ISSN 1068-1620, Russian Journal of Bioorganic Chemistry, 2017, Vol. 43, No. 2, pp. 186–196. © Pleiades Publishing, Ltd., 2017.

# Synthesis of Thiazole-Based Substituted Piperidinone Oximes: Profiling of Antioxidant and Antimicrobial Activity[1]

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Received May 10, 2016; in final form, October 22, 2016

**Abstract**—The synthesis of novel thiazole-based piperidinone oximes and screening of their antioxidant and antimicrobial activity are described. The obtained results revealed that the electronic effects of active substituents at C-4 terminals of phenyl rings on either side of piperidinone skeleton, as well as at 2-hydrazinyl thiazole, played a major role in development of antioxidant and antimicrobial activity. Antioxidant activity seems to be based also on radical dissipating ability of the thiazole ring. The nucleophilic character of sulfur in thiazole and lipophilic nature of piperidinone skeleton substantially influenced the observed antimicrobial activity of thiazole-based piperidinone oximes. Among the synthesized compounds, 2,6-bis(4-hydroxy-3-methoxyphenyl)-1-methylpiperidin-4-one *O*-(2-(2-(4-hydroxy-3-methoxybenzylidene)hydrazinyl)thiazol-4-yl) oxime exhibited excellent antioxidant activity whereas compound 2,6-bis(4-chloro phenyl)-1-methylpiperidin-4-one *O*-(2-(2-(4-nitrobenzylidene)hydrazinyl)thiazol-4-yl)oxime emerged as an outstanding antimicrobial agent.

*Keywords:* hydrazinyl thiazoles, piperidinone oximes, antioxidant activity, antibacterial activity, antifungal activity

**DOI:** 10.1134/S1068162017020042

## INTRODUCTION

The thiazole ring system is found in a diverse range of natural products and functional materials. It plays a central role in the biochemistry of life; the thiazole ring present in vitamin $B_1$ serves as an electron sink and its coenzyme form is important for the decarboxylation of α-keto acids [1]. Besides, thiazoles are also synthetic intermediates and common substructures in numerous biologically active compounds. Thus, the thiazole nucleus was much studied in the field of organic and medicinal chemistry. Owing to its interesting biological and pharmaceutical properties and synthetic utility, substantial interest has been demonstrated towards piperidin-4-one as another bioactive compound [2]; the compounds containing this substructure are widely prevalent in numerous natural alkaloids and synthetically derived compounds of biological importance. Specifically, piperidinone-based chemical entities with aryl substituents at C-2 and C-6 of the piperidinone ring were potent antioxidant and antimicrobial agents [3]. Moreover, thiosemicarbazones, oximes, or sulfur and nitrogen-containing heterocycles obtained by exploring the reactivity of keto group have been proven to exert better microbiological activities than their corresponding ketones [4]. In view of interest to the development of simpler and more convenient synthetic routes for achieving the biologically active thiazole-nucleated piperdinone analogues and in continuation of our research interest in functionalization of new tricyclic and heterocyclic compounds [5–7], we synthesized a series of novel thiazole based piperidinone oximes (**VIII**–**XXVII**) to explore their antioxidant and antimicrobial potential. The general structure and the proposed plan for substitution pattern of the thiazole-nucleated moieties is depicted in Figs. 1 and 2.

The installation of several active groups in thiazole nucleated moiety plays a preponderant role for the enhancement of antioxidant and antimicrobial activity.

## RESULTS AND DISCUSSION

In the present investigation, synthesis of thiazole-based library of compounds was aimed. Initially, 2-(substituted benzylidene)hydrazinecarbothioamides (**IIa**–**d**) were furnished by refluxing substituted benzaldehyde and thiosemicarbazide with catalytic amount of concentrated sulfuric acid [8]. The cyclisation of (**IIa**–**d**) with chloroacetyl chloride in ethanol (Scheme 1) affords key scaffolds of 4-chloro-2-(2-

[1] The article is published in the original.

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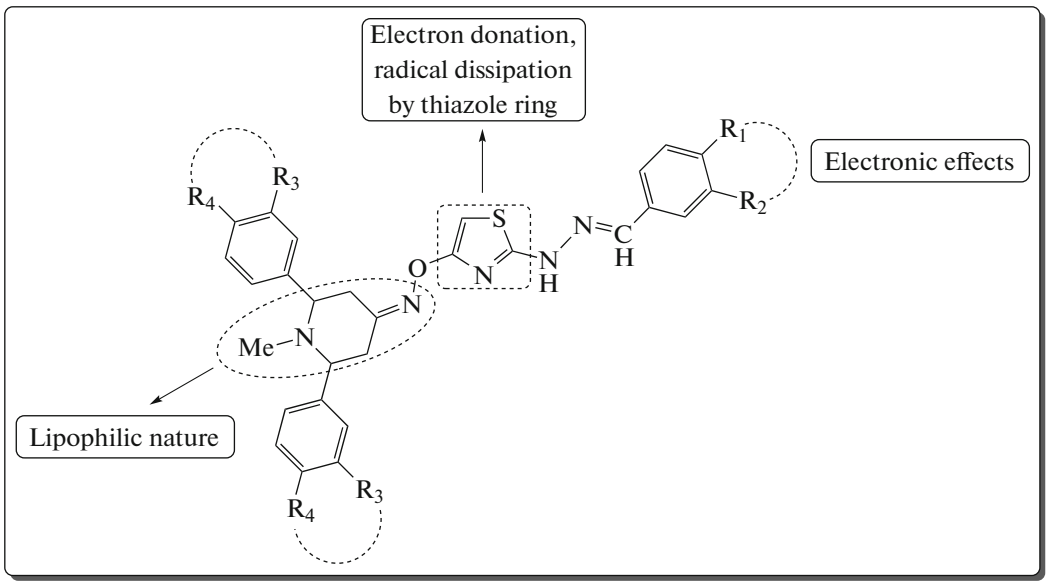
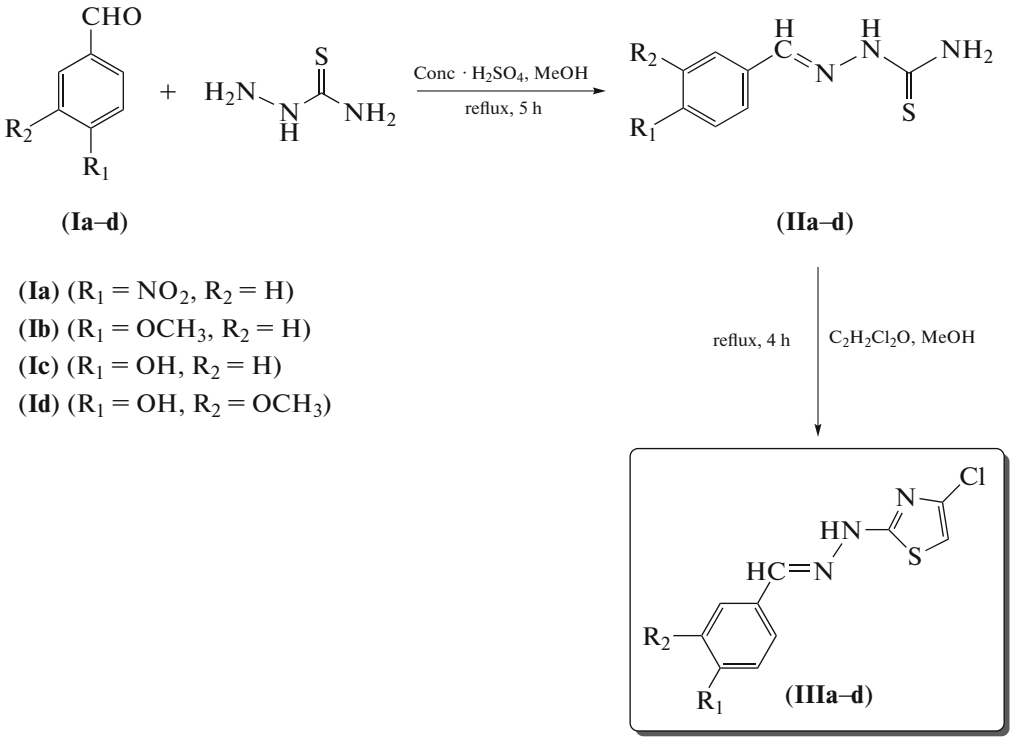
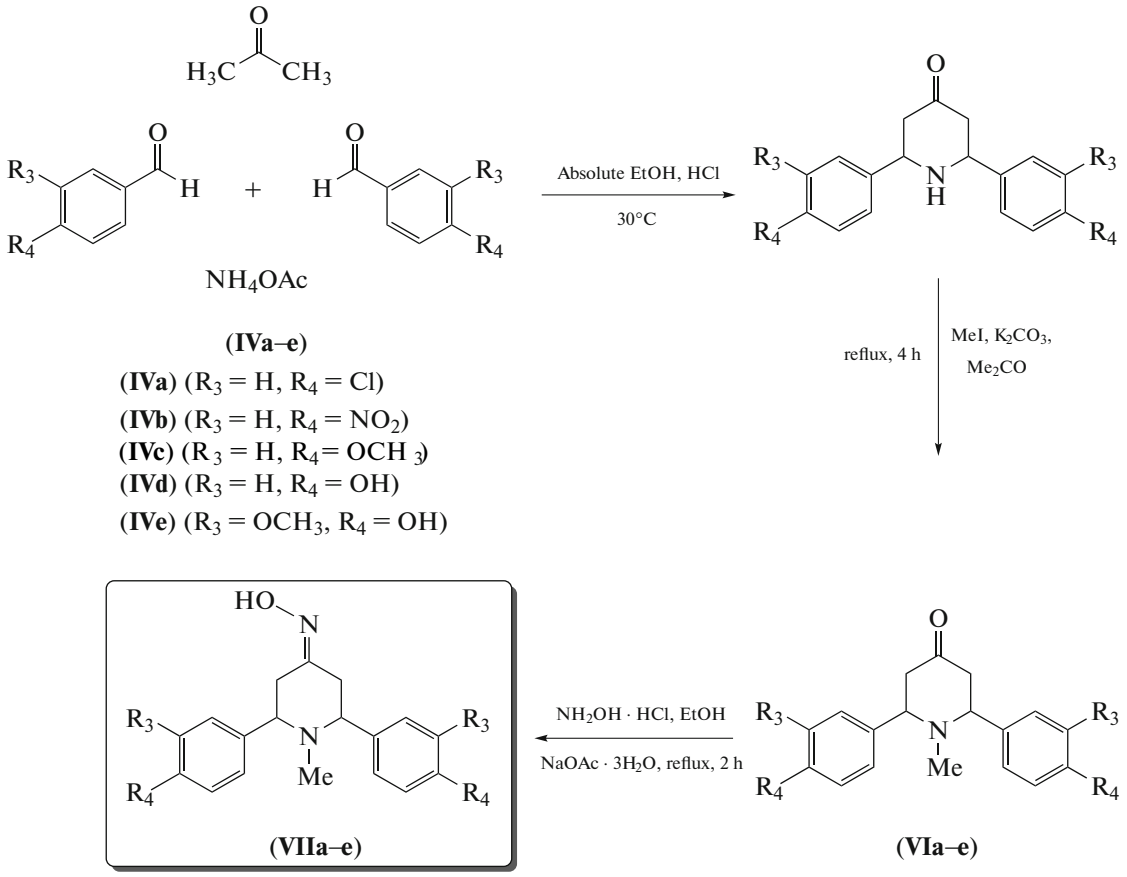



