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Stereospecific synthesis of oximes and oxime ethers of 3-azabicycles: A SAR study towards antimicrobial agents

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ABSTRACT

Libraries of 1-methyl-2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones/oximes/*O*-methyloximes **1–14/15–28/29–42** and 7-methyl-2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones/oximes/*O*-methyloximes **43–48/49–54/55–60** were synthesized and their stereochemistry was established by 1D/2D NMR spectral and single crystal XRD studies. All the synthesized oximes and oxime ethers were screened 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*) using Gentamicin and Fluconazole as standards, respectively. From the SAR profile, the lead molecules were identified.

Molecules with the 3-azabicyclo[3.3.1]nonane nucleus are of great interest due to their presence in a wide variety of naturally occurring diterpenoid/norditerpenoid alkaloids and biological activities.[1] The 3-azabicyclo[3.3.1]nonane nucleus itself contains an important class of piperidone pharmacophore[2] and the SAR studies on the piperidone heterocycle indicated that the nature and position of substituents were important factors towards significantly effect the biological actions.[3]

Reports reveal the antimicrobial efficacy of oximes and oxime ethers owing to the presence of —C═N—O—R functionality.[4] An essential component of the search for new leads in drug designing program is the synthesis of molecules, which are novel, yet resembling known biologically active molecules by virtue of the presence of some critical structural features.[5] Moreover, it would rather be achieved by an easier synthetic strategy with stereo controlled product.

Altogether with an expectation of enhanced antimicrobial profile, we synthesized new oximes and *O*-methyloximes of 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones with CH_3 group at C-1/C-7 and electron-withdrawing/donating F/Cl/Br/CH_3/OCH_3 substituents in *ortho/meta/para* positions of the phenyl at C-2 and C-4.

Synthetic strategy of 1-methyl-2,4-diaryl-3-azabicyclo[3.3.1]-nonan-9-ones **1–14** and their oximes/*O*-methyloximes **15–28/29–42** is depicted in Scheme 1.

All 1-methyl-2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones **1–14** were synthesized as single isomer with good yields in one-pot by a modified and an optimized Mannich reaction.[1a,6] Stereochemistry of the compounds were established by use of their H,H-COSY, NOESY, HSQC and HMBC spectral data. The long-range couplings by means of 'W' arrangement from the H,H-COSY as well as NOE (Fig. 1) indicate the twin-chair conformation for the 3-azabicycle with equatorial orientation of the aryl groups at C-2 and C-4. The bridge-head proton H-5 appeared as a quintet in the most of the compounds. However, in some compounds, it appeared as a broad singlet/unresolved multiplet with a half-width "$W_{1/2}$" of about 8 Hz, supporting the twin-chair conformation.[7]

E/*Z* isomerism is obvious while synthesizing the oximes or oxime ethers from unsymmetrical ketones. However, in all cases, only *E* isomer was achieved with >90% yields. The effect of oximation/oximination on $^1H/^{13}C$ NMR spectra was significant by the allylic ($A^{1,3}$) interaction between the N–O and C(5)–H bonds besides the decrease in electronegativity at C-9 by the reduction of C═O as C═N. In fact, $A^{1,3}$ interaction is noteworthy (Fig. 2a) as deshielded H-5 (*syn* α-proton) >1 ppm and shielded C-5 (*syn* α-carbon) about 7 ppm besides the electronegativity (oximation) effect on that proton/carbon. Thus, the effect of $A^{1,3}$ interaction dominated the electronegativity effect on consecutive (*syn*) β position and affect the γ-carbon. Although, $A^{1,3}$ effect was similar in oxime ethers, due to the presence of electron-donating CH_3 group at oxime functionality, the oximino carbon C-9 and *syn* α-proton

