Synthesis and Characterization of Chemical Compounds Derived From Benzohydrazide and Evaluation of Their Antibacterial Activities

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Abstract
Background: The antimicrobial resistance of pathogenic bacteria has emerged as a major health problem in recent years. Extensive research has been conducted to find new antimicrobial agents.

Objectives: The aim of this study was to examine the antibacterial activities of benzohydrazide derivatives.

Methods: Manganese hydrogen sulfate choline chloride was applied in a simple method for synthesizing benzohydrazide derivatives. Antimicrobial activities of the derivatives were assessed against Staphylococcus aureus, Escherichia coli, Enterococcus faecalis, Bacillus subtilis, diphtheroids, Salmonella enterica, Serratia marcescens, Pseudomonas aeruginosa, and Klebsiella pneumoniae. The structure of the synthesized compounds was determined employing 1H/13C NMR and Fourier-transform infrared (FTIR) spectroscopy. The reactions were carried out in choline chloride dissolved in water at room temperature.

Results: The results of this study showed that benzohydrazide derivatives had very desired antibacterial activities against the assessed bacteria.

Conclusions: Further investigations are required to assess the safety and efficacy of benzohydrazide derivatives as antibacterial agents in vivo and in vitro.

Keywords: Antibacterial activity, Benzohydrazide derivatives, Pathogenic bacteria

Background
Bacterial resistance has become a serious problem because of the widespread use of antibiotics either prophylactically or remedially without proper medical indications. The incorrect selection of alternative antimicrobials and numerous switching between them further contribute to antimicrobial resistance in bacteria (1).

The derivatives of benzohydrazide, a moiety present in the structure of various molecules, have been known to promote important biological activities. For example, studies have investigated pyrrolyl benzohydrazide for anticancer (3), N'-benzoyl-N-(3-hydroxybenzylidene) benzohydrazide (HHB) for anticancer (4), copper (II), manganese (II), and nickel (II) complexes of (Z)-2-hydroxy-(3-hydroxybenzylidene) benzohydrazides for in vitro antimicrobial and anticancer (4), copper (II), manganese (II), and nickel (II) complexes of (Z)-2-hydroxy-N',(2-oxoindolin-3-ylidene) benzohydrazide for in vitro antibacterial activities against Enterococcus faecalis (5), (3,4-disubstituted)-1,3-thiazol-2-ylidene]-4-hydroxybenzohydrazide (6) and quinolinaldehydrazines (7) also for anticancer, and finally 2-bromo-5-methoxy-N'-[4-(aryl)-1,3-thiazol-2-yl] benzohydrazide derivatives (8) for analgesic, antiinflammatory, and antibacterial activities. In a recent study, the biological effects of three benzohydrazide derivatives were screened, from which two compounds exhibited promising analgesic activities, and one showed in vitro antiproliferative activity (8). Furthermore, isonicotinohydrazide and benzohydrazide analogues were evaluated for their in vitro antimicrobial activities against Mycobacterium tuberculosis H₃₇Ra (MTB) (9). In other studies, benzoheterocyclic analogues of N'-benzoyl-N-(tert-butyl) benzohydrazide showed insecticidal activity against Spodoptera litura F. (10), and N',N'-dibenzyl benzoazidazides did in vitro antifungal activity against Botrytis cinerea phytopathogenic fungus (11).

The quinoline scaffold is prevalent in the structure of a variety of pharmacologically active synthetic and natural compounds. Quinolines are historically known as the most important antimalarial drugs ever used. Chloroquine which is the most famous drug of this group has dedicated to us great hopes for eradicating malaria. Other known drugs of this family include quinidine, quinine, ciprofloxacin, grepafloxacin, antrafenine, saquinavir, gemifloxacin, topotecan, balofloxacin, and levofloxacin. As a core essential molecule, quinoline in the form of chloroquinolone ring is often used for designing many synthetic compounds with diverse biological activities (12). Some studies, for example, have been conducted to assess 2-chloro-3-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl) quinoline derivatives for in vitro antifungal and antibacterial effects (13), (2-chloro-quinoline-3-yl)-
methanol for antioxidant and cytotoxic properties (14), 2-chloro-3-(I, 3-dioxolan-2-yl) quinolines for DPPH free radical scavenging activities (15), 2-chloro quinoline-3-carbaldehyde derived Schiff bases for antimicrobial activities (16), 7-chloro-4-quinolinylhydrzone derivatives for antitumoral properties (17), N-(2-(arylaldimine) ethyl)-7-chloroquinolone-4-amine derivatives for fighting with Zika virus function (18), 1-(7-Chloroquinolin-4-yl)-2-[1H-pyrryl-2-yl] methylene hydrazine as an anticancer agent (19), 4-[(p-Aminobenzensulfonylamide-N\'-[2-pyridinil]-7-chloroquinolone derivatives as promising antimalarial compounds, and the spots were visualized under UV light. To prepare manganese hydrogen sulfate choline chloride (m, 3H), 7.20 (m, 1H), 5.20 (s, 2H).

