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# Synthesis of Some Biological Active Compounds

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## ABBREVIATIONS

TMS – TriMethyl Silane  
DMF – Dimethyl Formamide  
THF- TetraHydroFuran  
CDCl<sub>3</sub>– Deuterated Chloroform  
DMSO - Dimethyl sulfoxide  
CCl<sub>4</sub>– Carbon tetrachloride  
Me--- Methyl  
Et--- Ethyl  
Ac--- Acetyl  
Ar---Aryl  
Ph. ----Phenyl  
R--- Alkyl  
IR--- Infra-red  
NMR—Nuclear Magnetic Resonance.  
M.Pts.- Melting points  
Mol—Moles  
Min—Minutes  
Hrs---Hours.  
PPM—Parts per millions  
Atm—atmosphere  
Het- Heteryl moiety.  
Fig—figure  
Calcd- Calculated

## PATENTS

Fr. Pat- france patents  
Belg.pat.- Belgium patents  
B.pat.---British patents  
Eur. Pat.—European Patents.  
Ger.Off-German Patents  
Ger. Pat—German patents  
Ita. Pat.- Japanese patents  
Jpn. Pat- Japanese patents  
Jpn. Kokai- Japanese patents  
Russ. Pat.- Russian patents  
U.S. Pat.-United state Patents.

# **PART – I**

## **General Introduction & Literature Survey**

Heterocyclic compounds are of interesting due to their physiological and industrial significance. The versatile application of nitrogen and / or oxygen heterocyclic compounds have made this area of extensive research of synthetic chemists. Nitrogen heterocyclic compounds like triazines, Benzimidazoles, pyrazoles, isoxazoles and pyridines have received considerable attention in recent years due to their wide physiological activities. These derivatives are very useful in various fields e.g. drugs dyes, polymers, textiles, agricultures etc. triazine derivatives have been used as antimicrobial herbicides, urinary antiseptics and anti-inflammatory agents. Benzimidazole derivatives have been reports to possess wide range of biological activities such as antibacterial, antifungal, antiviral and antihelmintic. Numerous physiological activities have been attributed to Isoxazole derivatives. The clinical use of Isoxazole derivatives has been well explored. Pyrazolines have shown marked analgesic properties. S-triazines or 1,3,5-triazines are among the earliest organic compounds reported in the chemical literature. Having been described by Serullas & Liebig in 1828. The parent compounds S-triazine having remarkable stability can be explained by the electronic configuration which resembles that of its  $\pi$ -electrons which are spread over all six ring atoms & this is responsible for its high aromatic character & thermal stability.

The essential difference exists in electronics configuration between S-triazine and benzene as consequence of the greater electro negativity of the nitrogen atoms as compared to that of the carbon atoms.

Thus the electrons in S-triazine ring are localized in the vicinity of the N-atom rather than being evenly distributed over the whole ring. A polar mesomeric form that bears an additional pair of unshared electrons on the N-atoms & the C-atoms will contribute to a certain degree to the actual structures of the S-triazine molecule (Fig-1). The delocalization effect in combination with inductive and mesomeric effects exerted by the substituents at C-2, C-4 & C-6 greatly influence the chemical behavior & physical properties of S-triazine derivatives. The relative electron deficiency of the ring C-atom, makes them susceptible to nucleophilic attack. Hence chlorines atoms of the moieties under selective reaction conditions. The majority of substitution reactions of S-triazines are nucleophilic substitutions of chlorotriazines.

Several reviews of the chemistry of cyanuric chloride are available the most complete of which was published by the American cyanamide company in 1955. An earlier summary was presented by Fierz-David and Matter in 1937 in a review of dyes containing the triazine ring, and reference may be made to a review by Migrdichian.

A series of nine papers from the laboratories of the American Cyanamide company constitutes an excellent source of information on the preparation. Properties and reactions of amino, alkoxy and aryloxy derivatives of cyanuric chloride therefore, the present treatment of this subject will be abbreviated with emphasis on more recent reactions of chlorotriazines. Cyanuric chloride was prepared as early as 1828 by Serullas<sup>5</sup>, who obtained it through by the action of chlorine on anhydrous hydrocyanic acid in direct sunlight.

Although reactions may occur at the ring Nitrogen atoms, most of the reactions of cyanuric chloride involve the chlorine atoms, which are nucleophilic reagents. Banks and co-workers<sup>6-8</sup> have reported the synthesis of a number of dialkoxy-s-triazines from chloro-s-triazines. Stepwise reaction of cyanuric chloride with phenols in aqueous sodium hydroxide has been effected. The triaryl cyanurates (Fig-2) were also obtained by the reaction of cyanuric chloride with sodium phenoxide or with phenol alone. The triaryl cyanurates react with amines to form trisubstituted melamines. The thermal rearrangement of 2-amino-4,6-dialkoxy-s-triazines has been studied. Such a rearrangement was to be expected at elevated temperatures in view of the known rearrangement of trialkyl and dialkyl cyanurates to isocyanurates<sup>10</sup>.

The chlorine atoms of cyanuric chloride may be replaced successively by various amino or substituted amino groups<sup>1-3</sup>.

The early work was reported by Fries<sup>11</sup> and Dials<sup>12</sup>. In general one atom of chlorine is replaced at 0°C, the second at 30-20°C, and the third at 90-100°C. This sequence of reaction is analogous to the stepwise replacement of the chlorine atoms of the less reactive 2,4,6-trichloro pyrimidine by ammonia or primary amine or secondary amines.

Different results can be achieved by variation of the reaction conditions or the reactivity of the amines. Pearlman and Banks<sup>7</sup> reported the replacement of all three chlorine atoms of cyanuric chloride at 25°C by secondary amines such as morpholine or piperidine.



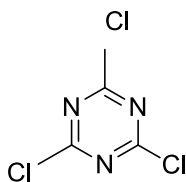


FIG. 1

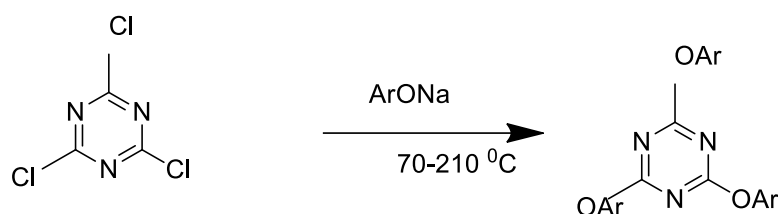


FIG. 2

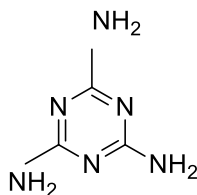


FIG. 3

The monoaminated triazines were obtained at sufficiently low temperature. Reaction of cyanuric chloride or its partially animated derivatives with ammonia or with primary or secondary amines affords a convenient route to substituted melamine's <sup>1,2</sup>. Melamine itself (Fig-3) is formed from ammonia and cyanuric chloride at 100 atm. Pressure. The reaction of cyanuric chloride with aminophenols, aminoesters, aminonitriles, aminoaryl sulphonamides,

semicarbazides or thiosemicarbazides hydrazides (Fig-4) and the metal salts or ureas, thioureas or monosubstituted cyanamides have been summarized<sup>1</sup>.

Diels<sup>12</sup> reported the hydrogenolysis of 2-amino-4,6-dichloro-s-triazines and formoguanmine (2,4-diamino-s-triazine) (Fig-6) respectively, by hydrogen iodide and phosphonium iodide.

Reduction of (Fig-5) to (Fig-6) has also been effected with hydrogen iodide alone<sup>13</sup>. Grundmann and Kober<sup>14</sup> have synthesized 2-diazo alkyl-s-triazines and have carried out a variety of transformations of these interesting intermediates. Cyanuric chloride reacts readily with two moles of diazomethane at room temperature in ether with formation of 2-diazo methyl-4,6-dichloro-s-triazine.

The first successful synthesis of s-triazine aldehydes was accomplished by the further reaction of 2-diazo methyl-s-triazines<sup>15</sup>. These compounds were selectively reduced to the corresponding s-triazine aldehyde hydrazones by means of hydrogen sulfide or preferably, lower alkyl mercaptans.

Grundmann and Weisse<sup>16</sup>, effected the reduction of 2,4,6-tris-(trichloromethyl)-s-triazine to a mixture of 2,4,6-trimethyl-s-triazine and 2-amino-4,6-dimethyl-s-triazine with zinc in ethanol and formamide. Kreutzberger<sup>17</sup> has studied the reactions of trichloro-methyl-s-triazines with amines. The action of concentrated aqueous ammonia on 2-methyl-4,6-bis-(trichloromethyl)-s-triazine under very mild conditions gave 2-methyl-4-amino-6-trichloromethyl-s-triazine and at higher temperatures afforded 2-methyl-4-amino-6-hydroxy-s-triazine. Goodman and Gilman<sup>18</sup> synthesized Methanamine or Urotropin, which is widely

used as a urinary antiseptic. The activity of the drug is attributed to the slow release of formaldehyde in acid urine by reversal of the equation for its synthesis. Although newer synthetic drugs and antibiotics have largely replaced it, Methanamine is still prescribed, particularly for certain resistant urinary infections.

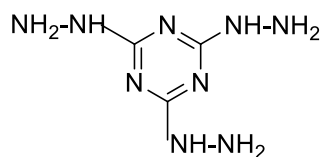


Fig. 4

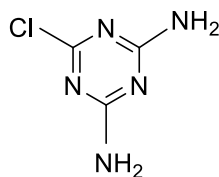


FIG. 5

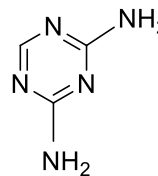


FIG. 6

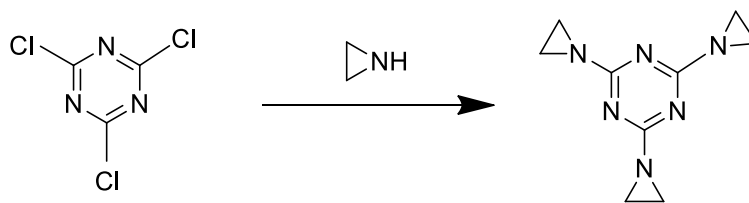


FIG.7

Triethylene melamine (2,4,6-tris-(ethylene imino)-s-triazine (Fig-7) prepared by condensation of ethylenimine and cyanuric chloride in benzene followed by triethylamine as an acid acceptor<sup>19</sup> was found to be an effective inhibitor of experimental tumors in animals by several investigators<sup>20-24</sup>. This compound has been useful in the treatment of lymphomas in man<sup>25-27</sup>.

Iensch<sup>28</sup> prepared surfen-C (Congasin) from Cyanuric chloride by reaction with 2-methyl-4,6-diaminoquinoline and aminolysis of the monochloro intermediates. Surfen- C is active against various forms of trypanosomiasis in cattle and has been used in tropical veterinary medicine. It has some effect against. *Cruzi* in infants, but causes toxix reaction in man.

Banks and Friedheim<sup>29-32</sup> prepared Melarsen oxide – 2,4,6- diamino-2-s-triazinyl) p-arsine oxide (Fig-8) by the reduction of the pentavalent analog. Melarsen oxide and Melarsen are reported to be effective against both early and late stages of African trypanosomiasis.

The cyclic disulphide (Fig-9) obtained by condensation of Melarsen oxide and 2,3-dimercaptopropanol, is know as arsobal or Mel-B and is valuable trypanocidal agant<sup>32</sup>. Sodium p-melaminyl stilbonate benzene (Fig-10), prepared by reaction of cyanuric chloride and stibanilic acid and subsequent amonolysis, has a prophylactic effect against *Trypanosoma equiperdum*<sup>33,34</sup> . Lipschitz and haddidian was found formoguanamine (2,4-diamino-s- triazine (Fig-11 ) to be active as an oral diuretic in experimental animals, and further studies indicated its effectiveness in man as an oral diuretic<sup>35-36</sup>

Clauder, Bulscu and Richter<sup>37</sup> synthesized a series of triazines diuretics (Fig-12) by the reaction of substituted biguanides with formic or acetic acid. Highest diuretic activity in rats. Greater than that of (Fig-10) is observed when R1 is phenyl or halophenyl and R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, & R<sub>5</sub>, are hydrogen's.

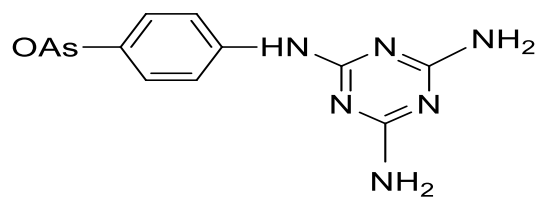


FIG. 8

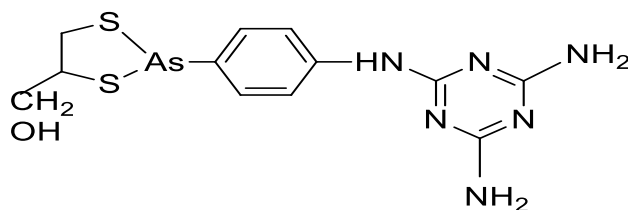


FIG. 9

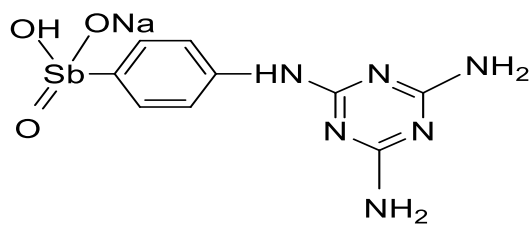


FIG. 10

The 4,6 -diamino-1aryl-1,2-dihydro-s-triazines possess a broad spectrum of biological activity. They act as antimetabolites in microbiological systems, interfering with folic acid metabolism<sup>38,39</sup>. In certain microbiological systems the primary mode of action of these compounds appears to be inhibition of the disphosphopyridine nucleotide linked reduction of folic acid<sup>40</sup>. They are active against avian and rodent malaria<sup>41,42</sup> and against malaria in monkeys<sup>43</sup>.

The dihydrotriazines also inhibit the growth of experimental tumors<sup>44,45</sup> and exhibit activity against coccidiosis in chick<sup>46</sup> and against murine

toxoplasmosis<sup>47</sup>. These compounds have also been shown to be active as antihelmintic agents, against *Syphacia obvelata* in mice, for example<sup>48-49</sup> 4,6-diamino-1-(p-chloro-phenyl)-1,2-dihydro-2,2-(1-methylcyclohexyl)-s-triazine hydrochloride (Fig-13) is now undergoing clinical trial as antihelmintic agent. Later investigations have demonstrated the inhibition in vitro of *Lactobacillus arabinosus* –p-amino- benzoic acid<sup>50</sup>, *Diplococcus pneumoniae* and *Streptococcus pyogenes*<sup>51</sup>, bioassay systems by a number of these dihydrotriazines and also the synergistic effect of sulfonamides in these systems.

In experiments in vivo the dihydrotriazines are effective against *D. pneumoniae*<sup>52</sup> and against several strains of streptococci<sup>53,54</sup> exhibiting a profound synergism with sulfonamides.

Kerutznerger et.al.<sup>55</sup> prepared substituted – 2-phenoxy-1,3,5- triazines by treating the dichloro triazine with substituted phenols. These compounds possessed antidiabetic activity. Campbell et.al.<sup>56</sup>, obtained 6-aryl-4-hydrazinyl-s-triazine-2-ones by treating 1,4-dimethyl isobutiret with  $\text{Ph-C(OMe)}_3$  to give 4-methoxy-1-methyl-(1-phenyl-1,2-dihydro-s-triazine-2-one) which was treated with methyl hydrazine. These compounds were possessed anti hypertensive's and cardiovascular activities. Boards et.al.<sup>57</sup> prepared 2-chloro-derivatives by reaction with thiourea in dilute inorganic acid at 60-95<sup>0</sup> which followed by neutralization with 10% aqueous NaOH.

Kreutzberger et al.<sup>58</sup>. Prepared Bis (isopropyl amino)- aniline- S-triazines by treating 2- chloro-4, 6-bis -(isopropyl) – s- triazines with substituted compounds the title compound is most pronounced trichomon acidal activity towards trichomonas uaginalis. Kavalek<sup>59</sup> synthesized 2- amino- 4- alkoxy -6- alkyl- s- triazines these compounds were known veterinary sedatives and herbicidal intermediates. Shasati and Hansa Parekh <sup>60</sup> were prepared Bis- (triazinyl- aminophenyl) –sulfones and found to possess antibacterial and antifungal activity. Weber et. Al <sup>61</sup>. prepared 1,3,5- triazine -2,4,6-trithiotri sodium salt monohydrate by treating Cyanuric chloride with aq. NaOH or Na<sub>2</sub>S.

Hasier et al.<sup>62</sup>. obtained thermotropic Bis-(S-triazinyamino) alkanes by treating 2-methoxy-dichloro triazine with diamines in aq. dioxane. Schering et. Al.<sup>63</sup>. Prepared triazine derivatives as herbicides microbicides and plant growth regulators. Wheeler et. al.<sup>64</sup>. prepared tri- substituted -s- triazine derivatives and possessed antizonants for rubber. Hutten et.al.<sup>65</sup> were prepared triazolo (1,5a) – s- triazines by cyclisation of hydrazino triazines in the presence of PPA-Silylester followed by condensation with amines. These compounds possessed adenosine antagonists. Coe and Jotham wordworth<sup>66</sup> obtained triazine derivatives by successive amination of cyanuric chloride for the use of P-glycoprotein inhibitors as enhancing antitumor activity.

Knueppel et. al.<sup>67</sup>. Prepared triazinyl amino acrylate derivatives and were found superior to know compound against cochilobolus, satires, venturia in aequalis, pyricularia oryzae and erysiphe graminis as potent pesticides. Adachi

et.al<sup>68</sup>. were attempted to synthesize 6-(halomethyl)-4- [(1-methyl-2-phenomethyl) amino]- s- triazine-2-amines as herbicides.

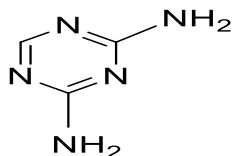


FIG. 11

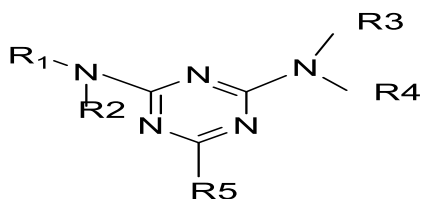


FIG. 12

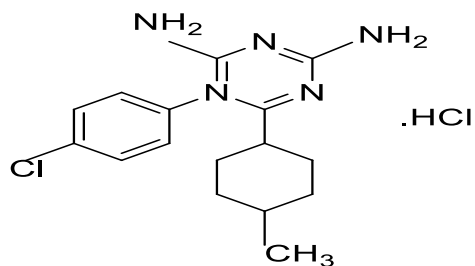


FIG. 13

Hasegawa et.al<sup>69</sup>. Prepared 2,4 -diamino-1,3,5- triazine derivatives as Leukotriene antagonists. Raspanti <sup>70</sup> were synthesized tris- (carbonyl aniline) – traizines by treating cyanuric chloride with cyclo hexyl- p- aminobenzoate in xylene and used in cosmetics, dermatol compounds as sunscreens. Tsista<sup>71</sup> synthesized crystal structure and biological properties of a new series of lipophilic s-triazine as a dihydro folate reductase inhibitors.



Hocquaux et. <sup>72</sup> prepared 2,4 –diamino- s-triazine derivatives treating 2,4-diamino 6- chloro-s-triazine with sodium butoxide in butanol diglyme mixture followed by N- oxidation with on substituted perbenzoic acid. These are useful in treatment and prevention hair loss. Mishina et.al<sup>73</sup> were prepared 2,4 – diamino-6 phenyl- s-triazine derivatives and analogous as sunscreen and light stabilizers. Lesmann et.al. <sup>76</sup>, prepared triazine tris- ( amino alkanoates) and used as fungicides and bactericidal additives for lubricants.

Benzimidazole is the commonest name of the parent compound of the series although other name such as 1,3- benzodiazole is often used. The benzimidazole (Fig-4) resembles the imidazoles in many ways. They process both acidic and basic characteristics. The – NH group in benzimidazole is very weakly basic and relatively strongly acidic. The outstanding property of benzimidazole is their pronounced chemical stability.

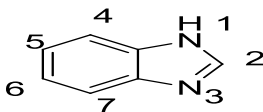


FIG. 14

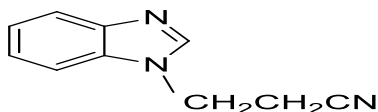


FIG. 15

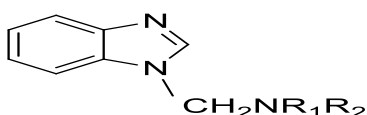


FIG. 16

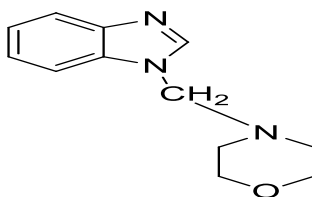


FIG. 17

Alkylation of Benzimidazoles at the 1-position takes place fairly with ethyl sulfate and alkyl iodides. A study of the methylation of 5 (6) -methyl benzimidazoles, 5, (6)- Nitro benzimidazoles,, 5, (6)- bromo benzimidazoles with methyl sulfate has led to conclusion that the presence of electron attracting substituent's in the benzene ring favors' the formation of the 1,6 isomer<sup>77</sup>. Excess of alkylating reagent leads to the formation of quaternary salts. Thus, when benzimidazole is heated with ethyl iodide in methanol solution in a sealed tube at 150-160<sup>0</sup> c, 1,3-diethyl benzimidazolium iodide<sup>78</sup> is formed. 1-Cyanoethyl benzimidazole (Fig-15) may be obtained by the treatment of acrylonitrile on

benzimidazole in the presence of a base catalyst<sup>79</sup>. The 1-substituted benzimidazole in the presence of a base catalyst<sup>79</sup>. The 1-substituted benzimidazoles have lower melting points as a result of their inability to form associates molecules. In 1953 the extent of the literature was such that Klaus Hafmann was able to cover the entire chemistry of monocyclic imidazoles and benzimidazoles in Imidazole and its derivatives.

The early 1950 was an important period regarding the biological significance of benzimidazoles and the closely related purines<sup>80</sup> and vital role of purines in biological system was established and it was discovered that 5,6-dimethyl-1-( $\alpha$ -D-ribofuranosyl) benzimidazole<sup>81</sup> is an integral part of the structure of vitamin B<sub>12</sub>. These findings stimulated great interest in the chemistry of Benzimidazoles and related compounds. A variety of benzimidazole derivatives of use as anthelmintic agents e.g. thiabendazole and fungicides are well established marketed products.

Systematic review on benzimidazoles appeared in 1951<sup>82</sup>, 1953<sup>83</sup>, and 1974<sup>84</sup>, although surveys have appeared in articles covering the chemistry of both imidazoles and benzimidazoles. The chemical reactivity of benzimidazole was governed by the functional behavior of the nitrogens, its salt formation, acylation and alkylation. The alkylation by Mannich procedure was firstly described by Bachman and Hiese<sup>88</sup>. This efficient method has subsequently applied to the preparation of a variety of benzimidazole derivatives including Benalate analogs<sup>89</sup> (Fig. 17). The amine exchange reaction<sup>90</sup> of Mannich bases has been successfully applied to the synthesis of 1-alkylated benzimidazoles

containing a T- carbonyl function. The literature survey reveals that, Varma and Chatterjer<sup>90</sup> synthesized 1,3-disubstituted benzimidazolin – 2 – thiones as anti-inflammatory agents.

Ries et.al.<sup>91</sup>, prepared N- [X-carboxyl alkoxy benzyl] – benzimidazoles and its analogous as angiotensin II antagonists. Huel Nobert et.al.,<sup>92</sup> synthesized [ Biphenyl) methyl] benzimidazoles as a antihypertensives with diuretic and saluretic activity as well. Yoshida et.al.,<sup>93</sup> prepared 2-[4- aminophenyl]-1-methoxy benzimidazole as a stomach secretion inhibitors which were prepared by hydrogenlysis of 2- [-4-nitro-phenyl-1- methoxy]- benzimidazoles in the presence of 10 % Pd/C in THF. Reddy et.al.,<sup>94</sup> prepared 1,3-di-p-chlorophenyl-2-aryl benzimidazoles starting from o- phenylene diamine. Dastimo et. al.,<sup>95</sup> prepared 1- sub -2- benzylamino) benzimidazole derivatives by condensation of aminobenzimidazole with acryl aldehyde derivatives followed by NaBH<sub>4</sub> reduction is used as antihistaminic activity . Yamada et. a.;<sup>96</sup> prepared 1- [biphenyl alkyl] benzimidazole derivatives as angiotensin II antagonists and antihypertensive agents. Hejos et.al.<sup>97</sup> prepared substituted imidazoles as antiulcer agents. Sexena et. al.,<sup>98</sup> prepared 1- (N-substituted aminomethyl) – 2 – [N-phenothiazinyl methyl ] benzimidazoles as antiviral agents by taking chloromethyl benzimidazole and phenothiazine followed by reaction with different secondary amines.

Dhaneshwar et. al.<sup>99</sup> were prepared benzimidazoles derivatives by Mannich reaction and reported their anthelmintic activity. Hublot et. al.<sup>100</sup> were synthesized 1- acryl-2-amino benzimidazoles by taking Me (CH=CH)<sub>2</sub> COCl in

THF at – 5 to 0° c with 2- aminobenzimidazole in THF containing triethylamine to give title compounds and reported as antiulcer agents.

Weston et.al.<sup>101</sup> were prepared benzimidazole derivatives as pesticides by taking 1- geranyl-2 methyl- benzimidazole. The 2,4-dimethyl benzimidazole and NaOH in DMF were treated with formyl chloride to give title compounds and Axelsson et.at.<sup>102</sup> benzimidazole prepared compounds and used as calcium channel blockers and as a useful pharmaceutical, such as in the treatment of Ischemia, anoxia, migraine and psychosts. Orjales et.al.,<sup>103</sup> synthesized new peperidine derivatives of benzimidazoles as antihistaminic and antiallergic agents. Recently Varma, et.al.,<sup>104</sup> synthesized 5- methoxy-1, 3- disubstituted.

Benzimidazolin – 2 thione as potential biological agents by taking 5- methoxybenzimidazolin-2 thione with formaldehyde and various amines under the Mannich condition.

In the light of the above literature survey it is observed that there is not a single attempt to synthesize s-triazine derivatives incorporating with dihydrophyridine and coumarinyl moieties. Benzimidazoles also received less attention incorporating with – N- substituted dihydropyridine, pyrazoline and Isoxazoline moieties, therefore the attempt was made to synthesize these compounds with hope that they may have enhanced biological activity, less side effects, unambiguous structures and better yields.

Therefore the present work entitled “Synthesis of Some biological active compounds” is described in five parts.

The part first consists of three sections. Section – A describes the synthesis of substituted dihydropyridines which were prepared by Hantzsch Synthesis, Section – B describes the Synthesis of substituted s- triazine derivatives. The Cyanuric chloride was converted into 2 – methyl amino- 4 – substituted aniline – 6- chlorotriazines by reaction of methyl amine and substituted anilines. 2 – Methyl amino – 4 – substituted aniline – 6 – chlorotriazines by reaction of methyl amine and substituted anilines 2- methyl amino- 4 – substituted aniline – 6 substituted dihydropyridino – s- triazines (Fig- IB) were prepared by the condensation of substituted aniline – 6- chloro- s- triazines. Section – C deals with the condensation of sodium salt of substituted coumarins with 2,4 – bis (substituted aniline) -6 chloro- s- triazines to give 2,4- bis (substituted aniline ) – 6- (Coumarinyl – 6 /-oxy) –s- triazines (Fig-IC).

