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Stereocontrolled facile synthesis and antimicrobial activity of oximes and oxime ethers of diversely substituted bispidines

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ABSTRACT

A small library of diversely substituted 2,4,6,8-tetraaryl-3,7-diazabicyco[3.3.1]nonan-9-ones, their oximes and O-methyloximes were achieved in a stereocontrolled manner by an easiest synthetic strategy as single isomers with high yields. Stereochemistry of all the synthesized compounds was established by their 1D/2D NMR spectral studies, further, witnessed by single-crystal XRD analysis. Accordingly, the compounds exist in a chair-boat conformation with equatorial orientation of the substituents in the chair part and boat-axial orientation in the boat part. Finally, all the synthesized oximes and oxime ethers were evaluated for their in vitro antimicrobial activity against a panel of pathogenic bacteria and fungi, and as a result of the structure–activity correlations, some lead molecules were known for further optimization.

Molecules with the bispidine nucleus are of great interest due to their presence in a wide variety of naturally occurring lupin alkaloids and various biologically active molecules.[1] In fact, bispidine is a piperidine scaffold, comprised by two-units of piperidine core, which is also a well-known pharmacophore, proved by their occurrence in numerous naturally occurring alkaloids and biologically active molecules as well as in drugs and active pharmaceutical ingredients.[2] Hence, synthesis of new molecules with the bio-active bispidine nucleus and their stereochemical investigation are all worthy in the field of medicinal chemistry.

On the other hand, the biological activities of oxime derivatives are known as very significant, and the introduction of substituents on the oxime functionality, C=N–O–R, exhibits an advance in their antimicrobial activity.[3] In the light of above all, we synthesized a mini-library of oximes and *O*-methylated oximes of 2,4,6,8-tetraaryl-3,7-diazabicyco[3.3.1]nonan-9-ones by combining the bispidine and oxime pharmacophores with an expectation of enhanced antimicrobial activity. Promisingly, the nature and position of the substituents were important factors toward significantly effect the biological actions.[4] Accordingly, we synthesized the target molecules with phenyl groups on both sides of the secondary amino groups (i.e., C-2, C-4, C-6 and C-8 positions of the 3,7-diazabicycle). Furthermore, to find the effective structure–activity correlations, electron-withdrawing/donating fluoro/chloro/bromo/methyl/ethyl/*iso*-propyl/thiomethyl/methoxy/ethoxy/*n*-propoxy/*n*-butoxy/phenoxy/benzyloxy/allyloxy substituents were used at *ortho*, *meta* and *para* positions of the phenyl groups.

The 2,4,6,8-tetraaryl-3,7-diazabicyclo[3.3.1]nonan-9-ones[5] were synthesized by a modified and an optimized successive double Mannich condensation of acetone, substituted benzaldehydes and ammonium acetate in 1:4:2 ratio in ethanol with good yields (Scheme 1). Although a number of stereomers are possible as witnessed by their stereogenic centers, all bicyclic ketones were achieved as single isomers. As stereochemistry of the molecules is a major criterion for their biological response, it is of immense help to establish the structure of newly synthesized compounds.

The stereochemistry of 2,4,6,8-tetrakis(2-fluorophenyl)-3,7-diazabicyclo[3.3.1]nonan-9-one and 2,4,6,8-tetrakis(3-methoxyphenyl)-3,7-diazabicyclo[3.3.1]nonan-9-one, respectively, an *ortho* and *meta* substituted bispidines is as shown in Figures 1 and 2, witnessed by their complete NMR studies. The NOE bears out the fact that both the *ortho* and *meta* isomers exhibit the same stereochemistry as *para* isomers. However, $^{1}H/^{13}C$ chemical shifts of the *ortho* isomers vary from the *meta* and *para* isomers, whereas they are closer between them. Furthermore, in *ortho* isomers **2**, **5** and **8**, chemical shift of the benzylic (H-2, H-4, H-6 and H-8) and

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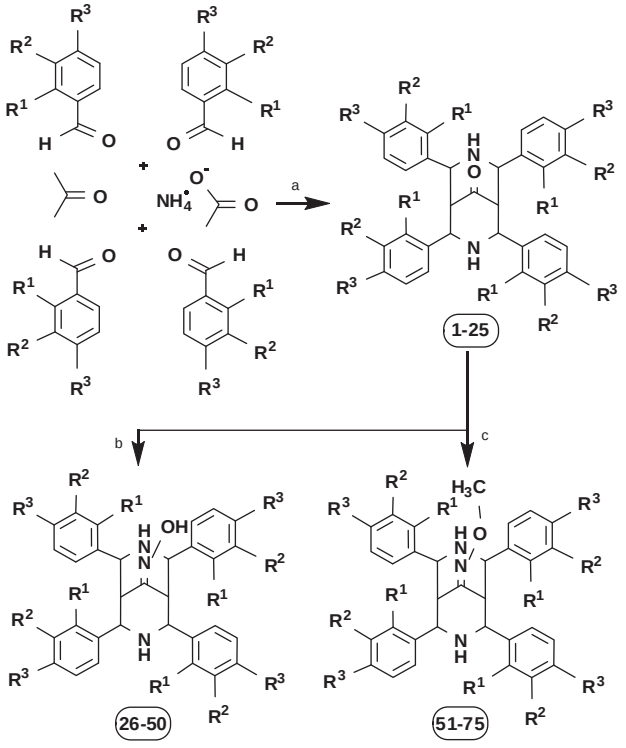

