STUDIES ON SYNTHESIS, CHARACTERIZATION AND INVITRO ANTI-INFLAMMATORY ACTIVITY OF METHOXYDIBENZOFURAN-1,3-THIAZOLE-CARBOXAMIDE DERIVATIVES

A Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY,

CHENNAI- 600 032

In partial fulfilment of the award of the degree of

MASTER OF PHARMACY

IN

Branch-I – PHARMACEUTICAL CHEMISTRY

Submitted by

Name: GNANA SAHAYA JEYANTHI.T

REG.No.261615203

Under the Guidance of

Dr. S.P.VINOTHKUMAR, M.Pharm., PhD., AIC.,

DEPARTMENT OF PHARMACEUTICAL CHEMISTRY

J.K.K. NATTRAJA COLLEGE OF PHARMACY

KUMARAPALAYAM – 638183

TAMILNADU.

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CERTIFICATES

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled "**STUDIES ON SYNTHESIS, CHARACTERIZATION AND INVITRO ANTI-INFLAMMATORY ACTIVITY OF METHOXYDIBENZOFURAN-1,3-THIAZOLE CARBOXAMIDE DERIVATIVES"** Submitted by the student bearing **Reg. No: 261615203** to "**The Tamil Nadu Dr. M.G.R. Medical University – Chennai**", in partial fulfilment for the award of Degree of **Master of Pharmacy** in **Pharmaceutical chemistry** was evaluated by us during the examination held on……..…….

Internal Examiner **External Examiner**

CERTIFICATE

This is to certify that the work embodied in this dissertation entitled "**STUDIES ON SYNTHESIS, CHARACTERIZATION AND INVITRO ANTI-INFLAMMATORY ACTIVITY OF METHOXYDIBENZOFURAN-1,3-THIAZOLE CARBOXAMIDE DERIVATIVES"** submitted to "**The TamilNadu Dr.M.G.R. Medical University- Chennai**", in partial fulfilment and requirement of university rules and regulation for the award of Degree of **Master of Pharmacy** in **Pharmaceutical Chemistry** is a bonafide work carried out by the student bearing Reg.No**. 261615203** during the academic year 2017-2018, under the guidance and supervision of **Dr.S.P.Vinothkumar,M.Pharm.,PhD.,** Associate Professor, J.K.K.Nattraja College of Pharmacy, Kumarapalayam.

Dr. S.P.Vinothkumar, M. Pharm., PhD.,
Associate professor,
Department of Pharmaceutical chemistry,
J.K.K. Nattraja College of Pharmacy.
Kumarapalayam - 638 183.

Dr. R. Sambathkumar, M. Pharm., PhD.,
Principal,
J.K.K. Nattraja College of Pharmacy,
Kumarapalayam - 638 183.

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Place: Kumarapalayam

Date:

Dr. Vijayabhaskaran, M. Pharm., PhD.,
Professor & Head,
Department of Pharmaceutical chemistry,
J.K.K. Nattraja College of Pharmacy,
Kumarapalayam - 638 183.

DECLARATON

I do hereby declared that the dissertation "**STUDIES ON SYNTHESIS, CHARACTERIZATION AND INVITRO ANTI-INFLAMMATORY ACTIVITYOF METHOXYDIBENZOFURAN - 1,3-THIAZOLE CARBOXAMIDE DERIVATIVES"** submitted to "**The Tamil Nadu Dr. M.G.R Medical University - Chennai",** for the partial fulfilment of the degree of **Master of Pharmacy** in **Pharmaceutical chemistry,** is a bonafide research work has been carried out by me during the academic year 2017-2018, under the guidance and supervision of **Dr.S.P.Vinothkumar,M.Pharm.,PhD.,AIC.,** Associate Professor,Department of Pharmaceutical chemistry, J.K.K. Nattraja College of Pharmacy, Kumarapalayam.

I further declare that this work is original and this dissertation has not been submitted previously for the award of any other degree, diploma, associate ship and fellowship or any other similar title. The information furnished in this dissertation is genuine to the best of my knowledge.

Place: Kumarapalayam **Mrs.T.GNANA SAHAYA JEYANTHI,**

Date: **Reg.no. 261615203**

Dedicated to Parents,

Teachers & My Family

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Mrs.T.GNANASAHAYA JEYANTHI

Registerno : 261615203

CONTENTS

LIST OF ABBREVIATIONS

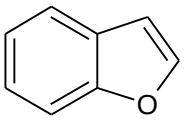
°C	-	Degree centigrade
µg	-	Microgram
µm	-	Micrometer
^{1}H-NMR	-	Proton nuclear magnetic resonance
DMSO	-	Dimethylsulfoxide
FTIR	-	Fourier transform infrared spectroscopy
g	-	Gram
hr	-	Hour
HRMS	-	High resolution mass spectroscopy
IUPAC	-	International union of pure and applied chemistry
KBr	-	Potassium bromide
Kg	-	Kilogram
M	-	Mole
m.p	-	Melting point
mg	-	Milligram
min	-	Minutes
TLC	-	Thin Layer Chromatography
UV	-	Ultraviolet
TBTU	-	2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetra flurosorate
PDE	-	Phosphodiesterase
TNF-α	-	Tumor necrosis factor
cAMP	–	Cyclic adenosine monophosphate
cGMP	-	Cyclic guanosine monophosphate

INTRODUCTION

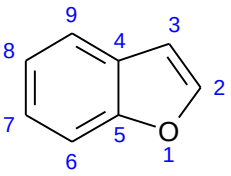
1.1 Introductoin & Dibenzofuran

The Chemistry of heterocyclic compound is one of the most complex branches of Chemistry. Heterocyclic compounds are widely distributed in the nature and play an important role in regulating biological processes. A large number of heterocyclic compounds are as chemotherapeutic agent, drugs, dyestuffs and copolymers. Among these benzofuran is very interesting class of oxygen containing heterocyclic compounds having wide range of application in medicinal of synthetic chemistry.

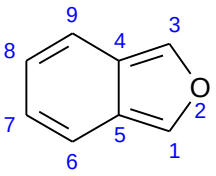
The benzofuran nucleus ae have considerable importance as pharmaceuticals, insecticides, it occur in coaltar & are isolated as picrates. It also synthesis via palladium protonated cyclization of O-substituted aryl aryl ether. Many synthetic benzofuran derivatives have interesting properties. These are further used as intermediates for the preparation of herbicides, fungicides & parasiticides.



Condensation of a benzene ring with furan to form benzofuran & depending on whether the benzene ring is condensed at the 2,3 (or) 3,4 position. The first one is known as coumaran (or) benzofuran and the later is known as isocoumaran or isobenzofuran.

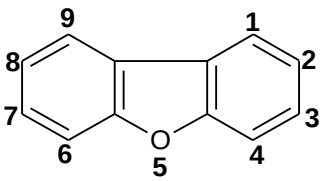


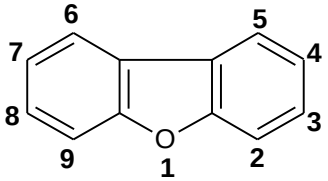
(1)
benzo (b) furan



(2)
benzo (c) furan

Among the other fused benzofuran derivatives furocoumarin, dibenzofurans and pyranobenzofuran are important class of oganic compounds. Particularly the dibenzofuran is somewhat confusing because of different systems of numbering employed by chemical abstracts prior to 1937.





Due to these divergent systems considerable care must be taken when consulting the

literature to ascertain the method of numbering. Benzofuran possessing various biological activities, particularly the dibenzofurans are reported to have analgesics, antiviral, anti-inflammatory, coughinhibiting, hypolipemics and herbicidal properties.

Thomas et al reported the synthesis of anticholestamic, dibenzofurnyl, N-alkyl carbamates and a new synthesis of novel dibenzofuran and two new xanthones from calophyllum panciflorum has been reported.

Introduction of Anti-inflammatory activity

Inflammation & Cell-Mediated Immune Response

"Inflammation is the reaction of vascular supporting elements to injury and results in formation of protein rich exudates provided the injury has not been so serious as to destroy the area". Inflammation is one of the most important mechanisms involved in the each disease. Inflammation is manifest by pain, swelling, redness, and loss of function in the affected tissue. The process is created by immune cells invading the tissue like an army in full battle mode. Cell-mediated immunity is initiated by several cell populations, including mast cells, macrophages, eosinophils, and neutrophils. The net effect of sustained immune activity in any target organ is inflammation with local dysfunction, associated with systemic symptoms from immune mediators released into the bloodstream. And create systemic symptoms by mediator or mediator release (Venkateshwaramurthi N 2010).

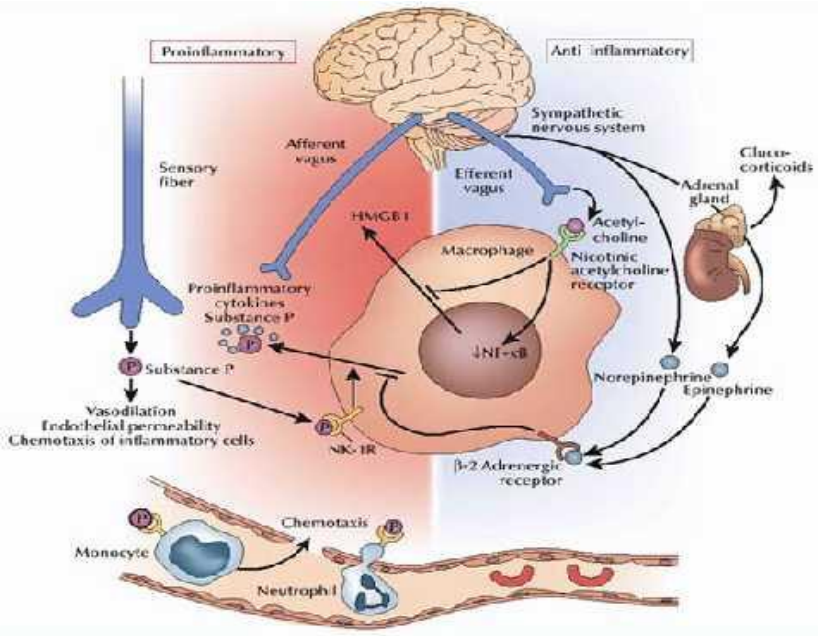


Fig-1: Different Stages Involved in Anti-inflammatory Cycle

Antibodies

The bone marrow is the major manufacturing area for immune cells. Some bone marrow cells migrate to the thymus gland and mature into T-lymphocytes. B- lymphocytes produce antibodies which identify specific foreign molecules and cell- surface markers and act against them. Immunity means that immune cells remember the identity of an antigen and initiate a defensive response. Antibodies are serum proteins or immunoglobulin. These proteins comprise of a memory system which detects antigens and then links antigens to an effecter system that defends against the antigen and associated structures. Antibodies are secreted by B-lymphocytes (transformed to plasma cells in tissue spaces). Antibodies may be free-floating in the blood and combine with antigen to form immune complexes (Masirkar J *et al* 2008).

B-Lymphocytes originate in the bone marrow and migrate to lymphatic tissues throughout the body. The main sites of serum antibody production are the spleen, lymph nodes and mucosa associated lymphatic tissues. In young children, serum immunoglobulin increase in concentration and variety as they grow an indication of expanding acquired immunity and hypersensitivity to a variety of potential antigens that arrive from the environment (Meena AK *et al* 2010).

There are 5 main antibody types:

- IgA: circulating and secreted on all defended body surfaces, as the first defense against invaders.
- IgD: surface receptors on lymphocytes.
- IgE: the antibody which produces typical allergy or immediate hypersensitivity reactions such hay fever, asthma, hives, and anaphylaxis.
- IgG: is the major circulating antibody which enters tissues freely, and participates in diverse immune events.
- IgM: the multivalent antibody, capable of capturing and binding antigens to form large insoluble complexes which are readily cleared from the blood.

Lymphocytes

Two major groups of lymphocytes are recognized as Thymus dependent or T-

lymphocytes; and Bursa dependent or B-lymphocytes. Adaptive immune responses require B cells to provide antibody and T cells to provide cell-mediated immunity. Cell surface receptors recognize antigens, B-lymphocytes learn make antibodies to specific antigens. Although T and B cells share a common progenitor, their development occurs in different locations in the body. B cells develop in the bone marrow and mature in lymphoid tissue. T lymphocyte progenitors leave the bone narrow and travel to the thymus where they mature (Vinothkumar *et al* 2009).

The identity of a foreign molecule, microorganism or cell, is recognized by an antigenic determinant, an amino acid sequence, usually contained in an intact protein. Once an antigenic determinant is recognized, its sequence is remembered by clones of antigen-specific B and T-memory cells which can activate other B lymphocytes that make antibodies against the antigen. T memory cells are also referred to a as helper T cells which are activated by the binding of a specific antigen encountered in the past, a signal that initiates defense against familiar pathogens(Krishnaswamy NR 2003).

Four cardinal signs of Inflammation:

- Calor - heat
- Rubor - redness
- Tumor - swelling
- Dolor - pain

Purpose of Immune Response:

A. Isolate, neutralize and remove cause of injury
B. Clear area of debris
C. Initiate healing and repair of injured tissue

CLASSIFICATIONS

Inflammation can be classified as

- Acute inflammation
- Chronic

Acute inflammation:

Acute inflammation is the initial response of the body to harmful stimuli and is

achieved by the increased movement of plasma and leukocytes from the blood in to the injured tissues. A cascade of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells with in the injured tissue. Acute inflammation is a short-term process, usually appearing within a few minutes, hours or one or two days and ceasing upon the removal of the injurious stimulus (Jayakar B 2010).

The cardinal signs are produced by

i. Changes in vascular flow
ii. Changes in vascular permeability
iii. Cellular events – Leucocytes exudation and phagocytes

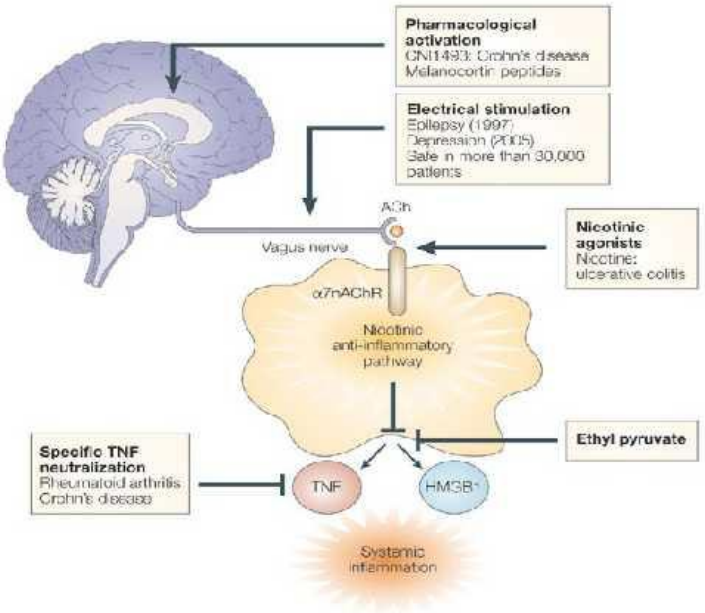


Fig 2: Mechanism of Acute inflammation

Chronic inflammation:

Prolonged inflammation is known as chronic inflammation, known as chronic inflammation, leads to a progressive shift in the type of cells which are present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process. It is of longer duration and is associated with presesnce of lymphocytes, macrophages, proliferation of blood vessels and connective tissue.

The causes of chronic inflammation are

i. Progression of acute inflammation
ii. Repeated bouts of acute inflammation
iii. Insidious low grade smoldering response

ANTI-INFLAMMATORY ACTIVITY:

Anti-inflammatory refers to the property of a substance or treatment that reduces inflammation. Anti-inflammatory drugs make up about half of analgesics, remedying pain by reducing inflammation as opposed to opioids which affect the central nervous system. Anti-inflammatory medications are often used to treat medical conditions that cause swelling or inflammation in various areas of the body. Some of these medical conditions may include pulled muscles, arthritis, or lupus. Anti-inflammatory medications are available both with and without a prescription (Mohammed Ali 2001).

Medications:

1. Steroids

Steroid medications such as cortisone are man-made or synthetic versions of natural hormones produced by the human body. These medications are often prescribed as anti-inflammatory medications. Steroid creams or ointments are often used externally to reduce swelling and inflammation associated with muscle, skin, or joint issues. Cortisone injections may be given by a doctor for deeper muscle or joint problems, including conditions such as arthritis. Many steroids, specifically glucocorticoids, reduce inflammation or swelling by binding to glucocorticoid receptors. These drugs are often referred to as corticosteroids (Kokate CK 2001).

Non-steroidal anti-inflammatory drugs:

Non-steroidal anti-inflammatory drugs, commonly referred to as NSAIDs, are the most commonly prescribed anti-inflammatory medications for conditions such as arthritis and muscle pain. Many of these medications are available over the counter and can be found in most drug stores. Non-steroidal anti-inflammatory drugs (NSAIDs) alleviate pain by counteracting the cyclooxygenase (COX) enzyme. On its own COX enzyme synthesizes prostaglandins, creating inflammation. In whole the NSAIDs prevent the prostaglandins from ever being synthesized, reducing or eliminating the pain. Some common examples of NSAIDs include aspirin, ibuprofen, and naproxen. The newer specific COX-inhibitors, although probably sharing a similar mode of action, are not classified together with the traditional NSAIDs.

On the other hand, there are analgesics that are commonly associated with anti-inflammatory drugs but that have no anti-inflammatory effects. An example is paracetamol, called acetaminophen in the U.S. and sold under the brand name of Tylenol. As opposed to NSAIDS, which reduce pain and inflammation by inhibiting COX enzymes, paracetamol has recently been shown to block the reuptake of cannabinoids. And which only reduces pain, likely explaining why it has minimal effect on inflammation.(Ashok D *et al* 2017).

2. Immune Selective Anti-Inflammatory Derivatives (ImSAIDs):

Early work in this area demonstrated that the submandibular gland released a host of factors which regulate systemic inflammatory responses and modulate systemic immune and inflammatory reactions. It is now well accepted that the immune, nervous and endocrine systems communicate and interact to control and modulate inflammation and tissue repair. One of the neuroendocrine pathways, when activated, results in the release of immune regulating peptides from the submandibular gland upon neuronal stimulation from sympathetic nerves. This pathway or communication is referred to as the cervical sympathetic trunk-submandibular gland (CST-SMG) axis, a regulatory system that plays a role in the systemic control of inflammation.