The part II includes two sections. The synthesis of heterocyclic diketones (Fig- II A) is described in Section – A. these were obtained from Baker – Venkatraman transformations by taking ester in presence of KOH in dry pyridine. Section – B gives the synthesis of 2,4 – Bis- (Substituted aniline) – 6- hydrazide – s- triazines (Fig- II- B) by taking cyanuric chloride and substituted anilines in the presence of tri ethylamine followed by hydrazine hydrate. It also covers the reaction of (II A) & (II B) in acetic acid to yield 2, 4- Bis- (Substituted aniline) – 6 (3'5' – substituted pyrazol- 1- yl)- s- triazines (Fig-IIC)

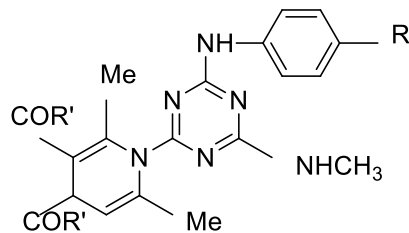


FIG. I B

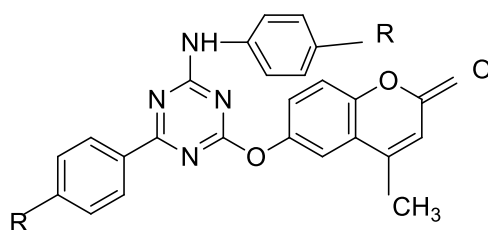


FIG. I C

The Part – III divided into three sections. The synthesis of 1,3- Bis (Propen- 1- onyl) – benzimidazolin – 2- thiones (fig- III A) is described in section – A. these compounds have been synthesized by the reaction of benzimidazolin – 2- thione with 1 – chloro – 3- substituted propenone in presence of pyridine. The section – B deals with the synthesis of 1, 3- [Bis – (5' substituted aryl / heteryl) 4'.5' – dihydro pyrazol – 3'-yl ] benzimidazolin – 2- thiones (Fig- III B) which were obtained by reaction of 1,3 – bis- (Propen- 1-onyl)- benzimidazolin – 2- thiones (Fig- IIIA) with hydrazine hydrate in acetic acid. Section – C describes the reaction of – 1,3- bis- (propen – 1- onyl) benzimidazolin – 2- thiones with hydroxyl amine hydrochloride to yield 1,3 – Bis – (5' - substituted ayrl / heteryl) 4'5' - dihydro isoxazol- 3 – yl) benzimidazolin – 2- thiones. (Fig- III-C).

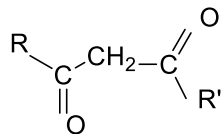


FIG. II A

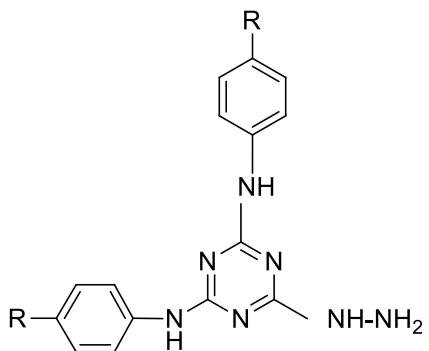


FIG. II B

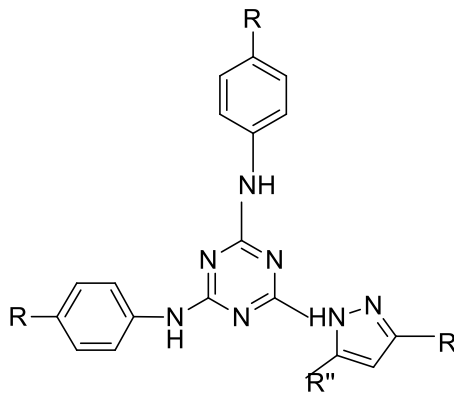


FIG. II C

The part IV describes in two section. The synthesis of N- substituted dihydropyridino methyl benzimidazoles (Fig- IV A). These were obtained by Mannich reaction of benzimidazoles and formaldehyde with substituted dihydropyridines is discussed in section –A The section-B describes the reaction of benzimidazolin – 2- thiones with substituted dihydropyridines under Mannich reaction conditions yielded 1,3 Bis- (N-substituted dihydropyridino methyl) – benzimidazolin – 2 – thiones (Fig- IV B)



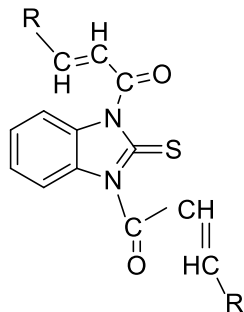


FIG. III - A

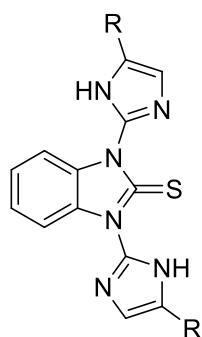


FIG. III - B

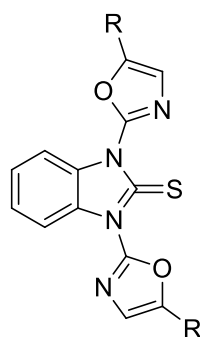


FIG. III - C

The part V describes the biological screening of the selected compounds of all the four parts.

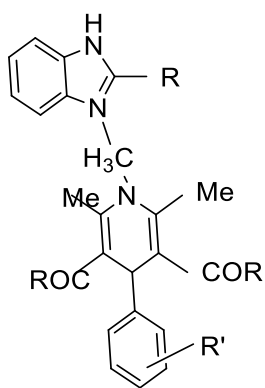


FIG. IV - A

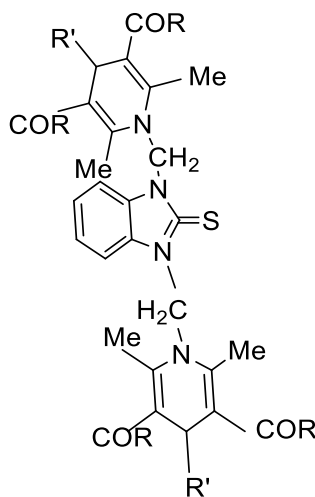


FIG. IV - B

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# **PART - I**

## **SECTION – A**

### **Synthesis of 1,4- DihydroPyridines by Hantzsch Method.**

## **SYNTHESIS OF 1,4- DIHYDROPYRIDINES BY HANTZSCH METHOD**

### **INTRODUCTION**

The dihydropyridines are hydrogen transferring coenzymes and utmost importance in the biological systems <sup>1,2</sup>. A few reports as weak analgesics<sup>3</sup>, antitumor<sup>4</sup>, and coronary dilating activities for dihydropyridines<sup>5</sup>. The literature survey shows that the recently prepared dihydropyridines and its importance in biological system.

Bonnet et. al<sup>6</sup>. Studied the effect of Nifedipine (Fig-IA<sub>1</sub>) on platelet function in normal subjects at rest and under exertion. Oral administration of 20mg nifedipine to healthy male volunteers had little effect on blood platelet parameters such as numbers aggregation behavior of dense granule content under both resting and exercise conditions. The antagonistic, electrophysiol and hemodynamic effects of nifedipine were studied in insolated, pefused guinea pig hearts and in anaesthesised, intubated dogs and compared with those of verapamil.

Iwazawa et.al<sup>7</sup>, prepared dihydropyridine derivatives (Fig-I<sub>2</sub>) and studied their pharmaceutically acceptable acid salts, which have strong vasodialating and antihypertensive activity with reduced side effects such as increase in heart beats and hypertension, heart failure, angim pectons and cardiac infractions, peglion et.al <sup>8</sup> synthesised 2- [(alkylamino) ethoxy methyl] 1,4-dihydropyridine 2,5-dicarbox lates as antitumor adjuncts. Oosumi et.al <sup>9</sup>. obtained 4- pheny;- 1,4-dihydropyridine – 3,5-dicarboxylates useful in treating drug resistant tumors.

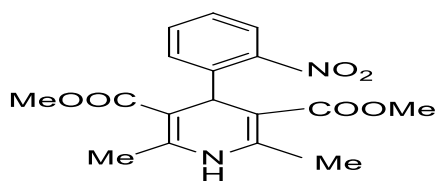


FIG. I - A<sub>1</sub>

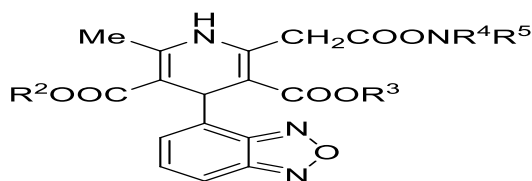


FIG. I - A<sub>2</sub>

Sato et.al.<sup>10</sup> prepared 1,4-dihydropyridine derivatives (Fig- IA<sub>3</sub>) as antihypertensive and vasodialators. Khandilkar et.al.<sup>26</sup> synthesised dihydropyridine compounds (Fig- IA<sub>4</sub>) and reported its calcium channel blocking and  $\beta$ - adrenergic blocking activity. Shingare and Shinde reported the dihydropyridines as active in antihypertensive active agents.

From the above literature survey it was thought worthwhile to use these dihydropyridine compounds as a starting material which were required for the section- B of part III and part IV of the present work. The various dihydropyridines were prepared by the Hantzsch method. This can be prepared either by treating a mixture of substituted aryl aldehyde ( 1 mol equiv) and liquor ammonia, with methyl or ethyl acetoacetate (2 mol equiv) or acetyl acetone, or by first preparing the aminocrotonate from methyl or ethyl acetoacetate or acetyl acetone by action of ammonia followed by its reaction with equimolar amounts of methyl or ethyl acetoacetate or acetyl acetone and aryl aldehydes.

## **METHODS FOR THE PREPARATIONS OF DIHYDROPYRIDINES.**

### **METHODS – I-**

To a equivalent mixture of methyl or ethyl acetoacetate or acetyl acetone , liquor ammonia in ethanol was added aryl aldehydes and the reaction mixture heated in the dark on a water bath for 30 min. The solid separated out was filtered and crystallized from ethanol to give title compounds<sup>26</sup> (Fig- IA<sub>5</sub>)

### **METHODS – II**

Ammonia gas was passed into methyl or ethyl acetoacetate or acetyl acetone with stirring for about 1 hr to yield methyl or ethyl – 3- amino crotonate. To this mixture of methyl or ethyl – 3 amino crotonate and methyl or ethyl acetoacetate was added to aryl aldehydes and the mixture was refluxed for 30 min to give title compounds<sup>26</sup>.

By following the first method all substituted dihydropyridines were prepared (Table – 1.1).

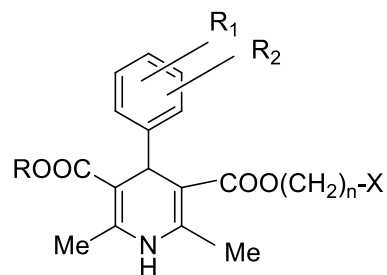


FIG. I - A<sub>3</sub>

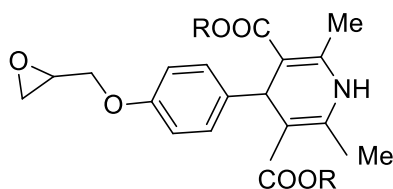


FIG. I - A<sub>4</sub>

**GENERAL METHOD FOR THE SYNTHESIS OF 1,4  
DIHYDROPYRIDINES (FIG- IA<sub>5</sub>).**

To a solution of substituted aldehyde (0.024 mol) in ethyl alcohol (50ml), B- ketoester (0.048 mol) and 2.1 ml of liquor ammonia was then added. The mixture was refluxed for about 30 min in dark. It was cooled and filtered, the solid obtained was washed with cold alcohol abs crystallized from ethyl alcohol. The purity of the compound was checked by TLC. The melting points, yields, and solvent of crystallization if these compounds have been tabulated in table 1.1.

## EXPERIMENTAL PROCEDURE

### EXPERIMENT NO.1

#### PREPARATION OF 1,4- DIHYDRO- [2,6 –DIMETHYL-4 (4' METHOXY PHENYL)]- PYRIDINE – 3,5- DICARBOXYLIC ESTER (11) TABLE- 1.0 :-

To a solution of 4- methoxy benzaldehyde (2.00 g; 0.24 mol) in ethanol (50 ml), methyl acetoacetate (5.56g; 0.048 mol) and 2.1 ml liquor ammonia was then refluxed for about 30 min in dark the solid thus obtained was filtered and washed with cold alcohol and crystallized from ethanol to give the title compound. M.pt.186 0c ; Yield -72 %.

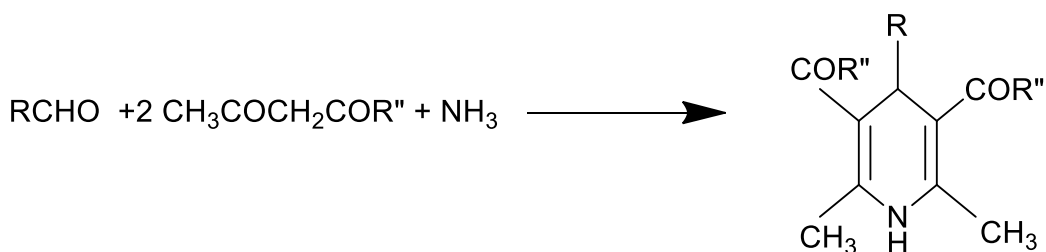


FIG. I A 5

Where ;

R = C<sub>6</sub>H<sub>5</sub>, 2 NO<sub>2</sub>-Ph, 3-NO<sub>2</sub>-Ph, 4-NO<sub>2</sub>-Ph,  
2-ClPh, 3ClPh, 4-ClPh, 3-BrPh, 2-MePh,  
3MePh,4-MePh,2-OMePh,3-MOePh,4-OMePh,  
2-OHC<sub>6</sub>H<sub>4</sub>, 4-OHC<sub>6</sub>H<sub>4</sub>,2- Furyl, 3- Pyridyl,  
2- Thienyl.

R'' = CH<sub>3</sub>, OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>.

## EXPERIMENT NO.2

### **PREPARATION OF 1,4- DIHYDRO- [2,6 –DIMETHYL-4 (3'- CHLORO PHENYL)]- PYRIDINE – 3,5- PYRIDINE DIONE (06) TABLE- 1.1 :-**

To a solution of 3- chloro benzaldehyde (3.61 g; 0.024 mol) in 50 ml ethanol, acetyl acetone (4.8g; 0.048 mol) and 2.1 ml liq. ammonia was added and the mixture was then refluxed for about 30 min in dark. The solid separated during refluxing was cooled and filtered, washed with cold ethanol and crystallized from hot ethanol. M.Pt.  $212^{\circ}\text{C}$  ; yield 89 %.

By following above procedure, the other compounds of this series were prepared.



**TABLE- 1.1****CHARACTERISATION DATA OF SUBSTITUTED DIHYDROPYRIDINES (FIG. IA 5)**

COMP. NO	R	R'	YIELD (%)	M.P.(OC)
1.	C <sub>6</sub> H <sub>5</sub>	Me	77	172
2.	2-NO <sub>2</sub> -ph	Me	80	226
3.	3- NO <sub>2</sub> -ph	Me	79	186
4.	4- NO <sub>2</sub> -ph	Me	75	293
5.	2-Cl-ph	Me	71	184
6.	3-Cl-ph	Me	89	212
7.	4-Cl-ph	Me	86	179
8.	3- Br-ph	Me	80	217
9.	2-OCH <sub>3</sub> -ph	Me	78	171
10.	3-OCH <sub>3</sub> -ph	Me	85	181
11.	4-OCH <sub>3</sub> -ph	Me	82	168
12.	2-tolyl	Me	80	181
13.	3-tolyl	Me	74	186
14.	4-tolyl	Me	78	178
15.	2-furyl	Me	74	158
16.	3-pyridyl	Me	84	246
17.	2-thienyl	Me	90	141
18.	-ph	OMe	82	197
19.	2- NO <sub>2</sub> -ph	OMe	75	235

COMP. NO	R	R'	YIELD (%)	M.P.(OC)
20.	2-NO <sub>2</sub> -ph	OMe	78	204
21.	2-NO <sub>2</sub> -ph	OMe	71	176
22.	2-Cl-ph	OMe	69	188
23.	3-Cl-ph	OMe	72	192
24.	4-Cl-ph	OMe	66	191
25.	3- Br-ph	OMe	73	193
26.	2- OMe-ph	OMe	76	157
27.	3- OMe-ph	OMe	79	163
28.	4- OMe-ph	OMe	72	186
29.	2- Me-Ph	OMe	80	176
30.	3- Me-Ph	OMe	82	194
31.	4- Me-Ph	OMe	84	179
32.	2-OH-ph	OMe	70	112
33.	4-OH-ph	OMe	85	223
34.	2-furyl	OMe	80	186
35.	3-pyridyl	OMe	80	246
36.	2-thienyl	OMe	69	190
37.	-ph	OEt	73	187
38.	2- NO <sub>2</sub> -ph	OEt	67	152
39.	3- NO <sub>2</sub> -ph	OEt	66	160

COMP. NO	R	R'	YIELD (%)	M.P.(OC)
40.	2-NO <sub>2</sub> -ph	OEt	70	189
41.	2-Cl-ph	OEt	70	160
42.	3-Cl-ph	OEt	74	166
43.	4-Cl-ph	OEt	68	178
44.	3- Br-ph	OEt	64	124
45.	4- Br-ph	OEt	76	110
46.	2- OMe-ph	OEt	70	119
47.	3- OMe-ph	OEt	79	130
48.	4- OMe-ph	OEt	81	98
49.	4- Me-Ph	OEt	80	112
50.	4-OH	OEt	76	146

❖ A\*All Compounds are Crystallized from the ethanol.

## **PART - I**

### **SECTION – B**

**Synthesis of 2- (Methyl amino)-4-**

**(Ethoxy aniline)-6- (substituted**

**Dihydropyridino)-**

**s- triazines.**

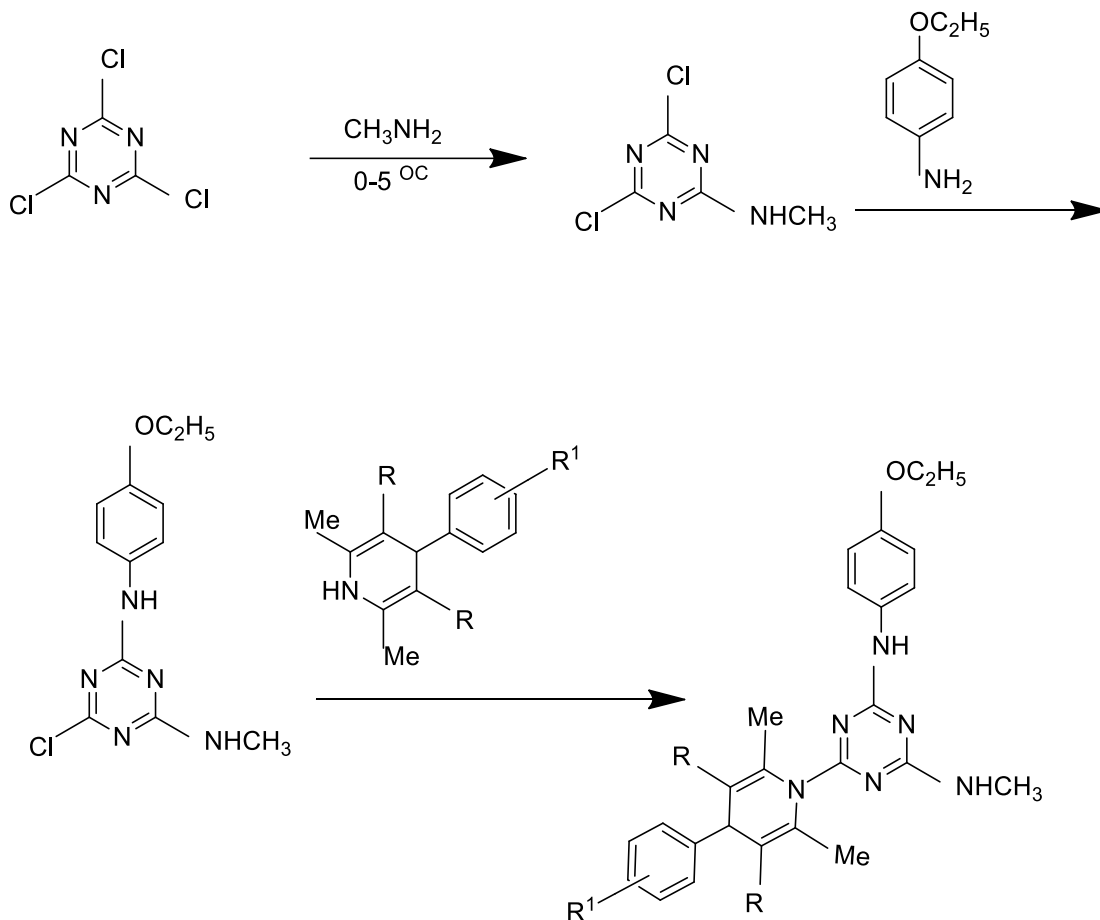
## INTRODUCTION

A good deal of importance is being given to S- triazine derivatives due to their wide use in medicinal field. The majority of substitution reactions of S-triazines are nucleophilic substitution of cyanuric chloride. The chlorines atoms of cyanuric chloride may be replaced successively by various amino or substituted groups <sup>12-14</sup>.

In general one atom of chlorine is replaced 0<sup>0</sup>. The second at 30-50<sup>0</sup> and the third at 90-100<sup>0</sup>. The replacement of all three chlorine atoms of cyanuric chloride at 25<sup>0</sup> by secondary amines such as morpholine or piperidine had reported by Pearlman banks. S-triazine nucleus <sup>15</sup> has a potential therapeutic agents for diseases due to bacteria & protozoa <sup>16</sup>. African sleeping sickness <sup>17,18</sup>, Malaria<sup>19,20</sup> , Cancer and antiviral<sup>21</sup>. While the dihydropyridines<sup>22-24</sup> are known to exhibit antihypertensive <sup>25,26</sup>, antimicrobial and calcium channel blocking activity.

2,4,6- substituted –s- triazines provide the bulk of the literature on S-triazines. A glance at the standard reference work shows that more studies have been carried out on s-triazine derivatives which originates from cyanuric chloride. From the diverse biological importance of s-triazine derivatives incorporating substituted dihydropyridine moiety. An attempt is made to synthesis 2,4,6-tri substituted –s- triazines and evaluate them for its pharmacological activities.

**PRESENT WORK :**



**FIG. I - B<sub>1</sub>**

The synthesis of 2- (methyl amino) – 4- (ethoxy aniline) – 6- (Substituted dihydropyridino) –s-triazines (Fig-IB<sub>1</sub>) were carried out in the present work. The 2-methyl amino – 4- ethoxy aniline – 6- chloro- s-triazines were treated with various substituted dihydropyridines at refluxed condition. The method gives better yield and unambiguous products and starting materials can be easily prepared. The formation of the product were confirmed by spectral and elemental analysis.

**GENERAL METHOD OF PREPARATION OF 2- (METHYL AMINO) -4-(4' ETHOXY ANILINO)- 6- (-N-(1'4'- DIHYDRO – [-4'- (SUBSTITUTED ARYL) – 3'5'- DIACETYL -2',6' – DIMETHYL- PYRIDINO] –S- TRIAZINES :- (FIG- IB1).**

A mixture of 2-methyl amino -4-(4'-ethoxy aniline) – 6- chloro –s-triazine (0.01 mol) and substituted dihydropyridine (0.01 mol) in acetone (20 ml) was refluxed for 4 hrs on a water bath. It was then cooled and poured on crushed ice and the resulting solid was filtered washed & dried. It was recrystallized from proper solvent . The melting points, yields solvents for crystallization are listed in table 1.2.

**DISCUSSION OF IR SPECTRA**

IR Spectra of the 2-methyl amino -4-(4'-ethoxy anilino -6- (N-1',4'- dihydro – [4'-(4'' –hydroxy phenyl) -3' ,5'- diacetyl 2',6'- diethyl- pyridine) –s- traizines were recorded on perkin elmer spectrophotometer model 1420 in nujol mulls.

Above compound have shows absorption bands at 3350 -3480 (-NH stretching & -OH group). 1660-1695 (-C=O stretching), 1620-1635 (C=N), 1610-1600 (C=C stretching ) & 890- 870 cm<sup>-1</sup> (C<sub>3</sub> N<sub>3</sub> stretching)

## **DISCUSSION OF PMR SPECTRA**

PMR spectra of the -s-triazine (Fig- IB<sub>1</sub>) were taken on FT - 80A Spectrometer in CDCl<sub>3</sub> using TMS as internal standard. Chemical shift is expressed in  $\delta$  (ppm) scale.

The presence of signals at  $\delta$  1.20- 1.02 (t, CH<sub>2</sub>- CH<sub>3</sub>),  $\delta$  (2.20 (s,6H,CH<sub>3</sub>),  $\delta$  3.56 (s,6H-CO-CH<sub>3</sub>),  $\delta$  3.60 (s' CH<sub>3</sub>),  $\delta$  3.74-3.96 (q, 2H,O-CH<sub>2</sub>-CH<sub>3</sub>)  $\delta$  5.70 (S, 1H,pyridyl H,C-4)  $\delta$  6.40-7.76 (m, 9H, Ar-H & NH). The spectrum No.2 represents the spectrum of 2- methyl amino - 4- ethoxy aniline- 6- (N-1'4' -dihydro - [(4'-chloro phenyl) -'5'- dicarbo methoxy - 2', 6'- dimethyl - pyridine] -s- triazines.

## **EXPERIMENTAL PROCEDURE :-**

### **SYNTHESIS OF 2- METHYLAMINO - 4- (ETHOXY ANILINO)- 6- (N-1,4-DIHYDRO - 4'- (4''- HYDROXY PHENYL) - 3',5' DIACETYL - 2' 6'- DIMETHYL PYRIDINO) - S TRIAZINES (17. TABLE 1.2) :-**

The mixture of 2 methyl amino - 4- (4'-ethoxy aniline) -6- chloro -s-triazine (2.63 g ; 0.01 mol) and 1,4- dihydro- [4-(4''-hydroxy phenyl) -3,5-dictyl-2,5 dimethyl]- pyridine (2.52 g; 0.01 mol) in acetone (20ml) was refluxed for 4 hrs on a boiling water bath. It was then cooled and poured on crushed ice and the resulting solids was filtered, washed and dried. It was crystallized from aq. Alcohol . M.P. 125<sup>0</sup>C; Yield 69% Similarly, all other compounds of this series were prepared.



