



Synthesis, spectral, crystal and antimicrobial studies of biologically potent oxime ethers of nitrogen, oxygen and sulfur heterocycles

Paramasivam Parthiban^{a,b}, Gopalakrishnan Aridoss^{a,b}, Paramasivam Rathika^c, Venkatachalam Ramkumar^d,
Senthamarai Kannan Kabilan^{a,*}

^a Department of Chemistry, Annamalai University, Annamalai Nagar, Chidambaram 608 002, India

^b Division of Image Science and Information Engineering, Pukyong National University, Busan 608 739, Republic of Korea

^c Department of Microbiology, Annamalai University, Annamalai Nagar, Chidambaram 608 002, India

^d Department of Chemistry, Indian Institute of Technology-Madras, Chennai 600 036, India

ARTICLE INFO

Article history:

Received 5 March 2009

Revised 9 April 2009

Accepted 10 April 2009

Available online 18 April 2009

Keywords:

Heterocycles

Oxime ethers

Stereochemistry

Antibacterial activity

Antifungal activity

ABSTRACT

Three series of oxime ethers viz, 2,6-diarylpiperidin-4-one *O*-benzyloximes **5a–o**, 2,6-diaryltetrahydropyran-4-one *O*-benzyloximes **7a–e** and 2,6-diaryltetrahydrothiopyran-4-one *O*-benzyloximes **11a–b** and **12a–c** were synthesized and stereochemistry is established by their spectral and single crystal analysis. A SAR study has been carried out for the above oxime ethers against a panel of antibacterial (*Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Salmonella typhi* and *Escherichia coli*) and antifungal agents (*Candida albicans*, *Candida-51*, *Rhizopus* sp., *Aspergillus niger*, *Aspergillus flavus* and *Cryptococcus neoformans*), respectively, using Ciprofloxacin and Amphotericin B as standards. Most of the chloro/methyl/methoxy substituted compounds exerted moderate to good activity against all the tested organisms; moreover, some compounds (**5i**, **5l**, **5n**, **5o**, **7c2**, **7d1**, **7d2**, **7e**, **11b** and **12c**) exhibited promising activity than standard drugs.

© 2009 Elsevier Ltd. All rights reserved.

Though infections caused by microorganisms are common, it is very serious and often leads to death.¹ Up to 19% patients are infected from hospital visits throughout the world.² Most of the nosocomial infections are associated with urinary tract and cause a wide range of severe infections including pneumonia, bloodstream and surgical wounds and infections of immunocompromised patients such as AIDS, cancer and organ transplant recipients. Majority of the nosocomial pathogens are resistant to most of the antibiotics.³ Beside the antibacterial, there are many studies focused on antifungal research due to the need of new, safe and potent antifungal molecules. The use of available antifungal drugs, polyene macrolides, azoles, flucytosine and candins are not ideal in terms of efficacy, antifungal spectrum and safety; and the invasive candidiasis and aspergillosis has increased dramatically.⁴ Though Amphotericin B is efficacious against both candidiasis and aspergillosis, it shows severe renal toxicity.⁵ Hence, the urgent need of new molecules to combat bacterial and fungal infections is immense.

Widespread interest in the chemistry of piperidones, pyrans and thiopyrans in a large number of natural products has attracted due to their biological activities.⁶ Structure–activity relationship (SAR) studies from piperidone heterocycles indicated that nature

and position of substituents were considerably important factors to effect the biological actions.⁷

On the other hand, oxime ether function of various heterocycles is reported to possess microbiological properties. Particularly, *O*-benzyl oxime ether functionality (Fig. 1) shows very significant antimicrobial activities.⁸ With a view of above, we have incorporated bio-active *N*, *O* and *S* heterocycles with *O*-benzyl moiety to make biologically potent oxime ether pharmacophore C=N–O–Bn.

As illustrated in Scheme 1, the oxime ethers **5a–o** were synthesized. Conversion of ketone into oxime ether primarily depends upon the substitution on active methylene carbons and phenyl. The C-3, C-5 unsubstituted and C-3 substituted ketones yield the corresponding oxime ethers respectively within 6 and 7–25 h, depending on nature and size of the substituent. But ketones with methyl substitution at C-3 and C-5 take more than 30 h for the conversion. All 3,5-unsubstituted/3-substituted compounds adopt chair conformation as in Figure 2 (refer Supplementary data for further details).

