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The Synthesis of Several 7H-Pyrrolo[2,3-d]Pyrimidin-4-amine Derivatives, Derived from Cyanobenzaldehyde, was Achieved Using Ultrasonic Waves

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Abstract- Benzaldehydes have been uswed as key intermediates in the synthesis of 7H-pyrrolo[2,3-d]pyrimidin-4-amine (PPA) derivatives. The structural identities of these newly synthesized compounds were thoroughly validated using a range of analytical techniques, including elemental analysis, infrared (IR) spectroscopy, nuclear magnetic resonance (NMR), and ultraviolet (UV) spectral data. To assess their biological activity, all of the synthesized compounds were subjected to in vitro testing to evaluate their cytotoxicity against Artemia salina. Furthermore, the antimicrobial potential of each compound was explored to determine its efficacy in inhibiting microbial growth. The antibacterial activity of these compounds was compared with that of known antibiotics, fluconazole and streptomycin, showing promising results. This study specifically emphasizes the antibacterial properties of these compounds and investigates the relationship between their chemical structure and biological activity, providing valuable insights into structure-activity relationships (SAR).

Keywords- 7H-pyrrolo[2,3-d]pyrimidin-4-amine, cyanobenzaldehyde, Element analysis, infrared spectroscopy

I. INTRODUCTION

Purines and pyrimidines, due to their crucial roles in various cellular processes, have emerged as promising candidates for drug discovery. Among the pyrimidine family, 2-thiopyrimidine (2-TP) and its related compounds, collectively referred to as 2-mercaptopyrimidine derivatives, have garnered significant interest [1]. One intriguing possibility involves replacing the oxygen atom currently attached to carbon-2 in the uridine base with a sulfur atom in the 2-TP ring, which could potentially alter its biological properties [2]. This concept has led synthetic biochemists to focus their attention on 2-TP derivatives, recognizing their unique potential [3]. Notably, the European patent provides a comprehensive overview of the use of 2-TP derivatives in the development of cardiotonic drugs [4]. In addition, Pathak et al. explored the antibacterial properties of 2-TP derivatives, specifically assessing their effectiveness against Mycobacterium tuberculosis (Mtb) [5]. Another notable compound in this context is 6-thiopurine (6-TP), a sulfur analog of hypoxanthine [6], which is a by-product of purine metabolism.

Over the past five decades, numerous biological studies have led to the synthesis and characterization of thousands of 6-TP derivatives. These compounds have proven particularly effective in treating leukemias [7], autoimmune and rheumatic disorders [7–10], and in providing

immunosuppression during organ transplantation procedures [7, 8]. Due to their structural similarity to both purines and pyrimidines, pyrrolo[3,2-d]pyrimidines have shown intriguing biological activities. As a class of 7-deazapurine analogues, they hold significant therapeutic potential. For example, well-known nonsteroidal anti-inflammatory drugs (NSAIDs) like Tolmetin (Rumatol) and Ketorolac (Ketolac) [11] exert their anti-inflammatory effects primarily through the inhibition of prostaglandin production. Additionally, PNU-142731A, a pyrrolopyrimidine with anti-inflammatory properties, inhibits cytokine production in living organisms [12]. Naturally occurring pyrrolo[2,3-d]pyrimidine nucleoside antibiotics, such as sangivamycin, tubercidin, and toyocamycin, are known to demonstrate potent antimicrobial activity [13, 14].

Previous studies have revealed that the presence of nitrogen or other heteroatoms in ring structures can enhance the antimicrobial and anti-inflammatory activity of various compounds [15–17]. Building on this knowledge and continuing the ongoing research in this area [15–17], we have sought to develop novel PPA derivatives based on substituted cyano benzaldehyde, aiming to further explore the structure-activity relationships and discover new compounds with improved therapeutic potential.

