Synthesis, Spectroscopic analysis, Antioxidant, and Anti-bacterial activities of (Z)-4-Chloro-N′-(3-methyl-2r,6c-diphenylpiperdin-4-ylidene) benzohydrazides

TANZEER AHMAD DAR[1], BALASANKAR THIRUNAVUKKARASU[2], KHURSHEED AHMAD DAR[3], AADIL FAROOQ SHAH[4], KAWSAR JAN[5]

[1, 2] *Department of Chemistry, Annamalai University, Annamalai Nagar, Tamil Nadu-India.*

[3] *Department of Zoology, Annamalai University, Annamalai Nagar, Tamil Nadu-India.*

[4] *Department of Botany, Annamalai University, Annamalai Nagar, Tamil Nadu-India.*

[5] *Dew drops educational Institute Kulgam, Kashmir-India*

Abstract- ***(Z)-4-Chloro-N'-(substituted benzlidenes) benzohydrazides 1(a-e) were blended by abridging 4-Chlorobenzohydrazide with appropriate aldehydes in the molar ratio of 1:1 in the methanol as solvent. For all the synthesized compounds, FT-IR, ^{1}H and ^{13}C NMR spectra have been recorded. The synthesized amalgams were curtained for their anti-oxidant and anti-bacterial activities.***

Indexed Terms- Chemical production, Anti-oxidant activity, 4-Chlorobenzhydrazide, NMR spectra

I. INTRODUCTION

The piperdin-4-one nucleus, an imperative class of pharamacophore found in a wide variety of natural alkaloids exhibits a wide range of biological activities ranging from anticancer to antibacterial [1, 2]. Many piperdin derivatives possess pharmacological activities including antimicrobial, antioxidant, and anticancer activities and form an essential part of the molecular structure of important drugs [3,4,5,6]. Furthermore, research over the hoary several decades has demonstrated that antioxidants play a protective role in the multistage carcinogenis [7,8,9]. Recently, considerable care has been focused on identifying synthetic antioxidants that target various signaling pathways that are aberrant in cancer. Hydrazide-hydrazone derivatives received the attention of various medicinal chemists as a result of their effectual biological potencies, viz., anti-microbial, anti-tubercular, and also anti-convulsant activities [2, 11, 12].

In the present study, a new series of 4-Chloro-N′-(3-methyl-2r, 6c-diphenylpiperidin-4-ylidene) benzohydrazides 1(a-e) were synthesized using a response of piperidin-4-one with 4-Chlorobenzohydrazide in existence of CH_3COOH in CH_3OH. The organic structures were confirmed using IR, ^{1}H-NMR, and ^{13}C-NMR. In addition, we implemented structure activity rapport studies of the freshly synthesized hydrazine derivatives with potent anti-oxidant and anti-bacterial activities.

II. RESULTS AND DISCUSSION

Synthesis of 4-Chloro-N′-(3-methyl-2r, 6c-diphenylpiperidin-4-ylidene) benzohydrazides 1(a-e) were carried out according to the steps shown in scheme 1. A detailed investigation of IR, ^{1}H NMR, and ^{13}C NMR spectra data, was performed to identify and establish the newly synthesized compounds 1(a-e).

In the ^{1}H NMR spectra for compound 1a, a broad and more downfield D_2O exchangeable singlet at 10.71 ppm was characteristic of the N-H amide group. Another broad singlet signal resonated at 2.010 ppm was assigned for the N-H proton of the piperidin-4-one ring. Signal enlargement is owing to the quicker exchange of the N-H proton with flush moisture than the resonance time-scale. 2- doublets were detected in the region 0.82 ppm and 3.02 ppm H2a and the CH_3 group of C3 at the piperdin ring. Three doublets were perceived in the province of 2.61 ppm, 2.63 ppm and 2.65 ppm is due to the H-5e, H-5a, and H-6a.