**Methods**

The materials were purchased from Merck and Sigma–Aldrich, Germany, and all the chemicals were used without further purification. The composition of the products was characterized by FT-IR, and 1H-NMR, and their physical and spectral data with those of authentic samples. FT-IR spectra were run in a Bruker, Equinox 55 spectrometer. The Bruker (DRX-500 Avanes) NMR device was used to record 1H NMR spectra. Thin-layer chromatography was performed to check the purity of compounds, and the spots were visualized under UV.

**Preparation of Green Catalyst Liquid**

To prepare manganese hydrogen sulfate choline chloride (MHSCC), MnCl2\·2H2O (0.1 mol) was poured in a 250-mL round-bottomed flask fitted with a calcium chloride drying tube, and concentrated sulfuric acid (98%, 10.8 mL, 0.2 mol) was added dropwise over 30 minutes at room temperature. After the addition of H2SO4, the mixture was shaken for 30 minutes to obtain a pale pink solid. To eliminate H2SO4, the solid was washed with absolute ethanol (25). Afterwards, in a 50-mL round-bottomed flask, 5.00 g (0.036 moles) choline chloride was dissolved in 10 mL water, and then the mixture was stirred. Finally, manganese hydrogen sulfate (0.50 g, 2.0 mmol) was added to obtain a transparent liquid.

Preparation of N\'-(2-Chloroquinolin-3-yl) Methylene Benzohydrazides (5a-5h)

Benzohydrazide derivatives (2 mmol) and 2-chloroquinoline-3-carbaldehyde (0.383 g, 2 mmol) were mixed and ground in a pestle. The mixed powder and MHSCC were transferred to a round-bottomed flask and heated up to 60°C. The progress of the reaction was monitored by thin-layer chromatography. After the completion of the reaction, 25 mL ethyl acetate was added to the mixture to precipitate and filter the product. The crude product was then recrystallized from ethanol to form pure benzohydrazide derivatives with the yields of 83% to 95%. All the products were identified by comparing their physical and spectral data with those of authentic samples.

**Entry 1:** N\'-(2-Chloroquinolin-3-yl) methylene)-2-methoxybenzohydrazide: Color Light orange, Yield of 93%, mp 144–145°C.

**FT-IR (KBr) vmax/cm⁻¹:** 3432, 3266, 2956, 1676, 1649, 1607, 1578. 1H NMR (DMSO-d6, 400 MHz) δ: 12.10 (1H, s), 9.00 (s, 1H), 8.90 (s, 1H), 8.25 (d, 1H, J 8.1 Hz), 8.00 (m, 3H, ArH), 7.90 (t, 1H, J 8.1Hz), 7.70 (t, 2H, J 7.8Hz), 7.10 (d, 1H, J 9.0 Hz), 3.06 (s, 3H).

**Entry 2:** N\'-(2-Chloroquinolin-3-yl) methylene)-4-nitrobenzohydrazide: Color Yellow, Yield of 89%, mp 257–258°C.

**FT-IR (KBr) vmax/cm⁻¹:** 3437, 3181, 2853, 1670, 1617, 1597, 1523; 1H NMR (DMSO-d6, 400 MHz) δ: 12.50 (s, 1H), 9.05 (s, 1H), 8.95 (s, 1H), 8.40 (d, 2H, J 7 Hz), 8.30 (m, 3H), 8.00 (d, 1H, J 8.4 Hz), 7.90 (t, 1H, J 6.9 Hz), 7.70 (t, 1H, J 7.5 Hz).

