Med Chem Res
DOI 10.1007/s00044-013-0624-2

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Novel 3-benzyl-2,6-diarylpiperidin-4-one derivatives: syntheses, characterization, and antimicrobial profile

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Received: 16 February 2013 / Accepted: 6 May 2013

Abstract The study was aimed at the syntheses and evaluation of a series of novel 3-benzyl-2,6-diarylpiperidine-4-ones. The newly synthesized compounds were characterized by elemental analysis, infrared, ^{1}H NMR, ^{13}C NMR, and mass spectral analyses. These compounds were screened for their inhibiting potential against various bacterial and fungal strains. The antimicrobial activity was performed against four Gram positive bacteria (*S. aureus, B. subtilis, B. pumilus, and M. luteus*), three Gram negative bacteria (*P. aeruginosa, P. fluorescens*, and *E. coli*), and two fungal strains (*A. niger* and *P. chrysogenum*) by cup-plate method and tube assay method. The results reveal that some of these compounds exhibited remarkable activity against the selected bacterial and fungal strains, with MIC values as low as 50 μg/mL. Interestingly, all the compounds exhibited better antifungal activity than antibacterial activity. Thus, it can be concluded that 3-benzyl-2,6-diarylpiperidine-4-ones may exhibit potent antifungal activity.

Keywords Piperidin-4-ones · Mannich reaction · Antifungal · Antibacterial · Antimicrobial

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Introduction

The widespread use of heterocyclic compounds is because their structures can be subtly manipulated to achieve the required modification in function (Gilchrist, 1997). Heterocyclic ring systems having piperidin-4-one nucleus have generated great interest in the past and recent years due to their wide variety of biological properties (Sahu *et al*., 2013) such as antibacterial (Ramalingan *et al*., 2004; Jayabharathi *et al*., 2007a, b; Gopalakrishnan *et al*., 2009; Srinivasan *et al*., 2006), antifungal (Aridoss *et al*., 2006, 2007a, b, 2009; Jayabharathi *et al*., 2005), analgesic and antipyretic (Kalaiselvan *et al*., 2004; Rameshkumar *et al*., 2003; Salima *et al*., 1986), anticancer (Dimmock *et al*., 1990, 2002; Das *et al*., 2007; Pati *et al*., 2008, 2009; Makarov *et al*., 2009; Patel *et al*., 2007), antiviral (Artico *et al*., 1998; Santo *et al*., 2003; El-Subbagh *et al*., 2000), antihypertensive (Zhang *et al*., 2009), and antimycobacterial activities (Das *et al*., 2008; Aridoss *et al*., 2008).

Piperidine-4-one nucleus is generally synthesized by Mannich reaction, producing β-amino-carbonyl compound, also known as a Mannich base. The biological activities of piperidones are associated with substitutions at 2, 3, and 6 positions. The biological activity was found to be significant in compounds possessing aromatic substituents at 2 and/or 6 positions (Rameshkumar *et al*., 2003). The substituted piperidin-4-ones, such as 1,3-dimethyl-2,6-diphenyl-4-piperidone, have been found to be versatile intermediates in different types of reactions since they have two reactive sites, carbonyl and keto methylene groups. This paved the pathway for the synthesis of some heterocyclic compounds such as tetrahydropyridine, diazepanone, oxazepanone, piperidone, pyridopyrimidone, pyrido-pyrimidinethione, thiazolopyridine, furanylmethylene, and pyridoindole (Padmavathi *et al*., 2005). Piperidin-4-one, when reacted with

Published online: 16 May 2013

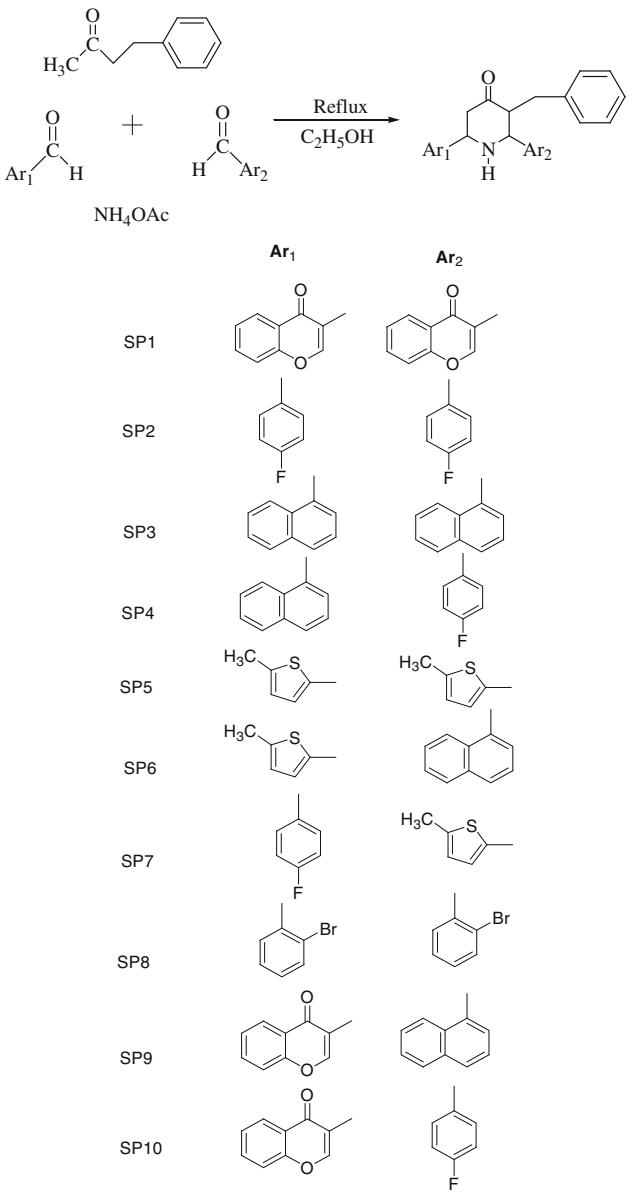
hydroxylamine hydrochloride, generates piperidin-4-one oxime which shows potent antimicrobial activity (Balasubramanian *et al*., 2006). Similarly, piperidin-4-one when refluxed with hydrazine hydrate, yields bispiperidine which shows anticonvulsant activity (Krapcho and Turk, 1979). Using piperidin-4-one as intermediate bicyclic pyrazolines, piperidin-4-one semicarbazones, thiosemicarbazones, and piperidin-4-one oxime ethers have also been synthesized which show central nervous system depressant, anti-inflammatory (Hemalatha *et al*., 2008), and antibacterial activity (Ramalingan *et al*., 2006), respectively. The aryl-piperidine scaffold is a key element involved in binding to a variety of receptors and therefore can be described as a privileged structure (Horton *et al*., 2003). Similarly, piperidone derivatives have also received wide interest among chemists and biologists due to their envisaged mode of interaction with cellular thiols, with modest or no affinity for the hydroxy and amine groups found in nucleic acids (Mutus *et al*., 1989; Ramachandran *et al*., 2008).

