IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

# PHASE – TRANSFER CATALYSED SYNTHESIS OF NEW $N^3$ SUBSTITUTED THIAZOLE DERIVATIVES AS ACTIVE ANTICONVULSANT COMPOUNDS

**Dr. Sangeeta Kamthan**
Associate Professor, Department of Chemistry,
Bareilly College, Bareilly (UP) INDIA.

***Abstract:*** Ten different thiazole substituted hydantoin derivatives were prepared by condensation of different chloro-acetylated heterocyclic moieties with alkali metal-cyanate in presence of quaternary ammonium salt as phase - transfer catalyst
The compounds were screened for anticonvulsant activity, Diphenyl hydantoin sodium was used as reference drug.
Two of the compounds showed significant anticonvulsant activity. Compound V, $N^3$ - 4- (p- hydroxy phenyl-thizole-2 yl) hydantoin exhibited maximum anticonvulsant activity.

***Index Terms*** **- Phase-** ***transfer catalyst, thiazole, anticonvulsant activity.***

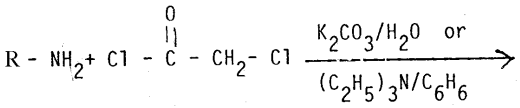
## I. INTRODUCTION

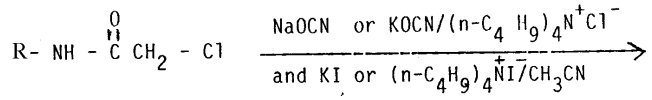
The field of medicinal chemistry has been enriched with progressive findings about the anticonvulsant activities of various substituted thiazole derivatives [1-8]. Workers have shown that $N^3$- substituted derivatives of 5 – phenyl – 5 – alkyl hydantoins can be prepared and the activity is strongly dependant on the type of substitution [9-12]. In view of great therapeutic activities of $N^3$- substituted hydantoins, it seemed desirable to synthesize some new derivatives with modifications of the parent structure which may enhance activity and also show less toxicity [3][13]. Thus, 2-amino – 4–phenyl-substituted thiazoles [14] were treated with chloro-acetyl derivatives which on treatment with an alkali-metal cyanate in presence of phase-transfer catalyst [15] to give hydantoin derivatives which were found to possess considerable anticonvulsive activity. The current article manages the blend and anticonvulsant action of ten substituted thiazole hydantoins.

## II. MATERIAL AND METHODS

### *Synthesis*

$N^3$- substituted hydantoin derivatives were synthesized by the method of Kim and Kwon, 1982, [15] in two stages. First, chloro-acetylated heterocyclic mixtures were prepared by treating the heterocyclic compounds with chloro-acetyl chloride in dry benzene. In second stage, chloro-acetylated derivatives were treated with potassium cyanate in presence of catalytic amount of tetra-n-butyl-ammonium iodide as phase- transfer catalyst [15] and potassium-iodide containing a polar solvent, acetonitrile. The general sequence of the chemical reaction may be depicted as follows:





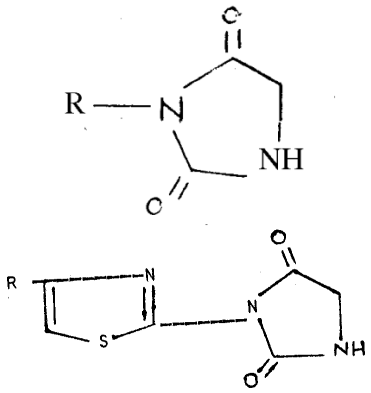




**Table 1.The molecular formula, melting-point & percentage yield of substituted hydantoins of thiazole.**

| S. No. | R | Molecule formula | M.P ℃ | Yield % |
|---|---|---|---|---|
| I | phenyl | $C_{12}H_9N_3O_2S$ | 162 | 62 |
| II | p-methoxyphenyl | $C_{13}H_{11}O_3N_3S$ | 126 | 54 |
| III | o-tolylphenyl | $C_{13}H_{11}N_3O_3S$ | 115 | 60 |
| IV | p-anisylphenyl | $C_{14}H_{12}N_3O_3S$ | 118 | 62 |
| V | p-hydroxy-phenyl | $C_{12}H_9N_3O_3S$ | 158 | 52 |
| VI | p-chloro-phenyl | $C_{12}H_8O_2N_3SCl$ | 165 | 68 |
| VII | o-chlorophenyl | $C_{12}H_8O_2N_3SCl$ | 166 | 64 |
| VIII | p-bromophenyl | $C_{12}H_8O_2N_3SBr$ | 160 | 61 |
| IX | p-fluorophenyl | $C_{12}H_8O_2N_3SF$ | 170 | 60 |
| X | p-nitrophenyl | $C_{12}H_9O_4N_4S$ | 170 | 74 |

**The analysis of N, Cl, Br, S and F found and calculated did not differ more than 0.4%**

## III. ANTIEPILEPTIC ACTIVITY

Male albino mice weighing 20-25 mg were used in the present study. They were maintained at an ambient temperature of 22 ± 1℃ and had food and water ad.libitum. The mice were divided into groups of six animals each except otherwise mentioned. The test compounds were dissolved in polysorbate (Tween 80) and diluted with distilled water and were injected i.p.in a dose of 100 mg/kg to the mice. One group received standard drug, di-phenyl hydantoin sodium in a dose of 25 mg/kg i.p. The control group received vehicle only. The animals were observed for behavioral changes, if any, up to 1 hour of drug administration.

