2- And 3-substituted imidazo[1,2-\(a\)]pyrazines as inhibitors of bacterial type IV secretion

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General Chemistry Methods

Melting points (Mpt) were recorded on a Gallenkamp Melting Point Apparatus and are uncorrected. Proton nuclear magnetic resonance spectra (\textsuperscript{1}H NMR) were recorded using Bruker AV400 (400 MHz), AV500 (500 MHz) and AV600 (600 MHz) spectrometers as indicated. Carbon nuclear magnetic resonance spectra (\textsuperscript{13}C NMR) were recorded using Bruker AV400 (100 MHz), AV500 (125 MHz) and AV600 (150 MHz) spectrometers as indicated. Spectra were obtained using CDCl\textsubscript{3}, CD\textsubscript{3}OD, CD\textsubscript{2}Cl\textsubscript{2} and DMSO-d\textsubscript{6} as solvents and chemical shifts are quoted on the δ scale in units of ppm using TMS as an internal standard. Coupling constants (J) are reported in Hz with the following splitting abbreviations: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), bs (broad singlet). Infra-Red (IR) spectroscopy was carried out using a PerkinElmer Spectrum 100 FT-IR Spectrometer using thin films. Absorption maxima (\nu max) are reported in wavenumbers (cm\textsuperscript{-1}). High Performance Liquid Chromatography (HPLC) was performed using a Varian ProStar instrument; A Chiralpak AD column for normal phase analytical HPLC; DiscoveryBIO wide pore C18-10 (25 cm x 4.6 mm, 10 µm) for reverse phase analytical HPLC; and a DiscoveryBIO wide pore C18 (25 cm x 21.2 mm, 10 µm) column for reverse phase preparative HPLC. Each solvent used contained 0.1% TFA buffer. Liquid Chromatography Mass Spectrometry (LCMS) was carried out using SQD-Waters Acquity UPLC/SQD with C18 (50 mm x 2.1 mm, 1.7 µm) column. A total run time of 5 minutes and flow rate of 0.6 mL/min was used with gradient elution: 95% H\textsubscript{2}O/ 5% MeCN (0 min), 5% H\textsubscript{2}O/ 95% MeCN (3 min), 95% H\textsubscript{2}O/ 5% MeCN (4.5 min). Each solvent contained 0.1% formic acid buffer. LRMS refers to low resolution mass spectrometry and HRMS refers to high resolution mass spectrometry. Electron Impact/Chemical Ionisation (EI/CI) MS was carried out using MAT900XP (Thermo Finnigan) instrument and electrospray ionization (ESI) accurate mass was determined using Waters LCT Premier XE instrumentation. Thin layer chromatography (TLC) was carried out using Fluka aluminium backed sheets coated with 60F\textsubscript{254} silica gel. Visualisation of the silica plates was achieved using a UV lamp (\lambda max = 245 nm) and/or potassium permanganate (KMnO\textsubscript{4} in 1M NaOH with 5% K\textsubscript{2}CO\textsubscript{3}). Flash chromatography was carried out using either Geduran (Merck) or ZEOprep (Apollo) Si60 40-63 µm silica gel.
Solvents and reagents were obtained from commercial sources and were used as received unless otherwise stated. Dry solvents were dried over anhydrous columns,\(^1\) moisture levels were usually <15 ppm by Karl Fischer titration. Pet. ether refers to the fraction of light petroleum ether boiling in the range 40-60 °C.

**First generation imidazo[1,2-α]pyrazine inhibitors**

**Synthesis of α-azido aryl ketones**

2-azido-1-(2-phenoxyphenyl)ethanone, 16b

2-bromo-1-(2-phenoxyphenyl)ethanone 15b (3.07 g, 10.5 mmol) was dissolved in DMSO (15 mL) and the mixture was cooled on ice. Sodium azide (824 mg, 12.68 mmol) was added in one portion and the reaction was stirred under argon at RT for 5 h. An extra portion of sodium azide (200 mg) was added and left to stir overnight. After 15 h, the reaction was quenched with H\(_2\)O (30 mL), and extracted with EtOAc (4 x 40 mL). The combined organic layers were washed with H\(_2\)O (5 x 20 mL) and then dried (Na\(_2\)SO\(_4\)) and filtered. The solvent was removed in vacuo to give the product as a brown liquid (2.52 g, 9.96 mmol, 95%). R\(_f\) = 0.4 (CH\(_2\)Cl\(_2\)); IR (\(\nu_{\text{max}}/\text{cm}^{-1}\), thin film): 3071, 2100, 1685, 1599; \(^{1}\)H NMR (500 MHz, CDCl\(_3\)): \(\delta_H = 4.60\) (s, 2H, 1-H), 6.87 (dd, \(J = 8.3, 0.9\) Hz, 1H, 7-H), 7.04-7.06 (m, 2H, 10,14-H), 7.18-7.23 (m 2H, 5,12-H), 7.40-7.43 (m, 2H, 11,13-H), 7.45-7.49 (m, 1H, 6-H), 7.92 (dd, \(J = 7.8, 1.5\) Hz, 1H, 4-H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta_C = 58.9\) (C-1), 118.0 (C-7), 119.2 (C-10), 123.2 (C-5), 124.4 (C-12), 126.2 (C-3), 130.0 (C-11), 130.8 (C-4), 134.5 (C-6), 155.0 (C-9), 157.0 (C-8), 193.6 (C-2); LRMS m/z (Cl\(^{+}\)): 198 [M-CH\(_2\)N\(_3\)]\(^{+}\), 85 [COCH\(_2\)N\(_3\)]\(^{+}\).
2-azido-1-(3,4-dimethoxyphenyl)ethanone, 16c

2-Bromo-1-(3,4-dimethoxyphenyl)ethanone\(^2\) (2.33 g, 8.61 mmol) was dissolved in anhydrous DMSO (10 mL) and the mixture was cooled on ice. Sodium azide (671 mg, 10.3 mmol) was added in one portion and the reaction was stirred under argon at RT for 2 h. An immediate colour change of yellow to orange was observed on addition of the sodium azide. The reaction was then quenched with H\(_2\)O (30 mL), and extracted with EtOAc (4 \times 40 mL). The combined organic layers were washed with H\(_2\)O (5 \times 20 mL) followed by brine (20 mL) and then dried (MgSO\(_4\)) and filtered. The solvent was removed \textit{in vacuo} to give an orange solid (1.87 g, 8.46 mmol, 98\%) with NMR data comparable with literature values:\(^3\) \(R_f = 0.22\) (CH\(_2\)Cl\(_2\)); IR (\(\nu_{\text{max}}/\text{cm}^{-1}\), thin film): 2106, 1682, 1595, 1515; \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta_H = 3.94\) (s, 3H, \(9-H\)), 3.96 (s, 3H, \(10-H\)), 4.52 (s, 2H, \(1-H\)), 6.90 (d, \(J = 8.4\) Hz, 1H, \(5-H\)), 7.47 (dd, \(J = 8.5, 2.0\) Hz, 1H, \(4-H\)), 7.52 (d, \(J = 2.1\) Hz, 1H, \(8-H\)); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta_C = 54.5\) (C-1), 56.1 (C-9), 56.2 (C-10), 110.0 (C-8), 110.1 (C-5), 122.5 (C-4), 127.5 (C-3), 149.4 (C-7), 154.1 (C-6), 191.8 (C-2); LRMS m/z (Cl\(^+\)): 222 [M+H]\(^+\), 165 [M-CH\(_2\)N\(_3\)]\(^+\); HRMS m/z (Cl\(^+\)): Found 222.0878 [M+H]\(^+\); C\(_{10}\)H\(_{12}\)N\(_3\)O\(_3\) requires 222.0879.

2-azido-1-(3,5-dimethylphenyl)ethanone, 16d

2-Bromo-1-(3,5-dimethylphenyl)ethanone\(^4\) (3.44 g, 15.1 mmol) was dissolved in anhydrous DMSO (15 mL) and the mixture was cooled on ice. Sodium azide (1.18 g, 18.2 mmol) was added in one portion and the reaction was stirred under argon at RT for 16 h. An extra portion of sodium azide (200 mg) was added and the reaction was left to stir for a further 1 h. A colour change from yellow to deep orange was observed. The
reaction was then quenched with H$_2$O (30 mL), and extracted with EtOAc (4 x 40 mL). The combined organic layers were washed with H$_2$O (5 x 20 mL) followed by brine (20 mL) and then dried (MgSO$_4$) and filtered. The solvent was removed in vacuo to give an orange solid (2.85 g, 15.1 mmol, 100%). $R_f = 0.59$ (CH$_2$Cl$_2$); IR ($\nu_{\text{max}}$/cm$^{-1}$, thin film): 2920, 2105, 1692, 1604; $^1$H NMR (500 MHz, CDCl$_3$): $\delta_H = 2.35$ (s, 6H, 7-H), 4.52 (s, 2H, 1-H), 7.20 (s, 1H, 6-H), 7.40 (s, 2H, 4-H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta_C = 21.3$ (C-7), 55.0 (C-1), 125.7 (C-4), 134.5 (C-3), 135.9 (C-6), 138.8 (C-5), 193.6 (C-2); LRMS m/z (Cl$^+$): 132 [M-CH$_2$N$_3$]$^{+}$.

2-azido-1-(3-thienyl)ethanone, 16e

2-bromo-1-(3-thienyl)-1-ethanone$^5$ 15e (573 mg, 2.80 mmol) was dissolved in DMSO (3 mL) and the mixture was cooled on ice. Sodium azide (218 mg, 3.35 mmol) was added in one portion and the reaction was stirred under argon at RT for 5 h. The reaction was quenched with H$_2$O (20 mL), and extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with H$_2$O (5 x 20 mL) followed by brine (20 mL), dried (Na$_2$SO$_4$) and filtered. The solvent was removed in vacuo to give the title compound as a brown/orange oil (460 mg, 2.75 mmol, 98%). $R_f = 0.27$ (CH$_2$Cl$_2$); IR ($\nu_{\text{max}}$/cm$^{-1}$, thin film): 3105, 2097, 1679, 1508; $^1$H NMR (500 MHz, CDCl$_3$): $\delta_H = 4.43$ (s, 2H, 1-H), 7.38 (dd, $J = 5.1$, 2.8 Hz, 1H, 5-H), 7.55 (dd, $J = 5.0$, 1.2 Hz, 1H, 4-H), 8.10 (dd, $J = 2.9$, 1.3 Hz, 1H, 7-H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta_C = 55.5$ (C-1), 126.6 (C-5), 127.2 (C-4), 132.7 (C-7), 139.1 (C-3), 187.6 (C-2); LRMS m/z (ES$^+$): 185 [M+18]$^+$, 168 [M+H]$^+$; HRMS m/z (ESI$^+$): Found 168.02354 [M+H]$^+$; C$_6$H$_6$N$_3$OS requires 168.02316.
Synthesis of α-azido aryl alcohols

2-azido-1-(2-phenoxyphenyl)ethanol, 17b

16b (2.52 g, 9.96 mmol) was dissolved in anhydrous MeOH (50 mL) and cooled on ice. Sodium borohydride (565 mg, 14.9 mmol) was added portion wise and the mixture was stirred on ice under argon for 1 h. The solvent was removed and the resulting residue was taken up in CH$_2$Cl$_2$ (50 mL) and carefully washed with H$_2$O (2 x 40 mL). Re-extraction of the aqueous layers with CH$_2$Cl$_2$ (3 x 30 mL), followed by washing the combined organic extracts with brine, drying (Na$_2$SO$_4$), filtering and concentrating in vacuo gave the title compound as a brown oil (2.47 g, 9.69 mmol, 97%). R$_f$ = 0.19 (CH$_2$Cl$_2$); IR (ν$_{max}$/cm$^{-1}$, thin film): 3413, 3039, 2102, 1583; $^1$H NMR (500 MHz, CDCl$_3$): δ$_H$ = 2.54 (bs, 1H, 15-H), 3.50 (dd, $J = 12.5$, 8.0 Hz, 1H, 1-H), 3.58 (dd, $J = 12.5$, 3.5 Hz, 1H, 1-H), 5.23 (dd, $J = 8.0$, 3.4 Hz, 1H, 2-H), 6.84 (dd, $J = 8.2$, 1.1 Hz, 1H, 7-H), 6.97-7.00 (m, 2H, 10-H), 7.13 (tt, $J = 7.4$, 1.1 Hz, 1H, 5-H), 7.17 (td, $J = 7.5$, 1.0 Hz, 1H, 12-H), 7.24-7.27 (m, 1H, 6-H), 7.34-7.37 (m, 2H, 11-H), 7.58 (dd, $J = 7.7$, 1.7 Hz, 1H, 4-H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ$_C$ = 56.5 (C-1), 68.7 (C-2), 118.0 (C-7), 118.3 (C-10), 123.4 (C-5), 123.5 (C-12), 127.1 (C-4), 129.6 (C-6), 129.6 (C-11), 130.8 (C-3), 153.5 (C-9), 156.3 (C-8); LRMS m/z (Cl$^+$): 200 [M-CH$_2$N$_3$]$^+$, 182 [M-OH,CH$_2$N$_3$]$^+$. 
2-azido-1-(3,4-dimethoxyphenyl)ethanol, 17c

16c (1.86 g, 8.40 mmol) was dissolved in anhydrous Et₂O (80 mL). Activated neutral alumina (8 g) and sodium borohydride (635 mg, 16.8 mmol) were added and the suspension was stirred at RT under argon. After 16 h the reaction mixture was filtered and washed with ether. The resulting filtrate was washed with H₂O (2 x 30 mL), followed by brine (2 x 30 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo to give the title compound as a yellow oil (1.64 g, 7.37 mmol, 88%). Rf = 0.65 (2:1 CH₂Cl₂/EtOAc); IR (νmax/cm⁻¹, thin film): 3497, 2938, 2839, 2106, 1516; \(^1\)H NMR (500 MHz, CDCl₃): δH = 2.67 (bs, 1H, 11-H), 3.36 (dd, \(J = 12.6, 3.8 \text{ Hz, 1H, 1-H}\)), 3.49 (dd, \(J = 12.6, 8.3 \text{ Hz, 1H, 1-H}\)), 3.84 (s, 3H, 9-H), 3.85 (s, 3H, 10-H), 4.78 (dd, \(J = 8.3, 3.8 \text{ Hz, 1H, 2-H}\)), 6.82 (d, \(J = 8.2 \text{ Hz, 1H, 5-H}\)), 6.86 (dd, \(J = 8.2, 1.9 \text{ Hz, 1H, 4-H}\)), 6.89 (d, \(J = 1.9 \text{ Hz, 1H, 8-H}\)); \(^1^3\)C NMR (125 MHz, CDCl₃): δC = 55.6 (C-9,10), 57.7 (C-1), 72.9 (C-2), 108.6 (C-8), 110.8 (C-5), 117.9 (C-4), 132.0 (C-3), 148.6 (C-7), 148.8 (C-6); LRMS m/z (EI⁺): 223 [M]⁺, 167 [M-CH₂N₃]⁺, 139 [M-CH(OH)CH₂N₃]⁺.

2-azido-1-(3,5-dimethylphenyl)ethanol, 17d

16d (2.85 g, 15.1 mmol) was dissolved in anhydrous MeOH (60 mL) and cooled on ice. Sodium borohydride (855 mg, 22.6 mmol) was added portion wise and the mixture was stirred on ice under argon for 1 h. The solvent was removed and the resulting orange oil was taken up in CH₂Cl₂ (60 mL) and washed with 2.0 M HCl (40 mL), H₂O (30 mL) and brine (30 mL). The combined organic extracts were dried (MgSO₄), filtered and
concentrated in vacuo to give the title compound as an orange oil (2.85 g, 14.9 mmol, 99%). \( R_f = 0.27 \) (CH\(_2\)Cl\(_2\)); IR (\( \nu_{\text{max}} / \text{cm}^{-1} \), thin film): 3395, 2918, 2099; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta_H = 2.32 \) (s, 6H, 7-H), 3.40 (dd, \( J = 12.6, 3.8 \) Hz, 1H, 1-H), 3.47 (dd, \( J = 12.6, 8.4 \) Hz, 1H, 1-H), 4.79 (dd, \( J = 8.4, 3.8 \) Hz, 1H, 2-H), 6.96 (s, 1H, 6-H), 6.97 (s, 2H, 4-H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta_C = 21.2 \) (C-7), 58.2 (C-1), 73.5 (C-2), 123.8 (C-4), 130.0 (C-6), 138.4 (C-5), 140.7 (C-3); LRMS m/z (Cl\(^+\)): 192 [M+H\(^+\)], 132 [M-OH-N\(_3\)]\(^+\).

2-azido-1-(3-thienyl)ethanol, 17e

\( 16e \) (278 mg, 1.67 mmol) was dissolved in anhydrous MeOH (10 mL) and cooled on ice. Sodium borohydride (94.5 mg, 2.45 mmol) was added portion wise and the mixture was stirred on ice under argon for 1 h. The solvent was removed and the resulting residue was taken up in CH\(_2\)Cl\(_2\) (30 mL) and carefully washed with H\(_2\)O (2 x 20 mL) followed by brine (20 mL). The organic extracts were dried (Na\(_2\)SO\(_4\)), filtered and concentrated in vacuo to give the title compound as a yellow oil (257 mg, 1.52 mmol 91%). \( R_f = 0.8 \) (1:1 pet. ether /EtOAc); IR (\( \nu_{\text{max}} / \text{cm}^{-1} \), thin film): 3372, 3105, 2096; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta_H = 3.51\text{-}3.54 \) (m, 2H, 1-H), 4.98 (dd, \( J = 4.7, 1.9 \) Hz, 1H, 2-H), 7.08 (dd, \( J = 5.0, 1.3 \) Hz, 1H, 4-H), 7.29\text{-}7.30 (m, 1H, 7-H), 7.34 (dd, \( J = 5.0, 3.0 \) Hz, 1H, 5-H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta_C = 57.5 \) (C-1), 69.9 (C-2) 122.0 (C-7), 125.4 (C-4), 126.7 (C-5), 142.0 (C-3); LRMS m/z (Cl\(^+\)): 152 [M-OH\(^+\)], 127 [M-N\(_3\)]\(^+\), 113 [M-CH\(_2\)N\(_3\)]\(^+\); HRMS m/z (Cl\(^+\)): Found 152.02859 [M-OH\(^+\)]; C\(_6\)H\(_8\)N\(_3\)S requires 152.02824.
Synthesis of α-amino aryl alcohols

2-amino-1-(2-phenoxyphenyl)ethanol, 14b

17b (2.46 g, 9.66 mmol) was dissolved in anhydrous MeOH (50 mL) and 10% Pd/C (246 mg, 10% wt/wt) was added. The vessel was evacuated and purged with Ar (3x), and under static vacuum a balloon of H₂ was added. The reaction was stirred at RT under H₂ atmosphere until completion, as determined by TLC and disappearance of N₃ peak by IR. After 22 h, the H₂ was carefully released, the vessel evacuated and purged Ar (3x), and the reaction mixture was filtered through Celite (pre-washed with MeOH). Solvent removal in vacuo gave the title compound as a brown oil (2.21 g, 9.66 mmol, 100%). Rf = 0.0 (CH₂Cl₂); IR (νmax/cm⁻¹, thin film): 3413, 3055, 2983; 1H NMR (600 MHz, CDCl₃): δₜH = 2.17 (bs, 3H, 15,16-H), 2.84 (dd, J = 13.2, 7.8 Hz, 1H, 1-H), 3.10 (dd, J = 13.2, 4.2 Hz, 1H, 1-H), 4.99 (dd, J = 7.8, 3.6 Hz, 1H, 2-H), 6.82 (dd, J = 8.4, 1.2 Hz, 1H, 7-H), 6.95 (d, J = 7.8 Hz, 2H, 10-H), 7.08-7.11 (m, 1H, 12-H), 7.13-7.15 (m, 1H, 5-H), 7.21 (td, J = 7.8, 1.8 Hz, 1H, 6-H), 7.30-7.33 (m, 2H, 11-H), 7.57 (dd, J = 7.8, 1.2 Hz, 1H, 4-H); 13C NMR (150 MHz, CDCl₃): δC = 47.7 (C-1), 69.4 (C-2), 118.2 (C-7), 118.5 (C-10), 123.4 (C-12), 123.9 (C-5), 127.5 (C-4), 128.6 (C-6), 130.0 (C-11), 133.3 (C-3), 153.8 (C-9), 157.2 (C-8); LRMS m/z (ES+): 230.1 [M+H]+, 212.1 [M-OH]+, 195.1 [M-OH, NH₂]+.
2-amino-1-(3,4-dimethoxyphenyl)ethanol, 14c

17c (1.58 g, 7.09 mmol) was dissolved in anhydrous MeOH (30 mL) and 10% palladium on carbon (158 mg, 10% w/w) was added. The vessel was evacuated and purged with Ar (3x), and under static vacuum a balloon of H₂ was added. The reaction mixture was stirred under hydrogen atmosphere until completion as determined by TLC and disappearance of N₃ peak by IR. After 2 h, the hydrogen was carefully released, and the reaction mixture was filtered through Celite (pre-washed with MeOH). Solvent removal in vacuo gave the crude compound as an orange oil. Flash chromatography (100% EtOAc followed by 100% MeOH), followed by re-dissolving in CH₂Cl₂ and filtering to remove silica yielded the title compound as a white solid (880 mg, 4.47 mmol, 63%). Spectroscopic data was consistent with that previously reported.⁶ Rᵣ = 0.3 (1:1 EtOAc/MeOH); IR (vmax/cm⁻¹, thin film): 3362, 2938, 2838; ¹H NMR (500 MHz, CDCl₃): δH = 2.14 (bs, 3H, 11,12-H), 2.80 (dd, J = 12.7, 7.9 Hz, 1H, 1-H), 2.96 (dd, J = 12.6, 4.0 Hz, 1H, 2-H), 3.86 (s, 3H, 9-H), 3.88 (s, 3H, 10-H), 4.56 (dd, J = 7.9, 4.0 Hz, 1H, 3-H), 6.82 (d, J = 8.2 Hz, 1H, 5-H), 6.86 (dd, J = 8.5, 1.8 Hz, 1H, 4-H), 6.91 (d, J = 1.8 Hz, 1H, 8-H); ¹³C NMR (125 MHz, CDCl₃): δC = 48.9 (C-1), 55.5 (C-9), 55.6 (C-10) 73.8 (C-2), 108.7 (C-8), 110.7 (C-5), 117.8 (C-4), 134.8 (C-3), 148.1 (C-7), 148.7 (C-6); LRMS m/z (EI⁺): 197 [M]⁺, 167 [M-CH₂NH₂]⁺; HRMS m/z (EI⁺): Found: 197.1049 [M]⁺; C₁₀H₁₅NO₃ requires 197.1046.
2-amino-1-(3,5-dimethylphenyl)ethanol, 14d

![Chemical Structure of 2-amino-1-(3,5-dimethylphenyl)ethanol, 14d](image)

17d (2.85 g, 14.9 mmol) was dissolved in anhydrous MeOH (60 mL) and 10% palladium on carbon (285 mg, 10% w/w) was added. The vessel was evacuated and purged with Ar (3x), and under static vacuum a balloon of H₂ was added. The reaction mixture was stirred under hydrogen atmosphere until completion as determined by TLC and disappearance of N₃ peak by IR. After 22 h, the hydrogen was carefully released, and the reaction mixture was filtered through Celite (pre-washed with MeOH). Solvent removal *in vacuo* gave the title compound as a sticky green/brown solid (2.37 g, 14.4 mmol, 97%). Rₓ = 0.0 (CH₂Cl₂); IR (vₓ/cm⁻¹, thin film): 3289, 3010, 2916, 2861; ¹H NMR (600 MHz, CDCl₃): δₓ = 2.31 (s, 6H, 7-H), 2.81 (dd, J = 12.6, 7.8 Hz, 1H, 1-H), 2.96 (dd, J = 13.2, 4.2 Hz, 1H, 1-H), 4.57 (dd, J = 7.8, 4.2 Hz, 1H, 2-H), 6.91 (s, 1H, 6-H), 6.96 (s, 2H, 4-H); ¹³C NMR (150 MHz, CDCl₃): δₓC = 21.5 (C-7), 49.3 (C-1), 74.5 (C-2), 123.8 (C-4), 130.6 (C-6), 138.1 (C-5), 142.5 (C-3); LRMS m/z (EI⁺): 224, 135 [M-CH₂NH₂]⁺, 117 [M-CH₂OHNH₂]⁺.

