SYNTHESIS OF ARYL/HETEROCYCLIC SULFONYL CYCLIC UREAS AS ANTIDIABETIC AGENTS

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Master of Philosophy

in

Organic Chemistry

By

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DECLARATION

This is to certify that this dissertation submitted by ***Iftikhar Ahmad*** in its present form is accepted by the Department of Chemistry, Quaid-i-Azam University, Islamabad as satisfying the dissertation requirements for the degree of ***Master of Philosophy in Organic Chemistry***.

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To

My loving parents and brothers, for their immense patience and perseverance for supporting me through thick and thin for making me, what I am today.

To

My nephews, Omer, Usman, Ali, **friends,** *Shoaib and Jahangir, to whom I love more today than yesterday, but not as much as tomorrow.*

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RESEARCH OBJECTIVES

The job of synthetic organic chemist is to synthesize new compounds using old or preferably new synthetic methods and utilize these compounds in industry. More and more efforts are being concentrated on the synthesis of new drugs. The main objective of this project was to synthesize aryl/heterocyclic sulfonyl cyclic urea derivatives having hypoglycemic activity. A concrete structure activity relationship can be concluded. Moreover, the toxicity of compounds can be tested and drugs having maximum pharmacological activity and low toxicity can be studied for further clinical trials. The major part of the project was the synthesis of these drugs, optimising the yield and elucidation of structure of intermediate compounds as well as final products by modern spectroscopic techniques.

INTRODUCTION

1. Introduction:

After the biguanides only one class of oral hypoglycemic agents is seen in the market, "the sulfonyl ureas". Tolbutamide, glibenclamide and tolazamide are the important sulfonyl urea drugs used for the treatment of non insulin dependent diabetes mellitus. Different pharmaceutical companies are marketing a number of antidiabetic drugs having these sulfonyl ureas as active ingredients under different trade names.

During the last two decades, literature is over-loaded with the synthesis and antidiabetic activity of many acyclic aryl/heterocyclic sulfonyl ureas. In recent literature some new aryl sulfonyl urea derivatives with appreciable hypoglycemic activity have been reported[1]. Among heterocyclic acyclic sulfonyl urea derivatives 3-methyl-5-phenyl-pyrazole-sulfonyl urea derivatives have been reported as hypglycemic agents[2]. The potency of these is more than that of phenformin. 3,4,5-Trisubstituted pyrazole sulfonyl urea derivatives[3] have also been reported as hypoglycemic agents and among them compound having carboxylic acid group at position-4 is much more active than the corresponding trisubstituted pyrazoles. It has also been reported that pyrazole sulfonyl urea derivatives are much more active than the corresponding thiourea analogues[4]. Amino acid derivatives of sulfonyl urea have also been reported as antidibetic agents[5].

Some zinc and cerum salts of sulfonyl urea have also been reported useful in reducing elevated blood sugar levels and for diabetes treatment[6]. Zinc-glyburide and Ce-glyburide were more effective in reducing blood sugar levels in rats than glyburide itself. These were also more effective than tolbutamide itself. More and more efforts are being concentrated on the synthesis of new acyclic sulfonyl urea derivatives as antidiabetic agents. However, a little attention has been paid to the synthesis of cyclic sulfonyl urea derivatives as antidiabetic agents.

Many researchers concentrated their attention to the synthesis of cyclic sulfonyl urea derivatives, "the sulfonyl hydantoins"[7-9]. A number of derivatives of 3-substituted-1-[p-(3-methyl-5-phenyl) pyrazol-1-yl] and [(3-methyl-4-bromo-5-phenyl) pyrazole-1-yl) benzene sulfonly]-2-thiohydantoins have been reported as having marked antidiabetic activity[4]. It was proved that the aryl/heterocyclic sulfonyl group at 1-postion of hydantoin greatly effects the physiochemical properties and intestinal absorption of the drugs and

they are much more active than those when 3-position is substituted by sulfonyl group[10]. A number of aryl/heterocyclic sulfonyl hydantoin derivatives have been prepared and tested as antidiabetic agents. The synthesis of 3-aryl sulfonyl hydantoins by coupling of corresponding sulfonyl chloride with substituted hydantoins have been reported which on rearrangement in the presence of sodium hydride lead to 1-sulfonyl hydantoin derivatives[11].

Among heterocyclic sulfonyl hydantoins, 1-(3-bromo-7-fluro benzo [b] furan-2-yl-sulfonyl) hydantoin, 1-(4,5-dichloro benzo [b] furan-2-yl-sulfonyl) hydantoin, 1-(5,6-dichloro benzo [b] furan-2-yl-sulfonyl) hydantoin and 1-(3-bromo-5,6-dichloro benzo [b] furan-2-yl-sulfonyl) hydantoin were found to be the most active.

An other class of oral hypoglycemic agents "the sulfonyliminoimidazolidine" have beèn reported[12]. By combining structural elements of sulfonyl ureas and bigaunides within one molecule, these compounds display hypoglycemic activity in nomral and streptozotocin diabetic rats. Sulfonyliminoimidazolidine have dual activity i.e. activity like sulfonyl urea derivatives and activity like biguanides. To test this hypothesis different studies have been carried out to study the effects of selected sulfonyliminoimidazolidines on insulin release in-vitro and in-vivo and as glucose oxidation by rat fat cells in vitro.

Synthesis of perhydro-1,3-diazepin-2,4-dione which is a seven membered cyclic urea have been reported[13]. However, its sulfonyl derivatives are not known. It may be possible to have sulfonyl perhydro 1,3-diazepin 2,4-dione as potent antidiabetic agents analogous to sulfonyl hydantoin derivatives. Similarly sulfonyl benzimidazolones, which are five membered cyclic urea derivatives have been reported[14], but their antidiabetic activity is still not reported. However, some benzimidazolones derivatives have been reported as psychopharmacological agents and are available in the market.

Currently an active search for antidiabetic agents is being conducted, while the known antidiabetic agents have been used to establish a role for the treatment of diabetes and diabetic complications such as cataract and peripheral neuropathy in diabetic and galactosemic animals. The present work was conducted as a part of search for potent antidiabetic agents. For this purpose we have prepared a number of new sulfonyl cyclic

urea derivatives using some new methods. These include 1,3-diaryl sulfonyl benzimidazolones **III, III′ (a-b)**, 3-mono aryl sulfonyl benzimidazolones **VI, VI′ (a-b)**, 1-ter.butoxy carbonyl-3-aryl sulfonyl benzimidazolones **V, V′ (a-b)**, 3-aryl sulfonyl hydantoins **VIIIa, VIIIf, VIIIh**, 1-aryl sulfonyl hydantoins **IXf** and **IXh** through a rearrangement in the presence of sodium hydride from 3-aryl sulfonyl hydantoins and 3-heterocyclic sulfonyl hydantoin **VIIIu**. The spectroscopy of intermediate compounds and the final products have been discussed in detail. The compounds **III, III′ (a-b), VI, VI′ (a-b), VIIIa, VIIIf, VIIIh, IXf** and **IXh** have been sent to F.R. Germany to be tested as antidiabetic agents.

BACKGROUND

2. Background:

2.1 Diabetes[15]:

Diabetes is the most common of the serious metabolic human diseases distributed world-wide. It is characterized by a series of hormone-induced metabolic abnormalities and by long term complications, involving eyes, kidneys, nerves and blood vessels.

Between 1 and 6% of the United States and about 13% of Pakistan's population has diabetes and almost as many other are believed to have this disease. It ranks third behind heart disease and cancer as a cause of death.

Diabetes is defined clinically as a disease in which the blood sugar level persists in being much higher than warranted by the dietary and nutritional status of the individual. Invariably, a person with untreated diabetes has glucosuria, and the discovery of this condition often triggers the clinical investigations that are necessary to diagnose diabetes.

Glucose is stored under normal conditions in the form of glycogin in the liver and muscles for later use and at this time it is reconverted in to glucose. Insulin is necessary for both the storage and reconversion of glycogen to glucose.

The fundamental problem in diabetes is the body's inability to metabolize glucose, which results in abnormal accumulation of sugar in the blood stream. As glucose accumulates above normal levels in the diabetics blood stream, it is filtered by kidneys and remains in urine. Additional amount of urine is produced to contain the excess glucose.

The body's need to obtain energy from glucose and to convert glucose to glycogen and vice versa is continuous, but always changing quantitatively. Meeting these needs requires constantly fluctuating amounts of effective insulin. Non-diabetics produce these amounts no matter, what they eat or do, thus maintaining a steady state of metabolism. Diabetics can not achieve this steady state simply by taking insulin, they must also control their diets and their activities. Diabetes is not an all-or-nothing phenomenon. It can be mild, moderate or severe and can fluctuate in degree in any one individual over a long period of time or even from day by day.

Diabetes is divided into two classes:

2.1.1 Diabetes Insipidus (DI):

It is characterized by excretion of excessive amount of dilute urine. Patient may pass 5-20 litres or more urine in 24 hours. It is further divided into diabetes insipidus cranial and diabetes insipidus nephrogenic.

Diabetes insipidus cranial is characterized by antidiuretic hormone (ADH) and arginin vesopressin (AVP) deficiency. This may be due to genetic defect, hypothalmia or high stalk tension and idiopathic.

Diabetes insipidus nephrogenic is characterized by unresponsiveness of the renal tabules to vesopressin. This may be due to genetic defect, metabolic abnormality, drug therapy and heavy metal poisoning.

2.1.2 Diabetes Mellitus (DM):

It is characterized by hyperglycemia due to absolute or relative deficiency of insulin. The name of this disorder is from the Greek, diabetes "to pass through a siphon", and mellitus, "honey-sweet", meaning to pass urine that contains sugar. Generally it is called "Diabetes".

Diabetes mellitus is further divided into three types:

Type-I: It is called insulin-dependent diabetes mellitus or IDDM. In this type β-cells of the pancreas are unable to make and secrete insulin. Insulin therapy is essential. Between 10 and 25% of all cases of diabetes are of this severe insulin-dependent variety. Most victims contract IDDM, before the age of 40, often as adolescent. So IDDM has sometimes been called as juvelin-onset diabetes.

IDDM, develops in six stages. Stage I is an existing genetic defect, most likely involving more than one gene. Genetic problem is associated with problem of the immune system. Stage II is a triggering incident, like a viral infection. For example, mumps virus causes diabetes in some cases. Stage III is the appearance of certain antibodies in the blood. In this case body's immune system fails to recognize the protection of its own body and sets out to destroy them and therefore, itself. Stage IV is

period in which the pancreas loses its ability to secrete insulin. Stage V is diabetes and persistent hyperglycemia. At this stage most of the pancreas β-cells have disappeared. Stage VI is the period following complete destruction of β-cells.

Type II: It is called non insulin-dependent diabetes mellitus or NIDDM. NIDDM is a chronic disorder of metabolism due particularly to disfunction of pancreatic β-cells. NIDDM patients secrete insulin, and their serum insulin levels may be diminished, normal or even increased. In this case most of the patients are over 40, so NIDDM has been called as adult-onset diabetes.

Type III: This type is the diabetes associated with genetic syndrome. The reason may be some viruses.

2.2 Complications Associated with Diabetes:

Many long term complications of diabetes are known. These relates to eyes, kidneys, nerves and blood vessels. However, complications relating to eyes and blood vessels are common. These are cataract and microangiopathy.

2.2.1 Cataract[16]:

Any opacity in the lens or its capsule weather developmental or acquired, is called cataract. Acquired cataract is due to degeneration of lens fibres already formed. The reason, are the factors which disturb the critical intra and extra-cellular equilibrium of water and electrolytes. This deranges the colloid system within the fibres and this tends to bring about opecification.

Developmental cataract occur during the process of lens development. Lens's development takes place in layers. Central nucleus is formed first, around which concentric zones are subsequently laid down. This process continue until adolescence. Developmental cataract has therefore a tendency to effect a particular zone, which was being formed, when this process was disturbed.

Diabetic patients very frequently acquire cataract in their eyes, due to which the lens of the eyes is damaged. This is the leading cause of new cases of blindness in the

United States and in Pakistan, and it is the second most common cause of blindness, overall.

Sugar cataract formation takes place due to the reduction of glucose to sorbitol. Glucose is reduced by the enzyme aldose-reductase to sorbitol. It is a minor reduction in cells of the lens of the eyes, but an abundance of glucose shifts equilibria in favour of too much sorbitol. Sorbitol, unlike glucose, tends to be trapped in lens cells and as the sorbitol concentrations rises, so does the osmotic pressure in the fluid. This draws water into the lens cells, which generates pressure and leads to cataract. Now-a-days this damaged lens is being replaced by intraocular lens through operation.

2.2.2 Microangiopathy[17]:

The presence of high levels of blood sugar in both IDDM and NIDDM patients shifts certain chemical equilibria in favour of glycosylated compounds. In such reactions Schiff-base formation takes place.

$$-CH{=}O + -NH_2 \rightleftharpoons -CH{=}N- + H_2O$$

Haemoglobin gives this reaction, and a high level of glucose shifts this equilibria to the right. The level of glycosylated haemoglobin thus increases. When the glucose level is brought down and kept within a normal range, the Schiff-base level also declines. The problem with Schiff-bases, in the long term, is that they undergo molecular rearrangements to more permanent products, called "Amadori Compounds", in which the (C=N) double bond has migrated to C=C positions. After a time, the formation of the amadori compounds, is not reversible when these reactions occur in the basement membrane of blood capillaries, they swell and thicken. This condition is called "migroangiopathy". Microangiopathy is believed to lead to other complications, most of which involves the vascular system or the neural network, kidney problems, gangrene of the lower limbs and blindness.

2.3 Medication:

First step for the medication of diabetes is the determination of level of blood sugar. A number of technologies are being used for this purpose. For example, an enzyme-based test is used to detect the blood sugar level. Another technology in use is a

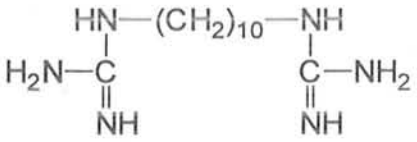
hand held battery driven source of infrared rays, which converts the amount of light absorbed into blood glucose level. In some diabetics, insulin pumps can be implanted, much like heart pacemakers. They monitor the blood sugar level and release insulin according to the need. The use of insulin nasal sprays immediately before a meal is another technique tested.

Several groups of scientists are working over insulin pills and transplantation of β-cells. Human β-cells work best, of course, but those form pigs and cows are also useable provided that they are encapsulated in very small plastic spheres. These spheres have microscopic holes, large enough to let insulin molecules escape but not large enough to let antibodies inside. This technique has cured type I diabetes (IDDM) in experimental animals. A test of this technique in human was begun in 1993, and early indications were very promising. However, the most common therapy of diabetes, besides dietary control and insulin resistance, is the administration of oral antidiabetic drugs.

A wide variety of compounds are capable of causing reduction of glucose in blood. These include biguanides[18], sulfonamides[19], pyrimidine[20], imidine[21], amines[22], triazines[23], oxazoles[24], flavonoids[25] and a variety of plant substances as well as other compounds. Although insulin is a practical and satisfactory agent for the treatment of diabetes, it has the disadvantage of requiring parental administration one or more times daily. The search continues for means of controlling hyperglycemia by the use of oral preparations of insulin or therapeutic agents other than insulin. Two types of compounds are used widely as antiabetic drugs in the market. These are biguanides and sulfonyl ureas.

2.3.1 Biguanides:

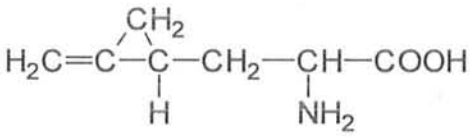
In early days, attempts were made to treat the diabetic patients with guanidine derivatives[26]. For this purpose synthalin (**1**) and hypoglycin[27] (**2**) were used but these attempts met with failure because of the toxicity of these compounds.



synthalin

(1)

(decamethylene diguanidine)



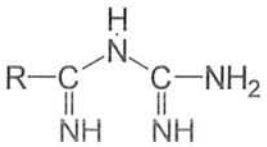
hypoglycin

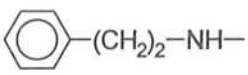
(2)

(α-amino-β-[2-methylene cyclopropyl] propionic acid)

However, later on, it was found that guanidine and some of its derivatives could produce hyperglycemia. In this connection three different biguanides were in use as hypoglycemic agents all over the world namely phenformin (3) buformin (4) and metformin (5), these are shown in Table-2.1.

Table-2.1: Biguanides having antidiabetic activity.



Comp. No.	Name	R
3	Phenformin	
4	Buformin	$CH_3–(CH_2)_3–NH–$
5	Metformin	$(CH_3)_2N–$

Although guanidine and many of its derivatives can produce hypoglycemia, yet only phenyl ethyl biguanide (phenformin) was in use as hypoglycemic agent. Its hypoglycemic effects in patients with diabetes are not well understood. It is of interest that compounds do not cause a reduction in blood glucose in normal human subjects. It has been shown to potentiate the effects of insulin in vivo and in vitro and may antagonize anti-insulin factors. The symptoms of an excessive dose include neusea, anorexia, foul breath, vomiting, diarrhoea and abdominal cramps. Some investigators have reported that phenformin leads to slow but consistent weight loss. This observation has yet been confirmed by carefully controlled studies. However, this agent lowers blood

sugar without promoting insulin release. Therefore, in addition to reducing the post prandial need for insulin from the pancreas, it might reduce the deposition of fat. Phenformin is often used in combination with sulfonyl urea or insulin. In patients, where diabetes is difficult to control, even with excess dose of insulin, the addition of phenformin to the therapeutic regimen has improved blood sugar control. Its use was accompanied by increased blood pressure and heart rates as well as an increase in fatal and non fatal events.

Table-2.2: Biguanides used as antidiabetic drugs available in the market.

Trade Name	Active ingredient	Daily Dose	Preparation available	Manufacturer
Glucophage	Metformin hydrochloride	500-1500 mg as three doses in a day.	White film coated tablets	Merck Marker (Pvt.) Ltd., Quetta, Pakistan.
Tabrophage	Metformin hydrochloride	500-1500 mg as three doses in a day.	Film coated tablets in aluminium foil skip.	Tabros Pharma, Karachi, Pakistan.
Metphage	Metformin hydrochloride	500-1500 mg as three doses in a day.	White film coated tablets.	Efroze Chemical Industries (Pvt.) Ltd., Karachi, Pakistan.

2.3.2 Sulfonyl ureas:

2.3.2.1 Aryl sulfonyl acylic ureas:

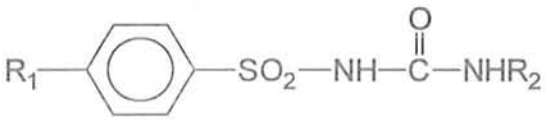
After the removal of biguanides from the U.S. market in 1977, only one class of oral hypoglycemic agents was left for the treatment of non-insulin dependent diabetes mellitus (NIDDM)[28], namely the sulfonyl ureas.

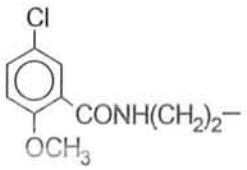
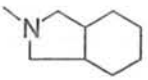
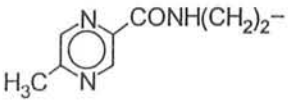
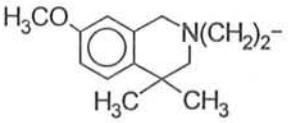
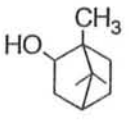
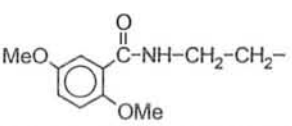
Sulfonyl ureas are divided into two classes:

i) Sulfonyl ureas with simpler substitution known as the first generation sulfonyl ureas [**6(a-e)** Table-2.3].

ii) Sulfonyl ureas with complex substitution known as the second generation sulfonyl ureas [**6(f-h)** Table-2.3].

Table-2.3: Sulfonyl ureas having antidiabetic activity.



Comp. No.	Name	R_1	R_2
6a	Acetohexamide	CH_3CO-	
6b	Chloropropamide	Cl	$-(CH_2)_2CH_3$
6c	Tolazamide	CH_3-	
6d	Carbutamide	NH_2-	$-(CH_2)_3CH_3$
6e	Tolbutamide	CH_3-	$-(CH_2)_3CH_3$
6f	Glibenclamide		
6g	Gliclazide	CH_3-	
6h	Glipizide		
6i	Gliquinidone		
6j	Glibornamide	$-CH_3$	
6k	Glyburide		

First generation sulfonyl ureas as well as second generation sulfonyl ureas are being widely used as antidiabetic agents. Different pharmaceutical companies are marketing these sulfonyl ureas under different trade names. Some of antidiabetic drugs, their trade names, and active ingredients available in the market are shown in Table-2.4.

Table-2.4: Sulfonyl urea drugs available in the market.

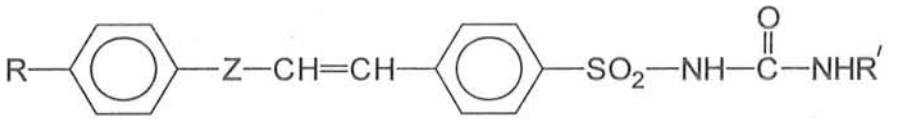
Trade Name	Active ingredient	Daily dose	Preparations available	Manufacturer
Euglucon	Glibenclamide	15-20 mg as three doses in a day.	White oblong scored tablets of 5mg in printed BME_4.	AGP (Pvt.), Ltd., Karachi, Pakistan.
Diamicron	Gliclazide	80-240 mg as a single dose in a day.	Boxos with 20 and 60 tablets of 80 mg each.	Less Laboratories, Servier, France.
Daonil	Glibenclamide	5-15 mg as two doses in a day.	5x10 oblong tablets of 5mg each.	Hoechst Pakistan Ltd; Karachi, Pakistan.
Diocid	Gliclazide	80-320 mg as a single dose in a day.	Pack of 30 tablets of 80 mg each.	Himont Pharma-ceutical (Pvt) Ltd., Lahore, Pakistan.
Glicon	Glibenclamide	5-20 mg as a two doses in a day.	Blister strips of 6x10 tablets of 5mg each.	Efroze Chemical Industries (Pvt) Ltd., Karachi, Pakistan.
Amaryl	Glimepiride	1-6 mg as a single dose in a day.	Tablets of 1-2 mg each.	Hoechst AG., Frankfurt, Germany.
Diclazide	Gliclazide	80-320 mg as two doses in a day.	Blister pack of 20 tablets of 80 mg each.	Wilson's Pharma-ceuticals, Islamabad, Pakistan.

Despite an improvement of 250-fold in potency, over the last 33 years e.g. Glibenclamide (**6f**), the sulfonyl ureas are still afflicated with serious and sometimes fatal problems of drug-induced hypoglycemia, apparantly the result of hypoinsulinema.

The most serious problems associated with the use of sulfonyl ureas are profound hypoglycemia and diabetic acidosis. CNS effects such as confusion, vertigo etaxia and weakness have been observed with the use of large doses. Sulfonyl ureas have also been

reported to produce hypothyroidim. The most serious toxic effects are granulocytopenia and cholestatic jaundice are frequently preceded by fever, malaise and skin eruptions or photosensitivity.

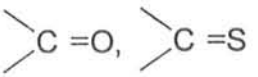
Some new sulfonyl urea derivatives with appreciable hypoglycemic activity have been reported in recent literature. For example, compound (7) has been reported to show hypoglycemic activity at 300 mg/kg in mice. This compound is prepared by refluxing chalconyl sulfonamide with isocyanate[1].



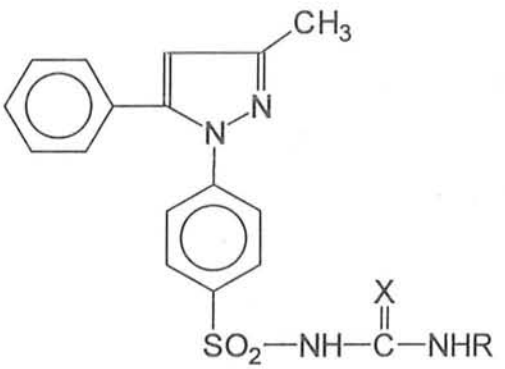
(7)

R = H, Me, OMe, Cl

R′ = Bu, C_6H_{10}

Z = 

Among heterocyclic sulfonyl urea derivatives, 3-methyl-5-phenylpyrazole sulfonyl urea derivatives (**8**) have been reported as hypoglycemic agents[2].

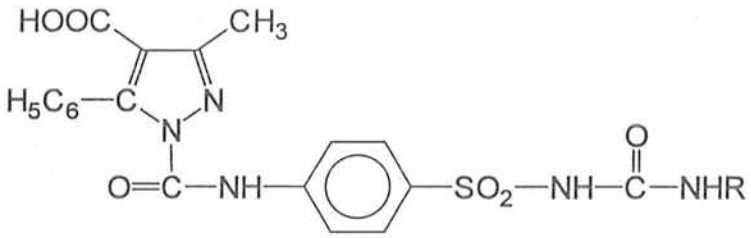


(**8**)

	R	**X**
a)	C_2H_5	O
b)	$(CH_2)_2CH_3$	O
c)	$(CH_2)_3CH_3$	O
d)	C_6H_{11}	O
e)	C_6H_5	S
f)	C_2H_5	S

All of these compounds were tested for hypoglycemic activity and it was found that compounds **8 (b-d)** possess marked hypoglycemic activity, and potency of these is more than that of phenformin.

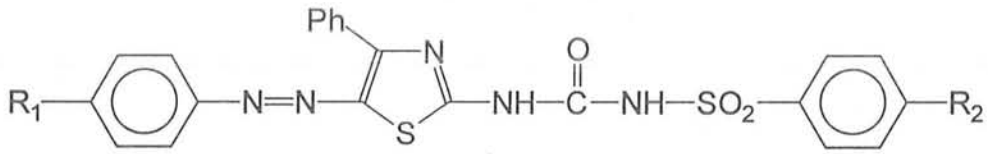
3,4,5-Trisubstituted pyrazoles sulfonyl urea derivatives[4] have also been reported as having potential hypoglycemic activity and among them compound (**9**) having carboxylic acid group at position-4 is much more active than the corresponding trisubstituted pyrazoles. The presence of 4-ethoxy carbonyl or carboxy group in the pyrazole ring reduces the hypoglycemic activity and it was also found that pyrazole sulfonyl urea derivatives are much more active than the corresponding thiourea analogous[4].



(**9**)

R = alkyl, aryl or H.

Some new N-[5-aryl_azo-4-phenyl-2-thiazolyl]-N-arylsulfonyl urea (**10**) were prepared as oral hypoglycemic agents[1].

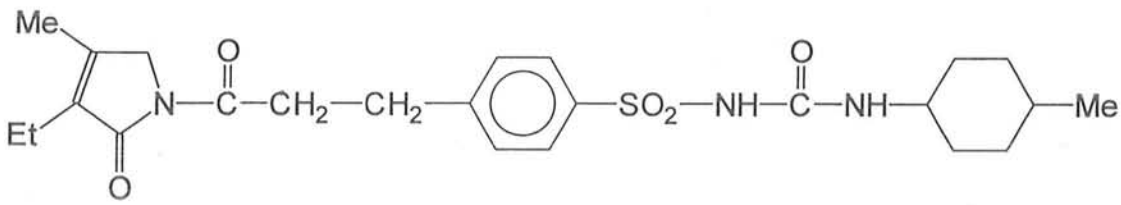


(**10**)

R_1 = H, NO_2, OMe, Cl

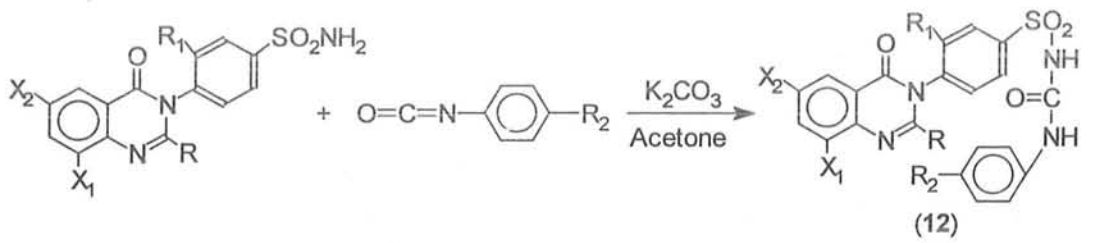
R_2 = H, Me, OMe, NHAc

Compound (**10**) decreased blood sugar in rats up to 21% at an oral dose of 250 mg/kg. Arylurieodoalkyl phenyl sulfonyl ureas, Glimepiride[29a] (**11**), prepared from lactams showed blood glucose lowering efficiency.



(**11**)

Quinazolinonyl sulfnilamides on condensation with aryl isocyanate in the presence of K_2CO_3/acetone gave new hypoglycemic agents[29b] (12).



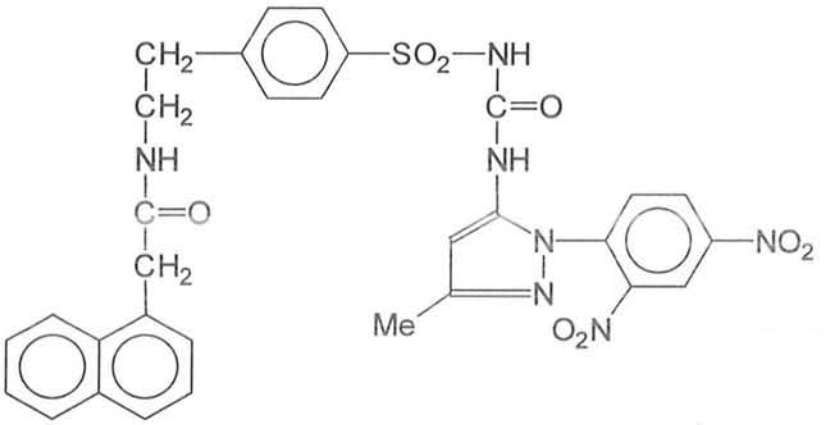
R = Me, Ph

R_1 = H, Me

R_2 = H, Me

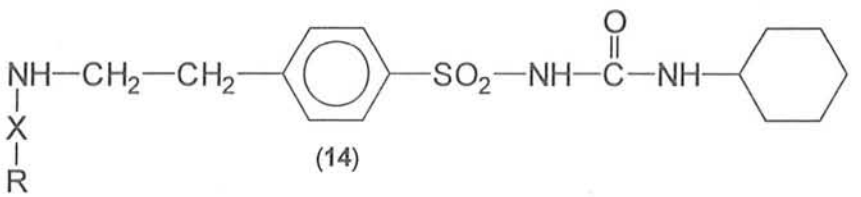
X_1, X_2 = H or halogens.

Compound (13) was prepared as oral hypoglycemic agent[30].



(13)

Amino acid derivatives of sulfonyl ureas[31] were also prepared as hypoglycemic agents e.g. compound (14). This compond having R=H, X=Val., Ph., were the most active hypoglycemic agents approximately 5-times more potent than carbutamide (6d)

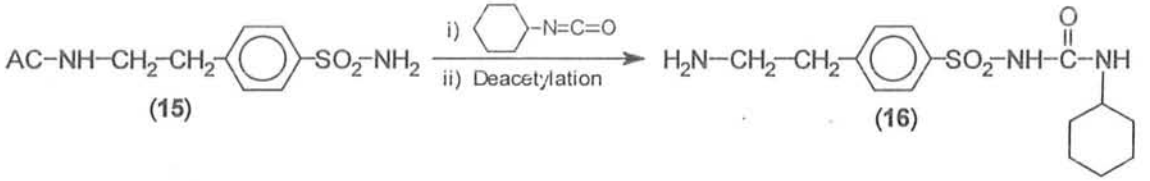


(14)

R = $PhCH_2O_2C$

X = Gly., Ala., Val., Leu., Phe., D-ala.

Compound (**15**) was condensed with cyclohexyl isocyanate and the resulting urea was deacetylated to give (**16**). This compound exhibited higher hypoglycemic activity in rats.



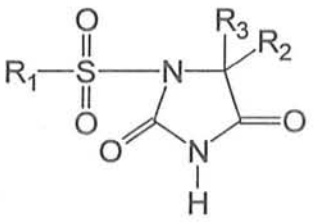
(**15**) (**16**)

Zinc and Cerium salts[6] of sulfonyl ureas were prepared as hypoglycemic agents and were useful in reducing elevated blood sugar levels and for diabetes treatment. Zinc-glyburide and Ce-glyburide were more effective in reducing blood sugar levels in rats than glyburide (**6h**) itself. Also the Zn and Ce-salts were more effective than tolbutamide (**6e**) itself.

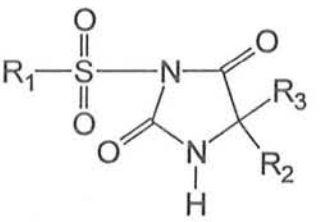
2.3.2.2 Sulfonyl cyclic ureas:

While surveying the market, it was found that only acyclic sulfonyl ureas are being used as antidiabetic drugs. The literature has revealed that very little attention has been paid to the synthesis of cyclic sulfonyl ureas. However, many researchers have paid attention to the synthesis of sulfonyl hydantoins derivatives, which can be included under the heading of cyclic sulfonyl ureas[7,32,33].

A wide variety of hydantoins have been used in medicines. Sulfonyl hydantoins have been reported as antidiabetic agent in general and as anticataract and aldose-reductase inhibitors in particular[34a]. It has been proved that the aryl/heterocyclic sulfonyl group at 1-position of hydantoin ring greatly effects the physico-chemical properties and intestinal absorption of drugs, and they are much more active than those where 3-position is substituted by R-sulfonyl group[10].



(**17**)
1-aryl/heterocyclic sulfonyl hydantoin

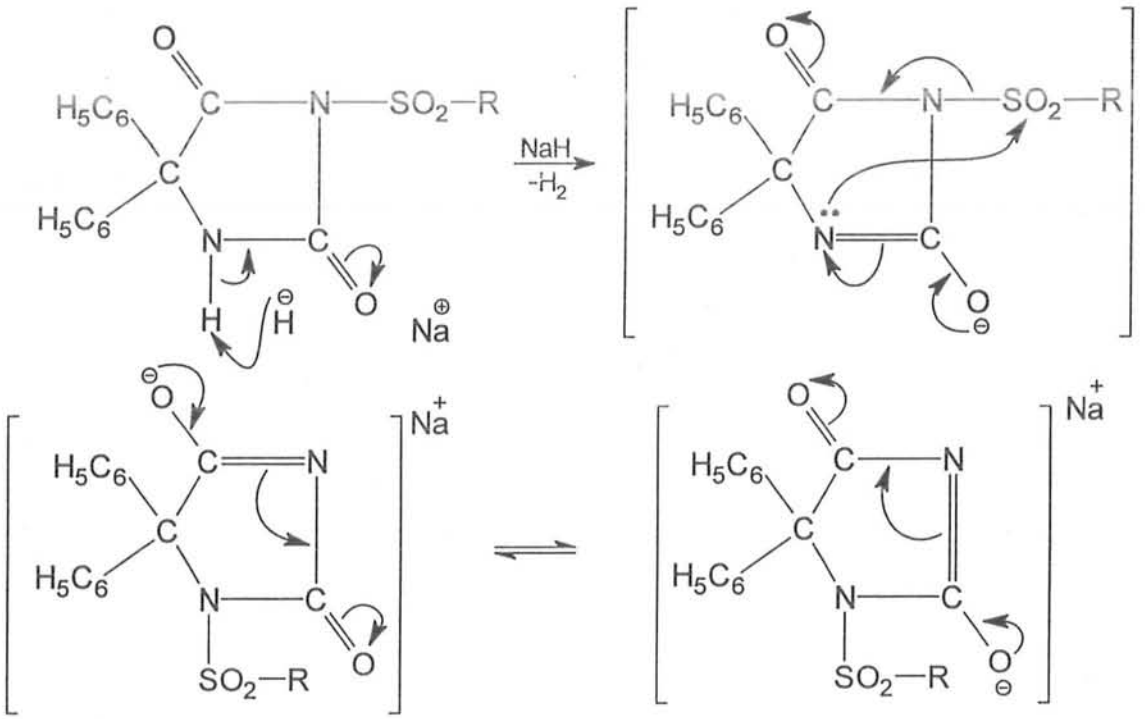


(**18**)
3-aryl/heterocyclic sulfonyl hydantoin

Where R_1 may be aryl or heterocyclic group and R_2 and R_3 may be alkyl or aryl groups.

It was found that substitution at 1-position of hydantoin increased the acid dissociation constants by 1000 fold and partition co-efficients were increased by 100-1000 fold in $CHCl_3/H_2O$ system and 10-100 fold in n-octanol/H_2O system. The solubilities of 1-benzene sulfonyl hydantoin derivatives increased with increasing PH of the solution. At PH more than '5' the intestinal absorption from solution was found to be caused by the passive transport according to the first order kinetics. The rate constants of absorption of 1-benzene sulfonyl hydantoin derivatives were rather large even under the condition where they were 99% ionized in the solution than that of a corresponding 1-unsubstituted hydantoin derivatives, which exist mainly as the ionized form under the same condition.

Some Japanese workers[11] prepared 3-aryl sulfonyl hydantoin by coupling the aryl sulfonyl chlorides with hydantoin and subjected these molecules to rearrangement in the presence of NaH in dry benzene to give 1-aryl sulfonyl hydantoin. The mechanism of rearrangement is depicted in Scheme-A.

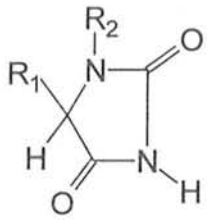


Scheme-A

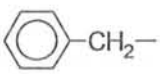
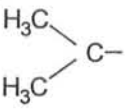
Some new chiral sulfonyl hydantoin derivatives have been prepared[34b] and their antidiabetic activity has been reported.

Compound **19a** and **19d** possessed inhibitory effect on insulin release at either 10^{-4} or 10^{-3} concentration and thus showed no antidiabetic activity. While compound **19b** and **19c** exhibited antidiabetic activity only at lower concentrations. However, it requires further confirmatory evidence from in vivo studies in animal experiments in order to ascertain their margin of safety and freedom from undesirable toxic effects.

Table-2.5: Chiral sulfonyl hydantoins having antidiabetic activity.

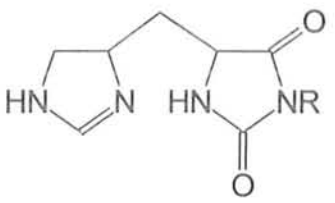


(19)

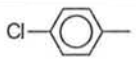
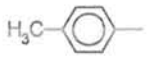
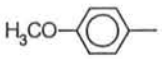
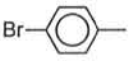
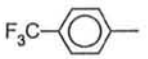
Comp. No.	R_1	R_2
19a	H	
19b	CH_3	"
19c		"
19d		"

Some L-[4(or5)imidazolylmethyl]3-substituted hydantoins have been prepared[35] and tested as antidiabetic agents. [**20(a-i)** Table-2.6]. All these compounds showed modest hypoglycemic activity. As sulfonyl ureas are being used as hypoglycemic agents, so these compounds may have good antidiabetic activity, after coupling them with sulfonyl chlorides, to prepare their sulfonyl derivatives.

