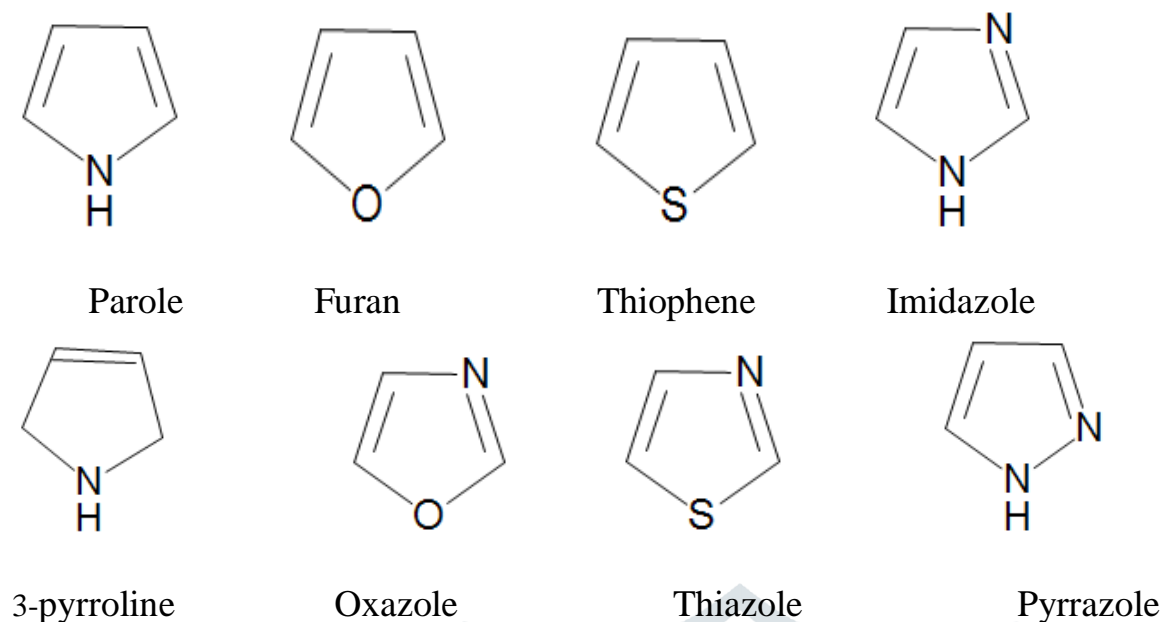


Fig 1.1: Various heterocyclic compounds

Most of the drugs belong to the class of heterogeneous compounds. Heterocyclic compounds played a vital role in the metabolism of all living cells; large number of them are five and six member heterocyclic compounds having one to three heteroatom's in their nucleus. Some of the common heterocyclic compounds used in medicines are as amino acids like proline, histidine and tryptophan, the vitamins and coenzyme precursors such as thiamine, riboflavin, pyridoxine, folic acid, biotin, B12 and E families of vitamins. Literature survey shows that a number of heterocyclic compounds having condensed ring system possess various types of physiological activities (Mukhtyar et al., 2013). Compounds classified as heterocyclic probably constitute the largest and most varied family of organic compounds. Heterocyclic compounds may be classified into aliphatic and aromatic. The aliphatic heterocyclics are the cyclic analogues of amines, ethers, thioethers, amides, etc. The properties are particularly influenced by the presence of strain in the ring. These compounds generally consist of small (3- and 4-membered) and common (5 to 7 member) ring systems. The aromatic heterocyclic compounds, in contrast, are those which have a heteroatom in the ring and behave in a manner similar to benzene in some of their properties. They are also the major components of biological molecules such as DNA and RNA, chlorophyll, hemoglobin, vitamins and many more. Heterocyclic compounds played a vital role in the metabolism of all living cells; large numbers of them are five and six member heterocyclic compounds having one to three heteroatom's in their nucleus (Gupta, 2015). Nitrogen heterocyclic possess a wide spectrum of antimicrobial activity and anti-pharmaceutical activities (Meenachi et al., 2014).

### **1.3 THEOPHYLLINE:**

The methylxanthine theophylline (a1, fig.1) and its derivative (i.e., 1b) have been extensively studied. For example they have been used (i.e., 1c) template in molecularly imprinting related research. Due to its multivalency with various hydrogen bonding donor and acceptor sites this base can be recognized by the binding site of molecularly imprinting polymer with specific structures. Also, theophylline and its derivative (i.e., 1d) been used for conjugation with different high molecular weight poly (ethylene glycol). Among the xanthine derivative theophylline shows greater bindings efficacy with DNA than theobromine and caffeine. It has been demonstrated that theophylline forms complexes with DNA through hydrogen bonds, while serving as a strong antioxidant that prevents DNA damage.

The biological effect of the theophylline is associated with its affinity with a family of adenosine receptors known as A1, A1a, A2b, and A3. These adenosine receptors (or p1 receptor) are a class of purinergic receptors, G-protein coupled receptors with adenosine as endogenous ligands. Structures, activity, and relationship of the

xanthine derivative in searching for more potent and highly A2b-selective legends. It has been found that substitution at position 8 of the theophylline (i.e., 1b.1e) play an important role in the antagonistic activity. For Example, compound 1e present an A2b K1 of 1.39nM.

Through the binding with the above adenosine receptors, theophylline derivative are well known to influence neuronal activities. We are interested in immobilizing them on silicon substrata.

We choose this compound for comparative structure activity analysis, since compounds 2 and 3 present an ethylene glycol derivative substituent at position 8 of theophylline, while compound 10a and 10e present the substitution over the N7 of the base. On the other hand, the presence of substitution at position N7 of the base in compounds 10a and 10e results in the reduction of its affinity for the receptor in corporation to that of 2. This fact can be attributed to the hypothesized activity of this nitrogen as a hydrogen-bonds acceptor at the binding pocket, which it is not allowed in tertiary N7. However compounds 10a still show higher affinity at A1 receptor than 3 and 10e. This may be related to a favorable distal electronic interaction with the receptor due to the combination in 10a of a long tetra (ethylene glycol) chain with a terminable electron rich grouped, similar to that in 2.

Finally, solubility in water and hydrophilic solvents is necessary for biological application of active compounds. This physicochemical property has been a major issue with xanthine and non xanthine antagonist of adenosine receptor, since the 8-phenyl substantial activity at adenosine.

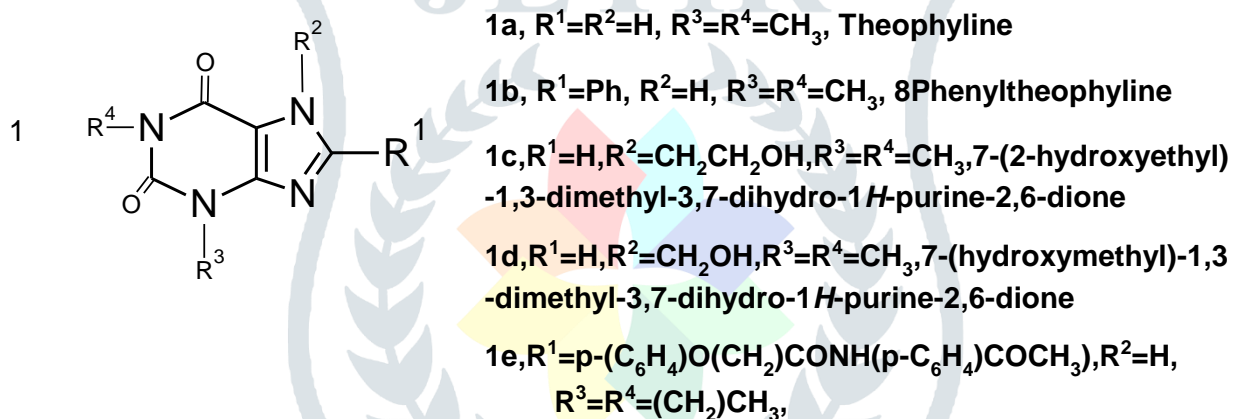


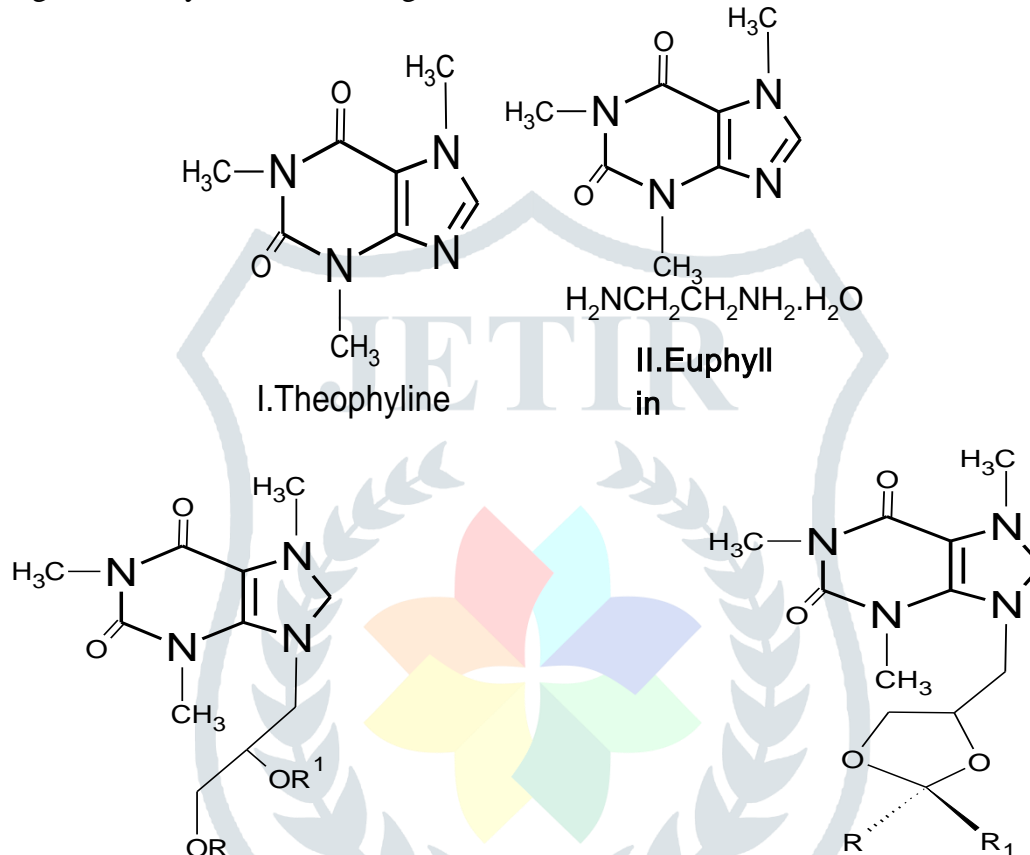
Fig.1.2.Strucher activity theophylline derivatives

### 1.3.1: Xanthine derivatives

Xanthine derivatives have attracted considerable attention due to their numerous biological activities. Although theophylline (I) and euphyllin II have diuretic effects, dyphylline (1) has no effect in spite of being a water soluble analogue of I. On the other hand, dyphylline (1) is much more effective than euphyllin (II) in the treatment of bronchial asthma.<sup>10</sup> Moreover, continuing our efforts to explore new types of acyclic nucleoside have been encouraged by the finding that acyclic nucleoside analogues possess potent selective antiherpes activity<sup>11-20</sup> and the S-enantiomer of 9-(2, 3-dihydroxypropyl) adenine has inhibitory activity towards a number of DNA and RNA viruses.<sup>21, 22</sup>

In the present work, two different approaches have been utilized by the derivatization of the glycerol residue of dyphylline as esters and acetals which may act as prod rugs as well as by the utilization of its periodate oxidation product to build different types of heterocyclic compounds of possible therapeutic value. Acetylation of dyphylline (1) with acetic anhydride in pyridine afforded the di-O-acetyl derivative 2 whose spectra agree with the assigned structure. The terminal methylene group appeared in the <sup>1</sup>H NMR spectrum as two doublets of doublets with a sufficient difference in their chemical shifts indicating the restricted rotation around C-2'-C-3' bond. Selective p-toluene sulfonylation of 1 afforded the mono tosylated derivative 3, based on the reactivity of the C-3 hydroxyl group. Isopropylideneation of 1 with acetone in presence of sulfuric acid afforded the 1,3-

dioxalane derivative 4. The difference in the chemical shifts of the two methyl groups ( $Dd = 0.07$ ) agreed with El Ashry's shift rule for a terminal isopropylidene ring. The rest of the spectrum agreed with the assignment. Benzylidenation of 1 with benzaldehyde in presence of zinc Chloride as a catalyst gave a mixture of the cis and Trans isomers of 5 with ratio (1:1) as deduced from the  $^1H$  NMR spectrum. The other approach to the chemical modification of dyphylline (1) utilized the synthesis of theophylline-7- acetaldehyde (6); reduction with sodium borohydride afforded 7-(2-hydroxyethyl)theophylline (7), acetylation of which gave 8. Treatment of 6 with hydroxylamine hydrochloride, thiosemicarbazide and benzoylhydrazine afforded the oxime, thiosemicarbazone and benzoylhydrazone derivatives 9, 10 and 11, respectively. Treatment of compounds 10 and 11 with boiling acetic anhydride caused their cyclization and subsequent acetylation to form the acylated 1, 3,4-thiadiazoline and oxadiazoline derivatives 12 and 13, respectively. Treatment of 6 with two molar equivalents of dimedone followed by boiling with 1N hydrochloric acid gave the xanthene derivative.



**Fig.1.3** Theophylline changes of different group

	R	R1
1)	H	H
2)	Ac	Ac
3)	Ts	H
4)	Me	Me
6)	CHO	
7)	CH <sub>2</sub> OH	
8)	CH <sub>2</sub> OAc	
9)	CH=N-OH	
10)	CH=NNHCSNH <sub>2</sub>	
11)	CH=NNHCOPh	

List of different groups R, and R1 position

### 1.3.2: Riboside theophylline

Cytotoxic nucleoside analogues and nucleobases were among the first chemotherapeutic agents to be introduced for the medical treatment of cancer.[1] This family of compounds has grown to include a variety of

purine and pyrimidine nucleosides with activity both against solid tumours and against malignant disorders of the blood.[1,2] These agents behave as antimetabolites, compete with physiological nucleosides and interact with a large number of intracellular targets to induce cytotoxicity.[3] Progress has recently been made in the identification and characterization of nucleoside transporters and the enzymes that metabolise them, in the optimisation of intracellular nucleoside accumulation and in the improvement of cancer cell selectivity. All this has provided a deeper understanding of the molecular mechanisms of anticancer nucleoside activity and opened up new prospects for potentiation of their antitumor effects.[4] The search for new antiviral agents, particularly for the treatment of human immunodeficiency virus (HIV)[5] and, more recently, hepatitis B virus (HBV, especially as regards the chronic disease),[6] and of new adenosine A1, A2 and A3 receptor antagonists (ribose nucleosides),[7] has stimulated the study of thiopurine and thiopyrimidine derivatives of nucleosides, which are components of transfer ribonucleic acids.[8] Among these, 6-thiopurines and 6-thiopurine nucleosides exhibit significant antitumor activity.[9] In addition, a number of alkylxanthines, such as those substituted at position 8 in theophylline, have aroused interest as adenosine receptor antagonists. 1, 3-Dialkyl-7-ribosylxanthines, for example, have been found to be partial Such important applications, which are continuously increasing, and the need to develop new building blocks with a view to devising useful combinatorial methodologies have fostered the application of modern synthetic methods to the synthesis of nucleoside analogues[11] (carbocyclic nucleosides included[12]) for the development of simple, flexible, efficient procedures for their production. Recent advances in the synthesis of modified purine nucleosides include the use of reactions such as Suzuki coupling,[13] Stille coupling,[14] Pd-mediated arylaminations,[15] organocuprate cross coupling[ 16] and, recently, the use of 6-bromopurine nucleosides as intermediates in the synthesis.[17] It is therefore of interest to design and prepare novel theophylline nucleosides. In this paper we report the synthesis of a series of new theophylline- ribopyranosyl and -ribofuranosyl nucleosides, as well as the corresponding 6-thio derivatives, all of which are of special interest on account of the ribose moiety, as present in nature. In addition, we examined some interesting conformational aspects of their peracetyl derivatives with a view to gaining better insight into their structure-activity relationship.