2-amino-1-(3-thienyl)ethanol, 14e

![Chemical Structure of 2-amino-1-(3-thienyl)ethanol, 14e](image)

14e (257 mg, 1.52 mmol) was dissolved in anhydrous MeOH (10 mL) and 10% palladium on carbon (25.7 mg, 10% w/w) was added. The vessel was evacuated and purged with Ar (3x), and under static vacuum the reaction vessel was then subjected to 3 bar hydrogen for 5 h. After this period the mixture was filtered through Celite and concentrated *in vacuo* to give a pale yellow solid (217 mg, 1.52 mmol, 100%). Rₓ = 0.0 (1:1 CH₂Cl₂/EtOAc); vₓ/cm⁻¹ (thin film): 3194, 3091, 2921; ¹H NMR (600 MHz, CDCl₃): δₓH = 1.91 (bs, 3H, 8,9-H), 2.88 (dd, J = 12.6, 7.8 Hz, 1H, 1-H), 3.04 (d, J = 10.2
Hz, 1H, 1-H), 4.75 (dd, J = 6.6, 3.6 Hz, 1H, 2-H), 7.08 (d, J = 5.4 Hz, 1H, 4-H), 7.23 (d, J = 2.4 Hz, 1H, 7-H), 7.31 (dd, J = 4.8, 3.0 Hz, 1H, 5-H); 13C NMR (150 MHz, CDCl3): δc = 48.4 (C-1), 70.9 (C-2), 121.1 (C-7), 125.6 (C-4), 126.3 (C-5), 144.0 (C-3); LRMS m/z (Cl⁺): 177, 159, 127 [M-NH2]+; (EI⁺): 131, 127 [M-NH2]+, 119, 114.

Synthesis of 2-[(3-chloropyrazin-2-yl)amino]-1-(2-aryl)ethanols

2-[(3-chloropyrazin-2-yl)amino]-1-(2-phenoxyphenyl)ethanol, 18b

14b (2.21 g, 9.66 mmol), 2,3-dichloropyrazine (1.11 mL, 10.6 mmol) and Et3N (1.88 mL, 13.5 mmol) were dissolved in 1,4-dioxane (22 mL) and the reaction was stirred under reflux, under argon. After 17 h, the reaction was cooled to RT, and the solvent removed in vacuo. The residue was taken up in CH2Cl2 and washed with H2O (3 x 20 mL) and brine (1 x 20 mL). The organic extracts were dried (Na2SO4), filtered and concentrated to give the crude product as a brown oil. Purification was carried out via flash chromatography (applied in CH2Cl2; eluted 0% to 10% EtOAc) to afford the title compound as an orange oil (2.09 g, 6.15 mmol, 64%). Rf = 0.42 (9:1 CH2Cl2/EtOAc); IR (νmax/cm⁻¹, thin film): 3423, 3060, 2924; 1H NMR (400 MHz, CDCl3): δH = 3.76-3.83 (m, 1H, 1-H), 3.92-3.98 (m, 1H, 1-H), 5.31 (dd, J = 7.2, 3.2 Hz, 1H, 2-H), 5.64 (1H, 16-H), 6.87 (dd, J = 8.1,1.1 Hz, 1H, 7-H), 6.99-7.02 (m, 2H, 10-H), 7.10-7.18 (m, 2H, 5,12-H), 7.25 (dd, J = 8.0, 1.7 Hz, 1H, 6-H), 7.33-7.38 (m, 2H, 11-H), 7.60 (d, J = 1.7 Hz, 1H, 4-H), 7.61 (d, J = 2.8 Hz, 1H, 19-H), 7.89 (d, J = 2.8 Hz, 1H, 18-H); 13C NMR (100 MHz, CDCl3): δc = 47.9 (C-1), 69.3 (C-2), 118.2 (C-7,10), 123.2 (C-5), 123.5 (C-12), 127.2 (C-4), 128.6 (C-6), 129.6 (C-11), 130.8 (C-19), 132.2 (C-3), 134.8 (C-20), 139.2 (C-18), 151.0 (C-17), 153.4 (C-9), 156.6 (C-8); LRMS m/z (Cl⁺): 325 [M(37Cl)-OH]+, 323 [M(35Cl)-OH]+; HRMS m/z (ESI⁺): Found 340.0867 [M(35Cl)-H]+; C18H15ClN3O2 requires 340.0853.
2-[(3-chloropyrazin-2-yl)amino]-1-(3,4-dimethoxyphenyl)ethanol, 18c

14c (827 g, 4.20 mmol), 2,3-dichloropyrazine (481 µL, 4.62 mmol) and Et3N (781 µL, 5.88 mmol) were dissolved in 1,4-dioxane (8 mL) and the reaction was stirred under reflux, under argon. After 16 h, the reaction was cooled to RT, and the solvent removed in vacuo. The residual brown oil was taken up in CH2Cl2 and washed with H2O (3 x 30 mL) and brine (1 x 20 mL). The organic extracts were dried (Na2SO4), filtered and concentrated to give the crude product as a brown oil. Purification was carried out via flash chromatography (applied in CH2Cl2; eluted 0% to 10% to 10% EtOAc) to afford the title compound as a light orange oil (748 mg, 2.42 mmol, 58%). Rf = 0.27 (2:1 CH2Cl2/EtOAc); IR (νmax/cm⁻¹, thin film): 3377, 2934; ¹H NMR (500 MHz, CDCl3): δH = 3.60-3.66 (m, 1H, 1-H), 3.83-3.89 (m, 1H, 1-H), 3.88 (s, 3H, 9-H), 3.89 (s, 3H, 10-H), 4.93 (dd, J = 7.6, 3.7 Hz, 1H, 2-H), 5.61 (s, 1H, 12-H), 6.87 (d, J = 8.2 Hz, 1H, 5-H), 6.93 (d, J = 8.2 Hz, 1H, 4-H), 6.97 (s, 1H, 8-H), 7.62 (d, J = 1.0 Hz, 1H, 16-H), 7.93 (d, J = 1.0 Hz, 1H, 15-H); ¹³C NMR (125 MHz, CDCl3): δC = 49.0 (C-1), 55.6 (C-9,10), 73.2 (C-2), 108.6 (C-8), 110.8 (C-5), 117.8 (C-4), 130.9 (C-16) 134.1 (C-3),134.7 (C-18),139.6 (C-15) 148.4 (C-7), 148.8 (C-6), 150.9 (C-13); LRMS m/z (Cl⁺): 312 [M(³⁷Cl)+H]⁺, 310 [M(³⁵Cl)+H]⁺, 294 [M(³⁷Cl)-OH]⁺ 292 [M(³⁵Cl)-OH]⁺; HRMS m/z (Cl⁺): Found 310.0956 [M(³⁵Cl)+H]⁺; C14H17ClN3O3 requires 310.0958.

2-[(3-chloropyrazin-2-yl)amino]-1-(3,5-dimethylphenyl)ethanol, 18d

14d (2.34 g, 14.2 mmol), 2,3-dichloropyrazine (1.62 mL, 15.6 mmol) and Et3N (2.76 mL, 19.8 mmol) were dissolved in 1,4-dioxane (24 mL) and the reaction was stirred under reflux, under argon. After 16 h, the reaction was cooled to RT, and the solvent removed
in vacuo. The residue was taken up in CH$_2$Cl$_2$ and washed with H$_2$O (3 x 30 mL) and brine (1 x 20 mL). The organic extracts were dried (MgSO$_4$), filtered and concentrated to give the crude product as a brown oil. Purification was carried out via flash chromatography (applied in CH$_2$Cl$_2$; eluted CH$_2$Cl$_2$ to 30:1 – 10:1 CH$_2$Cl$_2$/EtOAc) to afford the title compound as a light orange oil (2.58 g, 9.37 mmol, 65%). R$_f$ = 0.37 (9:1 CH$_2$Cl$_2$/EtOAc); IR (v$_{max}$/cm$^{-1}$, thin film): 3422, 2921; $^1$H NMR (600 MHz, CDCl$_3$): δ$_H$ = 2.33 (s, 6H, 7-H), 3.27 (s, 1H, 8-H) 3.61 (ddd, $J$ = 13.8, 7.8, 4.8 Hz, 1H, 1-H), 3.88 (ddd, $J$ = 13.8, 6.6, 3.6 Hz, 1H, 1-H), 4.91 (dd, $J$ = 7.9, 2.8 Hz, 1H, 2-H), 5.62 (bt, 1H, 9-H), 6.95 (s, 1H, 6-H), 7.02 (s, 2H, 4-H), 7.62 (d, $J$ = 3.0 Hz. 1H, 13-H), 7.93 (d, $J$ = 3.0 Hz, 1H, 12-H); $^{13}$C NMR (150 MHz, CDCl$_3$): δ$_C$ = 21.5 (C-7), 49.53 (C-1), 73.8 (C-2), 123.7 (C-4), 129.7 (C-6), 131.2 (C-13), 135.3 (C-15) 138.4 (C-5), 139.7 (C-12), 142.5 (C-3), 151.3 (C-10); LRMS m/z (Cl$^+$): 280 [M($^{37}$Cl)+H]$^+$, 278 [M($^{35}$Cl)+H]$^+$, 262 [M($^{37}$Cl)-OH]$^+$, 260 [M($^{35}$Cl)-OH]$^+$; HRMS m/z (Cl$^+$): Found 278.1059 [M($^{35}$Cl)+H]$^+$; C$_{14}$H$_{17}$N$_3$OCl requires 278.1060.

2-[(3-chloropyrazin-2-yl)amino]-1-(3-thienyl)ethanol, 18e

13e (232 mg, 1.63 mmol), 2,3-dichloropyrazine (183 µL, 1.79 mmol), Et$_3$N (316 µL, 2.27 mmol) and 1,4-dioxane (2.5 mL) were stirred under reflux, under argon for 18 h. The solvent was removed in vacuo and the residue was taken up in CH$_2$Cl$_2$ (30 mL), washed with H$_2$O (5 x 10 mL) and brine (10 mL). The organics were dried (MgSO$_4$), filtered and solvent removed to give a brown oil. Flash chromatography (applied in CH$_2$Cl$_2$; eluted CH$_2$Cl$_2$ to 2:1 CH$_2$Cl$_2$/EtOAc) afforded the title compound as an orange oil (193 mg, 0.753 mmol, 46%). R$_f$ = 0.46 (2:1 CH$_2$Cl$_2$/EtOAc); IR (v$_{max}$/cm$^{-1}$, thin film): 3420, 3091, 2920, 1583, 1525; $^1$H NMR (600 MHz,CDCl$_3$): δ$_H$ = 3.69-3.74 (m, 1H, 1-H), 3.96-4.00 (m, 1H, 1-H), 5.10 (dd, $J$ = 7.2, 3.0 Hz, 1H, 2-H), 5.72 (bs, 1H, 9-H), 7.13 (dd, $J$ = 4.8, 1.2 Hz, 1H, 4-H), 7.31-7.32 (m, 1H, 7-H), 7.35 (dd, $J$ = 5.4, 3.0 Hz, 1H, 5-H), 7.65 (d, $J$ = 3.0 Hz, 1H, 13-H), 7.93 (d, $J$ = 2.4 Hz, 12-H); $^{13}$C NMR (150 MHz, CDCl$_3$): δ$_C$ = 49.0
(C-1), 70.4 (C-2), 121.6 (C-7), 125.5 (C-4), 126.7 (C-5), 131.3 (C-13), 135.6 (C-15), 138.8 (C-12), 143.1 (C-3), 150.8 (C-10); LRMS m/z (ESI⁺): 240 [M(37Cl)-OH]^+, 238 [M(35Cl)-OH]^+; HRMS m/z (ESI⁻): Found 254.0145 [M-H]; C_{10}H_{9}N_{3}OSCl requires 254.0155.

Synthesis of 2-[(3-chloropyrazin-2-yl)amino]-1-(2-aryl)ethanones

2-[(3-chloropyrazin-2-yl)amino]-1-(2-phenoxyphenyl)ethanone, 19b

DMSO (1.13 mL, 15.98 mmol) was dissolved in anhydrous CH₂Cl₂ (100 mL) and the mixture was cooled to and maintained at -78°C. Oxalyl chloride (677 µL, 7.99 mmol) was added drop wise and the reaction was stirred for 20 min. 18b (2.10 g, 6.15 mmol), dissolved in CH₂Cl₂ (20 mL), was then added drop wise and after 20 min stirring, Et₃N (4.08 mL, 30.7 mmol) was added drop wise. The reaction was then allowed to slowly warm to RT over a period of 2.5 h. The reaction was quenched with H₂O (50 mL) and organics extracted followed by washing with 2.0 M HCl (2 x 40 mL), sat. NaHCO₃ (1 x 40 mL), H₂O (1 x 40 mL) and brine (1 x 40 mL). Drying (MgSO₄), filtration and concentration gave a brown/orange oil. Flash chromatography was carried out (applied in CH₂Cl₂; eluted 50:1 to 10:1 CH₂Cl₂/EtOAc) to afford the title compound as a yellow solid (1.33 g, 3.92 mmol, 64%). Mpt: 76-78 °C; R_f = 0.74 (9:1 CH₂Cl₂/EtOAc); IR (νmax/cm⁻¹, thin film): 3423, 3060, 2924; ¹H NMR (500 MHz, CDCl₃): δH = 4.95 (d, J = 4.8 Hz, 1H, 1-H), 6.30 (1H, 15-H), 6.90 (dd, J = 8.4, 0.8 Hz, 1H, 7-H), 7.11-7.13 (m, 2H, 10-H), 7.18-7.23 (m, 2H, 5,12-H), 7.40-7.44 (m, 2H, 11-H), 7.46-7.49 (m, 1H, 6-H), 7.59 (d, J = 2.7 Hz, 1H, 19-H), 7.88 (d, J = 2.7 Hz, 1H, 18-H), 8.01 (dd, J = 7.9, 1.8 Hz, 1H, 4-H); ¹³C NMR (125 MHz, CDCl₃): δC = 52.0 (C-1), 118.1 (C-7) 119.4 (C-10), 123.0 (C-5), 124.3 (C-12), 126.5 (C-3), 129.9 (C-11), 130.7 (C-4), 130.8 (C-19), 134.3 (C-6), 134.8 (C-21), 140.0 (C-18), 150.2 (C-16), 155.2 (C-9), 157.2 (C-8), 194.8 (C-2); LRMS

2-[(3-chloropyrazin-2-yl)amino]-1-(3,4-dimethoxyphenyl)ethanone, 19c

DMSO (417 µL, 5.89 mmol) was dissolved in anhydrous CH₂Cl₂ (25 mL) and the mixture was cooled to and maintained at -78°C. Oxalyl chloride (249 µL, 2.94 mmol) was added drop wise and the reaction was stirred for 15 min. 18c (700 mg, 2.26 mmol), dissolved in CH₂Cl₂ (20 mL), was then added drop wise and after 15 min stirring, Et₃N (1.5 mL, 11.31 mmol) was added drop wise. The reaction was then allowed to slowly warm to RT over a period of 2 h. The reaction was quenched with H₂O (20 mL) and organics extracted followed by washing with 2.0 M HCl (2 x 20 mL), sat. NaHCO₃ (1 x 20 mL), H₂O (1 x 20 mL) and brine (1 x 20 mL). Drying (MgSO₄), filtration and concentration gave an off white solid. Flash chromatography (CH₂Cl₂ applied in CH₂Cl₂; eluted 50:1 to 10:1 CH₂Cl₂/EtOAc) gave the title compound as a white solid (543 mg, 1.76 mmol, 78%). Mpt: 128-130 °C; Rᵣ = 0.31 (5:1 CH₂Cl₂/EtOAc); IR (νmax/cm⁻¹, thin film): 3399, 2936, 1677; ¹H NMR (500 MHz, CDCl₃): δH = 3.96 (s, 3H, 9-H), 3.97 (s, 3H, 10-H), 4.88 (d, J = 4.2 Hz, 1H, 1-H), 6.43 (s, 1H, 12-H), 6.94 (d, J = 8.2 Hz, 1H, 5-H), 7.57 (d, J = 1.7 Hz, 1H, 8-H), 7.64 (d, J = 2.9 Hz, 1H, 16-H), 7.70 (dd, J = 8.2, 2.0 Hz, 1H, 4-H), 7.96 (d, J = 2.5 Hz, 1H, 15-H); ¹³C NMR (125 MHz, CDCl₃): δC = 47.3 (C-1), 55.8 (C-9), 55.9 (C-10) 109.7 (C-8), 110.0 (C-5), 122.3 (C-4), 127.3 (C-3), 130.8 (C-16), 135.1 (C-18), 139.8 (C-15) 149.0 (C-7), 150.1 (C-13), 153.9 (C-6), 192.1 (C-2); LRMS m/z (Cl⁺): 310 [M⁺(37Cl)+H]⁺, 308 [M⁺(35Cl)+H]⁺; HRMS m/z (Cl⁺): Found 308.0814 [M⁺(35Cl)+H]⁺; C₁₄H₁₅ClN₃O₃ requires 308.0811.
2-[(3-chloropyrazin-2-yl)amino]-1-(3,5-dimethylphenyl)ethanone, 19d

DMSO (1.71 mL, 24.2 mmol) was dissolved in anhydrous CH$_2$Cl$_2$ (170 mL) and the mixture was cooled to and maintained at -78°C. Oxalyl chloride (1.02 mL, 12.1 mmol) was added drop wise and the reaction was stirred for 20 min. 18d (2.58 g, 9.30 mmol), dissolved in CH$_2$Cl$_2$ (30 mL), was then added drop wise and after 20 min stirring, Et$_3$N (6.18 mL, 46.6 mmol) was added drop wise. The reaction was then allowed to slowly warm to RT over a period of 2.5 h. The reaction was quenched with H$_2$O (50 mL) and organics extracted followed by washing with 2.0 M HCl (2 x 40 mL), sat. NaHCO$_3$ (1 x 40 mL), H$_2$O (1 x 40 mL) and brine (1 x 40 mL). Drying (MgSO$_4$), filtration and concentration gave a yellow solid (2.31, 8.37 mmol, 90%) which was carried through to the next stage without further purification. Mpt: Decomposed before melting; R$_f$ = 0.76 (9:1 CH$_2$Cl$_2$/EtOAc); IR (v$_{max}$/cm$^{-1}$, thin film): 3405, 2916, 1681, 1578, 1497; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$H = 2.40 (s, 6H, 7-H), 4.89 (d, $J = 4.0$ Hz, 1H, 1-H), 6.43 (s, 1H, 8-H), 7.27 (s, 1H, 6-H), 7.65 (d, $J = 3.0$ Hz, 1H, 12-H), 7.67 (s, 2H, 4-H), 7.97 (d, $J = 3.0$ Hz, 1H, 11-H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$C = 20.9 (C-7), 47.8 (C-1), 125.4 (C-4), 130.9 (C-12), 134.2 (C-3), 135.1 (C-14), 135.5 (C-6), 138.4 (C-5), 139.8 (C-11), 150.0 (C-9), 193.6 (C-2); LRMS m/z (ESI): 276 [M$(^{37}$Cl)-H]$^+$, 274 [M$(^{35}$Cl)-H]$^+$; HRMS m/z (ESI): Found 274.0762 [M$(^{35}$Cl)-H]$^+$; C$_{14}$H$_{13}$N$_3$OCl requires 274.0747.

