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Efficient one-pot synthesis of functionalised imidazo[1,2-*a*]pyridines and unexpected synthesis of novel tetracyclic derivatives by nucleophilic aromatic substitution†

Charles R. K. Changunda, B. C. Venkatesh, William K. Mokone, Amanda L. Rousseau, Dean Brady, Manuel A. Fernandes and Moira L. Bode *

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Novel tetracyclic imidazo[1,2-*a*]pyridine derivatives have been prepared by intramolecular nucleophilic aromatic substitution of 5-fluoroimidazo[1,2-*a*]pyridines under basic conditions. Use of the non-nucleophilic alcoholic solvent *tert*-butanol, rather than methanol, increased the yield of the tetracycles by reducing the competing intermolecular reaction observed for methanol. In addition, a modified protocol for the dehydration of formamides to isocyanides has been found to be tolerant of an unprotected hydroxyl functional group and one-pot conversion to imidazo[1,2-*a*]pyridyl-aminocyclohexanol analogues is reported.

Introduction

The imidazopyridine skeleton possesses unique electronic and chemical properties that make it an attractive starting point in the preparation of a broad spectrum of therapeutic agents[1] ranging from sedative drugs such as zolpidem **1**, antiviral agents **2**, anticancer compounds **3**, immunomodulators **4** (ref. 2) and antitubercular agents **5** (ref. 3) (Fig. 1), to mention just a few. Other reports indicate activity as gastric proton pump inhibitors[4] and as antifungal,[5] antibacterial[6] and anxiolytic[7] agents.

Largely as a result of their biological importance, the development of safe synthetic methodologies that efficiently access imidazopyridines and their associated derivatives continues to generate much research interest in synthetic chemistry.[8]

The utility of the multi-component Groebke–Blackburn–Bienaymé reaction[9] for preparation of imidazo[1,2-*a*]pyridines by reaction of an aldehyde, 2-aminopyridine and an isocyanide is well documented in synthetic chemistry literature.[1a,10a,b] Given that 2-aminopyridines and aldehydes are generally affordable, the versatility and robustness of this protocol is primarily disadvantaged by the limited variety and high procurement cost of commercially available isocyanides. This mandates researchers to prepare most of the isocyanides that are required to fulfil their research requirements.

More than one and a half centuries ago, Gautier and Hofmann[11] first described the preparation of isocyanides. Their apt description of isocyanides as possessing 'almost overpowering, horrible and extremely distressing odours' typifies the challenges associated with the preparation and handling of isocyanides even to this present day. Almost a hundred years later, the first generally applicable routes for accessing isocyanides were described, *via* the dehydration of *N*-formamides using acyl oxides of group IV–VI elements in the presence of bases.[12] Due to the high toxicity and handling difficulties associated with using phosgene,[13] phosphorus oxychloride (used together with Et_3N base), a method originally described by Ugi and Meyr,[14] has become one of the most commonly employed *N*-formamide dehydrating agents for the preparation of isocyanides in synthetic chemistry today.

Nevertheless, the increasing enactment of tightened environmental, health and safety management laws continues to drive the search for safer synthetic routes for accessing isocyanides. Thus, more research and development is still needed to develop safer methodologies that provide ease of access to a large variety of these key substrates. In an interesting development, Wang and co-workers[15] reported the identification of triphenylphosphine and iodine as mild and efficient *N*-formamide dehydrating agents for generating aromatic isocyanides. Guchhait and colleagues[16] reported the development of a one-pot reaction which employed *para*-toluenesulfonyl chloride (pTsCl) and DABCO for the dehydration of *N*-formamide substrates to generate isocyanides *in situ* for subsequent use in multicomponent reactions.

Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, Private Bag 3, PO WITS 2050, Johannesburg, South Africa. E-mail: Moira.Bode@wits.ac.za

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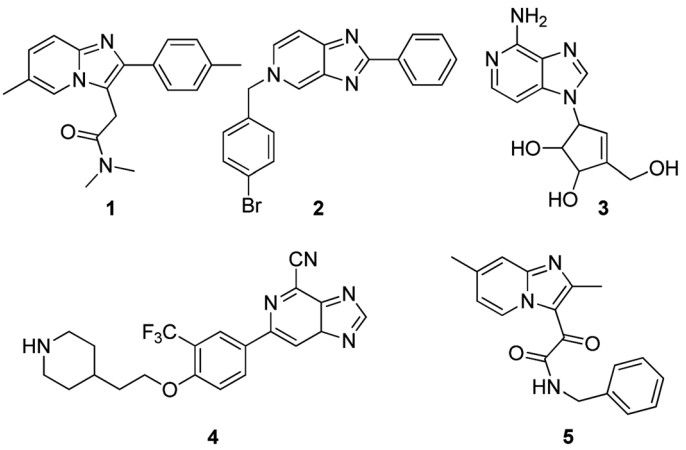


Fig. 1 Biologically active imidazopyridines.

We have previously reported the identification of novel imidazo[1,2-*a*]pyridine derivatives as non-nucleoside inhibitors of HIV-1 reverse transcriptase.[17] The novel lead compound, 2-(2-chlorophenyl)-3-(cyclohexylamino)imidazo[1,2-*a*]pyridine-5-carbonitrile **6** (Fig. 2) exhibited good antiviral activity (whole cell anti-HIV $IC_{50} = 0.18$ μM) and displayed excellent selectivity (SI = 868) when screened against the wild-type HI virus. Molecular modelling results indicated that introduction of groups capable of hydrogen-bonding to amino acids in the allosteric site would potentially lead to compounds with increased potency.

Therefore, as part of our ongoing efforts to discover compounds with better antiviral activity profiles against both wild-type and mutant viral strains we planned to expand our imidazo[1,2-*a*]pyridine library using compound **6** as a starting point. Thus compounds of general structure 7 (Fig. 2) were conceived for synthesis as promising targets for subsequent screening against the HI virus. In this paper, we report a highly efficient modified pTsCl/DABCO protocol[16] as a safe and OH functional group tolerant catalyst methodology for accessing novel imidazo[1,2-*a*]pyridine heterocyclic targets. In addition, we also report the unexpected ring-closure of 5-fluoro-imidazo [1,2-*a*]pyridine derivatives, giving rise to novel tetracyclic compounds.

Results and discussion

To access our initial small library of target compounds of general structure 7, 2-*trans*-hydroxyammonium hydrochloride (*rac*-**8**) was neutralised and formylated quantitatively to generate formamide *rac*-**9** using a previously reported method[18] (Scheme 1). After acetylation, compound *rac*-**10** was then dehydrated using $POCl_3/Et_3N$ to produce the isocyanide *rac*-**11** for subsequent multi-component Groebke–Blackburn–Bienaymé reaction. Acetylation was used as a means of protecting the OH group during the dehydration step, as free OH groups are incompatible with the $POCl_3/Et_3N$ methodology. Coupling of *rac*-**11** with 2-chlorobenzaldehyde **12a** and 6-substituted-2-aminopyridine **13** (Scheme 1) produced the target acetates **14a–d** in excellent yields, specifically over the multicomponent coupling step (v, Scheme 1). Nonetheless, it is noteworthy to point out that a respectable 85% yield of the isocyanide (*rac*-**11**) was only achieved at small scale (100 mg of *rac*-**10**) whilst efforts to scale up the reaction progressively gave poorer conversions. One of the difficulties of this reaction appeared to be a propensity of *rac*-**11** to undergo a rehydration reaction to regenerate the *N*-formamide *rac*-**10** during the aqueous work up, given the non-stoichiometric imbalance between the acid and base associated with this protocol.

The final step in the synthesis was KOH-catalysed hydrolysis of the respective acetates in MeOH to obtain alcohols **7**. Target compounds **7b** and **7c** were obtained in excellent yields from **14b** and **14c**, respectively, while unexpected hydrolysis of the nitrile group of **14d** under the basic conditions of the deprotection reaction gave rise to carboxamide **7e**. Attempted deprotection of compound **14a** also did not lead to the expected deprotected compound; instead a roughly equal mixture of two compounds was obtained. On initial inspection of the ^{1}H NMR spectrum of the first product **15** it was immediately evident that the acetyl group had been removed. The first clear indication that the expected product had not been obtained was the appearance of the signal at 6.17 ppm for H-6 as a doublet showing one *ortho*-coupling ($J = 7.2$ Hz). In the starting material **14a**, this proton appears at 6.38 ppm as a triplet as a result of *ortho*-coupling to both H-7 and F with very similar coupling constants ($J = 7.1$ Hz). The disappearance of F was further confirmed in the ^{13}C NMR spectrum of **15** where C-6 appeared as a singlet at 96.6 ppm, rather than the doublet ($^2J_{C-F} = 18$ Hz) observed at 93.1 ppm for **14a**. The signal for C-1′ appeared at

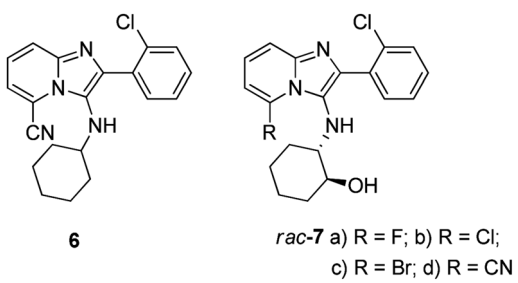
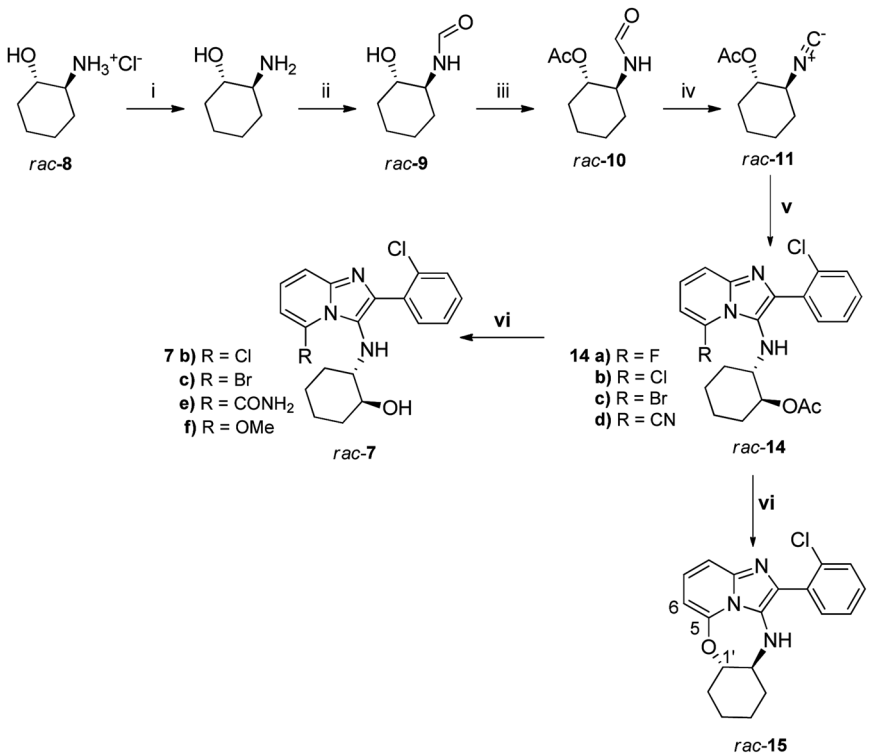


Fig. 2 Imidazopyridine lead compound **6**; modified target products **7**.

