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Synthesis and *In-Vitro* Antimicrobial Activity of *N*-Benzamide Derivatives

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Abstract: Amide derivatives of benzoic acids have a wide range of pharmacological effects, including analgesic, anti-inflammatory, anti-cancer, cardiovascular, and other biological effects, as well as antimicrobial, antibacterial, and antifungal effects. These biological implications draw the scientific community to create numerous novel benzamide derivatives. The synthesis of 12 benzamide compounds and their antibacterial activity profile are the subjects of the current investigation. Compound **5a** showed remarkably excellent activity against both the strains *B. subtilis* and *E. coli* with a diameter zone of inhibition 25 and 31 mm and MIC values of 6.25 for *B. subtilis* and 3.12 μg/mL for *E. coli*, respectively. However, compounds **6b** and **6c** showed better activity against *E. coli and B. subtilis* with a 24 mm diameter zone of inhibition and have 3.12 and 6.25 μg/mL MIC values, respectively.

Keywords: *para*-hydroxy benzoic acid; thionyl chloride; substituted amines; antimicrobial agents.

1. Introduction

Amides are important in synthesizing many molecules in various industries but especially important in the pharmaceutical industry [1]. Due to their anticonvulsant, analgesic, antitumor [2-6], antioxidant [7-11], antibacterial, antifungal [12-17], and insecticide [18] activities, amides have been found to be potent antimicrobial agents. A majority of the top-selling pharmaceuticals in the market today, about 25%, contain amides, showing their pervasive use in contemporary medicine. Plant-derived amino acids have antifungal, antiseptic, anti-inflammatory, insecticidal, antiviral, wound-healing, and antibacterial properties [19]. Recently substituted amides are gaining much importance and attention due to their wide range of biological activities, which include their antibacterial, antifungal, anticonvulsant, anesthetic, antiproliferative, antiplaque, antiplatelet-aggregation, antioxidant, and potassium channel activating potential [20,21]. In the last 20 years, patients with comparatively weakened immune systems are more likely to contract infections brought on by time-resolving fungal pathogens. Both single and multiple drug resistance exists in the strains of the AIDS epidemic and Mycobacterium TB [22]. In recent years, peptides are a novel class of therapeutic medicines that have gained attention due to their unique biochemical features and therapeutic potential [23]. Thus, the current state of medicine necessitates inventing new, powerful medications with original modes of action.

The current work focused on the synthesis, characterization, and biological activities of amide derivatives **5 (a-h)** and **6 (a-h)**. The synthesized compounds were tested for their antibacterial activity using the disc diffusion technique. As a result, three compounds, **5(a)** and **6b**, **6c**, showed good antibacterial activities.

2. Materials and Methods

2.1. Materials.

The reagents used in the synthesis were commercially available and of analytical grade. All solvents and reagents were used without further purification.

2.2. Methods.

The melting points of the compounds were determined in open capillary and are uncorrected. ^{1}H and ^{13}CNMR (DMSO) spectra were recorded on 400 MHz JEOL, model: JNM ECS400 instrument using TMS as a reference, chemical shift in δppm. Mass spectra were recorded in XEVO G2-XS QTOF (TOF MS ES+, 1.83e8). Melting points were determined in an open capillary tube and were uncorrected.

2.3. General procedure for the synthesis of acid chlorides 3 or 4.

A mixture of acid **1** or **2** (1 mol) thionyl chloride (1 mol) containing DMF was refluxed for 2 hrs. The mixture was evaporated, and toluene was used to dissolve the residue. The resulting solution was then evaporated to furnish acid chlorides 3 and **4,** respectively. The crude acid chlorides were immediately used for the next amidation step by dissolving them in anhydrous CH_2Cl_2 at 0°C.

2.4. General procedure for the synthesis of N-benzamides 5(a-f) or 6(a-f).

To the mixture of 3 or 4 in anhydrous CH_2Cl_2 at 0°C were added amines (10.12 mmol) dropwise. The reaction mixture was stirred at room temperature for 8 hrs. The solvent was removed *in vacuo*, and the crude was extracted using EtOAc. The combined organic extract was washed with water (2 × 50 ml), brine solution (50 ml), dried (Na_2SO_4), and the solvent was removed *in vacuo*. The crude product **5** or **6** was purified by column chromatography (SiO_2, 60–120 mesh; eluant: CH_2Cl_2).

