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Synthesis, antioxidant and antimicrobial activity of novel vanillin derived piperidin-4-one oxime esters: Preponderant role of the phenyl ester substituents on the piperidin-4-one oxime core

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ABSTRACT

The study has been achieved the efficient synthesis of vanillin derived piperidin-4-one oxime esters (**5a–m**) via four step reaction involved Mannich reaction of vanillin, acetone and ammonium acetate to obtain 2,6-bis(4-hydroxy-3-methoxyphenyl)-piperidin-4-one **2** followed by N-methylation and oximation. Further, to enhance the biological activity of vanillin derived piperidin-4-one oxime core, esterification of **4** with substituted benzoyl chlorides in the presence of strong organic base *t*-BuOK accomplished a series of vanillin derived piperidin-4-one oxime esters (**5a–m**). The synthesized analogues are screened for their antioxidant and antimicrobial studies and the preponderant effect of the phenyl ester substituents on the biological activity of piperidin-4-one oxime core was demonstrated. Among the tested compounds, **5i** and **5j** are emerged as outperformed antioxidants than standard Butylated hydroxy anisole (BHA) whereas, compounds **5b** and **5d** manifested potent antibacterial and antifungal activity than standard streptomycin and fluconazole respectively.

Heterocyclic compounds carrying piperidine skeleton are attractive targets of organic synthesis owing to their pharmacological activity and their wide occurrence in nature. Specifically, piperidine based chemical entities with aryl substituents at carbons 2 and 6 of the piperidine ring have been documented as potent antimicrobial agent.[1] Piperidinone derivatives and oxime analogues (Fig. 1) are found to possess diversified pharmacological activity and form an essential part of the molecular structures of some drugs.[2–4]

Vanillin (4-hydroxy-3-methoxybenzaldehyde) is a widely used flavor compound in food and cosmetics, with an estimated annual worldwide consumption of more than 2000 tons.[5] Vanillin has been reported to inhibit mutagenesis induced by chemical and physical mutagens and to suppress the invasion and migration of cancer cells.[6] It also displays chemopreventive effects in multiorgan carcinogenesis and hepatocarcinogenesis models in rats.[7] Moreover, vanillin displays antimicrobial and antioxidant properties and is used as a food preservative and for medicinal purposes.[8,9] In particular, piperidinone oximes and their derivatives represent an important class of organic molecules that attract the interest of both synthetic and medicinal chemists. But it is envisaged from the literature that there is scarcity of reports on synthesis and biological importance of piperidin-4-one oxime esters. Thus, in continuation of our interest in functionalization of tricyclic and heterocyclic compounds[10–12] and in searching of new biologically active piperidin-4-one analogues, the title compounds vanillin derived piperidin-4-one oxime esters (Fig. 2) was synthesized.

The numerous pharmacological activities of piperidin-4-ones and piperidin-4-one oxime prompted us to study the antioxidant and antimicrobial activity of newly synthesized compounds using various assays.

In the present work, four step synthetic strategies are adapted for the preparation of vanillin derived piperidin-4-one oxime esters (**5a–m**). The representation describing the routes of synthesis is depicted in the Scheme 1. The basic compound 2,6-bis(4-hydroxy-3-methoxyphenyl)piperidin-4-one **2** was synthesized by condensation reaction (Mannich reaction) of vanillin, acetone and ammonium acetate in 2:1:1 ratio respectively.[13,14] In the next step, compound **2** on N-methylation upon reflux with iodomethane in the presence of anhydrous potassium carbonate (K_2CO_3) as base in acetone afforded 2,6-bis(4-hydroxy-3-methoxyphenyl)-1-methylpiperidin-4-one **3** with excellent yield. Further, compound **3** was converted to corresponding oxime that is, 2,6-bis(4-hydroxy-3-methoxyphenyl)-1-methylpiperidin-4-one oxime **4** by treating with hydroxylamine hydrochloride ($NH_2OH{\cdot}HCl$) in the presence of sodium acetate trihydrate in absolute alcohol. In the present investigation, esterification of oxime **4** was done by using *t*-BuOK