**Fig. 1.** Structural requirements for the thiazole-nucleated piperidinone oximes.

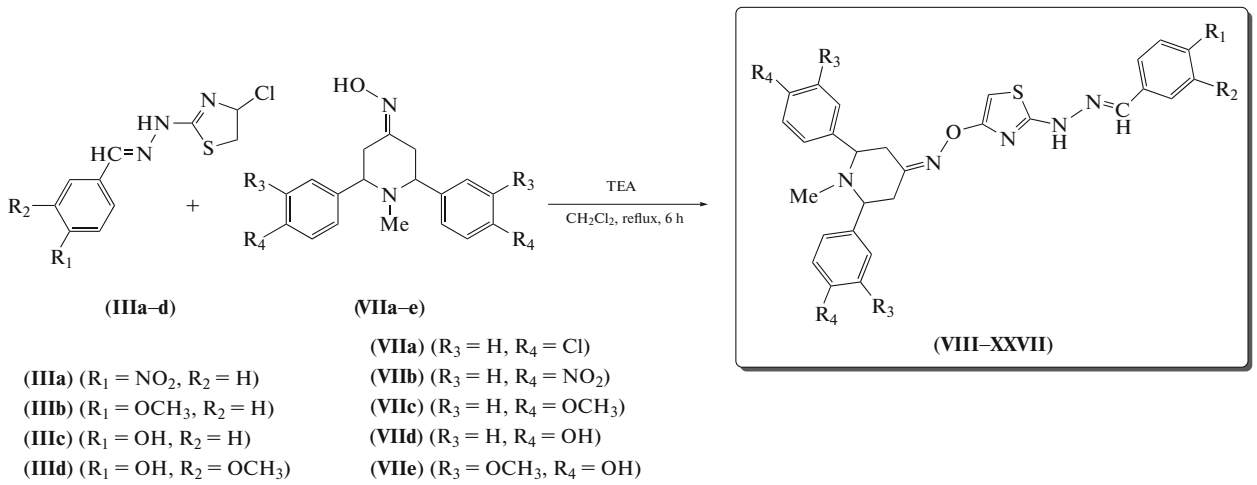
(substituted benzylidene)hydrazinyl)thiazoles (**IIIa–d**). IR spectrum showed the absence of $NH_2$ bands at 3417.57 $cm^{-1}$ and the presence of a sharp band at 3430.57–3435.0 $cm^{-1}$ due to NH. The $^1H$ NMR spectrum also revealed the absence of primary amine signals at δ (ppm) 8.40–8.52 (s, 2H, $NH_2$) and the presence of H-signal of the thiazole ring at δ (ppm) 7.0 (s, 1H, thiazole H) confirms the formation of key scaffolds (**IIIa–d**). The scaffolds 2,6-bis(substituted phenyl)-1-methylpiperidin-4-one oximes (**VIIa–e**) were accomplished via three-step reactions involving Mannich reaction of substituted benzaldehydes (**IVa–e**), acetone, and ammonium acetate to obtain 2,6-bis(substituted phenyl)-piperidin-4-one (**Va–e**) followed by *N*-methylation and oximation (Scheme 2) [3].




**Scheme 1.** Reaction protocol for the synthesis of 4-chloro-2-(2-(substituted benzylidene)hydrazinyl) thiazole (**IIIa–d**).




**Scheme 2.** Reaction protocol for the synthesis of 2,6-bis(substituted phenyl)-1-methylpiperidin-4-one oxime (**VIIa–e**).




**Scheme 3.** Synthesis of thiazole-based piperidinone oximes (**VIII–XXVII**).

Finally, 2,6-bis(substituted phenyl)-1-methylpiperidin-4-one oximes (**VIIa–e**) were incorporated with key scaffolds (**IIIa–d**) in the presence of triethylamine to obtain thiazole-based piperidinone oximes (**VIII–XXVII**) in good yields (Scheme 3). The $^1$H NMR spectrum showed the absence of oxime proton (N–OH) resonating at δ (ppm) 2.10–2.15 (s, 1H, NOH), which confirms the formation of target compounds (**VIII–XXVII**).

The results of the antioxidant assays revealed that majority of the synthesized compounds exerted a wide range of modest antioxidant activity [9]. Fifty percent inhibitory concentration ($IC_{50}$) values are depicted in Table 1. Initially, key scaffolds (**IIIa–d**) exhibited certain degree of antioxidant activity. Here, the thiazole nucleus itself acts as a reactive center towards the radical species and this reactivity may attribute to its high resonance stability and very low energy barrier towards

