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THE UNIVERSITY OF ALBERTA

AZAXANTHONES AS POTENTIAL LEUKOTRIENE INHIBITORS

BY

DALJIT VUDATHALA (C)

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF DOCTOR OF PHILOSOPHY

IN

PHARMACEUTICAL SCIENCES (MEDICINAL CHEMISTRY)

FACULTY OF PHARMACY AND PHARMACEUTICAL SCIENCES

EDMONTON, ALBERTA

FALL, 1990

ISBN 0-315-64796-5

THE UNIVERSITY OF ALBERTA

RELEASE FORM

NAME OF AUTHOR: DALJIT VUDATHALA

TITLE OF THESIS: AZAXANTHONES AS POTENTIAL LEUKOTRIENE INHIBITORS

DEGREE: PH.D

YEAR THIS DEGREE GRANTED: 1990

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To my parents

ABSTRACT

Arachidonic acid (AA) is metabolized by two major pathways: cyclooxygenase and 5-lipoxygenase. Metabolism by cyclooxygenase gives rise mainly to prostaglandins which are responsible for inflammation and by 5-lipoxygenase to leukotrienes (LTs). LTs have been found to be synthesized and released by many cells and organs. Elevated levels of LTs have been reported in inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, cutaneous allergic reactions, psoriasis, adult respiratory distress syndrome and asthma. Therefore, drugs which can lower the levels of leukotrienes may be helpful in these conditions.

A number of 1-azaxanthone derivatives were synthesized in our laboratory and some were found to inhibit the cyclooxygenase and 5-lipoxygenase pathways in an *in vitro* assay. The compounds which were found to exhibit the most promising biological results had imidazole, thiazole or pyridine rings incorporated on 1-azaxanthone to give tetracyclic ring systems or had a thiourea side chain at the C-7 position of 1-azaxanthone. Several compounds were found to exhibit bronchodilating properties.

On this basis their 4-azaxanthone, 4-azathioxanthone and 1-azathioxanthone analogs were synthesized and several modifications were made in these ring systems to further explore the structure-activity relationships. In imidazole derivatives (78-80), C_2-H was replaced with methyl to give compounds (82-84) and N-1 hydrogen was replaced with methyl to give derivatives (86-88), with ethyl to give compounds (90-92) and benzyl to give derivatives (94-96). The carbonyl group of imidazole (78) was reduced to give non-rigid pyridopyranobenzimidazole (100). The thiazole derivative (102) of 4-azaxanthone was synthesized and the strongly electron-donating amino-group was acetylated to give compound (103). Pyridine derivatives (105-108) were synthesized and the pyridine of (105) was replaced with pyrazine to give compound (109). A number of thiourea derivatives (116-117, 119-134) were also synthesized.

Biological testing was done on guinea pig isolated tracheal spirals and lung parenchymal strips. Tracheal spirals, in the presence of indomethacin, were used to screen for lipoxygenase inhibition and parenchymal strips for cyclooxygenase inhibition. Activity was compared to nafazatrom, piriprost, sodiun meclofenamate, NDGA, BW 755C and L-649, 923. Most of the compounds showed better or comparable activity to these standard drugs. Compounds were also tested for their bronchodilating activity.

ACKNOWLEDGEMENT

I wish to express my sincere thanks to Dr. F. M. Pasutto for his supervision of this work and preparation of this manuscript.

I also wish to thank Dr. John Burka, Department of Anatomy and Physiology, Atlantic Veterinary college, University of prince Edward Island, for conducting the pharmacological studies presented in this thesis. Thanks to Drs. Syed Abuzar and B. P. Setiloane for their help in my work.

Financial assistance from the Faculty of Pharmacy and Pharmaceutical Sciences and a studentship from Alberta Heritage Foundation for Medical Research was greatly appreciated.

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LIST OF ABBREVIATIONS

AA	---arachidonic acid
bp	---boiling point
$CDCl_3$	---deuterochloroform
CI	---chemical ionization
cm	---centimeter
CO	---cyclooxygenase
DMSO-d_6	---hexadeuterodimethyl sulphoxide
DSCG	---disodium chromoglycate
g	---gram
h	---hour
5-HETE	---5-hydroxyeicosatetraenoic acid
5-HPETE	---5-hydroperoxyeicosatetraenoic acid
ID_{50}	---50% inhibition dose
ir	---infrared
12-LO	---12-lipoxygenase
15-LO	---15-lipoxygenase
LT	---leukotriene
LTA_4	---leukotriene A_4
LTB_4	---leukotriene B_4
LTC_4	---leukotriene C_4
LTD_4	---leukotriene D_4
LTE_4	---leukotriene E_4
LTF_4	---leukotriene F_4
5-LO	---5-lipoxygenase
min	---minute
ml	---milliliter

mmol	---millimole
mol	---mole
mp	---melting point
NDGA	---nordihydroguaiaretic acid
nmr	---nuclear magnetic resonance
NSAIDs	---non-steroidal antiinflammatory drugs
PCA	---passive cutaneous anaphylaxis
PG	---prostaglandin
PGD_2	---prostaglandin D_2
PGE_2	---prostaglandin E_2
$PGF_{2\alpha}$	---prostaglandin $F_{2\alpha}$
PGG_2	---prostaglandin G_2
PGH_2	---prostaglandin H_2
PMN	---polymorphonuclear
PMNs	---polymorphonucleocytes
PPA	---polyphosphoric acid
psi	---pounds per square inch
TLC	---thin layer chromatography
Tx	---thromboxane
TXA_2	---thromboxane A_2
℃	---degree celsius

INTRODUCTION

1.0. Metabolism of arachidonic acid:

Arachidonic acid (AA) is an essential C_{20} unsaturated fatty acid which is present as an ester in phospholipids and glycerides . The first step in the metabolism of arachidonic acid is the release of free acid from its ester by enzyme phospholipase. There are two major metabolic pathways of arachidonic acid: cyclooxygenase and 5-lipoxygenase (5-LO). Arachidonic acid is also metabolized by 12-lipoxygenase (12-LO), 15-lipoxygenase (15-LO) and cytochrome P450.[1,2]

1.1. Cyclooxygenase pathway:

The cyclooxygenase pathway of the arachidonic acid cascade has been investigated most extensively. It gives rise to prostaglandins (PGs), thromboxane (Tx) and prostacyclin.[3,4]

1.1.1. *Prostaglandins:*

Prostaglandins were first discovered in human semen. Since the prostate gland was believed to be their major source, the term prostaglandins was introduced. It is now known that prostaglandins are produced by most cells except erythrocytes.[4] The prostaglandins are a group of C_{20} fatty acids containing a cyclopentane ring between C-8 and C-12. The compounds are divided into groups (A-J) according to the substituents on the cyclopentane ring and further subdivided according to the number of double bonds in the side chains. The latter are indicated by a relevant suffix.[4]

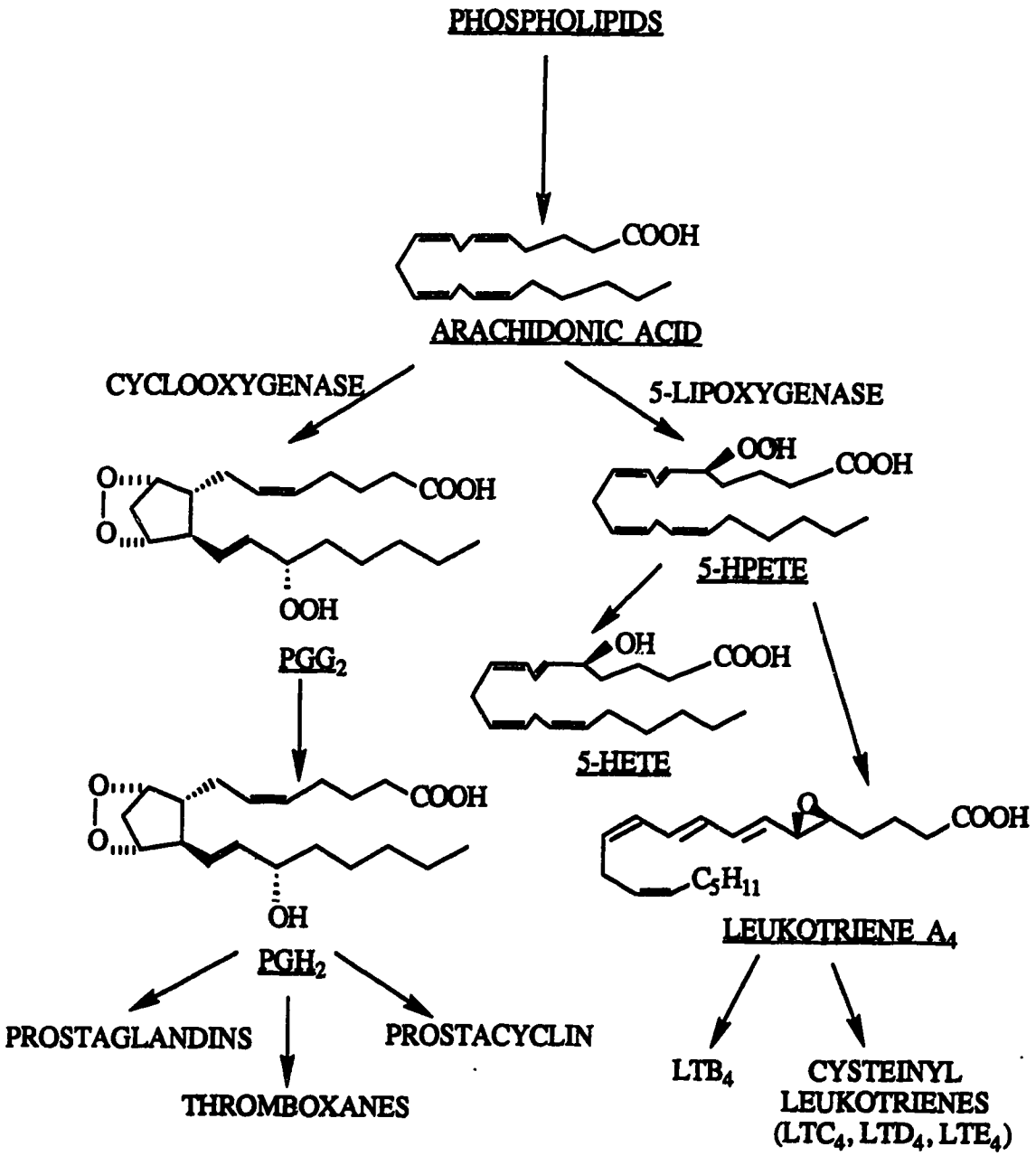


Fig. 1: Major metabolic pathways of arachidonic acid

The first step in the enzymatic synthesis of prostaglandins is the insertion of two molecules of oxygen into arachidonic acid to yield 15-hydroperoxy-9-11-endoperoxide

(PGG_2) which is then reduced to its 15-hydroxy analogue (PGH_2) (Fig. 1). PGH_2 is converted to prostaglandins (PGD_2, PGE_2 and $PGF_{2\alpha}$) (Fig. 2).[2,4]

1.1.2. *Biological effects of prostaglandins:*

Prostaglandins contribute to the important symptoms of inflammation[5,6] including erythema,[7] edema, pain and fever. In human, prostaglandins cause pain[8,9] along the veins into which they are infused, as well as headache. They exhibit powerful pyretic action when injected either into cerebral ventricles or directly into the anterior hypothalmus of unanesthesized cat, rabbit and rat.[10,11]

Free radicals (such as superoxide and hydroperoxy radicals) are formed during prostaglandin synthesis and these are believed to play an important role in inflammation by causing local tissue damage.[12]

1.1.3. *Thromboxanes and prostacyclin:*

Thromboxane A_2 (TXA_2) is synthesized in blood platelets (thrombocytes) from PGH_2 and contains an oxane ring instead of the cyclopentane ring present in the structure of prostaglandins (Fig. 2). Prostacyclin is also formed from PGH_2 but in the endothelial cells of blood cell walls. Both prostacyclin and TXA_2 are unstable at physiological pH and temperature and hydrolyse to 6-keto $PGF_{1\alpha}$ and TXB_2 respectively, which are less active than their precursors.[4]

1.1.4. *Biological effects of thromboxane and prostacylin:*

Thromboxane A_2 is a potent inducer of platelet aggregation and has vasoconstrictor properties, it is therefore prothrombotic.[13] On the other hand, prostacyclin is anti-thrombotic; it is the most powerful, naturally occurring inhibitor of platelet aggregation[14] and has vasodilator activity.

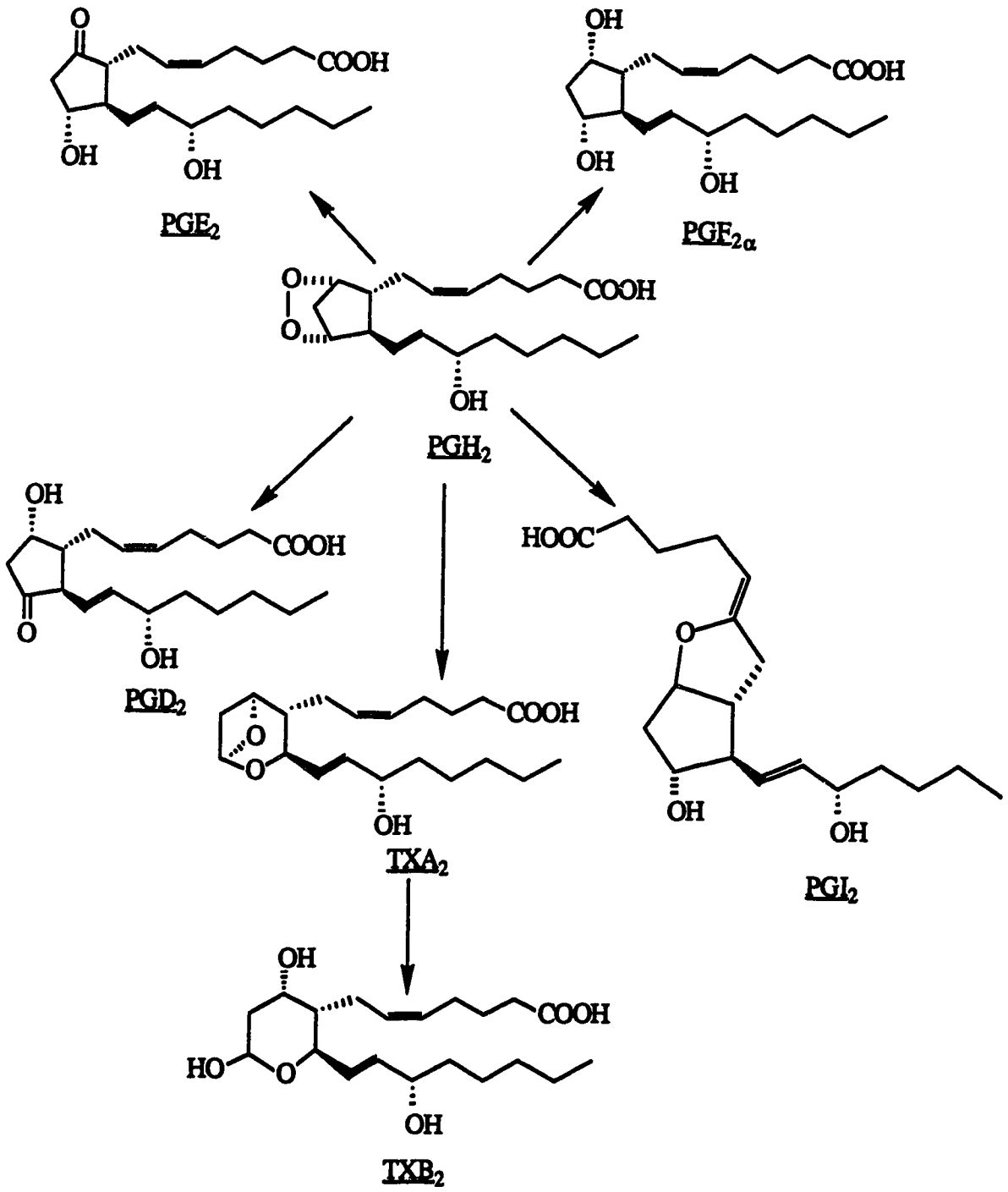


Fig. 2: Cyclooxygenase pathway

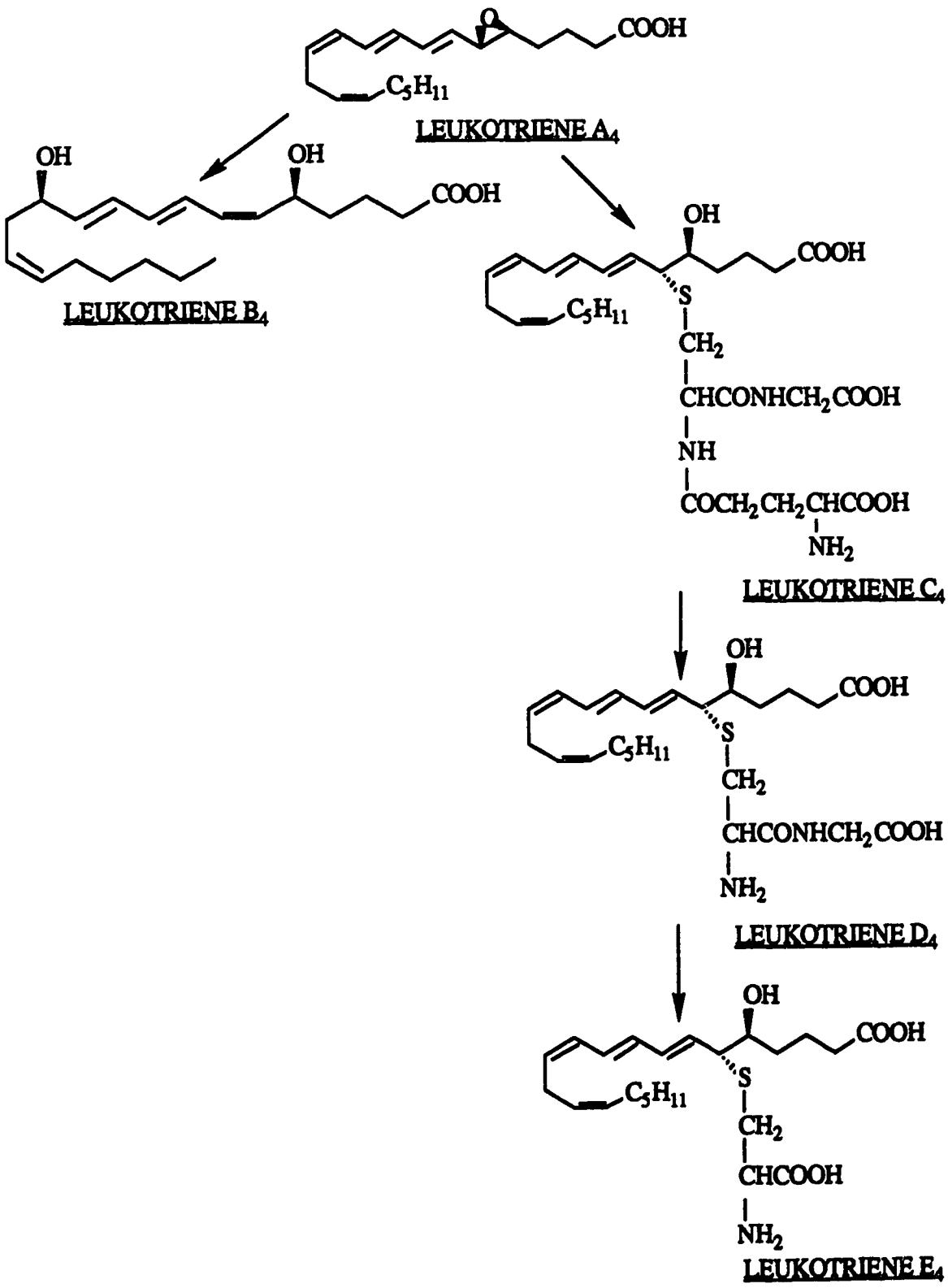


Fig. 3 : Lipoxygenase pathway

1.2. 5-Lipoxygenase pathway:

Metabolism of AA by 5-lipoxygenase gives 5-hydroperoxyeicosatetraenoic acid (5-HPETE) which is reduced to 5-hydroxyeicosatetraenoic acid (5-HETE) by glutathione peroxidase. Metabolism of 5-HPETE to biologically active leukotrienes is of more interest.[15]

1.2.1. *Leukotrienes:*

Leukotrienes (LTs) were discovered by Samuelsson et al. (1979-1980) and are the subject of intense research efforts.[3] The name leukotriene originates from the cellular origin of these mediators, the leukocytes, and the characteristic triene system found within their chemical structure. Unlike prostaglandins, leukotrienes do not contain a ring but have open chain structures. They are divided into groups (A-F) according to major structural differences and into sub-groups according to the number of double bonds in the side chains.[4]

The first step in the conversion of 5-HPETE to leukotrienes is the loss of water to form an unstable epoxide, leukotriene A_4[16] (LTA_4) (Fig. 1). From LTA_4 all other leukotrienes are formed (Fig. 3). LTA_4 gives 5(S),12(R)-dihydroxy-6,14-cis-8,10-trans-eicosatetraenoic acid (LTB_4) under the influence of LTA_4 hydrolase.[17,18] Alternatively, LTA_4 may be converted into a 5-hydroxy-6-glutathionyl derivative (LTC_4) by glutathione-S-transferase.[19] LTC_4 is metabolized successively by gamma-glutamyltranspeptidase and cysteinylglycine dipeptidase to LTD_4 and LTE_4 respectively.[2,20,21] The action of N-acetyltransferase on LTE_4 gives N-AcLTE_4.[1] Gamma-glutamyltranspeptidase can incorporate a glutamyl moiety on to LTE_4 to produce LTF_4. However, the production of LTF_4 by tissue or cells has not been observed.[2] LTC_4, LTD_4 and LTE_4 have a cysteine residue at C-6 and are therefore called cysteinyl leukotrienes. These cysteinyl leukotrienes were previously known as SRS-A (slow reacting substances of anaphylaxis).

Studies done with the rat basophilic leukemia cells and guinea pig peritoneal polymorphonuclear leukocytes have shown that the metabolism of arachidonic acid by 5-lipoxygenase pathway is stimulated by calcium in a concentration dependent fashion.[22-24]

1.2.2. *Biological effects of leukotrienes:*

The effects of leukotrienes on different biological systems have been studied and the results published in several review articles.[1,25,26,27] Although LTs were originally identified as products of leukocytes, it is now well recognized that LTs can be produced by a variety of other biological cell systems such as eosinophils, macrophages and mast cells.[4,28]

1.2.2.1. LEUKOTRIENES AND THE CARDIAC SYSTEM:

Leukotrienes play a potential role in cardiac anaphylaxis which in human is characterized by arrhythmias, myocardial depression, coronary constriction and ultimately heart failure. These effects vary from species to species.

In *in vivo* studies with several animal species LTs have been observed to cause coronary constriction. This has been reviewed by G. Feurestein.[26] Coronary constriction has not been investigated in human. On treatment with LTs, guinea pig and human cardiac tissue exhibited myocardial depression[29] but this effect was not observed in other studies.[30] LTs have also been shown to induce cardiac arrhythmias.[31]

1.2.2.2. LEUKOTRIENES AND THE VASCULAR AND MICROVASCULAR SYSTEM:

Although in general LTs cause vasoconstriction in blood vessels, there are certain exceptions[32]: 1) in humans LTs cause vasodilation of bronchial or pulmonary vessels ; 2) in several animal species LTs were found to have no constricting effect on coronary ring

preparations; and 3) LTs induced an endothelial-dependent relaxation in *in vitro* preparations of canine, mesenteric, and renal vessels.[33]

LTs not only affect large and small arteries and veins but also affect the microcirculation. LTs play an important role in microcirculatory and cellular events of inflammatory responses.[34, 35]

1.2.2.3. LEUKOTRIENES AND THE PULMONARY SYSTEM:

LTs are produced in lung parenchyma,[36] the bronchial tree and pulmonary vessels. It has been suggested that LTs play a role in asthma, perhaps by narrowing of the airways,[37-39] by mucus secretion[40] and consequent plugging of the airways, and also by producing edema of the bronchial mucosa. LTs may be involved in several other disease processes related to the pulmonary system such as adult respiratory distress syndrome,[41] chronic bronchitis[42] and cystic fibrosis.[43]

1.2.2.4. ROLE OF LEUKOTRIENES IN THE CENTRAL NERVOUS SYSTEM:

LTs have been shown to be produced in normal brain cells of rats.[44] Excessive production of LTs in the brain has been demonstrated in gerbil brain after ischemia and reperfusion.[45] It has also been demonstrated in brain tissue of spontaneously convulsing gerbil brain.[46] The effect of LTs on intracranial blood vessels is not clear. LTs caused constriction of intracranial circulation in the pig[47] but no relaxation or contractile response in human cerebral vessels *in vitro* or on the rabbit cerebral microcirculation *in vivo*.[26] However, in rat, LTs increased permeability and promoted vasogenic edema.[48]

1.2.2.5. LEUKOTRIENES IN INFLAMMATION:

LTB_4 has been identified in inflammatory exudates in patients with arthritis, gout[49] and psoriasis.[50] In inflammatory sites, leukotrienes are produced by polymorphonuclear

(PMN) leukocytes and macrophages.[51] PMNs produce LTB_4 which has potent chemotactic, chemokinetic activities and it causes aggregation of neutrophils.[52]

2.0. Inhibition of arachidonic acid metabolism:

2.1. Phospholipase inhibitors:

Corticosteroids are known to inhibit the clinical symptoms of arthritis, inflammation and asthma by interfering with the release of fatty acids from cell membrane phospholipids.[53,54] However, long term use of corticosteroids causes serious side effects which limits their use.[12]

2.2. Inhibition of cyclooxygenase pathway:

Unacceptable side effects associated with corticosteroids led to the search for non-steroidal antiinflammatory drugs (NSAIDs) which show their activity by inhibiting the enzyme cyclooxygenase, by affecting cell migration and enzyme release, and by inhibiting superoxide production.[12, 55, 56, 57] During inflammation there is a migration of PMN leukocytes which destroy foreign material by breaking it down with lysosomal enzymes. In a chronic inflammatory response, the usually useful degradative enzymes are released into the inflamed area which results in local tissue damage. NSAIDs have been shown to inhibit migration of PMNs into an inflamed area.[58] NSAIDs also inhibit the release of lysosomal enzyme from PMNs *in vitro* and *in vivo*.[59]

2.2.1. *NSAIDs in use:*

Most NSAIDs in clinical use are carboxylic acids with the exception of a few pyrazoles. Some of these drugs are listed below and representative structures for each class are given in Fig. 4.

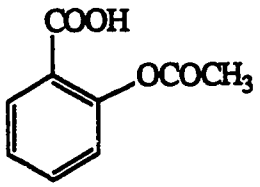
Carboxylic Acids

Salicylates	Acetic Acid	Fenamates	Propionic
Aspirin	Diclofenac	Mefenamic acid	Ibuprofen
Diflunisal	Indomethacin	Meclofenamate	Benoxaprofen
	Sulindac		Ketoprofen
	Tolmetin		Fenoprofen

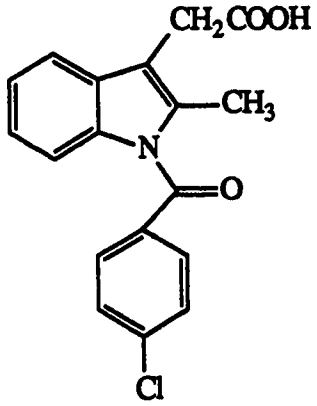
Pyrazoles

Phenylbutazone

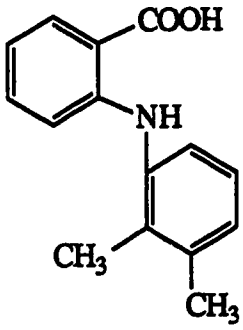
Oxyphenbutazone



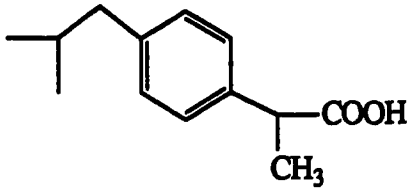
ASPIRIN



INDOMETHACIN



MEFENAMIC ACID



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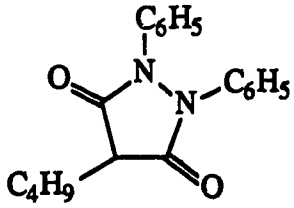


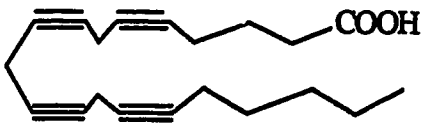
PHENYLBUTAZONE

Fig. 4: Structures of representative NSAIDs

2.3. Inhibitors of cyclooxygenase and 5-lipoxygenase:

5,8,11,14-Eicosatetraynoic acid (ETYA) is a general purpose inhibitor of arachidonate metabolism. It is a structural analog of arachidonic acid in which all double bonds are replaced with triple bonds. Although it has been assumed to be a dual inhibitor of both cyclooxygenase and the lipoxygenase pathways, its actions are more complex. For

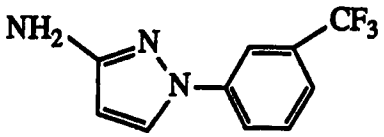
example, the dose that inhibits CO and 5-LO is ineffective on 12-LO.[60,61] There are other reports suggesting that doses that inhibit prostaglandin production do not affect leukotriene[62] formation but actually stimulate 5-HETE production.[63]



5, 8, 11, 14-EICOSATETRAYNOIC ACID

1

A variety of structurally diverse compounds have been reported to be dual inhibitors of both CO and 5-LO.[64-68] BW 755C, SKF 86 002 and L 652 345 are some examples of this class of inhibitors.



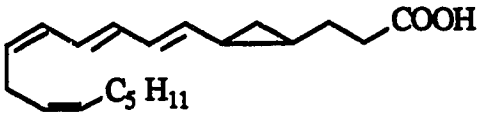
BW 755C

2

Dual inhibitors would be expected to possess the same anti-inflammatory activity as steroids. Like steroids they could also be useful in diseases, such as asthma, associated with leukotrienes. Dual inhibitors may be free from the unacceptable toxic effects associated with steroids.[69]

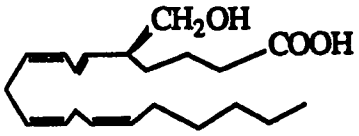
2.4. Inhibitors of 5-lipoxygenase:

The 5,6-methano analog of LTA_4 (the epoxy oxygen is replaced by CH_2 group) (3) and carba analog of HPETE (the peroxide function is replaced by CH_2OH) (4) have been reported to inhibit 5-lipoxygenase of guinea pig PMNs.[70]



5, 6-METHANO-LTA$_4$

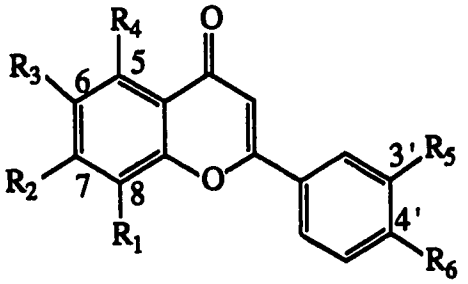
3



CARBA ANALOG OF HPETE

4

Natural products such as flavonoids (5) have been reported to be selective inhibitors of 5-lipoxygenase. Crisilol (3',4',5-trihydroxy-6,7-dimethoxyflavone) was found to be more potent than other flavonoids.[71] 12-LO was also inhibited but at higher concentrations. Some of these flavonoid compounds are present in plant extracts which have been used for centuries in Oriental medicine for the treatment of inflammatory diseases. Caffeic acid also acts as a 5-LO inhibitor.[72] Some retinoids, particularly retinol (Vitamin A), are also effective inhibitors of LTB4 synthesis[73] and have been used in the treatment of psoriasis.

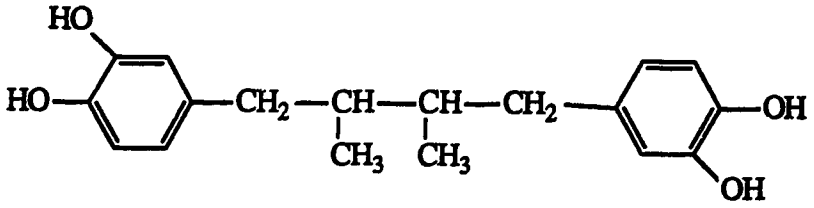


R_1, R_2, R_3, R_4, R_5, R_6=H, OH, OCH_3

FLAVONOIDS

5

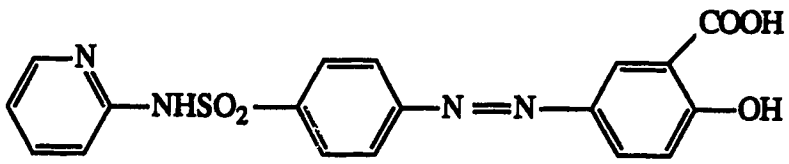
Nordihydroguaiaretic acid (NDGA) (6) , an anti-oxidant, has been shown to inhibit 5-LO selectively.[74] It will inhibit other lipoxygenases and cyclooxygenase but only at higher concentrations.



NDGA

6

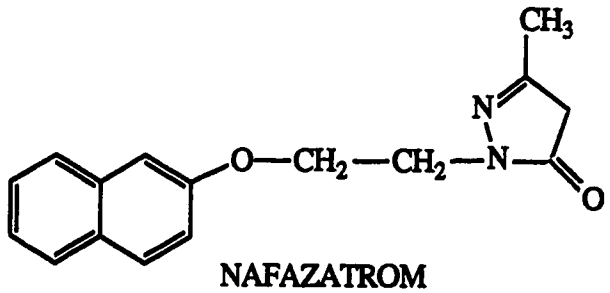
Sulfasalazine (7), used in the management of inflammatory bowel disease, has been proposed to inhibit lipoxygenase. The original rationale for its synthesis was the attempt to combine the antibacterial action of sulfa drugs with the anti-inflammatory action of salicylates.[75] It has been reported that a metabolite of sulfasalazine, 5-aminosalicyclic acid is most probably the active principle.[76]



SULFASALAZINE

7

Nafazatrom (8), 3-methyl-1-[2-(2-naphthyloxy)-ethyl]-2-pyrazoline-5-one, was originally developed as an antithrombotic agent but has been reported to be a selective lipoxygenase inhibitor.

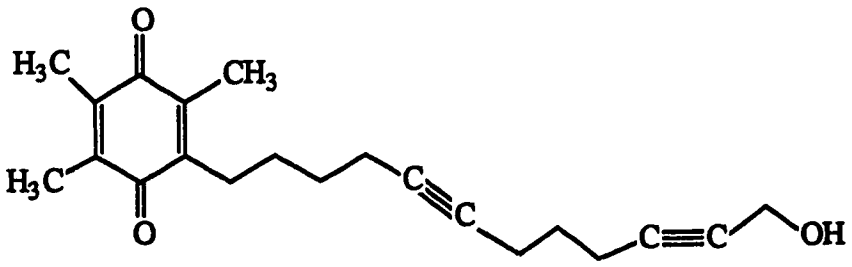


NAFAZATROM

8

Nafazatrom is also believed to be a free radical scavenger.[77]

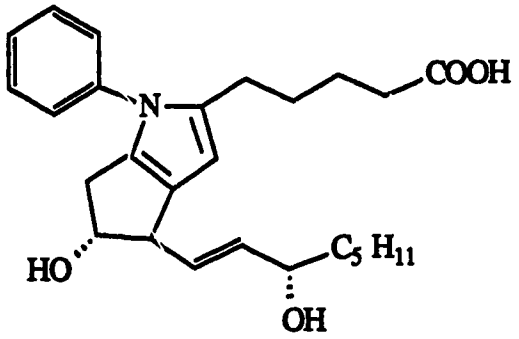
AA861 (9), a derivative of benzoquinone, is a selective inhibitor of 5-LO.[78] It has been shown to reduce allergic bronchoconstriction in guinea pigs and to reduce carrageenin-induced paw edema and pleurisy in rats.



AA861 (TAKEDA)

9

Piriprost (U-60,257) (10), which is under development by Upjohn, is an inhibitor of glutathione-S-transferase. The concentration of U-60,257 that completely inhibits leukotriene synthesis does not inhibit histamine release from the human lung. It antagonizes the contractile effect of LTC_4 and LTD_4 on guinea pig ileum[79] and inhibits enzyme release from human PMNs.[80] In Ascaris antigen-challenged rhesus monkeys, U-60,257 inhibits bronchoconstriction when given by aerosol (0.05-1%) or intravenously (0.01-5 mg/kg).



PIRIPROST
U-60,257

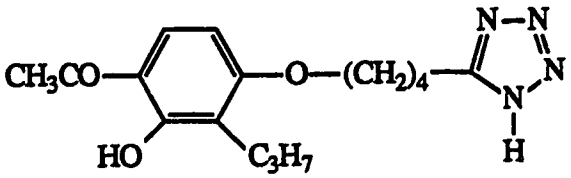
10

2.5. Leukotriene receptor antagonists:

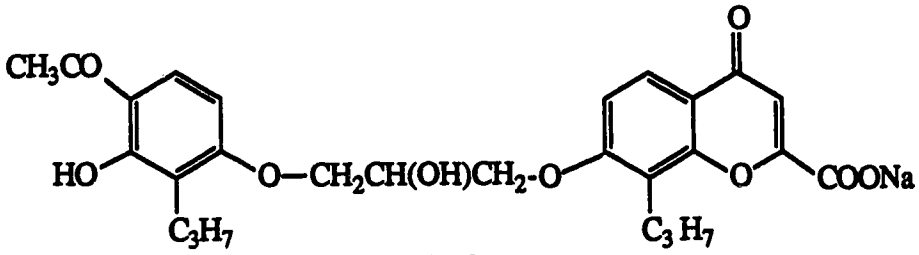
Leukotriene receptor antagonists could be important in the treatment of several disease processes in which leukotrienes are believed to play an important role. A number of compounds have been developed as leukotriene receptor antagonists. It has been suggested that the antagonist should have certain properties in order for it to progress to clinical trials. These properties include affinity for the receptor, lack of intrinsic activity, receptor selectivity, sufficient duration of action, lack of toxicity as well as bioavailability and efficacy in various animal models of the disorder.[81]

2.5.1. *Analogs of FPL 55712 which contain the acetophenone moiety:*

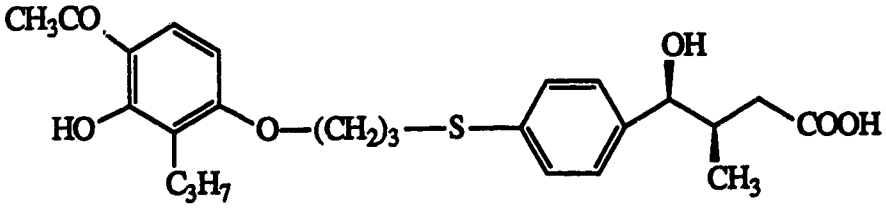
FPL 55712 (Fig. 5) was the first leukotriene receptor antagonist to be described and it played an important role in defining the pharmacology of cysteinyl leukotrienes.[82] However, its poor bioavailability and short half life limited its use in animal models.[83,84] LY 171883, LY 163443 and L-649, 923 are some of the analogs (Fig. 5) which have been developed to overcome the limitations of FPL 55712. These second generation antagonists have similar potencies to FPL 55712 and were able to block bronchoconstriction mediated by leukotrienes in guinea pigs at oral doses of 3-10 mg/kg.[85, 86, 87]



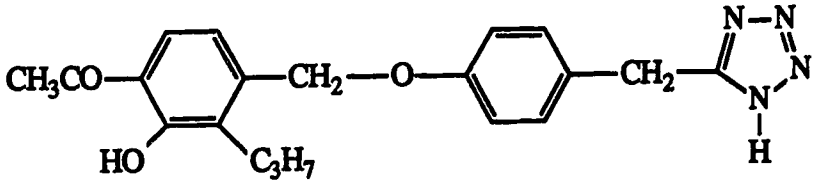
LY 171883



FPL 55712



L-649,923

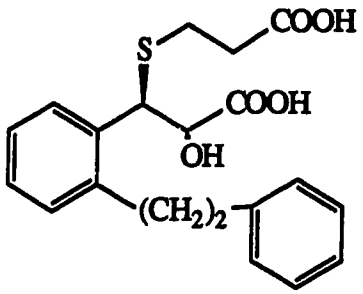


LY 163443

Fig. 5: FPL 55712 and some of its acetophenone analogs

2.5.2. *Analog of natural agonist:*

SKF 104353 is an example of a third generation antagonist the structure of which was derived from natural agonists. It has activity against LTD_4 induced contractions of guinea-pig trachea[85] and is more potent than the acetophenone analogs.



SKF 104353

11

2.5.3. *Miscellaneous*:

WY 48 252, ICI 204 219, ICI 198 615 and ONO RS 411 (Fig. 6) are structurally diverse antagonists. ICI 204 219 is the most active antagonist against LTD_4-induced contraction of guinea pig trachea.[89] It shows a high preference for LTD_4/LTE_4 receptors and does not have any activity against LTC_4-induced contractions.

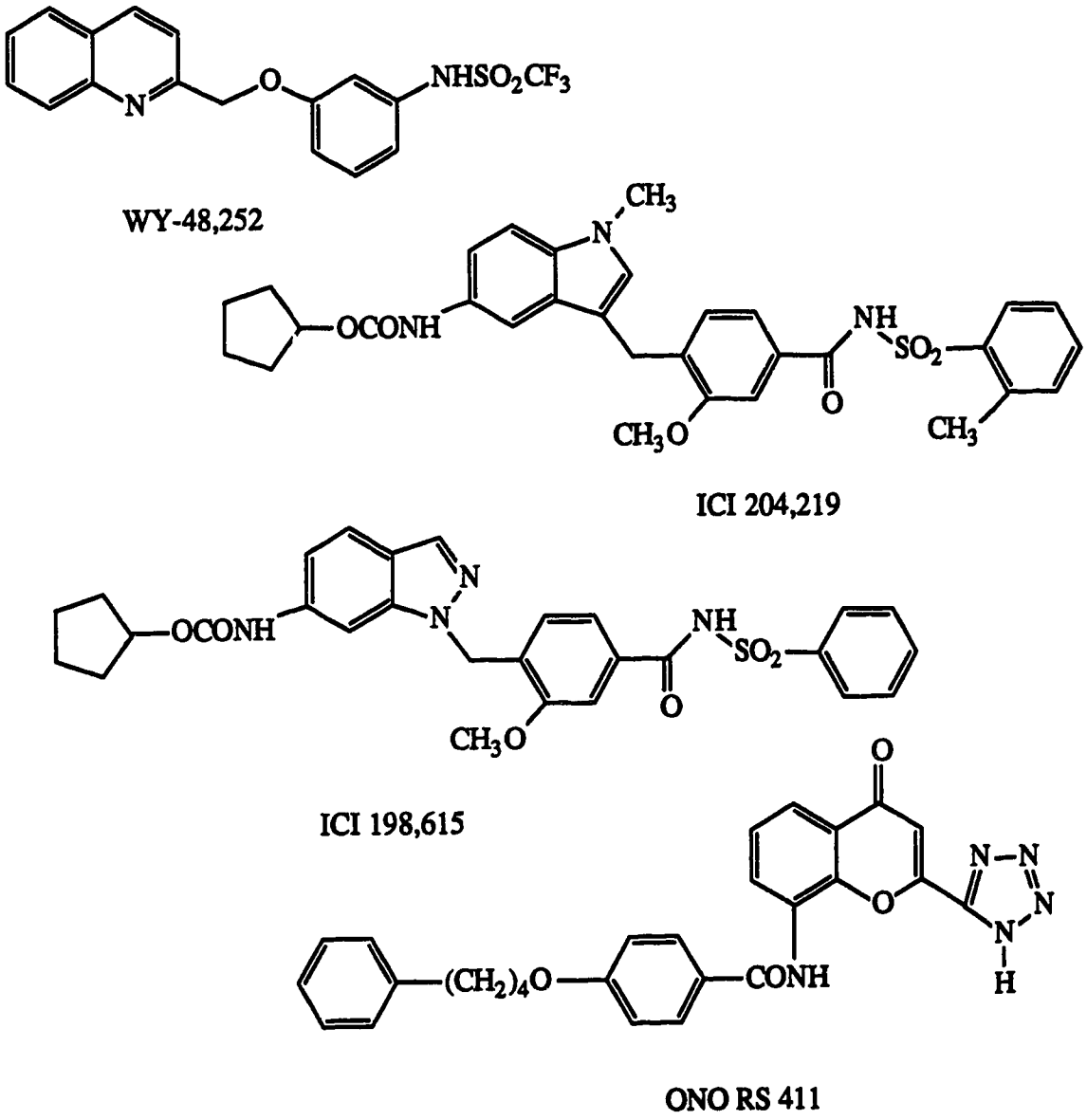


Fig. 6: Miscellaneous antagonists

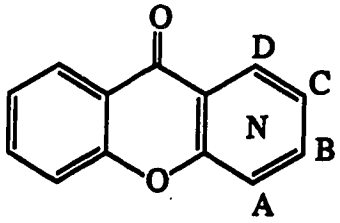
2.6. Drug development potential of leukotriene inhibitors and/or receptor antagonists:

Leukotrienes play a major role in many disease processes such as inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, cutaneous allergic reactions, psoriasis, asthma and adult respiratory distress syndrome. Therefore drugs which can act

as leukotriene inhibitors and/or receptor antagonists may become useful in the treatment of these conditions.[1,2,3,25,28]

3.0 Introduction to benzopyranopyridines:

Benzopyranopyridines, commonly known as azaxanthones, can be classified into four different types according to the position of the nitrogen in the pyridine ring.