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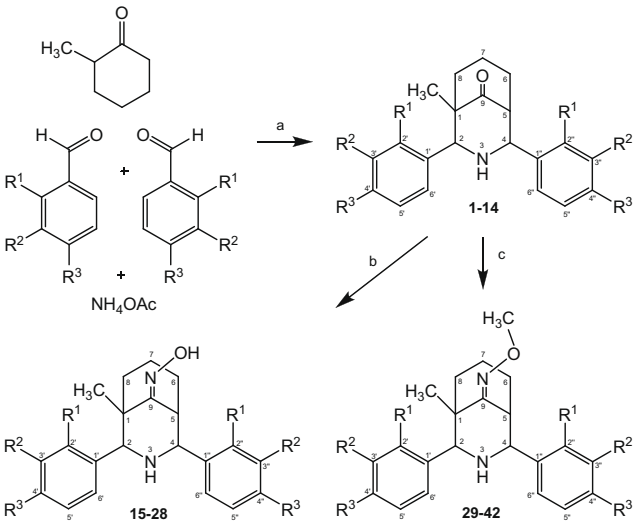


Compound	R^1	R^2	R^3	Compound	R^1	R^2	R^3
1, 15, 29	H	H	H	**8, 22, 36**	Br	H	H
2, 16, 30	F	H	H	**9, 23, 37**	H	H	Br
3, 17, 31	H	F	H	**10, 24, 38**	CH_3	H	H
4, 18, 32	H	H	F	**11, 25, 39**	H	H	CH_3
5, 19, 33	Cl	H	H	**12, 26, 40**	OCH_3	H	H
6, 20, 34	H	Cl	H	**13, 27, 41**	H	OCH_3	H
7, 21, 35	H	H	Cl	**14, 28, 42**	H	H	OCH_3

Scheme 1. Reagents and conditions: (a) EtOH, warm, stirring; (b) HO–NH_2.HCl, $CH_3COONa{\cdot}3H_2O$, EtOH, reflux; (c) CH_3–O–NH_2·HCl, $CH_3COONa{\cdot}3H_2O$, EtOH, reflux.

H-5 were shielded by ~1 and 0.15 ppm, respectively. On the basis of NMR studies, we conceived that the oximes **15–28** and oxime ethers **29–42** are exist in the twin-chair conformation with equatorial disposition of the aryl groups at C-2 and C-4 (Figs. 1a and 2), which was further proved by XRD analysis (Fig. 3). Refer Supplementary data for detailed NMR/XRD analysis.

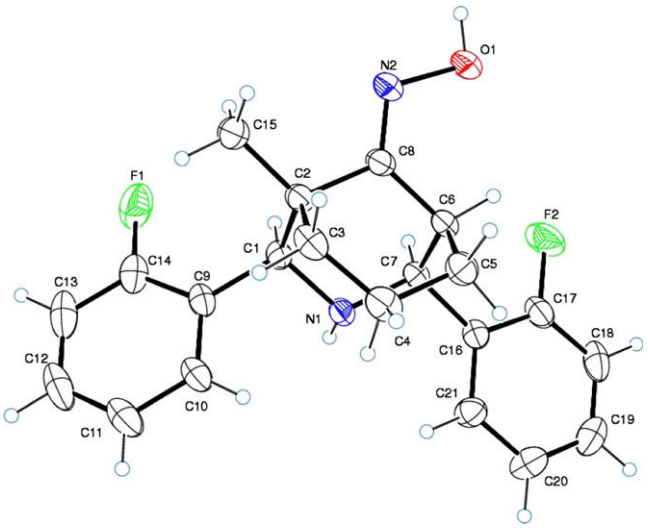


Figure 3. ORTEP of compound **16** with atoms represented as 30% probability ellipsoids. Single crystal XRD analysis proved that the bicycle exists in a twin-chair conformation with equatorial orientation of the *ortho*-fluorophenyl groups on both sides of the secondary amino group. The compound exists in *E* configuration.

