Identification and characterization of new structural scaffolds modulating the activity of *Mycobacterium tuberculosis* dihydroneopterin aldolase (FolB) *in vitro*

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Mycobacterium tuberculosis, dihydroneopterin aldolase (DHNA), Rv3607c (FolB), Folate precursor synthesis, drug screening

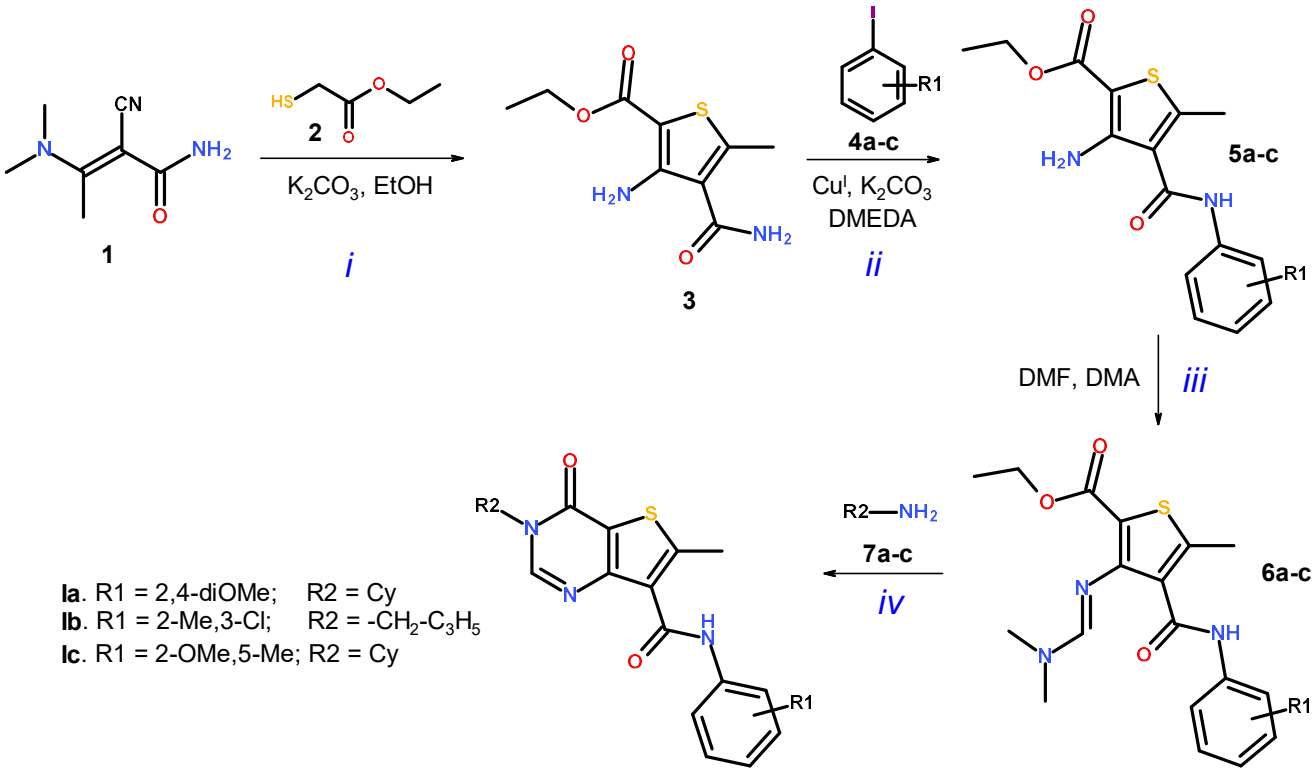
Supplementary methods

Chemistry

Reagents and solvents were obtained from commercial suppliers and used without purification or drying, unless otherwise stated. ^{1}H NMR spectrum were recorded using a Bruker instrument at 400 MHz. TMS was used as an internal standard. LC-MS analysis were performed using an Acquity UPLC column (BEH C18, 2.1×50 mm, 1.7 μm), under the following conditions: mobile phase A: 0.05% TFA in Water; mobile phase B: 0.05% TFA in Acetonitrile; gradient (T/% B): 0/50, 3/90, 5/90, 5.01/50; flow rate: 0.4 mL/min; Temperature: 35°C. All raw NMR and HPLC data are available upon request to the corresponding author.

Note: numbering for hit compounds in this section are following the red labels indicated in **Figure S2**.

