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Antibacterial activities of Groebke–Blackburn–Bienaymé-derived imidazo[1,2-*a*]pyridin-3-amines

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ABSTRACT

We sought to explore the imidazo[1,2-*a*]pyridin-3-amines for TLR7 (or 8)-modulatory activities. This chemotype, readily accessed via the Groebke–Blackburn–Bienaymé multi-component reaction, resulted in compounds that were TLR7/8-inactive, but exhibited bacteriostatic activity against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA). To investigate the mechanism of antibacterial activity of this new chemotype, a resistant strain of *S. aureus* was generated by serially passaging the organism in escalating doses of the most active analogue. A comparison of minimum inhibitory concentrations (MICs) of known bacteriostatic agents in wild-type and resistant strains indicates a novel mechanism of action. Structure–activity relationship studies have led to the identification of positions on the scaffold for additional structural modifications that should allow for the introduction of probes designed to examine cognate binding partners and molecular targets, while not significantly compromising antibacterial potency.

1. Introduction

The introduction of antibiotics into the therapeutic armamentarium in the early 20th century revolutionized the management of microbial infections. Once considered 'wonder drugs', antibiotics have perhaps become victims of their own success, and resistance to these drugs have almost invariably followed on the heels of their widespread use (and misuse). The incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) infections continues to increase alarmingly not only in hospital-associated settings (nosocomial infections), but in recent times, also in community settings in the United States, and throughout the globe. The increase in morbidity and mortality due to *S. aureus* infections[1] is a reflection of increased invasive procedures, indwelling devices, older age, and comorbidities, as well as the acquisition of resistance to commonly-used antimicrobial agents. Of particular concern is the emergence of multidrug-resistant strains of Gram-positive bacteria, with the loss of susceptibility to a wide range of reserve antibiotics such as vancomycin.[2] The need for the development of effective antibiotics is urgent, especially in the face of a diminishing pipeline of drugs for antimicrobial chemotherapy.

Our work in the recent past has focused on the discovery and development of vaccine adjuvants. Of particular interest to us are small molecule agonists of toll-like receptor-7 (TLR7). Given that the known small molecule agonistic chemotypes are limited to imidazoquinolines[3–5] and oxoadenines,[6–10] we are actively exploring related structures. We have recently noted that 1*H*-imidazo[4,5-*c*]pyridin-4-amines are TLR7-agonistic (Yoo, E. et al., manuscript submitted, Fig. 1). We therefore asked whether the structurally-related imidazo[1,2-*a*]pyridin-3-amines (Fig. 1) would possess TLR7-modulatory properties. This chemotype is readily amenable to a rapid elaboration of combinatorial libraries using the one-pot multi-component Groebke–Blackburn–Bienaymé reaction.[11–13] An initial test-library of 24 compounds proved to be neither agonistic nor antagonistic at TLR7. However, some of the initial compounds were found to have antibacterial activity against *S. aureus* with a clear indication of possible structure–activity relationships. Subsequent focused libraries of compounds were synthesized. These latter compounds, too, were not active in TLR7 screens, but displayed prominent bacteriostatic activity against several Gram-positive bacteria, including methicillin-resistant *S. aureus* (MRSA). To investigate the mechanism of antibacterial activity of this new chemotype, a resistant strain of *S. aureus* was generated by serially passaging the organism in escalating doses of the most active analogue. A comparison of minimum inhibitory

Abbreviations: ATCC, American Type Culture Collection; DavePhos, 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl; *E. fecalis*, *Enterococcus fecalis*; ESI-TOF, electrospray ionization-time of flight; HIV, human immunodeficiency virus; MBC, minimum bactericidal concentration; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MW, microwave; NF-κB, nuclear factor-κB; $Pd_2(dba)_3$, tris(dibenzylideneacetone)dipalladium(0); SAR, structure–activity relationship; ssRNA, single-stranded RNA; *S. pneumoniae*, *Streptococcus pneumoniae*; *S. pyogenes*, *Streptococcus pyogenes*; TLR, toll like receptor.

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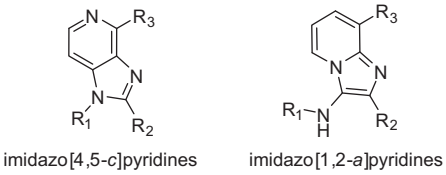
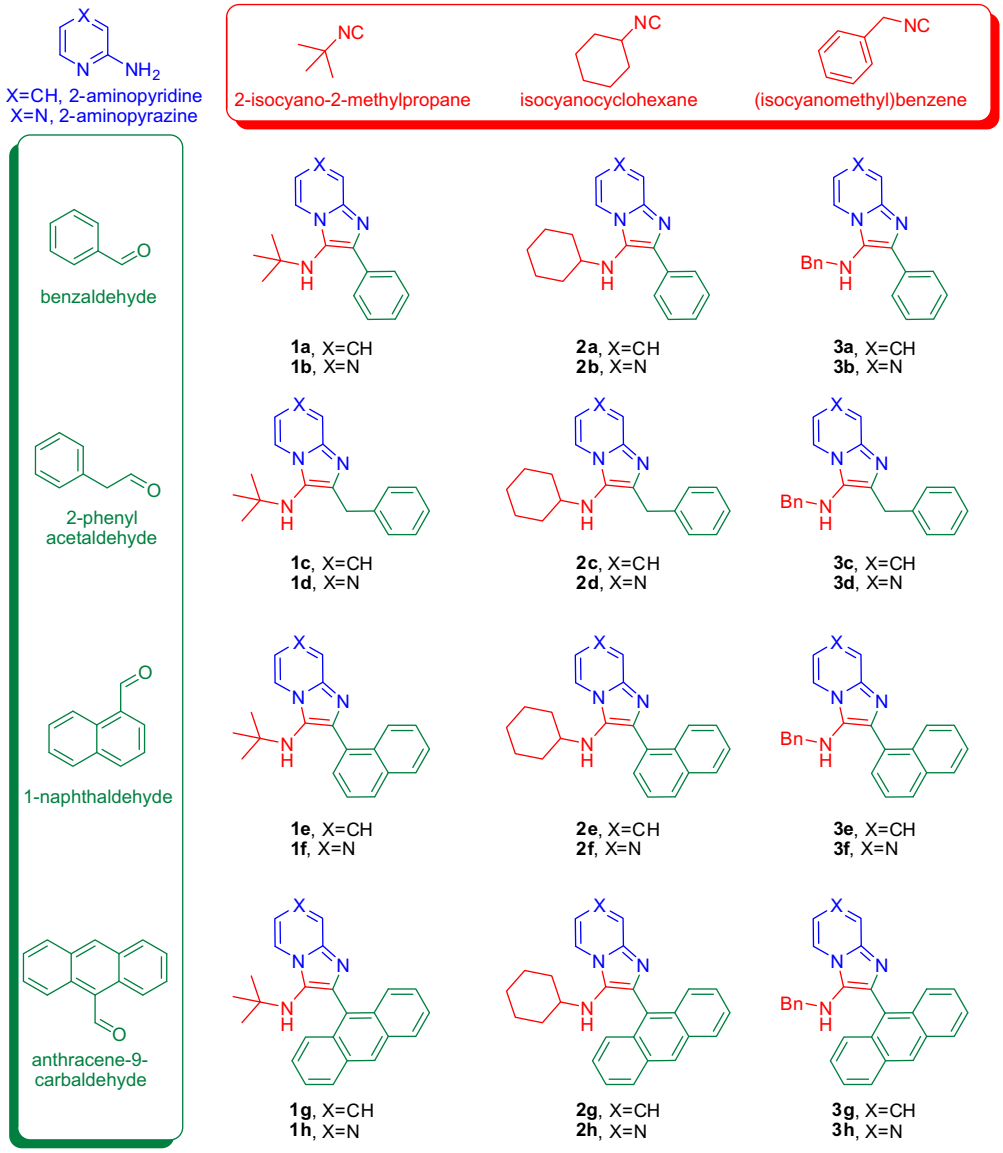


Figure 1. Structures of 1*H*-imidazo[4,5-*c*]pyridine and 1*H*-imidazo[1,2-*a*]pyridine scaffolds.

concentrations (MICs) of known bacteriostatic agents in wild-type and resistant strains indicate a novel mechanism of action. These findings served as a point of departure for further exploration of SAR and mechanisms of bacteriostatic activity in this chemotype.

2. Results and discussion

Our initial test-library comprising of twenty-four compounds was synthesized (Scheme 1) using two amidines (2-aminopyridine and 2-aminopyrazine), three isonitriles (2-isocyano-2-methylpropane, isocyanocyclohexane, (isocyanomethyl)benzene), and four aldehydes (benzaldehyde, 2-phenylacetaldehyde, 1-naphthaldehyde, anthracene-9-carbaldehyde). The syntheses of **1a**–**3h** (Scheme 1) proceeded smoothly. All compounds were tested in TLR7 agonism and antagonism assays using specific reporter gene-based cellular assays as described earlier[14–16]; to our disappointment, none of the compounds displayed any activity in these assays up to concentrations of 250 μM (data not shown). The assay plates were stored in the autoclave room at room temperature prior to disposal, and, quite by accident, we observed a dose-dependent inhibition of a bacterial contaminant in such plates. We therefore decided to examine the antibacterial activities of these compounds in antibacterial screens (*E. coli* ATCC 9637 and *S. aureus* ATCC 13709) routinely employed in our laboratory.[17,18] Four compounds were identified to be inhibitory to *S. aureus* ATCC 13709 but not *E. coli* ATCC 9637. Maximal antibacterial activity resided in compounds derived from 2-aminopyridine, bearing either a bulky *N*-*tert*-butyl or cyclohexyl groups at C3, and a large aromatic pendant group (naphthyl or anthracenyl) at C2 (**1e**, **1g**, **2e**,



Scheme 1. Synthesis of a library of compounds using Groebke multicomponent reaction using 2 different amidines, 3 different isonitriles and 4 different aldehydes. Reagents and conditions: (i) MW, 400 W, 110 °C, 20 min, HCl/dioxane, CH_3CN.

Table 1
Minimum inhibitory concentration values (μg/mL) of compounds[a]

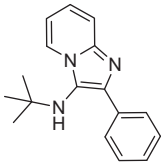
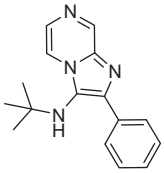
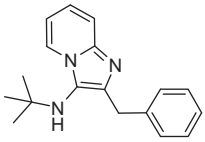
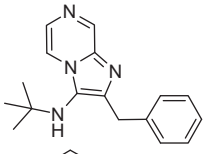
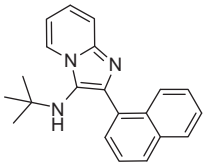
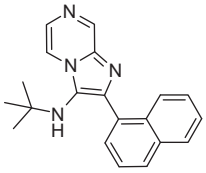
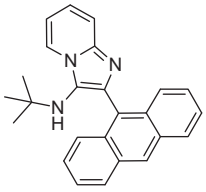
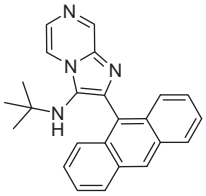
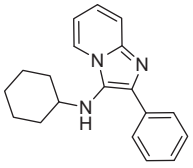
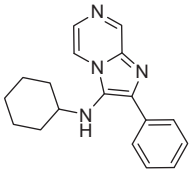
Structure	Compound number	MIC (μg/mL)	
		S. aureus	MRSA
	**1a**	ND	NT
	**1b**	ND	NT
	**1c**	ND	NT
	**1d**	ND	NT
	**1e**	62.5	31.25
	**1f**	ND	NT
	**1g**	3.91	3.91
	**1h**	ND	NT
	**2a**	ND	NT
	**2b**	ND	NT

Table 1 (*continued*)

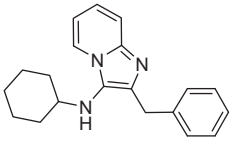
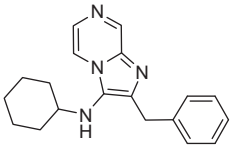
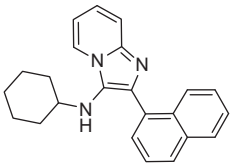
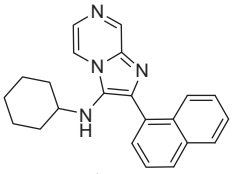
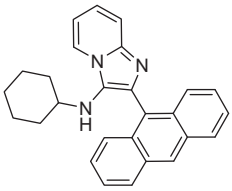
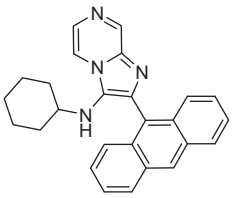
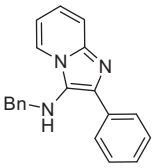
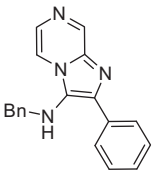
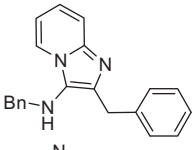
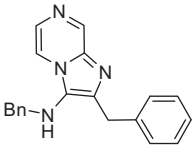
Structure	Compound number	MIC (μg/mL)	
		S. aureus	MRSA
	**2c**	ND	NT
	**2d**	ND	NT
	**2e**	7.81	15.62
	**2f**	ND	NT
	**2g**	3.91	3.91
	**2h**	7.81	NT
	**3a**	ND	NT
	**3b**	ND	NT
	**3c**	ND	NT
	**3d**	ND	NT

