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*Original Article*

# Synthesis of Benzimidazole and Phthaloylamino Acid derivatives and Antibacterial Activity

**Hussniya A. AlDifar[1,*], Basma S. Baaiu[1], Khalid M. A. Darwish[1], Mohamad F. Ali[1], Othman O. Dakhil[1], Mansour Abd-Alsalam[1], Haneen Al Difar[2]**

[1]*Associate Professor, Department of Chemistry, Faculty of Science, Benghazi University, Benghazi, Libya*
[2]*MSc Student, Department of Chemistry, Faculty of Science, Benghazi University, Benghazi, Libya*

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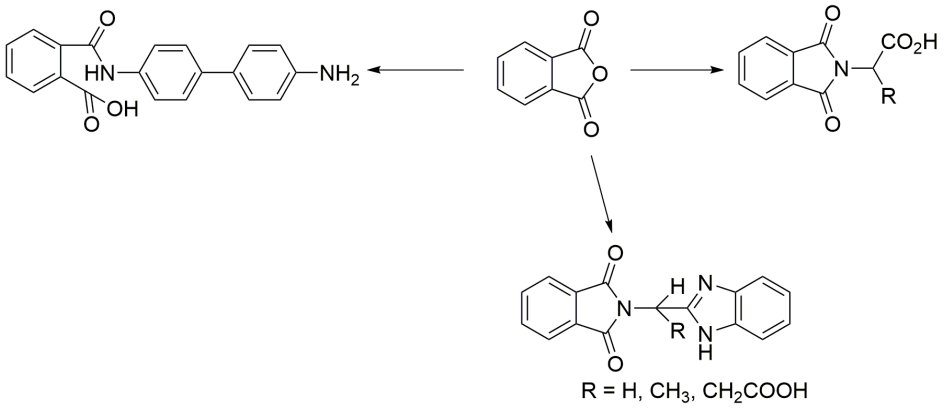
**ABSTRACT**

Seven novel benzimidazole and phthaloylamino acid derivatives were synthesized. In the presence of acetic acid, the phthalic anhydride reacted with benzidine in a cyclization reaction to obtain the biphenyl of 7 products. Likewise, when phthalic anhydride is reacted with different amino acids including D-glycine, D-alanine, and D-valine under solventless and fusion conditions using an oil bath, the N-phthaloylamino acids **1a** to **1c** were obtained. These were, in turn, reacted and again in a cyclization reaction with o-phenylenediamine (OPDA) under reflux conditions in the presence of dilute hydrochloric acid affording their corresponding benzimidazole derivatives **2a** to **2c**. The last compound 3a was synthesized in the existence of benzidine and acetic acid. The structures of synthesized complexes were identified by chromatographic, $^1$H-NMR, and mass spectrometry. The melting point and other physicochemical properties were found in this investigation. The biological screening of the products was made to evaluate and prove their antibacterial importance.

**GRAPHICAL ABSTRACT**




* Corresponding author: Hussniya A. AlDifar
✉ E-mail: Ha_Difar@yahoo.com

## Introduction

Phthalimide ($C_8H_5NO_2$) and *N*-substituted phthalimide derivatives are an important type of substrates and the bicyclic non-aromatic nitrogen heterocycle that has interesting applications in biological, pharmacological, industrial, and chemical applications. Both phthalimide and *N*-substituted phthalimide possessed biological efficiency such as anti-inflammatory [1, 2], analgesic, anti-depressant [3, 4], antioxidant [5], antimicrobial agent [5-7], and other activates [8-12]. The important applications of phthalimide due to the structural properties that are possessed like a hydrophobic aryl ring, the group of electron-donor, and hydrophobic 5-membered ring help to improve the biological activity of Phthalimide [13]. The study [14] has shown that, the possibility of using phthalimide and its derivatives in the biological field and used as an anti-bacterial. It is further used as a helping substance in medical productions and showed its effectiveness in cancer and other diseases [14]. In addition, the production of phthalimide derivatives via phthalic anhydride used in different applications like antinoceptive and anti-convulsants is summarized in the review [15]. Furthermore, Chi and his team examined the formation of some derivatives of phthalimide and subjected these complexes to various activities. One of these activities they tested, was the obtained complexes against some cancer cell lines, and their results showed positive effects of some complexes. Moreover, the same obtained compounds were tested toward some types of bacteria. The results also exhibited good and different effects as well as the inhibited bacteria that were used [16]. We further found some recent studies indicating the importance of these compounds as well as after modifying them with other functionally effective compounds. Besides, it showed the pharmacological importance of these compounds and their effectiveness in treating some chronic diseases, especially Alzheimer's disease, as those studies showed [17, 18].

