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Synthesis and anticonvulsant activity of 1-[(4, 5-dihydro-5-phenyl-3-(phenylamino)pyrazol-1-yl)]ethanone derivatives

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Abstract

In present study a series of chalcones of anilide and their corresponding product 1-[(4,5-dihydro-5-phenyl-3-(phenylamino)pyrazol-1-yl)]ethanone derivatives I-VI were synthesized and evaluated for their anticonvulsant activity against electric shock induced convulsion method in rat at a dose of 125 mg/kg and 250 mg/kg intraperitonially. The structures of compounds were confirmed by IR, H^1 NMR and Mass spectroscopy. The compounds of this series (III) and (V) were found to be most potent, which have shown higher percent of anti convulsant activity. Phenytoin was taken as reference drug. Their pharmacophoric groups are similar and the possible structure of suitable fused heterocyclic could be accepted to give anti convulsant activity.

Key word: Pyrazole derivatives, Anticonvulsant activity, Chalcones, *S*pectroscopy

Introduction

Many natural and synthetic products containing heterocyclic ring such as Pyrazol, the potent pharmacodynamic nucleus has been reported to possess a wide variety of biological Activity viz :anti-inflammatory[1], cardio vascular[2] and antibacterial activities[3]. Furthermore substitution on heterocyclic moiety at phenyl 2, 4 positions markedly induced the anticonvulsant activity. The conventional synthesis by Claisen Smidth condensation reaction of acetanilide with different substituted aromatic aldehydes. Encouraged by these observations we synthesized newer heterocyclic pyrazol derivatives in the hope of obtaining better anti convulsant agent. From a

structurally simple group of compounds, chalcons have displayed an impressive array of biological Activities, among which anti malarial[4], anti protozoal[5], anti inflammatory[6] and immunomodulatory[7] has been reported to possess varies biological activities.

These compounds obtained by convenient synthetic method in Ist step. The relatively simple structure and high affinity of chalcones towards colchicines binding site is because of similarity of the two-aryl group where unsaturated carbon-carbon double bond gets cyclized in synthesis of pyrazol-1-yl ethanone derivatives.These are to be inhibiting neural transmission effect. These observations places new emphasis on the need of as well as search for alternative new and more effective anticonvulsant with broad spectrum. In the interest of above, we planed to synthesize a system, which combines both bioactive chalconylanilide and pyrazol-1-yl ethanone derivatives to give a compact like structure of title compounds[8].

A structural variant of this drug may be conceived of possessing chalconylanilide moiety with attached phenyl rings and obtained potentially useful molecule. The biological activity of chalcones may be due to >C=0 linkage at nucleus of chalconylanilide and activity of 4,5 di hydro pyrazol-1-yl ethanone derivatives were may be due to –C-N = N- linkage. pyrazol derivatives have attracted considerable attention as they were also endowed with wide range of pharmaceutical activities[9-11]. The present methodology bears the merits of reduced worthwhile to synthesize the title compounds, as they appeared to be highly promising. The structures of all the compounds have been illustrated on the basis of analytical and spectral data.

Materials and Methods

General Procedure:

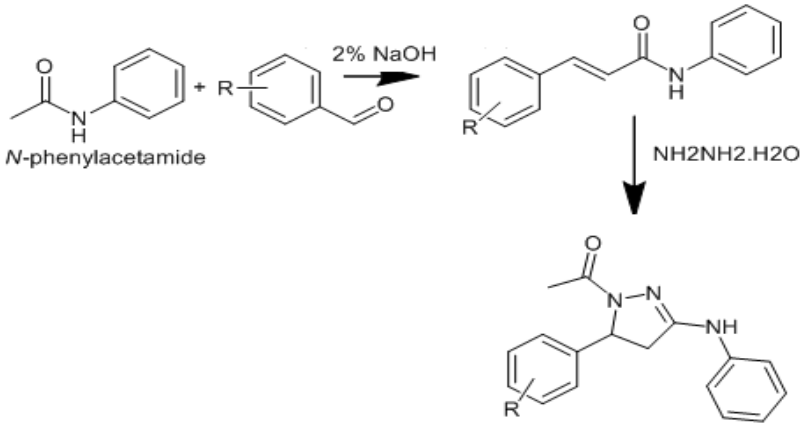
Step- I : In a clean and dry flat bottom flask (500ml) placed solution of acetanilide (0.01 mol) in methanol (dry 50 ml), substituted benzeldehyde (0.01 mol) were added in presence of 2% NaOH solution (5 ml). The reaction mixture was stirred for 10-12 hrs. at room temperature. The solvent was distilled off and crude product poured into ice water. The solid obtained, was washed with water and recrystallized from methanol.