**TABLE – 1.2****CHARACTRISATION DATA OF 2- (METHYLAMINO) – 4 – (ETHOXYANILINO) – 6-  
(SUBSTITUTED DIHYDROPYRIDINO – S- TRIAZINES (FIG- IB1).**

Comp. No.	R.	R1	Yield (%)	M.P.* (0c)	Mol.formula	% of Nitrogen	
						Found	Calcd
1.	-COCH <sub>3</sub>	H	65	120	C <sub>32</sub> H <sub>38</sub> N <sub>6</sub> D <sub>3</sub>	15.02	15.16
2.	-COCH <sub>3</sub>	2-CH <sub>3</sub>	61	130	C <sub>33</sub> H <sub>40</sub> N <sub>6</sub> D <sub>3</sub>	14.61	14.78
3.	-COCH <sub>3</sub>	5-CH <sub>3</sub>	68	122	C <sub>33</sub> H <sub>40</sub> N <sub>6</sub> D <sub>3</sub>	14.62	14.78
4.	-COCH <sub>3</sub>	4-CH <sub>3</sub>	63	116	C <sub>33</sub> H <sub>40</sub> N <sub>6</sub> O <sub>3</sub>	14.58	14.78
5.	-COCH <sub>3</sub>	2-OCH <sub>3</sub>	70	118	C <sub>33</sub> H <sub>40</sub> N <sub>6</sub> O <sub>4</sub>	14.20	14.38
6.	-COCH <sub>3</sub>	4-OCH <sub>3</sub>	65	128	C <sub>33</sub> H <sub>40</sub> N <sub>6</sub> O <sub>4</sub>	14.14	14.38
7.	-COCH <sub>3</sub>	5-OCH <sub>3</sub>	68	131	C <sub>33</sub> H <sub>40</sub> N <sub>6</sub> O <sub>4</sub>	14.31	14.38
8.	-COCH <sub>3</sub>	2-Cl	62	124	C <sub>32</sub> H <sub>37</sub> N <sub>6</sub> D <sub>3</sub> Cl	14.07	14.27
9.	-COCH <sub>3</sub>	3-Cl	66	131	C <sub>32</sub> H <sub>37</sub> N <sub>6</sub> D <sub>3</sub> Cl	14.14	14.27
10.	-COCH <sub>3</sub>	4-Cl	71	136	C <sub>32</sub> H <sub>37</sub> N <sub>7</sub> O <sub>3</sub> Cl	14.01	14.27
11.	-COCH <sub>3</sub>	2-NO <sub>2</sub>	72	140	C <sub>32</sub> H <sub>37</sub> N <sub>7</sub> O <sub>5</sub>	16.11	16.36
12.	-COCH <sub>3</sub>	3-NO <sub>2</sub>	63	129	C <sub>32</sub> H <sub>37</sub> N <sub>7</sub> O <sub>5</sub>	16.11	16.36
13.	-COCH <sub>3</sub>	4-NO <sub>2</sub>	68	136	C <sub>32</sub> H <sub>37</sub> N <sub>6</sub> O <sub>5</sub>	16.11	16.36
14.	-COCH <sub>3</sub>	3-Br	65	132	C <sub>32</sub> H <sub>37</sub> N <sub>7</sub> O <sub>5</sub> Br.	13.04	13.27
15.	-COCH <sub>3</sub>	4-Br	67	142	C <sub>32</sub> H <sub>37</sub> N <sub>6</sub> O <sub>3</sub> Br.	13.21	13.27

16.	-COCH <sub>3</sub>	2-OH	70	114	C <sub>32</sub> H <sub>38</sub> N <sub>6</sub> O <sub>4</sub> .	14.62	14.73
17.	-COCH <sub>3</sub>	4-OH	69	125	C <sub>32</sub> H <sub>38</sub> N <sub>6</sub> O <sub>4</sub> .	14.60	14.7
18.	-COCH <sub>3</sub>	H	65	127	C <sub>32</sub> H <sub>38</sub> N <sub>6</sub> O <sub>5</sub> .	14.13	14.33
19	-COOCH <sub>3</sub>	2-CH <sub>3</sub>	70	124	C <sub>33</sub> H <sub>40</sub> N <sub>6</sub> O <sub>5</sub> .	13.84	14.00
20.	-COOCH <sub>3</sub>	3-CH <sub>3</sub>	64	118	C <sub>33</sub> H <sub>40</sub> N <sub>6</sub> O <sub>5</sub> .	13.83	14.00
21.	-COOCH <sub>3</sub>	4-CH <sub>3</sub>	69	109	C <sub>33</sub> H <sub>40</sub> N <sub>6</sub> O <sub>5</sub> .	13.91	14.00
22	-COOCH <sub>3</sub>	2-OCH <sub>3</sub>	59	114	C <sub>33</sub> H <sub>40</sub> N <sub>6</sub> O <sub>6</sub>	13.49	13.63
23.	-COOCH <sub>3</sub>	3-OCH <sub>3</sub>	62	135	C <sub>33</sub> H <sub>40</sub> N <sub>6</sub> O <sub>6</sub>	16.11	16.36
24.	-COOCH <sub>3</sub>	4-OCH <sub>3</sub>	66	156	C <sub>33</sub> H <sub>40</sub> N <sub>6</sub> O <sub>6</sub>	13.28	13.63
25.	-COOCH <sub>3</sub>	2-C1	71	171	C <sub>32</sub> H <sub>37</sub> N <sub>6</sub> O <sub>5</sub> C1	13.34	13.53
26.	-COOCH <sub>3</sub>	3-C1	68	155	C <sub>32</sub> H <sub>37</sub> N <sub>6</sub> O <sub>5</sub> C1	13.26	13.53
27.	-COOCH <sub>3</sub>	4-C1	70	135	C <sub>32</sub> H <sub>37</sub> N <sub>6</sub> O <sub>5</sub> C1	13.38	13.35
28.	-COOCH <sub>3</sub>	3-Br	64	165	C <sub>32</sub> H <sub>37</sub> N <sub>6</sub> O <sub>5</sub> Br	12.49	13.69
29.	-COOCH <sub>3</sub>	4-Br	60	172	C <sub>32</sub> H <sub>37</sub> N <sub>6</sub> O <sub>5</sub> Br	12.34	12.63
30.	-COOCH <sub>3</sub>	2-NO <sub>2</sub>	69	128	C <sub>32</sub> H <sub>37</sub> N <sub>7</sub> O <sub>7</sub>	15.37	15.53
31.	-COOCH <sub>3</sub>	3-NO <sub>2</sub>	63	114	C <sub>32</sub> H <sub>37</sub> N <sub>7</sub> O <sub>7</sub>	15.39	15.53
32.	-COOCH <sub>3</sub>	2-NO <sub>2</sub>	71	110	C <sub>32</sub> H <sub>38</sub> N <sub>6</sub> O <sub>6</sub>	15.34	15.53
33.	-COOCH <sub>3</sub>	2-OH	77	98	C <sub>32</sub> H <sub>38</sub> N <sub>6</sub> O <sub>6</sub>	13.83	13.95
34.	-COOCH <sub>3</sub>	3-OH	71	120	C <sub>32</sub> H <sub>38</sub> N <sub>6</sub> O <sub>6</sub>	13.79	13.95
35	-COOCH <sub>3</sub>	4- OH	73	126	C <sub>32</sub> H <sub>38</sub> N <sub>6</sub> O <sub>6</sub>	13.72	13.95
36.	-COOC <sub>2</sub> H <sub>5</sub>	H	80	108	C <sub>34</sub> H <sub>42</sub> N <sub>6</sub> O <sub>5</sub>	13.44	13.68

37.	COOC <sub>2</sub> H <sub>5</sub>	2-CH <sub>3</sub>	78	129	C <sub>35</sub> H <sub>44</sub> N <sub>6</sub> O <sub>5</sub>	13.14	13.37
38.	COOC <sub>2</sub> H <sub>5</sub>	3-CH <sub>3</sub>	72	135	C <sub>35</sub> H <sub>44</sub> N <sub>6</sub> O <sub>5</sub>	13.17	13.37
39.	COOC <sub>2</sub> H <sub>5</sub>	4-CH <sub>3</sub>	70	144	C <sub>35</sub> H <sub>44</sub> N <sub>6</sub> O <sub>5</sub>	13.18	13.37
40.	COOC <sub>2</sub> H <sub>5</sub>	2-OCH <sub>3</sub>	68	130	C <sub>35</sub> H <sub>44</sub> N <sub>6</sub> O <sub>6</sub>	12.89	13.04
41.	COOC <sub>2</sub> H <sub>5</sub>	3-OCH <sub>3</sub>	66	141	C <sub>35</sub> H <sub>44</sub> N <sub>6</sub> O <sub>6</sub>	12.88	13.04
42.	COOC <sub>2</sub> H <sub>5</sub>	4-OCH <sub>3</sub>	71	152	C <sub>35</sub> H <sub>44</sub> N <sub>6</sub> O <sub>6</sub>	12.91	13.04
43.	COOC <sub>2</sub> H <sub>5</sub>	2-C1	67	132	C <sub>34</sub> H <sub>41</sub> N <sub>6</sub> O <sub>5</sub> C1	12.68	12.95
44.	COOC <sub>2</sub> H <sub>5</sub>	3-C1	69	139	C <sub>34</sub> H <sub>41</sub> N <sub>6</sub> O <sub>5</sub> C1	12.83	12.95
45.	COOC <sub>2</sub> H <sub>5</sub>	4-C1	67	138	C <sub>34</sub> H <sub>41</sub> N <sub>6</sub> O <sub>5</sub> C1	12.82	12.95
46.	COOC <sub>2</sub> H <sub>5</sub>	3Br	80	170	C <sub>34</sub> H <sub>41</sub> N <sub>6</sub> O <sub>5</sub> Br	12.09	12.28
47.	COOC <sub>2</sub> H <sub>5</sub>	2-NO <sub>2</sub>	77	140	C <sub>34</sub> H <sub>41</sub> N <sub>7</sub> O <sub>7</sub>	12.59	12.74
48.	COOC <sub>2</sub> H <sub>5</sub>	4-NO <sub>2</sub>	80	148	C <sub>34</sub> H <sub>41</sub> N <sub>7</sub> O <sub>7</sub>	12.67	12.74
49.	COOC <sub>2</sub> H <sub>5</sub>	2-OH	84	128	C <sub>34</sub> H <sub>42</sub> N <sub>6</sub> O <sub>6</sub>	13.27	13.31
50.	COOC <sub>2</sub> H <sub>5</sub>	4-OH	81	144	C <sub>34</sub> H <sub>42</sub> N <sub>6</sub> O <sub>6</sub>	13.15	13.31

- A\*All compounds recrystallized from Aq. alcohol & gives satisfactory C & H analysis.

# **PART - I**

## **SECTION – C**

### **Synthesis of 2,4-(substituted -anilino)- 6- (substituted coumarinyloxy)-s- triazines.**

## INTRODUCTION

The oxygen or nitrogen heterocyclic compounds like coumarins and triazines are widely used in the medicinal field. The unsaturated lactones have been known for their various physiological activities<sup>27-33</sup>. Coumarin, a lactone of coumarinic acid possesses different physiological activity<sup>34</sup>. The plants extract of umbelliferae and Rutaceae families are known to act as fish poison. It was shown by Priest<sup>35</sup> that activity of these plant extracts is attributed due to presence of coumarin derivatives. It was also found that coumarin derivatives act as narcotics to animals<sup>36</sup>. Kuhn showed that coumarin derivatives inhibit the growth of fungi and bacteria, hence coumarin derivatives have been used as preservatives for potato. Andus and Quastel<sup>37</sup> showed that coumarin exhibits double effects, they inhibit germination of seed and also arrest root growth.

3- substituted coumarins and furan coumarins are found to be useful as drugs<sup>38</sup>. Sodium salt of coumarin – 3- carboxylic acid is used in treatment of asthma along with adrenalin. Some coumarins are known to possess antifungal and antibacterial activities<sup>39-42</sup>. Several workers reported that substituted s-triazines possess wide range of physiological activities. Schering A. G<sup>43</sup> reported s- triazines (Fig-IC<sub>1</sub>) as herbimicrobicides and plant growth regulators. Hocquaus<sup>44</sup> et.al. prepared 2,4- diamine – 6- alkoxy – 1,3,5 – triazine derivatives and used for treating and preventing hair loss. Histsuka et. al.<sup>45</sup> synthesized substituted – triazines (Fig.IC<sub>2</sub>) as herbicides.

Kreutzberger<sup>46</sup> et. al. prepared six antidibetic triazines by treating the dichloro triazines with RR' C6, H3, OH. Kvalek<sup>47</sup> et.al reported the process for the production of 2- amino-4- alkoxy- - 6- alkyl – 1, 3, 5- triazines as useful veterinary sedatives and herbicidal intermediates. Desai<sup>48-49</sup> et.al prepared – s- triazines (Fig- IC<sub>3</sub>) and (Fig-IC<sub>4</sub>) as a antibacterial agents. Considering the literature survey described earlier on physiological active s- triazines and taking into account of the wide biological activities of coumarins.

It was though worth while to synthesize 2,4- Bis-(substituted aniline) – 6 – (4'-methyl- 5- substituted – B' – acetyl coumarinyl – ' 6 / 7' –oxy) – s- triazines in the hope to obtain new s- triazine with enhanced biological activities.

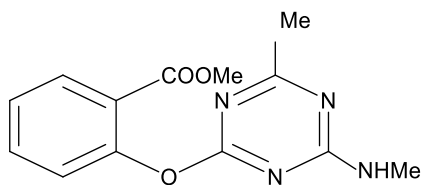


FIG. I C-1

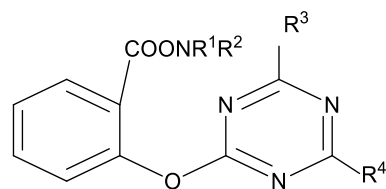


FIG. I C-2

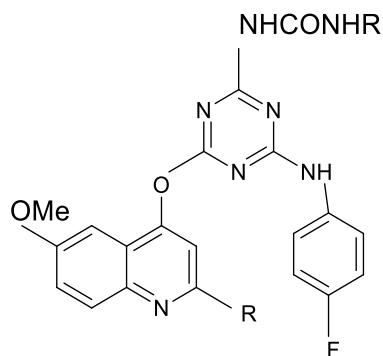


FIG. I C-3

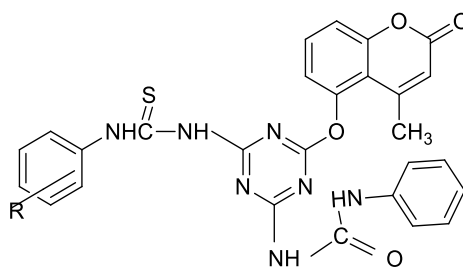


FIG. I C-4

## **PRESENT WORK**

Synthesis of 2, 4 – Bis- (substituted aniline) – 6 – (4' –methyl - 5' /6' substituted – 8' acetyl coumarinyl- 6'/7'- oxy) – s- triazine (Fig IC<sub>5</sub>) has been undertaken in the present work by known method. The title compounds have been prepared from Cynauric chloride and various substituted anilines in presence of aq. NaHCO<sub>3</sub>. The intermediate so obtained were treated with sodium salt of coumarins. The method was used because it offers.

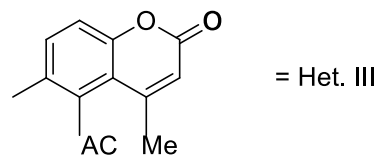
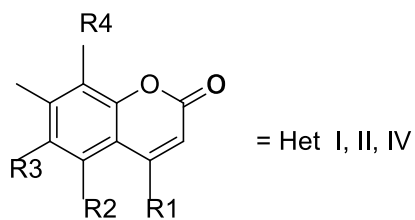
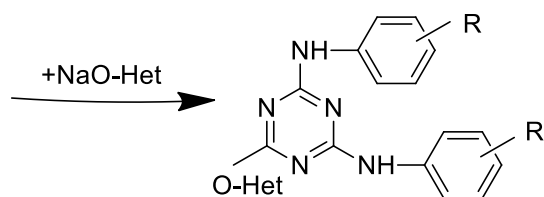
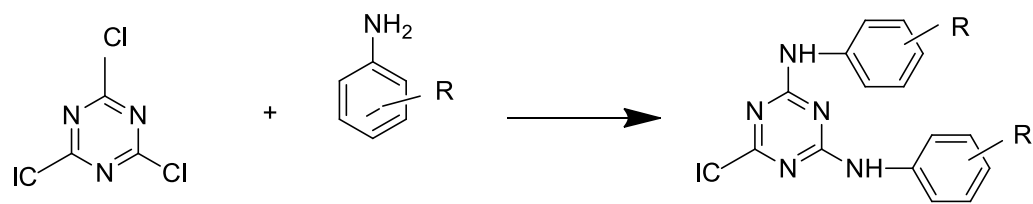
1. Moderate reaction conditions.
2. Starting materials were readily available.
3. Products having unambiguous structures.
4. Better yields.

The substituted coumarins used were prepared by known methods<sup>50-52</sup>.

### **GENERAL METHOD FOR THE SYNTHESIS OF 2, 4, BIS – (** **SUBSTITUTED ANILINO) – 6 – (SUBSTITUTED COUMARINYL- OXY)** **–S- TRIAZINES.**

A Mixture of 2, 4 – Bis – (Substituted aniline) – 6 –chloro – s- triazine and sodium salt of substituted coumarin in THF was stirred for 30 min. The mixture was refluxed for 3 hrs. It was cooled, and poured on crushed ice. The separated solid was filtered, washed with water dried and crystallized from aq. DMF. The purity of title compound was checked by TLC. The IR and NMR spectra indicates the formation of the desired product.

The M. pts. Yields, elements analysis and crystallization solvents of these compounds are tabulated in table 1.3



	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>
Het I = Me	Me	H	Ac	Me
Het I = Me	Me	H	H	Ac
Het I = H	H	AcOMe	H	Ac

FIG. 1 C 5



## **DISCUSSION OF IR SPECTRA**

The IR spectra of some of the representative compounds of this series were scanned on perkin –Elmer IR – 1420 Spectrophotometer using nujol mull.

The compounds showed absorption band in the region of 1710-1730  $\text{cm}^{-1}$  due to C=O stretching of coumarin moiety. 1600- 1630  $\text{cm}^{-1}$  band due to C=C or C=N stretching. It is observed that the absorption band at 1280  $\text{cm}^{-1}$  and 1070-1140  $\text{cm}^{-1}$  are present and can be attributed to ether linkage. The absence of O- H stretching in the region 3200-3500  $\text{cm}^{-1}$  indicate the formation of title compounds. The single weak band at the 3340  $\text{cm}^{-1}$  region are due to secondary amines.

The given IR spectrum No.3 represents spectrum of 2,4- Bis – (4'- chloro aniline) – 6- (4' –methyl – 8' – acetyl coumarinyl- 7'- oxy) – s- triazines.

## **DISCUSSION OF PMR SPECTRA**

The PMR spectra of few representative compounds were scanned of FT – BOA spectrometer using TMS as standard and DMSO- $\text{d}_6$  as solvent. Chemical shifts are in ppm scale. The given PMR spectrum no. 4 represents the spectrum of 2, 4 –Bis- (4'- chloro aniline) - 6 – (4' –methyl – 8' acetyl coumarinyl – 7 ' – oxy) – s- triazines as it displays following signals.

$\delta$  2.25 (s, 3H, -  $\text{COCH}_3$ ),  $\delta$  2.35 (s, 3H, - pyrone –  $\text{CH}_3$ ),  $\delta$  6.52- 7360 (m,Ar protons – 12H, & NH) stretching.

## EXPERIMENTAL PROCEDURE

### PREPARATION OF 2, 4 -BIS- (4' CHLORO ANILINO) – 6 -(4',8' – DIMETHYL- 6' ACETYL- COUMARINYL – 7' OXY ) – S- TRIAZINES : (04) TABLE 1.3.

To the sodium salt of 7 -hydroxy -4, 8 – dimethyl – 6- acetyl coumarin (2.54 g; 0.01 mol), 2, 4 – Bis – (4' - chloro aniline) – 6- chloro – s- triazine (3.66g; 0.01 mol) was added in portions. After the completion of addition the reaction mixture was stirred further for 45 min. by maintaining temperature to 60<sup>0</sup>C. Then it was refluxed for 3 hrs.

The reaction was monitored by TLC. After the completion of the reaction. The reaction mixture was cooled and poured over crushed ice. The solid obtained was filtered, washes with water and dried. Then it was crystallized from aq. DMF. M. Pt. 270 <sup>0</sup>c, yield - 66%.

The purity of the compound was checked by TLC. Finally this compound was confirmed by IR, PMR and elemental analysis.

Similarly other compounds of this series were also prepared and their physical parameters are tabulated in Table 1.3.

**TABLE – 1.3****CHARACTRISATION DATA OF 2,4 -BIS- (SUBSTITUTED ANILINO) – 6 –(SUBSTITUTED COUMARINYLOXY) –S – TRAIZINES (FIG. IC<sub>5</sub>)**

Comp. No.	Sub.R.	Het.	M.P.* (°c)	Yield (%)	Mol.formula	% of Nitrogen	
						Calcd	Found
1.	H	I	130	64	C <sub>28</sub> H <sub>23</sub> N <sub>5</sub> O <sub>4</sub>	14.19	13.85
2.	4-CH <sub>3</sub>	I	121	73	C <sub>30</sub> H <sub>27</sub> N <sub>5</sub> O <sub>4</sub>	13.43	13.30
3.	3-C1	I	206	68	C <sub>28</sub> H <sub>21</sub> N <sub>5</sub> O <sub>4</sub> C1 <sub>2</sub>	12.47	12.25
4.	4-C1	I	270	72	C <sub>28</sub> H <sub>21</sub> N <sub>7</sub> O <sub>8</sub>	12.47	12.25
5.	3-NO <sub>2</sub>	I	149	69	C <sub>28</sub> H <sub>21</sub> N <sub>7</sub> O <sub>8</sub>	16.80	16.42
6.	0-NO <sub>2</sub>	I	177	71	C <sub>28</sub> H <sub>21</sub> N <sub>7</sub> O <sub>8</sub>	16.80	16.42
7.	4-OCH <sub>3</sub>	I	139	67	C <sub>30</sub> H <sub>27</sub> N <sub>5</sub> O <sub>6</sub>	12.65	12.35
8.	4-002H <sub>5</sub>	I	146	64	C <sub>32</sub> H <sub>31</sub> N <sub>5</sub> O <sub>6</sub>	12.04	12.00
9.	4-Br	I	204	62	C <sub>28</sub> H <sub>21</sub> N <sub>5</sub> O <sub>4</sub> Br <sub>2</sub>	10.75	10.60
10.	4-OH	I	150	74	C <sub>28</sub> H <sub>23</sub> N <sub>5</sub> O <sub>6</sub>	13.33	13.12
11.	H	II	189	63	C <sub>27</sub> H <sub>21</sub> N <sub>5</sub> O <sub>4</sub>	14.61	14.49
12.	4-CH <sub>3</sub>	II	198	60	C <sub>29</sub> H <sub>25</sub> N <sub>5</sub> O <sub>4</sub>	13.86	13.54
13.	4-C1	II	187	59	C <sub>27</sub> H <sub>19</sub> N <sub>5</sub> O <sub>4</sub> C1 <sub>2</sub>	12.77	12.62
14.	3-NO <sub>2</sub>	II	208	68	C <sub>27</sub> H <sub>19</sub> N <sub>7</sub> O <sub>8</sub>	17.22	17.00
15.	4-NO <sub>2</sub>	II	215	62	C <sub>27</sub> H <sub>19</sub> N <sub>7</sub> O <sub>8</sub>	17.22	17.00
16.	4-OCH <sub>3</sub>	II	203	72	C <sub>29</sub> H <sub>25</sub> N <sub>5</sub> O <sub>6</sub>	12.98	12.70
17.	4-00 <sub>2</sub> H <sub>5</sub>	II	210	61	C <sub>31</sub> H <sub>29</sub> N <sub>5</sub> O <sub>6</sub>	12.34	12.10

18.	4-Br	II	219	64	C <sub>27</sub> H <sub>19</sub> N <sub>5</sub> O <sub>4</sub> Br <sub>2</sub>	10.98	10.75
19.	3-OH	II	238	67	C <sub>27</sub> H <sub>21</sub> N <sub>5</sub> O <sub>6</sub>	13.69	13.52
20.	4.OH	II	243	71	C <sub>27</sub> H <sub>21</sub> N <sub>5</sub> O <sub>6</sub>	13.69	13.52
21.	H	III	170	70	C <sub>27</sub> H <sub>21</sub> N <sub>5</sub> O <sub>6</sub>	14.61	14.39
22.	4-CH <sub>3</sub>	III	178	60	C <sub>29</sub> H <sub>25</sub> N <sub>5</sub> O <sub>4</sub>	13.86	13.40
23.	3-C1	III	175	69	C <sub>27</sub> H <sub>19</sub> N <sub>5</sub> O <sub>4</sub> C1 <sub>2</sub>	12.77	12.58
24.	4-C1	III	186	73	C <sub>27</sub> H <sub>19</sub> N <sub>5</sub> O <sub>4</sub> C1 <sub>2</sub>	12.77	12.58
25.	3-NO <sub>2</sub>	III	177	67	C <sub>27</sub> H <sub>19</sub> N <sub>7</sub> O <sub>8</sub>	17.22	17.10
26.	4-NO <sub>2</sub>	III	216	64	C <sub>27</sub> H <sub>19</sub> N <sub>7</sub> O <sub>8</sub>	17.22	17.10
27.	4-OCH <sub>3</sub>	III	181	73	C <sub>29</sub> H <sub>25</sub> N <sub>5</sub> O <sub>6</sub>	12.98	12.49
28.	4-OCH <sub>2</sub> H <sub>5</sub>	III	172	62	C <sub>31</sub> H <sub>29</sub> N <sub>5</sub> O <sub>6</sub>	12.34	12.05
29.	3-OH	III	219	68	C <sub>27</sub> H <sub>21</sub> N <sub>5</sub> O <sub>6</sub>	13.69	13.18
30.	4-OH	III	226	70	C <sub>27</sub> H <sub>21</sub> N <sub>5</sub> O <sub>6</sub>	13.69	13.18
31.	H	IV	149	67	C <sub>27</sub> H <sub>23</sub> N <sub>5</sub> O <sub>6</sub>	13.03	12.85
32.	4-CH <sub>3</sub>	IV	160	71	C <sub>31</sub> H <sub>27</sub> N <sub>5</sub> O <sub>6</sub>	12.04	11.90
33.	3-C1	IV	170	61	C <sub>29</sub> H <sub>21</sub> N <sub>5</sub> O <sub>6</sub> C1 <sub>2</sub>	11.25	11.12
34.	4-C1	IV	177	65	C <sub>29</sub> H <sub>21</sub> N <sub>5</sub> O <sub>6</sub> C1 <sub>2</sub>	11.25	11.12
35.	3-NO <sub>2</sub>	IV	182	64	C <sub>29</sub> H <sub>21</sub> N <sub>7</sub> O <sub>10</sub>	14.87	14.60
36.	4-NO <sub>2</sub>	IV	195	59	C <sub>29</sub> H <sub>21</sub> N <sub>7</sub> O <sub>10</sub>	14.87	14.60
37.	4-OCH <sub>3</sub>	IV	162	63	C <sub>31</sub> H <sub>27</sub> N <sub>5</sub> O <sub>8</sub>	11.72	11.50
38.	4-OO <sub>2</sub> H <sub>5</sub>	IV	165	65	C <sub>33</sub> H <sub>21</sub> N <sub>5</sub> O <sub>8</sub>	11.20	11.04

39.	4-OH	IV	207	68	C <sub>29</sub> H <sub>23</sub> N <sub>5</sub> O <sub>8</sub>	11.64	11.45
40.	4-OH	IV	238	70	C <sub>29</sub> H <sub>23</sub> N <sub>5</sub> O <sub>8</sub>	11.64	11.45

\* All compounds crystallized from aq. DMF. & gives satisfactory C & H. analysis.