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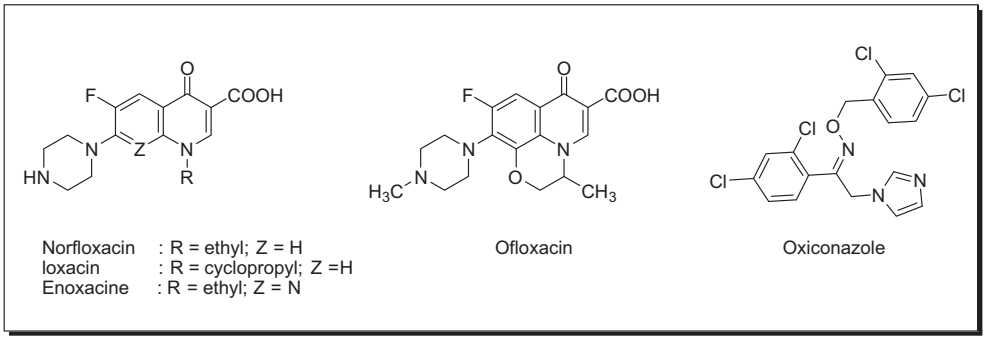


Figure 1. Structures of piperidinone and oxime derived pharmacologically active drugs.

as base proceeded with fair yields irrespective of substituted benzoyl chlorides used (Table 1). Very recently, the conversion of oxime into oxime esters by using triethylamine (Et_3N) as base has been reported.[15] The present communication represented an efficient and a mild variant potassium tertiarybutoxide (*t*-BuOK) assisted convenient procedure for the preparation of vanillin derived piperidin-4-one oxime esters **(5a–m).** The structure of compounds was elucidated by elemental analysis, IR, NMR (^1H, ^{13}C) and mass spectral studies.

In order to study the vital role of the phenyl ester substituents possessing diversified functional groups at different position on the piperidin-4-one oxime core towards antioxidant and antimicrobial potential, all the synthesized analogues (**5a–m**) were subjected to in vitro antioxidant and antimicrobial assays. Evaluation of antioxidant activity for the newly synthesized analogues was undertaken by using three in vitro assays such as 2,2′-diphenyl-1-picryl-hydrazyl (DPPH) radical scavenging activity, 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) ($ABTS^{\cdot+}$) radical scavenging activity and inhibition of microsomal lipid peroxidation (LPO).

The synthesized molecules (**5a–m**) can quench DPPH free radicals (i.e., by providing hydrogen atoms or by electron donation, conceivably via a free-radical attack on the DPPH molecule) and convert them to a colorless/bleached product (i.e., 2,2′-diphenyl-1-picryl-hydrazine, or a substituted analogous hydrazine), resulting in a decrease in absorbance at 517 nm. Hence, the more rapidly the absorbance decreases, the more potent the radical scavenging activity of the compound.[16] 50% inhibitory concentrations (IC_{50}) were calculated and are depicted in Table 2. Initially, vanillin derived piperidin-4-one oxime core **4** exhibited considerable activity. The reason would be the presence of electron releasing hydroxyl and electron donating methoxy groups on phenyl moiety on either side of the piperidin-4-one oxime skeleton. Further, inclusion of substituted benzoyl chlorides to **4** results the vanillin derived piperidin-4-one oxime esters endowed notable improvement in radical scavenging activity. Nearly, all the tested compounds (**5a–m**) exhibited positive efficacy for scavenging DPPH free radical. Among the synthesized molecules and the positive control BHA, the top two for scavenging radicals are compounds **5i** and **5j** having additional pair of hydroxyl groups on the aryl ester moiety. Generally, the more number of hydroxyl substituents on the phenyl moiety, more the antioxidant properties.[17] The next promising antioxidant activity was showed by compounds **(5f–h)** having one hydroxyl group at different position on aryl ester moiety. The incorporation of $–OCH_3$ groups on the phenyl ring at different position in the compounds (**5k–m**) demonstrated slight increase in the radical scavenging capabilities. This may be due to the presence of electron donating $–OCH_3$ groups.[18] The introduction of groups like F, Br, Cl and NO_2 on the phenyl ring at C-4 position demonstrated no affects for the enhancement of radical scavenging capacity. The reason might be the electron withdrawing capabilities of these groups.[19]

