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Synthetic Approach of Cyanopyridine Derivatives with Their Antibacterial Screening and ADME Profiling Studies

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ABSTRACT

By using Claisen Schmidt condensation method, various substituted acetophenones were reacted with 4-hydroxy-3,5-dimethoxybenzaldehyde to produce different chalcones (3a-k). The synthesis of substituted 2-amino-4-(4-hydroxy-3,5-dimethoxyphenyl)-nicotinonitrile (KMC-1 to KMC-11) was accomplished by condensing substituted chalcones (3a-k) with malononitrile and ammonium acetate in different solvents like methanol, ethanol, and DMSO, respectively. Cyanopyridines play an vital role in our life due to their biological significance in the struggle pathogens. All synthesized compounds underwent evaluation for their antibacterial properties. Compared to Tetracycline, the tested antibacterial compound showed significantly lower or moderate efficacy against both Gram-positive and Gram-negative bacteria. The most active compound was KMC-1 and KMC-5 against *Bacillus cereus,* with a 12.0-13.0 mm zone of inhibition (For Tetracycline, 21 mm). SwissADME assesses pharmacokinetic behavior and drug-likeness based on molecular structure, assisting in the prediction of compounds' suitability as oral medication candidates. The majority of KMC compounds exhibit high GI absorption, including KMC-1, KMC-2, KMC-3, KMC-4, KMC-7, KMC-8, KMC-9, KMC-10, and KMC-11. Good oral bioavailability and effective intestine absorption are indicated by high GI absorption. TPSA values for the majority of substances range from 101 to 147 Å². It is not anticipated that any will pass through the BBB.

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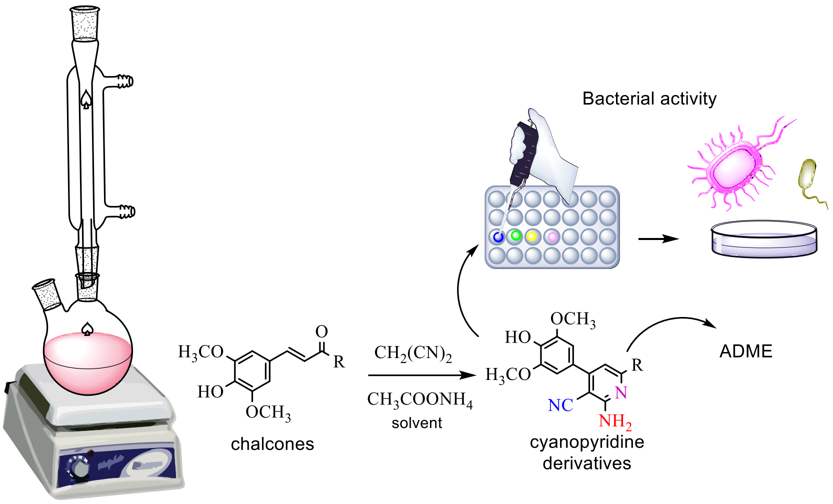


Graphical Abstract

***Keywords*:** Chalcone, Claisen Schmidt condensation, Cyanopyridine, Antibacterial activity, SwissADME.

1. INTRODUCTION

Because of their reactivity and adaptability in drug design, chalcones—a three-carbon α,β-unsaturated carbonyl system connecting two aromatic rings—form a crucial scaffold in medicinal chemistry[1]. In addition to defining the chalcone structure, their distinct α,β-unsaturated ketone functionality also leads to a variety of pharmacological benefits, such as anticancer, anti-inflammatory, and antibacterial actions, etc., documented in multiple investigations [2]. Since minor modifications to the substituents on the aromatic rings can increase the effectiveness and potency of pharmacological profiles, Chalcone derivatives have undergone significant modification to maximize therapeutic characteristics [3]. Chalcones are synthesised by many reactions, such as using SOCl2 [4], Claisen Schmidt condensation method [5], Heck coupling reaction [6], etc. Chalcones frequently reacted with hydrazine or substituted hydrazines to create pyrazoline derivatives, many of which have more biological activity than the original chalcone [7]. Chalcones easily react with nucleophiles through Michael addition reactions, producing derivatives with a variety of structural variations [8, 9]. Chalcones can be cyclocondensed with guanidine, urea, or thiourea to produce pyrimidine derivatives, demonstrating the chalcone scaffold's versatility as a precursor in heterocyclic synthesis. Chalcone reacts with different molecules to give many compounds like Pyrazoline, Phenyl pyrazoline, Aminopyrimidine, Cyanopyridine, Diazepines, Triazoles, etc. [10-14].

Cyanopyridines serve as highly adaptable synthetic intermediates in the pharmaceutical sector due to their notable biological and pharmacological properties. Cyanopyridine derivatives have garnered a lot of attention due to their extraordinary significance as anti-inflammatory, antipyretic [15], anti-convulsant, anti-depressant, antiparkinsonian, analgesic [16,17,18], antibacterial [19,20], and anti-cancer [21].

