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Synthesis of some new thiadiazole derivatives and their anticonvulsant activity

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A new series of 1,3,4-thiadiazole derivatives was synthesized and the structures of these compounds were established by means of IR, ^{1}H-NMR and elemental analysis. The compounds AR-5, AR-6, AR-7, AR-8 and AR-14 were screened for anticonvulsant activity on albino mice. Most of these compounds showed promising anticonvulsant activity. Structural modification of these compounds may lead to the discovery of more potent anticonvulsant agents with lower neurotoxicity.

Keywords: - I, 3, 4-thiadiazole, Anticonvulsant activity; Maximum Electroshock Seizure (MES)

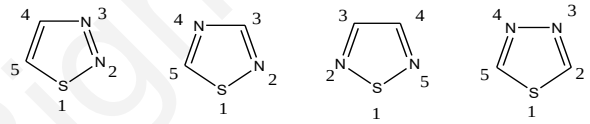
INTRODUCTION

1,3,4-thiadiazoles are associated with diverse biocidal activities [1-5]. A large number of 1,3,4-thiadiazoles have been reported as anticancer, antitubercular, anti-inflammatory, and pesticide agents. These observations prompted us to synthesize the title compounds presuming that incorporation of amine derivatives would produce new compounds with significant anticonvulsant activity.

Medicinal chemistry is offering today many complicated challenges [6]. The most difficult and sometimes the most rewarding challenge is the rational design of new therapic agents for treating human diseases. For many years the strategy for discovering new drugs consisted of taking a lead structure and developing a chemical program for finding analogue molecules which would exhibit the desired biological properties.

After several trial-and-error cycles, the medicinal chemist would select a candidate analogue for further development. The entire process is laborious, expensive and time consuming. However, the fact is that most of the drugs that are in use today have been provided by this process.

Thiadiazole is a five-membered heterocyclic compound. It contains two nitrogen atoms and one sulfur atom. The first thiadiazole was described by Fischer (1882), but the nature of the ring system was demonstrated by Freud and Kuhn (1890) [7, 8].



1,2,3-thiadiazole 1,2,4-thiadiazole 1,2,5-thiadiazole 1,3,4-thiadiazole

1,2,3-thiadiazole is an yellowish liquid at room temperature [10]. It boils at 157ºC at normal atmospheric pressure and is soluble in alcohol, ether and water [11]. It is stable in acids but decomposes in bases with evolution of nitrogen. The compound is a weak base and forms a deliquescent hydrochloride, which get decomposed by water to its components.

1,2,4-thiadiazole is a colorless, mobile liquid, boiling at 121ºC, freezing at 33ºC, possessing an odor similar to that of pyridine [12,13].

1,3,4-thiadiazole is a colorless quite stable compound melting at 42ºC and possessing no ultraviolet absorption maximum above 220 nm. Zinc and hydrochloric acid or 30 % hydrogen peroxide destroy the compound. 1,3,4-Thiadiazole is more stable towards the peroxide than the 1,2,4-isomer. Aqueous alkalis decompose the compound, however 1,3,4-thiadiazole is quite stable towards mineral acids [14].

1,3,4-thiadiazoles represent one of the most biologically active classes of compounds, possessing a wide spectrum of activities. A triazolo thiadiazole system may be viewed as a cyclic analogue of two very important components thiosemicarbazide and biguanide, which often display diverse biological activities, stopping multiplication of bacteria. This has made them

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unique for the control of deadly infectious diseases caused by a variety of pathogens.

Members of the 1,3,4-thiadiazole ring system have found diverse applications as pharmaceuticals, antioxidants, cyanine dyes and metal complexing agents [8] .

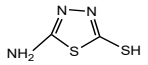
EXPERIMENTAL

General scheme for synthesis

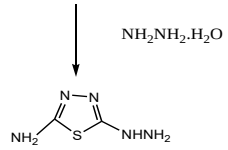
The general methods for the synthesis of compounds bearing a five-membered heterocyclic ring for obtaining new derivatives of thiadiazoles have been used in our laboratory for a long time. Various substituted amine derivatives, piperidine, aniline, and 2-amino-oxazole derivatives were prepared.

