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Original Article

Synthesis and evaluation of the antibacterial and antifungal activity of new ibuprofen hydrazone derivatives

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ABSTRACT

Background and Aims: The pursuit of new antimicrobial agents to address antimicrobial resistance remains a fundamental effort in supporting sustainable global health endeavours. Hydrazone compounds possess numerous advantages as biologically active agents because of their diverse properties. In our work, a series of hydrazone derivatives (**4a-f**) containing the ibuprofen moiety were synthesised and evaluated as antibacterial and antifungal agents.

Methods: Novel hydrazone derivatives were synthesised through the condensation of 2-[4-(2-methylpropyl)phenyl]propanehydrazide with suitable cyclohexanone derivatives. The structure of the new compounds was confirmed using spectral methods such as IR, ^{1}H-NMR, ^{13}C-NMR (APT) and electrospray ionisation mass spectrometry (ESI-MS). Testing involved six compounds and their standards against a range of bacterial and fungal strains, including Gram-positive and Gram-negative bacteria, as well as *Candida* spp. MIC values were determined using the microbroth dilution method.

Results: Each of the tested molecules exhibited varying inhibitory effects across six distinct targets, resulting in different MIC values. Compounds **4a, 4e,** and **4f** showed moderate antimicrobial activity compared with the standards.

Conclusion: Among the tested compounds, compound **4a** demonstrated the most potent antimicrobial activity against the *P. mirabilis* strain, with an MIC value of 312.5 µg/mL. Further modification and development of ibuprofen-hydrazone derivatives against targets may result in new antimicrobial drug candidates in the near future.

Keywords: Hydrazone; ibuprofen; antibacterial activity; antifungal activity; gram-positive bacteria; gram-negative bacteria.

INTRODUCTION

Antimicrobial resistance (AMR) is a critical health problem and development threat to the entire world. AMR occurs as a result of bacteria, fungi, viruses, and parasites changing over time and not responding to drugs; this makes infections more difficult to treat and increases the risk of disease spread, morbidity, and mortality (WHO 2023). The increase in high resistance rates observed after antibiotic treatment causes prolonged hospitalisations, treatment failures, and seriously high costs (Dadgostar, 2019). New antibiotics that are effective against resistant microorganisms are urgently needed.

Hydrazide-hydrazones have demonstrated a wide range of pharmacological activities, including anticancer, antimicrobial, antidiabetic, anticonvulsant, antitumor, anti-tuberculosis, antidepressant, antiinflammatory, and antiviral activities (Angelova, Karabeliov, Andreeva-Gateva, & Tchekalarova, 2016; Koçyiğit-Kaymakçıoğlu et al., 2006; Nasr, Bondock, & Youns, 2014; Paprocka et al., 2018; Salgin-Goksen et al., 2021; Taha et al., 2017; Tian et al., 2009). Among the biological activity profiles of hydrazide-hydrazones, antimicrobial properties are the most prevalent in the scientific literature. Several hydrazone have been reported to possess wide spectra of activity against both Gram-(+) and Gram-(-) bacteria as antibacterial agents (Masunari & Tavares, 2007), and some of them have also been reported to have an inhibitory effect on fungi (Evranos, Gürpinar, & Eryilmaz, 2020; Tatar et al., 2016; Vicini, Zani, Cozzini, & Doytchinova, 2002).

In this paper, we report the synthesis of novel hydrazone obtained from the condensation of 2-[4-(2-methylpropyl)phenyl]propanehydrazide and appropriate cyclohexanone derivatives. All the synthesised compounds were also screened for their in vitro antibacterial and antifungal activities.

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MATERIALS AND METHODS

Chemistry

Commercially available chemicals were purchased from Sigma-Aldrich or Merck. Melting points were determined in open capillary tubes using a Buchi B-540 melting point apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were run on Bruker 500 MHz and Bruker 600 MHz spectrophotometers. Microanalyses were performed using a Thermo Finnigan Flash EA 1112 elemental analyser. An AgilentAgilent 1260 Infinity II ESI/MS mass spectrometer was used to record the mass spectra with electrospray ionisation (IR: Infrared radiation, ^{1}H-NMR: Proton nuclear magnetic resonance, ^{13}C-NMR: Carbon-13 nuclear magnetic resonance, APT: Attached proton test).

