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SUSTAINABLE CHEMICAL ROUTES TO FIVE- AND SIX-MEMBERED HETEROCYCLES

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ABSTRACT

The present study deals with the synthesis and infrared (IR) identification of various heterocyclic and azo compounds using efficient and eco-friendly methodologies. Benzothiazine derivatives were successfully synthesized using a sonication technique, which significantly reduced reaction time and improved yield compared to conventional methods. The use of ultrasonic irradiation demonstrated advantages such as enhanced reaction efficiency, mild conditions, and reduced solvent consumption.

Azo dyes containing pyrazole moieties were synthesized through diazotization followed by coupling reactions, incorporating biologically active heterocyclic systems into the dye structure. The formation of azo dyes was achieved under controlled temperature and pH conditions, ensuring the stability of diazonium salts and effective coupling with suitable aromatic compounds. Additionally, azo chiral dyes were prepared to introduce optical activity, expanding their potential applications in advanced materials and asymmetric synthesis.

The synthesized compounds were characterized using IR spectroscopy, which confirmed the presence of key functional groups. Characteristic absorption bands corresponding to azo (–N=N–), C=N, aromatic C=C, N–H, and C–S groups validated the successful formation of the target molecules. Overall, the study highlights the importance of green synthesis techniques and spectroscopic analysis in developing novel compounds with potential pharmaceutical and industrial applications.

CHAPTER 1

INTRODUCTION

1.1 The ever-increasing awareness of the need to protect natural resources through the development of environmentally sustainable processes and the optimization of energy consumption has guided the actions of both the private and governmental sectors of society. Economic planning has been strongly impacted by this new paradigm, which has led to increasing demands by society for products produced in a sustainable way and to more stringent governmental regulatory policies. Thus, while in the past profit was often the major concern, in the current economic context more sustainable production processes are preferred.

This has triggered a demand in both industry and academy for the development of new, cleaner technologies. In medicinal chemistry, experience has shown that compounds with biological activity are often based on heterocyclic structures. In particular, azoles, azines and their derivatives have attracted increasing interest as versatile intermediates for the synthesis of biologically active compounds such as potent antitumor, antibacterial, antifungal, antiviral and antioxidizing agents. Azoles and azines are a large class of 5-membered and 6-membered ring heterocyclic compounds containing at least one nitrogen atom and one heteroatom in their structure.

The construction of this type of molecule has received great attention due to the wide spectrum of biological activities that have been attributed to structurally distinct azoles and azines. Fluconazole, itraconazole, voriconazole, Atorvastatin, Cimetidine, Losartan and posaconazole are antifungal agents commercially available that contain a heterocyclic nucleus. Celecoxib is a non-steroidal anti-inflammatory and analgesic agent of the pyrazole class. Isoxazole compounds such as valdecoxib are selective COX 2 inhibitors used in the treatment of pain. Heterocyclic make up an exceedingly important class of compounds more than half of all known organic compounds are heterocycles. Almost all the compounds we know as drugs, vitamins, and many other natural products are heterocycles.

The heterocyclic compounds usually possess a stable ring structure which does not readily hydrolyzed or decomposed. Heterocycles with three atoms in the ring are more reactive because of ring strain. Those containing one heteroatom are in general, stable. Those with two hetero atoms are more likely to occur as reactive intermediates. Heterocyclic chemistry is one of the most interesting, applied branches of organic chemistry and of utmost practical and theoretical importance. As a result, a great deal of research carried out in chemistry is devoted to heterocyclic chemistry. It is vast and expanding area of chemistry because of obvious application of compounds derived from heterocyclic rings in pharmacy, medicine, agriculture, plastic, polymer and other fields. Heterocyclic compounds are widely distributed in nature. By virtue of their therapeutic properties, they could be employed in the treatment of infectious diseases. Many heterocyclic compounds synthesized in laboratories have been successfully used as clinical agents. Heterocycles form by far the largest of classical organic divisions of organic chemistry and are of immense importance biologically and industrially.

The majority of pharmaceuticals and biologically active agrochemicals are heterocycles while countless additives and modifiers used in industrial applications ranging from cosmetics reprography, information storage and plastics are heterocycles in nature. One striking structural feature inherent to heterocycles, which continue to be to great advantage by the drug industry, lies in their ability to manifest substituent around a core scaffold in defined three-dimensional representations. For more than a century, heterocycles have constituted one of the largest areas of research in organic chemistry.

1.2 Introduction of Microwave

Microwave assisted organic synthesis has revolutionized organic synthesis. Small molecules can be built in a fraction of the time required by classical thermal methods. As a result, this technique has rapidly gained acceptance as a valuable tool for accelerating drug discovery and development processes. A microwave is a form of electromagnetic energy, which falls at the lower end of the electromagnetic spectrum and is defined in a measurement of frequency as 300 to 300,000 Megahertz, corresponding to wavelengths of 1 cm to 1 m.

The microwave region of the electromagnetic spectrum lies between infrared and radio frequencies. Wavelengths between 1 cm and 25 cm are extensively used for RADAR transmissions and remaining wavelength range is used for telecommunications. In order to avoid interference with radar and telecommunication activities, which also operate in this region, most commercial and domestic microwave ovens operate at 2450 MHz (12.25cm). The difference between microwave energy and other forms of radiation, such as X- and γ-rays, is that microwave energy is non-ionizing and therefore does not alter the molecular structure of the compounds being heated – it provides only thermal activation. The heating effect utilized in microwave assisted organic transformations is mainly due to dielectric polarization. When a molecule is irradiated with microwaves, it aligns itself with the applied field. The rapidly changing electric field (2.45 x 109 Hz) affects the molecule and consequently the molecule continually attempts to align itself with the changing field and energy is absorbed. The ability of a material to convert electromagnetic energy into thermal energy is dependent on the dielectric constant. The larger the dielectric constant the greater is the coupling with microwaves. Thus, solvents such as water, methanol, DMF, ethyl acetate, acetone, acetic acid, etc. are all heated rapidly when irradiated with microwaves.

However, solvents with low dielectric constants such as hexane, toluene, carbon tetrachloride, etc. do not couple and therefore do not heat that rapidly under microwave irradiation. Microwave heating has thus been found to be a very convenient thermal source not only in the kitchen but also in a chemical laboratory. Chemists have explored the possibility of the application of a conventional microwave oven to carry out chemical reactions. It has been found that many reactions progress much faster upon microwave irradiation than with traditional heating techniques.

The application of microwave irradiation to activate and accelerate organic reactions has taken a new dimension and has experienced exponential growth in the last ten years. Microwave chemistry is becoming increasingly popular both in industry and in academia. We hope to demonstrate in this article the utility of this technique, and the potential that this methodology can give to the bench chemist.

1.3 Microwave Heating

Microwave dielectric heating uses the ability of some liquids and solids to transform electromagnetic radiation into heat to drive chemical reactions. However, the advantages of using microwave dielectric heating for performing organic transformations have only emerged since the mid- 1980s. This technology opens up new opportunities to the synthetic chemist, in the form of new reactions that are not possible using conventional heating. Developments in this field have suggested that microwave-assisted chemistry could be used in most reactions that require heating.

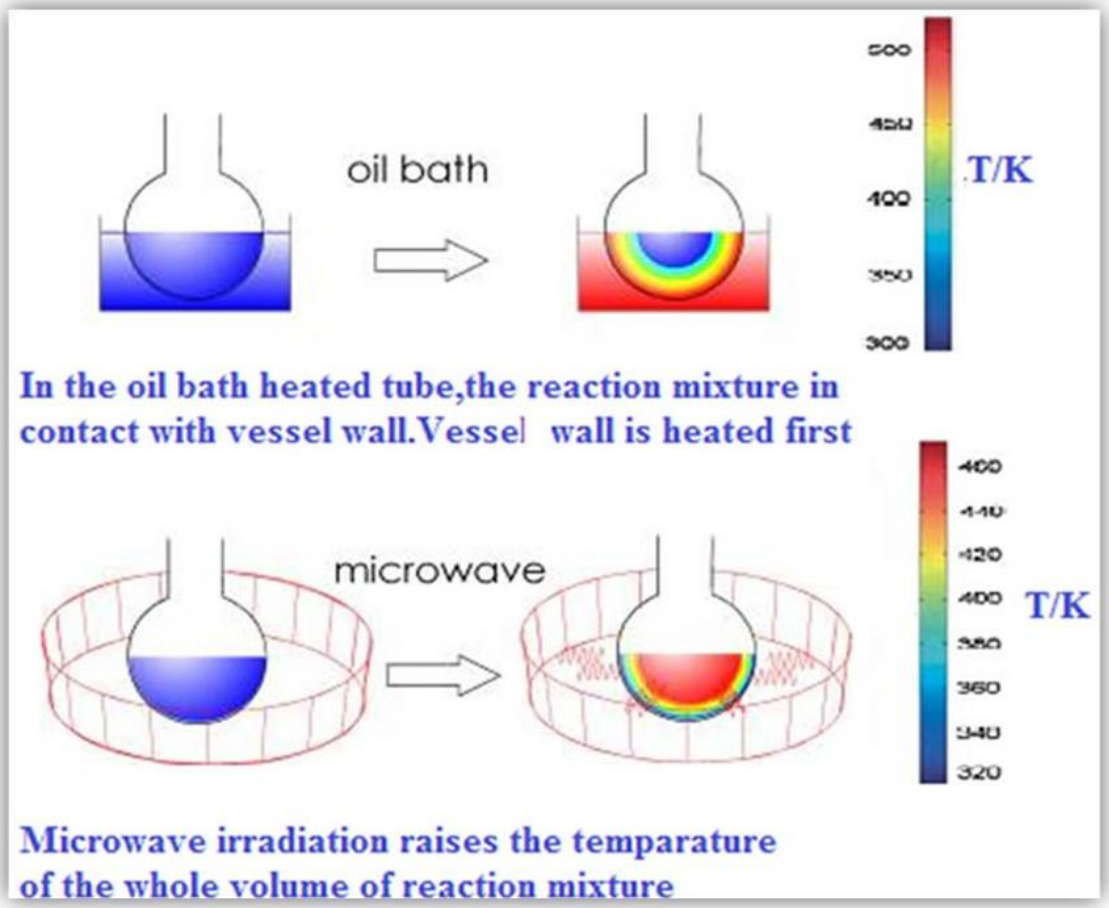

Figure 1.1: Microwave Heating

1.4 Advantages of microwave

In the past, microwave chemistry was often used only when all other options to perform a particular reaction had failed, or when exceedingly long reaction times or high temperatures were required to complete a reaction. This practice is now slowly changing and, due to the growing availability of microwave reactors in many laboratories, routine synthetic transformations are now also being carried out by microwave heating. Microwave include following advantages, over the conventional heating. Uniform heating occurs throughout the material Process speed is increased High efficiency of heating Reduction in unwanted side reaction Purity in final product Improve reproducibility Environmental heat loss can be avoided Reduce wastage of heating reaction vessel Low operating cost.

1.5 Environment friendly Techniques (EFT)

The term ―Environment friendly Techniques‖ is defined as ―the invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances‖. EFT can diminish the need for other approaches to environmental protection. Ideally, the application of green chemistry principles and practice renders regulation, control, clean-up, and remediation unnecessary, and the resultant environmental benefit can be expressed in terms of economic impact.

1.6 Microwave for Synthesis

While fire is now rarely used in synthetic chemistry, it was not until Robert Bunsen invented the burner in 1855 that the energy from this heat source could be applied to a reaction vessel in a focused manner. The Bunsen burner was later superseded by the isomantle, oil bath or hot plate as a source of applying heat to a chemical reaction. In the past few years, heating chemical reactions by microwave energy has been an increasingly popular theme in the scientific community. Since the first published reports on the use of microwave irradiation to carry out organic chemical transformations by the groups of Gedye, more than 5000 articles have been published in this fast moving and exciting field, today generally referred to as microwave-assisted organic synthesis. In the early days of microwave synthesis, experiments were typically carried out in sealed Teflon or glass vessels in a domestic household microwave oven without any temperature or pressure measurements. Kitchen microwave ovens are not designed for the rigors of laboratory usage: acids and solvents corrode the interiors quickly and there are no safety controls. The results were often violent explosions due to the rapid uncontrolled heating of organic solvents under closed vessel conditions. In the 1990s several groups started to experiment with solvent-free microwave chemistry (so-called dry-media reactions), which eliminated the danger of explosions19. Here, the reagents were reabsorbed onto either a more or less microwave transparent inorganic support (i.e., silica, alumina or clay) or a strongly absorbing one (i.e., graphite), that additionally may have been doped with a catalyst or reagent. In many of the published examples, microwave heating has been shown to dramatically reduce reaction times, increase product yields and enhance product purities by reducing unwanted side reactions compared to conventional heating methods.

The advantages of this enabling technology have, more recently, also been exploited in the context of multistep total synthesis, medicinal chemistry/drug discovery and have additionally penetrated related fields such as polymer synthesis, material sciences, nanotechnology and biochemical processes.

The use of microwave irradiation in chemistry has thus become such a popular technique in the scientific community that it might be assumed that, in a few years, most chemists will probably use microwave energy to heat chemical reactions on a laboratory scale. The statement that, in principle, any chemical reaction that requires heat can be performed under microwave conditions has today been generally accepted as a fact by the scientific community. Microwave-assisted heating has been shown to be an invaluable technology in synthesis, since it can often dramatically reduce reaction times, typically from days or hours to minutes or even seconds. It can also provide pure products in quantitative yield and selectivity.

Figure 1.2: Microwave oven for reactions.

1.7 Ultrasound in synthetic organic chemistry

Introduction of Sonication The use of ultrasound in chemistry (sonochemistry) offers the synthetic chemist a method of chemical activation which has broad applications and uses equipment which is relatively inexpensive. The driving force for sonochemistry is cavitation and so a general requirement is that at least one of the phases of the reaction mixture should be a liquid. When laboratory research in sonochemistry began it seemed to be mainly a method of initiating intransigent reactions especially those which depended upon the activation of metallic or solid reagents. Its development in the past 15 years however has revealed that it has far wider applicability than this and also that it presents a significant scientific challenge to understanding its underlying physical phenomenon—acoustic cavitation. The ever-expanding number of applications of sonochemistry in synthesis has made the subject attractive to many experimentalists and interest has spread beyond academic laboratories into industry and chemical engineering. It was in 1986 that the first ever International Symposium on Sonochemistry was held at Warwick University UK as part of the Autumn Meeting of the Royal Society of Chemistry. This meeting was significant in that it was the beginning of serious interest in the uses of ultrasound in chemistry as a study in itself. Of course, sonochemistry dates back much further than this. Its origins can be traced to the early part of this century with the discoveries of echo sounding and the mechanical use of power ultrasound for emulsification. The formation of the Royal Society of Chemistry Sonochemistry Group in 1987 followed by a European Society in 1990 and then other national groups has meant that the subject has expanded greatly over the last few years. There are a range of applications for the uses of ultrasound in chemistry which include synthesis, environmental protection (the destruction of both biological and chemical contaminants) and process engineering (improved extraction, crystallization, electroplating and new methods in polymer technology).

1.8 Fundamental aspects of Sonication

Ultrasound is defined as sound of a frequency beyond that to which the human ear can respond. The normal range of hearing is between 16 Hz and about 18 kHz and ultrasound is generally considered to lie between 20 kHz to beyond 100 MHz. Sonochemistry generally uses frequencies between 20 and 40 kHz because this is the range employed in common laboratory equipment. However, since acoustic cavitations can be generated well above these frequencies, recent researches into sonochemistry use a much broader range. High frequency ultrasound from around 5 MHz and above does not produce cavitation and this is the frequency range used in medical imaging. Like all sound energy, ultrasound is propagated via a series of compression and rarefaction waves induced in the molecules of the medium through which it passes. At sufficiently high power the rarefaction cycle may exceed the attractive forces of the molecules of the liquid and cavitations bubbles will form. These bubbles will grow over a few cycles taking in some vapor or gas from the medium (rectified diffusion) to an equilibrium size which matches the frequency of bubble resonance to that of the sound frequency applied. The acoustic field experienced by the bubble is not stable because of the interference of other bubbles forming and resonating around it. As a result, some bubbles suffer sudden expansion to an unstable size and collapse violently. It is the fate of these cavities when they collapse which generates the energy for chemical and mechanical effects. There are several theories which have been advanced to explain the energy release involved with cavitation of which the most understandable in a qualitative sense is the _hot spot approach. Each cavitation bubble acts as a localized microreactor which, in aqueous systems, generates temperatures of several thousand degrees and pressures in excess of one thousand atmospheres. In addition to the generation of extreme conditions within the bubble there are also major mechanical effects produced as a result of its rapid collapse. These are also of significance in synthesis and include very rapid degassing of the cavitating liquid (in the rarefaction cycle the newly formed bubbles will fill with gas and be expelled from the liquid) and rapid crystallization.

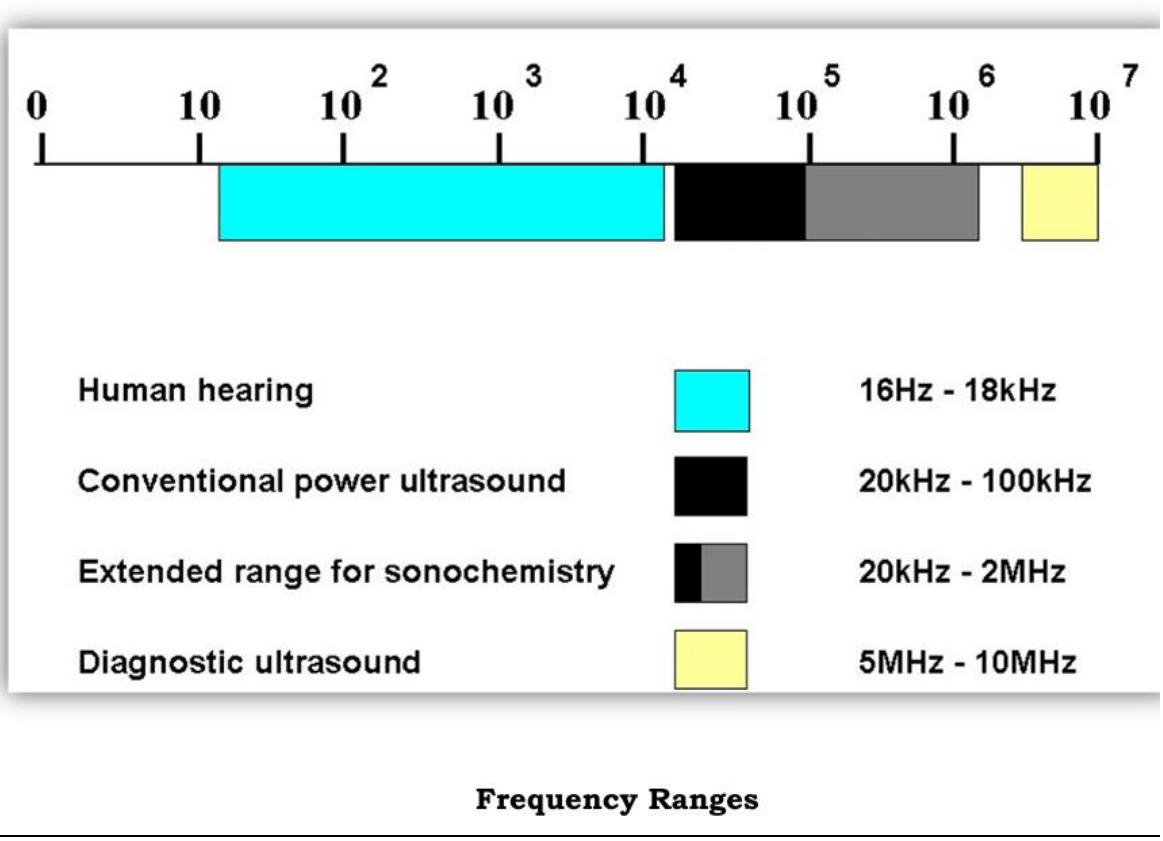

Figure 1.3: Frequency ranges of Sonication.

1.9 Laboratory equipment for sonication

The first requirement for sonochemistry is a source of ultrasound and whatever type of commercial instrument is used the energy will be generated via an ultrasonic transducer—a device by which mechanical or electrical energy can be converted to sound energy. There are three main types of ultrasonic transducer used in sonochemistry: liquid-driven (effectively liquid whistles), magneto strictive (based on the reduction in size of certain metals, e.g. nickel, when placed in a magnetic field) and piezoelectric. Most of the current equipment used for sonochemistry utilises transducers constructed of piezoelectric ceramics. These are brittle and so it is normal practise to clamp them between metal blocks for protection. The overall structure is known as a piezoelectric _sandwich '. Usually, two ceramic elements are combined so that their overall mechanical motion is additive. Piezoelectric transducers are very efficient and, depending on their dimensions, can be made to operate over the whole ultrasonic range. The two most common sources of ultrasound for laboratory sonochemistry are the ultrasonic cleaning bath and the ultrasonic horn or probe system. These generally operate at frequencies of around 40 and 20 kHz, respectively.

1.10 Ultrasonic cleaning bath

The simple ultrasonic cleaning bath is by far the most widely available and cheapest source of ultrasonic irradiation for the chemical laboratory. Although it is possible to use the bath itself as a reaction vessel this is seldom done because of problems associated with corrosion of the bath walls and containment of any evolved vapors and gases. The normal usage therefore involves the immersion of standard glass reaction vessels into the bath which provides a fairly even distribution of energy into the reaction medium. The reaction vessel does not need any special adaptation, it can be placed into the bath, thus an inert atmosphere or pressure can be

readily maintained throughout a sonochemical reaction. The amount of energy which reaches the reaction through the vessel walls is low. Temperature control in commercial cleaning baths is generally poor and so the system may require additional thermostatic control.

Ultrasonic cleaning bath

Figure 1.4: Ultrasonic Cleaning Bath

1.11 Ultrasonic probe

This apparatus allows acoustic energy to be introduced directly into the system rather than rely on its transfer through the water of a tank and the reaction vessel walls. The power of such systems is controllable and the maximum can be several hundred W. The probe system is more expensive than the bath and it is slightly less convenient in use because special seals will be needed if the horn is to be used in reactions which involve reflux, inert atmospheres or pressures above (or below) ambient.

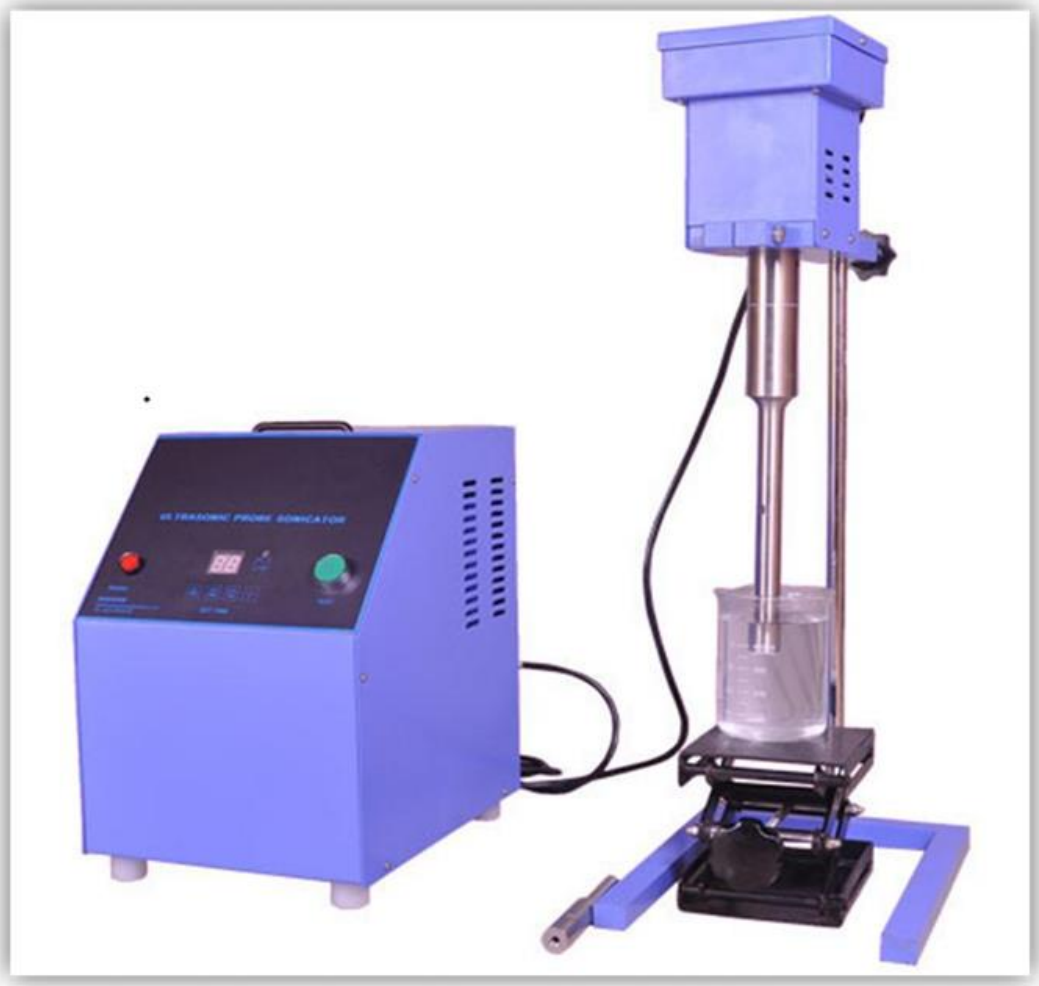

Figure 1.5: Ultrasonic Probe

1.12 Ultrasound and its chemical effects

The discovery of the piezoelectric effect provided the basis for the construction of modern ultrasonic devices. Piezoelectric materials generate mechanical vibrations in response to an applied alternating electrical potential. If the potential is applied at sufficiently high frequency, ultrasonic waves are generated. The phenomenon responsible for the beneficial effects of ultrasound on chemical reactions is cavitation. Ultrasonic waves are propagated via alternating compressions and rarefactions induced in the transmitting medium through which they pass.

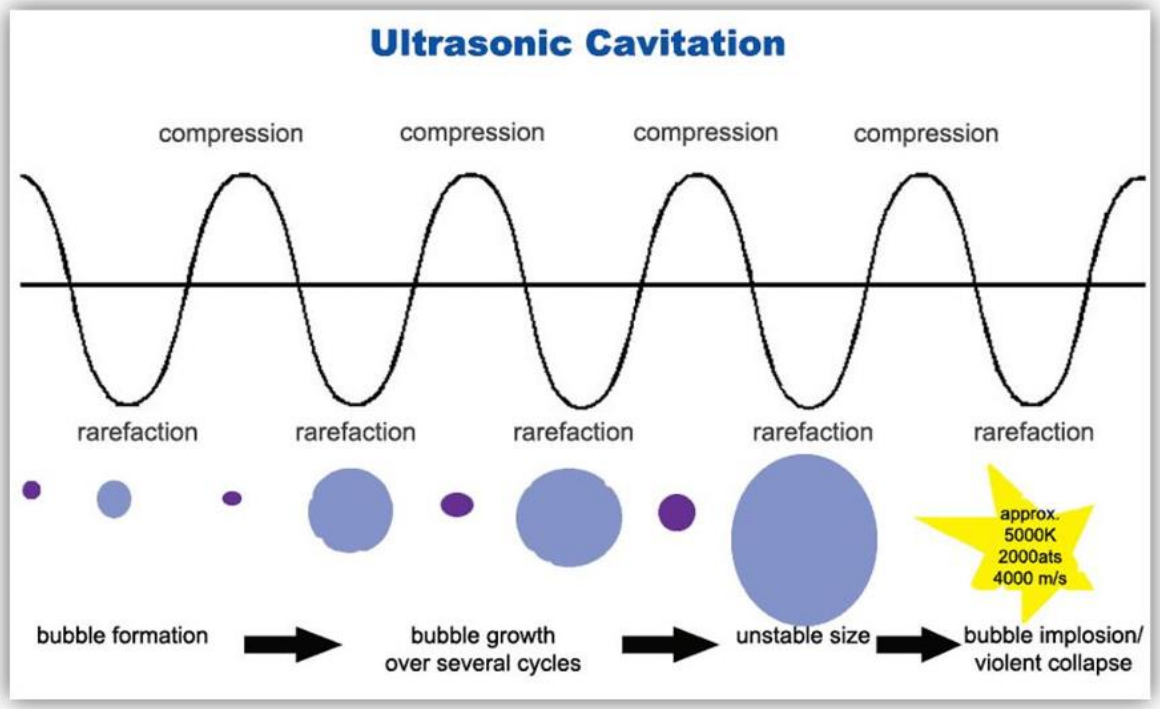

Figure 1.6: Ultrasonic Cavitation.

During the rarefaction cycle of the sound wave, the molecules of the liquid are separated, generating bubbles that subsequently collapse in the compression cycle. These rapid and violent implosions generate short-lived regions with local temperatures of roughly 5000 °C, pressures of about 2000 atm and heating and cooling rates that can exceed 10 billion °C per second. Such localized hot spots can be thought of as micro reactors in which the mechanical energy of sound is transformed into a useful chemical form. In addition to the generation of such hot spots, there can also be mechanical effects produced as a result of the violent collapse (Mason & Lorimer, 2002).

