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Synthesis of substituted diazino[*c*]quinolin-5(6*H*)-ones, diazino[*c*]isoquinolin-6(5*H*)-ones, diazino[*c*]naphthyridin-6(5*H*)-ones and diazino[*c*]naphthyridin-5(6*H*)-ones

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ABSTRACT

Substituted diazino[*c*]quinolin-5(6*H*)-ones and -isoquinolin-6(5*H*)-ones, diazino[*c*]naphthyridin-6(5*H*)- and -5(6*H*)-ones were obtained using two synthetic routes: one-pot cross-coupling/cyclisation and two-step cross-coupling/KOH-mediated anionic ring closure. The two strategies gave yields in the same order of magnitude and their choice depends on the availability of the starting material.

1. Introduction

Phenanthridines and their aza-analogues benzonaphthyridines have been the subject of many attention owing to their interesting biological activities, leading to tremendous efforts to obtain straightforward access to these structures.[1] To date, di- and triaza analogues of phenanthridines remain less studied[1b,2] probably because of the limited access to starting materials, thus preventing their use as valuable scaffolds in medicinal chemistry.

Substituted (aza)phenanthridin-6(5*H*)-ones constitute chemical precursors of choice to obtain the corresponding (aza)phenanthridines, offering the possibility to further insert additional substituents in position 6.[1a,b] Among the great number of chemical routes to substituted (aza)phenanthridin-6(5*H*)-ones, which have been described, three methods offer a general access to these tricyclic compounds: (1) Pd-catalysed C–H arylation of N-protected benzamides followed by intramolecular N-arylation,[3] (2) one-pot Pd-catalysed cross-coupling/cyclisation between anilines and benzoates derivatives[1i,2a,4] and (3) Pd-catalysed cross-coupling with benzonitriles and fluorobenzenes derivatives followed by an anionic ring closure.[5] If the first methodology constitutes to date the most straightforward access to substituted phenanthridin-6(5*H*)-ones, it has never been used to synthesize azaphenanthridin-6(5*H*)-ones derivatives and requires in most cases an additional deprotection step.[3b,c] We thought that the two last methodologies could be successfully adapted to the synthesis of new di- and triazaphenanthridin-6(5*H*)-ones derivatives, and we wish to report here our efforts toward the synthesis of the unknown substituted diazino[*c*]quinolin-5(6*H*)-ones and -isoquinolin-6(5*H*)-ones, diazino[*c*]naphthyridin-6(5*H*)- and -5(6*H*)-ones using the two synthetic paths depicted in Fig. 1.

2. Results and discussion

We started our investigations by exploring path A. The three boronic esters **1a**–**c** were prepared in 36–99% yield according to a literature procedure,[6] and starting, respectively, from ethyl benzoate, ethyl 4-trifluoromethylbenzoate and ethyl isonicotinate (Scheme 1).

The Suzuki–Miyaura cross-coupling reactions using commercially available 2-amino-3-chloropyrazine, 5-amino-4-chloropyrimidine and 4-amino-5-iodopyrimidine as starting materials with the boronates **1a**–**c** were realized using classical conditions with $Pd(PPh_3)_4$ as the catalyst and K_3PO_4 as the base.[7] The expected

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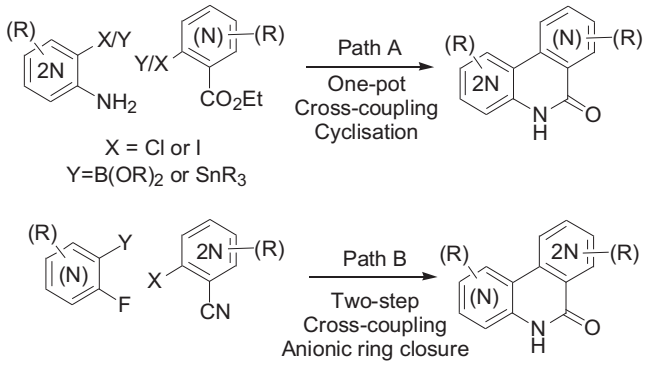
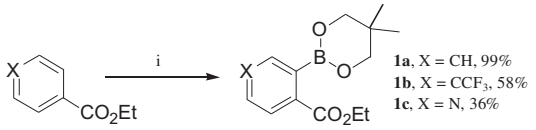


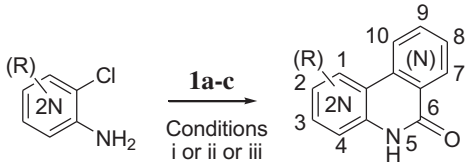
Fig. 1. Synthetic paths of diazino[*c*]quinolin-5(6*H*)-ones, diazino[*c*]isoquinolin-6(5*H*)-ones, diazino[*c*]naphthyridin-6(5*H*)-ones and diazino[*c*]naphthyridin-5(6*H*)-ones.



