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# Synthesis, spectral analysis and in vitro microbiological evaluation of 3-(3-alkyl-2,6-diarylpiperin-4-ylidene)-2-thioxoimidazolidin-4-ones as a new class of antibacterial and antifungal agents

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ABSTRACT

In the present work, a new series of bis hybrid heterocycle comprising both piperidine and thiohydantoin nuclei together namely 3-(3-alkyl-2,6-diarylpiperin-4-ylidene)-2-thioxoimidazolidin-4-ones **46–60** was synthesized by the treatment of the respective thiosemicarbazones **31–45** with chloroethyl acetate and anhydrous sodium acetate in refluxing ethanol for 4 h and were characterized by melting point, elemental analysis, MS, FT-IR, one-dimensional NMR ($^1$H, $D_2O$ exchanged $^1$H and $^{13}$C), two dimensional HOMOCOSY and NOESY spectroscopic data. In addition, the title compounds were screened for their antimicrobial activities against a spectrum of clinically isolated microbial organisms. Compounds **47–50**, **52–55** and **57–60** with fluoro, chloro, methoxy or methyl functions at the *para* position of phenyl rings attached to C-2 and C-6 carbons of piperidine moiety along with and without methyl substituent at position C-3 of the piperidine ring exerted potent biological activities against*Staphylococcus aureus, β-Hemolytic streptococcus, Vibrio cholerae, Escherichia coli, Pseudomonas aeruginosa, Aspergillus flavus, Candida albicans, Candida 6* and *Candida 51* at a minimum inhibitory concentration.



Small heterocyclic compounds act as highly functionalized scaffolds and were known pharmacophores of a number of biologically active and useful molecules. Baliah et al., have reviewed the importance of piperidin-4-ones as intermediates in the synthesis of several physiologically active compounds.[1,2] Similarly, Lijinsky and Taylor[3] have found that the presence of substituents at both the α-positions to that of N in piperidin-4-one is important to exert marked biological properties. Bioactive heterocyclic ring systems having 2,6-diaryl-piperidine-4-one nucleus with different substituents at 3- and 5-positions of the ring have aroused great interest due to their wide variety of biological properties such as antiviral, antitumour,[4,5] central nervous system,[6] local anesthetic,[7] anticancer,[8] antimicrobial activity[9] and their derivative piperidine are also biologically important and act as neurokinin receptor antagonists,[10] analgesic and anti-hypertensive agents.[11]

Thiohydantoins are sulfur analogs of hydantoins with one or both carbonyl groups replaced by thiocarbonyl groups.[12] Among the known thiohydantoins, 2-thiohydantoins were most notably known due of their wide applications as hypolipidemic,[13] anticarcinogenic,[14] antimutagenic,[15] antithyroidal[16] antiviral (e.g., against herpes simplex virus, HSV),[17] human immunodeficiency virus (HIV)[18] and tuberculosis[19]), antimicrobial (antifungal and antibacterial),[20] anti-ulcer and anti-inflammatory agents,[21] as well as pesticides.[22] Additionally, 2-thiohydantoins have been used as reference standards for the development of C-terminal protein sequencing,[23] as reagents for the development of dyes[24] and in textile printing, metal cation complexation and polymerization catalysis.[25]

In connection with our earlier work on the synthesis of structurally diverse biologically active hybrid heterocyclic ring systems and as part of our ongoing research programme,[26] we planned to design a system, which combines both bioactive piperidine and thiohydantoin components together to give a new series of bis hybrid heterocycles comprising both piperidine and thiohydantoin nuclei. In the present work, a new series of bis heterocycles comprising both piperidine and thiohydantoin nuclei together namely 3-(3-alkyl-2,6-diarylpiperin-4-ylidene)-2-thioxoimidazolidin-4-ones **46–60** was synthesized by the treatment of the respective thiosemicarbazones **31–45** with chloroethyl acetate and anhydrous sodium acetate in refluxing ethanol for 4 h . The synthetic route for the formation of compounds **46–60** was given in Scheme 1. The physical data was given in Table 1. A reaction mechanism was proposed and given in Scheme 2. The structures of all the synthesized compounds **46–60** are discussed with the help of mp's, elemental analysis, FT-IR, MS, one-dimensional Proton and Carbon NMR, $D_2O$ exchanged $^1$H NMR, $^{13}$C NMR, HOMOCOSY and NOESY spectra.[27]

