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Synthesis of Some New Substituted Pyridilimides From 2-Carboxy Nicotinic Acid By Reaction With Amines, and Evaluation of Their Antibacterial Activity.

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Abstract

In this paper, we synthesized some new substituted pyridilimides in three different ways. Firstly, by the reaction of 2-carboxy nicotinic acid with some amino acids to form 2- substituted (5,7- dioxo-5,7-dihydro -6H-pyrrolo [3,4-b] pyridine -6-yl) acetic acid (1- 2). In the next step, the resultant compounds were treated with phenylene diamine to form substituted 6-((1H-benzo[d]imidazol-2 -yl) methyl)-5H-pyrrolo [3,4-b] pyridine -5,7(6H)- dione (3-4). Secondly, 2- carboxy nicotinic acid, which was converted to anhydride (5), reacted with acetic anhydride and acetic acid. In the next step, two moles of (5) were used to react with some aliphatic or aromatic diamine to give substituted bis 5H-pyrrolo [3,4-b] pyridine-5,7(6H)-dione (6-11). Finally, (5) was treated with urea to form imide (12). The next step, imide (12) was treated with formaldehyde to give 6-(hydroxymethyl) -5H- pyrrolo [3,4- b] pyridine -5,7(6H)-dione (13). The next step was to react (13) with substituted aniline to form substituted 6-((phenylamino)methyl)-5H-pyrrolo [3,4-b] pyridine -5,7 (6H)- dione (14- 17). The resulting compounds were proven by their physical properties and by IR, ^{1}H-NMR, and CHN. The antibacterial assessment of many compounds produced to fight two pathogenic bacterial strains was carried out, and the outcomes were contrasted with two well-known antibiotics. Compounds (1, 8, 17) showed a high inhibition zone (20, 16, 19) mm respectively. Docking was carried out using CB-Dock2 against the shikimate kinase enzyme, where compound (8) had the highest docking score of -8.6 Kcal/mol. This result encourages the synthesis of more substituted pyrrolopyridin compounds as a future work.

Keywords: Amines, Amino acids, Imidazole, Nicotinic acid, Pyridilimides.

Introduction

Heterocyclic nitrogenous compounds represent a big class in organic chemistry. In most cases, nitrogen gives the compounds potent properties.

Pyridilimides are a class of organic compounds with a unique combination of aromatic and imide functionalities. These compounds have various applications in various fields due to their diverse biological, chemical, and physical properties.

The pyrrolo pyridine class of pyridilimides has been extensively studied for their potential as analgesic and sedative agents. In addition, these derivatives have shown promise in treating various diseases of the nervous and immune systems based on biological investigations. Some examples of their therapeutic applications include antidiabetic, antimycobacterial, antiviral, and antitumor activities. For instance, the compound depicted in Fig. 1 contains a pyrrolo pyridine scaffold that has been found to increase insulin sensitivity. The present compounds reduce blood glucose levels by enhancing the uptake of glucose into both muscle and adipose (fat) cells.[1-3]

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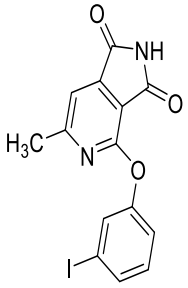
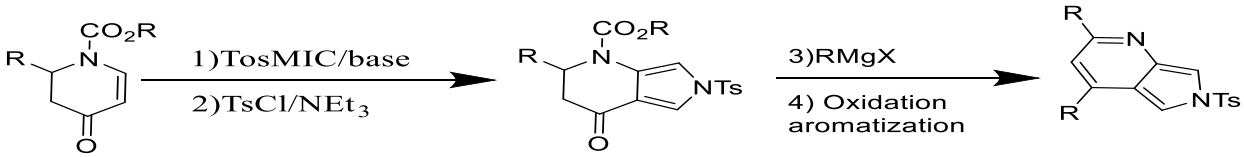


4-(3-iodophenoxy)-6-methyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3(2*H*)-dione

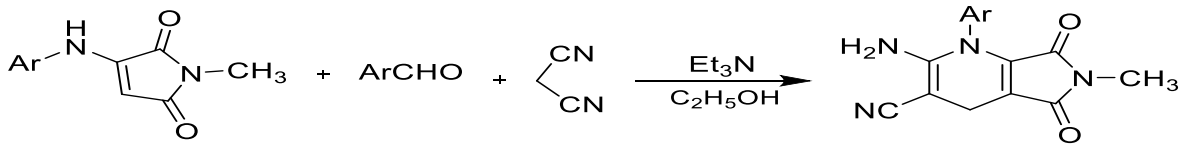
Figure 1. Bioactive compound

In a recent study by Kiren et al. a series of pyrrolopyridine compounds were synthesized from substituted N- acyl-2,3 -dihydro- 4-pyridones using a toluene sulfonyl methyl isocyanide reagent under basic conditions in four steps Scheme. 1.[4]



Scheme 1. Pyrrolopyridine synthesis

Jiang et al, revealed the preparation of pyrrolo pyridine using malononitrile, β-enamino imide, and aromatic aldehyde derivatives in the occurrence of triethylamine in a one-pot, three-element reaction. In mild circumstances, the reaction proceeded and formed the selected product in a good yield Scheme 2.[5]



Scheme 2. One-pot three-factor reaction

The preparation of new substituted pyridilimides from 2-carboxy nicotinic acid by reaction with amines is an important approach to expanding the structural diversity of pyridilimides and developing new compounds with improved properties. The reaction of 2-carboxy nicotinic acid with amines involves the formation of an imine intermediate, which can then undergo cyclization to form a pyridilimide. The choice of amine reactant, reaction conditions and catalyst can significantly impact the outcome of the reaction, including the yields, stereochemistry, and structural features of the resulting pyridilimides. The study of the synthesis of new substituted pyridilimides from 2-carboxy nicotinic acid by reaction with amines is a rapidly developing field with numerous recent advances.[6-8]

Materials and Methods

The experiment utilized chemicals or solvents acquired from readily existing sources, which were employed without further purification. The IR spectra (with the peak at Vmax in cm^{-1}) were acquired using a Shimadzu FT-IR 8400 spectrophotometer with a KBr disc. For the ^{1}H-NMR spectra, a Bruker spectrometer operating at 300 MHz was used, employing CD3OD, CD3CN, and acetone d6 as solvents and TMS served as the standard reference for the chemical shift. Access to the EAS superuser elemental analysis system GmbH was granted through the Vario EL superuser. In docking studies, CB-Dock2 was the software used.

Synthesis of 2- substituted (dioxo-dihydro -pyrrolo [3,4- b] pyridine -6-yl) Aetic Acid (1- 2). [9]
In a round bottom flask 50 ml 1g, 6 mmol of 2-carboxy nicotinic acid was added to the solution of 6 mmol, 0.336g and 0.450g of glycine and alanine respectively in 10 ml of glacial acetic acid. The resultant combination was refluxed for 4 hours, and then the solvent was removed under reduced pressure. After that, 30 ml of distilled water was added and waited for precipitation to be complete, then filtered and recrystallized from ethanol. The physical properties of (1) light yellow solid %80, m.p. 180-181^{o}C and (2) white solid %56 m.p. 142-143 ^{o}C.

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Synthesis of Substituted 6-((1H-benzo[d]imidazol-2-yl) methyl) pyrrolo [3,4- b] pyridine - dione (3-4).[10]
In 50 ml R. B. F., 5 mmol, 0.91g and 0.98g of 1 and 2 respectively, were added to the solution of (0.54g, 5mmol) of orthophenylene diamine in (10 ml) of (4N) HCl. The resultant was reflexed for about two hours, the precipitate was obtained after being cooled to room temperature, filtrated, and recrystallized from ethanol. The physical properties of the resulting compound are (3) white solid %51, m.p. 203-204 °C and (4) pale yellow solid %46 m.p. 204-205 °C.

2-(5,7-dioxo-5,7-dihydro-6H-pyrrolo[3,4-b] pyridin-6-yl) acetic acid (1): FT-IR (KBr, ν, cm^{-1}) 3260 (O-H), 2999 (=C-H), 1746 (C=O), 1693 (amide), 1612 (C=C), 1465 (C-H) bending, and 1396 (O-H) bending. ^{1}H-NMR (ppm): (CD_3OD, 400 MHz) δ:7.78–8.55 (m, 3H) aromatic protons, 4.20 (s, 2H) CH_2, 2.50 (s, 1H) OH.