Scheme 1. Boronic esters **1a**–**c** synthesis. Isolated yields starting from the corresponding substituted ethyl benzoates or ethyl isonicotinate: (i) LTMP 1.5 equiv, B(O*i*-Pr)$_3$ 2.0 equiv, THF, −78 °C, over 3.5 h then neopentyl glycol 1.5 equiv, AcOH 1.5 equiv.

pyrazino[2,3-*c*]-, pyrimidino[5,4-*c*]- and pyrimidino[4,5-*c*]isoquinolin-6(5*H*)-ones and their naphthyridin-6(5*H*)-ones analogues **5a**–**g** were obtained in yields ranging from 11 to 80% (Table 1). For pyrimidino derivatives **5d**–**g**, low yields could be explained by their higher solubility in MeOH/water medium used for purification process. Using the more hindered 4-amino-5-chloro-2,6-dimethylpyrimidine, the catalytic system had to be replaced by Pd(OAc)$_2$/*S*-Phos to achieve a good conversion to **5h**, which was isolated in a 71% yield (Table 1).[8]

Table 1
Synthesis of substituted diazino[*c*](iso)quinolin-6-(5*H*)-ones and diazino[*c*]-2,6-naphthyridin-6-(5*H*)-ones **5a**–**h** through path A

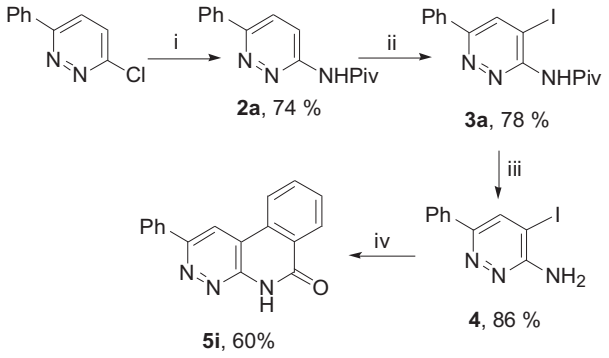


5 a-h

Coupling partners	Products				Isolated yields (%)
	N1	N2	N3	R	
2-NH$_2$–3-Cl–pyrazine/**1a**	1	4	—	—	**5a**, 61[i]
2-NH$_2$–3-Cl–pyrazine/**1b**	1	4	—	9-CF$_3$	**5b**, 50[i]
2-NH$_2$–3-Cl–pyrazine/**1c**	1	4	9	—	**5c**, 80[i]
5-NH$_2$–4-Cl–pyrimidine/**1a**	1	3	—	—	**5d**, 40[i]
5-NH$_2$–4-Cl–pyrimidine/**1b**	1	3	—	9-CF$_3$	**5e**, 11[i]
5-NH$_2$–4-Cl–pyrimidine/**1c**	1	3	9	—	**5f**, 43[i]
4-NH$_2$–5-I–pyrimidine·HCl/**1a**	2	4	—	—	**5g**, 41[ii]
4-NH$_2$–5-Cl–2,6-diMe–pyrimidine/**1a**	2	4	—	1,3-diMe	**5h**, 71[iii]

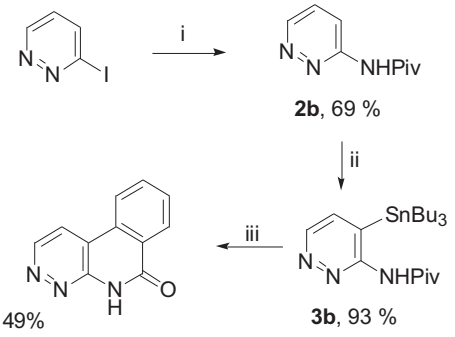
Conditions: (i) Sealed tube, Pd(PPh$_3$)$_4$ 8 mol %, diazine 1 equiv, boronic species 3.0 equiv, K$_3$PO$_4$ 3.0 equiv, dioxane/H$_2$O 12:1, reflux, overnight. (ii) Sealed tube, Pd(PPh$_3$)$_4$ 8 mol %, diazine 1 equiv, boronic species 3.0 equiv, K$_3$PO$_4$ 5.0 equiv, dioxane/H$_2$O 12:1, reflux, overnight. (iii) Sealed tube, diazine 1 equiv, boronic species 3.0 equiv, K$_3$PO$_4$ 3.0 equiv, Pd(OAc)$_2$ 5 mol %, *S*-Phos 10 mol %, dioxane/H$_2$O 12:1, reflux, overnight.

In the pyridazine series, we first prepared the 3-amino-4-iodo-6-phenylpyridazine (**4**) in an overall 50% yield as follows: 3-chloro-6-phenylpyridazine was aminated with pivalamide using Pd(OAc)$_2$/BINAP as catalyst affording the aminated pyridazine **2a** in 74% yield. Compound **2a** was then iodinated in 78% yield by metallation with LTMP (Lithium 2,2,6,6-TetraMethylPiperidinyl amide) as base and using I$_2$ as the electrophile. The resulting pivalamide **3a** was finally deprotected under acidic conditions to afford **4** in 86% yield. The coupling of pyridazine **4** with **1a** under the previous conditions gave the expected 2-phenylpyridazino[3,4-*c*]isoquinolin-6(5*H*)-one (**5i**) in 60% yield (Scheme 2).



Scheme 2. Synthesis of 2-phenylpyridazino[3,4-*c*]iso-quinolin-6(5*H*)-one **5i**. Isolated yields, conditions: (i) 2,2,2-trimethylacetamide 1.2 equiv, Binap 10 mol %, Pd(OAc)$_2$ 5 mol %, Cs$_2$CO$_3$, dioxane; (ii) LTMP 8.0 equiv, THF, −78 °C, over 1.5 h then I$_2$ 8.2 equiv; (iii) H$_2$SO$_4$ (5 M), reflux, overnight; (iv) sealed tube, Pd(PPh$_3$)$_4$ 8 mol %, **1a** 3.0 equiv, K$_3$PO$_4$ 3.0 equiv, dioxane/H$_2$O 12:1, reflux, overnight.

