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Synthesis of 4-pyrido-6-aryl-2-substituted amino pyrimidines as a new class of antimalarial agents

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Abstract—A series of 2,4,6-trisubstituted pyrimidines were synthesized and evaluated for their in vitro antimalarial activity against *Plasmodium falciparum*. Of the 18 compounds synthesized, 14 compounds showed MIC in the range of 0.25–2 μg/mL. These compounds are in vitro several fold more active than pyrimethamine.

1. Introduction

Despite continued efforts aimed at complete eradication of malaria, the disease remains a major health threat in many areas of the world, especially in tropical and subtropical countries. According to WHO estimates, 40% of the world's population presently lives under malarial threat. *Plasmodium falciparum* is the main cause of severe clinical malaria and death. Endemic mapping indicates that *P. falciparum* and *P. vivax* account for 95% of malarial infections. One of the most crucial obstacles for eradicating malaria is the widespread resistance of the malarial parasite to almost all chemotherapeutic agents. Therefore, it is very necessary to seek for new drugs attacking crucial targets in the malarial pathogen in order to combat and relieve this tremendous prevalence. The dihydrofolate reductase (DHFR) domain of *P. falciparum* is one of the few well-defined targets in malarial chemotherapy. Pyrimethamine is a specific inhibitor of the plasmodial DHFR that is essential for DNA synthesis.[1–3]

Polyamines, found in all living organisms, are required for cellular proliferation and differentiation. Malarial parasites have ornithine decarboxylase (ODC) for polyamine biosynthesis, and a number of polyamine analogues inhibit the ODC activity in *P. falciparum*. These drugs bind directly to the plasmodial DNA and thereby prevent the inhibition of DNA synthesis of the malarial parasites.[1,4]

Fatty acid biosynthesis (FAS) is another important target site in the discovery of new antimalarials. Pyridine-4-carboxylic hydrazide (isoniazid), which is a frontline drug in the treatment of tuberculosis, is an inhibitor of an important enzyme (enoyl-ACP reductase) in the fatty acid biosynthesis pathway. Thus, pyridine analogues inhibit the biosynthesis of fatty acids that are fundamental for the survival of *P. falciparum* in the host.[5]

Compounds that act on more than one target site are more liable to be active. On the basis of these observations, we have synthesized hybrid derivatives having a pyrimidine (DHFR inhibitor) along with a pyridine moiety (fatty acid inhibitor). We had previously found that triazines substituted with diamine chains (**11** and **22**) have potent in vitro antimalarial activity.[6] Our previous experience prompted us to synthesize pyrimidine derivatives having these diamine chains (**11** and **22**) at the 2nd position as polyamine inhibitors.

As part of our ongoing programme devoted to the synthesis of diverse heterocycles as anti-infective agents,[7] we had previously reported antimalarial activity in substituted triazines,[6] pyrimidines[6] and quinolines.[8] This communication describes the in vitro antimalarial activity of pyrimidine derivatives substituted with diamine chains at the 2nd position and a pyridine nucleus at the 4th position.

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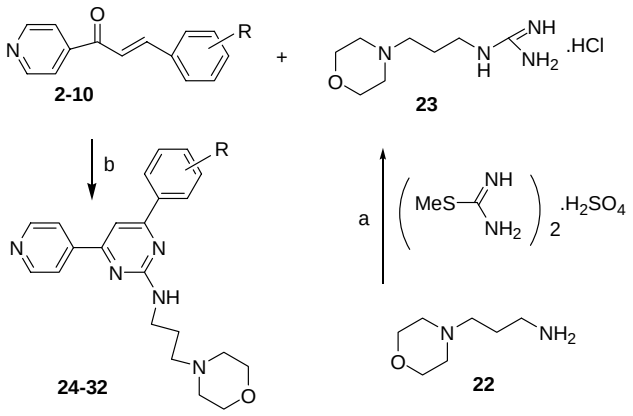
2. Chemistry

To synthesize the 2,4,6-trisubstituted pyrimidine compounds (**13**–**21** and **24**–32), 4-acetylpyridine was reacted with different aldehydes in 10% aq NaOH and methanol to yield the corresponding chalcones **2**–**10**.[9] *N*-(3-imidazol-1-yl-propyl)-guanidine (**12**) and *N*-(3-morpholin-4-yl-propyl)-guanidine (**23**) were synthesized by refluxing the corresponding amine (**11** and **22**) with *S*-methyl-isothiourea sulfate in water according to a reported procedure.[10] The chalcones **2**–**10** were further cyclized with substituted guanidine hydrochloride (**12** and **23**) in the presence of sodium isopropoxide (synthesized in situ by adding sodium metal in isopropanol) to afford the 2,4,6-trisubstituted pyrimidines **13**–**21** (Scheme 1) and **24**–**32** (Scheme 2).