Antitubercular [22], cytotoxic [23], antiproliferative [24], antifungal, larvicidal, and antioxidant activity [25] are only a few of its many attributes. The purpose of this work is to evaluate the antibacterial properties of chalcone derivatives, including cyanopyridine. It has been demonstrated that chalcone derivatives, including cyanopyridine, are essential for exhibiting and enhancing potent antibacterial qualities. In order to achieve this, we created, synthesised, and assessed a unique set of these compounds, paying particular attention to their ADME profiles [26, 27], and antibacterial activity.

The current strategy involves the synthesis of novel 3-cyanopyridines and the pharmacological profile of this class of compounds in light of these discoveries. This work synthesizes and evaluates a new series of these compounds to explore their potential as novel antibacterial agents against key pathogens. The antibacterial activity of each newly designed compound was tested against a variety of pathogens, including both Gram-positive (*Staphylococcus aureus, Bacillus cereus*) and Gram-negative (*Salmonella spp., Escherichia coli*) bacteria. [28, 29]

2. RESULTS AND DISCUSSION

2.1. Chemistry and Spectroscopic Discussion

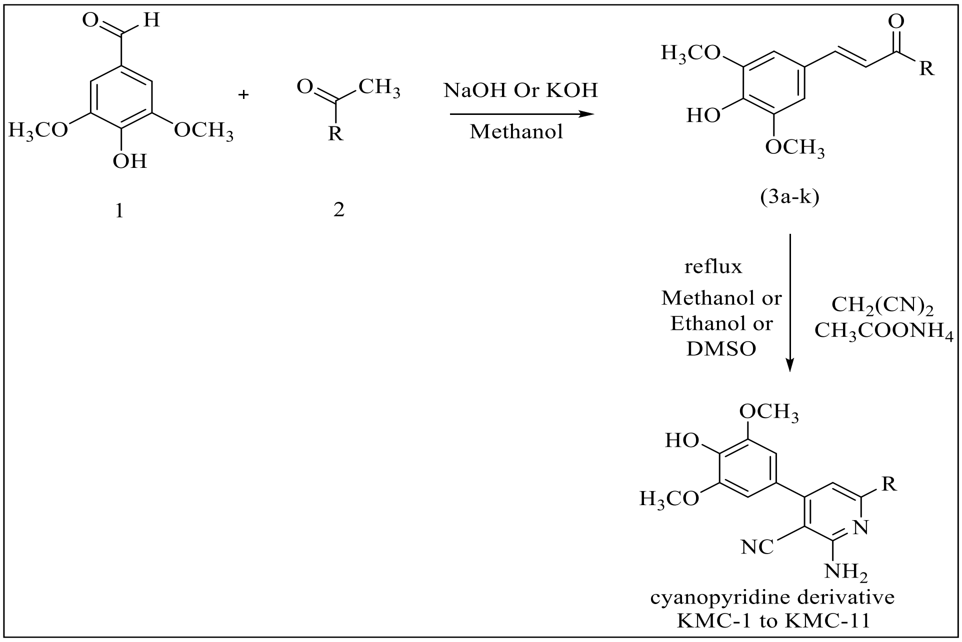
The synthesis of substituted chalcone (3a–k) by treating substituted acetophenone (2) with 4-hydroxy-3, 5-dimethoxybenzaldehyde (1) in methanol is completed. Different chalcones (3a-k) were synthesised by Claisen-Schmidt condensation. Reaction with malononitrile and ammonium acetate, the chalcones undergo ring formation to produce substituted Cyanopyridines (KMC-1 to KMC-11) (Table 1) (Scheme 1).

Yield comparison of cyanopyridine compounds (KMC-1 to KMC-11) by using different solvents. % Yield comparison to methanol, ethanol, and DMSO as a solvent, respectively. The KMC series (cyanopyridine) was synthesised, with methanol and ethanol proving to be the most effective solvents. Methanol and ethanol consistently delivered higher yields and less time compared to DMSO (Table 1).

The target cyanopyridines' successful synthesis and molecular structure were validated by spectral analysis. The compounds' structures were verified using spectral data from IR, ^{1}H NMR, ^{13}C NMR, Mass spectroscopy, and elemental analysis. The IR spectrum of substituted cyanopyridine KBr shows a characteristic band near the region of 2208.49-2212.35 cm^{-1} (C–N str.), 3352.28-3400.01 cm^{-1} (N–H str.), etc. Peaks at m/z 362.18, 378.18, and 364.17 confirm the molecular ion $[M+H]^+$ for KMC-1, KMC-2, and KMC-3, respectively. Additionally, its ^{1}H NMR (400 MHz, MeOD or DMSO-d6) spectrum signal at δ7.24-7.53 (s, 1H, -CH of pyridine ring), 6.83-6.99 (s, 2H, NH_2 of pyridine ring) and 3.81-3.95 (s, 6H, Ar-OCH_3) confirms the compound's two OCH_3 groups.