Scheme

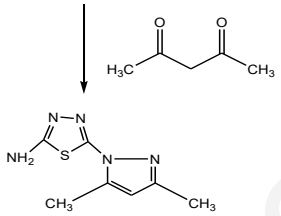
Step-1: Preparation of intermediate



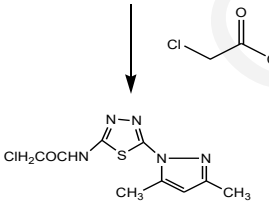
AR-1, 5-Amino-[1,3,4]thiadiazole-2-thiol



AR-2, 5-Hydrazino-[1,3,4]thiadiazol-2-ylamine



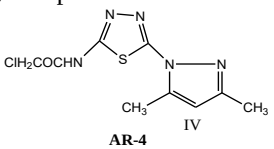
AR-3, 5-(3,5-Dimethyl-pyrazol-1-yl)-[1,3,4]thiadiazol-2-ylamine



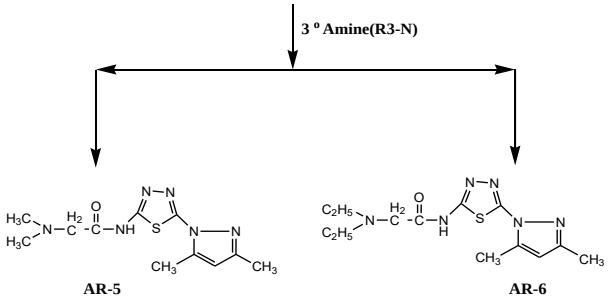
AR-4, 2-Chloro-*N*-[5-(3,5-dimethyl-pyrazol-1-yl)-[1,3,4]thiadiazol-2-yl] -acetamide

Step-2: Synthesis of derivativs:

