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Synthesis, stereochemistry and antimicrobial studies of novel oxime ethers of aza/diazabicycles

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ABSTRACT

Two series of bicyclic oxime ethers viz, 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-one *O*-benzyloximes **13**–**24** and 2,4,6,8-tetraaryl-3,7-diazabicyclo[3.3.1]nonan-9-one *O*-benzyloximes **31**–**36** were synthesized and stereochemistry was established by their spectral (1D and 2D NMR) and crystal studies. Synthesized oxime ethers were screened for their in vitro antimicrobial activity against a set of pathogenic bacteria (*Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Salmonella typhi*, *Escherichia coli* and *Klebsiella pneumoniae*) and fungi (*Candida albicans*, *Candida-51*, *Rhizopus* sp., *Aspergillus niger* and *Aspergillus flavus*) by two-fold serial dilution method, respectively, using Ciprofloxacin and Amphotericin B as standards. Most of the molecules expressed promising antimicrobial profile against the tested pathogens and even a few compounds **16**, **21**, **22**, **33** and **34** were better than standard drugs.

Microbes are customary in nature, air, water, on the surface that we touch in everyday life and even in our regular food. Infections caused by these small unicellular organisms can range from mild illness to a fatal one, leading to death.[1] Particularly, 2–19% patients are infected from hospital visits.[2] Apart from bacterial infections, the risk of opportunistic fungal infections has been greatly increased due to the increase of immunocompromised patients such as AIDS, cancer and organ transplant recipients. But the available antifungal drugs, polyene macrolides, azoles, flucytosine and candins are non-ideal in terms of efficacy, antifungal spectrum or safety; and, the invasive *candidiasis* and *aspergillosis* has increased dramatically.[3] Hence, the need for new and efficient antimicrobial agents is emerging nowadays.

3-ABN (3-azabicyclo[3.3.1]nonane) and 3,7-DABN (3,7-diazabicyclo[3.31]nonane) nucleus are of biological interest due to their presence in the molecular structure of various alkaloids (diterpene/norditerpene and lupin) and drugs.[4] Also, oxime ethers are more interested in current affairs due to their antimicrobial efficiency.[5] The *O*-benzyloxime/*O*-benzyl functionality (Fig. 1) of antifungal drugs (oxiconazole/econazole/miconazole) and antimicrobial agents (piperidone/chromanone/nafimidone oxime ethers and inverted oxime ethers of oxiconazole) prompted to synthesize *O*-benzyloximes of 3-ABN/3,7-DABN-9-ones with the expectation of effective antimicrobial profile.

As depicted in Scheme 1, 3-ABN-9-one oxime ethers **13**–**19** and their *N*-methyl analogs **20**–**24** were synthesized. The 1D (^{1}H and ^{13}C) and 2D (^{1}H–^{1}H COSY, ^{1}H–^{13}C COSY, HMBC and NOESY) NMR spectral studies of **13**–**24** suggested that all compounds (except **16**) exist in chair–chair conformation with equatorial orientation of aryl groups at C-2 and C-4 as in Figure 2. Single crystal XRD analysis of the representative compound **15** also proved the same (Fig. 3). Refer Supplementary data for detailed spectral and crystal analysis.

In the ^{1}H NMR spectrum of **16**, unlike other oxime ethers, doublets observed at 5.25 (1H, J = 12.21 Hz) and 5.17 (1H, J = 12.21 Hz) ppm. The ^{1}H–^{1}H COSY suggested that the doublets are due to *O*-benzyl methylene protons, which are diastereotopic in nature. Besides, the benzylic protons H-2a/H-4a are appeared in the higher frequency region than **13** and **17** by 0.5 ppm, and the observed vicinal coupling constant was appreciably less. These variations suggested that, there may be a change in its stereochemistry. To overcome this ambiguity, XRD analysis has been carried out. According to single crystal XRD analysis, compound **16** also exhibits similar stereochemistry as **15** (Fig. 4).