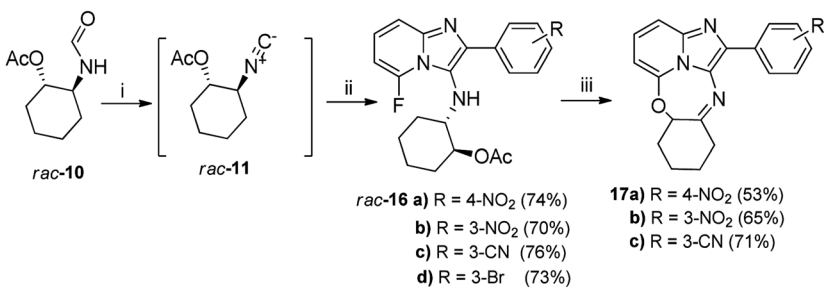


Scheme 1 Reagents: (i) NaOMe, MeOH, RT; (ii) methyl formate, RT, 12 h; (iii) Ac_2O, pyridine, 4 h; (iv) $POCl_3/Et_3N$, DCM; (v) 2-chlorobenzaldehyde **12a**, 6-substituted-2-aminopyridine **13a–d**, K-10 clay, MW 150W, 100 °C, 30 min; (vi) KOH, MeOH, RT, 4 h.

88.4 ppm, far more deshielded than for compound **14a**, where this signal appeared at 76.4 ppm. Thus, it appeared that ring-closure of the newly-deprotected hydroxyl group onto the carbon atom originally carrying F had taken place, giving rise to **15**. The second product was identified as **7f**, where the acetate group had been removed, but where F had been replaced by OMe (Scheme 1). Only these two unexpected products were obtained from the basic deprotection reaction of **14a** in MeOH, with none of the expected deprotected hydroxyl product being observed at all. Repeating the KOH hydrolysis reaction of **14a** in the non-nucleophilic solvent *tert*-butanol instead of methanol gave **15** as the sole product in 60% yield.

Excited by the unexpected formation of novel ring-closed heterocyclic product **15**, we explored the general applicability of this phenomenon using various fluorine-containing imidazopyridine analogues derived from four randomly selected aldehydes. Given the challenges encountered using the $POCl_3/Et_3N$ reagents as highlighted above, we explored the utility of an alternative *para*-toluenesulfonyl chloride-based protocol reported in literature[16] that employs equimolar quantities of acid and base as dehydrating agents (Scheme 2).

In our case, we observed that the efficiency of the dehydration protocol was highly dependent on the purity of the *p*TsCl. Thus, the literature reported purification procedure developed by Whitaker[19] in 2001 was utilized to purify the *p*TsCl, which was subsequently stored sealed to reduce moisture ingress. The *p*TsCl/DABCO protocol proved to be highly convenient and efficient with its main attractive feature being the *in situ* generation of the desired isocyanide *rac*-**11** which obviated the often tedious aqueous workups encountered during isocyanide

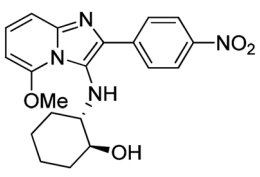


Scheme 2 Reagents: (i) DCM, anhydr. Na_2SO_4 (1 eq.), pTsCl/DABCO, 0 °C–RT, 6 h, (ii) 0–5 °C, aldehyde **12**, 2-amino-6-fluoropyridine **13a**, anhydr. Na_2SO_4 (1 eq.); then 50 °C, 12 h; (iii) KOH, MeOH or *t*-BuOH, RT, 4 h. Yields of **16** are quoted over two steps.

purification which are commonplace when employing the $POCl_3/Et_3N$ protocol. In addition, it removed the unpleasant odour usually associated with isocyanide isolation. The *in situ* generated isocyanide *rac*-**11** was then coupled with the requisite aldehydes **12b–e** and 2-amino-6-fluoropyridine **13a** under sealed conditions at moderate temperatures (50 °C) to obtain the respective fluorine-containing imidazopyridine acetates **16a–d**, with the *p*TsCl/DABCO adducts formed during the dehydration reaction subsequently catalysing the multicomponent coupling reaction (Scheme 2). As a slight deviation from the Guchhait protocol,[16] we observed that the addition of anhydrous Na_2SO_4 during the dehydration stage as well as the multicomponent coupling step, not only obviated the need for N_2 purging, but further simplified the overall preparation of the desired target compounds. These transformations translated to a minimum 70% yield across both the isocyanide generation as well as the multicomponent coupling phases. The *p*TsCl/DABCO-catalysed reactions were easily scalable without any discernible drop in target product yields, unlike the problems experienced using $POCl_3$-mediated dehydration. Secondly, the non-stoichiometric addition of dehydrating agents that oftentimes characterises most $POCl_3/Et_3N$ protocols makes it mandatory for preliminary aqueous workups to remove salts and excess reagents and purify the isocyanide. Such reactive salts and excess reagents could also be responsible for catalysing the hydration of the isocyanide to regenerate the formamide, thereby lowering yields.

Subsequent base-catalysed hydrolysis of the acetate **16a** in MeOH did indeed give rise to a ring-closed tetracycle **17a** in 53% yield (Scheme 2), together with compound *rac*-**18** (Fig. 3), in 47% yield. Close examination of the ^{1}H NMR spectrum for **17a** showed clearly that the fluorine atom had been displaced, as the proton at position 6 appeared as a dd, with one *ortho* and one *meta* coupling.

However, the signal for the proton on the cyclohexyl ring carbon atom carrying nitrogen had disappeared, together with the NH proton signal, showing that in fact **17a** was an imine, representing the oxidised form of compound **15**. Similarly, base-catalysed hydrolysis of acetates **16b–c**, this time in *t*-BuOH, gave rise to oxidised tetracycles **17b–c** in good yield (step iii, Scheme 2). Hydrolysis of the bromine containing acetate **16d** gave rise to an irresolvable mixture. The identities of the ring-closed products **17a** and **17c** were confirmed by single crystal X-ray crystallographic analysis (Fig. 4). The formation of the oxidised imine-containing products may possibly be attributed to the stronger electron withdrawing effect on the imidazopyridine skeleton by the nitro and the cyano groups as compared to



rac-**18**

Fig. 3 Compound **18** formed from **16a**.

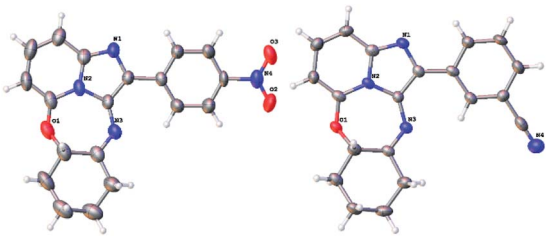
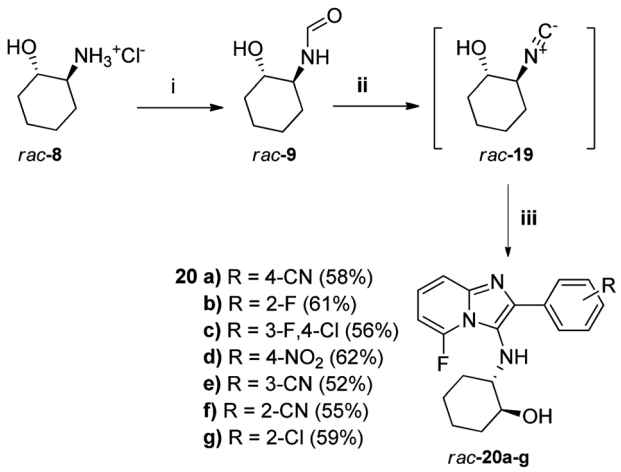


Fig. 4 ORTEP diagrams (50% probability level) of **17a** (left) and **17c** (right).

that exerted by the chlorine atom in the case of unoxidised ring-closed product **15**.