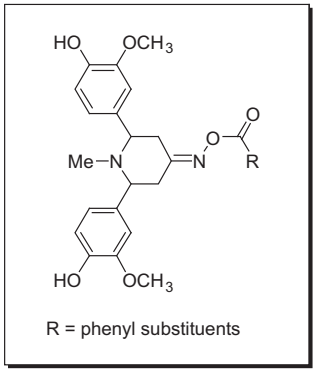
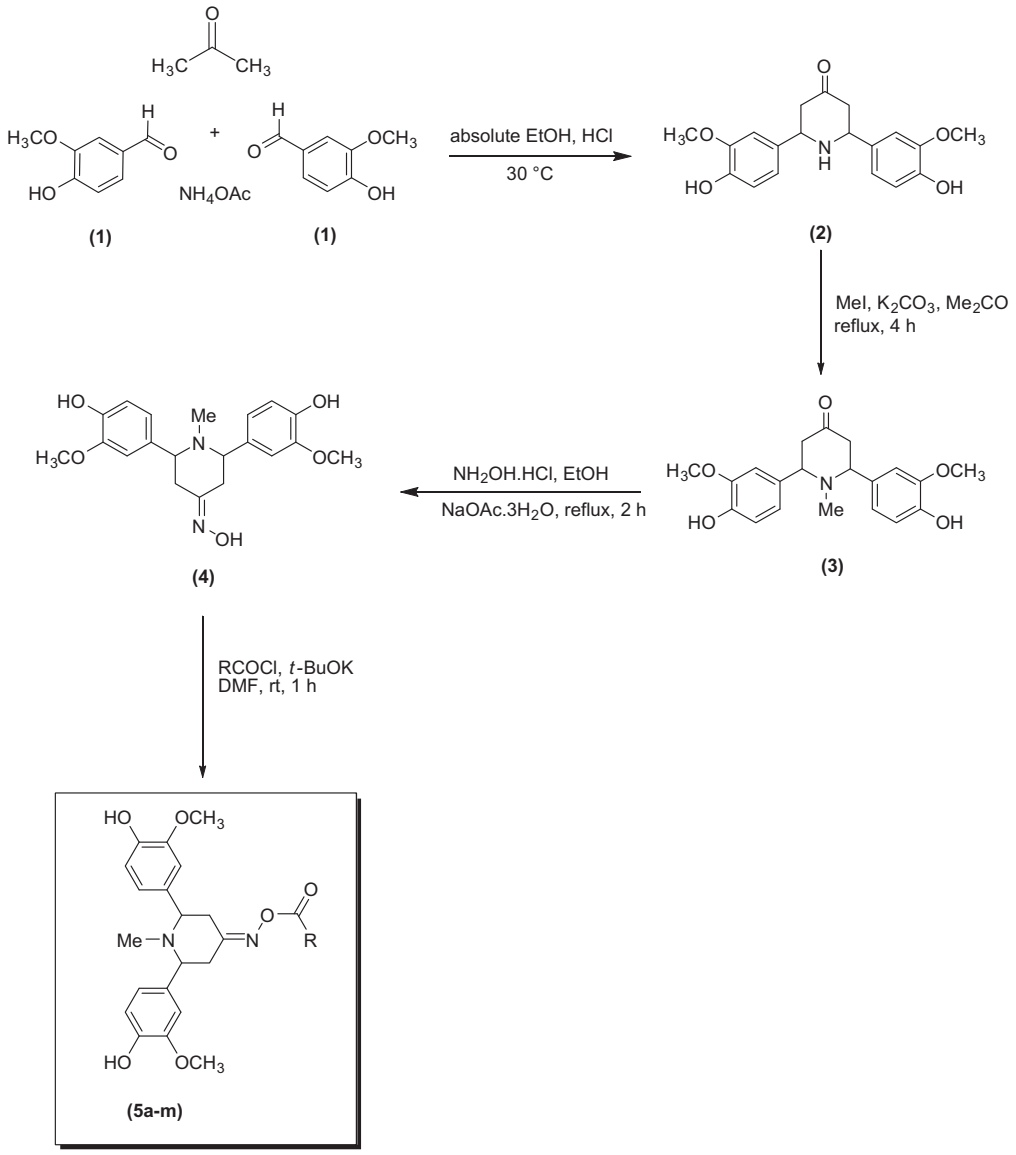