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## **PART - II**

### **SECTION – A**

#### **Synthesis of Substituted $\beta$ - Diketones**

## SYNTHESIS OF $\beta$ - DIKETONES

### INTRODUCTION

$\beta$  – diketones are widely used as starting materials for the preparation of the large number of synthetic products such as phenothiazines, 1,4 – Benzothiazines, 1, 5- benzothiazepines, pyrazolines, triazines etc.

The synthesis of  $\beta$  - diketones was accomplished through two steps. The first involved the etherification of substituted O – hydroxyl acetophenones with substituted acid<sup>1</sup>. Using pyridine and phosphorus oxychloride and the second step these esters were subjected to Baker – Venkatraman transformation<sup>2-4</sup> using pyridine and potassium hydroxide.

The synthesis of benzoyloxy esters of O- hydroxyl acetophenones from esterification of phenols<sup>5-6</sup> which then converted into diketones.

Claisen<sup>7</sup> devised a method for the preparation of propane- 1, 3 –diones. This method is applicable to the ketones containing x – hydrogen atom with respect to the ketonic group. This method involves the condensation of a ketone and an ester in presence of a base catalyst such as sodium ethoxide, sodamide or sodium hydroxide resulting in the formation of propane - 1 ,3, - dione (Fig- IIA). Bulow<sup>8</sup> applied this method for the preparation of dibenzoyl methane. Vila<sup>9</sup> observed that of the reaction is carried out with sodamide in the absence of ether, better yields are obtained.

Levine et.al. and Adams & Huser<sup>10-11</sup> synthesized propane 1, 3 – dione by acylating ketones with the help of  $\text{BF}_3$ <sup>10</sup> and sogamide<sup>12</sup>.

The another method proposed by Haury et. al<sup>13</sup>. In this method a monoketone has been treated with a primary amine or hydroxyl amine or phenyl hydrazine and the derivatives thus formed are then acylated by an acetylating agent to form nitrogen containing ketone. This gives propane – 1 ,3 –dione (Fig-IIA 2) on hydrolysis. Allen et.al<sup>14</sup>. prepared  $\beta$  - diketones from chalcone dibromide (Fig-IIA3). Thus, the methods which were available have some drawbacks. So, the Baker-Venkataraman transformation method were adopted in this present work for the preparation of  $\beta$  - diketones used for the next section- B as a starting material for the preparation of pyrazolyl – s triazines.

It is observed that when a mixture of an ester of O – hydroxyl acetophenone and potassium carbonate is boiled with toluene or benzene, the aryl group migrates and 1 , 3- diketone is formed. Baker<sup>2</sup> carried out this transformation using potassium carbonate and toluene / benzene. While Venkataraman and Mahal<sup>3</sup> carried out the same transformation using sodamide in dry ether at  $0^\circ\text{C}$ . Ullal and wheeler<sup>15</sup> used sodium ethoxide or sodium hydroxide in alcohol while virkar abd wheeler<sup>16</sup> suggested the use of sodium in dry ether or toluene. Thakar & Coworkers<sup>17-18</sup> have synthesized substituted propane – 1, 3 - diones using pyridine & KOH. Wheeler & other workers<sup>19-20</sup> have studied the mechanism of this transformation & suggested it is a base catalyzed intra molecular claisen condensation.

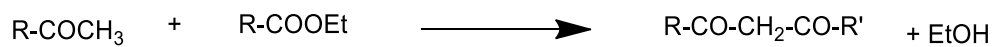


FIG. II A<sub>1</sub>

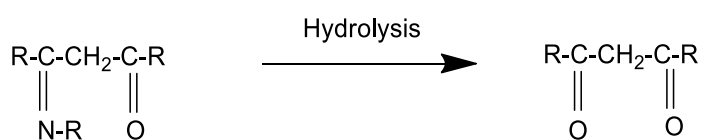
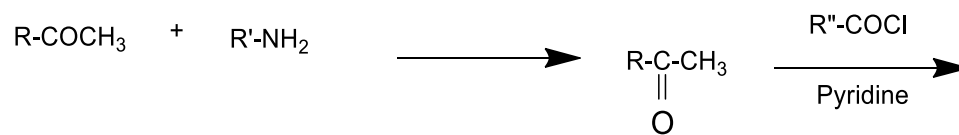


FIG. II A<sub>2</sub>

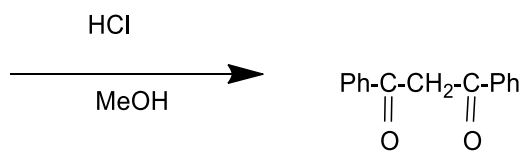
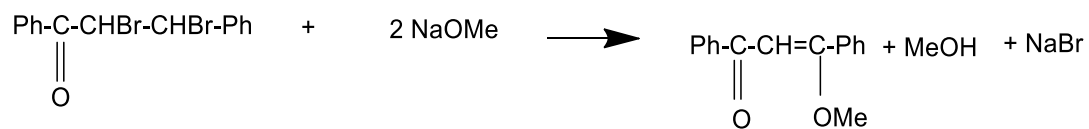


FIG. II A<sub>3</sub>

### **GENERAL PROCEDURE FOR ESTRIFICATION (FIG.IIA<sub>4</sub>) STEP – 1**

A mixture of substituted O- hydroxy acetophenone (0.04 mol) and substituted heterocyclic acid (0.05 mol) was dissolved in pyridine (20ml). This solution was ice cooled, and distilled phosphorus oxychloride (5ml) was added slowly with stirring. Maintaining the temperature below 40<sup>0</sup>C. The reaction mixture was kept at room temperature for two hours and poured on crushed ice containing HCl (25ml) Usually colourless solid separated out. Which was filtered, washed successively with water, 2 % NaOH and again with water. The product obtained was crystallized from proper solvent.

By following the above procedure, various benzoyloxy esters were prepared.

### **STEP 2 : - SYNTHESIS OF PROPANE – 1, 3 –DIONES FROM ESTERS.**

Chalcone dibromide and Baker – Venkataraman transformation are the suitable method for the preparation of substituted propane – 1, 3 – diones. The products obtained by these methods have unambiguous structures, where as Claisen condensation and other methods give products with ambiguous structures. Therefore, Baker – Venkataraman transformation is used in the present work for the preparation of substituted propane 1,3 – diones.

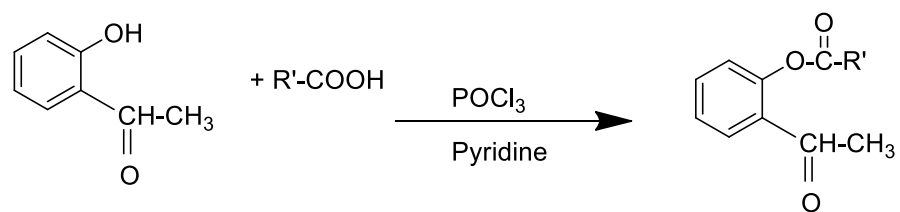
### **BAKER – VENKAT RAMAN METHOD :-**

The following general procedure is adopted to effect this transformation.

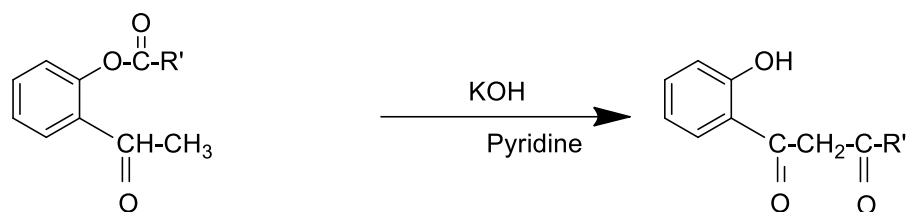
A mixture of an ester (0.01 mol), dry pyridine (12-20 ml) and powdered KOH (0.04 mol) was stirred for about 20 min. and allowed to stand for about half an hour. The reaction mixture was acidified by pouring it on ice and HCl. Usually a yellow product was obtained (Fig- IIA 4) . It was filtered, washed with water and crystallized by using proper solvent.

By using above method, following substituted propane – 1 , 3 –diones were synthesized and their physical parameters are listed in Table- 2.1.

STEP - I



STEP - II



Where,

R = Cl, CH<sub>3</sub>

R' = aryl

FIG II - A<sub>4</sub>



**The Following  $\beta$  – diketones were used as a starting material.**

1. 1 – (2' Hydroxy – 5' – methyl phenyl) – – (4'- phenyl) – propane- 1,3- dione.
2. 1 – (2' Hydroxy – 5' – methyl phenyl) – 3 – (4'- tolyl) – propane- 1,3- dione.
3. 1 – (2' Hydroxy – 5' – methyl phenyl) – 3 – (4'- methoxy phnyl) – propane- 1,3- dione.
4. 1 – (2' Hydroxy – 5' – methyl phenyl) – 3 – (3'- chlorophenyl) – propane- 1,3- dione.
5. 1 – (2' Hydroxy – 5' – methyl phenyl) – 3 – (4'- nitrophenyl) – propane- 1,3- dione.
6. 1 – (2' Hydroxy – 5' – chloro phenyl) – 3 – (4'- phenyl) – propane- 1,3- dione.
7. 1 – (2' Hydroxy – 5' – chloro phenyl) – 3 – (4'-methyl phenyl) – propane- 1,3- dione.
8. 1 – (2' Hydroxy – 5' – chloro phenyl) – 3 – (4'- methoxy phenyl) – propane- 1,3- dione.
9. 1 – (2' Hydroxy – 5' – chloro phenyl) – 3 – (4'-chloro phenyl) – propane- 1,3- dione.
10. 1 – (2' Hydroxy – 5' – chloro phenyl) – 3 – (4'- Nitro phenyl) – propane- 1,3- dione.

**TABLE – 2.1****1-(2' HYDROXY – 5' SUBSTITUTED PHENYL) – 3 (SUBSTITUTED PHENYL)-  
PROPANE 1.3 DIONES (FIG-IIA<sub>4</sub>)**

<u>Comp No.</u>	<u>Substituent</u>		<u>Yield* (%)</u>	<u>M.P.</u> <u>(°C)</u>
	<u>R</u>	<u>R'</u>		
1.	p-CH <sub>3</sub>	Phenyl	68	118
2.	p-CH <sub>3</sub>	4' methyl phenyl	80	124
3.	p-CH <sub>3</sub>	4' methyl phenyl	62	120
4.	p-(CH <sub>3</sub> )	3' chloro phenyl	78	160
5.	p-(CH <sub>3</sub> )	4' nitro phenyl	80	318
6.	P (Cl)	Phenyl	64	96
7.	P (Cl)	4' methyl phenyl	78	115
8.	P (Cl)	3' methyl phenyl	64	116
9.	P (Cl)	3' chloro phenyl	80	120
10.	P (Cl)	4' nitro phenyl	82	270

\* All the synthesized compounds are recrystallized from ethanol.

## **PART - II**

### **SECTION – B**

**Synthesis of 2,4 bis-(substituted  
aniline) – 6- (pyrazolyl) – s- triazines.**

## INTRODUCTION

The pyrazole ring system (Fig-IIB<sub>1</sub>) consists of a double unsaturated five membered ring containing two adjacent N atoms. Knorr<sup>21,22</sup> first synthesized a compound containing this system in 1883 by the reaction of ethyl acetoacetate with phenyl hydrazine to yield 1- phenyl – 3- methyl – 5- pyrazolone (Fig-IIB<sub>2</sub>). His interest in quinine led to test the antiferbrile action of this and related which resulted in the discovery of antipyrine<sup>23</sup>, (Fig-IIB<sub>3</sub>) , an important Febrifuge.

Knorr<sup>24</sup> introduced the name pyrazole for these compounds to denote that the nucleus was derived from pyrrole by replacement of a carbon by nitrogen. He synthesized many members of this class and systematically investigated their properties. Since many nucleus, the class has been widely studied. A biological activities review shows that, some of the aryl. Alkyl and heteryl derivatives of pyrazoles have quite significant bacteriostatic, bactericidal and fungicidal properties<sup>25-30</sup>. Alkyl and aryl pyrazoles possess a sharply pronounced sedative action on central nervous system<sup>31-32</sup>.

Tranquillizing central nervous relaxants and psychoanaleptic properties have been associated with the derivative<sup>33</sup>. A- Acylprazole are found to be analgesics, anti-inflammatory, muscle relaxants, sedative, hypolemic and plant growth regulating<sup>34</sup>. It is reported that pyrimidine pyrazoles are being studied in the fight against cancer<sup>35</sup>. Oxyphenbutazon (F-g. IIB<sub>4</sub>) is preferred clinically, since it does not cause gastrointestinal disturbances.

These drugs are most effective for the cause of acute inflammatory conditions such as osteoarthritis<sup>36</sup>.

Recently, pyrazole derivatives are found to possess insecticidal, herbicidal and nematocidal properties<sup>37</sup>. Antidiabetic<sup>38</sup> and antiviral<sup>39</sup> activities have been studied for pyrazole derivatives. The arylazopyrazoles were tested for anti- HIV activity<sup>40</sup>.

## **GENERAL METHODS FOR THE SYNTHESIS OF PYRAZOLE NUCLEUS**

### **METHOD I :- FROM 1,3 – DICARBONYL COMPOUNDS:-**

The reaction of hydrazine<sup>41-47</sup> or its derivatives such as aryl or alkyl hydrazine, semicarbazide<sup>48-53</sup> or aminoguanidine<sup>54</sup> with 1, 3 – dicarbonyl compounds in presence of neutral or acid medium gave pyrazole derivatives (Fig-IIB<sub>5</sub>). The synthesis of pyrazolines from  $\beta$  - Ketoesters is analogous (Fig-IIB<sub>6</sub>). The mono substituted hydrazines can yield isomeric pyrazoles and in many instances no attempt has been made to determine the type of isomer (Fig- IIB<sub>7</sub>). Benzoyl acetone gives both 1,3- dimethyl- 5- phenyl pyrazole and 1,5 dimethyl – 3-phenyl pyrazole by reaction with methyl hydrazine<sup>42</sup> but only 1,5- diphenyl – 3- methyl pyrazole with phenyl hydrazine<sup>55-56</sup>.

## **METHOD II :-**

### **FROM $\alpha,\beta$ - UNSATURATED CARBONYL COMPOUNDS.**

#### **Acetylenic Carbonyl Compounds<sup>42</sup> :-**

The synthesis of pyrazoles by the reaction of  $\alpha,\beta$ - acetylenic compounds with hydrazine and its derivatives is less common than the corresponding pyrazoline synthesis from  $\alpha,\beta$ - ethylenic carbonyl compounds because the acetylenic compounds are less readily available and the reaction is some what less general (Fig- IIB<sub>8</sub>). The reaction of semicarbazide with acetylenic aldehydes and ketones has been studied carefully in only a few instances<sup>57</sup>.

#### **Acetylenic Carbonyl Compounds<sup>42</sup> :-**

The most general method for pyrazoline synthesis is the reaction of hydrazines with  $\alpha,\beta$ - unsaturated ketones. When an  $\alpha,\beta$  - ethylenic carbonyl compound substituted at either  $\alpha$  or  $\beta$  position with a readily replaceable group is treated with hydrazine, a pyrazole is frequently formed. Only halogens, generally bromine, have been examined as the  $\alpha$ - substituent<sup>58</sup>. With hydrazine or phenyl hydrazine, these yield pyrazoles readily, although the intermediate hydrazone is some times insoluble. If it is of low solubility, some times refluxing with an alkaline reagent is necessary to form the pyrazoles (Fig-IIB<sub>9</sub>). Silver nitrate or other silver salts some times convert pyrazolines to pyrazoles<sup>59-60</sup> and potassium ferricyanide or lead tetra-acetate<sup>62</sup> has occasionally been employed for the same purpose.

### **METHOD III : FROM $\alpha$ , $\beta$ - UNSATURATED ESTERS AND DIAZO**

#### **COMPOUNDS:-**

Pyrazoles are readily obtained from  $\alpha,\beta$ -unsaturated esters and diazo compounds<sup>63</sup> (Fig-IIB<sub>10</sub>) and wide variety of  $\alpha,\beta$ - unsaturated esters and diazo compounds have been investigated and yield pyrazolines<sup>64</sup>. Pyrazoline containing conjugated system are readily distinguished from other pyrazolines by an appreciable exaltation in the molecular reaction<sup>65</sup>. The reactions of  $\alpha,\beta$  - unsaturated nitriles with diazo compounds has not been studied extensively. Secondary nitro – olefins react readily with diazo- compounds to give pyrazolines. Thus formed pyrazolines converted easily into pyrazoles.

### **METHOD IV :- CONVERSION OF 2-ARYL CHROMONES TO PYRAZOLES.**

Baker and Bhutt<sup>66</sup> carried out the reaction between 3 –aryl – 2- methyl chromone and phenyl hydrazine in an alcoholic medium and observed the formation of substituted pyrazole. The following sequence of the reaction has been proposed by them for the formation of 4 – aroyl- 1- phenyl – 5 (-O-hydroxyl phenyl)- 3 – methyl pyrazole <sup>67-69</sup> (Fig-II B 11) Bohdan and Zofia<sup>70</sup> have also drawn a conclusion in favor of a similar structure for pyrazole while studying the reaction of 3- acetyl – 2- phenyl- chromone with phenyl hydrazine.

They formulated the compound as 4 – acetyl – 5- (O-hydroxy phenyl) – 1, 3- diphenyl pyrazole (Fig.IIB<sub>12</sub>). But there is possibility of the formation of two

isomeric compounds. Holger and co-workers<sup>71</sup> did isolate the two isomeric products obtained by the action of phenyl hydrazine on 3- benzoyl chromone.

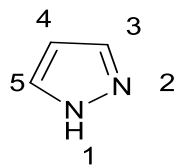


FIG. II B<sub>1</sub>

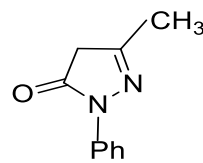


FIG. II B<sub>2</sub>

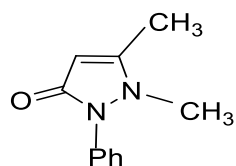


FIG. II B<sub>3</sub>

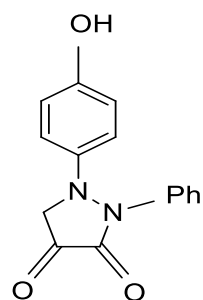


FIG. II B<sub>4</sub>



### SELECTION OF MEHOD:-

In the above mentioned four methods, method – I was followed. It was observed that the reaction of heterocyclic hydrazines with 1,3- diketones, invariably yields a pyrazole<sup>72</sup> derivatives instead of the reported triazepine or diazepine<sup>73-75</sup>. Thus substituted s- triazinyl hydrazides on treatment with several symmetrical and unsymmetrical diketones yielded a single isomer which may have substituent located at position- 3 & -5 of the pyrazole ring (TLC and NMR spectra).

The exclusive formation of the single isomers may be reationalised by the predominance of the more stable enol 73 (I) as compared to enol (II) in the equilibrium shown below.

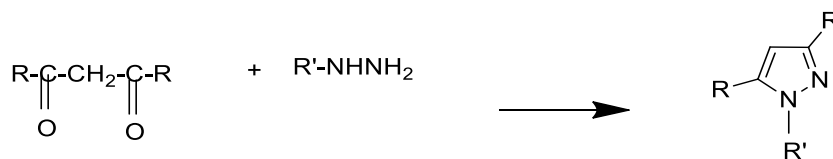


FIG. II B 5

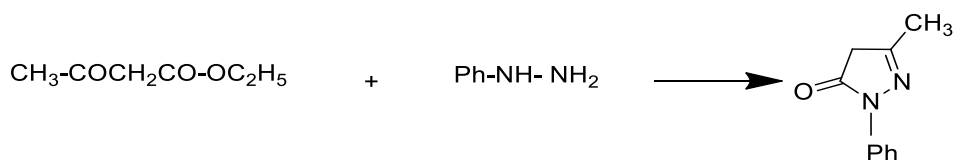


FIG. II B 6

## PRESENT WORK

2,4 - Bis - (substituted aniline) - 6- pyrazolyl - s- triazines has been prepared from the condensation of 1,3 - propane diones and triazinyl hydrazides in refluxing methanol for 4 hrs. The separated solid compound were confirmed by TLC & Spectral (IR & NMR) data and elemental analysis.

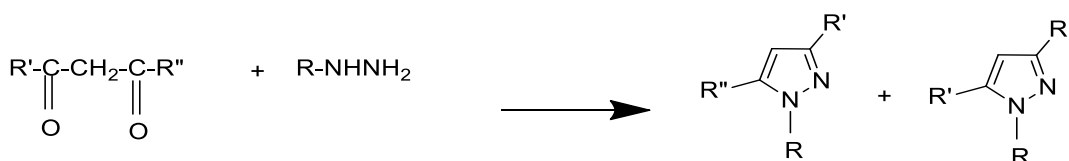


FIG. II B 7

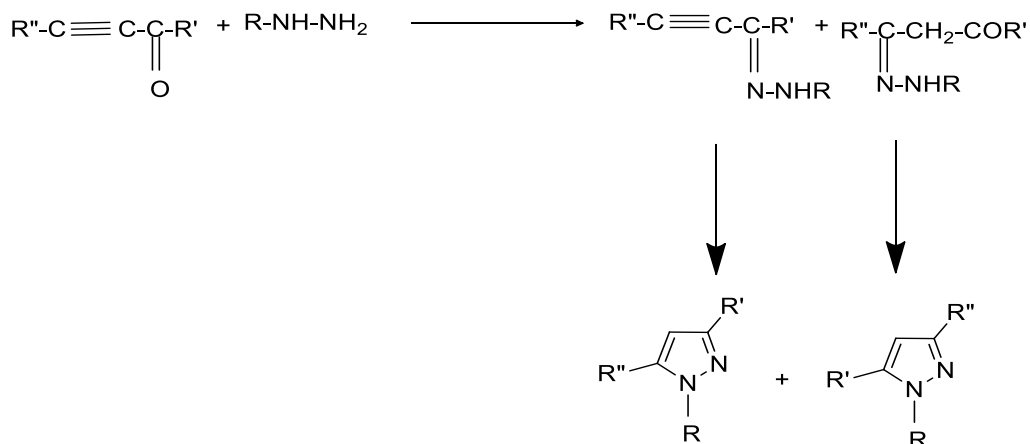


FIG. II B 8

## **1) GENERAL METHOD FOR THE SYNTHESIS OF 2, 4-BIS**

### **[SUBSTITUTED ANILINO]- 6- HYDRAZIDE- S- TRIAZINES :**

A mixture of 2,4- Bis- (substituted aniline) – 6 – chloro- s- triazines (0.01 mol) and hydrazine hydrate (80%) (0.015 mol) in THF was stirred for 1 hr in the presence of triethyl amine at 60-80<sup>0</sup> C on a boiling water bath. The above mixture consequently were refluxed for about half an hr. The reaction mixture was cooled and the obtained product was filtered and washed with cold water, dried and crystallized from suitable solvent. The m.pt., yields, solvents for crystallization and elemental analysis are recorded in Table- 2.21.

## **2) GENERAL METHOD FOR THE SYNTHESIS OF 2, 4-BIS**

### **[SUBSTITUTED ANILINO]- 6- [SUBSTITUTED PYRAZOL-1-YL] –S- TRIAZINES : (FIGII B<sub>13</sub>) :**

A mixture of 2,4- Bis- (substituted aniline) – 6 – hydrazide- s- triazine (0.01 mol) and 1- [(2' substituted aryl)-3- (substituted aryl)] – 1,3- propane dione (0.01 mol) in presence of conc. HCL in ethyl alcohol was refluxed for 4 hr. The reaction mixture was cooled and poured over ice water. The product was crystallized from proper solvent. The purity of the compounds were checked by TLC. The structures were confirmed by (IR & NMR) spectral and elemental analysis. The m.pt. yields, solvent for crystallization and element analysis were recorded in Table- 2.22.

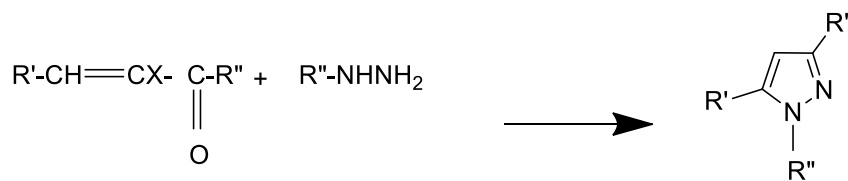


FIG. II B<sub>9</sub>

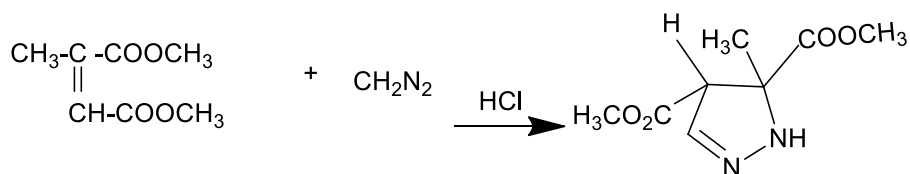


FIG. II B<sub>10</sub>

### DISCUSSION OF IR SPECTRA-

The IR spectra of some of the representative compounds of the series were scanned on Perkin- Elmer 1420 Spectrophotometer in nujol mulls.

All the compounds showed absorption at 3250-3380  $\text{cm}^{-1}$  due to - NH stretching. The absorption peak at 1650  $\text{cm}^{-1}$  due to > C=N stretching. The band at 870-860  $\text{cm}^{-1}$  due to  $\text{C}_3\text{N}_3$  stretching of s-triazine ring. The spectrum No.5 represent the spectrum of 2,4- Bis- (4'- chloro aniline)- 6- (3'5'- dimethyl- pyraazol-1-yl)- S-triazine.