1.4. CLASSIFICATION OF ANTI-INFLAMMATORY DRUGS

1. Chemical Classification

A: Salicylates

- Acetyl salicylic acid (aspirin)
- Sodium Salicylates
- Choline Salicylates,
- Sodium thio Salicylates
- Salicylic Salicylates

B: Propionic Acid Derivatives

- Ibuprofen
- Ketoprofen
- Naproxen
- Oxaprozin
- Flurbiprofen

C: Indole Acetic Acid

- Indomethacin
- Sulindac

D: Substituted Anthranilic Acids (Rarely Used)

- Mefenamic acid
- Meclofenamate Na

E: Pyrrole Alkanoic Acid (Rarely Used)

- Tolmetin

F: Oxicams

- Piroxicam
- Meloxicam

G: Di-fluoro phenyl Derivatives

- Diflunisal

H: Phenyl Acetic Acid

- Diclofenac

I: Acetic Acid Derivatives

- Etodolac

J: Naphthyl Acetic Acid Prodrugs

- Nabumetone

K: Para-Amino Phenol Derivatives
- Acetaminophen

2. According To Mechanism Of Action

A: Non-Selective Cox Inhibitors
- Diclofenac
- Etodolac
- Indomethacin
- Ketoprofen
- Ketorolac
- Naproxen
- Oxaprozin
- Ibuprofen
- Flurbiprofen
- Diflunisol
- Piroxicam
- Sulindac

(Tenoxicam, Tiattrofin, Tolmetin are rarely used and not available in USA)

B: Drugs More Effective Inhibitors of Cox-1
- Aspirin
- Indomethacin
- Piroxicam
- Sulindac

C: Cox-2 Selective Inhibitors
- Celecoxib
- Etoricoxib
- Meloxicam

3. Therapeutic Classification

A: Analgesics
- Aspirin
- Paracetamol

B: AntiInflammatory
- Indomethacin
- Naproxen
- Ibuprofen

C: Anti-Coagulants
- Aspirin

D: Anti-Pyretics
- Aspirin
- Paracetamol
- Indomethacin
- Celecoxib
- Ibuprofen

E: Inflammatory Bowel Disease
- Sulfasalazine
- Infiximab

F: Anti-Cancer Drugs
- Methotrexate

G: Anti-Malarial
- Chloroquine
- Hydroxychloroquine

H: Tissue Transplantation
- Cyclosporine

I: Chelating Agents in Wilson's disease
- Penicillamine

J: Anti-Gout Drugs
- Indomethacin
- Ibuprofen

4. WHO Classification:

A: Drugs with Weak Anti-Inflammatory Effect
- Acetaminophen

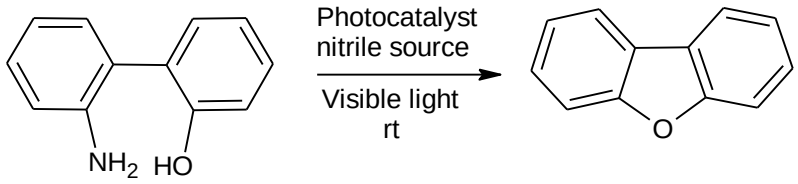
B: Drugs with Mild to Moderate Anti-Inflammatory Effect
- Propionic acid derivatives
- Anthranilic acid derivatives

C: Drugs with Marked Anti-Inflammatory Effects

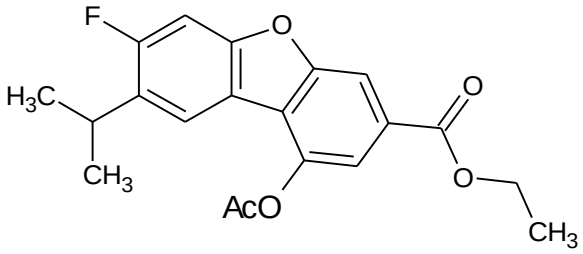
- Salicylates, acetic acid derivatives
- Oxicams
- Diclofenac
- Etodolac

Literature review

Ji young cho *et al* **(2018)** has been synthesized dibenzofuran derivatives via intra molecular C-O bond formation. This involves the in situ production of a diazonium salt.



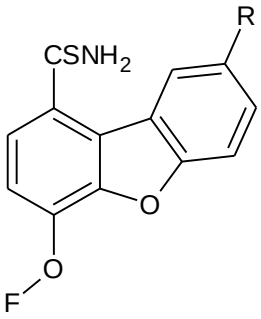
Ying Ma *et al* **(2017)** was performed the synthesis, bioactivity, 3D QSAR studies of novel dibenzofuran derivatives as PTP-MEG2 inhibitors. His finding provides a new strategy as useful insights for designing the effective PTP-MEG2 inhibitor.



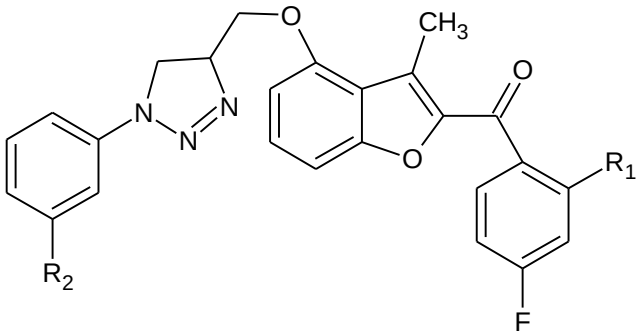
Ashok D *et al* **(2017)** has reported the synthesis, biological evaluation of spirofurochromanone derivative as anti-inflammatory and antioxidant activity. They found certain compounds have better anti-inflammatory activity in the albumin denaturation technique.

Ananthi R *et al* **(2016)** worked on antimicrobial and anti-inflammatroy activity of usnic acid and its acetyl derivative usnic acid diacetate. they concluded that the parent compound usnic acid was more active than usnic acid acetate.

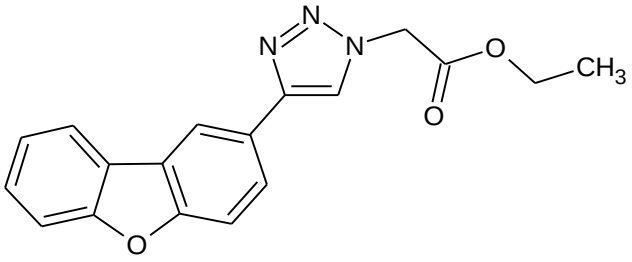
Gopalan B *et al* **(2016)** reported the synthesis of a few dibenzo(b,d) furan thiazole derivatives and exhibit promising in vitro PDE-4B and TNF- α inhibitor activities with promising result.



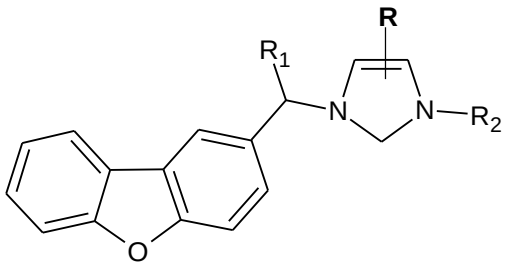
Zhen liang *et al* **(2016)** has designed and synthesized a series of benzofuran triazole hybrids. The target compounds were evaluated in vitro antifungal activity. They found the results indicated that the compounds exhibited moderate to satisfactory activity.



Thirumal Y *et al* **(2014)** has been reported a series of novel dibenzo(b,d)furan-1,2,3-triazole conjugate and evaluate the invitro antimycobacterial activity against mycobacterium tuberculosis H37Rv(ATCC27294) showed most promosing antitubercular agent with lowest cytotoxicity.



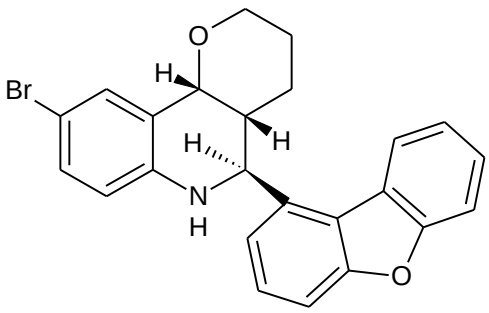
Lan –Xiang liu *et al* **(2013)** has been prepared a noval hybrid compounds between dibenzo(b,d) furan and imidazole also he evaluated in vitro antitumor activities and found to be more selective against Brest carcinoma (MCF-7) & myeloid liver carcinoma (SMMC-7721).



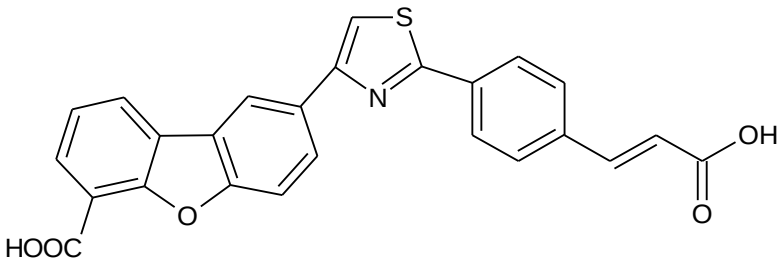
Sangita Chandra *et al* **(2012)** has evaluated the in vitro anti-inflammatory effect of aqueous extract of coffea arabica against the denaturation of protein concluded that coffee possessed marked in vitro anti-inflammatory effect against the denaturation of protein. The effect was plausibly due to the polyphenol content of coffee.

Zhiping che and Hui Xu **(2011)** has reported an efficient one –pot synthesis of dibenzofuran, via S_N Ar reaction of aryl halides and ortho bromo phenols in the presence of anhydrous K_2CO_3 and subsequent ligand free palladium-catalysed intramolecular aryl-aryl cross coupling cyclization under microwave irradiation. In end it concluded that they got the product at maximum 72-96% yield in short reaction times.

Srinivas kantevari *et al* **(2011)** reported a series of `noval dibenzo(b,d) furan and 9-methyl-9H-carbazole derived hexa hydro-2H-pyrano(3,2-c)quinolines via povarov reaction(imino diels-alder reaction) and evaluated for their invitro anti-mycobacterial activity against M.tuberculosis H37Rv.

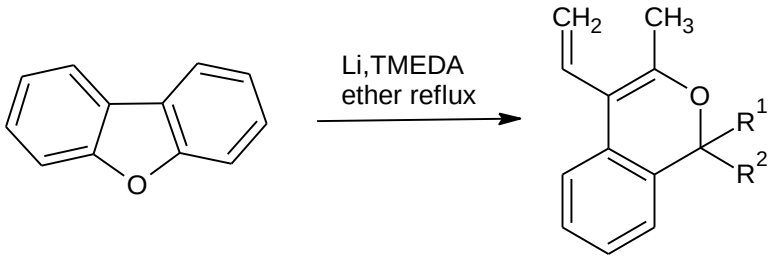


Lakshminarayana N *et al* **(2010)** reported a series of dibenzo(b,d) furan monocarboxylic acid derivatives and evaluated their ability to inhibit protein Tyrosin phosphate as potential anti diabetic agents.



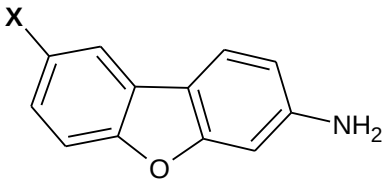
Perumal R *et al* **(2008)** have been synthesized pyrimidinoimidazolinones and evaluated for their antimicrobial activity. He observed that acceptable anti-inflammatroy activity by invitro model compared to standard diclofenac sodium.

Bin wang *et al* **(2006)** has worked on a general synthetic route to 6,6-substituted-6-H-dibenzo(b,d) pyran from dibenzofuran in good yield. The reaction undergoes reductive ring opening and cyclization.



Katashi iota *et al* **(1995)** have been reported the chlorination of dibenzofuran and some of its derivatives also he concluded that preparation of 2-chloro dibenzofuran was accomplished most effectively by direct chlorination in presence of iron powder, dichlorination (2, 8-dichloro derivative) archived by the use of chlorine and iron powder.

Barry reported 2-chloro (bromo) 7-aminodibenzofuran to completely inhibit M.Tuberculosis at a dilution of 1/4,00,000.



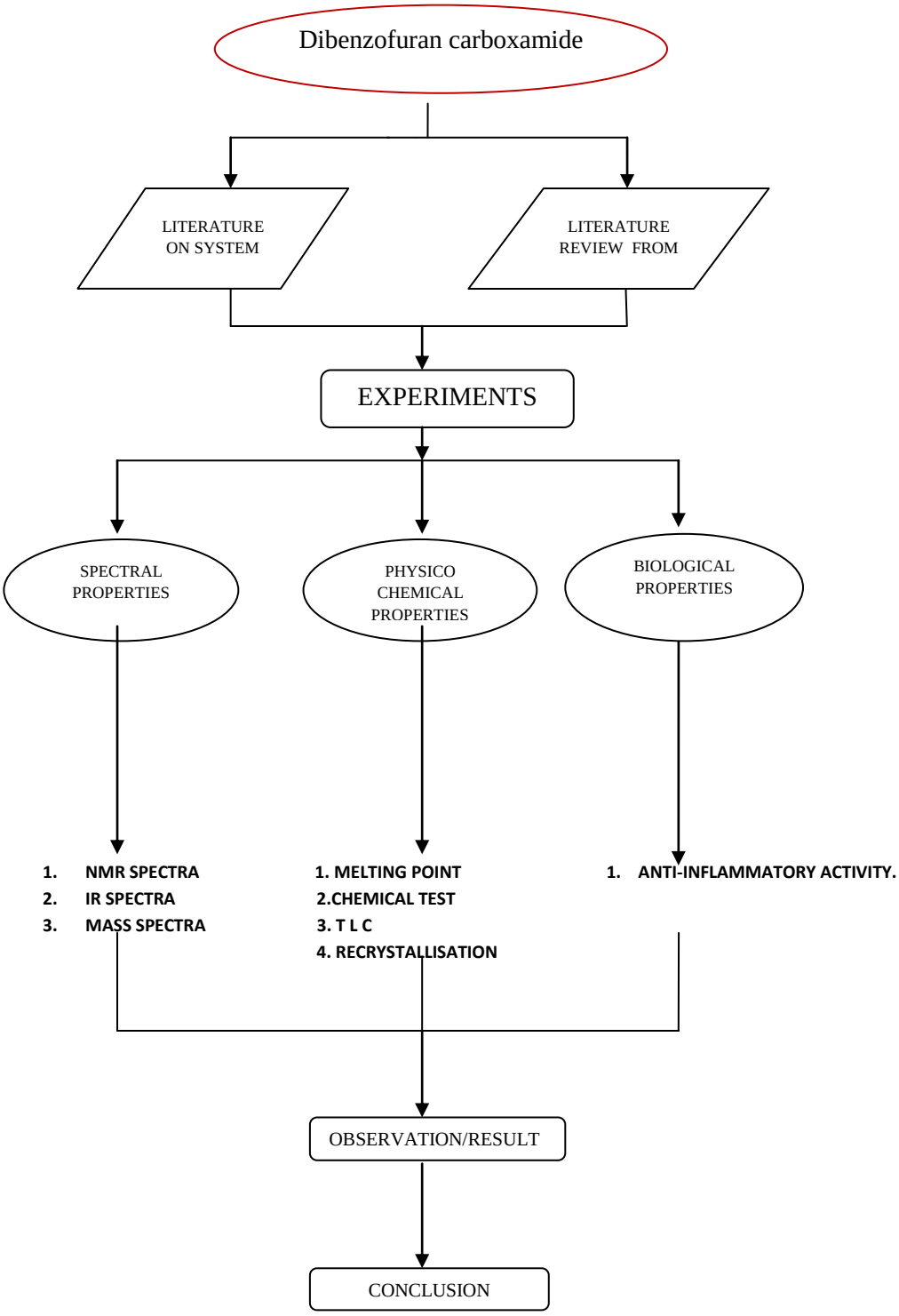
AIM OF THE WORK

Today's system of medicine has adopted highly sophisticated technological tools and discovered newer modern drugs. However beyond those success these drugs causes serious side effect also. That may be due to its reaction with cellular component of human system (tissues). In view of that the present work was aimed to synthesis some dibenzofuran-1,3-thiazole carboxamide derivatives by four step reactions with the substitution of various aromatic amines under suitable catalyst. All the synthesized compounds were characterized by physical, chemical and spectral data. Those synthesized compounds were further screened mainly for preliminary anti-inflammatory study and focused for further pharmacological evaluation.

The total plan of the work as follows

- The literature review done with the help of journals, scifinder, online sites and some books.
- To synthesize some dibenzofuran 1,3-thiazole carboxamide derivatives.
- Ten derivatives were synthesised by substituting aryl amine with suitable catalyst and solvents.
- The purity and progress of the reactions will be monitored by TLC with suitable solvent system.
- The purification of the compounds will be carried by purification methods like recrystallization by using suitable solvents.
- To characterize the structures of newly synthesized compounds by IR, ^{1}H NMR and Mass spectra.
- The anti-inflammatory activity of synthesised compounds done by protein denaturation assay method.

PLAN OF WORK


Dibenzofuran carboxamide
LITERATURE ON SYSTEM
LITERATURE REVIEW FROM
EXPERIMENTS
SPECTRAL PROPERTIES
PHYSICO CHEMICAL PROPERTIES
BIOLOGICAL PROPERTIES
1. NMR SPECTRA
2. IR SPECTRA
3. MASS SPECTRA
1. MELTING POINT
2.CHEMICAL TEST
3. T L C
4. RECRYSTALLISATION
1. ANTI-INFLAMMATORY ACTIVITY.
OBSERVATION/RESULT
CONCLUSION

SYNTHESIS AND EXPERIMENTAL PROCEDURE

Materials and Methods

The melting points were taken in open capillary tube and are uncorrected. The IR spectra of the compounds were recorded on FT-IR spectrometer-4100 typeA with potassium bromide pellets. The ^{1}H-NMR and spectra of the synthesized compounds were recorded on a JOEL 500 MHz NMR spectrometer in $CHCl_3$ / DMSO. Mass spectra were recorded on Shimadzu GCMS QP 5000. The purity of the compounds was checked by TLC on pre – coated SiO_2 gel (HF254 200 mesh) aluminum plates (E-merk) using ethyl acetate: n-hexane as eluent and visualized in UV- chamber.(Harbone JB 2005). The IR, ^{1}H-NMR, and mass spectra were consistent with the assigned structure.