1,3-Dioxoisoindoline is considered as one of the phthalimide derivatives products and it consists of heterocycles that contain nitrogen which has a wide range of pharmacological features [19]. Also, the phthalimides were modified by some types of amines, and activities of these compounds were increased and show positive effects when utilized and examined to combat plasmodium falciparum malaria [20], or used as an anti-plasmodial drug, as explained in [21].

Figure 1 displays different biological activities of *N*-substituted derivatives of 1*H*-isoindole-1,3(2*H*)-dione derivatives (R represents an alkyl group).

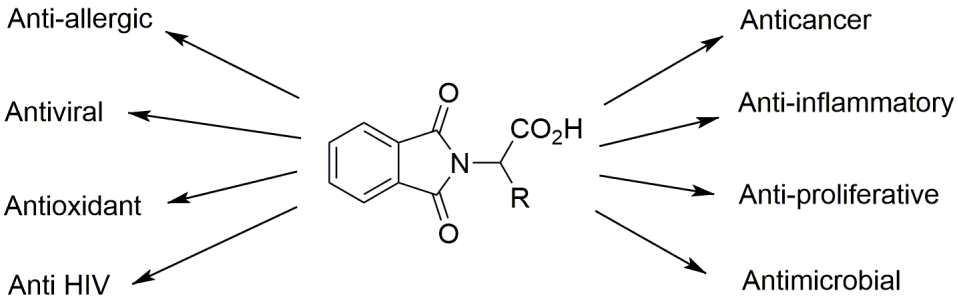



**Figure 1:** different biological activities of *N*-substituted derivatives of 1*H*-isoindole-1,3 (2*H*)-dione derivatives (R represents an alkyl group)

*N*-substituted phthalimide is synthesized by different methods such as traditional procedures and yield which found around 98% [22]. Microwave process was also used and the obtained yield was between 52 and 89% [23] or between 60 and 80% [24]. Similar to use a microwave technique without solvent, it helps to obtain compounds with good purity and high yields found as explained in [25] or used refluxing in organic solvents at high temperatures and the utilized solvent like acetic acid [11], water [7], or toluene [26].

In addition, phthalimide was synthesized by microwave irradiation with the help of urea and

phthalic anhydride, and the yield was 85% [27]. Other work used ionic liquid [bmim][Cl] which possessed hydrophilic properties as a solvent, and the reaction carry on the microwave heating. The obtained yield by this method was more than 95% [28].

The main objective of the present investigation is to synthesize new benzimidazole and phthaloylamino acid derivatives using phthalic anhydride, amino acids, and aromatic amines (used as precursors). The phthalimide derivatives were synthesized to obtain various complexes such as benzimidazole, phthaloylamino acid derivatives, and 2-[(4'-aminobiphenyl-4-yl) carbamoyl] benzoic acid. The structure of the obtained compounds was confirmed by FT-IR and $^1$H-NMR.

The obtained phthalimide derivatives are examined against some types of bacteria to study the activity of these products.

