(Research Article)

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Synthesis, spectral and biological evaluation of some hydrazone Derivatives

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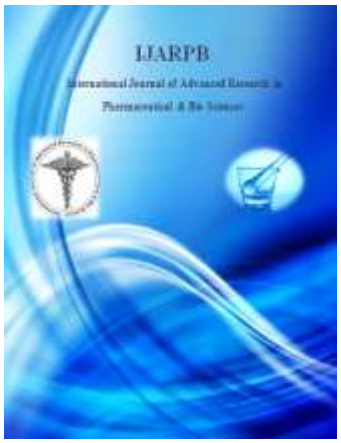

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ABSTRACT
Schiff's bases, hydrazone and guanidine derivatives are important heterocyclic molecules. The attempt to synthesize schiff bases of Phenyl acetic acid were successfully carried out as per the scheme mentioned. The synthesized compounds are primarily characterized by running T.L.C. and melting point analysis. The structures of the compounds synthesized are confirmed by I.R. and ^{1}HNMR. All compounds showed mild to moderate anti-inflammatory and anticonvulsant activity.

KEY WORDS- Schiff's base derivatives, Hydrazones, hydrazide-hydrazones, biological activity.

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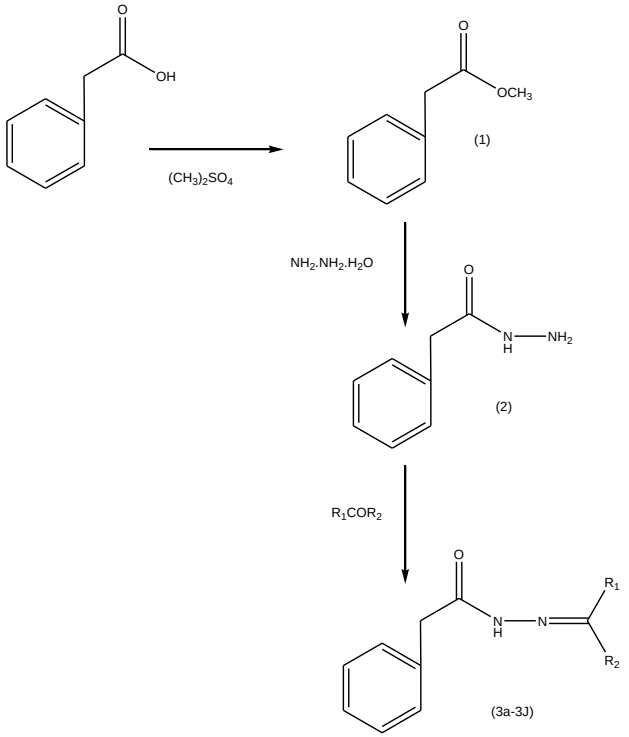
INTRODUCTION

Schiff bases, hydrazone and guanidine derivatives are important heterocyclic molecules. Schiffs bases, hydrazone and guanidine derivatives posses various types of biological activities such as anti-inflammatory, analgesic, anti-microbial, anti-fungal, anti-malarial activity etc. Schiffs bases are also employed as legand for the complexation of metal ions.Tempted by a variety of biological activities exhibited by Schiffs bases,hydrazone and guanidine derivatives and in continuation of earlier efforts in search of potent molecules exhibiting anti-inflammatory and analgesic activities a number of novel schiffs bases, hydrazone and guanidine derivatives have been synthesized[1-12].



Scheme: 1

MATERIALS AND METHODS

General Methodology

All the melting points reported were determined in open capillary tube method and are uncorrected. The IR spectra of the compounds were recorded on Bruker Tensor-27 FTIR spectrophotometer and are expressed in cm^{-1}. The NMR spectra of the compounds were recorded on Bruker DRX-300 spectrometer. The mass spectra of the compounds were recorded on Shimadzu 8201 PC spectrometer.

The progress of the reaction was monitored on precoated silica gel 60 F254 plates (Merck) using different solvent systems. Synthesis and analytical studies of the title compounds were carried out using laboratory grade and analytical grade reagents as the case may be standard procedures or reported methods were followed with or without modification appropriately as and when required.