Table 1 (*continued*)

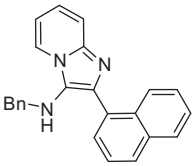
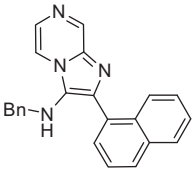
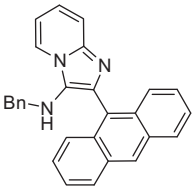
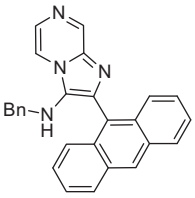
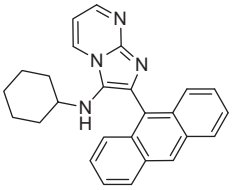
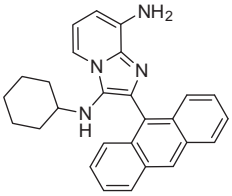
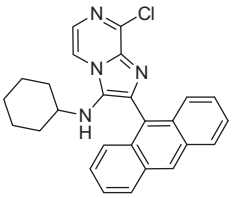
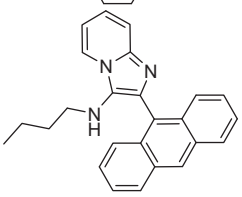
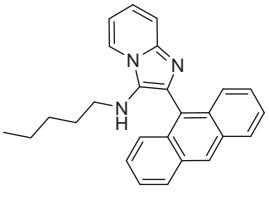
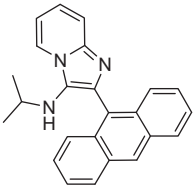
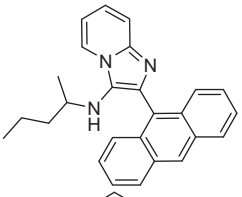
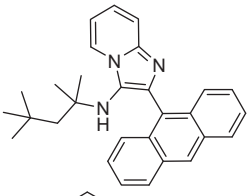
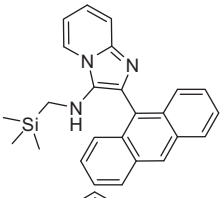
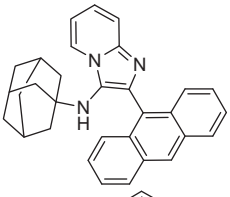
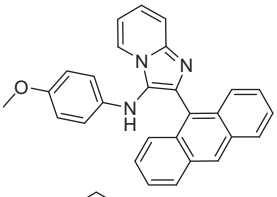
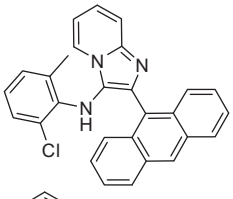
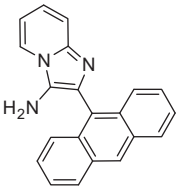
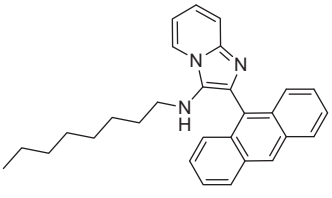
Structure	Compound number	MIC (μg/mL)	
		S. aureus	MRSA
	**3e**	15.62	NT
	**3f**	ND	NT
	**3g**	ND	NT
	**3h**	ND	NT
	**4a**	15.62	NT
	**4b**	15.62	NT
	**4c**	ND	NT
	**5a**	3.91	7.81
	**5b**	3.91	7.81

Table 1 (*continued*)

Structure	Compound number	MIC (μg/mL)	
		S. aureus	MRSA
	**5c**	15.62	15.62
	**5d**	7.81	3.91
	**5e**	3.91	3.91
	**5f**	15.62	NT
	**5g**	15.62	NT
	**5h**	ND	NT
	**5i**	ND	NT
	**6**	ND	NT
	**7a**	7.81	NT

(*continued on next page*)

Table 1 (*continued*)

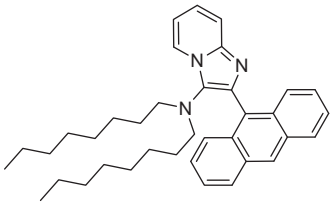
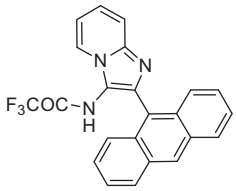
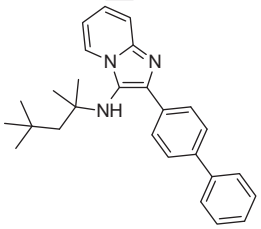
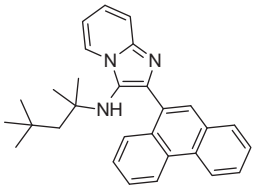
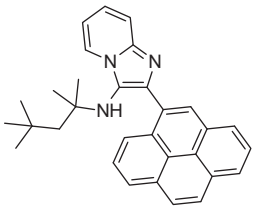
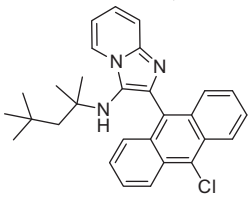
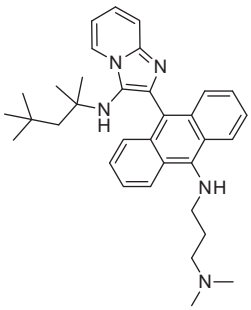
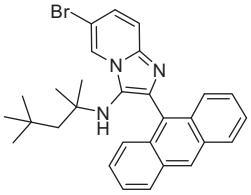
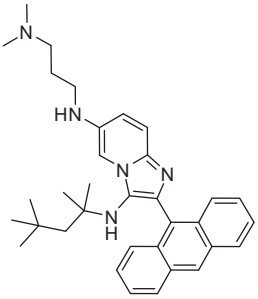
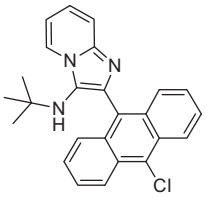
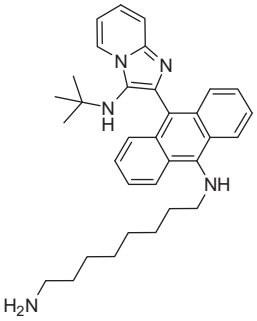
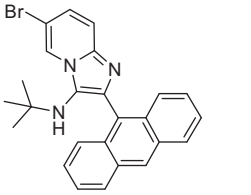
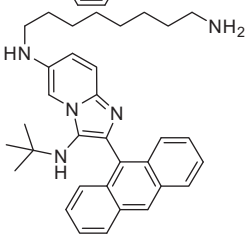
Structure	Compound number	MIC (μg/mL)	
		S. aureus	MRSA
	**7b**	31.25	NT
	**7c**	62.5	NT
	**8a**	ND	NT
	**8b**	7.81	NT
	**8c**	15.62	NT
	**9**	7.81	NT
	**10**	3.91	NT

Table 1 (*continued*)

Structure	Compound number	MIC (μg/mL)	
		S. aureus	MRSA
	**11**	15.62	NT
	**12**	3.91	NT
	**13**	7.81	NT
	**14**	7.81	15.62
	**15**	15.62	NT
	**16**	3.91	7.81

[a] ND denotes no activity detected at 100 μg/mL and NT denotes not tested.

2g, Scheme 1, Table 1). The MICs of both **1g** and **2g** for *S. aureus* ATCC 13709 and MRSA ATCC 33591 were 3.91 μg/mL, (Table 1), and 7.81 μg/mL for coagulase-negative *S. epidermidis* ATCC 35983 (Supplementary data). We examined the MIC values of representative leads (**1e**, **1g** and **2g**) against a variety of other Gram-positive organisms (*Enterococcus fecalis (E. fecalis*) clinical isolates of *Streptococcus pneumoniae (S. pneumoniae)* and *Streptococcus pyogenes (S. pyogenes)*); significant MICs (<10 μg/mL) were observed in all of the leads only against *S. pyogenes*, indicating a narrow spectrum of activity (data not shown).

The active compounds listed above were all determined to be bacteriostatic rather than bactericidal by conventional microplate MBC assays (Fig. 2).[19] The outer membrane of Gram-negative bacteria serves as a permeability barrier for hydrophobic antimicrobials[20,21], and we wondered if the lack of activity of these compounds against Gram-negative bacteria could be attributable to its bulky, nonpolar nature. We therefore performed additional assays using polymyxin B nonapeptide,[22–24] which is commonly used to permeabilize the outer-membranes of Gram-negative bacteria, rendering the organisms susceptible to otherwise impermeable antimicrobials[17]; however, the imidazopyridines did not exert any significant antibacterial effect even at high concentrations of polymyxin B nonapeptide (Fig. 2), confirming that the antibacterial spectrum of these compounds is specific to Gram-positive organisms.

Given that **1g** and **2g** demonstrated identical potencies, we arbitrarily selected isocyanocyclohexane and anthracene-9-carbaldehyde as the invariant components, and varied the amidine component; we chose 2-aminopyrimidine, 2,3-diaminopyridine, and 2-amino-3-chloropyrazine (Scheme 2). The 2-amino-3-chloropyrazine-derived compound **4c** was inactive, while **4a** and **4b** exhibited lower activities than **1g** (Table 1). Next, we varied the isonitrile component. We explored nine different isonitriles (Scheme 3) chosen to include linear aliphatic (as in **5a** and **5b**), branched aliphatic (**5c**–**5e**), silyl-containing (**5f**), adamantyl (**5g**), and aromatic substituents (**5h**, **5i**). We observed that the *N*-2,4,4-trimethylpentan-2-yl group of **5e**, could be dealkylated under strongly acidic conditions as has been reported recently,[25] affording the possibility of introducing alkyl or acyl substituents (represented by **7a**–**7c,** Scheme 4) that were not accessible through commercially available isonitriles. Optimal activity profiles appeared to correspond to compounds with branched-chain substituents (**5d**, **5e**), while compounds with aromatic substituents (**5h**, **5i**) were bereft of antibacterial activity (Table 1).

