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Synthesis, characterization, and antimicrobial evaluation of novel spiropiperidones

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Abstract: Novel spiro derivatives of piperidone **4a–f** were synthesized, characterized, and screened against a panel of different bacterial and fungal strains. The study revealed the potential of these molecules for further development as antimicrobial agents.

Keywords: antimicrobial activity; azomethines; piperidone; Schiff base.

Introduction

Many heterocyclic compounds bearing a piperidine skeleton show pharmacological activity and are widely distributed in nature [1–3]. Among these heterocycles, spiropiperidines have been identified as privileged structures in medicinal chemistry and have attracted increasing interest in the past few years. The most recent reports are representative of their wide range of biological activities as components of new stearoyl CoA desaturase 1(SCD-1) inhibitors, nociceptin receptor ligands, chemokine receptor type 5 (CCR5) antagonists, neuropeptide Y (NPYY) receptor antagonists, calcitonin gene-related peptide (CGRP), receptor antagonists, tryptase inhibitors, prostaglandin d2 (PGD2) receptor antagonists, and checkpoint (ChK1) kinase inhibitors. Piperidones were reported to possess analgesic, anti-inflammatory, central nervous system, local anesthetic, anticancer, and antimicrobial activity [4, 5].

The objective of the present study is to develop a novel cluster of spiro derivatives of *N*-methyl-4-piperidones with better pharmacological properties than the reference drugs gentamicin and fluconazole. Literature survey revealed chloro, methoxy, and nitro functional groups are important functionalities in medicinal chemistry [6]. In particular, the chloro substitution of piperidone derivatives increases the antibacterial potency, and the compounds substituted with a methoxy group show better antifungal activity [7]. Several studies have pointed out the major role of lipophilicity in antimicrobial activity [8, 9], and in particular, it has been suggested that the mode of action of piperidone derivatives with antibacterial activity involves an unspecific interaction, which is related to the hydrophobic character of the molecules on protein thiol groups [10–13]. In particular, the increased activity of spiro piperidone derivatives can be explained on the basis of that compounds have better fit at the receptor site and can be transformed into more effective compounds with antimicrobial activity point of view. It was therefore thought to synthesize some novel spiro derivatives of piperidone bearing methoxy and chloro and nitro groups to produce compounds with the expected enhanced activity.

Results and discussion

The synthetic route to the proposed compounds is shown in Scheme 1. The synthesis of 3,5-bis(4-substituted benzylidene)-1-methyl-2,6-diphenylpiperidin-4-ones **1a–c** and the subsequent formation of Schiff bases **2a–c** were achieved by using the known literature procedures [14]. The formation of thiazolidinone ring in **3a–c** was achieved by intermolecular cyclization of **2a–c** with mercaptoacetic acid. The Claisen condensation of **3a–c** with substituted benzaldehydes furnished the final products **4a–f**. The structural assignments of the compounds **4a–f** were based on the analysis of their ^{1}H NMR, ^{13}C NMR, and mass spectra. Satisfactory elemental analyses were obtained.

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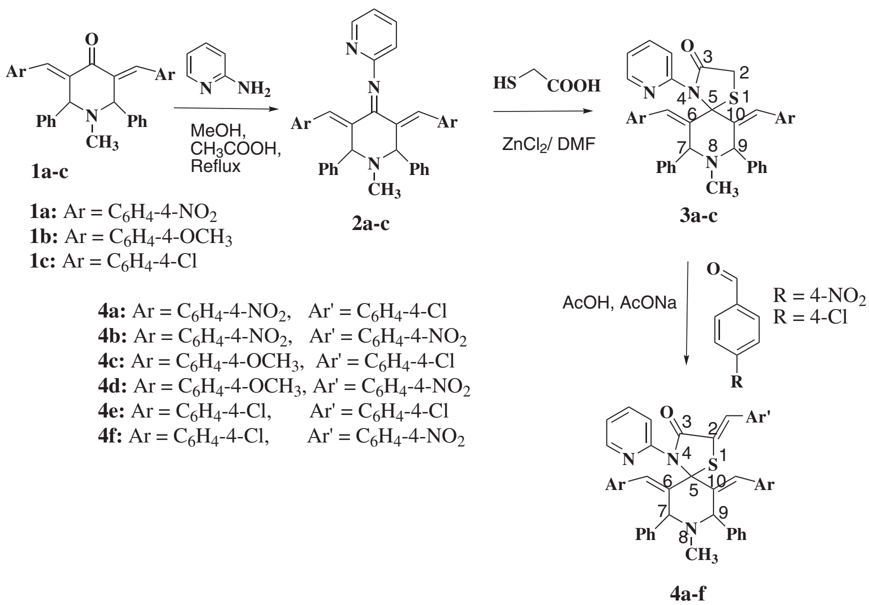

