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Post Groebke–Blackburn multicomponent protocol: Synthesis of new polyfunctional imidazo[1,2-a]pyridine and imidazo[1,2-a]pyrimidine derivatives as potential antimicrobial agents

Taleb H. Al-Tel [a,b,*], Raed A. Al-Qawasmeh [c]

[a] College of Pharmacy, University of Sharjah, University City Road, P.O. Box 27272, Sharjah, United Arab Emirates
[b] Sharjah Institute for Medical Research-Cancer Division, University of Sharjah, 27272, Sharjah, United Arab Emirates
[c] Department of Chemistry, University of Jordan, Amman 1194, Jordan

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ABSTRACT

New antimicrobial agents [imidazo[1,2-a]pyridine and imidazo[1,2-a]pyrimidine] have been synthesized. Their antimicrobial activities were conducted against various Gram-positive and Gram-negative bacteria including *Staphylococcus aureus*. Compounds **5d**, **7a**, **10a**, **11a** and **12a** proved to efficiently inhibit the growth of all the Gram-positive and Gram-negative strains investigated. Results of this study showed that the nature of the substituents on the armed phenyl groups determined the extent of the activity of the fused imidazopyridine and/or imidazopyrimidine derivatives. Preliminary structure–activity observations revealed that groups with positive sigma and positive bi values (e.g. **5d**, **6c**, **12a**, **12d**) were significantly more active compared to other bioisosteres (e.g. **5b**). Furthermore, increasing the molar refractivity of the substitution pattern (e.g. **5b**, **6b** and **6d**) sharply decreased the antibacterial activity.

1. Introduction

Infections caused by multi-drug resistant bacteria are of a major health concern worldwide. Particularly important, are infections caused by the Gram-positive bacteria *Staphylococcus aureus* and species of the genus *Enterococcus*, due to increasing incidence of infections caused by these microorganisms in hospitals and their ability of developing resistance to multiple antibiotics [1].

Patients undergoing organ transplants, anticancer chemotherapy or long treatment with antimicrobial agents, as well as patients with AIDS are immuno suppressed and very susceptible to life threatening systemic microbial infections by Candidiasis, Cryptococcosis and Aspergillosis. New antibacterial agents to treat infections caused by these Gram-positive bacteria have recently been introduced, including the semi-synthetic streptogramine, quinupristin/dalfopristin, daptomycin, the synthetic oxazolidinone linezolid, and tigecycline [2,3]. For the past several years, vancomycin has been considered the last line of defense against Gram-positive infections [4,5]. Such new treatment options are welcome additions to the arsenal against these invaders; however, the identification of intrinsically resistant strains, and the serious side effects caused by some of these new agents, makes the development of a diversified pipeline of antimicrobials, a necessity [6]. These observations place a new emphasis on the need to search for alternative new and more effective antimicrobial agents with a broad spectrum of activities. In this regard, extensive synthesis and design of new structural motifs in order to overcome the aforementioned problems and improve broad spectrum antimicrobial activity are highly desirable. The engine of such a strategy, however, will be driven by the development of novel scaffolds that will lead to a chemical space of skeletally diverse molecules [7–9].

As part of an ongoing program aiming at natural product synthesis and preparation of medicinally significant structures [10–12], we report herein an efficient process for the construction of polyfunctionalized imidazopyridine, and pyrimidine derivatives and their antibacterial evaluation. Recent studies from many laboratories, implicate the role of these scaffolds in the treatment of many of the most common human diseases, including diabetes [13], cancers [14], infection by microorganisms [15], and an array of neurological syndromes [16]. Furthermore, a literature search

* Corresponding author. College of Pharmacy, University of Sharjah, University City Road, P.O. Box 27272, Sharjah, United Arab Emirates. Tel.: +971 501732950; fax: +971 6 5585812.
E-mail address: taltal@sharjah.ac.ae (T.H. Al-Tel).

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indicated that benzimidazoles [17–19], oxadiazoles [20–22] and phenyl imidazoles [23,24] with different substitution patterns possess wide range of antimicrobial properties.

2. Results and discussion

2.1. Chemistry

We recently reported a protocol for the combination of Groebke–Blackburn/Ugi MCRs (multicomponent reaction) to achieve higher order seven component reaction (6CR) in one-pot [25]. Positioning the Groebke–Blackburn reaction [26–29] before the Ugi reaction [7,30], was the most straightforward because the former could carry with it an unprotected carboxylic acid group. Such a process involved the incorporation of a functional group in one of the primary inputs of the first MCR that does not participate in the reaction (e.g. carboxylic acid group as in our MCRs), but does react as one of the radical components in the second MCR. We next strove to arrive at the title motifs and study their growth inhibitory activity against Gram-positive bacteria *S. aureus*, *E. faecalis* and *Bacillus megaterium* and Gram-negative bacteria *E. coli*, *P. aeruginosa* and *E. aerogenes*. These synthetic motifs were obtained *via* the classical [4+1]-cycloaddition Groebke–Blackburn 3CR protocol of an aldehyde, aminopyridine derivatives and an isocyanide. More importantly, the primary input of this reaction required a carboxylic acid handle in order for the post Groebke–Blackburn product to be capable of being further differentiated and eventually integrated to deliver the intended scaffolds. Scheme 1 shows the general synthetic strategy followed for the arrival at compounds **5a**–**12e**. We started our plan by using 5-carboxy-2-aminopyridine (**2**) as the main component, which in turn, was subjected to condensation with *p*-substituted benzaldehydes **3a**–**g**, in the presence of a catalytic amount of $Sc(OTf)_3$ at rt for 45 min and subsequent reaction with phenyl isocyanide (**1**) to deliver the imidazopyridines **4a**–**g**. Having secured pure amounts from compounds **4a**–**g**, our synthetic plan contemplated three types of scaffolds, **5**, **6** and **7** as indicated in Scheme 1. Thus, derivatives of type **5** were prepared through the coupling between **4a**–**g** and phenylene diamine using TBTU (O-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate) and DIPEA (*N*,*N*-diisopropylethylamine) in DMF at 0 °C. After work up, the delivered amides from this step were refluxed in acetic acid for 2 h to produce, after chromatographic purifications, compounds **5a**–**g** (Table 1).

For the synthesis of substituted phenyl imidazoles **6a**–**d**, the desired imidazopyridines **4a**–**d** were reacted with the proper α-bromoacetophenone using DIPEA at 0 °C in DMF. After work up, the crude α-ketoesters were subjected without further purification to standard condensation protocol with ammonia using ACO_2NH_4 in refluxing acetic acid. After silica gel column chromatography, compounds **6a**–**d** (Table 1) were produced.

