

## N-Hydroxy-3,3-dimethyl-2,6-diarylpiperidin-4-one과 그것의 Thiosemicarbazide 유도체의 특이한 합성 및 항균 활성

M. Gopalakrishnan\*, P. Sureshkumar, J. Thanusu, and V. Kanagarajan  
Synthetic Organic Chemistry Laboratory, Department of Chemistry, Annamalai University,  
Annamalainagar-608 002, Tamil Nadu, India  
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## Unusual Formation of N-hydroxy-3,3-dimethyl-2,6-diarylpiperidin-4-one and its Thiosemicarbazide Derivative—Synthesis and Antimicrobial Activity

M. Gopalakrishnan\*, P. Sureshkumar, J. Thanusu, and V. Kanagarajan  
Synthetic Organic Chemistry Laboratory, Department of Chemistry, Annamalai University,  
Annamalainagar-608 002, Tamil Nadu, India  
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**요 약.** 다수의 새로운 N-Hydroxy-3,3-dimethyl-2,6-diarylpiperidin-4-one thiosemicarbazones들을 합성하였고 녹는점, 원소 분석, MS, FT-IR, NMR ( $^1\text{H}$  &  $^{13}\text{C}$ ) 데이터로 구조분석 하였으며, *in vitro* 항균성과 항진균성의 활성을 측정하였다. 합성되어진 모든 화합물중에서, 화합물 31은 대장균을 제외한 전체 시험되어진 gram-양성, gram-음성 박테리아들에 대해 광범위한 항균 활성을 보여주고 있다. 화합물 31은 *Aspergillus flavus*, 털곰팡이, *Microsporum gypseum*에 강한 항진균성을 보였다.

**주제어:** N-Hydroxy-3,3-dimethyl-2,6-diarylpiperidin-4-one thiosemicarbazones; *m*-chloroperbenzoic acid, 입체화학, 항균 활성도

**ABSTRACT.** An array of novel N-Hydroxy-3,3-dimethyl-2,6-diarylpiperidin-4-one thiosemicarbazones **28-32** are synthesized, characterized by melting point, elemental analysis, MS, FT-IR, NMR ( $^1\text{H}$  &  $^{13}\text{C}$ ) spectroscopic data and evaluated for their *in vitro* antibacterial and antifungal activities. Of all the compounds synthesized, compound **31**, exerted a wide range of antibacterial activities against the entire tested gram-positive and gram-negative bacterial strains except *Escherichia coli*. Compound **31** exerted strong antifungal activities against *Aspergillus flavus*, *Mucor* and *Microsporum gypseum*.

**Keywords:** N-Hydroxy-3,3-dimethyl-2,6-diarylpiperidin-4-one Thiosemicarbazones, *m*-chloroperbenzoic Acid, Stereochemistry, Antimicrobial Activity

### INTRODUCTION

Organo-sulfur compounds dominate much of synthetic, analytical and medicinal chemistry. A better understanding of their biological activity can be derived from their oxidation mechanisms. It is widely accepted that the prerequisite for thio compounds to express their physiological effects is

through S-Oxygenation.<sup>1</sup> Oxidation of organo-sulfur compounds appear to be involved in many cellular functions<sup>2</sup> including the reductive degradation of polypeptide hormones and proteins, regulation of protein synthesis, maintenance of intracellular redox potential, protection of cell from oxidative damage etc., The chemistry of hydrazine derivatives such as thiosemicarbazide and its hydrazones is of immense

interest owing to their wide synthetic and analytical applications and biological activities.<sup>3</sup> Biological activities of thiosemicarbazide derivatives include: antithyroid activity,<sup>4</sup> which leads to a disruption of the pituitary-thyroid hormonal regulatory system, effective antidotes to paraquat toxicity<sup>5</sup> in an HL 60 cell culture system, anticonvulsant effect,<sup>6</sup> pesticidal and fungicidal effect,<sup>7</sup> tuberculostatic,<sup>8</sup> bactericide,<sup>9</sup> CNS depressant activity,<sup>10</sup> treatment of liver diseases and disorders,<sup>11</sup> plant-growth promoting agents,<sup>12</sup> treatment<sup>13</sup> of influenza, small pox, protozoa, tumors etc.

Heterocyclic ring systems having piperidine-4-one nucleus have aroused great interest in the past and recent years due to their wide variety of biological properties such as antiviral, antitumour,<sup>14,15</sup> central nervous system,<sup>16</sup> local anesthetic,<sup>17</sup> anticancer,<sup>18</sup> and antimicrobial activity<sup>19</sup> and their derivative piperidine are also biologically important and act as neurokinin receptor antagonists,<sup>20</sup> analgesic and anti-hypertensive agents.<sup>21</sup>

In addition, hydroxylamines have been reported as anti-bacterial, antifungal and antileukemic agents. N-Hydroxy urea was one of the effective antineoplastic agent<sup>22</sup> and ciclopirox has broad-spectrum antifungal activity.<sup>23</sup>

