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**Brief communication**

# Green synthesis and antimicrobial activities of some aromatic hydrazones

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**ABSTRACT**

The condensation reaction of Benzil with semicarbazide followed by a triazine ring formation and then subsequent interaction with substituted aromatic aldehydes, resulted in synthesis of aromatic hydrazone derivatives **(C1–C4)**. These derivatives have been synthesized *via* greener method using acetic acid rather than conc. Sulfuric acid. The resultant compounds were analyzed using spectral (1H-NMR, IR) and elemental analysis. The *in-vitro* analysis of these compounds portrayed prominent activity against bacterial and fungal strains.

**Keywords:** Hydrazones, Green synthesis, Antibacterial activities, Antifungal activities.

## INTRODUCTION

Hydrazones are the organic compounds with basic structure>C=$NNH_2$. They are obtained by interaction of a carbonyl compound with a hydrazide (or hydrazine) in an organic solvent. However, recently there have been attractive developments leading to greener, efficient and economical methods for their synthesis such as-synthesis in aqueous medium, synthesis using grinding technique, microwave irradiation method, one-pot synthesis, biosynthesis, etc.[1-6]. Hydrazones and their complexes receive focus of researchers as they demonstrate prominent reactivity and showcase significance in multiple areas of research i.e.; materialistic chemistry, pharmaceutics and biological significance viz., anti-oxidant, anti-tumor, anti-malarial, anti-cancer, anti-inflammatory and antimicrobial activities, etc. [7-14]. The present scenario demands of newer drugs exhibiting microbial resistance against variety of pathogens including bacteria and fungi; along with easier synthetic approach[15,16]. Herein this research paper, we have reported green synthesis and antimicrobial activities of some Hydrazone derivatives.

## MATERIALS AND METHODS

The commercially procured chemicals (from Sigma Aldrich/Merck) were used without purification. Hydrogen, Carbon and Nitrogen were analyzed on a Perkin-Elmer C, H, N and S II series 2400 analyzer. IR spectra were recorded on a Perkin Elmer FTIR spectrophotometer (Spectrum version 10.4.00) using KBr pellets in the range

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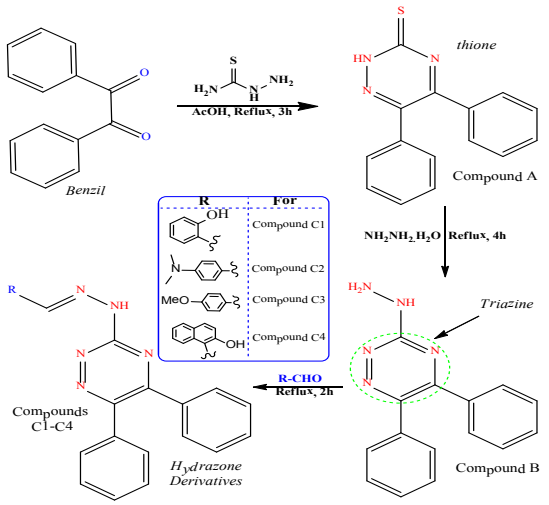
4000-400 $cm^{-1}$. $^1$H-NMR spectra were obtained on Bruker-Avance III 600 MHz using TMS as internal reference in DMSO-$d_6$.

**Green Synthesis of Thione (Scheme 1)**

To a mixture of Benzil (1mmol) and thiosemicarbazide (1mmol); acetic acid was added and contents were refluxed in water for about 3 hours. The obtained precipitate was filtered under vacuum, washed with water twice, dried in an oven for about 3-4 h to obtain solid orange-red compound A (m.p.: 221-223°C, Yield: 94%).




**Scheme 1. Synthetic route for Hydrazone derivatives**

**Synthesis of Hydrazone (Scheme 1)**

Thione (A, 2.5 g, 9.42mmol) and hydrazine hydrate (5 mL) in water were refluxed for about 4 h and then Acetic acid was added to neutralize the pH. The obtained precipitate was filtered under vacuum, washed with water, dried in an oven for about 3-4 h to obtain solid yellowish compound B (m.p.: 176-177°C, Yield: 89%).