Figure 2. General structure of vanillin derived piperidin-4-one oxime esters.

The synthesized piperidin-4-one oxime esters having different concentrations (10, 25, 50, 100, 200, 500 μM) were subjected to $ABTS^{\cdot+}$ radical scavenging activity.[20] ABTS radical scavenging assay is a facile and elegant method to exploit antioxidant activity of the array of newly synthesized compounds. The technique is based on direct production of the blue/green $ABTS^{\cdot+}$ chromophore through the reaction between ABTS and potassium persulfate. The findings of present study (Table 2) indicated that the majority of oxime esters exhibited moderate to high radical scavenging ability. The incorporation of these two substituted benzoyl chlorides (3,5 dihydroxy and 3,4,5 trihydroxy) to oxime core **4** led to compound **5i** and **5j** respectively, has showed twelve to fifteen fold more activity compared to piperidin-4-one oxime core **4** and these are outperformed antioxidants among the tested molecules. Introduction of electron withdrawing groups such as F, Br, Cl, NO_2 in compounds (**5b–e**) was inadequate to show enhanced activity. Whereas, the compounds (**5f–h**) having single electron releasing hydroxyl group at *ortho, meta* and *para* position of phenyl ester exhibited nine to 10-fold more radical scavenging capacity than **4**. Electron donating methoxy group holding compounds (**5k–m**) exhibited antioxidant activity slightly lesser than compounds (**5f–h**). Analogue **5a** which does not have any substituent on the phenyl ring showed least activity compared to other analogues.

In LPO assay, the abilities of the array of compounds to scavenge free radicals was further confirmed by inhibition of microsomal lipid peroxidation indices in a liposome model system. LPO has been broadly defined as the oxidative deterioration of polyunsaturated lipids.[21] IC_{50} values of LPO inhibition for the newly synthesized analogues are depicted in Table 2 and reflects whole of the tested compounds exhibited certain degree of antioxidant activity. The compounds (**5f–h**) possessing single hydroxyl group at different position on the phenyl ester moiety exhibits good activity whereas,



Scheme 1. Reaction protocol for the synthesis of vanillin derived piperidin-4-one oxime esters (**5a–m**).

compounds **5i** and **5j** holding two and three hydroxyl groups on the phenyl ester skeleton dominantly inhibits the lipid peroxidation compared to all analogues and standard BHA as well. Electron releasing methoxy group substituted compounds (**5k–m**) were the next most effective LPO inhibitors followed by rest of compounds (**5b–e**) and **5a.**

The antimicrobial activity of newly synthesized compounds (**5a–m**) was determined by well plate method.[22,23] The potentiality of the synthesized compounds as antimicrobials was appraised for their antibacterial studies against different strains of human pathogens namely *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 25923 and *Pseudomonas aeruginosa* ATCC 27853. Antifungal studies against human pathogen fungal strains such as *Aspergillus flavus* MTCC 3306, *Candida albicans* MTCC 3017 and *Chrysosporium keratinophilum* MTCC 2827.

