"Novel Diiodobenzaldehyde Derivatives of 4-Aminopyrrolo[2,3-d] pyrimidine: Synthesis, Characterization, and Biological Activity."

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Abstract: The main objectives of this study were to create new pyrrolopyrimidine compounds, analyze their properties, and assess their effectiveness against both fungi and bacteria. Specifically, the focus was on synthesizing diiodobenzaldehyde derivatives of pyrrolopyrimidine. Various spectroscopic methods were employed to characterize the chemically synthesized substances. These compounds were then tested for their ability to inhibit the growth of four bacterial strains (*S. aureus*, *B. subtilis, E. coli, P. aeruginosa*) and two fungal strains (*C. albicans, S. cerevisiae*). Each synthesized compound exhibited distinct peaks in FT(IR), ^{1}H, and ^{13}C NMR, as well as UV spectral studies. In vitro testing revealed that compound **2a** displayed significantly higher antibacterial and antifungal activity compared to streptomycin and fluconazole, the gold standards.

Keywords: Iodo benzaldehyde, 4-aminopyrrolo[2,3-*d*]pyrimidine, Cytotoxic study, Antibacterial activity

1. Introduction:

The importance of pyrimidines and related compounds is well-known. In nature, the most common heteroaromatic chemicals are pyrimidines and purines. The pharmacological and chemotherapeutic potential of pyrrolopyrimidine (PP) derivatives has piqued the curiosity of researchers. Their possible bioactive properties make fused heterocycles that have structural similarities intriguing. Inhibiting enzyme activity [1], inducing cell death [2], fighting viruses [3], lowering inflammation [4-6], treating allergies [7], combatting tumours [8-12], and serving as antibacterial and antifungal agents [13] are some of the documented biological roles of these compounds. Our research has identified a novel class of PP compounds generated from iodobenzaldehydes, and this study details their synthesis and antibacterial characteristics.

Experimental:

All materials were procured from commercial sources and utilized in their original, unprocessed states unless specified otherwise. Thin-layer chromatography (TLC) testing was conducted using silica gel plates. The accuracy of the melting point measurements is uncertain. FT(IR) spectra of the KBr pellet were obtained using a BRUKER FT-IR spectrophotometer, covering the spectral range from 4000 to 500 cm^{-1}. UV spectra were acquired using a JASCO V650 spectrophotometer in a methanol solution at room temperature. ^{1}H NMR spectra in DMSO d_6 were recorded at a frequency of 400 MHz using a Brucker spectrophotometer, with TMS as the internal reference. The carbon (C), hydrogen (H), and nitrogen (N) levels across the entire sample set were all within 0.4% of their expected values. Statistical data regarding the synthesized substances are summarized in **Table 1**.

Preparation of PP derivatives 2(a-c):

A mixture comprising 10 mmol of PP and 10 mmol of diiodo benzaldehyde derivatives (**a-c**) was synthesized by refluxing for 2 hours in a solution consisting of 50 ml of ethanol and 0.5 ml of concentrated hydrochloric acid (HCl). Subsequently, the resulting products, 2(a-c), were filtered, rinsed with methanol, and then dried.

PP-2,3-diodobenzaldehyde (2a):

Colour, Yellow; M.W., 474; Yield (%), 76.99; M.P. (°C), 211; Element content: C, 32.94; H, 1.70; I, 53.54; N, 11.82. FT-IR (cm^{-1}): 3322 (-OH), 3110 (NH), 3032 (C-H), 1586/1480 (>C=C<), 1676 (>C=N-), 1333 (C-N), 725 (disubstituted benzene ring (DSBR)), 690 (monosubstituted benzene ring (MSBR)). ^{1}H NMR (ppm): 11.22 (Ar-OH), 9.23 (-CH=), 7.44-7.70 (aromatic amine), UV spectrum (λ_{nm}): 290 ($\pi \rightarrow \pi^*$), 372 ($n \rightarrow \pi^*$).