II. EXPERIMENTAL

1. General Methods

The uncorrected melting points of various substances were determined using the Lab Junction Melting Point/Boiling Point Apparatus. To measure the infrared absorption bands, potassium bromide pellets were employed, and the measurements were taken using a BRUKER FT-IR spectrophotometer. Chemical shifts were recorded on a Bruker 400 MHz spectrometer, with the results expressed in parts per million (ppm) relative to tetramethylsilane (TMS), which served as the internal standard for calibration. Microanalysis was conducted using the VCarlo Erba 1108 analyzer, and the obtained results were within the acceptable range (±0.40) of the predicted values, ensuring the accuracy of the analysis. Ultraviolet (UV) absorption bands at room temperature were captured with a JASCO V650 spectrophotometer. For thin-layer chromatography (TLC), precoated silica gel plates were used in place of the traditional glass plates, and a solvent mixture of 9:1 pet ether and ethyl acetate was employed as the developing solvent. The spots on the TLC plates were visualized under ultraviolet (UV) light for detection.

2. Hydroxybenzaldehyde Derivatives of PPA (2a-2c)

In the presence of a catalytic amount of concentrated hydrochloric acid, a reaction was carried out by combining cyano benzaldehydes (a–c) (0.1 mol) with PPH A (0.1 mol). After the reaction reached completion, which was monitored using thin-layer chromatography (TLC), the reaction mixture was filtered to remove any solid residues. The filtrate was then washed sequentially with ether and water to remove impurities. Following this, the mixture was dried to eliminate any residual solvents and then recrystallized from ethanol to purify the resulting compound. To ensure thorough mixing and efficient reaction, the mixture was sonicated at room temperature for 30 minutes.

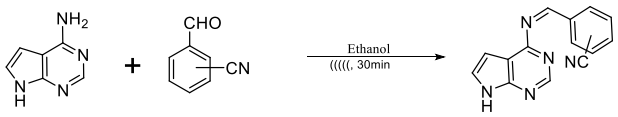


Figure 1: General preparation of compound 2a -2i

3. Biological Assay

Anti-microbial Activity

Materials and Methods

The antibacterial activity of the synthesized compounds was assessed using two standard methods: the disc-diffusion and minimum inhibitory concentration (MIC) techniques, both of which comply with the guidelines established by the National Committee for Clinical Laboratory Standards (NCCLS) [18]. A range of bacterial strains were selected for the in vitro antimicrobial testing, including Gram-positive bacteria Staphylococcus aureus MCC 2010 and Bacillus subtilis MCC 2010, as well as Gram-negative bacteria Pseudomonas aeruginosa MCC 2080, Escherichia coli MCC 2412, and the fungal strain Candida albicans MCC 1439.

These microbial strains were sourced from the Konkan Gyanpeeth Rahul Dharkar College of Pharmacy and Research Institute, located in Karjat, District Raigad, Maharashtra, India.

For the disc-diffusion method, the experiment utilized Hi-Media's nutrient agar and Muller Hinton agar (MHA), both of which were used for bacterial culture. The test compounds were dissolved in sterile dimethyl sulfoxide (DMSO) to prepare concentrations of 20 and 30 mg/mL. Following this, the solution was passed through 0.2 mm membrane filters to ensure purity. A 2 mL aliquot of the filtered solution was then placed in a sterile, screw-capped container, flash-frozen, and stored at -15°C for later use. Before being applied to the assay, the containers were thawed and refrozen. The antibacterial testing was conducted following the disc diffusion method outlined by Bauer et al. [19]. The DMSO itself showed no antimicrobial activity, thus serving as a negative control, while streptomycin and fluconazole were used as reference drugs.

To determine the minimum inhibitory concentration (MIC) of the compounds, the tests were performed on Mueller-Hinton agar plates, adhering to the 1997 NCCLS guidelines [20]. Bacterial subcultures were incubated overnight at 37°C, while fungal cultures were incubated at 35°C for 24-48 hours to ensure optimal growth. The microbial strains underwent at least two rounds of purification to confirm their viability and purity. The bacterial inoculum was then introduced into each well of microdilution trays, and the nutrient agar plates were incubated at the appropriate temperatures.