2-(5,7-dioxo-5,7-dihydro-6H-pyrrolo[3,4-b] pyridin-6-yl) propanoic acid (2): FT-IR (KBr,ν, cm^{-1}) 3241 (O-H), 2990 (=C-H), 2940 (C-H), 1750 (C=O), 1735 (C=O), 1678 amide, and 1383 (O-H) bending. ^{1}H-NMR (ppm): (CD_3OD, 400 MHz) δ:7.77-8.5 (m, 3H) aromatic, 4.57 (m, 1H) C-H, 2.51 (s, 1H) OH, 1.52 (d, 3H) CH_3.

6-((1H-benzo[d]imidazol-2-yl) methyl) -5H-pyrrolo[3,4-b] pyridine-5,7(6H) -dione (3): FT-IR (KBr, ν, cm^{-1}) 3330 (N-H), 2969 (=C-H), 2895 (C-H), 1698 amide, 1571 (C=C), 1320 (C-H) bending. ^{1}H-NMR (ppm): (CD_3OD, 400 MHz) δ: 13.06 (s, NH), 7.2–8.2 (m, 7H), 4.90 (s, CH_2). CHN elemental analysis calculated for $C_{15}H_{10}N_4O_2$: C, 64.74%; H, 3.59%; N, 20.13% Found: C, 64.50%; H, 4.10%; N, 20.62%.

6-(1-(1H-benzo[d]imidazol-2-yl)ethyl)-5H-pyrrolo[3,4-b] pyridine-5,7(6H) -dione (4): FT-IR (KBr, ν, cm^{-1}) 3446 (N-H), 3035 (=C-H), 2935 (C-H), 1678 amide, 1626 (C=C), 1606 (N-H) bending, and 1357 (C-H) bending. ^{1}H-NMR (ppm): (CD_3OD, 400 MHz) δ: 12.63 (s, NH), 7.20–8.20 (m, 7H), 4.98 (s, CH), 1.69 (s, CH_3). CHNS elemental analysis calculated for $C_{16}H_{12}N_4O_2$: C, 65.74%; H, 4.1%; N, 19.17% Found: C, 65.44%; H, 54.17%; N, 19.23%.

Synthesis of Furo [3,4 -b] pyridine 5,7- dione (5) [11]**:** In 50 ml R.B.F., 10 mmol, 1.66g of 2-carboxy nicotinic acid was dissolved in 15 ml of acetic acid with 0.02 mole and 2.2 ml of acetic anhydride. The resultant mixture was refluxed until it was clear, then cooled and filtered, followed by recrystallization from ethanol-water to give a beige solid product of 85% (mp. = 139–140 °C), IR: 3043, 1765 cm^{-1}. ^{1}H-NMR (ppm): (CD_3OD, 400 MHz) δ: 7.86–8.60 (m, 3H)

Synthesis of Substituted bis 5H-pyrrolo [3,4 -b] pyridine-dione (6- 11) [12]**:**
5 mmol, 0.44g, 0.51g, 0.65g, 0.78g, 1.04g and 0.49g of diamine compounds (R6-R11), respectively, were added to the solution of 10 mmol, 1.5g of (5) in 10 ml glacial acetic acid and refluxed for an hour. After that, the solvent was isolated under reduced pressure. The resultant solid was recrystallized in a suitable solvent. The physical properties of the resultant compounds are listed in Table. 1.

6,6'-(butane-1,4-diyl)bis(5H-pyrrolo[3,4-b] pyridine-5,7(6H)-dione)(6): FT-IR (KBr, ν, cm^{-1}) 3030 (=C-H), 2955 (=C-H), 1742 bis dione, 1699 amide, 1646 (C=N), 1386 (C-H) binding. ^{1}H-NMR (ppm): (CD_3CN, 400 MHz) δ 7.8–8.7 (m, 6H) aromatic, 3.38 (m, 4H) $2CH_2$, 1.65 (m, 4H) $2CH_2$. CHN elemental analysis calculated for $C_{18}H_{14}N_4O_4$: C, 61.71%; H, 3.99%; N, 15.99% Found: C, 61.91%; H, 4.11%; N, 16.20%.

6,6'-(azanediylbis(ethane-2,1-diyl))bis(5H-pyrrolo[3,4-b]pyridine-5,7(6H)-dione)(7): FT-IR (KBr, ν, cm^{-1}) 3371 (N-H), 2951 (=C-H), 2881 (C-H), 1758 bis dione, 1677 amide, 1596 (N-H) bending, and 1387 (C-H) bending ^{1}H-NMR (ppm): (CD_3CN, 400 MHz) δ: 7.82–7.48 (m, 6H), 3.66 (t, 4H), 2.87, 2.87 (t, 4H), 2.16 (s, 1H). CHN elemental analysis calculated for $C_{18}H_{15}N_5O_4$: C, 59.17%; H, 4.1%; N, 19.16% Found: C, 58.91%; H, 4.14%; N, 19.99%.

6,6'-(2-methylhexane-1,6-diyl)bis(5H-pyrrolo[3,4-b]pyridine-5,7(6H)-dione)(8): FT-IR (KBr, ν, cm^{-1}) 2966 (= C-H), 2863 (C-H), 1727 bis dione, 1699 amide, 1627 (C= N), 1381 (C-H) bending. ^{1}H-NMR (ppm): (CD_3OD, 400 MHz) δ: 7.89–7.67 (m, 6H), 3.65–3.25 (m, 4H), 2.15 (d, 2H), 1.75–1.65 (d, 2H), 1.35–1.15 (d, 3H), 0.95 (d, 3H). CHN elemental analysis calculated for $C_{21}H_{20}N_4O_4$: C, 64.27%; H, 5.09%; N, 14.27% Found: C, 64.30%; H, 5.12%; N, 14.29%.

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6,6'-(((1H-1,2,4-triazole-3,5-diyl) bis(azanediyl))bis(methylene))bis(5H-pyrrolo[3,4-b]pyridine-5,7(6H)-dione) (9): FT-IR (KBr, ν, cm^{-1}) 3187 (N-H), 3061 -H), 1776 pyrrolopyridine, 1773 bis dione, 1592, 1492, 1307. ^{1}H-NMR (ppm): (CD_3OD, 400 MHz) δ: 9.91 (s, 1H), 7.80–7.41 (m, 6H), 5.22- 4.89 (s, 4H), 4.11 (s, 2H). CHN elemental analysis calculated for $C_{18}H_{13}N_9O_4$: C, 51.55%; H, 3.10%;N, 30.06% Found: C, 51.60%; H, 3.76%; N, 30.66%.

6,6'-(acridine-3,6-diyl) bis(5H-pyrrolo[3,4-b] pyridine-5,7(6H)-dione) (10): FT-IR (KBr, ν, cm^{-1}) 3045 (=C-H), 1715 amide, 1609 (N-H) binding, 1367 (C-H) binding, 1105. ^{1}H-NMR (ppm): (CD_3OD, 400 MHz) δ: 8.35–7.2 (m, 13H). CHN elemental analysis calculated for $C_{27}H_{13}N_5O_4$: C, 68.78%; H, 2.75%; N, 14.85%. Found: C, 68.08%; H, 2.91%; N, 14.55%.

6,6'-(1H-1,2,4-triazole-3,5-diyl)bis(5H-pyrrolo[3,4-b] pyridine-5,7(6H)-dione) (11): FT-IR (KBr, ν, cm^{-1}) 3370 (N-H), 3032 (=C-H), 1760 bis dione, 1707 amide, and 1593 (N-H) bending ^{1}H-NMR (ppm): (acetone D6, 400 MHz) δ: 9.89 (s, 1H), 7.92–7.61 (m, 6H). CHN elemental analysis calculated for $C_{16}H_7N_7O_4$: C, 53.19%; H, 1.93%; N, 27.13% Found: C, 53.61%; H, 2.31%; N, 27.59%.

Synthesis of 5H-pyrrolo [3,4-b]-pyridine-dione (12) [13]:
In a 100 ml round-bottom flask, a mixture of 0.3 moles 2 g of urea and 0.15 moles 9 g of anhydride (5) was made. After 10 to 20 minutes of shaking and heating the mixture to a temperature range of (130 to 135 °C), the reaction volume increased. The reaction result was then allowed to cool until it reached room temperature. 10 ml of water were added and well mixed to neutralise the amide. After filtering and recrystallizing from ethanol, the resultant mixture produced white crystals with a melting point of (188–190 °C) and 83% purity. The infrared spectrum exhibited characteristic peaks at 3104, 1725, 1620, and 1391 cm^{-1}. ^{1}H-NMR (ppm): (CD_3OD, 400 MHz) δ: 13.2 (s, 1H) N-H, 7.76-8.61 (m, 3H).