2.5. Synthesis of 4-hydroxy-N-phenylbenzamide 5a.

Following the general procedure for synthesizing N-benzamide, compound **5a** was obtained as a light brown solid with a 74 % yield. M.p. 260-265°C. Mol. Formula: $C_{13}H_{11}NO_2$. ^{1}H NMR (DMSO, ppm): δ10.13(-NH-), 7.99(2H, d) 7.91(2H, d), 7.62(2H, d), 7.48(1H, t) 27.22 (2H, t). ^{13}CNMR (DMSO, ppm): δ164.8, 161.4, 135.4, 129.2, 124.4, 126.5, 128.9, 128.4, 123.6, 121.6, 117.5, 116.0. LC-MS (ESI) m/z: $[M+H]^+$213, found m/z = 214.

2.6. Synthesis of 4-hydroxy-N-p-tolylbenzamide 5b.

Following the general procedure for synthesizing N-benzamide, compound **5b** was obtained as a thick pale-yellow solid in 40 % yield. Mol. Formula: $C_{14}H_{13}NO_2$.; ^{1}HNMR (DMSO) δ10.35 (-NH-), 7.14–7.75 (m, 6H), 7.07 (d, 2H), 6.91 (d, 2H), 2.4 (s, 1H); ^{13}CNMR

(DMSO): δ165.5, 160.9, 134.5, 132.0, 129.5, 128.8, 126.5, 121.5, 115.8, 24.5; LC-MS (ESI) m/z: $[M+H]^+$= 227, found m/z = 228.

2.7. Synthesis of N-(4-bromophenyl)-4-hydroxybenzamide 5c.

Following the general procedure for synthesizing N-benzamide, compound **5c** was obtained as a white solid with a 60 % yield. M.p. 180-182°C; Mol. Formula: $C_{13}H_{10}BrNO_2$; ^{1}HNMR (DMSO, ppm): δ10.30 (1H, s), 7.80-7.88 (2H, m), 7.50-7.53 (2H, m), 7.40 (2H, m), 6.90 (2H, m); ^{13}CNMR (DMSO, ppm): δ163, 134.2, 131.5, 128.9, 128.2, 123.0, 118.2. 116.0; LC-MS (ESI) m/z: $[M+H]^+$= 290.99, found m/z= 292.00.

2.8. Synthesis of N-(4-chlorophenyl)-4-hydroxybenzamide 5d.

Following the general procedure for synthesizing N-benzamide, compound **5d** was obtained as a light brown solid with 72 % yield. M.p. 185-187°C; Mol. Formula: $C_{13}H_{10}ClNO_2$; ^{1}H NMR (DMSO, ppm): δ10.35 (s, 1H), 7.58-7.78 (m, 4H), 7.25 (2H, m), 6.90 (m, 2H); ^{13}CNMR (DMSO, ppm): δ163.5, 134.5, 130.2, 129.2, 128.2, 126.9, 116.0; LC-MS (ESI) m/z: $[M+H]^+$= 247, found m/z= 248.

2.9. Synthesis of 4-hydroxy-N-(4-nitrophenyl)benzamide 5e.

Following the general procedure for synthesizing N-benzamide, compound **5e** was obtained as a light-yellow solid with 83 % yield. M.p. 190-192°C; Mol. Formula: $C_{13}H_{10}N_2O_4$; ^{1}HNMR (DMSO, ppm): δ10.85(1H, s), 8.23 (2H, d), 7.75-7.95 (4H, m), 6.90 (2H, d); ^{13}CNMR (DMSO, ppm): δ164.60, 161.80, 144.30, 142.60, 128.60, 122.4, 121.20, 116.50, 95.2; LC-MS (ESI) m/z: $[M+H]^+$=258, found m/z= 259.

2.10. Synthesis of N-(3-cyanothiophen-2-yl)-4-hydroxybenzamide 5f.

Following the general procedure for synthesizing N-benzamide, compound **5f** was obtained as a light-yellow solid with an 80 % yield. Mol. Formula: $C_{12}H_8N_2O_2S$; **^{1}**H NMR (DMSO, ppm): δ10.15(-NH-), 7.78 (2H, d), 6.91 (2H, d), 6.71 (2H, d), 6.50 (2H, d). **^{13}**CNMR (DMSO, ppm): δ164.4, 161.8, 149.0, 129.0, 138.2, 135.14, 131.95, 129.25, 128.94, 126.80, 117.4, 116.3, 115.4; LC-MS (ESI) m/z: $[M+H]^+$= 244 found m/z=245.