Step-2(a):-Preparation of 3^0 amine derivatives

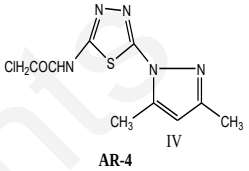


AR-4

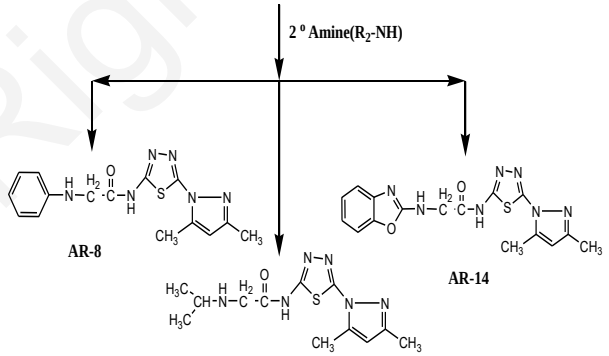


AR-5 **AR-6**

Step-2(b): Preparation of 2^0 amine derivatives

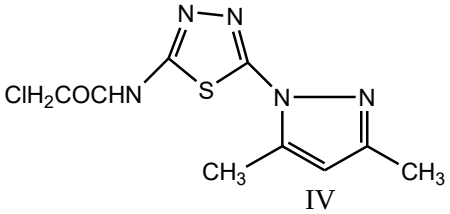


AR-4

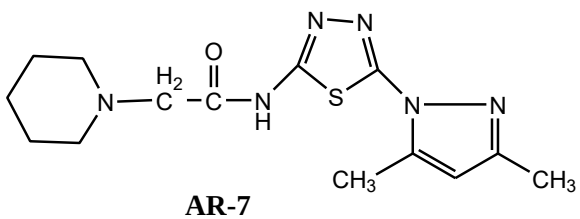


AR-8 **AR-14** **AR-10**

Step-2(c): Preparation of 1^0 amine derivatives



AR-4



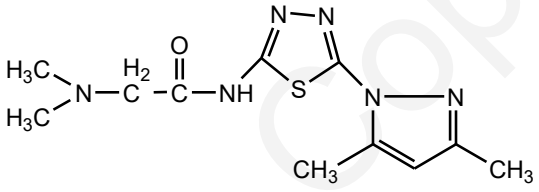
AR-7

RESULTS AND DISCUSSION

The synthesis started from 2-amino-5-mercapto-1,3,4-thiadiazole (**AR-1**), the thiol group of compound **AR-1** was readily converted into the hydrazino derivative **AR-2** by heating under reflux with an ethanolic solution of hydrazine hydrate. The resulting 2-amino-5-hydrazino-1,3,4-thiadiazole was used for the synthesis of interesting derivatives as a versatile key intermediate for the synthesis of some fused heterocyclic rings. Thus, the interaction of **AR-2** with acetyl acetone and carbon disulfide gave rise to the formation of 2-amino-5-(3,5-dimethyl-1H-pyrazole-1-yl)-1,3,4-thiadiazole (**AR-3)** which reacted with an equimolar quantity of chloroacetyl chloride and produced 2-chloro-N-[5-(3,5-dimethyl-pyrazol-1-yl)-[1,3,4] thiadiazol-2-yl]-acetamide (**AR-4**). The latter, on reaction with various amines (equimolar amounts in ethanol), produced the compounds **AR-5, AR-6, AR-7**, **AR-8**, **AR-10**, and **AR-14**. The structure of the synthesized compounds was established on the basis of ^{1}H-NMR and IR spectral data. In all cases TLC of the product showed the presence of one single spot referring to only one product.

Spectral characterization of the compounds

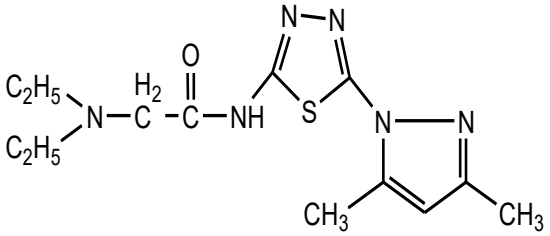
N-(5-(3,5-dimethyl-1-H-pyrazol-1-yl)-1,3,4-thiadiazol-2-yl)-2-(dimethyl amino) acetamide (AR-5)



IR (KBr) cm^{-1}

The spectrum of the compound showed absorption bands at: 3410 cm^{-1} (CO-NH$_2$ stretching), 2984 cm^{-1} (CH$_3$ stretching), 2363 cm^{-1} (aromatic CH$_3$ stretching), 1728 cm^{-1} (–NH stretching), 1600 cm^{-1} (C=O stretching), 1437 cm^{-1} (C=N stretching), 1295 cm^{-1} (C-N stretching), 1104 cm^{-1} (N-N stretching), 666 cm^{-1} (C-S-C stretching).

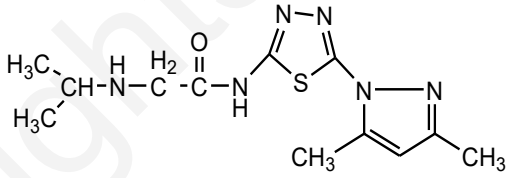
2-(Diethyl amino)-N-(3, 5-dimethyl-1H-pyrazol-1-yl)-1,3,4-thiadiazole-2-yl) acetamide (AR-6)



IR (KBr) cm^{-1}

The spectrum of the compound showed absorption bands at: 3423 cm^{-1} (CO-NH$_2$ stretching), 2968 cm^{-1} (aromatic CH$_3$ stretching), 2495 cm^{-1} (CH$_2$ stretching), 1591 cm^{-1} (C=O stretching), 1379 cm^{-1} (C=C stretching), 1281 cm^{-1} (C-N stretching), 1062 cm^{-1} (N-N stretching), 667 cm^{-1} (C-S-C stretching).

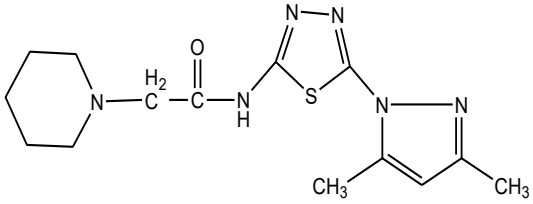
Synthesis of N-(5-(3,5-dimethyl-1H-pyrazol-1-yl)-1,3,4-thiadiazol-2-(isopropyl amino) acetamide (AR-10)



IR (KBr) cm^{-1}

The spectrum of the compound showed absorption bands at: 3410 cm^{-1} (CO-NH$_2$ stretching), 2981 cm^{-1} (aromatic CH$_3$ stretching), 2362 cm^{-1} (CH$_2$ stretching), 1722 cm^{-1} (C=O stretching), 1628 cm^{-1} (C=C stretching), 1026 cm^{-1} (N-N stretching), 667 cm^{-1} (C-S-C stretching).