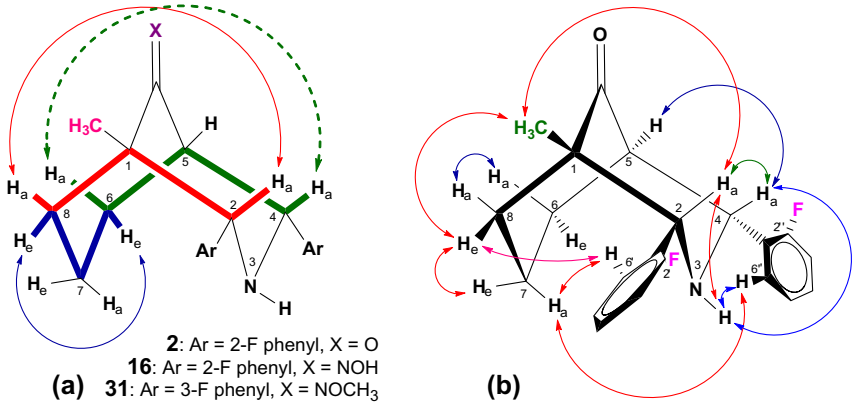


Figure 1. (a) Long-range couplings between the protons that are in 'W' arrangement. Accordingly, the compounds exist in the twin-chair conformation with equatorial orientation of the aryl groups at C-2 and C-4 of the 1-methyl-3-azabicycle. All compounds exhibited a weak correlation between H-4a and H-6a comparing to H-2a and H-8a; (b) Meaningful NOE observed in the NOESY spectrum of compound **2**.

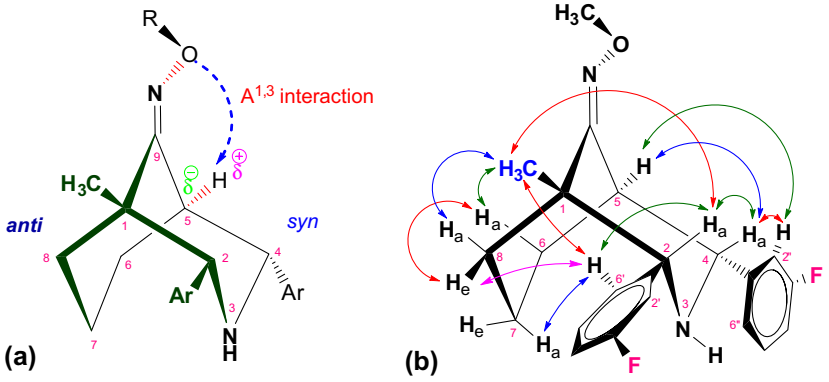
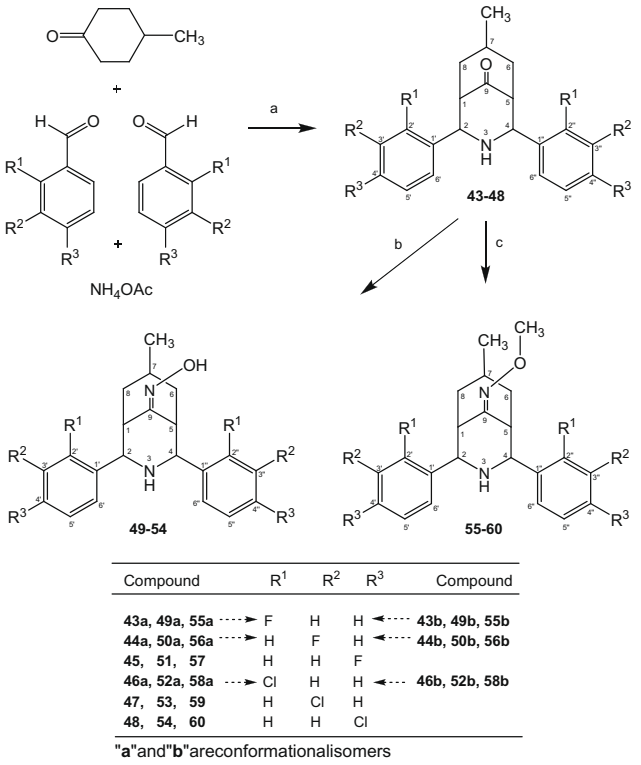


Figure 2. (a) Non-bonded 1,3-allylic interaction between the N–O and C(5)–H bonds; (b) significant NOE observed in the NOESY spectrum of compound **31**.



Scheme 2. Reagents and conditions: (a) EtOH, warm, stirring; (b) HO–NH_2·HCl, $CH_3COONa·3H_2O$, EtOH, reflux; (c) CH_3–O–NH_2·HCl, $CH_3COONa·3H_2O$, EtOH, reflux.

Synthesis of 7-methyl-2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones **43–48** and their oximes/*O*-methyloximes **49–54/55–60** are illustrated in Scheme 2.