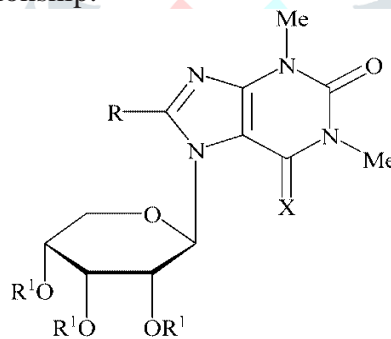


Fig-1.4- Ribosilexanthine derivative

	1	2	3	4	5	6	7	8
X	O	O	S	S	O	O	S	S
R	Me	Me	Me	Me	H	H	H	H
R <sup>1</sup>	H	Ac	H	Ac	H	Ac	H	Ac

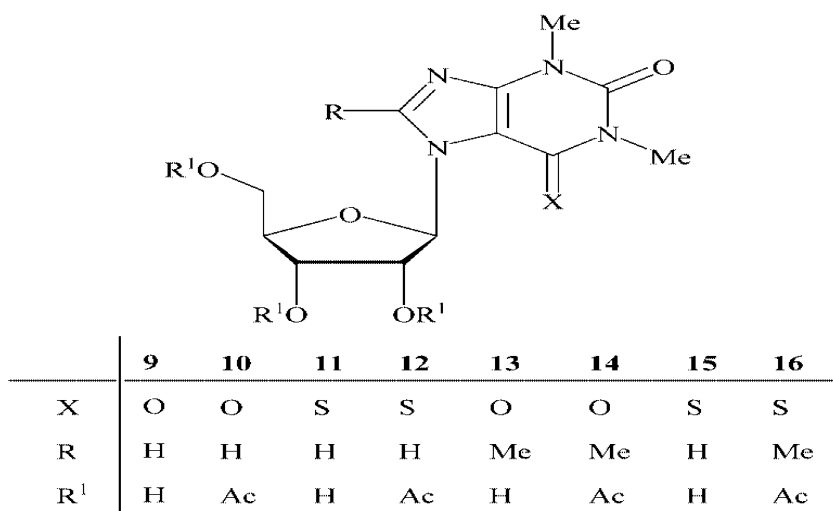
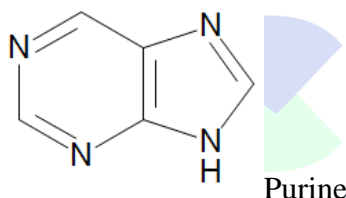


Fig-1.5- Ribosilexanthine derivative

### 1.3.3 About of Purine(7-Imidazol[4,5]pyrimidine)

Purine is a bicyclic compounds having structure. It is made of a five and a six-membered heterocyclic rings containing two nitrogen atoms. These are fused together along the carbon atoms 4 and 5.



The class of compounds such as uric acid, caffeine, Theobromine, Theophylline, and xanthenes witch could be regarded as a derivatives of purine, are designated as purine. At one time, uric acid and other purines were represented by rectangular formulas since they could be thought of as formed from two molecules of urea and a dicarboxylic acid (Diureides)

### 1.4:URIC ACID, 2,6,8-Purinetrione

This most important derivative of purine is, in fact, mixture of two tautomeric forms.

Uric acid is produced in humans by the degradation of proteins that constitute the tissue and muscles. Normally small amounts of uric acid (up to 0.3/100 ml) are present in blood. It is excreted in urine, about 0.7g/24 hours. Any excess of uric acid formed in blood is deposited in joints as crystals of monosodium urate, cussing gout, or kidney stone may form.

### 1.5:Theobrominene

Theobromine is prepared by the methyl urea and ethyl carboxamido acetate undergoes transesterification to yield a diamide which on treatment with alkali gives to a pyrimidone. The resulting product on reaction with nitrous acid followed by reduction gives a diamines witch on being treated with formic acid produces a purine and when subjected to monomethylation yields finally the theobromine

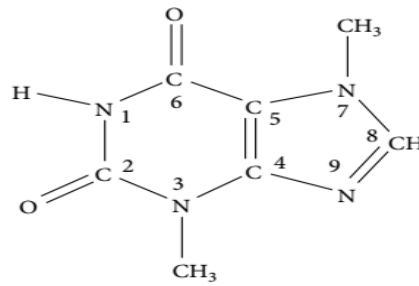


Fig.1.6 Theobromine

## 1.6: Theophylline

This compounds belong to the group of purine compounds they retained methyl groups in 1-and 3-position, various polar substitution were introduced in the 7-position in an attempt of making more water-soluble compounds, they reported to be generally less potent than theophylline, the introduction of small alkyl groups in the 8-position will not reduce the bronchodilator potency. Also, many 1, 3, 8-derivatives exhibit potent and interesting antiallergic properties. A common metabolic pathway with xanthine is oxidation in the 8-position to uric acids; 8-substituted xanthenes would therefore be predictably more stable compounds. The 1, 3, 7, 9-tetraalkyl derivatives are permanently more charged xanthenes that will not easily traverse lipid membranes.

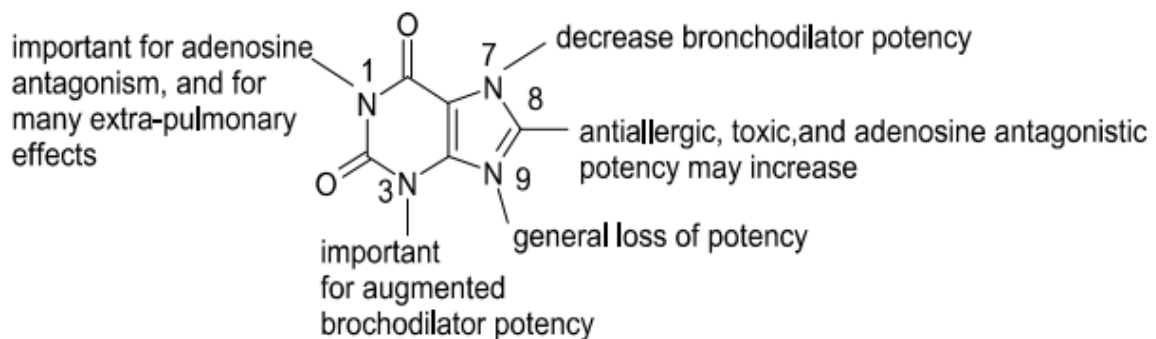


Fig.1.7 SAR of Theophylline

Useful finding and developments on the basis of their molecular features for xanthenes compounds (1) were reported to contribute in the development of new molecules.

Assessing the influence of methylation of the nitrogen at position 7 of several substituted theophylline (2), indicated that it depend on the receptor, in the case of A2B and A2A receptors a significant increase in affinity level was obtained, to show bronchodilator more effective than theophylline. 8-substituted theophylline-7-ribose (2h) was synthesized in an almost quantitative yield, and show low efficacy agonist or antagonist for the adenosine receptor.

	R1	R2	R3	R4
A	Ethyl	Benzyl	Theophen-2-ylmethyl	Methyl
B	Ethyl	Benzyl	Furfuryl	Methyl
C	Ethyl	Theophen-2-ylmethyl	Theophen-2-ylmethyl	Methyl
D	Ethyl	Theophen-2-ylmethyl	Furfuryl	Methyl
E	Ethyl	Theophen-2-ylmethyl	2,6-difluorobenzyl	Methyl
F	Methyl	Methyl	Bromo	Propylacitaaminophen
G	Methyl	Methyl	Imidazolyl	Propylacitaaminophen
H	Methyl	Methyl	Alkyl substitute	Ribosyl
I	Ethyl	Ethyl	Methyl	Styryl substitution



## 2. REVIEW OF LITERATURE

### Loay K. Abdulrahman-2012-

Theophylline a methyl xanthine compounds, is known as an efficient bronchodilator drug, having also anti-inflammatory and immunomodulatory effects. In order to improve its pharmacological profile and to reduce also the serious side effects that appear at high concentration, new 1, 3, 7, 8-tetrasubstituted theophylline derivatives have been synthesized. The new compounds are obtained

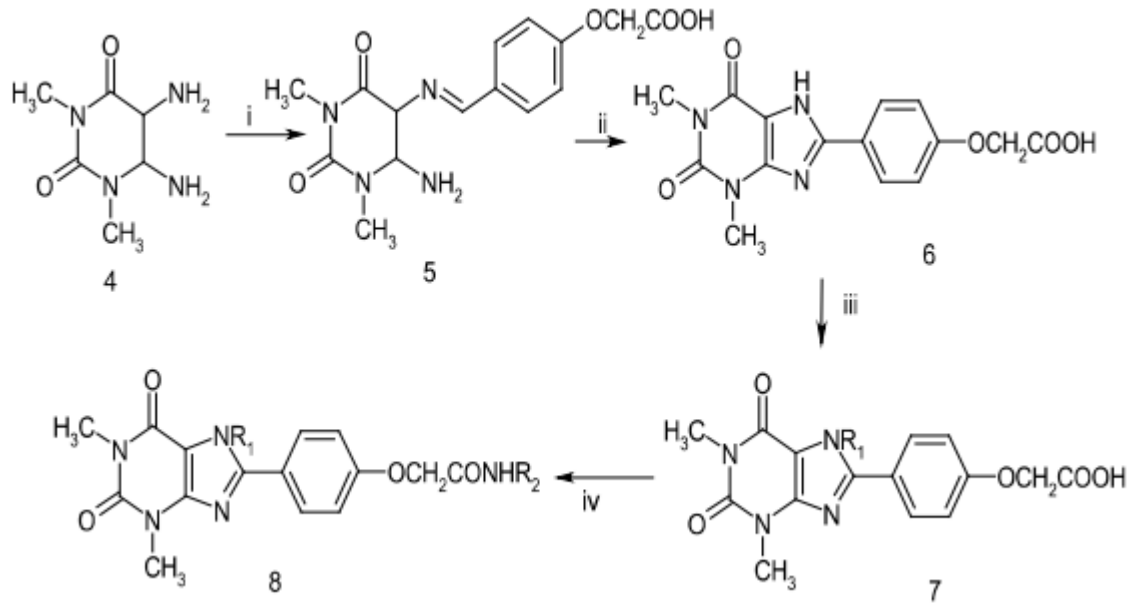


Fig 2.1 Structure of 1, 3, 7, 8-tetrasubstituted theophylline

### S. Gotsulia, P. S. Knyazevich, O. I. Panasenko, Ye. G. Knysh

To analyze the carbonyl derivatives of 7-((3-thio-4-R-4H-1,2,4-triazole-5-yl)methyl)theophylline their mother substance was synthesized and its interaction with  $\alpha$ -haloketones series was carried out.

2,4-Triazole derivatives are successfully used in medicine as antibacterial and antifungal agents. The combination of analeptic and diuretic effect of theophylline and triazole fragment may give unexpected results. Moreover, it is known that mesomeric effect manifestation, occurring in carbonyl group, shifts the electron density in the molecule. Therefore these derivatives spark the interest of scientific community. It is possible that carbonyl group contributes activity of transporting the agent through tissue. The manifestation of mesomeric effect in the carbonyl group provides great opportunity for the chemical molecule modification. In particular, ketones are featured by the reaction of reduction in  $H^+$ -ion excess and the reaction of hydrazinolysis thus creates a large amount of space for further research

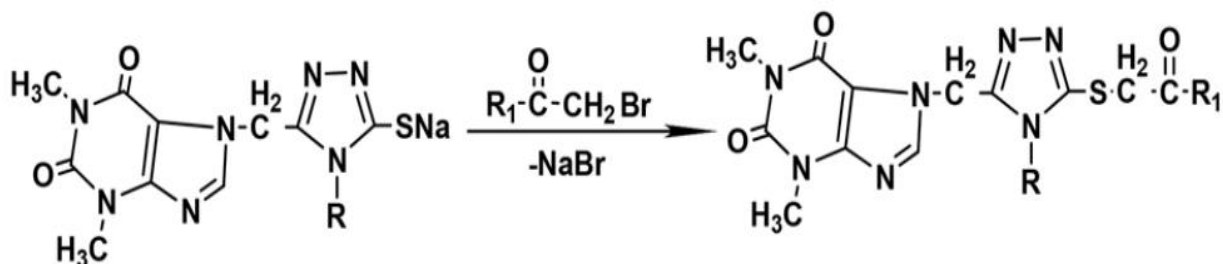


Fig.2.2- 1,2,4-triazoles, Theophylline

**LENUȚA PROFIRE<sup>1\*</sup>, VALERIU ȘUNEL<sup>4</sup>, DAN LUPAȘCU<sup>1</sup>, MIHAELA CRISTINA BAICAN<sup>2</sup>, NELA BIBIRE<sup>3</sup>, CORNELIA VASILE**

Theophylline, a methylxanthine compound, is known as an efficient bronchodilator drug, having also anti-inflammatory and immunomodulatory effects. In order to improve its pharmacological profile and to reduce also the serious side effects that appear at high concentrations, new theophylline derivatives have been synthesized. The new compounds are obtained in two steps by the reaction of 8-substituted-theophyllines with epoxy-propyl-acetaminophen. The chemical structure of the synthesized compounds has been elucidated by their <sup>1</sup>H-NMR spectra. The potential bronchodilator effects of the synthesized compounds have been also established.

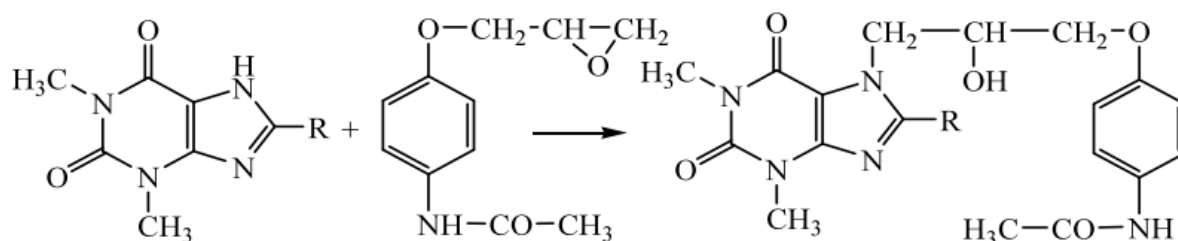


Figure: 2.3- The synthesis of new theophylline derivatives

**Heba A. Mohamed,<sup>a</sup> Benjamin R. M. Lake,<sup>a</sup> Thomas Laing,<sup>b</sup> Roger M. Phillips<sup>\*c</sup> and Charlotte**

**E. Willans,** A new library of silver(I)-N-heterocyclic carbene complexes prepared from the natural products caffeine, theophylline and theobromine is reported. The complexes have been fully characterised using a combination of NMR spectroscopy, mass spectrometry, elemental analysis and X-ray diffraction analysis. Furthermore, the hydrophobicity of the complexes has been measured. The silver(I)-N-heterocyclic carbenes have been evaluated for their antiproliferative properties against a range of cancer cell lines of different histological types, and compared to cisplatin. The data shows different profiles of response when compared to cisplatin in the same panel of cells, indicating a different mechanism of action. Furthermore, it appears that the steric effect of the ligand and the hydrophobicity of the complex both play a role in the chemosensitivity of these compounds, with greater steric bulk and greater hydrophilicity delivering higher cytotoxicity.