Single crystal XRD study has been carried out for **5b** to confirm the stereochemistry established by NMR studies.⁹ Analysis of torsion angles, asymmetry parameters and least-squares plane calculation¹⁰ shows that the piperidine ring adopts a chair conformation with deviation of ring atoms N1 and C9 from C7/C8/C10/C11 plane by $-0.672(4)$ and $0.597(2)$ Å, respectively (Fig. 3). The smallest displacement parameters $q_2 = 0.068(2)$ and $q_3 = -0.566(2)$ Å, total

* Corresponding author.

E-mail address: prskabilan@rediffmail.com (S. Kabilan).

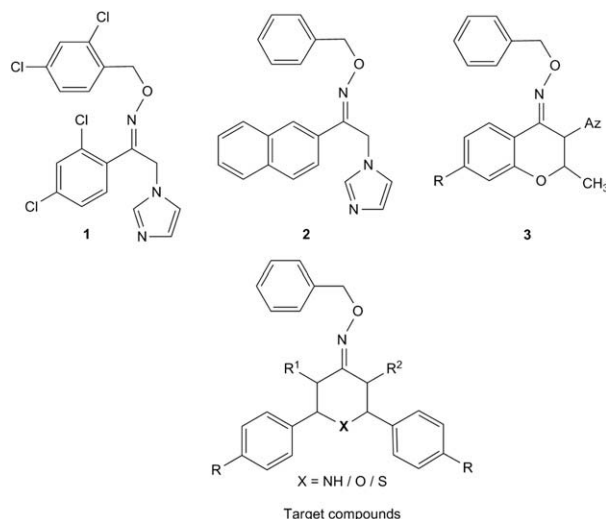
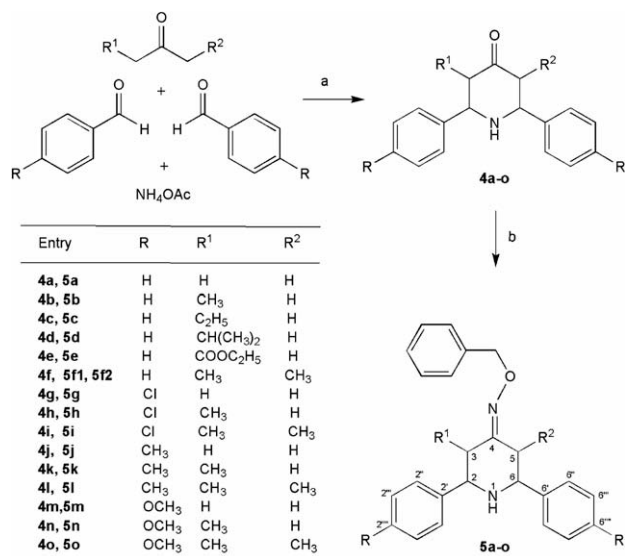


Figure 1. Structure of oxiconazole **1**, nafimidone oxime ether **2**, chromonone oxime ether **3** and target compounds.



Scheme 1. Reagents and conditions: (a) EtOH, warm; (b) C₆H₅CH₂-O-NH₂·HCl, CH₃COONa·3H₂O, MeOH, reflux.

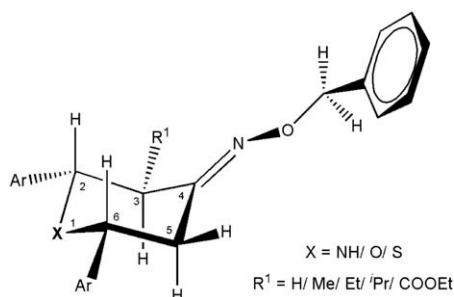


Figure 2. Chair conformation of compounds **5a–e**, **5g–h**, **5j–k**, **5m–n**, **7a–b** and **11a–b** with equatorial orientation of substituents at C-2, C-3 and C-6.

puckering amplitude, $Q_T = 0.570(2) \text{ \AA}$ and $\theta = 172.9(2)^\circ$. Dihedral angle between the two phenyl rings C1/C2/C3/C4/C5/C6 and C12/C13/C14/C15/C16/C17 is $56.56(4)^\circ$. Torsion angle of C6/C7/C8/C9 and C9/C10/C11/C12 are $174.27(4)$ and $178.27(4)^\circ$, respectively.