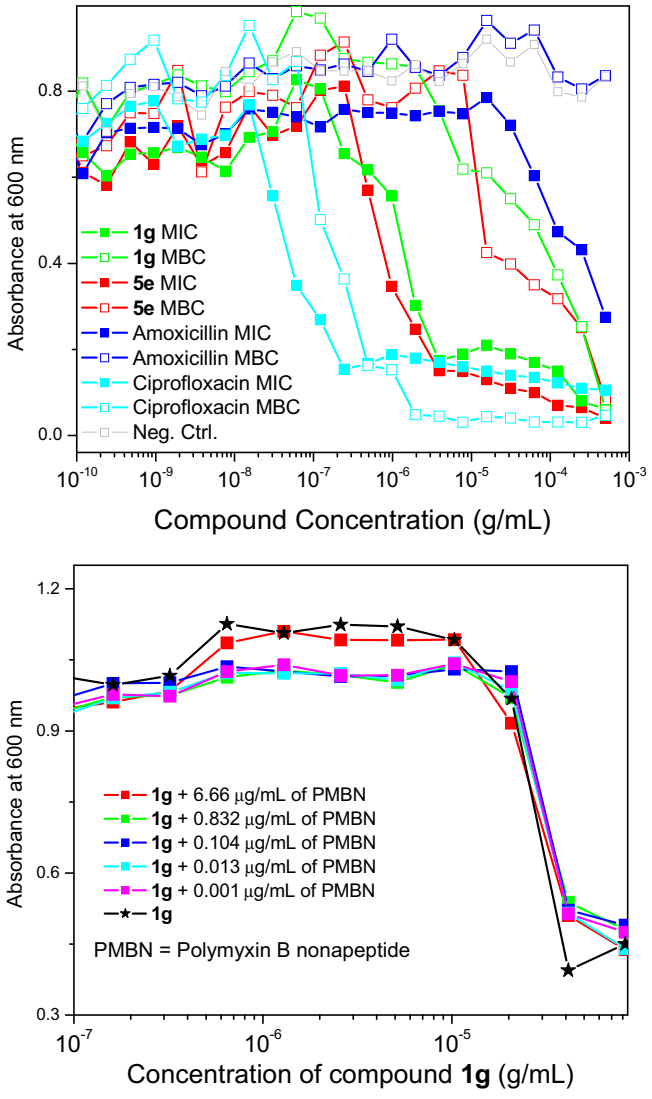


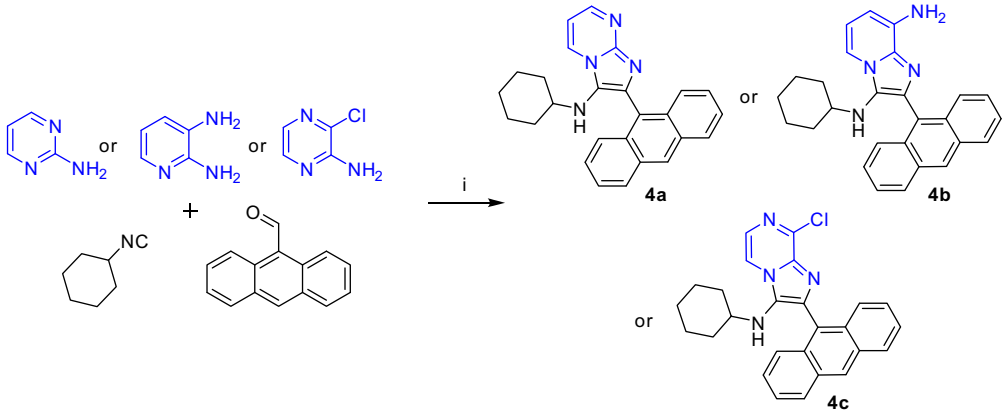
Figure 2. Top: Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) data of active 1*H*-imidazo[1,2-*a*]pyridine compounds. MICs were determined using MRSA (ATCC strain 33591) by broth microdilution method in Mueller–Hinton broth (MHB). Ciprofloxacin and amoxicillin were used as positive and negative controls, respectively. For MBC determinations, 0.5 μL of each of the 384 wells in the parent MIC plate was diluted into 80 μL of fresh MHB. Bottom: Lack of sensitization in *E. coli* (ATCC strain 9637) by polymyxin B nonapeptide to **1g**.

Noting that bulky, aldehyde-derived aromatic substituents at C2 corresponded to maximal activity (exemplified by the anthracenyl group in **1g**, **2g**, **5a**–**5g**), it was of interest to explore other similar functional groups. Compounds with biphenyl (**8a**), phenanthrenyl (**8b**), and pyrenyl (**8c**) substituents were therefore synthesized and evaluated (Scheme 5). Compounds **8b** and **8c** exhibited lower activity than the anthracenyl-bearing compound, while the biphenyl compound **8a** was inactive, pointing to the necessity of a large polycyclic, aromatic group at C2; the higher activity of **5e** with its bulky anthracenyl group would appear to suggest that the polycyclic group of a particular topology is a determinant of activity.

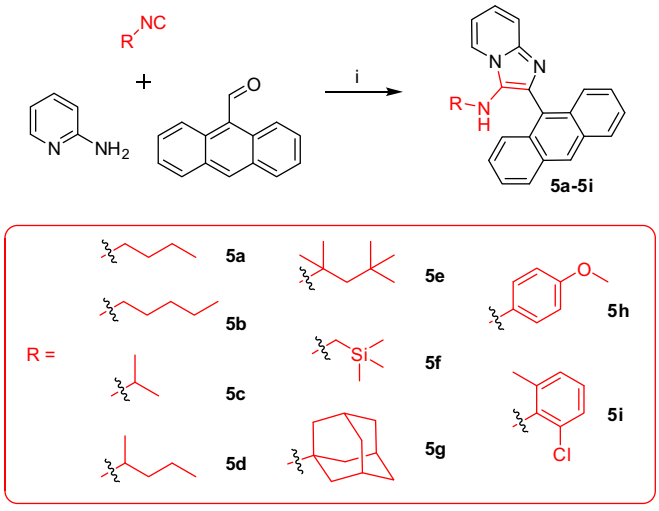
The compound that showed maximal activity thus far was the very lipophilic **5e**, and it was desirable to explore more polar analogues for future evaluation in in vivo models. We therefore attempted to introduce *N*,*N*-dimethylaminopropylamino groups on both the amidine- and aldehyde-derived portions of **5e**. This was achieved in a straightforward manner using appropriate halo-substituted components, followed by Buchwald–Hartwig coupling as depicted in Scheme 6. The antibacterial activities of **10** and **12** were found to be identical to that of **5e** (Table 1).

Although the lead compounds of this chemotype exhibit narrow-spectrum bacteriostatic activity against Gram-positive organisms, the substantial potency against MRSA warranted an attempt at understanding the mechanism of action. Our preliminary studies have been to examine the antibiograms of wild-type and **5e**-resistant *S. aureus* organisms, comparing a variety of antimicrobials with known mechanisms of action. **5e**-resistant *S. aureus* organisms were generated by exposing the bacterium to escalating doses of the compound. Within about 10 serial passages, organisms that withstood **5e** up to concentrations of 100 μg/mL emerged. The MICs of various classes of bacteriostatic and bactericidal antibiotics were found to be identical within experimental error for both the wild-type and **5e**-resistant *S. aureus*, suggesting that the molecular target of **5e** and related compounds were distinct and unique (Fig. 3).

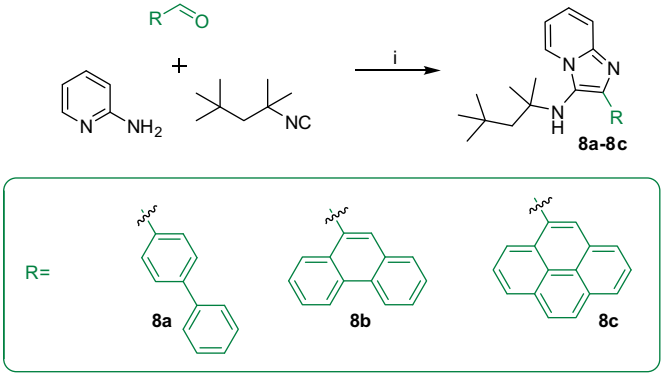
We noticed, however, that upon prolonged storage (~2 weeks), aqueous solutions of hydrochloride salts of both **10** and **12** were degrading gradually, giving rise to *N*-dealkylated products as was discussed earlier (LC–MS data in Supplementary data, Page S136). Furthermore, we were desirous of introducing a functional group that would permit facile coupling of probes such as fluorophores or biotin in order to identify the possible molecular target(s) of **5e**. We elected to replace the *N*-2,4,4-trimethylpentan-2-yl group with the more stable *tert*-butyl group, and the *N*,*N*-dimethylaminopropylamino group with a 1,8-diaminooctane, using the Buchwald-Hartwig coupling strategy employed earlier (Scheme 7). The introduction of the primary amine-bearing 1,8-diaminooctanyl group on either the anthrace-



Scheme 2. Groebke reaction using different amidines. Reagents and conditions: (i) MW, 400 W, 110 °C, 30 min, HCl/dioxane, CH_3CN.



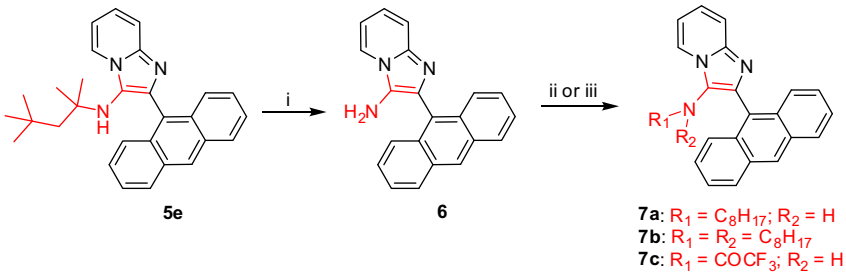
Scheme 3. Groebke reaction using various isonitriles. Reagents and conditions: (i) MW, 400 W, 110 °C, 20 min, HCl/dioxane, CH_3CN.



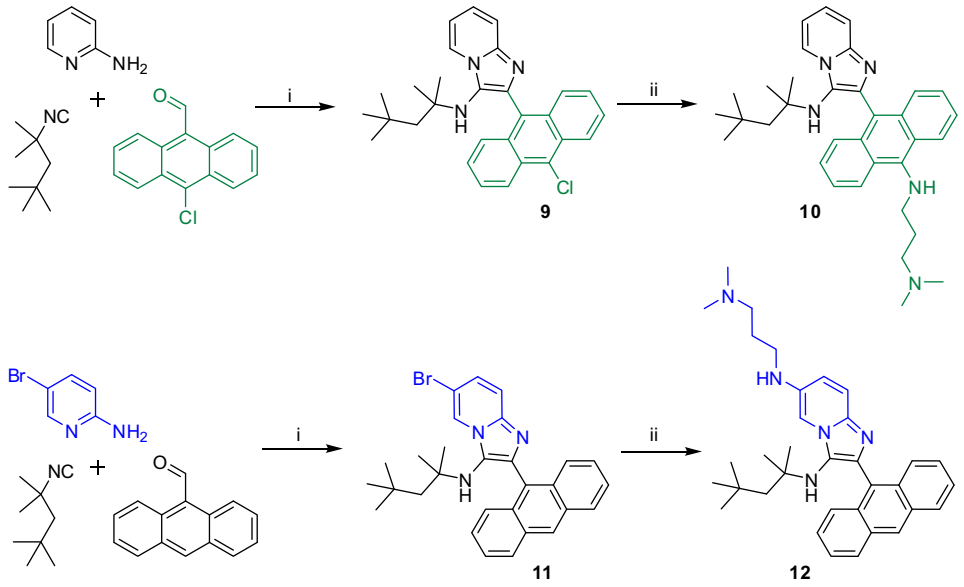
Scheme 5. Groebke reaction using various aldehydes. Reagents and conditions: (i) MW, 400 W, 110 °C, 20 min, HCl/dioxane, CH_3CN.

nyl or pyridinyl portions of the molecule do not result in significant attenuation of antibacterial activity relative to **1g** (Table 1), allowing the possibility of exploring the binding partners for these compounds.

In conclusion, our attempts at exploring imidazo[1,2-*a*]pyridin-3-amines for TLR7 (or 8)-modulatory activities have unexpectedly led to the identification of a novel chemotype with substantial bacteriostatic activity against Gram-positive bacteria, including methicillin-resistant *S. aureus* (MRSA). We note that antibacterial activities of the imidazo[1,2-*a*]pyridines have been reported earlier; the compounds reported herein show narrow-spectrum selectivity, only against Gram-positive organisms.[26,27] Our preliminary results suggest that the mechanism of action may be distinct from known bacteriostatics. Structure–activity relationship studies have led to the identification of positions on the scaffold for additional structural modifications that should allow for the introduction of probes designed to examine cognate binding partners and molecular targets, while not significantly compromising antibacterial potency.



Scheme 4. Derivatization of the C3-amine. Reagents and conditions: (i) HCl/dioxane. For compounds **7a** and **7b**; (ii) $C_7H_{15}CHO$, CH_3COOH, $NaCNBH_3$, MeOH. For compound **7c**; (iii) $(CF_3CO)_2O$, CH_2Cl_2.



Scheme 6. Syntheses of polar derivatives of **5e**. Reagents and conditions: (i) MW, 400 W, 110 °C, 30 min, HCl/dioxane, CH_3CN; (ii) K(O-tBu), $Pd_2(dba)_3$, DavePhos, NH_2–$(CH_2)_3$–$NH(CH_3)_2$, dioxane, 80 °C.

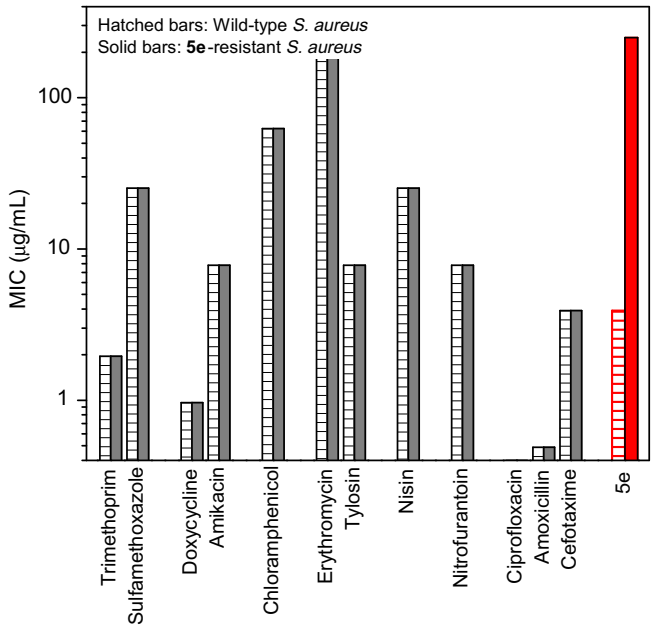


Figure 3. Comparison of antimicrobial susceptibility of wild-type *S. aureus* ATCC 13709 (hatched bars) and **5e**-resistant organism (solid bars) to a range of bacteriostatic antibiotics with known mechanisms of action, and **5e**. Bacteriostatics include trimethoprim and sulfamethoxazole (dihydrofolate reductase pathway), doxycycline and amikacin (30S ribosomal subunit), chloramphenicol (23S ribosomal subunit), erythromycin and tylosin (50S ribosomal subunit), nisin (lipid II), nitrofurantoin (bacterial DNA); also included were the bactericidal controls, ciprofloxacin, amoxicillin, and cefotaxime.