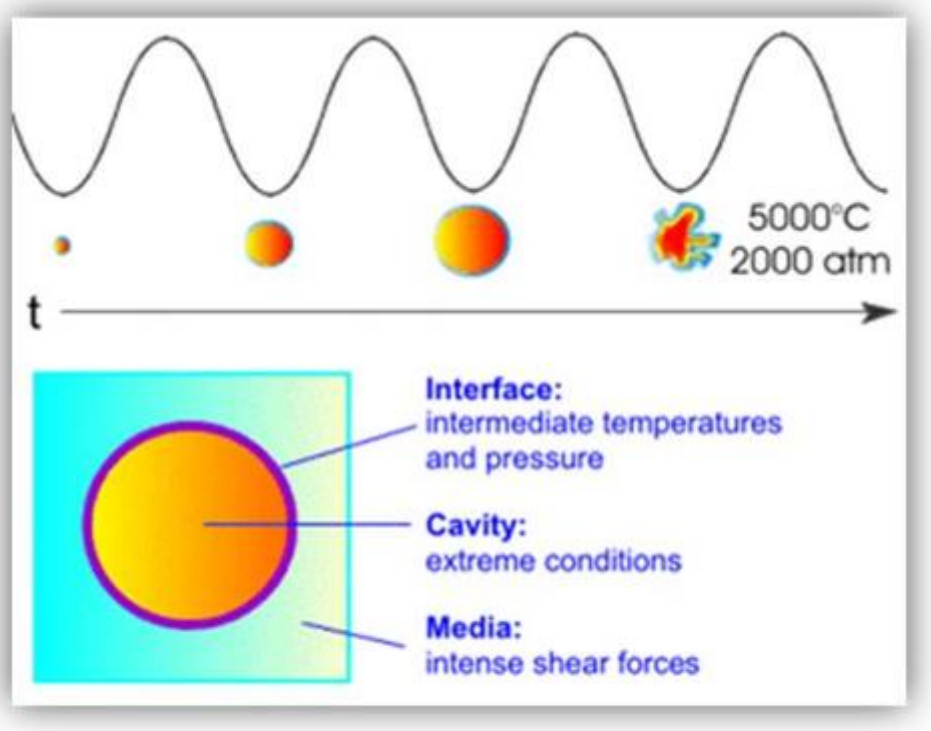

Figure 1.7: Hot spot generation.

More than 80 years have passed since the effect of ultrasound on reaction rates was first reported by Richards and Loomis (Richards & Loomis, 1927). However, this work received little attention at the time because it used a high frequency apparatus that was not commonly available to chemists. According to the review of Cravotta and Cintas, two classical papers, published in 1978 and 1980, provided a major stimulus for the development of modern sonochemistry.

The report by Fry and Herr (Fry & Herr, 1978) of the reductive dehalogenation of dibromo ketones with mercury dispersed by ultrasound (2) The work of Luche and Damiano (Luche & Damiano, 1980) on the Recent Advances in the Ultrasound-Assisted Synthesis of Azoles sonochemical preparation of organolithium and Grignard reagents and their coupling with carbonyls. In the ensuing four decades, numerous efficient and innovative applications of ultrasound in organic synthesis have appeared which have established sonochemistry as an important tool in the arsenal of Green Chemistry.

The two main sources of ultrasound in organic synthesis are ultrasonic cleaning baths and ultrasonic immersion probes, which typically operate at frequencies of 40 and 20 kHz, respectively (Mason, 1997). The former are more commonly employed in organic synthesis simply because they are less expensive and hence more widely available to chemists, even though the amount of energy transferred to the reaction medium is lower than that of ultrasonic probe systems, which deposit the acoustic energy directly into the reaction medium. In this context, the use of Ultrasound and Microwave to accelerate reactions has proven to be a particularly important tool for meeting the Green Chemistry goals of minimization of waste and reduction of energy requirements.

Considering the facts above facts new Thiazine, Oxadiazole, Piperidine, Pyrazole, Dioxine, Triazoles have been synthesized using Microwave and Sonication techniques.

CHAPTER 2

2.1 LITERATURE SURVEY

1. Florio and Leng (1977) reported the synthesis of 4H-2,3-dihydrobenzo-1,4-thiazine derivatives through addition and self-condensation reactions. Their work established an efficient route for constructing benzothiazine ring systems and laid the foundation for further investigations into the biological activities of these heterocyclic compounds.

2. Kamila and Kob (2006) synthesized a series of (Z)-hetaryl methylene and (Z)-substituted benzylidene derivatives of 4H-benzo[1,4]thiazine-3-thiones by reacting 4H-benzo[1,4]thiazine-3-thiones with various aldehydes. The study demonstrated the versatility of aldehyde condensation reactions in generating structurally diverse benzothiazine derivatives.

3. Parai and Panda (2008) developed a copper-catalyzed intramolecular N-aryl amination methodology for synthesizing 3,4-dihydro-2H-benzo[b][1,4]thiazine derivatives. The reaction employed substituted 2-(2-bromophenylthio)ethanamines and provided good yields under mild conditions.

4. Florio, Leng and Stirling (1978) synthesized 4-substituted-2,3-dihydrobenzo-1,4-thiazine derivatives and evaluated their antihypertensive properties. Several compounds exhibited promising pharmacological activity, highlighting the therapeutic potential of the benzothiazine scaffold.

5. Wu, Shang and Wang (2011) reported a DABCO-catalyzed one-pot three-component synthesis of 3,4-dihydro-2H-benzo[b]thiazine derivatives from 2-aminobenzenethiol, aromatic aldehydes and α-halogenated ketones. The method offered operational simplicity and high product yields.

6. Govindan and Valliappan (2010) synthesized a series of 3,5-diaryl-tetrahydro-N-formyl-1,4-thiazine-1,1-dioxides from corresponding thiazine precursors. The study demonstrated the utility of formylation reactions in generating novel sulfur-containing heterocycles.

7. Gupta et al. (2012) described a one-pot synthesis of 1,2,4-trichloro-7-fluoro-9-methyl-phenothiazine-3-one. The developed protocol reduced reaction time and improved overall synthetic efficiency.

8. Sundari et al. (2013) synthesized novel 1,4-thiazine derivatives through condensation of 3,5-diaryl-tetrahydro-1,4-thiazine-1,1-dioxide with formaldehyde and substituted anilines under acidic conditions. The resulting compounds were screened for biological activity.

9. Sheibani, Islami, Hassanpour and Hosseininasab (2010) developed efficient synthetic routes to 4H-benzo[b][1,4]thiazine derivatives under environmentally friendly conditions. The methodology afforded high yields with simplified purification procedures.

10. Dabholkar and Gavande (2011) synthesized 2H,4H-2-[(substituted-phenyl)-1,3,4-oxadiazol-5-yl]-methyl-3-oxo-1,4-benzothiazine derivatives using ultrasound-assisted reactions. Ultrasonic irradiation significantly reduced reaction times while improving product yields.

11. Kumar et al. (2012) synthesized a series of 3-substituted-1,4-dioxo-1,4-dihydronaphthalen-2-yl-thioalkanoates and naphtho[2,3-b][1,4]thiazine-5,10-diones. Biological evaluation revealed notable antibacterial and antifungal activities.

12. Rees, White and Williams (1998) reported the synthesis of 4-ethylbis[1,2]dithiolo[5,4-b][4′,5′-e][1,4]thiazine-3,5-dithione via reaction of disulfur dichloride in the presence of DABCO. Their work expanded the chemistry of sulfur-rich heterocyclic systems.

13. Deohate (2012) synthesized 6,7-di(substituted)-phenyl-3-pyridin-4-yl-5H-[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazines from substituted benzoins and triazole intermediates. The compounds displayed promising biological characteristics.

14. Sridhara et al. (2013) prepared 3,6-disubstituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles and corresponding thiadiazines through multistep synthetic transformations. The synthesized molecules were investigated for potential medicinal applications.

15. Dong et al. (2014) synthesized 7H-3-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-6-substituted-s-triazolo[3,4-b]-1,3,4-thiadiazines through cyclization reactions involving α-haloketones. Several compounds exhibited significant biological activity.

Pyrazole Derivatives

16. Mamaghani and Dastmard (2005) synthesized 1,5-diarylpyrazoles by reacting Baylis-Hillman adducts with phenylhydrazine hydrochloride under sonication. The ultrasonic method improved reaction rates and product yields.

17. Pathak et al. (2007) compared four activation methods for synthesizing N-acetyl pyrazolines. Ultrasound-assisted reactions completed within 10–25 minutes and afforded high yields.

18. Pizzuti et al. (2008) synthesized 1-thiocarbamoyl-3,5-diaryl-4,5-dihydropyrazoles from chalcones and thiosemicarbazide under KOH catalysis. The products were obtained rapidly with excellent purity.

19. Gupta et al. (2009) utilized ultrasonic irradiation to promote cyclization between chalcones and phenylhydrazine, producing pyrazole derivatives in high yields.

20. Nabid et al. (2010) developed a synthesis of bridgehead pyrazole derivatives under ultrasonic conditions. The methodology furnished 1H-pyrazolo[1,2-b]phthalazine-5,10-diones efficiently.

Piperidine Derivatives

21. Mane, Jaikumar and Dhavale (2004) synthesized γ-hydroxyalkyl substituted piperidine iminosugars from D-glucose. These compounds attracted interest due to their glycosidase inhibitory properties.

22. Balle and Perregaard (2002) prepared piperidinylethylamide derivatives possessing 5-HT1A antagonist and antihistaminic activities, indicating potential use as anxiolytic agents.

23. Costanzo et al. (2005) synthesized spirocyclic piperidine amides as potent tryptase inhibitors and demonstrated oral efficacy in animal models.

24. Barta, Becker and co-workers (2006) developed piperidine-based metalloprotease inhibitors with anti-inflammatory, antiangiogenic and antitumor properties.

25. Apodaca, Dvorak and Xiao (2007) synthesized neuroactive piperidine derivatives that exhibited potent 5-HT2A receptor antagonistic activity.

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Dioxine (Meldrum's Acid) Derivatives

26. Yonemitsu et al. (1987) reported a multicomponent reaction involving Meldrum's acid, aldehydes, and indoles in a one-pot process to afford indol-3-ylpropionic acid derivatives. This reaction became one of the most cited examples demonstrating the synthetic versatility of Meldrum's acid in heterocyclic chemistry.

27. Kraus and Chaudhary (1999) described the synthesis of indane esters through base-catalyzed hydrolysis of spirocyclic intermediates derived from Meldrum's acid. Their work highlighted the utility of Meldrum's acid as a valuable precursor for carbocyclic and heterocyclic frameworks.

28. Chang and Huang (2001) synthesized Gelastatin analogues containing partially unsaturated pyrone rings using Meldrum's acid as a key starting material. The methodology provided an efficient route to biologically important natural product analogues.

29. Dabholkar and Mohammed (2012) investigated a green synthetic approach for the preparation of Biginelli products using Meldrum's acid under environmentally benign conditions. The protocol offered improved yields with reduced environmental impact.

30. Cunha et al. (2013) synthesized novel N-substituted-1,2,3-triazole-4-acylhydrazone derivatives and evaluated their biological potential. The compounds exhibited promising antimicrobial and pharmacological properties.

Additional Pyrazole Derivatives

31. Kappe (2004) reported an efficient microwave-assisted synthesis of pyrazole derivatives through cyclocondensation of hydrazines with β-dicarbonyl compounds. The methodology significantly reduced reaction times and improved product yields.

32. Fustero et al. (2006) developed a regioselective synthetic strategy for highly substituted pyrazoles using fluorinated β-enamino diketones. The approach provided access to structurally diverse pyrazole derivatives with potential pharmaceutical applications.

33. Elguero and co-workers (2007) investigated the structural, physicochemical and biological properties of substituted pyrazoles. Their comprehensive study established pyrazoles as important scaffolds in medicinal chemistry.

34. Koretzky et al. (2008) synthesized novel pyrazole-containing heterocycles and evaluated their antimicrobial activities. Several compounds exhibited significant inhibitory effects against pathogenic microorganisms.

35. Shaabani et al. (2009) reported a one-pot multicomponent synthesis of pyrazole derivatives under solvent-free conditions. The environmentally friendly protocol afforded excellent yields and operational simplicity.

36. Abdel-Wahab et al. (2010) synthesized a series of fused pyrazole derivatives and evaluated their anticancer activities against different cancer cell lines. Several compounds demonstrated promising cytotoxic effects.

37. Chande et al. (2011) prepared substituted pyrazole analogues and investigated their anti-inflammatory activities. Biological studies revealed significant inhibition of inflammatory responses.

38. Desai et al. (2012) synthesized pyrazole-based Schiff bases and evaluated their antibacterial and antifungal activities. Many derivatives exhibited broad-spectrum antimicrobial properties.

39. Bekhit and co-workers (2013) developed novel pyrazole derivatives as selective cyclooxygenase inhibitors. The compounds demonstrated significant anti-inflammatory activity with improved selectivity profiles.

40. Bondock et al. (2014) synthesized pyrazole-containing compounds and evaluated their analgesic and anti-inflammatory properties. Several derivatives showed potent pharmacological effects comparable to standard drugs.

Additional Piperidine Derivatives

41. Dimmock et al. (2002) synthesized a series of piperidine derivatives and evaluated their anticancer activities against various tumor cell lines. Several compounds demonstrated potent cytotoxic effects and potential as anticancer agents.

42. Watson and Jiang (2003) developed stereoselective methodologies for the synthesis of substituted piperidines. Their work provided valuable synthetic tools for pharmaceutical and medicinal chemistry research.

43. Michael (2005) reviewed naturally occurring piperidine alkaloids and emphasized their structural diversity, biological activities and therapeutic significance in drug discovery.

44. O'Hagan (2007) discussed the synthesis and medicinal applications of piperidine-containing compounds. The review highlighted the importance of piperidine scaffolds in numerous clinically useful drugs.

45. Meanwell (2011) described piperidine as a privileged scaffold in medicinal chemistry and summarized its role in improving pharmacokinetic and pharmacodynamic properties of therapeutic agents.

46. Jeyachandran et al. (2012) synthesized novel piperidine derivatives and screened them for antimicrobial activity. Several compounds displayed promising antibacterial and antifungal effects.

47. Kumar et al. (2013) reported a green synthetic approach for functionalized piperidines using multicomponent reactions. The methodology offered high atom economy and environmentally friendly reaction conditions.

48. Roman et al. (2014) synthesized piperidine-containing heterocycles and investigated their antioxidant properties. Some derivatives showed significant free radical scavenging activity.

49. Singh and Desta (2015) reviewed recent advances in the synthesis, biological evaluation and therapeutic applications of piperidine derivatives. Their review highlighted emerging trends in piperidine-based drug design.

50. Choudhary et al. (2016) synthesized biologically active piperidine analogues and evaluated their enzyme inhibitory activities. Several compounds exhibited promising pharmacological profiles.

Additional Meldrum's Acid / Dioxine Derivatives

51. Tietze (2004) reported several multicomponent reactions involving Meldrum's acid for the construction of complex heterocyclic frameworks. These methodologies demonstrated the versatility of Meldrum's acid in diversity-oriented synthesis.

52. Dömling and Ugi (2005) described Meldrum's acid as an important reagent in multicomponent reactions and highlighted its applications in the rapid synthesis of heterocyclic compounds.

53. Zhu and Bienaymé (2006) reported the use of Meldrum's acid in diversity-oriented synthesis strategies aimed at generating structurally diverse compound libraries for drug discovery.

54. Alizadeh et al. (2008) developed environmentally benign methods for synthesizing dioxine derivatives using Meldrum's acid. Their approach emphasized green chemistry principles and sustainable synthesis.

55. Heravi et al. (2010) reviewed the utility of Meldrum's acid in organic synthesis and heterocyclic chemistry. The review summarized numerous applications in the preparation of biologically active molecules.

56. Kidwai et al. (2011) reported a microwave-assisted green protocol for synthesizing oxygen-containing heterocycles from Meldrum's acid. The methodology significantly reduced reaction times and improved yields.

57. Maghsoodlou et al. (2012) synthesized various dioxine derivatives through multicomponent reactions involving Meldrum's acid. The study demonstrated the broad applicability of Meldrum's acid in heterocyclic synthesis.

58. Teimouri (2013) developed catalyst-free synthetic methods for heterocyclic compounds utilizing Meldrum's acid as a key precursor. The protocol provided an environmentally friendly alternative to conventional methods.

59. Azizian et al. (2014) synthesized novel triazole and dioxine derivatives through one-pot multicomponent reactions under ultrasonic irradiation. The approach afforded excellent yields with reduced reaction times.

60. Rostamizadeh et al. (2015) reported efficient syntheses of biologically active oxygen-containing heterocycles derived from Meldrum's acid and evaluated their pharmacological potential. Several compounds exhibited promising antimicrobial and antioxidant activities.

CHAPTER 3

PLAN OF WORK

1. BENZOTHIAZINES SYNTHESIS BY SONICATION TECHNIQUE
2. AZO DYES CONTAINING PYRAZOLE MOITIES
3. FORMATION OF AZO DYES
4. FORMATION AZO CHITRAL DYES
5. CONCLUSION

CHAPTER 4

4.1 Materials and Reagents for Benzothiazines

All chemicals and reagents used in the present investigation were of Analytical Reagent (AR) grade and were used without further purification unless otherwise specified. Malonic acid, acetic anhydride, sulfuric acid, acetone, tetrahydrofuran (THF), hydrochloric acid, and absolute ethanol were procured from Merck Life Science. p-Toluidine was purchased from Sigma-Aldrich. Sulfur powder, iodine, and carbon disulfide (CS_2) were obtained from Loba Chemie. Distilled water used throughout the study was prepared in-house.

Meldrum's acid, the key intermediate employed in the synthesis of substituted 2,2-dimethyl-9H-1,3-dioxa-10-thia-9-aza-anthracen-4-one derivatives, was synthesized in the laboratory according to the reported procedure using malonic acid, acetic anhydride, sulfuric acid, and acetone. The synthesized product was purified by recrystallization from an acetone-water mixture and characterized by its melting point before further use.

Table 4.1 Chemicals and Reagents Used in the Study

S. No.	Chemical/Reagent	Molecular Formula	Grade	Manufacturer
1	Malonic Acid	$C_3H_4O_4$	AR	Merck Life Science
2	Acetic Anhydride	$C_4H_6O_3$	AR	Merck Life Science
3	Sulfuric Acid	H_2SO_4	AR	Merck Life Science
4	Acetone	C_3H_6O	AR	Merck Life Science
5	p-Toluidine	C_7H_9N	AR	Sigma-Aldrich
6	Sulfur Powder	S	AR	Loba Chemie
7	Iodine	I_2	AR	Loba Chemie
8	Tetrahydrofuran (THF)	C_4H_8O	AR	Merck Life Science
9	Hydrochloric Acid	HCl	AR	Merck Life Science
10	Carbon Disulfide	CS_2	AR	Loba Chemie
11	Absolute Ethanol	C_2H_5OH	AR	Merck Life Science
12	Distilled Water	H_2O	Laboratory Grade	Prepared In-house
13	Meldrum's Acid	$C_6H_8O_4$	Synthesized	Prepared in Laboratory

4.2 Instruments Used

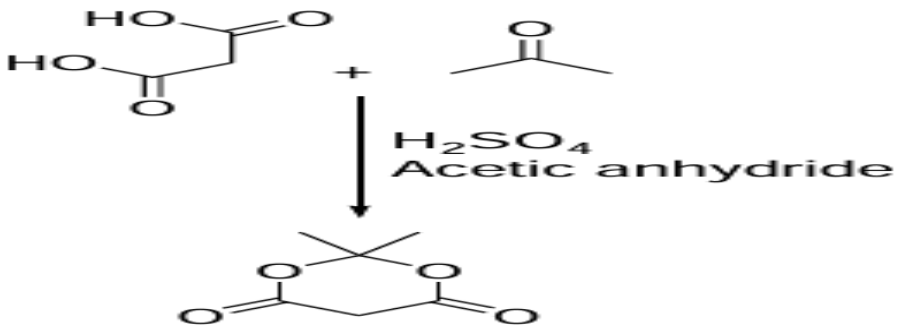
The melting points of synthesized compounds were determined using a digital melting point apparatus and were uncorrected. The progress of reactions and purity of compounds were monitored by thin-layer chromatography (TLC) using pre-coated silica gel G plates. Infrared spectra were recorded using FT-IR spectroscopy employing the KBr pellet technique. Proton Nuclear Magnetic Resonance (^1H NMR) and Carbon-13 Nuclear Magnetic Resonance (^13C NMR) spectra were recorded using deuterated solvents with tetramethylsilane (TMS) as the internal standard. Mass spectra were obtained using a mass spectrometer operating under electron impact ionization conditions. Sonication-assisted synthesis was carried out using an ultrasonic probe sonicator, while conventional synthesis was performed using a heating mantle equipped with a reflux condenser.

4.1 .1 SYNTHESIS BY SONICATION TECHNIQUE

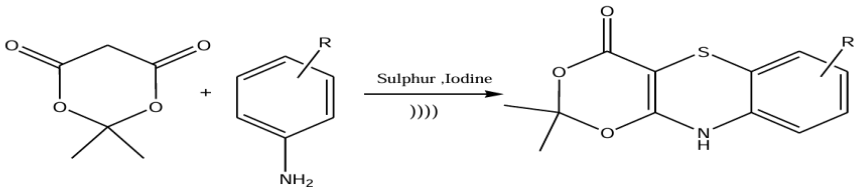
Preparation of Meldrums acid

To a mixture of malonic acid (5.2g 0.05 mol) and acetic anhydride (5.6 mL, 0.05 mol), (catalytic amount) sulfuric acid (0.16 mL) was added. Mixture was cooled and stirred, after 20 mins, acetone 5.0 mL (0.05 mol) was added, the mixture was stirred for 6 hrs. Kept overnight in refrigerator, obtained crude product was filter off and recrystallized from acetone/water. Yield 72%; M.P. 95-96°C.

Scheme 4.1



Scheme 4.2



Representative Procedure:

N H (74) Synthesis of 2, 2, 6-Trimethyl-9H-1, 3-dioxa-10-thia-9-aza-anthracen-4 one: Method A (Sonication)

Mixture of Meldrum ‘s acid (7.2g, 0.05 mol), p-toludine (5.35g, 0.05 mol) and Sulphur (1g), iodine (0.15g) and THF (5mL) as a solvent was Sonicated for 15 20 mins by a Sonication probe.

The progress of the reaction was monitored by TLC. After completion of the reaction, the concentrated reaction mixture was cooled and poured onto ice-cold water, solid separated was filtered off, washed with dilute HCl and CS2, dried, and recrystallized from absolute alcohol to obtain pure compound. Yield 56%; m.p 139-40°C.

Method B (Conventional)

Mixture of Meldrum ‘s acid (0.05 mol), p-toludine (0.05 mol) and Sulphur (1g), iodine (0.15g) and THF (5mL) as a solvent was reflux for 2-3 hrs. on heating mantle. The progress of the reaction was monitored by TLC. After completion of the reaction, the concentrated reaction mixture was cooled and poured onto ice-cold water, solid separated was filtered off, washed with dilute HCl and CS2, dried, and recrystallized from absolute alcohol to obtain pure compound (74a). Yield 78%; m.p 139-40°C.

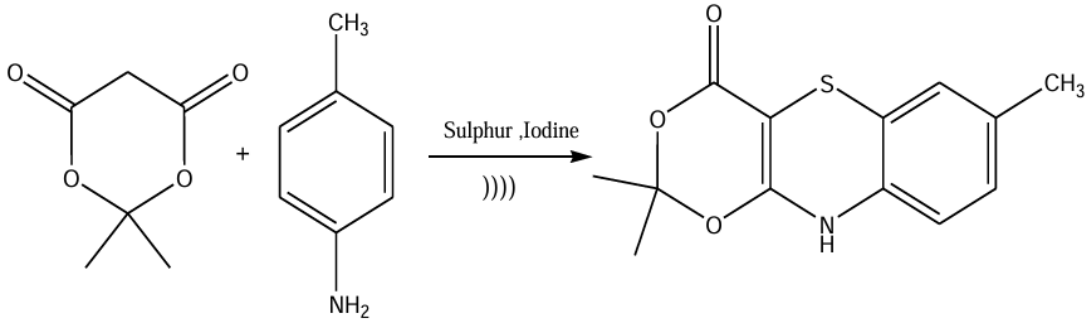


Table-4.1 Physical data of (substituted)-2, 2-dimethyl-9H-1, 3-dioxa-10-thia-9-aza anthracen-4-one

Compds (74)	R	M.F	MP (°C)	% Yield	Color	Time	
						Conv. Method (hrs)	Soni Method (min)
a	6-CH_3	$C_{13}H_{13}O_3NS$	139-41	72	Light Brown	2.5	18
b	6-Cl	$C_{12}H_{10}O_3NSCl$	135-38	76	Light Brown	2.5	18
c	H	$C_{12}H_{11}O_3NS$	113-15	78	Gray	2.5	20
d	6-OCH_3	$C_{13}H_{13}O_4NS$	144-146	82	Dark Brown	2.5	17
e	7-OCH_3	$C_{13}H_{13}O_4NS$	9092	76	Cream	2.5	20
f	8-CH_3	$C_{13}H_{13}O_3NS$	85-88	68	Light Green	2.5	20
g	7-CH_3	$C_{13}H_{13}O_3NS$	103-05	66	Green	2.5	20
h	6-Br	$C_{12}H_{10}O_3NSBr$	165-67	79	Buff	2	16
i	6-NO_2	$C_{12}H_{10}O_5N_2S$	196-99	69	Dark Yellow	2	15
j	8-NO_2	$C_{12}H_{10}O_5N_2S$	151-53	61	Light Yellow	2	15

4.2.1 Analysis of compound

Light brown compound was found to have the molecular composition C13H13O3NS showed the following result on elemental analysis.

Elemental analysis of the compound

Molecular formula	Calc./ Found		
	C	H	N
$C_{13}H_{13}O_3NS$	56.53	4.65	5.01
	56.22	4.52	5.34

4.3.1 Spectral characteristic data of 2, 2, 6-Trimethyl-9H-1, 3-dioxa-10-thia-9 aza-anthracen-4-one

IR Spectra: Fig 2.1 IR (cm-1): 3290(NH), 1730(C=O) 1H NMR interpretation: Fig 2.2 1H NMR (δ ppm): 1.72(s, 6H, 2xCH3), 2.05 (s, 3H, CH3), 4.32 (s, 1H, NH) 6.8 7.2 (m, 3H, Ar- H), 13C NMR interpretation: Fig 2.3 13C NMR (δ ppm): 20.1(CH3), 27.3(2xCH3), 77.78 (tetrahedral C), 115.36-131.7 (C=C, Ar-C), 165.47 (C=O). Mass interpretation: Fig 2.4 m/e: M+ 263

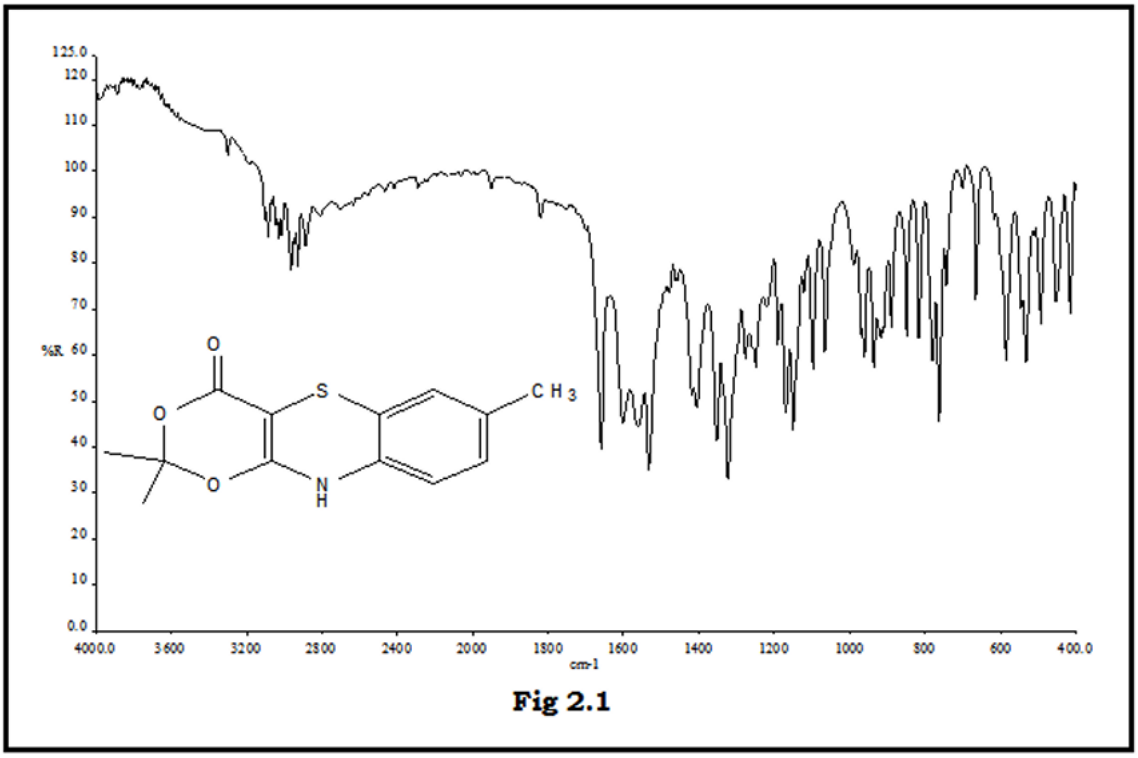


Fig 2.1

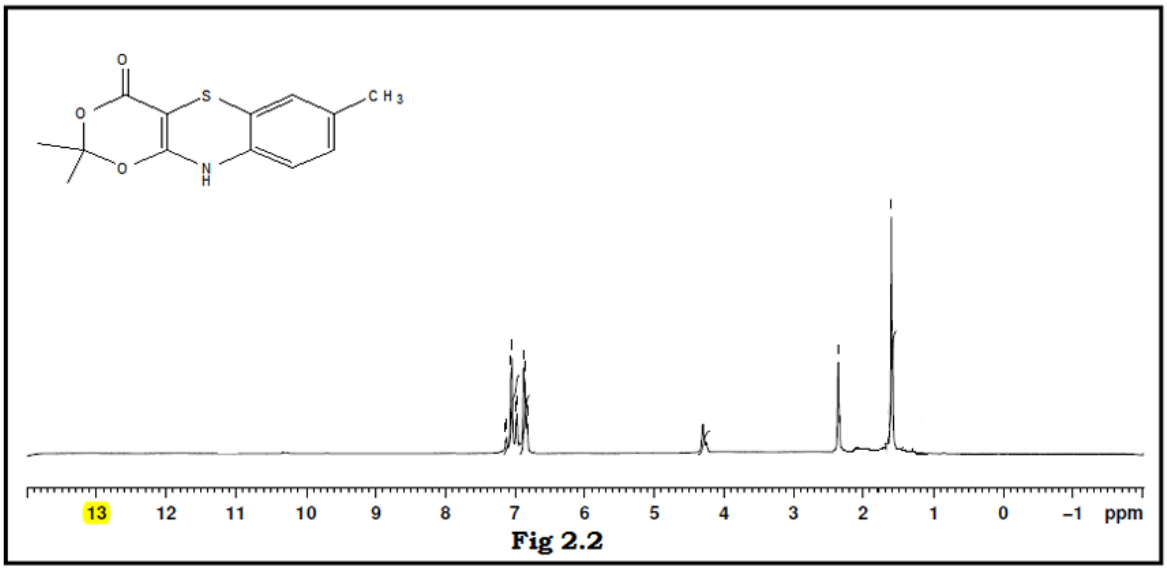
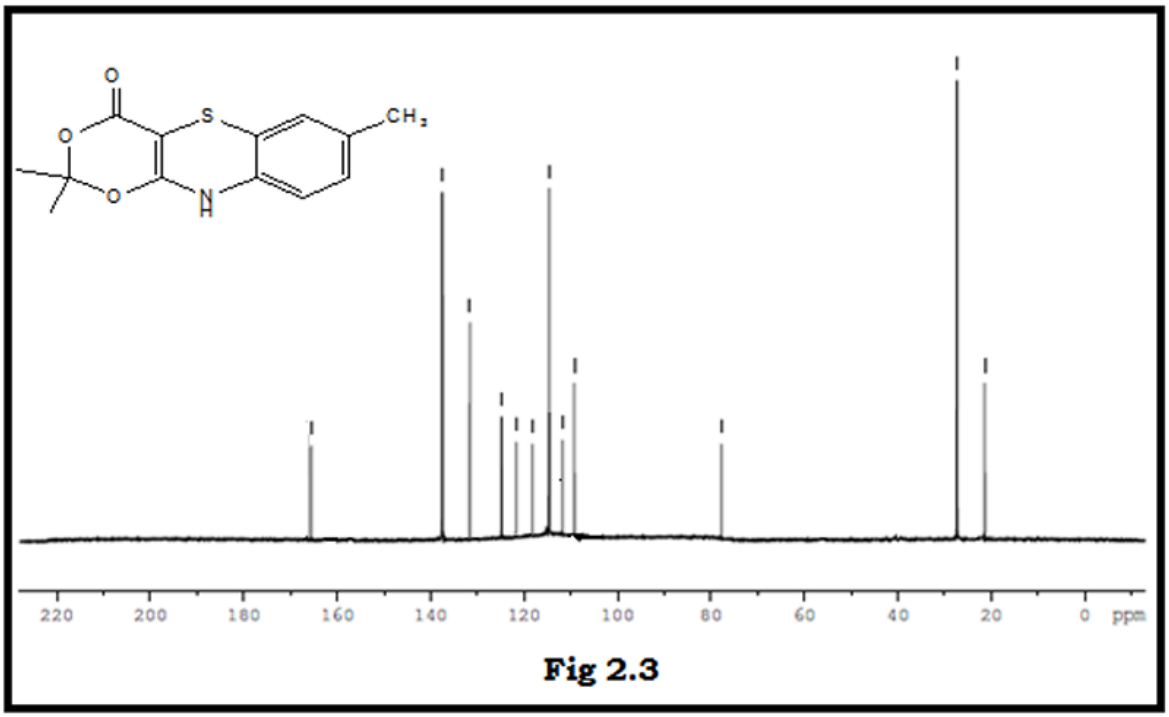