General procedure for the synthesis of Cluster I (compounds **Ia-c**)



i. To a stirred solution of **1** (5.00 g, 33.0 mmol) and **2** (4.75 g, 39.6 mmol) in EtOH (50.0 mL) was added K_2CO_3 (0.318 g, 2.30 mmol). The resulting reaction mixture was stirred at 80°C for 16h. Reaction progress was monitored by TLC (40% EtOAc in petroleum ether (PE)). After completion of the reaction, the mixture was poured into ice-cold water. The precipitate formed was filtered off and washed with water and PE to afford the desired product **3** as a white solid (4.50 g, 59.8% yield).

ii. To a stirred solution of **3** (1 eq., ~0.5 g) in toluene (10 mL) was added CuI (0.05 eq.), K_2CO_3 (2.0 eq.), *N*,*N*'-dimethylethylenediamine (DMEDA, 0.10 eq.) and the corresponding iodobenzene derivative **4a-c** (0.8 eq.) at room temperature. The resulting reaction mixture was stirred at 110°C for 16h. Reaction progress was monitored by TLC (**5a**: 40% EtOAc in PE, R_f = 0.6; **5b**: 30% EtOAc in PE, R_f = 0.8; **5c**: 40% EtOAc in PE, R_f = 0.8). After depletion of the starting material, the reaction mixture was poured into ice-cold water (50 mL) and

extracted with EtOAc (2 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude compound was purified by silica gel column (100-200 mesh) using 15% EtOAc in PE (**5a**), 20% EtOAc in PE (**5b**) or 8% EtOAc in PE (**5c**) as eluent to afford **5a-c** as off white to pale yellow solids (48-67% yield).

iii. To a stirred solution of **5a-c** (1.0 eq., ~0.20 g) in ethanol (10 mL) was added *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA; 2.0 eq.) at room temperature. The resulting reaction mixture was stirred at 80°C for 4h. Reaction progress was monitored by TLC (**6a**: 20% EtOAc in PE, R_f = 0.4; **6b**: 30% EtOAc in PE, R_f = 0.3; **6c**: 20% EtOAc in PE, R_f = 0.3). After depletion of the starting material, the reaction mixture was concentrated under reduced pressure to afford **6a-c** as pale yellow solids. Crude compounds were used in the next reaction without further purification.

iv. A 20 mL sealed tube was charged with **6a-c** (1 eq., ~0.150 g), the corresponding amine **7a-c** (2 eq.) and acetic acid (120 µL) at room temperature. The resulting reaction mixture was stirred at 160°C for 3h. Reaction progress was monitored by TLC (**7a**: 40% EtOAc in PE, R_f = 0.4; **7b**: 30% EtOAc in PE, R_f = 0.2; **7c**: 30% EtOAc in PE, R_f = 0.2). After depletion of the starting material, the reaction was quenched with saturated sodium bicarbonate solution (50 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude compound was purified by silica gel column (100-200 mesh) using 10% EtOAc in PE (**4a,b**) or 15% EtOAc in PE (**4c**) as eluent to afford **Ia-c** as off white to pale yellow solids (27-52% yield).

3-cyclohexyl-N-(2,4-dimethoxyphenyl)-6-methyl-4-oxo-thieno[3,2-d]pyrimidine-7-carboxamide (**Ia**)

Off white solid. ^{1}H NMR (400 MHz, DMSO-*d6*) *δ*: 1.23-1.29 (m, 1H), 1.33-1.45 (m, 2H), 1.69-1.72 (d, *J* = 12 Hz, 1H), 1.89-1.99 (m, 6H), 2.95 (s, 3H), 3.77 (s, 3H), 3.97 (s, 3H), 4.64-4.69 (m, 1H), 6.51-6.54 (dd, *J* = 2.8, 8.8 Hz, 1H), 6.68 (d, *J* = 2.4 Hz, 1H), 8.28-8.31 (dd, *J* = 1.6, 8.8 Hz, 1H), 8.76 (s, 1H), 11.58 (s, 1H). LC-MS: RT, 1.92, $[M+H]^+$ 428.23 m/z.