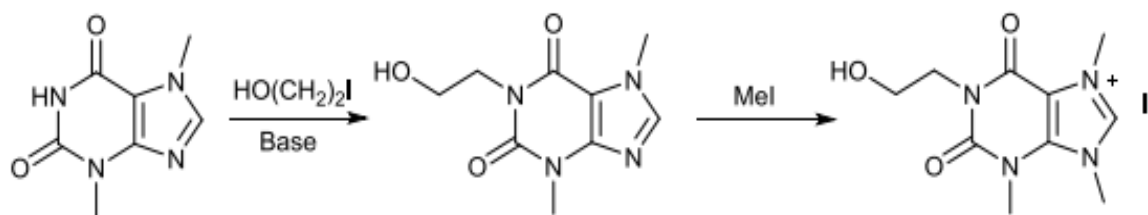


Figure: 2.4-Synthesis of imidazolium salts starting from theophylline theobromine

**Synthesis of some novel pyrazolo[3,4-*d*]pyrimidine derivatives as potential antimicrobial agents-**

A series of pyrazolo[3,4-*d*] pyrimidine nucleus containing 8-(trifluoromethyl)quinoline have been synthesized. The synthesis of this ring system has been accomplished from two pyrazole intermediates, 5-amino-1-[8-(trifluoromethyl)quinolin-4-yl]-1*H*-pyrazole-4-carboxylate and 5-amino-1-[8-(trifluoromethyl)quinolin-4-yl]-1*H*-pyrazole-4-carbonitrile. The antimicrobial activity study of the newly synthesized pyrazolo[3,4-*d*] pyrimidine ring system is discussed.

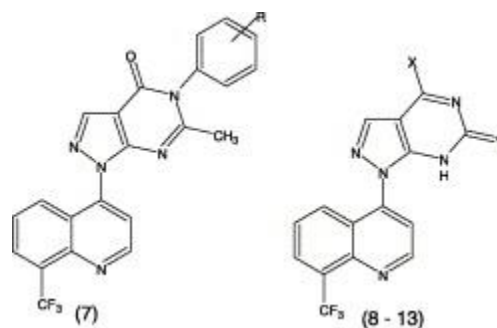


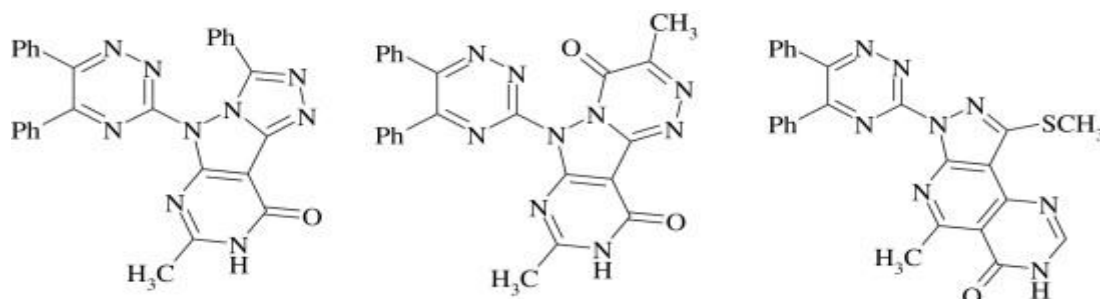
Figure: 2.5-Synthesis of 8-(trifluoromethyl)quinoline

The reaction of 4-hydrazino-8-(trifluoromethyl) quinoline (**2**) with ethoxymethylenecyanoacetate afforded ethyl 5-amino-1-[8-(trifluoromethyl)quinolin-4-yl]-1*H*-pyrazole-4-carboxylate (**3**) and that with ethoxymethylenemalononitrile afforded 5-amino-1-[8-(trifluoromethyl)quinolin-4-yl]-1*H*-pyrazole-4-carbonitrile (**5**). Compounds **3** and **5** were hydrolyzed to get 5-amino-1-[8-(trifluoromethyl)quinolin-4-yl]-1*H*-pyrazole-4-carboxylic acid and then reacted with acetic anhydride to afford 6-methyl-1-[8-(trifluoromethyl)quinolin-4-yl]pyrazolo[3,4-*d*]oxazin-4-one (**6**), which was condensed with different aromatic amines to give a series of 5-substituted 6-methyl-1-[8-(trifluoromethyl)quinolin-4-yl]-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-ones (**7**). Compounds **3** and **5** also reacted with formamide, urea, and thiourea affording the corresponding pyrazolo[3,4-*d*]pyrimidines (**8–13**), respectively. Structures of the products have been determined by chemical reactions and spectral studies. All compounds of the series have been screened for their antibacterial and antifungal activity studies. The results are summarized.

### **Tarik El-Sayed Ali- Synthesis of some novel pyrazolo[3,4-*b*]pyridine and pyrazolo[3,4-*d*]pyrimidine derivatives bearing 5,6-diphenyl-1,2,4-triazine moiety as potential antimicrobial agents.**

The reaction of 5,6-diphenyl-3-hydrazino-1,2,4-triazine (**1**) with bis(methylthio)methylene]malononitrile (**2**) afforded 5-amino-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-3-(methylthio)-1*H*-pyrazole-4-carbonitrile (**3**). Compound **3** reacted with thiourea to give 3,4-diaminopyrazolo[3,4-*d*]pyrimidine **5**, which was treated with benzoyl chloride to give pyrazolo[5,4,3-*kl*]pyrimido[4,3-*d*]pyrimidine **6**. Treatment of **3** with acetic anhydride produced 3-methylthio-pyrazolo[3,4-*d*]pyrimidine derivative **7**, which was allowed to react with hydrazine hydrate to give the corresponding hydrazino derivative **8**. Heterocyclization of **8** with benzoyl chloride and sodium pyruvate afforded the polyfused heterocycles **9** and **10**, respectively. Reaction of **3** with benzoylacetone yielded pyrazolo[3,4-*b*]pyridine **12**, which was allowed to react with malononitrile and acetanilide to get heterocyclic systems **13** and **14**, respectively. Interaction of **3** with cyanoacetone gave pyrazolo[3,4-*b*]pyridine **15**, which was refluxed in formic acid to yield pyrazolo[4',3':5,6]pyrido[4,3-*d*]pyrimidine **16**. Reaction of **3** with **2** afforded the triazinylpyrazole derivative **17**, which was reacted with hydrazine hydrate to give dipyrazolo[1,5-*a*:3',4'-*d*]pyrimidine **19**. Furthermore, treatment of the latter compound with methyl anthranilate furnished tetraheterocyclic compound **21**. Structures of the products have been determined by elemental analysis and spectral studies. All compounds have been screened for their antibacterial and antifungal activities. Compounds **9**, **10**, **13**, **19** and **21** showed maximum activity comparable to the standard drugs with lower toxicity in the case of **9** and **10**.

Novel pyrazolo[3,4-*b*]pyridine and pyrazolo[3,4-*d*]pyrimidine derivatives fused with nitrogen heterocycles and bearing 5,6-diphenyl-1,2,4-triazine moiety were synthesized and screened for their antimicrobial activity against bacterial and fungal strain. The results suggest that some of these compound to be potent antimicrobial agents with lower toxicity.

Figure: 2.6-Synthesis of pyrazolo[3,4-*b*]pyridine.

**Synthesis and biological evaluation of 3,6-diamino-1H-pyrazolo[3,4-b]pyridine derivatives as protein kinases inhibitors**-The synthesis and biological evaluation of a number of differently substituted 3,6-diamino-1H-pyrazolo[3,4-b]pyridine derivatives are reported. From the inhibition results on a selection of disease-relevant protein kinases [IC<sub>50</sub> (μM) DYRK1A = 11; CDK5 = 0.41; GSK-3 = 1.5] we have observed that 3,6-diamino-4-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (4) constitutes a potential new and simple lead compound in the search of drugs for the treatment of Alzheimer's disease.

**Synthesis of N-aryl-5-amino-4-cyanopyrazole derivatives as potent xanthine oxidase inhibitors**, Some pyrazolo[3,4-d]pyrimidines, structurally related with allopurinol, a well known xanthine oxidase inhibitor, clinically used in the therapy of gout, have also been reported as potent inhibitors of xanthine oxidase and the growth of several human tumor cell lines. Considering the potential interest of this family of compounds, the aim of the present study was to synthesis and provide a full chemical characterization of new N-aryl-5-amino-4-cyanopyrazole derivatives and their corresponding pyrazolo[3,4-d]pyrimidines. Their biological activity pertaining to the xanthine oxidase inhibition and effect on the growth of three tumor cell lines (MCF-7, NCI-H460, and SF-268) are also provided. With only one exception, the synthesized compounds showed no effect on the growth of the three tumors cell lines. However, a strong xanthine oxidase inhibitory activity was observed for almost all pyrazolo[3,4-d]pyrimidines tested, revealing some of them IC<sub>50</sub> values below 1 μM. The results of the molecular docking studies of these compounds, against xanthine oxidoreductase are also described, providing an atomistic explanation of the differences in the inhibitory efficiency. MEP calculations were used to explain different inhibitory efficiency of similar inhibitors.

**Nobuhiko Yui**, Synthesis of theophylline–polyrotaxane conjugates and their drug release via supramolecular dissociation Theophylline–polyrotaxane conjugates were synthesized by coupling theophylline with α-cyclodextrins (α-CDs) in the polyrotaxane. The polyrotaxane is a molecular assembly in which many α-CDs are threaded onto a poly(ethylene glycol) (PEG) chain capped with l-phenylalanine (l-Phe). Theophylline-7-acetic acid was activated by coupling with 4-nitrophenol, and then ethylenediamine was allowed to react with the active ester in order to obtain N-aminoethyl-theophylline-7-acetoamide. This derivative was coupled with a 4-nitrophenyl chloroformate-activated polyrotaxane to obtain the theophylline–polyrotaxane conjugates. The conjugates formed a specific association under physiological conditions, depending upon interactions between the theophylline molecules and/or the terminal l-Phe moiety in the conjugates. In vitro degradation of the conjugates revealed that theophylline-immobilized α-CDs were completely released by hydrolysis of the terminal peptide linkage in the polyrotaxane. This result indicates that the association of the conjugates does not induce the steric hindrance but rather enhances the accessibility of enzymes to the terminal peptide linkages. It is suggested that our designed drug–polyrotaxane conjugates can release the drugs via the dissociation of the supramolecular structure without steric hindrance of enzymatic accessibility to the terminal peptide linkages.

**Design and synthesis of N-benzylpiperidine–purine derivatives as new dual inhibitors of acetyl- and butyryl cholinesterase**-The synthesis and biological evaluation of N-benzyl-(piperidin or pyrrolidin)-purines are described. Compounds derived from N-benzylpiperidine and N-substituted purines showed moderate acetylcholinesterase inhibition. Preliminary structure–activity relationships and a superimposition of the best compound with the active conformation of donepezil have revealed structural features that have been used in the design of more potent N-benzylpiperidine inhibitors bearing an 8-substituted caffeine fragment and a methoxymethyl linker. These new compounds are interesting dual inhibitors of acetylcholinesterase and butyryl cholinesterase and have been chosen for further optimization.

**Jana Klimentová, Jakub Novotný-Synthesis and Enhancing Effect of Transkarbam 12 on the Transdermal Delivery of Theophylline, Clotrimazole, Flobufen, and Griseofulvin**, Dodecyl-6-aminohexanoate (DDEAC) is a transdermal permeation enhancer with excellent activity, low toxicity, and no dermal irritation. We hypothesized that DDEAC reacts with air CO<sub>2</sub> to form a two-chain ammonium carbamate—Transkarbam 12 (T12)—which is responsible for the enhancing effect. DDEAC and T12 were synthesized, their structures were confirmed by spectral methods, and their enhancing activity was studied using the Franz diffusion cell and human skin. A high-performance liquid chromatography method was developed for determination of T12, and its biodegradability was evaluated using porcine esterase.

**Fatimah A. Agili,** To prepare the target nucleosides, the branched chain sugars was converted to their active form (1-bromosugar derivatives). This conversion included the hydrolysis of bromination with hydrobromic acid (HBr) in glacial acetic acid, forming 1-bromo sugars (4,6-di-O-Acetyl-2,3-dideoxy-3,3-di-C-nitro methyl-Darabino-hexopyranosyl-bromide), which were subjected to condensation with theophyllinemercury salt to give acetylated nucleosides (7-(4',6'-di-O-Acetyl-2',3'-dideoxy-3',3'-di-C-nitromethyl-D-arabino-hexo- pyranosyl) theophylline). Deblocking of these nucleosides with sodium methoxide in methanol afforded our target the free nucleoside analogues type of 7-(2',3'-Dideoxy-3',3'-di-C-nitromethyl-D-arabino-hexopyranosyl) theophylline (V). In a similar manner Bis (Indole-1-yl) mercury were condensed with 1-bromo sugar derivatives mentioned above to give acetylated nucleoside analogues 1-(4',6'-di-O-Acetyl-2',3'-dideoxy-3',3'-di-C-nitromethyl-Darabino-hexo pyranosyl) indole, (VI) which upon hydrolysis afforded the target free nucleoside analogues as 1-(2',3'-Dideoxy-3',3'-di-C-nitromethyl-D-arabino-hexo pyranosyl)

**Lee D. W. ET all 24 August 2006 -Chitosan,-**A polymer derived from chitin, has been used for nasal drug delivery because of its biocompatibility, biodegradability and bioadhesiveness. Theophylline is a drug that reduces the inflammatory effects of allergic asthma but is difficult to administer at an appropriate dosage without causing adverse side effects. It was hypothesized that adsorption of theophylline to chitosan nanoparticles modified by the addition of thiol groups would improve theophylline absorption by the bronchial epithelium and enhance its anti-inflammatory effects. Theophylline alone exerts a moderate anti-inflammatory effect, as evidenced by the decrease in eosinophils in BAL fluid, the reduction of bronchial damage, inhibition of mucus hypersecretion and increased apoptosis of lung cells. The effects of theophylline were significantly enhanced when the drug was delivered by TCNs

**Alaa M. Hayallah, 2 Suzan A. Ispier and 2Amira-** Chronic airway inflammation plays a key role in asthma. This fundamental feature has been included in the most recent definitions of the disease. 8-substituted bronchodi especially theophylline derivatives are well known as potent bronchodilators for the relief of acute asthma and play pronounced role in inflammation process. The present work involves the design and synthesis of new 8-substituted theophylline derivatives. The chemical structures of these compounds were elucidated by IR, elemental analyses, and FAB-MS spectral data. The bronchodilator activity was evaluated using acetylcholine induced bronchospasm in guinea pigs, and most of the compounds showed significant anti-bronchoconstrictive activity in comparison with aminophylline as a standard. Also, anti-inflammatory activity of the target compounds was investigated using indomethacin as a reference drug. Results showed that some of the tested compounds have good anti-inflammatory activity. A pharmacophore model was computed to get useful insight on the essential structural features of bronchodilator activity.