Scheme 1

The synthesized compounds **4a–f** were screened for their antimicrobial activity against a panel of several bacterial strains [*Staphylococcus aureus* (*Sa*), *Bacillus subtilis* (*Bs*), *Pseudomonas aeruginosa* (*Pa*), *Escherichia coli* (*Ec*), and *Klebsiella pneumoniae* (*Kp*)] and fungal strains [*Candida albicans* (*Ca*), *Aspergillus niger* (*An*),

Table 1 Antibacterial and antifungal activities of compounds **4a–f**: diameter of zone of inhibition (mm) by disc-diffusion assay (μg/disc) and MIC values (μg/mL) by twofold serial dilution technique.

Compounds	Zone of inhibition (mm) and MIC values of bacterial strains					Zone of inhibition (mm) and MIC values of fungal strains				
	Sa	*Pa*	*Bs*	*Ec*	*Kp*	*Ca*	*Af*	*An*	*Pc*	*Tr*
4a	12	08[a]	08[a]	08[a]	09[a]	08[a]	09[a]	08[a]	08[a]	17
	100[a]	100[a]	100[a]	100[a]	100[a]	100[a]	100[a]	100[a]	100[a]	25.0
4b	25	08[a]	10	22	08[a]	09[a]	08[a]	08[a]	09[a]	08[a]
	6.25	100[a]	100[a]	**12.5**[b]	100[a]	100[a]	100[a]	100[a]	100[a]	100[a]
4c	08[a]	09[a]	08[a]	10	08[a]	20	08[a]	10	10	09[a]
	100[a]	100[a]	100[a]	100[a]	100[a]	100[a]	100[a]	100[a]	100[a]	100[a]
4d	12	08[a]	09[a]	08[a]	10	27[c]	09[a]	09[a]	08[a]	08[a]
	100[a]	100[a]	100[a]	100[a]	100[a]	**3.12**[c]	100[a]	100[a]	100[a]	100[a]
4e	10	08[a]	08[a]	08[a]	08[a]	10	10	08[a]	22[c]	19
	100[a]	100[a]	100[a]	100[a]	100[a]	100[a]	100[a]	100[a]	12.5	>12.5
4f	35[b]	38[b]	12	08[a]	08[a]	08[a]	08[a]	08[a]	08[a]	16
	3.12[b]	**3.12**[b]	100[a]	100[a]	100[a]	100[a]	100[a]	100[a]	100[a]	100[a]
Control	06	06	06	06	06	06	06	06	06	06
Gentamicin	22	23	22	20						
	6.25									
Ampicillin	29	20	18	19						
Ciprofloxacin	20–28	22–30	–	26						
Fluconazole						18				
						6.25				
Chloroamphenicol				32						

[a]No activity.
[b]Entries in bold font indicate lower MIC values than for the reference drugs gentamicin, ampicillin and ciprofloxacin, and chloroamphenicol [15].
[c]Entries in bold font indicate lower MIC values than for the reference drug fluconazole [16].