Methyl 2-[4-(2-methylpropyl)phenyl]propanoate (2)

Racemic acid (**1**) (0.1 mol) and a few drops of sulphuric acid (%98) in methanol (0.5 mol) were heated under reflux for 24 h. Saturated sodium bicarbonate was added, and the solvent was evaporated under vacuum. The solution was extracted with chloroform and dried over sodium sulphate. The yellowish oily residue was used without further purification (Allegretti et al., 2005) (CAS number: 61566-34-5).

2-[4-(2-Methylpropyl)phenyl]propanehydrazide (3)

A mixture of **2** (0.01 mol), ethanol (20 ml), and hydrazine hydrate was heated under reflux for 6 h. The resulting white powders were filtered off and recrystallised from C_2H_5OH (Bülbül et al., 2023) (CAS number: 127222-69-9).

General procedure for the synthesis of 2-[4-(2-methylpro pyl) phenyl]-N'-[4-(non)-substitutedcyclohexylidene] propanehydrazide (4a-f)

A solution of **3** (0.005 mol) in ethanol (25 ml) and an appropriate cyclohexanone (0.006 mol) was refluxed for 4-6 h. The resulting white solid was filtered off and recrystallised from C_2H_5OH-H_2O mixture.

N-(4-methylcyclohexylidene)-2-[4-(2-methylpropyl)phenyl] propanehydrazide (4b)

White crystals (84%); m.p. 122-124°C; IR(KBr): ν_{max} 3213, 3169 (N-H), 1656 (C=O), 1539, 1496, 1456 (C=N, C=C); ^{1}H-NMR ($CDCl_3$/600MHz): 8.49, 8.03 (1H, 2s, NH), 7.31-7.27, 7.26-7.21, 7.16-7.12, 7.08-7.03 (4H, 4m, Ar-H), 4.69-4.60, 3.69-3.60 (1H, 2m, -CH-CH_3), 2.63-2.38, 2.23-2.04, 1.92-1.43, 1.26-0.90 (18H, 4m, cyc-H, $(CH_3)_2$C**H**-, -CH-CH_2- and -CH-C**H**$_3$), 0.89 (6H, d, *J*= 6.6 Hz, CH_3); ^{13}C-NMR ($CDCl_3$/150MHz): 176.4, 170.2 (C=O), 161.2, 161.1, 154.8, 154.3 (C=N), 141.1, 139.8, 138.9, 138.8, 137.7 (C1, C4), 129.8, 129.0, 127.7, 127.5 (C2, C3, C5, C6), 45.9, 40.7, 40.5 (-CH-CH_3), 45.1, 44.9 (-CH-CH_2-), 35.0, 34.9, 34.8, 34.7, 34.6, 33.7, 33.5, 25.4, 25.0 (cyc-CH_2), 31.8, 31.6 (cyc-CH), 30.1 ($(CH_3)_2$CH), 22.4, 22.2 ($(CH_3)_2$CH-), 21.3, 21.2 (CH_3), 18.2, 18.1 (-CH-CH_3). LC-MS (ESI (+)) $C_{20}H_{30}N_2O$ $[M+H]^+$: 315.24309; Found: 315.2 (100, $[M+H]^+$), 316.2 (20, $[M+2H]^+$), 337.2 (95, $[M+Na]^+$), 338.2 (20, $[M+H+Na]^+$). Anal. calcd. for $C_{20}H_{30}N_2O$ (314.46) C: 76.39, H: 9.62, N: 8.91. Found C: 76.77, H: 9.13, N: 8.98.

N-(4-ethylcyclohexylidene)-2-[4-(2-methylpropyl)phenyl] propanehydrazide (4c)