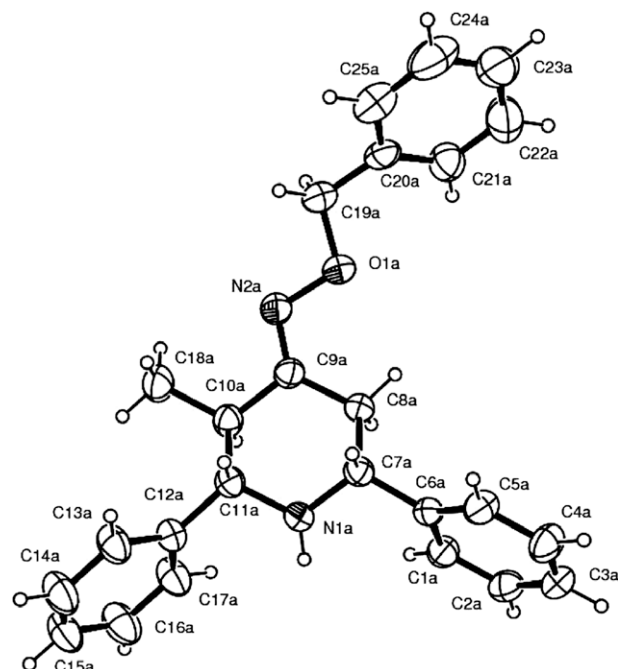


Figure 3. ORTEP of compound **5b** with atoms represented as 30% probability ellipsoids; exists in chair conformation with equatorial disposition of methyl and phenyl groups. The asymmetric unit of **5b** contains two crystallographically independent molecules; for clarity, one is eliminated.

While look at the chemical shifts and coupling constants, we can identify the variation in stereochemistry of 3,5-dimethyl substituted piperidone oxime ethers **5f**, **5i**, **5l** and **5o**. Among the four, **5f** gave two isomers **5f1** and **5f2**. Due to their close R_f values, the isomers could not be separated by TLC and hence are separated by HPLC^{11a} followed by their 1D (¹H–¹H COSY, NOESY) and 2D NMR (HSQC, HMBC) characterization. Since the chemical shifts and coupling constants of **5i**, **5l** and **5o** are similar to that of **5f2**, they should also adopt the same conformation as **5f2** (Fig. 4).

In the minor isomer **5f1**, doublets at 5.12 and 5.16 ppm are due to diastereotopic nature of methylene protons (–O–CH₂–Ph). The observed vicinal couplings $^3J_{2,3} = 5.3$ and $^3J_{5,6} = 9.0$ Hz are drastically deviated from its parent ketone ($^3J_{2a,3a} = ^3J_{5a,6a} = 10.3$ Hz), which exists in chair conformation with equatorial orientation of all substituents. Hence, the observed coupling constants $^3J_{2,3}$ and $^3J_{5,6}$ suggest that **5f1** is not in chair form. If it adopts a normal chair conformation with equatorial orientation of all substituents, the observed coupling constants $^3J_{2a,3a}$ and $^3J_{5a,6a}$ should be around 10.5 Hz. Moreover, the coupling constants are not favorable for boat conformation also. If it exists in a rigid boat form, the vicinal

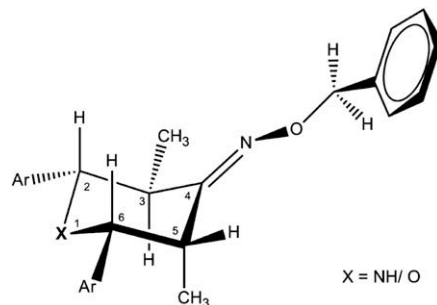


Figure 4. Chair conformation of compounds **5f2**, **5i**, **5l**, **5o** and **7c2–d2**. The phenyl at C-2, C-6 and methyl at C-3 adopt equatorial orientation while methyl at C-5 occupies axial position to avoid A^{1,3} interaction.

coupling constants should be about 4 Hz. Hence, the abnormal vicinal coupling constants indicate that piperidone ring adopts neither chair nor boat conformation and hence we suggest a twist boat conformation (Fig. 5). As well, carbon chemical shifts also support the existence of **5f1** in twist boat conformation.¹²

The synthetic method of 2,6-diaryltetrahydropyran-4-one *O*-benzyloximes is depicted in Scheme 2. With respect to substituent on *para* position of the phenyl at C-2 and C-6, **6c–e** required about 25–30 h reflux for the conversion to oxime ethers. However, the ketone without substitution on phenyl did not undergo oximation even at higher mole ratio of *O*-benzylhydroxylamine hydrochloride up to 120 h; and cannot lead to the desired product by other bases viz, pyridine or amberlyst A-21¹³ instead of sodium acetate.