Aspergillus fumigatus (*Af*), *Penicillium chrysogenum* (*Pc*), and *Trichophyton rubrum* (*Tr*)]. The antimicrobial activities were evaluated by measuring the diameter of zone of inhibition and minimal inhibitory concentrations (MIC) values against the test organisms. Ampicillin, chloramphenicol, ciprofloxacin, fluconazole, and gentamicin [15, 16] were used reference antibiotics (see Supplementary Information). Although all spiro derivatives of piperidone were found to show antimicrobial activity against different strains in these two assays, compounds **4d** and **4f** are clearly outstanding in their antimicrobial properties. For several pathogens, these compounds were more active than the reference drugs. Compound **4d** selectively inhibits the growth of *C. albicans*, and compound **4f** is highly active against *S. aureus* and *P. aeruginosa* with MIC values of 3.12 μg/mL. Detailed activity results are summarized in Table 1.

Conclusion

New piperidone derivatives were synthesized and screened for their antimicrobial activity. Compounds **4d** and **4f** exhibit outstanding antifungal and antibacterial properties.

Experimental

Melting points were determined in an open capillary tube and are uncorrected. IR spectra (KBr pellets) were recorded on a Perkin-Elmer FTIR spectrophotometer; ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ on a Bruker 400 MHz instrument. EI mass spectra were recorded on a Va 70–70H mass spectrometer at 70 eV. Elemental analysis was performed on a Perkin-Elmer 2400 series II elemental CHNS analyzer.

In vitro antibacterial and antifungal activities were conducted using a disc-diffusion method [17, 18] by standard microbroth dilution as per NCCLS protocol. 3,5-Bis(4-substituted benzylidene)-1-methyl-2,6-diphenylpiperidin-4-ones **1a–c** [19] and *N*-(3,5-bis(4-substituted benzylidene)-1-methyl-2,6-diphenyl piperidin-4-ylidene)pyridin-2-amines **2a–c** [20] were prepared by known literature procedures.

General procedure for the preparation of 6,10-bis(4-substituted benzylidene)-8-methyl-7,9-diphenyl-4-(pyridin-2-yl)-1-thia-4,8-diazaspiro[4,5]decan-3-ones (3a–c)

A well-stirred solution of *N*-(3,5-bis(4-substituted benzylidene)-1-methyl-2,6-diphenyl piperidin-4-ylidene)pyridin-2-amine (**2a–c**, 0.01 mol) in dry DMF containing a catalytic amount of anhydrous $ZnCl_2$ and thioglycolic acid (0.02 mol) was heated under reflux for 8–10 h. Excess of solvent was removed under reduced pressure, and the residue was poured on to crushed ice. The resultant solid was filtered, washed, and crystallized from ethanol.

6,10-Bis(4-nitrobenzylidene)-8-methyl-7,9-diphenyl-4-(pyridin-2-yl)-1-thia-4,8-diazaspiro-[4,5]decan-3-one (3a) This compound was obtained in 67% yield; mp 241–245°C; ^{1}H NMR: δ 2.67 (s, 3H, N-CH_3), 3.32 (s, 2H, 2-CH_2), 4.36 (br s, 2H, 7,9-H), 6.13 (s, 2H, 6,10-C=CH-Ar), 6.40 (br s, 2H, 3′,5′-H), 7.26–8.21 (m, 18 H, ArH and pyridine); EI-MS: *m/z* 681 (M^+), 682 (M^++1). Anal. Calcd for $C_{39}H_{31}N_5O_5S$: C, 68.72; H, 4.55; N, 10.27. Found: C, 67.93; H, 4.49; N, 10.14.