The results obtained as zone of inhibition (mm) are presented in Table 3 and Table 4, respectively. It is more attractive to speculate the observation that the result of the antimicrobial activity of the different derivatives of oxime esters appeared to be related to the nature of substituents on the phenyl unit. Among the derivatives, compounds (**5b–d**) showed enhanced antimicrobial activity at concentration of 1000 and 500 μg/mL. The reason would be more lipophilic nature of piperidin-4-one moiety[2] along with the presence of electronegative groups like halogens.

The results of antibacterial activities (Table 3) revealed that the majority of the synthesized compounds showed varying degree of inhibition against tested micro organisms. Compounds **5b** and **5d** possessing fluoro and chloro group at *para* position in phenyl moiety exhibited almost equipotent efficacy compared to standard drug streptomycin against *P. aeruginosa* and *E. coli*. Compound **5c** possessing bromo group exhibited slightly less antibacterial activity than standard followed by **5e** having electron withdrawing nitro group. Compounds bearing hydroxyl groups such as (**5f–j**) were demonstrated moderate activity against three tested bacterial strains. Introduction of methoxy groups in compounds (**5k–m**) were inadequate to show moderate antibacterial activity. The compound **5a** having no substitution on aryl ester moiety exhibited least antibacterial activity.

The investigation of antifungal activity (Table 4) reveals that compound **5b** possessing most electronegative fluoro group in *para* position of phenyl ester moiety emerged as active antifungal agent against *A. flavus* compared with standard fluconazole. Replacement

Table 1
Chemical structures and yields of vanillin derived piperidin-4-one oxime esters (**5a–m**)

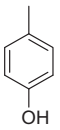
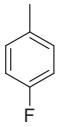
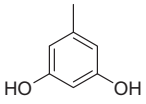
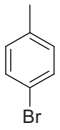
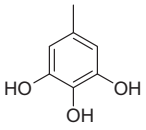
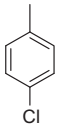
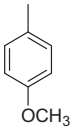
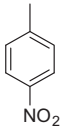
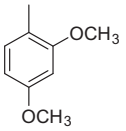
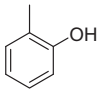
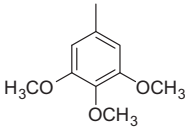
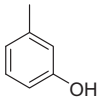
Compounds	Entry R	Yield (%)	Compounds	Entry R	Yield (%)
5a		88.00	**5h**		75.02
5b		77.00	**5i**		71.65
5c		78.30	**5j**		84.20
5d		77.00	**5k**		80.45
5e		85.00	**5l**		76.78
5f		79.32	**5m**		79.20
5g		76.21			

Table 2
Concentration required for 50% inhibition (IC_{50}) of $DPPH^{\cdot}$, $LPO^{\cdot}$ and $ABTS^{\cdot+}$ radicals by the compounds (**5a–m**) and the standard antioxidant compound BHA

Tested compounds	Scavenging activity[a] (IC_{50})		
	$DPPH^{\cdot}$	LPO	$ABTS^{\cdot+}$
4	144 ± 0.18	167 ± 0.56	158 ± 0.12
5a	141 ± 0.12	165 ± 0.21	156 ± 0.33
5b	133 ± 0.81	140 ± 0.54	141 ± 0.32
5c	103 ± 0.31	112 ± 0.12	108 ± 0.51
5d	110 ± 0.23	121 ± 0.45	112 ± 0.63
5e	76 ± 0.42	82 ± 0.55	79 ± 0.91
5f	14.8 ± 0.65	24.1 ± 0.61	15.9 ± 0.30
5g	15.6 ± 0.22	25.3 ± 0.81	16.5 ± 0.47
5h	14.2 ± 0.41	22.5 ± 0.26	15.1 ± 0.25
5i	10.8 ± 0.71	17.2 ± 0.41	12.3 ± 0.50
5j	10 ± 0.23	16.1 ± 0.22	11.8 ± 0.64
5k	28 ± 0.33	40 ± 0.57	33 ± 0.14
5l	32 ± 0.12	52 ± 0.71	41 ± 0.17
5m	40 ± 0.91	61 ± 0.22	53 ± 0.51
BHA	12 ± 0.21	18.5 ± 0.11	13 ± 0.42