Synthesis of 6-(hydroxymethyl) pyrrolo [3,4-b] pyridine-dione (13) [14]:
28 mmol, 5g of imide (12) and 30 mmol, 2.5 ml of 40% formaldehyde in water were mixed in 30 ml of distilled water and (10 ml) of DMF. The resultant mixture was stirred overnight till a white precipitate was noted; then, the white solid product was filtered and recrystallized from DMF/water (1:4). (m.p. 163–164 °C) 85% IRcm^{-1} 3608 (O-H), 2966 (=C-H), 2883 (C-H), bis dione 1733, 1708 amide, 1443 (c-H) bending, and 1399 (O-H) bending ^{1}H-NMR (ppm): (CD_3OD, 400 MHz) δ: 7.86–8.65 (m, 3H) aromatic, 4.94 (s, 2H) CH_2, 4.35 (s, 1H) O-H.

Synthesis of Substituted 6-((phenylamino)methyl)-5H-pyrrolo [3,4-b] pyridine-dione (14-17) [15]:
3 mmol, 0.53g from (13) was mixed with 3 mmol, 0.29 mL, 0.41g, 0.33mL and 0.45g of substituted aniline (R14 to R17) respectively with one drop of TEA and one drop of DMF. The blend was heated in an oil bath to (110- 120 °C) for about 10 minutes, and finally, the mixture was cooled by adding 5 ml of ice water. Then, the resultant precipitate was filtrated and recrystallized from acetone. The physical properties of the resulting compounds are in Fig. 2 and Table 1.

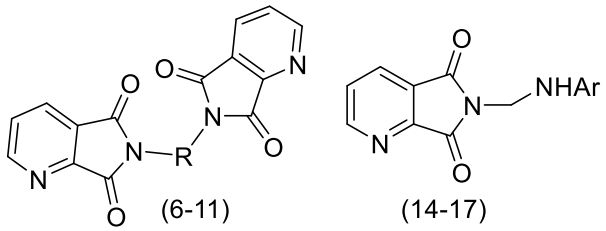
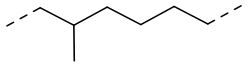
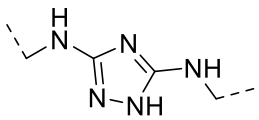


Figure 2. Proposed structures for compounds (6-11, 14-17)

Table 1. The physical properties of prepared compounds (6- 11, 14-17)

	R	m.p.	color	Solvent of recrystallization	% yield
6	$-CH_2CH_2CH_2CH_2-$	170- 171	white	ethanol	91
7	$-CH_2CH_2NHCH_2CH_2-$	183- 184	White	ethanol	80
8		156- 157	Gray	$CHCl_3$	61
9		185-186	Pale yellow	methanol	57

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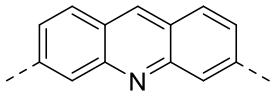
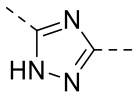
10		168- 170	Pale yellow	Ethanol	73
11		210- 211	White	Methanol	64
14	H	225- 227	yellow	Acetone	72
15	p-Ph-NO_2	142- 143	Yellow	Acetone	69
16	-CH_2-Ph	211-212	White	Acetone	70
17	-NH-CO-p-Pyridine	261- 263	Pale yellow	acetone	54

6-((phenylamino)methyl) -5H-pyrrolo[3,4-b] pyridine-5,7(6H) -dione (14): FT-IR (KBr,ν, cm^{-1}) 3333 (N-H), 2933 (=C-H), 2858 (C-H), 1766 bis dione, 1716 amide, and 1464 (C-H) bending CHN elemental analysis calculated for $C_{14}H_{11}N_3O_2$: C, 66.39%; H, 4.34%; N, 15.80%. Found: C, 66.78%; H, 4.62%; N, 15.15%. ^{1}H-NMR (ppm): (CD_3OD, 400 MHz) δ: 7.65–8.23 (m, 3H), 6.92–7.12 (m, 5H), 5.89 (s, 1H) N-H, 5.75 (s, 2H).

6-(((4-nitrophenyl)amino)methyl) -5H-pyrrolo[3,4-b] pyridine-5,7(6H) -dione (15): FT-IR (KBr, ν, cm^{-1}) 3362 (N-H), 3062 (=C-H), 2939 (C-H), 1767 bis dione, 1706 amide, 1603 (N-H) bending, 1500 asymmetric (N-O), 1362 symmetric (N-O), and 1284 (C-N) ^{1}H-NMR (ppm): (CD_3CN, 400 MHz) δ:8.08–8.06 (d, 1H), 7.85–7.82 (m, 2H), 6.98–6.66 (m, 4H), 5.16 (s, 2H), 3.16 (s, H). CHN elemental analysis calculated for $C_{14}H_{10}N_4O_4$: C, 56.37%; H, 3.35%; N, 18.78% Found: C, 56.67%; H, 3.76%; N, 18.79%.

6-((benzylamino)methyl) -5H-pyrrolo[3,4-b] pyridine-5,7(6H) -dione (16): FT-IR (KBr,ν, cm^{-1}) 3388 (N-H), 3037 (=C- H), 2907 (C-H), 1712 amide, 1592 (N-H) bending, and 1388 (C-H) bending ^{1}H-NMR (ppm): (CD_3CN, 400 MHz) δ 7.85 - 7.82 (m, 3H), 7.58 - 7.31 (m, 5H), 4.82 (s, 2H), 4.50 (s, 1H), 3.64 (s, 2H). CHN elemental analysis calculated for $C_{15}H_{13}N_3O_2$: C, 67.40%; H, 4.86%; N, 15.72% Found: C, 67.49%; H, 5.16%; N, 15.14%.

N'-((5,7-dioxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)methyl)benzohydrazide (17): FT-IR (KBr, ν, cm^{-1}) 3196 (N-H), 3045 (=C-H), 1750 bis dione, 1598 (N-H) bending, 1454 (C-H) bending, 1378, and 1295 (N-N).^{1}H-NMR (ppm): (CD_3CN, 400 MHz) δ: 9.12 (s, 1H), 8.33–7.67 (m, 7H), 5.19 (s, 2H). 4.09 (s, 1H). CHN elemental analysis calculated for $C_{14}H_{11}N_5O_3$: C, 56.56%; H, 3.70%; N, 23.55% Found: C, 56.65%; H, 3.89%; N, 23.72%.

Results and Discussion

The commercial availability of 2-carboxy nicotinic acid provides a convenient route for the building of substituted pyrrolo [3,4-b] pyridine derivatives, which can potentially be useful building blocks for the synthesis of various compounds.

The starting material, 2-carboxy nicotinic acid, was utilized in three different reactions. In the first step, it was reacted with either glycine or alanine in the presence of glacial acetic acid to produce substituted pyrrolo pyridine compounds (1-2) respectively. The resulting compounds were characterized by their physical properties colours and melting points compared with the starting material and the unique absorption spectra in IR, with strong and broad spikes in 1750 and 1735 corresponding to the carbonyl of carboxylic acids and at 1678 for amide. In the subsequent step, compounds (1-2) were further reacted with ortho-phenylenediamines in the presence of 4N hydrochloric acid to produce substituted benzoimidazole pyrrolo pyridine compounds (3-4). These products were characterized by their physical properties (colors and melting points and absorption bands in IR, with peaks at 3330 and 3446 corresponding to NH and at 1698 and 1678 for carbonyl of amide Fig. 3. The characterization was further supported by ^{1}H-NMR (ppm) at 13.06 and 12.63 for singlet NH and at 4.90 for two protons in CH_2 and 4.98 for one proton in CH, as shown in. Fig. 4. In addition, the C.H.N. analysis confirmed that the percentage of the elements was in perfect ratio. The percentage of resulted compounds fluctuated from good in (1) to moderate in (2 and 3) to week in (4).[16,17]