In ^{13}C NMR of compound 1a, two downfield resonances at 163.7 ppm and 160.1 ppm were assigned to C=N and C=O (=N-NH-CO-) carbons respectively. The carbon resonances were observed around 149.5 ppm and 141.7 ppm were due to ipso carbons. However, there are four signals around 67.7 ppm, 61.8 ppm, 39.3 ppm, and 29.7 ppm which were conveniently assigned to the C-2, C-3, C-5, and C-6 carbons respectively. The ^{13}C chemical shift values of two methyl carbons (C-3 at the piperdin ring and C-4 at the benzohydrazide ring) were observed at 13.8 ppm and 14.5 ppm. The signals at 166.2 ppm and 138.9 ppm were also assigned for C-4 and C-5 of the benzohydrazide ring. Taken together all the above observations substantiate the proposed structure of the 4-Chloro-N'-(3-methyl-2r, 6c-diphenylpiperdin-4-ylidene) benzohydrazide.

We have advanced the scheme that combines piperidin-4-one pharmacophore and hydrazones 1(a-e) with the anti-cipation of numerous encouraging anti-cancer, antioxidant and anti-microbial agents emerging. The current study also aimed to investigate the structure-activity relationship for the antioxidant activities of hybrid molecules containing the piperidin-4-one pharamacophore and hydrazones.

Five different hydrazone by-products were blended and evaluated for their *in vitro* free- radical scavenging activity against various free-radicals. Our findings provide evidence that synthetic compounds 1(a-e) showed a concentration-dependent antiradical activity resulting from the reduction of DPPH, Metal chelation, and lipid peroxidation radicals to their non-radical forms. IC_{50} values scavenging effects of various synthetic compounds 1(a-e) are shown in Table 1. It is well known that an increase in antioxidant activity is observed with the replacement of alkyl chains such as methyl, ethyl to phenyl rings due to the electron resonance effect of the phenyl group [13]. Several studies have confirmed that organic molecules incorporating an electron donating group (hydroxyl, amine, alkyl, and methoxy) at the para position of the phenyl loop can act as free- radical deceiving agents and are proficient of differing oxidative-challenges [1, 14,15, 16]. Compounds possessing electron-donating methoxy (1c) and methyl (1e) substitutions at the para positions of the phenyl loop attached to the C-2 and C-6 carbons of the piperdin moiety showed excellent free-radical scavenging effects compared to the standard antioxidant, a known antioxidant used as a positive control. These findings confirm reports by other workers on the *in vitro* free-radical scavenging special effects of organic molecules incorporating an electron donating group (amine, hydroxyl, methoxy, and alkyl) at the para position of the phenyl ring [14, 15, 16]. These admirable or less free radical- scavenging special effects of compounds with fluoro, chloro, bromo substitutions may be due to the electron-withdrawing inductive effect of halogens. Our consequences are in line with other findings [13, 16, 17]. The radical-scavenging effects are measured by the change in color from purple to light yellow and reading the absorbance at 517 nm. Samples were analyzed at four different concentrations (30, 60, 90, and 120 mg/ml) which revealed a significant ($p \leq 0.05$) increase in DPPH scavenging potential with the increase in concentration. The scavenging ability of the synthesized compounds 1(a-e) is depicted graphically in Fig.1. Research over the past decades has demonstrated that excessive production of toxic radical species is known to cause deleterious changes in DNA, lipid, and protein oxidation. Thus, free radicals may serve as a source of mutations that initiate carcinogenis [18, 19].

In vitro anti-bacterial action of the blended hydrazones was conceded out against B.subtilis, S.aureus, K.pneumoniae, P.aeruginosa and E.coli by the Two-fold sequential dilution method using Streptomycin as the standard. The MIC values are presented in Table 2. Analysis of the *in vitro* anti-microbial special effects of the 4-Chloro-N′-(3-methyl-2r,6c-diphenylpiperdin-4-ylidene)benzohydrazide 1(a-e) revealed a diverse range of inhibitory activity(6.25-200 μgml^{-1}) against all pathogens except compound 1a, which did not show activity against K.pneumoniae and P.aures, even at a maximum concentration of 200 μgml^{-1}. The compounds deprived of any substitutes at the para-position of the phenyl groups at the C-2 and C-6 positions of the heterocyclic ring (1a) hinder the growth of Bacillus subtilis, S.aureus and E.coli at the MIC value 50-100 μgml^{-1}. Substitution of electron withdrawing bromo(1d) and chloro(1b) functional groups at aryl groups showed modest anti-bacterial activity against B.subtilis, P.aeruginosa, K.pneumoniae, S.aureus, E.coli at MIC values of