Materials and methods

The chemicals and reagents were procured from S.D. Fine and Sigma-Aldrich and were used as such. Melting points were determined using melting point apparatus and are uncorrected. Progress of the reactions was monitored by thin layer chromatography on silica gel G plates, using iodine vapors and UV chamber as visualizing agents. The synthesized compounds were subjected to physical and spectral analysis.

Synthesis

The synthesis of 3-benzyl-2,6-diarylpiperidin-4-ones was achieved with a versatile and efficient synthetic route outlined in Scheme 1.



Scheme 1 Synthesis of 3-benzyl-2,6-diarylpiperidin-4-one derivatives

General procedure for the synthesis of 3-benzyl-2,6-diarylpiperidin-4-ones

Dry ammonium acetate (0.01 mol.) was dissolved in ethanol (3 ml), mixed with different aromatic/heteroaromatic aldehydes (0.02 mol.) and benzylacetone (0.01 mol.), refluxed for 10 min and allowed to stand at room temperature overnight. Then, ether (5 ml) was added followed by concentrated hydrochloric acid (3 ml) and cooled in ice water. The precipitated hydrochloride was filtered and washed with ethanol–ether (1:5) mixture. The hydrochloride was suspended in acetone and made alkaline using strong ammonia solution. On dilution with excess of water, the base was precipitated which was filtered and dried and recrystallized from chloroform. The purity of compounds was confirmed by thin layer chromatography using precoated silica gel G plates (20 × 20 cm) and a solvent system of dichloromethane and chloroform (1:99). The spots were developed in UV chamber (long and short wavelength) and Iodine chamber. Only **SP-1** was recrystallized from ethanol and its melting range was determined by open capillary method and is uncorrected. The other compounds were obtained as highly viscous sticky solids (Jayabharathi *et al*., 2007a; Rameshkumar *et al*., 2003).

Spectral data of synthesized compounds

*Compound **SP-1:** 3-benzyl-2,6-bis-(4-oxo-4H-chromen-3-yl)-piperidin-4-one*

% Yield (w/w): 27.10, Melting range (°C): 128–130, Elemental Analysis: C = 68.34 % H = 03.67 % N = 02.45 %;

IR KBr (cm^{-1}): 1,693.38 (C=O stretching), 3,415.70 (N–H stretching), 1,271.00 (C–N stretching); Mass *m/e* $[M+1]^+$: 478, ^1H NMR ($CDCl_3$, δ ppm): 2.17 (t, 1H, amine) 2.67 (s, 4H, methylene), 7.49–7.79 (m, 14H, benzene); ^{13}C NMR ($CDCl_3$, ppm): 33.7 (CH_2 aliphatic), 42.29 (CH_2 piperidine), 51.06 (CH piperidine), 56.86 (CH piperidine), 61.22 (CH piperidine), 117.66 (2CH chromene), 125.53 (2CH chromene), 126.12 (2CH chromene),125.91 (2C chromene), 126.44 (2C chromene), 134.21 (2CH chromene), 154.72 (2C chromene), 155.94 (2C chromene), 127.22 (CH benzene), 128.73–129.50 (4CH benzene), 138.86 (C benzene), 174.86 (2C chromene carbonyl), 204.53 (C piperidin carbonyl)

*Compound **SP-2:** 3-benzyl-2,6-bis-(4-fluorophenyl)-piperidin-4-one*

% Yield (w/w): 22.54; IR KBr (cm^{-1}): 1,712.67 (C=O stretching), 3,415.70 (N–H stretching), 1,230.50 (C–N stretching); Mass *m/e* $[M+1]^+$: 378; ^1H NMR ($CDCl_3$, δ ppm): 2.07–2.29 (m, 1H, amine), 3.75 (d, 1H, methine), 4.05 (d, 1H, methine), 6.91–7.27 (m, 12H, benzene); ^{13}C NMR ($CDCl_3$, ppm): 33.24 (CH_2 aliphatic), 45.81 (CH_2 piperidine), 58.68 (CH piperidine), 60.86 (CH piperidine), 64.73 (CH piperidine), 115.29 (4CH benzene), 127.22 (CH benzene), 128.73-130.55 (8CH benzene), 136.48 (C benzene), 138.53 (C benzene), 162.70 (C benzene), 207.08 (C piperidine carbonyl).