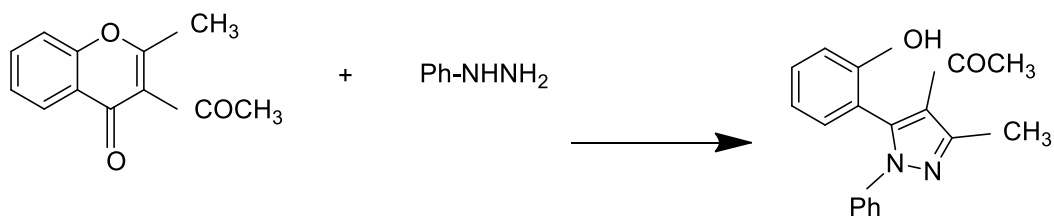


FIG II B 11

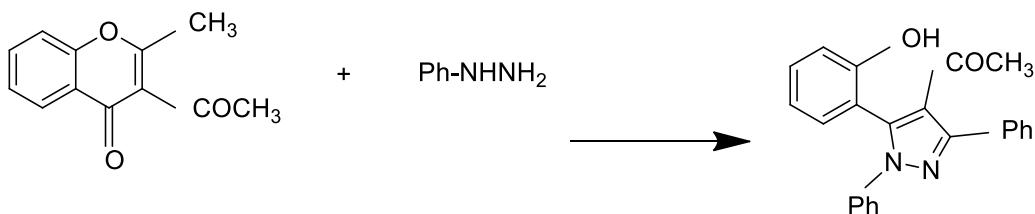
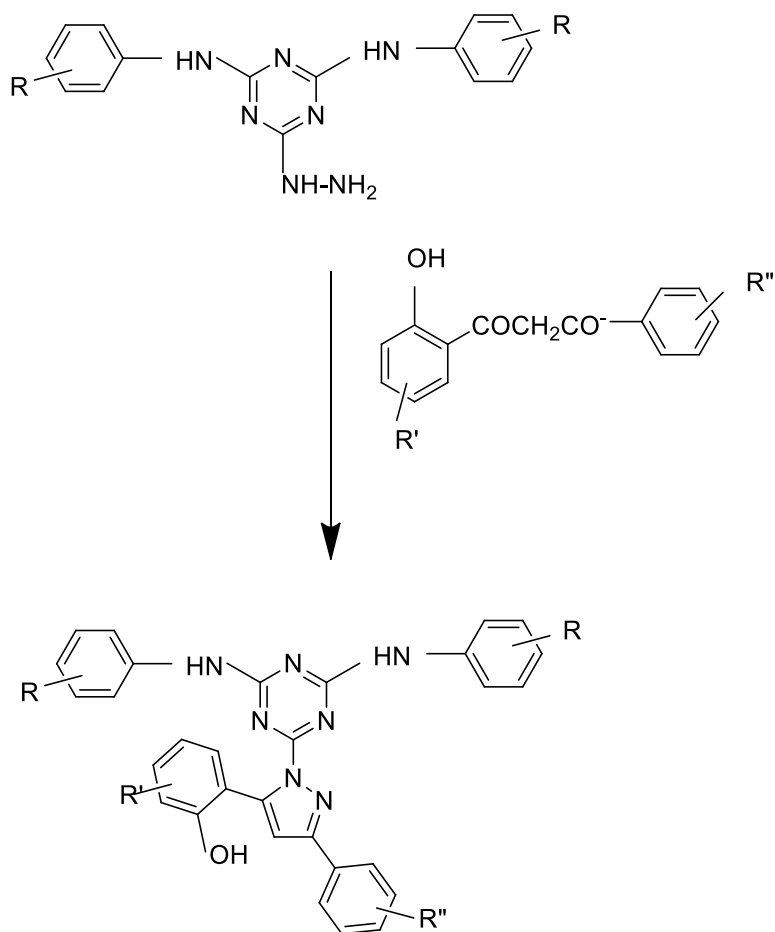


FIG II B 12

### DISCUSSION OF PMR SPECTRA-

The PMR spectra of some of the representative compounds of this series were scanned on FT-BOA spectrometer using TMS as an internal standard in DMSO-d<sub>6</sub> as solvent. Chemical shifts measured in  $\delta$  ppm. The PMR spectra of 2,4-bis-(4' methyl aniline) – 6- [(3'2(3''-chloro) -5'-(2''-hydroxy- 5''-methyl phenyl) – pyrazol- 1- yl)]-s-triazine (spectrum No.6) displays signals at  $\delta$  2.45 singlet due to six proton of –CH<sub>3</sub> group at 4' – position of aniline moiety.  $\delta$  2.50, singlet due to three protons of 5'CH<sub>3</sub>of aryl moiety of pyrazolyl at 5- position. The singlet at  $\delta$  6.15 due to one proton of pyrazolyl at-4- position.  $\delta$  6.65 – 7.80 multiplet due to aromatic protons and –C=CH of pyrazole 4'H protons and – NH proton &  $\delta$  10.55, singlet due to –OH proton.

PRESENT WORK



SCHEME - II

FIG. II - B<sub>13</sub>

Where,

R = H, CH<sub>3</sub>, OCH<sub>3</sub>, Cl, Br, NO<sub>2</sub>, OH

R' = CH<sub>3</sub>, Cl, ; R'' = CH<sub>3</sub>, Cl

## **EXPERIMENTAL PROCEDURE :-**

### **EXPERIMENT NO.1 :-**

#### **PREPARATION OF 2,4-BIS-(4'-NITROANILINO)-6- HYDRAZIDE –S- TRIAZINES (6):- TABLE- 2.21**

A mixture of 2,4 – Bis- (nitro anilino) -6- chloro- s- triazine (3.80 g; 0.01mol) and hydrazine hydrate (4ml; 0.015mol) in THF (20ml) was stirred for 1hr in presence of triethyl amine (5 ml) at 60-80<sup>0</sup> C on a boiling water bath. This was refluxed consequently for about half an hour. The reaction mixture was cooled and obtained solid was filtered, washed with cold water to give (6). M.Pt. 145<sup>0</sup> c; yield 64%. Similarly other compounds of the series were prepared.

### **EXPERIMENT NO. 2 :-**

#### **PREPARATION OF 2,4-BIS-(3'-NITRO ANILINO)- 6-[3-(4''-TOLYL)-5'- (2''-HYDROXY-5'' METHYL PHENYL) –PYRAZOL -1-YL] –S-TRIAZINE (12) :- (TABLE-2.22).**

A mixture of 2,4 – Bis- (4'-nitroanilino)-6 hydrazide –s- triazine (3.77g ; 0.01 mol) and 1- (4'-tolyl)—3- (2'hydroxy-5'- methyl phenyl)-1,3-propane dione (2.71g; 0.01 mol) in ethyl alcohol (25ml) was refluxed for 4 hr and then the reaction mixture was cooled and poured over crushed ice. The solid thus separated was filtered, washed with cold water and crystallized from ethanol to give (12) , M.P. 162<sup>0</sup> C; yield- 81%.

Similarly other compounds of the series were prepared.

**TABLE- 2.21****CHARACTERISATION DATA OF 2,4-BIS- (SUBSTITUTED ANILINO)****-6- HYDRAZIDE – S- TRIAZINES.**

Comp No.	Substituent R	Yield (%)	M.P* (°C)	Mol. Formula	% of Calcd.	Nitrogen Found.
1.	H	70	140	C <sub>15</sub> H <sub>15</sub> N <sub>7</sub>	34.26	34.07
2.	4'CH <sub>3</sub>	72	165	C <sub>17</sub> H <sub>19</sub> N <sub>7</sub>	30.50	29.85
3.	4'-OO <sub>2</sub> H <sub>5</sub>	78	190	C <sub>19</sub> H <sub>21</sub> N <sub>7</sub> O <sub>2</sub>	26.20	26.10
4.	4'Cl	68	231	C <sub>15</sub> H <sub>13</sub> N <sub>7</sub> Cl <sub>2</sub>	27.60	27.34
5.	4'NO <sub>2</sub>	64	145	C <sub>15</sub> H <sub>13</sub> N <sub>9</sub> O <sub>4</sub>	32.39	32.14

\* All compounds were recrystallized from aq. –DMF- Methanol.



**TABLE – 2.22****CHARACTRISATION DATA OF 2,4 -BIS- (SUBSTITUTED ANILINO) – 6****–(SUBSITUTED PYRAZOL-1-YL) –S – TRAIZINES (FIG. IIB<sub>13</sub>)**

Comp. No.	Sub.R.			Yield (%)	M.P.* (°c)	Mol.formula	% of Nitrogen	
	R	R'	R''				Found	Calcd.
1.	4'-Cl	5'-CH <sub>3</sub>	H	70	100	C <sub>31</sub> H <sub>22</sub> N <sub>7</sub> O <sub>1</sub> Cl <sub>2</sub>	16.60	16.95
2.	4'- Cl	5'-CH <sub>3</sub>	4'-CH <sub>3</sub>	75	146	C <sub>32</sub> H <sub>24</sub> N <sub>7</sub> O <sub>1</sub> Cl <sub>2</sub>	16.45	16.55
3.	4'- Cl	5'-CH <sub>3</sub>	4'-OCH <sub>3</sub>	68	135	C <sub>32</sub> H <sub>24</sub> N <sub>7</sub> O <sub>2</sub> Cl <sub>2</sub>	16.60	16.11
4.	4'- Cl	5'-CH <sub>3</sub>	3'-Cl	65	115	C <sub>31</sub> H <sub>21</sub> N <sub>7</sub> OCl <sub>3</sub>	16.60	16.95
5.	4'- Cl	5'-CH <sub>3</sub>	4'-NO <sub>2</sub>	71	307	C <sub>31</sub> H <sub>21</sub> N <sub>8</sub> O <sub>3</sub> Cl <sub>2</sub>	16.75	16.89
6.	4'- Cl	5'- Cl	H	80	79	C <sub>30</sub> H <sub>20</sub> N <sub>7</sub> OCl <sub>3</sub>	16.26	16.31
7.	4'- Cl	5'- Cl	4'-CH <sub>3</sub>	78	135	C <sub>31</sub> H <sub>23</sub> N <sub>7</sub> OCl <sub>3</sub>	15.85	15.92
8.	4'- Cl	5'- Cl	4'-OCH <sub>3</sub>	72	104	C <sub>31</sub> H <sub>22</sub> N <sub>7</sub> O <sub>2</sub> Cl <sub>3</sub>	14.50	14.54
9.	4'- Cl	5'- Cl	3'-Cl	70	115	C <sub>30</sub> H <sub>19</sub> N <sub>7</sub> OCl <sub>4</sub>	14.41	15.43
10	4'- Cl	5'- Cl	4'-NO <sub>2</sub>	74	248	C <sub>31</sub> H <sub>19</sub> N <sub>8</sub> O <sub>3</sub> Cl <sub>3</sub>	17.30	17.35
11.	3'-NO <sub>2</sub>	5'-CH <sub>3</sub>	H	75	102	C <sub>32</sub> H <sub>25</sub> N <sub>9</sub> O <sub>5</sub>	20.80	20.96
12.	3'-NO <sub>2</sub>	5'-CH <sub>3</sub>	4'-CH <sub>3</sub>	81	162	C <sub>32</sub> H <sub>25</sub> N <sub>9</sub> O <sub>5</sub>	20.32	20.48
13.	3'-NO <sub>2</sub>	5'-CH <sub>3</sub>	4'-OCH <sub>3</sub>	80	90	C <sub>32</sub> H <sub>25</sub> N <sub>9</sub> O <sub>6</sub>	19.76	19.96
14.	3'-NO <sub>2</sub>	5'-CH <sub>3</sub>	3'-Cl	74	144	C <sub>31</sub> H <sub>24</sub> N <sub>9</sub> O <sub>5</sub> Cl	19.68	19.82

15.	3'-NO <sub>2</sub>	5'-CH <sub>3</sub>	4'NO <sub>2</sub>	72	260	C <sub>31</sub> H <sub>24</sub> N <sub>10</sub> O <sub>7</sub>	21.45	21.67
16.	3'-NO <sub>2</sub>	5'-Cl	H	70	142	C <sub>30</sub> H <sub>20</sub> N <sub>9</sub> O <sub>5</sub> Cl	20.29	20.27
17.	3'-NO <sub>2</sub>	5'-Cl	5'-Cl	79	98	C <sub>31</sub> H <sub>22</sub> N <sub>9</sub> O <sub>5</sub>	19.74	19.82
18.	3'-NO <sub>2</sub>	5'-CH <sub>3</sub>	4'-OCH <sub>3</sub>	76	165	C <sub>31</sub> H <sub>22</sub> N <sub>9</sub> O <sub>6</sub>	19.20	19.82
19.	3'-NO <sub>2</sub>	5'-CH <sub>3</sub>	3'-Cl	78	135	C <sub>30</sub> H <sub>20</sub> N <sub>9</sub> O <sub>5</sub> Cl	19.09	19.35
20.	3'-NO <sub>2</sub>	5'-CH <sub>3</sub>	4'NO <sub>2</sub>	69	230	C <sub>30</sub> H <sub>20</sub> N <sub>10</sub> O <sub>7</sub> Cl	20.80	21.00
21.	4'-CH <sub>3</sub>	5'-CH <sub>3</sub>	H	64	101	C <sub>33</sub> H <sub>29</sub> N <sub>7</sub> O	18.06	18.18
22.	4'-CH <sub>3</sub>	5'-CH <sub>3</sub>	4'-CH <sub>3</sub>	74	110	C <sub>34</sub> H <sub>31</sub> N <sub>7</sub> O	17.45	17.68
23.	4'-CH <sub>3</sub>	5'-CH <sub>3</sub>	4'-OCH <sub>3</sub>	70	129	C <sub>34</sub> H <sub>31</sub> N <sub>7</sub> O	17.04	17.19
24.	4'-CH <sub>3</sub>	5'-CH <sub>3</sub>	3'-Cl	65	138	C <sub>33</sub> H <sub>29</sub> N <sub>7</sub> OCl	16.98	17.09
25.	4'-CH <sub>3</sub>	5'-CH <sub>3</sub>	4'NO <sub>2</sub>	60	285	C <sub>33</sub> H <sub>29</sub> N <sub>8</sub> O <sub>3</sub>	19.10	19.17
26.	4'-CH <sub>3</sub>	5'-Cl	H	72	79	C <sub>32</sub> H <sub>26</sub> N <sub>7</sub> OCl	17.50	17.51

\* All compounds were recrystallized from ethanol.

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## **PART - III**

### **SECTION – A**

**Synthesis of 1,3- Bis-(substituted  
propen – 1 – onyl)- Benzimidazolin –  
2- thiones.**



## INTRODUCTION

$\alpha,\beta$ - unsaturated ketones may be named as Chalcones and their aryl derivatives as acrylophenones. Chalcones can be represented by general structure (Fig- III A) chemical abstracts & ring index preferred the nomenclature of chalcone derivatives are well known as reactive intermediates in the synthesis of heterocyclic compounds and they have exhibited various biological activities.

Gieger and conn<sup>1</sup>, discovered that the presence of  $\alpha,\beta$ -unsaturated carbonyl system in antibiotics like clavacin and penicillic acid is the root cause for their activity. Thereafter several workers have synthesized a number of acrylophenones and tested them for biological activity. The antibacterial & antifungal activities of the class of compounds have been reported by Kushawa et, al<sup>2</sup>. Acrylophenones having heteryl moieties like quinolyl furyl and pyridyl at 3- positions also showed microbial activities<sup>3</sup>. Antitumor activity has been reported by David et. al.,<sup>4</sup> for the chalcones with heteryl substituent's like pyridyl and thienyl. The coronary dialating property for chalcones was investigated<sup>5</sup>. The anticancer activity and friends virus Leukemia were studied by Donely and co-workers in a series of acrylophenones<sup>6</sup>, germicidal<sup>7-9</sup>, fungicidal<sup>10</sup> and carcinogenic<sup>11</sup> properties have been claimed for these derivatives. These findings stimulated to attempt the synthesise benzimidazolin- 2 – thiones with different substituent at 1, 3-positions.

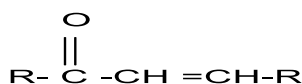


FIG. III A

## **METHODS FOR THE PREPARATION OF CHALCONES OR PROPEN –**

### **1- ONES :-**

Various methods have been devised for the synthesis of chalcones. The following methods are mostly used.

1. The claisen – Schmidt method.
2. Friedel – craft acylation method.
3. Reaction of benzene selenyl halide on ketone.

### **THE CLAISEN –SCHMIDI METHOD:-**

This is the most widely used method for the synthesis of chalcone. It involves the condensation of an aldehyde with ketone having active methylene group or  $\alpha$ - hydrogen atom in presence of an alkali (Fig- IIIA<sub>1</sub>). The reaction conditions are very simple, piperidine can be used for their condensation.

### **FRIEDEL CRAFT ACYLATION METHOD:-**

In this method aromatic hydrocarbon is acylated using  $\alpha, \beta$ - unsaturated acid chloride in presence of Lewis acid to get the chalcones (Fig-III A<sub>2</sub>). This method has limitations as it gives good yield but some unidentified solid as by – product. The starting material like  $\alpha, \beta$ - unsaturated acid chlorides are not easily available.

### METHODS FOR THE PREPARATION OF CHALCONES

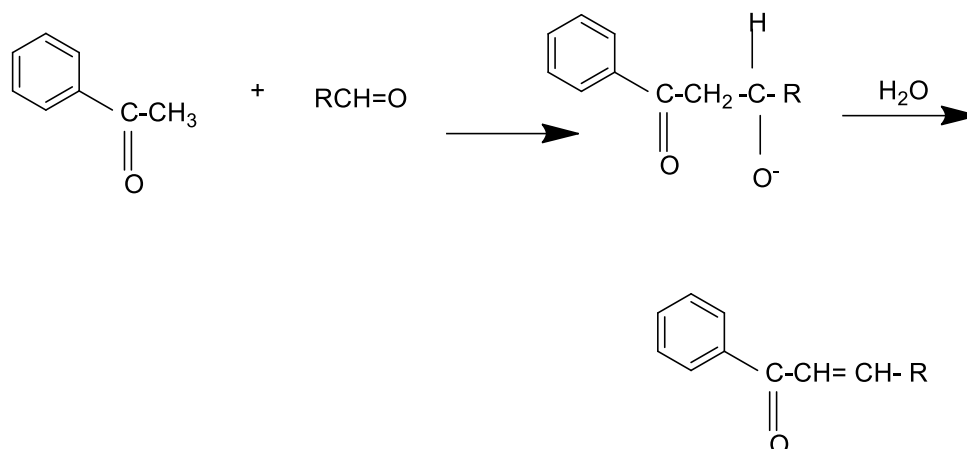


FIG. III A<sub>1</sub>

### REACTION OF BENZENE SELENYL HALIDE ON KETONE:-

Benzene selenyl halide first reacts with ketone and forms  $\alpha$ - phenyl seleno carbonyl compound which is oxidized by silver trifloro acetate<sup>15</sup> to yield corresponding  $\alpha,\beta$ - unsaturated ketone. Reaction course is presented in (Fig- IIIA<sub>3</sub>)

### PRESENT WORK AND METHOD

In the present work 1, 3- Bis- (Substituted propen – 1- onyl)- benzimidazolin – 2- thiones were obtained from 1- chloro 3- substituted aryl / heteraryl propenones with benzimidazolin- 2- thiones in presence of pyridine by following the modified friedel crafts acylation method (Fig-III A<sub>2</sub>). This is the only suitable method for the synthesis of chalcones, because it has moderate reaction condition, starting materials can be easily obtained and yields are also good.

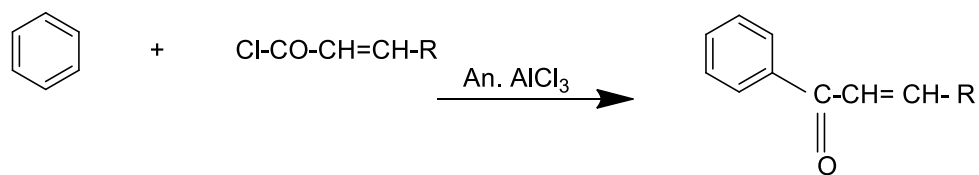


FIG. III A<sub>2</sub>

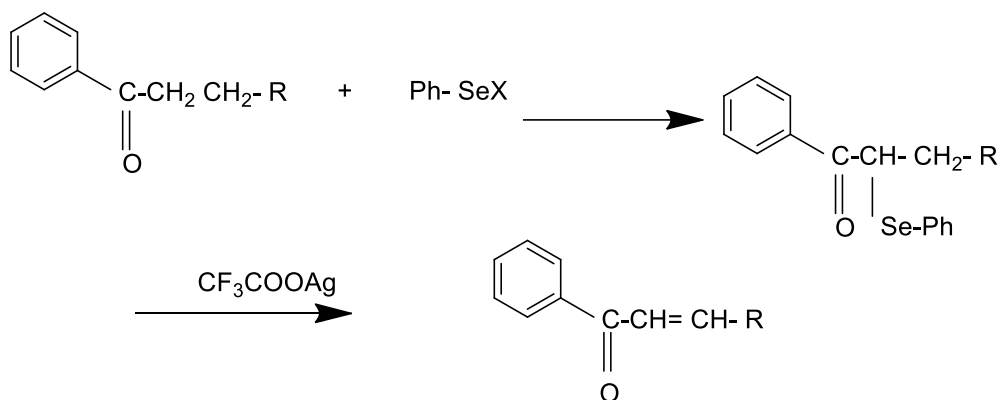


FIG. III A<sub>3</sub>

**GENERAL METHOD FOR THE SYNTHESIS OF 1,3- BIS-**  
**(SUBSTITUTED ARYL / HETERRYL) – PROPEN -1- ONLY) –**  
**BENZIMIDAZOLIN – 2- THIONES (FIG-III A<sub>4</sub>):-**

The benzimidazolin – 2- thiones were condensed with different 1 – chloro-3-(4'- chlorophenyl) –propen- 1- one in ethanol (50ml) in presence of pyridine by refluxing the mixture for 5hrs. The mixture were cooled to 0°C and the product obtained was filtered, washed and crystallized from proper solvent to gave faint brown crystallized from proper solvent to gave faint brown crystals which gave red colouration with conc. Sulphuric acid indicating the presence of α,β-unsaturated carbonyl compound. The purity of the product was checked by TLC.

The formation of compound confirmed by elemental analysis, IR and NMR spectra. The melting points yields, solvent for crystallization and elemental analysis are listed in table 3.1.

### **DISCUSSION OF IR SPECTRA.**

The IR spectra of some representative compounds from the series were recorded on Perkin- Elmer IR- 1420 Spectrophotometer in nujol mull. All the compounds have been shown absorption band in the region 1670-7000  $\text{cm}^{-1}$  for (C=O) stretching vibrations. Lowering of carbonyl frequency i.e. the shift of C=O, to lower wave number is due to the presence of  $\alpha,\beta$ - unsaturation. All compounds shown absorption due to ethylenic double bond in the region 1605-1650  $\text{cm}^{-1}$ . The absorption at 1220 $\text{cm}^{-1}$  is due to (C=S). The IR Spectrum NO.7 represents the spectrum of 1,3- Bis- [(4'-chlorophenyl) - propen - 1- onyl]- benzimidazolin - 2- thiones.

### **DISCUSSION OF PMR SPECTRA.**

The PMR spectra of few of the representative compounds were studied in DMSO- $\text{d}_6$  on FT-80A Spectrometer using TMS as internal standard. The chemical shift is measured in  $\delta$  ppm scale. The peak at  $\delta$  6.9 is due to olefinic proton absorption and the multiplet is in the region  $\delta$  6.6- 7.25 due to aromatic proton i.e. the presence of aromatic ring is confirmed. The spectrum No.8 represents the spectrum of 1,3-Bis - [(4'-chlorophenyl - propen- 1- onyl)] - benzimidazolin - 2- thiones.

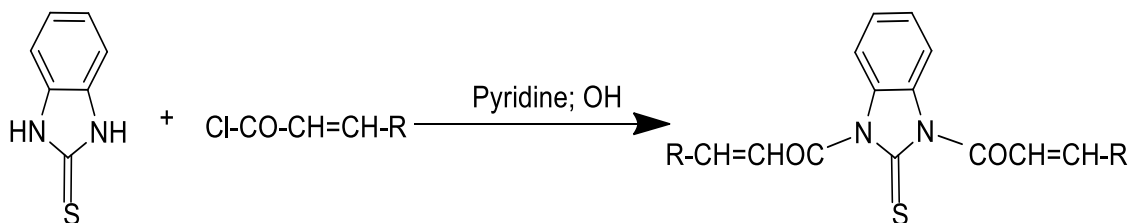
## EXPERIMENTAL

### PREPARATION OF 1,3-BIS- [(4'-CHLOROPHENYL)- PROPEN -1-ONLY]

#### -BENZIMIDAZOLIN – 2- THIONES (04) :- TABLE- 3.1.

A Mixture of benzimidazolin- 2- thione (1.5g; 0.01 mol) and 1- chloro- 3-(4'-chlorophenyl)- propen-1-one (4.07g; 0.01 mol) in ethanol (50 ml). The mixture was stirred in presence of pyridine for half an hr and refluxed further for 5 hr. The mixture were cooled to 0<sup>o</sup>c. The precipitated solid was filtered, washed with water, dried and crystallized from ethanol. M. Pt. 270 <sup>o</sup>c ; yield 69 %. Similarly the other members of the series were prepared.

#### PRESENT WORK



Where,

R = Ph, CH<sub>3</sub>-Ph, OCH<sub>3</sub>-Ph, O<sub>2</sub>N-Ph, Cl-Ph, Br-Ph

FIG. III A<sub>4</sub>

**TABLE – 3.1****CHARACTERISATION DATA OF 1,3-BIS- [(SUBSTITUTED ARYL)- PROPEN – 1-ONYL] – BENZIMIDAZOIN – 2- THIONES (FIG- IIIA<sub>4</sub>)**

Compd. No	R	M.P.* (°C)	Yield (%)	% of Nitrogen	
				Found	Calcd.
1.	C <sub>6</sub> H <sub>5</sub>	289	76	5.62	5.71
2.	2'- OH C <sub>6</sub> H <sub>4</sub>	252	70	6.21	6.33
3.	2'- CL C <sub>6</sub> H <sub>4</sub>	259	62	5.57	5.84
4.	4'- CL C <sub>6</sub> H <sub>4</sub>	270	69	5.60	5.84
5.	2'- CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	276	73	6.23	6.39
6.	3'- CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	285	65	6.14	6.39
7.	4'- CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	294	72	6.20	6.39
8.	2'- OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	265	79	5.81	5.95
9.	4'- OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	279	80	5.84	5.95
10.	2'- NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	276	70	11.13	11.20
11.	3'- NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	290	60	10.98	11.20
12.	4'- NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	309	61	11.10	11.20
13.	2'-furyl	298	70	7.04	7.17
14.	2'-pyridyl	262	73	6.54	6.79
15.	2'- Thiophene	295	68	6.48	6.63
16.	- CH <sub>3</sub>	162	76	9.60	9.79

\* All compounds Crystallized from Ethyl Alcohol.

## **PART - III**

### **SECTION – B**

**Synthesis of 1,3- bis-(substituted 4', 5'  
–dihydro- pyrazolyl)- benzimidazolin  
– 2- thiones.**



## INTRODUCTION

The pyrazole ring system consists of a doubly bonded unsaturated five membered ring containing two adjacent nitrogen as heteroatoms. Knorr<sup>16</sup> has synthesized first compound of pyrazoline and there after the investigated various derivatives and their properties of pyrazoles. The dihydro derivatives of pyrazoles are named as pyrazolines (Fig- III B<sub>1</sub>).

Various biological properties asn synthetic methods of pyrazoles and pyrazolines have been well reviewed by Elderfield<sup>17</sup>. Chelkov et.al.<sup>18</sup> have reported that 2 – pyrazolines are valuable as corrosion inhibitors. Fungicidal<sup>19-21</sup> activity of these compounds have been recorded. Some hydroxyl aryl pyrazolines have been evaluated for antibacterial activity. Some hydroxyl aryl pyrazoline derivatives have claimed local anaesthetic<sup>22</sup>, anticonvulsant<sup>23</sup> and antifertile<sup>24</sup> properties. 1-phenyl – 3- amino pyrazoline was found useful in developing cine films. CNS stimulant<sup>25</sup> and diuretic activities were also claimed in some derivatives of pyrazolines. The utility of pyrazole derivatives like phenyl butazone (Fig-III B<sub>2</sub>), oxyphenbutazone (Fig-III B<sub>3</sub>), Antipyrine (Fig-III B<sub>4</sub>) and Aminopyrine (Fig-III B<sub>5</sub>), as medicaments has been firmly established. Phenyl butazone has agent, causes marked retention of sodium and possesses mild uric cosuric properties. Oxyphenbutazone has equal anti-inflammatory and sodium retaining properties but less toxicity. Oxyphenbutazone is preferred clinically in the cases of acute inflammatory conditions, since in contrast to phenyl butazone. It does not cause gastro intestinal disturbances<sup>26</sup>.