The proton and carbon chemical shifts of **7a** and **7b** are assigned similar to that of piperidone analogs **5b** and **5c**. Due to the increase in electronegativity of oxygen than nitrogen, the benzylic protons (H-2, H-6) and carbons (C-2, C-6) are deshielded about 0.7–0.8 and 17–18 ppm, respectively. On the basis of observed coupling constants, chair conformation (Fig. 2) is suggested for both **7a** and **7b**; the conformation of the methyl and ethyl groups also same as in **5b** and **5c** (refer Supplementary data). Among the 3,5-dimethyl compounds **7c–e**, **7e** gave single isomer while **7c** and **7d** gave two isomers; of the two, **7d** separated as **7d1** and **7d2** by TLC whereas **7c** separated by HPLC.^{11b} Chemical shift pattern and coupling constants of **7c1**, **7d1** and **7e** suggest that these compounds adopt twist boat conformation like **5f1** whereas **7c2** and **7d2** adopt chair conformation with the stereochemistry as in Figure 4.

The synthesis of cis and trans-isomers of 2,6-diaryltetrahydrothiopyran-4-one *O*-benzyloximes **11a–b** and **12a–c** are shown in Scheme 3. The proton and carbon chemical shifts of the cis-isomers **11a–b** were assigned similar to that of corresponding piperidone oxime ethers; thereby adopt the similar conformation of corre-

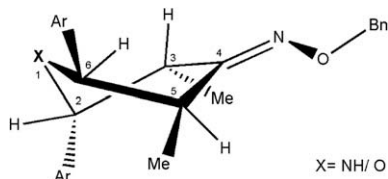
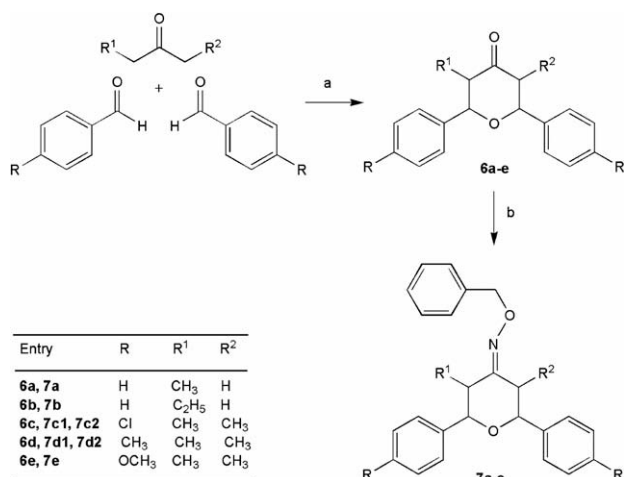
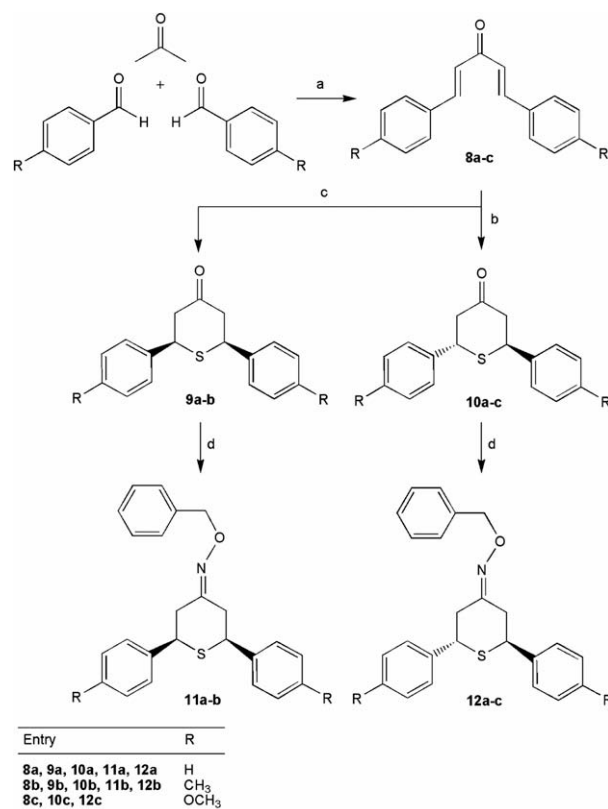


Figure 5. Twist boat conformation for compounds **5f1**, **7c1**, **7d1** and **7e**.



Scheme 2. Reagents and conditions: (a) KOH, aqueous EtOH, vigorous stirring; (b) C₆H₅CH₂-O-NH₂·HCl, CH₃COONa·3H₂O, MeOH, reflux.