*Compound **SP-3:** 3-benzyl-2,6-di-naphthalen-1-yl-piperidin-4-one*

% Yield (w/w): 17.68; Elemental Analysis: C = 80.63 % H = 06.22 % N = 02.42 %; IR KBr (cm^{-1}): 1,708.81 (C=O stretching), 3,309.62 (N–H stretching), 1,217.00 (C–N stretching); Mass *m/e* $[M+1]^+$: 442, ^1H NMR ($CDCl_3$, δ ppm): 2.28–2.32 (d, 1H, amine), 2.92 (s, 4H, methylene), 3.37 (s, 1H, methine), 4.35 (d, 1H, methine), 7.08–7.10 (d, 5H, benzene), 7.18–7.68 (m, 12H, naphthalene); ^{13}C NMR ($CDCl_3$, ppm): 33.24 (CH_2 aliphatic), 44.90 (CH_2 piperidine), 59.41 (CH piperidine), 60.55 (CH piperidine), 63.66 (CH piperidine), 123.60–124.12 (2CH naphthalene), 125.68–126.26 (8CH naphthalene), 132.79–134.27 (8CH naphthalene), 132.89–134.37 (2C naphthalene), 127.22 (CH benzene), 128.73–129.50 (4CH benzene), 138.86 (C benzene), 207.08 (C piperidine carbonyl).

*Compound **SP-4:** 3-benzyl-2-(4-fluorophenyl)-6-naphthalen-2-yl-piperidin-4-one*

% Yield (w/w): 36.37; IR KBr (cm^{-1}): 1,710.74 (C=O stretching), 3,311.55 (N–H stretching), 1,224.71 (C–N stretching); Mass *m/e* $[M+1]^+$: 410; ^1H NMR ($CDCl_3$, δ ppm): 2.12 (s, 1H, amine), 2.72–2.90 (m, 4H, methylene), 3.45–4.14 (m, 3H, methine), 7.18–7.74 (m, 7H, naphthalene), 6.92–7.16 (m, 9H, benzene); ^{13}C NMR ($CDCl_3$, ppm): 33.26 (CH_2 aliphatic), 44.9 0 (CH_2 piperidine), 59.41 (CH piperidine), 60.21 (CH piperidine), 64.73 (CH piperidine), 115.29 (2CH benzene), 130.55 (2CH benzene), 136.48 (C benzene),162.70 (C benzene), 128.73–129.50 (4CH benzene), 127.22 (CH benzene), 138.86 (C benzene),125.6–127.22 (8CH naphthalene), 123.60 (CH naphthalene), 134.27 (C naphthalene), 207.08 (C piperidine carbonyl).

*Compound **SP-5:** 3-benzyl-2,6-bis-(5-methyl-thiophen-2-yl)-piperidin-4-one*

% Yield (w/w): 13.91; Elemental Analysis: C = 70.36 % H = 05.88 % N = 02.98 %; IR KBr (cm^{-1}): 1,712.67 (C=O stretching), 3,456.20 (N–H stretching), 1,224.71 (C–N stretching); Mass *m/e* $[M+1]^+$: 382; ^1H NMR ($CDCl_3$, δ ppm): 2.43–2.52 (d, 6H, methyl), 2.87–3.05 (m, 4H, methylene), 3.98–4.01 (d, 1H, methine), 4.25–4.29 (t, 1H, methine), 6.56–6.81 (m, 4H, thiophene), 7.06–7.25 (m, 5H, benzene); ^{13}C NMR ($CDCl_3$, ppm): 16.83 ($2CH_3$), 33.70 (CH_2 aliphatic), 44.31 (CH_2 piperidine), 56.82 (CH piperidine), 59.70 (CH piperidine), 62.92 (CH piperidine), 122.98 (2CH thiophene), 126.70–128.10 (2CH thiophene), 141.84 (2C thiophene),147.03–149.61 (2C thiophene), 128.10–129.50 (4CH benzene), 127.22 (CH benzene), 138.86 (C benzene), 204.53 (C piperidine carbonyl).

*Compound **SP-6:** 3-benzyl-2-(5-methyl-thiophen-2-yl)-6-naphthalen-2-yl-piperidin-4-one*

% Yield (w/w), 29.19; Elemental Analysis: C = 79.15 % H = 06.32 % N = 02.36 %; IR KBr (cm^{-1}): 1,708.81 (C=O stretching), 3,407.98 (N–H stretching), 1,217.00 (C–N stretching); Mass *m/e* $[M+1]^+$: 412; ^1H NMR ($CDCl_3$, δ ppm): 2.08–2.32 (m, 1H, amine), 2.42–2.66 (m, 3H, methyl), 2.73–2.93 (m, 4H, methylene), 3.39–4.28 (m, 2H, methine), 6.68 (m, 2H, thiophene), 7.08–7.21 (m, 5H, benzene), 7.38–7.59 (m, 7H, naphthalene); ^{13}C NMR ($CDCl_3$, ppm): 16.83 (CH_3), 33.70 (CH_2 aliphatic), 44.31 (CH_2 piperidine), 56.62 (CH piperidine), 59.81 (CH piperidine), 62.71 (CH piperidine), 122.96 (CH thiophene), 126.67 (CH thiophene), 142.84 (C thiophene), 149.58 (C thiophene), 128.32–129.50 (4CH benzene), 127.22 (CH benzene), 138.86 (C benzene), 125.68–127.22 (8CH naphthalene), 123.60 (CH naphthalene), 134.27 (C naphthalene), 205.14 (C piperidine carbonyl).

*Compound **SP-7:** 3-benzyl-6-(4-fluorophenyl)-2-(5-methyl-thiophen-2-yl)-piperidin-4-one*

% Yield (w/w): 09.23; IR KBr (cm^{-1}): 1,711.10 (C=O stretching), 3,400.30 (N–H stretching), 1,217.50 (C–N

stretching); Mass *m/e* $[M+1]^+$: 380; ^{1}H NMR ($CDCl_3$,δ ppm): 2.24–2.29 (d, 1H, amine), 2.39–2.43 (d, 3H, methyl), 2.80–2.96 (m, 4H, methylene), 3.75 (m, 1H, methine) 4.04 (m, 1H, methine), 6.60 (d, 2H, thiophene), 6.94–7.29 (m, 9H, benzene), 7.47–6.94; ^{13}C NMR ($CDCl_3$, ppm): 16.83 (CH_3), 33.70 (CH_2 aliphatic), 44.31 (CH_2 piperidine), 56.62 (CH piperidine), 59.81 (CH piperidine), 62.71 (CH piperidine), 122.96 (CH thiophene), 126.67 (CH thiophene), 142.84 (C thiophene), 149.58 (C thiophene), 128.32–129.50 (4CH benzene), 127.22 (CH benzene), 138.86 (C benzene), 115.38 (2CH benzene), 129.39 (2CH benzene), 138.53 (C benzene), 162.85 (C benzene), 205.14 (C piperidine carbonyl).