Of the synthesized bicyclic ketones **43–48**, the *para*-F (**45**), *meta*-Cl (**47**) and *para*-Cl (**48**) compounds were achieved as single isomer in good yields, whereas, *ortho*-F (**43a, 43b**), *meta*-F (**44a, 44b**) and *ortho*-Cl (**46a, 46b**) compounds were obtained as mixtures of two conformational isomers. Stereochemistry of the bicyclic ketones **43–48** were established on the basis of the observed long-range couplings, NOE and $W_{1/2}$ of the bridge-head protons by H,H-COSY and NOESY spectra (Figs. 4 and 5). Accordingly, compounds **43a, 44a, 45, 46a** and **48** exist in the twin-chair conformation with equatorial orientation of all substituents, whereas **43b, 44b, 46b** and **47** exist in the chair-boat conformation with equatorial orientation of the aryl groups at C-2/C-4 and exocyclic orientation of the CH_3 group at C-7. The bridge-head protons in **43a, 44a, 45, 46a** and **48** appeared as broad singlets, whereas, in **43b, 44b, 46b** and **47**, they observed as doublets with *J* of 9–10 Hz. According to the α-effect by the introduction of CH_3 at C-7, it was deshielded about 6 ppm in **43–48**, whereas, the effect reversed at C-1 by the CH_3 at C-1 in **1–14**. The C-1 was shielded by 1–3 ppm depends on the nature and position of the substituents in phenyl.

According to NMR data, it is clear that all 7-methyl-2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones **43–48** afforded the corresponding oximes **49–54** and oxime ethers **55–60** with *syn* orientation of the N–O to C(5)–H bond. Owing to this phenomenon, a non-bonded interaction established between them, and as a consequence, the *syn*-α proton H-5 deshielded about 1 ppm, whereas the *anti*-α proton H-1 shielded by 0.05–0.1 ppm. Thus in oximes, the $\Delta\delta_{5,1}$ was $\geqslant$1.05 ppm, however, reduced to 0.90–0.95 ppm by O-methylation. Stereochemistry of the oximes and oxime ethers are shown in Figure 6 as witnessed by NMR studies, which were further witnessed by XRD analysis of **53** and **54** (Figs. 7 and 8). Refer Supplementary data for detailed NMR/XRD analysis.

All the synthesized oximes/oxime ethers were evaluated for their in vitro antimicrobial activity against a panel of pathogenic bacteria and fungi by standard broth micro-dilution technique

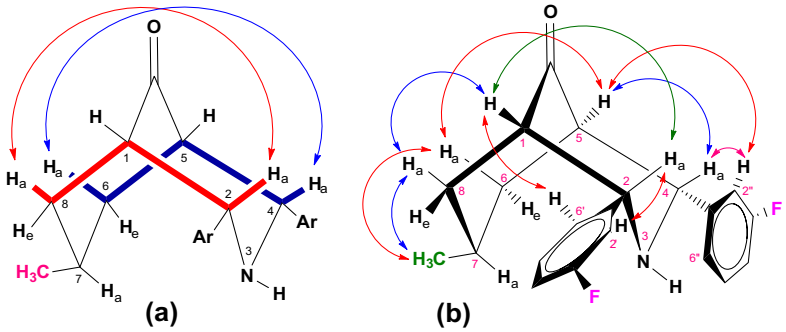


Figure 4. (a) Long-range couplings between the protons that are in 'W' arrangement, according to the H,H-COSY spectrum of compound **44a**; (b) significant NOE observed in the NOESY spectrum of **44a**. Both H,H-COSY and NOESY suggest that the bicycle exists in a twin-chair conformation with equatorial orientation of all substituents.

