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SYNTHESIS AND CHARACTERIZATION OF SUBSTITUTED 1,2,4-THIADIZOLES AND 1,2,4- DITHIAZOLES

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ABSTRACT

The present study is based on the various biological activities reported on 1,2,4–thiadiazoles and 1,2,4-dithiazoles by several scientists prompted the author to undertake the present work of synthesis of substituted 1,2,4–thiadiazole (86) and 1,2,4-dithiazole (87) and to evaluate them for a few selected biological activities.

KEYWORDS: 1,2,4–thiadiazole, 1,2,4-dithiazole, Heterocyclic compounds, anticonvulsants, antimicrobial angents.

INTRODUCTION

The synthetic drugs are obtained by simple modifications of the structures of naturally occurring drugs. By changes in structure of the natural drugs and following the leads, it has been possible to prepare many new analgesics, local anaesthetics, sympathomimetics, antispasmodics etc. Drugs like barbiturates, sulphonamides, anti-histaminics, certain antihypertensives, many diuretics, and antimalarials, have been of pure synthetic origin. Heterocyclic compounds are those which have a cyclic structure with two, or more, different kinds of atom in the ring.

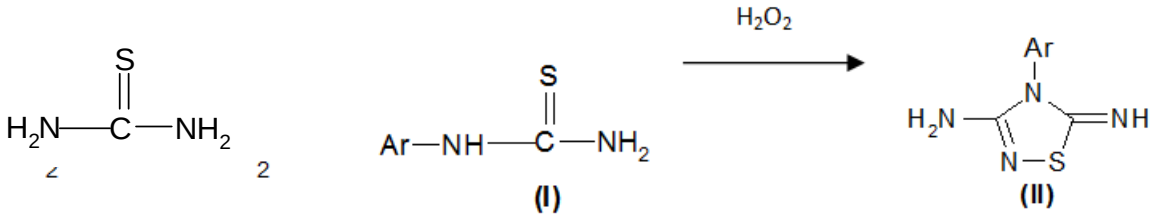
Synthesis And Characterization: Syntheses of substituted 1,2,4-thiadiazoles were accomplished through the following steps.

Step–1: Synthesis of Aryl thiourea (I)

Aromatic/Hetero aromatic amines were reacted with ammonium thiocyanate in the presence of concentrated hydrochloric acid to give arythiourea.[1]

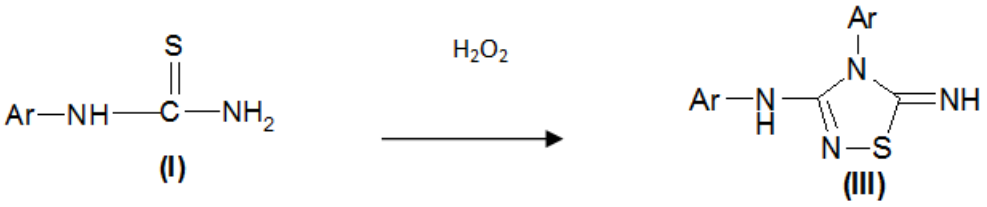
Step–2: Synthesis of 3-Amino-4-aryl-5-imino-Δ^2-1,2,4–thiadiazoline (II)

Compound **I** were oxidatively cyclised into 3-amino-4–aryl-5-imino-Δ^2-1,2,4–thiadiazoline by hydrogen peroxide in presence of excess thiourea.[2-4]



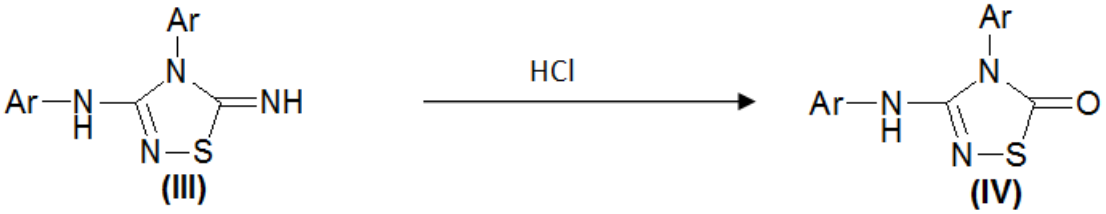
Step–3: Synthesis of 3-Aryl amino-4-aryl-5-imino--Δ^2-1,2,4–thiadiazoline (III)