PP-2,4-diiodobenzaldehyde (2b):

Colour, Yellow; M.W., 474; Yield (%), 73.25; M.P. (°C), 209; Element content: C, 32.94; H, 1.70; I, 53.54; N, 11.82. FT-IR (cm^{-1}): 3380 (-OH), 3113 (NH), 2992 (C-H), 1581/1476 (>C=C<), 1650 (>C=N-), 1332 (C-N), 726 (TSBR), 693 (DSBR). ^{1}H NMR (ppm): 11.22 (Ar-OH), 9.20 (-CH=), 7.40-7.72 (aromatic amine), UV spectrum (λ_{nm}): 230 ($\pi \rightarrow \pi^*$), 325 ($n \rightarrow \pi^*$).

PP-2,6-diiodobenzaldehyde (2c):
Colour, Yellow; M.W., 474; Yield (%), 69.87; M.P. (°C), 218; Element content: C, 32.94; H, 1.70; I, 53.54; N, 11.82. FT-IR (cm^{-1}): 3346 (-OH), 3110 (NH), 3000 (C-H), 1586/1477 (>C=C<), 1652 (>C=N-), 1335 (C-N), 724 (TSBR), 693 (DSBR). ^{1}H NMR (ppm): 11.22 (Ar-OH), 9.25 (-CH=), 7.40-7.73 (aromatic amine), UV spectrum (λ_{nm}): 233 ($\pi \rightarrow \pi^*$), 325 ($n \rightarrow \pi^*$).

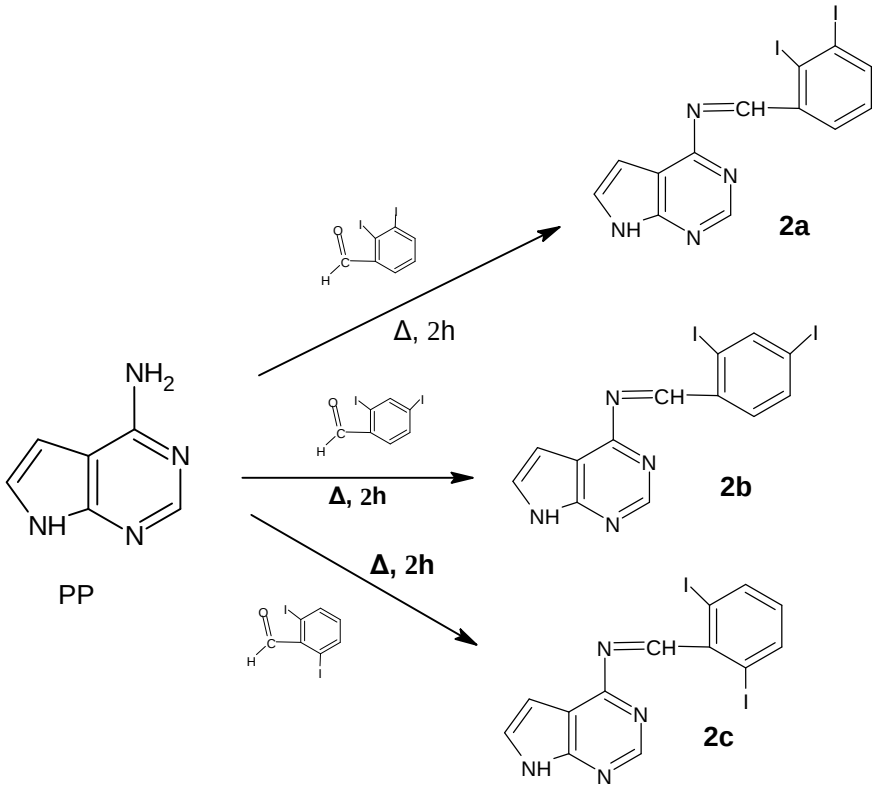

Figure 1: The synthesis of diiodobenzaldehyde-PP derivatives

Antimicrobial Assay:

Test Microorganisms:
The effectiveness of the newly synthesized compounds against both gram-positive and gram-negative microorganisms was assessed. Before antimicrobial testing, the Muller Hilton agar medium underwent autoclaving at a pressure of 15 pounds per square inch for 15 minutes. Researchers employed the disc diffusion method to ascertain the potential antibacterial properties of the synthesized chemicals [14]. Diluting the initial culture with sterile distilled water reduced its concentration to approximately 10^8 colony-forming units per ml (cfu/mL). Following a 15-minute incubation period, the cultures of various microbial strains were transferred to Petri plates containing 20 mL of Muller Hilton agar media. A sterile borer was utilized to create wells with a diameter of 6 mm. Subsequently, the inoculated plates were treated with 100 microliters of a medication solution at a concentration of 4.0 mg/mL. Following a 24-hour incubation period at 37 °C, all plates were examined. The diameter of the inhibition zone surrounding the wells was measured to assess the antibacterial activity of the synthesized compounds. Streptomycin served as a positive control, while DMF served as a negative control.