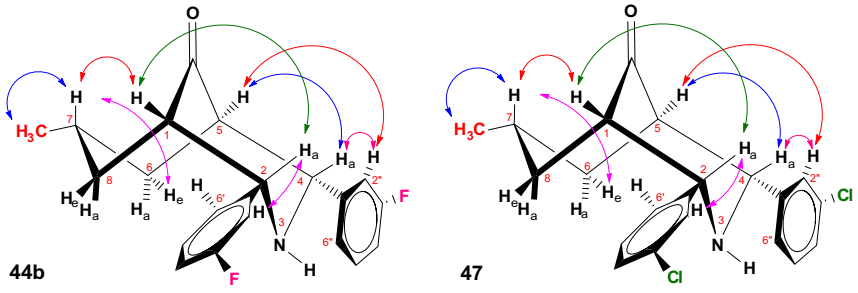


Figure 5. Significant NOE observed in the compounds **44b** and **47**, suggesting the chair-boat conformation. Also, the absence of long-range couplings in the H,H-COSY spectrum of **44b** and **47** support the non-existence of the bicycle in the twin-chair conformation. The NOE between H-7 and H-1 indicates the exocyclic orientation of the CH_3 group at C-7.

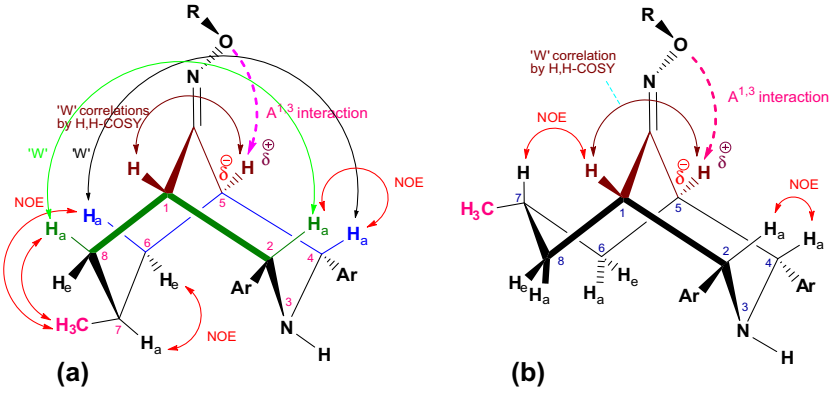


Figure 6. (a) Chair–chair conformation of compounds **49a, 50a, 51, 52a, 54, 55a, 56a, 57, 58a** and **60** with equatorial orientation of the aryl groups at C-2 and C-4 and exocyclic as well as equatorial orientation of the CH_3 at C-7. NOE and 'W' correlations (between H-1 and H-5, H-2a and H-8a, H-4a and H-6a; because H-6e and H-8e were merged, we could not get the correlation between them) strongly support the proposed stereochemistry; (b) chair–boat conformation of compounds **49b, 50b, 52b, 53, 55b, 56b, 58b** and **59** with equatorial orientation of the aryl groups at C-2/C-4 and exocyclic orientation of the CH_3 at C-7. Observed NOE and the absence of 'W' correlations (except H-1 and H-5 from H,H-COSY) insist that the compounds exist in chair–boat conformation. NOE between the H-7 and H-1 indicates the exocyclic orientation of the CH_3 at C-7.

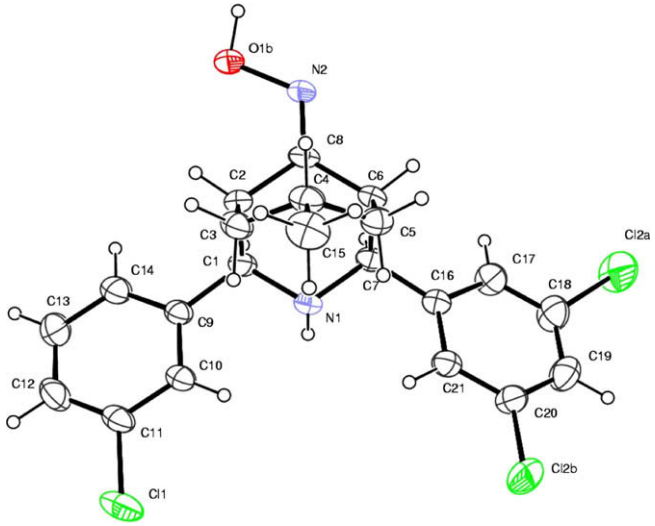


Figure 7. ORTEP of compound **53** with atoms represented as 30% probability ellipsoids. The bicycle exists in a chair–boat conformation with equatorial orientation of the *meta*-chlorophenyl groups on both sides of the secondary amino group. The molecule exists in *E* configuration with exocyclic orientation of the CH_3 group at C-7. Chlorine atom in one of the phenyl rings and oxygen atom of the oxime functionally are disordered over two positions with site occupancy factors of 0.5. One of the disordered oxygen atoms is omitted for clarity.