Given our failure to obtain the originally intended fluorine-containing imidazopyridine targets of general structure **7** *via* base-catalysed hydrolysis of their respective acetates **14** as explained above, an exploratory attempt was made to directly dehydrate the unprotected 2-*trans*-hydroxyformamide *rac*-**9** using the modified *p*TsCl/DABCO protocol and generate the isocyanide *rac*-**19** *in situ* for the subsequent multicomponent reaction with 2-amino-6-fluoropyridine **13a** and selected aldehydes **12** (Scheme 3). To our delight, the expected novel fluorine-containing targets **20a–g** were obtained in excellent overall yield, which also demonstrated the excellent OH functional group tolerance of the *p*TsCl/DABCO protocol. To the best of our knowledge, no similar successful attempts have previously been reported. Guchhait *et al.*[16] did not test their method on functionalised isocyanides. Although *rac*-**19** has not been prepared previously by dehydration of *rac*-**9**, it has been prepared by ring-opening of cyclohexene epoxide using TMSCN and ZnI_2, to give the TMS-protected alcohol that was subsequently deprotected.[20] One example of dehydration of a formamide containing a hydroxyl group to the corresponding isocyanide was reported by McCarthy *et al.* using Burgess reagent, but the reaction was low-yielding (<50%) and took 2



Scheme 3 Reagents: (i) NaOMe, methyl formate, MeOH, RT, 4 h; (ii) DCM, anhydr. Na_2SO_4 (1 eq.), pTsCl/DABCO, 0 °C–RT, 6 h, (iii) 0–5 °C, aldehyde **12**, 2-amino-6-fluoropyridine **13a**, anhydr. Na_2SO_4 (1 eq.), then 50 °C, 12 h. Yields for **20** are quoted over all three steps.

days.[21] Thus, the method reported here is superior in terms of ease of reaction and yield. The small library of novel imidazo [1,2-*a*]pyridines produced during the course of this research will be screened for activity against the HI virus and the findings will be reported in due course.

Experimental

General

All solvents were freshly distilled prior to use. Other reagents were used as purchased from Sigma-Aldrich. All infrared spectra were recorded neat using a Bruker TENSOR 27 single channel infrared spectrometer. All melting points are uncorrected and were performed using open capillary tubes on a Stuart SMP 10 melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded using either a Bruker AVANCE 111 300, 400 or 500 MHz spectrometer in deuterated chloroform ($CDCl_3$) with trimethylsilane (TMS) as internal standard ($\delta = 0$) for ^{1}H NMR, and $CDCl_3$ ($\delta = 77.0$ ppm) for ^{13}C NMR. The chemical shift (δ) is reported in ppm and the coupling constants (J) in Hz. High resolution mass spectral data was collected on a Waters Synapt G2 using an ESI positive source and a cone voltage of 15 V. TLC was performed on aluminium-backed Merck silica gel 60 F_{254} plates. The purification of compounds by column chromatography was performed using gravity (particle size 0.063–0.200 mm) or flash (particle size 0.040–0.063 mm) silica gel 60 purchased from Merck.

Synthetic procedures

Synthesis of *N*-(2-*trans*-hydroxycyclohexyl)formamide (*rac*-9). 2-*trans*-Hydroxycyclohexylammonium chloride *rac*-**8** (1 eq., 5.00 g, 33.0 mmol) was dissolved in methanol (40 ml) and treated with NaOMe (1.8 eq., 3.298 g, 10.0 ml, 61.0 mmol), to the resulting mixture was added methyl formate (4 eq., 8.00 ml, 130.6 mmol), and the reaction was allowed to stir for 24 h. A white solid precipitated out of the reaction mixture and was removed by filtration. An excess of hexane (relative to the volume of methanol) was added to the collected reaction mixture and was allowed to stand overnight, the resulting precipitate was again removed by filtration and the solvent removed *in vacuo* to obtain the desired product *rac*-**9** as a white-light grey solid (4.53 g, 96%). From NMR spectroscopy, it was evident that in solution this product occurs as a mixture of rotamers. Mp: 136–139 °C; IR (ν_{max}/cm^{-1}): 3341 (*N*–H), 3283 (O–H), 2858–2962 (C–H alkyl), 1635 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.26 (s, 0.7H), 8.06 (d, $J = 11.2$ Hz, 0.3H), 6.61 (br s, 0.3H), 6.28 (br s, 0.7H), 3.74–3.63 (m, 1H), 3.42–3.20 (m, 1.5H), 3.07–2.98 (m, 0.5H), 2.06–1.97 (m, 2H), 1.90–1.74 (m, 2H), 1.31–1.25 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.14, 162.54, 74.41, 73.23, 58.69, 54.60, 34.38, 33.69, 32.31, 31.57, 24.79, 24.16, 24.44, 24.04; HRMS (ES)$^+$: calculated for $C_7H_{14}NO_2$ [M + H]$^+$: 144.1019, found: 144.1019.

Synthesis of 2-*trans*-formamidocyclohexyl acetate (*rac*-10). Compound *rac*-**9** (1 eq., 1.20 g, 8.38 mmol) was dissolved in a solution of acetic anhydride (9 eq., 7.00 ml, 74.1 mmol) and pyridine (6 eq., 4.20 ml, 52.1 mmol, 6 eq.) for 4 h at room temperature. The reaction vessel was placed in an ice bath, and excess methanol was added to the resulting solution to quench the excess acetic anhydride. The excess pyridine was removed *in vacuo* as an azeotropic mixture with toluene to give the desired product *rac*-**10** as a yellow solid (1.50 g, 97%). Mp: 85–88 °C; IR (cm^{-1}): 3271 (NH str.), 2868 and 2937 (CH str.), 1726 (C=O ester), 1658 (C=O aldehyde); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.15–8.00 (m, 1H), 6.56–6.25 (m, *N*–H), 4.75–4.52 (m, 1H), 4.03–3.88 (m, 0.8H), 3.35–3.20 (m, 0.2H), 2.12–1.92 (m, 5H), 1.83–1.69 (m, 2H), 1.54–1.19 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.5, 170.3, 164.2, 160.9, 74.8, 74.3, 54.8, 51.1, 32.0, 31.7, 30.8, 30.6, 24.0, 23.9, 23.8, 23.5, 21.0, 20.9; HRMS (ES)$^+$: calculated for $C_9H_{16}NO_3$ [M + H]$^+$: 186.1125, found: 186.1127.

Synthesis of 2-*trans*-isocyanocyclohexyl acetate (*rac*-11). Compound *rac*-**10** (0.100 g, 0.540 mmol) and Et_3N (1.82 g, 18.0 mol) were mixed in dry DCM (10 ml) and the mixture treated with $POCl_3$ (0.30 ml, 3.21 mmol) at 0 °C. The reaction was warmed to room temperature under N_2, and left to stir for 24 h. The resulting mixture was gradually added to ice-cold water over a period of 30 min to quench the excess $POCl_3$. The organic layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 ml). The organic layers were combined and washed with saturated $NaHCO_3$ solution before being dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the residue purified by flash column chromatography (elution 4 : 1 EtOAc/Hex) to give the desired product *rac*-**11** as a light yellow oil (0.077 g, 85%). IR (cm^{-1}): 1736 (C=O), 2141 ($^+$N≡C$^-$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.83 (td, $J = 9.2$, 4.2 Hz, 1H), 3.59–3.47 (m, 1H), 2.25–2.01 (m, 5H), 1.84–1.58 (m, 3H), 1.52–1.20 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.0, 156.5 (t, $J_{C-N} = 9.5$ Hz), 73.4, 55.1 (t, $J_{C-N} = 13.5$ Hz), 31.3, 29.4, 22.9, 22.7, 20.9 ppm; HRMS (ES)$^+$: calculated for $C_9H_{14}NO_2$ [M + H] $^+$: 168.1019, found: 168.1017.

General procedure for microwave-assisted synthesis of novel imidazo[1,2-*a*]pyridine derivatives 14a–d

A mixture of a 6-substituted-2-aminopyridine **13a–d** (1 mmol), 2-chlorobenzaldehyde **12a** (1 mmol), isocyanide *rac*-**11** (170 mg, 1.02 mmol) and montmorillonite K-10 clay (100 mg) in 1,4-dioxane (2.0 ml) was irradiated in a sealed tube for 30 min (150 W, 100 °C). After cooling to room temperature, the K-10 clay was filtered off through Celite which was later washed with EtOAc and the combined organic solvents were removed *in vacuo* to give a crude residue that was purified using flash silica by eluting with 20–60% EtOAc/Hex.

Synthesis of 2-((2-(2-chlorophenyl)-5-fluoroimidazo[1,2-*a*]pyridin-3-yl)amino)cyclohexyl acetate (*rac*-14a). MW irradiation of 2-chlorobenzaldehyde **12a** (143 mg, 1.0 mmol), 2-amino-6-fluoropyridine **13a** (112 mg, 1.0 mmol) and isocyanide *rac*-**11** (167 mg, 1.0 mmol) in the presence of K-10 clay (110 mg) gave *rac*-**14a** (220 mg, 60%) as a black oil. IR (cm^{-1}): 3352 (NH str.), 2937 (CH str.), 1730 (C=O str.), 1651 (C=N). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61–7.58 (m, 1H), 7.50–7.47 (m, 1H), 7.37–7.34 (m, 3H), 7.12–7.08 (m, 1H), 6.38 (t, $J = 7.4$ Hz, 1H), 4.66–4.55 (m, 1H), 3.55–3.51 (m, 1H), 2.88–2.81 (m, 1H), 1.93–1.87 (m, 4H), 1.71–1.66 (m, 1H), 1.62–1.56 (m, 1H), 1.52–1.47 (m, 1H), 1.24–

1.15 (m, 2H), 1.02–0.91 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, δ 150.6 (d, $^1J_{C-F} = 268.1$ Hz), 143.6 (d, $^4J_{C-F} = 3.4$ Hz), 136.2, 133.4, 133.2, 132.5, 129.6, 129.5, 126.8, 126.1 (d, $^4J_{C-F} = 2.8$ Hz), 124.3 (d, $^3J_{C-F} = 6.4$ Hz), 113.8 (d, $^3J_{C-F} = 5.0$ Hz), 93.1 (d, $^2J_{C-F} = 17.4$ Hz), 76.4, 60.9, 30.9, 30.2, 23.7, 23.7, 21.1 ppm; HRMS (ES^+) calculated for $C_{21}H_{22}ClFN_3O_2$ $[M + H]^+$: 402.1379, found: 402.1400.

