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Original article

Design, synthesis and *in vitro* antimicrobial evaluation of novel Imidazo[1,2-*a*]pyridine and imidazo[2,1-*b*][1,3]benzothiazole motifs

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ABSTRACT

New antimicrobial agents, imidazo[1,2-*a*]pyridine and imidazo[2,1-*b*][1,3]benzothiazole, have been synthesized. Their antimicrobial activities were conducted against various Gram-positive, Gram-negative bacteria and fungi. Compounds **6c**, **7a**, **10b**, **11a**, **12b**, **14a**, **14b**, **15a** and **15b**, exerted strong inhibition of the investigated bacterial and fungal strains compared to control antibiotics amoxicillin and cefixime and the antifungal agent fluconazole. Results from this study showed that the nature of the substituents on the armed aryl groups determines the extent of the activity of the fused imidazopyridine and/or imidazobenzothiazole derivatives. Preliminary structure–activity observations revealed that bromo-fluoro substituents enhanced the antimicrobial activity significantly compared to other substituents.

1. Introduction

Despite significant progress in antimicrobial therapy, infectious diseases caused by bacteria and fungi remain a major health concern due to the development of resistance to existing antimicrobial drugs. The increasing incidence of bacterial resistance to large number of antibacterial agents such as glycopeptides, sulfonamides, β-lactams, nitroimidazoles, quinolones, tetracyclins, chloramphenicol and macrolides is becoming a major concern [1,2]. In particular, the emergence of multiple drug resistant Gram-positive and Gram-negative bacteria has caused life-threatening infectious diseases in many countries around the world [3].

On the other hand, systemic and dermal fungal infections have significantly increased, specifically in patients undergoing organ transplants [4], anticancer chemotherapy or long term treatment with antimicrobial agents [5–7]. Patients with AIDS are immuno suppressed, and very susceptible to life-threatening systemic fungal infections by Candidiasis, Cryptococcosis and Aspergillosis [5,6]. Reports are available on the development of resistance to currently available antifungal azoles in *Candida* spp., as well as clinical failures in the treatment of fungal infections [5–8]. Furthermore, most of the present antifungal drugs are not effective against invasive Aspergillosis and the only drug of choice in such patients is the injectable amphotericin B [9]. Therefore, there is an increasing need to design new antibacterial and antifungal agents with better activity profile.

The aim of this study is therefore, to synthesize hybrid molecules through the combination of different pharmacophores for the purpose of obtaining potent antibacterial and antifungal lead compounds. In continuation of an ongoing program aimed at natural product synthesis and preparation of medicinally active structures [10–12], we describe herein an efficient process for the construction of polyfunctionalized imidazo[1,2-*a*]pyridine and imidazo[2,1-*b*][1,3]benzothiazole derivatives and their antimicrobial evaluation. Recent studies from many laboratories implicate the activity of these scaffolds against many of the most common human diseases, including diabetes [13], cancers [14], infection by microorganisms [15], viral infections and an array of neurological syndromes [16]. A literature search indicated that benzimidazoles [17–19], oxadiazoles [20–22] and phenyl imidazoles [23,24] with different substitution patterns possess a wide range of biological activities [25–32].

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2. Results and discussion

2.1. Chemistry

In a previous article from our group [33], we reported on the synthesis and the antibacterial evaluation of imidazo[1,2-*a*]pyridine and imidazo[1,2-*a*]pyrimidine derivatives. These results encouraged us to further extend the scope of this methodology to build new systems for improving the spectrum of activity of these scaffolds. Although our previous studies provided some important information about the structure–activity relationship of the aforementioned motifs, several questions remained unanswered: How do the skeletal complexity and substitution patterns affect the activity? How will the spectrum of activity change by fine tuning the core structure and the substitution pattern [33]? To answer these questions, chemical and biological approaches were used. For the chemical strategy, we relied on the structure–activity relationship developed from our previous report. Furthermore, in this study, it was found that the introduction of substituted isoquinoline and/or indol groups on the heterocyclic framework enhanced the potencies of these novel scaffolds compared to simple substituted phenyl rings described before [33]. Moreover, a substituted benzothiazole fused to an imidazole ring was introduced and found to be highly active against the tested microorganisms.

For the biological tools, on the other hand, we followed the same guidelines reported previously from our laboratory. Thus, we tested all derivatives produced from the aforementioned chemical strategies against the Gram-positive bacteria *S*taphylococcus *aureus*, *E*nterococcus *faecalis* and *Bacillus megaterium* and the Gram-negative bacteria *E*scherichia *coli*, *P*seudomonas *aeruginosa* and *Enterobacter aerogenes*. For the antifungal activity, the synthesized motifs were biologically evaluated against *C*andida *albicans*, *C*andida *parapsilosis*, *Aspergillus flavus* and *Microsporum gypsuem*.

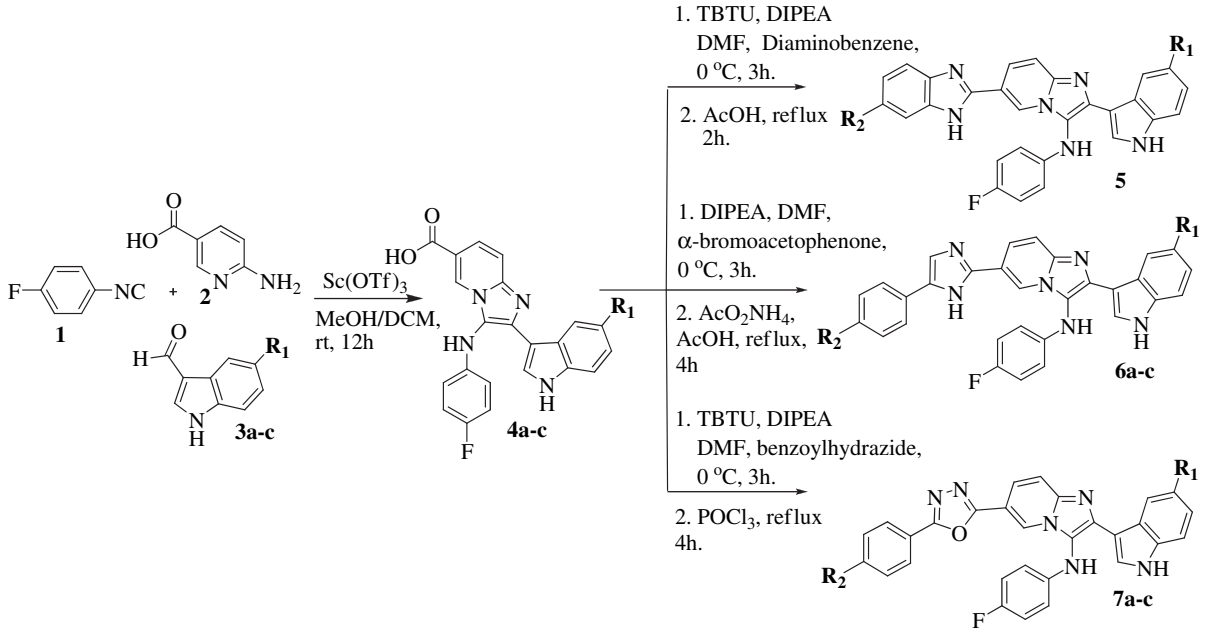
The title compounds were obtained *via* the Groebke–Blackburn 3CR [4+1]-cycloaddition protocol [34,35] of an aldehyde, aminoazole derivatives and an isocyanide. The primary input of this reaction must carry a carboxylic acid handle in order for the post Groebke–Blackburn 3CR product to be capable of being further differentiated and eventually integrated to deliver the intended scaffolds [36]. This strategy was recently developed in our laboratories for the purpose of producing a plethora of complex molecular scaffolds that could possibly become useful drug leads. Such a process involved the orthogonal union of Groebke–Blackburn 3CR and Ugi 4CR to arrive at a higher order 6CR reaction in a tandem one-pot protocol [36].