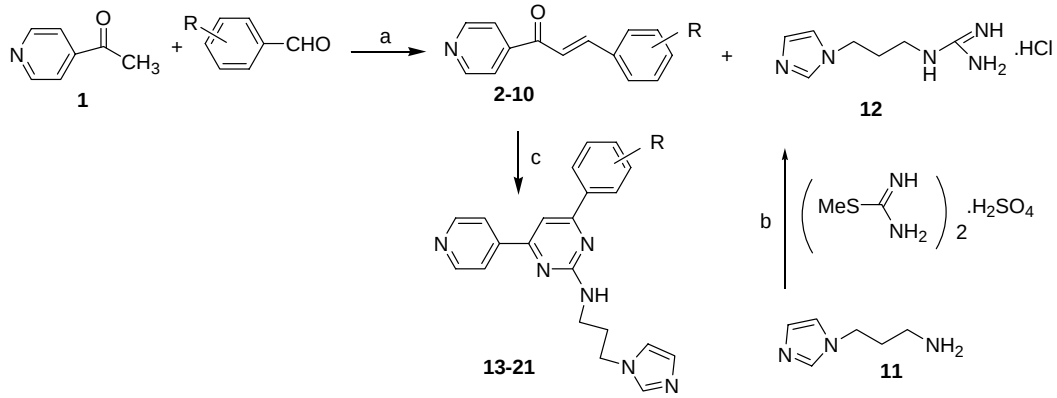
Scheme 2. Reagents and conditions: (a) (i) water, reflux, 15 min; (ii) barium chloride, reflux, 15 min; (b) sodiumisopropoxide, isopropanol, reflux, 8 h.

3. Biological activity

The in vitro antimalarial assay was carried out in 96-well microtitre plates according to the micro assay of Rieckmann et al.[11] The culture of *P. falciparum* NF-54 strain is routinely being maintained in the RPMI-1640 medium supplemented with 25 mM HEPES, 1% D-glucose, 0.23% sodium bicarbonate and 10% heat-inactivated human serum.[12] The asynchronous parasite of *P. falciparum* was synchronized after 5% D-sorbitol treatment to obtain parasitized cells harbouring only the ring stage.[13] For carrying out the assay, an initial ring-stage parasitaemia of ≈1% at 3% haematocrit in total volume of 200 μL of RPMI-1640 medium was uniformly maintained. The test compound in 20 μL volume at required concentration (ranging between 0.125 and 50 μg/mL) in duplicate wells were incubated with parasitized cell preparation at 37 °C in candle jar. After 36–40 h incubation, the blood smears from each well were prepared and stained with Giemsa stain. The slides were microscopically observed to record maturation of ring-stage parasites into trophozoites and schizonts in the presence of different concentrations of compounds. The test concentration, which inhibits the complete maturation into schizonts, was recorded as the minimum inhibitory concentration (MIC). Pyrimethamine was used as the standard reference drug. Activity of all the tested compounds is given in Table 1.

4. Results and discussion

The in vitro biological activities of the synthesized pyrimidine derivatives have shown encouraging results against *P. falciparum.* Of the 18 synthesized compounds, two compounds **15** and **16** have shown MIC of 0.25 μg/mL, whereas 12 compounds have shown MIC in the range of 1–2 μg/mL. Compound **13** having phenyl group showed a MIC of 2 μg/mL. Substitution on the phenyl ring with methyl (**14**), methoxy (**17**) or chloro (**21**) group increased the activity of compounds having a MIC of 1 μg/mL. Replacement of the methyl group on the phenyl ring with thiomethyl group (**15**) and disubstitution with methyl group (**16**) increased the activity to 0.25 μg/mL. Di- (**18**) or trisubstitution (**19** and **20**) with methoxy group reduced the activity having a MIC of 2 μg/mL. On substituting the imidazole propyl amine chain at 2nd position of the pyrimidine ring with morpholine propyl amine chain the activity followed almost similar pattern. In general,



Scheme 1. Reagents and conditions: (a) 10% aq NaOH, methanol 0 °C, rt, 30 min; (b) (i) water, reflux, 15 min; (ii) barium chloride, reflux, 15 min; (c) sodiumisopropoxide, isopropanol, reflux, 8 h.

Table 1. Antimalarial in vitro activity against *P. falciparum*

Compound	R	MIC (μg/mL)
13	H	2
14	4-Me	1
15	4-SMe	0.25
16	3,4-DiMe	0.25
17	4-OMe	1
18	2,5-DiOMe	2
19	2,4,5-TriOMe	2
20	3,4,5-TriOMe	2
21	4-Cl	1
24	H	10
25	4-Me	2
26	4-SMe	1
27	3,4-DiMe	1
28	4-OMe	2
29	2,5-DiOMe	10
30	2,4,5-TriOMe	10
31	3,4,5-TriOMe	10
32	4-Cl	2

MIC = minimum inhibiting concentration for the development of ring-stage parasite into the schizont stage during 40 h incubation. Standard drug, pyrimethamine; MIC 10 μg/mL.

the imidazole-propyl-amine-substituted compounds **13**–**21** showed better activities in comparison with their corresponding morpholine-propyl-amine-substituted compounds **24**–**32**. Monosubstitution on the phenyl ring improved the activity, whereas disubstitution on the phenyl ring with methyl group further increased the activity. Di- or trisubstitution with methoxy group decreased the activity.

5. Conclusion

The 18 2,4,6-trisubstituted pyrimidines **13**–**21** and **24**–**32** were synthesized as pyrimethamine analogues. Of the synthesized compounds, two compounds showed MIC of 0.25 μg/mL. Five compounds showed MIC of 1 μg/mL, whereas seven compounds showed MIC of 2 μg/mL. These compounds are 5–40 times more potent than pyrimethamine. These identified pyrimidines are new leads in antimalarial chemotherapy. These molecules can be very useful for further optimization work in malarial chemotherapy.

6. Experimental

IR spectra were recorded on Beckman Aculab-10, Perkin–Elmer 881 and FTIR 8210 PC, Scimadzu spectrophotometers either on KBr discs or in neat. Nuclear magnetic resonance (NMR) spectra were recorded on either Bruker Avance DRX-300 MHz or Bruker DPX 200 FT spectrometers using TMS as an internal reference. FAB mass spectra were recorded on JEOL SX 102/DA 6000 mass spectrometer using argon/xenon (6 kV, 10 mA) as the FAB gas. Chemical analyses were carried out on Carlo-Erba-1108 instrument. The melting points were recorded on an electrically heated melting point apparatus and were uncorrected.