In order to find the effect of potency of inhibitions in the title compounds 3-(3-alkyl-2,6-diarylpiperin-4-ylidene)-2-thioxoimi-

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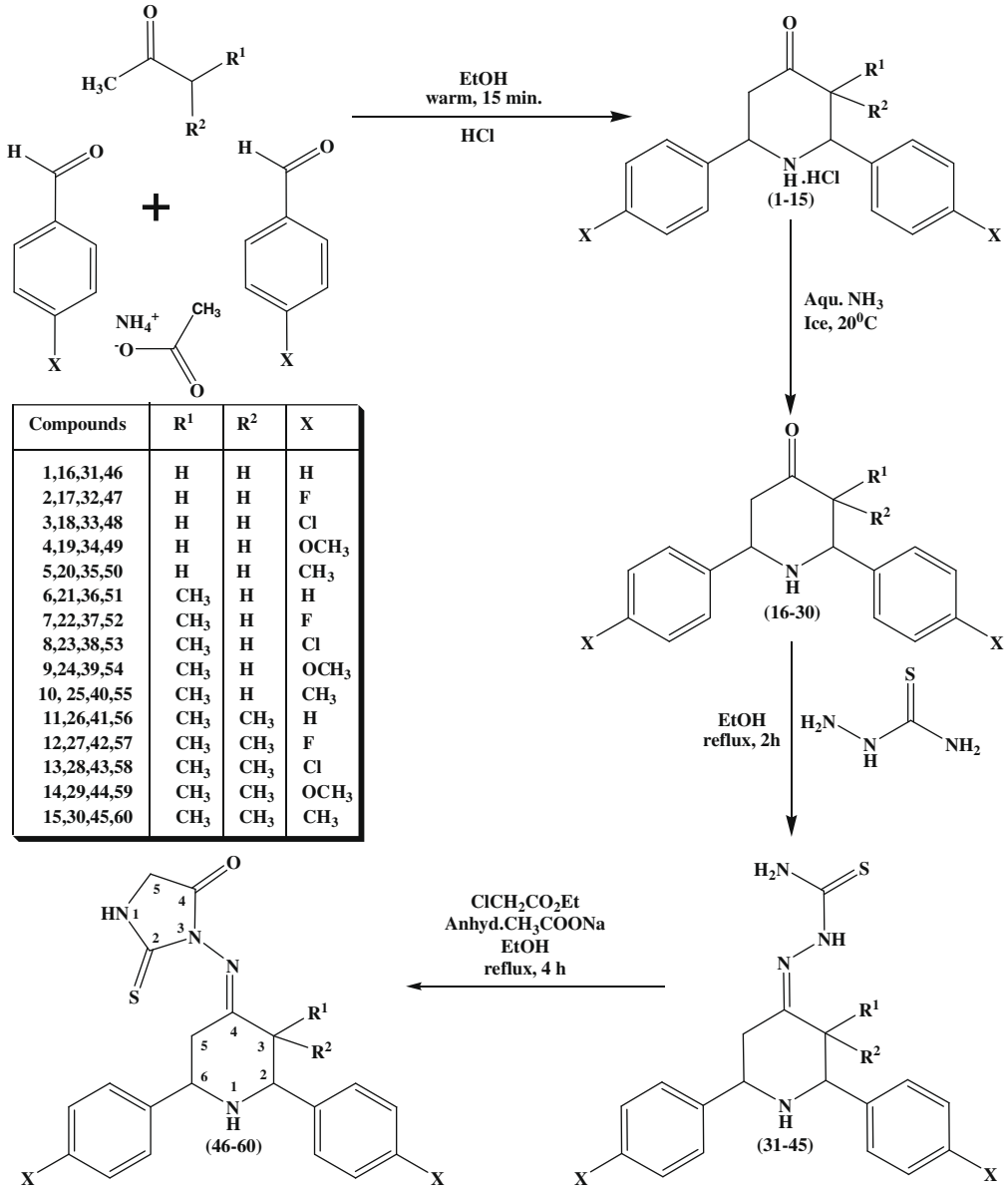