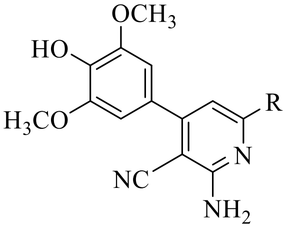
Both Gram-positive (*Staphylococcus aureus, Bacillus cereus*) and Gram-negative (*Salmonella spp., Escherichia coli*) bacteria were less to moderately effective against the investigated antibacterial substances. With a 13mm zone of inhibition against *Bacillus cereus*, KMC-1 was the most effective chemical. Activity did not surpass the potency or broad spectrum of the tetracycline standard (Table 2).

SwissADME predicts pharmacokinetic behavior and drug-likeness based on molecular structure. Most of KMC compounds show high GI absorption, including KMC-1, KMC-2, KMC-3, KMC-4, KMC-7, KMC-8, KMC-9, KMC-10, and KMC-11, which indicates Good oral bioavailability (Table 3).

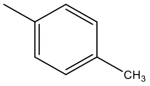
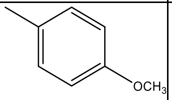
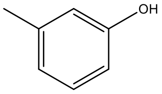
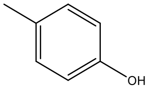


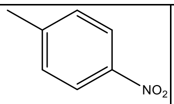
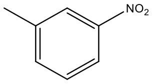
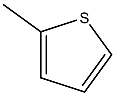
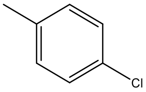
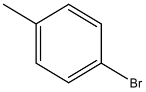
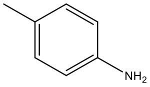
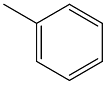
Scheme 1. Preparation of cyanopyridine compounds (KMC-1 to KMC-11)

Table 1. Properties and yield of cyanopyridine derivatives (KMC-1 to 11)



(KMC-1 to 11)

Code	*-R*	*Mole. Weight*	*Mole. Formula*	*% Yield*			*Time Taken*			*Melting point (°C)*
				Methanol	**Ethanol**	**DMSO**	**Methanol**	**Ethanol**	**DMSO**	
KMC-1		361.40	$C_{21}H_{19}N_3O_3$	68	67	66	8	9	10	260
KMC-2		377.40	$C_{21}H_{19}N_3O_4$	68	68	62	8	8	9	280
KMC-3		363.37	$C_{20}H_{17}N_3O_4$	61	59	53	12	11	12	240
KMC-4		363.37	$C_{20}H_{17}N_3O_4$	62	63	60	12	13	14	250

KMC-5		392.37	$C_{20}H_{16}N_4O_5$	66	65	61	6	6	7	260
KMC-6		392.37	$C_{20}H_{16}N_4O_5$	65	62	59	7	7	8	246
KMC-7		353.40	$C_{18}H_{15}N_3O_3S$	67	68	60	7	8	9	180
KMC-8		381.82	$C_{20}H_{16}ClN_3O_3$	65	63	62	9	9	11	246
KMC-9		426.27	$C_{20}H_{16}BrN_3O_3$	66	65	61	10	10	12	242
KMC-10		362.39	$C_{20}H_{18}N_4O_3$	67	66	59	8	8	10	180
KMC-11		347.37	$C_{20}H_{17}N_3O_3$	69	68	60	7	7	8	210