In recent years there has been a great deal of interest in exploiting more than one proximal functional groups for designing novel structures capable of performing a variety of functions. In the course of broad programme in developing biologically active molecules, we have recently reported the synthesis of 2,6-diarylpiperidin-4-one derivatives and evaluated their biological importance.<sup>24,25</sup> Aiming at extending our knowledge in structure-activity relationship, we considered that it is valuable to synthesis a system which unites biolabile functional groups like thiosemicarbazide and hydroxyl amines into 3,3-dimethyl-2,6-diarylpiperidin-4-one nucleus which together will give a compact structure of N-Hydroxy-3,3-dimethyl-2,6-diarylpiperidin-4-one thiosemicarbazones. The influence of some structural variations by varying the substituent at the phenyl ring in the synthesized compounds towards their biological activities is evaluated.

## CHEMISTRY

Four-step synthetic strategy yields the target molecule N-Hydroxy-3,3-dimethyl-2,6-diarylpiperidin-4-one thiosemicarbazones **28-32**. A mixture of 3-methyl-butan-2-one **1**, appropriate benzaldehyde **2-6** and ammonium acetate **7** in the ratio of 1:2:1, is warmed for 15 min. and hydrochloric acid was added to afford 3,3-dimethyl-2,6-diaryl-piperidin-4-ones hydrochloride **8-12**, which upon neutralization with aqueous ammonia at 0 °C gave the respective 3,3-dimethyl-2,6-diaryl-piperidin-4-ones **13-17**. Cyclic ketones normally undergo Baeyer-Villiger oxidation (oxygen insertion reaction) to yield lactones upon treatment with peracids.<sup>26,27</sup> But, when 3,3-dimethyl-2,6-diaryl-piperidin-4-ones are subjected to Baeyer-Villiger type of reaction by using *m*-chloroperbenzoic acid, N-hydroxy-3,3-dimethyl-piperidin-4-ones **23-27** resulted instead of lactones **18-22**. Compounds **23-27** are converted into their thiosemicarbazones **28-32** using thiosemicarbazide in refluxing ethanol. The importance of the title compounds is due to their diverse potential, broad-spectrum biological activity. The schematic representation and the analytical data of compounds **23-32** are given in *Scheme 1* and *Table 1*, respectively. In addition, compared to 3-alkyl-2,6-diarylpiperidin-4-ones,<sup>28</sup> all coupling constant values extracted for newly synthesized compounds **23-32** have no appreciable change, since the electro negativity of C=NNHCSNH<sub>2</sub> group is less than that of C=O. Hence it is concluded that they all exist in chair conformation only (*Fig. 1* and *Fig. 2*).

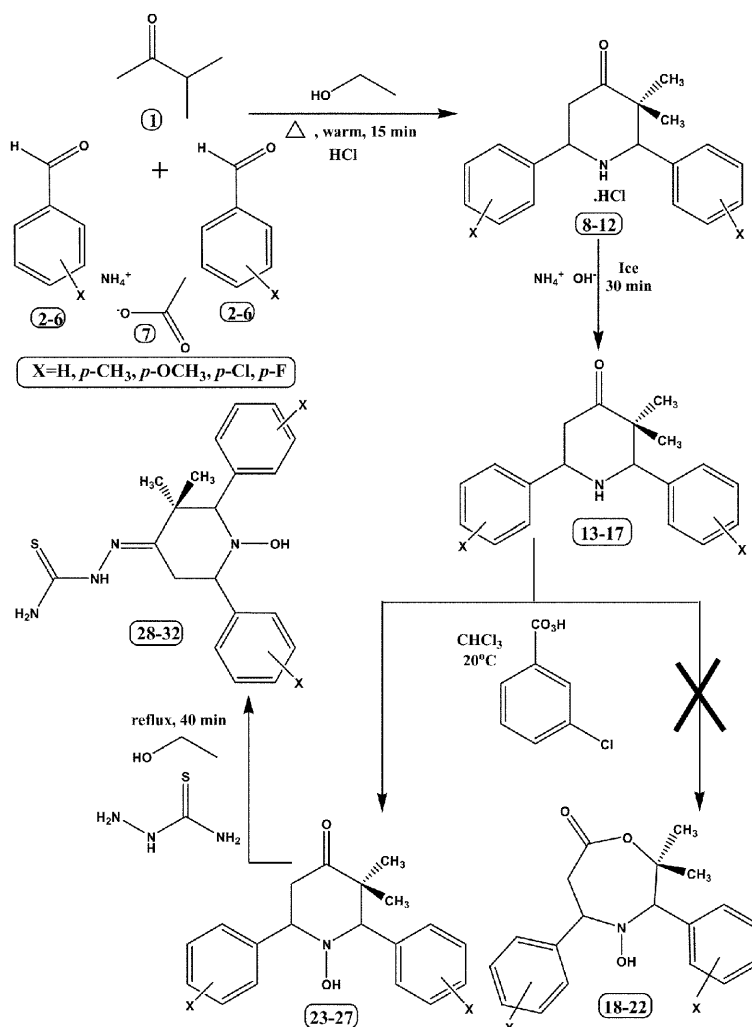
To grasp structure activity relationship well, numberings of the target compound are done (*Fig. 3*).