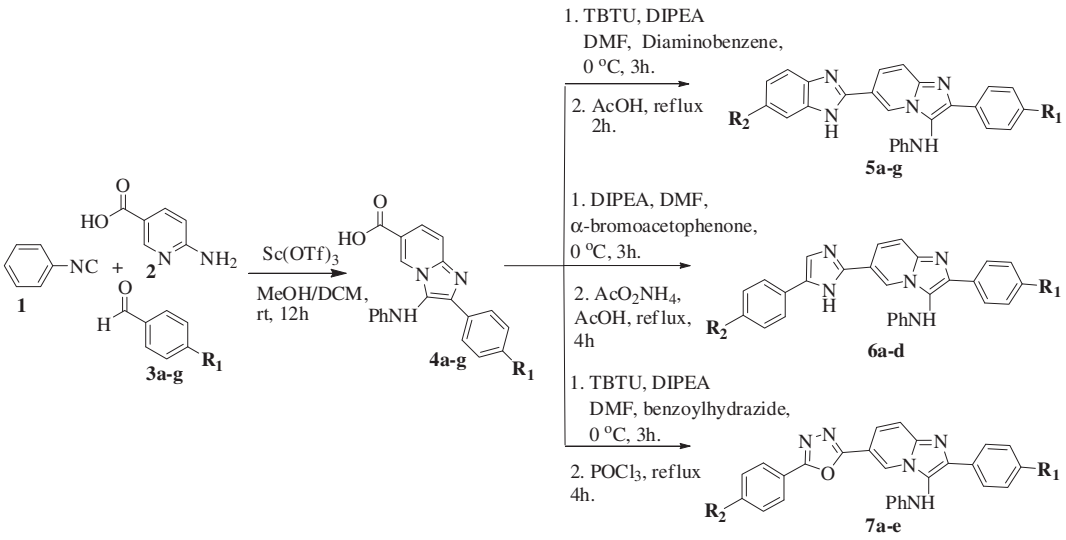
The last scaffolds, the oxadiazoles **7a**–**d** (Table 1), were visited after the intended derivatives from **4a**–**e** were coupled with the desired benzoylhydrazide using TBTU and DIPEA in DMF at 0 °C followed by reaction with $POCl_3$.

After the successful synthesis of the above described derivatives, the scope of these methodologies was extended toward the synthesis of imidazopyrimidine scaffolds (Scheme 2). In this regard, 5-carb oxy-2-aminopyrimidine (**8**) was chosen as the primary input. Following the same reaction sequence, compounds **10a**–**12e** (Table 1) were produced from the [4+1]-cycloaddition intermediates **9a**–**e**.

2.2. Biology

The antimicrobial activities of the compounds **5a**–**12e** were tested against Gram-positive bacteria *S. aureus*, *E. faecalis* and *B. megaterium* and Gram-negative bacteria *E. coli*, *P. aeruginosa* and *E. aerogenes*. Minimum inhibitory concentration (MIC) was measured as described in the experimental section. Cefixime, amoxicillin and vancomycin were used as positive controls. Solutions of different concentrations of cefixime, vancomycin or amoxicillin and compounds **5a**–**12e** were prepared by dissolving them in DMSO. Eleven serial dilutions were prepared by reducing the concentration of the stock solutions to half their original values, with an initial concentration of (200 μg/ml). Microorganism's suspensions at 5×10^5 CFU (colony forming units/mL) were inoculated into the wells. The plates were incubated at 37 °C for 24 h. The MIC values were determined using a turbidity test [31–33]. The results of *in vitro* antimicrobial activities of the synthesized compounds are listed in Table 1.

The results showed a wide range of antimicrobial activities among the different derivatives tested with MIC values, defined as the lowest concentration at which no visible growth is observed, from >127 μg/ml to 0.5 μg/ml (Table 1) with the most active compounds belonging to compounds having bromo–flouro substituents. Derivatives **5d**, **6a**, **6c**, **7a**, **10a**, **10b**, **11a**, **11b**, and **12b**

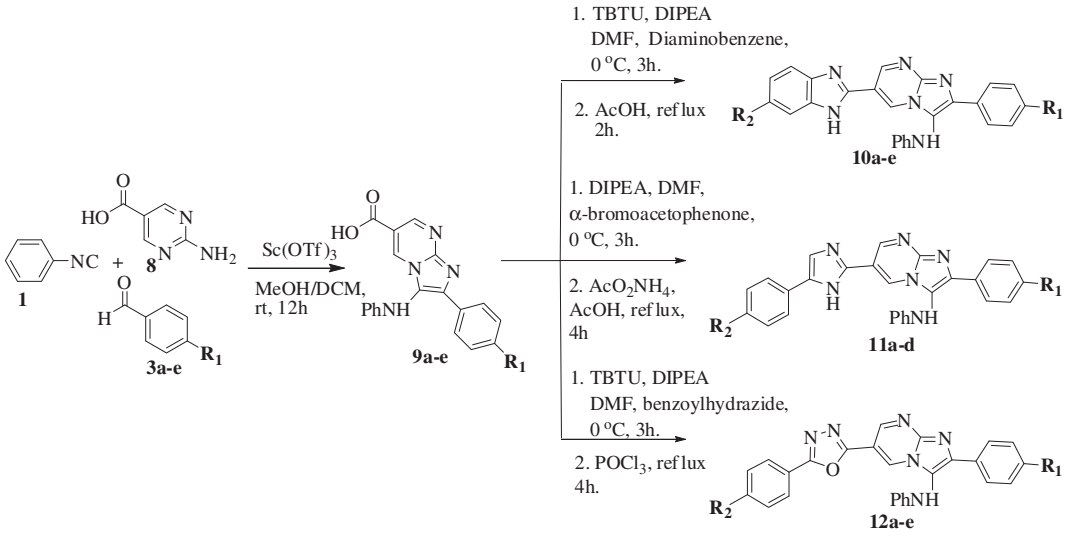


Scheme 1. Synthesis of imidazopyridine derivatives **5a**–**7e**.

Table 1
In vitro antimicrobial activity (MIC μg/ml) of compounds **5a**–**12e**.