3. Experimental section

3.1. Chemistry

All of the solvents and reagents used were obtained commercially and used as such unless noted otherwise. Moisture- or air-sensitive reactions were conducted under nitrogen atmosphere in oven-dried (120 °C) glass apparatus. The solvents were removed under reduced pressure using standard rotary evaporators. Flash column chromatography was carried out using RediSep Rf 'Gold' high performance silica columns on CombiFlash Rf instrument unless otherwise mentioned, while thin-layer chromatography was carried out on silica gel CCM pre-coated aluminum sheets. Microwave reactions were done in Synthos 3000 instrument (Anton Paar). IR spectra were recorded on Shimadzu 8400 series FTIR instrument and values are reported in cm^{-1}. Purity for all final compounds was confirmed to be greater than 95% by LC–MS using a Zorbax Eclipse Plus 4.6 × 150 mm, 5 μm analytical reverse phase C_{18} column with H_2O–isopropanol or H_2O–CH_3CN gradients and an Agilent ESI-TOF mass spectrometer (mass accuracy of 3 ppm) operating in the positive ion acquisition mode. Unless otherwise mentioned, the compounds synthesized were obtained as yellow solids.

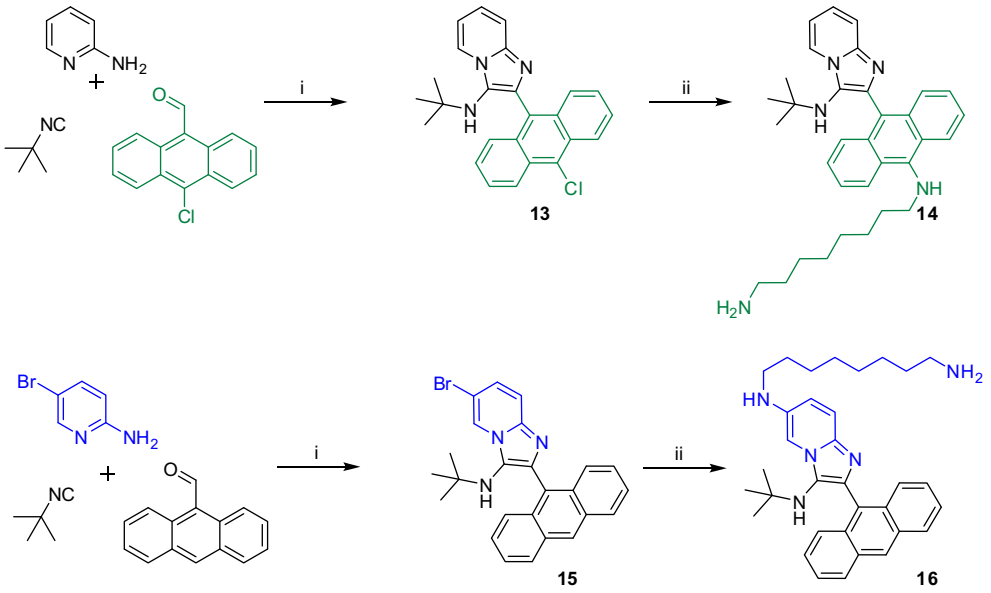
3.1.1. Synthesis of compound 1a: *N*-(*tert*-butyl)-2-phenylimidazo[1,2-*a*]pyridin-3-amine

To the solution of 2-aminopyridine (24 mg, 0.25 mmol) in anhydrous acetonitrile, were added benzaldehyde (28 μL, 0.28 mmol), a catalytic amount of 4 N HCl/dioxane (10 μL) and *tert*-butyl isonitrile (27 μL, 0.24 mmol). The reaction mixture was then heated under microwave conditions (400 W, 110 °C, 20 min). After the reaction mixture was cooled to room temperature, solvent was removed and the residue was purified using column chromatography to obtain the compound **1a** as white solid (44 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (dt, J = 6.9, 1.2 Hz, 1H), 7.90 (dt, J = 8.1, 1.6 Hz, 2H), 7.55 (dt, J = 9.0, 1.0 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.31 (t, J = 7.4 Hz, 1H), 7.13 (ddd, J = 9.0, 6.6, 1.3 Hz, 1H), 6.77 (td, J = 6.8, 1.1 Hz, 1H), 3.12 (s, 1H), 1.04 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.42, 128.43, 128.32, 127.52, 124.17, 123.64, 117.48, 111.46, 101.91, 56.59, 30.43. MS (ESI) calcd for $C_{17}H_{19}N_3$, m/z 265.16, found 266.17 $(M+H)^+$.

Compounds **1b–1f, 2a–2f** and **3a–3f** were synthesized similarly as compound **1a.**

3.1.2. Compound 1b: *N*-(*tert*-butyl)-2-phenylimidazo [1,2-*a*]pyrazin-3-amine (45 mg, 62%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (d, J = 1.4 Hz, 1H), 8.14 (dd, J = 4.6, 1.5 Hz, 1H), 7.91 (dd, J = 8.3, 1.3 Hz, 2H), 7.86 (d, J = 4.6 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 7.37 (t, J = 7.4 Hz, 1H), 3.19



Scheme 7. Syntheses of **1g** derivatives bearing terminal primary amines. Reagents and conditions: (i) MW, 400 W, 110 °C, 30 min, HCl/dioxane, CH_3CN; (ii) (a) K(O-tBu), $Pd_2(dba)_3$, DavePhos, NH_2–$(CH_2)_8$–NHBoc, dioxane, 80 °C; (b) 4 M HCl/dioxane.

(s, 1H), 1.05 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.54, 142.40, 137.43, 134.38, 129.04, 128.66, 128.38, 128.33, 125.17, 116.49, 100.13, 57.11, 30.45. MS (ESI) calcd for $C_{16}H_{18}N_4$, m/z 266.15, found 267.16 $(M+H)^+$.

3.1.3. Compound 1c: 2-benzyl-*N*-(*tert*-butyl)imidazo[1,2-*a*]pyridin-3-amine (41 mg, 61%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dt, J = 6.9, 1.1 Hz, 1H), 7.47 (dt, J = 9.0, 1.0 Hz, 1H), 7.28–7.23 (m, 4H), 7.21–7.14 (m, 1H), 7.08 (ddd, J = 9.0, 6.7, 1.3 Hz, 1H), 6.72 (td, J = 6.8, 1.1 Hz, 1H), 4.20 (s, 2H), 2.57 (s, 1H), 1.18 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.83, 139.62, 128.68, 128.48, 126.06, 123.41, 123.35, 117.06, 110.93, 101.78, 98.20, 55.71, 34.36, 30.45. MS (ESI) calcd for $C_{18}H_{21}N_3$, m/z 279.17, found 280.19 $(M+H)^+$.

3.1.4. Compound 1d: 2-benzyl-*N*-(*tert*-butyl)imidazo[1,2-*a*]pyrazin-3-amine (31 mg, 43%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, J = 1.4 Hz, 1H), 8.06 (dd, J = 4.6, 1.5 Hz, 1H), 7.81 (d, J = 4.6 Hz, 1H), 7.32–7.27 (m, 2H), 7.25–7.18 (m, 3H), 4.24 (s, 2H), 2.62 (s, 1H), 1.20 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.95, 142.78, 138.88, 137.32, 128.72, 128.67, 126.45, 116.28, 56.29, 34.39, 30.48. MS (ESI) calcd for $C_{17}H_{20}N_4$, m/z 280.17, found 281.18 $(M+H)^+$.

3.1.5. Compound 1e: *N*-(*tert*-butyl)-2-(naphthalen-1-yl)imidazo[1,2-*a*]pyridin-3-amine (56 mg, 74%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (dt, J = 6.9, 1.1 Hz, 1H), 8.02–7.85 (m, 3H), 7.68–7.44 (m, 5H), 7.19 (ddd, J = 9.0, 6.7, 1.3 Hz, 1H), 6.83 (td, J = 6.8, 1.1 Hz, 1H), 3.00 (s, 1H), 0.78 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.83, 132.94, 131.98, 128.48, 128.25, 128.15, 126.57, 125.73, 125.70, 125.34, 123.97, 123.64, 117.45, 111.37, 101.79, 100.00, 55.95, 29.76. MS (ESI) calcd for $C_{21}H_{21}N_3$, m/z 315.17, found 316.19 $(M+H)^+$.

3.1.6. Compound 1f: *N*-(*tert*-butyl)-2-(naphthalen-1-yl)imidazo[1,2-*a*]pyrazin-3-amine (29 mg, 38%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (d, J = 1.4 Hz, 1H), 8.24 (dd, J = 4.6, 1.5 Hz, 1H), 7.97–7.87 (m, 4H), 7.67–7.42 (m, 4H), 3.08 (s, 1H), 0.80 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.57, 141.83, 133.85, 131.76, 131.71, 128.98, 128.95, 128.67, 128.27, 126.94, 126.02, 125.31, 125.19, 116.54, 105.36, 98.21, 56.51, 29.81. MS (ESI) calcd for $C_{20}H_{20}N_4$, m/z 316.17, found 317.17 $(M+H)^+$.

3.1.7. Compound 1g: 2-(anthracen-9-yl)-*N*-(*tert*-butyl)imidazo[1,2-*a*]pyridin-3-amine (55 mg, 63%)

IR ($CHCl_3$) ν_{max} (cm^{-1}): 2970, 1500, 1473, 1342, 1311. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.40 (dt, J = 6.9, 1.2 Hz, 1H), 8.09–8.02 (m, 2H), 7.93–7.86 (m, 2H), 7.66 (dt, J = 9.0, 1.1 Hz, 1H), 7.51–7.38 (m, 4H), 7.29–7.20 (m, 1H), 6.89 (td, J = 6.8, 1.1 Hz, 1H), 2.69 (s, 1H), 0.64 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.71, 131.45, 130.94, 128.75, 127.60, 126.80, 126.34, 126.19, 125.06, 124.00, 123.62, 117.57, 111.40, 101.78, 97.01, 55.59, 29.72. MS (ESI) calcd for $C_{25}H_{23}N_3$, m/z 365.19, found 366.20 $(M+H)^+$.

3.1.8. Compound 1h: 2-(anthracen-9-yl)-*N*-(*tert*-butyl)imidazo[1,2-*a*]pyrazin-3-amine (50 mg, 57%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (d, J = 1.5 Hz, 1H), 8.57 (s, 1H), 8.31 (dd, J = 4.6, 1.5 Hz, 1H), 8.12–8.05 (m, 2H), 7.98 (d, J = 4.6 Hz, 1H), 7.83–7.75 (m, 2H), 7.53–7.42 (m, 4H), 2.75 (s, 1H), 0.65 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.65, 139.88, 138.08, 131.37, 130.86, 129.05, 128.96, 128.35, 127.48, 126.81, 125.52, 125.24, 116.55, 101.78, 56.14, 29.77. MS (ESI) calcd for $C_{24}H_{22}N_4$, m/z 366.18, found 367.19 $(M+H)^+$ and 389.18 $(M+Na)^+$.

3.1.9. Compound 2a: *N*-cyclohexyl-2-phenylimidazo[1,2-*a*]pyridin-3-amine white solid (51 mg, 73%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, J = 6.8 Hz, 1H), 8.05 (dd, J = 8.3, 1.2 Hz, 2H), 7.62 (d, J = 9.0 Hz, 1H), 7.45 (t, J = 7.8 Hz, 2H), 7.32 (t, J = 7.4 Hz, 1H), 7.17 (ddd, J = 8.9, 6.7, 1.2 Hz, 1H), 6.82 (td, J = 6.8, 0.9 Hz, 1H), 3.32 (s, 1H), 3.07–2.85 (m, 1H), 1.81 (d, J = 13.1 Hz, 2H), 1.68 (dd, J = 9.1, 3.6 Hz, 2H), 1.60–1.54 (m, 1H), 1.28–1.12 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.02, 135.43, 133.45, 128.74, 127.74, 127.20, 125.17, 125.04, 123.07, 116.94, 112.30, 57.02, 34.27, 25.81, 24.94. MS (ESI) calcd for $C_{19}H_{21}N_3$, m/z 291.17, found 292.18 $(M+H)^+$.