Position of Nitrogen

A	5H-[1]benzopyrano[2,3-b]pyridin-5-one
B	5H-[1]benzopyrano[2,3-c]pyridin-5-one
C	10H-[1]benzopyrano[3,2-c]pyridin-10-one
D	10H-[1]benzopyrano[3,2-b]pyridin-10-one

Fig. 7: General structure of benzopyranopyridines

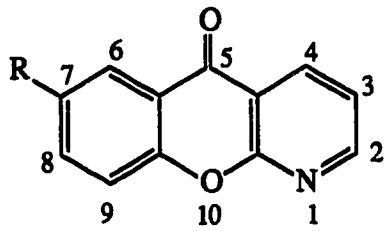
3.1. Pharmacology of benzopyranopyridines:

The patent literature describes a number of pharmacologically active benzopyranopyridines but for many of these compounds no detailed pharmacological data are included.

3.1.1. *Pharmacology of 5H-[1]benzopyrano[2,3-b]pyridin-5-one derivatives:*

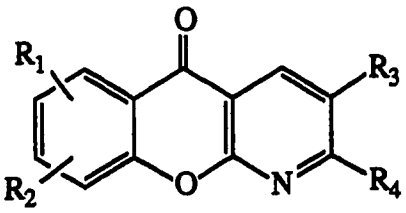
Various substituted 5H-[1]benzopyrano[2,3-b]pyridin-5-ones (12) have been studied. Compounds with R=carboxylic acid, alkyl, ester, ketone, hydroxyalkyl,

alkoxyalkyl and aminoalkyl substituents have been reported to possess antiallergic, anti-inflammatory or diuretic activity. [90-93]



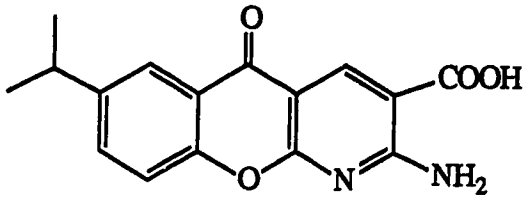
12

Other substituted 5H-[1]benzopyrano[2,3-b]pyridin-5-ones of general structure (13) have been shown to exhibit antiallergic, antiasthmatic and bronchodilating properties in which R_1, R_2=H, alkyl, halo, keto, nitro, hydroxy, COOH, CN, CHO; R_3=H, CN, COOH; R_4=alkyl, aryl, COOH, OH, alkoxy, NH_2.[94-99]



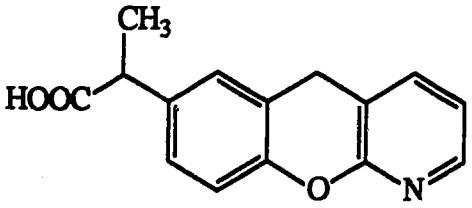
13

A number of 5-oxo-5H[1]benzopyrano[2,3-b]pyridine-3-carboxylic acids have been synthesized and evaluated for their antiallergic activity by Takeda Chemical Industries, Ltd.[100-102] The most promising compound in this series is Amoxanox {AA-673, 2-amino-7-(1-methylethyl)-5-oxo-5H-[1]benzopyrano[2,3-b]pyridine-3-carboxylic acid} (14), which is undergoing clinical trials. In experimental animal models of asthma, the compound inhibited IgE- and IgG-mediated asthma, and also inhibited bronchconstriction.



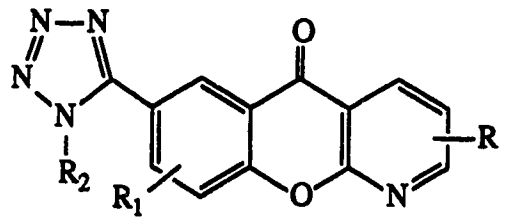
14

A series of benzopyranopyridinyl acetic acid and propionic acid derivatives have been found to show anti-inflammatory activity.[103] The most potent compound in this series is 2-(5H-[1]benzopyrano[2,3-b]pyridin-7-yl)propionic acid (15) which is now marketed under the name pranoprofen. This compound is structurally related to numerous NSAIDs which are currently on the market and are mainly CO inhibitors (e.g. ibuprofen).

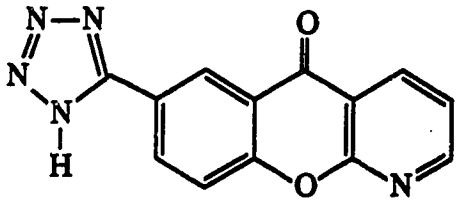


15

When tetrazole is present on the benzene ring (16) the compounds show anti-allergic, antiasthmatic, antihistaminic, anti-inflammatory and antidiuretic activities[104-110]; where R=H, Ph, substituted Ph, halogen, alkoxy, alkyl; R_1=Me, Cl, OMe, H; R_2=H, Me, allyl, vinyl, CH_2COOH, $Me_2NCH_2CH_2$, hydroxyalkyl. The most active compound in this series is (17) which is 5 times as active as disodium chromoglycate (DSCG). DSCG is used for the treatment of chronic asthma.

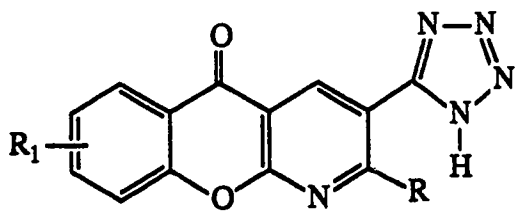


16

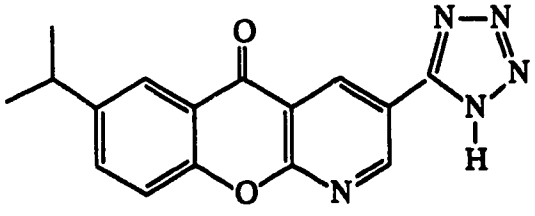


17

Compounds having tetrazolyl substituents on the pyridine ring (18) [where R=H, NH_2, OH, NHOMe; R_1=H, alkyl, alkylamino, aryl, alkoxy, halogen, NO_2, COOH, OH] (17) show bronchodilating and antiallergic activities.[101,104,105]

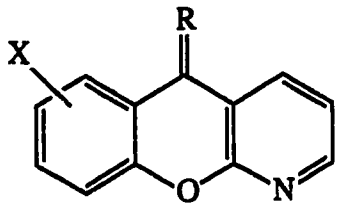


18



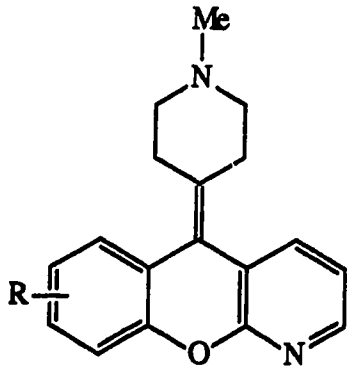
19

The most promising compound in this series is (19). It has ID_{50} (50% inhibition dose) value of 0.0096 mg/Kg in the rat PCA (passive cutaneous anaphylaxis) test and is 145 times as active as DSCG.[101]



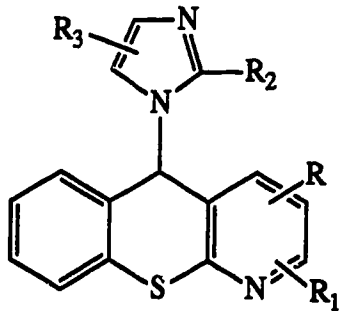
20

A series of compounds with general structure (20) [X is H, halogen, alkyl, alkoxy and R=quinuclidylidene, 1-methyl-4-piperidylidene, 1-methyl-3-piperidylmethylidene, 1-ethyl-3-piperidylidene] have been studied for their bronchodilating and antihistaminic activities.[111,112] Of considerable interest in this series are compounds (21) [R=H, Cl, F, CH_3, OCH_3, t-Bu] because they show both bronchodilating and antihistaminic properties.



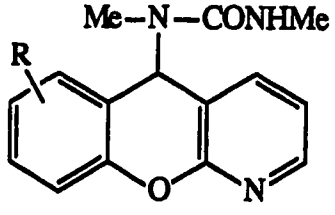
21

Compound (21) relaxes the bronchospasm induced by anaphylaxis in the isolated perfused lung of guinea pig and will protect against histamine both *in vitro* and *in vivo*.

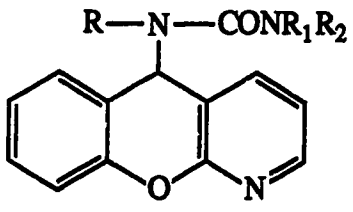


22

Compounds with general structure (22) have been found to show antiulcer activity at 30 mg/kg in rat, where R, R_1=H, halo, alkyl, alkoxy, cyano and R_2,R_3=H, alkyl, Ph, aminoalkyl.[113]



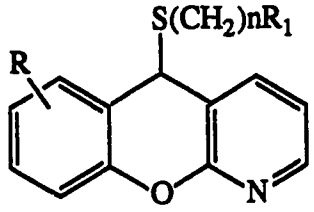
23



24

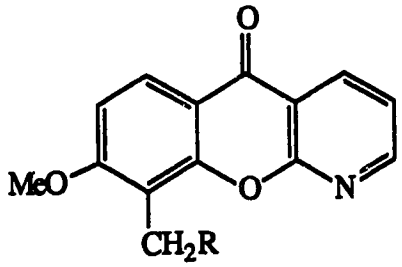
5H-[1]Benzopyrano[2,3-b]pyridin-5-ylurea (23) [R=H, halogen, NO_2, methyl, methoxy] and (24) [R=H or CH_3; -NR_1R_2=-NH_2, -$NHCH_3$, -$N(CH_3)_2$, morpholino, 4-

methyl-1-piperazinyl have been found to show antisecretory and antiulcer activity.[114] Some of the compounds showed activity better than or equal to cimetidine. Unlike cimetidine these compounds are much more potent following intravenous administration than when given orally. Oral activity was reported only at higher doses.



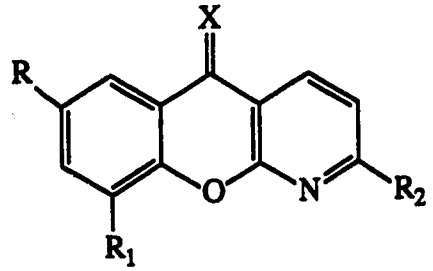
25

A series of 5-[(aminoalkyl)thio]-5H-[1]benzopyrano[2,3-b]pyridines (25) where R_1= amino, dimethylamino, morpholino, piperidino and R=H, OCH_3 possessing antisecretory activity in both rat and dog have been reported.[115]



26

5H-[1]benzopyrano[2,3-b]pyridin-5-one derivatives (26) [R=disubstituted N alkyl, piperidino, morpholino] have analeptic activity.[116]

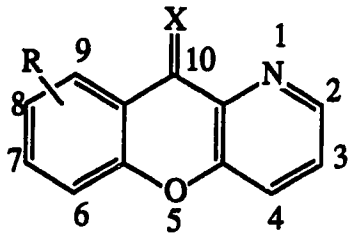


27

Compound (27) [R, R_1=H, Me, Ph, halogen; R_2=H, Me; X=alkylidene] shows CNS activity[117] and details of pharmacological activity have not been reported.

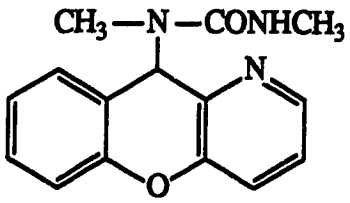
3.1.2. *Pharmacology of 10H-[1]benzopyrano[3,2-b]pyridin-10-one derivatives:*

A series of 10H-[1]benzopyrano[3,2-b]pyridin-10-one derivatives (28) where R=H, F or CH_3; X=1-methyl-4-piperidyl, 1-ethyl-4-piperidyl, 1-benzyl-4-piperidyl, 1-isopropyl-4-piperidyl and quinuclidyl have been studied for their bronchodilating and antihistaminic properties.[111,112]



28

10H-[1]Benzopyrano[3,2-b]pyridin-10-yl urea (29) has been found to show antisecretory and antiulcer activity.[114]

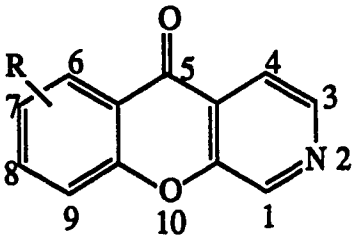


29

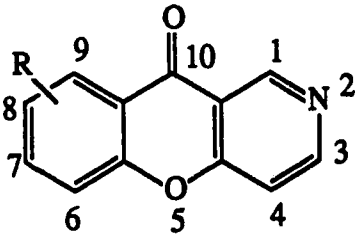
Compared to its 1-aza analog, (23), this compound is less active.

3.1.3. *Pharmacology of 5H-[1]benzopyrano[2,3-c]pyridin-5-one and 10H-[1]benzopyrano[3,2-c]pyridin-10-one derivatives:*

A number of 5H-[1]benzopyrano[2,3-c]pyridin-5-one (30A) and 10H-[1]benzopyrano[3,2-c]pyridin-10-one derivatives (30B) have been found to show antiallergic and antitumor activities[98, 118, 119] but detailed data were not provided.

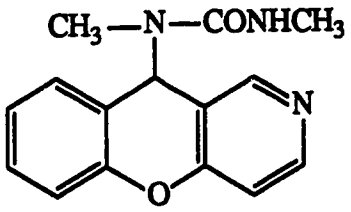


30A



30B

R=CN, COOH, $CONH_2$, tetrazol-5-yl .

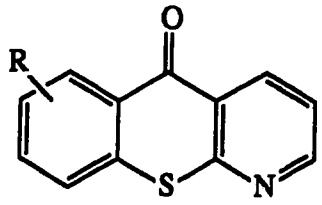


31

Compound (31) was also studied for antisecretory and antiulcer activity but unlike its analogs, (23) and (29), it was found to be inactive.[114]

3.2. Pharmacology of benzothiopyranopyridine derivatives:

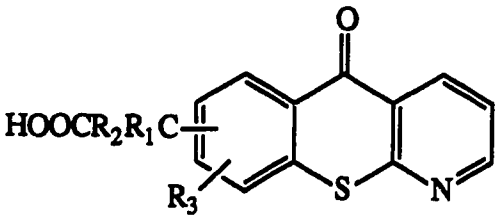
A number of pharmacologically active benzothiopyranopyridines have also been reported in the patent literature but, as for benzopyranopyridines, detailed pharmacological data was not provided.



32

Several derivatives of 5H-[1]benzothiopyrano[2,3-b]pyridin-5-one (32) {R=COOH, CN, CHO, alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl } have been found to show antiallergic, anti-inflammatory, diuretic and antitumor activities. [90, 93, 98, 119]

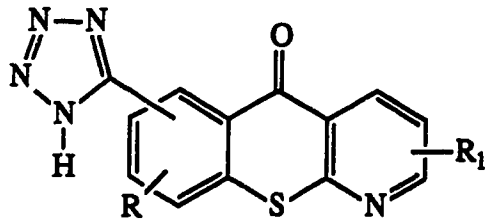
Several acid derivatives (33) show anti-inflammatory, antirheumatic, analgesic and antipyretic properties[120] while tetrazol-5-yl derivatives (34) exhibit antiallergic, antitumor, anti-inflammatory, diuretic and antihistaminic activities.[98,107,109,110]



33

R_1, R_2=H, alkyl

R_3=H, halo, alkoxy, alkyl

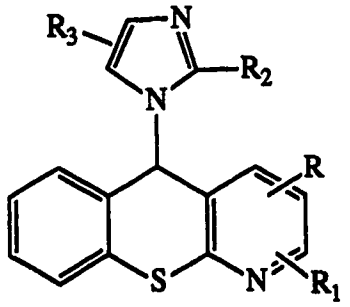


34

R=H,halo,Me,COOH, alkoxy

R_1=H, alkyl, Ph, p-ClC_6H_4-

When an imidazole ring is present at the C-5 position the compounds (35) exhibit antitumor activity at an oral dose of 30 mg/kg.[110]

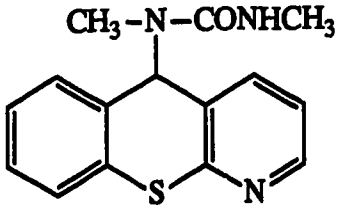


35

R, R_1=H, halo, alkyl, alkoxy, NO_2, CN

R_2, R_3=H, alkyl, Ph

5H-[1]Benzothiopyrano[2,3-b]pyridin-5-ylurea (36) was screened for its antisecretory and antiulcer activity and was found to be more potent than the oxygen analog (23). When sulphur is oxidized to the sulfoxide, the compound loses its activity.[115]

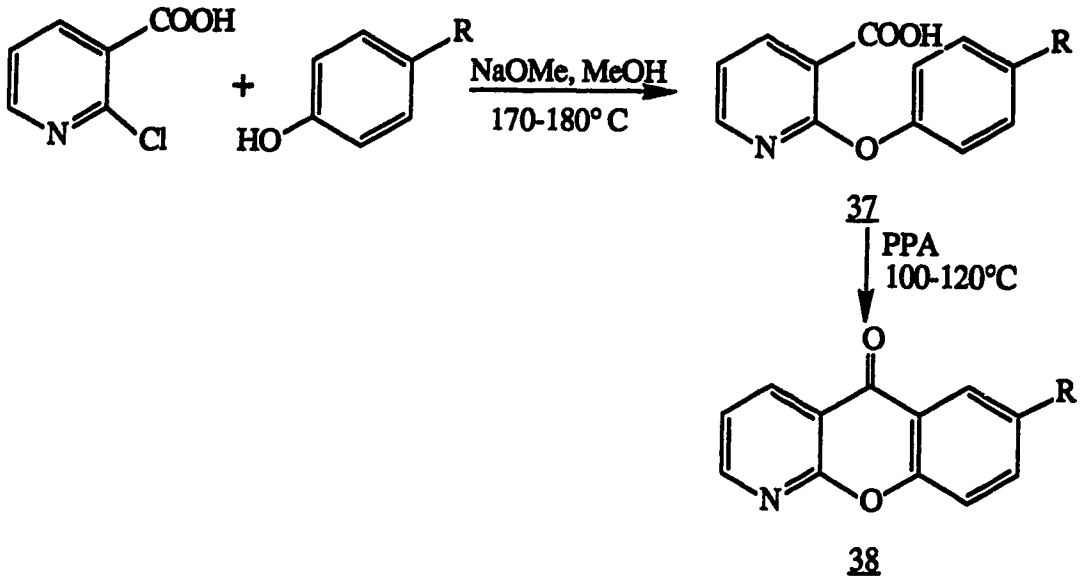


36

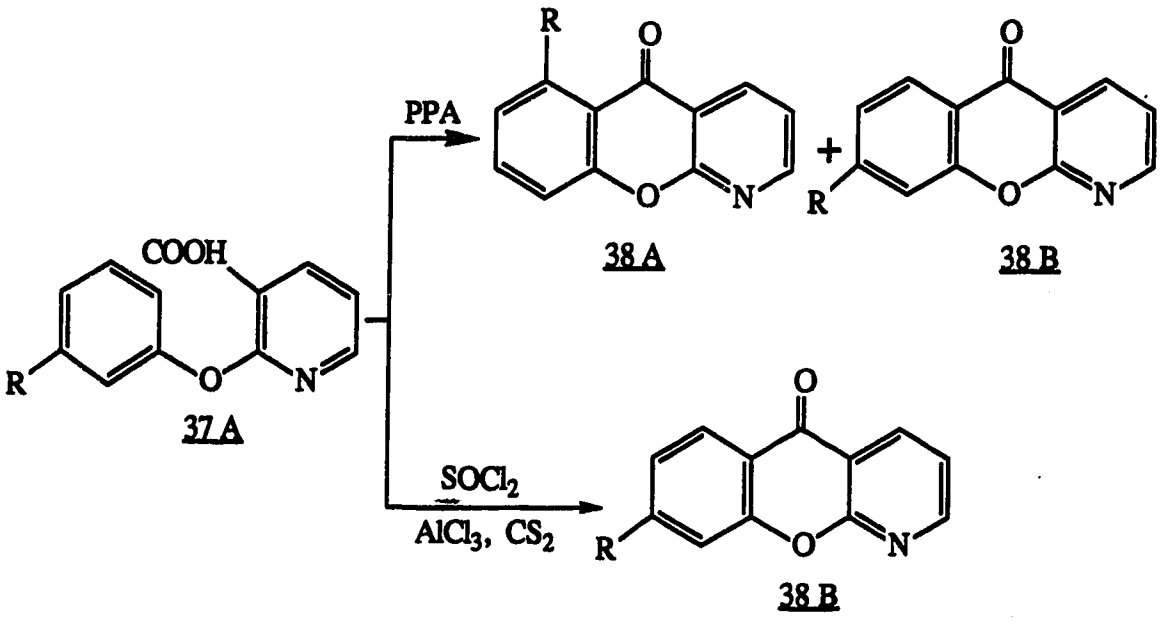
3.3. Chemistry of benzopyranopyridines:

3.3.1. *Synthesis of 5H-[1]benzopyrano[2,3-b]pyridin-5-one (38):*

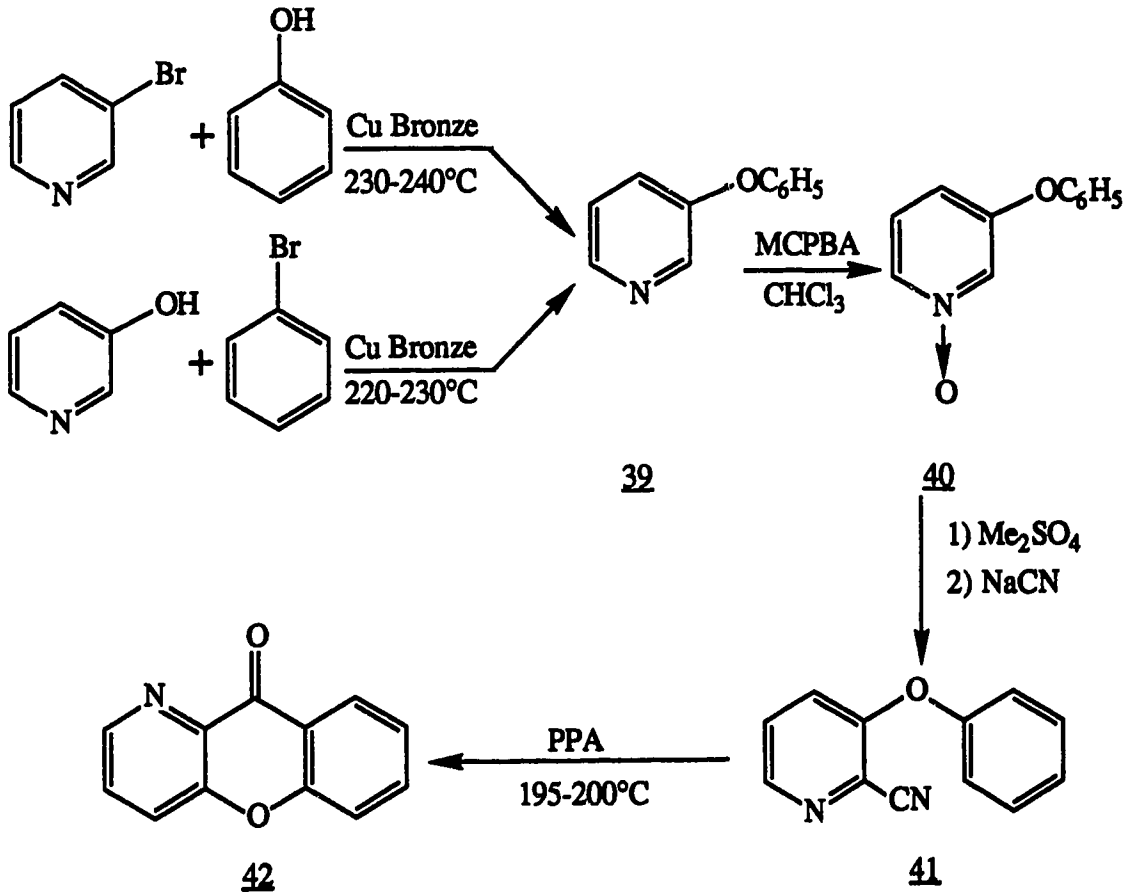
5H-[1]Benzopyrano[2,3-b]pyridin-5-one (38) [R=H, Cl, F, CH_3] ring system has been synthesized from 2-chloronicotinic acid in two steps.[111,112] The first step involves condensation of 2-chloronicotinic acid with phenol followed by cyclization with polyphosphoric acid (PPA). PPA is a better reagent than phosphorus oxychloride for cyclization of p-substituted phenoxy derivative of nicotinic acid as it gives superior yields [e.g. R=H, 98% (mp 178-182°C), R=Cl, 80% (mp 198-200°C)].



With this synthetic approach cyclization of meta-substituted phenoxy-derivative of nicotinic acid (37 A) gave a mixture of 6- and 8-substituted 5H-[1]benzopyrano[2,3-b]pyridin-5-ones (38 A) and (38 B) respectively. However, when the acid (37 A) was converted to its acid chloride and refluxed with $AlCl_3$ in carbon disulphide 8-substituted 5H-[1]benzopyrano[2,3-b]pyridin-5-one (38 B) was isolated.[122]

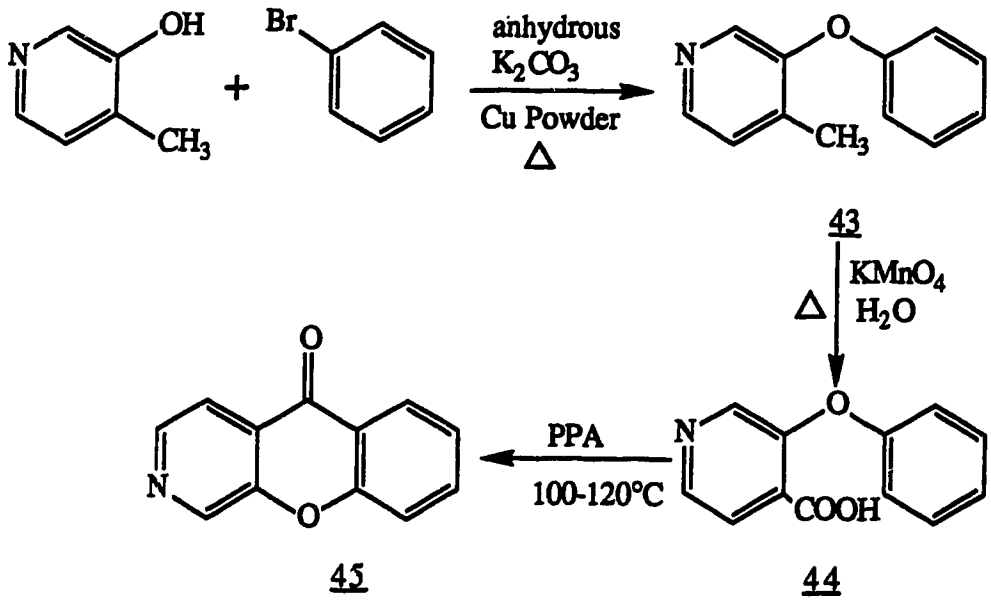


3.3.2. *Synthesis of 10H-[1]benzopyrano[3,2-b]pyridin-10-one (42):*



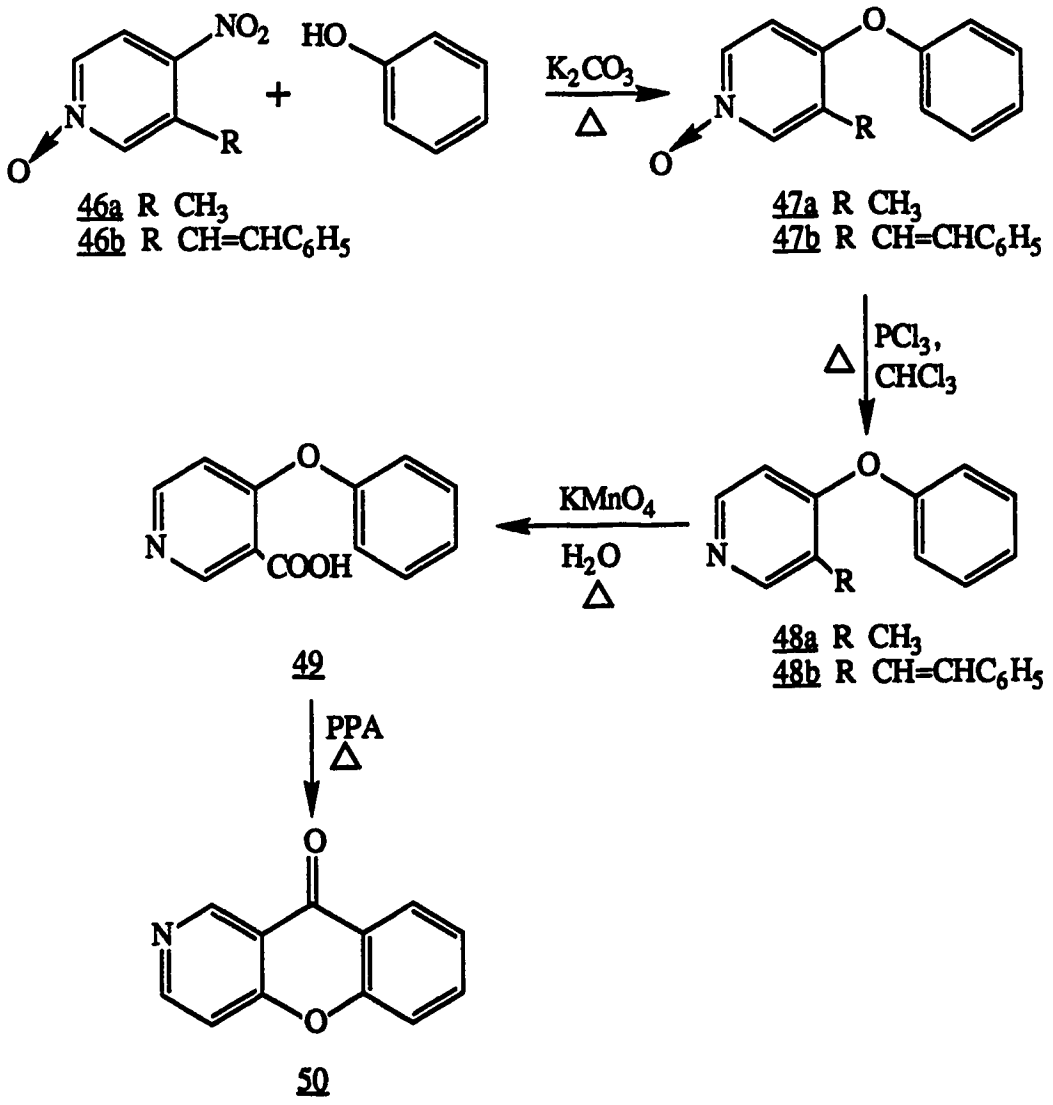
3-Phenoxypyridine (39) can be prepared from 3-bromopyridine and phenol in 59% yield, or alternatively from 3-pyridinol and bromobenzene in 57% yield by Ulmann condensation.[123] 3-Phenoxypyridine (39) was oxidized by meta-chloroperbenzoic acid (MCPBA) to give 3-phenoxypyridine-N-oxide (40) in 70% yield. The 3-phenoxypyridine-N-oxide (40) was warmed with dimethyl sulphate to give the N-methoxy methylsulphate salt which was dissolved in water and added under nitrogen into an aqueous solution of sodium cyanide at 0-5°C to give compound (41) in 53% yield. Direct ring closure of 2-cyano-3-phenoxypyridine gave 10H-[1]benzopyrano[3,2-b]pyridin-10-one (42) in 84% yields (mp 204-205°C).[111]

3.3.3. *Synthesis of 5H-[1]benzopyrano[2,3-c]pyridin-5-one (45):*



3-Phenoxy-4-picoline (43) was obtained by Ulmann condensation of 3-hydroxy-4-picoline with bromobenzene in 70% yield. Oxidation of the methyl group with potassium permanganate gave 3-phenoxyisonicotinic acid (44) in 25% yield. This was then cyclized with PPA to give final product (45) in 91% yield (mp 157-158°C).[111]

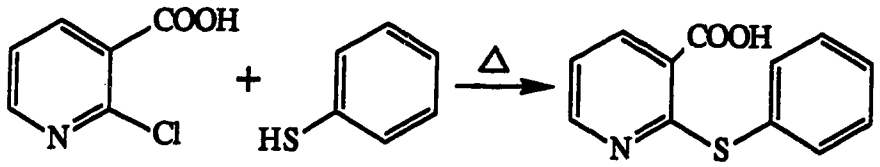
3.3.4. *Synthesis of 10H-[1]benzopyrano[3,2-c]pyridin-10-one (50):*



Phenyl ether (47a) was obtained by displacement of the nitro group from disubstituted pyridine N-oxide (46a)[125] and similarly (47b)[126] was obtained from (46b) in 47% yield. Compounds (47a) and (47b) were N-deoxygenated with PCl_3 in $CHCl_3$ in 79% and 63% yield respectively followed by oxidation with $KMnO_4$ to give 4-phenoxynicotinic acid (49). 4-Phenoxynicotinic acid (49) was cyclized with PPA to give final product (50) in 83% yield (mp 183-185°C).[111]

3.4. CHEMISTRY OF BENZOTHIOPYRANOPYRIDINES

3.4.1. *Synthesis of 5H-[1]benzothiopyrano[2,3-b]pyridin-5-one (52):*



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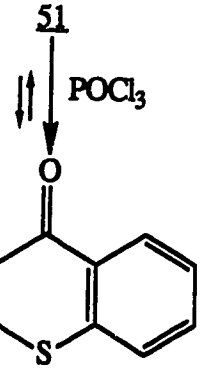
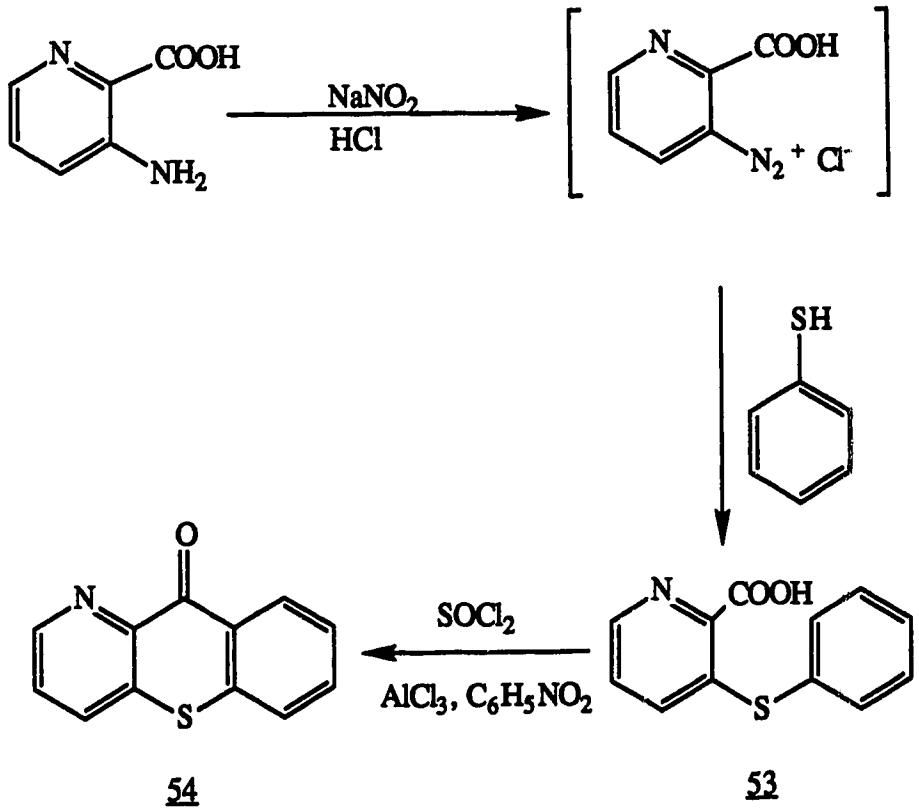


52

2-Chloronicotinic acid was condensed with thiophenol to give 3-carboxy-2-pyridyl phenyl sulphide (51) in 70% yield. 3-Carboxy-2-pyridyl phenyl sulphide was cyclized with phosphorus oxychloride to give 5H-[1]benzothiopyrano[2,3-b]pyridin-5-one (52) in 65% yield (mp 234°C).[127]

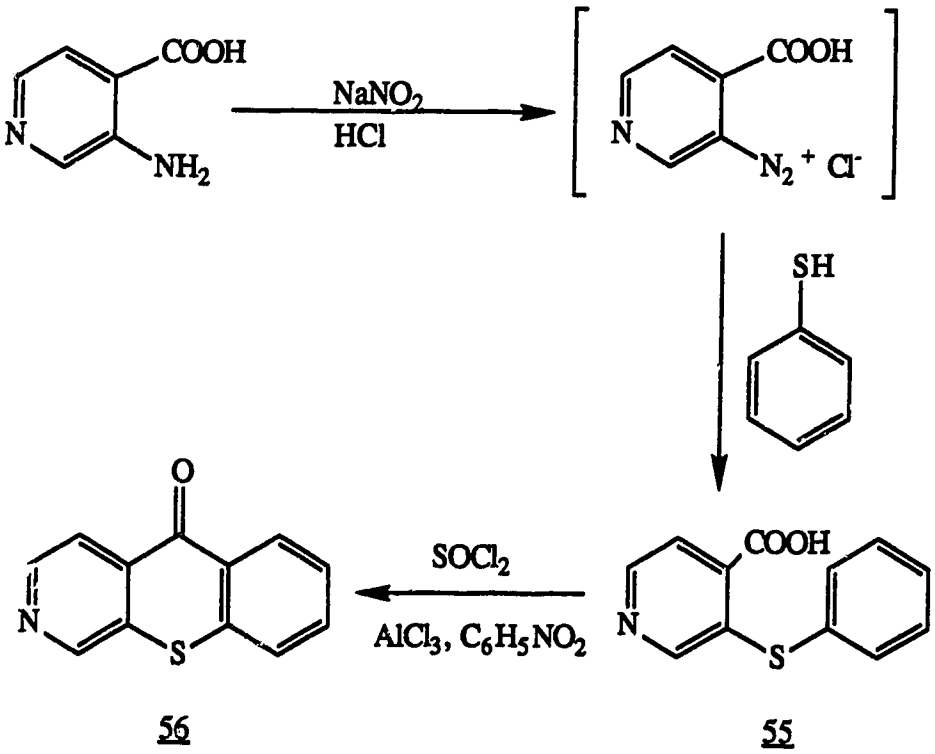
3.4.2. *Synthesis of 10H-[1]benzothiopyrano[3,2-b]pyridin-10-one (54):*



54 53

Diazotized 3-aminopicolinic acid was condensed at 95°C with thiophenol in alkaline solution to give 2-carboxy-3-pyridyl phenyl sulphide (53). This carboxylic acid was converted into the carbonyl chloride which was refluxed in nitrobenzene with aluminium chloride to give cyclized product (54) in 59% yield (mp 224°C).[128]

3.4.3. *Synthesis of 5H-[1]benzothiopyrano[2,3-c]pyridin-5-one (56):*



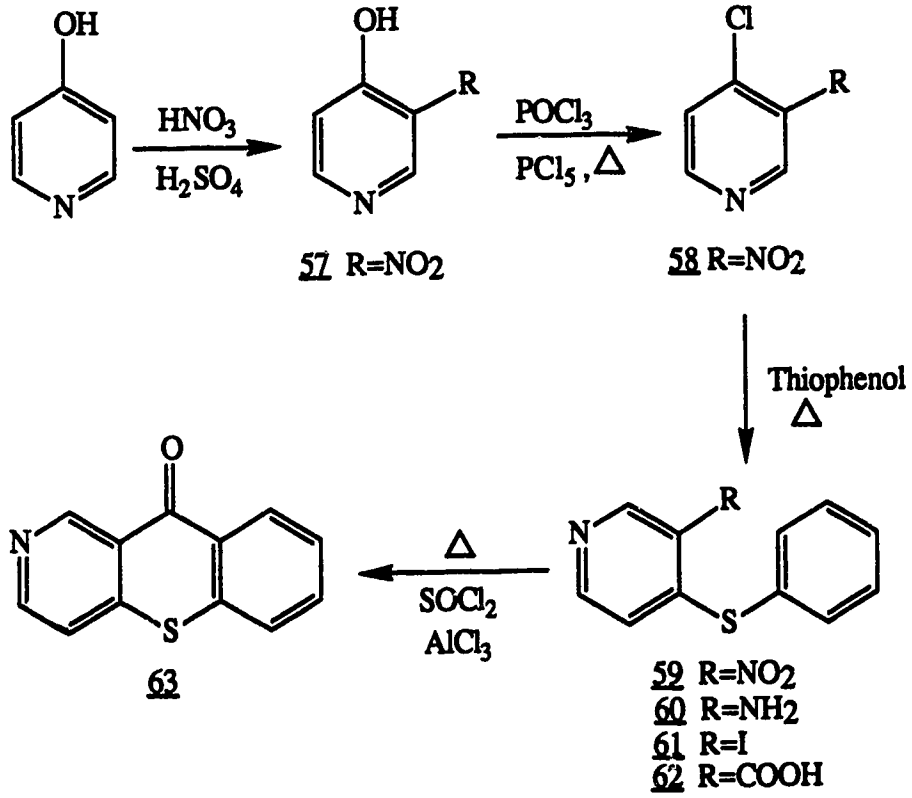
56 55

5H-[1]benzothiopyrano[2,3-c]pyridin-5-one (56)[128] was prepared from 3-amino-isonicotinic acid as reported for 10H-[1]benzothiopyrano[3,2-b]pyridin-10-one (54). 3-aminoisonicotinic acid was first converted into 4-carboxy-3-pyridyl phenyl sulphide (55) in 44% yield which on cyclization gave final product (56) in 72% yield (mp 165°C).