Table-2.6: L-[4(or 5)imidazolylmethyl]3-substituted hydantoins having antidiabetic activity.



(20)

Comp. No.	R	T_2[a]	T_3	T_4
20a		1[b]	2	2
		2	2	2
20b	$CH_3(CH_2)_3$–	1	2	1
		1	1	
20c		2	1	
20d		1	0	
20e	$CH_3(CH_2)_2$–	2	1	
20f		2	3	1
20g		2	1	
20h		2	2	2
20i		1	1	0
Cloropropamide[c]		4	4	

a = T_2, T_4, T_6-represents 2, 4 and 6 hr. post administration.

b = Percent fall in blood sugar from initial values, scored as follow 0 = 0 - 5% fall, 1 = 6 - 15%, 2 = 16 - 2 5%, 3 = 26 - 35%, 4 = 36 - 45%.

2.4 Sulfonyl Cyclic Ureas as Aldose Reductase Inhibitors:

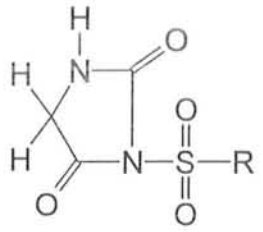
The diabetic patients very frequently acquire cataract in their eyes, due to which the lens of the eye is damaged. As discussed in Section 2.2.1, the reason for this disorder is the accumulation of excessive sorbitol and galactol in the lenses synthesized by the action of aldose reductase on glucose and galactose. These findings suggest that potent aldose reductase inhibitors may be great value in the treatment of these complications.

Flavonoids[7] have been reported as aldose-reductase inhibitors long time ago. Sulfonyl cyclic urea derivatives have also been reported as aldose-reductase inhibitors. Sorbinil, [d-6-fluoro-spiro[chroman-4,4′-imidazolidine]-2′,5′-dione which is a hydantoin derivative has been reported as a strong aldose-reductase inhibitor.

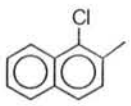
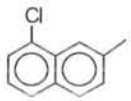
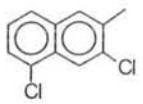
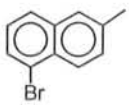
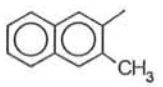
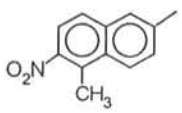
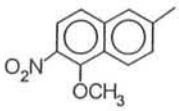
Some Japanese workers[7] have presented the results of a screening test for inhibitory activity of 54-hydantoin derivatives on rat and bovine lens aldsoe-reductase and have described the effects of structural alterations on the inhibitory activity. They have also reported the effect of PH on the inhibition of aldose-reductase by hydantoin derivatives.

A patent has been published in which the synthesis of more than 15-derivatives of (naphthalene-2-yl-sulfonyl)hydantoins[32] has been reported. IC^{50}(μ mole/L) i.e. concentration of typical (naphthalene-2-yl-sulfonyl)hydantoin derivatives required to produce 50% inhibition are listed in Table-2.7.

Table-2.7: IC_{50}-values of napthalene-2-yl-sulfonyl hydantoin derivatives for lens aldose reductase.

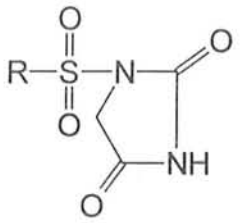


(22)

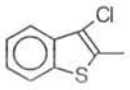
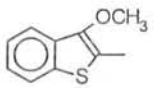
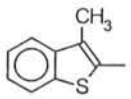
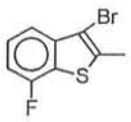
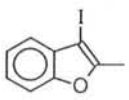
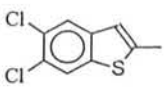
Comp. No.	R	IC_{50} (μ mole/L)
22a		0.16
22b		0.14
22c		0.46
22d		0.24
22e		0.17
22f		0.14
22g		0.027
22h		0.038

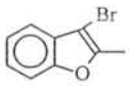
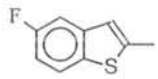
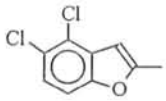
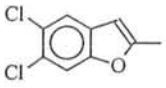
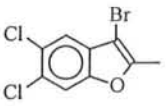
Many heterocyclic sulfonyl hydantoins[36] have also been reported as aldose reductase inhibitors. Their inhibitory activities were measured on bovine lens aldose reductase. IC_{50} (μ mole/L) concentrations are listed in Table-2.8. It was found that all of the compounds **23(a-k)** showed strong inhibitory activity against aldose reductase.

Table-2.8: IC_{50}-values of heterocyclic sulfonyl hydantoin derivatives for lens aldose reductase.



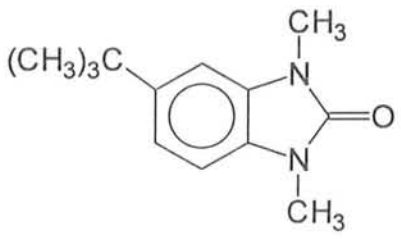
(23)

Comp. No.	R	IC_{50} (μ mole/L)
23a		0.12
23b		0.27
23c		0.38
23d		0.085
23e		0.24
23f		0.17

23g		0.16
23h		0.18
23i		0.061
23j		0.083
23k		0.054

2.5 Benzimidazolones: Another Class of Cyclic Ureas:

Benzimidazolones also have very interesting biological properties. 2(3H)-Benzimidazolone and its derivatives are useful heterocyclic building blocks that are prominent structural elements of compounds demonstrating a wide variety of interesting biochemical and pharmacological properties. These antogonize neurotransmitters[37], inhibit aldose-reductase[38], show antiulcer and antisecretory properties, enhance pulmonary surfactant secretion[39] and modulate ion channels[40]. Several of these compounds show activity against mouse leukemia[41]. One of the best compound exhibiting such activity is 1,3-dimethyl-5-t-butyl-benzimidazolone (**24**).



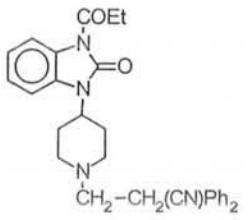
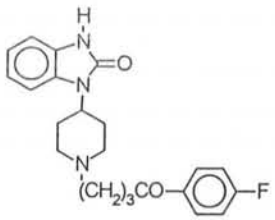
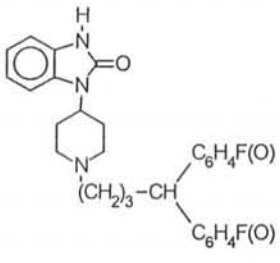
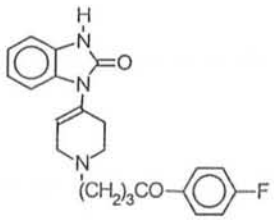
(**24**)

As a consequence of their interesting biological properties especially as antidiabetic agent in general and as aldose-reductase in particular, different synthetic

approaches have been developed to prepare benzimidazolones, exhibiting widely varied substitution pattern[42-45].

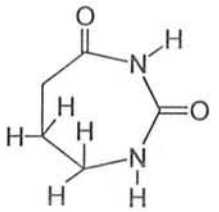
Some new methods[46] have been developed for selectively protecting one of the degenerate nitrogen atoms of the benzimidazolone and related cyclic urea derivatives, to get different mono substituted derivatives of benzimidazolone, which are otherwise difficult to obtain. The direct mono substitution of one of the nitrogen atoms of this heterocycle is not straight forward and mixtures of mono and disubstituted products are generally produced along with the starting materials.

Table-2.9: Some commercially available benzimidazolone derivatives along with their uses.

Comp. No.	Name	Proprietary Name	Structure	Uses	Manufacturer
25	Bezitramide	Burgodin		Analgesic	Janssen, UK.
26	Benperidol	Frenactil Glianimin		Psychophar-macological agent	Laboratories, Elin-Comav-Byla, France. Troponworke Dinklage, Germany.
27	Pimozide	Orap opiram		Psychophar-macological agent	Janssen, UK. Laboratories Gassenne, France.
28	Droperidol	Droleptan Inapsine		Psychophar-macological agent	Janssen, UK. Menell, USA.

2.6 Perhydro 1,3-diazepin 2,4-dione:

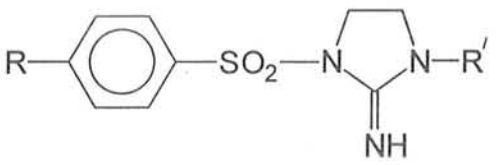
Among seven membered cyclic urea derivatives, synthesis of perhydro-1,3-diazepin-2,4-dione[13] have been reported. The functionalized perhydro-1,3-diazepin-2-one system has been the subject of recent interest in view of the potent inhibition of cytidine deaminase exhibited by some of its nucleosides[47]. The 5-oxo and 5-hydroxy perhydro-1,3-diazepin-2-one ring systems have been reported and attention is now focused on the 4-oxo isomer (**29**). This compound was first reported in 1972 as a natural product, isolated from the plant Anona squamosu and have named squamolone[48].



(**29**)

2.7 Sulfonyliminoimidazolidines:

Recently a new class of oral hypoglycemic agents, "sulfonyliminoimidazolidine"[49] have been reported, by combining structural elements of sulfonyl ureas and biguanides within one molecule (compound **30**). This type of compounds display hypoglycemic activity in normal and in streptozotocin diabetic rats.



(**31**)

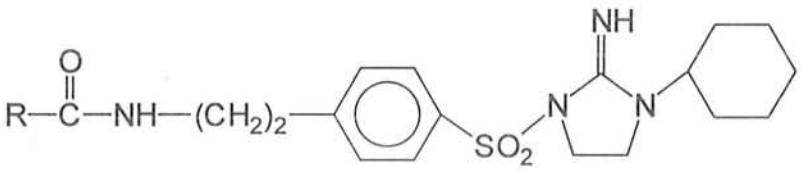
R may be an alkyl group and R′ an alkyl or aryl group.

As sulfonyl ureas lower blood glucose in normal animals by releasing insulin from the pancreas and are therefore inactive in the streptozotocin diabetic rats model. Biguanides, on the other hand produce hypoglycemic activity in diabetic animals by extrapancreatic mechanism and are devoid of significant activity in normal animals[50].

Sulfonyliminoimidazolidine has dual activity (i.e. hypoglycemic effect in normal and diabetic rats to a combination of mechanism operative in ureas and biguanides). Effects of selected sulfonyliminoimidazolidine on insulin release in vitro and in vivo (sulfonyl urea-type activity) and on glucose oxidation by rat fat cells in vitro (biguanide-type activity) have been studied using three models i.e. stimulation of insulin release by pieces of rabbit pancreas in vitro, increase of plasma insulin in normal rats in vivo and inhibition of glucose oxidation by isolated rat fat cells in vitro.

Sulfonyl ureas show no detectable activity in the latter model, while biguanides are inactive in the first two models. Effects of several sulfonyliminoimidazolidine (compounds **32-36**) in these tests are shown in Tables 2.11-2.13.

Table-2.10: Sulfonyliminoimidazolidine.



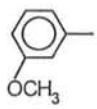
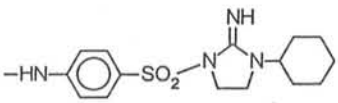
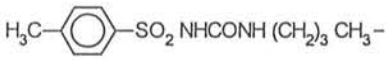
Comp. No.	R
32	$CH_3CH{=}CH-$
33	$CH_3CH_2CH_2-$
34	
35	
36	

Table-2.11: Insulin release*.

Comp. No.	0.003 mmol/L	0.01 mmol/L	0.03 mmol/L	0.1 mmol/L	0.3 mmol/L	0.9 mmol/L
32	1.88±0.56(3)	2.73±0.87(9)	—	—	1.82±0.44(4)	—
33	1.02±0.07(6)	1.84±0.24(6)	2.18±0.21(7)	2.51±0.22(6)	3.06±0.20(6)	—
34	0.98±0.06(6)	2.08±0.33(6)	2.24±0.14(6)	3.13±0.74(7)	3.60±0.51(6)	—
35	1.01±0.12(4)	1.22±0.29(4)	1.74±0.33(4)	3.21±0.52(12)	—	3.21±0.25(6)
36	0.95±0.19	1.81±0.23(5)	—	4.33±0.68(10)	—	4.23±0.29(7)

* Ratio of insulin release with test compounds to without test compounds present; means plus or minus SEM. (Number of experiments in parenthesis).

Table-2.12: Hypoglycemic effects and insulin release.

Comp. No.	Dose[a] mmol/kg	N[b]	Blood glucose[c] mmol/kg	Plasma insulin p mol/L
Control		11	5.87±0.12	95.8±11.0
32	0.0084	6	4.04±0.1 (-31%)**	163.3±35.5 (+71%)
	0.028	6	3.42±0.68 (-42%)**	476.3±28.0 (397%)**
33	0.008	5	4.86±0.27 (-27%)*	107.5±18.5 (+12%)
	0.024	6	3.62±0.08 (-36%)**	309.5±29.0 (233%)**
	0.072	6	363±0.11 (-38%)**	395.5±66.8 (+313%)**
34	0.18	5	3.08±0.12 (-17%)**	285±49.0 (+198%)**
35	0.60	11	4.66±6.1 (-21%)**	138.3±20.5 (+42%)
36 (Tolbutamide)	0.17	6	3.86±0.05 (-34%)**	273.5±34.3 (190%)**
Phenformin	2.0	7	5.52±0.09 (-6%)	86.1±18.9 (-10%)

a. Compounds were administered orally, 45 min before assay of blood glucose and plasma insulin.

b. Number of animal used.

c. Mean plus or minus SEM (percent change against control in parenthesis). Statistical significant of change against control:

* = PL 0.05 ** = PL 0.01 (Dunnet's test).

Table-2.13: Inhibition of glucose oxidation in isolated rat fat cells in vitro.

Comp. No.	IC^*_{50} mmol/L
32	0.18 ± 0.01 (5)
33	0.71 ± 0.004 (7)
34	0.020 ± 0.002 (4)
35	0.18 ± 0.02 (3)
36 (Tolbutamide)	$> 0.5^{**}$ (2)
Phenformin	0.18 ± 0.03 (7)

* = Concentration causing 50% inhibition, mean plus or minus SEM (number of experiments in parenthesis).

** = Highest concentration tested, inactive.

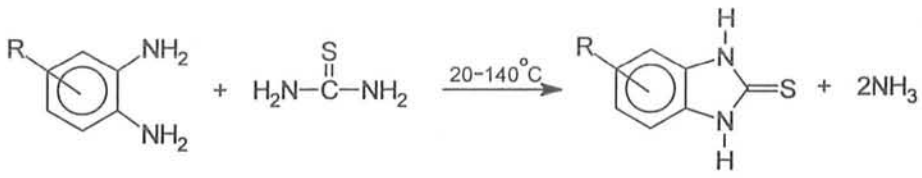
Sulfonyliminoimidazolidine and sulfonyl urea, tolbutamide, stimulated the insulin release in vitro (compounds **32-35**, Table-2.11). A two- to threefold increase above basal level was observed in case of sulfonyliminoimidazolidine, whereas an approximately fourfold increase was obtained with tolbutamide.

Sulfonyliminoimidazolidine also stimulated insulin release in vivo (compounds **32-35**, Table-2.12 and 2.13) increased plasma insulin in normal rats at hypoglycemic doses. A blood glucose decrease in the range of 30-50% correlated with a two to fourfold increase of plasma insulin was observed. The sulfonyl urea tolbutamide showed hypoglycemic activity, but the biguanide, phenformin was inactive, despite a very high dose (Table 2.12). Glucose oxidation in isolated fat cells was inhibited by the sulfonyliminoimidazolidine and by biguanide, phenformin with IC_{50} values between 0.15 and 0.020 mmol/L, while tolbutamide was inactive (Table-2.13).

As sulfonyliminoimidazolidines have dual activity i.e. activity of sulfonyl urea-type and activity of biguanide-type, they may be very useful as antidiabetic drugs.

A review[51] has been published in which the synthesis of sulfonyliminoimidazolidine type-compounds, using benzimidazoline-2-thione and N,N-dichloromethylamine has been reported. Benzimidazoline-2-thiones (**37**) have been synthesized by the general

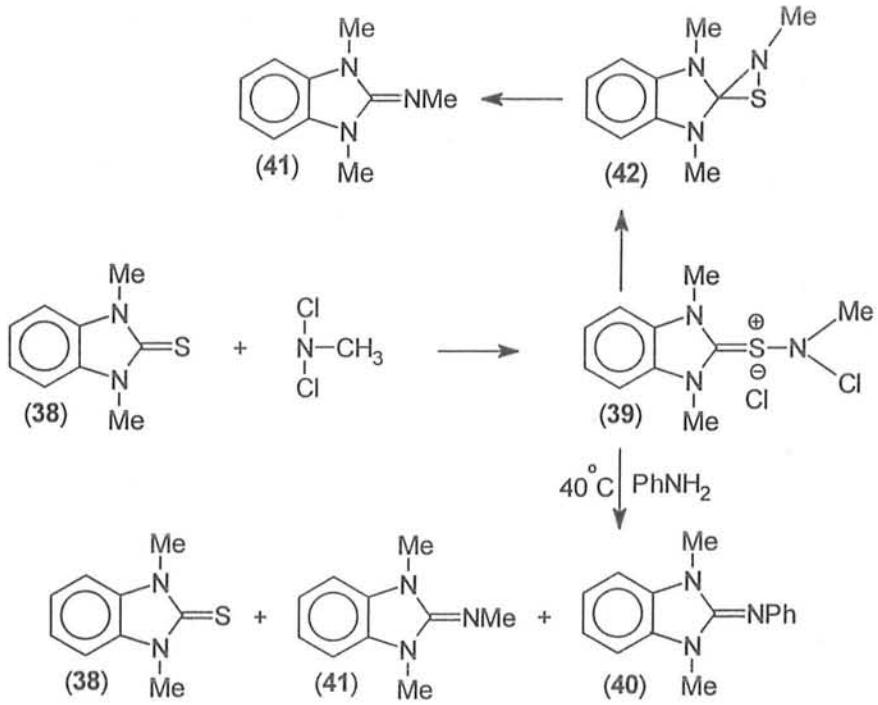
methods described by Van Allan and Deacon[52]. Some uncommon approaches to 2-thione are also present which include their formation from 4,5,6,7-tetrahydrobenzimidazole by thermal reactions in the presence of sulfur[53] and from 2-chlorobenzimidazoles by reaction with thiourea[54]. An other approach is the thermal reaction of ortho phenylenediamine with thiourea[55].



Benzimidazoline-2-thione

(37)

A sulfonium salt (**39**) has been isolated from the reaction of benzimidazoline-2-thione with N,N-dichloromethylamine and its chemistry has been briefly investigated. Certain modes of reactivity of this salt are nicely demonstrated by its behaviour with aniline in which nucleophilic attack at the benzimidazole-2-carbon atom or exocyclic nitrogen atom can occur. Formation of 1,3-dimethyliminobenzimidazoline (**40**) however is probably best rationalized[56] in terms of an intermediate thiaziride derivatives (**39** → **42** → **41**).



PLAN OF WORK

3. Plan of Work:

After going through the literature discussed in the background concerning the synthesis of cyclic urea derivatives having satisfactory antidiabetic activity, it was decided to synthesize new aryl/heterocyclic sulfonyl cyclic ureas and get them tested as antidiabetic/anticataract agents.

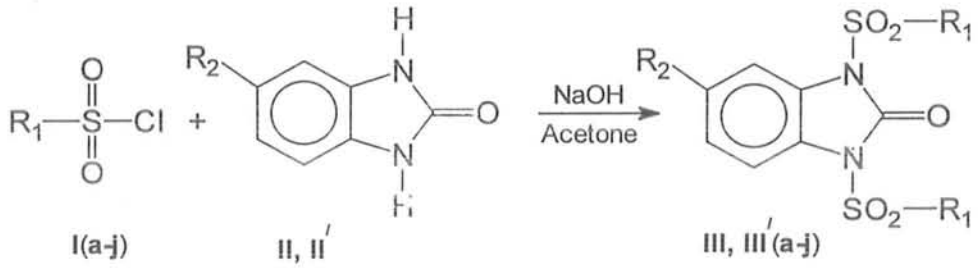
For this purpose it was decided to synthesize cyclic ureas like benzimidazolones **II, II′**, hydantoins **VII(a-e)** and perhydro 1,3-diazepin 2,4-dione **X(a-c)** on one hand and aryl/heterocyclic sulfonyl chlorides like naphthalene-2-yl-sulfonyl chloride **I(a)**, p-toluene sulfonyl chloride **I(b)**, 5-bromo benzo [b] furan-2-yl-sulfonyl chloride **I(c)**, 6,7-dichloro benzo [b] furan-2-yl-sulfonyl chloride **I(d)**, 5-bromo-3-methyl benzo [b] furan-2-yl-sulfonyl chloride **I(e)**, 5-chloro, 3-methyl benzo [b] furan-2-yl-sulfonyl chloride **I(f)**, 2-benzoyl benzo [b] furan-3-yl-sulfonyl chloride **I(g)**, 3,5-dimethyl isoxazole-4-yl-sulfonyl chloride **I(h)**, 3,5-phenyl methyl isoxazole-4-yl-sulfonyl chloride **I(i)** and 3,5-diphenyl isoxazole-4-yl-sulfonyl chloride **I(j)**, on the other hand. These two moieties can be coupled to give aryl/heterocyclic sulfonyl cyclic ureas.

In case of hydantoins and perhydro 1,3-diazepin 2,4-diones 3-aryl/heterocyclic sulfonyl cyclic urea derivatives are obtained, which can be subjected to rearrangement[11] in the presence of sodium hydride in benzene to give 1-aryl/heterocyclic sulfonyl cyclic urea derivatives, which are more active than 3-aryl/heterocyclic sulfonyl cyclic urea derivatives[4] as indicated in the background.

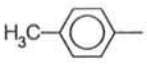
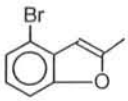
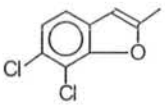
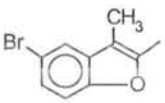
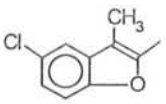
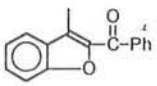
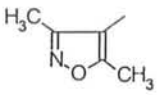
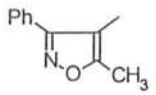
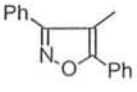
3.1 Synthesis of aryl/heterocyclic sulfonyl cyclic ureas:

3.1.1 Synthesis of 1,3-di-aryl/heterocyclic sulfonyl benzimidazolones[11] III, III′ (a-j):

Aryl/heterocyclic sulfonyl chlorides on reaction with benzimidazolones in basic media using sodium hydroxide in acetone give 1,3-di-aryl/heterocyclic sulfonyl benzimidazolones **III, III′ (a-j)**.



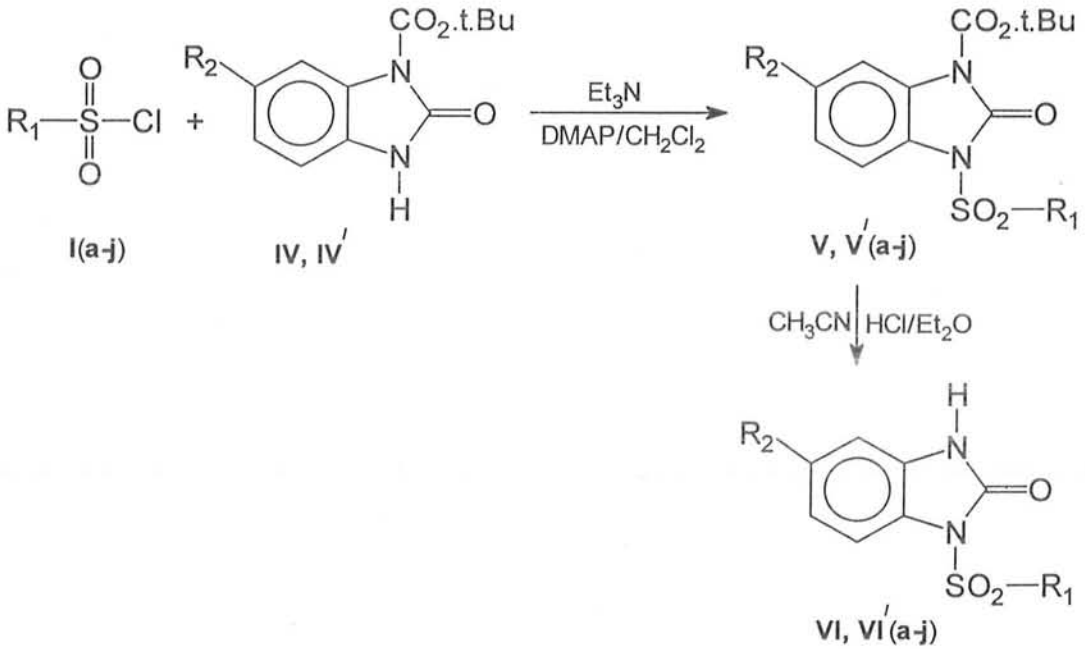
I(a-j) II, II′ III, III′(a-j)

	R_1		R_2
I(a)		II, III	H
I(b)		II′, III′	NO_2
I(c)			
I(d)			
I(e)			
I(f)			
I(g)			
I(h)			
I(i)			
I(j)			

Scheme-I

3.1.2 Synthesis of mono-aryl/heterocyclic sulfonyl benzimidazolones VI, VI′ (a-j):

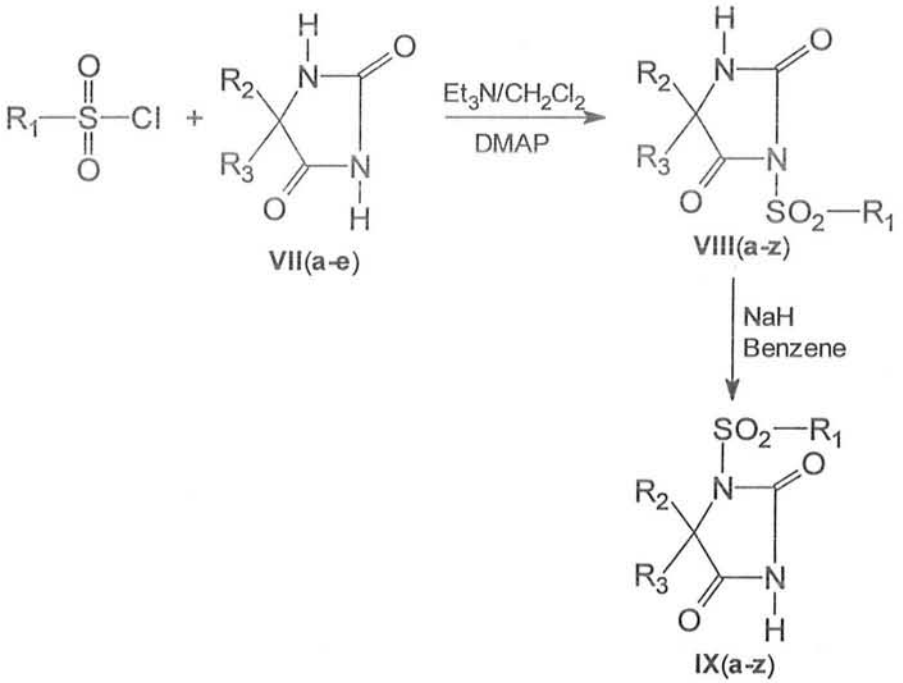
In order to synthesize mono substituted aryl/heterocyclic sulfonyl benzimidazolone derivatives VI, VI′ (a-j), it was necessary to protect one of the nitrogen of benzimidazolone. For the purpose 2,3-dihydro-2-oxo-1H-benzimidazole-1-carboxylic acid, 1,1-dimethyl ethyl ester IV, IV′, were prepared and then sulfonylated in the presence of Et_3N and dimethyl aminopyridine to give 2,3-dihydro-3-(aryl/heterocyclic sulfonyl)-2-oxo-1H-benzimidazole-1-carboxylic acid, 1,1-dimethyl ethyl ester V, V′(a-j). The deprotection was carried out by reported procedure[46] to give VI, VI′(a-j).

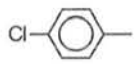
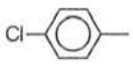
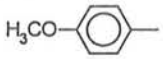
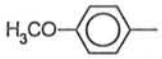
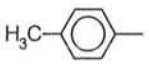
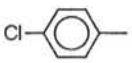
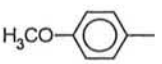
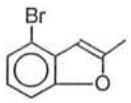
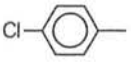


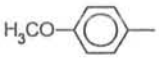
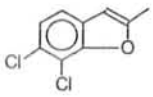
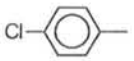
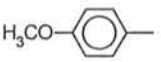
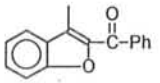
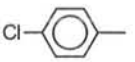
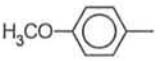
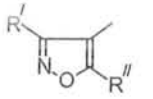
Scheme-II

3.1.3 Synthesis of aryl/heterocyclic sulfonyl hydantoins VIII, IX (a-z):

The aryl/heterocyclic sulfonyl chlorides on reaction with hydantoins in the presence of triethylamine as base and dimethylaminopyridine as catalyst give 3-aryl/heterocyclic sulfonyl hydantoins[46] VIII (a-y). These hydantoins can be converted to 1-aryl/heterocyclic sulfonyl hydantoins IX (a-y) in the presence of NaH via a rearrangement reaction[11].



	R_1	R_2		R_1	R_2	R_3
VII(a)	CH_3	C_6H_5	**VIII, IX (a)**		CH_3	C_6H_5
VII(b)	C_6H_5	C_6H_5	**VIII, IX (b)**	"	C_6H_5	C_6H_5
VII(c)	CH_3	CH_3	**VIII, IX (c)**	"	CH_3	CH_3
VII(d)		H	**VIII, IX (d)**	"		H
VII(e)		H	**VIII, IX (e)**	"		H
			VIII, IX (f)		CH_3	C_6H_5
			VIII, IX (g)	"	C_6H_5	C_6H_5
			VIII, IX (h)	"	CH_3	CH_3
			VIII, IX (i)	"		H
			VIII, IX (j)	"		H
			VIII, IX (k)		CH_3	C_6H_5
			VIII, IX (l)	"	C_6H_5	C_6H_5
			VIII, IX (m)	"	CH_3	CH_3
			VIII, IX (n)	"		H

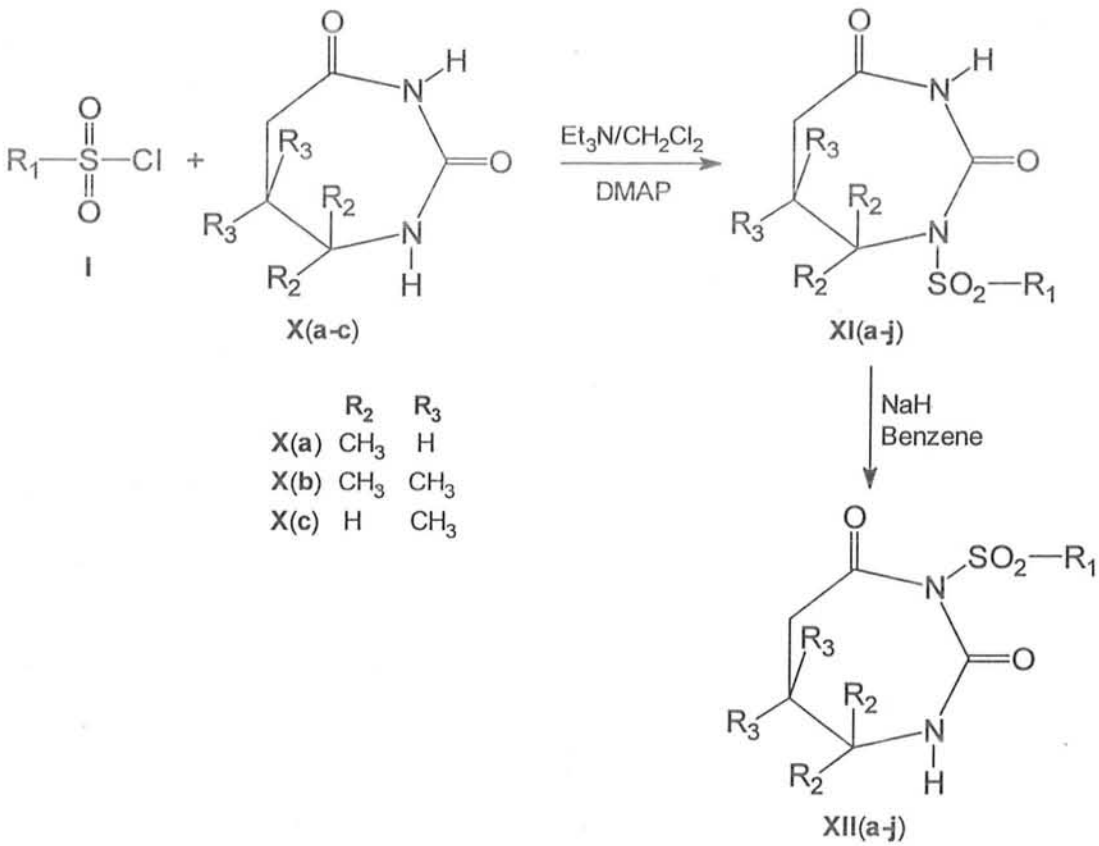
VIII, IX (o)	"		H
VIII, IX (p)		CH_3	C_6H_5
VIII, IX (q)	"	C_6H_5	C_6H_5
VIII, IX (r)	"	CH_3	CH_3
VIII, IX (s)	"		H
VIII, IX (t)	"		H
VIII, IX (u)		CH_3	C_6H_5
VIII, IX (v)	"	C_6H_5	C_6H_5
VIII, IX (w)	"	CH_3	CH_3
VIII, IX (x)	"		H
VIII, IX (y)	"		H
VIII, IX (z)		CH_3	C_6H_5

R′ and R″ may be CH_3 & CH_3, CH_3 & C_6H_5 or C_6H_5 & C_6H_5.

Scheme-III

3.1.4 Synthesis of aryl/heterocylic sulfonyl perhydro 1,3-diazepin 2,4-dione VII (a-j):

Perhydro 1,3-diazepin 2,4-dione is a seven membered cyclic urea. Its synthesis has been reported[13], as indicated in background. It was suggested that perhydro 1,3-diazepin 2,4-dione may be sulfonylated in the presence of triethylamine as base and dimethylaminopyridine as catalyst in dichloromethane to give 3-aryl/heterocyclic sulfonyl perhydro 1,3-diazepin 2,4-dione **XI (a-c)**. These aryl/heterocyclic sulfonyl perhydro 1,3-diazepin 2,4-diones might be converted to 1-aryl/heterocylic sulfonyl perhydro 1,3-diazepin 2,4-dione **XII (a-c)**, on reaction with sodium hydride, through a rearrangement analogous to hydantoins[11]. This may be very interesting in view of their biological activity as well as their spectroscopy.



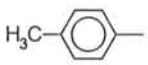
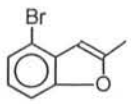
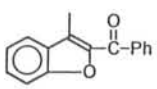
I

X(a-c)

	R_2	R_3
X(a)	CH_3	H
X(b)	CH_3	CH_3
X(c)	H	CH_3

XI(a-j)

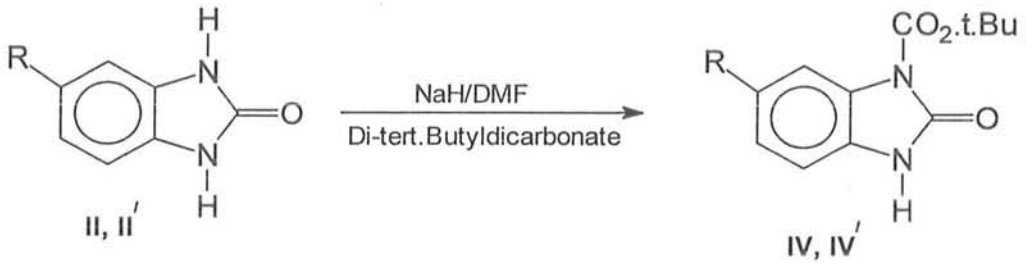
XII(a-j)

	R_1	R_2	R_3
XI, XII (a)		CH_3	H
XI, XII (b)	"	CH_3	CH_3
XI, XII (c)	"	H	CH_3
XI, XII (d)		CH_3	H
XI, XII (e)	"	CH_3	CH_3
XI, XII (f)	"	H	CH_3
XI, XII (g)		CH_3	H
XI, XII (h)	"	CH_3	CH_3
XI, XII (i)	"	H	CH_3
XI, XII (j)		CH_3	H

Scheme-IV

3.1.5 Protection of amino-group of benzimidazolone IV, IV′:

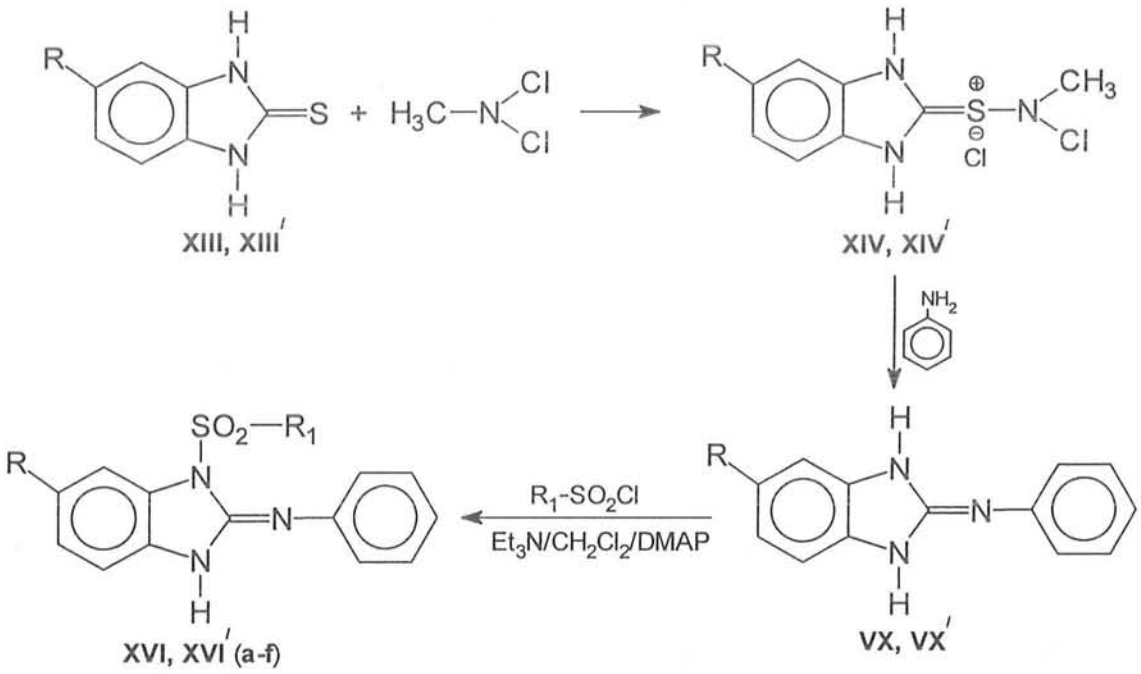
For the mono functionalization of benzimidazolone, it was necessary to protect one of the nitrogen atom of the benzimidazolone. For the protection of amino group of benzimidazolone, di-tert.butyl dicarbonate was reacted with benzimidazolone, using sodium hydride as base in dimethyl formamide[46]. Reaction was carried out under argon atmosphere.