Compounds **I** were oxidatively cyclised into 3-aryl amino-4-aryl-5-imino-Δ^2-1,2,4–thiadiazoline.[5]



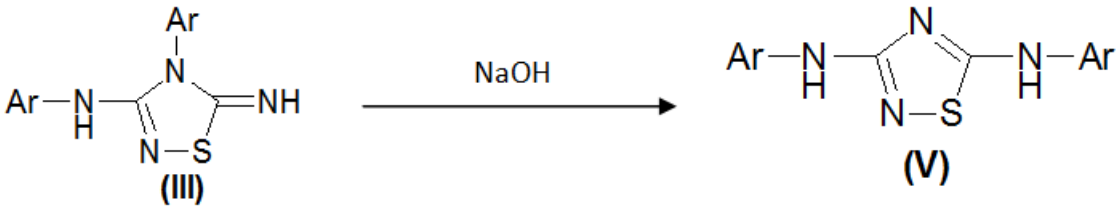
Step–4: Synthesis of 3-Aryl amino-4-aryl-5-oxo-Δ^2-1,2,4– thiadiazoline (IV)

Compounds **III** on refluxing with concentrated hydrochloric acid gave 3-aryl amino-4-aryl-5-oxo-Δ^2-1,2,4–thiadiazoline.[6]



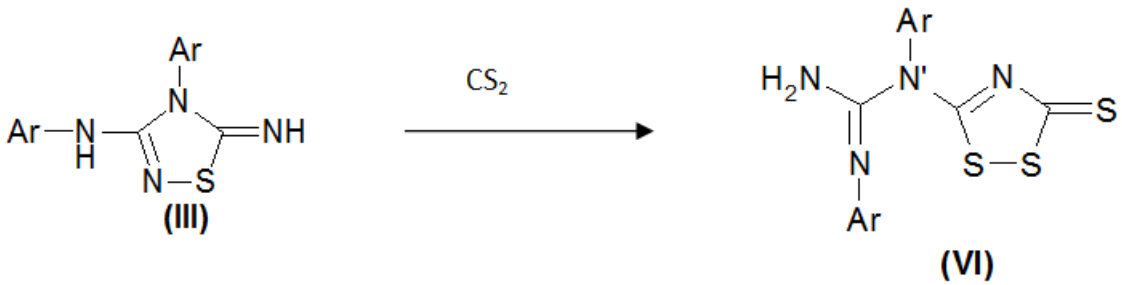
Step–5: Synthesis of 3,5–Diaryl amino-1,2,4–thiadiazole (V)

Compounds **III** isomerised to 3, 5-diarylamino–1, 2, 4 thiadiazole in presence of sodium hydroxide solution.[7]



Step–6: Synthesis of 3-Thio-5-(N'-aryl-N'-aryl guanyl)–1,2,4–dithiazole (VI)

Compounds **III** on reacting with carbon disulfide gave the corresponding 3-thio-5-(N'-aryl-N′-aryl guanyl)-1, 2,4–dithiazole.[8]