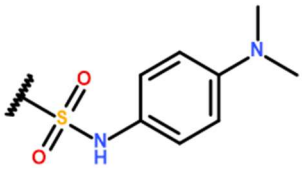
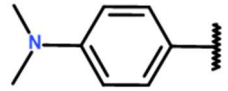
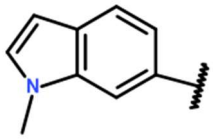
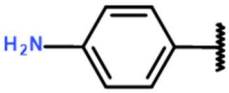
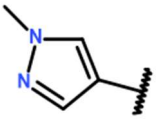
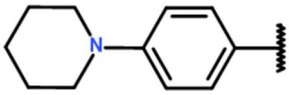
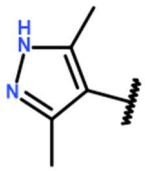
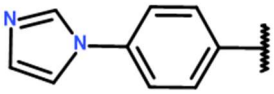
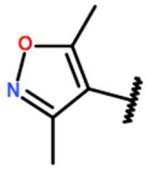
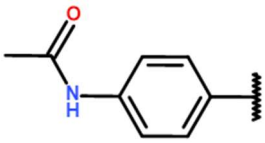
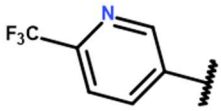
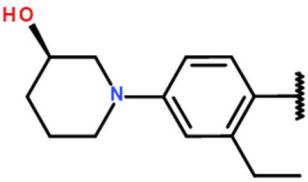
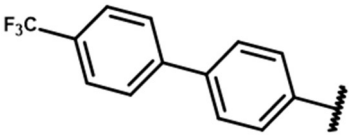
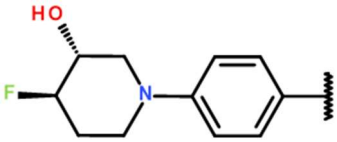
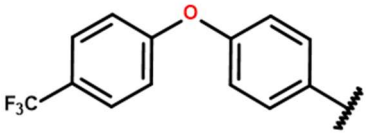
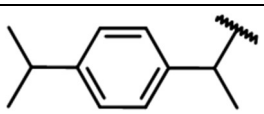
N-(3-chloro-2-methyl-phenyl)-3-(cyclopropylmethyl)-6-methyl-4-oxo-thieno[3,2-d]pyrimidine-7-carboxamide (**Ib**)

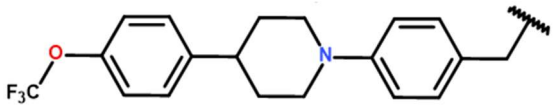
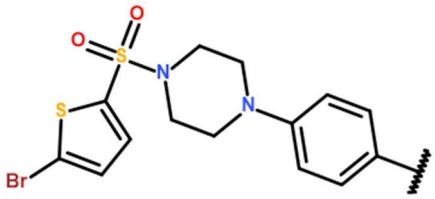
Pale yellow solid. ^{1}H NMR (400 MHz, DMSO-*d6*) *δ*: 0.47-0.5 (m, 2H), 0.52-0.55 (m, 2H), 1.29-1.33 (m, 1H), 2.46 (s, 3H), 2.94 (s, 3H), 3.92-3.94 (d, *J* = 7.2 Hz, 2H), 7.23-7.29 (m, 2H), 8.04-8.06 (dd, J = 2.4, 6.8 Hz, 1H), 8.80 (s, 1H), 11.30 (s, 1H). LC-MS: RT 2.11, $[M+H]^+$ 388.13 m/z.

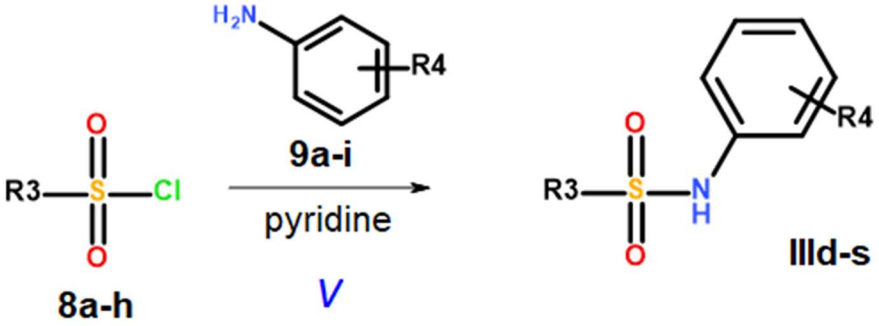
3-cyclohexyl-N-(2-methoxy-5-methyl-phenyl)-6-methyl-4-oxo-thieno[3,2-d]pyrimidine-7-carboxamide (**Ic**)

Off white solid. ^{1}H NMR (400 MHz, DMSO-*d6*) *δ*: 1.23-1.33 (q, *J* = 13.1 Hz, 1H), 1.39-1.48 (q, *J* = 12.5 Hz, 2H), 1.69 (d, *J* = 12.4 Hz, 1H), 1.87-1.99 (m, 6H), 2.27 (s, 3H), 2.96 (s, 3H), 3.96 (s, 3H), 4.63-4.69 (m, 1H), 6.87-6.90 (dd, *J* = 1.6, 8.4 Hz, 1H), 6.97 (d, *J* = 8 Hz, 1H), 8.32 (m, 1H), 8.76 (s, 1H), 11.74 (s, 1H). LC-MS: RT 2.38, $[M+H]^+$ 412.20 m/z.