2.11. Synthesis of N-phenylbenzamide 6a.

Following the general procedure for synthesizing N-benzamide, compound **6a** was obtained as a white solid with an 80 % yield. M.p. 158-160°C; Mol. Formula: $C_{13}H_{11}NO$; **^{1}**H NMR (DMSO, ppm): δ10.13(-NH-), 7.93-7.82 (m, 3H), 7.63 (d, 2H), 7.55 (t, 1H), 7.46 (t, 2H), 7.35 (t, 2 H). **^{13}**CNMR (DMSO, ppm): δ165.0, 138.2, 135.14, 131.95, 129.25, 128.94, 127.26, 124.73, 120.35; LC-MS (ESI) m/z: $[M+H]^+$ =197, found m/z=198.

2.12. Synthesis of N-p-tolylbenzamide 6b.

Following the general procedure for synthesizing N-benzamide, compound **6b** was obtained as a light brown solid with an 80% yield; M.p. 156-157°C; Mol. Formula: $C_{14}H_{13}NO$; ^{1}HNMR (DMSO, ppm) δ10.20 (s, 1H), 7.84 (d, 2H), 7.41–7.53 (m, 5H), 7.17 (d, 2H), 2.33 (s, 3H); ^{13}CNMR ($CDCl_3$) δ 165.9, 135.4, 135.0, 134.2, 131.6, 129.5, 128.6, 127.1, 120.5, 20.9; LC-MS (ESI) m/z: $[M+H]^+$= 211, found m/z = 212.

2.13. Synthesis of N-(4-bromophenyl)benzamide 6c.

Following the general procedure for synthesizing N-benzamide, compound **6c** was obtained as a light brown solid with 72 % yield. M.p. 190-192°C; Mol. Formula: $C_{13}H_{10}BrNO$; ^{1}H NMR (DMSO, ppm): δ10.35 (s, 1H), 7.96-7.90 (m, 2H), 7.85-7.67 (m, 2H), 7.60-7.49 (m, 5H); ^{13}CNMR (DMSO, ppm): δ165.3, 138.2, 135.2, 132.5, 132.1, 128.7, 128.2, 122.7, 115.6; LC-MS (ESI) m/z: $[M+H]^{+}$276.27, found m/z= 276.27.

2.14. Synthesis of N-(4-chlorphenyl)benzamide 6d.

Following the general procedure for synthesizing N-benzamide, compound **6d** was obtained as a white solid with a 75 % yield. M.p. 184-187°C; Mol. Formula: $C_{13}H_{10}ClNO$; ^{1}HNMR (DMSO, ppm): δ10.35(s, 1H), 8.20-7.85 (m, 2H), 7.90-7.75 (m, 2H), 7.65-7.52 (m, 3H), 7.50-7.25 (m, 2H); ^{13}CNMR (DMSO, ppm): δ166.1, 137.9, 135.24 132.4, 129.0, 128.8, 128.0, 127.6, 122.3; LC-MS (ESI) m/z: $[M+H]^{+}$231, found m/z= 232.

2.15. Synthesis of N-(4-Nitrophenyl)benzamide 6e.

Following the general procedure for synthesizing N-benzamide, compound **6e** was obtained as a brown oil with a 63 % yield. Mol. Formula: $C_{13}H_{10}N_2O_3$; ^{1}HNMR (DMSO, ppm): δ10.82(1H, s), 8.25 (2H, d), 8.05 (1H, d), 7.97 (2H, d), 7.60 (3H, m); ^{13}CNMR (DMSO, ppm): δ166.42, 161.35, 145.40. 142.60, 135.28, 132.33, 128.65, 128.0, 124.85, 119.90; LC-MS (ESI) m/z: $[M+H]^{+}$=242, found m/z= 243.