3.1.10. Compound 2b: *N*-cyclohexyl-2-phenylimidazo[1,2-*a*]pyrazin-3-amine (25 mg, 36%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99 (d, J = 1.4 Hz, 1H), 8.01 (ddd, J = 4.6, 3.2, 1.8 Hz, 3H), 7.85 (d, J = 4.6 Hz, 1H), 7.48 (t, J = 7.7 Hz,

2H), 7.38 (t, J = 7.4 Hz, 1H), 3.26 (s, 1H), 3.00 (s, 1H), 1.82 (dd, J = 6.6, 5.4 Hz, 2H), 1.70 (dd, J = 9.3, 3.3 Hz, 2H), 1.62–1.55 (m, 1H), 1.34–1.07 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.37, 139.08, 136.82, 133.62, 129.01, 128.90, 128.30, 127.42, 126.70, 115.73, 57.02, 34.41, 25.69, 24.91. MS (ESI) calcd for $C_{18}H_{20}N_4$, m/z 292.17, found 293.18 $(M+H)^+$.

3.1.11. Compound 2c: 2-benzyl-*N*-cyclohexylimidazo [1,2-*a*]pyridin-3-amine (51 mg, 70%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dt, J = 6.8, 1.1 Hz, 1H), 7.52–7.46 (m, 1H), 7.31–7.26 (m, 4H), 7.19 (qd, J = 5.3, 2.7 Hz, 1H), 7.10 (ddd, J = 9.0, 6.7, 1.3 Hz, 1H), 6.76 (td, J = 6.8, 1.1 Hz, 1H), 4.16 (s, 2H), 2.77 (s, 1H), 2.60 (s, 1H), 1.79–1.67 (m, 4H), 1.59 (s, 1H), 1.32–1.04 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.11, 139.62, 137.49, 128.68, 128.53, 126.20, 125.44, 123.43, 122.59, 116.93, 111.41, 57.32, 34.17, 34.11, 25.74, 24.85. MS (ESI) calcd for $C_{20}H_{23}N_3$, m/z 305.19, found 306.20 $(M+H)^+$.

3.1.12. Compound 2d: 2-benzyl-*N*-cyclohexylimidazo [1,2-*a*]pyrazin-3-amine (37 mg, 50%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 (d, J = 1.4 Hz, 1H), 7.93 (dd, J = 4.6, 1.5 Hz, 1H), 7.81 (d, J = 4.6 Hz, 1H), 7.33–7.25 (m, 4H), 7.22 (ddd, J = 6.2, 3.3, 1.6 Hz, 1H), 4.20 (s, 2H), 2.81 (s, 1H), 2.68 (s, 1H), 1.84–1.65 (m, 4H), 1.60 (d, J = 6.1 Hz, 1H), 1.24–0.95 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.19, 139.22, 137.30, 135.01, 127.27, 127.20, 127.17, 125.71, 125.04, 114.00, 55.65, 32.84, 32.76, 24.09, 23.31. MS (ESI) calcd for $C_{19}H_{22}N_4$, m/z 306.18, found 307.20 $(M+H)^+$.

3.1.13. Compound 2e: *N*-cyclohexyl-2-(naphthalen-1-yl) imidazo[1,2-*a*]pyridin-3-amine (24 mg, 29%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, J = 6.8 Hz, 1H), 7.95–7.88 (m, 3H), 7.72–7.64 (m, 2H), 7.59–7.54 (m, 1H), 7.53–7.45 (m, 2H), 7.25–7.20 (m, 1H), 6.90 (t, J = 6.8 Hz, 1H), 3.15 (s, 1H), 2.63 (t, J = 9.6 Hz, 1H), 1.58 (d, J = 12.6 Hz, 2H), 1.50–1.36 (m, 3H), 1.04–0.77 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.06, 133.76, 131.95, 128.57, 128.49, 128.15, 126.76, 126.65, 125.86, 125.50, 125.36, 124.30, 122.89, 117.21, 112.14, 56.32, 33.70, 25.47, 24.51. MS (ESI) calcd for $C_{23}H_{23}N_3$, m/z 341.19, found 342.20 $(M+H)^+$.

3.1.14. Compound 2f: *N*-cyclohexyl-2-(naphthalen-1-yl) imidazo[1,2-*a*]pyrazin-3-amine (50 mg, 61%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.05 (d, J = 1.5 Hz, 1H), 8.05 (dd, J = 4.6, 1.5 Hz, 1H), 7.96–7.93 (m, 2H), 7.92–7.89 (m, 2H), 7.61 (ddd, J = 15.2, 7.5, 4.2 Hz, 4H), 7.55–7.48 (m, 1H), 3.27 (s, 1H), 2.73 (s, 1H), 1.61 (dd, J = 9.5, 3.2 Hz, 2H), 1.44 (ddd, J = 14.5, 11.6, 4.6 Hz, 3H), 1.07–0.82 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.40, 138.38, 136.73, 133.80, 131.90, 130.80, 129.03, 128.84, 128.58, 128.53, 128.07, 126.87, 126.08, 125.30, 125.27, 115.67, 56.12, 33.85, 25.35, 24.50. MS (ESI) calcd for $C_{22}H_{22}N_4$, m/z 342.18, found 343.19 $(M+H)^+$ and 365.17 $(M + Na)^+$.

3.1.15. Compound 2g: 2-(anthracen-9-yl)-*N*-cyclohexylimidazo [1,2-*a*]pyridin-3-amine (83 mg, 88%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.23 (dt, J = 6.8, 1.2 Hz, 1H), 8.06 (d, J = 8.4 Hz, 2H), 7.83 (dd, J = 8.7, 0.8 Hz, 2H), 7.66 (dt, J = 9.0, 1.0 Hz, 1H), 7.49–7.44 (m, 2H), 7.40 (ddd, J = 8.6, 6.5, 1.3 Hz, 2H), 7.23 (ddd, J = 9.0, 6.7, 1.3 Hz, 1H), 6.90 (td, J = 6.8, 1.1 Hz, 1H), 2.80 (d, J = 7.4 Hz, 1H), 2.62–2.49 (m, 1H), 1.47 (d, J = 12.6 Hz, 2H), 1.35–1.24 (m, 3H), 0.89–0.77 (m, 3H), 0.68 (dt, J = 12.8, 6.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.02, 134.01, 131.38, 131.20, 128.59, 128.34, 128.10, 127.64, 126.25, 126.12, 125.10, 123.40, 122.81, 117.72, 111.60, 56.18, 33.62, 25.39, 24.38. MS (ESI) calcd for $C_{27}H_{25}N_3$, m/z 391.20, found 392.22 $(M+H)^+$.

3.1.16. Compound 2h: 2-(anthracen-9-yl)-*N*-cyclohexylimidazo [1,2-*a*]pyrazin-3-amine (17 mg, 18%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (d, J = 1.4 Hz, 1H), 8.59 (s, 1H), 8.13–8.06 (m, 3H), 7.97 (d, J = 4.6 Hz, 1H), 7.72 (dd, J = 8.7, 0.6 Hz, 2H), 7.46 (dddd, J = 10.0, 7.8, 6.5, 1.1 Hz, 4H), 2.91 (d, J = 6.2 Hz, 1H), 2.62 (s, 1H), 1.48 (d, J = 12.6 Hz, 2H), 1.29 (dd, J = 24.7, 8.3 Hz, 3H), 0.91–0.76 (m, 3H), 0.76–0.63 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.63, 136.28, 135.36, 130.29, 130.12, 128.74, 128.01, 127.76, 127.36, 125.75, 125.54, 124.62, 124.25, 114.68, 54.95, 32.71, 24.20, 23.32. MS (ESI) calcd for $C_{26}H_{24}N_4$, m/z 392.20, found 393.20 $(M+H)^+$.

3.1.17. Compound 3a: *N*-benzyl-2-phenylimidazo[1,2-*a*]pyridin-3-amine white solid (62 mg, 86%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (ddt, J = 3.7, 3.0, 1.6 Hz, 3H), 7.57 (dt, J = 9.0, 1.0 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 7.39–7.26 (m, 6H), 7.13 (ddd, J = 9.0, 6.7, 1.3 Hz, 1H), 6.74 (td, J = 6.8, 1.1 Hz, 1H), 4.20 (d, J = 6.1 Hz, 2H), 3.52 (t, J = 6.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.57, 139.06, 136.04, 134.13, 128.84, 128.30, 127.82, 127.65, 127.16, 125.77, 124.32, 122.50, 117.52, 111.94, 52.57. MS (ESI) calcd for $C_{20}H_{17}N_3$, m/z 299.14, found 300.15 $(M+H)^+$.

3.1.18. Compound 3b: *N*-benzyl-2-phenylimidazo[1,2-*a*] pyrazin-3-amine (45 mg, 62%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98 (d, J = 1.3 Hz, 1H), 7.94 (dt, J = 8.1, 1.6 Hz, 2H), 7.82 (dd, J = 4.6, 1.4 Hz, 1H), 7.77 (d, J = 4.6 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.39 (t, J = 7.4 Hz, 1H), 7.34–7.27 (m, 5H), 4.23 (d, J = 2.4 Hz, 2H), 3.66 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.46, 138.76, 138.56, 136.79, 133.34, 129.06, 129.03, 128.99, 128.46, 128.24, 128.08, 127.42, 127.18, 115.38, 52.39. MS (ESI) calcd for $C_{19}H_{16}N_4$, m/z 300.14, found 301.15 $(M+H)^+$.

3.1.19. Compound 3c: *N*,2-dibenzylimidazo[1,2-*a*] pyridin-3-amine (33 mg, 44%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (dt, J = 6.8, 1.1 Hz, 1H), 7.49 (dt, J = 9.1, 0.9 Hz, 1H), 7.38–7.15 (m, 10H), 7.09 (ddd, J = 9.0, 6.7, 1.3 Hz, 1H), 6.72 (td, J = 6.7, 1.1 Hz, 1H), 4.01 (s, 2H), 3.94 (d, J = 5.5 Hz, 2H), 2.99 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.18, 139.68, 139.24, 137.57, 128.69, 128.62, 128.57, 128.28, 127.59, 126.25, 125.93, 123.36, 122.14, 117.15, 111.44, 52.83, 34.13. MS (ESI) calcd for $C_{21}H_{19}N_3$, m/z 313.16, found 314.18 $(M+H)^+$.

3.1.20. Compound 3d: *N*,2-dibenzylimidazo[1,2-*a*] pyrazin-3-amine (19 mg, 25%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.72 (m, 2H), 7.35–7.25 (m, 5H), 7.25–7.18 (m, 4H), 7.16 (dd, J = 7.0, 2.2 Hz, 2H), 4.03 (s, 2H), 3.96 (d, J = 3.9 Hz, 2H), 3.15–3.05 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.87, 139.52, 137.76, 137.68, 135.44, 128.01, 127.89, 127.75, 127.71, 127.66, 127.63, 127.59, 127.56, 127.26, 127.19, 126.97, 126.84, 126.75, 125.57, 114.09, 51.49, 51.46, 33.19. MS (ESI) calcd for $C_{20}H_{18}N_4$, m/z 314.15, found 315.17 $(M+H)^+$.

3.1.21. Compound 3e: *N*-benzyl-2-(naphthalen-1-yl) imidazo[1,2-*a*]pyridin-3-amine (42 mg, 50%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15–8.10 (m, 1H), 8.01 (d, J = 8.3 Hz, 1H), 7.94–7.86 (m, 2H), 7.61 (d, J = 9.0 Hz, 1H), 7.55–7.44 (m, 4H), 7.18 (ddd, J = 9.0, 6.7, 1.3 Hz, 1H), 7.15–7.11 (m, 3H), 7.02 (dd, J = 6.5, 3.0 Hz, 2H), 6.83 (td, J = 6.8, 1.0 Hz, 1H), 3.92 (d, J = 4.9 Hz, 2H), 3.53 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.35, 138.75, 135.57, 133.79, 132.14, 131.50, 128.45, 128.37, 128.33, 127.88, 127.34, 127.31, 126.49, 125.88, 125.82, 125.27, 123.69, 122.50, 117.60, 111.80, 52.42. MS (ESI) calcd for $C_{24}H_{19}N_3$, m/z 349.16, found 350.18 $(M+H)^+$.

3.1.22. Compound 3f: *N*-benzyl-2-(naphthalen-1-yl)imidazo [1,2-*a*]pyrazin-3-amine (12 mg, 14%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (d, J = 1.5 Hz, 1H), 7.97–7.89 (m, 4H), 7.83 (d, J = 4.6 Hz, 1H), 7.49 (tddd, J = 10.0, 6.8, 3.6, 1.4 Hz, 4H), 7.17–7.08 (m, 3H), 7.01–6.94 (m, 2H), 3.96 (d, J = 5.8 Hz, 2H), 3.78 (t, J = 5.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.50, 138.21, 137.83, 136.53, 133.78, 131.90, 130.44, 129.08, 128.95, 128.89, 128.49, 128.46, 128.02, 127.77, 127.73, 127.58, 126.78, 126.06, 125.45, 125.21, 115.35, 51.83. MS (ESI) calcd for $C_{23}H_{18}N_4$, m/z 350.15, found 351.18 $(M+H)^+$.