White powders (88%); m.p. 112-114°C; IR(KBr): ν_{max} 3223, 3176 (N-H), 1660 (C=O), 1541, 1512, 1463 (C=N, C=C); ^{1}H-NMR ($CDCl_3$/500MHz): 8.52, 8.17 (1H, 2s, NH), 7.31, 7.25, 7.15, 7.07 (4H, 4d, *J*=7.8 Hz, Ar-H), 4.70-4.64, 3.71-3.62 (1H, 2m, -CH-CH_3), 2.68-0.80 (20H, m, cyc-H, $(CH_3)_2$C**H**-, -C**H**-CH_2- and -CH-C**H**$_3$),0.91 (6H, d, *J*= 6.6 Hz, CH_3); ^{13}C-NMR ($CDCl_3$/125MHz): 176.4 (C=O), 155.3, 154.8 (C=N), 141.0, 139.9, 138.8, 137.6 (C1, C4), 129.7, 129.0, 127.7, 127.5 (C2, C3, C5, C6), 45.8, 40.7, 40.5 (-**C**H-CH_3), 45.0, 44.9 (-CH-**C**H_2-), 38.5, 38.4 (cyc-CH), 34.7, 34.4, 32.6, 32.4, 31.4,25.6, 25.0 (cyc-CH_2), 28.7, 28.5, 28.2 (CH_2), 30.1 ($(CH_3)_2$**C**H-), 22.4, 22.2 ($(CH_3)_2$CH-), 18.2, 18.1 (-CH-**C**H_3), 11.5 (CH_3). LC-MS (ESI (+)) $C_{21}H_{32}N_2O$ $[M+H]^+$: 329.25874; Found: 329.2 (100, $[M+H]^+$), 351.2 (90, $[M+Na]^+$), 352.3 (25, $[M+H+Na]^+$). Anal. calcd. for $C_{21}H_{32}N_2O$ (328.49) C: 76.78, H: 9.82, N: 8.53, Found C: 76.99, H: 9.46, N: 8.59.

N-(4-propylcyclohexylidene)-2-[4-(2-methylpropyl)phenyl] propanehydrazide (4d)

White crystals (80%); m.p. 122-124°C; IR(KBr): ν_{max} 3224, 3174 (N-H), 1660 (C=O), 1541, 1512, 1456 (C=N, C=C); ^{1}H-NMR ($CDCl_3$/600MHz): 8.46, 8.02 (1H, 2s, NH), 7.29, 7.24 (2H, 2d, *J*= 7.8 Hz, Ar-H), 7.16-7.12, 7.08-7.03 (2H, 2m, Ar-H), 4.68-4.61, 3.68-3.62 (1H, 2m, -C**H**-CH_3), 2.62-2.39, 2.22-2.05, 1.95-0.85 (22H, 3m, cyc-H, $(CH_3)_2$C**H**-, -CH-C**H**$_2$- and -CH-C**H**$_3$), 0.89 (6H, d, *J*= 6.6 Hz, CH_3); ^{13}C-NMR ($CDCl_3$/150MHz): 176.4, 170.2 (C=O), 161.6, 161.5, 155.1, 154.7 (C=N), 141.1, 139.9, 139.8, 138.9, 137.7 (C1, C4), 129.8, 129.0, 127.7, 127.5 (C2, C3, C5, C6), 45.9, 40.7, 40.5 (-**C**H-CH**3**), 45.1, 44.9 (-**C**H-CH_2-), 38.2, 38.1 (CH_2), 36.5, 36.3, 36.2 (cyc-CH), 34.7, 34.5, 33.0, 32.8, 32.5, 25.4, 25.0 (cyc-CH_2), 31.7, 31,6, 31.5 ($(CH_3)_2$**C**H-), 22.4, 22.2 ($(CH_3)_2$CH-), 20.1(CH2), 18.3, 18.2, 18.1 (-CH-CH_3), 14.2 (CH_3). LC-MS (ESI (+)) $C_{22}H_{34}N_2O$ $[M+H]^+$: 343.27439; Found: 343.2 (10, $[M+H]^+$). Anal. calcd. for $C_{22}H_{34}N_2O$ (342.51): C: 77.14, H: 10.01, N: 8.18. Found C: 77.50, H: 10.20, N: 8.27.

