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Synthesis and Antimicrobial Activity of Some Novel Schiff Bases and 4-Thiazolidinones Containing N-Benzyl Piperidine Moiety

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ABSTRACT

A series of novel schiff bases containing N-benzyl piperidine moiety **(1*a-d*)** were synthesized by the reaction of N-benzylpiperidine-4-carbaldehyde with suitable aromatic amines. And synthesized schiff bases were converted to a series of novel 4-thiazolidinones **(2*a-d*)** by the reaction of Schiff base with mercaptoacetic acid. The chemical structures of the synthesized compounds were confirmed by using spectroscopic and chemical analysis techniques. All the above compounds were screened for their antimicrobial activity against some selected pathogenic microorganism. Good level of antimicrobial activity has been displayed by both categories of compounds against tested pathogenic microorganism. Thiazolidinone derivatives (**2*a-d***) showed higher activity than schiff base derivatives **(1*a-d*)**.

Keywords: N-benzylpiperidine-4-carbaldehyde, 4-Thiazolidinone, antimicrobial activity, Schiff base, Heterocyclic compounds, N-benzyl piperidine moiety.

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INTRODUCTION

One of the major objectives of organic and medicinal chemistry is the design, synthesis and production of molecules having highly therapeutic nature. The rapidly increasing resistance of pathogenic bacteria towards available antibiotics, as well as fungal infections continues to increase rapidly in the number of immuno compromised patients is a serious problem. So, the design of new molecules to deal with resistant bacteria and fungi has become one of the most important areas of antimicrobial research today.

This study is a serious effort towards the development of biologically more active molecule. The wide range of biological activities exhibited by 4-thiazolidinones and piperidine derivatives, the aim of this study is to prepare thiazolidinones containing piperidine ring in the molecule and to explore the pharmacological activity of this combination product.

4-Thiazolidinones are among the most studied heterocyclic compounds due of their biologically active nature. 4-thiazolidinones gained attraction by researchers due to their broad spectrum of biological and pharmacological activities. Several substituted thiazolidinone have been found to be possessed a number of pharmacological activities like antibacterial,[1-4] anticancer,[5] antitubercular,[6,7] antifungal,[8] anti-inflammatory,[9] antiviral,[10] and analgesic.[11]

On the other hand Piperidine and its derivatives has high impact on medical filed due to its wide variety of pharmacological action like antifungal[12], antihypertensive[13], hypoglycemic and hypolipidemic[14], anticonvulsant activity[15], neuroprotective agents[16], antidepressants[17], antimicrobial agents[18] and in the management of pain[19].

MATERIALS AND METHODS

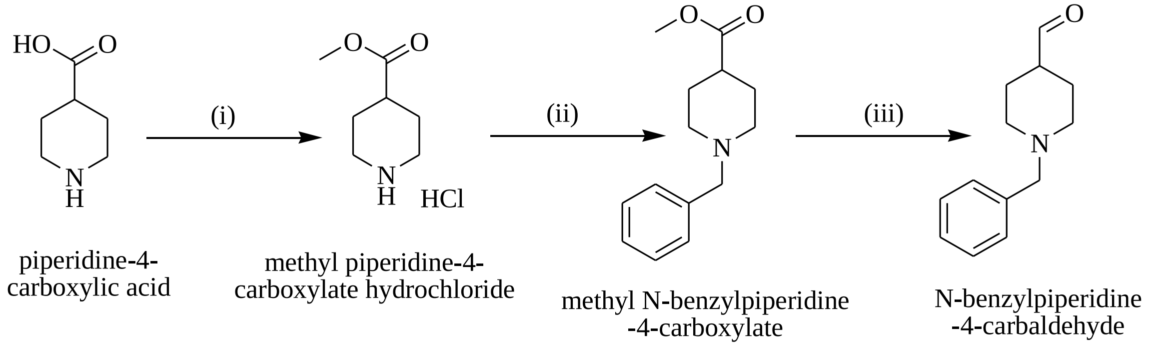
All solvents and chemicals used were of commercial or LR grade, and were used without further purification. Purity of the compounds was checked by TLC. Melting points were measured on Buchi melting point apparatus and are uncorrected. The IR spectra were recorded on Perkin-Elmer spectrometer, using KBr pellets. ^{1}H-NMR spectra were scanned on Bruker-NMR spectrometer at 500 MHz, using TMS as an internal standard and DMSO d6/ $CDCl_3$ as solvent and mass spectra were recorded on Waters Q-T of MS.