2-[(3-chloropyrazin-2-yl)amino]-1-(3-thienyl)ethanone, 19e

DMSO (128 µL, 1.81 mmol) was dissolved in anhydrous CH$_2$Cl$_2$ (9 mL) and the mixture was cooled to and maintained at -78°C. Oxalyl chloride (77.0 µL, 0.906 mmol) was added drop wise and the reaction was stirred for 20 min. 18e (178 mg, 0.697 mmol), dissolved in CH$_2$Cl$_2$ (5 mL), was then added drop wise and after 20 min stirring, Et$_3$N (463 µL, 3.48 mmol) was added drop wise. The reaction was then allowed to slowly
warm to RT over a period of 2 1/2 h. The reaction was quenched with H$_2$O (20 mL) and organics extracted followed by washing with 2.0 M HCl (2 x 10 mL), sat. NaHCO$_3$ (1 x 10 mL), H$_2$O (1 x 10 mL) and brine (1 x 10 mL). Drying (MgSO$_4$), filtration and concentration gave an orange sticky solid. Flash chromatography (applied in CH$_2$Cl$_2$; eluted 50:1 to 20:1 CH$_2$Cl$_2$/EtOAc) gave the title compound as a yellow solid (135 mg, 0.531 mmol, 76%). Mpt: 130 - 134°C; R$_f$ = 0.85 (2:1 CH$_2$Cl$_2$/EtOAc); IR ($\nu_{\text{max}}$/cm$^{-1}$, thin film): 3407, 3107, 2917, 1682, 1582; $^1$H NMR (600 MHz, CDCl$_3$): $\delta$H = 4.84 (d, $J = 4.4$ Hz, 1H, 1-H), 6.33(s, 1H, 9-H), 7.41 (dd, $J = 5.0$, 2.8 Hz, 1H, 5-H), 7.65 (dd, $J = 5.0$, 1.2 Hz, 1H, 4-H), 7.66 (d, $J = 2.8$ Hz, 1H, 13-H), 7.96 (d, $J = 2.7$ Hz, 12-H), 8.26 (dd, $J = 5.4$, 3.0 Hz, 1H, 7-H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$C = 49.0 (C-1), 70.4 (C-2), 121.6 (C-4), 125.5 (C-7), 126.7 (C-5), 131.3 (C-13), 135.6 (C-15), 138.8 (C-12), 143.1 (C-3), 150.8 (C-10); LRMS m/z (Cl$^+$): 256 [M($^{37}$Cl)+H]$^+$, 254 [M($^{35}$Cl)+H]$^+$; HRMS m/z (Cl$^+$): Found 254.0147 [M($^{35}$Cl)+H]$^+$; C$_{10}$H$_9$N$_3$OSCl requires 254.0155.

**Synthesis of 3-aryl-8-chloro-imidazo[1,2-a]pyrazines**

8-chloro-3-(2-phenoxyphenyl)imidazo[1,2-a]pyrazine, 20b

19b (1.33 g, 3.92 mmol) was dissolved in anhydrous toluene (50 mL) and the mixture was cooled on ice. Trifluoroacetic acid (2.11 mL, 24.7 mmol) was added and the reaction was allowed to stir on ice for 30 min, followed by the addition of trifluoroacetic anhydride (3.81 mL, 24.7 mmol). The reaction mixture was then stirred on ice for a further 30 min and then at RT for 68 h. The reaction was then diluted with toluene (50 mL) and washed with NaHCO$_3$ solution (10% w/v, 3 x 30 mL) and brine (1 x 40 mL). The organics were dried (MgSO$_4$), filtered and concentrated to give crude brown oil. Purification was carried out via flash chromatography (applied in CH$_2$Cl$_2$; eluted 50:1 to 5:1 CH$_2$Cl$_2$/EtOAc to afford the title compound as a yellow sticky solid (1.26 g, 3.92 mmol, 100%). R$_f$ = 0.25 (9:1 CH$_2$Cl$_2$/EtOAc); IR ($\nu_{\text{max}}$/cm$^{-1}$, thin film): 1460, 1231; $^1$H
NMR (600 MHz, CDCl₃): δ_H = 6.83–6.85 (m, 2H, 18-H), 7.05-7.10 (m, 2H, 14,20-H), 7.23-7.26 (m, 2H, 19-H), 7.29 (td, J = 7.8, 1.2 Hz, 1H, 12-H), 7.46-7.49 (m, 1H, 13-H), 7.53 (dd, J = 7.2, 1.2 Hz, 1H, 11-H), 7.70 (d, J = 4.2 Hz, 1H, 6-H), 7.86 (s, 1H, 2-H), 8.01 (d, J = 4.2 Hz, 1H, 5-H); ¹³C NMR (150 MHz, CDCl₃): δ_c = 118.3 (C-5), 118.5 (C-18), 118.8 (C-22), 124.2 (C-10,12,20), 126.1 (C-3), 130.0 (C-19), 131.5 (C-13), 132.0 (C-11), 135.6 (C-2), 138.4 (C-9), 143.9 (C-8), 155.0 (C-15), 156.0 (C-17); LRMS m/z (EI⁺): 323 [M(³⁷Cl)]⁺, 321 [M(³⁵Cl)]⁺; HRMS m/z (EI⁺): Found: 321.0659 [M(³⁵Cl)]⁺; C₁₈H₁₂ClN₃O requires 321.0663.

8-chloro-3-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyrazine, 20c

19c (280 mg, 0.912 mmol) was dissolved in anhydrous toluene (20 mL) and the mixture was cooled on ice. Trifluoroacetic acid (490 µL, 6.39 mmol) was added and the reaction was allowed to stir on ice for 30 min, followed by the addition of trifluoroacetic anhydride (887 µL, 6.39 mmol). The reaction mixture was then stirred on ice for a further 30 min and then at RT for 68 h. The reaction was then diluted with toluene (50 mL) and washed with NaHCO₃ solution (10% w/v, 3 x 30 mL) and brine (1 x 40 mL). The organics were dried (MgSO₄), filtered and concentrated to give crude yellow solid. Purification was carried out via flash chromatography (applied in CH₂Cl₂; eluted 9:1 to 2:1 CH₂Cl₂/EtOAc) to afford the title compound as a white solid (46.8 mg, 0.162 mmol, 18%). Mpt: > 200 °C; R_f = 0.32 (2:1 CH₂Cl₂/EtOAc); IR (ν_max/cm⁻¹, thin film): 2960, 2924, 1732; ¹H NMR (400 MHz, CDCl₃): δ_H = 3.93 (s, 3H, 16-H), 3.96 (s, 3H, 17-H), 6.99 (d, J = 2.0 Hz, 1H, 15-H), 7.03 (d, J = 8.2 Hz, 1H, 12-H), 7.10 (dd, J = 8.3, 2.0 Hz, 1H, 11-H), 7.67 (d, J = 4.6 Hz, 1H, 6-H), 7.84 (s, 1H, 2-H), 8.15 (d, J = 4.6 Hz, 1H, 5-H); ¹³C NMR (100 MHz, CDCl₃): δ_c = 56.1 (C-16), 56.2 (C-17), 111.4 (C-15), 111.8 (C-12), 116.3 (C-5), 119.8 (C-10), 121.0 (C-11), 128.2 (C-6), 129.2 (C-3), 134.2 (C-2), 138.0 (C-9), 144.3 (C-8), 149.8 (C-14), 150.1 (C-13); 290 [M(³⁵Cl)+H]⁺, 292
[M(37Cl)+H]+; HRMS m/z (ESI+): Found 290.0683 [M(35Cl)+H]+; C14H13N2O2Cl requires 290.0696.

8-chloro-3-(3,5-dimethylphenyl)imidazo[1,2-a]pyrazine, 20d

19d (2.29 g, 8.31 mmol) was dissolved in anhydrous toluene (90 mL) and the mixture was cooled on ice. Trifluoroacetic acid (4.48 mL, 58.1 mmol) was added and the reaction was allowed to stir on ice for 30 min, followed by the addition of trifluoroacetic anhydride (8.09 mL, 58.1 mmol). The reaction mixture was then stirred on ice for a further 30 min and then at RT for 68 h. The reaction was then diluted with toluene (50 mL) and washed with NaHCO3 solution (10% w/v, 3 x 40 mL) and brine (1 x 40 mL). The organics were dried (MgSO4), filtered and concentrated to give crude orange sticky solid. Purification was carried out via flash chromatography (applied in CH2Cl2; eluted 40:1 CH2Cl2/EtOAc) to afford the title compound as a yellow solid (531.7 g, 2.06 mmol, 25%). Mpt: 178-180 °C; Rf = 0.32 (9:1 CH2Cl2/EtOAc); IR (νmax/cm⁻¹, thin film): 2918, 1603; 1H NMR (600 MHz, CDCl3): δH = 2.41 (s, 6H, 14-H), 7.14 (s, 1H, 13-H), 7.16 (s, 2H, 11-H), 7.69 (d, J = 4.6 Hz, 1H, 6-H), 7.87 (s, 1H, 2-H), 8.21 (d, J = 4.6 Hz, 1H, 5-H); 13C NMR (150 MHz, CDCl3): δC = 21.5 (C-14), 116.6 (C-5), 125.9 (C-11), 127.4 (C-10), 128.3 (C-6), 129.6 (C-3), 131.3 (C-13), 134.5 (C-2), 138.3 (C-9), 139.5 (C-12), 144.4 (C-8); LRMS m/z (EI+): 259 [M(37Cl)]+, 257 [M(35Cl)]+; HRMS m/z (Cl+): Found: 257.0717 [M(35Cl)]+; C14H12ClN3 requires 257.0714.
8-chloro-3-(3-thienyl)imidazo[1,2-α]pyrazine, 20e

19e (345 mg, 1.36 mmol) was dissolved in anhydrous toluene (15 mL) and the mixture was cooled on ice. Trifluoroacetic acid (790 µL, 10.3 mmol) was added and the reaction was allowed to stir on ice for 30 minutes, followed by the addition of trifluoroacetic anhydride (1.43 L, 10.3 mmol). The reaction mixture was then stirred on ice for a further 30 minutes and then at RT for 68 h. The reaction was then diluted with toluene (20 mL) and washed with NaHCO₃ solution (10% w/v, 3 x 10 mL) and brine (1 x 10 mL). The organics were dried (MgSO₄), filtered and concentrated to give crude orange oil. Purification was carried out via flash chromatography (applied in CH₂Cl₂; eluted 20:1 to 5:1 CH₂Cl₂/EtOAc) to afford the title compound as an off white solid (105 mg, 0.477 mmol, 33%). Mpt: 178-180 °C; Rf = 0.34 (5:1 CH₂Cl₂/EtOAc); IR (νmax/cm⁻¹, thin film): 3098, 1462; ¹H NMR (600 MHz, CDCl₃): δH = 7.34–7.36 (m, 1H, 12-H), 7.58 (s, 1H, 14-H), 7.59 (d, J = 0.7 Hz, 1H, 11-H), 7.73 (d, J = 4.6 Hz, 1H, 6-H), 7.91 (s, 1H, 2-H), 8.19 (d, J = 4.6 Hz, 1H, 5-H); ¹³C NMR (150 MHz, CDCl₃): δc = 116.7 (C-5), 124.2 (C-14), 125.0 (C-10), 126.7 (C-12), 127.7 (C-3), 128.0 (C-11), 128.6 (C-6), 134.6 (C-2), 138.1 (C-9), 144.5 (C-8); LRMS m/z (Cl⁺): 238 [M(³⁷Cl)+H]⁺, 236 [M(³⁵Cl)+H]⁺; HRMS m/z (Cl⁺): Found 236.0057 [M(³⁵Cl)+H]⁺; C₁₀H₇N₃SCl requires 236.0049.
Synthesis of 2-aryl-8-chloro-imidazo[1,2-α]pyrazines

8-chloro-2-(2-phenoxyphenyl)imidazo[1,2-α]pyrazine, 21b

15b (438 mg, 1.50 mmol), 2-amino-3-chloropyrazine (195 mg, 1.50 mmol), NaHCO₃ (158 mg, 1.88 mmol) and BuOH (9 mL) were stirred under reflux for 48 h. The reaction was cooled to RT and solvent removed in vacuo. The sample was taken up in CH₂Cl₂ (25 mL) and washed with H₂O (3 x 10 mL). The combined aqueous extracts were further washed with CH₂Cl₂ (4 x 10 mL), and the organic extracts were combined, dried (MgSO₄), filtered and solvent removed. Flash chromatography (applied in pet. ether; eluted 25:1 to 10:1 to 5:1 to 3:1 pet. ether/EtOAc) afforded a pale yellow solid. (156 mg, 0.485 mmol, 32%). Mpt: > 200 °C; Rₚ = 0.75 (1:1 pet. ether/EtOAc); IR (ʋₑₓₐₚ/cm⁻¹, thin film): 1071 – 1225; ¹H NMR (600 MHz, CDCl₃): δH = 6.97 (dd, J = 1.5, 8.2 Hz, 1H, 14-H), 7.07 (d, J = 7.6 Hz, 2H, 18-H), 7.16 (t, J = 7.4 Hz, 1H, 20-H), 7.29 – 7.34 (m, 2H, 12,13-H), 7.38 (dd, J = 8.6, 7.5 Hz, 2H, 19-H), 7.65 (d, J = 4.5 Hz, 1H, 6-H), 7.99 (d, J = 4.5 Hz, 1H, 5-H), 8.31 (s, 1H, 3-H), 8.59 (dd, J = 7.6, 1.9 Hz, 1H, 11-H); ¹³C NMR (150 MHz, CDCl₃): δC = 115.3 (C-3), 118.5 (C-5), 118.8 (C-18), 119.0 (C-14), 123.7 (C-20), 123.8 (C-10), 124.1 (C-12), 127.8 (C-6), 129.7 (C-13), 129.9 (C-19), 130.1 (C-11), 137.1 (C-9), 143.2 (C-2), 143.3 (C-8), 154.6 (C-15), 156.5 (C-17); LRMS m/z (ESI⁺): 324 [M(³⁷Cl)+H]⁺, 322 [M(³⁵Cl)+H]⁺; HRMS m/z (Cl⁺): Found 322.07554 [M(³⁵Cl)+H]⁺; C₁₈H₁₃ClN₃O requires 322.0747.
8-chloro-2-(3,4-dimethoxyphenyl)imidazo[1,2-α]pyrazine, 21c

A mixture of 15c (229 mg, 0.885 mmol), 2-amino-3-chloropyrazine (115 mg, 0.885 mmol) and NaHCO₃ (93.0 mg, 1.11 mmol) in tBuOH (5 mL) were stirred under argon, under reflux for 40 h. After this point, the reaction mixture was cooled to RT and solvent removed in vacuo. The resulting orange solid was dissolved in CH₂Cl₂ (30 mL) and washed with H₂O (3 x 30 mL). The aqueous layers were extracted further with CH₂Cl₂ (2 x 20 mL) before the combined organics were washed with brine (20 mL), dried (MgSO₄), filtered and solvent removed to give a light brown solid. Flash chromatography (applied in pet. ether; eluted 3:1 pet. ether/EtOAc) was carried out to afford the title compound (155 mg, 0.536 mmol, 61%). Mpt: Decomposed before melting; Rf = 0.11 (1:1 pet. ether/EtOAc); IR (ν_max/cm⁻¹, thin film): 3142, 2933, 2833, 1498; ¹H NMR (600 MHz, CDCl₃): δ_H = 3.93 (s, 3H, 16-H), 4.00 (s, 3H, 17-H), 6.93 (d, J = 8.3 Hz, 1H, 12-H), 7.48 (dd, J = 8.2, 2.1 Hz, 1H, 11-H), 7.59 (d, J = 2.1 Hz, 1H, 15-H), 7.65 (d, J = 4.5, 1H, 6-H), 7.96 (s, 1H, 3-H), 8.02 (d, J = 4.5 Hz, 1H, 5-H); ¹³C NMR (150 MHz, CDCl₃): δ_C = 56.0 (C-16), 56.1 (C-17), 109.6 (C-15), 110.6 (C-3), 111.2 (C-12), 118.3 (C-5), 119.3 (C-11), 125.2 (C-10), 128.0 (C-6), 138.0 (C-9), 143.1 (C-8), 148.3 (C-2), 149.3 (C-13), 149.9 (C-14); LRMS m/z (ESI⁺): 292 [M³⁷Cl⁺]+, 290 [M³⁵Cl⁺]+; HRMS m/z (ESI⁺): Found 290.0687 [M³⁵Cl⁺]+; C₁₄H₁₃ClN₃O₂ requires 290.0696.

8-chloro-2-(3,5-dimethylphenyl)imidazo[1,2-α]pyrazine, 21d

A mixture of 15d (530 mg, 2.33 mmol), 2-amino-3-chloropyrazine (302 mg, 2.33 mmol) and NaHCO₃ (245 mg, 2.92 mmol) in tBuOH (11 mL) were stirred under argon, under reflux for 40 h. After this point, the reaction mixture was cooled to RT and solvent
removed *in vacuo*. The resulting orange solid was dissolved in CH$_2$Cl$_2$ (100 mL) and washed with H$_2$O (3 x 40 mL). The aqueous layers were extracted further with CH$_2$Cl$_2$ (2 x 50 mL) before the combined organics were washed with brine (75 mL), dried (MgSO$_4$), filtered and solvent removed to give crude orange solid. Flash chromatography (1st: applied in pet. ether; eluted 9:1 to 5:1 to 2:1 pet. ether/EtOAc; 2nd: applied in CH$_2$Cl$_2$; eluted 9:1 CH$_2$Cl$_2$/EtOAc) was carried out to afford the title compound (245 mg, 0.951 mmol, 41%). Mpt: 158-162 °C; R$_f$ = 0.68 (2:1 CH$_2$Cl$_2$/EtOAc); IR (ν$_{max}$/cm$^{-1}$, thin film): 2920, 1365; $^1$H NMR (500 MHz, CDCl$_3$): δH = 2.38 (s, 6H, 14-H), 7.05 (s, 1H, 13-H), 7.62 (s, 2H, 11-H), 7.66 (d, J = 4.5 Hz, 1H, 6-H), 7.99 (s, 1H, 3-H). 8.02 (d, J = 4.5 Hz, 1H, 5-H); $^{13}$C NMR (125 MHz, CDCl$_3$): δC = 21.3 (C-14), 111.3 (C-3), 118.4 (C-5), 124.5 (C-11), 128.0 (C-6), 131.1 (C-13), 132.1 (C-10), 138.2 (C-9), 138.6 (C-12), 143.4 (C-8). 148.6 (C-2); LRMS m/z (EI$^+$): 257 [M($^{35}$Cl)]$^+$, 259 [M($^{37}$Cl)]$^+$; HRMS m/z (EI$^+$): Found 257.0719 [M($^{35}$Cl)]$^+$; C$_{14}$H$_{12}$ClN$_3$ requires 257.0714.

**8-chloro-2-(3-thienyl)imidazo[1,2-a]pyrazine, 21e**

15e (293 mg, 1.43 mmol), 2-amino-3-chloropyrazine (185 mg, 1.43 mmol), NaHCO$_3$ (150 mg, 1.79 mmol) and BuOH (6 mL) were stirred under reflux for 41 h. The reaction was cooled to RT and solvent removed *in vacuo*. The sample was taken up in water (15 mL) and extracted with DCM (2 x 20 mL). The combined organics were washed with H$_2$O (2 x 15 mL) and brine (15 mL) before they were dried (MgSO$_4$), filtered and concentrated to give crude brown/orange solid. Flash chromatography (applied in pet. ether; eluted 2:1 pet. ether /EtOAc) afforded a pale yellow solid (109 mg, 0.464 mmol, 32.4%). Mpt: decomposed before melting; R$_f$ = 0.33 (1:1 pet. ether /EtOAc); IR (ν$_{max}$/cm$^{-1}$, thin film): 1240 – 1480; $^1$H NMR (600 MHz, CDCl$_3$): δH = 7.44 (dd, J = 5.0, 3.0 Hz, 1H, 12-H), 7.58 (dd, J = 5.0, 1.3 Hz, 1H, 11-H), 7.69 (d, J = 4.4 Hz, 1H, 6-H), 7.93 (s, 1H, 3-H), 7.96 (dd, J = 3.0, 1.3 Hz, 1H 14-H), 8.04 (d, J = 4.4 Hz, 1H, 5-H); $^{13}$C NMR (150 MHz, CDCl$_3$): δC = 111.1 (C-3), 118.4 (C-5), 123.6 (C-14), 126.0 (C-12),
126.6 (C-11), 128.1 (C-6), 134.1 (C-10), 138.0 (C-9), 143.3 (C-8), 144.3 (C-2); LRMS m/z (ESI+) 238 [M(37Cl)+H]+, 236 [M(35Cl)+H]+; HRMS m/z (ESI+): Found: 236.0056 [M(35Cl)+H]+; C10H7ClN3S requires 236.0049.