For the MIC determination, serial two-fold dilutions of the synthesized compounds and reference drugs were prepared in DMSO, yielding concentrations of 1000, 500, 250, 125, 65, 30, and 15 mg/mL. The trays were incubated for 24 hours at 37°C in a humidified environment, after which the MIC endpoints were evaluated. The MIC was defined as the lowest concentration of a compound that completely inhibited macroscopic growth. Control wells containing only DMSO, sterile microorganisms, and sterile growth medium were included to account for any experimental variables.

III. RESULTS AND DISCUSSION

Figure 1 illustrates the step-by-step synthetic procedures employed to produce the desired compounds in this study. The primary focus of the research was to explore the interaction between cyanobenzaldehydes and PPA. The synthesis of these compounds was carefully monitored to ensure the successful formation of the targeted structures. The resulting compounds, designated 2a–c, were characterized and their physicochemical properties are compiled in Table 1. This table provides a detailed summary of the physical and chemical characteristics of each compound, which were analyzed to assess their potential applicability and reactivity in further studies.

1. FT(IR) Spectra

We evaluated the attachment of PPA to cyano-substituted benzaldehydes by comparing the FT(IR) spectra of the synthesized compounds with those of the free PPA. The effect of PPA's vibrations on the cyanobenzaldehydes was analyzed through several significant bands observed in the infrared spectra. Notably, the absence of the typical aldehyde (CHO) and amino (NH_2) stretching vibrations confirmed that all the synthesized compounds had undergone the expected reactions and had fully matured. Instead of these original vibrations, a new solid band appeared in the 1511-1539 cm^{-1} region, characteristic of the azomethine (HC=NN) group [21]. This confirmed the successful formation of the imine linkage. According to references [22, 23], the presence of an aromatic NH group in the compounds was suggested by the broad absorption band between 3178 and 3293 cm^{-1}. The aldehyde (-CH=) stretching vibrations were detected between 2815 and 3063 cm^{-1} for all compounds, further confirming the incorporation of the aldehyde functional group in the structures. The infrared spectra of compounds 2a–c revealed two significant bands at 1582–1590 and 1447–1455 cm^{-1}, which are associated with the C=C stretching vibrations in the aromatic ring. Additional bands observed at 712–739 cm^{-1} and 1315–1333 cm^{-1}

correspond to various ring modes, including aromatic (C-N), and di-substituted benzene. For compounds 2a–c, an FT-IR peak was detected in the range of 1969–2232 cm-1, which is indicative of the -CN group. These detailed FT-IR spectral features provided essential evidence for the structural identification of the synthesized compounds.

Table 1: FT(IR) spectral data of compounds 2a-2c

Comp	NH-aromatic)	-CH=	(>C=C<)	>C=NN-	-N-N-	Di sub Benz ring	-CN
2a	3283	3063	1587/1447	1511	1040	712	1969
2b	3178	2815	1582/1451	1526	1070	741	2237
2c	3293	2884	1590/1455	1539	1039	739	2232

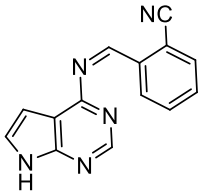
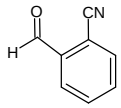
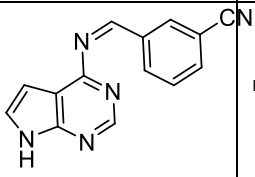
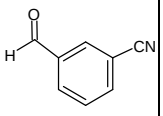
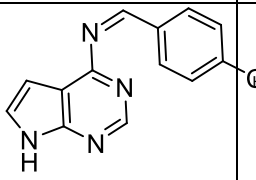
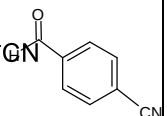
2. 1H NMR Spectra