Scheme 3. Reagents and conditions: (a) EtOH, 10% NaOH, cold condition, stirring; (b) fast stream of H₂S gas, excess of CH₃COONa, EtOH, reflux, 30 min.; (c) slow stream of H₂S gas, CH₃COONa, EtOH, reflux, 6 h; (d) C₆H₅CH₂-O-NH₂·HCl, CH₃COONa·3H₂O, MeOH, reflux, 5 h.

sponding piperidone oxime ethers as in Figure 2. However the trans-isomers **12a–c**, differ drastically in their coupling constants, which indicates that these compounds are not in twist boat form instead exist in a small contribution of boat form along with the predominant chair form. Moreover, there are two possibilities in chair conformation according to NMR data; one with *axial* orientation of the phenyl *syn* to oximino group another is *anti* to oximino group. Of the two, *syn* axial phenyl should be populated largely (Fig. 6) since in *anti* axial phenyl, steric interactions experienced by the *ortho* protons of phenyl with axial proton at C-3, destabilize that conformation.

The crystal analysis shows that thiopyran ring adopts a distorted chair conformation with deviation of ring atoms S1 and C3 from C1/C2/C4/C5 plane by −0.953 and 0.575 Å, respectively (Fig. 7). The ring puckering parameters q_2 and $q_3 = 0.1697(17)$ and $0.6279(18)$ Å; $Q_T = 0.6505(2)$ Å and $\theta = 15.14(15)^\circ$. Dihedral angle between the two phenyl rings C6/C7/C8/C9/C10/C11 and

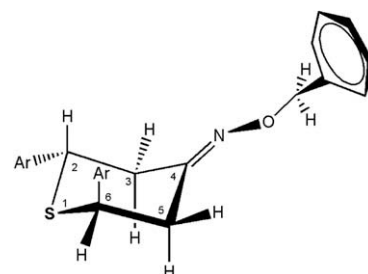


Figure 6. Predominant chair conformation of compounds **12a–c** with equatorial and axial orientations of aryl groups, respectively, at C-2 and C-6, in solution.

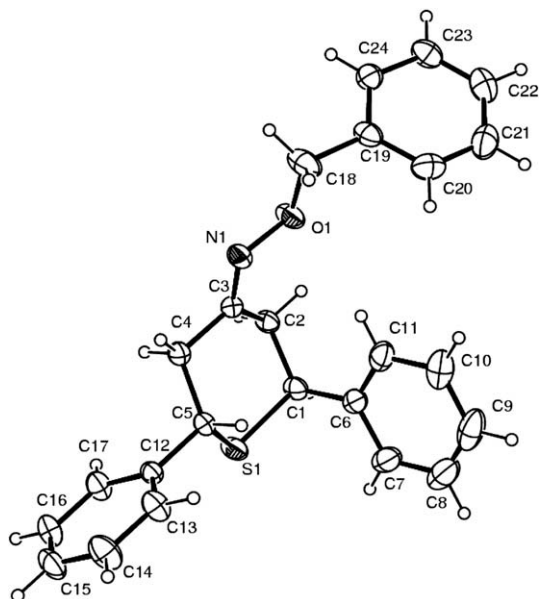


Figure 7. ORTEP of compound **12a** with atoms represented as 30% probability ellipsoids. The molecule exists in chair conformation with axial and equatorial dispositions of phenyl groups, respectively *syn* and *anti* to oximino group.

C12/C13/C14/C15/C16/C17 is 73.01(4)°. Torsion angle of C3/C2/C1/C6 and C3/C4/C5/C12 are −73.13(4)° and 177.51(4)°, respectively.

All the synthesized compounds were screened for their *in vitro* antimicrobial activity against pathogenic bacteria and fungi by twofold serial dilution method.¹⁴ A prudent perusal of the MICs

of synthesized compounds against the bacterial strains viz, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Salmonella typhi* and *Escherichia coli* with comparison of MICs of Ciprofloxacin in Table 1 provides an understandable structure–activity relationship. In all N, O and S heterocycles, irrespective of the nature of hetero atom, the compounds with substitution neither on active methylene centers C-3/C-5 nor phenyl at C-2/C-6 show poor or negligible activity. And the substitution of Me/Et/ⁱPr/COOEt at C-3 also does not show any significant enhancement in their antibacterial activity. However, activity increased with incorporation of alkyl substituent at C-3 along with the substitution of Cl/Me/OMe at C-2''' and C-6''' of compounds **5g**, **5j** and **5m**. Further, inhibition potency increased with the introduction of methyl substituent on both active methylene carbons C-3 and C-5 of **5g**, **5j** and **5m**.

