Supplementary Figures

Supplementary Figure 1
Correlations between principal components and calculated properties.

a. Correlations in tree latent space
### b. Correlations in graph latent space

|       | PKA | JUN-D | SAS | TRPA | HRO | HBA | LCCD |
|-------|-----|-------|-----|------|-----|-----|------|
| 0     | 0.1 | -0.0  | 0.2 | 0.1  | 0.1 | 0.1 | 0.8  |
| 1     | 0.0 | -0.0  | -0.0| 0.1  | -0.0| 0.1 | -0.0 |
| 2     | -0.0| -0.0  | -0.0| 0.1  | -0.0| 0.1 | -0.1 |
| 3     | 0.0 | 0.1   | -0.0| 0.0  | 0.0 | -0.1| 0.0  |
| 4     | 0.1 | 0.1   | 0.0 | 0.1  | 0.0 | 0.1 | 0.0  |
| 5     | -0.1| -0.1  | 0.0 | 0.0  | -0.1| 0.0 | 0.0  |
| 6     | -0.0| -0.1  | -0.2| 0.1  | -0.0| 0.1 | 0.0  |
| 7     | 0.0 | 0.1   | -0.1| 0.0  | -0.0| 0.0 | 0.0  |
| 8     | 0.0 | 0.1   | -0.1| 0.0  | 0.0 | 0.1 | 0.0  |
| 9     | 0.0 | -0.0  | -0.2| 0.1  | 0.0 | 0.1 | 0.0  |
| 10    | 0.0 | -0.0  | -0.2| 0.1  | 0.0 | 0.1 | 0.0  |
| 11    | 0.2 | 0.1   | 0.0 | 0.0  | 0.0 | 0.1 | 0.0  |
| 12    | 0.1 | -0.0  | 0.2 | 0.1  | 0.0 | 0.1 | 0.0  |
| 13    | 0.0 | -0.0  | 0.1 | 0.0  | 0.1 | 0.1 | 0.0  |
| 14    | -0.1| 0.1   | 0.0 | 0.0  | 0.1 | 0.1 | 0.0  |
| 15    | -0.0| -0.1  | 0.2 | 0.0  | 0.0 | 0.1 | 0.0  |
| 16    | 0.0 | 0.0   | 0.0 | 0.0  | 0.1 | 0.0 | 0.0  |
| 17    | 0.1 | 0.1   | 0.0 | 0.0  | 0.1 | -0.0| 0.0  |
| 18    | 0.1 | 0.0   | 0.1 | 0.0  | -0.1| 0.1 | 0.0  |
| 19    | -0.0| 0.1   | 0.0 | 0.0  | -0.1| 0.1 | 0.0  |
| 20    | 0.0 | 0.0   | 0.0 | 0.0  | 0.1 | -0.0| 0.0  |
| 21    | 0.0 | 0.0   | 0.0 | 0.0  | 0.0 | 0.1 | 0.0  |
| 22    | -0.1| 0.0   | 0.0 | 0.0  | 0.0 | 0.0 | 0.0  |
| 23    | 0.0 | 0.0   | 0.0 | 0.0  | 0.0 | 0.0 | 0.0  |
| 24    | 0.0 | 0.0   | 0.0 | 0.0  | 0.0 | 0.0 | 0.0  |
| 25    | 0.0 | -0.1  | 0.0 | 0.0  | 0.0 | 0.0 | 0.0  |
| 26    | 0.0 | -0.1  | 0.0 | 0.0  | -0.1| 0.0 | 0.0  |
| 27    | 0.0 | -0.1  | 0.0 | 0.0  | -0.1| 0.0 | 0.0  |
Supplementary Figure 2

Scatterplots between calculated properties and projections on principal component with the highest correlation

a. Scatterplots between calculated properties and projections on principal component in tree latent space with the highest correlation

| MW   | cLogP  | SAS    |
|------|--------|--------|
| ![MW Scatterplot](image) | ![cLogP Scatterplot](image) | ![SAS Scatterplot](image) |

| TPSA | HBD    | HBA    |
|------|--------|--------|
| ![TPSA Scatterplot](image) | ![HBD Scatterplot](image) | ![HBA Scatterplot](image) |

| pIC50 |
|-------|
| ![pIC50 Scatterplot](image) |
b. Scatterplots between calculated properties and projections on principal component in graph latent space with the highest correlation

| MW | cLogP | SAS |
|----|-------|-----|
| ![MW](image1) | ![cLogP](image2) | ![SAS](image3) |

| TPSA | HBD | HBA |
|------|-----|-----|
| ![TPSA](image4) | ![HBD](image5) | ![HBA](image6) |

| pIC\text{50} |
|--------------|
| ![pIC\text{50}](image7) |

MW – Molecular weight
TPSA – Topological polar surface area
HBD – Number of hydrogen bond donors
HBA – Number of hydrogen bond acceptors
SAS – Synthetic accessibility score
cLogP – calculated log P
Supplementary Figure 3