Synthetic Methods

For the synthesis of substituted dibenzofuran carboxamide, at first 2-(4-methoxydibenzo [b, d] furan-1-yl)-5-methyl-N-benzyl-1, 3-thiazole-4-carboxamide was prepared in four steps using 4-methoxy dibenzo [b, d] furan as a starting compound. In the first step, 4-methoxy dibenzo [b, d] furan gets converted to 4-methoxydibenzo[b, d]furan -1-carbothiamide, in the second step next Ethyl 2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-1,3-thiazole-4-carboxylate was obtained which in third step gets converted as carboxylic acid derivatives and then in fourth step we got 2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-benzyl-1,3-thiazole-4-carboxamide. Finally from the fourth step we produced series of ten aryl amine derivatives and the detailed procedures and scheme are given below.(Gopal B *et al* 2012).

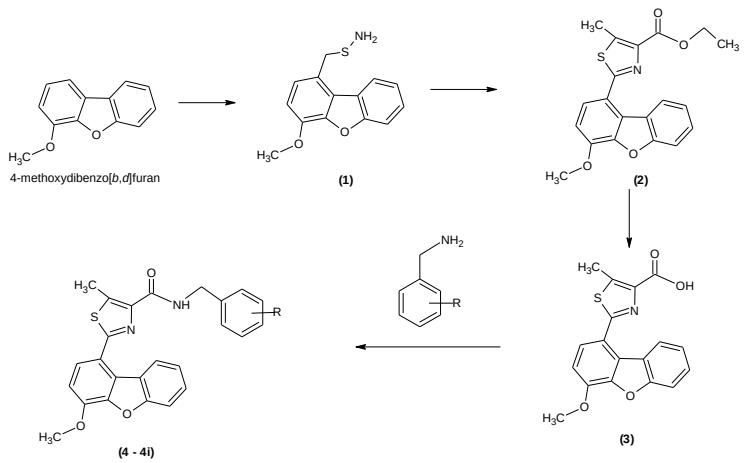


Fig.:3

Synthesis of 4-methoxydibenzo [b, d] furan-1-carbothioamide (1)

4-methoxy dibenzo[b,d]furan 1 g, (5.05 mmol) in 11 ml of methane sulfonic acid was taken in a round bottom flask then 1 g potassium thiocyanate was added (10.29 mmol) slowly, the reaction was kept at 0–5 ° C in ice and salt mixture, after the addition the reaction mass was stirred at room temperature. Finally the mixture was poured into crushed ice and the solid obtained was filtered. It was triturated with n-hexane and dried to get a pale brown coloured solid (0.9 g). Yield—70%; mass m/z: 258.2 (M+1).

Synthesis of Ethyl 2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-1,3-thiazole-4-carboxylate (2)

4-methoxydibenzo [b, d] furan-1-carbothioamide (1.0 mmol) was taken with 5ml ethanol and stirred to become a solution, then potassium carbonate (1.5 mmol) followed by ethyl 3-bromo-2-oxobutanoate (1.2 mmol) was added at room temperature. The reaction mixture was refluxed at 80°C for 2 hr with occasional shaking, subsequently it was poured into 25 ml of cold water and the precipitate which obtained was filtered to get a peach coloured solid, yield - 50%; mass m/z: 354.1 (M+1).

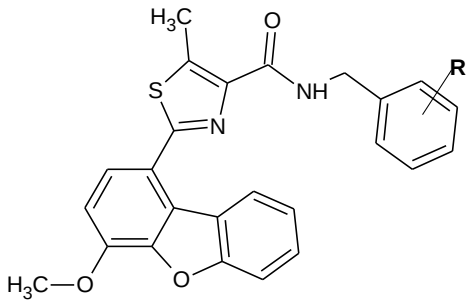
Synthesis of 2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-1,3-thiazole-4-carboxylic acid (3)

To a slurry of ethyl 2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-1,3-thiazole-4-carboxylate (50 mg,0.116 mmol) in ethanol (5 mL) was added potassium hydroxide (30 mg, 0.535 mmol) followed by water (0.5 mL) and the mass was stirred at rt for 2 h. Subsequently the reaction mixture was poured into cold water, acidified with 1 N HCl to a pH of 3–4; and the precipitated solid was filtered and triturated with ether followed by n–hexane to give a off-white solid; Yield—42% m/z: 403.1 (M+1).

Synthesis of 2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-benzyl-1,3-thiazole-4-carboxamide (4)

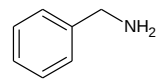
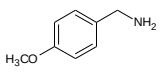
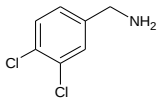
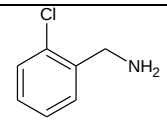
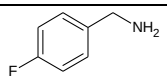
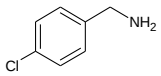
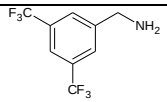
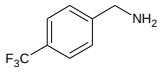
In a 50ml round bottom flask 0.2 g (0.00048mol) of 2-(4-methoxydibenzo [b,d]furan-1-yl)-5-methyl-1,3-thiazole-4-carboxylic acid was dissolved in 10ml dichloromethane. To that solution 0.32g (0.00096 mol) TBTU and 0.15 ml (0.0014 mol)Triethylamine was added and stirred for 5 min under nitrogen atmosphere. Then benzyl amine (0.632 mmol) was added and stirred for 3hr under room temperature. The completion of the reaction was monitored by TLC and the reaction mixture was

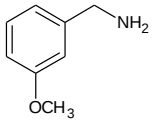
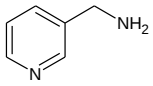
extracted with ethyl acetate. The organic layer was washed with sodium bicarbonate solution, water, brine solution, which was separated and dried over anhydrous sodium sulphate. The evaporation of solvent yielded the target compounds. 0.13g, Yield: 76%. m/z: 429.1 (M+1).(Katashi O *et al* 1955.)



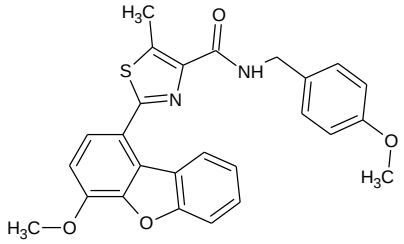
General structure

Table :.1

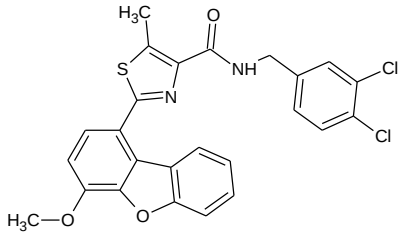
S.No	Code	R	IUPAC Name	M.P °C	Yield %
1	4		2-(4-methoxydibenzo(b,d)furan-1-yl)-5-methyl-n-benzyl-1,3-thiazole-4-carboxamide	192	76
2	4a		2-(4-methoxydibenzo(b,d)furan-1-yl)-5-methyl-n-(4-methoxybenzyl)-1,3-thiazole-4-carboxamide	152	79.13
3	4b		2-(4-methoxydibenzo(b,d)furan-1-yl)-5-methyl-N-(3,4-dichlorobenzyl)1,3thiazole-4-carboxamide	164	61.26
4	4c		2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-(2chlorobenzyl)-1,3-thiazole-4-carboxamide	120	55.46
5	4d		2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-(4-fluorobenzyl)-1,3-thiazole-4-carboxamide	194	59.21
6	4e		2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-(4-chlorobenzyl)-1,3-thiazole-4-carboxamide	182	54.04
7	4f		2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-[(3,5-bis tri fluoro methyl)benzyl]-1,3-thiazole-4-carboxamide	198	71.90
8	4g		2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-[(4-tri fluoro methyl)benzyl]-1,3-thiazole-4-carboxamide	184	72.16

9	4h		2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-(3-methoxybenzyl)-1,3-thiazole-4-carboxamide	170	83.24
10	4i		2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-(pyridine-3-yl)-1,3-thiazole-4-carboxamide	226	87.83

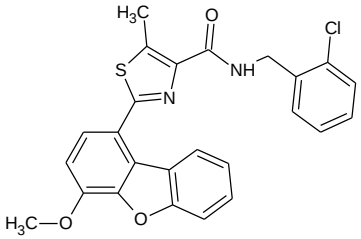
Synthesis of 2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-(4-methoxybenzyl)-1,3-thiazole-4-carboxamide(4a)



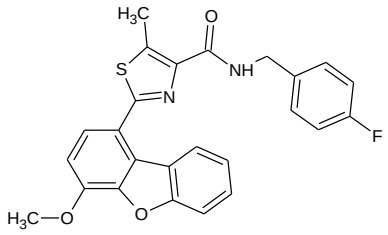
Synthesis of 2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-(3,4-dichlorobenzyl)-1,3-thiazole-4-carboxamide(4b)



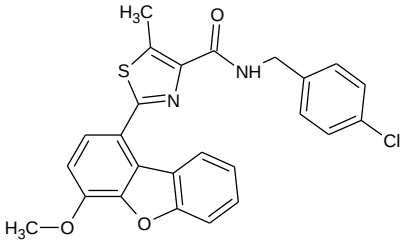
Synthesis of 2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-(2chlorobenzyl)-1,3-thiazole-4-carboxamide(4c)



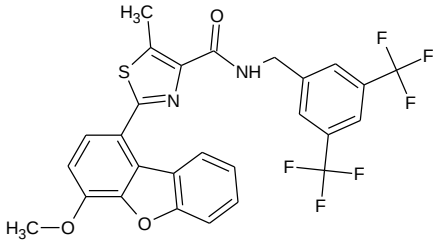
Synthesis of 2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-(4-fluorobenzyl)-1,3-thiazole-4-carboxamide(4d)



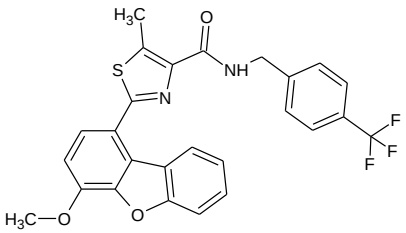
Synthesis of 2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-(4-chlorobenzyl)-1,3-thiazole-4-carboxamide(4e)



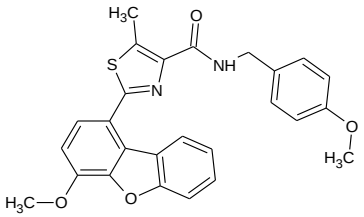
Synthesis of 2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-[(3,5-bistrifluoromethyl)benzyl]-1,3-thiazole-4-carboxamide(4f)



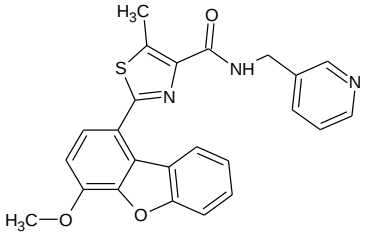
Synthesis of 2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-[(4-trifluoromethyl)benzyl]-1,3-thiazole-4-carboxamide(4g)



Synthesis of 2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-(3-methoxybenzyl)-1,3-thiazole-4-carboxamide(4h)

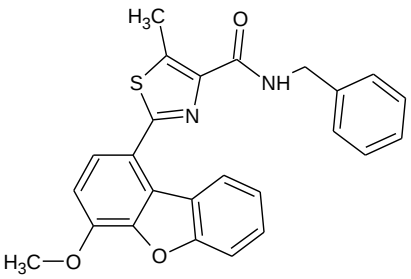


Synthesis of 2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-(pyridine-3-yl)-1,3-thiazole-4-carboxamide(4i)



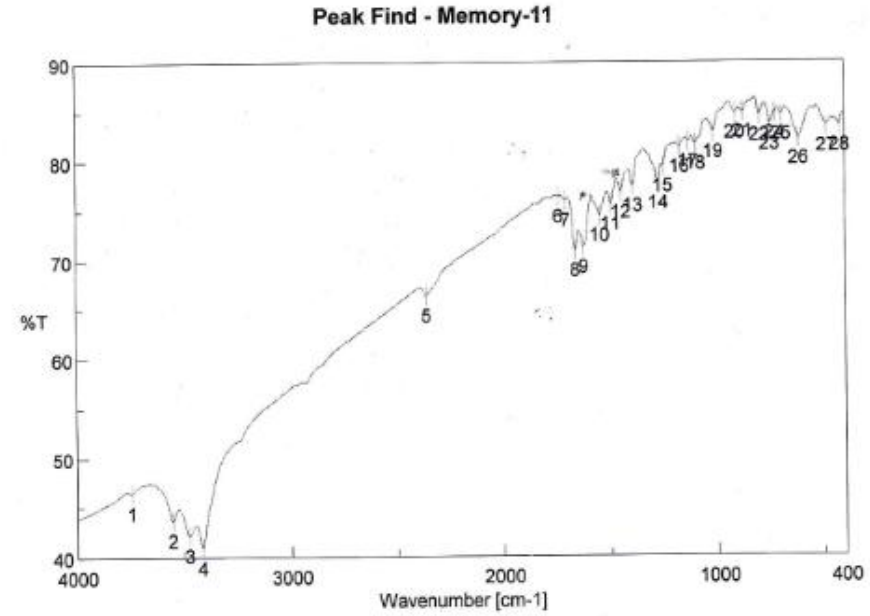
PHYSICO-CHEMICAL PROPERTIES AND SPECTRAL DATA OF THE SYNTHESISED COMPOUNDS (Mc MURRY J 1992).

Table:2. Physical data of compound - 4



Compound	4
IUPAC NAME	*2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-benzyl-1,3-thiazole-4-carboxamide*
Molecular formula	$C_{25}H_{20}N_2O_3S$
Molecular weight	428
M.P.	192^0C
Yield (%)	76
IR (KBr),ν (cm^{-1})	3415 N-H bend (amide), 3476 C=C-H. (Ar carbon), 1741, C=O stretch (carbonyl amide), 1624 – 1446 C=C stretch (Ar ring),1018 C-N stretch (amine) 799 (Para substitution)
^{1}H-NMR δ (ppm)	^{1}H-NMR (500 MHz, $CDCl_3$) ppm: 2.97 (s, 3H, CH_3); 4.11 (s, 3H, OCH_3); 4.64 - 4.65 (d, 2H, CH_2); 6.97-7.03 (m, 2H, Ar-H); 7.29 (m, 1H, Ar-H); 7.33 – 7.39 (m, 4H, Ar-H); 7.43 (t, 1H, Ar-H); 7.48 - 7.50 (d, 1H, Ar-H); 7.62 - 7.63 (d, 1H, Ar-H); 7.90 - 7.92 (t, 1H, Ar-H); 8.38 – 8.40(d, 1H, N-H).
HRMS (m/z):	429(M^{+1})

Figure:4. Infrared spectra of compound – 4



[Comments]
Sample name
Comment
User
Division
Company NAWAL ANALYTICAL LBORATORIES

[Detailed Information]		[Measurement Information]	
Creation date	19-Feb-18 11:59 AM	Model Name	FT/IR-4100typeA
		Serial Number	C251661016
Data array type	Linear data array		
Horizontal axis	Wavenumber [cm-1]	Measurement Date	19-Feb-18 11:56 AM
Vertical axis	%T		
Start	399.193 cm-1	Light Source	Standard
End	4000.6 cm-1	Detector	TGS
Data interval	0.964233 cm-1	Accumulation	16
Data points	3736	Resolution	4 cm-1
		Zero Filling	On
		Apodization	Cosine
		Gain	Auto (2)
		Aperture	Auto (7.1 mm)
		Scanning Speed	Auto (2 mm/sec)
		Filter	Auto (30000 Hz)

[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	3743.15	46.4218	2	3553.2	43.6908