Among the three sets of compounds **5g**, **5j**, **5m** (no Me at C-3 and C-5), **5h**, **5k**, **5n** (Me at C-3) and **5i**, **5l**, **5o** (Me at C-3 and C-5) with substituted phenyl at C-2 and C-6, the introduction of Me group at C-3 and C-5 shows constant increase in inhibition efficiency of oxime ethers **5i**, **5l** and **5o** than **5h**, **5k**, **5n** and **5g**, **5j**, **5m**. Noticeably, compounds **5i** and **5l** are eightfold potent than **5h** and **5k** against *S. aureus* and *E. coli*, respectively. As well, **5i** is fourfold potent than **5h** against *P. aeruginosa* and *E. coli*. Distinctly **5i**, which possess the electron withdrawing chloro substituent at C-2''' and C-6''' along with methyl at C-3 and C-5 is better than other similar compounds **5l** and **5o**, respectively having methyl and methoxy substituents, instead of chlorine. Compound **5i** is twofold potent against *S. aureus*, *S. typhi* and *E. coli* and fourfold stronger against *P. aeruginosa* than Ciprofloxacin to inhibit the visible growth of organisms. Like **5i**, compound **5l** also respectively two and four times potent than standard, against *E. coli* and *P. aeruginosa* while register a twofold less inhibition potency against *S. aureus*.

In the pyran series also, compounds **7a** and **7b** with unsubstituted phenyl at C-2 and C-6 show poor activity; but, the oxygen heteroatom in place of NH shows an increase in activity for compounds **7a** and **7b** than corresponding nitrogen analogs **5b** and **5c**. Among the pyran oxime ethers **7a–e**, compounds with methyl substituents at C-2''' and C-6''' in addition to C-3 and C-5 (**7d1**, **7d2**) are better than chloro or methoxy compounds **7c1** and **7e**. Of the two isomers in each compound **7c** and **7d**, the isomers **7c1** and **7d1** with twist boat conformation show better activity than isomers **7c2** and **7d2** with chair conformation. The oxime ether **7d1** shows MICs 12.5–25 µg/mL against all the tested pathogens; twice over potent than standard against *S. aureus* and *S. typhi*.

In thiopyran oxime ethers **11a–12c**, the antibacterial activity against all the tested organisms is not better than corresponding piperidone analog except *para*-Me compounds. The sulfur analog of **5j**, that is, compounds **11b** and **12b** show good activity than **5j**. Particularly, the *cis*-isomer **11b** is far better than *trans*-isomer **12b**; its inhibition potency against *S. aureus* and *S. typhi* is twofold higher than Ciprofloxacin.

Table 2 explains SAR study of synthesized compounds against a panel of fungal strain viz, *Candida albicans*, *Candida-51*, *Rhizopus* sp., *Aspergillus niger*, *Aspergillus flavus* and *Cryptococcus neoformans*. The unsubstituted piperidone oxime ether does not show activity against most of the strains, whose activity against *C. albicans*, *Candida-51* and *A. flavus* lies in the range of 200 µg/mL. Moreover, the introduction of Me/Et/ⁱPr/COOEt at C-3 and Me at C-3, C-5 of **5a** also have no improvement in their antifungal potency, except against a few organisms. Compounds **5c** against *Rhizopus* sp. and *A. niger*, **5d** against *Rhizopus* sp. and *C. albicans*, **5e** and **5f2**, respectively, against *C. albicans* and *Rhizopus* sp. and **5f1** against *C. albicans* and *Candida-51* show the MIC at the level of 50 µg/mL. The incorporation of Cl/Me/OMe substituents at C-2''' and C-6''' of **5a** (i.e., compounds **5g**, **5j** and **5m**) shows the improvement in their inhibition potency; **5g** against *C. albicans* and *A. niger* and **5m**

Table 1
Antibacterial activity of compounds **5a–o**, **7a–e** and **11a–12c**

Compds	Minimum inhibitory concentration ^a (µg/mL)			
	<i>P. aeruginosa</i>	<i>S. aureus</i>	<i>S. typhi</i>	<i>E. coli</i>
5a	200	>200 ^b	100	>200
5b	200	200	100	200
5c	100	25	50	100
5d	200	>200	100	100
5e	50	200	200	100
5f1	50	200	100	50
5f2	200	100	100	100
5g	50	50	100	50
5h	25	50	50	50
5i	6.25	6.25	25	12.5
5j	50	200	100	200
5k	50	50	100	100
5l	25	6.25	50	12.5
5m	50	50	50	100
5n	50	25	25	50
5o	50	25	25	25
7a	100	100	200	100
7b	100	200	100	50
7c1	25	50	50	50
7c2	50	50	100	50
7d1	12.5	12.5	25	25
7d2	25	25	50	50
7e	25	50	50	25
11a	200	>200	100	200
11b	25	12.5	25	50
12a	>200	>200	200	200
12b	100	100	100	50
12c	25	50	50	50
Ciprofloxacin	12.5	25	50	25

^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.

