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Design and Synthesis of Novel Pyrazole Based Heterotricycles and their Derivatization via Automated Library Synthesis

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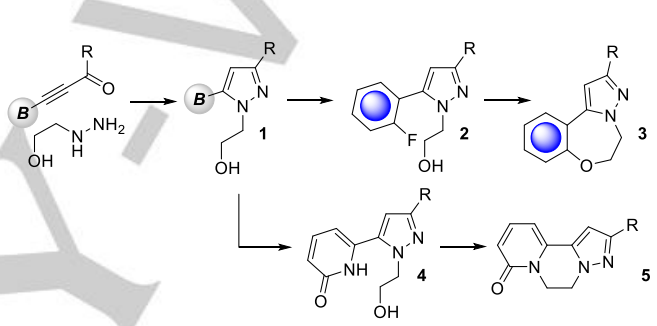
Abstract: Small molecule heterocycles bearing orthogonal functionality have the potential to deliver diverse structural motifs that aid the drug discovery effort. This work highlights how a readily assembled *N*-hydroxyethyl pyrazole trifluoroborate offers rapid access to architecturally distinct 5-6-6 and 5-7-6 fused tricyclic compounds. This chemistry is not only amenable to single compound synthesis, but also to high throughput experimentation. It enables easy access to diverse compound arrays with varying physchem and ADME profiles by fully automated library synthesis. The combination of the high throughput experimentation with rapid testing of the compounds in an integrated physchem and ADME profiling workflow allows accelerated design of novel lead compounds in drug discovery projects.

Introduction

Heteroaromatic scaffolds are prominent structural motifs in pharmaceutical agents, agrochemicals and functional materials; this aspect has motivated synthetic chemists to devise new strategies for their efficient and selective incorporation into a broad range of biologically active molecules. Boronic acid chemistry provides one of the most widely used approaches for the coupling of heteroaromatic systems because of the synthetic versatility of these compounds.[1] Several complementary strategies are available that enable rapid access to heterocyclic boronic acid derivatives, including borylation of C-X/C-H bonds,[2] cycloadditions[3] and cyclization[4] processes. In preceding publications, we have described the efficient synthesis of *N*-substituted pyrazole-5-trifluoroborate salts[5] and thiophene-5-trifluoroborates[6] from a common intermediate: an ynone trifluoroborate. We have demonstrated the compatibility of the trifluoroborate handle with condensation reactions, yielding heterocycles bearing the borate group readily installed.

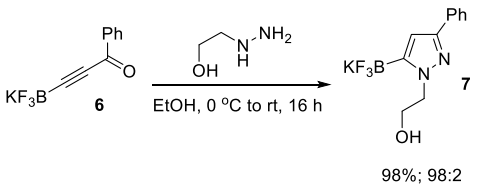
Pyrazoles are a remarkably prevalent moiety in drug discovery,[7] and we envisaged that our route to *N*-substituted pyrazole-5-trifluoroborate salts would allow easy access to novel types of fused tricyclic scaffolds with this privileged heterocycle at their core. Specifically, as shown in Scheme 1, condensation of hydroxyethyl hydrazide with the ynone would provide intermediate **1** that could be elaborated in a divergent manner to an oxazepane bridged tricycle **3**, or a piperazine bridged tricycle **5**. We report herein the successful implementation of this strategy and their profiling with regard to physicochemical and eADME properties.



Scheme 1. Divergent strategy to pyrazole-based tricycles.