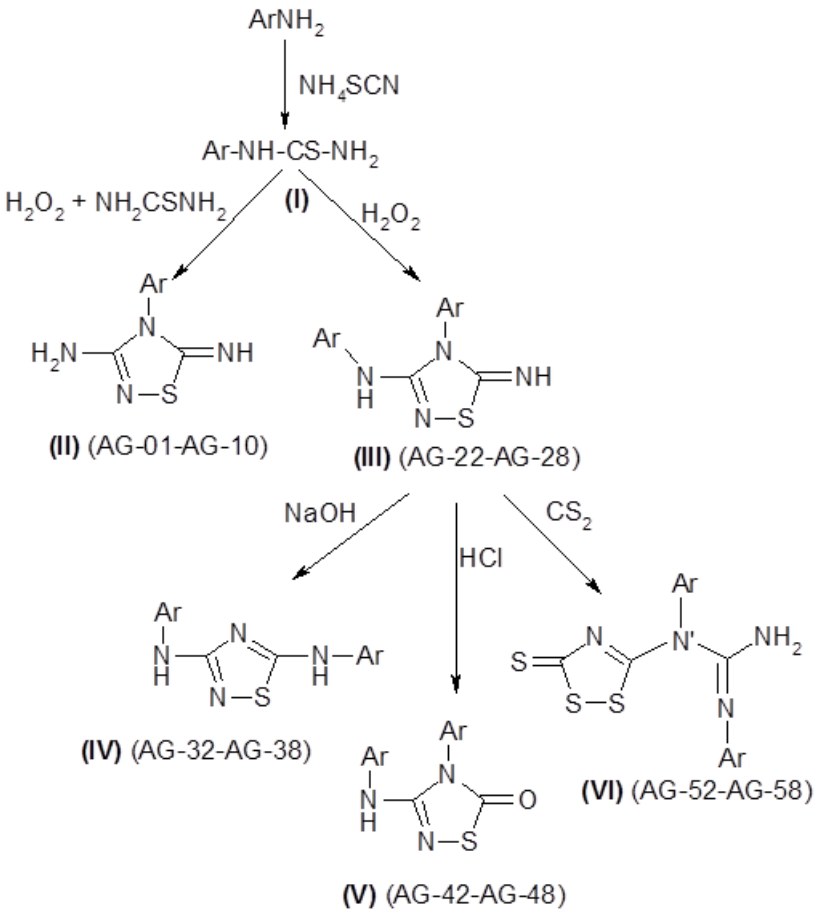


Phenobarbitone Induced Hypnosis Potentiation Test

The study for Phenobarbitone induced hypnosis was carried out for only those compounds which gave anticonvulsant effect at a dose level of 100 mg/kg. Most of the compounds were found to be devoid of hypnosis in Phenobarbitone induced hypnosis potentiation test at the dose level of 30 mg/kg. Compounds AG-04($p<0.05$), AG-42($p<0.05$), AG-03($p<0.01$), AG-43($p<0.01$) and AG-23($p<0.001$), AG-33($p<0.001$), AG-48($p<0.001$) have increased the sleeping time in rats significantly and thus showing sedation properties at 100 mg/kg i.p. dose level (Table-4.16). Significance of sleeping time is that the drug may be having antipsychotic potential property.

Prompted by these reports the present author undertook the present investigation on 1,2,4-thiadiazoles. As 1,2,4-thiadiazole on simple reaction gives 1,2,4-dithiazoles and very less work has been reported related to biological activities of 1,2,4-dithiazoles so the present work includes work on 1,2,4-dithiazoles also.

The syntheses of the title compounds consist of the following schemes.



Thirty-eight compounds were synthesised a list of which is given below on Table No. 1 to.4.

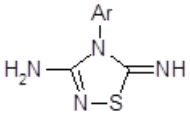
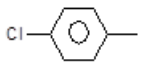
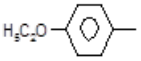
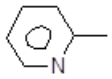
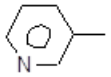
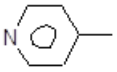
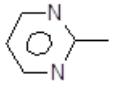
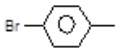
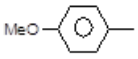


Table 1: List of Synthesized compounds.

Compound No.	Chemical Name	Ar
AG-01	3-Amino-4-(4'-chlorophenyl)-5-imino-Δ2-1,2,4-thiadiazoline	
AG-02	3-Amino-4-(1'-naphthyl)-5-imino-Δ2-1,2,4-thiadiazoline	
AG-03	3-Amino-4-(4'-ethoxyphenyl)-5-imino-Δ2-1,2,4-thiadiazoline	
AG-04	3-Amino-4-(4'-fluorophenyl)-5-imino-Δ2-1,2,4-thiadiazoline	

