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# Novel 4-hydroxy-N'-[(1E)-substituted-phenylmethylidene] benzohydrazide analogs (hydrazones) as potent antibacterial and anti-oxidant agents

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**ABSTRACT**

In the present study, a series of 4-hydroxy-N′-[(1E)-substituted-phenylmethylidene] benzohydrazide analogs was synthesized, characterized, and evaluated for their antibacterial and anti-oxidant activity. All the tested compounds show high antibacterial activity with compound $AR_7$, N′-(3,4,5-trimethoxybenzylidene)-4-hydroxybenzohydrazide as the most active compound, whereas compounds $AR_{10}$ (hydrogen peroxide scavenging) and $AR_8$ (2,2-diphenyl-1-picrylhydrazyl radical scavenging activity method) were found to possess maximum anti-oxidant activity indicating that different mechanisms are involved in different anti-oxidant determination methods.

## INTRODUCTION

Multi-drug resistant microbial infection, a major problem in the treatment of infectious disease, is increasing considerably from the last decades (Ahmad *et al*., 2012; Makki *et al*., 2015) and to overcome this problem, development of new antimicrobial agents is the need of the hour (Lindahl, 2015; Venkatesh *et al*., 2016). Hydrazones, belonging to Schiff base family with chemical formula $R_2C=NNR_2$, are of incredible interest because of their various biological activities reported in literature, viz., anti-bacterial, anti-fungal, anti-convulsant, anti-inflammatory, anti-cancer, anti-viral, anti-malarial & anti-tuberculosis, anti-oxidant, and antidepressant (Alam *et al*., 2012; Kumar and Chauhan, 2014; Marwa and Ahmed, 2018; Neda *et al*., 2018; Nurkenov *et al*., 2017; Popiolek, 2017; Rayam *et al*., 2015; Verma *et al*., 2014). Along with the diverse activities, their ease of synthesis, increased stability, and tendency toward crystallinity make hydrazones a perfect choice to synthesize more effective and novel antimicrobial agents (Bala *et al*., 2011; 2013; Singh *et al*., 2016).

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The antimicrobial (Chaudhary *et al*., 2008; Kapoor and Dahiya, 2016; Khatkar *et al*., 2017) and anti-oxidant (Velika and Kron, 2012; Pontiki and Litina, 2019) perspective of organic acids can be well recognized from the literature. Phenolic compounds (Abouzeed *et al*., 2018; Benslama *et al*., 2017; Fu *et al*., 2016; Sahloul *et al*., 2014) are also proved as successful antibacterial as well as anti-oxidant activity which might be due to the fact that anti-oxidants act by creating scavenging environment which may inhibit bacterial growth. p-hydroxy benzoic acid, a phenolic derivative, is also found to possess various pharmacological activities, viz., antimicrobial, antialgal, antisickling, antimutagenic, antiviral, anti-inflammatory, anti-oxidant, etc., (Manuja *et al*., 2013). Antimicrobial potential of p-hydroxy benzoic acid derivatives, viz., N′-(4-methoxybenzylidene)-4-hydroxybenzohydrazide, N′-benzylidene-4-hydroxybenzohydrazide have also been reported (Sapra *et al*., 2014; Suzana *et al*., 2017). Therefore, the present study was designed with the aim of synthesizing novel hydrazone derivatives of p-hydroxy benzoic acid for exploring their antimicrobial and anti-oxidant potential.

## MATERIALS AND METHODS

Ester of 4-hydroxy benzoic acid was synthesized using Fischer esterification which was further treated with hydrazine hydrate in ethanol to yield corresponding 4-hydroxybenzoic acid

hydrazides. The synthesized hydrazides were further reacted with substituted aldehydes (aromatic) in presence of glacial acetic acid (2–3 drops) to yield 4-hydroxy-N′-[(1E)-substituted phenylmethylidene] benzohydrazide ($AR_1$–$AR_{10}$) (Scheme 1) which were then characterized by spectral and analytical means (Harer *et al*., 2010; Narang *et al*., 2012; Rajput and Rajput, 2009).

