SYNTHESIS AND EVALUATION OF NOVEL IODINATED PHENYL BENZAMIDES

M.Sc Thesis

A DISSERTATION SUBMITTED IN THE PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF SCIENCE (M.Sc) IN CHEMISTRY

SUBMITTED

BY

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SESSION: OCTOBER-2014

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BANGLADESH UNIVERSITY OF ENGINEERING AND TECHNOLOGY (BUET)

DHAKA-1000, BANGLADESH

January-2022

BANGLADESH UNIVERSITY OF ENGINEERING AND TECHNOLOGY (BUET), DHAKA-1000, BANGLADESH.

DEPARTMENT OF CHEMISTRY

THESIS ACCEPTANCE LETTER

The thesis titled "**Synthesis and Evaluation of Novel Iodinated Phenyl Benzamides**" Submitted by Ummey Salma, Roll No: 1014032605 F, Registration No: 1014032605, Session: October, 2014 has been accepted as satisfactory in partial fulfilment of the requirement for the degree of Master of Chemistry (M.Sc) in Chemistry on 11 January, 2022.

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Name of the Candidate

Dedicated
To
My Family

ACKNOWLEDGEMENT

All praise and admiration for almighty Allah, the most kind and merciful who has enabled me in carrying out the research work presented in this dissertation.

I am extremely delighted to express my deepest gratitude and sincere thanks to my respected teacher and supervisor, Assistant Prof. Dr. Md. Ayub Ali, for this helpful advice, keen interest, patience, motivation, worthy suggestions and encouragement throughout the progress of my research work.

I am grateful to all my respected teachers of this department for their helpful suggestions at different stages of studies in chemistry.

I owe my deepest gratitude to the BANGLADESH UNIVERSITY OF ENGINEERING AND TECHNOLOGY (BUET), Dhaka, Bangladesh for giving me the financial support to carry out my research work and I am also grateful to the Department of Chemistry to give me opportunity to do M.Sc program. I thank all staffs in the Department of Chemistry, BUET for their kind co-operations.

I would like to extend my thanks to Laila Anjum, Saidul Hoque, Md. Sajib Hossain, Anamika Biswas, Dilruba Pervin, Iffat Ara Tazin, Rabeya Akter, Sharmin Binte Sahid and all lab members for their cooperation and generous help in the laboratory.

Finally, I must express my very profound gratitude to my parents for providing me with unfailing support and continuous encouragement throughout my years of study and through the process of researching and writing this thesis. This accomplishment would not have been possible without them.

UMMEY SALMA
Author

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LIST OF ABBREVIATIONS

Ac	acetyl, acetate
aq.	Aqueous
Bp	boiling point
br	Broad
d	Doublet
dec.	Decomposition
DMF	*N*, *N* – dimethylformamide
Equiv.	Equivalent
Et	Ethyl
EtOAc	ethyl acetate
h	Hour
HPLC	high performance liquid chromatography
hν	Light
Hz	Hertz
IR	infra red spectra
J	coupling constant
m	multiplet or medium
M	mass or metal
min	Minutes
mmol	Millimole

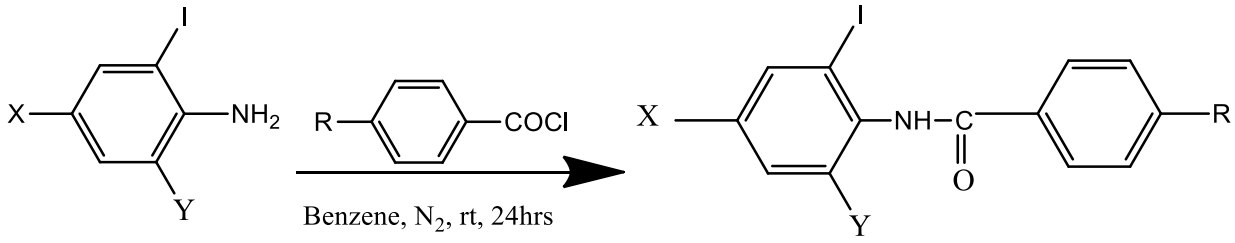
mol	Mole
mol%	mole percent
Mp	melting point
NMR	nuclear magnetic resonance
OAc	Acetate
Ph	Phenyl
PhH	Benzene
ppm	perts per million
rt	room temperature
s	singlet, strong, or second
sec	Seconds
t	Triplet
TLC	thin layer chromatography
TMS	Trimethylsilane
UV	ultra violet
w	Weak
Δ	heat or reflux
δ	chemical shift
λ_{max}	ultraviolet absorption in nm
ν_{max}	infrared absorption in per centimeter

Thesis title: SYNTHESIS AND EVALUATION OF NOVEL IODINATED PHENYL BENZAMIDES

Abstract

As a class, iodo benzamide derivatives are of great interest in natural products, pharmaceuticals, functional materials, and medicines. Synthesis and biological evaluation of iodo benzamide derivatives have been a topic of special demand to organic and medicinal chemist. Without catalyst here a convenient method for the synthesis of N-substituted benzamide derivatives is reported. In this purpose, 2-iodo – 4 –substituted anilines were synthesized by the iodination of the parent sustituted aniline using KI, KIO_3 in methanol. The reaction study on 2-iodo–4–substituted anilines with acid chlorides were carried out in benzene at room temperature for 24-48 hrs under N_2 atmosphere to yield N-(2-iodo-4-substituted phenyl)- p-substituted benzamide **01, 02.** The reaction went for two step. At first step is designed for the iodination.

Second step is for aryl acid chloride derivatives addition.



X= Cl, Y= H R= CH_3, NO_2

On the other reaction the benzamide was prepared directly with the reaction of 4- substituted aniline 02 and acid chloride. And then the reaction was subjected to go iodination with KI and KIO_3 but it was not successful.

In vitro antimicrobial activities of the synthesized compound 01 was evaluated. The compound 01 showed resistance against the gram positive and gram negative bacteria.

Summary

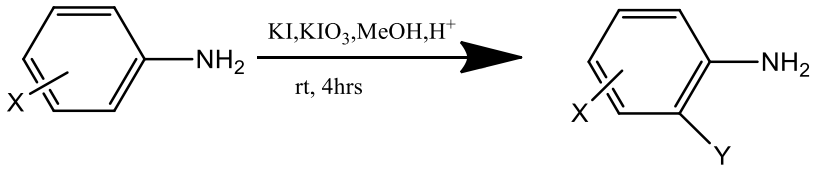
Investigation incorporated in this dissertion titled,'Synthesis and evaluation of novel iodinated phenylbenzamides''have been presented in three chapters. The first chapter is introductory section, in which the back ground, biological action and the important synthesis are presented. The chapter II deals with rationale, results and discussion, and conclusion for the synthesis of iodinated substituted phenyl benzamides. The chapter III deals with the detailed methodologies and experimental procedure for the synthesis of iodinated phenyl benzamides derivatives, spectra, and references.

Chapter-I

It represents the importance and synthesis of iodo phenylbenzamide derivatives. Iodo amides are a class of amide bond that are of increasing interest in synthetic and pharmaceutical chemistry. Iodo amides have proved considerable interest due to their pharmalogical activities. Various methods are known for the synthesis of iodo amide derivatives but without catalyst for the synthesis of indole derivatives are limited in number.

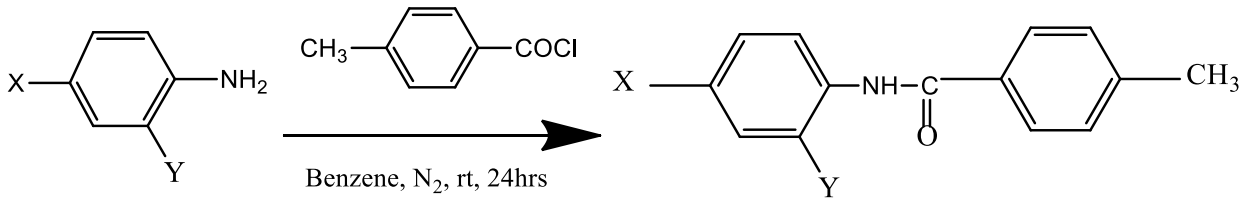
Chapter-II

In the experimental section the general procedure for the synthesis of iodo amide is described. For this purpose, first of all, different aryl iodide were synthesized from substituted aniline using potassium iodide and potassium iodate in methanol at room temperature (**Scheme 1**). The aryl iodide on treatment with different acid chloride in benzene at room temperature for 24 hrs produced substituted different iodo benzamides **01-02** (**Scheme 2**) with good yields (%).

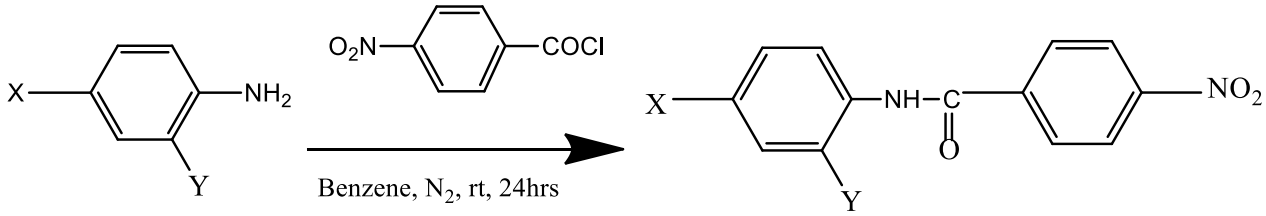


X= Cl, Y= I

Scheme -1



01



02

Scheme -2

Chapter-III

In this section results and discussion are presented. Here a strategy for the synthesis of iodo amide derivatives is reported without catalyzed N-substituted aniline with aryl acid chlorides.

Chapter-I

Introduction

INTRODUCTION

1.1 Application of Iodo compounds

Organic compounds containing iodine are known as iodo compounds. Iodo amide compounds are important in organic chemistry and very useful in medicine. The element iodine plays important roles within the human body and human health. For want of, lists of iodine uses often start with biological uses of iodine within the human body. This leads simply onto uses of iodine in health related contexts, such as its use as an antiseptic and disinfect, then to various medical uses of iodine e.g. as a radiocontrast agent for medical imaging such as CT scan and X-ray imaging etc. In human medicine iodo compounds, such as thyroxine and triiodothyronine, play a vital biological role as thyroid hormones. Iodoarenes participate in variety of organic transformations. To prepare Grignard reagents which are widely used in organic synthesis iodo compounds are used a lot. Iodo compounds (e.g. triiodomethane) are involved in a haloform reaction, which is used as a test for the detection of the CH_3-CO- group in analytical chemistry. Like organobromo compounds, organoiodo compounds are employed in coupling reactions just like the Buchwald-Hartwig amination, in which the aryl iodide undergoes a palladium-catalyzed cross-coupling reaction with amines to make a carbon-nitrogen bond. This reaction has gained wide use not only in the pharmaceutical but also chemical industries, because it involves the facile formation of aryl C-N bonds. Organoiodo compounds are also used in the Wurtz - Fittig reaction. Additionally, for the chlorination and oxidation of various organic substrates, dichloroiodo arenes are used as reagents. Many polyiodo organic compounds are employed as X-ray contrast agents, and in medical imaging. A triiodo compound like sodium acetrizoate (sodium 3-(acetylamino)-2,4,6-triiodobenzoate), is used as a contrast agent for several radiographic studies including pyelography, angiography of the brain, and cholecystography. Similarly, 3,5-diacetamido-2,4,6-triiodobenzoic acid is also a radiocontrast agent. Iodophors are used in the chemical industry to sanitize equipment and bottles and many of the iodo compounds possess antibacterial and antiphlogistic properties. Besides, there are also various other chemical use of iodine- both historical and current. Common examples include the traditional photographic chemical silver iodide.

1.1.1 Neuroprotection

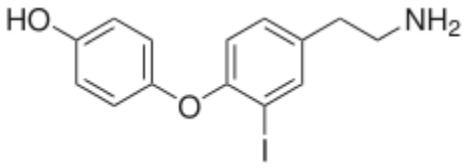


Figure 1: 3-Iodothyronamine (T1AM)

Thyroid hormone and thyroid hormone metabolites, including 3-iodothyronamine (T1AM) are furnished with neuroprotective features including memory stimulation and retrieval,[1] reduction of spinal cord injury and protection of hippocampal neuron cell death induced by KA (kainic acid) . Recently reported that both thyroid hormone and thyroid hormone metabolites activated hippocampal AKT and this activation was responsible for the neuroprotective effect of the 3-iodothyroacetic acid (TA1), the main oxidative metabolite of T1AM produced ubiquitously. The neuroprotective mechanism of T1AM at this setting remained instead to be demonstrated. T1AM is the last iodinated thyronamine which is produced by thyroid hormone alternative metabolism. For the presence of a short half-life being rapidly degraded to TA1 by monoamine oxidases (MAO) or by deiodinases so T1AM pharmacologically delivered to rodents. Typically, T1AM pharmacological effects generate within 15 min from amine administration describing inverted dose-effect curves which are modulated by monoamine oxidase inhibitors, thus suggesting that the production of TA1 may be part of T1AM effects including memory stimulation and hyperalgesia. Recently, it is assured that the participation of TA1 in the T1AM-induced activation of neuroprotective pathways including autophagy. From the pharmacodynamics perspective, T1AM is indicated as a multi-targets molecule able to interact at several G-protein coupled receptors, including the ex-orphan trace amine associated receptor isoform1(TAAR1). Not only T1AM is considered as an agonist of TAAR1 but also a biased agonist at dopaminergic type 2 (D2R) and serotoninergic type 1 B (5HT1BR) receptors which can be found heterodimerized with TAAR1. In really, it is excluded the effect of T1AM on the reduction of spinal cord injury, few of the

pharmacological effects reported for T1AM may be attributed unequivocally to TAAR1 activation. Overall, irrespective of which is the plasma membrane receptor recognized, T1AM may also generate, inside cells TA1, a metabolite which is endowed of an its own signaling capacity and pharmacological activities. Between these mechanisms (the plasma membrane and the intracellular ones) prevails could depend on the expression levels of plasma membrane targets and on the amine oxidase cell kit.

1.1.2 Activity of tumor tissue

The function of cytotoxic drugs is outlined by their selectivity of uptake and action in tumor tissue. In the latter clinical responses achieved by treating metastatic malignant melanoma with therapeutic combination based on gene expression profiling showed that malignant melanoma is flexible to systemic treatment [2]. Malignant melanoma is the fifth most common cancer in men and the sixth most common cancer in women in the United States of America. Rapidly the incidence rates of malignant melanoma are rising. Despite taking a lot of aggressive efforts, the estimated 5-y survival of only 6% has not been significantly improved. The poor outcomes are responsible for the frequent multifocality of metastases. Once metastasized, malignant melanomas are no longer curable by surgical and external radiation therapies. Unfortunately, a trial with dacarbazine, which is considered the gold standard for the treatment of metastatic melanoma, response rates of less than 20%, with only a small fraction of persisting responses, are achieved. In contrast, based on a targeted internal radiotherapy (radiopharmaceutical therapy) considered as a systemic therapy could be effective because melanoma is often sufficiently radiosensitive [3]. For this attempt one prerequisite is the selective targeting of melanoma cells with cytotoxic radiopharmaceuticals. N-(2-(diethylamino) ethyl) benzamides have been shown to selectively accumulate in metastatic melanoma. For the importance of radionuclide therapy of malignant melanoma, the benzamide BA52 (benzo (1,3) dioxolo-5-carboxylic acid (4-(2-diethylamino-ethylcarbamoyl)-2-iodo-5-methoxy-phenyl)-amide) can be radiolabeled with ^{131}I-iodine, a b-particle emitting radionuclide with a physical half-life of 8d. ^{123}I, the g-emitting diagnostic counterpart of ^{131}I, with a physical half-life of 13.2h, can be employed to identify patients with positive tumor uptake of this drug. It is reported that on the synthesis, radiolabeling, pharmacokinetics, preliminary dosimetry data, and

initial therapeutic observations of $^{123}I/^{131}I$-BA52, a novel benzamide, in adult patients with metastatic malignant melanoma.

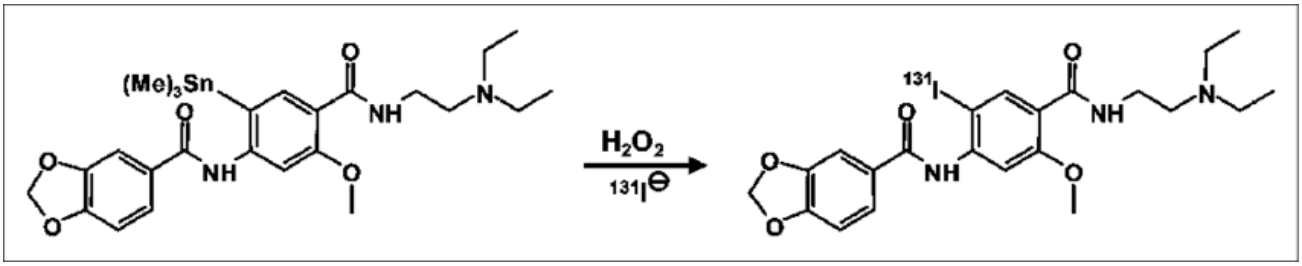


Fig 1: Chemical structure of novel melanin-binding benzamide ^{131}I-BA52

1.1.3. Catalysis

One of the most important application of iodine is as co-catalyst for the production of acetic acid by the Monsanto and Cativa processes. In the technologies, which support the world's demand for acetic acid converts the methanol feedstock into methyl iodide, which undergoes carbonylation. Hydrolysis of the resulting acetyl iodide regenerates hydroiodic acid and gives acetic acid [4].

1.1.4. Nutritional Supplement

The production of ethylene diammonium diiodide (EDDI) consumes a large fraction of available iodine. EDDI is used to livestock as a nutritional supplement [4].

1.1.5. Disinfectant and water treatment

Elemental iodine is used as a disinfectant in various forms almost 100 years. The iodine exists as the element or as the water-soluble triiodide anion I^-_3 generated in situ by adding iodide to poorly water-soluble elemental iodine (the reverse chemical reaction makes some free elemental iodine available for antisepsis)[5]. In alternative fashion, iodine may come from iodophors, which contain iodine complexed with a solubilizing agent (iodide ion may be thought of loosely as the iodophor in triiodide water solutions). Examples of such preparation include [6]:

Povidone iodine is noted for its wide range of uses. Its major applications are in the field of proplylaxis:

*Skin and mucous membrane antisepsis

*Surgical and hygienic hand disinfection.

