Synthesis, Stereochemistry, and Antimicrobial Activity of 2,6-Diaryl-3-(arylthio)piperidin-4-ones

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A series of novel 2,6-diaryl-3-(arylthio)piperidin-4-ones have been synthesized by reaction of arylthioacetones, substituted aromatic aldehydes, and methylamine/ammonium acetate and their structures elucidated by ^{1}H, ^{13}C, and 2D NMR (H, H-COSY, C, H-COSY, HMBC, and NOESY) spectroscopy. The NMR data reveal that all these piperidones exist in chair conformation with the 2,6-diaryl groups equatorially oriented, while the arylthio group prefers to be in either an equatorial or axial orientation depending on whether the substituent in the 2,6-diaryl rings is present in 4- or 2-position, respectively. In the case of NH-2,6-diaryl-3-(arylthio)piperidin-4-ones with *o*-substituted 2,6-diaryl groups, the arylthio group prefers the axial orientation presumably in a bid to minimize the steric and/or electronic repulsion. The arylthiopiperidin-4-ones exhibit significant antibacterial activity against *Staphylococcus aureus*, *Vibrio cholerae*, *Salmonella typhi*, and *Escherichia coli* and antifungal activity against *Candida albicans* and *Aspergillus niger*.

Key words piperidin-4-one; NMR; stereochemistry; antibacterial activity; antifungal activity

Piperidin-4-ones display a number of important biological properties such as bactericidal, fungicidal, and herbicidal activities.[1—3] Piperidone derivatives have also been found to act as potential inhibitors of human placental aromatase *in vitro*.[4] 3,5-Bis(arylidene)piperidin-4-ones behave as cytotoxic and anticancer agents.[5,6] 2,2,6,6-Tetramethylpiperidin-4-one hydrochloride has been used as a spin trap in several EPR studies[7,8] and its hydrazones are used as antioxidants for lubricating greases.[9] 2-Arylpiperidin-4-ones are used as key intermediates for the synthesis of tachykinin antagonists[10] and indolizidine alkaloids.[11]

Many saturated and unsaturated piperidin-2-ones have been used as key chiral intermediates in the preparation of numerous natural and synthetic compounds with significant anticancer,[12] anti-HIV,[13] and glycosidase inhibition[14] activities. 3,3-Diethylpiperidin-2-one behaves as an effective anticonvulsant.[15] *N*-Substituted-3-aminopiperidin-2-ones possess tryptase inhibition activity.[16] 3-Aminopiperidin-2-ones have been used as constrained surrogates of the Ser-Leu dipeptides.[17,18] Piperidin-3-one derivatives are used as precursors for the synthesis of antimalarial agents febrifugine and isofebrifugine.[19]

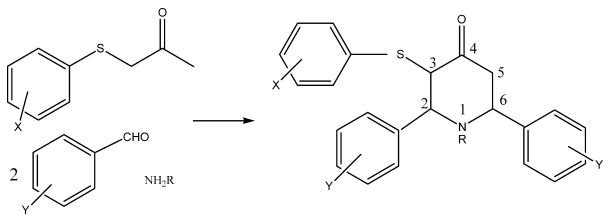
Earlier reports have indicated that biological activity is significant in piperidone systems possessing aromatic substitutions in the 2- and/or 6-positions.[3] Biological activities are also ascribed to the presence of chloro substituents in 2- and/or 4-positions.[20] Therefore it was considered likely that the new series of 2,6-diaryl-3-(arylthio)piperidin-4-ones and their *N*-methyl analogues (Chart 1) synthesized in the present study could possess potent biological activity. Thus, in continuation of our research programme on the synthesis of heterocycles,[21,22] we hereby report our results on the synthesis and stereochemical investigation of the 2,6-diaryl-3-(arylthio)piperidin-4-ones along with their antimicrobial activities.

Results and Discussion

In the present work, a series of new 2,6-diaryl-3-(arylthio)piperidin-4-ones (**1a**—**p**) and *N*-methyl-2,6-diaryl-3-(arylthio)piperidin-4-ones (**1q**—**t**) was synthesized by four-component reaction of arylthioacetones, substituted aromatic aldehydes, and methylamine or ammonium acetate with about 32—50% yields by following the method reported for the preparation of 2,6-diarylpiperidin-4-ones by Baliah *et al.*[23] The yield and mp of various arylthiopiperidin-4-ones (**1a**—**t**) are given in Table 1.