12.50 μgml^{-1} similar to that of standard streptomycin. Several studies have documented that electron withdrawing substitues like bromo,fluoro, and chloro substituted 2,6-diphenyl piperidone derivatives exerted excellent antibacterial and antifungal activities [1,2,11,14,20]. Compounds 1c and 1e having electron donating methoxy and methyl substitutions at the para-position of phenyl rings devoted to C-2 and C-6 carbons of the piperdine moiety show restrained anti-bacterial activity against all the tested bacterial strains in the range 0f 25-200 μgml^{-1}.

III. EXPERIMENTAL

All the substances that were purchased were used without further purification. All the stated melting points remained measured in open capillaries were uncorrected. FT-IR analysis was done making a pellet of the compound with KBr. Both 1D and 2D- NMR spectra were documented in the NMR spectrometer. A sample was prepared with a 5mm diameter tube using CdCl3-d6 solvent (10 mg in 0.5 ml). ^{1}H- NMR and ^{13}C-NMR data were collected in 400.13 MHz and 100.62 MHz operating frequency, respectively. Chemical shifts (δ) were expressed in ppm with respect to TMS. Splitting patterns were designated as follows: s-singlet, d-doublet, t-triplet, q-quartet, and m-mutiplet.

IV. GENERAL PROCEDURE

The 3-methyl-2r,6c-diphenyl piperidin-4-one A(1-5) were prepared by the condensation of suitable ketones, aldehydes, and ammonium acetate in a 1:2:1 ratio, according to the method described Noller and Baliah [21]. A reaction mixture containing 3-methyl-2r,6c-diphenyl piperidin-4-one (1 mmol) and 4-Chlorobenzhydrazide (1.5 mmol) was liquefied in the solvent of methanol and acetic acid (2ml) was added as a catalyst. The response mixture was refluxed for 4-5 hours. After accomplishment of the reaction the product and were recrystallized with ethanol. The pure compounds 1(a-e) were obtained.

4-Chloro-N′-(3-methyl-2r,6c-diphenylpiperidin-4-ylidene) benzohydrazide (1a):
White solid, yield: 73%, m.p:179˚c. IR (KBr, V-$_{max}$ Cm^{-1}): 1634.935(C=N), 3211.439(N-H), 3031.616 (C-H $_{arom}$), 1604.337, 1446.326 (C=C $_{arom}$). ^{1}H NMR spectrum (δ, 400MHz, $CdCl_3$-d6, ppm): 1.10(d,3H, CH_3 at piperdin ring), 2.01(s,1H, C-5-1Ha), 2.65(m,1H, C3-1H), 3.05(dd,1H,C5-1He),3.55(d,1H,C2-1H),7.17-7.53(m,10H, Ar-H),10.71(s,1H, N-H amide N-H). ^{13}C NMR spectrum (δ 400 MHz-$CdCl_3$-d6, ppm): 13.88(CH_3 at piperdin ring), 29.7(C-5), 39.7(C-3), 61.8(C-6), 67.7(C-2), 126.8-128.9 (Ar-C), 138.9 and 141.7 (ipso Carbons), 160.10 (C-4), 163.7(NHCO), 166.2(C-4 at benzohydrazide).

4-Chloro-N′-(3-methyl-2r,6c-bis(p-chlorophenyl)piperidin-4-ylidene) benzohydrazide (1b):
white solid, yield: 75%, m.p:206˚c, IR(KBr,$V_{max,}$ Cm^{-1}): 1637(C=N),3230(N-H), 3056(C-H $_{arom}$), 1592, 1567, 1505(C=C $_{arom}$). ^{1}H NMR spectrum (δ, 400 MHz-$CdCl_3$-d6, ppm): 1.17(s,3H, CH_3 at piperdin ring), 2.51(s,1H, NH at piperdin ring),2.21(dd,1H,C5-1Ha), 2.51(s,1H,C3-1H), 6.99-7.45(m,8H,Ar-H), 10.49(s,1H,N-H, amide N-H).^{13}C NMR spectrum (δ, 400 MHz-$CdCl_3$-d6): 9.9(CH_3 at piperdin ring), 29.7(C-5), 38.2(C-3), 62.3(C-6), 69.2(C-2), 1238.7-129.9(Ar-C), 132.0(C-5), 136.7 and 147.9(ipso Carbons), 154.5(C-4), 163.7 (NHCO). 166.5(C-4 at benzohydrazide ring).