6.1. General procedure for the synthesis of compounds 2–10

6.1.1. Method A. To a cooled solution of 10% NaOH, 1.0 equiv of liquid aldehydes were added. To this solution, 1.0 equiv of 4-acetylpyridine was added dropwise in about a period of 30 min. The solution was maintained at 0 °C for an hour and then allowed to stir at room temperature. After some time, a solid started separating out. The solution was further stirred for about 1 h. The solid was filtered and recrystallized from methanol or ethanol to afford crystals of the chalcone having yield in the range 60–75%.

6.1.2. Method B. In case of aldehydes that were solid, the aldehyde (1 equiv) was first dissolved in minimum quantity of ethanol or methanol (approximately 25 mL) and then 10% NaOH solution (approximately 100 mL) was added to it to give a clear solution. The solution was cooled up to 0 °C in an ice bath placed below it. Then, 1 equiv of 4-acetylpyridine was added dropwise to it, in around a period of 30 min. The solution was maintained at 0 °C for 1 h and then allowed to stirred at room temperature. After some time, a solid started separating out. This was stirred for about an hour. The solid was filtered and recrystallized from methanol or ethanol to give crystals of the chalcone having yield in the range 50–60%.

6.1.3. 3-Phenyl-1-pyridin-4-yl-propenone (2). The compound was synthesized using the method A. Yield: 75%; mp 172–174 °C; MS: 210 (M+1); IR (KBr) 3521, 1956, 1673, 1595, 1411, 1225 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.84 (d, 2H, $J = 6.0$ Hz), 8.01 (d, 2H, $J = 7.8$ Hz), 7.86 (d, 1H, $J = 15.1$ Hz), 7.76 (d, 2H, $J = 6.0$ Hz), 7.44–7.40 (m, 3H), 7.36 (d, 1H, $J = 15.1$ Hz). Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.56; H, 5.53; N, 6.78.

6.1.4. 1-Pyridin-4-yl-3-*p*-tolyl-propenone (3). The compound was synthesized using the method A. Yield: 76%; mp 138–140 °C; MS: 224 (M+1); IR (KBr) 3290, 1967, 1689, 1598, 1492, 1412, 1238 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.84 (d, 2H, $J = 6.0$ Hz), 7.84 (d, 1H, $J = 15.6$ Hz), 7.74 (d, 2H, $J = 6.0$ Hz), 7.54 (d, 2H, $J = 8.2$ Hz), 7.37 (d, 1H, $J = 15.6$ Hz), 7.24 (d, 2H, $J = 8.2$ Hz), 2.39 (s, 3H). Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.82; H, 5.62; N, 6.42.

6.1.5. 3-(4-Methylsulfanyl-phenyl)-1-pyridin-4-yl-propenone (4). The compound was synthesized using the method A. Yield: 70%; mp 94–96 °C; MS: 256 (M+1); IR (KBr) 3412, 1956, 1682, 1595, 1415, 1225 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.83 (d, 2H, $J = 6.1$ Hz), 7.82 (d, 1H, $J = 14.9$ Hz), 7.76 (d, 2H, $J = 6.1$ Hz), 7.55 (d, 2H, $J = 8.6$ Hz), 7.38 (d, 1H, $J = 14.9$ Hz), 7.26 (d, 2H, $J = 8.6$ Hz), 2.52 (s, 3H). Anal. Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49. Found: C, 70.74; H, 5.34; N: 5.34.

6.1.6. 3-(3,4-Dimethyl-phenyl)-1-pyridin-4-yl-propenone (5). The compound was synthesized using the method

A. Yield: 67%; mp 168–170 °C; MS: 238 (M+1); IR (KBr) 3392, 1952, 1687, 1597, 1424, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.84 (d, 2H, J = 6.0 Hz), 7.89 (d, 2H, J = 7.8 Hz), 7.83 (d, 1H, J = 15.2 Hz), 7.74 (d, 2H, J = 6.0 Hz), 7.51 (s, 1H), 7.40 (d, 1H, J = 15.2 Hz), 7.29 (d, 2H, J = 7.8 Hz), 2.37 (s, 3H), 2.34 (s, 3H). Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.24; H, 6.09; N, 5.68.

6.1.7. 3-(4-Methoxy-phenyl)-1-pyridin-4-yl-propenone (6). The compound was synthesized using the method A. Yield: 67%; mp 104–106 °C; MS: 240 (M+1); IR (KBr) 3420, 1946, 1683, 1598, 1489, 1411, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.83 (d, 2H, J = 6.1 Hz), 7.89 (d, 2H, J = 8.6 Hz), 7.82 (d, 1H, J = 15.4 Hz), 7.75 (d, 2H, J = 6.1 Hz), 7.37 (d, 1H, J = 15.4 Hz), 6.92 (d, 2H, J = 8.6 Hz), 3.88 (s, 3H, OMe). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.54; H, 5.59; N, 5.71.