Synthesis of N-benzylpiperidine-4-carbaldehyde

10.13g (0.085mol) of thionyl chloride was added drop wise to a suspension of 10g (0.077mol) of piperidine-4-carboxylic acid in 50 ml of methanol at 0-5°C, after complete addition temperature was allowed to rise to room temperature and stirred at room temperature for 4 hours. Clear reaction mass indicates the completion of reaction, solvent evaporated completely under reduced pressure to yield 13.4g methyl piperidine-4-carboxylate hydrochloride as white solid (96% yield).8.4g (0.066mol) of benzyl chloride was added drop wise to a solution of 10g (0.055mol) of methyl piperidine-4-carboxylate hydrochloride, 16.7g (0.165mol) of triethylamine in 50 ml of dichloromethane at 0-5°C, after complete addition reaction mixture stirred at room temperature for 1 hour and progress of the reaction monitored by TLC. Organic layer washed twice with water, solvent evaporated completely under reduced pressure to yield 11.7g methyl N-benzylpiperidine-4-carboxylate as viscous liquid (90% yield).

A mixture of 5ml pyrrolidine and 5ml methyl tertiary butyl ether (MTBE) was added slowly to a mixture of 17.2ml 70% vitride solution in toluene and 17.2 ml methyl tertiary butyl ether (MTBE) at -20 to -30°C and stirred at 10-15°C for 1hour followed by addition of a suspension of 0.35g Potassium tertiary butoxide (PTB) in 5ml tetrahydrofuran (THF) under stirring. Above solution was added slowly at -20 to -30°C to a solution of 7.5g (0.032mol) of methyl N-benzylpiperidine-4-carboxylate in 15ml methyl tertiary butyl ether (MTBE). pH of the reaction mixture adjusted to 2 using 2N HCl, layer separated, pH of the aqueous layer adjusted to 9 using 4N NaOH, aqueous layer extracted with ethyl acetate, ethyl acetate layer washed with water and evaporated completely under reduced pressure to yield 5g N-benzylpiperidine-4-carbaldehyde (Reaction scheme-1) as light brown colored viscous liquid (77% yield).[20]

Reaction scheme-1: Synthesis of N-benzylpiperidine-4-carbaldehyde



(i) Methanol, thionyl chloride
(ii) Benzyl chloride, triethylamine, dichloromethane
(iii) Vitride (70% sol in toluene), pyrrolidine, MTBE, PTB, THF

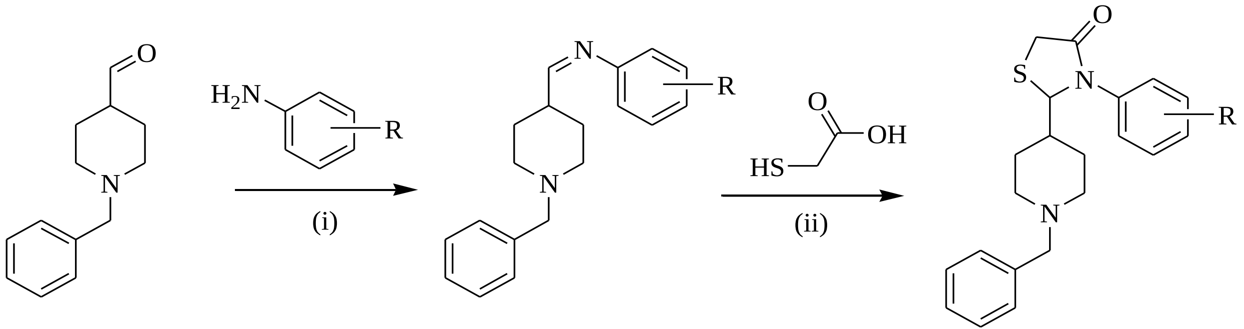
General method for the synthesis of schiff bases

N-benzylpiperidine-4-carbaldehyde was refluxed with equimolar amount of suitable aromatic amine in presence of catalytic amount of acetic anhydride in the media of absolute ethanol for four to eight hours depending upon the reaction completion. Progress of the reaction was monitored on TLC. After complete reaction solvent evaporated completely under reduced pressure and residue crystallized from suitable solvents (Reaction scheme-2).

General method for the synthesis of 4-thiazolidinones

Obtained schiff bases were refluxed with 1.2 molar equivalent amount of mercapto acetic acid in presence of catalytic amount of fused zinc chloride in the media of 1,4-dioxane for four to eight hours depending upon the reaction completion. Progress of the reaction was monitored on TLC. After complete reaction solvent evaporated completely under reduced pressure, residue dissolved in dichloromethane, washed twice with water to remove access amount of mercapto acetic acid, dichloromethane layer evaporated after drying over sodium sulphate and residue was crystallized from suitable solvents (Reaction scheme-2).