O
O
S
CH3
O
N
H
13
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
ppm

Fig 2.2


O
O
S
CH3
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ppm

Fig 2.3

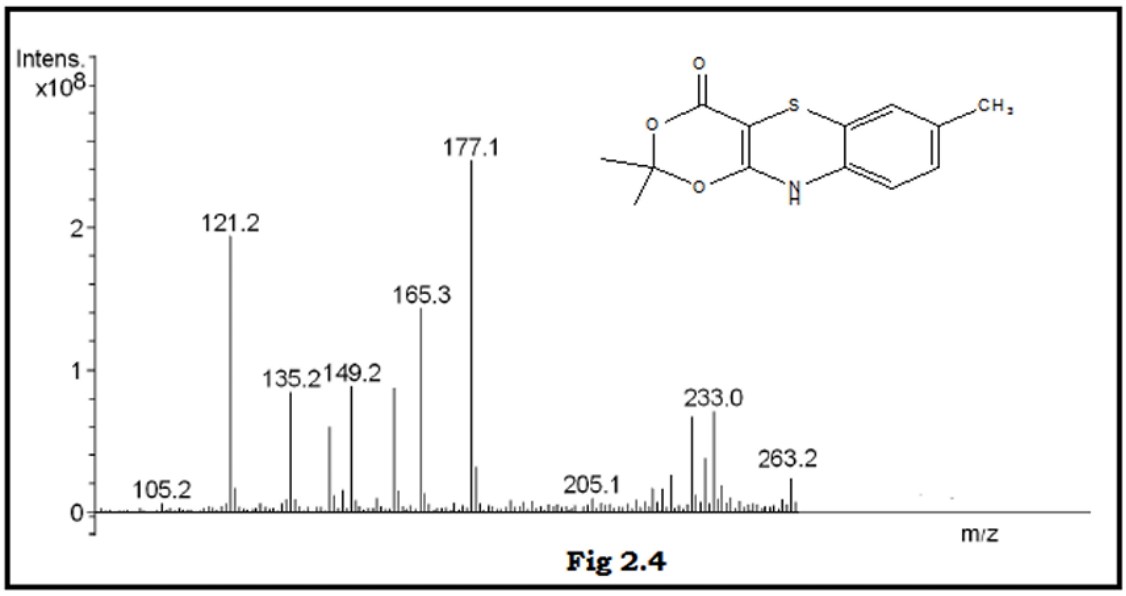


Fig 2.4

Figure 4.1: I R spectral characteristics.

4.4.1 Analysis of compound

Dark Brown compound was found to have the molecular composition C13H13O4NS showed the following result on elemental analysis.

Elemental analysis of the compound

Molecular formula	Calc./ Found		
	C	H	N
$C_{13}H_{13}O_4NS$	56.53	4.65	5.01
	56.22	4.52	5.34

Spectral characteristic data of 6-Methoxy-2,2-dimethyl-9H-1,3-dioxa-10 thia-9-aza-anthracen-4-one:

IR Spectra: Fig 2.5

IR (cm-1): 3290(NH), 1730(C=O) 1H NMR interpretation:

Fig 2.6 1H NMR (δ ppm): 2.02(s, 6H, 2xCH3), 3.32 (s, 3H, OCH3), 4.35 (s, 1H, NH), 6.8 7.2 (m, 3H, Ar-H),

13C NMR interpretation: Fig 2.7

13C NMR (δ ppm): 27.3(2xCH3), 56.1(OCH3), 77.78 (tetrahedral C), 114.23 133.57 (C=C, Ar-C), 167.54 (C=O).

Mass interpretation: Fig 2.8 m/e: M+ 279

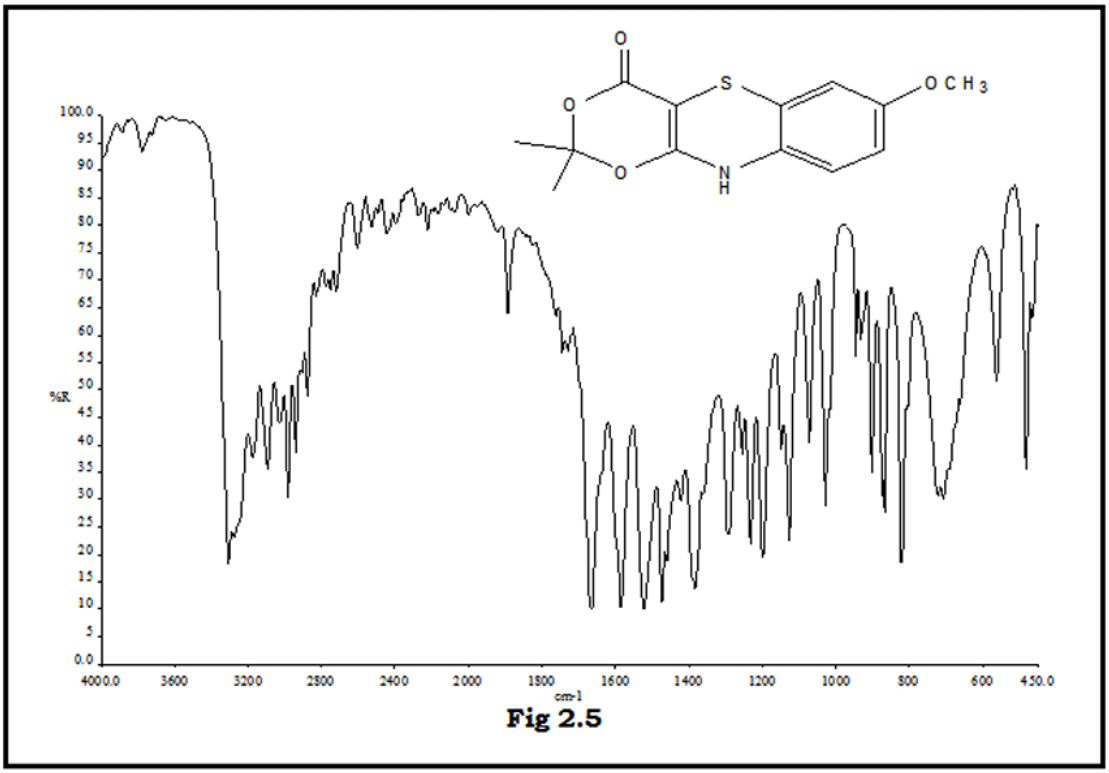


Fig 2.5

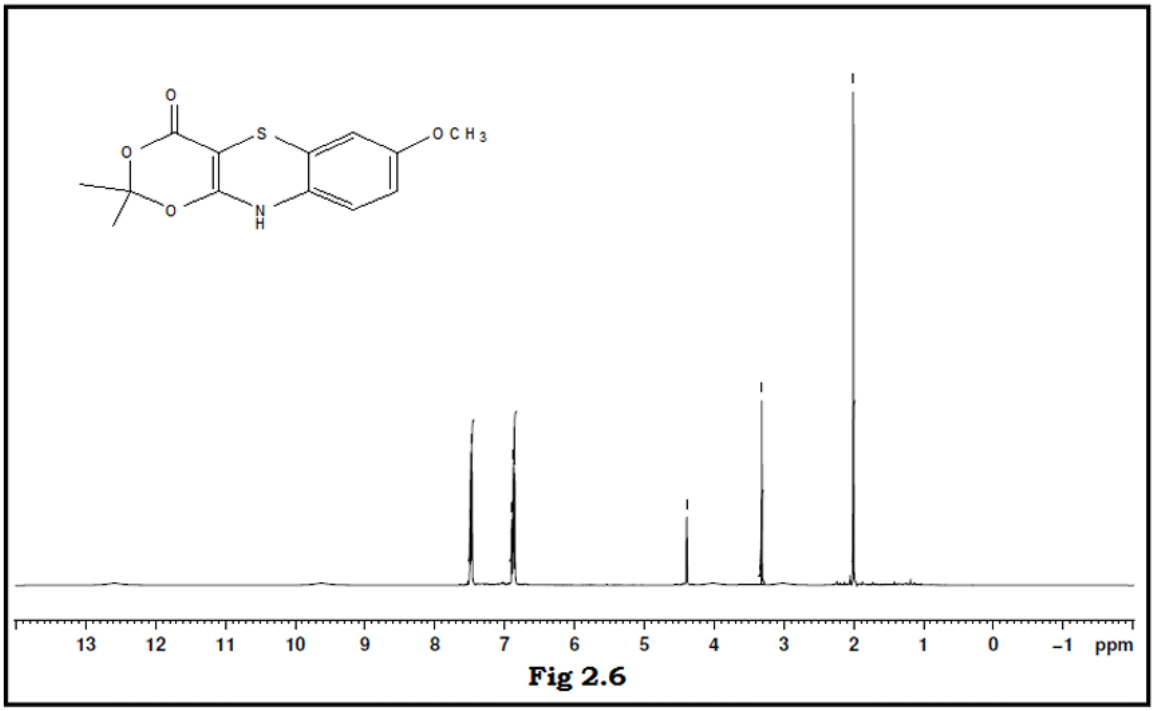


Fig 2.6

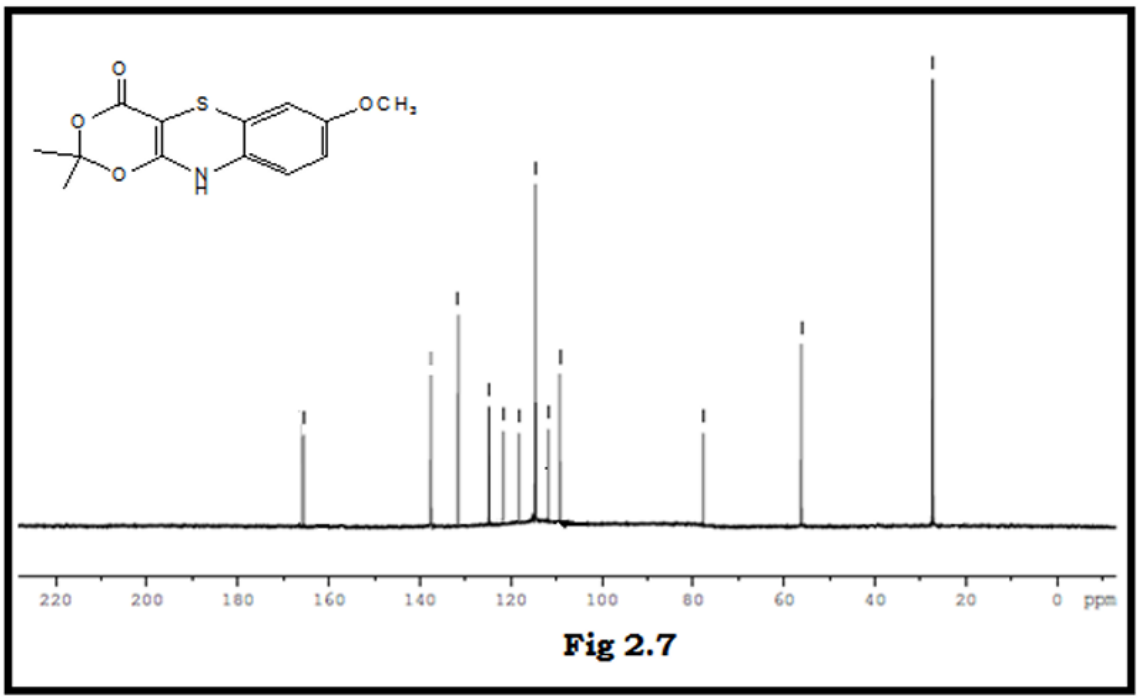


Fig 2.7

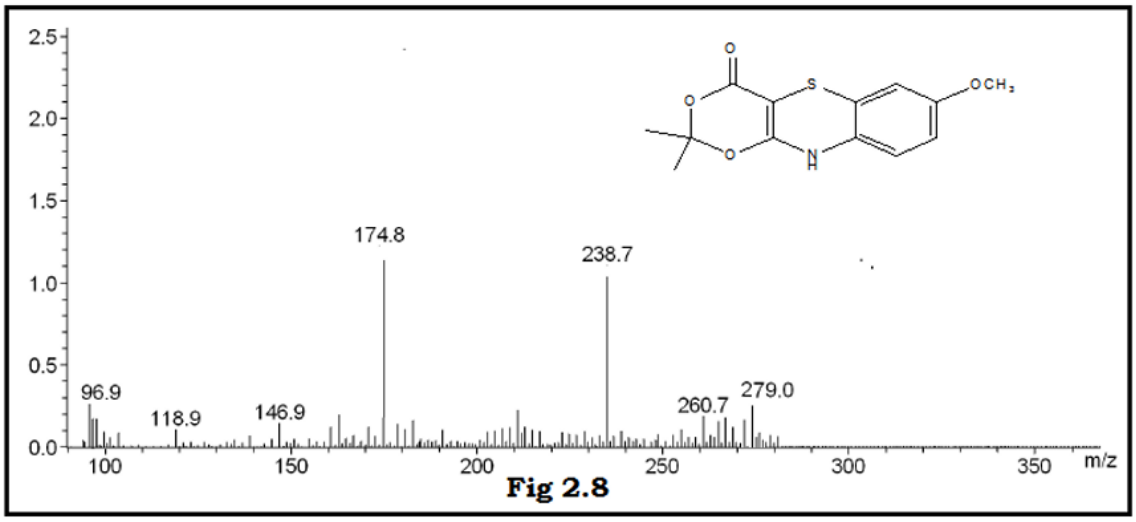


Fig 2.8

Figure 4.2:IR spectral characteristics

4.5.1 Analysis of compound

Light yellow compound was found to have the molecular composition C12H10O5N2S showed the following result on elemental analysis.

Elemental analysis of the compound

Molecular formula	Calc./ Found		
	C	H	N
$C_{12}H_{10}O_5N_2S$	46.19	3.21	8.98
	47.02	3.52	9.06

Spectral characteristic data of 6-Nitro-2, 2-dimethyl-9H-1, 3-dioxa-10 thia-9-aza-anthracen-4-one:

IR Spectra: Fig 2.9

IR (cm-1): 3290(N-H), 1735(C=O), 1340 – 1550 (NO_2) 1H NMR interpretation: Fig 2.10

1H NMR (δ ppm): 1.72(s, 6H, 2xCH3), 4.35(s, 1H, NH) 6.8-7.3 (m, 3H, Ar- H),

13C NMR interpretation: Fig 2.11

13C NMR (δ ppm): 27.5(2xCH3), 77.78 (C), 114.25-133.58 (C=C, Ar-C), 168.35 (C=O). Mass interpretation: Fig 2.12 m/e: M+ 294

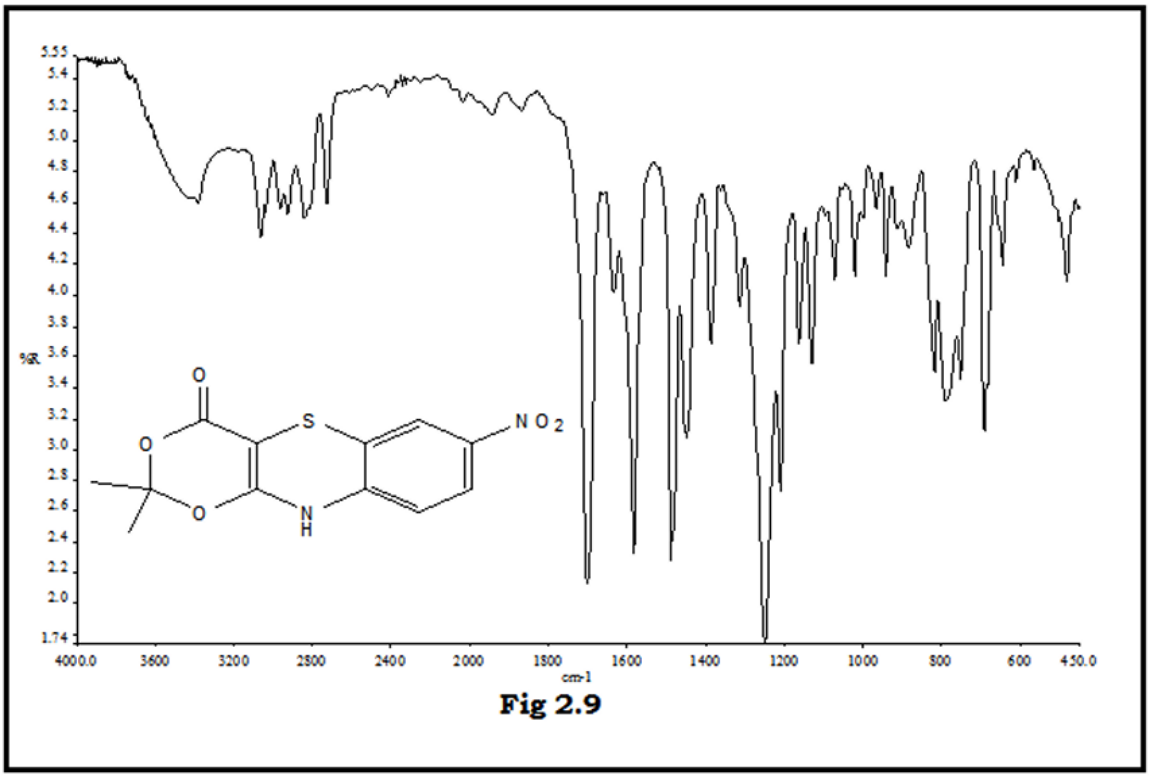


Fig 2.9

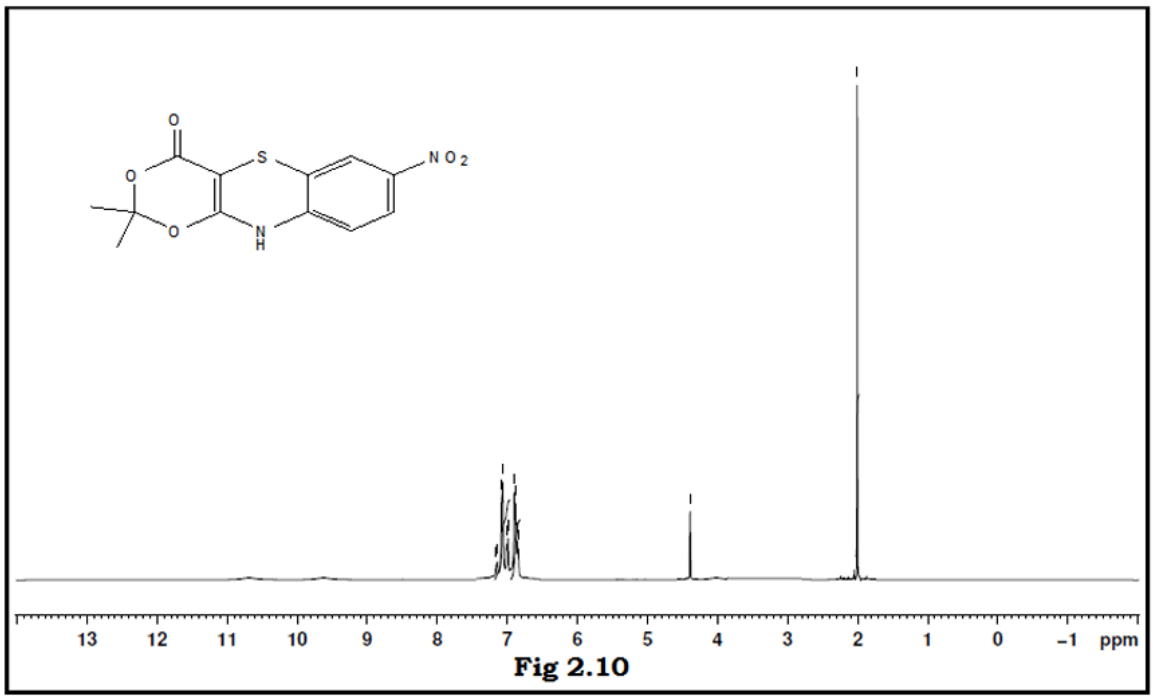


Fig 2.10

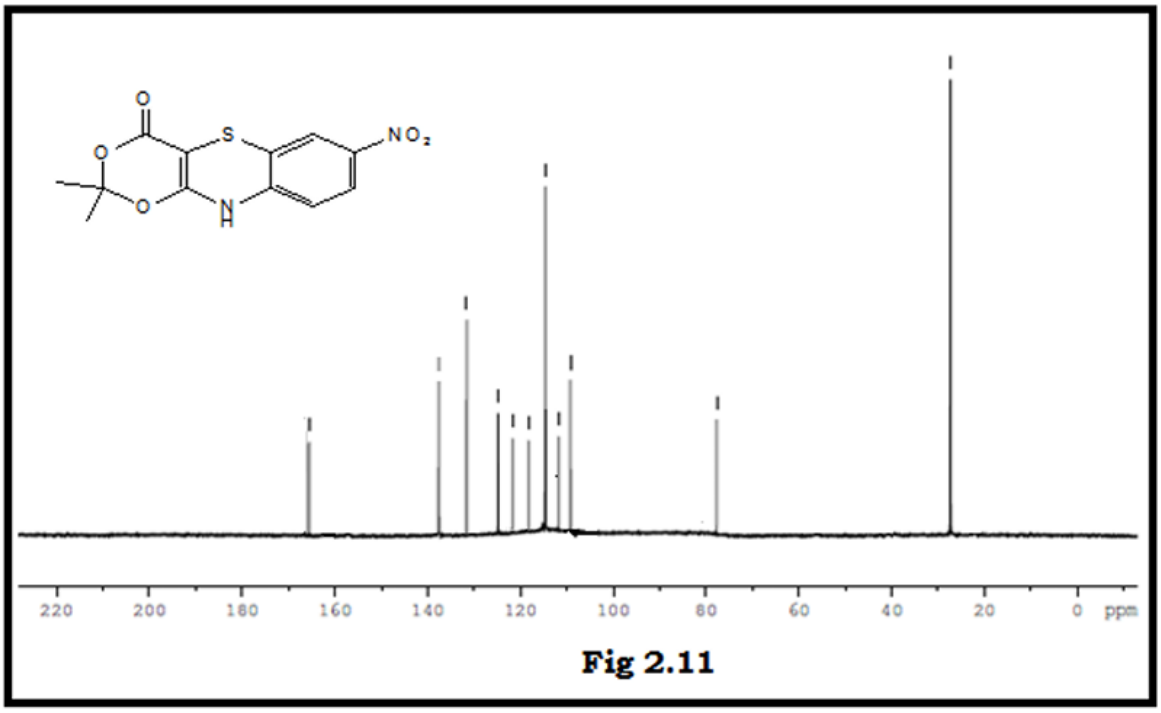


Fig 2.11

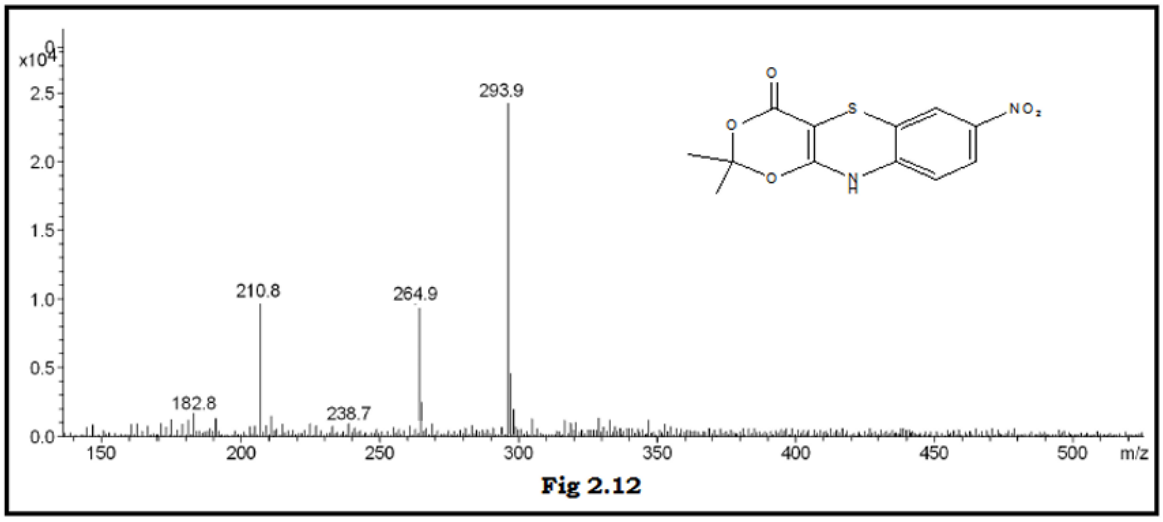


Fig 2.12

Figure 4.3:IR spectral characteristics.

5.1 Materials and Reagents for Azo Dyes Containing Pyrazole Moieties

All chemicals and reagents used in the synthesis of azo dyes containing pyrazole moieties were of Analytical Reagent (AR) grade and were used as received without further purification unless otherwise stated. p-Chlorobenzaldehyde, ethyl acetoacetate, ethanol, piperidine, sodium hydroxide, hydrochloric acid, urea, potassium hydroxide, thionyl chloride, dichloromethane, methanol, hydrazine hydrate, sodium nitrite, sodium acetate, glacial acetic acid, triethylamine, and ethyl bromoacetate were procured from reputed commercial suppliers. Distilled water was prepared in-house and used throughout the study. The progress of all reactions was monitored by thin-layer chromatography (TLC) using silica gel-G precoated plates.

Table 5.1 Chemicals and Reagents Used in the Study

S. No.	Chemical/Reagent	Molecular Formula	Grade	Manufacturer
1	p-Chlorobenzaldehyde	C7H5ClO	AR	Merck Life Science
2	Ethyl Acetoacetate	C6H10O3	AR	Merck Life Science
3	Ethanol	C2H5OH	AR	Merck Life Science
4	Piperidine	C5H11N	AR	Sigma-Aldrich
5	Sodium Hydroxide	NaOH	AR	Merck Life Science
6	Hydrochloric Acid	HCl	AR	Merck Life Science
7	Urea	CH4N2O	AR	Loba Chemie
8	Potassium Hydroxide	KOH	AR	Loba Chemie
9	Thionyl Chloride	$SOCl_2$	AR	Sigma-Aldrich
10	Dichloromethane (DCM/MDC)	CH_2Cl_2	AR	Merck Life Science
11	Methanol	CH_3OH	AR	Merck Life Science
12	Hydrazine Hydrate	$N_2H_4 \cdot H_2O$	AR	Sigma-Aldrich
13	Aromatic Primary Amines	Various	AR	Sigma-Aldrich
14	Sodium Nitrite	$NaNO_2$	AR	Loba Chemie
15	Sodium Acetate	CH_3COONa	AR	Loba Chemie
16	Glacial Acetic Acid	CH_3COOH	AR	Merck Life Science
17	Triethylamine	$C_6H_{15}N$	AR	Sigma-Aldrich
18	Ethyl Bromoacetate	$C_4H_7BrO_2$	AR	Sigma-Aldrich
19	Petroleum Ether	Petroleum Fraction	AR	Loba Chemie
20	Distilled Water	H_2O	Laboratory Grade	Prepared In-house

5.2 Instruments Used

The melting points of synthesized compounds were determined using a digital melting point apparatus and are reported uncorrected. Thin-layer chromatography (TLC) was performed on silica gel-G precoated aluminum plates, and spots were visualized under ultraviolet light. Infrared spectra were recorded using an FT-IR spectrophotometer employing the KBr pellet technique. Proton Nuclear Magnetic Resonance (^1H NMR) and Carbon-13 Nuclear Magnetic Resonance (^13C NMR) spectra were recorded using deuterated solvents with tetramethyl silane (TMS) as an internal standard. Mass spectra were obtained using an electron impact mass spectrometer. Reflux reactions were carried out using standard round-bottom flasks fitted with water-cooled condensers, while solvent removal was performed under reduced pressure using a rotary vacuum evaporator.