General procedure for the synthesis of Cluster III (compound **IIId** and derivatives)

N-Series (8a + 9a-j)		**S-Series (9a + 8b-h)**	
			
	IIId		IIIn
	IIIe		IIIo
	IIIf		IIIp
	IIIg		IIIq
	IIIh		IIIr
	IIIi		IIIs
	IIIj		IIIt
	IIIk		

	IIII		
	IIIm		



v. To a solution of the desired substituted heterocyclic sulfonyl chloride **8a-h** (1.2 eq.) in pyridine were added the desired heterocyclic anilines **9a-j** (1.0 eq.) and the mixture was stirred at room temperature for 2 hours. The reaction was diluted with EtOAc (20 mL), washed with water (10 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by flash column chromatography (20% EtOAc in *n*-hexane) to afford the target compounds **IIId-m**. Compounds **IIId-m** (N-series) were obtained by reacting the same 5-bromothiophene-2-sulfonyl chloride **8a** with anilines **9a-j**. Compounds **IIIn-t** (S-series) were obtained by reacting the same N4,N4-dimethylbenzene-1,4-diamine **9a** with various sulfonyl chloride **8b-h**.

Structures of the target compounds are summarized in the table below:

5-bromo-N-(4-(dimethylamino)phenyl)thiophene-2-sulfonamide (**IIId**)

Brown solid, Yield 86%; ^{1}H NMR (400 MHz, DMSO-*d6*) δ: 2.82 (s, 6H), 7.26 (d, J = 9.2 Hz, 2H), 6.93 (d, J = 9.2 Hz, 1H), 7.23 (d, J = 4.0 Hz, 1H), 7.60 (d, J = 4.0 Hz, 1H), 9.90 (s, 1H);

MS (ESI): $[M+H]^{2+}$ 362 m/z.

N-(4-aminophenyl)-5-bromothiophene-2-sulfonamide (**IIIe**)

Brown solid; ^{1}H NMR (400 MHz, DMSO-*d6*) *δ*: 5.04 (s, 2H), 6.46 (d, *J* = 8.4 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 3.6 Hz, 1H), 7.27 (d, *J* = 3.2 Hz, 1H), 9.37 (s, 1H); MS (ESI): $[M+H]^+$ 333 m/z.

5-bromo-N-(4-(piperidin-1-yl)phenyl)thiophene-2-sulfonamide (**IIIf**)

Brown solid; Yield 82%; ^{1}H NMR (400 MHz, DMSO-*d6*) *δ*: 1.58-1.50 (br, 6H), 3.07 (t, *J* = 4.8 Hz, 4H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 7.27 (dd, *J* = 12 Hz, 8.0 Hz, 2H), 10.03 (s, 1H); MS (ESI): $[M+H]^{2+}$ 342 m/z.

N-(4-(1H-imidazol-1-yl)phenyl)-5-bromothiophene-2-sulfonamide (**IIIg**)

White solid; ^{1}H NMR (400 MHz, DMSO-*d6*) *δ*: 7.08 (s, 1H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 4.0 Hz, 1H), 7.41 (d, *J* = 4.0 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.67 (s, 1H), 8.18 (s, 1H), 10.70 (s, 1H); MS (ESI): $[M+H]^{2+}$ 385 m/z.

N-(4-((5-bromothiophene)-2-sulfonamido)phenyl)acetamide (**IIIh**)

Brown solid; ^{1}H NMR (400 MHz, DMSO-*d6*) *δ*: 1.99 (s, 3H), 7.05 (d, *J* = 8.8 Hz, 2H), 7.29 (dd, *J* = 9.6 Hz, 5.6 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H), 9.90 (s, 1H), 10.31 (s, 1H); MS (ESI): $[M+H]^{2+}$ 376 m/z.

(R)-5-bromo-N-(2-ethyl-4-(3-hydroxypiperidin-1-yl)phenyl)thiophene-2-sulfonamide (**IIIi**)

Brown solid; ^{1}H NMR (400 MHz, DMSO-*d6*) *δ*: 1.28 (t, *J* = 12.4 Hz, 3H), 1.88-1.47 (m, 5H), 2.67-2.43 (m, 3H), 3.46 (d, *J* = 11.2 Hz, 1H), 3.57 (d, *J* = 9.2 Hz, 2H), 4.77 (s, 1H), 6.73-6.63 (m, 3H), 7.22 (s, 2H), 7.31 (s, 1H), 9.56 (s, 1H); MS (ESI): $[M+H]^+$ 445 m/z.