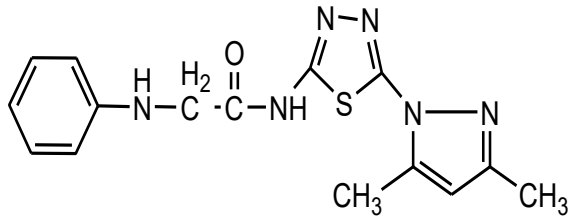
Synthesis of N-(5-(3,5-dimethyl-1H-pyrazol-1-yl)-1,3,4-thiadiazol)-2- (piperidin-1-yl) acetamide (AR-7)



IR (KBr) cm^{-1}

The spectrum of the compound showed absorption bands at: 3437 cm^{-1} (CO-NH$_2$ stretching), 2949 cm^{-1} (aromatic CH$_3$ stretching), 2532 cm^{-1} (CH$_2$ stretching), 1572 cm^{-1} (C=O stretching), 1499 cm^{-1} (C=N stretching), 1024 cm^{-1} (N=N stretching), 667 cm^{-1} (C-S-C stretching).

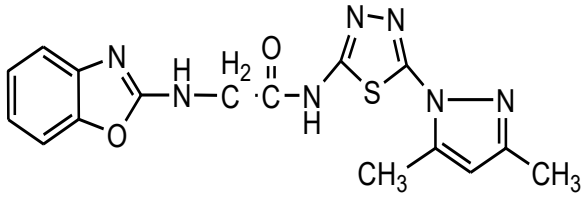
Synthesis of N-(5-(3,5-dimethyl-1H-pyrazol-1-yl)-1,3,4-thiadiazol-2-yl)-2-(phenyl amino) acetamide (AR-8)



IR (KBr) cm^{-1}

The spectrum of the compound showed absorption bands at: 3374 cm^{-1} (CO-NH_2 stretching), 3008 cm^{-1} (aromatic CH_3 benzene), 2365 cm^{-1} (CH_2 stretching), 1603 cm^{-1} (C=O stretching), 1562 cm^{-1} (C=N stretching), 1492 cm^{-1} (C=C stretching), 1028 cm^{-1} (N=N stretching), 667 cm^{-1} (C-S-C stretching).

Synthesis of 2-(benzo[d]oxazol-2-yl amino)-N-(5-(3,5-dimethyl-1H-pyrazol-1-yl)-1,3,4-thiadiazol-2-yl) acetamide (AR-14)



IR (KBr) cm^{-1}

The spectrum of the compound showed absorption bands at: 3776 cm^{-1} (CO-NH_2 stretching), 3429 cm^{-1} (CH_3 stretching), 3023 cm^{-1} (aromatic CH_3 benzene stretching), 2364 cm^{-1} (CH_2 stretching), 1628 cm^{-1} (C=O stretching), 1438 cm^{-1} (C=N stretching), 1022 cm^{-1} (N=N stretching), 670 cm^{-1} (C-S-C stretching).

Doses of 30, 100 and 300 mg/kg were administered i.p. The values in the table indicate the minimum dose whereby bioavailability was demonstrated in half or more of the mice. The animals were examined 0.5 and 4 h after injections were made. The dash (-) indicates an absence of activity at the maximum dose administered (300 mg/kg).

Table 1: Anticonvulsant activity of the synthesized derivatives

S.No.	Compound No.	MES	
		0.5h	4h
1.	AR-5	100	300
2.	AR-6	30	100
3.	AR-8	100	100
4.	AR-14	300	300
5.	AR-7	30	100
6.	Phenytoin	30	30
7.	Carbamazepine	30	100

Table 2: Minimum motor impairment of the synthesized derivatives

S.No.	Compound No.	TOXICITY SCREEN	
		0.5h	4h
1.	AR-5	100	300
2.	AR-6	30	100
3.	AR-8	300	300
4.	AR-14	30	300
5.	AR-7	30	300
6.	Phenytoin	30	30
7.	Carbamazepine	30	100

Doses of 30, 100 and 300 mg/kg were administered i.p. The figures in the table indicate the minimum dose whereby bioavailability was demonstrated in half or more of the mice. The animals were examined 0.5 and 4 h after injections were made. The dash (-) indicates an absence of activity at maximum dose administered (300mg/kg).

Anticonvulsant activity

The anticonvulsant activity was tested using a reported procedure. Albino mice (Swiss strain) of either sex weighing 20-25 g were acclimatized to their environment for at least two days before the experiment. The animals were allowed to free access to water before the test.