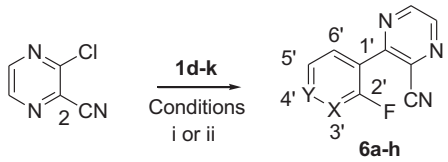
In order to access the unsubstituted analogue of **5i**, we first applied the metallation/iodination sequence as described in Scheme 2. Unfortunately, this procedure let to degradation of the starting material **2b**. We then prepared the 4-stannylated pyridazine **3b** according to the same route as for **3a** starting from 3-iodopyridazine[9] and using Bu$_3$SnCl as the electrophile after the metallation step. Unsubstituted pyridazino[3,4-*c*]isoquinolinone (**5j**) was then obtained in 49% yield according to a Stille cross-coupling[10] between ethyl 2-iodobenzoate and **3b** using Pd(OAc)$_2$/*S*-Phos in refluxing toluene (Scheme 3).



Scheme 3. Synthesis of pyridazino[3,4-*c*]isoquinolin-6(5*H*)one **5j**. Isolated yields, conditions: (i) 2,2,2-trimethylacetamide 1.2 equiv, Binap 10 mol %, Pd(OAc)$_2$ 5 mol %, Cs$_2$CO$_3$, dioxane; (ii) LTMP 4.0 equiv, THF, −78 °C, over 1.5 h then Bu$_3$SnCl 2.1 equiv; (iii) ethyl 2-iodobenzoate 1.1 equiv, Pd(OAc)$_2$ 5 mol %, *S*-Phos 10 mol %, toluene, reflux, overnight.

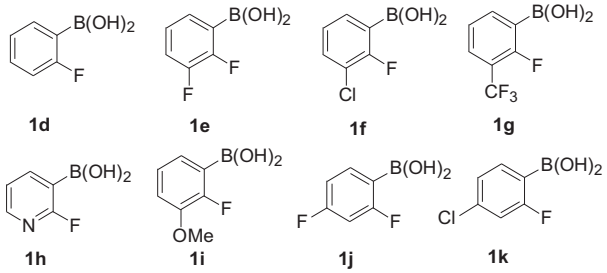
The previous one-pot cross-coupling/cyclisation for the synthesis of diaza-analogues of phenanthridinones and benzonaphthyridinones **5a**–**j** appeared to be efficient, provided that the starting materials were available. We were then interested in the alternative route B, for which we have already demonstrated it was a very general way for the synthesis of phenanthridinones and benzonaphthyridinones.[5] The key-step of this route is the KOH-mediated anionic ring closure involving a biaryl compound bearing a cyano group in position 2 and a fluorine atom in position 2′ (see scheme of Table 2). We first synthesized the biaryl compounds **6a**–**h** using commercially available substituted 2-fluoroarylboronic acids **1d**–**k** (Scheme 4), which were coupled to 3-chloro-2-cyanopyrazine in the presence of Pd(OAc)$_2$/*S*-Phos as the catalyst.

Table 2
Synthesis of substituted 3-(2-fluoroaryl or -pyridinyl)pyrazine-2-carbonitriles **6a**–**h** via Suzuki cross-coupling (path B)



Boronic species	Products		Isolated yield (%)
	X	Y	
1d	CH	CH	**6a**, 83[i]
1e	CF	CH	**6b**, 61[ii]
1f	CCl	CH	**6c**, 69[i]
1g	CCF_3	CH	**6d**, 56[ii]
1h	N	CH	**6e**, 55[i]
1i	COMe	CH	**6f**, 84[i]
1j	CH	CF	**6g**, 71[ii]
1k	CH	CCl	**6h**, 72[i]

Conditions: (i) $Pd(OAc)_2$ 5 mol %, *S*-Phos 10 mol %, 3-chloro-2-cyanopyrazine 1 equiv, boronic species 1.05 equiv, Na_2CO_3 4 equiv, DME/H_2O 2:1, reflux, 15 min. (ii) $Pd(OAc)_2$ 5 mol %, *S*-Phos 10 mol %, 3-chloro-2-cyanopyrazine 1 equiv, boronic species 1.5 equiv, Na_2CO_3 4 equiv, DME/H_2O 2:1, reflux, overnight.

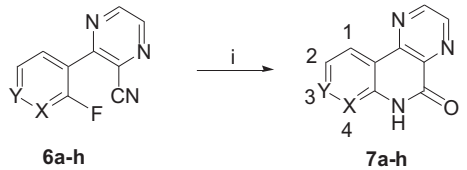


Scheme 4. Commercially available boronic acids **1d**–**k** selected for path B.

The biaryl compounds **6a**–**h** were obtained in 55–84% yields (Table 2).

Biaryls **6a**–**h** were then submitted to KOH-mediated anionic ring closure in *t*-BuOH at 150 °C for 1.5 h. The expected pyrazino [2,3-*c*]quinolin-5(6*H*)-ones **7a**–**d**,**f**–**h** were isolated after precipitation and filtration in 64–97% yields. Using the same conditions, pyrazino[2,3-*c*]-[1,8]naphthyridin-5(6*H*)-one **7e** was isolated with a lower 52% yield, probably due to competitive direct substitution of the fluorine atom adjacent to the nitrogen atom by the hydroxide anion (Table 3).

Table 3
Synthesis of substituted pyrazino[2,3-*c*]quinolin-5(6*H*)-ones and pyrazino[2,3-*c*]-[1,8]naphthyridin-5(6*H*)-one **7a**–**h** via KOH-mediated anionic ring closure (path B)



Starting material	Products		Isolated yield (%)
	X	Y	
6a	CH	CH	**7a**, 67
6b	CF	CH	**7b**, 88
6c	CCl	CH	**7c**, 69
6d	CCF_3	CH	**7d**, 73
6e	N	CH	**7e**, 52
6f	COMe	CH	**7f**, 64
6g	CH	CF	**7g**, 97
6h	CH	CCl	**7h**, 88

Conditions: (i) Sealed tube, KOH 5 equiv, *t*-BuOH, 150 °C, 1.5 h.

