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Research Article

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Synthesis and Antimalarial Activity of Some Novel aminopyrimidine derivatives

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Abstract
Malaria remains a significant global health challenge, necessitating the development of new therapeutic agents to combat drug-resistant *Plasmodium* strains. This study focuses on the design, synthesis, and evaluation of novel aminopyrimidine derivatives as potential antimalarial agents. A series of aminopyrimidine derivatives were synthesized through a multi-step reaction process involving the condensation of substituted aromatic aldehydes with guanidine derivatives, followed by appropriate functionalization. The chemical structures of the synthesized compounds were confirmed using spectroscopic techniques, including IR, NMR, and mass spectrometry. The synthesized compounds screened by evaluating their ability to inhibit heme polymerization, their blood schizonticidal activity, or their impact on the in vitro growth of the *Plasmodium falciparum* NF-54 strain.

Keywords: Synthesis, Antimalarial Activity, aminopyrimidine derivatives

1. Introduction

Malaria is a life-threatening disease caused by protozoan parasites of the genus *Plasmodium*. It remains one of the most significant global health concerns, particularly in tropical and subtropical regions [1-3]. According to the World Health Organization (WHO), there were an estimated 247 million cases of malaria worldwide in 2021, resulting in over 619,000 deaths, with children under the age of five being the most vulnerable. Despite advances in public health interventions, such as insecticide-treated bed nets, indoor residual spraying, and antimalarial drugs, malaria continues to pose a significant burden on health systems, economies, and human lives. This underscores the urgent need for new therapeutic agents, particularly in the face of increasing resistance to existing antimalarial drugs [4-6].

The treatment of malaria has evolved significantly over the years. Historically, quinine and chloroquine were the mainstays of antimalarial therapy [7-9]. However, the emergence of chloroquine-resistant *Plasmodium falciparum* strains in the 1950s marked the beginning of a major challenge in malaria control [10-13]. Subsequent drugs, such as sulfadoxine-pyrimethamine, mefloquine, and artemisinin-based combination therapies (ACTs), have been developed, yet resistance to these drugs is also emerging. For instance, resistance to artemisinin, a cornerstone of modern malaria treatment, has been reported in Southeast Asia and parts of Africa. These developments highlight the need for novel chemotherapeutic agents that can overcome resistance mechanisms and provide effective treatment [14-17].

The search for new antimalarial agents involves the exploration of diverse chemical scaffolds and the identification of molecular targets critical to the survival of *Plasmodium* parasites. Among the promising candidates, aminopyrimidine derivatives have garnered significant attention due to their versatile pharmacological properties and

their potential as antimalarial agents [18-21]. Aminopyrimidines are heterocyclic compounds characterized by a pyrimidine ring with an amino group substitution. The pyrimidine scaffold is found in several biologically active compounds, including nucleotides, vitamins, and therapeutic agents, making it a valuable pharmacophore in drug design [22-25].

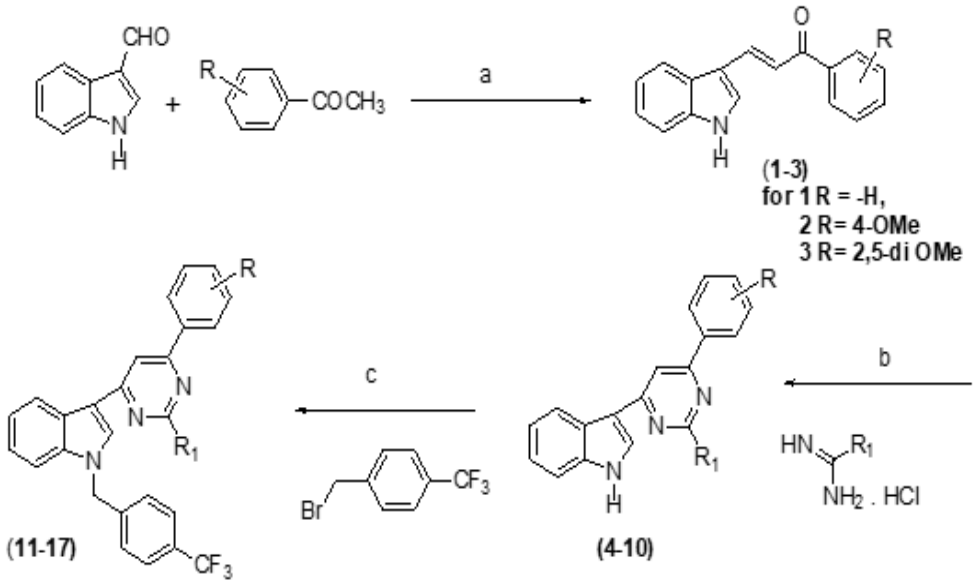
Aminopyrimidines have demonstrated efficacy against a variety of diseases, including cancer, bacterial infections, and viral infections. Their application in antimalarial research is particularly compelling due to their ability to target critical enzymes and pathways in the *Plasmodium* life cycle. For instance, aminopyrimidine derivatives are known to inhibit dihydrofolate reductase (DHFR), an enzyme essential for folate metabolism in *Plasmodium*. Inhibition of DHFR disrupts nucleotide synthesis, impairing DNA replication and cell division in the parasite. This mechanism forms the basis of antifolate drugs such as pyrimethamine, which have been used in malaria treatment [26-28].