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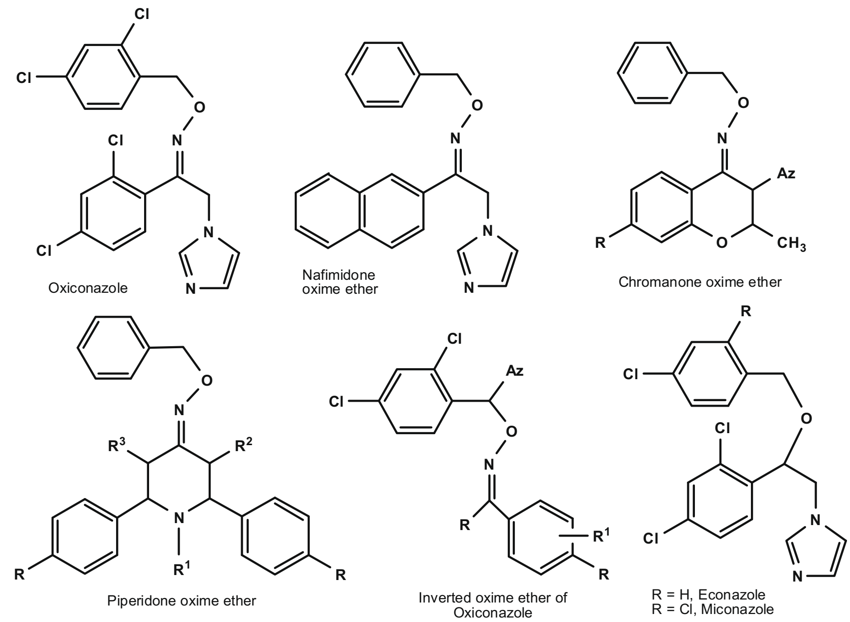
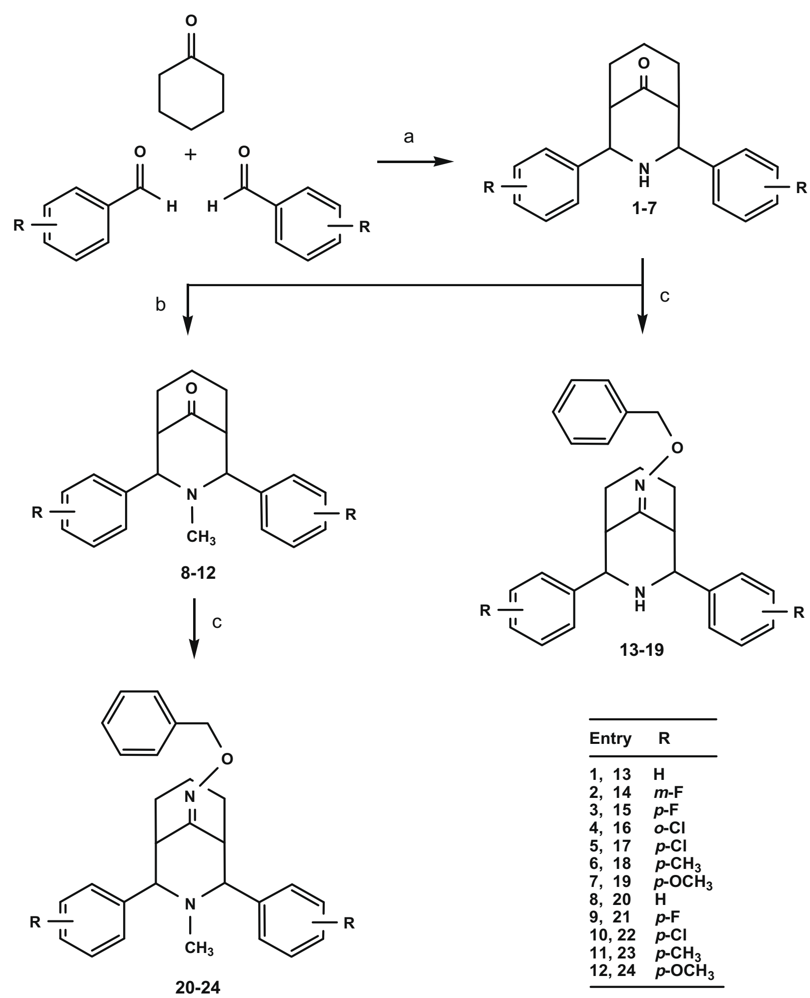


Figure 1. Structures of some analogous antimicrobial agents.