Results and Discussion

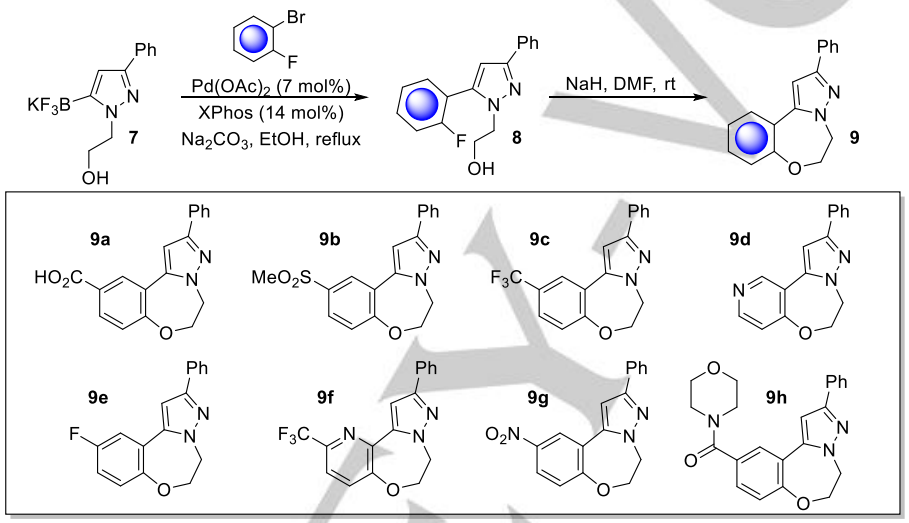
We began our studies by undertaking the condensation of *N*-ethanolhydrazine with phenylynone trifluoroborate **6**. We were pleased to find that this cyclization proceeded smoothly, furnishing potassium 2-(3-phenyl-5-(trifluoroboranyl)-1*H*-pyrazol-1-yl)ethan-1-ol **7** in excellent yield and regioselectivity (98%, 98:2; Scheme 2). Due to the significant difference in solubility of both regioisomers in acetone, the isolation of the desired major isomer in pure form was straightforward; this regioisomer was then used to generate two types of libraries, one leading to 5-7-6 fused tricycles, the other furnishing the 5-6-6 fused chemotype. Suzuki-Miyaura cross-coupling reactions were performed using an automated library synthesis/purification system available at Sanofi R&D in Frankfurt, Germany.



Scheme 2. Condensation of trifluoroborate **6** with *N*-ethanolhydrazine.

Synthesis of oxazepane bridged tricycles: For this first library, we had envisioned the introduction of an *ortho*-fluoride in the arene introduced during the Suzuki cross-coupling step, enabling a cyclization via nucleophilic aromatic substitution (Scheme 1, **2** → **3**). This approach complements the elegant synthesis of this class of tricycles by Virelli et al.[8] In the event, this two-step sequence worked well in general, and all compounds were characterized by ^{1}H NMR spectroscopy and LC-MS (with a small selection submitted for full characterization). These compounds were subsequently subjected to physchem and eADME profiling, and the results are summarized in Table 1. This approach allowed us to access diverse compounds with an attractive range of molecular weights and logD values spanning from 0 to 5. The generated scaffolds show limited solublity in water (pH 7.4) with only three candidates exhibiting a solubility >20 mg/mL, highlighting the importance of the substitution pattern for this parameter. Whereas the cell permeability (Caco-2 measurements) was generally good with values >20x10^{-7} cm/s for four of the compounds, the metabolic lability of these compounds in human microsomes was generally high; only 3 compounds showed values below 40% (**9a**, **9b** and **9h**). Finally, all but **9d** showed CYP Inhibition values with IC_{50} values >30.0 µM, which is not surprising given the presence of an unsubstituted pyridine moiety in this particular example.[9]

Table 1. Physical and biological properties of oxazepane bridged tricycles.