Recent studies have also explored the potential of aminopyrimidine derivatives to inhibit other molecular targets, including plasmepsins (proteases involved in hemoglobin degradation) and kinases essential for parasite survival. These findings highlight the versatility of the aminopyrimidine scaffold and its potential for further optimization [29-32].

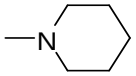
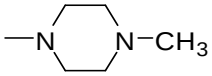
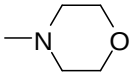
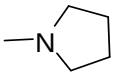
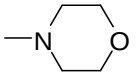
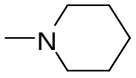
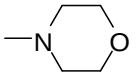
The primary objective of this research is to synthesize and evaluate the antimalarial activity of novel aminopyrimidine derivatives.

2. Material and Methods

Titration gradient microchromatography (TLC) with basic alumina coatings and silica gel-G was used to monitor all the reactions. The developing agents used to create the spots on the TLC plates were iodine vapours, potassium permagnate spray, or Dragendroff spray. The melting points were measured using an melting point instrument which was heated electrically. IR spectra were obtained using FTIR 8210 PC and Perkin Elmer 881, Beckman Aculab-10, Shimadzu spectrophotometers either in neat or on KBr discs and values were reported in cm-1. NMR spectra were obtained using either Bruker DRX 200 or Bruker Avance DRX-300 MHz FT spectrometers, with TMS serving as the internal reference. Electron impact mass spectra were obtained using a JEOL JMS-D-300 spectrometer with an ionization potential of 70 eV, and electrospray mass spectra were recorded on a Quantro-II micro mass spectrometer. Silica gel (230-400 mesh) for flash column chromatography and Silica gel (60-120mesh) for column chromatography were utilized. Anhydrous solvents were made according to the standard process outlined in A.I. Vogel's textbook of practical organic chemistry.



Scheme 1: Synthetic scheme of aminopyrimidine derivatives

Compound No.	R	R_1
4,11	-H	
5,12	4-OMe	
6,13	4-OMe	
7,14	4-OMe	
8,15	2,5-diOMe	
9,16	2,5-diOMe	
10,17	-H	

Synthesis of 1-(1*H*-indol-3-yl)-3-substituted –propenone

General Procedure for the synthesis of compounds (1-3)

A mixture of indole-3-carboxaldehyde (1.0 equiv.) substituted acetophenone (1.1 equiv.) and piperidine (1.5 equiv.) was refluxed in 50mL of methanol or ethanol for 10h. After a period of time the chalcone starts separating out[1]. The solid was filtered out and washed with methanol or ethanol to afford the pure product in 80-90% yield.

1-(1*H*-indol-3-yl)-3-phenyl-propenone (1)

MP :182-184ºC; **MS:** 248 (M+1); **IR (KBr):** 3222, 1630, 1577, 1543, 1433, 1357 cm^{-1}; **Yield:** 83%.

1-(1*H*-indol-3-yl)-3-(4-methoxy-phenyl)-propenone (2)

MP: 164-166ºC; **MS:** 278 (M+1); **IR (KBr)**:3166, 2939, 176, 163, 1551, 1486, 1361 cm^{-1}; **Yield:** 88%.