## Materials and Methods

The chemicals and solvent used in this investigation are purchased and utilized in an analytical grade. Melting point is measured using griffin apparatus (Stuart 3) and applied without calibration. The structure of the obtained compounds was confirmed using $^1$H-NMR, Varian Gemini 300 MHz, and JNM-LA 400 FT-NMR system spectrometer and chemical shifts are expressed in ppm units using TMS as an internal reference. The DMSO-$d_6$ used as a solvent. Mass spectrometry (MS) were recorded on a GC-MS QP1000 EX Shimadzu.

*General procedure for synthesis*

*N-phthaloylamino acid (**1a** to **1c**)*

An equimolar ratio of phthalic of phthalic anhydride and amino acids (D-glycine, D-alanine, and D-valine) were used and reacted under fusion conditions in an oil bath at temperatures between 170 °C and 190 °C for 30 minutes. Chromatography (TLC) was utilized to observe the reaction. The solution is poured into ice, filtered, and then washed with distilled water. The final product is dried and re-crystallized from ethanol.

*2-(1, 3-dioxoisoindolin-2-yl) acetic acid (**1a**)*

White crystal, yield 70%, mp 191-193 °C, $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ 4.73 (s, 2 H, $CH_2$), 7.87 (m, 4 H, Ar-H), MS: m/z: 205.04 (100 %) and 206.04 (10.8 %), Anal. Calcd. for $C_{10}H_7NO_4$: Found: C, 58.54%, H, 3.44 %; N, 6.83 %, and O, 31.19 %. Calculated: C 58.54%, H, 3.44%; N, 6.83%, and O, 31.19%.

*2-(1, 3-dioxoisoindolin-2-yl) propionic acid (**1b**)*

White crystal, yield 60%, mp 153-155 °C, $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ 1.33 (d, 3H, $CH_3$), 5.13 (q, 1 H, CH), 7.88 (m, 4 H, Ar-H), MS: m/z: 219.05 (100 %), 220.06 (11.9 %), Anal. For $C_{11}H_9NO_4$; Found: C, 60.31%, H, 4.16%; N, 6.40%, and O, 29.19%. Calculated: C, 60.28%, H, 4.14%; N, 6.39%, and O, 29.2%.

*2-(1, 3-dioxoisoindolin-2-yl) succinic acid (**1c**)*

White crystal, yield 65%, mp 200-202 °C, (DMSO-$d_6$, 300 MHz): $\delta$ 3.09 (d, 2 H, $CH_2$), 5.58 (t, 1 H, CH), 7.88 (m,4 H, Ar-H), MS: m/z: 263.04 (100 %), 264.05 (13.0 %), and 265.05 (1.2%), Anal. For $C_{13}H_{13}NO_4$: Found: C, 54.76 %, H, 3.45 %; N, 5.32%, and O, 36.47%. Calculated: C, 63.15%, H, 5.3%; N, 5.67%, and O, 25.88%.

*Benzimdazoles (**2a** to **2c**)*

In a round-bottom flask (250 mL), 0.01 mL of o-phenylene diamine, 0.01 mL N-phthaloylamino acid, and 5 mL of dilute hydrochloric acid were put. The solution was refluxed for 2 hours, the reaction solution was cooled, and 10% of sodium hydroxide was slowly added to the flask with constant stirring. The pH was monitored using a pH meter to reach an alkaline level. Thereafter, the final solution is filtered, and then washed with cold water affording the product.

*2-((1l2, 3l4-benzo[d]imidazol-2-yl) methyl) isoindoline-1, 3-dione (**2a**)*

Pale orange crystal, yield 76%, mp 220-222 °C, $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ 5.28 (s, 2 H, -$CH_2$), 6.18-7.70 (m, 4 H, Benzimidazole-H), 7.87-7.88 (m, 4 H, Isoindole-H), MS: m/z: 277.28 (100 %) and 278.28 (11.9 %), Anal. For $C_{16}H_{11}N_3O_2$: Found: C, 69.31%, H, 3.98%; N, 15.15%, and O,

11.53%. Calculated: C, 69.31%, H, 4%; N, 15.15%, and O, 11.54%s.