Synthesis of first generation 2- and 3-substituted 8-aminoimidazo[1,2-a]pyrazines 4-methyl-N-[2-(2-naphthyl)imidazo[1,2-a]pyrazine-8-yl]benzenesulfonamide, 1

All glassware was evacuated and flushed with argon prior to use. 20a (12.3 mg, 0.044 mmol), 4-toluenesulfonamide 22 (9.10 mg, 0.053 mmol), K2CO3 (7.30 mg, 0.053 mmol), 1 mol% Pd(dba)2 (0.120 mg) and 5 mol% tert-butyl XPhos (0.600 mg) were weighed into a 5 mL round bottom flask. tBuOH (1 mL) was added and the reaction was stirred under reflux for 40 h. The reaction mixture was cooled to RT, diluted with MeOH and filtered through Celite (pre-washed with MeOH). Flash chromatography (applied in CH2Cl2; eluted 10:1 to 1:1 CH2Cl2/EtOAc) afforded the target compound as a white solid (7.50 mg, 0.018 mmol, 41%). Mpt: Decomposed before melting; Rf = 0.62 (1:1 CH2Cl2/EtOAc); IR (νmax/cm⁻¹, thin film): 3258, 3112, 2923, 2854, 1579; ¹H NMR (600 MHz, DMSO-d6): δH = 2.36 (s, 3H, 26-H), 7.16 (bs, 1H, 6-H), 7.39 (d, J = 8.2 Hz, 2H, 24-H), 7.60 - 7.62 (m, 2H, 15,16-H), 7.74 (d, J = 8.9 Hz, 1H, 11-H), 7.87 (bd, J = 6.8 Hz, 1H, 5, 23-H) 7.91 (s, 1H, 2-H), 8.00 - 8.04 (m, 2H, 14,17-H), 8.11 (d, J = 8.2 H, 12-H), 8.21 (s, 1H, 19-H), 11.70 (s, 1H, 20-H); ¹³C NMR (150 MHz, DMSO-d6): δC = 21.0 (C-26), 108.7 (C-5), 116.8 (C-6), 124.6 (C-10), 125.7 (C-11), 126.1 (C-23), 127.1 (C-15,16), 127.4 (C-19), 128.1 (C-14,17), 129.0 (C-12), 129.6 (C-24), 130.6 (C-3), 132.8 (C-13,18), 133.3 (C-2), 135.6 (C-9), 140.1 (C-22), 142.6 (C-25), 144.5 (C-8); LRMS m/z (ESI+): 415 [M+H]+, 260 [M-SO2C6H4CH3]+; HRMS m/z (ESI+): Found 415.1230 [M+H]+; C23H19N4O2S requires 415.1229.
4-methyl-N-[2-phenoxyphenyl]imidazo[1,2-a]pyrazine-8-yl]benzenesulfonamide, 2

All glassware was evacuated and flushed with argon prior to use. 20b (516 mg, 1.60 mmol), 4-toluenesulfonamide 22 (330 mg, 1.93 mmol), K2CO3 (266 mg, 1.93 mmol), 1 mol% Pd(dba)2 (5.20 mg) and 5 mol% tert-butyl XPhos (26.0 mg) were weighed into a 50 mL round bottom flask. tBuOH (10 mL) was added and the reaction was stirred under reflux for 40 h. The reaction mixture was cooled to RT, diluted with MeOH and filtered through Celite (pre-washed with MeOH). Flash chromatography was carried out (applied in CH2Cl2; eluted 10:1 CH2Cl2/EtOAc to 1:1 gradient followed by 10% MeOH/CH2Cl2) to afford the title compound as yellow solid (188 mg, 0.412 mmol 26%). Mpt: > 200 °C; Rf = 0.18 (2:1 CH2Cl2/EtOAc); IR (νmax/cm⁻¹, thin film): 3243, 2917, 1588; 1H NMR (600 MHz, CDCl3): δH = 2.37 (s, 3H, 27-H), 6.85 (d, J = 7.8 Hz, 2H, 18-H), 7.04 (d, J = 8.4 Hz, 2H, 6, 14H), 7.07 (t, J = 7.2 Hz, 1H, 20H), 7.23-7.27 (m, 5H, 12, 19, 25-H), 7.43-7.46 (m, 3H, 5, 11, 13-H), 7.65 (s, 1H, 2-H), 7.94 (bs, 2H, 24-H), 11.45 (bs, 1H, 21-H); 13C NMR (150 MHz, CDCl3): δC = 21.7 (C-27), 109.5 (C-5), 115.1 (C-6), 118.6 (C-10), 118.8 (C-18), 118.9 (C-14), 124.0 (C-12), 124.2 (C-20), 126.8 (C-24), 128.1 (C-3), 129.4 (C-25), 130.0 (C-19), 131.5 (C-13), 132.1 (C-11), 134.6 (C-2), 136.0 (C-9), 139.5 (C-23), 143.2 (C-26), 146.0 (C-8), 155.0 (C-15), 155.9 (C-17); LRMS m/z (ESI⁺): 457 [M+H]+, 302 [M-C6H5-SO2]+. HRMS m/z (ESI): Found: 455.1183 [M-H]−; C23H19N4O3S requires 455.1178.
All glassware was evacuated and flushed with argon prior to use. 20c (95.0 mg, 0.033 mmol), 4-toluenesulfonamide 22 (67.5 mg, 0.039 mmol), K$_2$CO$_3$ (54.4 mg, 0.039 mmol), 1 mol% Pd(dba)$_2$ (0.950 mg) and 5 mol% tert-butyl XPhos (4.75 mg) were weighed into a 10 mL round bottom flask. tBuOH (2 mL) was added and the reaction was stirred under reflux for 40 h. The reaction mixture was cooled to RT, diluted with MeOH and filtered through Celite (pre-washed with MeOH). Flash chromatography was carried out (applied in CH$_2$Cl$_2$; eluted 50:1 to 20:1 to 5:1 to 2:1 to 1:1 CH$_2$Cl$_2$/EtOAc) to afford the title compound as a yellow solid (42.3 mg, 0.010 mmol, 30.5%). Mpt: >200 °C; R$_f$ = 0.08 (1:1 CH$_2$Cl$_2$/EtOAc); IR (ν$_{max}$/cm$^{-1}$, thin film): 3244, 3129, 2838, 1582; $^1$H NMR (600 MHz, CDCl$_3$): δ$_H$ = 2.34 (s, 3H, 24-H), 3.89 (s, 3H, 16-H), 3.93 (s, 3H, 17-H), 6.93 (d, $J$ = 1.8 Hz, 1H, 15-H), 6.98 (d, $J$ = 8.3 Hz, 1H, 12-H), 7.02 (dd, $J$ = 8.2, 1.8 Hz, 11-H), 7.13 (bs, 1H, 6-H), 7.21 (d, $J$ = 8.1 Hz, 2H, 22-H), 7.41 (bs, 1H, 5-H), 7.64 (s, 1H, 2-H), 7.92 (d, $J$ = 8.1 Hz, 2H, 21-H), 11.53 (s, 1H, 18-H); $^{13}$C NMR (150 MHz, CDCl$_3$): δ$_C$ = 21.5 (C-24), 56.1 (C-16), 56.2 (C-17), 108.0 (C-5), 111.5 (C-15), 111.7 (C-12), 116.1 (C-6), 119.5 (C-10), 121.2 (C-11), 126.6 (C-21), 129.4 (C-22), 131.4 (C-3), 133.1 (C-2), 135.6 (C-9), 139.3 (C-20), 143.2 (C-23), 145.8 (C-8), 149.6 (C-14), 150.1 (C-13); LRMS m/z (ESI$^+$): 425 [M+H]$^+$, 447 [M+Na]$^+$, HRMS m/z (ESI): Found 423.0940 [M-H]$^+$; C$_{21}$H$_{21}$N$_4$O$_4$S requires 423.0949.
All glassware was evacuated and flushed with argon prior to use. 20d (93.8 mg, 0.364 mmol), 4-toluenesulfonamide 22 (74.8 mg, 0.437 mmol), K$_2$CO$_3$ (60.4 mg, 0.437 mmol), 1 mol% Pd(dba)$_2$ (2.10 mg) and 5 mol% tert-butyl XPhos (7.70 mg) were weighed into a 10 mL round bottom flask. tBuOH (2 mL) was added and the reaction was stirred under reflux for 40 h. The reaction mixture was cooled to RT, diluted with MeOH and filtered through Celite (pre-washed with MeOH). Flash chromatography was carried out (applied in CH$_2$Cl$_2$; eluted 9:1 to 1:1 CH$_2$Cl$_2$/EtOAc followed by 5% MeOH/CH$_2$Cl$_2$) to afford the title compound as a pale yellow solid (96.2 mg, 0.245 mmol, 67%). Mpt: >200 °C; R$_f$ = 0.5 (CH$_2$Cl$_2$/10% MeOH); IR (ν$_{\text{max}}$/cm$^{-1}$, thin film): 3253, 1591; $^1$H NMR (600 MHz, CD$_2$Cl$_2$): δ$^H$ = 2.38 (s, 6H, 14-H), 2.39 (s, 3H, 21-H), 6.98 (bs, 1H, 6-H), 7.11 (s, 2H, 11-H), 7.13 (s, 1H, 13-H), 7.30 (d, $J$ = 8.0 Hz, 2H, 19-H), 7.50 (bs, 1H, 5-H), 7.64 (s, 1H, 2-H), 7.90 (bd, $J$ = 6.1 Hz, 2H, 18-H), 11.33 (bs, 1H, 15-H); $^{13}$C NMR (150 MHz, CD$_2$Cl$_2$): δ$^C$ = 21.4 (C-14), 21.7 (C-21), 108.9 (C-5), 115.8 (C-6), 125.9 (C-3), 126.4 (C-11), 126.8 (C-18), 129.8 (C-19), 131.4 (C-13), 132.2 (C-10), 133.6 (C-2), 136.1 (C-9), 139.4 (C-12), 139.7 (C-17), 143.9 (C-20), 146.2 (C-8); LRMS m/z (ESI$^+$): 415 [M+Na]$^+$, 393 [M+H]$^+$; HRMS m/z (ESI$^+$): Found: 393.1366 [M+H]$^+$; C$_{21}$H$_{21}$N$_4$O$_2$S requires 393.1385.
**4-methyl-N-[4-[3-(3-thienyl)imidazo[1,2-a]pyrazine-8-yl]amino]phenyl]benzenesulfonamide, 6**

All glassware was evacuated and flushed with argon prior to use. 20e (94.9 mg, 0.403 mmol), N-(4-aminophenyl)-4-methylbenzenesulfonamide 23 (126.8 mg, 0.484 mmol, 1.2 equiv.), NaO\textsubscript{t}Bu (54.2 mg, 0.564 mmol, 1.4 equiv.), 1 mol% Pd(dba)\textsubscript{3} (3.7 mg) and 3 mol% DavePhos (4.8 mg) were weighed into a 25 mL round bottom flask. Toluene (4 mL) was added and the reaction was stirred under reflux for 18 h. The reaction mixture was cooled to RT and the solvents removed in vacuo. Flash chromatography (applied in pet.
er; eluted 2:1 to 1:1 pet.
er/EtOAc) was carried out to give a mixture of the product and starting sulfonamide. Reverse phase preparative HPLC (35 to 55% MeCN/H\textsubscript{2}O over 10 min) was carried out to afford title compound (RT 15.5 min) as off white solid (56.7 mg, 0.123 mmol, 30%). Mpt: 108-110 °C; R\textsubscript{f} = 0.62 (1:1 CH\textsubscript{2}Cl\textsubscript{2}/EtOAc); IR (ν\textsubscript{max}/cm\textsuperscript{-1}, thin film): 3112, 1624, 1542, 1506; \textsuperscript{1}H NMR (600 MHz, CD\textsubscript{3}OD): δ\textsubscript{H} = 2.38 (s, 3H, 26-H), 7.17 (d, J = 5.4 Hz, 1H, 6-H), 7.28 (d, J = 9.0 Hz, 2H, 17-H), 7.33 (d, J = 8.4 Hz, 2H, 24-H), 7.48 (d, J = 9.0 Hz, 2H, 18-H), 7.49, (dd, J = 5.4, 1.2 Hz, 1H, 11-H), 7.72-7.73 (m, 3H, 12-H, 23-H), 7.92 (dd, J = 2.4, 1.2 Hz, 1H, 14-H), 7.96 (bs, 1H, 2-H), 8.02 (d, J = 5.4 Hz, 1H, 5-H); \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}): δ\textsubscript{H} = 2.38 (s, 3H, 26-H), 6.69 (s, 1H, 20-H), 7.07 (d, J = 8.8 Hz, 2H, 18-H), 7.22 (d, J = 8.2 Hz, 2H, 24-H), 7.34 (dd, J = 4.0, 2.0 Hz, 1H, 11-H), 7.52 (d, J = 4.7 Hz, 1H, 6-H), 7.54-7.56 (m, 2H, 12,14-H), 7.63 (d, J = 8.2 Hz, 2H, 23-H), 7.64 (s, 1H, 2-H), 7.71 (d, J = 4.7 Hz, 1H, 5-H), 7.79 (d, J = 8.8 Hz, 2H, 17-H), 8.34 (bs, 1H, 15-H); \textsuperscript{13}C NMR (150 MHz, CD\textsubscript{3}OD): δ\textsubscript{C} = 21.4 (C-26), 112.2 (C-5), 119.8 (C-6), 122.7 (C-17), 126.1 (C-14), 126.6 (C-18), 128.0 (C-11), 128.3 (C-10), 128.3 (C-23), 128.9 (C-12), 129.1 (C-3), 130.7 (C-24), 132.1 (C-19), 133.0 (C-9), 134.2 (C-2), 138.2 (C-22), 138.8 (C-16), 145.3 (C-25),
$^{13}$C NMR (150 MHz, CDCl$_3$): 21.7 (C-26), 109.7 (C-5), 120.3 (C-17), 123.6 (C-12), 123.9 (C-18), 124.5 (C-10), 126.9 (C-11), 127.4 (C-14), 127.5 (overlapping signals, C-2, 23), 128.1 (C-3), 129.1 (C-6), 129.8 (C-24), 131.2 (C-19), 132.9 (C-9), 136.2 (C-22), 137.4 (C-16), 143.9 (C-25), 146.1 (C-8); LRMS m/z (ES$^+$): 484 [M+Na]$^+$, 462 [M+H]$^+$; HRMS m/z (ES$^+$): Found 462.1065 [M+H]$^+$; C$_{23}$H$_{20}$N$_5$S$_2$O$_2$ requires 462.1058.

4-methyl-N-[2-(2-naphthyl)imidazo[1,2-a]pyrazine-8-yl]benzenesulfonamide, 7

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\begin{align*}
\text{All glassware was evacuated and flushed with argon prior to use.} & \text{ 21a (50.0 mg, 0.178 mmol), 4-toluenesulfonamide 22 (36.9 mg, 0.215 mmol, 1.2 equiv.), NaO'Bu (24.1 mg, 0.250 mmol, 1.4 equiv.), 1 mol\% Pd$_2$(dba)$_3$ (1.6 mg) and 3 mol\% DavePhos (2.1 mg) were weighed into a 25 mL round bottom flask. Toluene (2 mL) was added and the reaction was stirred under reflux for 24 h. The reaction mixture was cooled to RT and the solvents removed in vacuo. The residue was taken up in CH$_2$Cl$_2$ (30 mL) and washed with water (3 x 30 mL). The combined aqueous extracts were washed with CH$_2$Cl$_2$ (30 mL). The CH$_2$Cl$_2$ layers were combined, washed with brine (30 mL), dried over MgSO$_4$ and the solvents removed in vacuo to give an orange oil. The crude product was dry loaded onto a column and purified by flash chromatography (applied in pet. ether; eluted 4:1 to 1:1 pet. ether/EtOAc) to give the target compound as a white solid (68.7 mg, 0.166 mmol, 93%).} \\
\text{Alternative microwave procedure:} & \text{In a 2 mL microwave vial, Pd$_2$(dba)$_3$ (0.7 mg, 1 mol\%), DavePhos (0.8 mg, 3 mol\%) and NaO'Bu (9.6 mg, 0.100 mmol, 1.4 equiv.) were dissolved in anhydrous toluene (1 mL). 21a (20 mg, 0.072 mmol) and 22 (14.7 mg, 0.086 mmol, 1.2 equiv.) were added and the}
\end{align*}
\]
reaction mixture was stirred at 160 °C for 10 min with a 20 bar pressure limit. The solvent was removed in vacuo and the crude mixture was purified via flash chromatography (applied pet. ether; eluted 4:1 to 1:2 pet. ether) to give 7 as a white solid (13.6 mg, 46%).

Mpt: >200 °C; Rf = 0.32 (1:1 CH₂Cl₂/EtOAc); IR (νmax/cm⁻¹, thin film): 3253; ¹H NMR (600 MHz, DMSO-d₆): δH = 2.37 (s, 3H, 26-H), 7.16 (bd, J = 5.2 Hz, 1H, 6-H), 7.39 (d, J = 8.2 Hz, 2H, 24-H), 7.51 - 7.54 (m, 2H, 15,16-H), 7.86 (bd, J = 5.2 Hz, 1H, 5-H), 7.89 (d, J = 8.0 Hz, 2H, 23-H), 7.92 (d, J = 7.7 Hz, 1H, 14-H), 7.98 (d, J = 8.6 Hz, 1H, 12-H), 8.01 - 8.05 (m, 2H, 11,17-H), 8.52 (s, 1H, 19-H), 8.59 (s, 1H, 3-H), 11.69 (s, 1H, NH: 20-H); ¹³C NMR (150 MHz, DMSO-d₆): δC = 21.0 (C-26), 111.0 (C-5), 115.3 (C-3), 116.8 (C-6), 123.8 (C-11), 124.2 (C-19), 126.2 (C-23), 126.3 (C15/16), 126.6 (C-15/16), 127.7 (C-14), 128.3 (C-17), 128.4 (C-12), 129.5 (C-24), 130.0 (C-10), 132.8 (C-13), 133.2 (C-18), 135.6 (C-9), 140.0 (C-22), 142.7 (C-25), 144.5 (C-8), 145.3 (C-2); LRMS m/z (ESI⁺): 415 [M+H]+, (ESI⁻): 413 [M-H]⁻, HRMS m/z (ESI⁺): Found 415.1219 [M+H]+; C₂₃H₁₉N₄O₂S requires 415.1229.

4-methyl-N-[2-(2-phenoxyphenyl)imidazo[1,2-a]pyrazine-8-yl]benzenesulfonamide, 8

All glassware was evacuated and flushed with argon prior to use. 21b (130 mg, 0.405 mmol), 4-toluenesulfonamide 22 (83.1 mg, 0.486 mmol), K₂CO₃ (67.1 mg, 0.127 mmol), Pd(dba)₂ (1.30 mg) and 5 mol% tert-butyl XPhos (6.50 mg) were weighed into a 10 mL round bottom flask. tBuOH (3 mL) was added and the reaction was stirred under reflux for 48 h. The reaction mixture was cooled to RT, diluted with MeOH (100 mL) and filtered through Celite (pre-washed with MeOH). Flash chromatography was carried out
(applied in CH$_2$Cl$_2$; eluted 100% CH$_2$Cl$_2$ to 40:1 to 30:1 to 1:1 CH$_2$Cl$_2$/EtOAc) to afford the title compound as a yellow solid (23.9 mg, 0.052 mmol 13%). Mpt: >200 °C; R$_f$ = 0.18 (9:1 CH$_2$Cl$_2$/EtOAc); IR (ν$_{max}$/cm$^{-1}$, thin film): 3245, 1586; $^1$H NMR (600 MHz, CD$_2$Cl$_2$): δ$_H$ = 2.43 (s, 3H, 27-H), 6.91 (bs, 1H, 6-H), 6.96 (d, $J$ = 8.1 Hz, 1H, 14-H), 7.08 (dd, $J$ = 8.8, 0.7 Hz, 2H, 18-H), 7.17 (t, $J$ = 7.1 Hz, 1H, 20-H), 7.27 (t, $J$ = 7.3 Hz, 1H, 12-H), 7.31 – 7.37 (m, 4H, 5,13,25-H), 7.38 – 7.41 (m, 2H, 19-H), 7.91 (bd, $J$ = 5.7 Hz, 2H, 24-H), 8.12 (s, 1H, 3-H), 8.48 (dd, $J$ = 7.8,1.7 Hz 1H, 11-H), 11.41 (s, 1H, 21-H); $^{13}$C NMR (150 MHz, CD$_2$Cl$_2$): δ$_C$ = 21.3 (C-27), 110.2 (C-5), 115.0 (C-6), 117.7 (C-3), 118.8 (C-18), 118.9 (C-14), 123.7 (C-20), 123.8 (C-10), 123.9 (C-12), 126.2 (C-24), 129.1 (C-11), 129.5 (C-15,25), 130.0 (C-19), 134.7 (C-9), 139.4 (C-23), 142.1 (C-2), 143.5 (C-26), 145.5 (C-8), 154.3 (C-15), 156.5 (C-17); LRMS m/z (ESI$^+$): 457 [M+H]$^+$, HRMS m/z (ESI$^+$): Found 455.1167 [M +H$^+$]; C$_{25}$H$_{19}$N$_4$O$_3$S requires 455.1178.