3-(2,5-Dimethoxy-phenyl)- 1-(1*H*-indol-3-yl)-propenone (3)

MP: 211-213ºC; **MS:** 308 (M+1); **IR (KBr):** 3187, 2945, 1767, 1644, 1554, 1487, 1362 cm^{-1}; **Yield:** 84%.

Synthesis of 3-[substituted-pyrimidin-4-yl]-1*H*-indole (4-10)

To a solution of 1.0 equiv. of 4-methyl-piperazine-1-carboxamidine[2] hydrochloride in 50 mL of isopropanol, 1.1 equiv. of sodium metal was added. The reaction mixture was refluxed for 2h and then different chalcones (**1-3**, 1.0 equiv) were added to it and refluxed for 10h. Under reduced pressure, the solvent was withdrawn from the reaction mixture. After adding water, the aqueous phase was chloroformed extracted and rinsed with brine solution. After passing the organic phase through a filter, it was concentrated after drying over anhydrous Na_2SO_4. To obtain the pure chemicals in 60-75% yields, the crude product was refined using crystallization from ethanol or methanol or, on occasion, by column chromatography on silica gel (5% Methanol in chloroform).

3-(6-Phenyl-2-piperidin-1-yl-pyrimidin-4-yl)-1*H*-indole (4)

MP: 224-226ºC; **MS:** 355 (M+1); **IR (KBr):** 3020, 2359, 2147, 1566, 1435, 1216, cm^{-1}; **Yield:** 62%.

3-[6-(4-Methoxy-phenyl)-2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yl]-1*H*-indole (5)

MP: 128-130ºC; **MS:** 400 (M+1); **IR (KBr)** 2935, 1607, 1567, 1433, 1443, 1364, 1264 cm^{-1}; **Yield:** 72%.

3-[6-(4-Methoxy-phenyl)-2morpholin-4-yl-pyrimidin-4-yl]-1*H*-indole (6)

MP: >250ºC; **MS:** 387 (M+1); **IR (KBr):** 3020, 2361, 1572, 1478, 1426, 1215 cm^{-1};

Yield: 69%.

3-[6-(4-Methoxy-phenyl)-2-pyrrolidin-1-yl-pyrimidin-4-yl)-1*H*-indole (7)

MP: Decomposes at 240ºC; **MS:** 371 (M+1); **IR (KBr):** 3390, 2937, 2856, 1609, 1563, 1540, 1507, 1480,1456, 1339, 1257 cm^{-1}; **Yield:** 68%.

3-[6-(2,5-Dimethoxy-phenyl)-2-morpholin-4-yl-pyrimidin-4-yl]-1*H*-indole (8)
MP: 236-238ºC; **MS:** 417 (M+1); **IR (KBr):** 2952, 2846, 1569, 1538, 1487, 1360, 1266, 1216cm^{-1}; **Yield:** 71%.
3-[6-(2,5-Dimethoxy-phenyl)-2-piperidin-1-yl-pyrimidin-4-yl]-1*H*-indole (9)
MP: 198-200ºC; **MS:** 415 (M+1); **IR (KBr):** 3019, 2937, 1663, 1565, 1493, 1438, 1216 cm^{-1}; **Yield:** 69%.
3-[2-(Morpholin-4-yl)-6-phenyl-pyrimidin-4-yl]-1*H*-indole (10)
MP: 224-226ºC; **MS:** 357 (M+1); **IR (KBr):** 2966, 2852, 1569, 1538, 1481, 1427, 1338, 1265 cm^{-1}; **Yield:** 75%.