AG-05	3-Amino-4-(2'-pyridyl)-5-imino-Δ2-1,2,4-thiadiazoline	
AG-06	3-Amino-4-(3'-pyridyl)-5-imino-Δ2-1,2,4-thiadiazoline	
AG-07	3-Amino-4-(4'-pyridyl)-5-imino-Δ2-1,2,4-thiadiazoline	
AG-08	3-Amino-4-(2'-pyrimidyl)-5-imino-Δ2-1,2,4-thiadiazoline	
AG-09	3-Amino-4-(4'-bromophenyl)-5-imino-Δ2-1,2,4-thiadiazoline	
AG-10	3-Amino-4-(4'-methoxyphynyl)-5-imino-Δ2-1,2,4-thiadiazoline	

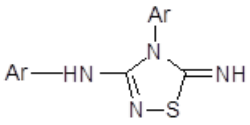
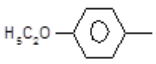
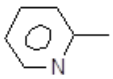
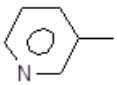
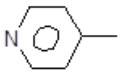
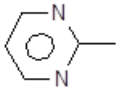


Table 2: List of Synthesized compounds.

Compound No.	Chemical Name	Ar
AG-22	3-(1'-Napthylamino)-4-(1'-napthyl)-5-imino-Δ2-1,2,4-thiadiazoline	
AG-23	3-(4'-Ethoxyphenylamino)-4-(4'-ethoxyphenyl)-5-imino-Δ2-1,2,4-thiadiazoline	
AG-24	3-(4'-Fluorophenylamino)-4-(4'-fluorophenyl)-5-imino-Δ2-1,2,4-thiadiazoline	
AG-25	3-(2'-Pyridylamino)-4-(2'-pyridyl)-5-imino-Δ2-1,2,4-thiadiazoline	
AG-26	3-(3'-Pyridylamino)-4-(3'-pyridyl)-5-imino-Δ2-1,2,4-thiadiazoline	
AG-27	3-(4'-Pyridylamino)-4-(4'-pyridyl)-5-imino-Δ2-1,2,4-thiadiazoline	
AG-28	3-(2'-Pyrimidylamino) -4-(2'-pyrimidyl)-5-imino -Δ2-1,2,4-thiadiazoline	

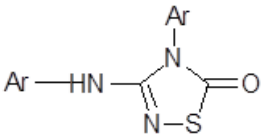
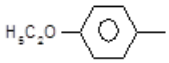
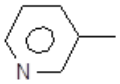
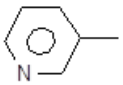
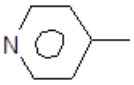
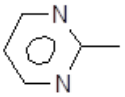


Table 3: List of Synthesized compounds.

Compound No.	Chemical Name	Ar
AG-32	3-(1'-Napthylamino)-4-(1'-napthyl)-5 -oxo-Δ2-1,2,4-thiadiazoline	
AG-33	3-(4'-Ethoxyphenylamino)-4-(4'-ethoxyphenyl)-5-oxo-Δ2-1,2,4-thiadiazoline	
AG-34	3-(4'-Fluorophenylamino)-4-(4'-fluorophenyl)-5-oxo-Δ2-1,2,4-thiadiazoline	
AG-35	3-(2'-Pyridylamino)-4-(2'-pyridyl)-5-oxo-Δ2-1,2,4-thiadiazoline	
AG-36	3-(3'-Pyridylamino)-4-(3'-pyridyl)-5-oxo-Δ2-1,2,4-thiadiazoline	
AG-37	3-(4'-Pyridylamino)-4-(4'-pyridyl)-5-oxo-Δ2-1,2,4-thiadiazoline	
AG-38	3-(2'-Pyrimidylamino)-4-(2'-pyrimidyl)-5-oxo -Δ2-1,2,4-thiadiazoline	

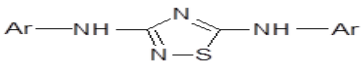
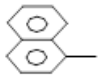
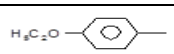
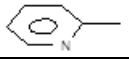
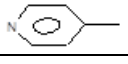
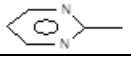


Table 4: List of Synthesized compounds.