Step - II : In clean and dry round bottom flask (500ml) took product obtained in stepI (0.01 mol) in absolute ethanol then add hydrazine hydrate 99% (0.02 mol) and few drops of glacial acetic acid. The reaction mixture was refluxed for 6–8 hr. The excess of solvent was distilled off and crude product poured into ice water, the separated solid were filtered and recrystallized from methanol.

3-chalconylanilides were condensed according to Claisen-Schmidt reaction mechanism. The condensation of substituted aromatic aldehydes, having no α-hydrogen, with ketone having active hydrogen, in the presence of 2% alkali(2% NaOH) solution to give-α, β-unsaturated ketone is called as Claisen-Schmidt or Claisen reaction. Condensation is catalyzed by sodium ethoxide. The ethoxide ion from sodium ethoxide removes a proton from a molecule of acetanilide to give the carbanion. The carbanion added to the carbonyl group of the second molecule of substituted benzeldehyde[12]. Oxygen is more electronegative than carbon which attracts the electron produced have slightly **-ve** charge. Both involve nucleophilic attack by carbanion on an electron-deficient carbonyl carbon. However, in the aldol condensation, nucleophilic attack results in addition of aldehyde and ketones and alcoholic intermediate formed

in further step, donate their electrons; withdraw the proton furnished in carbon–carbon double bond. Unsaturated hydrocarbons with aromatic substitution with single carbonyl group are called chalcones. R-substituted chalconylanilide compounds were cyclized in acidic medium with addition of hydrazine hydrate removes water molecules furnished final compounds 4, 5-dihydropyrazol-1-yl ethanone derivatives successfully.

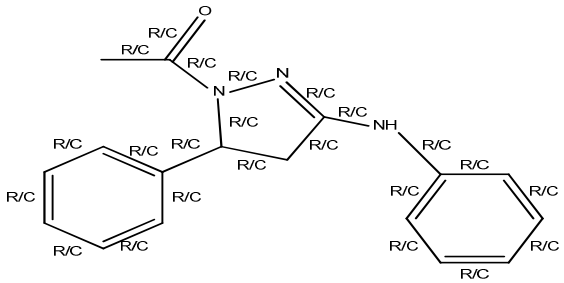
Fig. 1: Reaction Scheme



Characterization of the compounds-

The 4, 5-dihydropyrazol-1-yl ethanone derivatives are synthesized by the reaction between substituted benzeldehyde and acetanilide in presence of base.

Table 1. Physiochemical Properties of synthesized compounds



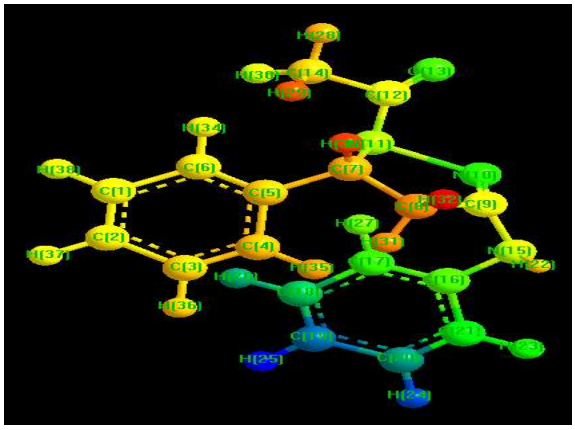
Compd.	Mol. formula	M. wt.	λ max nm	M.P.(°C)	% yield	R*f* value
I	$C_{19}H_{22}N_4O$	322	390.8	213	75	0.76
II	$C_{17}H_{16}N_4O_3$	324	336.0	93	65	0.62
III	$C_{17}H_{16}N_3OCl$	313.5	257.5	112	70	0.7
IV	$C_{17}H_{17}N_3O$	279	245.5	102	60	0.66
V	$C_{17}H_{15}N_3OCl_2$	348	308.0	107	74	0.86
VI	$C_{17}H_{17}N_3O_2$	295	321.5	124	67	0.58

The reaction scheme is as figure 1. All Melting points (m.p.) were determined in open capillaries on Jindal melting point apparatus and are uncorrected. The purity of the compounds was routinely checked by thin layer chromatography (TLC) using silica gel G (Merck). The instruments used for spectroscopic data are IR: Jasco IR-470 spectrophotometer (KBr) with diffuse reflectance method; MS-JEOL SX102 Mass spectroscopy by using Argon/Xenone (6Kv, 10mA) as the FAB gas and m-nitro benzyl alcohol (NBA) as the matrix. H^1NMR: JEOL GSX-400, 60MHz spectrometer in $CDCl_3$, TMS (tetra methyl saline) as an internal standard.

