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Synthesis OF N-(Substituted Phenyl)-2-[5-Phenyl-2H-1, 2, 4-triazol-3ylamino] Acetamide as Anticonvulsant

Dayanand Kadadevar[1]*, Chaluvaraju K C[1],Niranjan M S[1], Chandrashekar Sultanpur[1] Santosh Kumar Madinur[1], Nagaraj[1], Manjunath Hegde[1], Smitha M[1], Krishna Chakraborty[1].

***[1]Department of Pharmaceutical Chemistry, Government College of Pharmacy, Subbaiah Circle, Bengaluru- 560 027,India.**

Corres.author : daya_kadadevar@yahoo.co.in
Mob. No: +91-9902592245

Abstract: In the present study about five N-(substituted phenyl)-2-[5-phenyl-2H-1, 2, 4-triazol-3ylamino] acetamide (T_1-T_5) were synthesized and tested for anticonvulsant activity by MES method. Cyclocondensation of benzamidoguanidine in sodium ethoxide gives 5-amino-3-phenyl-1, 2, 4-triazole. This on reaction with 2- chloro-N-substituted phenylacetamide gives the title compounds. The synthesized compounds were purified and characterized by TLC, IR, and ^{1}HNMR spectral data. Phenytoin was used as standard anticonvulsant drug in screening. The compounds T_3 and T_4 were stastically significant compared to control.
Key words: Benzamidoguanidine, 1, 2, 4-triazole, anticonvulsant, Phenytoin.

INTRODUCTION:

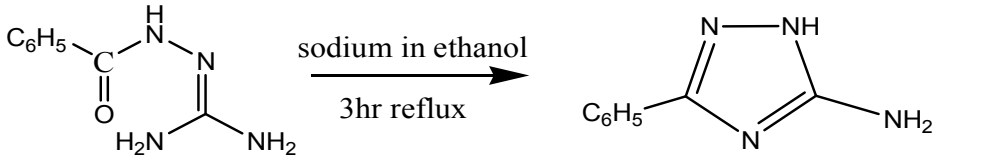
In recent years triazoles and its derivatives have received considerable attention owing to their synthetic and effective biological importance[(1)]. The Heterocycles bearing a symmetrical triazoles moiety were reported to show a broad spectrum of pharmacological properties viz., anticonvulsant[(2)],antifungal[(3)],antibacterial[(4)],antiviral[(5)] ,anti-inflammatory[(6)] activities etc.

Epilepsy is a neurological disorder characterised by unprovoked seizures that affecting millions of people worldwide[(7)]. The treatment of convulsion is symptomatic with available drugs, but neither effective prophylaxis nor cure is available. Loreclezole[(8)], (1-(2-chloro-2-(3,4-dichloropheyl)-1H-1,2,4-triazole) is a positive modulator of $GABA_A$ receptors containing a β_2/β_3 subunit and Estazolam[(9)] a Benzodiazepine agonist having triazolobenzo diazepine ring are known to have potent anticonvulsant properties. This importance of triazole nucleus and continuing demand for new anticonvulsant agents, in the present study about five 1, 2, 4-triazole derivatives were synthesized.

EXPERIMENTAL:

The chemicals required for the study were obtained from commercial source and were used without purification. The melting points of these synthesized compounds were determined in open capillary tube and were uncorrected. The IR spectra were recorded by preparing pellets dispersed in 1% KBr on FTIR-8400 spectrometer and the ^{1}HNMR spectra was taken on a Bruker AMX (400MHz) NMR spectrometer. The structures of synthesized compounds are in good agreement with the proposed ones.

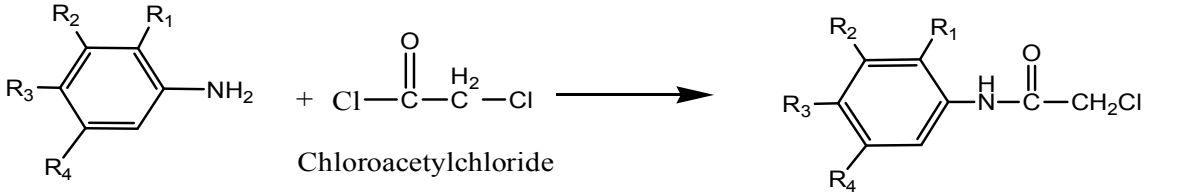
SCHEME: 1 Synthesis of 5-amino-3-phenyl-1, 2, 4-triazole