**El Sayed H. El Ashry ET, al, 2001, 0440–0450-** Xanthine derivatives have attracted considerable attention due to their numerous biological activities. Although theophylline (I) and ephyllin II have diuretic effects, dyphylline (1) has no effect in spite of being a water soluble analogue of I. On the other hand, dyphylline (1) is much more effective than ephyllin (II) in the treatment of bronchial asthma. Moreover, continuing our efforts to explore new types of acyclo- nucleoside have been encouraged by the finding that acyclo nucleoside analogues possess potent selective antiherpes activity 11-20 and the S-enantiomer of 9-(2,3-dihydroxypropyl)adenine has inhibitory activity towards a number of DNA and RNA viruses. 21,22 a In the present work, two different approaches have been utilized by the derivatization of the glycerolyl residue of dyphylline as esters and acetals which may act as prodrugs as well as by the utilization of its periodate oxidation product to build different types of heterocyclic compounds of possible therapeutic value. Acetylation of dyphylline (1) with acetic anhydride in pyridine afforded the di-O-acetyl derivative 2 whose spectra agree with the assigned structure. The terminal methylene group appeared in the  $^1\text{H}$  and Hanna A. Rasheed Chemistry Department, Faculty of Science, Alexandria University, Alexandria, Egypt  $^1\text{H}$  NMR spectrum as two doublets of doublets with a sufficient difference in their chemical shifts indicating the restricted rotation around C-2'- C-3' bond. Selective p-toluene sulfonylation of 1 afforded the mono tosylated derivative 3, based on the reactivity of the C-3 hydroxyl group. Isopropylideneation of 1 with acetone in presence of sulfuric acid afforded the 1,3-dioxalane derivative 4. The difference in the chemical shifts of the two methyl groups ( $\Delta\delta = 0.07$ ) agreed with El Ashry's shift rule for a terminal isopropylidene ring. The rest of the spectrum agreed with the assignment. Benzylideneation of 1 with benzaldehyde in presence of zinc trum. The other approach to the chemical modification of dyphylline (1) utilized the synthesis of theophylline-7acetaldehyde (6); reduction with sodium borohydride afforded 7-(2-hydroxyethyl)theophylline (7), acetylation of which gave

Treatment of 6 with hydroxylamine hydrochloride, thiosemicarbazide and benzoylhydrazine afforded the oxime, thiosemicarbazone and benzoylhydrazone derivatives 9, 10 and 11, respectively. Treatment of compounds 10 and 11 with boiling acetic anhydride caused their cyclization and subsequent acetylation to form the acylated 1,3,4-thiadiazoline and oxadiazoline derivatives 12 and 13, respectively. Treatment of 6 with two molar equivalents of dimedone followed by boiling with 1N hydrochloric acid gave the xanthene derivative 15

### 3. OBJECTIVE

Drug is any substance or product that is used or is intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient. The development of a novel drug from natural sources might follow the following pattern.

- Screening of Synthesized Compounds for biological activity.
- Isolation and purification of the active principle.
- Determination of structure.
- Structure-activity relationships (SARs).
- Synthesis of analogues.
- Receptor theories.
- Design and synthesis of novel drug structures.

Thus the present investigation in titled “STRUCTURAL MODIFICATION AND STUDY OF PHARMACOLOGICAL ACTIVITY OF THEOPHYLLINE” was planned with following objectives.

- To establish the method of synthesis for the proposed compounds.
- To elucidate the structure of synthesized compounds by FT-IR, <sup>1</sup>H NMR, and Mass, Spectroscopy.
- To evaluate biological activity of synthesized derivatives.  
-Antitussive, activity

### 4. PLAN OF WORK

The plan of work is broadly classified under two main categories.

#### 4.1: Synthesis and characterization

##### Chemical Synthesis

- Synthesis of theophylline

##### Characterization of synthesized compounds

- Solubility
- Mass analysis
- <sup>1</sup>H NMR analysis
- IR analysis

## 4.2: Biological activity evaluation

The synthesized compounds were evaluated for the following activity.

- Antitussive and bronchodilator activity

## 5. METHODOLOGY

### • 5.1 EXPERIMENTAL PROCEDURE

- In the present dissertation, the 7-(undec-10-ene)theophylline and 8-(7-chloroquinoline)theophylline derivatives have been synthesized by using theophylline and 11-Bromoundec-1-ene and 4,7-Dichloroquinoline as the precursor compounds. The synthesis consists of following steps:

#### • A-Synthesis of the 7-(undec-10-ene)theophylline

- A solution of theophylline (1.80g, 10mmol), Triethylamine (1.4mL, 10mmol) in dry  $\text{CH}_2\text{Cl}_2$  (20mL) was stirred under argon atmosphere at  $20^\circ\text{C}$  for 20 min. Then 11-Bromoundec-1-ene (2.4mL, 11mmol) was added drop wise. The mixture was refluxed for 4 hours. After this period, dichloromethane (40mL) was added, and the solution was washed successively with 1M HCl (5mL), saturated  $\text{NaHCO}_3$  (5mL) and water (3\*5mL). Then the solution was dried over  $\text{MgSO}_4$ , filtered and the solvent eliminated in vacuum. The crude residue was separated by Colum chromatography eluting with cyclohexane/Dichloromethane 6:4 and then Dichloromethane/Methanol 9.5:0.5 to obtain white solid

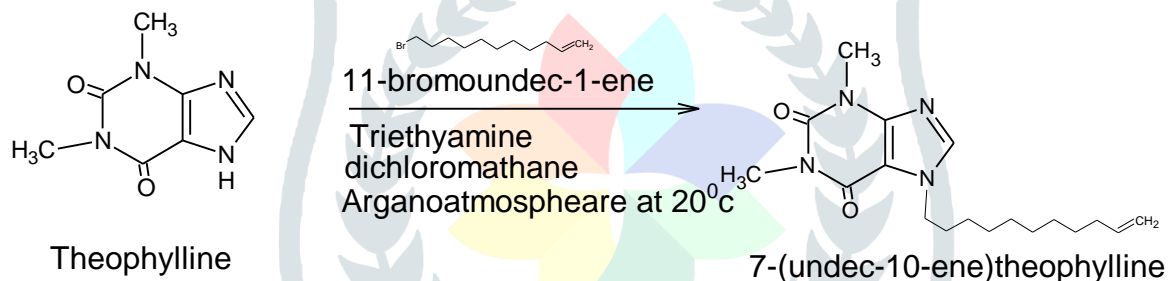


Figure-5.1.A. Synthesis of 7-(undec-10-ene)Theophylline

#### • B--Synthesis of the 8-(7-Chloroquinoline)-7-(undec-10-ene)theophylline

- A solution of 7-(undec-10-ene)theophylline (2.7g, 3 equivalent mmol) in Methanol 20mL was stirred  $20^\circ\text{C}$  until a clear solution was obtained. 1g 4,7-Dichloroquinoline (equivalent 1mol) were then slowly added to the solution. The latter was refluxed for 26 hours and cooled to room temperature. The resulting suspension was filtered and the solvent removed under reduced pressure. The oil is obtained was washed with water (40ml) until solid precipitate occurred. The precipitate was filtered and was with with water to obtained crystalline 8-(7-Chloroquinoline)-7-(undec-10-ene)theophylline.

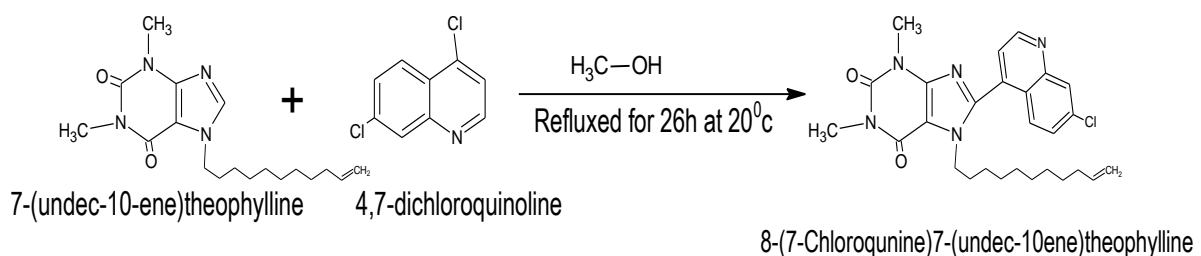


Figure-5.1.B. Synthesis of 8-(7-Chloroquinoline)-7-(undec-10-ene)Theophylline

#### • C- Synthesis of 7-(7-Chloroquinoline)theophylline

- An anhydrous solution of Theophylline 14.8g (3mol) in Methanol 80ml was stirred until a clear solution was obtained. Then adding drop wise Triethyleamine 15ml. Then 4,7-Dichloroquinoline were slowly added to

the solution. The latter was refluxed for 38 hours and cooled to room temperature. The resulting suspension was filtered and the solvent removed under reduced pressure. The oil obtained was washed with water (240ml) until solid precipitate occurred. The precipitate was filtered and washed with water to obtaining 7-(7-Chloroquinoline)theophylline.

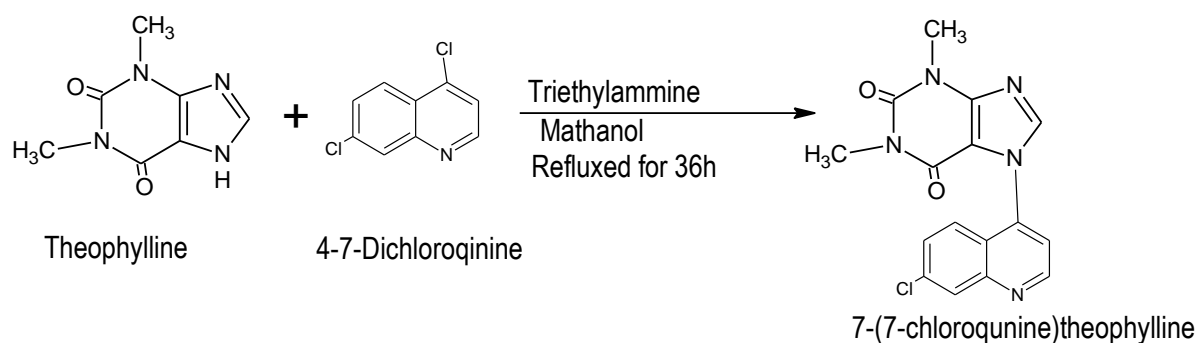


Figure-5.1.C. Synthesis of 7-(7-Chloroquinoline)Theophylline

## • 5.2: CHARACTERIZATION OF SYNTHESIZED COMPOUNDS

### • 5.2.1: Solubility studies

Compound A and C dissolve in Methanol. Compound A, B and C are completely dissolved in DMS solution. Compound B are completely soluble in 0.1M NaOH, solution. The observation and recorded on the basis of following ranges, 0.1M HCl solution drug are soluble.

### • 5.2.2: Melting Points

- Compound-A, 52-54 °C;
- Compound-B, 58-62 °C;
- Compound-C, 44-47 °C;

## 6. Pharmacological Activity

### • 6.1- Pharmacological Activity evaluation

Theophylline is a widely used bronchodilator with antitussive narrow therapeutic index and undergoes extensive metabolism by CYP1A2, and this drug are diuretic action show. The purpose of this study was to investigate the effect of theophylline derivatives on the pharmacokinetics of theophylline in swish albino mice. Theophylline is a widely used bronchodilator and diuretics characterized by a narrow therapeutic index with high inter individual variation in plasma concentration 1, 2 hours. Plasma concentrations below 10µg/ml may be associated with inadequate therapy while those above 20µg/ml potentially cause a variety of serious side effects in humans<sup>3</sup>. Theophylline is thought to be primarily oxidized by two isozymes CYP1A2 and CYP2E1 of the hepatic microsomal mono-oxygenase system via N-demethylation and 8-hydroxylation pathways, respectively

### • 6.2-Materials

Theophylline, saline, Methanol, ammonium hydroxide, sodium hydrogen sulfate, sulfuric acid, and ammonium chloride, sodium bicarbonate, were used in the antitussive study. Where purchased from Sigma Chemical Co., St Louis. Theophylline derivative was further purified by Silica gel column chromatography.

### • 6.3-Evaluation of Antitussive Activity

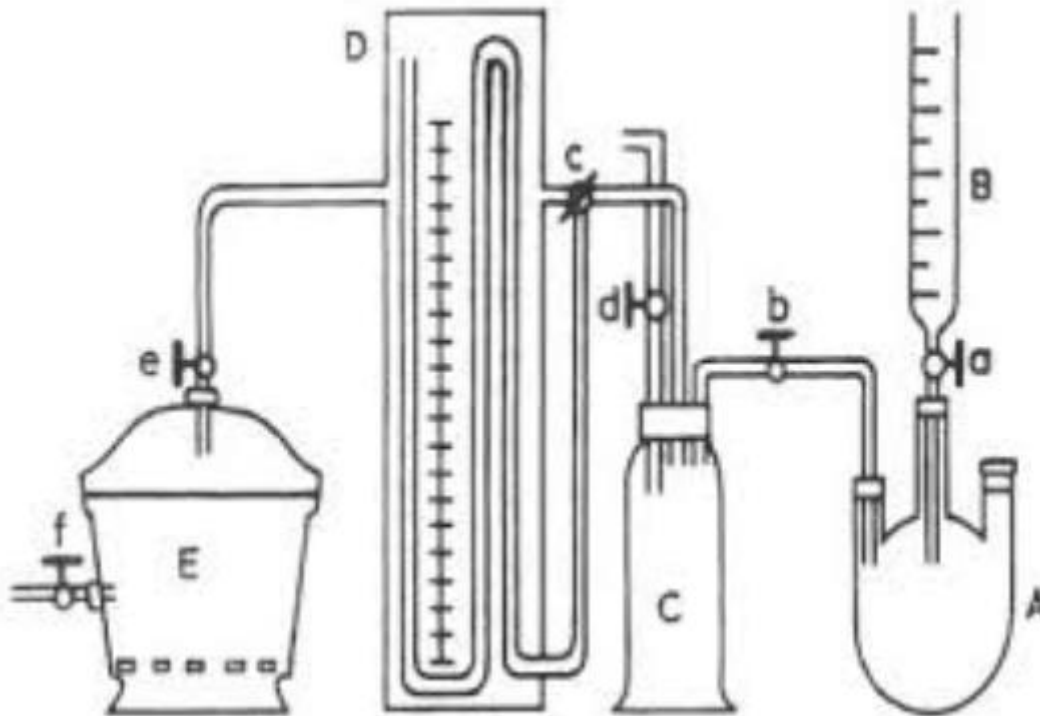
The experiments were carried out in Albino mice of either sex weighing between 20–30 g obtained from animal house of k.n.i.m.t college of Pharmacy sultanpur (u.p) were kept in the animal house at 26±2oC in polyacrylic cages with not more than six animals per cage and maintained under standard laboratory conditions with Standard food and water *ad libitum*. The animals were used for the experiment after an acclimatization period of one week before experimental sessions. Animals were divided into six groups, containing 6 mice each.



The animal experiment was performed according to the college's ethical committee approval. The control group was treated with saline solution orally, and the positive control was treated with theophylline. The remaining groups were treated with the *Theophylline derivative* at doses of 60 and 80 mg/Kg body weight

#### • 6.4-Sulfur Dioxide Gas Induced Cough Reflex in Mice

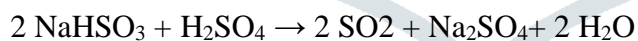
The experimental model is shown in Figure 1 where A is a 500 ml three-necked flask which contains aqueous saturated sodium hydrogen sulphite solution. By opening the stop-cock of a burette (B), the concentrated sulphuric acid was introduced to generate sulphurdioxide gas.