And in the field of treatment:

*Treatment of burns, decube and varicose ulcers

*Use in the treatment of dermatomycosis pyoderma and acne

*Use in the treatment of vaginitis

The advantage of Povidone iodine is that it can be incorporated in a wide range of formulation

1.1.6. Radiocontrast agent

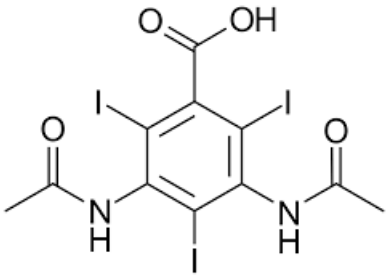


Figure-2:3-acetamido-5- (acetamidomethyl)-2,4,6-triiodobenzoic acid (Diatrizoic acid)

Diatrizoic acid, a radiocontrast agent

- As physically dense element with high electron density and high atomic number, Iodine is quite radio-opaque (i.e., it absorbs X-rays well). And for this nature iodine substituted benzene derivatives are available in medicine as X-ray radiocontrast agents for intravenous injection. This is often in conjunction with advanced X-ray techniques such as angiography and Computed Tomography (CT scanning).
- Generally, radiocontrast agents are compound of either barium or iodine. At present, all water-soluble radiocontrast agents rely on iodine. For example, iodine-based radiocontrast agent incl. iopamidol (Isovue 370), iohexol (Omnipaque 350), ioxilan (Oxilan 350), iopromide (Ultravist 370) and iodixanol (Visipaque 320).

1.1.7 Inorganic Iodo compounds

Iodine makes bond to form compounds with all the elements except for the noble gases. From the perspective of commercial applications, an important compound is hydro iodic acid, used as a co-catalyst in the Cativa process for the production of acetic acid. Titanium and aluminium iodides are used in the production of butadiene which is a precursor to rubber tires. Alkali metal salts are common colourless solids that are highly soluble in water. Potassium iodide is used as a convenient source to form iodide anion. It is easier to handle than sodium iodide because of its hygroscopic nature. Both salts are mainly used in in the production of iodized salt. Sodium iodide is especially useful in the Finkelstein reaction, because it is soluble in acetone, comparatively potassium iodide is less so. In this reaction, an alkyl chloride is converted to an alkyl iodide. This relies on the insolubility of sodium chloride in acetone to drive the reaction.

$$\text{R-Cl(acetone)} + \text{NaI (acetone)} \rightarrow \text{R-I (acetone)} + \text{NaCl (s)}$$

Despite having the lowest electronegativity of the common halogens, iodine reacts violently with some metals, such as aluminium:

$$3I_2 + 2Al \rightarrow 2AlI_3$$

This reaction produces 314kj per mole of aluminium, comparable to thermite's 425kJ. Yet the reaction initiates spontaneously, and if unconfined, causes a cloud of gaseous iodine due to the high temperature.

1.1.8. Organic Iodo compounds

A lot of organo iodo compounds exist; the simplest is iodomethane, approved as a soil fumigant. Iodinated organic compounds are used as synthetic reagents. Organoiodo compounds can be made in many ways. Exemplary, methyl iodide can be prepared from methanol, red phosphorus, and iodine [7]. The iodinating reagent is phosphorus triiodide that is formed in situ.

$$3CH_3OH + PI_3 = 3CH_3I + H_3PO_3$$

The iodoform test uses an alkaline solution of iodine to react with methyl ketones to give the labile triiodomethide leaving group, forming iodoform with precipitation reaction. Aryl and alkyl iodides

both form Grignard reagents. Iodine is something used to activate magnesium to prepare Grignard reagents. Alkyl iodides such as iodomethane acts as good alkylating agents. Some flaws to use of organoiodine compounds in chemical synthesis are:

- Iodine compounds are not cheaper than the corresponding bromides and chlorides, in that order
- Iodides are much stronger alkylating agents, and so are more toxic (e.g., methyl iodide is very toxic (T+) [8]. Low-molecular-weight iodides tend to have a much higher equivalent weight, compared to other alkylating agents (e.g., methyl iodide verses dimethyl carbonate), owing to the atomic mass of iodine.

The organoiodine compound, erythrosine ($C_{20}H_6I_4Na_2O$) is also known as Red no.3, E127 and by other synonyms. It is used as a food colouring agent as well as in printing inks which is known to biological stain. It is also known as dental plaque disclosing agent. Commercial bakeries add usually sodium iodate to certain kinds of flour to improve the quality of the bread.

1.1.9 Biological Role

In the Unites States, the Drug Enforcement Administration (DEA) regards iodine and compounds containing iodine (ionic iodides, iodoform, ethyl iodide and so on) as reagents useful for the clandestine manufacture of methamphetamine [9,10].

Thyroxines are iodine-containing hormones that justify the widespread use of iodised salt. Iodine's main role in animal biology is as a constituent of the thyroid hormones *thyroxines* (T4) and *triiodothyromine* (T3)

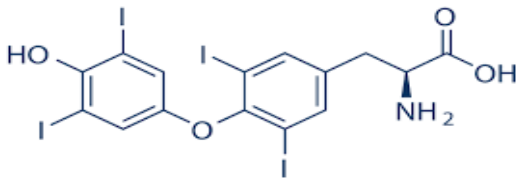


Figure-3: Structure of Thyroxine(3,5,3',5'-tetraiodothyronine)-T_4

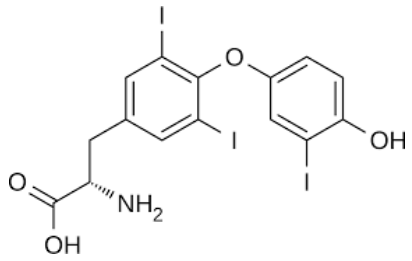


Figure-4: Structure of Triiodothyronine-T3

These are made from addition condensation products of the amino acid tyrosine, and are stored prior to release in an iodine-containing protein called thyroglobulin. T4 and T3 contain four and three atoms od iodine per molecule, respectively. The thyroid gland actively absorbs iodide from the blood to make and release these hormones into the blood, actions that are regulated by a second hormone TSH from the pituitary. Thyroid hormones are phylogenetically very old molecules that are synthesized by most unicellular organisms.

Thyroid hormones play a basic role in biology, acting on gene transcription to regulate the basal metabolic rate. The total deficiency of thyroid hormones can reduce basal metabolic rate up to 50%, while in excessive production of thyroid hormones the basal metabolic rate can be increased by 100%. T4 acts as a precursor to T3, which is (with minor exceptions) the biologically active hormone.

Iodine has a nutritional relationship with selenium. A family of selenium-dependent enzymes called deiodinases converts T4 and T3 (the active hormone) by removing an iodine atom from the outer tyrosine ring. These enzymes also convert T4 to reverse T3(rT3) by removing an inner ring iodine atom, and convert T3 to 3,3’-diiodothyronine (T2) also by removing an inner ring iodine atom. Both of the latter are inactivated hormones that are ready for disposal and have, in essence, no biological effects. A family of non-selenium-dependent enzymes then further deiodinates the products of these reactions.

Iodine accounts for 65% of the molecular weight of T4 and 59% of the T3. Fifteen to 20mg of iodine concentrated in thyroid tissue and hormones, but 70% of the body’s iodine is distributed in other tissue, including mammary glands, gastric mucosa, the cervix, and salivery glands. In the

cells of these tissue is related, iodide enters directly by sodium-iodide symporter(NIS). Its role in mammary tissue is related to fetal and neonatal development, but its role in the other tissues is unknown [11].

1.1.10. As a food colouring agent

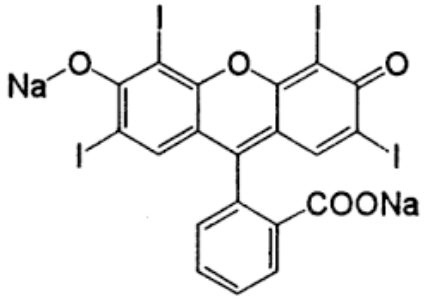


Figure-5: Structure of Erythrosine [2-(6-Hydroxy-2,4,57-tetraiodo-3-oxo xanthen-9- yl) benzoic acid]

Erythrosine[11], also known as Red No. 3, is an organoiodine compound, specifically a derivative of fluorone. It is a pink dye which is primarily used for food coloring. It is the disodium salt of 2,4,5,7-tetraiodofluorescein. Its maximum absorbance is at 530 nm in an aqueous solution, and it is subject to photodegradation.

It is used as a:

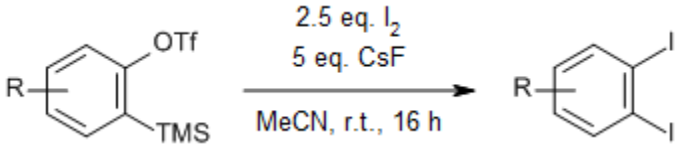
- Food colouring agent
- Printing ink
- Biological stain
- Dental plaque disclosing agent
- sensitizer for orthochromatic photographic films
- Visible light photoredox catalyst

Erythrosine is commonly used in sweets such as some candies and popsicles, and even more widely used in cake-decorating gels. As a food additive, it has the E number E127.

1.2 Iodination of aromatic compounds

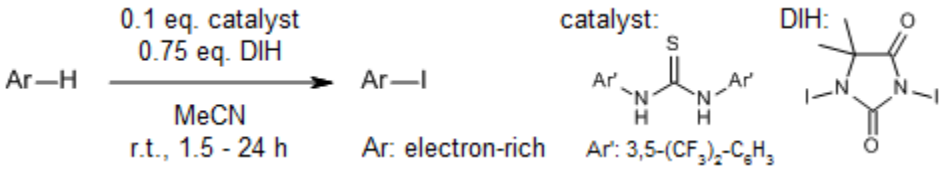
1.2.1 Aryne Insertion into I-I σ bonds

A new protocol for the efficient synthesis of o-diiodoarenes [12] has been developed. This method allows the synthesis of substituted and polycyclic o-diiodoarenes, which are difficult to obtain by classical methods.



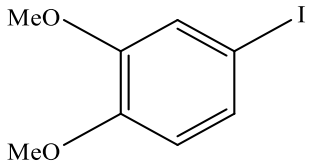
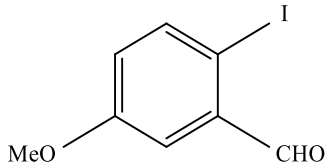
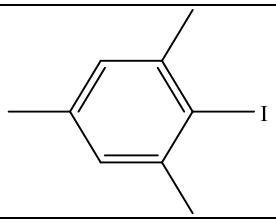
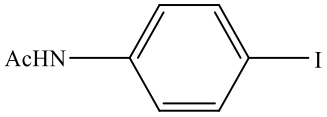
1.2.2. Organocatalytic Iodination of Aromatic Compounds

An organocatalytic iodination of activated compounds using 1,3-diiodo-5,5-dimethylhydantion (DIH)[13] as the iodine source with thiourea catalysts in acetonitrile is applicable to a number of aromatic substrates with significantly different steric and electric properties.



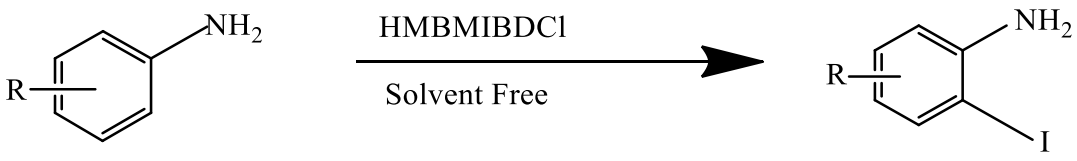
The iodination is generally highly regioselective and provides high yields of isolated products.

Table -1 : Iodination by DIH with Thiourea catalysts

Sl No	Product	Selectivity	Yield (%)
1.		49:1	68
2.		6:1	66
3.		50:1	83
4.		50:1	92

1.2.3 Iodination by Ionic Liquid Iodinating Reagent

An ionic liquid iodinating agent as Hexamethylene bis (N-methylimidazolium) bis (dichloroiodate)(HMBMIBDCI) [14] has been prepared and characterized. Its ability to perform iodination reactions reagent with a variety of substrates has been explored. In general, iodination reactions of aromatic and heteroaromatic amines proceed with good yields in the absence of solvent.

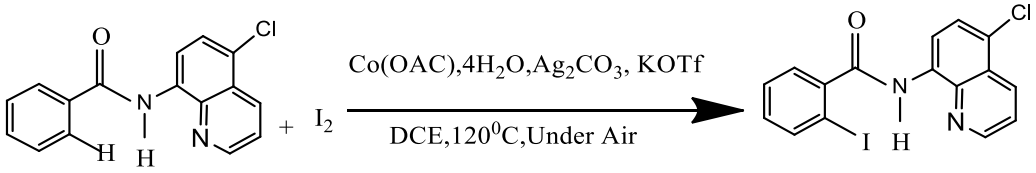


1.2.4 Acts as best leaving group

Almost all organoiodine compounds feature iodide connected to one carbon center. These are usually classified as derivatives of I^-. Some organoiodine compounds feature iodine in higher oxidation states [15]. The C–I bond is the weakest of the carbon–halogen bonds. These bond strengths correlate with the electronegetivity of the halogen, decreasing in the order F > Cl > Br > I. This periodic order also follows the atomic radius of halogens and the length of the carbon-halogen bond. For example, in the molecules represented by CH_3X, where X is a halide, the carbon -X bonds have strengths, or bond dissociation energies, of 115, 83.7, 72.1, and 57.6 kcal/mol for X = fluoride, chloride, bromide, and iodide, respectively [16]. Of the halides, iodide usually is the best leaving group. Because of the weakness of the C-I bond, samples of organoiodine compounds are often yellow due to an impurity of I_2.

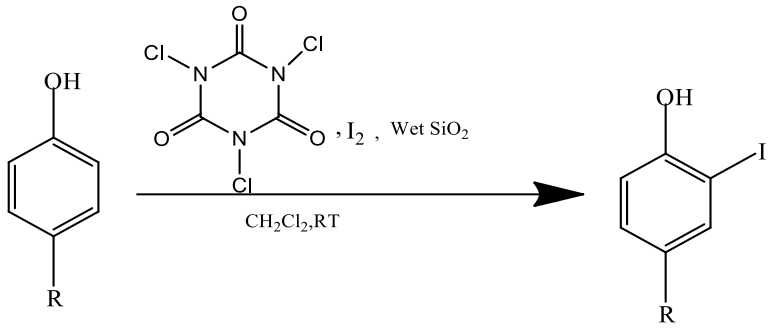
1.2.5 Cobalt(II)- catalyzed chelation assisted C-H Iodination

The cobalt-catalyzed chelation-assisted iodination of aromatic amides using molecular I_2 as an iodinating reagent is reported. 8-Amino-5-chloroquinoline[17] functions as an efficient directing group. This mild and air stable catalytic system shows a wide functional group tolerance and improved synthetic accessibility.



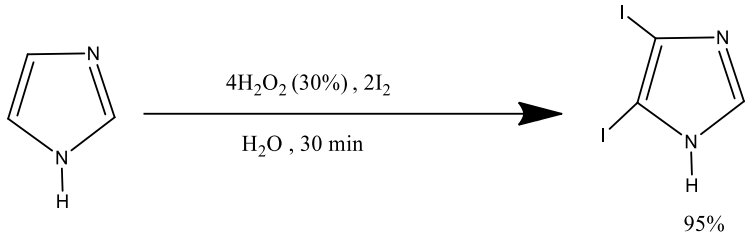
1.2.6. Mild Iodination by Trichloroisocyanuric Acid

Molecular iodine in the presence of trichloroisocyanuric acid[18] and wet SiO_2 has been utilized efficiently for iodination of phenols under mild reaction conditions. It is desirable to apply a simple, inexpensive and non-toxic reagent system for iodination of aromatic compounds. Trichloroisocyanuric acid,[19,20] which used primarily as a disinfectant has found little application in organic chemistry so far.



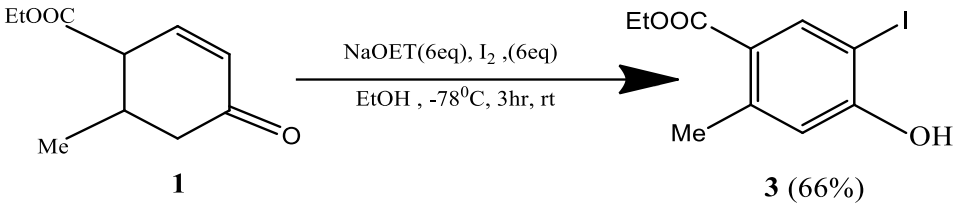
1.2.7 Rapid protocol for iodination

A rapid and efficient ultrasound promoted protocol for iodination of aromatic and hetero aromatic compounds, using molecular iodine in the presence of aqueous hydrogen peroxide in water without any solvent, has produced versatile iodinated organic molecules with potential application in organic synthesis and medicine in short reaction times and good to excellent yield.[21]

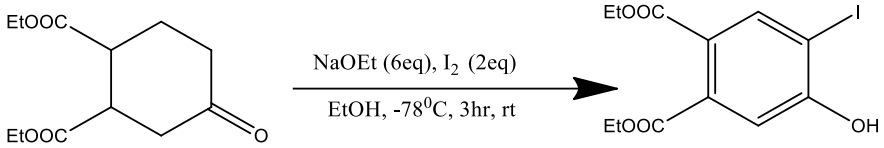


1.2.8 Transformation using Iodine and Sodium Ethoxide

Transformation of a wide variety of easily 2-cyclohexane-4-carboxylates 1-2 to the corresponding iodophenols 3-4 in high yield has been accomplished **[22]** with iodine and sodium ehtoxide in ethanol. 2-propanols are versatile building blocks for synthesis of a variety of benzoheterocyclic systems. Several unsaturated cyclohexanone derivatives undergo oxidative aromatization **[23]** with iodine-cerium (iv) ammonium nitrate in alchohol (methanol,ethanol,1-propanol,2-propanol) affording the corresponding alkylphenyl ethers in good yield.

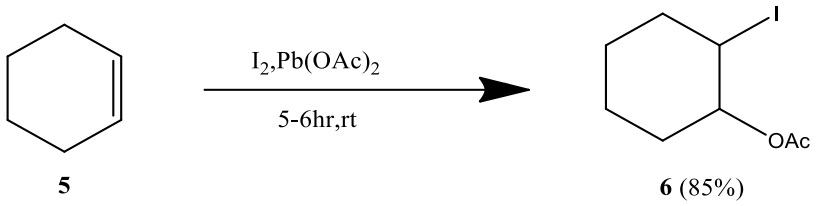


1 **3** (66%)

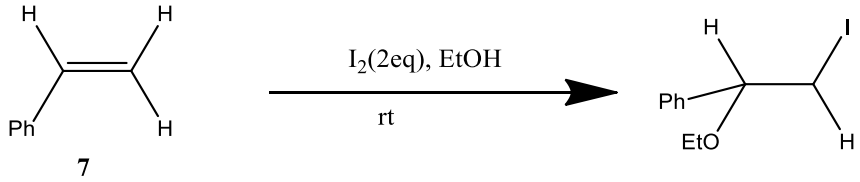


2 **4** (77%)

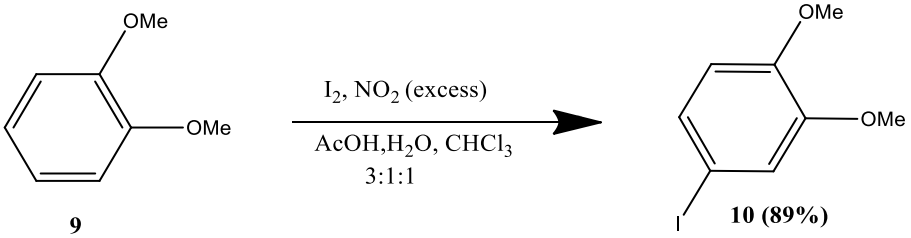
Iodination of double bond [24] **5-6, 7-8** and aromatic compounds **9-10, 11-12** has been realized in high yield.