Determination of MIC:
We employed the adapted disc diffusion technique to determine the minimum inhibitory concentrations (MICs) of all the substances. The synthetic concentrations of the compounds were adjusted, ranging from 10 to 1000 µg/mL, derived from a stock solution of 4 mg/mL in DMF. A volume of 100 µL of the targeted microorganism was spread onto agar using a standard inoculum of 10^8 cfu/mL. Following each dilution, three separate wells were inoculated. After 24 hours of incubation at 37°C, the plates were examined for inhibitory zones. Streptomycin served as the standard antibiotic for comparison.

Antifungal Activity:
Employing the cup-and-plate method, the compounds underwent testing against two distinct fungal species, namely C. albicans and S. cerevisiae [16–17]. Using micropipettes, the test solution was dispensed onto discs measuring 5 mm in diameter and 1 mm in thickness. Subsequently, the plates were incubated at 37°C for 72 hours, allowing sufficient time for the test solution to permeate the substance and influence fungal growth. After

an initial 36-hour incubation period at 37°C, the size of the inhibitory zone was evaluated. The minimal inhibitory dosages of chemicals showing promise against fungus were determined. The MIC of an antifungal medication was defined as the lowest dosage inhibiting microbial growth during a 24-hour incubation period. Clinical laboratories utilize the minimum inhibitory concentration (MIC) to confirm bacterial resistance to antibiotics and assess the efficacy of novel antimicrobial agents.

In vitro cytotoxicity:
We utilized a bioassay involving brine prawns to assess the cytotoxicity of the synthesized compounds. One side of the tank contained prawn eggs, while artificial saltwater (comprising 38 grams of sodium chloride per 1000 milliliters of tap water) was placed on the other side. The entire life cycle of a prawn egg, from egg to nauplii, occurred within 48 hours. Newly hatched prawns were removed for examination. Each test tube contained varying concentrations of the dehydrated complex: 2.5, 5.0, 7.5, 10.0, and 12.0 mg/10 mL. The complexes were dissolved in DMSO to evaluate their cytotoxicity. Ten live prawns were added to each test tube using a Pasteur pipette, with a control group included to ensure the reliability of the cytotoxicity test and its results. Following a 24-hour incubation period, the tubes were observed under a microscope, and the number of surviving nauplii and any notable occurrences were recorded. The experiment was conducted in five separate trials, each with three sets of duplicates. From the collected data, we determined the LC50, LC90, chi-square value, and 95% confidence interval. Adjustments were made to the values using Abbott's formula to account for any deaths in the control groups.

Results and Discussion:

The discussed compounds are formed through the reaction of PP with diiodobenzaldehydes under reflux conditions for a duration of 2 hours. The desired compounds were obtained with yields ranging from 69.87% to 76.99%. **Figure 1** depicts the process of synthesizing diiodobenzaldehydes-PP derivatives. Although incompatible with water, the synthesized compounds exhibit compatibility with a wide range of organic solvents. Elemental analysis results confirm that all derivatives have the expected compositions. These substances manifest as colored powders with minimal water absorption properties. Following synthesis, the purity of the compounds was assessed using thin-layer chromatography (TLC).

FT(IR) spectra:
To elucidate the interaction between PP and diiodobenzaldehydes, we analyzed the FT(IR) spectra of both the synthesized compounds and the unreacted material. We specifically investigated the impact of PP vibration on substituted diiodobenzaldehydes by selecting appropriate bands for our study. A distinct and prominent band attributed to the azomethine group (HC=NN-) was evident in the spectrum within the range of 1650 to 1675 cm^{-1}. This observation confirms the formation of all synthesized compounds and indicates that the stretching vibrations of the amino derivatives are hindered by the presence of the aldehyde (CHO) and amino (NH_2) groups. The identification of a continuous spectrum range at 3109-3113 cm-1 suggests the presence of aromatic (NH) moieties in their modified states. Additionally, features characteristic of aldehydic compounds are discernible within the spectral range of 2999–3033 cm^{-1}. The infrared spectra of compounds **2a-c** exhibit two distinct bands at 1581–1585 and 1475–1481 cm^{-1}, respectively, attributable to the >C=C functional group of the aromatic ring. Furthermore, a band corresponding to aromatic (C-N) bonds is observed between 1330 and 1336 cm^{-1} in the FT spectra of compounds **2a–c**. Moreover, trisubstituted benzene rings are identified at 723-725 cm^{-1}, while monosubstituted benzene rings are detected at 683-689 cm^{-1}.