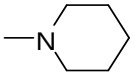
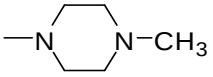
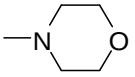
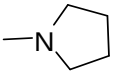
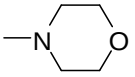
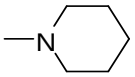
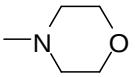
Synthesis of 3-(substituted -pyrimidin-4-yl)-1-(4-trifluoromethyl-benzyl)-1H-indole (11-17)
Synthesized molecules **4-10** were alkylated using 4-trifluoromethylbenzyl bromide. To synthesized aminopyrimidine 1.0 equivalent solution in 75 ml THF, 1.0 equivalent of 4-trifluoromethylbenzyl bromide and 1.5 equivalent sodium hydride was added. The reaction was stirred for 1.5 hours at room temperature. The alkylated compound was evaporated to remove any THF. Water and chloroform were used for the extraction. Using column chromatography, the produced chemical was isolated and made pure.
3-(6-Phenyl-2-piperidin-1-yl-pyrimidin-4-yl)-1-(4-trifluoromethyl-benzyl)-1H-indole (11)
mp: 173-175ºC; **MS:** 513 (M+1); **IR (KBr)** 3020, 2933, 2358, 1566, 1434, 1324, 1216, 1033cm^{-1} ; **^{1}H NMR** ($CDCl_3$, 300MHz): δ (ppm) 8.45 (d, 1H, J = 7.5Hz, Ar-CH), 8.13-8.07 (m, 3H,Ar-CH), 7.57 (d, 2H, J = 7.8 Hz,Ar-CH), 7.49-7.47 (m, 3H,Ar-CH), 7.31-7.25 (m, 6H,Ar-CH), 5.47 (s, 2H,N-CH_2-Ar), 4.04 (s, 4H,CH_2), 1.73(s,6H, CH_2).; **^{13}C** ($CDCl_3$, 50MHz): 140.72, 137.30, 130.27, 128.60, 127.19, 126.97, 126.50, 125.93, 125.88, 123.01, 122.17, 121.65, 110.14, 101.37, 96.16, 50.07, 45.51, 25.99, 25.00; **Yield:** 72%.
3-[6-(4-Methoxy-phenyl)-2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yl]-1-(4-trifluoromethyl-benzyl)-1H-indole (12)
mp: 165-167ºC; **MS:** 558 (M+1); **IR (KBr):** 3447,2926, 2363, 1572, 1516, 1445, 1324, 1259, 1168, 1123, 1065, 1013 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 200MHz): δ (ppm) 8.45-8.41 (m, 1H, Ar-H), 8.07 (d, 2H, J = 8.8Hz,Ar-H), 7.89 (s, 1H,Ar-H), 7.57 (d, 2H,J =8.1,Ar-H), 7.34-7.21 (m, 6H,Ar-H), 6.98 (d, 2H, J =8.7, N-CH_2), 5.45 (s, 2H, N-CH_2-Ar), 4.21 (t, 4H, J = 5.2Hz, N-CH_2), 3.87 (s, 3H,O-CH_3), 2.79 (t, 4H, J = 4.6Hz), 2.53 (s, 3H, N-CH_2) ; **^{13}C** ($CDCl_3$, 50MHz): 163.6, 162.2, 162.1, 161.4, 140.7, 137.3, 130.8, 129.7, 128.4, 126.8, 126.5, 125.9, 125.8, 122.9, 122.2, 121.5, 116.2, 113.9, 109.9, 101.4, 96.1, 55.2, 54.8, 49.9, 45.7, 43.3, 29.7; **Yield:** 67%.
3-[6-(4-Methoxy-phenyl)-2-morpholin-4-yl-pyrimidin-4-yl]-1-(4-trifluoromethyl-benzyl)-1H-indole (13)
mp:208-210ºC; **MS:** 545 (M+1); **IR (KBr):** 3020, 2923, 2358, 1580, 1525, 1431, 1323, 1215, 1040 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300MHz): δ (ppm) 8.49 (d, 1H, J = 7.2,Ar-H), 8.11 (d, 2H, J = 8.7Hz,Ar-H), 7.93 (s, 1H,Ar-H), 7.59 (d, 2H,J = 8.1Hz,Ar-H), 7.35-7.25 (m, 6H,Ar-H), 7.03 (d, 2H, J = 8.9Hz,Ar-H), 5.48 (s, 2H, N-CH_2-Ar), 4.05 (t, 4H, J = 4.8 Hz, N-CH_2), 3.90 (s,br 7H, J = 5.10Hz, O-CH_2,O-CH_3), ; **^{13}C** ($CDCl_3$, 50MHz): 163.7, 162.4, 162.2, 161.4, 140.7, 137.3, 130.8, 129.9, 128.4, 126.9, 126.5, 125.9, 122.9, 122.2, 121.5, 116.1, 113.9, 110.1, 55.4, 50.0, 44.6, 29.7; **Yield:** 77%.
3-[6-(4-Methoxy-phenyl)-2-pyrrolidin-1-yl-pyrimidin-4-yl]-1-(4-trifluoromethyl-benzyl)-1H-indole (14)
mp:158-160ºC; **MS:** 529 (M+1); **IR (KBr):** 2961, 2867, 2362, 1609, 1566, 1509, 1462, 1397, 1325, 1252, 1170, 1123 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300MHz): δ (ppm) 8.54-8.51 (m, 1H,Ar-H), 8.15-8.08 (m, 3H,Ar-H), 7.29-7.23 (m, 4H, Ar-H), 6.96 (d, 3H, J=8.6 Hz, N-CH_2), 5.47 (s, 2H, N-CH_2-Ar), 3.90-3.84 (m, 8H, CH_2,O-CH_3), 2.06 (s, 4H, CH_2); **^{13}C** ($CDCl_3$, 50MHz): 161.6, 143.3, 140.7, 137.2, 131.4, 130.8, 130.3, 129.9, 128.8, 127.9, 127.1, 126.6, 125.9, 125.8, 123.1, 122.6, 122.1, 121.6, 114.9, 113.8, 110.1, 100.3, 96.1, 55.3, 50.1, 47.3, 34.5, 29.7, 29.4, 25.6; **Yield:** 71%.
3-[6-(2,5-Dimethoxy-phenyl)-2-morpholin-4-yl-pyrimidin-4-yl]-1-(4-trifluoromethyl-benzyl)-1H-indole (15)
mp: 85-87ºC; **MS:** 575 (M+1); **IR (KBr):** 3017, 2855, 2363, 1564, 1440, 1324, 1265, 1216, 1172 cm$^{-1;}$ **^{1}H NMR** ($CDCl_3$, 300MHz): δ (ppm) 8.44 (d, 1H, J = 7.2Hz, Ar-H), 7.87 (s, 1H, Ar-H), 7.67 (s, 1H, Ar-H), 7.61 (s, 1H Ar-H), 7.55 (s, 1H, Ar-H), 7.53 (s,1H, Ar-H), 7.24-7.19(m, 5H, Ar-H), 6.94-6.92 (m, 2H, N-CH_2), 5.43 (s, 2H, N-CH_2-Ar), 3.99 (t, 4H, J=4.6Hz, CH_2), 3.86-3.78 (m, 10H, CH_2,O-CH_3); **^{13}C** ($CDCl_3$, 50MHz): 162.3, 161.9, 161.4, 153.9, 152.4, 140.7, 137.3, 130.5, 130.1, 128..6, 126.8, 126.5, 125.9, 125.8, 122.9, 122.1, 121.4, 116.1, 116.0, 113.5, 111.2, 109.9, 107.5, 96.1, 56.6, 55.6, 49.9, 44.7, 44.4; **Yield:** 62%.