Scheme 1 shows the general synthetic strategy followed for the preparation of compounds **5a**–**7c**. The synthetic plan was started by using 5-carboxy-2-aminopyridine (**2**) as the main component, which in turn, was subjected to condensation with substituted 1*H*-indole-3-carbaldehyde **3a**–**c**, in the presence of a catalytic amount of $Sc(OTf)_3$ and subsequent reaction with *p*-fluorophenyl isocyanide (**1**) to deliver the imidazopyridines **4a**–**c**. Having secured pure amounts from compounds **4a**–**c**, our synthetic plan contemplated three types of scaffolds **5**, **6** and **7** as indicated in Scheme 1. Thus, compound **5** was produced through the coupling of **4a** with phenylene diamine derivative using TBTU and DIPEA in DMF. After work up, the delivered amide intermediate from this step was refluxed in acetic acid for 5 h to produce compound **5** (Scheme 1, Table 1).

The synthesis of substituted phenyl imidazoles **6a**–**c**, was achieved through the reaction of the desired imidazopyridines **4a**–**c** with the proper α-bromoacetophenone using DIPEA. The delivered α-ketoesters intermediates were subjected without further purification, to a standard condensation protocol using ACO_2NH_4 in refluxing acetic acid to produce compounds **6a**–**c** (Scheme 1, Table 1).

The third class of scaffolds, oxadiazoles **7a**–**c** (Scheme 1, Table 1), were synthesized from compounds **4a**–**c** by coupling with the desired benzoylhydrazide using TBTU and DIPEA followed by reaction with $POCl_3$.

After the successful synthesis of the above described derivatives, the scope of this methodology was extended toward the synthesis of imidazopyridine scaffolds containing substituted quinoline moiety (Scheme 2). In this regard, 5-carboxy-2-aminopyridine (**2**) was chosen as the primary input. Following the same reaction sequence described in Scheme 1, the preparation of compounds



Scheme 1. Synthesis of imidazopyridine carrying indole derivatives **5**–**7c**.

Table 1
In vitro antibacterial activity (MIC μg/mL) of compounds **5**–**15e**.

			Gram-negative			Gram-positive		
Compd	R_1	R_2	*E. coli*	*P. aeruginosa*	*E. aerogenes*	*S. aureus*	*E. faecalis*	*B. megaterium*
5	Br	F	1.12 ± 1.03	1.51 ± 0.01	1.15 ± 0.02	1.12 ± 0.07	1.36 ± 0.04	1.43 ± 0.03
6a	Br	NO_2	2.13 ± 0.08	2.11 ± 0.09	2.35 ± 0.05	2.52 ± 0.04	3.17 ± 0.25	4.24 ± 0.41
6b	Br	CH_3	6.11 ± 1.31	8.28 ± 1.34	6.22 ± 1.14	5.13 ± 0.22	7.32 ± 0.35	1.25 ± 0.03
6c	Br	F	0.42 ± 0.02	0.52 ± 0.01	0.17 ± 0.03	0.23 ± 0.02	1.96 ± 0.12	1.13 ± 0.22
7a	Br	F	0.11 ± 0.003	0.21 ± 0.001	0.35 ± 0.004	0.31 ± 0.002	0.37 ± 0.02	1.97 ± 0.15
7b	Br	CH_3	6.72 ± 1.32	5.64 ± 1.20	4.42 ± 1.12	3.13 ± 1.21	7.56 ± 1.11	6.44 ± 1.17
7c	Br	NO_2	3.32 ± 0.12	2.45 ± 0.31	3.13 ± 0.44	2.45 ± 0.46	2.11 ± 0.10	4.34 ± 0.21
10a	Br	CH_3	6.21 ± 1.11	5.45 ± 0.92	5.35 ± 0.77	7.43 ± 1.15	7.34 ± 1.21	7.54 ± 1.12
10b	Br	F	1.34 ± 0.04	1.35 ± 0.06	1.55 ± 0.02	1.46 ± 0.01	1.47 ± 0.04	2.53 ± 1.01
10c	Br	NO_2	2.14 ± 0.11	2.32 ± 0.15	3.15 ± 0.10	2.12 ± 0.26	3.36 ± 0.18	4.12 ± 0.53
11a	Br	F	1.15 ± 0.11	1.34 ± 0.04	0.81 ± 0.03	0.63 ± 0.02	1.21 ± 0.11	4.07 ± 0.65
11b	Br	CH_3	3.42 ± 0.92	2.89 ± 0.53	2.78 ± 0.59	1.95 ± 0.12	2.26 ± 0.15	5.14 ± 0.45
12a	Br	CH_3	2.43 ± 0.21	2.57 ± 0.21	1.74 ± 0.16	1.24 ± 0.13	2.32 ± 0.37	3.15 ± 0.45
12b	Br	F	0.75 ± 0.01	0.75 ± 0.03	0.41 ± 0.02	0.46 ± 0.01	1.38 ± 0.02	2.21 ± 0.32
12c	Br	NO_2	1.72 ± 0.14	1.58 ± 0.11	1.27 ± 0.15	1.45 ± 0.13	2.13 ± 0.45	3.11 ± 0.59
14a	Br	F	0.35 ± 0.01	0.34 ± 0.02	0.51 ± 0.01	0.43 ± 0.01	0.51 ± 0.01	1.12 ± 0.05
14b	F	F	0.23 ± 0.01	0.15 ± 0.02	0.34 ± 0.01	0.26 ± 0.01	0.21 ± 0.01	0.83 ± 0.05
14c	OCH_3	F	10.42 ± 1.52	11.89 ± 1.35	13.43 ± 1.31	12.43 ± 1.11	11.17 ± 1.13	19.15 ± 1.25
14d	CH_3	F	10.38 ± 1.61	9.66 ± 1.54	9.57 ± 1.62	8.63 ± 1.21	9.45 ± 1.19	18.65 ± 1.35
15a	Br	F	0.44 ± 0.02	0.53 ± 0.01	0.32 ± 0.02	0.18 ± 0.03	0.87 ± 0.01	1.69 ± 0.12
15b	F	F	0.14 ± 0.03	0.11 ± 0.01	0.23 ± 0.03	0.18 ± 0.01	0.41 ± 0.02	1.52 ± 0.11
15c	CH_3	F	14.52 ± 1.95	16.18 ± 1.78	14.63 ± 1.92	10.13 ± 1.81	9.17 ± 1.63	22.15 ± 2.75
15d	Br	OCH_3	8.12 ± 1.52	9.69 ± 1.35	8.13 ± 1.31	7.33 ± 1.11	10.57 ± 1.13	13.25 ± 2.15
15e	OCH_3	F	19.71 ± 1.65	18.53 ± 1.45	17.84 ± 1.34	17.39 ± 1.42	19.54 ± 1.73	23.45 ± 1.88
Amoxicillin			15.32 ± 1.12	14.67 ± 1.11	3.45 ± 0.21	12.92 ± 1.32	1.62 ± 0.03	2.28 ± 0.12
Cefixime			2.12 ± 0.01	16.43 ± 1.21	27.13 ± 1.33	34.64 ± 2.32	28.56 ± 1.32	126.32 ± 4.35