Compd	R1	R2	*E. coli*	*P. aeruginosa*	*E. aerogenes*	*S. aureus*	*E. faecalis*	*B. megaterium*
5a	Br	NO_2	11.32 ± 1.34	14.51 ± 2.12	12.85 ± 2.17	10.32 ± 1.79	13.36 ± 2.41	17.53 ± 2.32
5b	CH_3	OPh	34.77 ± 3.80	45.43 ± 3.65	57.33 ± 4.75	54.86 ± 4.32	46.51 ± 4.21	65.54 ± 6.75
5c	CH_3	Br	3.18 ± 0.17	5.22 ± 0.34	7.15 ± 1.20	5.11 ± 0.89	6.28 ± 1.11	13.96 ± 1.72
5d	Br	F	2.15 ± 0.11	3.44 ± 0.13	2.05 ± 0.10	1.51 ± 0.09	5.23 ± 0.45	10.25 ± 1.42
5e	OPh	F	10.71 ± 1.55	12.44 ± 1.83	11.54 ± 1.26	12.13 ± 1.21	15.32 ± 2.27	21.61 ± 3.64
5f	Br	OPh	31.83 ± 3.14	41.13 ± 3.78	58.45 ± 5.35	56.17 ± 5.32	44.71 ± 4.65	58.67 ± 5.14
5g	Br	CH_3	10.34 ± 0.97	13.37 ± 1.09	11.79 ± 1.15	9.51 ± 0.76	13.64 ± 1.31	18.58 ± 1.96
6a	Br	F	1.33 ± 0.08	2.12 ± 0.09	1.55 ± 0.05	0.72 ± 0.04	3.17 ± 0.15	8.34 ± 0.41
6b	OPh	Br	12.21 ± 1.31	11.78 ± 1.34	10.72 ± 1.14	10.23 ± 1.00	13.72 ± 1.35	19.85 ± 2.13
6c	Br	Cl	1.42 ± 0.08	2.52 ± 0.12	1.17 ± 0.07	0.93 ± 0.02	2.96 ± 0.12	9.13 ± 0.52
6d	Br	OPh	33.28 ± 3.32	44.29 ± 3.11	53.41 ± 3.42	58.37 ± 4.18	39.64 ± 3.31	53.16 ± 4.11
7a	Br	F	1.11 ± 0.03	2.43 ± 0.10	0.85 ± 0.04	0.51 ± 0.008	1.57 ± 0.02	4.97 ± 0.13
7b	OPh	F	11.72 ± 1.22	9.64 ± 1.00	8.42 ± 1.21	11.13 ± 1.31	12.56 ± 1.61	17.44 ± 1.87
7c	CH_3	NO_2	13.42 ± 1.12	12.55 ± 1.41	10.17 ± 1.14	9.85 ± 1.46	11.38 ± 1.50	15.47 ± 1.71
7d	Br	CH_3	12.37 ± 113	10.19 ± 0.84	11.27 ± 1.19	12.27 ± 0.78	11.79 ± 1.18	16.55 ± 2.11
7e	Br	NO_2	7.37 ± 0.61	5.45 ± 0.61	4.12 ± 0.52	6.36 ± 0.31	8.22 ± 0.73	12.73 ± 1.12
10a	Br	F	2.29 ± 0.11	2.85 ± 0.12	2.25 ± 0.17	1.23 ± 0.05	6.64 ± 0.21	11.74 ± 1.22
10b	Br	Cl	2.78 ± 0.14	2.55 ± 0.16	2.75 ± 0.19	1.84 ± 0.12	5.87 ± 0.34	13.73 ± 1.51
10c	CH_3	F	3.44 ± 0.13	4.72 ± 0.25	6.18 ± 1.10	6.32 ± 0.76	5.76 ± 1.18	17.16 ± 2.13
10d	OPh	F	10.53 ± 1.78	7.38 ± 1.25	6.12 ± 1.13	9.43 ± 1.42	10.39 ± 1.45	19.78 ± 2.31
10e	Br	NO_2	11.66 ± 1.41	12.23 ± 1.49	10.64 ± 1.21	9.32 ± 0.81	11.45 ± 0.91	15.44 ± 1.89
11a	Br	F	1.15 ± 0.06	2.34 ± 0.07	1.11 ± 0.04	0.63 ± 0.01	4.21 ± 0.11	9.17 ± 0.55
11b	Br	Cl	3.11 ± 0.12	1.82 ± 0.13	1.89 ± 0.09	1.76 ± 0.10	4.28 ± 0.14	11.64 ± 0.45
11c	Br	CH_3	8.11 ± 0.99	11.45 ± 0.76	10.85 ± 1.23	9.49 ± 0.77	11.67 ± 1.10	15.56 ± 1.51
11d	Br	NO_2	5.33 ± 0.56	7.81 ± 0.74	9.33 ± 1.23	4.22 ± 0.57	9.61 ± 0.88	17.44 ± 2.11
12a	Br	F	1.33 ± 0.01	1.87 ± 0.01	0.94 ± 0.06	0.64 ± 0.03	1.92 ± 0.07	5.45 ± 0.15
12b	CH_3	F	2.78 ± 0.11	3.65 ± 0.13	5.29 ± 0.90	5.47 ± 0.85	4.58 ± 0.39	15.29 ± 1.78
12c	Br	NO_2	3.12 ± 0.14	4.45 ± 0.31	2.23 ± 0.15	3.35 ± 0.17	6.18 ± 0.25	11.22 ± 1.59
12d	Br	Cl	2.34 ± 0.09	1.56 ± 0.06	3.16 ± 0.23	2.45 ± 0.18	5.37 ± 0.32	8.45 ± 0.78
12e	Br	CH_3	8.56 ± 1.23	7.64 ± 0.79	6.43 ± 0.26	5.31 ± 0.45	8.71 ± 0.87	13.61 ± 1.11
Amoxicillin			16.43 ± 1.12	14.53 ± 1.22	3.65 ± 0.31	13.32 ± 0.92	1.22 ± 0.07	2.75 ± 0.15
Cefixime			2.34 ± 0.10	17.23 ± 1.31	28.16 ± 1.53	33.87 ± 2.11	27.92 ± 1.13	127.76 ± 5.78
Vancomycin			6.65 ± 0.33	23.47 ± 1.75	0.52 ± 0.09	2.75 ± 0.21	4.21 ± 0.42	6.37 ± 0.38

exhibited potent activities against *E. coli*, *E. aerogenes* and *S. aureus* compared to the control antibiotics amoxicillin and cefixime. Some qualitative structure–activity relationships could be concluded from Table 1. The superiority of the compounds having R_1 = bromine at the phenyl moiety resident on the imidazopyridine ring and a halogen substituent on the benzimidazole rings (e.g. **5d**, **6a**, **6c**, **12a**) is obviously evident from Table 1. Furthermore, if R_1 is a methyl, and R_2 is a halogen (e.g. **5c**, **10c** and **12b**) the activity is reduced to about three folds in all series. Interestingly, introduction of a phenoxy group (e.g. **5b**, **5e**, **6b**, **7b**, **10d**) at either side of our motifs demolishes the activities of these compounds. Another important finding is the activity difference between the three different scaffolds resident on the pyridine and pyrimidine rings. Clearly, compounds having fused benzimidazole group (e.g. **5d**, **10a**) are less active than compounds having substituted phenyl imidazole moiety (e.g. **6a**, **11a**). The latter in turn is less active than the substituted phenyl oxadiazole handle (e.g. **7a**, **12a**). Among the most active halogenated derivatives (where R_1 and R_2 are halogens), is the oxadiazole motifs which are two folds more active than the imidazole analogs. The latter in turn are more potent than the



Scheme 2. Synthesis of imidazopyrimidine derivatives **10a**–**12e**.

benzimidazole counter parts. It is worth noting that all the derivatives are more potent against *B. megaterium* compared to cefixime. Moreover, all of the synthesized scaffolds showed more activity against *E. coli* (except **5b**, **5f** and **6d**) compared to amoxicillin. However, none of these motifs exhibited good activity against *B. megaterium* compared to amoxicillin. Further investigations in this direction are currently under progress in our laboratories.

3. Conclusions

In summary, we have synthesized and introduced new antimicrobial agents with potent activity against various Gram-negative and Gram-positive bacterial strains. Many of the synthesized motifs showed potent antimicrobial activity compared to the control antibiotics amoxicillin and cefixime. Characterization of the antimicrobial spectrum of the synthesized compounds (e.g. **7a**, **10a**, **11a** and **12a**), as shown in Table 1, indicating a broad spectrum of antibacterial activity against the tested strains. These results form the foundation for further investigations in our laboratories.

4. Experimental section

4.1. General methods

All reagents were used as purchased from commercial suppliers without further purification. The reactions were carried out in oven dried or flamed graduated vessels. Solvents were dried and purified by conventional methods prior use. Flash column chromatography was performed with Silica gel 60, 0.040–0.063 mm (230–400 mesh). Aluminum backed plates pre-coated with silica gel 60 (UV254) were used for thin layer chromatography. ^{1}H, ^{13}C spectra were recorded on 300 MHz/75 MHz spectrometer. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Chemical shifts (δ) are given in ppm relative to the resonance of their respective residual solvent peak, $CHCl_3$ (7.27 ppm, ^{1}H; 77.16 ppm, the middle peak, ^{13}C). Elemental analysis was carried out at the University of Jordan instrument. High and low resolution mass spectroscopic analyses were conducted at the University of Jordan using positive ion mode by Electrospray Ionization (ESI). The samples were dissolved in acetonitrile, diluted in spray solution (methanol/water 1:1 v/v + 0.1% formic acid) and infused using a syringe pump with a flow rate of 2 μL/min. External calibration was conducted using Arginine cluster in a mass range *m*/*z* 175–871.