3.4.4. *Synthesis of 10H-[1]benzothiopyrano[3,2-c]pyridin-10-one (63):*

4-Hydroxypyridine was nitrated in 88% yield to give 4-hydroxy-3-nitropyridine (57). Phosphorous oxychloride was added to a mixture of powdered 4-hydroxy-3-nitropyridine (57) and phoshorous pentachloride to give 4-chloro-3-nitropyridine (58) in 82% yield. A cold equimolar mixture of 4-chloro-3-nitropyridine (58) and thiophenol was heated to 20°C to give 3-nitro-4-pyridyl phenyl sulphide (59) in 99% yield which was

reduced by heating with tin in concentrated HCl to give 3-amino-4-pyridyl phenyl sulphide (60) in 58% yield. Diazotization and treatment with potassium iodide in water gave 3-iodo-4-pyridyl phenyl sulphide (61) in 72% yield. A cold solution of 3-iodo-4-pyridyl phenyl sulphide (61) in anhydrous toluene was treated with n-butyl lithium followed by treatment with powdered carbon dioxide at -38°C to give acid (62) in 73% yield. The acid (62) was boiled in thionyl chloride to give the corresponding acid chloride, which on heating at 100°C in nitrobenzene with powdered aluminum chloride, gave the final product in 89% yield (mp 181°C).[129]



OBJECTIVES OF RESEARCH

Arachidonic Acid (AA) is an essential C_{20} unsaturated fatty acid formed from the breakdown of disrupted cell membranes by the enzyme phospholipase. Metabolism of arachidonic acid via cyclooxygenase gives rise to prostaglandins and via lipoxygenase to leukotrienes. Elevated levels of LTs have been reported in inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, cutaneous allergic reactions, psoriasis, adult respiratory distress syndrome and asthma. Therefore drugs which can lower the enhanced concentrations of leukotrienes may be helpful in these conditions.

The literature has several examples of benzopyranopyridine derivatives with antiallergic, antihistaminic and bronchodilating activity. Studies done by Villani et al. showed that 5H-[1]benzopyrano[2,3-b]pyridin-5-one and 10H-[1]benzopyrano[3,2-b]pyridin-10-one are more active and less toxic than 5H-[1]benzopyrano[2,3-c]pyridin-5-one and 10H-[1]benzopyrano[3,2-c]pyridin-10-one. On this basis, a number of 5H-[1]benzopyrano[2,3-b]pyridin-5-one derivatives were synthesized in our laboratory and several of these compounds were found to inhibit cyclooxygenase and/or lipoxygenase pathways in *in vitro* assays.[139] In the studies with 5H-[1]benzopyrano[2,3-b]pyridin-5-one derivatives, it was observed that when the ring oxygen was replaced by sulphur, activity increased by almost ten-fold. These compounds showed LT antagonist activity higher or comparable to standard compounds (nafazatrom and piriprost). Several compounds were also found to exhibit bronchodilating properties.

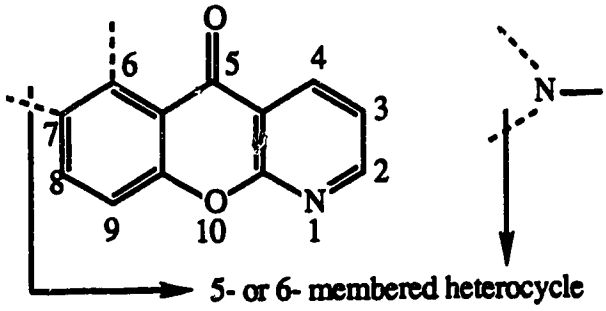
Compounds which showed the most promising pharmacological results were found to possess 5 or 6-membered heterocyclic ring systems, such as imidazole, thiazole and pyridine fused on the benzene ring of 5H-[1]benzopyrano[2,3-b]pyridin-5-one (64). On this basis it was proposed to synthesize similar derivatives of 10H-[1]benzopyrano[3,2-b]pyridin-5-one and benzothiopyranopyridines and make a number of modifications to further explore the structure-activity relationship.

In substituted imidazoles the N-H can be present on either of the two nitrogens in the ring system due to its tautomeric forms. If hydrogen is present at the 1-position (adjacent to carbonyl of benzopyranopyridine) it can undergo hydrogen bonding with the carbonyl oxygen and it could also bind with the receptor site. It was proposed to substitute the N-1 position of the imidazole with different alkyl substituent as these compounds would not undergo intramolecular-hydrogen bonding. Reduction of the carbonyl group would give reduced imidazole which would not undergo intramolecular-hydrogen bonding and this compound would have reduced conformational rigidity.

The thiazole derivative of 5H-[1]benzopyrano[2,3-b]pyridin-5-one was also found to inhibit the 5-lipoxygenase pathway. On this basis it was proposed to synthesize thiazole derivatives of 10H-[1]benzopyrano[3,2-b]pyridin-10-one and also to acetylate the strongly electron-donating amino group on the thiazole ring to a moderately electron-donating acetamido group.

Pyridine derivatives also increased the activity of the 5H-[1]benzopyrano[2,3-b]pyridin-5-one. It was proposed to synthesize a similar derivative in the 10H-[1]benzopyrano[3,2-b]pyridin-10-one series and replace the pyridine ring with pyrazine.

A number of thiourea derivatives of general structure (65) were found to be potent lipoxygenase inhibitors.[139] It was proposed to synthesize similar derivatives of 10H-[1]benzopyrano[3,2-b]pyridin-10-ones and their sulphur analogs.



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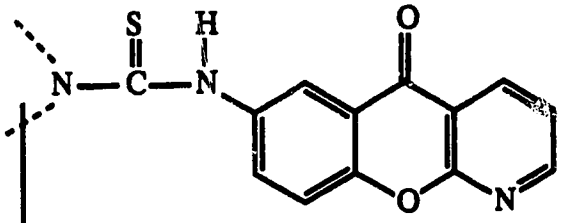


65

RESULTS AND DISCUSSION

4.0. Nomenclature:

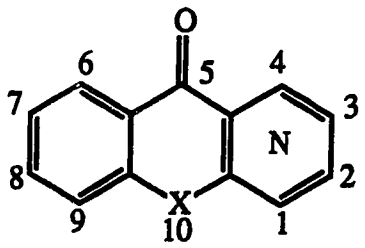
For convenience, compounds (66a-d) will be designated as 1-azaxanthone, 4-azaxanthone, 1-azathioxanthone and 4-azathioxanthone respectively. The chemical abstract names for these compounds are as follows:

compound (66a): 5H-[1]benzopyrano[2,3-b]pyridin-5-one

compound (66b): 10H-[1]benzopyrano[3,2-b]pyridin-10-one

compound (66c): 5H-[1]benzothiopyrano[2,3-b]pyridin-5-one

compound (66d): 10H-[1]benzothiopyrano[3,2-b]pyridin-10-one



66

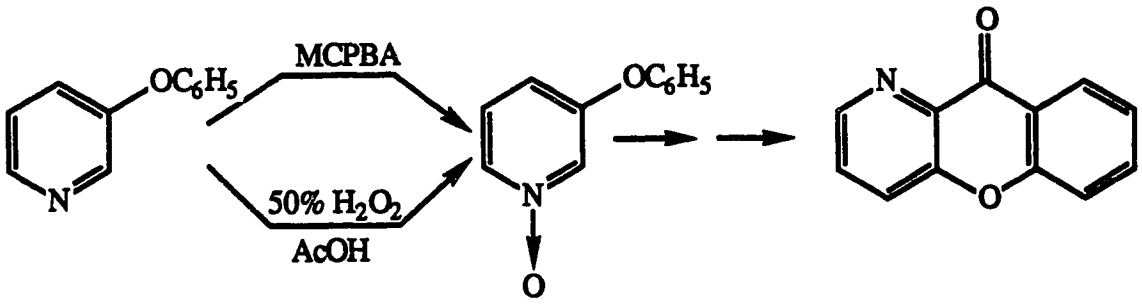
	X	Position of Nitrogen
a)	O	1
b)	O	4
c)	S	1
d)	S	4

Fig. 8: General structure of azaxanthones or azathioxanthones

5.0. Modification in synthesis of 4-azaxanthone (42):

Although 4-azaxanthone (42) was synthesized as described by Villani,[111] a modification in the oxidation of 3-phenoxypyridine (39) to 3-phenoxypyridine-N-oxide (40) was made. In Villani's method, oxidation with m-chloroperbenzoic acid gave a yield of 70% and involved washing with 10% KI, 20% $Na_2S_2O_7$, 10% NaOH and H_2O.

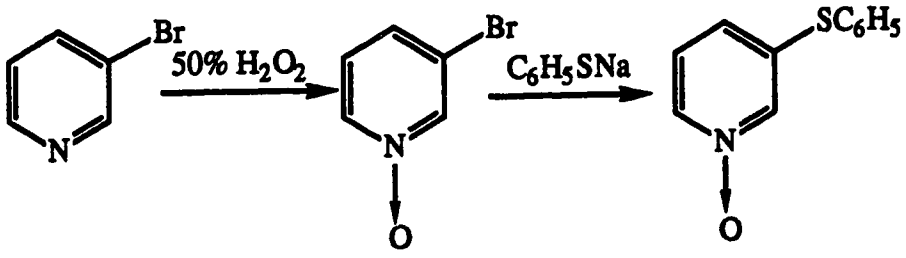
Improvement over this method was obtained by oxidizing with 50% H_2O_2 in glacial acetic acid[130] which gave a yield of 92%.



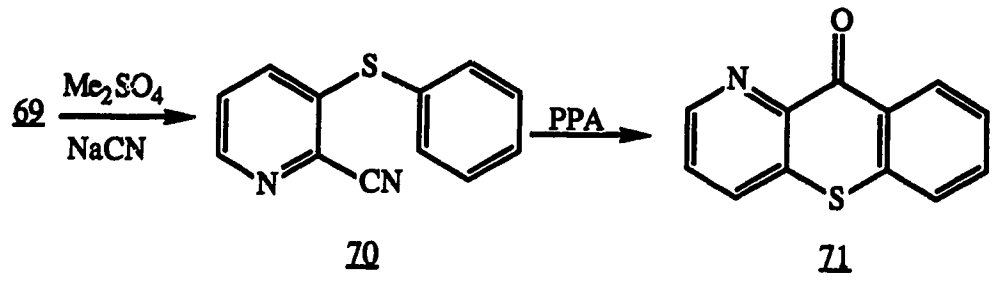
39 40 42

6.0. Synthesis of 4-azathioxanthone (71):

The synthesis of 4-azathioxanthone (71) was reported by Kruger and Mann[128] in 28% yield from 3-aminopicolinic acid. Diazotized 3-aminopicolinic acid was condensed with thiophenol to give 2-carboxy-3-pyridyl phenyl sulphide. 2-Carboxy-3-pyridyl phenyl sulphide was cyclized by refluxing in nitrobenzene with aluminium chloride to give 4-azathioxanthone (71). However, in our own hands, diazotization of 3-aminopicolinic acid followed by condensation with thiophenol resulted in recovery of 3-aminopicolinic acid instead of the desired product, 2-carboxy-3-pyridyl phenyl sulphide. However, 4-azathioxanthone was prepared sucessfully from 3-bromopyridine (67) in an overall yield of 37% yield.

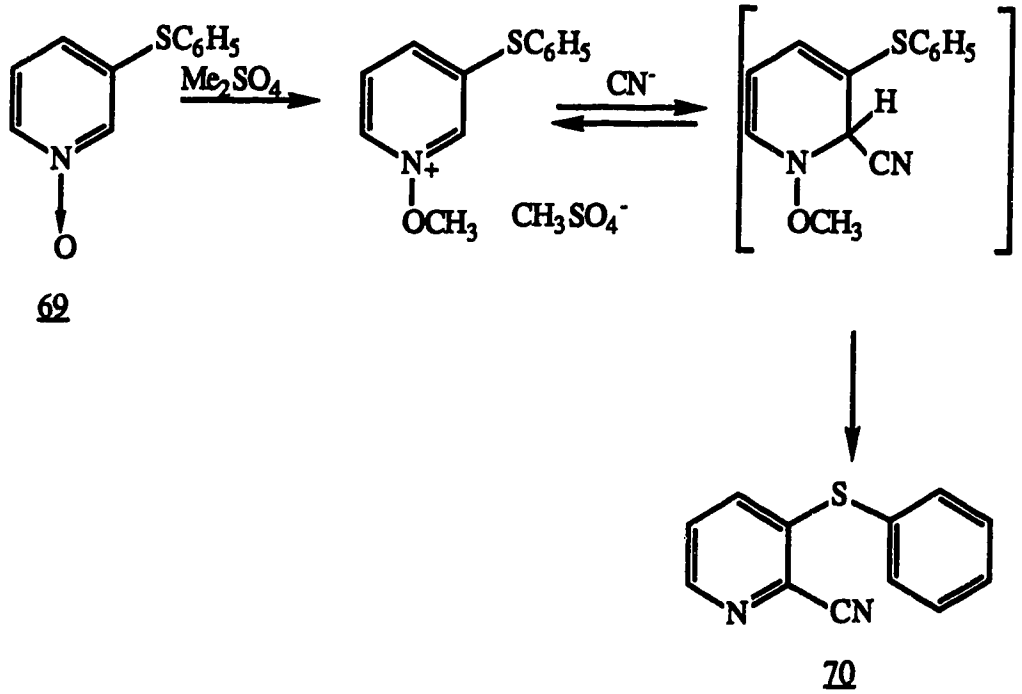


67 68 69



70 71

3-Bromopyridine (67) was oxidized with 50% H_2O_2 in glacial acetic acid to give 3-bromopyridine-1-oxide (68)[130] which was condensed with sodium thiophenoxide in a sealed tube to give 3-(phenylthio)pyridine-1-oxide (69).[131, 132] 3-(Phenylthio)pyridine-1-oxide (69) on heating with dimethyl sulphate gave the N-methoxymethyl sulphate salt of (69). This salt, without purification, was dissolved in water and added to an aqueous solution of sodium cyanide to give 2-cyano-3-(phenylthio)pyridine (70).[124] The driving force of this reaction would be the loss of alkoxide ion with the formation of aromatic ring system as shown in Fig. 9.



69 70

Fig. 9: Mechanism of synthesis of 2-cyano-3-(phenylthio)pyridine

2-Cyano-3-(phenylthio)pyridine (70) was conveniently cyclized in PPA to give the final product (71) in 82% yield.[111] Although there is an improvement in the overall yield, this

method is more tedious and time-consuming as compared to the one reported by Kruger and Mann.

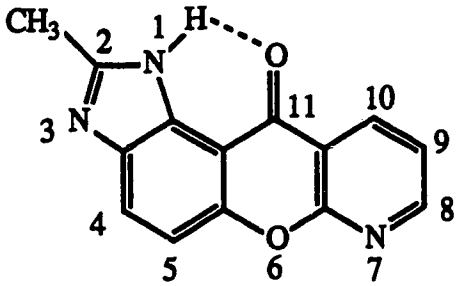
7.0. Modification of azaxanthones:

7.1. Spectral data:

For sake of convenience spectral data of only 4-azaxanthone derivatives will be discussed in this chapter and rest of the data is given in experimental. The ^1H nmr integrations of all peaks were consistent with the expected number of protons.

7.2. Benzimidazol-11-ones:

Pyridopyranobenzimidazolone (72) synthesized by another investigator in our laboratory[139] was found to inhibit contraction of guinea pig isolated trachea by more than 50% at 10^{-6}M concentration when challenged with arachidonic acid and was found to be a better leukotriene inhibitor than standard compounds, nafazatrom and piriprost (see page 84 for assay methods). Based on this preliminary pharmacological result, 4-azaxanthone and azathioxanthone analogs (78-80, 82-84) were synthesized and evaluated.



72

Hydrogen on the imidazole ring component of (72) can be present at either 1- or 3-position. If hydrogen is present at N-1, it can undergo hydrogen bonding with oxygen at C-11 position. To evaluate the role of hydrogen in activity several derivatives were synthesized in which the N-1 hydrogen was replaced with methyl (86-87), ethyl (89-91) or

benzyl (93-95) groups. To further evaluate the role of hydrogen-bonding, the carbonyl group was reduced to -CH_2- to give methylpyridopyranobenzimidazole (100) (section 7.2.6.). This compound can not undergo intramolecular-hydrogen bonding. With the reduction of C=O (sp^2 carbon) to CH_2 (sp^3 carbon) the molecule would lose conformational rigidity present in benzimidazoles which could effect the activity.

7.2.1. *Synthesis of pyridopyrano-/thiopyranobenzimidazolones (78-80):*

7-Amino-4-azaxanthone (73a), 7-amino-4-azathioxanthone (73b) and 7-amino-1-azathioxanthone (73c) were prepared from their 7-nitro precursors by reduction with stannous chloride in concentrated HCl.[111] Acetylation of amines (73a-c) was carried out with acetic anhydride to give the corresponding 7-acetamido derivatives (74a-c). 7-Acetamido-4-azaxanthone (74a) was nitrated with KNO_3 in H_2SO_4 to give 7-acetamido-6-nitro-4-azaxanthone (75a). This was found to be the only product although the C-5 carbonyl is expected to deactivate the C-6 position. The position of nitration was established by ^1H nmr and assignments were made by comparing chemical shift values with corresponding 7-acetamidoazaxanthones. If substitution was at C-8 position, ^1H nmr would have shown doublet due to para coupling of C-6 and C-9. Substitution at C-9 would show doublet due to meta coupling for C-6 and C-8 protons. The ^1H nmr of compound (75a) showed a doublet (J=9.6 Hz) at δ 8.14 for C_8-H and a doublet for C_9-H is buried under the multiplet at δ 7.98. The value of the coupling constant indicates that these proton are adjacent to each other. Nitration of 7-acetamidoazathioxanthones (74b) and (74c) showed similar results. The spectrum of compound (75b) showed doublets (J=9.4 Hz) at δ 8.04 and δ 8.14 for C_9-H and C_8-H respectively. Compound (75c) also

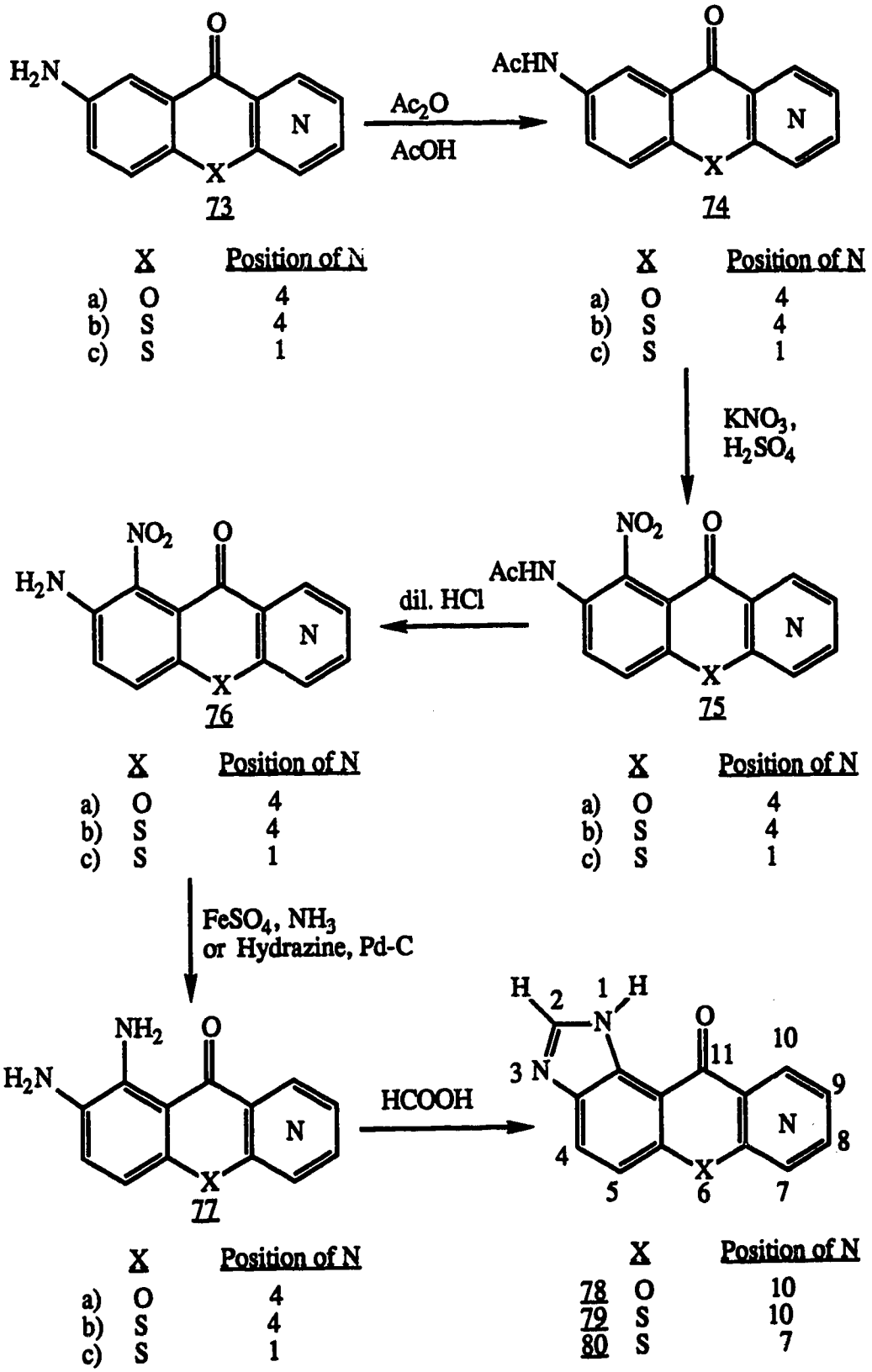
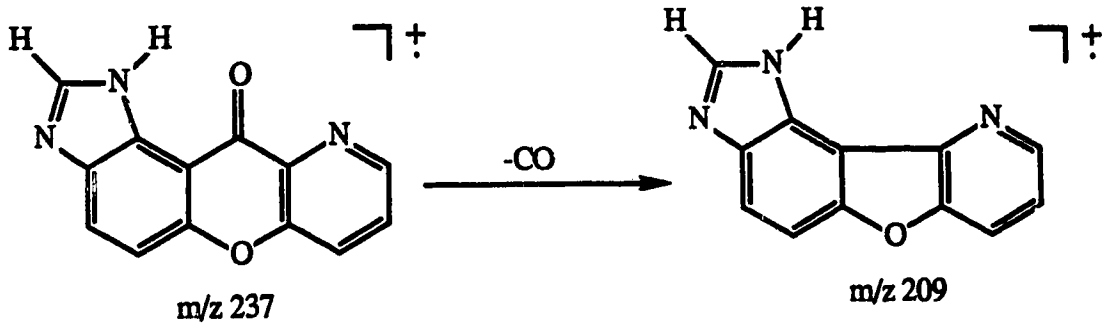


Fig.10: Synthesis of pyridopyrano-/thiopyranobenzimidazol-11-ones

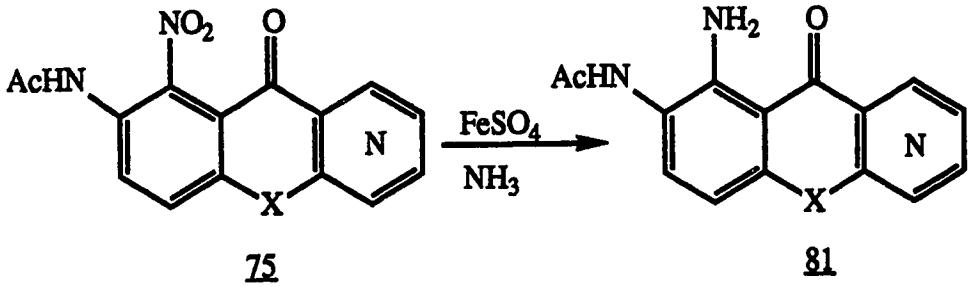
showed doublets (J=8.4 Hz) for C9-H at δ 8.12 and for C8-H at δ 8.22. Previous studies done in our laboratory showed that nitration of 7-acetamido-1-azaxanthone gave 7-acetamido-6-nitro-1-azax[illegible] eatment with KNO_3 in H_2SO_4, while nitration of 7-acetamido-1-azaxanthene [illegible]ical conditions gave 7-acetamido-8-nitro-1-azaxanthene. This [illegible] the ketone group of azaxanthone influences the substitution of nitro at the C-6 position.[139]

Hydrolysis of 7-acetamido-6-nitro-4-azaxanthone (75a) with 5% aqueous HCl solution gave 7-amino-6-nitro-4-azaxanthone (76a). Hydrolysis of azathioxanthones (75b) and (75c) with 5% HCl resulted in incomplete reaction (40% and 45% yields respectively) but with 10% HCl yields of 85% and 90% were obtained. 7-Amino-6-nitro-azaxanthone/azathioxanthones (76a-c) were reduced with $FeSO_4$ and NH_4OH to give 6,7-diaminoazaxanthone/azathioxanthones (77a-c) in 81%, 51% and 50% yields respectively. However, by reducing 7-amino-6-nitroazathioxanthones (76a-b) with hydrazine hydrate in 10% Pd on charcoal improved yields of (77a-b) (56% and 58% respectively) were obtained. Compounds (77a-c) were cyclized by refluxing in formic acid to give products (78-80) in 69%, 61% and 70% yields respectively.

The 300 MHz ^1H nmr (δ) spectrum of (78) showed a doublet at 7.54 (J=9.1 Hz) which was assigned to C_4-H. A doublet of doublets at 7.94 (J=8.3, 4.0 Hz) was attributed to C_8-H. A multiplet at 8.26 was assigned to a doublet of C_5-H and a doublet of doublets of C_7-H. A singlet at 8.36 was due to C_2-H. A doublet at 8.84 (J=4.0 Hz) was assigned to C9-H. A singlet at 13.2 was due to the NH and was exchangeable with D_2O. The i.r. spectrum showed absorptions (cm^{-1}) at 3402 (NH) and 1663 (CO). The EI mass spectrum exhibited major ions of m/z (relative intensity): 238 (15%), 237 (100%) and 209 (12%). The molecular ion loses CO to give the ion of m/z 209. The high resolution mass spectrum showed a molecular ion peak corresponding to $C_{13}H_7N_3O_2$ [237.0539 found; 237.0538 calculated]. The structures of compounds (79) and (80) were similarly confirmed from spectral data.



7.2.2. ***Synthesis of 2-methylpyridopyrano-/thiopyranobenzimidazol-11-ones (82-84):***

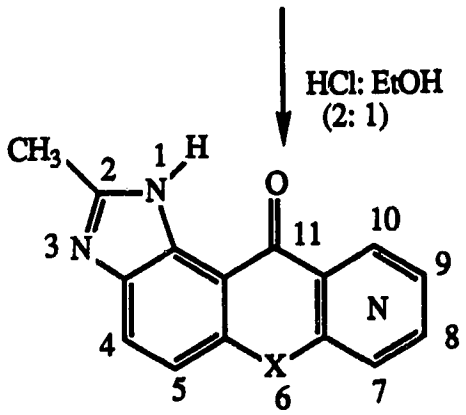


75

	X	Position of N
a)	O	4
b)	S	4
c)	S	1

81

	X	Position of N
a)	O	4
b)	S	4
c)	S	1



	X	Position of N
82	O	10
83	S	10
84	S	7

7-Acetamido-6-nitro-4-azaxanthone (75a) and 7-acetamido-6-nitro-1-azathioxanthone (75c) were reduced with $FeSO_4/NH_4OH$ to give the corresponding 7-acetamido-6-amino-4-azaxanthone (81a) in 70% yield and 7-acetamido-6-amino-1-azathioxanthone (81c) in 78% yield. Improved yields were obtained by reducing (75a) and (75c) with NH_2NH_2 in the presence of 10% Pd on carbon to give (81a) and (81c) in 96% and 82% yields respectively. 7-Acetamido-6-nitro-4-azathioxanthone (75b) was reduced with NH_2NH_2 in the presence of 10% Pd on carbon to give (80b) in 68% yield. 7-Acetamido-6-aminoazaxanthone/azathioxanthones (81a-c) were cyclized by refluxing in a mixture of HCl: EtOH (2:1) to give 2-methylpyridopyrano-/thiopyranobenzimidazolones (82-84).

The structures of these benzimidazolones (82-84) have been confirmed from spectral data. For example, the ^1H nmr (δ) spectrum of (82) exhibited a singlet at 2.60 which has been attributed to C_2-methyl group. The doublet at 7.48 (J=8.5 Hz) was due to C_5-H. A doublet of doublets at 7.94 (J=8.0, 4.0 Hz) was assigned to C_8-H. A doublet at 8.10 (J=8.5 Hz) and doublet of doublets at 8.28 (J=8.0, 1.5 Hz) were attributed to C_4-H and C_7-H respectively. A doublet of doublets at 8.88 (J=4.0, 1.5 Hz) was due to C_9-H. The singlet at 12.14 was assigned to -NH and was exchangeable with D_2O. The i.r. spectrum showed absorptions (cm^{-1}) at 3427 (NH) and 1663 (CO). The EI mass spectrum exhibited major ions of m/z (relative intensity): 252 (16%), 251 (100%), 250 (38%) and 222 (6%) and the major fragmentation pathways are shown in Fig.11. Microanalysis was found to be within $\pm$0.4% of calculated values.

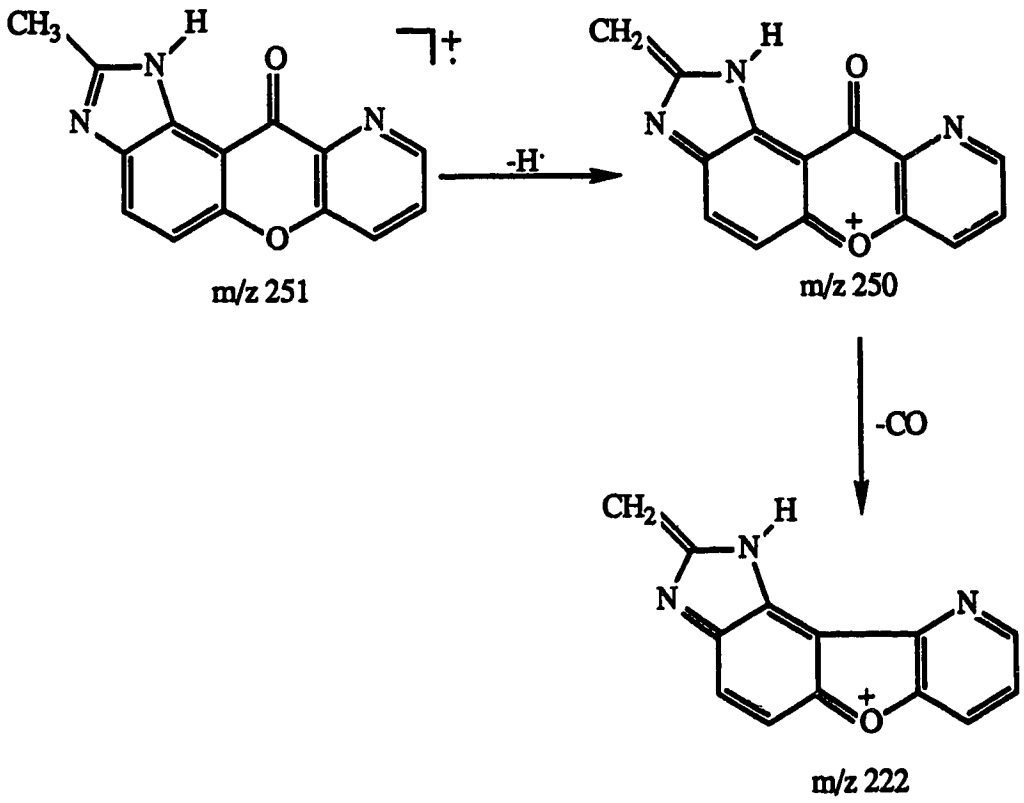
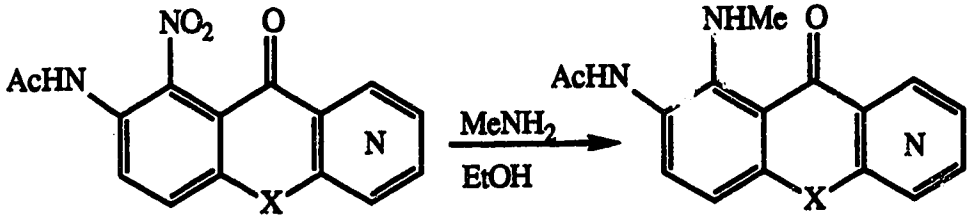


Fig. 11: Postulated major fragmentation pathways of 2-methylpyrido[2',3':5,6]pyrano[3,2-e](1H,11H)benzimidazol-11-one

7.2.3. *Synthesis of 1,2-dimethylpyridopyrano-/thiopyranobenzimidazol-11-ones (86-88):*

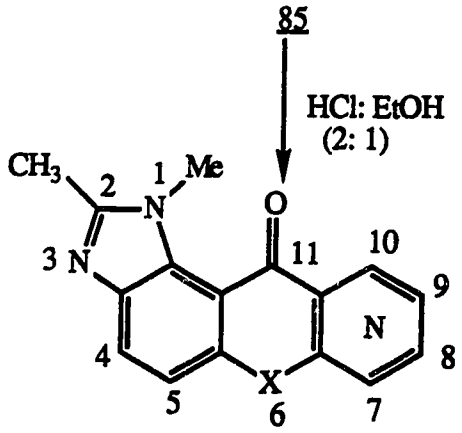


75

	X	Position of N
a)	O	4
b)	S	4
c)	S	1

85

	X	Position of N
a)	O	4
b)	S	4
c)	S	1



	X	Position of N
86	O	10
87	S	10
88	S	7

7-Acetamido-6-nitroazaxanthone/azathioxanthones (75a-c) were heated with methylamine in ethanol to give 7-acetamido-6-methylaminoazaxanthone/azathioxanthones (85a-c). 7-Acetamido-6-methylaminoazaxanthone/azathioxanthones (85a-c) were refluxed in HCl: EtOH mixture to give corresponding 1,2-dimethylpyridopyrano-/thiopyrano-benzimidazol-11-ones (86-88).

The structures of these compounds have been established from spectal data. For example, the ^1H nmr spectrum of (86) showed singlets at δ 3.36 and at δ 4.20 which were attributed to C_2-CH_3 and N-CH_3 respectively. A doublet at δ 7.48 (J=8.9 Hz) was due to C_5-H. A doublet of doublets at δ 7.92 (J= 8.9, 4.5 Hz) was assigned to C_8-H and a doublet at δ 8.06 (J=8.9 Hz) was due to C_4-H. Two doublets of doublets at δ 8.24 (J=8.9, 1.3 Hz) and at δ 8.84 (J=4.5, 1.3 Hz) were attributed to C_7-H and C_9-H respectively. The i.r. spectrum exhibited absorption at 1663 cm^{-1} (CO). The EI mass spectrum exhibited (Fig. 12) major ions with m/z (relative intensity): 266 (17%), 265 (100%), 264 (85%) and 250 (62%). Microanalysis values were found to be within ±0.4% of calculated values.

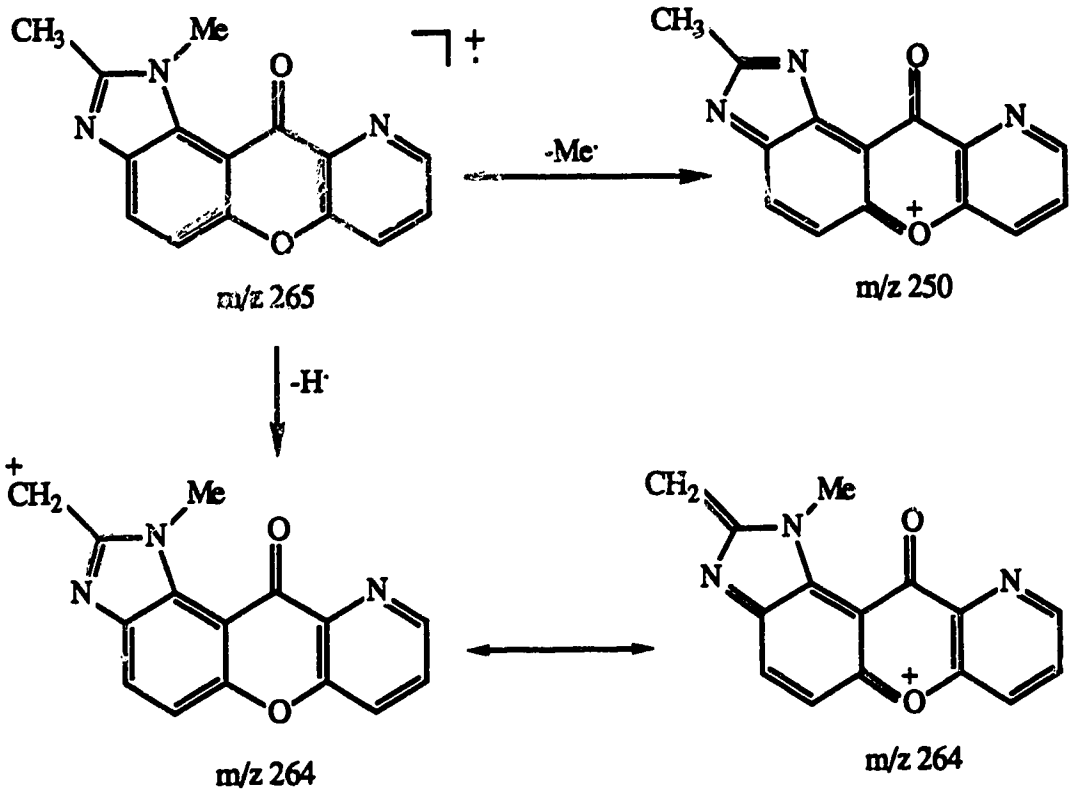
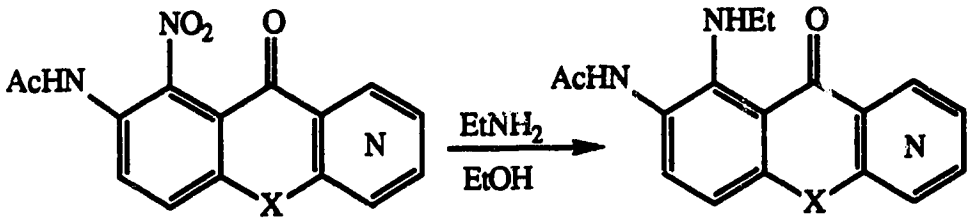


Fig. 12: Postulated major fragmentation pathways of 1,2-dimethylpyrido[2',3':5,6]pyrano[2,3-g](1H,11H)benzimidazol-11-one

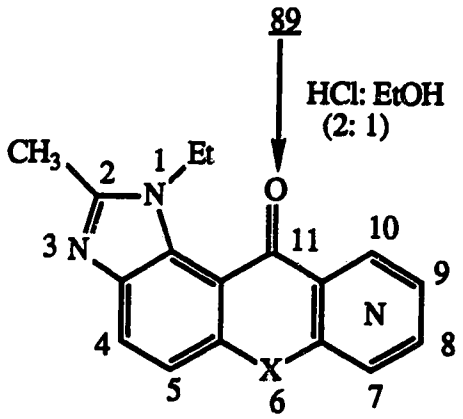
7.2.4. *Synthesis of 1-ethyl-2-methylpyridopyrano-/thiopyranobenzimidazol-11-ones (90-92):*



75 89

	X	Position of N
a)	O	4
b)	S	4
c)	S	1

	X	Position of N
a)	O	4
b)	S	4
c)	S	1



	X	Position of N
90	O	10
91	S	10
92	S	7

7-Acetamido-6-nitroazaxanthone/azathioxanthones (75a-c) were treated with ethylamine to give 7-acetamido-6-ethylaminoazaxanthone/azathioxanthones (89a-c). Compounds (89a-c) underwent HCl promoted cyclization to give N-ethyl substituted benzimidazol-11-ones (90-92) respectively.

The structures of compounds (90-92) were confirmed from the spectral data. For example, the ^1H nmr (δ) spectrum of (90) displayed a triplet at 1.46 (J=6.8 Hz) due to CH_3 of ethyl and a singlet at 2.18 due to C_2-CH_3. A quartet at 5.00 (J=6.8 Hz) was assigned to the -CH_2- of the ethyl group. A doublet at 7.42 (J=9.1 Hz) and a doublet of doublets at 7.70 (J=8.0, 3.4 Hz) were attributed to C_5-H and C_8-H respectively. A doublet at 7.96 (J=9.1 Hz) was due to C_4-H. Two doublet of doublet at 8.08 (J=8.0, 1.1 Hz) and 8.86 (J=3.4, 1.1 Hz) were assigned to C_7-H and C_9-H respectively. The i.r. spectrum displayed a carbonyl absorption at 1655 cm^{-1}. The EI mass spectrum (Fig. 13) exhibited major ions of m/z (relative intensity): 280 (14%), 279 (76%), 278 (8%), 264 (17%) and 251 (16%). Elemental analysis values were found to be within ±0.4% of calculated values.

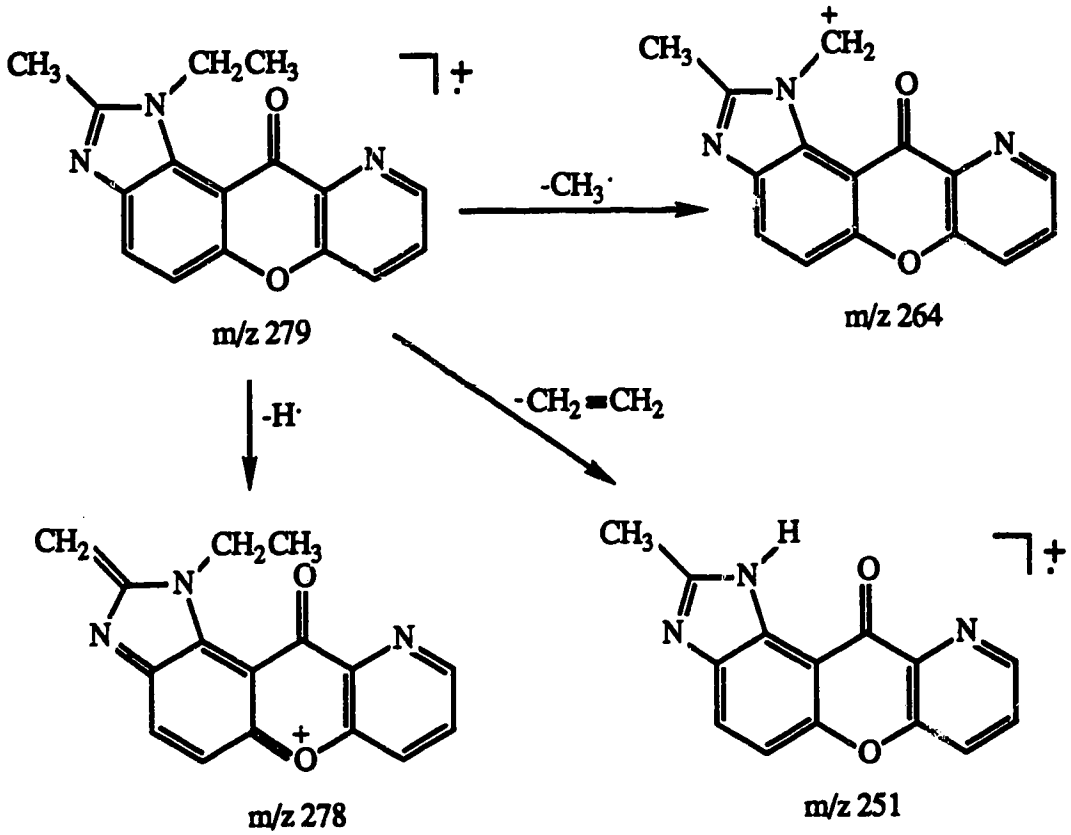
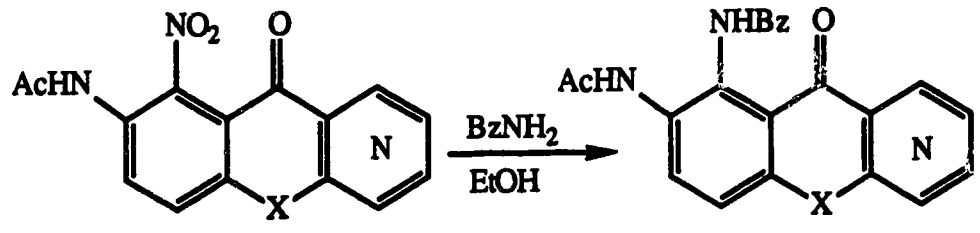


Fig. 13: Postulated major fragmentation pathways of 1-ethyl-2-methylpyrido[2',3':5,6]pyrano[2,3-g](1H,11H)benzimidazol-11-one

7.2.5. *Synthesis of 1-benzyl-2-methylpyridopyrano-/thiopyranobenzimidazol-11-ones (94-96):*

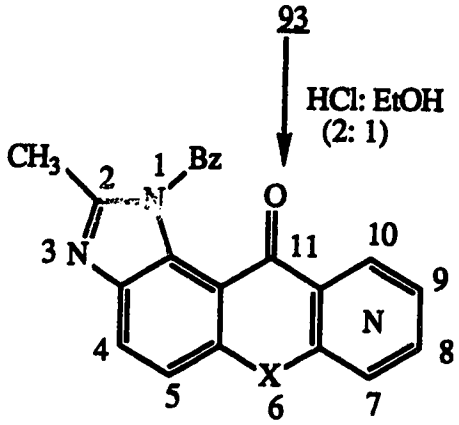


75

	X	Position of N
a)	O	4
b)	S	4
c)	S	1

93

	X	Position of N
a)	O	4
b)	S	4
c)	S	1



	X	Position of N
94	O	10
95	S	10
96	S	7

7-Acetamido-6-nitroazaxanthone/azathioxanthones (75a-c) were refluxed with benzylamine followed by treatment with an HCl: EtOH (2:1) mixture to give N-benzyl-2-methylpyridopyrano-/thiopyranobenzimidazolones (94-96).