Reaction scheme-2: Synthesis of schiff bases and 4-thiazolidinones



N-benzylpiperidine
-4-carbaldehyde

1*a-d*

2*a-d*

(i) Absolute ethanol, Acetic anhydride (cat.), Reflux
(ii) 1,4-Dioxane, Fused zinc chloride (cat.), Reflux

RESULTS AND DISCUSSION

Chemical synthesis

The chemical synthesis started with the conversion of commercially available piperidine-4-carboxylic acid to methyl piperidine-4-carboxylate hydrochloride by the treatment of methanol and thionyl chloride, methyl piperidine-4-carboxylate hydrochloride was reacted with benzyl chloride in presence of triethyl amine to form N-benzylpiperidine-4-carboxylate, ester of N-benzylpiperidine-4-carboxylate was then reduced to aldehyde with vitride to form N-benzylpiperidine-4-carbaldehyde. Chemical structure of the synthesized N-benzylpiperidine-4-carbaldehyde was confirmed by means of spectroscopic techniques and elemental analysis.

N-benzylpiperidine-4-carbaldehyde

1H NMR (500 MHz, CDCl3) 1.60-1.91 (m, 4H, piperidine), 2.16-2.30 (m, 4H, piperidine), 2.32-2.36 (m, 4H, piperidine), 3.52 (s, 2H), 7.10-7.24 (m, 5H, phenyl), 9.67 (s, 1H, CHO); 13C NMR (175 MHz, CDCl3) 26.44, 26.51,44.18, 52.45, 52.53 (5C, piperidine), 61.41 (CH_2), 127.00, d-128.10, d-128.17, 136.42 (6C, phenyl), 204.11 (1C,CHO); Elemental analysis calculated for C13H17NO: C=76.81; H=8.43; N=6.89. Found: C=76.66; H=8.40; N=6.88.

N-benzylpiperidine-4-carbaldehyde was condensed with equimolar amount of suitable aromatic amine in presence of catalytic amount of acetic anhydride in the media of absolute ethanol to yield schiff base derivatives **(1*a-d*)** four aromatic amines were used namely aniline, p-chloroaniline, p-toluidine and 3-chloro-4-fluoroaniline.

Table-1:Physical data of schiff bases and 4-thiazolidinones

Compound	Mol. Formula	Mol. Weight	MP (°C)	Yield (%)	Elemental Analysis (calculated and found)		
					C	H	N
1*a*	$C_{19}H_{22}N_2$	278.39	160	61	81.97	7.97	10.06
					81.90	7.88	10.00
1*b*	$C_{19}H_{21}ClN_2$	312.84	172	60	72.95	6.77	8.95
					72.90	6.70	8.90
1*c*	$C_{20}H_{24}N_2$	292.42	155	61	82.15	8.27	9.58
					81.95	8.20	9.50
1*d*	$C_{19}H_{20}ClFN_2$	330.83	177	57	68.98	6.09	8.47
					68.79	5.99	8.40
2*a*	$C_{21}H_{24}N_2OS$	352.49	141	40	71.55	6.86	7.95
					71.46	6.80	7.88
2*b*	$C_{21}H_{23}ClN_2OS$	386.94	152	44	65.18	5.99	7.24
					65.05	5.80	7.18
2*c*	$C_{22}H_{26}N_2OS$	366.52	138	42	72.09	7.15	7.64
					71.98	7.09	7.60
2*d*	$C_{21}H_{22}ClFN_2OS$	404.93	140	40	62.29	5.48	6.92
					62.15	5.54	6.78

Obtained schiff bases were refluxed with 1.2 molar equivalent amount of mercapto acetic acid in presence of catalytic amount of fused zinc chloride in the media of 1,4-dioxane to yield 4-thiazolidinones **(2*a-d*)**. Purity of the synthesized compounds was confirmed by TLC and structures were confirmed by mass, infrared, nuclear magnetic spectroscopic techniques and elemental analysis. Physical data of the prepared compounds are tabulated in table-1.

N-((1-benzylpiperidin-4-yl)methylene) benzenamine (1*a*)

Pale yellow colored crystals; yield 61 %; mp 160 °C; IR (KBr / cm^{-1}) absorption band at 1628 (C=N); ^1H NMR (500 MHz, CDCl3) 1.31-1.61 (m, 5H, piperidine), 2.16-2.26 (m, 4H, piperidine), 3.66 (s, 2H, CH_2), 7.04-7.24 (m, 10H, Ar.), 7.56 (s, 1H, N=CH); Elemental analysis calculated for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06; Found: C, 81.90; H, 7.88; N, 10.00. Mass (TOF MS ES+) 279.08 (M+H).