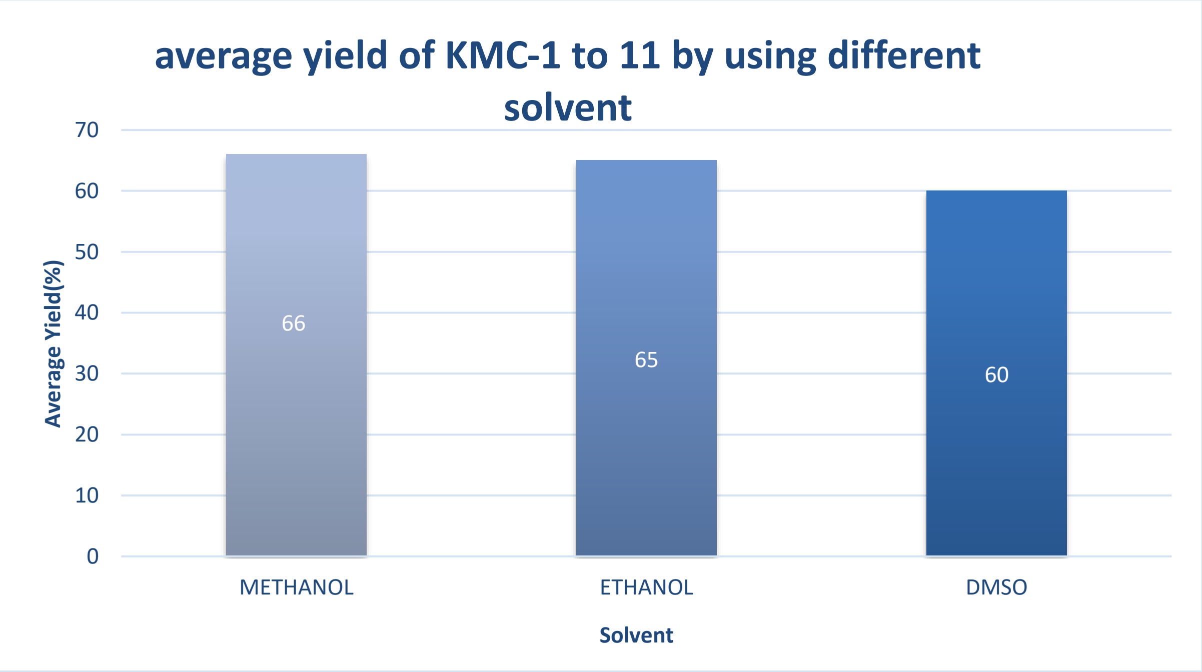


Figure 1. Average yield of KMC-1 to 11 by using different solvents.

2.2. Biological Activity

When compared to Tetracycline, newly prepared tested antibacterial compounds (KMC-1 to KMC-11) exhibited much lower to moderate efficacy at a concentration of 10 mg/mL against both Gram-positive (*Staphylococcus aureus, Bacillus cereus*) and Gram-negative (*Salmonella spp., Escherichia coli*) bacteria (Table 2). The agar well diffusion method [30-35] is a low-cost and rapid way to assess antibacterial activity. To obtain actively growing cells, bacterial strains were initially cultivated in nutrient broth and incubated at 37 °C for the entire night. Following conventional protocols, nutrient agar was made, transferred onto sterile Petri dishes, and allowed to solidify. An aliquot of 100 µL of the bacterial suspension was then uniformly spread over the agar surface, and the plates were left to dry at room temperature for 15-20 min. The test compounds were produced at a concentration of 10 mg/mL in DMSO, and 50 µL of each was added to wells that were punched into the agar with a diameter of 6 mm. The positive control was tetracycline (10 mg/mL), while the negative control was DMSO. For 24 hours, the inoculation plates were incubated at 37 °C, after which antibacterial activity was assessed by measuring the zones of inhibition around each well. All assays were performed in triplicate, and mean values were calculated to ensure reliability and reproducibility. Evaluation of a compound's antibacterial activity, its ability to work against particular bacterial strains (such as Gram-positive and Gram-negative), and its possible comparison with conventional antibiotics are the study's goals. For antibacterial activity, Tetracycline as a standard drug. Millimeters were used to measure the zone of inhibition (Table 2).

Table 2. Antibacterial activities of synthesized compounds (KMC-1 to KMC-11).

Compound code	**Antibacterial activity (zone of inhibition in mm)**			
	Salmonella spp.	***E.coli***	***Staphylococcus aureus***	***Bacillus cereus***
KMC-1	0	0	3	13
KMC-2	0	0	4	9
KMC-3	0	0	2	9
KMC-4	1	0	3	10
KMC-5	0	0	2	12
KMC-6	0	0	2	7
KMC-7	0	0	2	9
KMC-8	1	0	1	6
KMC-9	0	0	4	8
KMC-10	0	3	6	7
KMC-11	2	0	5	9
Tetracycline	17	19	16	21

2.3. ADME Properties

In silico ADME (Absorption, Distribution, Metabolism, and Excretion) predictions generated by the SwissADME web tool. In SwissADME, according to Lipinski's rule, the number of atoms that can form hydrogen bonds (such as N and O) with a typical drug-like range of ≤10 is crucial for solubility and receptor binding. Permeability and binding affinity are affected by the number of atoms that can donate hydrogen bonds (such as NH and OH). The ideal range for molar refractivity (MR) is between 40 and 130. P-glycoprotein substrates may have shown drug resistance issues.

Topological Polar Surface Area, or TPSA, has a significant impact on BBB penetration (TPSA<90 Å²) and oral absorption (TPSA <140 Å²). BBB permeability indicates whether a compound can cross the blood–brain barrier. High GI absorption indicates optimal and efficient intestinal uptake and oral bioavailability, whereas low GI absorption, often associated with high TPSA, suggests limited oral absorption and potential formulation challenges. ADME investigation of KMC-1 to KMC-11 is shown in Table 3.