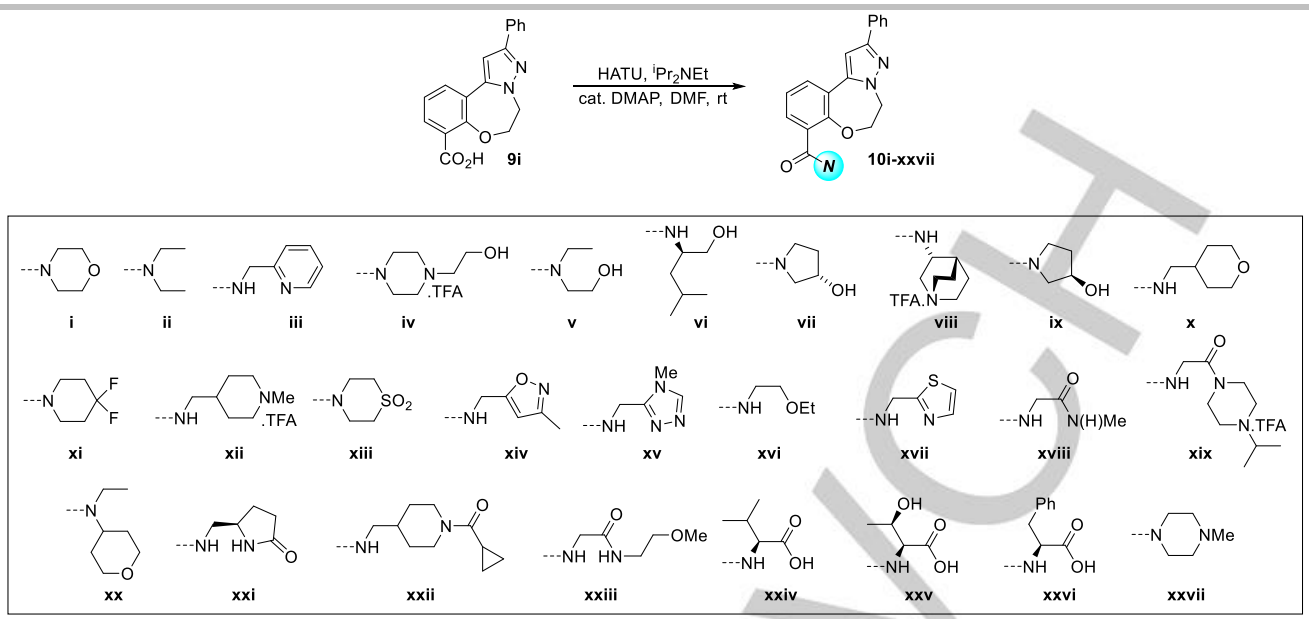


Product	Mol. Wt.	Caco-2[a]	Metabolic lability[b]	logD[c]	CYP inhibition[d]	Solubility[e]
9a	306.3	63.9	20	-0.04	> 30.0	1632
9b	340.4	53.6	-9	2.10	> 30.0	3
9c	330.3	NoVal	45	4.39	> 30.0	3
9d	263.3	NoVal	NoVal	1.48	14.6	87
9e	280.3	80.2	65	3.58	> 30.0	4
9f	331.3	NoVal	46	4.08	> 30.0	3
9g	307.3	NoVal	68	3.44	> 30.0	3
9h	375.4	154.7	38	1.77	> 30.0	26

[a] Caco-2; Mean; PTotal (A2B) (10^{-7} cm/s). [b] Metabolic lability in human microsomes; Total Metabolism (%), no CYP inhibitor added. [c] LogD (pH 7.4). [d] CYP inhibition, IC_{50} (INH) (µM), Isoform: CYP3A4, Substrate: Midazolam. [e] Solubility (pH 7.4; mg/ml), Mean. NoVal: Insufficient sample to perform the assay in this case.

The successful synthesis of compound **9a** highlighted that carboxylic acids could be tolerated in the coupling-cyclization sequence. We recognized that this offered a platform to exploit this vector in amide bond forming reactions, and we therefore prepared a further library with a range of amines coupled with carboxylic acid **9i**. The physchem and eADME profile of this new library is summarized in Table 2.

Table 2. Physical and biological properties of tricycle amide library.



Product	Mol. Wt.	Caco-2[a]	Metabolic Lability[b]	logD[c]	CYP inhibition[d]	Solubility[e]	Product	Mol. Wt.	Caco-2[a]	Metabolic lability[b]	logD[c]	CYP inhibition[d]	Solubility[e]
10i	375.4	205.2	13	1.80	> 30.0	230	**10xv**	400.4	57.2	6	1.17	> 30.0	80
10ii	361.5	189.1	31	2.69	> 30.0	29	**10xvi**	377.5	186.5	91	2.42	> 30.0	54
10iii	396.5	149.3	43	2.24	> 30.0	< 3	**10xvii**	402.5	184.8	63	2.23	5.8	< 3
10iv	532.5	80.9	22	1.11	> 30.0	> 939	**10xviii**	376.4	136.8	13	1.36	> 30.0	4
10v	377.5	141.8	30	1.71	> 30.0	> 1325	**10xix**	587.6	82.7	70	1.96	> 30.0	11
10vi	405.5	NoVal	93	2.64	> 30.0	< 3	**10xx**	417.5	210.7	90	2.32	> 30.0	> 1198
10vii	375.4	NoVal	6	1.25	> 30.0	> 1332	**10xxi**	402.5	36.0	14	1.26	> 30.0	227
10viii	528.5	14.2	8	1.07	> 30.0	> 946	**10xxii**	470.6	182.4	91	2.23	> 30.0	< 2
10ix	375.4	79.9	7	1.26	> 30.0	> 1332	**10xxiii**	420.5	131.1	18	1.53	> 30.0	4
10x	403.5	178.3	83	2.09	> 30.0	3	**10xxiv**	419.5	0.9	-2	1.00	> 30.0	1233
10xi	409.4	186.3	24	2.96	> 30.0	3	**10xxv**	421.5	0.0	1	0.54	> 30.0	1227
10xii	530.6	21.6	4	1.02	> 30.0	> 942	**10xxvi**	453.5	0.1	-6	1.43	> 30.0	1103
10xiii	423.5	90.2	7	1.74	> 30.0	83	**10xxvii**	388.5	120.3	57	1.54	> 30.0	1287
10xiv	400.4	172.4	31	2.4	27.6	< 3							