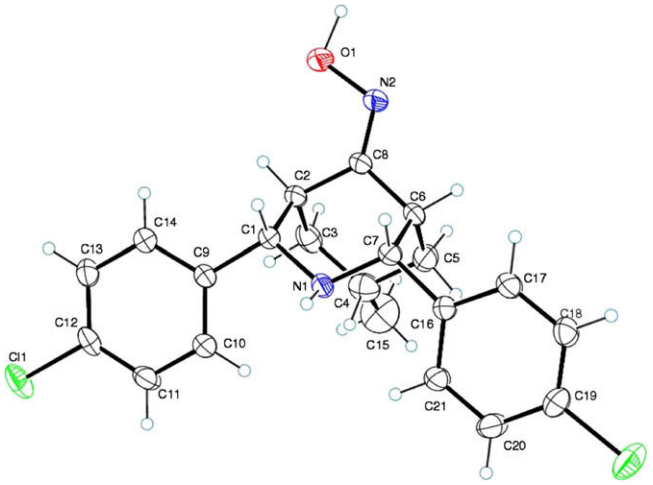


Figure 8. ORTEP of compound **54** with atoms represented as 30% probability ellipsoids. According to XRD analysis, the bicycle exists in a twin-chair conformation with equatorial orientation of the *para*-chlorophenyl groups. Also, the analysis witnessed the equatorial as well as exocyclic orientation of the CH_3 group at C-7 and *E* configuration of the molecule.

according to NCCLS guidelines,[8] using Gentamicin and Fluconazole as standards.

Data of the Table 1 describe the antibacterial activity of the synthesized oximes/oxime ethers against pathogenic bacteria and suggest the lead molecules. Among the oxime derivatives, compounds with electron-withdrawing F/Cl/Br substituents at phenyl expressed moderate to good activity. Especially, the F and Cl substituents at *ortho* or *para* positions of the phenyl showed maximum activity. Among the 1-methyl oximes **15–28**, **16, 18, 19** and **21** exhibited moderate activity against all strains and enhanced by the introduction of a CH_3 group at oxime functionality. Thus, **30, 32, 33** and **35** expressed a good activity profile against all strains with the MIC range of 4–16 μg/mL as Gentamicin (MIC range 2–16 μg/mL). Likewise, the oxime ethers **55a, 57, 58a** and **60** also exhibited broad-spectrum antibacterial activity, their MIC lies in the range of 2–16 μg/mL against all strains, except **60** against *Pseudomonas aeruginosa*.

Careful analysis of the MICs in Table 2 provides the lead molecules with good antifungal profile. Despite the position of CH_3 in the bicycle, all oxime ethers exhibited comparatively better activity than their oximes. Both 1- and 7-methyl substituted oxime ethers with F/Cl substituents at *ortho/para* positions (**30, 32, 33, 35, 55a, 55b, 57, 58a, 58b** and **60**) expressed promising antifungal profile. Particularly, 7-methyl oxime ethers **55b** and **58b** registered their best MIC in the range of 2–4 μg/mL against all tested fungi. In addition, analogous oximes **49b** and **52b** exhibited their best MIC at 4 μg/mL against *Aspergillus niger* and *Candida albicans*, respectively.

In summary, libraries of 3-azabicyclo[3.3.1]nonan-9-ones/oximes/*O*-methyloximes with F/Cl/Br/CH_3/OCH_3 substituents at *ortho/meta/para* position of the phenyl groups at C-2/C-4 and CH_3 group at C-1/C-7 were synthesized in a stereospecific manner by an easier strategy with high yield. All oximes and oxime ethers were achieved only as *E*-isomers. Among the oxime derivatives, irrespective of the nature and position of the substituents, all 1-methyl compounds **15–42** exist in the twin-chair conformation