$N$-[2-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyrazine-8-yl]-4-methyl-benzene-sulfonamide, 9

![Chemical Structure](image)

All glassware was evacuated and flushed with argon prior to use. 21c (200 mg, 0.691 mmol), 4-toluensulfonamide 22 (142 mg, 0.829 mmol), K$_2$CO$_3$ (115 mg, 0.829 mmol), 1 mol% Pd(dba)$_2$ (2.00 mg) and 5 mol% tert-butyl XPhos (10.0 mg) were weighed into a 10 mL round bottom flask. tBuOH (4 mL) was added and the reaction was stirred under reflux for 48 h. The reaction mixture was cooled to RT, diluted with MeOH (100 mL) and filtered through Celite (pre-washed with MeOH). Flash chromatography was carried out (applied in CH$_2$Cl$_2$; eluted 100% CH$_2$Cl$_2$ to 50:1 to 1:9 CH$_2$Cl$_2$/EtOAc followed by CH$_2$Cl$_2$/10% MeOH) gave the title compound as a yellow sticky solid (5.2 mg, 0.012 mmol, 2%). Mpt: >200 °C; R$_f$ = 0.26 (1:1 CH$_2$Cl$_2$/EtOAc); IR (ν$_{max}$/cm$^{-1}$, thin film): 3274, 3138, 1584; $^1$H NMR (600 MHz, DMSO-d$_6$): δ$_H$ = 2.36 (s, 3H, 24-H), 3.78 (s, 3H, 16-H), 3.83 (s, 3H, 17-H), 7.02 (d, $J$ = 8.2 Hz, 1H, 12-H), 7.13 (bd, $J$ = 4.9 Hz, 1H, 6-H), 7.2 - 7.37 (m, 4H, 5,13,25-H), 7.38 – 7.41 (m, 2H, 19-H), 7.91 (bd, $J$ = 5.7 Hz, 2H, 24-H), 8.12 (s, 1H, 3-H), 8.48 (dd, $J$ = 7.8,1.7 Hz 1H, 11-H), 11.41 (s, 1H, 21-H); $^{13}$C NMR (150 MHz, CD$_2$Cl$_2$): δ$_C$ = 21.3 (C-27), 110.2 (C-5), 115.0 (C-6), 117.7 (C-3), 118.8 (C-18), 118.9 (C-14), 123.7 (C-20), 123.8 (C-10), 123.9 (C-12), 126.2 (C-24), 129.1 (C-11), 129.5 (C-15,25), 130.0 (C-19), 134.7 (C-9), 139.4 (C-23), 142.1 (C-2), 143.5 (C-26), 145.5 (C-8), 154.3 (C-15), 156.5 (C-17); LRMS m/z (ESI$^+$): 457 [M+H]$^+$, HRMS m/z (ESI$^+$): Found 455.1167 [M +H$^+$]; C$_{25}$H$_{19}$N$_4$O$_3$S requires 455.1178.
7.37 (d, J = 8.2 Hz, 1H, 22-H), 7.45 (bs, 1H, 11-H), 7.47 (bs, 1H, 15-H), 7.81 (d, J = 5.5 Hz, 1H, 5-H), 7.87 (d, J = 8.0 Hz, 2H, 21-H), 8.41 (s, 1H, 3-H), 11.63 (s, 1H, 18-H); 13C NMR (150 MHz, DMSO-d6): δC = 21.0 (C-24), 55.5 (C-16), 55.6 (C-17), 108.9 (C-15), 111.0 (C-5), 111.9 (C-12), 114.3 (C-3), 116.6 (C-6) 118.2 (C-11), 125.3 (C-10), 126.1 (C-21), 129.5 (C-22), 135.0 (C-9), 139.8 (C-20), 142.7 (C-23), 144.4 (C-8), 145.6 (C-2), 149.0 (C-14), 149.1 (C-13); LRMS m/z (ES+): 423 [M+H]+; HRMS m/z (ES+): Found 423.1115 [M+H]+; C21H21N4O4S requires 423.1127.

N-[2-(3,5-dimethylphenyl)imidazo[1,2-a]pyrazine-8-yl]-4-methylbenzene-sulfonamide, 10

A mixture of 21d (100 mg, 0.388 mmol), 4-toluene sulfonamide 22 (79.8 mg, 0.466 mmol), Pd(dppf)Cl2 (6.30 mg, 2 mol%) and Cs2CO3 (152 mg, 0.466 mmol) in anhydrous toluene (3 mL) were stirred under reflux, under Ar. After 21 h, the reaction was cooled to RT, diluted with toluene (20 mL) and washed with H2O (10 mL) and brine (10 mL). Further extraction of the aqueous layers was carried out using CH2Cl2 (3 x 10 mL). The combined organics were dried (MgSO4), filtered and solvent removed in vacuo. Flash chromatography (applied in CH2Cl2; eluted 19:1 CH2Cl2/EtOAc) afforded the title compound as a yellow solid (43.4 mg, 0.111 mmol, 29%). Mpt: >200 °C; Rf = 0.37 (2:1 CH2Cl2/EtOAc); IR (vmax/cm⁻¹, thin film): 2928, 1595; 1H NMR (600 MHz, (CD3)2SO): δH = 2.31 (s, 6H, 14-H), 2.36 (s, 3H, 21-H), 6.97 (s, 1H, 13-H), 7.13 (t, J = 5.4 Hz, 1H, 6-H), 7.38 (d, J = 8.1 Hz, 2H, 19-H), 7.54 (s, 2H, 11-H), 7.81 (d, J = 5.4 Hz, 1H, 5-H), 7.87 (d, J = 8.1 Hz, 2H, 18-H), 8.42 (s, 1H, 3-H), 11.63 (bd, J = 5.4 Hz, 1H, 7/15-H); 13C NMR (150 MHz, (CD3)2SO): δC = 21.0 (overlapping signals, C-14,21), 111.0 (C-5), 114.8 (C-3), 116.7 (C-6), 123.3 (C-11), 126.1 (C-18), 129.5 (C-19), 129.8 (C-13), 132.4 (C-10), 135.2 (C-9), 137.9 (C-12), 139.9 (C-17), 142.6 (C-20), 144.5 (C-8), 145.5 (C-2); LRMS m/z (ES+): 393 [M+H]+, HRMS m/z (ES+): Found 391.1236 [M-H]+; C21H19N4O2 requires 391.1229.
4-methyl-N-[4-[(2-(2-naphthyl)imidazo[1,2-a]pyrazine-8-yl)amino]phenyl]benzenesulfonamide, 11

In a 2 mL microwave vial, Pd$_2$(dba)$_3$ (0.7 mg, 1 mol%), DavePhos (0.8 mg, 3 mol%) and NaO$^t$Bu (9.6 mg, 0.100 mmol, 1.4 equiv.) were dissolved in anhydrous toluene (1 mL). 21a (20 mg, 0.072 mmol) and 23 (22.5 mg, 0.086 mmol, 1.2 equiv.) were added and the reaction mixture was stirred at 160 °C for 10 min with a 20 bar pressure limit. The solvent was removed in vacuo and the crude mixture was purified via flash chromatography (applied in toluene, eluted 3:1 toluene:EtOAc) to give 11 as a light brown solid (17 mg, 47%).
4-methyl-N-[4-[2-(3-thienyl)imidazo[1,2-a]pyrazine-8-yl]amino]phenyl]benzenesulfonamide, 12

All glassware was evacuated and flushed with argon prior to use. 21e (128 mg, 0.540 mmol), N-(4-aminophenyl)-4-methylbenzenesulfonamide 23 (171 mg, 0.650 mmol), K$_2$CO$_3$ (90.1 mg, 0.652 mmol), 1 mol% Pd(dba)$_2$ (3.12 mg) and 5 mol% tert-butyl XPhos (11.5 mg) were weighed into a 25 mL round bottom flask. tBuOH (5 mL) was added and the reaction was stirred under reflux for 40 h. The reaction mixture was cooled to RT, diluted with MeOH (100 mL) and filtered through Celite (pre-washed with MeOH). LCMS indicated the correct product mass was present, and flash chromatography (applied in pet. ether; eluted 1:1 pet. ether /EtOAc) was carried to give the title compound as a yellow solid (19.2 mg, 0.042 mmol, 8%). Mpt: 158-164 ºC; R$_f$ = 0.57 (1:1 CH$_2$Cl$_2$/Et$_2$O); IR (v$_{max}$/cm$^{-1}$, thin film): 1140; $^1$H NMR (600 MHz, CD$_3$OD): δ$_H$ = 2.41 (s, 3H, 26-H), 7.17 (d, J = 4.5 Hz, 1H, 6-H), 7.29 (d, J = 8.8 Hz, 2H, 17-H), 7.35 (d, J = 8.0 Hz, 2H, 24-H), 7.53 (d, J = 8.8, 2H, 18-H), 7.57 (dd, J = 4.9, 2.9 Hz, 1H, 12-H), 7.66 (dd, J = 4.9, 1.1 Hz, 1H, 11-H), 7.75 (d, J = 8.4, 2 H, 23-H), 7.96 (d, J = 5.4, 1H, 5-H), 7.98 (dd, J = 1.1, 2.8 Hz, 1H, 14-H), 8.30 (s, 1H, 3-H); $^{13}$C NMR (150 MHz, CD$_3$OD): δ$_C$ = 20.0 (C-26), 112.6 (C-5), 114.3 (C-3), 118.8 (C-6), 121.4 (C-17), 122.3 (C-14), 122.6, 124.8 (C-18), 125.5 (C-11), 126.5 (C-12), 127.0 (C-23), 129.3, (C-24), 131.4 (C-16), 134.0 (C-9 +C-10), 136.8 (C-19 + C-22), 143.2 (C-2), 143.8 (C-25), 144.4 (C-8); LRMS m/z (ESI$^+$) 462 [M+H]$^+$; HRMS m/z (ESI$^+$): Found 462.1047 [M+H]$^+$; C$_{23}$H$_{20}$N$_5$O$_2$S$_2$ requires 462.1058.
4-Methyl-N-(4-(2-(2-phenoxyphenyl)imidazo[1,2-a]pyrazin-8-ylamino)phenyl)-benzenesulfonamide 13

NaO'Bu (12.5 mg, 130 μmol), 1 mol% Pd₂(dba)₃ (1 mg, 1.1 μmol) and 3 mol% DavePhos (1 mg, 2.5 μmol) were weighed into a 25 mL round bottom flask and dissolved in anhydrous toluene (5 mL). 21b (30 mg, 93.4 μmol) and N-(4-aminophenyl)-4-methylbenzenesulfonamide 23 (29 mg, 112 μmol) were added under argon atmosphere. The reaction was stirred under reflux for 24 h. The reaction was cooled to room temperature and the solvent removed in vacuo. The product was taken up in dichloromethane (2 mL) and filtered. The filtrate was washed with water (3 x 1 mL) and the combined aqueous extracts were further washed with dichloromethane (2 x 1 mL). The organic layers were combined, dried over MgSO₄ and the solvent was removed in vacuo. flash chromatography (applied in pet. ether; eluted 3:1 pet. ether/EtOAc) was performed to give the product as a yellow, sticky solid (4.8 mg, 8.8 μmol, yield: 9%). Mpt: decomposed before melting; Rₛ = 0.14 (3:1 pet. ether/EtOAc); IR (vₘₐₓ/cm⁻¹, thin film): 1489-1542; ¹H NMR (600 MHz, CDCl₃), δ (ppm): 2.38 (s, 3H, CH₃: 32-H), 6.36 (bs, 1H, NH: 21-H), 6.96 (dd, J = 6.7, 2.3 Hz, 1H, CH: 14-H), 7.06 (d, J = 7.5 Hz, 2H, CH: 18-H), 7.07 (d, J = 8.6 Hz, 1H, CH: 24-H), 7.14 (t, J = 7.2 Hz, 1H, CH: 20-H), 7.22 (d, J = 8.3 Hz, 2H, CH: 30-H), 7.21-7.31 (m, 2H, CH: 12-H, CH: 13-H), 7.35-7.38 (m, 3H, CH: 6-H, CH: 19-H), 7.48 (d, J = 4.5 Hz, 1H, CH: 5-H), 7.62 (d, J = 8.2 Hz, 2H, CH: 29-H), 7.79 (d, J = 8.3 Hz, 2H, CH: 23-H), 8.05 (s, 1H, CH: 3-H), 8.45 (dd, J = 6.2, 2.2 Hz, 1H, CH: 11-H); ¹³C-NMR (125 MHz, CDCl₃), δ (ppm): 21.7 (C-32), 111.9 (C-5), 115.0 (C-3), 118.8 (C-18), 119.4 (C-14), 120.1 (C-23), 123.7 (C-20), 124.1 (C-24), 124.2 (C-12), 124.8 (C-10), 127.4 (C-29), 127.8 (C-6), 129.1 (C-11), 129.3 (C-13), 129.7 (C-30), 130.1 (C-19), 130.8 (C-25), 132.6 (C-9), 136.1 (C-28), 137.6 (C-22), 140.0 (C-2), 143.9 (C-8), 145.9 (C-31), 154.3 (C-15); LRMS m/z (ES⁺): 550
[M\(^{37}\)Cl+H]\(^+\), 549, 548 [M\(^{35}\)Cl+H]\(^+\); HRMS m/z (ES\(^+\)): Found 548.1733 [M+H]\(^+\); C\(_{31}\)H\(_{26}\)N\(_5\)O\(_2\)S requires 548.1756.

**Reaction conditions screen for the synthesis of 7**

**Method A**

All glassware was evacuated and flushed with Ar prior to use. 214\(^a\) (50.0 mg, 0.178 mmol), 4-toluene sulfonamide 22 (36.9 mg, 0.215 mmol), K\(_2\)CO\(_3\) (29.7 mg, 0.215 mmol), Pd(dba)\(_2\) (1.03 mg, 1 mol%) and tBu-XPhos (3.80 mg, 5 mol%) were taken up in tBuOH (3 mL) and the reaction was stirred under reflux for 24 h. The reaction mixture was cooled to RT, diluted with MeOH (100 mL) and filtered through Celite (pre-washed with MeOH). Flash chromatography (applied in CH\(_2\)Cl\(_2\); eluted 5% to 10% to 20% EtOAc; or applied in pet. ether; eluted 20% to 33% to 50% to 66% EtOAc) afforded the target compound as a white solid (28.0 mg, 0.068 mmol, 38%).

**Method B (Microwave):**

In a 2 mL microwave vial, catalyst, ligand and base were dissolved in solvent. 21\(^a\) and 4-toluene sulfonamide 22 (1.2 eq) were added and the reaction mixture was stirred at the stated temperature and for the given time with a 20 bar pressure limit. The solvent was removed in vacuo and the crude mixture was purified via flash chromatography (applied in CH\(_2\)Cl\(_2\); eluted 5% to 10% to 20% EtOAc; or applied in pet. ether; eluted 20% to 33% to 50% to 66% EtOAc) afforded the title compound.

**Method C:**

21\(^a\), 4-toluene sulfonamide 22 (2 eq) and base (in the case of NaH, the base was pre-activated by stirring in anhydrous hexanes and drying) were dissolved in solvent and stirred at the stated temperature for the given time. The reaction was cooled to RT and quenched with brine (in the case of NaH: with NH\(_4\)Cl (Sat.Aq)) and extracted EtOAc (3x). The combined organic layers were washed with H\(_2\)O (5x) and brine, dried (MgSO\(_4\)), filtered and solvent removed. Flash chromatography (applied in CH\(_2\)Cl\(_2\); eluted 5% to 10% to 20% EtOAc; or applied in pet. ether; eluted 20% to 33% to 50% to 66% EtOAc) afforded the title compound.

**Method D (Microwave):**
In a 2 mL microwave vial, 21a, 4-toluene sulfonamide 22 (1.2 eq) and base were added and the reaction mixture was stirred at the stated temperature and for the given time, with a 20 bar pressure limit. The solvent was removed in vacuo and the crude mixture was purified via flash chromatography (applied in CH₂Cl₂; eluted 5% to 10% to 20% EtOAc; or applied in pet. ether; eluted 20% to 33% to 50% to 66% EtOAc) afforded the title compound.

*Method E:*

NaH was washed by stirring in anhydrous hexanes, syringing out the solvent and drying. Under Ar, the reaction solvent was added to the flask, followed by 4-toluene sulfonamide (2 eq) in solvent. The contents were then stirred at RT for 20 min before 24 in solvent was added dropwise, and the reaction was stirred at the stated temperature for the given time. The reaction was cooled to RT and quenched with NH₄Cl (Sat. Aq) and extracted EtOAc (3x). The combined organic layers were washed with H₂O (5x) and brine, dried (MgSO₄), filtered and solvent removed. Flash chromatography (applied in pet. ether; eluted 20% to 33% to 50% to 66% EtOAc) afforded the title compound.

*Method F (Microwave):*

In a 2 mL microwave vial, 24, 4-toluene sulfonamide (2 eq) and base were added and the reaction mixture was stirred at the stated temperature and for the given time with a 20 bar pressure limit. The solvent was removed in vacuo and the crude mixture was purified via flash chromatography (pet. ether; 20% to 33% to 50% to 66% EtOAc) to afford the title compound.

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<td>DavePhos (3 mol%)</td>
<td>Cs$_2$CO$_3$ (1.4 eq)</td>
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<td>Reflux</td>
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<td>Pd(dba)$_2$ (1 mol%)</td>
<td>DavePhos (3 mol%)</td>
<td>NaO'Bu (1.4 eq)</td>
<td>toluene</td>
<td>Reflux</td>
<td>24</td>
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<td>DavePhos (3 mol%)</td>
<td>Cs$_2$CO$_3$ (1.4 eq)</td>
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<td>DavePhos (3 mol%)</td>
<td>NaO'Bu (1.4 eq)</td>
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<td>NaO'Bu (1.4 eq)</td>
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<td>160</td>
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<td>DavePhos (3 mol%)</td>
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<td>17</td>
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<td>Pd(OAc)$_2$ (0.5 mol%)</td>
<td>DavePhos (3 mol%)</td>
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<tr>
<td>18</td>
<td>B</td>
<td>Pd(PPh)$_3$ (5 mol%)</td>
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<td>NaO'Bu (1.4 eq)</td>
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<td>NaO'Bu (1.4 eq)</td>
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<td>10 min</td>
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<td>20</td>
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<td>Cul (15 mol%)</td>
<td>Diamine$^b$ (30 mol%)</td>
<td>K$_2$CO$_3$ (2 eq)</td>
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<td>-</td>
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<td>DIPEA (1.5 eq)</td>
<td>MeCN</td>
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<td>10</td>
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<tr>
<td>27</td>
<td>E</td>
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<td>29</td>
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<td>30</td>
<td>F</td>
<td>-</td>
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<td>DIPEA (2 eq)</td>
<td>MeCN</td>
<td>160</td>
<td>10</td>
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Table S1: Reaction optimisation for the formation of 7.  

a Reaction carried out in sealed tube; b N,N’-dimethylcyclohexane-1,2-diamine; c 1.4 eq of 4-toluene sulfonamide used
Second generation imidazo[1,2-a]pyrazine inhibitors, variants at 8-position.

2-(Naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-amine (25)

In a sealed tube, 24 (21.0 mg, 0.065 mmol) was dissolved in 2.0 M NH₃/IPA (2 mL), and the mixture was heated at 100 °C for 16 h. Removal of solvent in vacuo followed by flash chromatography (applied in CH₂Cl₂; eluted 1% to 10% MeOH) afforded the title compound as a sticky yellow solid (3.40 mg, 0.013 mmol, 20%). Mpt: >200 °C; \( R_f = 0.49 \) (20:1 CH₂Cl₂/MeOH); IR (\( \nu_{\text{max}}/\text{cm}^{-1} \), thin film): 3314, 2956-3055, 1620; \(^1\)H NMR (600 MHz, CDCl₃): \( \delta_H = 6.10 \) (bs, 2H, 20-H), 7.29 (d, \( J = 4.7 \) Hz, 1H, 6-H), 7.47-7.52 (m, 2H, 15,16-H), 7.54 (d, \( J = 4.7 \) Hz, 1H, 5-H), 7.85 (d, \( J = 8.4 \) Hz, 1H, 17-H), 7.90 (d, \( J = 1.0 \) Hz, 2H, 12,14-H), 7.92 (s, 1H, 3-H), 8.00 (d, \( J = 8.5 \) Hz, 1H, 11-H), 8.44 (s, 1H, 19-H); \(^{13}\)C NMR (150 MHz, CDCl₃): \( \delta_C = 111.4 \) (C-3), 112.8 (C-5), 123.8 (C-11), 125.2 (C-19), 126.6 (C-15), 126.7 (C-16), 127.8 (signals overlapping, C-6,17), 128.4 (C-12), 128.8 (C-14), 129.4 (C-10), 133.5 (signals overlapping, C-9,13,18), 146.1(C-8), 148.4 (C-2); LRMS m/z (EI\(^+\)): 260 [M\(^+\)]; HRMS m/z (Cl\(^+\)): Found 261.1141 [M+H\(^+\)]; \( C_{16}H_{13}N_{4} \) requires 261.1140.