Projection of training molecules onto principal components with highest correlation to the molecules' pIC$_{50}$ in tree latent space.
Supplementary Figure 4
Cumulative explained variances computed through PCA

a. Tree space

b. Graph space
Supplementary Note – Chemical synthesis and analytical data

Synthetic scheme for compound 1

Reagents:
Step 1: 2,5-dichloropyridine(1.0eq.), K₂CO₃ (3.5eq.), Pd(OAc)₂ (0.1eq), BIINAP(0.1eq), toluene(20vol), molecular sieves, 110°C, 16h.
Step 2: 1: (COCl)₂(1.2eq), DMF(1drop), DCM(20vol), rt, 2h.
   2: Int-3(1.0eq), NaH(10.0eq), DIPEA(10.0eq), THF(30vol), 80°C, microwave, 3h.
Step 3: NBS(1.0eq), DCM(20vol), -78°C, 1h.
Step 4: Int-7(1.0eq), Na₂CO₃ (3.0eq), Pd(dppf)Cl₂, DCM(0.1eq), dioxane:water(4:1), 100°C, 2h.

Step 1. 5-chloro-N-(4-fluorophenyl)pyridin-2-amine.
In a 250.0 mL flask, 4-fluoroaniline (2.00 g, 18.0 mmol), 2,5-dichloro pyridine (2.65 g, 18.0 mmol) and toluene (20.0 vol) were mixed. Molecular sieves were added followed by slow portionwise addition of potassium carbonate (8.37 g, 63.1 mmol) under nitrogen purging. After 15 minutes BINAP (1.10 g, 1.08 mmol) was added portionwise, followed by addition of Pd(OAc)$_2$ (0.400 g, 1.08 mmol) under nitrogen purging. Reaction mixture was stirred at 110°C for 16h. After completion of reaction the mixture was diluted with ethyl acetate (100 mL) and washed with brine (50 mL). The organic layers were dried over sodium sulfate and concentrated. Crude compound was purified by silica gel column chromatography and eluted with 10% ethyl acetate-hexane to afford a brown solid compound, 5-chloro-N-(4-fluorophenyl)pyridin-2-amine (0.800 g, 20.0% yield). LCMS (m/z): 223.1 [M+H]$^+$. $^1$H NMR (400 MHz, Chloroform-d) δ 8.12 (d, $J = 2.4$ Hz, 1H), 7.49 (m, 1H), 7.32 (m, 2H), 7.09 (m, 2H), 6.8 (s, 1H), 6.71 (d, $J = 9.2$ Hz, 1H).

**Step 2. N-(5-chloropyridin-2-yl)-N-(4-fluorophenyl)pyrazolo[1,5-a]pyridine-5-carboxamide.**

A solution of pyrazolo[1,5-a]pyridine-5-carboxylic acid (0.300 g, 1.85 mmol) in DCM (20.0 vol) was cooled to 0°C and a drop of DMF was added followed by dropwise addition of oxalyl chloride (0.270 g, 2.22 mmol). The reaction mixture was stirred at room temperature for 2h. After completion of the reaction, the solvent was evaporated. 5-chloro-N-(4-fluorophenyl)pyridin-2-amine (0.410 g, 1.85 mmol) was dissolved in THF (40.0 vol) in 30 mL microwave vial. Sodium hydride (0.133 g, 5.56 mmol) was added to the mixture at 0°C, followed by addition of DIPEA (0.700 g, 5.56 mmol), and acid chloride in THF at 0°C. The reaction mixture was irradiated in microwave at 80°C for 3h. After completion the reaction mixture was diluted with ethyl acetate (100 ml) and washed with water (2 x 50 ml). The organic layer was dried over sodium sulfate, filtered, and evaporated to dryness. The residue was column purified by silica gel column chromatography.
and eluted with 25% ethylacetate-hexane to afford, \(\text{N-(5-chloropyridin-2-yl)-N-(4-fluorophenyl)pyrazolo[1,5-a]pyridine-5-carboxamide}\) (0.22 g, 32% yield). LCMS (m/z): 367.5 [M+H]\(^+\). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.62 (m, 1H), 8.40 (s, 1H), 8.05 (s, 1H), 8.01 (d, 1H), 7.87 (d, 1H), 7.54 (m, 1H), 7.37 (m, 2H), 7.27 (m, 2H), 6.87 (m, 1H), 6.73 (d, \(J = 1.6\) Hz, 1H).