The ^1H nmr spectrum of (94) exhibited two singlets at δ 2.54 and δ 6.36; the singlet at δ 2.54 was due to -CH_3 and the singlet at δ 6.36 was due to -CH_2- of the benzyl group. A doublet at δ 6.92 (J=8.7 Hz) was assigned to the ortho protons of the benzyl group and the multiplet at δ 7.88 was assigned to the meta and the para protons of the benzyl group. A doublet at δ 7.54 (J=8.7 Hz) and a doublet of doublets at δ 7.88 (J=8.7, 4.7 Hz) were attributed to C_5-H and C_8-H respectively. A doublet at δ 8.16 (J=8.7 Hz) was assigned to C_4-H. A doublet of doublets at δ 8.20 (J=8.7, 1.3 Hz) was due to C_7-H and the doublet at δ 8.76 (J=4.7, 1.3 Hz) was due to the C_9-H. The i.r. absorption at 1638 cm^{-1} was assigned to CO. The E^+ mass spectrum (Fig. 14) exhibited major ions with m/z (relative intensity): 342 (21%), 341 (95%), 340 (20%), 326 (46%), 264 (100%), 250 (17%) and 91 (28%). Microanalysis values were found to be within ±0.4% of calculated values. The structures of compounds (95) and (96) were similarly confirmed from spectral data.

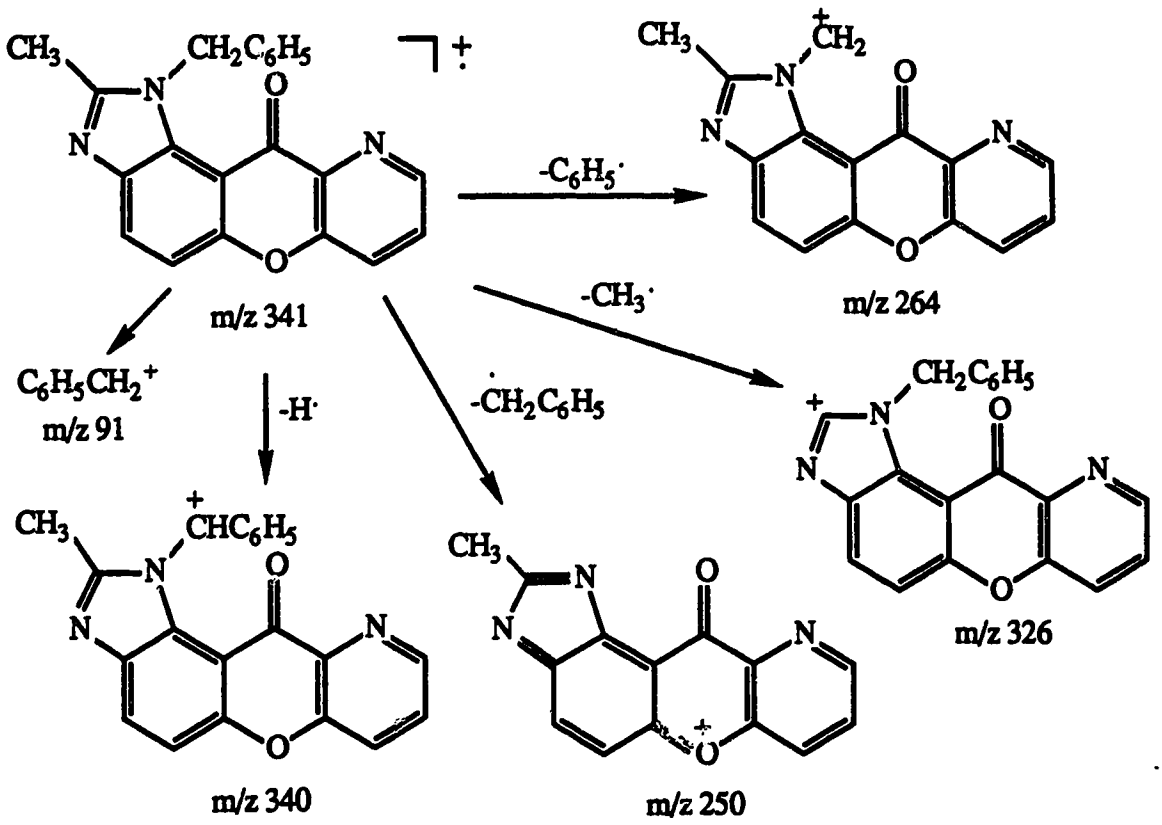
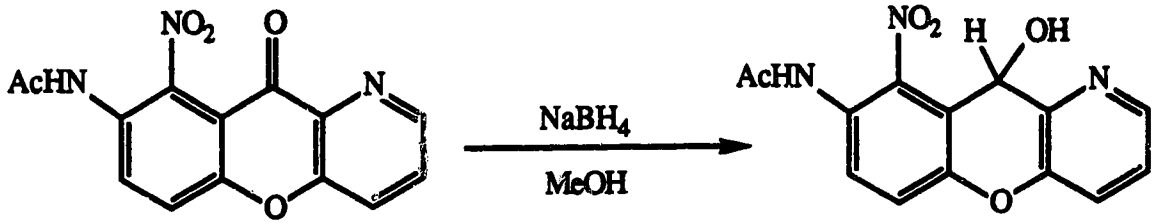


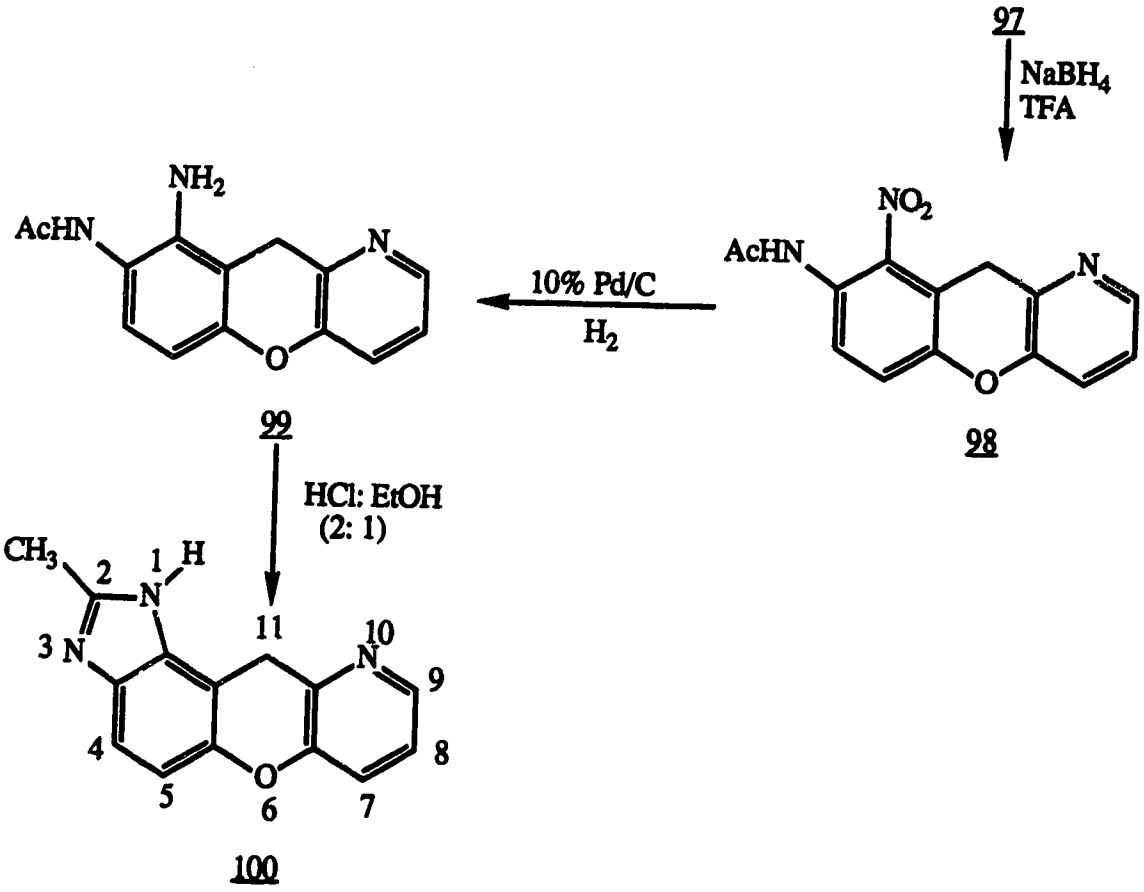
Fig. 14: Postulated major fragmentation pathways of 1-benzyl-2-methylpyrido[2',3':5,6] pyrano[2,3-g](1H,11H)benzimidazol-11-one

7.2.6. *Synthesis of 2-methylpyrido[2',3':5,6]pyrano[3,2-e](1H,11H) benzimidazole (100):*



75a

97



7-Acetamido-6-nitro-4-azaxanthone (75a) was reduced with $NaBH_4$ in MeOH to give 7-acetamido-6-nitro-4-azaxanthen-5-ol (97) which was reduced with $NaBH_4$ in trifluoroacetic acid to give 7-acetamido-6-nitro-4-azaxanthene (98). 7-Acetamido-6-nitro-4-azaxanthene (98) was reduced to the corresponding amino compound (99) with 10% Pd/C and hydrogen at 50 psi in a Parr Hydrogenator using ethanol as solvent. Cyclization of 7-acetamido-6-amino-4-azaxanthene (99) was achieved with HCl: EtOH (2:1) mixture to give compound (100) in 75% yield.

The ^1H nmr (δ) spectrum of (100) showed two singlets at 2.54 and 4.36; a singlet at 2.54 was attributed to $-CH_3$ and the singlet at 4.36 to C_{11}-Hs. C_{11}-Hs appeared downfield due to electron-withdrawing effects of aromatic rings especially pyridine. A doublet at 6.94 (J=8.7 Hz) was assigned to C_5-H. A multiplet at 7.36 was due to C_4-H and C_8-H. Two doublets at 7.52 (J=8.2 Hz) and at 8.32 (J=4.3 Hz) were

attributed to C7-H and C9-H respectively. The C7-H and C9-H are expected to exhibit doublets of doublets but in this compound coupling between C7-H and C9-H was not observed. The i.r. absorption at 3164 cm^{-1} was assigned to the -NH group. The EI mass spectrum exhibited major ions of m/z (relative intensity): 238 (14%), 237 (95%), 236 (100%) and the formation of base peak of m/z 236 is shown in Fig. 15. The high resolution mass spectrum showed a molecular ion peak corresponding to $C_{14}H_{11}N_3O_2$ [237.0894 found; 237.0902 calculated].

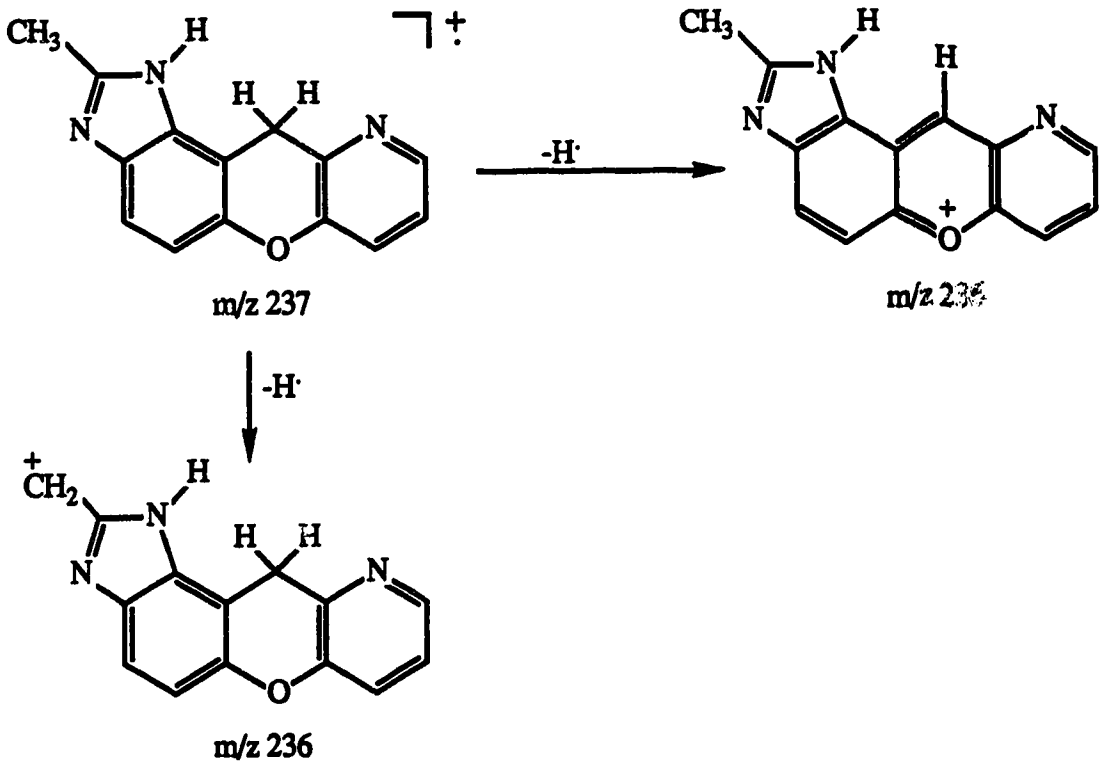
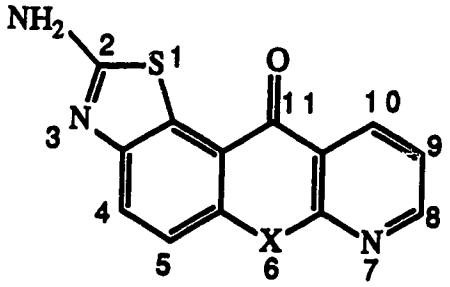


Fig. 15: Postulated major fragmentation pathways of 2-methylpyrido[2',3':5,6]pyrano[3,2-e](1H,11H)benzimidazole

7.3. Benzothiazol-11-ones:

Pharmacological evaluation of benzothiazolones (101a) and (101b) has shown that these compounds are promising dual inhibitors of both 5-lipoxygenase and

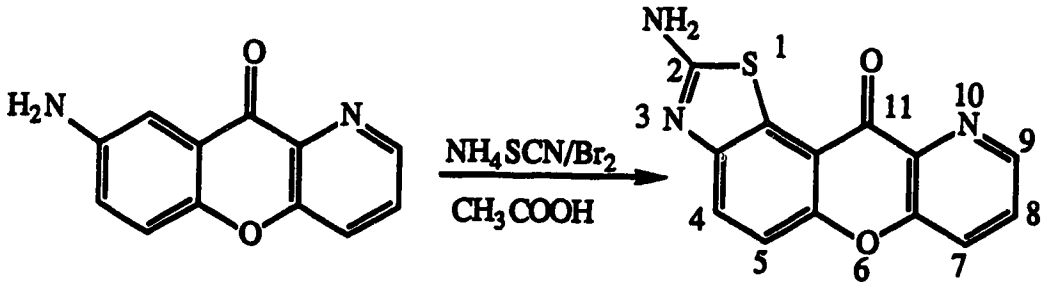
cyclooxygenase pathways.[139] Therefore, the 4-azaxathone analog (102) was synthesized.



101a X=O

101b X=S

7.3.1. *Synthesis of 2-aminopyrido[2',3':5,6]pyrano[2,3-g]benzothiazol-11(11H)-one (102):*



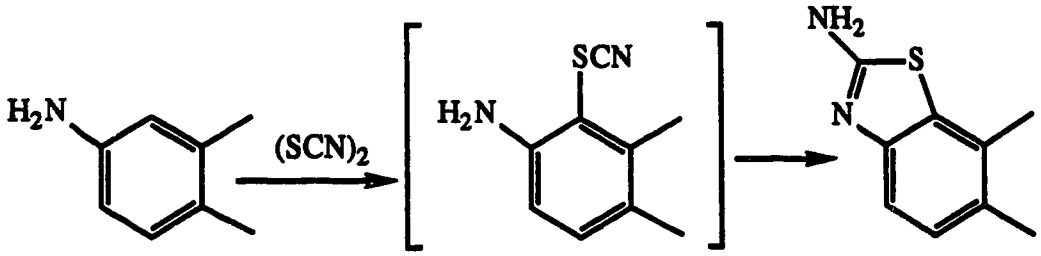
73a

102

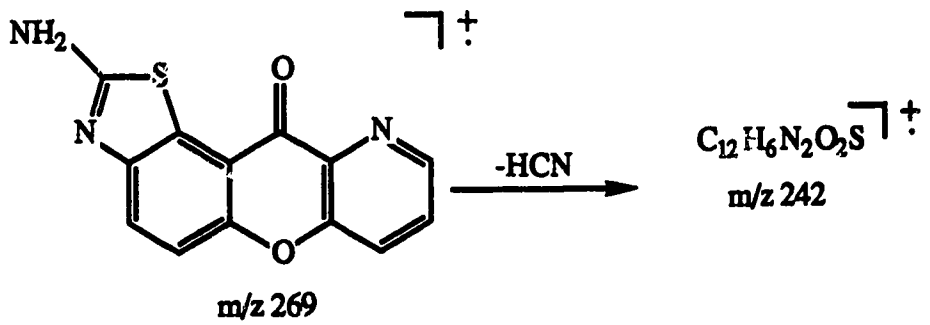
7-Amino-4-azaxanthone (73a) on treatment with ammonium thiocyanate and bromine[133,134] was converted to the title compound (102) in 70% yield.

The combination of thiocyanate and bromine generates thiocyanogen which attaches ortho to the amino group when the para position is occupied.[135] In the case of 7-amino-4-azaxanthone 73a the thiocyanate group attaches exclusively at the C_6-position to form 7-

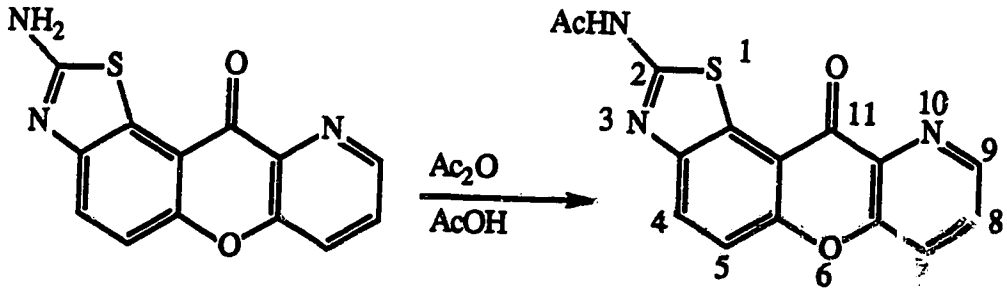
amino-6-thiocyanato-4-azaxanthone *in situ*, which spontaneously rearranges to give the cyclic compound (102).



The position of thiazole fusion on the 4-azaxanthone nucleus (73a) was confirmed by ^1H nmr. If fusion was between C_7-C_8 of compound (73a), ^1H nmr would have shown doublets for C_6-H and C_9-H due to para coupling. The ^1H nmr of compound (102) exhibited a doublet at δ 7.68 (J=9.0 Hz) due to C_4-H; such a large coupling constant showed it to be ortho coupled with C_5-H which is located under the multiplet at δ 7.96. The position of fusion is similar to that observed in case of benzimidazoles (section 7.2.1.). A singlet at δ 7.72 was due to amino group which was exchangable with D_2O. The C_8-H appeared at same position as C_5-H under the multiplet at δ 7.96. Two doublet of doublets at δ 8.28 (J=9.0, 1.5 Hz) and δ 8.88 (J=3.7, 1.5 Hz) were assigned to C_7-H and C_9-H respectively. The i.r. absorptions (cm^{-1}) were observed at 3336 (N-H) and 1642 (CO). The EI mass spectrum exhibited major ions with m/z (relative intensity): 270 (16%), 269 (100%) and 242 (31%). Elemental analysis was within ± 0.4% of calculated values.



7.3.2. *Synthesis of 2-acetamidopyrido[2',3':5,6]pyrano[2,3-g]benzothiazol-11-(11H)-one (103):*



102 103

To evaluate the effect of the amino group,which is highly electron donating, on activity the amine was converted to the moderately electron donating acetamido group.[136] 2-Aminopyrido[2',3':5,6]pyrano[2,3-g]benzothiazol-11-(11H)-one (102) was acetylated with acetic anhydride in acetic acid to give 2-acetamidopyrido[2',3':5,6]pyrano[2,3-g]-benzothiazol-11(11H)-one (103) in 86% yield.

The 300 MHz ^{1}H nmr (δ) spectrum of (103) showed a singlet at 2.26 due to the CH_3 of the acetamido group. A doublet at 7.84 (J=9.0 Hz) was assigned to C_4-H and a doublet of doublets at 7.96 (J=8.6, 4.1 Hz) was due to C_8-H. A multiplet at 8.30 was attributed to C_5-H and C_7-H. The C_9-H appeared as a doublet at 8.98 (J=4.1 Hz) instead of doublet of doublets as coupling between C_7-H and C_9-H was not observed in the nmr. The i.r. spectrum (cm^{-1}) showed absorption at 3480 which was assigned to N-H and two strong absorptions in the carbonyl region at 1696 and 1655. On comparing these values with that of aminothiazolone (102), absorption at 1696 was attributed to NHCO and at 1655 to C_{11}-CO. The EI mass spectrum (Fig.16) exhibited major ions of m/z (relative intensity): 311 (22%), 270 (16%), 269 (100%) and 242 (14%). The base peak in the mass spectrum at m/z 269 is formed by loss of ketene molecule from molecular ion which

loses a molecule of HCN from the pyridine ring to give fragment $C_{12}H_6NO_3S$ with m/z 242. The molecular ion peak corresponded to $C_{15}H_9N_3O_3S$ [311.0371, found; 311.0366 calculated].

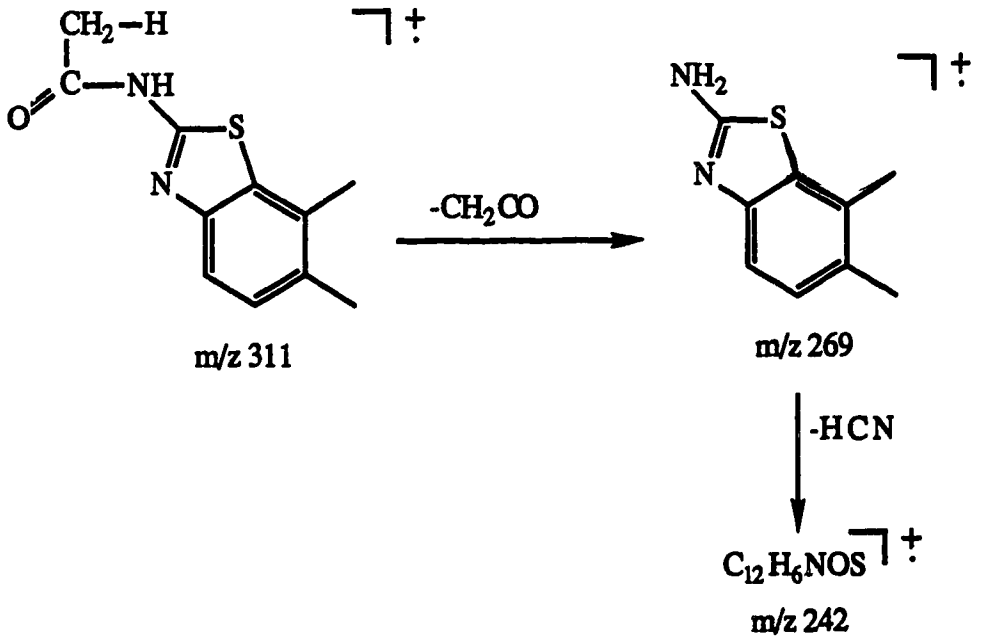
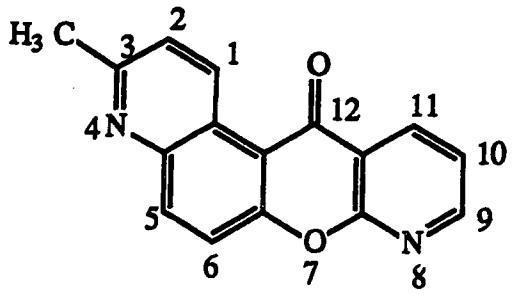


Fig 16: Postulated major fragmentation pathways of 2-acetamidopyrido[2',3':5, 6]pyrano[2,3-g]benzothiazol-11(11H)-one

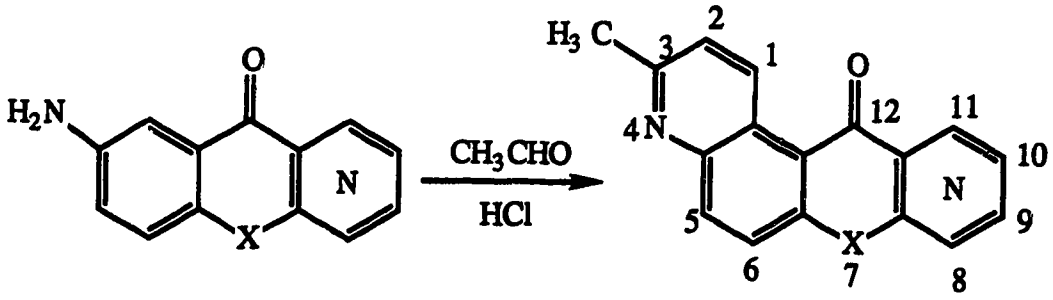
7.4. Quinolin-12-ones:

3-Methylpyrido[3',2':5,6]pyrano[3,2-f]quinolin-12(12H)-one (104)[139] synthesized by other personnel in our laboratory was found to show more than 50% inhibition at 10^{-6}M concentration on guinea pig isolated trachea. This suggested that this compound is a potent inhibitor of the 5-lipoxygenase pathway. Therefore sulphur and selenium analogs of 1-azaxanthone (107, 108) as well as oxygen and sulphur analogs of 4-azaxanthone (105, 106) were synthesized.



104

7.4.1. *Synthesis of 3-methylpyridopyrano-/thiopyrano-/selenopyrano-quinolin-12-ones (105-108):*



73

	X	Position of N
a)	O	4
b)	S	4
c)	S	1
d)	Se	1

	X	Position of N
105	O	11
106	S	11
107	S	8
108	Se	8

The synthesis of compounds (73a-c) have been reported in section **7.2.1.** 7-Amino-1-azaselenoxanthone (73d) was provided by another researcher from our laboratory. 7-Amino-4-azaxanthone (73a), 7-amino-4-azathioxanthone (73b), 7-amino-1-azathioxanthone (73c) and 7-amino-1-azaselenoxanthone (73d), on refluxing with acetaldehyde in concentrated HCl, gave quinolin-12-ones (105-108) respectively.

This reaction is an example of the Doebner Von Miller procedure, a modification of the Skraup synthesis, for the synthesis of quinolines.[137] The first step of the mechanism

involves self-condensation of acetaldehyde to give an α,β-unsaturated aldehyde which reacts with the amine as shown in Fig. 17 (same as in ref. 137).

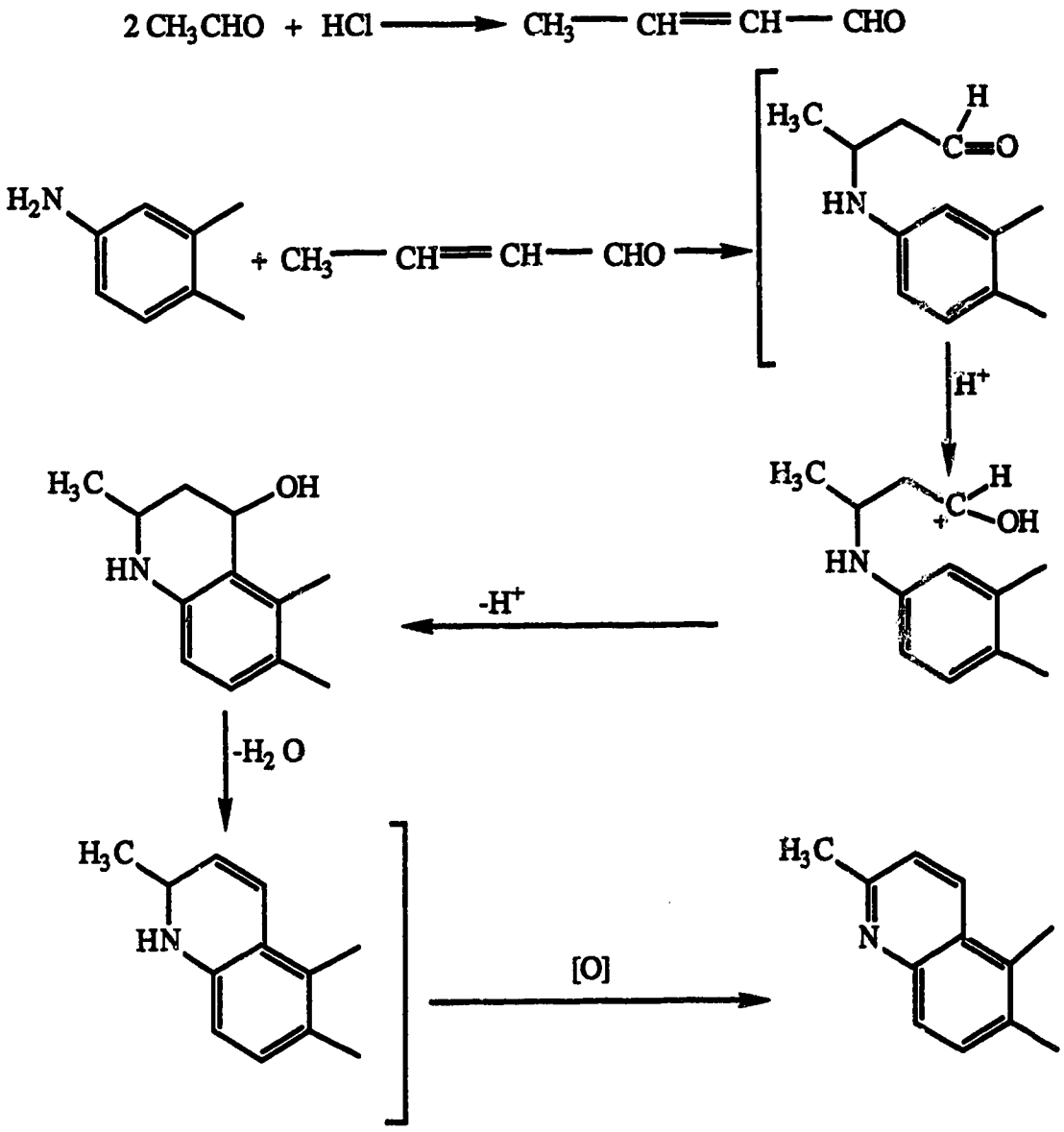


Fig. 17: Mechanism of formation of quinolines

The structures of these quinolin-12-ones were established by spectral data. For example, the ^1H nmr (δ) spectrum of (105) showed a singlet at 2.74 due to the methyl group. A doublet at 7.78 (J=8.5 Hz) was assigned to the C_2-H and a doublet of doublets

at 7.98 (J=7.7, 3.9 Hz) was attributed to the C9-H. A doublet at 8.04 (J=9.3 Hz) was due to the C_6-H and a doublet of doublets at 8.32 (J=7.7, 1.5 Hz) was assigned to the C8-H. A doublet at 8.42 (J=9.3 Hz) was due to the C_5-H and a doublet of doublets at 8.92 (J=3.9, 1.5 Hz) was assigned to the C_{10}-H. The C_1-H appeared as a doublet at very low field of 10.18 (J=8.5 Hz) which could be caused by its orientation in the deshielding area of C_{12}-CO. The i.r. spectrum showed absorption at 1663 cm^{-1} which was due to -CO and microanalysis values were found to be within ±0.4% of the calculated values. The EI mass spectrum exhibited (Fig. 18) major ions with m/z (relative intensity): 263 (17%), 262 (100%), 234 (10%), 221 (8%) and 193 (5%).

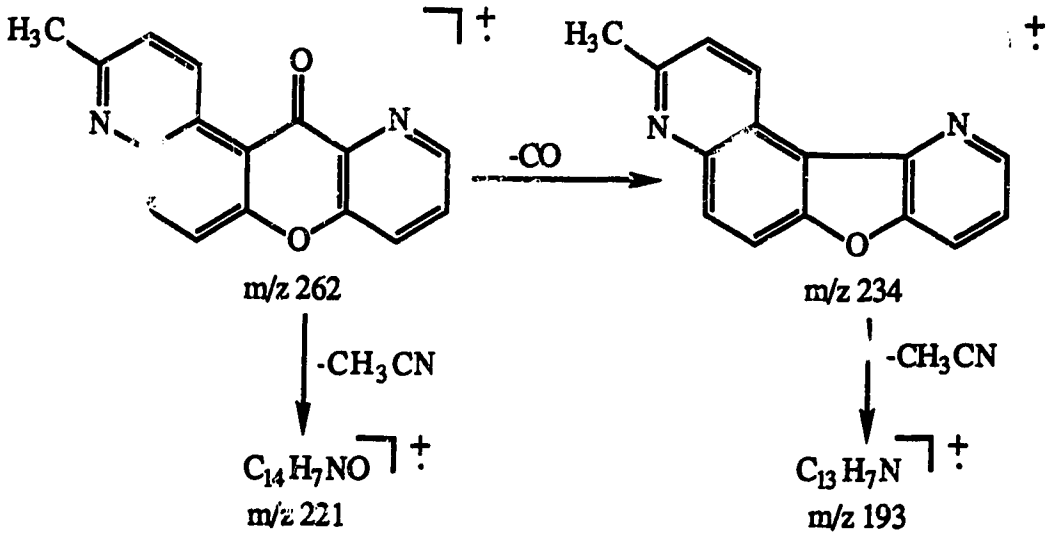
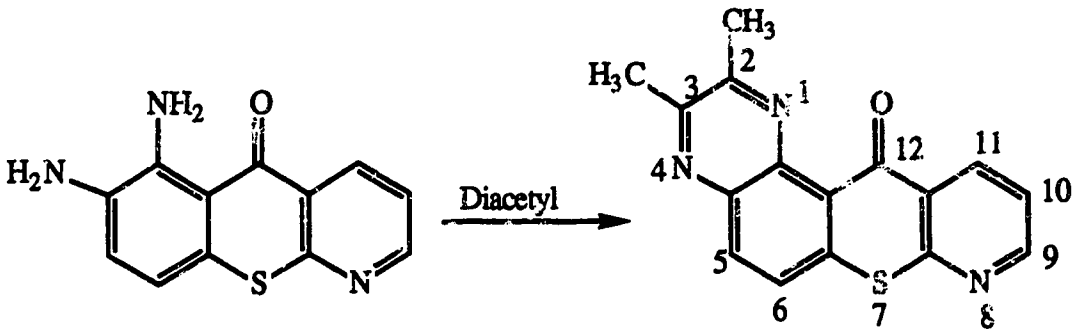


Fig. 18: Postulated major fragmentation pathways of 3-methylpyrido[2',3':5,6]pyrano[3,2-f]quinolin-12(12H)-one

7.5. Quinoxalin-12-one

7.5.1. *Synthesis of 2,3-dimethylpyrido[3',2':5,6]thiopyrano[3,2-f] quinoxalin-12(12H)-one (109):*



77c 109

2,3-Dimethylpyrido[3',2':5,6]thiopyrano[3,2-f]quinoxalin-12(12H)-one (109) was prepared from 6,7-diamino-1-azathioxanthone (77c) by condensation with diacetyl.[138]

The ^{1}H nmr (δ) spectrum of (109) exhibited two singlets at 2.72 and 2.76 which have been assigned to C_2-CH_3 and C_3-CH_3 respectively. A doublet of doublets at 7.74 (J=8.4, 4.6 Hz) was assigned to the C_{10}-H. Two doublets, one at 8.12 (J=8.8 Hz) and the other at 8.26 (J=8.8 Hz), have been assigned to C_6-H and C_5-H respectively. Two doublet of doublets at 8.74 (J=8.4, 1.4 Hz) and 8.94 (J=4.6, 1.4 Hz) have been attributed to C_{11}-H and C_9-H respectively. The i.r. absorption at 1646 cm^{-1} was assigned to CO. The EI mass spectrum exhibited major ions of m/z (relative intensity): 294 (20%), 293 (100%), 292 (22%), 252 (16%) and fragmentation pathways are shown in Fig. 19. The molecular ion peak corresponded to $C_{16}H_{11}N_3OS$ [293.0621 found; 293.0624 calculated].

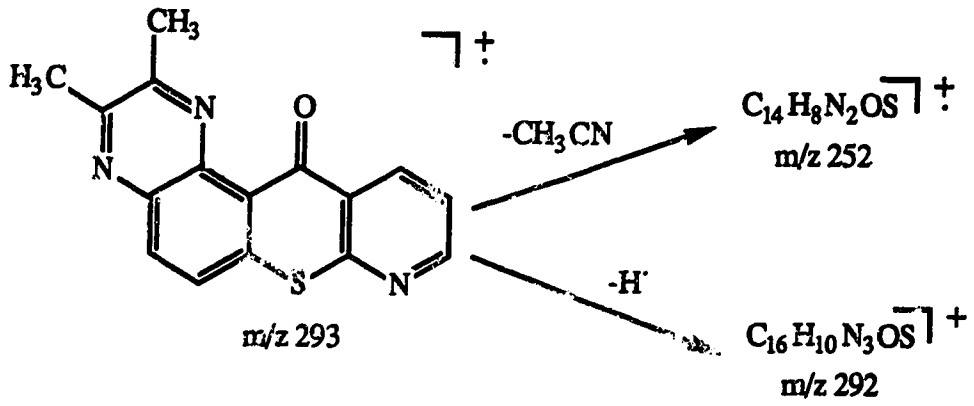
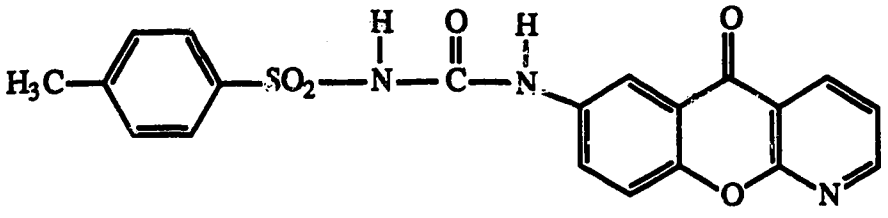


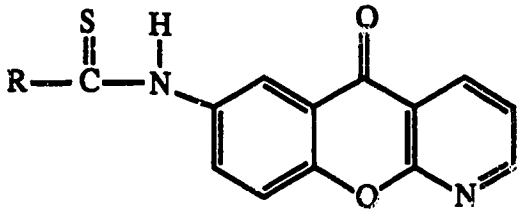
Fig. 19: Postulated major fragmentation pathways of 2,3-dimethylpyrido[3',2':5,6]thiopyrano[3,2-f]quinoxalin-12(12H)-one

7.6. 7-Substituted azaxanthone ureas:

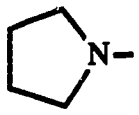
Several 1-azaxanthones derivatives (110-115) containing urea substituents at the 7-position, which were synthesized by other personnel in our laboratory were found to show excellent leukotriene inhibitory properties.[139]

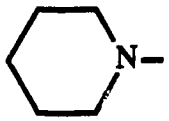


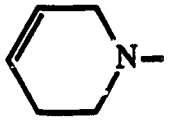
110

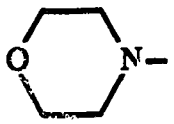


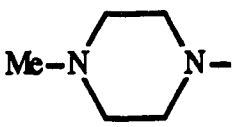
R

111 

112 

113 

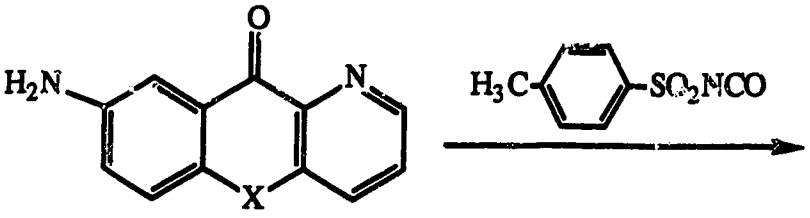
114 

115 

From these results it was felt that the 1-azathioxanthone, 4-azaxanthone and 4-azathioxanthone analogs should be synthesized and evaluated.

7.6.1. *Synthesis of 7-(p-toluenesulphonylurea)-4-azaxanthone/4-azathioxanthone (116,117):*

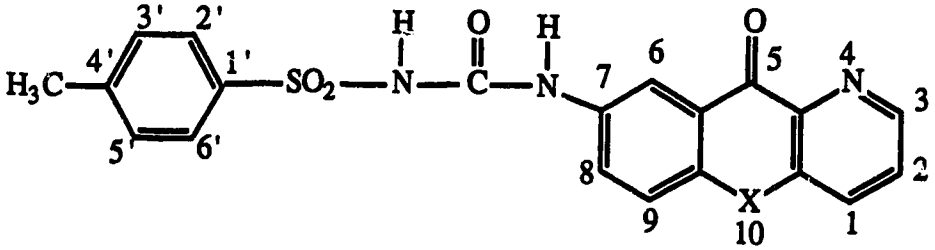
Solutions of 7-amino-4-azaxanthone (73a) and 7-amino-4-azathioxanthone (73b) in THF, on refluxing with p-toluenesulphonylisocyanate, gave 7-(p-toluenesulphonylurea)-4-azaxanthone (116) and 7-(p-toluenesulphonylurea)-4-azathioxanthone (117), respectively.



73

a) X=O

b) X=S



116 X=O

117 X=S

The ^1H nmr (δ) spectrum of 7-(p-toluenesulphonylurea)-4-azaxanthone (116) showed a singlet at 2.40 due to the methyl group. A doublet at 7.48 (J=8.5 Hz) was assigned to C_3'-H and C_5'-H due to shielding effect of the methyl group. A doublet at 7.70 (J=9.1 Hz) was attributed to the C_9-H and a doublet of doublets at 7.86 (J=9.1, 2.4 Hz) was due to the C_8-H. A multiplet at 7.92 was assigned to C_2-H, C_2'-H and C_6'-H. The C_2'-H and C_6'-H signal appeared at low field relative to C_3'-H and C_5'-H due to the deshielding effect of the sulphonyl group. A doublet of doublets at 8.22 (J=8.5, 1.2 Hz) and doublet at 8.32 (J=2.4 Hz) were due to C_1-H and C_6-H respectively. A doublet of doublets at 8.84 (J=4.2, 1.2 Hz) was assigned to the C_3-H. A singlet at 9.32 was due to the two N-Hs and these hydrogens were exchangeable with D_2O. The i.r. spectrum (cm^{-1}) exhibited strong absorptions at 1728 ($SO_2NHCONH$), 1671 (C_5-CO), 1326 (SO_2), 1171 (SO_2). The EI mass spectrum exhibited major ions of m/z (relative intensity): 238 (22%), 212 (87%), 211 (9%), 197 (18%), 171 (6%), 155 (49%), 129 (7%), 91 (100%), 65 (27%), 64 (7%) and 39 (17%). Major fragmentation pathways are shown in Fig. 20. Microanalysis values were found to be within ±0.4% of calculated values. The structure of compound (117) was similarly confirmed from spectral data.

