# Synthesis, Characterization and evaluation of antioxidant potential of 2, 6-diphenylpiperidine-4-one compounds and their novel imine derivatives

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**Abstract**: In search of potent molecules having antioxidant activity the present work was designed to synthesize 2, 6-diphenylpiperidine-4-one compounds (1a and 1b) and their imine derivatives (2a, 2b, 3a, and 3b). Compounds 1a and 1b were synthesized by Mannich condensation reaction. The method was found to be simple, convenient with high yield and products were easily separated. Compounds 1a and 1b serves as an intermediate for the preparation of highly functionalized novel imine derivatives. Oxime (2a, 2b) and carbothioamide (3a, 3b) derivatives of 1a and 1b compounds were produced by condensation reaction with hydroxyl amine hydrochloride and thiosemicarbazide respectively. These compounds were characterized by IR, EI-mass and $^1$HNMR spectroscopy. The antioxidant activity of compounds was analyzed by 1, 1- dipheny1-2-picrylhydrazyl (DPPH) assay method. It was found that substituted aryl derivatives containing phenol and methoxy groups (1b, 2b and 3b) showed better antioxidant activity ($IC_{50}$ values rang from 1.84-4.53µg/ml) than unsubstituted aryl derivative (1a, 2a and 3a) ($IC_{50}$ rang from 6.46-11.13µg/ml). Compound 1b exhibited excellent antioxidant activity ($IC_{50}$ 1.84±0.15µg/ml) comparable to standard ascorbic acid ($IC_{50}$1.65± 0.16µg/ml).

**Keywords**: Piperidine-4-one, oxime, thiosemicarbazide, total synthesis, characterization, antioxidant.

## INTRODUCTION

Piperidine is one of the most common structural entities among nitrogen containing heterocyclic molecules. The piperidine ring is present in numerous natural alkaloids, having diverse pharmacological properties including anticancer, antioxidant, antihistamine, bactericidal, fungicidal, insecticidal, stimulant and depressant of central nervous system (Alphonsa, Loganathan *et al*., 2015, Savithiri, Rajarajan *et al*., 2014, Singh, Chawla *et al*., 2012, Naicker, Venugopala *et al*., 2015). The abundance of piperidine nucleus in biologically active natural and synthesized compounds provides a considerable interest for synthesis of highly functionalized piperidine derivatives with potential biological activity (Ponnuswamy, Sethuvasan *et al*., 2015, Schneider, 1996, Watson, Jiang *et al*., 2000). In piperidine derivatives, piperidine-4-one is mostly used as an intermediate for preparation of highly functionalized heterocyclic compounds. Presences of carbonyl and amino functional groups in piperidine-4-one are the reason of substitution on the ring. In designing and discovering of a novel hybrid compound by combination of two bioactive pharmacophores produced a single compound with potential to treat number of diseases (Ahmad Bhat, Al-Omar *et al*., 2018), considering this approach, bioactive 2,6- diphenylpiperidine-4-one derivatives were combined with imine molecule having diverse bioactivity including antimicrobial, anticancer, antinflammatory, antituberculosis and antioxidants (Ghosh, Misra *et al*., 2009, Ley and Bertram, 2002, Liu, Wang *et al*., 2009, da Silva, da Silva Araújo *et al*., 2015, Islam, Shafiq *et al*., 2015, Miyabe, Ueda *et al*., 2000, Song, Liu *et al*., 2013). The presences of electronegative nitrogen, sulphur and oxygen elements in the functional groups of modified structure may increases the potential of compounds to interact with various biological targets.

Antioxidants protect from various pathological conditions including cancer, arthritis, cirrhosis, Alzheimer and kidney disease by neutralizing excess free radical, which is produced due to oxidative stress (Kelly, 1998, Tiwari, 2001). The importance of antioxidants in protecting the body from chronic disease insistence to synthesized new potent effective antioxidant compounds.