Synthesis of 2-((5-chloro-2-(2-chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)amino)cyclohexyl acetate (*rac*-14b). Reaction of 2-chlorobenzaldehyde **12a** (87.5 μL, 0.778 mmol), 2-amino-6-chloropyridine **13b** (100 mg, 0.778 mmol) and isocyanide *rac*-**11** (130 mg, 0.778 mmol) under MW irradiation in the presence of K-10 clay (110 mg) gave *rac*-**14b** (240 mg, 76%) as a black solid. Mp: 89–91 °C; IR (cm^{-1}): 3355 (NH str.), 2944 (CH str.), 1728 (C=O str.), 1653 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61–7.59 (m, 1H), 7.50–7.48 (m, 2H), 7.37–7.34 (m, 2H), 7.06–7.02 (m, 1H), 6.78–6.76 (m, 1H), 4.57–4.52 (m, 1H), 3.67–3.64 (m, 1H), 2.89–2.84 (m, 1H), 1.91–1.84 (m, 4H), 1.61–1.53 (m, 2H), 1.48–1.43 (m, 1H), 1.22–1.07 (m, 2H), 1.02–0.92 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 143.8, 138.3, 133.5, 133.4, 132.5, 129.6, 129.5, 127.6, 126.8, 126.3, 123.7, 116.8, 114.2, 76.9, 60.8, 30.3, 30.0, 23.6, 23.6, 21.1 ppm; HRMS (ES^+) calculated for $C_{21}H_{22}N_3O_2Cl_2$ $[M + H]^+$: 418.1089, found: 418.1080.

Synthesis of 2-((5-bromo-2-(2-chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)amino)cyclohexyl acetate (*rac*-14c). 2-Chlorobenzaldehyde **12a** (81.2 mg, 0.578 mmol), 2-amino-6-bromopyridine **13c** (100 mg, 0.578 mmol) and isocyanide *rac*-**11** (96.5 mg, 0.578 mmol) were reacted under MW irradiation in the presence of K-10 clay (110 mg) to give *rac*-**14c** (210 mg, 81%) as a black oil. IR (cm^{-1}): 3352 (NH str.), 2938 (CH str.), 1732 (C=O str.), 1652 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62–7.60 (m, 1H), 7.55–7.52 (m, 1H), 7.49–7.47 (m, 1H), 7.38–7.34 (m, 2H), 7.00–6.94 (m, 2H), 4.58–4.53 (m, 1H), 3.64–3.60 (m, 1H), 2.88–2.82 (m, 1H), 1.92–1.85 (m, 4H), 1.58–1.52 (m, 2H), 1.49–1.43 (m, 1H), 1.22–1.14 (m, 1H), 1.11–1.03 (m, 2H), 0.98–0.90 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 143.9, 138.8, 133.6, 133.3, 132.4, 129.6, 129.5, 127.9, 126.8, 124.0, 118.8, 117.3, 112.5, 60.4, 30.1, 29.9, 23.7, 23.6, 21.1 ppm; HRMS (ES^+) calculated for $C_{21}H_{22}BrClN_3O_2$ $[M + H]^+$: 462.0578, found: 462.0555.

Synthesis of 2-((2-(2-chlorophenyl)-5-cyanoimidazo[1,2-*a*]pyridin-3-yl)amino)cyclohexyl acetate (*rac*-14d). Reaction of 2-chlorobenzaldehyde **12a** (118 mg, 0.84 mmol), 2-amino-6-cyanopyridine **13d** (100 mg, 0.84 mmol) and isocyanide *rac*-**11** (140.33 mg, 0.84 mmol) under MW irradiation in the presence of K-10 clay (110 mg) gave *rac*-**14d** (150 mg, 44%) as a yellow solid. Mp: 236–238 °C. IR (cm^{-1}): 3348 (NH str.), 2939 (CH str.), 2215 (CN str.), 1733 (C=O str.), 1653 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, $J = 8.9$ Hz, 1H), 7.68–7.64 (m, 1H), 7.55–7.51 (m, 1H), 7.45–7.40 (m, 3H), 7.20 (dd, $J = 9.0$, 7.1 Hz, 1H), 4.59 (td, $J = 9.7$, 4.4 Hz, 1H), 3.73–3.68 (m, 1H), 2.93–2.86 (m, 1H), 2.00–1.92 (m, 1H), 1.84 (s, 3H), 1.65–1.51 (m, 3H), 1.34–1.21 (m, 3H), 1.12–0.98 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 141.3, 139.3, 133.2, 133.0, 132.4, 130.2, 129.9, 127.8, 127.3, 124.3, 123.0, 122.3, 113.8, 108.4, 77.1, 60.0, 30.4, 29.9, 23.8, 23.7, 21.1 ppm; HRMS (ES^+) calculated for $C_{22}H_{22}ClN_4O_2$ $[M + H]^+$: 409.1426, found: 409.1413.

Typical procedure for the preparation of compounds 16a–d

A mixture of 2-*trans*-hydroxycyclohexylammonium chloride *rac*-**8** (2.00 g, 17.12 mmol), sodium methoxide (20 ml, 6.58 mmol) and methyl formate (2 ml) were stirred at room temperature for 2 h. Thereafter, MeOH (20 ml) was added to the reaction and the mixture was stirred at 40 °C for 2 h, and then at room temperature for a further 24 h. After removing the organic solvent *in vacuo*, acetone (25 ml) was added to the off-white residue and the precipitated salts were removed by filtration. The solvent was evaporated *in vacuo* to afford an off-white oily product, 2-*trans*-hydroxycyclohexyl formamide *rac*-**9** (1.83 g. 99% yield). To a mixture of the formamide *rac*-**9** (1.70 g, 16.18 mmol) and a catalytic amount of dimethylaminopyridine (171 mg) in acetonitrile (20 ml) was added acetic anhydride (15 ml) and the reaction mixture stirred at room temperature for 12 h. After evaporating the solvent, the pale-yellow oil was diluted with acetone (20 ml) and after adding sodium bicarbonate (1.2 eq.), the reaction mixture was filtered to afford 2-formamidocyclohexyl acetate *rac*-**10** as a pale yellow oil in quantitative yield.

An appropriate amount of 2-formamidocyclohexyl acetate *rac*-**10** (1.0 mmol (185 mg)–2 mmol (371 mg)), anhydrous Na_2SO_4 (284 mg, 2 mmol) and a magnetic stirrer were added to freshly distilled dichloromethane (10–15 ml) and chilled in an ice bath (10 min). *p*-Toluenesulfonyl chloride (pTsCl) (1.0 mmol (191 mg)–2.0 mmol (382 mg)) and DABCO (1.0 mmol (112 mg)–2.0 mmol (225 mg)) were added in succession and the closed reaction mixture was stirred under ice-chilled conditions for 1 h. Thereafter, the reaction mixture was allowed to gradually warm to room temperature with stirring for a further 2 h. To this chilled *in situ* generated isocyanide *rac*-**11** crude mixture was added anhydrous Na_2SO_4 (284 mg, 2 mmol), an appropriate aldehyde **12** (1.0–2.0 mmol) and 2-amino-6-fluoropyridine **13a** (1.0–2.0 mmol) and the sealed reaction mixture was heated at 50–60 °C in an oil bath for 10–12 h. Thereafter, the reaction was cooled to room temperature, diluted with DCM (20 ml) and filtered. The filtrate was washed successively with distilled water (2 × 10 ml) and saturated brine solution (10 ml). After drying over Na_2SO_4, the solvent was removed *in vacuo* and the crude mixture was purified by silica gel flash column chromatography, eluting the title compounds **16a–d** with 25–50% EtOAc/hexane.

Synthesis of 2-((5-fluoro-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridin-3-yl)amino)cyclohexyl acetate (*rac*-16a). 4-Nitrobenzaldehyde (303 mg, 2.0 mmol), 2-amino-6-fluoropyridine **13a** (225 mg, 2.0 mmol) and the *in situ* generated isocyanide *rac*-**11** were reacted to generate product *rac*-**16a** (454 mg, 74% from *rac*-**10**) as a yellow solid. Mp: 196–197 °C; IR (cm^{-1}): 3333 (NH str.), 3081 and 2943 (CH str.), 1727 (C=O str.), 1659 (C=N), 1566 (NH bend), 1451 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53–8.48 (m, 2H), 8.30–8.26 (m, 2H), 7.36 (d, $J = 9.0$, Hz, 1H), 7.17–7.12 (m, 1H), 6.41 (t, $J = 7.3$ Hz, 1H), 4.79 (td, $J = 10.0$, 4.5 Hz, 1H), 3.63–3.61 (m, 1H), 3.11–3.06 (m, 1H), 2.09–2.05 (m, 1H), 1.94 (s, 3H), 1.78–1.74 (m, 1H), 1.71–1.68 (m, 1H), 1.62–1.58 (m, 1H), 1.33–1.22 (m, 3H), 1.12–1.06 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 150.5 (d, $^1J_{C-F} = 262.5$ Hz), 146.7, 144.1 (d, $^4J_{CF} = 3.7$ Hz), 140.5, 134.7, 127.7, 126.0 (d, $^4J_{C-F} = 1.7$ Hz), 125.4 (d, $^3J_{C-F} = 6.8$ Hz) 123.7, 114.2 (d, $^3J_{C-F} = 4.9$

Hz), 93.4, (d, $^2J_{CF}$ = 17.6 Hz), 77.4, 61.4 (d, $^5J_{C-F}$ = 2.1 Hz), 31.2, 30.7, 24.1, 24.0, 21.1; HRMS (ES^+) calculated for $C_{21}H_{22}FN_4O_4$ $[M + H]^+$: 413.1620, found: 413.1615.