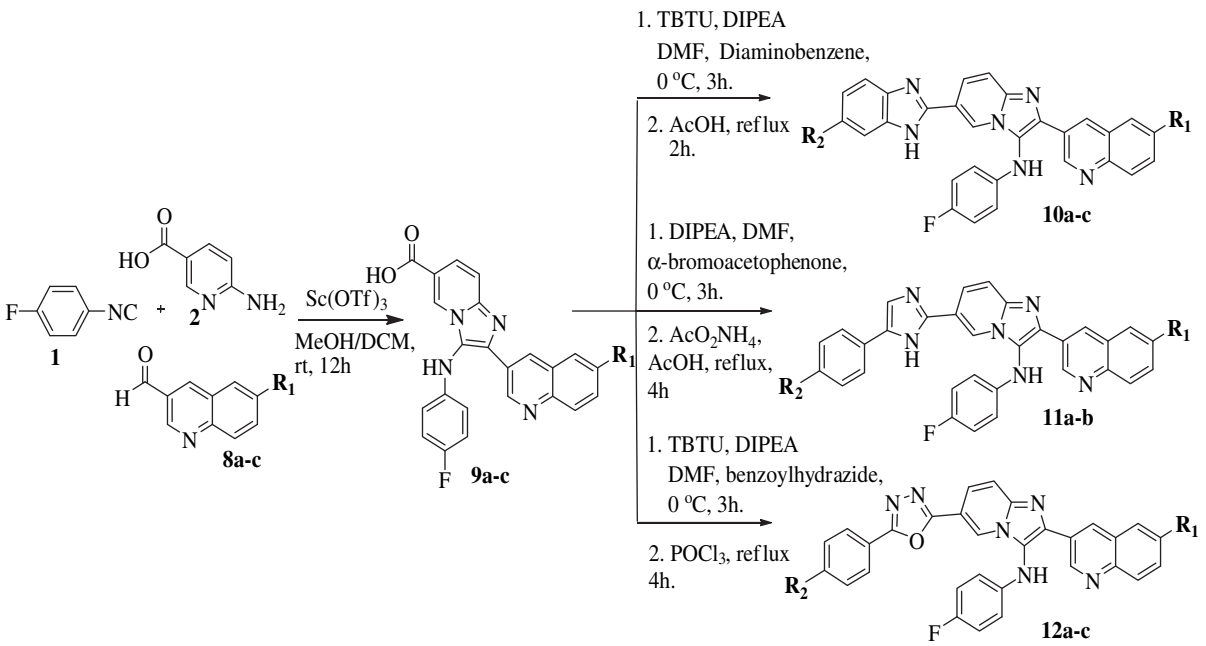
10a–**12c** (Scheme 2, Table 1) were produced from the [4+1]-cycloaddition intermediates **9a**–**c**.

After successfully demonstrating the underlying utility of this strategy for the rapid preparation of complex heterocycles (Schemes 1 and 2), it remained to be applied to the synthesis of more complex heterocyclic scaffolds with different frameworks. Thus, substituted benzo[*d*]thiazol-2-amine derivatives **13a**–**d** (Scheme 3), were reacted with substituted quinoline-3-carbaldehyde derivatives **8a**–**d** followed by reaction with *p*-fluorophenyl isocyanide (**1**) to give the polycyclic compounds **14a**–**d** (Scheme 3, Table 1).

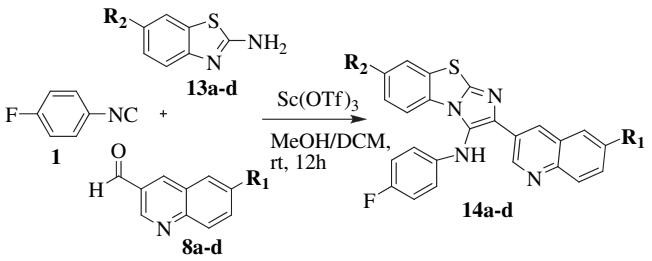
The versatility of this approach was expanded to arrive at derivatives **15a**–**e**. Thus, reaction of 2-aminobenzothiazoles **13a**–**d** with 1*H*-indole-3-carbaldehyde **3a**–**e** followed by the addition of isocyanide **1** (Scheme 4, Table 1), gave compounds **15a**–**e** (Scheme 4, Table 1).

2.2. Biological assay and SAR

The title compounds were tested for their antibacterial activity against Gram-positive bacteria *S. aureus*, *E. faecalis* and *B. megaterium* and Gram-negative bacteria *E. coli*, *P. aeruginosa* and



Scheme 2. Synthesis of imidazopyridine carrying quinoline derivatives **10a**–**12c**.



Scheme 3. Synthesis of imidazo[2,1-*b*][1,3]benzothiazole carrying quinoline derivatives **14a**–**d**.

E. aerogenes. For the antifungal activity, the synthesized motifs were screened against *C. albicans*, *C. parapsilosis*, *A. flavus* and *M. gypsuem*. Ampicillin, cefixime and fluconazole were used as antibacterial and antifungal references, respectively.

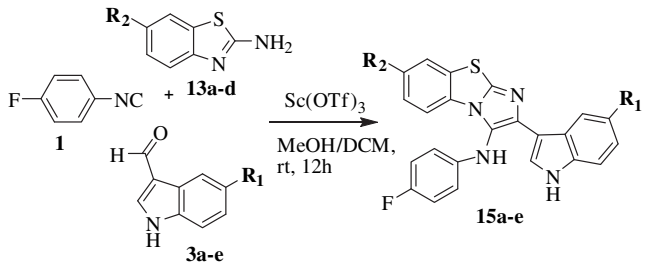
As shown in Table 1, the synthesized scaffolds exhibited a broad spectrum activity with MIC values of 0.11–23.45 μg/mL against both Gram-positive and Gram-negative bacteria. Among the Gram-positive bacteria tested, *S. aureus* showed a relatively high sensitivity toward the title compounds. Compounds **6c**, **7a**, **14a**, **14b** and **15b**, gave the best inhibitory activity against *S. aureus* with MIC values <0.5 μg/mL. Furthermore, compounds **7a**, **14a**, **14b** and **15b** showed potent activity against *E. faecalis* with MIC values <0.5 μg/mL.

With respect to antifungal activities (Table 2), all compounds displayed potent activity against *C. albicans*, *C. parapsilosis*, *A. flavus* and *M. gypsuem*, with MIC values of 1.11–19.65 μg/mL. Compounds **10b**, **11a**, **12b**, **14a**, **14b** and **15b** possess strong antifungal activities compared to the reference antifungal agent, fluconazole.

At this stage, some structure–activity relationships could be concluded from the data described in Tables 1 and 2. As a result, imidazopyridines and imidazobenzothiazoles that carry fluoro-bromo substituents, were found to be more potent as antimicrobial agents compared to compounds carrying other types of substitution patterns. Furthermore, the introduction of substituted isoquinoline and/or indol groups on the heterocyclic framework enhanced the potencies of these novel scaffolds compared to simple substituted phenyl rings described in our previous report [33]. Moreover, a substituted benzothiazole fused to an imidazole ring was introduced and found to be highly active against the investigated microorganisms.

3. Conclusion

In summary, we have synthesized new antimicrobial leads with a potent activity against various Gram-negative, Gram-positive bacterial and fungal strains. Many of the synthesized motifs, possessed potent antimicrobial activity compared to the control antibiotics amoxicillin and cefixime and the antifungal drug fluconazole. Characterization of the antimicrobial spectrum of the synthesized compounds (e.g. **12b**, **14a**, **14b**, **15a** and **15b**), as could be concluded from Tables 1 and 2, indicated a broad spectrum antibacterial and antifungal activities. The results described here, merit further investigations in our laboratories using a forward chemical genetics approach for finding lead molecules as anti-infective agents. Furthermore, we are currently engaged in a process directed toward the identification of the molecular target of these motifs in a reversed chemical genetics approach. The later will allow us to understand the specific biological target as well as the biochemical mechanism of action of these novel scaffolds.



Scheme 4. Synthesis of imidazo[2,1-*b*][1,3]benzothiazole carrying indole derivatives **15a**–**e**.

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 or flamed dried vessels. Solvents were dried and purified by conventional methods prior to use. Flash column chromatography was performed with Silica gel 60, 0.040–0.063 mm (230–400 mesh). Aluminum packed plates, pre-coated with silica gel 60 (UV254) were used for thin layer chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a 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, 1H; 77.16 ppm, the middle peak, ^{13}C). Both elemental analysis and high and low resolution mass spectroscopic analyses were conducted at the University of Jordan using positive ion mode 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–4c*, *9a–9e*, *14a–d* and *15a–e*

A mixture of 2-aminopyridine-5-carboxylic acid (**2**) or substituted 2-aminobenzothiazole (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 purification.