The structures of the compounds were elucidated by elemental analysis and ^{1}H, ^{13}C, and 2D NMR spectroscopic data. The ^{1}H- and ^{13}C-NMR spectroscopic data of **1a**—**t** are given in Tables 2 and 3 respectively.

^{1}H-NMR Spectra The ^{1}H-NMR spectrum of **1q** has ABX and AX spin systems for heterocyclic ring protons. The H-6, H-5ax, and H-5eq of the ABX spin system afford three doublets of doublets at 3.56, 2.91, and 2.80 ppm respectively, assigned as below on the basis of the magnitudes of their *J*



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1	R	X	Y	**1**	R	X	Y
1a	H	H	H	**1k**	H	*p*-Cl	*o*-Cl
1b	H	H	*p*-Cl	**1l**	H	*p*-Me	H
1c	H	H	*p*-CH_3	**1m**	H	*p*-Me	*p*-Cl
1d	H	H	*p*-OCH_3	**1n**	H	*p*-Me	*p*-CH_3
1e	H	H	*o*-Cl	**1o**	H	*p*-Me	*p*-OCH_3
1f	H	*p*-Cl	H	**1p**	H	*p*-Me	*o*-Cl
1g	H	*p*-Cl	*p*-Cl	**1q**	Me	*p*-Cl	H
1h	H	*p*-Cl	*p*-CH_3	**1r**	Me	*p*-Cl	*p*-Cl
1i	H	*p*-Cl	*p*-OCH_3	**1s**	Me	*p*-Cl	*p*-CH_3
1j	H	*p*-Cl	*p*-F	**1t**	Me	*p*-Cl	*o*-Cl

Chart 1

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Table 1. Yields and Melting Points of 2,6-Diaryl-3-(arylthio)piperidin-4-ones (**1**)

Comp.	mp (°C)	Yield (%)	Elemental analysis					
			Calculated (%)			Found (%)		
			C	H	N	C	H	N
1a	188	45	76.84	5.89	3.90	76.81	5.91	3.87
1b	181	48	64.49	4.47	3.27	64.44	4.45	3.29
1c	168	41	77.48	6.50	3.61	77.45	6.51	3.62
1d	152	38	71.57	6.01	3.34	71.60	6.03	3.37
1e	174	41	64.49	4.47	3.27	64.38	4.41	3.21
1f	185	34	70.13	5.12	3.56	70.04	5.25	3.64
1g	183	32	59.69	3.92	3.03	59.75	3.88	3.12
1h	172	38	71.16	5.73	3.32	71.10	5.62	3.28
1i	170	33	66.14	5.33	3.09	66.24	5.23	3.14
1j	180	40	64.26	4.22	3.26	64.15	4.34	3.22
1k	176	42	59.69	3.92	3.03	59.78	3.97	3.08
1l	177	46	77.17	6.21	3.75	77.19	6.19	3.72
1m	179	50	65.16	4.78	3.17	65.14	4.76	3.19
1n	163	39	77.77	6.78	3.49	77.80	6.81	3.47
1o	152	37	72.03	6.28	3.23	72.04	6.25	3.26
1p	161	46	65.16	4.78	3.17	65.07	4.81	3.12
1q	182	47	70.66	5.44	3.43	70.63	5.35	3.31
1r	178	48	60.45	4.23	2.94	60.52	4.24	3.02
1s	175	45	71.62	6.01	3.21	71.68	5.94	3.12
1t	173	44	60.45	4.23	2.94	60.54	4.12	2.99

Table 2. ^{1}H-NMR Spectral Data of 2,6-Diaryl-3-(arylthio)piperidin-4-ones (**1**)