*2-(1-(1l2, 3l4-benzo[d]imidazol-2-yl) ethyl) isoindoline-1,3-dione (**2b**)*

Brown crystal, yield 75%, mp 230-231 °C, $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ 1.44 (d, 3 H, $CH_3$), 5.65 (q, 1 H, CH), 6.93-7.70 (m, 4 H, Benzimidazole-H), 7.87-7.88 (m, 4 H, isoindole-H), MS: m/z: 291.30 (100 %) and 292.30 (11.5%), Anal. For $C_{17}H_{13}N_3O_2$: Found: C, 70.03%, H, 4.42%; N, 14.39%, and O, 11.01%. Calculated: C, 70.09%, H, 4.5%; N, 14.42%, O, 10.98%.

*3-(1l2, 3l4-benzo[d]imidazol-2-yl)-3-(1, 3-dioxoisoindolin-2-yl)propanoic acid (**2c**)*

Pale orange crystal, yield 70%, mp 246-248 °C, $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ 3.03 (d, 2 H; -$CH_2$), 5.84 (t, 1 H, CH), 6.94-7.70 (m, 4 H; Benzimidazole-H), and 7.88-7.94 (m, 4 H; Isoindole-H), MS: m/z: 335.31 (100 %) and 336.30, Anal. For $C_{18}H_{13}N_3O_4$: Found: C, 64.42%, H, 3.88%; N, 12.54%, and O, 19.11%. Calculated: C, 64.48%, H, 3.91%; N, 12.53%, and O, 19.09%.

*2-[(4'-aminobiphenyl-4-yl)carbamoyl]benzoic acid (**3a**)*

In a round-bottom flask, 1.48 g of phthalic anhydride, 0.05 mL benzidine, and 50 mL acetic acid were put, and then the solution was refluxed for two hours. The obtained solution was poured into ice, filtered, and washed with cold water affording the complex.

*2-[(4'-aminobiphenyl-4-yl) carbamoyl] benzoic acid (**3a**)*

Brown crystal, yield 80%, mp 251-253 °C, $^1$H-NMR (DMSO-$d_6$, 300 MHz): $\delta$ 6.90-7.21 (m, 4 H, Terminal Phenylene-H), 7.45-7.87 (m, 4 H, Middle phenylene-H), 7.59-7.83 (m, 4 H, Benzoic-H). MS: m/z: 332.04 (100 %) and 333.04 (12.9 %). Anal. For $C_{20}H_{16}N_2O_3$: Found: C, 72.20%; H, 4.83%; N, 8.41%, and O, 14.46%. Calculated: C, 72.28%; H, 4.85%; N, 8.43%, and O, 14.44%.

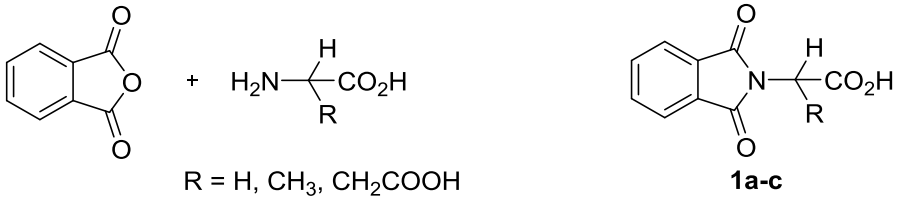
## Results and Discussion

The process used to synthesize seven types of compounds with a help of phthalic anhydride and different types of amino acids at a high temperature showed moderate to good yield while the **3a** product show a high yield compared to other products reached to 80%. Schemes 1, 2, and 3 showed the processes for synthesizing all compounds. Scheme 1 shows the synthesized of *N*-phthaloylamino acid (**1a** to **1c**). The values of elemental analysis (calculated values) of 3 compounds (**1a** to **1c**) are in agreement with the obtained values.