Table : 2 Characterization of Synthesized Compounds

Comp name	Spectroscopic data
I	IR(KBr/cm^{-1})=3450(N-H), 3010 (Ar.C-H), 2930 (C-H), 1770 (C=O), 1580 (C=N), 1670 (Ar.C=C), 1510 (N-N), 2880 (C-H); mass(m/e)= 236, 250, 293, 294, 309; Elemental analysis for $C_{34}H_{34}N_4O_4$ Calculated C 72.58; H 6.09; N 9.96 found C 72.11; H 5.78; N 9.62; O 11.02
II	IR(KBr/cm^{-1})=3460 (N-H), 3028 (Ar.C-H), 2941 (C-H), 1750 (C=O), 1560 (C=N), 1650 (Ar.C–C), 1530 (N-N), 1650 (N=O); Mass(m/e)= 314, 332, 450; Elemental analysis for $C_{34}H_{34}N_4O_4$ Calculated C 72.58; H 6.09; N 9.96 found C 72.11; H 5.78; N 9.62; O 11.02
III	IR(KBr/cm^{-1})=3470 (N-H), 3030(Ar.C-H), 2910 (C-H), 1740 (C=O), 1550 (C=N), 1655 (Aromatic C-C), 1550 (N-N), 892 (C-Cl); Mass(m/e)= 257, 271, 298, 329, 424; Elemental analysis for $C_{34}H_{34}N_4O_4$ Calculated C 72.58; H 6.09; N 9.96 found C 72.11; H 5.78; N 9.62; O 11.02
IV	IR(KBr/cm^{-1})=3420 (N-H), 3000 (Ar-CH), 2950 (C-H), 1720 (C=O), 1540 (C=N), 1540 (Ar. C-C), 1550 (N-N); Mass(m/e)= 227, 289, 406, 433; Elemental analysis for $C_{34}H_{34}N_4O_4$ Calculated C 72.58; H 6.09; N 9.96 found C 72.11; H 5.78; N 9.62; O 11.02
V	IR(KBr/cm^{-1})=3130 (N-H), 3020 (Ar.C-H), 2940 (CH_2)1750 (C=O), 1660 (C=N), 1600 (C-N), 1510 (Ar. C-C), 1515 (N-N), 1095 (Ar. C-Cl); Mass(m/e)= 391, 406, 449; Elemental analysis for $C_{34}H_{34}N_4O_4$ Calculated C 72.58; H 6.09; N 9.96 found C 72.11; H 5.78; N 9.62; O 11.02
VI	IR(KBr/cm^{-1})=3140 (N-H), 3040 (Ar.CH), 2900 (CH_2)1730 (C=O), 1630 (C=N), 1620 (C-N)1540 (Ar. C-C), 1530 (N-N), 3077 (Ar.C-OH); Mass(m/e)= 220, 307, 411; Elemental analysis for $C_{34}H_{34}N_4O_4$ Calculated C 72.58; H 6.09; N 9.96 found C 72.11; H 5.78; N 9.62; O 11.02

Fig: 2. Energy minima three dimension of synthesized title compound



H^1NMR, C^{13}NMR and IR spectra were consistent with the assigned structure. Elemental analysis(C, H, N analysis) were done on a CHN rapid analyser. All the compounds gave satisfactory analysis with in 0.4 of the expected values.

Physiochemical Properties and analytical data of all compounds are given in **table .1&2.**