benzamidoguanidine

5-phenyl-2*H*-1,2,4-triazol-3-amine

SCHEME: 2 Synthesis of 2-chloro-N-substituted-phenyl-acetamide



2-chloro-N-substituted-phenyl-acetamide

Where,

	R_1	R_2	R_3	R_4
2a	**Cl**	**H**	**H**	**NO_2**
2b	**NO_2**	**H**	**OCH_3**	**H**
2c	**H**	**H**	**NO_2**	**H**
2d	**H**	**H**	**Cl**	**H**
2e	**NO_2**	**H**	**H**	**H**

PROCEDURE:

Step-1: Synthesis of 5-amino-3-phenyl-1, 2, 4-triazole [(10)]

Benzamidoguanidine (0.0109 mol, 1.8g) was refluxed with a solution of sodium (0.065 mol,1.5g) in alcohol (100 CC) for 3 hours and the solvent was removed in reduced pressure. Water was added, the insoluble residue filtered off and the filterate was made acidic with acetic acid (**Scheme : 1).** The precipitate obtained was collected and crystallized from water. Yield (%) 59.95, m.p. 185-186ºC, IR1350Cm^{-1}(C-N stretching), 3458 Cm^{-1} (NH- stretching),1570 Cm^{-1}(NH bend),TLC Ethyl acetate: Hexane (7:3).

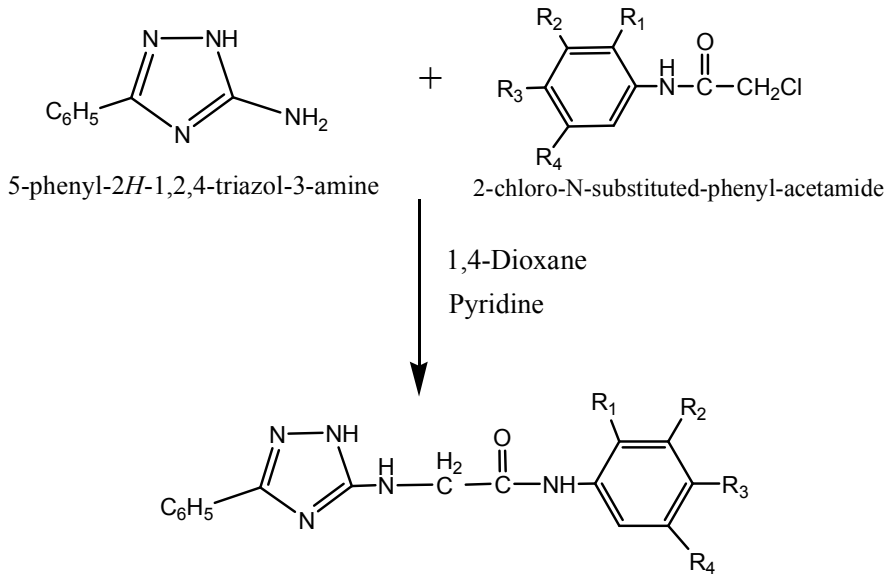
Step-2: Synthesis of 2-chloro-N-substituted-phenyl-acetamide[(11)] (2a to 2e)

Substituted aromatic amines (0.05mol) were dissolved in glacial acetic acid (25ml) containing (25ml) saturated solution of sodium acetate, warmed and then the solution was cooled in ice bath with stirring. To this chloroacetyl chloride (0.06mol) was added drop wise in 30 minutes. The white colored product was separated and filtered. The product was washed with 50% aqueous acetic acid and finally with water. It was then recrystallised from aqueous alcohol (**Scheme: 2). Table -01** summarizes the physical and analytical data of compounds.

TABLE NO-01: PHYSICOCHEMICAL CHARACTERIZATION OF 2-CHLORO-N-SUBSTITUTED-PHENYL-ACETAMIDE (2a to 2e)

	Mol.formula	M.P	**IR (Cm^{-1})**
2a	$C_8H_6Cl_2N_20_3$	120-122°C	**3329 (NH-stretch),1647 (C=O), 3186 (Ar-H)**
2b	$C_9H_9ClN_20_4$	118-120°C	**3322(NH-stretch),1681 (C=O), 3146 (Ar-H)**
2c	$C_8H_7ClN_20_3$	121-123°C	**3414 (NH-stretch),1662 (C=O), 3032 (Ar-H)**
2d	$C_8H_7Cl_2N0$	116-118°C	**3373 (NH-stretch),1685 (C=O), 3142 (Ar-H)**
2e	$C_8H_7ClN_20_3$	122-124°C	**3348(NH-stretch),1664 (C=O), 3130 (Ar-H)**

SCHEME: 3 Synthesis of N-(substituted phenyl)-2-[5-phenyl-2H-1, 2, 4-triazol-3ylamino] acetamide (T_1-T_5).