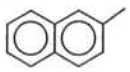
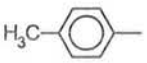
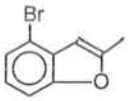
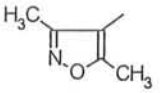
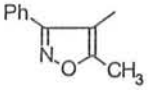
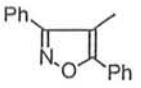


Scheme-V

3.2 Synthsis of sulfonyl benzimidazolidine XVI (a-d):

Sulfonyl iminoimidazolidines are another class of oral hypoglycemic agents recently reported[49]. Sulfonyl iminoimidazolidines have dual activity i.e. hypoglycemic effect, similar to sulfonyl urea and inhibition of glucose oxidation in vitro similar to biguanide type activity, as indicated in background. Sulfonyl iminoimidazolidines have been prepared by combining the structural elements of sulfonyl ureas and biguanides within one molecule. Keeping in view the interesting structural feature and biological activity of sulfonyl iminoimidazolidine, it was planned to synthesize sulfonyl benziminoimidazolidine. It was suggested to synthesize **VX**, **VX′** starting from benzimidazoline-2-thiones and N,N-dichloromethylamine by reported mehtod[56]. These benziminoimidazolidines on reaction with aryl/heterocylic sulfonyl chloride in the presence of triethylamine as base and dimethylaminopyridine as catalyst might give sulfonlybenziminoimidazolidine **XVI, XVI′ (a-d)**.



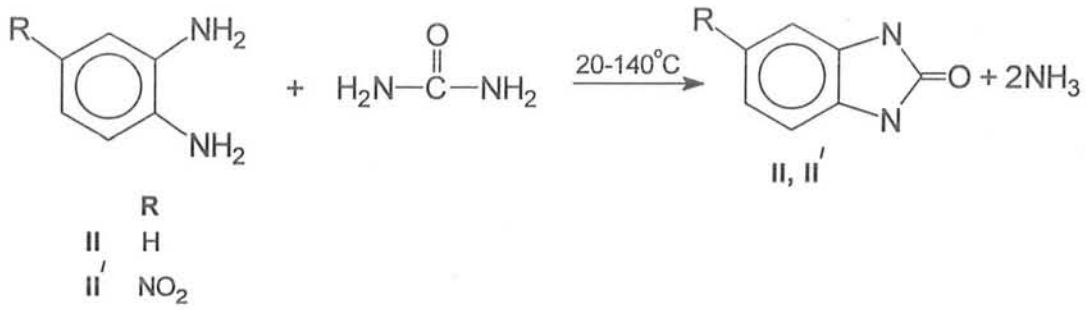
	R_1
XVI, XVI′(a)	
XVI, XVI′(b)	
XVI, XVI′(c)	
XVI, XVI′(d)	
XVI, XVI′(e)	
XVI, XVI′(f)	

Scheme-VI

3.3 Synthesis of cyclic ureas:

3.3.1 Synthesis of benzimidazolones [55] II, II′:

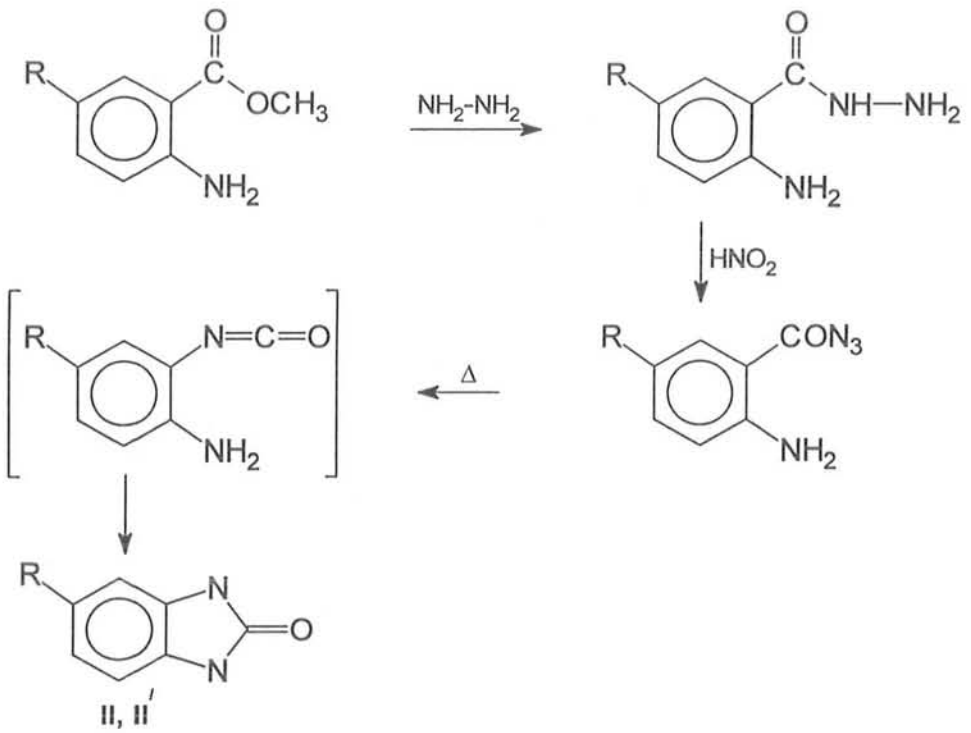
O-Phenylenediamine was fused with urea at 20-140°C under inert atmosphere to give benzimidazolone.



	R
II	H
II′	NO_2

Scheme-VIIa

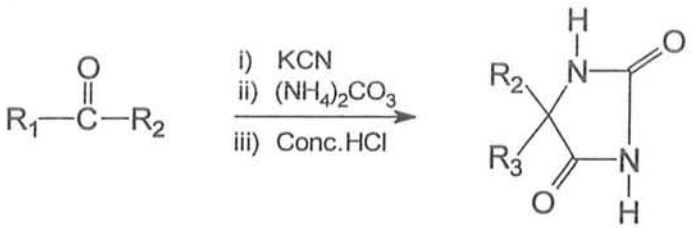
Benzimidazolone may be synthesized by another method. Methyl anthranilate on reaction with hydrazine hydrate gives anthranilohydrazide. Anthranilohydrazide on reaction with nitrous acid gives anthranilic acid azide, which on heating rearranges to benzimidazolone through an isocyanate intermediate[57].



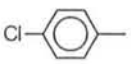
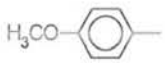
Scheme-VIIb

3.3.2 Synthesis of hydantoins VII (a-e):

1-Ketones/aldehydes on reaction with KCN, $(NH_4)_2CO_3$ and Conc. HCl give the 5,5-disubstituted hydantoins[58]. The nature of substitution depends upon the nature of aldehydes/ketones selected.



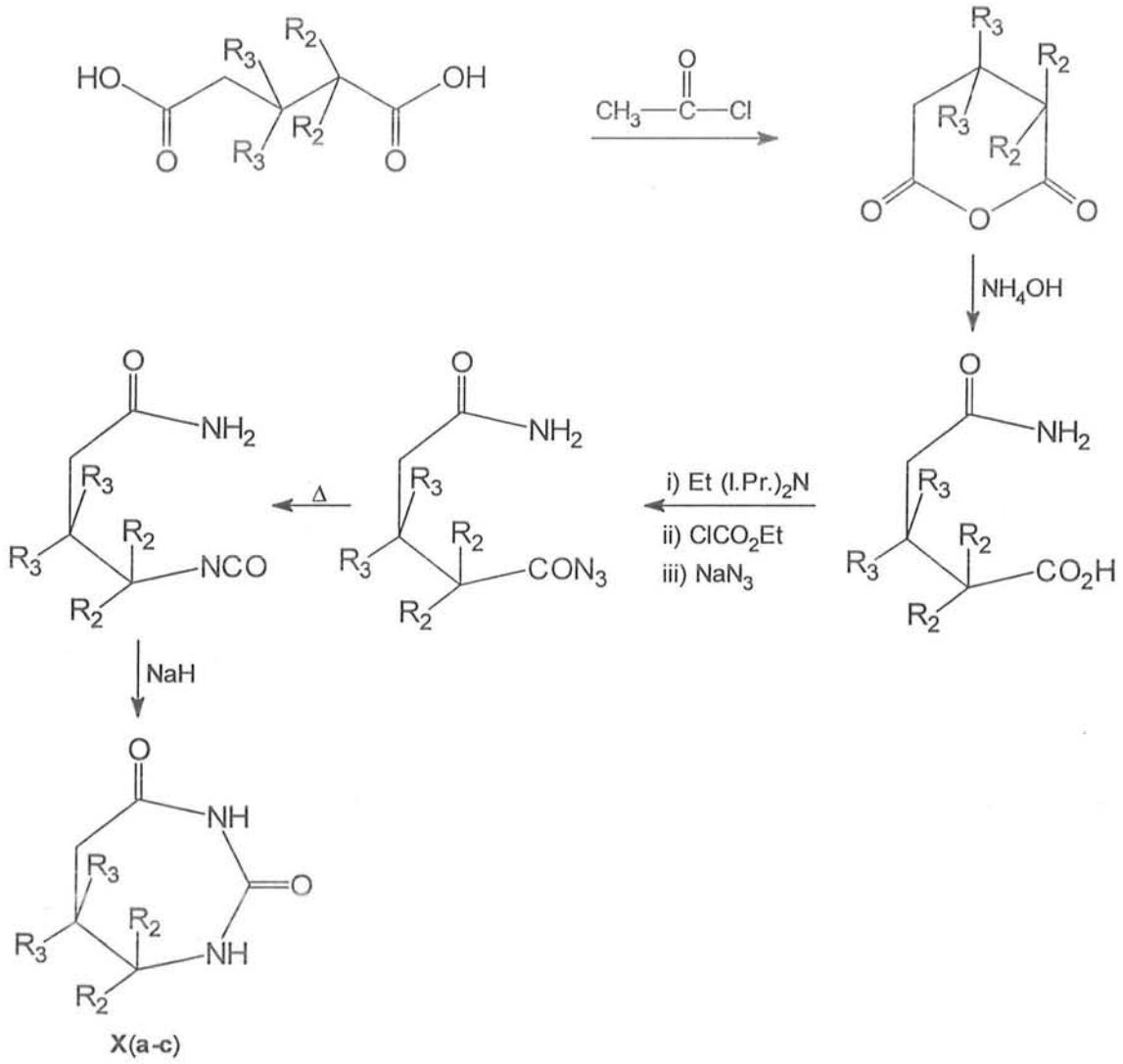
VII (a-e)

	R_1	R_2
VII (a)	CH_3	C_6H_5
VII (b)	C_6H_5	C_6H_5
VII (c)	CH_3	CH_3
VII (d)		H
VII (e)		H

Scheme-VIII

3.3.3 Synthesis of perhydro 1,3-diazepin 2,4-dione X (a-c):

Perhydro 1,3-diazepin 2,4-dione was planned to be synthesized from glutaric acid. Glutaric acid on reaction with acetyl chloride is converted into glutaric anhydride. Glutaric anhydride is treated with ammonium hydroxide to give glutaric acid monoamide. Glutaric acid monoamide is reacted with sodium azide in the presence of diisopropylethylamine and ethyl chloroformte to give the corresponding acyl azide, which on slight heating changes to isocyante. This isocyante on reation with sodium hydride gives perhydro 1,3-diazpin 2,4-dione[13] **X (a-c)**.

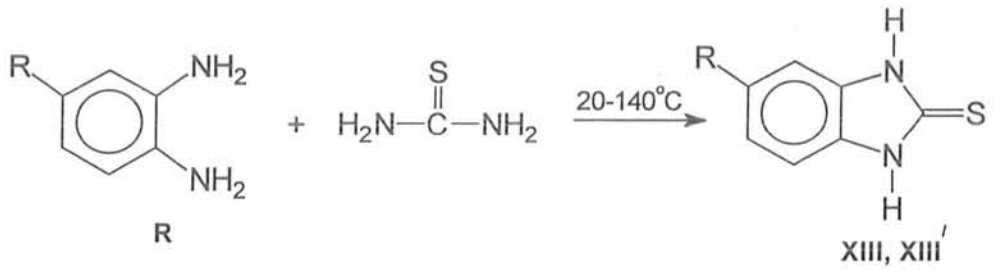


	R_2	R_3
X(a)	CH_3	H
X(b)	CH_3	CH_3
X(c)	H	CH_3

Scheme-IX

3.3.4 Synthesis of benzimidazoline-2-thione VIII, VIII':

O-Phenylene diamine is fused with thiourea at 20-140°C under inert atmosphere to give benzimidazoline-2-thione[55].

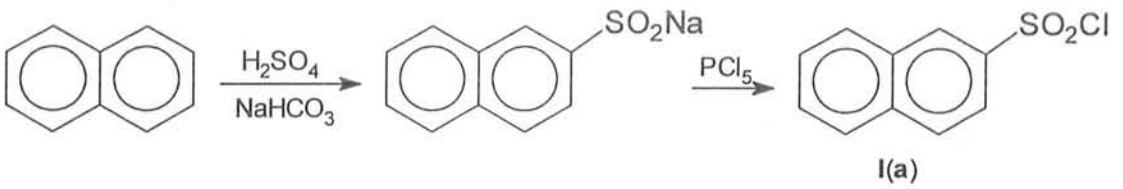


Scheme-X

3.4 Synthesis of sulfonyl chlorides:

3.4.1 Synthesis of aryl sulfonyl chlorides I(a):

Naphthalene on reaction with conc. sulfuric acid gives naphthalene sulfonic aicd, which on treatment with sodiumbicarbonate gives sodium salt of naphthalene sulfonic acid. This salt on reaction with PCl_5 gives naphthalene-2-sulfonyl chloride[59] **I(a)**.

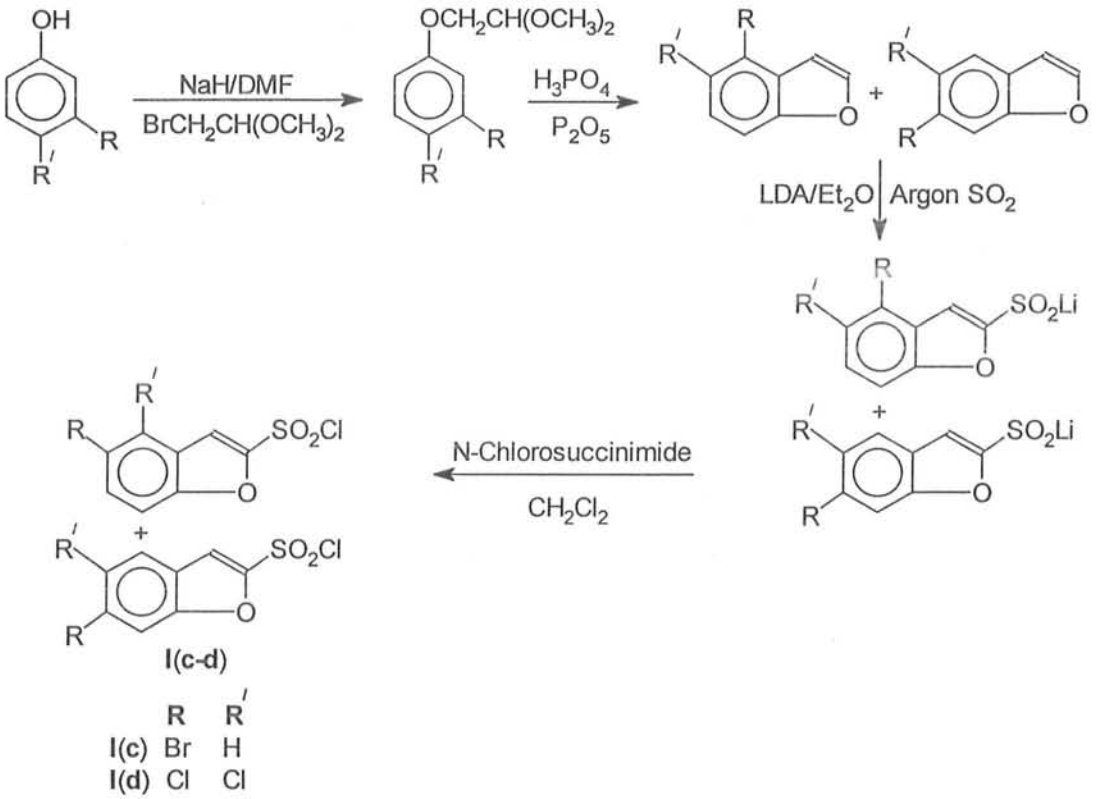


Scheme-XI

3.4.2 Synthesis of heterocyclic sulfonyl chlorides:

3.4.2.1 Synthesis of 3,4 and 4,5-halo benzo [b] furan-2-yl-sulfonyl chlorides I(c-d):

Substituted phenols on reaction with bromoacetaldehyde dimethylacetal in the presence of sodium hydride give (phenyloxy) acetaldehyde dimethylacetals, which on reaction with phosphoric acid and phosphorous pentaoxide give substituted benzofurans. These benzofurans are reacted with lithium diisopropylamide (LDA) in tetrahydrofuran, under argon to generate reactive carbanions. These anions on reaction with SO_2 leads to the formation of lithium benzo [b] furan sulfinates. These compounds on reaction with N-chlorosuccinimide lead to 3,4 and 4,5-halo-benzo [b] furan-2-yl-sulfonyl chlorides[60] **I(c-d)**.



I(c-d)

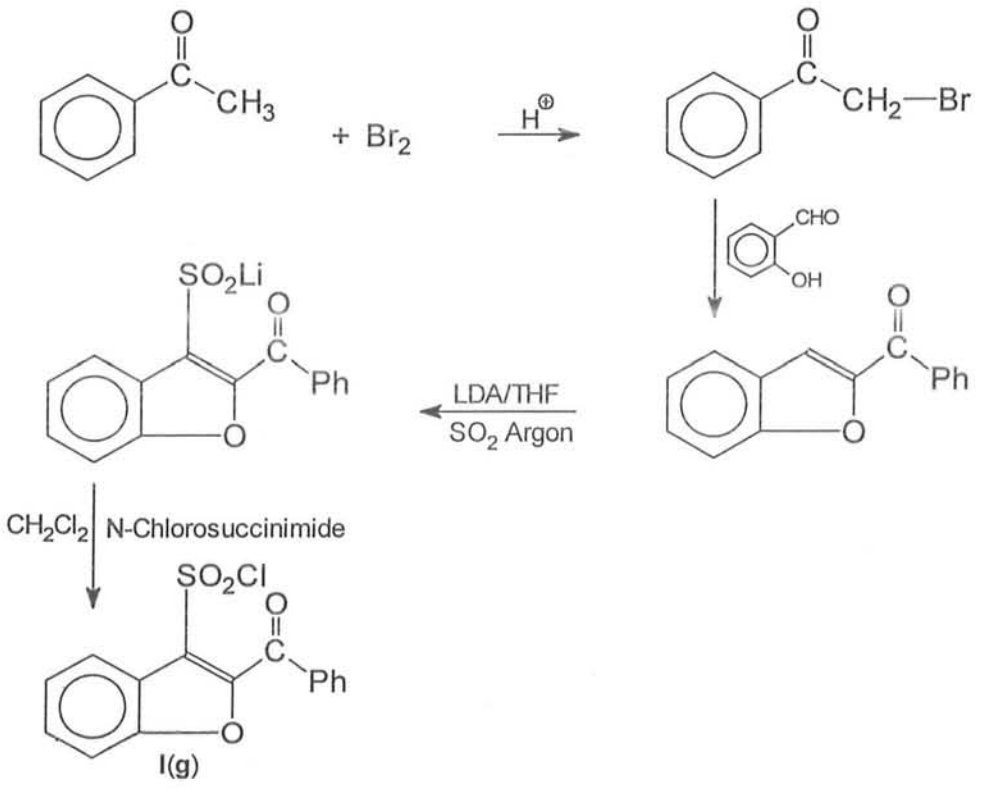
	R	R′
I(c)	Br	H
I(d)	Cl	Cl

Scheme-XII

3.4.2.2 Synthesis of 2-benzoyl benzo [b] furan-3-yl-sulfonyl chloride I(g):

Acetophenone on reaction with Br_2 in the presence of acid gives α-bromoacetophenone. Under basic conditions α-bromoacetophenone condenses with o-hydroxy benzaldehyde to yield benzoyl benzo [b] furan[61].

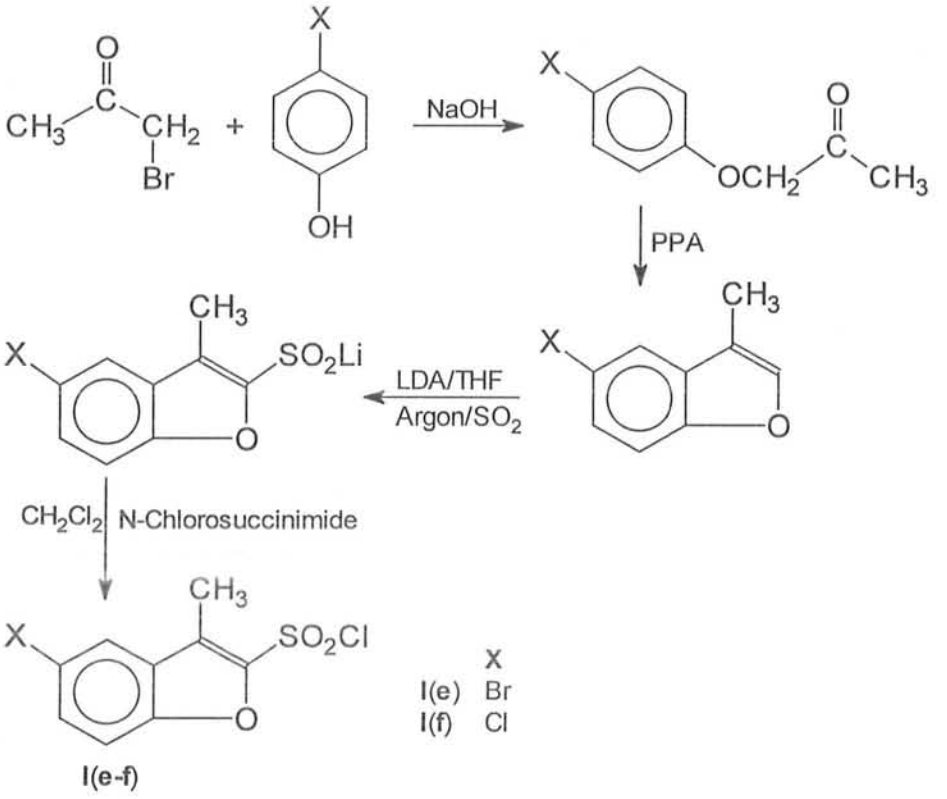
Benzoyl benzo [b] furan is reacted with lithium diisoprolylamide (LDA) in THF under argon to generate reactive carbanion. This reactive carbanion is reacted with sulferdioxide to give lithium benzo [b] furan sulfinate, which on reaction with N-chlorosuccinimide in dichloromethane leads to 2-benzoyl benzo [b] furan-3-yl-sulfonyl chloride[60] I(g).



Scheme-XIII

3.4.2.3 Synthesis of 5-halo-3-methyl benzo [b] furan-2-yl-sulfonyl chlorides I(e-f):

P-Halophenols on reaction with α-bromoacetone in the presence of NaOH give p-halophenyloxy acetone which on reaction with poly phosphoric acid give 5-halo-3-methyl benzo [b] furan[92]. These 5-halo-3-methyl benzo [b] furans are chlorosulfonylated as described in section 3.4.2.2, to give respective sulfonyl chlorides.

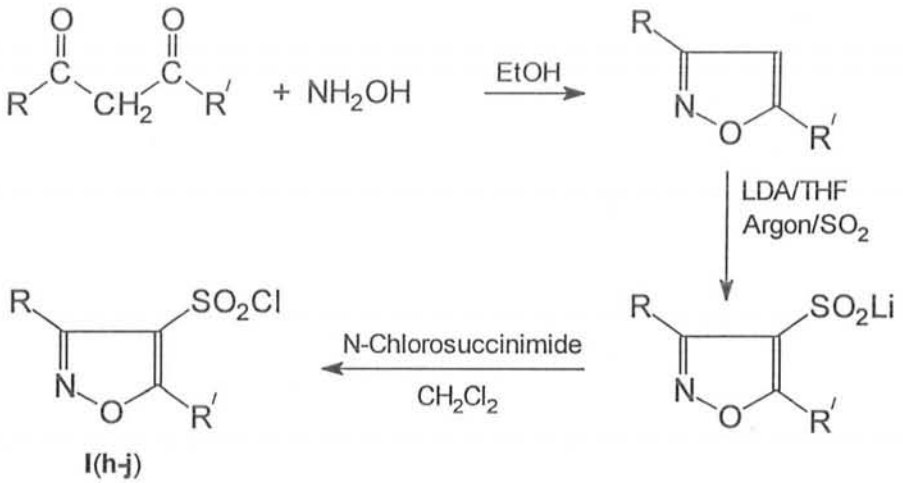


I(e-f)

Scheme-XIV

3.4.2.4 Synthesis of 3,5-disubstituted isoxazoles 4-yl-sulfonyl chlorides I(h-j):

β-Diketones on reaction with hydroxylamine hydrochloride give monoximes, which readily cyclize to give substituted isoxazoles[63]. These isoxazoles are chlorosulfonylated as described in section 3.4.1.2 to give respective sulfonyl chlorides.



I(h-j)

	R	R′
I(h)	CH_3	CH_3
I(i)	CH_3	C_6H_5
I(j)	C_6H_5	C_6H_5

Scheme-XV

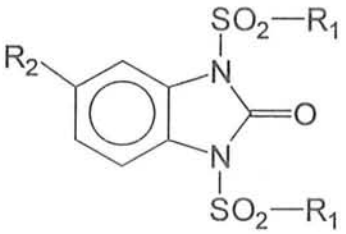
RESULTS & DISCUSSION

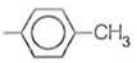
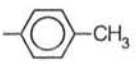
4. Results and Discussion:

4.1 Synthesis of 1,3-diaryl sulfonyl benzimidazolones:

1,3-Di(p-toluene/naphthalene) sulfonyl benzimidazolones **III(a-b)** and 1,3-di(p-toluene/naphthalene)-6-nitro benzimidazolones **III'(a-b)** were synthesized following the methods reported in literature[11] (Scheme-I). The yields were good in all cases ranging from 62.24-96.77%. The physical data of these compounds have been tabulated in Table 4.1.1.

Table 4.1.1: Physical data of compounds III,III'(a-b).



S. No.	Compound	R_1	R_2	m.p. °C	Yield %	R_f-Value
1.	**IIIa**		H	187	83.79	0.31 Cyclohexane:Chloroform (2:1)
2.	**IIIb**		H	186-188	62.24	0.62 Pet.ether:Chloroform (2:1)
3.	**III'a**		NO_2	219-220	96.77	0.89 Et.Acetate:Pet.ether (1:1)
4.	**III'b**		NO_2	206	72.81	0.81 Cyclohexane:Chloroform (2:1)

The IR spectra showed a bond at 1152 cm^{-1} and 1340 cm^{-1} for R-SO_2-N asymmetric and symmetric stretching in all these compounds. Compounds **III(a-b)** exhibited ⟩C=O stretching at 1756-1760 cm^{-1}. Both the compounds exhibited C-H, aromatic in plane deformation at 1184 cm^{-1} and 1194 cm^{-1}, C=C aromatic vibration at 1596 cm^{-1} & 1588 cm^{-1} and C=CH stretching at 3052 cm^{-1}. Compound **IIIa** exhibited CH_3- stretching at 2956 cm^{-1}, which was absent in compound **IIIb**, and this was the clear indication of the introduction of (p-toluene)sulfonyl group at nitrogen of

benzimidazolones. IR spectra of compounds **III'(a-b)** exhibited C-H, aromatic in-plane deformation at 1192 cm^{-1} & 1184 cm^{-1}, C=C, aromatic vibrations at 1444 cm^{-1} & 1588 cm^{-1}, C-N, vibration at 856 cm^{-1} & 860 cm^{-1}, C=C-H aromatic stretching at 3068 cm^{-1} and 3056 cm^{-1}. The presence of nitro group at the benzimidazolone was indicated by Ar-NO_2 asymmetric stretching at 1528 cm^{-1} in IR spectra of **III'(a-b)**. In **III'a** CH_3-stretching was observed at 2952 cm^{-1}, which was the indication of the introduction of (p-toluene)sulfonyl group at nitrogen of nitrobenzimidazolones. IR spectroscopic data of compounds **III(a-b)** and **III'(a-b)** is tabulated in Tables 4.1.2 and 4.1.3.

^{1}H-NMR spectra of compound **III(a-b)** showed that the protons H-4 and H-7 resonated in the region 7.30-7.60 ppm as doublet of doublet with ortho coupling constants of 6.2-7.0 Hz and meta coupling constants of 3.2-3.4 Hz. The protons H-5 and H-6 appeared in the region 7.70-8.0 ppm as a complex multiplet due to the same chemical environment of these protons. The aromatic protons H-a/a′ resonated at 7.95 ppm as multiplet and H-b/b′ as a doublet at 7.31 ppm with a coupling constant of 8.5 Hz, which indicates the ortho coupling. The methyl protons of tosyl group resonated as a sharp singlet at 2.4 ppm. Aromatic protons of naphthoyl group H-f and H-f′ appeared as triplet at 7.68 ppm and 7.75 ppm. Down field shift of H-f′ is due to the resonance effect in naphthalene, due to which the proton H-f′ becomes deshielded. The protons H-e/e′ and H-d resonated at 7.82 ppm as a multiplet and H-c/c′ resonated as doublet at 7.94 ppm. The reason for down filed shift of these protons is the presence of a more electronegative group in the vicinity of these protons, in addition to resonance effect. The ^{1}H-NMR data of compounds **III(a-b)** is shown in Table 4.1.4.

The ^{1}H-NMR-Spectra of compound **III'(a-b)**, showed that the proton H-4 appeared at 8.16-8.8 ppm as doublet with coupling constant of 8.63-9.63 Hz, which indicates the ortho coupling. The proton H-5 resonated at 8.22-8.25 ppm as a doublet of doublet, with ortho coupling constant of 9.03 Hz and meta coupling constant of 2.0 Hz. Protons H-7 appeared at 8.08-8.87 ppm as a doublet with coupling constants of 9.03 Hz and 2.0 Hz. The reason of down filed shift in case of H-4 is the presence of nitro group at meta-position of H-4, due to which the position-4 become deshielded and a down filed shift is observed. The aromatic protons H-a/a′ resonated as a multiplet in the region 7.74-8.01 ppm and H-b′/b′ as a doublet in the region 7.36 ppm with coupling constant of 8.0

Hz. Methyl proton resonated at 2.4 as a sharp singlet. Aromatic protons of naphthyl group followed the same pattern as in the case of **IIIb**. H-f and H-f' resonated at 7.64 and 7.71 ppm as triplets, H-e/e', H-d as multiplet at 7.86 ppm and H-c/c' as doublet at 8.10 ppm with a coupling constant of 8.9 Hz. ^{1}H-NMR data of compounds **III'(a-b)** is shown in Table 4.1.5.

In order to understand the coupling interaction between different protons, ^{1}H-^{1}H-Cosy experiment was carried out. The ^{1}H-^{1}H-Cosy spectrum of **IIIa** is reproduced in Fig.4.1.1. From this spectrum ^{1}H/^{1}H interactions can be easily observed.

To determine the spacial orientation of protons NOE experiment has been carried out in compound **III'a**. When proton H-4, which appeared at 8.86 ppm is irradiated 100%, signal at 8.0 ppm is enhanced, which is signal for protons H-a/a'. This means that proton H-4 is close to protons H-a/a' in space. This suggests the orientation for the tosyl group in space, in such a way that H-4, proton come closer to protons H-a/a' in space. Also, when we irradiate the methyl protons of tosyl group, signal at 7.22 ppm is enhanced, which is due to H-b/b', which indicates that H-b/b' are close to methyl group. From this it is confirmed that signal at 7.22 ppm is due to H-b/b', because these are the only protons, which are near the methyl group. No other orientation is possible. The NOE-spectra of compound **III'a** are shown in Fig. 4.1.2 and 4.1.3.

The ^{13}C-NMR spectra of compounds **III(a-b)**, showed that methyl carbon of tosyl group appeared at 22.0 ppm, carbonyl carbon (C-2) appeared at 147-147.5 ppm, C-4/7 appeared at 125-125.5 ppm, C-5/6 appeared at 147-147.5 ppm, C-4/7 appeared at 125-125.5 ppm, C-5/6 appeared at 128 ppm. Due to similar chemical environment C-4/7 and C-5/6 showed single peak of two carbons each. Aromatic carbons of tosyl group appeared in the region 126-132 ppm. However C-3'/5' appeared at 114.0 ppm. The aromatic carbons of naphthoyl group appeared in the region 122-134 ppm, however in this case C-6' appeared at 113.0 ppm. Detailed ^{13}C-NMR data of compounds **III(a-b)** is listed in Table 4.1.6.

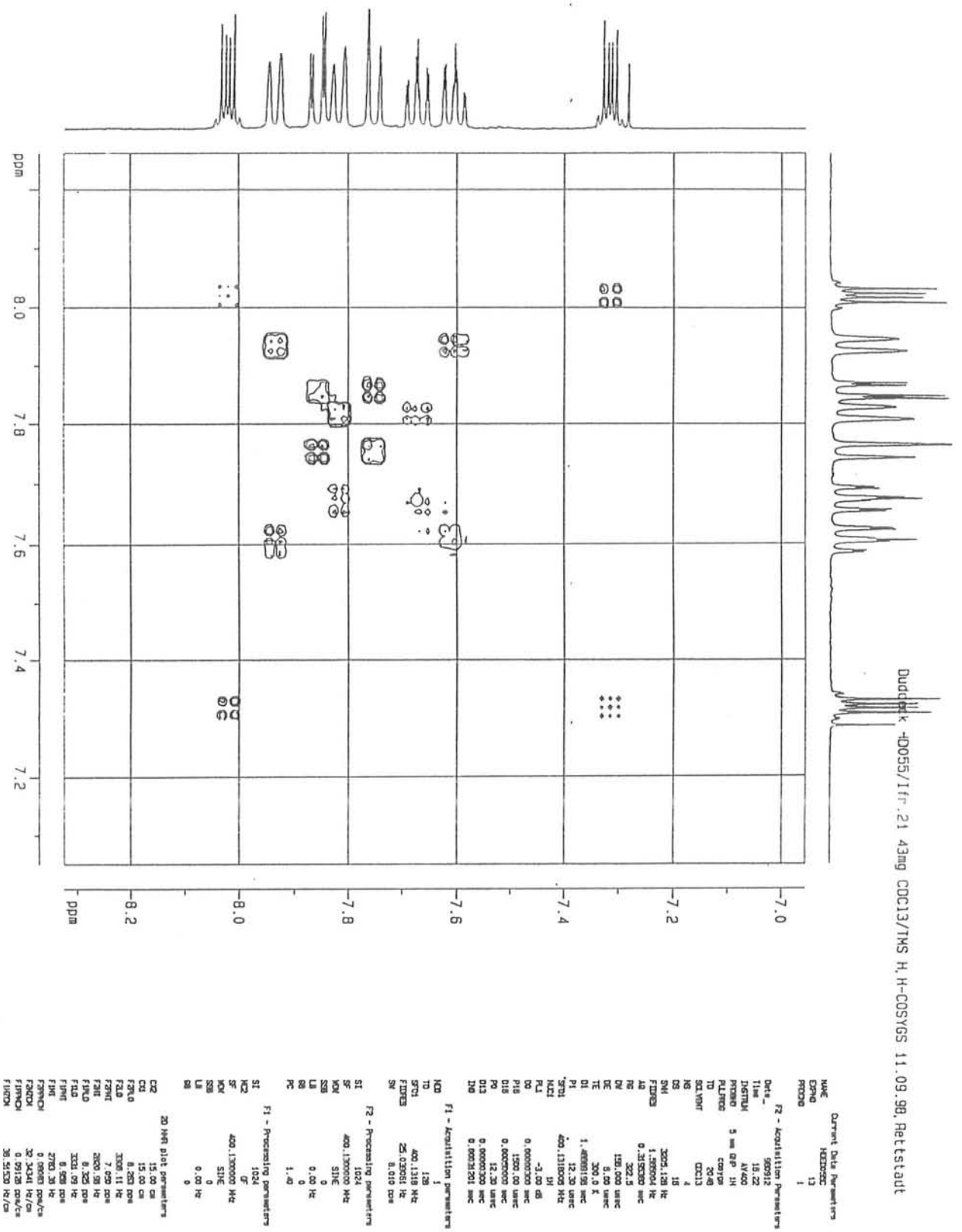


Fig. 4.1.1 H/H-Cosy spectrum of compound IIIa.

Fig. 4.1.3 NOE-Spectrum of compound III'a.