In the present study synthesized compounds were investigated for free radical scavenging activity using 1, 1-diaphenyl-2-picryl-hydrazyl-hydrate (DPPH)

## MATERIALS AND METHODS

Reagents used in synthesis were purchased from TCI (Japan) chemical company. Analytical grade solvents

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such as methanol, ethanol, acetic acid and ether were purchased from E. Merck. TLC plate Kieselgel60 (GF-254) was used to monitor the completion of reaction. Melting points of synthesized compounds was recorded in open capillaries on Buchi 434 instrument and are uncorrected. Shimadzu UV-1600 Spectrophotometer was used for ultraviolet-visible (UV/vis.) spectra using methanol as solvent. Jasco 302 Fourier transform infrared (FTIR) spectrophotometer was used to analyze infra-red (IR) spectra by making KBR disc method. The electronic impact (EI) low resolution mass spectra were recorded using MAT112 and JEOL mass spectrometer (JMS) 600H. $^1$HNMR analysis was performed on Brucker AM 300, and 400 spectrometer using tetramethylsilane (TMS) as an internal standard and chloroform ($CDCl_3$) as solvent.

***Synthesis and spectral analysis of 2, 6 diphenylpiperidine-4-one derivatives***

***(1a) 3-octyl-2, 6-diphenylpiperidin-4-one and (1b) 2, 6-bis (4-hydroxy-3-methoxyphenyl)-3-methylpiperidin-4-one***

Both of these compounds (1a, 1b) were synthesized by adopting one pot total synthesis method as reported by Noller and Baliah (Noller and Baliah, 1948). In reaction flask ammonium acetate (0.1M), ketone (0.1M) and benzaldehyde (0.2M) were taking in ethanol (30ml) and allow refluxing. After the completion of reaction confirm by using TLC, the mixture was treated with dilute hydrochloric acid to form precipitates of product. Precipitates were filter and washed with ethanol-ether (4:1) solution. The precipitate in acetone were treated with aqueous ammonia followed by addition of excess water which librates product in the form of free base. Compounds were recrystallized from absolute ethanol.

For the synthesis of 1a, 2-undecanone and benzaldehyde were used and for 1b reactants ethyl methyl ketone and vanillin were used (Scheme-1).

***Compound*** (1a) $C_{25}H_{33}NO$; Yield: 78%; colorless powder; mp: 128±2ºC; $UV_{\lambda max}$ (MeOH) nm: 215; EIMS m/z (%): 363.2 $M^+$ (53.7), 264.1(100.0), 208.1(95.2), 194.1(39.4), 106.0(87.5), 55.0(55.3); IRυ(KBr) $cm^{-1}$:3750, 2361, 1715, 992; $^1$H-NMR ($CDCl_3$, 300MHz) δ(ppm): 7.816-7.417(m,10 ArH, H-8, 9, 10, 11, 12, 23, 24, 25, 26, 27), 4.979-4.909(t, 3H, H-5a), 4.730 - 4.657(t, 3H, H-5b), 3.702 - 3.608(t, 3H, H-6), 3.552 - 3.494 (m, 4H, H-3), 2.717-2.669(d, J=14.4Hz, 2H, H-2), 1.392 - 1.367(m, 4H, H-13), 1.242 - 1.194 (m, 12H, H-14, 15, 16, 17, 18, 19), 0.846 - 0.799(t, 5H, H-20).

***Compound*** (1b) $C_{20}H_{23}NO_5$; Yield: 88%; colorless powder; mp: 132±2ºC; $UV_{\lambda max}$ (MeOH) nm: 257, 280; EIMS m/z (%): 357.16 $M^+$ (47.41), 285.9(48.05), 178.0(45.53), 152.0(100.00), 134.9(55.76), 77.0(40.23); IRυ(KBr) $cm^{-1}$: 3328, 2927, 2841, 1710, $^1$H-NMR($CDCl_3$, 400MHz) δ(ppm): 8.834 - 8.813 (s, 2H, H-23, H-26), 7.027 - 6.694 (m, 6ArH, H-8, 11, 12, 16, 19, 20), 3.896 - 3.860 (dd, 2H, H-6), 3.764 - 3.751 (s, 6H, H-22, H-25), 3.44 - 3.41 (d, J= 6.4Hz, 2H, H-2), 2.736 - 2.623 (m, 5H, H-3), 2.397 - 2.390 (d, J=2.8Hz, 2H, H-5a), 2.365 - 2.358(d, J= 2.8Hz, 2H, H-5b) 0.671- 0.655 (d, J = 6.4Hz, 4H, H-13).

***(2a) (Z)-3-octyl-2, 6-diphenylpiperidin-4-one oxime and (2b) (Z)-2, 6-bis(4-hydroxy-3-methoxyphenyl)-3-methylpiperidin-4-one oxime***

Imine derivatives, oxime of parent compounds were synthesized by boiling mixture of parent (1a and 1b) compound (0.02M) and sodium acetate trihydrate (0.06M) in ethanol (30ml). After ten minutes of boiling hydroxylamine hydrochloride (0.03M) was added to reaction mixture and allow refluxing for three hours with continuous stirring. After cooling the mixture was poured into crushed ice, product appears in the form of precipitates. The obtained precipitates were filtered, washed with cold water, vacuum dried and recrystallized from ethanol (Scheme 1).