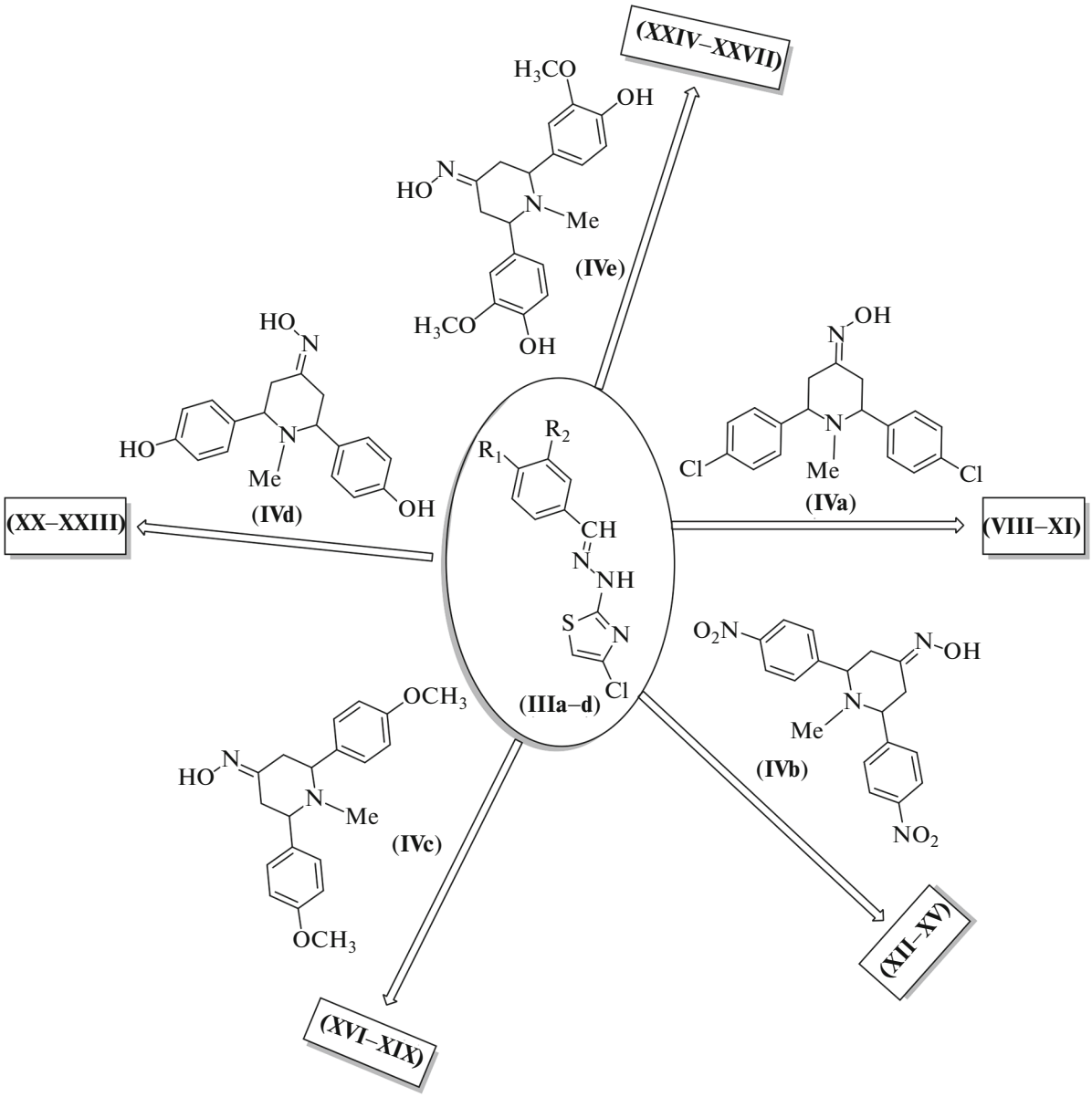



**Fig. 2.** Pathway rationale of target compounds.

radical reactions. In addition, the radical dissipation inside the thiazole system would be mandatory for the observed antioxidant activity [1]. Further, to explore the better antioxidant motifs, the key scaffolds (**IIIa–d**) were coupled with 2,6-bis(substituted phenyl)-1-methylpiperidin-4-one oximes (**VIIa–e**). Inclusion of piperidinone oximes into the key scaffolds played a vital role for significant enhancement of antioxidant activity. The electronic effects of substituents on C-4 terminals of phenyl ring attached to piperidin-4-one skeleton may also play an important role for enhanced antioxidant activity.

Nearly all the tested compounds, except (**VIII–XV**), acted as effective 2,2'-diphenyl-1-picrylhydrazyl (DPPH) free radical scavengers. Among the synthesized molecules, compounds (**XIX**), (**XXII**), (**XXIII**), (**XXVI**), and (**XXVII**) demonstrated significant radical scavenging activity (RSA) up to 13–15-fold higher than the key scaffolds (**IIIa–d**), which were more active than standard butylated hydroxy anisole (BHA). This may be due to the plenty electron donating hydroxyl and methoxy groups in the phenyl ring present on the either side of the piperidinone skeleton, as well as on phenyl ring attached to 2-hydrazinyl thiazole. Thus, free radical scavenging capacity primarily attributed to the high reactivity of hydroxyl substituents [10]. Compounds (**XXI**), (**XXIV**), (**XXV**), and (**XVIII**) also showed appreciable RSA, bearing 8–9 folds more activity than initial scaffolds (**IIIa–d**),

**Table 1.** Concentration required for 50% inhibition ($IC_{50}$) of DPPH and LPO radicals by the compounds (**IIIa**–**d**) and (**VIII**–**XXVII**) and the standard antioxidant compound BHA

| Compounds | Scavenging activity* | |
|---|---|---|
| | DPPH• | LPO• |
| **(IIIa)** | 162.1 ± 0.9 | 112.0 ± 0.1 |
| **(IIIb)** | 158.0 ± 0.5 | 105.0 ± 0.1 |
| **(IIIc)** | 151.0 ± 0.7 | 98.0 ± 0.2 |
| **(IIId)** | 140.0 ± 0.8 | 89.0 ± 0.1 |
| **(VIII)** | 132.0 ± 0.1 | 82.1 ± 0.4 |
| **(IX)** | 119.0 ± 0.1 | 77.2 ± 0.1 |
| **(X)** | 102.0 ± 0.6 | 68.3 ± 0.1 |
| **(XI)** | 98.0 ± 0.3 | 62.3 ± 0.4 |
| **(XII)** | 129.0 ± 0.1 | 78.2 ± 0.9 |
| **(XIII)** | 112.0 ± 0.4 | 72.1 ± 0.1 |
| **(XIV)** | 96.0 ± 0.7 | 62.0 ± 0.5 |
| **(XV)** | 79.0 ± 0.1 | 59.5 ± 0.1 |
| **(XVI)** | 51.0 ± 0.2 | 32.6 ± 0.8 |
| **(XVII)** | 38.0 ± 0.0 | 36.1 ± 0.2 |
| **(XVIII)** | 12.1 ± 0.3 | 5.8 ± 0.1 |
| **(XIX)** | 9.2 ± 0.1 | 4.8 ± 0.1 |
| **(XX)** | 32 ± 0.3 | 28.2 ± 0.4 |
| **(XXI)** | 19 ± 0.1 | 12.0 ± 0.5 |
| **(XXII)** | 10.2 ± 0.4 | 5.2 ± 0.7 |
| **(XXIII)** | 8.9 ± 0.2 | 4.5 ± 0.3 |
| **(XXIV)** | 26 ± 0.6 | 23.4 ± 0.7 |
| **(XXV)** | 15.2 ± 0.2 | 7.2 ± 0.3 |
| **(XXVI)** | 9.8 ± 0.5 | 5.0 ± 0.8 |
| **(XXVII)** | 8.2 ± 0.4 | 4.8 ± 0.2 |
| BHA | 12.0 ± 0.1 | 5.3 ± 0.2 |

* The values are expressed as μM concentration; lower $IC_{50}$ values indicate higher radical scavenging activity.

but slightly less than the reference compound. Meanwhile, derivatives (**XX**), (**XIV**), (**XV**), and (**XVII**) exhibited enhanced activity with 5–6 fold higher than that of (**IIIa**–**d**) because of the presence of electron-donating hydroxyl and methoxy groups on the piperidinone phenyl moiety and electron-withdrawing chloro/nitro group as C-4 substituent on phenyl ring attached to 2-hydrazinyl thiazole moiety. Compounds (**X**) and (**XI**) demonstrated marked decrease in RSA compared to standard. On the other hand, compounds (**VIII**) and (**XII**) showed least antioxidant activity. This could be due to the presence of chloro/nitro function at *para*-position of the phenyl rings.

The arrays of compounds having abilities to scavenge free radicals were further confirmed by inhibition of lipid peroxidation (LPO) assay in a liposome model system [11]. $IC_{50}$ values of LPO inhibition for the newly synthesized analogues are depicted in Table 1. The tested compounds (**VIII**–**XXVII**) exhibited varying range of antioxidant potency. Indeed, compounds (**XXII**), (**XXIII**), (**XXVI**), (**XXVII**), and (**XIX**) revealed potent LPO radical scavenger properties. Probably, this result is associated with the presence of hydroxyl groups at *para*-position of the phenyl rings and the unique geometry of the compounds. The next promising lipid peroxidation inhibitors are (**XXI**), (**XXIV**), (**XXV**), and (**XVIII**). On the other hand, compounds (**VIII**), (**IX**), (**X**), (**XI**), (**XII**), and (**XIII**) having electron-withdrawing chloro/nitro groups had appreciable antioxidant activity. The increasing order of LPO activity is as follows (**XXVII**) > (**XXIII**) > (**XIX**) > (**XXVI**) > (**XXII**) > **BHA** > (**XVIII**) > (**XXV**) > (**XXI**) > (**XXIV**) > (**XX**) > (**XVI**) > (**XVIII**) > (**XV**) > (**XIV**) > (**XI**) > (**X**) > (**XIII**) > (**IX**) > (**XII**) > (**VIII**) > (**IIId**) > (**IIIc**) > (**IIIb**) > (**IIIa**). The results of this assay revealed that most of the synthesized compounds exerted a wide range of modest antioxidant activity.