Table 1
Antibacterial activity of compounds **15–42** and **49–60**

Compounds	Minimum inhibitory concentration (MIC_{90})[a] in μg/mL			
	B. Subtilis	*S. aureus*	*K. pneumoniae*	*P. aeruginosa*
15	>128	128	>128	>128
16	32	8	16	32
17	128	64	32	128
18	64	16	32	64
19	64	8	16	32
20	>128	64	64	>128
21	>128	64	16	>128
22	128	64	128	>128
23	>128	64	>128	>128
24	64	128	128	>128
25	128	128	>128	>128
26	64	64	128	128
27	128	128	>128	>128
28	128	32	64	>128
29	>128	64	128	>128
30	16	4	4	8
31	128	16	32	32
32	32	8	16	16
33	32	4	8	8
34	128	64	32	64
35	64	32	16	64
36	64	64	64	128
37	64	32	32	>128
38	32	32	128	128
39	32	64	64	128
40	32	32	32	64
41	64	32	128	>128
42	64	16	64	128
49a	16	8	16	32
49b	32	32	64	128
50a	128	32	32	64
50b	>128	32	64	32
51	64	8	32	64
52a	32	16	32	32
52b	64	16	32	>128
53	32	64	32	64
54	32	32	16	32
55a	4	2	2	8
55b	8	16	16	32
56a	16	16	64	64
56b	32	32	64	64
57	16	4	8	16
58a	8	4	4	4
58b	32	8	16	16
59	64	32	32	128
60	16	16	8	32
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 millilitre.

Table 2
Antifungal activity of compounds **15–42** and **49–60**

Compounds	Minimum inhibitory concentration (MIC_{90}) in μg/mL			
	C. albicans	*C. parapsilosis*	*A. niger*	*C. neoformans*
15	>128	>128	>128	>128
16	8	8	64	64
17	32	64	128	>128
18	16	32	64	32
19	64	8	16	8
20	64	64	>128	128
21	32	64	64	32
22	64	64	128	>128
23	>128	>128	128	128
24	128	>128	64	>128
25	128	>128	64	128
26	>128	128	128	64
27	>128	>128	>128	128
28	128	>128	128	>128
29	128	>128	>128	>128
30	4	8	16	8
31	16	64	64	128
32	8	8	32	16
33	32	4	16	4
34	32	32	128	64
35	16	16	8	8
36	64	32	32	128
37	64	128	32	64
38	64	128	64	128
39	128	>128	32	64
40	64	64	128	128
41	>128	64	>128	128
42	64	128	128	>128
49a	64	128	64	64
49b	16	32	4	16
50a	128	64	64	>128
50b	64	32	32	64
51	32	64	64	32
52a	16	32	>128	32
52b	4	16	32	64
53	64	128	64	>128
54	64	64	32	64
55a	8	32	16	16
55b	2	2	2	4
56a	32	32	64	64
56b	8	16	16	32
57	16	64	16	8
58a	8	16	32	16
58b	4	4	2	2
59	16	8	32	32
60	32	16	64	16
Fluconazole	1	2	4	2

with equatorial orientation of the aryl substituents at C-2 and C-4 of the 3-azabicycle. Of the 7-methyl compounds **49–60**, **49a/50a/51/52a/54/55a/56a/57/58a/60** and **49b/50b/52b/53/55b/56b/58b/59**, respectively, adopted the chair–chair and chair–boat conformations with exocyclic substitution of the methyl at C-7 along with equatorial orientation of the aryl groups at C-2 and C-4. Among the synthesized compounds, oximes with electron-withdrawing F/Cl substituents at *ortho/para* positions of the phenyl exhibited remarkable antibacterial as well as antifungal activity. Further, the activity was enhanced by the introduction of a methyl group at oxime functionality. Thus, the present SAR provides some lead molecules with worthy antibacterial and antifungal activities. Furthermore, to optimize the lead molecules and to develop better antimicrobial agents, toxicity and mechanistic studies are planned to carry out.

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Supplementary data

Complete experimental details, IR, ^{1}H and ^{13}C NMR data of all compounds, 2D NMR data of the representative compounds, and single crystal XRD data of **16, 53** and **54** were provided as supplementary material. Supplementary crystallographic data for **16** (CCDC No. 753535), **53** (CCDC No. 753536) and **54** (CCDC No. 753537) 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.2010.01.048.