4-Chloro-N′-(3-methyl-2r,6c-bis(p-methoxyphenyl)piperdin-4-ylidene)benzohydrazide (1c):
White solid, yield: 76%, m.p:163˚c, IR (KBr, Vmax, cm^{-1}): 1633(C=N), 3208(N-H),3038(C-H arom),1503,1445, 1418(C=C arom). 1H NMR spectrum (δ, 400 MHz-$Cdcl_3$-d6, ppm): 0.78(d, 3H, CH_3 at piperdin ring), 1.69(s, 1H, NH at piperdin ring), 2.00(s, 1H, C5-1Ha), 2.50(s, 1H, C3-1H), 3.70(s, 6H, OCH_3), 6.79-7.71(Ar-H).^{13}C NMR spectrum (δ, 400MHz-$Cdcl_3$-d6, ppm):11.8(CH_3 at piperdin ring), 68.1(C-2), 55.3(C-6), 40.5(OCH_3), 29.7(C-3), 114.2-129.3(Ar-C), 129.7 and 133.1(ipso carbons), 159.5(C-4), 161.9(NHCO), and 166.1(C-4 at benzohydrazide ring).

4-Chloro-N′-(3-methyl-2r,6c-bis(p-bromophenyl)piperdin-4-ylidene)benzohydrazide (1d):
White solid, yield: 69%, m.p: 225˚c, IR (KBr, Vmax, cm^{-1}): 1639(C=N), 3159(N-H), 2963(C-H arom), 1559, 1503, 1485(C=C arom). ^{1}H NMR spectrum(δ, 400 MHz-$CdCl_3$-d6, ppm): 0.75(d, 3H, CH_3 at

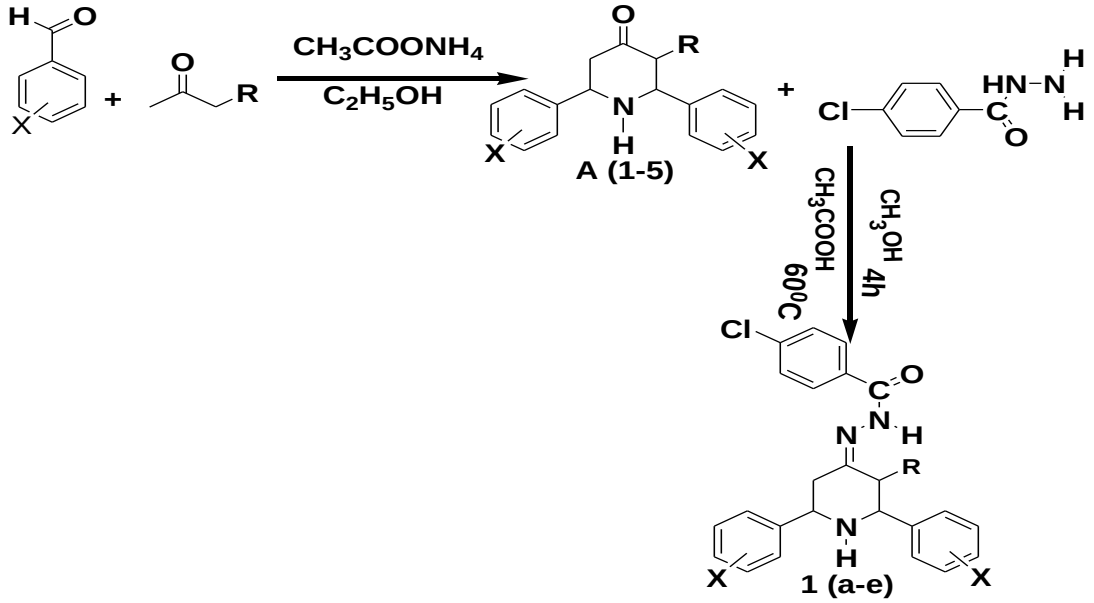
piperdin ring), 2.00(s, 1H, NH at piperdin ring), 2.48(dd, 1H, C5-1Ha), 2.52(m, 1H, C3-1H), 3.50 (dd, 1H, C5—1He),3.91(d,1H,c6-1H), 7.01-7.33(m, 8H, Ar-H), 1.17(s, 1H, N-H amide NH).^{13}C NMR spectrum (δ, 400 MHz-$CdCl_3$-d6, ppm):10.09(CH_3 at piperdin ring), 40.98(C-5), 56.75(C-3), 60.93(C-6), 67.72(C-2), 126.39-129.41(Ar-C), 140.71-141.58(ipso Carbons), 147.92(C-4), 163.53(NHCO), and 169.72(C-4 at benzohydrazide ring).