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 (gram-negative), *Staphylococcus aureus* ATCC 25923 **(**gram-positive), and *Pseudomonas aeruginosa* ATCC 27853 (gram-negative) by well plate method [12]. The results were obtained as zone of inhibition (mm). The majority of the synthesized compounds showed varying degree of inhibition against tested bacterial strains (Table 2). The reason would be the presence of sulfur in thiazole nucleus resulting. The nucleophilic character of sulfur might help in penetrating through the microbial cell wall easily, thereby arresting cell growth [13]. Among the synthesized derivatives, compounds (**VIII**) and (**XII**) exhibited enhanced antibacterial activity, which was also higher than that of standard streptomycin. The lipophilic nature of piperidinone core [14], along with the presence of electron withdrawing groups, like chloro/nitro groups at *para* position of all the phenyl rings, may contribute to the enhanced antibacterial activity. Halogens like chlorine, are very useful to modulate the electronic effects in phenyl rings. Chlorine has strong inductive electron-attracting effects, moreover these atoms may also influence the steric characteristics and the hydrophilic–hydrophobic balance of the molecules [15]. It is indicative that lipophilic and steric parameters are the prerequisites for these molecules to act as potent antimicrobial agents. The replacement of the nitro group by electron donating methoxy/hydroxyl functions as C-4 substituent in phenyl ring attached to 2-hydrazinyl thiazole in compounds (**IX**), (**X**), (**XIII**), and (**XIV**) resulted in slightly reduced activity compared to (**VIII**) and (**XII**). Substitution of methoxy and hydroxyl groups in phenyl ring attached to piperidinone skeleton in (**XVI**) and (**XX**) resulted in appreciable activity against *E. coli* and *P. aeruginosa* strains. Compounds (**XI**), (**XV**), (**XXI**), (**XXIV**), (**XXV**), (**XVII**), and (**XVIII**) showed moderate activity. Compounds (**XIX**), (**XXII**), (**XXIII**), (**XXVI**),

**Table 2.** Inhibitory zone (diameter, mm) of the synthesized compounds (**IIIa–d**) and (**VIII–XXVII**) against tested bacterial strains by well plate method

| Compounds | *Escherichia coli* | | *Staphylococcus aureus* | | *Pseudomonas aeruginosa* | |
|---|---|---|---|---|---|---|
| | 1000 | 500 | 1000 | 500 | 1000 | 500 |
| | Concentration, μg/mL | | | | | |
| **(IIIa)** | 5.0 ± 0.1 | 4.2 ± 0.2 | 4.4 ± 0.2 | 3.1 ± 0.1 | 6.3 ± 0.1 | 4.2 ± 0.2 |
| **(IIIb)** | 4.1 ± 0.2 | 3.1 ± 0.1 | 3.5 ± 0.1 | 2.3 ± 0.2 | 5.5 ± 0.1 | 2.3 ± 0.1 |
| **(IIIc)** | 3.0 ± 0.2 | 3.5 ± 0.3 | 2.6 ± 0.1 | 1.2 ± 0.1 | 3.4 ± 0.2 | 2.4 ± 0.2 |
| **(IIId)** | 3.4 ± 0.1 | 2.8 ± 0.1 | 2.4 ± 0.2 | 1.4 ± 0.2 | 3.3 ± 0.2 | 1.5 ± 0.1 |
| **(VIII)** | 20.1 ± 0.1 | 13.2 ± 0.1 | 18.8 ± 0.1 | 12.3 ± 0.1 | 23.7 ± 0.1 | 14.6 ± 0.1 |
| **(IX)** | 15.4 ± 0.2 | 12.0 ± 0.1 | 13.4 ± 0.1 | 9.2 ± 0.1 | 18.0 ± 0.1 | 10.3 ± 0.2 |
| **(X)** | 13.1 ± 0.2 | 11.5 ± 0.2 | 14.7 ± 0.2 | 8.2 ± 0.2 | 17.5 ± 0.2 | 9.3 ± 0.2 |
| **(XI)** | 12.2 ± 0.2 | 10.5 ± 0.1 | 11.0 ± 0.1 | 8.0 ± 0.2 | 14.3 ± 0.2 | 8.4 ± 0.1 |
| **(XII)** | 18.8 ± 0.3 | 10.1 ± 0.2 | 16.8 ± 0.1 | 10.5 ± 0.2 | 20.8 ± 0.2 | 12.4 ± 0.2 |
| **(XIII)** | 12.6 ± 0.1 | 8.3 ± 0.1 | 9.1 ± 0.2 | 8.4 ± 0.2 | 10.3 ± 0.1 | 8.1 ± 0.1 |
| **(XIV)** | 8.4 ± 0.1 | 7.3 ± 0.1 | 9.8 ± 0.1 | 7.7 ± 0.1 | 12.2 ± 0.1 | 8.2 ± 0.1 |
| **(XV)** | 11.6 ± 0.1 | 8.2 ± 0.1 | 9.3 ± 0.2 | 6.3 ± 0.1 | 12.5 ± 0.2 | 6.3 ± 0.1 |
| **(XVI)** | 13.4 ± 0.1 | 9.7 ± 0.1 | 10.9 ± 0.2 | 8.6 ± 0.1 | 17.3 ± 0.1 | 9.3 ± 0.1 |
| **(XVII)** | 10.2 ± 0.1 | 7.5 ± 0.2 | 8.7 ± 0.1 | 6.3 ± 0.1 | 11.7 ± 0.2 | 7.2 ± 0.1 |
| **(XVIII)** | 9.7 ± 0.2 | 5.1 ± 0.1 | 7.9 ± 0.2 | 5.4 ± 0.2 | 10.3 ± 0.2 | 6.6 ± 0.1 |
| **(XIX)** | 4.7 ± 0.1 | 3.4 ± 0.1 | 5.1 ± 0.2 | 3.8 ± 0.1 | 8.4 ± 0.1 | 4.5 ± 0.1 |
| **(XX)** | 11.0 ± 0.2 | 8.3 ± 0.1 | 9.7 ± 0.1 | 7.5 ± 0.1 | 14.5 ± 0.1 | 7.2 ± 0.2 |
| **(XXI)** | 8.3 ± 0.1 | 6.4 ± 0.1 | 8.2 ± 0.2 | 6.7 ± 0.2 | 10.5 ± 0.2 | 7.5 ± 0.2 |
| **(XXII)** | 6.5 ± 0.1 | 4.0 ± 0.2 | 5.2 ± 0.1 | 3.2 ± 0.1 | 9.1 ± 0.1 | 3.7 ± 0.2 |
| **(XXIII)** | 4.3 ± 0.2 | 3.8 ± 0.2 | 4.4 ± 0.1 | 2.3 ± 0.1 | 7.3 ± 0.1 | 3.3 ± 0.1 |
| **(XXIV)** | 7.7 ± 0.1 | 5.2 ± 0.2 | 8.9 ± 0.2 | 6.7 ± 0.2 | 12.4 ± 0.2 | 8.8 ± 0.1 |
| **(XXV)** | 7.1 ± 0.1 | 5.8 ± 0.2 | 7.5 ± 0.1 | 5.4 ± 0.1 | 8.3 ± 0.1 | 6.7 ± 0.1 |
| **(XXVI)** | 4.0 ± 0.2 | 3.1 ± 0.2 | 5.4 ± 0.1 | 2.1 ± 0.1 | 7.5 ± 0.1 | 2.5 ± 0.2 |
| **(XXVII)** | 10.2 ± 0.1 | 7.5 ± 0.2 | 8.7 ± 0.1 | 6.3 ± 0.1 | 11.7 ± 0.2 | 7.2 ± 0.1 |
| Streptomycin | 18.3 ± 0.1 | 10.2 ± 0.1 | 15.0 ± 0.2 | 10.5 ± 0.1 | 18.2 ± 0.1 | 125 ± 0.2 |

and (**XXVII**), holding electron-donating methoxy and hydroxyl substituents in phenyl rings, demonstrated least antibacterial activity compared to other analogues.

In vitro antifungal activity was evaluated against three pathogenic fungal species, namely *Aspergillus flavus* MTCC 3306, *Candida albicans* MTCC 3017, and *Chrysosporium keratinophilum* MTCC 2827 by well plate method [16]. Compounds (**XIX**), (**XXII**), (**XXIII**), (**XXVI**), and (**XXVII**) possessing electron donating methoxy and hydroxyl substituents failed to show good antifungal activity even at higher concentrations (Table 3). Compounds (**VIII**) and (**XII**) possessing chloro/nitro substituent at *para*-position of piperidinone phenyl rings emerged as active antifungal agents against all tested fungal strains compared with standard fluconazole. The introduction of methoxy function instead of nitro group at *para*-position on phenyl ring attached to 2-hydrazinyl thiazole in compounds (**IX**) and (**XIII**) made them the next potent antifungal agents. Meanwhile, the presence of hydroxyl substituent at C-4 atom in phenyl ring of 2-hydrazinyl thiazole, along with chloro group (compound (**X**)) and nitro group (compound (**XI**)) at *para*-position of phenyl rings attached to piperidinone skeleton resulted in moderate activity. However, compounds (**XI**), (**XV**), (**XVII**), (**XX**), and (**XXIV**) showed appreciable activity against the *C. keratinophilum* strain whereas its activity against *C. albicans* and *A. flavus* was diminished. Notable decrease in antifungal activity was observed for compounds (**XXIII**) and (**XXVII**) with electron-withdrawing nitro/chloro group replaced by hydroxyl/methoxy substituents. It is tempting to speculate that the results of the antimicrobial activity of the different derivatives appear to be related to the nature of substituent on the *para*-position of the phenyl rings.