N-((1-benzylpiperidin-4-yl)methylene)-4-chlorobenzenamine (1*b*)

Off white colored crystals; yield 60 %; mp 172 °C; IR (KBr / cm^{-1}) absorption band at 1622 (C=N); ^1H NMR (500 MHz, CDCl3) 1.29-1.60 (m, 5H, piperidine), 2.11-2.21 (m, 4H, piperidine), 3.56 (s, 2H, CH_2), 7.06-7.26 (m, 9H, Ar.), 7.55 (s, 1H, N=CH); Elemental analysis calculated for $C_{19}H_{21}ClN_2$: C, 72.95; H, 6.77; Cl, 11.33; N, 8.95; Found: C, 72.90; H, 6.70; N, 8.90. Mass (TOF MS ES+) 313.54 (M+H).

N-((1-benzylpiperidin-4-yl)methylene)-4-methylbenzenamine (1*c*)

Off white colored crystals; yield 61 %; mp 155 °C; IR (KBr / cm^{-1}) absorption band at 1620 (C=N); ^{1}H NMR (500 MHz, CDCl3) 1.30-1.59 (m, 5H, piperidine), 2.11-2.21 (m, 4H, piperidine), 2.33 (s, 3H, CH_3), 3.51 (s, 2H, CH_2), 7.01-7.22 (m, 9H, Ar.), 7.50 (s, 1H, N=CH); Elemental analysis calculated for $C_{20}H_{24}N_2$: C, 82.15; H, 8.27; N, 9.58; Found: C, 81.95; H, 8.20; N, 9.50. Mass (TOF MS ES+) 293.34 (M+H).

N-((1-benzylpiperidin-4-yl)methylene)-3-chloro-4-fluorobenzenamine (1*d*)

Pale yellow colored crystals; yield 57 %; mp 177 °C; IR (KBr / cm^{-1}) absorption band at 1629 (C=N); ^{1}H NMR (500 MHz, CDCl3) 1.30-1.60 (m, 5H, piperidine), 2.09-2.18 (m, 4H, piperidine), 3.50 (s, 2H, CH_2), 7.10-7.31 (m, 8H, Ar.), 7.50 (s, 1H, N=CH); Elemental analysis calculated for $C_{19}H_{20}ClFN_2$: C, 68.98; H, 6.09; Cl, 10.72; F, 5.74; N, 8.47; Found: C, 68.79; H, 5.99; N, 8.40. Mass (TOF MS ES+) 331.60 (M+H)

The structures of schiff bases **(1*a-d*)** and thiazolidinone derivatives **(2*a-d*)** were supported by elemental analyses and IR spectra, conversion of schiff bases to thiazolidinone derivatives confirmed by IR as disappearance of 1620 - 1630 $cm^{-1}$for -N=CH- band of schiff base with appearance of 1680 - 1690 cm^{-1} for >C=O of thiazolidinone. The double doublet signals in the ^{1}H-NMR of cyclilized thiazolidinones were observed at δ 3.33–3.49, corresponding to $-CH_2-$ in the thiazolidinone ring and other peak also support the formation of compound.

2-(1-benzylpiperidin-4-yl)-3-phenylthiazolidin-4-one (2*a*)

Yellow colored crystals; yield 40 %; mp 141 °C; IR (KBr / cm^{-1}) absorption band at 1681 (C=O of thiazolidinone ring); ^{1}H NMR (500 MHz, CDCl3) 1.22-1.49 (m, 4H, piperidine), 2.15-2.35 (m, 5H, piperidine), 3.39-3.49 (dd, 2H, CH_2 of thiazolidinone), 3.60 (s, 2H, CH_2 of benzyl), 4.60 (d, 1H, CH of thiazolidinone), 7.00-7.30 (m, 10H, Ar.); Elemental analysis calculated for $C_{21}H_{24}N_2OS$: C, 71.55; H, 6.86; N, 7.95; O, 4.54; S, 9.10; Found: C, 71.46; H, 6.80; N, 7.88. Mass (TOF MS ES+) 353.06 (M+H).