Synthesis of 2-((5-fluoro-2-(3-nitrophenyl)imidazo[1,2-*a*]pyridin-3-yl)amino)cyclohexyl acetate (*rac*-16b). 3-Nitrobenzaldehyde (303 mg, 2.0 mmol), 2-amino-6-fluoropyridine **13a** (225 mg, 2.0 mmol) and the *in situ* generated isocyanide *rac*-**11** were reacted to give product *rac*-**16b** (406 mg, 70% from *rac*-**10**) as a yellow solid. Mp: 169–171 °C; IR (cm^{-1}): 3341 (NH str.), 3083, 2967 and 2936 (CH str.), 1728 (C=O str.), 1654 (C=N), 1568 (NH bend), 1434 (C=C);.^{1}H NMR (500 MHz, $CDCl_3$) δ 9.20 (t, J = 2.0 Hz, 1H), 8.66 (dt, J = 7.9, 1.3 Hz, 1H), 8.17–8.15 (m, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 7.16–7.12 (m, 1H), 6.40 (t, J = 7.2 Hz, 1H), 4.77 (td, J = 10.1, 4.5 Hz, 1H), 3.63–3.58 (m, 1H), 3.14–3.08 (m, 1H), 2.09–2.03 (m, 1H), 1.85 (s, 3H), 1.70–1.61 (m, 2H), 1.34–1.22 (m, 4H), 1.16–1.08 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 150.5 (d, $^1J_{C-F}$ = 265.7 Hz), 148.6, 143.9 (d, $^4J_{C-F}$ = 3.7 Hz), 135.8, 134.8, 133.1, 129.2, 125.1 (d, $^3J_{C-F}$ = 6.3 Hz), 122.1 (d, $^3J_{C-F}$ = 9.5 Hz), 114.0 (d, $^4J_{C-F}$ = 4.9 Hz), 93.4 (d, $^2J_{C-F}$ = 17.6 Hz), 77.7, 61.1 (d, $^5J_{C-F}$ = 2.2 Hz), 31.2, 30.7, 24.1, 24.0, 21.0; HRMS (ES^+) calculated for $C_{21}H_{22}FN_4O_4$ $[M + H]^+$: 413.1620, found: 413.1617.

Synthesis of 2-((2-(3-cyanophenyl)-5-fluoroimidazo[1,2-*a*]pyridin-3-yl)amino)cyclohexyl acetate (*rac*-16c). Reaction of 3-cyanobenzaldehyde (262 mg, 2.0 mmol), 2-amino-6-fluoropyridine **13a** (225 mg, 2.0 mmol) and the *in situ* generated isocyanide *rac*-**11** gave target product *rac*-**16c** (448 mg, 76% from *rac*-**10**) as a yellow solid. Mp: 185–187 °C; IR (cm^{-1}): 3335 (NH str.), 3055, 2937 and 2855 (CH str.), 2229 (CN str.), 1729 (C=O str.), 1657 (C=N), 1583 (NH bend), 1443 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (d, J = 1.7 Hz, 1H), 8.57 (dt, J = 7.9, 1.5 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H), 7.34 (d, J = 9.0 Hz, 1H), 7.15–7.11 (m, 1H), 6.40 (t, J = 7.2 Hz, 1H), 4.77 (td, J = 10.0, 4.5 Hz, 1H), 3.58–3.55 (m, 1H), 3.11–3.04 (m, 1H), 2.08–2.05 (m, 1H), 1.94 (s, 3H), 1.77–1.73 (m, 1H), 1.70–1.66 (m, 1H), 1.63–1.57 (m, 1H), 1.33–1.20 (m, 3H), 1.14–1.04 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 150.4 (d, $^1J_{C-F}$ = 265.9 Hz), 143.9 (d, $^4J_{C-F}$ = 3.8 Hz), 135.2, 134.8, 131.4, 130.8, 130.7, 129.1, 125.1 (d, $^3J_{C-F}$ = 6.3 Hz), 124.9 (d, $^4J_{C-F}$ = 2.5 Hz), 119.0, 113.9 (d, $^3J_{C-F}$ = 5.0 Hz), 112.5, 93.3 (d, $^2J_{C-F}$ = 17.6 Hz), 77.3, 61.1 (d, $^5J_{C-F}$ = 2.2 Hz), 31.2, 30.7, 24.0, 21.0; HRMS (ES^+) calculated for $C_{22}H_{22}FN_4O_2$ $[M + H]^+$: 393.1721, found: 393.1719.

Synthesis of 2-((2-(3-bromophenyl)-5-fluoroimidazo[1,2-*a*]pyridin-3-yl)amino)cyclohexyl acetate (*rac*-16d). 3-Bromobenzaldehyde (370 mg, 2.0 mmol), 2-amino-6-fluoropyridine **13a** (225 mg, 2.0 mmol) and the *in situ*-generated isocyanide *rac*-**11** were reacted to give title compound *rac*-**16d** (472 mg, 73% from *rac*-**10**) as a yellow solid. Mp: 151–152 °C; IR (cm^{-1}): 3341 (NH str.), 3083, 2957 and 2936 (CH str.), 1728 (C=O str.), 1654 (C=N), 1568 (NH bend), 1434 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (t, J = 1.9 Hz, 1H), 8.24 (dt, J = 7.8, 1.3 Hz, 1H), 7.44–7.42 (m, 1H), 7.34 (d, J = 9.0 Hz, 1H), 7.31–7.27 (m, 1H), 7.11–7.07 (m, 1H), 6.36 (t, J = 7.2, Hz, 1H), 4.75 (td, J = 10.0, 4.5 Hz, 1H), 3.52 (s, 1H), 3.08–3.06 (m, 1H), 2.08–2.04 (m, 1H), 1.89 (s, 3H), 1.79–1.76 (m, 1H), 1.69–1.66 (m, 1H), 1.61–1.58 (m, 1H), 1.32–1.20 (m, 3H), 1.10–1.08 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 150.5 (d, $^1J_{C-F}$ = 265.7 Hz), 143.9 (d, $^4J_{C-F}$ = 3.7 Hz), 136.0, 135.4, 130.4, 130.1, 129.8, 125.8, 125.7, 124.7 (d, $^1J_{C-F}$ = 6.3 Hz), 122.6, 113.8 (d, $^4J_{C-F}$ = 5.0 Hz), 93.1 (d, $^2J_{C-F}$ = 17.6 Hz), 77.6, 60.9 (d, $^5J_{C-F}$ = 2.1 Hz), 31.1, 30.7, 24.1, 24.0, 21.1; HRMS (ES^+) calculated for $C_{21}H_{22}{}^{79}BrN_3O_2$ $[M + H]^+$: 446.0874, found: 446.0875.

General procedure for the preparation of imidazo[1,2-*a*] pyridines 7b–c, 7e, 18 and ring-closed products 15, 17a–c

An appropriate aminocyclohexyl acetate derivative (**14** or **16**) and powdered KOH (4 eq.) were stirred in MeOH or *tert*-butanol (3–5 ml) at room temperature for 4 h. After removing solvent *in vacuo*, the crude residue was diluted with DCM (15–20 ml) and then washed successively with distilled water (2 × 10 ml) and saturated brine solution (10 ml). After drying over Na_2SO_4, the solvent was removed *in vacuo* and the crude mixture was purified by silica gel flash column chromatography, eluting the title compound with 25–50% EtOAc/hexane.

Synthesis of 2-((5-chloro-2-(2-chlorophenyl)imidazo[1,2-*a*] pyridin-3-yl)amino)cyclohexanol (*rac*-7b). Compound *rac*-**7b** (72 mg, 83%) obtained as a yellow solid from the hydrolysis of acetate *rac*-**14b** (100 mg, 0.24 mmol) in methanol. IR (cm^{-1}): 3423 (OH str.), 3340 (NH str.), 2943 (CH str.), 1651 (NH bend), 1442 (C=C); Mp: 183–185 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60–7.56 (m, 1H), 7.53–7.48 (m, 2H), 7.38–7.34 (m, 2H), 7.05 (dd, J = 8.9, 7.2 Hz, 1H), 6.79 (dd, J = 7.2, 1.1 Hz, 1H), 3.85–3.78 (m, 1H), 3.27–3.21 (m, 1H), 2.70–2.63 (m, 1H), 2.43–2.38 (m, 1H), 1.92–1.86 (m, 1H), 1.61–1.54 (m, 2H), 1.50–1.44 (m, 1H), 1.16–1.07 (m, 2H), 1.11–0.89 (m, 1H), 0.78–0.71 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.9, 138.1, 133.6, 133.5, 132.6, 129.8, 129.6, 127.8, 126.8, 126.0, 123.7, 117.0, 114.2, 74.6, 65.3, 33.4, 30.3, 24.4, 24.0; HRMS (ES^+) calculated for $C_{19}H_{20}N_3OCl_2$ $[M + H]^+$: 376.0983, found: 376.0974.

Synthesis of 2-((5-bromo-2-(2-chlorophenyl)imidazo[1,2-*a*] pyridin-3-yl)amino)cyclohexanol (*rac*-7c). Compound *rac*-**7c** (60 mg, 83%) obtained as a yellow solid from the hydrolysis of acetate *rac*-**14c** (80 mg, 0.204 mmol) in methanol. Mp: 156–158 °C; IR (cm^{-1}): 3431 (OH str.), 3328 (NH str.), 2940 (CH str.), 1656 (NH bend), 1437 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60–7.54 (m, 2H), 7.51–7.47 (m, 1H), 7.37–7.33 (m, 2H), 7.02–6.95 (m, 2H), 3.90 (s, 1H), 3.27–3.19 (m, 1H), 2.70–2.60 (m, 1H), 2.33 (s, 1H), 1.90–1.80 (m, 1H), 1.57–1.44 (m, 3H), 1.15–1.06 (m, 2H), 0.98–0.90 (m, 1H), 0.85–0.76 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 144.0, 138.5, 133.7, 133.5, 132.5, 129.8, 129.6, 128.0, 126.8, 124.0, 118.8, 117.5, 112.2, 74.7, 64.7, 33.4, 30.1, 24.4, 24.1; HRMS (ES^+) calculated for $C_{19}H_{20}BrClN_3O$ $[M + H]^+$: 420.0473, found: 420.0465.