Each value represents mean ± SD ($n = 3$).
[a] The values are expressed as μM concentration. Lower IC_{50} values indicate higher radical scavenging activity.

of fluoro group by chloro led to compound **5d** was the next effective antifungal agent. Compounds **5c** and **5e** bearing Br, NO_2 groups exhibited moderate growth inhibitory activities. The rest of the compounds showed weak to moderate antifungal activity against all the tested fungal strains.

Thus, the most remarkable result of these antioxidant and antimicrobial assays is the critical influence of the phenyl ester substituents on the vanillin derived piperidin-4-one oxime core.

In conclusion, we have achieved a convenient protocol for the synthesis of vanillin derived piperidin-4-one oxime esters (**5a–m**) through the pathway involved Mannich reaction of vanillin, acetone and ammonium acetate to obtain 2,6-bis(4-hydroxy-3-methoxyphenyl)-piperidin-4-one **2** followed by N-methylation and oximation. In order to improve the pharmacological activity of piperidin-4-one oxime core, esterification of 2,6-bis(4-hydroxy-3-methoxyphenyl)-1-methylpiperidin-4-one oxime **4** with substituted benzoyl chlorides was successfully done by employing a *t*-BuOK assisted reaction. The synthesized molecules were assessed for their antioxidant and antimicrobial capacities. It is noteworthy that compounds **5i** and **5j** possessed dominant antioxidant capacity than standard because of having highest phenolic content. The antimicrobial study was undertaken to evaluate their inhibitory activities on the growth of pathogenic bacteria and fungi. Presence of electron withdrawing substituent particularly fluoro and chloro group at *para* position of aryl ester in compounds **5b** and **5d** found to be essential for potent antimicrobial. Overall, the biological tests revealed the determinant influence of the phenyl ester substituents on the antioxidant and antimicrobial activity of vanillin derived piperidin-4-one oxime core. Our results prompt that, further studies on these compounds may be operating as a positive reinforce for the construction of novel chemical entities with better pharmacological profiles.

Table 3
Inhibitory zone (diameter) mm of the synthesized compounds (**5a–m)** against tested bacterial strains by well plate method

Compound no.	*Escherichia coli*		*Staphylococcus aureus*		*Pseudomonas aeroginosa*	
	Concentration (μg/mL)					
	1000	500	1000	500	1000	500
4	01 ± 0.01	00 ± 0.02	01 ± 0.02	00 ± 0.03	01 ± 0.01	00 ± 0.02
5a	03 ± 0.02	02 ± 0.01	04 ± 0.02	03 ± 0.01	02 ± 0.01	01 ± 0.01
5b	18 ± 0.03	13 ± 0.02	15 ± 0.01	13 ± 0.02	16 ± 0.02	13 ± 0.02
5c	11 ± 0.01	07 ± 0.01	09 ± 0.02	07 ± 0.01	09 ± 0.01	07 ± 0.01
5d	17 ± 0.02	12 ± 0.01	13 ± 0.01	09 ± 0.01	15 ± 0.01	012 ± 0.02
5e	08 ± 0.02	04 ± 0.01	08 ± 0.01	05 ± 0.01	08 ± 0.01	05 ± 0.02
5f	06 ± 0.01	04 ± 0.01	05 ± 0.02	05 ± 0.02	04 ± 0.02	03 ± 0.02
5g	07 ± 0.01	06 ± 0.02	07 ± 0.01	05 ± 0.01	05 ± 0.01	03 ± 0.01
5h	05 ± 0.02	04 ± 0.02	06 ± 0.02	04 ± 0.02	03 ± 0.02	02 ± 0.02
5i	04 ± 0.01	05 ± 0.01	05 ± 0.01	05 ± 0.01	05 ± 0.01	04 ± 0.01
5j	07 ± 0.02	05 ± 0.01	06 ± 0.02	04 ± 0.02	04 ± 0.02	03 ± 0.01
5k	03 ± 0.01	02 ± 0.02	04 ± 0.01	02 ± 0.01	04 ± 0.01	03 ± 0.02
5l	06 ± 0.02	04 ± 0.02	05 ± 0.01	03 ± 0.01	06 ± 0.01	06 ± 0.02
5m	05 ± 0.02	04 ± 0.01	06 ± 0.02	04 ± 0.02	05 ± 0.02	03 ± 0.01
Streptomycin (standard)	18 ± 0.01	12 ± 0.01	15 ± 0.02	12 ± 0.01	16 ± 0.01	13 ± 0.02