Table 3. ADME properties profile of the synthesized compounds (KMC-1 to 11)

Molecule	H-bond acceptors	H-bond donors	MR	TPSA	GI absorption	BBB permeant	Pgp substrate
KMC-1	5	2	104.2	101.39	High	No	No
KMC-2	6	2	105.73	110.62	High	No	No
KMC-3	6	3	101.26	121.62	High	No	No
KMC-4	6	3	101.26	121.62	High	No	No
KMC-5	7	2	108.06	147.21	Low	No	No
KMC-6	7	2	108.06	147.21	Low	No	No
KMC-7	5	2	97.11	129.63	High	No	No
KMC-8	5	2	104.25	101.39	High	No	No
KMC-9	5	2	106.94	101.39	High	No	No
KMC-10	5	3	103.64	127.41	High	No	Yes
KMC-11	5	2	99.24	101.39	High	No	No

3. EXPERIMENTAL

3.1. Materials and Methods

FTIR Shimadzu was used to record the IR spectra and to measure molecular weight using a mass spectrometer with a QDa detector. First, calibrate the instrument, then, without any correction, melting points were measured in open capillaries on a Mel-Temp apparatus. The progress of the reaction and the purity of each compound were analyzed by TLC (thin-layer chromatography). Metal plates coated with Silica Gel 60F254as the stationary phase and a mixture of ethyl acetate and hexane in a 3:7 proportion as the mobile phase UV light (254 nm) was then used to view the plates. A Bruker ADVANCE II was used to record the 1H (400 MHz) and 13C (100 MHz) NMR spectra taken in MeOD or DMSO-d6. Tetramethylsilane was employed as an internal standard.

3.2. General Procedure

3.2.1. General Synthesis of Chalcone (3a-k) by

Claisen Schmidt condensation or base-catalyst reaction:

Throughout the procedure, equimolar amounts of substituted aromatic aldehyde and substituted acetophenone condense. In the presence of aqueous alcoholic alkali, α, β-unsaturated ketones, commonly known as chalcones, were produced by the Claisen-Schmidt condensation reaction. To synthesize compound (3a-k), 4-hydroxy-3,5-dimethoxybenzaldehyde(1) (0.01 M) was dissolved in around 25 ml of methanol, and substituted acetophenone (2) (0.01 M) was added with continuous stirring at room temperature for 30 minutes. Subsequently, sodium hydroxide (40% w/v) was introduced to the reaction mixture, which was then stirred at room temperature.

Once the reaction reached completion, after the reaction was completed, as verified by TLC. Following response marking, crushed ice was added, and diluted HCl was used to neutralize it. The different Chalcone (3a-k) was created by separating the isolated material, washing it with water, drying it, and then recrystallizing it from ethanol [5] (Scheme 1).

3.2.2. Synthesis of substituted 2-amino-4-(4-hydroxy-3,5-dimethoxyphenyl)-nicotinonitrile (KMC-1 to KMC-11)

Ammonium acetate (6.16 gm, 0.08 mol), malononitrile (0.66 gm, 0.01 mol), and the chalcone (3a-k) (0.01 mol) were dissolved in around 20-25 ml of methanol, ethanol, or DMSO, and then refluxed for a period of 6–12 hours. It was allowed to cool and then subsequently poured over crushed ice. After being separated, the product was filtered and given a water wash. Recrystallization of the products was achieved using ethanol (Table-1) (Scheme 1).

3.3. Physical and Spectral Data

3.3.1 2-amino-4-(4-hydroxy-3, 5-dimethoxyphenyl)-6-(p-tolyl) nicotinonitrile (KMC-1)

$C_{21}H_{19}N_3O_3$; Molecular Weight:361.40; M.P: 260°C; Dark yellow solid; Elemental Analysis: C, 69.79; H, 5.30; N, 11.63; O, 13.28; IR (KBr, cm-1): 3464.15 cm-1(O-H str.), 3352.28 cm-1(N-H str.), 2208.49 cm-1(C≡N str.), 1610.56 cm-1(C=N str.), 1571.99 cm-1(N-H def.), 1311.59 cm-1(C-N str.), 1255.66 cm-1(Ar-O-R str.); 1H NMR (400 MHz, MeOD) δ 7.99 (dd, 2H, Ar-H), 7.31 (dd, 2H, Ar-H), 7.24 (s, 1H, Ar-H of pyridine ring), 6.99 (s, 2H, $-NH_2$ of pyridine ring), 3.96 (s, 2H, Ar-H), 3.95 (s, 6H, 2 $-OCH_3$), 2.43 (s, 3H, $-CH_3$); 13C NMR (101 MHz, DMSO-D6) δ 161.48, 158.80, 155.50, 148.44, 140.33, 137.74, 135.48, 129.75, 127.76, 127.25, 118.17, 109.27, 106.76, 86.70, 56.74, 21.47.