## RESULTS AND DISCUSSION

Structure activity relationship results.

### Antibacterial activity

Novel N-Hydroxy-3,3-dimethyl-2,6-diarylpiperidin-4-one thiosemicarbazones **28-32** were tested for their antibacterial activity *in vitro* (*Table 2*) against *Staphylococcus aureus*,  $\beta$ -*Haemolytic streptococcus*, *Vibrio cholerae*, *Salmonella typhi*, *Shigella*



Scheme 1. Synthetic scheme for N-Hydroxy-3,3-dimethyl-2,6-diaryl-piperidin-4-one thiosemicarbazones.

Table 1. Analytical data of compounds 23-32

Compound	Yield (%)	m.p. °C	Elemental analysis (%)			m/z (M <sup>+</sup> ) Molecular formula
			C Found (calculated)	H Found (calculated)	N Found (calculated)	
23	70	150-52	77.20(77.26)	7.13(7.17)	4.70(4.74)	(296)C <sub>19</sub> H <sub>11</sub> NO <sub>2</sub>
24	72	148-50	77.92(77.98)	7.75(7.79)	4.29(4.33)	(324)C <sub>21</sub> H <sub>13</sub> NO <sub>2</sub>
25	80	156-58	70.91(70.96)	7.04(7.09)	3.91(3.94)	(356)C <sub>23</sub> H <sub>15</sub> NO <sub>2</sub>
26	70	169-70	62.22(62.25)	5.22(5.26)	3.82(3.85)	(365)C <sub>19</sub> H <sub>10</sub> Cl <sub>2</sub> NO <sub>2</sub>
27	75	173-75	68.81(68.87)	5.73(5.78)	4.20(4.23)	(332)C <sub>19</sub> H <sub>10</sub> F <sub>2</sub> NO <sub>2</sub>
28	85	156-58	65.17(65.19)	6.54(6.56)	15.17(15.20)	(369)C <sub>20</sub> H <sub>14</sub> N <sub>4</sub> OS
29	82	151-52	66.58(66.63)	7.07(7.12)	14.09(14.13)	(397)C <sub>22</sub> H <sub>16</sub> N <sub>4</sub> OS
30	80	155-56	61.62(61.66)	6.54(6.59)	13.02(13.07)	(429)C <sub>23</sub> H <sub>15</sub> N <sub>4</sub> O <sub>2</sub> S
31	83	166-68	54.87(54.92)	5.02(5.07)	12.77(12.81)	(438)C <sub>22</sub> H <sub>15</sub> Cl <sub>2</sub> N <sub>4</sub> OS
32	85	170-72	59.34(59.39)	5.43(5.48)	13.81(13.85)	(405)C <sub>20</sub> H <sub>12</sub> F <sub>2</sub> N <sub>4</sub> OS

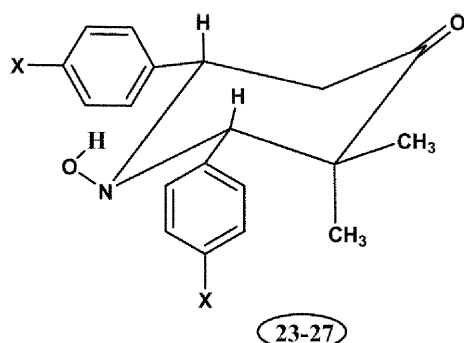


Fig. 1. Preferred chair conformation.

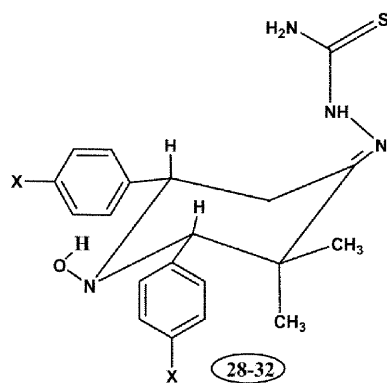


Fig. 2. Preferred chair conformation.

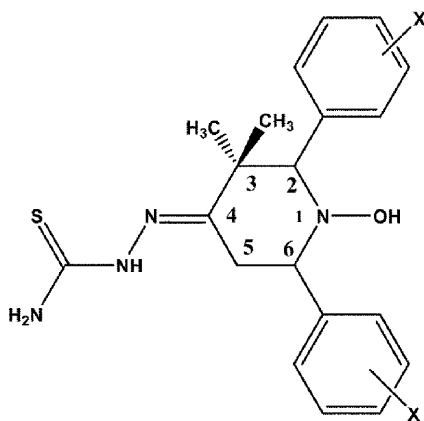


Fig. 3. Numberings of the target compound.