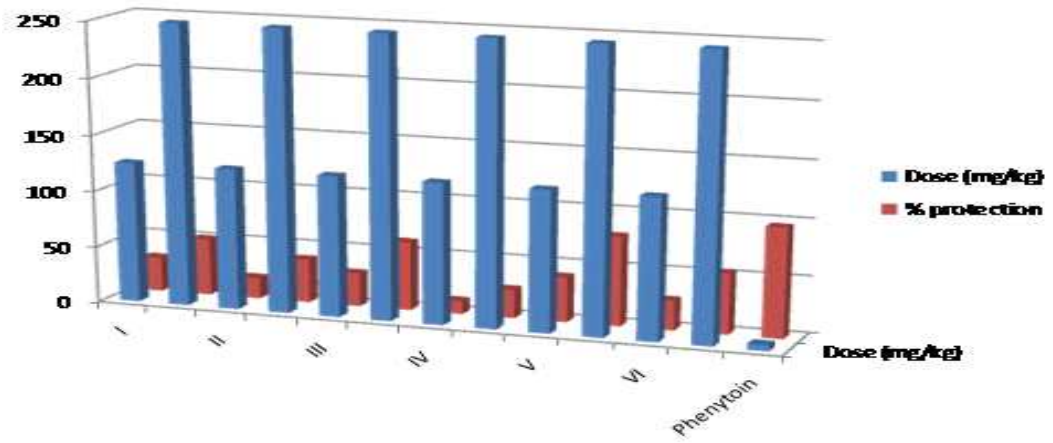
Anticonvulsant Screening

The anti epileptic activity was determined by MES (electroshock induced convulsions) method. The protocol was approved by animal ethical committee (A70/ac/08/CPCSEA/88). The synthesized compounds were dissolved in DMSO to prepare stock solution of concentration 5mg/ml and 2.5 mg/ml. These stock solutions were utilized for the evaluation of the anti epileptic activity. Anti-consultant activity was determined against electric shock induced seizure in mice 25-30 gm of either sex. Two group of 12 animals each was divided and marked to serve as control and test group. To the control group, vehicle DMSO was injected instead of the test compounds. To the test group, the synthesized compounds were administered in two doses: 125 mg/kg body weight and 250 mg/kg body weight intra peritoneally. Phenytoin (5 mg/kg) was used as reference for the evaluation of the anti epileptic activity. After 30 minutes of the injection of the test compounds, both the groups were injected, and then produced current (electric shock). Each animal in the test group as well as the control group, occurrence of convulsion was observed for a period of 60 minutes. The number of protected animals in treated groups was calculated as percentage of affected animals in the control group.

Table : 3. Anticonvulsant activity of the synthesized compound

Compounds	Dose (mg/kg)	% protection
I	125	30.62
	250	50.72
II	125	18.51
	250	38.80
III	125	29.66
	250	61.03
IV	125	11.51
	250	25.30
V	125	39.95
	250	79.20
VI	125	26.30
	250	53.66
Phenytoin	5	96.5

Fig. : 3 Graphical representation of anticonvulsant activity



Results and Discussion

4, 5-dihydropyrazol-1-yl ethanone derivatives were synthesized in moderate yields by reacting acetanilide with substituted benzaldehyde. It obtained significant yield of all synthesized compounds. The structure confirmation of the compounds is done by IR, UV-visible and mass spectroscopy. All the obtained spectroscopic data are given in Table. 2. All the synthesized compounds shows peak in the IR spectrum at wave number (cm^{-1}) - 3200, 3160, 2980, 2890, 1760, 1610, 1580, 1370 and 1095. These peaks are characteristics of N-H, C-H (aromatic), C-H, C=O, C=N and C-C stretching and C–H bending. Mass spectrum peaks of compound I-VI found at m/z (236, 250, 293, 294, 309), (314, 332, 450), (257, 271, 298, 329, 424), (391, 406, 449), (220, 307, 411) respectively.

All the synthesized 4, 5-dihydropyrazol-1-yl ethanone derivatives show antiepileptic activity by electric shock method. The compounds are found to be active against the epilepsy in comparatively higher dose than that required for the activity against epilepsy in most of cases. Antiepileptic activity of the synthesized compound and the reference drug shown in table 5, indicate that compounds I-VI inhibit *in vivo* transmission of epilepsy. Compounds III and V are found to be the most potent compounds of all synthesized compounds. Other remaining I, II, IV and VI compounds are found to be almost equipotent to the as usual synthesized compounds. Chlorine substitution at 2-position of phenyl plays an important role in the anti-convulsant activity to the compounds. In addition to the compounds V at the position of 2, 4 of the same phenyl ring substituted at this position enhance the activity of the compound against convulsion. The results also indicate that the substitution of an aryl derivative at the 2-position and 4-position of chlorine lead to more potent anticonvulsant agent as compared to the other groups at R-substitutions. 4, 5-dihydropyrazol-1-yl ethanone derivatives showed comparable activity.

Conclusion

The study of epileptic condition for over last 30 years has led us to the basic understanding of the physiology and the pathological process helped in elucidating the mode of action of several antiepileptic drugs such as valproic acid, gabapentin, succinamide etc. and revealed newer

targets for the development of novel therapeutic agents. The study of various newer compounds by chemists all over the world has lead to the discovery of napthyridine derivatives as novel anticonvulsant compounds. The present work involved the synthesis of 4, 5-dihydropyrazol-1-yl ethanone derivatives then characterization and *in-vivo* evaluation of anticonvulsant activity given in table 3. Overall synthesized and physico-chemical parameters of 4, 5-dihydropyrazol-1-yl ethanone derivatives are given in table1. Characterization of the synthesized compounds was carried out by determining their melting points, UV absorption maximum (λ_{max}), IR Spectra, Mass spectra and R_f value. The compounds were evaluated for anticonvulsant activity by electric shock method. All the synthesized compounds possess anticonvulsant activity. Chlorine substitution at the position–2 in compound II and position–2,4 in compound V have significant anticonvulsant activity. In conclusion, as 4, 5-dihydropyrazol-1-yl ethanone derivatives cyclic analogues showed comparable activity. We may say that their pharmacophoric groups are similar and the possible structure of suitable fused heterocyclic could be accepted to give anticonvulsant activity and may have various pharmacological activities.

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