**Synthesis of Hydrazone Derivatives (Scheme 1)**

A mixture of Hydrazone (B, 1mmol) and aldehyde (R-CHO, 1mmol) in ethanol was refluxed for about 2 hours. Contents were cooled and the obtained precipitate was filtered under vacuum, washed twice with water and dried in electric oven for about 3-4 h to obtain the final compounds C1-C4.

## RESULTS AND DISCUSSION

All the resultant hydrazine derivatives (C1-C4) were synthesized as shown in Scheme 1. In the very first step, A was prepared via a condensation pathway using acetic acid, skipping the use of conc. sulfuric acid. In the next step, compound A and hydrazine hydrate interacted to produce the Hydrazone B. In the final step, compound B and substituted aromatic aldehydes reacted to result in the formation of respective Hydrazone derivatives C1-C4. Final compounds were obtained in 83-91% yield. Physical and analytical results are given in Table 1.

**Table 1: Analytical and physical data for compounds C1-C4**

| S. No | Compound | Molecular Formula | m.p. (°C) | %Observed Yield (% Yield while using conc. $H_2SO_4$) | Elemental Analysis % found (% calcd.) C | H | N |
|---|---|---|---|---|---|---|---|
| 1 | Compound C1 | $C_{22}H_{17}N_5O$ | 271-272 | 86(83) | 72.13(71.92) | 4.47(4.66) | 18.88(19.06) |
| 2 | Compound C2 | $C_{24}H_{22}N_6$ | 262-263 | 91(78) | 73.19(73.07) | 5.78(5.62) | 21.11(21.30) |
| 3 | Compound C3 | $C_{23}H_{19}N_5O$ | 266-267 | 87(82) | 72.29(72.42) | 5.18(5.02) | 18.42(18.36) |
| 4 | Compound C4 | $C_{26}H_{19}N_5O$ | 310-311 | 83(88) | 74.68(74.80) | 4.63(4.59) | 16.64(16.78) |

**IR Spectra (Table 2)**

IR Spectra of the Hydrazone derivatives were observed in region of 4000-400 $cm^{-1}$. These spectra were studied and analyzed based upon some key peaks as recorded[17-20]. The presence of signals in spectra of all the derivatives C1-C4 in region 3250-3210 $cm^{-1}$ correspond to ν(N-H) which was originally present in compound B, confirming that no deprotonation occurred during synthesis of final compounds[18]. Presence of peaks in 1520-1515 $cm^{-1}$ range assigned to ν(N=C), confirms the formation of azomethine link[20].

Signals in the region 1620-1595 $cm^{-1}$ and 1285-1245 $cm^{-1}$ are attributed to ν(C=C) and ν(C-C), respectively. Peaks observed in 1065-1050 $cm^{-1}$ region are assigned to ν(C-H, aromatic) present in all the compounds.

**Table 2: IR spectral data for compounds C1-C4**

| S. No | Compound | ν(N-H) | ν(C=C) | ν(C=N) | ν(C-C) | ν(C-H) |
|---|---|---|---|---|---|---|
| 1 | Compound C1 | 3240 | 1620 | 1515 | 1280 | 1060 |
| 2 | Compound C2 | 3210 | 1595 | 1505 | 1275 | 1050 |
| 3 | Compound C3 | 3250 | 1615 | 1510 | 1245 | 1055 |
| 4 | Compound C4 | 3245 | 1610 | 1520 | 1285 | 1065 |

**$^1$H-NMR Spectra (Table 3)**

The presence of signals observed in 12.33-11.65 ppm region in the proton spectra of compounds C1, C2, C3 and C4 can be attributed to –NH protons[17]. Additionally, signals observed in the regions 9.68-8.20 ppm and 8.24-6.78 ppm are assigned to =CH and aromatic protons; respectively[19,20]. Peak observed at 2.99 ppm in C2 and 3.75 ppm in C3 have been assigned to the methyl protons; whereas peaks observed at 11.44 ppm in C1 and 12.79 ppm in C4 have been assigned to the hydroxyl (-OH) protons.