5-bromo-N-(4-((3R,4R)-4-fluoro-3-hydroxypiperidin-1-yl)phenyl)thiophene-2-sulfonamide (**IIIj**)

Brown solid; ^{1}H NMR (400 MHz, DMSO-*d6*) *δ*: 1.67-1.62 (m, 1H), 2.06 (br, 1H), 2.59 (t, *J* = 12.4 Hz, 1H), 2.77 (t, *J* = 12.4 Hz, 1H), 3.57-3.52 (br, 3H), 4.45 (br, 1H), 5.36 (d, *J* = 4.4 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 6.8 Hz, 2H), 10.06 (s, 1H); MS (ESI): $[M+H]^{2+}$ 436 m/z.

5-bromo-N-(1-(4-isopropylphenyl)ethyl)thiophene-2-sulfonamide (**IIIk**)

Brown solid; Yield 56%; ^{1}H NMR (400 MHz, DMSO-*d6*) *δ*: 1.17(d, *J* = 6.8 Hz, 6H), 1.28 (d, *J* = 6.8 Hz, 3H), 2.83-2.79 (m, 1H), 4.40 (d, *J* = 6.8 Hz, 2H), 7.12-7.05 (m, 5H), 8.5 (s, 1H); MS (ESI): $[M+H]^{2+}$ 389 m/z.

5-bromo-N-(4-(4-(4-(trifluoromethoxy)phenyl)piperidin-1-yl)benzyl)thiophene-2-sulfonamide (**IIIl**)

Brown solid; ^{1}H NMR (400 MHz, DMSO-*d6*); *δ*: 1.88-1.72 (m, 4H), 2.74 (t, *J* = 12.0 Hz, 3H), 3.80 (d. *J* = 12.0 Hz, 2H), 3.98 (s, 2H), 6.91 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 4.8 Hz, 3H), 7.42-7.37 (m, 3H), 8.36 (s, 1H); MS (ESI): $[M+H]^{2+}$ 576 m/z.

5-Bromo-N-(4-(4-((5-bromothiophen-2-yl)sulfonyl)piperazin-1-yl)phenyl)thiophene-2-sulfonamide (**IIIm**)

Brown solid; Yield 34%; ^{1}H NMR (400 MHz, DMSO-*d6*) *δ*: 3.08-3.05 (br, 4H), 3.02-3.18 (br, 4H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 2.8 Hz, 2H), 7.48 (d, *J* = 4 Hz, 1H), 7.54 (d, *J* = 4 Hz, 1H), 10.11 (s, 1H). MS (ESI): $[M+H]^{2+}$ 627 m/z.

N-(4-(dimethylamino)phenyl)-1-methyl-1H-indole-6-sulfonamide (**IIIn**)

Brown solid; Yield 84%; ^{1}H NMR (400 MHz, DMSO-*d6*) *δ*: 2.84 (s, 6H), 3.80 (s, 3H), 6.52 (d, *J* = 8.8 Hz, 2H), 6.56 (d, *J* = 3.2 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H). 7.47-7.45 (m, 2H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.90 (s, 1H), 9.41 (s, 1H); MS (ESI): $[M+H]^+$ 330 m/z.

N-(4-(dimethylamino)phenyl)-1-methyl-1H-pyrazole-4-sulfonamide (**IIIo**)

Brown solid; ^{1}H NMR (400 MHz, DMSO-*d6*) *δ*: 2.83 (s, 6H), 3.82 (s, 3H), 6.62 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 9.2 Hz, 2H), 7.53 (s, 1H), 8.05 (s, 1H), 9.41 (s, 1H); MS (ESI): $[M+H]^+$ 281 m/z.

N-(4-(dimethylamino)phenyl)-3,5-dimethyl-1H-pyrazole-4-sulfonamide (**IIIp**)

Brown solid; Yield 38%; ^{1}H NMR (400 MHz, DMSO-*d6*) *δ*: 2.09 (s, 6H), 2.82 (s, 6H), 6.60 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 9.18 (s, 1H), 12.72 (s, 1H); MS (ESI): $[M+H]^+$ 295 m/z.

N-(4-(dimethylamino)phenyl)-3,5-dimethyl-isoxazole-4-sulfonamide (**IIIq**)

Brown solid; ^{1}H NMR (400 MHz, DMSO-*d6*) *δ*: 2.14 (s, 3H), 2.29 (s, 3H), 2.85 (s, 6H), 6.65 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 9.70 (s, 1H); MS (ESI): $[M+H]^+$ 296 m/z.