Figure:5. NMR spectra of compound – 4

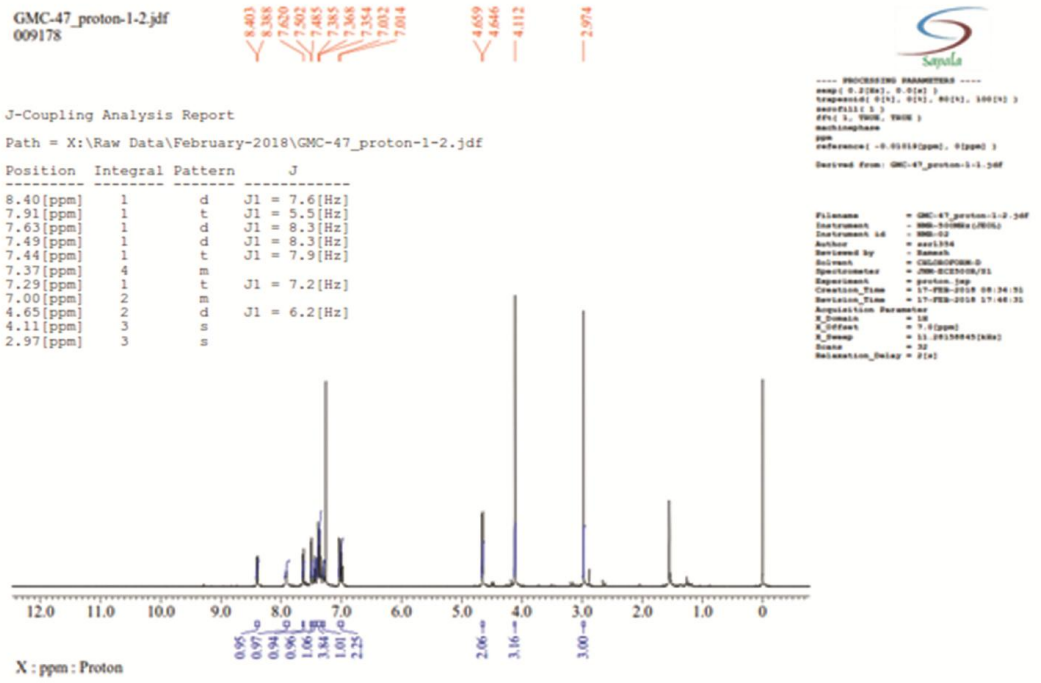


Figure:6. Mass spectra of compound – 4

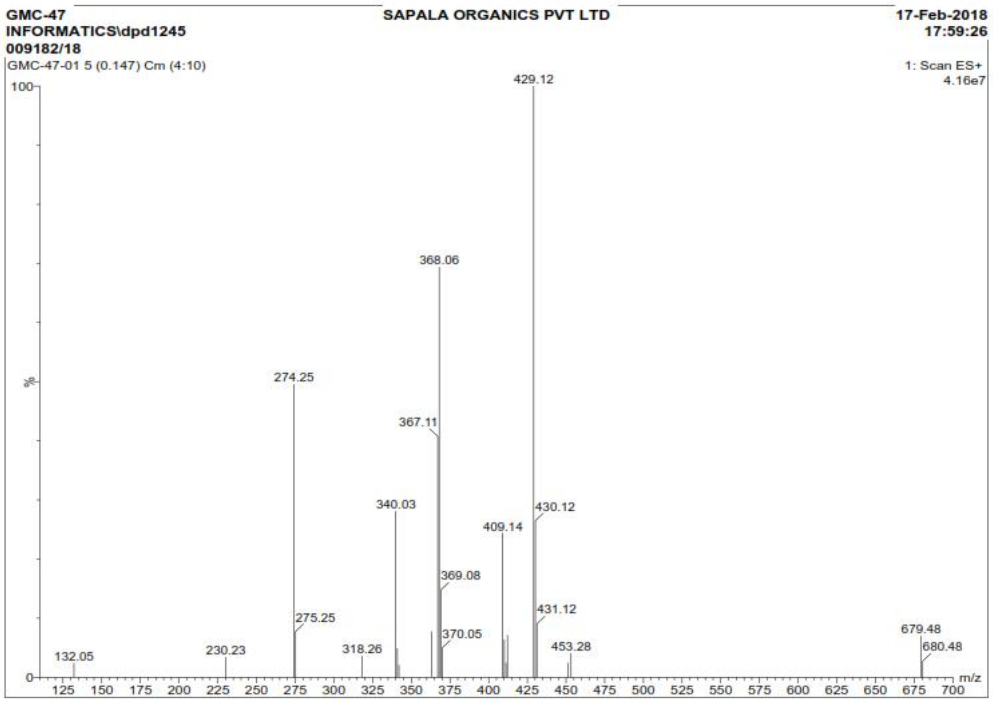
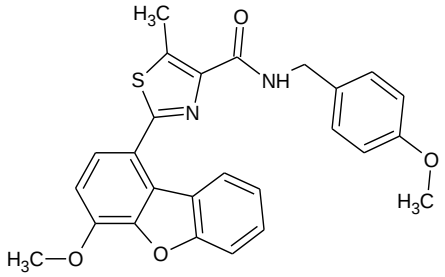
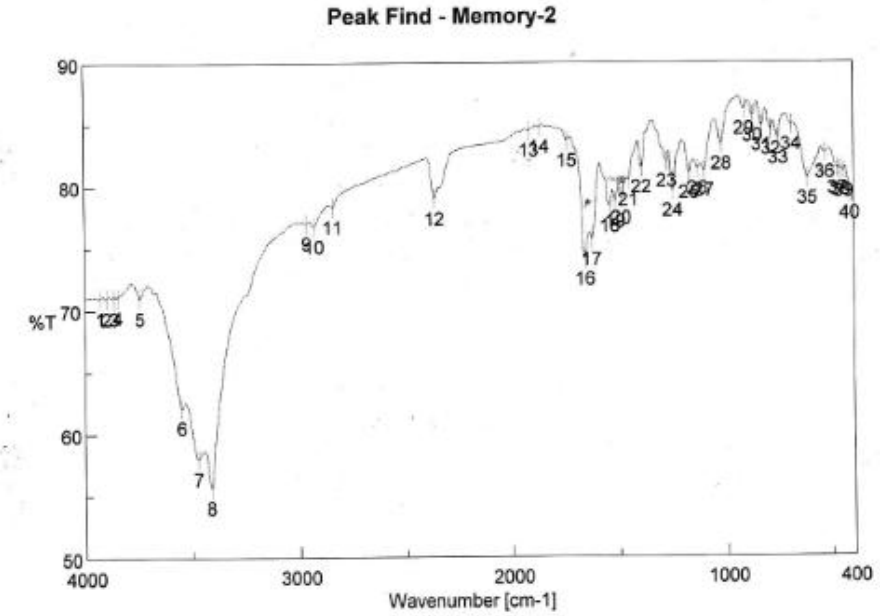


Table:3. Physical data of compound – 4a



Compound	4a
IUPAC NAME	*2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-(4-methoxybenzyl)-1,3-thiazole-4-carboxamide*
Molecular formula	$C_{26}H_{22}N_2O_4S$
Molecular weight	458
M.P.	152^0C
Yield (%)	79.13
IR (KBr),ν (cm^{-1})	3413 N-H bend (amide), 3473 C=C-H. (Ar carbon), 1740 C=O stretch (carbonyl amide), 1625 – 1454 C=C stretch (Ar ring),1021 C-N stretch (amine) 787,754 (Para substitution)
^{1}H-NMR δ(ppm)	^{1}H-NMR (500 MHz, $CDCl_3$) ppm: 2.96 (s, 3H, CH_3); 3.80 (s, 3H, OCH_3); 4.11 (s, 3H, OCH_3); 4.57 - 4.58 (d, 2H, CH_2); 6.87- 6.88 (d, 2H, Ar-H); 7.00 - 7.03 (m, 2H, Ar-H); 7.29 – 7.31 (m, 2H, Ar-H); 7.44 (t, 1H, Ar-H); 7.48 - 7.49 (d, 1H, Ar-H); 7.62 - 7.63 (d, 1H, Ar-H); 7.83 - 7.85 (t, 1H, Ar-H); 8.37 – 8.39 (d, 1H, N-H).
HRMS (m/z):	459(M^{+1})

Figure:7 Infrared spectra of compound – 4a



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[Detailed Information]	
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Horizontal axis	Wavenumber [cm-1]
Vertical axis	%T
Start	399.193 cm-1
End	4000.6 cm-1
Data interval	0.964233 cm-1
Data points	3736

[Measurement Information]	
Model Name	FT/IR-4100typeA
Serial Number	C251661016
Measurement Date	19-Feb-18 12:13 PM
Light Source	Standard
Detector	TGS
Accumulation	16
Resolution	4 cm-1
Zero Filling	On
Apodization	Cosine
Gain	Auto (2)
Aperture	Auto (7.1 mm)
Scanning Speed	Auto (2 mm/sec)
Filter	Auto (30000 Hz)

[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	3925.39	70.964	2	3896.47	70.9362

Figure:8 NMR spectra of compound – 4a

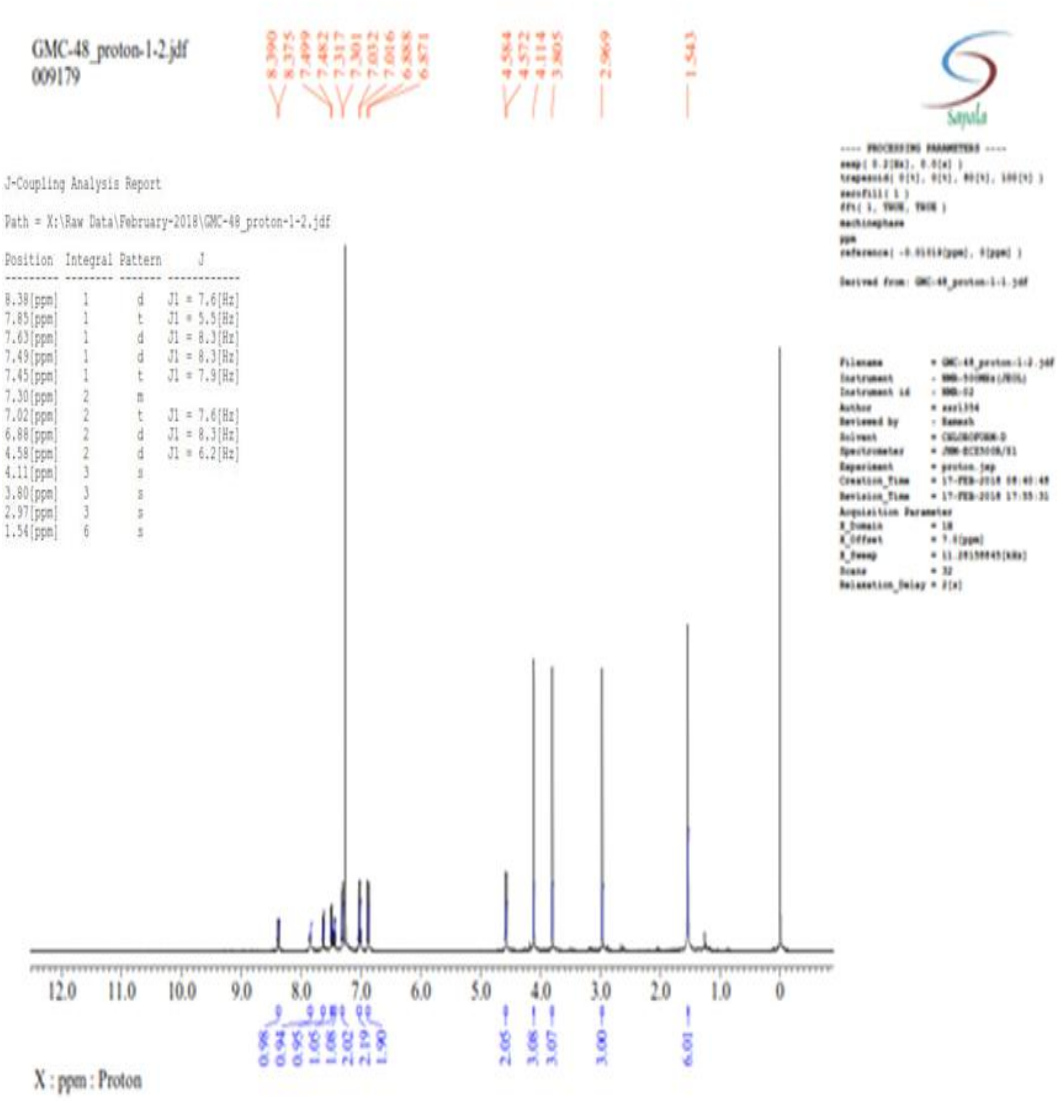


Figure:9 Mass spectra of compound – 4a

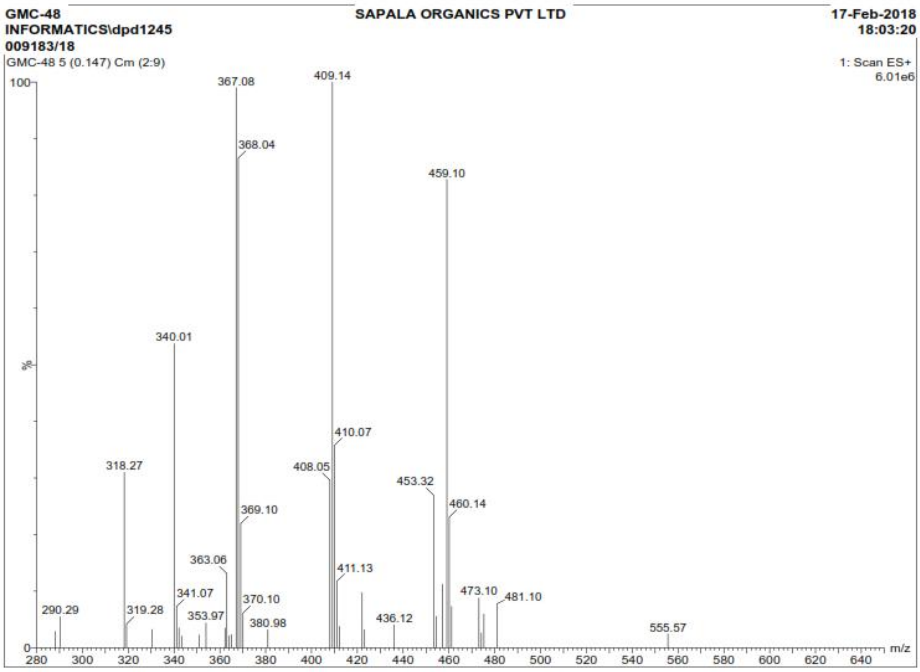
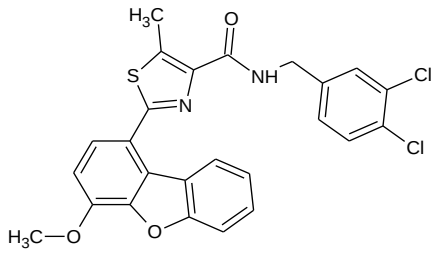
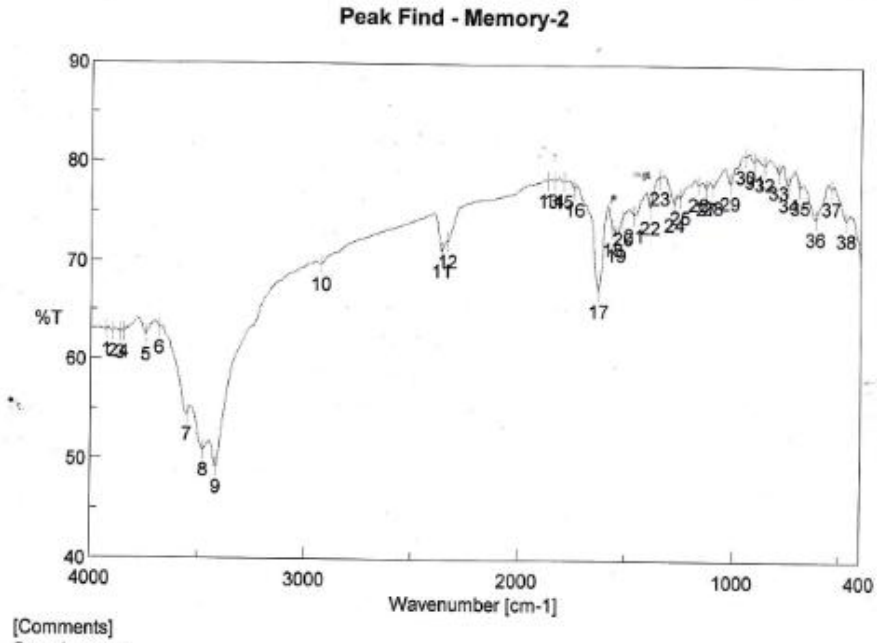


Table:4. Physical data of compound – 4b



Compound	4b
IUPAC NAME	*2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-(3,4- di chloro benzyl)-1,3-thiazole-4-carboxamide*
Molecular formula	$C_{25}H_{18}Cl_2N_2O_3S$
Molecular weight	497
M.P.	164^0C
Yield (%)	61.26
IR (KBr),ν (cm^{-1})	3414 N-H bend (amide), 3474 C=C-H. (Ar carbon), 1740 C=O stretch (carbonyl amide), 1627 – 1464 C=C stretch (Ar ring),1165,1130 (Ar-Cl stretch), 1019 (C-N stretch amine), 791 (Para substitution), 744(ortho substitution).
^{1}H-NMR δ(ppm)	^{1}H-NMR (500 MHz, $CDCl_3$) ppm: 2.95 (s, 3H, CH_3); 4.11 (s, 3H, OCH_3); 4.57 - 4.59 (d, 2H, CH_2); 7.01 - 7.04 (m, 1H, Ar-H); 7.08 - 7.12 (t, 1H, Ar-H); 7.21 - 7.23 (m, 1H, Ar-H); 7.40 – 7.42 (d, 1H, Ar-H); 7.46 - 7.51 (m, 3H, Ar-H); 7.64 - 7.66 (d, 1H, Ar-H); 7.94 - 7.97 (t, 1H, Ar-H); 8.34 – 8.35 (d, 1H, N-H).
HRMS (m/z):	495(M^{-1})

Figure:10 Infrared spectra of compound – 4b



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[Detailed Information]		[Measurement Information]	
Creation date	19-Feb-18 12:26 PM	Model Name	FT/IR-4100typeA
		Serial Number	C251661016
Data array type	Linear data array		
Horizontal axis	Wavenumber [cm-1]	Measurement Date	19-Feb-18 12:26 PM
Vertical axis	%T		
Start	399.193 cm-1	Light Source	Standard
End	4000.6 cm-1	Detector	TGS
Data interval	0.964233 cm-1	Accumulation	16
Data points	3736	Resolution	4 cm-1
		Zero Filling	On
		Apodization	Cosine
		Gain	Auto (2)
		Aperture	Auto (7.1 mm)
		Scanning Speed	Auto (2 mm/sec)
		Filter	Auto (30000 Hz)

[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	3925.39	62.8618	2	3896.47	62.7478