3-[6-(2,5-Dimethoxy-phenyl)-2-piperidin-1-yl-pyrimidin-4-yl]-1-(4-trifluoromethyl-benzyl)-1H-indole (16)
mp: semisolid; **MS:** 573 (M+1); **IR (KBr):** 3019, 2928, 2360, 1747, 1562, 1440, 1324, 1216, 1170 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300MHz): δ (ppm) 8.44-8.40 (m, 1H, Ar-H), 7.98 (s, 1H, Ar-H), 7.61-7.54 (m, 4H, Ar-H), 7.26-7.24 (m, 5H, Ar-H), 6.95 (d, 2H, J = 2.1Hz, N-CH_2), 5.46 (s, 2H, N-CH_2-Ar), 3.99 (t, 4H, J= 4.6 Hz,CH_2), 3.88 (s, 3H, O-CH_3), 3.85(s, 3H, O-CH_3) ; **^{13}C** ($CDCl_3$, 50MHz): 153.9, 152.4, 140.8, 137.2, 130.4, 130.0, 126.8, 126.6, 125.9, 125.8, 125.7, 122.8, 122.1, 121.4, 116.1, 115.9, 113.4, 109.9, 106.4, 96.1, 56.6, 55.7, 49.9, 45.3, 29.7, 25.9, 25.1; **Yield:** 79%.

