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# SYNTHESIS AND ANTICONVULSANT ACTIVITY OF 3-ARYLAMINO-4-ARYL-5-(N-4-CHLOROPHENYLTHIOCARBAMIDO)-1,2,4-THIADIAZOLES

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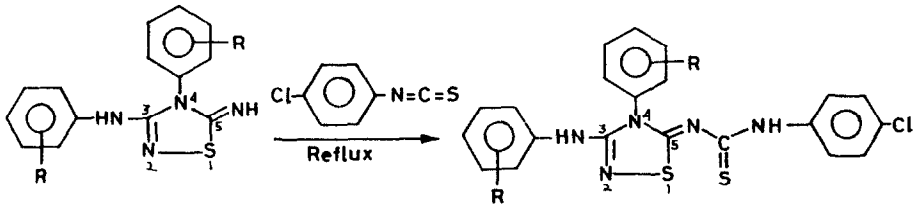
**Abstract:** The 3-(4-chlorophenyl)amino-4-(4-chlorophenyl)-5-(N-4-chlorophenylthiocarbamido)-1,2,4-thiadiazole possesses significant anticonvulsant activity, devoid of side effect, sedation.

Hydantoins and related cyclic ureids have served as an important source in the search for new anticonvulsants.[1] The sulfonyl analogues of Phenytoin, i.e., 1,2,5-thiadiazoles have been reported as potent anticonvulsants.[2] Recently, we have reported the synthesis anticonvulsant activities and related biological properties of 1,2,4-thiadiazoles.[3,4,5,6,7,8] 1,2,4-thiadiazoles could be considered bioisosterically equivalent to earlier reported 1,3,4-thiadiazoles[9] and 1,2,5-thiadiazoles[2]. The anticonvulsant properties observed for 1,2,5-thiadiazoles provided the impetus for the delineation of many of the structural parameters necessary for anticonvulsant activity within this class of compounds. In view of this, and in continuation with our investigations on 1,2,4-thiadiazole derivatives, we describe here the synthesis of some substituted derivatives of 1,2,4-thiadiazoles and screening them for the identification of anticonvulsant activity. It was also the aim to test for sedation, which is chronic side effect in most anticonvulsants. Anticonvulsant profile of synthesized compounds are compared with the standard drugs phenytoin. In our earlier reports [4,5,7] the parachlorophenyl group attached to amino nitrogen at 3 and directly to nitrogen at 4 positions of the thiadiazole ring have produced the compounds with moderate anticonvulsant activity. Hence, it was proposed to introduce the parachlorophenyl group to the imino nitrogen at 5 position of the thiadiazole ring, in an adduct form in order to observe a compound with enhanced activity. Various substituents were planned to be introduced into the two aryl rings of amino nitrogen at 3 and nitrogen at 4 positions of thiadiazole ring. The synthesis leading to the title compound (1-10) is depicted in SCHEME. The 4-aryl-3-arylamino-5-imino-1,2,4-thiadiazoles on condensation with 4-chlorophenylisothiocyanate forms 1:1 adduct, i.e., 3-arylamino-4-aryl-5-(N-4-chlorophenyl thiocarbamido)-1,2,4-thiadiazoles.[10] The 4-arylamino-3-aryl-5-imino-1,2,4-thiadiazoles were prepared by the method described in literature.

SCHEME : Synthesis of 3-arylamino-4-aryl-5-(N-4-chlorophenyl thiocarbamido)-1,2,4-thiadiazoles




4-Aryl-3-arylamino-5-imino 1,2,4-thiadiazoles

3-Arylamino-4-aryl-5-(N-4-chlorophenyl thiacarbamido)-1,2,4-thiadiazoles (1-10)

Where, R=H, 2-$CH_3$, 3-$CH_3$, 4-$CH_3$, 2-$OCH_3$, 3-$OCH_3$, 4-$OCH_3$, 2-Cl, 3-Cl and 4-Cl