Figure:11 NMR spectra of compound – 4b

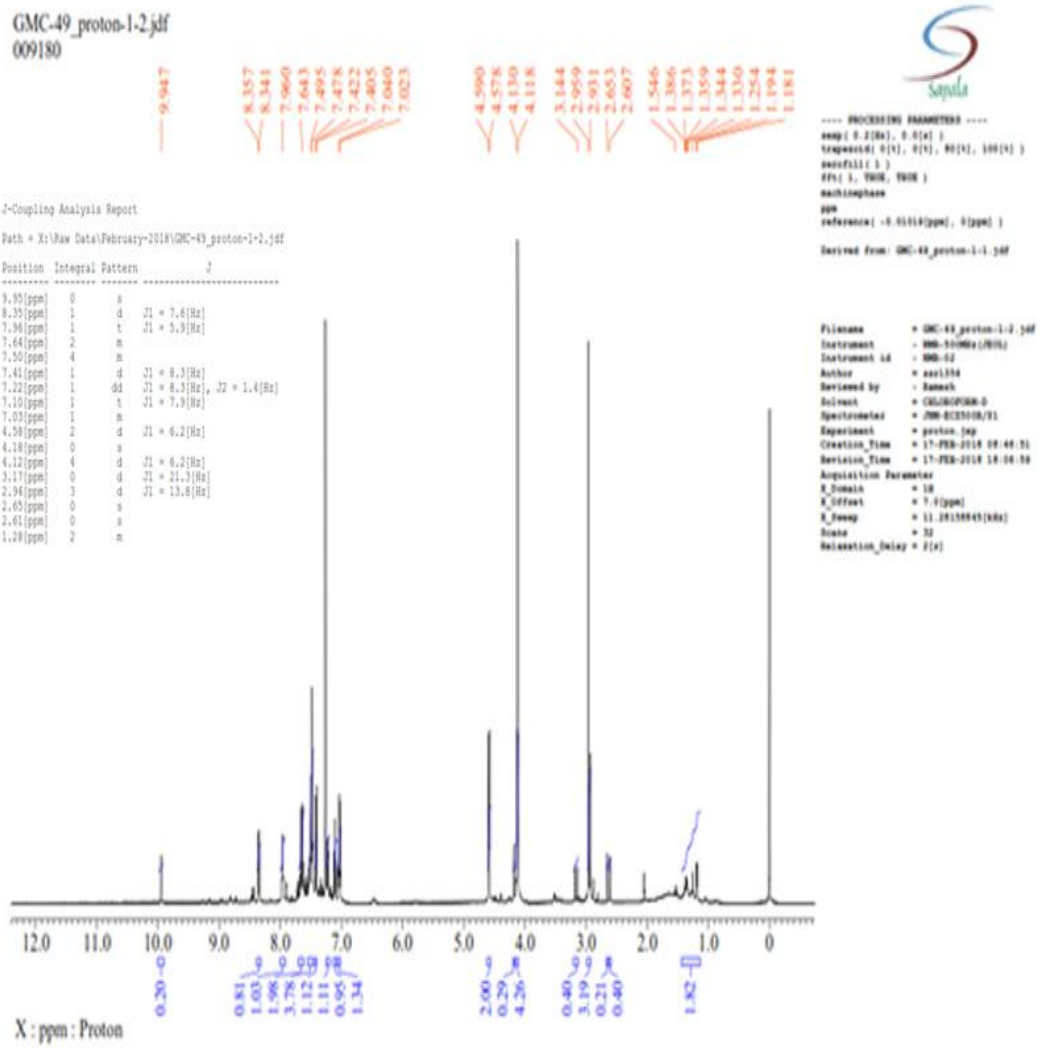


Figure:12 Mass spectra of compound – 4b

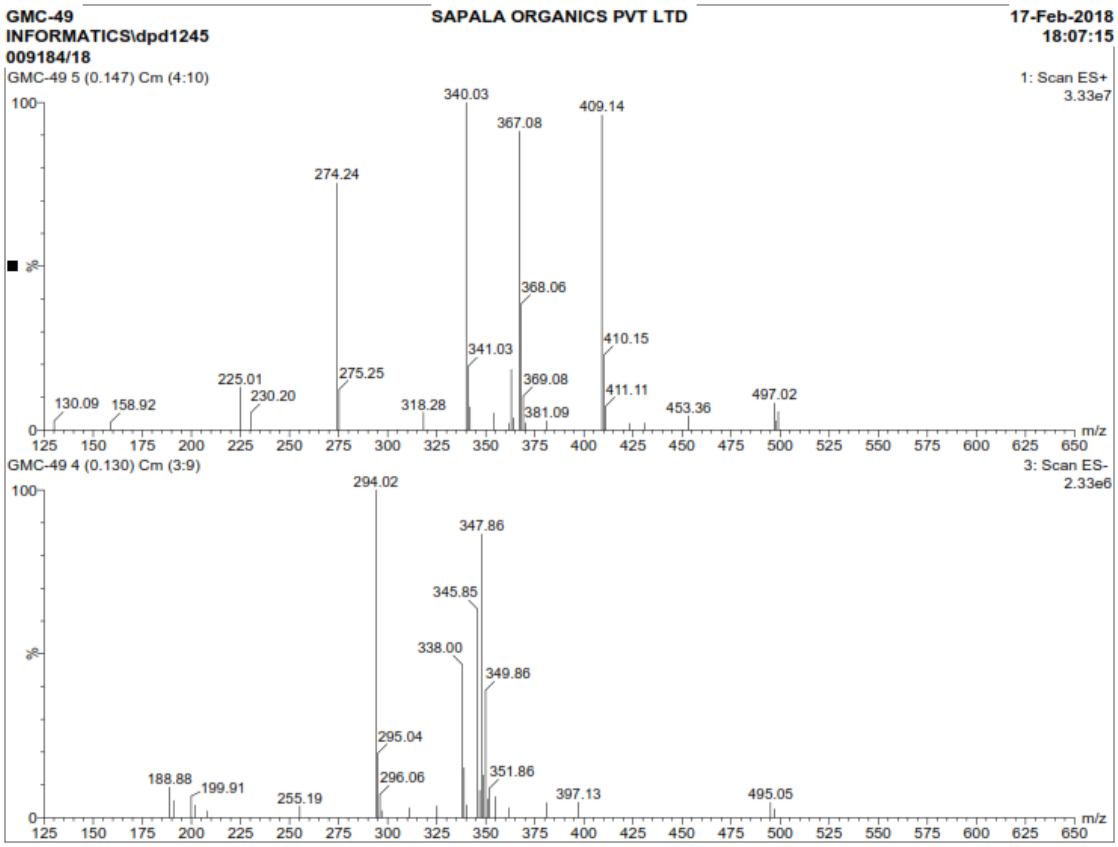
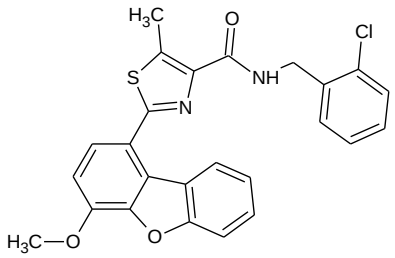
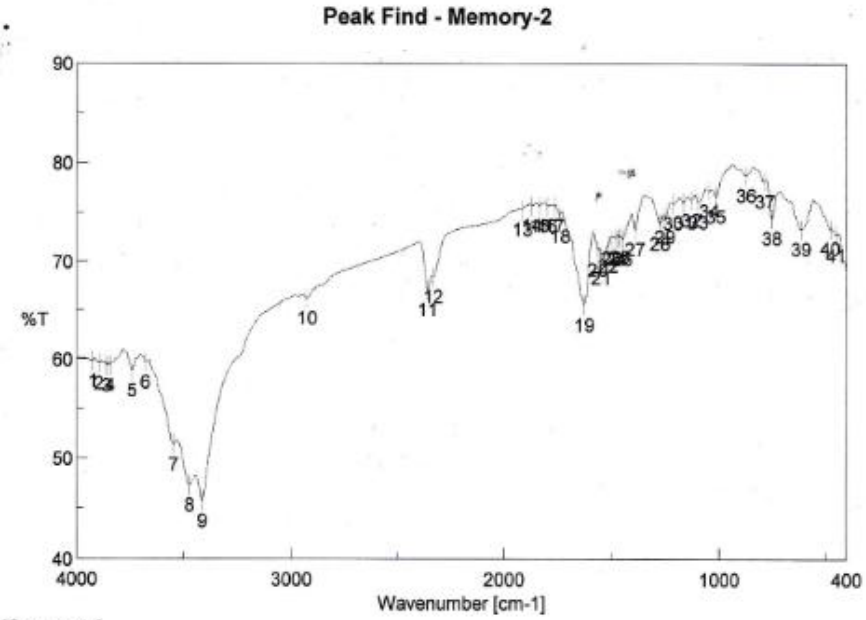


Table:5. Physical data of compound – 4c



Compound	4c
IUPAC NAME	*2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-(2chlorobenzyl)-1,3-thiazole-4-carboxamide*
Molecular formula	$C_{25}H_{19}$ Cl N_2 O_3 S
Molecular weight	462
M.P.	120^0C
Yield (%)	55.46
IR (KBr),ν (cm^{-1})	3414 N-H bend (amide), 3474 C=C-H. (Ar carbon), 1740 C=O stretch (carbonyl amide), 1627 – 1450 C=C stretch (Ar ring),1131(Ar-Cl stretch), 1047 C-N stretch (amine), 785 (Para substitution), 753(ortho substitution).
HRMS (m/z):	463 (M^{+1})

Figure:13 Infrared spectra of compound – 4c



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[Detailed Information]		[Measurement Information]	
Creation date	19-Feb-18 12:40 PM	Model Name	FT/IR-4100typeA
		Serial Number	C251661016
Data array type	Linear data array		
Horizontal axis	Wavenumber [cm-1]	Measurement Date	19-Feb-18 12:40 PM
Vertical axis	%T		
Start	399.193 cm-1	Light Source	Standard
End	4000.6 cm-1	Detector	TGS
Data interval	0.964233 cm-1	Accumulation	16
Data points	3736	Resolution	4 cm-1
		Zero Filling	On
		Apodization	Cosine
		Gain	Auto (2)
		Aperture	Auto (7.1 mm)
		Scanning Speed	Auto (2 mm/sec)
		Filter	Auto (30000 Hz)

[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	3924.43	59.7638	2	3896.47	59.5206

Figure:14 Mass spectra of compound – 4c

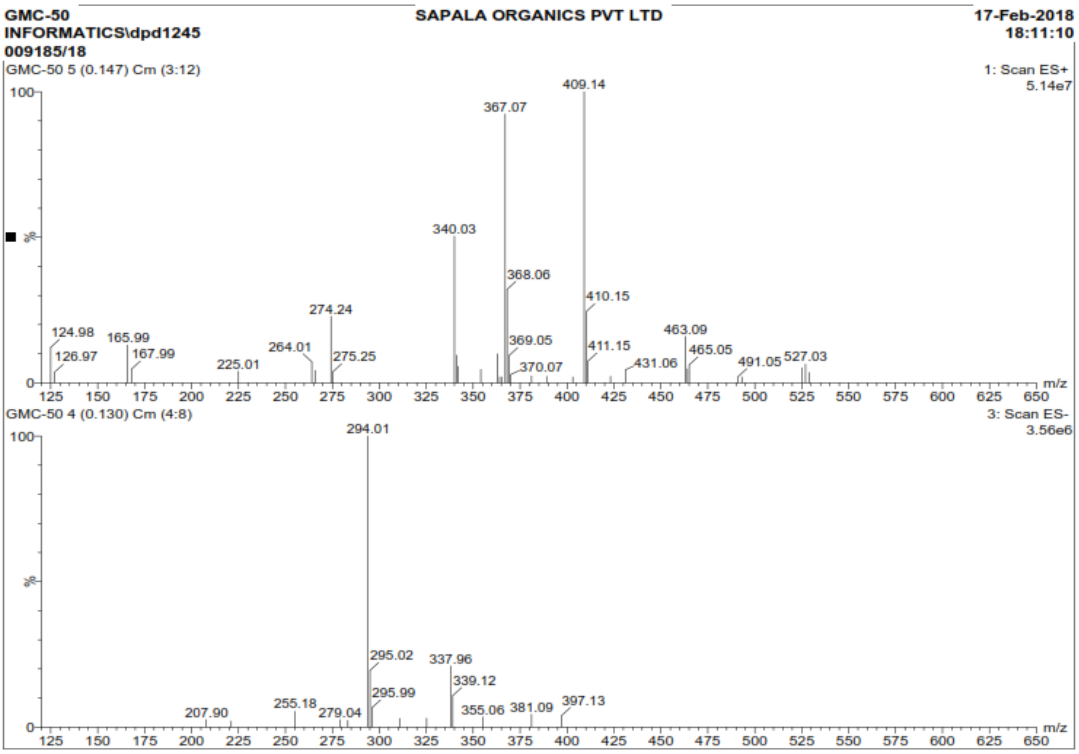
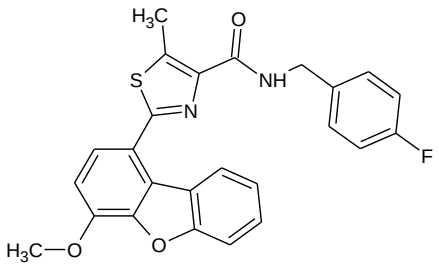
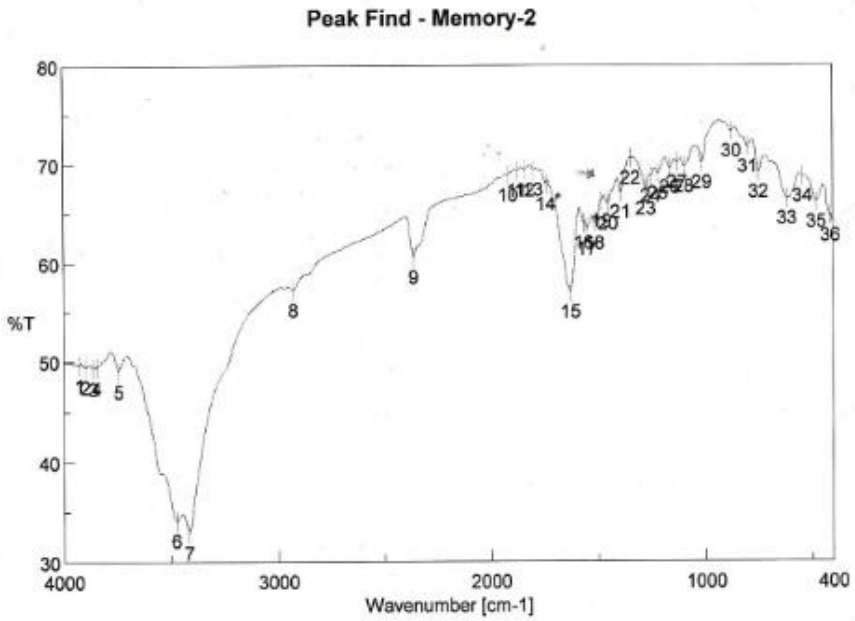


Table:6. Physical data of compound – 4d



Compound	4d
IUPAC NAME	*2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-(4-fluorobenzyl)-1,3-thiazole-4-carboxamide*
Molecular formula	$C_{25}H_{19}FN_2O_3S$
Molecular weight	446
M.P.	194^0C
Yield (%)	59.21
IR (KBr),ν (cm^{-1})	3415 N-H bend (amide), 3473 C=C-H. (Ar carbon), 1740 C=O stretch (carbonyl amide), 1627 – 1450 C=C stretch (Ar ring),1098 (C-F stretch), 1014 C-N stretch (amine), 799 (Para substitution).
HRMS (m/z):	447 (M^{+1})

Figure:15 Infrared spectra of compound – 4d



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[Detailed Information]		[Measurement Information]	
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		Serial Number	C251661016
Data array type	Linear data array		
Horizontal axis	Wavenumber [cm-1]	Measurement Date	19-Feb-18 12:54 PM
Vertical axis	%T		
Start	399.193 cm-1	Light Source	Standard
End	4000.6 cm-1	Detector	TGS
Data interval	0.964233 cm-1	Accumulation	16
Data points	3736	Resolution	4 cm-1
		Zero Filling	On
		Apodization	Cosine
		Gain	Auto (2)
		Aperture	Auto (7.1 mm)
		Scanning Speed	Auto (2 mm/sec)
		Filter	Auto (30000 Hz)

[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	3924.43	49.5952	2	3896.47	49.4064

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Figure:16 Mass spectra of compound – 4d

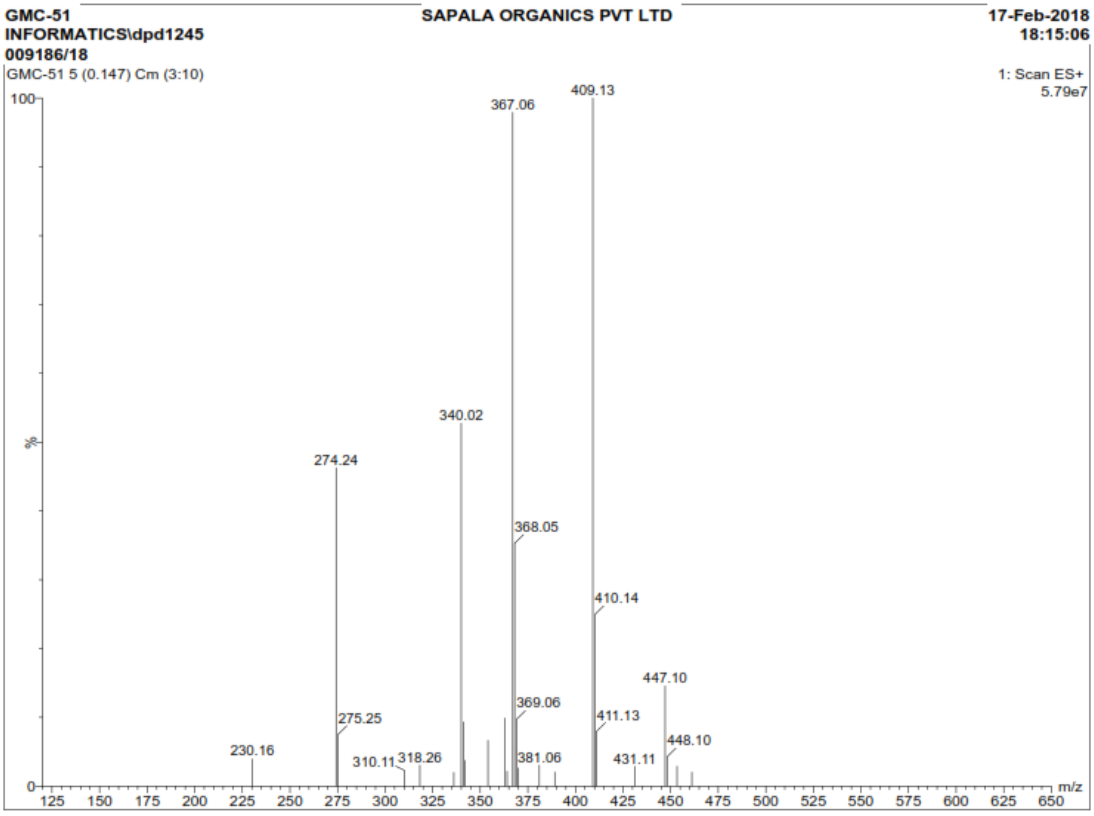
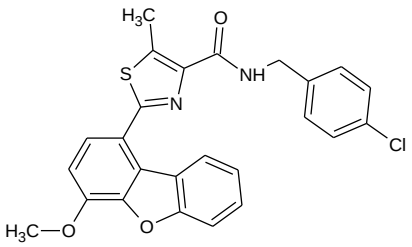
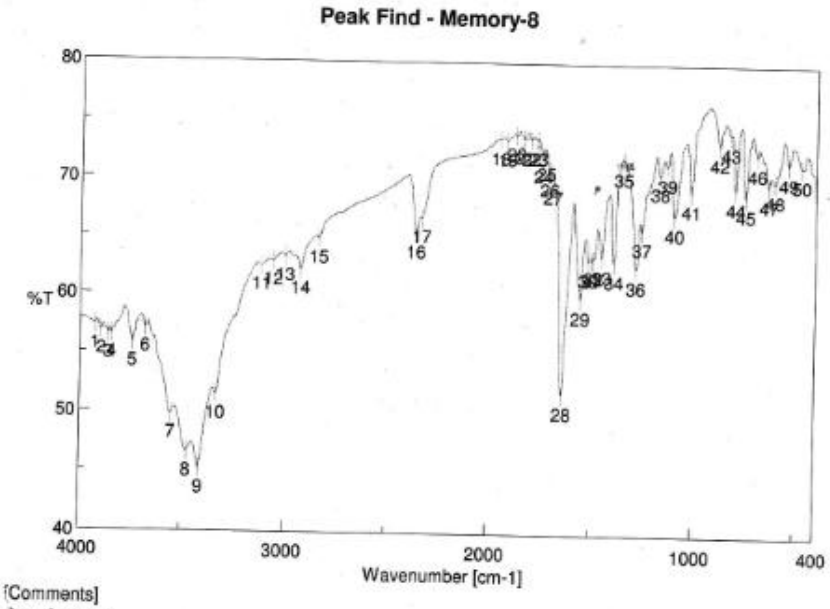