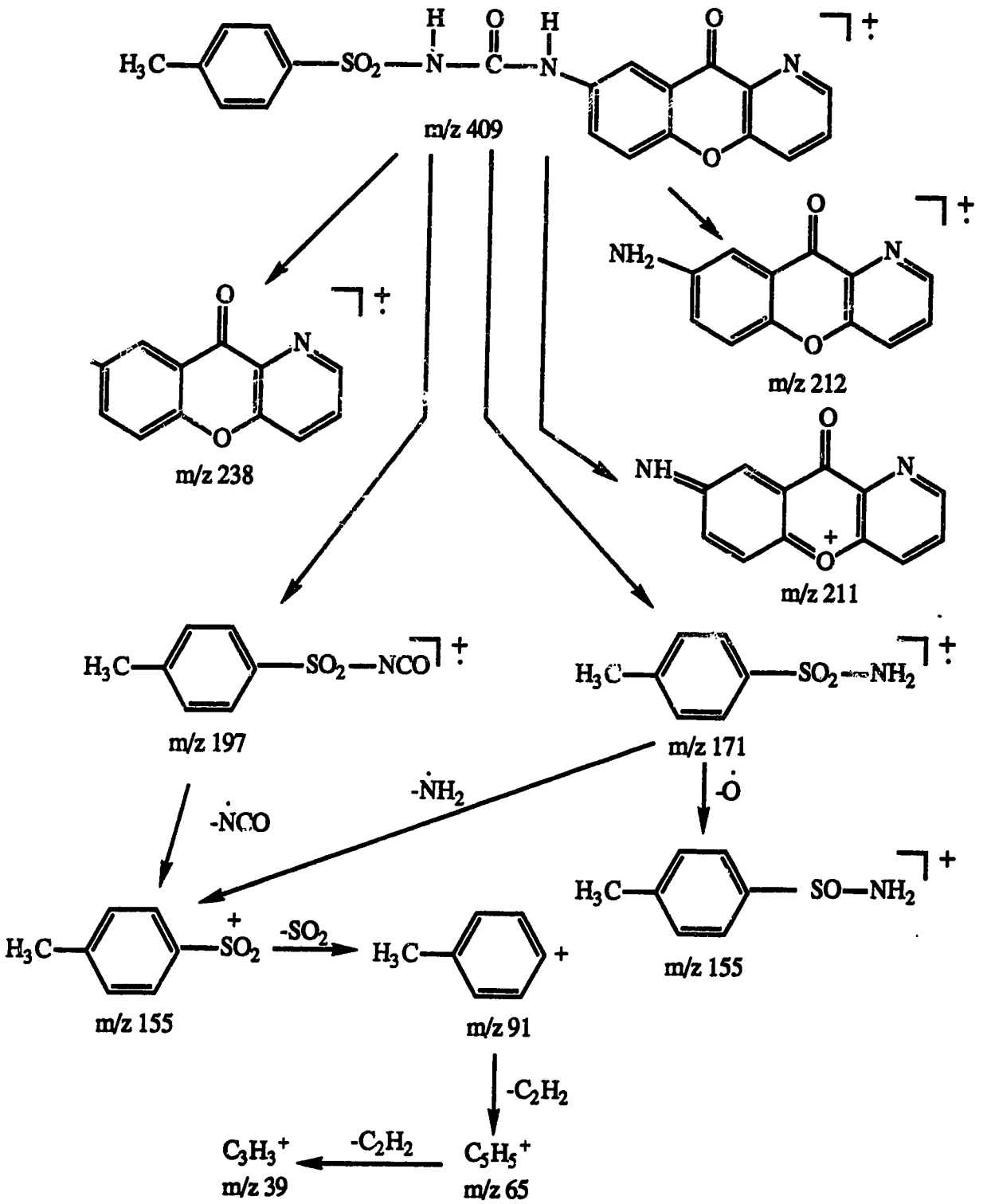
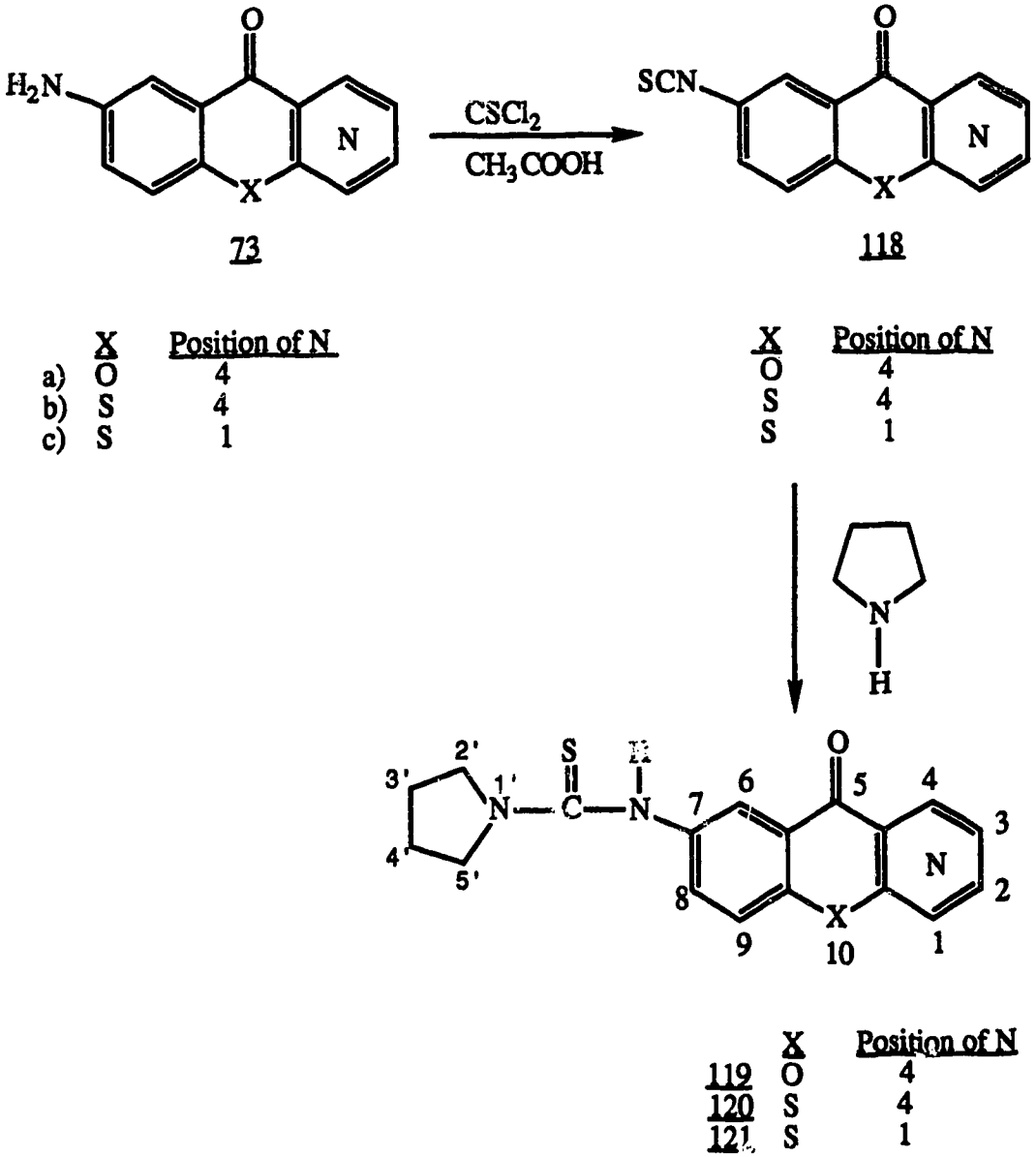


Fig. 20: Postulated major fragmentation pathways of 7-(p-toluenesulphonylurea)-4-azaxanthone

7.6.2.Synthesis of 7-(1-pyrrolidinylthiocarboxamido)azaxanthone/azathioxanthones (119-120):



Solutions of 7-aminoazaxanthone/azathioxanthones (73a-c) in acetic acid were refluxed with an equimolar quantity of thiophosgene to give 7-isothiocyanatoazaxanthone/azathioxanthones (118a-c). The i.r. spectra of these compounds showed characteristic strong absorption for the -NCS group near 2125 cm^{-1}. 7-Isothiocyanatoazaxanthones/azathioxanthones (118a-c) were condensed with different cyclic amines to

give a variety of ureas. For example, on treatment with equimolar quantity of pyrrolidine, 7-isothiocyanatoazaxanthones/azathioxanthones (118a-c) solutions in acetone gave thioureas (119-121) respectively.

The 300 MHz ^1H nmr of (119) showed singlets at δ 1.96 and δ 3.68; the singlet at δ 1.96 was assigned to the C_3'-H and C_4'-H methylenes while the singlet at δ 3.68 was due to the C_2'-Hs and C_5'-Hs. The C_2'-Hs and C_5'-Hs are deshielded due to the pyrrolidine nitrogen which is attached to an electron-withdrawing C=S group. A doublet at δ 7.68 (J=8.7 Hz) was assigned to C_9-H. Two doublet of doublets at δ 7.92 (J=8.7, 4.1 Hz) and δ 8.10 (J=8.7, 3.1 Hz) were due to C_2-H and C_8-H respectively. A doublet at δ 8.16 (J=3.1 Hz) was attributed to C_6-H. Two doublet of doublets at δ 8.22 (J=8.7, 1.5 Hz) and δ 8.84 (J=4.1, 1.5 Hz) were assigned to C_1-H and C_3-H respectively. A singlet at δ 9.26 was due to the N-H and was exchangeable with D_2O. The ir absorptions (cm^{-1}) were at 3312 (-NH), 1663 (CO) and 1622 (CS). The EI mass spectrum (Fig. 21) exhibited fragments with m/z (relative intensity): 254 (100%), 227 (6%), 226 (10%), 71 (4%) and 70 (9%). The molecular ion peak was not observed in the mass spectrum. The base peak at m/z 254 resulted from loss of the pyrrolidine molecule. The peak at m/z 71 corresponds to the pyrrolidine fragment and m/z 70 is formed by loss of a H radical from pyrrolidine as shown in Fig. 21. The structures of compounds (120) and (121) were similarly confirmed from spectral data.

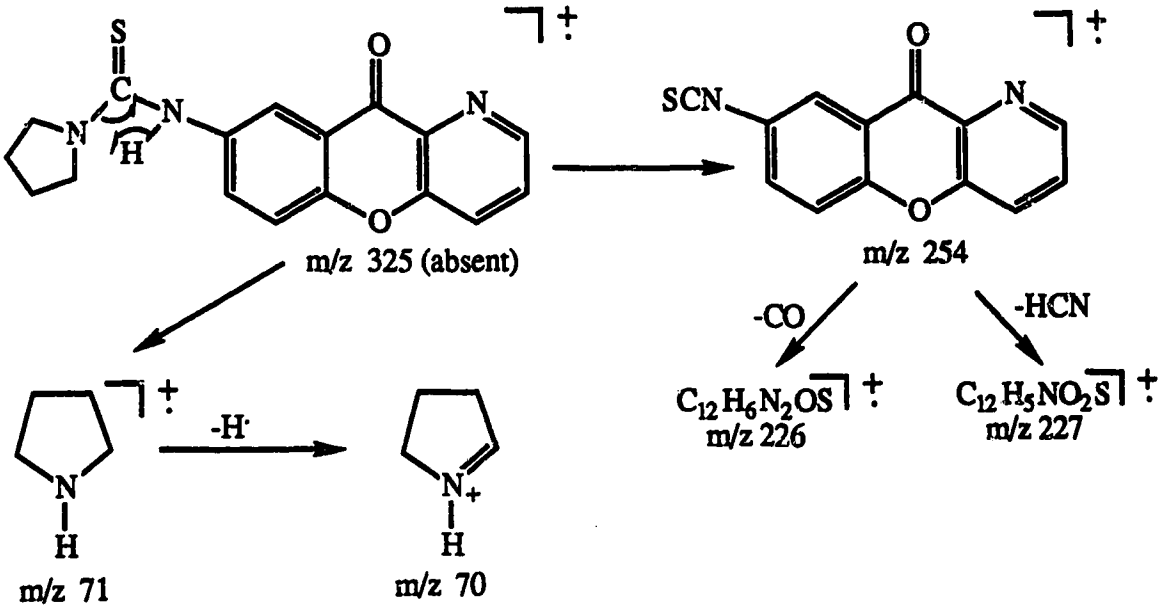
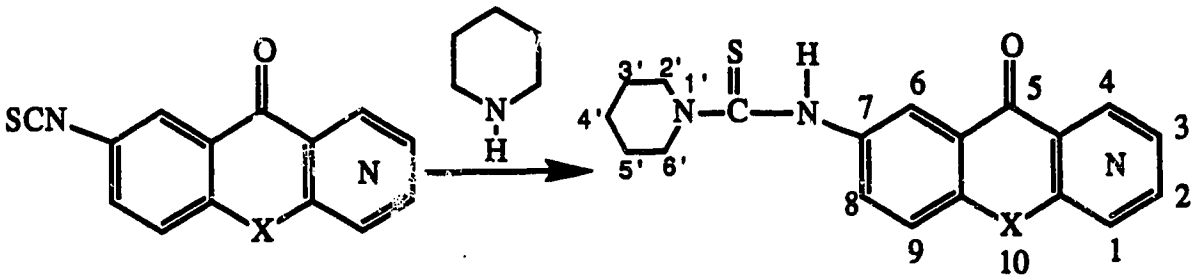


Fig 21: Postulated fragmentation pathways of 7-(1-pyrrolidinylthiocarboxamido)-4-azaxanthone

7.6.3. *Synthesis of 7-(piperidinothiocarboxamido)azaxanthone/aza-thioxanthones (122-124):*



118

	X	Position of N
a)	O	4
b)	S	4
c)	S	1

	X	Position of N
122	O	4
123	S	4
124	S	1

7-Isothiocyanatoazaxanthone/azathioxanthones (118a-c) solutions in acetone were reacted with piperidine to give thioureas (122-124) respectively.

The ^1H nmr spectrum of (122) exhibited a singlet at δ 1.64 which was assigned to the C_3'-Hs, C_4'-Hs, C_5'-Hs and a singlet at δ 3.94 assigned to C_2'-Hs and C_6'-Hs. The C_2'-Hs and C_6'-Hs appeared at lower field due to the piperidyl nitrogen which is attached to electron withdrawing C=S. A doublet at δ 7.56 (J=8.7 Hz) was assigned to C_9-H and a doublet of doublets at δ 7.84 (J=8.7, 4.3 Hz) to C_2-H. A multiplet at δ 8.1 was due to C_1-H and C_8-H. A doublet at δ 8.14 (J=2.9 Hz) was assigned to the C_6-H and a doublet of doublets at δ 8.84 (J=4.3, 1.4 Hz) was attributed to the C_3-H. A singlet at δ 9.48 was due to the N-H and was exchangeable with D_2O. The significant i.r. absorptions were at 3312 (-NH), 1663 (CO) and 1622 (CS). The EI mass spectrum exhibited fragments of m/z (relative intensity): 254 (100%), 227 (15%), 226 (21%), 85 (26%), 84 (47%), 57 (20%), 56 (22%) and 43 (9%). Major fragmentation pathways are shown in Fig. 22. Microanalysis values were found to be within ±0.4% of calculated value. The structures of compounds (123) and (124) were similarly confirmed from spectral data.

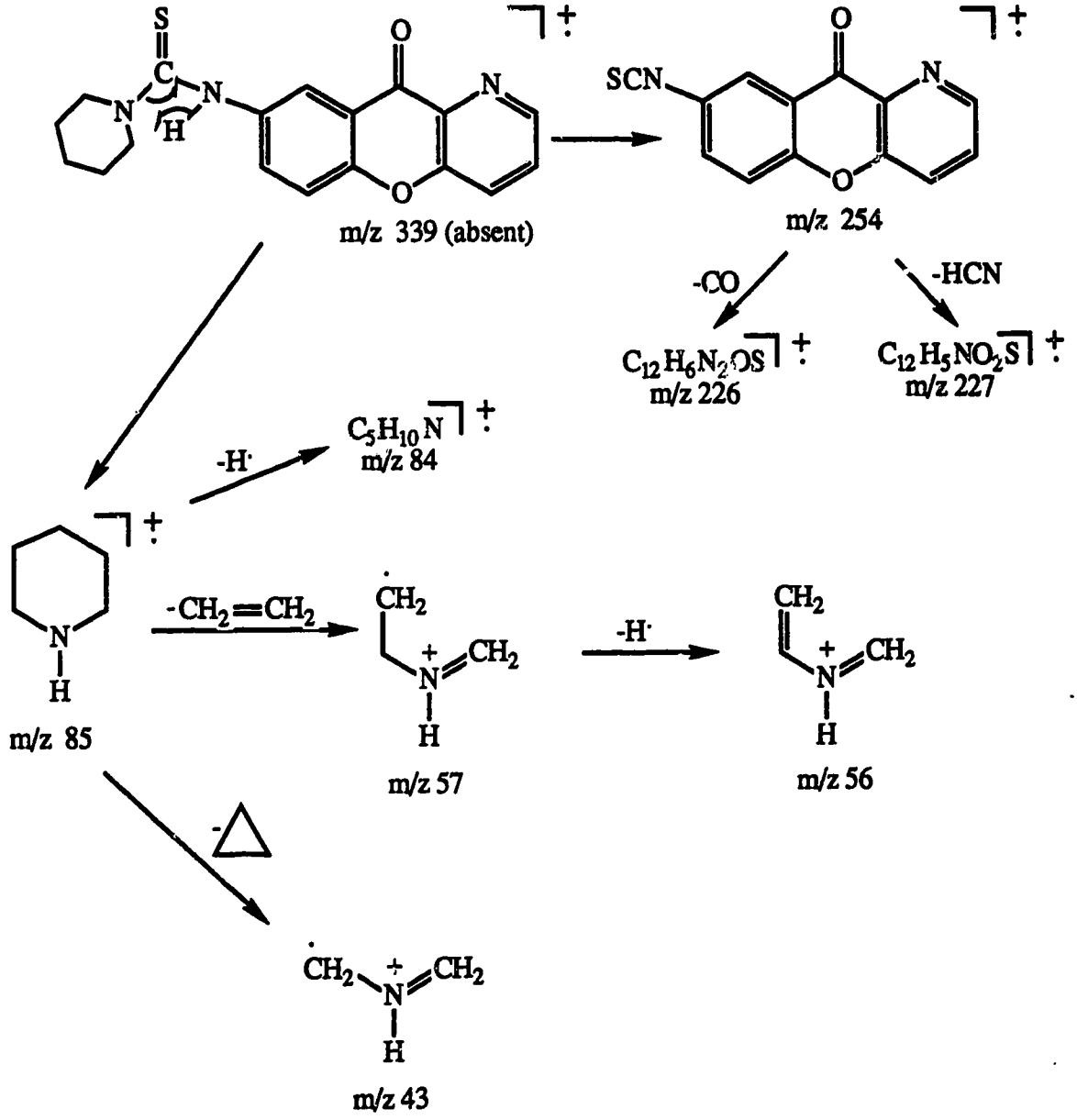
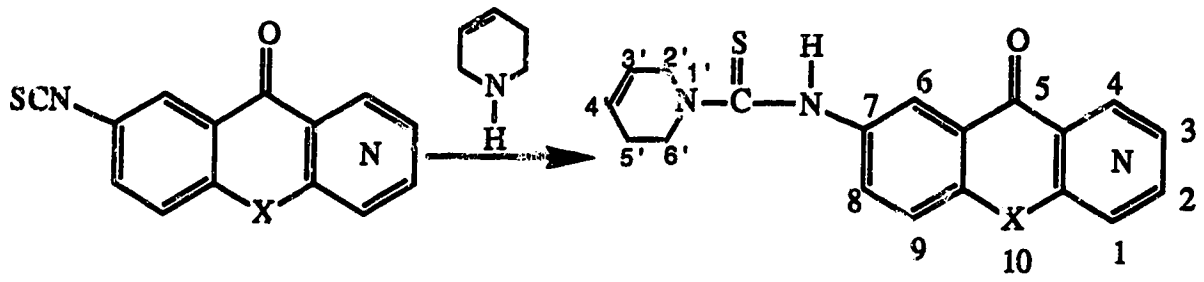


Fig. 22: Postulated major fragmentation pathways of 7-(piperidinothiocarboxamido)-4-azaxanthone

7.6.4. *Synthesis of 7-[1-(1',2',5',6'-tetrahydropyridinyl)thiocarboxamido]azaxanthone/azathioxanthones (125-127):*



118

	X	Position of N
a)	O	4
b)	S	4
c)	S	1

	X	Position of N
125	O	4
126	S	4
127	S	1

Thioureas (125-127) were prepared from 7-isothiocyanatoazaxanthone/azathioxanthones (118a-c) by condensation with 1,2,5,6-tetrahydropyridine.

The structures of compounds (125-127) have been confirmed by spectral data. For example, the 300 MHz ^{1}H nmr (δ) spectrum of (125) showed a multiplet at 2.26 due to C_5'-H. A triplet at 4.04 (J=6.0 Hz) was due to C_6'-Hs and multiplet at 4.38 was assigned to C_2'-Hs. The latter are further downfield due to the inductive effect of the double bond. Multiplets at 5.78 and 5.96 were assigned to C_4'-H and C_3'-H respectively. This difference in chemical shift is due to the fact that the nitrogen has a greater deshielding on C_3'-H than C_4'-H. A doublet at 7.68 (J=9.3 Hz) was attributed to C_9-H. Two doublet of doublets at 7.92 (J=8.1, 4.6 Hz) and 8.02 (J=9.3, 2.3 Hz) were assigned to C_2-H and C_8-H respectively. A doublet at 8.08 (J=2.3 Hz) was due to the C_6-H. Two doublet of doublets at 8.24 (J=8.1, 1.2 Hz) and 8.84 (J=4.6, 1.2 Hz) were attributed to C_1-H and C_3-H respectively. A singlet at 9.62 was due to the N-H and was exchangeable with D_2O. The i.r. absorption (cm^{-1}) were observed at 3312 (-NH) and 1663 (-CO). The

positive ions chemical ionization mass spectrum of this compound showed characteristic ions with m/z (relative intensity): 509 (9%), 340 (7%), 339 (17%), 338 (60%), 255 (100%), 253 (27%), 84 (63%), 83 (18%) and 82 (17%). The quasimolecular ion $[M+1]^+$ had the expected m/z 338 and fragments of m/z 255, 84 and m/z 82 are the protonated equivalent fragments of m/z 254, 83 and 81 as shown in Fig. 23. Ions of m/z 509 is postulated to be a dimer of m/z 254. Microanalysis values were found to be within ±0.4% of calculated values.

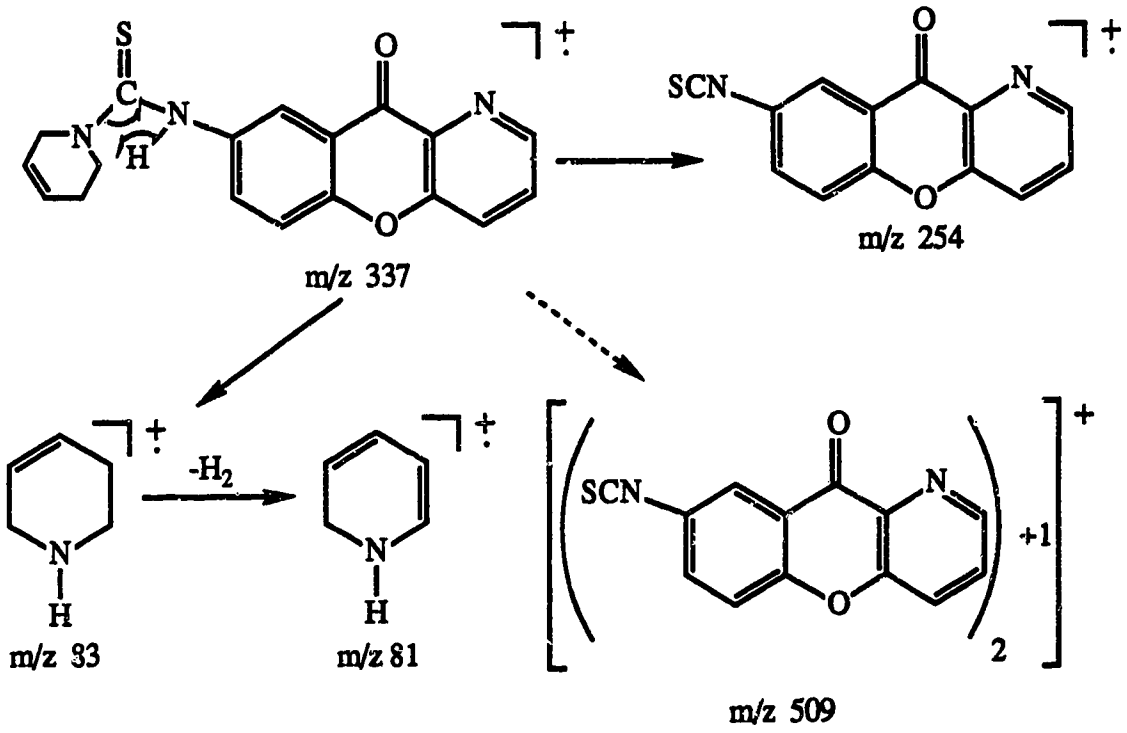
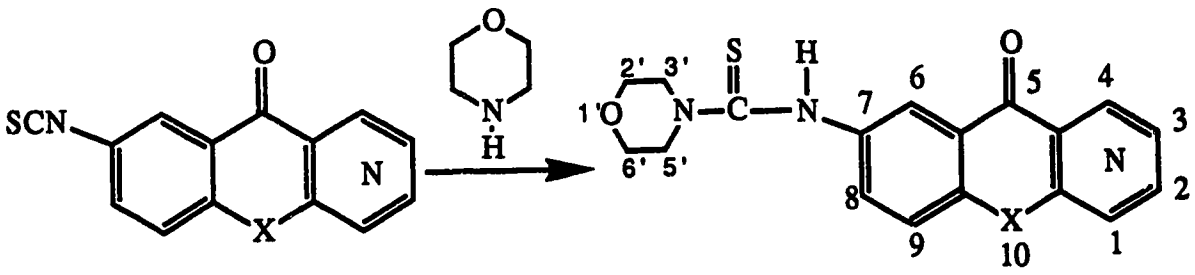


Fig. 23: Postulated chemical ionization fragmentation pathways of 7-[1-(1',2',5',6'-tetrahydropyridinyl)thiocarboxamido]-4-azaxanthone

7.6.5. *Synthesis of 7-(morpholinothiocarboxamido)azaxanthone/aza-thioxanthones (128-129):*



118

	X	Position of N
a)	O	4
b)	S	4
c)	S	1

	X	Position of N
128	O	4
129	S	4
130	S	1

Solutions of 7-isothiocyanatoazaxanthone/azathioxanthones (118a-c) in acetone on treatment with morpholine, gave thioureas (128-130) respectively.

The ^1H nmr spectrum of (128) showed two triplets, one at δ 3.70 (J=4.6 Hz) assigned to C_2'-Hs and C_6'-Hs and the other at δ 3.96 (J=4.6 Hz) due to C_3'-Hs and C_5'-Hs. In case of a morpholine molecule protons adjacent to oxygen are at approximately δ 3.7 and are more deshielded than those adjacent to nitrogen which are at approximately δ 2.9. But in compound (128) protons adjacent to nitrogen are more deshielded as they are attached to electron-withdrawing thiocarbonyl group. A doublet at δ 7.68 (J=8.6 Hz) was attributed to the C_9-H. Two doublet of doublets at δ 7.92 (J=8.6, 4.1 Hz) and δ 8.02 (J=8.6, 2.8 Hz) were assigned to C_2-H and C_8-H respectively. A doublet at δ 8.10 (J=2.8 Hz) was due to the C_6-H. Two doublet of doublets at δ 8.22 (J=8.6, 1.4 Hz) and δ 8.82 (J=4.1, 1.4 Hz) were attributed to C_1-H and C_3-H respectively. A singlet at δ 9.66 was assigned to the N-H which was exchangeable with D_2O. Positive ion CI mass

exhibited ions with m/z (relative intensity): 509 (24%), 342 (84%), 255 (100%), 88 (28%) and 87 (16%). The quasimolecular ion had the expected m/z 342 and fragment ions of m/z 255, 88 and 87 are protonated equivalents of fragment ions of m/z 254, 87 and 86 as shown in Fig. 24. Ion of m/z 509.09 was postulated to be a dimer as showm in Fig. 24 and its mass was calculated to be 509.04 which confirmed its identity. Elemental analysis values were found to be within ±0.4% of calculated values. The structures of compounds (129) and (130) were similarly confirmed from spectral data.

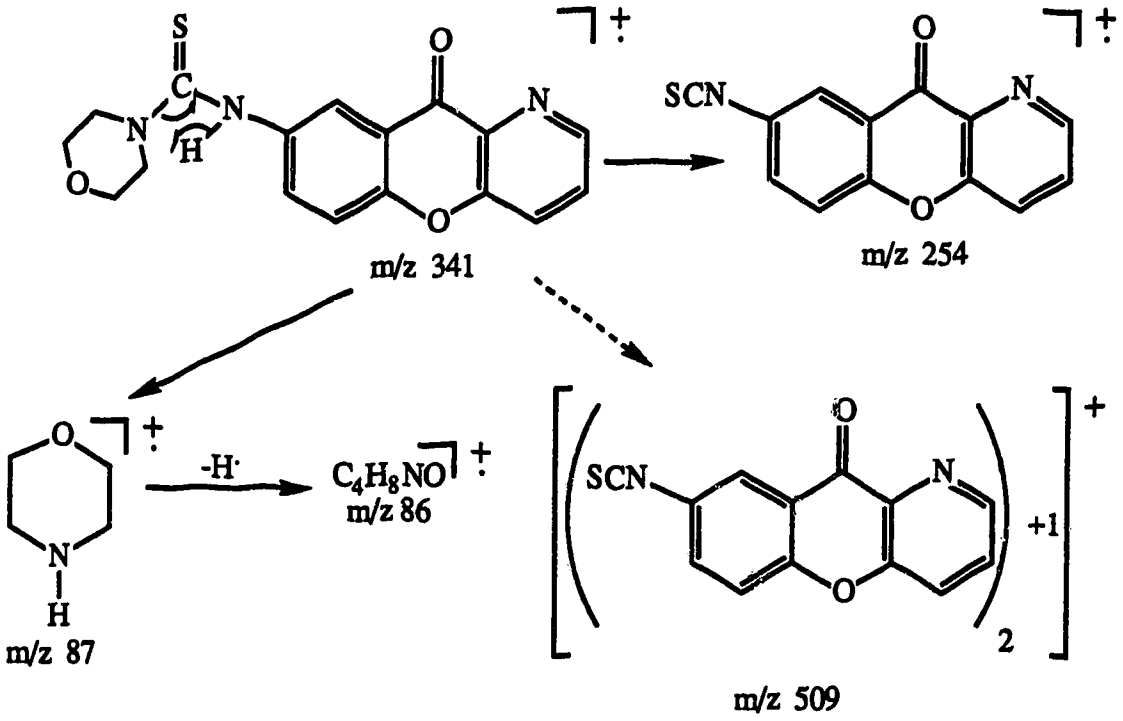
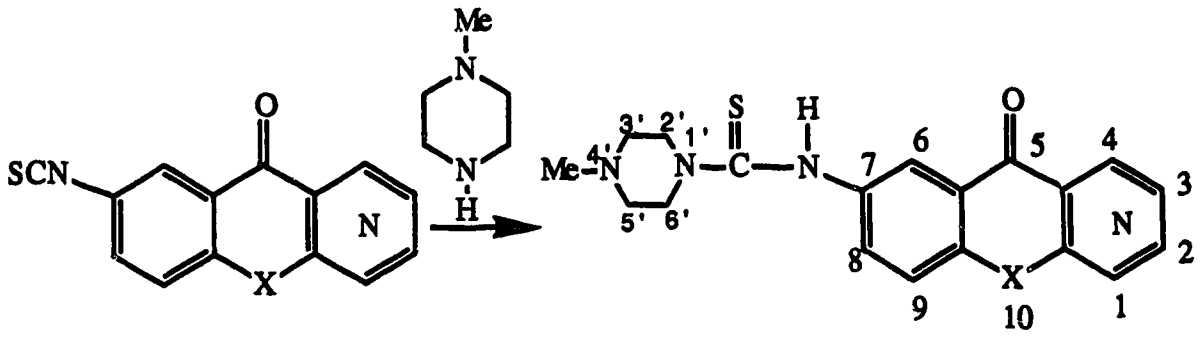


Fig. 24: Postulated major chemical ionization fragmentation pathways of 7-(morpholinothiocarboxamido)-4-azaxanthone

7.6.6. *Synthesis of 7-[1-(N-methylpiperazinyl)thiocarboxamido]-azaxanthone/azathioxanthones (131-133):*



118

	X	Position of N
a)	O	4
b)	S	4
c)	S	1

	X	Position of N
131	O	4
132	S	4
133	S	1

7-Isothiocyanato-4-azaxanthone (118a) was treated with equimolar quantity of N-methylpiperazine to give thiourea (131). Similarly compounds (132) and (133) were synthesized from (118b) and (118c) respectively.

The structures of these compounds were confirmed by spectral data. For example, the ^1H nmr spectrum (δ) of (131) showed a singlet at 2.24 due to the methyl group. A triplet at 2.40 (J=4.5 Hz) was assigned to C_3'-Hs, C_5'-Hs and a triplet at 3.94 (J=4.5 Hz) was assigned to C_2'-Hs, C_6'-Hs. A doublet at 7.68 (J=8.9 Hz) was assigned to the C_9-H. Two doublet of doublets at 7.92 (J=8.9, 4.4 Hz) and 7.98 (J=8.9, 2.5 Hz) were attributed to C_2-H and C_8-H respectively. A doublet at 8.06 (J=2.5 Hz) was assigned to C_6-H. Two doublet of doublets at 8.22 (J=8.9, 1.9 Hz) and 8.82 (J=4.4, 1.9 Hz) were due to C_1-H and C_3-H respectively. A singlet at 9.66 was assigned to the N-H and was exchangeable with D_2O. The i.r. spectrum (cm^{-1}) exhibited absorptions at 3213 (-NH)

and 1655 (-CO). The EI mass spectrum exhibited peaks with m/z (relative intensity): 255 (18%), 254 (100%), 227 (5%), 226 (9%), 100 (17%), 58 (81%) and 56 (17%). A molecular ion peak at m/z 354 was not observed. The peak at m/z 100 was assigned to N-methylpiperazine fragment which fragmented further to give fragment ions of m/z 58 and 56 as shown in Fig. 25.

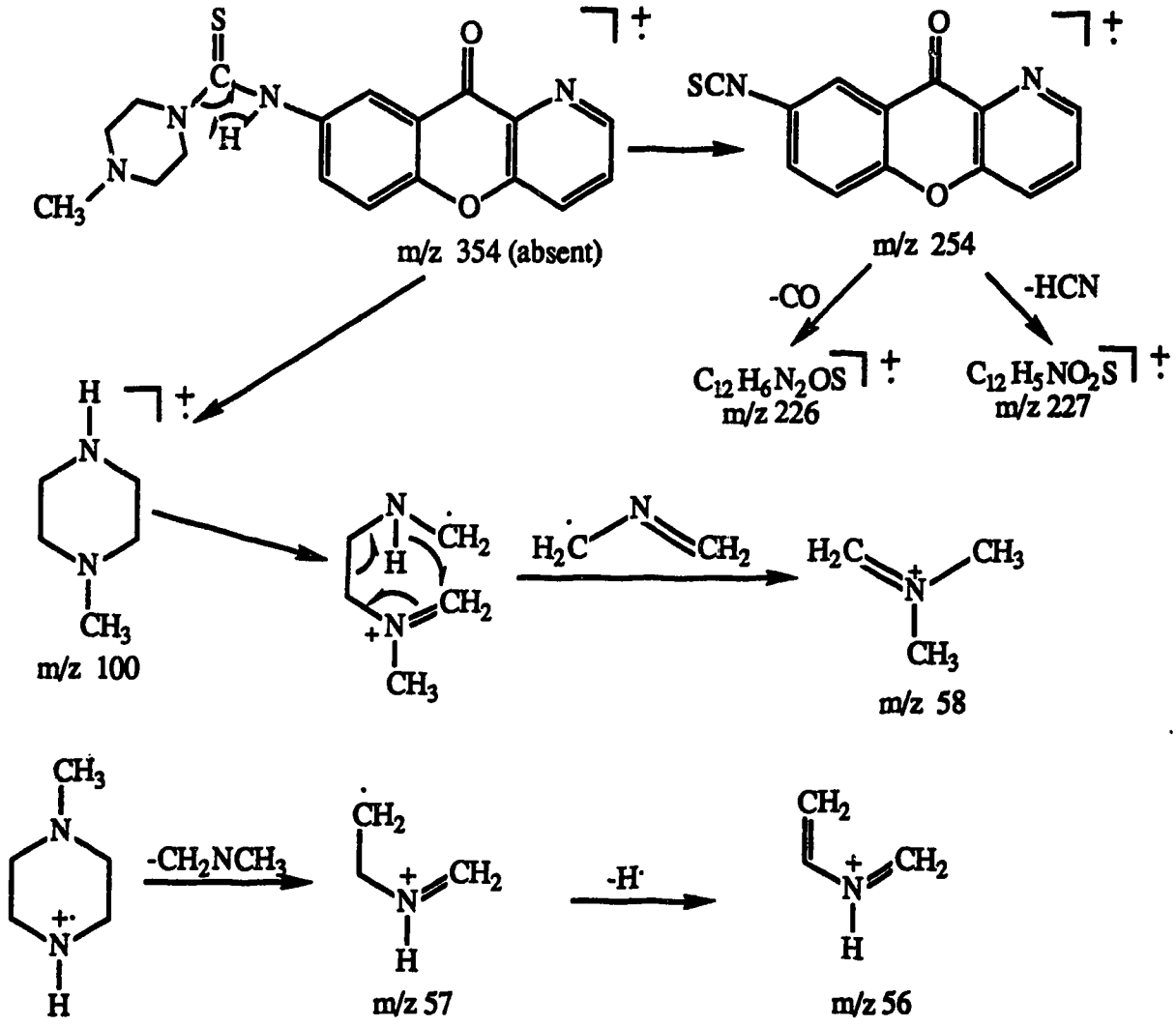
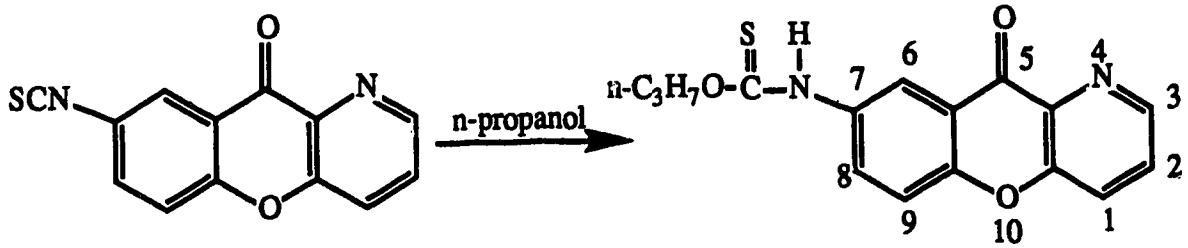


Fig 25: Postulated major fragmentation pathways of 7-[1-(N-methylpiperazinyl)-thiocarboxamido]-4-azaxanthone

The chemical ionization mass spectrum showed ions of m/z 509 (11%), 355 (7%), 256 (22%), 255 (100%), 254 (20%) and 101(15%). Ions of m/z 355, 255 and 101 are protonated equivalent of molecular ion of m/z 354 and its two fragment of m/z 254 and 100 respectively. The peak at m/z 509 is postulated to be a dimer as shown in Fig. 23.

7.6.7. *Synthesis of 7-(n-propoxythiocaboxamido)-4-azaxanthone (134):*



118a 134

7-Isothiocyanato-4-azaxanthone (118a) was refluxed in n-propanol to give thiocarbamate (134).

The 300 MHz ^1H nmr spectrum (δ) of (134) showed a triplet at 0.98 (J=6.0 Hz) due to the methyl group. A multiplet at 1.76 was assigned to -$OCH_2\underline{CH_2}CH_3$ and a broad singlet at 4.44 was assigned to $O\underline{CH_2}CH_2CH_3$. A doublet at 7.70 (J=8.4 Hz) was due to C_9-H and a doublet of doublets at 7.90 (J=8.4, 4.4 Hz) was assigned to C_2-H. A doublet at 8.18 (J=8.4 Hz) was due to C_1-H. Two broad singlets at 8.30 and 8.62 were attributed to C_8-H and C_6-H respectively. These broad singlets for C_8-H and C_6-H were also observed for 1-azaxanthone and 1-azathioxanathone.[139] A doublet at 8.82 (J=4.4 Hz) was assigned to the C_3-H. A singlet at 11.40 was due to the N-H and was exchangeable

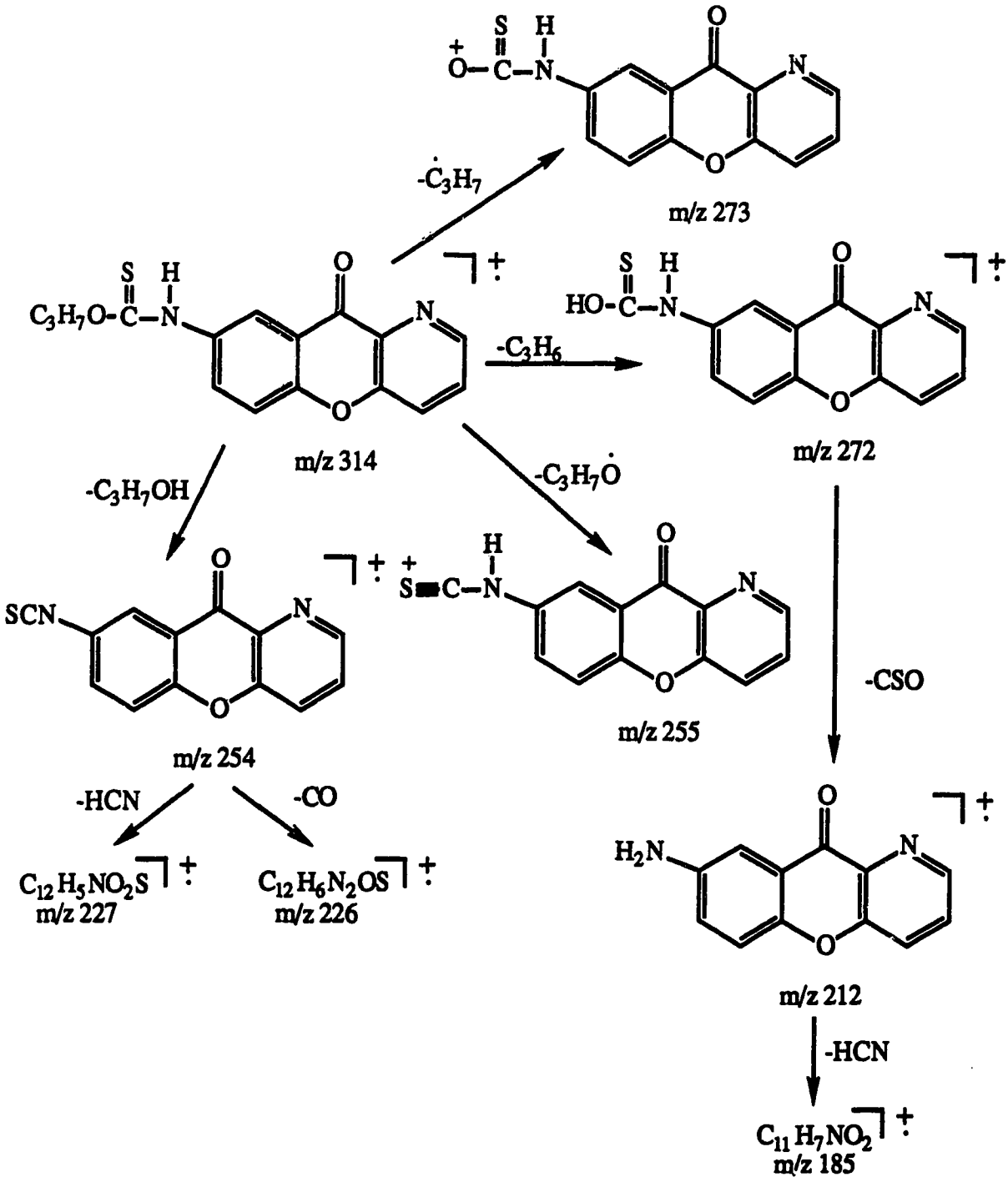


Fig. 26: Postulated major fragmentation pathways of 7-(n-propoxythiocaboxamido)-4-azaxanthone

with D_2O. The i.r. absorptions (cm^{-1}) were at 3287 (-NH) and 1671 (-CO). The EI mass exhibited diagonstic ions of m/z (relative intensity): 314 (21%), 273 (23%), 272 (54%), 255 (68%), 254 (100%), 253 (60%), 227 (48%), 226 (54%), 212 (53%) and 185 (5%). Major fragments are shown in Fig. 26. Microanalysis values were found to be within ±0.4% of calculated value.