References and notes

1. (a) Jeyaraman, R.; Avila, S. *Chem. Rev.* **1981**, *81*, 149; (b) Hardick, D. J.; Blagbrough, I. S.; Cooper, G.; Potter, B. V. L.; Critchley, T.; Wonnacott, S. *J. Med. Chem.* **1996**, *39*, 4860; (c) Henry, A. *Plant Alkaloids*; Churchill: London, 1966. p 75; (d) Barker, D.; Lin, D. H.-S.; Carland, J. E.; Chu, C. P.-Y.; Chebib, M.; Brimble, M. A.; Savage, G. P.; Mc Leod, M. D. *Bioorg. Med. Chem.* **2005**, *13*, 4565; (e) Parthiban, P.; Aridoss, G.; Rathika, P.; Ramkumar, V.; Kabilan, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6981; (f) Parthiban, P.; Rathika, P.; Park, K. S.; Jeong, Y.T. *Monatsh. Chem*., in press, doi:10.1007/s00706-009-0221-8.
2. (a) Baliah, V.; Jeyaraman, R.; Chandrasekaran, L. *Chem. Rev.* **1983**, *83*, 379; (b) Katritzky, A. R.; Fan, W. *J. Org. Chem.* **1990**, *55*, 3205. and references cited therein; (c) Perumal, R. V.; Adiraj, M.; Shanmugapandian, P. *Indian Drugs* **2001**, *38*, 156; (d) Aridoss, G.; Parthiban, P.; Ramachandran, R.; Prakash, M.; Kabilan, S.; Jeong, Y. T. *Eur. J. Med. Chem.* **2009**, *44*, 577.
3. (a) Prostakov, N. S.; Gaivoronskaya, L. A. *Chem. Rev.* **1978**, *47*, 447; (b) Lijinsky, W.; Taylor, H. W. *Int. J. Cancer* **1975**, *16*, 318; (c) Parthiban, P.; Aridoss, G.; Rathika, P.; Ramkumar, V.; Kabilan, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2981.
4. (a) Parthiban, P.; Balasubramanian, S.; Aridoss, G.; Kabilan, S. *Med. Chem. Res.* **2005**, *14*, 523; (b) Ramalingan, C.; Park, Y. T.; Kabilan, S. *Eur. J. Med. Chem.* **2006**, *41*, 683; (c) Bhandari, K.; Srinivas, N.; Kesava, G. B. S.; Shukla, P. K. *Eur. J. Med. Chem.* **2009**, *44*, 437; (d) Emami, S.; Falahati, M.; Banifatemi, A.; Amanlouc, M.; Shafiee, A. *Bioorg. Med. Chem.* **2004**, *12*, 3971; (e) Balasubramanian, S.; Aridoss, G.; Parthiban, P.; Ramalingan, C.; Kabilan, S. *Biol. Pharm. Bull.* **2006**, *29*, 125; (f) Rameshkumar, N.; Veena, A.; Ilavarasan, R.; Adiraj, M.; Shanmugapandiyan, P.; Sridhar, S. K. *Biol. Pharm. Bull.* **2006**, *26*, 188.
5. (a) Silverman, R. B. *Organic Chemistry of Drug Design and Drug Action*; Academic Press: San Diego, 1992; (b) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555.
6. (a) Jeyaraman, R.; Manoharan, M. *Heterocycles* **1989**, *29*, 1191; (b) Parthiban, P.; Ramkumar, V.; Jeong, Y. T. *Acta Cryst.* **2010**, *E66*, o194.
7. Iriepa, I.; Madrid, A. I.; Galvez, E.; Bellanato, J. *J. Mol. Struct.* **2003**, *651–653*, 579. and references cited therein.
8. (a) National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, Approved Standard, 5th ed.; NCCLS: Villanova, PA, 2000; pp M7–A5.; (b) National Committee for Clinical Laboratory Standard. Reference method for broth dilution antifungal susceptibility testing of yeast, Approved Standard. Document M27-A; NCCLS: Wayne, PA, USA, 1997.; (c) National Committee for Clinical Laboratory Standard. Reference method for broth dilution antifungal susceptibility testing of conidium forming filamentous fungi, Proposed Standard. Document M38-P; NCCLS: Wayne, PA, USA, 1998.