^{1}H NMR spectra:
^{1}H NMR spectra serve as a means to identify various chemical components. Noteworthy singlet signals between 10.83 and 10.88 ppm indicate the presence of a -NH- group within the pyrrolyl ring in this instance. Singlet peaks within the ranges of 10.20–11.23 ppm (attributed to aromatic –OH) and 9.20–9.23 ppm (corresponding to aldehydic –CH=) are observed in all synthesized compounds. The 1H NMR spectra of all synthesized derivatives were examined to verify the successful substitution of the amino group with the Schiff base. The wide singlet signal at 9.84 ppm (2H) can be attributed to the -NH_2 group of 4-chloro-7H-pyrrolo[2, 3-d] pyrimidine. Under previous findings, the $_1$H NMR spectra were recorded.

UV-Visible spectra:
The UV spectra of synthetic compounds **2a-c** were obtained at ambient temperature following their dissolution in DMF. The aromatic band observed in **2a-c**, ranging from 230 to 290 nm, is attributed to the $\pi \rightarrow \pi^*$ transition occurring within the benzene ring. Additionally, compounds **2a-c** display a band spanning from 324 to 372 nm, which arises from the $n \rightarrow \pi^*$ transition within the nitrogen of the azomethine groups.

Biological studies:

The synthesized compounds underwent in vitro testing to assess their antibacterial effectiveness against various strains of bacteria and fungi. All of the active antibacterial compounds tested against S. aureus, B. subtilis, E. coli, and P. aeruginosa displayed MIC values ranging from 12.5 to 22.5 mm. In comparison to streptomycin, the synthesized compounds exhibited more potent inhibitory effects against Staphylococcus aureus, with inhibitory values ranging from 18.5 to 20.5 mm.

Compound	Antibacterial Activity (zone of inhibition)			
	S. aureus	***B. subtilis***	***E. coli***	***P. aeruginosa***
2a	20.5	12.5	22.5	17.5
2b	18.5	19.0	16.5	21.5
2c	19.0	16.5	17.0	20.5
Streptomycin	15.5	14.5	12.0	14.0

Antifungal studies:
Research conducted on two fungal strains, Candida albicans and S. cerevisiae, demonstrated that the synthetic compounds exhibited approximately double the efficacy of the standard antifungal medication, fluconazole, with antifungal activity ranging from 22.5 to 24.0 mm.

Compound	***Candida albicans***	***Saccharomyces cerevisiae***
2a	24.0	22.5
2b	23.5	23.0
2c	22.0	21.5
Fluconazole	10.5	14.0

In vitro cytotoxicity:
With LD50 values estimated to range from 8.50 to 9.50 x10^{-4} M/mL, all the synthesized compounds displayed cytotoxic effects against Artemia salina.

Table 3: Brine shrimp bioassay of **2a-c** compounds

Compound	**LD_{50} (M)**
2a	$>9.50 \times 10^{-4}$
2b	$>8.50 \times 10^{-4}$
2c	$>9.00 \times 10^{-4}$

Conclusion

Our research has been centered on PP, and we have successfully synthesized numerous novel derivatives of substituted diiodobenzaldehydes (**2a-c**). Spectral investigations, electrochemical data, and analytical results collectively support the synthesis of the proposed compounds. Spectral and elemental analyses were conducted to assess the composition of benzaldehyde-based molecules produced. The results endorse the utilization of a 1:1 ratio of PP to diiodobenzaldehydes. Moreover, the antibacterial efficacy of each synthesized molecule was found to be significant. Additionally, all synthetic compounds exhibited notable cytotoxicity when evaluated on sensitive cell lines.

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