Compound ***SP-8:*** *3-benzyl-2,6-bis-(2-bromo-phenyl)-piperidin-4-one*

% Yield (w/w): 51.50; Elemental Analysis: C = 56.57 % H = 04.41 % N = 01.31 %; IR KBr (cm^{-1}): 1,709.60 (C=O stretching), 3,435.60 (N–H stretching), 1,216.80 (C–N stretching); Mass *m/e* $[M+1]^+$: 500; ^{1}H NMR ($CDCl_3$,δ ppm): 2.13–2.25 (d, 1H, amine), 2.89–2.97 (m, 4H, methylene), 4.48–4.53 (t, 2H, methine), 6.90–7.39 (m, 13H, benzene); ^{13}C NMR ($CDCl_3$, ppm): 33.24 (CH_2 aliphatic), 44.66 (CH_2 piperidine), 56.83 (CH piperidine), 60.83 (CH piperidine), 63.50 (CH piperidine), 127.04–128.29 (5CH benzene), 127.11–128.29 (2C benzene), 138.65–140.99 (2C benzene), 128.29–129.50 (4CH benzene), 138.86 (C benzene), 130.77–133.78 (4CH benzene), 207.08 (C piperidine carbonyl).

Compound ***SP-9:*** *3-benzyl-2-naphthalen-1-yl-6-(4-oxo-4H-chromen-3-yl)-piperidin-4-one*

% Yield (w/w): 20.69; Elemental Analysis: C = 70.32 % H = 04.81 % N = 00.50 %; IR KBr (cm^{-1}): 1,690.90 (C=O stretching), 3,392.30 (N–H stretching), 1,217.50 (C–N stretching); Mass *m/e* $[M+1]^+$: 460; ^{1}H NMR ($CDCl_3$,δ ppm): 2.14 (s, 1H, amine), 2.56–2.60 (t, 2H, methylene), 2.73–2.78 (t, 2H, methylene), 3.90 (s, 1H, methine), 4.06 (s, 1H, methine), 7.16–7.30 (m, 9H, benzene), 7.41–7.72 (m, 7H, naphthalene); ^{13}C NMR ($CDCl_3$, ppm): 33.24 (CH_2 aliphatic), 42.29 (CH_2 piperidine), 51.55 (CH piperidine), 60.55 (CH piperidine), 63.39 (CH piperidine), 117.66

(CH chromene), 127.20 (C chromene), 125.53–125.91 (2CH chromene), 126.12 (CH chromene), 134.21 (CH chromene), 151.04 (CH chromene), 155.94 (C chromene), 127.22 (CH benzene), 128.73–129.50 (4CH benzene), 138.86 (C benzene), 124.12 (CH naphthalene), 125.70–128.34 (6CH naphthalene), 132.20–134.15 (3C naphthalene), 174.86 (C chromene carbonyl), 206.85 (C piperidin carbonyl),

Compound ***SP-10:*** *3-benzyl-2-(4-fluorophenyl)-6-(4-oxo-4H-chromen-3-yl)-piperidin-4-one*

% Yield (w/w): 21.31; IR KBr (cm^{-1}): 1,700.00 (C=O stretching), 3,402.30 (N–H stretching), 1,219.50 (C–N stretching); Mass *m/e* $[M+1]^+$: 428; ^{1}H NMR ($CDCl_3$,δ ppm): 2.14–2.19 (d, 1H, amine), 2.55–2.62 (t, 2H, methylene), 2.82–2.87 (t, 2H, methylene), 3.90 (d, 1H, methine), 4.06 (s, 1H, methine), 7.07–7.76 m,

(13H, benzene); ^{13}C NMR ($CDCl_3$, ppm): 33.24 (CH_2 aliphatic), 42.29 (CH_2 piperidine), 51.55 (CH piperidine), 60.55 (CH piperidine), 64.19 (CH piperidine), 117.66 (CH chromene), 127.20 (C chromene), 125.53–125.91 (2CH chromene), 126.12 (CH chromene), 134.21 (CH chromene), 151.04 (CH chromene), 155.94 (C chromene), 127.22 (CH benzene), 128.73–129.50 (4CH benzene), 138.86 (C benzene), 115.29 (2CH benzene), 130.55 (2CH benzene), 136.48 (C benzene),162.70 (C benzene), 174.86 (C chromene carbonyl), 206.85 (C piperidin carbonyl),

In vitro evaluation of antimicrobial activity

The synthesized compound was tested for in vitro antimicrobial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *B. pumilus*, *Micrococcus luteus*, *Pseudomonas aeruginosa*, *P. fluorescens*, *Escherichia coli*, *Aspergillus niger*, and *Penicillium chrysogenum* using cup-plate and tube assay method. A previously liquefied medium with the requisite quantity of suspension of the microorganism was inoculated. Then, the suspension was added to the medium at room temperature and the inoculated medium was poured immediately into Petri dishes with uniform thickness, by placing the dishes on a uniform level surface. The prepared dishes were stored in a manner so as to ensure that no significant growth or death of test organism occurred before the dishes were used and that surface of agar layer was dry at the time of use. The solutions of antimicrobial agents **SP-1** to **SP-10** (25–250 μg/mL in DMSO) were applied to the surface of the solid medium in cavities (6 mm) prepared in the agar. Standard drugs used (norfloxacin and fluconazole) were taken in reported quantities, i.e., 50 μg/mL. The volumes of the solutions were added to each cavity in uniform and sufficient quantities to almost fill the holes. The plates were left for 1–4 h at room temperature, as a period of pre-incubation diffusion, to minimize the effects of variation in the time between the applications of the different solutions. They were incubated for 18 h at the temperature suitable for individual microorganism. The diameters of the circular zones of inhibition were measured (Indian Pharmacopoeia, Ministry of Health and Family Welfare, Controller of Publications, Govt. of India, Delhi, II (P-Z) 1996).