In order to reveal the potential anticonvulsant profile of the synthesized compounds, the MES model was employed in accordance with the anticonvulsant drug development (ADD) Protocol. The anticonvulsant activity of compounds **AR-5, AR-6, AR-7, AR-8** and **AR-14** in mice was evaluated at dose levels of 30, 100 and 300 mg/kg i.p. MES-maximum electroshock seizure and NT-neurotoxicity screening are summarized in tables **1 and 2** together with literature data on standard drugs (phenytoin and carbamazepine) (fig.1&2).

The compounds **AR-6, AR-7** exhibited fifty percent or more protection after 0.5 h at a lower dose of 30 mg/kg. These compounds showed activity comparable to phenytoin and carbamazepine. Compounds **AR-5** and **AR-8** were also active at low doses. At 100 mg/kg the compounds that showed protection were **AR-5(0.5h, 4h), AR-6(0.5h, 4h), AR-7(0.5h),** and **AR-8(4h)**; compound 14 showed activity only at a higher dose level (300 mg/kg). This shows that all synthesized compounds are more or less active against the spread of seizures.

It is evident from table **2** that the compounds are less neuro-toxic than the standard drugs phenytoin and carbamazepine.

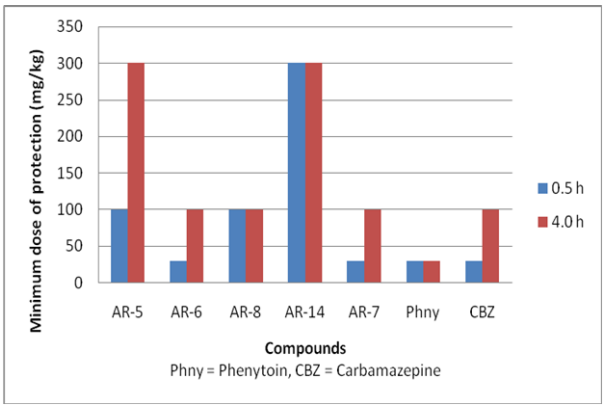


Fig. 1. Anticonvulsant activity of the synthesized compounds (AR-5,6,7,8,14)

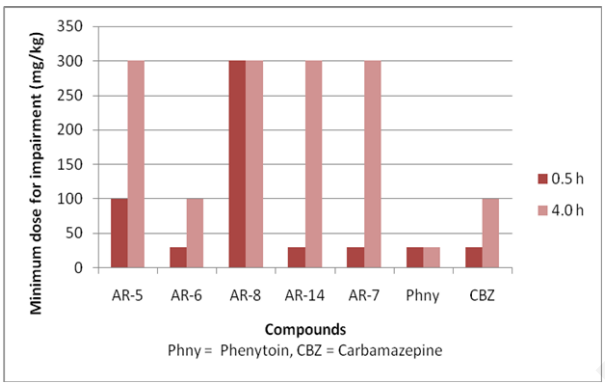


Fig. 2. Minimum motor impairment of the synthesized compounds (AR-5,6,7,8,14)

SUMMARY

The present study showed that the anticonvulsant activity of the investigated compounds depends upon the lipophilic nature of the ring due to the "**S"** moiety. We reported in this study the general approach for preparation of substituted 1,3,4-thiadiazole derivatives having various biological activities. The synthesized compounds were identified on the basis of their spectral data [15-17].

The results indicate that the constituents (dimethylamine, diethylamine, 2-aminobenzoxazole, aniline and piperidine) significantly affect the anticonvulsant activity. Thus, **AR-5, AR-8,** and **AR-14** have emerged as the lead compounds with activity in the MES test at 0.5h and 4h. The compounds **AR-6 and AR-7** were found less neurotoxic. Structural modification of these compounds may lead to the discovery of more potent anticonvulsant agents with lower neurotoxicity.

5-amino-1, 3, 4-thiadiazole-2-thiol (AR-1)

m.p. 232 ^{0}C, Rf value 0.78

^{1}H-NMR (400 MHz, DMSO-d6, TMS) ppm 7.99 (2H, s, NH_2), 12.93 (H, s, SH). FTIR (KBr) _max cm^{-1} 2553 (S-Hstr, thiol).

2-amino-5-hydrazino-1, 3, 4-thiadiazole (AR-2)

m.p. 242-244 ^{0}C, Rf value 0.65

IR: 3400-3250($NHNH_2$), 3200, 3168(NH_2), 1600(C=N), 688(C-S). ^{1}H-NMR (DMSO-d6) δ: 5.27(s, 2H, NH_2) (D2O exchange, disappear), 6.00(s, 1H, NH) (D2O exchange, disappear), 7.08(s, 2H, NH2) (D_2O exchange, disappear). ^{13}C-NMR (DMSO-d6) δ: 154.7, 161.5 (thiadiazole carbons).