8.0. Biological activity:

Compounds were evaluated by Dr. John Burka, Atlantic Veterinary College, University of Prince Edward Island, for their 5-lipoxygenase and/or cyclooxygenase inhibition.[140-150]

8.1. Biological model used:

Compounds were tested on guinea pig isolated tracheal spiral and lung parenchymal strips challenged with arachidonic acid.

Arachidonic acid, on metabolism via the cylooxygenase pathway gives rise to prostaglandins and by the 5-lipoxygenase pathway to leukotrienes. In the presence of indomethacin, guinea pig isolated trachea, on administration of arachidonic acid, shows contraction of the smooth muscle. This is due to the formation of 5-lipoxygenase pathway products such as LTC_4, LTD_4 and LTE_4. On the other hand, parenchymal strips show arachidonic acid induced contraction in the absence of indomethacin. Therefore, contraction of the parenchymal strips is due to cyclooxygenase products i.e., prostaglandins. Thus, if a compound inhibits contraction of trachea induced by arachidonic acid in the presence of indomethacin, it is inhibiting the 5-lipoxygenase pathway or it is blocking the receptor site of leukotrienes. Similarly, if a compound inhibits contraction of lung parenchmal strips induced by arachidonic acid, it is blocking the cyclooxygenase pathway. Trial studies with indomethacin (a known cyclooxygenase inhibitor), NDGA (a known lipoxygenase inhibitor) and L649, 923 (Merck Frosst leukotriene receptor antagonist) have shown that this model works effectively.

8.2. Biological test method

To the organ bath containing tracheal tissue, indomethacin (8.4 mM) was added 45 minutes before challenge with arachidonic acid (66 mM). The test compound (10^{-6} M) was added to the organ bath 30 minutes before addition of arachidonic acid. Testing was previously done using 10^{-5} M but since many of the synthesized compounds are active at lower concentration (10^{-7}M -10^{-8}M) test is now done with concentration of 10^{-6}M. The contractions are compared to those from paired tracheal strips over a period of 60 minutes. If the inhibition was more than 50%, the pD_2 value was calculated. pD_2 is the negative log of concentration of drug that inhibits arachidonic acid induced contraction of the tissue by 50%. Results were compared with the nafazatrom, piriprost, sodium meclofenamate, NDGA, BW 755C and L-649, 923.

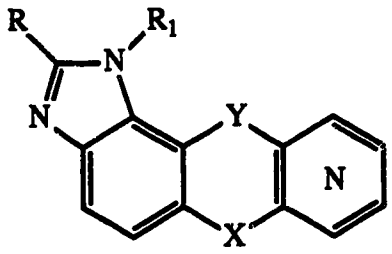
In a similar fashion, compounds were tested using parenchymal strips in the absence of indomethacin and results were compared with the cyclooxygenase inhibitor indomethacin.

8.3. Study for bronchodilating activity

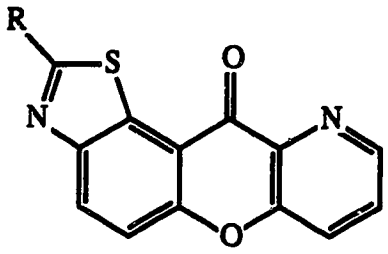
Beside exhibiting cyclooxygenase and/or lipoxygenase inhibition several compounds were found to have airway smooth muscle relaxing activity, even when added to tissues already relaxed with indomethacin. Tracheal spirals and lung parenchymal strips were contracted with histamine (10^{-5}M) and cumulative concentration-response curves for each agent were established. For each tissue, maximum contraction was determined by adding isoprenaline (10^{-6}M) after no further relaxation was obtained with the test compounds. Bronchodilating activity of test compounds was compared with isoprenaline and L-649, 923.

RESULTS

TABLE 1: INHIBITION OF ARACHIDONIC ACID INDUCED CONTRACTIONS

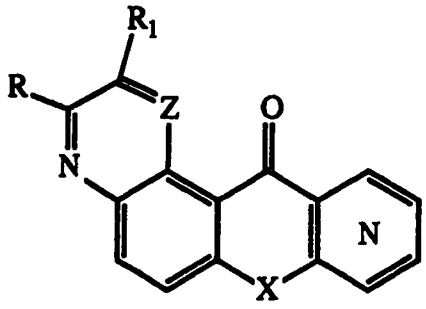


						pD2 values	
No	R	R_1	N	X	Y	Trachea	Parenchyma
78	H	H	4	O	CO	7.51±0.36	-
79	H	H	4	S	CO	CE	
80	H	H	1	S	CO	6.38±0.16	4.09±0.32
82	Me	H	4	O	CO	Biophasic-	
						pD_2±1 7-8	4.67±0.51
						pD_2±2 4-5	
83	Me	H	4	S	CO	~6	-
84	Me	H	1	S	CO	6.48±0.20	>7
86	Me	Me	4	O	CO	6	-
87	Me	Me	4	S	CO	CE	
88	Me	Me	1	S	CO	CE	
90	Me	Et	4	O	CO	>>6	-
91	Me	Et	4	S	CO	CE	
92	Me	Et	1	S	CO	CE	
94	Me	Bz	4	O	CO	CE	
95	Me	Bz	4	S	CO	CE	
96	Me	Bz	1	S	CO	CE	
100	Me	H	4	O	CH_2	<5	-



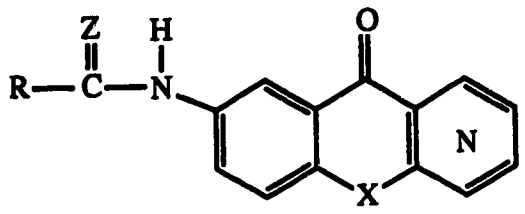
pD2 values

No	R	Trachea	Parenchyma
102	NH_2	< 5	-
103	NHAc	not soluble at 10^{-6}M	



pD2 values

No	R	R_1	N	X	Z	Trachea	Parenchyma
105	Me	H	4	O	C-H	< 6	-
106	Me	H	4	S	C-H	CE	
107	Me	H	1	S	C-H	CE	
108	Me	H	1	Se	C-H	CE	
109	Me	Me	1	S	N	CE	



					pD2 values	
No	R	N	X	Z	Trachea	Parenchyma
116	$C_7H_8NO_2S$	4	O	O	CE	
117	$C_7H_8NO_2S$	4	S	O	CE	
119	C_4H_8N	4	O	S	< 6	-
120	C_4H_8N	4	S	S	CE	
121	C_4H_8N	1	S	S	CE	
122	$C_5H_{10}N$	4	O	S	< 6	-
123	$C_5H_{10}N$	4	S	S	CE	
124	$C_5H_{10}N$	1	S	S	CE	
125	C_5H_8N	4	O	S	< 6	-
126	C_5H_8N	4	S	S	CE	
127	C_5H_8N	1	S	S	CE	
128	C_4H_8NO	4	O	S	~ 6	-
129	C_4H_8NO	4	S	S	CE	
130	C_4H_8NO	1	S	S	CE	

131	$C_5H_{11}N_2$	4	O	S	6.77±0.57	5.82
132	$C_5H_{11}N_2$	4	S	S	CE	
133	$C_5H_{11}N_2$	1	S	S	CE	
134	C_3H_7O	4	O	S	< 6	-
Indomethacin					-	5.26±0.37
Sod. meclofenamate					5.80±0.19	6.28±0 53
NDGA					5.31±0.18	-
Nafazatrom					4.15	-
Piriprost					4.68	-
BW 755C					-	-
L-649,923					6.48±0.37	4.49±0.19

CE: currently being evaluated; - pD_2 <4-5; pD_2 values are mean ± SEM of the -ve logarithms; $C_7H_8NO_2S$ is p-toluenesulphonyl; C_4H_8N is pyrrolidinyl: $C_5H_{10}N$ is piperidino; C_5H_8N is 2,5,6-tetrapyridinyl: C_4H_8NO is morpholino; $C_5H_{11}N_2$ is N-methyl piperazinyl; C_3H_7O is n-propoxy

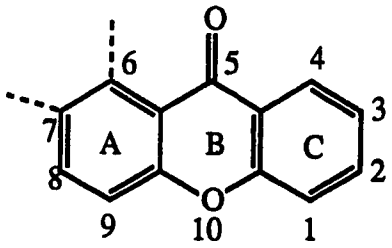
TABLE 2: BRONCHODILATING ACTIVITY

	pD_2 values	
No	Trachea	Parenchyma
78	+	+
90	+	+
128	+	+
131	+	+
Forskolin	6.01	-
Aminophylline	4.13	-
L-649, 923	6.06±0.15	6.92±0.27
Isoprenaline	7.54±0.05	6.96±0.10

CE: currently being evaluated; - $pD_2 < 4\text{-}5$; + $pD_2 > 5$; pD_2 values are mean ± SEM of the -ve logarithms

8.5. Structure-activity relationships:

Based on the biological results of 1-azaxanthone,[139] 4-azaxanthone, 4-azathioxanthone and 1-azathioxanthone derivatives, the following structure-activity relationships can be drawn:

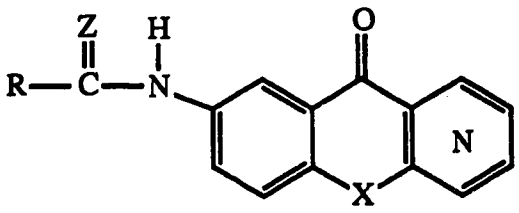


Modification of ring A:

1) The most active compounds were tetracyclic ring systems in which a heteroaromatic ring, such as imidazole, thiazole or pyridine, is fused on the C-6,7 position of the parent tricyclic ring system. Replacement of N-1 hydrogen of benzoimidazole (e.g.82) by an alkyl group (e.g.90) resulted in retention of activity. The thiazole derivative of 1-azaxanthone showed dual inhibitory properties whereas the 4-azaxanthone derivative (102) exhibited only lipoxygenase inhibitory properties. Replacement of the amino-group by an acetamido-group resulted in an insoluble compound (103) which could not be tested. The pyridine derivative (e.g.105) has been found to be active and its pyrazine analog (109) has yet to be evaluated.

2) Five membered heterocyclic ring systems with dihydrofuran and furan present across C-6,7 position did not show appreciable activity which indicates that presence of nitrogen in the ring could be important for activity.

3) The C-7 substitution of azaxanthone with a thiourea side chain resulted in potent lipoxygenase inhibitors. The most active compounds were those in which R=pyrrolidinyl, piperidino, tetrahydropyrdinyl, morpholino and N-methylpiperazinyl.



Modification of ring B:

1) Replacement of oxygen by sulphur resulted in improved activity.

2) Ring opening at the oxygen bridge resulted in loss of activity.

3) Reduction of the C-5 carbonyl group of imidazole (82) in 4-azaxanthone to CH_2 to give reduced imidazole (100) resulted in reduced activity while in case of 1-azaxanthone it resulted in little change in activity.

Modification of ring C:

1) Reduction of the pyridine ring to dihydropyridine and replacement of pyridine by benzene resulted in complete loss of activity.

2) By comparing biological results of 1-azaxanthone with 4-azaxanthone it has been observed that the position of nitrogen in the pyridine ring is apparently not an important factor for activity.

9.0. Summary and conclusions:

A number of azaxanthone derivatives have been synthesized in our laboratory which have potent lipoxygenase inhibitory properties, in some cases better or comparable to those of standard agents. Most of these compounds showed weak cyclooxygenase inhibition. From the biological activity results the following three important conclusions have been made:

1) A nitrogen containing heterocycle fused across C-6,7 position of azaxanthone improves activity as does the thiourea side chain at C-7 postion.

2) The pyridine ring of the azaxanthone is important for activity.

3) Presence of sulphur at the bridge position is more favourable than oxygen.

Metabolism of arachidonic acid by 5-lipoxygenase gives leukotrienes which have been implicated as mediators in a variety of disease processes such as inflammation, inflammatory distress syndrome, psoriasis and asthma. The roles played by leukotrienes in different diseases remain to be defined, in part due to the poor specificity and potency of the available LT receptor antagonists and 5-lipoxygenase inhibitors. The azaxanthone derivatives offer the promise of insight into the contributions of leukotrienes to the pathophysiology of the diseases in which leukotrienes are believed to play a major role.

In most of the diseases a whole array of mediators (such as prostanoids, platelet-activating factor and histamine) are believed to play a role. Therefore, it is expected that successful therapy in diseases like asthma would include interference with several mediators in addition to leukotrienes. A number of the compounds synthesized in our laboratory also exhibited bronchodilating properties. These results are particularly encouraging since bronchodilation is desirable in the treatment of asthma.

Therefore, it will be desirable to further explore the mechanism of action of these azaxanthone derivatives as 5-lipoxygenase inhibitors, leukotriene antagonists and bronchodilators.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point appartaus and are uncorrected. The i.r. spectra were obtained on a Nicolet 5DX fourier transform spectrometer. ^1H nmr spectra were recorded on a Bruker AM 300 fourier transform spectrometer using TMS as an internal standard. Mass spectra were recorded on an AEI MS 12 and ammonia gas was used for chemical ionization mass spectra. Elemental analyses were performed on a Perkin-Elmer 240 B analyzer. Exact mass measurements were obtained when elemental analyses were not within ±0.4%. Column chromatography was performed with 100-200 mesh silica gel (pH 7.3, equivalent to Merck 7734).

10.1. 2-Cyano-3-(thiophenyl)pyridine (70):

3-(Thiophenyl)pyridine-N-oxide (69) (12.75 g, 6.28 mmol) was warmed with stirring to 75-80°C and Me_2SO_4 (7.91 g, 6.28 mmol) was added dropwise maintaining the temperature at 80-85°C during the addition. The mixture was heated for 2 h and dissolved in 50 ml of H_2O. This solution was added dropwise to NaCN (10.86 g) in 30 ml of water, under nitrogen, at a temperature of 0-5°C. The reaction mixture was stirred for 6 h in an ice bath and allowed to warm to room temperature overnight. The mixture was extracted with $CHCl_3$ (3x100 ml) and the solvent removed *in vacuo*. The residue was dissolved in $CHCl_3$ and chromatographed on a silica gel column using 10% $CHCl_3$ in hexane as eluent. The crude product was recrystallized from hexane to give white crystals of 2-cyano-3-(thiophenyl)pyridine (70) in 55% yield. Mp 87-92°C; i.r.($CHCl_3$) (cm^{-1}): 2240 (CN); ^1H-nmr ($CDCl_3$) δ: 7.46 (m, 2H, C_4-H, C_5-H); 7.50 (m, 5H, C_{Ph}-H), 8.58 (dd, 1H, C_6-H, J=4.5, 2.0 Hz); microanalysis for $C_{12}H_8N_2S$: found (calc) C-68.19 (67.90), H-3.96 (3.80), N-13.46 (13.20).

10.2. 4-Azathioxanthone (71):

A mixture of compound (70) (3.25 g, 15.3 mmol) and 40 times its weight of polyphosphoric acid (PPA) was heated with stirring at 185°C for 6 h. The cooled mixture was poured into ice water (500 ml) and basified with NaOH. The precipitate formed was

filtered, washed with water (4 x125 ml) and recrystallized to give cyclized product (71) in 82% yield. Mp observed 225-228°C, reported 224°C (C_6H_6); i.r.(KBr)(cm^{-1}): 1663 (CO); ^1H nmr (DMSO-d_6) δ : 7.68 (1H, C_7-H, J=7.5, 1.0 Hz), 7.88 (m, 3H, C_2-H, C_8-H, C_9-H), 8.42 (dd, 1H, C_1-H, J=8.0, 1.0 Hz), 8.54 (dd, 1H, C_6-H, J=7.5, 1.5 Hz), 8.96 (dd, 1H, C_3-H, J=4.0, 1.0 Hz); microanalysis for $C_{12}H_7NOS$: found (calc) C-67.20 (67.59), H-3.22 (3.31), N-6.51 (6.57).

10.3. General procedure for the synthesis of 7-acetamidoazaxanthone/aza-thioxanthones (74a-c):

Acetic anhydride (1.0 ml) was added to a hot stirred suspension of (73a) (1.0 g, 4.7 mmol) in glacial acetic acid (10 ml) and stirring was continued for 2 h. The product which crystallized from solution was filtered, washed with water (3x20 ml), dried and recrystallized to give (74a) in 87% yield. Mp >300°C (CH_3CN); i.r. (KBr) (cm^{-1}): 3287 (N-H), 1687 (NHCO), 1663 (CO); ^1H nmr (DMSO-d_6) δ : 2.14 (s, 3H, -CH_3), 7.68 (d, 1H, C_9-H, J=9.6 Hz), 7.94 (dd, 1H, C_2-H, J=8.6, 4.1 Hz), 8.12 (dd, 1H, C_8-H, J=9.6, 2.7 Hz), 8.18 (dd, 1H, C_1-H, J=8.6, 1.4 Hz), 8.58 (d, 1H, C_6-H, J=2.7 Hz), 8.84 (dd, 1H, C_3-H, J=4.1, 1.4 Hz), 10.34 (s, 1H, -NH, exch.); microanalysis for $C_{14}H_{10}N_2O_3$: found (calc) C-66.20 (66.14), H-3.91 (3.96), N-11.11(11.02).

By the same procedure, (74b) was obtained from (73b) (3.57 g,15.6 mmol) in 68% yield. Mp >300°C (EtOH); i.r. (KBr) (cm^{-1}): 3312 (NH), 1687 (NHCO), 1630 (CO); ^1H-nmr (DMSO-d_6) δ : 2.10 (s, 3H, -CH_3), 7.76 (dd, 1H, C_2-H, J=8.4, 4.4 Hz), 7.86 (d, 1H, C_9-H, J=9.1 Hz), 8.08 (dd, 1H, C_8-H, J=9.1, 2.2 Hz), 8.38 (dd, 1H, C_1-H, J=8.4, 1.4 Hz), 8.76 (d, 1H, C_6-H, J=2.2 Hz), 8.90 (dd, 1H, C_3-H, J=4.4, 1.4 Hz), 10.5 (s, 1H, -NH, exch.); microanalysis for $C_{14}H_{10}N_2O_2S$: found (calc) C-62.07 (62.21), H-3.80 (3.73), N-10.58 (10.36).

Using the same procedure, (73c) (2.25 g, 9.86 mmol) was acetylated to give (74c) in 94% yield. Mp 205°C (EtOH); i.r. (KBr) (cm^{-1}): 3262 (NH), 1673 (NHCO), 1642 (CO); ^1H nmr (DMSO-d_6) δ: 2.18 (s, 3H, -CH_3), 7.70 (dd, 1H, C_3-H, J=8.1, 4.4 Hz),

7.90 (d, 1H, C9-H, J=8.6 Hz), 8.12 (dd, 1H, C8-H, J=8.6, 2.2 Hz), 8.78 (d, 1H, C6-H, J=2.2 Hz), 8.80 (dd, 1H, C4-H, J=8.1, 1.7 Hz), 8.96 (dd, 1H, C2-H, J=4.4, 1.7 Hz), 10.46 (s, 1H, -NH, exch.); microanalysis for $C_{14}H_{10}N_2O_2S$: found (calc) C-62.07 (62.21), H-3.74 (3.73), N-10.23 (10.36).

10.4. General procedure for the synthesis of 7-acetamido-6-nitro-azaxanthone/azathioxanthones (75a-c):

A solution of KNO_3 (0.7 g) in concentrated H_2SO_4 (2 ml) was added dropwise to a stirred solution of (74a) (1.0 g, 3.9 mmol) in concentrated H_2SO_4 (7 ml) at 0-5°C. The reaction was slowly returned to room temperature, stirred for 3 h and poured over crushed ice. The precipitate was filtered, washed with excess water and recrystallized to give (75a) as light yellow crystals in 87% yield. Mp 290°C (THF); i.r. (KBr) (cm^{-1}): 3620 (NH), 1676 (NHCO), 1683 (CO), 1549 (NO_2), 1324 (NO_2); ^1H nmr (DMSO-d_6) δ: 2.10 (s, 3H, $-CH_3$), 7.98 (m, 2H, C2-H, C9-H), 8.14 (d, 1H, C8-H, J=9.6 Hz), 8.28 (d, 1H, C1-H, J=7.7 Hz), 8.88 (d, 1H, C3-H, J=3.8 Hz), 10.08 (s, 1H, -NH, exch.); microanalysis for $C_{14}H_9N_3O_5$ found (calc) C-55.93 (56.19), H-2.86 (3.03), N-13.97 (14.04).

Using a slight modification in the above procedure, compound (75b) was prepared from (74b) in 60% yield. In this reaction, after pouring over crushed ice, the mixture was cooled overnight to obtain a precipitate of (75b). Mp > 300°C (THF); i.r. (KBr) (cm^{-1}): 3279 (NH), 1671 (NHCO), 1655 (CO), 1556 (NO_2), 1359 (NO_2); ^1H nmr (DMSO-d_6) δ: 2.04 (s, 3H, $-CH_3$), 7.84 (dd, 1H, C2-H, J=8.8, 4.4 Hz), 8.04 (d, 1H, C9-H, J=9.4 Hz), 8.14 (d, 1H, C8-H, J=9.4 Hz), 8.44 (dd, 1H, C1-H, J=8.8, 1.3 Hz), 8.94 (dd, 1H, C3-H, J=4.4, 1.3 Hz), 10.06 (s, 1H, -NH, exch.); microanalysis for $C_{14}H_9N_3O_4S$: found (calc) C-53.59 (53.33), H-2.79 (2.88), N-13.32 (13.33).

7-Acetamido-1-azathioxanthone (74c) (2.5 g, 9.25 mmol) was nitrated with KNO_3 and H_2SO_4, as described for (75a), to give 7-acetamido-6-nitro-1-azathioxanthone (75c) in 63% yield. Mp 283°C (MeOH); i.r. (KBr) (cm^{-1}): 3246 (N-H), 1671 (NHCO),

1638 (CO), 1540 (NO_2), 1302 (NO_2); ^1H nmr (DMSO-d_6) δ: 2.14 (s, 3H, -CH_3), 7.76 (dd, 1H, C_3-H, J=8.2, 4.6 Hz), 8.12 (d, 1H, C_9-H, J=8.4 Hz), 8.22 (d, 1H, C_8-H, J=8.4 Hz), 8.72 (dd, 1H, C_4-H, J=8.2, 1.6 Hz), 9.00 (d, 1H, C_9-H, J=8.4 Hz), 10.10 (s, 1H, -NH, exch.); exact mass measurement for $C_{14}H_9N_3O_4S$: [315.0311 found, 315.0314 calculated].

10.5. General procedure for the synthesis of 7-amino-6-nitroaza-xanthone/azathioxanthones (76a-c):

A solution of (75a) (1.08 g, 3.61 mmol) in 5% HCl was refluxed for 30 min. The product which precipitated out on cooling was filtered, washed with water and recrystallized to give (76a) as yellow solid in 96% yield. Mp >300°C (CH_3COOH); i.r. (KBr) (cm^{-1}) : 3451 (NH), 3320 (NH), 1663 (CO), 1540 (NO_2), 1335 (NO_2); ^1H nmr (DMSO-d_6) δ: 6.16 (s, 2H, -NH, exch.), 7.50 (d, 1H, C_8-H, J=10.2 Hz), 7.68 (d, 1H, C_9-H, J=10.2 Hz), 7.88 (dd, 1H, C_2-H, J=9.4, 4.5 Hz), 8.16 (dd, 1H, C_1-H, J=9.4, 1.6 Hz), 8.80 (dd, 1H, C_3-H, J=4.5, 1.6 Hz); microanalysis for $C_{12}H_7N_3O_4$: found (calc) C-55.70 (56.04), H-2.69 (2.74), N-16.09 (16.34).

Compound (75b) (1.02 g, 3.23 mmol) was refluxed in 10% HCl for 1 h. The product which precipitated out on cooling was filtered, washed with water, dried and recrystallized to give product (76b) in 85% yield as yellow powder. Mp >300°C (CH_3COOH); i.r. (KBr) (cm^{-1}): 3427 (NH), 3312 (NH), 1646 (CO), 1523 (NO_2), 1359 (NO_2); ^1H nmr (DMSO-d_6) δ: 6.44 (s, 2H, -NH_2, exch.), 7.42 (d, 1H, C_9-H, J=9.4 Hz), 7.78 (m, 2H, C_2-H, C_8-H), 8.40 (d, 1H, C_1-H, J=8.8 Hz), 8.88 (d, 1H, C_3-H, J=3.5 Hz); microanalysis for $C_{12}H_7N_3O_3S$: found (calc) C-52.65 (52.74), H-2.70 (2.58), N-15.00 (15.38).

Using the above procedure, (75c) was refluxed in 10% HCl to give (76c) in 90% yield. Mp 205°C (CH_3COOH); i.r. (KBr) (cm^{-1}) : 3458 (NH), 3378 (NH), 1623 (CO), 1539 (NO_2), 1371 (NO_2); ^1H nmr (DMSO-d_6) δ: 6.34 (s, 2H, -NH_2, exch.), 7.42 (d,

1H, C_9-H, J=8.7 Hz), 7.66 (dd, 1H, C_3-H, J=8.7, 4.3 Hz), 7.80 (d, 1H, C_8-H, J=8.7 Hz), 8.62 (dd, 1H, C_4-H, J=8.7, 2.2 Hz), 8.90 (dd, 1H, C_2-H, J=4.3, 2.2 Hz).

10.6. 6,7-Diamino-4-azaxanthone (77a):

A hot ferrous sulphate solution (5g of $FeSO_4$ in aqueous ammonia) was added to a hot solution (60°C) of (76a) (0.42g, 1.63 mmol) in acetone (200 ml) and aqueous ammonia (100 ml). The mixture was heated for 1.5-2 h, cooled and extracted with ethyl acetate. Ethyl acetate was removed *in vacuo* to obtain a solid product in 81% yield. The product was used without further purification.

10.7. 6,7-Diaminoazathioxanthones (77b-c):

Method A: Using the procedure described above, compound (76b) (0.5 g, 1.83 mmol) was reduced with $FeSO_4$ and aqueous ammonia in 45% yield.

Method B: Compound (76b) (0.5 g, 1.83 mmol) was refluxed with hydrazine hydrate (0.4 ml, 12.6 mmol) and palladium-charcoal (0.1 g, 10%) in 95% EtOH (50 ml) for 2 h. The hot reaction mixture was filtered though Celite and washed with hot ethanol (3x10 ml). The combined filtrate was evaporated *in vacuo* to give an orange solid of (77b) in 56% yield. The product was used without further purification.

Compound (76c) (0.5 g, 1.83 mmol) was similarly reduced to give (77c) by method A in 50% yield and by method B in 58% yield.

10.8. General procedure for the synthesis of pyridopyrano-/thiopyrano-benzimidazol-11-ones (78-80)

A solution of (77a) (0.25g, 1.10 mmol) in formic acid (10 ml) was refluxed for 1.5 h, cooled and basified with ammonia solution. The solid which seperated was filtered, washed with water, dried and recrystallized to give (78) in 69% yield. Mp >300°C (CH_3CN); i.r. (KBr) (cm^{-1}): 3402 (NH), 1663 (CO); ^1H nmr (DMSO-d_6) δ: 7.54 (d, 1H, C_4-H, J=9.1 Hz), 7.94 (dd, 1H, C_8-H, J=8.3, 4.0 Hz), 8.26 (m, 2H, C_5-H, C_7-H), 8.36 (s, 1H, C_2-H), 8.84 (d, 1H, C_9-H, J=4.0 Hz), 13.2 (s, 1H, N-H, exch.); EI mass

m/z (relative abundance): 238 (15%), 237 (100%), 209 (12%), 154 (5.28), 105 (10%); exact mass measurement for $C_{13}H_7N_3O_2$: [237.0539 found, 237.0538 calculated].

Using the same procedure, compound (79) was obtained from (77b) in 61% yield. Mp >300°C (MeOH); i.r. (KBr) (cm^{-1}): 3197 (NH), 1630 (CO); ^1H nmr (DMSO-d_6) δ: 7.72 (d, 1H, C_5-H, J=7.9 Hz), 7.82 (dd, 1H, C_8-H, J=8.3, 4.4 Hz), 8.20 (d, 1H, C_4-H, J=7.9 Hz), 8.38 (s, 1H, C_2-H), 8.46 (dd, 1H, C_7-H, J=8.3, 1.6 Hz), 8.96 (dd, 1H, C_9-H, J=4.4, 1.6 Hz); EI mass m/z (relative abundance): 255 (5%), 254 (15%), 253 (100%), 198 (12%), 197 (8%), 113 (8%), 99 (7%); microanalysis for $C_{13}H_7N_3OS$: found (calc) C-61.94 (61.65), H-2.97 (2.79), N-16.39 (16.59).

Using the same procedure, (77c) (0.25 g, 1.02 mmol) was cyclized to give (80) in 70% yield. Mp >300°C (MeOH); i.r. (KBr) (cm^{-1}): 3057 (NH), 1638 (CO); ^1H nmr (DMSO-d_6) δ: 7.78 (m, 2H, C_5-H, C_9-H), 8.26 (d, 1H, C_4-H, J=8.6 Hz), 8.44 (s, 1H, C_2-H), 8.94 (dd, 1H, C_{10}-H, J=8.1, 1.5 Hz), 9.00 (dd, 1H, C_8-H, J=4.5, 1.5 Hz); EI mass m/z (relative intensity): 255 (5%), 254 (15%), 253 (100%), 225 (24%), 198 (8%), 197 (6%), 170 (8%), 126 (7%), 99 (6%); exact mass measurement for $C_{13}H_7N_3OS$: [253.0312 found, 253.0310 calculated].

10.9. General procedure for the synthesis of 7-acetamido-6-amino-4-azaxanthone/azathioxanthones (81a-c):

7-Acetamido-6-nitro-4-azaxanthone (75a) (0.5 g, 1.67 mmol) was refluxed with hydrazine hydrate (0.4 ml,12.6 mmol) and palladium-charcoal (0.1g, 10%) in 95% EtOH (100 ml) for 2 h. The hot reaction mixture was filtered through Celite and washed with hot ethanol (3x25 ml). The combined filterate was evaporated *in vacuo* to give (81a) in 96% yield. Mp 248°C (CH_3CN); i.r. (KBr) (cm^{-1}): 3420 (NH), 3320 (NH), 3287 (NH), 1679 (NHCO), 1638 (CO); ^1H nmr (DMSO-d_6) δ: 2.10 (s, 3H, $-CH_3$), 6.70 (d, 1H, C_9-H, J=8.7 Hz), 7.56 (d, 1H, C_8-H, J=8.7 Hz), 7.70 (s, 2H, $-NH_2$, exch.), 7.88 (dd, 1H, C_2-H, J=8.2, 4.2 Hz), 8.12 (dd, 1H, C_1-H, J=8.2, 1.6 Hz), 8.88 (dd, 1H, C_3-H, J=3.7,

1.6 Hz), 9.26 (s, 1H, -NHAc, exch.); microanalysis for $C_{14}H_{11}N_3O_3$: found (calc) C-62.69 (62.45), H-4.25 (4.12), N-15.71 (15.61).

Using the above procedure, (75b) (0.73 g, 2.32 mmol) was reduced to give (81b) in 68% yield. Mp 270°C (EtOH); i.r. (KBr) (cm^{-1}): 3402 (NH), 3279 (NH), 1679 (NHCO), 1640 (CO); ^{1}H-nmr (DMSO-d_6) δ: 2.08 (s, 3H, -CH_3), 6.86 (d, 1H, C_9-H, J=8.4 Hz), 7.48 (d, 1H, C_8-H, J=8.4 Hz), 7.68 (dd, 1H, C_2-H, J=8.4, 4.2 Hz), 7.94 (s, 2H, -NH_2, exch.), 8.22 (dd, 1H, C_1-H, J=8.4, 1.4 Hz), 8.82 (dd, 1H, C_3-H, J=4.2, 1.4 Hz), 9.28 (s, 1H, -NH, exch.); exact mass measurement for $C_{14}H_{11}N_3O_2S$: [285.0569 found, 285.0573 calculated].

Compound (75c) (1.0g, 3.17 mmol) was reduced with $FeSO_4$-aqueous ammonia as described for (77a) (section **10.6.**) to give 81c in 77% yield. Mp 255°C (CH_3CN); i.r. (KBr) (cm^{-1}): 3484 (NH), 3320 (NH), 3271 (NH), 1663 (NHCO), 1631 (CO); ^{1}H nmr (DMSO-d_6) δ: 2.08 (s, 3H, -CH_3), 6.84 (d, 1H, C_9-H, J=7.8 Hz), 7.44 (d, 1H, C_8-H, J=7.8 Hz), 7.54 (dd, 1H, C_3-H, J=8.6, 1.6 Hz), 7.94 (s, 2H, -NH_2, exch.), 8.64 (dd, 1H, C_4-H, J=8.6, 1.6 Hz), 8.76 (dd, 1H, C_2-H, J=4.7, 1.6 Hz), 9.26 (s, 1H, -NH, exch.).

10.10. General procedure for the synthesis of 2-methylpyridopyrano/-thiopyranobenzimidazol-11-one (82-84):

A solution of (81a) (0.25 g, 0.93 mmol) in concentrated HCl-EtOH (2:1, 12ml) was refluxed for 8 h. After cooling, ethanol was removed *in vacuo* and the residue was taken up in aqueous ammonia. The precipitate which formed was filtered, washed with water, followed by washing with cold acetone (10 ml) and recrystallized to give (82) as tan crystals in 60% yield. Mp > 310°C (CH_3CN); i.r. (KBr) (cm^{-1}): 3427 (NH), 1663 (CO); ^{1}H nmr (DMSO-d_6) δ: 2.60 (s, 3H, -CH_3), 7.48 (d, 1H, C_5-H, J=8.5 Hz), 7.94 (dd, 1H, C_8-H, J=8.0, 4.0 Hz), 8.10 (d, 1H, C_4-H, J=8.5 Hz), 8.28 (dd, 1H, C_7-H, J=8.0, 1.5 Hz), 8.88 (dd, 1H, C_9-H, J=4.0, 1.5 Hz), 12.14 (s, 1H, -NH, exch.); EI mass m/z

(relative abundance): 252 (16%), 251 (100%), 250 (38%), 222 (7%); microanalysis for $C_{14}H_9N_3O_2$: found (calc) C-66.78 (66.93), H-3.59 (3.61), N-16.79 (16.72).

Compound (81b) (0.35 g, 1.22 mmol) was similarly cyclized to give (83) as yellow crystals in 79% yield. Mp >300°C (CH_3CN); i.r. (KBr) (cm^{-1}): 3418 (NH), 1630 (CO); ^1H nmr (DMSO-d_6) δ: 2.64 (s, 3H, $-CH_3$), 7.64 (d, 1H, C_5-H, J=7.9 Hz), 7.82 (dd, 1H, C_8-H, J=9.0, 4.5 Hz), 8.06 (d, 1H, C_4-H, J=7.9 Hz), 8.46 (dd, 1H, C_7-H, J=9.0, 1.7 Hz), 8.98 (dd, 1H, C_9-H, J= 4.5, 1.7 Hz), 13.14 (s, 1H, -NH, exch.); EI mass m/z (relative abundance): 269 (6%), 268 (17%), 267 (100%), 266 (11%), 239 (24%), 238 (21%), 133 (7%); microanalysis for $C_{14}H_9N_3OS$: found (calc) C-63.03 (62.91), H-3.23 (3.39), N-16.02 (15.72).

From (81c) (0.25 g, 0.87 mmol) by using the same procedure (84) was obtained in 65% yield. Mp 247°C (CH_3CN); i.r. (KBr) (cm^{-1}): 3410 (-NH), 1638 (CO);^1H nmr (DMSO-d_6) δ: 2.62 (s, 3H, $-CH_3$), 7.62 (d, 1H, C_9-H, J=8.4 Hz), 7.68 (dd, 1H, C_3-H, J=8.4, 4.5 Hz), 8.02 (d, 1H, C_8-H, J=8.4 Hz), 8.84 (dd, 1H, C_4-H, J=8.4, 1.9 Hz), 8.92 (dd, 1H, C_2-H, J= 4.5, 1.9 Hz), 12.15 (s, 1H, -NH, exch.); EI mass m/z (relative abundance): 269 (6%), 268 (17%), 267 (100%), 266 (16%), 239 (10%), 238 (11%); microanalysis for $C_{14}H_9N_3OS$: found (calc) C-62.72 (62.91), H-3.27 (3.39), N-15.80 (15.72).

10.11. General procedure for the synthesis of 7-acetamido-6-methylamino-azaxanthone/azathioxanthones (85a-c):

To a hot solution of 7-acetamido-6-nitro-4-azaxanthone (75a) (0.52 g, 1.73 mmol) in 95% EtOH (20 ml), methylamine (5 ml, 25-30% aqueous solution) was added. The mixture was refluxed for 1 h and the completion of reaction monitored by TLC. The mixture was cooled, the solvent removed and the residue washed with water and recrystallized to give (85a) in 78% yield. Mp 254°C (EtOH); i.r. (KBr) (cm^{-1}): 3254 (-NH), 1638 (CO); ^1H nmr (DMSO-d_6) δ: 2.04 (s, 3H, $-NHCOCH_3$), 3.06 (d, 3H, $-NHCH_3$, J=5.9 Hz), 6.70 (d, 1H, C_9-H, J=8.4 Hz), 7.36 (d, 1H, C_8-H, J=8.4 Hz),

7.86 (dd, 1H, C_2-H, J=8.4, 4.2 Hz), 8.08 (dd, 1H, C_1-H, J=8.4, 1.7 Hz), 8.76 (dd, 1H, C_3-H, J=4.2, 1.7 Hz), 9.54 (s, 1H, -NHAc, exch.), 9.74 (q, 1H, -NHMe, J=5.9, exch.); microanalysis for $C_{15}H_{13}N_3O_3$: found (calc) C-63.49 (63.60), H-4.83 (4.63), N-14.81(14.83).

By the same procedure, (85b) was obtained from (75b) (0.5 g, 1.58 mmol) in 88% yield. Mp 246-248°C (CH_3CN); i.r. (KBr) (cm^{-1}): 3230 (NH), 1646 (NHCO), 1614 (CO); ^1H nmr (DMSO-d_6) δ: 2.06 (s, 3H, -NHCOCH_3), 3.00 (d, 3H, -NHCH_3, J=6.0 Hz), 6.94 (d, 1H, C_9-H, J=8.3 Hz), 7.34 (d, 1H, C_8-H, J=8.3 Hz), 7.68 (dd, 1H, C_2-H, J=8.3, 4.1 Hz), 8.22 (d, 1H, C_1-H, J=8.3 Hz), 8.80 (s, 1H, -NHMe, exch.), 9.56 (s, 1H, -NHAc, exch.), 9.90 (dd, 1H, C_3-H, J=4.1 Hz); microanalysis for $C_{15}H_{13}N_3O_2S$: found (calc) C-60.16 (60.19), H-4.54 (4.38), N-14.11 (14.04).

Using the above procedure, (75c) (0.5 g, 1.58 mmol) was converted to (85c) in a yield of 80%. Mp 244-246°C (EtOH); i.r. (KBr) (cm^{-1}): 3238 (NH), 1655 (CO), 1614 (CO); ^1H nmr (DMSO-d_6) δ: 2.06 (s, 3H, -NHCOCH_3), 3.04 (d, 3H, -NHCH_3, J=4.7 Hz), 6.96 (d, 1H, C_9-H, J=7.6 Hz), 7.36 (d, 1H, C_8-H, J=7.6 Hz), 7.60 (dd, 1H, C_3-H, J=8.5, 4.7 Hz), 8.68 (dd, 1H, C_4-H, J=8.5, 1.9 Hz), 8.84 (dd, 1H, C_2-H, J=4.7, 1.9 Hz), 9.58 (s, 1H, -NHAc, exch.), 10.02 (q, 1H, -NHMe, J=4.7 Hz, exch.); microanalysis for $C_{15}H_{13}N_3O_2S$: found (calc) C-60.40 (60.19), H-4.47 (4.38), N-14.16 (14.04).

10.12. General procedure for the synthesis of 1,2-dimethylpyridopyrano/-thiopyranobenzimidazol-11-ones (86-88):

A solution of (85a) (0.3 g, 1.06 mmol) in concentrated HCl:EtOH (2:1, 15 ml) was refluxed for 8 h. The reaction was then cooled, ethanol was removed *in vacuo* and the residue was taken up in aqueous ammonia. The precipitate which formed was filtered, washed with water, followed by washing with acetone (10 ml) and recrystallized to give (86) in 75% yield. Mp 248°C (CH_3CN); i.r.(KBr) (cm^{-1}): 1663 (CO); ^1H nmr (DMSO-d_6) δ: 3.34 (s, 3H, C_2-CH_3), 4.20 (s, 3H, N_1-CH_3), 7.48 (d, 1H, C_5-H, J=8.9 Hz),

7.92 (dd, 1H, C_8-H, J=8.9, 4.5 Hz), 8.08 (d, 1H, C_4-H, J=8.9 Hz), 8.24 (dd, 1H, C_7-H, J=8.9, 1.3 Hz), 8.84 (dd, 1H, C_9-H, J=4.5, 1.3 Hz); EI mass m/z (relative abundance): 266 (17%), 265 (100%), 264 (85%), 251 (10%), 250 (62%), 169 (9%), 140 (9%), 132 (8%); microanalysis for $C_{15}H_{11}N_3O_2$: found (calc) C-67.76 (67.92), H-4.14 (4.18), N-15.97 (15.84).

By the same procedure, (87) was obtained from (85b) (0.3g, 1.00 mmol) in 64% yield. Mp 234°C (CH_3CN); i.r. (KBr) (cm^{-1}): 1646 (CO); ^1H nmr (DMSO-d_6) δ: 2.62 (s, 3H, C_2-CH_3), 3.86 (s, 3H, N_1-CH_3), 7.60 (d, 1H, C_5-H, J=8.9 Hz), 7.78 (dd, 1H, C_8-H, J=8.5, 4.5 Hz), 8.00 (d, 1H, C_4-H, J=8.9 Hz), 8.40 (dd, 1H, C_7-H, J=8.5, 1.5 Hz), 8.90 (dd, 1H, C_9-H, J=4.5, 1.5 Hz); EI mass m/z (relative abundance): 283 (6%), 282 (20%), 281 (100%), 280 (65%), 267 (9%), 266 (51%), 185 (13%), 184 (10%), 140 (8%); microanalysis for $C_{15}H_{11}N_3OS$: found (calc) C-63.86 (64.04), H-4.04 (3.94), N-14.54 (14.94).

By the same procedure, (88) was obtained from (85c) (0.37 g, 1.23 mmol) in 92% yield. Mp 207-208°C (CH_3CN); i.r. (KBr) (cm^{-1}): 1638 (CO); ^1H nmr (DMSO-d_6) δ: 3.38 (s, 3H, C_2-CH_3), 3.94 (s, 3H, N_1-CH_3), 7.62 (d, 1H, C_5-H, J=9.0 Hz), 7.70 (dd, 1H, C_9-H, J=8.2, 4.3 Hz), 8.02 (d, 1H, C_4-H, J=9.0 Hz), 8.74 (dd, 1H, C_{10}-H, J=8.2, 1.7 Hz), 8.94 (dd, 1H, C_8-H, J=4.3, 1.7 Hz); EI mass m/z (relative abundance): 283 (6%), 282 (20%), 281(100%), 280 (62%), 267 (8%), 266 (47%), 185 (5%), 184 (5%), 140 (7%); microanalysis for $C_{15}H_{11}N_3OS$: found (calc) C-63.76 (64.04), H-3.91 (3.94), N-15.03 (14.94).