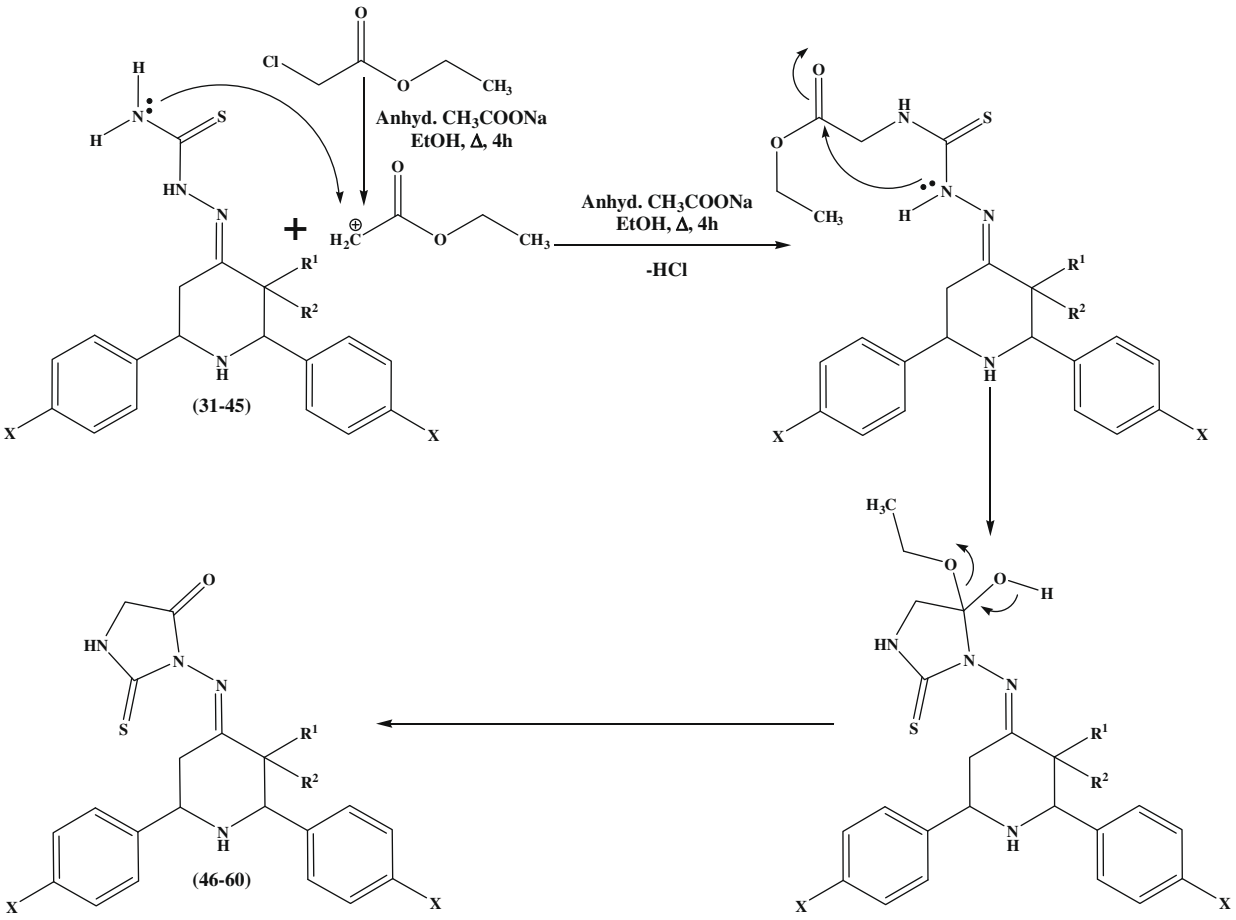

| Compounds | $R^1$ | $R^2$ | X |
|---|---|---|---|
| 1,16,31,46 | H | H | H |
| 2,17,32,47 | H | H | F |
| 3,18,33,48 | H | H | Cl |
| 4,19,34,49 | H | H | $OCH_3$ |
| 5,20,35,50 | H | H | $CH_3$ |
| 6,21,36,51 | $CH_3$ | H | H |
| 7,22,37,52 | $CH_3$ | H | F |
| 8,23,38,53 | $CH_3$ | H | Cl |
| 9,24,39,54 | $CH_3$ | H | $OCH_3$ |
| 10, 25,40,55 | $CH_3$ | H | $CH_3$ |
| 11,26,41,56 | $CH_3$ | $CH_3$ | H |
| 12,27,42,57 | $CH_3$ | $CH_3$ | F |
| 13,28,43,58 | $CH_3$ | $CH_3$ | Cl |
| 14,29,44,59 | $CH_3$ | $CH_3$ | $OCH_3$ |
| 15,30,45,60 | $CH_3$ | $CH_3$ | $CH_3$ |

**Scheme 1.** Synthetic route for the formation of 3-(3-substituted-2,6-diaryl-piperidin-4-ylideneamino)-2-thioxoimidazolidin-4-ones.

**Table 1**
Physical data for the title compounds **46–60**

| Compounds | $R^1$ | $R^2$ | X | Yield (%) | Mp (°C) |
|---|---|---|---|---|---|
| **46** | H | H | H | 74 | 108 |
| **47** | H | H | F | 78 | 103 |
| **48** | H | H | Cl | 67 | 167 |
| **49** | H | H | $OCH_3$ | 72 | 158 |
| **50** | H | H | $CH_3$ | 70 | 142 |
| **51** | $CH_3$ | H | H | 75 | 171 |
| **52** | $CH_3$ | H | F | 78 | 182 |
| **53** | $CH_3$ | H | Cl | 75 | 187 |
| **54** | $CH_3$ | H | $OCH_3$ | 72 | 182 |
| **55** | $CH_3$ | H | $CH_3$ | 70 | 136 |
| **56** | $CH_3$ | $CH_3$ | H | 76 | 148 |
| **57** | $CH_3$ | $CH_3$ | F | 77 | 134 |
| **58** | $CH_3$ | $CH_3$ | Cl | 75 | 176 |
| **59** | $CH_3$ | $CH_3$ | $OCH_3$ | 72 | 132 |
| **60** | $CH_3$ | $CH_3$ | $CH_3$ | 71 | 124 |