2-amino-5-(3, 5-dimethyl-1H-pyrazole-1-yl)-1, 3, 4-thiadiazole (AR-3)

m.p. 150-152 ^{0}C, Rf value 0.72

IR: 3300, 3250(NH_2), 3078(=CH-), 2977, 2850(CH aliphatic). 1H-NMR (DMSO-d6) *δ*: 3.32, 3.48(s, 3H, CH_3), 6.01(s, 1H, =CH-), 7.08(s, 2H, NH_2) (D_2O exchange, disappear). ^{13}C-NMR (DMSO-d6) *δ*: 17.6(1C, CH3), 52.1, 56.4(2C, C-CH_3), 96.6(1C, =CH-), 152.1, 163.2 (thiadiazole carbons).

N-(5-(3, 5-dimethyl-1-H-pyrazol-1-yl)-1, 3, 4-thiadiazol-2-yl)- 2-(dimethyl amino) acetamide (AR-5)

m.p. **198-200 ^{0}C.**R_f value 0.78
IR (KBr): 3410 N-H str 2984-C-H str
1670-**CONH- str** 1600 **C=C st r**
1217, 1104, 1026, 866 1,3,4-thiadiazole nucleus

2-(diethyl amino)-N-(3,5-dimethyl-1H-pyrazol-1-yl)-1,3,4- thiadiazole-2-yl) acetamide (AR-6)

m.p. **210-212 ^{0}C.** R_f value **0.65**
3423 N-H str 2985 -C-H str.
1650 **-CONH- str** 1590 **C=C str**
1218, 1062, 99 1,3,4-thiadiazole

N-(5-(3,5-dimethyl-1H-pyrazol-1-yl)1,3,4-thiadiazol-2-(isopropyl amino) acetamide (AR-10),

M.P. 220-222 ^{0}C.R_f value **0.65**
3410 N-H str,2981 -C-H str.
1628 **-CONH- str,**1600 **C=C str**
1218, 1026, 892 1,3,4-thiadiazole

N-(5-(3,5-dimetyl-1H-pyrazol-1-yl)-1,3,4-thiadiazol)-2-(piperidin-1-yl) acetamide (AR-7),

m.p. 192-194 ^{0}C
R_f value **0.65**
3410 N-H str 2981-C-H str. 1628 **-CONH- str**

1600 **C=C str** 1218, 1026, 892 1,3,4-thiadiazole

N-(5-(3,5-dimethyl-1H-pyrazol-1-yl)-1,3,4-thiadiazol-2-yl)-2-(phenyl amino) acetamide (AR-8)

m.p. 205 -207 ^{0}C.
R_f value **0.65**
3374-NH, 3008 Ar-H, 2970 -CH str.
1951, Mono substituted phenyl ring
1690-**NH-CO-,** 1603, 1572 **C=C** stretching,
1218, 1119, 1054, 999 1,3,4-thiadiazole nucleus

2-(benzo[d] oxazl-2-ylamino)-N-(5-(3,5-dimethyl-1H- pyrazol-1-yl)-1,3,4-thiadiazol-2-yl) acetamide (AR-14)

m.p. 234-235 ^{0}C.
R_f value **0.65**
3374 NH stretching, 3008 Ar-H,
2970-CH,1951 Mono substituted phenyl ring
1690-**NH-CO-,** 1603, 1572 **C=C** stretching
1218, 1119, 1054, 999, 1,3,4-thiadiazole nucleus

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СИНТЕЗА НА НЯКОИ НОВИ ТИАДИАЗОЛОВИ ПРОИЗВОДНИ ТЯХНОТО АНТИ-КОНВУЛСИВНО ДЕЙСТВИЕ

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(Резюме)

Синтезирана е нова серия производни на 1,3,4-тиадиазол и е установена структурата им чрез IR, ^{1}H-NMR и елементен анализ. Съединенията AR-5, AR-6, AR-7, AR-8 и AR-14 са изследвани за анти-конвулсивно действие върху бели мишки. Повечето от тези съединения показват обещаваща активност. Структурните модификации на тези съединения може да доведат до откриване на по-мощни анти-конвулсивни агенти с ниска невро-токсичност.