4.2.2. General experimental procedure B for the synthesis of compounds *5* and *10a–10e*

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 was 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 then H_2O. The organic layer was dried over $MgSO_4$, and concentrated in vacuo, which was

Table 2
In vitro antifungal activity (MIC μg/mL) of compounds **5**–**15e**.

Compd	R_1	R_2	*C. albicans*	*C. parapsilosis*	*A. flavus*	*M. gypsuem*
5	Br	F	11.34 ± 1.13	10.41 ± 1.11	12.21 ± 1.12	9.14 ± 1.17
6a	Br	NO_2	8.72 ± 1.18	6.22 ± 1.19	9.35 ± 1.25	7.44 ± 1.24
6b	Br	CH_3	19.53 ± 1.31	18.41 ± 1.34	16.46 ± 1.14	15.61 ± 1.22
6c	Br	F	3.21 ± 1.22	4.61 ± 1.01	3.25 ± 1.23	8.12 ± 1.22
7a	Br	F	2.54 ± 0.13	2.22 ± 0.11	3.13 ± 0.14	4.25 ± 0.12
7b	Br	CH_3	11.63 ± 1.32	10.43 ± 1.20	6.55 ± 1.12	13.41 ± 1.21
7c	Br	NO_2	6.63 ± 0.12	5.71 ± 0.31	8.31 ± 0.44	11.22 ± 0.46
10a	Br	CH_3	16.35 ± 1.11	15.53 ± 1.92	15.41 ± 1.77	17.53 ± 1.15
10b	Br	F	1.11 ± 0.04	1.22 ± 0.06	1.36 ± 0.02	1.21 ± 0.01
10c	Br	NO_2	4.23 ± 1.11	5.34 ± 1.15	7.63 ± 1.10	9.41 ± 1.26
11a	Br	F	1.05 ± 0.01	1.15 ± 0.04	0.72 ± 0.03	0.84 ± 0.02
11b	Br	CH_3	13.14 ± 1.92	12.56 ± 1.53	12.63 ± 1.59	11.52 ± 1.12
12a	Br	CH_3	12.24 ± 1.21	12.24 ± 1.21	11.31 ± 1.16	11.15 ± 1.13
12b	Br	F	1.22 ± 1.01	1.35 ± 1.03	1.32 ± 1.02	1.14 ± 1.01
12c	Br	NO_2	6.40 ± 0.14	5.34 ± 0.11	7.15 ± 0.15	8.27 ± 0.13
14a	Br	F	1.21 ± 0.01	1.13 ± 0.02	1.30 ± 0.01	1.24 ± 0.01
14b	F	F	1.12 ± 0.01	1.14 ± 0.02	1.23 ± 0.01	1.20 ± 0.01
14c	OCH_3	F	11.21 ± 1.52	13.56 ± 1.35	15.32 ± 1.31	17.51 ± 1.11
14d	CH_3	F	12.15 ± 1.41	14.44 ± 1.44	13.36 ± 1.32	18.41 ± 1.11
15a	Br	F	2.23 ± 0.12	2.32 ± 0.11	2.13 ± 0.12	3.15 ± 0.13
15b	F	F	1.15 ± 0.03	1.24 ± 0.01	1.15 ± 0.03	1.23 ± 0.01
15c	CH_3	F	14.62 ± 1.35	16.48 ± 1.18	14.57 ± 1.22	10.53 ± 1.41
15d	Br	OCH_3	4.12 ± 0.22	5.63 ± 0.25	3.21 ± 0.21	4.14 ± 0.21
15e	OCH_3	F	17.51 ± 1.65	16.63 ± 1.45	15.54 ± 1.34	19.65 ± 1.42
Fluconazole			2.11 ± 0.11	4.35 ± 0.54	9.22 ± 1.15	6.57 ± 0.47

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 and 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 experimental procedure C for the synthesis of compounds *6a*–*6d* and *11a*–*11d*

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, 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, saturated $NaHCO_3$ aqueous solution, H_2O, dried over $MgSO_4$, concentrated in vacuo and 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 $NaHCO_3$ solution and H_2O, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (DCM/EtOAc, 8/2 to 7/3) to give 1*H*-imidazol-2-yl-*N*-phenylimidazo[1,2-*a*]pyridin-3-amine derivatives **6a**–**11d**.

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

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 was stirred at the same temperature for 30 min. Then benzoylhydrazide (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 1 N HCl aqueous solution, saturated $NaHCO_3$ solution, H_2O, dried over $MgSO_4$, concentrated in vacuo and was used in the next step without further purification. To this diamide $POCl_3$ (10 ml) was added 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 and washed thoroughly with water. The crude was dissolved in EtOAc, washed with a saturated $NaHCO_3$ solution, H_2O, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (DCM/EtOAc, 8/2 to 7/3) to give 1,3,4-oxadiazol-2-yl-*N*-phenylimidazo[1,2-*a*]pyridin-3-amine derivatives **7a**–**12e**.

4.2.5. 6-(6-Bromo-1H-benzo[d]imidazol-2-yl)-2-(5-fluoro-1H-indol-3-yl)-N-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-amine (*5*)

This derivative was synthesized according to the general experimental procedure B. Yield 66%, white solid, m.p. 198–199 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 10.05 (s, 1H), 8.96 (d, $J = 9.6$ Hz, 1H), 8.79 (bs, 1H), 8.64 (d, $J = 8.6$ Hz, 1H), 8.14 (dd, $J = 7.1$, 8.7 Hz, 1H), 7.94 (bs, 1H), 7.82 (bs, 1H), 7.49 (d, $J = 1.7$ Hz, 1H), 7.38–6.99 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 160.5, 158.6, 155.9, 149.8, 142.3, 140.6, 134.5, 132.1, 130.2, 128.8, 128.3, 125.7, 124.6, 120.5, 119.3, 118.6, 117.2, 115.1, 112.8, 111.4, 110.7, 105.3, 105.1, 98.6. HRMS (ESI): calcd. for $C_{28}H_{17}BrF_2N_6$ $[M + Na]^+$: 577.05638; found 577.05631.

4.2.6. 2-(5-Bromo-1H-indol-3-yl)-N-(4-fluorophenyl)-6-(5-(4-nitrophenyl)-1H-imidazol-2-yl)imidazo[1,2-a]pyridin-3-amine (*6a*)

This derivative was synthesized according to the general experimental procedure C. Yield 61%, white solid, m.p. 208–209 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.99 (s, 1H), 9.32 (s, 1H), 8.46 (d, $J = 1.6$ Hz, 1H), 8.22–7.95 (m, 8H), 7.47 (m, 2H), 7.39 (d, $J = 7.9$ Hz,

2H), 7.21 (d, J = 7.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 149.3, 147.5, 140.9, 134.3, 132.4, 130.7, 129.6, 127.8, 125.6, 124.5, 122.3, 121.8, 120.4, 119.2, 118.7, 118.1, 115.5, 113.3, 112.6, 98.4. HRMS (ESI): calcd. for $C_{30}H_{19}BrFN_7O_2$ $[M + Na]^+$: 630.06653; found 630.06662.

4.2.7. 2-(5-Bromo-1H-indol-3-yl)-N-(4-fluorophenyl)-6-(5-p-tolyl-1H-imidazol-2-yl)imidazo[1,2-a]pyridin-3-amine (**6b**)

This derivative was synthesized according to the general experimental procedure C. Yield 56%, white solid, m.p. 199–200 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 10.31 (s, 1H), 9.39 (bs, 1H), 8.52 (d, J = 1.4 Hz, 1H), 8.25 (dd, J = 3.5, 9.8 Hz, 2H), 8.11 (bs, 2H), 7.95 (s, 1H), 7.45–7.34 (m, 6H), 7.19 (d, J = 7.3 Hz, 1H), 2.49 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 148.6, 147.4, 137.5, 134.8, 132.1, 131.9, 130.4, 128.7, 128.3, 125.6, 124.1, 122.9, 122.3, 120.4, 119.3, 115.7, 113.2, 112.5, 98.7, 22.4. HRMS (ESI): calcd. for $C_{31}H_{22}BrFN_6$ $[M + Na]^+$: 599.09710; found 599.09717.