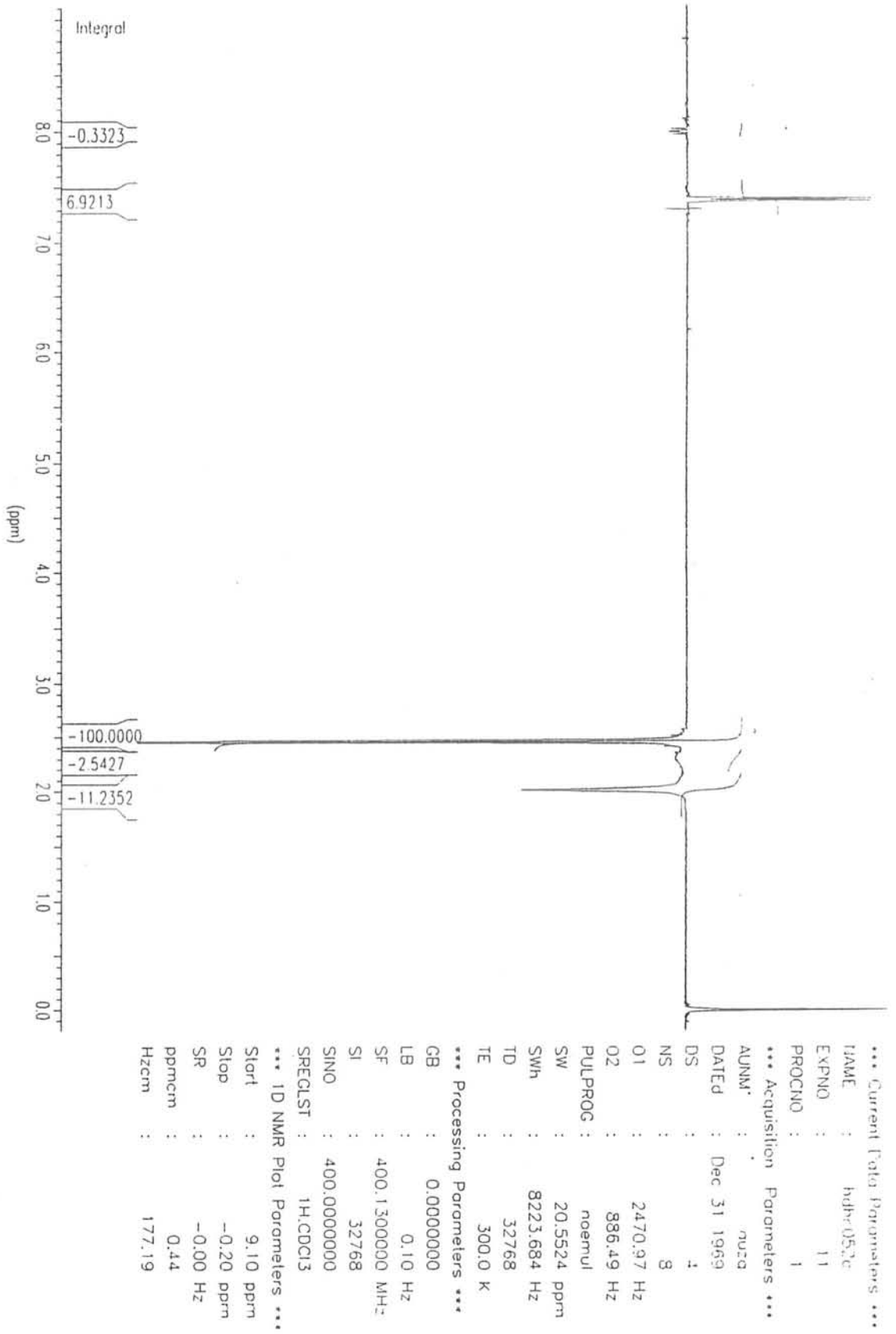
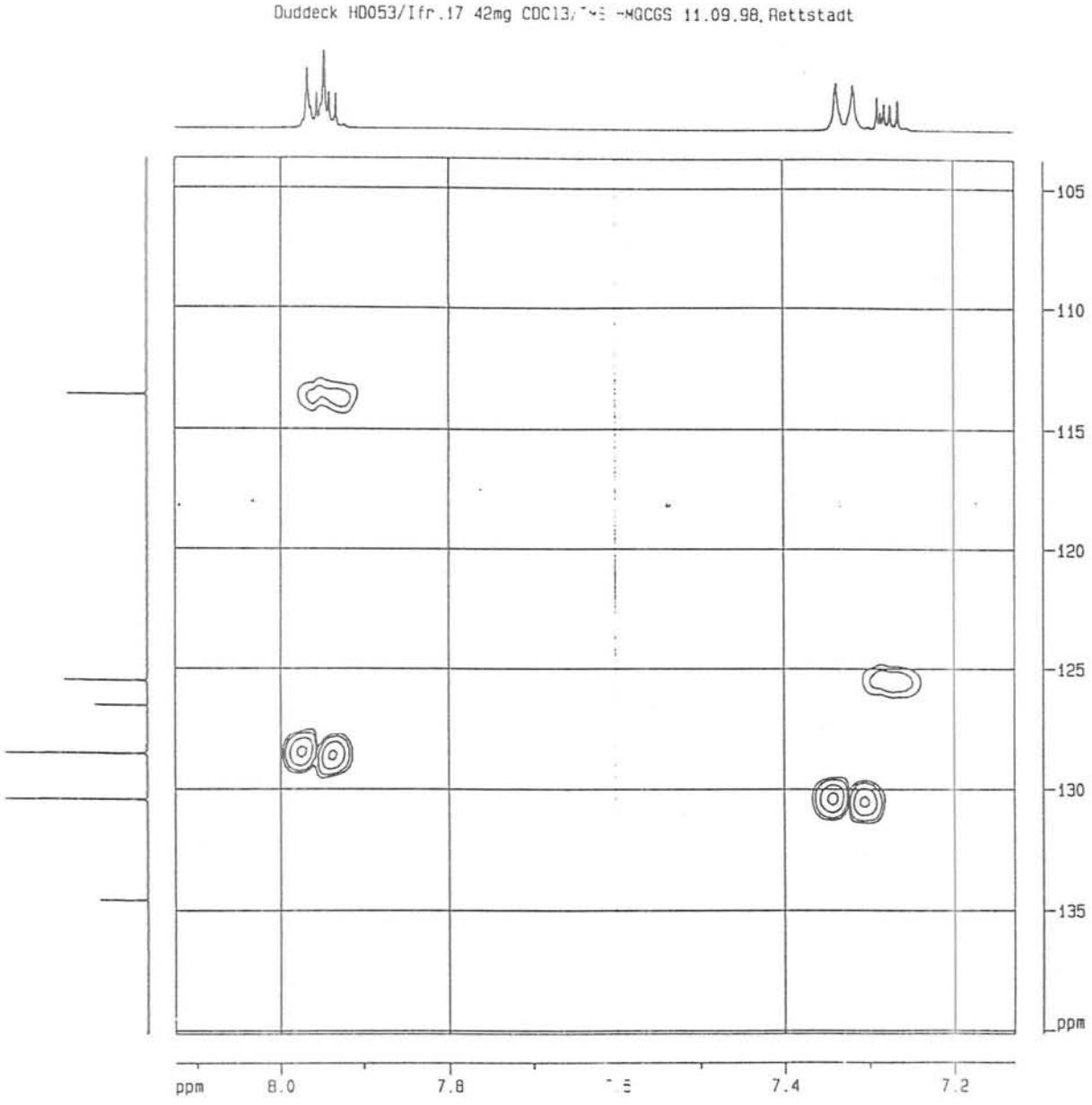


Fig. 4.1.2 NOE-Spectrum of compound III'a.

The ^{13}C-NMR spectra of compounds **III′(a-b)** showed similar pattern. Carbon of methyl group appeared at 22.0 ppm. Carbonyl carbon appeared at 147-147.3 ppm. In this case C-6, which is directly attached with nitro group appeared at 145-147.2 ppm, C-4 at 113.0 ppm, C-5 at 121 ppm and C-7 at 109 ppm, due to different chemical environment. Aromatic carbons of tosyl group appeared in the region 126-133 ppm, while the aromatic carbons of naphthyl group appeared in the region 122-133 ppm, with similar pattern as in compounds **III(a-b)**. ^{13}C-NMR data of compounds **III′(a-b)** is tabulated in Table 4.1.7.

In order to determine the interaction between the chemical shifts of proton and chemical shifts of carbon atoms, to which these protons are attached, HMQCGS-spectra of compounds **III(a-b)** and **III′(a-b)** have been recorded. From these spectra ^{13}C/^{1}H-interactions can be conveniently determined. For example, the spectrum of **IIIa** showed that H-4/7 at 7.26 ppm interacted with C-4/7 at 125.0 ppm. H-5/6 at 7.0-7.92 ppm interacted with C-5/6 at 128.0 ppm and H-b/b′ at 7.30 ppm interacted with C-3′/5′ at 132.0 ppm. Similarly in **IIIb** and **III′(a-b)** different ^{13}C/^{1}H-interactions have been observed. HMQCGS spectra of compounds **III(a-b)** and **III′(a-b)** are reproduced in Fig.4.1.4-4.1.7.

The detailed Mass-spectroscopic data of compounds **III(a-b)** and **III′(a-b)** is tabulated in Table 4.1.8 and 4.1.9. The Mass spectra of compounds **III(a-b)**, showed molecular ion peaks with good intensities (21.38-44.46%). Mass spectra of compound **IIIa**, showed the base peak (m/z=91) formed by the loss of SO_2 molecule from M^+-$C_{14}H_{11}N_2O_3S\rceil^\bullet$ which has good intensity (93.90%). Other major peaks in **IIIa** are II-$C_7H_7\rceil^\bullet$ (m/z=287), III-SO_2 (m/z=223), II-$C_7H_6\rceil^\bullet$ (m/z=288), X-C_2H_2 (m/z=65) and XIII-$C_8H_7O_3NS$ (m/z=180). The formation of peaks II, III, X and VIII is shown in fragmentation pattern of compounds **IIIa** (Fig. 4.1.8).



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PULPROG	inv4gs
TD	1024
SOLVENT	CDCl3
NS	4
DS	16
SWH	4006.410 Hz
FIDRES	3.912510 Hz
AQ	0.1278452 sec
RG	8502
DW	124.800 usec
DE	6.00 usec
TE	300.0 K
D12	0.00002000 sec
D2	0.00345000 sec
P16	1500.00 usec
D13	0.00000300 sec
d20	0.00192700 sec
D1	2.00000000 sec
P1	12.30 usec
SFO1	400.1316005 MHz
NUC1	1H
PL1	-3.00 dB
PL2	-3.00 dB
P3	8.00 usec
SFO2	100.6207780 MHz
NUC2	13C
D0	0.00000300 sec
D16	0.00050000 sec
P2	24.60 usec
PL12	18.00 dB
CPDPRG2	garp
PCPD2	85.00 usec
DW	0.00002750 sec

F1 - Acquisition parameters

ND0	2
TD	128
SFO1	100.6266 MHz
FIDRES	141.530792 Hz
SW	180.042 ppm

F2 - Processing parameters

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SF	400.1300000 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	1.40

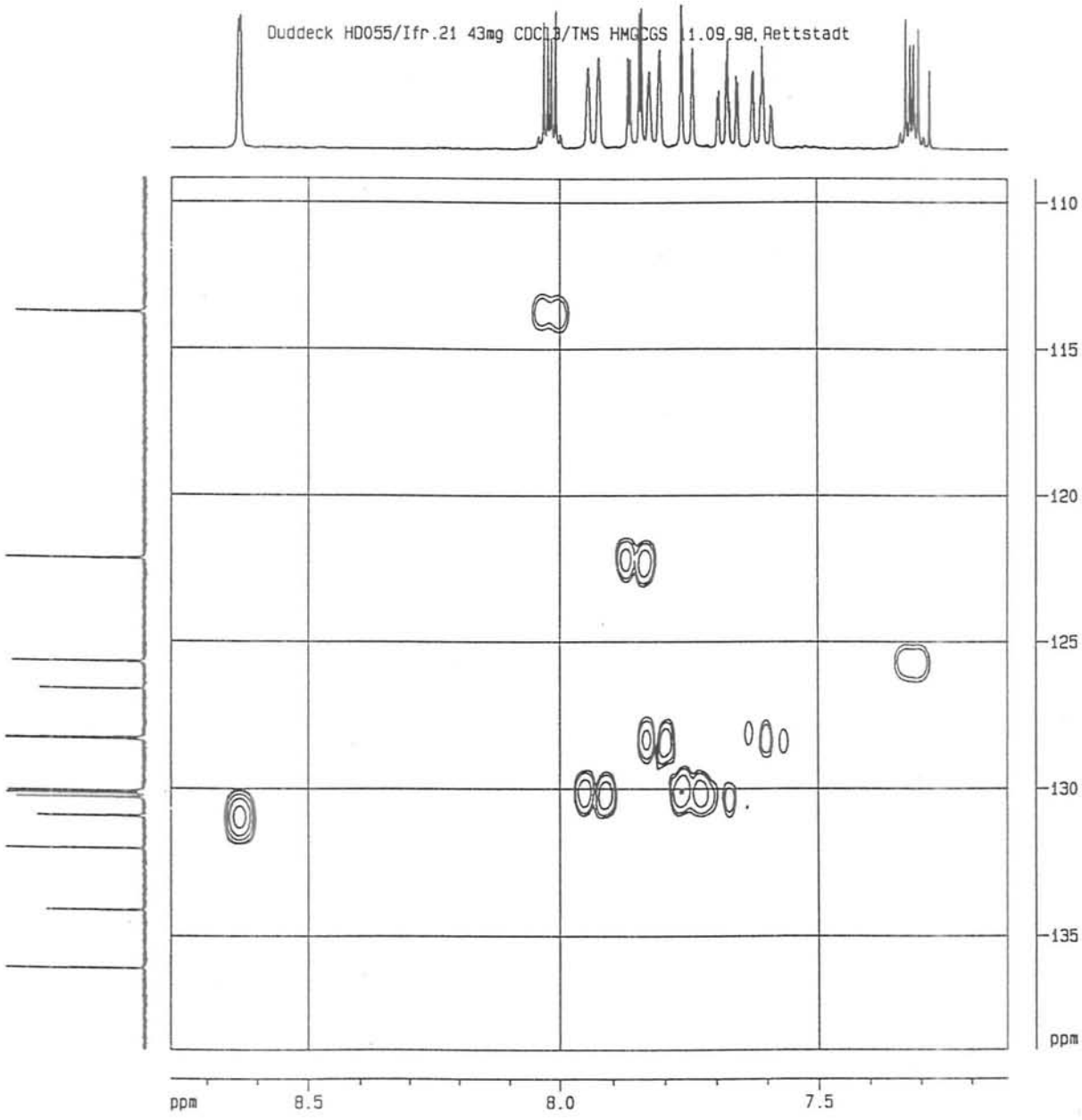
F1 - Processing parameters

SI	1024
MC2	QF
SF	100.6127250 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CY1	15.00 cm
F2PLO	8.125 ppm
F2LO	3251.60 Hz
F2PHI	7.129 ppm
F2HI	2852.52 Hz
F1PLO	140.135 ppm
F1LO	14098.48 Hz
F1PHI	103.736 ppm
F1HI	10437.35 Hz
F2PPMCM	0.06548 ppm/cm
F2HZCM	26.50507 Hz/cm
F1PPMCM	2.42554 ppm/cm
F1HZCM	244.14062 Hz/cm

Fig. 4.1.4 HMQCGS-Spectrum of compound IIIa.



Current Data Parameters

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PROCNO	1

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PULPROG	inv4gs
TD	1024
SOLVENT	CDCl3
NS	4
DS	16
SWH	4006.410 Hz
FIDRES	3.912510 Hz
AQ	0.1278452 sec
RG	8502
DW	124.800 usec
DE	6.00 usec
TE	300.0 K
D12	0.00002000 sec
D2	0.00345000 sec
P16	1500.00 usec
D13	0.00000300 sec
d20	0.00192700 sec
D1	2.00000000 sec
P1	12.30 usec
SFO1	400.1318005 MHz
NUC1	1H
PL1	-3.00 dB
PL2	-3.00 dB
P3	9.00 usec
SFO2	100.6207780 MHz
NUC2	13C
D9	0.00000300 sec
D15	0.00050000 sec
P2	24.80 usec
PL12	18.00 dB
CPDPRG2	garp
PCPD2	85.00 usec
IN0	0.00002780 sec

F1 - Acquisition parameters

NDO	2
TD	128
SFO1	100.6206 MHz
FIDRES	141.530752 Hz
SW	180.042 ppm

F2 - Processing parameters

SI	2048
SF	400.1300000 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	1.40

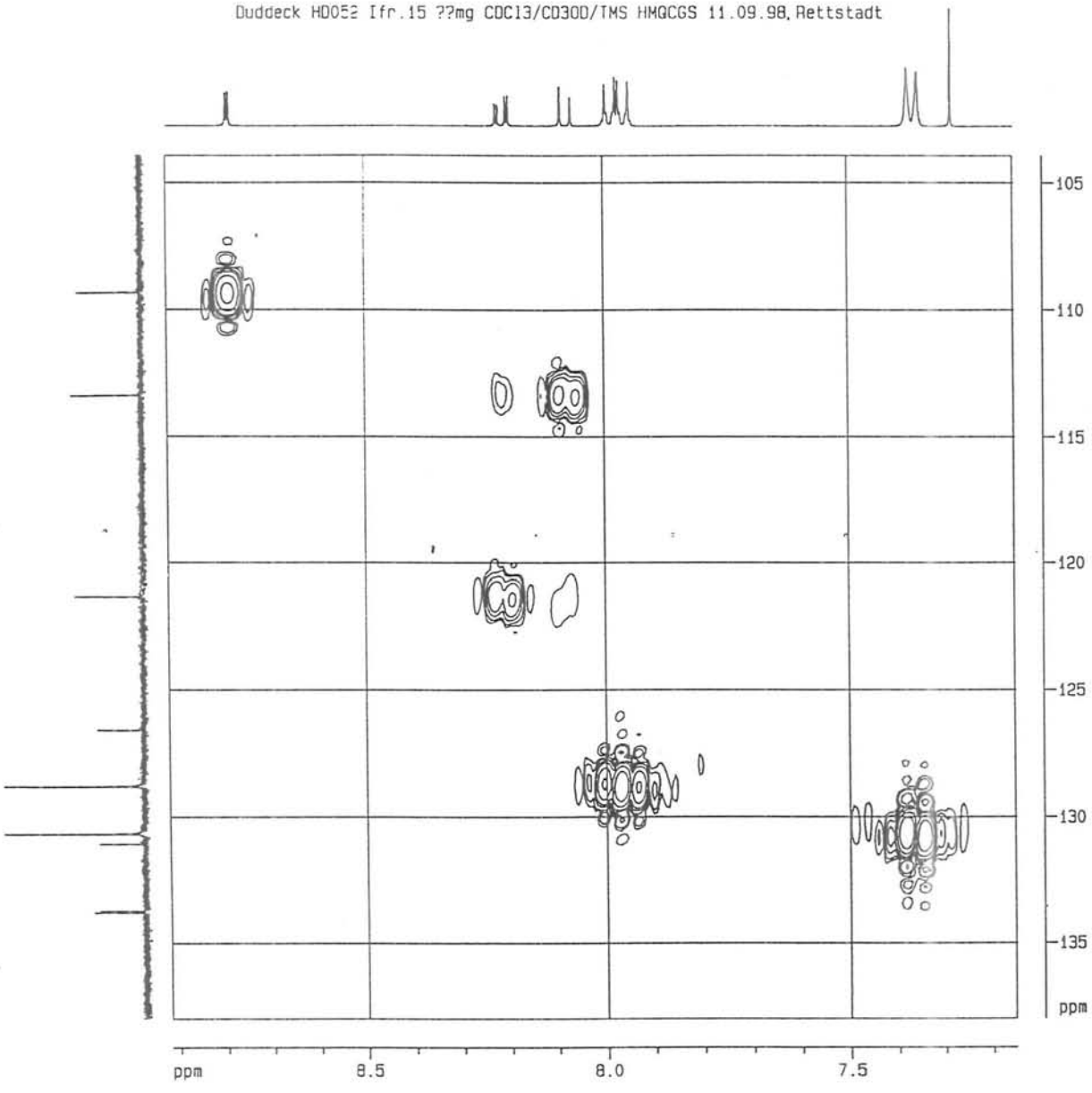
F1 - Processing parameters

SI	1024
MC2	QF
SF	100.6127250 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	8.777 ppm
F2LO	3511.78 Hz
F2PHI	7.128 ppm
F2HI	2852.52 Hz
F1PLO	138.905 ppm
F1LO	13875.62 Hz
F1PHI	109.188 ppm
F1HI	10905.79 Hz
F2PPMCM	0.10984 ppm/cm
F2HZCM	43.95054 Hz/cm
F1PPMCM	1.98109 ppm/cm
F1HZCM	198.32256 Hz/cm

Fig. 4.1.5 HMQCGS-Spectrum of compound IIIb.

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PULPROG                 inv4gs
TD                        1024
SOLVENT                   CDCl3
NS                           24
DS                           16
SWH                   4008.410 Hz
FIDRES                3.912510 Hz
AQ                    0.1278452 sec
RG                         9502
DW                     124.800 usec
DE                       6.00 usec
TE                       300.0 K
D12                   0.00002000 sec
D2                    0.003450000 sec
P16                      1800.00 usec
D13                   0.00000300 sec
d20                   0.00192700 sec
D1                    2.00000000 sec
P1                       12.30 usec
SFO1                400.1318005 MHz
NUC1                        1H
PL1                      -3.00 dB
PL2                      -3.00 dB
P3                        9.00 usec
SFO2                100.5207780 MHz
NUC2                        13C
D9                    0.00000300 sec
D16                   0.00050000 sec
P2                       24.80 usec
PL12                     18.00 dB
CPDPRG2                  garp
PCPD2                    85.00 usec
IN0                   0.00002780 sec

                F1 - Acquisition parameters
NDO                          2
TD                         128
SFO1                100.5206 MHz
FIDRES              141.530782 Hz
SW                     180.042 ppm

                F2 - Processing parameters
SI                        2048
SF                  400.1300000 MHz
WDW                        SINE
SSB                           0
LB                         0.00 Hz
GB                            0
PC                         1.40

                F1 - Processing parameters
SI                        1024
MC2                         SF
SF                  100.6127290 MHz
WDW                        SINE
SSB                           0
LB                         0.00 Hz
GB                            0