3. Conclusion

In summary, we have demonstrated that the two routes A and B are both efficient to provide an easy access to di- and triazaphenanthridin-6(5*H*)-ones. The one-pot cross-coupling/cyclisation method (Path A) gave the expected diazino[*c*]isoquinolin-6(5*H*)-ones and diazino[*c*]-[2,6]-naphthyridin-6(5*H*)-ones in 11–80%. The two-step cross-coupling/anionic ring closure route (path B) afforded pyrazino[2,3-*c*]quinolin-5(6*H*)-ones and pyrazino [2,3-*c*]-[1,8]-naphthyridin-5(6*H*)-one in 29–69% overall yields. If the one-pot procedure can appear more attractive, the two-step route gave yields in the same order of magnitude and the choice depends on the availability of the starting material.

4. Experimental section

4.1. General

Reagents and solvents were bought from chemical suppliers and generally used without further purification except compounds **1a**,[6] 3-iodopyridazine[9] and 5-iodopyrimidin-4-amine hydrochloride[11] prepared from literature procedures. THF and toluene were dried and distilled over sodium and benzophenone under N_2. Reactions were followed by ^1H or ^{19}F NMR of the crude mixture or by Thin Layer Chromatography (TLC) on silica gel (Merck, Darmstadt, Germany) and revealed using UV light. Most of the compounds were purified by flash silica gel column chromatography (70–200 μm). The purity of synthetic products was established by NMR spectroscopic data, and MS analysis. MS: Thermo Finnigan, LCQ Advantage Max, Electrospray Ionisation, Source heater *T*=220 °C, capillary voltage=33 V. High Resolution Mass Spectra (HRMS) were recorded with a Q-TOF Micromass Instrument in the positive ESI (CV=30 V) mode. ^1H (300 MHz), ^{19}F (282 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker Avance DMX 300 instrument. TMS signal or the residual signal of deuterated solvent was taken as internal reference for ^1H and ^{13}C spectra and $CFCl_3$ signal for ^{19}F spectra. Melting points were determinate on a Kofler melting point apparatus. IR spectra were recorded on Perkin–Elmer IRFT 1650 spectrometer.

4.2. General procedure for the synthesis of boronic esters (1a–c)

To a solution of 2,2,6,6-tetramethylpiperidine (TMPH, 1.5 equiv) in THF (2 mL/mmol of ester), a solution of *n*-butyllithium (1.45 M in hexane, 1.5 equiv) was added at −30 °C over 30 min. After cooling at −78 °C, tris(isopropyl)borate (2.0 equiv) was added over 20 min. Ethyl benzoate or 4-(trifluoromethyl)benzoate or ethyl isonicotinate (1.0 equiv) was added via syringe to the reaction mixture over 10 min and the mixture was stirred at −78 °C for 3.5 h. After warming to −30 °C, glacial acetic acid (1.5 equiv) was added causing the internal temperature rising to −10 °C. Neopentyl glycol (1.5 equiv) was added and the mixture was stirred at room temperature for 2 h. Dichloromethane (20 mL/mmol of ester) was then added. The organic phase was successively washed three times with satd aqueous NH_4Cl, with satd aqueous $NaHCO_3$ and with water, dried over $MgSO_4$ and evaporated to give the desired compounds.

*4.2.1. Ethyl 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate (**1a**).*[6] Following general procedure **1a** was obtained as a yellow oil (3.30 g, 99%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J*=7.8 Hz, 1H), 7.53–7.48 (m, 2H), 7.42–7.34 (m, 1H), 4.38 (q, *J*=7.1 Hz, 2H), 3.80 (s, 4H), 1.39 (t, *J*=7.1 Hz, 3H), 1.11 (s, 6H).

*4.2.2. Ethyl 2-(5,5-dimethyl-[1,3]-dioxoborinan-2-yl)-4-trifluoromethylbenzoate (**1b**).* Following general procedure **1b** was

obtained as a dark oil (1.45 g, 58%). IR (neat) ν (cm^{-1}) 2965, 1714 (C=O), 1478, 1343, 1276, 1167, 1124, 1088; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J=8.2 Hz, 1H), 7.76 (s, 1H), 7.64 (d, J=8.2 Hz, 1H), 4.41 (q, J=7.1 Hz, 2H), 3.80 (s, 4H), 1.41 (t, J=7.1 Hz, 3H), 1.12 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 136.6 (q, J=1.2 Hz), 133.2 (q, ^2J=32.6 Hz), 128.8 (2C), 128.3 (q, ^3J=3.6 Hz), 125.4 (q, ^3J=3.8 Hz), 123.8 (d, ^1J=272.9 Hz), 72.6 (2C), 61.8, 31.9, 22.1 (2C), 14.3. ^{19}F NMR (282 MHz, $CDCl_3$): δ −63.5 (s); MS (ESI^+): 331 [M+H], 313, 259, 231, 158.

*4.2.3. Ethyl 2-(5,5-dimethyl-[1,3]-dioxoborinan-2-yl)isonicotinate (**1c**).* Following general procedure **1c** was obtained as a yellow oil (1.88 g, 36%). IR (neat) ν (cm^{-1}) 2914, 2863, 1715 (C=O), 1310, 1293, 1095; ^1H NMR (300 MHz, $CDCl_3$) δ 8.95 (d, J=5.0 Hz, 1H), 8.74 (s, 1H), 7.90 (d, J=5.0 Hz, 1H), 4.15 (q, J=7.1 Hz, 2H), 3.64 (s, 4H), 1.13 (t, J=7.1 Hz, 3H), 0.97 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 152.3, 148.7, 142.8, 133.9, 122.9, 72.9 (2C), 62.6, 29.7, 21.5 (2C), 13.6; MS (ESI^+): 257, 236, 218, 164.