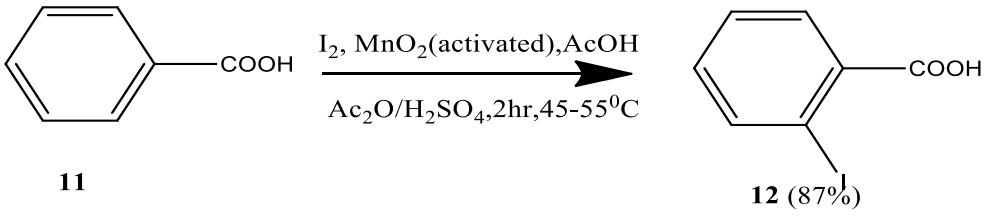
5 **6** (85%)



7 **8** (75%)



9 **10 (89%)**



11 **12** (87%)

1.2.9. Iodination of Methoxybenzenes with N-Iodosuccinimide in Acetonitrile

Derivatives of Methoxy aromatic used in this study were submitted to reaction with NIS in CH_3CN at different temperatures [25]. The results are collected in the **Table-2**. As can be seen , the products obtained in all cases resulted from the regiospecific iodination of the aromatic ring. The observed regiochemistry was the result of reaction through the persumably more electron rich and less sterically encumbered aromatic ring position. Thus , para positions of methoxybenzens (entries **1,5** and **6**) and 4- and 1- position of methoxynapthalenes (entries **9** and **10**) were exclusively iodinated, whereas the ortho-iodination only ocurred when the para position was occupied (enties **4** and **7**). As was found with NBS, chain iodination products were not detected in the reactions of NIS with methylanisoles under refluxing acetonitrile (entries **2-4**).

The reactivity of the substrates seems to be associated to the electronic density of the aromatic rings. Thus, iodination of 1,3- and 1,4- dimethyoxybenzene (entries **6** and **7**) and 1,2,4-trimethoxybenzene (entry **8**) took place at rt whereas the rections of methoxybenzens and naothalenes (entries **1-4** and **9-10**) and 1,2-dimethoxybenzene (entry **5**) required refluxing acetonitrile to be completed. It is noteworthy that the activiting effect of the substitutents is only additive when they are not arranged on adjacent carbons. Thus, the influence is scarce (compare entries **1** with **2** and with **8**) or even negative (compare entries **1** with **5**) when iodination can take place on a free para position. In the case of 1,2- dimethoxybenzene (entry **5**), this could be a consquence of the lower activation of the reactive position 4 due to the OMe group situated at C-2 (meta) .

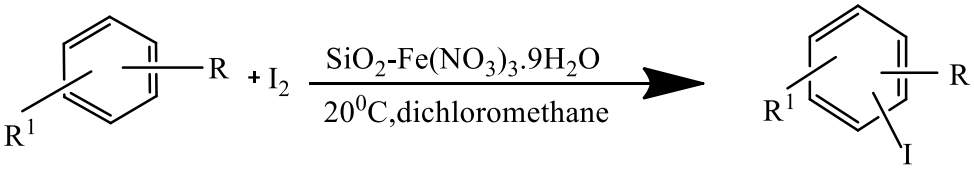
Table -2: Iodination of Methoxybenzenes and Napthalenes with NIS in CH_3CN

Entry	Substrate	NIS (Eqv.)	Temp	Time	Product	Yield (%)
1	Anisole	1.5	82^0C	6h	4-Iodoanisole	95%
2	2-Methylanisole	1.5	82^0C	8h	4-Iodo-2-Methylanisole	96%
3	3-Methylanisole	1.5	82^0C	2h	4-Iodo-3-Methylanisole	90%
4	4-Methylanisole	1.5	82^0C	8h	2-Iodo-4-Methylanisole	90%
5	1,2-Dimethoxybenzene	1.5	82^0C	18h	4-Iodo-1,2-Dimethoxybenzene	85%
6	1,3- Dimethoxybenzene	1.1	20^0C	5h	1-Iodo-2,4-Dimethoxybenzene	90%
7	1,4-- Dimethoxybenzene	1.1	20^0C	19h	2-Iodo-1,4-Dimethoxybenzene	95%
8	1,2,4-Trimethoxybenzene	1.1	20^0C	4h	1-Iodo-2,4,5-trimethoxybenzene	95%
9	1-Methoxy-Napthalene	1.5	82^0C	6h	4-Iodo-1-methoxy Napthalene	97%
10	2-meyhoxy-napthalene	1.5	82^0C	24h	1-Iodo-2-Methoxy napthalene	96%

1.2.10. Iodination of activated arenes using silfen

Iodoarenes are valuable and versatile synthetic intermesiates with wide applications in medicine and biochemsistry. Recent progress in oraganotransition metal chemsitry has renewed the importance of these iodoarenes. The transformations of iodine in iodoarenes,to diverse functional groups, by transition metal catalysts has been a popular and fruitful area if investigation.[26] A simple and direct method for the iodination of activated arenes,using molecular iodine and silfen(silica supported ferric nitrate nonahydrate) as an oxidant, is presented. The reactions are performed at 20^0C in dichloromethane.[27] The method provides an easy access to the corresponding iodinated products in good yields. Synthetic methods involving a source of positive iodine i.e. I^+ as the reactive species , seem to be the most convenient procedure for the direct iodination of

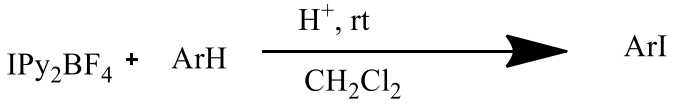
arenes. A side array of reagents and methods involving molecular iodine, in combination with oleum, CrO_3 , F_2, $Pb(OAc)_4$, Hg salts, nitrogen dioxide and CF_3SO_3Ag have been documented. However , most of these methods require large volumes of mineral acids, high reaction temperatures , the use of expensive/ non ecofriendly / sensitive mettalic reagents and the generation of largge amount of toxic waste. Hence , a convenient method involving mild reaction conditions is highly desirable. So, it is wished to report a mild,efficient and regioselective monoiodination of activated arenes, using molecular iodine and silfen. Silfen is prepared under solvent free conditions and possesses no handling and storage problems.



where R, R^1 = -H, alkoxy,alkyl, aryloxy, halogen etc.

1.2.11. A selective and general iodination method by IPy_2BF_4

Reaction of aromatic compounds with bis(pyridine) iodinoium(I) tetrafluroborate (IPy_2BF_4) in the presence of HBF_4 or CF_3SO_3H in CH_2Cl_2 at room temperature furnishes monoiodo derivates with excellent regioselectivity and yields[28]. Use of either acid gives compareble results with activated aromatics, whereas CF_3SO_3H is much more effective in the iodination of deactiveted aromatics. Treating a mixture of IPy_2BF_4 and an aromatic compound with an acid dichloromethane at room temperature gave monoiodinated products in good yields.



H^+ : HBF_4 or CF_3SO_3H

Initially reactions are carried out using HBF_4 as the acid neutralize pyridine and liberate the iodination agent **Table-3**.

Table-3: Room temperature Iodination of Aromatic Compounds by Acid Treatment of Ipy_2BF_4

Entry	Starting Material	Acid	Time (h)	ArI (Yield%)
1	Benzene	HBF_4	0.25	48
2	Benzene	CF_3SO_3H	0.25	60
3	1,3,5-trimethoxybenzene	CF_3SO_3H	0.25	86
4	Aniline	HBF_4	0.10	90
5	N,N-dimethylaniline	HBF_4	0.10	98
6	Methylbenzoate	CF_3SO_3H	14	84
7	Benzoic acid	CF_3SO_3H	10	86
8	Benzaldehyde	CF_3SO_3H	10	80
9	Nitrobenzene	CF_3SO_3H	14	82

1.2.12 A Practical Iodination of Aromatic Compounds Using Tetrabutylammonium Peroxydisulfate ($(TBA)_2S_2O_8$) and Iodine

A combination of tetrabutylammonium peroxydisulfate ($(TBA)_2S_2O_8$) and iodine has been found to be an excellent reagent for the efficient iodination of aromatic compounds such as methoxybenzene,phenol, and aniline in acetonitrile under mild **co**nditions [29]. This reaction has an advantage to be carried out at 20^0C under the neutral condition in acetonitrile.

Tetrabutylammonium peroxydisulfate was successfully prepared and turned out to be a useful source of tetrabutylammonium sulfate radical, which can be readily converted to sulfate anion by one electron transfer from a substrate [30].

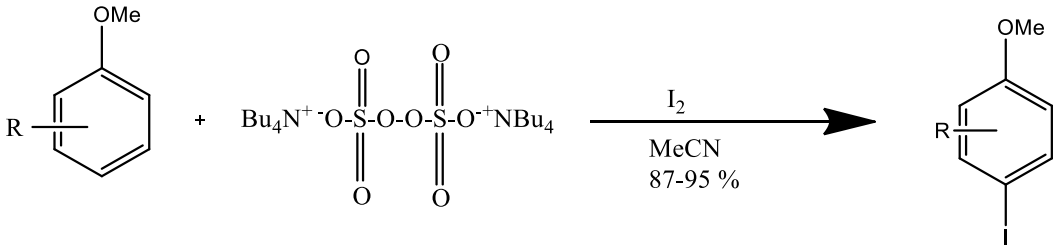
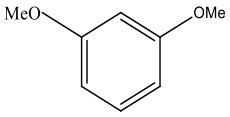
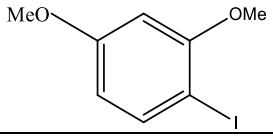
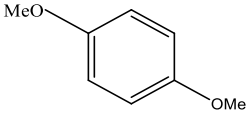
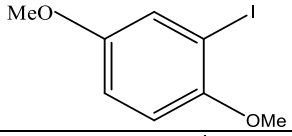
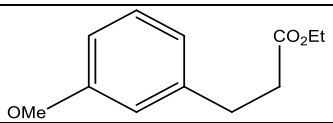
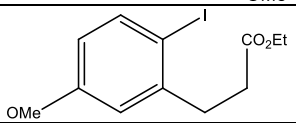
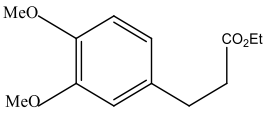
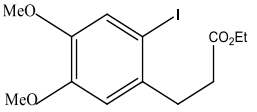
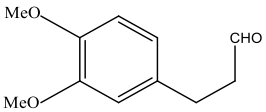
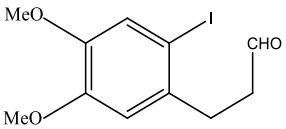
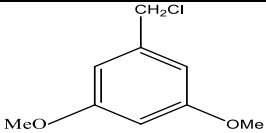
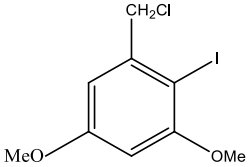
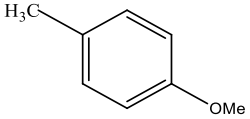
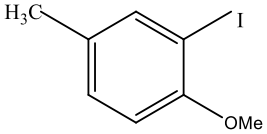
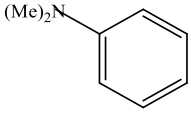
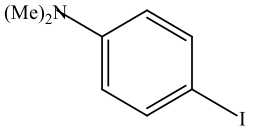
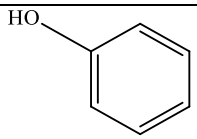
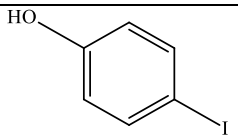
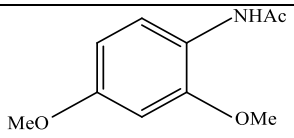
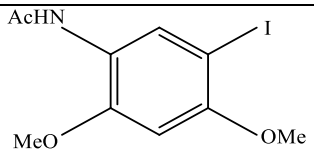
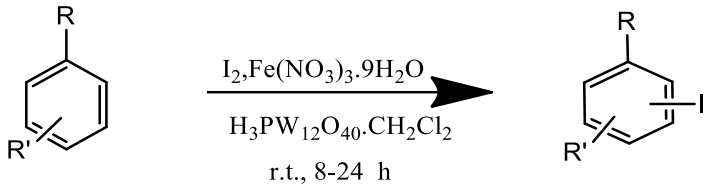


Table-4 : Iodination of Aromatic Compounds Using $(TBA)_2S_2O_8$ and Iodine

Run	Substrate	Time (h)	Temp (^{0}C)	Product	Yield (%)
1		0.7	20		95
2		3	20		92
3		6	50		92
4		7	50		93
5		7	50		87
6		2	20		91
7		20	20		87
8		24	20		88
9		30	20		92
10		20	20		93

1.2.13. Efficient and regioselective iodination of arenes using iron(III) nitrate in the presence of tungstophosphoric acid

An easy, cheap,and effective method for iodination of various aromatic compounds takes place with molecular iodine and iron nitrate nonahydrate as the oxidant in the presence of a catalytic amount of tungstophosphoric acid in dichloromethane [31], with good yields and high regioselective in mild conditions.



R=OCH_3, CH_3, OH, NH_2, $NHCOCH_3$

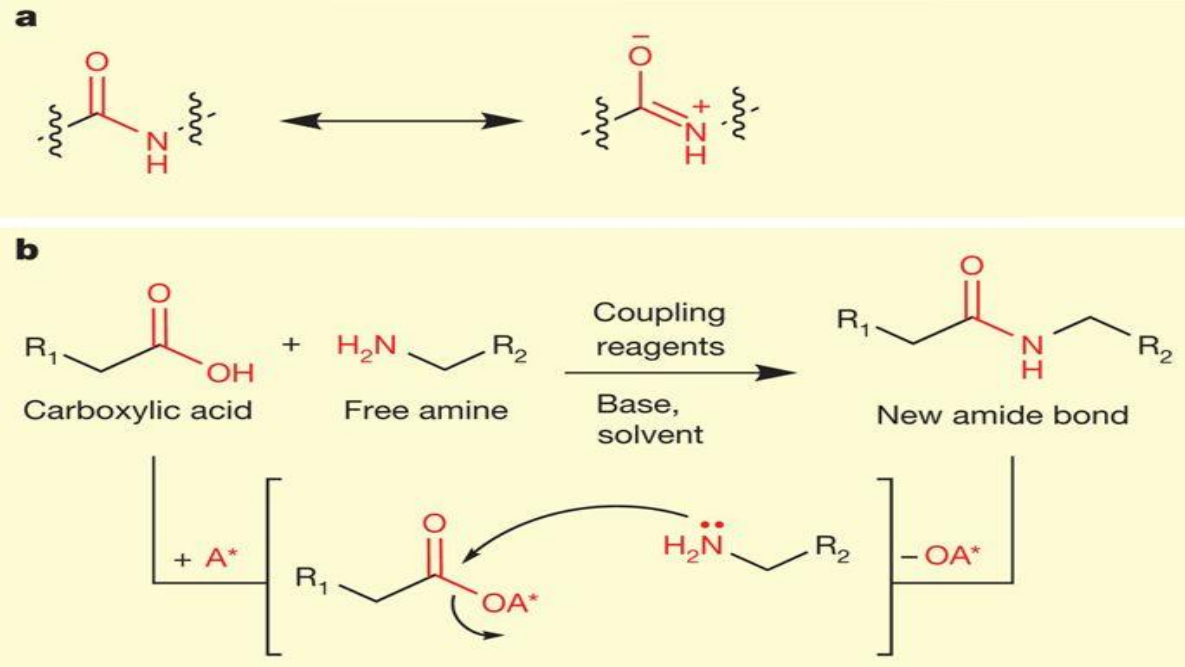
R'= OCH_3, CH_3,NO_2, Br, H

1.3 Amide Bond Activation

The presence of carboxamide groups is found in a large array of biologically important compounds. Peptides and proteins play an important role in modern biology. A key step in peptide production is the formation of the peptide bond, which involves amide bond formation[32]. Amide bonds are the most prevalent structures found in organic molecules and various biomolecules such as peptides, proteins, DNA, and RNA. The unique feature of amide bonds is their ability to form resonating structures, thus, they are highly stable and adopt particular three-dimensional structures, which, in turn, are responsible for their functions. The main focus of this review article is to report the methodologies for the activation of the unactivated amide bonds present in molecules, which includes the enzymatic approach, metal complexes, and non-metal based methods. This article also discusses some of the applications of amide bond activation approaches in the sequencing of proteins and the synthesis of peptide acids, esters, amides, and thioesters. Chemical synthesis of large peptides by intermolecular coupling of smaller peptides using conventional peptide bond-forming techniques did not realize its potential advantages until recently. Using an approach based on highly specific and efficient chemical ligation has extended the concept by creating catalytic amide bond formation, synthesizing of native therapeutic peptides and providing new approaches to peptides and protein engineering.

Amide linkage [33] are not only the key chemical connections of proteins but they are also the basis for some of the most versatile and widely used synthetic polymers. Chemical reactions for their formation are among the most executed transformations in organic chemistry (Fig-6). The prevalence of amide functionally, particularly in peptides and proteins [34], sometimes gives the incorrect impression that there are no remaining synthetic challenges. This is surprising, as it is often the case that even simple amidest resist formation, forcing practitioners to resort to ever more exotic and expensive reagents for their synthesis. Furthermore, the favourable properties of amides, such as high polarity, stability and conformational diversity, make it one of the most popular and reliable functional groups in all branches of organic chemistry. Improved methods for the synthesis of amide functionality, whether catalytic and waste-free or chemoselective and suitable for fragment coupling, are in great demand.

Figure-6: Chemical structure of amides and the conventional chemical method for amide bond synthesis



a.Resonance structures of an amide group. **b** the conventional method for formation of an amide bond. It involves activation of a carboxylic acid by an activating group(A*), followed by nucleophilic displacement by a free amine to generate a new amide bond in the presence of coupling reagent, base and solvent. R_1 and R_2, small molecules, peptides or proteins.

The amide functionality is a common feature in small or complex synthetic or natural molecules. For example, it is ubiquitous in life, as proteins play a crucial role in virtually all biological processes such as enzymatic catalysis (nearly all known enzymes are proteins), transport/storage (haemoglobin), immune protection (antibodies) and mechanical support (collagen). Amides also play a key role for medicinal chemists. An in-depth analysis of the Comprehensive Medicinal Chemistry database revealed that the carboxamide group appears in more than 25% of known drugs[35]. This can be expected, since carboxamides are neutral, are stable and have both hydrogen-bond accepting and donating properties. In nature, protein synthesis involving a sequence of peptide coupling reactions (amide bond formation between two a-amino acids or peptides) is very complex, probably to safeguard the unique and precisely defined amino acid sequence of every

protein. This barrier is overcome in vivo by a selective activation process catalysed by enzymes, where the required amino acid is transformed into an intermediate amino ester. This intermediate is then involved in a process mediated by the coordinated interplay of more than a hundred macromolecules, including mRNAs, tRNAs, activating enzymes and protein factors, in addition to ribosomes[36].