6,10-Bis(4-methoxybenzylidene)-8-methyl-7,9-diphenyl-4-(pyridin-2-yl)-1-thia-4,8 diazaspiro[4,5]decan-3-one (3b) This compound was obtained in 61% yield; mp 228–230°C; ^{1}H NMR: δ 2.87 (s, 3H, N-CH_3), 3.22 (s, 2H, 2-CH_2), 3.74, 3.77 (s, 6H, 4′,4″-OCH_3), 4.26 (br s, 2H, 7,9-H), 6.13 (s, 2H, 6,10-C=CH-Ar), 6.91 (br s, 4H, 3′,5′,3″,5″-H), 7.36–8.17 (m, 18 H, ArH and pyridine); IR (cm^{-1}): 1738 (C=O, str), 1637 (C=N, str.), 1610 (C=C, str), 1240 (C-N, str),1216, (C-O, str.), 688 (C-S-C, str); EI-MS: *m/z* 651 (M^+), 653(M^++1). Anal. Calcd for $C_{41}H_{37}N_3O_3S$: C, 75.57; H, 5.68; N, 6.45. Found: C, 75.11; H, 5.56; N, 6.50.

6,10-Bis(4-chlorobenzylidene)-8-methyl-7,9-diphenyl-4-(pyridin-2-yl)-1-thia-4,8-diazaspiro[4,5]decan-3-one (3c) This compound was obtained in 65% yield; mp 167–168°C; ^{1}H NMR: δ 2.93 (s, 3H, N-CH_3), 3.17 (s, 2H, 2-CH_2), 4.48 (br s, 2H, 7,9-H), 6.19 (s, 2H, 6,10-C=CH-Ar), 7.24–8.21 (m, 18H, ArH and pyridine); IR (cm^{-1}): 1743 (C=O, str), 1631 (C=N, str), 1602 (C=C, str), 1249 (C-N, str), 733 (C-Cl), 688 (C-S-C, str); EI-MS: *m/z* 659 (M^+), 660 (M^++1). Anal. Calcd for $C_{39}H_{31}N_3Cl_2OS$: C, 70.90; H, 4.69; N, 6.36. Found: C, 71.02; H, 4.39; N, 6.19.

General procedure for the preparation of 2-(4-substitutedbenzylidene)-8-methyl-6,10-bis(4-substitutedbenzylidene)-7,9-diphenyl-4-(pyridin-2-yl)-1-thia-4,8-diazaspiro-[4,5]-decan-3-ones (4a–f)

To a refluxing mixture of 6,10-bis(4-substitutedbenzylidene)-8-methyl-7,9-diphenyl-4-(pyridin-2-yl)-1-thia-4,8-diazaspiro[4,5]decan-3-one (**3a–c**) (0.01 mol) and sodium acetate (0.01 mol) in glacial acetic acid, 4-substituted benzaldehydes (0.01 mol) was added and refluxing was continued for 12–14 h. After completion of reaction, ice-cold water was added to the reaction mixture to get crude product which was filtered, washed, and recrystallized from ethanol.

2-(4-Chlorobenzylidene)-8-methyl-6,10-bis(4-nitrobenzylidene)-7,9-diphenyl-4-(pyridin-2-yl)-1-thia-4,8-diazaspiro[4,5] decan-3-one (4a) This compound was obtained in 64% yield; mp 256–260°C; ^{1}H NMR: δ 2.62 (s, 3H, N-CH_3), 4.41 (br s, 2H, 7,9-H), 6.28 (s, 2H, 6,10-C=CH-Ar), 6.56 (t, 1H, 5′-H of pyridine), 6.90–8.20 (m, 26 H, pyridine and ArH); ^{13}C NMR: δ 39.4 (CH_3), 52.6, 52.7 (7,9-C), 76.9 (5-C), 116.9 (5′-C of pyridine), 121.2–146.9 (pyridine and aromatic C), 147.5 (6′-C=N of pyridine), 153.0 (2′=C-N of pyridine), 162.2 (C=O); IR (cm^{-1}): 3026 (C-H, str, ArH), 2952, 2859 (C-H, str, CH_3), 1721 (C=O, str), 1633 (C=N, str), 1612, 1510, 1446 (C=C, str), 1533, 1360 (NO_2, str), 1238 (C-N, str), 771 (C-Cl), 696 (C-S-C, str); EI-MS: *m/z* 803 (M+), 804 (M+1). Anal. Calcd for $C_{46}H_{34}N_5ClO_5S$: C, 68.69; H, 4.23; N, 8.71; S, 3.98. Found: C, 67.96; H, 4.19; N, 8.63; S, 4.02.