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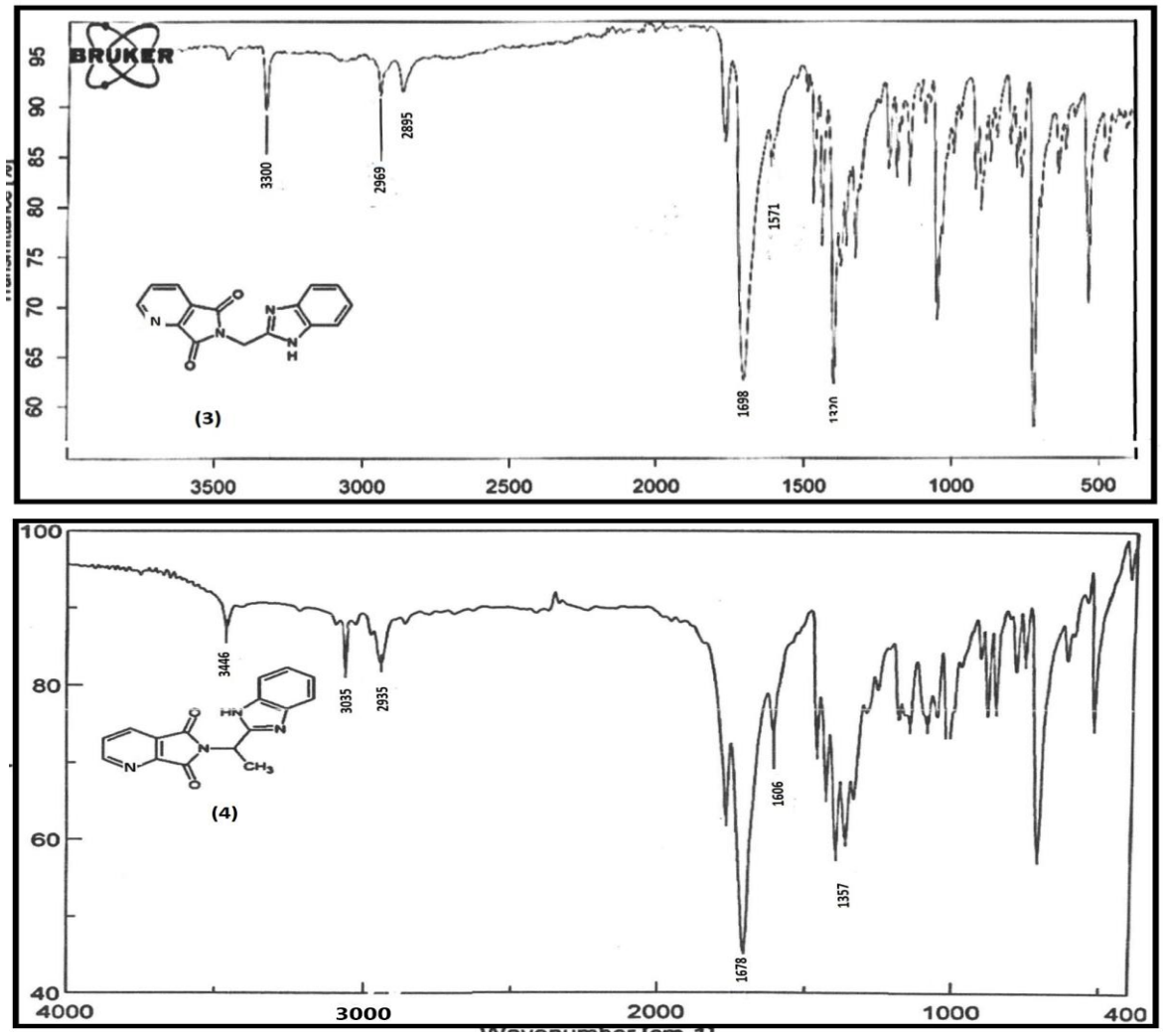
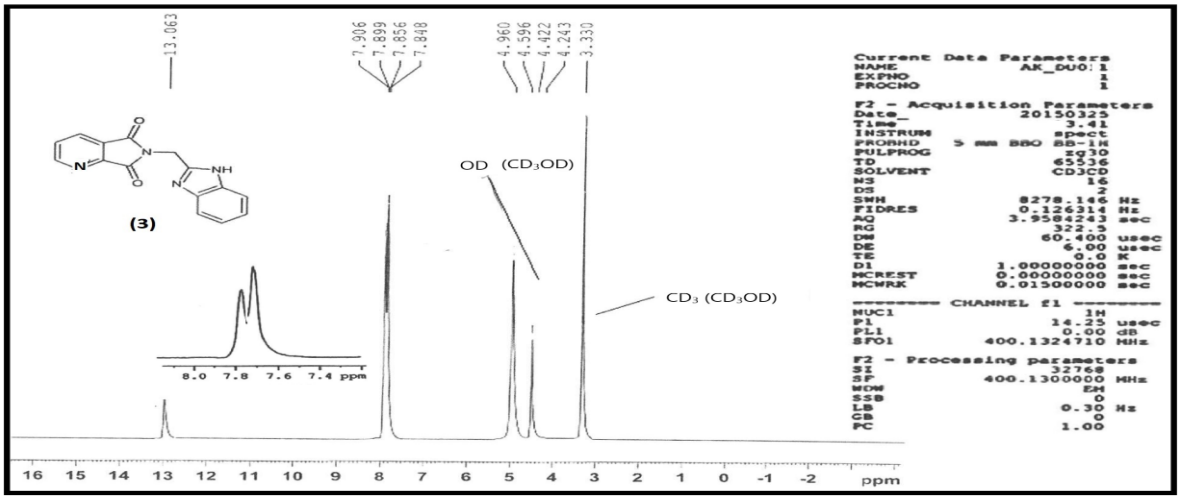


Figure 3. IR spectra for (3,4)



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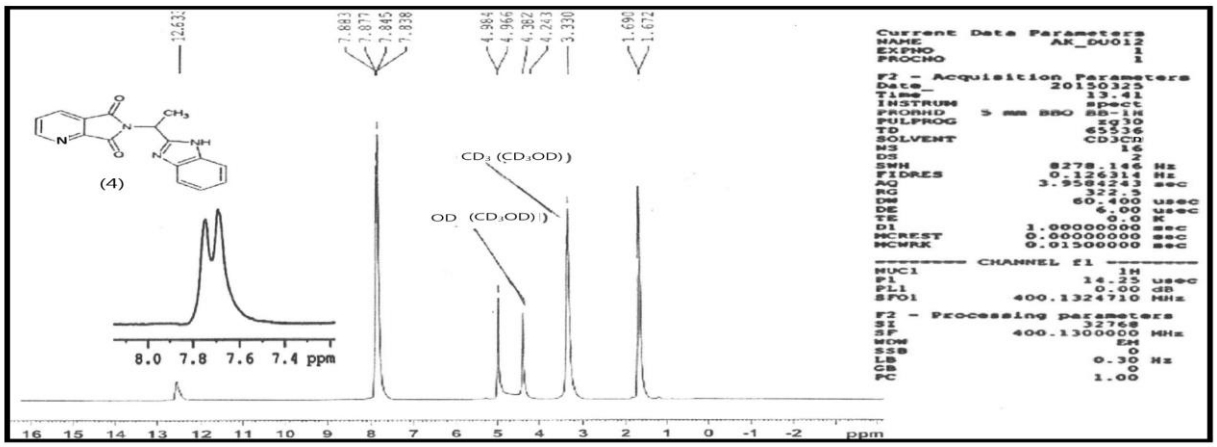
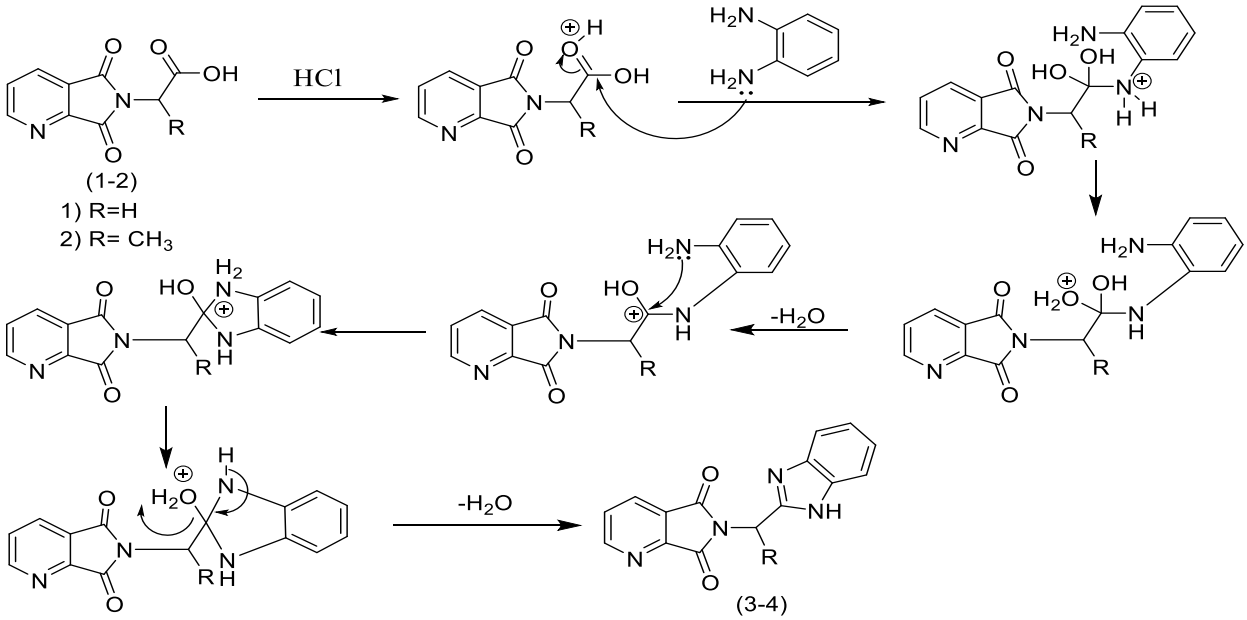