Compound	R^1	R^2	R^3
1, 26, 51	H	H	H
2, 27, 52	F	H	H
3, 28, 53	H	F	H
4, 29, 54	H	H	F
5, 30, 55	Cl	H	H
6, 31, 56	H	Cl	H
7, 32, 57	H	H	Cl
8, 33, 58	Br	H	H
9, 34, 59	H	Br	H
10, 35, 60	H	H	Br
11, 36, 61	CH_3	H	H
12, 37, 62	H	H	CH_3
13, 38, 63	H	H	CH_2CH_3
14, 39, 64	H	H	$CH(CH_3)_2$
15, 40, 65	H	H	SCH_3
16, 41, 66	OCH_3	H	H
17, 42, 67	H	OCH_3	H
18, 43, 68	H	H	OCH_3
19, 44, 69	OCH_2CH_3	H	H
20, 45, 70	H	H	OCH_2CH_3
21, 46, 71	H	H	$OCH_2CH_2CH_3$
22, 47, 72	H	H	$OCH_2CH_2CH_2CH_3$
23, 48, 73	H	OC_6H_5	H
24, 49, 74	H	H	OCH_2-C_6H_5
25, 50, 75	H	H	$OCH_2CH{=}CH_2$

Scheme 1. Reagents and conditions: (a) EtOH, warm, stirring; method A: (b) HO–NH_2·HCl, $CH_3COONa·3H_2O$, EtOH/$CHCl_3$, reflux 1–3 days; (c) CH_3–O–NH_2·HCl, $CH_3COONa·3H_2O$, EtOH/$CHCl_3$, reflux 1–3 days. Method B: (b) HO–NH_2·HCl, pyridine, EtOH/$CHCl_3$, reflux 5–6 h; (c) CH_3–O–NH_2·HCl, pyridine, EtOH/$CHCl_3$, reflux 5–6 h.

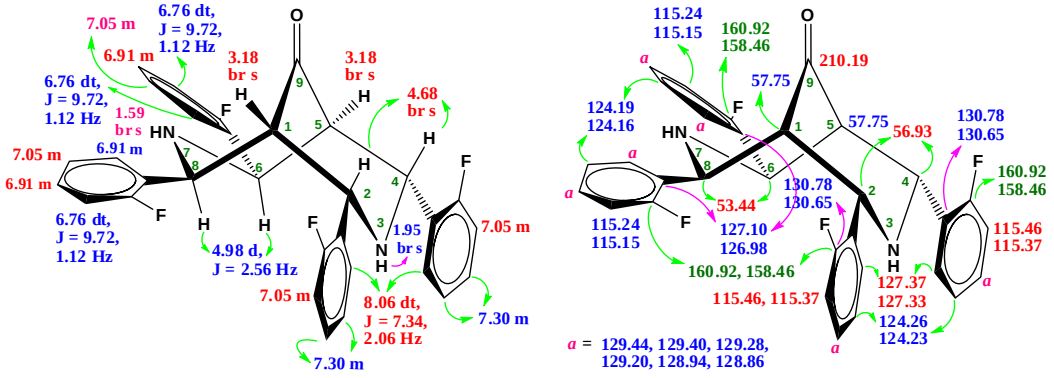

Figure 1. The ^1H and ^{13}C chemical shifts of compound **2** are assigned by H,H-COSY/NOESY and HSQC/HMBC, respectively. The 3,7-diazabicycle exists in a chair-boat conformation with equatorial orientation of the *ortho*-fluorophenyl groups at C-2/C-4 of the chair form and with boat-axial at C-6/C-8 of the boat form.