*felxneri*, *Escherichia coli*, *Klebsiella pneumonia* and *Pseudomonas*. Ciprofloxacin was used as standard drug; whose zone of inhibition (mm) values for *Staphylococcus aureus*,  $\beta$ -*Heamolytic streptococcus*, *Vibreo cholerae*, *Salmonella typhi*, *Shigella felxneri*, *Escherichia coli*, *Klebsiella pneumonia*

and *Pseudomonas are* 25, 28, 23, 22, 23, 24, 26 and 23 respectively. All the synthesized novel N-Hydroxy-3,3-dimethyl-2,6-diaryl piperidin-4-one thiosemicarbazones **28-32** exerted a wide range of modest antibacterial activity *in vitro* against the tested organisms. But their activity decreased upon dilution. All the compounds **28-32** are active against all the tested bacterial strains. Generally compounds containing electron withdrawing functional groups (-Cl, -F) exhibited more potent than the electron donating functional groups (-CH<sub>3</sub>, -OCH<sub>3</sub>) present on the aryl rings attached to piperidones.<sup>22</sup> Of all the compounds synthesized, compound **31**, which contains electron withdrawing chloro functional group on the *para* position of the two phenyl rings of the respective thiosemicarbazone, exerted a wide range of antibacterial activities against the entire tested gram-positive and gram-negative bacterial strains except *Escherichia coli*, besides compound **32**, which contains electron withdrawing fluoride moiety on the *para* position of the two phenyl rings of the N-Hydroxy-3,3-dimethyl-2,6-bis(*p*-fluorophenyl)piperidin-4-one thiosemicarbazone which is more active against *Staphylococcus aureus*, gram-positive cocci.

#### Antifungal activity

The *in vitro* antifungal activity (Table 2) of the synthesized novel heterocyclic compounds, **28-32** was studied against the fungal strains viz., *Aspergillus flavus*, *Mucor. Rhizopus* and *Microsporium gypsuum*. Fluconazole was used as a standard drug whose zone of inhibition (mm) values for *Aspergillus flavus*, *Mucor, Rhizopus* and *Microsporium gypsuum* are 20 + 0.5 zone of inhibition (mm) against all the tested fungi. In general, all the synthesized compounds exerted a wide range of modest *in vitro* antifungal activity against all the tested organisms. But their activity decreased upon dilution. Compound **31** exerted strong antifungal activities against *Aspergillus flavus*, *Mucor* and *Microsporium gypsuum*. In addition, compound **32** is more potent against *Microsporium gypsuum*. The strong antifungal activity of compounds **31** and **32** is due to the presence of electron withdrawing functional groups like fluoro and chloro moieties attached to the aryl

Table 2. *In vitro* outline of compounds 28-32 against test bacteria and fungi

Micro organisms	Compound 28			Compound 29			Compound 30			Compound 31			Compound 32		
	100 ppm	200 ppm	500 ppm	100 ppm	200 ppm	500 ppm	100 ppm	200 ppm	500 ppm	100 ppm	200 ppm	500 ppm	100 ppm	200 ppm	500 ppm
<i>Staphylococcus aureus</i>	+	++	+++	+	++	+++	+	++	+++	+	++	++++	+	++	++++
<i>β-Heamolytic streptococcus</i>	-	+	+++	-	+	+++	-	+	+++	+	+++	++++	+	+	++
<i>Vibreo cholerae</i>	+	++	+++	-	+	+++	+	++	+++	+	+	++++	+	++	+++
<i>Salmonella typhi</i>	+	+	+++	+	+	+++	+	+	+++	-	++	++++	+	++	++
<i>Shigella flexneri</i>	+	++	+++	+	++	+++	+	++	+++	+	++	++++	++	++	+++
<i>Escherichia coli</i>	-	-	++	-	+	+++	-	+	+++	-	+	+++	++	+++	+++
<i>Klebsiella pneumonia</i>	-	+	+++	+	++	+++	+	++	+++	+	+++	++++	+	++	+++
<i>Pseudomonas</i>	-	-	++	+	+	+++	+	++	+++	-	++	++++	-	+	++
<i>Aspergillus flavus</i>	+	++	+++	-	+	+++	+	+	+++	+	+++	++++	-	+	++
<i>Mucor</i>	-	+	++	+	++	+++	-	++	+++	-	++	++++	+	++	+++
<i>Rhizopus</i>	-	+	++	+	++	+++	-	+	+++	+	++	+++	+	++	+++
<i>Microsporium gypsuem</i>	+	+	+++	-	++	+++	+	++	+++	-	++	++++	+	+++	++++

(-)=inactive. (+)=weakly active (12-16 mm). (-)(+)=moderately active (17-21 mm). (-)(+)(+)=strong active (22-29). (-)(+)(+)(-)=highly active (30-33).

rings than the other compounds 28-30, which contain electron donating CH<sub>3</sub>, OCH<sub>3</sub> groups attached to the *para* position of the aryl rings.