### Evaluation of antibacterial activity

Antibacterial activity of synthesized products was evaluated against *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), *Staphylococcus aureus* (ATCC 25923), and *Enterococcus faecalis* (ATCC 29212) using Norfloxacin standard as it is the most widely used antibiotic in bacterial infections (Table 2) (Cappucino and Sherman, 1999) by tube dilution method using double strength nutrient broth IP followed by incubation at 37°C ± 1°C.

### Antioxidant activity

*Hydrogen peroxide radical scavenging ($H_2O_2$) assay*

Hydrogen peroxide plays an important role as bactericidal agent (Halliwell, 1995) by acting directly or indirectly via its reduction product, $OH^-$ (second messenger in synthesis and activation of several inflammatory mediators) (Sprong *et al*., 1998).

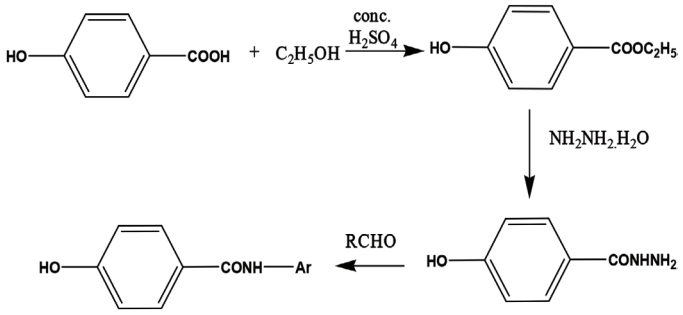
Anti-oxidant activity by the $H_2O_2$ method was determined as per the method reported (Ruch *et al*., 1989). Different dilutions of synthesized (20–60 µg/ml), as well as standard compound (Ascorbic acid) in distilled water, were added to 40 mM $H_2O_2$ solution prepared in phosphate buffer and absorbance was measured at 230 nm after 10 minutes against a blank solution.

### DPPH radical scavenging activity

DPPH radical scavenging, a standard rapid assay for antioxidant studies (Soares *et al*., 1977), was done by adding ethanolic DPPH solution (0.1 Mm) to test solutions as well as standard compound to make different dilutions (20–60 µg/ml) and then by measuring their absorbance at 517 nm after 30 minutes. Scavenging activity in both methods was expressed as inhibition percentage and calculated using the following formula:

$$\% \text{ inhibition} = (A_o - A_t)/A_o \times 100$$

where $A_o$ is the absorbance control (blank); $A_t$ is the absorbance of the test (Shukla *et al*., 2009).




**Scheme 1.** Synthesis of 4-hydroxy-N'-[(1E)-substituted-phenylmethylidene] benzohydrazide analogs.

## RESULTS AND DISCUSSION

Melting points of synthesized compounds were determined (Elico melting point apparatus, India) and purity was ascertained using single spot TLC (Table 1). The structures were confirmed by spectral studies (IR spectra on FTIR-Shimadzu spectrometer and $^1$H NMR spectra on BRUKER AVANCE II 400 NMR spectrometer using DMSO). The data obtained from spectral studies were in agreement with assigned molecular structures.

### Analytical data for compound $AR_1$

**M.P.(°C)**: 243–247; **Yield**: 77.4%; **IR** ($cm^{-1}$): 1,738.90 (C=O stretch), 1,627.99 (C=N stretch), 3,731.45 (OH stretch), 1,547.47 (C=C stretch), 3,227.35 (NH stretch), 2,995.45 (C-H stretch) ; $^1$H NMR: (δ) 9.9 (s, 1H, N=CH), 8.4 (s, 1H, NH-N=), 7.8 (d, 2H, Ar-H), 7.5 (m, 2H, Ar-H), 7.4 (m, 3H, Ar-H), 6.9 (m, 2H, Ar-H), 5.2 (s, 1H, OH).

### Analytical data for compound $AR_2$

**M.P.(°C):** 211–214; **Yield:** 72%; **IR** ($cm^{-1}$)**:** 1,720.13 (C=O stretch), 1,625.98 (C=N stretch), 3,636.48 (OH stretch), 3,279.74 (NH stretch), 3,035.96 (Aromatic CH stretch), 1,521.84 (Aromatic C=C stretch), 671.23 (C-Cl stretch), 2,961.45 (C-H stretch), 630.42 (CH Rocking), 1,148.46 (C-C stretch); **$^1$H NMR:** (δ) 9.1 (s, 1H, -NH-N=), 8.1 (s, 1H, -N=CH-), 7.8 (d, 2H, Ar-H), 7.6 (d, 2H, Ar-H), 7.3 (d, 2H, Ar-H), 6.9 (d, 2H, Ar-H), 5.4 (s, 1H, OH).