4.2.8. 2-(5-Bromo-1H-indol-3-yl)-N-(4-fluorophenyl)-6-(5-(4-fluorophenyl)-1H-imidazol-2-yl)imidazo[1,2-a]pyridin-3-amine (**6c**)

This derivative was synthesized according to the general experimental procedure C. Yield 69%, white solid, m.p. 203–204 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.89 (s, 1H), 9.32 (bs, 1H), 8.64 (d, J = 1.5 Hz, 1H), 8.36 (d, J = 9.1 Hz, 2H), 8.08 (d, J = 7.1 Hz, 1H), 7.85 (s, 1H), 7.64 (s, 1H), 7.41 (dd, J = 1.6, 7.2 Hz, 1H), 7.39 (d, J = 7.9 Hz, 2H), 7.22 (s, 1H), 7.13 (dd, J = 1.7, 7.2 Hz, 2H), 7.03 (dd, J = 1.4, 8.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 163.6, 159.1, 148.4, 147.2, 140.7, 134.5, 132.3, 130.2, 128.4, 126.5, 125.7, 125.4, 122.6, 120.3, 119.6, 118.5, 115.3, 115.1, 113.2, 112.9, 97.9. HRMS (ESI): calcd. for $C_{30}H_{19}BrF_2N_6$ $[M + Na]^+$: 603.07203; found 603.07211.

4.2.9. 2-(5-Bromo-1H-indol-3-yl)-N-(4-fluorophenyl)-6-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)imidazo[1,2-a]pyridin-3-amine (**7a**)

This derivative was synthesized according to the general procedure D. Yield 55%, white solid, m.p. 189–190 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.29 (s, 1H), 8.59 (s, 1H), 8.24 (d, J = 7.3 Hz, 2H), 7.89 (s, 1H), 7.75 (d, J = 5.3 Hz, 2H), 7.63 (d, J = 5.9 Hz, 2H), 7.44 (m, 2H), 7.40 (d, J = 1.5 Hz, 1H), 7.38 (m, 3H), 7.13 (dd, J = 1.7, 5.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 167.4, 163.7, 157.6, 154.8, 147.4, 134.8, 132.3, 130.4, 128.7, 126.5, 125.9, 125.3, 124.8, 120.4, 119.7, 119.1, 115.6, 115.3, 114.5, 113.2, 110.1, 98.2. HRMS (ESI): calcd. for $C_{29}H_{17}BrF_2N_6O$ $[M + Na]^+$: 605.05130; found 605.05123.

4.2.10. 2-(5-Bromo-1H-indol-3-yl)-N-(4-fluorophenyl)-6-(5-p-tolyl-1,3,4-oxadiazol-2-yl)imidazo[1,2-a]pyridin-3-amine (**7b**)

This derivative was synthesized according to the general experimental procedure D. Yield 67%, white solid, m.p. 202–203 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.31 (s, 1H), 8.61 (s, 1H), 8.15 (m, 4H), 7.56–7.45 (m, 7H), 7.34 (d, J = 7.1 Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 158.1, 154.3, 147.5, 138.7, 137.6, 134.4, 132.5, 130.8, 129.1, 127.5, 127.3, 125.6, 124.9, 124.4, 120.7, 120.3, 119.1, 114.8, 112.7, 109.9, 97.6, 22.1. HRMS (ESI): calcd. for $C_{30}H_{20}BrFN_6O$ $[M + Na]^+$: 601.07637; found 601.07629.

4.2.11. 2-(5-Bromo-1H-indol-3-yl)-N-(4-fluorophenyl)-6-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)imidazo[1,2-a]pyridin-3-amine (**7c**)

This derivative was synthesized according to the general experimental procedure D. Yield 71%, white solid, m.p. 213–214 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.27 (s, 1H), 8.56 (s, 1H), 8.42 (m, 4H), 8.20 (d, J = 7.3 Hz, 2H), 7.94 (bs, 1H), 7.49–7.38 (m, 5H), 6.97 (d, J = 7.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 158.5, 154.1, 152.3, 147.4, 139.1, 137.5, 136.2, 134.3, 132.6, 130.4, 129.2, 127.9, 126.1, 125.7, 124.3, 120.5, 119.6, 119.2, 115.4, 113.2, 110.3, 98.7. HRMS (ESI): calcd. for $C_{29}H_{17}BrFN_7O_3$ $[M + Na]^+$: 632.04579; found 632.04570.

4.2.12. 2-(6-Bromoquinolin-3-yl)-N-(4-fluorophenyl)-6-(6-methyl-1H-benzo[d]imidazol-2-yl)imidazo[1,2-a]pyridin-3-amine (**10a**)

This derivative was synthesized according to the general experimental procedure B. Yield 73%, white solid, m.p. 207–208 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 10.58 (s, 1H), 9.17 (d, J = 8.4 Hz, 1H), 8.75 (s, 1H), 8.49 (s, 1H), 8.42 (s, 1H), 8.23 (d, J = 8.1 Hz, 2H), 7.94 (dd, J = 7.1, 8.4 Hz, 2H), 7.79 (d, J = 1.4 Hz, 1H), 7.74 (bs, 1H), 7.39 (m, 4H), 7.21 (bs, 1H), 7.09 (d, J = 6.9 Hz, 1H), 2.49 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 160.2, 151.1, 149.5, 145.9, 145.3, 144.4, 143.1, 136.7, 135.8, 134.2, 131.3, 129.7, 128.5, 126.1, 124.5, 121.3, 120.6, 120.2, 118.4, 117.1, 22.3. HRMS (ESI): calcd. for $C_{30}H_{20}BrFN_6$ $[M + Na]^+$: 585.08145; found 585.08153.

4.2.13. 2-(6-Bromoquinolin-3-yl)-6-(6-fluoro-1H-benzo[d]imidazol-2-yl)-N-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-amine (**10b**)

This derivative was synthesized according to the general experimental procedure B. Yield 65%, white solid, m.p. 215–216 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 10.49 (s, 1H), 9.21 (s, 1H), 8.97 (s, 1H), 8.77 (s, 1H), 8.59 (d, J = 8.7 Hz, 1H), 8.39 (d, J = 8.2 Hz, 1H), 8.14 (dd, J = 7.2, 8.3 Hz, 2H), 7.89–7.71 (m, 3H), 7.46 (d, J = 8.4 Hz, 2H), 7.31 (dd, J = 1.5, 5.6 Hz, 1H), 7.13 (d, J = 7.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 159.8, 151.4, 149.5, 145.9, 145.3, 140.6, 137.3, 136.4, 134.5, 131.2, 130.7, 129.8, 128.5, 125.2, 124.8, 122.5, 120.7, 120.3, 118.6, 111.5, 110.9, 106.1, 105.8. HRMS (ESI): calcd. for $C_{29}H_{17}BrF_2N_6$ $[M + Na]^+$: 589.05638; found 589.05645.

4.2.14. 2-(6-Bromoquinolin-3-yl)-N-(4-fluorophenyl)-6-(6-nitro-1H-benzo[d]imidazol-2-yl)imidazo[1,2-a]pyridin-3-amine (**10c**)

This derivative was synthesized according to the general experimental procedure B. Yield 53%, white solid, m.p. 205–206 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 10.81 (s, 1H), 9.17 (d, J = 7.0 Hz, 1H), 8.96 (s, 1H), 8.73 (d, J = 2.7 Hz, 1H), 8.37 (d, J = 8.4 Hz, 1H), 8.09 (bs, 1H), 7.94 (dd, J = 7.1, 8.3 Hz, 2H), 7.78–7.73 (m, 3H), 7.52 (d, J = 5.6 Hz, 1H), 7.39 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 7.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 159.7, 151.5, 150.3, 145.2, 141.4, 137.6, 136.5, 134.3, 131.4, 130.1, 129.2, 126.7, 122.4, 120.8, 120.2, 119.7, 117.9, 116.5, 108.1. HRMS (ESI): calcd. for $C_{29}H_{17}BrFN_7O_2$ $[M + Na]^+$: 616.05088; found 616.05079.