**Entry 3:** N\'-(2-Chloroquinolin-3-yl) methylene)-2-hydroxybenzohydrazide: Color Off white, Yield of 90%, mp 159–161°C.

**FT-IR (KBr) vmax/cm⁻¹:** 3196, 3051, 1669, 1590, 1556; 1H NMR (DMSO-d6, 400 MHz) δ: 12.20 (s, 1H, NH), 11.75 (s, 1H, OH), 9.00 (s, 1H), 8.95 (1H, s), 8.45 (d, 1H, J 7.5 Hz), 8.00 (d, 1H, J 8.4 Hz), 7.90 (t, 2H, J 7.2 Hz), 7.50 (t, 1H, J 7.2 Hz), 7.00 (t, 2H, J 7.8 Hz).

**Entry 4:** N\'-(2-Chloroquinolin-3-yl) methylene)-2,4-dinitrobenzohydrazide: Color Yellow, Yield of 85%, mp 142–143°C.

**FT-IR (KBr) vmax/cm⁻¹:** 3414, 3250, 2916, 1665, 1630, 1619, 1582, 1563; 1H NMR (DMSO-d6, 400 MHz) δ: 12.40 (1H, s, NH), 8.69 (1H, s), 8.68 (s, 1H), 8.26 (d, 1H, J 8 Hz), 8.00–7.86 (m, 2H), 7.72 (t, 1H, J 7.8 Hz), 7.57–7.56 (m, 1H), 6.19–6.10 (m, 2H).

**Entry 5:** N\'-(2-Chloroquinolin-3-yl) methylene)-2,3,5-trichlorophenoxoacylidyrazide: Color White, Yield of 88%, mp 199–200°C.

**FT-IR (KBr) vmax/cm⁻¹:** 3192, 3113, 2987, 1685, 1635, 1616, 1583; 1H NMR (DMSO-d6, 400 MHz) δ: 12.10 (s, 1H, NH), 9.03 (s, 1H), 8.70 (s, 1H), 8.22 (d, 1H, J 12 Hz), 7.98 (d, 1H, J 8 Hz), 7.88 (t, 1H, J 8 Hz), 7.70–7.34 (m, 3H), 7.20 (m, 1H), 5.20 (s, 2H).

**Entry 6:** 4-Chloro-N\'-((2-Chloroquinolin-3-yl) methylene) benzohydrazide: Color Off white, Yield of 85%, mp 268–269°C.

**FT-IR (KBr) vmax/cm⁻¹:** 3174, 3053, 2902, 1651, 1618, 1593, 1552; 1H NMR (DMSO-d6, 400 MHz) δ: 12.40 (s,
Bacterial Isolates

The antibacterial activities of the benzohydrazide derivatives were examined against four Gram-positive bacteria, namely, *S. aureus*, *E. faecalis*, *Bacillus subtilis*, and diphtheroids, as well as five Gram-negative bacteria including *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *S. marcescens*, and *S. enterica*. The bacteria were obtained from clinical samples, propagated on nutrient agar (Merck, Germany) at 37°C, and maintained at 4°C until use.

In Vitro Antibacterial Assessment

In this study, the antibacterial activities of the benzohydrazide derivatives were assessed by the agar well-diffusion method. A suspension containing 1.5×10⁸ CFU/mL bacteria in sterile normal saline (adjusted to 0.5 McFarland standard) was initially prepared (26). Muller-Hinton agar (Merck, Company) with a depth of 4 mm was poured into petri dishes to give a solid plate. Next, 100 μL of the bacterial suspension was inoculated into the medium by sterile cotton swabs. Afterward, 6-mm diameter punctures were created within the culture media by sterile cork borers and filled with 20 μL of each benzohydrazide derivative. The first used concentration was 80 mg/mL, and the plates were incubated at 37°C for 24 hours. Following incubation, the antibacterial activity was determined by measuring the zones of inhibition (mm) around each well. All the tests were performed in triplicate. DMSO: methanol (1:1 v/v) solvent and tetracycline were considered as negative and positive controls, respectively. To determine minimum inhibitory concentration (MIC), a two-fold dilution series (80, 40, 20, 10, 5, 2.5, 1.25, 0.625, and 0.3 mg/mL) of each benzohydrazide derivative was prepared in DMSO: methanol (1:1 v/v) solvent and bioassayed using the agar well-diffusion method as mentioned above. The cultures were then incubated at 37°C for 24 hours.