Table 1 In vitro antifungal and antibacterial activities of compounds **SP-1** to **SP-10**

Diameter of zone of inhibition (mm)										
Compounds	Concn. (μg/mL)	Fungal strains		Bacterial strains						
		AN	PC	SA	BS	BP	ML	PA	PF	EC
SP-1	25	–	–	–	–	–	–	–	12.1 ± 0.1	–
	50	13.3 ± 0.1	12.0 ± 1.0	12.37 ± 0.2	12.2 ± 0.1	12.3 ± 0.3	14.9 ± 0.5	12.0 ± 0.4	15.0 ± 0.2	12.3 ± 0.2
	100	14.2 ± 0.2	14.1 ± 0.1	13.1 ± 0.6	14.3 ± 0.2	13.6 ± 0.7	17.0 ± 0.5	14.1 ± 0.2	16.8 ± 0.3	15.1 ± 0.5
	150	15.2 ± 0.5	15.0 ± 0.1	15.7 ± 0.6	17.3 ± 1.0	13.7 ± 0.7	18.1 ± 0.3	16.1 ± 0.6	19.5 ± 0.5	17.2 ± 0.3
	200	17.1 ± 0.3	16.0 ± 0.2	17.1 ± 0.2	18.9 ± 0.1	15.3 ± 0.2	19.4 ± 0.3	18.5 ± 0.5	21.2 ± 1.0	18.1 ± 0.1
	250	19.4 ± 1.0	18.3 ± 0.5	18.1 ± 0.1	20.8 ± 1.0	17 ± 1.0	21.0 ± 0.5	21.1 ± 0.2	23.0 ± 1.0	20.5 ± 0.5
SP-2	25	14.0 ± 1.0	14.4 ± 0.1	–	12.9 ± 0.6	–	–	–	–	13.1 ± 0.2
	50	15.0 ± 1.0	15.1 ± 0.7	11.4 ± 0.1	15.4 ± 0.1	14.1 ± 0.2	11.2 ± 0.1	14.1 ± 1.0	15.5 ± 0.3	16.2 ± 0.3
	100	16.2 ± 0.4	17.5 ± 0.4	12.2 ± 0.5	16.4 ± 0.1	15.1 ± 0.4	16.0 ± 0.5	17.3 ± 0.3	18.1 ± 0.8	17.0 ± 1.0
	150	18.5 ± 0.1	18.1 ± 0.2	14.0 ± 1.0	17.5 ± 0.2	16.3 ± 0.1	18.1 ± 0.3	18.4 ± 0.5	20.0 ± 0.5	18.2 ± 0.4
	200	19.0 ± 1.0	19.6 ± 0.5	15.3 ± 0.3	18.5 ± 0.4	17.0 ± 0.5	20.1 ± 0.1	19.0 ± 1.0	21.2 ± 0.1	19.3 ± 0.5
	250	20.1 ± 0.6	21.3 ± 0.2	18.0 ± 1.0	20.1 ± 0.1	19.3 ± 0.4	22.0 ± 1.0	21.1 ± 0.4	24.3 ± 0.1	22.0 ± 1.0
SP-3	25	13.2 ± 0.2	13.0 ± 0.4	–	12.1 ± 0.3	–	–	–	–	14.5 ± 0.6
	50	15.0 ± 1.0	16.9 ± 0.5	12.1 ± 0.1	14.7 ± 0.5	15.2 ± 0.4	11.6 ± 0.7	15.3 ± 0.2	14.5 ± 0.3	16.4 ± 0.1
	100	17.6 ± 0.2	18.3 ± 0.1	13.5 ± 0.8	16.1 ± 0.4	17.3 ± 0.5	15.1 ± 0.2	17.3 ± 0.1	16.5 ± 1.0	18.1 ± 0.3
	150	18.0 ± 2.0	19.8 ± 0.3	14.5 ± 0.1	17.3 ± 0.2	18.2 ± 0.3	16.3 ± 0.3	19.1 ± 0.8	18.6 ± 0.3	19.0 ± 1.0
	200	19.5 ± 0.5	20.5 ± 0.5	16.1 ± 0.2	19.0 ± 0.1	19.1 ± 0.5	18.6 ± 0.1	20.6 ± 0.6	20.2 ± 0.7	20.3 ± 0.4
	250	20.4 ± 0.1	21.0 ± 1.0	18.8 ± 0.9	21.0 ± 0.2	20.5 ± 0.5	23.0 ± 0.1	22.4 ± 0.5	23.0 ± 1.0	22.2 ± 0.5
SP-4	25	13.1 ± 0.2	13.2 ± 0.3	–	12.4 ± 0.5	–	–	–	–	14.5 ± 0.2
	50	16.4 ± 0.8	15.0 ± 0.5	12.5 ± 0.7	14.9 ± 0.2	13.4 ± 0.2	14.1 ± 0.2	14.5 ± 0.5	14.3 ± 0.4	16.0 ± 1.0
	100	17.1 ± 0.1	17.0 ± 0.5	14.3 ± 0.1	15.2 ± 0.0	15.2 ± 0.1	15.0 ± 0.5	15.1 ± 0.4	16.5 ± 0.5	18.5 ± 0.1
	150	19.0 ± 0.1	18.3 ± 0.2	16.8 ± 0.3	17.2 ± 0.7	16.1 ± 0.3	17.0 ± 0.8	18.4 ± 0.2	19.1 ± 0.2	19.3 ± 0.4