Entry	R
1, 13	H
2, 14	*m*-F
3, 15	*p*-F
4, 16	*o*-Cl
5, 17	*p*-Cl
6, 18	*p*-CH_3
7, 19	*p*-OCH_3
8, 20	H
9, 21	*p*-F
10, 22	*p*-Cl
11, 23	*p*-CH_3
12, 24	*p*-OCH_3

Scheme 1. Reagents and conditions: (a) CH_3COONH_4, EtOH, warm; (b) CH_3I, anhydrous K_2CO_3, dry acetone, reflux; (c) $C_6H_5CH_2$–O–NH_2·HCl, $CH_3COONa·3H_2O$, MeOH, reflux.

In **20–24**, owing to the effect of N-methylation, the benzylic carbons C-2/C-4 and their protons H-2a/H-4a were deshielded and shielded by 9.5 and 0.8 ppm, respectively.[6] Moreover, the vicinal coupling constants $J_{2a,1}$ and $J_{4a,5}$ were higher than corresponding

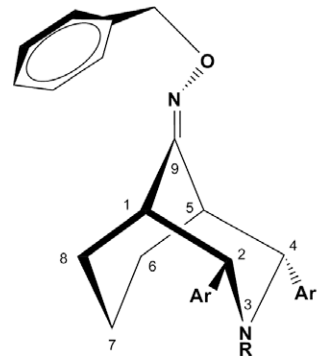


Figure 2. Chair–chair conformation with equatorial orientation of the phenyl/substituted phenyl groups at C-2 and C-4 of compounds **13**–**24** in $CDCl_3$ solution, according to one and two dimensional NMR data.

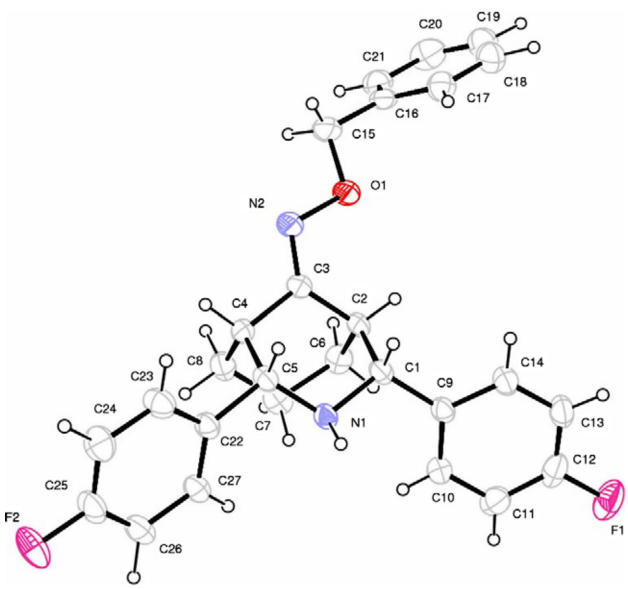


Figure 3. ORTEP of compound **15** with atoms represented as 30% probability ellipsoids; shows the existence in chair–chair conformation with equatorial orientation of *para*-fluorophenyl group on both sides of the secondary amino group. Of the chairs, the piperidine ring is in near ideal chair whereas cyclohexane deviates from the ideal chair.

non N-methylated oxime ethers, due to the lower electronegativity of N-CH_3 group than NH.