4.3. General procedure for the synthesis of *N*-(pyridazin-3-yl) pivalamides (2a,b)

To degassed dioxane (3 mL/mmol of halide), 3-chloro-6-phenylpyridazine or 3-iodopyridazine (1 equiv), trimethylacetamide (1.2 equiv), Cs_2CO_3 (2.5 equiv), BINAP (10 mol %) and $Pd(OAc)_2$ (5 mol %) were introduced. The mixture was heated at 100 °C for 24 h under Ar. The resulting solution was filtered and washed with dioxane. The filtrate was evaporated to dryness and purified by column chromatography (eluent: PE/AcOEt (7:3)) to afford the desired compounds.

*4.3.1. N-(6-Phenylpyridazin-3-yl)pivalamide (**2a**).* Following general procedure, **2a** was obtained as a white powder (199 mg, 74%); mp 172–173 °C; IR (neat) ν (cm^{-1}) 3382 (NH), 2973, 1686 (C=O), 1509, 1486, 1351, 1294, 1141, 1121; ^1H NMR (300 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.55 (d, J=9.3 Hz, 1H), 8.02 (dd, J=7.9, 1.6 Hz, 2H), 7.87 (d, J=9.3 Hz, 1H), 7.56–7.45 (m, 3H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 156.7, 154.1, 136.1, 129.7, 129.0 (2C), 126.7 (2C), 125.9, 119.0, 40.1, 27.4; HRMS (ESI^+): calcd for $C_{15}H_{18}N_3O$ m/z 256.1450 [M+H], found 256.1451.

*4.3.2. N-(Pyridazin-3-yl)pivalamide (**2b**).*[12] Following general procedure **2b** was obtained as a white powder (1.21 g, 69%). ^1H NMR (300 MHz, $CDCl_3$): δ 8.91 (dd, J=4.6, 1.5 Hz, 1H), 8.52 (s, 1H), 8.48 (dd, J=9.0, 1.5 Hz, 1H), 7.47 (dd, J=9.0, 4.6 Hz, 1H), 1.25 (s, 9H). HRMS (ESI^+): calcd for $C_9H_{14}N_3O$ m/z 180.1137 [M+H], found 180.1140.

4.4. Synthesis of *N*-(4-iodo-6-phenylpyridazin-3-yl)pivalamide (3a)

A solution of *n*-butyllithium (24.1 mL, 1.3 M in hexane, 31.3 mmol, 8.0 equiv) was added to a cold (−78 °C) and anhydrous solution of TMPH (5.3 mL, 31.3 mmol, 8.0 equiv) in THF (25 mL). The mixture was warmed to 0 °C. After 30 min, the mixture was cooled to −78 °C and a cold (−78 °C) solution of *N*-(6-phenylpyridazin-3-yl)pivalamide (**2a**) (1.01 g, 3.9 mmol) in THF (20 mL) was added dropwise. Then, the mixture was stirred for 90 min. At −78 °C, iodine (8.20 g, 32.1 mmol, 8.2 equiv) was introduced and stirring was maintained for 90 min at the same temperature. Hydrolysis was then carried out at −78 °C using satd aqueous NH_4Cl (50 mL). Temperature was raised to room temperature and the solution was decolorized with satd aqueous sodium thiosulfate (30 mL) and evaporated nearly to dryness. The residue was extracted with dichloromethane (4×40 mL), then the combined organic extracts were dried over magnesium sulfate and evaporated in vacuum. The residue was purified by column chromatography (eluent: PE/EtOAc (7:3)) to give the desired compound **3a** as a bright orange powder (1.17 g, 78%); mp 135–137 °C; IR (neat) ν (cm^{-1}) 3241 (NH), 2973, 2927, 1656 (C=O), 1485, 1447, 1400, 1180, 1019; ^1H NMR (300 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.26 (s, 1H), 7.91–7.87 (m, 2H), 7.56–7.46 (m, 3H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 157.2, 155.7, 136.8, 134.4, 130.4, 129.1 (2C), 127.2 (2C), 101.3, 39.8, 27.4 (3C); HRMS (ESI^+): calcd for $C_{15}H_{17}IN_3O$ m/z 382.0416 [M+H], found 382.0425.

4.5. Synthesis of *N*-(4-(tri(*n*-butyl)stannyl)pyridazin-3-yl)pivalamide (3b)

A solution of *n*-butyllithium (17.6 mL, 1.53 M in hexane, 24 mmol, 4.0 equiv) was added to a cold (−78 °C) and anhydrous solution of TMPH (4.6 mL, 27 mmol, 4.0 equiv) in THF (40 mL). The mixture was warmed to 0 °C. After 20 min, the mixture was cooled to −78 °C and a solution of *N*-(pyridazin-3-yl)pivalamide **2b** (1.21 g, 6.7 mmol) in THF (20 mL) was added dropwise. The mixture was then stirred for 1 h 15 min. At −78 °C, tri(*n*-butyl)tin chloride (7.5 mL, 27.7 mmol, 4.1 equiv) was introduced and the stirring was maintained for 90 min at the same temperature. Hydrolysis was then carried out at −78 °C using satd aqueous NH_4Cl (50 mL). Temperature was raised to room temperature and the reaction mixture was evaporated to dryness. The residue was extracted with dichloromethane (5×40 mL). The combined organic extracts were then dried over magnesium sulfate and evaporated in vacuum. The residue was purified by column chromatography (eluent: PE/EtOAc (8:2)) to give the desired compound **3b** as a yellow solid (2.94 g, 93%); mp<50 °C; IR (neat) ν (cm^{-1}) 3160 (NH), 2957, 2918, 1670 (C=O), 1498, 1405, 1337, 1279, 1179; ^1H NMR (300 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.74 (d, J=5.4 Hz, 1H), 7.57 (d, J=5.4 Hz, 1H), 1.53–1.43 (m, 6H), 1.36–1.24 (m, 6H), 1.32 (s, 9H), 1.08–1.03 (m, 6H), 0.92–0.84 (m, 9H); Selected ^{13}C NMR data (75 MHz, $CDCl_3$) δ 178.6, 160.2, 147.5, 139.9, 137.7, 39.5, 27.3 (3C); HRMS (ESI^+): calcd for $C_{21}H_{40}N_3OSn$ m/z 470.2193 [M+H], found 470.2199.