\( N'-(2-(Naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-yl)benzene-1,4-diamine \) (26)

All glassware was dried and purged with Ar prior to use. Pd\(_2\)(dba\(_3\)) (9.17 mg, 1 mol%), DavePhos (11.8 mg, 3 mol%) and NaO'Bu (135 mg, 1.402 mmol) were dissolved in anhydrous toluene (10 mL). 21a (280 mg, 1.00 mmol) and 1,4-diaminobenzene (130 mg, 1.20 mmol) were added and the reaction was stirred under reflux under Ar for 16 h. The
reaction was cooled to RT and solvent removed in vacuo, before the residue was taken up in CH₂Cl₂ (100 mL) and washed with H₂O (3 x 50 mL) and brine (30 mL), dried (MgSO₄), filtered and concentrated in vacuo. Flash chromatography (applied in CH₂Cl₂; eluted 15:1 to 5:1 to 1:1) afforded the title compound as a sticky brown solid (95.0 mg, 0.271 mmol, 27%). \( R_f = 0.22 \) (1:1 CH₂Cl₂/EtOAc); IR \( (\nu_{\text{max}}/\text{cm}^{-1}, \text{thin film}) \): 3335, 3051, 1622, 1541, 1507; \(^1\text{H NMR} (600 \text{ MHz, CDCl}_3) \): \( \delta_H = 3.71 \text{ (bs, 2H, 25-H)}, 6.76 \text{ (ap.d, J = 8.7 Hz, 2H, 23-H)}, 7.42 \text{ (d, J = 4.6 Hz, 1H, 6-H)}, 7.48-7.53 \text{ (m, 3H, 5,15,16-H)}, 7.61 \text{ (d, J = 9.5 Hz, 2H, 22-H)}, 7.86 \text{ (d, J = 7.5 Hz, 1H, 14-H)}, 7.90 \text{ (s, 1H, 3-H)}, 7.92-7.94 \text{ (m, 3H, 12,17,20-H)}, 8.02 \text{ (dd, J = 8.5, 1.7 Hz, 1H, 11-H)}, 8.48 \text{ (s, 1H, 19-H)}; \(^{13}\text{C NMR} (150 \text{ MHz, CDCl}_3) \): \( \delta_C = 110.8 \text{ (C-5)}, 111.0 \text{ (C-3)}, 115.8 \text{ (C-23)}, 122.4 \text{ (C-22)}, 124.1 \text{ (C-11)}, 124.9 \text{ (C-19)}, 126.3 \text{ (C-15,16)}, 127.9 \text{ (C-14)}, 128.4 \text{ (overlapping signals, C-12,17)}, 128.7 \text{ (C-6)}, 130.6 \text{ (overlapping signals, C-10,21)}, 133.4 \text{ (C-13)}, 133.7 \text{ (C-9)}, 133.8 \text{ (C-18)}, 142.7 \text{ (C-24)}, 144.7 \text{ (C-2)}, 146.8 \text{ (C-8)}; \text{LRMS m/z (ES\textsuperscript{+}): 352 [M+H]\textsuperscript{+}, 338, 181; HRMS m/z (ES\textsuperscript{+}): Found 352.1563 [M+H]\textsuperscript{+}; C\textsubscript{22}H\textsubscript{18}N\textsubscript{5} requires 352.1562.

\textit{N-(4-(2-(Naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-ylamino)phenyl)methanesulfonamide (27)}

All glassware was dried and purged with Ar prior to use. Pd\textsubscript{2}(dba\textsubscript{3}) (1.64 mg, 1 mol%), DavePhos (2.11 mg, 3 mol%) and NaO\textsubscript{t}Bu (24.1 mg, 0.250 mmol) were dissolved in anhydrous toluene. \textbf{21a} (50.0 mg, 0.179 mmol) and \textit{N-(4-aminophenyl)methanesulfonamide\textsuperscript{7}} (39.9 mg, 0.215 mmol) were added and the reaction was stirred under reflux, under Ar for 20 h. The reaction was cooled to RT and the solvent removed in vacuo, before the residue was taken up in CH₂Cl₂ (50 mL) and washed with NaHCO\textsubscript{3} (30 mL), H₂O (30 mL) and brine (30 mL), dried (MgSO₄), filtered and concentrated in vacuo. Flash chromatography (applied in toluene; eluted 2:1
toluene/EtOAc) afforded the title compound as an off white solid (5.2 mg, 0.012 mmol, 7%). Mpt: Decomposed before melting; \( R_f = 0.32 \) (1:1 toluene/EtOAc); IR (\( \nu_{\text{max}}/\text{cm}^{-1}, \text{thin film} \)): 3248, 3056, 2926, 2854, 1624, 1543, 1508; \(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta_H \) = 3.01 (s, 3H, 27-H), 6.39 (s, 1H, 25-H), 7.27-7.29 (m, 2H, 23-H), 7.47 (d, \( J = 4.6 \) Hz, 1H, 6-H), 7.49-7.54 (m, 2H, 15,16-H), 7.60 (d, \( J = 4.6 \) Hz, 1H, 5-H), 7.87 (d \( J = 7.8 \) Hz, 1H, 14-H), 7.92-7.95 (m, 5H, 3,12,17,22-H), 8.02 (dd, \( J = 8.5, 1.6 \) Hz, 1H, 11-H), 8.18 (s, 1H, 20-H), 8.48 (s, 1H, 19-H); \(^1^3\)C NMR (150 MHz, CDCl\(_3\)): \( \delta_C \) = 39.3 (C-27), 111.2 (C-3), 111.9 (C-5), 128.2 (C-6), 120.8 (C-22), 123.3 (C-23), 124.1 (C-11), 125.0 (C-19), 126.4 (C-15), 126.6 (C-16), 127.9 (C-14), 128.2 (C-17), 128.8 (C-12), 130.4 (C-10), 131.1 (C-24), 133.4 (C-13), 133.7 (overlapping signals, C-9,18), 137.7 (C-21), 145.1 (C-2), 146.1 (C-8); LRMS m/z (ES\(^+\)): 430 [M+H\(^+\)]; HRMS m/z (ES\(^+\)): Found 430.1324 [M+H\(^+\)]; C\(_{23}\)H\(_{30}\)N\(_5\)O\(_2\)S requires 430.1338.

4-Methyl-N-(4-(2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-yloxy)phenyl)benzenesulfonamide (28)

NaH (60% in mineral oil; 12.4 mg, 0.310 mmol) was washed by stirring in anhydrous hexanes (3 mL) for 20 min, removing the solvent using a syringe and drying the contents under high vacuum. DMF (0.5 mL) was added followed by \( N \)-(4-hydroxyphenyl)-4-methylbenzenesulfonamide\(^8\) (81.4 mg, 0.310 mmol) in DMF (1 mL) and the mixture was stirred at RT for 20 min. 24 (50.0 mg, 0.155 mmol) in DMF (1.5 mL) was added and the resulting deep red solution was heated at 100 °C under Ar for 16 h. The mixture was then diluted with EtOAc (50 mL) and washed with NH\(_4\)Cl (sat. aq. 20 mL) and H\(_2\)O (5 x 20 mL). The combined aqueous layers were then re-extracted with EtOAc (2 x 30 mL), followed by washing the combined organics with brine (30 mL), drying (MgSO\(_4\)),

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filtering and concentrating *in vacuo*. The crude material was purified via flash chromatography (applied in toluene; eluted 25% EtOAc/toluene) to give the title compound as an off white-pink solid (36.4 mg, 0.072 mmol, 47%). Mpt: 128 °C; $R_f = 0.21$ (2:1 toluene/EtOAc); IR ($\nu_{\text{max}}$/cm$^{-1}$, thin film): 3568, 3049, 1488; $^1$H NMR (600 MHz, (CD$_3$)$_2$SO): δ$H = 2.39$ (s, 3H, 31-H), 7.15-7.17 (m, 2H, 23-H), 7.21-7.13 (m, 2H, 22-H), 7.33 (d, $J = 4.6$ Hz, 1H, 6-H), 7.39 (d, $J = 8.2$ Hz, 2H, 29-H), 7.52-7.56 (m, 2H, 15,16-H), 7.70 (d, $J = 8.2$ Hz, 2H, 28-H), 7.94 (d, $J = 7.6$ Hz, 1H, 17-H), 8.01-8.04 (m, 2H, 12,14-H), 8.15 (dd, $J = 8.5$, 1.6 Hz, 1H, 11-H), 8.32 (d, $J = 4.6$ Hz, 1H, 5-H), 8.61 (s, 1H, 19-H), 8.74 (s, 1H, 3-H), 10.34 (s, 1H, 25-H); $^{13}$C NMR (150 MHz, (CD$_3$)$_2$SO): δ$C = 21.0$ (C-31), 112.9 (C-3), 116.9 (C-5), 121.3 (C-23), 122.7 (C-22), 124.0 (C-11), 124.5 (C-19), 125.5 (C-6), 126.4 (C-15), 126.6 (C-16), 126.8 (C-28), 127.7 (C-17), 128.3 (C-14), 128.5 (C-12), 129.9 (C-29), 130.4 (C-10), 132.8 (C-9), 132.9 (C-13), 133.2 (C-18), 135.0 (C-24), 136.7 (C-27), 143.4 (C-30), 145.1 (C-2), 148.7 (C-21), 153.1 (C-8); LRMS m/z (ES$^-$): 505 [M-H]$^-$; HRMS m/z (ES$^-$): Found 505.1323 [M+H]$^+$; C$_{29}$H$_{33}$N$_4$O$_3$S requires 505.1334.

*N-(4-Aminobenzyl)-2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-amine*

All glassware was dried and purged with Ar prior to use. Pd$_2$(dba)$_3$ (1.64 mg, 1 mol%), DavePhos (2.11 mg, 3 mol%) and NaO'Bu (24.1 mg, 0.250 mmol) were dissolved in anhydrous toluene (2 mL). 21a (50.0 mg, 0.179 mmol) and 4-(aminomethyl)aniline (24.3 µL, 0.215 mmol) were added and the reaction was stirred under reflux, under Ar for 20 h. The reaction was cooled to RT and solvent removed *in vacuo*, before the residue was taken up in CH$_2$Cl$_2$ (50 mL) and washed with NaHCO$_3$ (sat. aq. 30 mL), H$_2$O (30 mL) and brine (30 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo*. Flash
chromatography (applied in pet. ether; eluted 4:1 to 3:1 to 2:1 to 1:1 to 1:3 pet.
ether/EtOAc) afforded the title compound as a light yellow oil (20.1 mg, 0.055 mmol,
31%). \( R_f = 0.52 \) (3:1 EtOAc/pet. ether); IR (\( \nu_{\text{max}}/\text{cm}^{-1} \), thin film): 3326, 1619, 1544,
1519; \( ^1H \) NMR (600 MHz, CD\(_3\)OD): \( \delta_H = 4.58 \) (s, 2H, \( 21-H \)), 6.71-6.74 (m, 2H, \( 24-H \)),
7.19 (d, \( J = 8.4 \) Hz, 2H, \( 23-H \)), 7.25 (d, \( J = 4.7 \) Hz, 1H, \( 6-H \)), 7.44-7.49 (m, 2H, \( 15,16-H \)),
7.65 (d, \( J = 4.7 \) Hz, 1H, \( 5-H \)), 7.82-7.84 (m, 1H, \( 14-H \)), 7.85-7.88 (m, 2H, \( 12,17-H \)),
7.94 (dd, \( J = 8.5, 1.6 \) Hz, 1H, \( 11-H \)), 8.16 (s, 1H, \( 3-H \)), 8.34 (s, 1H, \( 19-H \)); \( ^{13}C \) NMR
(150 MHz, CD\(_3\)OD): \( \delta_C = 45.5 \) (C-21), 111.5 (C-5), 113.1 (C-3), 116.7 (C-24), 124.9 (C-
11), 125.5 (C-19), 127.2 (C-15), 127.5 (C-16), 128.7 (C-14), 129.1 (C-6), 129.2 (C-17),
129.9 (C-22), 129.5 (C-12), 131.7 (C-10), 134.6 (overlapping signals, C-
9,13), 135.0 (C-18), 145.4 (C-2), 148.1 (C-25), 149.8 (C-8); LRMS m/z (ES\(^+\)): 366
[M+H]\(^+\), 273 [M-aniline]\(^+\), 261 [M-CH\(_2\)-aniline]\(^+\); HRMS m/z (ES\(^+\)): Found 366.1716
[M+H]\(^+\); C\(_{23}\)H\(_{20}\)N\(_5\) requires 366.1719.

4-Methyl-N-(4-((2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-ylamino)methyl)-
phenyl)benzenesulfonamide (29)

N-(4-Aminobenzyl)-2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-amine (18.0 mg, 0.049
mmol) was dissolved in anhydrous pyridine (1 mL) and the mixture was cooled on ice.
4-Methylbenzene-1-sulfonyl chloride (11.3 mg, 0.059 mmol) was added and the deep
yellow/orange solution was stirred under Ar at RT for 16 h. The solvent was then
removed \textit{in vacuo} and the crude material was purified \textit{via} flash chromatography (applied
in CH$_2$Cl$_2$; eluted 10% to 20% EtOAc) to afford the title compound as pale green sticky solid (8.20 mg, 0.016 mmol, 32%). $R_f = 0.44$ (20% EtOAc/CH$_2$Cl$_2$); IR ($\nu_{\text{max}}$/cm$^{-1}$, thin film): 3240, 3050, 2923, 2823, 1544, 1509; $^1$H NMR (600 MHz, CDCl$_3$): $\delta_H = 2.47$ (s, 3H, 32-H), 4.76 (bs, 2H, 21-H), 6.49 (bs, 1H, 20-H), 6.73 (bs, 1H, 26-H), 7.03 (d, $J = 8.5$ Hz, 2H, 24-H), 7.22 (d, $J = 8.2$ Hz, 2H, 30-H), 7.29 (d, $J = 8.5$ Hz, 2H, 23-H), 7.35 (d, $J = 4.5$ Hz, 1H, 6-H), 7.46-7.51 (m, 3H, 5,15,16-H), 7.64 (d, $J = 8.2$ Hz, 2H, 29-H), 7.83-7.85 (m, 1H, 14-H), 7.87-7.90 (m, 3H, 3,12,17-H), 7.95 (dd, $J = 8.6$, $1.2$ Hz, 1H, 11-H), 8.40 (s, 1H, 19-H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta_C = 21.7$ (CH$_3$), 44.2 (C-21), 110.3 (C-5), 111.0 (C-3), 122.0 (C-24), 124.0 (C-11), 124.8 (C-19), 126.3 (C-15), 126.6 (C-16), 127.4 (C-29), 127.9 (Overlapping signals, C-12,17), 128.7 (C-6), 129.0 (C-23), 129.8 (C-30), 130.5 (C-10), 133.3 (C-13), 133.6 (C-9), 133.7 (C-18), 135.6 (C-22), 135.8 (C-25), 136.2 (C-28), 144.0 (C-31), 144.6 (C-2), 148.8 (C-8); LRMS m/z (ES$^-$): 518 [M-H$^-$]; HRMS m/z (ES$^-$): Found 518.1658 [M-H$^-$]; C$_{30}$H$_{24}$N$_5$O$_2$S requires 518.1651.

**N-(3-aminopropyl)-4-methylbenzenesulfonamide**

![](image)

1,3-Diaminopropane (2.0 g, 27 mmol) and triethylamine (5.5 g, 54 mmol) were dissolved in a 2/1 solvent mixture of CH$_2$Cl$_2$/THF (50 mL). The resulting solution was stirred at room temperature and 4-methylbenzenesulfonyl chloride (2.5 g, 13 mmol) was added portion-wise over 2 h. The reaction was quenched by addition of 1 M HCl (50 mL). The biphasic mixture was extracted with 1 M HCl (20 mL x 2). The combined aqueous layers were basified with 2 M NaOH (50 mL) and extracted with CH$_2$Cl$_2$ (3 x 50 mL). The organic layers were combined, dried (MgSO$_4$), filtered and concentrated under reduced pressure to give a colourless solid (1.45 g, 49% yield) suitably pure for subsequent synthetic steps. Mpt: Decomposed before melting; $R_f = 0.25$ (15% MeOH in CH$_2$Cl$_2$); IR ($\nu_{\text{max}}$/cm$^{-1}$, thin film): 3359, 2673, 1598, 1492, 1318; $^1$H NMR (600 MHz, CDCl$_3$): $\delta_H = 1.58$ (app. qt, $J = 6.9$ Hz, 2H, 9-H), 2.43 (s, 3H, CH$_3$), 2.62 (t, $J = 6.2$ Hz, 2H, 10-H), 2.87 (t, $J = 6.2$ Hz, 2H, 8-H), 7.38 (d, $J = 8.2$ Hz, 2H, 3-H and 5-H), 7.72 (d, $J = 8.2$ Hz, 2H, 2-H and 6-H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta_C = 21.6$ (CH$_3$), 30.8 (C-9), 41.1 (C-10), 46.2 (C-3), 46.4 (C-11), 115.6 (C-5), 116.7 (C-15), 117.5 (C-16), 122.0 (C-29), 122.9 (Overlapping signals, C-12,17), 123.7 (C-6), 124.8 (C-19), 126.3 (C-14), 126.9 (C-23), 129.8 (C-30), 130.5 (C-10), 133.3 (C-13), 133.6 (C-9), 133.7 (C-18), 135.6 (C-22), 135.8 (C-25), 136.2 (C-28), 144.0 (C-31), 144.6 (C-2), 148.8 (C-8); LRMS m/z (ES$^-$): 518 [M-H$^-$]; HRMS m/z (ES$^-$): Found 518.1658 [M-H$^-$]; C$_{30}$H$_{24}$N$_5$O$_2$S requires 518.1651.
43.3 (C-8), 127.2 (C-2 and C-6), 129.8 (C-3 and C-5), 137.2 (C-1), 143.2 (C-4); HRMS m/z (Cl+): Found 229.10124 [M+H]+; C10H17N2O2S requires 229.10107.

4-Methyl-N-(3-(2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-ylamino)propyl)-benzenesulfonamide (30)

To a solution of N-(3-aminopropyl)-4-methylbenzenesulfonamide (73.1 mg, 0.322 mmol) in anhydrous DMF (2 mL) was added DIPEA (56.1 µL, 0.322 mmol) followed by 24 (52.0 mg, 0.161 mmol) and the reaction mixture was stirred at 100 °C for 16 h. Cooling to RT and removal of the solvent was followed by flash chromatography (applied in toluene; eluted 2:1 toluene/EtOAc), which yielded the title compound as a white solid (24.9 mg, 0.053 mmol, 33%). Mpt: Decomposed before melting; Rf = 0.26 (3:1 EtOAc/pet. ether); IR (νmax/cm−1, thin film): 3023, 2971, 1740, 1548, 1370, 1217; 1H NMR (600 MHz, CDCl3): δH = 1.79-1.81 (m, 2H, 22-H), 2.35 (s, 3H, 30-H), 3.00 (bd, J = 5.4 Hz, 2H, 23-H), 3.68 (q, J = 5.8 Hz, 2H, 21-H), 6.27 (bs, 1H, 20-H), 7.02 (bs, 1H, 24-H), 7.21 (d, J = 8.2 Hz, 2H, 28-H), 7.33 (d, J = 4.7 Hz, 1H, 6-H), 7.43 (d, J = 4.6 Hz, 1H, 5-H), 7.46-7.51 (m, 2H, 15,16-H), 7.72 (d, J = 8.2 Hz, 2H, 27-H), 7.84-7.85 (m, 2H, 12,17-H), 7.95 (dd, J = 8.5, 1.6 Hz, 1H, 11-H), 8.38 (s, 1H, 19-H); 13C NMR (150 MHz, CDCl3): δC = 21.6 (C-30), 30.3 (C-22), 38.3 (C-21), 39.7 (C-23), 110.2 (C-5), 111.1 (C-3), 124.0 (C-11), 124.7 (C-19), 126.3 (C-15), 126.6 (C-16), 127.1 (C-27), 127.9 (C-14), 128.1 (C-6), 128.4 (C-17), 128.7 (C-12), 129.7 (C-28), 130.5 (C-10), 133.3 (C-9,13), 133.7 (C-18), 137.6 (C-26), 143.1 (C-29),
144.8 (C-2), 149.7 (C-8); LRMS m/z (ES\(^+\)) 472 [M+H]\(^+\); HRMS m/z (EI\(^+\)): Found 471.1726 [M]\(^+\); \(\text{C}_{26}\text{H}_{25}\text{N}_{5}\text{O}_{2}\text{S}\) requires 471.1724.