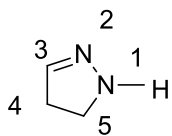


FIG. III B<sub>1</sub>

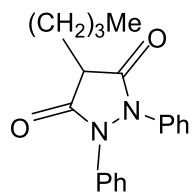


FIG. III B<sub>2</sub>

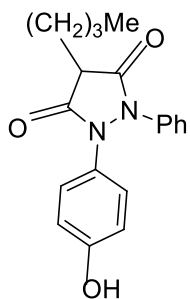


FIG. III B<sub>3</sub>

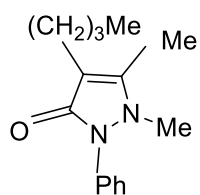


FIG. III B<sub>4</sub>

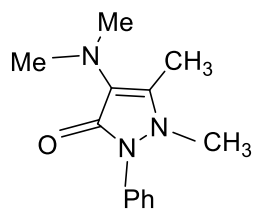


FIG. III B<sub>5</sub>

## **METHODS FOR THE PREPARATION OF PYRAZOLINES.**

Various methods have been devised for the synthesis of pyrazolines. Some important methods are given below.

### **PYRAZOLINES FROM PYRAZOLES.**

The reduction of 1 aryl pyrazolines to pyrazolines by sodium and alcohol is well known. The reduction can proceed beyond the pyrazoline (Fig-B<sub>6</sub>) stage with ring opening<sup>27,28</sup>. Catalytic hydrogenation of a pyrazole has been rarely attempted and it gives pyrazolines or pyrrolidines<sup>29</sup>. This is a poor preparative method because other synthesis methods are easier.

### **PYRAZOLINES FROM $\alpha,\beta$ - UNSATURATED CARBONYL COMPOUNDS.**

The pyrazolines can be synthesized from  $\alpha,\beta$ -ethylenic carbonyl compounds with hydrazine hydrate is rarely very common. Phenyl hydrazones can be isolated in many instances with phenyl hydrazine and these intermediates generally rearrange to pyrazolines on refluxing in acetic acid. Aliphatic and aromatic  $\alpha,\beta$ -unsaturated aldehydes and ketones directly or in hot aqueous sodium hydroxide when react with hydrazine hydrate yield pyrazoline derivatives. The more detailed survey of this method is given in "Heterocyclic compounds" by Elderfield<sup>30</sup>.

Recently Aziz et.al.<sup>31</sup> have reported the hydrazones first formed can be easily cyclised to pyrazolines on refluxing with Acetic acid. They independently carried out these reactions in acidic and neutral media. In acidic conditions they

independently carried out these reactions in acidic and neutral media. In acidic conditions they obtained compound (A) whereas in neutral medium the isomer (B) was isolated. They proposed that (A) is formed by 1 : 2- addition of hydrazine hydrate to the carbonyl group of the chalcone whereas (B) is obtained by 1 :4- addition of hydrazine hydrate on chalcone. The hydrazone thus formed, then undergoes dehydration, cyclisation and rearrangement to form pyrazoline (Fig-III B7).

### **FROM $\beta$ - SUBSTITUTED CARBONYL COMPOUNDS**

pyrazolines are also synthesized from a variety of  $\beta$ - substituted carbonyl compounds in which the  $\beta$ - substituent is a readily displayed group such as dialkylamino or halogen. The reaction is especially valuable with Mannich bases, which often gives pyrazoline under the usual conditions<sup>32</sup>. The exact course of pyrazoline formation has not been determined, their phenyl hydrazones may be intermediates, but a displacement of the dialkyl amino group of the phenyl hydrazone of the Mannich base by the hydrazine nitrogen is equally likely. The phenyl hydrazones of  $\beta$  - dialkyl amino ethyl  $\alpha,\beta$  -unsaturated ketones isomerise readily to pyrazolines by ring closure to the double bond<sup>33</sup>. Other  $\beta$  - substituents which can be eliminated to yield pyrazolines in a similar fashion to dialkylamino group of Mannich bases include chloro<sup>34</sup>, hydroxy<sup>35</sup>, mercapto<sup>35</sup> and aryl seleno<sup>36</sup>.

METHOD I

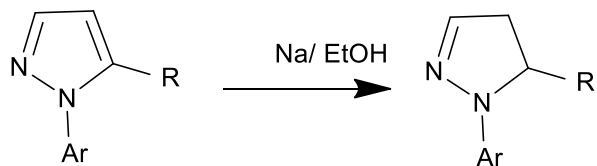


FIG. III B<sub>6</sub>

METHOD II

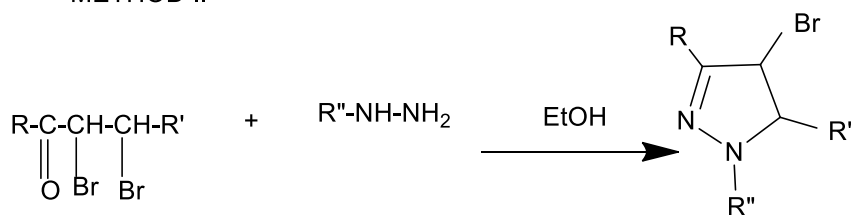


FIG. III B<sub>9</sub>

**PYRAZOLINES FROM DIAZO COMPOUNDS AND OLEFINS.**

Pyrazolines are readily obtained from  $\alpha$ ,  $\beta$  - unsaturated esters and diazo compounds. A wide variety of  $\alpha$ ,  $\beta$  - unsaturated esters and diazo compounds have been investigated and yield pyrazolines. The reaction of  $\alpha$ ,  $\beta$  - unsaturated nitriles with diazo compounds has not been studied extensively. Acrylonitrile gave polymers in preliminary experiments but has recently been reported to give pyrazolines in good yield<sup>37</sup>.

Secondary nitro olefins such as (w- nitrostyrene) react readily with diazomethane to give pyrazolines (Fig-IIIB<sub>8</sub>) that lose the nitro groups as oxides of nitrogen on heating or with diazomethane in cold ether to give pyrazoline and styrene behaves similarly. Diazo compounds react with  $\alpha$ -N- unsaturated esters to yield unstable pyrazolines which give pyrazoles with loss of hydrochloride under mild conditions<sup>39</sup>.

### **FROM CHALCONE DIBROMIDE**

Recently Dora et.al.<sup>40</sup> have obtained substituted pyrazolines by refluxing chalcone dibromide with phenyl hydrazine in alcohol – benzene mixture (Fig-III B<sub>9</sub>).

METHOD II

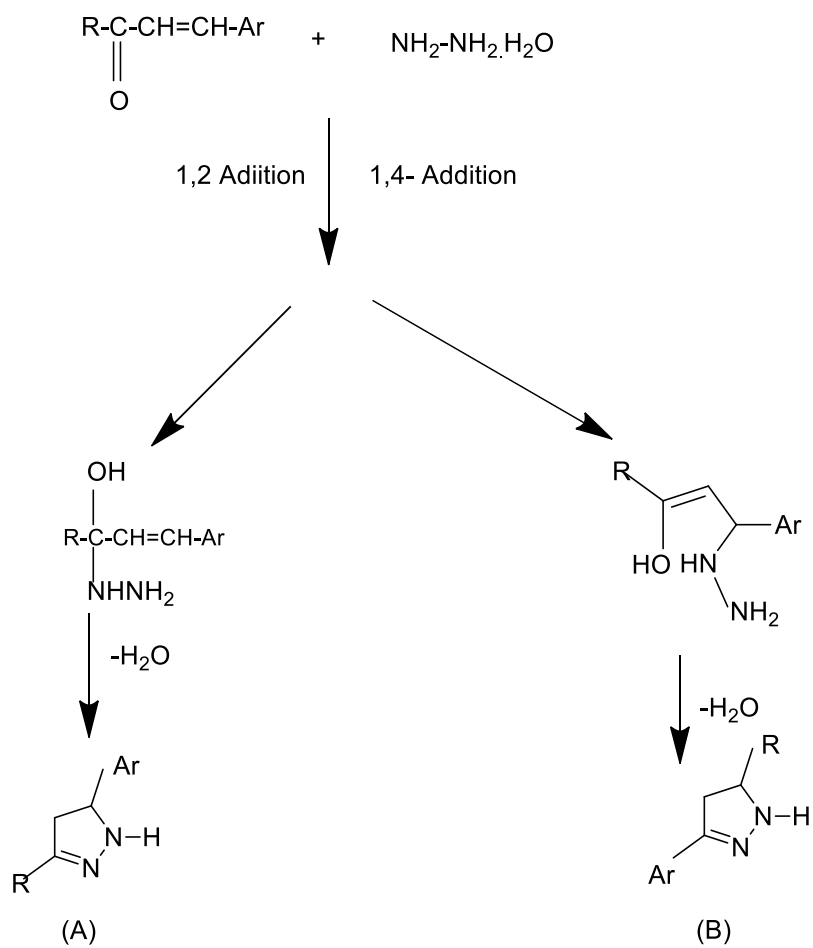


FIG. III B<sub>7</sub>

METHOD IV

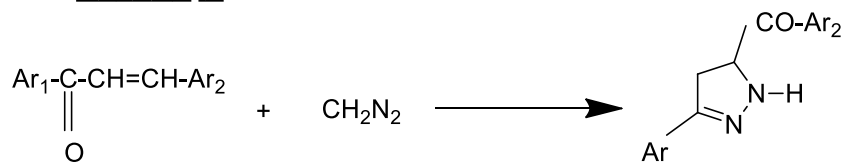


FIG. III B<sub>8</sub>

## PRESENT WORK AND METHOD.

The synthesis of 1,3- Bis- (5'-(4''-Chloro phenyl))- 4' 5-<sup>4</sup> dihydropyrazol - 3'-yl)- benzimidazolin - 2- thiones (Fig-IIIB10) has been carried out in the present work. These com- pounds were obtained by treating 1, 3 - (Bis(substituted aryl / heteryl)- propen - 1- only)- benzimidazolin - 2- thiones with hydrazine hydrate in alcohol. This method gave better yields and unambiguous products.

### PRESENT WORK

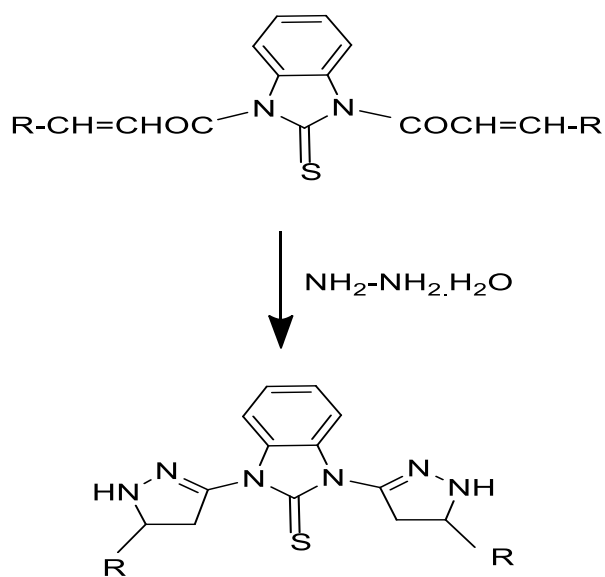


FIG. III- B<sub>10</sub>

Where,

$\text{R} = \text{Ph}, \text{CH}_3\text{-Ph}, \text{OCH}_3\text{-Ph}, \text{Cl-Ph}, \text{Br-Ph}, \text{NO}_2\text{-Ph}$



**GENERAL METHOD FOR THE SYNTHESIS OF -5'- (SUBSTITUTED  
ARYL / HETERYL) – 4',5'- DIHYDRO PYRAZOL -3'-YL) –  
BENZIMIDAZOLIN 2- THIONES :- (FIG. III B<sub>10</sub>).**

Hydrazine hydrate (0.03 mol) was added to 1,3 – [Bis- (4'- substituted aryl / heteryl )- propen – 1- onyl] – benzimidazolin – 2- thiones (0.01 mol) in ethanol (50ml) containing 5 ml glacial acetic acid. Then the reaction mixture was refluxed for 4 he on a water bath. The solvent was reduced to half of its volume. The crystalline product was separated out on cooling, then it was filtered, washed with water, dried and crystallized from ethanol. The purity of product was checked by TLC. The course of the reaction is represented as in Fig. IIIB<sub>10</sub>. The structure of the compounds was confirmed on the basis of IR and NMR spectra. The characterization of these compounds are recorded in Table 3.2. The compounds does not give colouration with conc. H<sub>2</sub>SO<sub>4</sub> indicating that the  $\alpha,\beta$ -unsaturated carbonyl group has taken part in the reaction.

### **DISCUSSION OF IR SPECTRA**

The IR spectra of few pyrazolines were recorded on Perkin-Elmer Infra-Red Spectrophotometer in nujol mull. The absorption for  $>C=N$  is found in the region of  $1560-1630\text{ cm}^{-1}$  indicating the conversion of ( $>C=O$ ) group into ( $>C=N$ ), the strong sharp band at  $336.-3375\text{ cm}^{-1}$  is due to  $>NH$  stretching. The absorption of  $>C=S$  is found in the region of  $1210-1220\text{ cm}^{-1}$ . The IR Spectrum No. 9 represents the spectrum of compound No. 4 (Table 3.2).

### **DISCUSSION OF PMR SPECTRA**

The PMR Spectra of few of the representative compounds were studied in  $DMSO-d_6$  on FT-80A Spectrometer using TMS as internal standard. The spectrum No.10, have the following PMR data. Chemical shifts in  $\delta$  3.7 (d,4H, $CH_2$  of pyrazoline ring),  $\delta$  4.9-5.1 (t,2H-pyrazoline ring),  $\delta$  6.8-7.8 (m,16H, Ar-H and -NH). Thus the structure of the compound 1,3- [Bis-(Substituted aryl / heteryl)-4', 5'-dihydropyrazol- 3'-yl]- benzimidazolin- 2- thiones is consistent with the PMR data. The spectrum No. 10 represents the spectrum of compound No.4 (Table- 3.2).

## EXPERIMENTAL PROCEDURE

### EXPERIMENT NO.1

#### PREPARATION OF 1,3 [BIS- (5'-(4"-CHLOROPHENYL)- 4',5'

#### DIHYDROPIRAZOL-3-YL)- BENZIMIDAZOLIN-2- THIONES:-( 04)

#### TABLE – 3.2.

Hydrazine Hydrate (1.28 g; 0.030 mol) was added to 1,3-Bis- (4'-chlorophenyl)- propen-1- only) – benzimidazolin – 2- thiones (4.79 g; 0.01mol) in ethanol (50 ml) containing 5ml glacial acetic acid. It was refluxed for six hrs, cooled and poured on ice-cold water. The solid separated was filtered, washed with cold water and dried. The crude product was crystallized from ethyl alcohol. M.P. 284 °C and yield 65 %.

Other compounds of the series were also prepared by following above procedure.

**TABLE – 3.2****CHARACTERISATION DATA OF 1,3-BIS- [(SUBSTITUTED ARYL- SUBSTITUTED PYRAZOLYL)- BENZIMIDAZOLIN – 2- THIONES (FIG-IIIB<sub>10</sub>).**

Compd. No	R	M.P.*	Yield	% of Nitrogen	
		(OC)		(%)	Found
1	-C <sub>6</sub> H <sub>5</sub>	275	65	18.62	18.96
2	-OHC <sub>6</sub> H <sub>4</sub>	241	68	17.49	17.68
3	-ClC <sub>6</sub> H <sub>4</sub>	246	79	16.26	16.40
4	-ClC <sub>6</sub> H <sub>4</sub>	284	65	16.20	16.40
5	-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	282	70	17.54	17.83
6	-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	286	66	17.59	17.83
7	-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	292	71	17.63	17.83
8	-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	281	74	16.51	16.69
9	-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	293	79	16.49	16.69
10	-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	260	69	15.60	15.75
11	-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	278	68	15.60	15.75
12	-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	285	76	15.60	15.75
13	-Furyl	273	72	19.68	20.09
14	-Pyridyl	249	69	18.90	19.09
15	-Thiophen	281	70	18.52	18.66
16	-CH <sub>3</sub>	180	79	26.40	26.75

\* All compounds Crystallized from Ethyl Alcohol.

## **PART - III**

### **SECTION – C**

**Synthesis of 1,3- bis-(substituted**

**4', 5'- dihydroisoxazole)-**

**Benzimidazolin- 2- Thiones**

## INTRODUCTION

A good deal of importance is being given to isoxazoline derivatives due to their wide use in medicinal chemistry. The isoxazole ring system, as its name indicated, is one containing a nitrogen and an oxygen atom adjacent to each other in the five membered cycle (Fig-III<sub>C1</sub>)

Although isoxazole derivatives have known for more than eighty years, the investigation of their chemistry commences rather slowly. Creasol<sup>41</sup> obtained the isoxazole in the year 1884 by the action of hydroxyl amine hydrochloride on benzoyl acetone. Dihydro isoxazoles or isoxazolines are biologically important compounds.

Theoretically, three isoxazolines are possible depending on the location of  $\alpha$ ,  $\alpha$  double bond.

1. 22-Isoxazoline.
2. 33- Isoxazoline.
3. 44- Isoxazoline, (as shown in Fig-III<sub>C 2-4</sub>)

2- Isoxazolines (Fig-III<sub>C2</sub>) are comparatively more stable and much important.

Until recently, no natural product containing the isoxazole ring was known, except the glycosides, hipilagen isolated in 1920 from *Malpighicea hipatogo mudobalata*<sup>42</sup>. In the year 1955, Blue et.al.<sup>43</sup> isolated the antibiotic cycloserin or oxamycin from *streptomyces* or orchideneous a simple derivative of 4- amino isoxazolidone.



ISOXAZOLE

FIG. III- C<sub>1</sub>



2- ISOXAZOLINE

FIG. III- C<sub>2</sub>



3- ISOXAZOLINE

FIG. III- C<sub>3</sub>



4- ISOXAZOLINE

FIG. III- C<sub>4</sub>

It is a well known broad spectrum antibiotic and is found useful in the treatment of tuberculosis<sup>44</sup> and leprosy<sup>45</sup>. Similarly, a number of isoxazole derivatives have been shown to possess potential antibacterial, antitubercular, antifungal and antiviral activities<sup>46</sup>. Anilido isoxazolines synthesized by Khalil and others<sup>47</sup> were found to possess remarkable bactericidal activity against some gram(+ve) and gram (-ve) bacteria. A number of isoxazoline have been used as photosensitizer and super sensitizer<sup>48,49</sup>. Recently, it was observed. That pregnan<sup>55,56</sup> d-2-isoxazolines<sup>50</sup> were useful for fertility control and pregnancy maintenance. Some substituted isoxazolines have been reported as herbicides and plant growth regulants<sup>51</sup>. Many of them are used for the control of plant phytopathogens<sup>52</sup>. Antimicrobial and antifungal activities have been reported in 3-methyl-4- isoxazolines by Mittal and others<sup>53</sup>. A number of isoxazolin – 3- one derivatives have been synthesized as antiinflammants<sup>54</sup> and analgesics<sup>55</sup>.

Keeping this in view the attempt was made to synthesize some new 1,3-Bis- (Substituted aryl /heteryl)- benzimidazolyl isoxazolines which may have significant chemotherapeutic activities.

METHOD- I

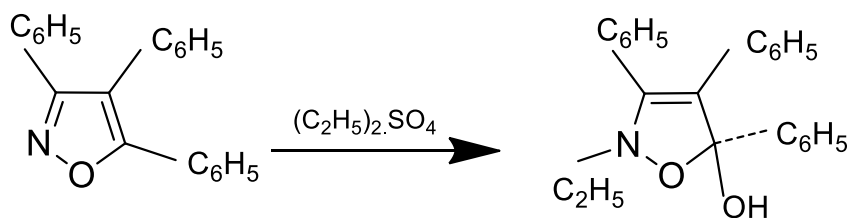


FIG. III C<sub>5</sub>

METHOD- II

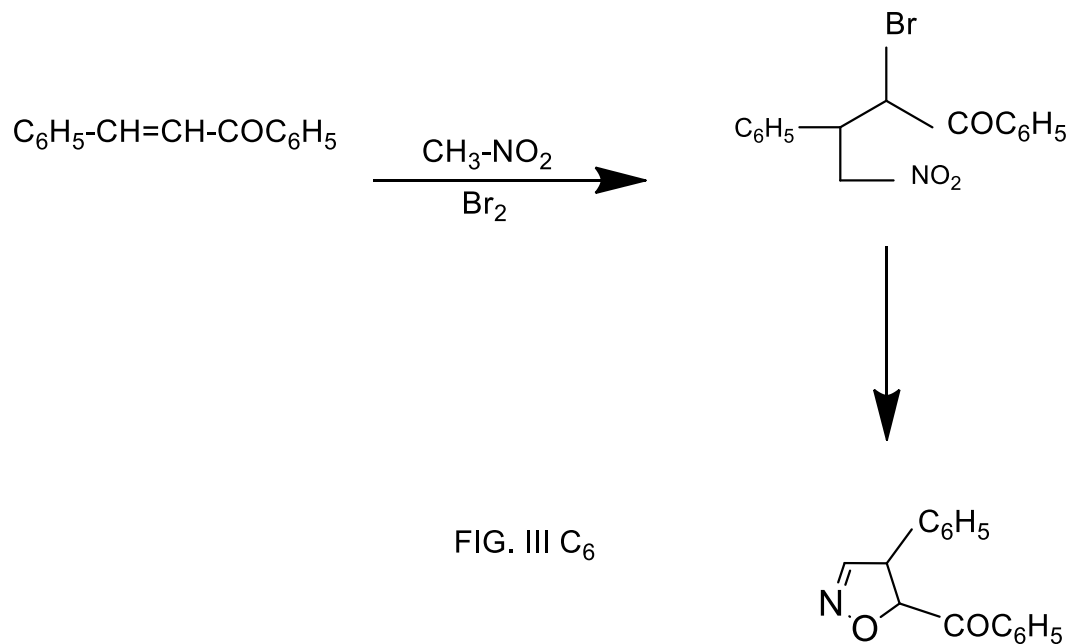


FIG. III C<sub>6</sub>



## **METHODS FOR THE PREPARATION OF ISOXAZOLINES**

A Number of methods can be used for the preparation of isoxazolines. The most widely used methods are discussed here.

### **FROM ISOXAZOLES :-**

Isoxazoles may be converted to 5- hydroxyl isoxazolines. This transformation is essentially the formation of pseudo base<sup>56</sup>. The reaction can be represented in Fig- IIC<sub>5</sub>.

### **FROM NITRO COMPOUNDS :-**

Isoxazoline oxides can be prepared from properly substituted nitro compounds as shown in Fig-IIC<sub>6</sub>

### **FROM B- HALOKETONES :-**

When  $\alpha, \beta$ - haloketone<sup>57</sup> is treated with hydroxyl amine in alkaline solution, the isoxazoline is obtained by the displacement of halo atom by an anion of the normal ketoxine. A similar reaction takes place when the oxime of Mannich base<sup>58</sup> is treated with aqueous alcoholic sodium hydroxide. In this case trialkyl amine is displaced instead of halo ion. The reaction can be shown in Fig-IIC<sub>7</sub>.

METHOD - III

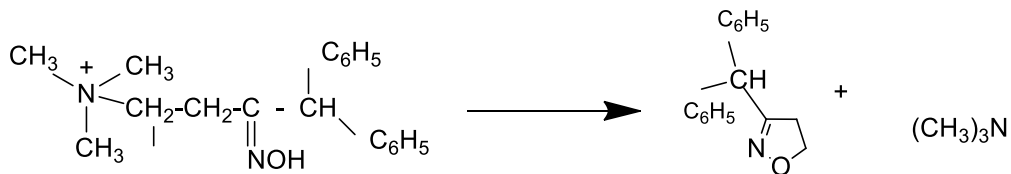


FIG. III C<sub>7</sub>

METHOD - IV

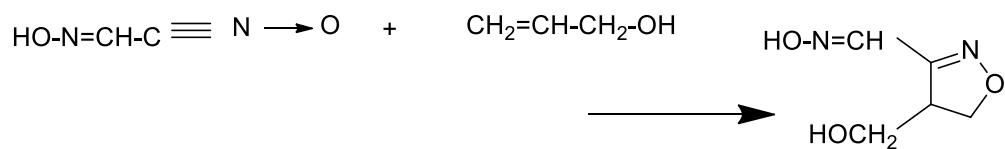


FIG. III C<sub>8</sub>

**FROM OLEFINS :-**

The reaction of olefins with nitrile oxide is a general method for preparing isoxazolines. This synthesis is successful with benzonitrile oxide and varied olefins such as allyl alcohol, vinyl chloride, styrene stillbene and eugenol<sup>60</sup>, Fig- IIC<sub>8</sub>.

METHOD -V

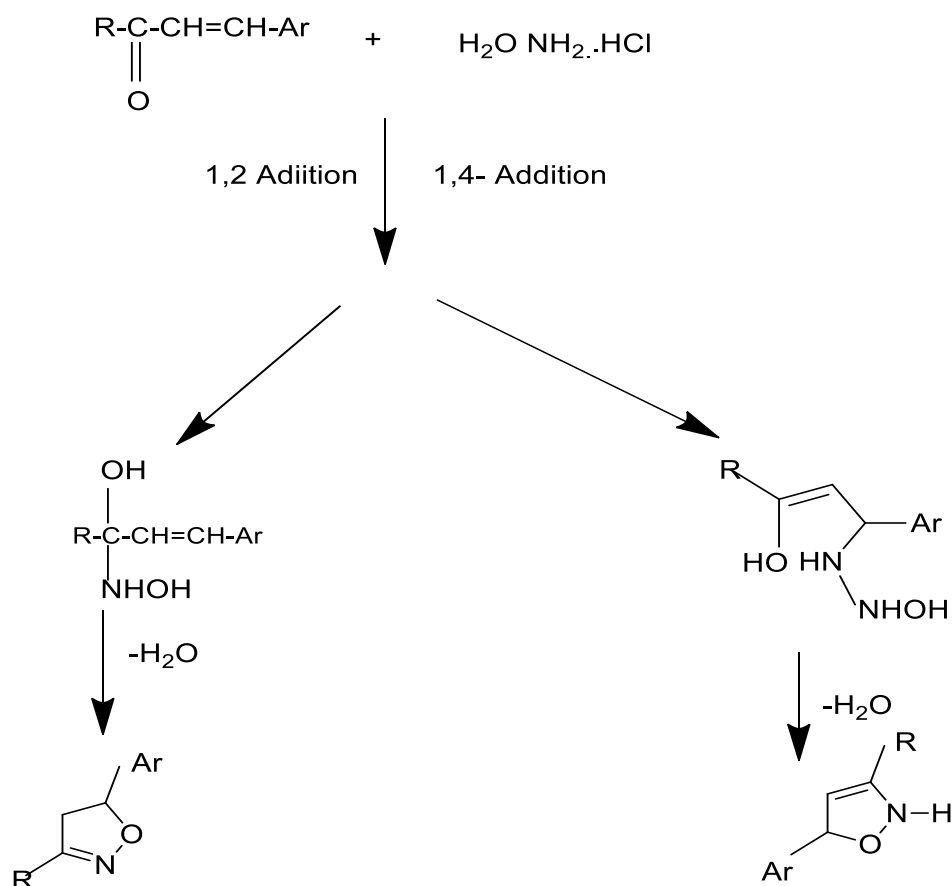


FIG. III C<sub>9</sub>

**FROM  $\alpha$ ,  $\beta$ - UNSATURATED KETONES :-**

Generally isoxazolines are prepared by this method. It involves the reaction of an  $\alpha$ ,  $\beta$  unsaturated ketone with hydroxyl amine in basic medium. The mechanism is not definitely established. Both 1, 4 and 1, 2 addition of hydroxylamine may take place depending on the experimental conditions. Van Answers et. al.<sup>61</sup> have reported that the isoxazolines are not directly formed by cyclisation of unsaturated ketoximes.