Table 2
Antifungal activity of compounds **5a–o**, **7a–e** and **11a–12c**

Compds	Minimum inhibitory concentration (μg/mL)					
	<i>C. albicans</i>	<i>Candida-51</i>	<i>Rhizopus sp.</i>	<i>A. niger</i>	<i>A. flavus</i>	<i>C. neoformans</i>
5a	200	200	>200	>200	200	>200
5b	100	200	200	200	100	>200
5c	100	100	50	50	>200	200
5d	50	200	50	200	200	100
5e	50	100	200	200	100	100
5f1	50	50	100	100	200	100
5f2	100	100	50	100	>200	200
5g	50	200	>200	50	200	100
5h	25	50	100	50	50	50
5i	25	25	50	25	25	25
5j	200	100	100	200	100	200
5k	50	50	25	100	100	100
5l	50	6.25	12.5	50	25	50
5m	100	50	50	100	100	100
5n	25	12.5	25	50	50	25
5o	12.5	6.25	25	25	100	12.5
7a	100	100	200	200	200	100
7b	100	100	100	200	100	50
7c1	50	50	50	100	50	25
7c2	12.5	25	25	50	25	12.5
7d1	25	50	50	50	50	50
7d2	6.25	6.25	25	50	25	25
7e	50	12.5	25	50	100	6.25
11a	>200	200	200	100	>200	>200
11b	100	100	50	50	100	200
12a	200	>200	>200	200	100	200
12b	50	200	50	100	100	50
12c	25	25	50	25	25	12.5
Std ^a	25	25	25	50	50	25

^a Amphotericin B.

against *Candida-51* and *Rhizopus sp.* inhibit the visible growth of fungi at 50 μg/mL. Compounds **5g**, **5j** and **5m** show better MICs while incorporating methyl at C-3 (compounds **5h**, **5k** and **5n**) and C-5 (compounds **5i**, **5l** and **5o**). Among those, **5l** and **5o** are doubly potent than Amphotericin B against *Rhizopus sp.*, *A. flavus* and *C. albicans*, *A. niger*, *C. neoformans*, respectively; in specific, both register their best MIC at 6.25 μg/mL against *Candida-51*.

Pyran analogs **5b** and **5c**, that is, compounds **7a** and **7b** show activity in the range of 50–200 μg/mL. The *para* substitution along with methyl at C-3 and C-5 show better activity than corresponding piperidone analog in the range of 25–50 μg/mL for most of the tested pathogens. In specific, the Me substitution at C-2''' and C-6''' show better MICs than others; of the two isomers **7d1** and **7d2**, the isomer with chair conformation **7d2** is potent than **7d1**. Compounds **7d2** and **7e** show remarkable MIC at 6.25 μg/mL against *C. albicans*, *Candida-51* and *C. neoformans*, respectively.

Both stereomers **11a** and **12a** have no activity against most of the tested pathogenic fungi whereas the introduction of methyl group at C-2''' and C-6''' of **11a** and **12a** show better activity against all the strains. Of the two, trans-isomer **12b** is more potent than **11b**. Among the synthesized thiopyran oxime ethers **11a–12c**, the trans-isomer **12c** shows more potency against all the tested fungal strains, whose MICs fall in the range of 12.5–50 μg/mL. When compare to the cis-isomer of the piperidone analog **5m**, the MICs of the trans-isomer **12c** are considerably better; especially **12c** register its best MIC at 12.5 μg/mL against *C. neoformans*, which is respectively two- and eightfold better than standard and **5m**.

In overall, the hetero atom of synthesized compounds paved by chloro/methyl/methoxy-phenyl on either side along with alkyl

groups at C-3 and/or C-5 positions play a significant role in eliciting good antimicrobial properties. Hence, these classes of oxime ethers can be used as sketch to conquer both bacterial and fungal infections.

Acknowledgments

The authors would like to acknowledge NMR research center, IISc-Bangalore and Department of Chemistry, IIT-Madras, respectively, for recording NMR and single crystal XRD. We extend our thanks to RMMCH, Annamalai University for the antimicrobial studies.

Supplementary data

Complete experimental details, analytical, IR, mass and NMR data of all compounds. Conformation of alkyl group at C-3 of **5b–d**, **5h**, **5k**, **5n** and **7a–b**. Crystal data for **5b** and **12a**. Supplementary crystallographic data for **5b** (CCDC No. 717888) and **12a** (CCDC No. 717889) 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.2009.04.038](https://doi.org/10.1016/j.bmcl.2009.04.038).