N-(substituted phenyl)-2-[5-phenyl-2H-1, 2, 4-triazol-3ylamino] acetamide

Where,

	R1	**R_2**	**R2**	**R3**	**R4**
T1	Cl	**H**	H	NO_2	NO_2
T2	NO_2	**H**	OCH_3	H	H
T3	H	**H**	NO_2	H	H
T4	H	**H**	Cl	H	H
T5	NO_2	**H**	H	H	H

TABLE NO-02: PHYSICOCHEMICAL CHARACTERISTICS OF COMPOUNDS (T_1 –T_5)

	R_1	**R_2**	**R_3**	**Mol. Formula (Mol. Wt)**	**M.P (% yield)**	**IR (Cm^{-1})**	**^{1}H NMR (CDCl3)**
T_1	Cl	H	NO_2	$C_{16}H_{13}ClN_6O_3$ (372.8g)	82-84°C (50%)	3120 (Ar-H), 1290 (C-N),1595 (NH bend), 3410 (NH stretch), 1685 (C=O)	4.08(s,2H,CH2),7.55(s,1H,NH),8.06(s,1H,NH-amide),7.44-8.53(m,8H,Ar)
T_2	NO_2	OCH_3	H	$C_{17}H_{16}N_6O_4$ (368.3g)	78-80°C (37.5%)	3009 (Ar-H), 1310 (C-N),1580 (NH bend), 3380 (NH stretch), 1670 (C=O)	4.2(s,2H,CH2),3.85(S,3H,OCH_3)7.80(s,1H,NH),9.35(s,1H,NH-amide),7.28-8.07(m,8H,Ar)
T_3	H	NO_2	H	$C_{16}H_{14}N_6O_3$ (338.3g)	174-176°C (56.08%)	3109 (Ar-H), 1342 (C-N),1627 (NH bend), 3273 (NH stretch), 1695 (C=O)	4.3(s,2H,CH2),7.72(s,1H,NH), 9.26(s,1H,NH-amide),7.44-8.17(m,9H,Ar)
T_4	H	Cl	H	$C_{16}H_{14}ClN_5O$ (327.8g)	94-96°C (56.08%)	3120 (Ar-H), 1280 (C-N),1560 (NH bend), 3340 (NH stretch), 1660 (C=O)	4.4(s,2H,CH2),8.32(s,1H,NH), 8.36(s,1H,NH-amide),7.36-8.07(m,9H,Ar)
T_5	NO_2	H	H	$C_{16}H_{14}N_6O_3$ (338.3g)	85-87°C (43.75%)	3156 (Ar-H), 1306 (C-N),1598 (NH bend), 3410 (NH stretch), 1676 (C=O)	4.2(s,2H,CH2),7.69(s,1H,NH), 8.67(s,1H,NH-amide),7.36-8.53(m,9H,Ar)

Step-3: Synthesis of N-(substituted phenyl)-2-[5-phenyl-2H-1, 2, 4-triazol-3ylamino] acetamide (T_1-T_5).

A solution of the 2-chloro-N-substituted-phenyl-acetamide (0.01mol) in dioxane (5ml) was added drop wise to a mixture of compound 1 (1.6g, 0.01 mol), pyridine (1.2ml, 0.015 mol) and dioxane (10ml) with constant stirring at 0-5^{o}C for 30min. The temperature was raised to 50 ^{o}C and further stirred for 7 hours. The mixture was then poured in to water (50ml) and the formed precipitate was filtered, washed with water and recrystallized from methanol (Scheme 3). Table -02 summarizes the physical and analytical data of compounds.