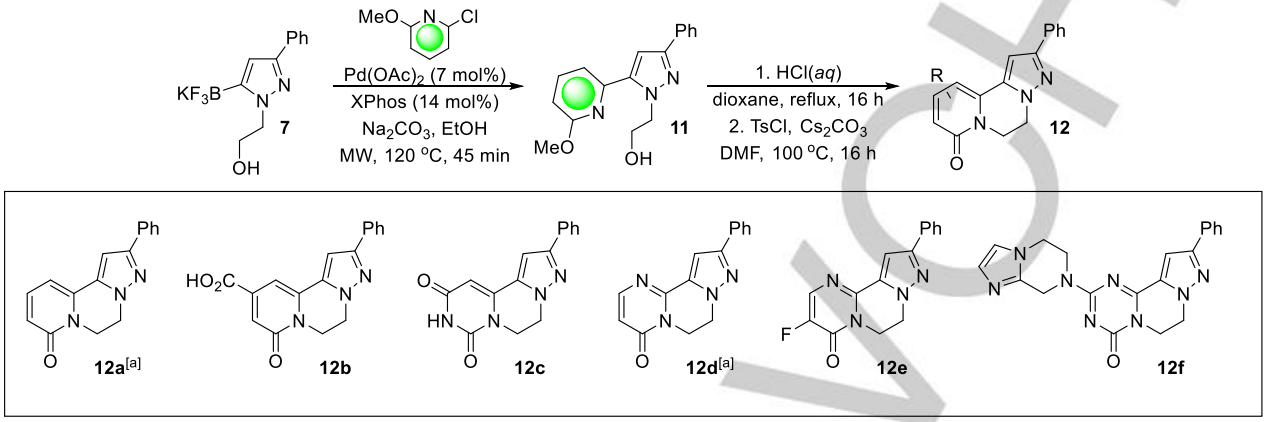
[a] Caco-2; Mean; PTotal (A2B) (10^{-7} cm/s). [b] Metabolic lability in human microsomes; Total Metabolism (%), no CYP inhibitor added. [c] LogD (pH 7.4). [d] CYP inhibition, IC_{50} (INH) (μM), Isoform: CYP3A4, Substrate: Midazolam. [e] Solubility (pH 7.4; mg/ml), Mean. NoVal: Insufficient sample to perform the assay in this case.

Interestingly, results arising from this library showed that the introduction of a series of amides could lead to a much broader range of values for both permeability and metabolic lability as compared to the parent tricycle system. These compounds showed acceptable permeability apart from 4 examples **10viii**, **10xxiv**, **10xxv** and **10xxvi**. The proportion of compounds showing acceptable metabolic lability was marginally improved over the previous library, albeit over a much larger number of examples. As expected, the use of amino acid coupling partners resulted in compounds with the lowest metabolic lability in this series. As observed in the previous library, CYP inhibition was not a general issue with this series and only compounds **10xiv** and **10xvii** providing measurable inhibition. As a conclusion, we identified compounds **10i**, **10iv**, **10v**, **10ix**, **10xiii** and **10xv** as having the most interesting overall physchem and eADME properties, albeit the latter two examples have relatively low solubility.

Synthesis of piperazine bridged tricycles: Our synthetic strategy to access the 5,6,6-fused tricyclic pyrazole series involved the cross coupling of our common precursor **7** with 2-bromo 6-alkoxyazine derivative, followed by hydrolysis and cyclization.

This synthetic route together with physchem and eADME profile data of this library is summarized in Table 3.

Table 3. Physical and biological properties of piperazine bridged tricycles.