4.2.15. 2-(6-Bromoquinolin-3-yl)-N-(4-fluorophenyl)-6-(5-(4-fluorophenyl)-1H-imidazol-2-yl)imidazo[1,2-a]pyridin-3-amine (**11a**)

This derivative was synthesized according to the general experimental procedure C. Yield 59%, white solid, m.p. 195–196 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 10.54 (s, 1H), 9.28 (dd, J = 0.9, 9.7 Hz, 1H), 8.92 (s, 1H), 8.49 (m, 2H), 8.28 (d, J = 8.3 Hz, 1H), 8.14 (d, J = 8.7 Hz, 2H), 7.92 (dd, J = 7.2, 8.5 Hz, 2H), 7.79 (m, 2H), 7.45 (bs, 1H), 7.37 (m, 2H), 7.18 (d, J = 4.5 Hz, 2H), 7.03 (d, J = 7.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 163.2, 159.5, 151.3, 148.6, 147.4, 145.8, 141.3, 136.7, 134.5, 131.3, 130.2, 127.6, 126.4, 125.9, 123.7, 120.8, 120.1, 119.6, 119.2, 115.4, 114.3. HRMS (ESI): calcd. for $C_{31}H_{19}BrF_2N_6$ $[M + Na]^+$: 615.07203; found 615.07213.

4.2.16. 2-(6-Bromoquinolin-3-yl)-N-(4-fluorophenyl)-6-(5-p-tolyl-1H-imidazol-2-yl)imidazo[1,2-a]pyridin-3-amine (**11b**)

This derivative was synthesized according to the general experimental procedure C. Yield 72%, white solid, m.p. 196–197 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 10.19 (s, 1H), 9.15 (d, J = 8.3 Hz, 1H), 9.08 (s, 1H), 8.81 (bs, 1H), 8.49 (m, 2H), 8.31 (d, J = 8.1 Hz, 1H),

7.98 (m, 3H), 7.79 (d, $J = 1.6$ Hz, 1H), 7.65 (d, $J = 8.8$ Hz, 1H), 6.61 (bs, 1H), 7.43–7.37 (m, 5H), 7.21 (d, $J = 7.5$ Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 151.5, 148.3, 147.6, 146.1, 141.2, 136.5, 134.4, 131.3, 130.7, 129.6, 127.2, 125.4, 124.6, 123.2, 122.9, 120.7, 120.3, 119.6, 22.7. HRMS (ESI): calcd. for $C_{32}H_{22}BrFN_6$ $[M + Na]^+$: 611.09710; found 611.09717.

4.2.17. 2-(6-Bromoquinolin-3-yl)-N-(4-fluorophenyl)-6-(5-p-tolyl-1,3,4-oxadiazol-2-yl)imidazo[1,2-a]pyridin-3-amine (**12a**)

This derivative was synthesized according to the general experimental procedure C. Yield 70%, white solid, m.p. 178–179 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 8.97 (s, 1H), 8.71 (s, 1H), 8.57 (d, $J = 8.3$ Hz, 2H), 7.99 (m, 2H), 7.94 (dd, $J = 7.1$, 8.4 Hz, 2H), 7.81 (bs, 1H), 7.75 (m, 3H), 7.48 (m, 4H), 6.99 (d, $J = 7.4$ Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 158.5, 154.7, 151.3, 146.4, 140.9, 136.4, 134.8, 131.5, 130.7, 128.4, 126.2, 125.3, 124.9, 124.6, 120.2, 119.8, 119.5, 118.7, 117.5. 21.5. HRMS (ESI): calcd. for $C_{31}H_{20}BrFN_6O$ $[M + Na]^+$: 613.07637; found 613.07645.

4.2.18. 2-(6-Bromoquinolin-3-yl)-N-(4-fluorophenyl)-6-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)imidazo[1,2-a]pyridin-3-amine (**12b**)

This derivative was synthesized according to the general experimental procedure D. Yield 66%, white solid, m.p. 185–186 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.14 (s, 1H), 8.53 (s, 1H), 8.48 (d, $J = 8.2$ Hz, 1H), 7.98 (dd, $J = 7.3$, 8.4 Hz, 2H), 7.77 (m, 3H), 7.56 (dd, $J = 5.1$, 8.6 Hz, 2H), 7.43 (d, $J = 8.1$ Hz, 2H), 7.24 (d, $J = 7.3$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 167.5, 164.3, 158.7, 154.4, 151.5, 145.9, 145.4, 144.1, 136.7, 134.5, 131.6, 130.2, 126.1, 125.7, 125.4, 125.1, 121.1, 120.5, 120.1, 119.6, 115.2, 115.3. HRMS (ESI): calcd. for $C_{30}H^{17}BrF^2N_6O$ $[M + Na]^+$: 617.05130; found 617.05139.

4.2.19. 2-(6-Bromoquinolin-3-yl)-N-(4-fluorophenyl)-6-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)imidazo[1,2-a]pyridin-3-amine (**12c**)

This derivative was synthesized according to the general experimental procedure D. Yield 64%, white solid, m.p. 189–190 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.07 (s, 1H), 8.67 (m, 4H), 8.39 (d, $J = 8.4$ Hz, 1H), 8.21 (dd, $J = 7.1$, 8.5 Hz, 2H), 7.94 (s, 1H), 7.89 (m, 3H), 7.81 (d, $J = 1.5$ Hz, 2H), 7.49 (d, $J = 7.2$ Hz, 2H), 7.18 (d, $J = 7.1$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 158.3, 154.5, 152.2, 151.7, 146.5, 145.6, 144.7, 136.4, 134.8, 131.2, 130.5, 126.6, 126.1, 125.4, 123.9, 121.2, 120.8, 119.7, 118.3. HRMS (ESI): calcd. for $C_{30}H_{17}BrFN_7O_3$ $[M + Na]^+$: 644.04579; found 644.04586.

4.2.20. 2-(6-Bromoquinolin-3-yl)-7-fluoro-N-(4-fluorophenyl) imidazo[2,1-b][1,3]benzothiazol-3-amine (**14a**)

This derivative was synthesized according to the general experimental procedure A. Yield 71%, white solid, m.p. 219–220 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.34 (d, $J = 2.9$ Hz, 1H), 8.97 (d, $J = 3.3$ Hz, 1H), 8.71 (dd, $J = 2.2$, 8.3 Hz, 2H), 8.41 (s, 1H), 7.63 (bs, 1H), 7.52 (bs, 2H), 7.49–7.24 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 164.7, 161.3, 160.5, 156.4, 148.1, 147.4, 144.3, 142.5, 138.6, 137.4, 134.8, 127.5, 121.4, 121.1, 120.9, 119.6, 117.5, 117.2, 116.8, 116.3, 114.5, 111.4, 110.8, 110.2, 56.6. HRMS (ESI): calcd. for $C_{24}H_{13}BrF_2N_4S$ $[M + Na]^+$: 528.99101; found 528.99114.

4.2.21. 7-Fluoro-N-(4-fluorophenyl)-2-(6-fluoroquinolin-3-yl) imidazo[2,1-b][1,3]benzothiazol-3-amine (**14b**)

This derivative was synthesized according to the general experimental procedure A. Yield 53%, white solid, m.p. 211–212 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.41 (s, 1H), 8.74 (m, 3H), 8.47 (m, 2H), 7.98 (d, $J = 8.1$ Hz, 1H), 7.41–7.11 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 165.3, 164.5, 161.2, 160.8, 159.5, 156.4, 148.2, 146.7, 144.5, 143.9, 138.6, 137.2, 134.5, 129.1, 122.4, 120.8, 120.4, 117.6, 116.7, 116.4, 115.8, 115.1, 114.5, 111.3, 110.6. HRMS (ESI): calcd. for $C_{24}H_{13}F_3N_4S$ $[M + Na]^+$: 469.07107; found 469.07113.