**Table 3: $^1$H-NMR spectral data for compounds C1-C4**

| S. No | Compound | $^1$H NMR (600 MHz, $Me_2SO$–$d_6$) |
|---|---|---|
| 1 | Compound C1 | δ12.23 (1H, NH), 11.44 (1H, OH), 8.42 (1H, =CH-), 7.45-7.33 (11H, Ar-H), 7.23 (1H, Ar-H), 6.91–6.87 (2H, Ar-H) |
| 2 | Compound C2 | δ11.65 (1H, NH), 9.68 (1H, =CH-), 7.56 (2H, Ar-H), 7.48 (3H, Ar-H), 7.41–7.38 (7H, Ar-H), 6.78 (2H, Ar-H), 2.99 (6H, $CH_3$) |
| 3 | Compound C3 | δ11.78 (1H, NH), 8.20 (1H, =CH-), 7.64 (2H, Ar-H), 7.44 (3H, Ar-H), 7.34 (7H, Ar-H), 6.98 (2H, Ar-H), 3.75 (3H, $CH_3$) |
| 4 | Compound C4 | δ12.79 (1H, OH), 12.33 (1H, NH), 9.35 (1H, =CH-), 8.24 (1H, Ar-H), 7.92 (2H, Ar-H), 7.63 (1H, Ar-H), 7.54 (2H, Ar-H), 7.49 (1H, Ar-H), 7.46–7.40 (8H, Ar-H), 7.33 (1H, Ar-H) |

**Antimicrobial Activities (Table 4, Figure 1)**

The synthesized derivatives were tested for their antimicrobial significance against *B. subtilis* ATCC 6051, *E. coli* ATCC 8739, *C. glabrata* ATCC 15545 and *A. niger* ATCC 1015). Ciprofloxacin and Itraconazole were used as control drugs using Kirby-Bauer well diffusion method[21-23]. Strains were swabbed on Sabouraud's Dextrose Agar as MH (Muller Hinton) Agar medium and plates were incubated for about 48 hours at 28°C.

Anti-microbial evaluation reveals that the derivatives (C1-C4) show promising activities against all these pathogens. Compound C2 showcased the best activity against all the strains in comparison to other derivatives, which may be owed to the presence of the tertiary amino group. Overall; the derivatives showed better anti-fungal significance in comparison to their anti-bacterial activities.

**Table 4: Antimicrobial activity results for compounds C1-C4**

| S. No | Compound | MIC concentrations (µg/mL) | | | |
|---|---|---|---|---|---|
| | | Bacterial strain | | Fungal Strain | |
| | | *B. subtilis* ATCC 6051 | *E. coli* ATCC 8739 | *C. glabrata* ATCC 15545 | *A. niger* ATCC 1015 |
| 1 | Compound C1 | 1000 | 750 | 500 | 500 |
| 2 | Compound C2 | 500 | 250 | 250 | 250 |
| 3 | Compound C3 | 750 | 750 | 750 | 500 |
| 4 | Compound C4 | 500 | 500 | 500 | 500 |
| 5 | Ciprofloxacin | 25 | 25 | --- | --- |
| 6 | Itraconazole | --- | --- | 10 | 5 |

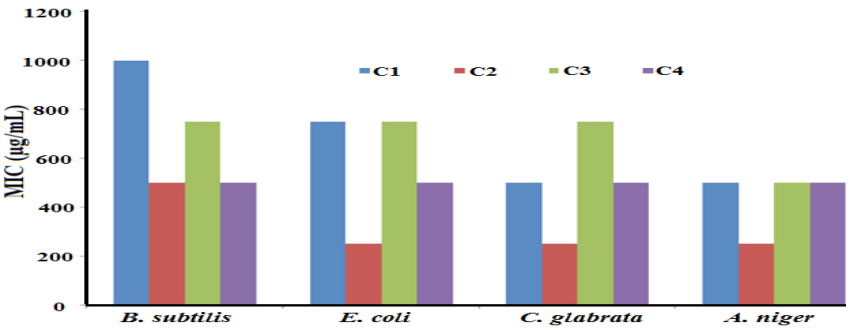



**Fig. 1. Antimicrobial activities (MIC values) of synthesized compounds C1-C4**

## CONCLUSION

In the present work; green syntheses of some Hydrazone derivatives have been reported. The use of organic solvents and sulfuric acid was eliminated as the reactions were carried out in aqueous medium. The anti-microbial evaluation of these compounds demonstrates significant biological activity against *B. subtilis, E.coli, C. glabrata* and *A. niger*. In comparison to other analogues, compound C2 showed best activities against the bacterial and fungal strains.

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**Conflict of Interest**

There are no conflicts of interest.

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