## CONCLUSION

A close examination of the *in vitro* antibacterial and antifungal activity profile in differently substituted novel N-Hydroxy-3,3-dimethyl-2,6-diarylpiperidin-4-one thiosemicarbazones 28-32 against the tested bacterial strains *viz.* *Staphylococcus aureus*, *β-Heamolytic streptococcus*, *Vibreo cholerae*, *Salmonella typhi*, *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas* and the fungal strains *viz.* *Aspergillus flavus*, *Aspergillus fumigatus*, *Mucor*, *Candida albicans* and *Rhizopus* respectively, provides a better structure activity relationship correlate, which may be summarized as follows:

Results of this study show that the nature of substituent on the phenyl ring *viz.*, chloro as well as the fluoro functions at the *para* positions of the aryl moieties are determinant for the nature and extent of the anti-bacterial and anti-fungal activities of the synthesized compounds, which might have influ-

ences on their inhibiting mechanism of actions. Further development of this group of N-Hydroxy-3,3-dimethyl-2,6-diarylpiperidin-4-one thiosemicarbazones may lead to compounds with better pharmacological profile than standard drugs and serve as templates for the construction of better drugs to come to blows bacterial and fungal infections.

## EXPERIMENTAL

### Microbiology

#### Materials

All the bacterial strains namely *Staphylococcus aureus*, *β-Heamolytic streptococcus*, *Vibreo cholerae*, *Salmonella typhi*, *Shigella flexneri*, *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas* and fungal strains namely *Aspergillus flavus*, *Mucor*, *Rhizopus* and *Microsporium gypsuem* are get hold of from Faculty of Medicine, Annamalai University, Annamalainagar-608 002, Tanuil Nadu, India.

#### *In vitro* antibacterial and antifungal activity

The *in vitro* activities of the compounds were tested in Sabourauds dextrose broth (SDB) (Hi-media, Mumbai) for fungi and nutrient broth (NB)

(Hi-media, Mumbai) for bacteria by the Disc Diffusion method.<sup>29</sup> The respective hydrochlorides of the test compounds **28-32** were dissolved in water to obtain 1 mg ml<sup>-1</sup> stock solution and the different concentrations (100, 200, 500 ppm) are prepared from the stock solution. Seeded broth (broth containing microbial spores) was prepared in NB from 24 h old bacterial cultures on nutrient agar (Hi-media, Mumbai) at 37±1 °C while fungal spores from 1 to 7 days old Sabourauds agar (Hi-media, Mumbai) slant cultures were suspended in SDB. Sterile paper disc of 5 mm diameter is saturated with the three different concentrations and such discs are placed in each seeded agar plates. The petri plates are incubated in BOD incubator at 37 °C for bacteria and at 28 °C for fungi. The zone of inhibition is recorded by visual observations after 24 hrs of inhibition for bacteria and after 72-96 hrs of inhibition for fungi. Moreover, the zone of inhibition is measured by excluding the diameter of the paper disc. Ciprofloxacin was used as standards for bacteria and fluconazole as standard for fungi under analogous conditions.

### Chemistry

Performing TLC assessed the reactions and the purity of the products. All the reported melting points were taken in open capillaries and were uncorrected. IR spectra were recorded in KBr (pellet forms) on a Nicolet-Avatar-360 FT-IR spectrophotometer and note worthy absorption values (cm<sup>-1</sup>) alone are listed. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at 400 MHz and 100 MHz respectively on Bruker AMX 400 NMR spectrometer using CDCl<sub>3</sub> as solvent. The ESI +ve MS spectra were recorded on a Bruker Daltonics LC-MS spectrometer. Satisfactory microanalysis was obtained on Carlo Erba 1106 CHN analyzer.

By adopting the literature precedent,<sup>30</sup> 3,3-dimethyl-2,6-diarylpiperidin-4-ones were prepared **13-17** were prepared.

**Experimental method for the synthesis of N-Hydroxy-3,3-dimethyl-2,6-diphenylpiperidin-4-one 23:** A solution of 3,3-dimethyl-2,6-diphenylpiperidin-4-one **13** (0.01 mol) and *m*-chloroperbenzoic acid

(0.01 mol) in 50 mL of chloroform was stirred for 1 hr and kept aside for overnight at 20 °C. Then the mixture was extracted with chloroform and washed with 10% sodium bicarbonate solution. The chloroform layer was dried over anhydrous magnesium sulphate and distilled off under reduced pressure. Purifications with silica gel column chromatography with ethyl acetate: petroleum ether (bp60-80) 2:8 mixture yielded the product N-Hydroxy-3,3-dimethyl-2,6-diphenylpiperidin-4-one **23**. IR (KBr) (cm<sup>-1</sup>): 3485, 3031, 2985, 2938, 1710, 723, 702; <sup>1</sup>H NMR (δ ppm): 0.93 (s, 3H, CH<sub>3</sub> at C-3), 1.23 (s, 3H, CH<sub>3</sub> at C-3), 3.09 (t, 1H, H<sub>5a</sub>); 2.52 (dd, 1H, H<sub>5e</sub>, J<sub>5a,6e</sub>=14.6; J<sub>5e,6a</sub>=3.8 Hz), 3.77 (d, 1H, H<sub>2a</sub>), 3.96 (dd, 1H, H<sub>6a</sub>, J<sub>5a,5e</sub>=13.2 Hz), 4.48 (s, 1H, H<sub>1</sub>), 7.28-7.49 (m, 10H, H<sub>arom</sub>); <sup>13</sup>C NMR (δ ppm): 21.3 CH<sub>3</sub> at C-3, 45.4 C-5, 49.6 C-3, 70.9 C-6, 78.7 C-2, 126.8-130.2 -C<sub>arom</sub>, 137.7, 142.0 *ipso*-C, 210.1 C-4.