	200	20.5 ± 0.4	19.1 ± 0.6	18.0 ± 1.0	18..5 ± 0.3	17.0 ± 1.0	19.9 ± 0.2	20.4 ± 0.7	21.3 ± 0.4	20.2 ± 0.1
	250	21.7 ± 0.3	20.2 ± 0.5	21.1 ± 0.2	20.0 ± 1.0	18.2 ± 0.5	23.6 ± 0.4	22.0 ± 0.1	23.2 ± 0.2	22.5 ± 0.8
SP-5	25	–	–	–	–	–	–	–	12.0 ± 0.1	–
	50	14.0 ± 0.9	13.8 ± 0.3	11.2 ± 0.6	13.5 ± 1.0	13.2 ± 0.7	15.0 ± 0.5	14.1 ± 0.3	15.7 ± 0.2	13.9 ± 0.4
	100	16.2 ± 0.7	14.2 ± 0.4	13.1 ± 0.5	15.2 ± 0.7	15.5 ± 0.3	16.4 ± 0.4	15.1 ± 0.3	17.4 ± 0.8	15.3 ± 0.6
	150	17.4 ± 0.3	16.0 ± 0.5	14.4 ± 0.1	16.0 ± 0.5	16.2 ± 0.3	18.2 ± 0.2	16.0 ± 1.0	19.5 ± 0.1	17.3 ± 0.1
	200	19.2 ± 0.6	18.1 ± 0.3	17.0 ± 0.7	18.2 ± 0.9	17.0 ± 0.3	19.4 ± 0.8	18.6 ± 0.3	20.4 ± 0.5	19.6 ± 0.1
	250	20.0 ± 0.1	19.5 ± 0.8	19.1 ± 1.0	20.0 ± 0.5	19.0 ± 0.5	22.1 ± 0.7	19.6 ± 0.1	23.0 ± 0.5	22.5 ± 0.3
SP-6	25	–	–	–	–	11.1 ± 0.5	–	–	–	–
	50	14.1 ± 0.3	13.4 ± 0.5	13.1 ± 0.7	12.1 ± 0.9	13.5 ± 0.3	14.0 ± 0.5	13.5 ± 0.2	15.0 ± 0.0	12.1 ± 0.2
	100	15.5 ± 0.4	14.0 ± 0.5	14.3 ± 0.4	14.1 ± 0.1	15.0 ± 0.7	16.2 ± 0.3	15.1 ± 0.4	17.4 ± 0.5	14.3 ± 0.5
	150	16.5 ± 0.1	15.2 ± 0.2	15.5 ± 0.5	16.6 ± 0.6	16.6 ± 0.8	18.0 ± 1.0	16.2 ± 0.6	18.2 ± 0.2	16.2 ± 0.3
	200	18.3 ± 0.3	17.0 ± 1.0	16.1 ± 0.9	17.1 ± 0.7	18.5 ± 0.1	20.0 ± 1.0	17.0 ± 0.5	20.5 ± 0.3	18.2 ± 0.7
	250	19.0 ± 0.1	19.3 ± 0.2	20.4 ± 0.7	19.5 ± 0.1	20.6 ± 0.5	23.0 ± 0.1	18.4 ± 0.8	22.1 ± 0.6	21.0 ± 1.0
SP-7	25	13.0 ± 0.1	13.6 ± 0.3	–	12.2 ± 0.5	12.0 ± 1.0	–	12.1 ± 0.3	–	–
	50	14.0 ± 0.3	15.1 ± 0.4	11.2 ± 0.8	14.4 ± 0.3	14.0 ± 0.4	14.3 ± 0.5	14.4 ± 0.2	14.5 ± 0.3	12.1 ± 0.3
	100	15.3 ± 0.7	16.1 ± 0.3	13.0 ± 0.6	15.2 ± 0.9	16.1 ± 0.5	17.4 ± 0.3	16.0 ± 0.5	16.2 ± 1.0	13.0 ± 0.5
	150	16.6 ± 0.8	17.0 ± 0.1	16.5 ± 0.2	17.5 ± 0.1	17.3 ± 0.8	18.2 ± 0.7	17.0 ± 0.1	18.4 ± 0.4	14.3 ± 1.0
	200	18.3 ± 0.5	19.3 ± 0.3	18.0 ± 1.0	19.3 ± 0.4	18.2 ± 0.2	19.3 ± 0.5	18.1 ± 0.8	20.0 ± 0.1	16.5 ± 0.6
	250	19.2 ± 0.8	20.2 ± 0.5	19.7 ± 0.3	21.3 ± 0.2	20.0 ± 0.5	23.1 ± 0.5	19.1 ± 0.3	22.3 ± 0.5	18.1 ± 0.5
SP-8	25	12.5 ± 0.2	–	–	–	12.0 ± 1.0	–	–	–	–
	50	14.0 ± 0.5	14.4 ± 0.2	12.2 ± 0.1	13.5 ± 0.5	14.6 ± 0.2	13.3 ± 0.6	12.5 ± 1.0	–	12.1 ± 0.2
	100	15.5 ± 1.0	15.1 ± 0.5	13.4 ± 0.6	15.1 ± 0.3	15.5 ± 0.2	15.0 ± 0.7	13.2 ± 0.1	15.6 ± 0.4	14.0 ± 0.5
	150	17.2 ± 0.7	16.2 ± 0.1	16.2 ± 1.0	16.3 ± 0.5	16.5 ± 0.3	19.1 ± 0.7	14.2 ± 0.0	18.1 ± 0.9	15.3 ± 0.6