5.3 Solvents Used for Synthesis and Purification

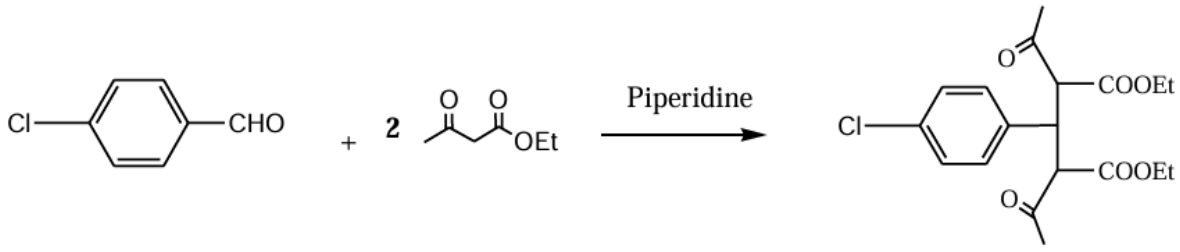
The following solvents were used during synthesis, extraction, recrystallization, and purification procedures:

- Ethanol
- Methanol
- Dichloromethane (DCM)
- Glacial Acetic Acid
- Petroleum Ether
- Distilled Water
- Aqueous Hydrochloric Acid
- Aqueous Sodium Hydroxide Solution
- Aqueous Potassium Hydroxide Solution

5.1.1 AZO DYES CONTAINING PYRAZOLE MOITIES

Synthesis of 2, 6-Diacetyl-3-(4'-chlorophenyl) diethylpentanedioate (75): A mixture of p-chloro benzaldehyde (14.05g, 0.1mol), ethyl acetoacetate (26g, 0.2 mol) in ethanol (50mL) and piperidine 0.34mL (0.004 mol) was stirred at room temperature for 3hrs. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was poured into ice-cold water. The product thus obtained, was filtered, washed with cold water, followed by pet ether to get 75. Yield: 82%, M.P. 182- 184 °C;

Scheme 3.1

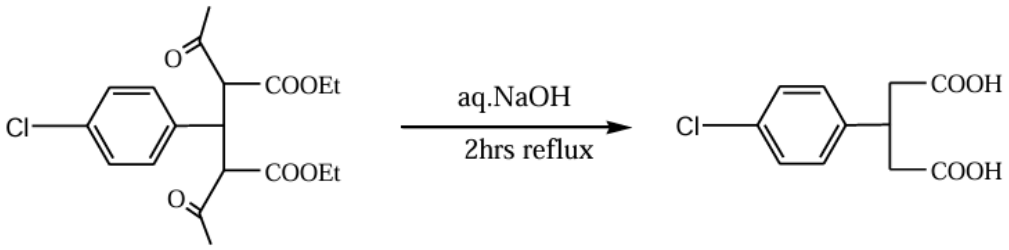


(75)

5.2.1 Synthesis of 3-(4'-chlorophenyl) pentane-1, 5-dioicacid (76):

A suspension of 75 (2.42g, 0.01 mol) and sodium hydroxide (6g, 0.15 mol) in water (20mL) was stirred at 120-140°C for 2 hrs. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was poured into ice-cold water and acidified with Conc.HCl. The solid thus obtained, was filtered, washed with cold water, followed by pet ether to get 76. Yield: 62%, M.P. 176-178 °C

Scheme 3.2

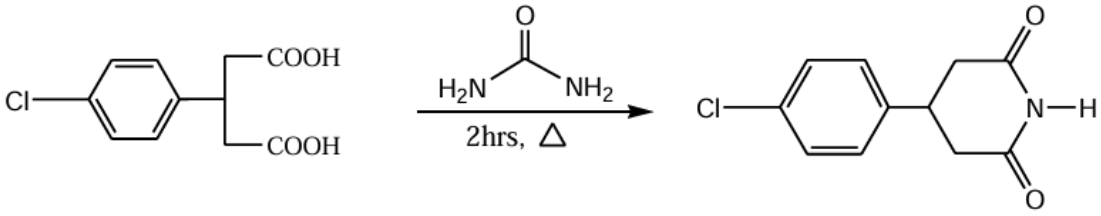


(75) **(76)**

5.3.1 Synthesis of 2, 6-Dioxo-4-(4'-chlorophenyl) piperidine (77):

Equimolar mixture of compound 76 (2.42g, 0.01mol) and urea (0.9g, 0.015mol) were heated at 120-140°C for 2-3 hrs. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was poured into cold water. The solid thus obtained, was filtered, washed and recrystallized from aqueous alcohol to get 77. Yield: 80%, m.p. 160 -163 °C.

Scheme 3.3

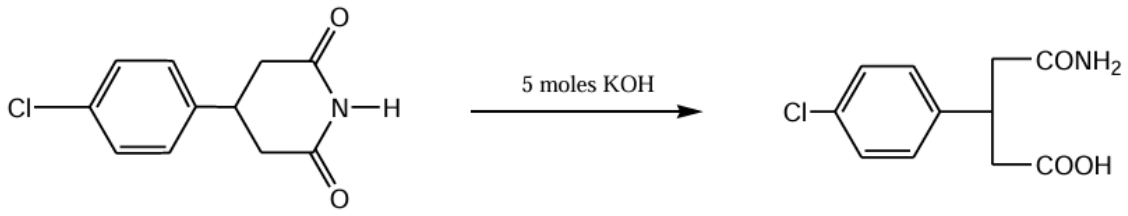


(76) **(77)**

5.4.1 Synthesis of 4-Carbamoyl-3-(4'-chlorophenyl) butyric acid (78):

Compound 77 (2.235g, 0.01mol) was mixed with aq. KOH (2g, 0.05mol in 10mL H2O) and stirred for 1hr at room temperature to obtained Clear solution; the progress of the reaction was monitored by TLC. Upon Completion, the reaction mixture was poured into ice- water. To this clear solution, dil. HCl was added drop wise till complete precipitation. The solid thus obtained, was filtered, washed thoroughly with water to obtained white solid compound 78. Yield: 88%, M.P. 206-208 °C

Scheme 3.4

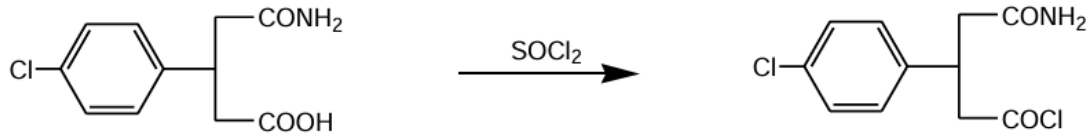


(77) **(78)**

5.5 .1 Synthesis of acyl chloride (79):

In a 150 mL round bottom flask, thionyl chloride (6g, 0.12 mol) added to a solution of 78 (12.1g, 0.1 mol) in dichloromethane (25mL). The solution was further stirred for 3hrs. The progress of reaction was monitored by TLC (by making methyl ester of acid chloride). Upon completion, solvent was removed under reduce pressure and crude product was used as such for next step.

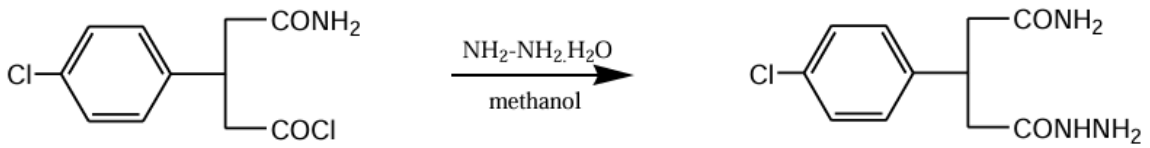
Scheme 3.5



(78) **(79)**

5.6.1 Synthesis of 3-(4'-Chlorophenyl)-4-hydrazinocarbonyl-butyramide (80): Compound 78(12.1g, 0.01mol), SOCl2 (6g, 0.01mol) and MDC (10 mL) were allowed to stirred at room temperature for 2-3 hrs to obtained compound 79. Excessive solvent was distilled out by vacuum distillation. As this product was unstable it was used in -situ to obtained compound 80 by adding hydrazine hydrate (1g, 0.02mol) in methanol and refluxed for 2 hrs. The completion of reaction was monitored by TLC. Upon the completion of reaction, the mass was poured into ice-water and the separated product was filtered and recrystallized in absolute alcohol. Yield: 85%, M.P. 250-252 °C.

Scheme 3.6

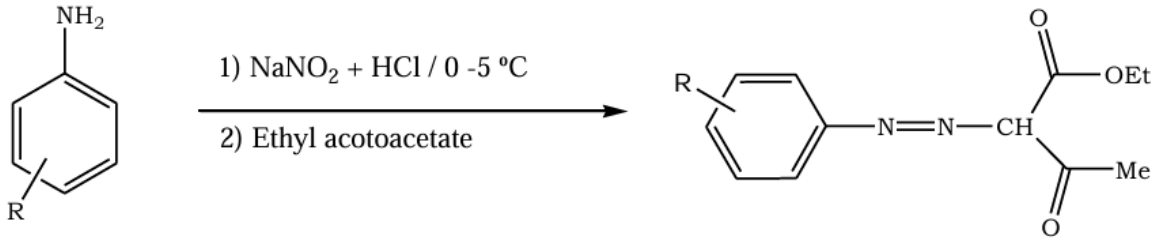


(79) **(80)**

5.7.1 Synthesis of ethyl-2-(substituted) phenylazo-3-oxobutanoate (81):

Compound (81) required for the reaction was prepared by reported procedure [73]. General Procedure: To an ice-cold solution of aromatic primary amine (0.02mol), concentrated Hydrochloric acid (8mL) and water (11mL), a cold aqueous solution of sodium nitrite (1.40g) was added in portions under ice-cold condition. The diazonium salt so formed was then filtered into an already cooled (0ºC) solution containing sodium acetate (16g, 0.196mol) and ethyl acetoacetate (2.46g, 0.02mol) in ethanol (50mL), the solution was then stirred vigorously. Separated solid was washed with water and recrystallized from ethanol to obtained 81. Under similar procedure compound 81 (a- k) were prepared and listed in table 3.1.

Scheme 3.7



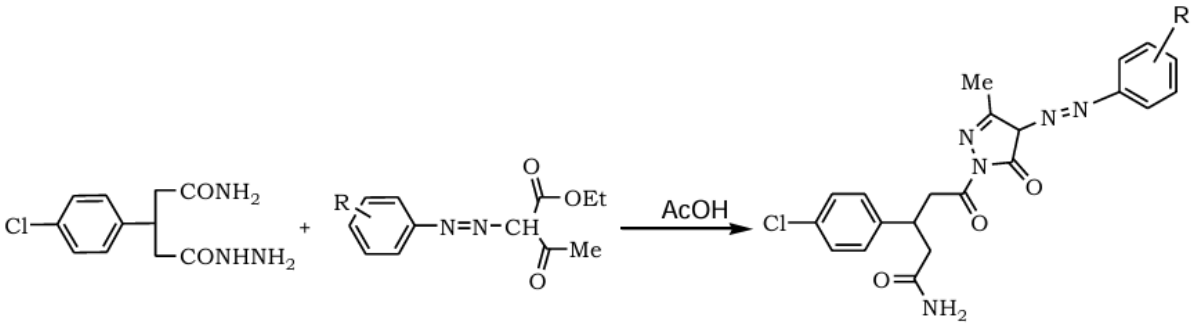
(81)

Table 3.1

Physical data of Ethyl-2-(substituted) phenylazo-3-oxobutanoate (81)

Compds (81)	R	MF	MW	M.P (°C)	% Yield	
					Lit[73]	Obt.
a	4-H	$C_{12}H_{14}N_2O_3$	234	58-60	70	69
b	4-Cl	$C_{12}H_{13}N_2O_3Cl$	268.5	45-46	71	72
c	4-NO_2	$C_{12}H_{13}N_3O_5$	279	75-76	70	75
d	4-CH_3	$C_{13}H_{16}N_2O_3$	248	50-52	72	75
e	4-Br	$C_{12}H_{13}N_2O_3Br$	313	40-42	64	72
f	2-NO_2	$C_{12}H_{13}N_3O_5$	279	43-45	66	70
g	2-Cl	$C_{12}H_{13}N_2O_3Cl$	268.5	32-33	68	68
h	2-CH_3	$C_{13}H_{16}N_2O_3$	248	30-32	65	65
i	3-CH_3	$C_{13}H_{16}N_2O_3$	248	31-33	68	68
j	3-NO_2	$C_{12}H_{13}N_3O_5$	279	90-91	68	66
k	4-OCH_3	$C_{13}H_{16}N_2O_4$	264	42-44	75	76

General Scheme:

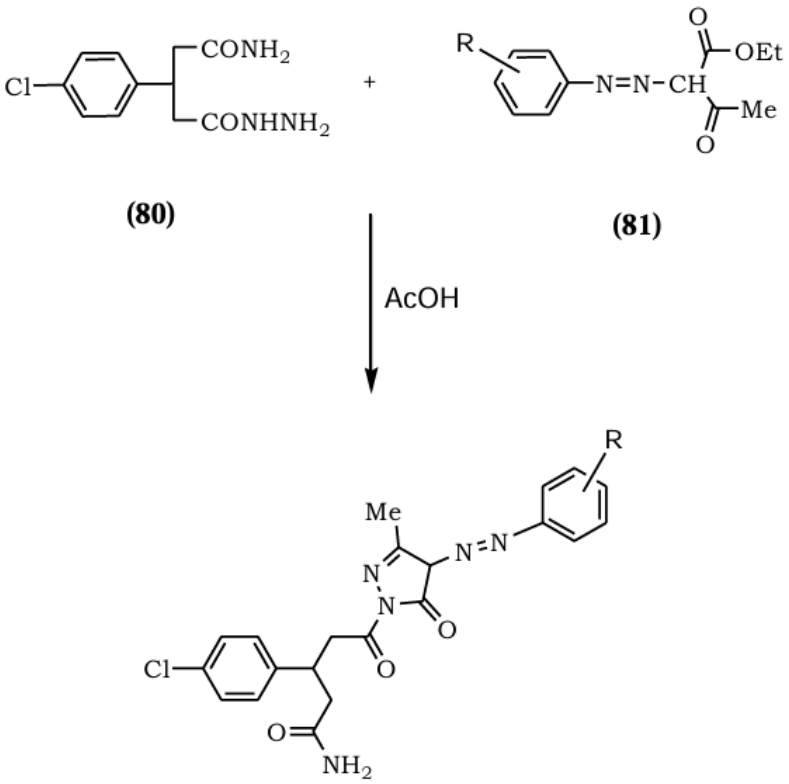


(80) **(81)** **(82)**

5.8.1 Representative Procedure:

Synthesis of 3-(4'-Chloro-phenyl)-5-(3-methyl-5-oxo-4-p-tolylazo-4,5 dihydro-pyrazol-1-yl)-5-oxo-pentanoic acid amide (82 a) Equal mole of compound 80 (2.55g, 0.01mol) and compound 81 (0.01mol) in glacial acetic acid (8 mL) were refluxed in a round bottom flask for 2-3 hrs. After completion of the reaction monitored by TLC the reaction mixture was quenched onto crushed ice; the separated solid mass was filtered, washed with water and recrystallized with ethanol to obtain the desired compound 82a. Under similar conditions 82b-k were prepared & listed in table-3.2.

Scheme 3.8



(80) **(81)**

(82)

Table 3.2

Physical data of 3-[4'-chlorophenyl-5-{(substituted)-phenylazo)-3-methyl-5-oxo-4, 5-dihydro-pyrazol-1-yl}]-5-oxo-pentanoic acid amide (82)

Compds (82)	R	MF	MW	MP (°C)	% Yield	Color
a	4-H	$C_{21}H_{20}ClN_5O_3$	425.5	276-78	73	Yellow
b	4-Cl	$C_{21}H_{19}Cl_2N_5O_3$	460	280-82	78	Yellow
c	4-NO_2	$C_{21}H_{19}ClN_6O_5$	470.5	274-76	77	Dark Yellow
d	4-CH_3	$C_{22}H_{22}ClN_5O_3$	439.5	254-56	79	Orange
e	4-Br	$C_{21}H_{19}BrClN_5O_3$	504.5	290-92	72	Yellow
f	2-NO_2	$C_{21}H_{19}ClN_6O_5$	470.5	236-38	62	Yellow
g	2-Cl	$C_{21}H_{19}Cl_2N_5O_3$	460	256-58	63	Yellow
h	2-CH_3	$C_{22}H_{22}ClN_5O_3$	439.5	244-46	66	Orange
i	3-CH_3	$C_{22}H_{22}ClN_5O_3$	439.5	255-57	69	Orange
j	3-NO_2	$C_{21}H_{19}ClN_6O_5$	470.5	264-96	69	Yellow
k	4-OCH_3	$C_{22}H_{22}ClN_5O_4$	455.5	297-99	79	Orange

5.9.1 Analysis of compound (82a)

Yellow compound obtained was found to have the molecular composition C21H20N5O3Cl showed the following results on elemental analysis. Elemental analysis of the compound (82a).

5.10.1 Synthesis [4-(5,6-Dimethoxy-1-oxo-indan-2-yl-methyl)-piperidin-1-yl] acetic acid ethyl ester (84):

Equimolar mixture of 83 (7.2g, 0.025 mol), tri ethyl amine (2.525g, 0.025 mol) and Ethyl bromoacetate (4.175g, 0.025mol), in dichloromethane (100mL) was Stirred for 2 hrs, the progress of the reaction was monitored by TLC, upon completion, the content was poured into cold water. The separated organic layer was washed with water to yield 84. Yield = 68 %, B.P =215-218 °C.

Molecular Formula	Elemental analysis Calc./ Found		
	C	H	N
$C_{21}H_{20}ClN_5O_3$	59.22	4.21	16.45
	59.61	4.33	16.23

5.11.1 Spectral Characteristic data of 3-[4'-chlorophenyl-5-{(phenylazo)-3-methyl 5-oxo-4, 5-dihydro-pyrazol-1-yl}]-5-oxo-pentanoic acid amide (82 a)

IR spectra: Fig. 3.1

IR (cm-1): 3341, 3102 (NH2), 1660 (C=O); 1100 (C-N); 700-750 1H NMR interpretation: Fig. 3.2

1H NMR (δ ppm): 2.20 (s, 3H, CH3), 2.44 (d, 2H, CH2), 2.54 (d, 2H, CH2), 3.36 (m, 1H, CH), 4.96 (s, 1H, CH), 5.96 (s, 2H, NH2), 6.89 – 7.40 (m, 9H, ArH) 13C NMR interpretation:

Fig. 3.3 13C NMR (δ ppm): 20.02 (CH3), 28.46 (CH), 38.60 (CH2), 42.75 (CH2), 65.53 (CH), 120.15-140.36 (ArC),156.23(C=N), 170.20 (C=O), 174.25 (C=O), 176.85(C=O).

Mass interpretation: Fig. 3.4 m/e: M+ 425.5

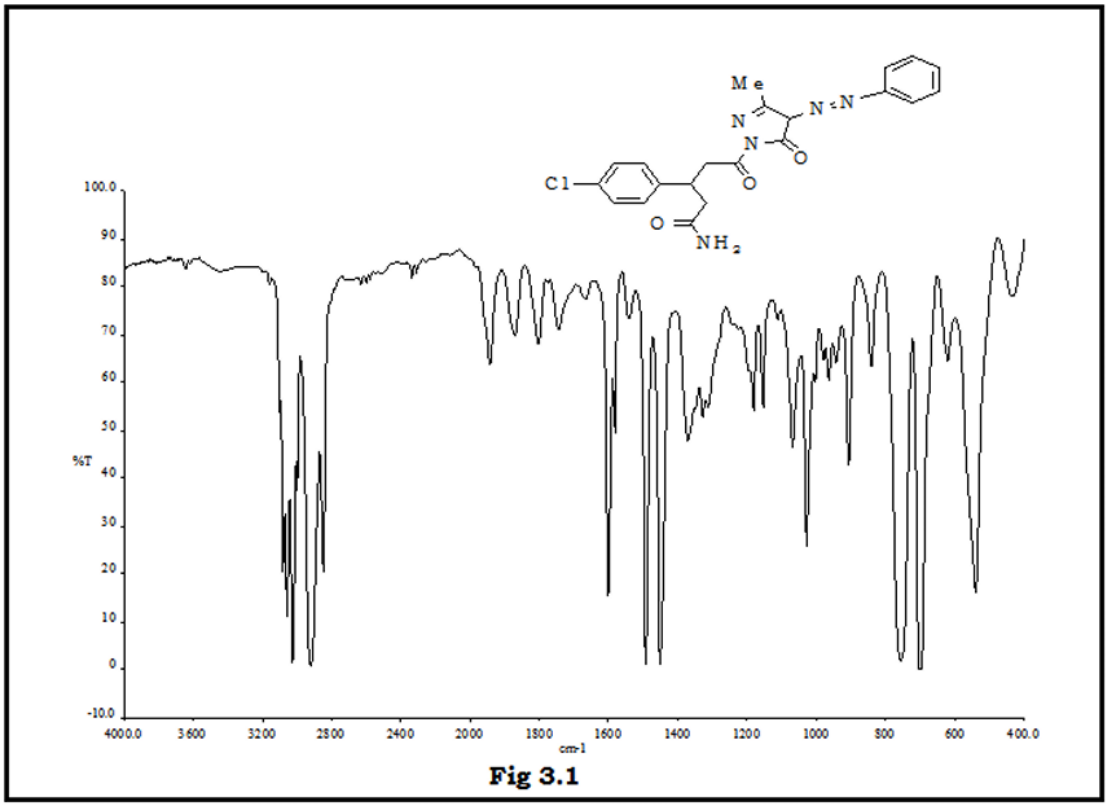

Me
N
N
N
N
O
O
Cl
O
NH2
100.0
90
80
70
60
50
%T
40
30
20
10
0
-10.0
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400.0
cm-1

Fig 3.1

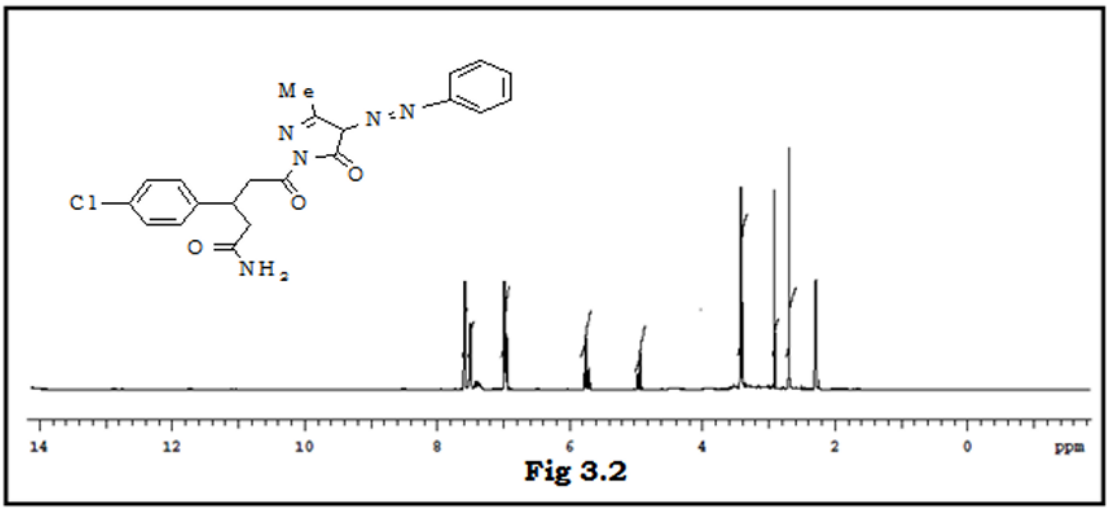

Me
N
N
N
N
O
O
Cl
O
NH2
14
12
10
8
6
4
2
0
ppm

Fig 3.2

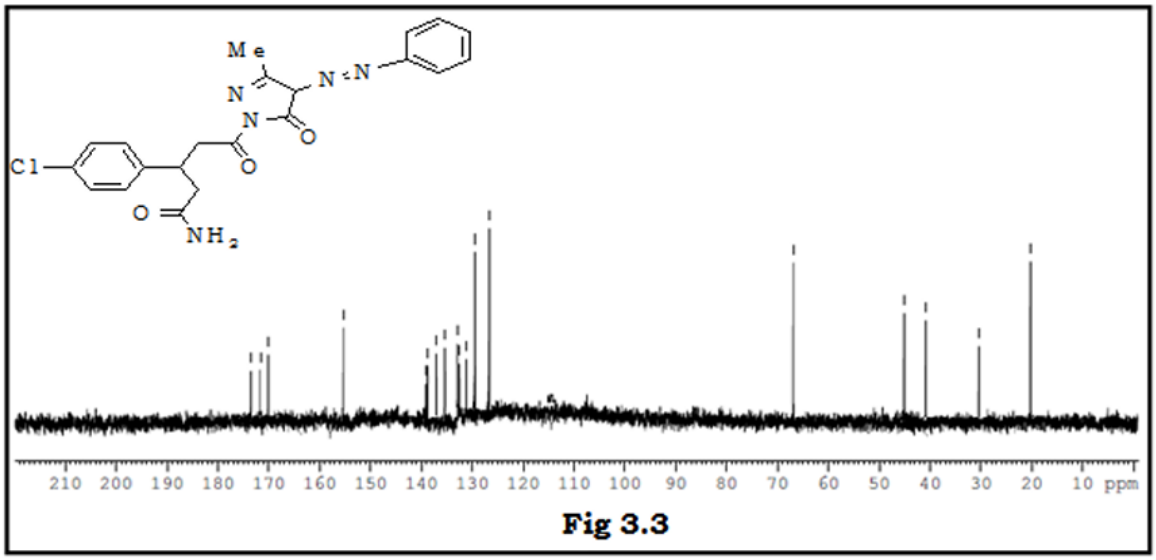


Fig 3.3

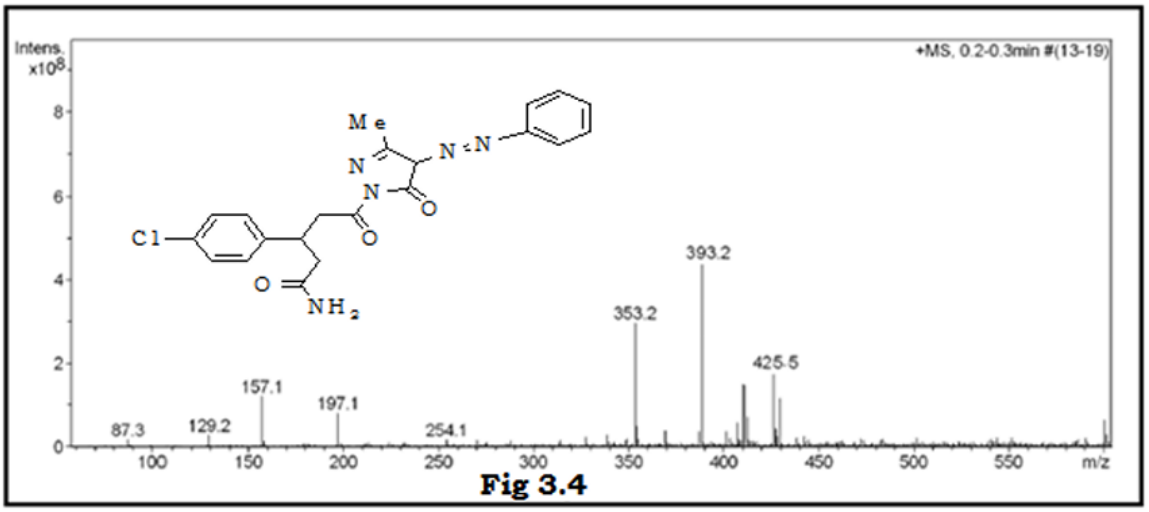


Fig 3.4

5.12.1 Analysis of compound (82d)

Yellow compound obtained was found to have the molecular composition C22H22ClN5O3 showed the following results on elemental analysis.