                2D NMR plot parameters
CX2                       15.00 cm
CY1                       15.00 cm
F2PLO                     8.918 ppm
F2LO                   3568.51 Hz
F2PHI                     7.153 ppm
F2HI                   2862.30 Hz
F1PLO                   138.026 ppm
F1LO                  13887.17 Hz
F1PHI                   103.814 ppm
F1HI                  10446.06 Hz
F2PPMCM                0.11786 ppm/cm
F2HZCM                47.08084 Hz/cm
F1PPMCM                2.27415 ppm/cm
F1HZCM                228.80808 Hz/cm
```

Fig. 4.1.6 HMQCGS-Spectrum of compound III'a.

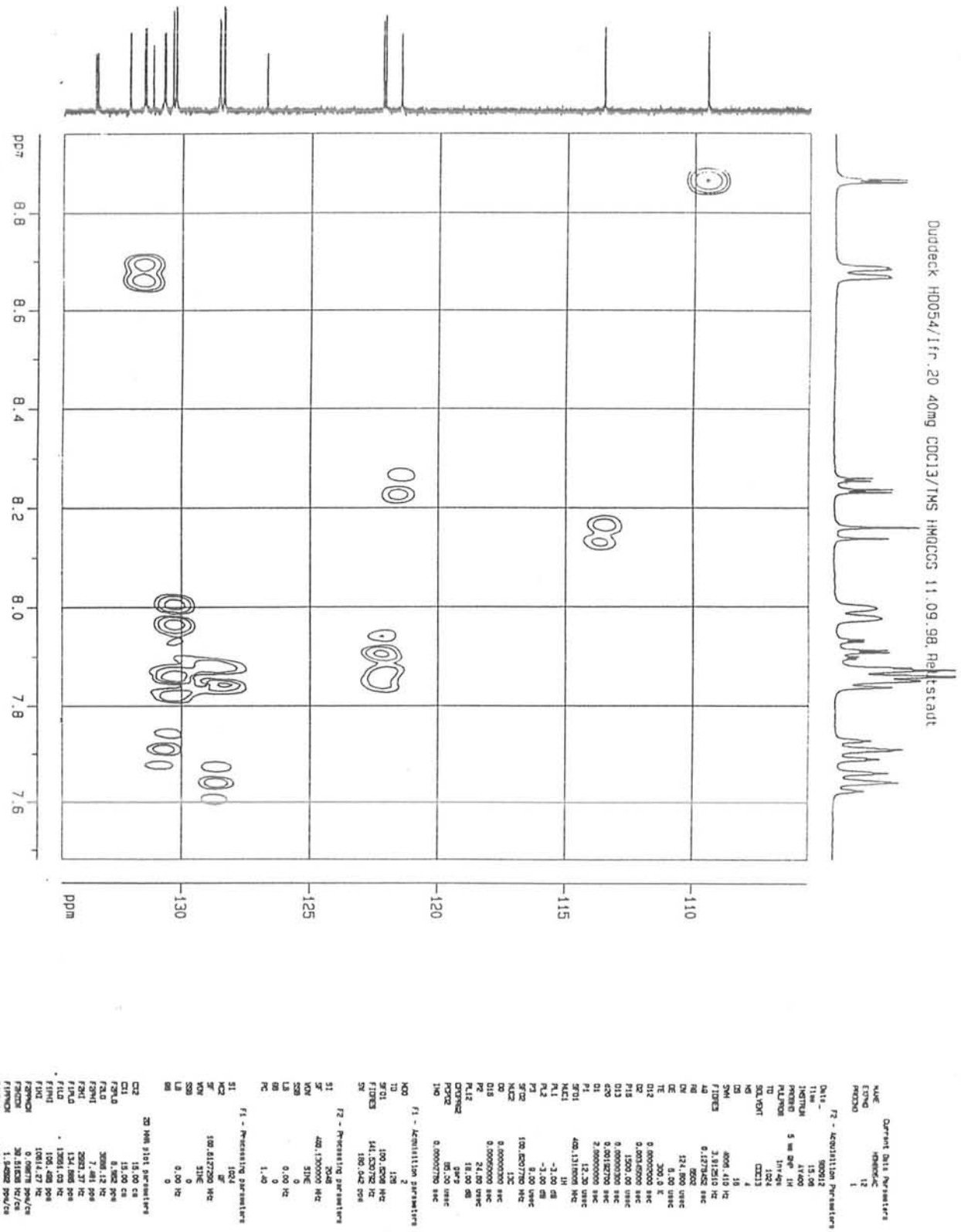


Fig. 4.1.7 HMQCGS-Spectrum of compound III'b.

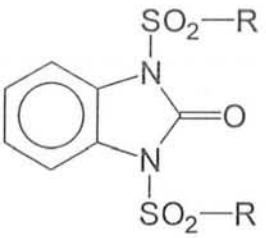
The mass spectrum of compound **IIIb**, showed base peak (m/z=127) due to the loss of $C_{17}H_{11}N_2O^{\bullet}$ from XIX. Peak XIX (m/z=386) was formed by the loss of SO_2 molecule from $M^{+\bullet}$ peak. $M^{+\bullet}$ peak was at m/z=514 with 21.38% intensity. Other major peaks in **IIIb** are II-$C_{10}H_7^{\bullet}$ (m/z=323), XV-SO_2 (m/z=259), XXI (m/z=191). The peak XXI was the most prominent peak after the base peak with 46.60% intensity. This peak was formed by the loss of $C_{17}H_{17}N_2O_3S^{\bullet}$ from the $M^{+\bullet}$ peak. Peak II (m/z=450) was observed by the loss of SO_2 molecule from the $M^{+\bullet}$ peak. Formation of XV and others is shown in fragmentation pattern of compound **IIIb** in Fig. 4.1.9.

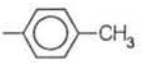
Mass-spectrum of compound **III'a**, showed $M^{+\bullet}$-peak at m/z 487, with 26.05 intensity. Base peak (m/z=155) was observed due to II-$C_{14}H_{10}N_3O_3^{\bullet}$. Peak II (m/z=423) was observed due to loss of SO_2 molecule from $M^{+\bullet}$ peak. Other major peaks in **III'a** are $M^{+\bullet}$-SO_2 (m/z=423), III-$C_{14}H_{10}N_3O_5^{\bullet}$ (m/z=92), V-SO_2 (m/z=91) and VI-C_2H_5 (m/z=65). Formation of peaks III, VI, V is shown in fragmentation pattern of compound **III'a** in Fig. 4.1.10.

The mass-spectrum of compound **III'b**, showed $M^{+\bullet}$-peak at m/z=559, with 9.89% intensity. Base peak at (m/z=157) was due to III-$C_{17}H_{10}N_3O_3$. Peak III was formed in similar way as in **III'a**. Other major peaks are $M^{+\bullet}$-SO_2 (m/z=495), XV-SO_2 (m/z=305), XVI-$C_{11}H_7NO$ (m/z=91), II-$C_{10}H_7^{\bullet}$ (m/z=369) and XV-SO_2 (m/z=304). Formation of all the peaks is shown in fragmentation pattern of compound **III'b** in Fig. 4.1.11. All these findings suggest that molecular ion peak in all the four compounds consists of a heterocyclic moiety with two nitrogen atoms and an aromatic ring and at both the nitrogen atoms, aryl sulfonyl groups are attached. These findings confirm the disubstitution of nitrogen atoms of benzimidazolones.

Elemental analysis of compounds **III(a-b)** and **III'(a-b)** were in accordance to the proposed structure.

Table 4.1.2: IR Spectroscopic data of Compounds III(a-b).

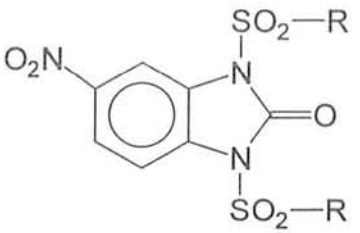


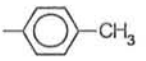
IIIa = R = 

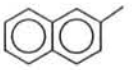
IIIb = R = 

S. No.	Vibrational Mode	IIIa (cm^{-1})	IIIb (cm^{-1})
1.	R–SO_2–N, asym. stretching	1152	1152
2.	R–SO_2–N, sym. stretching	1340	1304
3.	 stretching	1760	1756
4.	C–H, aromatic in-plane deformation	1192	1184
5.	C=C aromatic vib.	1596	1588
6.	CH_3– stretching	2956	—
7.	C=C–H str.	3052	3056
8.	=S=O asym. str. vibration	—	1156

Table 4.1.3: IR Spectroscopic data of Compounds III′(a-b).

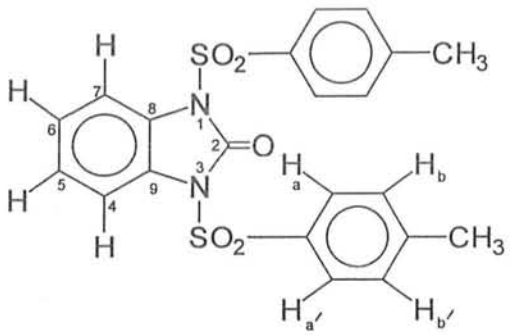


III′a = R = 

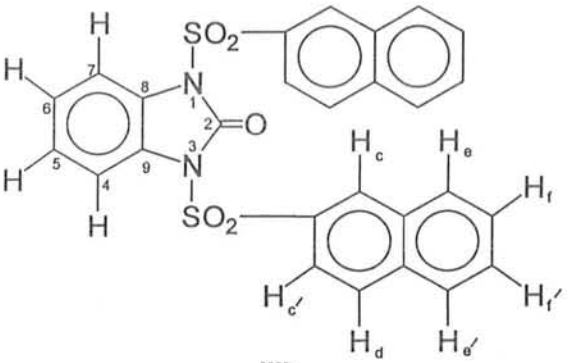
III′b = R = 

S. No.	Vibrational Mode	III′a (cm^{-1})	III′b (cm^{-1})
1.	R–SO_2–N, asym. stretching	1152	1152
2.	R–SO_2–N, sym. stretching	1344	1344
3.	⟩C=O str.	1772	1768
4.	C–H, aromatic inplane deformation	1192	1184
5.	C=C, aromatic vib.	1444	1488
6.	Ar–NO_2, asym. str.	1528	1528
7.	C–N, vib.	856	860
8.	CH_3– str. vib.	2952	—
9.	=C–H, aromatic. Str.	3068	3056
10.	C–H, aromatic out of plane vib.	—	888

Table 4.1.4: ^{1}H-NMR-Spectroscopic data of Compounds III(a-b).



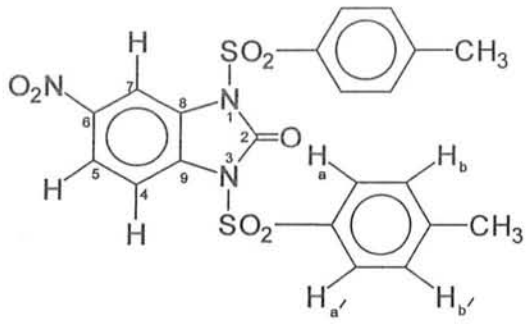
IIIa



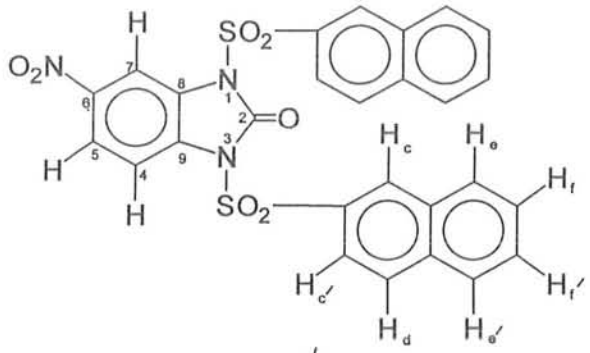
IIIb

S. No.	No. of Protons	IIIa (ppm)	IIIb (ppm)
1.	H-4/7	7.26 (dd, 2H), $J_{7\text{-}6}$ = 7.0 Hz, $J_{7\text{-}5}$ = 3.4 Hz	7.30 (dd, 2H), $J_{7\text{-}6}$ = 6.2 Hz, $J_{7\text{-}5}$ = 3.2 Hz
2.	H-5/6	7.70-7.92 (m, 2H)	7.80-8.0 (m, 2H)
3.	H-a/a′	7.95 (m, 4H)	—
4.	H-b/b′	7.31 (d, 4H), $J_{b\text{-}a}$ = 8.5 Hz	—
5.	H-CH_3	2.4 (s, 6H)	—
6.	H-f	—	7.68 (t, 2H)
7.	H-f′	—	7.75 (t, 2H)
8.	H-e/e′, H-d	—	7.82 (m, 6H)
9.	H-c/c′	—	7.94 (d, 4H), $J_{c'\text{-}d}$ = 8.7 Hz

Table 4.1.5: ^{1}H-NMR-Spectroscopic data of Compounds III′(a-b).



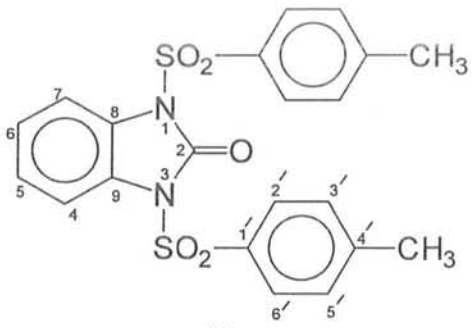
III′a



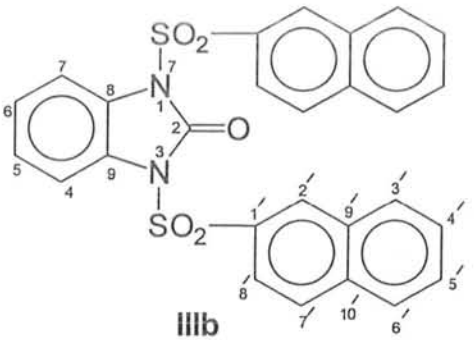
III′b

S. No.	No. of Protons	III′a (ppm)	III′b (ppm)
1.	H-4	8.88 (d, 1H), J_{4-5} = 8.03 Hz	8.16 (d, 1H), J_{4-5} = 9.03 Hz
2.	H-5	8.22 (dd,1H), J_{5-4} = 9.03 Hz, J_{5-7} = 2.0 Hz	8.25 (dd, 1H), J_{5-7} = 2.0 Hz, J_{5-4} = 9.03 Hz
3.	H-7	8.92 (d, 1H), J_{7-5} = 2.03 Hz	8.87 (d, 1H), J_{7-5} = 2.0 Hz
4.	H-a/a′	7.94-8.01 (m, 4H)	—
5.	H-b/b′	7.36 (d, 1H), J_{b-a} = 8.0 Hz	—
6.	H-CH_3	2.4 (s, 6H)	—
7.	H-f	—	7.64 (t, 2H)
8.	H-f′	—	7.71 (t, 2H)
9.	H-e/e′, H-d	—	7.86 (m, 6H)
10.	H-c/c′	—	8.10 (d, 4H), $J_{c'-d}$ = 8.9 Hz

Table 4.1.6: ^{13}C-NMR data of Compounds III(a-b).



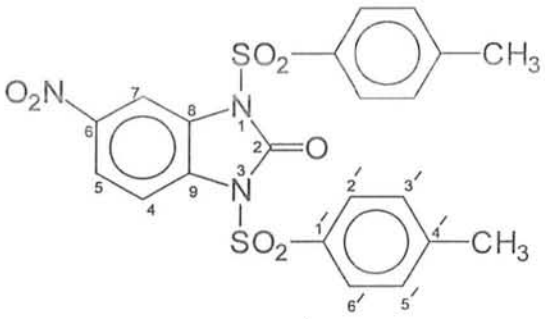
IIIa



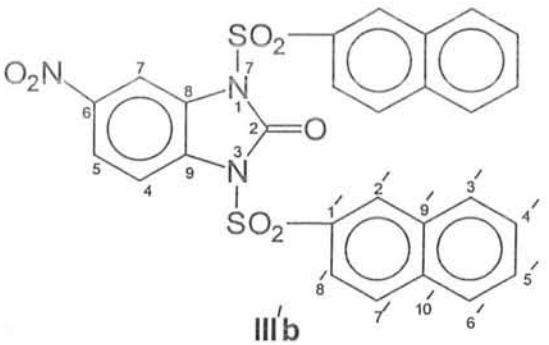
IIIb

S. No.	No. of Carbons	IIIa (ppm)	IIIb (ppm)
1.	C-4/7	125.0	125.25
2.	C-5/6	128.0	128.0
3.	C-2′/6′	132.0	—
4.	C-3′/5′	114.0	—
5.	C-8/9	146.0	135.5
6.	C-1′	134.0	134.0
7.	C-4′	126.0	—
8.	C-CH_3	22.0	—
9.	C-CO	147.0	147.5
10.	C-3′/4′/7′	—	122.0
11.	C-6′	—	113.0
12.	C-5′	—	129.5
13.	C-2′/8′	—	130.5
14.	C-9′/10′	—	131.0

Table 4.1.7: ^{13}C-NMR data of Compounds III′(a-b).



III′a



III′b

S. No.	No. of Carbons	III′a (ppm)	III′b (ppm)
1.	C-2	147.0	147.3
2.	C-4	113.0	113.0
3.	C-5	121.0	121.0
4.	C-6	147.2	145.0
5.	C-7	144.8	129.5
6.	C-8	144.8	129.5
7.	C-9	130.0	126.0
8.	C-1′	133.3	133.0
9.	C-2′/6′	128.3	—
10.	C-3′/5′	130.1	—
11.	C-4′	126.0	—
12.	C-CH_3	22.0	—
13.	C-2′/8′	—	131.5
14.	C-3′/4′/7′	—	122.0
15.	C-5′	—	131.0
16.	C-6′	—	128.0
17.	C-9′/10′	—	129.0

Table 4.1.8: Mass Spectroscopic data of Compounds III(a-b).

S. No.	Peak	IIIa		IIIb	
		m/z	%	m/z	%
I	$M^{+\bullet}$	442	44.46	514	21.38
II	$M^{+\bullet}$-SO_2	378	6.39	450	6.96
III	II-$C_7H_7]^{\bullet}$	287	39.87	—	—
IV	III-SO_2	223	9.84	—	—
V	IV-CO	195	1.66	—	—
VI	IV-C_8H_7NO	90	3.35	—	—
VII	II-$C_7H_6]^{\bullet}$	288	8.95	—	—
VIII	VII-SO_2	224	2.19	—	—
IX	$M^{+\bullet}$-$C_{14}H_{11}N_2O_3S]^{\bullet}$	155	90	—	—
X	IX-SO_2	91	100.0	—	—
XI	X-C_2H_2	65	14.84	—	—
XII	$M^{+\bullet}$-$H]^{\bullet}$	441	—	—	—
XIII	XII-SO_2	377	—	—	—
XIV	XIII-$C_8H_7O_3NS$	180	30.78	—	—
XV	II-$C_{10}H_7]^{\bullet}$	—	—	323	8.42
XVI	XV-SO_2	—	—	259	13.63
XVII	XVI-$C_{11}H_7NO$	—	—	90	—
XVIII	II-SO_2	—	—	386	1.14
XIX	XIX-$C_{17}H_{11}N_2O]^{\bullet}$	—	—	127	100.0
XX	$M^{+\bullet}$-$C_{17}H_{17}N_2O_3S]^{\bullet}$	—	—	191	47.60
XXI	XXI-SO_2	—	—	127	100

Table 4.1.9: Mass Spectroscopic data of Compounds III'(a-b).

S. No.	Peak	III'a		III'b	
		m/z	%	m/z	%
I	$M^{+\bullet}$	487	26.05	559	9.89
II	$M^{+\bullet}$-SO_2	423	5.66	495	8.85
III	II-SO_2	359	—	431	—
IV	III-$C_{14}H_{10}N_3O_3]^{\bullet}$	92	9.47	—	—
V	II-$C_{14}H_{10}N_3O_3]^{\bullet}$	155	100.0	—	—
VI	V-SO_2	91	77.17	—	—
VII	VI-C_2H_2	65	11.15	—	—
VIII	$M^{+\bullet}$-$C_7H_7SO_2]^{\bullet}$	332	—	—	—
IX	III-SO_2	268	—	—	—
X	IX-C_8H_7NO	90	3.98	—	—
XI	$M^{+\bullet}$-$2C_7H_7SO_2]^{\bullet}$	177	—	—	—
XII	XI-CO	149	2.65	—	—
XIII	XII-N_2	121	—	—	—
XIV	III-$C_{17}H_{10}N_3O_3]^{\bullet}$	—	—	127.0	100.0
XV	$M^{+\bullet}$-$C_{10}H_7SO_2]^{\bullet}$	—	—	368	—
XVI	XV-SO_2	—	—	304	1.82
XVII	XVI-$C_{11}H_7NO$	—	—	91	1.48
XVIII	$M^{+\bullet}$-$2C_{10}H_7SO_2]^{\bullet}$	—	—	177	—
XIX	XVIII-CO	—	—	149	1.79
XX	II-$C_{10}H_7]^{\bullet}$	—	—	369	1.97
XXI	XX-SO_2	—	—	305	1.55

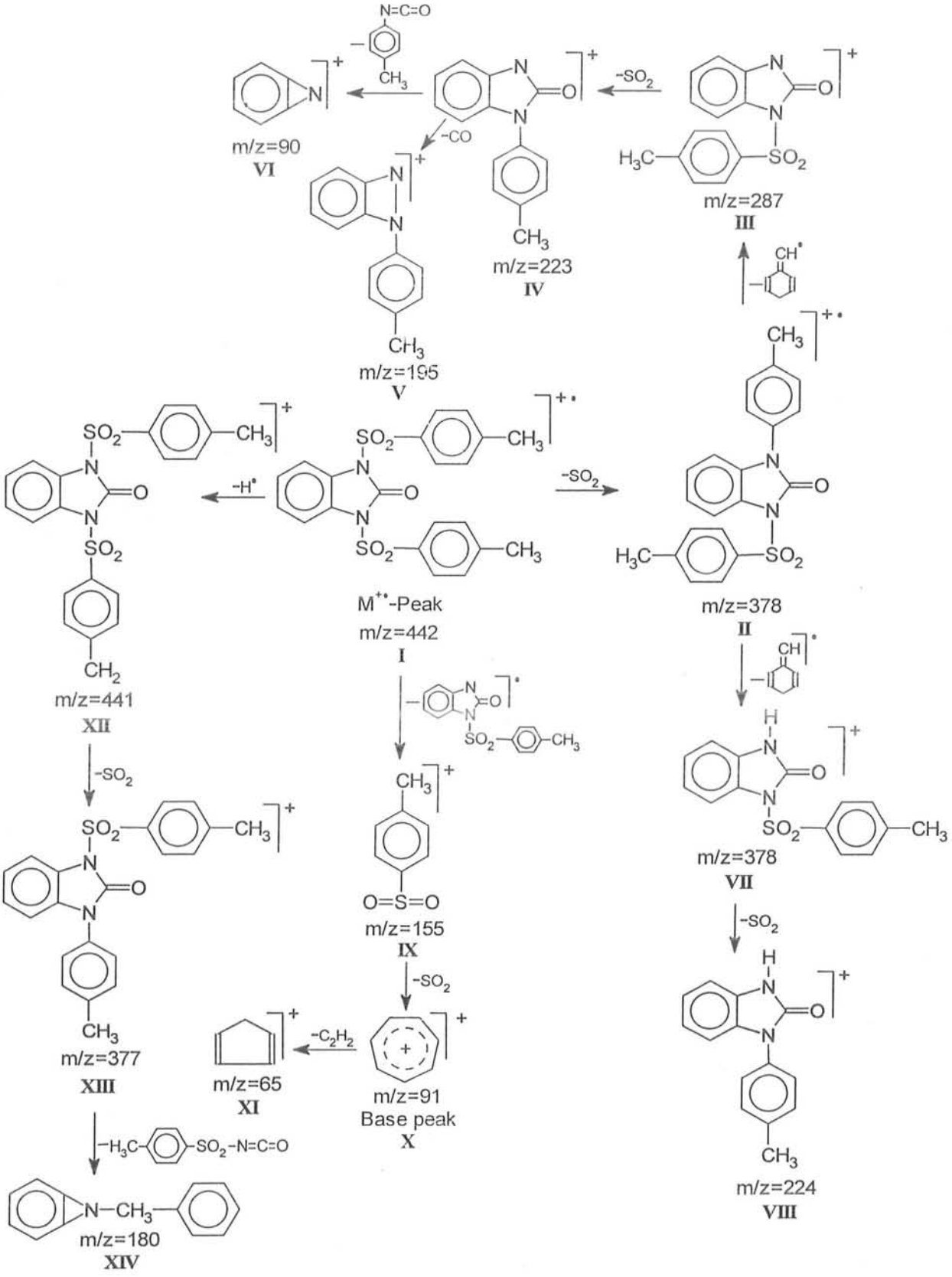


Fig. 4.1.8: Mass Fragmentation Pattern of Compound IIIa.

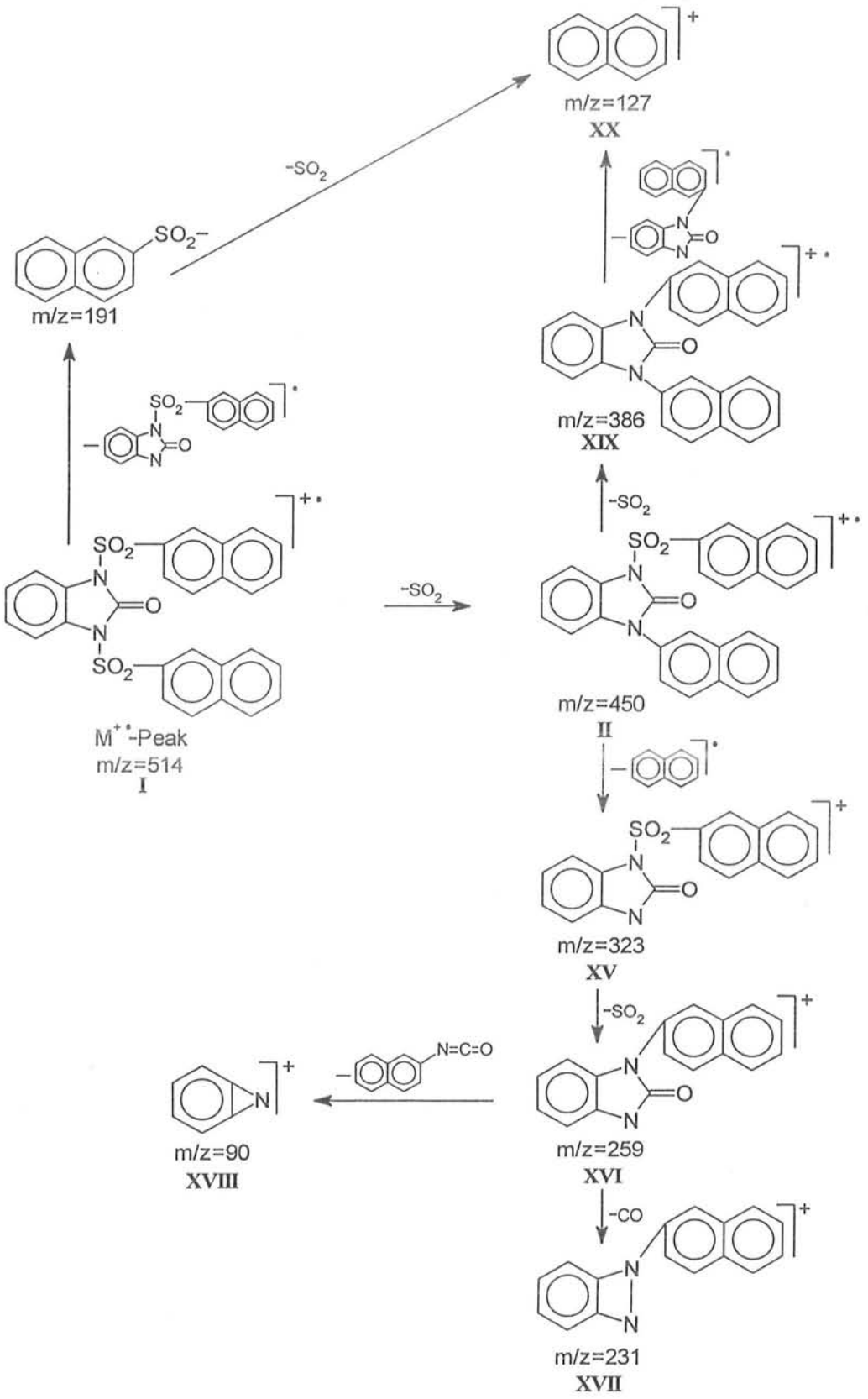


Fig. 4.1.9: Mass Fragmentation Pattern of Compound IIIb.

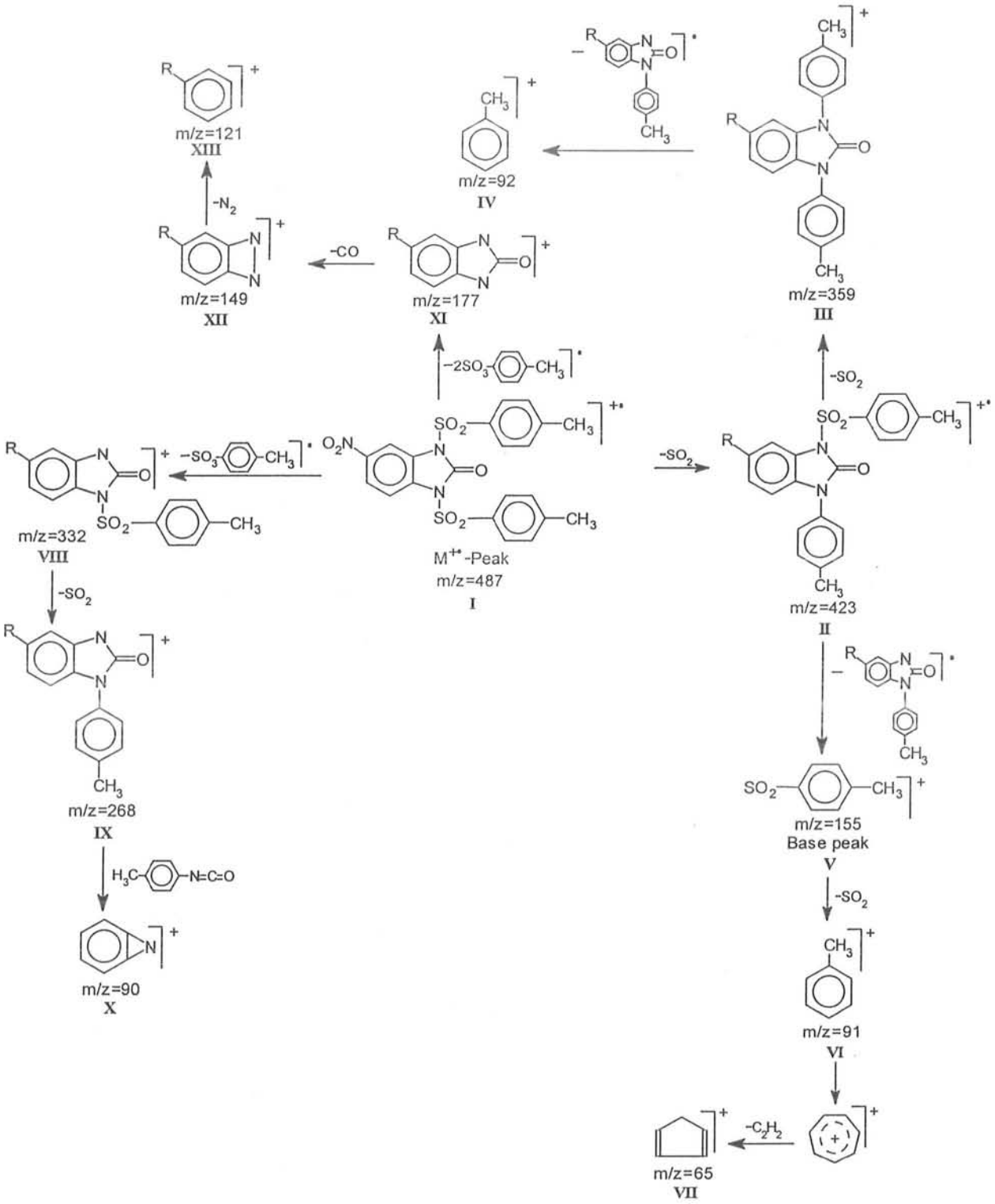


Fig. 4.1.10: Mass Fragmentation Pattern of Compound III a.

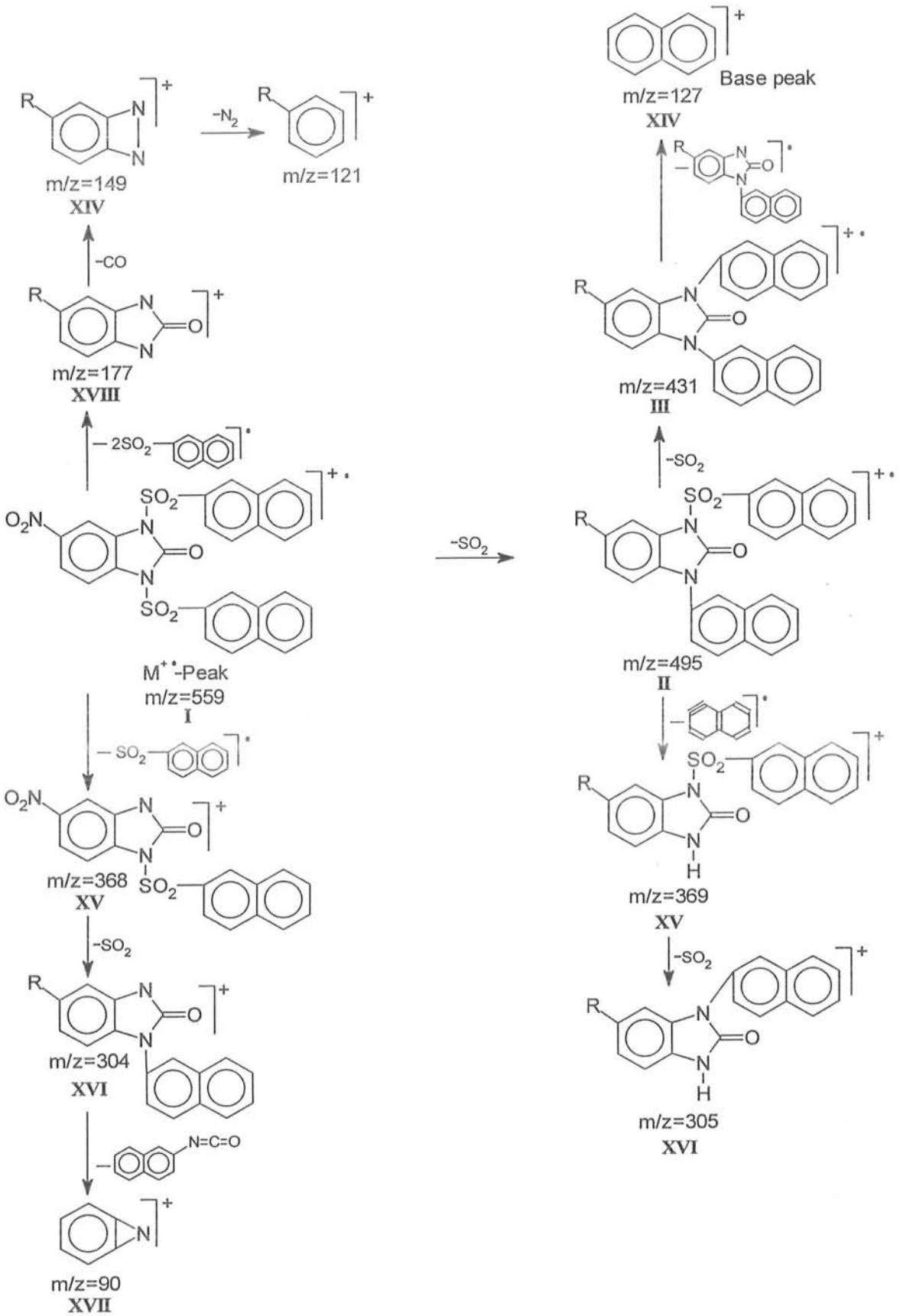


Fig. 4.1.11: Mass Fragmentation Pattern of Compound III'b.

Table 4.1.10: Elemental Analysis of Compounds III, III'(a-b).

S. No.	Elements	IIIa		IIIb		III'a		III'b	
		% (Cal.)	% (Found)	% (Cal.)	% (Found)	% (Cal.)	% (Found)	% (Cal.)	% (Found)
1.	C	57.00	56.84	63.02	62.18	51.74	51.32	57.95	57.60
2.	H	4.10	4.03	3.53	3.46	3.51	3.38	3.06	2,97
3.	N	6.33	6.26	5.44	5.19	8.62	8.48	7.51	7.39

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4.2 Synthesis of monoprotected benzimidazolones:

Protection of one of the nitrogen atoms of benzimidazolones was carried out according to Scheme-V, following the methods reported in the literature[46]. The purity of all synthesized monoprotected benzimidazolones **IV**, **IV′** was established by TLC. In case of compound **IV**, only one spot was observed and yield was quite good (70.25%), but in case of **IV′**, two spots appeared at TLC. This indicated the presence of two regio isomers. These two regio isomers have been separated by Flash Column Chromatography using silica gel as a adsorbent and n-hexane : ethyl acetate (4:1) as solvent. In this case yields were quite low. The physical data of compounds **IV**, **IV′** and **IV″** has been tabulated in Table 4.2.1.

The IR spectra of compounds **IV**, **IV′** and **IV″** showed a band at 1740 cm^{-1} due to $-NCO_2-$ stretching. These compounds exhibited $\rangle C=O$ stretching for amide at 1760-1779 cm^{-1}, C–H aromatic inplane deformation at 1110 cm^{-1}, C–H vib. deformation at 1337-1365 cm^{-1}, C=C aromatic vib. at 1390-1394 cm^{-1}, C–H aromatic out of plane vib. at 832-888 cm^{-1}, =C–H aromatic stretching at 3185-3195 cm^{-1}. In all the compounds CH_3- stretching was exhibited at 2975 cm^{-1}, which indicated the presence of t-butoxy carbonyl group at nitrogen atom of the benzimidazolones. Presence of nitro group at aromatic ring of benzimidazolone was indicated by the $Ar-NO_2$ asym. stretching at 1520-1521 cm^{-1}. The presence of free –NH group was indicated by a band at 3361-3365 cm^{-1} in IR spectra of all these compounds. IR spectroscopic data of compounds **IV**, **IV′** and **IV″** is shown in Table 4.2.2.

The ^{1}H-NMR spectra of compounds **IV**, **IV′** and **IV″** showed that –NH–proton resonated at 9.48-10.5 ppm. H-4/5/6, appeared at 7.10-7.20 as a multiplet in compound **IV**. However, H-7 resonated at 7.72 ppm as doublet with coupling constant of 8.0 Hz. The down field shift in H-7 is due to its presence in the vicinity of t-butoxy carbonyl group. Protons of t-butoxy group resonated at 1.25-1.7 ppm as a singlet of 9-protons in all three compounds. In compound **IV′** and **IV″**, due to the presence of nitro group at 6-postion of benzimidazolone, chemical environment of H-4, H-5 and H-7 becomes different. Thus H-4 resonated at 7.18-7.87 ppm as a doublet with coupling constant of 8.66-8.9 Hz, H-5 resonated at 8.10-8.18 ppm as a doublet of doublet with ortho coupling

constant of 8.66-8.9 Hz and meta coupling constant of 2.13-2.26 Hz. Proton H-7 resonated at 8.70-8.0 ppm as a doublet with coupling of 2.13-2.30 Hz. Down field shift in H-7, of compound **IV′**, indicates that H-7 is in the vicinity of some electron withdrawing group other than nitro group, because H-7, in **IV″** is relatively up field with respect to **IV′**. This indicates that t-butoxy carbonyl group in **IV′** is at 1-position of nitrobenzimidazolone. In case of compound **IV″**, the H-4 resonated at 7.87 ppm, whereas in compound **IV′** it resonated at 7.18 ppm. This down field shift suggests that H-4 in compound **IV″** is near to some electron withdrawing group. This indicates that in **IV″**, t-butoxy carbonyl group is at position-3 of the nitrobenzimidazolone. It is seen that down field shift in case of H-4 in **IV″** is less than down field shift of H-7 in **IV′**. The reason for this is the chemical environment due to the presence of nitro group at position-6, which is ortho to H-7, but is meta to H-4, due to it down field shift due to t-butoxy carbonyl group, is more at H-7 than H-4. The ^{1}H-NMR spectroscopic data of compounds **IV**, **IV′** and **IV″** is tabulated in Table 4.2.3.

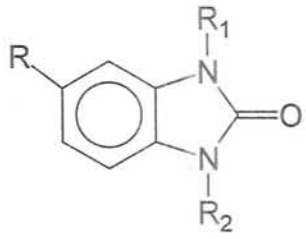
Mass spectra of **IV**, **IV′**showed $M^{+\bullet}$-peaks (m/z=234, 279) with low intensities (10.2%, 9.14%). Base peak in both compounds was observed due to II-C_4H_8 (m/z=134, 179) peak. Peak II was formed by the loss of CO_2 molecule from $M^{+\bullet}$ peak. Other major peaks were III-CO (m/z=106, 151), IV-N_2 (m/z=78, 123), $M^{+\bullet}$–O-t-Bu$]^{\bullet}$ (m/z=161, 206, VI-CO (m/z=133, 178), VII-CO (m/z=105, 150) and VIII-N_2 (m/z=77, 122).

The formation of peaks III, IV, VI, VII and VIII is shown in fragmentation pattern of these compounds in Fig. 4.2.1 and Fig. 4.2.2.

All these findings suggest that molecular ion peak in both compounds consists of heterocyclic moiety with two nitrogen atoms and one aromatic ring. At one of the nitrogen atoms, t-butoxy carbonyl group is attached, which indicates that monoprotection of amino group of benzimidazolone has occurred.

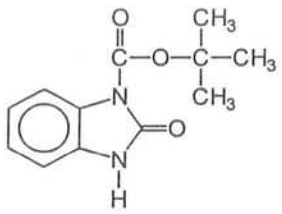
Elemental analysis of these compounds **IV**, **IV′** and **IV″** was in accordance to the proposed structure.

Table 4.2.1: Physical data of Compounds IV, IV′ and IV″.

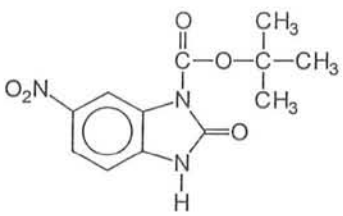


S.No.	Compound	R	R_1	R_2	m.p.°C	% Yield	R_f-Value
1.	IV	H	$-CO_2-C(CH_3)_2-CH_3$	H	165-168	70.25	0.25 (Ethylacetate:n-hexane) (1:3)
2.	IV′	NO_2	"	H	320	35.25	0.47 (Ethylacetate:n-hexane) (1:3)
3.	IV″	NO_2	H	$-CO_2-C(CH_3)_2-CH_3$	327	40.00	0.35 (Ethylacetate:n-hexane) (1:3)

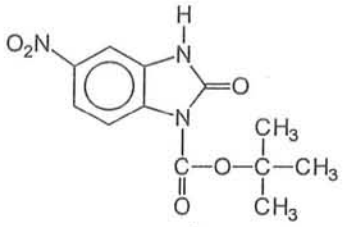
Table 4.2.2: IR Spectroscopic data of Compounds IV, IV′ and IV″.



IV



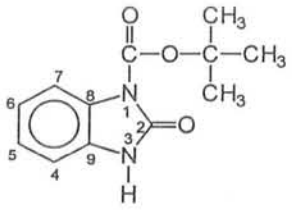
IV′



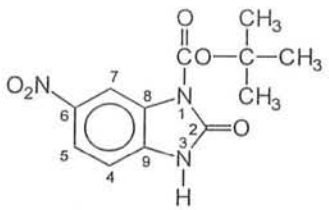
IV″

S. No.	Vibrational Mode	IV (cm^{-1})	IV′ (cm^{-1})	IV″ (cm^{-1})
1.	 amide, str.	1760	1777	1779
2.		1740	1740	1740
3.	C–H, aromatic in-plane deformation	1110	1110	1110
4.	C–H, vib. deformation	1337	1365	1365
5.	C=C, vib., aromatic	1394	1394	1390
6.	C–H, aromatic out of plane vib.	888	832	871
7.	=C–H, aromatic str.	3195	3195	3195
8.	CH_3– str.	2975	2975	2975
9.	Ar–NO_2, asym. str.	—	1520	1521
10.	–NH, str.	3367	3365	3365

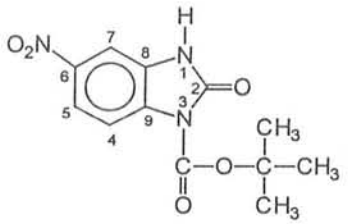
Table 4.2.3: ^{1}H-NMR data of Compounds IV, IV′ and IV″.



IV



IV′



IV″

S. No.	No. of Protons	IV (ppm)	IV′ (ppm)	IV″ (ppm)
1.	H-3 (H-NH)	10.7 (s, 1H)	9.70 (s, 1H)	9.48 (s, 1H)
2.	H-4/5/6	7.10-7.20 (m, 3H)	—	—
3.	H-7	7.72 (d, 1H), J_{7-6} = 8.0 Hz	—	—
4.	H-4	—	7.18 (d,1H), J_{4-5} = 8.66 Hz	7.87 (d, 1H), J_{4-5} = 8.9 Hz
5.	H-5	—	8.18 (dd, 1H), J_{5-4} = 8.66 Hz, J_{5-7} = 2.26 Hz	8.10 (dd, 1H), J_{5-4} = 8.9 Hz, J_{5-7} = 2.13 Hz
6.	H-7	—	8.70 (d, 1H), J_{7-5} = 2.13 Hz	8.0 (d, 1H), J_{7-5} = 2.3 Hz
7.	H-t.Bu	1.7 (s, 9H)	1.25 (s, 9H)	1.25 (s, 9H)

Table 4.2.4: Mass Spectroscopic data of Compounds IV, IV'.

S. No.	Peak	IV		IV'	
		m/z	%	m/z	%
I	$M^{+\bullet}$	234	10.02	279	9.14
II	$M^{+\bullet}$-CO_2	190	—	235	—
III	II-C_4H_8	134	100.00	179	100.00
IV	III-CO	106	11.44	151	8.50
V	IV-N_2	78	2.66	123	3.16
VI	$M^{+\bullet}$-o-t.Bu$]^{\bullet}$	161	2.03	206	3.0
VII	VI-CO	133	4.94	178	5.31
VIII	VII-CO	105	3.09	150	2.91
IX	VIII-N_2	77	1.11	122	2.11

Table 4.2.5: Elemental Analysis of Compounds IV, IV' and IV''.

S. No.	Elements	IV		IV'		IV''	
		%(Cal.)	%(Found)	%(Cal.)	%(Found)	%(Cal.)	%(Found)
1.	C	61.54	62.28	51.6	51.91	51.6	51.95
2.	H	5.98	6.25	4.66	4.31	4.66	4.23
3.	N	11.96	11.41	15.05	14.95	15.05	14.95

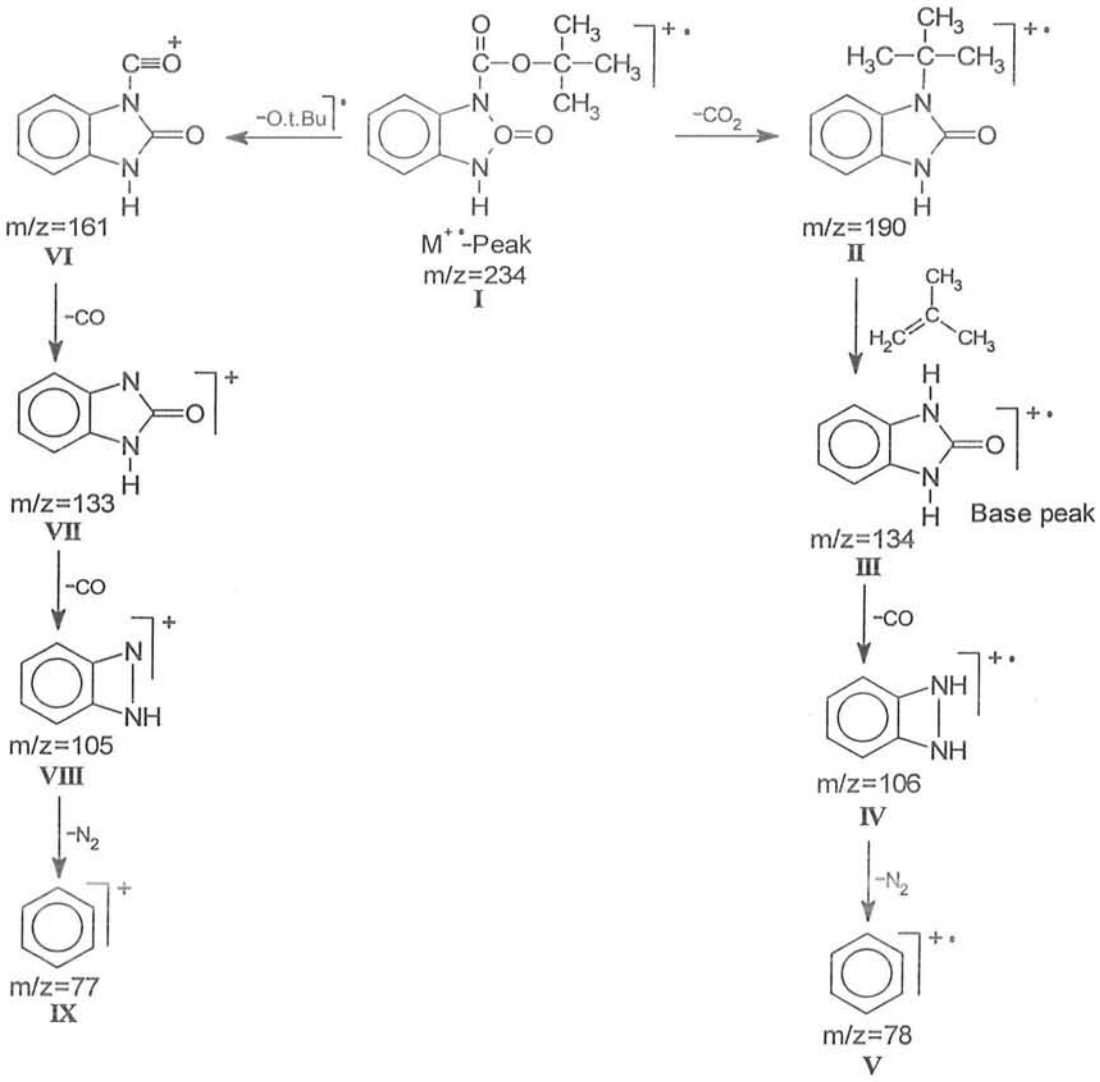


Fig. 4.2.1: Mass Fragmentation Pattern of Compound IV.

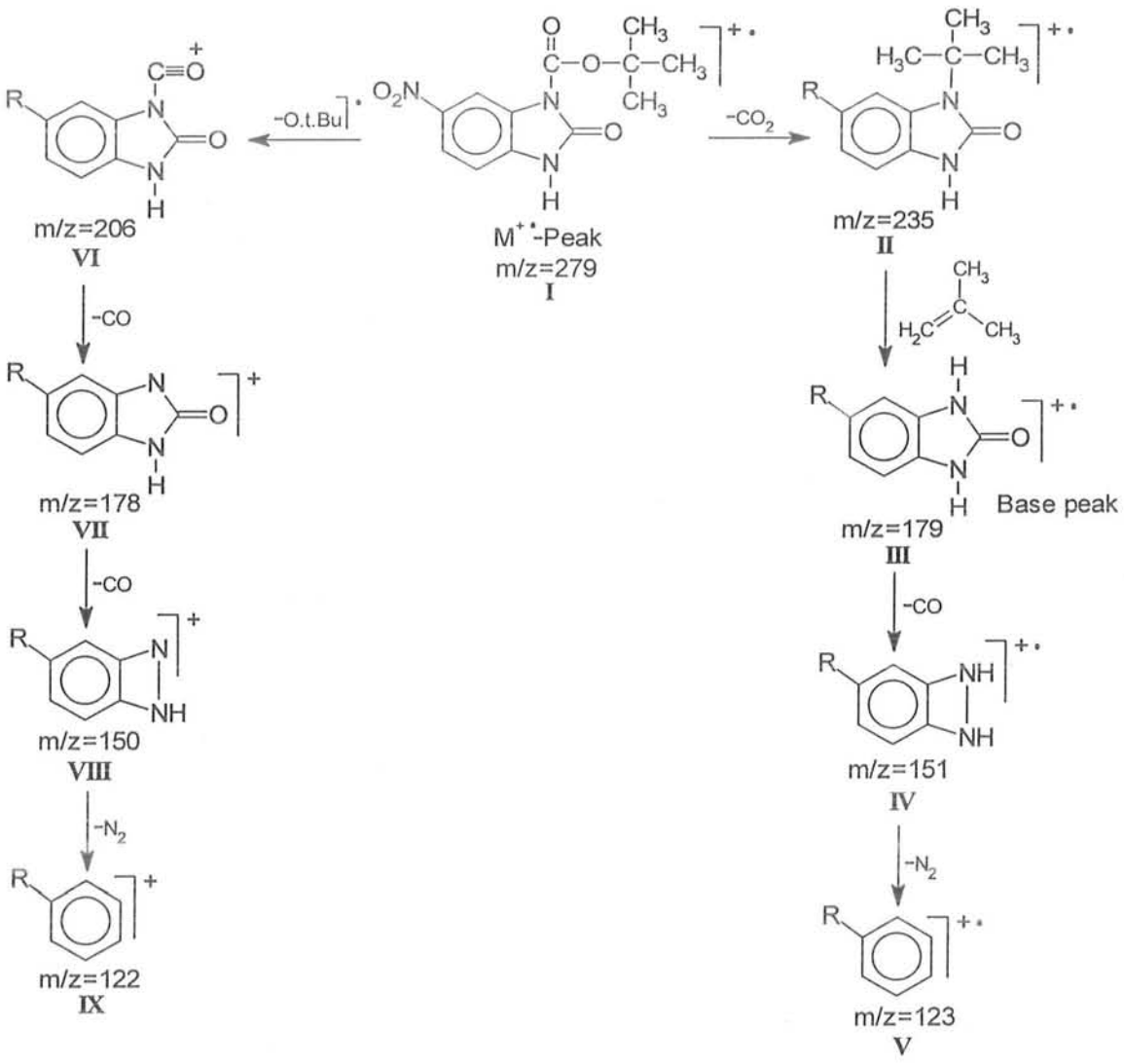


Fig. 4.2.2: Mass Fragmentation Pattern of Compound IV'.

4.3 Synthesis of monoaryl sulfonyl benzimidazolones:

For the synthesis of monoaryl sulfonyl benzimidazolones, monoprotected benzimidazolones were sulfonylated and then deprotection was carried out according to Scheme-II following the methods reported in the literature[46]. Purity of all the monoprotected sulfonylated benzimidazolones **VI(a-b)** and **VI'b**, was established by TLC. Yields were quite good ranging from 55.56-87.5%. Physical data of compounds **V(a-b)**, **V'b** and **VI(a-b)**, **VI'b** is shown in Table 4.3.1.

The IR spectra of all these compounds showed a band at 1182-1193 cm^{-1} for $R-SO_2-N$ asymmetric stretching and 1340-1345 cm^{-1} for symmetric stretching. Disappearance of band at 3361-3365 cm^{-1} for NH stretching in IR spectra of **V(a-b)**, **V'b**, also indicated the sulfonylation of the benzimidazolone, and then again appearance of this band in IR spectra of **VI(a-b)**, **VI'b**, indicated the deprotection. IR spectra showed a band for CH_3- stretching at 2925-2975 cm^{-1} in compounds **V(a-b)**, **V'b**, which was absent in **VI(a-b)**, **VI'b**. That was the indication of successful deprotection of the protected nitrogen of the benzimidazolones. Other major bands in IR spectra of these compounds were due to $\rangle C=O$ str. at 1765-1770 cm^{-1}, C-H aromatic in-plane deformation at 1331-1345 cm^{-1}, C=C aromatic vib. at 1374-1391 cm^{-1}, C-H aromatic out of plane vib. at 890-902 cm^{-1} in all compounds and Ar-No_2 stretching at 1515 cm^{-1} only in compounds **V'b** and **VI'b**. IR spectroscopic data of **V(a-b)**, **V'b** and **VI(a-b)**, **VI'b** is tabulated in Table 4.3.2.

The ^{1}H-NMR spectra of compounds **V(a-b)**, **V'b** and **VI(a-b)**, **VI'b**, showed that proton H-4 resonated at 7.36-8.10 ppm. H-5/6/7 resonated at 7.11-7.34 ppm, H-5 at 8.21-8.35 ppm as doublet of doublet with coupling constant of 8.2-8.6 and 2.2-2.3 Hz. H-7 at 8.71 ppm as doublet with coupling constant of 2.14 Hz. H-a/a' at 7.98-8.03 ppm as doublet of doublet with coupling constant of 7.0-8.2 Hz as ortho coupling constant and 1.2-2.1 Hz as meta coupling constant. Protons H-b/b' resonated at 7.28-7.33 ppm as doublet with coupling constant of 8.0-8.1 Hz. Aromatic protons of naphthyl group resonated in the range of 7.60-8.98 ppm.

The ^{1}H-NMR spectra of **VI(a-b)** and **VI'b** showed that NH-proton resonated at 7.27-9.8 ppm. signal for NH-proton in **VI(a-b)** and **VI'b** indicated the successful deprotection of amine group of benzimidazolones and the formation of monoaryl sulfonyl benzimidazolones. Detailed ^{1}H-NMR data of compounds **V(a-b)**, **V'b** and **VI(a-b)**, **VI'b** is shown in Tables 4.3.3. and 4.3.4.

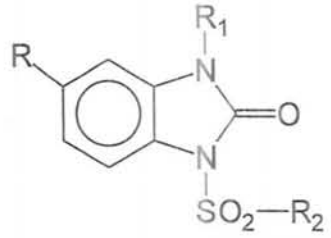
Mass spectroscopic studies of compounds **V(a-b)** and **VI(a-b)** have been carried out. The mass spectra of compounds **V(a-b)** showed molecular ion peaks with low intensities (8.73-9.43%). Base peak in **Va** was observed due to II-C_4H_8 (m/z=288). Peak II was formed by the loss of CO_2 molecule from $M^{+\bullet}$-peak. In compound **Vb**, base peak was observed due to XII-SO_2 (m/z=127), which is a peak of naphthyl group. Other major peaks with their relative intensities are tabulated in Table 4.3.5.

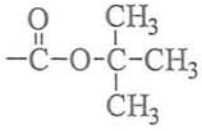
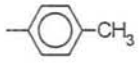
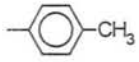
Molecular ion peaks in compounds **VI(a-b)** was observed with relatively high intensities (35.62-64.66%). Base peak in **VIa** was due to $M^{+\bullet}$-$C_7H_7SO_2]^{\bullet}$ (m/z=133). Other major peaks were VI-SO_2 (m/z=91), $M^{+\bullet}$-$C_7H_5SO_2]^{\bullet}$ (m/z=155). In compound **VIb**, base peak was due to XV-SO_2 (m/z=127). The peak XV was formed by the loss of $C_7H_5N_2O]^{\bullet}$ from the $M^{+\bullet}$-peak. Other major peaks with their relative intensities are listed in Table 4.3.6. Mass fragmentation pattern of all these compounds **V(a-b)** and **VI(a-b)** are shown in Fig. 4.3.1-4.3.4.

From the mass fragmentation patterns of these compounds, it is indicated that in compound **V(a-b)**, $M^{+\bullet}$-peak consists of a heterocyclic moiety with two nitrogen atoms. One of the two nitrogen atoms have t-butoxy carbonyl group and at other nitrogen, aryl sulfonyl group is present. These finding suggests the successful functionalization of free nitrogen atom of all nonprotected benzimidazolones. In compounds **VI(a-b)**, it is indicated that deprotection of protected nitrogen of the benzimidazolones has occurred and one of the nitrogen atom of the benzimidazolones is free. Other nitrogen atom has aryl sulfonyl group, which confirms the mono sulfonylation of the benzimidazolones.

Elemental analysis of these compounds **V(a-b)** and **VI(a-b)** was in accordance to the proposed structure (Table 4.3.7).

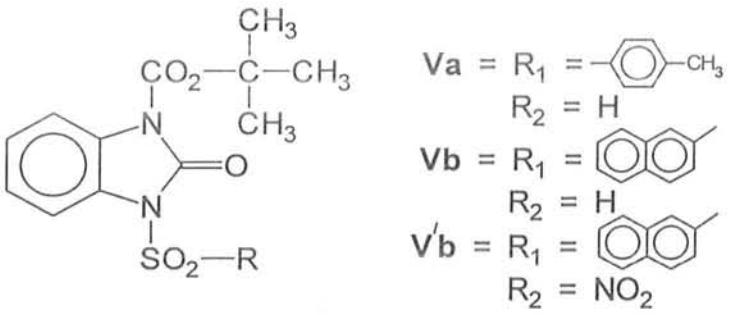
Table 4.3.1: Physical data of Compounds V(a-b), V′b, VI(a-b), VI′b.



S. No.	Comp.	R_1	R_2	R	m.p.°C	% Yield	R_f-Value
1.	Va			H	130-132	87.5	0.67 (Ethylacetate:n-hexane, 1:4)
2.	Vb	"		"	127	75.20	0.42 (Ethylacetate:n-hexane, 1:4)
3.	V′b	"	"	NO_2	295-297	55.56	0.59 (Ethylacetate:n-hexane, 1:4)
4.	VIa	H		H	208-210	81.08	0.18 (Ethylacetate:n-hexane, 1:2)
5.	VIb	H		H	206	70.21	0.21 (Ethylacetate:Pet.ether, 1:2)
6.	VI′b	H	"	NO_2	325	62.15	0.15 (Ethylacetate:Pet.ether, 1:2)

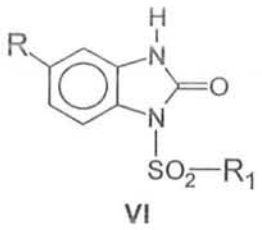
81

Table 4.3.2: IR Spectroscopic data of Compounds Va, Vb and V'b.

