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Original Article

Synthesis and Anticonvulsant Activity of Some Novel Hydrazone Derivatives

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Abstract

In the present study a series of hydrazone derivatves (III, IIIa, IV) were synthesized and characterized by their spectral data and screened for anticonvulsant properties against seizures induced by maximal electroshock (MES) and toxicity screening. The purity of the newer compounds was checked by m.p. and TLC analysis. The structures of these compounds were established on the basis of their spectral (FT-IR, ^{1}H-NMR) data analysis. These newly synthesized derivatives of phenytoin were evaluated in terms of anticonvulsant activity. Some of the investigated compounds showed significant anticonvulsant activity. Some of these may be chosen as a prototype for development of new anticonvulsants.

Keywords: Hydrazones, Anticonvulsant, Epilepsy.

Introduction

Epilepsy is a common disorder of the central nervous system (CNS). Approximately 0.4%~1% of the population worldwide suffers from this disorder. The conventional antiepileptic drugs suffer from a range of side effects. Furthermore, the convulsions of 25% of epileptics are inadequately controlled by currently available medications. During the past decade several new drugs were approved, e.g., felbamate, fosphenytoin, gabapentin, lamotrigine, vigabatrin and zonisamide. However none of the available antiepileptic drug is ideal as they can be associated with chronic and adverse side effects. Thus the search for new anticonvulsant drugs continues to be an active area of investigation in medicinal chemistry. Hydrazones and their derivatives constitute a versatile class of compounds in organic chemistry. These compounds have interesting biological properties(1),(5), such as anti-inflammatory(7), analgesic(8), anticonvulsant, antituberculosis(3),(10), antitumor, anti-HIV and antimicrobial activity(2),(6),(7),(9). Hydrazones are important compounds for drug design, as possible ligands for metal complexes, organocatalysis and also for the synthesis of heterocyclic compounds. Hydrazone has been prepared because during initial screening it has shown activity in the MES test. In view of potent anticonvulsant activity of hydrazone, we have synthesized a novel series hydrazone derivative by following reaction and evaluate them for their anticonvulsant activity.

Materials and Methods

Chemistry

The entire chemicals used were procured from Qualigens, Himedia and C.D.H. Purity of starting

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materials used for reaction was confirmed by checking their melting point or boiling point and by thin layer chromatography. Melting points were determined in open capillary tube using precision melting point apparatus and uncorrected. FT-IR (KBr) spectra were recorded on "SHIMADZU FT-IR 8400S" spectrophotometer from GLA University, Institute Of Pharmaceutical Research, Mathura (UP). 1H NMR spectra of synthesized compounds were recorded on "FTNMR AVANCE" spectrometer in DMSO using TMS as internal standard (chemical shift ä ppm) at Punjab University, Chandigarh. CHN analyzer was recorded on "ELEMENTOR" at Punjab University, Chandigarh. Physical properties of the synthesized compounds are listed in **Table 1** whereas scheme of synthesis is given in **Figure 1, 2** and **3.**

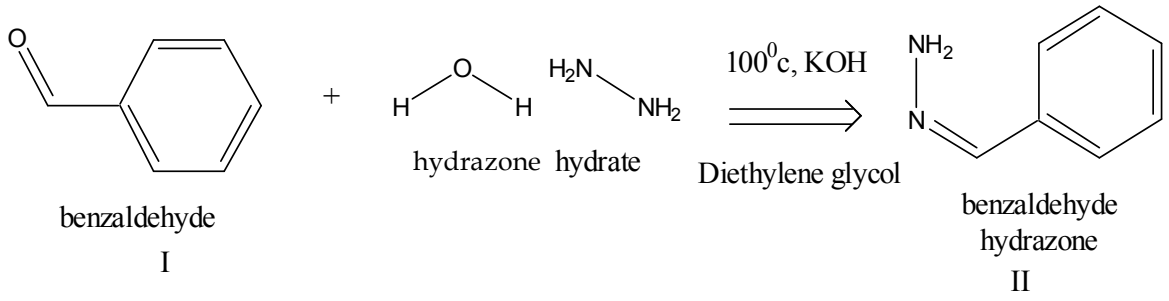


Figure 1: Synthesis of Benzaldehyde Hydrazone.