**Table 3.** Inhibitory zone (diameter, mm) of the synthesized compounds (**IIIa–d**) and (**VIII–XXVII**) against tested fungal strains by well plate method

| Compounds | *Aspergillus flavus* | | *Chrysosporium keratinophilum* | | *Candida albicans* | |
|---|---|---|---|---|---|---|
| | 1000 | 500 | 1000 | 500 | 1000 | 500 |
| | Concentration, μg/mL | | | | | |
| **(IIIa)** | 5.2 ± 0.1 | 4.2 ± 0.2 | 6.5 ± 0.1 | 5.1 ± 0.2 | 8.3 ± 0.1 | 5.2 ± 0.1 |
| **(IIIb)** | 4.1 ± 0.2 | 3.3 ± 0.2 | 4.7 ± 0.2 | 2.4 ± 0.1 | 6.4 ± 0.2 | 4.3 ± 0.1 |
| **(IIIc)** | 2.4 ± 0.2 | 2.2 ± 0.1 | 3.1 ± 0.2 | 2.3 ± 0.2 | 4.7 ± 0.2 | 2.1 ± 0.2 |
| **(IIId)** | 2.7 ± 0.1 | 2.3 ± 0.2 | 3.4 ± 0.1 | 1.9 ± 0.1 | 4.0 ± 0.1 | 1.8 ± 0.1 |
| **(VIII)** | 15.5 ± 0.2 | 12.2 ± 0.1 | 19.3 ± 0.2 | 17.2 ± 0.1 | 23.4 ± 0.1 | 22.3 ± 0.2 |
| **(IX)** | 12.7 ± 0.2 | 9.5 ± 0.1 | 16.4 ± 0.1 | 13.5 ± 0.1 | 18.2 ± 0.1 | 17.7 ± 0.2 |
| **(X)** | 9.8 ± 0.2 | 7.1 ± 0.2 | 15.6 ± 0.2 | 12.4 ± 0.2 | 17.3 ± 0.2 | 16.3 ± 0.2 |
| **(XI)** | 8.4 ± 0.2 | 6.2 ± 0.1 | 14.3 ± 0.2 | 11.8 ± 0.2 | 13.9 ± 0.2 | 10.9 ± 0.1 |
| **(XII)** | 13.4 ± 0.3 | 10.5 ± 0.2 | 17.6 ± 0.1 | 15.4 ± 0.2 | 20.7 ± 0.2 | 21.4 ± 0.2 |
| **(XIII)** | 10.8 ± 0.1 | 8.4 ± 0.1 | 10.3 ± 0.2 | 9.7 ± 0.2 | 12.8 ± 0.2 | 10.9 ± 0.1 |
| **(XIV)** | 8.3 ± 0.1 | 5.4 ± 0.1 | 9.3 ± 0.1 | 8.3 ± 0.1 | 12.2 ± 0.1 | 10.4 ± 0.1 |
| **(XV)** | 6.4 ± 0.1 | 5.2 ± 0.1 | 13.6 ± 0.2 | 10.6 ± 0.1 | 12.3 ± 0.2 | 9.5 ± 0.1 |
| **(XVI)** | 11.8 ± 0.1 | 9.3 ± 0.1 | 15.8 ± 0.2 | 14.6 ± 0.1 | 17.3 ± 0.1 | 19.3 ± 0.1 |
| **(XVII)** | 7.4 ± 0.1 | 4.7 ± 0.2 | 9.5 ± 0.1 | 8.6 ± 0.1 | 11.2 ± 0.2 | 10.6 ± 0.1 |
| **(XVIII)** | 4.1 ± 0.2 | 3.3 ± 0.1 | 7.5 ± 0.2 | 6.4 ± 0.2 | 10.1 ± 0.2 | 9.3 ± 0.1 |
| **(XIX)** | 3.8 ± 0.1 | 2.5 ± 0.2 | 5.7 ± 0.1 | 4.5 ± 0.1 | 9.2 ± 0.1 | 8.3 ± 0.1 |
| **(XX)** | 6.4 ± 0.2 | 5.8 ± 0.1 | 16.8 ± 0.1 | 12.4 ± 0.1 | 16.4 ± 0.1 | 14.8 ± 0.2 |
| **(XXI)** | 6.3 ± 0.1 | 5.6 ± 0.1 | 8.6 ± 0.2 | 7.7 ± 0.2 | 10.1 ± 0.2 | 11.2 ± 0.2 |
| **(XXII)** | 3.2 ± 0.1 | 2.5 ± 0.2 | 6.4 ± 0.1 | 5.5 ± 0.1 | 9.3 ± 0.1 | 8.5 ± 0.2 |
| **(XXIII)** | 3.1 ± 0.3 | 2.6 ± 0.1 | 4.2 ± 0.2 | 2.7 ± 0.1 | 5.1 ± 0.1 | 3.1 ± 0.1 |
| **(XXIV)** | 5.6 ± 0.1 | 3.6 ± 0.2 | 11.5 ± 0.2 | 10.2 ± 0.2 | 13.7 ± 0.2 | 12.9 ± 0.1 |
| **(XXV)** | 5.9 ± 0.1 | 4.6 ± 0.2 | 6.9 ± 0.1 | 5.5 ± 0.1 | 8.5 ± 0.1 | 7.6 ± 0.1 |
| **(XXVI)** | 3.0 ± 0.2 | 3.7 ± 0.2 | 6.5 ± 0.1 | 4.7 ± 0.1 | 9.8 ± 0.1 | 6.3 ± 0.2 |
| **(XXVII)** | 2.3 ± 0.1 | 1.4 ± 0.1 | 3.4 ± 0.1 | 2.3 ± 0.1 | 5.4 ± 0.1 | 4.3 ± 0.1 |
| Fluconazole | 13.2 ±0.1 | 12.3 ± 0.2 | 17.7 ± 0.2 | 16.2 ± 0.1 | 22.3 ± 0.2 | 20.4 ± 0.2 |

## EXPERIMENTAL

All the reagents used were purchased from Merck (Darmstadt, Germany); chemicals were of AR grade and were used without further purification. Melting points were determined by using an open capillary method and are uncorrected. Thin layer chromatography (TLC) was performed with aluminum sheets–Silica gel 60 F254 purchased from Merck. The synthesized compounds were purified using column chromatography with silica gel (60–120 mesh) in hexane–ethylacetate (8 : 2) as eluent. IR spectra (ν, $cm^{-1}$) were recorded with a Nicolet 5700 FT-IR spectrophotometer using KBr Wafer technique. $^1H$ NMR and $^{13}C$ NMR spectra were recorded at 400 and 100 MHz, respectively, in a Bruker spectrometer using DMSO-$d_6$ as a solvent for all the compounds. Micro analytical data were obtained by Elemental-Vario EL-III and mass spectra were recorded with a Waters-Q-TOF Ultima spectrometer.

### *Preparation of 2,6-bis(Substituted phenyl)-1-Methylpiperidin-4-one O-2-(2-(4-Chlorobenzylidene)hydrazinyl)thiazol-4-yl Oximes (VIII–XXVII)*

An equimolar mixture of 4-chloro-2-(2-(substituted benzylidene)hydrazinyl)thiazoles (**IIIa–d**) (1 mmol), 2,6-bis(substituted phenyl)-1-methylpiperidin-4-one oximes (**VIIa–e**) (1 mmol), and triethylamine (1 mmol) was refluxed for 6 h in dichloromethane (10 mL). Then, the product was poured into ice-cold water. The precipitate was collected by filtration and recrystallized with methanol to obtain products (**VIII–XXVII**) in good yields.

**2,6-Bis(4-chlorophenyl)-1-methylpiperidin-4-one *O*-(2-(2-(4-nitrobenzylidene)hydrazinyl)thiazol-4-yl) oxime (VIII).** White solid; yield 82%; mp 120–123°C.

Anal. calcd. for $C_{28}H_{24}Cl_2N_6O_3S$ (594.16): C, 56.47; H, 4.06; N, 14.11; found: C, 56.44; H, 4.02; N, 14.08%. IR: 3417.57 (N–H), 3051–2956 (Ar-CH), 1628 (C=N). $^1$H NMR: 8.03 (s, 1H, HC=N), 7.68–6.97 (m, 13H, Ar-H), 4.01 (s, 1H, NH), 3.90–3.86 (t, 2H, CH), 3.11–2.71 (m, 4H, $CH_2$), 1.92 (s, 3H, N–$CH_3$). $^{13}$C NMR: 172.0, 170.35, 160.0, 158.1, 156.41, 143.82, 139.1, 134.0, 133.3, 132.41, 131.8, 129.69, 127.77, 110.1, 67.78, 66.0, 42.0, 41.43, 37.38, 36.29.