The 1H NMR spectra of all the synthesized compounds exhibited singlet signals with chemical shifts ranging from 11.27 to 13.08 ppm, which aligns with the expected presence of an aromatic NH group attached to the pyrrolyl ring. A singlet peak in the 8.58–9.36 ppm region was also observed, representing the aldehydic -CH= group, which was present in all of the synthesized compounds. The absence of a broad singlet peak at 9.84 ppm (2H) in the derivatives suggests that the substitution of the amino group with the Schiff base [24] was successfully carried out, as this peak typically corresponds to the -NH2 group in PPA. Furthermore, a distinct peak was observed in the 1H NMR spectra of compounds 2a–c, which corresponds to the pyrimidine proton, located within the chemical shift range of 8.05–8.74 ppm. These observed 1H NMR signals are consistent with those reported in previous studies [24–25], confirming the molecular structures of the synthesized compounds.

Table 2: NMR spectral data of compounds 2a-2c

Comp	NH aromatic (s, 1H)	-CH= (s, 1H)	pyrimidine-H (s, 1H)	aromatic-H (m, 6H)
2a	11.27	9.36	8.05	6.87-8.05
2b	13.08	8.97	8.74	7.21-8.56
2c	12.97	8.58	8.57	7.18-8.47

Table 3: Yield, color, reaction time, and physical constants of the product (2a-c)

Products	Aldehyde	Color	Yield (%)	Reaction time (min.)	m.p. (°C)
 2a	 a	White	72.90	30	185
 2b	 b	Yellow	79.00	30	180
 2c	 c	Yellow	75.35	30	177

3. Antimicrobial Evaluation

In vitro screening was conducted on the newly synthesized compounds to evaluate their antibacterial and antifungal properties. The compounds' effectiveness against Candida albicans (MCC 1439), Saccharomyces cerevisiae (MCC 1033),

as well as a range of Gram-positive and Gram-negative bacterial strains, was assessed using the broth microdilution method. The bacterial strains tested included Staphylococcus aureus (MCC 2010), Bacillus subtilis (MCC 2010), and Pseudomonas aeruginosa (MCC 2080).

To prepare the bacterial cultures, all isolates were grown in a nutrient-rich broth medium, incubated at 37 °C for 24 hours. In contrast, the fungal cultures were grown in Sabouraud dextrose agar and transferred to malt broth for incubation at 25 °C for 24 hours. Fungal spore suspensions were made using Tween 80 from fungi that had been cultured for 7 days. The final optical densities (OD) of the bacterial and fungal inoculums were adjusted to 0.2–0.3 for bacteria and 0.5 for fungi to ensure proper growth conditions.

It was confirmed that the dimethyl sulfoxide (DMSO) used to prepare the stock solutions did not have any noticeable effect on the microorganisms at the concentrations used. The bacterial and fungal populations showed a twofold increase at a concentration of 1000 µg/mL. Fluconazole and streptomycin, well-known therapeutic agents, were used as controls to compare the antimicrobial efficacy of the synthesized compounds. The antibacterial activity was evaluated after 24 hours of incubation at 37 °C, while the antifungal activity was assessed after 48 hours of incubation at 25 °C.

Antibacterial Activity

The reference antibiotic used in this study was Streptomycin, known for its broad-spectrum antimicrobial activity. Streptomycin displayed a minimum inhibitory concentration (MIC) of 1 mg/mL against the bacterial strains tested. The zones of inhibition observed for Escherichia coli (MCC 2412), Bacillus subtilis (MCC 2010), Pseudomonas aeruginosa (MCC 2080), and Staphylococcus aureus (MCC 2010) ranged from 19–20 mm, 18–21 mm, 19–23 mm, and 17–21 mm, respectively. The antibacterial results summarized in Table 4 reveal that the newly synthesized compounds demonstrated activity against all the tested microorganisms, with their minimum inhibitory concentrations (MICs) falling between 35 and 70 µg/mL. These findings confirm that the compounds possess significant antibacterial properties, comparable to the reference drug.