Synthesis of 2-(2-chlorophenyl)-3-((2-hydroxycyclohexyl)amino) imidazo[1,2-*a*]pyridine-5-carboxamide (*rac*-7e). Compound *rac*-**7e** (65 mg, 68%) obtained as a yellow solid from the hydrolysis of acetate *rac*-**14d** (100 mg, 0.25 mmol) in methanol. Mp: 156–158 °C; IR (cm^{-1}): 3431 (OH str.), 3328 (NH str.), 2940 (CH str.), 1656 (NH bend), 1437 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.97 (s, 1H), 7.62–7.52 (m, 3H), 7.44–7.39 (m, 2H), 7.23–7.18 (m, 1H), 7.11 (d, J = 6.8 Hz, 1H), 4.36 (d, J = 4.7 Hz, 1H), 4.24 (d, J = 3.2 Hz, 1H), 3.13–3.05 (m, 1H), 1.69–1.60 (m, 1H), 1.48–1.37 (m, 1H), 1.33–1.21 (m, 2H), 1.09–0.92 (m, 2H), 0.79–0.57 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ 165.6, 140.7, 134.4, 133.2, 132.6, 131.8, 129.3, 129.2, 127.9, 126.6, 121.7, 118.8, 113.6, 71.9, 59.3, 32.6, 29.0,

23.0, 22.8.; HRMS (ES^+) calculated for $C_{20}H_{22}N_4O_2Cl$ $[M + H]^+$: 385.1431, found: 385.1418.

Synthesis of 2-((2-(2-chlorophenyl)-5-methoxyimidazo[1,2-*a*]pyridin-3-yl)amino)cyclohexanol (*rac*-7f). Both compound *rac*-**7f** (30 mg, 40%) and *rac*-**15** (50%), which were readily separated by silica gel column chromatography, were obtained from the hydrolysis of *rac*-**14a** (80 mg, 0.21 mmol) in methanol. *Rac*-**7f**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58–7.56 (m, 1H), 7.48–7.46 (m, 1H), 7.35–7.30 (m, 2H), 7.17 (d, $J = 8.9$ Hz, 1H), 7.05–7.3 (m, 1H), 5.97 (d, $J = 7.4$ Hz, 1H), 4.04 (s, 3H), 3.85–3.56 (m, 1H), 3.40 (s, 1H), 3.26–3.18 (m, 1H), 2.58–2.51 (m, 1H), 2.00–1.92 (m, 1H), 1.67–1.56 (m, 2H), 1.51–1.44 (m, 1H), 1.18–1.01 (m, 2H), 0.99–0.89 (m, 1H), 0.71–0.62 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.8, 143.4, 133.9, 133.8, 133.4, 132.6, 129.7, 129.4, 127.6, 126.8, 124.6, 110.8, 88.4, 74.0, 66.0, 56.3, 33.1, 31.2, 24.8, 24.0; HRMS (ES^+) calculated for $C_{21}H_{23}N_3O_2Cl$ $[M + H]^+$: 372.1479, found: 372.1466.

Synthesis of 1-(2-chlorophenyl)-7,8,9,10,10*a*,11-hexahydro-6*aH*-6-oxa-2,2*a*1,11-triazadibenzo[*cd*,*g*]azulene (*rac*-15). Compound *rac*-**15** (30 mg, 60%) was obtained as an orange oil from the hydrolysis of *rac*-**14a** (80 mg, 0.21 mmol) in *tert*-butanol. IR (cm^{-1}): 3301 (*N*–H), 3067 (=C–H), 2937 (C–H), 1638 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, $J = 7.6$ Hz, 1H), 7.46 (d, $J = 8.0$ Hz, 1H), 7.35 (t, $J = 7.5$ Hz, 1H), 7.30–7.26 (m, 1H), 7.17 (d, $J = 9.0$ Hz, 1H), 6.92 (t, $J = 8.1$ Hz, 1H), 6.17 (d, $J = 7.2$ Hz, 1H), 4.13–4.07 (m, 1H), 3.84 (s, 1H), 3.42–3.35 (m, 1H), 2.29–2.23 (m, 1H), 2.06–2.00 (m, 1H), 1.87–1.81 (m, 1H), 1.76–1.62 (m, 2H), 1.50–1.40 (m, 1H), 1.39–1.23 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.6, 142.6, 133.4, 133.0, 132.4, 129.8, 128.8, 128.2, 127.1, 124.3, 123.6, 111.7, 96.6, 88.4, 60.4, 32.8, 31.6, 23.9, 23.6 ppm; HRMS (ES^+) calculated for $C_{19}H_{19}N_3OCl$ $[M + H]^+$: 340.1217, found: 340.1205.

Synthesis of 1-(4-nitrophenyl)-7,8,9,10-tetrahydro-6*aH*-6-oxa-2,2*a*1,11-triazadibenzo[*cd*,*g*]azulene (17a). Compound **17a** (46 mg, 53%) was obtained as a dark brown solid and a co-product with 18 (47%) from the hydrolysis of 2-((5-fluoro-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridin-3-yl)amino)cyclohexyl acetate *rac*-**16a** (105 mg, 0.25 mmol) in methanol. Mp: 188–189 °C; IR (cm^{-1}): 3082 and 2946 (CH str.), 1655 (C=N), 1445 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67–8.65 (m, 2H), 8.31–8.28 (m, 2H), 7.35 (dd, $J = 8.9$, 1.0 Hz, 1H), 7.25–7.22 (m, 1H), 6.40 (dd, $J = 7.3$, 1.0 Hz, 1H), 4.72 (dd, $J = 9.4$, 6.2 Hz, 1H), 2.96–2.90 (m, 1H), 2.69–2.61 (m, 1H), 2.46–2.41 (m, 1H), 2.06–1.94 (m, 3H), 1.85–1.76 (m, 1H), 1.73–1.63 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.5, 148.7, 147.0, 145.8, 140.4, 138.7, 129.1, 128.0, 127.1, 123.4, 112.3, 98.7, 83.8, 36.6, 31.6, 23.3, 20.9 ppm; HRMS (ES^+) calculated for $C_{19}H_{17}N_4O_3$ $[M + H]^+$: 349.1295, found: 349.1287.

Synthesis of 1-(3-nitrophenyl)-7,8,9,10-tetrahydro-6*aH*-6-oxa-2,2*a*1,11-triazadibenzo[*cd*,*g*]azulene (17b). Compound **17b** (45 mg, 65%) was obtained as a yellow solid from the hydrolysis of *rac*-**16b** (85 mg, 0.20 mmol) in *tert*-butanol. Mp: 164–166 °C; IR (cm^{-1}): 3080 and 2952 (CH str.), 1653 (C=N), 1450 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.43 (t, $J = 2.0$ Hz, 1H), 8.75 (d, $J = 7.8$ Hz, 1H), 8.17 (dd, $J = 8.2$, 2.4 Hz, 1H), 7.59 (t, $J = 8.9$, 1H), 7.34 (d, $J = 8.9$ Hz, 1H), 7.22 (dd, $J = 8.9$, 7.3 Hz, 1H), 6.39 (d, $J = 7.3$ Hz, 1H), 4.73–4.69 (m, 1H), 2.96–2.91 (m, 1H), 2.69–2.62 (m, 1H), 2.44–2.41 (m, 1H), 2.05–1.94 (m, 3H), 1.85–1.75 (m, 1H), 1.71–1.64 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9, 148.6, 148.4, 145.6, 138.6, 135.6, 134.1, 129.0, 127.8, 126.4, 123.7, 122.4, 112.1, 98.7, 83.8, 36.6, 31.7, 23.4, 21.0 ppm; HRMS (ES^+) calculated for $C_{19}H_{17}N_4O_3$ $[M + H]^+$: 349.1295, found: 349.1290.

Synthesis of 3-(7,8,9,10-tetrahydro-6*aH*-6-oxa-2,2*a*1,11-triazadibenzo[*cd*,*g*]azulen-1-yl)benzonitrile (17c). Hydrolysis of *rac*-**16c** (100 mg, 0.25 mmol) with KOH (4 eq.) in *tert*-butanol gave product **17c** (60 mg, 71%) as a brown solid. Mp: 130–132 °C; IR (cm^{-1}): 3078 and 2955 (CH str.), 2225 (CN str.), 1653 (C=N), 1445 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (t, $J = 1.7$ Hz, 1H), 8.66 (dt, $J = 8.0$, 1.5 Hz, 1H), 7.60 (dt, $J = 7.7$, 1.5 Hz, 1H), 7.53 (t, $J = 7.8$ Hz, 1H), 7.32 (d, $J = 8.9$ Hz, 1H), 7.22 (dd, $J = 8.9$, 7.3 Hz, 1H), 6.38 (d, $J = 7.3$ Hz, 1H), 4.71–4.68 (m, 1H), 2.94–2.88 (m, 1H), 2.65–2.61 (m, 1H), 2.42–2.40 (m, 1H), 2.01–1.93 (m, 3H), 1.80–1.78 (m, 1H), 1.71–1.64 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8, 148.6, 145.6, 138.8, 135.1, 132.6, 132.4, 131.0, 128.9, 127.8, 126.3, 119.2, 112.3, 112.1, 98.6, 83.8, 36.5, 31.6, 23.3, 20.9 ppm; HRMS (ES^+) calculated for $C_{20}H_{17}N_4O$ $[M + H]^+$: 329.1397, found: 329.1394.

Synthesis of 2-((5-methoxy-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridin-3-yl)amino)cyclohexanol (*rac*-18). Compound *rac*-**18** (46 mg, 47%) was obtained as an orange solid co-product with **17a** from the hydrolysis of 2-((5-fluoro-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridin-3-yl)amino)cyclohexyl acetate *rac*-**16a** (105 mg, 0.25 mmol) in methanol. Mp: 179–180 °C; IR (cm^{-1}): 3401 (OH str.), 3343 (NH str.), 3079 and 2948 (CH str.), 1648 (C=N), 1559 (NH bend), 1448 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, $J = 8.6$ Hz, 2H), 8.24 (d, $J = 8.6$ Hz, 2H), 7.19–7.07 (m, 2H), 5.97 (d, $J = 7.2$ Hz, 1H), 4.49 (br s, 1H), 4.07 (s, 3H), 3.54–3.49 (m, 1H), 2.79–2.74 (m, 1H), 2.04–1.95 (m, 1H), 1.70–1.61 (m, 1H), 1.56–1.47 (m, 2H), 1.28–1.17 (m, 3H), 1.04–0.93 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0, 146.3, 144.0, 141.5, 133.6, 128.2, 127.8, 125.9, 123.5, 110.7, 88.6, 75.2, 65.5, 56.4, 34.2, 30.1, 24.4, 24.3; HRMS (ES^+) calculated for $C_{20}H_{23}N_4O_4$ $[M + H]^+$: 383.1714, found: 383.1704.