**2,6-Bis(4-chlorophenyl)-1-methylpiperidin-4-one *O*-2-(2-(4-methoxybenzylidene) hydrazinyl)thiazol-4-yl oxime (IX).** Yellow solid; yield 87%; mp 160–162°C. Anal. calcd. for $C_{29}H_{27}Cl_2N_5O_2S$ (579.15): C, 60.00; H, 4.69; N, 12.06; found: C, 60.12; H, 4.72; N, 12.51%. IR: 3407.87 (N–H), 3058–2967 (Ar-CH), 1627 (C=N). $^1$H NMR: 8.07 (s, 1H, HC=N), 7.89–7.27 (m, 13H, Ar-H), 7.12 (s, 1H, thiazole carbon), 4.40 (s, 1H, NH), 3.90–3.86 (m, 2H, CH), 3.82 (s, 3H, $OCH_3$), 3.29–3.14 (m, 4H, $CH_2$), 1.92 (s, 3H, N–$CH_3$). $^{13}$C NMR: 170.35, 156.41, 143.82, 139, 127, 134, 133.3, 132.41, 131.8, 129.69, 127.77, 67.78, 65.38, 41.43, 37.38, 36.29.

**2,6-Bis(4-chlorophenyl)-1-methylpiperidin-4-one *O*-2-(2-(4-hydroxybenzylidene)hydrazinyl) thiazol-4-yl oxime (X).** White solid; yield 92%; mp 134–136°C. Anal. calcd. for $C_{28}H_{25}Cl_2N_5O_2S$ (565.13): C, 59.36; H, 4.45; N, 12.36; found: C, 59.34; H, 4.41; N, 12.38%. IR: 3419.57 (N–H), 3072–2941 (Ar-CH), 1625 (C=N). $^1$H NMR: 8.14–7.72 (m, 13H, Ar-H),8.01 (s, 1H, HC=N), 7.10 (s, 1H, thiazole carbon), 5.30 (s, 1H, OH), 4.10 (s, 1H, NH), 3.86–3.78 (m, 2H, CH), 3.21–3.14 (m, 4H, $CH_2$), 1.76 (s, 3H, N–$CH_3$). $^{13}$C NMR: 170.35, 156.41, 143.82, 139, 127, 134, 133.3, 132.41, 131.8, 129.69, 127.77, 67.78, 65.38, 41.43, 37.38, 36.29.

**2,6-Bis(4-chlorophenyl)-1-methylpiperidin-4-one *O*-(2-(2-(4-hydroxy-3-methoxy benzylidene)hydrazinyl)thiazol-4-yl) oxime (XI).** Yellow solid; yield 88%; mp 167–169°C. Anal. calcd. for $C_{29}H_{27}Cl_2N_5O_3S$ (595.19): C, 58.39; H, 4.56; N, 11.74; found: C, 58.31; H, 4.53; N, 11.71%. IR: 3416.57 (N–H), 3047–2958 (Ar-CH), 1629 (C=N). $^1$H NMR: 8.03 (s, 1H, HC=N), 8.01–7.57 (m, 12H, Ar-H), 7.04 (s, 1H, thiazole carbon), 5.34 (s, 1H, OH), 3.96 (s, 1H, NH), 3.89–3.85 (m, 2H, CH), 3.81 (s, 3H, $OCH_3$), 3.29–3.14 (m, 4H, $CH_2$), 1.84 (s, 3H, N–$CH_3$). $^{13}$C NMR: 169.25, 155.81, 142.82, 138, 129, 134.52, 133.55, 131.41, 130.08, 129.19, 126.77, 66.78, 64.58, 55.62, 42.53, 38.38, 36.89.

**1-Methyl-2,6-bis(4-nitrophenyl)piperidin-4-one *O*-2-(2-(4-nitrobenzylidene)hydrazinyl)thiazol-4-yl oxime (XII).** Yellow solid; yield; 79%; mp 117–119°C. Anal. calcd. for $C_{28}H_{24}N_8O_7S$ (616.16): C, 54.54; H, 3.92; N, 18.17; found: C, 54.52 H, 3.90; N, 18.16%. IR: 3417.67 (N–H), 3058–2959 (Ar-CH), 1624 (C=N). $^1$H NMR: 8.29–6.92 (m, 13H, Ar-H), 8.03 (s, 1H, HC=N), 7.11 (s, 1H, thiazole carbon), 4.00 (s, 1H, NH), 3.90–3.86 (m, 2H, CH), 3.29–3.14 (m, 4H, $CH_2$), 1.92 (s, 3H, N–$CH_3$). $^{13}$C NMR: 172.44, 158.23, 144.82, 139, 128, 136.56, 134.53, 132.05, 131.82, 130.54, 128.17, 67.72, 66.47, 41.11, 37.58, 34.29.

**1-Methyl-2,6-bis(4-nitrophenyl)piperidin-4-one *O*-2-(2-(4-methoxybenzylidene)hydrazinyl)thiazol-4-yl oxime (XIII).** Yellow solid; yield; 88%; mp 160–162°C. Anal. calcd. for $C_{29}H_{27}N_7O_6S$ (601.17) C, 57.23; H, 4.29; N, 16.69 found: C, 57.24; H, 4.25; N, 16.61%. IR: 3421.57 (N–H), 3068–2967 (Ar-CH), 1629 (C=N). $^1$H NMR: 7.93 (s, 1H, HC=N), 7.73–7.07 (m, 13H, Ar-H), 7.05 (s, 1H, thiazole carbon), 4.03 (s, 1H, NH), 3.88–3.84 (m, 2H, CH), 3.80 (s, 3H, $OCH_3$), 3.21–3.10 (m, 4H, $CH_2$), 1.92 (s, 3H, N–$CH_3$). $^{13}$C NMR: 171.05, 155.11, 143.52, 138.41, 126.45, 135.36, 133.43, 132.62, 130.73, 128.69, 127.41, 67.69, 65.58, 41.52, 37.38, 36.52.

**1-Methyl-2,6-bis(4-nitrophenyl)piperidin-4-one *O*-2-(2-(4-hydroxybenzylidene)hydrazinyl)thiazol-4-yl oxime (XIV).** Pale yellow solid; yield 94%; mp 156–158°C. Anal. calcd. for $C_{28}H_{25}N_7O_6S$ (587.19): C, 57.23; H, 4.29; N, 16.69; found: C, 57.24; H, 4.25; N, 16.61%. IR: 3417.17 (N–H), 3067–2953 (Ar-CH), 1630 (C=N). $^1$H NMR 7.93 (s, 1H, HC=N), 7.73–7.07 (m, 13H, Ar-H), 7.05 (s, 1H, thiazole carbon), 5.35 (s, 1H, OH), 4.03 (s, 1H, NH), 3.88–3.84 (m, 2H, CH), 3.21–3.10 (m, 4H, $CH_2$), 1.92 (s, 3H, N–$CH_3$). $^{13}$C NMR 171.05, 155.11, 143.52, 138.41, 126.45, 135.36, 133.43, 132.62, 130.73, 128.69, 127.41, 67.69, 65.58, 41.52, 37.38, 36.52.

**1-Methyl-2,6-bis(4-nitrophenyl)piperidin-4-one *O*-(2-(2-(4-hydroxy-3-methoxybenzylidene)hydrazinyl)-thiazol-4-yl) oxime (XV).** Brown solid; yield 92%; mp 147–149°C. Anal. calcd. for $C_{29}H_{27}N_7O_7S$ (617.13) C, 56.39; H, 4.41; N, 15.87; found: C, 56.35; H, 4.46; N, 15.88%. IR: 3417.97 (N–H), 3045–2956 (Ar-CH), 1624 (C=N). $^1$H NMR: 7.78 (s, 1H, HC=N), 7.72–7.35 (m, 12H, Ar-H), 7.11 (s, 1H, thiazole carbon), 5.30 (s, 1H, OH), 4.00 (s, 1H, NH), 3.90–3.86 (m, 2H, CH), 3.29–3.14 (m, 4H, $CH_2$), 1.92 (s, 3H, N–$CH_3$). $^{13}$C NMR: 170.55, 156.62, 143.83, 138.52, 126.63, 134.15, 133.31, 130.41, 130.58, 129.19, 127.72, 69.78, 65.35, 55.41, 41.53, 37.52, 36.51.

**2,6-Bis(4-methoxyphenyl)-1-methylpiperidin-4-one *O*-(2-(2-(4-nitrobenzylidene)hydrazinyl)thiazol-4-yl) oxime (XVI).** Off white solid; yield 81%; mp 146–148°C. Anal. calcd. for $C_{30}H_{30}N_6O_5S$ (586.17): C, 61.42; H, 5.15; N, 14.33; found: C, 61.45; H, 5.14; N, 14.31%. IR: 3417.17 (N–H), 3025–2948 (Ar-CH), 1631 (C=N). $^1$H NMR: 8.30–6.59 (m, 13H, Ar-H), 8.03 (s, 1H, HC=N), 7.09 (s, 1H, thiazole carbon), 4.20 (s, 1H, NH), 3.90–3.86 (m, 2H, CH), 3.84 (s, 3H, $OCH_3$), 3.82 (s, 3H, $OCH_3$), 3.25–3.16 (m, 4H, $CH_2$), 1.78 (s, 3H, N–$CH_3$). $^{13}$C NMR: 172.35, 155.31, 144.82, 139.45, 129.52, 134.59, 133.56, 132.51,

131.58, 128.69, 127.14, 67.68, 65.28, 41.53, 36.38, 35.59.