Elemental analysis of the compound (82d)

Molecular Formula	Elemental analysis Calc./ Found		
	C	H	N
$C_{22}H_{22}ClN_5O_3$	60.06	5.00	15.92
	59.76	4.90	15.02

5.13 Spectral Characteristic data of 3-(4'-Chloro-phenyl)-5-(3-methyl-5-oxo-4-p tolylazo-4, 5-dihydro-pyrazol-1-yl)-5-oxo-pentanoic acid amide (82 d)

IR spectra: Fig. 3.5

IR (cm-1): 3284, 3202 (NH2), 1650 (C=O), 1100 (C-N), 800. 1H NMR interpretation: Fig. 3.6

1H NMR (δ ppm): 2.14 (s, 3H, CH3), 2.35 (s, 3H, CH3), 2.45 (d, 2H, CH2), 2.65 (d, 2H, CH2), 3.26 (m, 1H, CH), 5.10 (s, 1H, CH), 6.05 (s, 2H, NH2), 7.07 – 7.72 (m, 8H, ArH) 13C NMR interpretationFig. 3.7

13C NMR (δ ppm): 19.45 (CH3), 21.20 (CH3), 30.46 (CH), 39.81 (CH2), 43.81 (CH2), 67.83 (CH), 122.26-147.65 (ArC), 157.35 (C=N), 171.33 (C=O), 175.75 (C=O), 176.47(C=O). Mass interpretation: Fig. 3.8

m/e: M+ 439.5

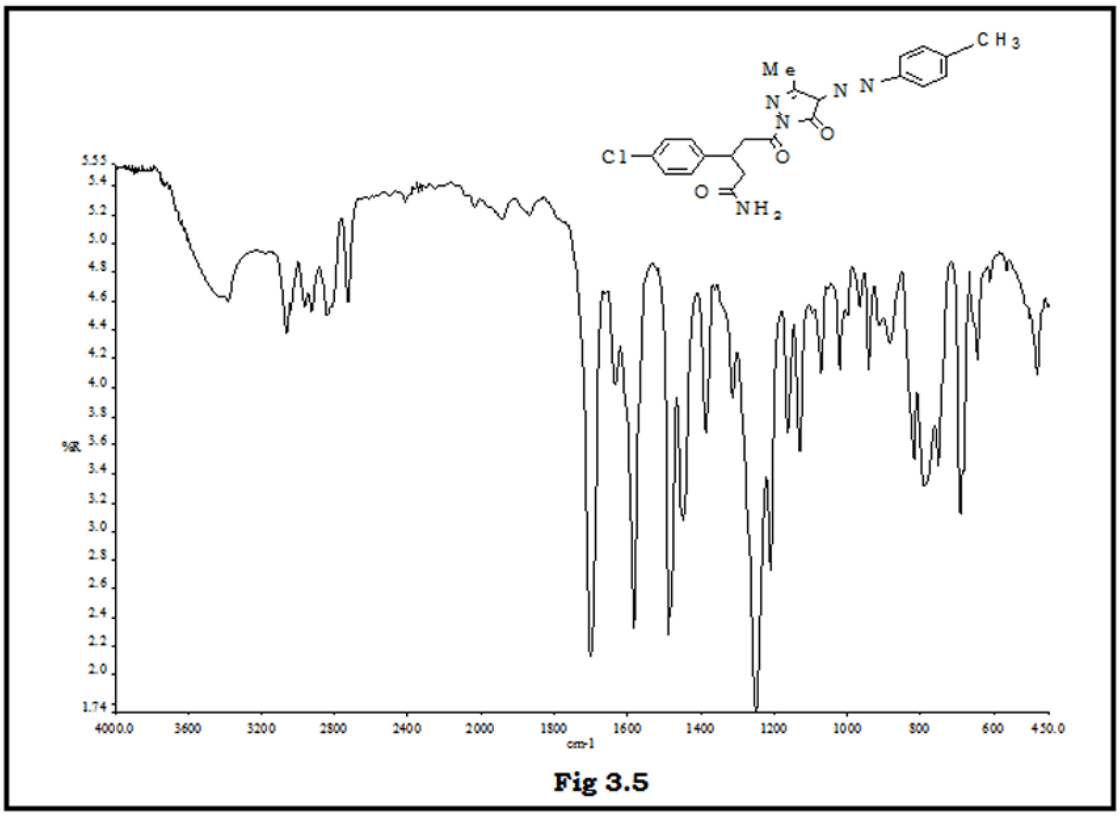


Fig 3.5

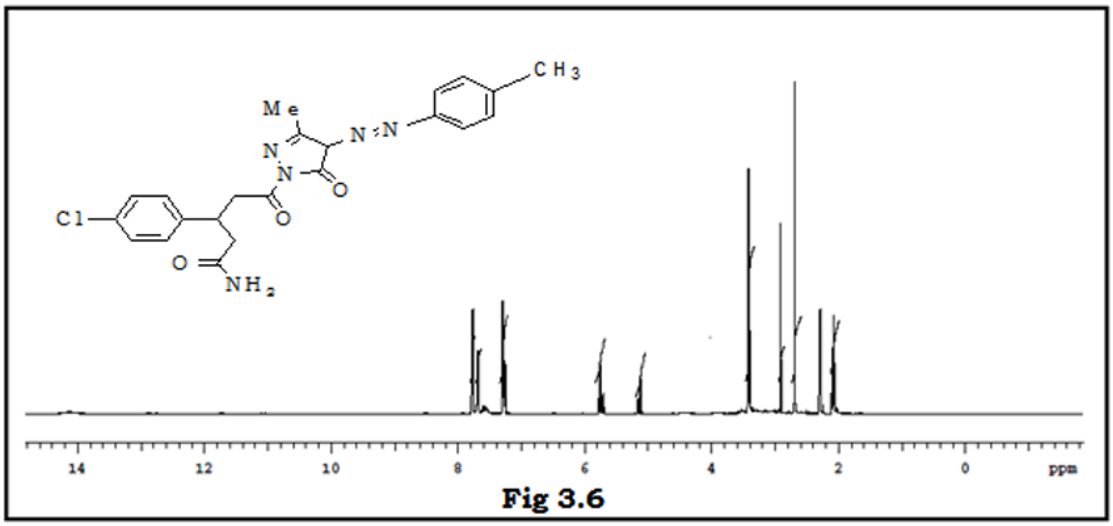


Fig 3.6

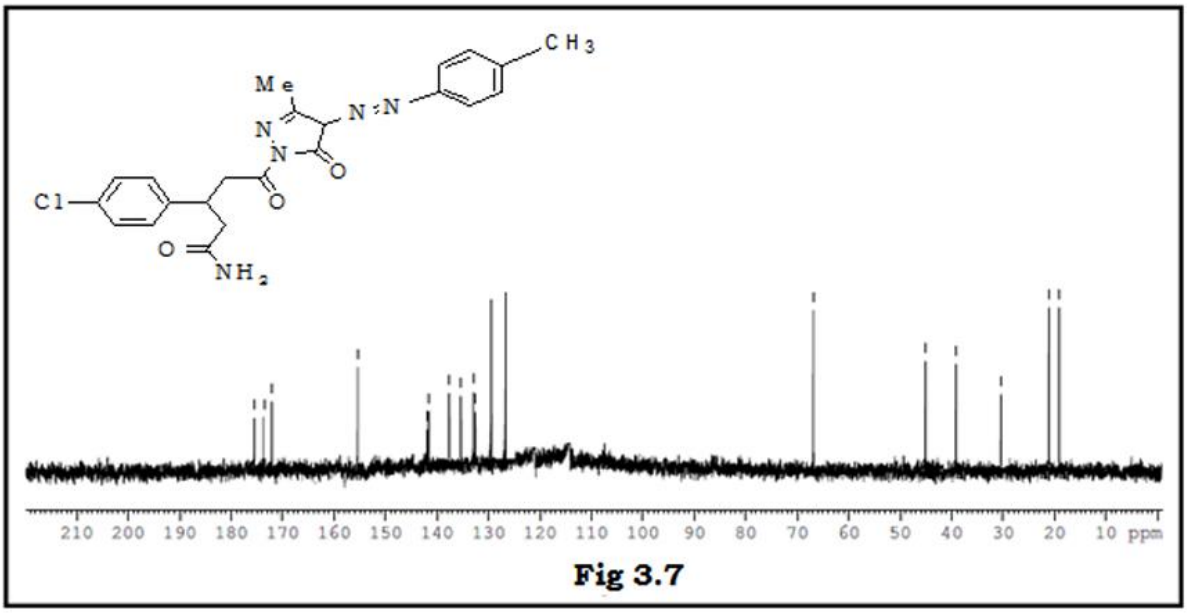

CH3
Me
N
N
N
N
O
Cl
O
O
NH2
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

Fig 3.7

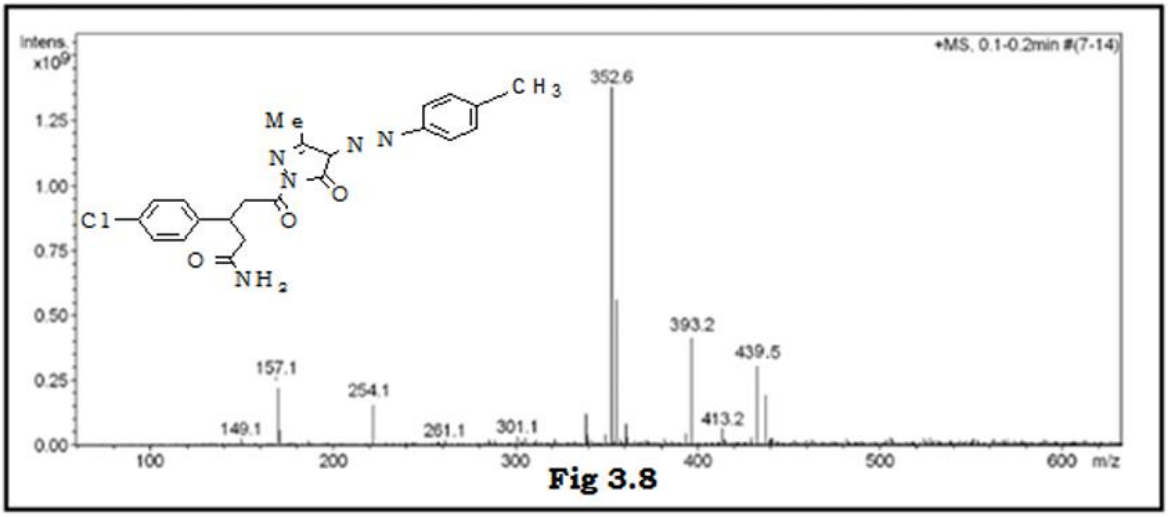

Intens.
x10^9
+MS, 0.1-0.2min #(7-14)
352.6
CH3
Me
N
N
N
N
O
Cl
O
O
NH2
393.2
439.5
157.1
254.1
149.1
261.1
301.1
413.2
1.25
1.00
0.75
0.50
0.25
0.00
100
200
300
400
500
600
m/z

Fig 3.8

5.14.1 Analysis of compound (82k)

Orange compound obtained was found to have the molecular composition C22H22ClN5O4 showed the following results on elemental analysis. Elemental analysis of the compound (82k)

Molecular Formula	Elemental analysis Calc./ Found		
	C	H	N
$C_{22}H_{22}ClN_5O_4$	57.95	4.82	15.36
	57.76	4.50	14.72

5.15.1 Spectral Characteristic data of 3-(4'-Chloro-phenyl)-5-[4-(4-methoxy phenylazo)-3-methyl-5-oxo-4, 5-dihydro-pyrazol-1-yl]-5-oxo-pentanoic acid amide (82 k)

IR spectra: Fig. 3.9 IR (cm-1): 3284, 3223 (NH2), 1689 (C=O), 1120 (C-N), 800. 1H NMR interpretation: Fig. 3.10

1H NMR (δ ppm): 2.24 (s, 3H, CH3), 2.45 (d, 2H, CH2), 2.65 (d, 2H, CH2), 3.24 (m, 1H, CH), 3.56 (s, 3H, OCH3), 5.14 (s, 1H, CH), 6.15 (s, 2H, NH2), 7.07 – 7.80 (m, 8H, ArH). 13C NMR interpretation: Fig. 3.11

13C NMR (δ ppm): 21.46 (CH3), 29.26 (CH), 39.56 (CH3), 40.81 (CH2), 43.98 (CH2), 67.86 (CH), 123.25-148.23 (ArC), 156.13 (C=N), 172.33 (C=O), 176.75 (C=O), 176.87(C=O)

Mass interpretation: Fig. 3.12

m/e: M+ 455.5

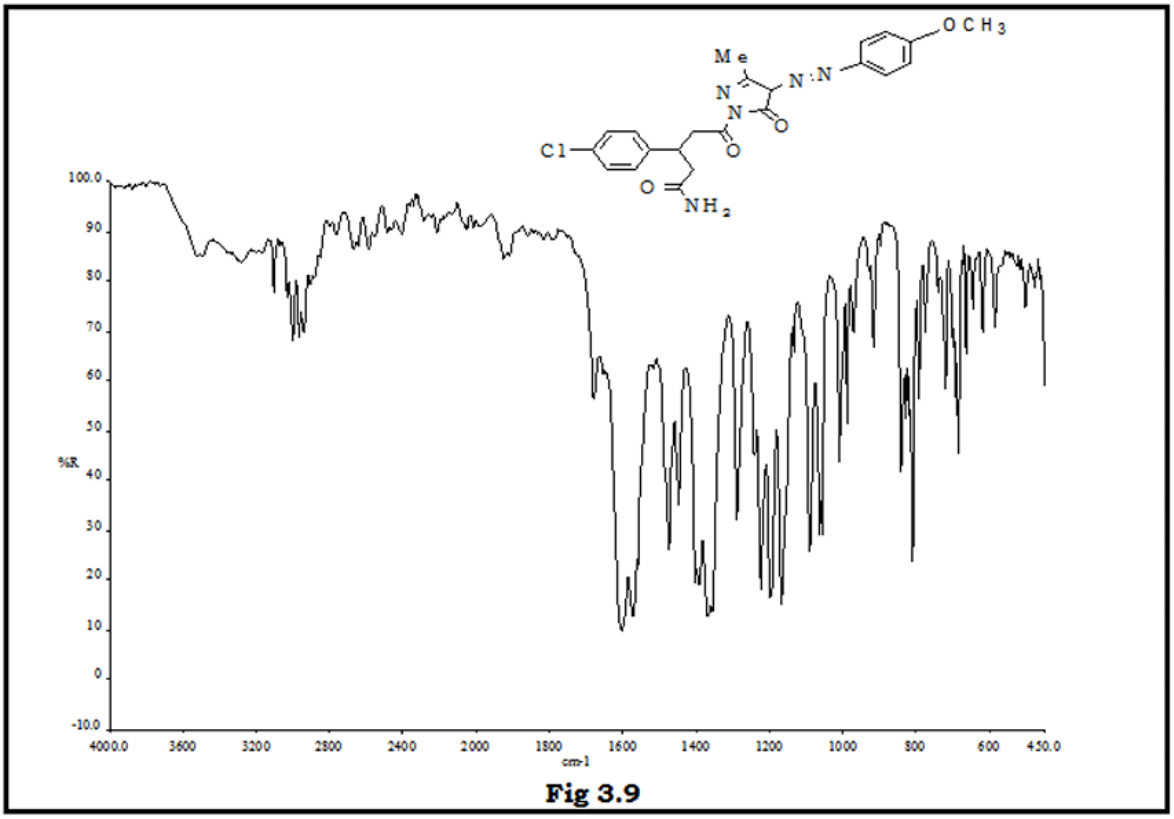


Fig 3.9

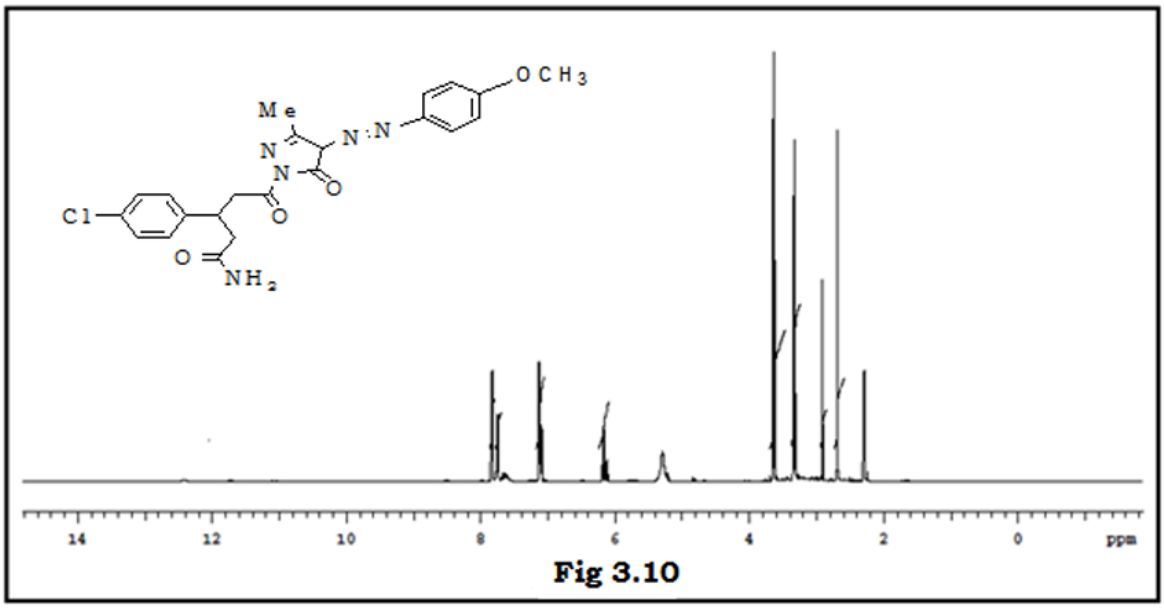


Fig 3.10

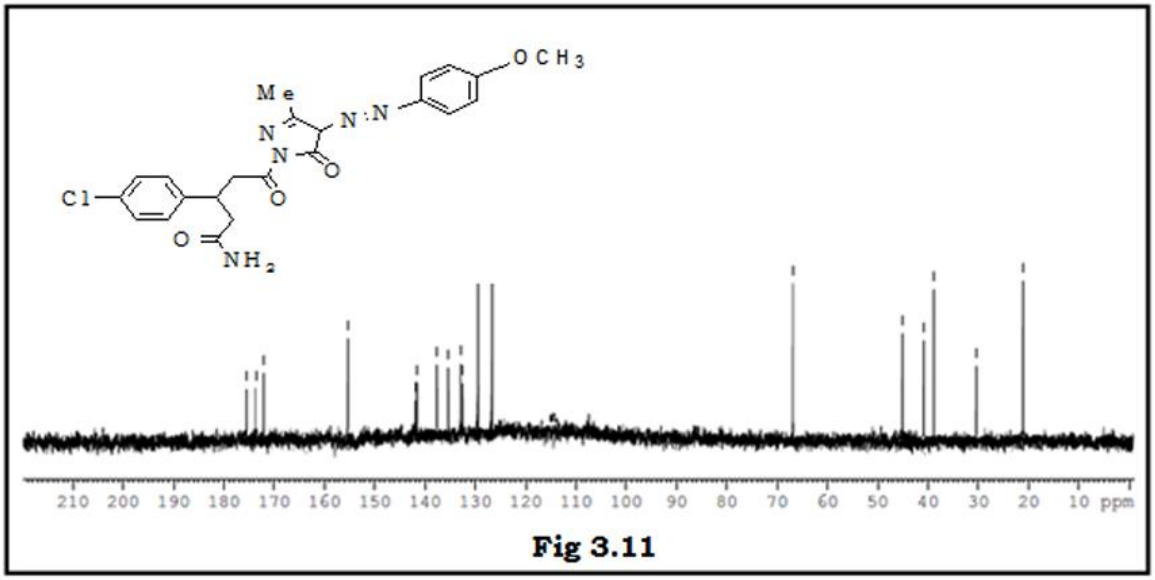


Fig 3.11

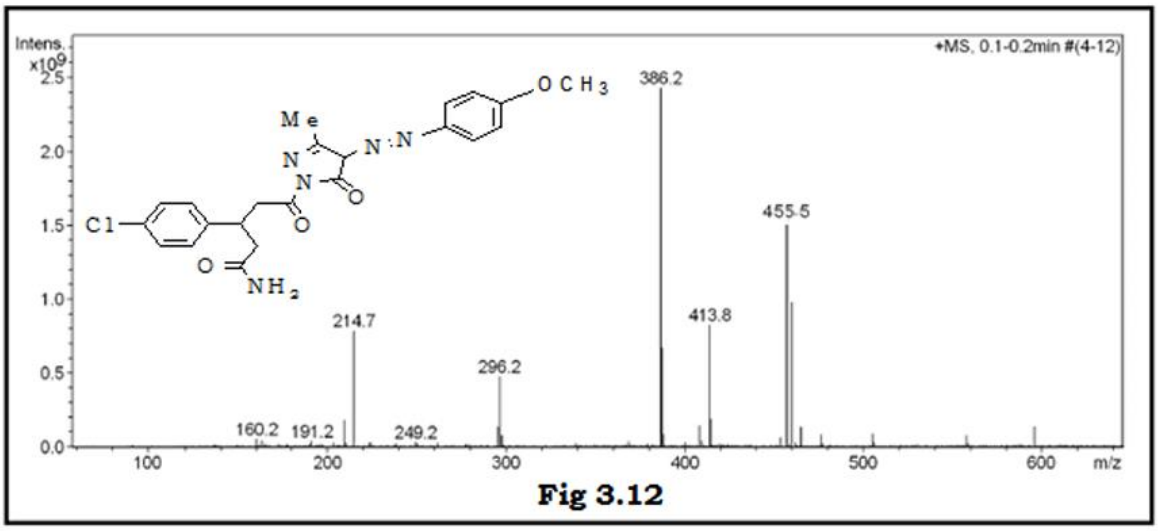


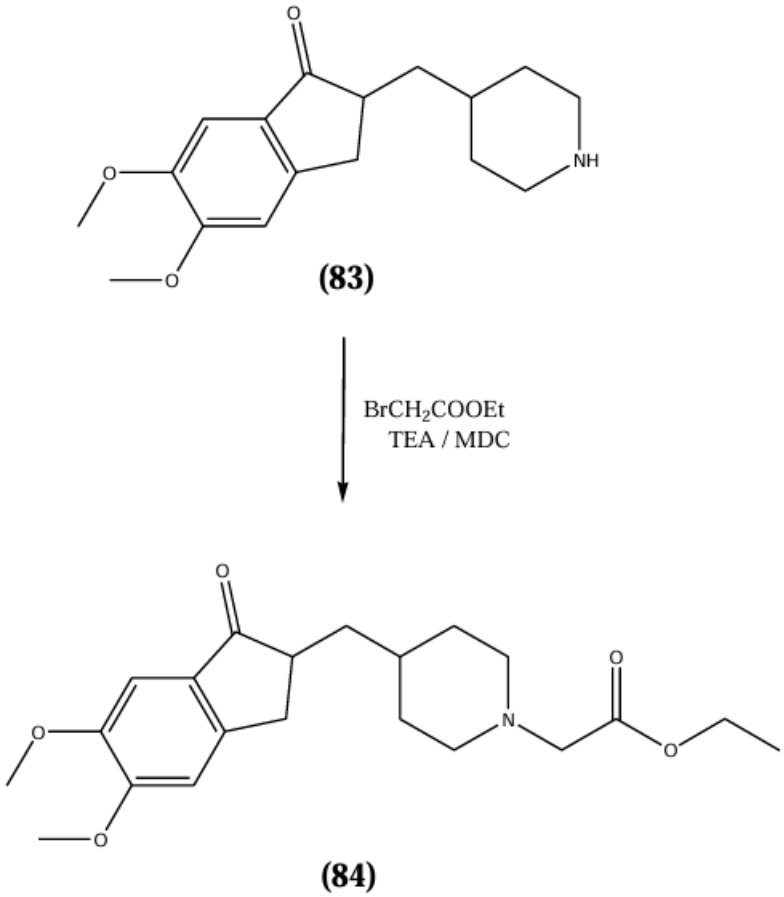
Fig 3.12

6.1 FORMATION OF AZO DYES

6.2 Synthesis [4-(5,6-Dimethoxy-1-oxo-indan-2-yl-methyl)-piperidin-1-yl] acetic acid ethyl ester (84):

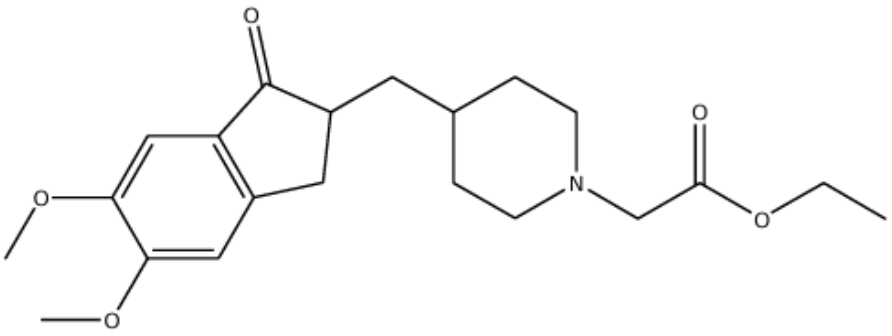
Equimolar mixture of 83 (7.2g, 0.025 mol), tri ethyl amine (2.525g, 0.025 mol) and Ethyl bromoacetate (4.175g, 0.025mol), in dichloromethane (100mL) was Stirred for 2 hrs, the progress of the reaction was monitored by TLC, upon completion, the content was poured into cold water. The separated organic layer was washed with water to yield 84. Yield = 68 %, B.P =215-218 °C.

Scheme 4.1

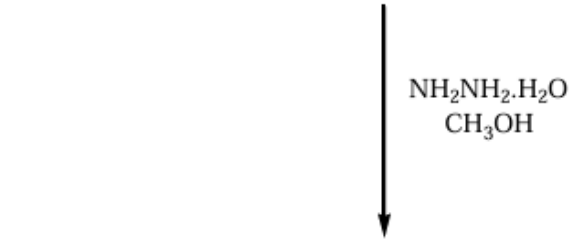


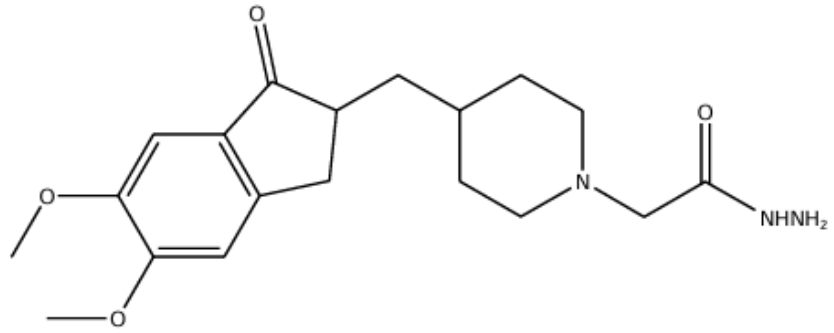
6.3 Synthesis of [4-(5, 6-Dimethoxy-1-oxo-indan-2-yl-methyl)-piperidin-1-yl] acetic acid hydrazide (85):

A mixture of 84 (9.375g, 0.025 mol) and hydrazine hydrate (1.75g, 0.035 mol) in methanol (25mL) was refluxed for 6- 7 hrs. The progress of reaction was monitored by TLC, upon completion, the reaction mass was cooled to 0 to 5 ºC. Yellow color solid thus obtained, was filtered and washed with cold methanol to yield 85. Yield = 78%, M.P = >300 °C



(84)

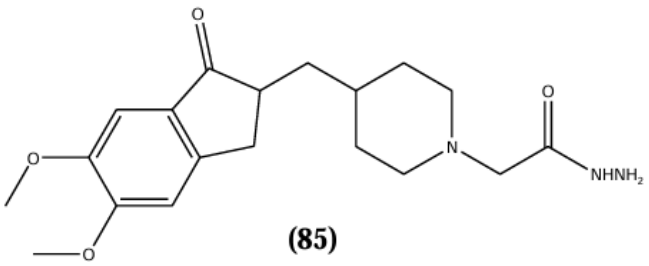




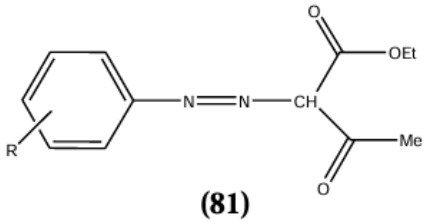
(85)

6.4 Synthesis of 2-{2-[4'-(5,6-Dimethoxy-1-oxo-indan-2-ylmethyl)-piperidin-1 yl]-acetyl} -4-(substituted phenylazo) -5-methyl -2,4-dihydro-pyrazol-3-one (86) General procedure: Equimolar mixture of compound 85 (9.025g, 0.025mol) and compound 81 (1mol) in glacial acetic acid (8 mL) were refluxed in a round bottom flask for 2-3 hrs, the reaction was monitored by TLC, after completion the reaction mixture was quenched onto crushed ice, the separated solid mass was filtered, washed with water and recrystallized with ethanol to give the desired compound 86 Under similar conditions (86a-k) were prepared & listed in table-4.1

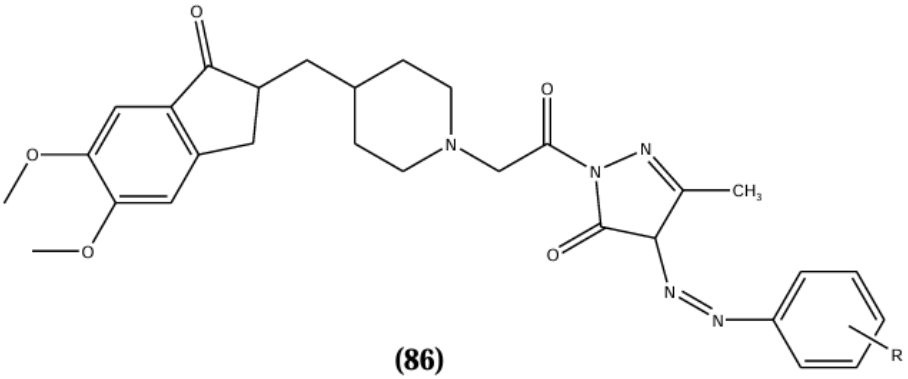
Scheme 4.3



(85)



(81)



(86)

Table-4.1

Physical data of 2-{2-[4'-(5, 6-Dimethoxy-1-oxo-indan-2-ylmethyl)-piperidin-1-yl]-acetyl}-5-methyl-4-(substtitutedphenylazo)-2, 4-dihydro-pyrazol-3-one (86 a-k)

Compds (86)	R	MF	MW	MP (°C)	% Yield
a	4-H	$C_{29}H_{33}N_5O_5$	531	264-66	68
b	4-Cl	$C_{29}H_{32}ClN_5O_5$	566.5	270-72	71
c	4-NO_2	$C_{29}H_{32}N_6O_7$	576	>300	70
d	4-CH_3	$C_{30}H_{35}N_5O_5$	545	268-70	69
e	4-Br	$C_{29}H_{32}BrN_5O_5$	610	295-97	65
f	2-NO_2	$C_{29}H_{32}N_6O_7$	576	280-80	66
g	2-Cl	$C_{29}H_{32}ClN_5O_5$	566.5	266-269	67
h	2-CH_3	$C_{30}H_{33}N_5O_5$	545	253-257	63
i	3-CH_3	$C_{30}H_{35}N_5O_5$	545	256-58	68
j	3-NO_2	$C_{29}H_{32}N_6O_7$	576	285-87	65
k	4-OCH_3	$C_{30}H_{35}N_5O_6$	561	279-81	72

6.5 Analysis of compound (86a)

Yellow compound obtained was found to have the molecular composition C29H33N5O5 showed the following results on elemental analysis.