4.2. Chemistry

4.2.1. General experimental procedure A for the synthesis of compounds *4a–g* and *9a–e*

A mixture of aminopyridine (3.0 mmol) in MeOH-DCM (2:3, 15.0 mL) and aldehyde (3.0 mmol) containing 5 mol% of $Sc(OTf)_3$ was stirred for 1 h at room temperature, followed by the addition of 3 mmol of the phenyl isocyanide, and the mixture was stirred for another 12 h at rt. Then 1 mL of hexane was added and the resulting yellowish solid was filtered, washed three times with hexane–ethyl acetate mixture (5:1, 20 mL) and triturated with ethyl acetate–hexane. The crude product was used in the next step without further purifications.

4.2.2. General procedures A for the synthesis of compounds *5a–g* and *10a–e*

To a solution of methyl 2-(4-bromophenyl)-3-(phenylamino) imidazo[1,2-a]pyridine-6-carboxylic acid (**4**) (407 mg, 1.0 mmol, 1 equiv) in DMF (8 mL) at 0 °C was added DIPEA (0.21 mL, 1.2 mmol, 1.2 equiv). After 10 min, TBTU (551 mg, 1.2 mmol, 1.2 equiv) was added and the resulting mixture stirred at the same temperature for 30 min. Then the desired diaminobenzene (1.1 mmol, 1.1 equiv) was added. The resulting mixture was stirred at 0 °C for 4 h, and then quenched with ice-water. The precipitated solid was filtered, washed with water and dissolved in EtOAc. The organic phase was washed with a 1 N HCl aqueous solution, then with a saturated $NaHCO_3$ aqueous solution, and finally H_2O, dried over $MgSO_4$, and concentrated in vacuo, which was used in the next stage without further purification. To this amide was added AcOH (30 mL) and the resulting suspension was refluxed for 5 h, cooled to room temperature, concentrated in vacuo and diluted with crushed ice. The brown solid was filtered, washed thoroughly with water. The crude was dissolved in EtOAc washed with a saturated $NaHCO_3$ aqueous solution and with H_2O, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (DCM/AcOEt, 8/2 to 7/3) to give 1*H*-benzo[d]imidazol-2-yl-N-phenylimidazo[1,2-a]pyridin-3-amine derivatives **6a–e**.

4.2.3. General procedure B for the synthesis of compounds *6a–d* and *11a–d*

To a solution of 2-(4-bromophenyl)-3-(phenylamino)imidazo [1,2-a]pyridine-6-carboxylic acid (**4**) (407 mg, 1.0 mmol, 1 equiv) in DMF (10 mL) at 0 °C was added DIPEA (0.21 mL, 1.2 mmol, 1.2 equiv). The resulting mixture was stirred at 0 °C for 30 min followed by dropwise addition of the appropriate α-bromoketone (1.1 mmol, 1.1 equiv) in DMF. The resulting mixture was stirred at 0 °C for 4 h, then quenched with ice-water. The precipitated solid was filtered, washed with water and dissolved in EtOAc. The organic phase was washed with a 1 N HCl aqueous solution, and then a saturated $NaHCO_3$ aqueous solution, then H_2O, dried over $MgSO_4$, and concentrated in vacuo, which was used in the next stage without further purification. To this product, AcOH (25 mL) and $AcONH_4$ (924 mg, 12 mmol, 12 equiv) was added and the resulting suspension was refluxed for 5 h, cooled to room temperature, concentrated in vacuo and diluted with crushed ice. The brown solid was filtered, washed thoroughly with water. The crude cake was dissolved in EtOAc washed with a saturated $NaHCO_3$ aqueous solution and with H_2O, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (DCM/AcOEt, 8/2 to 7/3) to give 1*H*-imidazol-2-yl-N-phenylimidazo[1,2-a] pyridin-3-amine derivatives **5a–g**.

4.2.4. General procedure C for the synthesis of compounds *7a–e* and *12a–e*

To a solution of methyl methyl 2-(4-bromophenyl)-3-(phenylamino)imidazo[1,2-a]pyridine-6-carboxylic acid (**4**)(407 mg, 1.0 mmol, 1 equiv) in DMF (8 mL) at 0 °C was added DIPEA (0.21 mL, 1.2 mmol, 1.2 equiv). After 10 min, TBTU (551 mg, 1.2 mmol, 1.2 equiv) was added and the resulting mixture stirred at the same temperature for 30 min. Then benzohydrazide (1.1 mmol, 1.1 equiv) was added. The resulting mixture was stirred at 0 °C for 6 h, and then quenched with ice-water. The precipitated solid was filtered, washed with water and dissolved in EtOAc. The organic phase was washed with a 1 N HCl aqueous solution, then with a saturated $NaHCO_3$ aqueous solution, and finally H_2O, dried over $MgSO_4$, and concentrated in vacuo, which was used in the next stage without further purification. To this diamide was added $POCl_3$ (10 mL) and the resulting suspension was refluxed for 3 h, cooled to room temperature, concentrated under vacuum and diluted with crushed ice. The brown solid was filtered, washed thoroughly with water. The crude was dissolved in EtOAc washed with a saturated $NaHCO_3$ aqueous solution and with H_2O, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (DCM/AcOEt, 8/2–7/3) to give 1,3,4-oxadiazol-2-yl-N-phenylimidazo[1,2-a]pyridin-3-amine derivatives **7a–f** (58%).

4.2.5. 2-(4-Bromophenyl)-6-(6-nitro-1H-benzo[d]imidazol-2-yl)-N-phenylimidazo[1,2-a]pyridin-3-amine (**5a**)

This derivative was synthesized according to the general procedure A. Yield 66%, as white solid, m.p. 197–199 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 10.88 (s, 1H), 8.94 (d, J = 9.6 Hz, 2H), 8.52 (s, 1H), 8.51 (d, J = 2.7 Hz, 1H), 8.0 (s, 1H), 7.87 (d, J = 1.2 Hz, 2H), 7.75 (d, J = 9.0 Hz, 1H), 7.56 (s, 1H), 7.31 (m, 5H), 6.98 (d, J = 7.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 161.1, 150.0, 142.2, 140.1, 138.5, 132.9, 131.7, 131.2, 130.3, 128.9, 127.8, 122.1, 119.4, 119.0, 117.5, 115.9, 109.1. HRMS (ESI): calcd. for C26H17BrN6O2 $[M + H]^+$: 525.06746; found 525.06751.

4.2.6. 6-(6-Phenoxy-1H-benzo[d]imidazol-2-yl)-N-phenyl-2-p-tolylimidazo[1,2-a]pyridin-3-amine (**5b**)

This derivative was synthesized according to the general procedure A. Yield 71%, white solid, m.p. 168–169 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 10.74 (s, 1H), 8.95 (d, J = 9.6 Hz, 2H), 8.64 (s, 1H), 7.89 (dd, J = 1.2, 7.2 Hz, 2H), 7.79 (s, 2H), 7.64 (s, 1H), 7.61 (s, 1H), 7.28 (m, 7H), 7.03 (m, 4H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 160.4, 157.8, 150.5, 147.9, 137.1, 131.6, 131.2, 130.9, 129.8, 129.2, 129.0, 127.5, 126.0, 123.2, 120.3, 129.7, 118.9, 117.5, 114.4, 104.6, 22.4. HRMS (ESI): calcd. for $C_{33}H_{25}N_5O$ $[M + H]^+$: 508.21374; found 508.21369.