The compounds **24-27** were synthesized similarly.

**N-Hydroxy-3,3-dimethyl-2,6-bis(p-methylphenyl)piperidin-4-one 24:** IR (KBr) (cm<sup>-1</sup>): 3477, 3030, 2985, 2921, 1710, 817; <sup>1</sup>H NMR (δ ppm): 0.92 (s, 3H, CH<sub>3</sub> at C-3), 1.24 (s, 3H, CH<sub>3</sub> at C-3), 2.35 (s, 6H, CH<sub>3</sub> at phenyl rings), 2.53 (t, 1H, H<sub>5a</sub>); 3.15 (dd, 1H, H<sub>5e</sub>, J<sub>5a,6e</sub>=14.6; J<sub>5e,6a</sub>=3.7 Hz), 3.76 (d, 1H, H<sub>2a</sub>), 3.96 (dd, 1H, H<sub>6a</sub>, J<sub>5a,5e</sub>=13.2 Hz), 4.75 (s, 1H, H<sub>1</sub>), 7.19-7.40 (m, 8H, H<sub>arom</sub>); <sup>13</sup>C NMR (δ ppm): 21.0 CH<sub>3</sub> at phenyl rings, 21.3 CH<sub>3</sub> at C-3, 45.5 C-5, 49.7 C-3, 70.6 C-6, 78.5 C-2, 126.7-129.4 -C<sub>arom</sub>, 134.7, 137.1, 137.3, 139.1 *ipso*-C, 210.4 C-4.

**N-Hydroxy-3,3-dimethyl-2,6-bis(p-methoxyphenyl)piperidin-4-one 25:** IR (KBr) (cm<sup>-1</sup>): 3488, 3035, 2988, 2927, 2835, 1708, 831; <sup>1</sup>H NMR (δ ppm): 0.91 (s, 3H, CH<sub>3</sub> at C-3), 1.22 (s, 3H, CH<sub>3</sub> at C-3), 3.07 (t, 1H, H<sub>5a</sub>); 2.50 (dd, 1H, H<sub>5e</sub>, J<sub>5a,6e</sub>=14.6; J<sub>5e,6a</sub>=3.4 Hz), 3.71 (d, 1H, H<sub>2a</sub>), 3.80 (s, 6H, OCH<sub>3</sub> at phenyl rings), 3.91 (dd, 1H, H<sub>6a</sub>, J<sub>5a,5e</sub>=13.1 Hz), 4.60 (s, 1H, H<sub>1</sub>), 6.90-7.41 (m, 8H, H<sub>arom</sub>); <sup>13</sup>C NMR (δ ppm): 21.3 CH<sub>3</sub> at C-3, 45.5 C-5, 49.8 C-3, 55.1, 55.2 OCH<sub>3</sub> at phenyl rings, 70.3 C-6, 78.2 C-2, 114.0-129.8 -C<sub>arom</sub>, 131.2, 134.1, 158.8, 159.0 *ipso*-C, 210.5 C-4.

**N-Hydroxy-3,3-dimethyl-2,6-bis(p-chlorophenyl)piperidin-4-one 26:** IR (KBr) (cm<sup>-1</sup>): 3474, 3030, 2984, 2946, 2926, 1711, 831; <sup>1</sup>H NMR (δ ppm):

0.92 (s, 3H, CH<sub>3</sub> at C-3), 1.20 (s, 3H, CH<sub>3</sub> at C-3), 3.05 (t, 1H, H<sub>3a</sub>); 2.50 (dd, 1H, H<sub>5e</sub>, J<sub>5a,6e</sub>=14.7; J<sub>5e,6a</sub>=3.8 Hz), 3.75 (d, 1H, H<sub>2a</sub>), 3.94 (dd, 1H, H<sub>6a</sub>, J<sub>5a,5e</sub>=13.2 Hz), 4.49 (s, 1H, H<sub>1</sub>), 7.26-7.48 (m, 8H, H<sub>arom</sub>); <sup>13</sup>C NMR (δ ppm): 21.2 CH<sub>3</sub> at C-3, 45.1 C-5, 49.6 C-3, 70.4 C-6, 78.2 C-2, 128.2-129.0 -C<sub>arom</sub>, 131.6, 133.6, 135.8, 139.9 *ipso*-C, 209.1 C-4.

