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RAPID, ENVIRONMENTALLY GREENER AND ULTRASOUND-ASSISTED ONE-POT SYNTHESIS OF QUINOLINE, BENZIMIDAZOLE AND PYRIMIDINE COMBINED MOIETY AS POTENTIAL ANTIMICROBIAL AGENTS

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Abstract – An efficient and environmentally benign greener synthesis of 2-amino-4-(substituted quinoline)-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitriles under ultrasonic irradiation was achieved. Here, we have developed a one-pot three-component reaction between 2-chloroquinoline-3-carbaldehyde, malononitrile, and 2-aminobenzimidazole in the presence of ammonium acetate as a catalyst and ethanol solvent. All the synthesized compounds (**TF-1** to **TF-8**) were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, and Mass spectroscopic analysis. All the synthesized compounds were screened and evaluated for their antimicrobial activities.

In the current research framework, greener synthesis[1] is widely used for the synthesis of organic molecules. Ultrasonic-assisted, microwave-assisted, ionic liquid and bio-based catalysts are currently developed to synthesize organic compounds. Ultrasonic-assisted (US)[2] organic synthesis is familiar to encourage conventional heating methods, and the ultrasonic-assisted method shows better results on competitive reactions[3] in organic chemistry. In this technique, heating is broadly used for an appropriate derivation of heating in organic molecular synthesis. In the organic synthesis using US techniques, the purpose is to develop a comfortable handle, economic criteria, cleaner, faster, efficient, and rapid techniques.[4] We focus on these techniques to develop and determine parameters related to conventional heating methods and ultrasonic-assisted methods effects.

The literature has reported many methods to synthesize 1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine via one-pot three-component reaction of 2-aminobenzimidazole, aldehydes, and malononitrile.[5] This reaction proceeded using different catalysts and conditions like microwave techniques,[6] MgO,[7] triethylamine,[8] pyridine,[9] N_2H_4[10] and *p*-toluenesulphonic acid.[11] All the above-discussed conditions

followed to suffer drawbacks such as costly catalyst used, low reaction yield, the hazardous reagent used, and prolonged reaction period. In the present study, we report the use of ammonium acetate as catalyst and ethanol as solvent to minimize the drawbacks.

The quinoline nucleus fused with pyridine derivatives is the cornerstone of the biologically active compounds and valuable synthetic intermediates. The structures of quinoline derivatives are observed in natural products and are frequently targeted pharmacological activity, such as anti-cancer,[12] antimalarial,[13] antiviral,[14] antimycobacterial,[15] antifungal,[16] insecticidal,[17] HIV-1 integrase inhibitors,[18] antileishmanial activity,[19] antimicrobial,[20] antiproliferative activity,[21] and Covid-19.[22] Some marketed drug of quinoline derivatives are shown in **Figure 1**.