Elemental analysis of the compound (86a)

Molecular Formula	Elemental analysis Calc./ Found		
	C	H	N
$C_{29}H_{33}N_5O_5$	65.54	6.21	13.18
	65.52	6.13	14.08

6.6 Spectral Characteristic data of 2-{2-[4-(5, 6-Dimethoxy-1-oxo-indan-2-ylmethyl) piperidin-1-yl]-acetyl}-5-methyl-4-(phenylazo)-2, 4-dihydro-pyrazol-3-one (86 a) IR spectra: Fig. 4.1

IR (cm-1): 3282 (NH), 1710, 1680 (C=O), 1170 (C-O), 690-750 1H NMR interpretation: Fig. 4.2

1H NMR (δ ppm): 1.23 (m, 4H, 2XCH2), 1.49 (m, 1H, CH), 2.15(m, 1H,CH), 2.19 (s, 3H,CH3), 2.28 (d, 2H,CH2), 2.44 (t, 2H, CH2), 2.70 (t, 4H, 2XCH2), 3.73 (s, 6H, 2X OCH3), 3.90 (s, 2H, CH2), 4.46 (s, 1H, CH), 7.23 – 7.60 (m, 7H, ArH) 13C NMR interpretation: Fig. 4.3

13C NMR (δ ppm): 13.6 (CH3), 20.9 (CH3), 28.8(CH), 29.3 (CH2), 30.6 (2 x CH2), 32.9 (CH2), 48.6 (CH), 50.5 (CH), 51.9 (CH2), 58.6 (2 x OCH3), 60.5 (CH2), 110.15-151.36 (ArC),156 (C=N), 163 (C=O), 174.25 (C=O), 200.53(C=O).

Mass interpretation: Fig. 4.4

m/e: M+ 531

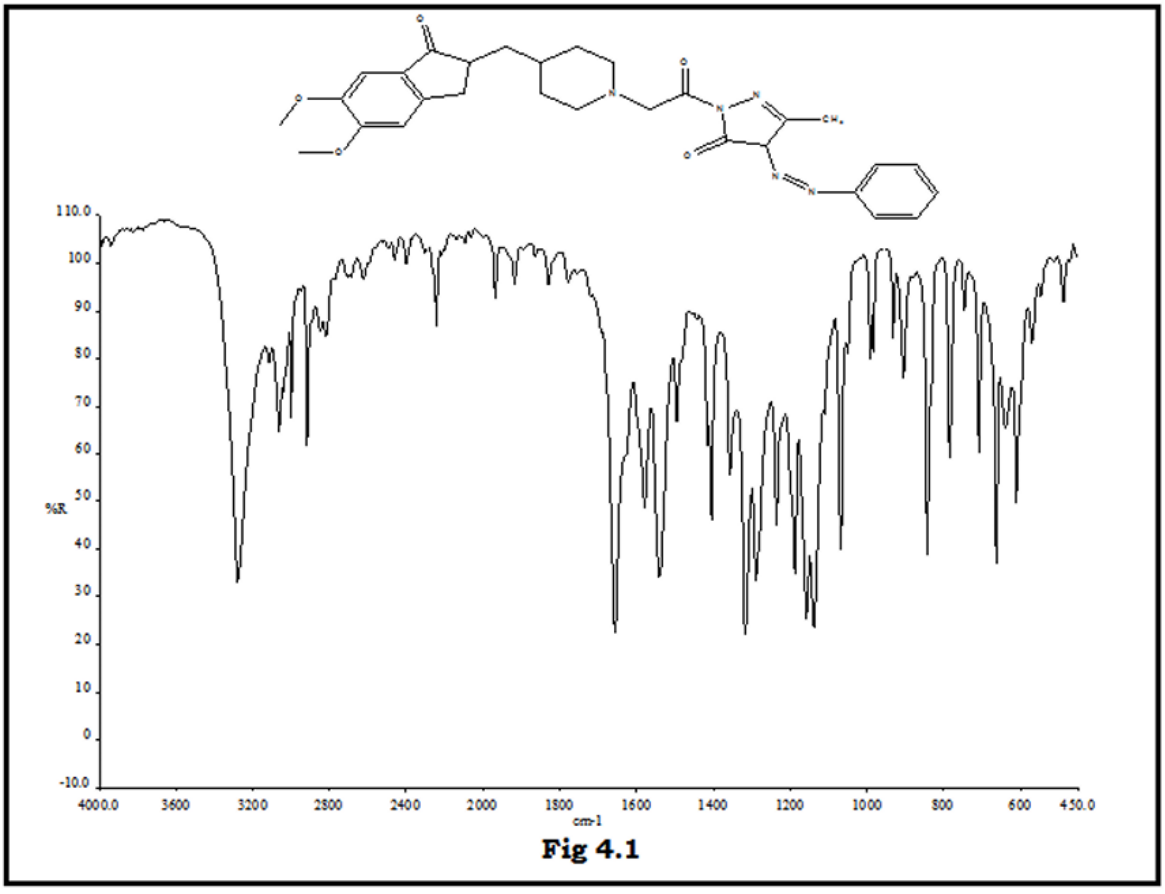


Fig 4.1

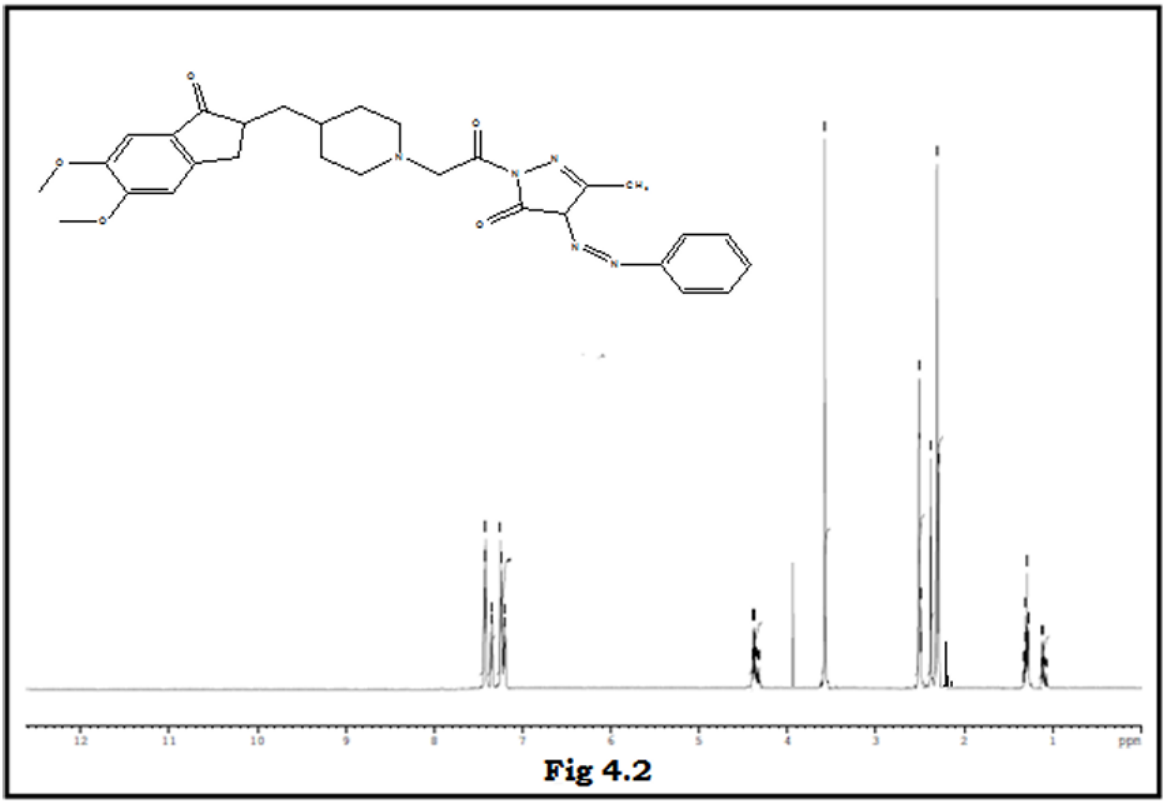

12
11
10
9
8
7
6
5
4
3
2
1
ppm

Fig 4.2

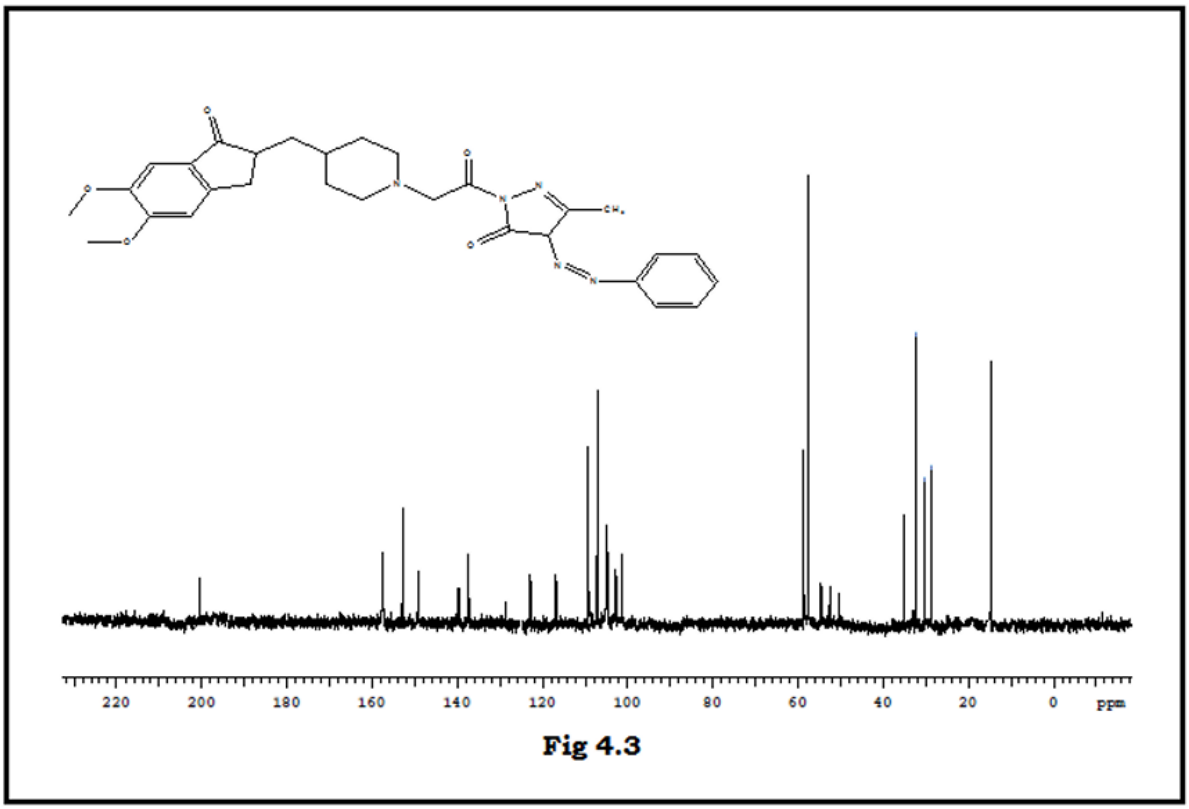

220
200
180
160
140
120
100
80
60
40
20
0
ppm

Fig 4.3

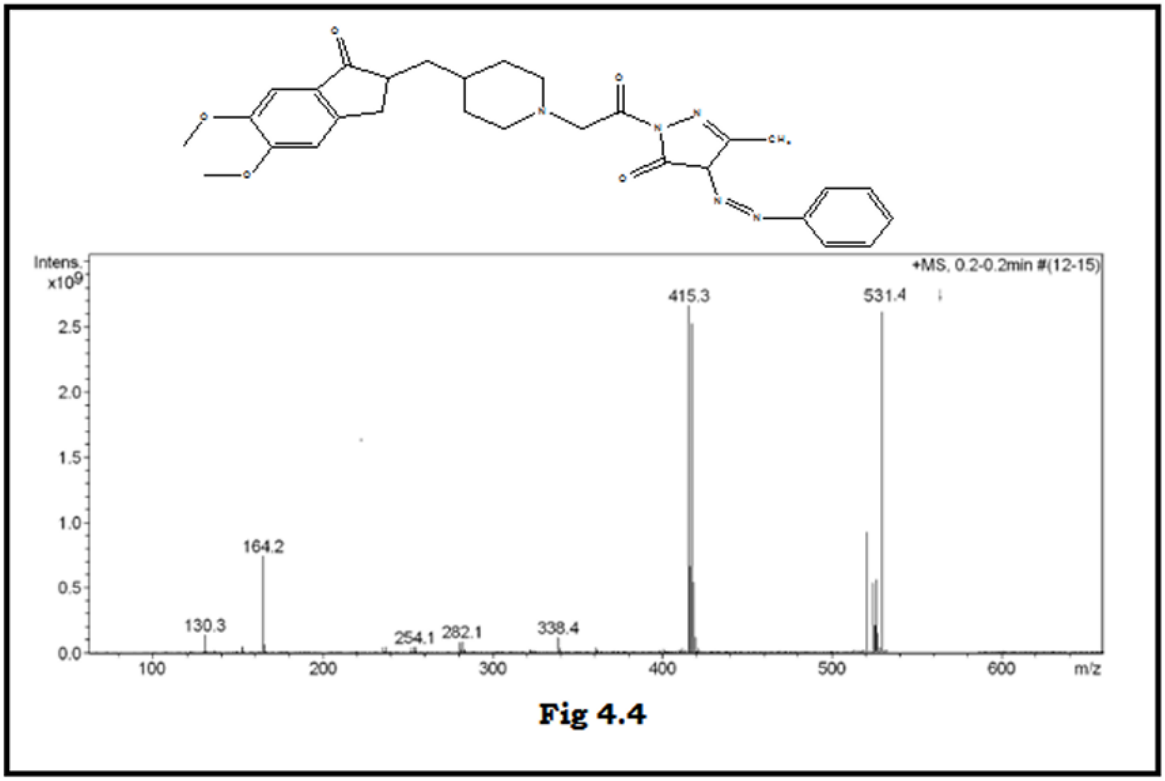


Fig 4.4

6.7 Analysis of compound (86d)

Yellow compound obtained was found to have the molecular composition C30H35N5O5 showed the following results on elemental analysis.

Elemental analysis of the compound (86d)

Molecular Formula	Elemental analysis Calc./ Found		
	C	H	N
$C_{30}H_{35}N_5O_5$	66.06	6.42	12.84
	66.72	6.23	13.25

6.8 Spectral Characteristic data of 2-{2-[4-(5, 6-Dimethoxy-1-oxo-indan-2-ylmethyl) piperidin-1-yl]-acetyl}-4-(4'-methylphenylazo) -5-methyl -2,4-dihydro-pyrazol-3 one (86 d) IR spectra: Fig. 4.5

IR (cm-1): 3221 (NH), 1705, 1678 (C=O); 1080 (C-O); 680-800 1H NMR interpretation: Fig. 4.6

1H NMR (δ ppm): 1.28 (m, 4H, 2XCH2), 1.51 (m, 1H, CH), 2.18(m, 1H, CH), 2.23 (s, 3H, CH3), 2.26(s, 3H, CH3), 2.30 (d, 2H, CH2), 2.45 (t, 2H, CH2), 2.78 (t, 4H, 2XCH2), 3.75 (s, 6H, 2X-OCH3), 3.96 (s, 2H, CH2), 5.23 (s, 1H, CH), 7.31 – 7.63 (m, 6H, ArH) 13C NMR interpretation: Fig. 4.7

13C NMR (δ ppm): 14.6 (CH3), 29.8(CH), 30.3 (CH2), 30.9 (2 x CH2), 32.65 (CH2), 48.6 (CH), 50.5 (CH), 51.8 (CH2), 58.6 (2 x OCH3), 60.3 (CH2), 110.20-150.46 (ArC),158 (C=N), 165 (C=O), 171.98 (C=O), 201.02(C=O).

Mass interpretation: Fig. 4.8

m/e: M+ 545

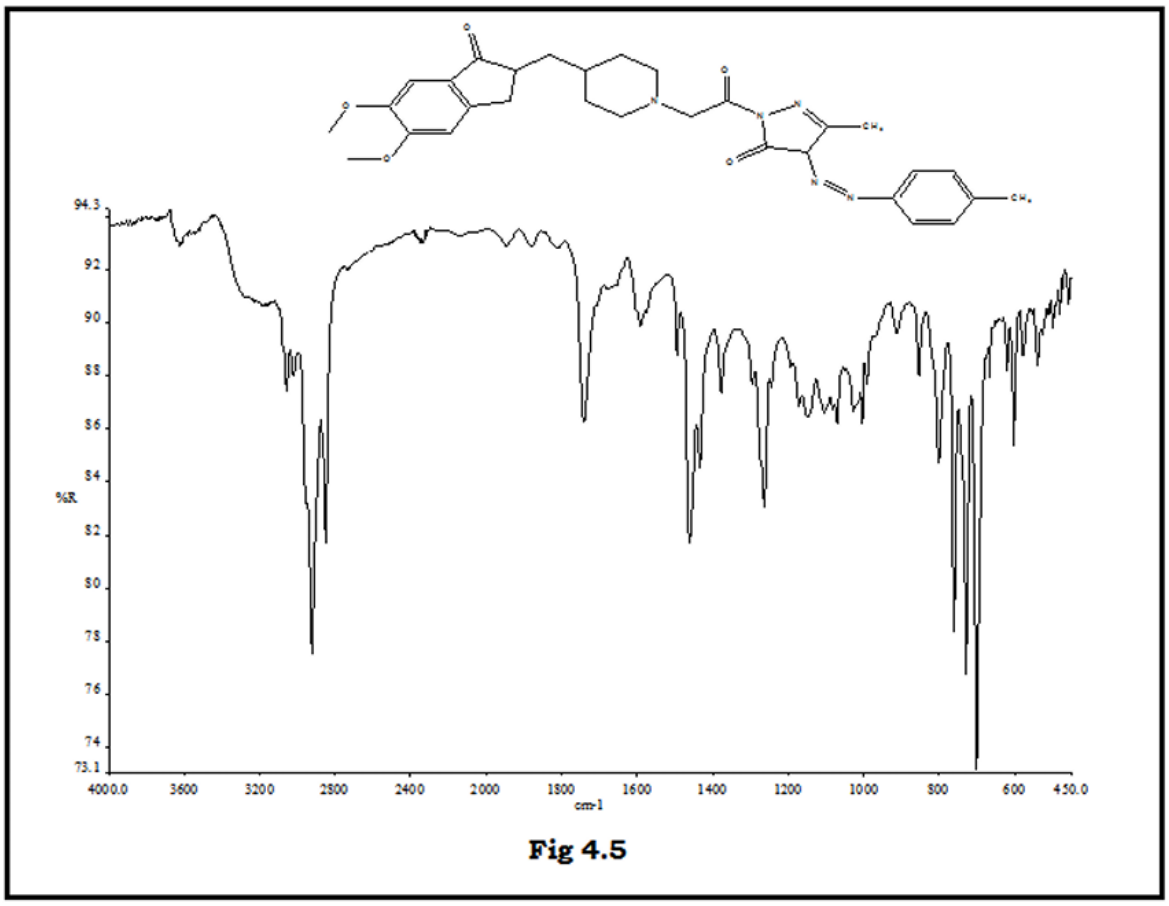


Fig 4.5

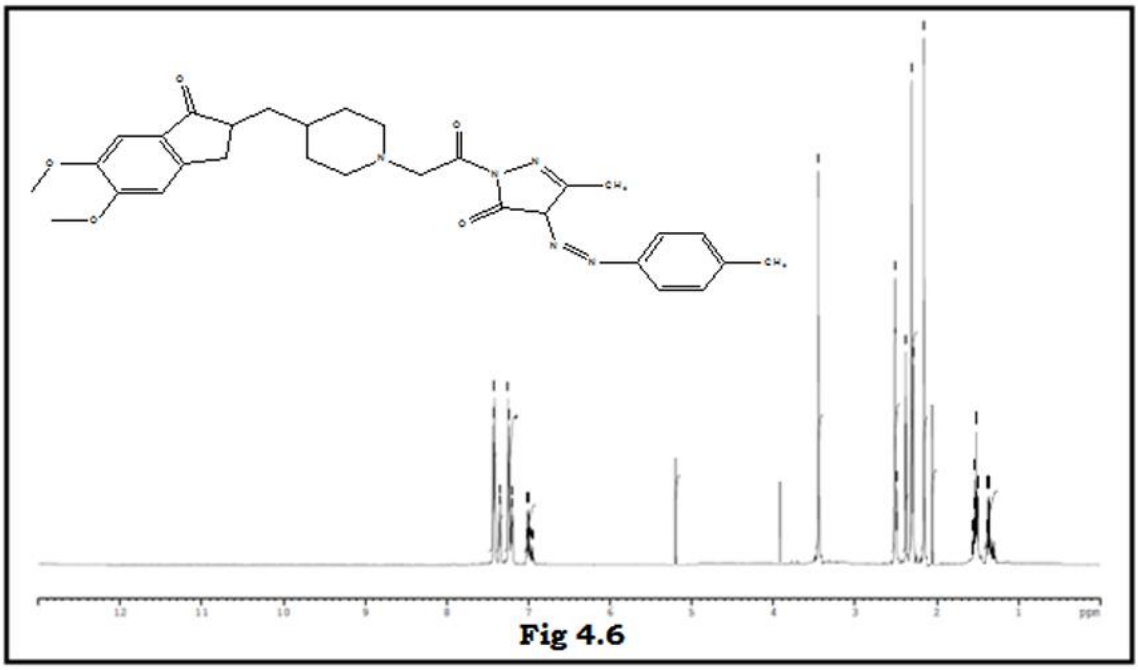


Fig 4.6

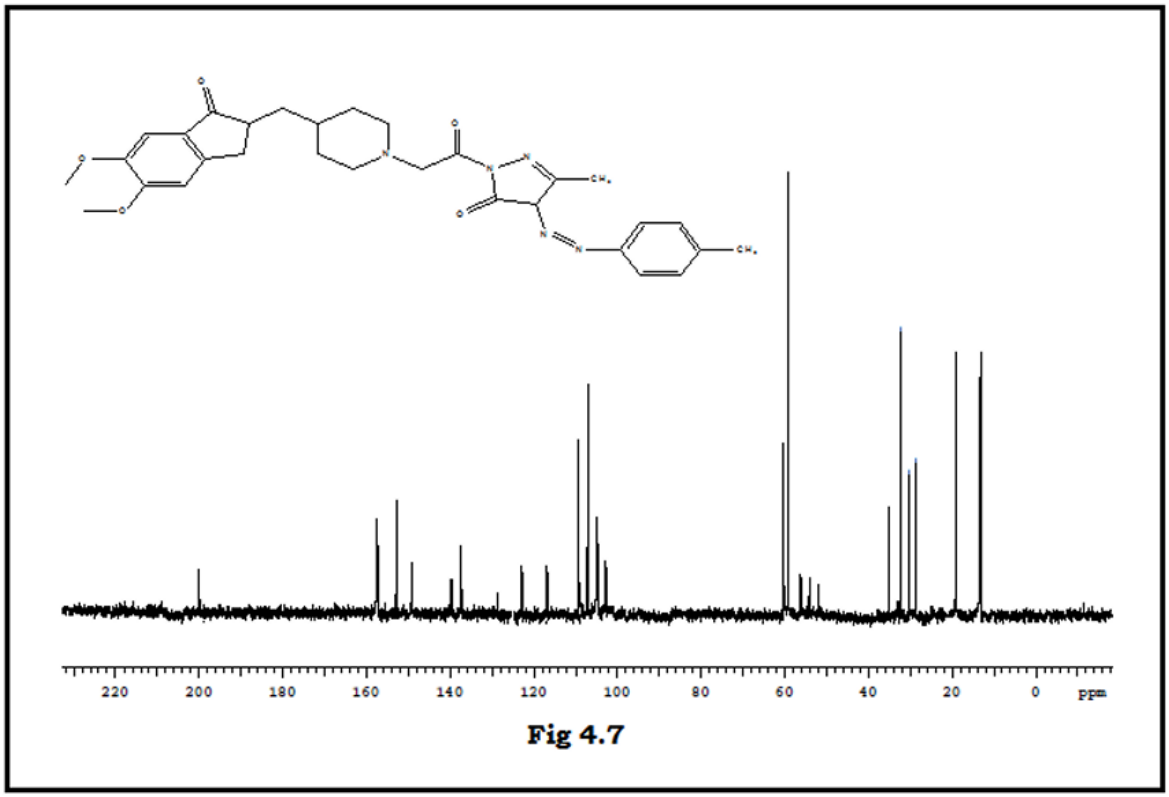


Fig 4.7

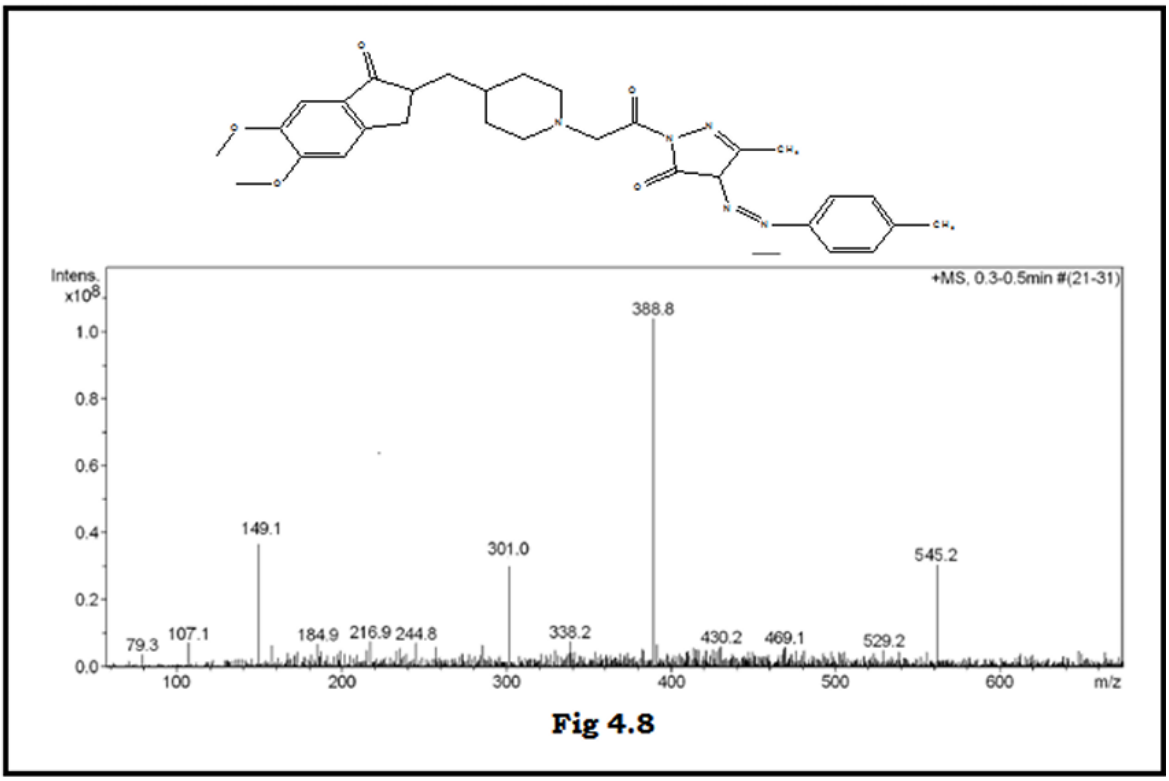


Fig 4.8

6.9 Analysis of compound (86k)

Yellow compound obtained was found to have the molecular composition C30H35N5O6 showed the following results on elemental analysis.

Elemental analysis of the compound (86k)

Molecular Formula	Elemental analysis Calc./ Found		
	C	H	N
$C_{30}H_{35}N_5O_6$	64.17	6.24	12.48
	63.97	5.99	13.12

6.10 Spectral Characteristic data of 2-{2-[4-(5,6-Dimethoxy-1-oxo-indan-2-ylmethyl) piperidin-1-yl]-acetyl}-4-(4'-methoxy-phenylazo)-5-methyl-2,4-dihydro-pyrazol-3 one (86k)

IR spectra: Fig. 4.9

IR (cm-1): 3222 (NH), 1710, 1690 (C=O); 1210 (C-O); 600-800 1H NMR interpretation: Fig. 4.10

1H NMR (δ ppm): 1.26 (m, 4H, 2XCH2), 1.45 (m, 1H, CH), 2.18(m, 1H,CH), 2.23 (s, 3H,CH3), 2.28 (d, 2H,CH2), 2.45 (t, 2H, CH2), 2.74 (t, 4H, 2XCH2), 3.52(s, 3H, OCH3), 3.73 (s, 6H, 2X-OCH3), 3.94 (s, 2H, CH2), 5.03 (s, 1H, CH), 7.20 – 7.63 (m, 6H, ArH) 13C NMR interpretation: Fig. 4.11

13C NMR (δ ppm): 13.6 (CH3), 28.8(CH), 29.3 (CH2), 30.6 (2 x CH2), 32.9 (CH2), 48.6 (CH), 50.5 (CH), 51.9 (CH2), 57.5 (OCH3), 58.6 (2 x OCH3), 60.5 (CH2), 110.15-151.36 (ArC),159.32(C=N), 163.23 (C=O), 174.25 (C=O), 200.53(C=O).