N-(4-(dimethylamino)phenyl)-6-(trifluoromethyl)pyridine-3-sulfonamide (**IIIr**)

Brown solid; ^{1}H NMR (400 MHz, DMSO-*d6*) *δ*: 2.83 (s, 6H), 6.60 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 8.13 (d, *J* = 8.4 Hz, 1H), 8.28 (d, *J* = 8.4 Hz, 1H), 8.93 (s, 1H), 10.07 (s, 1H); MS (ESI): $[M+H]^+$ 346 m/z.

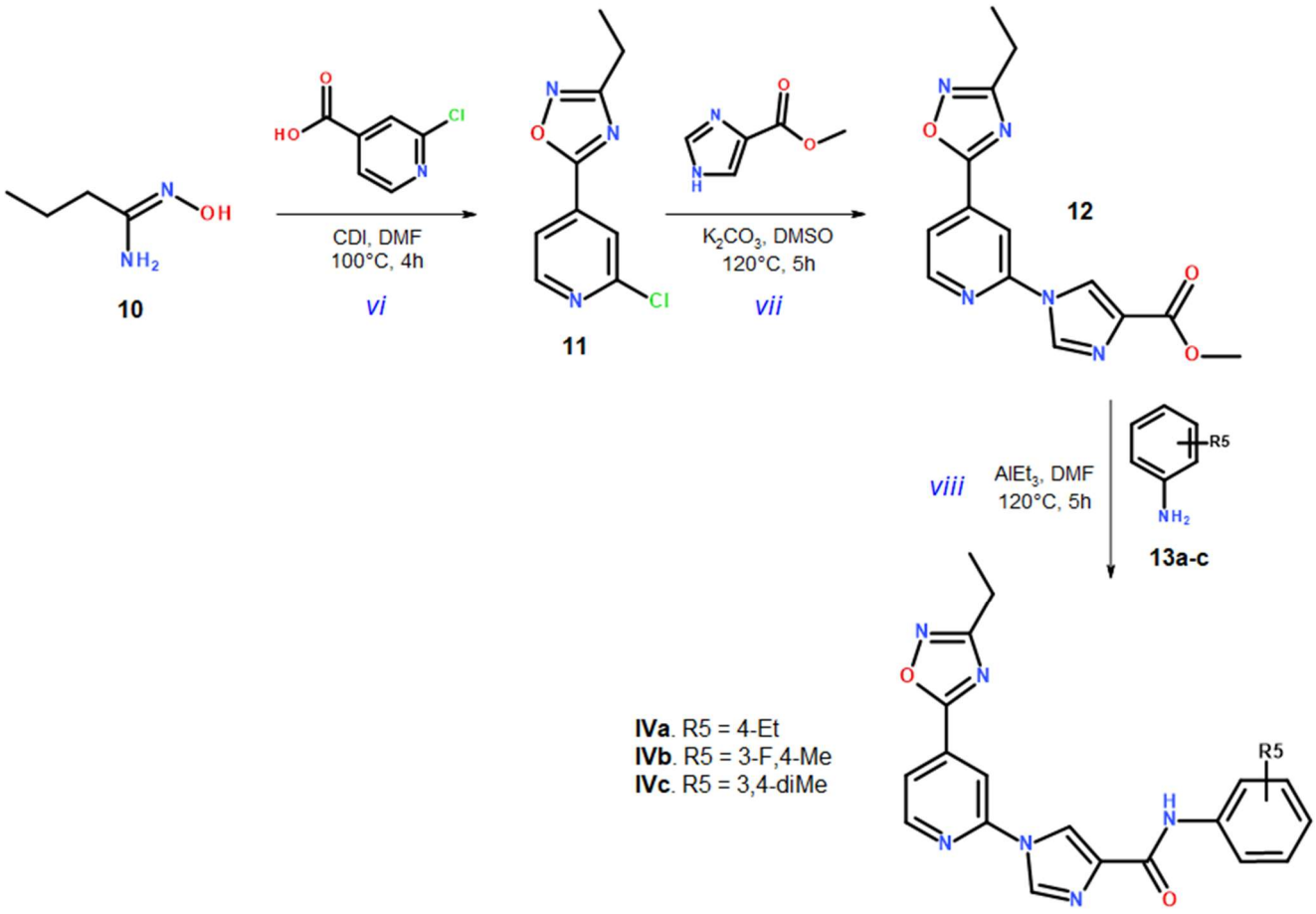
N-(4-(dimethylamino)phenyl)-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-sulfonamide (**IIIs**)

Brown solid; ^{1}H NMR (400 MHz, DMSO-*d6*) *δ*: 2.80 (s, 6H), 6.59 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.95-7.90 (m, 4H), 9.74 (s, 1H); MS (ESI): $[M+H]^+$ 421 m/z.