General procedure for the preparation of imidazo[1,2-*a*]pyridines 20a–g

To a chilled solution of 2-*trans*-hydroxycyclohexyl formamide *rac*-**9** (287 mg, 2 mmol) (prepared as described previously) in freshly distilled DCM (10–15 ml) was added a stirrer bar, dried *p*-TsCl (382 mg, 2 mmol) and DABCO (225 mg, 2 mmol). The sealed reaction mixture was stirred under chilled conditions for 1 h and allowed to warm to room temperature with stirring for a further 3 h. Thereafter, an appropriate aromatic aldehyde **12** (2 mmol), 2-amino-2-fluoropyridine **13a** (2 mmol) and anhydrous Na_2SO_4 (282 mg, 2 mmol) were added. The closed reaction mixture was heated at 50–60 °C in an oil bath for 10–12 h and later cooled to room temperature. Thereafter, the mixture was washed consecutively with distilled water (2 × 15 ml) and saturated brine solution (10 ml). After drying with anhydrous Na_2SO_4, the organic was evaporated *in vacuo* to leave a crude residue which was purified on flash silica gel by eluting with 25–80% EtOAc/Hex to afford title compounds **20a–g**.

Synthesis of 4-(5-fluoro-3-((-2-hydroxycyclohexyl)amino)imidazo[1,2-*a*]pyridin-2-yl)benzonitrile (*rac*-20a). 4-Cyanobenzaldehyde (303 mg, 2.0 mmol), 2-amino-6-fluoropyridine **13a** (225 mg, 2.0 mmol) and the *in situ* generated isocyanide *rac*-**19** were

reacted to give product *rac*-**20a** (407 mg, 58% overall yield from *rac*-**8**) as a brown solid. Mp: 102–103 °C IR (cm^{-1}): 3305 (NH str.), 3016 and 2933 (CH str.), 2224 (CN str.), 1652 (C=N), 1555 (NH bend), 1434 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49–8.41 (m, 2H), 7.71–7.66 (m, 2H), 7.39 (d, J = 9.0 Hz, 1H), 7.20–7.13 (m, 1H), 6.41 (t, J = 7.2 Hz, 1H), 3.97 (br. s, 1H), 3.57–3.53 (m, 1H), 2.84–2.81 (m, 1H), 2.07–1.93 (m, 2H), 1.69–1.65 (m, 1H), 1.59–1.50 (m, 2H), 1.31–1.20 (m, 2H), 1.07–0.97 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6 (d, $^1J_{C-F}$ = 267.1 Hz), 144.1 (d, $^4J_{CF}$ = 2.5 Hz), 138.3, 135.9, 132.1, 128.5, 128.0, 125.6 (d, $^3J_{CF}$ = 12.0 Hz), 119.2, 113.9 (d, $^3J_{C-F}$ = 5.0 Hz), 110.8, 93.5 (d, $^2J_{C-F}$ = 17.6 Hz), 75.3, 65.0 (d, $^5J_{C-F}$ = 2.6 Hz), 34.4, 30.1, 24.4, 24.2 ppm; HRMS (ES^+) calculated for $C_{20}H_{20}FN_4O$ $[M + H]^+$: 351.1616, found: 351.1617.

Synthesis of 2-((5-fluoro-2-(2-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)amino)cyclohexanol (*rac*-20b). Reaction of 2-fluorobenzaldehyde (245 mg, 2.0 mmol), 2-amino-6-fluoropyridine **13a** (225 mg, 2.0 mmol) and the *in situ* generated isocyanide *rac*-**19** gave title compound *rac*-**20b** (430 mg, 61% overall yield from *rac*-**8**) as a brown solid. Mp: 146–147 °C; IR (cm^{-1}): 3389 (NH str.), 3078, 2940 and 2861 (CH str.), 1651 (C=N), 1504 (NH bend), 1430 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (td, J = 7.6, 1.8 Hz, 1H), 7.43–7.34 (m, 2H), 7.30–7.25 (m, 1H), 7.20–7.09 (m, 2H), 6.40 (t, J = 7.3 Hz, 1H), 3.58 (br. s, 1H), 3.37–3.31 (m, 1H), 3.18 (br s, 1H), 2.69–2.63 (m, 1H), 2.02–1.98 (m, 1H), 1.63–1.58 (m, 2H), 1.51–1.44 (m, 1H), 1.27–1.12 (m, 2H), 1.03–0.93 (m, 1H), 0.79–0.65 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6 (d, $^1J_{C-F}$ = 245.7 Hz), 150.5 (d, $^1J_{C-F}$ = 268.4 Hz), 144.2 (d, $^4J_{C-F}$ = 3.8 Hz), 133.2, 131.9 (d, $^4J_{C-F}$ = 3.8 Hz), 129.9 (d, $^3J_{C-F}$ = 7.6 Hz), 126.5 (d, $^4J_{C-F}$ = 2.5 Hz), 124.73, 124.69 (d, $^4J_{C-F}$ = 3.2 Hz), 121.6 (d, $^3J_{C-F}$ = 15.1 Hz), 115.9 (d, $^1J_{C-F}$ = 22.7 Hz), 113.7 (d, $^3J_{C-F}$ = 5.0 Hz), 93.4 (d, $^2J_{C-F}$ = 17.6 Hz), 74.2, 65.5, 33.2, 30.9, 24.6, 24.0 ppm; HRMS (ES^+) calculated for $C_{19}H_{20}F_2N_3O$ $[M + H]^+$: 344.1582, found: 344.1569.

Synthesis of 2-((2-(4-chloro-3-fluorophenyl)-5-fluoroimidazo[1,2-*a*]pyridin-3-yl)amino)cyclohexanol (*rac*-20c). 4-Chloro-3-fluorobenzaldehyde (318 mg, 2.0 mmol), 2-amino-6-fluoropyridine **13a** (225 mg, 2.0 mmol) and the *in situ* generated isocyanide *rac*-**19** were reacted to give product *rac*-**20c** (423 mg, 56% overall yield from *rac*-**8**) as a brown solid. Mp: 105–107 °C; IR (cm^{-1}): 3400 (OH str.), 3328 (NH str.), 2932 and 2861 (CH str.), 1653 (C=N), 1512 (NH bend), 1435 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (dd, J = 8.3, 1.9 Hz, 1H), 8.04 (dd, J = 8.3, 2.0 Hz, 1H), 7.41 (t, J = 8.1 Hz, 1H), 7.35 (d, J = 8.9 Hz, 1H), 7.15–7.10 (m, 1H), 6.38 (t, J = 7.3 Hz, 1H), 3.91 (s, 1H), 3.58–3.53 (m, 1H), 2.87–2.81 (m, 1H), 2.07–1.99 (m, 2H), 1.69–1.65 (m, 1H), 1.59–1.52 (m, 2H), 1.29–1.24 (m, 2H), 1.06–1.02 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.5 (d, $^1J_{C-F}$ = 247 Hz), 150.5 (d, $^1J_{C-F}$ = 265.9 Hz), 144.1 (d, $^4J_{C-F}$ = 3.8 Hz), 136.4 (d, $^3J_{C-F}$ = 5.0 Hz), 134.6 (d, $^3J_{C-F}$ = 7.6 Hz), 130.3, 125.2 (d, $^3J_{C-F}$ = 10.1 Hz), 124.5 (d, $^4J_{C-F}$ = 1.3 Hz), 123.9 (d, $^4J_{C-F}$ = 3.8 Hz), 119.4 (d, $^2J_{C-F}$ = 17.6 Hz), 115.6 (d, $^2J_{C-F}$ = 22.7 Hz), 113.8 (d, $^3J_{C-F}$ = 5.0 Hz), 93.2 (d, $^2J_{C-F}$ = 17.6 Hz), 75.2, 64.9 (d, $^5J_{C-F}$ = 2.7 Hz), 34.4, 29.9, 24.8, 24.4, 24.2 ppm; HRMS (ES^+) calculated for $C_{19}H_{19}ClF_2N_3O$ $[M + H]^+$: 378.1179, found: 378.1167.

Synthesis of 2-((5-fluoro-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridin-3-yl)amino)cyclohexanol (*rac*-20d). Reaction of 4-nitrobenzaldehyde (303 mg, 2.0 mmol), 2-amino-6-fluoropyridine **13a** (225 mg, 2.0 mmol) and the *in situ* generated isocyanide *rac*-**19** generated product *rac*-**20d** (460 mg, 62% overall yield from *rac*-**8**) as a brown solid. Mp: 218–220 °C; IR (cm^{-1}): 3361 (OH str.), 3196 (NH str.), 2936 and 2858 (CH str.), 1652 (C=N), 1515 (NH bend), 1439 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55–8.51 (m, 2H), 8.29–8.26 (m, 2H), 7.38 (d, J = 9.0 Hz, 1H), 7.18–7.13 (m, 1H), 6.41 (td, J = 7.3, 0.9 Hz, 1H), 4.01 (s, 1H), 3.60–3.57 (m, 1H), 2.88–2.82 (m, 1H), 2.05–1.99 (m, 1H), 1.80 (s, 1H), 1.70–1.49 (m, 3H), 1.32–1.22 (m, 2H), 1.09–0.98 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6 (d, $^1J_{C-F}$ = 265.9 Hz), 146.8, 144.4 (d, $^4J_{C-F}$ = 3.8 Hz), 140.7, 136.0, 128.1, 126.0 (d, $^4J_{C-F}$ = 2.5 Hz), 125.5 (d, $^3J_{C-F}$ = 7.6 Hz), 123.6, 114.1 (d, $^3J_{C-F}$ = 5.0 Hz), 93.4 (d, $^2J_{C-F}$ = 17.6 Hz), 75.3, 65.0 (d, $^5J_{C-F}$ = 2.5 Hz), 34.5, 30.0, 24.4, 24.2 ppm; HRMS (ES^+) calculated for $C_{19}H_{20}FN_4O_3$ $[M + H]^+$: 371.1514, found: 371.1510.