Table 4
Inhibitory zone (diameter) mm of the synthesized compounds (**5a–m)** against tested fungal strains by well plate method

Compound no.	*Aspergillus flavus*		*Chrysosporium keratinophilum*		*Candida albicans*	
	Concentration (μg/mL)					
	1000	500	1000	500	1000	500
4	01 ± 0.03	00 ± 0.03	01 ± 0.02	01 ± 0.01	01 ± 0.01	00 ± 0.01
5a	02 ± 0.02	01 ± 0.01	03 ± 0.02	02 ± 0.01	03 ± 0.01	02 ± 0.01
5b	17 ± 0.03	13 ± 0.02	12 ± 0.01	14 ± 0.02	20 ± 0.02	18 ± 0.02
5c	06 ± 0.01	05 ± 0.01	07 ± 0.02	05 ± 0.01	09 ± 0.01	08 ± 0.01
5d	15 ± 0.02	12 ± 0.01	10 ± 0.01	12 ± 0.01	19 ± 0.01	16 ± 0.02
5e	04 ± 0.02	03 ± 0.01	05 ± 0.01	04 ± 0.01	06 ± 0.01	07 ± 0.02
5f	04 ± 0.01	03 ± 0.01	06 ± 0.02	04 ± 0.02	06 ± 0.02	02 ± 0.02
5g	02 ± 0.01	01 ± 0.02	02 ± 0.01	01 ± 0.01	03 ± 0.01	01 ± 0.01
5h	01 ± 0.02	12 ± 0.02	03 ± 0.02	02 ± 0.02	02 ± 0.02	02 ± 0.02
5i	02 ± 0.01	01 ± 0.01	01 ± 0.01	02 ± 0.01	03 ± 0.01	03 ± 0.01
5j	04 ± 0.02	02 ± 0.01	04 ± 0.02	03 ± 0.02	08 ± 0.02	06 ± 0.01
5k	06 ± 0.01	05 ± 0.02	04 ± 0.01	04 ± 0.01	07 ± 0.01	05 ± 0.02
5l	05 ± 0.02	04 ± 0.02	05 ± 0.01	04 ± 0.01	06 ± 0.01	04 ± 0.02
5m	03 ± 0.02	04 ± 0.01	06 ± 0.02	03 ± 0.02	03 ± 0.02	03 ± 0.01
Fluconazole (standard)	14 ± 0.01	12 ± 0.02	17 ± 0.02	16 ± 0.01	22 ± 0.02	20 ± 0.02

All the antioxidant assays were carried out in triplicate for 3 separate experiments. The amount of compound needed to inhibit DPPH, $ABTS^{+\cdot}$ and LPO radical by 50% inhibitory concentration (IC_{50}) was graphically estimated using a linear regression algorithm.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.10.019.

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