***Compound*** (2a) $C_{25}H_{34}N_2O$; Yield: 57%; colorless powder; mp: 123±2ºC; $UV_{\lambda max}$ (MeOH) nm: 252, 279.50; EIMS m/z (%): 378.27 $M^+$ (54.0), 361.0(89.7), 264.9(56.1), 256.0(33.8), 193.9(80.4), 106.0(100.0), 91.0(23.2); IRυ (KBr) $cm^{-1}$: 3231, 2908, 2847, 1687, 702; $^1$H-NMR($CDCl_3$, 400MHz) δ(ppm): 7.823 - 7.027(m, 10 ArH, H-8, 9, 10, 11, 12, 24, 25, 26, 27, 28), 4.261 - 4.231(d, 3H, H-5), 3.934-3.870(t, 3H, H-6), 3.625 - 3.597 (m, 4H, H-3), 2.631-2.612(d, J=5.7 Hz, 2H, H-2), 1.525 (m, 4H, H-13), 1.236 - 1.136 (m, 12H, H-14, 15, 16, 17, 18, 19), 0.849 - 0.814(t, 5H, H-20).

***Compound*** (2b) $C_{20}H_{24}N_2O_5$; Yield: 69%; colorless powder; mp: 153±1ºC; $UV_{\lambda max}$ (MeOH) nm: 249, 275; EIMS m/z (%): 372.17 $M^+$ 62.2), 286.2(10.6), 204.1(20.2), 152.1(100.0), 83.0(53.2); IRυ(KBr) $cm^{-1}$:3047.90, 2908.8, 2843, 1603, 745; $^1$H-NMR ($CDCl_3$, 400MHz) δ(ppm): 10.521(s, IH, H-15), 8.932-8.912 (s, 2H, H-24, H-27), 6.861-6.792 (m, 6Ar H, H-8, 11, 12, 17, 20, 21), 3.962-3.940 (dd, 2H, H-6), 3.742-3.739 (s, 6H, H-23, H-26), 3.422-3.411 (d, J= 4 Hz, 2H, H-2), 2.836 - 2.723 (m, 5H, H-3), 2.497 - 2.490 (d, J =2.8 Hz, 2H, H-5a), 2.476-2.468(d, J= 2.8MHz, 2H, H-5b) 1.052 - 1.047 (d, J = 2Hz, 4H, H-13).

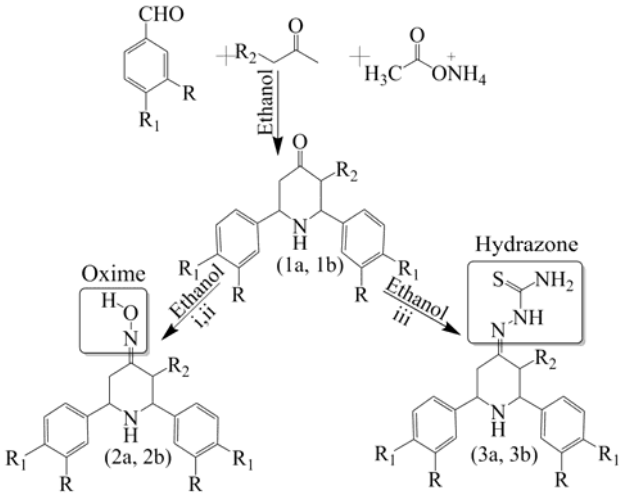
***(3a) (Z)-2-(3-octyl-2,6-diphenylpiperidin-4-ylidene)hydrazine-1-carbothioamide and (3b) (Z)-2-(2, 6-bis(4-hydroxy-3-methoxyphenyl)-3-methylpiperidin-4-ylidene) hydrazine-1-carbothioamide***

Imine derivative, hydrazine-carbothioamide of parent compounds were synthesized by refluxing equimolar amount of parent (1a and 1b) compound (0.01M) with thiosemicarbazide (0.01M) in acidic ethanol (30ml) with continuous stirring on steam bath for three hours. The content were cooled and poured into crushed ice, precipitate obtained was filtered, washed with cold water,

vacuum dried and recrystallized from hot ethanol (Scheme- 1).