References and notes

- Potera, C. *Science* **1999**, *46*, 4830.
- (a) Facts sheet-Swiss Hand Hygiene Campaign, **2007**. <http://www.swiss-noso.ch/>; (b) Gastmeier, P.; Sohr, D.; Geffers, C.; Behnke, M.; Rüden, H. *Infect. Control Hosp. Epidemiol.* **2007**, *28*, 466; (c) http://www.wrongdiagnosis.com/n/nosocomial_infections/stats-country.
- (a) Talbot, G. H.; Bradley, J.; Edwards, J. E.; Gilbert, D.; Scheld, M.; Bartlett, J. G. *Clin. Infect. Dis.* **2006**, *42*, 657; (b) Gastmeier, P.; Sohr, D.; Geffers, C.; Behnke, M.; Daschner, F.; Rüden, H. *Infection* **2005**, *33*, 148.
- (a) Fridkin, S. K.; Jarvis, W. R. *Clin. Microbiol. Rev.* **1996**, *9*, 499; (b) Marr, K. A. *Oncology* **2004**, *18*, 9; (c) Akins, R. A. *Med. Mycol.* **2005**, *42*, 285.
- Masubuchi, M.; Ebiike, H.; Kawasaki, K.; Sogabe, S.; Morikami, K.; Shiratori, Y.; Tsujii, S.; Fujii, T.; Sakata, K.; Hayase, M.; Shindoh, H.; Aoki, Y.; Ohtsuka, T.; Shimma, N. *Bioorg. Med. Chem.* **2003**, *11*, 4463.
- (a) Baliah, V.; Jeyaraman, R.; Chandrasekaran, L. *Chem. Rev.* **1983**, *83*, 379; (b) Aridoss, G.; Parthiban, P.; Ramachandran, R.; Prakash, M.; Kabilan, S.; Jeong, Y. T. *Eur. J. Med. Chem.* **2009**, *44*, 577; (c) Aridoss, G.; Amirthaganesan, S.; Kumar, N. A.; Kim, J. T.; Lim, K. T.; Kabilan, S.; Jeong, Y. T. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6542; (d) Aridoss, G.; Balasubramanian, S.; Parthiban, P.; Kabilan, S. *Eur. J. Med. Chem.* **2007**, *42*, 851; (e) Dell, L. P. *Curr. Med. Chem.* **1998**, *5*, 179; (f) Singh, V. et al *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4209.
- (a) Prostavkov, N. S.; Gaivoronskaya, L. A. *Chem. Rev.* **1978**, *47*, 447; (b) Lijinsky, W.; Taylor, H. W. *Int. J. Cancer* **1975**, *16*, 318.
- (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) Mixich, G.; Thiele, K. *Arzneim.-Forsch./Drug Res.* **1979**, *29*, 1510; (e) Polak, A. *Arzneim.-Forsch./Drug Res.* **1982**, *32*, 17; (f) Rossello, A.; Bertini, S.; Lapucci, A.; Macchia, M.; Martinelli, A.; Rapposelli, S.; Herreros, E.; Macchia, B. J. *Med. Chem.* **2002**, *45*, 4903; (g) Emami, S.; Falahati, M.; Banifatemi, A.; Amanlou, M.; Shafiee, A. *Bioorg. Med. Chem.* **2004**, *12*, 3971; (h) Karakurt, A.; Dalkara, S.; Ozalp, M.; Ozbey, S.; Kendy, E.; Stables, J. P. *Eur. J. Med. Chem.* **2001**, *36*, 421.
- Parthiban, P.; Balasubramanian, S.; Aridoss, G.; Kabilan, S. *Spectrochim. Acta Part A* **2008**, *70*, 11.
- Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354.
- (a) Semi-preparative HPLC, solvent system (mobile phase): MeOH–water mixture, 9:1, flow rate: 5.0 mL/min, column (stationary phase): symmetry ODS column[®], condition: isocratic, instrument: Waters 486 Tunable absorbance detector, solution: 50 mg/mL; (b) solvent system: acetonitrile–water mixture, 1:1, flow rate: 3.5 mL/min.
- Geneste, P.; Durand, R.; Kamenka, J. M.; Beierbeck, H.; Martino, R.; Saunders, J. K. *Can. J. Chem.* **1978**, *56*, 1940.
- (a) Parthiban, P.; Ramachandran, R.; Aridoss, G.; Kabilan, S. *Magn. Reson. Chem.* **2008**, *46*, 780; (b) Ballini, R.; Barboni, L.; Filippone, P. *Chem. Lett.* **1997**, *5*, 475.
- Dhar, M. L.; Dhar, M. M.; Dhawan, B. N.; Mehrotra, B. N.; Ray, C. *Indian J. Expt. Biol.* **1968**, *6*, 232.