3.1.23. Compound 3g: 2-(anthracen-9-yl)-*N*-benzylimidazo [1,2-*a*]pyridin-3-amine (47 mg, 49%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.18 (dt, J = 6.9, 1.2 Hz, 1H), 8.07 (d, J = 8.5 Hz, 2H), 7.82 (dd, J = 8.8, 0.9 Hz, 2H), 7.66 (dt, J = 9.0, 1.1 Hz, 1H), 7.50–7.43 (m, 2H), 7.39 (ddd, J = 8.7, 6.5, 1.3 Hz, 2H), 7.22 (ddd, J = 9.0, 6.7, 1.3 Hz, 1H), 7.05–6.95 (m, 3H), 6.90–6.82 (m, 3H), 3.74 (d, J = 6.3 Hz, 2H), 3.25 (t, J = 6.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.88, 137.71, 132.57, 130.36, 130.23, 127.77, 127.54, 127.15, 127.02, 126.76, 126.63, 126.10, 125.31, 125.10, 124.09, 122.54, 121.46, 116.74, 110.71, 51.19. MS (ESI) calcd for $C_{28}H_{21}N_3$, m/z 399.17, found 400.20 $(M+H)^+$.

3.1.24. Compound 3h: 2-(anthracen-9-yl)-*N*-benzylimidazo [1,2-*a*]pyrazin-3-amine (8 mg, 8%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.09 (d, J = 1.4 Hz, 1H), 8.59 (s, 1H), 8.08 (d, J = 8.5 Hz, 2H), 8.01 (dd, J = 4.6, 1.5 Hz, 1H), 7.91 (d, J = 4.6 Hz, 1H), 7.69 (dd, J = 8.8, 0.7 Hz, 2H), 7.52–7.45 (m, 2H), 7.41 (ddd, J = 8.6, 6.5, 1.2 Hz, 2H), 7.06–6.94 (m, 3H), 6.83–6.77 (m, 2H), 3.78 (d, J = 5.3 Hz, 2H), 3.44 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.66, 138.12, 137.10, 135.78, 131.32, 131.19, 130.28, 129.06, 128.75, 128.50, 128.33, 127.55, 127.41, 126.56, 126.53, 125.74, 125.28, 115.37, 51.61. MS (ESI) calcd for $C_{27}H_{20}N_4$, m/z 400.17, found 401.19 $(M+H)^+$.

Compounds **4a**–**4c** were synthesized similarly as compound **1a.**

3.1.25. Compound 4a: 2-(anthracen-9-yl)-*N*-cyclohexylimidazo [1,2-*a*]pyrimidin-3-amine (40 mg, 43%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (dd, J = 4.1, 2.1 Hz, 1H), 8.56 (s, 1H), 8.54 (dd, J = 6.8, 2.1 Hz, 1H), 8.07 (d, J = 8.4 Hz, 2H), 7.83 (dd, J = 8.7, 0.8 Hz, 2H), 7.49–7.44 (m, 2H), 7.41 (ddd, J = 8.6, 6.5, 1.3 Hz, 2H), 6.97 (dd, J = 6.8, 4.1 Hz, 1H), 2.83 (s, 1H), 2.47 (s, 1H), 1.43 (d, J = 12.9 Hz, 2H), 1.29 (d, J = 7.4 Hz, 3H), 0.82 (t, J = 6.6 Hz, 3H), 0.75–0.62 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.91, 144.93, 135.89, 131.34, 131.05, 130.37, 128.66, 128.12, 127.26, 126.67, 126.29, 126.07, 125.18, 108.17, 56.46, 33.55, 25.28, 24.28. MS (ESI) calcd for $C_{26}H_{24}N_4$, m/z 392.20, found 393.22 $(M+H)^+$.

3.1.26. Compound 4b: 2-(anthracen-9-yl)-N^3-cyclohexylimidazo [1,2-*a*]pyridine-3,8-diamine (15 mg, 15%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.06 (d, J = 8.4 Hz, 2H), 7.86 (dd, J = 8.7, 0.7 Hz, 2H), 7.70 (dd, J = 6.7, 0.9 Hz, 1H), 7.49–7.44 (m, 2H), 7.43–7.37 (m, 2H), 6.74 (t, J = 7.0 Hz, 1H), 6.40 (dd, J = 7.3, 0.9 Hz, 1H), 4.57 (s, 2H), 2.77 (s, 1H), 2.56 (s, 1H), 1.49 (d, J = 12.4 Hz, 2H), 1.29 (d, J = 5.7 Hz, 3H), 0.94–0.75 (m, 3H), 0.75–0.61 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.97, 135.69, 132.06, 131.45, 131.37, 129.03, 128.57, 128.36, 127.62, 126.37, 126.06, 125.12, 113.22, 112.69, 101.65, 56.09, 33.63, 25.41, 24.41. MS (ESI) calcd for $C_{27}H_{26}N_4$, m/z 406.22, found 407.23 $(M+H)^+$.

3.1.27. Compound 4c: 2-(anthracen-9-yl)-8-chloro-*N*-cyclohexylimidazo[1,2-*a*]pyrazin-3-amine (20 mg, 20%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.10–8.06 (m, 3H), 7.77 (d, J = 4.5 Hz, 1H), 7.70 (dd, J = 8.7, 0.7 Hz, 2H), 7.52–7.47 (m, 2H), 7.46–7.41 (m, 2H), 2.93 (d, J = 6.8 Hz, 1H), 2.66–2.58 (m, 1H), 1.48 (d, J = 12.4 Hz, 2H), 1.32 (d, J = 6.9 Hz, 3H), 0.92–0.79 (m, 3H), 0.69 (dd, J = 22.4, 11.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.61, 136.76, 134.02, 131.59, 131.27, 131.26, 128.77, 128.58, 127.43, 126.61, 126.17, 125.63, 125.29, 115.63, 56.13, 33.74, 25.16, 24.33. MS (ESI) calcd for $C_{26}H_{23}ClN_4$, m/z 426.16, found 427.17 $(M+H)^+$.

Compounds **5a–5i** were synthesized similarly as compound **1a.**

3.1.28. Compound 5a: 2-(anthracen-9-yl)-*N*-butylimidazo [1,2-*a*]pyridin-3-amine (22 mg, 25%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.19 (dt, J = 6.8, 1.2 Hz, 1H), 8.06 (d, J = 8.4 Hz, 2H), 7.84 (dd, J = 8.7, 0.8 Hz, 2H), 7.67 (dt, J = 9.1, 1.0 Hz, 1H), 7.48–7.44 (m, 2H), 7.40 (ddd, J = 8.6, 6.5, 1.3 Hz, 2H), 7.22 (ddd, J = 9.0, 6.7, 1.3 Hz, 1H), 6.90 (td, J = 6.8, 1.1 Hz, 1H), 2.89 (t, J = 6.1 Hz, 1H), 2.64 (q, J = 6.6 Hz, 2H), 1.09–0.97 (m, 2H), 0.86–0.72 (m, 2H), 0.43 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.97, 133.07, 131.52, 131.47, 129.40, 128.68, 128.39, 127.80, 126.46, 126.21, 125.25, 123.46, 122.61, 117.92, 111.80, 47.92, 32.18, 19.67, 13.53. MS (ESI) calcd for $C_{25}H_{23}N_3$, m/z 365.19, found 366.20 $(M+H)^+$.

3.1.29. Compound 5b: 2-(anthracen-9-yl)-*N*-pentylimidazo [1,2-*a*]pyridin-3-amine (35 mg, 38%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.19 (dt, J = 6.8, 1.2 Hz, 1H), 8.06 (d, J = 8.4 Hz, 2H), 7.84 (dd, J = 8.7, 0.8 Hz, 2H), 7.67 (dt, J = 9.0, 1.1 Hz, 1H), 7.49–7.44 (m, 2H), 7.40 (ddd, J = 8.6, 6.5, 1.3 Hz, 2H), 7.22 (ddd, J = 9.0, 6.7, 1.3 Hz, 1H), 6.90 (td, J = 6.8, 1.1 Hz, 1H), 2.91 (t, J = 6.4 Hz, 1H), 2.65 (q, J = 6.7 Hz, 2H), 1.02 (dt, J = 14.3, 7.0 Hz, 2H), 0.82–0.65 (m, 4H), 0.52 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.85, 132.95, 131.40, 131.34, 129.24, 128.56, 128.26, 127.67, 126.32, 126.10, 125.13, 123.31, 122.48, 117.81, 111.67, 48.05, 29.68, 28.58, 22.07, 13.70. MS (ESI) calcd for $C_{26}H_{25}N_3$, m/z 379.20, found 380.22 $(M+H)^+$.

3.1.30. Compound 5c: 2-(anthracen-9-yl)-*N*-isopropylimidazo [1,2-*a*]pyridin-3-amine (15 mg, 18%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.25 (dt, J = 6.8, 1.2 Hz, 1H), 8.08–8.04 (m, 2H), 7.84 (dd, J = 8.7, 0.9 Hz, 2H), 7.66 (dt, J = 9.0, 1.1 Hz, 1H), 7.49–7.44 (m, 2H), 7.41 (ddd, J = 8.6, 6.5, 1.3 Hz, 2H), 7.23 (ddd, J = 9.0, 6.7, 1.3 Hz, 1H), 6.90 (td, J = 6.8, 1.1 Hz, 1H), 2.86 (dq, J = 12.5, 6.3 Hz, 1H), 2.71 (d, J = 6.4 Hz, 1H), 0.69 (d, J = 6.3 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.10, 134.36, 131.39, 131.13, 128.63, 128.31, 128.29, 127.69, 126.23, 126.17, 125.11, 123.56, 122.78, 117.69, 111.64, 49.20, 23.15. MS (ESI) calcd for $C_{24}H_{21}N_3$, m/z 351.17, found 352.19 $(M+H)^+$.

3.1.31. Compund 5d: 2-(anthracen-9-yl)-*N*-isopropylimidazo [1,2-*a*]pyridin-3-amine (37 mg, 41%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.23 (dd, J = 6.8, 1.0 Hz, 1H), 8.06 (d, J = 8.3 Hz, 2H), 7.89–7.83 (m, 2H), 7.67 (dt, J = 9.0, 1.0 Hz, 1H), 7.50–7.37 (m, 4H), 7.23 (ddd, J = 9.0, 6.7, 1.3 Hz, 1H), 6.90 (td, J = 6.8, 1.1 Hz, 1H), 2.79–2.61 (m, 2H), 1.12–0.95 (m, 2H), 0.92–0.82 (m, 2H), 0.79–0.67 (m, 1H), 0.63 (d, J = 6.2 Hz, 2H), 0.39 (t, J = 7.1 Hz, 2H), 0.29 (t, J = 7.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.03, 134.21, 131.41, 131.39, 131.36, 131.19, 131.13, 128.62, 128.61, 128.59, 128.36, 128.34, 127.64, 127.61, 126.26, 126.15, 126.13, 125.09, 123.45, 123.34, 122.68, 122.60, 117.74, 117.71, 111.62, 59.63, 53.06, 39.14, 26.01, 20.85, 18.53, 13.58, 9.01. MS (ESI) calcd for $C_{26}H_{25}N_3$, m/z 379.20, found 380.22 $(M+H)^+$.

3.1.32. Compound 5e: 2-(anthracen-9-yl)-*N*-(2,4,4-trimeth ylpentan-2-yl)imidazo[1,2-*a*]pyridin-3-amine (51 mg, 50%)

IR ($CHCl_3$) ν_{max} (cm^{-1}): 2956, 1519, 1481, 1365, 1340. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.41 (d, J = 6.9 Hz, 1H), 8.05 (d, J = 7.7 Hz, 2H), 7.88 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 9.0 Hz, 1H),

7.50–7.38 (m, 4H), 7.24 (ddd, *J* = 8.9, 6.7, 1.2 Hz, 1H), 6.88 (td, *J* = 6.8, 1.0 Hz, 1H), 2.89 (s, 1H), 0.97 (s, 2H), 0.68 (s, 6H), 0.52 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.71, 137.08, 131.44, 131.01, 129.27, 128.71, 127.53, 126.78, 126.32, 126.24, 125.05, 123.94, 123.70, 117.51, 111.35, 59.61, 55.82, 31.20, 30.95, 28.61. MS (ESI) calcd for $C_{29}H_{31}N_3$, *m*/*z* 421.25, found 422.27 $(M+H)^+$.