6.1.8. 3-(2,5-Dimethoxy-phenyl)-1-pyridin-4-yl-propenone (7). The compound was synthesized using the method B. Yield: 67%; mp 128–130 °C; MS: 270 (M+1); IR (KBr) 3299, 1956, 1685, 1597, 1456, 1411, 1259 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.85 (d, 2H, J = 6.0 Hz), 7.82 (d, 1H, J = 15.4 Hz), 7.77 (d, 2H, J = 6.0 Hz), 7.39 (d, 1H, J = 15.4 Hz), 7.36 (s, 1H), 7.24 (d, 1H, J = 7.2 Hz), 6.76 (d, 1H, J = 7.2 Hz), 3.88 (s, 3H, OMe), 3.85 (s, 3H, OMe). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.58; H, 5.86; N, 4.97.

6.1.9. 1-Pyridin-4-yl-3-(2,4,5-trimethoxy-phenyl)-propenone (8). The compound was synthesized using the method B. Yield: 67%; mp 160–162 °C; MS: 300 (M+1); IR (KBr) 3282, 1939, 1689, 1598, 1468, 1420, 1232 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.82 (d, 2H, J = 5.9 Hz), 7.84 (d, 1H, J = 15.6 Hz), 7.72 (d, 2H, J = 5.9 Hz), 7.64 (s, 1H), 7.37 (d, 1H, J = 15.6 Hz), 6.72 (s, 1H), 3.96 (s, 3H, OMe), 3.92 (s, 3H, 2OMe). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 67.98; H, 5.94; N, 4.91.

6.1.10. 1-Pyridin-4-yl-3-(3,4,5-trimethoxy-phenyl)-propenone (9). The compound was synthesized using the method B. Yield: 67%; mp 194–196 °C; MS: 300 (M+1); IR (KBr) 3278, 1943, 1687, 1596, 1457, 1445, 1245 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.79 (d, 2H, J = 6.0 Hz), 7.82 (d, 1H, J = 15.2 Hz), 7.70 (d, 2H, J = 6.0 Hz), 7.37 (d, 1H, J = 15.2 Hz), 7.30 (s, 2H), 3.98 (s, 3H, 2OMe), 3.95 (s, 3H, OMe). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.47; H, 5.98; N, 4.31.

6.1.11. 3-(4-Chloro-phenyl)-1-pyridin-4-yl-propenone (10). The compound was synthesized using the method B. Yield: 68%; mp 205–207 °C; MS: 244 (M+1); IR (KBr) 3297, 1948, 1684, 1598, 1489, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.85 (d, 2H, J = 6.1 Hz), 7.86 (d, 1H, J = 15.6 Hz), 7.75 (d, 2H, J = 6.1 Hz), 8.09 (d, 2H, J = 8.6 Hz), 7.38 (d, 1H, J = 15.6 Hz), 7.52 (d, 2H, J = 8.6 Hz). Anal. Calcd for $C_{14}H_{10}ClNO$: C, 69.00; H, 4.14; N, 5.75. Found: C, 68.74; H, 4.32; N, 5.44.

6.2. General procedure for the synthesis of compounds 13–21

To a solution of 1.0 equiv of *N*-(3-imidazol-1-yl-propyl)-guanidine hydrochloride in 50 mL of isopropanol, 1.1 equiv of sodium metal was added. The reaction mixture was refluxed for 2 h and then different chalcones (**2**–**10**, 1.0 equiv) were added to it and refluxed for 8 h. The solvent was removed from the reaction mixture under reduced pressure. Water was added and the aqueous phase was extracted with chloroform and washed with brine solution. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by crystallization from methanol or ethanol or sometimes by column chromatography on neutral alumina (chloroform/hexane, 1:2) to yield the pure compounds.

6.2.1. (3-Imidazol-1-yl-propyl)-(4-phenyl-6-pyridin-4-yl-pyrimidin-2-yl)-amine (13). Yield: 65%; mp decomposes at 210 °C; MS: 357 (M+1); IR (KBr) 3416, 2932, 1645, 1574, 1484, 1319, 1280 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.77 (d, 2H, J = 6.0 Hz), 8.06 (d, 2H, J = 7.8 Hz), 7.92 (d, 2H, J = 6.0 Hz), 7.55 (s, 1H), 7.52–7.47 (m, 3H), 7.45 (s, 1H), 7.09 (d, 1H, J = 4.4 Hz), 6.97 (d, 1H, J = 4.4 Hz), 5.44 (s, 1H, NH), 4.13 (t, 2H, J = 5.1 Hz), 3.64 (m, 2H), 2.25 (t, 2H, J = 5.1 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): 166.4, 165.4, 162.7, 150.3, 145.4, 137.8, 137.1, 127.8, 129.6, 128.9, 125.1, 120.8, 119.2, 103.4, 44.8, 39.1, 31.5. Anal. Calcd for $C_{21}H_{20}N_6$: C, 70.77; H, 5.66; N, 23.58. Found: C, 70.52; H, 5.44; N, 23.34.

6.2.2. (3-Imidazol-1-yl-propyl)-(4-pyridin-4-yl-6-*p*-tolyl-pyrimidin-2-yl)-amine (14). Yield: 76%; mp 168–170 °C; MS: 371 (M+1); IR (KBr) 3412, 2926, 1638, 1580, 1480, 1325, 1272 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.75 (d, 2H, J = 6.1 Hz), 7.99 (d, 2H, J = 7.9 Hz), 7.90 (d, 2H, J = 6.1 Hz), 7.51 (s, 1H), 7.44 (s, 1H), 7.30 (d, 2H, J = 7.9 Hz), 7.08 (d, 1H, J = 4.9 Hz), 6.95 (d, 1H, J = 4.9 Hz), 5.51 (s, 1H, NH), 4.09 (t, 2H, J = 4.6 Hz), 3.60 (t, 2H, J = 4.6 Hz), 2.43 (s, 3H, Me), 2.19 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 166.8, 165.5, 163.5, 150.9, 145.6, 141.7, 137.5, 134.9, 131.8, 129.9, 127.4, 121.4, 119.3, 103.5, 44.9, 39.0, 31.6, 21.8. Anal. Calcd for $C_{22}H_{22}N_6$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.52; H, 5.68; N, 22.34.