ANTICONVULSANT ACTIVITY[12]:

The compounds were screened for their anticonvulsant activity by electroshock seizure method (MES).Male Albino rats, (150-250g) were weighed and divided in to seven groups of 4 animals each. Of the seven groups, one group was used as control, one group for phenytoin (standard) and the remaining five groups were used to study the effect of synthesized compounds. The animals were kept at room temperature (25–30 °C) on an adequate diet and allowed free access to food and water except during the short time they were removed from the cages for testing. All the experimental protocols were carried out with the permission from Institutional Animal Ethics Committee.

The suspensions of the compound were prepared in 3% acacia in distilled water. The controlled animals were treated with 0.5ml acacia suspension (solvent control) orally. An electric shock of 150 mA strength for 0.2 sec was applied to the animals from an electroconvulsiometer by means of an ear electrode, at 0, 30, 60, 90, 120, 150, 180 minutes after drug administration. The time (in sec) spent by the animals in each phase of the convulsions (tonic flexion, tonic extension, clonus and stupor) were noted (Table-03). A reduction or abolition of tonic extensor phase is considered as anticonvulsant property of a drug. The results were stastically compared by analysis of variance (Table-04).

TABLE NO- 03: THE EFFECTS OF SYNTHESIZED COMPOUND ON TONIC EXTENSOR PHASE OF CONVULSION IN ALBINO RATS

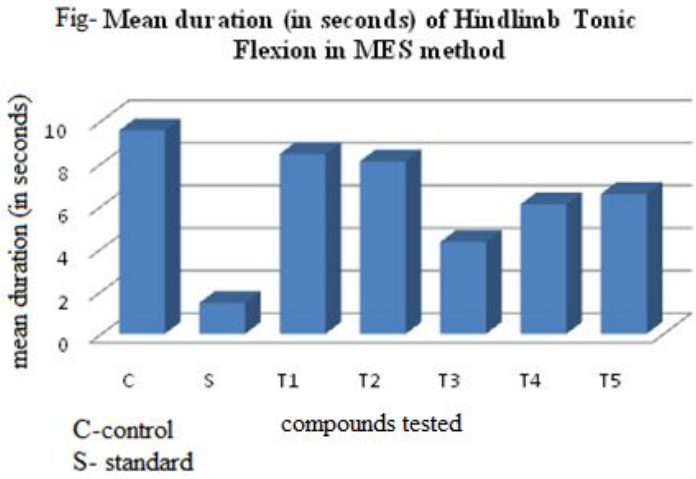
Sl N	Treatment	Avg .Wt	Dose mg/Kg	Hind limb extension (in seconds)						
				0	30	60	90	120	150	180
1.	Control	190	0.5ml of acacia suspension	11	10.2	9.6	9.8	9.6	9.2	7.4
2.	Phenyto	210	30	10.	0.0	0.0	0.0	0.0	0.0	0.0
3.	T1	180	30	12	8.5	7	6.8	8.0	7.8	9
4.	T2	190	30	11.	9.6	9.0	8.0	4.0	7.5	7.0
5.	T3	185	30	9.8	7.0	4.4	3.0	0.0	2.0	4.0
6.	T4	188	30	10	7.5	5.0	3.6	4.5	4.0	8
7.	T5	200	30	8.8	7.8	8.2	3.6	1.2	7.0	9.4

m-minutes

TABLE NO-04: COMPARISON OF MEAN & SE VALUES OF HIND LIMB TONIC FLEXION IN MES METHOD

Sl.No	Treatment	Mean ± SEM	P Value
1.	control	9.54 ± 0.566	----
2.	Standard	1.45 ± 6.880**	0.007
3.	T_1 (30mg/Kg)	8.44 ± 1.416^{ns}	0.329
4.	T_2(30mg/Kg)	8.10 ± 2.599^{ns}	0.312
5.	T_3(30mg/Kg)	4.31 ± 4.868*	0.022
6.	T_4(30mg/Kg)	6.08 ± 2.716*	0.041
7.	T_5(30mg/Kg)	6.57 ± 4.242^{ns}	0.115

*P < 0.05 (significant)
**P < 0.01(highly significant)
ns- not satisfactory



RESULT AND DISCUSSION:

The synthesized compounds (T_1-T_5) were screened for anticonvulsant activity by MES method and were compared with that of control for anticonvulsant activity. Among the synthesized compounds (T_1-T_5), T_3 and T_4 were found to be active as they reduced the time of extensor phase compared to control and the values are stastically significant compared to control. The remaining compounds T_1, T_2 and T_3 did not show stastically significant anticonvulsant activity in the parameter tested.

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