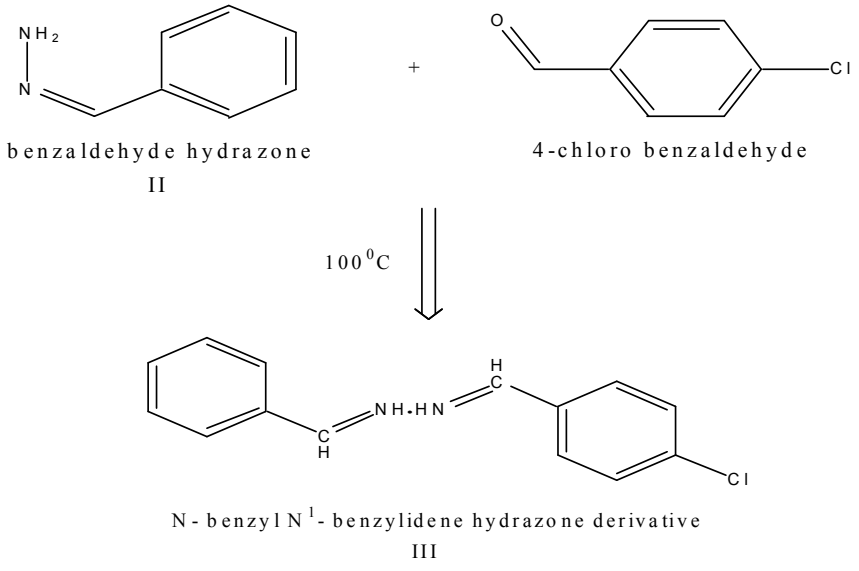
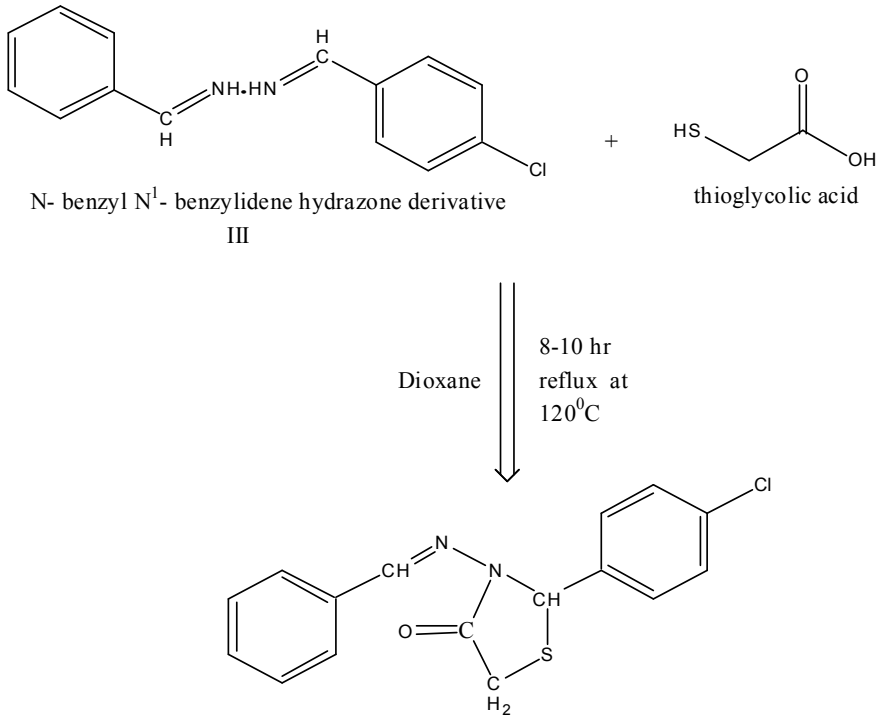


Fig. 2: Scheme 1 Synthesis of N {2 Substituted phenyl} 4 chloro benzyl hydrazone.



N- benzyl N[1]- benzylidene hydrazone derivative

III

+ thioglycolic acid

N[1] [2 (substituted phenyl) 4-oxo -1,3-thiazolan-3-yl] 4-chloro benzyl hydrazone

IV

Fig. 3: Scheme 2 Synthesis of N1 [2 (substituted phenyl) 4-oxo-1,3-thiazolan-3-yl] 4-chloro benzyl hydrazone.

General procedure for the Synthesis of Benzaldehyde hydrazone.

Intially placed 9 g. of benzaldehyde, 60 ml. of diethylene glycol, 8 ml of 90% hydrazine hydrate and 10 g. of potassium hydroxide pellets in a 100 ml round bottom flask. After that warmed the mixture on a boiling water bath until most of the potassium hydroxide has dissolved and then refluxed for 1 hour.