***N*-(4-*tert*-butylcyclohexylidene)-2-[4-(2-methylpropyl) phenyl]propanehydrazide (4e)**

White crystals (81%); m.p. 113-125°C; IR(KBr): ν_{max} 3219, 3169 (N-H), 1662 (C=O), 1543, 1512, 1450 (C=N, C=C); ^{1}H-NMR ($CDCl_3$/600MHz): 8.43, 8.01 (1H, 2s, NH), 7.29, 7.24 (2H, 2d, *J*= 7.8 Hz, Ar-H), 7.17-7.12, 7.08-7.03 (1H, 2m, -C**H**-CH_3), 4.68-4.61, 3.68-3.62 (1H, 2m, -C**H**-CH_3), 2.63-2.40, 2.22-2.06, 1.97-0.85 (24H, 3m, cyc-H, $(CH_3)_2$C**H**-, -C(C**H**$_3)_3$ and -CH-CH_3**)**, 0.89 (6H, d, *J*= 6.6 Hz, CH_3); ^{13}C-NMR ($CDCl_3$/150MHz): 176.3, 170.2 (C=O), 161.6, 161.5, 155.1, 154.6 (C=N), 141.1, 139.9, 139.8, 138.9, 137.6 (C1, C4), 129.8, 129.0, 128.9, 127.7, 127.5, 127.3 (C2, C3, C5, C6), 45.9, 40.7, 40.6 (-**C**H-CH_3), 45.1, 44.9 (-CH-CH_2-), 38.5, 38.4, 38.3, 38.2 (cyc-CH), 34.7, 34.6, 34.5, 32.6, 32.4, 32.1, 31.4, 31.2, 25.4, 25.0 (cyc-CH_2), 30.1 (($CH_3)_2$CH-), 28.7, 28.5 (-C$(CH_3)_3$), 22.4, 22.2 (($\mathbf{C}H_3)_2$CH-), 18.3, 18.2, 18.1 (-CH-**C**H_3), 11.5 (CH_3). LC-MS (ESI (+)) $C_{23}H_{36}N_2O$; $[M+H]^+$: 357.29004; Found: 357.3 (10, $[M+H]^+$). Anal. calcd. for $C_{23}H_{36}N_2O$ (356.54) C: 77.48, H: 10.18, N: 7.86, Found C: 77.08, H: 10.22, N: 7.88.

Determination of Minimum Inhibitory Concentrations (MICs)

The ibuprofen hydrazone analogues in vitro antibacterial properties were determined through the application of the Clinical and Laboratory Standards Institute's microbroth dilution procedure (CLSI, 2008; CLSI, 2020).

The compounds were tested for their minimum inhibitory concentrations (MICs) against the following bacteria: *Escherichia coli* ATCC 25922, *Proteus mirabilis* ATCC 14153, *Staphylococcus aureus* ATCC 29213, *Staphylococcus epidermidis* ATCC 12228, *Klebsiella pneumoniae* ATCC 4103, and three yeasts: *Candida albicans* ATCC 10231, *Candida parapsilosis* ATCC 22019, and *Candida tropicalis* ATCC 750. As test media, Mueller-Hinton broth (MHB) (Difco, Detroit, MI, USA) was created for the bacteria through serial 2-fold dilutions ranging from 1250 to 0.6 µg/mL, while RPMI-1640 medium (Sigma, St. Louis, MO, USA) was prepared for the yeasts and buffered to pH 7.0 using MOPS. For the molecules, dimethyl sulfoxide (DMSO) was used as a solvent. To achieve a final concentration of 5 x10^5 CFU/mL for the bacteria and 0.5 x10^3 to 2.5 x10^3 CFU/mL for the yeasts in the test trays, respectively, 50 µl of a 4–6 h broth culture was added to each well. To prevent the trays from evaporating, they were covered and sealed in plastic bags. Trays containing MHB were incubated for 24 h at 37 °C, whereas trays containing RPMI-1640 media were incubated for 48 h at 30 °C. The minimum inhibitory concentration (MIC) is the lowest concentration of a chemical that completely inhibits observable development. The antibacterial properties of DMSO were examined using test microorganisms as a control. The values of the controls were used to evaluate the outcomes.

RESULTS AND DISCUSSION

Chemistry

The synthetic pathways for the preparation of the target products are illustrated in Figure 1. The reaction of 2-[4-(2-methylpropyl)phenyl]propanehydrazide and appropriate cyclohexanones in ethanol gives the corresponding hydrazone/hydrazide compounds in good to excellent yields. The molecular structure of the synthesized compounds was confirmed by spectroscopic methods including ^{1}H NMR, ^{13}C NMR, and mass spectrometry. In addition, compounds **4a** and **4f**, previously described by Halim et al. in the literature (Apaydın, Hasbal Çelikok, Yılmaz Özden, & Cihan Üstündağ, 2022), were synthesized and confirmed by spectral and analytical data (experimental information for these molecules was given in the Supplementary Material).