4.2.7. 6-(6-Bromo-1H-benzo[d]imidazol-2-yl)-N-phenyl-2-p-tolylimidazo[1,2-a]pyridin-3-amine (**5c**)

This derivative was synthesized according to the general procedure A. Yield 58%, white solid, m.p. 199–200 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.66 (s, 1H), 8.92 (d, J = 9.3 Hz, 2H), 8.61 (s, 1H), 7.96 (d, J = 2.7 Hz, 1H), 7.88 (dd, J = 1.1, 8.6 Hz, 2H), 7.74 (s, 2H), 7.38 (s, 1H), 7.26 (m, 5H), 6.88 (d, J = 7.3 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 159.8, 149.1, 141.2, 137.4, 136.7, 134.1, 131.6, 130.5, 129.7, 128.4, 127.2, 125.3, 124.8, 121.5, 120.1, 119.9, 117.8, 111.6, 110.3, 21.9. HRMS (ESI): calcd. for $C_{27}H_{20}BrN_5$ $[M + H]^+$: 494.09803; found 494.09807.

4.2.8. 2-(4-Bromophenyl)-6-(6-fluoro-1H-benzo[d]imidazol-2-yl)-N-phenylimidazo[1,2-a]pyridin-3-amine (**5d**)

This derivative was synthesized according to the general procedure A. Yield 63%, white solid, m.p. 169–170 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.73 (s, 1H), 8.99 (d, J = 9.3 Hz, 2H), 8.61 (s, 1H), 8.33 (d, J = 8.7 Hz, 1H), 7.86 (dd, J = 1.1, 7.0 Hz, 2H), 7.58 (s, 1H), 7.53 (dd, J = 1.6, 8.4 Hz, 1H), 7.36–7.30 (m, 6H), 7.18 (s, 1H), 6.92 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 161.1, 158.5, 150.2, 142.7, 141.1, 139.8, 137.5, 133,6, 131.7, 131.2, 130.1, 127.6, 125.3, 119.7, 119.5, 117.8, 111.3, 110.1, 105.9, 105.4. HRMS (ESI): calcd. for $C_{26}H_{17}BrFN_5$ $[M + Na]^+$: 520.05490; found 520.05498.

4.2.9. 6-(6-Fluoro-1H-benzo[d]imidazol-2-yl)-2-(4-phenoxyphenyl)-N-phenylimidazo[1,2-a]pyridin-3-amine (**5e**)

This derivative was synthesized according to the general procedure A. Yield 79%, white solid, m.p. 179–180 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 10.02 (s, 1H), 8.93 (d, J = 9.2 Hz, 2H), 8.64 (s, 1H), 8.30 (d, J = 8.9 Hz, 1H), 7.91 (s, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.65 (s, 1H), 7.54 (s, 1H), 7.33–7.31 (m, 4H), 7.18–7.05 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 160.3, 157.8, 157.3, 152.9, 150.2, 143.1, 141.5, 139.2, 137.3, 132.5, 130.4, 130.1, 129.1, 127.8, 125.6, 123.4, 119.5, 119.3, 118.2, 116.7, 110.8, 110.3, 105.6, 105.1. HRMS (ESI): calcd. for $C_{32}H_{22}FN_5O$ $[M + Na]^+$: 534.17061; found 534.17066.

4.2.10. 2-(4-Bromophenyl)-6-(6-phenoxy-1H-benzo[d]imidazol-2-yl)-N-phenylimidazo[1,2-a]pyridin-3-amine (**5f**)

This derivative was synthesized according to the general procedure A. Yield 71%, white solid, m.p. 177–176 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 10.65 (s, 1H), 8.75 (d, J = 8.4 Hz, 1H), 8.71 (s, 1H), 7.69 (m, 2H), 7.58 (d, J = 8.6 Hz, 1H), 7.34–7.27 (m, 8H), 7.08–6.94 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 161.2, 157.1, 150.5, 149.2, 141.9, 137.7, 133.8, 132.1, 130.9, 130.8, 130.5, 129.8, 129.3, 127.7, 123.6, 120.2, 119.4, 119.1, 118.7, 113.6, 104.5. HRMS (ESI): calcd. for $C_{32}H_{22}BrN_5O$ $[M + Na]^+$: 594.09054; found 594.09060.

4.2.11. 2-(4-Bromophenyl)-6-(6-methyl-1H-benzo[d]imidazol-2-yl)-N-phenylimidazo[1,2-a]pyridin-3-amine (**5g**)

This derivative was synthesized according to the general procedure A. Yield 61%, white solid, m.p. 189–190 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.78 (s, 1H), 9.14 (d, J = 8.3 Hz, 2H), 8.72 (bs, 1H), 8.11 (d, J = 9.3 Hz, 2H), 7.87 (d, J = 8.5 Hz, 1H), 7.30 (m, 8H), 7.09 (d, J = 9.1 Hz, 1H), 7.00 (dd, J = 5.1, 8.7 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 159.5, 149.4, 141.0, 137.1, 134.0, 133.8, 131.9, 131.5, 130.8, 130.3, 129.6, 128.1, 120.8, 119.7, 119.5, 119.2, 117.4, 114.4, 22.3. HRMS (ESI): calcd. for $C_{27}H_{20}BrN_5$ $[M + H]^+$: 494.09803; found 494.09810.

4.2.12. 2-(4-Bromophenyl)-6-(5-(4-fluorophenyl)-1H-imidazol-2-yl)-N-phenylimidazo[1,2-a]pyridin-3-amine (**6a**)

This derivative was synthesized according to the general procedure B. Yield 71%, white solid, m.p. 181–182 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.78 (s, 1H), 8.98 (d, J = 8.6 Hz, 1H), 8.76 (s, 1H), 8.06 (d, J = 7.0 Hz, 2H), 7.87 (dd, J = 1.4, 7.3 Hz, 2H), 7.61 (d, J = 8.9 Hz, 1H), 7.42 (s, 1H), 7.32–7.29 (m, 5H), 7.14 (d, J = 3.8 Hz, 2H), 6.96 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 162.7, 159.9, 148.5, 147.2, 141.8, 137.6, 134.3, 131.5, 130.0, 129.4, 125.7, 125.2, 122.5, 120.8, 119.6, 118.3, 115.4, 114.5, 113.9. HRMS (ESI): calcd. for $C_{28}H_{19}BrFN_5$ $[M + H]^+$: 524.08861; found 524.08855.

4.2.13. 6-(5-(4-Bromophenyl)-1H-imidazol-2-yl)-2-(4-phenoxyphenyl)-N-phenylimidazo[1,2-a]pyridin-3-amine (**6b**)

This derivative was synthesized according to the general procedure B. Yield 67%, white solid, m.p. 176–177 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.61 (s, 1H), 9.21 (d, J = 8.4 Hz, 1H), 8.75 (s, 1H), 7.96 (bs, 2H), 7.87 (bs, 2H), 7.66 (s, 1H), 7.43 (bs, 3H), 7.42 (m, 4H), 7.32 (m, 4H), 7.07 (m, 3H), 7.05 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 158.7, 153.2, 147.9, 146.7, 141.3, 137.1, 133.2, 130.4, 129.5, 128.8, 125.3, 125.0, 122.1, 120.6, 119.9, 118.7, 118.3, 117.8, 113.0. HRMS (ESI): calcd. for $C_{34}H_{24}BrN_5O$ $[M + Na]^+$: 620.10619; found 620.10623.