6.2.3. [4-(4-Methylsulfanyl-phenyl)-6-pyridin-4-yl-pyrimidin-2-yl]-(3-imidazol-1-yl-propyl)-amine (15). Yield: 74%; mp 90–92 °C; MS: 403 (M+1); IR (KBr) 3420, 2948, 1636, 1584, 1486, 1325, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.77 (d, 2H, J = 6.0 Hz), 7.99 (d, 2H, J = 8.7 Hz), 7.89 (d, 2H, J = 6.0 Hz), 7.53 (s, 1H), 7.43 (s, 1H), 7.35 (d, 2H, J = 8.7 Hz), 7.09 (d, 1H, J = 4.1 Hz), 6.96 (d, 1H, J = 4.2 Hz), 5.43 (s, 1H, NH), 4.11 (t, 2H, J = 4.9 Hz), 3.60 (t, 2H, J = 4.8 Hz), 2.54 (s, 3H, SMe), 2.20 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 166.7, 165.1, 163.7, 150.8, 145.8, 142.8,

137.6, 134.4, 127.8, 126.4, 125.1, 121.4, 119.5, 103.6, 45.1, 39.2, 31.7, 18.7. Anal. Calcd for $C_{22}H_{22}N_6S$: C, 65.65; H, 5.51; N, 20.88. Found: C, 65.22; H, 5.75; N, 20.54.

6.2.4. [4-(3,4-Dimethyl-phenyl)-6-pyridin-4-yl-pyrimidin-2-yl]-(3-imidazol-1-yl-propyl)-amine (16). Yield: 65%; mp 126–128 °C; MS: 385 (M+1); IR (KBr) 3426, 2924, 1648, 1576, 1486, 1328, 1284 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.75 (d, 2H, J = 6.0 Hz), 7.90 (d, 2H, J = 6.0 Hz), 7.83 (s, 1H), 7.77 (d, 1H, J = 6.9 Hz), 7.51 (s, 1H), 7.44 (s, 1H), 7.28 (d, 1H, J = 6.9 Hz), 7.07 (d, 1H, J = 4.2 Hz), 6.96 (d, 1H, J = 4.2 Hz), 5.43 (s, 1H, NH), 4.10 (t, 2H, J = 4.9 Hz), 3.62 (t, 2H, J = 4.9 Hz), 2.37 (s, 3H), 2.34 (s, 3H), 2.19 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 167.0, 163.5, 163.3, 150.8, 145.7, 140.4, 137.5, 137.2, 135.2, 130.6, 129.9, 128.6, 125.0, 121.5, 119.3, 103.5, 44.9, 38.9, 31.6, 20.4, 20.2. Anal. Calcd for $C_{23}H_{24}N_6$: C, 71.85; H, 6.29; N, 21.86. Found: C, 71.52; H, 6.55; N, 21.64.

6.2.5. (3-Imidazol-1-yl-propyl)-[4-(4-methoxy-phenyl)-6-pyridin-4-yl-pyrimidin-2-yl]-amine (17). Yield: 72%; mp 140–142 °C; MS: 387 (M+1); IR (KBr) 3422, 2926, 1638, 1580, 1480, 1325, 1272 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.76 (d, 2H, J = 6.0 Hz), 8.05 (d, 2H, J = 8.8 Hz), 7.91 (d, 2H, J = 6.0 Hz), 7.53 (s, 1H), 7.41 (s, 1H), 7.08 (d, 1H, J = 4.2 Hz), 7.01 (d, 2H, J = 8.8 Hz), 6.96 (d, 1H, J = 4.2 Hz), 4.12 (t, 2H, J = 4.9 Hz), 3.88 (s, 3H, OMe), 3.60 (t, 2H, J = 4.9 Hz), 2.19 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 166.8, 163.6, 162.9, 161.2, 150.4, 145.5, 137.6, 129.9, 128.6, 125.0, 121.0, 119.3, 114.0, 103.6, 55.4, 44.9, 38.9, 31.6. Anal. Calcd for $C_{22}H_{22}N_6O$: C, 68.38; H, 5.74; N, 21.75. Found: C, 68.52; H, 5.98; N, 21.51.

6.2.6. [4-(2,5-Dimethoxy-phenyl)-6-pyridin-4-yl-pyrimidin-2-yl]-(3-imidazol-1-yl-propyl)-amine (18). Yield: 59%; mp 114–116 °C; MS: 417 (M+1); IR (KBr) 3439, 2993, 1652, 1575, 1509, 1462, 1465, 1350 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.77 (d, 2H, J = 5.9 Hz), 7.95 (d, 2H, J = 5.9 Hz), 7.56 (s, 1H), 7.38 (s, 1H), 7.32 (s, 1H), 7.22 (d, 1H, J = 6.8 Hz), 7.08 (d, 1H, J = 4.3 Hz), 6.95 (d, 1H, J = 4.3 Hz), 6.71 (d, 1H, J = 6.8 Hz), 4.12 (t, 2H, J = 4.7 Hz), 3.87 (t, 2H, J = 4.6 Hz), 3.84 (s, 3H, OMe), 3.82 (s, 3H, OMe), 2.21 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 164.9, 162.6, 162.2, 154.3, 152.9, 150.8, 146.1, 137.7, 128.3, 125.1, 121.6, 119.4, 116.9, 116.6, 113.7, 107.9, 56.9, 56.3, 44.9, 39.0, 31.6. Anal. Calcd for $C_{23}H_{24}N_6O_2$: C, 66.33; H, 5.81; N, 20.18. Found: C, 66.49; H, 5.62; N, 20.54.