Figure 4. ^{1}H-NMR charts for (3,4)

According to the proposed mechanism, the reaction proceeds in two steps, each involving the release of a water molecule upon attack by the nucleophilic amine groups on the carbon of the C-O bonds, as illustrated in Scheme 3.



Scheme 3. Mechanism of the reaction

In the second route, 2-carboxy nicotinic acid was dehydrated by treating it with acetic anhydride to give furo pyridine dione (5) in 85%. The confirmation of this previously prepared compound was based on its physical properties (color and melting point) matching those of literature [11]. In addition, the absorption in the IR spectrum showed peaks at 3043 cm^{-1} for aromatic C-H and 1765 cm^{-1} for the carbonyl of anhydride. At the same time, the ^{1}H-NMR chart gives peaks representing the three protons of the pyridine ring.

Next, two moles of (5) were reacted with one mole of various diamino compounds to give (6-11). The percentage of resultant compounds fluctuated from excellent in (6) to moderate in (9). These compounds were confirmed by their physical properties Table. 1 and their absorption in the IR spectrum. For example, the absorption at 3371, 3187, and 3370 cm^{-1} belonged to N-H in (7, 9, 11), respectively. The absorption range from 2955 to 2966 cm^{-1} belonged to C-H in (6-9) while it disappeared in (10-11). The absorption range from 1776 to 1699 cm^{-1} belonged to the two rings of bis pyrrolo pyridine dione (6-11) Fig. 5.

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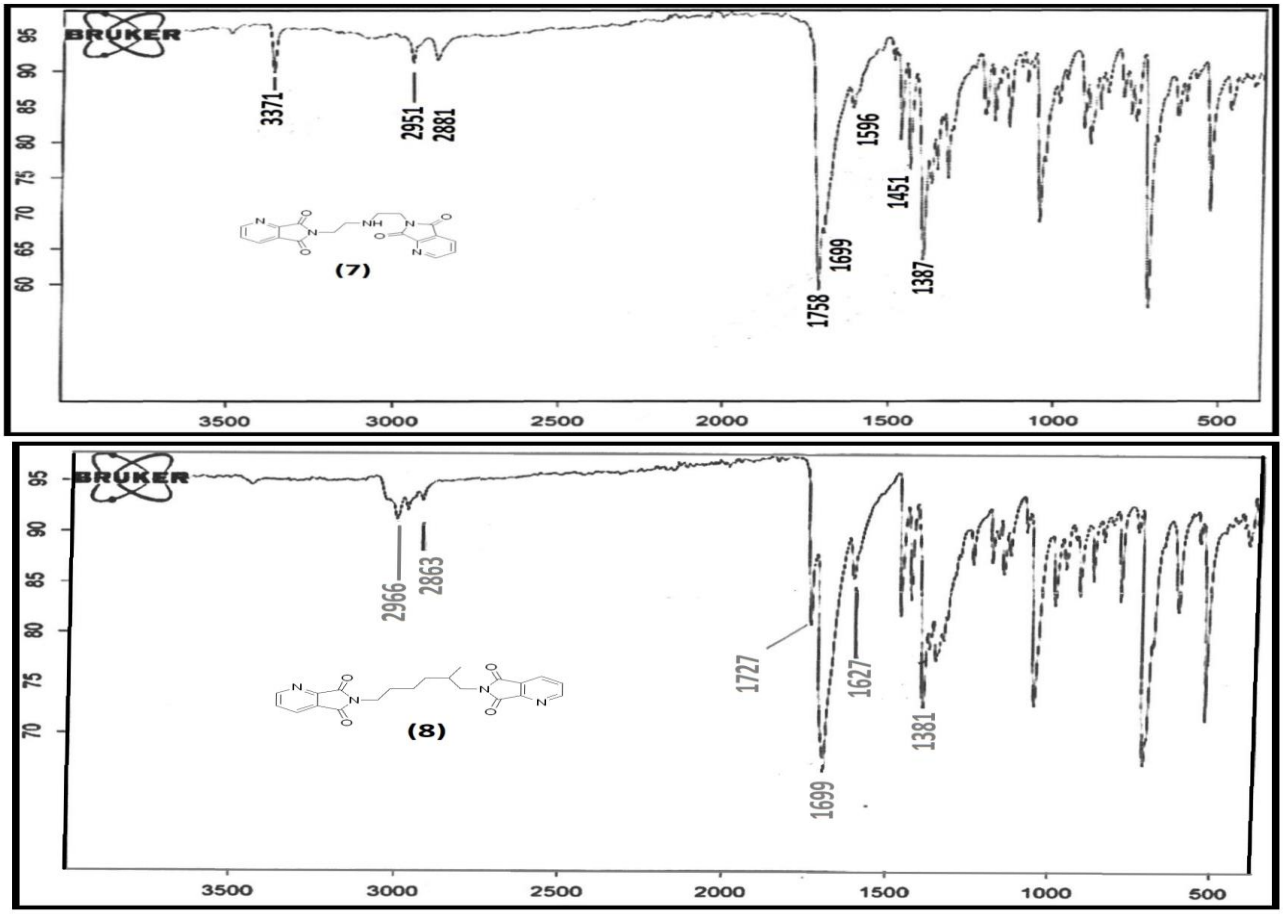
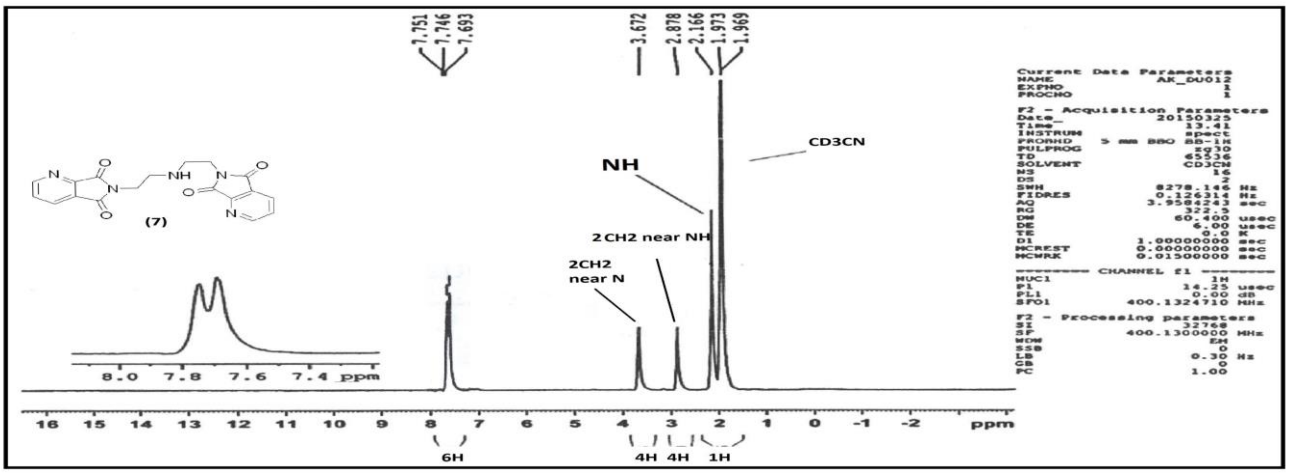


Figure 5. IR charts for (7, 8)