dazolidin-4-ones **46–60** by in vitro method, we modified different substituents at the phenyl rings in 3-(3-alkyl-2,6-diarylpiperin-4-ylidene)-2-thioxoimidazolidin-4-ones. Compounds, **46–60** were assessed to elicit their antibacterial activity in vitro against *Staphylococcus aureus, β-Hemolytic streptococcus, Vibrio cholerae*, *Escherichia coli,* and *Pseudomonas aeruginosa*. The antibacterial potency of the synthesized compounds was compared with broad spectrum antibiotic namely Ciprofloxacin and their minimum inhibitory concentration (MIC) values were summarized in Table 2. A close survey of the MIC values indicate that all the compounds exhibited a varied range (6.25–200 μg/mL) of antibacterial activity against all the tested bacterial strains except **50** and **59** which did not show activity against *S. aureus* and *E. coli* even at a maximum concentration of 200 μg/mL. The compounds without any substituents at the *para* position of the phenyl groups at the C-2 and C-6 positions of the piperidine ring (**46**, **51** and **56**) showed antibacterial activity in the range of 25–200 μg/mL. Compounds **47** and **48**, which were having electron withdrawing fluoro and chloro substitutions, respectively, at the *para* position of phenyl rings attached to C-2 and C-6 carbons of piperidine moiety shows fourfold increased activity against β-*H. streptococcus* and *P. aeruginosa* at a MIC value of 6.25 μg/mL and shows twofold increased activity