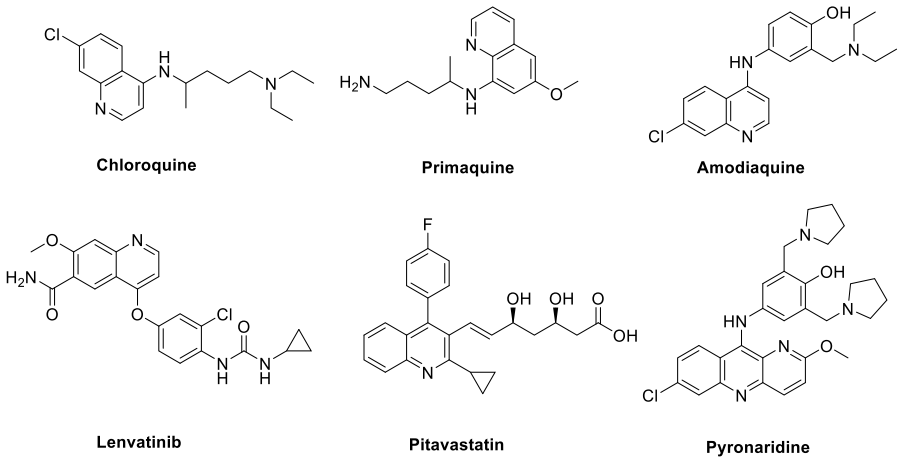


Figure 1. Marketed drug of quinoline derivatives

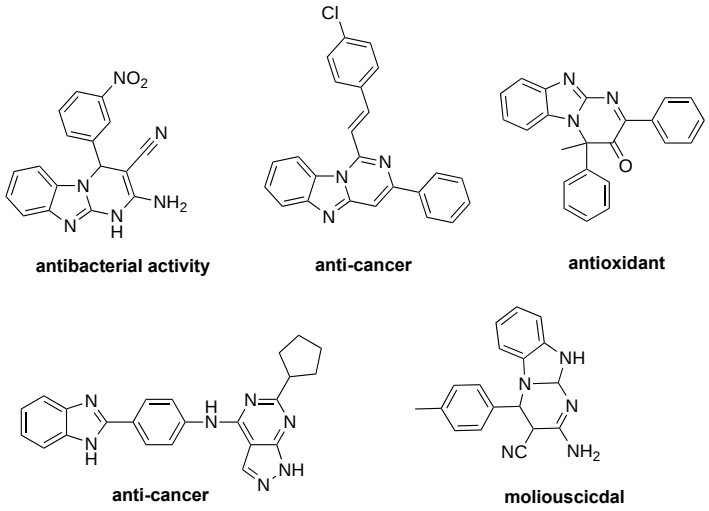
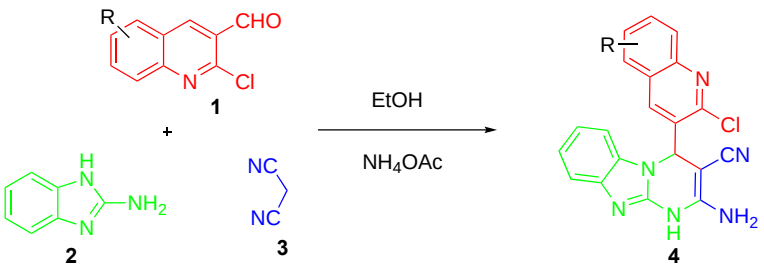


Figure 2. Biological active drug

Herein, we have developed a new, rapid, and efficient method for the synthesis of 2-amino-4-(substituted quinoline)-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitriles *via* ultrasonic irradiation.

Chemistry

All the synthesized compounds **(TF-1** to **TF-8)** were prepared by ultrasonic and conventional heating methods in the presence of an ammonium acetate catalyst shown in **Scheme 1**.



where R = H, Cl, CH_3, Br, OMe

Scheme 1. Reagents and conditions: 2-chloroquinoline-3-carbaldehyde **1** (2.0 mmol), 2-aminobenzimidazole **2** (2.0 mmol), malononitrile **3** (2.0 mmol) and NH_4OAc (0.10 mmol), EtOH.

The reaction was successfully performed using a one-pot three-component reaction of 2-chloro-quinoline-3-carbaldehyde **(1)**, malononitrile **(3)**, and 2-aminobenzimidazole **(2)** in the presence of NH_4OAc catalyst and EtOH solvent to furnished the new 2-amino-4-(substituted quinoline)-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitriles **(4)**. We have carried out the model reaction protocol using the ultrasonic irradiation method. Ultrasonic techniques provided better yields and shorter reaction time than the conventional heating method.