Table:7. Physical data of compound – 4e



Compound	4e
IUPAC NAME	*2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-(4-chlorobenzyl)-1,3-thiazole-4-carboxamide*
Molecular formula	$C_{25}H_{19}$ Cl N_2 O_3 S
Molecular weight	462
M.P.	182^0C
Yield (%)	54.04
IR (KBr),ν (cm^{-1})	3414 N-H bend (amide), 3474 C=C-H, (Ar carbon), 1740 C=O stretch (carbonyl amide), 1636 – 1448 C=C stretch (Ar-C),1133 (Ar-Cl stretch), 1014 C-N stretch (amine), 799 (Para substitution).
HRMS (m/z):	463(M^{+1})

Figure:17 Infrared spectra of compound – 4e



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[Detailed Information]
Creation date 19-Feb-18 1:16 PM

Data array type Linear data array
Horizontal axis Wavenumber [cm-1]
Vertical axis %T
Start 399.193 cm-1
End 4000.6 cm-1
Data interval 0.964233 cm-1
Data points 3736

[Measurement Information]
Model Name FT/IR-4100typeA
Serial Number C251661016

Measurement Date 19-Feb-18 1:12 PM

Light Source Standard
Detector TGS
Accumulation 16
Resolution 4 cm-1
Zero Filling On
Apodization Cosine
Gain Auto (2)
Aperture Auto (7.1 mm)
Scanning Speed Auto (2 mm/sec)
Filter Auto (30000 Hz)

[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	3924.43	57.2619	2	3895.5	56.8432

Figure:18 Mass spectra of compound – 4e

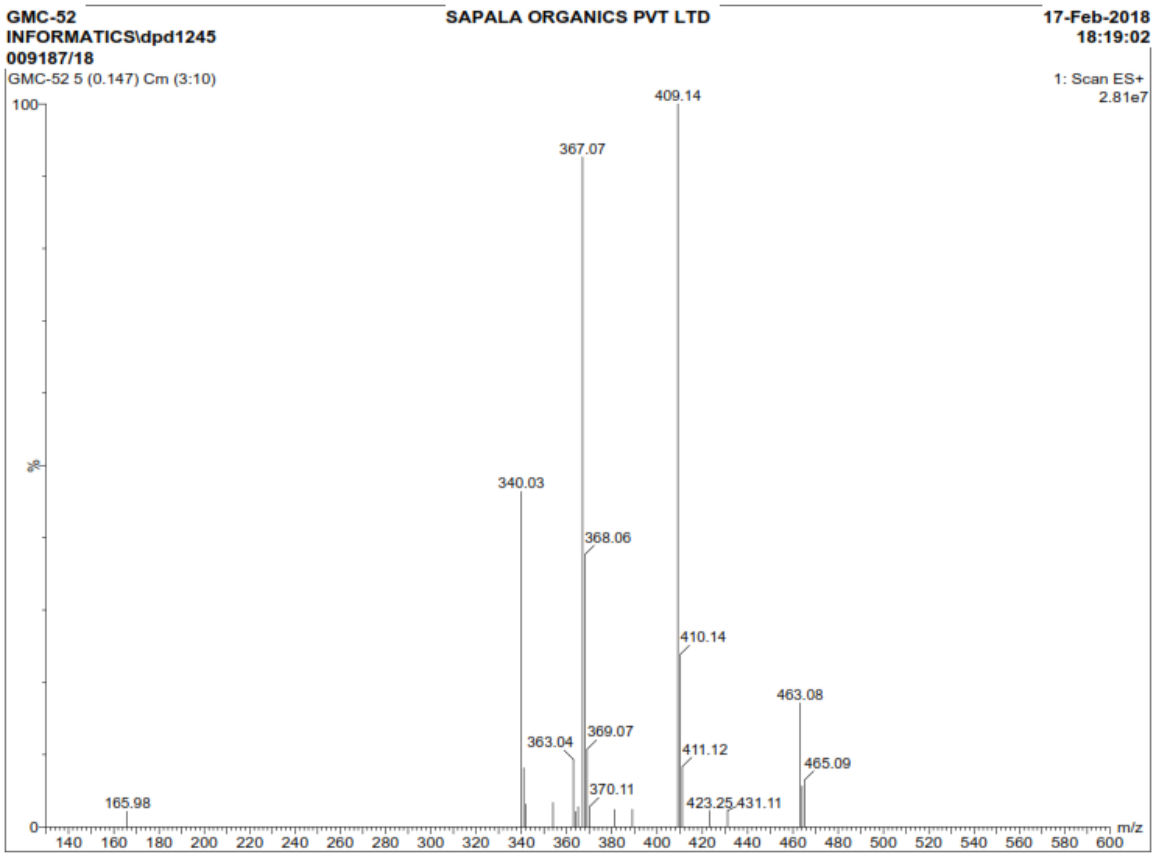
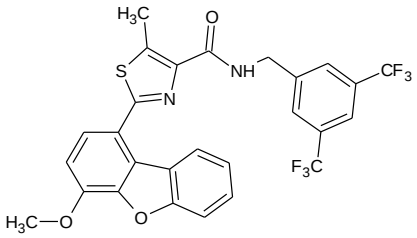
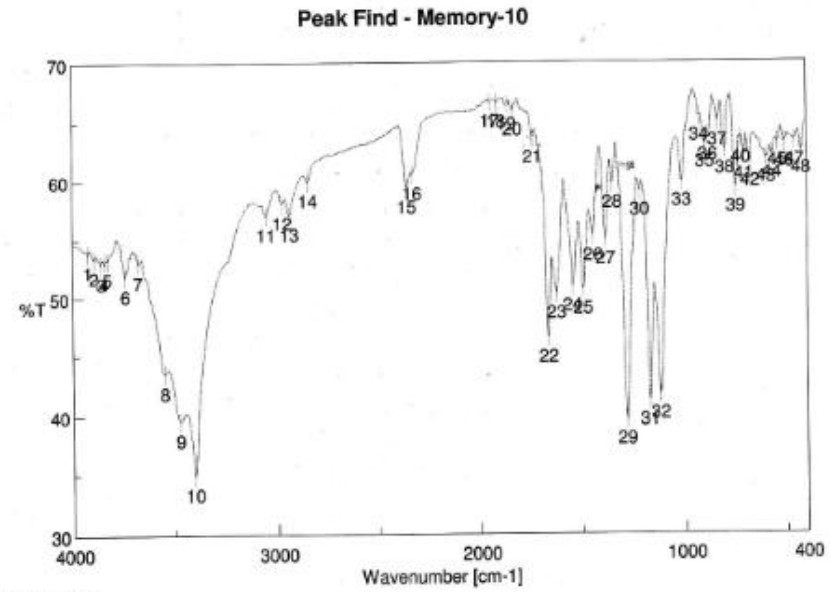


Table:.8 Physical data of compound – 4f



Compound	4f
IUPAC NAME	*2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-[(3,5-bis tri fluoro methyl)benzyl]-1,3-thiazole-4-carboxamide*
Molecular formula	$C_{27}H_{18}F_6N_2O_3S$
Molecular weight	564
M.P.	198^0C
Yield (%)	71.90
IR (KBr),ν (cm^{-1})	3474N-H bend (amide), 3550 C=C-H (Ar carbon), 1740 C=O stretch (carbonyl amide), 1627 – 1448 C=C stretch (Ar ring),1172,1121(CF_3 stretch), 1014 (C-N stretch amine), 802 (Para substitution), 899 (Meta Substitution).
HRMS (m/z):	563 (M^{-1})

Figure:19 Infrared spectra of compound – 4f



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[Detailed Information]	
Creation date	19-Feb-18 1:32 PM
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Horizontal axis	Wavenumber [cm-1]
Vertical axis	%T
Start	399.193 cm-1
End	4000.6 cm-1
Data interval	0.964233 cm-1
Data points	3736

[Measurement Information]	
Model Name	FT/IR-4100typeA
Serial Number	C251661016
Measurement Date	19-Feb-18 1:32 PM
Light Source	Standard
Detector	TGS
Accumulation	16
Resolution	4 cm-1
Zero Filling	On
Apodization	Cosine
Gain	Auto (2)
Aperture	Auto (7.1 mm)
Scanning Speed	Auto (2 mm/sec)
Filter	Auto (30000 Hz)

[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	3924.43	53.8313	2	3895.5	53.3382

Figure:20 Mass spectra of compound – 4f

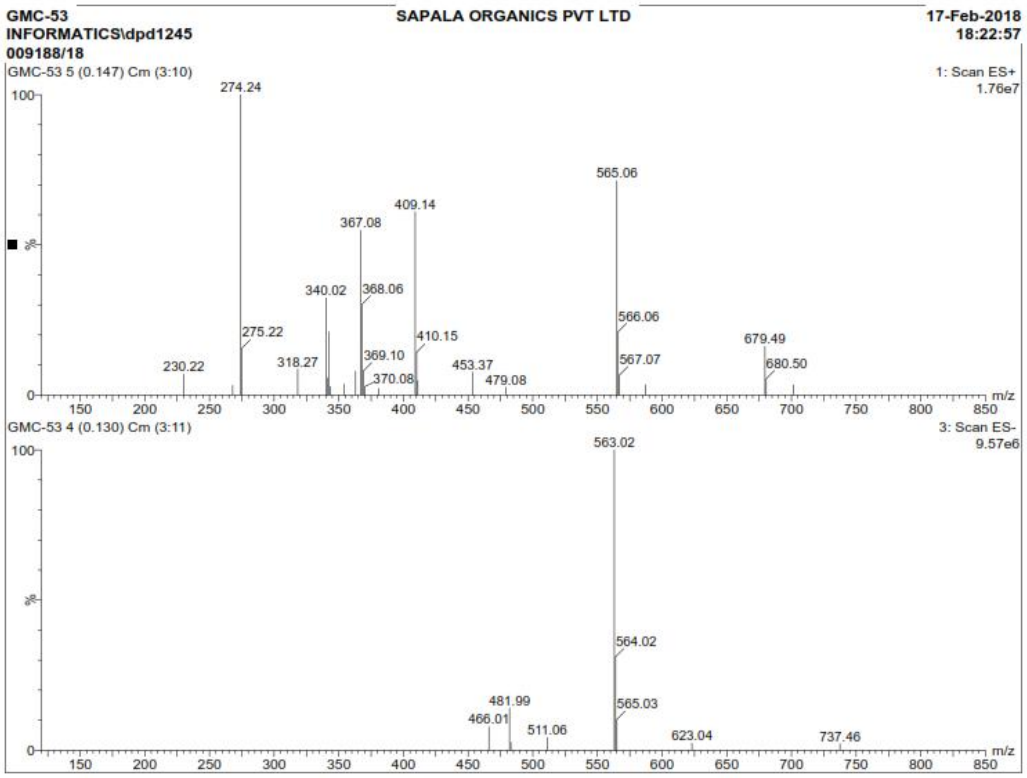
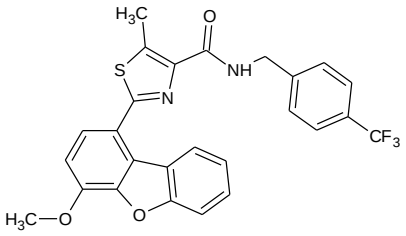
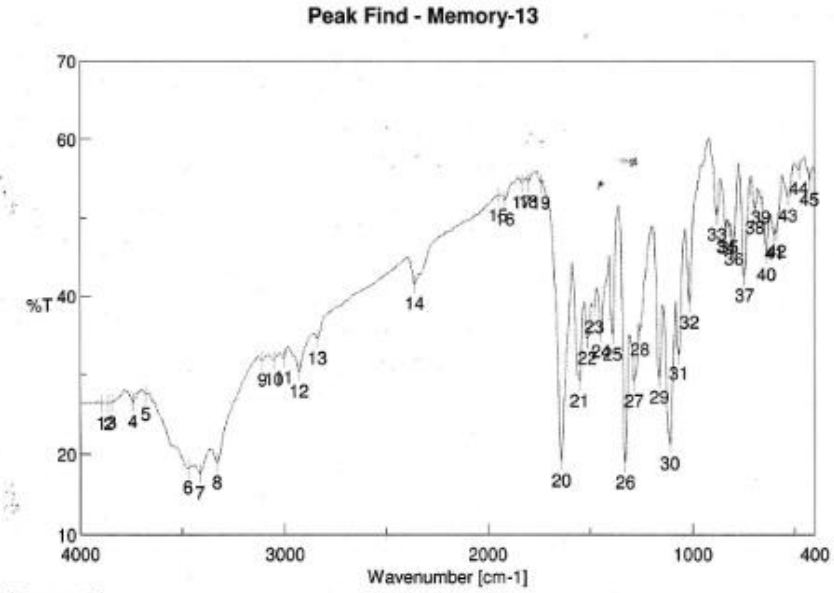


Table:9 Physical data of compound – 4g



Compound	4g
IUPAC NAME	*2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-[(4-tri fluoro methyl)benzyl]-1,3-thiazole-4-carboxamide*
Molecular formula	$C_{26}H_{19}F_3N_2O_3S$
Molecular weight	496
M.P.	184^0C
Yield (%)	72.16
IR (KBr),ν (cm^{-1})	3414 N-H bend (amide), 3472 C=C-H. (Ar carbon), 1740 C=O stretch (carbonyl amide), 1639 – 1446 C=C stretch (Ar ring),1162 (CF_3 stretch), 1016 (C-N stretch (amine), 798 (Para substitution).
HRMS (m/z):	495(M^{-1})

Figure:21 Infrared spectra of compound – 4g



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[Detailed Information]		[Measurement Information]	
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		Serial Number	C251661016
Data array type	Linear data array		
Horizontal axis	Wavenumber [cm-1]	Measurement Date	19-Feb-18 1:47 PM
Vertical axis	%T		
Start	399.193 cm-1	Light Source	Standard
End	4000.6 cm-1	Detector	TGS
Data interval	0.964233 cm-1	Accumulation	16
Data points	3736	Resolution	4 cm-1
		Zero Filling	On
		Apodization	Cosine
		Gain	Auto (4)
		Aperture	Auto (7.1 mm)
		Scanning Speed	Auto (2 mm/sec)
		Filter	Auto (30000 Hz)

[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	3896.47	26.2431	2	3860.79	26.2082

Figure:22 Mass spectra of compound – 4g

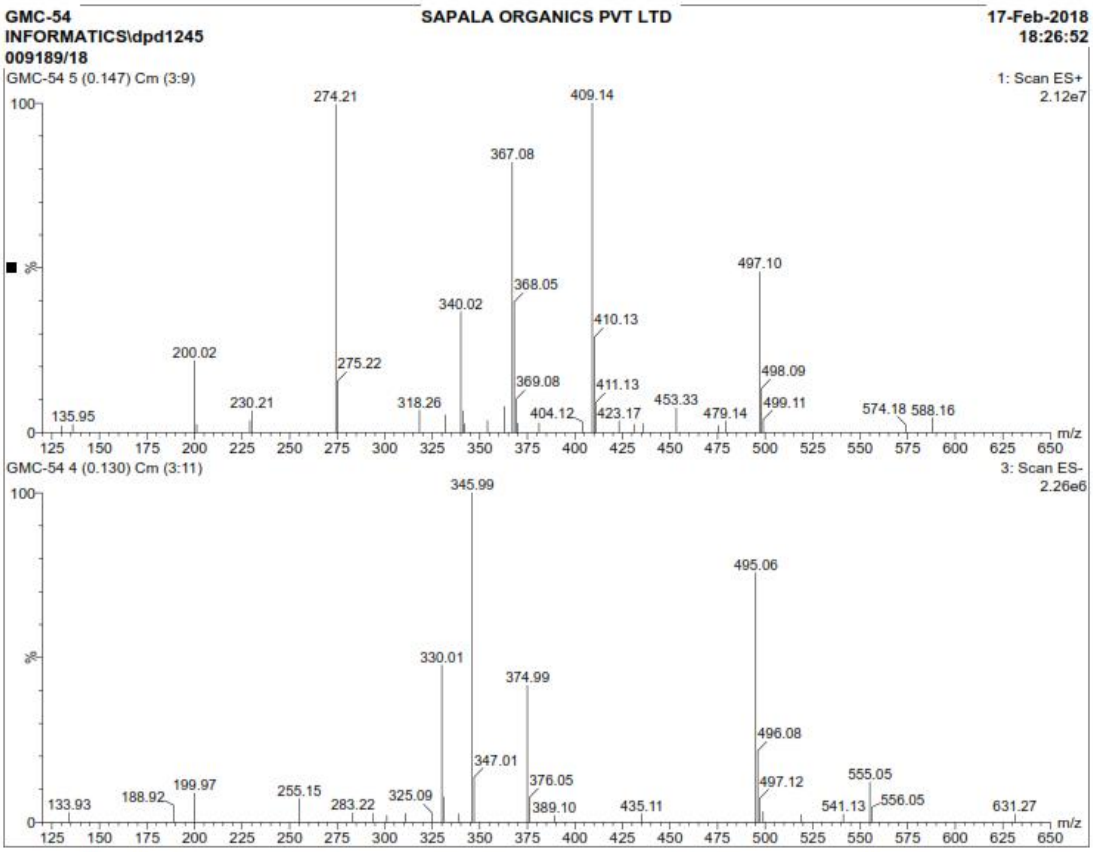
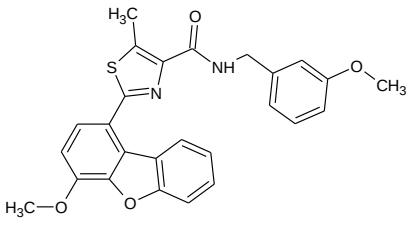
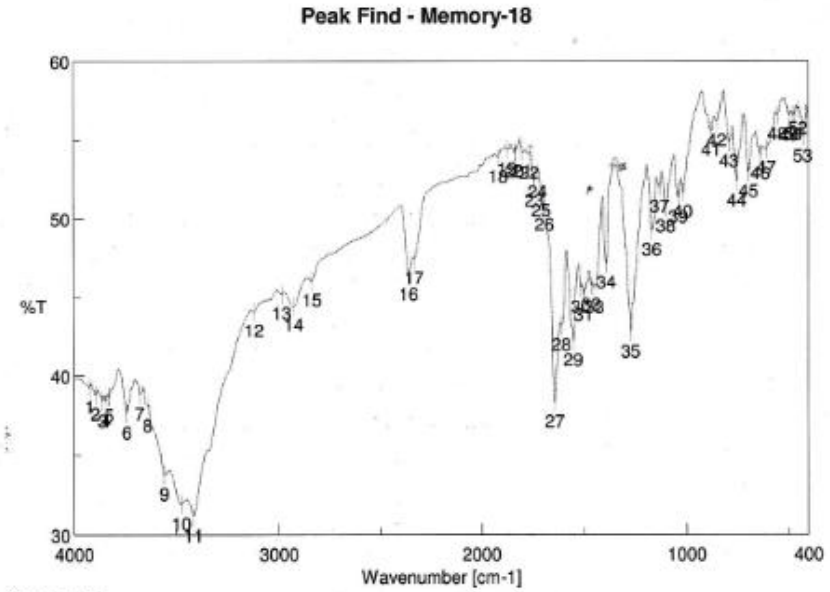