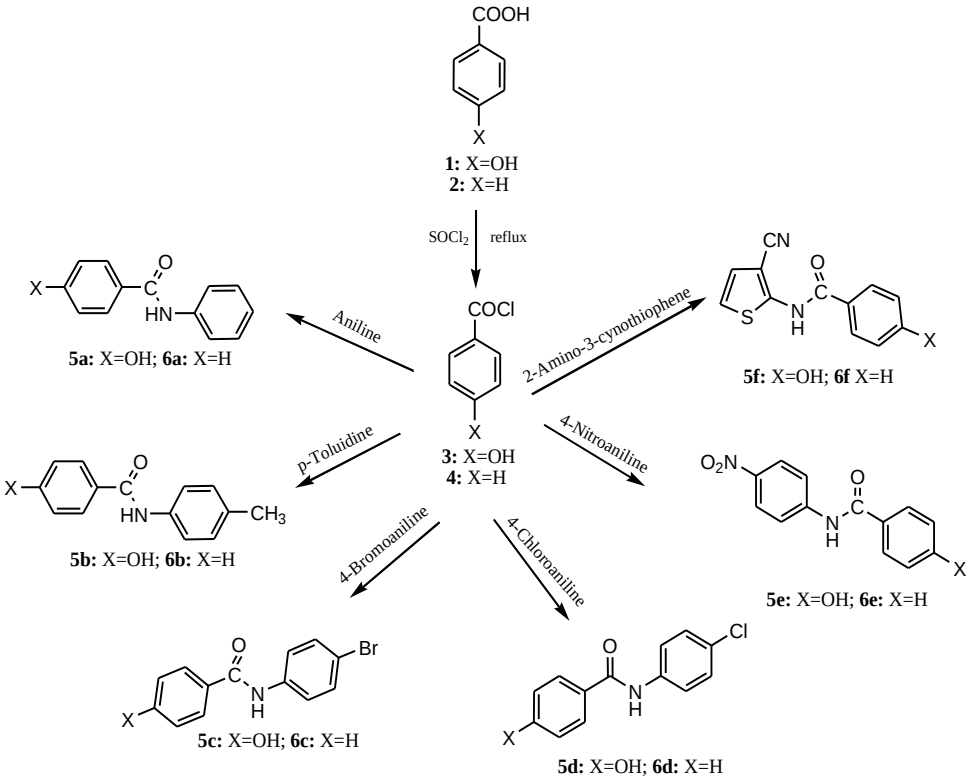
2.16. Synthesis of N-(3-cyano-4,5-dihydrothiophen-2-yl)benzamide 6f.

Following the general procedure for synthesizing *N-benzamide*, compound **6f** was obtained as a yellow solid with 85 % yield. M.p. 197-199°C; Mol. Formula: $C_{12}H_8N_2OS$; ^{1}HNMR (DMSO, ppm): δ 2.81 (2H, d), 3.61 (2H, d), 7.50-7.64 (3H, m), 8.01 (2H, d); ^{13}CNMR (DMSO, ppm): δ164.80, 150.2, 135.2 132.8, 128.7, 128.6, 61.80, 144.30, 142.60, 128.60, 127.4, 115.0, 96.0; LC-MS (ESI) m/z: $[M+H]^{+}$=228, found m/z= 228.3.

3. Results and Discussion

3.1. Chemistry.

Many scientists have synthesized amide from various acids and amines and studied their biological importance. Thus, we intended to synthesize amide derivatives based on the literature review on "bioactive amides and their analogous". We visualized that acid chlorides **3** and **4** are activated synthon and can be examined to obtain the target compounds **5(a-h)** and **6(a-h)** depicted in Scheme 1. The commercially available p-hydroxy benzoic acid **1** and benzoic acid **2** are used as starting materials. Upon their activation with thionyl chloride in reflux conditions [24] furnish corresponding acid chlorides **3** and **4,** which were next coupled with a set of different aromatic amines to obtain target compounds **5(a-h)** and **6(a-h)**. The aromatic amines were selected based on their easy availability, low cost, and presence as substituents in some novel antimicrobial agents. All the compounds were characterized by the ^{1}H and ^{13}CNMR and Mass spectrometry. The distinct peak of -NH-amide observed as a singlet at δ10.13 ppm to 10.85 ppm in ^{1}HNMR and -CO- observed at δ163-166 ppm in ^{13}CNMR confirms the structure of **5(a-f)** and **6(a-f)**.



Scheme 1. Synthetic route of 5(a-f) and 6(a-f) compounds.

3.2. Antibacterial activity.

The synthesized compounds **5(a-g)** were tested using the disc diffusion method for their antibacterial activity against Gram-positive *Bacillus subtilis* ATCC 6633 and Gram-negative *Escherichia coli* ATCC 25922. The mixture was thoroughly mixed, and the pH was set to 7.5 + 0.2. Then, the mixture was heated to dissolve the components completely. It was sterilized by autoclaving it for 45 minutes at 121°C with 15 lbs of pressure. After autoclaving,15-20 ml of that media was placed in a petri dish. The bacterial culture (B. subtilis MTCC no 441) was aseptically added to the agar medium, thoroughly mixed, and immediately poured into sterilized petri plates. The surface of each bacterium was spread with 0.1 ml of the obtained microorganism. The Whatman No. 1 filter paper discs were sterilized in an autoclave for 1 hour at 121°C. Antimicrobial activities were evaluated by measuring the diameter of the zone of inhibition (mm) [25,26] and Minimal Inhibitory Concentration (MIC) by two-fold serial dilution method [27,28]. Ampicillin and Gentamicin were used as standard antibacterial drugs. The zone of inhibition surrounding bacterial growth was measured to determine the antibacterial activity [29,30]. The antibacterial activity of all the 12 compounds **5(a-f)** and **6(a-f)** displayed interesting results. Each compound showed different activity for a different strain. Compound **5a** showed remarkably excellent activity against both the strains B. subtilis and E. coli with a diameter zone of inhibition 25 and 31 mm and MIC values of 6.25 for B. subtilis and 3.12 µg/mL for E. coli, respectively. However, compounds **6b** and **6c** showed better activity against E. coli and B. subtilis with a 24 mm diameter zone of inhibition and have 3.12 and 6.25 µg/mL MIC values, respectively.