Comp.	Chemical shifts (δ) (J, Hz)							
	NMe/NH	H-2	H-3	H-5		H-6	Aromatic protons	Other protons
				ax	eq			
1a	2.19	3.96 (J=11)	4.05 (J=11)	2.70—2.83		4.12 (J=11, 4)	7.03—7.42	—
1b	2.23	3.95 (J=11)	4.06 (J=11)	2.71—2.85		4.19 (J=11, 4)	6.99—7.40	
1c	2.17	3.91 (J=11)	4.03 (J=11)	2.72—2.85		4.11 (J=11, 4)	7.01—7.48	2.22, 2.25 (Me)
1d	2.16	3.93 (J=11)	4.04 (J=11)	2.76—2.84		4.13 (J=11, 4)	6.91—7.45	3.70, 3.71 (OMe)
1e	1.99	4.95 (J=2)	3.99 (J=2)	3.26 (J=14, 12)	2.62 (J=14, 3)	4.65 (J=11, 4)	6.72—7.95	—
1f	2.24	3.97 (J=11)	4.06 (J=11)	2.80—2.84		4.13 (J=11, 4)	6.96—7.41	—
1g	2.16	3.90 (J=11)	4.02 (J=11)	2.80—2.86		4.28 (J=11, 4)	6.77—7.44	—
1h	2.17	3.93 (J=11)	4.08 (J=11)	2.78—2.83		4.10 (J=11, 4)	6.97—7.42	2.32, 2.33 (Me)
1i	2.18	3.91 (J=11)	4.03 (J=11)	2.77—2.80		4.12 (J=11, 4)	6.75—7.42	3.78, 3.79 (OMe)
1j	2.16	3.90 (J=11)	4.04 (J=11)	2.81—2.87		4.30 (J=11, 4)	6.72—7.47	—
1k	1.99	4.95 (J=2)	3.93 (J=2)	3.20 (J=14, 12)	2.63 (J=14, 3)	4.65 (J=12, 3)	6.98—7.93	—
1l	2.24	3.95 (J=11)	4.02 (J=11)	2.67—2.82		4.09 (J=11, 4)	6.89—7.47	2.27 (Me)
1m	2.18	3.91 (J=11)	4.03 (J=11)	2.69—2.79		4.12 (J=11, 4)	6.87—7.53	2.22 (Me)
1n	2.11	3.89 (J=11)	4.01 (J=11)	2.71—2.89		4.17 (J=11, 4)	6.77—7.65	2.24, 2.26, 2.25 (Me)
1o	2.04	3.92 (J=11)	3.99 (J=11)	2.65—2.87		4.08 (J=11, 4)	6.98—7.66	2.27 (Me) 3.77, 3.79 (OMe)
1p	2.04	4.96 (J=2)	3.91 (J=2)	3.28 (J=14, 12)	2.62 (J=14, 3)	4.67 (J=12, 3)	6.92—7.98	2.21 (Me)
1q	1.77	3.42 (J=11)	4.12 (J=11)	2.91 (J=14, 11)	2.80 (J=14, 4)	3.56 (J=11, 4)	6.94—7.38	—
1r	1.68	3.30 (J=11)	4.09 (J=11)	2.90 (J=14, 11)	2.78 (J=14, 4)	3.50 (J=11, 4)	6.88—7.28	—
1s	1.78	3.21 (J=11)	4.11 (J=11)	2.92 (J=14, 11)	2.78 (J=14, 4)	3.48 (J=11, 4)	6.91—7.39	2.22, 2.35(Me)
1t[a)]	1.81	4.25 (J=11)	4.14 (J=11)	2.71 (J=14, 11)	2.93 (J=14, 4)	4.38 (J=11, 4)	6.89—7.98	3.75, 3.78 (OMe)

a) Chemical shifts of major isomer.

Table 3. ^{13}C-NMR Spectral Data of 2,6-Diaryl-3-(arylthio)piperidin-4-ones (**1**)