3.1.33. Compound 5f: 2-(anthracen-9-yl)-*N*-((trimethylsilyl) methyl)imidazo[1,2-*a*]pyridin-3-amine (33 mg, 35%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.15 (dt, *J* = 6.8, 1.1 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 2H), 7.89 (dd, *J* = 8.7, 0.7 Hz, 2H), 7.69–7.65 (m, 1H), 7.49–7.44 (m, 2H), 7.43–7.38 (m, 2H), 7.22 (ddd, *J* = 9.0, 6.7, 1.3 Hz, 1H), 6.91 (td, *J* = 6.8, 1.0 Hz, 1H), 2.60 (s, 1H), 2.15 (s, 2H), -0.31 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.55, 132.06, 131.73, 131.42, 131.23, 128.58, 128.10, 127.65, 126.45, 126.02, 125.11, 123.20, 122.44, 117.79, 111.61, 38.69, -3.37. MS (ESI) calcd for $C_{25}H_{25}N_3Si$, *m*/*z* 395.18, found 396.20 $(M+H)^+$.

3.1.34. Compound 5g: *N*-(adamantan-1-yl)-2-(anthracen-9-yl) imidazo[1,2-*a*]pyridin-3-amine (46 mg, 43%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.45 (dt, *J* = 6.9, 1.1 Hz, 1H), 8.08–8.03 (m, 2H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.65 (dt, *J* = 9.0, 1.0 Hz, 1H), 7.44 (dddd, *J* = 10.0, 7.9, 6.5, 1.3 Hz, 4H), 7.23 (ddd, *J* = 9.0, 6.7, 1.3 Hz, 1H), 6.88 (td, *J* = 6.8, 1.1 Hz, 1H), 2.66 (s, 1H), 1.65 (s, 3H), 1.34 (d, *J* = 12.1 Hz, 3H), 1.19 (d, *J* = 11.4 Hz, 3H), 1.13 (d, *J* = 2.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.80, 137.17, 131.51, 131.15, 129.27, 128.82, 127.68, 126.39, 126.35, 125.99, 125.17, 123.99, 123.87, 117.61, 111.43, 55.78, 43.30, 36.03, 29.50. MS (ESI) calcd for $C_{31}H_{29}N_3$, *m*/*z* 443.24, found 444.26 $(M+H)^+$.

3.1.35. Compound 5h: 2-(anthracen-9-yl)-*N*-(4-methoxyphenyl) imidazo[1,2-*a*]pyridin-3-amine (36 mg, 36%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.01 (d, *J* = 8.5 Hz, 2H), 7.90–7.83 (m, 3H), 7.74 (d, *J* = 9.1 Hz, 1H), 7.46–7.39 (m, 2H), 7.38–7.28 (m, 3H), 6.87 (td, *J* = 6.8, 1.0 Hz, 1H), 6.61–6.56 (m, 2H), 6.37–6.29 (m, 2H), 5.29 (s, 1H), 3.63 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.58, 142.85, 137.63, 136.25, 131.45, 131.34, 128.69, 128.04, 127.61, 126.28, 126.18, 125.19, 124.47, 123.39, 123.21, 118.11, 115.45, 114.84, 112.22, 55.69. MS (ESI) calcd for $C_{28}H_{21}N_3O$, *m*/*z* 415.17, found 416.19 $(M+H)^+$.

3.1.36. Compound 5i: 2-(anthracen-9-yl)-*N*-(2-chloro-6-methylphenyl)imidazo[1,2-*a*]pyridin-3-amine (11 mg, 11%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.21 (dt, *J* = 6.8, 1.1 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 2H), 7.75 (ddd, *J* = 15.6, 8.3, 4.8 Hz, 3H), 7.41–7.35 (m, 2H), 7.34–7.28 (m, 3H), 6.97 (td, *J* = 6.8, 1.1 Hz, 1H), 6.61 (dd, *J* = 7.9, 1.0 Hz, 1H), 6.41–6.35 (m, 1H), 6.29 (t, *J* = 7.7 Hz, 1H), 5.43 (s, 1H), 1.48 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.20, 139.32, 137.26, 131.22, 129.58, 128.96, 128.51, 127.69, 127.36, 126.96, 126.32, 125.86, 124.98, 124.43, 124.33, 122.77, 121.59, 118.07, 112.53, 18.14. MS (ESI) calcd for $C_{28}H_{20}ClN_3$, *m*/*z* 433.13, found 434.15 $(M+H)^+$.

3.1.37. Synthesis of Compound 6: 2-(anthracen-9-yl) imidazo[1,2-*a*]pyridin-3-amine

Compound **5e** (50 mg, 0.12 mmol) was stirred in a solution of 4 M HCl/dioxane for 3 h, followed by removing the solvent under vacuum. The residue was then purified using column chromatography to obtain the compound **6** in quantitative yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.12 (d, *J* = 6.8 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 2H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.66 (d, *J* = 9.1 Hz, 1H), 7.49–7.45 (m, 2H), 7.44–7.38 (m, 2H), 7.23–7.17 (m, 1H), 6.91 (td, *J* = 6.8, 0.9 Hz, 1H), 3.07 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.49, 131.62, 131.32, 130.44, 128.77, 127.97, 127.79, 126.54, 126.32, 125.88, 125.33, 123.00, 122.10, 117.82, 111.89. MS (ESI) calcd for $C_{21}H_{15}N_3$, *m*/*z* 309.13, found 310.14 $(M+H)^+$.

3.1.38. Syntheses of Compounds 7a and 7b

To a solution of compound **6** (20 mg, 0.065 mmol) in anhydrous methanol, were added octyl aldehyde (15 μL, 0.098 mmol), 4 drops of acetic acid and sodium cyanoborohydride (6 mg, 0.098 mmol). The reaction mixture was stirred for 18 h and the solvent was then removed under vacuum. The residue was purified using column chromatography to obtain compounds **7a** (3% methanol/CH_2Cl_2) and **7b** (2% methanol/CH_2Cl_2).

3.1.39. Compound 7a: 2-(anthracen-9-yl)-*N*-octylimidazo [1,2-*a*]pyridin-3-amine (10 mg, 36%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.20 (dt, *J* = 6.8, 1.1 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 2H), 7.84 (dd, *J* = 8.7, 0.7 Hz, 2H), 7.67 (d, *J* = 9.0 Hz, 1H), 7.50–7.43 (m, 2H), 7.42–7.37 (m, 2H), 7.23 (ddd, *J* = 9.0, 6.7, 1.3 Hz, 1H), 6.91 (td, *J* = 6.8, 1.1 Hz, 1H), 2.92 (s, 1H), 2.70–2.61 (m, 2H), 1.21–1.11 (m, 2H), 0.99 (ddd, *J* = 15.6, 8.8, 7.1 Hz, 4H), 0.90–0.84 (m, 2H), 0.82 (t, *J* = 7.3 Hz, 3H), 0.73–0.66 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.95, 132.96, 131.54, 131.48, 129.37, 128.73, 128.28, 127.86, 126.44, 126.28, 125.28, 123.54, 122.65, 117.92, 111.86, 48.16, 31.79, 30.06, 29.11, 29.10, 26.56, 22.70, 14.22. MS (ESI) calcd for $C_{29}H_{31}N_3$, *m*/*z* 421.25, found 422.27 $(M+H)^+$.

3.1.40. Compound 7b: 2-(anthracen-9-yl)-*N*,*N*-dioctylimidazo[1,2-*a*]pyridin-3-amine (7 mg, 20%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.30 (d, *J* = 6.8 Hz, 1H), 8.04 (d, *J* = 8.5 Hz, 2H), 7.63 (d, *J* = 8.7 Hz, 3H), 7.46–7.40 (m, 2H), 7.31 (ddd, *J* = 8.6, 6.5, 1.1 Hz, 2H), 7.26–7.21 (m, 1H), 6.90 (td, *J* = 6.8, 1.0 Hz, 1H), 2.51–2.45 (m, 4H), 1.32–1.19 (m, 8H), 1.19–1.08 (m, 8H), 1.08–0.93 (m, 8H), 0.85 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.02, 135.49, 132.12, 131.84, 131.45, 129.90, 128.41, 127.72, 127.10, 125.49, 125.20, 123.93, 123.19, 117.77, 111.74, 54.71, 31.92, 29.51, 29.38, 29.16, 27.09, 22.75, 14.25. MS (ESI) calcd for $C_{37}H_{47}N_3$, *m*/*z* 533.38, found 534.38 $(M+H)^+$.

3.1.41. Synthesis of compound 7c: *N*-(2-(anthracen-9-yl) imidazo[1,2-*a*]pyridin-3-yl)-2,2,2-trifluoro acetamide

To a solution of compound **6** (10 mg, 0.024 mmol) in anhydrous CH_2Cl_2, was added trifluoroacetic anhydride (4 μL, 0.03 mmol) and the reaction mixture was stirred for 12 h. The solvent was then removed under vacuum and the residue was purified using column chromatography (3% methanol/CH_2Cl_2) to obtain the compound **7c** (10 mg, 73%). IR ($CHCl_3$) ν_{max} (cm^{-1}): 1730, 1494, 1355, 1315, 1240, 1195, 1157. ^{1}H NMR (500 MHz, MeOD) δ 8.89 (s, 1H), 8.76 (d, *J* = 6.8 Hz, 1H), 8.28–8.14 (m, 3H), 8.10 (d, *J* = 9.0 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.72 (dd, *J* = 10.0, 4.0 Hz, 1H), 7.59 (ddt, *J* = 9.9, 6.6, 3.9 Hz, 4H). ^{13}C NMR (126 MHz, MeOD) δ 161.71, 161.41, 161.11, 160.82, 159.55, 159.23, 158.92, 158.61, 140.74, 135.66, 132.62, 132.61, 132.47, 130.22, 129.81, 129.06, 127.34, 127.00, 125.58, 118.91, 118.54, 113.88. MS (ESI) calcd for $C_{23}H_{14}F_3N_3O$, *m*/*z* 405.11, found 406.12 $(M+H)^+$.

Compound **8a**–**8c** were synthesized similarly as compound **1a.**

3.1.42. Compound 8a: 2-([1,1'-biphenyl]-4-yl)-*N*-(2,4,4-trimethylpentan-2-yl)imidazo[1,2-*a*]pyridin-3-amine (60 mg, 63%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 6.9 Hz, 1H), 7.99–7.95 (m, 2H), 7.71–7.65 (m, 4H), 7.61 (d, *J* = 9.0 Hz, 1H), 7.46 (dd, *J* = 10.5, 4.8 Hz, 2H), 7.38–7.33 (m, 1H), 7.21–7.15 (m, 1H), 6.82 (dd, *J* = 6.6, 6.2 Hz, 1H), 3.29 (s, 1H), 1.61 (s, 2H), 1.05 (s, 9H), 0.99 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.75, 140.14, 128.92, 128.78, 128.70, 127.31, 127.27, 127.26, 127.00, 126.96, 124.63,

123.66, 123.48, 117.04, 111.69, 60.86, 57.09, 31.86, 31.76, 29.02. MS (ESI) calcd for $C_{27}H_{31}N_3$, m/z 397.25, found 398.25 $(M+H)^+$.

3.1.43. Compound 8b: 2-(phenanthren-9-yl)-*N*-(2,4,4-trimethylpentan-2-yl)imidazo[1,2-*a*]pyridin-3-amine (79 mg, 78%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (d, J = 8.2 Hz, 1H), 8.74 (d, J = 8.1 Hz, 1H), 8.37 (dt, J = 6.9, 1.1 Hz, 1H), 8.04 (dd, J = 8.2, 1.0 Hz, 1H), 7.92 (dd, J = 7.9, 1.2 Hz, 1H), 7.90 (s, 1H), 7.68 (dddd, J = 8.3, 6.9, 4.2, 1.4 Hz, 2H), 7.65–7.56 (m, 3H), 7.21 (ddd, J = 9.0, 6.7, 1.3 Hz, 1H), 6.86 (td, J = 6.8, 1.1 Hz, 1H), 3.21 (s, 1H), 1.26 (s, 2H), 0.78 (s, 6H), 0.73 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.35, 139.07, 131.88, 131.67, 131.27, 130.82, 130.44, 129.27, 128.91, 127.17, 126.89, 126.83, 126.72, 126.63, 125.55, 124.24, 123.90, 123.18, 122.72, 117.53, 111.59, 60.24, 56.39, 31.63, 31.45, 28.78. MS (ESI) calcd for $C_{29}H_{31}N_3$, m/z 421.25, found 422.26 $(M+H)^+$ and 444.25 $(M + Na)^+$.