All the other compounds displayed moderate to minimal antibacterial activity. Therefore, it can be inferred that the active compounds may either penetrate the peptidoglycan bacterial cell wall easily or may have a better fit at the receptor site. Compounds **5a**, **6b,**

and **6c** exhibited promising antibacterial activity and could be the future scope as drug lead. Antibacterial screening results of benzamides **5(a-f)** and **6(a-f)** are shown in Table 1.

Table 1. Antibacterial activity of compounds **5 (a-f)** and **6(a-f)** diameter zone of inhibition (mm) by disc-diffusion assay (µg/disc) and MIC values (µg/mL) by two-fold serial dilution technique.

Compound	Gram-positive	Gram-negative
	B. subtilis	***E. coli***
5a	**25[b](6.25[b])**	**31[b](3.12[b])**
5b	11(100[a])	24(>12.5)
5c	08[a](100[a])	20(25.0)
5d	17(>50.0)	28[b](6.25[b])
5e	10[a](100[a])	26(6.25)
5f	10(100[a])	22(25.0)
6a	09[a](100[a])	20 (25.0)
6b	18(50.0)	**24[b](>3.12[b])**
6c	**24[b](6.25[b])**	26(6.25)
6d	09[a](100[a])	21(>12.5)
6e	10[a](100[a])	20(25.0)
6f	09[a](100[a])	20(25.0)
Control	6	6
Gentamicin	22	20
Ampicillin	18	19

[a] No activity.; [b] Entries in bold font indicate better activity than reference drugs Gentamicin and Ampicillin.

3.3. Lipinski rule of five compliance.

In addition, Lipinski's rule of five compliance of the synthesized compounds was also examined, and the findings are listed in Table 2. A molecule must meet no more than one of the following four requirements [31]: log P (octanol-water partition coefficient) ≤5, molecular weight ≤500, number of hydrogen bond acceptors ≤10, and number of hydrogen bond donors ≤5. The majority of the synthesized compounds met the aforementioned requirements, according to calculations made using the www.molinspiration.com software [32]. These substances, therefore, have a good chance of being developed into oral medications in the future and could be strong drug candidates.

Table 2. Molinspiration calculation of molecular properties for the Lipinski rule.

Compound	nViol	MW	miLog P	nON	nOHNH	natoms	Nrotb
5a	0	213.24	2.35	3	2	16	2
5b	0	227.26	2.8	3	2	17	2
5c	0	292.13	3.16	3	2	17	2
5d	0	247.68	3.03	3	2	17	2
5e	0	258.23	2.31	6	2	19	3
5f	0	244.28	1.82	4	2	17	2
6a	0	197.24	2.83	2	1	15	2
6b	0	211.26	3.28	2	1	16	2
6c	0	276.13	3.64	2	1	16	2
6d	0	231.68	3.51	2	1	16	2
6e	0	242.23	2.79	5	1	18	3
6f	0	228.28	2.29	3	1	16	2
Acceptable range	≤1	≤500	≤5	≤10	≤5	—	—

nViol, no. of violations; MW, molecular weight; miLog P, molinspiration predicted Log P; nON, no. of hydrogen bond acceptors; nOHNH, no. of hydrogen bond donors; natoms, no. of atoms; nrotb, no. of rotatable bond.

4. Conclusions

This work used reactions with activation and acylation phases to successfully create benzamide compounds **5(a-f)** and **6(a-f)**. ^{1}HNMR and ^{13}CNMR spectroscopy techniques were used to perform structural studies on the synthesized compounds. The antibacterial activity of each compound was examined using the disc diffusion method. As a consequence, the studied compounds **5a**, **6b**, and **6c** exhibited promising antibacterial activity.

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Conflicts of Interest

The authors declare no conflict of interest.

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