Table 1. Physical constant of synthesized compounds (TF-1 to TF-8)

Comp. Code	Subs. R	M.F.	M.W. (gm/mole)	CH[a] (min)		US[b] (min)		*MP (°C)
				Time (min)	Yield[c] (%)	Time (min)	Yield[c] (%)	
TF-1	-H	$C_{20}H_{13}ClN_6$	372	60	76	**30**	**90**	198-200
TF-2	7-Cl	$C_{20}H_{12}Cl_2N_6$	407	60	74	**30**	**89**	208-210
TF-3	7-Me	$C_{21}H_{15}ClN_6$	386	65	73	**35**	**92**	200-202
TF-4	6-Br	$C_{20}H_{12}BrClN_6$	452	70	75	**35**	**94**	240-242
TF-5	6-Me	$C_{21}H_{15}ClN_6$	386	72	70	**35**	**92**	198-202

TF-6	8-Me	$C_{21}H_{15}ClN_6$	386	75	64	**35**	**80**	202-204
TF-7	6-OMe	$C_{21}H_{15}ClN_6O$	402	80	70	**40**	**85**	206-208
TF-8	6-Cl	$C_{20}H_{12}Cl_2N_6$	407	80	68	**30**	**84**	208-212

[CH[a]: Conventional heating method, US[b]: Ultrasonic irradiation method,

Yield[c]: Reagents and conditions: 2-chloroquinoline-3-carbaldehyde (2.0 mmol), 2-aminobenzimidazole (2.0 mmol), malononitrile (2.0 mmol) and NH_4OAc (10 mol%), EtOH.

*The MP of all synthesized compounds was measured by using open capillary apparatus.]

Reaction Optimization:

Our preliminary examination for the synthesis of 2-amino-4-(substituted quinoline)-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitriles **(TF-1)** from the reaction of malononitrile, 2-aminobenzimidazole with quinolinealdehyde under various reaction conditions are shown in **Table 2**.

Table 2. Optimization table for compound TF-1

Entry	Solvent	Catalyst	Loading (mol%)	Condition	Temp. (°C)	Time (min)	Yield (%)
1	EtOH	NH_4OAc	5	rt	-	80	52
2	EtOH	NH_4OAc	5	Reflux	80	60	68
3	EtOH	NH_4OAc	5	Microwave	80	6	70
4	EtOH	NH_4OAc	5	Ultrasonic	80	30	80
5	EtOH	NH_4OAc	10	rt	-	80	64
6	EtOH	NH_4OAc	10	Reflux	80	60	76
7	EtOH	NH_4OAc	10	Microwave	80	6	78
8	**EtOH**	**NH_4OAc**	**10**	**Ultrasonic**	**80**	**30**	**90**
9	MeOH	NH_4OAc	10	Microwave	80	8	77
10	MeOH	Et_3N	10	Microwave	80	8	65

Scheme 1 represents the construction of new quinoline fused with pyridine derivatives. The furnished compound **TF-1** to **TF-8** was achieved in NH_4OAc and EtOH under ultrasonic irradiation for 30 to 40 min. The optimization of reaction conditions was studied using two different solvents, loading catalysts, different reaction conditions, reaction time, and product yield.

The final compound **TF-1** was synthesized by using the presence of two different catalysts. We have performed the reaction using triethylamine catalyst and methanol solvent, but the product yield was low compared to other conditions. The desired product **TF-1** was obtained from various reaction conditions like room temperature, microwave irradiation, conventional heating method, and ultrasonic-assisted techniques shown in **Table 2**. We have observed that the ultrasonic irradiation method gave enhanced yield **(Table 2 entry 4 and 8)**. To furnish the final molecule, **TF-1** was obtained from two different solvents like MeOH and EtOH. From these, we have proven that EtOH is a perfect solvent for excellent yield **(Table 2 entry 8)**. Our observation for optimization the catalyst, catalyst loading, temperature and condition of results are summarised in **Table 2**. The current reaction preferred with the loading of 10 mol% NH_4OAc catalyst to furnished 90% yield is shown in **Table 3**, **entry 3**. Increasing the NH_4OAc catalyst amount 20 mol% to no improvement observed **(Table 3 entry 5)**.