Product	Mol. Wt.	Caco-2[b]	Metabolic lability[c]	logD[d]	CYP inhibition[e]	Solubility[f]
12a	263.3	187.7	76	1.11	> 30.0	278
12b	307.3	3.5	5	1.31	> 30.0	> 1172
12c	280.3	173.9	58	0.54	> 30.0	26
12d	264.3	284.2	94	0.79	> 30.0	86
12e	282.3	NoVal	60	2.17	> 30.0	9
12f	386.4	25.3	23	0.99	14.5	69

[a] The coupling reaction used the corresponding arylbromide. [b] Caco-2; Mean; PTotal (A2B) (10^{-7} cm/s). [c] Metabolic lability in human microsomes; Total Metabolism (%), no CYP inhibitor added. [d] LogD (pH 7.4). [e] CYP inhibition, IC_{50} (INH) (μM), Isoform: CYP3A4, Substrate: Midazolam. [f] Solubility (pH 7.4; mg/ml), Mean. NoVal: Insufficient sample to perform the assay in this case.

Pleasingly, the coupling conditions applied earlier were also found to be successful in introducing the azine groups using either aryl bromides or chlorides. Acidic hydrolysis followed by tosylation of the primary alcohol promoted in situ cyclization to the desired tricyclic compounds **12a-f**. This series exhibited generally high metabolic lability, with only **12b** and **12f** showing promising properties. However, the permeability of the cyclized compounds was encouraging and the solubility values were good to excellent. Overall however, as a conclusion, these 5-6-6 fused tricyclic compounds have less favorable overall properties as compared to the previous 5-7-6 fused systems, although only a limited selection of substitution patterns were evaluated.

Conclusion

We have successfully shown that pyrazole trifluoroborates are suitable precursors for automated parallel synthesis of novel tricyclic heteroaromatics. Efficient and regioselective synthesis of *N*-ethanol-pyrazole-5-trifluoroborate **1** and careful design of Suzuki partners enabled straightforward access to two unique classes of fused pyrazolotricycles with a broad range of physicochemical and eADME properties. The extension of this chemistry to the library synthesis of polycycles based on alternative heteroaromatic cores is underway and will be reported in due course.

Experimental Section

Potassium 2-(3-phenyl-5-(trifluoroboranyl)-1*H*-pyrazol-1-yl)ethan-1-ol (7). To a solution of ynone **6** (200 mg, 0.847 mmol) in ethanol (6 mL) at 0 °C was added 2-hydroxyethylhydrazine (186 mg, 2.03 mmol) dropwise under nitrogen. The reaction was followed by ^{19}F NMR spectroscopy, and upon completion, the mixture was evaporated to dryness. The residue was redissolved in the minimum of acetone and addition of Et_2O provided the title compound as a 92:8 mixture of regioisomers (244 mg, 98%). Removal of the minor isomer was achieved by trituration in acetone, and the major product isolated as an orange oil after removal of solvent. ^1H NMR (400 MHz, DMSO-d_6): δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.32 (t, *J* = 8.0 Hz, 2H), 7.19 (t, *J* = 8.0 Hz, 1H), 6.29 (s, 1H), 4.67 (t, *J* = 6.0 Hz, 1H), 4.17 (t, *J* = 7.0 Hz, 2H), 3.73 – 3.69 (m, 2H)); ^{13}C NMR (101 MHz, DMSO-d_6): δ 147.9, 134.9, 128.3, 126.2, 124.8, 105.4, 61.1, 52.6; ^{19}F NMR (376 MHz, DMSO-d_6): δ -136.7; ^{11}B NMR (128 MHz, DMSO-d_6): δ 2.2; FTIR: ν_{max} 3364 (br. w), 2947 (w), 1604 (w), 1430 (m), 1189 (s), 1139 (s); HRMS calculated for $C_{11}H_{11}{}^{11}BOF_3N_2$ (ESI^-): 255.0922. Found: 255.0928.

General Procedure for the Synthesis of oxazepane bridged tricycles 9. In a RG24-flask, the aryl bromide partner (0.5 mmol, 1 equiv) was put under argon atmosphere. Na_2CO_3 (1.5 mmol, 3 equiv) was added, followed by compound **7** (0.6 mmol, 1.2 equiv) in ethanol (3 mL). Palladium(II) acetate (0.04 mmol, 0.07 equiv) and XPhos ligand (0.07 mmol, 0.14 equiv) were added in ethanol (2 mL). The mixture was then heated at 80 °C until completion of the reaction (as judged by LC-MS analysis). Si-TMT-Scavenger (150 mg) was added and the reaction was stirred at rt for 4 h, filtered and washed with ethanol (2 mL). The crude was evaporated and redissolved in DMF and purified by preparative HPLC to yield the corresponding biaryl products. In the case of **9d**, the oxazepane product was formed directly in this step.