Table 1 continued

Diameter of zone of inhibition (mm)										
Compounds	Concn. (μg/mL)	Fungal strains		Bacterial strains						
		AN	PC	SA	BS	BP	ML	PA	PF	EC
	200	18.2 ± 0.5	18.4 ± 0.7	18.3 ± 0.2	18.1 ± 0.2	18.5 ± 0.5	21.0 ± 0.1	16.2 ± 0.4	20.4 ± 0.1	17.1 ± 0.7
	250	20.4 ± 0.1	19.4 ± 0.8	20.5 ± 0.2	20.0 ± 1.0	19.3 ± 0.8	24.5 ± 0.5	18.2 ± 0.3	23.3 ± 0.2	18.0 ± 1.0
SP-9	25	12.3 ± 0.3	–	–	12.1 ± 0.7	11.2 ± 0.4	–	–	–	–
	50	14.1 ± 0.0	12.1 ± 0.1	12.0 ± 0.3	14.3 ± 0.8	12.2 ± 0.2	14.1 ± 0.2	12.2 ± 0.7	12.0 ± 0.5	13.2 ± 0.6
	100	15.2 ± 0.7	15.5 ± 0.1	14.3 ± 0.8	16.2 ± 0.2	14.5 ± 1.0	16.2 ± 0.5	15.3 ± 0.5	15.1 ± 0.2	15.1 ± 0.4
	150	17.1 ± 0.6	16.2 ± 0.1	15.1 ± 0.1	18.5 ± 0.3	15.4 ± 0.3	20.5 ± 0.1	17.0 ± 0.1	17.3 ± 1.0	16.0 ± 0.2
	200	18.0 ± 0.3	18.1 ± 0.9	17.2 ± 0.7	20.1 ± 0.5	17.3 ± 0.7	22.3 ± 0.3	18.1 ± 0.3	20.5 ± 0.5	18.5 ± 0.1
	250	19.4 ± 0.1	19.0 ± 0.5	19.3 ± 0.3	22.1 ± 0.4	18.5 ± 0.1	24.3 ± 0.5	21.2 ± 0.3	22.1 ± 0.2	20.2 ± 0.5
SP-10	25	12.2 ± 0.2	–	–	–	–	–	–	–	–
	50	13.0 ± 0.5	12.0 ± 0.5	12.1 ± 0.7	14.0 ± 0.9	12.1 ± 0.5	18.1 ± 0.4	12.1 ± 0.1	11.1 ± 0.4	13.1 ± 0.5
	100	15.3 ± 0.4	14.2 ± 0.2	14.5 ± 0.1	16.1 ± 0.4	15.5 ± 1.0	20.4 ± 0.4	15.4 ± 0.4	16.2 ± 0.6	15.5 ± 0.1
	150	16.4 ± 0.9	15.5 ± 1.0	16.4 ± 0.6	17.2 ± 0.6	16.1 ± 0.5	21.1 ± 0.3	16.3 ± 0.7	18.1 ± 0.5	17.2 ± 0.4
	200	17.1 ± 0.3	17.3 ± 1.0	18.1 ± 0.2	20.0 ± 0.2	18.0 ± 1.0	22.0 ± 0.2	18.1 ± 0.2	20.0 ± 1.0	19.1 ± 0.3
	250	19.1 ± 0.8	19.3 ± 0.4	21.2 ± 0.5	22.5 ± 0.1	19.2 ± 0.6	24.2 ± 0.7	21.0 ± 0.5	23.1 ± 0.4	21.5 ± 0.1
A	50	–	–	25.3 ± 0.5	23.5 ± 0.2	28.2 ± 0.5	26.3 ± 0.7	28.3 ± 1.0	25.5 ± 1.0	36.2 ± 0.4
B	50	28.8 ± 0.2	20.0 ± 1.0	–	–	–	–	–	–	–
C	–	–	–	–	–	–	–	–	–	–

Values are expressed in triplicates, i.e., mean ± SD ($n = 3$)

A norfloxacin, *B* fluconazole, *C* control (DMSO)

AN *Aspergillus niger* (MTCC No. 2546), PC *Penicillium chrysogenum* (MTCC No. 161), SA *Staphylococcus aureus* (MTCC No. 1430), BS *Bacillus subtilis* (MTCC No. 441), BP *Bacillus pumilus* (MTCC No. 1456), ML *Micrococcus luteus* (MTCC No. 1538), PA *Pseudomonas aeruginosa* (MTCC No. 424), PF *Pseudomonas fluorescens* (MTCC No. 2421), EC *Escherichia coli* (MTCC No. 1573)

Determination of minimum inhibitory concentration (MIC)

Tube assay method was performed to determine the MICs of the synthesized compounds. MICs are considered the "gold standard" for determining the susceptibility of organisms to antimicrobials and are therefore used to judge the performance of all other methods of susceptibility testing. To the test tubes containing 4.5 mL of nutrient medium previously seeded with the appropriate test organism, 1.0 mL of each concentration (25, 50, 100, 150, 200, and 250 μg/mL) of the sample solution was added. Standard drugs used (norfloxacin and fluconazole) were taken in reported quantities, i.e., 50 μg/mL. An inoculated broth containing no antibiotic was included as growth control and a tube of uninoculated broth was used as sterility control. These test tubes were then, incubated for 24 h at suitable temperature. Then, optical density was recorded using Labotronics Digital Photo Colorimeter Model No. 13 at 530 nm. The sharp fall in the readings of optical density was considered as MIC.