**Scheme 2.** Proposed reaction mechanism for the formation of target molecules **46**–**60**.

against *V. cholerae and E. coli* at a MIC value of 12.5 μg/mL. Electron withdrawing substituents like fluoro and chloro substituted 2,6-diarylpiperidone derivatives exerted excellent antibacterial and antifungal activities.[26c,d] Fluorination increases the lipophilicity due to strong electron withdrawing capability of fluorine.[28] Moreover, fluorine substitution was commonly used in contemporary medicinal chemistry to improve metabolic stability, bioavailability and protein ligand interactions.[29] Compounds **49** and **50**, which were having electron donating methoxy and methyl substitutions, respectively, at the *para* position of phenyl rings attached to C-2 and C-6 carbons of piperidine moiety shows moderate antibacterial activity against all the tested bacterial strains in the range of 100–25 μg/mL. Introduction of mono methyl or dimethyl groups at C-3 of the piperidine ring in compounds **52** and **57**, which also having electron withdrawing fluoro substitution at the *para* position of phenyl rings attached to C-2 and C-6 carbons of piperidine moiety exerted excellent activity with a MIC value of 6.25–12.5 μg/mL against all the tested bacterial strains. Compound **53**, which have electron donating methyl group at C-3 of the piperidine ring and having electron withdrawing fluoro substitution at the *para* position of phenyl rings attached to C-2 and C-6 carbons of piperidine moiety shows good antibacterial activity against *S. aureus* and *V. cholerae* at a MIC of 6.25 and 12.5 μg/mL, respectively. Compound **58**, which have electron donating dimethyl groups at C-3 of the piperidine ring and also have electron withdrawing chloro substitution at the *para* position of phenyl rings attached to C-2 and C-6 carbons of piperidine moiety exerted good activity against β-*H. streptococcus* with a MIC value of 12.5 μg/mL. Moreover, introduction of electron donating dimethyl group at C-3 of the piperidine ring in compounds **59** and **60**, which were having electron donating methoxy and methyl substitutions, respectively, at the *para* position of phenyl rings attached to C-2 and C-6 carbons of piperidine moiety exerted modest antibacterial activity against all the tested bacterial strains in the range of 25–200 μg/mL. Compound **51**, which have $CH_3$ group at C-3 position of the piperidine ring exerted moderate activity against all the tested bacterial strains at a MIC of 200 μg/mL when compared to compounds **46**, which was having no $CH_3$ group at C-3 position of the piperidine

**Table 2**
In vitro antibacterial activity of compounds **46**–**60** against clinically isolated bacterial strains

| Compounds | Minimum inhibitory concentration (MIC) in μg/mL | | | | |
|---|---|---|---|---|---|
| | *S. aureus* | β-*H. streptococcus* | *V. cholerae* | *E. coli* | *P. aeruginosa* |
| **46** | 100 | 50 | 100 | 50 | 50 |
| **47** | 50 | 6.25 | 12.5 | 12.5 | 6.25 |
| **48** | 50 | 6.25 | 12.5 | 12.5 | 6.25 |
| **49** | 50 | 100 | 50 | 50 | 100 |
| **50** | — | 100 | 100 | 200 | 25 |
| **51** | 200 | 100 | 50 | 50 | 50 |
| **52** | 6.25 | 12.5 | 6.25 | 12.5 | 6.25 |
| **53** | 6.25 | 50 | 12.5 | 50 | 50 |
| **54** | 50 | 25 | 50 | 100 | 25 |
| **55** | 25 | 50 | 100 | 50 | 50 |
| **56** | 100 | 25 | 100 | 100 | 100 |
| **57** | 12.5 | 6.25 | 12.5 | 6.25 | 6.25 |
| **58** | 25 | 12.5 | 50 | 50 | 25 |
| **59** | 200 | 50 | 100 | — | 50 |
| **60** | 25 | 25 | 100 | 50 | 100 |
| Ciprofloxacin | 25 | 50 | 50 | 25 | 25 |