### Analytical data for compound $AR_3$

**M.P. (°C):** 225–227; **Yield:** 56.5%; **IR** ($cm^{-1}$)**:** 1,706.11 (C=O stretch), 1,665.45 (C=N stretch), 3,715.31 (OH stretch), 3,269.13 (NH stretch), 3,056.34 (Aromatic CH stretch), 1,504.54 (Aromatic C=C stretch), 2,921.32 (C-H stretch), 640.39 (CH Rocking), 1,148.46 (C-C stretch); **$^1$H NMR:** (δ) 8.0 (s, 1H, -NH-N=), 8.1 (s, 1H, -N=CH), 7.8 (d, 2H, Ar-H), 7.5 (d, 2H, Ar-H), 7.1 (d, 2H, Ar-H), 6.9 (d, 2H, Ar-H), 5.1 (s, 1H, OH).

### Analytical data for compound $AR_4$

**M.P. (°C):** 170–173; **Yield:** 55.3%; **IR** ($cm^{-1}$): 1,717.68 (C=O stretch), 1,627.99 (C=N stretch), 3,558.27 (OH stretch), 3,237.65 (NH stretch), 1,573.98 (NH band), 3,024.51 (Aromatic CH stretch), 1,544.08 (Aromatic C=C stretch), 1,302.01 (C-O stretch), 3,042.44 (C-H stretch), 659.68 (CH Rocking). 1,023.28 (C-C stretch); **$^1$H NMR:** δ 9.2 (s, 1H,-NH-N=), 8.1 (s, 1H,-N=CH-), 7.8 (d, 2H, Ar-H), 7.0 (m, 2H, Ar-H), 6.9 (d, 2H, Ar-H), 6.7 (d, 2H, Ar-H), 5.6 (s, 1H, OH), 3.7 (s, 3H, -$OCH_3$).

### Analytical data for compound $AR_5$

**M.P. (°C):** 247–249; **Yield:** 67.9%; **IR** ($cm^{-1}$): 1,710.70 (C=O stretch), 1,638.00 (C=N stretch), 3,562.60 (OH stretch), 1,560.92 (NH band), 3,081.60 (Aromatic CH-stretch), 1,590.92 (NH band), 1,545.65 (C=C stretch), 636.51 (CH rocking); **$^1$H NMR:** δ 9.8 (s,1H,NH), 8.4 (s,1H,OH), 7.8 (d, 2H, Ar-H), 7.7 (d, 2H, Ar-H), 7.6 (d, 2H, Ar-H), 7.3 (d, 2H, Ar-H), 7.1 (d, 2H, Ar-H), 7.0 (s, 1H, $OCH_3$), 6.8 (d, 2H, Ar-H).

### Analytical data for compound $AR_6$

**M.P. (°C):** 177–177; **Yield:** 87.8%; **IR** ($cm^{-1}$): 1,690.68 (C=O stretch), 1,636.67 (C=N stretch), 3,554.41 (OH stretch),