**2,6-Bis(4-methoxyphenyl)-1-methylpiperidin-4-one *O*-(2-(2-(4-methoxybenzylidene)hydrazinyl)thiazol-4-yl) oxime (XVII).** Brown solid; yield 76%; mp 150–152°C. Anal. calcd. for $C_{31}H_{33}N_5O_4S$ (571.21) C, 65.13; H, 5.82; N, 12.25; found: C, 65.13; H, 5.82; N, 12.25%. IR: 3417.27 (N–H), 3029–2956, (Ar-CH), 1625 (C=N). $^1$H NMR: 8.07–6.75 (m, 13H, Ar-H), 8.03 (s, 1H, HC=N), 7.03 (s, 1H, thiazole carbon), 4.00 (s, 1H, NH), 3.93–3.87 (m, 2H, CH), 3.85 (s, 3H, $OCH_3$), 3.83 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 3.16–3.01 (m, 4H, $CH_2$), 1.68 (s, 3H, N–$CH_3$). $^{13}$C NMR: 171.52, 155.21, 142.82, 138.58, 126.75, 134.51, 133.59, 132.21, 130.56, 129.99, 126.57, 67.78, 66.38, 55.65, 55.21, 42.53, 37.68, 36.19.

**2,6-Bis(4-methoxyphenyl)-1-methylpiperidin-4-one *O*-(2-(2-(4-hydroxybenzylidene)hydrazinylthiazol-4-yl) oxime (XVIII).** Off white solid; yield 91%; mp 148–150°C. Anal. calcd. for $C_{30}H_{31}N_5O_4S$ (557.21): C, 64.61; H, 5.60; N, 12.56; found: C, 64.64; H, 5.62; N, 12.58%. IR: 3414.57 (N–H), 3064–3029 (Ar-CH), 1631 (C=N); $^1$H NMR: 8.25–7.65 (m, 13H, Ar-H), 8.03 (s, 1H, HC=N), 7.05 (s, 1H, thiazole carbon), 5.29 (s, 1H, OH), 4.00 (s, 1H, NH), 3.98 (s, 3H, $OCH_3$), 3.96 (s, 3H, $OCH_3$), 3.90–3.86 (m, 2H, CH), 3.29–3.14 (m, 4H, $CH_2$), 1.92 (s, 3H, N–$CH_3$). $^{13}$C NMR: 170.41, 157.41, 143.86, 138.26, 128.63, 135.54, 134.51, 130.41, 129.86, 128.69, 127.27, 69.78, 66.38, 55.89, 42.03, 37.18, 36.59.

**2,6-Bis(4-methoxyphenyl)-1-methylpiperidin-4-one *O*-(2-(2-(4-hydroxy-3-methoxybenzylidene)hydrazinyl)thiazol-4-yl) oxime (XIX).** Yellow solid; yield 94%; mp 155–157°C. Anal. calcd. for $C_{31}H_{33}N_5O_5S$ (587.24) C, 63.36; H, 5.66; N, 11.92; found: C, 63.32; H, 5.61; N, 11.90%. IR: 3417.67 (N–H), 3032–2986 (Ar-CH), 1628 (C=N). $^1$H NMR: 7.81 (s, 1H, HC=N), 7.52–6.95 (m, 12H, Ar-H), 7.11 (s, 1H, thiazole carbon), 5.29 (s, 1H, OH), 4.04 (s, 1H, NH), 3.84 (s, 3H, $OCH_3$), 3.83–3.80 (m, 2H, CH), 3.82 (s, 3H, $OCH_3$), 3.73 (s, 3H, $OCH_3$), 3.34–3.14 (m, 4H, $CH_2$), 1.71 (s, 3H, N–$CH_3$). $^{13}$C NMR: 172.35, 157.28, 144.82, 138.54, 129.51, 135.25, 133.45, 132.10, 131.15, 129.68, 127.12, 68.78, 66.38, 55.78, 42.03, 37.30, 35.20.

**2,6-Bis(4-hydroxyphenyl)-1-methylpiperidin-4-one *O*-(2-(2-(4-nitrobenzylidene)hydrazinyl)thiazol-4-yl) oxime (XX).** Off white solid. yield 84%; mp 165–168°C. Anal. calcd. for $C_{28}H_{26}N_6O_5S$ (558.12): C, 60.20; H, 4.69; N, 15.04 found: C, 60.21; H, 4.65; N, 15.03%. IR: 3417.49 (N–H), 3081–2954 (Ar-CH), 1625 (C=N). $^1$H NMR: 8.33–6.89 (m, 13H, Ar-H), 8.01 (s, 1H, HC=N), 7.08 (s, 1H, thiazole carbon), 6.10 (s, 1H, OH), 6.13 (s, 1H, OH), 4.12 (s, 1H, NH), 3.90–3.86 (m, 2H, CH), 3.29–3.14 (m, 4H, $CH_2$), 1.94 (s, 3H, N–$CH_3$). $^{13}$C NMR: 168.35, 158.41, 144.82, 138.25, 129.24, 135.48, 134.71.3, 132.41, 131.8, 129.71, 126.81, 68.78, 65.53, 40.43, 38.28, 36.29.

**2,6-Bis(4-hydroxyphenyl)-1-methylpiperidin-4-one *O*-(2-(2-(4-methoxybenzylidene)hydrazinyl)thiazol-4-yl) oxime (XXI).** Brown solid; yield 78%; mp 158–160°C. Anal. calcd. for $C_{29}H_{29}N_5O_4S$ (543.14): C, 64.07; H, 5.38; N, 12.88; found: C, 64.05; H, 5.36; N, 12.85%. IR: 3417.43 (N–H), 3064-2953 (Ar-CH), 1628 (C=N). $^1$H NMR: 8.13 (s, 1H, HC=N), 7.64–7.27 (m, 13H, Ar-H), 7.10 (s, 1H, thiazole carbon), 6.28 (s, 1H, OH), 6.26 (s, 1H, OH), 4.08 (s, 1H, NH), 3.81 (s, 3H, $OCH_3$), 3.78–3.69 (m, 2H, CH), 3.29–3.14 (m, 4H, CH2), 1.92 (s, 3H, N–$CH_3$). $^{13}$C NMR: 170.54, 156.01, 143.80, 138.45, 128.47, 134.47, 133.45, 132.89, 131.63, 129.79, 128.33, 67.15, 65.19, 55.52, 41.52, 37.26, 35.69.

**2,6-Bis(4-hydroxyphenyl)-1-methylpiperidin-4-one *O*-(2-(2-(4-hydroxybenzylidene)hydrazinyl)thiazol-4-yl) oxime (XXII).** White solid; yield 89%; mp 131–133°C. Anal. calcd. for $C_{28}H_{27}N_5O_4S$ (529.15): C, 63.50; H, 5.14; N, 13.22; found: C, 63.52; H, 5.12; N, 13.20%. IR: 3417.87 (N–H), 3057–2972 (Ar-CH), 1628 (C=N). $^1$H NMR 8.03 (s, 1H, HC=N), 7.89–7.32 (m, 13H, Ar-H), 7.01 (s, 1H, thiazole carbon), 6.35 (s, 1H, OH), 6.33 (s, 2H, OH), 4.04 (s, 1H, NH), 3.86–3.75 (m, 2H, CH), 3.29–3.14 (m, 4H, $CH_2$), 1.94 (s, 3H, N–$CH_3$). $^{13}$C NMR: 168.78, 156.65, 142.82, 139.58, 127.61, 134.41, 132.45, 131.41, 130.25, 129.32, 128.77, 67.88, 65.36, 41.44, 37.32, 34.85.

**2,6-Bis(4-hydroxyphenyl)-1-methylpiperidin-4-one *O*-(2-(2-(4-hydroxy-3-methoxybenzylidene)hydrazinyl)thiazol-4-yl) oxime (XXIII).** Yellow solid; yield 93%; mp 164–166°C. Anal. calcd. for $C_{29}H_{29}N_5O_5S$ (559.15): C, 62.24; H, 5.22; N, 12.51; found: C, 62.22; H, 5.20; N, 12.53%. IR: 3418.57 (N–H), 3057–2983 (Ar-CH), 1628 (C=N). $^1$H NMR: 7.82 (s, 1H, HC=N), 7.76–7.35 (m, 12H, Ar-H), 7.04 (s, 1H, thiazole carbon), 6.55 (s, 1H, OH), 6.53 (s, 1H, OH), 5.83 (s, 1H, OH), 4.05 (s, 1H, NH), 3.86–3.90 (m, 2H, CH), 3.82 (s, 3H, $OCH_3$), 3.27–3.14 (m, 4H, $CH_2$), 1.92 (s, 3H, N–$CH_3$). $^{13}$C NMR: 172.35, 155.42, 145.72, 139.41, 128.31, 134.12, 133.78, 132.45, 131.44, 129.69, 125.17, 67.75, 64.18, 41.42, 36.51, 35.29.