10.13. General procedure for the synthesis of 7-acetamido-6-ethylamino-azaxanthone/azathioxanthones (89a-c):

A solution of (75a) (0.5 g, 1.67 mmol) in EtOH (10 ml) was refluxed with ethylamine (1.0 ml) to give (89a) in 77% yield. Mp (sublimes) 263°C (EtOH); i.r. (KBr) (cm^{-1}): 3451 (NH), 3238 (NH), 1649 (CO); ^1H nmr (DMSO-d_6) δ: 1.28 (t, 3H, -$CH_2\underline{CH_3}$, J=6.0 Hz), 2.14 (s, 3H, -NHCO$\underline{CH_3}$), 3.54 (m, 2H, -$\underline{CH_2}CH_3$), 6.66 (d, 1H, C_9-H,

J=8.6 Hz), 7.46 (d, 1H, C_8-H, J=8.6 Hz), 7.74 (dd, 1H, C_2-H, J=8.6, 4.8 Hz), 7.90 (dd, 1H, C_1-H, J=8.6, 1.9 Hz), 8.76 (dd, 1H, C_3-H, J=4.8, 1.9 Hz), 9.30 (s, 1H, -NHAc, exch.), 9.62 (t, 1H, -NHEt, J=3.8 Hz, exch.); microanalysis for $C_{16}H_{15}N_3O_3$: found (calc) C-64.54 (64.64), H-5.14 (5.09), N-14.16 (14.13).

By the same procedure, (89b) was obtained from (75b) (0.5 g, 1.58 mmol) in 90% yield. Mp 254-256°C (EtOH); i.r. (KBr) (cm^{-1}): 3443 (NH), 3246 (NH), 1663 (NHCO), 1622 (CO); ^1H nmr (DMSO-d_6) δ: 1.18 (t, 3H, -CH_2CH_3, J=7.0 Hz), 2.04 (s, 3H, -NHCOCH_3), 3.38 (q, 2H, -CH_2CH_3, J=7.0, 4.9 Hz), 7.00 (d, 1H, C_9-H, J=8.1 Hz), 7.42 (d, 1H, C_8-H, J=8.1 Hz), 7.70 (dd, 1H, C_2-H, J=8.1, 4.1 Hz), 8.24 (d, 1H, C_1-H, J=8.1 Hz), 8.82 (d, 1H, C_3-H, J=4.1 Hz), 9.56 (s, 1H, -NHAc, exch.), 9.84 (t, 1H, -NHEt, J=4.9 Hz, exch.); exact mass measurement for $C_{16}H_{15}N_3O_2S$: [313.0888 found, 313.0886 calculated].

Using the above procedure, (75c) (0.5 g, 1.58 mmol) was converted to (89c) in a yield of 90%. Mp 258°C (EtOH); i.r. (KBr) (cm^{-1}): 3246 (-NH), 1649 (-NHCO), 1614 (CO); ^1H nmr (DMSO-d_6) δ: 1.22 (t, 3H, -CH_2CH_3, J=7.0 Hz), 2.08 (s, 3H, -NHCOCH_3), 3.46 (m, 2H, -CH_2CH_3), 7.02 (d, 1H, C_9-H, J=8.1 Hz), 7.44 (d, 1H, C_8-H, J=8.1 Hz), 7.64 (dd, 1H, C_3-H, J=8.1, 4.0 Hz), 8.74 (dd, 1H, C_4-H, J=8.1, 1.6 Hz), 8.86 (dd, 1H, C_2-H, J=4.0, 1.6 Hz), 9.58 (s, 1H, -NHAc, exch.), 9.96 (t, 1H, -NHEt, J=4.9 Hz, exch.); microanalysis for $C_{16}H_{15}N_3O_2S$: found (calc) C-61.33 (61.34), H-4.87 (4.82), N-13.31 (13.41).

10.14. General procedure for the synthesis of 1-ethyl-2-methylpyrido-pyrano/thiopyranobenzimidazol-11-ones (90-92):

Compound (89a) (0.5 g, 1.68 mmol) was refluxing with HCl: EtOH (2:1) to give (90) in 61% yield as described in section **10.12**. Mp 192°C (CH_3CN), i.r. (KBr) (cm^{-1}): 1655 (CO); ^1H nmr (DMSO-d_6) δ: 1.46 (t, 3H, -CH_2CH_3, J=6.8 Hz), 2.18 (s, 3H, -NHCOCH_3), 5.00 (q, 2H, -CH_2CH_3, J=6.8 Hz), 7.42 (d, 1H, C_5-H, J=9.1 Hz), 7.70 (dd, 1H, C_8-H, J=8.0, 3.4 Hz), 7.96 (d, 1H, C_4-H, J=9.1 Hz), 8.08 (dd, 1H, C_7-H,

J=8.0, 1.1 Hz), 8.86 (dd, 1H, C9-H, J=3.4, 1.1 Hz); EI mass m/z (relative abundance): 280 (14%), 279 (76%), 278 (8%), 265 (17%), 264 (100%), 251 (16%), 140 (5%); microanalysis for $C_{16}H_{13}N_3O_2$: found (calc) C-68.81 (68.81), H-4.71 (4.69), N-14.95 (15.04).

Using the above procedure, (89b) (0.38 g, 1.20 mmol) was converted to (91) in 35% yield. Mp 190°C (CH_3CN), i.r. (KBr) (cm^{-1}): 1638 (CO); ^1H nmr (DMSO-d_6) δ: 1.14 (t, 3H, -$CH_2\underline{CH_3}$, J=7.0 Hz), 2.66 (s, 3H, -NHCO$\underline{CH_3}$) , 4.60 (q, 2H, -$\underline{CH_2}CH_3$, J=7.0 Hz), 7.62 (d, 1H, C_5-H, J=8.4 Hz), 7.78 (dd, 1H, C_8-H, J=8.4, 4.4 Hz), 8.02 (d, 1H, C_4-H, J=8.4 Hz), 8.40 (dd, 1H, C_7-H, J=8.4, 1.5 Hz), 8.90 (dd, 1H, C9-H, J=4.4, 1.5 Hz); EI mass m/z (relative abundance): 297 (5%), 296 (17%), 295 (88%), 294 (7%), 282 (6%), 281 (18%), 280 (100%), 278 (12%), 268 (8%), 267 (18%), 253 (6%), 225 (6%), 213 (7%); exact mass measurement for $C_{16}H_{13}N_3OS$: [295.0780 found, 295.0781 calculated].

By the same procedure, (92) was obtained from (89c) (0.26 g, 0.8 mmol). The compound was dissolved in 10% MeOH in $CHCl_3$ and chromatographed on a silica gel column using $CHCl_3$ as eluent. The crude product was recrystallization from acetonitrile to give pure product in 37% yield. Mp 166°C; i.r. (KBr) (cm^{-1}): 1646 (CO); ^1H nmr (DMSO-d_6) δ: 1.22 (t, 3H, -$CH_2\underline{CH_3}$, J=6.6 Hz), 3.38 (s, 3H, C_2-CH_3), 4.68 (q, 2H, -$\underline{CH_2}CH_3$, J=6.6 Hz), 7.66 (d, 1H, C_5-H, J=8.6 Hz), 7.72 (dd, 1H, C9-H, J=7.4, 3.7 Hz), 8.08 (d, 1H, C_4-H, J=8.6 Hz), 8.78 (dd, 1H, C_{10}-H, J=7.4, 1.2 Hz), 8.96 (dd, 1H, C9-H, J=3.7, 1.2 Hz); EI mass m/z (relative abundance): 296 (12%), 295 (62%), 282 (8%), 281 (23%), 280 (100%), 267 (9%), 266 (5%), 185 (5%), 184 (5%), 140 (7%); microanalysis for $C_{16}H_{13}N_3OS$: found (calc) C-65.02 (65.04), H-4.40 (4.44), N-14.13 (14.23).

10.15. General procedure for the synthesis of 7-acetamido-6-benzylamino-azaxanthone/azathioxanthones (93a-c):

Compound (75a) (0.52 g, 1.74 mmol) on treatment with an equimolar quantity of benzylamine in EtOH (20 ml), gave (93a) after recrystallization in 74% yield. Mp 234-236°C (EtOH); i.r. (KBr) (cm^{-1}): 3262 (NH), 1658 (NHCO), 1639 (CO); ^1H nmr (DMSO-d_6) δ: 2.00 (s, 3H, $-CH_3$), 4.66 (d, 2H, $-CH_2-$, J=5.8 Hz), 6.82 (d, 1H, C_9-H, J=8.3 Hz), 7.40 (m, 5H, $-C_6H_5$), 7.48 (d, 1H, C_8-H, J=8.3 Hz), 7.86 (dd, 1H, C_2-H, J=9.1, 4.2 Hz), 8.12 (dd, 1H, C_1-H, J=9.1, 1.7 Hz), 8.76 (dd, 1H, C_3-H, J=4.2, 1.7 Hz), 9.56 (s, 1H, -NHAc, exch.), 9.96 (t, 1H, -NHBz, J=5.8 Hz, exch.); microanalysis for $C_{21}H_{17}N_3O_3$: found (calc) C-69.78 (70.18), H-4.82 (4.77), N-11.66 (11.69).

Using the above procedure, (75b) (0.5 g, 1.58 mmol) was converted to (93b) in 79% yield. Mp 233°C (EtOH); i.r. (KBr) (cm^{-1}): 3246 (NH), 1669 (NHCO), 1614 (CO); ^1H nmr (DMSO-d_6) δ: 2.04 (s, 3H, $-CH_3$), 4.54 (d, 2H, $-CH_2$, J=6.4 Hz), 7.04 (d, 1H, C_9-H, J=8.0 Hz), 7.36 (m, 5H, $-C_6H_5$), 7.48 (d, 1H, C_8-H, J=8.0 Hz), 7.66 (dd, 1H, C_2-H, J=8.0, 4.8 Hz), 8.24 (dd, 1H, C_1-H, J=8.0, 1.6 Hz), 8.78 (dd, 1H, C_3-H, J=4.8, 1.6 Hz), 9.56 (s, 1H, -NHAc, exch.), 10.02 (t, 1H, -NHBz, J=6.4 Hz, exch.); microanalysis for $C_{21}H_{17}N_3O_2S$: found (calc) C-66.97 (67.19), H-4.74 (4.56), N-11.13 (11.19).

By the same procedure, (93c) was obtained from (75c) (0.5 g, 1.58 mmol) in 79% yield. Mp 234°C (EtOH); i.r. (KBr) (cm^{-1}): 3238 (NH), 1655 (NHCO), 1605 (CO); ^1H-nmr (DMSO-d_6) δ: 2.04 (s, 3H, $-CH_3$), 4.58 (d, 2H, $-CH_2$, J=5.0 Hz), 7.08 (d, 1H, C_9-H, J=8.4 Hz), 7.38 (m, 5H, $-C_6H_5$), 7.48 (d, 1H, C_8-H, J=8.4 Hz), 7.60 (dd, 1H, C_3-H, J=8.4, 4.2 Hz), 8.66 (dd, 1H, C_4-H, J=8.4, 1.7 Hz), 8.84 (dd, 1H, C_2-H, J=4.2, 1.7 Hz), 9.62 (s, 1H, -NHAc, exch.), 10.16 (t, 1H, -NHBz, J=5.0 Hz, exch.); microanalysis for $C_{21}H_{17}N_3O_2S$: found (calc) C-66.88 (67.18), H-4.56 (4.56), N-10.97 (11.19).

10.16. General procedure for the synthesis of 1-benzyl-2-methylpyrido-pyrano/thiopyranobenzimidazol-11-ones (94-96):

Compound (93a) (0.45 g, 1.25 mmol) on refluxing with HCl: EtOH (2:1) gave (94) after recrystallization in 61% yield. Mp 203-206°C (CH_3CN), i.r. (KBr) (cm^{-1}): 1663 (CO); ^1H nmr (DMSO-d_6) δ: 2.54 (s, 3H, -CH_3), 6.36 (s, 2H, -CH_2), 6.92 (d, 1H, C-Ph*ortho*, J=8.7 Hz), 7.24 (m, 3H, C-Ph*meta,para*), 7.54 (d, 2H, C_5-H, J=8.7 Hz), 7.88 (dd, 1H, C_8-H, J=8.7, 4.7 Hz), 8.16 (d, 1H, C_4-H, J=8.7 Hz), 8.20 (dd, 1H, C_7-H, J=8.7, 1.3 Hz), 8.76 (dd, 1H, C_9-H, J=4.7, 1.3 Hz); EI mass m/z (relative abundance): 342 (21%), 341 (95%), 340 (20%), 327 (11%), 326 (46%), 299 (14%), 265 (17%), 264 (100%), 250 (17%), 170 (10%), 91 (28%); microanalysis for $C_{21}H_{15}N_3O_2$: found (calc) C-73.88 (73.89), H-4.39 (4.43), N-12.45 (12.31).

By the same procedure, (95) was prepared from (93b) (0.35 g, 0.93 mmol) in 75% yield. Mp 236-238°C (CH_3CN), i.r. (KBr) (cm^{-1}): 1646 (CO); ^1H nmr (DMSO-d_6) δ: 2.66 (s, 3H, -CH_3), 5.86 (s, 2H, -CH_2), 6.84 (dd, 2H, Ph*ortho*, J=7.9, 1.7 Hz), 7.22 (m, 3H, C-Ph*meta,para*), 7.60 (d, 1H, C_5-H, J=7.9 Hz), 7.70 (dd, 1H, C_8-H, J=9.0, 4.5 Hz), 8.02 (d, 1H, C_4-H, J=7.9 Hz), 8.32 (dd, 1H, C_7-H, J=9.0, 1.7 Hz), 8.84 (d, 1H, C_9-H, J=4.5, 1.7 Hz); EI mass m/z (relative abundance): 359 (7%), 358 (25%), 357 (100%), 356 (19%), 343 (8%), 342 (34 %), 315 (10%), 281 (14%), 280 (74%), 266 (28%), 185 (5%), 178 (10%), 91 (28%); microanalysis for $C_{21}H_{15}N_3OS$: found (calc) C-70.55 (70.57), H-4.38 (4.23), N-11.68 (11.76).

Using the above procedure, (93c) (0.40 g, 1.06 mmol) was converted to (96) in a yield of 65%. Mp 286°C (CH_3CN); i.r. (KBr) (cm^{-1}): 1630 (CO); ^1H nmr (DMSO-d_6) δ: 2.68 (s, 3H, -CH_3), 5.96 (s, 2H, -CH_2), 6.84 (d, 1H, Ph*ortho*, J=7.5 Hz), 7.16 (m, 3H, C-Ph*meta,para*), 7.64 (m, 2H, C_5-H, C_9-H), 8.10 (d, 1H, C_4-H, J=8.7 Hz), 8.60 (dd, 1H, C_{10}-H, J=8.1, 1.7 Hz), 8.88 (dd, 1H, C_8-H, J=5.2, 1.7 Hz); EI mass m/z (relative abundance): 359 (7%), 358 (25%), 357 (99%), 356 (19%), 343 (11%), 342 (48%), 315 (7%), 282 (6%), 281 (18%), 280 (100%), 266 (11%), 178 (9%), 91 (63%);

microanalysis for $C_{21}H_{15}N_3OS$: found (calc) C-70.49 (70.57), H-4.23 (4.23), N-11.83 (11.76).

10.17. 7-Acetamido-6-nitro-4-azaxanthen-5-ol (97):

To a solution of (75a) (0.5 g, 1.67 mmol) in MeOH, $NaBH_4$ (0.07 g, 1.85 mmol) was added with stirring. Stirring was continued for 3-4 h and solvent removed *in vacuo*. Water (25 ml) was added to the residue which was filtered, washed with water, dried and recrystallized to give (97) in 85% yield. Mp: 242°C (CH_3OH); i.r. (KBr) (cm^{-1}): 3466-3100 (OH), 3262 (NH), 1664 (CO), 1540 (NO_2), 1369 (NO_2); ^1H nmr (DMSO-d_6) δ: 2.12 (s, 3H, -CH_3), 6.12 (d, 1H, C_5-H, J=7.4 Hz), 6.40 (d, 1H, C_5-OH, J=7.4 Hz), 7.42 (m, 2H, C_2-H, C_9-H), 7.60 (dd, 1H, C_1-H, J=8.2, 1.4 Hz), 7.66 (d, 1H, C_8-H, J=9.0 Hz), 8.52 (dd, 1H, C_3-H, J=4.5, 1.4 Hz), 9.82 (s, 1H, -NH, exch.); microanalysis for $C_{14}H_{11}N_3O_5$: found (calc) C-55.86 (55.82), H-3.57 (3.68), N-13.99 (13.95).

10.18. 7-Acetamido-6-nitro-4-azaxanthene (98):

To a solution of (97) (0.4 g, 1.33 mmol) in trifluoroacetic acid (10 ml), $NaBH_4$ (0.06 g, 1.58 mmol) was added portionwise with stirring. Stirring was continued and the completion of reaction was checked by TLC. The reaction mixture was diluted with ice water and the precipitate which formed was filtered and washed with water. To obtain a second crop filtrate was basified to pH 12 with NaOH to give (98) in a total yield of 79% after recrystallization. Mp 215°C (CH_3CN); i.r. (KBr) (cm^{-1}): 3246 (NH), 1687 (NHCO), 1548 (NO), 1376 (NO); ^1H nmr (DMSO-d_6) δ: 2.04 (s, 3H, -CH_3), 4.22 (s, 2H, C_5-H), 7.46 (m, 3H, C_2-H, C_8-H, C_9-H), 7.70 (dd, 1H, C_1-H, J=8.2, 1.1 Hz), 8.40 (dd, 1H, C_3-H, J=4.5, 1.1 Hz), 10.10 (s, 1H, -NH, exch.).

10.19. 7-Acetamido-6-amino-4-azaxanthene (99):

Compound (98) (0.5 g, 1.75 mmol) was hydrogenated in a Parr Hydrogenator using 5% Pd/C (0.05 g) and hydrogen at 50 psi in EtOH (100 ml) for 4 h. The solution was filtered through Celite and washed with hot ethanol (25 ml). The combined filtrate

was evaporated *in vacuo* and recrystallized to give (99) in 87% yield. Mp 245-247 °C (EtOH); i.r. (KBr) (cm^{-1}): 3427 (NH), 3353 (NH), 3262 (NH), 1646 (NHCO); ^1H nmr (DMSO-d_6) δ: 2.04 (s, 3H, -CH_3), 3.92 (s, 2H, C_5-H), 5.06 (s, 2H, -NH_2, exch.), 6.32 (d, 1H, C_9-H, J=8.7 Hz), 7.02 (d, 1H, C_8-H, J=8.7 Hz), 7.28 (dd, 1H, C_2-H, J=8.1, 4.5 Hz), 7.46 (dd, 1H, C_1-H, J=8.1, 1.3 Hz), 8.28 (dd, 1H, C_3-H, J=4.5, 1.3 Hz), 9.14 (s, 1H, -NHAc, exch.); microanalysis for $C_{14}H_{13}N_3O_2$: found (calc) C-66.27 (65.87), H-5.02 (5.13), N-16.62 (16.46).

10.20. 2-Methylpyrido[2',3':5,6]pyrano[3,2-e](1H,11H)benzimidazole (100):

A solution of (99) (0.5 g, 1.96 mmol) in HCl: EtOH (2:1, 25 ml) was refluxed for 8 h, cooled and the ethanol removed *in vacuo*. Cold water (25 ml) was added to the residue and mixture was taken up in aqueous ammonia. The precipitate which formed was filtered and washed with water, followed by washing with acetone and recrytallized to give (100) in 75% yield. Mp 265-269°C (EtOH); i.r. (KBr) (cm^{-1}): 3164 (-NH); ^1H nmr (DMSO-d_6) δ: 2.52 (s, 3H, -CH_3), 4.34 (s, 2H, C_{11}-H), 6.94 (d, 1H, C_5-H, J=8.7 Hz), 7.36 (m, 2H, C_4-H, C_8-H), 7.52 (d, 1H, C_7-H, J=8.2 Hz), 8.32 (d, 1H, C_9-H, J=4.3 Hz), 12.30 (s, 1H, -NH, exch.); EI mass m/z (relative abundance): 238 (14%), 237 (95%), 236 (100%), 208 (9%), 140 (6%), 118 (14%); exact mass measurement for $C_{14}H_{11}N_3O$: [237.0894 found, 237.0902 calculated].

10.21. 2-Aminopyrido[2',3':5,6]pyrano[2,3-g]benzothiazol-11-(11H)-one (102):

To a cooled solution of 7-amino-4-azaxanthone (73a) (1.5 g, 7.0 mmol) and ammonium thiocyanate (1.2 g, 15.8 mmol) in glacial acetic acid (150 ml), bromine (0.71 ml, 14.0 mmol) was added dropwise. Stirring was continued for an additional hour. The solid which formed was filtered, washed with aqueous sodium carbonate solution followed by washing with water and recrystallized to give (102) in 70% yield. Mp >320°C (CH_3COOH), i.r. (KBr) (cm^{-1}): 3336 (NH), 3256 (NH), 1642 (CO); ^1H nmr (DMSO-

d_6) δ: 7.68 (d, 1H, C_4-H, J=9.0 Hz), 7.72 (s, 2H, -NH_2, exch.), 7.96 (m, 2H, C_5-H, C_8-H), 8.28 (dd, 1H, C_7-H, J=9.0, 1.5 Hz), 8.88 (dd, 1H, C_9-H, J=3.7, 1.5 Hz); EI mass m/z (relative abundance): 271 (6%), 270 (16%), 269 (100%), 242 (31%), 134 (8%); microanalysis for $C_{13}H_7N_3O_2S$: found (calc) C-57.90 (57.99), H-2.65 (2.62), N-15.20 (15.60).

10.22. 2-Acetamidopyrido[2',3':5,6]pyrano[2,3-g]benzothiazol-11(11H)-one (103):

A solution of (102) (0.5 g, 1.85 mmol) in glacial acetic acid (50 ml) was refluxed for 2 h with acetic anhydride (1.0 ml). The reaction mixture was cooled and the solid which formed was filtered, washed with water and recrystallized to give (103) as yellow solid in 86% yield. Mp > 300°C (MeOH); i.r. (KBr) (cm^{-1}): 3480 (NH), 1696 (NHCO), 1655 (CO); ^1H nmr (DMSO-d_6) δ: 2.26 (s, 3H, -CH_3), 7.84 (d, 1H, C_4-H, J=9.0 Hz), 7.96 (d, 1H, C_8-H, J=8.6, 4.1 Hz), 8.30 (d, 2H, C_5-H, C_7-H), 8.98 (d, 1H, C_9-H, J=4.1 Hz); EI mass m/z (relative abundance): 311 (22%), 271 (6%), 270 (16%), 269 (100%), 242 (14%); exact mass measurement for $C_{15}H_9N_3O_3S$: [311.0371 found, 311.0366 calculated].

10.23. General procedure for the synthesis of 3-methylpyridopyrano/-thiopyrano/selenopyranoquinolin-12-ones (105-108):

Acetaldehyde (0.1 g) was added to a solution of 7-amino-4-azaxanthone (73a) (0.27 g, 1.27 mmol) in concentrated HCl. This was refluxed for 2 h, cooled, basified with aqueous ammonia, filtered and washed with water followed by washing with acetone. The residue was dissolved in mixture of MeOH:$CHCl_3$ (1:1) and chromatographed on a silica gel column using chloroform as the eluent. The crude product was recrystallized from acetonitrile to give pure (105) in 25% yield. Mp 243°C (CH_3CN), i.r. (KBr) (cm^{-1}): 1663 (CO); ^1H nmr (DMSO-d_6) δ: 2.74 (s, 3H, -CH_3), 7.78 (d, 1H, C_2-H, J=8.5 Hz), 7.98 (dd, 1H, C_9-H, J=7.7, 3.9 Hz), 8.04 (d, 1H, C_6-H, J=9.3 Hz), 8.32 (dd, 1H, C_8-H, J=7.7, 1.5 Hz), 8.42 (d, 1H, C_5-H, J=9.3 Hz), 8.92 (dd, 1H, C_{10}-H, J=3.9, 1.5 Hz),

10.18 (d, 1H, C_1-H, J=8.5 Hz); EI mass m/z (relative abundance): 263 (17%), 262 (100%), 234 (10%), 221 (8%), 193 (5%), 177 (7%), 149 (18%), 131 (6%), 97 (6%), 85 (7%), 83 (6%), 71 (10%), 69 (8%), 57 (13 %), 55 (9%), 43 (13 %), 41 (8%); micro-analysis for $C_{16}H_{10}N_2O_2$: found (calc) C-73.56 (73.27), H-3.92 (3.84), N-10.73 (10.68).

Using the above procedure, 7-amino-4-azathioxanthone (73b) (1.0 g, 4.38 mmol) was converted to (106) which was similarly chromatographed on silica gel column using chloroform as the eluent. This crude material was recrystallized from methanol to give pure product in 33% yield. Mp (decomp.) 271-274°C; i.r. (KBr) (cm^{-1}): 1630 (CO); ^1H nmr (DMSO-d_6) δ: 2.70 (s, 3H, $-CH_3$), 7.72 (d, 1H, C_2-H, J=9.1 Hz), 7.82 (dd, 1H, C_9-H, J=8.4, 4.2 Hz), 8.14 (d, 1H, C_6-H, J=9.1 Hz), 8.26 (d, 1H, C_5-H, J=9.1 Hz), 8.50 (dd, 1H, C_8-H, J=8.4, 1.4 Hz), 8.98 (dd, 1H, C_{10}-H, J=4.2, 1.4 Hz), 9.94 (d, 1H, C_1-H, J=9.1 Hz); EI mass m/z (relative abundance): 280 (6%), 279 (19%), 278 (100%), 277 (8%), 250 (25 %), 249 (13%), 209 (6%), 149 (7%), 139 (10%); exact mass measurement for $C_{16}H_{10}N_2OS$: [278.0515 found, 278.0515 calculated].

Using the same procedure, 7-amino-1-azathioxanthone (73c) (1.0g, 4.38 mmol) gave (107) which was similarly purified by passing through silica gel column using chloroform as the eluent. Recrystallization from acetonitrile gave pure product in 37% yield. Mp 265°C; i.r. (KBr) (cm^{-1}): 1638 (CO); ^1H nmr ($CDCl_3$) δ: 2.80 (s, 3H, $-CH_3$), 7.58 (m, 2H, C_2-H, C_{10}-H), 7.88 (d, 1H, C_6-H, J=8.9 Hz), 8.28 (d, 1H, C_5-H, J=8.9 Hz), 8.88 (dd, 1H, C_9-H, J=4.1, 1.6 Hz), 8.94 (dd, 1H, C_{11}-H, J=8.9, 1.6 Hz), 10.18 (d, 1H, C_1-H, J=8.9 Hz); EI mass m/z (relative abundance): 280 (6%), 279 (20%), 278 (100%), 277 (7%), 250 (21%), 249 (8%), 237 (9%), 139 (12%); microanalysis for $C_{16}H_{10}N_2OS$: found (calc) C-68.83 (69.05), H-3.62 (3.62), N-9.92 (10.06).

Compound (108) was obtained from 7-amino-1-azaselenoxanthone (73d) as described above and purified by passing through silica gel column using chloroform as the eluent. Recrystallization from acetonitrile gave (108) in 34% yield. Mp 260°C; i.r. (KBr)

(cm^{-1}): 1622 (CO); ^1H nmr ($CDCl_3$) δ: 2.82 (s, 3H, $-CH_3$), 7.56 (m, 2H, C_2-H, C_{10}-H), 7.94 (d, 1H, C_6-H, J=8.7 Hz), 8.22 (d, 1H, C_5-H, J=8.7 Hz), 8.84 (dd, 1H, C_9-H, J=4.3, 2.2 Hz), 8.92 (dd, 1H, C_{11}-H, J=8.0, 2.2 Hz), 9.92 (d, 1H, C_1-H, J=8.7 Hz); EI mass m/z (relative abundance): 328 (18%), 327 (19%), 326 (100 %), 325 (13%), 324 (51%), 323 (21%), 322 (19%), 298 (44%), 297 (12%), 295 (13%), 294 (11%), 246 (54%), 245 (9%), 231 (5%), 218 (17%), 217 (12%), 190 (10%), 177 (14%), 164 (10%), 163 (11%), 141 (10%), 140 (13%), 74 (10 %), 63 (9%), 51 (10%), 50 (13%); microanalysis calculated for $C_{16}H_{10}N_2OSe$: found (calc) C-58.74 (59.09), H-3.09 (3.10), N-8.60 (8.61).

10.24. 2,3-Dimethyl[3',2':5,6]thiopyrano[3,2-f]quinoxalin-12(12H)-one (109):

6,7-Diamino-1-azathioxanthone (77c) (0.15 g, 0.61 mmol) was refluxed with diacetyl (0.08 ml, 0.93 mmol) in ethanol (15 ml) for 2 h. The cooled solution was poured into cold water (50 ml) and the white product which formed was filtered, washed with water and dried to give (109) in 90% yield. Mp (decomp.) 220°C (CH_3CN); i.r. (KBr) (cm-1): 1646 (CO); ^1H nmr (DMSO-d_6) δ: 2.72 (s, 3H, $-CH_3$), 2.76 (s, 3H, $-CH_3$), 7.74 (dd, 1H, C_{10}-H, J=8.4, 4.6 Hz), 8.12 (d, 1H, C_6-H, J=8.8 Hz), 8.26 (d, 1H, C_5-H, J=8.8 Hz), 8.74 (dd, 1H, C_{11}-H, J=8.4, 1.4 Hz), 8.94 (dd, 1H, C_9-H, J=4.6, 1.4 Hz); EI mass m/z (relative abundance): 295 (11%), 294 (20%), 293 (100%), 292 (22%), 252 (16%), 184 (16%), 166 (5%), 165 (19%), 156 (17%), 149 (6%), 147 (21%), 139 (43%), 138 (15%), 114 (6%), 112 (31%), 105 (32%); exact mass measurement for $C_{16}H_{11}N_3OS$ [293.0621 found; 293.0624 calculated].

10.25. General procedure for the synthesis of 7-(p-toluenesulphonylurea)-4-azaxanthone/4-azathioxanthone (116, 117):

To a hot solution of (73a) (0.12 g, 0.56 mmol) in THF (50 ml), p-toluenesulphonyl chloride (0.11 g, 0.56 mmol) was added. This was stirred for 15 min and the precipitate which formed was filtered and washed with hot MeOH to give (116) as yellow powder in

86% yield. Mp 282°C; i.r. (KBr)(cm^{-1}): 3450 (NH), 1728 (NHCONH), 1671 (CO), 1326 (SO_2), 1171 (SO_2); ^1H nmr (DMSO-d_6) δ : 2.40 (s, 3H, -CH_3), 7.48 (d, 2H, C_3'-H, C_5'-H, J=8.5 Hz), 7.70 (d, 1H, C_9-H, J=9.1 Hz), 7.86 (dd, 1H, C_8-H, J=9.1, 2.4 Hz), 7.92 (m, 3H, C_2-H, C_2'-H, C_6'-H), 8.22 (dd, 1H, C_1-H, J=8.5, 1.2 Hz), 8.32 (d, 1H, C_6-H, J=2.4 Hz), 8.84 (dd, 1H, C_3-H, J=4.2, 1.2 Hz), 9.36 (s, 2H, -NH, exch.); EI mass m/z (relative abundance): 238 (22%), 213 (13%), 212 (87%), 211 (9%), 210 (6%), 197 (18%), 185 (7%), 184 (10%), 171 (6%), 157 (6%), 156 (9%), 155 (49%), 129 (7%), 128 (6%), 92 (8%), 91 (100%), 90 (8%), 89 (8%), 79 (6%), 78 (6%), 77 (8%), 65 (27%), 64 (7%), 63 (13%), 62 (5%), 52 (8 %), 51 (10%), 50 (7%), 41 (6%), 39 (17%); microanalysis for $C_{20}H_{15}N_3O_5S$: found (calc), C-58.35 (58.67), H-3.83 (3.69), N-10.36 (10.26).

Using the above procedure, (73b) (0.14g, 0.62 mmol) was converted to (117) in 88% yield. Mp (decomp.) 283°C (MeOH); i.r. (KBr) (cm^{-1}): 3262 (N-H), 1720 (NHCONH), 1638 (CO), 1343 (SO_2), 1154 (SO_2); ^1H nmr (DMSO-d_6) δ : 2.38 (s, 3H, -CH_3), 5.78 (s, 1H, CONH, exch.), 7.12 (dd, 1H, C_8-H, J=8.4, 2.6 Hz), 7.30 (s, 1H, SO_2NHCO, exch.), 7.38 (d, 2H, C_3'-H, C_5'-H, J=7.8 Hz), 7.56 (d, 1H, C_9-H, J=8.4 Hz), 7.70 (m, 4H, C_2-H, C_6-H, C_2'-H, C_6'-H), 8.30 (dd, 1H, C_1-H, J=8.9, 1.6 Hz), 8.84 (dd, 1H, C_3-H, J=4.2, 1.6 Hz); EI mass m/z (relative abundance): 254 (17%), 231 (7%), 230 (53%), 229 (79%), 228 (100%), 227 (8%), 202 (7%), 201 (25%), 200 (77%), 199 (23%), 198 (24%), 197 (84%), 196 (30%), 195 (7%), 174 (5%), 173 (21%), 171 (16%), 157 (10%), 156 (17%), 155 (84%), 107 (5%), 92 (11%), 91 (82%); microanalysis for $C_{20}H_{15}N_3O_4S_2$: found (calc), C-56.73 (56.46), H-3.41 (3.55), N-9.81 (9.88).

10.26. General procedure for the synthesis of 7-isothiocyanato-azaxanthone/azathioxanthones (118a-c):

To a solution of 7-amino-4-azaxanthone (73a) (0.42 g, 1.98 mmol) in glacial acetic acid (100 ml), thiophosgene (0.15 ml, 1.98 mmol) was added with stirring. Stirring was continued for another 15 min and filtered. The filtrate was diluted with ice-cold water and

the precipitate which formed was filtered, washed with water and recrytallized to give (118a) in 83% yield. Mp 212°C (CH_3CN); i.r. (KBr) (cm^{-1}): 2139 (NCS), 1679 (CO); ^1H nmr ($CDCl_3$) δ : 7.64 (d, 1H, C_9-H, J=8.9 Hz), 7.68 (dd, 1H, C_8-H, J=8.9, 2.1 Hz), 7.80 (dd, 1H, C_2-H, J=8.9, 3.7 Hz), 8.02 (dd, 1H, C_1-H, J=8.9, 1.6 Hz), 8.38 (d, 1H, C_6-H, J=2.1 Hz), 8.96 (dd, 1H, C_3-H, J=3.7, 1.6 Hz); microanalysis for $C_{13}H_6N_2O_2S$: found (calc) C-61.28 (61.41), H-2.57 (2.38), N-11.05 (11.02).

Using the above procedure, (73b) (1.31 g, 5.74 mmol) was converted to (118b) in 70% yield. Mp 260°C (CH_3CN); i.r. (KBr) (cm^{-1}): 2114 (NCS), 1646 (CO); ^1H nmr (DMSO-d_6) δ : 7.80 (dd, 1H, C_2-H, J=8.7, 4.4 Hz), 7.88 (dd, 1H, C_8-H, J=9.1, 2.2 Hz), 8.04 (d, 1H, C_9-H, J=9.1 Hz), 8.38 (d, 1H, C_6-H, J=2.2 Hz), 8.44 (dd, 1H, C_1-H, J=8.7, 1.4 Hz), 8.94 (dd, 1H, C_3-H, J=4.4, 1.4 Hz); microanalysis for $C_{13}H_6N_2OS_2$: found (calc) C-57.87 (57.76), H-2.54 (2.24), N-10.67 (10.36).

By the same procedure, (118c) was obtained from (73c) (0.22 g, 0.81 mmol) in 86% yield. Mp 205°C (CH_3CN); i.r. (KBr) (cm^{-1}): 2155 (NCS), 1649 (CO); ^1H nmr (DMSO-d_6) δ : 7.68 (dd, 1H, C_3-H, J=8.3, 4.5 Hz), 7.88 (dd, 1H, C_8-H, J=9.0, 2.2 Hz), 8.02 (d, 1H, C_9-H, J=9.0 Hz), 8.30 (d, 1H, C_6-H, J=2.2 Hz), 8.76 (dd, 1H, C_4-H, J=8.2, 1.5 Hz), 8.92 (dd, 1H, C_2-H, J=4.5, 1.5 Hz) microanalysis for $C_{13}H_6N_2OS_2$: found (calc) C-57.40 (57.76), H-2.24 (2.24), N-10.39 (10.36).

10.27. 7-(1-Pyrrolidinylthiocarboxamido)azaxanthone/azathioxanthones (119-121):

To a hot soution of 7-isothiocyanato-4-azaxanthone (118a) (0.09 g, 0.35 mmol) in acetone (10 ml), pyrrolidine (0.03 g, 0.42 mmol) was added with stirring. Stirring was continued for another 15 min and the precipitate which formed was filtered, washed with water and recrystallized to give (119) in 87% yield. Mp 272-274°C (CH_3OH); i.r. (KBr)(cm^{-1}): 3312 (NH), 1663 (CO), 1622 (CS); ^1H nmr (DMSO-d_6) δ : 1.96 (br s, 4H, C_3'-H, C_4'-H), 3.68 (s, 4H, C_2'-H, C_5'-H), 7.68 (d, 1H, C_9-H, J=8.7 Hz), 7.92 (dd, 1H, C_2-H, J=8.7, 4.1 Hz), 8.10 (dd, 1H, C_8-H, J=8.7, 3.1 Hz), 8.16 (d, 1H, C_6-H,

J=3.1 Hz), 8.22 (dd, 1H, C_1-H, J=8.7, 1.5 Hz), 8.84 (dd, 1H, C_3-H, J=4.1, 1.5 Hz), 9.26 (s, 1H, -NH, exch.); EI mass m/z (relative abundance): 257 (5%), 256 (6%), 255 (18%), 254 (100%), 253 (16%), 227 (6%), 226 (10%), 222 (7%), 210 (7%), 207 (6%), 194 (8%), 168 (7%), 149 (7%), 140 (11%), 137 (9%), 71 (4%), 70 (9%), 65 (12%).

Using a slight modification of the above procedure, compound (120) was prepared. A solution of 7-isothiocyanato-4-azathioxanthone (118b) (0.20 g, 0.75 mmol) in acetone was refluxed with pyrrolidine (0.06 g, 0.84 mmol) for 2 h. This was then cooled and acetone was removed *in vacuo* . The residue was washed with water followed by washing with hot MeOH to give (120) in 97% yield. Mp (decomp.) 285°C; i.r. (KBr)(cm^{-1}): 3303 (NH), 1647 (CO), 1638 (CS); ^{1}H nmr (DMSO-d_6) δ : 1.96 (br s, 4H, C_3'-H, C_4'-H), 3.68 (s, 4H, C_2'-H, C_5'-H), 7.76 (dd, 1H, C_2-H, J=7.9, 3.9 Hz), 7.84 (d, 1H, C_9-H, J=8.7 Hz), 8.06 (dd, 1H, C_8-H, J=8.7, 2.2 Hz), 8.38 (dd, 1H, C_1-H, J=7.9, 1.3 Hz), 8.44 (d, 1H, C_6-H, J=2.2 Hz), 8.88 (dd, 1H, C_3-H, J=3.9, 1.3 Hz), 9.32 (s, 1H, -NH, exch.); EI mass m/z (relative abundance): 272 (12%), 271 (18%), 270 (100%), 269 (8%), 243 (6 %), 242 (23%), 241 (5%), 210 (7%), 198 (8%), 184 (17%), 183 (6%), 140 (12%), 114 (5%), 83 (6%), 82 (7%), 75 (5%), 71 (9%), 70 (14%), 69 (8%), 63 (5%), 43 (27%), 42 (6%), 41 (5%), 39 (9%); microanalysis for $C_{17}H_{15}N_3OS_2$: found (calc) C-59.54 (59.80), H-4.52 (4.43), N-12.04 (12.31).

Compound (121) was prepared, by the same procedure described for (120), from 7-isothiocyanato-1-azathioxanthone (118c) (0.11 g, 0.41 mmol) in 98% yield. Mp 179°C (MeOH); i.r. (KBr) (cm^{-1}): 3290 (NH), 1641 (CO); ^{1}H nmr (DMSO-d_6) δ : 1.98 (s, 4H, C_3'-H, C_4'-H), 3.72 (s, 4H, C_2'-H, C_5'-H), 7.72 (dd, 1H, C_3-H, J=8.7, 4.8 Hz), 7.98 (d, 1H, C_9-H, J=9.2 Hz), 8.10 (dd, 1H, C_8-H, J=9.2, 2.4 Hz), 8.50 (d, 1H, C_6-H, J=2.4 Hz), 8.82 (dd, 1H, C_4-H, J=8.7, 2.4 Hz), 8.96 (dd, 1H, C_2-H, J=4.8, 2.4 Hz), 9.36 (s, 1H, -NH, exch.); +ve CI mass m/z (relative abundance): 342 (2%), 341 (6%), 271 (16%), 270 (27%), 269 (16%), 143 (26%), 73 (8%), 72 (100%).

10.28. 7-(1-Piperidinothiocarboxamido)azaxanthone/azathioxanthones (122-124):

To a hot solution of (118a) (0.15 g, 0.59 mmol) in acetone, piperidine (0.52g, 0.61 mmol) was added with stirring. Stirring was continued for 15 min. The precipitate which formed was filtered, washed with water and recrystallized to give (122) in 70% yield. Mp 255-261°C (CH_3COCH_3); i.r. (KBr) (cm^{-1}): 3295 (NH), 1655 (CO); ^1H nmr (DMSO-d_6) δ : 1.64 (br s, 6H, C_3'-H, C_4'-H, C_5'-H), 3.94 (s, 4H, C_2'-H, C_6'-H), 7.56 (d, 1H, C_9-H, J=8.7 Hz), 7.84 (dd, 1H, C_2-H, J=8.7, 4.3 Hz), 8.10 (m, 2H, C_1-H, C_8-H), 8.14 (d, 1H, C_6-H, J=2.9 Hz), 8.84 (dd, 1H, C_3-H, J=4.3, 1.4 Hz), 9.48 (s, 1H, -NH, exch.); EI mass m/z (relative abundance): 256 (16%), 255 (43%), 254 (100%), 253 (38%), 252(5%), 228 (6%), 227 (15%), 226 (21%), 222 (9%), 210 (18%), 199 (6%), 194 (10%), 171 (6%), 168 (9%), 154 (6%), 140 (31%), 139 (6%), 127 (11%), 114 (6%), 113 (17%), 99 (6%), 88 (5%), 85 (26%), 84 (47%), 83 (6%), 76 (5%), 75 (10%), 74 (6%), 70 (7%), 63 (13%), 57 (20%), 56 (22%), 50 (8%), 44 (12%), 43 (9%), 42 (11%), 41 (6%), 39 (18%), 38 (7%); microanalysis for $C_{18}H_{17}N_3O_2S$: found (calc) C-63.74 (63.70), H-5.03 (5.05), N-12.58 (12.38).

Compound (118b) (0.21g, 0.80 mmol) was refluxed for 2 h with piperidine (0.08g, 1.00 mmol) in acetone. The residue was cooled and the solvent removed *in vacuo*. The residue was washed with water followed by washing with hot MeOH to give (123) in 85% yield. Mp (sublime) 240-242°C; i.r. (KBr) (cm^{-1}): 3320 (NH), 1646 (CO), 1638 (CS); ^1H nmr (DMSO-d_6) δ : 1.62 (s, 6H, C_3'-H, C_4'-H, C'5-H), 3.94 (br s, 4H, C_2'-H, C_6'-H), 7.78 (dd, 1H, C_2-H, J=8.2, 3.6 Hz), 7.82 (d, 1H, C_9-H, J=8.8 Hz), 7.96 (dd, 1H, C_8-H, J=8.8, 2.1 Hz), 8.34 (d, 1H, C_6-H, J=2.1 Hz), 8.38 (dd, 1H, C_1-H, J=4.3, 1.4 Hz), 8.90 (dd, 1H, C_3-H, J=3.6, 1.5 Hz), 9.52 (s, 1H, -NH, exch.); microanalysis for $C_{18}H_{17}N_3OS_2$: found (calc) C-61.08 (60.82), H-4.62 (4.82), N-11.82 (11.82).