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Synthesis of methyl 2-phenylacetate (1)

A mixture of phenyl acetic acid (0.003mole) in acetone, dimethyl Sulphate (0.007mole), anhydrous potassium carbonate (0.02mol) was refluxed on a water bath for 2hr with occasional stirring. After the completion of the reaction, the mixture was allowed to cool at room temperature and poured into crushed ice. The dried crude product was recrystallized with methanol. The completion of the reaction was monitored by T.L.C. Solvent system: Chloroform: Methanol(8:2)

Synthesis of 2-phenylacetohydrazide(2)

Methyl 2-phenylacetate (0.01mole) in alcohol was refluxed with hydrazine hydrate (0.01mole) for 8hrs. The reaction mixture was allowed to cool at room temp. by pouring into crushed ice and extracted with chloroform. The chloroform extract was evaporated to dryness in order to get the product and recrystallized by chloroform. The completion of the reaction was monitored by T.L.C. Solvent system: Chloroform: Methanol (8:1)

Synthesis of Schiff's bases of 2-phenylacetohydrazide(3a-3j)

A mixture of equimolar amount of appropriate benzaldehyde and 2-phenyl acetohydrazide were dissolved in methanol then two drops of conc. HCl were added as catalyst and stirred at room temperature for 2-3hr. the reaction mixture was poured into ice and filtered. The crude product so obtained was dried and recrystallized with methanol. Solvent system: Chloroform: Methanol (8:2)

TABLE 1: The physico-chemical data of synthesized compound

Comp.	Mol. Formula	Mol. Wt .	R_f	Colour (Appearance)	m.p. (°C)	λ_{max}
1.	$C_9H_{16}O_2$	156	0.82[a]	Dark brown	70	281.334
2.	$C_8H_{16}ON_2$	130	0.89[b]	Dark yellow	74.5	207.278
3a	$C_{15}H_{13}N_2O_2$	279	0.85[a]	Brown	133	331.806
3b	$C_{15}H_{15}N_2O$	281	0.66[a]	Dark Brown	81	238.976
3c	$C_{15}H_{13}N_3O_2$	267	0.86[a]	Black	52	206.739
3d	$C_{15}H_{13}N_2Ocl$	272	0.95[a]	Brown	61	307.008
3e	$C_{15}H_{13}N_2OCl$	272	0.90[a]	Light brown	60.5	331.806
3f	$C_{13}H_{12}N_2O_2$	228	0.90[a]	Light green	55.5	298.652
3g	$C_{18}H_{20}N_2O_4$	328	0.82[a]	Carbon black	50.5	207.278
3h	$C_{17}H_{17}N_2O_2$	281	0.80[a]	Light brown	71	291.375
3i	$C_{16}H_{16}N_2O_2$	268	0.90[b]	Black	51	286.523
3j	$C_{16}H_{16}N_2O_2$	268	0.85[b]	Black	53	258.329
3k	$C_{16}H_{16}N_2O$	252	0.90[c]	Light brown	61.5	330.805

Solvent System: a. (Chloroform : Methanol 8 :2)
b. (Chloroform : Methanol 8 : 1)
c. (Chloroform : Methanol 9 : 1)

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TABLE 2: Spectral data of the synthesized compounds

Compound	
3a	IR: 3327.32(NH), 3284.88(NH), 2951.19(Ar-CH), 1702.47 (C=O), 1595.18(C=C), 1564.32(C=N), ^{1}H NMR(ppm): 9.8(s,1H,OH), 8.5(s,1H,NH), 7.2-7.8(m,9H,Ar-H), 5.5(s,2H,CH_2), 1.6(s,1H,CH).
3b	IR: 3385.18(NH), 3319.60(NH), 2951.19(Ar-CH), 1697.41(C=O), 1525.74(C=N), ^{1}H NMR(ppm): 8.9(s,1H,NH), 7.7-8.3(m,9H,Ar-H), 7.09(s,2H,CH_2), 1.47(s,1H,CH), 3.1(s,6H,N(CH_3)$_2$).
3c	IR: 3432.87(OH), 3398.09(NH), 3318.59(NH), 3050.26(Ar-CH), 1614. 24(C=O),1529.77(C=N).
3d	IR: 3034.68(NH), 2827.69(Ar-CH), 1648.89(C=O), 1543.64(C=N) , ^{1}H NMR(ppm): 8.6(s,1H,NH), 7.2-8.0(m,9H,Ar-H), 6.7(s,2H,CH_2), 1.2(s1H,CH).
3e	IR: 3564.58(OH), 3105.18(Ar-CH), 3104.44(NH), 1693.38(C=O), 1503.57(C=N), 1125.35(OCH_3).
3f	IR: 3469.70(OH), 3301.91(NH), 3301.91(NH), 3195.91(NH), 3031.89(Ar-CH), 1701.10(C=O), 1546.8(CH).
3g	IR: 3124.95(NH), 2923.24(Ar-CH), 1679.12(C=O), 1632.30(C=N).
3h	IR: 3359.90(NH), 3199.24(NH), 3097.28(Ar-CH), 1696.54(C=O), 1516.19(C=N), 1299.60(N(CH_3)$_2$) , ^{1}H NMR(ppm): 8.3(s1H,NH), 7.2-8.2(m,7H,Ar-H), 7.0(s,2H,CH_2), 4.0(s,9H,OCH_3).
3i	IR: 3591.21(OH), 3369.41(NH), 3249.83(NH), 1701.23(C=O), 1519.80(C=N), 1192.2(OCH_3) , ^{1}H NMR(ppm): 7.8(s,1H,OH), 7.2(s,1H,NH), 6.8-7.35(m,9H,Ar-H), 6.7(s,2H,CH_2), 5.3(s,3H,CH_3), 1.25(s,1H,CH).
3j	IR: 3396.67(OH), 3157.1(NH), 2951.76(Ar-CH), 2896(CH_3)$_3$, 1685.3(C=O), 1630.54(C=N).