4.6. Synthesis of 3-amino-4-iodo-6-phenylpyridazine (4)

In sealed tube, **3a** (1.0 g, 2.6 mmol) was dissolved into aqueous 5 M H_2SO_4 (7.9 mL, 3 mL/mmol) and the resulting solution was heated at 95 °C for 7 h. After cooling to room temperature, the mixture was diluted with water (30 mL) and the aqueous phase was washed with ethyl acetate (3×20 mL). The pH of combined aqueous phase was fixed at 10 with an aqueous 2 M sodium hydroxide solution (20 mL) and the resulting aqueous phase was extracted with ethyl acetate (3×20 mL). The combined organic phase was dried over magnesium sulfate and evaporated to dryness, giving the desired compound **4** as a bright brown solid (0.67 g, 86%); mp 178–179 °C; IR (neat) ν (cm^{-1}) 3468, 3276, 1636, 1510, 1490, 1450, 1433, 1262, 1184, 1015; ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.92 (dd, J=8.0, 1.5 Hz, 2H), 7.52–7.39 (m, 3H), 5.34 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 152.2, 135.7, 135.4, 129.1, 128.9 (2C), 126.2 (2C), 89.7; HRMS (ESI^+): calcd for $C_{10}H_9IN_3$ m/z 297.9841 [M+H], found 297.9833.

4.7. General procedure for tandem Suzuki cross coupling–cyclisation reactions (compounds 5a–i)[13]

In a sealed tube and under argon atmosphere, the appropriate diazine (1.0 equiv) and the corresponding boronic ester (3.0 equiv) were dissolved in a mixture of dioxane/water 12:1 (7.7 mL/mmol of diazine), then K_3PO_4 (3.0 or 5.0 equiv) and palladium catalyst ($Pd(PPh_3)_4$ 8 mol % or $Pd(OAc)_2$ 5 mol %+*S*-Phos 10 mol %) were added. The reaction mixture was refluxed overnight and then cooled to room temperature. The crude product was evaporated to dryness and purified using column chromatography or precipitated in MeOH/water (2:1) (20 mL/mmol of diazine).

*4.7.1. Pyrazino[2,3-c]isoquinolin-6(5H)-one (**5a**).* Starting from 2-amino-3-chloropyrazine (100 mg, 0.77 mmol) and boronic ester **1a**, following general procedure, **5a** was obtained after precipitation as a yellow powder (94 mg, 61%); mp>260 °C; IR (neat) ν (cm^{-1}) 3010, 2876, 1653 (C=O), 1607, 1504, 1414, 1341, 1073; ^1H NMR (300 MHz, DMSO-d_6) δ 12.34 (s, 1H), 8.70 (d, J=7.6 Hz, 1H), 8.58 (d, J=2.4 Hz, 1H), 8.56 (d, J=2.4 Hz, 1H), 8.33 (d, J=7.6 Hz, 1H), 7.97 (dd, J =7.6, 7.6 Hz, 1H), 7.82 (dd, J =7.6, 7.6 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.0, 144.6, 143.7, 139.1, 133.6, 133.3, 131.9, 130.5, 127.4 (2C), 123.4; HRMS (ESI^+): calcd for $C_{11}H_8N_3O$ m/z 198.0667 [M+H], found 198.0668.

*4.7.2. 9-(Trifluoromethyl)pyrazino[2,3-c]-isoquinolin-6(5H)-one (**5b**).* Starting from 2-amino-3-chloropyrazine (91 mg, 0.70 mmol) and boronic ester **1b**, following general procedure, **5b** was obtained after precipitation as a white powder (94 mg, 50%); mp>260 °C; IR (neat) ν (cm^{-1}) 3300 (NH), 2926, 2868, 1690, 1664 (C=O), 1409, 1351, 1298, 1254, 1179, 1125, 1067; ^1H NMR (300 MHz, DMSO-d_6) δ 12.60 (s, 1H), 8.89 (s, 1H), 8.63 (d, J=2.4 Hz, 1H), 8.62 (d, J=2.4 Hz, 1H), 8.50 (d, J=8.3 Hz, 1H), 8.12 (dd, J=8.3, 1.1 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.6, 145.1, 144.8, 139.5, 134.3, 132.9 (q, ^2J=32.2 Hz), 131.0, 130.3, 129.1, 126.4 (q, ^3J=3.2 Hz), 123.6 (q, ^1J=266.6 Hz), 120.2 (q, ^3J=4.1 Hz); ^{19}F NMR (282 MHz, DMSO-d_6): δ −61.7 (s); HRMS (ESI^+): calcd for $C_{12}H_7F_3N_3O$ m/z 266.0541 [M+H], found 266.0550.