Results

In our ongoing search for bioactive substances and in connection with our efforts to synthesize benzohydrazide derivatives, we here investigated the antibacterial activities of these chemical adducts. First, we described an efficient protocol for preparing these compounds. The results of antimicrobial tests showed that these derivatives were active against *S. aureus*, *E. coli*, *E. faecalis*, *B. subtilis*, diphtheroids, *S. enterica*, *S. marcescens*, *P. aeruginosa*, and *K. pneumoniae*. Initially, we examined the efficiency of the synthesis process of N’-((2-Chloroquinolin-3-yl) methylene)-2-phenoxyacetohydrazide. To this end, 2-methoxybenzhydrazide (0.332 g, 2 mmol) and 2-chloroquinoline-3-carbaldehyde (0.383 g, 2 mmol) were mixed and ground in a pestle. The mixed powder was transferred to a round-bottomed flask containing the green catalyst liquid. Overall, we here presented a simple method for synthesizing benzohydrazide derivatives using the green catalyst liquid as an eco-friendly, inexpensive, and efficient reagent. Short reaction times, high yield, the simplicity of the process, and an easy work-up procedure are some of the advantages of this method. Our promising results suggest the necessity of evaluating the antibacterial activities of other structural derivatives of benzohydrazide. The results of FT-IR and ¹H NMR analyses of N’-((2-Chloroquinolin-3-yl) methylene)-2-methoxybenzohydrazide have been shown in Figures 1 and 2.

According to the antibiogram test (i.e. agar well-diffusion assay), all of the bacterial isolates were sensitive to the used benzohydrazide derivatives at 80 mg/mL concentration, delivering inhibition zones ranging from 11 to 42 mm (Table 1). The MIC values of benzohydrazide derivatives have been shown in Table 2.

Discussion

Increased resistance to antibiotics is an alarming health threat as treating the infections caused by resistant bacterial strains can be problematic (28). This study aimed to examine the antibacterial activities of benzohydrazide...
Table 1. Inhibition Zones (mm) of Eight Benzohydrazide Derivatives at 80 mg/mL Concentration Against Nine Bacteria as Assessed by Agar Well-diffusion Assay

| Bacteria   | 4-Chloro-N'-((2-chloroquinolin-3-yl)methylene) benzohydrazide | N'-((2-Chloroquinolin-3-yl)methylene)-2,4-dinitrobenzohydrazide | N'-((2-Chloroquinolin-3-yl)methylene)-2-phenoxyacetohydrazide | N'-((2-Chloroquinolin-3-yl)methylene)-2-(3,5-dichlorophenoxy) acetohydrazide | N'-((2-Chloroquinolin-3-yl)methylene)-4-nitrobenzohydrazide | N'-((2-Chloroquinolin-3-yl)methylene) benzohydrazide | N'-((2-Chloroquinolin-3-yl)methylene)-2-hydroxybenzohydrazide |
|------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|------------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|------------------------------------------------------------------|
| S. aureus  | -                                                             | 12                                                            | 15                                                            | 20                                                               | 17                                                             | 17                                                            |
| E. faecalis| 11                                                            | 16                                                            | 10                                                            | 24                                                               | 25                                                             | 25                                                             | 25                                                               |
| B. subtilis| -                                                             | 13                                                            | 20                                                            | 17                                                               | 25                                                             | 25                                                             | 20                                                               |
| Diphtheroids| 12                                                           | -                                                             | 25                                                            | 40                                                               | 34                                                             | 34                                                             | 42                                                               |
| E. coli    | 12                                                            | 20                                                            | 19                                                            | 18                                                               | 22                                                             | 12                                                             | 18                                                               |
| S. enterica| 11                                                            | 17                                                            | 12                                                            | 24                                                               | 21                                                             | 15                                                             | 22                                                               |
| S. marcescens| 12                                                           | 20                                                            | 16                                                            | 23                                                               | 23                                                             | 14                                                             | 21                                                               |
| P. aeruginosa| 11                                                          | 15                                                            | 16                                                            | 13                                                               | 24                                                             | 11                                                             | 18                                                               |
| K. pneumonia| 11                                                          | 21                                                            | 18                                                            | 26                                                               | 21                                                             | 13                                                             | 21                                                               |