**Table 1.** Physical data of synthesized derivatives.

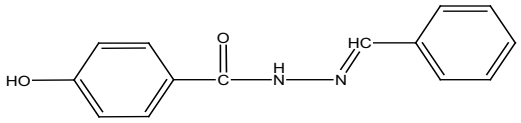
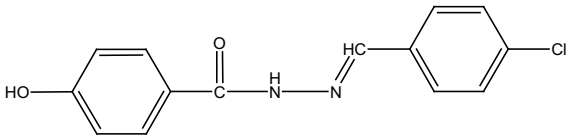
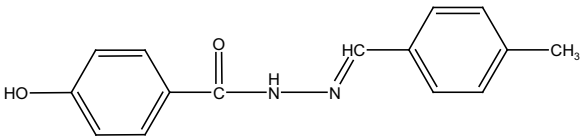
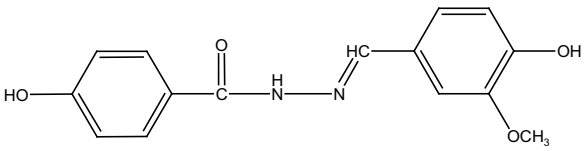
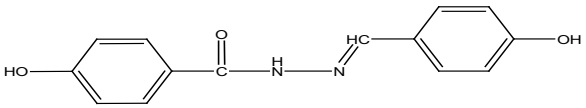
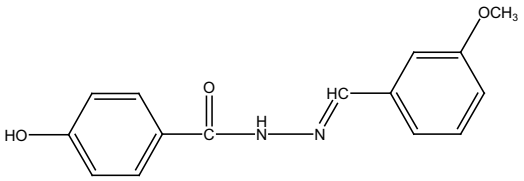
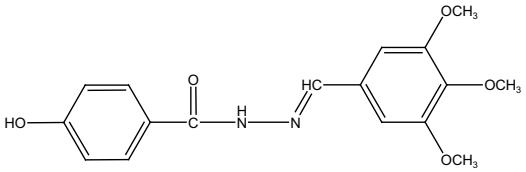
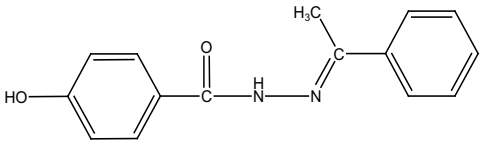
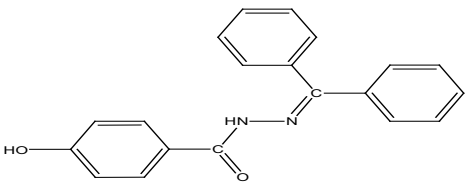
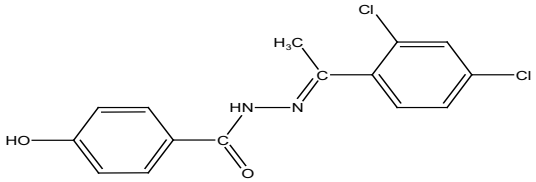
| S. No. | Compound | Structure | Molecular Formula | Mol. wt. | % yield | M. P | $R_f$ |
|---|---|---|---|---|---|---|---|
| 1 | $AR_1$ |  | $C_{14}H_{12}N_2O_2$ | 240.26 | 77.4 | 243–247 (Suzana *et al*., 2017) | 0.776 |
| 2 | $AR_2$ |  | $C_{14}H_{11}ClN_2O_2$ | 274.71 | 72 | 211–214 | 0.795 |
| 3 | $AR_3$ |  | $C_{15}H_{14}N_2O_2$ | 254.29 | 56.5 | 227–230 | 0.88 |
| 4 | $AR_4$ |  | $C_{15}H_{14}N_2O_4$ | 286.29 | 55.3 | 170–173 (Sapra *et al*., 2014) | 0.906 |
| 5 | $AR_5$ |  | $C_{14}H_{12}N_2O_3$ | 256.26 | 67.9 | 245–248 | 0.48 |
| 6 | $AR_6$ |  | $C_{15}H_{14}N_2O_3$ | 270.29 | 87.8 | 177–180 | 0.94 |
| 7 | $AR_7$ |  | $C_{17}H_{18}N_2O_5$ | 330.34 | 74.9 | 164–168 (Sapra *et al*., 2014) | 0.70 |
| 8 | $AR_8$ |  | $C_{15}H_{14}N_2O_2$ | 254.29 | 59.8 | 212–215 | 0.692 |
| 9 | $AR_9$ |  | $C_{20}H_{16}N_2O_2$ | 316.36 | 65.5 | 125–128 | 0.864 |
| 10 | $AR_{10}$ |  | $C_{15}H_{12}Cl_2N_2O_2$ | 323.18 | 71.8 | 112–115 | 0.783 |