In the IR spectra, some significant stretching bands due to N–H, C=O, C=N, and C=C were at 3226-3169 cm^{-1}, 1662-1656 cm^{-1} and 1543-1448 cm^{-1} respectively.

The ^{1}H NMR spectra of **4a-f** displayed two sets of signals for most of the protons. NH protons were observed as two separate singlets at about δ 8.69-8.01 ppm. In the ^{1}H NMR spectra of **4a-f**, protons were observed at δ 2.84-0.85 ppm due to the existence of aliphatic protons in the cyclohexylidene residue.

Carbon resonances were assigned using the APT experiments. Observation of C=N (δ 161.6-153.2 ppm) resonances in the ^{13}C NMR spectra of **4a-f** verified the presence of hydrazone compounds. The ^{13}C NMR spectra of compound **4a-f** showed the characteristic amide C = O carbon at δ 176.5-170.2 ppm as two signal sets, except for **4c**. N-acylhydrazone can exist in four possible forms, as geometric isomers (E/Z) regarding the C=N double bonds and as rotamers (cis/trans) regarding the amide N-C(O) (Apaydın, Hasbal Çelikok, Yılmaz Özden, & Cihan Üstündağ, 2022; Cihan Üstündağ, Mataracı Kara, & Çapan, 2019). All compounds were found to exist as racemic mixtures of two isomers, as indicated by ^{1}H-NMR and ^{13}C-NMR spectra.

Protonated $[M+H]^+$ molecular ions observed in ESI-MS confirmed the molecular weights of the compounds.

In vitro Antibacterial and Antifungal Activity

Ibuprofen is approved for over-the-counter (OTC) usage at a dosage of 200 mg per single dose, with a maximum daily limit of 1200 mg (Moore, 2007). Antimicrobial properties are usually discovered later and considered as side effects in non-antibiotic drugs (Obad J, Suskovic J, & Kos, 2015). Similarly, the antimicrobial capabilities of ibuprofen are viewed solely as a side effect and are not addressed in the patient information leaflets accompanying ibuprofen drugs. In the disc diffusion test conducted to investigate the antimicrobial properties of ibuprofen, inhibition zones were obtained with concentrations greater than

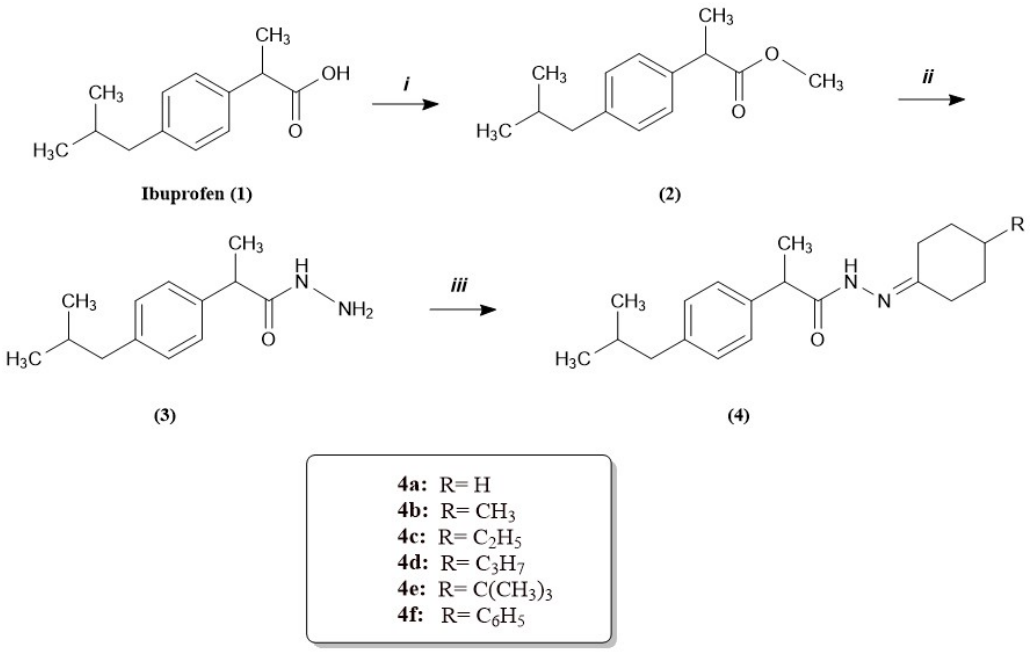

Figure 1. Synthesis route of hydrazide-hydrazone derivatives (**4a-f**) (i): CH_3OH, conc. H_2SO_4, reflux, 24 h; (ii): $NH_2NH_2.H_2O/C_2H_5OH$, reflux, 6 h (iii): C_2H_5OH/cyclic ketones, 4-6 h.