4.2.22. 7-Fluoro-N-(4-fluorophenyl)-2-(6-methoxyquinolin-3-yl) imidazo[2,1-b][1,3]benzothiazol-3-amine (**14c**)

This derivative was synthesized according to the general experimental procedure A. Yield 59%, white solid, m.p. 216–217 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.31 (d, $J = 2.9$ Hz, 1H), 8.74 (s, 1H), 8.61 (d, $J = 6.4$ Hz, 2H), 8.13 (d, $J = 8.6$ Hz, 1H), 7.41–7.13 (m, 6H), 3.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 165.1, 162.3, 161.2, 156.4, 149.1, 147.3, 144.5, 142.2, 138.7, 137.8, 134.4, 127.6, 121.5, 120.8, 120.2, 117.4, 116.5, 116.1, 114.3, 110.9, 110.4, 109.8. HRMS (ESI): calcd. for $C_{25}H_{16}F_2N_4OS$ $[M + Na]^+$: 481.09106; found 481.09113.

4.2.23. 7-Fluoro-N-(4-fluorophenyl)-2-(6-methylquinolin-3-yl) imidazo[2,1-b][1,3]benzothiazol-3-amine (**14d**)

This derivative was synthesized according to the general experimental procedure A. Yield 60%, white solid, m.p. 227–228 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 9.27 (d, $J = 3.1$ Hz, 1H), 8.71 (d, $J = 6.2$ Hz, 2H), 8.39 (d, $J = 2.9$ Hz, 1H), 8.17 (bd, $J = 3.0$ Hz, 1H), 7.39–7.14 (m, 7H), 2.59 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 165.2, 161.3, 159.1, 156.4, 147.6, 146.9, 140.3, 136.3, 133.2, 128.8, 126.5, 124.1, 120.8, 120.2, 116.9, 116.3, 116.1, 115.7, 114.9, 114.2, 111.3, 110.6, 22.5. HRMS (ESI): calcd. for $C_{25}H_{16}F_2N_4S$ $[M + Na]^+$: 465.09614; found 465.09621.

4.2.24. 2-(5-Bromo-1H-indol-3-yl)-7-fluoro-N-(4-fluorophenyl) imidazo[2,1-b][1,3]benzothiazol-3-amine (**15a**)

This derivative was synthesized according to the general experimental procedure A. Yield 64%, white solid, m.p. 203–204 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 8.72 (d, $J = 1.6$ Hz, 2H), 8.17 (d, $J = 2.1$ Hz, 1H), 8.09 (s, 1H), 7.37–7.09 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 164.1, 160.4, 159.3, 156.5, 143.3, 142.1, 139.7, 138.2, 134.5, 133.4, 131.3, 130.6, 125.5, 124.1, 121.2, 117.4, 116.1, 115.3, 114.7, 113.3, 112.6, 110.5, 109.7. HRMS (ESI): calcd. for $C_{23}H_{13}BrF_2N_4S$ $[M + Na]^+$: 516.99101; found 516.99109.

4.2.25. 7-Fluoro-2-(5-fluoro-1H-indol-3-yl)-N-(4-fluorophenyl) imidazo[2,1-b][1,3]benzothiazol-3-amine (**15b**)

This derivative was synthesized according to the general experimental procedure A. Yield 67%, white solid, m.p. 213–214 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 8.54 (d, $J = 3.5$ Hz, 1H), 8.47 (dd, $J = 6.2$, 8.3 Hz, 2H), 8.17 (s, 1H), 7.63 (bs, 1H), 7.35–7.12 (m, 7H), 6.72 (d, $J = 2.8$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 163.9, 160.7, 160.1, 159.2, 155.8, 154.9, 142.3, 137.8, 136.5, 135.7, 133.4, 129.3, 124.1, 117.4, 115.2, 114.8, 114.3, 113.6, 110.5, 109.7, 109.2, 108.9, 107.5, 106.7. HRMS (ESI): calcd. for $C_{23}H_{13}F_3N_4S$ $[M + Na]^+$: 457.07107; found 457.07113.

4.2.26. 7-Fluoro-N-(4-fluorophenyl)-2-(5-methyl-1H-indol-3-yl) imidazo[2,1-b][1,3]benzothiazol-3-amine (**15c**)

This derivative was synthesized according to the general experimental procedure A. Yield 61%, white solid, m.p. 206–207 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 8.64 (dd, $J = 5.7$, 6.4 Hz, 2H), 8.23 (bs, 1H), 7.89 (s, 1H), 7.34–7.28 (m, 6H), 7.23 (d, $J = 5.2$ Hz, 1H), 7.13 (d, $J = 5.7$ Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 164.3, 160.7, 158.9, 156.3, 146.1, 142.3, 138.5, 137.6, 131.8, 130.3, 130.1, 127.6, 126.5, 123.4, 119.7, 117.4, 115.3, 115.1, 114.6, 113.5, 110.4, 109.5, 21.9. HRMS (ESI): calcd. for $C_{24}H_{16}F_2N_4S$ $[M + Na]^+$: 453.09614; found 453.09621.

4.2.27. 2-(5-Bromo-1H-indol-3-yl)-N-(4-fluorophenyl)-7-methoxyimidazo[2,1-b][1,3]benzothiazol-3-amine (**15d**)

This derivative was synthesized according to the general experimental procedure A. Yield 65%, white solid, m.p. 199–200 °C.

^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 8.67 (dd, $J = 5.8$, 6.3 Hz, 2H), 8.17 (d, $J = 2.2$ Hz, 1H), 8.09 (s, 1H), 7.83 (d, $J = 8.4$ Hz, 1H), 7.37–7.29 (m, 4H), 7.14 (d, $J = 3.1$ Hz, 1H), 6.29 (d, $J = 5.8$ Hz, 1H), 3.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 164.7, 161.2, 159.5, 143.1, 141.3, 139.7, 138.5, 134.3, 131.4, 130.6, 129.8, 125.3, 124.2, 123.6, 121.3, 117.5, 115.8, 115.1, 114.8, 113.5, 110.7, 108.4, 55.9. HRMS (ESI): calcd. for $C_{24}H_{16}BrFN_4OS$ $[M + Na]^+$: 529.01099; found 529.01089.

4.2.28. 7-Fluoro-N-(4-fluorophenyl)-2-(5-methoxy-1H-indol-3-yl) imidazo[2,1-b][1,3]benzothiazol-3-amine (**15e**)

This derivative was synthesized according to the general experimental procedure A. Yield 63%, white solid, m.p. 198–199 °C. ^{1}H NMR (300 MHz, $CDCl_3$, in ppm): δ 8.71 (dd, $J = 5.7$, 6.4 Hz, 2H), 8.23 (s, 1H), 7.49(s, 1H), 7.31–7.19 (m, 5H), 6.87 (d, $J = 5.7$ Hz, 1H), 4.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, in ppm): δ 163.8, 160.3, 159.4, 156.1, 153.9, 145.5, 142.3, 138.4, 134.6, 133.7, 130.5, 126.2, 117.4, 115.8, 114.6, 113.5, 113.2, 112.7, 112.1, 110.8, 110.2, 101.5, 56.1. HRMS (ESI): calcd. for $C_{24}H_{16}F_2N_4OS$ $[M + Na]^+$: 469.09106; found 469.09112.