After a careful comparison of the observed coupling constants of **13** with corresponding monocyclic oxime ether **37** (2,6-diphenylpiperidin-4-one *O*-benzyloxime)[7] provided the insight; in **37**, the vicinal coupling constant on the *syn* side ($J_{5e,6a}$ = 3.0 Hz) was more than *anti* side ($J_{2a,3e}$ = 2.9 Hz), but in **13**, the vicinal coupling constant on the *syn* side was ($J_{4a,5}$ = 1.97 Hz) less than *anti* side ($J_{2a,1}$ = 2.09 Hz). This divergence was due to *syn* α-proton; in **37**, the *syn* α-proton presumably moved toward the *syn* β-proton whereas in **13**, the *syn* α-proton moved away from the *syn* β-proton to minimize the interaction with the oximino group.

According to Scheme 2, the 3,7-DABN-9-one oxime ethers **31**–**36** were synthesized. Based on the 1D and 2D NMR studies,[8] dynamic chair–boat conformation (Fig. 5) was proposed to them.

Single crystal XRD analysis of **31** proved that, one of the piperidine rings C1–C2–N1–C3–C4–C7 adopted the near ideal chair conformation with the deviation of ring atoms N1 and C7 from the C1–C2–C3–C4 plane by −0.665 and 0.687 Å, respectively. However, another piperidine ring C1–C7–C4–C5–N2–C6 adopted boat conformation with the deviation of ring atoms N2 and C7 from

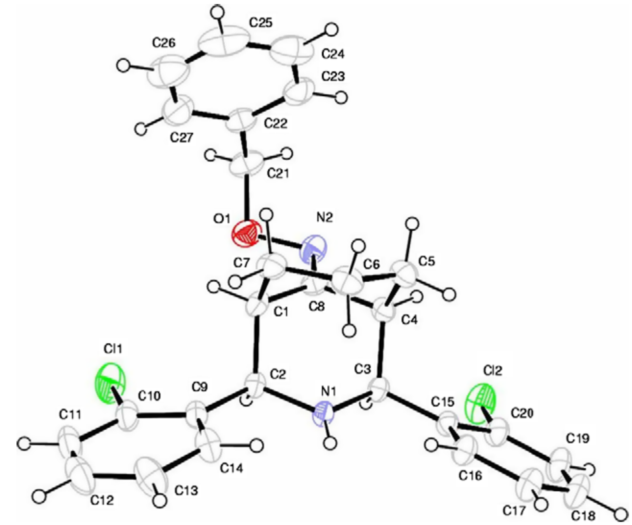


Figure 4. ORTEP of compound **16** with atoms represented as 30% probability ellipsoids. Compound **16** also exists in chair–chair conformation with equatorial orientation of *ortho*-chlorophenyl groups; both Cl atoms are pointed upward, that is, towards the C=N group.

the plane C1–C4–C5–C6 by −0.673 and 0.707 Å, respectively. Hence, **31** exists in chair–boat conformation as in Figure 6. Akin to **31**, compound **35** also revealed the chair–boat conformation (Fig. 7).

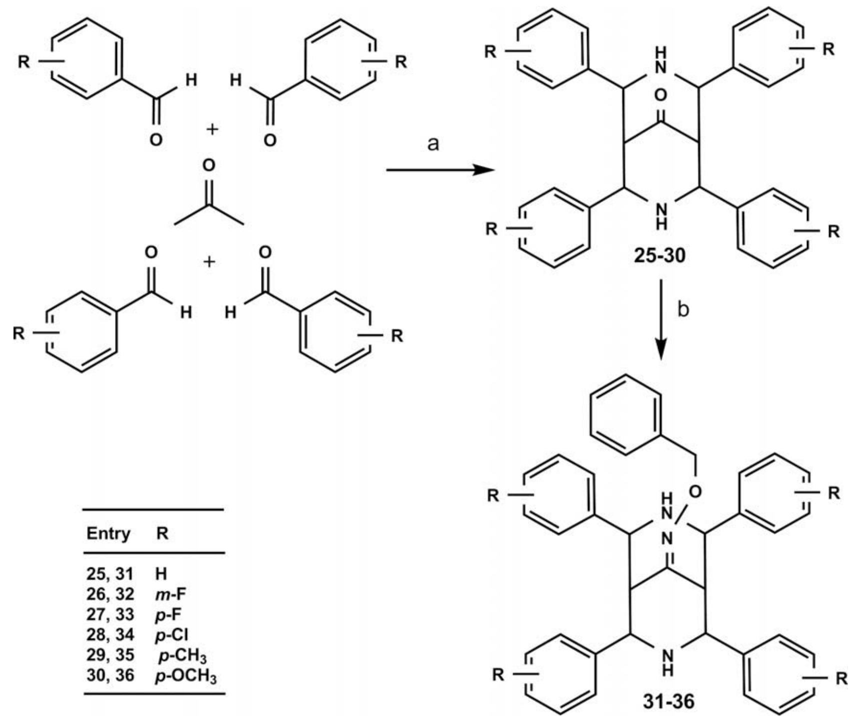
In vitro antibacterial activity of the synthesized oxime ethers was carried out against *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Salmonella typhi*, *Escherichia coli* and *Klebsiella pneumoniae* by twofold serial dilution method[9] using Ciproflaxacin as standard. The MIC values are presented in Table 1.