***Compound*** (3a) $C_{26}H_{36}N_4S$; Yield: 88%; colorless powder; mp: 173±0.5ºC; $UV_{\lambda max}$ (MeOH) nm: 257, 280; EIMS m/z (%): 436.27 $M^+$ (47.4), 320.2(22.9), 264.1(83.9), 208.1(100.0), 194.1(54.4), 131.1(25.4), 106.1(65.1), 55.1(19.4); IRυ (KBr) $cm^{-1}$: 3217, 2913, 2843.59, 1669.43, 1225.43, 690l $^1$H-NMR($CDCl_3$, 300MHz) δ(ppm):10.695 (s, 1H, H-22), 8.336(s, 2H, H-31), 7.669 - 7.294 (m, 10 ArH, H-8, 9, 10, 11, 12, 26, 27, 28, 29, 30), 4.607-4.482(d, J= 37.5, 2H, H-2), 3.834 - 3.770(t, 3H, H-6), 3.125 - 3.297 (m, 4H, H-3), 1.890 - 1.804(m, 2H, H-5), 1.578 (m, 4H, H-13), 1.214 - 0.970 (m, 12H, H-14, 15, 16, 17, 18, 19),0.843-0.735(t, 5H, H-20).

***Compound*** (3b) $C_{21}H_{26}N_4O_4S$; Yield: 63%; colorless powder; mp: 182±1ºC; $UV_{\lambda max}$ (MeOH) nm: 257, 280; EIMS m/z (%): 430.17 $M^+$ (4714.0), 353.2(100.0), 286.1(31.1), 262.1(29.3), 152.1(48.0), 137.1(44.9); IRυ(KBr) $cm^{-1}$:3514, 2937.57, 2851.76, 2369.58, 1651.69, 690 ; $^1$H-NMR ($CDCl_3$, 400MHz) δ(ppm): 10.981(s, 1H, H-15),7.177 - 7.157 (s, 2H, H-26, H-30), 7.751(s, 2H, H-27),6.627 - 6.772 (m, 6ArH, H-8, 11, 12, 19, 22, 23), 3.963 - 3.960 (dd, 2H, H-6), 3.774 (s, 6H, H-25, H-29), 3.447 - 3.441 (d, J= 2.4Hz, 2H, H-2), 2.774 - 2.723 (m, 5H, H-3), 2.395 - 2.389 (d, J=2.4Hz, 2H, H-5a), 2.362 - 2.351(d, J= 4.4Hz, 2H, H-5b) 0.674 - 0.656 (d, J = 7.2 Hz, 4H, H-13).




i: hydroxylamine HCl, ii: sodium acetate trihydrate, iii: thiosemicarbazide
1a, 2a, 3a (R = H, $R_1$= H, $R_2$=$C_7H_{15}$)
1b, 2b, 3b (R = $OCH_3$, $R_1$=OH, $R_2$=$CH_3$)

**Scheme 1**: Synthetic scheme of compound 1a, 1b, 2a, 2b, 3a and 3b

***Free radical scavenging activity***

*Method*

Freshly prepared 2ml of 0.1mM DPPH radical solution in methanol were added to 2ml solution of synthesized compounds (1a, 2a, 3a, 1b, 2b and 3b) of different concentrations (20, 15, 10, 5.0, 1.0, 0.05 µg/ml) in methanol. These mixture contents were shaken vigorously and allowed to stand at room temperature in dark for 30 minutes. DPPH blank and standard compound ascorbic acid were also kept under same condition. The absorbance was recorded in triplicate at 517nm by using UV/visible spectrophotometer. The DPPH scavenging effect in percentage is calculated by using absorbance value of test, standard and blank in the following equation

$$\text{DPPH scacenging effect (\%)} = \frac{A_o - A_1}{A_o} \times 100$$

Where:
$A_o$ = absorbance of blank,
$A_1$= absorbance of test

## RESULTS

2, 6-diphenylpiperidine-4-one compounds and their imine derivatives were successfully synthesized in quantitative yield and characterized by spectroscopic procedures. Presences of carbonyl stretching bond in infrared spectra at frequency of 1715 and1710$cm^{-1}$ and N-H stretching at 3750 and 3328$cm^{-1}$ in 1a and 1b respectively confirmed the formation of 4-piperidone nucleus. In imine derivatives C=N stretching vibration appears around 1603-1687$cm^{-1}$. Synthesized compounds were evaluated for their potential antioxidant activity. The percentage scavenging activity of synthesized compounds on DPPH radical and $IC_{50}$ values were shown in fig. 1 and Table- 1 respectively.