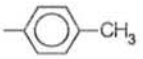


S. No.	Vibrational Mode	Va(cm^{-1})	Vb(cm^{-1})	V'b(cm^{-1})
1.	O ‖ –C– amide, str.	1765	1770	1715
2.	O ‖ –C–O–, str.	1790	1791	1761
3.	C–H, aromatic inplane deformation	1152	1152	1182
4.	C–H, vib. deformation	1345	1345	1331
5.	C=C, vib., aromatic	1390	1391	1374
6.	C–H, aromatic out of plane vib.	890	891	902
7.	=C–H, aromatic str.	3195	3190	3125
8.	CH_3– str.	2975	2970	2925
9.	R–SO_2–N, asym. str.	1193	1190	1182
10.	R–SO_2–N, sym. Str.	1345	1340	1345
11.	Ar–NO_2	—	—	1515

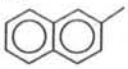
Table 4.3.3: IR Spectroscopic data of Compounds VIa, VIb and VI'b.



VI

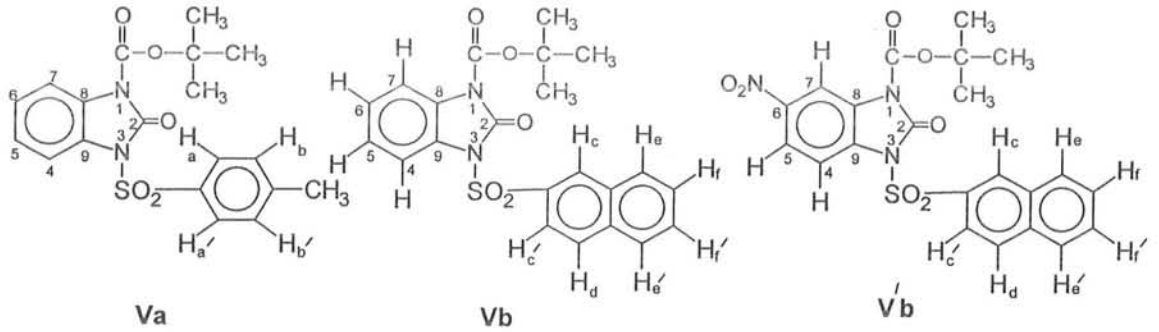
VIa = R_1 =  R_2 = H

VIb = R_1 =  R_2 = H

VI'b = R_1 =  R_2 = NO_2

S. No.	Vibrational Mode	VIa (cm^{-1})	VIb (cm^{-1})	VI'b (cm^{-1})
1.	$-\overset{O}{\overset{\|\|}{C}}-$, amide, str.	1760	1765	1701
2.	C–H, aromatic inplane deformation	1152	1152	1152
3.	C–H, vib. deformation	1340	1340	1333
4.	C=C, vib., aromatic	1389	1880	1375
5.	C–H, aromatic out of plane vib.	888	870	902
6.	=C–H, aromatic str.	3160	3182	3128
7.	CH_3– str.	2975	—	—
8.	R–SO_2–N, asym. str.	1190	1180	1183
9.	R–SO_2–N, sym. str.	1340	1340	1346
10.	Ar–NO_2 str.	—	—	1525

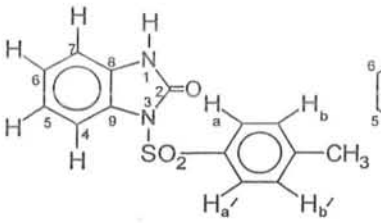
Table 4.3.4: ^{1}H-NMR data of Compounds V(a-b), V'b.



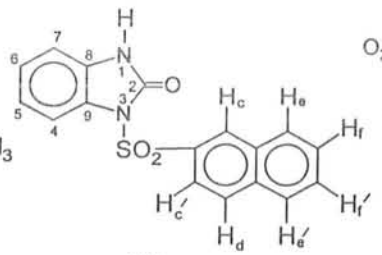
Va Vb V'b

S. No.	No. of Protons	Va (ppm)	Vb (ppm)	V'b (ppm)
1.	H-4	7.8 (dd, 1H), J_{4-5} = 1.63 Hz, J_{4-6} = 1.0 Hz	7.7 (dd, 1H), J_{4-5} = 1.7 Hz, J_{4-6} = 1.3 Hz	7.36 (d, 1H), J_{4-5} = 8.0 Hz
2.	H-5	—	—	8.21 (dd, 1H), J_{5-4} = 8.6 Hz, J_{5-7} = 2.26 Hz
3.	H-7	—	—	8.71 (d, 1H), J_{7-5} = 2.14 Hz
4.	H-5/6/7	720-7.27 (m, 3H)	7.23-7.34 (m, 3H)	—
5.	H-a/a′	8.03 (dd, 2H), J_{a-b} = 7.0 Hz, $J_{a-a'}$ = 1.2 Hz	—	—
6.	H-b/b′	7.33 (d, 2H), J_{b-a} = 8.0 Hz	—	—
7.	Hf	—	7.58 (t, 1H)	7.60 (t, 1H)
8.	Hf'	—	7.70 (t, 1H)	7.72 (t, 1H)
9.	H-e/e′, Hd	—	7.82 (m, 3H)	7.83 (m, 3H)
10.	H-c/c′	—	7.94 (d, 2H), $J_{c'-d}$ = 8.7 Hz	7.90 (d, 2H), $J_{c'-d}$ = 8.17 Hz
11.	H-Ar-CH_3	2.4 (s, 3H)	—	—
12.	H-t.Bu	1.6 (s, 9H)	1.6 (s, 9H)	1.6 (s, 9H)

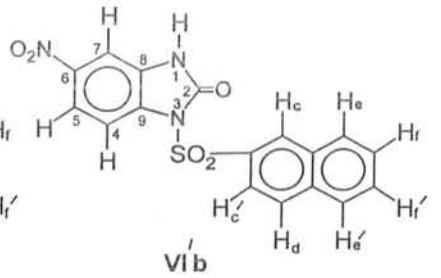
Table 4.3.5: ^{1}H-NMR data of Compounds VI(a-b), VI'b.



VIa



VIb



VI'b

S. No.	No. of Protons	VIa (ppm)	VIb (ppm)	VI'b (ppm)
1.	H-4	7.90 (d, 1H), J_{4-5} = 8.0 Hz	7.93 (d, 1H), J_{4-5} = 8.0 Hz	8.10 (d, 1H), J_{4-5} = 8.0 Hz
2.	H-5	—	—	8.35 (dd, 1H), J_{5-4} = 8.2 Hz, J_{5-7} = 2.3 Hz
3.	H-7	—	—	8.71 (d, 1H), J_{7-5} = 2.1 Hz
4.	H-5/6/7	7.11-7.21 (m, 3H)	7.13-7.20 (m, 3H)	—
5.	H-a/a′	7.98 (dd, 2H), J_{a-b} = 8.2 Hz, $J_{a-b'}$ = 2.1 Hz	—	—
6.	H-b/b′	7.28 (d, 2H), J = 8.1 Hz	—	—
7.	H-f	—	7.71 (t, 1H)	7.69 (t, 1H)
8.	H-f′	—	7.64 (t, 1H)	7.63 (t, 1H)
9.	H-e/e′, Hd	—	8.98 (m, 3H)	8.87 (m, 3H)
10.	H-c/c′	—	8.67 (d, 2H), J = 8.7 Hz	8.70 (d, 2H), J = 8.2 Hz
11.	H-Ar-CH_3	2.4 (s, 3H)	—	—
12.	H-NH	9.8 (s, 1H)	9.7 (s, 1H)	7.27 (s, 1H)

Table 4.3.6: Mass Spectroscopic data of Compounds Va and Vb.

S. No.	Peak	Va		Vb	
		m/z	%	m/z	%
I	$M^{+\bullet}$	388	9.43	424	8.73
II	$M^{+\bullet}$-CO_2	344	—	380	—
III	II-C_4H_8	288	100	324	47.65
IV	III-SO_2	224	15.42	260	13.30
V	IV-CO	196	1.66	232	2.71
VI	V-$C_7H_7]^{\bullet}$	106	12.53	105	11.53
VII	VI-N_2	77	3.81	77	3.81
VIII	IV-$C_7H_7]^{\bullet}$	133	73.40	—	—
IX	III-$C_7H_7SO_2]^{\bullet}$	155	50.47	—	—
X	IX-SO_2	91	47.65	—	—
XI	X-C_2H_2	65	8.38	—	—
XII	III-$C_7H_5N_2O]^{\bullet}$	—	—	191	35.06
XIII	XII-SO_2	—	—	127	100.00
XIV	$M^{+\bullet}$-$C_{10}H_7SO_2]^{\bullet}$	—	—	233	—
XV	XIV-CO_2	—	—	189	1.86
XVI	XV-C_5H_9NO	—	—	90	11.2

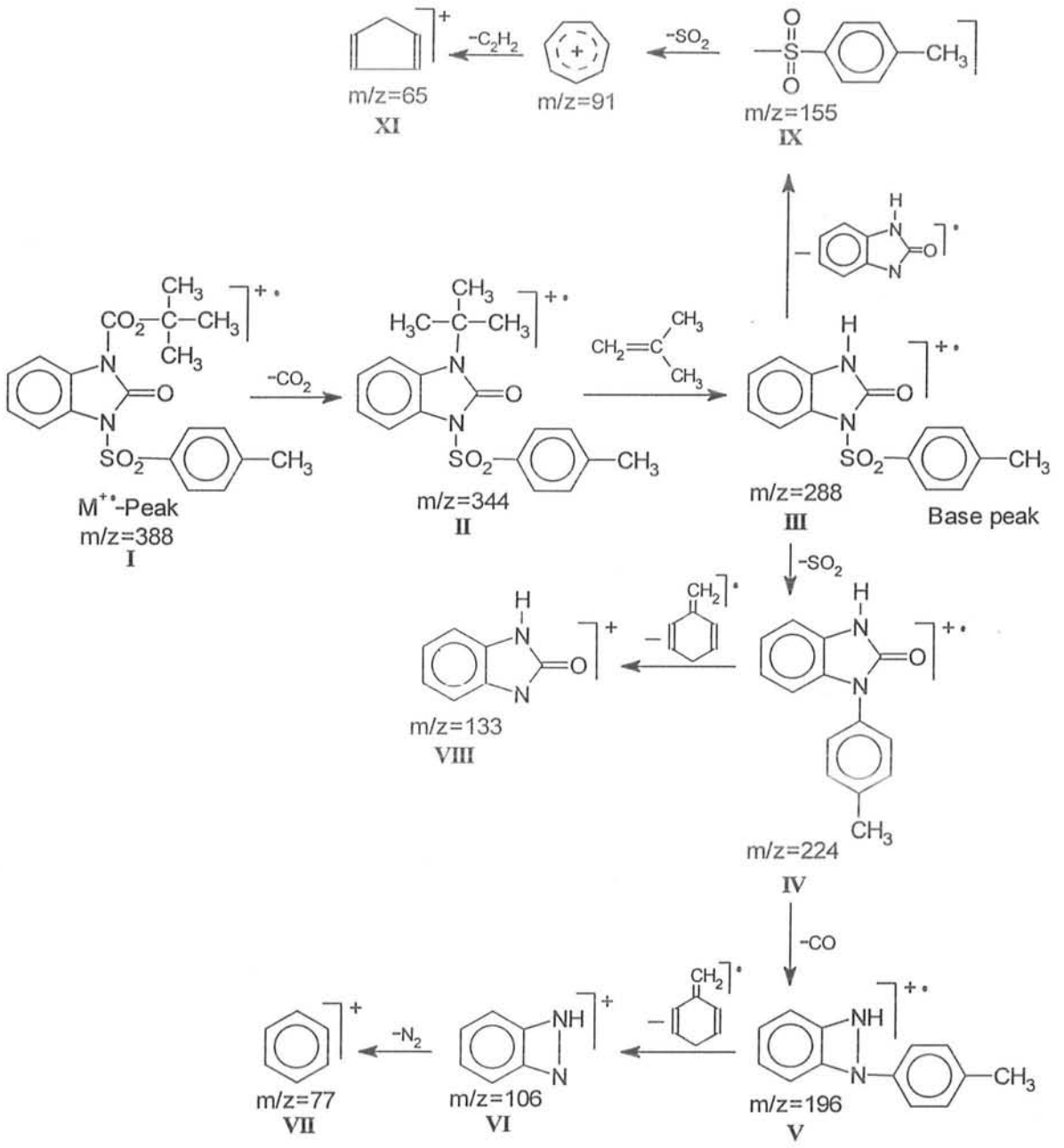


Fig. 4.3.1: Mass Fragmentation Pattern of Compound Va.

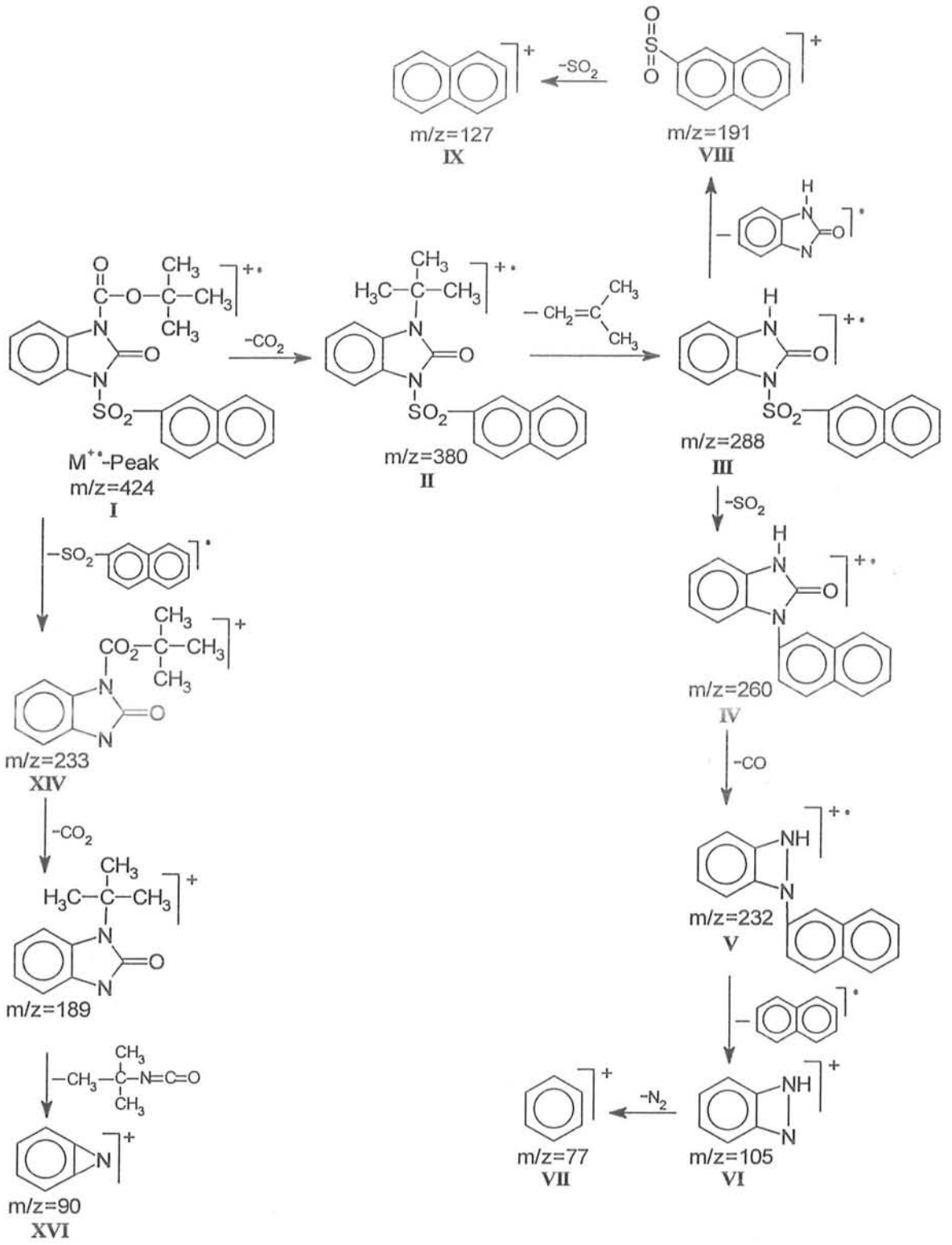


Fig. 4.3.2: Mass Fragmentation Pattern of Compound Vb.

Table 4.3.7: Mass Spectroscopic data of Compounds VIa and VIb.

S. No.	Peak	VIa		VIb	
		m/z	%	m/z	%
I	$M^{+\bullet}$	288	64.66	324	35.62
II	$M^{+\bullet}$-SO_2	224	16.27	260	15.27
III	II-CO	195	4.47	232	3.29
IV	III-$C_7H_7]^{\bullet}$	105	13.28	—	—
V	IV-N_2	77	5.88	—	—
VI	$M^{+\bullet}$-$C_7H_5N_2O]^{\bullet}$	155	41.39	—	—
VII	VI-SO_2	91	58.88	—	—
VIII	VII-C_2H_2	65	14.27	—	—
IX	$M^{+\bullet}$-$C_7H_7SO_2]^{\bullet}$	133	100.00	—	—
X	III-$C_{10}H_7]^{\bullet}$	—	—	105	10.23
XI	X-N_2	—	—	77	3.81
XII	$M^{+\bullet}$-$C_{10}H_7SO_2]^{\bullet}$	—	—	133	78.19
XIII	II-$H]^{\bullet}$	—	—	259	2.87
XIV	XIII-$C_{11}H_7NO$	—	—	90	11.2
XV	$M^{+\bullet}$-$C_7H_5N_2O]^{\bullet}$	—	—	191	15.21
XVI	XV-SO_2	—	—	127	100.00

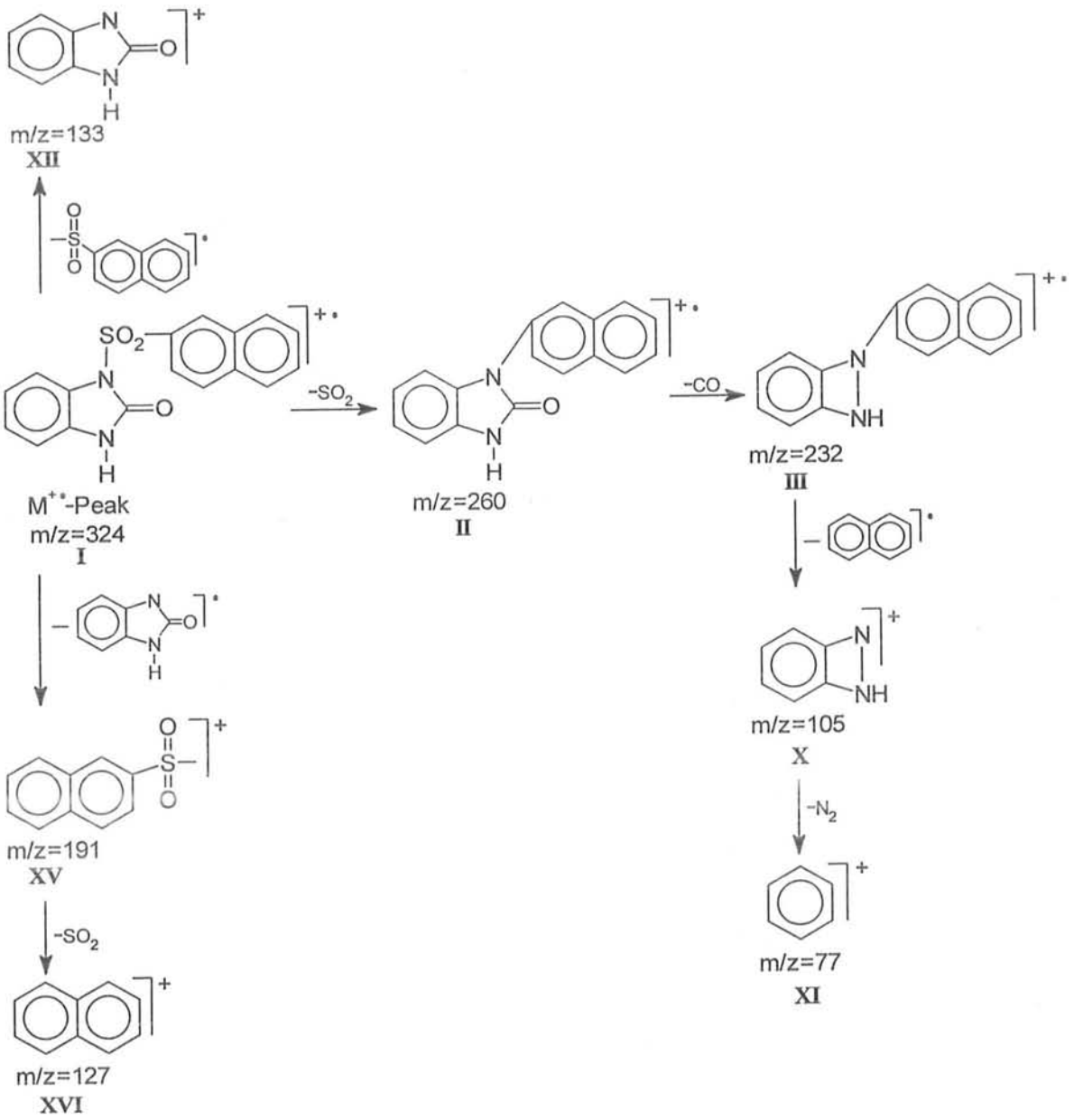


Fig. 4.3.4: Mass Fragmentation Pattern of Compound VIb.

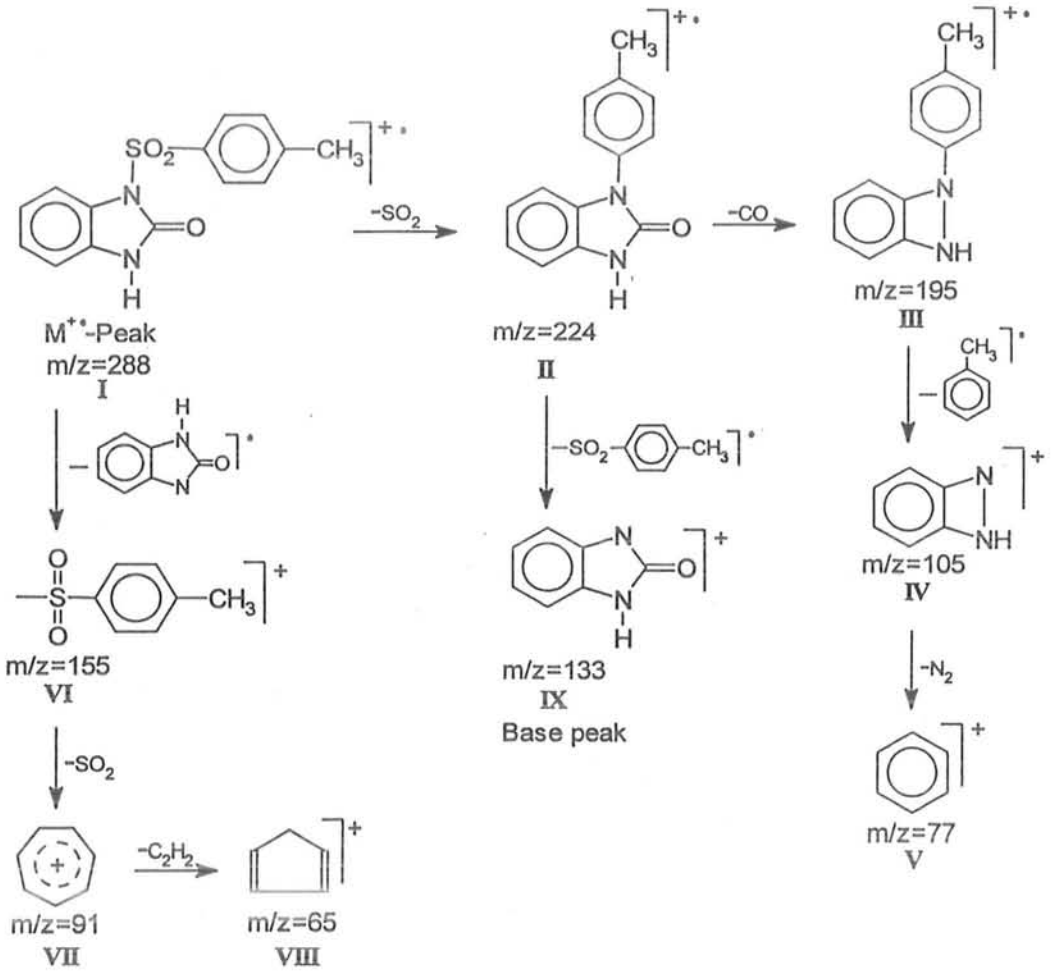


Fig. 4.3.3: Mass Fragmentation Pattern of Compound VIa.

Table 4.3.8: Elemental Analysis of Compounds V(a-b), V′b and VI(a-b), V′b.

S. No.	Elements	Va		Vb		V′b		VIa		VIb		VI′b	
		% Cal.	% Found	% Cal.	% Found	% Cal.	% Found	% Cal.	% Found	% Cal.	% Found	% Cal.	% Found
1.	C	58.61	59.66	62.26	62.12	56.28	56.62	58.33	58.22	62.96	62.01	55.28	55.31
2.	H	5.40	5.29	4.72	4.31	4.05	4.01	4.17	4.24	3.70	3.59	2.98	2.95
3.	N	7.20	7.31	6.60	6.54	8.95	8.84	9.72	9.72	8.64	8.54	11.38	19.31

4.4 Synthesis of aryl/heterocyclic sulfonyl hydantoins:

As mentioned in plan of work, the aim of the project was to synthesize aryl/hetrocyclic sulfonyl cyclic ureas. Aryl/heterocyclic sulfonyl hydantoins are also the cyclic ureas in which the aryl/heterocyclic sulfonyl group may be attached to N-1 or N-3. Normally, when the hydantoins are coupled with sulfonyl chlorides, the major product is 3-sulfonyl hydantoins, which can be rearranged to 1-sulfonyl hydantoins. It is well known fact that 1-substituted hydantoins are more active than 3-substituted sulfonyl hydantoins in their antidiabetic activity.

For this purpose 3-aryl/heterocyclic sulfonyl hydantoins **VIIIa, VIIIf, VIIIh, VIIIu** and 1-aryl sulfonyl hydantoins **IXf** and **IXh** were prepared by following the methods reported in literature[11,46]. Yields were quite good in case of aryl sulfonyl hydantoins, but was low in case of heterocyclic sulfonyl hydantoin **VIIIu**. 3-Aryl/heterocyclic sulfonyl hydantoins, were prepared by coupling aryl/heterocyclic sulfonyl chlorides with hydantoins in the presence of Et_3N and dimethyl aminopyridine (DMAP). (Scheme-III). 1-Aryl sulfonyl hydantoins **IXf** and **IXh** were prepared from 3-aryl sulfonyl hydantoins **VIIIf** and **VIIIh** through a rearrangement, using sodium hydride in dry benzene. Compounds **VIIIa, VIIIf, VIIIh VIIIu** and **IXf**, were found pure, but compound **IXh** was found to be impure after ^{1}H-NMR spectroscopic studies. It was found that it contains 3-aryl sulfonyl hydantoin along with 1-aryl sulfonyl hydantoin, which indicated that rearrangement of the aryl sulfonyl group was not occurred completely in this case. This was also evident from the % yield of **IXh**, which is 51.25%. In case of compound **IXf** % yield is 70%. Observed melting points, % yields and R_f-values of all 3-aryl/heterocyclic sulfonyl hydantoins and 1-aryl sulfonyl hydantoins are listed in Table 4.4.1.

IR spectra of all these compounds showed band at 1329-1347 cm^{-1} due to R–SO_2–N stretching. All these compounds exhibited –CO_2–NH– stretching vib. at 3350-3385 cm^{-1}, ⟩C=O stretching at 1714-1765 cm^{-1}, aromatic C=C stretching vib. at 1592-1607 cm^{-1}, CH_3– stretching at 2875-2960 cm^{-1}, C–H aromatic out of plane deformation at 1329-1347 cm^{-1} and CH_3– deformation vib. at 1442-1446 cm^{-1}. In case of heterocyclic sulfonyl hydantoin, band for heterocyclic moiety also appeared in IR spectrum of the

compound **VIIIu**. The most prominent band was due to =C–O– at 1246 cm^{-1}. This indicated the presence of heterocyclic moiety in the structure of the compound. IR spectroscopic data of these compounds is shown in Table 4.4.2.

The ^{1}H-NMR spectra of compounds **VIIIf** and **VIIIh** showed that methyl protons attached with hydantoin ring resonated at 1.8 ppm as a singlet. Methyl protons of aromatic ring in both the cases resonated at 2.3-2.45 ppm as singlet. Down field shift in aromatic methyl protons was due to resonance effect. In compounds **VIIIf** and **VIIIh**, H-a/a′ resonated at 7.95-8.0 ppm as doublet. In **VIIIh** H-b/b′ resonated at 7.36 ppm. In **VIIIf** H-b/b′was not distinguishable due to the overlapping of aromatic protons of phenyl group at 5-postion of hydantoin ring. Thus remaining aromatic protons in **VIIIf** appeared at 7.26-7.4 ppm as multiplet. NH–proton in both cases appeared at 6.40-6.70 ppm.

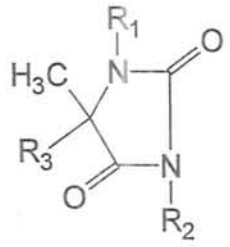
The ^{1}H-NMR spectra of **IXf** and **IXh**, showed that methyl protons of hydantoin ring appeared at 1.7-1.8 ppm as singlet, while methyl proton of aromatic ring appeared at 2.2-2.5 ppm. NH–proton appeared at 3.8-7.52 ppm. Other aromatic protons were not distinguishable due to overlapping of aromatic protons of phenyl group and tosyl group. It was observed that in case of 3-aryl sulfonyl hydantoin **VIIIf**, H-a/a′ and H-b/b′ were distinguishable, but in **VIIIf** only H-a/a′ was distinguishable. In case of **IXf** and **IXh** a complex multiplet is observed due to the overlapping of aromatic protons at 5-position of hydantoin. ^{1}H-NMR spectroscopic data of these compounds **VIIIf**, **VIIIh** and **IXf**, **IXh** is shown in Table 4.4.3.

Mass spectroscopic studies of compounds **VIIIf** and **IXf** has also been carried out. In both compounds $M^{+\bullet}$–peak was not observed. In compound **IXh**, peak with m/z=280 was observed due to the loss of SO_2– molecule from $M^{+\bullet}$–peak. The intensity of the peak was 21.30%. Peak with m/z=189 was observed in both the compounds due to the loss of $C_7H_7\rceil^{\bullet}$ from II. The intensity of this peak in **VIIIf** was 100% that means, it was base peak, while in **IXf** its intensity was 14.24%. This clearly indicates the stability of two regio isomers. Similarly base peak in **VIIIf** was V–NHCO (m/z=146), which was 31.95% in intensity in compound **VIIIf**. Other major peaks were XII-SO_2 (m/z=91) with intensity 14.92% in compound **VIIIf** and 73.62% in compound **IXf**. Peak XVI–CO (m/z=104) with intensity 16.50% in compound **VIIIf** and 34.52% in compound **IXf**.

Formation of peaks II, IV, V, XIII, XVI is shown in mass fragmentation patterns of compounds **VIIIf** and **IXh** in Fig. 4.4.1.

These findings suggests that $M^{+\bullet}$–peak in three compounds consists of a heterocyclic moiety with two nitrogen atoms and an aryl sulfonyl group attached at one of the two nitrogen atoms of the heterocyclic moiety. Mass spectroscopic data of compounds **VIIIf** and **IXf** is tabulated in Table 4.4.4.

Table 4.4.1: Physical data of Compounds VIIIa, VIIIf, VIIIh and IXa, IXf, IXh.



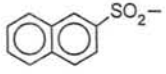
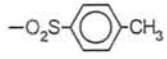
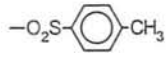
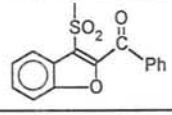
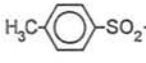
S. No.	Compound	R_1	R_2	R_3	m.p.°C	% Yield	R_f-Value
1.	**VIIIa**	H			380	70	0.53 (Ethylacetate:Pet.ether, 1:2)
2.	**VIIIh**	H		CH_3	173-174	67.87	0.87 (Ethylacetate:Pet.ether, 1:2)
3.	**VIIIf**	H			191	77.78	0.69 (Ethylacetate:Pet.ether, 1:2)
4.	**VIIIu**	H		"	270	31	0.8 (Ethylacetate:Pet.ether, 1:2)
5.	**IXh**		H	CH_3	144-145	51.25	0.35 (Ethylacetate:Pet.ether, 1:2)
6.	**IXf**	"	"		178-180°C	70	0.89 (Ethylacetate:Pet.ether, 1:2)

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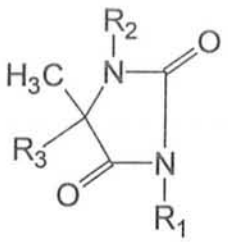
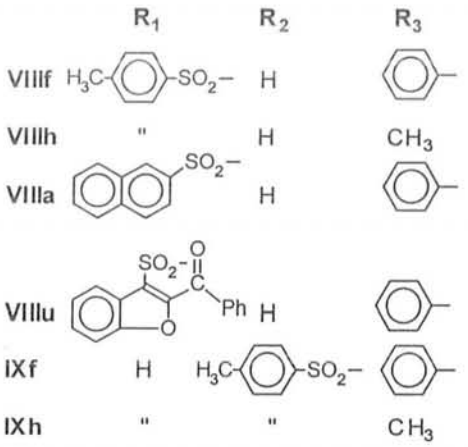
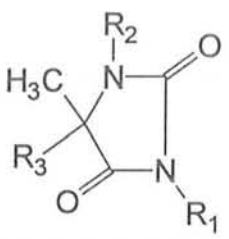
Table 4.4.2: IR spectroscopic data of Compounds VIIIf, VIIIh, VIIIa, VIIIu, IXf and IXh.

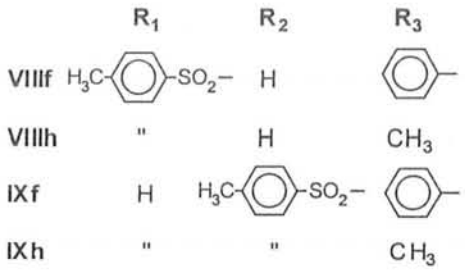




S.No.	Vibrational Mode	VIIIf (cm^{-1})	VIIIh (cm^{-1})	VIIIa (cm^{-1})	VIIIu (cm^{-1})	IXf (cm^{-1})	IXh (cm^{-1})
1.	–C(=O)–NH, Sec.amide str. vib.	3385	3385	3350	3270	3385	3385
2.	>C=O, Str.	1715	1714	1746	1751	1765	1765
3.	C=C, Ar. str. vib.	1607	1606	1592	1596	1606	1607
4.	CH_3– Str.	2958	2960	2875	2934	2950	2958
5.	C–H, aromatic out of plane deformation	775	776	907	873	812	814
6.	R–SO_2–N–, Str. vib.	1336	1329	1329	1333	1347	1347
7.	CH_3-deformation	1442	1442	1446	1441	1442	1442
8.	=C–O– Str. vib.	—		—	1246	—	—

Table 4.4.3: ^{1}H-NMR spectroscopic data of Compounds VIIIf, VIIIh and IXf, IXh.





S.No.	No. of Protons	VIIIf (ppm)	VIIIh (ppm)	IXf (ppm)	IXh (ppm)
1.	H–CH_3	1.8(s,3H)	—	1.8(s,3H)	—
2.	H–Ar–CH_3	2.45(s,3H)	2.3(s,3H)	2.25(3H)	2.5(s,3H)
3.	H-a/a′	7.95(d,2H)	8.0(d,2H)	—	—
4.	H-b/b′	—	7.36(d,2H, J=10.29 Hz	—	—
5.	H–2CH_3	—	1.9(s,6H)	—	1.7(s,6H)
6.	H–NH	6.40(s,1H)	6.70(s,1H)	3.8(s,1H)	7.52(s,1H)
7.	Other aromatic protons	7.26-7.4 (m,7H)	—	6.5-7.5 (m,9H)	7.2-8.2 (m,4H)

Table 4.4.4: Mass Spectroscopic data of Compounds VIIIf and IXf.

S. No.	Peak	VIIIf		IXf	
		m/z	%	m/z	%
I	$M^{+\bullet}$	344	—	344	—
II	$M^{+\bullet}$-SO_2	280	—	280	21.36
III	II-$C_6H_7]^{\bullet}$	189	100.00	189	14.24
IV	III-CO	161	—	161	7.23
V	$M^{+\bullet}$-$C_7H_5SO_2]^{\bullet}$	189	100	189	14.24
VI	V-NHCO	146	31.95	146	100.00
VII	VI-CO	118	1.87	118	9.06
VIII	$M^{+\bullet}$-$C_{11}H_{11}N_2O_4S]^{\bullet}$	77	10.00	77	—
IX	$M^{+\bullet}$-$C_6H_5]^{\bullet}$	267	—	267	—
X	IX-SO_2	203	—	203	—
XI	X-C_8H_7NO	70	14.23	70	11.90
XII	$M^{+\bullet}$-$C_{10}H_9]^{\bullet}$	155	2.70	155	—
XIII	XII-SO_2	91	14.92	91	73.62
XIV	VIII-C_2H_2	65	6.76	65	—
XV	II-$CH_3]^{\bullet}$	265	1.50	265	6.36
XVI	XV-C_8H_7NO	132	2.01	132	2.67
XVI	XVI-CO	104	16.50	104	34.52

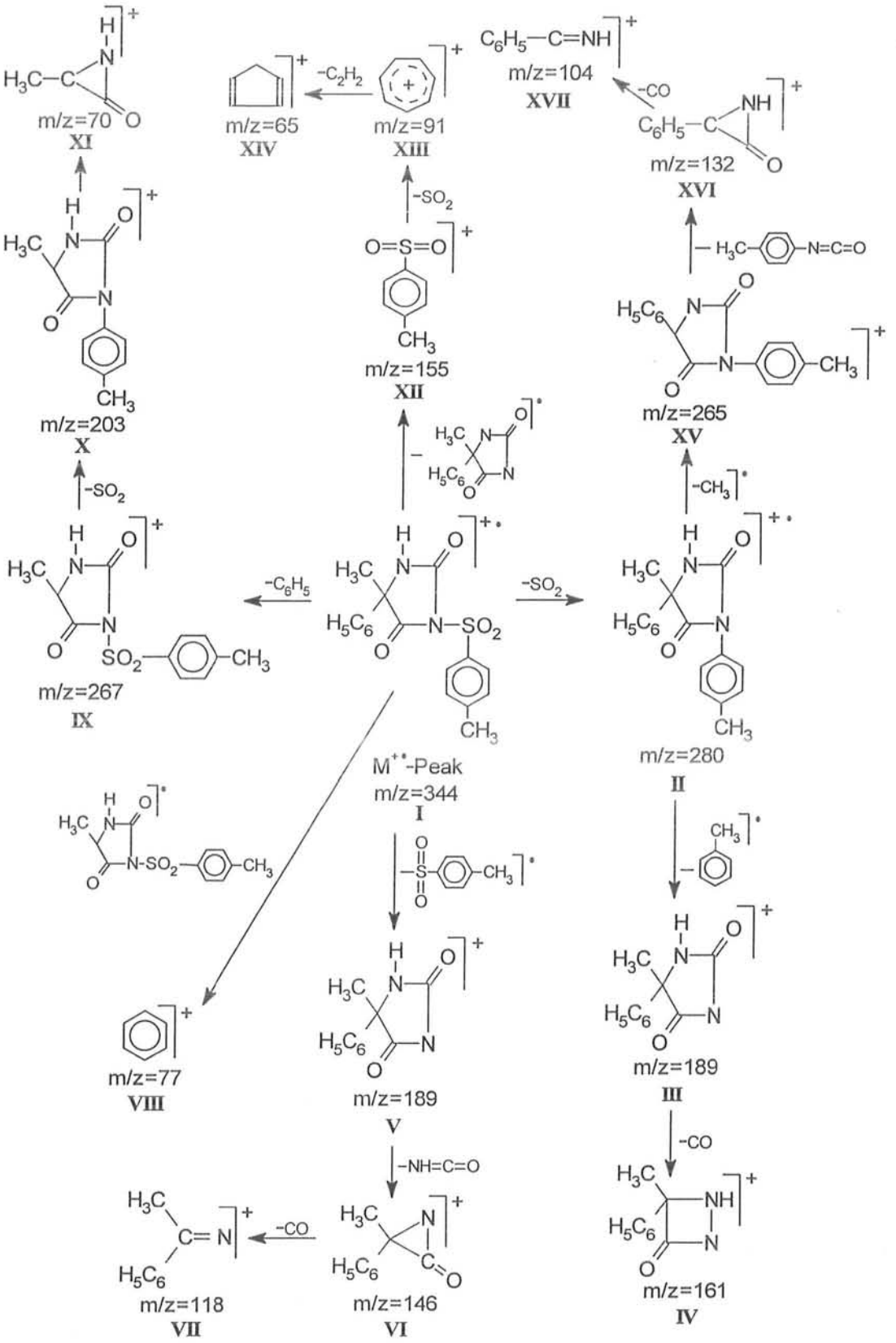


Fig. 4.4.1: Mass Fragmentation Pattern of Compound VIIIf and IXf.

Table 4.4.5: Elemental Analysis of Compounds VIIIa, VIIIf, VIIIh, IXf and IXh.

S.No.	Elements	VIIIa		VIIIf		VIIIh		IXf		IXh	
		%Cal.	%Found	%Cal.	%Found	%Cal.	%Found	%Cal.	%Found	%Cal.	%Found
1.	C	63.18	62.94	59.29	59.12	50.05	52.0	59.29	58.92	51.05	50.13
2.	H	4.24	4.11	4.68	4.6	5.0	4.69	4.68	4.63	5.0	5.93
3.	N	7.36	7.37	8.13	7.97	9.92	9.60	8.13	7.80	9.92	9.79

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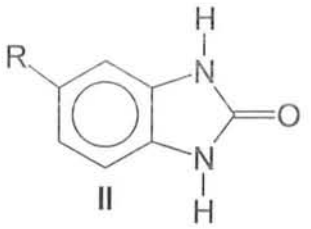
4.5 Synthesis of cyclic ureas:

Three types of cyclic urea,s, "benzimidazolone", "hydantoins" and "perhydro 1,3-diazepin 2,4-dione" were under consideration. Benzimidazolones and hydantoins were successfully prepared, but perhydro 1,3-diazepin 2,4-dione was not prepared due to non-availability of chemicals especially ethyl chloroformate. However, we were able to prepare the starting material glutaric anhydride and glutaric acid monoamide following the methods reported in literature[13] (Scheme-VIII). Physical data of gultaric anhydride and gultaric acid monoamide is tabulated in Table 4.5.4.

Benzimidazlones were prepared by two methods[55,57] (Scheme VIa & VIb). For unsubstituted benzimidazolone yield was good in method a, but for nitrosubstituted benzimidazolones yield was not good. Compounds synthesized by both the methods were highly pure and their purity was established by TLC. Two benzimidazolones **II** and **II'** were prepared. Observed melting points, % yield and R_f-values are listed in Table 4.5.1.

Five different hydantoins **VII** (**a-e**) were prepared according to Scheme-VII. All the five hydantoins prepared were pure and had sharp melting points. Yields were good (75-78%) and purification was done only by simple recrystallization. Physical data of compounds **VII** (**a-e**) is listed in Table 4.5.2. These five hydantoins synthesized were identified by IR spectroscopic studies. The IR spectra of all these compounds showed $-CO_2-NH-$ sec.amide str. vib. at 3215-3280 cm^{-1}, $\rangle C=O$ stretching at 1760-1775 cm^{-1}, CH_3- stretching vib. at 2928-3090 cm^{-1}, aromatic C–H, out of plane deformation at 766-871 cm^{-1}, C=C aromatic vib. at 1550-1605 cm^{-1}, C–Cl at 752 cm^{-1}, CH_3-O- at 1019 cm^{-1} and $C-CH_3$ deformation vib. were exhibited at 1456 cm^{-1}. IR spectroscopic data of all these compounds is tabulated in Table 4.5.3.

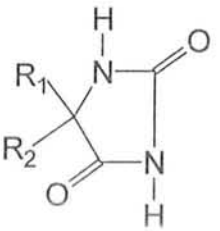
Table 4.5.1: Physical data of Compounds II and II'.



II

S. No.	Comp.	R	m.p.°C	% Yield	R_f-Value
1.	II	H	>300	75 (lit. 70)	0.75 (Ethylacetate:Pet.ether, 1:2)
2.	II'	NO_2	>300	30 (lit. 40)	0.55 (Ethylacetate:Pet.ether, 1:2)

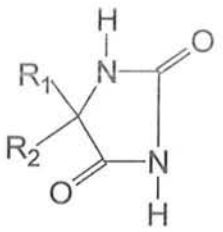
Table 4.5.2: Physical data of Compounds VII (a-b).



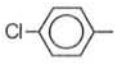
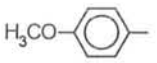
VII

S. No.	Comp.	R_1	R_2	m.p.°C	% Yield	R_f-Value
1.	VIIa	CH_3	C_6H_5	210 (lit.212)	78(lit.70)	0.64 (Ethylacetate:Pet.ether) (2:1)
2.	VIIb	C_6H_5	C_6H_5	290 (lit.289)	75(lit.69)	0.7 (Ethylacetate:Pet.ether) (2:1)
3.	VIIc	CH_3	CH_3	180 (lit.182)	78(lit.75)	0.59 (Ethylacetate:Pet.ether) (2:1)
4.	VIId		H	176 (lit.178)	76(lit.78)	0.6 (Ethylacetate:Pet.ether) (2:1)
5.	VIIe		H	190 (lit.195)	75(lit.76)	0.55 (Ethylacetate:Pet.ether) (2:1)

Table 4.5.3: IR spectroscopic data of Compounds VII (a-e).



VII(a-e)

	R_1	R_2
a)	CH_3	C_6H_5
b)	C_6H_5	C_6H_5
c)	CH_3	CH_3
d)		H
e)		H

S.No.	Vibrational Mode	VIIa (cm^{-1})	VIIb (cm^{-1})	VIIc (cm^{-1})	VIId (cm^{-1})	VIIe (cm^{-1})
1.	 str. vib.	3280	3280	3271	326	3215
2.	>C=O, Str.	1763	1760	1760	1767	1715
3.	CH_3– Str. vib.	2990		2981		
4.	C–H, aromatic out of plane deformation	766	871	—	858	823
5.	C=C, aromatic vib.	1593	1592	—	1550	1605
6.	C–CH_3, deformaiton vibration	1441	—	1441	—	—
7.	C–Cl, Vib. str.	—	—	—	752	—
8.	CH_3–O– Vib. str.	—	—	—	—	1019

Table 4.5.4: Physical data of Glutaric anhydrides and Glutaric acid monoamides.

S. No.	Compound Name	m.p.°C	% Yield	R_f-Value
1.	2,4-dimethylglutaric anhydride	80 (lit.80)	96.85 (lit.90)	0.8 (Benzene
2.	2,2-dimethylglutaric anhydride	34-35 (lit.35)	87.6 (lit.90)	0.52 (Benzene)
3.	3,3-dimethylglutaric anhydride	120-121 (lit.22)	90.14 (lit.90)	0.54 (Benzene)
4.	2,2-dimethylglutaric acid monoamide	125	69	0.73 (Ethylacetate:Pet.ether) (1:1)
5.	3,3-dimethylglutaric acid monoamide	112	71.42	0.51 (Ethylacetate:Pet.ether) (1:1)

4.6 Synthesis of aryl/heterocyclic sulfonyl chlorides:

As mentioned in the previous section, the aim of this project was the synthesis of aryl/heterocyclic sulfonyl cyclic ureas. For this purpose aryl/heterocyclic sulfonyl chlorides were required. Thus a major portion of this project was the synthesis of different aryl/heterocyclic sulfonyl chlorides. Two aryl sulfonyl chlorides were selected, p-toluene sulfonyl chloride and 2-naphthalene sulfonyl chloride. P-toluene sulfonyl chloride was available in the lab. So we decided to prepare 2-naphthalene sulfonyl chloride only. 2-Naphthalene sulfonyl chloride was prepared[59] from naphthalene, conc. H_2SO_4 and PCl_5 by heating at 170-180°C (Scheme-X). Naphthalene sulfonyl chloride was purified by fractional distillation under reduced pressure. Yield was good.

For the synthesis of heterocyclic sulfonyl chlorides, a number of heterocyclic compounds were prepared, which includes, 5-bromobenzo [b] furan[60], 6,7-dichloro benzo [b] furan[60], 5-bromo-3-methyl benzo [b] furan[62], 5-chloro-3-methyl benzo [b] furan[62], 2-benzoyl benzo [b] furan[61], 3,5-dimethyl isoxazole[63], 3,5-methyl phenyl isoxazole[63] and 3,5-diphenyl isoxazole[63]. All these heterocyclic compounds were synthesized according to the Schemes XI, XII, XIII and XIV. Yields were good in all the cases ranging from 52-89%. 3,5-Disubstituted isoxazoles were prepared by the reaction of β-diketone and hydroxyl amine. Physical data of all the synthesized compounds along with their UV and IR spectroscopic data is shown in Table 4.5.1.

The chlorosulfonylation of these heterocyclic compounds was carried out according to the methods reported in literature[60], in which heterocycles having one removable hydrogen are treated with lithiumdiisopropylamide (LDA) to generate the carbanion. Lithiumdiisopropylamide was also prepared in the lab using n-butyl lithium and diisopropyl amine. This reactive carbanion was reacted with SO_2 to give lithium heterocycle sulfinate (Scheme XI, XII, XIII, XIV).

Sulferdioxide for the sulfonylation was also prepared in the lab, by the action of conc. H_2SO_4 on sodium sulfite. Sulferdioxide prepared was dried by passing it through conc. H_2SO_4 and calcium chloride towers. A special type of apparatus was designed to have the continuous supply of sulferdioxide. The lithium salt produced was reacted with N-chlorosuccinimide to give the chlorosulfonylated compounds **Ic**, **I** (**g-j**). All the

reactions were carried out under argon atmosphere at -50 to -78°C. Isolated products were send to Germany for spectroscopic studies. The ^{1}H-NMR and Mass spectroscopic studies revealed that different spectra of these compounds were not in accordance with the proposed structure. It appeared that succinimide was isolated in all the cases. Literature was surveyed to find out some other methods for chlorosulfonylation of heterocycles. It was found that in most of the cases LDA and n-butyl lithium was used to generate the reactive carbnaion. One thing was that, the n-butyl lithium we, were using was too much old. So we decided to have the fresh n-butyl lithium and decided to use n-butyl lithium directly instead of LDA for the generation of carbanion.

Reaction was carried out using n-butyl lithium, isolated product was subjected to UV spectroscopic studies. There was a difference in the UV spectrum of starting material and product isolated. Then IR spectrum of the compound was recorded, which indicated the $-SO_2Cl$ stretching vib. at 1374 cm^{-1} and =C–C=O stretching at 1665 cm^{-1}. IR spectrum indicated that chlorosulfonylation has been taken place. However, yield was quite low about 17.85%. Physical data of the heterocyclic sulfonyl chloride is shown in Table 4.6.1.