Amide or ester bond formation between an acid and, respectively, an amine or an alcohol are formally condensations. The usual esterifications are an equilibrium reaction, whereas, on mixing an amine with a carboxylic acid, an acid– base reaction occurs first to form a stable salt. In other words, the amide bond formation has to fight against adverse thermodynamics as the equilibrium shown in **figure -7** and lies on the side of hydrolysis rather than synthesis[37].

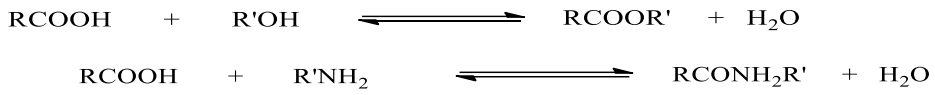


Figure-7: Ester Bond vs Amide Bond Formation

The direct condensation of the salt can be achieved at high temperature (160–180 ^{0}C)[38], which is usually quite incompatible with the presence of other functionalities Therefore, activation of the acid, attachment of a leaving group to the acyl carbon of the acid, to allow attack by the amino group is necessary (**figure-8**).

Figure-8: acid activation and aminolysis steps

Hence, a plethora of methods and strategies have been developed and these are now available for the synthetic, medicinal or combinatorial chemist. Relevant examples of these methods are indicated in this report. The chemist might have to screen a variety of such conditions to find the method best adapted to his situation. For example, due to poor reactivity or steric constraints in some extreme cases, the challenge will be to get the amide formed at all. In other situations, the chemist will require the reaction to avoid racemisation. In general, the aim could also be to

optimise the yield, to reduce the amount of by-products, to improve selectivity, to facilitate the final purification, to define a scalable process or to exploit more economical reagents. In the last two decades, the combined rapid development of solid-phase technologies and coupling methods has enabled parallel synthesis to become a tool of choice to produce vast amounts of diverse compounds for early discovery in the pharmaceutical industry

Carboxy components can be activated as acyl halides, acyl azides, acylimidazoles, anhydrides, esters etc. There are different ways of coupling reactive carboxy derivatives with an amine:

- an intermediate acylating agent is formed and isolated then subjected to aminolysis
- a reactive acylating agent is formed from the acid in a separate steps , followed by immediate treatment with the amine
- the acylating agent is generated in situ from the acid in the presence of the amine, by the addition of an activating or coupling agent.

Amide bond formation can often present difficulties such as low yields, racemisation, degradation, difficult purification etc. To face these challenges, numerous mild coupling reagents and methods have been developed that not only are high yielding, but that potentially help to prevent racemisation of neighbouring chiral centres. A classical example of racemisation is encountered in peptide synthesis when the terminal acid peptide is activated, leading to the formation of the corresponding oxazolone **1a**. Under mild basic conditions, the oxazolone undergoes racemisation via the formation of conjugated anionic intermediate 2. The resulting oxazolone **1a**, **1b** mixture reacts then with a nucleophile, explaining the loss of chiral integrity of the coupled material **3a**, **3b** (figure-9). Therefore, peptides are usually grown at the N-terminus and mild activation conditions are needed. In this latter approach, the activation is advantageously performed on an N-protected a-amino acid, thus avoiding the oxazolone formation. Acyl chlorides (also called acid chlorides) are one of the easiest methods to activate an acid and numerous acyl chlorides are commercially available. This is usually a two-step process, involving first the conversion of the acid into the acyl halide followed by the coupling itself.

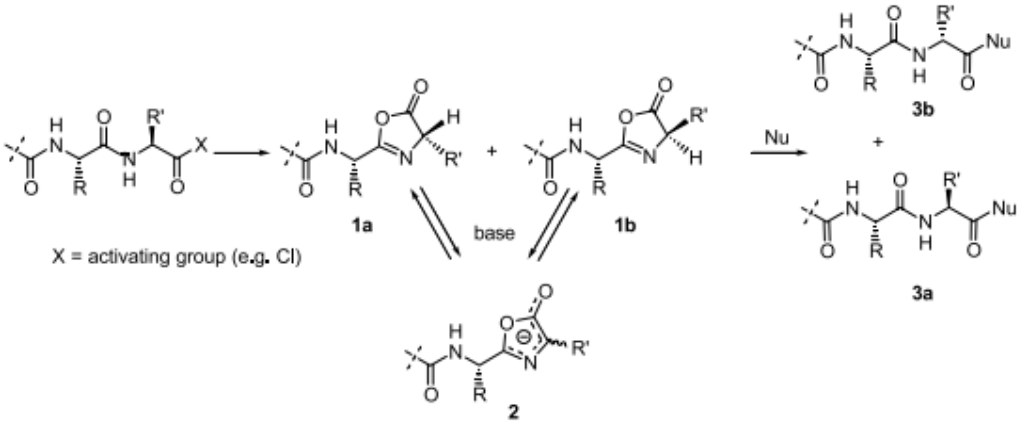


Figure-9: Oxazolone-mediated racemisation occurring during peptide coupling

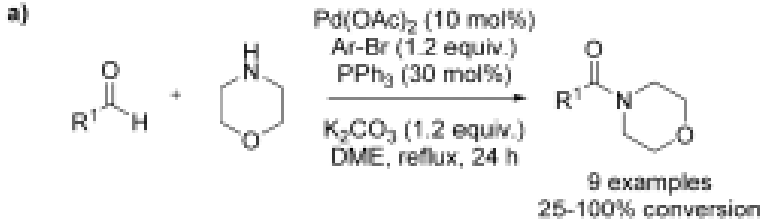
Thionyl chloride $SOCl_2$ [38], 5 oxalyl chloride $(COCl)_2$ [39,40], phosphorus trichloride PCl_3[41], phosphorus oxychloride $POCl_3$ [42] and phosphorus pentachloride PCl_5[43] are commonly used to generate acyl chlorides from their corresponding acids. Phoshonium pentachloride is generally used for aromatic acids, which contains electron-withdrawing substituents and which do not react readily with thionyl chloride [44].

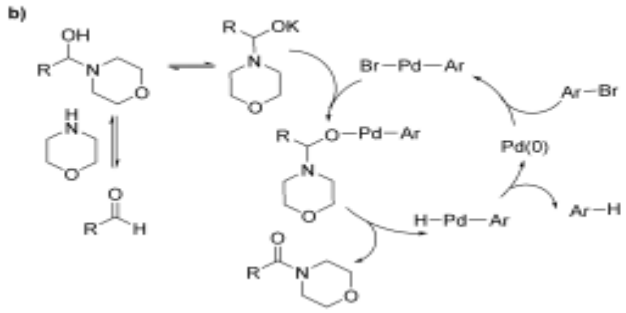
Recently, several elegant strategies have been explored for the formation of amide bonds by employing metal-catalyzed and metal-free conditions. In this context, the direct coupling of carboxylic acids or thioacids with amines or amine surrogates[45], the transamidation of amides[46], synthesis from oximes and ketones[47], or amine surrogates[48], the hydration of organonitriles[49], the N-formylation or oxidation of amines [50] , the oxidative/reductive amidation of aldehydes [51] ,and the oxidative amidation of alchols [52] have all been explored. Another powerful method is the aminocarbonylation of aryl halides[53], alkynes [54] and olefins [55]. Of these methods, the formation of amide bonds from carbonyl compounds (aldehydes, oximes, and ketones) has received much attention, owing to their accessibility and non-toxicity. Over the past few years, several groups have reviewed the scope and development of amide synthesis[56].Although the synthesis of amides from carbonyl compounds has already been described in some of these previous reviews, no comprehensive review of this special topic has hitherto been reported. Recent developments and current challenges in the formation of amide bonds has been reported on a variety of stylish metal-catalyzed and metal-free methods (including the use of N-heterocyclic carbenes or ionic liquid catalysts,biocatalysts, photocatalysts, and Lewis acid or

base catalysts) for the synthesis of amides from carbonyl compounds, such as aldehydes, oximes, and ketones.

1.3.1 Transition-metal catalyzed reaction

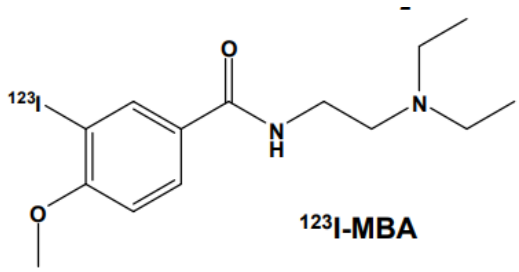
Over the past few years, several transition-metal-catalyzed approaches have been explored for the amidation of aldehydes with amines. In 1983, Tamaru et al. reported the first palladium-catalyzed oxidative amidation strategy for the synthesis of morpholine-based amides through the coupling of aldehydes with morpholine in the presence of [$Pd(OAc)_2$] as a catalyst, ArBr as an oxidant, and K_2CO_3 as a base (Scheme 4a).



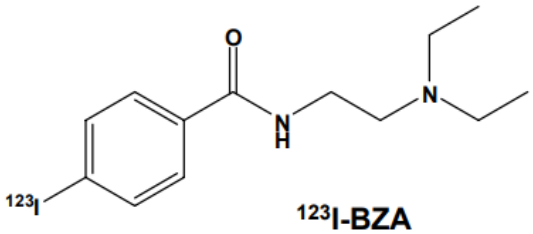


1.4 Application of iodo benzamides

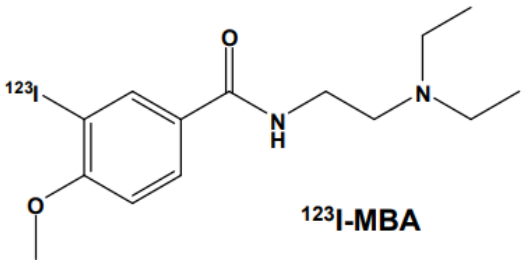
1.4.1 As radiotherapeutic agent



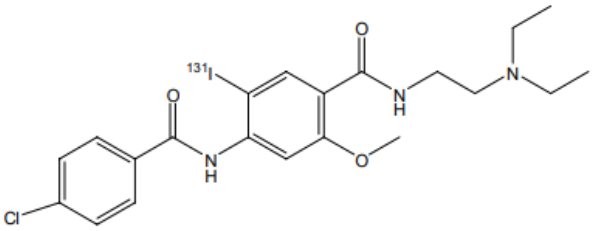
^{123}I-MBA



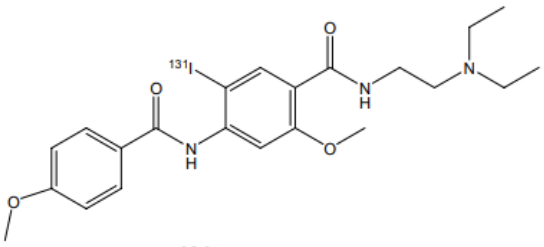
^{123}I-BZA



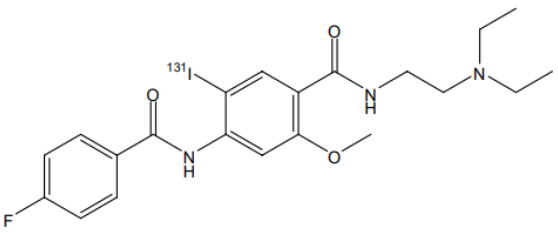
^{123}I-MBA



^{131}I-MIP-1143



^{131}I-MIP-1144

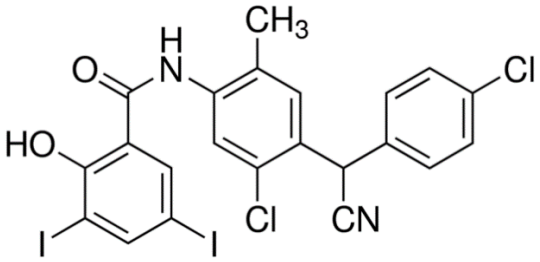


^{131}I-MIP-1145

1.4.2 Anti dopaminergic activity

1.4.3 Anti parasite activity

Claude et al and Ernest et al [57] reported the anti parasite activity of the compound.



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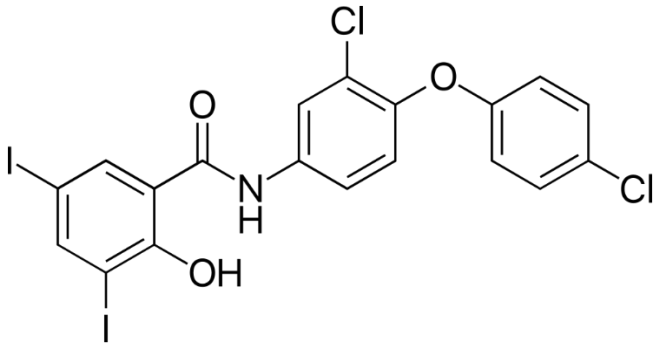
Lanusse et al, Alvarez et al,Virkel et al [58] also showed that the compound has anti parasite activity. The compound trade name rafoxanide.



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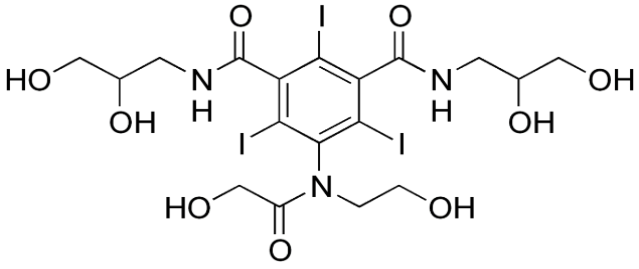
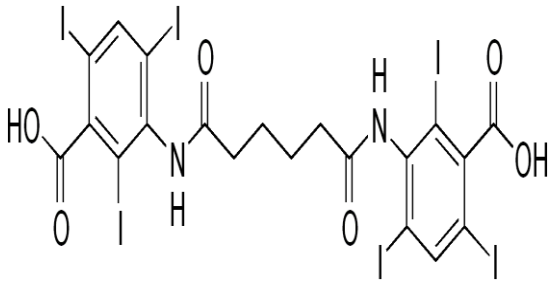
1.4.4. As Radio Contrast Materials

Over 75 million doses of radiocontrast media (RCM) are administered annually to patients worldwide [59]. Despite the seemingly low risk, one can extrapolate that a fair number of hypersensitivity reactions to RCM will be observed. In addition, the field of interventional pain management has grown rapidly. For example, in 2005, 4 million interventional pain procedures were performed on Medicare patients; the vast majority of these procedures utilized fluoroscopy for guiding injections. Frequently, RCM is employed to facilitate visualization of the spread of medications during pain procedures. Contrast media is helpful for the identification of spread within neural structures and the epidural space, and are helpful for the detection of inadvertent intravascular injection.



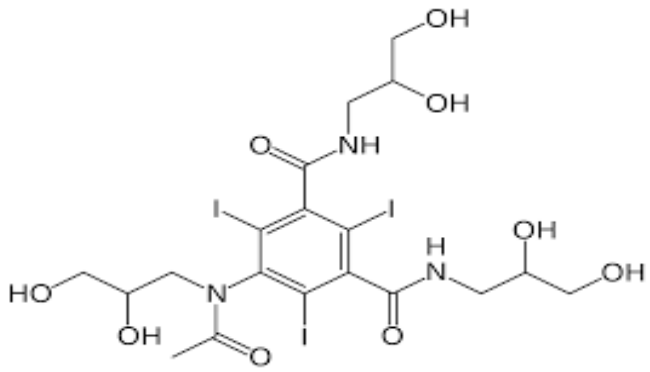
Loversol (Optiray)

3



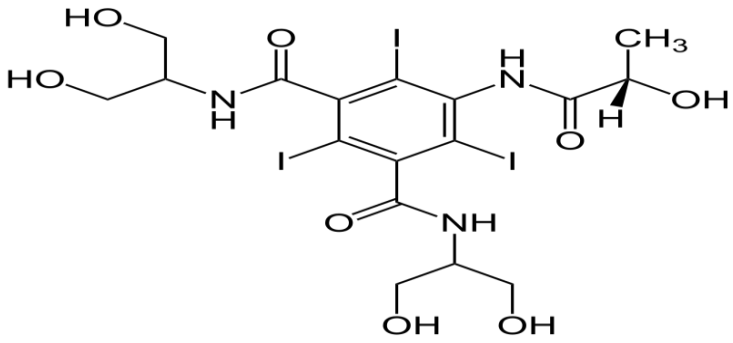
Iodipamide

4



Iohexol

5



Iopamidol

6

Chapter -2

Experimental

Experimental

2.0 General Experimental

All the solvents for reaction separation, extraction and recrystallization were purified and the test was used as available commercially.

2.1.1 Chemicals and reagents

Analytical or laboratory grade solvents and chemicals were used in all experiments and these were procured from E. Merck (Germany) and Fluka (Switzerland). Reagents grade of chloroform, n-hexane, ethyl acetate, ethanol, acetone etc. were purified by distillation at the boiling point of the respective solvent.

Others reagents and chemicals which were used in this research are given below:

1. Dry ethanol
2. Acetone
3. n-hexane
4. Chloroform
5. Ethyl acetate
6. Solid iodine
7. Potassium iodide
8. Potassioum iodate
9. Aniline and aniline derivatives
10. Acyl chloride derivatives
11. TLC plate

2.1.2. Instruments

The synthesized iodo amides were analysed using the following instruments:

- UV-visible Spectrophotometer (Shimadzu-1800)
- Fourier Transform Infrared Spectrophotometer (Shimadzu FTIR-8400)
- Nuclear Magnetic Resonance Spectrophotometer (Bruker BPX-400)
- Digital Balance (Precision electrical balance)
- Stirrer
- Rotatory evaporator

- UV-light
- Guard tube containing calcium chloride
- Büchner funnel

2.1.3. Purification of solvents and reagents

The following methods were used for the purification and drying of the solvents.

a) Dry ethanol (EtOH)

About 2 gm of clean and dry magnesium turnings and 0.125 gm of iodine were placed in a dry 500 ml round bottom flask containing 30-40 ml of reagent grade ethanol. The flask was then fitted with a double surface condenser carrying a calcium chloride guard tube on the top. The mixture was warmed until the iodine disappeared, if a lively evolution of hydrogen did not set in a further little amount of iodine was added. Heating was continued until all the magnesium was covered into pasty mass ethanol. About 230 ml of commercial grade ethanol was then added to the flask and refluxed the mixture for an additional hour. The resulting mixture was distilled off and the first 10-15 ml of distillate was discarded. Then the dry ethanol was collected into a receiving flask from which it was stored into a quick fit bottle.

b) Ethyl acetate

Ethyl acetate from E. Mark (Germany) was used directly as it was bought commercially.

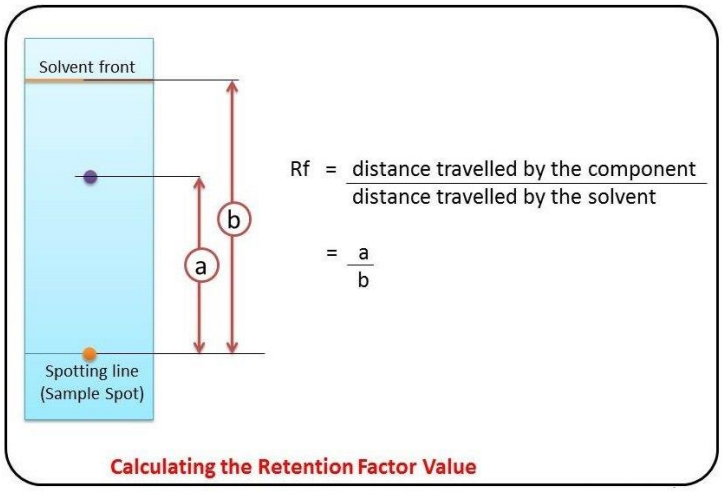
2.2 characterization of synthesized product

2.2.1 Melting point

Melting point were determined on Gallenkamp (England) melting point apparatus.