The unsubstituted phenyl groups at C-2 and C-4 of 3-ABN-9-one oxime ether **13** showed poor activity or inactivity even at 200 μg/mL. However, N-methylation (**20**) exerted a marginal improvement against all the tested bacterial strains. Likewise, the introduction of CH_3/OCH_3 substituents at phenyl groups exhibited a marginal improvement. Surprisingly, the F substituent on **13** and **20**, that is, compounds **14**/**15** (non *N*-methyl) and **21** (*N*-methyl) exerted significant improvement in their activity. In specific, **21** registered its best MIC at 12.5 μg/mL against *P. aeruginosa* and *E. coli*. Also, the Cl substituent on **13** and **20**, that is, compounds **16**, **17** and **22** expressed an appreciable improvement against all strains. Amongst, **16** (*ortho*-Cl) recorded remarkable MICs at 6.25 and 12.5 μg/mL against *P. aeruginosa* and *S. aureus*/*E. coli*, respectively.

The 3,7-DABN-9-one oxime ether **31** exerted poor activity against all the tested bacterial strains while the incorporation of fluorine on *meta*/*para* position (compounds **32**/**33**) enhanced their activity. The activity of *para*-F compound **33** was better than **32** and lies in the range of 6.25–12.5 μg/mL. The replacement of F by Cl/CH_3/OCH_3 in **33** afforded **34**/**35**/**36**. Astonishingly, all of them exerted a remarkable inhibition against *P. aeruginosa* (6.25–12.5 μg/mL) whereas decreased against rest of the strains.

All the synthesized oxime ethers were tested for their in vitro antifungal activity against *Candida albicans*, *Candida-51*, *Rhizopus* sp., *Aspergillus niger* and *Aspergillus flavus* using Amphotericin B as standard. The MIC values are summarized in Table 2.

When compared to **13**, its *N*-methyl analog **20** exhibited improvement against *C. albicans* and *Rhizopus* sp. at 50 μg/mL. Like **20**, the *para*-F compound **21** was better than non *N*-methyl analog **15** against all strains, whose best MIC was 12.5 μg/mL against *C. albicans*. The replacement of F by Cl in **15** and **21** provided **17** and **22**; both exerted improvements against all strains except **22**



Scheme 2. Reagents and conditions: (a) CH_3COONH_4, EtOH, warm; (b) $C_6H_5CH_2–O–NH_2·HCl$, $CH_3COONa·3H_2O$, $CHCl_3$/EtOH (1:1), reflux.