Table:10 Physical data of compound – 4h



Compound	4h
IUPAC NAME	*2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-(3-methoxybenzyl)-1,3-thiazole-4-carboxamide*
Molecular formula	$C_{26}H_{22}N_2O_4S$
Molecular weight	458
M.P.	170^0C
Yield (%)	83.24
IR (KBr),ν (cm^{-1})	3415 N-H bend (amide), 3474(C=C-H (Ar carbon), 1740 C=O stretch (carbonyl amide), 1641 – 1448 C=C stretch (Ar ring), 1015 C-N stretch (amine), 877 (Meta substitution).
HRMS (m/z):	459(M^{+1})

Figure:23 Infrared spectra of compound – 4h



[Comments]
Sample name
Comment
User
Division
Company NAWAL ANALYTICAL LBORATORIES

[Detailed Information]		[Measurement Information]	
Creation date	19-Feb-18 2:03 PM	Model Name	FT/IR-4100typeA
		Serial Number	C251661016
Data array type	Linear data array		
Horizontal axis	Wavenumber [cm-1]	Measurement Date	19-Feb-18 2:02 PM
Vertical axis	%T		
Start	399.193 cm-1	Light Source	Standard
End	4000.6 cm-1	Detector	TGS
Data interval	0.964233 cm-1	Accumulation	16
Data points	3736	Resolution	4 cm-1
		Zero Filling	On
		Apodization	Cosine
		Gain	Auto (2)
		Aperture	Auto (7.1 mm)
		Scanning Speed	Auto (2 mm/sec)
		Filter	Auto (30000 Hz)

[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	3923.47	39.2118	2	3895.5	38.7592

Figure:24 Mass spectra of compound – 4h

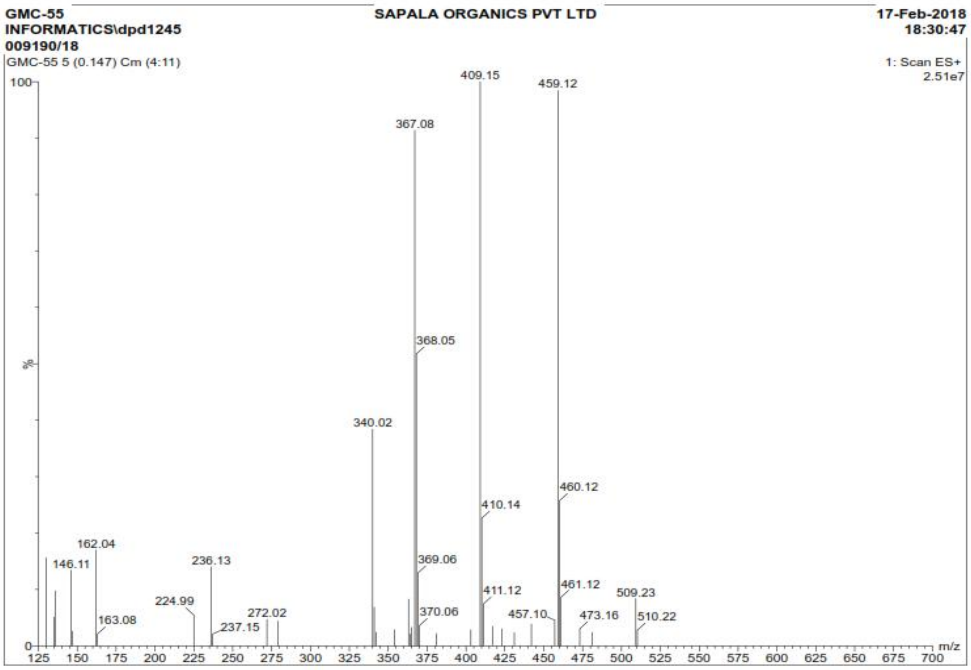
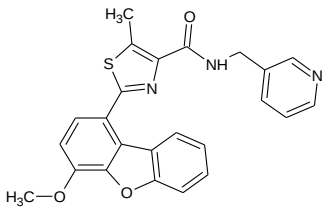
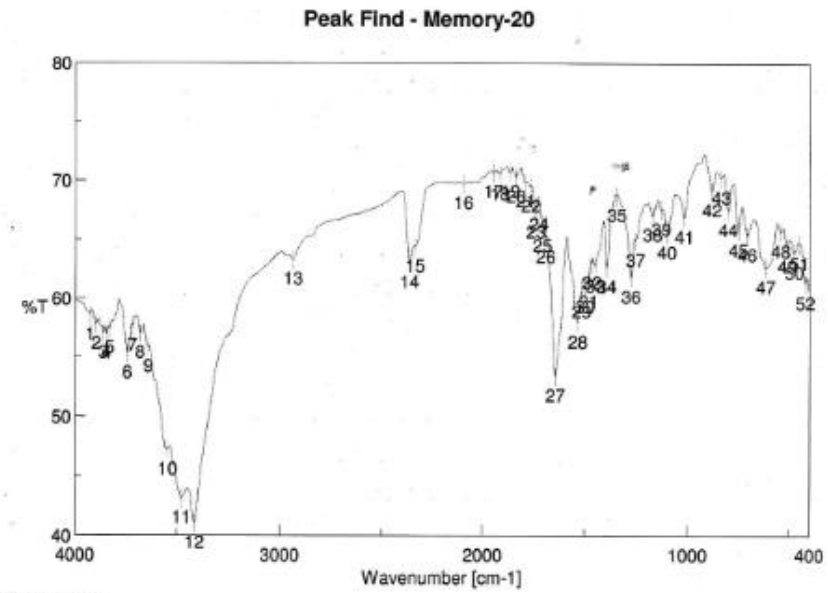


Table:11 Physical data of compound – 4i



Compound	4i
IUPAC NAME	*2-(4-methoxydibenzo[b,d]furan-1-yl)-5-methyl-N-(pyridine-3-yl)-1,3-thiazole-4-carboxamide*
Molecular formula	$C_{24}H_{19}N_3O_3S$
Molecular weight	429
M.P.	226^0C
Yield (%)	87.83
IR (KBr),ν (cm^{-1})	3414N-H bend (amide), 3477 C=C-H. (Ar carbon), 1740 C=O stretch (carbonyl amide), 1643 – 1449 C=C stretch (Ar ring),1016 C-N stretch (amine).
^{1}H-NMR δ (ppm)	^{1}H-NMR (500 MHz, $CDCl_3$) ppm: 2.84 (s, 3H, CH_3); 4.06 (s, 3H, OCH_3); 4.51 - 4.52 (d, 2H, CH_2); 7.20 -7.23 (t, 1H, Ar-H); 7.30 (d, 1H, Ar-H); 7.42 – 7.43 (m, 1H, Ar-H); 7.57 – 7.58 (t, 1H, Ar-H); 7.64 - 7.65 (d, 1H, Ar-H); 7.76 - 7.77 (d, 1H, Ar-H); 7.80 - 7.82 (d, 1H, Ar-H); 8.47 - 8.51 (d, 2H, Ar-H); 8.64 (s, 1H, Ar-H), 8.93 - 8.96 (t, 1H, N-H).
HRMS (m/z):	430(M^{+1})

Figure:25 Infrared spectra of compound – 4i



[Comments]
Sample name
Comment
User
Division
Company NAWAL ANALYTICAL LBORATORIES

[Detailed Information]		[Measurement Information]	
Creation date	19-Feb-18 2:15 PM	Model Name	FT/IR-4100typeA
		Serial Number	C251661016
Data array type	Linear data array		
Horizontal axis	Wavenumber [cm-1]	Measurement Date	19-Feb-18 2:14 PM
Vertical axis	%T		
Start	399.193 cm-1	Light Source	Standard
End	4000.6 cm-1	Detector	TGS
Data interval	0.964233 cm-1	Accumulation	16
Data points	3736	Resolution	4 cm-1
		Zero Filling	On
		Apodization	Cosine
		Gain	Auto (2)
		Aperture	Auto (7.1 mm)
		Scanning Speed	Auto (2 mm/sec)
		Filter	Auto (30000 Hz)

[Result of Peak Picking]

No.	Position	Intensity	No.	Position	Intensity
1	3924.43	58.5303	2	3895.5	57.7318

Figure:26 NMR spectra of compound – 4i

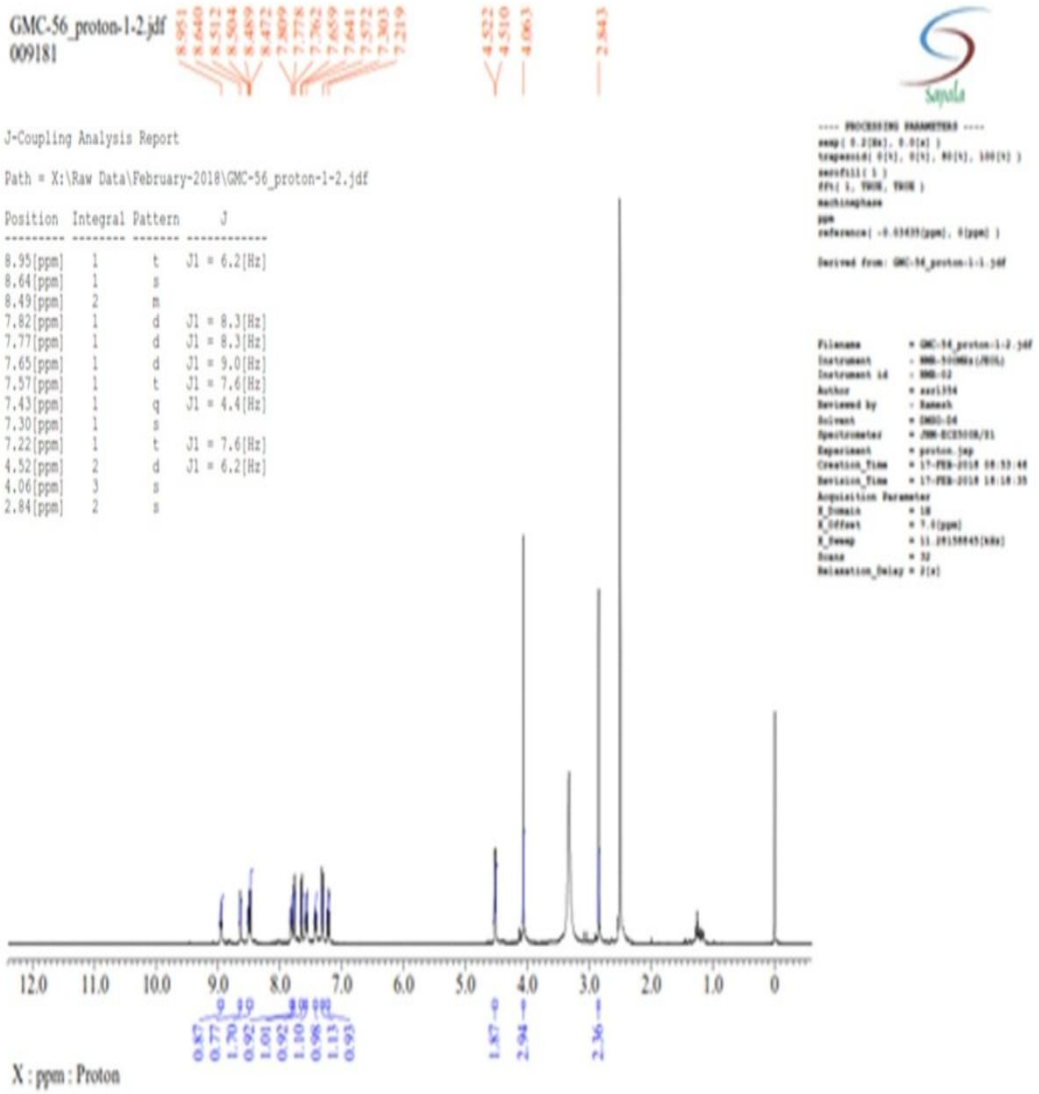
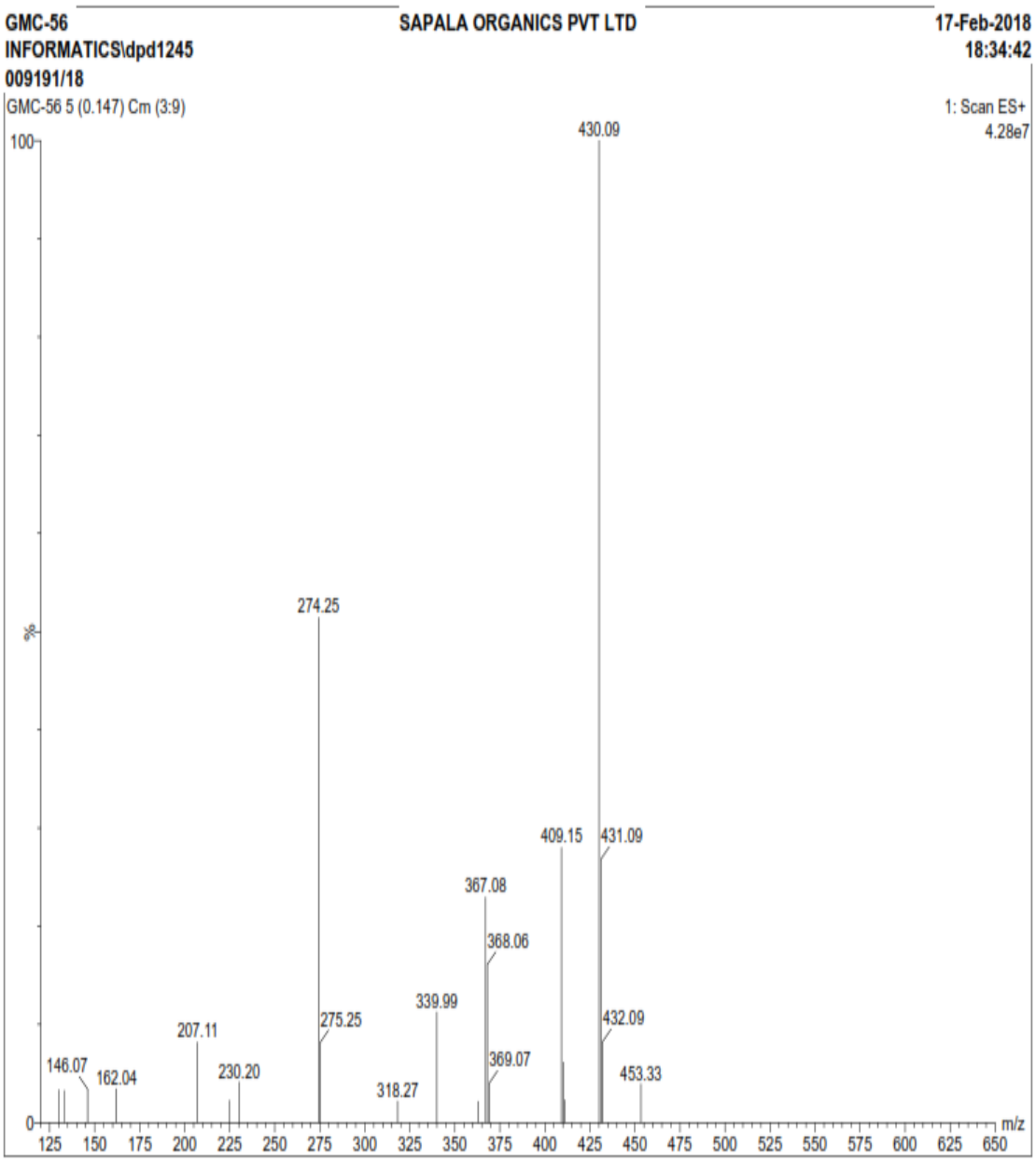


Figure:27 Mass spectra of compound – 4i



Evaluation of in vitro anti-inflammatory activity

Introduction

Inflammation is a bodily response to injury, infection or destruction characterized by heat, redness, pain, swelling and disturbed physiological functions. Inflammation is a normal protective response to tissue injury caused by physical trauma, noxious chemical or microbial agents. It is triggered by the release of chemical mediators from injured tissues and migrating cells. The present study was focused to evaluate the possible in vitro anti-inflammatory effect of synthesized compounds against the denaturation of protein.(Heendeniya SN *et al* 2018).

Anti-denaturation assay method

The denaturation of protein as one of the causes as inflammation is well documented. Production of auto-antigen in certain rheumatic diseases may be due to in vivo denaturation of proteins. A number of anti inflammatory drugs are known to inhibit the denaturation of protein. Based on that we have employed protein denaturation as in vitro screening model for anti-inflammatory compounds.(Sangita C *et al* 2012).