2.2.2 Chromatographic techniques

Thin layer chromatography (TLC) is a chromatographic technique used to separate the compounds of a mixture. In planar chromatography in particular, the retardation factor (R_f) is defined as the ratio of the distance traveled cy the center of a spot to the distance traveled by the solvent front.



2.2.3 Infra-red (IR) spectra

The infra–red spectra were recorded on KBr pellet for films with a Shimadzu FTIR spectrophotometer from the Department of Chemistry, (BUET), Dhaka, Bangladesh.

2.2.4 Ultra-violet spectra

The UV spectra were recorded in dry EtOH with a Shimadzu UV spectrophotometer from the Department of Chemistry, (BUET), Dhaka, Bangladesh.

2.2.5 Nuclear Magnetic Resource (NMR) spectra

The NMR spectroscopy is very widely used for the detailed investigation of an unknown compound. With the help of this spectroscopy the structure or pattern of an unknown compound can be set up. ^{1}H NMR (400 MHz) and^{13}C NMR (100 MHz) spectra were recorded in deuteriochloroform ($CDCl_3$) with a Bruker DPX-400 spectrophotometer using tetramethylsilane (TMS) as internal standard at the Wazed Miah Science Research Center (WMSRC), Jahangirnagar University, Dhaka, and BCSIR, Bangladesh.

2.2.6 Drying

All organic extracts were dried over anhydrous sodium sulfate (Na_2SO_4) or magnesium sulfate ($MgSO_4$) before concentration.

2.2.7 Evaporation

All evaporation were carried out under reduced pressure in Buchi rotatory evaporator (W. Germany) with a bath temperature below 40^0C.

2.2.8 Column chromatography

Column chromatography has been successfully applied to separate the individual components (having different R_f values) of mixture obtained from the reaction. This technique was also employed for purification of the product.

A long cylindrical column (70 cm long and 2 cm in diameter usually a burette type is used) made of glass drowns out at once end and packed with glass wool. To the lower constricted end of the column a stop cork was fitted in order to control the flow of the eluant. A seperatory funnel fitted with a specially made quick fit stopper and fitted with the eluent was placed the top of the column and this served as a store of eluent.

Adjusting the stop cork controlled the flow of the eluent. The column was prepared by slurry method, silica gel being used as the stationary phase; the column was made half filled with various types of solvents as light petroleum, ethyl acetate, chloroform, n-hexane etc. and slurry of silica gel in the chosen solvent was poured into it, so that the packing was compact and uniform.

Making the column as quickly as possible and following the solvent to fall drop by drop through the stop cork of the column removed air bubble. The mixture of the components was then placed on the upper surface of the slurry of the silica gel and the mixture was covered in limited area by some amount of dry silica gel. Then the solvent mixture was passed through the column. The fractions were collected in the test tubes about 20 to 30 ml each at a regular interval of time and respective fractions were detected by TLC. The solvent used for elution was chromatographically pure.

2.2.9 Gas chromatography mass spectrum (GC-MS) analysis

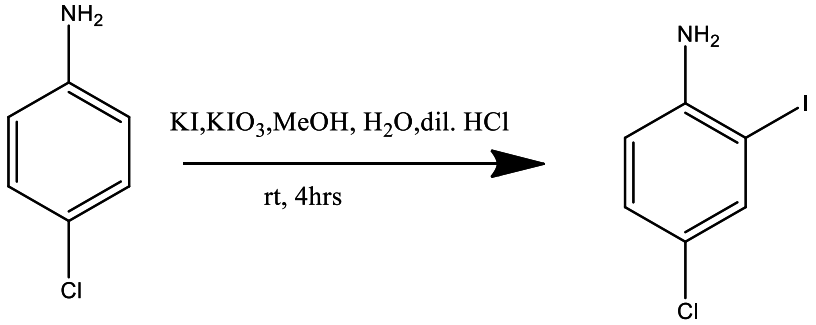
Retention time and mass spectrum for iodo amide derivatives was recorded using column: Rxi-5ms, 30m, 0.25mm ID, 0.25µ df by Shimadzu GC-MS. To determine mass spectrum, the molecule bombarded with high electron beam then form molecular ion again fragmentation of molecular ion occurs form many fragment ions.

2.3 synthesis of starting materials

2.3.1 synthesis of N-(2-iodo-4-chloro phenyl)-4 methyl benzamide 01

As scheme -01

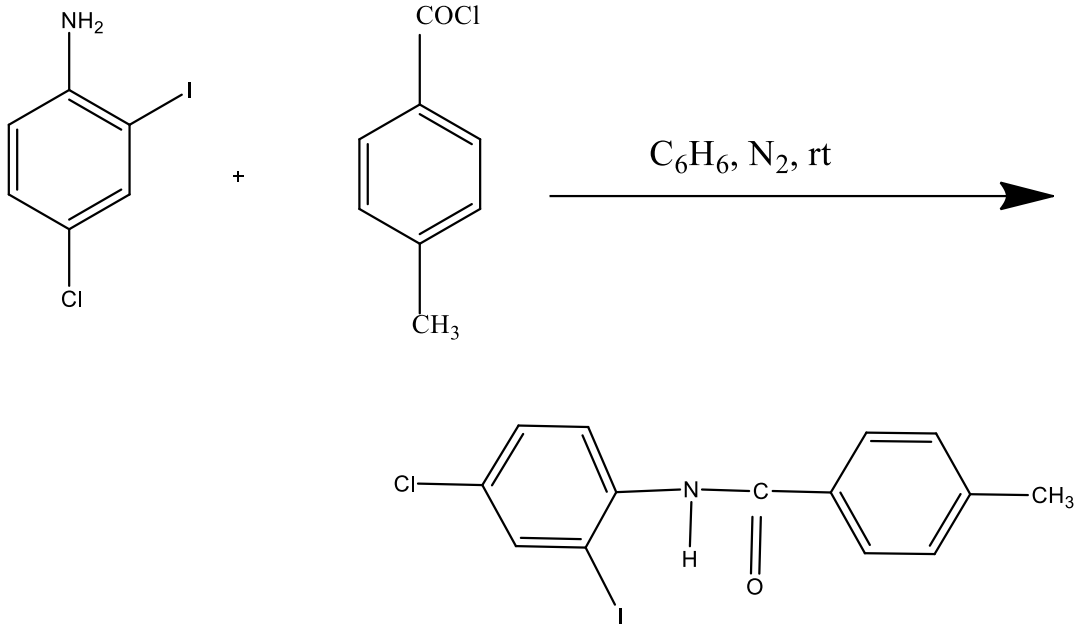
In a 250ml round bottom flask, a mixture of 2g (15.7mmol) of 4-chloro aniline , 3.13g of potassium iodide and 3.5g potassium iodate was prepared in 5ml of methanol and 30 ml of water. The reaction mixture was treated at room temperature with dilute hydrochloric acid 1.3mL over 40-45 minutes and stirred for an additional 2-3 hours. The progress of the reaction was monitored by TLC (n-hexane: chloroform, 1:1). After completion of the reaction, the mixture was diluted with water and extracted with dichloromethane(3×25mL), combined dichloromethane extract was washed with sodium thiosulfate solution, distilled water, brine, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using n-hexane: ethyl acetate (4:1) as eluent and compound **3** was isolated.



As scheme -02

The compound **1** was synthesized from 2-iodo-4-chloro aniline (0.3g) dissolved in benzene (10ml) and p-tolouylchloride (0.220g,0.18mL) by stirring thoroughly at room temperature for about 24 hrs. The progress was monitored by TLC (n-hexane: chloroform,1:1). After completion of the reaction the mixture was then filtered, washed with n-hexane and collected the white colored solid

compound. This solid compound was purified by column chromatography with ethyl acetate : n-hexane(1:9) to obtain the white compound **1** (0.320g; 75%), m.p 196^{0}C.



01

Physical state : a white solid

Yield : 75%

Molecular Formula : $C_{14}H_{11}NOClI$

Molecular Weight : 371.5

Melting Point : 195-196^{0}C

IR (KBr) : ν_{max} 3354.0 (-NH), 3034.13 (Ar C-H),1655.0(C=O), 1597.11 & 1524.78(C=C), 1250.6 & 1317.43(C-N) and 750.3(NH, out of plane bend) cm^{-1}

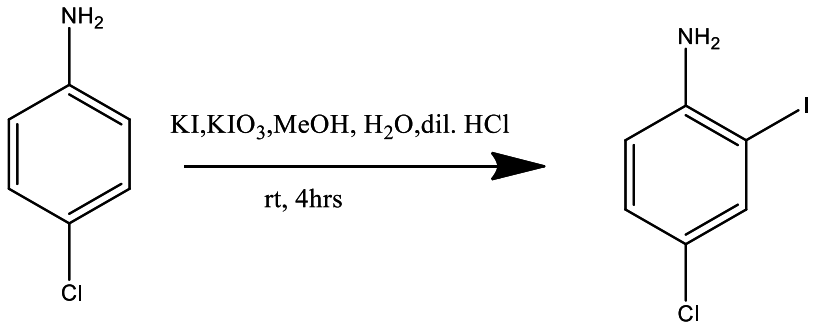
^{1}H NMR : δ_H 2.451 (s, 3H,Ar-CH_3) ,δ_H 7.81 (s,1H, -NH) ,δ_H 7.61 (d,2H,Ar-CH) δ_H 7.3-7.4(m,4H,Ar-CH), δ_H 7.8-7.9 (d,2H, Ar-CH)

^{13}C NMR spectrum : It was observed that the chemical shift at δ_C 165.56(-NHCO), δ_C 127.01 (Ar-C,2C), δ_C 129.12 (Ar-C,2C), 129.43(Ar-C,1C), δ_C 129.54(Ar-C,2C), δ_C 121.35(Ar-CH,2C), δ_C 21.52 (1C,$CH_{3)}$

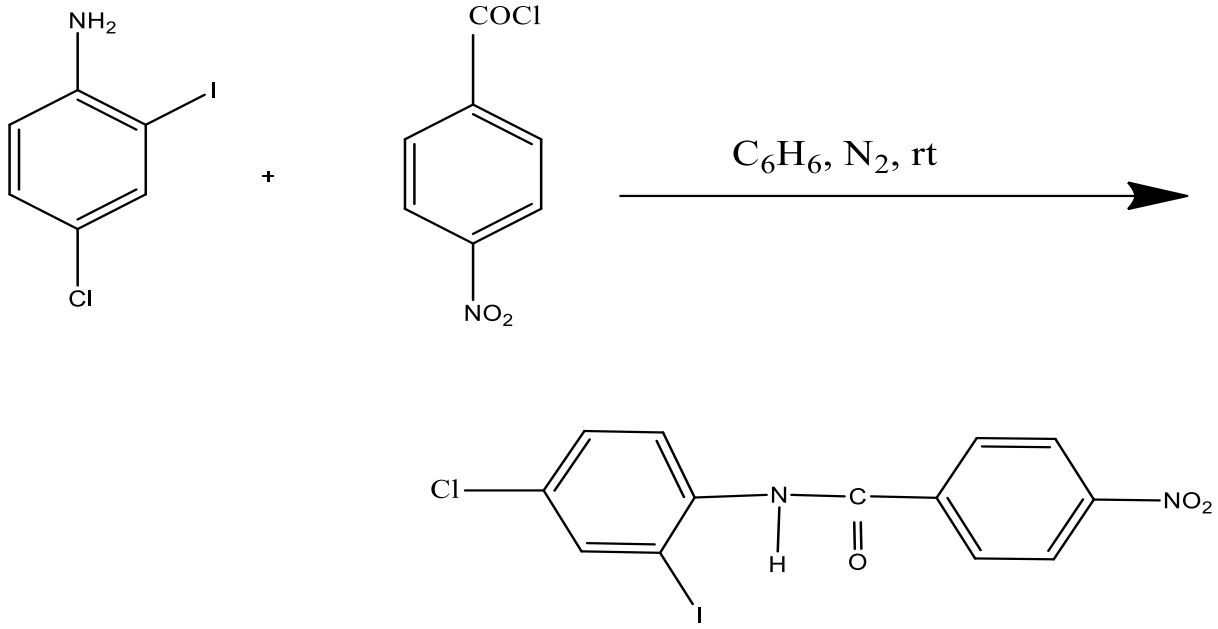
Mass spectroscopic data (ESI^+ m/z) : 245.1(M^+), 119.1, 91.1,63

2.3.2. Synthesis of N-(2-iodo-4-chloro phenyl)-4 nitro benzamide 02

In a 250ml round bottom flask, a mixture of 2g (15.7mmol) of 4-chloro aniline 1, 3.13g of potassium iodide and 3.5g potassium iodate was prepared in 5ml of methanol and 30 ml of water. The reaction mixture was treated at room temperature with dilute hydrochloric acid 1.3mL over 40-45 minutes and stirred for an additional 2-3 hours. The progress of the reaction was monitored by TLC (n-hexane: chloroform, 1:1). After completion of the reaction, the mixture was diluted with water and extracted with dichloromethane(3×25mL), combined dichloromethane extract was washed with sodium thiosulfate solution, distilled water, brine, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using n-hexane: ethyl acetate (4:1) as eluent and compound **4** was isolated.



The compound **2** was synthesized from 2-iodo-4-chloro aniline **(**0.3g) dissolved in benzene (10ml) and p-tolouylchloride (0.266g) by stirring thoroughly at room temperature for about 24 hrs. The progress was monitored by TLC (n-hexane: chloroform,1:1). After completion of the reaction the mixture was then filtered, washed with n-hexane and collected the white colored solid compound. This solid compound was purified by column chromatography with ethyl acetate: n-hexane (1:9) to obtain a pale yellow compound 8 (0.315g; 71%), m.p 220^0C.



2

Physical state : a pale yellow solid

Yield : 71%

Molecular Formula : $C_{13}H_8N_2O_3ICl$

Molecular Weight : 402.5

Melting Point : 219-220^{0}C

R_f value : 0.62 (n-hexane: choloform= 1.1)

IR(KBr) : ν_{max} 3350.3 (-NH), 3034.13 (Ar C-H),1698.0 (C=O), 1597.11 & 1524.78(C=C), 1250.6 & 1317.43(C-N),1604.7(N-O) and 750.3(NH, out of plane bend) cm^{-1}.

^1H NMR : δ_H 8.3-8.4(m,4H, Ar-H), δ_H 8.25-8.27 (m,3H,Ar-CH)

Mass spectroscopic data (ESI^+ m/z) : 280(M+) , 276, 150, 120

Chapter-03

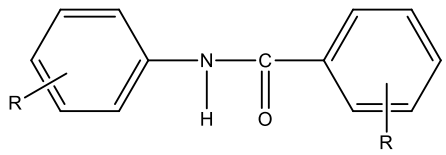
Results and Discussions

3.0 Present work: Synthesis of Substituted Novel Iodo benzamide Derivatives.

3.1 Rationale

In organic synthesis, aromatic iodides have long been utilized, because they can be readily functionalizd through carbon-carbon bond formation of diarenes, ethylenic or acetylenic condensations using transition metals or carbon-heteroatom bonds. Recent progress in organotransition metal chemistry has renewed the importance of iodoarenes, thus, the chemistry of transformations of iodoarenes to a variety of functional compounds by transition metal catalysis has been a popular and effective area of investigation. A number of functional groups transformations, for example, Heck reactions as well as Stille and Negishi cross couplings originating from aryl iodides make these compounds valuable synthetic intermediates.

Selective iodination of aromatic compounds is an important reaction in organic synthesis. There have been a number of reports on direct aromatic iodination but few Lewis acids have been evaluated. The iodination of aromatic compounds has been the subject of numerous studies due to a potential ability as intermediates in organic synthesis and also as bacterial and fungicidal agents. Iodoarenes are valuable and versatile intermediates with wide application in medicine and biochemistry and aromatic iodides have long been utilized in organic synthesis. There fore it was planned to develop a facile and efficient method for the synthesis of substituted novel iodobenzamides **1**



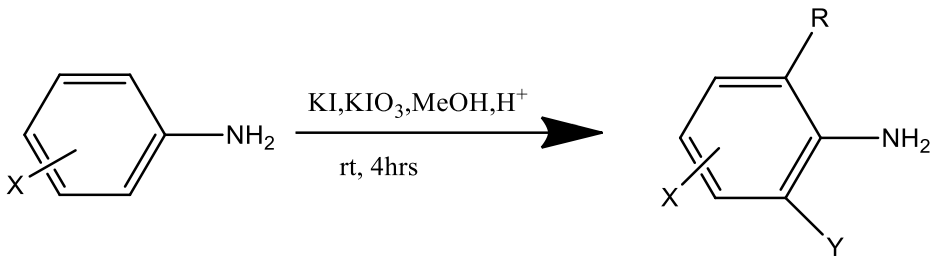
1

The ultimate goal of this work was to synthesize N-substituted iodobenzamide from readily available starting materials and reagents inn the most efficient way. It was also planned to develop the synthesis of starting materials, substituted iodoaniline in a facile way.

Then, a convenient method for the synthesis of substituted iodobenzamide would be developed through coupling reaction of iodoaniline with aryl and alkyl amine.

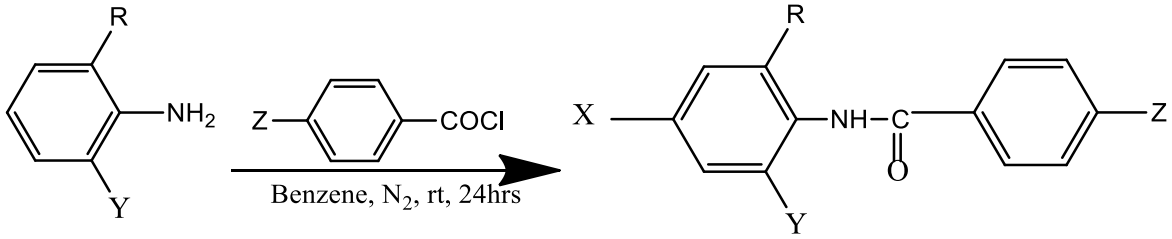
3.2 Results and Discussions

Here a convenient approach for the synthesis substituted aniline through the treatment with potassium iodate and potassium iodide is reported. The required starting materials N-substituted iodo- 4-chloro aniline was prepared by a convenient procedure using potassium iodide and potassium iodate in methanol and dilute hydrochloric acid from their parent substituted anilines (**scheme-1**). After usual workup, the crude product was purified by column chromatography on silica gel using n-hexane/ethyl acetate (4:1) as eluent and products were isolated.



Scheme-1

Substituted Iodo aniline Compound was stirred with aryl acid chloride in the presence of benzene in inert environment. After that compound **01-02** was synthesized.