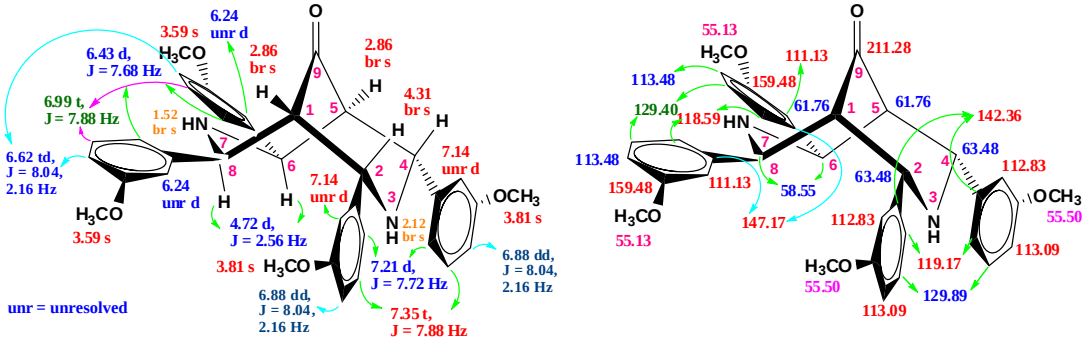

Figure 2. The proton and carbon chemical shifts of compound **17** are assigned by H,H-COSY/NOESY and HSQC/HMBC, respectively. Compound **17** also adopts the same stereochemistry as compound **2**.

bridge-head protons (H-1 and H-5) as well as carbons differ largely. Compared to **1** (H-2,4/H-6,8/H-1,5 and C-2,4/C-6,8/C-1,5 are 4.39/4.74/2.89 and 63.28/58.64/61.76 ppm), the ^{1}H and ^{13}C of **2** (4.68/4.98/3.18 and 57.89/53.55/57.07), **5** (4.73/5.28/3.52 and 60.54/55.82/55.70) and **8** (4.68/5.31/3.62 and 62.74/55.44/57.89) are deshielded and shielded, respectively, according to the varying impact on the chemical shifts with varying magnitude of the electronegativity of the substituents. This deshielding of protons is reasonably attributed by the interaction between the halogens and benzylic/bridge-head protons, indeed, which is more with the bridge-head protons than the benzylic protons, by their spatial proximity. In the above cases, in fact, the C–X bonds prefer to be *syn* to the benzylic protons to avoid the C–X and C–N dipole–dipole interaction. Owing to this, the *ortho* protons in the chair are more exposed to the axially oriented nitrogen lone pair, thus deshielded, and appear at 8.06, 8.21 and 8.22 ppm of **2**, **5** and **8**, respectively, than 7.60 ppm of **1**. Though the bridge-head and *ortho* protons are deshielded in the CH_3 and OCH_3/OC_2H_5 bispidines **11** and **16**/**19** by spatial proximity, particularly in **16**/**19**, the benzylic protons in the chair are significantly shielded by the electronic effect of OCH_3/OC_2H_5 groups attached β to them.

The oximes and oxime ethers of bispidines[5a] were synthesized as depicted in Scheme 1, using sodium acetate trihydrate as base (method A). Since the reaction required up to three days for the completion, alternatively tried with pyridine as base (method B). As an outcome, the desired product was achieved by 5–6 h reflux, but the yield reduced largely.

The complete proton and carbon chemical shifts of all compounds were assigned by 1D/2D NMR spectra (refer Supplementary data). Because of oximation, the ring carbons and their protons appear as distinct signals. Moreover, due to $A^{1,3}$-interaction (Fig. 3), the *syn*-α proton H-5 is deshielded. In **26**, the H-5 is deshielded by 1.13 ppm but the *anti*-α proton H-1 appears at 2.88 ppm as in **1**. Thus the difference between the bridge-head protons $\Delta\delta_{5,1}$ is 1.13 ppm, obviously by the allylic interaction since there was no impact by the electronegativity effect on the α protons.

In general, decrease in electronegativity of a particular group in a six-membered ring shields the α-carbons and deshields the β and γ carbons.[6] Accordingly, the α carbons are shielded by the reduction of C=O as C=N, however, the trend violated in the β and γ carbons. According to $A^{1,3}$-interaction, the H-5 and C-5 are acquired the positive and negative charges, respectively. Thus in **26**, C-5 is shielded by 6.67 ppm by the acquired negative charge besides the shielding of 10.43 ppm exerted by the electronegativity effect on the *syn* carbons. Then the excess of negative charge on the *syn*-α carbon transmitted to the *syn*-β carbon and some extent to the *syn*-γ carbon also. Hence, the expected deshielding by the electronegativity effect is overturned on the *syn*-β carbons C-4 and C-6 by the shielding of 1.24 and 1.19 ppm, respectively. This result indicates that the impact of $A^{1,3}$-interaction is significantly better than the electronegativity effect on the β carbons; in fact, the deshielding might be about 2.1 ppm since the *anti*-β carbon C-2 is deshielded by 0.91 ppm. Of the two *syn*-β carbons, one in the chair form C-4 is more shielded than the C-6 in the boat form, rationalized by the comparative shorter bond length of C(5)–C(4) [1.557 (2) Å] than C(5)–C(6) [1.566 (2) Å]. In accordance with the above electronegativity rule, all the γ carbons C-2′, C-4′, C-6′ and C-8′ are deshielded by 0.71, 0.61, 0.82 and 0.95 ppm, respectively. However, the *syn*-γ carbons C-4′ and C-6′ are less deshielded than corresponding *anti*-γ carbons C-2′ and C-8′ by the transmittance of a small magnitude of negative charge from C-5 to C-4′/C-6′ through C-4/C-6 as a consequence of the above mentioned effect of $A^{1,3}$-interaction. However, the impact experienced by them is lesser than the β carbons. Another interesting observation is, of the *anti*-β carbons, the C-2 is deshielded by 0.91 ppm in accordance with the rule, whereas, another *anti*-β carbon C-8 is shielded by 1.10 ppm. Moreover, this shielding is very closer to the *syn*-β carbon C-6 (1.19 ppm) by the consequence of $A^{1,3}$-interaction but such effect is not possible at C-8 if the molecule is rigid, instead of the dynamic behavior as outlined in Figure 6.