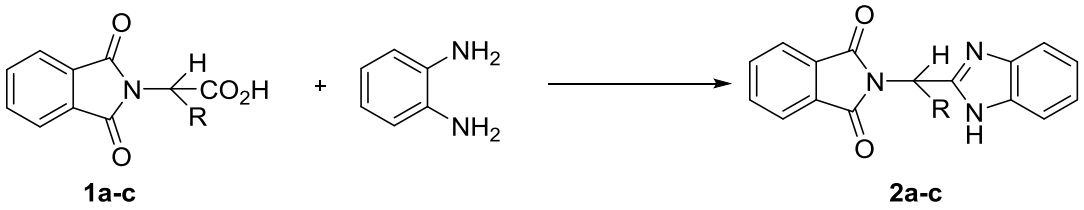
Table 1 presents the physical properties of 3 compounds (**1a** to **1c**) and Table 2 lists the name of the compound, molecular formula, and molecular structure of 3 compounds. Tables 1, 3, and 5 present the physical properties of compounds, and also Tables 2, 4, and 6 list the name of the compound as well as molecular formula and structure of the compounds.

Scheme 2 shows the synthesis of Benzimdazoles (**2a** to **2c**). The elemental analysis values for 3 compounds (**2a** to **2c**) are in agreement with the obtained values.

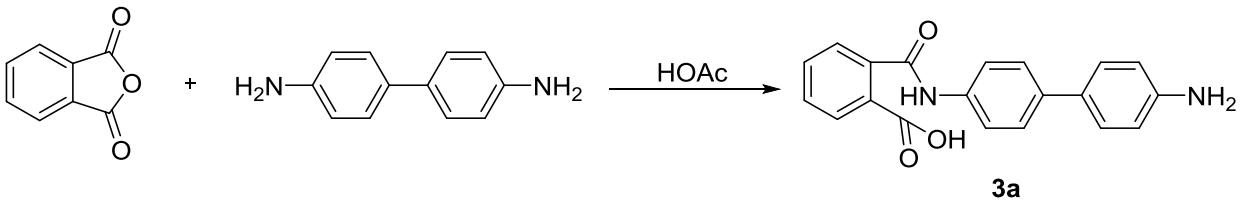
Table 3 provides the physical properties of 3 compounds (**2a** to **2c**) and Table 4 shows the name of compound, molecular formula, and molecular structure of 3 compounds.




**Scheme 1**: Synthesis of *N*-phthaloylamino acid (**1a-c**)




**Scheme 2:** Benzimdazoles synthesis (**2a-c**)




**Scheme 3:** Synthesis of 2-[(4'-aminobiphenyl-4-yl)carbamoyl]benzoic acid (**3a**)

**Table 1:** Physical properties of 3 compounds (**1a** to **1c**)

| Compound No. | Molecular weight | Yield (%) | mp (°C) | Reaction time (min) | Color of precipitate |
|---|---|---|---|---|---|
| **1a** | 205 | 70 | 191-193 | 15 | White |
| **1b** | 219 | 60 | 153-155 | 15 | White |
| **1c** | 247 | 65 | 200-202 | 16 | White |

**Table 2:** Molecular formula and structure of the 3 compounds (**1a** to **1c**)

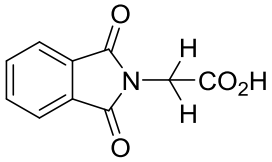
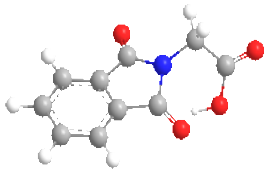
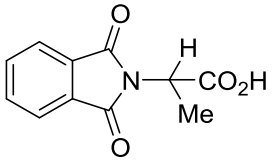
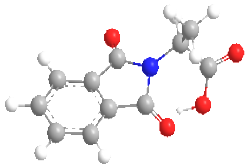
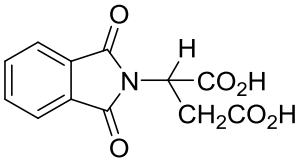
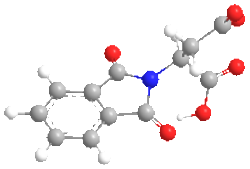
| IUPAC name | Molecular structure | Molecular formula | 3D structure |
|---|---|---|---|
| 2-(1,3-dioxoisoindolin-2-yl)acetic acid |  | $C_{10}H_7NO_4$ |  |
| 2-(1,3-dioxoisoindolin-2-yl)propanoic acid |  | $C_{11}H_9NO_4$ |  |
| 2-(1,3-dioxoisoindolin-2-yl)succinic acid |  | $C_{13}H_{13}NO_4$ |  |