Table 3. Screening of NH_4OAc proportion for compound TF-1

Entry	NH_4OAc (mol%)	Time (min)	Yield [a] (%)
1	2	30	70
2	5	30	78
3	**10**	**30**	**90**
4	15	30	84
5	20	30	80

[[a] Experiments were performed under ultrasonic-assisted method.]

The target quinoline structure fused with pyridine compounds was characterized by ^1H NMR, ^{13}C NMR, IR, and Mass spectrometry analysis. The two peaks observed in the IR spectra of the compounds near 3300 cm^{-1} and 2200 cm^{-1} confirmed that the amine ($-NH_2$) group and CN group were present in all compounds. The second sharp peak was observed at 1600-1650 cm^{-1}, indicating that –C=N stretching for aromatic compounds, and one peak observed near 1500-1500 cm^{-1} confirmed that –NH group presence in final molecules. In ^1H NMR spectra, one sharp peak singlet for one proton of a secondary amine was observed near 6.96 δ ppm two protons for the primary $–NH_2$ group. According to the presence of these peaks, we have confirmed the entire compounds in which the primary $–NH_2$ and –NH groups are present. We have also confirmed NMR by D_2O NMR exchange to prove the removal of amine peak in NMR. ^{13}C NMR spectrum explained the confirmation of carbon atoms in the assigned particular molecule of the synthesized compounds.

Biological evaluation:

The final adduct **TF-1** to **TF-8** were screened *in-vitro* activity for their antibacterial and antifungal strain. We have used the broth dilution technique to determine the minimum inhibitory concentration (MIC) of the synthesized compounds **TF-1** to **TF-8**. For that, we have used the bacterial strain of *Staphylococcus aureus* MTCC 96 and *Streptococcus pyogenes* MTCC 442 for a Gram-positive group. We have also used *Escherichia colli* MTCC 443 and *Pseudomonas aeruginosa* MTCC 1688 for the bacterial strain's Gram-negative group. For the evaluation study of antifungal activity, we have used *Aspergillus niger* MTCC 282, *Candida albicans* MTCC 227, and *Aspergillus clavatus* MTCC 1323 as a fungal strain. The MIC values of the tested compounds are summarized in **Table 4**.

Table 4. Antimicrobial activity of final compounds (TF-1 to TF-8)

Sr. No.	**Antibacterial activity**				**Antifungal activity**		
	Minimum inhibitory concentration µg/mL				**Minimum inhibitory concentration µg/mL**		
	Gram +*ve* Bacteria		**Gram -*ve* Bacteria**				
	S. aureus	***S. pyogenus***	***E. coli***	***P. aeruginosa***	***C. albicans***	***A. niger***	***A. clavatus***
TF-1	200	200	250	250	**100**	250	500
TF-2	200	**100**	500	250	500	250	500
TF-3	**100**	250	200	500	500	1000	250
TF-4	250	**100**	250	250	250	1000	>1000
TF-5	**100**	250	250	500	200	**100**	500
TF-6	**100**	200	200	250	250	200	500
TF-7	**100**	200	**100**	250	500	250	250
TF-8	**100**	250	200	500	500	1000	250
A.	250	100	100	100	-	-	-
Cl.	50	50	50	50	-	-	-
C.	50	50	25	25	-	-	-
N.	-	-	-	-	100	100	100
G.	-	-	-	-	500	100	100

A: Ampicillin, **Cl**: Chloramphenicol, **C**: Ciprofloxacin, **N**: Nystatin, **G**: Griseofulvin

The evaluation study of the final adduct for antimicrobial activity data screened that compounds **TF-1, TF-2, TF-3, TF-4, TF-5, TF-6, TF-7,** and **TF-8** are shown excellent activity. Compounds **TF-2, TF-3,**

TF-4, TF-5, TF-6, TF-7, and **TF-8** gave antibacterial activity (100 μg/mL) compared with ampicillin and chloramphenicol against Gram-positive bacteria. The compounds **TF-7** have shown good antibacterial activity (100 μg/mL) against Gram-negative compared to nystatin and griseofulvin as standard drugs. The compound **TF-1** and **TF-5** gave moderated activity for antifungal strain.