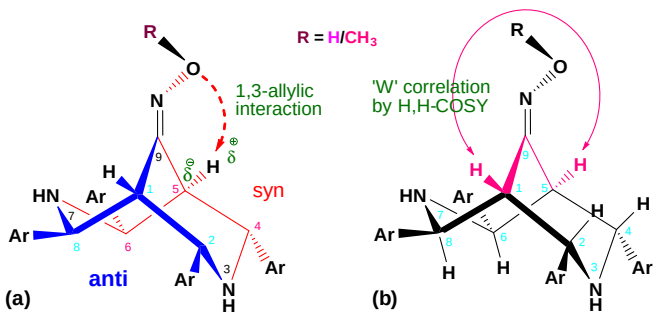

Figure 3. (a) Non-bonded $A^{1,3}$-interaction between the N–O and C(5)–H bonds in **26**–**75**; (b) Long-range coupling between the bridge-head protons H-1 and H-5 by 'W' arrangement, from the H,H-COSY spectrum of **51**, **52** and **53**.

Other than 0.1 ppm less deshielding of the H-5, a similar effect is observed in **51** by the introduction of a methyl group on oxime functionality of **26**. Further, in ^{13}C, the methyl group shields the oximino carbon C-9 and deshields the *syn*-α carbon C-5 by 1.13 and 0.72 ppm, respectively. Likewise, all other oximes **27**–**50** and oxime ethers **52**–**75** are exhibiting the trend. The ^{1}H and ^{13}C NMR chemical shifts of **53** are represented in Figures 4 and 5. On the basis of 1D/2D NMR studies in solution, we perceived that the oximes **26**–**50** and oxime ethers **51**–**75** are exist in an interconvertable dynamic chair-boat conformation with equatorial disposition of the aryl groups at C-2/C-4 (in the chair form) and axial-like orientation at C-6/C-8 (in the boat form) as in Figure 6.

Single-crystal analysis of **26** (Figs. 7 and 8) shows that one of the piperidine rings C1–C7–C4–C5–N2–C6 adopts a near ideal chair conformation with the deviation of ring atoms N2 and C7 from the best plane C1–C4–C5–C6 by −0.657 and 0.673 Å, respectively. According to Nardelli,[7] the smallest displacement asymmetry parameters q_2 and q_3 are 0.0391(17) and 0.6133(17) Å, respectively. In accordance with Cremer and Pople,[8] the ring puckering parameters such as total puckering amplitude 'Q_T' and the phase angle 'θ' are 0.6145(17) Å and 176.32(6)°. Thus all parameters strongly support the near ideal chair conformation. Likewise, the puckering analysis of another piperidine ring C1–C2–N1–C3–C4–C7 indicates that the ring adopts a boat conformation with the deviation of ring atoms N1 (−0.652 Å) and C7 (0.708 Å) from the best plane C1–C2–C3–C4. Further, it is confirmed by the Q_T = 0.7681(17) Å and θ = 89.43(13)° as well as q_2 [0.768(17)] and q_3 [0.0077(17) Å]. Thus, the detailed crystallographic studies such as asymmetry parameters, ring puckering parameters, torsion angles and least-square planes calculated for **26** proved that the bicycle exists in a chair-boat conformation with equatorial orientation of the phenyl rings in the chair form with the torsion angles of 177.23(13) [C7–C4–C5–C20] and 179.43(14)° [C7–C1–C6–C26], whereas the torsion angles of the phenyl rings C8–C9–C10–C11–C12–C13 and C14–C15–C16–C17–C18–C19 in the boat form are 120.27(16) [C7–C1–C2–C8] and −122.85(16)° [C7–C4–C3–C14], respectively. The phenyl groups in the chair form are orientated at an angle of 19.36(3)° with respect to one another whereas in the boat form, they are oriented at an angle of 40.09(5)°.