Procedure

The experiment was carried out with minor modification. The standard drug and extract was dissolved in minimum quantity of Dimethyl Formamide (DMF) and diluted with phosphate buffer (0.2 M, PH 7.4). Final concentration of DMF in all solution was less than 2.5%. Test Solution (4ml) containing different concentrations of drug was mixed with 1 ml of 1mM albumin solution in phosphate buffer and incubated at 37°C in incubator for 15 min. Denaturation was induced by keeping the reaction mixture at 70°C in water bath for 15 min. After cooling, the turbidity was measured at 660 nm. Percentage of Inhibition of denaturation was calculated from control where no drug was added. The diclofenac sodium was used as standard drug. The percentage inhibition of denaturation was calculated by using following formula.(Banerjee M *et al* 2011)

$$\text{Percentage of inhibition} = \frac{(A_{Test} - A_{Control})}{(A_{Test})} \times 100$$

At = O.D. of test solution

Ac = O.D. of control

Table :12 Anti inflammatory activity of Compounds (4 - 4i)

Compound code	**Concentrations in µg/ml**					
	100	**200**	**300**	**400**	**500**	**1000**
4	4.06	21.85	43.26	49.57	63.91	80.30
4a	7.08	8.52	26.70	29.76	35.16	51.63
4b	9.92	29.34	44.07	46.11	58.59	71.77
4c	26.70	44.60	61.68	66.85	72.99	80.36
4d	35.86	54.96	70.71	76.30	79.37	89.06
4e	27.16	30.99	47.08	51.83	52.61	67.03
4f	27.60	28.91	46.11	47.08	48.91	65.49
4g	38.54	44.60	62.30	64.98	66.85	79.96
4h	32.57	41.87	52.03	63.00	67.58	78.38
4i	5.60	7.08	9.92	14.49	29.76	59.16
Diclofinac sodium	25.31	51.44	64.77	72.49	77.22	84.94

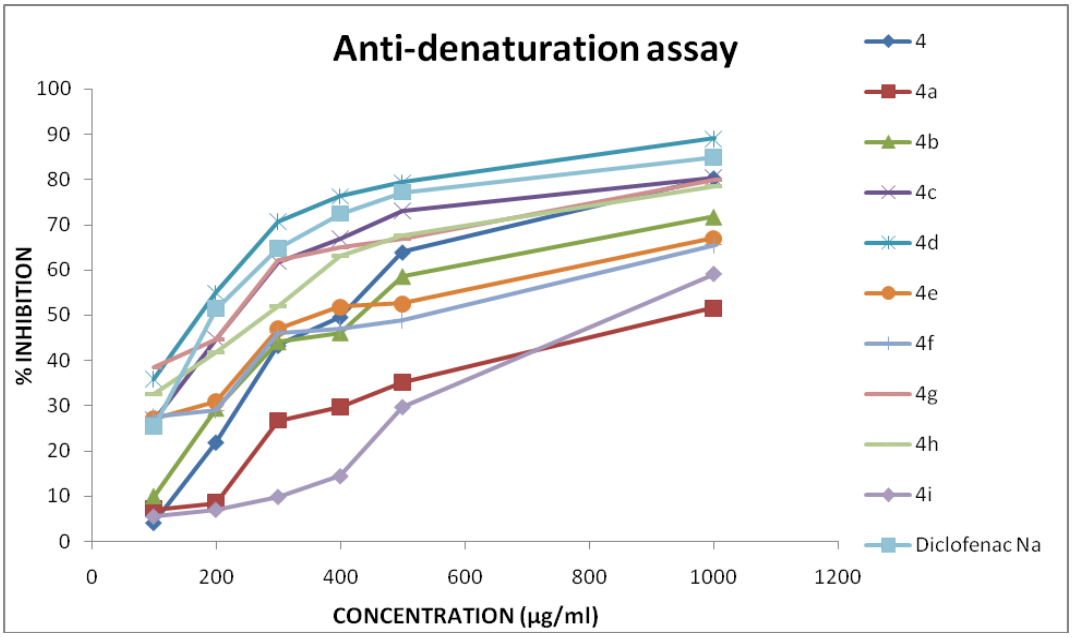
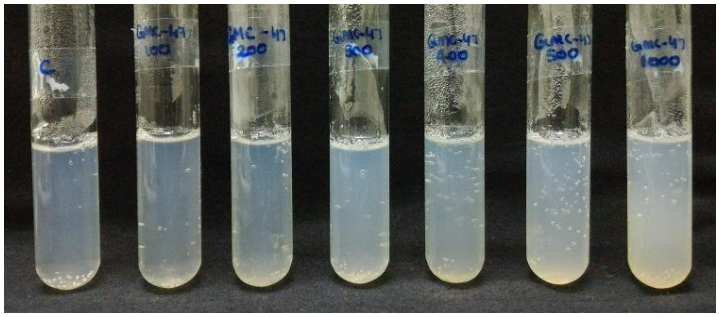


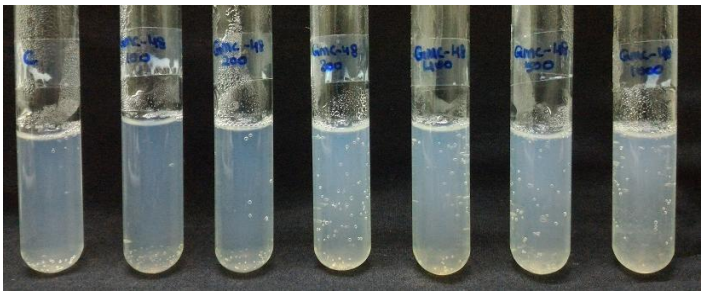
Fig:28

Photocopies representing anti inflammatory activity screening

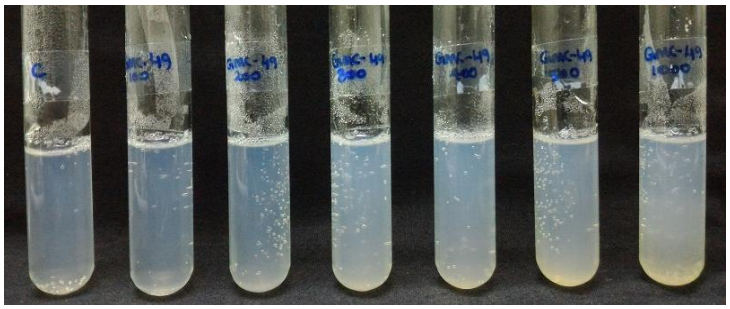
Synthesised of compound 4 (Fig.29)



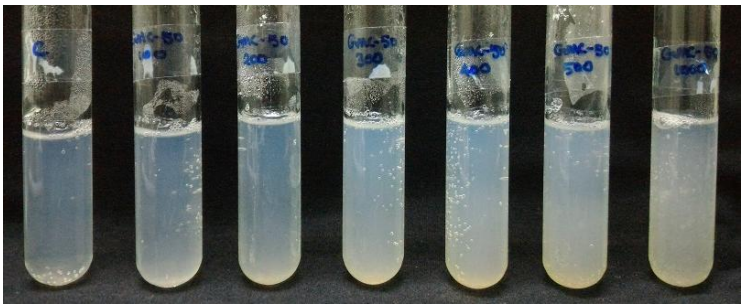
Synthesised of compound 4a (Fig.30)



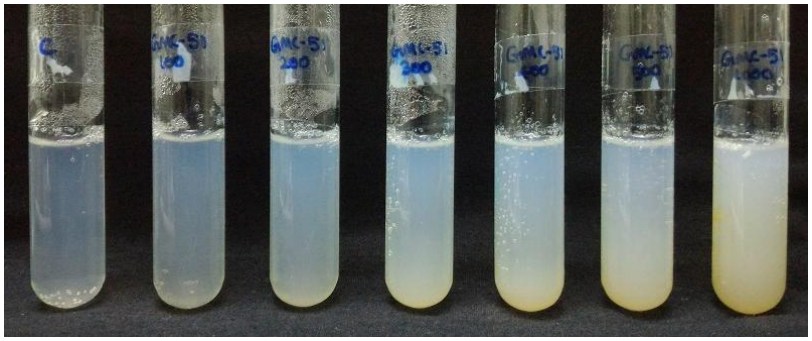
Synthesised of compound 4b (Fig.31)



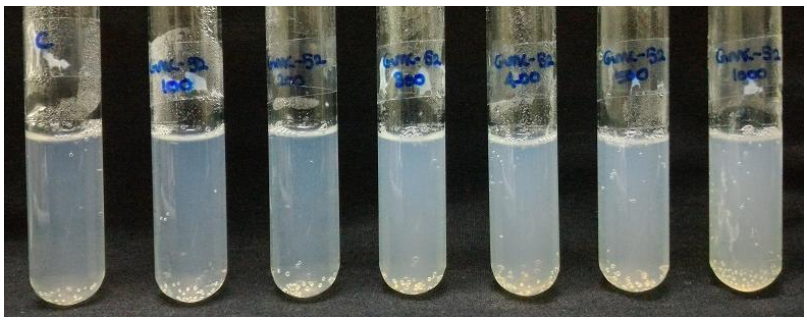
Synthesised of compound 4c (Fig.32)



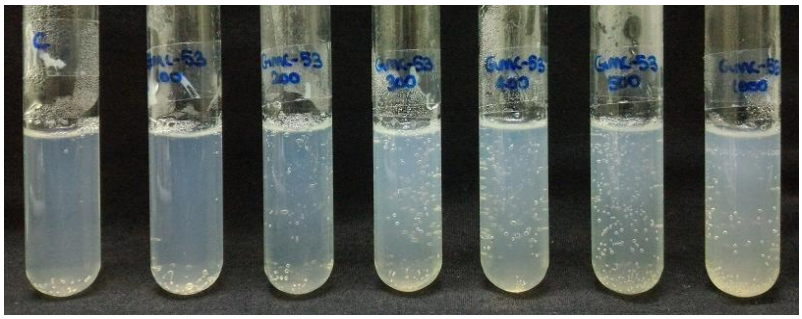
Synthesised of compound 4d (Fig.33)



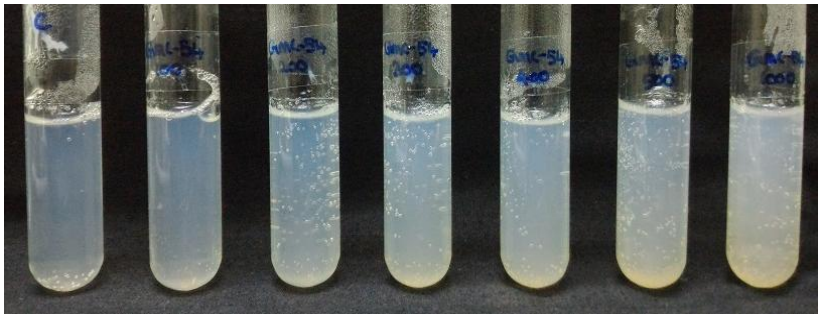
Synthesised of compound 4e (Fig.34)



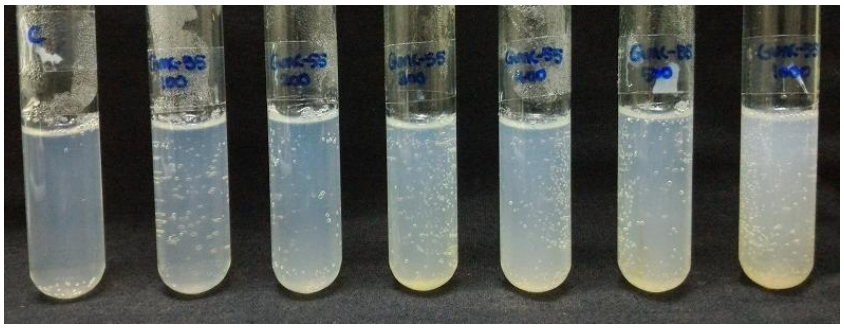
Synthesised of compound 4f (Fig.35)



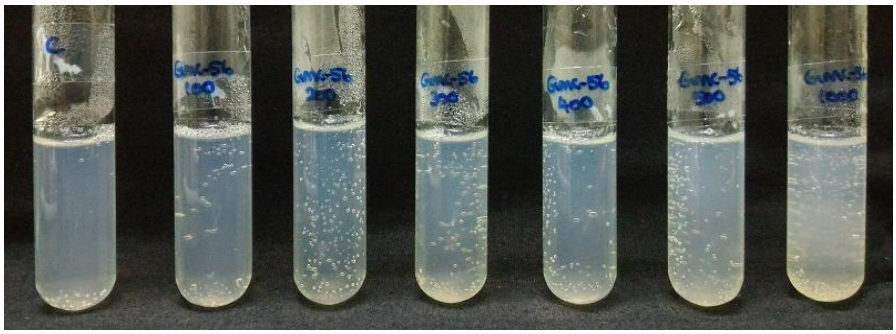
Synthesised of Compound 4g (Fig.36)



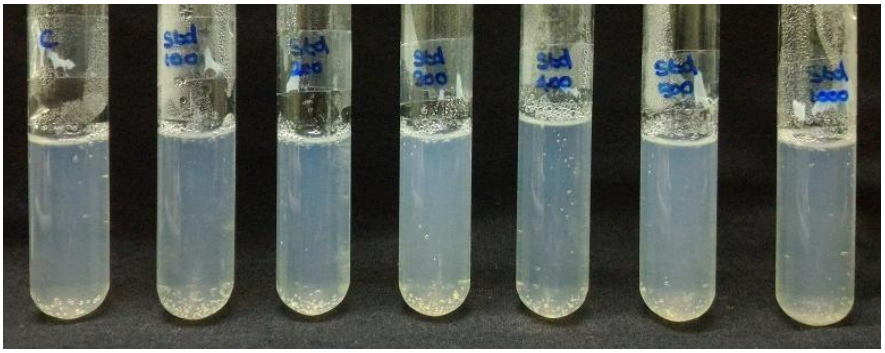
Synthesised of Compound 4h (Fig.37)



Synthesised of Compound 4i (Fig.38)



Std Diclofenac Sodium (Fig.39)



RESULTS AND DISCUSSION

The dibenzofuran carboxamide, a well known derivative. It has been synthetically prepared in four step procedure. In the first step methoxydibenzofuran was converted in to methoxydibenzofuran carbothiamide and in second methoxydibenzofuran carrboxylate. Next in third methoxydibenzofuran carboxylic acid and finally in to a methoxydibenzofuran carboxamide as a parent compound. The introduction of aryl amine groups in to the aforesaid parent molecule was done by coupling reaction.

The purity of all the synthesized derivatives was confirmed by melting point, thin layer chromatography and FTIR spectroscopy mainly. In addition to that ^{1}H NMR, Mass spectra studies were also done with most of the compounds. The yields of all the synthesized compounds were between 54-87%. All the derivatives were non-hygroscopic.

Different spectral data of the derivatives were taken in to the consideration. Thus the IR absorbtion band at 3413 to 3474cm^{-1} and 1740 to 1741 cm^{-1} showed the presence of N-H bend (amide) and C=O stretch (carbonyl amide) group respectively also 1098 to 1133cm^{-1} are indicate Ar – Cl stretch, 3473 to 3550 cm^{-1} are C=C-H of aromatic compound, 1636 -1446 cm^{-1} for C=C stretch of aromatic ring. Benzen substitution pattern confirmed for ortho (741-753 cm^{-1}) meta (899 cm^{-1}) and para (754 - 799 cm^{-1}) positions too. The ^{1}H NMR spectra of the selected derivatives showed the expected integration and peak multipilicites. In all the derivatives a typical singlet at δ 8.34 -8.96 was observed that was assigned to the N-H protons. The aromatic protons were present in the region of δ 6.87-8.69 respectively and the methyl, methoxy substitution of each compound were at δ 2.84 -2.97, δ 3.80 - 4.11 region in the decreasing order. The Mass spectra of all the derivatives were recorded and the suggested formulae were confirmed by the respective molecular ion peaks.

Anti-inflammatory activity of the synthesized compounds were studied by protein denaturation assay method and the results of such studies leading ultimately to their percentage inhibition values have been reported in tables and graphs.

All the synthesized compounds were capable of moderate inhibition effect. Among these compounds 4c, 4d, 4e, 4f, 4g and 4h showed promising activity when compared to STD drug diclofenac sodium at low concentration (100 µg/ml) and the percentage of inhibition are found to be 35.86, 26.70, 27.16, 27.60, 38.54 and 32.57 µg/ml respectively. Where STD drug diclofenac sodium was 25.31 µg/ml. particularly the compound 4d shows very good inhibiting property at all concentrations when compared to the standard drug.

SUMMARY AND CONCLUSION

The present work entitled “studies on synthesis, characterization and biological activity methoxydibenzofuran-1,3-thiazole carboxamide derivatives”, has described the synthesis of ten compounds. It is well established that the presence of dibenzofuranthiazole in molecules has resulted in pharmacologically and biologically active agents these are having a varied type of heterocyclic or otherwise, straight chain structures. Many of the existing drugs, for example, Tetomilast, oglemilast and ciliomilast are potent anti-inflammatory agents, they do have serious side effects. These include nausea, emesis and gastric acid secretion. Many other standard drugs of today also, have other types of unwanted effects one important being drug resistance. Thus, newer agents with out such undesirable side effects and better potency are the need of the day. This work, thus, was undertaken to study a few new compounds.

Based on the literature survey tetomilast a PDE inhibitor from otsuka contain thiazole moiety in it and oglemilast contain a new series of dibenzofuran nucleus, also the cilomilast carrying aryl derivatives with the conclusion in mind we forwarded to synthesis dibenzofuran thiazole carboxamide derivatives. All the compounds were prepared in the laboratory and purified by crystallization with suitable solvents. Furthermore, all the structures of the compounds were confirmed by melting point, FTIR, ^{1}H-NMR and High resolution Mass spectroscopy.

The cyclic nucleotide phosphodiesterase are a family of enzyme that selectively catalyse the hydrolysis of cAMP and cGMP. The inhibition of the PDEs in the cell effectively elevates the intracellular cAMP level. This in turn inhibits the release of inflammatory mediators (TNF-α, interleukin-2, interleukin -12) and act as a anti inflammatory drug.(Banerjee M *et al* 2011) In view of that we focused the biological evaluation for all the synthesized compounds. The results of short term in vitro anti-inflammatory screening against protein denaturation method show a moderate inhibitory effect. Among these particularly compounds 4c, 4d, 4e, 4f, 4g and 4h showed promising activity when compared to standard drug diclofenac sodium at lowest concentration of 100 µg/ml and the percentage of inhibition are found to be 26.70, 35.86, 27.16, 27.60,

38.54 and 32.57 µg/ml respectively. Where the standard drug diclofenac sodium was 25.31 µg/ml. Particularly the compound 4d shows a very good inhibiting property at all concentrations (100 -1000µg/ml) when compared to the standard drug. This experiment suggest that the anti-inlammatory activity of dibenzofuranthiazole carboxamide derivatives mainly due to the halogenic derivative with para substitution. The fluro, chloro substitution was one of the key groups to enhance greatly the activity with para and ortho substituent, as well as the methoxy derivatives with meta substituent also shows moderate activity.

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