The anticonvulsant activity was studied by maximum electro-shock seizures (MES).The electro-shock (48mA,0.2 sec.) was delivered 1 hr. after the drug administration through a convulsiometer (Techno) by using ear electrodes according to the method of Swinyard et.al.,[16]. After the delivery of shocks, duration of various phases of MES (tonic flexion, tonic extensor and clonus) and of post seizure depression, defined as the time required to regain the righting- reflux (RR), was taken as the index for protection. The statistical significance of the difference in the mean values were calculated by the student's't' test.

**Table 2. Effect of substituted hydantoins of thiazole on components of electro-shock-induced seizures in male albino mice.**

| Compound No. | No. of Animals | Mean duration in seconds ± SEM | | | |
|---|---|---|---|---|---|
| | | Flexor | Extensor | Clonus | Stupor |
| Vehicle Control | 11 | 2.29 ± 0.16 | 15.09 ± 1.35 | 11.80 ± 3.19 | 53.80 ± 10.06 |
| I | 6 | 1.65 ± 0.11*** | 17.65 ± 0.80 | 5.40 ± 2.23 | 34.60 ± 11.10 |
| II | 6 | 2.10 ± 0.31 | 17.56 ± 01.50 | 5.50 ± 1.28 | 70.80± 22.20 |
| III | 6 | 1.28 ± 0.41** | 15.61 ± 0.84*** | 6.41 ± 1.41** | 40.42 ± 10.61*** |
| IV | 6 | 1.92 ± 0.51** | 15.91 ± 0.91 | 5.98 ± 1.91 | 51.56 ± 11.64 |
| V | 6 | 2.60 ± 0.77 | 13.20 ± 1.29 | 7.00 ± 1.38* | 73.30 ± 25.98 |
| VI | 6 | 1.78 ± 0.26** | 20.11 ± 0.82*** | 7.50 ± 0.92 | 18.33 ± 2.87*** |
| VII | 6 | 1.84 ± 0.08*** | 24.21 ± 0.92*** | 8.20 ± 0.96 | 18.92 ± 2.89*** |
| VIII | 6 | 1.84 ± 0.31 | 33.41± 2.10 | 9.14 ± 1.12 | 18.98 ± 3.01*** |
| IX | 6 | 1.97 ± 0.41 | 20.48 ± 2.41 | 9.98 ± 2.01 | 19.24 ± 3.91 |
| X | 6 | 2.41 ± 0.91 | 1.72 ± 1.22**** | 7.01 ± 2.81 | 74.81 ± 13.41 |
| Diphenyl hydantoin sodium | 6 | 1.63 ± 0.24* | 0.00 ± 0.00**** | 2.20 ± 1.04**** | 4.73 ± 1.79*** |

**P value in comparison to control group -*P: - < 0.05, **P :-< 0.025, ***P :-< 0.01, ****P: -< 0.001**

**'a' : Dose of 25 mg/kg i.p**

## IV. RESULTS

A series of thiazole substituted hydantoins were synthesized and their structure, physical and chemical properties are summarized in Table 1.

The yield of the compound varied from 52 to 74%. The p-nitro derivative showed the maximum yield. Almost all the compounds showed high melting point ranging from 115 to $170^0$C.

The compounds were evaluated for their anticonvulsant action and were contrasted with the standard medication, Di-phenyl-hydantoin sodium. There was a marked variation in the anticonvulsant activity of $N^3$ – substituted thiazole hydantoins. The results are signified in Table 2.

The compound II and V offered significant anti convulsant activity against electro-shock-induced seizures. However, compounds VII, IX and X did not show any anticonvulsant activity. The compound II and V exhibited maximum anticonvulsant action on extensor component of electro-shock, although the flexor duration was almost same for both the compounds. Compound II had an added advantage of decreased clonus and stupor component.

The mortality rate was 100% in the compounds I & X, as observed after 1 hour and 24 hours of chemo shock - induced seizures. The compounds III, IV offered lowest percent mortality rate in 50% of the animals. Almost all the animals showed tremors and depressant effects. The compounds VI and VII also showed moderately high mortality rate.