*4.7.3. Pyrazino[2,3-c]-2,6-naphthyridin-6(5H)-one (**5c**).* Starting from 2-amino-3-chloropyrazine (142 mg, 1.08 mmol) and boronic ester **1c**, following general procedure, **5c** was obtained after precipitation as a yellow powder (172 mg, 80%); mp>260 °C; IR (neat) ν (cm^{-1}) 3372 (NH), 2665, 1672 (C=O), 1538, 1397, 1326, 1107, 1019; ^1H NMR (300 MHz, DMSO-d_6) δ 12.66 (s, 1H), 9.94 (s, 1H), 8.98 (d, J=5.2 Hz, 1H), 8.64 (d, J=2.2 Hz, 1H), 8.63 (d, J=2.2 Hz, 1H), 8.15 (d, J=5.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.7, 150.4, 146.8, 145.2, 144.4, 139.6, 133.1, 130.8, 127.7, 119.8; HRMS (ESI^+): calcd for $C_{10}H_7N_4O$ m/z 199.0620 [M+H], found 199.0609.

*4.7.4. Pyrimido[5,4-c]isoquinolin-6(5H)-one (**5d**).* Starting from 5-amino-4-chloropyrimidine (91 mg, 0.69 mmol) and boronic ester **1a**, following general procedure, **5d** was obtained after precipitation as a dark brown powder (55 mg, 40%); mp>260 °C; IR (neat) ν (cm^{-1}) 3014, 2877, 1667 (C=O), 1610, 1585, 1434, 1398, 1355, 1334, 1300; ^1H NMR (300 MHz, DMSO-d_6) δ 11.97 (s, 1H), 9.08 (s, 1H), 8.81 (s, 1H), 8.76 (dd, J=7.7, 1.0 Hz, 1H), 8.36 (dd, J=7.7, 1.0 Hz, 1H), 8.00 (ddd, J = 7.7, 7.7 Hz and J=1.0 Hz, 1H), 7.90 (ddd, J = 7.7, 7.7 Hz and J=1.0 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.0, 152.0, 145.0, 140.6, 133.4, 133.1, 131.8, 130.3, 129.1, 127.4, 123.7; HRMS (ESI^+): calcd for $C_{11}H_8N_3O$ m/z 198.0667 [M+H], found 198.0668.

*4.7.5. 9-(Trifluoromethyl)pyrimido[5,4-c]-isoquinolin-6(5H)-one (**5e**).* Starting from 5-amino-4-chloropyrimidine (92 mg, 0.71 mmol) and boronic ester **1b**, following general procedure, **5e** was obtained after precipitation as a grey powder (21 mg, 11%); mp>260 °C; IR (neat) ν (cm^{-1}) 3375 (NH), 2874, 1675 (C=O), 1407, 1314, 1289, 1262, 1174, 1121, 1066; ^1H NMR (300 MHz, DMSO-d_6) δ 12.19 (s, 1H), 9.08 (s, 1H), 8.88 (s, 1H), 8.81 (s, 1H), 8.47 (d, J=8.3 Hz, 1H), 8.16 (dd, J=8.3, 1.6 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.1, 152.2, 145.6, 139.5, 133.7, 132.9 (q, ^2J=32.5 Hz), 131.9, 130.7, 129.1, 127.7 (q, ^3J=3.3 Hz), 123.6 (q, ^1J=273.1 Hz), 120.4 (q, ^3J=4.0 Hz); ^{19}F NMR (282 MHz, DMSO-d_6): δ −61.8 (s); HRMS (ESI^+): calcd for $C_{12}H_7F_3N_3O$ m/z 266.0541 [M+H], found 266.0547.

*4.7.6. Pyrimido[5,4-c]-2,6-naphthyridin-6(5H)-one (**5f**).* Starting from 5-amino-4-chloropyrimidine (146 mg, 1.13 mmol) and boronic ester **1c**, following general procedure, **5f** was obtained after precipitation as a brown powder (96 mg, 43%); mp>260 °C; IR (neat) ν (cm^{-1}) 3410 (NH), 3018, 2753, 1680 (C=O), 1593, 1547, 1408, 1359, 1319, 1180, 1108; ^1H NMR (300 MHz, DMSO-d_6) δ 12.28 (s, 1H), 9.98 (s, 1H), 9.14 (s, 1H), 9.06 (d, J=5.2 Hz, 1H), 8.85 (s, 1H), 8.18 (d, J=5.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.1, 152.4, 151.7, 146.9, 145.4, 139.6, 134.8, 130.8, 127.2, 119.9; HRMS (ESI^+): calcd for $C_{10}H_7N_4O$ m/z 199.0620 [M+H], found 199.0626.

*4.7.7. Pyrimido[4,5-c]isoquinolin-6(5H)-one (**5g**).* Starting from 4-amino-5-iodopyrimidine hydrochloride (326 mg, 1.30 mmol) and boronic ester **1a**, following general procedure, **5g** was obtained after precipitation as a brown powder (103 mg, 41%); mp>260 °C; IR (neat) ν (cm^{-1}) 3342 (NH), 3036, 2869, 1686 (C=O), 1594, 1419, 1405, 1316, 1147; ^1H NMR (300 MHz, DMSO-d_6) δ 12.40 (s, 1H), 9.72 (s, 1H), 8.97 (s, 1H), 8.64 (d, J=7.9 Hz, 1H), 8.33 (d, J=7.9 Hz, 1H), 7.93 (dd, J =7.9, 7.9 Hz, 1H), 7.74 (dd, J =7.9, 7.9 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.6, 157.7, 152.7, 143.1, 133.5, 131.3, 129.5, 127.9, 126.2, 122.8, 111.4; HRMS (ESI^+): calcd for $C_{11}H_8N_3O$ m/z 198.0667 [M+H], found 198.0659.