N-(4-(dimethylamino)phenyl)-4-(4-(trifluoromethyl)phenoxy)benzenesulfonamide (**IIIt**)

Brown solid; ^{1}H NMR (400 MHz, DMSO-*d6*); *δ*: 2.81 (s, 6H), 6.60 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 2H), 9.62 (s, 1H); MS (ESI): $[M+H]^+$ 437 m/z.

General procedure for the synthesis of Cluster IV (compounds **IVa-c**)



vi. A mixture of 2-chloroisonicotinic acid (1.0 equiv.), carbonyldiimidazole (CDI, 2.5 equiv.) and the desired amidoxime **10** (2.0 equiv.) in DMF (5 mL) was heated at 100°C for 4 hours to produce the 2-chloroisonicotinic oxadiazole **11**. After reaction completion, the mixture was cooled down to room temperature, washed with EtOAc, water and the solvent was evaporated. The crude was purified by flash column chromatography (15% EtOAc in *n*-hexane) to give compound **11**.

vii. A mixture of compound **11** (1.0 equiv.), K_2CO_3 (3.0 equiv.), methyl 4-imidazolecarboxylate (2.0 equiv.) and KI (0.1 equiv.) in DMSO (5 mL) was heated at 120°C for 5 hours to afford compound **12**. After reaction completion, the mixture was cooled down to room temperature,

washed with EtOAc, water and the solvent was evaporated. Compound **12** was obtained after purification of the crude by flash column chromatography (20% EtOAc in *n*-hexane).

viii. A mixture of compound **12** (1.0 equiv.), triethylaluminium (2.0 equiv.) and the desired aniline **13a-c** (1.0 equiv.) in DMF (5 mL) was heated at 120°C for 5 hours. After reaction completion, the reaction mixture was cooled down to room temperature, washed with EtOAc, water and the solvent evaporated. The crude was purified by flash column chromatography (50% EtOAc in *n*-hexane) to give the target compounds **IVa-c**.

1-(4-(3-ethyl-1,2,4-oxadiazol-5-yl)pyridin-2-yl)-N-(4-ethylphenyl)-1H-imidazole-4-carboxamide (**IVa**)

White solid; ^{1}H NMR (400 MHz, DMSO-*d6*) *δ*: 1.87 (t, *J* =7.6 Hz, 3H), 1.34 (t, *J* = 7.6 Hz, 3H), 2.58 (dd, *J* = 14.8 Hz, 7.6 Hz, 2H), 2.90 (dd, *J* = 14.8 Hz, 7.6 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 2H), 8.07 (d, *J* = 4.0 Hz, 1H), 8.62 (s, 1H), 8.74 (s, 1H), 8.83 (d, *J* = 4.8 Hz, 1H), 8.89 (s, 1H), 9.95 (s, 1H); MS (ESI): $[M+H]^{+}$ 389 m/z.

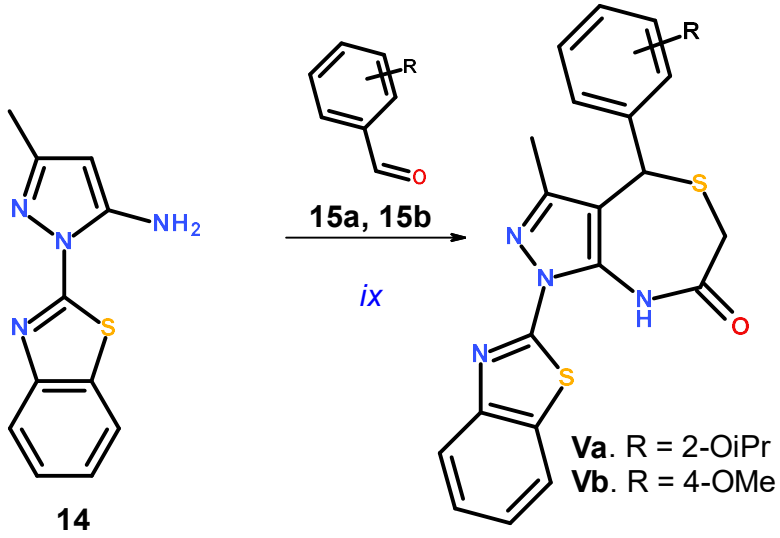
1-(4-(3-ethyl-1,2,4-oxadiazol-5-yl)pyridin-2-yl)-N-(3-fluoro-4-methylphenyl)-1H-imidazole-4-carboxamide (**IVb**)