**Figure 6.1-** Apparatus used in sulfur dioxide gas induced cough model

**A:** Saturated NaHSO<sub>3</sub> solution in 500ml flask, **B:** Conc. H<sub>2</sub>SO<sub>4</sub> in burette, **C:** Gas Cylinder, **D:** Water manometer, **E:** Desiccators and a, b, c, d, e, f are stop cocks

- The chemical reaction which occurred in flask, 'A' is as follows:



Flask A and gas cylinder C were filled with sulphur dioxide (SO<sub>2</sub>) gas. Cocks c and b were opened to elevate pressure in gas cylinder C, which was recorded by water manometer D. Stop-cock b was then closed and stop-cock d was opened slightly until pressure in D (11 mm, i.d.) reached 75 mm H<sub>2</sub>O, when stop-cock d was closed. The procedures were conducted in a draught. Cough response of all the groups are observed (0 minute) by placing the animals in desiccators E. The cocks c, f and e are opened in order and when the pressure in D became 0 mm of H<sub>2</sub>O, all the cocks are closed immediately. A certain amount, 5ml sulfur dioxide gas is induced into the desiccators and this way. After a minute of introducing the gas, the animal is taken out of the desiccator and frequency of cough is observed for five minutes in an un-ended filter funnel with a stethoscope at the tip in which mice is confined. In the same fashion the frequency of cough are observed for all the animal groups after every 30 minutes.

#### • 6.5-Statistical Analysis

- The results of pharmacological studies were reported as Mean ± S.E.M. The total variations present in data were analyzed by using one way analysis of variance (ANOVA) followed by Dunnett's Test

### • 6.5.1-Result and Discussion

• 7-(undec-10-ene)-8-(7-Chloroquinoline)theophylline derivative in two doses, High dose showed good dose dependent antitussive activity (Table 1). High dose (80 mg/kg) exhibited significant activity i.e. 46.362%, but lower dose of it showed less activity i.e. 36.251% inhibition in Sulfur dioxide gas induced cough.

#### • Selection of Animal and grouping

#### • Selection of Animal Control Group

Marking	Body weight	Dosing of drug (ml)	Drug (mg)	Bouts of cough
H	26.60	0.2	No drug	80
N	26.25	0.2	No drug	87
LF	27.10	0.2	No drug	78
RF	28.10	0.2	No drug	84
T	26.90	0.2	No drug	89
U	25.85	0.2	No drug	73

(Symbol: H- Head, N- Neck, LF- Left foot, RF- Right foot, T- Tail, U-Un-Mark)

#### • Selection of Animal Standards Group

Marking	Body weight	Dosing of drug (ml)	Drug (mg)	Bouts of cough
H	25.70	0.16	1.54	48
N	24.50	0.15	1.44	44
LF	24.90	0.15	1.49	51
RF	26.85	0.17	1.62	55
T	27.55	0.17	1.66	49
U	28.15	0.18	1.69	53

(Symbol: H- Head, N- Neck, LF- Left foot, RF- Right foot, T- Tail, U-Un-Mark )

#### • Selection of Animal Test Group Low dose

Marking	Body weight	Dosing of drug (ml)	Drug conc. (mg)	Bouts of cough
H	28.20	0.17	1.70	46
N	25.40	0.15	1.53	53
LF	25.70	0.15	1.55	41
RF	25.00	0.15	1.5	58
T	26.65	0.17	1.60	49
U	27.15	0.17	1.63	55

• Symbol: H- Head, N- Neck, LF- Left foot, RF- Right foot, T- Tail, U- Un-Mark

#### • Selection of Animal Test Group High dose

Marking	Body weight	Dosing of drug (ml)	Drug conc. (mg)	Bouts of cough
H	25.10	0.14	2.00	31
N	25.10	0.14	2.00	38
LF	28.60	0.16	2.29	29
RF	26.20	0.14	2.10	39
T	27.60	0.16	2.21	33

U	26.25	0.14	2.10	35
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(Symbol: H- Head, N- Neck, LF- Left foot, RF- Right foot, T- Tail, U- Un-Mark)

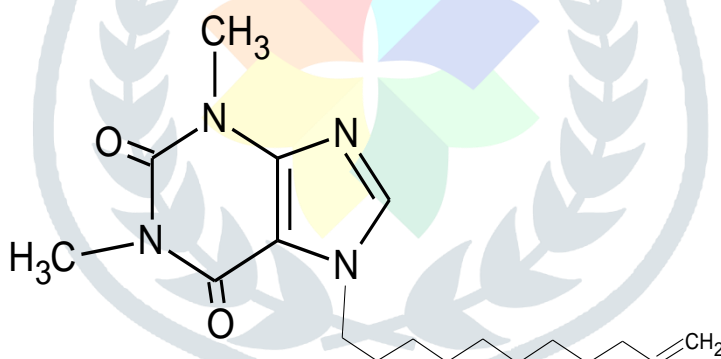
**Table1.6.1- Effect of 7-(undec-10-ene)-8-(7-Chloroquinoline)theophylline on cough frequency in sulfur dioxide gas induced cough mice**

Treatment	Dose(mg/kg)	Number of cough	Percentage of inhibition
Control	.....	81.83±6-7	.....
Theo.7-undec10	60	50.00 ± 6-7	35.495
Theo.4-Chloro	80	34.17 ±6-7	46.362
Theophylline	60	52.33 ± 6-7	36.251

Values expressed as mean±SEM (n=6). \*P<0.05, \*\*P<0.01, and \*\*\*P<0.001 for comparison of treated groups with control

## 7. RESULT

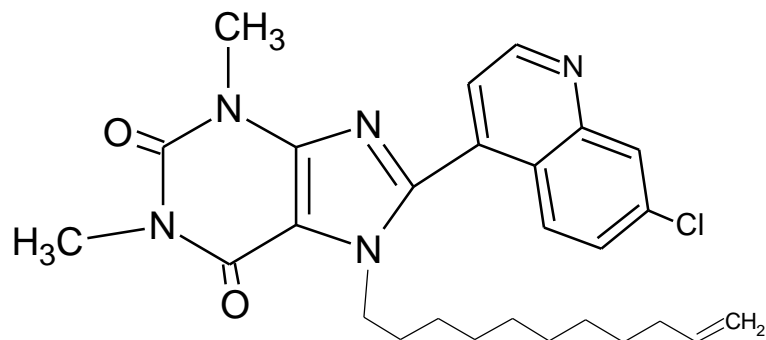
- 7.1: Experimental Analysis
- Compound A



**Fig 7.1:** 7-(undec-1-enyl)Theophylline

- Molecular formula: C<sub>18</sub>H<sub>22</sub>N<sub>4</sub>O<sub>2</sub>
- Molecular Weight: 332.45
- Solubility: 0.1M Sodium Hydroxide Solution
- Percentage of yield: 20%

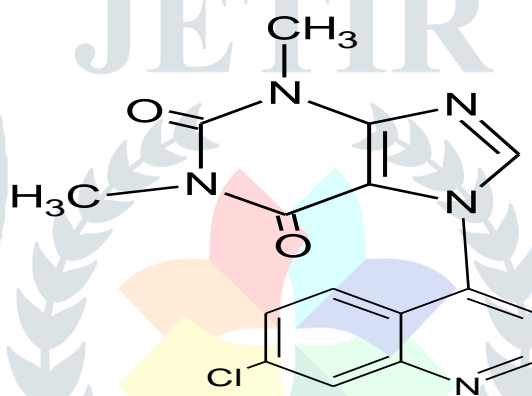
- **Compound B**



**Fig 7.2:** 7-(undec-1-enyl)-8-(7-Chloroquinoline)Theophylline

- Molecular formula:  $C_{27}H_{32}Cl_1N_5O_2$
- Molecular Weight: 494.02
- Solubility: 0.1M Sodium Hydroxide Solution
- Percentage of yield: 36.25%

- **Compound C**



**Fig 7.3:** 7-(7-Chloroquinoline)Theophylline

- Molecular formula:  $C_{16}H_{12}Cl_1N_5O_2$
- Molecular Weight: 341.751
- Solubility: 0.1M Sodium Hydroxide Solution
- Percentage of yield: 26.37%

- **7.2: Spectral Analysis**

- **Ultraviolet Spectroscopy (UV)**

- Ultraviolet spectroscopy were recorded on UV-Vis Analyst\bin\macroeasy.uva.analyst

- **Infrared Spectroscopy (IR)**

- Infrared (IR) spectra were recorded on SHIMADZU PERKIN EKMER 8201 PC IR SPECTROMETER.

- **<sup>1</sup>HNMR Spectroscopy:**

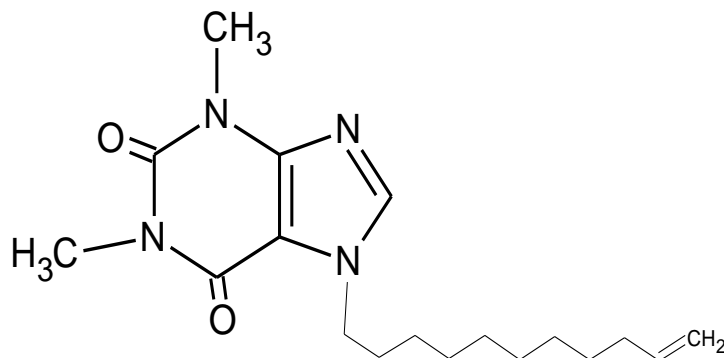
- <sup>1</sup>HNMR spectra were recorded on BRUKER AVANCE II 400 NMR SPECTROMETER.

- **Mass Spectroscopy:**

- Mass spectra were recorded on JEOL SX-102/DA-6000 Mass SPECTROMETER

- **Spectral features for compounds A**

- Molecular Weight: 332.45



- **UV  $\lambda_{max}$**

- The  $\lambda_{max}$  at 295nm recorded.

- **IR in  $cm^{-1}$**

- Peak at 3116 corresponds to C-H m.

Peak at 2975 corresponds to Ar.CH m-s.

Peak at 1706 corresponds to  $>C=O$  stretching.

Peak at 1575 corresponds to C=C vending.

Peak at 1310 corresponds to C-N< vending.

Peak at 690 corresponds to C-C stretching

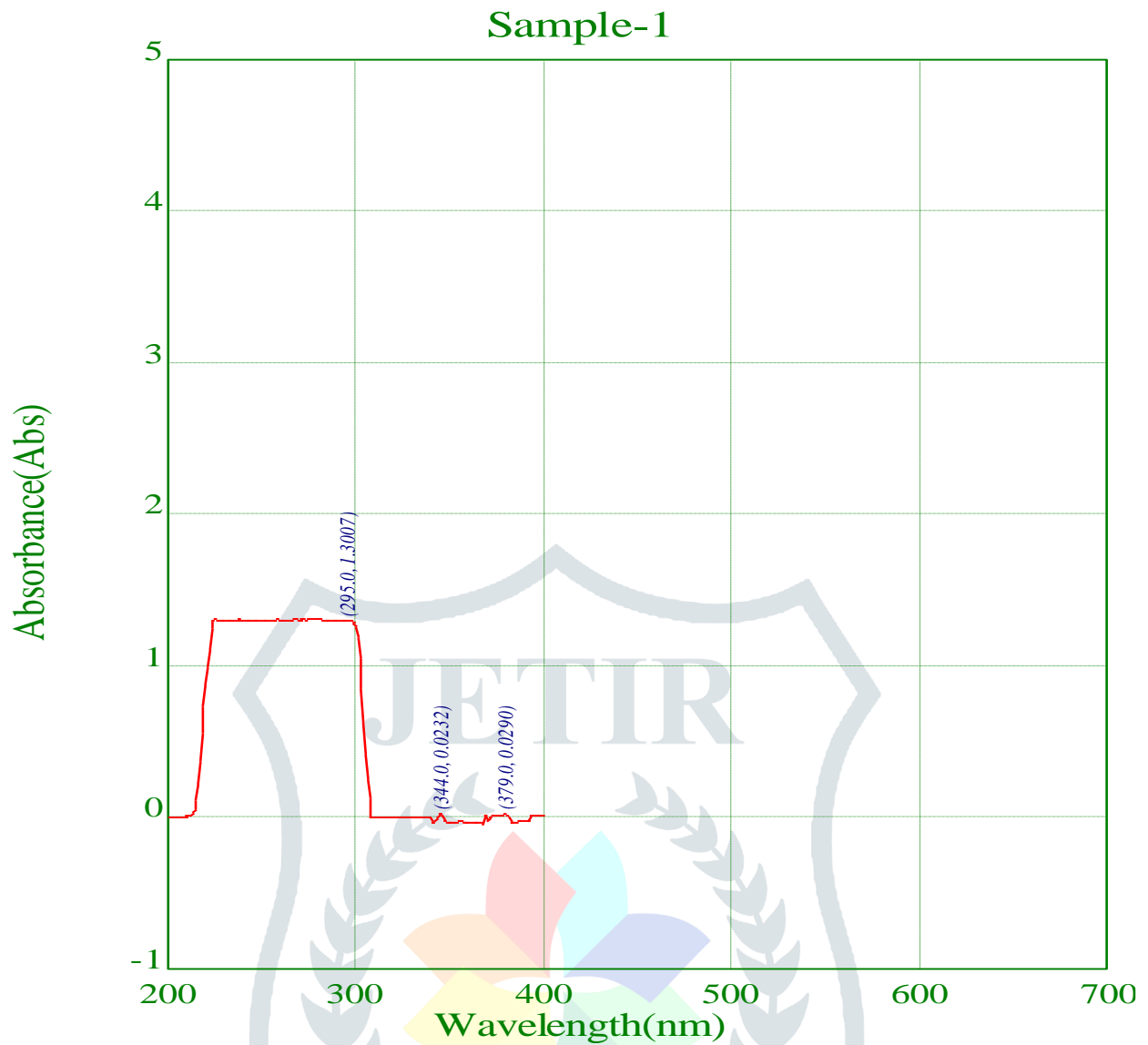
- **Mass: in m/z**

Further evidence of the structure of the compound was obtained by recording mass spectra of the sample. The mass spectrum revealed.