The theory of 1, 4- addition of hydroxyl amine to  $\alpha, \beta$ -unsaturated ketone was formerly accepted by Barnes and co-workers<sup>62</sup>, But recently, they have proposed the 1, 2 –addition mechanism for the formation of 2- isoxazolines. Intermediate products formed by 1, 2 – addition of hydroxyl amine to unsaturated ketones are decomposed to have isoxazolines. The structural and spectral evidences have also supported the 1, 2 –addition of hydroxyl; amine.

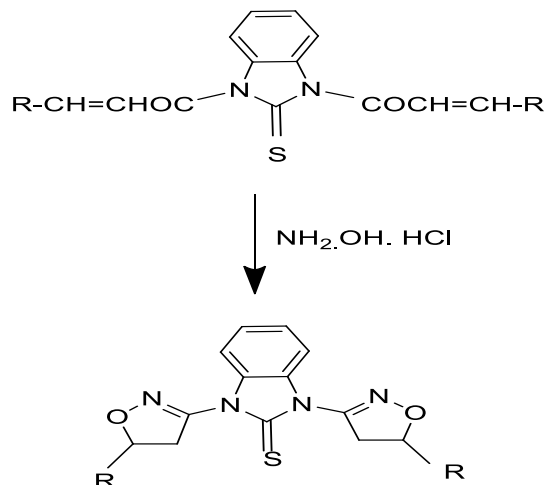
A mechanism involving 1, 4- addition was shown to be inconsistent with the experimental results by Blatt<sup>63, 64</sup>. The isoxazoline formation in basic or neutral medium is reported. Some workers have reported the synthesis of isoxazoline in presence of strong mineral acids. Recently Aziz<sup>65</sup> claimed the formation of 2- isoxazolines from  $\alpha, \beta$ - unsaturated ketone by 1, 2- addition mechanism in basic medium (Fig- III C<sub>9</sub>).

## **PRESENT WORK**

Few isoxazolines containing heterocyclic substituent's have been synthesized by Shingare and Siddiqui<sup>66</sup>. Some isoxazolines have been reported by Thakar and Padhye<sup>67</sup>. But there is no report on the synthesis of isoxazolines having benzimidazolin – 2- thiones at their 1 and 3- position. Therefore it was thought worthwhile to synthesize some new isoxazolines because of their use in pharmacology.

In the present work 1, 3- Bis- (5' substituted aryl / heteryl) – benzimidazolin – 2- thiones were synthesized by the interaction of  $\alpha,\beta$  - unsaturated ketones (described in section A of this part) and hydroxyl amine hydrochloride in presence of sodium hydroxide. The method is easy to carryout. The yields are better and the  $\alpha,\beta$  -unsaturated ketones were readily available.

PRESENT WORK



Where,

R = Ph, CH<sub>3</sub>-Ph, OCH<sub>3</sub>-Ph, Cl-Ph, Br-Ph, NO<sub>2</sub>-Ph

FIG. III- C 10

**GENERAL METHOD FOR THE SYNTHESIS OF 1,3 – BIS  
SUBSTITUTED- 4', 5' –DIHYDRO ISOXAZOL – 3' – YL) –  
BENZIMIDAZOLIN – 2- THIONES :- (FIG- IIC<sub>10</sub>).**

A Mixture of 1,3 – Bis – (N- (Substituted aryl / heteryl) – propen – 1- onyl) – benzimidazolin – 2- thiones and hydroxyl amine hydrochloride (0.03 mol) and 40% aqueous sodium hydroxide solution was refluxed in ethyl alcohol for 5-6 hrs. After cooling the reaction mixture was poured into ice cold water. The solid thus obtained was filtered, washed with water and crystallized from proper solvent. Purity of the product was checked by TLC.

The structure of the compounds was established by IR, NMR and elemental analysis. The M. Pts., yields, solvent for crystallization and nitrogen analysis are given in Table-3.3.

### **DISCUSSION OF IR SPECTRA**

The IR spectrum of the substituted dihydro isoxazol – 3'-yl-benzimidazolin – 2- thiones were scanned on Perkin- Elmer Infra- Red Spectrophotometer in nujol mull. Following frequencies are observed for different groups.

The absorption band at 1610- 1660  $\text{cm}^{-1}$  is due to C=N of isoxazoline ring & 1225  $\text{cm}^{-1}$  absorption due to C=S stretching. All compounds showed characteristic bands of isoxazoline ring at 1460,1240  $\text{cm}^{-1}$  are due to N-O-C. The IR spectrum No. 11 represents the spectrum of 1, 3-Bis-[(5'-(4''-chloro phenyl)-4', 5'- dihydro isoxazol- 3'- yl)] –benzimidazolin – 2- thiones.

### **DISCUSSION OF PMR**

The PMR spectra of few representative compounds were studied in DMSO-  $\text{d}_6$  on varian FT-BOA Spectrophotometer using TMS as internal standard.

The chemical shift in  $\delta$  ppm displayed a doublet due to 4H, of  $\text{CH}_2$ -isoxazoline ring at  $\delta$  3.6. The triplet appears at  $\delta$  4.9 – 5.0 due to 2H, isoxazolin – 5H, proton and showed multiplet due to 12 H, aromatic proton at  $\delta$  6.7 to 7.8. The PMR spectrum No. 12 represents the spectrum of 1, 3- [Bis-(5'-(4''- chloro phenyl)- 4',5'- dihydro isoxazol -3'-yl)] – benzimidazolin – 2- thiones.

## EXPERIMENTAL

### SYNTHESIS OF 1,3-[BIS-(5'-(4'-CHLOROPHENYL)-4',5' DIHYDRO

### ISOAZOL-3'-YL)- BENZIMIDAZOLIN-2- THIONES (04) :-

To a refluxing mixture of 1,3- (bis-(4'-chloro phenyl)- propen-1-only)- benzimidazolin – 2- thiones (4.8 g; 0.01 mol) and hydroxyl amine hydrochloride (2.08g; 0.03 mol) in ethanol (25 ml) was added an aqueous solution of sodium hydroxide (40%) portion wise during a period of half an hour. Refluxing was continued for 4 hr. The solvent was reduced to half its volume and the solid product which separated out on cooling was filtered, washed with cold aq. Ethanol followed by water, dried and crystallized from methanol-DMF mixture. M.P. 298 °C; yield 69 %.

Similarly other compounds of the series were prepared. Table 3.3.



**TABLE – 3.3****CHARACTERISATION DATA OF 1,3-BIS- [(SUBSTITUTED ARYL- SUBSTITUTED ISOXAZOLYL)- BENZIMIDAZOLIN – 2- THIONES (FIG-IIIC<sub>10</sub>).**

Compd. No	R	M.P.*	Yield	% of Nitrogen	
		( <sup>o</sup> C)		Found	Calcd.
1	-C <sub>6</sub> H <sub>5</sub>	273	75	12.32	12.58
2	2'-OH-C <sub>6</sub> H <sub>4</sub>	246	72	11.62	11.74
3	2'-Cl-C <sub>6</sub> H <sub>4</sub>	239	73	10.71	10.89
4	4'-Cl-C <sub>6</sub> H <sub>4</sub>	298	70	10.74	10.89
5	2'-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	280	66	11.60	11.83
6	3'-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	282	68	11.58	11.83
7	4'-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	290	72	11.70	11.83
8	2'-OCH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	276	76	10.84	11.08
9	4'-OCH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	290	68	10.90	11.08
10	2'-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	263	70	15.63	15.70
11	3'-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	270	72	15.59	15.70
12	4'-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	281	69	15.65	15.70
13	2'-Furyl	269	68	13.11	13.33
14	2'-Pyridyl	241	70	12.32	12.66
15	2'-Thiophen	283	73	12.12	12.38
16	-CH <sub>3</sub>	186	76	17.50	17.72

\* All compounds Crystallized from Methanol + DMF and gives C & H analysis satisfactory

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(M.S.) India.

## **PART – IV**

### **SECTION – A**

# **Synthesis of 2- alkyl / aryl )-1-(N-Substituted dihydropyridino- methyl )- Benzimidazoles**

## INTRODUCTION

The benzimidazole possesses wide biological activities, such as , Antibacterial<sup>1</sup> , Antifungal<sup>2</sup> , Antihelminthic<sup>3,4</sup> , Antiviral<sup>5</sup> activities. The Mannich reaction involves the condensation of a compound containing at least one active hydrogen atom such b-ketoester, phenols, b-cyanoesters, Benzimidazoles etc., with formaldehyde and ammonia or a primary or secondary amines. The net change during this reaction is the replacement of active hydrogen atom by an aminomethyl group or substituted aminomethyl group. The product is called Mannich base (Fig.IVA<sub>1</sub>) and is of great physiological value in therapy<sup>6-9</sup>. The Mannich bases of benzimidazoles were prepared by using dihydropyridines with the hope that to obtain antimicrobial active compounds.

Benzimidazole derivatives with substituent's such as amino, nitro, mercapto or chloro groups when present at position 4 or 6 have been found to inhibit the growth of certain viruses<sup>10</sup>, Besides various benzimidazoles are effective inhibitors of the growth of yeasts<sup>11</sup>, Lactobacilli<sup>12</sup>, Vacciniaviruses<sup>13</sup>, and influenza viruses<sup>14</sup>, similarly 2-polynitro phenyl thio benzimidazoles have been found to possess marked fungitoxicity.

On the other hand, it has been suggested by many chemists to synthesize therapeutically important compounds in which benzimidazoles is fused with other biologically active heterocyclic nuclei. It was also established that introduction of N,N-substituted amino alkyl moiety at 2-position of benzimidazole potentiates its biological activities<sup>15</sup>.

These findings prompted to synthesize some 1-[N,N-substituted dihydropyridino methyl]-benzimidazoles (fig- IV<sub>2</sub>) and evaluate for their antimicrobial activity.



## PRESENT WORK

The synthesis of 2-(alkyl / aryl )-1-[substituted dihydropyridino methyl]- benzimidazoles (Fig- IVA<sub>2</sub> ) has been carried out in the present work. 2-substituted alkyl / aryl benzimidazoles on Mannich reaction with appropriate secondary bases and formaldehyde in presence of conc. HCl gave 2- alkyl / aryl -1-[N-substituted dihydropyridino methyl]- benzimidazoles.

The formation of the compounds were characterized by TLC. These compounds were screened for their antimicrobial activity. The physical characterization data of the synthesized compounds are given in table 4.1. The required dihydropyridines <sup>16</sup> were used from the part I (section –A). The substituted benzimidazoles were prepared by known methods <sup>17-19</sup>.

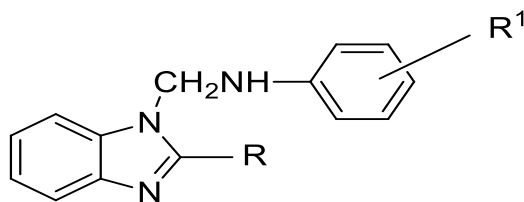
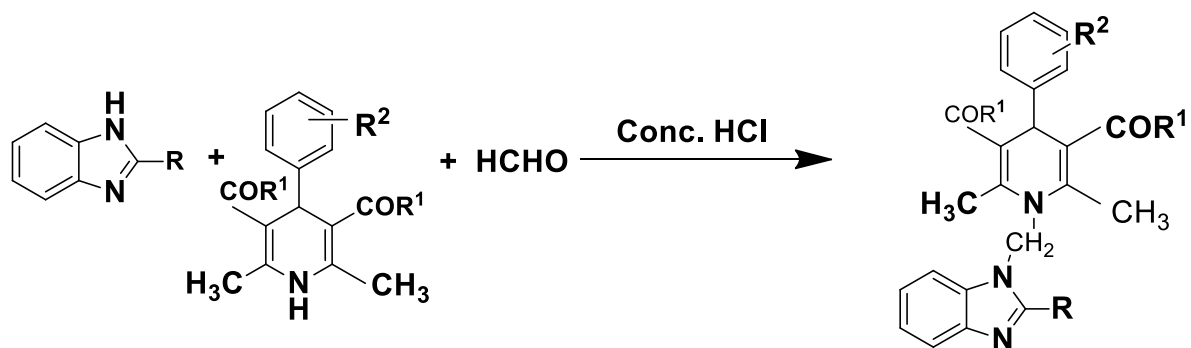


FIG. IV - A<sub>1</sub>

PRESENT WORK



Where ,  
R = H, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, C<sub>6</sub>H<sub>5</sub>  
R<sub>1</sub> = CH<sub>3</sub>, OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>  
R<sub>2</sub> = CH<sub>3</sub>, OCH<sub>3</sub>, Cl, NO<sub>2</sub>, Br

Fig. IV- A<sub>2</sub>

**GENERAL METHOD FOR SYNTHESIS OF 2- ALKYL / ARYL )-1-N-SUBSTITUTED  
DIHYDROPYRIDINO-METHYL- BENZIMIDAZOLES : (FIG-IVA<sub>2</sub>) :-**

To a mixture of equimolar quantities of 2-substituted alkyl / aryl benzimidazoles and substituted dihydropyridines and 40 % formaldehyde solution in ethanol was added and the mixture was refluxed on a water bath for 2 hr. The reaction mixture were cooled and poured on crushed ice. The solid product separated was filtered, washed with cold water, dried and crystallized from aq. Alcohol. The M.Pts., yields., elemental analysis and solvent for crystallization of these compounds have been tabulated in Table 4.1.

**EXPERIMENTAL PROCEDURE**

**PREPARATION OF 2-METHYL-1-N-[(1', 4' - DIHYDRO-4-4''-TOLYL)-3',5'-  
DIACETYL 2',6' - DIMETHYL PYRIDINO -METHYL) - BENZIMIDAZOLES (16) :**

**TABLE 4.1 :-**

To the mixture of Benzimidazole (1.18g ; 0.01 mol) in methanol (25ml) and formaldehyde (0.5 ml) were stirred for 30 min. and 1,4-dihydro -4'-3'' -chlorophenyl )-3,5-diacetyl -2,6-dimethyl pyridine (2.85 g ; 0.01 mol) was added with 1-2 drops of conc. HCl and then the mixture were refluxed on a boiling water bath for 2 hr. the reaction mixture were cooled and poured on crushed ice. The solid product separated was filtered, washed with cold water, dried and crystallized form aq. Ethanol to give compound no. 16. M. P. 177 0° ; yield 70 %.

Similarly other compounds of this series were prepared.

## DISCUSSION OF IR SPECTRA

The IR spectra of some of the representative compounds from this series have been scanned on Perkin-Elmer IR-1420 Spectrophotometer using nujol mull.

The IR spectrum No. 13 represents the spectrum of 2-methyl-1-[1',4'-dihydro-3',5'-diacetyl -2',6'-dimethyl )-4'-tolyl-pyridino methyl )-benzimidazoles (compound No. 16) were displayed the bands around 1545-1575  $\text{cm}^{-1}$  due to C-N stretching and at 1629-1635  $\text{cm}^{-1}$  due to C=N. the bands at 1685-1695  $\text{cm}^{-1}$  represents the presence of  $>\text{C}=\text{O}$  group and the bands at 1610-1620  $\text{cm}^{-1}$  are assignable to C=C stretchings.

## DISCUSSION OF PMR SPECTRA

The PMR spectra of few representative compounds were scanned on FT-80A PMR spectrometer using TMS as internal standard in  $\text{CDCl}_3$ . Chemical shifts are in  $\delta$  ppm scale. The spectrum No. 14 represents the PMR spectra of 2-methyl-1-[1',4'-dihydro-3',5'-diacetyl -2',6'-dimethyl )-4'-(tolyl)-pyridino methyl )-benzimidazoles (compound No. 16) as it displayed following PMR signals. At  $\delta$  2.50 singlet due to two protons of  $\text{N-CH}_2\text{-N}$ ,  $\delta$  2.26 singlet due to 6 H of pyridyl  $\text{CH}_3$ ,  $\delta$  1.60 singlet due to 3 H of benzimidazole of  $\text{CH}_3$ ,  $\delta$  3.41 singlet due to six protons of  $\text{COCH}_3$ ,  $\delta$  6.85-7.30 multiplet is assignable to eight protons of aromatic rings. The PMR data of other members of the series were also in agreement with their structures assigned.

Table 4.1

CHARACTERISATION DATA OF 2-ALKYL 1-(n-SUBSTITUTED DIHYDROPYRIDINO)-  
BENZIMIDAZOLES. (Fig. IV A<sub>2</sub>)

Comp. No.	R	R <sup>1</sup>	R <sup>2</sup>	YIELD %	M.P °C	MOL. FORMULA	% OF N found	% OF N calcd.
1	H	CH <sub>3</sub>	H	70	174	C <sub>25</sub> H <sub>25</sub> N <sub>3</sub> O <sub>2</sub>	10.39	10.52
2	H	CH <sub>3</sub>	4'-CH <sub>3</sub>	79	175	C <sub>26</sub> H <sub>27</sub> N <sub>3</sub> O <sub>2</sub>	10.04	10.16
3	H	CH <sub>3</sub>	4'-OCH <sub>3</sub>	70	165	C <sub>26</sub> H <sub>27</sub> N <sub>3</sub> O <sub>2</sub>	9.34	9.56
4	H	CH <sub>3</sub>	H	73	145	C <sub>25</sub> H <sub>25</sub> N <sub>3</sub> O <sub>4</sub>	9.56	9.74
5	H	OCH <sub>3</sub>	2'-CH <sub>3</sub>	82	178	C <sub>26</sub> H <sub>27</sub> N <sub>3</sub> O <sub>4</sub>	9.32	9.43
6	H	OCH <sub>3</sub>	3'-OCH <sub>3</sub>	86	165	C <sub>26</sub> H <sub>24</sub> N <sub>3</sub> O <sub>5</sub>	9.10	9.11
7	H	OCH <sub>3</sub>	3'-Cl	81	191	C <sub>25</sub> H <sub>24</sub> N <sub>3</sub> O <sub>4</sub> Cl	8.89	9.04
8	H	OCH <sub>3</sub>	3'-NO <sub>2</sub>	70	186	C <sub>25</sub> H <sub>24</sub> N <sub>4</sub> O <sub>6</sub>	11.56	11.76
9	H	OCH <sub>3</sub>	4'-NO <sub>2</sub>	74	204	C <sub>25</sub> H <sub>24</sub> N <sub>4</sub> O <sub>6</sub>	11.62	11.76
10	H	OCH <sub>3</sub>	4'-OH	81	224	C <sub>25</sub> H <sub>25</sub> N <sub>3</sub> O <sub>5</sub>	9.28	9.39
11	H	OC <sub>2</sub> H <sub>5</sub>	H	80	180	C <sub>27</sub> H <sub>29</sub> N <sub>3</sub> O <sub>4</sub>	10.39	10.52
12	H	OC <sub>2</sub> H <sub>5</sub>	4'-CH <sub>3</sub>	76	149	C <sub>28</sub> H <sub>31</sub> N <sub>3</sub> O <sub>4</sub>	8.61	8.87
13	H	OC <sub>2</sub> H <sub>5</sub>	4'-OCH <sub>3</sub>	85	129	C <sub>28</sub> H <sub>31</sub> N <sub>3</sub> O <sub>4</sub>	8.39	8.58
14	H	OC <sub>2</sub> H <sub>5</sub>	4'-Cl	68	135	C <sub>27</sub> H <sub>30</sub> N <sub>3</sub> O <sub>4</sub> Cl	8.29	8.47
15	CH <sub>3</sub>	CH <sub>3</sub>	H	80	170	C <sub>26</sub> H <sub>27</sub> N <sub>3</sub> O <sub>2</sub>	10.04	10.17
16	CH <sub>3</sub>	CH <sub>3</sub>	4'-CH <sub>3</sub>	70	177	C <sub>27</sub> H <sub>29</sub> N <sub>3</sub> O <sub>2</sub>	9.62	9.83
17	CH <sub>3</sub>	CH <sub>3</sub>	4'-OCH <sub>3</sub>	66	179	C <sub>27</sub> H <sub>29</sub> N <sub>3</sub> O <sub>3</sub>	9.36	9.48

Comp. No.	R	R <sup>1</sup>	R <sup>2</sup>	YIELD %	M.P °C	MOL. FORMULA	% OF N found	% OF N calcd.
18	CH <sub>3</sub>	OCH <sub>3</sub>	2'-CH <sub>3</sub>	79	168	C <sub>27</sub> H <sub>29</sub> N <sub>3</sub> O <sub>4</sub>	9.02	9.15
19	CH <sub>3</sub>	OCH <sub>3</sub>	4'-OCH <sub>3</sub>	76	179	C <sub>27</sub> H <sub>29</sub> N <sub>3</sub> O <sub>5</sub>	9.68	8.84
20	CH <sub>3</sub>	OCH <sub>3</sub>	3'-NO <sub>2</sub>	81	206	C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O <sub>6</sub>	11.31	11.42
21	CH <sub>3</sub>	OCH <sub>3</sub>	4'-NO <sub>2</sub>	78	184	C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O <sub>6</sub>	11.29	11.42
22	CH <sub>3</sub>	OCH <sub>3</sub>	2'-Cl	72	174	C <sub>26</sub> H <sub>26</sub> N <sub>3</sub> O <sub>4</sub> Cl	8.59	8.75
23	CH <sub>3</sub>	OC <sub>2</sub> H <sub>5</sub>	H	79	184	C <sub>28</sub> H <sub>31</sub> N <sub>3</sub> O <sub>4</sub>	8.62	8.87
24	CH <sub>3</sub>	OC <sub>2</sub> H <sub>5</sub>	4'-CH <sub>3</sub>	70	128	C <sub>29</sub> H <sub>33</sub> N <sub>3</sub> O <sub>4</sub>	8.34	8.62
25	CH <sub>3</sub>	OC <sub>2</sub> H <sub>5</sub>	4'-OCH <sub>3</sub>	75	139	C <sub>29</sub> H <sub>33</sub> N <sub>3</sub> O <sub>5</sub>	8.27	8.34
26	CH <sub>3</sub>	OC <sub>2</sub> H <sub>5</sub>	4'-Cl	79	128	C <sub>28</sub> H <sub>30</sub> N <sub>3</sub> O <sub>4</sub> Cl	8.14	8.27
27	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	H	69	139	C <sub>27</sub> H <sub>29</sub> N <sub>3</sub> O <sub>2</sub>	9.62	9.83
28	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	4'-CH <sub>3</sub>	78	181	C <sub>28</sub> H <sub>30</sub> N <sub>3</sub> O <sub>4</sub>	8.58	8.89
29	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	4'-OCH <sub>3</sub>	71	168	C <sub>28</sub> H <sub>30</sub> N <sub>3</sub> O <sub>4</sub>	8.41	8.60
30	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	4'-Br	82	177	C <sub>27</sub> H <sub>28</sub> N <sub>3</sub> O <sub>2</sub> Br	8.28	8.30
31	C <sub>2</sub> H <sub>5</sub>	OCH <sub>3</sub>	2'-CH <sub>3</sub>	68	170	C <sub>28</sub> H <sub>30</sub> N <sub>3</sub> O <sub>4</sub>	8.69	8.89
32	C <sub>2</sub> H <sub>5</sub>	OCH <sub>3</sub>	3'-OCH <sub>3</sub>	72	160	C <sub>28</sub> H <sub>30</sub> N <sub>3</sub> O <sub>5</sub>	8.42	8.58
33	C <sub>2</sub> H <sub>5</sub>	OCH <sub>3</sub>	2'-Cl	79	184	C <sub>27</sub> H <sub>28</sub> N <sub>3</sub> O <sub>4</sub> Cl	8.28	8.51
34	C <sub>2</sub> H <sub>5</sub>	OCH <sub>3</sub>	3'-NO <sub>2</sub>	72	195	C <sub>27</sub> H <sub>28</sub> N <sub>4</sub> O <sub>6</sub>	11.02	11.11
35	C <sub>2</sub> H <sub>5</sub>	OCH <sub>3</sub>	4'-NO <sub>2</sub>	70	180	C <sub>27</sub> H <sub>28</sub> N <sub>4</sub> O <sub>6</sub>	10.96	11.11
36	C <sub>2</sub> H <sub>5</sub>	OC <sub>2</sub> H <sub>5</sub>	H	79	183	C <sub>29</sub> H <sub>33</sub> N <sub>3</sub> O <sub>4</sub>	8.48	8.62
37	C <sub>2</sub> H <sub>5</sub>	OC <sub>2</sub> H <sub>5</sub>	4'-CH <sub>3</sub>	72	125	C <sub>30</sub> H <sub>35</sub> N <sub>3</sub> O <sub>4</sub>	8.12	8.38

Comp. No.	R	R <sup>1</sup>	R <sup>2</sup>	YIELD %	M.P °C	MOL. FORMULA	% OF N found	% OF N calcd.
38	C <sub>2</sub> H <sub>5</sub>	OC <sub>2</sub> H <sub>5</sub>	4'-OCH <sub>3</sub>	69	146	C <sub>30</sub> H <sub>35</sub> N <sub>3</sub> O <sub>5</sub>	7.98	8.12
39	C <sub>2</sub> H <sub>5</sub>	OC <sub>2</sub> H <sub>5</sub>	4'-Cl	74	130	C <sub>29</sub> H <sub>32</sub> N <sub>3</sub> O <sub>4</sub> Cl	7.89	8.05
40	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	H	78	140	C <sub>31</sub> H <sub>29</sub> N <sub>3</sub> O <sub>2</sub>	8.59	8.84
41	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	4'-OCH <sub>3</sub>	75	152	C <sub>31</sub> H <sub>29</sub> N <sub>3</sub> O <sub>3</sub>	8.28	8.31
42	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	4'-CH <sub>3</sub>	70	149	C <sub>32</sub> H <sub>31</sub> N <sub>3</sub> O <sub>3</sub>	8.40	8.58
43	C <sub>6</sub> H <sub>5</sub>	OCH <sub>3</sub>	H	79	160	C <sub>32</sub> H <sub>29</sub> N <sub>3</sub> O <sub>4</sub>	8.17	8.28
44	C <sub>6</sub> H <sub>5</sub>	OCH <sub>3</sub>	4'-CH <sub>3</sub>	73	146	C <sub>32</sub> H <sub>31</sub> N <sub>3</sub> O <sub>4</sub>	7.89	8.06
45	C <sub>6</sub> H <sub>5</sub>	OCH <sub>3</sub>	4'-Cl	82	172	C <sub>31</sub> H <sub>28</sub> N <sub>3</sub> O <sub>4</sub> Cl	7.48	7.75
46	C <sub>6</sub> H <sub>5</sub>	OCH <sub>3</sub>	4'-NO <sub>2</sub>	78	184	C <sub>31</sub> H <sub>28</sub> N <sub>3</sub> O <sub>6</sub>	10.11	10.14
47	C <sub>6</sub> H <sub>5</sub>	OC <sub>2</sub> H <sub>5</sub>	H	72	157	C <sub>33</sub> H <sub>33</sub> N <sub>3</sub> O <sub>4</sub>	7.77	7.85
48	C <sub>6</sub> H <sub>5</sub>	OC <sub>2</sub> H <sub>5</sub>	4'-CH <sub>3</sub>	78	130	C <sub>34</sub> H <sub>35</sub> N <sub>3</sub> O <sub>4</sub>	7.39	7.65
49	C <sub>6</sub> H <sub>5</sub>	OC <sub>2</sub> H <sub>5</sub>	4'-OCH <sub>3</sub>	80	170	C <sub>34</sub> H <sub>35</sub> N <sub>3</sub> O <sub>5</sub>	7.28	7.43
50	C <sub>6</sub> H <sub>5</sub>	OC <sub>2</sub> H <sub>5</sub>	4'-Cl	79	220	C <sub>34</sub> H <sub>32</sub> N <sub>3</sub> O <sub>4</sub>	7.20	7.37

\*All compounds gave satisfactorily C, H analysis and recrystallized from ethanol.