All the synthesized oximes and O-methyloximes were tested for their in vitro antimicrobial activity against a panel of pathogenic bacteria (*Bacillus subtilis*, *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*) and fungi (*Candida albicans*, *Candida parapsilosis*, *Aspergillus niger* and *Cryptococcus neoformans*) by standard broth micro-dilution technique by NCCLS

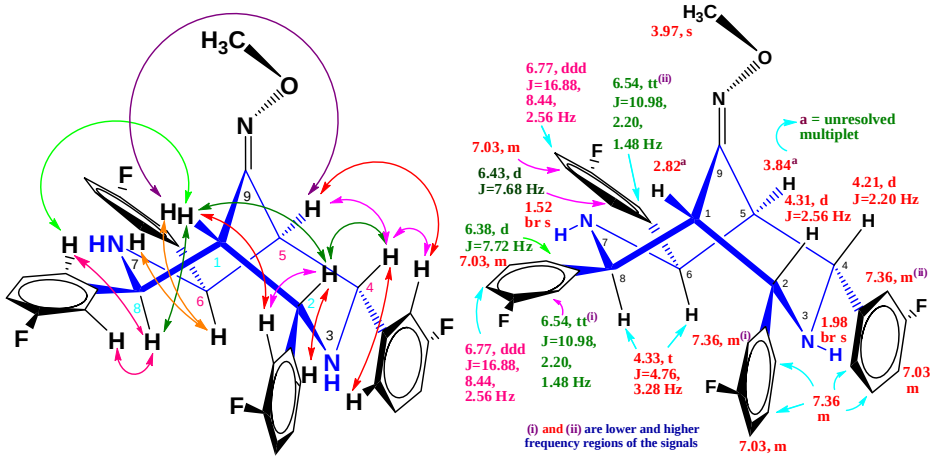

Figure 4. Significant NOE observed in the NOESY spectrum of **53**, suggesting the chair-boat conformation with equatorial orientation of the *meta*-fluorophenyl groups on the chair form. The proton chemical shifts of **53** are assigned by H,H-COSY and NOESY.

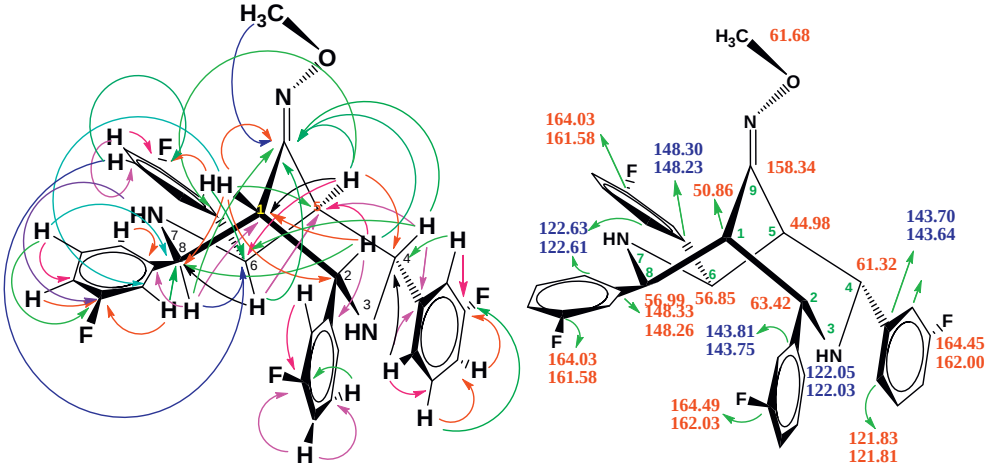

Figure 5. Connectivities found in the HMBC spectrum of **53**. The red, green and blue linkages are representing α, β and γ correlations, respectively. The carbon chemical shifts are unambiguously assigned by the use of one and multiple bond $^{1}H–^{13}C$ correlations.

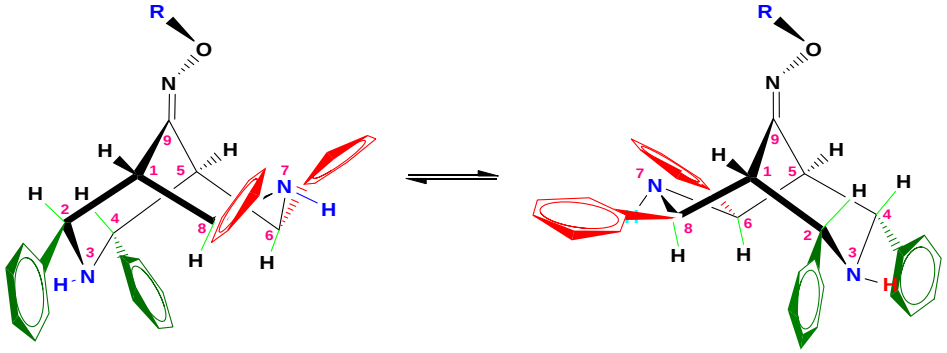

Figure 6. Dynamic behavior of the bicycle. The molecule is flexible and dynamic, in that a chair/boat conversion involves both rings; when one ring is chair, the other is boat and vice versa. This suggests that the oximes and methyloximes with their fixed double bond configuration are chiral molecules and the dynamics outlined above, is a racemization process. Very probably, this interconversion is fast on the NMR time scale but since NMR cannot differentiate enantiomers, the spectra suggest a rigid molecular framework. The phenyl groups are equatorial in the chair conformation but when this flips to the boat, their position is boat-axial.

guidelines,[9] using Gentamicin and Fluconazole as standards, respectively.