In a sealed tube, the biaryl intermediate (1 equiv) was dissolved in DMF (0.07 M) together with NaH (60% in paraffin; 1.1 equiv) and the mixture heated at 80 °C. The reaction was left to stir overnight and quenched by addition of water. The aqueous layer was acidified to pH 1 with HCl (37%) and extracted with CH_2Cl_2. The organic layer were dried over Na_2SO_4, filtered and all volatiles were removed. The residue was purified using reversed phase chromatography to yield compounds **9**.

Representative example: 2-(5-(3-fluoro-6-(trifluoromethyl)pyridin-2-yl)-3-phenyl-1*H*-pyrazol-1-yl)ethanol (9f). Following the general procedure, 2-bromo-3-fluoro-6-(trifluoromethyl)pyridine (127 mg, 0.50 mmol), **7** (163 mg, 0.55 mmol), $Pd(OAc)_2$ (7 mg, 0.04 mmol), XPhos (33 mg, 0.08 mmol) and Na_2CO_3 (109 mg, 1.00 mmol) were heated in ethanol (2.5 mL), the biaryl intermediate was obtained after reverse phase chromatography as a colourless oil (100 mg, 55%).

Following the general procedure using the biaryl product from the previous step (69 mg, 0.20 mmol) and NaH (60% in mineral oil, 9 mg, 0.22 mmol) in DMF (3.5 mL), the title compound was obtained after reverse phase chromatography as a colourless oil (46 mg, 71%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.89 (d, *J* = 7.0 Hz, 2H), 7.82 (d, *J* = 8.5 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.47 – 7.39 (m, 3H), 7.34 (t, *J* = 7.0 Hz, 1H), 4.81 – 4.79 (m, 2H), 4.69 – 4.67 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 154.2, 149.6, 141.5, 140.0 (d, *J* = 35.0 Hz), 135.7, 132.5, 130.4 (br), 128.7, 127.8, 125.2, 121.9 (d, *J* = 168.0 Hz), 120.6 (d, *J* = 102.5 Hz), 104.5, 68.5, 54.4; ^{19}F NMR (376 MHz, DMSO-d_6): δ -65.6; FTIR: ν_{max} 1593 (w), 1487 (m), 1455 (m), 1441 (m), 1354 (s), 1333 (s), 1286 (s), 1223 (s), 1163 (s), 1142 (s), 1120 (s); HRMS calculated for $C_{17}H_{12}F_3N_3O$ (ESI^+): 332.1005. Found: 332.1011.

Representative example: 2-Phenyl-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine-8-carboxylic acid (9i). Following the general procedure, 3-bromo-2-fluorobenzoic acid (110 mg, 0.50 mmol), **7** (163 mg, 0.55 mmol), $Pd(OAc)_2$ (8 mg, 0.04 mmol), XPhos (34 mg, 0.08 mmol) and Na_2CO_3 (111 mg, 1.00 mmol) were heated in ethanol (2.5 mL), the biaryl intermediate was obtained after reverse phase chromatography as a colourless oil (87 mg, 48%).

Following the general procedure using the biaryl product from the previous step (396 mg, 1.21 mmol) and NaH (60% in mineral oil, 243 mg, 6.07 mmol) in DMF (17 mL), the title compound was obtained after reverse phase chromatography as an off-white amorphous solid (141 mg, 38%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.06 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 2H), 7.57 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.38 (s, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 4.70 – 4.62 (m, 2H), 4.62 – 4.53 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 158.7, 156.3, 152.0, 149.7, 140.1, 132.8, 129.0, 128.7, 127.7, 125.3, 125.0, 120.6, 115.5, 103.1, 68.4, 54.5; FTIR: ν_{max} 3316 (w), 3047 (w), 2961 (w), 2906 (w), 1703 (m), 1288 (m); HRMS calculated for $C_{18}H_{14}N_2O_3$ (ESI^+): 307.1077. Found: 307.1081.