6.2.7. (3-Imidazol-1-yl-propyl)-(4-pyridin-4-yl-6-(2,4,5-trimethoxy-phenyl)-pyrimidin-2-yl)-amine (19). Yield: 60%; mp 129–131 °C; MS: 447 (M+1); IR (KBr) 3429, 2929, 2864, 1662, 1577, 1549, 1510, 1460, 1359 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.75 (d, 2H, J = 6.1 Hz), 7.91 (d, 2H, J = 6.1 Hz), 7.81 (s, 1H), 7.65 (s, 1H), 7.52 (s, 1H), 7.07 (d, 1H, J = 4.2 Hz), 6.96 (d, 1H, J = 4.2 Hz), 6.62 (s, 1H), 4.12 (t, 2H, J = 4.6 Hz), 3.97 (s, 3H, OMe), 3.92 (s, 6H, 2OMe), 3.62 (t, 2H, J = 4.6 Hz), 2.21 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 164.5, 162.6, 162.1, 154.1, 152.3, 150.8, 146.3, 143.9, 137.5, 125.0, 121.6, 119.3, 118.9, 114.2, 107.6, 98.3, 57.2, 57.0, 56.6, 44.9, 38.9, 31.5. Anal. Calcd for $C_{24}H_{26}N_6O_3$: C, 64.56; H, 5.87; N, 18.82. Found: C, 64.35; H, 5.98; N, 18.57.

6.2.8. (3-Imidazol-1-yl-propyl)-(4-pyridin-4-yl-6-(3,4,5-trimethoxy-phenyl)-pyrimidin-2-yl)-amine (20). Yield: 64%; mp 134–136 °C; MS: 447 (M+1); IR (KBr) 3427, 2930, 2864, 1658, 1591, 1513, 1442, 1356 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.78 (d, 2H, J = 5.9 Hz), 7.93 (d, 2H, J = 5.9 Hz), 7.53 (s, 1H), 7.35 (s, 1H), 7.30 (s, 2H), 7.08 (d, 1H, J = 4.2 Hz), 6.96 (d, 1H, J = 4.2 Hz), 4.12 (t, 2H, J = 4.8 Hz), 3.60 (t, 2H, J = 4.8 Hz), 2.20 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 167.2, 162.8, 163.2, 154.1, 150.8, 145.4, 140.8, 137.6, 134.6, 125.1, 121.6, 119.3, 105.1, 102.7, 61.4, 56.8, 44.8, 39.0, 31.6. Anal. Calcd for $C_{24}H_{26}N_6O_3$: C, 64.56; H, 5.87; N, 18.82. Found: C, 64.41; H, 5.65; N, 18.62.

6.2.9. [4-(4-Chloro-phenyl)-6-pyridin-4-yl-pyrimidin-2-yl]-(3-imidazol-1-yl-propyl)-amine (21). Yield: 67%; mp decomposes at 170 °C; MS: 391 (M+1); IR (KBr) 3426, 2933, 2839, 1656, 1510, 1448, 1356 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.77 (d, 2H, J = 5.9 Hz), 8.06 (d, 2H, J = 7.9 Hz), 7.94 (d, 2H, J = 5.9 Hz), 7.47 (d, 2H, J = 7.9 Hz), 7.53 (s, 1H), 7.40 (s, 1H), 7.07 (d, 1H, J = 4.5 Hz), 6.96 (d, 1H, J = 4.5 Hz), 4.12 (t, 4H, J = 4.7 Hz), 3.60 (t, 4H, J = 4.7 Hz), 2.22 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 165.6, 162.4, 161.9, 158.9, 145.6, 137.7, 135.2, 134.4, 130.2, 128.8, 125.1, 121.2, 119.4, 104.1, 44.9, 38.9, 31.7. Anal. Calcd for $C_{21}H_{19}ClN_6$: C, 64.53; H, 4.90; N, 21.50. Found: C, 64.34; H, 4.76; N, 21.65.

6.3. General procedure for the synthesis of compounds 24–32

The chalcones **2**–**10** were cyclized with *N*-(3-morpholin-4-yl-propyl)-guanidine hydrochloride by a similar method as that of compounds **13**–**21**.

6.3.1. (3-Morpholin-4-yl-propyl)-(4-phenyl-6-pyridin-4-yl-pyrimidin-2-yl)-amine (24). Yield: 70%; mp 202–204 °C; MS: 376 (M+1); IR (KBr) 3431, 2949, 1816, 1649, 1593, 1507, 1461, 1355 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.77 (d, 2H, J = 5.9 Hz), 8.11 (d, 2H, J = 7.8 Hz), 7.96 (d, 2H, J = 5.9 Hz), 7.52–7.49 (m, 3H), 7.42 (s, 1H), 3.79 (t, 4H, J = 4.6 Hz), 3.66 (t, 2H, J = 4.2 Hz), 2.63 (t, 2H, J = 4.5 Hz), 2.56 (t, 4H, J = 4.6 Hz), 1.96–1.91 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 165.2, 162.1, 161.7, 150.3, 145.4, 137.2, 127.8, 129.6, 128.9, 120.8, 103.4, 66.5, 45.6, 44.1, 39.5, 31.5. Anal. Calcd for $C_{22}H_{25}N_5O$: C, 70.38; H, 6.71; N, 18.65. Found: C, 70.52; H, 6.43; N, 18.37.