**Step 3.** 3-bromo-N-(5-chloropyridin-2-yl)-N-(4-fluorophenyl)pyrazolo[1,5-a]pyridine-5-carboxamide.

![Chemical Structure](image)

To a solution of N-(5-chloropyridin-2-yl)-N-(4-fluorophenyl)pyrazolo[1,5-a]pyridine-5-carboxamide (0.22g, 1.358 mmol) in DCM(40vol) was added NBS(0.24g, 1.358mmol) at -78°C. The reaction was stirred at -78°C for 1h. After completion, the reaction was diluted with DCM (50ml), washed with water(2x25ml). The organic layers was dried over sodium sulfate, filtered, and evaporated to dryness to afford a white solid, 3-bromo-N-(5-chloropyridin-2-yl)-N-(4-fluorophenyl)pyrazolo[1,5-a]pyridine-5-carboxamide (0.28g,46% yield). LCMS (m/z): 447.2 [M+2H]\(^+\).

**Step 4.** 3-(4-carbamoylphenyl)-N-(5-chloropyridin-2-yl)-N-(4-fluorophenyl)pyrazolo[1,5-a]pyridine-5-carboxamide.

![Chemical Structure](image)

In a 30.0 ml sealed tube, 3-bromo-N-(5-chloropyridin-2-yl)-N-(4-fluorophenyl)pyrazolo[1,5-a]pyridine-5-carboxamide (0.200 g, 0.449mmol) was suspended in a mixture of dioxane : water (4:1, 20vol). To the mixture was added sodium carbonate (0.140 g, 1.35mmol) followed by addition of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (0.110g, 0.449mmol) under
nitrogen purging. Finally, Pd(dppf)Cl₂.DCM (0.037g, 0.004mmol) was added in one portion under nitrogen purging. Reaction mixture was stirred at 100°C for 2h. The reaction mixture was diluted with ethyl acetate (50ml) washed by cold water (2x50ml). The organic layer was dried over sodium sulfate, filtered, and evaporated to dryness. The residue was purified by PREP-HPLC to afford 3-(4-carbamoylphenyl)-N-(5-chloropyridin-2-yl)-N-(4-fluorophenyl)pyrazolo[1,5-a]pyridine-5-carboxamide (0.043 g, 30.0% yield). LCMS(M/Z) : 486.4(M+H) +. ¹H NMR (400 MHz, DMSO-d₆) δ 8.73 (d, J = 1.6 Hz, 1H), 8.50 (m, 2H), 8.07 (m, 5H), 7.65 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.44 (m, 3H), 7.28 (m, 2H), 7.00 (d, J = 6.4 Hz, 1H).

| Prep. Method       |
|--------------------|
| Mobile Phase:      |
| (A) 0.1% NH₃ in water |
| (B) 100% ACN       |
| Column:            |
| YMC AQUA C18 (250*20)MM,5µ |
| Column Flow:       |
| 15 mL/min          |
| Gradient:          |
| Time(Min) | % B |
| 0.01  | 35  |
| 24.00 | 80  |
| 25.00 | 80  |
| 25.01 | 100 |
| 27.00 | 100 |
| 27.01 | 35  |
| 32.00 | 35  |
Synthetic scheme for compound 2

Reagents:
Step 1: 2-chloro-5-fluoropyridine (1.0eq), K₂CO₃ (3.5eq.), Pd(OAc)₂ (0.1eq), BINAP(0.1eq), toluene(20vol), molecular sieves, 110°C, 16h.
Step 2: 1: (COCl)₂(1.2eq), DMF(1drop), DCM(20vol), rt, 2h.
2: Int-3(1.0eq), NaH(10.0eq), DIPEA(10.0eq), THF(30vol), 80°C, microwave, 3h.
Step 3: NBS(1.0eq), DCM(20vol), -78°C, 1h.
Step 4: Int-7(1.0eq), Na₂CO₃(3.0eq), Pd(dppf)Cl₂.DCM(0.1eq), dioxane:water(4:1), 100°C, 2h.

Step 1. N-(4-chlorophenyl)-5-fluoropyridin-2-amine.

In a 50.0 mL flask, 4-chloroaniline (1.00g, 7.87mmol), 2-chloro-5-fluoropyridine (1.03g, 7.87mmol), and toluene(20ml) were combined with molecular sieves. Potassium carbonate(3.8g, 27.6mmol) was added to the reaction mixture slowly portionwise under nitrogen purging. After 15
minutes BINAP (0.48g, 0.78mmol) was added portionwise, followed by addition of Pd(OAc)$_2$ (0.17g, 0.78mmol) under nitrogen purging. The reaction mixture was stirred at 110°C for 16h. After completion of reaction, reaction mixture was diluted with ethyl acetate (100ml), washed by brine (2X50ml). The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with 10% ethylacetate-hexane to afford a brown solid, **N-(4-chlorophenyl)-5-fluoropyridin-2-amine** (0.50g, 28% yield). LCMS (m/z): 223.1 [M+H]$^+$.  