Comp.	δ (ppm)						
	C-2	C-3	C-4	C-5	C-6	Aromatic carbons	Other carbon
1a	67.1	65.6	202.6	50.9	60.2	127.0, 127.8, 128.4, 128.6, 129.0, 129.4, 132.3, 133.8, 134.0, 134.1, 138.6, 139.7	—
1b	67.3	65.2	203.4	50.7	60.4	126.8, 127.5, 128.3, 128.5, 128.8, 129.3, 132.1, 133.5, 133.8, 134.2, 138.7, 139.9	—
1c	67.2	65.3	202.8	50.8	60.5	126.7, 127.6, 128.2, 128.7, 129.0, 129.2, 132.3, 133.7, 134.1, 134.2, 138.7, 139.6	21.1, 21.2 (Me)
1d	67.1	65.7	203.6	50.9	60.3	127.0, 127.7, 128.4, 128.8, 129.1, 129.5, 132.4, 133.8, 134.2, 134.3, 138.4, 139.2	54.7, 54.9 (OMe)
1e	59.8	59.5	203.8	43.1	56.6	126.6, 127.4, 127.6, 127.8, 128.1, 129.0, 129.1, 129.4, 129.7, 130.0, 131.7, 132.2, 132.5, 134.2, 136.1, 139.5	—
1f	67.3	65.1	203.8	50.8	60.5	126.4, 127.7, 128.8, 129.0, 129.7, 132.7, 133.2, 133.5, 137.2, 137.6, 138.4, 139.6	—
1g	67.3	65.2	203.2	50.9	60.5	126.2, 127.6, 128.4, 128.9, 129.5, 132.7, 133.2, 133.9, 137.4, 137.8, 138.2, 139.1	—
1h	67.6	65.7	203.4	51.2	60.7	126.3, 127.9, 128.6, 129.0, 129.4, 132.9, 133.0, 133.8, 137.2, 137.9, 138.5, 139.5	21.0, 21.1 (Me)
1i	67.1	65.2	203.8	50.2	60.3	126.3, 127.9, 128.6, 129.0, 129.4, 132.9, 133.0, 133.8, 137.2, 137.8, 137.9, 138.6	54.9, 55.1 (OMe)
1j	67.2	65.4	203.3	50.7	60.6	126.4, 127.9, 128.4, 129.0, 129.2, 132.7, 132.9, 133.2, 133.5, 133.8, 137.3, 137.7, 137.9, 138.4	—
1k	59.8	59.5	203.8	43.1	56.6	126.6, 127.4, 127.6, 127.8, 128.1, 129.0, 129.1, 129.4, 129.7, 130.0, 131.7, 132.2, 132.5, 134.2, 136.1, 139.5	—
1l	67.0	65.6	202.8	50.8	60.1	127.8, 128.4, 128.9, 129.4, 129.5, 130.2, 132.9, 133.8, 134.0, 137.4, 138.8, 140.4	21.0 (Me)
1m	67.1	65.6	203.1	50.7	60.3	127.3, 128.1, 128.5, 129.1, 129.6, 130.2, 132.6, 133.9, 134.2, 137.5, 138.7, 140.2	21.1 (Me)
1n	67.3	65.3	202.8	50.6	60.1	127.2, 128.2, 128.4, 129.5, 129.6, 130.1, 132.7, 133.8, 133.9, 137.2, 138.9, 139.9	21.0, 21.1, 21.2 (Me)
1o	67.1	65.5	203.1	50.7	60.2	127.1, 128.3, 128.6, 129.7, 129.9, 130.3, 132.9, 133.9, 134.1, 137.5, 138.9, 140.3	21.0 (Me), 54.9, 55.0 (OMe)
1p	60.1	59.7	203.7	43.1	56.5	126.5, 127.6, 127.9, 128.9, 129.0, 129.4, 129.6, 129.8, 130.0, 132.3, 132.4, 132.5, 136.2, 137.8, 139.6	21.1 (Me)
1q	75.5	65.2	202.4	50.1	69.4	127.0, 127.8, 128.1, 128.4, 128.5, 128.7, 128.9, 132.8, 133.4, 133.7, 140.9, 142.7	41.2 (N<u>Me</u>)
1r	75.3	64.9	202.8	50.6	69.1	127.0, 127.8, 128.0, 128.3, 128.7, 128.9, 129.8, 133.2, 133.6, 134.4, 139.6, 140.9	41.0 (N<u>Me</u>)
1s	74.8	65.0	202.2	50.8	68.8	126.3, 126.7, 127.3, 127.8, 128.7, 129.3, 129.9, 135.2, 137.1, 137.5, 138.2, 139.7	41.5 (N<u>Me</u>), 21.0 (Me)
1t[a)]	61.9	60.1	203.8	44.7	58.1	125.4, 126.1, 127.5, 128.4, 128.8, 129.3, 129.6, 129.8, 130.5, 132.6, 132.8, 133.3, 136.6, 137.8, 138.5	41.0 (N<u>Me</u>)

a) Chemical shifts of major isomer.

values. The signal at 3.56 ppm with J values of 11 and 4 Hz, ascribable to $^3J_{H6,H5ax}$ and $^3J_{H6,H5eq}$, respectively, is assigned to H-6, while the signal at 2.91 ppm with J values of 14 Hz (geminal) and 11 (diaxial) is assigned to H-5ax. The signal at 2.80 ppm with J values of 14 Hz (geminal) and 4 (axial-equatorial) can be assigned to H-5eq similarly. The protons H-2 and H-3 of the AX spin system give doublets at 3.42 and 4.12 ppm with a J value of 11 Hz, indicating that these two protons are diaxially oriented.

The above signal assignments are evident from the NOESY spectrum of **1q**, which correlates the H-6 signal at 3.56 ppm with the signal at 3.42 ppm but not with the signal at 4.12 ppm (Fig. 1A). The HMBC correlations also support the above assignment. For instance, the signal at 1.77 ppm of **1q,** assigned to the *N*-methyl protons, correlates with the signal at 69.4 ppm and with the signal at 75.5 ppm. From these correlations, these two signals are assigned to C-6 and C-2, respectively (Fig. 1B). This is also confirmed by the C, H-COSY and H, H-COSY correlations. From the above, it follows that *N*-methyl-2,6-diphenyl-3-(4-chlorophenylthio)-piperidin-4-one adopts a chair conformation with all the substituents oriented equatorially.