Careful analysis of the MICs in Table 1 provides some lead molecules with good antibacterial activity. Of the oximes and oxime ethers **26**–**75** tested, compounds with electron-withdrawing F and Cl at *ortho* or *para* positions of the phenyl expressed a moderate to good activity against most of the tested pathogens; specifically, they would rather inhibited the Gram-negative than the Gram-positive pathogens. Compounds **29**, **52**, **54**, **55** and **57** required about 8–32 μg/mL against *B. subtilis* or *S. aureus*, whereas

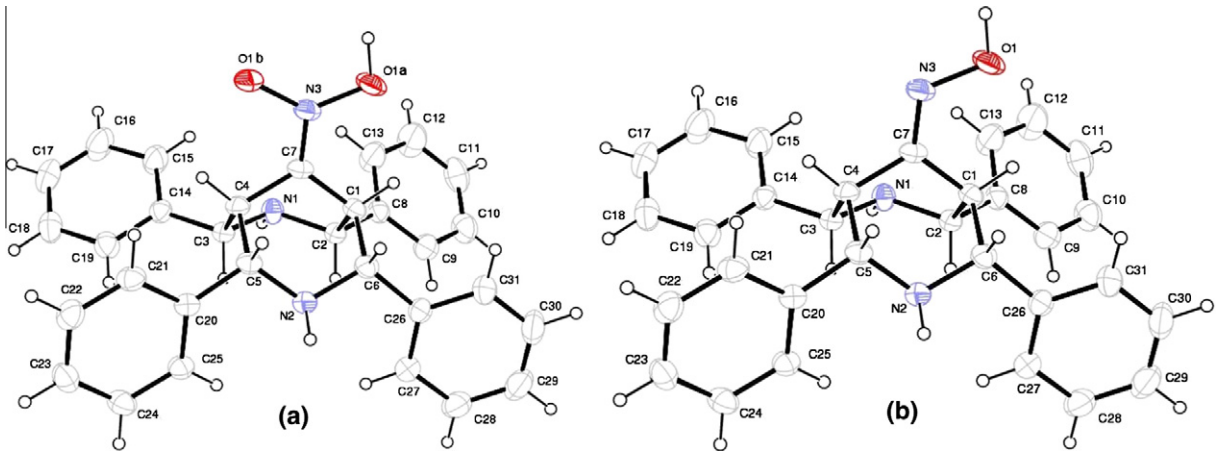

Figure 7. (a) Anisotropic displacement representation of the molecule **26** with atoms represented with 30% probability ellipsoids. The 3,7-diazabicycle exists in a chair-boat conformation with equatorial orientation of the phenyl groups in the chair form. As a matter of fact, the oxygen atom of the oxime functionally is disordered over two positions with a complementary occupancy factor (i.e., 0.52:0.48). The oxime molecule **26**, $C_{31}H_{29}N_3O$, crystallized in a monoclinic system under the space group $P2_1/c$ with cell parameters, a = 14.4165(12) Å, b = 7.0762(5) Å, c = 24.5488(18) Å, β = 96.913(3) and Z = 4; (b) For the clarity of structure, one of the disordered oxygen atoms was omitted.