Synthesis of 3-(5-fluoro-3-((2-hydroxycyclohexyl)amino)imidazo[1,2-*a*]pyridin-2-yl)benzonitrile (*rac*-20e). 3-Cyanobenzaldehyde (263 mg, 2.0 mmol), 2-amino-6-fluoropyridine **13a** (225 mg, 2.0 mmol) and the *in situ* generated isocyanide *rac*-**19** were reacted and gave product *rac*-**20e** (365 mg, 52% overall yield from *rac*-**8**) as a brown solid). Mp: 120–121 °C; IR (cm^{-1}): 3328 (overlapping br. OH and NH str.), 2931 and 2858 (CH str.), 2229 (CN str.), 1652 (C=N), 1516 (NH bend), 1446 (C=C^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68–8.66 (m, 1H), 8.55 (dt, J = 8.1, 1.5 Hz, 1H), 7.55 (dt, J = 7.8, 1.5 Hz, 1H), 7.49 (t, J = 7.8, Hz, 1H), 7.39 (d, J = 9.0 Hz, 1H), 7.19–7.15 (m, 1H), 6.42 (t, J = 7.1 Hz, 1H), 4.04 (s, 1H), 3.58–3.52 (m, 1H), 2.85–2.81 (m, 1H), 2.05–1.90 (m, 2H), 1.69–1.63 (m, 1H), 1.57–1.47 (m, 2H), 1.31–1.21 (m, 2H), 1.04–0.97 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6 (d, $^1J_{C-F}$ = 267.1 Hz), 143.9 (d, $^4J_{C-F}$ = 3.8 Hz), 135.4, 134.8, 131.8, 131.2, 130.9, 129.1, 126.0 (d, $^3J_{C-F}$ = 6.3 Hz), 125.1 (d, $^3J_{C-F}$ = 6.3 Hz), 119.0, 113.5 (d, $^4J_{C-F}$ = 5.0 Hz), 112.3, 93.7 (d, $^2J_{C-F}$ = 17.6 Hz), 75.0, 64.8 (d, $^5J_{C-F}$ = 2.6 Hz), 34.4, 30.0, 24.4, 24.2 ppm; HRMS (ES^+) calculated for $C_{20}H_{20}FN_4O$ $[M + H]^+$: 351.1616, found: 351.1615.

Synthesis of 2-(5-fluoro-3-((2-hydroxycyclohexyl)amino)imidazo[1,2-*a*]pyridin-2-yl)benzonitrile (*rac*-20f). 2-Cyanobenzaldehyde (263 mg, 2.0 mmol), 2-amino-6-fluoropyridine **13a** (225 mg, 2.0 mmol) and the *in situ* generated isocyanide *rac*-**19** were reacted and generated title compound *rac*-**20f** (386 mg, 55% overall yield from *rac*-**8**) as a brown solid. Mp: 152–153 °C; IR (cm^{-1}): 3328 (OH and NH br. str.), 2931 and 2851 (CH str.), 2225 (CN str.), 1652 (C=N), 1446 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (dd, J = 7.9, 1.2 Hz, 1H), 7.77 (dd, J = 7.8, 1.5 Hz, 1H), 7.67 (td, J = 7.7, 1.4 Hz, 1H), 7.47 (td, J = 7.7, 1.3 Hz, 1H), 7.39 (dd, J = 9.0, 0.9 Hz, 1H), 7.18–7.13 (m, 1H), 6.42 (t, J = 7.3 Hz, 1H), 3.83–3.77 (m, 1H), 3.34–3.30 (m, 1H), 2.78 (br s, 1H), 2.70–2.61 (m, 1H), 1.92–1.88 (m, 1H), 1.61–1.55 (m, 1H), 1.54–1.42 (m, 2H), 1.19–1.10 (m, 2H), 1.00–0.93 (m, 1H), 0.77–0.68 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.5 (d, $^1J_{C-F}$ = 267.1 Hz), 144.3 (d, $^4J_{C-F}$ = 3.8 Hz), 137.7, 136.7, 133.4, 132.6, 131.1, 128.2, 125.7 (d, $^4J_{C-F}$ = 2.5 Hz), 125.3 (d, $^3J_{C-F}$ = 6.3 Hz), 119.1, 114.1 (d, $^3J_{C-F}$ = 5.0 Hz), 112.4, 93.5 (d, $^2J_{C-F}$ = 17.6 Hz), 74.3, 65.0 (d, $^5J_{C-F}$ = 1.9 Hz), 33.5, 30.3, 24.2, 24.1 ppm; HRMS (ES^+) calculated for $C_{20}H_{20}FN_4O$ $[M + H]^+$: 351.1616, found: 351.1615.

Synthesis of 2-((2-(2-chlorophenyl)-5-fluoroimidazo[1,2-*a*]pyridin-3-yl)amino)cyclohexanol (*rac*-20g). Reaction of 2-chlorobenzaldehyde (210 mg, 1.0 mmol), 2-amino-6-fluoropyridine **13a** (113 mg, 1.0 mmol) and the *in situ* generated isocyanide

rac-**19** gave product *rac*-**20g** (212 mg, 59% overall yield from *rac*-**8**) as a brown solid. Mp: 149–151 °C; IR (cm^{-1}): 3400 (OH br. str.), 3221 (NH str.), 2928 and 2857 (CH str.), 1650 (C=N), 1432 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62–7.57 (m, 1H), 7.52–7.47 (m, 1H), 7.44–7.34 (m, 3H), 7.17–7.14 (m, 1H), 6.43 (t, J = 7.3, 1H), 3.53–3.36 (m, 1H), 3.30–3.25 (m, 1H), 3.08–2.71 (m, 1H), 2.66–2.59 (m, 1H), 2.00–1.94 (m, 1H), 1.66–1.58 (m, 2H), 1.53–1.44 (m, 1H), 1.20–1.10 (m, 2H), 1.02–0.93 (m, 1H), 0.73–0.64 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.5 (d, $^1J_{C-F}$ = 267.2 Hz), 143.6 (d, $^4J_{C-F}$ = 3.2 Hz), 135.7, 133.2, 132.7, 132.6, 129.8, 129.7, 127.0, 126.2 (d, $^4J_{C-F}$ = 2.9 Hz), 124.8 (d, $^3J_{C-F}$ = 6.8 Hz), 113.8 (d, $^3J_{C-F}$ = 5.0 Hz), 93.6 (d, $^2J_{C-F}$ = 17.7 Hz), 74.1, 65.4, 33.2, 31.0, 24.6, 24.0 ppm; HRMS (ES^+) calculated for $C_{19}H_{20}ClFN_3O$ $[M + H]^+$: 360.1273, found: 360.1272.

Crystallography

Crystal structure and refinement. Intensity data for **17a** and **17c** were collected on a Bruker Apex-II CCD area detector diffractometer with graphite monochromated Mo Kα radiation (50 kV, 30 mA). The collection method involved ω- and φ-scans of width 0.5° and 1024 × 1024 bit data frames. Using *Olex2*,[22] the crystal structures were solved by with the *ShelXT* structure solution program using Intrinsic Phasing and refined with the *ShelXL* refinement package using Least Squares minimisation.[23,24] Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F^2.

Crystal data for **17a**: $C_{19}H_{16}N_4O_3$ (M =348.36 g mol^{-1}): monoclinic, space group $C2/c$ (no. 15), a = 20.8879(15) Å, b = 7.2791(5) Å, c = 21.5015(15) Å, β = 96.086(5)°, V = 3250.8(4) $Å^3$, Z = 8, T = 173.15 K, μ(MoKα) = 0.100 mm^{-1}, D_{calc} = 1.424 g cm^{-3}, 10 492 reflections measured (3.81° ≤ 2θ ≤ 49.998°), 2857 unique (R_{int} = 0.1096, R_{sigma} = 0.1327) which were used in all calculations. The final R_1 was 0.0444 ($I > 2\sigma(I)$) and wR_2 was 0.0847 (all data). CCDC 1970362.

Crystal data for **17c**: $C_{20}H_{16}N_4O$ (M =328.37 g mol^{-1}): monoclinic, space group $P2_1/n$ (no. 14), a = 12.0432(7) Å, b = 7.3016(4) Å, c = 18.3346(12) Å, β = 96.116(4)°, V = 1603.07(17) $Å^3$, Z = 4, T = 173.15 K, μ(MoKα) = 0.088 mm^{-1}, D_{calc} = 1.361 g cm^{-3}, 11 067 reflections measured (3.866° ≤ 2θ ≤ 49.98°), 2831 unique (R_{int} = 0.1479, R_{sigma} = 0.2114) which were used in all calculations. The final R_1 was 0.0410 ($I > 2\sigma(I)$) and wR_2 was 0.0687 (all data). CCDC 1970363.

Conclusions

In summary, we have successfully developed a methodology for the synthesis of novel tetracyclic derivatives through intramolecular nucleophilic aromatic substitution of fluorine at position 5 of the imidazo[1,2-*a*]pyridine ring. In addition, we have demonstrated the improved utility, convenience and practicality of the *p*TsCl/DABCO-catalysed isocyanide *in situ* generation protocol over the conventional $POCl_3$/Et_3N protocol. Furthermore, we have managed to improve and simplify the existing *p*TsCl/DABCO *N*-formamide dehydration methodology to such an extent that it can be employed efficiently and cheaply in the absence of any preliminary purging of the reaction with nitrogen. Of particular importance is that it has also proved to be effective for preparing functionalised isocyanides *in situ* without the requirement for protection of reactive hydroxyl groups.

Conflicts of interest

There are no conflicts to declare.

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