3.3.2 2-amino-4-(4-hydroxy-3,5-dimethoxyphenyl)-6-(4-methoxyphenyl) nicotinonitrile (KMC-2)

$C_{21}H_{19}N_3O_4$; Molecular Weight: 377.40; M.P:280°C; Dark yellow solid; Elemental Analysis: C, 66.83; H, 5.07; N, 11.13; O, 16.96; IR (KBr): 3460.30 cm-1(O-H str.), 3348.42 cm-1(N-H str.), 2212.35 cm-1(C≡N str.), 1627.92 cm-1(C=N str.), 1606.70 cm-1(N-H def.), 1313.52 cm-1(C-N str.), 1259.62 cm-1(Ar-O-R str.); 1H NMR (400 MHz, DMSO-D6) δ 8.12 – 8.04 (dd, 2H, Ar-H), 7.22 (s, 1H, Ar-H of pyridine ring), 7.06 – 6.96 (dd, 2H, Ar-H), 6.94 (s, 2H, $-NH_2$ of pyridine ring), 3.83 (s, 2H, Ar-H), 3.81 (s, 6H, 2 -OCH3), 3.79 (s, 3H, $-OCH_3$); 13C NMR (101 MHz, DMSO-D6) δ 161.51, 161.35, 158.37, 155.54, 148.44, 137.75, 130.47, 129.42, 127.28, 118.23, 114.55 (d, J = 5.9 Hz), 108.88, 106.75, 86.23, 56.73, 55.86.

3.3.3. 2-amino-4-(4-hydroxy-3,5-dimethoxyphenyl)-6-(3-hydroxyphenyl) nicotinonitrile (KMC-3)

$C_{20}H_{17}N_3O_4$; Molecular Weight: 363.37; M.P:240°C; Brown solid; Elemental Analysis: C, 66.11; H, 4.72; N, 11.56; O, 17.61; IR (KBr): 3736.12cm-1(O-H str.), 3400.01cm-1(N-H str.), 2210.43 cm-1(C≡N str.), 1641.42 cm-1(C=N str.), 1612.49cm-1(N-H def.), 1313.52 cm-1(C-N str.), 1220.94cm-1(Ar-O-R str.); 1H NMR (400 MHz, DMSO-D6) δ 9.55 (s, 1H, -OH), 8.84 (s, 1H, -OH), 7.53 – 7.49 (s, 1H, Ar-H of pyridine ring), 7.48 (d, 1H, Ar-H), 7.26 (t, 1H, Ar-H), 7.17 (s, 1H, Ar-H), 6.94 (s, 2H, Ar-H), 6.85 (d, 1H, Ar-H), 6.83 (s, 2H, $-NH_2$ of pyridine ring), 3.82 (s, 6H, 2 $-OCH_3$); 13C NMR (101 MHz, DMSO-D6) δ 161.46, 159.06, 158.16, 155.51, 148.46, 139.78, 137.74, 130.11, 127.22, 118.68, 118.13, 117.54, 114.59, 109.69, 106.73, 86.99, 56.73.

3.3.4. 2-amino-4-(4-hydroxy-3,5-dimethoxyphenyl)-6-(4-hydroxyphenyl)nicotinonitrile (KMC-4)

$C_{20}H_{17}N_3O_4$; Molecular Weight: 363.37; M.P: 250°C; Dark yellow; Elemental Analysis: C, 66.11; H, 4.72; N, 11.56; O, 17.61; IR (KBr): 3636.12cm-1(O-H str.) 3402.01cm-1(N-H str.), 2210.47 cm-1(C≡N str.), 1641.42 cm-1(C=N str.), 1612.49cm-1(N-H def.), 1313.56 cm-1(C-N str.), 1220.94cm-1(Ar-O-R str.); 1H NMR (400 MHz, DMSO-D6) δ 9.67 (s, 1H, -OH), 8.73 (s, 1H, -OH), 8.04 (s, 1H, Ar-H of pyridine ring), 7.77 (dd, 2H, Ar-H), 6.86 (dd, 2H, Ar-H), 6.85 (s, 2H, -NH_2 of pyridine ring), 6.45 (s, 2H, Ar-H), 3.83 (s, 6H, 2 -OCH_3)

3.3.5. 2-amino-4-(4-hydroxy-3,5-dimethoxyphenyl)-6-(4-nitrophenyl)nicotinonitrile (KMC-5)

$C_{20}H_{16}N_4O_5$; Molecular Weight: 392.37; M.P: 260°C; Dark red; Elemental Analysis: C, 61.22; H, 4.11; N, 14.28; O, 20.39; IR (KBr): 3460.31cm-1(O-H str.), 3360.08cm-1(N-H str.), 2210.33cm-1(C≡N str.), 1650.70cm-1(N-H def.), 1640.93cm-1(C=N str.), 1313.52cm-1(C-N str.), 1260.63cm-1(Ar-O-R str.); 1H NMR (400 MHz, DMSO-D6) δ 8.73 (s, 1H, -OH), 8.36 (dd, 2H, Ar-H), 8.26 (dd, 2H, Ar-H), 8.04 (s, 1H, Ar-H of pyridine ring), 6.85 (s, 2H, -NH_2 of pyridine ring), 6.45 (s, 2H, Ar-H), 3.83 (s, 6H, 2 -OCH_3)