General Procedure for the Synthesis of piperazine bridged tricycles 12. In a RG24-flask, the aryl bromide partner (0.5 mmol, 1 equiv) was placed under argon atmosphere. Na_2CO_3 (1.5 mmol, 3 equiv) was added, followed by compound **7** (0.6 mmol, 1.2 equiv) in ethanol (3 mL). Palladium(II) acetate (0.04 mmol, 0.07 equiv) and XPhos ligand (0.07 mmol, 0.14 equiv) were added in ethanol (2 mL). The mixture was then heated at 80 °C until completion of the reaction (as judged by LC-MS analysis). Si-TMT-Scavenger (150 mg) was added and the reaction was stirred at rt for 4 h, filtered and washed with ethanol (2 mL). The crude was evaporated and redissolved in DMF and purified by preparative HPLC to yield the corresponding biaryl products.

A solution of HCl (4 M in 1,4-dioxane or water) was added to a solution of biaryl product (1 equiv) in 1,4-dioxane (0.15 M). The mixture was heated at reflux in a sealed tube. Upon completion, all volatiles were removed and the crude material was purified by column chromatography to yield the desired 2-pyridone product.

Tosyl chloride (2 equiv) and cesium carbonate (6 equiv) were added to a solution of 2-pyridone product from the previous step (1 equiv) in DMF (0.04 M) and the mixture was heated at reflux. Upon completion, water was added and the mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and filtered. All volatiles were removed and the crude was purified by column chromatography to afford the desired compounds **12**.

Representative example: 2-Phenyl-5*H*-pyrazolo[1,5-a]pyrido[2,1-c]pyrazin-8(6*H*)-one (12a). Following the general procedure, 2-bromo-6-methoxypyridine (370 µL, 3.00 mmol), **7** (970 mg, 3.30 mmol), $Pd(OAc)_2$ (48 mg, 0.21 mmol), XPhos (207 mg, 0.42 mmol) and Na_2CO_3 (637 mg, 6.00 mmol) were heated in ethanol (15 mL), the biaryl intermediate was obtained after reverse phase chromatography as an orange oil (851 mg, 96%).

Following the general procedure, the biaryl product (204 mg, 0. 62 mmol) was heated HCl in 1,4-dioxane (3.1 mL), the title compound was obtained after reverse phase chromatography as a colourless oil (161 mg, 91%).

Following general procedure, using the 2-pyridone from the previous step (145 mg, 0.52 mmol), tosyl chloride (204 mg, 1.03 mmol) and cesium carbonate (1.02 g, 3.09 mmol) in DMF (14 mL), the title compound was obtained after reverse phase chromatography as a colourless oil (116 mg, 85%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.84 (dd, J = 8.0, 1.0 Hz, 2H), 7.54 (dd, J = 9.0, 7.0 Hz, 1H), 7.48 – 7.40 (m, 3H), 7.34 (t, J = 7.0 Hz, 1H), 6.79 (dd, J = 7.0, 1.0 Hz, 1H), 6.46 (dd, J = 9.0, 1.0 Hz, 1H), 4.55 – 4.47 (m, 2H), 4.47 – 4.41 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 160.6, 150.9, 139.5, 135.3, 134.3, 132.5, 128.8, 128.0, 125.1, 118.7, 102.7, 100.8, 45.1, 39.7; FTIR: ν_{max} 3111 (w), 3065 (w), 2923 (w), 1653 (s), 1575 (s), 1529 (s), 1514 (m), 1458 (m), 1143 (s); HRMS calculated for $C_{16}H_{13}N_3O$ (ESI^+): 264.1131. Found: 264.1134.

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Keywords: ADME • boron • compound libraries • physicochemical • pyrazoles

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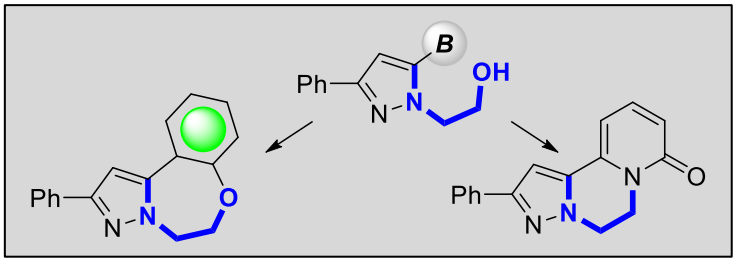

Taking shape! A readily accessible bifunctional pyrazole can be easily elaborated to architecturally distinct 5-6-6 and 5-7-6 fused tricyclic compounds. These have been further modified to new compound libraries bearing a broad range of physicochemical and eADME properties.