01-02

Z=NO_2, CH_3

Scheme-2

3.2.1 Synthesis of starting materials

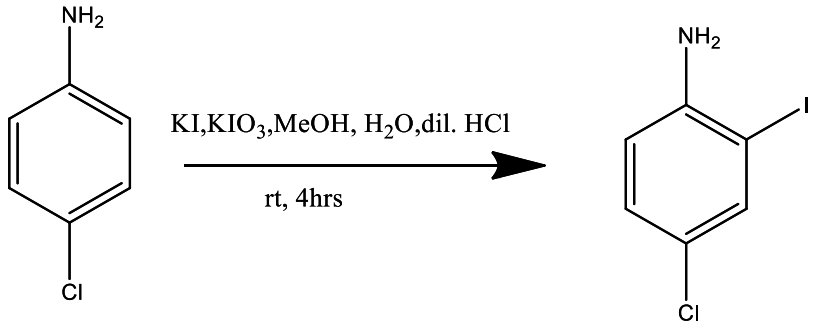
Commercially available p-Cl aniline was used to prepare the required starting materials. Iodination of reaction of the aromatic nucleus was done as shown in the **scheme -1.**

Iodination of 4-chloro aniline was carried out using potassium iodide, potassium iodate in methanol and dilute hydrochloric acid to yield substituted iodo aniline. In order to optimize the iodination reaction condition, temperature was maintained room temperature and the reaction was carried out for several hours.

After usual work up the crude was purified by column chromatography on silica gel with hexane/ethyl acetate (4:1) as eluent

Step-01

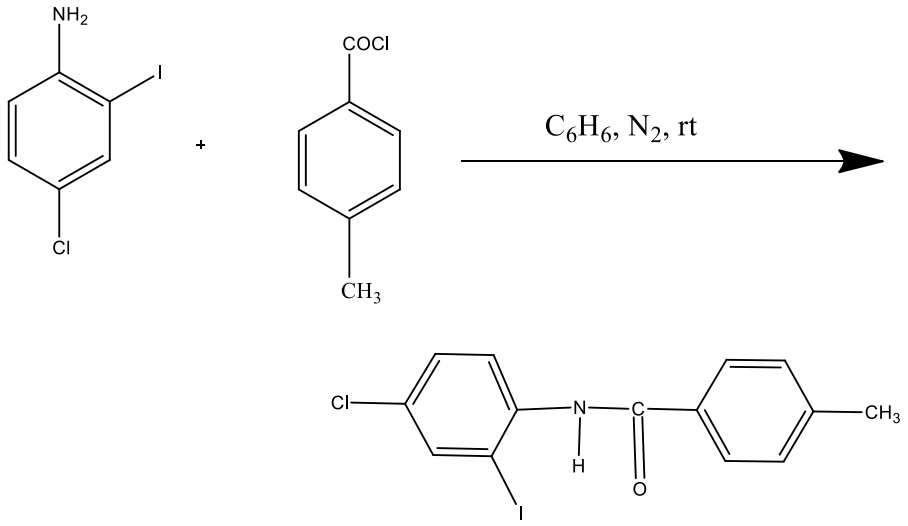
a) **Iodination of substituted aniline with KI, KIO_3 with dil. HCl**



Step -02

b) substituted iodo aniline and aryl acid chloride

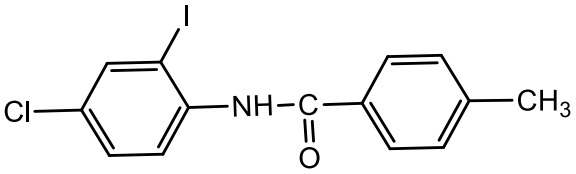
Substituted Iodo aniline Compound was stirred with aryl acid chloride in the presence of benzene in inert environment. After that compound **01** was synthesized



01

3.2.2 Characterization of substituted benzamide compound 01

3.2.2.1 N-(2-iodo-4-chloro phenyl)-4 methyl benzamide 01



A white solid, m.p. 195-196^{0}C

The IR spectrum of the compound showed absorption band at ν_{max} 3354.3 cm^{-1} due to the stretching vibration of secondary amine -NH. The absorption band at 3034.13cm^{-1} was caused by stretching vibration of Ar-C-H. The absorption band at 1649.0 cm^{-1} appeared due to carbonyl group(C=O) of amide and the stretching vibration at 1597.11 & 1524.78 cm^{-1} were afforded by the C=C. The bands at 1250.6 cm^{-1} and 1317.43 cm^{-1} were due to the stretching vibration of C-N and 750.3cm^{-1} out of plane bending of –NH of the compound.

In the ^{1}H NMR spectrum of the compound one doublet was found at δ_H 7.61 (d,2H,Ar-CH) for the presence of aromatic proton, a multiplet at δ_H 7.3-7.4 (m,4H,Ar-CH) because of aromatic proton. A doublet was found at δ_H 7.8-7.9(d, 2H, Ar-H) due to aromatic proton. A sharp singlet at δ_H 7.81 (s,1H, -NH) was found in favor of amido (-NH) group. A sharp singlet was found at 2.45 (s,3H, Ar-CH_3)

Further analysis the structure of **01** confirmed by its ^{13}C NMR spectrum. It was observed that the chemical shift at δ_C 165.95 for the carbonyl group of amide (-NHCO), δ_C 129.54 (Ar-C,2C), δ_C 129.12 (Ar-C,2C), δ_C 127.01(Ar-C,2C), δ_C 121.35(Ar-C,2C), δ_C 136.63(Ar-CH,1C), δ_C 129.43(Ar-CH,1C),δ_C 142.68(Ar-CH,1C),δ_C 131.78(Ar-CH,1C) and at 21.52 (Ar-CH_3, 1C). Thus the ^{13}C NMR spectrum suggested the formation of the compound **01.**

Mass spectroscopic data (ESI^+ m/z) : 245.1(M^+), 118, 119.1, 91.1,63

On the basis of complete analysis of the IR, Mass, ^{1}H NMR and ^{13}C NMR spectra the structure of this compound was accorded as N-(2-iodo-4-chloro phenyl)-4 methyl benzamide **01.**

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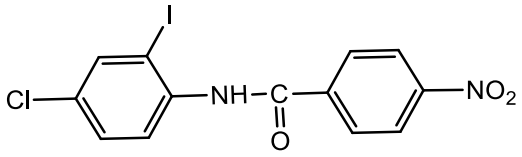
3.2.2.2 N-(2-iodo-4-chloro phenyl)-4 nitro benzamide 02



A pale yellow solid, m.p. 220^0C

The IR spectrum of the compound showed the absorption bans at ν_{max} 3354.0 cm^{-1} due to the stretching vibration of secondary amine –NH. The absorption band at 2923.9 cm^{-1} was caused by stretching vibration of –CH_3 attached to the aromatic ring. The absorption band at 1687.6cm^{-1} appeared due to the carbonyl group (C=O) of amide and the stretching vibration at 1604.7 and

1494.7 cm^{-1} were afforded by the N-O and C=C respectively. The bands at 360.0 and 1298.0cm^{-1} were due to the asymmetric and symmetric vibration od C-N stretching of the compound.

In the ^{1}H NMR spectrum of the compound a multiplet was found at 8.3-8.4 (m,4H,Ar-CH) for the aromatic proton, another multiplet was found at 8.25-8.27 (m,3H,Ar-CH) for the aromatic proton.

Mass spectroscopic data (ESI^{+} m/z): 280(M^{+}), 276, 150, 120

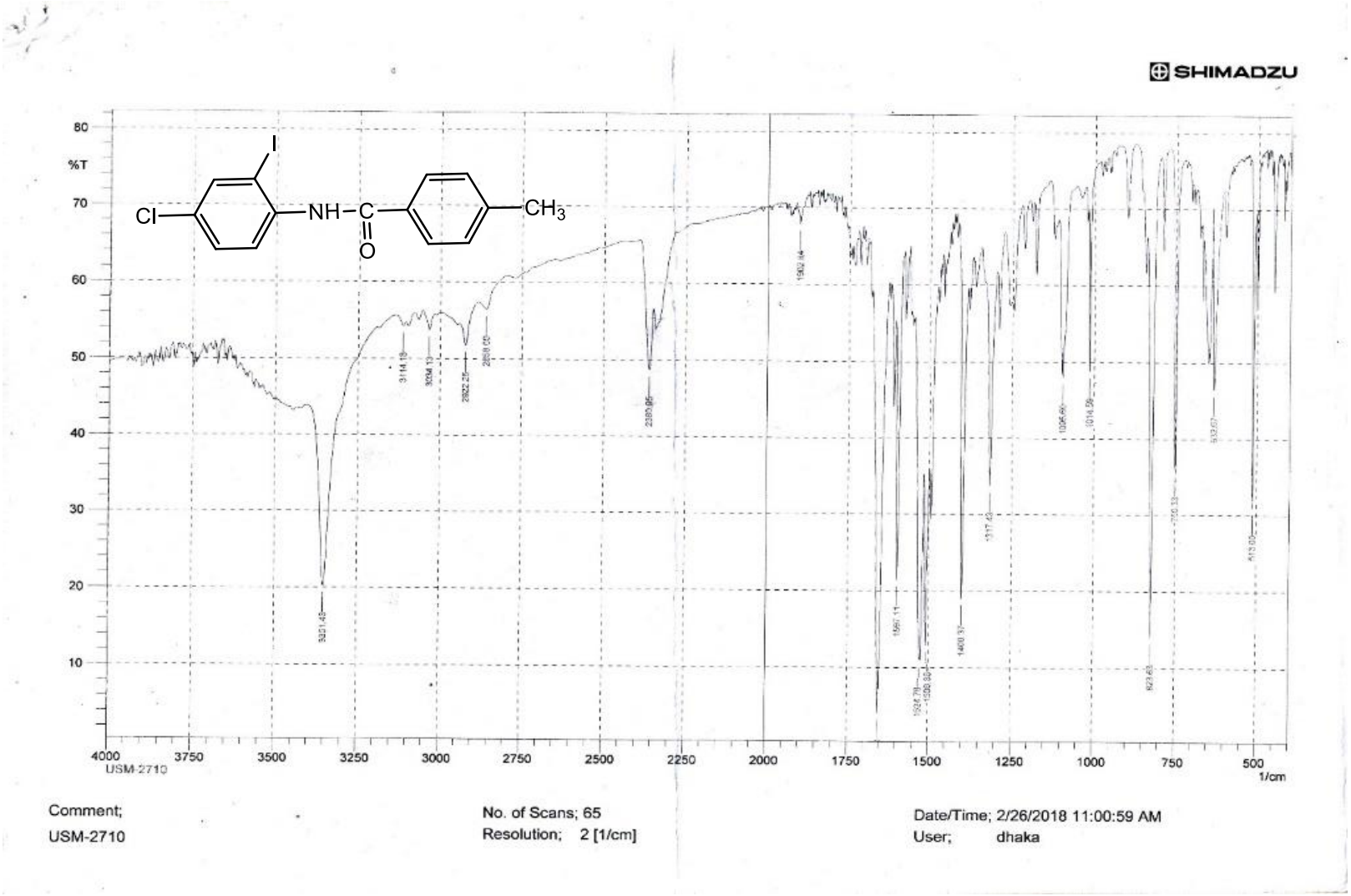
On the basis of complete analysis of the IR, mass, ^{1}H NMR and ^{13}C NMR spectra the structure of this compound was accorded as N-(2-iodo-4-chloro phenyl)-4 nitro benzamide **02**.

3.3 Conclusion

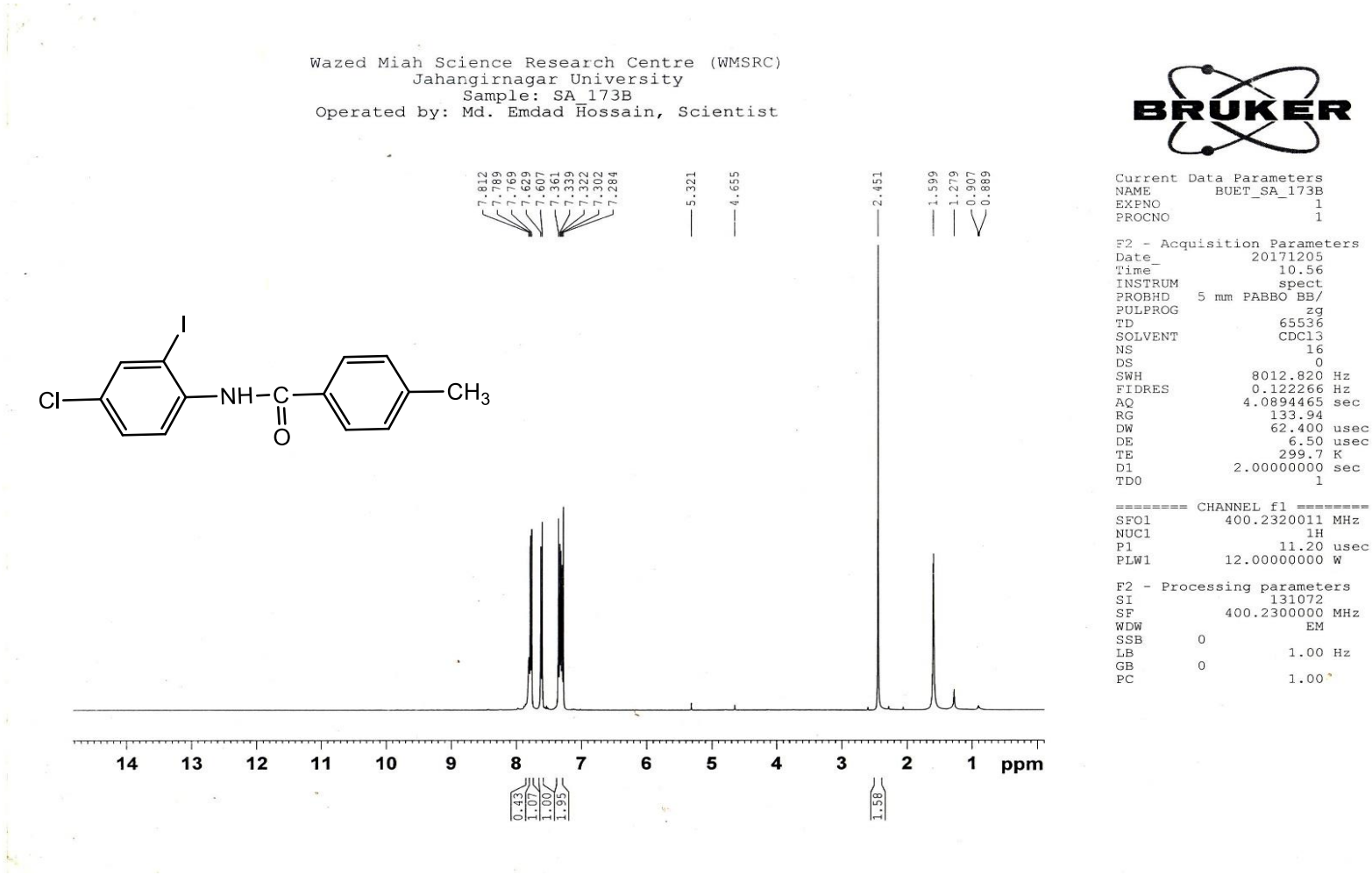
Here we have developed a convenient and facile method for the synthesis of novel iodinated phenyl benzamide with and without catalyst. The most important feature of the synthesis was that—

- Readily available inexpensive starting materials were used under relatively mild conditions.
- Various iodoaniline compounds were synthesized successfully.
- The approach of synthesis of benzamide from substituted iodo aniline without catalyst was found to be convenient.
- All the reactions are developed in mild conditions and follow the green chemistry methodology.
- The yield of substituted benazmide in the case of p-chlorobenzyl chloride was better than any of that substituted benzamide.
- This methodology is also expected to be widely used in synthesis of indole derivatives.
- The synthesized benzamide derivative show antibacterial activity.