The NH-piperidin-4-ones **1a**—**p** also show similar ^{1}H-NMR spectroscopic and conformational features as evident from the observation that the H-2 and H-3 of **1h** give doublets at 3.93 and 4.08 ppm, respectively, with a J value of 11 Hz while the benzylic proton (H-6) gives a doublet of doublets at 4.10 ppm (J=11, 4 Hz).

In piperidin-4-ones (**1e**, **1k**, and **1p**) with *o*-substituted phenyl rings at C-2,6 positions, the arylthio group prefers an axial orientation as evident from the J value of 2 Hz of the signals of H-2 and H-6 of **1e**, **1k**, and **1p**. While the equatorial arylthio group in piperidones **1a**—**d**, **1f**—**j**, **1l**—**o**, and **1q**—**s** has (i) an almost eclipsing interaction with the carbonyl group with probable electronic repulsion between the oxygen and sulphur atoms and (ii) a gauche interaction with the 2-aryl ring, the axial arylthio group in piperidones **1e**, **1k**, and **1p** has (i) a syn-axial interaction with the H-5ax and (ii) a gauche interaction with the 2-aryl ring. The syn-axial interaction may presumably be of lesser importance due to the longer C–S bond diminishing the effective "bulk" of the arylthio group. It is pertinent to note that in a recent study[24] on the conformational analysis of α-(*p*-substituted phenylthio)cyclohexanones employing semi-empirical PM3 calculations, the conformer with the axial orientation for the phenylthio group is found to be preferred.

From the observed preference of equatorial and axial orientations of the arylthio group in the case of *p*- and *o*-substituted 2,6-diaryl rings, respectively, it appears that the unfavourable gauche interaction between the arylthio and 2-aryl groups is less when the arylthio group takes up (i) an equatorial orientation in the case of *p*-substituted 2,6-diaryl (Fig. 2A) and (ii) an axial orientation in the case of *o*-substituted 2,6-diaryl (Fig. 2B) than the alternative orientation in each case. This orientation-dependence of the arylthio group on the position of the substituent in the 2-aryl group may presumably be ascribed to the variation in rotameric preference of the *o*- and *p*-substituted aryl rings at the 2-position and the concomitant changes in the magnitude of the gauche interaction. It is pertinent to note that the signal of H-2 of **1e**, **1k**, and **1p** occurs significantly downfield at 4.95 ppm relative to

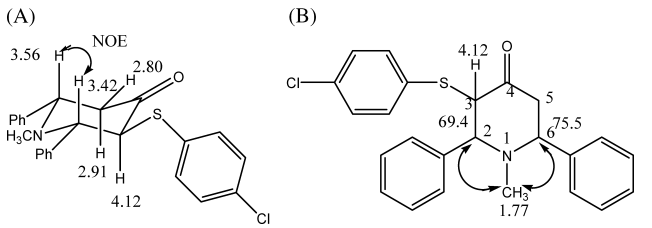
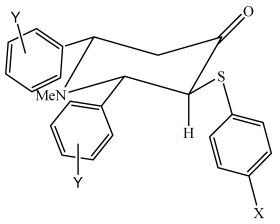
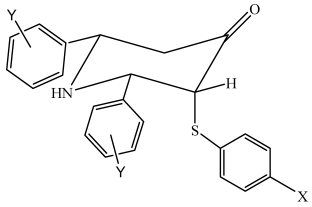


Fig. 1. NOESY Correlation in **1q** (A) and HMBC Correlation in **1q** (B)



1t: X = Cl; Y = *o*-Cl
(Major)

Fig. 2A



1e: X = H; Y = *o*-Cl
1k: X = Cl; Y = *o*-Cl
1p: X = Me; Y = *o*-Cl

Fig. 2B

that of **1f**—**j** (*ca.* 3.90 ppm) due to the preference of the rotameric form of **1e**, **1k**, and **1p** wherein the C–Cl bond of the *o*-chlorophenyl ring is oriented almost in an eclipsing manner with H-2, as is found in some 2,6-diarylpiperidin-4-ones wherein the aryl groups bear an *o*-substituent.