Table 2. MIC (mg/mL) Values of Eight Benzohydrazide Derivatives Against Nine Bacteria as Determined by Agar Well-diffusion Assay

| Bacteria   | 4-Chloro-N'-((2-chloroquinolin-3-yl)methylene) benzohydrazide | N'-((2-Chloroquinolin-3-yl)methylene)-2,4-dinitrobenzohydrazide | N'-((2-Chloroquinolin-3-yl)methylene)-2-phenoxyacetohydrazide | N'-((2-Chloroquinolin-3-yl)methylene)-2-(3,5-dichlorophenoxy) acetohydrazide | N'-((2-Chloroquinolin-3-yl)methylene)-4-nitrobenzohydrazide | N'-((2-Chloroquinolin-3-yl)methylene) benzohydrazide | N'-((2-Chloroquinolin-3-yl)methylene)-2-hydroxybenzohydrazide |
|------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|------------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|------------------------------------------------------------------|
| S. aureus  | aa                                                            | 20                                                            | 40                                                            | 5                                                               | 20                                                             | 20                                                             | 10                                                               |
| E. faecalis| 40                                                            | 20                                                            | 2.5                                                           | 5                                                               | 10                                                             | 2.5                                                             | 10                                                               |
| B. subtilis| -                                                             | 10                                                            | 10                                                            | 2.5                                                              | 0.625                                                          | 0.625                                                          | 10                                                               |
| Diphtheroids| 0.625                                                        | 10                                                            | 10                                                            | 0.625                                                            | 0.625                                                          | 0.625                                                          | 2.5                                                              |
| E. coli    | 40                                                            | 20                                                            | 40                                                            | 10                                                               | 0.625                                                          | 0.625                                                          | 10                                                               |
| S. enterica| 20                                                            | 10                                                            | 10                                                            | 10                                                               | 1.25                                                           | 5                                                               | 0.625                                                            |
| S. marcescens| 40                                                          | 10                                                            | 2.5                                                           | 5                                                               | 0.625                                                          | 0.625                                                          | 10                                                               |
| P. aeruginosa| 40                                                          | 10                                                            | 5                                                             | 0.625                                                            | 0.625                                                          | 5                                                               | 20                                                               |
| K. pneumonia| 40                                                          | 20                                                            | 40                                                            | 10                                                               | 10                                                             | 80                                                             | 10                                                               |

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derivatives against some pathogenic bacteria using in vitro assays. To achieve this goal, we challenged nine bacterial isolates with different concentrations of benzohydrazide derivatives. Based on the obtained results, the benzohydrazide derivatives showed significant antimicrobial activities against the evaluated bacteria. Similar studies have investigated the antimicrobial effects of some biologically active chemical reagents. In one study, a synthetic series of [3/4-bromo-N\&apos;\&(substituted benzylidene/furan-2-ylmethylene/5-oxopentylidene/3-phenylallylidene), benzohydrazides (1-23)] were subjected to physicochemical and spectral characterization. The synthesized compounds were also screened for their antimicrobial and anticancer features. Antimicrobial tests indicated that one of the compounds (number 12, pMICam = 1.67 μM/mL) delivered the most potent antimicrobial activity (29). Furthermore, in another study, 14 derivatives of 4-substituted [N&apos;-benzofuroxan-5-yl] benzohydrazides nifuroxazide were synthesized and tested against the standard multidrug-resistant S. aureus strains. Twelve out of the 14 compounds exhibited bacteriostatic activities against the evaluated strains (30). In the study of Ghasemi et al, thiazole derivatives significantly inhibited the growth of B. cereus and L. monocytogenes, but not E. coli and S. typhimurium (31). Setyawati et al also synthesized chalcone-like benzohydrazide derivatives applying natural vanillin and wintergreen oil and investigated their potential as natural antiseptic coatings for materials surfaces and for a variety of other environmental and biomedical applications.

Conclusions
Our findings revealed the potential of benzohydrazide derivatives as potent antibacterial agents. Hence, these compounds can be exploited as antiseptic coatings for materials surfaces and for a variety of other environmental and biomedical applications.

Conflict of Interests
Authors have no conflict of interests to declare.

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Authors’ Contribution
We confirm that the manuscript, as well as the order of authors listed in the manuscript, has been contributed, reviewed and approved by all named authors.

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