In summary, we have developed a powerful one-pot three-component greener protocol to provide efficient and environmentally benign greener synthesis of 2-amino-4-(substituted quinoline)-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitriles from readily available starting materials. We have used a cheaper and nontoxic NH_4OAc catalyst to improve the desired compounds in excellent yield. We have used ultrasonic-irradiation synthesis techniques to minimize the impurity and reaction time compared to the conventional heating method. Furthermore, we have evaluated their antimicrobial activity. The *in-vitro* antimicrobial study of newly synthesized adducts indicates that the entire compound shows good activity against different microbes.

EXPERIMENTAL

Materials and Methods:

In the synthesis, we have used purchased chemicals without further purification. Reactions were monitored by (TLC) thin-layer chromatography on silica gel-G plates (G60 F254 (Merck)) of 0.5 mm thickness, visualizing with ultraviolet light (254 and 365 nm). IR data were recorded on a Shimadzu FT-IR-8400 instrument using DRS (diffusive reflectance system) method and are reported in cm^{-1} (KBr). NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer (400 MHz for ^1H NMR and 101 MHz for ^{13}C NMR), respectively, in deuterated solvents like DMSO-d_6 and chemical shifts are referenced to the solvent residual signals for tetramethylsilane. Ultrasonic irradiation experiments were carried out in a Digital ultrasound cleaner (LMUC-12) with an output power of 300 W and frequency range of 20-60 kHz. A ruby thermometer monitored the control of reaction temperature. Mass spectra were recorded on a Shimadzu GC-MS-QP-2010 mass spectrometer in ESI (70eV) model using direct inlet probe technique, and *m/z* is reported in atomic units per elementary charge.

Antibacterial assay

We have to use the broth dilution method for the evaluation of antibacterial activity. It is one of the non-automated *in-vitro* bacterial susceptibility tests. This technique shows that quantitative result for the amount of antimicrobial agents that is needed to inhibit growth of specific microorganisms. The synthesized compounds were screened for their antibacterial activity in triplicate sets against these bacteria at different concentrations of 1000, 500, 250, and 200 μg/mL. The drugs which were found to be active in primary analysis were further diluted and evaluated. 10 μg/mL suspensions were further

inoculated on appropriate media and the growth was noted after one or two days. Minimum inhibitory concentration is the lowest concentration, which showed no growth of microbes after spot subculture for each drug. The test mixture should contain 100 μg/mL

Here, in our case for evaluation of antibacterial activity, we have to use *Staphylococcus aureus* MTCC 96 and *Bacillus subtilis* MTCC 441 from Gram-positive group of bacterial strain and *Escherichia colli* MTCC 443 and *Salmonella typhimurium* MTCC 98 from Gram-negative group of bacterial strain. The strains were procured from department of microbiology, R.K. University, Rajkot.

Antifungal assay

The newly prepared compounds (**TF-1** to **TF-8**) were screened for their antifungal activity as primary screens in six sets against *C. albicans*, *A. niger*, and *A. clavatus* at various concentrations of 1000, 500, and 250 μg/mL. The primary active compounds were similarly diluted to obtain 200, and 100 μg/mL concentrations for secondary screening to test in a second set of dilutions against all fungi. The fungal activity of each compound was compared with nystatin as a standard drug, which showed 100, 100, and 100 μg/mL MIC against *C. albicans*, *A. niger*, and *A. clavatus*, respectively.

Here are in our case evaluation of antifungal activity, we have to use *Aspergillus niger* MTCC 282 and *Aspergillus clavatus* MTCC 1323 as a fungal strains. The strains were procured from department of microbiology, R.K. University, Rajkot.