2-(1-benzylpiperidin-4-yl)-3-(4-chlorophenyl)thiazolidin-4-one (2*b*)

Off white crystals; yield 44 %; mp 152 °C; IR (KBr / cm^{-1}) absorption band at 1687 (C=O of thiazolidinone ring); ^{1}H NMR (500 MHz, CDCl3) 1.32-1.50 (m, 4H, piperidine), 2.14-2.34 (m, 5H, piperidine), 3.33-3.43 (dd, 2H, CH_2 of thiazolidinone), 3.62 (s, 2H, CH_2 of benzyl), 4.60 (d, 1H, CH of thiazolidinone), 7.03-7.31 (m, 9H, Ar.); Elemental analysis calculated for

$C_{21}H_{23}ClN_2OS$: C, 65.18; H, 5.99; Cl, 9.16; N, 7.24; O, 4.13; S, 8.29; Found: C, 65.05; H, 5.80; N, 7.18. Mass (TOF MS ES+) 387.60 (M+H).

2-(1-benzylpiperidin-4-yl)-3-p-tolylthiazolidin-4-one (2*c*)

Off white crystals; yield 42 %; mp 138 °C; IR (KBr / cm^{-1}) absorption band at 1688 (C=O of thiazolidinone ring); ^{1}H NMR (500 MHz, CDCl3) 1.34-1.59 (m, 4H, piperidine), 2.15-2.37 (m, 5H, piperidine and 3H, CH_3), 3.35-3.45 (dd, 2H, CH_2 of thiazolidinone), 3.67 (s, 2H, CH_2 of benzyl), 4.67 (d, 1H, CH of thiazolidinone), 6.89-7.21 (m, 9H, Ar.); Elemental analysis calculated for $C_{22}H_{26}N_2OS$: C, 72.09; H, 7.15; N, 7.64; O, 4.37; S, 8.75; Found: C, 71.98; H, 7.09; N, 7.60. Mass (TOF MS ES+) 367.50 (M+H).

2-(1-benzylpiperidin-4-yl)-3-(3-chloro-4-fluorophenyl)thiazolidin-4-one (2*d*)

Yellow colored crystals; yield 40 %; mp 140 °C; IR (KBr / cm^{-1}) absorption band at 1684 (C=O of thiazolidinone ring); ^{1}H NMR (500 MHz, CDCl3) 1.21-1.43 (m, 4H, piperidine), 2.11-2.30 (m, 5H, piperidine), 3.33-3.43 (dd, 2H, CH_2 of thiazolidinone), 3.62 (s, 2H, CH_2 of benzyl), 4.64 (d, 1H, CH of thiazolidinone), 6.89-7.19 (m, 8H, Ar.); Elemental analysis calculated for $C_{21}H_{22}ClFN_2OS$: C, 62.29; H, 5.48; Cl, 8.76; F, 4.69; N, 6.92; O, 3.95; S, 7.92. Found: C, 62.15; H, 5.54; N, 6.78. Mass (TOF MS ES+) 367.50 (M+H).

Antimicrobial Testing

For Inhibition zone measurements the tested compounds were dissolved in dimethylsulfoxide at a concentration of 1 mg/ml. The suitable medium (nutrient agar for bacteria namely *P. aeruginosa*, *S. aureus* and yeast extract peptone dextrose for fungi namely *C. albicans*) was inoculated with the test organisms.

Table 2:Antimicrobial activity: Inhibition zone diameter data

Compound	Diameter of inhibition zone (mm)		
	P. aeruginosa	***S. aureus***	***C. albicans***
1*a*	12	06	05
1*b*	12	15	15
1*c*	11	08	06
1*d*	11	14	14
2*a*	16	09	08
2*b*	14	16	16
2*c*	16	10	11
2*d*	16	16	18
Streptomycin	22	Not tested	Not tested
Benzyl penicillin	Not tested	20	Not tested
Fluconazole	Not tested	Not tested	22

A volume of the solution of each the test compounds equivalent to 100 mg was placed separately in cups cut in the agar[21]. The plates were incubated at 37 ◦C for 24 h for bacteria and 48h for fungi, and the resulting inhibition zones were measured (table-2). Dimethylsulfoxide, exhibited no antimicrobial activity against the test organisms and used as a negative control. Streptomycin, Benzyl penicillin and Fluconazole were used during the test procedures as reference anti pathogens for gram negative, gram positive bacteria and fungi respectively. In general, all synthesized compounds exhibited good inhibitory activity against tested pathogenic microorganism. Thiazolidinone derivatives (**2*a-d***) showed higher activity than schiff base derivatives **(1*a-d*)**.

CONCLUSION

The present study reports the successful synthesis of Schiff bases **(1*a-d*)** and thiazolidinone derivatives (**2*a-d***) containing N-benzyl piperidine moiety with several structural variations. Pharmacological examination of synthesized compounds exhibited good inhibitory activity against tested pathogenic microorganism. Thiazolidinone derivatives (**2*a-d***) showed higher activity than schiff base derivatives **(1*a-d*)**.

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