6.3.2. (3-Morpholin-4-yl-propyl)-(4-pyridin-4-yl-6-*p*-tolyl-pyrimidin-2-yl)-amine (25). Yield: 77%; mp 123–125 °C; MS: 390 (M+1); IR (KBr) 3429, 2934, 2872, 1638, 1579, 1510, 1468, 1356, 1278 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.75 (d, 2H, J = 6.1 Hz),

8.03 (d, 2H, $J = 7.9$ Hz), 7.94 (d, 2H, $J = 6.1$ Hz), 7.41 (s, 1H), 7.30 (d, 2H, $J = 7.9$ Hz), 3.78 (t, 4H, $J = 4.5$ Hz), 3.63 (t, 2H, $J = 4.3$ Hz), 2.62 (t, 2H, $J = 4.1$ Hz), 2.56 (t, 4H, $J = 4.5$ Hz), 2.43 (s, 3H, Me), 1.94–1.90 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 165.5, 162.5, 162.0, 150.2, 145.4, 138.1, 133.6, 130.1, 127.2, 121.2, 101.5, 66.6, 45.7, 44.2, 39.5, 31.5, 18.9. Anal. Calcd for $C_{23}H_{27}N_5O$: C, 70.92; H, 6.99; N, 17.98. Found: C, 70.68; H, 6.74; N, 17.74.

6.3.3. [4-(4-Methylsulfanyl-phenyl)-6-pyridin-4-yl-pyrimidin-2-yl]-(3-morpholin-4-yl-propyl)-amine (26). Yield: 74%; mp 124–126 °C; MS: 422 (M+1); IR (KBr) 3427, 2930, 2864, 1654, 1591, 1513, 1442, 1345 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.77 (d, 2H, $J = 6.2$ Hz), 8.06 (d, 2H, $J = 8.6$ Hz), 7.95 (d, 2H, $J = 6.2$ Hz), 7.40 (s, 1H), 7.36 (d, 2H, $J = 8.6$ Hz), 3.79 (t, 4H, $J = 4.6$ Hz), 3.66 (t, 2H, $J = 4.2$ Hz), 2.63 (t, 2H, $J = 4.5$ Hz), 2.56 (t, 4H, $J = 4.6$ Hz), 2.52 (s, 3H, SMe), 1.96–1.91 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 165.7, 163.1, 162.7, 150.8, 145.8, 142.8, 134.4, 127.8, 126.4, 121.4, 102.2, 66.2, 45.5, 44.0, 39.5, 31.5, 18.4. Anal. Calcd for $C_{23}H_{27}N_5OS$: C, 65.53; H, 6.46; N, 16.61. Found: C, 65.41; H, 6.32; N, 16.37.

6.3.4. [4-(3,4-Dimethyl-phenyl)-6-pyridin-4-yl-pyrimidin-2-yl]-(3-morpholin-4-yl-propyl)-amine (27). Yield: 70%; mp 92–94 °C; MS: 404 (M+1); IR (KBr) 3424, 2976, 2864, 1668, 1589, 1506, 1456, 1356 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.77 (d, 2H, $J = 6.1$ Hz), 7.97 (d, 2H, $J = 6.1$ Hz), 7.87 (s, 1H), 7.82 (d, 1H, $J = 6.9$ Hz), 7.42 (s, 1H), 7.23 (d, 1H, $J = 6.9$ Hz), 3.77 (t, 4H, $J = 4.7$ Hz), 3.62 (t, 2H, $J = 4.4$ Hz), 2.60 (t, 2H, $J = 4.1$ Hz), 2.56 (t, 4H, $J = 4.7$ Hz), 2.37 (s, 3H, Me), 2.34 (s, 3H, Me), 1.94–1.90 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 166.6, 162.9, 162.7, 150.8, 145.9, 140.2, 137.4, 135.6, 130.5, 128.6, 125.0, 121.5, 102.6, 66.4, 45.5, 44.1, 39.5, 31.5, 20.4, 20.2. Anal. Calcd for $C_{24}H_{29}N_5O$: C, 71.44; H, 7.24; N, 17.36. Found: C, 71.24; H, 7.36; N, 17.57.

6.3.5. [4-(4-Methoxy-phenyl)-6-pyridin-4-yl-pyrimidin-2-yl]-(3-morpholin-4-yl-propyl)-amine (28). Yield: 68%; mp 122–124 °C; MS: 406 (M+1); IR (KBr) 3439, 2934, 2865, 1673, 1575, 1510, 1462, 1350 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.77 (d, 2H, $J = 6.0$ Hz), 8.11 (d, 2H, $J = 8.8$ Hz), 7.96 (d, 2H, $J = 6.0$ Hz), 7.39 (s, 1H), 7.03 (d, 2H, $J = 8.8$ Hz), 3.88 (s, 3H, OMe), 3.77 (t, 4H, $J = 4.8$ Hz), 3.65 (t, 2H, $J = 4.7$ Hz), 2.61 (t, 2H, $J = 4.1$ Hz), 2.56 (t, 4H, $J = 4.8$ Hz), 1.92–1.88 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 165.4, 162.4, 162.2, 161.9, 150.4, 145.5, 129.9, 128.6, 121.0, 114.0, 101.6, 66.5, 55.5, 45.6, 44.1, 39.5, 31.5. Anal. Calcd for $C_{23}H_{27}N_5O_2$: C, 68.13; H, 6.71; N, 17.27. Found: C, 68.35; H, 6.65; N, 17.39.