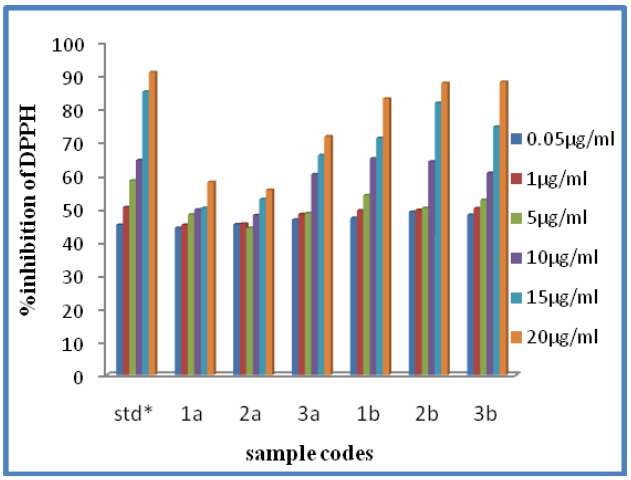



**Fig. 1**: Antioxidant activity of synthesized compound and standard

## DISCUSSION

Synthesis of new compounds having potential to protect the body from oxidative damage by neutralizing the free radicals, have become an important task in organic synthesis. Natural and synthetic antioxidants reduced the

risk of chronic diseases by inhibiting the oxidation of substrate (Odeyemi, Afolayan *et al*., 2017). Various *in vitro* procedures provide a useful indication of antioxidant capabilities of compound by analyzing the capacity of compounds for radical capture or inhibition of radical formation. The *in vitro* DPPH method is preferred over other methods because this method is convenient, reliable and fast. The DPPH free radical is scavenged by receiving hydrogen or electron from antioxidant and become colorless in reduced form (Mishra, Ojha *et al*., 2012). The percent inhibitions with relation to concentration of synthesized compounds along standard ascorbic acid have been reported in fig. 1. Our analytical data shown that with increase in concentration percent inhibition also increases, the maximum inhibition was found between 15-20 µg/ml (Biswas, Haldar *et al*., 2010). On the bases of chemical structure features two different kind of compounds were synthesized and analyzed and it is indicated from structure activity relation ship that presences of substitution on phenyl ring effect the potency of antioxidant compound. Especially presence of phenol moiety enhanced the scavenging effect. Results confirmed the concept that phenolic compounds showed better antioxidant activity (Moalin, Van Strijdonck *et al*., 2011, Rasineni and Reddy, 2008, Simić, Manojlović *et al*., 2007). Antioxidant activity also influenced by the substitution of carbonyl group of 1a and 1b with oxime and thiocarboamide functional groups, presence of N-H, C=N, C=O and C=S functional moieties also potentiates the scavenging effect (Espinosa, Inchingolo *et al*., 2015, Kim and Lee, 2004, Leopoldini, Russo *et al*., 2011). Synthesized compounds showed moderate to good antioxidant activates as compared with standard ascorbic acid.

**Table 1**: $IC_{50}\pm$ SEM of compounds and standard

| S. No. | Code | $IC_{50}\pm$ SEM[a](µg/ml) |
|---|---|---|
| 1 | 1a | 9.85 ± 0.12 |
| 2 | 2a | 11.13 ± 0.17 |
| 3 | 3a | 6.46 ± 0.20 |
| 4 | 1b | 1.84 ± 0.15 |
| 5 | 2b | 4.53 ± 0.41 |
| 6 | 3b | 4.44 ± 0.14 |
| Std | Ascorbic acid[b] | 1.65 ± 0.16 |

a= SEM (Standard error mean)
b= (standard antioxidant)

## CONCLUSION

In these synthetic and biological studies it was observed that compounds with substituted phenyl ring showed better antioxidant activities and it may be due to better hydrogen donating ability of substituted phenyl ring attributed to its resonance stabilizing effects by donating hydrogen. These effects are responsible for antioxidant property shown by our compounds; intensity of these effects is in order of 1b ℘ 3b ℘ 2b ℘ 3a ℘ 1a ℘ 2a. These finding are also useful in designing new and improved antioxidant compounds in future.

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