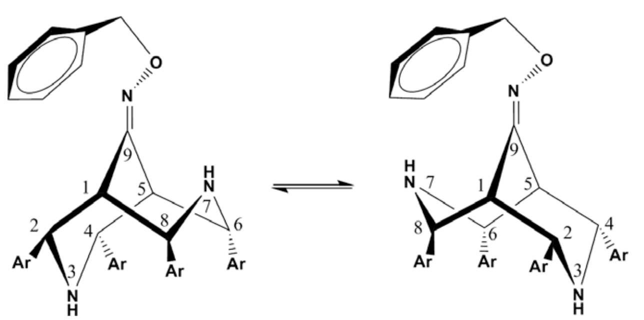


Figure 5. Dynamic chair–boat conformation of compounds **31–36** in $CDCl_3$ solution, according to one and two dimensional NMR data. The phenyl/substituted phenyl groups at C-2/C-4 and C-6/C-8 adopted the equatorial and axial orientations in chair and boat forms, respectively.

against *A. flavus* and *C. albicans*. In specific, **17** and **22** recoded their best MIC at 12.5 μg/mL against *Rhizopus* sp. and *Candida-51/Rhizopus* sp./*A. niger*, respectively. Of the compounds tested, **16** (*ortho*-Cl) was distinctively registered a remarkable inhibition against *Candida-51* at 6.25 μg/mL. The CH_3/OCH_3 substituents of **13** (i.e., **18/19**) and their *N*-methyl analogs (**23/24**) did not show inhibition profile as F/Cl compounds.

Other than *C. albicans* and *A. niger* (100 μg/mL), **31** required 200 μg/mL or more concentration to inhibit the visible growth of the tested fungal strains. Introduction of fluoro substituent on *meta*/*para* position of the above provided **32/33**. Of the two, **33** expressed better inhibition against all except *A. flavus*, which recorded the best MIC at 12.5 μg/mL against *C. albicans* and *Rhizopus* sp. The replacement of F by Cl (**34**) also registered best MIC at 12.5 μg/mL against *C. albicans* and *A. flavus* whereas required 25 μg/mL against *Rhizopus* sp. However, the activity was reduced by the replacement of F by CH_3 (**35**) and OCH_3 (**36**) substituents.

In summary, among the synthesized oxime ethers, **16**, **21**, **22**, **33** and **34** were potent against most of the tested pathogens. Also, **15**, **17** and **35** were moderately active. This preliminary structure–activity study reveals that compounds with electron withdrawing substituents at *ortho*/*para* position played a vital role in antimicrobial efficacy and was further enhanced by the introduction of a methyl group at ring nitrogen. Albeit the exact molecular mechanism of this SAR profile is unknown, presently, we consider that the aforementioned substituents may influence their mechanism of inhibition action. The present study provides new classes of

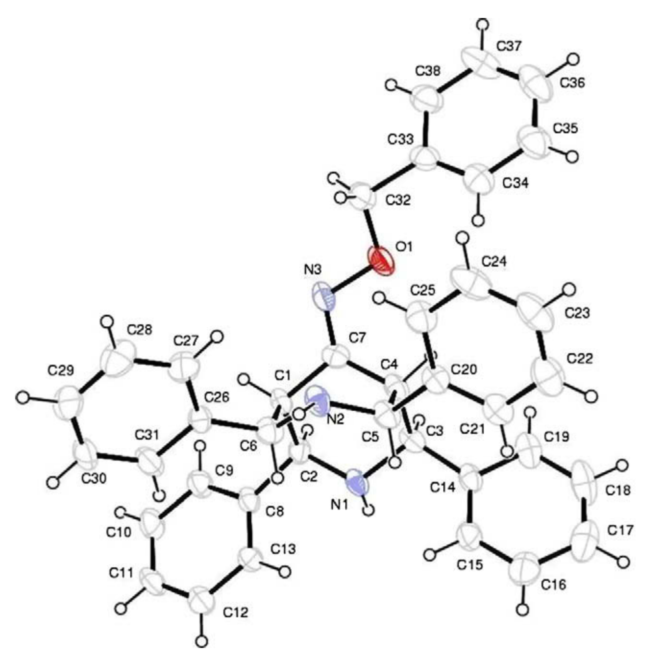


Figure 6. ORTEP of compound **31** with atoms represented as 30% probability ellipsoids; shows the existence of the molecule in chair–boat conformation with equatorial and axial orientations of the phenyl groups in chair and boat forms, respectively.