Compound No.	Chemical Name	Ar
AG-42	3,5-Di-(1'-napthylanimo)-1,2,4-thiadiazole	
AG-43	3,5-Di-(4'-ethoxyphenylamino)-1,2,4-thiadiazole	
AG-44	3,5-Di-(4'-fluorophenylamino)-1,2,4-thiadiazole	
AG-45	3,5-Di-(2'-pyridylamino)-1,2,4-thiadiazole	
AG-46	3,5-Di-(3'-pyridylamino)-1,2,4-thiadiazole	
AG-47	3,5-Di-(4'-pyridylamino)-1,2,4-thiadiazole	
AG-48	3,5-Di-(2'-pyrimidylamino)-1,2,4-thiadiazole	

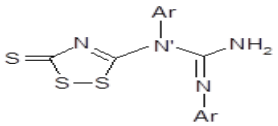
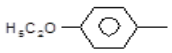
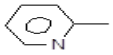
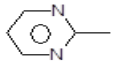


Table 5: List of Synthesized compounds.

Compound No.	Chemical Name	Ar
AG-52	3-Thio-5-[N'-(1'-napthyl)-N'-(1'-napthylguanyl)]-1,2,4-dithiazole	
AG-53	3-Thio-5-[N'-(4'-ethoxyphenyl)-N'-(4'-ethoxyphenylguanyl)]-1,2,4-dithiazole	
AG-54	3-Thio-5-[N'-(4'-fluorophenyl)-N'-(4'-fluorophenylguanyl)]-1,2,4-dithiazole	
AG-55	3-Thio-5-[N'-(2'-pyridyl)-N'-(2'-pyridylguanyl)]-1,2,4-dithiazole	
AG-56	3-Thio-5-[N'-(3'-pyridyl)-N'-(3'-3'-pyridylguanyl)]-1,2,4-dithiazole	
AG-57	3-Thio-5-[N'-(4'-pyridyl)-N'-(4'-pyridylguanyl)] -1,2,4-dithiazole	
AG-58	3-Thio-5-[N'-(2'-pyrimidyl)-N'-(2'-pyrimidylguanyl)]-1,2,4-dithiazole	

Pharmacological Studies

Anticonvulsant

As the earlier workers on the nuclei stressed over the anticonvulsant activities, so the present author evaluated the synthesised compounds for anticonvulsant activities. In the present study two well known models i.e. maximal electroshock induced seizure (MES) and pentylene tetrazole induced convulsions (ScPTZ) were used. The anticonvulsant activities were compared to phenytoin and carbamazepine.

The compounds AG-01, AG-02, AG-03, AG-22, AG-23, AG-24, AG-28, AG-32, AG-33, AG-34, AG-42, AG-43, AG-44 and AG-53 showed appreciable anticonvulsant activities as compared to the standard drugs.

Analgesic Activity

The study involve the tail flick method. Those compounds which showed analgesic activities are AG-02, AG-22, AG-23, AG-24, AG-32, AG-33, AG-34, AG-37, AG-42, AG-43, AG-44, AG-45, AG-47, AG-52. AG-53, AG-54 and AG-57.

Barbiturates Hypnosis Potentiation Effect

This study was undertaken for only those compounds which gave promising anticonvulsant activities. Those compounds which showed barbiturates hypnosis potentiation effect are : AG-03, AG-04, AG-23, AG-33, AG-42, AG-43 and AG-48.

Neurotoxicity test

As an ideal anticonvulsant should be devoid of Neurotoxicity, therefore rotorod test was performed to evaluate for neurotoxicity.

Microbiological Studies

Antibacterial Activity

Following strains procured from IMTECH, Chandigarh were used.

1. Staphylococus aureus (Gram +ve)
2. Bacillus subtilis (Gram +ve)
3. Pseudomonas aeruginosa (Gram –ve)
4. Escherechia coli (Gram –ve).

Antifungal Activity

Antifungal studies were carried out using the following fungal cultures.

1. Aspergillus niger
2. Candida albicans

Most of the compounds were found to be active against antibacterial and antifungal screening but overall antifungal effect of the compounds was better than the antibacterial effect.

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