## **PART IV**

### **SECTION – B**

*Synthesis of 1,3-Bis-(Substituted  
dihydropyridino methyl)-Benzimidazolin-2-  
thiones*



## INTRODUCTION

The synthesis of several types of benzimidazole compounds including their varied biological and pharmacological activities have been reported in the recent years. The benzimidazole derivatives exhibit a wide spectrum of biological activities such as antibacterial<sup>20</sup>, insecticidal<sup>21</sup>, Fungicidal<sup>22</sup>, anticonvulsant<sup>23</sup>, and antimicrobial<sup>24</sup>. While substituted dihydropyridines are well known for its b-adrenergic blockers<sup>25</sup> and calcium channel blockers<sup>26</sup> are the two important classes of drug clinically used in the treatment of hypertension<sup>29</sup> and some other cardiac disorders. Though the use of b-blocker has been dominating the scene, the emergence of nifedipine is leading to supplementary to the calcium channel blocking drugs. Calcium channel blockers are increasingly becoming the drug of primary line of treatment supported by b-blockers, though sometimes adhesive b-blockers alone are being used as a combined therapy, they are useful in the treatment of consumption<sup>27</sup>. Due to these wide spectrum of biological activity prompted to synthesize 1,3- Bis-(N-substituted dihydropyridino- methyl)-benzimidazolin-2- thiones<sup>30</sup> by the reaction of benzimidazolin-2-thione with paraformaldehyde and various dihydropyridines by Mannich reaction with hope to get enhanced biological activity.

## PRESENT WORK

The Synthesis of 1,3-Bis-(N-Substituted dihydropyridino methyl)- Benzimidazolin-2-thiones has been carried out in the present work. Benzimidazolin-2-thiones on Mannich reaction with paraformaldehyde and traces of Conc. HCl and with appropriate dihydropyridine gave title compounds. This method gives better yields, Unambiguous product and the reaction conditions are moderate. The starting materials can be easily prepared.

### GENERAL METHOD FOR SYNTHESIS OF 1,3-BIS-(N-SUBSTITUTED DIHYDROPYRIDINO METHYL)- BENZIMIDAZOLIN-2-THIONES : (Fig. IVB<sub>1</sub>)

To synthesise the title compounds following starting materials have been used.

1. Benzimidazolin-2-thiones<sup>28</sup>
2. Substituted dihydropyridines

Benzimidazolin-2-thiones (0.01 mol) in methanol (20 ml) was stirred with paraformaldehyde (0.03 mol) for about 30 min. and substituted dihydropyridines (0.02 mol) were added with traces of conc. HCl and then refluxed on a water bath for one hr. The reaction mixture were cooled and poured on crushed ice and neutralized by 10 % NaHCO<sub>3</sub>. the separated solid was filtered, washed with cold water, dried and crystallized from the aqueous alcohol to give the title compounds (Fig- IVB<sub>1</sub>). The purity of the product was checked by TLC. The structure of the compounds were confirmed by IR, NMR and elemental analysis. The M. Pts., yields, elemental analysis and crystallization solvents of these compounds have been recorded in Table 4.2.

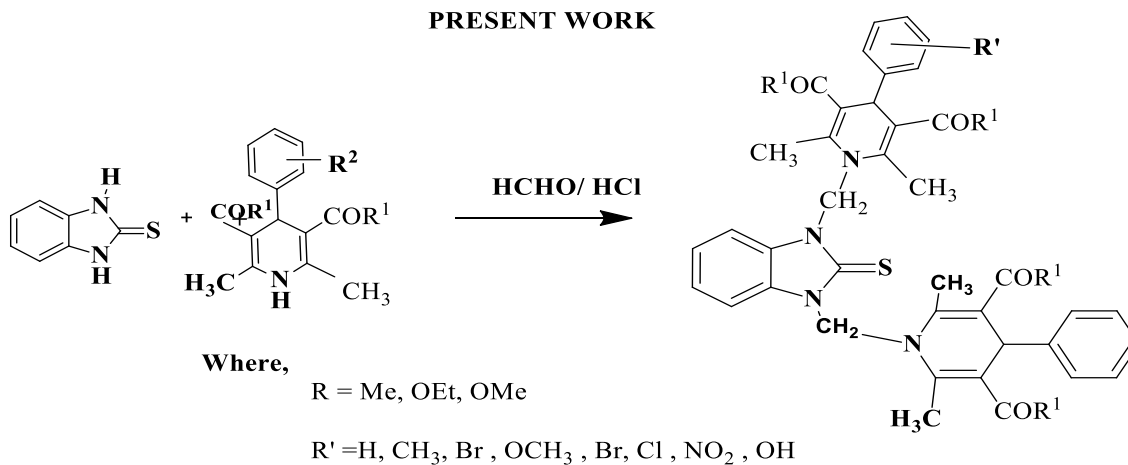


Fig.IV - B<sub>1</sub>

### DISCUSSION OF IR SPECTRA :-

The IR spectra of the representative compounds of this series were scanned on Perkin-Elmer IR-1420 Spectrophotometer in nujol mulls. All these compounds showed absorption bands in the region of 1670-1705 cm<sup>-1</sup> which were attributed to >C=O stretching of pyridyl carbonyl in acetate. The presence of bands at 1590-1610 cm<sup>-1</sup> are due to C=C stretching. The bands at 1210-1225 cm<sup>-1</sup> due to C-N stretching. The band at 1270-1300 cm<sup>-1</sup> attributed to C-N stretching. The spectrum No. 15 represents the spectrum of 1,3-Bis-(N-(1',4'- dihydro-[4'-(4''-chloro-phenyl)-2',6'-dimethyl - 3',5'-diacetyl])-pyridino methyl)- benzimidazoline-2-thione.

### DISCUSSION OF PMR SPECTRA

The PMR spectra of few the representative compounds were scanned on FT-BOA Spectrometer using TMS as internal standard and CDCl<sub>3</sub> as solvent. The chemical shifts measured in δ ppm scale. The given spectrum No. 16 represents a spectrum of 2-methyl-1-[1',4'- dihydro-3',5'-diacetyl -2',6'-dimethyl)-4'-(tolyl)-pyridino methyl)-benzimidazoles

(compound No. 16) displays following PMR signals.

$\delta$  1.90–2.25 (s, 6H, –XH<sub>3</sub>),  $\delta$  3.20–3.62 (s, 6H, COOCH<sub>3</sub>),  $\delta$  3.70–3.80, 6H, Ar-CH<sub>3</sub> ),  
4.10-4.90 (s, 4H, N-CH<sub>2</sub>-N),  $\delta$  6.50-7.20 (12, Ar- protons).

## **EXPERIMENTAL :**

### **EXPERIMENT NO. 1**

#### **PREPARATION OF 1,3-BIS-[N-1',4'- DIHYDRO (4'-CHLORO PHENYL)= 3',5'-DIACETYL -2',6'-DIMETHYL PYRIDINO METHYL )- BENZIMIDAZOLIN-2- THONES (07) (TABLE 4.2) :-**

Benzimidazoli-2-thione (1.5g; 0.01 mol) in methanol (20 ml) was stirred with paraformaldehyde (0.9 g ; 0.03 mol ) for 30 min and 1,4-dihydro-4-(4'-chlorophenyl)-3,5-diacetyl 2,6- dimethyl pyridine (5.99 g ; 0.02 mol ) were refluxed for one hr on a water bath. The reaction mixture were cooled and poured on crushed ice and neutralized by 10 % aq. NaHCO<sub>3</sub>, the separated solid was filtered, washed with cold water, dried and crystallized from ethanol to gives title compound M. P. 180 0C ; yield 74 % .

The formation of the compound were confirmed by TLC, IR, NMR and Elemental analysis. Similarly all other compounds of this series were synthesized by the following the same procedure.

Table 4.2

CHARACTERISATION DATA OF 1,3-BIS-[N-1',4'- DIHYDRO (4'-CHLORO PHENYL)=  
3',5'=DIACETYL -2',6'-DIMETHYL PYRIDINO METHYL )- BENZIMIDAZOLIN-2-  
THONES (Fig. IV B<sub>1</sub>)

Comp. No.	R	R <sup>1</sup>	YIELD %	M.P °C	MOL. FORMULA	% OF N found calcd.	
1	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	76	158	C <sub>43</sub> H <sub>42</sub> N <sub>4</sub> O <sub>4</sub> S	7.89	7.70
2	3-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	74	155	C <sub>45</sub> H <sub>46</sub> N <sub>4</sub> O <sub>4</sub> S	7.59	7.41
3	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	68	162	C <sub>45</sub> H <sub>46</sub> N <sub>4</sub> O <sub>4</sub> S	7.59	7.42
4	3-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	80	135	C <sub>45</sub> H <sub>46</sub> N <sub>4</sub> O <sub>5</sub> S	7.42	7.25
5	4-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	72	139	C <sub>45</sub> H <sub>46</sub> N <sub>4</sub> O <sub>5</sub> S	7.42	7.25
6	2-ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	75	169	C <sub>43</sub> H <sub>41</sub> N <sub>4</sub> O <sub>4</sub> ClS	7.52	7.34
7	4-ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	74	188	C <sub>43</sub> H <sub>41</sub> N <sub>4</sub> O <sub>4</sub> ClS	7.52	7.40
8	4-BrC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	68	160	C <sub>43</sub> H <sub>41</sub> N <sub>4</sub> O <sub>4</sub> BrS	7.10	7.04
9	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	70	178	C <sub>43</sub> H <sub>46</sub> N <sub>6</sub> O <sub>6</sub> S	10.92	10.62
10	C <sub>6</sub> H <sub>5</sub>	OCH <sub>3</sub>	74	149	C <sub>43</sub> H <sub>46</sub> N <sub>4</sub> O <sub>5</sub> S	7.24	7.15
11	3-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	OCH <sub>3</sub>	81	121	C <sub>45</sub> H <sub>46</sub> N <sub>4</sub> O <sub>6</sub> S	6.98	6.67
12	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	OCH <sub>3</sub>	95	126	C <sub>45</sub> H <sub>46</sub> N <sub>4</sub> O <sub>6</sub> S	6.98	6.65

Comp. No.	R	R <sup>1</sup>	YIELD %	M.P °C	MOL. FORMULA	% OF N found	% OF N calcd.
13	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	OCH <sub>3</sub>	80	130	C <sub>45</sub> H <sub>46</sub> N <sub>4</sub> O <sub>8</sub> S	6.98	6.69
14	3-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	OCH <sub>3</sub>	79	176	C <sub>45</sub> H <sub>46</sub> N <sub>4</sub> O <sub>10</sub> S	6.71	6.55
15	4-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	OCH <sub>3</sub>	72	165	C <sub>45</sub> H <sub>46</sub> N <sub>4</sub> O <sub>10</sub> S	6.71	6.49
16	2-ClC <sub>6</sub> H <sub>4</sub>	OCH <sub>3</sub>	77	210	C <sub>43</sub> H <sub>41</sub> N <sub>4</sub> O <sub>8</sub> ClS	6.93	6.74
17	3-ClC <sub>6</sub> H <sub>4</sub>	OCH <sub>3</sub>	78	140	C <sub>43</sub> H <sub>41</sub> N <sub>4</sub> O <sub>8</sub> ClS	6.93	6.60
18	4-ClC <sub>6</sub> H <sub>4</sub>	OCH <sub>3</sub>	69	168	C <sub>43</sub> H <sub>41</sub> N <sub>4</sub> O <sub>8</sub> ClS	6.93	6.42
19	2-BrC <sub>6</sub> H <sub>4</sub>	OCH <sub>3</sub>	66	175	C <sub>43</sub> H <sub>41</sub> N <sub>4</sub> O <sub>8</sub> BrS	9.71	9.52
20	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	OCH <sub>3</sub>	68	186	C <sub>43</sub> H <sub>41</sub> N <sub>6</sub> O <sub>12</sub> S	9.71	9.52
21	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	OCH <sub>3</sub>	71	154	C <sub>43</sub> H <sub>41</sub> N <sub>6</sub> O <sub>12</sub> S	9.71	9.55
22	C <sub>6</sub> H <sub>5</sub>	OCH <sub>3</sub>	75	171	C <sub>47</sub> H <sub>48</sub> N <sub>4</sub> O <sub>8</sub> S	6.76	6.62
23	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	OC <sub>2</sub> H <sub>5</sub>	76	158	C <sub>49</sub> H <sub>54</sub> N <sub>4</sub> O <sub>8</sub> S	6.52	6.50
24	4-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	OC <sub>2</sub> H <sub>5</sub>	72	195	C <sub>49</sub> H <sub>54</sub> N <sub>4</sub> O <sub>10</sub> S	6.52	6.48
25	3-ClC <sub>6</sub> H <sub>4</sub>	OC <sub>2</sub> H <sub>5</sub>	74	205	C <sub>47</sub> H <sub>47</sub> N <sub>4</sub> O <sub>8</sub> S	6.49	6.37
26	4-ClC <sub>6</sub> H <sub>4</sub>	OC <sub>2</sub> H <sub>5</sub>	64	215	C <sub>47</sub> H <sub>47</sub> N <sub>4</sub> O <sub>12</sub> S	6.49	6.30
27	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	OC <sub>2</sub> H <sub>5</sub>	60	132	C <sub>49</sub> H <sub>47</sub> N <sub>6</sub> O <sub>12</sub> S	9.14	9.04
28	4-BrC <sub>6</sub> H <sub>4</sub>	OC <sub>2</sub> H <sub>5</sub>	65	152	C <sub>49</sub> H <sub>54</sub> N <sub>4</sub> O <sub>8</sub> BrS	6.17	6.02

All compounds crystallized from aq. Alcohol and gives C & H analysis satisfactory.

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## **PART – V**

# **BIOLOGICAL ACTIVITY**

## **BIOLOGICAL SCREENING**

The biological activity may be measured in different ways depending on the level at which the investigation is conducted, when the critical site and mechanism of action of chemicals are known. Biological activity can be measured directly in terms of the degree of inhibition or enhancement of an enzyme system as measured in Vitro. More usually, however, biological activity is measured in an indirect manner through in vivo, observations of the end results of chain of events by the interaction of chemicals with some unknown biochemical component.

## **MICROBIAL SCREENING**

The wide spectrum of biological activity of S- Triazines and Benzimidazole derivatives have been observed in the literature survey. So, the attempt was made to screen the synthesized compounds for its antibacterial, antifungal and antiviral activities. Some of the representative compounds synthesized in the present work were screened for antimicrobial activities against gram (+ve) and gram (-ve) bacteria and on some selected fungi. While some Pyrazolyl-S-triazines were tested against various viruses.

The antimicrobial activity of some compounds were tested using Cup-plate Method <sup>1,2</sup> i.e. Disc –diffusion method <sup>3</sup> at 500 ppm and 250 ppm concentrations using 5mm size filter paper disc at similar conditions standard drug used were Carbendazim, Tetracycline, Streptomycine and Amphotericin.

The Following micro-organisms were used,

- 1) Staphylococcus Aureus gr (+ve).

- 2) Proteus Vulgaris gr (-ve)
- 3) Sarcina Leutea gr (-ve)
- 4) Bacillus Megaterium gr (-ve)
- 5) Alternaria Brassicicola gr (+ve)
- 6) Pseudomonas Florescence gr (-ve)
- 7) Fusarium Udam
- 8) E. Coli gr (-ve)
- 9) Aspergillus Niger

It is essential to know the few important points about some of the micro-organisms were used in the present work.

Staphylococcus Aureus are gram (+ve) bacteria. They are Cocci. The organs of human like throat, mouth and intestine are the harbors to these bacteria and so they produces infections to these organs of human. There are some reports on staphylococci in frozen vegetable like asparagus, spinach, peas, beans and corn. They are enter toxic <sup>4</sup>.

Lactobacillus are very important bacteria in the milk industries for the production of ghee, curd, cheese, butter etc., They ferments the milk while some species are harmful to vegetables <sup>5</sup>. E. Coli are gram (-ve) bacteria, it is used as index of water pollution and are important experimental material in biotechnology, since it requires only 20 minutes to complete its life cycle and simple media for its growth.

It is a normal intestinal flora of human body, but some times it acts as opportunistic when defense power of body get impaired. They contaminates herbs and spress products like chilli, paper black <sup>6</sup>.

Where as , all living organisms are surrounded by fungi. Numerous fungi have their biological habitat in the soil. Some on trees , in grass and in woodlands. Others in habit at the fur

on our pets while still others on our skin and in our hair and beards. Some species, for example, *Agaricus bisporus* are excellent to eat with bacon and eggs. Some of fungi produces diseases. Fungal diseases of humans are termed mycoses and in recent years there has been an increase in the all types of mycoses. Cutaneous and sub-cutaneous infections spread as a result of community living. Foot infections in coal mines for instance, are a major problem of occupational health. The most common pathogens identified are candid species, because of the many similarities between human cells and fungal cells both are eukaryotic and possess similar highly evolved metabolic processes.

The fungus *Aspergillus Niger*, which known as plant pathogens. It is soil born and also occurs on various types of substrates, including plants and animals. It causes diseases known as collar rot in ground nut. This organisms also helps in the soil formation and solvalisation of various elements.

*Alternaria Brassicicola* is deteuromycities fungus. It produces the disease of vegetable and crop plants like cereals. The potatos infected by this fungi and the disease is called as early blite. Many leaf spots and blites are produced by this serious fungi. Some alternaria species are newly found on grapes producing blite of leaf. The wilt diseases of pulses, banana and other co plants comes under fusarium udam and its elated species. The wilt of pigeon pea and gram is caused by fusarium.

### **EXPERIMENTAL :**

The czapke medium was used as a basal solution for the growth of microbials and was prepared by dissolving sucrose (30g) , sodium nitrate (3 g), potassium hydrogen phosphate (1g) Magnesium sulphate (0.01g) and Agar- Agar powder (20g ) in one liter of distilled water in clean conical flask. The flask was stoppered with non-absorbent cotton and were sterlised in autoclave at 15 lb/sq. inch pressure for about half an hour. The pure well developed culture of

fungi and bacteria were then well spread in separate dishes, then filter paper disc dipped in test solution and standard drug solution of same concentration was inoculated. The inoculation was done in presterilised (UV) chamber and under totally aseptic conditions.

The plates were incubated at 25 (+ or -) 10c for 2-3 days. The results i.e. zones of inhibition measured in mm. All the experiments were carried out in twice and average results were noted.

Table 5.1

ANTIMICROBIAL ACTIVITY OF THE 2- (METHYLAMINO)-4-(ETHOXYANILINO)-6-(SUBSTITUTED DIHYDROPYRIDINO)-S-TRIAZINES (FIG.IB<sub>1</sub>) :-

Comp. No.	Alternaria Brassicicola	Fusarium udam	Staphylococcus Aureus	E. Coli
1	+7	+6	+8	-
3	+8	+7	+8	-
7	+7	+6	+8	+9
8	+12	+10	-	+7
9	+13	+11	+6	-
11	+13	+10	+7	-
12	+12	+11	+8	+9
13	+14	+13	+15	+13
20	+8	-	+7	+9
25	+15	+13	+12	+13
27	+11	+9	+9	+8
30	+14	+10	+11	+12
32	+11	+10	+9	+11
40	+8	+9	+9	+6
43	+12	+8	+10	-
45	+11	+8	+10	+9
47	+13	+10	+9	+13
Standard	Carbendazim +13	+14	Streptomycin +12	+13

+mm → Antagonistic zones of inhibition in mm.

-mm → Zone of inhibition nil.

**Table 5.2****BIOLOGICAL ACTIVITY DATA OF THE 2,4-BIS- (SUBSTITUTED)-6-(SUBSTITUTED COUMARINYL-6',7'-OXY)-S-TRIAZINES (FIG.IC5) :-**

Comp. No.	Staphylococcus Aureus	Pseudomonas Florescence
3	+15	+9
4	+35	+15
5	+37	+17
8	+18	+17
13	+14	+10
15	+39	+18
17	+11	+7
24	+36	+18
25	+42	+26
26	+40	+20
32	+16	+8
33	+34	+12
34	+38	+14
36	+33	+15
38	+18	+7
40	+20	+8
Standard (Streptomycin)	+40	+30

+ mm → Antagonistic zones of inhibition in mm.

**Table 5.3****ANTIMICROBIAL ACTIVITY DATA OF THE 1,3-BIS- (5-ARYL / HETERYL  
SUBSTITUTED-4,5-DIHYDROPIRAZOL-3YL-BENZIMIDAZOLIN-2-THIONES  
(FIG.III B<sub>10</sub>) :-**

Comp. No.	Alternaria Brassicicola	Fusarium udam	Salmonella typhi (gr +ve)	E. Coli (gr -ve)
1	+6	+7	-	+6
3	+8	+6	+8	+7
4	+10	+9	+9	+11
7	+7	+6	+7	-
9	+6	-	+9	-
11	+14	+12	+11	+12
13	+10	+9	+8	+11
15	+9	+8	+7	+10
Standard	Carbendazim		Tetracyclin	
	+16	+14	+11	+13

+mm → Antagonistic zones of inhibition in mm.

-mm → Zone of inhibition nil.



**Table 5.4****ANTIMICROBIAL ACTIVITY DATA OF THE 1,3-BIS- (5-ARYL / HETERYL  
SUBSTITUTED-4,5-DIHYDROISOXAZOL-3-YL-BENZIMIDAZOLIN-2-THIONES  
(FIG.III C<sub>10</sub>) :-**

Comp. No.	Proteus Vulgaris	Sarcina Leutea (gr -ve)	E. Coli (gr -ve)	Pseudomonas Florescence
1	+7	+6	-	+7
3	+9	+8	+7	+8
4	+11	+8	+10	+9
6	+6	+7	+7	-
7	-	+6	+7	-
9	+6	-	+7	+6
11	+13	+10	+10	+9
12	+16	+12	+13	+12
13	+10	+9	+10	+8
15	+11	+11	+9	+10
16	+10	+8	+8	+9
Standard	Carbendazim +16	+14	+12	Tetracyclin +13

+mm → Antagonistic zones of inhibition in mm.

-mm → Zone of inhibition nil.

**Table 5.5****BIOLOGICAL ACTIVITY DATA OF 2-ALKYL-1-(1'- DIHYDROPYRIDYL METHYL-  
BENZIMIDAZOLES (FIG.IV A<sub>2</sub>) :-**

Comp. No.	Alternaria Brassicicola	Proteus Vulgaris (gr +ve)	Bacillus Megaterium(gr -ve)
7	+18	+10	+9
8	+19	+12	-
9	+17	+9	+10
13	+11	+10	+9
14	+15	+14	+12
15	+16	+11	+10
20	+22	+14	+13
21	+20	+15	-
22	+18	+16	+14
34	+23	+17	+11
35	+20	+12	+10
38	+19	+9	-
43	+8	+7	+6
45	+21	+13	+11
46	+23	+16	+13
Standard	Carbendazim	Amphicillin	
	+26	+18	+20

+mm → Antagonistic zones of inhibition in mm.

-mm → Zone of inhibition nil.

**Table 5.6**  
**BIOLOGICAL ACTIVITY DATA OF 1,3-BIS-(NSUBSTITUTED**  
**DIHYDROPYRIDINO- METHYL-BENZIMIDAZOLIN- THIONES (FIG.IV B<sub>1</sub>) :-**

Comp. No.	Bacillus subtilis (gr +ve)	Sarcina Lutea (gr +ve)	Pseudomonas araginose(gr +ve)
6	++	++	++
7	+++	+++	++
9	+++	+++	++++
14	++	++	++
15	+	++	++
16	++++	+++	+++
17	++++	++++	++++
18	+++	+++	++
20	++++	++++	++++
21	++++	++++	++++
24	++	++	++
25	+++	+++	+++
26	++++	++++	++++
27	++++	++++	++++
Standard			
Amphicillin	++++	++++	++++

Key for interpretation : +mm → Antagonistic zones of inhibition in mm.

++++ → 11-14 mm Highly active .      +++ → 8-11 mm Moderately active

++ → 5-8 mm Slightly active      + → 5 mm Inactive

## **RESULT AND DISCUSSION**

From the activity data it was observed that the most of the compounds showed promising activity and other are inactive. The compounds are highly active at high concentration and less active at low concentration.

It is reveals that the Table 5.1 that the compound Nos. 8,9, 13,25,30, and 47 were showed good activity against bacteria. It was also established that those S-triazines had –Cl and NO<sub>2</sub> groups substituted in its dihydropyridine moiety were showing good antimicrobial activity. While groups such as Br, OCH<sub>3</sub>, CH<sub>3</sub> and H were showing moderate activity against both fungi and bacteria. The most active compound was found to be compound nos. 13 and 45.

The activity data of 2,4-Bis-(substituted aniline)-6-(substituted coumarinyloxy)-S-triazines (Table 5.2) reveals that the compound Nos. 4, 5, 15, 24, 25, 33, 34 and 36 were showing good activity against staphylococcus Aureus (gram +ve) and Pseudomonas Florescence, while remaining compounds shows moderate activity. These observations leads to the conclusion that introduction of methoxy , chloro, nitro groups in aniline moiety shows good activity whereas the groups such as H, CH<sub>3</sub> showing mild activity. The most active compound of the series found to be 25 and 26.

From the antimicrobial activity data (Table 5.3) , the compound nos. 4, 11 , 12 and 13 showed good activity, while other compounds showed less activity. Whereas the activyt of Isoxazolyl-benzimidazolin-2-thiones (Table 5.4) , were tested against proteus vulgarius, Sarcina Leutea , E. Coli and Pseudomonas Florescence. The compound Nos. 4,11,12 and 13 showed good activity while other shows moderate activity.

The biological activity data of 2-alkyl-1-(N-substituted dihydropyridinyl methyl )-benzimidazoles were tested against Alternaria Brassicicola, Proteus Vulgarius and Bacillus Megaterium (Table 5.5). The high activity observed in compound nos. 20, 34 and 46 while

remaining compounds of the series were shows good activity and some of them were moderately active.

From the activity data of 1,3-Bis- N-substituted dihydroxyridino methyl)-benzimidazolin-2-thiones (Table 5.6), it is observed that compound nos. 7, 9, 16, 17,18, 20, 26 and 27 were showed good activity against bacteria while other compounds were moderately active. It was also concluded that those dihydroxyridine moiety having –Cl and NO<sub>2</sub> groups in its aryl moiety enhanced the activity while other groups such as H, CH<sub>3</sub>, OCH<sub>3</sub> and Br were showing less activity . The most active compounds of the series were found to be compound nos. 9, 17, 20 , 21, 26 and 27.

The activity of pyrazolyl-s-triazines (Fig- IIB) is in process which is tested against HIV in National Institute of Virology, Pune the results are not encouraging.

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