In contrast to the NH piperidones with an *o*-chlorophenyl ring (**1e**, **1k**, and **1p**), where 2B is the exclusive product, the corresponding *N*-methylpiperidin-4-one bearing *o*-chlorophenyl rings at 2,6-positions (**1t**) was obtained as a mixture in which the diastereomer (2A) was identified as the major product (91%) along with the minor isomer, 2B (9%). From the above observation, it appears that the sum of the interactions between the N–Me group and the *o*-chlorophenyl ring at the 2-position and the gauche interaction between the *o*-chlorophenyl ring at the 2-position and the equatorial 3-(*p*-chlorophenylthio) ring appears to be less than that in the corresponding piperidones with the 3-(*p*-chlorophenylthio) ring in axial orientation. This could probably be explained as follows: the destabilizing steric interactions between the N–Me and the 2- and 6-aryl rings could cause a rotameric preference of the aryl rings in such a way that these aryl rings and axial arylthio group in 2A sterically repel each other to a larger extent than when the arylthio ring is in equatorial orientation (2B). Thus it appears that in the case of **1t** the diastereomer with equatorial arylthio ring (2A) is thermodynamically more stable than the diastereomer with axial arylthio ring (2B) disclosing thermodynamic control of the stereoselectivity of these reactions. The above results thus reveal that the configurational preference of the arylthio group is delicately influenced by an interplay of different interactions involved in these piperidones, which, in turn, could be envisaged subtly to influence their biological activities as well.

^{13}C-NMR Spectra The ^{13}C-NMR spectra of the compounds of **1a**—**t** are in accord with the conclusions reached on their structural and stereochemical features from ^{1}H-NMR spectroscopic studies. All the heterocyclic ring carbons, except carbonyl, have been readily assigned from the connected proton chemical shifts and the C, H-COSY correlations as

Table 4. ^{1}H and ^{13}C Chemical Shift Assignments of **1q** from C, H-COSY Correlations

H-atom	δ_H	δ_C
N–CH_3	1.77 (s, 3H)	41.2
2	3.42 (d, J=11 Hz, 1H)	75.5
3	4.12 (d, J=11 Hz, 1H)	65.2
5ax	2.91 (dd, J=14, 11 Hz, 1H)	50.1
5eq	2.80 (dd, J=14, 4 Hz, 1H)	
6	3.56 (dd, J=11, 4 Hz, 1H)	69.4
Aromatic	6.94—7.38 (m, 14H)	127.0, 127.8, 128.1, 128.4, 128.5, 128.7, 128.9, 132.8, 133.4, 133.7, 140.9, 142.7

depicted in Table 4 for a representative example, **1q**. These carbon chemical shifts lying in the range 43—76 ppm are found to be sensitive to the position of substituent in the 2,6-aryl rings and orientation of the arylthio group. In the case of **1e**, **1k**, and **1p** with axial arylthio ring and *o*-chloroaryl rings at the 2- and 6-positions, the heterocyclic ring carbons C-2, C-3, C-5, and C-6 undergo significant upfield shifts, relative to those with *p*-substituted aryl rings, indicating that these molecules have considerable steric interactions such as syn-axial and gauche. In the case of *N*-methylpiperidones with *p*-substituted aryl rings at the 2- and 6-positions, the C-2,6 chemical shifts are significantly shifted downfield, while the C-3, 5 carbon chemical shifts remain almost the same. This is understandable in view of the proximity of the aryl rings at the 2- and 6-positions to the *N*-methyl substituent. The carbonyl carbon signals of these molecules occurring in the range 202—205 ppm remain almost unaffected by the orientation of the arylthio group as well as the position of the substituent in the 2- and 6-aryl rings, disclosing that the steric and/or electronic environment of the carbonyl functionality are essentially independent of either the orientation of the arylthio ring or substituent position in the 2- and 6-aryl rings. This probably could be ascribed to (i) the longer C–S bond leading to lesser steric interaction with the carbonyl group irrespective of whether the arylthio group is in the axial or equatorial orientation and (ii) large spacing between the 2,6-aryl rings and the carbonyl group. The individual assignment of the aromatic carbon signals of these compounds has not been made in view of the difficulty in the assignment of the individual proton chemical shifts of the aryl rings, which are required to assign the chemical shifts of carbons using C, H-COSY correlations. The chemical shifts of the carbons of aromatic rings **1a**—**t** lie in the range 126—143 ppm, among which the less intense ones in the region, 132—143 ppm, are ascribable to the *ipso* carbons. The ^{13}C chemical shifts of **1a**—**t** are listed in Table 3.