3.3.6. 2-amino-4-(4-hydroxy-3,5-dimethoxyphenyl)-6-(3-nitrophenyl)nicotinonitrile (KMC-6)

$C_{20}H_{16}N_4O_5$; Molecular Weight: 392.37; M.P: 246°C; Dark yellow; Elemental Analysis: C, 61.22; H, 4.11; N, 14.28; O, 20.39; IR (KBr): 3460.30cm-1(O-H str.), 3350.08cm-1(N-H str.), 2210.35cm-1(C≡N str.), 1637.92cm-1(C=N str.), 1610.70cm-1(N-H def.), 1313.59 cm-1(C-N str.), 1260.62 cm-1(Ar-O-R str.);1H NMR (400 MHz, DMSO-D6) δ 8.99 (s, 1H, Ar-H), 8.73 (s, 1H, -OH), 8.62 (d, 1H, Ar-H), 8.32 (d, 1H, Ar-H), 8.04 (s, 1H, Ar-H of pyridine ring), 7.84 (t, 1H, Ar-H), 6.76 (s, 2H, -NH_2 of pyridine ring), 6.45 (s, 2H, Ar-H), 3.82 (s, 6H, 2 -OCH_3)

3.3.7. 2-amino-4-(4-hydroxy-3,5-dimethoxyphenyl)-6-(thiophen-2-yl)nicotinonitrile (KMC-7)

$C_{18}H_{15}N_3O_3S$; Molecular Weight: 353.40; M.P: 180°C; Dark brown; Elemental Analysis: C, 61.18; H, 4.28; N, 11.89; O, 13.58; S, 9.07; IR (KBr): 3463.15 cm-1(O-H str.), 3352.28 cm-1(N-H str.), 2209.49 cm-1(C≡N str.), 1609.56 cm-1(C=N str.), 1571.99 cm-1(N-H def.), 1311.59 cm-1(C-N str.), 1255.66 cm-1(Ar-O-R str.); 1H NMR (400 MHz, DMSO-D6) δ 8.73 (s, 1H, -OH), 8.27 (s, 1H, Ar-H of pyridine ring),7.85 (dd, 2H, Ar-H), 7.66 (dd, 2H, Ar-H), 7.19 (t, 1H, thiophenes ring-H), 6.75 (s, 2H, -NH_2 of pyridine ring), 6.45 (s, 2H, Ar-H), 3.83 (s, 6H, 2 -OCH_3)

3.3.8. 2-amino-6-(4-chlorophenyl)-4-(4-hydroxy-3,5-dimethoxyphenyl)nicotinonitrile (KMC-8)

$C_{20}H_{16}ClN_3O_3$; Molecular Weight: 381.82; M.P: 246°C; Dark brown; Elemental Analysis: C, 62.92; H, 4.22; Cl, 9.28; N, 11.01; O, 12.57; IR (KBr): 3460.30 cm-1(O-H str.), 3350.42 cm-1(N-H str.), 2212.35 cm-1(C≡N str.), 1630.92 cm-1(C=N str.), 1608.70 cm-1(N-H def.), 1312.52 cm-1(C-N str.), 1259.62 cm-1(Ar-O-R str.); 1H NMR (400 MHz, DMSO-D6) δ 8.73 (s, 1H, -OH), 8.36 (dd, 2H, Ar-H), 8.04 (s, 1H, Ar-H of pyridine ring), 7.66 (dd, 2H, Ar-H), 6.76 (s, 2H, -NH_2 of pyridine ring), 6.46 (s, 2H, Ar-H), 3.81 (s, 6H, 2 -OCH_3)

3.3.9. 2-amino-6-(4-bromophenyl)-4-(4-hydroxy-3,5-dimethoxyphenyl)nicotinonitrile (KMC-9)

$C_{20}H_{16}BrN_3O_3$; Molecular Weight: 426.27; M.P: 242°C; Dark brown; Elemental Analysis: C, 56.35; H, 3.78; Br, 18.74; N, 9.86; O, 11.26; IR (KBr): 3460.30 cm-1(O-H str.), 3350.42 cm-1(N-H str.), 2210.35 cm-1(C≡N str.), 1629.92 cm-1(C=N str.), 1608.70 cm-1(N-H def.), 1312.52 cm-1(C-N str.), 1259.62 cm-1(Ar-O-R str.); 1H NMR (400 MHz, DMSO-D6) δ 8.73 (s, 1H, -OH), 8.17 (dd, 2H, Ar-H), 8.04 (s, 1H, Ar-H of pyridine ring), 7.55 (dd, 2H, Ar-H), 6.76 (s, 2H, -NH_2 of pyridine ring), 6.45 (s, 2H, Ar-H), 3.83 (s, 6H, 2 -OCH_3)