4-Chloro-N′-(3-methyl-2r,6c-bis(p-methylphenyl)piperdin-4-ylidene) benzohydrazide (1e):

White powder, yield: 71%, m.p:170˚c. IR (KBr, Vmax cm^{-1}):1636(C=N), 3216(N-H), 3023(C-H arom), 1504, 1438, 1408(C=C arom). ^{1}H NMR spectrum (δ, 400 MHz-$CdCl_3$-d6, ppm): 1.12(d, 3H, CH_3 at piperdin ring), 2.09(s,1H, NH at piperdin ring), 2.34(dd, 1H, C5-1Ha), 2.43(s, 6H, CH_3 at phenyl ring), 2.70(m, 1H, C3-1H), 3.60(d, 1H,C2-1H), 5.40(s, 1H-NH), 7.03-7.57(Ar-H),7.98(s,1H), 11.04(s, 1H, N-H, amide). ^{13}C NMR spectrum: (δ, 400 MHz-$CdCl_3$-d6, ppm): 13.9(CH3 at piperdin ring), 21.14(CH_3 at phenyl ring), 33.93(C-5), 50.86(C-3), 61.34(C-6), 68.24(C-2), 126.43-129.38(Ar–C), 137.52 and 139.73(ipso carbons), 149.73(C-4), 163.76(NHCO), and 166.19 (C-4 at benzohydrazide ring).

Scheme 1: Representation of the synthesis of 4-Chloro-N′-(3-methyl-2r,6c-diphenylpiperdin-4-ylidene) benzohydrazides 1(a-e).

Sample code		R	X
1	a	-CH_3	H
2	b	-CH_3	P-Cl
3	c	-CH_3	P-OCH_3
4	d	-CH_3	P-Br
5	e	-CH_3	P-CH_3



Scheme 1

- Antioxidant activity:

Different sample concentrations (w/v) were made by dispersing 30, 60, 90, and 120 mg of starch in 1ml of doubl- distilled H_2O followed by sonication for 20.0 minutes to ensure better mixing. The mixture obtained was then utilized for determining different antioxidant assays.

- DPPH activity:

The DPPH (1, 1-diphenyl-2, picrylhydrazyl) activity of samples was determined by the method proposed by Ashwar et al [22] with some modifications. 5ml of each sample of varying concentrations (30, 60, 90, and 120 mg/ml) was mixed with a 60 mM solution of DPPH in methanol (5ml). The mixture was vortexed for about a min and kept at 25˚c for 35 min in a dark room. The absorbance of the resulting mixture was

determined at 517nm using a UV-Vis spectrophotometer (U-2900, Hitachi, Tokyo, Japan) against the blank α-tocopherol was taken as positive control dissolved in double-distilled water.

- Metal chelating activity:

Metal chelation ability was evaluated according to the method of Shah et al [22]. The absorbance of the resulting mixture was measured at room temperature against blank at 562 nm and compared to citric acid (standard).