2,6,10-tris(4-nitrobenzylidene)-8-methyl-7,9-diphenyl-4-(pyridin-2-yl)-1-thia-4,8-diazaspiro[4,5] decan-3-one (4b) This compound was obtained in 59% yield; mp 279–280°C; ^{1}H NMR: δ 2.26 (s, 3H, N-CH_3), 4.59 (br s, 2H, 7,9-H), 6.35 (s, 2H, 6,10-C=CH-Ar), 7.90 (s, 1H, 5′-H of pyridine), 6.62–8.21 (m, 26 H, pyridine and ArH); ^{13}C NMR: δ 39.2 (CH_3), 51.90, 51.94 (7,9-C), 76.2 (5-C), 113.5–138.0 (pyridine and aromatic C), 147.8 (6′-C=N of pyridine), 153.1 (2′=C-N of pyridine), 161.95 (C=O); IR (cm^{-1}): 3036.5 (C-H, str, ArH), 2957, 2865 (C-H, str, CH_3), 1718.1 (C=O, str), 1650.3 (C=N, str), 1603, 1514, 1452 (C=C, str), 1533, 1360 (NO_2, str), 1238 (C-N, str), 696 (C-S-C, str); EI-MS: *m/z* 814 (M^+), 815 (M^++1). Anal. Calcd for $C_{48}H_{40}N_3ClO_3S$: C, 67.81; H, 4.17; N, 10.31; S, 3.93. Found: C, 68.06; H, 4.11; N, 10.19; S, 3.90.

2-(4-Chlorobenzylidene)-6,10-bis(4-methoxybenzylidene)-8-methyl-7,9-diphenyl-4-(pyridin-2-yl)-1-thia-4,8-diazaspiro[4,5]-decan-3-one (4c) This compound was obtained in 66% yield; mp 168–170°C; ^{1}HNMR (400 MHz, $CDCl_3$)δ: 2.78 (s, 3H, N-CH_3), 4.53 (br s, 2H, 7,9-H), 6.16 (s,2H, 6,10-C=CH-Ar), 6.43 (t, 1H, 5′-H of pyrid), 6.87 (s, 4H, 3′,5′,3″,5″-H), 7.11–8.06 (m, 22H, pyrid and ArH protons); ^{13}CNMR (100 MHz, $CDCl_3$)δ: 39.26 (CH_3), 51.93, 51.97 (7,9-C), 56.02, 56.10(4″,4‴-OCH_3), 76.26 (5-C), 113.53–138.02 (pyrid and aromat C), 139.17 (2-C-S),147.82 (6′-C=N of pyridine), 153.16 (2′, =C-N), 158.78, 158.81 (4″,4‴ =C-O), 161.97(C=O); IR (KBr) cm^{-1}: 3036 (C-H, str, ArH), 2957, 2865 (C-H, str, CH_3), 1718 (C=O, str), 1650 (C=N, str), 1603, 1514, 1452 (C=C, str), 1251 (C-N, str), 1218, 1030 (C-O, str, OCH_3), 769 (C-Cl), 686 (C-S-C, str); EI-MS: m/z 773 (M^+), 775 (M^++1). Anal. Calcd for $C_{48}H_{40}N_3ClO_3S$: C, 74.46; H, 5.17; N, 5.42; S, 4.13. Found: C, 74.12; H, 5.06; N, 5.29; S, 4.08.