The molecular ion peak was observed at m/z 333

- **$^1H$  NMR ( $\delta$ ) in PPM**

- 6.47-8.10 (9H, m, Ar.), 5.86 (1H, s, NH), 4.19-4.29 (3H, m, CH<sub>3</sub>), 4.08 (1H, C=O, NH), 1.19-1.29 (2H, m, CH<sub>2</sub>)

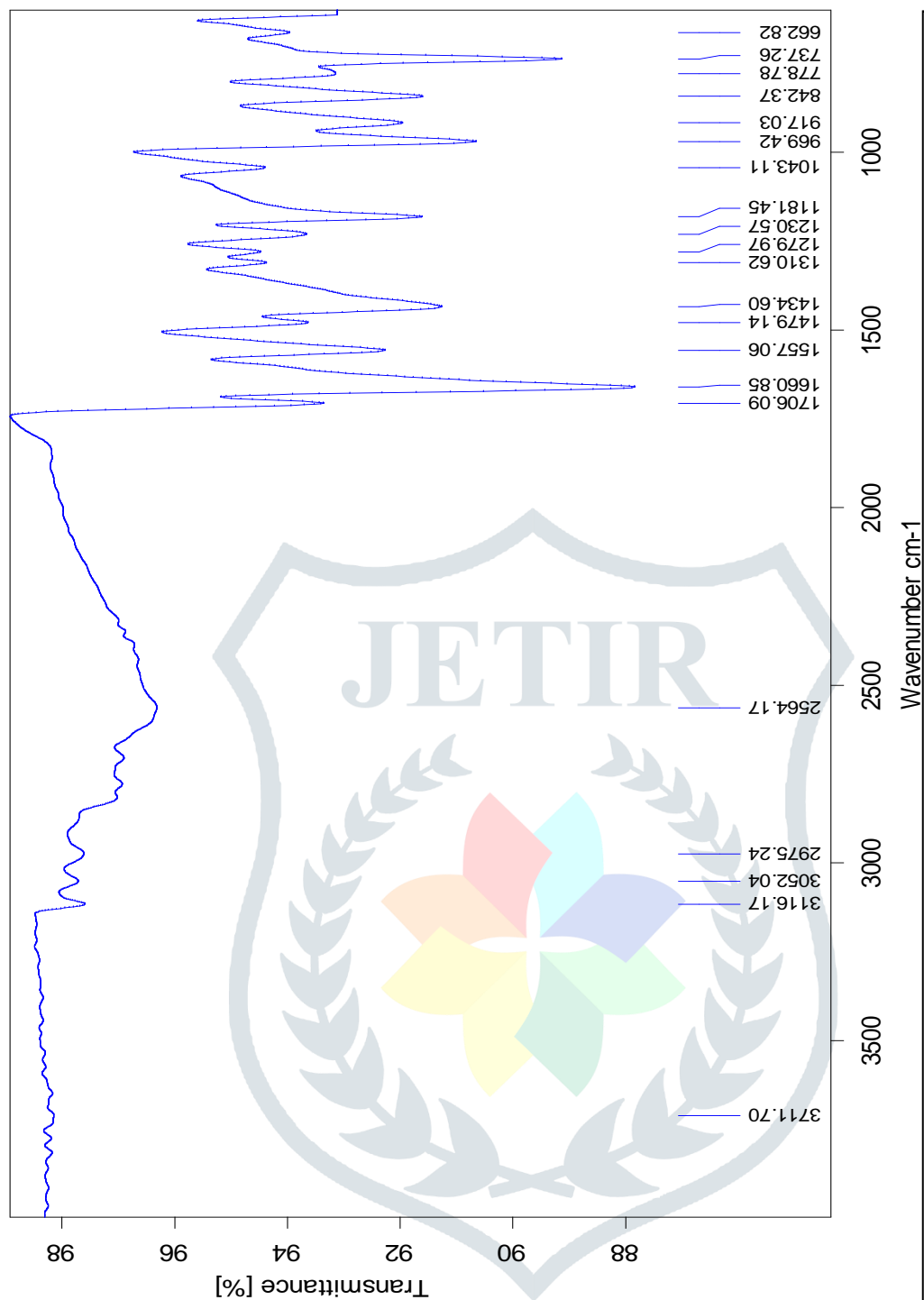


**Figure-7.4: 7-(UNDEC-1-ENYL)THEOPHYLLINE  $\lambda$  max**

KNIMT/PC/THEOPHYLLINE/15-16/01

M.PHARM/PHARMACEUTICAL CHEMISTRY

28/09/2016



**Figure-7.5:- FTIR- 7-(UNDEC-1-ENYL)THEOPHYLLINE**  
 M.PHARM/PHARMACEUTICAL CHEMISTRY 28/09/2016  
 KNIMT/PC/THEOPHYLLINE/15-16/001

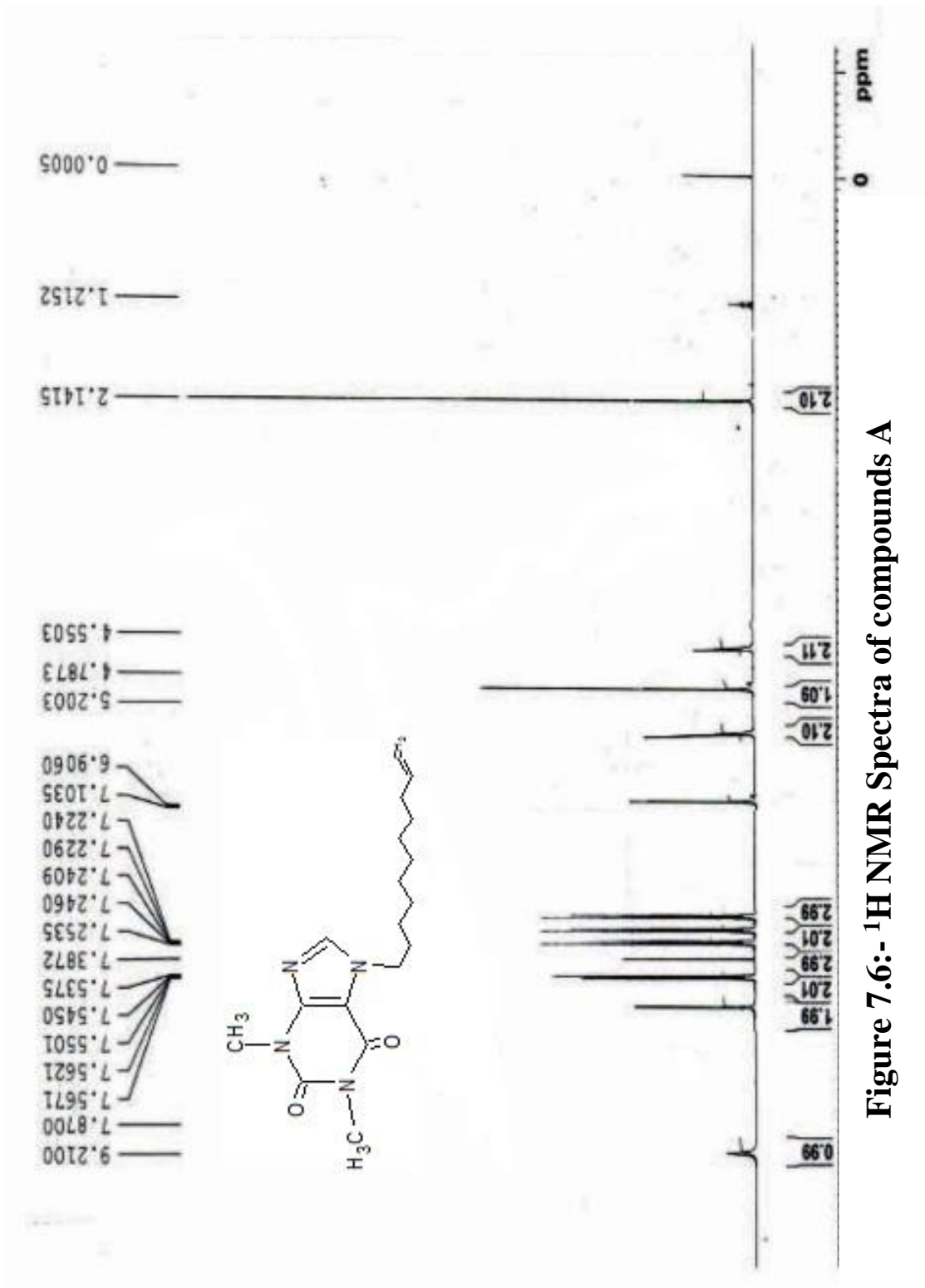


Figure 7.6:- <sup>1</sup>H NMR Spectra of compounds A



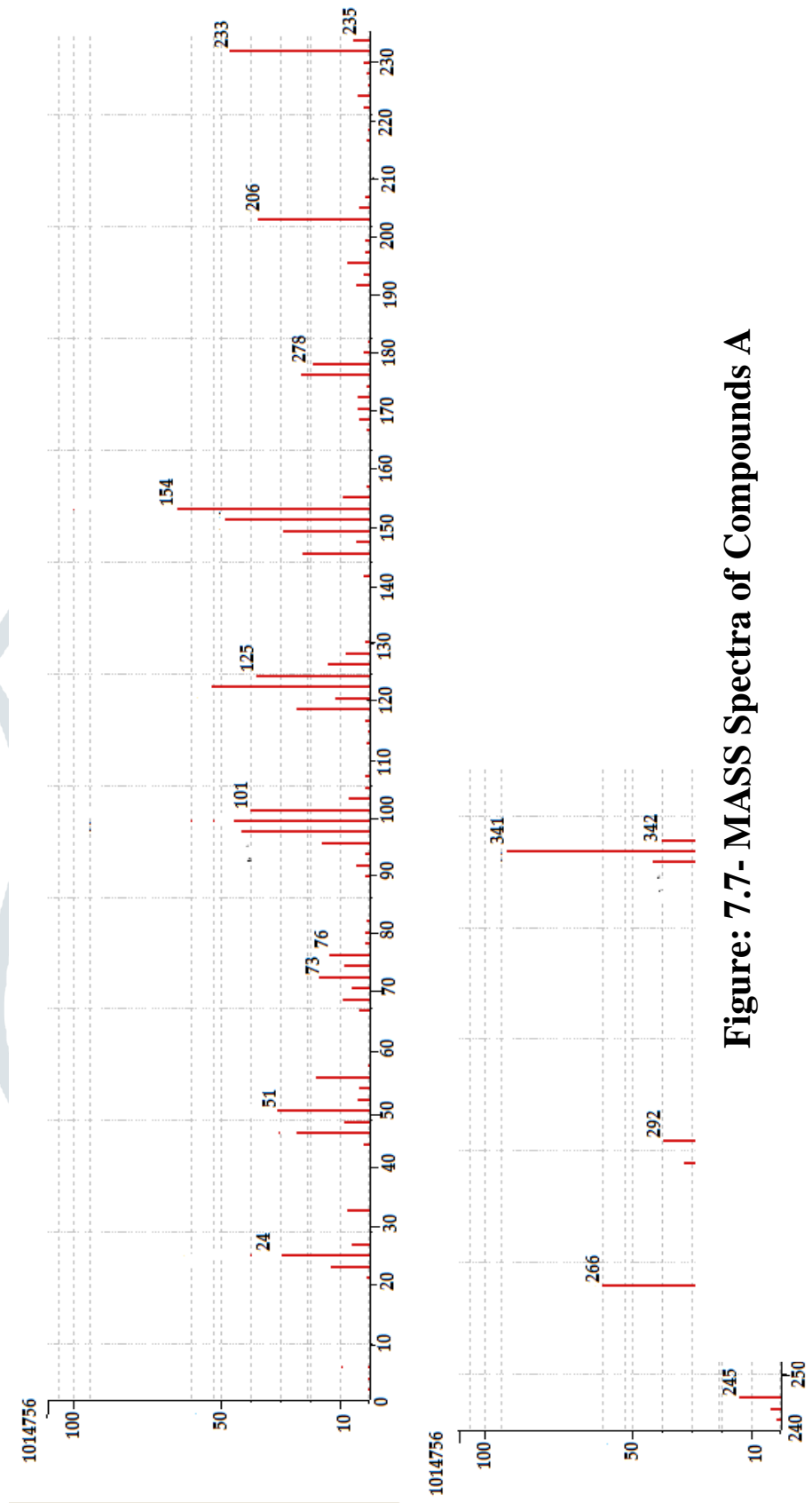
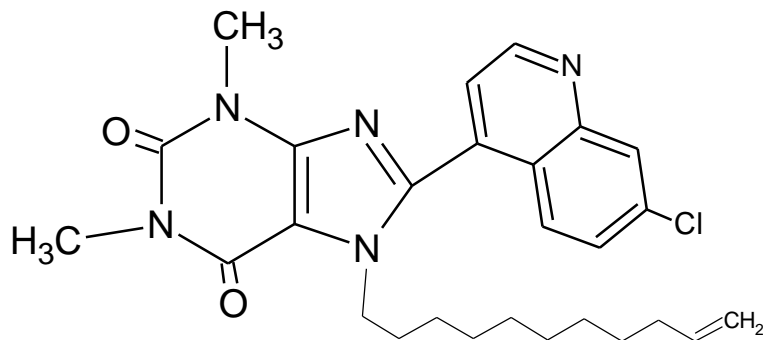


Figure: 7.7- MASS Spectra of Compounds A

**Spectral features for compounds B**

- Molecular Weight: 464.02



- **UV  $\lambda_{max}$**

- $\lambda_{max}$  at 295nm

- **IR in  $cm^{-1}$**

- Peak at 3366 corresponds to Amine –N-H stretching.

Peak at 3090 corresponds to Ar. C-H m.

Peak at 2805 corresponds to Alkenes –C-H m-s.

Peak at 2639 corresponds to –C =C- vending.

Peak at 1670 corresponds to –C-N- vending.

Peak at 1083 corresponds to C-C stretching

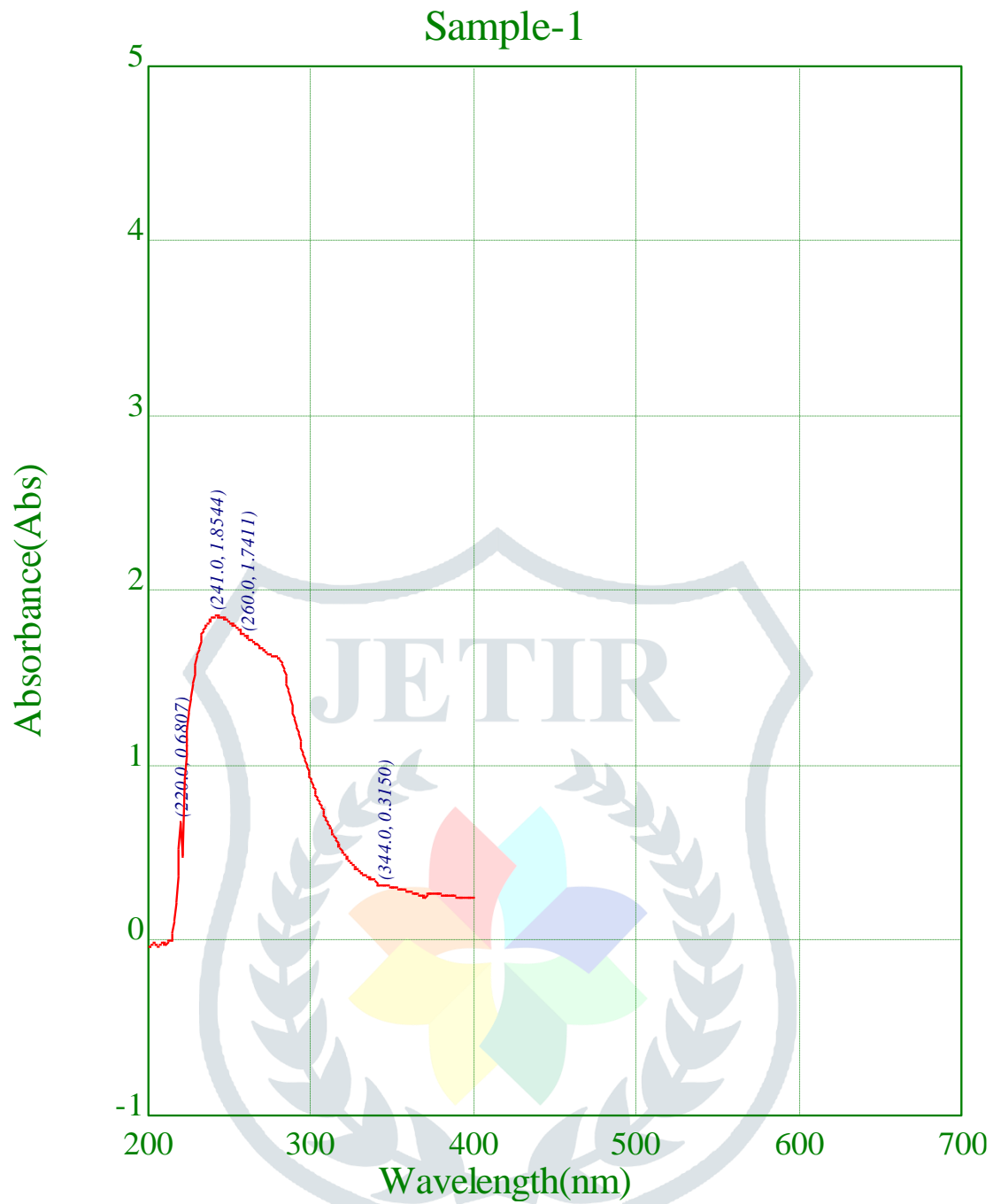
- **Mass: in m/z**

• Further evidence of the structure of the compound was obtained by recording mass spectra of the sample. The mass spectrum revealed:

The molecular ion peak was observed at m/z 464

- **$^1H$  NMR ( $\delta$ ) in PPM**

• 6.47-8.10 (9H, C=O m), 5.86 (1H, s, NH), 4.19-4.29 (3H, m, CH<sub>3</sub>), 4.08 (1H, Cl, NH), 1.19-1.29 (2H, m, CH<sub>2</sub>)



**Figure: 7.8:** 7-(UNDEC-1-ENYL),8-(7-CHLOROQUINOLINE)THEOPHYLLINE

KNIMT/PC/TBQ/15-16/02

M.PHARM/PHARMACEUTICAL CHEMISTRY

28/09/2016

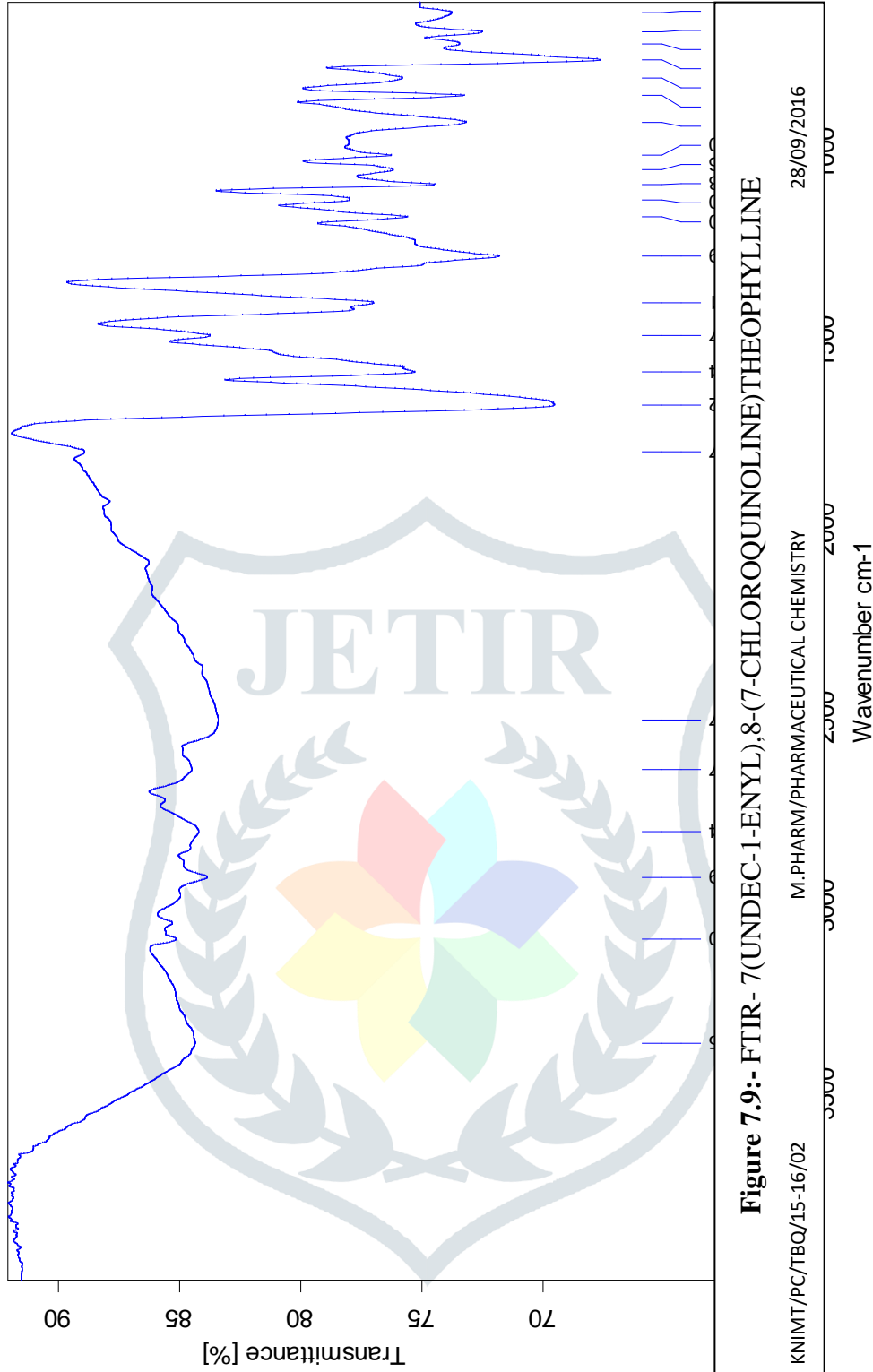


Figure 7.9:- FTIR- 7-(UNDEC-1-ENYL), 8-(7-CHLOROQUINOLINE)THEOPHYLLINE

KNIMT/PC/TBQ/15-16/02

M.PHARM/PHARMACEUTICAL CHEMISTRY

28/09/2016

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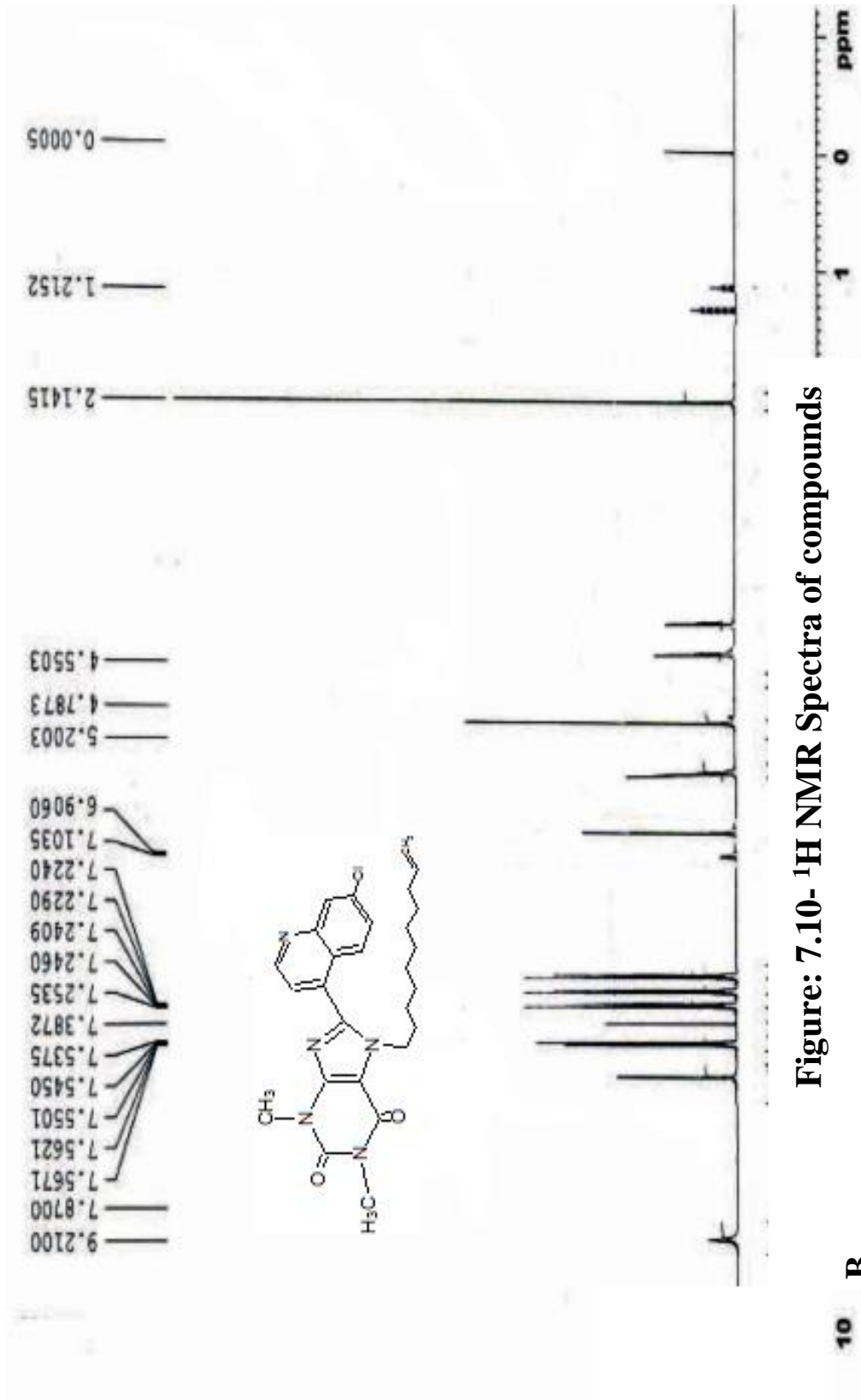
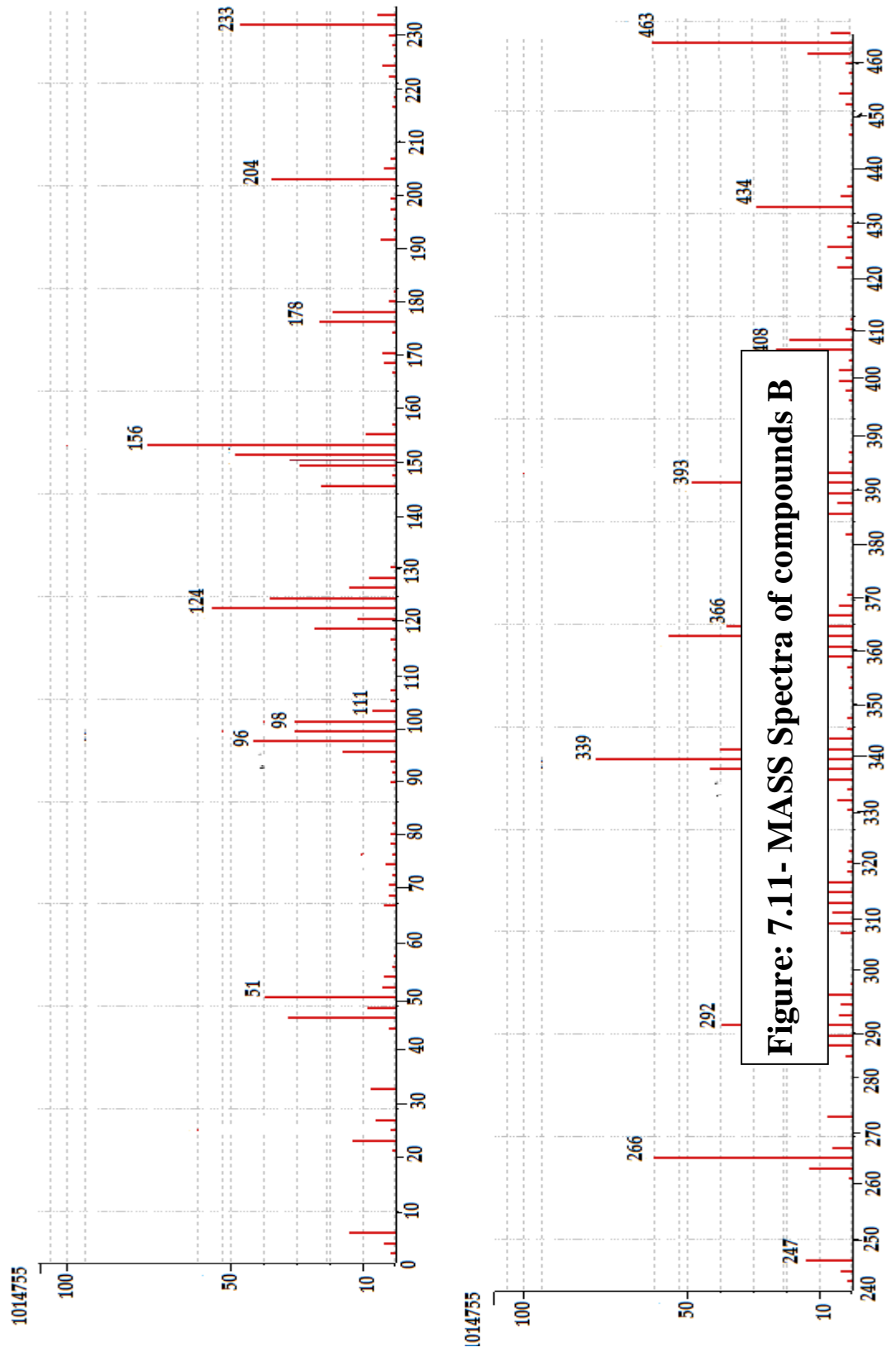


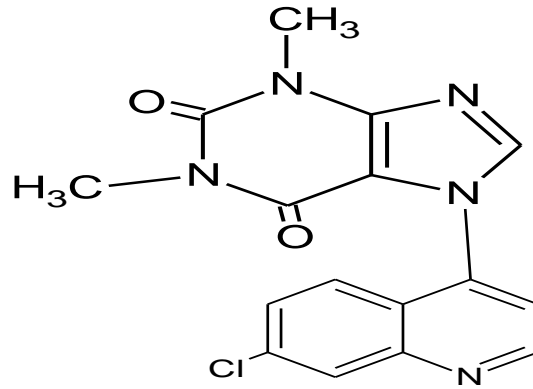
Figure: 7.10- <sup>1</sup>H NMR Spectra of compounds

10 B



## Spectral features for compounds C

- Molecular Weight: 341.76



- UV  $\lambda_{max}$

- $\lambda_{max}$  at 251nm

- IR in  $\text{cm}^{-1}$

- Peak at 1678 corresponds to C=O stretching.

- Peak at 1589 corresponds to Ar.CH stretching.

- Peak at 1282 corresponds to C-N vending.

- Peak at 1173 corresponds to C=C stretching.

- Peak at 1088 corresponds to C=C vending.