**Table 3:** Physical properties of 3 compounds (**2a** to **2c**)

| Compound No. | Molecular weight | Yield (%) | mp (°C) | Reaction time (h) | Color of precipitate |
|---|---|---|---|---|---|
| **2a** | 277 | 76 | 220-222 | 2 | Pale orange |
| **2b** | 291 | 75 | 230-231 | 2.3 | Brown |
| **2c** | 319 | 70 | 246-248 | 3 | Pale orange |

**Table 4:** Molecular formula and molecular structure of 3 compounds (**2a** to **2c**)

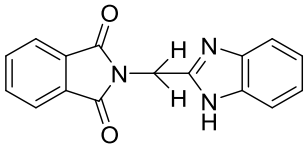
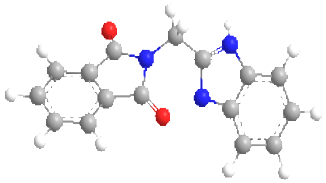
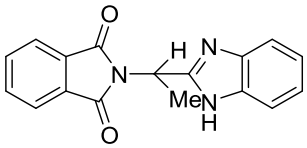
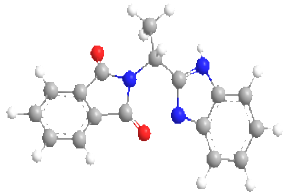
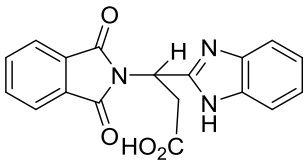
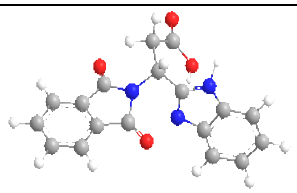
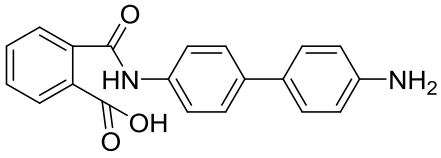
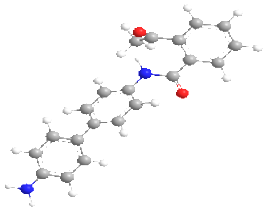
| IUPAC name | Molecular structure | Molecular formula | 3D structure |
|---|---|---|---|
| 2-((1l2,3l4-benzo[d]imidazol-2-yl)methyl)isoindoline-1,3-dione |  | $C_{16}H_{11}N_3O_2$ |  |
| 2-(1-(1l2,3l4-benzo[d]imidazol-2-yl)ethyl)isoindoline-1,3-dione |  | $C_{17}H_{13}N_3O_2$ |  |
| 3-(1l2,3l4-benzo[d]imidazol-2-yl)-3-(1,3-dioxoisoindolin-2-yl)propanoic acid |  | $C_{18}H_{13}N_3O_4$ |  |

**Table 5:** Physical properties of compound (3a)

| Compound No. | Molecular weight | Yield (%) | mp (°C) | Reaction time (h) | Color of precipitate |
|---|---|---|---|---|---|
| **3a** | 332 | 80 | 251-253 | 2 | Brown |

**Table 6:** Molecular formula and structure of the compound (**3a**)

| IUPAC name | Molecular structure | Molecular formula | 3D structure |
|---|---|---|---|
| 2-[(4'-aminobiphenyl-4-yl) carbamoyl] benzoic acid |  | **$C_{20}H_{16}N_2O_3$** |  |

Scheme 3 shows the synthesized of 2-[(4'-aminobiphenyl-4-yl)carbamoyl]benzoic acid (**3a**). Therefore, the elemental analysis values for **3a** product are in agreement with the obtained values. Table 5 presents the physical properties of **3a,** and also Table 6 lists the name of compound, molecular formula, and molecular structure of the **3a**.