To further confirm the structures of these compounds, ^{1}H-NMR spectroscopy was used. Specific bands were observed at 2.16 ppm for aliphatic NH in (7) and at 9.92 and 9.89 ppm for aromatic NH in (9, 11), respectively Fig. 6. The bands between 8.35 and 7.20 ppm belonged to the aromatic protons. Furthermore, the (C.H.N.) results for (6- 11) match the theoretical percentage of the elements.[16]



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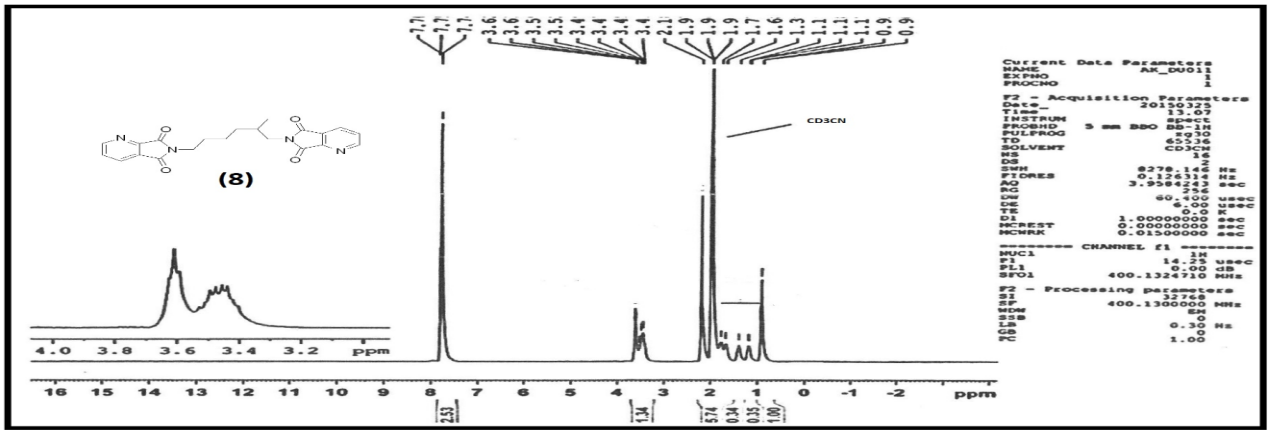

Figure 6. ^{1}H-NMR charts of (7, 8)

Overall, the results showed the successful synthesis of pyridine dione (5) and its reaction with diamino compounds (6-11) to produce new compounds with distinct physical and spectral properties. These findings may have implications for the development of new therapeutic agents.

In the final step of the route, compound (5) was subjected to a reaction with two moles of urea under heat, yielding pyrrolo pyridine dione (12) in a very good percent of 83%. This compound was confirmed through physical properties, IR analysis and ^{1}H-NMR. The IR spectrum showed unique bands at 3104 cm^{-1} for aromatic C-H and 1725 cm^{-1} for carbonyl groups. At the same time the proton of the N-H gives a signal at 13.2. Subsequently, (12) was reduced with formaldehyde in water in the presence of DMF to form methyl alcohol amide (13) in 85%, which was identified through its physical properties and IR absorption, showing a hydroxyl group band at 3608 cm^{-1} instead of the typical amide bands at 1733 and 1708 cm^{-1} Fig. 7.

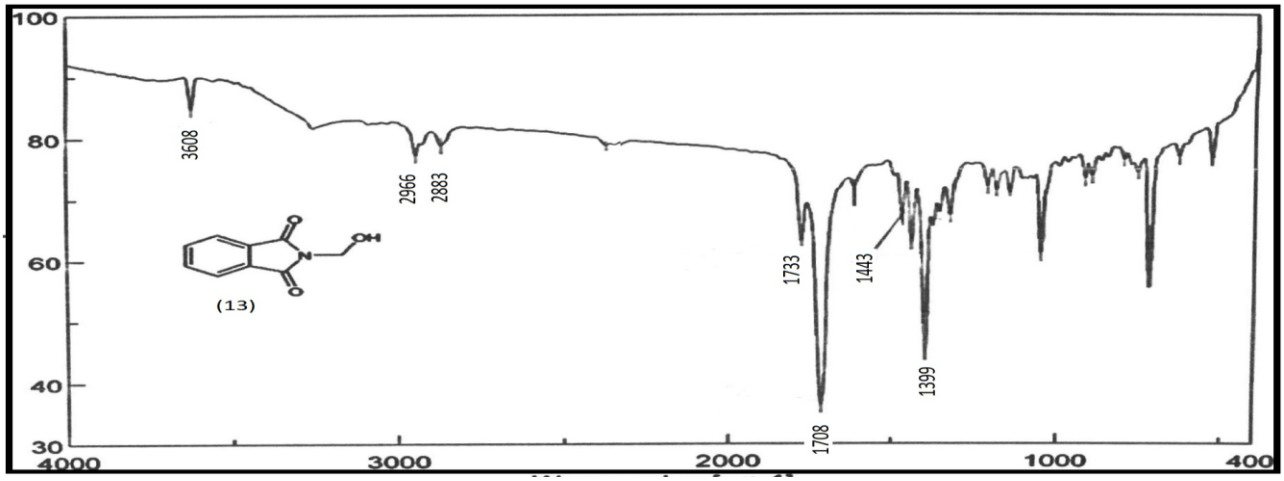

Figure 7. IR spectra of (13)

In the last step of the reaction, (13) was reacted with various amines through a simple SN2 one-step reaction, resulting in the formation of compounds (14-17) in a moderate to good percentage. The resulting compounds were identified through IR absorption at 3333, 3362, 3388, and 3196 cm^{-1}, corresponding to N-H groups. Furthermore, the nitro group [18] of (15) has a unique value belonging to the stretches of asymmetric (one oxygen atom bonds by a single bond to the nitrogen while the other oxygen has a double bond with nitrogen) at 1500 cm^{-1} and symmetric (the two oxygen atoms are bonded by a single bond to the nitrogen) at 1362cm^{-1}. In addition, the ^{1}H-NMR spectra showed singlet signals between 3.64 and 3.16 for (14-16) and at 9.13 and 4.09 for the two protons in the hydrazine group in (17) Fig. 8. Furthermore, the (C.H.N.) results for (14- 17) match the theoretical percentage of the elements. The total reaction synthesis is illustrated in Scheme 4.[19]