Antimicrobial Activity The compounds (**1a**—**t**) were screened for (i) antibacterial activity *in vitro* against four species of Gram-positive bacteria, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Vibrio cholerae*, and *Salmonella typhi*, and one Gram-negative bacterium *Escherichia coli* and (ii) antifungal activity against *Candida albicans* and *Aspergillus niger* using Muller–Hinton agar medium. All the compounds employed for biological screening consisted of only one diastereomer except **1t**,which existed as a mixture of 91% and 9% of two diastereomers. NMR data are shown in Tables 2 and 3. Separation of these isomers of **1t** proved difficult in view of the close *Rf* values of these isomers. Standard drugs used were streptomycin and nystatin.[25] For each biological activity test, three to four experiments were performed and the average zone of inhibition is reported in this work.

Table 5. Antibacterial Activity of 2,6-Diaryl-3-(arylthio)-piperidin-4-ones (**1**)

Comp.	Zone of inhibition in mm			
	Staphylococcus aureus	*Vibrio cholerae*	*Escherichia coli*	*Salmonella typhi*
1a	14	15	14	13
1b	17	16	17	16
1c	13	14	13	14
1d	13	13	14	13
1e	17	17	17	16
1f	16	16	15	16
1g	19	18	19	18
1h	16	15	16	15
1i	17	16	17	16
1j	17	16	17	16
1k	20	19	20	19
1l	13	12	12	13
1m	16	16	17	15
1n	13	13	12	13
1o	12	12	11	12
1p	16	17	17	16
1q	14	14	13	14
1r	19	18	19	18
1s	15	15	16	15
1t	17	16	17	18
Streptomycin	21	21	23	22

Antibacterial Activity It was found that compounds **1g**, **1k**, and **1r** possess pronounced antibacterial activity against all organisms tested (Table 5). The piperidones **1g**, **1k**, and **1r** possessed broader antibacterial activity against both Gram-positive and Gram-negative bacteria in comparison with the other piperidones. Interestingly, compounds with chlorine, **1b** and **1e**, exhibited higher activity than those that lack chlorine, **1a**, **1c**, and **1d**. The piperidones **1g**, **1k**, and **1r** showed growth-inhibitory action almost equal to that of reference drug streptomycin against *Staphylococcus aureus*, *Vibrio cholerae*, *Escherichia coli*, and *Salmonella typhi*, indicating that the presence of chlorine in all three phenyl rings enhances inhibitory activity. Compounds **1c**, **1h**, **1n**, and **1s** with a *p*-methyl group and compounds **1d**, **1i**, and **1o** with a *p*-methoxy group displayed weak to moderate activity against all bacterial pathogens. It was also found that the compounds with N–Me had lower activity than those with N–H. For instance, **1k** and **1g** had higher antibacterial activity than the corresponding compounds **1t** and **1r**, respectively. This suggests that the accessibility of the lone pair of electrons on the nitrogen and/or the hydrogen-bonding ability of the N–H proton could also make an important contribution to the biological activity of these compounds. All arylthiopiperidones **1a**—**t** were inactive against *Klebsiella pneumoniae*.

Antifungal Activity In the case of antifungal activity as well as antibacterial activity, compounds with chloro substituent *viz*. **1g**, **1k**, and **1r** exhibited considerably more antifungal activity than the other compounds (Table 6).

Compounds that exhibited high inhibitory activities were selected for further minimum inhibitory concentration assay (MIC) with different concentrations of test compounds (50, 100, 200 $\mu g\,ml^{-1}$). Broth cultures were incubated at 37 °C for 24 h with various concentrations of each compound, *viz.* **1a**—**t**. Test compounds **1g**, **1k**, and **1r** showed a MIC of 50 $\mu g\,ml^{-1}$ against all organisms tested (Tables 7, 8). It is important to note that these three compounds showed almost the same antibacterial activity as streptomycin and antifungal activity as nystatin at 200 $\mu g\,ml^{-1}$. Since the compounds with one or two chlorine atom(s) were found to be highly potent, it may be reasoned that compounds with more chlorines such as di- or tri-chloroaryl rings at the 2- and 6-positions and di- or tri-chloroarylthio rings could display more pronounced activity. Similarly, introduction of one more functionality such as arylthio/amide/amine/sulfonamide at the 6-position of the piperidones could also influence the stereochemistry and activity of these compounds. Introduction of substituents such as amino, amide, or sulfonamide on the aryl rings with scope for hydrogen bonding and their concomitant influence on biological activity also appear worth investigating. Such work, which could enable broadening of the investigation of structure–activity relationships in this piperidone ring system so as to bring the factors underlying the biological activity to light and suggest molecules with optimum structural features for maximizing activity, is currently under investigation by our research group.