4.2.14. 2-(4-Bromophenyl)-6-(5-(4-chlorophenyl)-1H-imidazol-2-yl)-N-phenylimidazo[1,2-a]pyridin-3-amine (**6c**)

This derivative was synthesized according to the general procedure B. Yield 71%, white solid, m.p. 204–205 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.81 (s, 1H), 8.95 (d, J = 8.2 Hz, 1H), 8.91 (bs, 1H), 8.43 (d, J = 6.6 Hz, 2H), 7.92–7.87 (m, 4H), 7.83 (d, J = 8.3 Hz, 1H), 7.36–7.31 (m, 8H), 7.11 (d, J = 3.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 148.3, 147.4, 141.9, 133.1, 131.2, 130.6, 129.8, 125.1, 123.5, 122.8, 121.7, 120.6, 119.9, 119.6, 119.4, 113.4. HRMS (ESI): calcd. for $C_{28}H_{19}BrClN_5$ $[M + Na]^+$: 562.04100; found 562.04108.

4.2.15. 2-(4-Bromophenyl)-6-(5-(4-phenoxyphenyl)-1H-imidazol-2-yl)-N-phenylimidazo[1,2-a]pyridin-3-amine (**6d**)

This derivative was synthesized according to the general procedure B. Yield 73%, white solid, m.p. 187–188 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 10.43 (s, 1H), 9.25 (d, J = 8.6 Hz, 1H), 8.89 (s, 1H), 7.98 (d, J = 1.1 Hz, 2H), 7.90 (dd, J = 1.7, 8.3 Hz, 2H), 7.41 (bs, 1H), 7.36–7.15 (m, 17H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 158.2, 152.1, 148.3, 146.4, 141.7, 133.9, 131.6, 130.4, 129.5, 128.7, 125.0, 124.3, 122.2, 121.4, 120.5, 119.8, 118.7, 117.1, 112.8. HRMS (ESI): calcd. for $C_{34}H_{24}BrN_5O$ $[M + H]^+$: 598.12425; found 598.12431.

*4.2.16. 2-(4-Bromophenyl)-6-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-N-phenylimidazo[1,2-a]pyridin-3-amine (**7a**)*

This derivative was synthesized according to the general procedure C. Yield 70%, white solid, m.p. 197–198 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.10 (s, 1H), 8.99 (s, 1H), 8.33 (d, J = 8.9 Hz, 1H), 7.93 (dd, J = 1.4, 8.3 Hz, 2H), 7.92 (s, 1H), 7.78 (bs, 2H), 7.49 (dd, J = 3.5, 5.1 Hz, 2H), 7.31–7.27 (m, 5H), 6.95 (dd, J = 1.8, 5.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 167.8, 163.2, 158.4, 154.1, 145.8, 141.1, 137.2, 133.7, 133.2, 131.5, 130.5, 129.7, 125.9, 120.2, 119.8, 119.1, 118.0, 115.7, 111.2. HRMS (ESI): calcd. for $C_{27}H_{17}BrFN_5O$ $[M + H]^+$: 526.06787; found 526.06791.

*4.2.17. 6-(5-(4-Fluorophenyl)-1,3,4-oxadiazol-2-yl)-2-(4-phenoxyphenyl)-N-phenylimidazo[1,2-a]pyridin-3-amine (**7b**)*

This derivative was synthesized according to the general procedure C. Yield 65%, white solid, m.p. 172–174 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.13 (bs, 1H), 8.31 (bd, J = 3.9 Hz, 1H), 7.97–7.74 (m, 6H), 7.51(d, J = 8.5 Hz, 2H), 7.37–7.32 (m, 4H), 7.12 (m, 3H), 7.10 (bs, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 166.9, 163.7, 158.1, 157.5, 153.2, 145.9, 141.4, 138.6, 136.9, 130.5, 129.4, 129.2, 128.6, 126.3, 125.7, 123.8, 119.7, 119.4, 118.1, 115.9, 110.8. HRMS (ESI): calcd. for $C_{33}H_{22}FN_5O_2$ $[M + H]^+$: 540.18358; found 540.18361.

*4.2.18. 6-(5-(4-Nitrophenyl)-1,3,4-oxadiazol-2-yl)-N-phenyl-2-p-tolylimidazo[1,2-a]pyridin-3-amine(**7c**)*

This derivative was synthesized according to the general procedure C. Yield 60%, white solid, m.p. 209–210 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 8.97 (bs, 1H), 8.44 (bs, 1H), 8.34 (d, J = 8.6 Hz, 2H), 7.91(dd, J = 1.0, 8.1 Hz, 2H), 7.83 (m, 3H), 7.42 (m, 4H), 6.89 (dd, J = 1.2, 5.3 Hz, 1H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 158.6, 153.8, 152.1, 150.5, 146.2, 141.8, 141.1, 137.4, 136.7, 136.1, 133.4, 132.9, 130.3, 128.8, 125.4, 123.7, 119.6, 119.3, 118.3, 110.4, 22.3. HRMS (ESI): calcd. for $C_{28}H_{20}N_6O_3$ $[M + Na]^+$: 511.14946; found 511.14939.

*4.2.19. 2-(4-Bromophenyl)-N-phenyl-6-(5-p-tolyl-1,3,4-oxadiazol-2-yl)imidazo[1,2-a]pyridin-3-amine (**7d**)*

This derivative was synthesized according to the general procedure C. Yield 61%, white solid, m.p. 193–194 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 8.82 (bs, 1H), 8.23 (d, J = 3.2 Hz, 1H), 8.00–7.88 (m, 4H), 7.84(d, J = 1.5 Hz, 1H), 7.39–7.31 (m, 8H), 6.98 (d, J = 7.1 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 158.1, 154.2, 153.4, 146.3, 142.6, 140.9, 137.1, 136.7, 133.9, 132.8, 131.7, 129.5, 127.6, 124.5, 124.1, 120.8, 119.7, 118.9, 117.9, 110.3, 20.6. HRMS (ESI): calcd. for C28H20BrN5O $[M + Na]^+$: 544.07489; found 544.07494.

*4.2.20. 2-(4-Bromophenyl)-6-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)-N-phenylimidazo[1,2-a]pyridin-3-amine (**7e**)*

This derivative was synthesized according to the general procedure C. Yield 57%, white solid, m.p. 186–187 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 8.95 (bs, 1H), 8.46 (m, 4H), 8.32 (d, J = 8.8 Hz, 1H), 7.91(dd, J = 1.3, 7.1 Hz, 2H), 7.82 (dd, J = 1.5, 8.7 Hz, 1H), 7.36–7.32 (m, 5H), 6.94 (dd, J = 1.1, 7.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 157.9, 153.8, 152.1, 145.7, 141.4, 140.5, 136.6, 136.1, 133.5, 132.9, 132.7, 131.4, 130.5, 129.4, 125.3, 123.8, 120.2, 119.5, 118.9, 118.3, 111.0. HRMS (ESI): calcd. for $C_{27}H_{17}BrN_6O_3$ $[M + Na]^+$: 575.04432; found 575.04428.

*4.2.21. 2-(4-Bromophenyl)-6-(6-fluoro-1H-benzo[d]imidazol-2-yl)-N-phenylimidazo[1,2-a]pyrimidin-3-amine (**10a**)*

This derivative was synthesized according to the general procedure A. Yield 59%, white solid, m.p. 166–167 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.79 (s, 1H), 9.12 (bs, 1H), 8.61 (d, J = 8.3 Hz, 1H), 8.29 (d, J = 1.4 Hz, 1H), 8.11 (d, J = 7.1 Hz, 2H), 7.72 (bs, 1H), 7.48–7.39 (m, 4H), 7.31 (d, J = 8.1 Hz, 2H), 7.10 (bs, 1H), 6.89 (dd, J = 1.1, 5.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 160.0, 155.8, 155.6, 153.0, 152.7, 146.4, 141.8, 138.7, 133.4, 132.8, 132.1, 131.5, 130.6, 130.1, 129.7, 125.3, 119.9, 119.5, 112.4, 111.8, 107.1, 106.0, 94.6. HRMS (ESI): calcd. for $C_{25}H_{16}BrFN_6$ $[M + Na]^+$: 521.05015; found 521.05023.