- Peak at 759 corresponds to C-C stretching

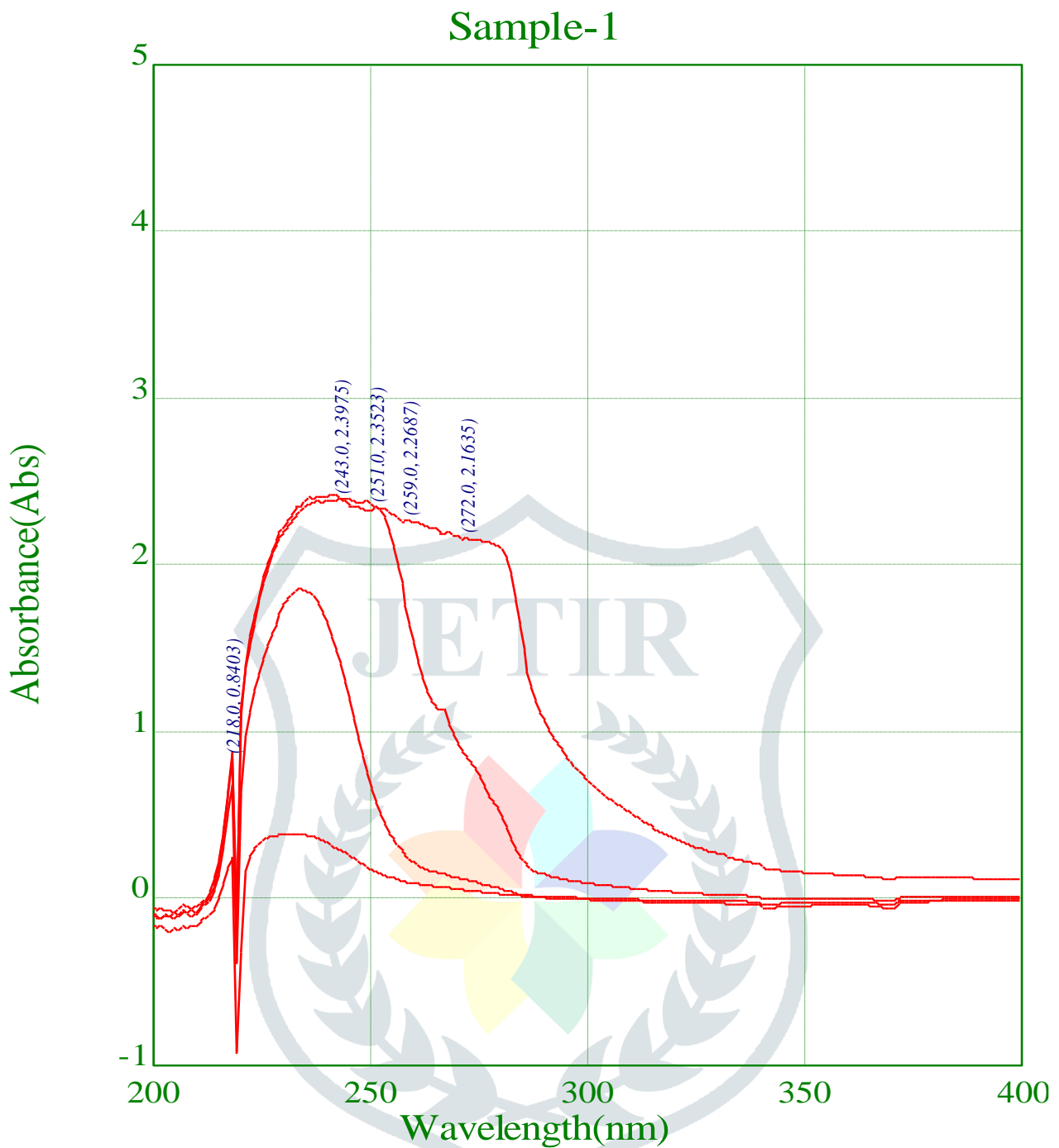
- Mass: in m/z

- Further evidence of the structure of the compound was obtained by recording mass spectra of the sample. The mass spectrum revealed:

The molecular ion peak was observed at m/z 342

- $^1\text{H}$  NMR ( $\delta$ ) in PPM

- 6.47-8.10 (9H, C=O m), 5.86 (1H, s, NH), 4.19-4.29 (3H, m, CH<sub>3</sub>), 4.08 (1H, Cl, NH), 1.19-1.29 (2H, m, CH<sub>2</sub>)



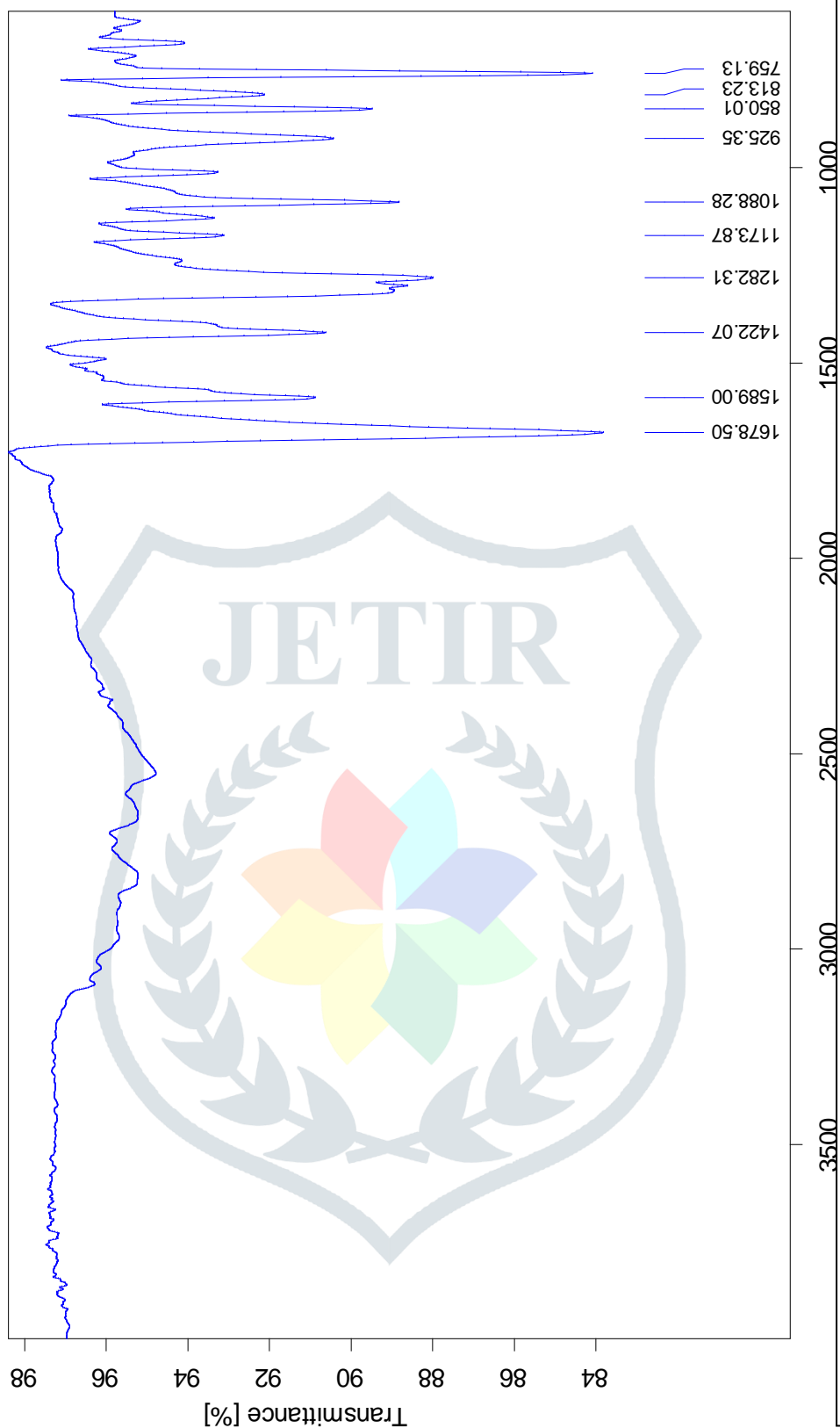
**Figure -7.12:- 8-(7-CHLOROQUINOLINE)THEOPHYLLINE  $\lambda$  max**

KNIMT/PC/THEOPHYLLINE/15-16/03

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**Figure-7.13:- 8-(7-CHLOROQUINOLINE)THEOPHYLLINE**

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Instrument type and / or accessory

04/10/2016

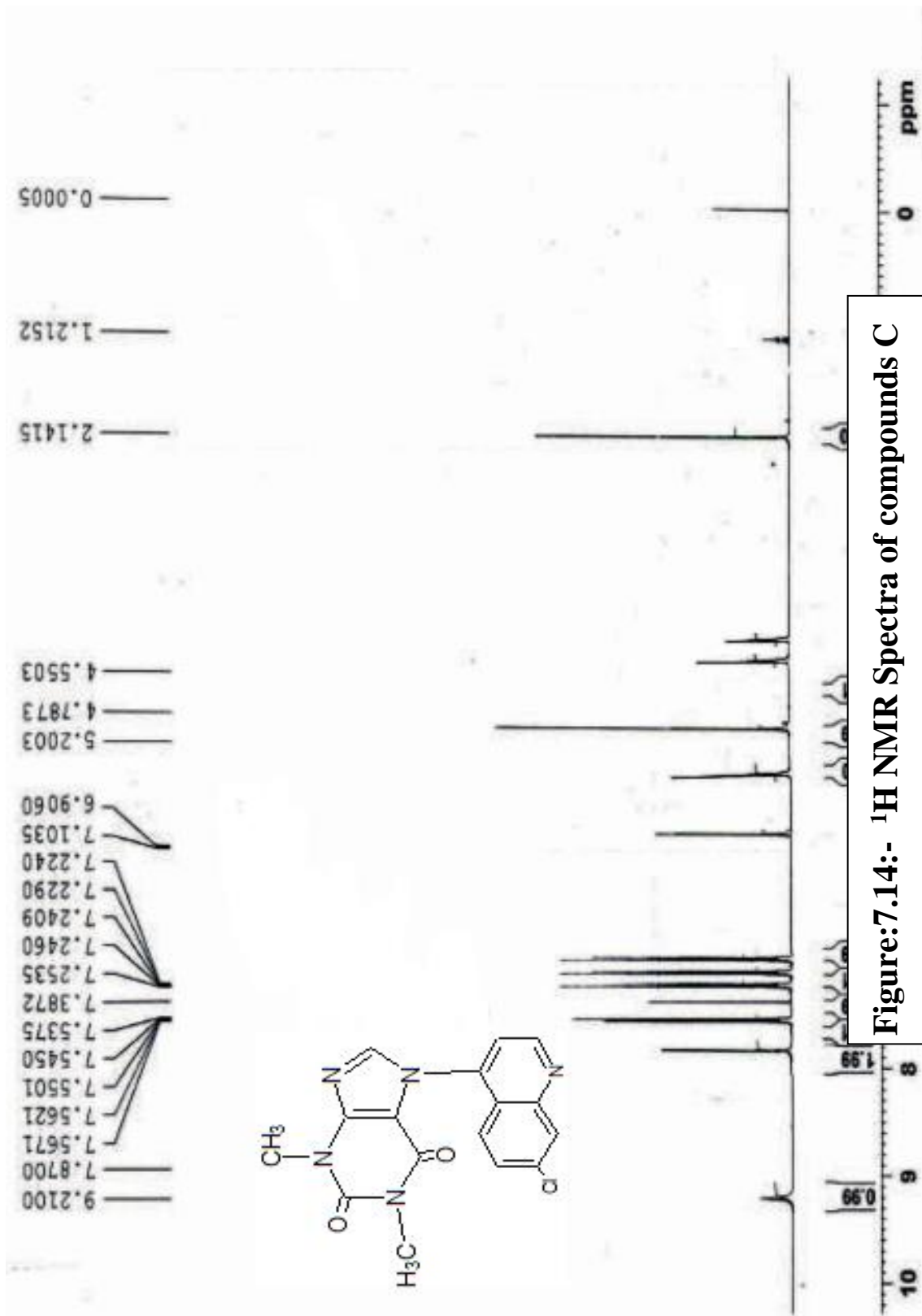
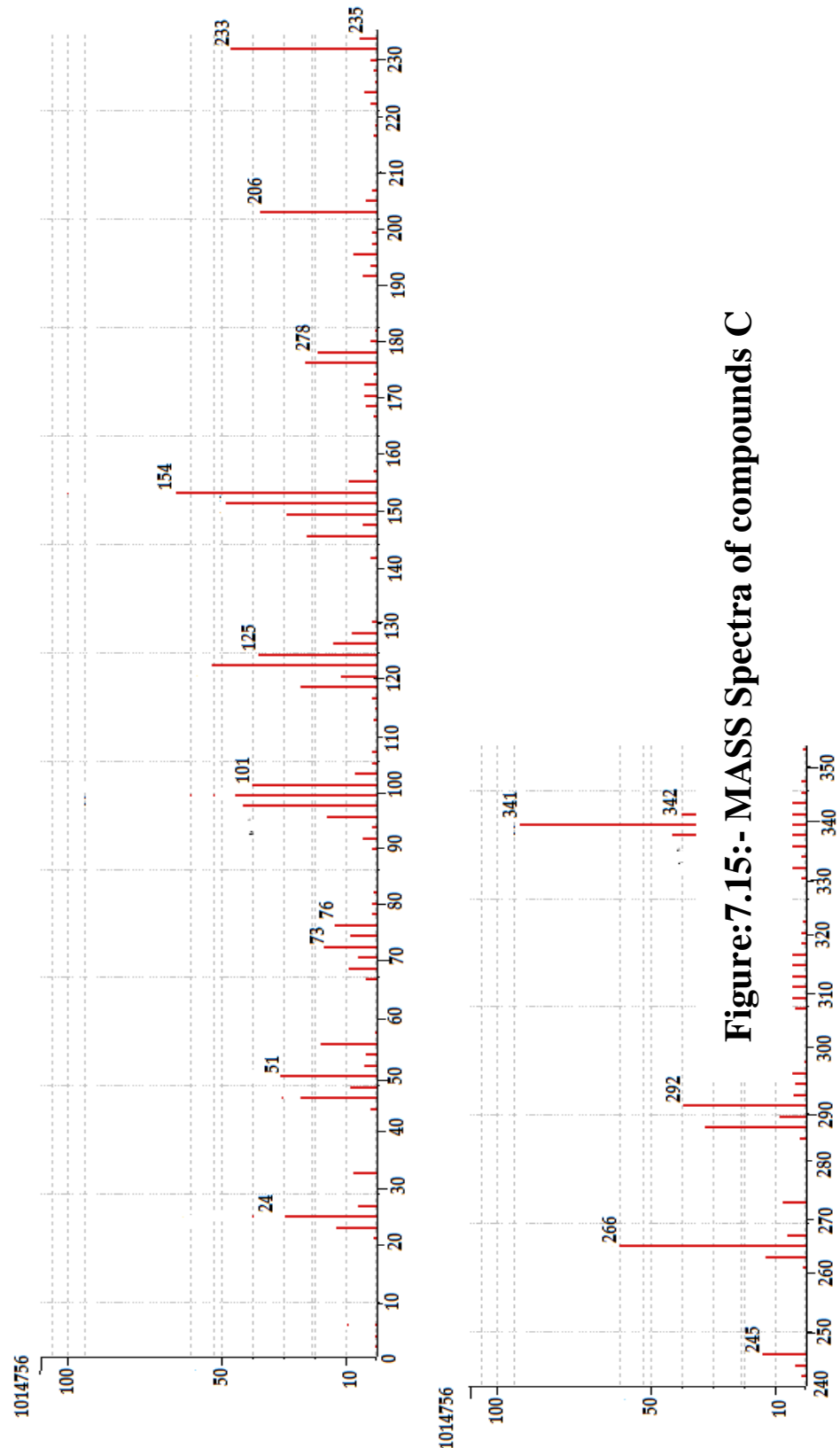


Figure:7.14:- <sup>1</sup>H NMR Spectra of compounds C



**Figure:7.15:- MASS Spectra of compounds C**

## 8. CONCLUSION

The objective of the present studies was to synthesize and characterize some novel Theophylline derivatives and to carry out the Antitussive and Bronchodilator activities.

Synthesis of all the 7, 8-theophylline derivatives by the above described method results in products with good yields.

IR, <sup>1</sup>H NMR and mass spectroscopic analysis was done to confirm the structures of the newly synthesized compounds. Some of the synthesized compounds showed moderate to good antitussive and Bronchodilator activity when compared with the standard drugs Theophylline.

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