Conclusions

The present work describes the synthesis of twenty novel 2,6-diaryl-3-(arylthio)piperidin-4-ones and the results of their screening for antibacterial and antifungal activities. Investigation of the structure and stereochemistry of these compounds by proton and carbon NMR spectra has brought to light a delicate interplay of various factors determining the stereoselectivity of the piperidin-4-ones. Some of these compounds display antimicrobial activity similar to that of streptomycin and nystatin. The results of the present investigation also suggested probable factors that could contribute to the activities, which, in turn, can provide valuable information in synthesizing compounds of maximum activity.

Table 6. Antifungal Activity of 2,6-Diaryl-3-(arylthio)piperidin-4-ones (**1**)

Comp.	Zone of inhibition in mm		Comp.	Zone of inhibition in mm	
	Candida albicans	*Aspergillus niger*		*Candida albicans*	*Aspergillus niger*
1a	13	13	**1k**	18	18
1b	16	15	**1l**	11	12
1c	14	13	**1m**	14	14
1d	13	12	**1n**	12	12
1e	16	16	**1o**	10	11
1f	15	15	**1p**	15	16
1g	17	17	**1q**	13	14
1h	16	15	**1r**	17	17
1i	15	14	**1s**	14	14
1j	16	15	**1t**	17	16

Nystatin: *Candida albicans*=19 mm; *Aspergillus niger*=20 mm.

Experimental

The melting points reported in the work are uncorrected. The ^1H- and ^{13}C-NMR spectra of the 2,6-diaryl-3-(arylthio)piperidin-4-ones (**1a**—**t**) were measured at 300 MHz and 75 MHz, respectively, by Bruker (Avance) NMR instrument in $CDCl_3$ and the chemical shifts referenced to tetramethylsilane. All one- and two-dimensional NMR spectra were measured using standard Bruker software throughout.

Synthesis of 2,6-Diaryl-3-(4-arylthio)piperidin-4-ones (1a—t) Methylamine or ammonium acetate (0.0048 mol) was dissolved in ethanol (2 ml) by heating. Aromatic aldehyde (0.0096 mol) and arylthioacetone (0.0048 mol) were added to this solution and the mixture was heated until the color of the solution changed yellow. After cooling, the viscous liquid obtained was dissolved in ether (10 ml) and shaken with hydrochloric acid (10 ml) and water (10 ml). The precipitated hydrochloride of piperidin-4-one was removed by filtration and washed with ether. The base was liberated from an alcoholic solution of the hydrochloride by adding a slight excess of aqueous ammonia and diluting with water in ice-cold condition. The piperidin-4-ones were recrystallized from ethanol or ethanol–ethyl acetate mixture.

Evaluation of Antimicrobial Activity—Procedure Antimicrobial activity was investigated following the method of Bauer *et al.*[25] Muller–Hinton agar medium (100 ml) was prepared, sterilized, poured on sterilized petriplates and left for solidification. Broth cultures of each test organism were then swabbed on the Muller–Hinton agar plates. The tested compounds (10 mg) were dissolved in chloroform (1 ml) and impregnated into 6 mm of Whatman No. 1 filter paper (sterilized) and left for evaporation of the solvent. Then the impregnated paper disc was placed on the test organism-seeded plates and kept for incubation at 37 °C for 24 h. After the incubation period, the plates were observed for zone of inhibition around the disc. Zone of inhibition was measured in mm and the results are shown in Table 4.

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Table 8. Antifungal Activity of Compounds (**1g**, **1k**, **1r**)

Comp.	Zone of inhibition in mm					
	Candida albicans			*Aspergillus niger*		
Conc. ($\mu g\,ml^{-1}$)	50	100	200	50	100	200
1g	6	8	11	6	8	10
1k	7	10	12	6	9	12
1r	6	8	11	7	9	12
Nystatin	8	10	12	7	9	12

Table 7. Antibacterial Activity of Compounds (**1g**, **1k**, **1r**)

Comp.	Zone of inhibition in mm											
	Staphyloccocus aurus			*Vibrio cholerae*			*Escherichia coli*			*Salmonella typhi*		
Conc. ($\mu g\,ml^{-1}$)	50	100	200	50	100	200	50	100	200	50	100	200
1g	6	9	11	7	9	11	7	9	11	6	8	10
1k	7	8	12	7	9	12	6	8	12	7	9	12
1r	8	9	13	8	10	12	7	8	13	6	10	11
Streptomycin	8	10	13	8	10	12	7	10	13	8	10	12

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