**Table 2.** Antibacterial activity of synthesized compounds.

| Compound | $pMIC_{E.\ coli}$ | $pMIC_{P.\ aeruginosa}$ | $pMIC_{S.\ aureus}$ | $pMIC_{E.\ faecilis}$ |
|---|---|---|---|---|
| $AR_1$ | 0.0983 | 1.284 | 0.983 | 1.585 |
| $AR_2$ | 1.04 | 1.041 | 0.74 | 1.337 |
| $AR_3$ | 1.309 | 1.007 | 1.007 | 1.007 |
| $AR_4$ | 0.757 | 1.061 | 1.06 | 2.523 |
| $AR_5$ | 1.036 | 1.036 | 0.733 | 1.638 |
| $AR_6$ | 0.312 | 1.62 | 0.312 | 1.62 |
| $AR_7$ | 1.42 | 1.119 | 1.423 | 2.699 |
| $AR_8$ | 1.309 | 1.009 | 1.309 | 2.523 |
| $AR_9$ | 1.403 | 1.102 | 1.102 | 1.703 |
| $AR_{10}$ | 1.412 | 1.114 | 1.114 | 1.114 |
| SD* | 0.18 | 0.22 | 0.17 | 0.09 |
| Std. (Norfloxacin) | 2.61 | 2.61 | 2.61 | 2.61 |

3,277.20 (NH stretch), 3,037.05 (Aromatic CH stretch), 1,540.23 (Aromatic C=C stretch), 1,092.72 (C-O stretch), 2,772.79 (C-H stretch), 659.68 (CH Rocking), 1,033.89 (C-C stretch); **$^1$H NMR:** δ 8.0 (s, 1H, -NH-N=)**,** 8.1 (s, 1H, -N=CH-)**,** 7.7 (d, 2H, Ar-H), 7.1 (m, 2H, Ar-H)**,** 7.2 (m, 2H, Ar-H)**,** 6.9 (d, 2H, Ar-H)**,** 5.4 (s, 1H, OH)**,** 3.7 (s, 3H, -OCH3).

### Analytical data for compound $AR_7$

**M.P. (°C):** 164–168 (°C); **Yield:** 74.9%; **IR (cm$^{-1}$):** 1,730.11(C=O stretch), 1,690.25(C=N stretch), 3,675.15(OH stretch), 3,234.45 (NH stretch), 3,024.11 (Aromatic CH stretch), 1,560.45(Aromatic C=C stretch), 1,290.25 (C-O stretch), 2,755.31(C-H stretch); **$^1$H NMR:** δ 10.5 (s, 1H, CH), 9.9 (s, 1H, NH), 7.9 (s, 1H, OH), 6.8 (d, 2H, Ar-H), 3.1 (s, 6H, $2OCH_3$), 2.4 (d, 2H, Ar-H), 2.2 (s, 3H, $CH_3$).

### Analytical data for compound $AR_8$

**M.P. (°C):** 212–215; **Yield:** 59.8%; **IR (cm$^{-1}$):** 1,690.68 (C=O stretch), 1,691.64 (C=N stretch), 3,758.27 (OH stretch), 3,282.99 (NH stretch), 1,576.87 (NH band), 3,026.44 (Aromatic CH stretch), 1,544.68 (Aromatic C=C stretch), 1,105.26 (C-O stretch), 2,779.54 (C-H stretch), 660.65 (CH Rocking), 1,026.17 (C-C stretch); **$^1$H NMR:** δ 9.6(s, 1H, NH), 8.4(s, 1H, OH), 7.8(d, 2H, Ar-H), 7.7(d, 3H, Ar-H), 7.6(d, 2H, Ar-H), 7.5 (d, 2H, Ar-H), 3.2(s, 3H, $CH_3$).

### Analytical data for compound $AR_9$

**M.P. (°C):** 125–128; **Yield:** 48.1%; **IR (cm$^{-1}$):** 1,705.10 (C=O stretch), 1,645.74 (C=N stretch), 3,575.45 (OH stretch), 3,258.90 (NH stretch), 3,021.45 (Aromatic CH stretch), 2,650.45 (C-H stretch), 1,510.64 (Aromatic C=C stretch), 675.71 (CH Rocking). 1,019.21 (C-C stretch); **$^1$H NMR:** δ 7.8 (d, 2H, Ar-H), 7.7 (d, 2H, Ar-H), 7.4 (m, 2H, Ar-H), 6.9 (d, 2H, Ar-H), 7.0 (s, 1H, -NH-N=), 5.1 (s, 1H, OH).