*4.2.22. 2-(4-Bromophenyl)-6-(6-chloro-1H-benzo[d]imidazol-2-yl)-N-phenylimidazo[1,2-a]pyrimidin-3-amine (**10b**)*

This derivative was synthesized according to the general procedure A. Yield 70%, white solid, m.p. 202–203 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 10.71 (s, 1H), 9.22 (bs, 1H), 8.45 (s, 1H), 8.12 (d, J = 9.4 Hz, 21H), 7.93 (d, J = 2.8 Hz, 1H), 7.74 (d, J = 9.1 Hz, 1H), 7.50–7.42 (m, 7H), 7.13 (d, J = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 155.9, 153.1, 152.8, 146.7, 142.1, 133.9, 132.7, 132.6, 131.7, 130.8, 129.9, 129.4, 128.1, 122.6, 120.1, 119.8, 119.5, 115.7, 94.6. HRMS (ESI): calcd. for $C_{25}H_{16}BrClN_6$ $[M + Na]^+$: 537.02060; found 537.02058.

*4.2.23. 6-(6-Fluoro-1H-benzo[d]imidazol-2-yl)-N-phenyl-2-p-tolylimidazo[1,2-a]pyrimidin-3-amine (**10c**)*

This derivative was synthesized according to the general procedure A. Yield 72%, white solid, m.p. 185–186 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 10.14 (s, 1H), 9.31 (bs, 1H), 8.53 (d, J = 8.5 Hz, 1H), 8.31 (d, J = 1.3 Hz, 1H), 8.13 (d, J = 7.2 Hz, 2H), 7.94 (d, J = 6.4 Hz, 2H), 7.87 (dd, J = 2.6, 7.3 Hz, 1H), 7.42 (m, 5H), 7.31 (m, 2H), 6.99 (dd, J = 1.0, 5.6 Hz, 1H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 159.7, 155.9, 155.1, 153.2, 152.4, 146.8, 141.4, 139.3, 137.2, 133.0, 130.1, 129.9, 129.3, 126.2, 125.1, 120.7, 119.6, 112.1, 111.5, 107.3, 106.1, 93.8, 22.5. HRMS (ESI): calcd. for $C_{26}H_{19}FN_6$ $[M + Na]^+$: 457.15529; found 457.15533.

*4.2.24. 6-(6-Fluoro-1H-benzo[d]imidazol-2-yl)-2-(4-phenoxyphenyl)-N-phenylimidazo[1,2-a]pyrimidin-3-amine (**10d**)*

This derivative was synthesized according to the general procedure A. Yield 55%, white solid, m.p. 178–179 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 10.09 (s, 1H), 9.05 (bs, 1H), 8.61 (d, J = 8.8 Hz, 1H), 8.28 (d, J = 1.2 Hz, 1H), 8.15 (bs, 2H), 7.99 (bd, J = 7.1 Hz, 2H), 77.454–7.33 (m, 4H), 7.21 (m, 2H), 7.17 (m, 2H), 7.11 (d, J = 7.2 Hz, 2H), 6.74 (bd, J = 6.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 159.2, 157.8, 155.7, 155.5, 153.3, 152.8, 152.4, 146.9, 141.6, 139.1, 136.3, 132.8, 130.4, 129.2, 125.1, 123.9, 119.8, 119.7, 119.2, 118.5, 111.9, 111.3, 106.1, 105.7, 93.5. HRMS (ESI): calcd. for $C_{31}H_{21}FN_6O$ $[M + Na]^+$: 535.16586; found 535.16579.

*4.2.25. 2-(4-Bromophenyl)-6-(6-nitro-1H-benzo[d]imidazol-2-yl)-N-phenylimidazo[1,2-a]pyrimidin-3-amine (**10e**)*

This derivative was synthesized according to the general procedure A. Yield 75%, white solid, m.p. 194–195 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 10.51 (s, 1H), 9.13 (bs, 1H), 8.71 (d, J = 2.6 Hz, 1H), 8.27 (d, J = 1.5 Hz, 1H), 8.15 (bs, 1H), 8.03 (d, J = 7.3 Hz, 2H), 7.92 (d, J = 6.9 Hz, 1H), 7.51–7.34 (m, 4H), 6.89 (d, J = 7.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 155.7, 153.0, 152.6, 146.5, 142.6, 141.4, 139.8, 133.7, 132.8, 132.4, 131.3, 129.7, 129.2, 121.9, 120.2, 119.7, 118.4, 107.3, 109.1, 93.6. HRMS (ESI): calcd. for $C_{25}H_{16}BrN_7O_2$ $[M + Na]^+$: 548.04465; found 548.04471.

*4.2.26. 2-(4-Bromophenyl)-6-(5-(4-fluorophenyl)-1H-imidazol-2-yl)-N-phenylimidazo[1,2-a]pyrimidin-3-amine (**11a**)*

This derivative was synthesized according to the general procedure B. Yield 77%, white solid, m.p. 183–184 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.71 (s, 1H), 9.21 (s, 1H), 8.33 (d, J = 1.4 Hz, 1H), 8.11 (d, J = 8.7 Hz, 2H), 8.10 (d, J = 7.1 Hz, 2H), 7.61 (bs, 1H), 7.48–7.19 (m, 6H), 7.15 (d, J = 4.1 Hz, 2H), 6.81 (bd, J = 6.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 162.5, 159.1, 155.1, 148.7, 147.4, 145.5, 142.3, 134.7, 132.8, 132.4, 132.1, 131.3, 130.7, 129.5, 128.6, 125.9, 121.6, 122.0, 120.1, 114.9, 114.4, 103.6. HRMS (ESI): calcd. for $C_{27}H_{18}BrFN_6$ $[M + H]^+$: 525.08386; found 525.08391.

*4.2.27. 2-(4-Bromophenyl)-6-(5-(4-chlorophenyl)-1H-imidazol-2-yl)-N-phenylimidazo[1,2-a]pyrimidin-3-amine (**11b**)*

This derivative was synthesized according to the general procedure B. Yield 71%, white solid, m.p.203–204 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.82 (s, 1H), 9.181 (bs, 1H), 8.41 (d, J = 6.7 Hz, 2H), 8.31 (d, J = 1.3 Hz, 1H), 8.12 (d, J = 7.2 Hz, 2H), 7.84 (d, J = 8.4 Hz, 2H), 7.55 (bs, 1H), 7.48–7.34 (m, 6H), 6.94 (bd, J = 6.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 155.3, 149.8, 145.2, 142.1, 134.2, 133.5, 132.7, 131.2, 130.8, 129.9, 128.7, 125.6, 124.6, 123.4, 120.2, 119.6, 103.8. HRMS (ESI): calcd. for $C_{27}H_{18}BrClN_6$ $[M + Na]^+$: 563.03625; found 563.03619.