General procedure for the Synthesis of N {2 Substituted phenyl}4 chloro benzyl hydrazone.(2)

In the second step a mixture of previously synthesized hydrazone (0.005 mol) and different substituted arylaldehydes (0.005 mol) was taken in absolute ethanol (15ml) as solvent in round bottom flask and refluxed for 2-3 hrs, on cooling a solid mass separated out that was filtered and then recrystalized from ethanol.

General procedure for the Synthesis of N1 [2(substituted phenyl) 4oxo,1, 3thiazolan3yl] 4-chloro benzyl hydrazone.(4)

At last in a round bottom flask the compound (0.002mol) in dioxane (50ml) was taken and thioglycolic acid (0.002mol) was added to it and the mixture was refluxed for 8-10 hrs at 120⁰C, after that the reaction mixture was concentrated on crushed ice and neutralized with 2% sodium bicarbonate solution, the solid mass that separated out was filtered and recrystallized from ethanol.

Table 1. Physicochemical characteristics of hydrazone derivatives.

Compound	(r) substitution	% yield	Molecular formula	Molecular weight	Rf value	Melting point °c
III	Para Chloro benzaldehyde	60	$C_{14}H_{11}N_2Cl$	242.5	0.84	127
IIIa	3 methoxy 4 hydroxy benzaldehyde	72	$C_{15}H_{14}N_2O_2$	254	0.45	105
IV	4 oxo 3 thiazolanyl p chlorobenzaldehyde	74	$C_{13}H_{13}ClN_2OS$	280.5	0.88	150

Spectral Data

N^1[2(substituted phenyl) 4oxo,1, 3thiazolan3yl] 4 chloro benzyl hydrazone. {IV}

IR (KBr, cm^{-1}): Aromatic-H at 3050 cm^{-1}, Ar-(C=C) at 1624 cm^{-1}, 1580 cm^{-1}, 1500 cm^{-1},1450 cm^{-1}, Cl-752.24 cm^{-1}, Aromatic mono substitution at 692.44 cm^{-1}, C=N at 1710 cm^{-1}; ^{1}HNMR 8.509 (3, 1H), 7.330 (4, 1H, J=6.887, J=1.406, J=1.405), 7.335 (5, 1H, J=7.410, J=6.887, J=5.446, J=0.000), 7.335 (6, 1H, J=7.412, J=6.887, J=5.453, J=0.000), Anal. Calcd. For $C_{13}H_{13}ClN_2OS$: C, 55.61,H,4.67, Cl, 12.64, N, 9.98, S, 11.40, O, 5.70;

N benzyl N^1{4 chloro benzylidene}hydrazone. {III}

IR (KBr, cm^{-1}): Aromatic-H at 3000 cm^{-1}, Ar-(C=C) at 1614 cm^{-1}, 1563 cm^{-1}, 1519 cm^{-1},1454 cm^{-1}, C-C at 1556 cm^1, Cl-744 cm^{-1}, Aromatic mono substitution at 690 cm^{-1}, C=N at 1768 cm^{-1}, C=O at 1643 cm^{-1}, C-S at 731 cm^{-1}, N-H at 3321 cm^{-1}; ^{1}HNMR 8.558 (2, 1H), 8.612 (3, 1H), 7.471 (4, 1H, J=7.546, J=7.438, J=1.423, J=1.418), 7.538 (5, 1H, J=8.196, J=7.546, J=2.074, J=0.440), 7.393 (6, 1H, J=7.775, J=7.438, J=2.074), Anal. Calcd. For $C_{14}H_{11}N_2Cl$: C, 69.27, H, 4.57, Cl, 14.62, N, 11.55;

N benzyl N^1{3 methoxy 4 hydroxy benzylidene}hydrazone. {IIIa}

IR (KBr, cm^{-1}): Aromatic-H at 3020 cm^{-1}, Ar-(C=C) at 1600 cm^{-1}, 1570 cm^{-1}, 1450 cm^{-1},1410 cm^{-1}, OH-3650 cm^{-1}, Aromatic mono substitution at 710 cm^{-1}, C=N at 1710 cm^{-1}, OCH3 (C-O) at 1090 cm^{-1}, OCH3 (C-H) at 2895-2885 cm^{-1}; ^{1}HNMR 1.407 (1, 3H), 1.407 (2, 3H), 1.407 (3, 3H), 8.502 (5, 1H), 8.605 (6, 1H), 7.284 (7, 1H, , J=7.958, J=1.420, J=1.395), 7.363 (8, 1H, J=7.958, J=7.643, J=0.548, J=0.000), 7.363 (9, 1H, J=7.958, J=7.827, J=0.728, J=0.000), 8.085 (10, 1H, J=7.643, J=1.451, J=1.395, J=0.728), 8.123 (11, 1H, J=7.827, J=1.451, J=1.420, J=0.548), 7.532 (12, 1H, J=8.427, J=1.780), 6.839 (13, 1H, J=8.427, J=1.631), 7.265 (14, 1H, J=1.780, J=1.631) ,Anal. Calcd. For $C_{14}H_{11}N_2Cl$: C, 70.84, H, 5.55, N, 11.02, O, 12.59;