Results and discussion

A series of novel 3-benzyl-2,6-diarylpiperidine-4-one derivatives were synthesized by reacting dry ammonium acetate, different aromatic/heteroaromatic aldehydes, and benzylacetone in ethanol. All the synthesized compounds were characterized by IR, MS, and ^{1}H NMR spectra as well as elemental analysis so as to assign the structures. IR spectra were recorded on Shimadzu 8400S and Perkin Elmer Spectrum RX1 FTIR spectrophotometers. The KBr pellet technique was adopted to record the spectra. The tentative assignment of the vibrational frequencies of the synthesized compounds were compared with those reported in the literature. The spectral shifts and intensity changes observed explain the influence of the substituents. Mass spectra were recorded on JEOL-AccuTOF JMS-T100LC spectrometer from Central Drug Research Institute, Lucknow, India. ^{1}H NMR spectra were recorded at 400 MHz on Bruker DRX-300 spectrometer and ^{13}C NMR data were recorded on Advance-400 MHz, Bruker (Switzerland) spectrometer using tetramethyl silane as internal standard from Central Drug Research Institute, Lucknow, India. ^{1}H

Table 2 In vitro antifungal and antibacterial activities of compounds **SP-1** to **SP-10**

Minimum inhibitory concentration (MIC, μg/mL)									
Fungal strains			Bacterial strains						
Compounds	AN	PC	SA	BS	BP	ML	PA	PF	EC
SP-1	150	200	150	150	150	150	150	50	150
SP-2	50	50	250	50	200	250	150	150	50
SP-3	50	50	150	50	150	250	150	150	50
SP-4	50	50	200	50	200	150	150	150	100
SP-5	150	150	200	150	200	150	150	100	150
SP-6	150	150	150	150	100	150	150	150	150
SP-7	50	100	200	50	50	150	100	150	150
SP-8	100	150	150	150	100	150	150	200	150
SP-9	50	200	200	50	50	150	150	150	150
SP-10	100	150	200	150	50	150	200	200	150
A	–	–	50	50	50	50	50	50	50
B	50	50	–	–	–	–	–	–	–

Each value is mean of three independent experiments ($n = 3$). Minimum inhibitory concentrations were determined by seriel dilution method for microdilution plates

A norfloxacin, *B* fluconazole

AN *Aspergillus niger* (MTCC No. 2546), PC *Penicillium chrysogenum* (MTCC No. 161), SA *Staphylococcus aureus* (MTCC No. 1430), BS *Bacillus subtilis* (MTCC No. 441), BP *Bacillus pumilus* (MTCC No. 1456), ML *Micrococcus luteus* (MTCC No. 1538), PA *Pseudomonas aeruginosa* (MTCC No. 424), PF *Pseudomonas fluorescens* (MTCC No. 2421), EC *Escherichia coli* (MTCC No. 1573)

NMR and ^{13}C NMR spectra of 3-benzyl-2,6-diaryl-4-piperidones were analyzed and effect of varying the substituents was observed on the ^{1}H and ^{13}C chemical shifts. The signals in the region of 6.32–7.8 ppm are due to the aryl/heteroaryl group protons at C-2, C-6 merged together to give multiplet with benzylic protons. Deshielding of the *ortho* protons of aryl/heteroaryl and benzylic protons can be attributed to the lone pair of electrons on the nitrogen in piperidone. Elemental analysis was carried out on Elemental Vario EL III analyzer from Central Drug Research Institute, Lucknow, India.

The in vitro antibacterial activity of the compounds was studied by cup-plate method as well as by tube assay method against *S. aureus* (MTCC No. 1430), *B. subtilis* (MTCC No. 441), *B. pumilus* (MTCC No. 1456), *M. luteus* (MTCC No. 1538), *P. aeruginosa* (MTCC No. 424), *P. fluorescens* (MTCC No. 2421), and *E. coli* (MTCC No. 1573). Norfloxacin was taken as the standard drug for the antibacterial activity studies. All of the synthesized compounds demonstrated antimicrobial activity as shown in Table 1. A close examination of MIC values indicates that all the compounds exhibited a varied range (50–250 μg/mL) of antibacterial potency against the tested bacterial strains (Table 2). Compounds **SP-2, SP-3, SP-4, SP-7**, and **SP-9** exhibited maximum activity against *B. subtilis* (50 μg/mL); **SP-7** and **SP-9** against *B. pumilus* (50 μg/mL); and compounds **SP-2** and **SP-3** showed maximum activity against *E. coli* (50 μg/mL). The remaining compounds showed moderate to good activity against all the bacterial strains.

The in vitro antifungal activity of compounds was examined against the fungal strains *A. niger* (MTCC No. 2546) and *P. chrysogenum* (MTCC No. 161). Fluconazole was chosen as the standard drug for the antifungal study. MIC values of all the compounds fall in the range of 50–250 μg/mL. Compounds **SP-2, SP-3, SP-4, SP-7,** and **SP-9** showed maximum activity against *A. niger* (50 μg/mL); **SP-2, SP-3,** and **SP-4** against *P. chrysogenum* (50 μg/mL), whereas the remaining compounds exhibited moderate to good activity (Tables 1, 2).

Conclusions

Among the compounds tested for antibacterial activity, compounds with symmetrical substitution at C-2 and C-6 by aryl groups exhibited promising activity. Further, it was found that 4-fluorophenyl, naphthalen-1-yl, and 4-oxo-4*H*-chromen-3-yl groups were important in eliciting good antibacterial activity. Similarly, among the antifungal profile of the compounds tested, the presence of 4-fluorophenyl and naphthalen-1-yl groups at C-2 and C-6 positions of piperidin-4-one ring played an important role in eliciting inhibition of all the fungi under test. Thus, a close examination of in vitro antibacterial and antifungal activity profiles for the 3-benzyl-2,6-diarylpiperidin-4-ones, against

the tested bacterial and fungal strains, clearly indicates that compounds **SP-2** and **SP-3** were the most potent antimicrobial agents in the series. Significantly, all the compounds showed better antifungal activity as compared to the antibacterial activity and may thus hold promise as antifungal agents. This finding increases the importance of this work because most of the antimicrobial agents are antibacterial, rather than antifungal, and there is an urgent need for antifungal agents.

The study reveals that several modifications are possible in the piperidin-4-one ring system. Piperidin-4-ones when reacted with thiosemicarbazide and hydroxylamine hydrochloride give thiosemicarbazone and oxime, respectively, which themselves have their own activity and could lead to more potent and highly active compounds.

Acknowledgments We express our sincere gratitude to Central Drugs Research Institute, Lucknow, India for providing the library facilities and sophisticated analytical instrument facilities.

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