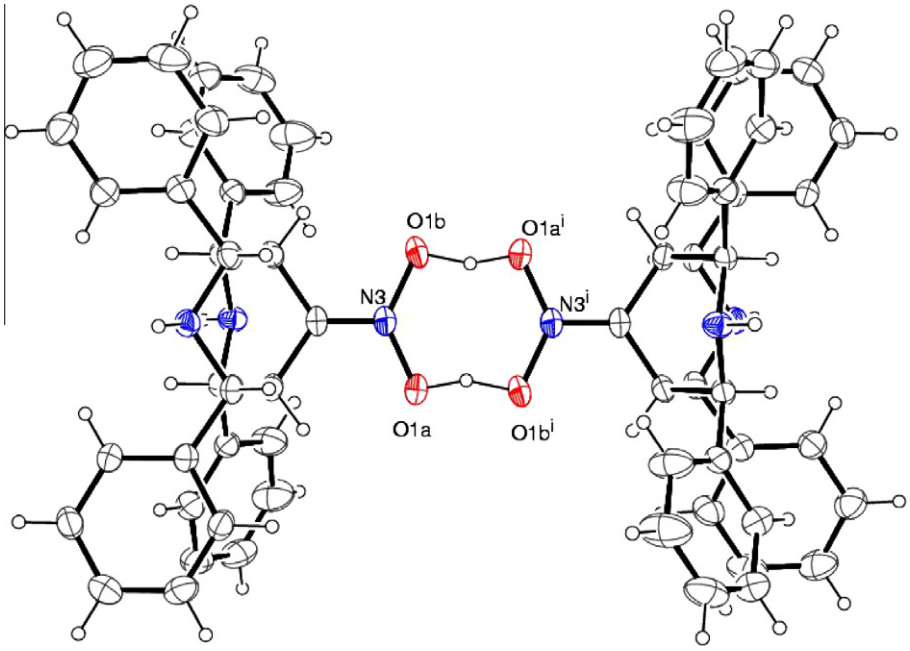

Figure 8. The molecule exists as a centrosymmetric dimer, connected by intermolecular hydrogen bonds with $R_2^2(8)$ graph-set motif.

they (except **29**) required only 4–8 μg/mL against *K. pneumonae* and/or *P. aeruginosa*. Also, **16**, **30**, **32**, **53**, **54** and **55** registered their MIC at 16 μg/mL against Gram-negative bacteria. However, the Br substituent did not exhibit activity even at 128 μg/mL, except **35** and **60** against *B. subtilis* at 64 μg/mL.

Introduction of the electron-donating substituents on the phenyl groups of **26** showed an improvement in their activity against Gram-negative strains; in addition, **68** inhibited the growth of *S. aureus* at 32 μg/mL. Of the two Gram-negative strains, *P. aeruginosa* was susceptible to the oximes **39**/**40**/**41**/**43** and oxime ethers **61**/**64**/**66**/**68** at 16 μg/mL (similar to Gentamicin) whereas against *K. pneumoniae*, **61**/**71** and **62**/**65**/**66** showed MIC at 16 and 8 μg/mL, respectively (they are eight and fourfold less potent than Gentamicin). Moreover, the oxime ethers **62** and **65** registered an outstanding MIC at 4 μg/mL against *P. aeruginosa*, which is four-fold potent than Gentamicin.

Table 2 describes the antifungal activity of synthesized oximes/oxime ethers and suggests some lead molecules with good antifungal profile. The oxime derivatives with unsubstituted phenyl did not exhibit activity even at 128 μg/mL. However, the introduction of F/Cl substituents exhibited moderate to excellent activity against *C. albicans* and *A. niger* (additionally, *ortho*-Cl oxime **30** and oxime ether **55** exerted activity against *C. neoformans* at 16 μg/mL), whereas, except the *para*-Br oxime **35** (MIC 32 μg/mL) and oxime ether **60** (MIC 16 μg/mL) against *C. parapsilosis*, no improvement for the Br substituent. Of the halo-substituted compounds, oximes **27**/**29** and oxime ether **52** registered a similar activity of Fluconazole at 4 μg/mL against *A. niger*; also, oxime ethers **54** and **55** recorded an outstanding activity at 2 μg/mL, which is twofold higher than standard Fluconazole. In addition, against *C. albicans*, **54** registered the best MIC at 2 μg/mL.

Introduction of the Me/Et/^{i}Pr groups on **26**/**51** exhibited a remarkable activity against *C. parapsilosis* (of them, **36**, **61**, **62** and **64** registered an excellent activity about 2–8 μg/mL) while, introduction of the alkoxy substituents moderately inhibited the growth of *C. neoformans* and *A. niger* (**65** and **70** showed their best

Table 1
Antibacterial activity of oximes **26**–**50** and oxime ethers **51**–**75**

Compounds	Minimum inhibitory concentration (MIC_{90})[a] in μg/mL			
	B. Subtilis	*S. aureus*	*K. pneumoniae*	*P. aeruginosa*
26	>128	>128	>128	>128
27	64	>128	32	16
28	128	>128	64	64
29	64	16	64	32
30	>128	64	32	16
31	>128	>128	>128	64
32	>128	64	16	32
33	>128	>128	>128	>128
34	>128	>128	>128	>128
35	64	>128	128	>128
36	>128	128	>128	32
37	>128	>128	>128	32
38	>128	>128	>128	32
39	>128	128	128	16
40	>128	>128	32	16
41	>128	>128	64	16
42	>128	>128	>128	128
43	>128	64	64	16
44	>128	>128	64	32
45	>128	>128	32	32
46	>128	>128	64	64
47	>128	>128	64	64
48	>128	>128	>128	>128
49	>128	>128	>128	>128
50	128	>128	64	>128
51	>128	>128	>128	128
52	32	64	16	4
53	>128	>128	64	16
54	64	8	16	4
55	>128	16	4	16
56	>128	>128	64	>128
57	128	32	4	8
58	>128	>128	>128	>128
59	>128	>128	>128	>128
60	64	>128	>128	>128
61	>128	>128	16	16
62	64	>128	8	4
63	>128	>128	64	32
64	>128	128	128	16
65	64	>128	8	4
66	64	>128	8	16
67	>128	128	>128	64
68	64	32	>128	16
69	>128	>128	64	32
70	>128	>128	32	32
71	>128	>128	16	64
72	>128	>128	64	64
73	>128	>128	>128	>128
74	>128	>128	64	>128
75	64	>128	16	64
Gentamicin	16	4	2	16

[a] MIC_{90} is the lowest concentration of an antimicrobial agent to significantly inhibit the 90% growth of a pathogen after a period of incubation; MIC values are represented in micrograms per milliliter.