3.1.44. Compound 8c: 2-(pyren-4-yl)-N-(2,4,4-trimethylpentan-2-yl)imidazo[1,2-*a*]pyridin-3-amine (47 mg, 44%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (dt, J = 6.9, 1.1 Hz, 1H), 8.28 (d, J = 7.8 Hz, 1H), 8.23–8.16 (m, 4H), 8.11 (dd, J = 12.1, 5.0 Hz, 3H), 8.02 (t, J = 7.6 Hz, 1H), 7.67 (dt, J = 9.0, 0.9 Hz, 1H), 7.23 (ddd, J = 9.0, 6.7, 1.3 Hz, 1H), 6.87 (td, J = 6.8, 1.1 Hz, 1H), 3.24 (s, 1H), 1.20 (s, 2H), 0.73 (s, 9H), 0.67 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.45, 139.49, 131.39, 131.00, 130.94, 130.62, 129.17, 128.39, 128.17, 127.55, 127.46, 125.92, 125.48, 125.20, 125.05, 125.01, 124.95, 124.79, 124.06, 123.77, 117.46, 111.40, 60.22, 56.27, 31.54, 31.32, 28.53. MS (ESI) calcd for $C_{31}H_{31}N_3$, m/z 445.25, found 446.26 $(M+H)^+$ and 468.25 $(M + Na)^+$.

Compound **9** was synthesized similarly as compound **1a.**

3.1.45. Compound 9: 2-(10-chloroanthracen-9-yl)-*N*-(2,4,4-trimethylpentan-2-yl)imidazo[1,2-*a*]pyridin-3-amine (128 mg, 59%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, J = 8.8 Hz, 2H), 8.41 (d, J = 6.9 Hz, 1H), 7.90 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 9.0 Hz, 1H), 7.62–7.57 (m, 2H), 7.50–7.45 (m, 2H), 7.28–7.25 (m, 1H), 6.90 (t, J = 6.8 Hz, 1H), 2.83 (s, 1H), 0.96 (s, 2H), 0.68 (s, 6H), 0.52 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.73, 136.53, 131.45, 129.61, 129.14, 128.64, 127.24, 127.01, 126.69, 126.58, 126.55, 125.21, 124.28, 123.73, 117.53, 111.57, 59.62, 55.90, 31.20, 31.00, 28.67. MS (ESI) calcd for $C_{29}H_{30}ClN_3$, m/z 455.21, found 456.23 $(M+H)^+$.

3.1.46. Synthesis of compound 10: N^1,N^1-dimethyl-N^3-(10-(3-((2,4,4-trimethylpentan-2-yl)amino)imidazo[1,2-*a*]pyridin-2-yl)anthracen-9-yl)propane-1,3-diamine

To a solution of compound **9** (50 mg, 0.11 mmol) in anhydrous dioxane, were added potassium *tert*-butoxide (38 mg, 0.34 mmol), N^1,N^1-dimethylpropane-1,3-diamine (69 μL, 0.55 mmol) and catalytic amounts of *tris*(dibenzylideneacetone)-dipalladium [$Pd_2(dba)_3$] and 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino) biphenyl [DavePhos]. The reaction was heated in a sealed tube at 80 °C for 4 h. The solvent was then removed under vacuum and the residue was purified using column chromatography to obtain the compound **10** (15 mg, 26%). ^{1}H NMR (500 MHz, MeOD) δ 8.53 (dt, J = 6.9, 1.0 Hz, 1H), 8.47 (d, J = 8.7 Hz, 2H), 7.74 (d, J = 8.5 Hz, 2H), 7.60v7.56 (m, 1H), 7.51–7.45 (m, 2H), 7.44–7.35 (m, 3H), 7.04 (td, J = 6.8, 1.1 Hz, 1H), 3.45 (t, J = 7.1 Hz, 2H), 2.57–2.52 (m, 2H), 2.30 (s, 6H), 2.02–1.91 (m, 2H), 0.95 (s, 2H), 0.74 (s, 6H), 0.45 (s, 9H). ^{13}C NMR (126 MHz, MeOD) δ 144.90, 143.81, 137.83, 133.18, 128.54, 127.84, 127.32, 126.52, 126.46, 125.51, 125.31, 125.08, 124.09, 117.18, 113.25, 60.30, 58.65, 56.77, 51.56, 45.43, 44.86, 32.49, 31.81, 31.76, 29.47, 29.44. MS (ESI) calcd for $C_{34}H_{43}N_5$, m/z 521.35, found 522.37 $(M+H)^+$.

Compound **11** was synthesized similarly as compound **1a**.

3.1.47. Compound 11: 2-(anthracen-9-yl)-6-bromo-*N*-(2,4,4-trimethylpentan-2-yl)imidazo[1,2-*a*]pyridin-3-amine

(150 mg, 63%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54–8.51 (m, 2H), 8.08–8.04 (m, 2H), 7.82 (dd, J = 8.6, 0.9 Hz, 2H), 7.56 (dd, J = 9.4, 0.7 Hz, 1H), 7.49–7.41 (m, 4H), 7.30 (dd, J = 9.4, 1.9 Hz, 1H), 2.91 (s, 1H), 0.96 (s, 2H), 0.68 (s, 6H), 0.50 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.22, 138.24, 131.56, 131.08, 128.94, 128.70, 127.97, 127.51, 127.30, 126.66, 126.08, 125.26, 124.04, 118.41, 106.62, 59.88, 55.93, 31.31, 31.07, 28.78. MS (ESI) calcd for $C_{29}H_{30}BrN_3$, m/z 499.16, found 500.18 $(M+H)^+$.

Compound **12** was synthesized similarly as compound **10**.

3.1.48. Compound 12: 2-(anthracen-9-yl)-N^6-(3-(dimethylamino)propyl)-N^3-(2,4,4-trimethylpentan-2-yl)imidazo[1,2-*a*]pyridine-3,6-diamine (21 mg, 40%)

^{1}H NMR (500 MHz, MeOD) δ 8.61 (s, 1H), 8.11 (d, J = 8.2 Hz, 2H), 7.83 (d, J = 8.6 Hz, 2H), 7.65 (d, J = 1.9 Hz, 1H), 7.52–7.42 (m, 4H), 7.39 (d, J = 9.5 Hz, 1H), 7.04 (dd, J = 9.5, 2.1 Hz, 1H), 3.18 (t, J = 6.8 Hz, 2H), 2.60–2.54 (m, 2H), 2.34 (s, 6H), 1.98–1.90 (m, 2H), 0.93 (s, 2H), 0.73 (s, 6H), 0.46 (s, 9H). ^{13}C NMR (126 MHz, MeOD) δ 140.23, 138.50, 136.47, 133.04, 132.49, 130.41, 129.86, 128.71, 128.35, 127.41, 127.33, 126.29, 121.96, 117.07, 103.72, 60.35, 58.54, 56.85, 45.44, 43.56, 31.78, 31.70, 29.50, 27.45. MS (ESI) calcd for $C_{34}H_{43}N_5$, m/z 521.35, found 522.36 $(M+H)^+$.

Compound **13** was synthesized similarly as compound **1a.**

3.1.49. Compound 13: *N*-(*tert*-butyl)-2-(10-chloroanthracen-9-yl)imidazo[1,2-*a*]pyridin-3-amine (242 mg, 84%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, J = 8.8 Hz, 2H), 8.40 (dt, J = 6.9, 1.1 Hz, 1H), 7.91 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 9.0 Hz, 1H), 7.60 (ddd, J = 8.8, 6.5, 1.1 Hz, 2H), 7.48 (ddd, J = 8.7, 6.5, 1.1 Hz, 2H), 7.28–7.23 (m, 1H), 6.90 (td, J = 6.8, 1.1 Hz, 1H), 2.63 (s, 1H), 0.65 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.88, 136.60, 131.47, 129.77, 129.12, 128.75, 127.13, 126.76, 126.72, 126.67, 125.36, 124.42, 123.78, 117.69, 111.71, 55.76, 29.90. MS (ESI) calcd for $C_{25}H_{22}ClN_3$, m/z 399.15, found 400.17 $(M+H)^+$.

Compound **14** was synthesized similarly as compound **10.**

3.1.50. Compound 14: N^1-(10-(3-(*tert*-butylamino)imidazo[1,2-*a*]pyridin-2-yl)anthracen-9-yl)octane-1,8-diamine Red solid (20 mg, 32%)

^{1}H NMR (500 MHz, MeOD) δ 9.01 (d, J = 6.8 Hz, 1H), 8.55 (d, J = 8.8 Hz, 2H), 8.15–8.08 (m, 1H), 7.99 (dd, J = 13.0, 4.8 Hz, 3H), 7.85 (dd, J = 8.4, 7.0 Hz, 2H), 7.80–7.71 (m, 2H), 7.67 (dd, J = 10.0, 4.0 Hz, 1H), 3.79 (dd, J = 16.7, 8.6 Hz, 2H), 2.94 (dd, J = 14.0, 6.6 Hz, 2H), 2.00–1.91 (m, 2H), 1.72–1.63 (m, 2H), 1.46–1.38 (m, 6H), 0.81 (s, 9H). ^{13}C NMR (126 MHz, MeOD) δ 139.74, 135.47, 135.36, 132.83, 130.52, 129.36, 129.01, 128.07, 127.63, 127.26, 127.03, 125.59, 123.03, 118.21, 113.15, 56.34, 54.29, 40.75, 30.28, 30.13, 29.99, 28.55, 27.62, 27.38, 27.35. MS (ESI) calcd for $C_{33}H_{41}N_5$, m/z 507.34, found 508.35 $(M+H)^+$.

Compound **15** was synthesized similarly as compound **1a.**

3.1.51. Compound 15: nthracen-9-yl)-6-bromo-*N*-(*tert*-butyl)imidazo[1,2-*a*]pyridin-3-amine (260 mg, 81%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54–8.52 (m, 2H), 8.08–8.04 (m, 2H), 7.83 (d, J = 8.6 Hz, 2H), 7.56 (dd, J = 9.4, 0.6 Hz, 1H), 7.49–7.42 (m, 4H), 7.30 (dd, J = 9.4, 1.9 Hz, 1H), 2.68 (s, 1H), 0.64 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.20, 138.13, 131.52, 130.96, 128.97, 128.47, 128.04, 127.60, 127.27, 126.67, 125.99, 125.25, 123.94, 118.41, 106.67, 55.85, 29.83. MS (ESI) calcd for $C_{25}H_{22}BrN_3$, m/z 443.10, found 444.10 $(M+H)^+$.

Compound **16** was synthesized similarly as compound **10.**

3.1.52. Compound 16: N^6-(8-aminooctyl)-2-(anthracen-9-yl)-N^3-(*tert*-butyl)imidazo[1,2-*a*]pyridine-3,6-diamine Brown solid (55 mg, 47%)

^{1}H NMR (500 MHz, MeOD) δ 8.81 (s, 1H), 8.20 (dd, J = 6.5, 2.3 Hz, 2H), 7.85–7.80 (m, 2H), 7.72–7.56 (m, 7H), 3.23 (t, J = 7.0 Hz, 2H), 2.97–2.90 (m, 2H), 1.80 (dt, J = 14.5, 7.1 Hz, 2H), 1.72–1.64 (m, 2H), 1.59–1.51 (m, 2H), 1.45 (s, 6H), 0.78 (s, 9H). ^{13}C NMR (126 MHz, MeOD) δ 141.50, 141.40, 134.23, 132.75, 132.52, 131.64, 130.29, 128.91, 128.20, 127.68, 126.85, 126.05, 121.64, 112.69, 104.55, 56.28, 45.40, 40.78, 30.46, 30.35, 30.30, 29.46, 28.65, 28.27, 27.52. MS (ESI) calcd for $C_{33}H_{41}N_5$, m/z 507.34, found 508.35 $(M+H)^+$.

3.2. Microbiological methods

MICs of the compounds were determined by broth microdilution method per CLSI (formerly NCCLS) guidelines as described earlier.[36] Mid-log phase Mueller-Hinton broth (MHB; noncation supplemented) cultures of organisms (40 μL; optical density at 600 nm adjusted to 0.5 AU, and diluted 10-fold) were added to equal volumes of 2-fold serially diluted compounds in a 384-well microtiter plate with the help of a Biotek Precision 2000 automated microplate pipetting system. The MICs of known antibiotics were included as reference compounds for comparison of activity. The microtiter plates were sealed and incubated overnight at 37 °C. The plates were read at an absorbance of 600 nm. The lowest concentration of an agent inhibiting growth of the organisms was recorded as the MIC.

For MBC determinations, conventional microdilution techniques were employed wherein 0.5 μL of each of the 384 wells in the parent MIC plate was diluted into 80 μL of fresh MHB using the Biotek Precision 2000 automated liquid handling device. The microtiter plates were incubated overnight at 37 °C. The plates were read at an absorbance of 600 nm.

5e-resistant *S. aureus* organisms were generated by exposing *S. aureus* ATCC 13709 to escalating doses of the compound. Within about 10 serial passages, organisms that withstood **5e** up to concentrations of 100 μg/mL emerged.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2012.07.052.

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