Mass interpretation: Fig. 4.12

m/e: M+ 561

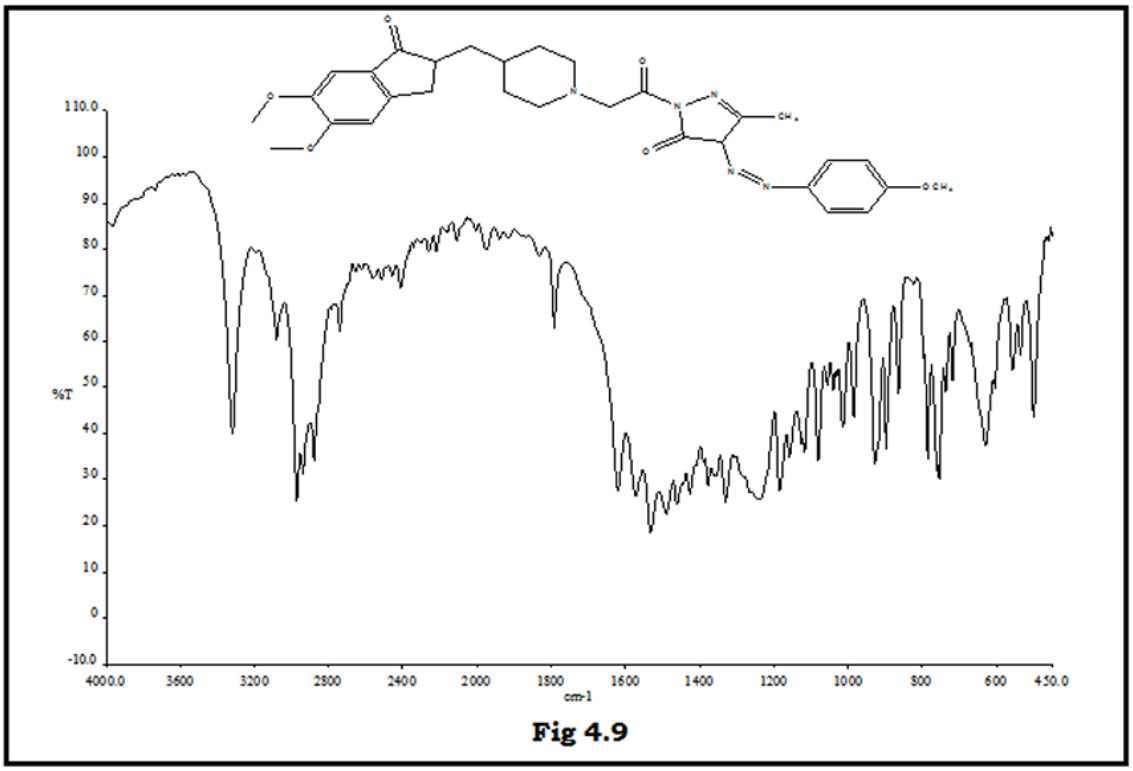


Fig 4.9

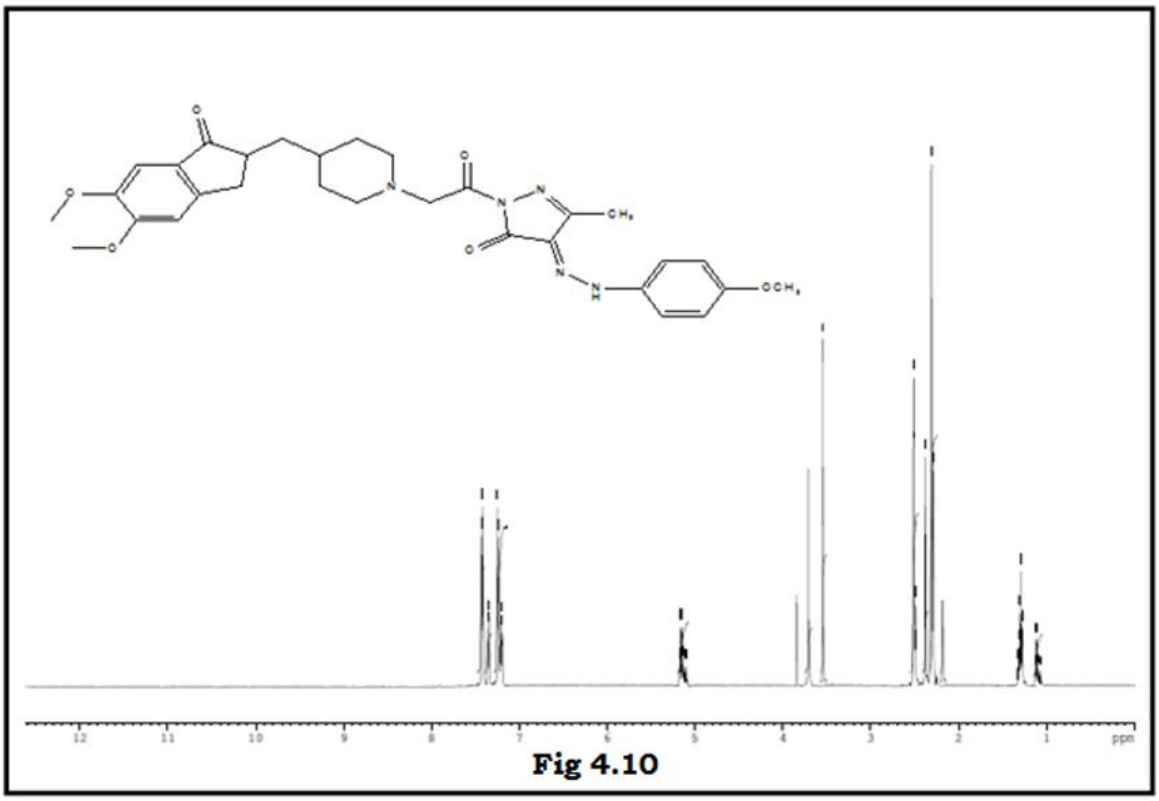


Fig 4.10

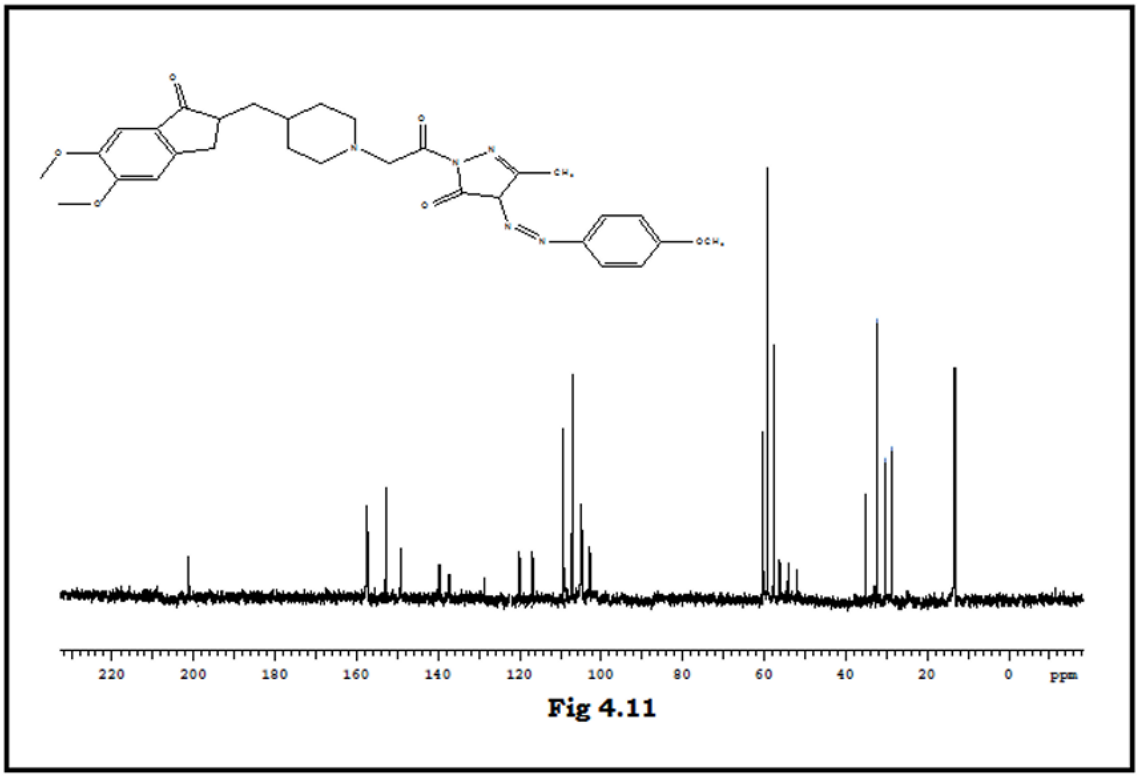


Fig 4.11

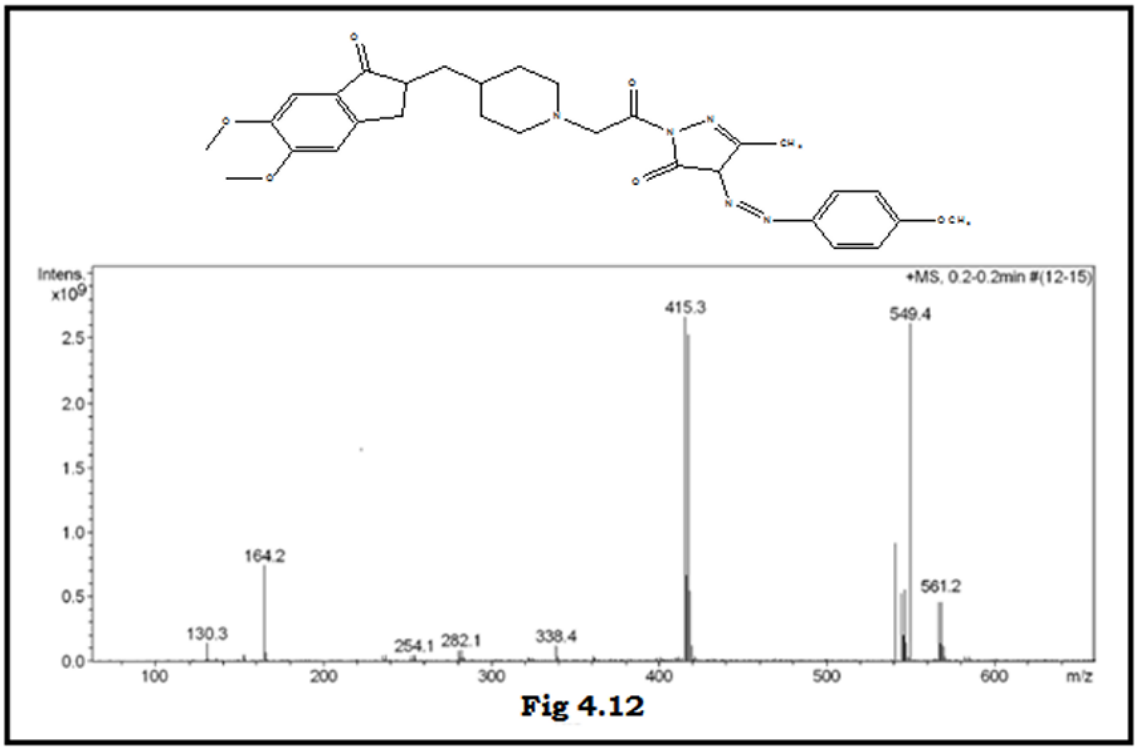


Fig 4.12

Materials and Reagents

Chemicals

For Synthesis of Compound 2-(1-Carbamoylmethylcyclopentyl) ethanoic acid

- 8-Azaspiro [4.5] decane-7,9-dione (87)
- Potassium hydroxide (KOH)
- Hydrochloric acid (HCl)
- Distilled water
- Methanol
- Crushed ice

For Synthesis of Compound 89

2-(1-Hydrazinocarbonylmethylcyclopentyl) ethanamide (89)

- Compound 88
- Thionyl chloride ($SOCl_2$)
- Hydrazine hydrate
- Dichloromethane (DCM/MDC)
- Methanol

For Synthesis of Azo Pyrazole Derivatives (90a–g)

- Compound 89 (hydrazide intermediate)
- 3-Oxo-2-(substituted phenylazo) ethylbutanoates (81a–g)
- Phenylazo derivative
- p-Tolylazo derivative
- p-Methoxyphenyl derivative
- Other substituted phenylazo analogues
- Glacial acetic acid
- Crushed ice
- Distilled water

Solvents

- Methanol
- Dichloromethane (DCM)
- Glacial acetic acid
- Distilled water

Reagents for Purification

- Methanol (recrystallization)
- Ice-cold methanol (washing)
- Distilled water
- Crushed ice

Reagents for TLC Monitoring

- Silica gel G TLC plates
- Ethyl acetate
- Hexane
- Chloroform
- Methanol
- Iodine chamber or UV lamp

(Solvent system may be optimized depending upon Rf values.)

Reagents for Spectral Characterization

FT-IR Analysis

- Potassium bromide (KBr) powder (for pellet preparation)

^{1}H NMR and ^{13}C NMR Analysis

- Deuterated dimethyl sulfoxide (DMSO-d6)
  or
- $CDCl_3$ (Deuterated chloroform)

Mass Spectrometry

- HPLC-grade methanol
- Acetonitrile
- Formic acid (if ESI-MS is employed)

Glassware Required

- 250 mL Round-bottom flask
- 100 mL Round-bottom flask
- Reflux condenser
- Measuring cylinders
- Beakers
- Conical flasks
- Dropping funnel
- Glass rod

- Pipettes
- Buchner funnel
- Vacuum filtration flask
- TLC developing chamber
- Watch glasses

Instruments Required

- Magnetic stirrer with hot plate
- Heating mantle
- Analytical balance
- Melting point apparatus
- TLC chamber
- UV lamp
- FT-IR spectrophotometer
- NMR spectrometer (400 MHz or higher)
- Mass spectrometer (ESI-MS)
- Vacuum pump
- pH meter

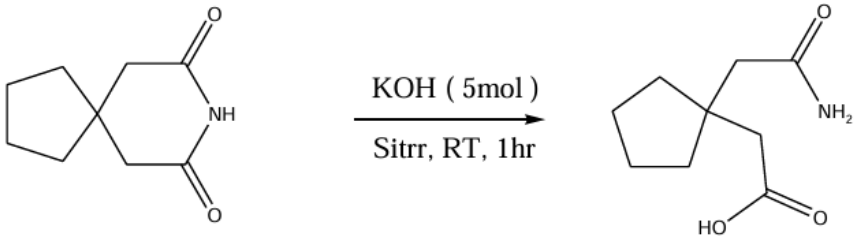
Summary of Key Reagents Consumed

S. No.	Reagent	Purpose
1	8-Azaspiro [4.5] decane-7,9-dione	Starting material
2	KOH	Ring opening/hydrolysis
3	HCl	Neutralization
4	$SOCl_2$	Acid chloride formation
5	Hydrazine hydrate	Hydrazide synthesis
6	Substituted phenylazo β-ketoesters	Pyrazole ring formation
7	Acetic acid	Cyclization medium
8	Methanol	Recrystallization/washing
9	DCM	Reaction solvent
10	Water and Ice	Work-up and precipitation

7.1 FORMATION AZO CHITRAL DYES

Synthesis of 2(1-Carbamoylmethylcyclopentyl) ethanoic acid (88) 8-Azaspiro [4.5] decane-7,9-dione 87 (16.7g, 0.1 mol) and KOH (20g, 0.5 mol) were transferred in 250 mL round bottom flask and stirred for 1hr at room temperature to obtained compound 88. After completion of the reaction (monitored by TLC), the reaction mixture was cooled, poured on crushed ice, on neutralization of the contents with HCl a solid mass separated out, which was filtered, washed with water, dried and recrystallised from methanol to obtained 88. Yield: 80%, m.p: 117-120 ºC

Scheme 5.1

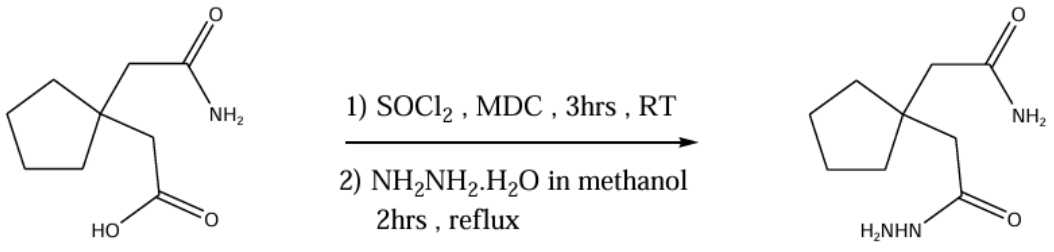


(87) **(88)**

7.2 Synthesis of 2-(1-Hydrazinocarbonylmethylcyclopentyl)-ethanamide (89)

A mixture of compound 88 (9.25g, 0.05 mol) and SOCl2 (5.95g, 0.05 mol) in MDC (100mL) was stirred at room temperature for 3hrs. After completion of reaction hydrazine hydrate (2.4g, 0.06 mol) in methanol (40mL) was added and reflux for 6 hrs. The progress of reaction was monitor by TLC. Upon completion, the reaction mass was cooled 0 to 5 ºC. Yellow color solid thus, was filtered and washed with cold methanol to yield 89. Yield: 73%, m.p: 133-135 ºC.

Scheme 5.2

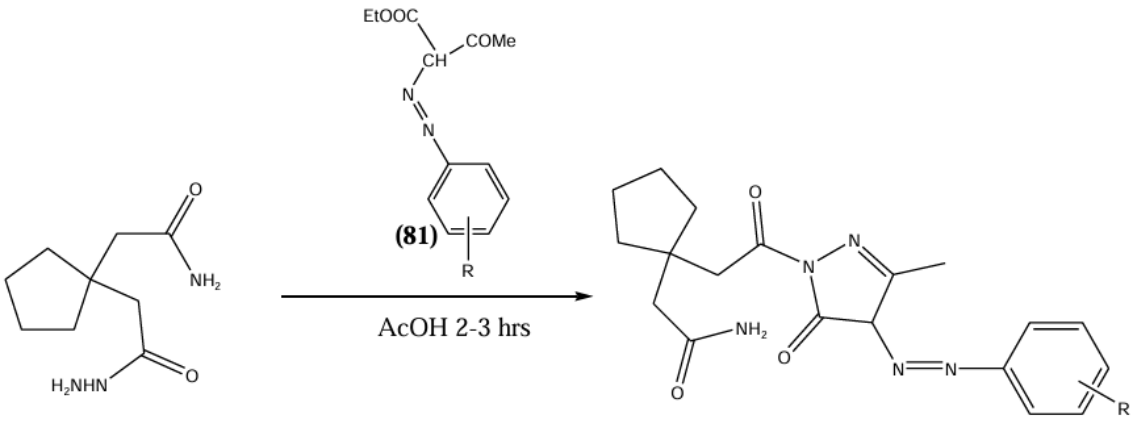


(88) **(89)**

7.3 Synthesis of 2-(1-{2-[4-(substituted phenylazo)-3-methyl-5-oxo-4,5 dihydropyrazol-1-yl]-2-oxoethyl} cyclopentyl)acetamide (90)

General Procedure: Equimolar mixture of compound 87 (9.95g, 0.05 mol) and 3-Oxo-2 (substitutedphenyl) azoethylbutanoate 81 (0.05 mol) in acetic acid (50mL) was transferred in 250 mL round bottom flask and stirred for 2-3hrs. After completion of the reaction (monitored by TLC), the reaction mixture was poured onto crushed ice, separated solid mass was filtered, washed with water and dried to yield 90. Under similar conditions 90a-g were prepared & listed in table-5.1.

Scheme 5.3



(89) **(90)**

Table-5.1

Physical data of 2-(1-{2-[4-(substituted phenylazo)-3-methyl-5-oxo-4, 5-dihydropyrazol-1-yl]-2-oxoethyl} cyclopentyl)acetamide (90)

Compds (90)	R	MF	MP (°C)	% Yield
a	H	$C_{19}H_{23}O_3N_5$	158-60	70
b	4-CH_3	$C_{20}H_{25}O_3N_5$	168-70	72
c	4-OCH3	$C_{20}H_{25}O_4N_5$	176-78	76
d	2-CH3	$C_{20}H_{25}O_3N_5$	114-15	79
e	2-NO2	$C_{19}H_{22}O_5N_6$	230-32	77
f	2-Cl	$C_{19}H_{22}O_3N_5Cl$	180-81	80
g	2-Br	$C_{19}H_{22}O_3N_5Br$	201-02	77

7.4 Analysis of compound (90a)

Yellow compound obtained was found to have the molecular composition C19H23N5O3 showed the following results on elemental analysis.

Elemental analysis of the compound (90a)

Molecular Formula	Elemental analysis Calc./ Found		
	C	H	N
$C_{19}H_{23}N_5O_3$	61.79	6.23	18.97
	61.99	6.53	19.09

7.5 Spectral Characteristic data of 2-{1-[2-(3-Methyl-5-oxo-4-phenylazo-4,5 dihydro-pyrazol-1-yl)-2-oxo-ethyl]-cyclopentyl}-acetamide (90 a)

IR spectra: Fig. 5.1

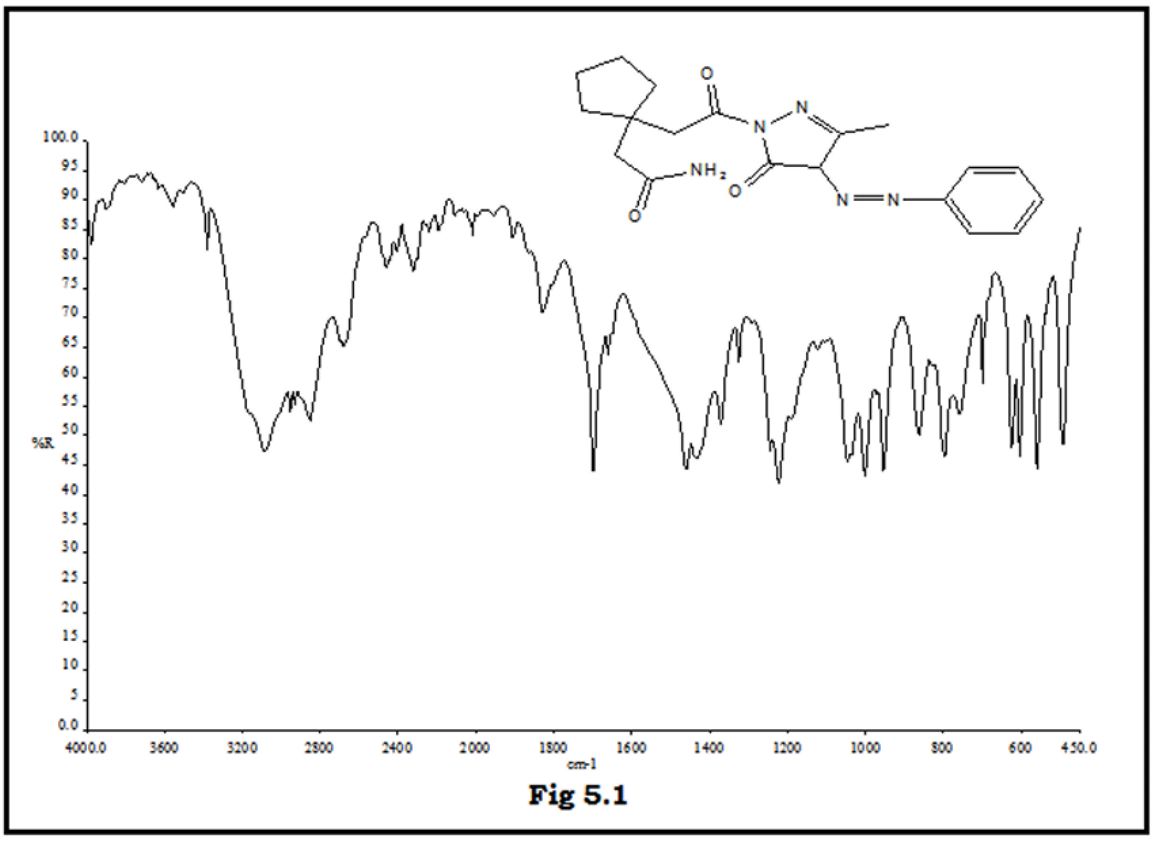
IR (cm-1): 3288, 3282 (NH2), 1680 (CONH2), 1170 (C-N), 700-760. 1H NMR interpretation: Fig. 5.2

1H NMR (δ ppm): 1.43(m, 4H, 2 X CH2), 1.51(t, 4H, 2X CH2), 2.10 (s, 2H, CH2), 2.23(s, 2H, CH2), 2.45(s, 3H, CH3), 5.8(s, 1H, CH), 6.2 (s, 2H, NH2), 7.1-7.3(m, 5H, ArH). 13C NMR interpretation: Fig. 5.3

13C NMR (δ ppm): 20.2(2 X CH2), 20.8(CH3), 29.6(CH), 34.9(2X CH2), 40.4(CH2), 44.2 (CH2), 61.8 (C), 122-147.7(ArC), 156 (C=N), 170.20 (C=O), 174.25 (C=O), 176.85(C=O).

Mass interpretation: Fig. 5.4

m/e: M+ 369.3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N
NH2
O
O
N
N
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95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%R
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
450.0
cm-1

Fig 5.1

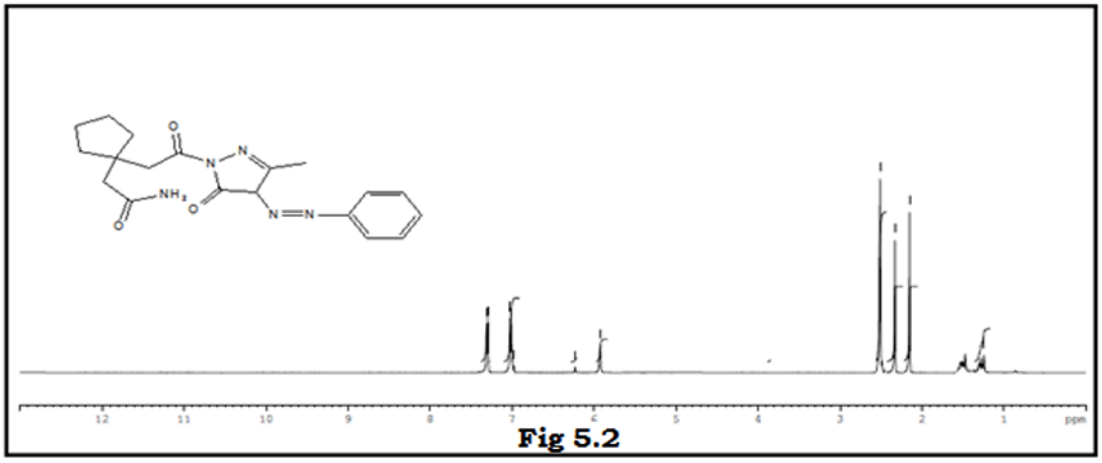


Fig 5.2

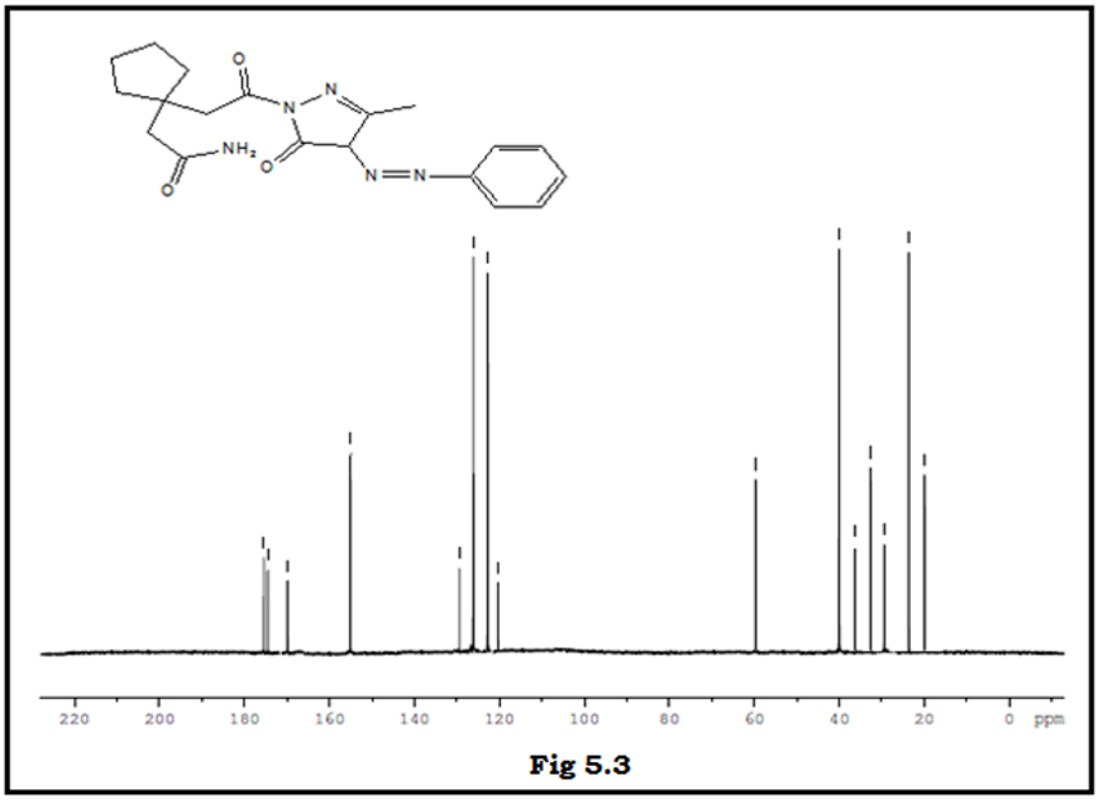


Fig 5.3

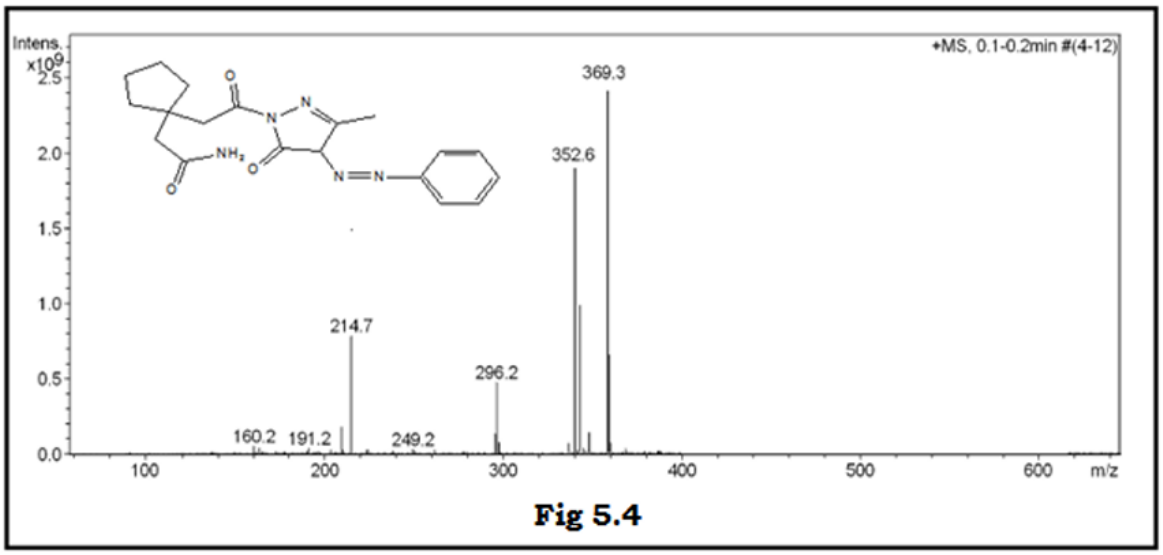


Fig 5.4

7.6 Analysis of compound (90b)

Yellow compound obtained was found to have the molecular composition C20H25N5O3 showed the following results on elemental analysis.