### Analytical data for compound $AR_{10}$

**M.P. (°C):** 112–115; **Yield:** 97.7%; **IR (cm$^{-1}$):** 1,720.18 (C=O stretch), 1,685.71 (C=N stretch), 3,658.27 (OH stretch), 3,368.85 (NH stretch), 3,156.44 (Aromatic CH stretch), 1,642.55 (Aromatic C=C stretch), 1,576.87 (NH band), 3,079.54 (C-H stretch), 742.32 (C-Cl stretch), 670.55 (CH Rocking). 1,026.17 (C-C stretch); **$^1$H NMR:** δ 7.8 (d, 2H, Ar-H), 7.3 (m, 2H, Ar-H), 7.2 (m, 2H, Ar-H), 6.9 (d, 2H, Ar-H), 7.0 (s, 1H, -NH-N=), 5.1 (s, H, OH), 1.3 (s, 3H, $-CH_3$)

### Antibacterial evaluation

In *E. coli*, compounds **$AR_7$** (pMIC = 1.420) and **$AR_{10}$** (pMIC = 1.412); in *P. aeruginosa*, compounds **$AR_1$** (pMIC = 1.62) and **$AR_6$** (pMIC = 1.284); in *S. aureus,* compounds **$AR_7$** and **$AR_8$** and in *E. faecilis*, compounds **$AR_4$, $AR_7$, and $AR_8$** were emerged as the most active one.

From antibacterial studies, compound **$AR_7$**, N′-(3,4,5-trimethoxybenzylidene)-4-hydroxybenzohydrazide in case of *E. coli, S. aureus*, and *E. faecilis* and compound **$AR_6$**, N′-(3-methoxybenzylidene)-4-hydroxybenzohydrazide in case of *P. aeruginosa* were emerged as the most active compound indicating that methoxy group (e-donating group) on benzene ring is essential for antibacterial activity (Emami *et al*., 2008). All compounds show good antibacterial property which may be due to the presence of benzylidene/1-phenyl-ethylidene which imparts lipophillicity, a parameter responsible for penetration of molecules across the microbial membrane. In case of *E. coli*, the compound **$AR_{10}$** containing electron withdrawing chlorine group was also found effective which confirmed the fact that different structural requirements are requisite for activity against different microorganisms (Sortino *et al*., 2011). The above facts are summarized in Figure 1.

### Antioxidant evaluation

To verify the fact that antibacterial compounds also possess anti-oxidant activity, the synthesized compounds were evaluated and it was observed that compound **$AR_{10}$** possesses maximum anti-oxidant activity followed by compounds $AR_3$ and $AR_7$ as governed by **hydrogen peroxide scavenging activity** method, whereas in **DPPH scavenging activity,** compound **$AR_8$** possesses maximum antioxidant activity followed by compound $AR_9 > AR_{10}$. All these compounds show even better antioxidant activity than reference compound Ascorbic acid as depicted by their $IC_{50}$ (Table 3; Fig. 2a and b)

The high activity of compounds **$AR_2$** and **$AR_{10}$** can be explained by the fact that halogens like chloro enhance antioxidant activity due to its redox activity through one electron transfer mechanism (Bala *et al*., 2012; Dudhe *et al*., 2013; Hossain *et al*.,