'—' no inhibition even at a higher concentration of 200 μg/mL.

ring. Mono methyl substituted compounds **52** and **53** at C-3 of piperidine ring were more active against *S. aureus* and they show fourfold increases in activity when compared to the standard drug Ciprofloxacin. Compound **52** show eightfold increases in activity against β-*H. streptococcus* and *P. aeruginosa* whereas fourfold increases in activity against *E. coli* was noted when compared to the standard antibacterial drug. Compound **53**, which have $CH_3$ group at C-3 position of the piperidine ring exerted a fourfold increase in activity against *V. cholerae* whereas compound **58**, a dimethyl substituted compound at position C-3 of piperidine ring exerted equal activity as that of the antibacterial drug. Compounds **54** and **55**, which were having electron donating methoxy and methyl substitutions, respectively, at the *para* position of phenyl rings attached to C-2 and C-6 carbons of piperidine moiety and have electron donating methyl group at C-3 of the piperidine ring shows modest antibacterial activity against all the tested bacterial strains in the range of 25–100 μg/mL. Dimethyl substitution at position C-3 of the piperidine ring for compound **56** exerted moderate activity similar to that of compounds **51** and **46**. There was no change in activity by incorporating two methyl groups at C-3 position. But for compound **57**, which was having strong electron withdrawing fluoro function groups at the phenyl rings along with two methyl groups at C-3 position of the piperidine ring exerted strong activity against *S. aureus* at a MIC of 12.5 μg/mL when compared to that of compound **46** which have no substitution at the C-3 position. Also, dimethylated compound **59** did not show any activity against *E. coli* even at a higher concentration of 200 μg/mL whereas as unsubstituted compound **49** and mono methyl substituted compound **54** exerted activity at a MIC of 50 and 100 μg/mL.