Elemental analysis of the compound (90b)

Molecular Formula	Elemental analysis Calc./ Found		
	C	H	N
$C_{20}H_{25}N_5O_3$	62.66	6.53	18.28
	62.86	6.96	18.63

7.7 Spectral Characteristic data of 2-{1-[2-(3-Methyl-5-oxo-4-p-tolylazo-4,5 dihydro-pyrazol-1-yl)-2-oxo-ethyl]-cyclopentyl}-acetamide (90 b)

IR spectra: Fig. 5.5

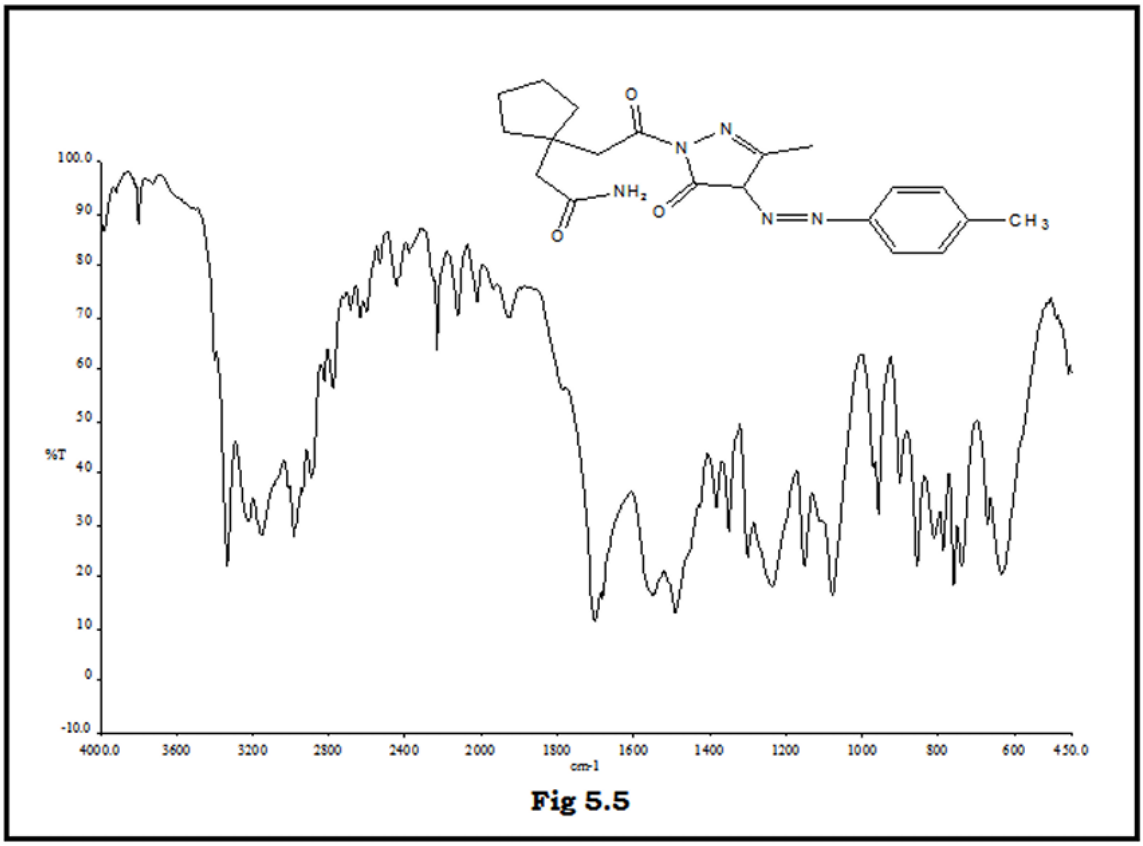
IR (cm-1): 3288, 3282 (NH2), 1680 (CONH2), 1170 (C-N), 700-750. 1H NMR interpretation: Fig. 5.6

1H NMR (δ ppm): 1.47(m, 4H, 2 X CH2), 1.53(t, 4H, 2X CH2), 2.12 (s, 2H, CH2), 2.21(s, 2H, CH2), 2.37(s, 3H, CH3), 2.48(s, 3H, CH3), 5.8(s, 1H, CH), 6.2 (s, 2H, NH2), 7.2-7.4(m, 4H, ArH). 13C NMR interpretation:

Fig. 5.7 13C NMR (δ ppm): 19.8(2 X CH2), 20.6(CH3), 25.5(CH3), 29.8(CH), 35.2(2XCH2), 40.6(CH2), 43.9 (CH2) , 61.5 (C), 121.3-146.9(ArC), 157.3 (C=N), 169.89 (C=O), 174.53 (C=O), 176.78(C=O).

Mass interpretation: Fig. 5.8

m/e: M+388.1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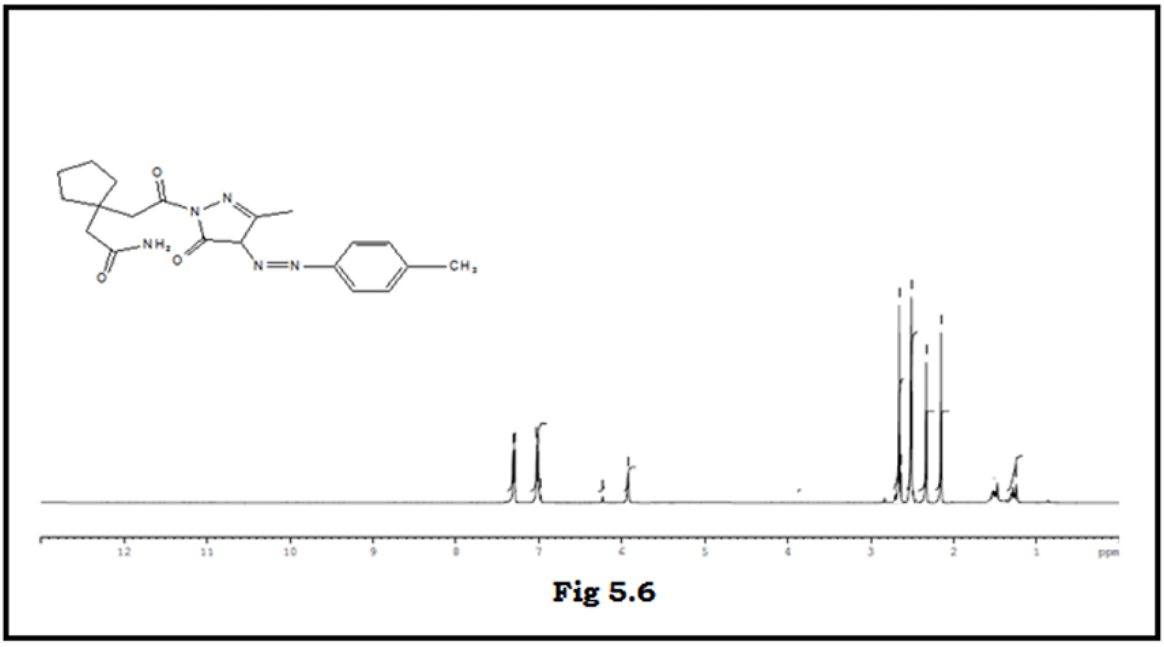
80
70
60
50
%T
40
30
20
10
0
-10.0
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
450.0
cm-1
O
N
N
NH2
O
O
N=N
CH3

Fig 5.5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N
N
NH2
O
O
N=N
CH3
12
11
10
9
8
7
6
5
4
3
2
1
ppm

Fig 5.6

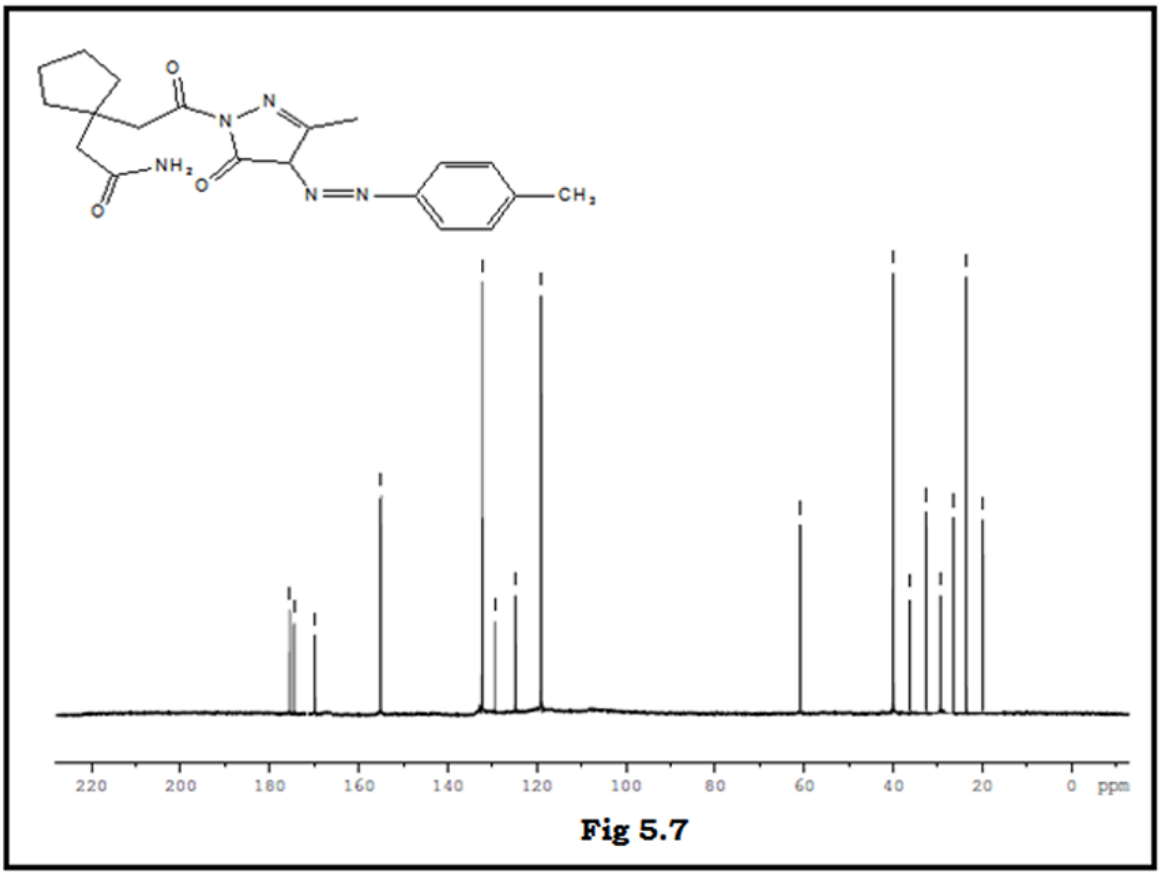
O
N
N
NH2
O
O
N=N
CH3
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Fig 5.7

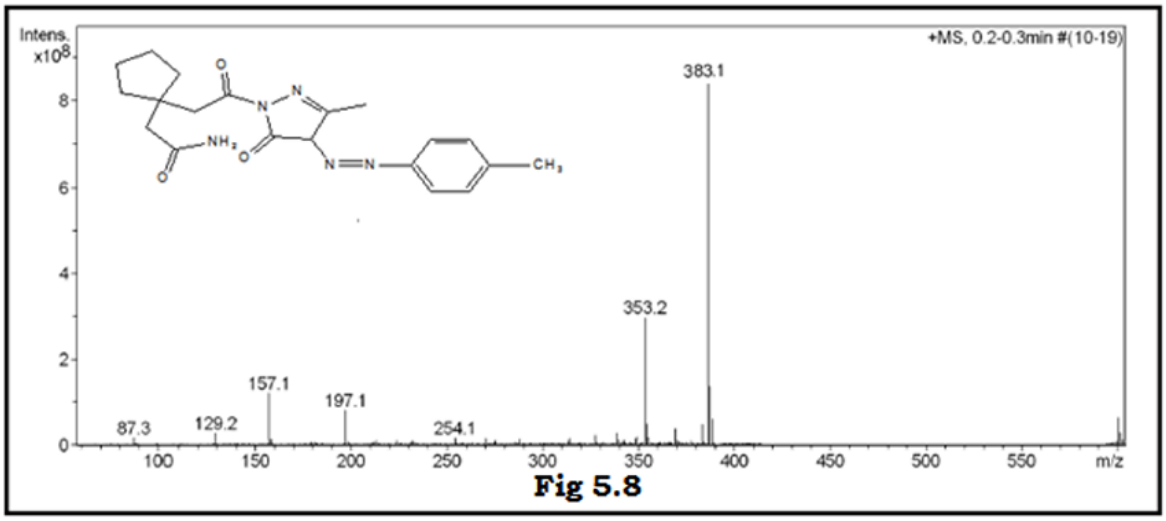

Fig 5.8

7.8 Analysis of compound (90c)

Yellow compound obtained was found to have the molecular composition C20H25N5O4 showed the following results on elemental analysis.

Elemental analysis of the compound (90c)

Molecular Formula	Elemental analysis Calc./ Found		
	C	H	N
$C_{20}H_{25}N_5O_4$	60.15	6.27	17.54
	60.12	6.54	17.95

7.9 Spectral Characteristic data of 2-{1-[2-(3-Methyl-5-oxo-4-p methoxyphenylazo-4,5-dihydro-pyrazol-1-yl)-2-oxo-ethyl]-cyclopentyl} acetamide (90c)

IR spectra: Fig. 5.9

IR (cm-1): 3288, 3282 (NH2), 1690 (CONH2), 1170 (C-N), 750-820. 1H NMR interpretation: Fig. 5.10

1H NMR (δ ppm): 1.45(m, 4H, 2 X CH2), 1.59(t, 4H, 2X CH2), 2.15 (s, 2H, CH2), 2.23(s, 2H, CH2), 2.45(s, 3H, CH3), 3.55(s, 3H, OCH3), 5.9(s, 1H, CH), 6.3(s, 2H, NH2), 7.1-7.5(m, 4H, ArH). 13C NMR interpretation: Fig. 5.11

13C NMR (δ ppm): 20.3(2 X CH2), 20.8(CH3), 29.6(CH), 35.2(2X CH2), 41.4 (CH2), 44.3(CH2) , 45.5(OCH3), 61.8 (C), 122.6-148.9(ArC), 156.5 (C=N), 171.25 (C=O), 174.53 (C=O), 177.85(C=O).

Mass interpretation: Fig. 5.12

m/e: M+ 399.3

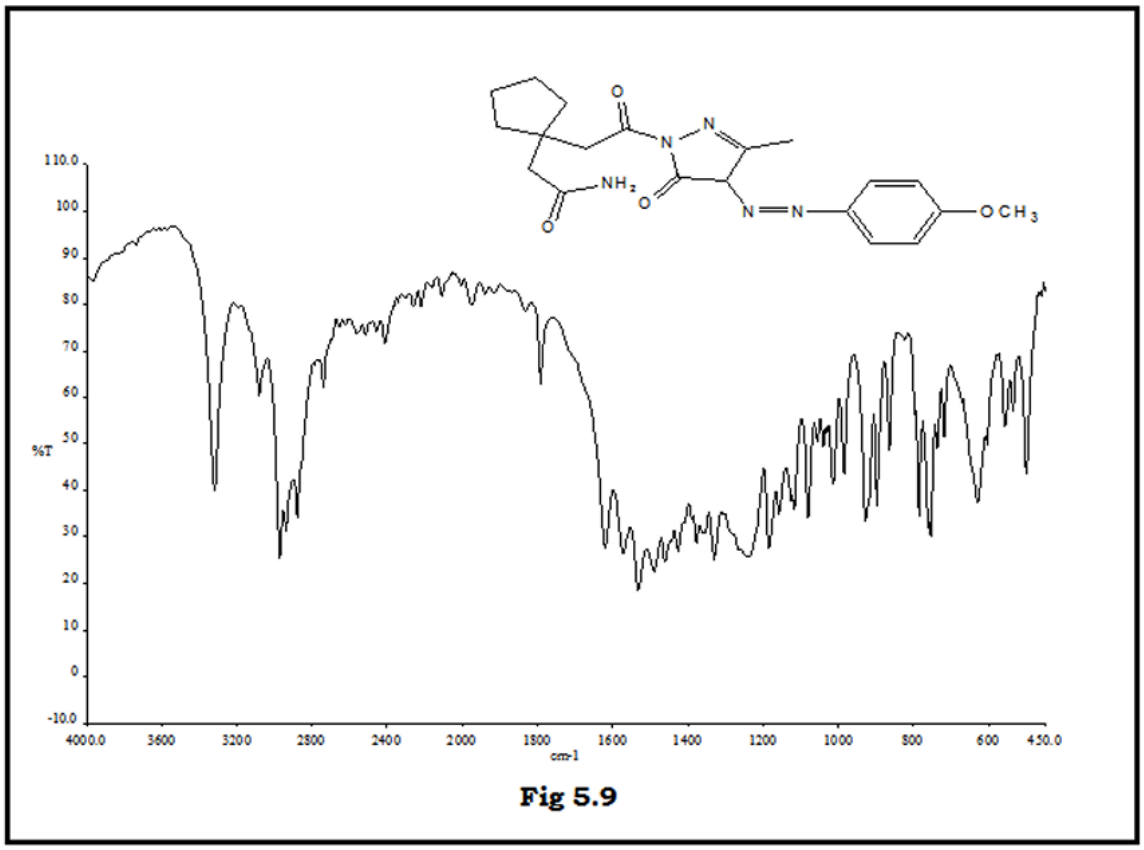

Fig 5.9

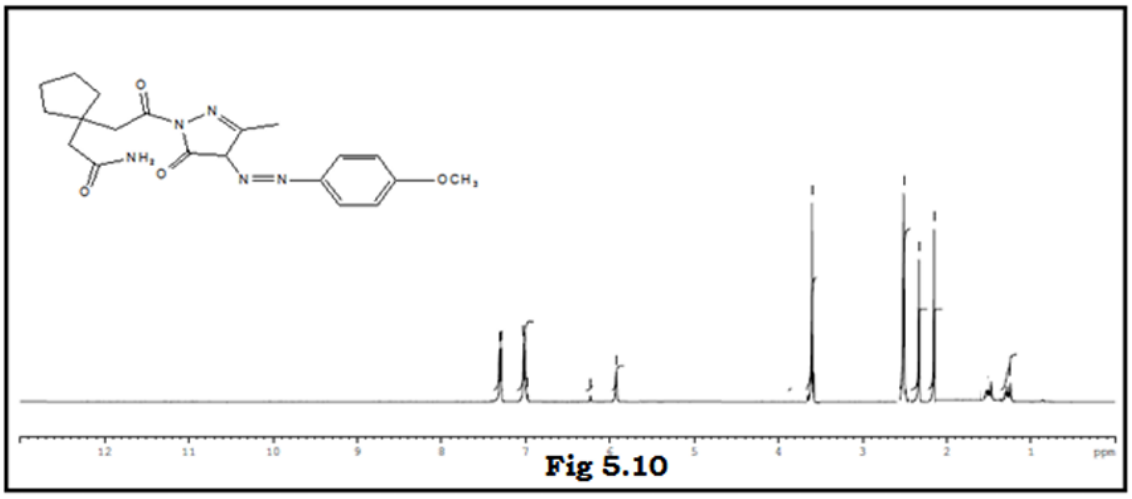

Fig 5.10

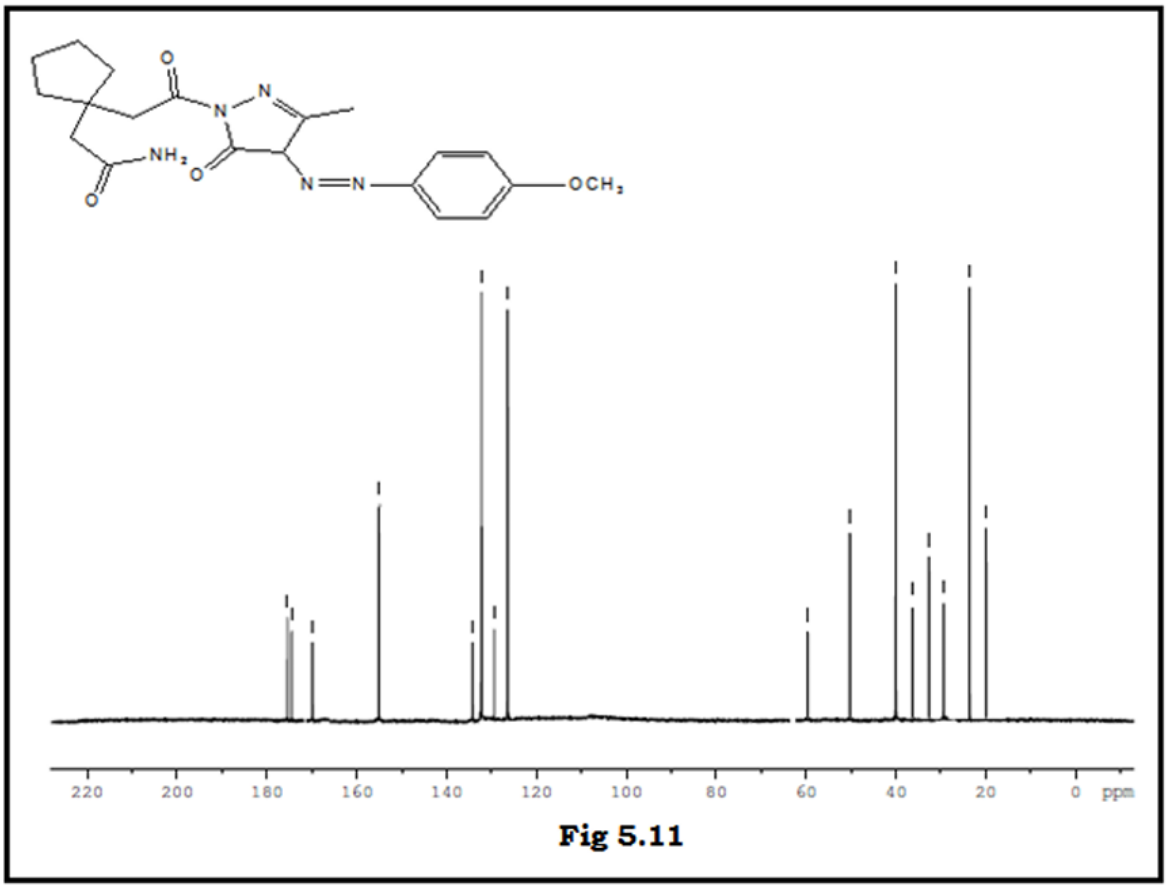

Fig 5.11

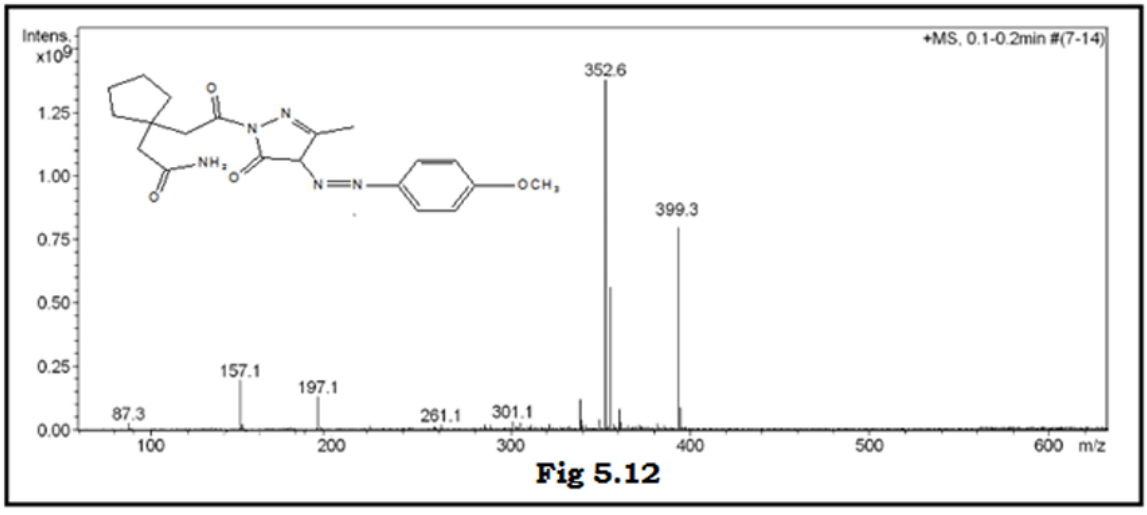

Fig 5.12

CHAPTER 5

RESULT & CONCLUSION

Novel heterocycles were synthesized by Microwave, Sonication and Conventional rout with good yield.

Structures of synthesized compounds were established by Physico-chemical test as well as by different spectral techniques.

The present study successfully demonstrated the synthesis and characterization of various heterocyclic and azo compounds using efficient and modern methodologies.

The **synthesis of benzothiazines by sonication technique** proved to be a rapid, eco-friendly, and high-yielding method compared to conventional heating. Ultrasonic irradiation enhanced reaction rates, reduced reaction time, and improved product purity, indicating its significance in green chemistry approaches.

The **synthesis of azo dyes containing pyrazole moieties** highlighted the importance of combining azo functionality with biologically active heterocycles. These compounds exhibited good stability and potential applications in pharmaceuticals and dye industries due to the presence of both chromophoric (-N=N-) and pharmacophoric pyrazole groups.

The **formation of azo dyes** through diazotization and coupling reactions was successfully carried out under controlled conditions. The reactions confirmed the importance of temperature control and pH in achieving high yields and desired substitution patterns.

Similarly, the **formation of azo chiral dyes** demonstrated the incorporation of chirality into azo systems, which can influence optical activity and enhance applications in asymmetric synthesis, optical materials, and advanced dye chemistry.

IR spectral analysis played a crucial role in confirming the successful synthesis of all compounds.

Future Scope and Applications

Future Scope

The synthesized compounds, including benzothiazines and azo dyes with pyrazole moieties, offer significant potential for further research and development in multiple scientific domains.

The **sonication-assisted synthesis of benzothiazines** can be further explored for:

- Scaling up to **industrial-level production** using green chemistry principles
- Application to other heterocyclic systems to improve **reaction efficiency and sustainability**
- Optimization using different solvents and catalysts to enhance **yield and selectivity**

The **azo dyes containing pyrazole moieties** open avenues for:

- Structural modification to improve **biological activity**, especially antimicrobial, anti-inflammatory, and anticancer properties
- Development of **target-specific drug molecules** due to the pharmacological relevance of pyrazole derivatives
- Investigation of **structure–activity relationships (SAR)** for better therapeutic outcomes

The **azo and azo chiral dyes** provide future research opportunities in:

- Designing **optically active materials** for advanced technologies
- Use in **asymmetric synthesis** and chiral recognition systems
- Development of **smart materials** such as pH-sensitive or photo responsive dyes

Further studies can also focus on:

- Advanced characterization techniques like **NMR, Mass Spectrometry, and X-ray crystallography**
- Computational modelling for predicting **molecular interactions and stability**
- Toxicological and environmental impact studies for safe application

Applications

The synthesized compounds have wide-ranging applications in pharmaceutical, industrial, and material sciences:

1. Pharmaceutical Applications

- Benzothiazine derivatives may exhibit **antimicrobial, analgesic, anti-inflammatory, and anticancer activities**
- Pyrazole-containing azo compounds can be explored as **drug candidates** due to their biological versatility
- Potential use in **drug delivery systems and medicinal chemistry research**

2. Dye and Textile Industry

- Azo dyes are extensively used as **colorants in textiles, leather, paper, and food industries**
- These compounds show **high color strength, stability, and tunable shades**

- Chiral azo dyes may be used in **specialty dyes and high-performance materials**

3. Analytical and Chemical Applications

- Azo compounds can act as **indicators and sensors** for detecting pH and metal ions
- Useful in **analytical chemistry for colorimetric analysis**

4. Material Science

- Application in **organic electronics, optical devices, and liquid crystals**
- Development of **photochromic and thermochromic materials**
- Use in **data storage and molecular switching devices**

5. Environmental Applications

- Potential use in **wastewater treatment and pollutant detection**
- Development of **eco-friendly dyes** using green synthesis techniques like sonication.

Overall Perspective

The integration of **efficient synthetic techniques (sonication)** with **functional heterocyclic and azo systems** presents a promising platform for developing novel compounds with diverse applications. With further research, these compounds can contribute significantly to advancements in **pharmaceutical sciences, industrial chemistry, and advanced material technologies**.

CHAPTER 6

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