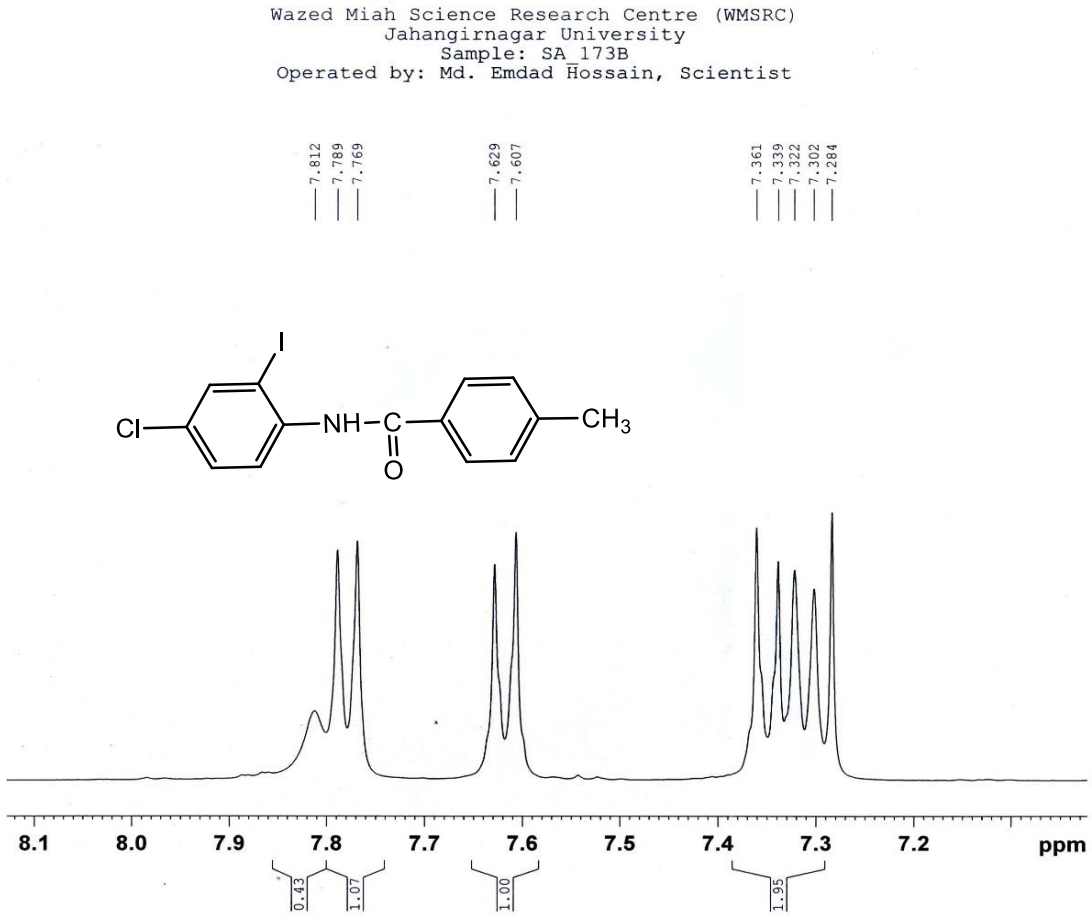
Spectra



IR Spectra of Compound 01



^{1}H NMR Spectra of Compound 01

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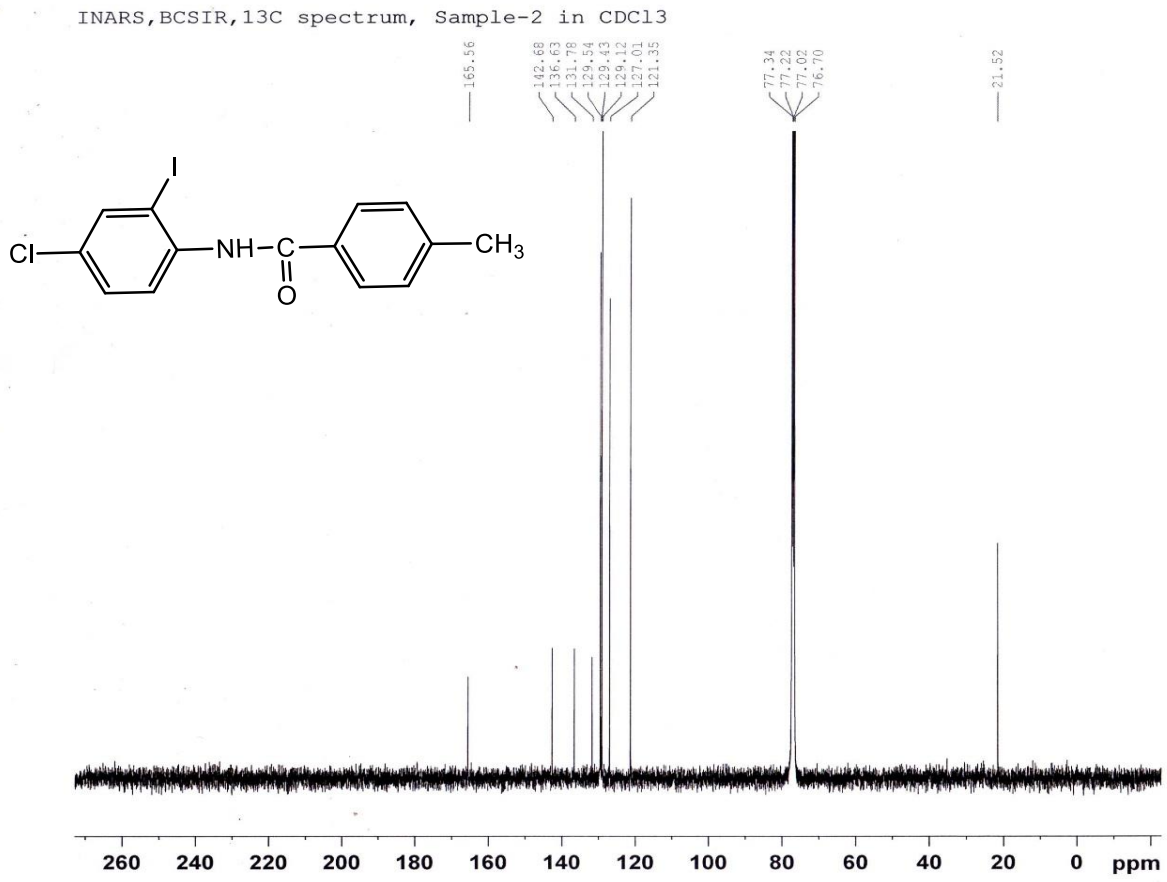

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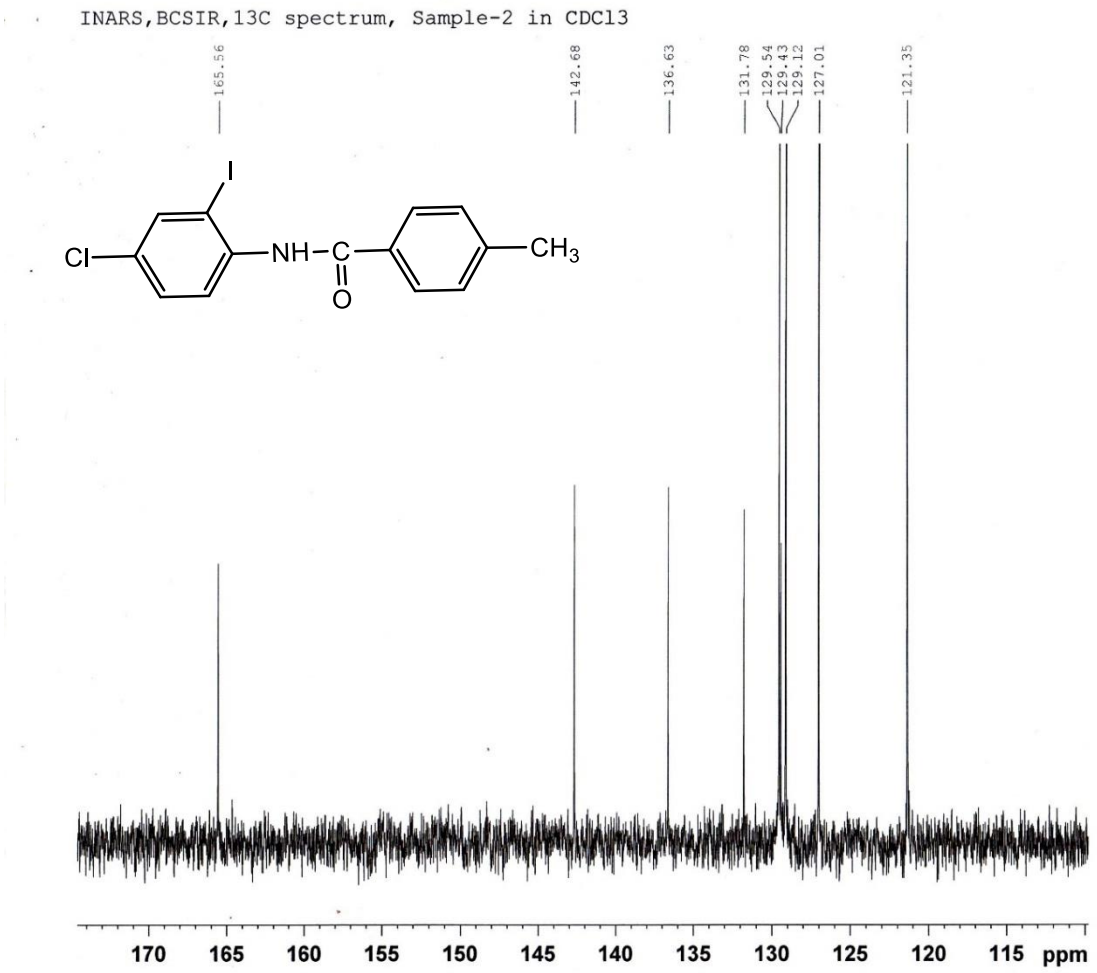


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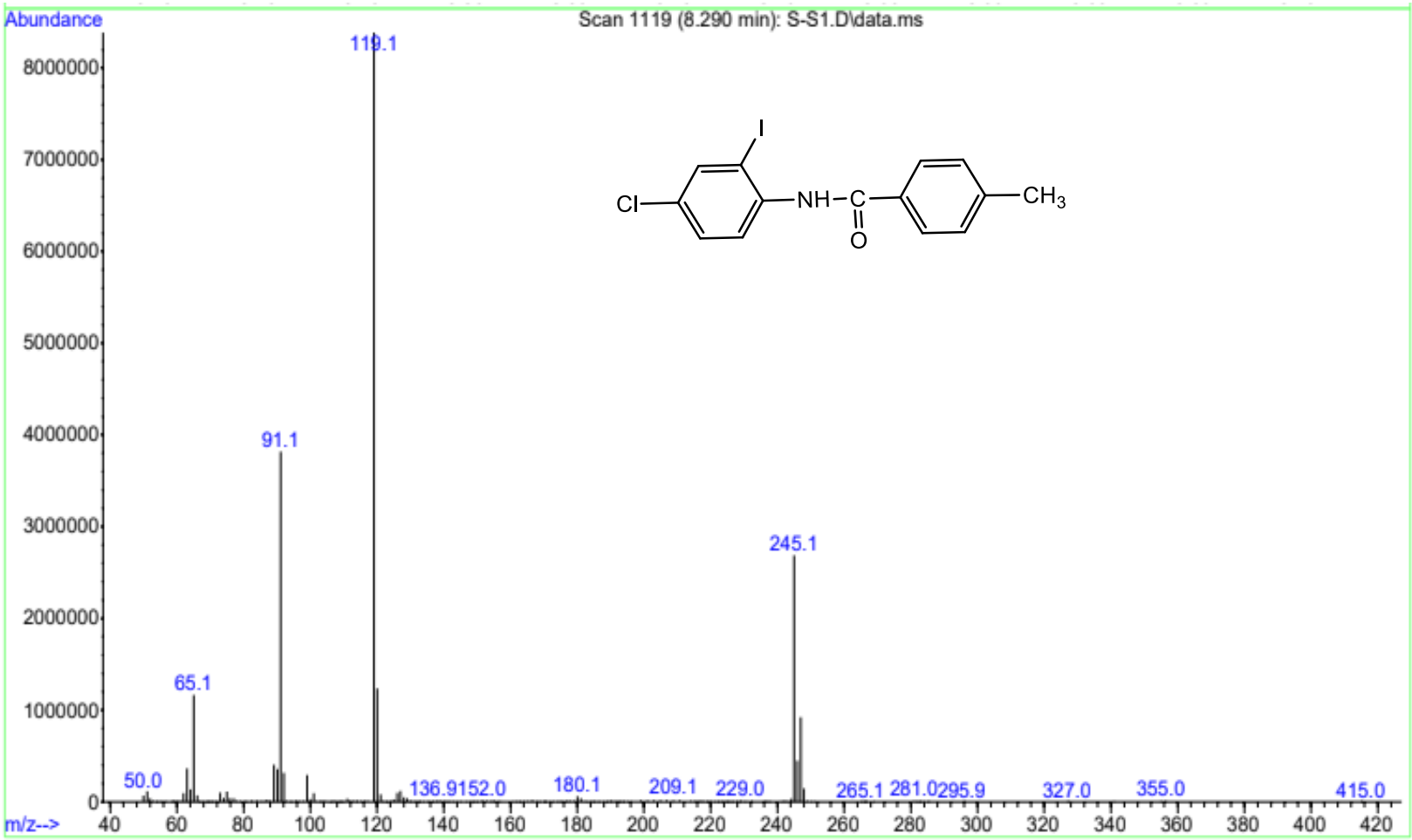
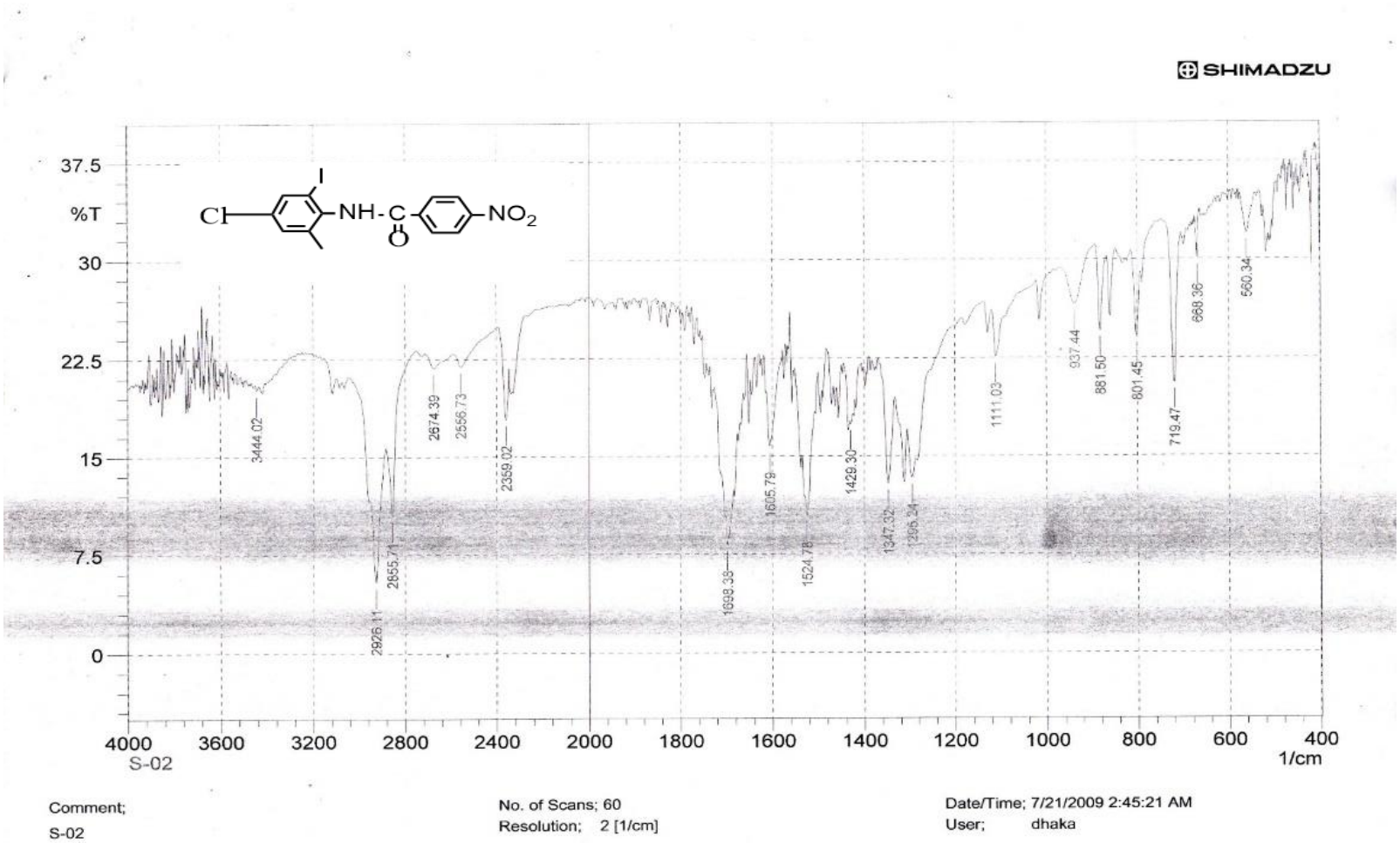
^{13}C NMR of compound 01



Mass Spectra of compound-01



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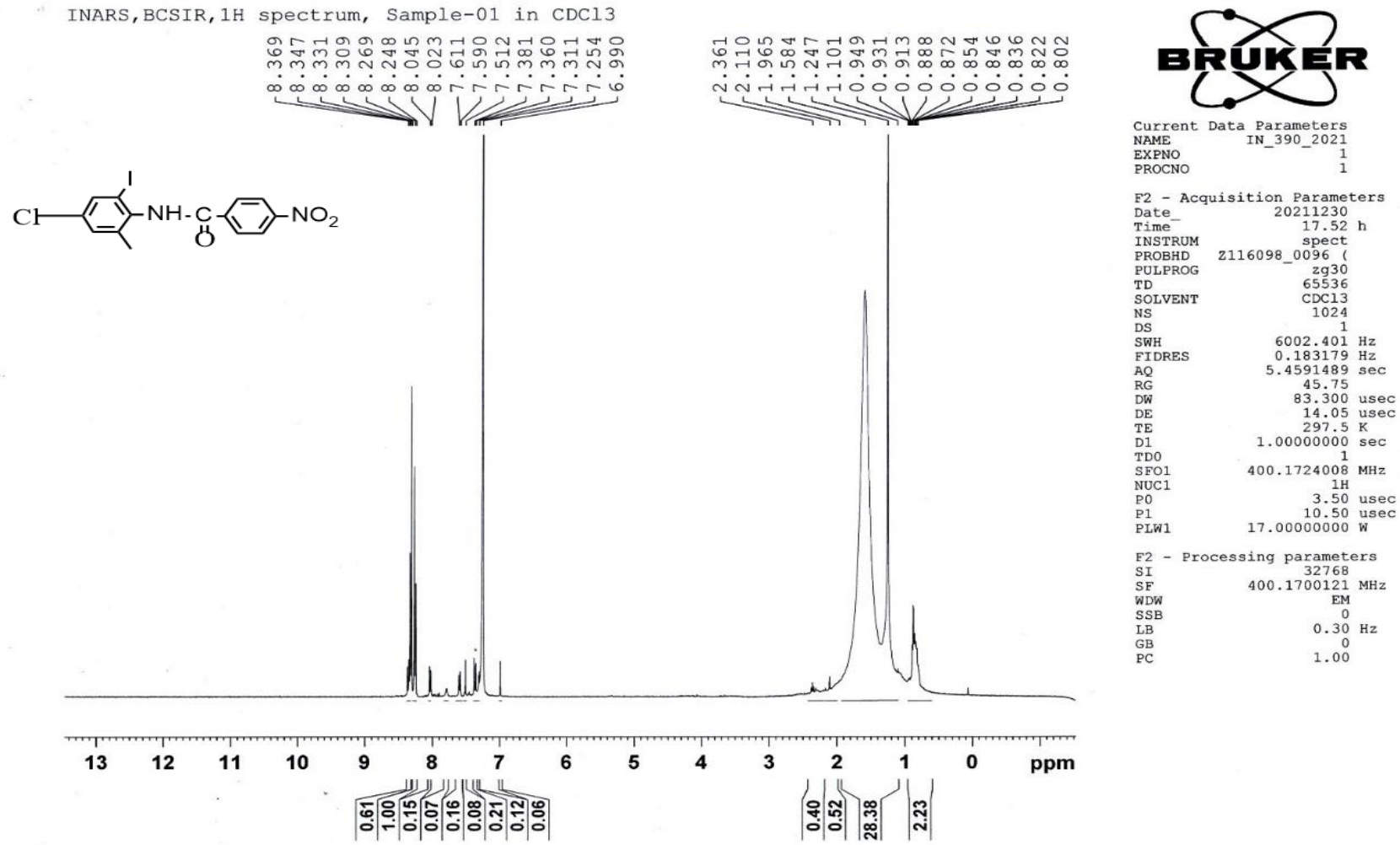