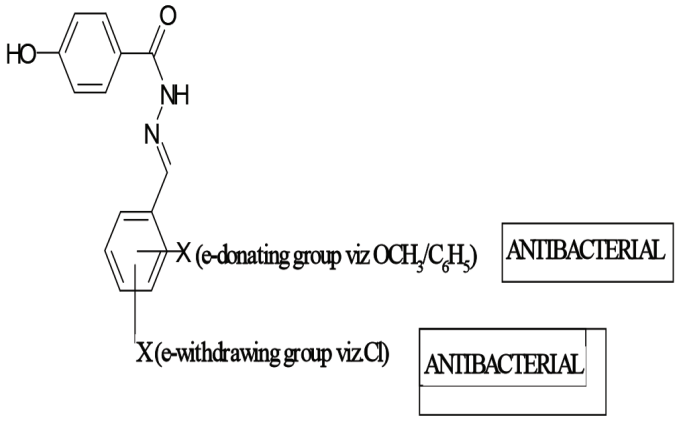
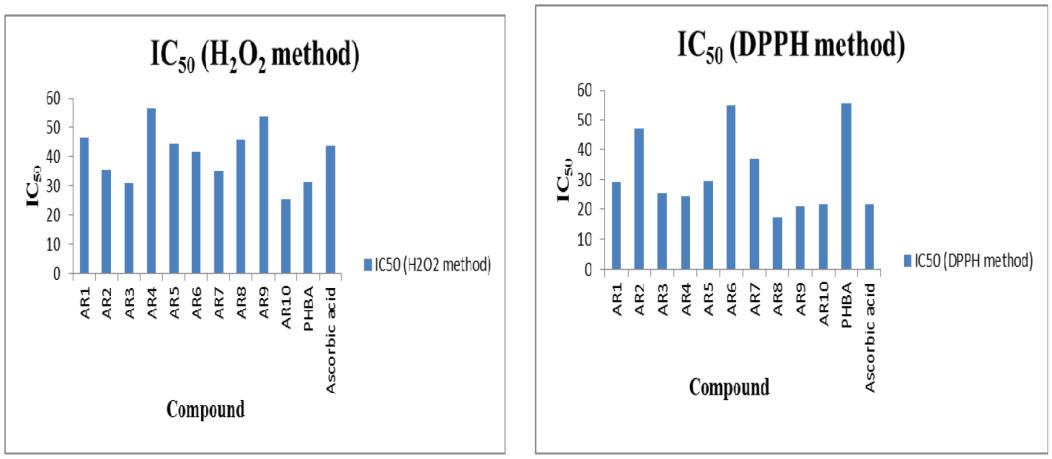



**Figure 1.** SAR studies.

**Table 3.** $IC_{50}$ of synthesized derivatives.

| Compound | $IC_{50}$ ($H_2O_2$ method) | $IC_{50}$ (DPPH method) |
|---|---|---|
| $AR_1$ | 46.73 | 29.38095 |
| $AR_2$ | 35.52 | 46.875 |
| $AR_3$ | 30.79 | 25.46939 |
| $AR_4$ | 56.595 | 24.53252 |
| $AR_5$ | 44.22 | 29.49458 |
| $AR_6$ | 41.747 | 55.05128 |
| $AR_7$ | 35.136 | 36.88525 |
| $AR_8$ | 46.05 | 17.3617 |
| $AR_9$ | 54.037 | 20.97087 |
| $AR_{10}$ | 25.253 | 21.68182 |
| PHBA | 31.368 | 55.67442 |
| Ascorbic acid | 43.53 | 21.60417 |




a) b)

**Figure 2.** (a and b) $IC_{50}$ of synthesized compounds ($H_2O_2$ and DPPH method).

2009). The high activity of compounds $AR_3$, $AR_7$, $AR_6$, $AR_8$, and $AR_9$ can be explained by the fact that methoxy and alkyl/aryl enhanced the stabilization of the generated radical during oxidation (Hadi *et al*., 2013). There is no correlation between results obtained by both methods, which governs that completely different mechanisms are involved in these two anti-oxidant determination methods.

## CONCLUSION

A series of 4-hydroxy-N′-[(1E)-substituted-phenylmethylidene] benzohydrazide derivatives were synthesized and evaluated for its antibacterial and anti-oxidant activity. Compound **$AR_7$** was found most potent antimicrobial against *E. coli*, *S. aureus*, *E. faecilis*, and and compound **$AR_6$** against *P. aeruginosa* which might be due to the presence of methoxy group (electron donating group) on benzene ring indicating the importance of electronic parameters in governing potency. Compounds **$AR_{10}$** and **$AR_8$** show maximum anti-oxidant activity when governed by hydrogen peroxide and DPPH scavenging activity, respectively, signifying different mechanisms are involved in antioxidant determination.

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## CONFLICT OF INTEREST

The authors declared no conflict of interest.

## FUNDING

None.

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