BIOLOGICAL ACTIVITY

Anticonvulsant activity:

The anticonvulsant activity was carried out of all the five synthesized amino acid incorporated bicyclo compounds by maximal electric shock method using phenytoin sodium as reference drug. Animals were weighed, numbered and divided into three groups each consisting of 6 rats. One group was used as normal control received dimethyl sulphoxide i.v., second group was standard control received phenytoin sodium at dose of 25mg/kg body wt i.v. and the third group received sample treatment at dose of 25mg/kg body wt. i.v. The corneal electrodes were placed on the cornea of the animal[14]. The whole procedures were repeated with the animals of all the three groups. After 30 min of drug treatment, the animals were subjected to a electric shock of 150 M.A. by convulsiometer for 0.2 sec. The reduction in time or abolition of tonic extensor phase of MES- convulsions was noted.

TABLE 3

COMPOUND	Mean±SEM	%Protection
Control(DMSO)	9.825±0.2658	0
Phenytoin Sod.	1.700 ±0.07071	82.69
3a	6.725±0.4679	31.55
3b	7.200±0.3764	26.71
3c	6.675 ±0.1887	32.06
3d	5.200±0.1155	47.07
3e	4.925±0.6292	49.87
w3f	4.950±0.6455	49.61
3g	5.950±0.6455	39.44
3h	7.050±0.5123	28.24
3i	5.675±0.1931	42.23
3j	5.175±0.1931	47.32

ANTI-INFLAMMATORY ACTIVITY

Anti-inflammatory activity was determined *in vivo* using the carrageenan-induced rat paw edema test. Animals of either sex were divided into seven groups of four each. A solution of 0.1 mL of 1% carrageenan in saline was injected subplantarly into the right hind paw of the rats 1 h after i.p. administration of the compounds. Paw thickness was measured from the ventral to the dorsal surfaces immediately prior to carrageenan injection and then at each hour, up to four hours after the subplantar injection. Edema was calculated as the thickness variation between the carrageenan and control treated paws. Anti-inflammatory activity expressed as the percent of inhibition of the edema when compared with the control group and was calculated by using the formula[12].

% inhibition of edema = $(V_c - V_c / V_c) \times 100$

Where V_t and V_c are the mean paw volumes of the test and control groups, respectively.

TABLE 4

COMPOUND	VOLUME OF EDEMA	% INHIBITION
Control(DMSO)	.09375-±0.00625	0
Diclofenac sodium	.03125±0.00625	66.66
3a	.0500±0.01768	46.69
3b	.0375±0.007217	46.66
3c	.0500±0.01768	46.69
3d	.05625±0.01573	40
3e	.08750±0.007217	56.69
3f	.0500±0.01021	46.66
3g	.05625±0.01573	40
3h	.0375±0.007217	46.66
3i	.0625±0.0375	33.33
3j	.03125±0.00625	66.66

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RESULTS AND DISCUSSION

The synthesis of the title compounds were affected as outlined in the scheme. All the synthesized title compounds were subjected for *in-vivo* anticonvulsant and anti-inflammatory activity. The results showed that substitution with electron withdrawing moiety favours significant reduction in the seizures and substitution with electron donating moiety favours reduction in paw volume.

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