4.3. In vitro antimicrobial procedure

Minimum inhibitory concentration (MIC) values for the synthesized compounds were determined by using broth microdilution. Standard and isolated strains of the bacteria; Gram-positive: *S. aureus*, *E. faecalis* and *B. megaterium* and Gram-negative bacteria: *E. coli*, *P. aeruginosa* and *E. aerogenes* were used to determine antibacterial activity. For antifungal activity, standard strains of *C. albicans*, *C. parapsilosis*, *A. flavus* and *M. gypsuem* were used. Ampicillin, cefixime and fluconazole were used as references. All bacteria were cultivated in Mueller–Hinton Agar and were diluted with Mueller–Hinton Broth (Oxoid). All fungi were cultivated in Sabouraud Dextrose Agar. The fungi inoculums were prepared in Sabouraud liquid medium (Oxoid), which were kept at 37 °C 12 h, and were diluted with RPMI-1640 medium and L-glutamine and buffered with 3-[*N*-morpholino]-propansulfonic acid (MOPS) at pH 7. The synthesized compounds and references were dissolved in DMSO/H_2O (50%), at a concentration of 1000 μg/mL. Two-fold dilutions of the synthesized compounds and reference compounds were added to the wells (500, 250…0.20 μg/mL). Then, a suspension of the microorganisms was inoculated into all wells. Final inoculum concentrations in the wells were 100 cfu/mL for bacteria and 2.5 × 100 cfu/mL for fungi. The sealed microplates were incubated at 37 °C for 24 h for antibacterial activity and at 37 °C for 48 h for antifungal activity in a humid chamber. At the end of the incubation period, MIC values were recorded as the lowest concentrations of the substances that had no visible turbidity.

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References

[1] J. Davies, Nature 383 (1996) 219–220.
[2] D.T.W. Chu, J.J. Plattner, L. Katz, J. Med. Chem. 39 (1996) 3853–3874.
[3] M. Grare, M. Mourer, S. Fontanay, J.B. Regnouf-de-Vains, C. Finance, R.E. Duval, J. Antimicrob. Chemother. 60 (2007) 575–581.
[4] M.A. Ghannoum, L.B. Rice, Clin. Microbiol. Rev. 12 (1999) 501–517.
[5] D.A. Williams, T.L. Lemke, Foye's Principles of Medicinal Chemistry, fifth ed. Lippincott Williams and Wilkins, 2002.
[6] F.C. Odds, J. Antimicrob. Chemother. 31 (1993) 463–471.
[7] C.A. Hitchock, Biochem. Soc. Trans. 21 (1993) 1039–1047.
[8] E.M. Johnson, D.W. Warnock, J. Luker, S.R. Porter, J. Antimicrob. Chemother. 35 (1995) 103–114.
[9] J.H. Rex, M.G. Rinaldi, M.A. Pfaller, Antimicrob. Agents Chemother. 39 (1995) 1–8.
[10] T.H. Al-Tel, R.A. Al-Qawasmeh, M.F. Schmidt, A. Al-Aboudi, S.N. Rao, S.S. Sabri, W. Voelter, J. Med. Chem. 52 (2009) 6484–6488.
[11] T.H. Al-Tel, R.A. Al-Qawasmeh, S.S. Sabri, W. Voelter, J. Org. Chem. 74 (2009) 4690–4696.
[12] T.H. Al-Tel, Eur. J. Med. Chem. 45 (2010) 5724–5731.
[13] S. Kuehnert, S. Oberboersch, C. Sundermann, M. Haurand, R. Jostock, K. Schiene, T. Tzschentke, T. Christoph, D. Kaulartz, (Gruenenthal GmbH, Germany). PCT Int. Appl. WO2006029980, (2006).
[14] C. Berset, S. Audetat, J. Tietz, T. Gunde, A. Barberis, A. Schumacher, P. Traxler. PCT Int. Appl. WO2005120513, (2005).
[15] D.S. Goldfarb. U.S. patent Appl. Publ. US 2008-341615, (2009).
[16] M.B. Van Niel, A. Miah, Brit. UK patent Appl. GB 2008-7129, 20080421, (2008).
[17] B. Venkata, S. Kumar, S.D. Vaidya, R.V. Kumar, S.B. Bhirud, R.B. Mane, Eur. J. Med. Chem. 41 (2006) 599–604.
[18] Y. Özkay, Y. Tunali, H. Karaca, I. Isikdag, Eur. J. Med. Chem. 45 (2010) 3293–3298.
[19] G. Coban, S. Zencir, I. Zupko, B. Rethy, H.S. Gunes, Z. Topcu, Eur. J. Med. Chem. 44 (2009) 2280–2285.
[20] N.P. Rai, V.K. Narayanaswamy, T. Govender, B.K. Manuprasad, S. Shashikanth, P.N. Arunachalam, Eur. J. Med. Chem. 45 (2010) 2677–2682.
[21] B. Chandrakantha, P. Shetty, V. Nambiyar, N. Isloor, A.M. Isloor, Eur. J. Med. Chem. 45 (2010) 1206–1210.
[22] S.L. Gaonkar, K.M.L. Rai, B. Prabhuswamy, Eur. J. Med. Chem. 41 (2006) 841–846.
[23] B.S. Dawane, S.G. Konda, G.G. Mandawad, B.M. Shaikh, Eur. J. Med. Chem. 45 (2010) 387–392.
[24] R. Rohini, K. Shanker, P.M. Reddy, Y.-P. Ho, V. Ravinder, Eur. J. Med. Chem. 44 (2009) 3330–3339.
[25] A. Naflous, N. Benchat, M. Mimouni, S. Abouricha, T. Ben-Hadda, B. El-Bali, A. Hakkou, B. Hacht, Lett. Drug Des. Discovery 1 (2004) 224–229.
[26] M.A. Martinez-Urbina, A. Zentella, M.A. Vilchis-Reyes, A. Guzman, O. Vargas, M.T.R. Apan, J.L.V. Gallegos, E. Diaz, Eur. J. Med. Chem. 45 (2010) 1211–1219.
[27] K.S. Gudmundsson, S.D. Boggs, J.G. Catalano, A. Svolto, A. Spaltenstein, M. Thomson, P. Wheelan, S. Jenkinson, Bioorg. Med. Chem. Lett. 19 (2009) 6399–6403.
[28] J.T. Starr, R.J. Sciotti, D.L. Hanna, M.D. Huband, L.M. Mullins, H. Cai, J.W. Gage, M. Lockard, M.R. Rauckhorst, R.M. Owen, M.S. Lall, M. Tomilo, H. Chen, S.P. McCurdy, M.R. Barbachyn, Bioorg. Med. Chem. Lett. 19 (2009) 5302–5306.
[29] Y. Imaeda, T. Kawamoto, M. Tobisu, N. Konishi, K. Hiroe, M. Kawamura, T. Tanaka, K. Kubo, Bioorg. Med. Chem. 16 (2008) 3125–3140.
[30] K.S. Gudmundsson, B.A. Johns, Bioorg. Med. Chem. Lett. 17 (2007) 2735–2739.
[31] C. Hamdouchi, B. Zhong, J. Mendoz, E. Collins, C. Jaramillo, J.E. De Diego, D. Robertson, C.D. Spencer, B.D. Anderson, S.A. Watkins, F. Zhanga, H.B. Brooks, Bioorg. Med. Chem. Lett. 15 (2005) 1943–1947.
[32] Z. Wu, M.E. Fraley, M.T. Bilodeau, M.L. Kaufman, E.S. Tasber, A.E. Balitza, G.D. Hartman, K.E. Coll, K. Rickert, J. Shipman, B. Shi, L. Sepp-Lorenzino, K.A. Thomas, Bioorg. Med. Chem. Lett. 14 (2004) 909–912.
[33] T.H. Al-Tel, R.A. Al-Qawasmeh, Eur. J. Med. Chem. 45 (2010) 5848–5855.
[34] K. Groebke, L. Weber, F. Mehlin, Synlett (1998) 661–663.
[35] C. Blackburn, B. Guan, P. Fleming, K. Shiosaki, S. Tsai, Tetrahedron Lett. 39 (1998) 3635–3638.
[36] T.H. Al-Tel, R.A. Al-Qawasmeh, W. Voelter, Eur. J. Org. Chem. (2010) 5586–5593.