**N-Hydroxy-3,3-dimethyl-2,6-bis(p-fluorophenyl)piperidin-4-one 27:** IR (KBr) (cm<sup>-1</sup>): 3472, 3029, 2981, 2944, 2928, 1120, 1710, 829; <sup>1</sup>H NMR (δ ppm): 0.91 (s, 3H, CH<sub>3</sub> at C-3), 1.18 (s, 3H, CH<sub>3</sub> at C-3), 3.02 (t, 1H, H<sub>3a</sub>); 2.49 (dd, 1H, H<sub>5e</sub>, J<sub>5a,6e</sub>=14.7; J<sub>5e,6a</sub>=3.8 Hz), 3.73 (d, 1H, H<sub>2a</sub>), 3.92 (dd, 1H, H<sub>6a</sub>, J<sub>5a,5e</sub>=13.1 Hz), 4.47 (s, 1H, H<sub>1</sub>), 7.24-7.42 (m, 8H, H<sub>arom</sub>); <sup>13</sup>C NMR (δ ppm): 21.0 CH<sub>3</sub> at C-3, 45.2 C-5, 49.4 C-3, 70.1 C-6, 78.0 C-2, 127.2-128.8 -C<sub>arom</sub>, 131.4, 133.3, 135.2, 139.4 *ipso*-C, 208.1 C-4.

**Experimental method for the synthesis of N-Hydroxy-3,3-dimethyl-2,6-diphenylpiperidin-4-one thiosemicarbazone 28:** A mixture of N-Hydroxy-3,3-dimethyl-2,6-diarylpiperidin-4-one **23** (0.01 mol) and thiosemicarbazide (0.01 mol) in ethanol (40 mL) was refluxed on a steam bath for 40 min and was concentrated to one-third of its original volume. After cooling, the mixture was poured over crushed ice. The solid product thus obtained was filtered off and the solid was subjected to column chromatography using ethyl acetate: petroleum ether (60:80) 2:8 as eluent to give 3,3-dimethyl-2,6-diphenylpiperidin-4-one thiosemicarbazone as crystalline solid. IR (KBr) (cm<sup>-1</sup>): 3482, 3426, 3358, 3158, 3065, 3030, 2976, 2931, 2863, 1587, 1493, 1287, 1075, 733, 702; <sup>1</sup>H NMR (δ ppm): 0.94 (s, 3H, CH<sub>3</sub> at C-3), 1.24 (s, 3H, CH<sub>3</sub> at C-3), 2.34 (t, 1H, H<sub>3a</sub>); 2.61 (dd, 1H, H<sub>5e</sub>, J<sub>5a,6e</sub>=14.5; J<sub>5e,6a</sub>=3.9 Hz), 3.67 (d, 1H, H<sub>2a</sub>), 3.73 (dd, 1H, H<sub>6a</sub>, J<sub>5a,6a</sub>=13.2 Hz), 4.53 (s, 1H, H<sub>1</sub>), 6.38 (s, 2H, CSNH<sub>2</sub>), 8.57 (s, 1H, HNCS), 7.26-7.50 (m, 10H, H<sub>arom</sub>); <sup>13</sup>C NMR (δ ppm): 21.4 CH<sub>3</sub> at C-3, 22.4 CH<sub>3</sub> at C-3, 31.5 C-5, 45.5 C-3, 70.1 C-6, 79.5 C-2, 126.9-128.8 -C<sub>arom</sub>, 138.1, 143.5 *ipso*-C, 156.1 C-4, 179.6 C=S.

The compounds **29-32** were synthesized similarly.

**N-Hydroxy-3,3-dimethyl-2,6-bis(p-methylphenyl)piperidin-4-one thiosemicarbazone 29:** IR (KBr) (cm<sup>-1</sup>): 3476, 3426, 3324, 2980, 2922, 2863, 1587,

1511, 1280, 1127, 817; <sup>1</sup>H NMR (δ ppm): 0.95 (s, 3H, CH<sub>3</sub> at C-3), 1.32 (s, 3H, CH<sub>3</sub> at C-3), 2.35 (t, 1H, H<sub>3a</sub>); 2.35 (s, 6H, CH<sub>3</sub> at phenyl rings), 2.63 (dd, 1H, H<sub>5e</sub>, J<sub>5e,5a</sub>=14.5; J<sub>5e,6a</sub>=3.7 Hz), 3.91 (d, 1H, H<sub>2a</sub>), 4.08 (dd, 1H, H<sub>6a</sub>, J<sub>5a,6a</sub>=13.3 Hz), 4.86 (s, 1H, H<sub>1</sub>), 5.73 (s, 2H, CSNH<sub>2</sub>), 8.72 (s, 1H, HNCS), 7.19-7.45 (m, 8H, H<sub>arom</sub>); <sup>13</sup>C NMR (δ ppm): 21.0 CH<sub>3</sub> at phenyl rings, 22.4 CH<sub>3</sub> at C-3, 23.3 CH<sub>3</sub> at C-3, 29.9 C-5, 45.5 C-3, 70.7 C-6, 78.6 C-2, 126.8-129.4 -C<sub>arom</sub>, 134.6, 137.1, 137.3, 138.9 *ipso*-C, 156.4 C-4, 179.6 C=S.