*Antibacterial activity*

The seven synthesized compounds of *N*-substituted phthalimide derivatives were examined against some types of bacteria such *S. aureus, P. aeruginosa* (gram-positive), *E. coli*, and *K. pneumonia* (gram-negative). The activity of synthesized compounds exhibited good activity in both types of bacterial and the (**3a**) compound showed better inhibitory activity against *S.aureus* and *P. aeruginosa* bacterial more than the other 6 compounds (Figure 2) while the 3 compounds (**2a** to **2c**) exhibited better inhibitory activity against *E .coli* and *K. pneumonia* more than other compounds (Figure 3). The results of antibacterial activity indicated the synthesized *N*-substituted phthalimide possess good activity toward microorganism due to the structural properties and the functional groups of the synthesized compound. Table 7 indicates the zone of inhibition in mm for both kinds of bacteria and Figures 2 and 3 display the inhibition zone of gram-positive and gram-negative, respectively.

**Table 7:** Inhibition zone in (mm) for both kinds of bacteria for all synthesized compounds

| Sample | *Gram-positive* | | *Gram-negative* | |
|---|---|---|---|---|
| | *S. aureus* | *P. aeruginosa* | *E. coli* | *K. pneumonia* |
| | Zone of inhibition (mm) | | | |
| **Std.** | 12.7 | 13.9 | 13.9 | 13.9 |
| **1a** | 13.2 | 11.8 | 12.6 | 12.6 |
| **1b** | 13.9 | 11.8 | 13.9 | 14.6 |
| **1c** | 13.9 | 10.8 | 14.6 | 13.9 |
| **2a** | 13.9 | 12.8 | 15.8 | 14.6 |
| **2b** | 12.8 | 13.9 | 14.6 | 15.8 |
| **2c** | 13.9 | 11.8 | 15.9 | 15.9 |
| **3a** | 13.9 | 14.6 | 14.6 | 14.6 |