Compound X has marked irritant effect accompanied by trimerogenic effect.

Di-phenyl hydantoin sodium (25mg/kg) offered total protection against electro-shock- induced seizures. The percent mortality rate was also found to be nil after 1 hour as well as 24 hours of drug administration.

## V. DISCUSSION

There was a marked variation in the results of compounds having p-alkoxy, p-hydroxy and ortho or para halo-atoms in the heterocyclic nuclei of hydantoins. In general, few have shown moderate anticonvulsant activity as shown in Table 2.

Results have shown that almost all the compounds were active as compared to vehicle control as indicated by decreased duration of extensor component of electro-shock seizure, except the para nitro derivative of thiazole hydantoin.

Compound V with p-hydroxy substitution has significant activity as compared to other derivatives.

The substitution of chlorine atom at para position, compound VI, shows slightly higher anticonvulsant activity as compared to ortho substituted chloro-atom, compound VII, by decreasing the time duration of stupor phase. On the contrary, the para substituted derivatives of bromine and fluorine, Compound VIII and IX, does not show any remarkable difference.

The para substituted nitro compound X, was found to be least anticonvulsant and highly toxic as shown by their mortality rate of chemo-shock-induced seizures. The phenyl substituted thiazole-2-yl compound I also showed 100% mortality rate of chemo-shock induced seizure immediately after drug administration.

The compound II, V and VI have also found to possess CNS depressant effect, which may be responsible for its anticonvulsant activity.

The order of anticonvulsant effect against electroshock and chemo-shock induced seizures was, thus, found to be compound V > II > VI.

In conclusion, it is suggested that hydantoins with substituted thiazole moiety are moderately anticonvulsants and may represent a starting point to allow a better understanding of antiepileptic therapeutic developments as well as to suggest ideas for designing and synthesizing a noval series of antiepileptic compounds.

## VI. ACKNOWLEDGEMENT

**The author is thankful to Principal, Bareilly College, Bareilly, Director IVRI, Izatnagar and Head, Division of Pharmacology and Toxicology, IVRI, Izatnagar, Bareilly for providing necessary lab facilities**

## VII. REFERENCES

[1] Wilby, M.J.; hutchinson, P.J. The pharmacology of chloromethiazole: A potential neuroprotective agent. CNS *Drug Rev*. 2004, *10*, 281–294. [Google Scholar] [CrossRef] [PubMed]

[2] Harnett, J.J.; Roubert, V.; Dolo, C.; Charnet, C.; Spinnewyn, B.; Cornet, S.; Rolland, A.; Marin, J.G.; Bigg, D.; Chabrier, P.E. Phenolic thiazoles as novel orally-active neuroprotective agents. *Bioorg. Med. Chem. Lett.* 2004, *14*, 157–160. [Google Scholar] [CrossRef] [PubMed]

[3] Pranabandhu Tripathy, H. K. Pujari, and M.K. Raut: J. Indian Chem.Soc., 407, 35 (1958)

[4] R. Charonnet, P.Lachat and J.Chereton. Therapie, 68, 12 (1957)

[5] Adolph H. Philip, Leslie G, Humber and Rene R. Martel: J Heterocycl. Chem., 413, 15 (1978).

[6] Dennis Big: Eur. Pat. Appl.EP. 69,623 (Cl.C 07 D 513/04) (1983).

[7] Francois Debarre, Claude Jean Mart, and Pierre Edouard Simon N: Ger. Offen. 2,359, 864, (Cl. C 07 d) (1964).

[8] Eugene E E. Galanty: Ger. Offen. 2, 003,090, (Cl. C 07 d) (1970).

[9] K.Schlogal, F. Weisley, D.Kraupp and H. Stormann: J.Med. Pharm. Chem. 4231 (1961).

[10] M.B. Winstead and C.R. Hamel:J. Med. Chem. , 8 120 (1965)

[11] M.B. Wintead, D.E Barr, C.R. Hamel, D.J.Renn, H.I. Parker and R.M. Neumann: J. Med. Chem., 8 117 (1965)

[12] J.W.Shaffer, E.Steinberg, V. Krimsley and M.B. Winstead J. Med. Chem. , 11 , 462 (1968).

[13] R.Charonnet, P.Lachat and J.Cherton. Therapie, 68, 72 (1957)

[14] L.C.King, and R.M. Dodson: J. Chem. Soc. 67, 2242 (1945); 68, 871 (1946).

[15] Kim, S.C. and Kwon, B.M. (1982). A new convenient synthesis of hydantoin derivatives by phase transfer method. *Synthesis 795-796*

[16] Swinyard, E.A. Brown, W.C. and Goodman, L.S. (1952). Comparative assays of antiepileptic drug in mice and rats, *J. Phamac. Exp. Ther. 106: 319-330.*