Table 4: Antibacterial studies of 2a-c compounds

Compound	Antibacterial Activity (zone of inhibition)			
	S. aureus	B. subtilis	E. coli	P. aeruginosa
(2d)	21.00	18.00	20.00	23.00
(2e)	20.00	19.00	20.00	22.00
(2f)	17.00	21.00	19.00	19.00
Streptomycin	20.00	21.00	20.00	19.00

Regarding the antibacterial efficacy against each bacterial species, it was noted that compound (2a) exhibited superior activity against Staphylococcus aureus (S. aureus) with a zone of inhibition of 21 mm, surpassing the effectiveness of the reference drug. On the other hand, compound (2b), showed reduced effectiveness against Pseudomonas aeruginosa (P. aeruginosa), with compound (2a) again demonstrating greater efficacy than the reference drug for this strain as well. All of the synthesized compounds showed the strongest antibacterial activity against Escherichia coli (E. coli), whereas compound (2b) exhibited the highest activity against Bacillus subtilis (B. subtilis). The observed antibacterial activity can likely be attributed to the increased ability of the compounds to penetrate the microbial cell walls, which may be facilitated by their reduced lipophilicity. This characteristic allows the compounds to more easily traverse the cell membranes, particularly in Gram-negative bacteria. The likely explanation for these findings lies in the presence of a lipophilic alkyl chain in the molecules, which enables them to pass through the lipid-rich membranes of Gram-negative bacteria. Additionally, the results suggest an inverse correlation between the length of the carbon chain and the antibacterial potency. Larger carbon chains may cause steric hindrance, making it more difficult for the molecules to penetrate bacterial cell membranes, thereby reducing their antibacterial effectiveness [26].

Antifungal Activity

In the study, fluconazole, the standard antifungal drug, demonstrated an inhibitory effect on the tested fungi with a minimum inhibitory concentration (MIC) of 50 µg/mL. The inhibition zones for Candida albicans ranged from 20 to 29 mm, while Saccharomyces cerevisiae showed inhibition zones between 22 and 24 mm. The compounds listed in Table 5 exhibited notable fungicidal activity, outperforming the conventional treatment. Their minimum inhibitory concentrations (MICs) against Candida albicans and Saccharomyces cerevisiae were also found to be 50 µg/mL, indicating their significant antifungal potential. These results suggest that the synthesized compounds possess potent antifungal properties, comparable to or exceeding those of the standard drug fluconazole, making them promising candidates for further development in fungal infection treatments.

Table 5: Antifungal studies of 2a-c compounds

Compound	Candida albicans	Saccharomyces cerevisiae
(2a)	22.00	23.00
(2b)	29.00	24.00
(2c)	20.00	22.00
Fluconazole	22.00	21.00

V. CONCLUSION

The present study focused on the synthesis of a series of novel substituted 7H-pyrrolo[2,3-d]pyrimidin-4-amine (PPA) derivatives, specifically compounds ranging from 2a to 2c. The successful preparation of these compounds was validated through an extensive set of analytical techniques, including FT-IR, UV-vis, NMR spectroscopy, and electrochemical analysis. The compounds, which were based on cyanobenzaldehydes, underwent characterization through various spectroscopic methods, such as 1H NMR, UV-vis, elemental analysis (for carbon, hydrogen, nitrogen, and halogens), and FT-IR spectroscopy. The results indicated that a 1:1 ratio of PPA to cyanobenzaldehydes is optimal for the synthesis of these compounds. Additionally, all the synthesized compounds exhibited outstanding antibacterial activity, highlighting their potential as effective antimicrobial agents. These findings demonstrate the promising prospects of these novel PPA derivatives for further development and application in combating bacterial infections.

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