The in vitro antifungal activity of 3-(3-alkyl-2,6-diarylpiperin-4-ylidene)-2-thioxoimidazolidin-4-ones **46–60** was studied against the fungal strains viz., *Aspergillus flavus*, *Candida albicans*, *Candida 6* and *Candida 51*. Fluconazole was used as a standard drug. Minimum inhibitory concentration (MIC) in μg/mL values was reproduced in Table 3. A close survey of the MIC values indicates that all the compounds **46–60** exhibited a varied range (6.25–200 μg/mL) of antifungal activity against all the tested fungal strains except compounds **49** and **56** which were not having antifungal activity against *Candida 51* and *A. flavus*. Compound **46**, which have no substituent at the *para* position of the phenyl groups at the C-2 and C-6 positions of the piperidine ring showed threefold increase in antifungal activity against *A. flavus* and *C. albicans* at a MIC value of 12.5 μg/mL. Compounds **47** and **48**, which have electron withdrawing fluoro or chloro substitution at the *para* position of phenyl rings attached to C-2 and C-6 carbons of piperidine moiety exerted threefold increased in antifungal activity against *A. flavus* and *Candida 6* at a MIC value of 12.5 μg/mL, respectively. Compounds **49** and **50**, which were having electron donating methoxy and methyl substitutions, respectively, at the *para* position of phenyl rings attached to C-2 and C-6 carbons of piperidine moiety shows admirable antifungal activity against all the tested fungal strains in the range of 6.25–12.5 μg/mL except compound **49** which did not show activity against *Candida 51* even at a higher concentration of 200 μg/mL. Compound **51**, which have electron donating mono methyl group at position C-3 of the piperidine ring, exerted reasonable antifungal activity against all the tested strains at a MIC value of 50 μg/mL. In addition to electron donating mono methyl group at position C-3 of the piperidine ring, compound **52** have electron withdrawing fluoro substitution at the *para* position of phenyl rings attached to C-2 and C-6 carbons of piperidine moiety exerted activity in the range of 6.25–12.5 μg/mL. Compound **53**, which have electron withdrawing chloro substitution at the *para* position of phenyl rings attached to C-2 and C-6 carbons of piperidine moiety as well electron donating methyl substituent at position C-3 of the piperidine ring exerted good antifungal activity against *A. flavus* and *Candida 51* at a MIC of 12.5 μg/mL. Compounds **54** and **55** which have electron donating methoxy and methyl substitution, respectively, at the *para* position of phenyl rings attached to C-2 and C-6 carbons of piperidine moiety as well electron donating methyl substituent at position C-3 of the piperidine ring were potent against *A. flavus*, *Candida 6* and *Candida 51*. Besides having electron donating dimethyl group at C-3 of the piperidine ring, compounds **59** and **60** which were having electron donating methoxy and methyl substitutions at the *para* position of phenyl rings attached to C-2 and C-6 carbons of piperidine moiety shows admirable antifungal activity against all the tested fungal strains in the range of 6.25–25 μg/mL. Dimethyl substituted compound **56** did not exhibit antifungal activity against *A. flavus*, whereas monomethyl substituted compound **51** at position C-3 of piperidine ring and unsubstituted compound **46** exerted activities at a MIC of 50 and 12.5 μg/mL, respectively. Electron donating dimethyl substituents at position C-3 of the piperidine ring in compound **59** exerted excellent antifungal activity against all the tested *A. flavus* strains whereas mono methyl substituted compound **54** and C-3 unsubstituted compound **49** exerted activity at a MIC of 12.5 μg/mL. Two and fourfold increased in activities were noticed for monomethyl substituted compound **54** and dimethyl substituted compound **59**, respectively, when compared to that of the standard antifungal drug Fluconazole. Fluoro substituted compound **52**, which have methyl group at position 3 of the piperidine ring exerted excellent antifungal activity against all the tested fungal strains. Eightfold increased in activity was noted against *A. flavus*, *C. albicans* and *Candida 51* and a fourfold increased in activity when compared to standard drug was noticed against *Candida 6* for compound **52**. But compound **47** which have no methyl substitution pronounced moderate activity against all the tested fungal strains except *A. flavus*, which exhibit fourfold increased in antifungal activity when compared to that of the drug, Fluconazole. Compound **60** which have dimethyl substituents at C-3 position of the phenyl ring exhibit fourfold and twofold increased in activity against *Candida 6* and *Candida 51,* respectively, whereas monomethyl substituted compound **55** and compound **50** which have no methyl substituent at C-3 of piperidine ring exerted fourfold increased in activity against all the tested fungal strains when compared to Fluconazole.

In crisp, we have synthesized a novel biologically active 3-(3-alkyl-2,6-diarylpiperin-4-ylidene)-2-thioxoimidazolidin-4-ones and their structures were characterized by their spectral and analytical

**Table 3**
In vitro antifungal activity of compounds **46–60** against clinically isolated fungal strains

| Compound | Minimum inhibitory concentration (MIC) in μg/mL | | | |
|---|---|---|---|---|
| | *A. flavus* | *C. albicans* | *Candida 6* | *Candida 51* |
| **46** | 12.5 | 12.5 | 50 | 100 |
| **47** | 12.5 | 50 | 50 | 50 |
| **48** | 50 | 50 | 12.5 | 25 |
| **49** | 12.5 | 12.5 | 6.25 | — |
| **50** | 6.25 | 12.5 | 6.25 | 6.25 |
| **51** | 50 | 50 | 50 | 50 |
| **52** | 6.25 | 6.25 | 12.5 | 6.25 |
| **53** | 12.5 | 50 | 50 | 12.5 |
| **54** | 12.5 | 50 | 12.5 | 12.5 |
| **55** | 12.5 | 50 | 6.25 | 12.5 |
| **56** | — | 50 | 100 | 50 |
| **57** | 25 | 50 | 50 | 50 |
| **58** | 25 | 50 | 50 | 50 |
| **59** | 6.25 | 12.5 | 25 | 6.25 |
| **60** | 25 | 25 | 6.25 | 12.5 |
| Fluconazole | 50 | 50 | 25 | 25 |