**N-(2-Aminoethyl)-4-methylbenzenesulfonamide**

\[
\begin{align*}
\text{S} & \quad \text{O} \\
\text{N} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{NH}_2 & 
\end{align*}
\]

1,2-Diaminoethane (2.0 g, 33 mmol) and triethylamine (6.7 g, 75 mmol) were dissolved in a 2/1 solvent mixture of \(\text{CH}_2\text{Cl}_2/\text{THF}\) (50 mL). The resulting solution was stirred at room temperature and 4-methylbenzenesulfonyl chloride (3.2 g, 17 mmol) was added portion-wise over 2 h. The reaction was quenched by addition of 1 M HCl (50 mL). The biphasic mixture was extracted with 1 M HCl (20 mL x 2). The combined aqueous layers were basified with 2 M NaOH (50 mL) and extracted with \(\text{CH}_2\text{Cl}_2\) (50 mL x 3). The organic layers were combined, dried (MgSO\(_4\)), filtered and concentrated under reduced pressure to give a colourless solid (2.1 g, 59% yield) suitably pure for subsequent synthetic steps. Mpt: Decomposed before melting; \(R_f = 0.22\) (15% MeOH in \(\text{CH}_2\text{Cl}_2\)); IR (\(v_{\text{max}}/\text{cm}^{-1}\), thin film): 3360, 2644, 1598, 1493, 1317; 1H NMR (600 MHz, CD\(_3\)OD): \(\delta_H = 2.42\) (s, 3H, \(\text{CH}_3\)), 2.65 (t, \(J = 6.2\) Hz, 2H, \(\text{8-H}\)), 2.89 (t, \(J = 6.2\) Hz, 2H, \(\text{7-H}\)), 7.38 (d, \(J = 8.2\) Hz, 2H, \(\text{3-H and 5-H}\)), 7.73 (d, \(J = 8.2\) Hz, 2H, \(\text{2-H and 6-H}\)); 13C NMR (150 MHz, CD3OD): \(\delta_C = 21.4\) (\(\text{CH}_3\)), 42.2 (C-8), 46.4 (C-7), 128.0 (C-2 and C-6), 130.8 (C-3 and C-5), 138.8 (C-1), 144.7 (C-4); HRMS m/z (EI\(^+\)): Found 215.08564 [M+H]\(^+\); \(\text{C}_{9}\text{H}_{15}\text{O}_{2}\text{N}_{3}\text{S}\) requires 215.08542.
4-Methyl-N-(2-(2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-ylamino)ethyl)benzene-sulfonamide (31)

To a solution of N-(2-aminoethyl)-4-methylbenzenesulfonamide (65.9 mg, 0.310 mmol) in anhydrous DMF (2 mL) was added DIPEA (53.9 µL, 0.310 mmol) followed by 24 (50.0 mg, 0.155 mmol) and the reaction mixture was stirred at 100 °C for 16 h. Cooling to RT and removal of the solvent was followed by flash chromatography (applied in toluene; eluted 2:1 toluene/EtOAc), which yielded the title compound as a white solid (15 mg, 0.033 mmol, 21%). Mpt: 158-160 °C; Rf = 0.26 (3:1 EtOAc/pet. ether); IR (νmax/cm⁻¹, thin film): 3412, 3029, 2924, 2853, 1621, 1538; ¹H NMR (600 MHz, CDCl₃): δH = 2.24 (s, 3H, 29-H), 3.32 (bd, J = 4.7 Hz, 2H, 22-H), 3.70-3.73 (m, 2H, 21-H), 6.32 (bs, 1H, 20-H), 6.55 (bs, 1H, 23-H), 7.10 (d, J = 8.1 Hz, 2H, 27-H), 7.29 (d, J = 4.6 Hz, 1H, 6-H), 7.45 (d, J = 4.6 Hz, 1H, 5-H), 7.48-7.52 (m, 2H, 15,16-H), 7.63 (d, J = 8.2 Hz, 2H, 26-H), 7.85-7.86 (m, 2H, 3,14-H), 7.88-7.91 (m, 2H, 12,17-H), 7.94 (d, J = 8.4 Hz, 1H, 11-H), 8.37 (s, 1H, 19-H); ¹H NMR (600 MHz, (CD₃)₂SO): δH = 2.30 (s, 3H, 29-H), 3.03 (q, J = 6.3 Hz, 2H, 22-H), 3.53 (q, J = 6.3 Hz, 2H, 21-H), 7.23-7.24 (m, 3H, 6,27-H), 7.45 (t, J = 5.9 Hz, 1H, 20-H), 7.50-7.56 (m, 2H, 15,16-H), 7.63 (d, J = 8.2 Hz, 2H, 26-H), 7.67 (t, J = 5.5 Hz, 1H, 23-H), 7.77 (d, J = 4.6 Hz, 1H, 5-H), 7.94 (d, J = 7.9 Hz, 1H, 14-H), 7.96 (d, J = 7.9 Hz, 1H, 17-H), 8.00 (d, J = 8.6 Hz, 1H, 12-H), 8.11 (dd, J = 8.6, 1.6 Hz, 1H, 11-H), 8.46 (s, 1H, 3-H), 8.52 (s, 1H, 19-H); ¹³C NMR (150 MHz, CDCl₃): δc = 21.6 (C-29), 40.7 (C-21), 45.0 (C-22), 110.6 (C-5), 111.0 (C-3), 124.0 (C-11), 124.8 (C-19), 126.4 (C-15), 126.6 (C-16), 127.0 (C-26), 127.9 (C-6,14), 128.4 (C-17), 128.7 (C-12), 129.5 (C-27), 130.4 (C-10), 133.2 (C-9), 133.4 (C-13), 133.7 (C-18), 137.0 (C-25), 143.3 (C-28), 144.9 (C-2), 149.5 (C-8); ¹³C NMR (150 MHz, (CD₃)₂SO):
δC = 21.0 (C-29), 40.1 (C-21), 41.6 (C-22), 110.3 (C-5), 112.0 (C-3), 123.8 (C-19), 124.1 (C-11), 126.1 (C-15), 126.6 (C-16), 126.6 (C-26), 127.7 (C-14), 128.0 (C-17), 128.1 (C-6), 128.3 (C-12), 129.4 (C-27), 131.0 (C-10), 132.6 (C-13), 132.9 (C-9), 133.2 (C-18), 137.3 (C-25), 142.4 (C-28), 143.0 (C-2), 148.4 (C-8); LRMS m/z (ES⁺): 458 [M+H]⁺; HRMS m/z (EI⁺): Found 458.1656 [M+H]⁺; C_{25}H_{24}N_{5}O_{2}S requires 458.1651.

2-(Naphthalen-2-yl)-N-(3-(pyridin-3-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (32)

All glassware was dried and purged with Ar prior to use. Pd₂(dba)₃ (1.28 mg, 1 mol%), DavePhos (1.65 mg, 3 mol%) and NaO'Bu (18.8 mg, 0.195 mmol) were dissolved in anhydrous toluene (2 mL). 21a (39.0 mg, 0.140 mmol) and 3-(pyridin-3-yl)aniline⁹ (28.5 mg, 0.168 mmol) were added and the reaction was stirred under reflux, under Ar for 16 h. The reaction was cooled to RT, and solvent removed in vacuo. The crude material was taken up in CH₂Cl₂ (50 mL) and washed H₂O (30 mL) and NaHCO₃ (sat. aq. 30 mL). The combined aqueous layers were then re-extracted with CH₂Cl₂ (2 x 30 mL) followed by washing the combined organics with brine (30 mL), drying (MgSO₄), filtering and concentrating in vacuo. Purification by flash chromatography (applied in toluene; eluted 20% to 33% EtOAc) afforded the title compound as a sticky brown solid (18.9 mg, 0.046 mmol, 33%). Rₚ = 0.26 (1:1 toluene/EtOAc); IR (νₑₑₑ/cm⁻¹, thin film): 2922, 1514; ¹H NMR (600 MHz, CDCl₃): δH = 7.32 (d, J = 7.8 Hz, 1H, 24-H), 7.42 (dd, J = 7.8, 4.8 Hz, 1H, 31-H), 7.49-7.53 (m, 4H, 6,15,16,25-H), 7.61 (d, J = 4.6 Hz, 1H, 5-H), 7.87 (d, J = 7.8 Hz, 1H, 14-H), 7.92 (dd, J = 8.2, 1.6 Hz, 1H, 26-H), 7.93-7.95 (m, 3H, 3,12,17-H), 7.98 (dt, J = 7.8, 1.9 Hz, 1H, 32-H), 8.03 (dd, J = 8.5, 1.6 Hz, 1H, 11-H), 8.28 (bt, J = 1.6 Hz, 1H, 22-H), 8.32 (bs, 1H, 20-H), 8.49 (s, 1H, 19-H), 8.62 (dd, J = 4.8, 1.4 Hz, 1H, 30-
H), 8.94 (d, J = 1.9 Hz, 1H, 28-H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$C = 111.2 (C-3), 111.8 (C-5), 118.3 (C-22), 119.3 (C-26), 121.8 (C-24), 123.8 (C-31), 124.1 (C-11), 125.0 (C-19), 126.4 (C-15), 126.6 (C-16), 127.9 (C-14), 128.4 (C-17), 128.5 (C-6), 128.7 (C-12), 129.9 (C-25), 130.4 (C-10), 133.4 (C-13), 133.7 (C-18), 133.8 (C-9), 134.9 (C-32), 136.8 (C-27), 138.7 (C-23), 140.2 (C-21), 145.0 (C-2), 146.2 (C-8), 148.4 (C-28), 148.4 (C-30); LRMS m/z (ES$^+$): 414 [M+H]$^+$; HRMS m/z (ES$^+$): Found 414.1706 [M+H]$^+$; C$_{27}$H$_{20}$N$_5$ requires 414.1719.

N-(4-(2-(Naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)phenyl)quinoline-8-sulfonamide (33)

To a stirred solution of 26 (10.0 mg, 0.029 mmol), quinoline-8-sulfonyl chloride (14.3 mg, 0.062 mmol, 2.2 eq.) and DMAP (cat.) in anhydrous CH$_2$Cl$_2$ (2 mL), under N$_2$, was added Et$_3$N (23 $\mu$L, 0.165 mmol, 5.7 eq.) and the reaction stirred at room temperature for 16h. The crude reaction mixture was washed with H$_2$O (5 mL) and sat. NaHCO$_3$ (5 mL). The organic fractions were dried (MgSO$_4$), concentrated and purified by column chromatography (applied in CH$_2$Cl$_2$; eluted 100% to 20% EtOAc/CH$_2$Cl$_2$) to give the product as a pale green oil (2.5 mg, 0.005 mmol, 16%). $R_f$ = 0.58 (1:1 EtOAc/CH$_2$Cl$_2$); $^1$H NMR (600 MHz, CDCl$_3$): $\delta$H = 7.01 (d, J = 8.8 Hz, 2H, 23-H), 7.35 (d, J = 4.6 Hz, 1H, 6-H), 7.47-7.51 (m, 2H, 15,16-H), 7.52 (d, J = 4.6 Hz, 1H, 5-H), 7.58 (t, J = 7.6 Hz, 1H, 31-H), 7.63-7.66 (m, 3H, 22,35-H), 7.85 (d, J = 7.7 Hz, 1H, 14-H), 7.89 (s, 1H, 3-H), 7.90-7.92 (m, 2H, 12,17-H), 7.95 (bs, 1H, 19-H), 7.98 (dd, J = 1.6 and 8.5 Hz, 1H, 32-H), 8.03 (dd, J = 1.3 and 8.2 Hz, 1H, 11-H), 8.31 (dd, J = 1.7 and 8.4 Hz, 1H, 34-H), 8.34 (dd, J = 1.3 and 7.4 Hz, 1H, 30-H), 8.40 (bs, 1H, H-27), 8.43 (bs, 1H, H-20), 9.18 (dd, J = 1.7 and 4.3 Hz, 1H, 36-H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$C = 111.1, 111.7,
120.0, 122.5, 123.7, 124.0, 124.9, 126.0, 126.3, 126.6, 127.9-128.9 (overlap), 131.8, 132.1, 133.4, 133.7, 135.5, 137.2, 137.4, 143.3, 151.4; LRMS m/z (CI\(^+\)): 542 [M]\(^+\); HRMS m/z (CI\(^+\)): Found 542.15172 [M]\(^+\); C\(_{31}\)H\(_{22}\)N\(_6\)O\(_2\)S requires 542.15195.

**N-(2-(Naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-yl)benzene-1,3-diamine**

All glassware was dried and purged with Ar prior to use. Pd\(_2\)(dba)\(_3\) (16.4 mg, 2 mol%), DavePhos (17.6 mg, 5 mol%) and NaO'Bu (172 mg, 1.78 mmol) were dissolved in anhydrous toluene (5 mL). 21a (250 mg, 0.89 mmol) and 1,3-diaminobenzene (97 mg, 0.89 mmol) were added and the reaction was stirred at 120 °C in a sealed tube for 16 h. The reaction was cooled to RT and solvent removed in vacuo, before the residue was taken up in CH\(_2\)Cl\(_2\) (25 mL) and washed with H\(_2\)O (2 x 50 mL) and brine (50 mL), dried (MgSO\(_4\)), filtered and concentrated in vacuo. Flash chromatography (applied in CH\(_2\)Cl\(_2\); eluted 15:1 to 5:1 to 1:1 CH\(_2\)Cl\(_2\)/EtOAc) afforded the title compound as a sticky brown oil (90 mg, 0.26 mmol, 29%). \(R_f = 0.59\) (1:1 CH\(_2\)Cl\(_2\)/EtOAc); \(^1\)H NMR (600 MHz, CDCl\(_3\)); \(\delta_H = 3.76\) (bs, 2H, 27-H), 6.44 (app d, \(J = 7.6\) Hz, 1H, 24-H), 7.13-7.19 (m, 2H, 5, 15, 16-H), 7.56 (d, \(J = 4.5\) Hz, 1H, 26-H), 7.86 (d, \(J = 7.7\) Hz, 1H, 17-H), 7.92-7.95 (m, 3H, 3, 12, 14-H), 8.02 (dd, \(J = 1.6\) Hz and 8.5 Hz, 1H, 11-H), 8.06 (s, 1H, 20-H), 8.48 (s, 1H, 19-H); \(^13\)C NMR (150 MHz, CDCl\(_3\)); \(\delta_C = 106.3, 110.1, 110.1, 111.1, 111.4, 124.1, 124.9, 126.3, 126.6, 127.9, 128.4, 128.4, 128.7, 129.9, 130.6, 133.4, 133.8, 140.4, 144.9, 146.3, 147.3; LRMS m/z (CI\(^+\)): 351 [M]\(^+\); HRMS m/z (CI\(^+\)): Found 351.14749 [M]\(^+\); C\(_{22}\)H\(_{17}\)N\(_5\) requires 351.14785.
N-(3-((2-(Naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)phenyl)quinoline-8-sulfonamide (34)

To a stirred solution of N-(2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-yl)benzene-1,3-diamine (10.0 mg, 0.029 mmol), quinoline-8-sulfonyl chloride (14.3 mg, 0.062 mmol, 2.2 eq.) and DMAP (cat.) in anhydrous CH₂Cl₂ (2 mL), under N₂, was added Et₃N (23 µL, 0.165 mmol, 5.7 eq.) and the reaction stirred at room temperature for 16 h. The crude reaction mixture was washed with H₂O (5 mL) and sat. NaHCO₃ (5 mL), organic fractions dried (MgSO₄), concentrated and purified by column chromatography (applied in CH₂Cl₂; eluted 100% to 20% EtOAc/CH₂Cl₂) to give the product as a pale green oil (3.4 mg, 0.006 mmol, 21%). Rᵣ = 0.68 (1:1 EtOAc/CH₂Cl₂); ¹H NMR (600 MHz, CDCl₃): 6.75 (d, J = 7.9 Hz, 2H, 24-H), 7.12 (t, J = 8.5 Hz, 2H, 23-H), 7.34 (d, J = 4.4 Hz, 1H, 6-H), 7.49-7.54 (m, 2H, 15,16-H), 7.55 (d, J = 4.5 Hz, 1H, 5-H), 7.58 (t, J = 7.8 Hz, 1H, 31-H), 7.63 (m, 3H, 22,26,35-H), 7.87 (d, J = 7.9 Hz, 1H, 14-H), 7.91 (s, 1H, 3-H), 7.92-7.96 (m, 3H, 12,17,19-H), 7.99-8.02 (m, 2H, 11,32-H), 8.29 (d, J = 8.3 Hz, 1H, 34-H), 8.40 (d, J = 7.3 Hz, 1H, 30-H), 8.47 (s, 1H, H-27), 8.48 (s, 1H, H-20), 9.21 (dd, J = 1.4 and 4.2 Hz, 1H, 36-H); ¹³C NMR (150 MHz, CDCl₃): 111.1, 116.5, 122.4, 124.0, 125.9, 126.6, 127.9, 128.1, 128.5, 128.9, 129.6, 132.1, 133.8, 135.4, 137.3, 137.8, 140.0, 143.3, 151.4; LRMS m/z (Cl⁺): 542 [M⁺]; HRMS m/z (Cl⁺): Found 542.15113 [M⁺]; C₃₁H₂₂N₆O₂S requires 542.15195.
Second generation imidazo[1,2-a]pyrazine inhibitors, variants at 2- and 6-positions.

8-Chloroimidazo[1,2-a]pyrazine

![Chemical Structure](image)

2-Amino-3-chloropyrazine (200 mg, 1.54 mmol) and NaHCO₃ (162 mg, 1.93 mmol) were suspended in tBuOH. Chloroacetaldehyde (50% w/v in H₂O; 200 µL, 1.54 mmol) was added and the reaction mixture was stirred under reflux for 40 h. The reaction was then cooled to RT and solvent removed in vacuo. The residual material was taken up in CH₂Cl₂ (100 mL) washed H₂O (40 mL) and brine (40 mL), dried (MgSO₄), filtered and concentrated in vacuo. Flash chromatography (applied in pet. ether; eluted 3:1 to 2:1 to 1:3 pet. ether/EtOAc) afforded the title compound as an off white solid (118 mg, 0.773 mmol, 50%). Mp: Decomposed before melting; \( R_f = 0.17 \) (2:1 EtOAc/pet. ether); IR (\( \nu_{max}/\text{cm}^{-1}, \text{thin film} \)): 3144, 3105, 1432; \(^1\)H NMR (600 MHz, (CD₃)₂SO): \( \delta_H = 7.73 \) (d, \( J = 4.5 \) Hz, 1H, 6-H), 7.87 (d, \( J = 0.9 \) Hz, 1H, 2-H), 8.28 (d, \( J = 0.9 \) Hz, 1H, 3-H), 8.66 (d, \( J = 4.5 \) Hz, 1H, 5-H); \(^{13}\)C NMR (150 MHz, (CD₃)₂SO): \( \delta_C = 117.3 \) (C-3), 120.8 (C-5), 127.3 (C-6), 135.5 (C-2), 137.1 (C-9), 141.7 (C-8); LRMS m/z (Cl⁺): 154 [M(\(^{35}\)Cl)+H⁺], 156 [M(\(^{37}\)Cl)+H⁺]; HRMS m/z (Cl⁺): Found 154.0166 [M(\(^{35}\)Cl)+H⁺]; C₆H₅ClN₃ requires 154.0172.

\( N-(4-(\text{Imidazo}[1,2-a]\text{pyrazin-8-ylamino})\text{phenyl})-4\text{-methylbenzenesulfonamide (35)} \)

![Chemical Structure](image)

All glassware was dried and purged with Ar prior to use. Pd₂(dba)₃ (2.97 mg, 1 mol%), DavePhos (3.83 mg, 3 mol%) and NaO'Bu (43.8 mg, 0.456 mmol) were dissolved in anhydrous toluene (3 mL). 8-Chloroimidazo[1,2-a]pyrazine (49.8 mg, 0.324 mmol) and \( N-(4\text{-aminophenyl})-4\text{-methylbenzenesulfonamide} \) 23 (106 mg, 0.389 mmol) were added
and the reaction was stirred under reflux, under Ar for 16 h. The reaction was cooled to RT and solvent removed in vacuo, before the residue was taken up in CH₂Cl₂ (50 mL) and washed with H₂O (3 x 30 mL) and brine (30 mL), dried (MgSO₄), filtered and concentrated in vacuo. Flash chromatography (applied in pet. ether; eluted 2:1 pet. ether/EtOAc) afforded the title compound as a brown solid (69.7 mg, 0.184 mmol, 56%). Mpt: Decomposed before melting; Rₜ = 0.30 (3:1 EtOAc/pet. ether); IR (νmax/cm⁻¹, thin film): 3338, 3045, 1537, 1505; ¹H NMR (600 MHz, CDCl₃): δH = 2.37 (s, 3H, 21-H), 6.88 (s, 1H, 15-H), 7.06 (d, J = 8.8 Hz, 2H, 13-H), 7.21 (d, J = 8.3 Hz, 2H, 19-H), 7.45 (d, J = 4.6 Hz, 1H, 6-H), 7.56-7.57 (m, 3H, 2,3,5-H), 7.63 (d, J = 8.3 Hz, 2H, 18-H), 7.76 (d, J = 8.8 Hz, 2H, 12-H), 8.19 (s, 1H, 10-H); ¹³C NMR (150 MHz, CDCl₃): δC = 21.7 (C-21), 111.9 (C-5), 115.2 (C-3), 120.3 (C-12), 123.9 (C-13), 127.4 (C-18), 128.4 (C-6), 129.7 (C-19), 131.1 (C-14), 131.9 (C-2), 133.2 (C-9), 136.2 (C-17), 137.4 (C-11), 143.9 (C-20), 146.0 (C-8); LRMS m/z (ES⁺): 380 [M+H]⁺, 402 [M+Na]⁺; HRMS m/z (ES⁺): Found 380.1168 [M+H]⁺; C₁₉H₁₈N₅O₂S requires 380.1181.

2-(8-Chloroimidazo[1,2-α]pyrazin-2-yl)quinoxaline

2-Bromo-1-(quinoxalin-2-yl)ethanone¹⁰ (648 mg, 2.58 mmol), 2-amino-3-chloropyrazine (334 mg, 2.58 mmol) and NaHCO₃ (271 mg, 3.23 mmol) in tBuOH (15 mL) were stirred under reflux for 40 h. The solvent was removed in vacuo and the resulting residual was taken up in CH₂Cl₂ (100 mL) and washed H₂O (2 x 40 mL) and brine (40 mL), dried (MgSO₄), filtered and solvent removed in vacuo. Flash chromatography (applied in pet. ether; eluted 3:1 to 1:1 to 1:3 pet. ether/EtOAc) afforded the title compound as an orange solid (342 mg, 1.21 mmol, 47%). Mpt: >200 °C; Rₜ = 0.11 (1:1 pet. ether/EtOAc); IR (νmax/cm⁻¹, thin film): 2924, 1675, 1495; ¹H NMR (600 MHz, (CD₃)₂SO): δH = 7.84 (d, J = 4.5 Hz, 1H, 6-H), 7.89-7.95 (m, 2H, 14,15-H), 8.15-8.17 (m, 2H, 13,16-H), 8.73 (d, J = 4.5 Hz, 1H, 5-H), 9.08 (s, 1H, 3-H), 9.71 (s, 1H, 19-H); ¹³C NMR (150 MHz, (CD₃)₂SO): δC = 116.9 (C-3), 121.0 (C-5), 128.3 (C-6), 129.0 (C-13), 129.1 (C-16), 130.5 (C-15),
131.1 (C-14), 137.7 (C-9), 141.4 (C-12), 141.8 (C-17), 142.2 (C-8), 143.4 (C-19), 143.9 (C-10), 146.4 (C-2); LRMS m/z (CI): 282 [M^{35}Cl]+H]^+, 284 [M^{37}Cl]+H]^+; HRMS m/z (CI): Found 282.0552 [M^{35}Cl]+H]^+; C_{14}H_{9}ClN_{5} requires 282.0547.