Table 2
Antifungal activity of oximes **26**–**50** and oxime ethers **51**–**75**

Compounds	Minimum inhibitory concentration (MIC_{90}) in μg/mL			
	C. albicans	*C. parapsilosis*	*A. niger*	*C. neoformans*
26	>128	>128	>128	>128
27	32	64	4	>128
28	32	>128	64	>128
29	4	>128	4	128
30	16	>128	8	16
31	>128	>128	64	>128
32	8	128	64	>128
33	>128	>128	>128	>128
34	>128	>128	>128	>128
35	>128	32	>128	>128
36	64	8	64	>128
37	64	32	>128	>128
38	>128	64	>128	>128
39	>128	32	>128	>128
40	32	32	16	32
41	>128	32	16	32
42	>128	>128	64	>128
43	>128	64	16	64
44	>128	>128	32	64
45	>128	>128	16	64
46	>128	>128	32	32
47	>128	>128	32	32
48	128	128	>128	>128
49	>128	>128	128	>128
50	>128	64	64	>128
51	128	>128	>128	>128
52	8	64	4	>128
53	32	>128	16	>128
54	2	>128	2	32
55	16	>128	2	16
56	>128	>128	64	>128
57	4	>128	16	>128
58	>128	64	>128	>128
59	>128	>128	>128	>128
60	>128	16	>128	>128
61	64	8	64	>128
62	64	2	64	>128
63	128	32	>128	>128
64	128	8	128	>128
65	32	16	4	8
66	64	32	4	8
67	128	>128	64	>128
68	>128	128	16	16
69	>128	64	16	16
70	>128	128	8	16
71	>128	>128	16	32
72	>128	>128	32	32
73	64	128	>128	>128
74	>128	>128	64	>128
75	>128	32	64	>128
Fluconazole	1	2	4	2

MIC at 4 and 8 μg/mL against *A. niger*). Instead of *C. neoformans*, phenoxy, benzyloxy and allyloxy substituted compounds inhibited the growth of *C. parapsilosis*; of them, **75** registered its best MIC at 32 μg/mL.

In summary, a small library of bispidines, their oximes and oxime ethers were synthesized by an easiest synthetic strategy as single isomers with high yields. According to NMR and single-crystal XRD studies, all the compounds exist in a chair-boat conformation with equatorial orientation of the aryl groups in the chair form. An SAR was carried out by changing the substituents on the phenyl groups that flanked the secondary amino groups of **26**, which afforded **27**–**50** with antimicrobial response; in addition, a methyl group was introduced on the oxime functionality of **26**–**50**, which yielded **51**–**75** with enhanced activity than corresponding oximes. According to this study, both the electron-withdrawing and donating groups exhibited a noteworthy antimicrobial profile, which can be rationalized as follows. Of the tested electron-withdrawing groups (F/Cl/Br), F/Cl at *ortho*/*para* positions exhibited a significant broad-spectrum activity against both the tested Gram-negative and Gram-positive strains. Of the tested electron-donating groups (Me/Et/^{i}Pr/SMe/OMe/OEt/OPr/OBu/OPh/OBn/allyloxy), majority of the substituents expressed their activity against the Gram-negative strains. Particularly, against *P. aeruginosa*, a very closer and even better activity of Gentamycin was observed despite the nature of the substituents.

The F/Cl substituents registered their significant fungal activity against *C. albicans* and *A. niger* whereas the electron-donating alkyl and alkoxy substituents mainly inhibited the growth of *C. parapsilosis* and *C. neoformans*/*A. niger*, respectively. A few of them, that is, compounds **27**, **29**, **62**, **65** **65** and **66** exerted a similar activity of Fluconazole against *C. parapsilosis* or *A. niger*. Surprisingly, thiomethyl (SMe) substituted oxime and oxime ether **40**/**65** expressed

a broad-spectrum activity at the MIC of 4–32 μg/mL against all the tested fungal strains, which are closer to Fluconazole. According to these structure–activity correlations, some lead molecules were known with valuable antimicrobial profile. Thus, deserves further optimization toward the development of a better class of antimicrobial agents.

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Supplementary data

Complete experimental details, NMR spectra/data of all compounds and single-crystal XRD data of **26**. Supplementary crystallographic data for **26** (CCDC No. 673684) can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.09.079.

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