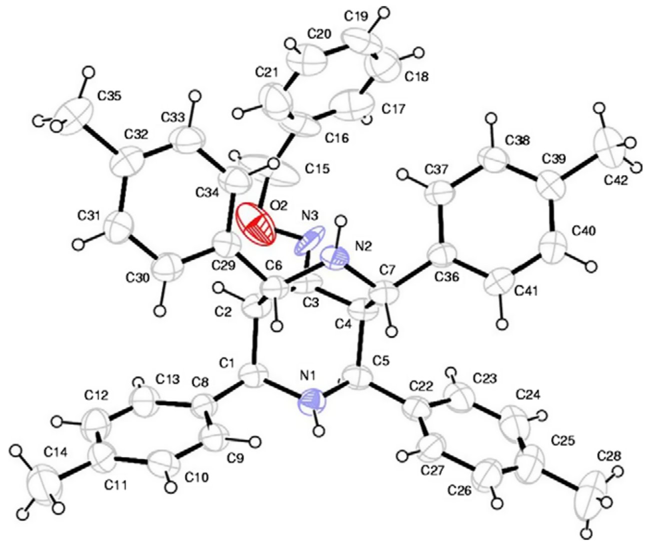


Figure 7. ORTEP of compound **35** with atoms represented as 30% probability ellipsoids. The bicycle exists in chair–boat conformation with equatorial and axial orientations of the *para*-methylphenyl groups in chair and boat forms, respectively.

Table 1
Antibacterial activity of compounds **13**–**24** and **31**–**36**

Compds	Minimum inhibitory concentration[a] (μg/mL)				
	P. aeruginosa	*S. aureus*	*S. typhi*	*E. coli*	*K. pneumoniae*
13	200	>200[b]	200	100	>200
14	25	100	100	25	100
15	25	100	50	25	50
16	6.25	12.5	50	12.5	50
17	12.5	25	25	50	100
18	25	25	100	100	200
19	50	100	50	50	100
20	100	200	100	100	200
21	12.5	50	25	12.5	25
22	12.5	12.5	25	50	50
23	25	25	50	100	100
24	25	50	50	25	100
31	100	200	100	100	>200
32	12.5	12.5	25	25	50
33	6.25	12.5	25	12.5	25
34	6.25	25	25	50	50
35	6.25	25	50	25	100
36	12.5	25	100	50	100
Std[c]	12.5	25	50	25	50

[a] MIC is the lowest concentration of an antimicrobial agent to significantly prevent the visible growth of a pathogen after a period of incubation; MIC values are represented in micrograms per milliliter (μg/mL).
[b] No activity up to 200 μg/mL.
[c] Ciprofloxacin.

oxime ethers with antibacterial and antifungal efficiency. They may be used as templates to construct better antimicrobial agents.

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Table 2
Antifungal activity of compounds **13**–**24** and **31**–**36**

Compds	Minimum inhibitory concentration (μg/mL)				
	C. albicans	*Candida-51*	*Rhizopus* sp.	*A. niger*	*A. flavus*
13	100	200	>200	>200	200
14	50	200	50	100	100
15	25	100	50	50	100
16	12.5	6.25	50	50	12.5
17	25	50	12.5	25	50
18	50	100	25	100	100
19	50	50	50	100	100
20	50	200	50	200	>200
21	12.5	25	25	25	50
22	25	12.5	12.5	12.5	100
23	50	50	50	100	25
24	25	50	50	25	100
31	100	>200	200	100	200
32	25	50	50	50	25
33	12.5	25	12.5	25	50
34	12.5	50	25	25	12.5
35	25	50	50	50	25
36	50	100	50	25	50
Std[a]	25	25	25	50	50

[a] Amphotericin B.

Supplementary data

Supplementary crystallographic data for **15** (CCDC No. 711365), **16** (CCDC No. 711364), **31** (CCDC No. 715424) and **35** (CCDC No. 715425) 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.2009.10.042.

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