**2,6-Bis(4-hydroxy-3-methoxyphenyl)-1-methylpiperidin-4-one *O*-2-(2-(4-nitro benzyli-dene)hydrazinyl)thiazol-4-yl oxime (XXIV).** Yellow solid; yield 76%; mp 134–136°C. Anal. calcd. for $C_{30}H_{30}N_6O_7S$ (618.20): C, 58.24; H, 4.89; N, 13.58; found: C, 58.28; H, 4.82; N, 13.51%. IR: 3416.57 (N–H), 3067–2958 (Ar-CH), 1624 (C=N). $^1$H NMR: 8.30–6.69 (m, 10H, Ar-H), 7.96 (s, 1H, HC=N), 7.10 (s, 1H, thiazole carbon), 6.33 (s, 1H, OH), 6.29 (s, 1H, OH), 4.08 (s, 1H, NH), 3.77–3.68 (m, 2H, CH), 3.86 (s, 3H, $OCH_3$), 3.88 (s, 3H, $OCH_3$), 3.34–2.18 (m, 4H, $CH_2$), 1.88 (s, 3H, N–$CH_3$). $^{13}$C NMR: 168.35,

156.41, 143.12, 138.41, 127.23, 133.58, 133.01, 132.41, 131.16, 129.29, 127.77, 66.54, 65.38, 55.62, 54.23, 41.23, 37.21, 35.29.

**2,6-Bis(4-hydroxy-3-methoxyphenyl)-1-methylpiperidin-4-one *O*-2-(2-(4-methoxybenzylidene)hydrazinyl)thiazol-4-yl oxime (XXV).** Brown solid; yield 75%; mp 172–174°C. Anal. calcd. for $C_{31}H_{33}N_5O_6S$ (603.20): C, 61.68; H, 5.51; N, 11.60; found: C, 61.65; H, 5.49; N, 11.58%. IR: 3417.14 (N–H), 3045–2967 (Ar-CH), 1628 (C=N). $^1$H NMR: 7.98 (s, 1H, HC=N), 7.70–6.57 (m, 11H, Ar-H) 7.03 (s, 1H, thiazole carbon), 5.50 (s, 1H, OH), 5.47 (s, 1H, OH), 4.06 (s, 1H, NH), 3.82 (s, 3H, $OCH_3$), 3.80 (s, 3H, $OCH_3$), 3.69 (s, 3H, $OCH_3$), 3.51–3.41 (m, 2H, CH), 3.18–2.04 (m, 4H, $CH_2$), 1.87 (s, 3H, N–$CH_3$). $^{13}$C NMR: 169.52, 155.41, 146.81, 139.46, 128.47, 134.54, 133.74, 132.21, 131.98, 129.22, 127.77, 67.72, 64.38, 55.58, 54.23, 42.13, 36.68, 36.21.

**2,6-Bis(4-hydroxy-3-methoxyphenyl)-1-methylpiperidin-4-one *O*-2-(2-(4-hydroxybenzylidene)hydrazinyl)thiazol-4-yl oxime (XXVI).** Off white solid; yield 84%; mp 125–127°C. Anal. calcd. for $C_{30}H_{31}N_5O_6S$ (589.23): C, 61.11; H, 5.30; N, 11.88; found: C, 61.14; H, 5.32; N, 11.86%. IR: 3417.67 (N–H), 3067–2938 (Ar-CH), 1628 (C=N). $^1$H NMR: 7.93 (s, 1H, HC=N), 7.69–6.67 (m, 11H, Ar-H) 7.01 (s, 1H, thiazole carbon), 5.50 (s, 1H, OH), 5.48 (s, 1H, OH), 5.40 (s, 1H, OH), 4.06 (s, 1H, NH), 3.82 (s, 3H, $OCH_3$), 3.80 (s, 3H, $OCH_3$), 3.47–3.41 (m, 2H, CH), 3.18–2.04 (m, 4H, $CH_2$), 1.87 (s, 3H, N–$CH_3$). $^{13}$C NMR: 172.45, 157.41, 142.82, 137.41, 128.29, 134.11, 133.35, 131.41, 130.38, 129.09, 127.70, 67.71, 65.26, 56.15, 55.46, 40.58, 37.22, 35.29.

**2,6-Bis(4-hydroxy-3-methoxyphenyl)-1-methylpiperidin-4-one *O*-(2-(2-(4-hydroxy-3-methoxy benzylidene)hydrazinyl)thiazol-4-yl) oxime (XXVII).** Off white solid; yield 89%; mp 157–159°C. Anal. calcd. for $C_{31}H_{33}N_5O_7S$ (619.42) C, 60.08; H, 5.37; N, 11.30; found: C, 60.04; H, 5.32; N, 11.33%. IR: 3417.77 (N–H), 3089–2951 (Ar-CH), 1628 (C=N). $^1$H NMR: 7.78 (s, 1H, HC=N), 7.72–6.67 (m, 10H, Ar-H), 7.01 (s, 1H, thiazole carbon), 6.53 (s, 1H, OH), 6.52 (s, 1H, OH), 6.50 (s, 1H, OH), 4.06 (s, 1H, NH), 3.90–3.87 (m, 2H, CH), 3.85 (s, 3H, $OCH_3$), 3.83 (s, 3H, $OCH_3$) 3.80 (s, 3H, $OCH_3$), 3.29–3.14 (m, 4H, $CH_2$), 1.90 (s, 3H, N–$CH_3$). $^{13}$C NMR: 171.10, 154.41, 145.82, 140.45, 134.52, 133.49, 132.43, 131.28, 129.56, 127.67, 127.23, 67.78, 65.38, 55.52, 54.23, 54.02, 40.83, 37.35, 36.21.

In **DPPH radical scavenging assay**, solutions of different concentrations (10, 25, 50, 100, 200, and 500 μM) of the synthesized compounds (**VIII**–**XXVII**) were prepared in distilled ethanol. To 1 mL of each compound solution, 4 mL of 0.1 mM ethanol solution of DPPH was added, and the tube was shaken vigorously. Then, they were incubated in the dark room at RT for 20 min. BHA was used as internal standard. A DPPH blank was prepared without the compounds and ethanol was used for the baseline correction. Changes (decrease) in the absorbance at 517 nm were measured using a UV-visible spectrophotometer and the remaining DPPH was calculated. The percent decrease in the absorbance was recorded for each concentration and percent quenching of DPPH was calculated on the basis of the observed decrease in absorbance of the radical. The radical scavenging activity was expressed as the inhibition percentage.

In the **inhibition of microsomal lipid peroxidation assay**, liver excised from adult male Wistar rat, was homogenized in 0.02 M Tris buffer, pH 7.4 (20 g/100 mL liquid). Microsomes were isolated by the calcium aggregation method. In the assay, 100 μL of liver microsomal suspension (0.5 mg protein) was incubated with 1 mmol/L each of $FeSO_4$ and ascorbic acid with or without compounds in a total volume of 1 mL in 0.1 mol/L phosphate buffer (pH 7.4). After incubation at 37°C for 60 min, the reaction mixture was boiled with thiobarbituric acid (TBA) (0.67 g/100 mL water) for 15 min. Formation of TBA reactive substances (TBARS) was calculated from the absorbance at 535 nm. BHA was used as the positive control.

**The antibacterial activity assay** was carried out against 24-h cultures of various bacterial strains. The test compounds were dissolved in dimethyl sulfoxide (DMSO) at concentrations of 1000 and 500 μg/mL. Twenty milliliter of sterilized agar media was poured into each pre-sterilized Petri dish. Excess of suspension was decanted and plates were dried by placing in an incubator at 37°C for an hour. About 60 mL of 24-h culture suspension were poured and neatly swabbed with the pre-sterilized cotton swabs. Six millimeter diameter wells were then punched carefully using a sterile cork borer and 30 μL of test solutions of different concentrations were added into each labeled well. The plates were incubated for 24 h at 37°C. The inhibition zone that appeared after 24 h around the well in each plate was measured as zone of inhibition in mm. Experiments were carried out in triplicates and standard deviation was calculated.

**Antifungal studies** were carried out using Sabouraud agar media. Normal saline was used to make a suspension of spore of fungal strains for inoculation. A loopful of particular fungal strain was transferred into 3 mL of saline to get a suspension of corresponding species. Twenty milliliter of agar media was poured into each Petri dish. Excess of suspension was decanted and plates were dried by placing in the incubator at 37°C for 1 h. Carefully punched wells were placed on these seeded agar plates and 30 μL of test solution of different concentrations in DMSO were added into each labeled well. A control was also prepared for the plates in the same way using DMSO as a solvent. The Petri dishes were prepared in triplicate and maintained at 25°C for 72 h. Antifungal activity

was determined by measuring the diameter of the inhibition zone.

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