**N-Hydroxy-3,3-dimethyl-2,6-bis(p-methoxyphenyl)piperidin-4-one thiosemicarbazone 30:** IR (KBr) (cm<sup>-1</sup>): 3489, 3429, 3368, 2994, 2931, 2836, 1587, 1512, 1268, 1036, 831; <sup>1</sup>H NMR (δ ppm): 0.99 (s, 3H, CH<sub>3</sub> at C-3), 1.47 (s, 3H, CH<sub>3</sub> at C-3), 2.04 (t, 1H, H<sub>3a</sub>); 2.72 (dd, 1H, H<sub>5e</sub>, J<sub>5a,6e</sub>=14.5; J<sub>5e,6a</sub>=3.7 Hz), 3.80 (s, 6H, OCH<sub>3</sub> at phenyl rings), 4.14 (d, 1H, H<sub>2a</sub>), 4.27 (dd, 1H, H<sub>6a</sub>, J<sub>5a,6a</sub>=13.6 Hz), 4.72 (s, 1H, H<sub>1</sub>), 6.09 (s, 2H, CSNH<sub>2</sub>), 8.09 (s, 1H, HNCS), 6.90-7.58 (m, 8H, H<sub>arom</sub>); <sup>13</sup>C NMR (δ ppm): 21.3 CH<sub>3</sub> at C-3, 22.3 CH<sub>3</sub> at C-3, 29.6 C-5, 45.3 C-3, 55.2 OCH<sub>3</sub> at phenyl rings, 70.2 C-6, 78.4 C-2, 114.0, 128.2-129.4 -C<sub>arom</sub>, 133.5, 138.4 *ipso*-C, 156.3 C-4, 179.4 C=S.

**N-Hydroxy-3,3-dimethyl-2,6-bis(p-chlorophenyl)piperidin-4-one thiosemicarbazone 31:** IR (KBr) (cm<sup>-1</sup>): 3473, 3426, 3371, 2977, 2926, 2853, 1589, 1490, 1288, 1090, 830; <sup>1</sup>H NMR (δ ppm): 1.10 (s, 3H, CH<sub>3</sub> at C-3), 1.34 (s, 3H, CH<sub>3</sub> at C-3), 2.44 (t, 1H, H<sub>3a</sub>); 2.73 (dd, 1H, H<sub>5e</sub>, J<sub>5a,6e</sub>=15.0; J<sub>5e,6a</sub>=3.7 Hz), 3.93 (d, 1H, H<sub>2a</sub>), 4.18 (dd, 1H, H<sub>6a</sub>, J<sub>5a,6a</sub>=13.6 Hz), 4.94 (s, 1H, H<sub>1</sub>), 6.53 (s, 2H, CSNH<sub>2</sub>), 8.57 (s, 1H, HNCS), 7.36-7.60 (m, 8H, H<sub>arom</sub>); <sup>13</sup>C NMR (δ ppm): 21.3 CH<sub>3</sub> at C-3, 22.1 CH<sub>3</sub> at C-3, 29.6 C-5, 45.0 C-3, 70.6 C-6, 78.6 C-2, 128.5-128.8 -C<sub>arom</sub>, 133.6, 138.6, 141.9 *ipso*-C, 156.5 C-4, 179.5 C=S.

**N-Hydroxy-3,3-dimethyl-2,6-bis(p-fluorophenyl)piperidin-4-one thiosemicarbazone 32:** IR (KBr) (cm<sup>-1</sup>): 3470, 3423, 3370, 2974, 2924, 2851, 1591, 1491, 1280, 1089, 830; <sup>1</sup>H NMR (δ ppm): 1.09 (s, 3H, CH<sub>3</sub> at C-3), 1.31 (s, 3H, CH<sub>3</sub> at C-3), 2.41 (t, 1H, H<sub>3a</sub>); 2.71 (dd, 1H, H<sub>5e</sub>, J<sub>5a,6e</sub>=15.1; J<sub>5e,6a</sub>=3.6 Hz), 3.90 (d, 1H, H<sub>2a</sub>), 4.15 (dd, 1H, H<sub>6a</sub>, J<sub>5a,6a</sub>=13.6 Hz), 4.97 (s, 1H, H<sub>1</sub>), 6.49 (s, 2H, CSNH<sub>2</sub>), 8.52 (s, 1H,

HNCS), 7.31-7.55 (m, 8H, H<sub>arom</sub>); <sup>13</sup>C NMR (δ ppm): 21.0 CH<sub>3</sub> at C-3, 21.9 CH<sub>3</sub> at C-3, 29.8 C-5, 45.5 C-3, 70.4 C-6, 78.4 C-2, 128.9-129.8 -C<sub>arom</sub>, 133.4, 138.3, 141.5 *ipso*-C, 156.2 C-4, 179.1 C=S.

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