'—' no inhibition even at a higher concentration of 200 μg/mL.

data. A close survey of the in vitro antibacterial and antifungal activity profile of the new 3-(3-alkyl-2,6-diarylpiperin-4-ylidene)-2-thioxoimidazolidin-4-ones **46–60** against the tested clinically isolated bacterial and fungal strains gave a clear picture about the structure–activity correlations among compounds **45–60** under study. Compounds **47–50**, **52–55** and **57–60** with fluoro, chloro, methoxy or methyl functions at the *para* position of phenyl rings attached to C-2 and C-6 carbons of piperidine moiety along with and without methyl substituent at position C-3 of the piperidine ring exerted a varied range of biological activities, while the activity was not significant for compounds **46**, **51** and **56** without any substituents at C-3 of the piperidine ring and the *para* position of the phenyl groups. Furthermore, the observed marked antibacterial and antifungal activities may be considered as key steps for the building of novel chemical entities with comparable pharmacological profiles to that of the standard drugs.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.11.074.

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27. *Spectral data for compound* **46**: IR (KBr) ($cm^{-1}$): 3400, 3306, 3060, 3029, 2980, 2896, 2797, 1728, 1635, 1598, 1215, 701, 758, 1041; MS: $m/z = 365$ $(M+1)^+$. Elemental Anal. Calcd: C, 65.91; H, 5.53; N, 15.37. Found: C, 65.87; H, 5.50; N, 15.33. $^1$H NMR ($\delta$ ppm): 1.97–2.05 (m, 1H, $H_{3a}$), 2.37–2.41 (dd, 1H, $H_{3e}$, $J_{3e,3a} = 13.64$ Hz, $J_{3e,2a} = 2.96$ Hz); 2.43–2.52 (m, 1H, $H_{5a}$), 2.83 (s, 1H, NH of piperidine), 3.62–3.66 (dd, $H_{5e}$, $J_{5e,5a} = 2.96$ Hz, $J_{5e,6a} = 13.52$ Hz), 3.80 (s, 2H, $CH_2$ of imidazolidine), 3.88–3.92 (dd, 1H, $H_{2a}$, $J_{2a,3e} = 3.08$ Hz, $J_{2a,3a} = 11.76$ Hz), 4.15–4.19 (dd, 1H, $H_{6a}$, $J_{6a,5e} = 3.20$ Hz, $J_{6a,5a} = 11.88$ Hz), 7.23–7.50 (m, 10H, Ar–H's), 11.78 (s, NH of imidazolidine); In the $D_2O$ exchanged $^1$H NMR spectrum, two peaks at 2.83 ppm and 11.78 ppm which resonances due to NH of piperidine and imidazolidine, respectively, disappeared; $^{13}$C NMR ($\delta$ ppm): 29.6 C-3, 37.3 C-5, 43.6 $CH_2$ of imidazolidine, 60.2 C-2, 61.1 C-6, 126.5–128.1 Ar–C's, 144.0, 144.1 *ipso*-C, 163.1 C=N, 167.6 C=O, 173.8 C=S. In six-membered heterocycles, a decrease in electronegativity of a group in the ring deshields β-carbons and shields β-protons. Hence for compound **46**, the deshielding of anti β-C-6 carbon with respect to thioxoimidazoline ring was in accordance with the expected electronegativity effect whereas the syn β-C-2 carbon was shielded.[30]
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