General procedure for the synthesis of 2-amino-4-(substituted quinoline)-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitriles (TF-1 to TF-8)

Ultrasonic-irradiation (US) method: Take a mixture of 2-aminobenzimidazole (2.0 mmol), malononitrile (2.0 mmol) and 2-chloroquinoline-3-carbaldehyde (2.0 mmol) in EtOH (10 mL) with ammonium acetate in a catalytic amount. The reaction mass was placed in the ultrasound and irradiated with 100 W radiation for 30 min. After completing the reaction (checked by TLC), the resulting solution was cooled to room temperature. Filtered the solid formed and washed with water. The crude product was recrystallized from 95% EtOH to give a pure solid product. (**TF-1** to **TF-8**); yield (80%-94%).

Conventional heating (CH) method: Solution of an equimolar mixture of 2-aminobenzimidazole (2.0 mmol), malononitrile (2.0 mmol) and 2-chloroquinoline-3-carbaldehyde (2.0 mmol) in EtOH (10 mL) with ammonium acetate was refluxed for 1-1.5 h. After completion of the reaction (checked by TLC), the resulting solution was cooled to room temperature. Filtered the solid formed and washed with water. The crude product was recrystallized from 95% EtOH to afford a pure solid product. (**TF-1** to **TF-8**); yield (64%-76%).

2-Amino-4-(2-chloroquinolin-3-yl)-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile (TF-1):

White solid; Yield: US, 90%, CH, 80%, MP: 198-200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.55 (s, 2H amine), 8.11 (d, *J* = 8.4 Hz 1H Ar-H), 8.00 (d, *J* = 8.8 Hz 1H Ar-H), 7.86 (m, 1H), 7.70 (m, 2H), 7.26 (d, *J* = 7.6 Hz 1H Ar-H), 7.14 (m, 1H), 7.03 (m, 3H), 5.81 (s, 1H).; ^{13}C NMR (101 MHz, DMSO-d_6): δ 151.64, 149.78, 148.58, 146.50, 141.50, 137.90, 131.80, 129.72, 129.30, 127.85, 126.38, 124.77, 123.09, 120.12, 118.50, 116.18, 112.50, 60.32, 51.42; IR(KBr, ν_{max}, cm^{-1}): 3333 (-NH_2, str., amine), 3147 (C-H, str., alkene), 2216 (-CN, str., Ar), 1649 (C=N, str. Ar), 1570 (C=C, str., Ar), 1085 (C-N str. Ar), 1043 (=C-H bend.), 698 (C-Cl, str.); Exact Mass $C_{20}H_{13}ClN_6$ (*m/z*): 372.1, Found: 372.1

2-Amino-4-(2,7-dichloroquinolin-3-yl)-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile (TF-2):

White solid; Yield: US, 89%, CH, 74%, MP: 208-210 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.64 (s, 1H amine), 8.64 (s, 1H), 8.11 (m, 2H Ar-H), 7.85 (m, 1H), 7.69 (m, 2H), 7.24 (m, 4H), 5.72 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 151.24, 149.75, 148.60, 146.84, 141.58, 137.94, 131.70, 129.75, 129.31, 127.89, 126.39, 124.97, 123.30, 120.17, 118.06, 116.24, 112.30, 60.20, 51.32; IR(KBr, ν_{max}, cm^{-1}): 3342 (-NH_2, str., amine), 3063 (C-H, str., alkene), 2212(-CN, str., Ar), 1631 (C=N, str. Ar), 1568 (C=C, str., Ar), 1550 (-NH., ben., Ar), 1068 (C-N str. Ar), 997 (=C-H bend.), 846 (*p*-disubstituted), 671 (C-Cl, str.); Exact Mass $C_{20}H_{12}Cl_2N_6$ (*m/z*): 406.1, Found: 406.1

2-Amino-4-(2-chloro-7-methylquinolin-3-yl)-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile (TF-3):