2-(4-Nitrobenzylidene)-6,10-bis(4-methoxybenzylidene)-8-methyl-7,9-diphenyl-4-(pyridin-2-yl)-1-thia-4,8-diazaspiro[4,5]-decan-3-one (4d) This compound was obtained in 66% yield; mp 157–160°C; ^{1}H NMR: δ 2.26 (s, 3H, N-CH_3), 3.83 (s,6H, OCH_3), 4.59 (br s, 2H, 7,9-H), 6.21 (s,2H, 6,10-C=CH-Ar), 7.90 (s, 1H, 5′-H of pyrid), 6.62–8.21 (m, 22 H, pyridine and ArH); ^{13}C NMR: δ 40.1 (CH_3), 61.7 (7,9-C), 55.80, 55.84 (4″,4‴-OCH_3), 84.4 (5-C), 114.2–159.8 (pyridine and aromatic C), 138.8 (=C-S),148.1 (6′-C=N of pyridine), 152.7 (2′=C-N of pyridine), 158.80, 158.84 (4″,4‴=C-O), 162.3 (C=O); IR (cm^{-1}): 3036.2 (C-H, str, ArH), 2957, 2865 (C-H, str, CH_3), 1718.3 (C=O, str), 1650 (C=N, str), 1603, 1514, 1452 (C=C, str), 1524, 1343 (NO_2, str), 1251 (C-N, str), 1218, 1030 (C-O, str, OCH_3), 686 (C-S-C str.); EI-MS: *m/z* 814 (M^+), 815 (M^++1). Anal. Calcd for $C_{48}H_{40}N_4O_5S$: C, 72.18; H, 5.01; N, 8.77; S, 4.01. Found: C, 71.97; H, 4.96; N, 8.61; S, 3.98.

2,6,10-Tris(4-chlorobenzylidene)-8-methyl-7,9-diphenyl-4-(pyridin-2-yl)-1-thia-4,8-diazaspiro[4,5]-decan-3-one (4e) This compound was obtained in 70% yield; mp 198–200°C; ^{1}H NMR: δ 2.55 (s, 3H, N-CH_3), 4.73 (br s, 2H, 7,9-H), 6.19 (s, 2H, 6,10-C=CH-Ar), 6.60 (t, 1H, 5′-H of pyridine), 6.82–8.01 (m, 26H, pyridine and ArH); IR (cm^{-1}): 3039 (C-H, str, ArH), 2965, 2854 (C-H, str, CH_3), 1723 (C=O, str), 1643 (C=N, str), 1607, 1509, 1446 (C=C, str), 1259 (C-N, str), 752 (C-Cl), 681 (C-S-C, str); EI-MS: *m/z* 781 (M^+), 783 (M^++1). Anal. Calcd for $C_{46}H_{34}N_3Cl_3OS$: C, 70.63; H, 5.37; N, 5.37; S, 4.09. Found: C, 70.31; H, 5.31; N, 5.31; S, 4.02.

2-(4-Nitrobenzylidene)-6,10-bis-(4-chlorobenzylidene)-8-methyl-7,9-diphenyl-4-(pyridin-2-yl)-1-thia-4,8-diazaspiro[4,5]-decan-3-one (4f) This compound was obtained in 73% yield; mp 182–183°C; ^{1}H NMR: δ 2.67 (s, 3H, N-CH_3), 4.56 (br s, 2H, 7,9-H), 6.24 (s, 2H, 6,10-C=CH-Ar), 6.64 (t, 1H, 5′-H of pyridine), 6.79–8.19 (m, 26H, pyridine and ArH); ^{13}C NMR: δ 38.9 (CH_3), 52.96, 53.00 (7,9-C), 76.1 (5-C), 117.6 (5′-C of pyridine), 122.7–146.9 (pyridine and aromatic C), 148.3 (6′-C=N of pyridine), 152.9 (2′=C-N of pyridine), 163.4 (C=O); IR (cm^{-1}): 3030 (C-H, str, ArH), 2951, 2863 (C-H, str, CH_3), 1703 (C=O, str), 1636 (C=N, str), 1599, 1517, 1445 (C=C, str), 1524, 1343 (NO_2, str), 1243 (C-N, str.), 758 (C-Cl), 698 (C-S-C, str); EI-MS: *m/z* 792 (M^+), 794 (M^++1). Anal. Calcd for $C_{46}H_{34}N_4Cl_2O_3S$: C, 69.60; H, 4.28; N, 7.06; S, 4.03. Found: C, 70.02; H, 4.24; N, 6.96; S, 3.99.

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