Table 4.6.1: Physical data along with IR Spectroscopic data of heterocyclic Compounds and heterocyclic suflonyl chloride Ig.

S.No.	Name of Compound	m.p/ b.p°C	% Yield	R_f-Value	$\lambda_{max}(\varepsilon)$	IR data (cm^{-1})
1.	6-bromo benzo [b] furan	178(b.p)	72.52	0.87 (Et.A:n-hex) 1:9	—	—
2.	6,7-dichloro benzo [b] furan	200(b.p)	62	0.72 (Et.A:n-hex) 1:9	—	—
3.	2-benzoyl benzo [b] furan	86-87 (lit.89)	70 (lit.69)	0.64 (Et.A:n-hex) 1:2	310.47 ($5.36x10^4$)	1636(⟩C=O), 1118(C-O-C), 1593(C=C)
4.	3,5-dimethyl isoxazole	142(b.p) (lit.142)	53 (lit.50)	0.55 (Et.A:P.Et) 1:1	225.93 ($1.34x10^5$)	—
5.	3,5-methyl phenyl isoxazole	59.7-61.2 (lit.60-62)	89.9 (lit.90)	0.56 (Et.A:P.Et) 1:1	240.02 ($1.58x10^5$)	1607 (C=C), 1566(C=N), 1598, Ar
6.	3,5-diphenyl isoxazole	138 (lit.138)	76 (lit.75)	0.58 (Et.A:P.Et) 1:1	250.94 ($1.44x10^5$)	1609 (C=C), 1587 (C=N), 1576, Ar
7.	5-chloro-3-methyl benzo [b] furan	192 (b.p)	65	0.68 (Et.A:P.Et) 1:1	—	—
8.	5-bromo-3-methyl benzo [b] furan	190 (b.p)	52	0.58 (Et.A:P.Et) 1:1	—	—
9.	2-benzoyl benzo [b] furan-3-yl-sulfonyl chloride	30	17.85	0.6 (Et.A:P.Et) 1:1	—	1118(C-O-C), 1665(⟩C=O), 1374(-SO_2Cl)

EXPERIMENTAL

5. Experimental:

All the solvents used were distilled. Dry solvents were used, where required. Diethyl ether, cyclohexane and n-hexane were dried using sodium wire. Tetrahydrofuran was dried using KOH and sodium wire. N,N-dimethyl formamide was dried by distilling over calcium hydride. Dichloromethane was dried by distilling over phosporus pentaoxide. Drying of compounds was carried out using drying pistol and vacuum desiccator with calcium chloride, silica gel, phosphorus pentaoxide and potassium hydroxide as desiccants.

All the reactions were monitored by thin layer chromatography (TLC), using Precoated Kieselgel-60 HF_{254} TLC plates, using different solvent systems. For the purification of compounds and for the separation of isomeric mixtures, column chromatography was used. Silica gel-60 (70-230 mesh ASTM) was used for packing the columns. For the purification of sulfonyl chlorides, flash column chromatography, under nitrogen atmosphere, was used. Columns of different sizes packed with silica gel were used. Melting points were recorded on Galenkamp digital melting point apparatus MGB-595-010-M. IR spectra were recorded on Schimadzu IR-460 spectrometer. UV spectra were recorded on UV-Spectrophotometer model Lambda 20. ^{1}H-NMR spectra of the synthesized compounds were scanned in $CDCl_3$ and D_2O on Brüker ^{1}H-NMR machine (400 MHz). Mass spectra, ^{13}C-NMR and elemental analysis were carried out at Hannover University, F.R. Germany.

5.1 General method for the preparation of 1,3-di-aryl/ heterocyclic sulfonyl benzimidazolones:

The standard procedure was followed[11]. Benzimidazolone (0.01 mol) was suspended in acetone (63 ml) in a three neck round bottomed flask, fitted with an air condenser and two dropping funnels. In one dropping funnel was taken IN NaOH solution (20 ml) and in other, solution of p-toluene/naphthalene sulfonyl chloride (0.02 mol) in acetone. To this suspension was added 1N NaOH solution and p-toluene/naphthalene sulfonyl chloride alternatively, dropwise with constant stirring. Temperature was maintained at 20-30°C. Mixture was stirred for one hour. Acetone was

removed in vacuo and residue was washed with water and recrystallized from chloroform and methanol (3:1).

5.1.1 1,3-Di(p-toluene sulfonly) benzimidazolone IIIa:

Yield = 83.79%, m.p. = 187°C.

R_f = 0.4 (Cyclohexane : Chloroform, 2:1).

IR (ν_{max}, KBr, cm^{-1})

3564, 3500, 3440, 3120, 3092, 2976, 2956, 2924, 1760, 1688, 1644, 1596, 1492, 1468, 1384, 1340, 1260, 1152, 1120, 1084, 1032, 980, 812, 664.

^{1}H-NMR ($CDCl_3$, 400 MHz), δ(ppm)

7.60 (dd, 2H, H-4, H-7, J_{7-6} = 7.0 Hz, J_{7-5} = 3.4 Hz), 7.70-7.92 (m, 2H, H-5, H-6), 7.95 (m, 4H, HaHa′), 7.31 (d, 4H, HbHb′, J_{a-b} = 8.5 Hz), 2.4 (s, 6H, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz), δ(ppm)

22 (C-CH_3), 128 (C-5/6), 132 (C-2′/6′), 114 (C-3′/5′), 146 (C-8/9), 134 (C-1′), 126 (C-4′), 147 (C-CO).

Mass: EI-MS, m/z (rel. int.%)

442 ($M^{+\bullet}$, 44.46), 379 (1.65), 378 (6.39), 289 (2.91), 288 (8.95), 287 (39.87), 224 (2.07), 223 (9.84), 222 (2.19), 221 (1.45), 209 (1.03), 208 (4.03), 195 (1.66), 193 (1.15), 181 (2.55), 180 (3.78), 179 (1.50), 167 (1.07), 165 (1.35), 159 (1.23), 157 (5.52), 156 (9.02), 155 (93.90), 141 (1.26), 140 (2.06), 139 (14.92), 134 (1.74), 133 (3.57), 124 (1.68), 107 (1.05), 106 (2.32), 105 (1.38), 104 (4.32), 93 (1.26), 92 (8.35), 91 (100.00), 90 (3.35), 89 (3.57), 79 (1.42), 78 (1.76), 77 (4.23), 66 (1.20), 66 (1.20), 65 (14.84).

Elemental analysis

Elements	% (calculated)	% (found)
C	57.00	56.84
H	4.10	4.03
N	6.33	6.26

5.1.2 1,3-Di(naphthalene-2-yl- sulfonyl) benzimidazolone IIIb:

Yield = 62.24%, m.p. = 186-188°C.

R_f = 0.31 (Cyclohexane : Chloroform, 2:1).

IR (ν_{max}, KBr, cm^{-1})

3496, 3432, 3116, 3056, 2928, 1812, 1756, 1624, 1588, 1504, 1468, 1384, 1304, 1260, 1184, 1156, 1072, 1032, 980, 952, 904, 856, 816, 784, 700, 565, 556.

^{1}H-NMR ($CDCl_3$, 400 MHz), δ(ppm)

7.30 (dd, 2H, H-4, H-7, J_{7-5} = 3.5 Hz, J_{7-6} = 6.2 Hz), 7.80-8.0 (m, 2H, H-5, H-6) 7.75 (t, 2H, $H_{f'}$), 7.68 (t, 2H, H_f), 7.94 (d, 4H, H-C, H-C′), 7.82 (m, 6H), H-e/e′, Hd).

^{13}C-NMR ($CDCl_3$, 100 MHz), δ(ppm)

125.25 (C-4/7), 128 (C-5/6), 135.5 (C-8/9), 134 (C-1′), 147.5 (C-CO), 122 (C-3′/4′/7′), 113 (C-6′), 129.5 (C-5′), 130.5 (C-2′/8′), 131 (C-9′/10′).

Mass: EI-MS, m/z (rel. int.%)

514 ($M^{+\bullet}$, 21.38), 452 (1.13), 451 (2.54), 450 (6.96), 386 (1.14), 326 (0.94), 325 (1.41), 324 (4.22), 323 (8.43), 261 (1.07), 260 (4.57), 259 (13.63), 256 (2.08), 253 (1.62), 252 (2.41), 232 (0.83), 231 (1.68), 229 (1.16), 218 (1.56), 217 (4.32), 216 (1.56), 215 (0.86), 204 (0.91), 193 (3.47), 192 (5.55), 191 (47.60), 176 (1.91), 175 (8.20), 161 (8.20), 160 (3.21), 159 (0.92), 147 (1.89), 134 (2.49), 133 (3.75), 129 (1.70), 128 (15.97), 127 (100.00), 126 (7.03), 125 (0.93), 116 (1.09), 115 (5.64), 106 (1.61), 104 (1.58), 102 (1.03), 101 (3.13), 91 (0.92), 79 (1.05), 78 (1.22), 77 (5.36), 76 (1.23), 75 (1.26), 74 (0.92), 69 (0.99).

Elemental analysis

Elements	% (calculated)	% (found)
C	63.02	62.18
H	3.53	3.46
N	5.44	5.19

5.1.3 1,3-Di(p-toluene sulfonyl)6-nitrobenzimidazolone IIIa′:

Yield = 96.77%, m.p. = 219-220°C.

R_f = 0.89 (Pet.ether : Ethylacetate, 1:1).

IR (ν_{max}, KBr, cm^{-1})

3436, 3132, 3068, 2952, 2924, 2860, 1772, 1596, 1528, 1472, 1442, 1396, 1344, 1280, 1192, 1152, 1116, 1084, 1040, 1004, 964, 888, 856, 812, 772, 744, 712, 660, 580.

^{1}H-NMR ($CDCl_3$, 400 MHz), δ(ppm)

8.88 (d, 1H, 4-H), 8.22 (dd, 1H, H-5, J_{5-4} = 9.03 Hz, J_{5-7} = 2.0 Hz), 8.92 (d, 1H, H-7, J_{7-5} = 2.03 Hz), 7.94-8.01 (m, 4H, HaHa′), 7.36 (d, 4H, HbHb′, J_{b-a} = 8.0 Hz), 2.4 (s, 6H, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz), δ(ppm)

147 (C–CO), 113 (C–4), 121 (C–5), 147.2 (C–6), 109 (C–7), 144.8 (C–8), 130 (C–9), 133.3 (C–1′), 128.3 (C–2′/6′), 130.1 (C–3′/5′), 126 (C–4′), 22 (C–CH_3).

Mass: EI-MS, m/z (rel. int.%)

487 ($M^{+\bullet}$, 26.05), 423 (5.66), 159 (2.51), 157 (5.69), 156 (9.49), 155 (100.00), 149 (2.65), 148 (2.84), 140 (2.67), 139 (9.32), 124 (3.83), 92 (9.47), 91 (77.17), 89 (3.98), 85 (4.44), 83 (5.03), 68 (2.75), 65 (11.15).

Elemental analysis

Elements	% (calculated)	% (found)
C	51.74	51.32
H	3.51	3.38
N	8.62	8.48

5.1.3 1,3-Di(naphthalene-2-yl- sulfonyl)6-nitrobenzimidazolone IIIb′:

Yield = 72.81%, m.p. = 206°C.

R_f = 0.82 (Cyclohexane : Chloroform, 2:1).

IR (ν_{max}, KBr, cm^{-1})

3442, 3132, 3104, 3056, 2928, 2856, 1768, 1629, 1604, 1588, 1528, 1468, 1444, 1396, 1344, 1272, 1184, 1152, 1112, 1068, 1004, 964, 888, 860, 816, 772, 744, 708, 656, 576.

^{1}H-NMR ($CDCl_3$, 400 MHz), δ(ppm)

8.16 (d, 1H, 4-H, J_{4-5} = 9.03 Hz), 8.25 (dd, 1H, H-5, J_{5-7} = 2.0 Hz, J_{5-4} = 9.0 Hz), 8.87 (d, 1H, H-7, J_{7-5} = 2.0 Hz), 8.67 (dis. d, 2H, $H_{c'}$), 7.64 (t, 2H, H_f), 7.71 (t, 2H, H_f), 7.86 (m, 6H, He, Hd, He′), 8.10 (d, 2H, Hc/c′, J_{e-d} = 8.9 Hz).

^{13}C-NMR ($CDCl_3$, 100 MHz), δ(ppm)

197.3 (C–CO), 121.0 (C–5), 113.0 (C–4), 129.5 (C–7), 145 (C–6), 129.5 (C–8), 126 (C–9), 131.5 (C-2′/8′), 122 (C-3′/4′/7′), 131 (C-5′), 128 (C-6′), 129 (C-9′/10′).

Mass: EI-MS, m/z (rel. int.%)

559 ($M^{+\bullet}$, 9.89), 497 (1.51), 496 (3.17), 495 (8.85), 369 (1.97), 305 (1.55), 304 (1.82), 304 (1.82), 252 (1.64), 193 (3.50), 192 (7.14), 191 (51.69), 179 (1.51), 176 (1.66), 175 (5.57), 163 (1.46), 161 (2.30), 160 (4.33), 149 (1.79), 148 (1.77), 147 (2.46), 129 (2.06), 128 (18.60), 127 (100.00), 126 (6.49), 116 (1.66), 115 (5.07), 105 (1.50), 102 (2.04), 101 (3.04), 91 (1.48), 77 (5.03), 76 (1.88), 75 (1.67).

Elemental analysis

Elements	% (calculated)	% (found)
C	57.95	57.60
H	3.06	2.97
N	7.51	7.39

5.2 General method for the protection of one of the amino group of benzimidazolones:

The standard procedure was followed[46]. Benzimidazolone (0.01 mol) was taken in a three neck round bottomed flask in dry DMF. Fitted the flask with a condenser. To one neck of the flask fitted a dropping funnel and remaining one neck was connected with argon inlet. A mercury trap was connected with upper end of the condenser. To the solution of benzimidazolone in DMF, was added sodium hydride (0.1 mol) under argon. The solution was stirred for half an hour. To this stirred solution was added di-tert-butyl dicarbonate (0.1 mol) drop-wise with the help of dropping funnel, with constant stirring. The solution was stirred for 24 hours at room temperature. DMF was removed in vacuo and residue was diluted with saturated ammonium chloride solution and extracted with ethyl acetate. Ethyl acetate was removed in vacuo and residue was purified by flash column chromatography using ethyl acetate : n-hexane (1:4) as solvent. In case of nitrobenzimidazolone two isomers were obtained, which were separated by column chromatography.

5.2.1 2,3-Dihydro-2-oxo-1H-benzimidazole-1-carboxylic acid, 1,1-dimethyl ethyl ester IV:

Yield = 67.57%, m.p. = 165-167°C.

R_f = 0.4 (n-hexane : Ethyl acetate, 4:1).

IR (ν_{max}, KBr, cm^{-1})

888, 1110, 1152, 1192, 1337, 1394, 1596, 1598, 1760, 2975, 3052, 3195, 3280.

^{1}H-NMR ($CDCl_3$, 400 MHz), δ(ppm)

7.72 (d, 1H, H-7, $J_{7\text{-}6}$ = 8.0 Hz), 7.10-7.20 (m, 3H, H_4, H_5, H_6), 1.7 (s, 9H, 3-CH_3), 10.5 (s, 1H, H-NH).

Mass: EI-MS, m/z (rel. int.%)

234 ($M^{+\bullet}$, 10.02), 161 (2.03), 135 (9.20), 134 (100.00), 133 (4.94), 106 (11.44), 105 (3.09), 90 (1.40), 79 (4.06), 78 (2.66), 77 (1.11), 67 (1.10).

Elemental analysis

Elements	% (calculated)	% (found)
C	61.54	62.28
H	5.98	6.25
N	11.96	11.41

5.2.2 6-Nitro, 2,3-dihydro-2-oxo-1H-benzimidazole, 1-carboxylic acid, 1,1-dimethyl ethyl ester IV′:

Yield = 28.93%, m.p. = 320°C.

R_f = 0.48 (Ethyl acetate : n-hexane, 1:3).

IR (ν_{max}, KBr, cm^{-1})

3965, 3795, 3195, 2975, 2850, 2730, 1798, 1777, 1729, 1647, 1614, 1575, 1520, 1480, 1394, 1365, 1337, 1289, 1259, 1236, 1150, 1110, 1069, 1037, 996, 950, 926, 888, 832, 769, 685, 654, 630, 552.

^{1}H-NMR ($CDCl_3$, 400 MHz), δ(ppm)

8.70 (d, 1H, H-7, J = 2.13 Hz), 8.18 (dd, 1H, H-5, $J_{5,4}$ = 8.66 Hz, J_{5-7} = 2.6 Hz), 7.18 (d, 1H, H-4, J = 8.66 Hz), 1.25 (s, 9H, H-t.Bu), 9.70 (s, 1H, H-NH).

Mass: EI-MS, m/z (rel. int.%)

279 (9.14), 179 (100), 151 (8.50), 123 (3.16), 135 (1.50), 206 (3.00), 178 (5.31), 150 (2.91), 122 (2.11).

Elemental analysis

Elements	% (calculated)	% (found)
C	51.6	50.91
H	4.66	4.31
N	15.65	14.95

5.2.3 6-Nitro, 2,3-dihydro-2-oxo-1H-benzimidazole, 3-carboxylic acid, 1,1-dimethyl ethyl ester IV'':

Yield = 33%, m.p. = 327°C.

R_f = 0.33 (Ethyl acetate : n-hexane, 1:3).

IR (ν_{max}, KBr, cm^{-1})

3965, 3785, 3185, 2970, 2850, 2730, 1798, 1779, 1720, 1640, 1614, 1570, 1521, 1485, 1390, 1360, 1350, 1289, 1259, 1230, 1150, 1110, 1069, 998, 951, 925, 871, 831, 759, 627, 552.

^{1}H-NMR ($CDCl_3$, 400 MHz), δ(ppm)

8.00 (d, 1H, H-7, J = 2.3 Hz), 8.10 (dd, 1H, H-3, $J_{3,4}$ = 8.7 Hz, $J_{3,1}$ = 2.13 Hz), 7.87 (d, 1H, H-4, J = 8.9 Hz), 1.25 (s, 9H, H-t.Bu), 9.48 (s, 1H, H-NH).

Elemental analysis

Elements	% (calculated)	% (found)
C	51.6	51.95
H	4.66	4.23
N	15.05	14.95

5.3 General method for the sulfonylation of mono-protected benzimidazolones:

The standard procedure was followed[46]. Mono-protected benzimidazolone (0.01 mol) was taken in a two neck round bottomed flask fitted, with a condenser. Added dry dichloromethane (500 ml) to the flask. To this was added Et_3N as base and DMAP (dimethylaminopyridine) as catalyst. Stirred the solution well. To this well stirred solution added p-toluene/naphthalene sulfonly chloride (0.11 mol) portionwise with constant stirring. Stirred the mixture at room temperature for further 3 hours. Diluted the mixture with IN HCl solution and extracted with dichloromethane. Removed the solvent in vacuo and crude product was recrystallized from chloroform : n-hexane (1:3).

5.3.1 2,3-Dihydro-3-(p-toluene sulfonyl)-2-oxo-IH-benzimidazole, 1-carboxylic acid, 1,1-dimethyl ethyl ester Va:

Yield = 87.5%, m.p. = 130-132°C.

R_f = 0.76 (Ethyl acetate : n-hexane, 1:4).

IR (ν_{max}, KBr, cm^{-1})

890, 1152, 1193, 1345, 1390, 1595, 1765, 1790, 2950, 2975, 3195.

^{1}H-NMR ($CDCl_3$, 400 MHz), δ(ppm)

7.20-7.27 (m, 3H, H-5, H-6, H-7), 7.84 (dd, 1H, H-4, J_{4-6} = 1.0 Hz, J_{4-5} = 1.63 Hz), 8.03 (dd, 2H, Ha, Ha′, $J_{a-a'}$ = 1.2 Hz), J_{a-b} = 7.0 Hz), 7.33 (d, 2H, Hb, Hb′, J_{b-a} = 8.0 Hz), 2.4 (s, 3H, 1-CH_3), 1.6 (s, 9H, 3-CH_3).

Mass: EI-MS, m/z (rel. int.%)

388 ($M^{+\bullet}$, 9.43), 291 (1.95), 290 (19.74), 288 (100.00), 234 (2.22), 225 (2.50), 224 (15.42), 223 (4.22), 213 (2.14), 198 (1.66), 195 (2.44), 182 (2.44), 182 (1.56), 181 (2.21), 161 (1.76), 160 (3.34), 157 (4.43), 156 (5.53), 155 (50.47), 149 (1.60), 139 (2.87), 135 (3.82), 134 (38.44), 133 (73.40), 111 (1.57), 107 (1.85), 106 (12.53), 105 (3.93), 104 (3.93), 104 (3.34), 99 (3.34), 97 (1.95), 92 (5.39), 91 (47.65), 90 (2.23), 89 (2.46), 86 (1.73), 85 (2.66), 83 (1.76), 80 (1.65), 79 (3.32), 78 (5.88), 77 (3.81), 77 (4.19), 69 (2.35), 65 (8.38).

Elemental analysis

Elements	% (calculated)	% (found)
C	58.61	59.06
H	5.40	5.29
N	7.20	7.31

5.3.2 2,3-Dihydro-3-(naphthalene-2-yl-sulfonyl)-2-oxo-1H-benzimidazole, 1-carboxylic acid, 1,1-dimethyl ethyl ester Vb:

Yield = 75.20%, m.p. = 127°C.

R_f = 0.42 (Ethyl acetate : n-hexane, 1:4).

IR (ν_{max}, KBr, cm^{-1})

891, 1152, 1190, 1345, 1391, 1770, 1791, 3190, 1770, 1340.

^{1}H-NMR ($CDCl_3$, 400 MHz), δ(ppm)

7.32 (dd, 2H, H-4, H-7, J_{7-6} = 6.2 Hz, J_{7-5} = 3.2 Hz), 8.01 (dd, 2H, H-5, H-6, J_{6-7} = 6.2 Hz, J_{6-4} = 3.4 Hz), 7.59-7.87 (m, 7H, H-Ar) 2.24 (s, 9H, H-t.Bu).

Mass: EI-MS, m/z (rel. int.%)

424 ($M^{+\bullet}$, 8.73), 324 (47.65), 260 (13.30), 232 (2.71), 105 (11.53), 77 (3.81), 191 (35.06), 127 (100), 189 (1.86), 90 (11.2).

Elemental analysis

Elements	% (calculated)	% (found)
C	62.26	62.12
H	4.72	4.31
N	6.60	6.54

5.3.3 6-Nitro, 2,3-dihydro-3-(naphthalene-2-yl-sulfonyl)-2-oxo-1H-benzimidazole, 3-carboxylic acid, 1,1-dimethyl ethyl ester Vb′:

Yield = 55.56%, m.p. = 295-297°C.

R_f = 0.59 (Ethyl acetate : n-hexane, 1:4).

IR (ν_{max}, KBr, cm^{-1})

3920, 3795, 3465, 3255, 3125, 2925, 2735, 2620, 2605, 2360, 1761, 1715, 1646, 1619, 1555, 1515, 1480, 1451, 1406, 1374, 1331, 1298, 1267, 1218, 1182, 1131, 1070, 1047, 992, 965, 902, 857, 806, 745, 721, 693, 662, 634.

^{1}H-NMR ($CDCl_3$, 400 MHz), δ(ppm)

7.26 (d, 1H, H-4, J_{4-5} = 8.0 Hz), 8.21 (dd, 1H, H-5, J_{5-4} = 8.6 Hz, J_{5-7} = 2.26 Hz), 8.71 (d, 1H, J_{7-5} = 2.14 Hz), 7.60 (t, 1H, Hf), 7.72 (t, 1H, Hf'), 7.83 (m, 3H, H-e/e', Hd), 7.90 (d, 2H, H-c/c, J = 3.17 Hz), 1.6 (s, 9H, H-t.Bu).

Elemental analysis

Elements	% (calculated)	% (found)
C	56.28	56.02
H	4.05	4.01
N	8.95	8.89

5.4 General method for the synthesis of mono-sulfonylated benzimidazolones:

For the deprotection of mono-protected sulfonylated benzimidazolones, standard procedure was followed[46].

In a 100 ml round bottomed flask taken (0.0013 mol) of monoprotected sulfonylated benzimidazolone in CH_3CN (5 ml). To this was added Conc. HCl (2.5 ml) in diethyl ether (6 ml). Stirred the mixture at room temperature for three hours. Concentrated the mixture using rotary evaporator and triturated with diethyl ether to give the mono sulfonylated benezimidazolone.

5.4.1 2,3-Dihydro-3-(p-toluene sulfonyl)-2-oxo-IH-benzimidazole VIa:

Yield = 81.08%, m.p. = 208-210°C.

R_f = 0.76 (Ethyl acetate : Pet.ether, 1:2).

IR (ν_{max}, KBr, cm^{-1})

1760, 1771, 1152, 1340, 1389, 888, 3166, 2975, 1190, 1340.

^{1}H-NMR ($CDCl_3$, 400 MHz), δ(ppm)

7.90 (d, 1H, H-4, J = 8.0 Hz), 7.11-7.21 (m, 3H, H-5, H-6, H-7), 7.98 (d, d', 2H, H-a/a', $J_{a-b'}$ = 2.1 Hz, J_{a-b} = 8.2 Hz), 7.28 (d, 2H, H-b, H-b', J = 8.1 Hz), 2.4 (s, 3H, H-CH_3), 9.8 (s, 1H, H-NH).

Mass: EI-MS, m/z (rel. int.%)

288 ($M^{+\bullet}$, 64.66), 225 (4.40), 224 (16.27), 223 (6.46), 195 (4.97), 167 (4.23), 157 (4.57), 156 (5.44), 155 (41.39), 149 (6.83), 139 (5.51), 135 (4.23), 157 (4.57), 156 (5.44), 155 (41.39), 149 (6.83), 139 (5.51), 135 (8.18), 134 (81.43), 133 (100.00), 107 (6.29), 106 (35.61), 105 (13.29), 104 (4.67), 99 (17.21), 92 (6.93), 91 (58.88), 90 (4.46), 89 (6.43), 85 (5.44), 83 (5.85), 79 (17.82), 78 (11.80), 77 (5.88), 71 (6.83), 70 (4.87), 69 (6.19), 67 (7.27), 65 (14.27).

Elemental analysis

Elements	% (calculated)	% (found)
C	58.33	58.22
H	4.17	4.24
N	9.72	9.72

5.4.2 2,3-Dihydro-3-(naphthalene-2-yl-sulfonyl)-2-oxo-1H-benzimidazolone VIb:

Yield = 70.21%, m.p. = 206°C.

R_f = 0.21 (Ethyl acetate : Pet. ether, 1:2).

IR (ν_{max}, KBr, cm^{-1})

1765, 1770, 1152, 1340, 1380, 3182, 2770, 1180, 1340.

^{1}H-NMR ($CDCl_3$, 400 MHz), δ(ppm)

7.93 (d, 1H, H-4, J = 8.0 Hz), 7.13-7.20 (m, 3H, H-5/6/7), 8.98 (m, 3H, H-e/e', Hd), 7.71 (t, 1H, Hf), 7.64 (t, 1H, H-f'), 8.67 (d, 2H, H-c/c', J = 8.7 Hz).

Mass: EI-MS, m/z (rel. int.%)

324 ($M^{+\bullet}$, 35.62), 260 (15.27), 259 (2.87), 232 (3.29), 191 (15.21), 133 (78.19), 127 (100.0), 105 (10.23), 90 (11.2), 77 (3.81).

Elemental analysis

Elements	% (calculated)	% (found)
C	62.96	62.01
H	3.70	3.59
N	8.64	8.54

5.4.3 6-Nitro, 2,3-dihydro-3-(naphthalene-2-yl-sulfonyl)-2-oxo-1H-benzimidazole VIb′:

Yield = 62.15%, m.p. = 325°C.

R_f = 0.59 (Ethyl acetate : Pet.ether, 1:2).

IR (ν_{max}, KBr, cm^{-1})

1761, 1767, 1152, 1333, 1375, 902, 3128, 2925, 1183, 1346, 1525.

^{1}H-NMR ($CDCl_3$, 400 MHz), δ(ppm)

8.10 (d, 1H, H-4, J = 8.0 Hz), 8.35 (dd, 1H, H-5, J_{5-4} = 8.2 Hz, J_{5-7} = 2.3 Hz), 8.71 (d, 1H, H-7, J_{7-5} = 2.14 Hz), 7.69 (t, 1H, H6), 7.63 (t, 1H, H6′), 8.87 (m, 3H, H-e/e′, Hd), 8.70 (d, 2H, Hc/c′, J = 8.2 Hz), 7.27 (s, 1H, H-NH).

Elemental analysis

Elements	% (calculated)	% (found)
C	55.28	55.31
H	2.98	2.95
N	11.38	11.31

5.5 General method for the synthesis of 3-aryl/heterocyclic sulfonyl hydantoins:

Standard procedure was followed[46]. In a 100 ml round bottomed flask took hydantoins (0.04 mol) triethylamine (0.04 mol) in dichloromethane (28 ml). Added dimethylaminopyridine (DMAP) as catalyst and stirred the solution well. Added the solution of aryl/heterocyclic sulfonyl chloride in dichloromethane dropwise and stirred the solution at room temperature for three hours. It was diluted with 1N HCl and

extracted with dichloromethane. The solvent was removed under vacuum and the crude product was recrystallized with ethyl acetate.

5.5.1 3-(p-toluene sulfonyl)-5,5-phenyl methyl hydantoin VIIIf:

Yield = 77.78%, m.p. = 191°C.

R_f = 0.69 (Ethyl acetate : Pet.ether, 1:2).

IR (ν_{max}, KBr, cm^{-1})

3385, 2960, 2958, 1714, 1606, 1491, 1442, 1404, 1347, 1307, 1260, 1184, 1162, 1136, 1086, 1040, 916, 844, 812, 776.

^{1}H-NMR ($CDCl_3$, 400 MHz), δ(ppm)

1.8 (s, 3H, H-CH_3), 2.45 (s, 3H, H-Ar-CH_3), 7.95 (d, 2H, H-a/a'), 7.26-7.41 (m, 7H, H-Ar).

Mass: EI-MS, m/z (rel. int.%)

281(8.64), 265 (1.50), 191 (1.62), 190 (12.74), 189 (100.00), 175 (2.72), 155 (2.70), 148 (1.12), 147 (5.89), 146 (31.95), 139 (1.06), 132 (2.01), 122 (1.27), 121 (6.85), 119 (5.21), 118 (1.87), 108 (1.01), 105 (2.37), 104 (16.50), 103 (19.81), 92 (2.69), 91 (14.92), 90 (1.17), 89 (1.92), 87 (1.80), 78 (2.80), 77 (10.00), 76 (1.16), 70 (14.23), 69 (1.23), 65 (6.76).

Elemental analysis

Elements	% (calculated)	% (found)
C	59.29	59.12
H	4.68	4.6
N	8.13	7.97

5.5.2 3-(p-toluene sulfonyl)-5,5-dimethyl hydantoin VIIIh:

Yield = 67.87%, m.p. = 173-174°C.

R_f = 0.87 (Ethyl acetate : Pet. ether, 1:2).

IR (ν_{max}, KBr, cm^{-1})

3385, 2960, 2958, 1765, 1715, 1607, 1491, 1442, 1405, 1347, 1308, 1260, 1184, 1162, 1136, 1086, 1040, 917, 812, 775.

^{1}H-NMR ($CDCl_3$, 400 MHz), δ(ppm)

1.9 (s, 6H, H-2CH_3), 2.3 (s, 3H, H-Ar-CH_3), 7.36 (d, 2H, H-b/b′), 8.0 (d, 2H, H-a/a′, J = 10.29).

Elemental analysis

Elements	% (calculated)	% (found)
C	51.05	52.0
H	5.0	4.69
N	9.92	9.63

5.5.3 3-(Naphthalene-2-yl-sulfonyl)-5,5-phenylmethyl hydantoin VIIIa:

Yield = 70%, m.p. = 380°C.

R_f = 0.53 (Ethyl acetate : Pet.ether, 1:2).

IR (ν_{max}, KBr, cm^{-1})

3350, 3855, 2875, 2735, 2360, 1803, 1746, 1592, 1488, 1446, 1379, 1329, 1291, 1232, 1187, 1096, 1065, 907, 814.

Elemental analysis

Elements	% (calculated)	% (found)
C	63.18	62.94
H	4.24	4.11
N	7.36	7.37

5.5.4 3-[2-Benzoyl benzo [b] furan-3-yl-sulfonyl] 5,5-phenylmethyl hydantoin VIIIu:

Yield = 31.50%, m.p. = 270°C.

R_f = 0.88