*4.2.28. 2-(4-Bromophenyl)-N-phenyl-6-(5-p-tolyl-1H-imidazol-2-yl)imidazo[1,2-a]pyrimidin-3-amine (**11c**)*

This derivative was synthesized according to the general procedure B. Yield 74%, white solid, m.p. 196–197 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.98 (s, 1H), 9.14 (bs, 1H), 8.39 (d, J = 1.3 Hz, 1H), 8.21 (d, J = 6.8 Hz, 2H), 7.91 (bd, J = 7.0 Hz, 2H), 7.52 (d, J = 9.6 Hz, 2H), 7.61 (bs, 1H), 7.44–7.36 (m, 6H), 6.85 (bd, J = 6.6 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 155.0, 150.4, 146.4, 145.3, 141.2, 142.1, 135.1, 133.1, 132.3, 131.1, 130.5, 129.2, 128.4, 125.3, 121.2, 120.4, 120.0, 119.8, 103.5, 22.6. HRMS (ESI): calcd. for $C_{28}H_{21}BrN_6$ $[M + Na]^+$: 543.09088; found 543.09092.

*4.2.29. 2-(4-Bromophenyl)-6-(5-(4-nitrophenyl)-1H-imidazol-2-yl)-N-phenylimidazo[1,2-a]pyrimidin-3-amine (**11d**)*

This derivative was synthesized according to the general procedure B. Yield 64%, white solid, m.p. 169–170 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.95 (s, 1H), 9.18 (bs, 1H), 8.35 (d, J = 1.2 Hz, 1H), 8.20 (bs, 2H), 7.98 (d, J = 6.9 Hz, 2H), 7.79–7.76 (m, 3H), 7.49–7.32 (m, 6H), 6.81 (bd, J = 7.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 154.8, 150.0, 146.8, 145.1, 144.5, 141.0, 134.1, 133.1, 132.5, 131.6, 130.7, 129.5, 128.6, 125.8, 123.4, 120.1, 119.5, 119.0, 102.6. HRMS (ESI): calcd. for $C_{27}H_{18}BrN_7O_2$ $[M + Na]^+$: 574.06030; found 574.06028.

*4.2.30. 2-(4-Bromophenyl)-6-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-N-phenylimidazo[1,2-a]pyrimidin-3-amine (**12a**)*

This derivative was synthesized according to the general procedure C. Yield 68%, white solid, m.p. 178–179 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.19 (s, 1H), 8.47 (s, 1H), 8.12 (d, J = 6.9 Hz, 2H), 7.83 (bs, 2H), 7.52–7.35 (m, 8H), 6.91 (bd, J = 6.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 167.1, 163.5, 158.2, 153.9, 150.2, 146.4, 141.5, 133.8, 133.1, 132.8, 131.6, 130.8, 129.2, 126.7, 126.5, 120.0, 119.6, 117.2, 114.8, 111.0. HRMS (ESI): calcd. for $C_{26}H_{16}BrFN_6O$ $[M + Na]^+$: 549.04507; found 549.04511.

*4.2.31. 6-(5-(4-Fluorophenyl)-1,3,4-oxadiazol-2-yl)-N-phenyl-2-p-tolylimidazo[1,2-a]pyrimidin-3-amine (**12b**)*

This derivative was synthesized according to the general procedure C. Yield 71%, white solid, m.p. 201–202 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.10 (s, 1H), 8.39 (s, 1H), 8.22 (d, J = 7.1 Hz, 2H), 7.89–7.75 (m, 4H), 7.53 (dd, J = 5.5, 8.7 Hz, 2H), 7.39–7.31 (m, 4H), 6.94 (bd, J = 6.7 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 166.8, 163.7, 158.0, 153.5, 150.1, 146.8, 141.0, 136.5, 133.4, 130.6, 129.4, 129.2, 126.9, 126.7, 125.6, 119.8, 119.4, 115.7, 114.5, 111.6, 23.3. HRMS (ESI): calcd. for $C_{27}H_{19}FN_6O$ $[M + Na]^+$: 485.15021; found 485.15029.

*4.2.32. 2-(4-Bromophenyl)-6-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)-N-phenylimidazo[1,2-a]pyrimidin-3-amine (**12c**)*

This derivative was synthesized according to the general procedure C. Yield 62%, white solid, m.p. 198–199 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.04 (s, 1H), 8.47–8.41 (m, 5H), 8.15 (d, J = 7.5 Hz, 2H), 7.53–7.315 (m, 6H), 7.12 (bd, J = 6.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 158.1, 153.8, 151.7, 149.6, 146.9, 141.6, 136.1, 133.7, 133.0, 132.6, 131.9, 130.4, 130.2, 125.3, 119.9, 119.2, 111.3. HRMS (ESI): calcd. for $C_{26}H_{16}BrN_7O_3$ $[M + Na]^+$: 576.03957; found 576.03965.

*4.2.33. 2-(4-Bromophenyl)-6-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)-N-phenylimidazo[1,2-a]pyrimidin-3-amine (**12d**)*

This derivative was synthesized according to the general procedure C. Yield 72%, white solid, m.p. 189–191 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.21 (s, 1H), 8.39 (s, 1H), 8.25 (d, J = 6.7 Hz, 2H), 8.13 (d, J = 7.3 Hz, 2H), 6.71 (d, J = 8.2 Hz, 2H), 7.49–7.34 (m, 6H), 7.08 (bd, J = 6.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 166.4, 163.1, 159.3, 154.2, 151.0, 146.8, 142.6, 134.3, 133.9, 132.6, 132.2, 131.6, 130.5, 127.4, 126.3, 121.5, 120.6, 118.3, 115.7, 110.8. HRMS (ESI): calcd. for $C_{26}H_{16}BrClN_6O$ $[M + Na]^+$: 565.01552; found 565.01559.

*4.2.34. 2-(4-Bromophenyl)-N-phenyl-6-(5-p-tolyl-1,3,4-oxadiazol-2-yl)imidazo[1,2-a]pyrimidin-3-amine (**12e**)*

This derivative was synthesized according to the general procedure C. Yield 71%, white solid, m.p. 193–194 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.88 (s, 1H), 9.15 (bs, 1H), 8.35 (d, J = 1.7 Hz, 1H), 8.31 (d, J = 7.1 Hz, 2H), 7.94 (bd, J = 3.1 Hz, 1H), 7.72 (bs, 1H), 7.51–7.39 (m, 8H), 7.14 (bd, J = 5.2 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 158.1, 154.2, 150.3, 146.7, 142.5, 141.8, 133.9, 133.3, 132.5, 131.7, 130.8, 129.6, 128.8, 125.7, 124.2, 120.5, 119.6, 111.3, 21.9. HRMS (ESI): calcd. for $C_{27}H_{19}BrN_6O$ $[M + Na]^+$: 545.07014; found 545.07021.

4.3. In vitro antimicrobial procedure

The determination of minimum inhibitory concentration [19,20] was done with six isolates of Gram-positive bacteria *S. aureus*, *E. faecalis* and *B. megaterium* and Gram-negative bacteria *E. coli*, *P. aeruginosa* and *E. aerogenes* which were inoculated into Luria broth medium containing 1% tryptone, 0.5% yeast extract, 0.5% sodium chloride. The pH of the medium was adjusted to 7.2 with sterile phosphate buffered saline and incubated at 37 °C for 24 h. The optical density of the bacteria from mid-log phase of growth was measured at 540 nm and diluted in fresh medium to obtain an optical density of 0.004 (corresponding to 5×10^5 colony forming units/mL). To each well of the ELISA plate, 200 μL of diluted bacterial suspension was added and graded concentrations (0.2–500 μg/50 μL) of the synthesized compounds and standard antibiotics (Amoxicillin, Cefixime and Vancomycin) in 20% H_2O/DMSO were added and incubated at 37 °C for 24 h. At the end of incubation the effect of the drugs on the growth of organisms was monitored by measuring the optical density at 540 nm using an ELISA reader. The MIC was defined as the lowest concentration of the antibiotic or test sample allowing no visible growth.

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