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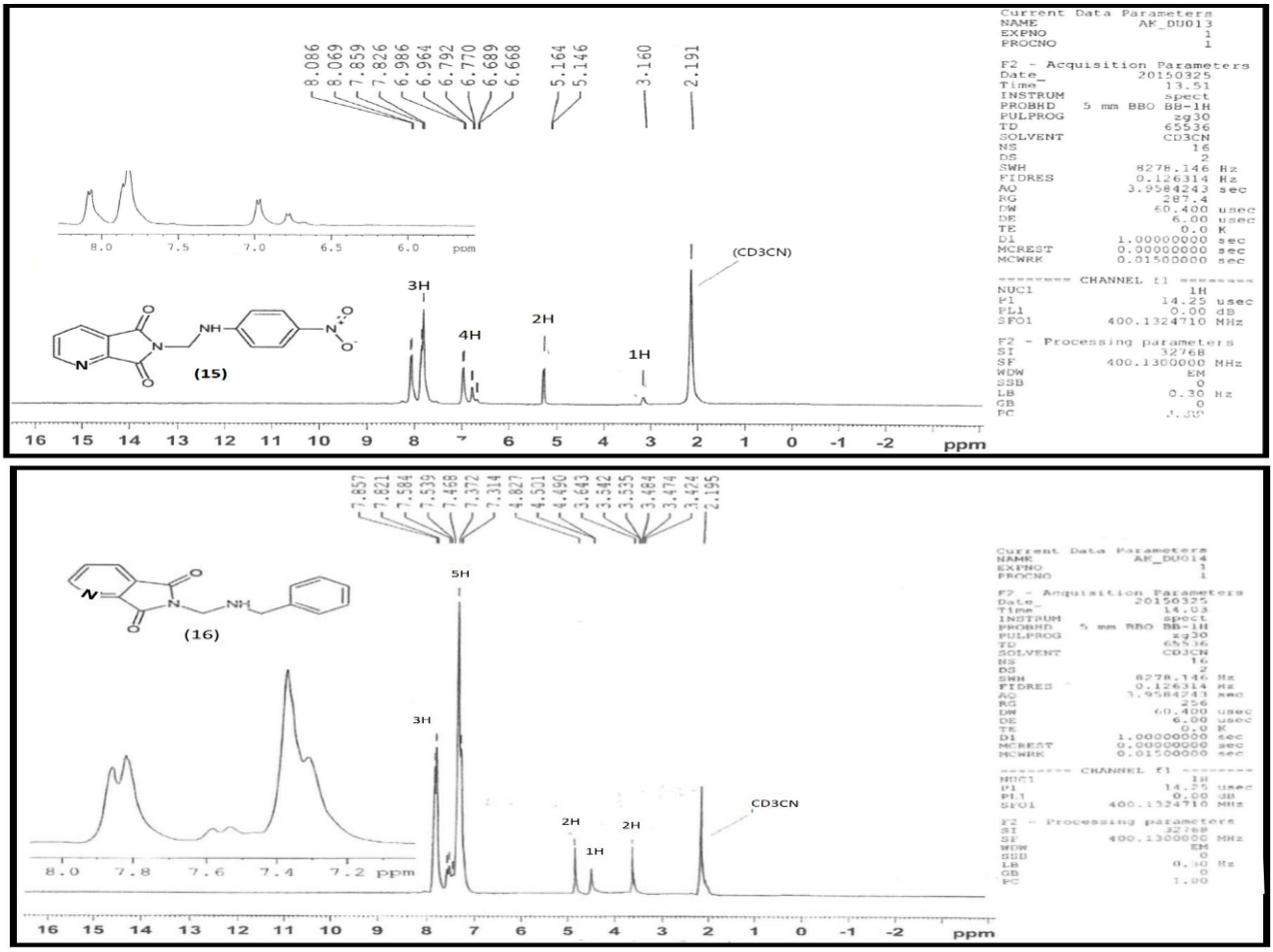
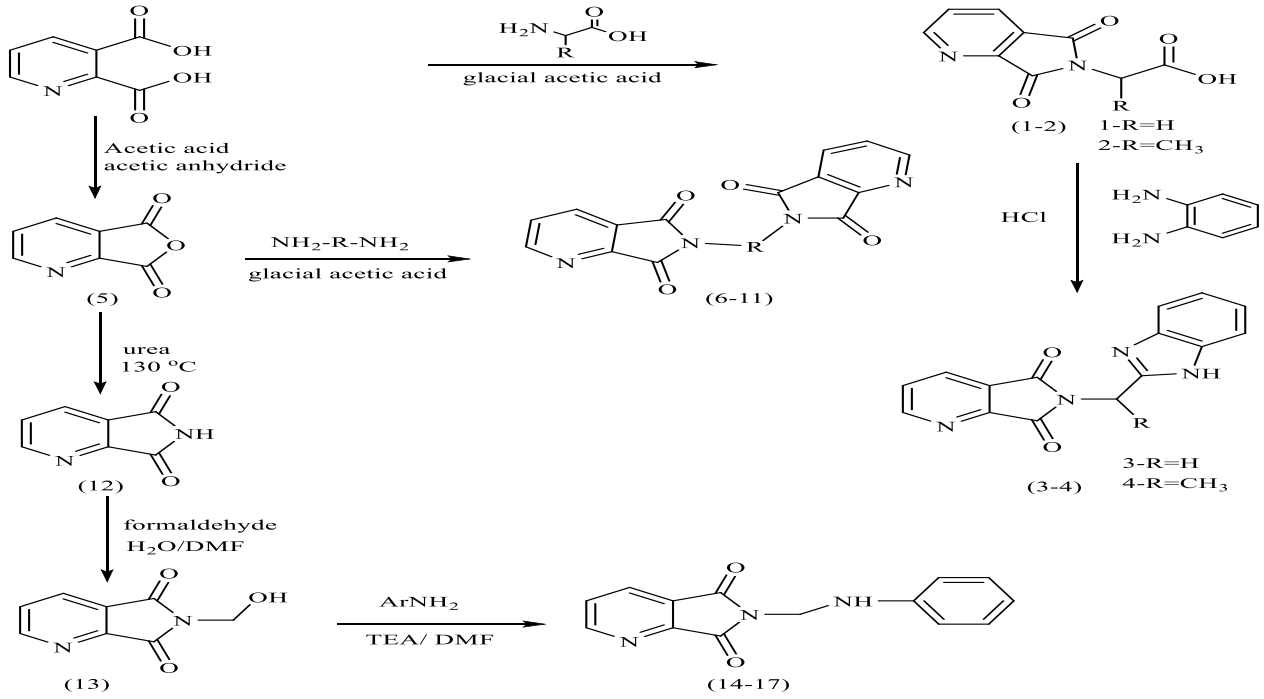


Figure 8. ^{1}H-NMR charts for (15, 16)



Scheme 4. Total synthesis reactions

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The Antimicrobial Activity:

In this study, the inhibitory efficacy of some compounds on the growth of two different sorts of Gram-positive and Gram-negative bacteria carrying the Klebsiella strain was tested using the sensitivity test. The following types of bacteria were used in this study: Gram-positive *Staphylococcus Aureus* and Gram-negative *Escherichia Coli.*

The Bauer and his group method [20] were adopted for sensitivity testing. Colonies of these types of bacteria were transferred to a nutrient broth intermediate and incubated at a temperature of 37 °C for 15-16 hours. The saline solution was then diluted, and 0.1 ml of the bacterial suspension was moved to the nutrient agar medium and spread on the surface of the plates. Plates were left to stand for approximately 30 minutes.

To measure the inhibitory effect of the chemical compounds obtained, discs were taken from filter paper and immersed in varying concentrations of the chemical compounds using dimethyl sulfoxide as a solvent for preparing the chemical compound solutions. The saturated discs with the solutions were distributed on the surface of the agar plates at suitable intervals and incubated for 18-20 hours. The antibiotics ampicillin and cefalexin were used as control samples for the bacteria Table 2.[21]

Table 2. The biological activity of prepared compounds

*Compound	Conc. Of (Mg/disk)			
	E. coli (10mg/disk) **ZI mm.	*E. coli* (1mg/disk) ZI mm.	*S. aureus* (10mg/ml) ZI mm.	*S. aureus* (1mg/disk) ZI mm.
1	20	9	15	7
2	13	7	11	6
4	10	6	-ve	-ve
8	16	7	16	7
11	-ve	-ve	6	2
17	19	12	19	12
Cephalexin	22	13		
Ampicillin			19	15

*Inhibition levels ranging from 1-6 mm. are considered to have low inhibition, those from 6- 12 mm. have moderate inhibition, and those above 12mm. have a high impact and inhibition. **ZI Zone of inhibition

The impact of some compounds prepared in this study (1, 2, 4, 8, 11, 17) on the growth of two different types of bacteria, both Gram-negative and Gram-positive has been examined. The results presented in the table indicate that the tested compounds possess the ability to inhibit the utilized bacteria. It was observed that with an increase in the substance's concentration, the diameter of the bacterial growth inhibition zone increased. Furthermore, it was observed that the inhibition of Gram-negative *Escherichia coli* was more sensitive compared to that of Gram-positive *Staphylococcus aureus*. This difference in potency refers to many factors such as the variance in composition of the cell wall of the bacteria, the resistance mechanism and the concentration of the inhibitor. The lactam antibiotics (cephalexin) cause bacterial lysis by affecting peptidoglycan synthesis, while bacteria develop antimicrobial resistance by various mechanisms such as horizontal gene transfer in *Staphylococcus aureus* .[22, 23]

The zone of inhibition results fluctuated from high (1, 8, 17) to moderate (2, 4) to low (11). Regarding compound (17), it exhibited the highest inhibitory capacity. This may be attributed to it being among the derivatives of hydrazides, which are considered biologically active compounds.[24]

The minimum inhibitory concentration (MIC) was made by preparing the following dilutions (1, 10 Mg/disk) of each compound, and the minimum inhibitory concentration that prevents the growth of the bacteria was identified.

Docking Study

Shikimate kinase was downloaded from protein bank database (https://www.rcsb.org/) having PDB ID: 1L4Y. The compounds were docked using CB-Dock2 online server [24], presented at: https://cadd.labshare.cn/cb-dock2/php/index.php**.** Table 3. and Fig.9.