λ_{max} (E) = 204.96 ($1.8x10^5$)

IR (ν_{max}, KBr, cm^{-1})

3470, 3270, 3060, 2934, 2905, 2575, 2470, 1909, 1751, 1596, 1533, 1488, 1441, 1395, 1365, 1333, 1288, 1246, 1167, 1156, 1104, 1069, 1015, 958, 873.

5.6 General method for the synthesis of 1-aryl/heterocyclic sulfonyl hydantoins:

Standard procedure was followed[11]. In a 100 ml two neck round bottomed flask took 3-aryl/heterocyclic sulfonyl hydantoins (0.001 mol) in dry benzene (15 ml). To this was added sodium hydride (0.0012 mol) and refluxed the mixture under argon for two hours. After two hours, evaporated the solvent and added pet. ether to it. White precipitates were obtained. Collected the precipitates and dried them. This was the sodium salt of the respective 1-sulfonyl hydantoin. Dissolved the precipitates in water and neutralized with IN HCl (one drop) and extracted with ethyl acetate. Rearranged product was recrystallized from ethyl acetate.

5.6.1 1-(p-toluene sulfonyl), 5,5-phenyl methyl hydantoin IXf:

Yield = 70%, m.p. = 178-180°C.

R_f = 0.89

IR (ν_{max}, KBr, cm^{-1})

3385, 2960, 2950, 2590, 1945, 1765, 1714, 1606, 1491, 1442, 1404, 1347, 1260, 1184, 1162, 1086, 1040, 812.

^{1}H-NMR ($CDCl_3$, 400 MHz), δ(ppm)

1.8 (s, 3H, H-CH_3), 2.2 (s, 3H, H-Ar-CH_3), 6.5-7.5 (m, 9H, H-Ar), 3.8 (s, 1H, H-NH).

Mass: EI-MS, m/z (rel. int.%)

280 (21.36), 275 (7.98), 274 (7.98), 265 (6.36), 246 (8.68), 223 (6.96), 191 (7.23), 190 (9.39), 189 (14.24), 182 (6.74), 178 (6.58), 175 (22.33), 171 (12.19), 161 (7.23), 156 (7.66), 154 (32.30), 149 (10.14), 147 (16.07), 146 (100.00), 145 (12.62), 139 (8.04), 136 (10.84), 132 (6.47), 128 (7.98), 120 (15.86), 119 (49.89), 118 (9.06), 111 (7.71), 109 (18.61), 107 (7.82), 105 (14.72), 104 (34.52), 103 (14.72), 99 (21.47), 97 (10.25), 96 (11.33), 95 (8.04), 93 (9.76), 91 (73.62), 84 (8.90), 85 (8.79), 84 (6.47), 83 (13.32), 82 (9.06), 81 (11.00), 78 (9.44), 76 (7.28), 71 (19.96), 70 (11.92), 69 (9.49), 68 (6.74), 67 (7.39), 65 (23.46).

Elemental analysis

Elements	% (calculated)	% (found)
C	59.29	58.92
H	4.68	4.63
N	8.13	7.80

5.6.2 1-(p-toluene sulfonyl) 5,5-dimethyl hydantoin IXh:

Yield = 51.25%, m.p. = 144-145°C.

R_f = 0.35 (Ethyl acetate : Pet. ether, 1:2).

IR (ν_{max}, KBr, cm^{-1})

3385, 2960, 2958, 1765, 1715, 1607, 1491, 1442, 1405, 1347, 1308, 1260, 1155, 1136, 1086, 1045, 915, 814, 760.

^{1}H-NMR ($CDCl_3$, 400 MHz), δ(ppm)

1.7 (s, 6H, H-2CH_3), 2.5 (s, 3H, H-Ar-CH_3), 7.2-8.2 (m, 4H, H-Ar).

^{1}H-NMR data showed that compound was not pure. There were so many other peaks, which were to be due to 3-(p-toluene sulfonyl) hydantoin. This showed that compound was a mixture of 1-(p-toluene sulfonyl) and 3-(p-toluene sulfonyl) hydantoin.

Elemental analysis

Elements	% (calculated)	% (found)
C	51.05	50.13
H	5.00	4.93
N	9.92	9.79

5.7 Synthesis of cyclic ureas:

5.7.1 General method for the synthesis of benzimidazolones:

Two methods were used as shown in plan of work. (Scheme **VIa, VIb**).

Method A

Standard procedure was followed[55]. o-Phenylenediamine (0.05 mol) and urea (0.05 mol) were mixed and ground finely. This finely ground mixture was taken in a 100 ml round bottomed two neck flask fitted with a condenser. Heated the mixture on oil bath from 20-140°C. After some time mixture melted and became solid. Heated the mixture till the evolution of NH_3. The evolution of NH_3 was checked with a filter paper soaked in HCl or with pH-paper. Dissolved the solid mixture in 2.5 NaOH solution. Filtered the solution and neutralized the filtrate with Conc. HCl under ice cooling. Precipitates were obtained and recrystallized from methanol.

Method B

In method B benzimidazolone was prepared in three steps[57] (Scheme **VIb**).

1. Synthesis of anthranilohydrazide:

In a 100 ml round bottomed flask, heated under reflux a solution of hydrazine hydrate (12 ml) and methyl anthranilate (10 gm, 8.5 ml) in ethanol (10 ml) for two hours. Reaction mixture was cooled in ice bath for ten minutes. White crystals appeared, which were filtered and washed with cold ethanol. Recrystallized the product from hot ethanol.

Yield = 52%, (lit. 50), m.p. = 115-116°C (lit. 117).

2. Synthesis of anthranilic acid azide:

To the solution of anthranilohydrazide (5gm) in HCl (10 ml) and water (10 ml) added ice colded solution of sodium nitrite (2.6 gm) in distilled water (10 ml) under ice cooling. Stirred the mixture for 10 minutes. Filtered off the solution and retained the filtrate. To this filtrate added excess sodium carbonate to basify it. Stirred the solution vigorously and filtered off the precipitates, washed the crude product with water and dried and recrystallized from ethanol.

Yield = 37.3% (lit. 23), m.p. = 78-80°C (lit. 78-80)

3. Synthesis of benzimidazolone:

In a 100 ml round bottomed flask took anthranilic acid azide (1 gm) in dry benzene (50 ml). Refluxed the mixture for more than three hours. Cooled the reaction mixture and filtered the solid material. Recrystallized the benzimidazolone from ethanol.

Yield = 85%, (lit. 80) m.p. = >300°C.

5.7.1.1 2,3-Dihydro-2-oxo-1H-benzimidazole II:

Yield = 75%, (lit. 70) m.p. = >300°C.

R_f = 0.75 (Ethyl acetate : Pet.ether, 1:2).

5.7.1.2 6-Nitro, 2,3-dihydro-2-oxo-1H-benzimidazole II':

Yield = 30%, (lit. 40) m.p. = = >300°C.

R_f = 0.55 (Ethyl acetate : Pet.ether, 1:2).

5.7.2 General method for the synthesis of hydantoins:

Standard procedure was followed[58].

In a 100 ml round bottomed flask, took aldehyde/ketone (0.1 ml) and ammonium carbonate (0.4 mol). Added KCN (0.1 mol) dissolved in ethanol (50-70%). The mixture was heated in oil bath at 55-60°C for 10 hours. The solvent was evaporated and product was acidified with Conc. HCl. The precipitates were filtered and dissolved in NaOH solution. The solution was extracted with ether. The aqueous phase was acidified to get

the precipitates of hydantoins. These precipitates were filtered, dried and recrystallized from ethanol/water.

5.7.2.1 **5,5-Methyl phenyl hydantoin VIIa:**

Yield = 78% (lit. 70) m.p. = 210°C (lit. 212).

R_f = 0.64 (Ethyl acetate : Pet.ether, 2:1).

IR (ν_{max}, KBr, cm^{-1})

3475, 3280, 2990, 2860, 2705, 2120, 1950, 1881, 1763, 1718, 1593, 1534, 1489, 1441, 1390, 1361, 1315, 1299, 1248, 1227, 1189, 1157, 1105, 1070, 1016, 959, 874.

5.7.2.2 **5,5-Diphenyl hydantoin VIIb:**

Yield = 75% (lit. 69), m.p. = 290°C (lit. 289).

R_f = 0.7 (Ethyl acetate : Pet.ether, 2:1).

IR (ν_{max}, KBr, cm^{-1})

3470, 3280, 2850, 2860, 2705, 2119, 1951, 1881, 1760, 1719, 1592, 1535, 1489, 1441, 1392, 1362, 1316, 1299, 1249, 1227, 1189, 1152, 1105, 1070, 1012, 950, 871.

5.7.2.3 **5,5-Dimethyl hydantoin VIIc:**

Yield = 78% (lit. 75), m.p. = 180°C (lit. 182).

R_f = 0.59 (Ethyl acetate : Pet.ether, 2:1).

IR (ν_{max}, KBr, cm^{-1})

3480, 3271, 2981, 2851, 2861, 2705, 2119, 1951, 1882, 1760, 1719, 1593, 1535, 1489, 1441, 1391, 1363, 1315, 1295, 1249, 1227, 1198, 1152, 1110, 1070, 1012, 952, 872.

5.7.2.4 **5-(p-Chlorophenyl) hydantoin VIId:**

Yield = 76% (lit. 78), m.p. = 176°C (lit. 175).

R_f = 0.6 (Ethyl acetate : Pet.ether).

IR (ν_{max}, KBr, cm^{-1})

3386, 3075, 1951, 1823, 1767, 1719, 1550, 1519, 1489, 1400, 1376, 1322, 1295, 1185, 1053, 1014, 918, 858.

5.7.2.5 **5-(p-Methoxyphenyl) hydantoin VIIe:**

Yield = 75% (lit. 76), m.p. = 190°C (lit. 195).

R_f = 0.55 (Ethyl acetate : Pet.ether, 2:1).

IR (ν_{max}, KBr, cm^{-1})

3215, 2755, 2365, 2165, 1775, 1745, 1605, 1511, 1456, 1426, 1406, 1332, 1306, 1282, 1246, 1191, 1122, 1019, 918, 869, 823.

5.8 Synthesis of perhydro 1,3-diazepin 2,4-diones:

Synthesis of perhydro 1,3-diazepin 2,4-dione consists of five steps. (Scheme-VIII).

a) Synthesis of glutaric anhydride.

b) Synthesis of glutaric acid monoamide.

c) Synthesis of acylazide.

d) Coversion of acylazide into isocynate.

e) Conversion of isocynate into perhydro 1,3-diazepin 2,4-dione.

Due to non availability of chemicals, especially ethylchloroformate, we were not able to carry out the work up to final step. We were only able to synthesize glutaric anhydride and glutaric acid monoamide.

5.8.1 General method for the synthesis of glutaric anhydride:

In a 100 ml round bottomed single neck flask took glutaric acid (0.027 mol). Added acetyl chloride (0.08 mol) to the flask. Refluxed the mixture for three hours. Cooled the reaction mixture and distilled out the excess acetyl chloride and acetic acid formed. Cooled the contents of the flask. It solidify on cooling. Recrystallized the product from a non aqueous solvent.

5.8.1.1 2,4-Dimethyl glutaric anhydride:

Yield = 96.85% (lit. 90), m.p. = 80-84°C (lit. 80).

R_f = 0.8 (Benzene).

5.8.1.2 2,2-Dimethyl glutaric anhydride:

Yield = 87.6% (lit. 90), m.p. = 34-35°C (lit. 35).

R_f = 0.52 (Benzene).

5.8.1.3 3,3-Dimethyl glutaric anhydride:

Yield = 90.14% (lit. 90), m.p. = 120-121°C (lit. 122).

R_f = 0.54 (Benzene).

5.8.2 General method for the synthesis of glutaric acid monoamide:

Standard procedure was followed[13].

In a 100 ml round bottomed flask took glutaric anhydride (0.013 mol). Added concentrated ammonia (14.5 ml) to the round bottomed flask at room temperature. Dissolved all the glutaric anhydride in NH_4OH by stirring and then refluxed the solution for more than 3 hours. It was reduced to dryness. Solid material was dried in vacuum oven at 60°C. A thick syrup was obtained which was treated with cation exchange resion (Dowex, 50 W-X8) with about 10 ml of water. Evaporated the water, dissolved the solid material in ethyl acetate and treated with activated charcoal to remove the colour. Removed the solvent slightly and then recrystallized the solid material from ethyl acetate.

5.8.2.1 3,3-Dimethyl glutaric acid monoamide:

Yield = 71.42%, m.p. = 112°C.

R_f = 0.51 (Ethyl acetate : Pet. ether, 1:1).

5.8.2.2 2,2-Dimethyl glutaric acid monoamide:

Yield = 69%, m.p. = 125°C.

R_f = 0.73 (Ethyl acetate : Pet. ether, 1:1).

5.9 General method for the synthesis of aryl sulfonyl chlorides:

Standard procedure was followed[59].

In a 100 ml round bottomed two neck flask took naphthalene/benzene (0.78 mol). Heated the flask up to 160±5°C. Stirred the contents with a mechanical stirrer. Added Conc. H_2SO_4 (160 gm) with the help of dropping funnel. Maintained the stirring at 180±5°C. Stirred the solution for 15 minutes and poured the solution into cold water (750 ml). Boiled the solution with activated charcoal. Filtered and neutralized by adding solid sodiumbicarbonate. Heated the solution to boiling, saturated with NaCl and then set a side for crystallization. Filtered the crude product and recrystallized from 10% sodium chlorides solution. It was the sodium salt of the corresponding sulfonic acid. Took sodium salt of the sulfonic acid (0.078 mol) in a round bottomed flask and added PCl_5 (0.078 mol). Heated the mixture at 170-178°C for 12-15 hours. After every three hours, flask was removed from oil bath, cooled and shaked well, keeping the flask stoppered. After the heating period, flask was removed. Contents were thrown in to crushed ice and extracted with CCl_4. Extract was washed with Na_2CO_3 solution. Evaporated the solvent and got the crude product. Purification was carried out by vacuum distillation.

5.9.1 Naphthalene-2-yl-sulfonyl chloride (Ib):

Yield = 94.0%, m.p. = 76°C.

5.10 Synthesis of heterocyclic compounds:

5.10.1 Synthesis of 3,4 and 4,5 halo benzo [b] furans:

Synthesis of 3,4 and 4,5 halo benzo [b] furans consists of two steps.

a) General method for the synthesis of (3,4 and 4,5 halo phenyloxy) acetaldehyde dimethyl acetal.

Standard procedure was followed[60].

To a suspension of sodium hydride (0.08 mol) in N,N-dimethylformamide (47 ml), was added dropwise 3,4 halo phenol (0.08 mol) under ice cooling. After stirring for 10 minutes to the solution was added dropwise bromoacetaldehyde dimethyl acetal (0.09 mol) and mixture was heated with stirring for 3 hours at 90°C. After cooling, water was

added to the resulting solution and acidified with IM hydrochloric acid solution and then extracted with ether (200 ml). The organic layer was washed with successive water, saturated aqueous sodium bicarbonate solution and saturated sodium chloride solution. After drying over anhydrous sodium-sulfate ether was removed in vacuo and the residue was purified by silica gel column chromatography to give the objective compound.

(3-Bromophenyloxy) acetaldehyde dimethyl acetal:

Yield = 72.64%

R_f = 0.8 (Ethyl acetate : Pet. ether, 1:3).

IR (Neat, ν_{max}, cm^{-1})

2941, 2835, 1615, 1506, 1458.

NMR ($CDCl_3$, ppm)

3.44 (6H, s), 3.96 (2H, d, J = 5.0 Hz), 4.69 (1H, t, J = 5.0 Hz), 6.77-7.26 (4H, m).

(3,4-Dichloro phenyloxy) acetaldehyde dimethyl acetal:

Yield = 85.32%, R_f = 0.65

IR (Neat, ν_{max}, cm^{-1})

2940, 2830, 1595, 1475, 1297, 1235.

NMR ($CDCl_3$, ppm)

3.45 (6H, s), 3.96 (2H, d, J = 5.3 Hz), 4.69 (1H, t, J = 5.3 Hz), 6.76 (1H, dd, J = 8.9, 3.0 Hz), 7.02 (1H, d, J = 3.0 Hz), 7.31 (1H, d, J = 8.9 Hz).

b) General method for the synthesis of 3,4 and 4,5 halo benzo [b] furans:

Standard procedure was followed[60].

Under ice cooling to phosphoric acid (0.24 mol) was added phosphorous pentaoxide (0.08 mol) and chlorobenzene (30 ml). The resulting mixture was heated up to 125°C. To the mixture was added dropwise the solution of (halo phenyloxy) acetaldehyde dimethyl acetal (0.02 mol) in chlorobenzene at 125°C and heated with stirring for 1 hour at 125°C. After cooling the resulting mixture was poured in to ice water and extracted with ether. The organic layer was washed with successive saturated

aqueous sodium bicarbonate solution and saturated aqueous NaCl solution. After drying over anhydrous sodium sulfate ether and chlorobenzene was removed in vacuo and residue was purified by silica gel column chromatography to give the objective compound.

5.10.1.1 Mixture of 4-bromo and 6-bromo benzo [b] furan:

Yield = 72.52%, R_f = 0.87 (Ethyl acetate : n-hexane, 1:9).

5.10.1.2 Mixture of 3,4- and 4,5-dichlor benzo [b] furan:

Yield = 62%, R_f = 0.72 (Ethyl acetate : n-hexane, 1:9).

5.10.2 Synthesis of 2-benzoyl benzo [b] furan:

5.10.2.1 Synthesis of α-broomoacetophenone[61].

In a 500 ml three neck round bottomed flask, took a solution of acetophenone (0.5 mol) in glacial acetic acid (200 ml). Fitted a mechanical stirrer to it. Added slowly Br_2 (0.5 mol) to the acetophenone solution with stirring, with the help of dropping funnel. Stirred the mixture vigorously during the addition and kept the temperature below 20°C. Let the reaction mixture to attain the room temperature. Added water and put it in ice. On scratching we got yellowish crystals of α-bromoacetophenone. Recrystallized it from ethanol water pair.

Yield = 72%, m.p. = 86-87°C.

R_f = 0.67 (n-hexane : ethyl acetate, 2:1).

5.10.2.2 Synthesis of 2-benzoly benzo [b] furan[61].

In 250 ml round bottomed flask, took α-bromoacetophenone (0.1 mol) and salicylaldehyde (0.1 mol) in dry ethanol (20 ml). To this was added anhydrous potassium carbonate (0.1 mol). The reaction mixture was heated for 1.5 hours at 100°C. added distilled water (150 ml) to it and product was separated in the form of solid lumps. These were broken with glass rod and filtered off. Washed with water and recrystallized from ethanol.

Yield = 70%, m.p. = 86-87°C.

R_f = 0.64 (n-hexane : ethyl acetate, 2:1).

IR (ν_{max}, KBr, cm^{-1})

3060, 1897, 1715, 1663, 1607, 1572, 1538, 1467, 1437, 1367, 1326, 1230, 1186, 1157, 1118, 1074, 1001, 969, 935, 846, 839, 741.

5.10.3 General method for the synthesis of 5-halo-3-methyl benzo [b] furan:

5.10.3.1 Synthesis of α-bromoacetone[62].

In 500 ml round bottomed two neck flask took acetone (125 ml) and mixed with glacial acetic acid (93 ml) and water (150 ml). Heated the mixture at 70-80°C. Added bromine (88.5 ml) dropwise, within 1-2 hours, till the decolourization of bromine stopped. Reaction mixture was diluted with water (200 ml) and cooled to 10°C and then neutralized with sodium carbonate. The oily fraction was separated out and dried over $CaCl_2$. Purification was done by distilling the crude product under reduced pressure.

5.10.3.2 Synthesis of α-(p-halo phenyloxy) acetone[62].

In 250 ml round bottomed two neck flask took p-halophenol (0.12 mol) and NaOH (0.12 mol) in water (150). To this solution was added bromoacetone (0.12 mol) and stirred the solution at room temperature for 45 minutes. The reaction mixture was extracted with ether (3x75 ml). The extracts were combined and dried over $MgSO_4$. Evaporated the solvent and distilled the crude product to get the pure product.

5.10.3.3 Synthesis of 5-halo-3-methyl benzo [b] furan[62].

In 250 ml round bottomed flask, took p-halophenyloxy acetone (0.54 mol) and poly phosphoric acid (100 gm). Stirred the mixture for 45 minutes with a mechanical stirrer. The temperature was kept at 125-130°C. the resultant mixture was dropped in ice cold water (300 ml) and extracted with ether. Ether was removed by evaporation using rotary evaporator to get the 5-halo-3-methyl benzo [b] furan.

5.10.3.3.1 *5-Bromo-3-methyl benzo [b] furan:*

Yield = 52%, R_f = 0.58 (Ethyl acetate : n-hexane, 1:4).

5.10.3.3.2 *5-Bromo-3-methyl benzo [b] furan:*

Yield = 65%, R_f = 0.68 (Ethyl acetate : n-hexane, 1:4).

5.10.4 Synthesis of 3,5-substituted isoxazoles:

Standard procedure was followed[63].

In a 250 ml round bottomed single neck flask, took hydroxylamine hydrochloride (0.215 mol) in water (30 ml). To this was added a solution of β-diketone (0.215 mol) in ethanol. Heated the reaction mixture under reflux till the -ve $FeCl_3$ test. Then poured the mixture in to cold water (120 ml). Aqueous mixture was extracted with ether. Then the extracts were combined and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and crude product was purified by distillation/recrystallization.

5.10.4.1 3,5-Dimethyl isoxazole:

Yield = 53%, b.p. = 140-142°C.

R_f = 0.55 (Ethyl acetate : Pet. ether, 1:1).

λ_{max} (E) = 225.93 (1.34×10^5).

IR (ν_{max}, KBr, cm^{-1})

3120, 3071, 1509, 1497, 1366, 1336, 1286, 1237, 1216, 1171, 1091, 1051, 1022, 877, 765, 707, 675.

5.10.4.2 3-Phenyl, 5-methyl isoxazole:

Yield = 89.9%, m.p. = 59.7-61.2°C.

R_f = 0.56 (Ethyl acetate : Pet. ether, 1:1).

λ_{max} (E) = 240.2 (1.58×10^5).

IR (ν_{max}, KBr, cm^{-1})

3119, 3068, 1609, 1567, 1497, 1466, 1435, 1409, 1366, 1336, 1286, 1237, 1216, 1161, 1098, 1051, 1020, 897, 765, 707, 676.

5.10.4.3 3,5-Diphenyl isoxazole:

Yield = 76%, m.p. = 138°C.

R_f = 0.5 (Ethyl acetate : Pet. ether, 1:1).

λ_{max} (E) = 250.94 ($1.44x10^5$).

IR (ν_{max}, KBr, cm^{-1})

3165, 3045, 1644, 1607, 1566, 1537, 1447, 1397, 1333, 1290, 1255, 1197, 1106, 1073, 1014, 948, 913, 918, 763, 705, 663, 527.

5.11 Synthesis of heterocyclic sulfonyl chlorides:

5.11.1 Synthesis of lithium di-isopropylamide[60] (LDA):

In a 100 ml round bottomed two neck flask di-isopropylamine (0.032 mol) were mixed with THF (54 ml) under argon. The solution was cooled at 0°C and added n-butyl lithium (0.032 mol) in n-hexane dropwise under argon. The solution was stirred for half an hour at 0°C and then cooled to -78°C. Now it was ready for further use.

5.11.2 Preparation of sulferdioxide gas:

Sulferdioxide gas required for the sulfonylation of heterocyclic compounds, was prepared in the laboratory by the action of conc. sulfuric acid on sodium sulfite. Sulferdioxide prepared was dried by passing it through conc. H_2SO_4 and calcium chloride towers. A special type of assembly was designed for this purpose to obtain the continuous supply of sulferdioxide.

5.11.3 General method for the chlorosulfonylation of heterocyclic compounds:

Standard procedure was followed[60].

To a solution of heterocyclic compound (0.006 mol) in anhydrous ether (5 ml) was added solution of LDA (0.007 ml) under argon at -70°C. After stirring for 30 minutes, into the solution was bubbled sulferdioxide for one hour with constant stirring at -60°C. then the solution was stirred for three hours at room temperature and formed precipitates were separated by filtration to give lithium sulfinate of the respective heterocyclic compound. To the suspension of the lithium sulfinate in dichloromethane

(20 ml) was added N-chlorosuccinimide (0.007 mol) at -50°C and stirred for three hours under ice cooling. Insoluble matters were filtered off and dichloromethane was removed in vacuo and residue was purified by flash column chromatography under nitrogen using silica gel as adsorbent.

5.11.3.1 5-Bromo benzo [b] furan-2-yl-sulfonyl chloride Ic:

Yield = 86.66%, m.p. = 85-86°C.

R_f = 0.09 (Ethyl acetate : n-hexane, 1:2).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm)

From ^{1}H-NMR data, it was observed that compound isolated after column chromatography was not the required one.

5.11.3.2 2-Benzoyl benzo [b] furan-3-yl-sulfonyl chloride Ig:

Yield = 88.46%, m.p. = 98-102°C.

R_f = 0.64 (Ethyl acetate : n-hexane).

From ^{1}H-NMR data, it was observed that compound isolated after column chromatography was not the required one.

5.11.3.3 3,5-Dimethyl isoxazole-4-yl-sulfonyl chloride Ih:

Yield = 52%, m.p. = 117-119°C.

R_f = 0.31

From ^{1}H-NMR data, it was observed that compound isolated after column chromatography was not the required one.

5.11.3.4 3-Methyl, 5-phenyl isoxazole-4-yl-sulfonyl chloride Ii:

Result same as in 5.11.3.3.

5.11.3.5 3,5-Diphenyl isoxazole-4-yl-sulfonyl chloride Ij:

Result same as in 5.11.3.3.

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