6.3.6. [4-(2,5-Methoxy-phenyl)-6-pyridin-4-yl-pyrimidin-2-yl]-(3-morpholin-4-yl-propyl)-amine (29). Yield: 66%; mp 112–114 °C; MS: 436 (M+1); IR (KBr) 3409, 2943, 1645, 1574, 1484, 1319, 1280 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.77 (d, 2H, $J = 6.0$ Hz), 7.95 (d, 2H, $J = 6.0$ Hz), 7.40 (s, 1H), 7.33 (s, 1H), 7.22 (d, 1H, $J = 6.8$ Hz), 6.74 (d, 1H, $J = 6.8$ Hz), 6.01 (s, 1H, NH), 3.84 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.77 (t, 4H, $J = 4.8$ Hz), 3.65 (t, 2H, $J = 4.6$ Hz), 2.61 (t, 2H, $J = 4.4$ Hz), 2.56 (t, 4H, $J = 4.8$ Hz), 1.92–1.88 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 164.9, 162.7, 162.3, 154.2, 152.9, 150.8, 146.1, 128.3, 121.6, 116.9, 116.5, 113.7, 107.8, 67.2, 56.9, 56.3, 45.5, 44.8, 39.5, 31.6. Anal. Calcd for $C_{24}H_{29}N_6O_3$: C, 66.19; H, 6.71; N, 16.08. Found: C, 66.42; H, 6.43; N, 16.37.

6.3.7. (3-Morpholin-4-yl-propyl)-(4-pyridin-4-yl-6-(2,4,5-trimethoxy-phenyl)-pyrimidin-2-yl)-amine (30). Yield: 68%; mp 121–123 °C; MS: 466 (M+1); IR (KBr) 3402, 2926, 1638, 1580, 1480, 1325, 1272 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.74 (d, 2H, $J = 6.1$ Hz), 7.93 (d, 2H, $J = 6.1$ Hz), 7.77 (s, 1H), 7.71 (s, 1H), 6.61 (s, 1H), 6.01(s, 1H, NH), 3.97 (s, 3H, OMe), 3.93 (s, 6H, 2OMe), 3.79 (t, 4H, $J = 4.6$ Hz), 3.66 (t, 2H, $J = 4.2$ Hz), 2.63 (t, 2H, $J = 4.5$ Hz), 2.56 (t, 4H, $J = 4.6$ Hz), 1.96–1.91 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 164.8, 162.6, 162.1, 154.3, 152.5, 150.7, 146.3, 143.9, 121.6, 118.9, 114.2, 107.6, 98.3, 67.3, 57.2, 57.0, 56.6, 45.6, 44.8, 39.5, 31.5. Anal. Calcd for $C_{25}H_{31}N_5O_4$: C, 64.50; H, 6.71; N, 15.04. Found: C, 64.76; H, 6.54; N, 15.32.

6.3.8. (3-Morpholin-4-yl-propyl)-(4-pyridin-4-yl-6-(3,4,5-trimethoxy-phenyl)-pyrimidin-2-yl)-amine (31). Yield: 65%; mp 137–139 °C; MS: 466 (M+1); IR (KBr) 3415, 2948, 1636, 1584, 1486, 1325, 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.76 (d, 2H, $J = 6.1$ Hz), 7.95 (d, 2H, $J = 6.1$ Hz), 7.35 (s, 1H), 7.32 (s, 2H), 3.97 (s, 6H, OMe), 3.92 (s, 3H, OMe), 3.77 (t, 4H, $J = 4.8$ Hz), 3.65 (t, 2H, $J = 4.7$ Hz), 2.61 (t, 2H, $J = 4.1$ Hz), 2.56 (t, 4H, $J = 4.8$ Hz), 1.92–1.88 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 167.2, 162.8, 163.2, 154.1, 150.8, 145.4, 140.8, 134.6, 121.6, 105.1, 102.7, 67.3, 61.4, 56.8, 45.6, 44.8, 39.5, 31.5. Anal. Calcd for $C_{25}H_{31}N_5O_4$: C, 64.50; H, 6.71; N, 15.04. Found: C, 64.68; H, 6.54; N, 15.36.

6.3.9. [4-(4-Chloro-phenyl)-6-pyridin-4-yl-pyrimidin-2-yl]-(3-morpholin-4-yl-propyl)-amine (32). Yield: 70%; mp 116–118 °C; MS: 410 (M+1); IR (KBr) 3412, 2936, 1642, 1578, 1488, 1324, 1284 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.76 (d, 2H, $J = 6.1$ Hz), 8.04 (d, 2H, $J = 8.4$ Hz), 7.93 (d, 2H, $J = 6.1$ Hz), 7.47 (d, 2H, $J = 8.4$ Hz), 7.37 (s, 1H), 6.1 (s, 1H, NH), 3.79 (t, 4H, $J = 4.8$ Hz), 3.65 (t, 2H, $J = 4.4$ Hz), 2.60 (t, 2H, $J = 4.3$ Hz), 2.52 (t, 4H, $J = 4.8$ Hz), 1.97–1.92 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 165.6, 162.4, 161.9, 158.9, 145.6, 135.2, 134.4, 130.2, 128.8, 121.2, 104.1, 66.5, 45.6, 44.1, 39.5, 31.5. Anal. Calcd for $C_{22}H_{24}ClN_5O$: C, 64.46; H, 5.90; N, 17.09. Found: C, 64.65; H, 5.68; N, 17.42.

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