White solid; ^{1}H NMR (400 MHz, DMSO-*d6*) *δ*: 1.34 (t, *J* = 7.2 Hz, 3H), 2.20 (s, 3H), 2.90 (dd, *J* = 14.8 Hz, *J* = 7.2 Hz, 2H), 7.22 (t, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 12.4 Hz, 1H), 8.07 (d, *J* = 4.4 Hz, 1H), 8.62 (s, 1H), 8.76 (s, 1H), 8.83 (d, *J* = 4.4 Hz, 1H), 8.89 (s, 1H), 10.19 (s, 1H); MS (ESI): $[M+H]^{+}$ 393 m/z.

N-(3,4-dimethylphenyl)-1-(4-(3-ethyl-1,2,4-oxadiazol-5-yl)pyridin-2-yl)-1H-imidazole-4-carboxamide (**IVc**)

White solid, Yield 68%; ^{1}H NMR (400 MHz, DMSO-*d6*) *δ*: 1.34 (t, *J* = 7.6 Hz, 3H), 2.19 (s, 3H), 2.22 (s, 3H), 2.90 (dd, *J* = 14.8 Hz, 7.2 Hz, 2H), 7.09 (d, *J* = 8.4Hz, 1H), 7.57 (d, *J* = 8.4Hz, 1H), 7.64 (s, 1H), 8.06 (d, *J* = 4.8 Hz, 1H), 8.61 (s, 1H), 8.72 (s, 1H), 8.84(d, *J* = 4.8 Hz, 1H), 8.89 (s, 1H), 9.82 (s, 1H); MS (ESI): $[M+H]^{+}$ 389 m/z.

General procedure for the synthesis of Cluster V (compounds **Va**, **Vb**)



ix. A 10 mL microwave vial was charged with compound **14** (1 eq., ~0.50 g), **15a** or **15b** (1 eq.) and thioglycolic acid (1 eq.) at room temperature. The resulting reaction mixture was stirred at 120°C for 15-20 min under microwave irradiation. The reaction progress was monitored by TLC (20% EtOAc in PE, **Va**: R_f = 0.3; **Vb**: R_f = 0.4). After completion of the reaction, the crude reaction mixture was purified by silica gel column (100-200 mesh) using 10% EtOAc in PE as eluent to afford **Va** (11% yield) or **Vb** (14% yield) as off white solids.

1-(1,3-benzothiazol-2-yl)-4-(2-isopropoxyphenyl)-3-methyl-4,8-dihydropyrazolo[3,4-e][1,4]thiazepin-7-one (**Va**)

Off white solid. ^{1}H NMR (400 MHz, DMSO-*d6*) *δ*: 1.32-1.34 (d, *J* = 4.8 Hz, 6H), 1.74 (s, 3H), 3.82-3.49 (q, *J* = 14.1 Hz, 2H), 4.73-4.79 (m, 1H), 5.59 (s, 1H), 6.83-6.87 (t, *J* = 7.4 Hz, 1H), 7.06-7.12 (q, *J* = 7.9 Hz, 2H), 7.26-7.29 (t, *J* = 7.0 Hz, 1H), 7.43-7.46 (t, *J* = 7.6 Hz, 1H), 7.54-7.58 (t, *J* = 7.6 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 7.6 Hz, 1H), 11.00 (s, 1H). LC-MS: RT 2.71, $[M+H]^+$ 451.44 m/z.

1-(1,3-benzothiazol-2-yl)-4-(4-methoxyphenyl)-3-methyl-4,8-dihydropyrazolo[3,4-e][1,4]thiazepin-7-one (**Vb**)

Off white solid. ^{1}H NMR (400 MHz, DMSO-*d6*) *δ*: 1.82 (s, 3H), 3.26 (s, 1H), 3.47 (d, *J* = 15.6 Hz, 1H), 3.75 (s, 3H), 5.54 (s, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.43-7.47 (td, *J* = 1.0, 7.7 Hz, 1H), 7.53-7.58 (td, *J* = 1.2, 7.6 Hz, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 8.10 (d, *J* = 7.2 Hz, 1H), 11.03 (s, 1H). LC-MS: RT 2.70, $[M+H]^{+}$ 423.23 m/z.