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Table 3. Docking result with the interactions [25]

compound	Docking score	Contact residues	Hydrogen bonding	Hydrophobic interactions
1	**-7.0**	**Chain A**: PRO11 LYS15 ASP34 ILE45 PHE49 GLU54 ARG58 GLY79 GLY80 GLY81 ALA82 PRO118 LEU119 ARG136	Arg58, Gly80, Gly81, Arg136	Pro11, Leu19, Glu54, Phe49, Pro118
8	**-8.6**	**Chain A**: PRO11 LYS15 SER16 ASP34 ALA46 PHE49 ALA50 GLU54 GLY79 GLY80 GLY81 VAL116 ARG117 PRO118 LEU119 ARG136	Lys16	Pro11, Ser16, Asp34, Phe49, Glu54, Arg117, Pro118, Leu119
17	**-8.4**	**Chain A**: LEU10 PRO11 GLY12 SER13 GLY14 L YS15 SER16 THR17 ASP34 LEU78 GLY79 GLY80 GLY81 VAL116 ARG117 PRO118 LEU119 ARG136	Gly14, Lys15, Gly80, Arg117	Pro11, Gly12, Ser16, Thr17, Gly79, Arg136

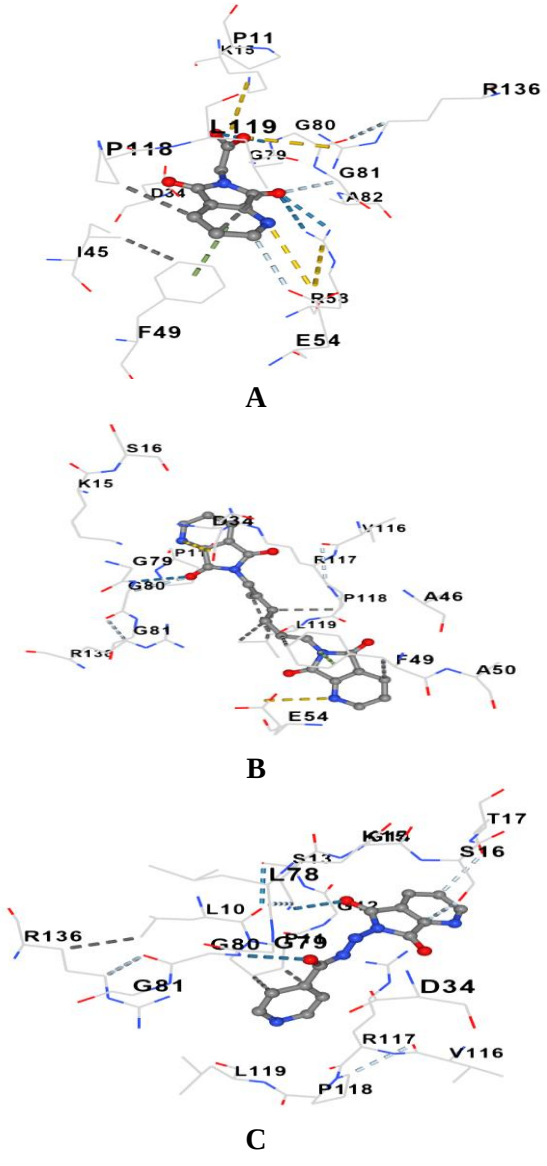

Figure 9. Interaction of shikimate kinase with (A) compound 1, (B) compound 8 and (C) compound 17.visualized by Lig plot [26]

Docking scores in Table 3 are essential for virtual screening and lead optimization in drug discovery, as they help prioritize potential drug candidates and select those with the highest predicted binding affinities for further experimental validation. However, it's important to note that docking scores are predictions and may not always correlate perfectly with actual experimental binding affinities So, they are often used as a preliminary filtering step in the drug development process. At the same time, contact residues are important for understanding the molecular details of protein-ligand interactions. It can provide insights into the binding interface and the key amino acids responsible for the interaction. Fig. 9, shows the binding of compounds (1, 8, 17) Figs. A, B and C respectively, to the enzyme with the interacting amino acid residues by dotted lines.[27]

The results of docking experiments indicate that these chemicals interact with the shikimate kinase enzyme. This enzyme plays an important role in the biosynthesis pathway for aromatic amino acids. Because the enzyme might serve as a molecular target in bacteria, these chemicals might prove valuable in the research and development of new antimicrobial drugs.

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Conclusion

This study reports the effective synthesis of several novel pyrrolo pyridines. The synthesis of these new amines provides building blocks for the construction of more complex molecular structures and has potential uses in a variety of medicinal applications. Furthermore, three compounds (1, 8, 17) showed considerable suppression against two species of bacteria (Escherichia coli and Staphylococcus aureus), while compounds (2, 4) exhibited moderate sensitivity. Promising results are obtained from the biological activity that has been seen and the compounds' potential as medications or drug precursors. The compounds (1, 8, 17) can bind to the target enzyme of bacteria with effectiveness, as further shown by the docking investigation. All things considered, this study provides insightful information about the intentional synthesis of novel pyrrolo pyridines, highlighting the potential.

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Authors' Declaration

- Conflicts of Interest: None.
- We hereby confirm that all figures and tables in the manuscript are ours. Furthermore, figures and images, that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.
- No animal studies are present in the manuscript.
- No human studies are present in the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee at at University of Mosul

Authors' Contributions Statement

S. S. I. accomplished the experiment portion of the study with all needed testing, A. A. F. carried out the research plan with the biological activity section. As a corresponding author, Y. S. A. investigated the data and wrote the manuscript. Every author has read and reviewed the work.

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تحضير بعض معوضات البيريديليمايد الجديدة من تفاعل 2-كاربوكسي حامض النيكوتنيك مع الامينات وتقييم فعاليتها ضد البكتريا

انوار عبد الغني فتحي ، ياسر شكيب محمد، شيماء سمير إسماعيل

قسم الكيمياء، كلية التربية للعلوم الصرفة ، جامعة الموصل، الموصل، العراق.

الخلاصة

تم في هذا البحث تحضير بعض معوضات البيريديليمايد من خلال تصعيد 2-كاربوكسي حامض النيكوتنك مع الاحماض الامينية لتكوين 2-معوضات (5,7-ثنائي اوكسي-5,7- ثنائي هايدرو- 6هايدرو- بايرولو[b,3,4] بريدين -6- يل حامض الخليك (1,2), ثم تم تصعيد المركبات الناتجة مع اورثو فنيل ثنائي الأمين بوجود حامض الهيدروكلوريك لتكوين معوضات 6- ((1- بنزو [d] اميدازول -2- يل) مثيل) – 5هايدرو- بايرولو[b,3,4] بريدين -5,7- (6هايدرو) داينون (3-4). وكذلك 2- كاربوكسي حامض النيكوتنك حول الى فيورو[b,3,4] بريدين -5,7- دايينون (5) من خلال تفاعله مع انهدريد الخليك وحامض الخليك, وكذلك معاملة مولين من الناتج السابق مع ثنائي الأمين لاعطاء معوضات بس 5هايدرو- بايرولو[b,3,4] بريدين -5,7- (6هايدرو) داينون (6- 11). واخيرا تم مفاعلة (5) مع اليوريا لاعطاء 5هايدرو- بايرولو[b,3,4] بريدين -5,7- (6هايدرو) داينون (12) والذي تم مفاعلته مع الفورمالديهايد لاعطاء 6-(هايدروكسي ميثايل)-5هايدرو- بايرولو[b,3,4] بريدين -5,7- (6هايدرو) داينون (13), وبدوره تم مفاعلته مع معوضات الانلين بوجود ثلاثي اثيل امين لاعطاء معوضات 6-((فينايل امينو) ميثايل) 5هايدرو- بايرولو[b,3,4] بريدين -5,7- (6هايدرو) داينون (14- 17). تم التحقق من صحة المركبات الناتجة بواسطة خواصها الفيزيائية بالإضافة الى (IR, NMR, C.H.N). قيست الفعالية البايولوجية لعدد من المركبات المحضرة ضد نوعين من البكتريا المرضية وقورنت النتائج مع نوعين من المضادات الحيوية المعروفة. أظهرت النتائج ان المركبات (1, 8 ,17) تمتلك فعالية عالية ضد البكتريا بينما (2 و 4) متوسطة الفعالية بالمقارنة مع (11) الذي لا يمتلك فعالية. أجريت دراسة ال Dockingباستخدام برنامج CB-Docke2ضد انزيم الشيكيمات كيناز حيث اظهر المركب (8) فعالية عالية تعادل 8.6- كيلوكالوري/ مول. هذه النتيجة تشجع على تحضير المزيد من مركبات البايرولو بريدين لما تمتلك من فعالية حيوية.

الكلمات المفتاحية: أمينات، أحماض أمينية، أميدا زول، حامض النيكوتينك، البيريديليمايد.