**Table I:** Physical properties of 3-arylamino-4-aryl-5-(N-4-chlorophenylthiocarbamido)-1,2,4-thiadiazoles.

| S.No. | R | m.p[a,b] °C | % yield | Formula[c] |
|---|---|---|---|---|
| 1. | H | 211 | 60 | $C_{21}H_{16}N_5S_2Cl$ |
| 2. | 2-$CH_3$ | 208 | 50 | $C_{23}H_{22}N_5S_2Cl$ |
| 3. | 3-$CH_3$ | 226 | 65 | $C_{23}H_{22}N_5S_2Cl$ |
| 4. | 4-$CH_3$ | 240 | 68 | $C_{23}H_{22}N_5S_2Cl$ |
| 5. | 2-$OCH_3$ | 186 | 50 | $C_{23}H_{22}N_5O_2S_2Cl$ |
| 6. | 3-$OCH_3$ | 168 | 66 | $C_{23}H_{22}N_5O_2S_2Cl$ |
| 7. | 4-$OCH_3$ | 218 | 70 | $C_{23}H_{22}N_5O_2S_2Cl$ |
| 8. | 2-Cl | 198 | 95 | $C_{21}H_{16}N_5S_2Cl_3$ |
| 9 | 3-Cl | 172 | 88 | $C_{21}H_{16}N_5S_2Cl_3$ |
| 10. | 4-Cl | 230 | 90 | $C_{21}H_{16}N_5S_2Cl_3$ |

[a]Melting points are uncorrected, [b]Solvent for Crystallization: Ethanol
[c]All compounds gave satisfactory analyses for C,H,N,S (± 0.4%). IR and $^1H$ NMR spectra of the synthesized compounds were consistent with the assigned structures.

**Synthesis** (Representative example, compound 4): The reaction mixture containing 4-(4-methylphenyl)-3-(4-methylphenylamino)-1,2,4-thiadiazole (2.96 g, 0.01 mol) and 4-chlorophenylisothiocyanate (1.69 g, 0.01 mol) in ethanol (10.0 mL) refluxed at 70°C for 4h. The reaction mixture was cooled and the solid was filtered, washed first with Petroleum ether and then with dilute hydrochloric acid. Solid was then dried and crystallised from ethanol to give compound 4: mp,240°C,yield,68%;

IR(KBr,$cm^{-1}$)3210(m,NH)1610(s,C=N)1200(s C=S); $^1H$ NMR($CDCl_3$)7.5(m,12H, 3Ar)5.1(brs,2H,2NH,$D_2O$ exchangeable)2.1(2s,6H,$2CH_3$). Similarly other compounds were synthesized and their physical properties are given in Table I.

**Biologial Activity:** Wistar strain albino rats of either sex in the weight range (100-150g) were used in of maximal electroshock seizure test, subcutaneous pentylenetetrazole seizure test,[13] Barbiturate hypnosis potentiation effect test[14] and $LD_{50}$ test. The assessment of anticonvulsant activity was done in two test areas, viz., MES and Sc-PTZ test. The biological results are summarized in Table II.

The results obtained in anticonvulsant identification in 3-arylamino-4-aryl-5-(N-4-chlorophenylthiocarbamido)-1,2,4-thiadiazoles shows that the parent compound (R=H,1) was partially inhibiting the MES induced convulsions (25% protection) at the dose of 20 mg/kg, i.p.. Substitution of parent compound with 2-$CH_3$(2), 3-$CH_3$(3), 2-$OCH_3$(5) and 3-$OCH_3$(6) groups produced the inactive compounds in MES test at the same dose level. the 4-$CH_3$(4) and 4-$OCH_3$(7) substituted compounds were partially protecting (50%) the MES induced seizures at the dose 20 mg/kg,i.p.. It was found that the chlorosubstitution [2-Cl(8); 3-Cl(9) and 4-Cl(10)] in phenyl rings at 3 and 4 positions of thiadiazole ring have produced the compounds with significant anticonvulsant activity, of which the 4-Cl(10) substituted compound being most active (87% protection in MES test, $P<0.01$). Compounds 8 and 9 were found equipotent ($P<0.05$) to standard drug phenytoin and compound 10 was comparatively more active ($P<0.01$) than the standard drug phenytoin.

All of the synthesized compounds (1-10) were assessed for the broad spectrum of activity in Sc-PTZ test at the dose level of 20 mg/kg,i.p. only 3-Cl(9) and 4-Cl(10) substituted compounds were partially inhibiting the PTZ induced convulsions, whereas rest of the compounds of this series were found totally inactive (0% protection) in Sc-PTZ test.