3.3.10. 2-amino-6-(4-aminophenyl)-4-(4-hydroxy-3,5-dimethoxyphenyl)nicotinonitrile (KMC-10)

$C_{20}H_{18}N_4O_3$; Molecular Weight: 362.39; M.P:180°C; Dark yellow; Elemental Analysis: C, 66.29; H, 5.01; N, 15.46; O, 13.24; IR (KBr): 3465.16 cm-1(O-H str.), 3352.28 cm-1(N-H str.), 2209.49 cm-1(C≡N str.), 1611.56 cm-1(C=N str.), 1571.99 cm-1(N-H def.), 1312.59 cm-1(C-N str.), 1256.67 cm-1(Ar-O-R str.); 1H NMR (400 MHz, DMSO-D6) δ 8.73 (s, 1H, -OH), 8.04 (s, 1H, Ar-H of pyridine ring), 8.02 (dd, 2H, Ar-H), 6.76 (s, 2H, $-NH_2$ of pyridine ring), 6.58 (dd, 2H, Ar-H), 6.45 (s, 2H, Ar-H), 5.24 (s, 2H, Ar-NH2), 3.82 (s, 6H, 2 $-OCH_3$)

3.3.11. 2-amino-4-(4-hydroxy-3,5-dimethoxyphenyl)-6-phenylnicotinonitrile (KMC-11)

$C_{20}H_{17}N_3O_3$; Molecular Weight: 347.37; M.P: 210°C; Dark yellow; Elemental Analysis: C, 69.15; H, 4.93; N, 12.10; O, 13.82; IR (KBr): 3347.42 cm-1(N-H str.), 3460.30 cm-1(O-H str.), 2208.37 cm-1(C≡N str.), 1628.82 cm-1(C=N str.), 1608.70 cm-1(N-H def.), 1315.52 cm-1(C-N str.), 1256.62 cm-1(Ar-O-R str.); 1H NMR (400 MHz, DMSO-D6) δ 8.84 (s, 1H, -OH), 8.33 (d, 2H, Ar-H), 8.04 (s, 1H, Ar-H of pyridine ring), 7.55 (d, 2H, Ar-H), 7.49 (t, 1H, Ar-H), 6.74 (s, 2H, $-NH_2$ of pyridine ring), 6.45 (s, 2H, Ar-H), 3.82 (s, 6H, 2 $-OCH_3$)

4. CONCLUSIONS

Novel cyanopyridine derivatives were created from different chalcones. The studied antibacterial compounds demonstrated weaker to moderate effectiveness against both Gram-positive (Staphylococcus aureus, Bacillus cereus) and Gram-negative (Salmonella spp., Escherichia coli) bacteria. When compared to Tetracycline, as indicated by the results of the antibacterial activity test. When compared to the common standard tetracycline, which is significantly more effective against all tested bacteria, the produced compounds KMC-1 to KMC-11 exhibit weaker to moderate antibacterial activity. Instead of being broad-spectrum, activity is selective. In Salmonella spp. The majority of chemicals have modest but detectable activity (1–6 mm) in Staphylococcus aureus. The chemicals work best in Bacillus cereus. The most active zones are KMC-1 (13 mm) and KMC-5 (12 mm), with zones ranging from 6 to 13 mm. This suggests that Gram-positive bacteria, particularly B. cereus, are clearly preferred. While some of the produced compounds exhibit promise as lead-like activity against Gram-positive bacteria, their potency is much lower. Bacillus cereus is the most vulnerable to the selective antibacterial activity of the KMC series, which primarily targets Gram-positive bacteria. These substances might be regarded as weak antibacterial leads that could be helpful for additional structural optimization as opposed to acting alone.

In SwissADME, every chemical is within permissible HBA ranges in between 5 and 7. Every KMC compound has two to three HBDs. Every compound exhibits MR values (typical range 40-130) between approximately 97 and 108, indicating appropriate polarizability and molecular size. The majority of chemicals have TPSA values between 101 and 147 Å². **KMC-5 and KMC-6** (TPSA = 147.21 Å²) surpass the optimal oral threshold, which accounts for their poor GI absorption. All compounds are predicted **not to be BBB permeant,** suggesting **low CNS exposure.** All compounds except KMC-10, being a P-gp substrate, may face efflux-related limitations. Due to their very high TPSA, compounds KMC-5 and KMC-6 show **low absorption**. All KMC compounds generally comply with **Lipinski's rule of five,** ensuring that their physicochemical properties fall within acceptable drug-like ranges. Most compounds are predicted to have **good oral absorption.** Most KMC compounds like **KMC-1, KMC-2, KMC-3, KMC-4, KMC-7, KMC-8, KMC-9, KMC-10, and KMC-11** show **high GI absorption**, which suggests lower Drug development risk and dose requirement.

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The authors declare no conflict of interest.

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