Lipid peroxidation activity: This assay was assessed by the method Shah et al [22]Starch suspension(1ml) of varying concentrations was added to linoleic acid (1 ml, 0.1% w/v), hydrogen peroxide (0.2ml,30mM), ascorbic acid (0.2ml, 100mM),and ferric nitrate (0.2ml,20mM). This mixture was allowed to incubate at 37˚c for ½ of an hour. After this, the termination of the reaction was carried out by adding trichloroacetic acid (1.o ml, 10 % w/v) and thiobarbituric acid (1.0 ml, 1% w/v). Reaction mixture tubes were kept in a hot water bath for 25 min followed by centrifugation at 6000 rpm for 5 min. The supernatant was collected and its absorbance was determined at 535 nm against a blank and compared to EDTA (standard).

Table 1. IC_{50} values for free radical scavenging activity (µg/ml)

Compound	IC_{50} values for free radical scavenging		
	DPPH	Lipid peroxidation	Metal Chelation
1a	3.38	4.67	3.50
1b	3.87	3.67	3.88
1c	1.55	1.34	1.44
1d	3.54	3.37	3.54
1e	1.54	1.54	0.95
Standard Used	1.98 (α-Tocopherol)	1.97 (EDTA)	1.64 (Citric acid)

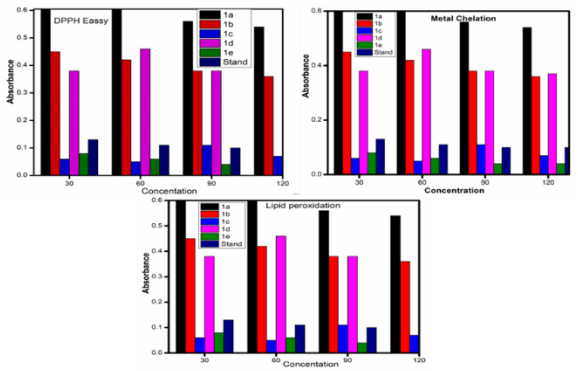


Fig.1. Anti-oxidant potential of synthesized compounds 1(a-e). Standard used are α-tocopherol, EDTA, and citric acid respectively. Data with different superscripts are significantly different at $p \leq 0.05$. EDTA represent butylated hydroxytoluene, α-tocopherol, and citric acid respectively.

- *In vitro* bacterial activity by twofold serial dilution method:

Bacterial strains such as Bacillus subtillis, Klebsiella pneumonaie, Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus obtained from factulty of Medicine, Annamalai University, Annamalainagar-608002, Tamil Nadu-Idia, were used to screen the anti-bacterial activity of the newly blended compounds 1(a-e). The bacterial-strains were cultured in nutrient broth(NB) at PH 5.6 (Hi-media, Mumbai).

The *in vitro* potency of compounds 1(a-e) was examined by 2F(Two fold) serial dilution method [23]. Stock solutions of 1(a-e) were made in DMSO (1 µg ml^{-1}). Compounds were tested in the concentrations of 200, 100, 50, 25,12.5, 6.25 and 3.12 µgml^{-1}(Twofold serial dilution method) with NB. Then NB were suspended with 100µL of bacterial spores for 24 h old bacterial cultures on NB at 37± 1˚ c. Drug standard for antibacterial activity are streptomycin.

Table 2.
In vitro antibacterial (MIC µm/ml) of compounds 1(a-e) of compounds by 2-fold dilution method.

compounds	B.subtills	S.aureus	K.pneumoniae	S.aeruginosa	E.coli
1a	50	200	200	100	100
1b	12.5	12.5	25	25	25

1c	25	25	50	50	100
1d	12.5	25	25	50	50
1e	100	50	100	200	200
Streptomycin	25	12.5	25	12.5	12.5

CONCLUSION

We have developed five newly compounds (Z)-4-Chloro-N′-(substituted benzlidenes) benzohydrazides. For their early antioxidant and antibacterial activity, all the recently produced compounds were tested. Due to the existence of the electron-confer set, all of these compounds exhibit strong antibacterial and antioxidative properties. According to recent investigations, these molecules may serve as a blueprint for the creation of new anti-oxidant and antibacterial drugs.

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The authors affirm that they have no known financial or interpersonal conflicts that would have appeared to have an impact on the research presented in this study.

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