**Step 2. N-(4-chlorophenyl)-N-(5-fluoropyridin-2-yl)pyrazolo[1,5-a]pyridine-5-carboxamide.**

![Chemical Structure](image)

In a 25.0 mL flask, a drop of DMF followed by dropwise added oxalyl chloride (0.135g, 1.11mmol) at 0°C was added to a solution of pyrazolo[1,5-a]pyridine-5-carboxylic acid (0.15g, 0.93mmol) in DCM (3ml). The reaction mixture was stirred at room temperature for 2h. After completion of the reaction the solvent was evaporated to generate the acid chloride. N-(4-chlorophenyl)-5-fluoropyridin-2-amine (0.210g, 0.962mmol) was dissolved in THF(40vol) in 30 ml microwave vial. To the solution was added NaH (0.065g, 2.75mmol) at 0°C, followed by addition of DIPEA (0.350g, 2.75mmol), and acid chloride in THF (1ml) at 0°C. The reaction mixture was irradiated in a microwave at 80°C for 3h. After completion of reaction, the reaction mixture was diluted with ethyl acetate (50ml) and washed with water (2x25ml). The organic layer was dried over sodium sulfate, filtered, and evaporated to dryness. The residue was purified by silica gel column chromatography and eluted with 25% ethylacetate-hexane to afford **N-(4-chlorophenyl)-N-(5-fluoropyridin-2-yl)pyrazolo[1,5-a]pyridine-5-carboxamide** (0.065 g, 26.0% yield). LCMS (m/z): 367.5 [M+H]$^+$.  

**Step 3. 3-bromo-N-(4-chlorophenyl)-N-(5-fluoropyridin-2-yl)pyrazolo[1,5-a]pyridine-5-carboxamide.**
To a solution of N-(5-chloropyridin-2-yl)-N-(4-fluorophenyl)pyrazolo[1,5-a]pyridine-5-carboxamide (0.065g, 0.175 mmol) in DCM(2ml) was added NBS(0.031g, 0.175mmol) at -78°C. The reaction mixture was stirred at -78°C for 1h. After completion of the reaction, the mixture was diluted with DCM (25ml), washed with water (2x20ml). The organic layers were dried over sodium sulfate, filtered, and evaporated to dryness to afford a white solid, 3-bromo-N-(4-chlorophenyl)-N-(5-fluoropyridin-2-yl)pyrazolo[1,5-a]pyridine-5-carboxamide (0.07g, 88% yield). LCMS (m/z): 447.2 [M+2H]+.

Step 4. 3-(4-carbamoylphenyl)-N-(4-chlorophenyl)-N-(5-fluoropyridin-2-yl)pyrazolo[1,5-a]pyridine-5-carboxamide.

In a 30.0 ml sealed tube, 3-bromo-N-(4-chlorophenyl)-N-(5-fluoropyridin-2-yl)pyrazolo[1,5-a]pyridine-5-carboxamide (0.07 g, 0.15mmol) was suspended in a mixture of dioxane : water (4:1, 20vol). To the mixture was added sodium carbonate (0.049 g, 0.460mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (0.037g, 0.150mmol), and Pd(dppf)Cl2.DCM (0.013g, 0.015mmol) under nitrogen purging. The reaction mixture was stirred at 100°C for 2h. Reaction mixture was diluted with ethyl acetate (25ml) washed with cold water(2X10ml). The organic layers was dried over sodium sulfate, filtered, and evaporated to dryness. The residue was purified by Prep-HPLC to afford 3-(4-carbamoylphenyl)-N-(4-chlorophenyl)-N-(5-fluoropyridin-2-yl)pyrazolo[1,5-a]pyridine-5-carboxamide (0.008 g, 10.0% yield). LCMS(M/Z) : 486.4(m+H)+.1H NMR (400 MHz, Chloroform-d) δ 8.40 (d, J = 7.2 Hz, 1H), 8.28 (d,
J = 7.2 Hz, 1H), 8.22 (s, 1H), 7.96 (m, 3H), 7.54 (m, 3H), 7.49 (d, J = 7.2 Hz, 3H), 7.41 (m, 2H), 6.92 (m, 1H), 6.14 (s, 1H), 5.71 (s, 1H).

| Prep. Method |
|--------------|
| Mobile Phase:  (A) 0.1% NH₃ in water |
|              (B) 100% ACN |
| Column:       YMC AQUA C18 (250*20)MM,5µ |
| Column Flow:  15 mL/min |
| Gradient:     | Time (Min) | % B |
|               |            | 0.01 | 35  |
|               |            | 24.00 | 80  |
|               |            | 25.00 | 80  |
|               |            | 25.01 | 100 |
|               |            | 27.00 | 100 |
|               |            | 27.01 | 35  |
|               |            | 32.00 | 35  |

Molecular Weight: 381.55