Pharmacology

All the compounds were screened for their anticonvulsant activity by electroshock seizure method. Albino rats of Wistar strains, weighing 100-200g, of either sex were used. . Accommodation conditions were maintained at 200C and the number of animals were used in different experiments. Polyethylene glycol was used for dissolving the test compounds in rotarod test. The control experiments were performed with solvents alone. Four animals were used in the control test. The test compounds were administered intraperitoneally to rat, at doses of 30.100,300 mg/Kg to 1 to 4 rat. The anticovulsant activity of III, IIIa, IV has been detailed in Table No. 2.

Anticonvulsant Screening

Maximal Electroshock Seizure Test (MES)(11)

Maximal seizures were elicited by a 60Hz alternating current of 50mA intensity delivered for 0.2 seconds via corneal electrodes.. A drop of 0.9% w/v sodium chloride instilled in each eye prior to application of electrodes assured adequate electrical contact. Test solutions of all the compounds were prepared in 30% v/v polyethylene glycol 400 (PEG 400) and animals were dosed intraperitoneally 30 min prior to testing. Abolition of the hind limb tonic extension component of the seizure was defined as protection in the MES test.

Result and Discussion

The anticonvulsant activity studies following MES method revealed that, the compounds evaluated **III,**

IIIa, **IV** have found to be possessing significant anticonvulsant activity. The compounds that exhibited most potent anti-MES activity included **IIIa** which have activity comparable with phenytoin. The compounds **IV** were found to be more lipophilic having potent anticonvulsant activity. The other compounds **IIIa** were also lipophilic having same potency. The compounds **III,** are less lipophilic and are less active in MES test. The present study reveals the anticonvulsant potential of fused 4-thiazolidinone derivatives. The results indicated that electron withdrawal group in position 2 and 4 [disubstituted phenyl-4-oxo-1,3-thiazolan-3-yl]-4 chloro hydrazone(12) was essential for the activity. Thus a number of novel *N* 1-[2-(substituted phenyl)-4-oxo-1,3-thiazolan-3-yl]- 4 chloro hydrazone derivatives exhibited anticonvulsant Screening by using MES test. The compounds N benzyl N1 {4 chloro benzylidene} hydrazone. {III} were lipophilic but were less active in MES test. Some of the compounds have shown higher degree of protection and obviously may have future commitment.

Table : 2 Anticonvulsant activity (Maximal electroshock induced convulsions)

Sr no.	Treatment	Duration of tonic flexion (sec)	Duration of tonicextensor (sec)	%Protection (24h)
1	Control(propylene glycol 400)	NO	14.17 ± 0.872	16.66
2	Phenytoin(25 mg/kg)	5.83 ± 0.9804	NO ***	100
3	III(30 mg/kg)	2.9 ± 0.3	8.3 ± 0.577	33.33
4	III(100 mg/kg)	3.4 ± 0.7	7.1 ± 1.5	49.99
5	III(300 mg/kg)	3.1±0.3	6.2±0.4***	66.66
6	IIIa(30 mg/kg)	3.2±0.2	8.1±0.5***	60.0
7	IIIa(100 mg/kg)	3.5 ± 0.4	7.83 ± 0.60*	83.33
8	IIIa(300 mg/kg)	3.3±0.4	7.3±0.4***	65.34
9	IV(30 mg/kg)	2.4±0.5	8.4±0.2***	70.77
10	IV(100 mg/kg)	3.2±0.3	9.7±0.4***	80.12
11	IV(300 mg/kg)	2.3±0.2	7.6±0.3***	63.66

Values are expressed as mean ± SEM, from 6 mice. Significant at *P<0.05 and ***P<0.001 as compare to control using one way ANOVA followed by Tukey - kramer's post hoc test.

Conclusion

In this study synthesized hydrazones mimicking the effects of anti epileptic drug by reducing tonic convulsion and mortality. It also reveals that those compounds which was more lipophilic in nature tends to have better anticonvulsant effects. The present research will guide our future development of potent and selective anticonvulsant drugs. However further studies on other species of animals is recommended, and comparison with other antiepileptic drugs in different species need to perform to fill the future need of model drug.

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