Brown solid; Yield: US, 92%, CH, 77%, MP: 200-202 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.52 (s, 1H amine), 8.48 (m, 1H), 7.98 (d, *J* = 7.4 Hz 1H Ar-H), 7.78 (s, 1H), 7.70 (d, *J* = 8.0 Hz 1H Ar-H), 7.52 (d, *J* = 8.4 Hz 1H Ar-H), 7.26 (d, *J* = 8.0 Hz 1H Ar-H), 7.14 (T, *J* = 8.0, 7.2 Hz 1H Ar-H), 7.05 (m, 1H), 6.96 (m, 2H), 5.79 (s, 1H), 2.54 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 151.70, 149.71, 148.65, 146.80, 141.58, 137.91, 131.70, 129.75, 129.31, 127.89, 126.39, 124.97, 123.39, 120.02, 118.56, 116.14, 112.50, 60.23, 51.51, 21.40; IR(KBr, ν_{max}, cm^{-1}): 3336 (-NH_2, str., amine), 3068 (C-H, str., alkene), 2216 (-CN, str., Ar), 1633 (C=N, str. Ar), 1595 (C=C, str., Ar), 1546 (-NH., ben., Ar), 1072 (C-N str. Ar), 1022 (=C-H bend.), 827 (*p*-disubstituted), 690 (C-Cl, str.); Exact Mass $C_{21}H_{15}ClN_6$ (*m/z*): 386.1, Found: 386.0

2-Amino-4-(6-bromo-2-chloroquinolin-3-yl)-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile (TF-4):

Brown solid; Yield: US, 94%, CH, 75%, MP: 240-242 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.60 (s, 1H amine), 8.60 (s, 1H), 8.10 (m, 2H Ar-H), 7.86 (m, 1H), 7.68 (m, 2H), 7.28 (m, 4H), 5.70 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 151.75, 149.80, 148.62, 146.80, 141.54, 137.90, 131.78, 129.76, 129.29, 127.88, 126.38, 124.90, 123.32, 120.16, 118.16, 116.28, 112.30, 60.22, 51.30; IR(KBr, ν_{max}, cm^{-1}): 3340 (-NH_2, str., amine), 3066 (C-H, str., alkene), 2210(-CN, str., Ar), 1628 (C=N, str. Ar), 1560 (C=C, str.,

Ar), 1552 (-NH., ben., Ar), 1060 (C-N str. Ar), 993 (=C-H bend.), 840 (*p*-disubstituted), 672 (C-Cl, str.); Exact Mass $C_{20}H_{12}BrClN_6$ (*m/z*): 450.0, Found: 450.0

2-Amino-4-(2-chloro-6-methylquinolin-3-yl)-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile (TF-5):

Brown solid; Yield: US, 92%, CH, 78%, MP: 198-202 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.50 (s, 1H amine), 8.45 (m, 1H), 7.98 (d, *J* = 7.4 Hz 1H Ar-H), 7.76 (s, 1H), 7.70 (d, *J* = 8.0 Hz 1H Ar-H), 7.52 (d, *J* = 8.4 Hz 1H Ar-H), 7.26 (d, *J* = 8.0 Hz 1H Ar-H), 7.14 (T, *J* = 8.0, 7.2 Hz 1H Ar-H), 7.05 (m, 1H), 6.96 (m, 2H), 5.79 (s, 1H), 2.52 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 151.71, 149.65, 148.80, 146.58, 141.56, 137.90, 131.72, 129.75, 129.31, 127.89, 126.39, 124.97, 123.39, 120.02, 118.58, 116.10, 112.50, 60.33, 51.50, 21.42; IR(KBr, ν_{max}, cm^{-1}): 3330 (-NH_2, str., amine), 3062 (C-H, str., alkene), 2220 (-CN, str., Ar), 1630 (C=N, str. Ar), 1589 (C=C, str., Ar), 1542 (-NH., ben., Ar), 1062 (C-N str. Ar), 1034 (=C-H bend.), 688 (C-Cl, str.); Exact Mass $C_{21}H_{15}ClN_6$ (*m/z*): 386.1, Found: 386.0

2-Amino-4-(2-chloro-8-methylquinolin-3-yl)-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile (TF-6):