Using the same procedure, (124) was obtained from (118c) (0.23 g, 0.85 mmol) in 73% yield. Mp 216°C (CH_3CN); i.r. (KBr) (cm^{-1}): 3344 (NH), 1646 (CO); ^1H nmr (DMSO-d_6) δ: 1.64 (s, 6H, C_3'-H, C_4'-H, C_5'-H), 3.96 (s, 4H, C_2'-H, C_6'-H), 7.70 (dd, 1H, C_3-H, J=7.7, 4.4 Hz), 7.86 (d,1H, C_9-H, J=8.8 Hz), 7.98 (dd, 1H, C_8-H, J=8.8, 2.2 Hz), 8.38 (d, 1H, C_6-H, J=2.2 Hz), 8.82 (dd, 1H, C_4-H, J=7.7, 2.2 Hz), 8.96 (dd, 1H, C_2-H, J-4.41, 2.2 Hz), 9.64 (s, 1H, -NH, exch.); EI mass m/z (relative abundance): 272 (28%), 271 (50%), 270 (100%), 269 (31%), 244 (8%), 243 (21%), 242 (62%), 241 (16%), 238 (20%), 226 (15%), 215 (11%), 211 (5%), 210 (31%), 209 (7%), 198 (23%), 197 (10%), 185 (7%), 184 (42%), 183 (18%), 165 (9%), 157 (7%), 140 (35%), 139 (8%), 135 (10%), 133 (6%), 121 (10%), 114 (5%), 113 (13%), 107 (9 %), 106 (6%),105 (6%), 99 (16%), 85 (25%), 84 (49%), 83 (11%), 82 (15%), 75 (8%), 74 (6%), 70 (5%), 69 (15%), 63 (10%), 57 (20%), 56 (23%), 55 (5%), 50 (6%),44 (11%), 43 (8%), 42 (10%), 39 (16%); microanalysis for $C_{18}H_{17}N_3OS_2$: found (calc) C-60.86 (60.82), H-4.87 (4.82), N-11.94 (11.82).

10.29. 7-[1-(1',2',5',6'-tetrahydropyridinyl)thiocarboxamido]aza-xanthone/azathioxanthones (125-127):

To a hot stirred solution of (118a) (0.13 g, 0.51 mmol) in acetone (15 ml) 1,2,5,6-tetrahydropyridine (0.05 g, 0.60 mmol) was added with stirring. Stirring was continued for 15 min and the solid which formed was filtered, washed with water and recrystallized to give (125) in 69% yield. Mp 255-259°C (MeOH); i.r. (KBr) (cm^{-1}): 3312 (NH), 1663 (CO); ^1H nmr (DMSO-d_6) δ: 2.26 (br s, 2H, C_5'-H), 4.04 (t, 2H, C_6'-H, J=6.0 Hz), 4.38 (br s, 1H, C_2'-H), 5.78 (m, 1H, C_4'-H), 5.96 (m, 1H, C_3'-H), 7.68 (d, 1H, C_9-H, J=9.3 Hz), 7.92 (dd, 1H, C_2-H, J=8.1, 4.6 Hz), 8.02 (dd, 1H, C_8-H, J=9.3, 2.3 Hz), 8.08 (d, 1H, C_6-H, J=2.3 Hz), 8.24 (dd, 1H, C_1-H, J=8.1, 1.2 Hz), 8.84 (dd, 1H, C_3-H, J=4.6, 1.2 Hz), 9.62 (s, 1H, -NH, exch.); +ve CI mass m/z (relative abundance): 509 (9%), 340 (7%), 339 (17%), 338 (60%), 257 (10%), 256 (27%), 255 (100%), 253

(27%), 84 (68%), 83 (18%), 82 (17%); microanalysis for $C_{18}H_{15}N_3O_2S$: found (calc) C-63.71 (64.08), H-4.42 (4.48), N-12.49 (12.45).

A solution of (118b) (0.20 g, 0.75 mmol) in acetone (20 ml) was refluxed with 1,2,5,6-tetrahydropyridine (0.066 g, 0.80 mmol) for 2 h. The reaction mixture was cooled, the solvent removed *in vacuo* and the residue washed sequentially with water, with hot MeOH and dried to give (126) in 95% yield. Mp 247°C; i.r. (KBr) (cm^{-1}): 3312 (NH), 1646 (CO), 1630 (CS); ^1H nmr (DMSO-d_6) δ: 2.26 (br s, 2H, C_5'-H), 4.06 (t, 2H, C_6'-H, J=5.7 Hz), 4.36 (t, 2H, C_2'-H, J=2.9 Hz), 5.76 (m, 1H, C_4'-H), 5.94 (m, 1H, C_3'-H), 7.74 (dd, 1H, C_2-H, J=8.0, 3.7 Hz), 7.80 (d, 1H, C_9-H, J=9.0 Hz), 7.96 (dd, 1H, C_8-H, J=9.0, 2.7 Hz), 8.34 (d, 1H, C_6-H, J=2.7 Hz), 8.36 (dd, 1H, C_1-H, J=8.0, 1.6 Hz), 8.86 (dd, 1H, C_3-H, J=3.7, 1.6 Hz), 9.66 (s, 1H, -NH, exch.); EI mass m/z (relative abundance): 273 (10%), 272 (65%), 271 (78%), 270 (100%), 269 (63%), 268 (15%), 244 (17%), 243 (36%), 242 (83%), 241 (34%), 238 (23%), 228 (9%), 226 (30%), 215 (22%), 210 (46%), 209 (11%), 198 (46 %), 197 (18%), 185 (15%), 184 (75%), 183 (32%), 165 (15%), 157 (14%), 140 (63%), 139 (12%), 135 (19%), 133 (14%), 121 (19%), 114 (11%), 113 (22%), 107 (18%), 106 (12%), 99 (34%), 83 (89%), 82 (94%), 81 (15%), 80 (24%), 76 (12%), 75 (20%), 74 (14%), 69 (35%), 68 (44%), 63 (24%), 62 (11%), 55 (27%), 54 (78%), 53 (26%), 52 (11%), 51 (17%), 50 (20%), 45 (14%), 42 (10%), 41 (13%), 39 (67%); microanalysis for $C_{18}H_{15}N_3OS_2$: found (calc) C-61.17 (61.17), H-4.22 (4.28), N-11.54 (11.89).

Using the same conditions, (119c) (0.223 g, 0.85 mmol) was converted into (127) and recrystallized to give pure product in 66% yield. Mp 196°C (CH_3CN); i.r. (KBr) (cm^{-1}): 3205 (NH), 1646 (CO); ^1H nmr (DMSO-d_6) δ: 2.28 (s, 2H, C_5'-H), 4.06 (t, 2H, C_6'-H, J=5.8 Hz), 4.40 (t, 2H, C_2'-H, J=2.9 Hz), 5.80 (m, 1H, C_4'-H), 5.96 (m, 1H, C_3'-H), 7.68 (dd, 1H, C_3-H, J=8.0, 4.6 Hz), 7.86 (d, 1H, C_9-H, J=8.6 Hz), 7.98 (dd, 1H, C_8-H, J=8.6, 2.3 Hz), 8.38 (d, 1H, C_6-H, J=2.3 Hz), 8.80 (d, 1H, C_4-H, J=8.0, 2.3 Hz), 8.94 (dd, 1H, C_2-H, J=4.6, 2.3 Hz), 9.68 (s, 1H, -NH, exch.); EI

mass m/z (relative abundance): 272 (25%), 271 (41%), 270 (100%), 242 (15%), 83 (33%), 82 (21%), 68 (13%) and 54 (10%).

10.30. 7-(Morpholinothiocarboxamido)azaxanthone/azathioxanthones (128-130):

To a hot solution of (118a) (0.07 g, 0.31 mmol) in acetone (10 ml) morpholine (0.03 g, 0.35 mmol) was added with stirring. Stirring was continued for a period of 15 min. The solid which precipitated was filtered, washed with water, dried and recrystallized to give (128) in 75 % yield. Mp 249-252°C (MeOH); i.r. (KBr)(cm^{-1}): 3205 (NH), 1655 (CO); ^1H nmr (DMSO-d_6) δ : 3.70 (t, 4H, C_2'-H, C_6'-H, J=4.6 Hz), 3.96 (t, 4H, C_3'-H, C_5'-H, J=4.6 Hz), 7.68 (d, 1H, C_9-H, J=8.6 Hz), 7.92 (dd, 1H, C_2-H, J=8.6, 4.1 Hz), 8.02 (dd, 1H, C_8-H, J=8.6, 2.8 Hz), 8.10 (d, 1H, C_6-H, J=2.8 Hz), 8.22 (dd, 1H, C_1-H, J=8.6, 1.4 Hz), 8.82 (dd, 1H, C_3-H, J=4.1, 1.4 Hz), 9.66 (s, 1H, -NH, exch.); +ve CI mass m/z (relative abundance): 596 (6%), 510 (9%), 509 (24%), 344 (8%), 343 (23%), 342 (84%), 339 (6%), 300 (5%), 257 (10%), 256 (36%), 255 (100%), 212 (7%), 88 (28%), 86 (16%); microanalysis for $C_{17}H_{15}N_3O_3S$: found (calc) C-59.57 (59.82), H-4.24 (4.39), N-12.38 (12.31).

Compound (118b) (0.28 g, 1.03 mmol) was refluxed with morpholine (0.10 g, 1.17 mmol) in acetone (25 ml) for 2 h. Acetone was removed *in vacuo* and the residue washed with water, followed by washing with hot MeOH and dried to give (129) in 92% yield. Mp (decomp.) 257-260°C ; i.r. (KBr) (cm^{-1}): 3296 (NH), 1646 (CO), 1632 (CS); ^1H nmr (DMSO-d_6) δ: 3.68 (t, 4H, C_2'-H, C_6'-H, J=4.5 Hz), 3.94 (t, 4H, C_3'-H, C_5'-H, J=4.5 Hz), 7.74 (dd, 1H, C_2-H, J=8.1, 4.4 Hz), 7.82 (d, 1H, C_9-H, J=8.4 Hz), 7.94 (dd, 1H, C_8-H, J=8.4, 2.0 Hz), 8.32 (d, 1H, C_6-H, J=2.0 Hz), 8.36 (dd, 1H, C_1-H, J=8.1, 1.7 Hz), 8.86 (dd, 1H, C_3-H, J=4.4, 1.7 Hz), 9.72 (s, 1H, -NH, exch.); EI mass m/z (relative abundance): 273 (5%), 272 (36%), 271 (58%), 270 (100%), 269 (29%), 268 (8%), 244 (10%), 243 (21%), 242 (71%), 241 (18%), 238 (10%), 226 (16%), 215 (12%), 210 (27%), 198 (27%),197 (12%), 184 (56%), 183 (19%), 140

(37%), 113 (13%), 107 (6%), 106 (7%), 99 (13%), 87 (35%), 86 (14%), 83 (18%), 82 (22%), 75 (15%), 69 (25%), 63 (18%), 57 (60%), 56 (23%), 50 (14%), 45 (12%), 42 (11%), 39 (18%); microanalysis for $C_{17}H_{15}N_3O_2S_2$: found (calc) C-57.15 (57.12), H-4.28 (4.23), N-11.41 (11.76).

Using the same procedure, (118c) (0.22 g, 0.81 mmol) gave (130) was obtained in 86% yield. Mp 230-232°C (MeOH); i.r. (KBr) (cm^{-1}): 3180 (NH), 1646 (CO); ^1H nmr (DMSO-d_6) δ: 3.72 (t, 4H, C_2'-H, C_6'-H, J=4.8 Hz), 3.98 (t, 4H, C_3'-H, C_5'-H, J=4.8 Hz), 7.70 (dd, 1H, C_3-H, J=8.4, 4.2 Hz), 7.88 (d, 1H, C_9-H, J=8.7 Hz), 8.00 (dd, 1H, C_8-H, J=8.7, 1.9 Hz), 8.40 (d, 1H, C_6-H, J=1.9 Hz), 8.82 (dd, 1H, C_4-H, J=8.4, 1.5 Hz), 8.96 (dd, 1H, C_2-H, J=4.2, 1.5 Hz), 9.80 (s, 1H, -NH, exch.); EI mass m/z (relative abundance): 272 (12%), 271 (20%), 270 (100%), 242 (16%), 238 (11%), 87 (10%), 57 (11%); microanalysis for $C_{17}H_{15}N_3O_2S_2$: found (calc) C-57.07 (57.12), H-4.32 (4.23), N-11.76 (11.76).

10.31. 7-[1-(N-methylpiperazinyl)thiocarboxamido]azaxanthone/azathioxanthones (131-133):

A hot solution of (118a) (0.05 g, 0.19 mmol) in acetone (10 ml) was stirred with N-methylpiperazine (0.02 g, 0.21 mmol) for 15 min. The solid which formed was filtered, washed with water, dried and recrystallized to give (131) in 74% yield. Mp 239-240°C (CH_3CN); i.r. (KBr) (cm^{-1}): 3213 (NH), 1655 (CO); ^1H nmr (DMSO-d_6) δ : 2.24 (s, 3H, -CH_3), 2.40 (m, 4H, C_3'-H, C_5'-H, J=4.5 Hz), 3.94 (m, 4H, C_2'-H, C_6'-H, J=4.5 Hz), 7.66 (d, 1H, C_9-H, J=8.9 Hz), 7.92 (dd, 1H, C_2-H, J=8.9, 4.4 Hz), 7.98 (dd, 1H, C_8-H, J=8.9, 2.5 Hz), 8.06 (d, 1H, C_6-H, J=2.5 Hz), 8.22 (dd, 1H, C_1-H, J=8.9, 1.9 Hz), 8.80 (dd, 1H, C_3-H, J=4.4, 1.9 Hz), 9.66 (s, 1H, -NH, exch.); EI mass m/z (relative abundance): 256 (6%), 255 (18%), 254 (100%), 253 (14%), 227 (5%), 226 (9%), 210 (7%), 140 (14%), 100 (17%), 75 (8%), 74 (6%), 63 (10%), 62 (6%), 58 (81%), 56 (17%); +ve CI mass m/z (relative abundance): 509 (11%), 355 (7%), 256 (22%), 255 (100%), 254 (20%), 101 (15%).

Compound (118b) (0.21 g, 0.78 mmol) was refluxed with N-methylpiperazine (0.08 g, 0.80 mmol) in acetone (20 ml) for 2 h. The reaction was cooled, solvent was removed *in vacuo* , and the residue washed with water and dried to give (132) in 90% yield. Mp 253-259°C; i.r. (KBr) (cm^{-1}): 3451 (NH), 1646 (CO), 1638 (CS); ^1H nmr (DMSO-d_6) δ : 2.22 (s, 3H, $-CH_3$), 2.40 (t, 4H, C_3'-H, C_5'-H, J=4.5 Hz), 3.94 (t, 4H, C_2'-H, C_6'-H, J=4.5 Hz), 7.74 (dd, 1H, C_2-H, J=8.1, 3.8 Hz), 7.80 (d,1H, C_9-H, J=8.7 Hz), 7.92 (dd, 1H, C_8-H, J=8.7, 2.2 Hz), 8.32 (d, 1H, C_6-H, J=2.2 Hz), 8.36 (dd, 1H, C_1-H, J=8.1, 1.6 Hz), 8.86 (dd, 1H, C_3-H, J=3.8, 1.6 Hz), 9.66 (s, 1H, -NH, exch.); EI mass m/z (relative abundance): 273 (8%), 272 (60%), 271 (100%), 242 (75%), 241 (24%), 238 (12%), 226 (24%), 210 (27%), 198 (30%), 197 (13%), 184 (62%), 183 (22%), 140 (49%), 134 (24%), 133 (10%), 120 (18%), 113 (15%), 107 (18%), 100 (25%), 99 (29%), 83 (12%), 82 (%), 75 (10%), 68 (19%), 63 (13%), 58 (60%); +ve mass m/z (relative abundance): 541 (7%), 540 (20%), 370 (7%), 272 (25%), 270 (100%), 269 (56%), 228 (5%).

Using the above conditions, (118c) (0.20 g, 0.74 mmol) was converted to (133) in 62% yield. Mp 234-238°C (CH_3CN); i.r. (KBr) (cm^{-1}): 3324 (NH), 1646 (CO); ^1H nmr (DMSO-d_6) δ : 2.24 (s, 3H, $-CH_3$), 2.42 (t, 4H, C_3'-H, C_5'-H, J=4.7 Hz), 3.96 (t, 4H, C_2'-H, C_6'-H, J=4.7 Hz), 7.68 (dd, 1H, C_3-H, J=8.3, 4.3 Hz), 7.86 (d, 1H, C_9-H, J=9.0 Hz), 7.98 (dd, 1H, C_8-H, J=9.0, 2.2 Hz), 8.38 (d, 1H, C_6-H, J=2.2 Hz), 8.80 (dd, 1H, C_4-H, J=8.3, 1.4 Hz), 8.94 (dd, 1H, C_2-H, J=4.3, 1.4 Hz), 9.76 (s, 1H, -NH, exch.); EI mass m/z (relative abundance): 273 (14%), 272 (70%), 271 (81%), 270 (100%), 269 (11%), 254 (25%), 244 (21%), 243 (37%), 242 (86%), 241 (26%), 238 (45%), 228 (27%), 215 (21%), 212 (31%), 210 (52%), 209 (10%), 206 (15%), 198 (47%), 197 (21%), 185 (17%), 184 (77%), 183 (38%), 178 (10%), 171 (10%), 165 (19%), 157 (18%), 141 (10%), 140 (71%), 139 (17%), 135 (42%), 133 (15%), 121 (37%), 113 (28%), 107 (14%), 106 (11%), 100 (16%), 99 (43%), 94 (11%), 93 (11%), 88 (10%), 85 (10%), 83 (20%), 82 (29%), 77 (15%), 76 (13%), 75 (21%), 74 (15%), 69

(36%), 63 (28%), 62 (13%), 58 (19%), 51 (13%); microanalysis for $C_{18}H_{18}N_4OS_2$: found (calc) C-58.35 (58.36), H-4.82 (4.90), N-15.13 (15.12).

10.32. 7-(n-propoxythiocarboxamido)-4-azaxanthone (134):

7-Isothiocyanato-4-azaxanthone (118a) (0.2 g, 0.78 mmol) was refluxed in isopropanol (50 ml) for 2 h. The reaction was cooled and the solid which formed was filtered and recrystallized to give (134) in 77% yield. Mp 233-235°C (EtOH); i.r. (KBr)(cm^{-1}): 3287 (NH), 1671 (CO); ^1H nmr (DMSO-d_6/$CDCl_3$) δ: 0.98 (t, 3H, $-CH_3$, J=6.0 Hz), 1.76 (m, 2H, $-OCH_2\underline{CH_2}CH_3$), 4.44 (br s, 2H, $-O\underline{CH_2}CH_2CH_3$), 7.70 (d, 1H, C_9-H, J=8.4 Hz), 7.90 (dd, 1H, C_2-H, J=8.4, 4.4 Hz), 8.18 (d, 1H, C_1-H, J=8.4 Hz), 8.30 (br s, 1H, C_8-H), 8.62 (br s, 1H, C_6-H), 8.82 (d, 1H, C_3-H, J=4.4 Hz), 11.40 (s, 1H, -NH, exch.); EI mass m/z (relative abundance): 314 (21%), 274 (8%), 273 (23%), 272 (54%), 271 (7%), 270 (9%), 257 (29%), 256 (58%), 255 (68%), 254 (100%), 253 (60%), 252 (36%), 239 (20%), 238 (15%), 229 (8%), 228 (23%), 227 (48%), 226 (54%), 225 (9%), 223 (7%), 222 (37%), 213 (13%), 212 (53%), 211 (21%), 210 (52%), 199 (15%), 198 (16%), 197 (10%), 196 (22%), 194 (20%), 185 (5%), 182 (12%), 171 (11%), 168 (21%), 154 (9%), 140 (30%), 76 (5%), 60 (34%), 59 (51%), 43 (8%), 42 (44%), 41 (13%); microanalysis for $C_{16}H_{14}N_2O_3S$: found (calc) C-61.00 (61.13), H-4.48 (4.49), N-9.16 (8.91).

BIBLIOGRAPHY

1) G. Feurstein and J. M. Hallenbeck, *FASEB J.*, **1**(3), 186 (1987).

2) P. Needlemann, J. Turk, B. A. Jakschik, A. R.Morrison and J. B, Lefkowith, *Ann. Rev. Biochem.*, **55**, 69 (1986).

3) Z. Chustecka in " The Scrip Leukotriene Report", PJB Publications, Surrey, England (1985).

4) J. A. Salmon, " Advances in Drug Research", Bernard Testa, Ed., **15**, Academic Press Inc., London, 111 (1986).

5) R. D. Zipser and G. Laffi, *West. J. Med.*, **143**, 485 (1985).

6) J. R. Vane, *J. Allergy Clin. Immunol.*, **58** (6), 691 (1976).

7) L. M. Solomon, L. Juhlin and M. B. Kirshenbaum, *J. Invest. Dermatol.*, **51**, 280 (1968).

8) J. G. Collier, S. M. M. Karim, B. Robinson and K. Somer, *Br. J. Pharmacol.*, **44**, 374 (1972).

9) S. Bergstrom, H. Duner, U. S. V. Euler, B. Pernow and J. Sjovall, *Acta Physiol. Scand.*, **45**, 145 (1959).

10) A. S. Milton and S. Wendlandt, *J. Physiol.*, **218**, 325 (1971).

11) W. Feldberg and P. N. Saxena, *J. Physiol.*, **217**, 547 (1971).

12) J. G. Lombardino, *Eur. J. Rheum. Inflam.*, **6**, 24 (1983).

13) S. Moncada and J. R. Vane, *Br. Med. Bull.*, **34** (2), 129 (1978).

14) O. V. Miller, J. W. Aiken, R. J. Shebushi and R. R. Gorman, *Prostaglandins*, **20**, 391 (1980).

15) G. W. Taylor and H. R. Morris, *Br. Med. Bull.*, **39** (3), 219 (1983).

16) P. Borgeat and B. Samuelsson, *Proc. Natl. Acad. Sci. USA*, **76**, 3213 (1979).

17) O. Radmark, T. Shimizu, H. Jornvall and B. Samuelsson, *J. Biol. Chem.*, **259**, 12339 (1984).

18) J. F. Evan, P. Dupuis and A. W. Ford-Hutchinson, *Biochim. Biophys. Acta* , **840**, 43 (1985).

19) R. C. Murphy, S. Hammarstrom and B. Samuelsson, *Proc. Natl. Acad. Sci. USA*, **76**, 4275 (1979).

20) H. R. Morris, G. W. Taylor, P. J. Piper and J. R . Tippins, *Nature*, **285**, 104 (1980).

21) H. R. Morris and G. W. Taylor, *Prostaglandins*, **19** , 185 (1980).

22) B. A. Jackshik , F. F. Sun, L. H. Lee and M. G. Steinhoff, *Biochem. Biophys. Res. Commun.*, **95**, 103 (1980).

23) B. A. Jackshik and L. H. Lee, *Nature,* **287**, 51 (1980).

24) K. Ochi, T. Yoshimoto and S. Yamamoto, *J. Biol. Chem.*, **258**, 5754 (1983).

25) B. Samuelsson, *Science* , **220**, 568 (1983).

26) G. Feuerstein, *J. Auton. Pharmacol.*, **5**, 149 (1985).

27) P. J. Piper, "The Leukotrienes", Raven, New York, (1986).

28) W. Kreutner and M. I. Siegel, *Ann. Rep. Med. Chem.*, **24**, 241 (1984).

29) R. Levi, Y. Hattori, J. A. Burke, Z.-G. Guo, U. H. DEL Baltzo, W. A. Scott and C. A. Rouzer,"Prostaglandins, Leukotrienes and Lipoxins", J. M. Bailey ed.,Plenum, New York, 275 (1985).

30) A. M. Lefer and D. M. Roth, "Leukotrienes in Cardiovascular and Pulmonary Function", A. M. Lefer and M.H. Gee eds., Liss, New York, 59 (1985).

31) Z. Zukowska-Grojec, M. A. Bayorh, I. J. Kopin and G. Feuerstein, *J. Pharmacol. Exp. Ther.*, **223**, 183 (1982).

32) G. Feurstein, *Adv. Prostaglandin Thromboxane Leukotriene Res.*,**16**, 299 (1986).

33) R. J. Secrest, E. J. Olsen and B. M. Chapnick, *Circ. Res.*, **57**, 323 (1985).

34) N. A. Soter, R. A. Lewis, E. J. Corey and K. F. Austen, *J. Invest. Dermatol.*, **80**, 115 (1983).

35) K. Sugio, K. Ohuchi, M. Sugata and S. Tsurufuji, *Prostaglandins*, **21**, 649 (1981).

36) R. A. Lewis, K. F. Austen, J. M. Drazen, D. A. Clark, A. Marfat and E. J. Corey, *Proc. Natl. Acad. Sci.* USA, **77**, 3710 (1980).

37) S. E. Dahlen, J. Raud, C. N. Serhan, J. Bjork and B. Samuelsson, *Acta Physiol. Scand.*, **130**, 643 (1987).

38) T. R. Jones, C. Davis and E. E. Daniel, *Can. J. Physiol. Pharmacol.*, **60**, 638 (1982).

39) R. R. Schellenberg and A Foster, *Int. Arch. Allergy Appl. Immunol.*, **75**, 237 (1984).

40) A. C. Peatfield, P. J. Piper and R. S. Richardson, *Br. J. Pharmacol.*, **77**, 391 (1982).

41) M. L. Ogletree, J. R. Snapper and K.L. Brigham, *Am. Physiol. Soc.*, Fall 1982 Abstract.

42) L. W. Turnbull, L. S. Turnbull, J. Crofton and A. B. Kay, *Lancet*, **2**, 184 (1978).

43) O. Cromwell, H. R. Morris, M. E. Hodson. M. J. Walport, G. W. Taylor, J. Batten and A. B. Kay, *The Lancet*, **2**, 164 (1981).

44) A. Dembinska-Kiec, T. Simmet and B. A. Peskar, *Eur. J. Pharmacol.*, **99**, 57 (1984).

45) M. A. Moskowitz, K. J. Kiwak, K. Hekimian and L. Levine, *Science*, **224**, 886 (1984).

46) Th. Simmet, A. Seregi and G. Hertting, *Neuropharmacology*, **26**, 107 (1987).

47) P. J. Piper and A. W. B. Stanton, *Adv. Prostaglandin, Thromboxane and Leukotriene Res.* **16**, 255 (1980).

48) K. L. Black, *Prostaglandin, Leukotriene Med.*, **14**, 339 (1984).

49) E. M. Davidson, S. A. Rae and M. J. H. Smith, *J. Pharm. Pharmacol.*, **34**, 410 (1982).

50) S. D. Brain, R. D. R. Camp, P. M. Dowel, A. K. Black, P.W. Woollard, A. I. Mallet and M. W. Greaves, *Lancet*, **2**, 762 (1982).

51) L. B. Klickstein, C. Shapleigh and E.J.Goetzl, *J. Clin. Invest.*, **66**, 1166 (1980).

52) A. W. Ford-Hutchinson, M. A. Bay, M. V. Doig, M. E. Shipley and M. J. H. Smith, *Nature*, **286**, 264 (1980).

53) R. J. Gryglewski, B. Panczenko, P. Korbut, L. Grodzinska and A. Ocetkiewicz, *Prostaglandins*, **10**, 343 (1975).

54) F. P. Nijkamp, R. J. Flower, S. Monacada and J. R. Vane, *Nature*, **263**, 479 (1976).

55) R. J. Flower , S. Moncada and J.R. Vane, "The Pharmacological Basic of Therapeutics", 6th ed.,Macmillan Publishing Co. Inc., New York, P 682 (1980).

56) S. A. Metz, *Med. Clin. North Am.*, **65**, 713 (1981).

57) L. E. Trang, *Semin. Arthritis Rheum.*, **9**, 153 (1980).

58) G. A. Higgs, K. E. Eakins, K. G. Mugridge, S. Monacada and J. R. Vane, *Eur. J. Pharmacol.*, **66**, 81 (1980).

59) B. J. Northover, *Br. J. Pharmacol.*, **59**, 253 (1977).

60) H. R. Morris, P. J. Piper, G. W. Taylor and J. R. Tippins, *Br. J. Pharmacol.*, **66**, 452 (1979).

61) W. D. Busse, M. Mardin, R. Cruetzmann, J. R. Dunn, M. Theodoreau, B. F. Sloane and K. V. Honn, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **41**, Abstract 8464 (1982).

62) D. M. Engineer, U. Niederhauser, P. J. Piper and P. Sirois, *Br. J. Pharmacol.*, **62**, 61 (1978).

63) P. Borgeat, Bernard Fruteau de Laclos, S. Picard, J. Drapeau, P. Vallerand and E. J. Corey, *Prostaglandins*, **23**, 713 (1982).

64) J. H. Musser, A. F. Kreft and A. J. Lewis, *Ann. Rep. Med. Chem.*, **20**, 71 (1985).

65) J. G. Gleason, C. D. Perchonock and T. J. Torphy, *Ann. Rep. Med. Chem.*, **21**, 73 (1986).

66) J. J. Piwinski, W. Kreutner and M. J. Green, *Ann. Rep. Med. Chem.*, **22**, 73 (1987).

67) T. J. Carty, A. Marfat and H. Masamune, *Ann. Rep. Med. Chem.*, **23**, 181 (1988).

68) H. Masamune and L. S. Melvin, Jr., *Ann. Rep. Med. Chem.*, **24**, 71 (1989).

69) G. A. Higgs and J. R. Vane, *Brit. Med. Bull.*, **39**, 265 (1983).

70) Y. Arai, M. Konno, K. Shimojo, Y. Konishi, H. Niwa, M. Toda and M. Hayashi, *Chem. Pharm. Bull.*, **30**, 379 (1982).

71) T. Yoshimoto, M. Furukawa, S. Yamamoto, T. Horie and S. Watanabe-Kohno, *Biochem. and Biophys. Res. Commun.*, **116** (2), 612 (1983).

72) Y. Koshiara, T. Neichi, S-I. Mouroto, A-N. Lao, Y. Fujimoto and T. Tatsuno, *Biochim. Biophys. Acta*, **792**, 92 (1984).

73) M. A. Bray, *Eur. J. Pharmacol.*, **98**, 61, (1984).

74) M. Hamberg, *Biochim. Biophys. Acta*, **431**, 651 (1976).

75) M. K. Bach," The Leukotrienes Chemistry and Biology", L. W. Chakrin and D. M. Bailey ed., Academic Press Inc, Florida, P 167 (1984).

76) H. Allgayer, J. Eisenburg and G. Paumgartner, *Eur. J. Clin. Pharmacol.*, **26**, 449 (1984).

77) M. D. Sevillla, P. Neta and L. J. Marnett, *Biochem. Biophys. Res. Commun.*, **115**, 800 (1983).

78) T. Yoshimoto, C. Yokoyama, K. Ochi, S. Yamamoto, Y. Maki, Y. Ashida, S. Terao and M. Shiraishi, *Biochim. Biophys. Acta*, **713**, 470 (1982).

79) M. K. Bach, J. R. Brashler, H. W. Smith, F. A. Fitzpatrick, F. F. Sun and J. C. McGuire, *Prostaglandins*, **23**, 759 (1982).

80) R. J. Smith, F. F. Sun, B. J. Bowman, S. S. Iden, H. W. Smith and J. C. McGuire, *Biochem. Biophys. Res. Commun.*, **109**, 943 (1982).

81) D. W. Synder and J. H. Fleisch, *Annu. Rev. Pharmacol. Toxicol.*, **29**, 123 (1989).

82) J. Augstein, J. B. Farmer, T. B. Lee, P. Shrard, M. L. Tattersall, *Nat. New Biol.*, **245**, 215 (1973).

83) P. Sheard, T. B. Lee and M. L. Tattersall, *Monogr. Allergy,* **12**, 245 (1977).

84) B. Mead, L. H. Patterson and D. A. Smith, *J. Pharm. Pharmacol.,* **33**, 682 (1981).

85) J. H. Fleisch, L. E. Rinkema, K. D. Haisch, D. Swanson-Bean, T. Goodson, P. P. K. Ho and W. S. Marshall, *J. Pharmacol. Exp. Ther.*, **233** (1), 148 (1985).

86) J. H. Fleisch, L. E. Rinkema, K. D. Haisch, D. McCullough, F. Patrick Carr and R. D. Dillard, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **333**, 70 (1986).

87) T. R. Jones, R. Young, E. Champion, L. Charette, D. Denis, A. W. Ford - Hutchinson, R. Frenette, J-Y. Gauthier, Y. Guindon, M. Kakushima, P. Masson, C. McFarlane, H.Piechuta, J.Rokach and R. Zamboni, *Can. J. Physiol. Pharmacol.*, **64**, 1068 (1986).

88) D. W. P. Hay, R. M. Muccitelli, S. S. Tucker, L. M. Vickery-Clark, K. A. Wilson, J. G. Gleason, R. F. Hall, M. A. Wasserman and T. J. Torphy , *J. Pharmacol. Exp. Ther.*, **243**, 474 (1987).

89) C. Buckner, J. Fedyma, R. Krell, J. Robertson, R. Keith, V. Matassa, F. Brown, P. Bernstein, Y. Yee, J. Will, J. Fishleder, R. Saban, B. Heap and F. Gileg, *FASEB J* , **2**: A1264 (Abstr.) (1988).

90) M. Nakanishi, T. Ohe and M. Tsuruda (Yoshitomi Pharm. Ind Ltd) Japan Kokai 75, 140, 498, 11 Nov 1975, Appl. 74/44,685, 19 April 1974, *Chem. Abst.*, **85**, 32977 (1976).

91) T. Oe and M. Tsuruda (Yoshitomi Pharm Ind. Ltd) Japan Kokai 76, 52, 199, 08 May 1976, Appl. 74/126,392, 31 Oct 1974, *Chem. Abstr.*, **85**, 192694 (1976).

92) T. Oe and M. Tsuruda (Yoshitomi Pharm. Ind. Ltd) Japan Kokai 76, 88, 997, 04 Aug 1976, Appl. 75/12,760, 29 Jan 1975, *Chem. Abstr.*, **86**, 89786 (1977).

93) T. Oe and M. Tsuruda (Yoshitomi Pharm Ind Ltd) Japan Kokai 76, 88, 998, 04 Aug 1976, Appl. 75/14,726, 03 Feb 1975, *Chem. Abstr.*, **86**, 89785(1977).

94) M. Nakanishi, T. Ohe and M. Tsuruda (Yoshitomi Pharm Ind Ltd) Japan Kokai 75, 130, 794, 16 Oct 1975, Appl. 74/37,490, 02 Apr 1974, *Chem. Abstr.*, **84**, 150612 (1976).

95) M. Nakanishi, T. Ohe and M. Tsurada (Yoshitomi Pham Ind. Ltd.) Japan Kokai 75, 130, 795, 16 Oct 1975, Appl. 74/38,512, 03 April 1974, *Chem. Abstr.*, **85**, 46621 (1976).

96) A. Nohara, H. Sugihara and K. Ukawa (Takeda Chem. Ind. Ltd.) Ger. Offen. 2, 809, 720, 14 Sept 1978, Japan Appl., 77/25,654, 08 March 1977, *Chem. Abstr.*, **89**, 215391 (1978).

97) A. Nohara, H. Dugihara and K.. Ukawa (Takeda Chem. Ind. Ltd.) Japan Kokai 79, 88, 298,13 July 1979, Appl. 77/153,898, 20 Dec. 1977, *Chem. Abstr.*, **91**, 193285 (1979).

98) Yoshitomi Pharm. Ind. Ltd., Japan Kokai 80, 122, 785, 20 Sept 1980, Appl. 79/30, 623, 15 Mar 1979, *Chem. Abstr.*, **94**, 156933 (1981).

99) T. Oe and M. Tsurada (Yoshitomi Pharm. Ind. Ltd.) Japan Kokai 76, 95, 097, 20 Aug 1976, appl.75/16,537, 08 Feb. 1975, *Chem. Abstr.*, **86**, 171424 (1977).

100) I. Toshihiri, K. Ukawa, H. Sugihara and A. Nohara, *Heterocycles*, **16**, 733 (1981).

101) A. Nohara, T. Ishiguro, K. Ukawa, H. Sugihara, Y. Maki and Y. Sanna, *J. Med. Chem.*, **28**, 559 (1985).

102) T. Saiho, H. Kuriki, Y. Ashida, H. Makino and Y. Maki, *Int. Arch. Allergy Appl. Immunol.*, **78**(1), 43 (1985).

103) A. Nakanishi et al, *Yakugaku Zasshi* , **96**(1), 99 (1976).

104) A. Nohara, T. Ishiguro and K. Ukawa (Takeda Chem. Ind. Ltd.) Ger. Offen., 2, 841, 644, 05 Apr. 1979, Japan Appl. 77/115,817, 26 Sept 1977, *Chem. Abstr.*, **91**, 91643 (1979).

105) A. Nohara, T. Ishiguro and K. Ukawa (Takeda Chem. Ind. Ltd.) S. African 78, 05, 054, 10 Jul. 1979, Japan Appl. 77/115, 817, 26 Sept. 1977, *Chem. Abstr.*, **92**, 76518 (1980).

106) T. Oe and M. Tsuruda (Yoshitomi Pharm. Ind. Ltd.) Ger. offen. 2, 521, 980, 18, Dec. 1975, Japan Appl. 74/60,632, 28 May 1974, *Chem. Abstr.*, **84**, 121842 (1976).

107) T. Oe and M. Tsuruda (Yoshitomi Pharm. Ind. Ltd.) Japan Kokai 76, 113, 899, 07 Oct. 1976, Appl. 75/37,646, 27 Mar. 1975, *Chem. Abstr.*, **86**, 189950 (1977).

108) T. Oe ansd M. Tsurada (Yoshitomi Pharm. Ind. Ltd.) Japan Kokai 75, 151, 897, O6 Dec. 1975, Appl. 74/60,632, 28 May 1974, *Chem. Abstr.*, **85**, 21376 (1976).

109) T. Oe ansd M. Tsurada (Yoshitomi Pharm. Ind. Ltd.) Japan Kokai 76, 96, 299, 30 Aug. 1976, Appl. 75/22, 043, 21 Feb. 1975, *Chem. Abstr.*, **86**, 121340 (1977).

110) T. Oe ansd M. Tsurada (Yoshitomi Pharm. Ind. Ltd.) Japan Kokai 77, 105, 197, 03 sept. 1977, Appl. 76/22, 544, 01 Mar. 1976, *Chem. Abstr.*, **88**, 89668 (1978).

111) F. J. Villani, T. A. Mann, E. A. Wefer, J. Hannon, L.L. Larca, M. J. Landon, W. Spivak and D. Vashi, *J. Med. Chem.*, **18**, 1 (1975).

112) F. J. Villani, T. A. Mann and E. A. Wefer, *J. Med. Chem.*, **18**, 666 (1975).

113) Yoshitomi Pharm. Ind. Ltd., Japan Kokai , 81, 100, 789, 12 Aug. 1981, Appl. 80/2919, 14 Jan 1980; 5pp, *Chem. Abstr.*, **96**, 6726 V (1982).

114) J. A. Bristol, E. H. Gold and R. J. Lovey, *J. Med. Chem.*, **24**, 927 (1981).

115) J. A. Bristol, E. H. Gold, I. Gross and R. J. Lovey, *J. Med. Chem.*, **24**, 1010 (1981).

116) P. Valenti, A. Borracini, G. Priofiore and P. D. Re, *Chim Ther.*, **6**, 652 (1973).

117) P. N. Namishi, J. Piechaczek and J. Wrotek, *Acta Pol. Pharm.*, **34**, 1 (1977).

118) N. Michio, T. Oe, T. Mineo (Yoshitomi Pharm. Ind. Ltd.) Japan Kokai 74, 117, 498 (cl. 16 E623), 09 Nov 1974, Appl. 73/32,109, 19 Mar. 1973, 6pp, *Chem. Abstr.*, **83**, 10033r (1975).

119) M. Nakanishi, T. Oe, O. Nakatasu and M. Tsurauda (Yoshitomi Pharm. Ind. Ltd.) Ger. offen. 2, 413, 150, 03 Oct 1974, Japan Appl. 73, 32 109, 19 Mar. 1973, *Chem. Abstr.*, **82**, 4230 (1975).

120) M. Nakanashi, T. Oe, M. Tsuruda (Yoshitomi Pharmaceutical Industries Ltd.), Japan Kokai, 75 05, 399 (cl. 16 E623), 21 Jan 1975, Appl. 73 59, 185, 25 May 1973, 4 pp, *Chem. Abstr.*, **83**, P28207 K (1975).

121) F. G. Mann and J. H. Turnbull, *J. Chem. Soc.*, 761 (1951).

122) F. J. Villani, P. J. L. Daniels, C. A. Ellis, T. A. Mann and K. C. Wang, *J. Heterocyclic Chem.*, **8**, 73 (1971).

123) R. R. Renshaw and R. C. Conn, *J. Amer. Chem. Soc.*, **59**, 297 (1937).

124) W. E. Feeley and E. M. Beavers, *J. Amer. Chem. Soc.*, **60**, 1698 (1938).

125) E. C. Taylor and A. J. Croveti, "Organic Synthesis," volume 4, Wiley, New York, 654 (1963).

126) D. Jerchel and H. E. Heck, *Justus Liebigs Ann. Chem.*, **613**, 171 (1958).

127) F. G. Mann and J. A. Reid, *J. Chem. Soc.*, 2057 (1952).

128) S. Kruger and F. G. Mann, *J. Chem. Soc.*, 3905 (1954).

129) S. Kruger and F. G. Mann, *J. Chem. Soc.*, 2755 (1955).

130) Evans and Brown, *J. Org. Chem.*, **27**, 1329 (1962).

131) C.W. Muth, R.S. Darlak and J. C. Patton, *J. Heterocyclic Chem.*, **9**, 1003 (1972).

132) M. Hamana, M. Yamazaki, Y. Zasshi, 80, 1519 (1960); *Chem. Abstr.*, **55**, 8405b (1961).

133) A. Lin and S. Kasina, *J. Heterocyclic Chem.*, **18**, 759 (1981).

134) R. Q. Brewster and F. B. Dains, *J. Am. Chem. Soc.*, 2148 (1969).

135) G. Hilgetag and A. Martini, "Preparative Organic Chemistry", 4th Ed., John Wiley and Sons, New York, P 202 (1972).

136) R. T. Morrison and R. N. Boyd, "Organic Chemistry" 3rd Ed., Allyn and Bacon Inc., Boston, P 342 (1973).

137) L. A. Paquette, "Principles of Modern Heterocyclic Chemistry" , Benjamin Inc., New York, P 277 (1968).

138) C. L. Groves, J. T. Ralph and A. F. Temple, *J. Heterocyclic Chem.*, **24**, 27 (1987).

139) Unpublished results from our laboratory.

140) J. F. Burka, *Br. J. Pharmac.*, **77**, 3 (1982).

141) J. F. Burka, *Agents and Actions*, **13**, 318 (1983).

142) J. F. Burka, *Can. J. Physiol. Pharmacol.*, **61**, 581 (1983).

143) J. F. Burka, *J. Pharmacol. Exp. Ther.*, **225**, 427 (1983).

144) M. H. Saad and J. F. Burka, *Can. J. Physiol. Pharmacol.*, **61**, 876 (1983).

145) J. F. Burka and M. H. Saad, *Br. J. Pharmac.*, **81**, 465 (1984).

146) M. H. Saad and J. F. Burka, *Eur. J. Pharmacol.*, **100**, 13 (1984).

147) J. F. Burka, *Br. J. Pharmac.*, **85**, 411 (1985).

148) J. F. Burka, *Br. J. Pharmac.*, **85**, 421 (1985).

149) J. F. Burka, Proc. 5th Symposium on Veterinary Pharmacology and Therapeutics, H. R. Adams ed. (1985).

150) J. F. Burka, H. Briand, P. Scott-Savage and F. M. Pasutto, *Can. J. Physiol. Pharmacol.*, **67**, 483 (1989).