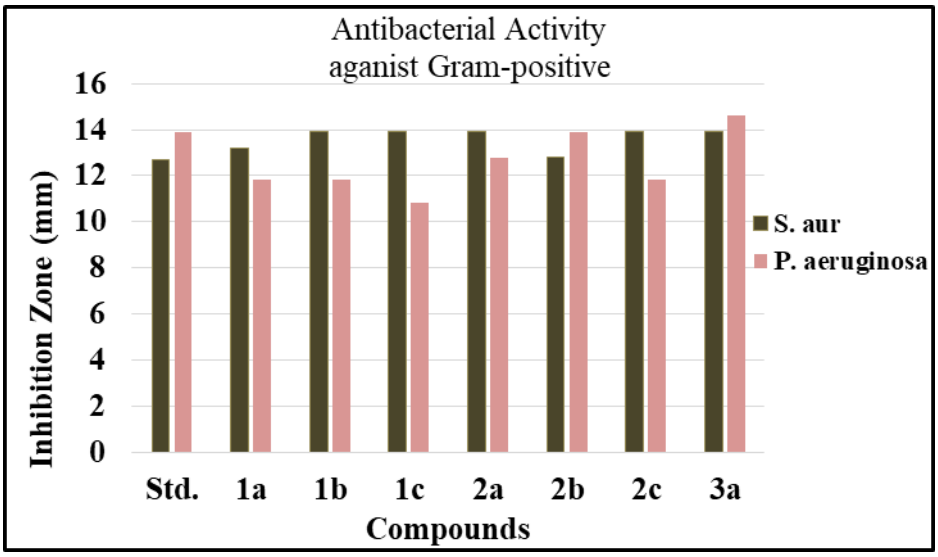



**Figure 2:** Inhibition zone of gram-positive of all synthesized compounds

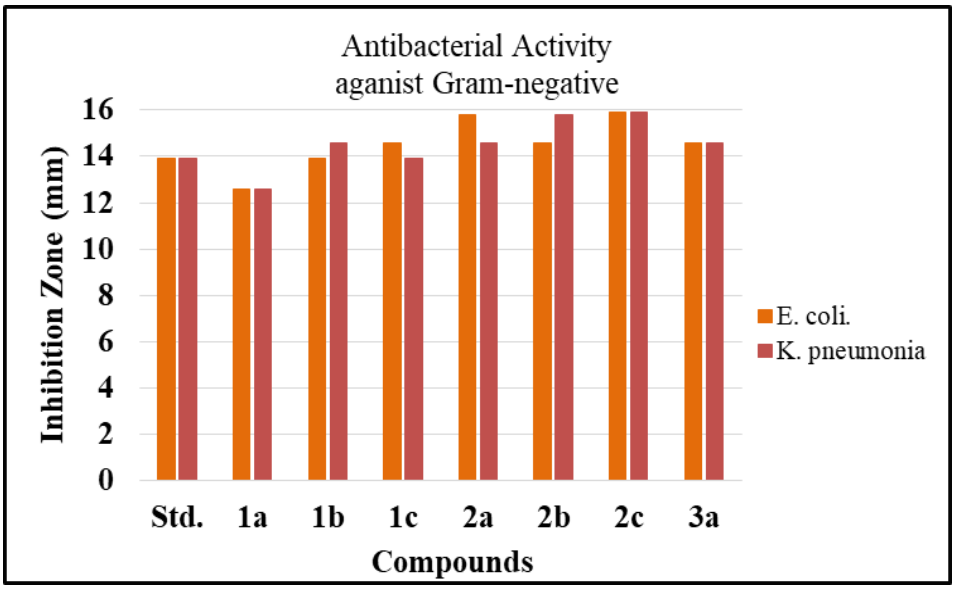



**Figure 3:** Inhibition zone of gram-negative of all synthesized compounds

## Antibacterial activity

The synthesized compounds of N-substituted phthalimide were screened against two kinds of bacteria. The disc diffusion approach was to study the compounds activity. Gram-positive and gram-negative bacteria are used in the work. The inhibition zone was observed and measured after 24 hours from incubation and the results were compared to DMSO which is used as a standard.

## Conclusion

In this study, a number of *N*-substituted phthalimide derivatives were synthesized. A high yield was found for seven products and it was found between 60% and 80%. The structure of synthesized compounds was identified by helping of $^{1}$H-NMR, mass spectrometry, and other physicochemical properties. The biological activity of the products was examined and the results show good inhibitory activity against used bacteria.

## Academic Contribution

In the current work, we seek to synthesize new phthalimide complexes due to the importance of these complexes in various applications, especially in the field of pharmacy and biology because of the biological properties of these compounds and their containment of functional groups that contribute and help to prepare some combinations of medicine and treatment of some diseases like inflammatory, Alzheimer, cancer, and others.

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## Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

## ORCID

*Hussniya A.AlDifar*
https://orcid.org/0000-0002-8685-1994
*Basma S.Baaiu*
https://orcid.org/0000-0002-1675-4670
*Khalid M. A. Darwish*
https://orcid.org/0000-0001-6518-6836
*Mohamad F.Ali*
https://orcid.org/0000-0002-6327-7264
*Othman O.Dakhil*
https://orcid.org/0000-0003-4656-6985
*Mansour Abd-Alsalam*
https://orcid.org/0000-0002-6126-2771
*Haneen Al Difar*
https://orcid.org/0000-0001-8039-158X

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