Brown solid; Yield: US, 80%, CH, 64%, MP: 202-204 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.43 (s, 1H amine), 7.96 (d, *J* = 8.4 Hz 1H Ar-H), 7.78 (s, 2H), 7.68 (d, *J* = 8.0 Hz 1H Ar-H), 7.53 (3, 2H Ar-H), 7.29 (d, *J* = 8.0 Hz 1H Ar-H), 7.18 (m, 1H Ar-H), 7.09 (m, 2H), 5.79 (s, 1H), 2.67 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 151.71, 149.65, 148.80, 146.58, 141.91, 137.70, 131.75, 129.31, 129.09, 127.39, 126.97, 124.70, 123.02, 120.56, 118.14, 116.50, 112.58, 60.20, 51.45, 21.83; IR(KBr, ν_{max}, cm^{-1}): 3332 (-NH_2, str., amine), 3060 (C-H, str., alkene), 2224 (-CN, str., Ar), 1635 (C=N, str. Ar), 1585 (C=C, str., Ar), 1540 (-NH., ben., Ar), 1060 (C-N str. Ar), 1034 (=C-H bend.), 680 (C-Cl, str.); Exact Mass $C_{21}H_{15}ClN_6$ (*m/z*): 386.1, Found: 386.0

2-Amino-4-(2-chloro-6-methoxyquinolin-3-yl)-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile (TF-7):

Brown solid; Yield: US, 85%, CH, 70%, MP: 206-208 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.56 (s, 1H amine), 8.47 (m, 1H), 7.94 (d, *J* = 7.4 Hz 1H Ar-H), 7.80 (s, 1H), 7.78 (d, *J* = 8.0 Hz 1H Ar-H), 7.50 (d, *J* = 8.4 Hz 1H Ar-H), 7.24 (d, *J* = 8.0 Hz 1H Ar-H), 7.12 (T, *J* = 8.0, 7.2 Hz 1H Ar-H), 7.08 (m, 1H), 6.78 (m, 2H), 5.64 (s, 1H), 3.80 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 151.97, 149.84, 148.60, 146.72, 141.54, 137.41, 131.14, 129.65, 129.49, 127.82, 126.42, 124.40, 123.24, 120.04, 118.50, 116.04, 112.20, 60.28, 51.56, 39.40; IR(KBr, ν_{max}, cm^{-1}): 3325 (-NH_2, str., amine), 3124 (C-H, str., alkene), 2225 (-CN, str., Ar),1629 (C=N, str. Ar), 1568 (C=C, str., Ar), 1550 (-NH., ben., Ar), 1072 (C-N str. Ar), 1008 (=C-H bend.), 684 (C-Cl, str.); Exact Mass $C_{21}H_{15}ClN_6O$ (*m/z*): 402.1, Found: 402.0

2-Amino-4-(2,6-dichloroquinolin-3-yl)-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonitrile (TF-8):

White solid; Yield: US, 84%, CH, 68%, MP: 208-212 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.62 (s, 1H amine), 8.62 (s, 1H), 8.12 (m, 2H Ar-H), 7.82 (m, 1H), 7.70 (m, 2H), 7.20 (m, 4H), 5.74 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 151.20, 149.74, 148.64, 146.88, 141.54, 137.90, 131.75, 129.71, 129.30, 127.87, 126.37, 124.99, 123.34, 120.17, 118.08, 116.20, 112.34, 60.22, 51.31; IR(KBr, ν_{max}, cm^{-1}): 3342 (-NH_2, str., amine), 3063 (C-H, str., alkene), 2212 (-CN, str., Ar), 1631 (C=N, str. Ar), 1568 (C=C, str., Ar), 1550 (-NH., ben., Ar), 1068 (C-N str. Ar), 997 (=C-H bend.), 846 (*p*-disubstituted), 671(C-Cl, str.); Exact Mass $C_{20}H_{12}Cl_2N_6$ (*m/z*): 406.1, Found: 406.1

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