4-Methyl-N-(4-(2-(quinoxalin-2-yl)imidazo[1,2-a]pyrazin-8-ylamino)phenyl)-benzenesulfonamide (36)

All glassware was dried and purged with Ar prior to use. Pd(dba)$_2$ (2.04 mg, 1 mol%), DavePhos (4.19 mg, 3 mol%) and Cs$_2$CO$_3$ (162 mg, 0.497 mmol) were stirred in dissolved in 1,4-dioxane (5 mL). 2-(8-Chloroimidazo[1,2-a]pyrazin-2-yl)quinoxaline (100 mg, 0.355 mmol) and N-(4-aminophenyl)-4-methylbenzenesulfonamide 23 (112 mg, 0.426 mmol) were added and the reaction was stirred under reflux for 40 h. The reaction was cooled to RT and solvent removed in vacuo. The resulting residue was taken up in CH$_2$Cl$_2$ (60 mL) and washed with NaHCO$_3$ (sat. aq. 40 mL), H$_2$O (30 mL) and brine (30 mL), dried (MgSO$_4$), filtered and solvent removed in vacuo. Flash chromatography (applied in toluene; eluted 0% to 50% EtOAc) afforded the title compound as a light yellow solid (12.3 mg, 0.024 mmol, 7%). Mpt: Decomposed before melting; $R_f = 0.49$ (1:1 CH$_2$Cl$_2$/EtOAc); IR ($\nu_{\max}$/cm$^{-1}$, thin film): 3135, 3061, 1495; $^1$H NMR (600 MHz, (CD$_3$)$_2$SO): $\delta_H = 2.34$ (s, 3H, 31-H), 7.05 (d, $J = 8.9$ Hz, 2H, 23-H), 7.35 (d, $J = 8.3$ Hz, 2H, 29-H), 7.44 (d, $J = 4.6$ Hz, 1H, 6-H), 7.64 (d, $J = 8.3$ Hz, 2H, 28-H), 7.84-7.86 (m, 1H, 15-H), 7.88-7.90 (m, 3H, 14,22-H), 8.03 (d, $J = 4.6$ Hz, 1H, 5-H), 8.10-8.14 (m, 2H, 13,16-H), 8.80 (s, 1H, 3-H), 9.61 (s, 1H, 20-H), 9.78 (s, 1H, 19-H), 10.06 (bs, 1H, 25-H); $^{13}$C NMR (150 MHz, (CD$_3$)$_2$SO): $\delta_C = 21.0$ (C-31), 112.5 (C-5), 115.9 (C-3), 121.1 (C-23), 121.2 (C-22), 126.8 (C-28), 128.2 (C-6), 128.8 (C-13), 129.1 (C-16), 129.7 (C-29), 129.9 (C-15), 130.9 (C-14), 132.1 (C-24), 133.4 (C-9), 136.6 (C-21), 136.7 (C-27), 138.9 (C-11), 139.5 (C-2).
141.2 (C-10), 141.4 (C-17), 141.5 (C-12), 143.1 (C-30), 143.7 (C-19), 146.1 (C-8), 147.0 (C-2) ; LRMS m/z (ES⁺): 530 [M+Na]⁺, 508 [M+H]⁺; HRMS m/z (ES⁺): Found 508.1565 [M+H]⁺; C₂₇H₂₂N₇O₂S requires 508.1556.

**3,5-Dibromopyrazin-2-amine**

![3,5-Dibromopyrazin-2-amine](image)

Pyrazin-2-amine (2.0g, 21 mmol) was dissolved in dichloromethane (50 mL) and the resulting solution was stirred at room temperature. N-bromosuccinimide (9.4g, 53mmol) was added. After completion, the mixture was concentrated under reduced pressure to give brown solid crude which was subsequently purified by chromatography (applied in hexane; eluted 10% EtOAc/hexane) to give the title compound as a pale yellow solid (3.6g 14 mmol, 68%). Mpt: 106-108 °C; Rf = 0.80 (1:1 EtOAc/hexane); IR (ν_max/cm⁻¹, thin film): 3447, 3280, 3154, 1621, 1549, 1506, 1450; ¹H NMR (600 MHz, CDCl₃): δ_H = 5.04 (brs, 2H, NH₂), 8.04 (s, 1H, 6-H); ¹³C NMR (150 MHz, CDCl₃): δ_C = 123.8 (C-5), 124.0 (C-3), 143.3 (C-6), 152.0 (C-2); HRMS m/z (CI⁺): found 251.87731 [M+H]⁺, C₄H₄Br₂N₃ requires 251.87720.
6,8-Dibromo-2-(naphthalene-2-yl)imidazo[1,2-a]pyrazine (39)

\[
\begin{array}{c}
\text{Br} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{Br} \\
\text{Br} \\
\text{N}
\end{array}
\]

3,5-Dibromopyrazin-2-amine (200 mg, 0.79 mmol) and 2-bromo-1-(naphthalene-2-yl)ethanone (490 mg, 2.0 mmol) were dissolved in ethanol (50 mL). A drop of concentrated HCl was added and the mixture was refluxed for 3 days at 80 °C. After completion, the mixture was allowed to reach room temperature and concentrated under reduced pressure. The resulting crude was subsequently purified by chromatography (applied in hexane; eluted 15% EtOAc/hexane) to give the title compound (80 mg, 0.19 mmol, 25%). R_f = 0.25 (1/3 EtOAc/hexane); IR (v_{max}/cm^{-1}, thin film): 3135, 1622, 1592, 1505, 1481, 1447; ¹H NMR (600 MHz, CDCl₃): δ_H = 7.52-7.56 (m, 2H, 15-H and 16-H), 7.85-7.88 (m, 1H, 14-H), 7.91-7.96 (m, 2H, 12-H and 17-H), 8.02-8.05 (m, 1H, 11-H), 8.13 (s, 1H, 3-H), 8.26 (s, 1H, 5-H), 8.54 (s, 1H, 19-H); ¹³C NMR (150 MHz, CDCl₃): δ_C = 111.9, 118.9, 120.3, 123.2, 124.1, 126.3, 126.8, 126.9, 127.9, 128.7, 128.8, 133.5, 133.9, 138.8, 149.6, 152.0; HRMS m/z (EI+): Found 400.91624 [M]+; C₁₆H₉Br₂N₃ requires 400.91577;

N-(4-((6-Bromo-2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)phenyl)-4-methylbenzenesulfonamide (37)

\[
\begin{array}{c}
\text{SO} \\
\text{O} \\
\text{N} \\
\text{NH} \\
\text{N} \\
\text{N} \\
\text{Br}
\end{array}
\]

23 (30 mg, 114 μmol) and N,N-diisopropylethylamine (31 μL, 178 μmol) were dissolved in n-butanol (10 mL) and the reaction was stirred at 120 °C for 14 h. After completion, the reaction mixture was concentrated under reduced pressure and purified by normal phase chromatography with a 25% EtOAc in hexane eluent. 34 mg (58 μmol, 51% yield)
of the product was isolated. \( R_f = 0.45 \) (2:1 EtOAc/hexane); 1H NMR (600 MHz, CDCl₃): \( \delta_H = 2.39 \) (s, 3H, 24-H), 7.10 (d, \( J = 8.4 \) Hz, 2H, 13-H and 15-H), 7.24 (d, \( J = 8.2 \) Hz, 2H, 20-H and 22-H), 7.48–7.56 (m, 2H, 30-H and 31-H), 7.63 (d, \( J = 8.2 \) Hz, 2H, 19-H and 23-H), 7.74 (s, 1H, 3-H), 7.81 (d, \( J = 8.4 \) Hz, 2H, 12-H and 16-H), 7.87 (d, \( J = 8.4 \) Hz, 1H, 29-H), 7.88 (s, 1H, 5-H), 7.81 (d, \( J = 8.4 \) Hz, 2H, 27-H and 32-H), 7.98 (dd, \( J = 1.5 \) and 8.5 Hz, 1H, 26-H), 8.44 (s, 1H, 34-H); 13C NMR (150 MHz, CDCl₃): \( \delta_C = 21.6, 111.1, 111.3, 120.0, 120.1, 121.8, 123.9, 124.0, 125.1, 126.5, 126.7, 127.4, 127.9, 128.4, 128.8, 129.8, 130.0, 131.5, 132.4, 133.5, 133.7, 134.8, 136.1, 143.9, 144.0; HRMS m/z (Cl+): 584.07632 [M+H]+; \( C_{29}H_{23}N_5BrO_2N_5S \) requires 584.07558.

\[ \text{N-} (2-((6\text{-Bromo-2-(naphthalen-2-yl)} \text{imidazo[1,2-\text{a}]} \text{pyrazin-8-yl)} \text{amino)} \text{ethyl})\text{-4-methylbenzenesulfonamide} \] (38)

6,8-Dibromo-2-(naphthalene-2-yl)imidazo[1,2-\text{a}]pyrazine (30 mg, 74 \( \mu \)mol), \( N\)-(2-aminoethyl)-4-methylbenzenesulfonamide (23 mg, 108 \( \mu \)mol) and \( N,N\)-diisopropylethylamine (31 \( \mu \)L, 178 \( \mu \)mol) were dissolved in n-butanol (10 mL) and the reaction was stirred at 80 °C for 14 h. After completion, the reaction mixture was concentrated under reduced pressure and purified by chromatography (applied in hexane; eluted 25% EtOAc/hexane) to give the title compound (33 mg, 62 \( \mu \)mol, 83%). \( R_f = 0.50 \) (2:1 EtOAc/hexane); IR (\( v_{\text{max}}/\text{cm}^{-1}, \text{thin film} \): 3287, 3107, 2868, 1600, 1545; 1H NMR (600 MHz, CDCl₃): \( \delta_H = 2.30 \) (s, 3H, 20-H), 3.34 (q, \( J = 5.5 \) Hz, 2H, 12-H), 3.71 (q, \( J = 5.5 \) Hz, 2H, 11-H), 5.71 (t, \( J = 5.3 \) Hz, 1H, 10-H), 6.39 (m, 1H, 13-H), 7.18 (d, \( J = 8.0 \) Hz, 2H, 16-H and 18-H), 7.47-7.53 (m, 2H, 25-H and 26-H), 7.60 (s, 1H, 3-H), 7.73 (d, \( J = 8.2 \) Hz, 2H, 15-H and 19-H), 7.81 (s, 1H, 5-H), 7.85-7.95 (m, 4H, 24-H, 27-H, 29-H and 30-H), 8.37 (s, 1H, 22-H); 13C NMR (150 MHz, CDCl₃): \( \delta_C = 21.6, 29.8, 44.1, 109.8, 110.9, 122.2, 123.9, 124.9, 126.5, 126.6, 126.7, 127.1, 128.4, 128.8, 129.6, 129.9, 144.0; HRMS m/z (Cl+): 584.07632 [M+H]+; \( C_{29}H_{23}N_5BrO_2N_5S \) requires 584.07558.
132.0, 133.5, 133.7, 137.0, 143.4, 145.0, 147.8; HRMS m/z (EI+): Found 536.0757 [M+H]+; C_{25}H_{23}BrN_{5}O_{2}S requires 536.0756.
**Figure S1** HMBC spectrum of 21a, indicating coupling of H₃ with C₅ and H₅ with C₃

Molecular docking studies were carried out using AutoDock Vina.¹¹ The crystal structure of ADP-HP0525 was retrieved from RSCB Protein Data Bank (PDB entry: IG60). All heteroatoms (H₂O, PEG, ADP) were removed from the .pdb file, which was then converted to pdbqt format “enzyme.pdbqt” using AutoDock Tools (ADT)¹² with the addition of polar hydrogens and Kollman charges. The docking grid box (located at the nucleotide binding site) had a size of 14 x 16 x 24 with a grid center of -12.034, 24.627 and 22.363 in the x, y, and z coordinates respectively. All ligand structures were generated in mol2 format (“ligand.mol2”) using chem3D professional Cambridge software (no energy minimization was carried out) and were converted to “ligand.pdbqt” format using ADT. The docking file, “ligand.txt” was prepared containing receptor and ligand information (in .pdbqt format), output file “out_ligand.pdbqt” and docking grid box coordinates and size. An “exhaustiveness” parameter was set to a value of 8. The window command prompt was used to script the docking.
2-Bromo-1-2-phenoxypyphenylethanone 15b
2-(3-Chloropyrazin-2-ylamino)-1-2-naphthyl)ethanol 18a.
2-(3-Chloropyrazin-2-ylamino)-1-(2-naphthyl)ethanone 19a.
8-Chloro-3-(2-naphthyl)imidazo[1,2-a]pyrazine 20a.
4-Methyl-N-[4-[3-(2-naphthyl)imidazo[1,2-\(a\)]pyrazine-8-yl]aminophenyl]benzene-
sulfonamide 5.
8-Chloro-2-(2-naphthyl)imidazo[1,2-a]pyrazine 21a.
4-Methyl-N-[4-(2-ethyl-imidazol-1,2-a-pyrazine-8-ylaminophenyl]benzene-
8-(Methylsulfonyl)-2-(naphthalen-2-yl)imidazo[1,2-a]pyrazine 24.
70 4-Methyl-N-(2,2-naphthyl)imidazo[1,2-a]pyrazine-8-yl]benzenesulfonamide
2-Azido-1-(2-phenoxyphenyl)ethanone 16b
2-Azido-1-(3,5-dimethylphenyl)ethanone 16d
2-Azido-1-(2-phenoxynaphenyl)ethanol, 17b
2-Azido-1-(3,5-dimethylphenyl)ethanol, 17d
2-Azido-1-(3-thienyl)ethanol, 17e
2-Amino-1-(2-phenoxyphenyl)ethanol, 14b
2-Amino-1-(3,5-dimethylphenyl)ethanol, 1,4d
2-Amino-1-(3-thienyl)ethanol, 14e
2-[(3-Chloropyrazin-2-yl)amino]-1-(2-phenoxyphenyl)ethanol, 18b
2-[(3-Chloropyrazin-2-yl)amino]-1-(3,4-dimethoxyphenyl)ethanol, 18c
2-[(3-Chloropyrazin-2-yl)amino]-1-(3,5-dimethylphenyl)ethanol, 18d
2-[(3-Chloropyrazin-2-yl)amino]-1-(3-thienyl)ethanol, 18e
2-[(3-Chloropyrazin-2-yl)amino]-1-(2-phenoxyphenyl)ethanone, 19b
2-(3-Chloropyrazin-2-ylamino)-1-(3,4-dimethoxyphenyl)ethanone, 19c
2-(3-Chloropyrazin-2-ylamino)-1-(3,5-dimethylphenyl)ethanone, 19d
2-(3-Chloropyrazin-2-yl)amino)-1-(3-thienyl)ethanone, 19e
8-Chloro-3-(2-phenoxyphenyl)imidazo[1,2-a]pyrazine, 20b
8-Chloro-3-(3,4-dimethoxyphenyl)imidazo[1,2-\(\alpha\)]pyrazine, 20c
8-Chloro-3-(3,5-dimethylphenyl)imidazo[1,2-α]pyrazine, 20d
8-Chloro-2-(2-phenoxyphenyl)imidazo[1,2-a]pyrazine, 21b
8-Chloro-2-(3,4-dimethoxyphenyl)imidazo[1,2-\text{a}]pyrazine, 21c
8-Chloro-2-(3-thienyl)imidazo[1,2-a]pyrazine, 21e
JS3v2 C
PROTON.ucl DMSO (C:\Bruker\TOPSPIN) abt 2

8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 ppm

11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
4-Methyl-\(N\)-[2-phenoxophenyl]imidazo[1,2-\(a\)]pyrazine-8-yl]benzenesulfonamide, 2
N-(3,4-Dimethoxyphenyl)imidazo[1,2-a][pyrazine-8-yl]-4-methyl-benzene-
sulfonamide, 3
N-(3,5-Dimethylphenyl)imidazo[1,2-a]pyrazine-8-yl-4-methyl-benzenesulfonamide.
4-Methyl-N-[4-[[[3-(thienyl)imidazo[1,2-a]pyrazine-8-yl]amino]phenyl]benzenesulfonamide, 6
4-Methyl-N-[4-(2-phenoxyphenoxy)imidazo[1,2-a]pyrazine-8-yl]benzenesulfonamide,
N-[2-(3,4-Dimethoxyphenyl)imidazo[1,2-α]pyrazine-8-yl]-4-methyl-benzene-sulfonamide, 9
N-(2,3,5-Trimethylphenyl)imidazol[1,2-a]pyrazine-8-yl-4-methylbenzenesulfonamide, 10
4-N-methyl-N-[4-[12-(3-thienyl)imidazo[1,2-a]pyrazine-8-yl]amino]phenyl]benzene-sulfonamide, 12
4-Methyl-N-(4-(2-(2-phenoxyphenyl)imidazo[1,2-a]pyrazin-8-y lamino)phenyl)-benzenesulfonamide 13
2-(Naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-amine (25)
N'-(2-Naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-yl)benzene-1,4-diamine (26)
$N$-(4-(2-(Naphthalen-2-yl)imidazo[1,2-$a$]pyrazin-8-ylamino)phenyl)methanesulfonamide (27)
4-Methyl-N-(4-(2-(naphthalen-2-yl)imidazo[1,2-α]pyrazin-8-yl)oxy)phenyl)benzene-sulfonamide (28)
4-Methyl-N-(4-((2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-ylamino)methyl)-phenyl)benzenesulfonamide (29)
benzene sulphonamide (30)
4-Methyl-N-(2-(2-(naphthalen-2-yl)imidazo[1,2-a]pyrazin-8-ylamino)ethyl)benzenesulfonamide (31)
2-((Naphthalen-2-yl)-N-((3-pyridin-3-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (32)
N-(4-(2-(Naphthalen-2-yl)imidazol-1,2,3-triazin-8-yl)aminophenyl)quinoline-8-
sulfonamide (33)
N-(3-((2-(Naphthalen-2-yl)imidazo[1,2-α]pyrazin-8-yl)amino)phenyl)quinoline-8-sulfonamide (34)
N-(4-(4-(imidazo[1,2-a]pyrazin-8-ylamino)phenyl)-4-methylbenzenesulfonamide (35)
4-Methyl-N-(4-(2-quinolin-2-yl)imidazo[1,2-a]pyrazin-8-ylamino)phenyl-benzenesulfonylamide (36)
$N^\text{-}4(4$-Bromo-2-(naphthalen-2-yl)imidazo[1,2-$a$]pyrazin-8-yl)amino)phenyl)-4-
methylbenzenesulfonamide (37)
\[N-(2-((6\text{-Bromo-2-(naphthalen-2-yl)imidazo}[1,2-\alpha]pyrazin-8-yl]amino)ethyl)-4-methylbenzenesulfonamide \ (38)\]
References


ATPase assay.

ATPase activity measurements were carried out using a colorimetric in vitro ATPase assay kit (Innova Biosciences), using 96-well ELISA microplates (Greiner Bio-One) with reaction volumes of 100 μL in each well. Multi-pipettes with either 8 tips or 96 tips were used. Enzymatic reactions were performed for 30 min at 37 ºC followed by measuring the absorbance at 620 nm, detecting the presence of inorganic phosphate product. Each reaction contained 100 mM Tris–HCl, pH 7.5; 2.5 mM MgCl₂; 125 μM ATP; 5% DMSO; 25 mM NaCl; 0.5 mM DTT and 0.053 μM HP0525, with or without inhibitor. In detail, the assay can be described in steps. Step 1: 48 μL of substrate buffer mix (providing the components Tris–HCl, pH 7.5; MgCl₂; ATP and DMSO) was dispensed to each well. Step 2: 2 μL of compound (solublized in DMSO) was added to corresponding well. Step 3: Enzymatic reaction was started by the addition of 50 μL of protein (in 50 mM Tris-HCl, pH 7.5; 50 mM NaCl and 1 mM DTT) to the wells. Step 4: Reaction plates were incubated at 37 degrees for 30 min. Step 5: The reaction was stopped by the addition of 25 uL of Gold mix reagent, followed by vigorous mixing. After 2-5 min, 10 uL of stabilizer solution was added to the reaction. Step 6: After an additional 30 min incubation at room temperature, the absorbance at 620 nm was measured using a microplate reader.

Data was normalized using non-inhibited HP0525 as positive control (100% enzyme activity) and fully inhibited enzyme as negative control (0% enzyme activity). In the negative control, the protein was added after the Gold mix, as described in the standard protocol of the Innova Biosciences ATPase assay kit. As an alternative negative control,
providing equivalent readouts, 10 mM EDTA could also be added at Step 2, then removing the catalytically essential Mg ions from the active site of HP0525.

Michaelis-Menten kinetics were performed under the same conditions as above but with various concentrations of ATP ranging from 0 to 500 μM, with and without 10 μM of compound 11. Negative controls for each ATP concentration were used. GraphPad Prism version 5.0d for Mac OS X (GraphPad Software, San Diego California USA, www.graphpad.com) was used for the IC\textsubscript{50} calculations using the Prism equation for non-linear normalized dose-response ‘Log(Inhibitor) vs. normalized response’ with Hill slope set to 1; and for Michaelis-Menten and Lineweaver-Burk analysis.
Figure S2. IC50 curves corresponding to compounds presented in Table 3 and 4. Curves corresponding to compounds 11 and 32 are presented in Figure 2. 100% activity corresponds to 100% protein activity.