Table 1. Antimicrobial properties of compounds 4a-f against selected bacteria and fungi

	MIC (µg/mL)						
Microorganism	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**	**Reference antimicrobials**
***S. aureus* ATCC 29213**	-[a]	-	-	-	-	-	**1.2 (Cefuroxime-Na)**
***P. mirabilis* ATCC 14153**	**312.5**	-	-	-	**625**	**625**	**2.4 (Cefuroxime-Na)**
***S. epidermidis* ATCC 1228**	**625**	-	-	-	**625**	**625**	**9.8 (Cefuroxime)**
***E. coli* ATCC 25922**	**625**	-	-	-	-	**625**	**4.9 (Cefuroxime-Na)**
***E. fecalis* ATCC 29212**	**625**	-	-	-	**625**	**625**	**128 (Amikacin)**
***K. pneumoniae* ATCC 4352**	**625**	-	-	-	-	-	**4.9 (Cefuroxime-Na)**
***P. aeruginosa* ATCC 27853**	-	-	-	-	-	-	**2.4 (Ceftazidime)**
***C. albicans* ATCC 10231**	-	-	-	-	-	**625**	**4.9 (Clotrimazole)**
***C. tropicalis* ATCC 750**	-	-	-	-	-	-	**1 (Amphotericin B)**
***C. parapsilosis* ATCC 22019**	-	-	-	-	-	-	**0.5 (Amphotericin B)**

[a] No activity at the highest concentration tested.

62.5 µg and 250 µg for *Staphylococcus aureus*, 125 µg and 250 µg for *Bacillus subtilis*, 31.3 µg and 125 µg for *Candida albicans*, 31.3 µg and 62.5 µg for *Aspergillus brasiliensis* using ibuprofen/disc and ibuprofen lysine/disc, respectively. However, inhibition zones were not obtained for *Escherichia coli, Pseudomonas aeruginosa*, and *Salmonella typhimurium* (Obad J, Suskovic J, & Kos, 2015).

The antibacterial and antifungal activities of the new hydrazone derivatives (**4a-f**) were evaluated *in vitro* against the following strains: four Gram-negative bacteria [*Pseudomonas*

aeruginosa (ATCC 27853), *Escherichia coli* (ATCC 25922), *Klebsiella pneumoniae* (ATCC 4352), and *Proteus mirabilis* (ATCC 14153), three Gram-positive bacteria [*Staphylococcus aureus* (ATCC 29213), *Staphylococcus epidermidis* (ATCC 12228), and Enterococcus faecalis (ATCC 29212); and three yeasts [*Candida albicans* (ATCC 10231), *Candida parapsilosis* (ATCC 22019), and *Candida tropicalis* (ATCC 750). The structures of the new hydrazone derivatives used in this work and their MICs compared with standard agents are shown in **Table 1.** With regard to the antibacterial activity, **4b, 4c**, and **4d** exhibited no activity against any of the tested reference strains. Surprisingly, **4a, 4e**, and **4f** showed weak activity against some Gram-positive and Gram-negative *strains*, with an MIC value at 625 g/mL. The best antimicrobial activity result from our study was obtained from **4a** when tested against the P. mirabilis strain with a MIC value at 312.5 g/mL. Additionally, antifungal activity was observed against *C. albicans* with **4f**.

CONCLUSION

In this study, we evaluated the ibuprofen hydrazone derivatives in terms of antibacterial and antifungal efficacy. The structures of newly hydrazone products were verified by ^{1}H-NMR, ^{13}C-NMR, MS, and elemental analysis. The compounds **4a, 4e** and **4f** showed moderate antibacterial activity. The data obtained from the antimicrobial activity studies showed that some ibuprofen hydrazone analogs have a potential for the further studies.

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