Quantification of anticonvulsant activity of the active compounds were done by the determination of a median effective dose ($ED_{50}$) and acute toxicity ($LD_{50}$) values, compounds 8 and 10 were

**Table II**: Biological activities of 3-arylamino-4-aryl-5-(N-4-chlorophenylthiocarbamido)-1,2,4-thiadiazoles.

| S.N. | R | MES, 1h(n=8) | | Sc-PTZ, 1h (n=8) | | $LD_{50}$ (mg/kg) (n=8) | T.I.** | Sleeping time (min n=5) Mean ± S.E. | hypnosis potentiation (%) |
|---|---|---|---|---|---|---|---|---|---|
| | | % Protection | $ED_{50}$ (mg/kg) | % Protection | $ED_{50}$ (mg/kg) | | | | |
| 1. | H | 25 | 76 54 | 0 | | 250 | 3.26 | $68.50\pm3.35^{NS}$ | 4.98 |
| 2. | 2-$CH_3$ | 0 | i | 0 | j | | | | |
| 3. | 3-$CH_3$ | 0 | i | 0 | j | | | | |
| 4. | 4-$CH_3$ | 50 | 46.71 | 0 | i | 300 | 6.42 | $75.45\pm4.50^{NS}$ | 15.63 |
| 5. | 2-$OCH_3$ | 0 | i | 0 | j | | | | |
| 6. | 3-$OCH_3$ | 0 | i | 0 | j | | | | |
| 7. | 4-$OCH_3$ | 50 | 20.31 | 0 | k | 210 | 10.33 | $67.30\pm4.32^{NS}$ | 3.14 |
| 8. | 2-Cl | $75^{+}$ | 12 | 0 | 35.15 | 175 | 14.58 | $78.68\pm6.25^{NS}$ | 20.58 |
| 9. | 3-Cl | $75^{+}$ | 17.5 | $75^{+}$ | 26.20 | 120 | 6.85 | $69.15\pm4.68^{NS}$ | 5 97 |
| 10. | 4-Cl | $87.5^{++}$ | 10 | $75^{+}$ | 22.10 | 117 | 11.7 | $72\ 81\pm5.54^{NS}$ | 11.58 |
| Phenytoin | | $75^{+}$ | 9.5 | 37.5 | i | 65.5 | 6.89 | $100.5\ \pm4.45^{+}$ | 54 02 |
| [1]Pentobarbitone-sodium(control) | | | | | | | | $65.25\pm4.42$ | |

i=No protection upto 100 mg/kg,i.p.; j=No protection upto 120 mg/kg,i.p.;
k=No protection upto 150 mg/kg,i.p ; [1]Dose = 30 mg/kg,i.p.
[m]non-significant activity upto 80 mg/kg i.p. at 95% C.I.; $^{+}P<0.05$; $^{++}P<0.01$, $^{NS}$Non-significant

$$^{**}\text{Therapeutic index(T.I.)} = \frac{LD_{50}}{\text{MES } ED_{50}}$$

having wide safety margin as is evident by their high therapeutic indices. For inactive compounds in MES test and Sc-PTZ test, the higher dose tested are mentioned in Table II.

Compounds which have shown significant anticonvulsant activities, were also tested for side effect, sedation, and none of the compounds have increased the sleeping time in rats statistically significantly in the Barbiturate hypnosis potentiation effect test at the dose level of 20 mg/kg,i.p. as compared to the reference drug, phenytoin. These compounds have also shown non-signficant hypnotic activity even at the higher doses up to 80 mg/kg,i.p. thereby exhibiting non-sedative activity. (Compound 1,4,7,8,9,10)

In conclusion, the 3-(4-chlorophenyl)amino-(4-chlorophenyl)-5-(N-4-chlorophenylthiocarbamido)-1,2,4 thiadiazole (compound 10) was possessing broad spectrum of anticonvulsant activity (active both in MES and Sc-PTZ tests) and devoid of sedation, as compared to the standard drug, Phenytoin. It was found that the adduct formed between imino nitrogen at 5 position of thiadiazole ring and 4-chlorophenylisothiocyanate is responsible for the significantly enhanced anticonvulsant activity.

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**References and Notes**:

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