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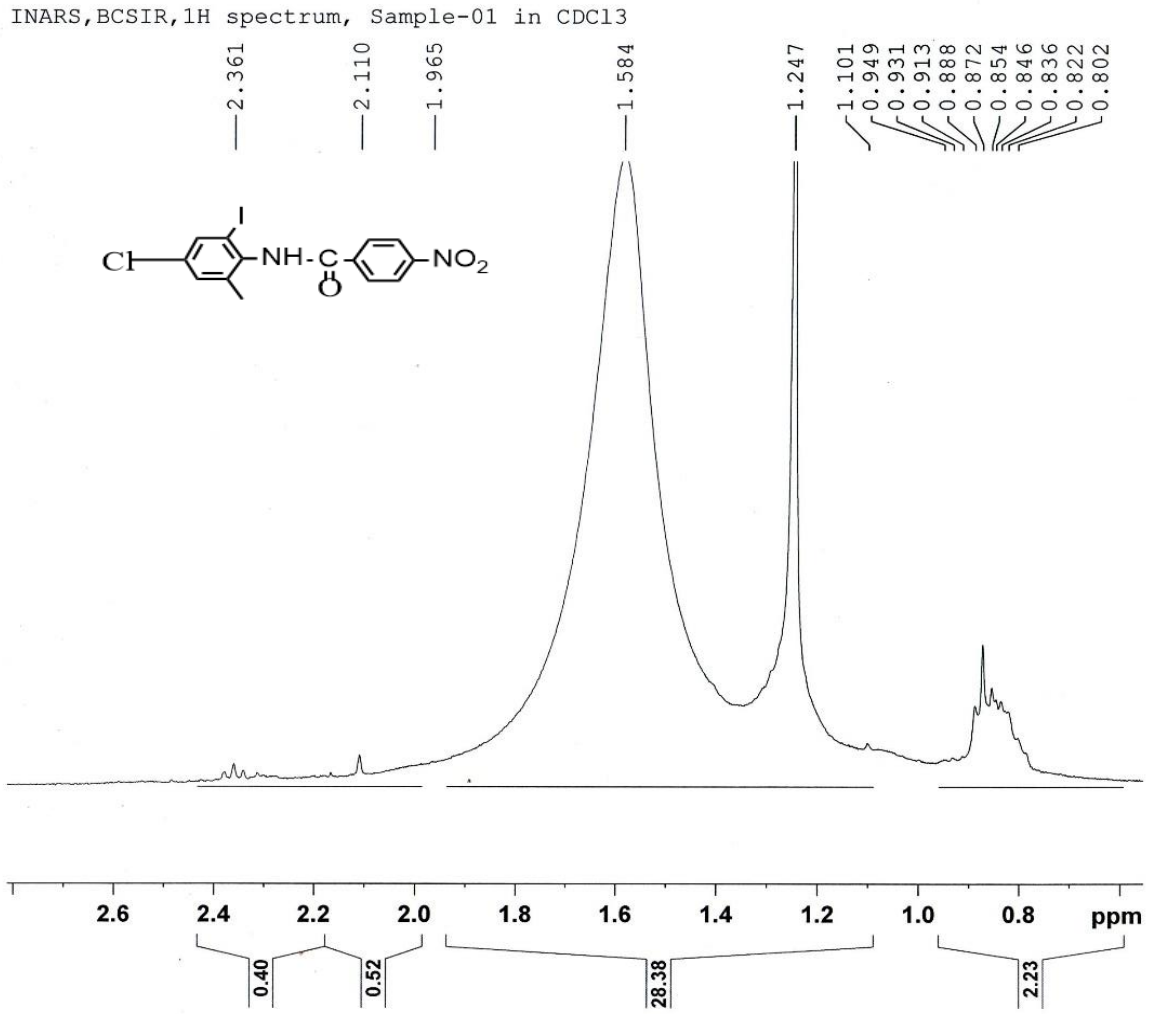
^{1}H NMR spectra of compound-02



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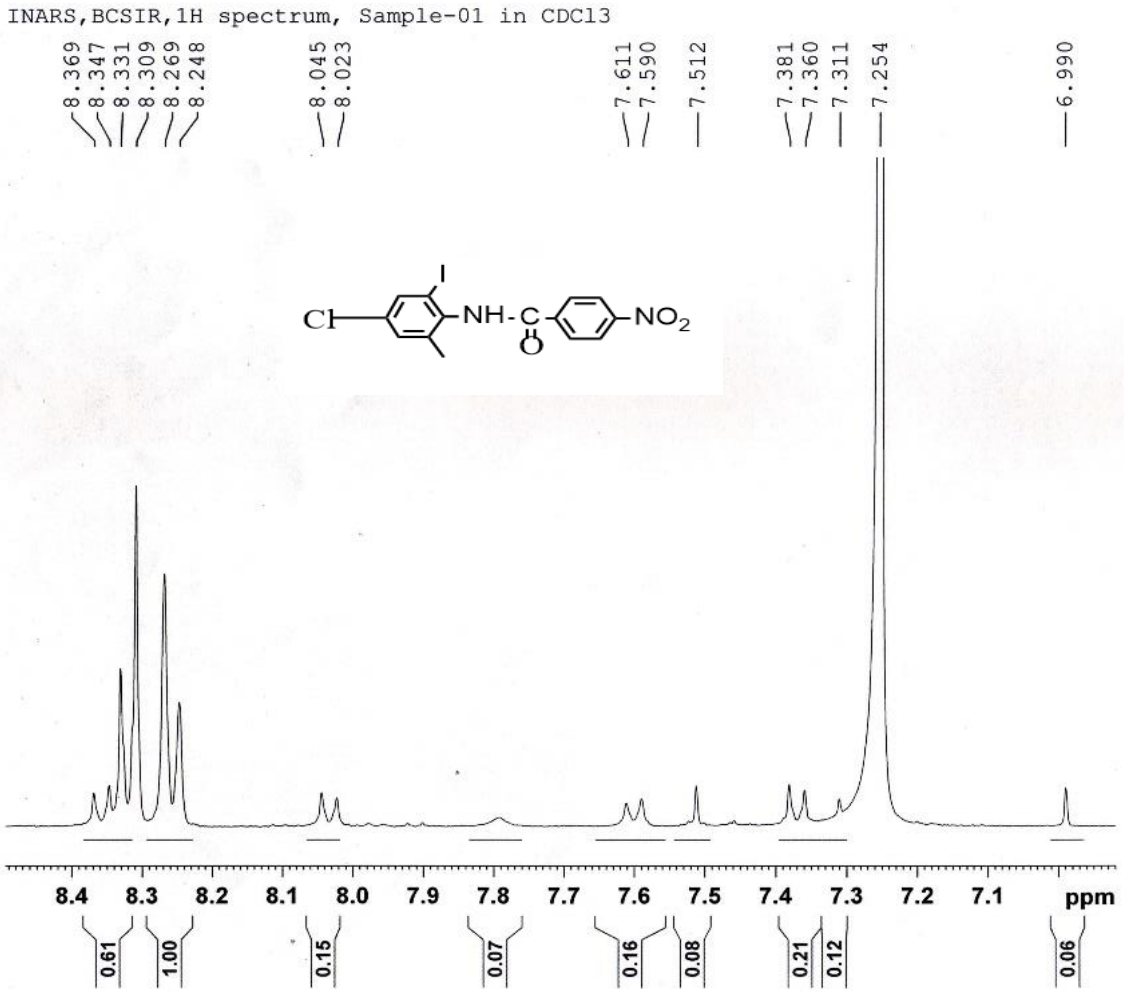
^{1}H NMR of compound 02



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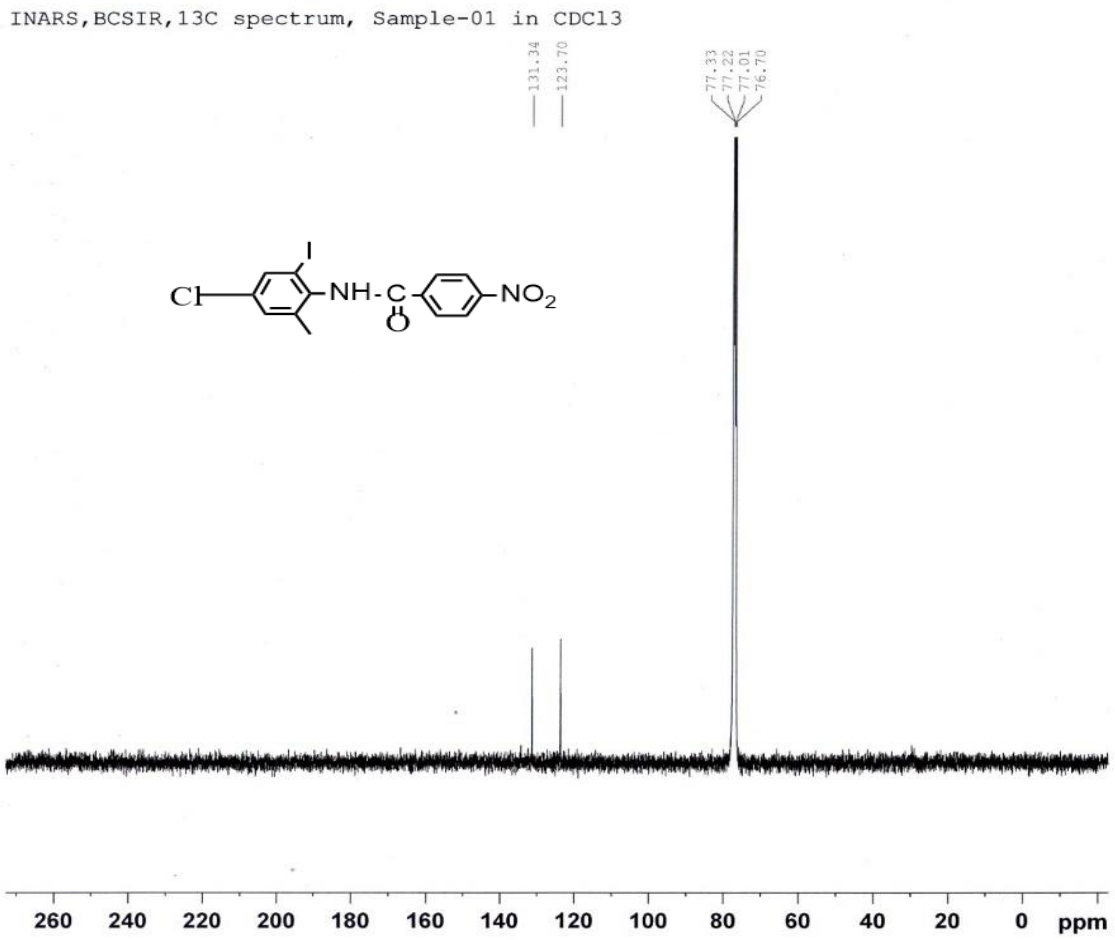
^{1}H NMR of Compound 02



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AQ 1.1010048 sec
RG 197.33
DW 16.800 usec
DE 7.55 usec
TE 299.3 K
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SFO1 100.6354023 MHz
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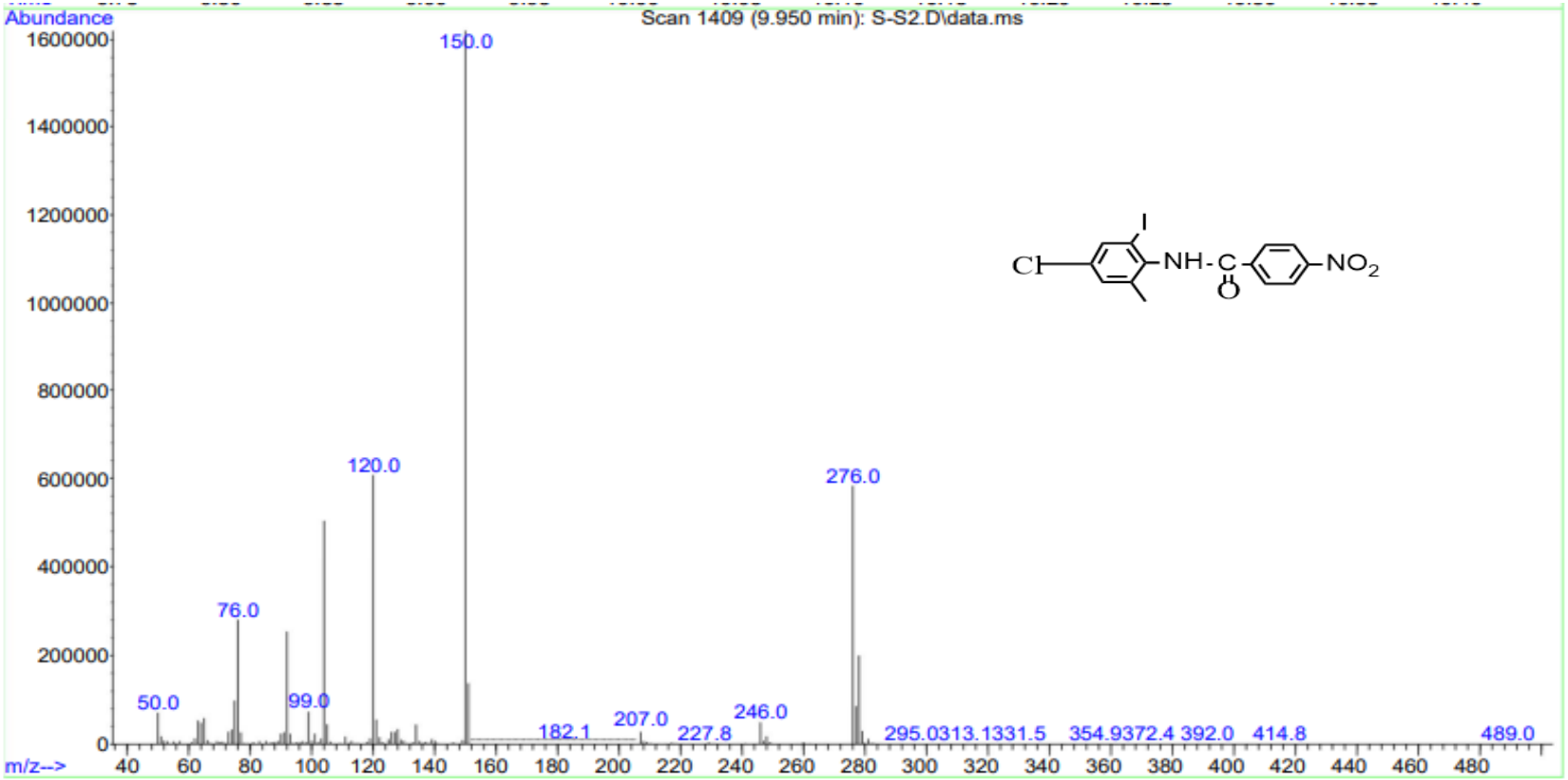
^{13}C NMR of compound 02



Mass Spectra of Compound 02

Chapter-04

Biological Screening

4.0 Determination of antimicrobial activity

The antimiocrobial activity of the synthesized iodo phenylbenzamide compound was determined by discs diffusion method by measuring the diameter of the inhibitory zone in millimeter by a transparent scale. The tested compound solution was prepared in chloroform and evaluated them for their in vitro antimicrobial and antifungal activity against Escherichia Coli, Shigella flexneri, respectively. 0.1 ml culture of microbial culture was taken and spread plate technique on nutrient agar plate was applied. After spreading the culture, 16 mm diameter disk placed on the plate which is soaked with intended compound with different concentration (10 mm, 11mm, 8 mm). Incubate the plate at 38^0C for 24 hours than investigate the plate for inhibition zone and measure the diameter of inhibition zone.

Fig 10 : Zone of Inhibition exhibited N-(2-iodo-4-chloro phenyl)-4 methyl benzamide (10 mm) by Staphylococcus aureus

Fig 11 : Zone of Inhibition exhibited N-(2-iodo-4-chloro phenyl)-4 methyl benzamide (11 mm) by Shigella flexneri

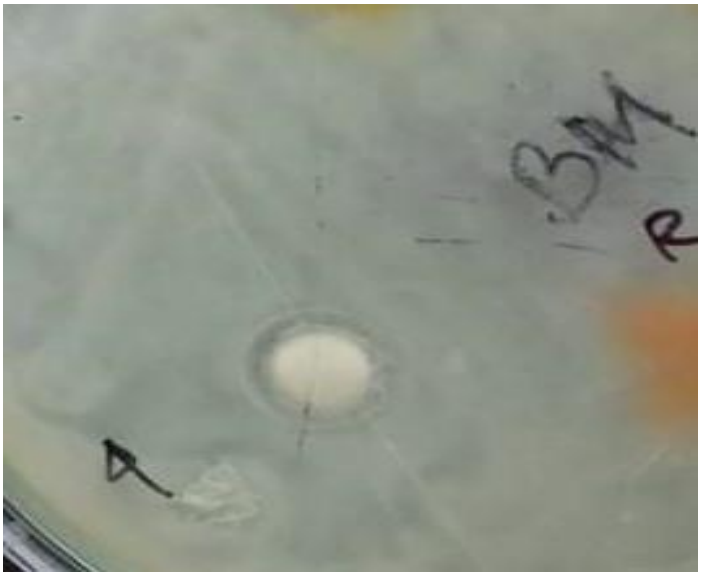


Fig 12: Zone of Inhibition exhibited N-(2-iodo-4-chloro phenyl)-4 methyl benzamide (11 mm) by Bacillus megaterium

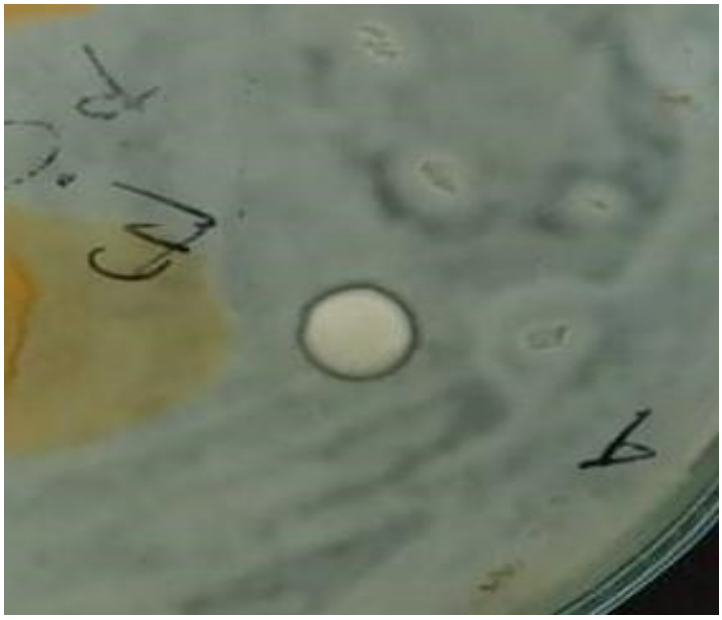


Fig13 : Zone of Inhibition exhibited N-(2-iodo-4-chloro phenyl)-4 methyl benzamide (8 mm) by Escherichia coli

Table -05: Antimicrobial activity of test sample of compound 01

Test microorganisms	**Diameter of zone of inhibition (mm)**	
	Compound-01	**Ceftriaxone**
Gram positive bacteria		
Bacillus cereus	-	20
Bacillus megaterium	11	50
Bacillus subtilis	-	20
Staphylococcus aureus	10	40
Gram negative bacteria		
Escherichia coli	8	38
Salminella typhumurium	-	31
Salminella paratyphi	-	50
Salminella typhi	-	44
Shigella boydii	-	25
Shigella dysentery	-	47
Shigella sonnei	-	40
Enterotoxigenic Escherichia coli	-	45
Enteropathogenic Escherichia coli	-	46
Shigella flexneri	11	39

The entire synthesized compounds were tested for in vitro antimicrobial activity by the disk diffusion technique. The results are summerized in table-05 that includes the activity of reference compound Ceftriaxone. The tested compound exhibited mild to moderate antibacterial activity this four bacteria.

References

References:

1.Bellusci, L., Laurino, A.,New insights into the potential roles of 3-iodothyronamine (T1AM) and newly developed thyronamine-like TAAR1 agonists in neuroprotection". *Pharmacol*,**2017,** 12 (8), 905.

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