3-(2-Morpholin-4-yl-6-phenyl-pyrimidin-4-yl)-1-(4-trifluoromethyl-benzyl)-1H-indole (17)
mp: 193-195ºC; **MS:** 515 (M+1); **IR (KBr):** 3020, 2359, 1568, 1529, 1425, 1324, 1216, 1041 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300MHz): δ (ppm) 8.46 (m, 1H, Ar-H), 8.13-8.08 (m, 2H, Ar-H), 7.91 (s, 1H, Ar-H), 7.59-7.45 (m, 6H, Ar-H), 7.36 (s, 1H, Ar-H), 7.26-7.22 (m, 4H, Ar-H), 5.46 (s, 2H, N-CH_2-Ar), 4.04 (t, 4H, J = 4.8Hz, CH_2),3.80(t,4H, J =4.4Hz, CH_2).; **^{13}C** ($CDCl_3$, 50MHz): 164.2, 162.4, 162.2, 140.7, 138.3, 137.3, 130.2, 130.1, 128.6, 127.1, 126.9, 126.4, 125.9, 125.8, 123.1, 122.2, 121.6, 115.9, 110.1, 102.2, 96.1, 67.1, 50.0, 44.7, 29.7; **Yield:** 63%.

3. Antimalarial Screening of Synthesized Compounds

Screenings of the produced compounds can be conducted through the heme polymerization activity of the parasites, blood schizonticidal activity or by assesinng in vitro growth against NF-54 strain of P. falciparum. The in vitro antimalarial experiment was conducted on 96-well microtitre plates following Rieckmann's micro assay methodology. The P. falciparum NF-54 strain is consistently cultured in RPMI-1640 medium enriched with 1% D-glucose, 25 mM HEPES, 10% heat-inactivated human serum and 0.23% sodium bicarbonate. Following treatment with 5% D-Sorbitol, the asynchronous P. falciparum parasite was brought into synchronization, allowing the isolation of parasitized cells containing solely the ring stage. To conduct the experiment, an initial ring stage parasitaemia of around 1% at 3% haematocrit was consistently maintained in a total volume of 200µL of RPMI-1640 medium. The test drug, in a volume of 20 µL at the specified concentration (varying from 0.25 µg to 50 µg/mL), was incubated in duplicate wells with the parasitized cell preparation at 37˚C in a candle jar. Following 36 to 40 hours of incubation, blood smears from each well were produced and stained with Giemsa stain. The slides were examined microscopically to document the maturation of ring-stage parasites into trophozoites and schizonts in the presence of varying quantities of chemicals. The concentration that prevents full growth into schizonts was noted as the minimal inhibitory concentration (MIC). Pyrimethamine served as the standard reference medication. The activity of all examined substances is presented in the tables. The table displays the activity of just those drugs that exhibited considerable efficacy [33].

S. No.	Compound	R	R_1	MIC (µg/ml)
1.	11	-H		>10
2.	12	4-Ome		2
3.	13	4-OMe		>10
4.	14	4-OMe		>10
5.	15	2,5-diOMe		>10
6.	16	2,5-diOMe		>10
7.	17	-H		>10

MIC of Pyrimethamine: 10 µg/mL

4. Results and Discussion

Aminopyrimidine derivatives (11-17) were synthesized and purity checked. The structures of compounds were confirmed by IR and NMR spectral studies. The synthesized compounds screened by evaluating their ability to inhibit heme polymerization, their blood schizonticidal activity, or their impact on the in vitro growth of the *Plasmodium falciparum* NF-54 strain. Aminopyrimidine derivatives molecules exhibited MIC of >10 μg/mL, while 1 molecule 12 has demonstrated MIC of 2μg/mL. A MIC of 2μg/mL was observed for the compound, which had an N-methyl piperazine group at the 2nd position of the pyrimidine ring.

5. Conclusion

In this study, some novel aminopyrimidine derivatives were successfully synthesized following the proposed scheme, with their structures confirmed through spectral analysis. The antimicrobial evaluation revealed significant activity among the synthesized compounds. Compound 12 exhibited the highest potency with an MIC of 2 μg/mL, attributed to the presence of an N-methyl piperazine group at the 2nd position of the pyrimidine ring. These findings highlight the potential of aminopyrimidine derivatives as promising candidates for further development in antimicrobial research, particularly compound 12, which warrants further investigation to optimize and understand its mechanism of action.

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