*4.7.8. 1,3-Dimethylpyrimido[4,5-c]isoquinolin-6(5H)-one (**5h**).* Starting from 4-amino-5-chloro-2,6-dimethylpyrimidine (151 mg, 0.96 mmol), boronic ester **1a**, following general procedure, **5h** was obtained after precipitation as a grey powder (153 mg, 71%); mp>260 °C; IR (neat) ν (cm^{-1}) 3359 (NH), 2843, 2702, 1679 (C=O), 1588, 1570, 1440, 1417, 1324; ^1H NMR (300 MHz, DMSO-d_6) δ 12.23 (s, 1H), 8.45 (d, J=8.3 Hz, 1H), 8.39 (dd, J=7.6, 1.3 Hz, 1H), 7.92 (ddd, J = 8.3, 8.3 Hz and J=1.3 Hz, 1H), 7.70 (dd, J=8.3, 7.6 Hz, 1H), 2.98 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.7, 164.0, 161.9, 154.1, 133.3, 132.3, 128.2, 127.9, 126.9, 126.5, 107.6, 27.7, 25.2; HRMS (ESI^+): calcd $C_{13}H_{12}N_3O$ m/z 226.0980 [M+H], found 226.0985.

*4.7.9. 2-Phenylpyridazino[3,4-c]isoquinolin-6(5H)-one (**5i**).* Starting from 3-amino-4-iodo-6-phenylpyridazine **4** (84 mg, 0.28 mmol) and boronic ester **1a**, following general procedure, and using column chromatography (eluent: PE/EtOAc (6:4)) **5i** was obtained as a yellow powder (46 mg, 60%); mp>260 °C; IR (neat) ν (cm^{-1}) 3322 (NH), 3080, 1678 (C=O), 1605, 1480, 1388, 1344, 1310, 1161, 1135; ^1H NMR (300 MHz, DMSO-d_6) δ 11.35 (s, 1H), 9.03 (s, 1H), 8.90 (d, J=7.6 Hz, 1H), 8.49 (d, J=7.6 Hz, 1H), 8.32 (d, J=7.1 Hz, 2H), 7.99 (dd, J =7.6, 7.6 Hz, 1H), 7.91 (dd, J = 7.6, 7.6 Hz, 1H), 7.61−7.52 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.2, 154.4, 150.1, 135.9, 133.4, 131.4, 130.8, 129.6, 128.9 (2C), 127.7, 127.5, 126.7 (2C), 125.3, 118.2, 117.9; HRMS (ESI^+): calcd for $C_{17}H_{12}N_3O$ m/z 274.0980 [M+H], found 274.0985.

4.8. Synthesis of pyridazino[3,4-*c*]isoquinolin-6(5*H*)-one (5j)

S-Phos (13 mg, 0.03 mmol, 10 mol %) was introduced in dry toluene (0.5 mL) under Argon, then $Pd(OAc)_2$ (4 mg, 0.02 mmol, 5 mol %) was added. The resulting solution was heated at 80 °C for 10 min. A solution of *N*-(4-(tri(*n*-butyl)stannyl)pyridazin-3-yl)pivalamide **3b** (150 mg, 0.32 mmol, 1.0 equiv) in dry toluene (0.8 mL) and ethyl 2-iodobenzoate (80 μL, 0.48 mmol, 1.5 equiv) were successively added. The solution was refluxed overnight and the resulting mixture was evaporated to dryness. The crude product was purified by column chromatography (eluent: PE/EtOAc (6:4)) to give the desired product **5j** (31 mg, 49%) as a yellow powder; mp>260 °C; IR (neat) ν (cm^{-1}) 3156 (NH), 3047, 2918, 1654 (C=O), 1606, 1479, 1436, 1345, 1324; ^1H NMR (300 MHz, DMSO-d_6) δ 12.55 (s, 1H), 9.17 (d, J=5.3 Hz, 1H), 8.67 (d, J=7.9 Hz, 1H), 8.60 (d, J=5.3 Hz, 1H), 8.36 (d, J=7.9 Hz, 1H), 7.97 (dd, J=7.9, 7.5 Hz, 1H), 7.84 (dd, J=7.9, 7.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.3, 151.0, 147.2, 133.5, 131.3, 130.7, 127.7, 127.5, 124.7, 120.4, 116.8; HRMS (ESI^+): calcd for $C_{11}H_8N_3O$ m/z 198.0667 [M+H], found 198.0673.

4.9. General procedure for Suzuki cross-coupling (compounds 6a–h)[14]

In a degassed solution of DME/H_2O (2:1) (12 mL/mmol of diazine), were successively introduced *S*-Phos (10 mol %) and $Pd(OAc)_2$ (5 mol %). The solution was heated at 80 °C for 10 min then sodium carbonate (4.0 equiv), appropriate boronic acid (1.05 or 1.5 equiv) and appropriate diazine (1.0 equiv) were added. The solution was then refluxed (15 min or overnight) under Ar. The resulting mixture was filtered on Celite and washed with ethyl acetate and water. The aqueous phase was then extracted three times with ethyl acetate. The combined organic phase was dried over $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography (eluent: PE/EtOAc) to give the desired product.

*4.9.1. 3-(2′-Fluorophenyl)pyrazine-2-carbonitrile (**6a**).* Starting from 2-chloro-3-cyanopyrazine (81 mg, 0.58 mmol) and boronic acid **1d**, following general procedure, **6a** was obtained after purification by column chromatography (eluent: PE/EtOAc (85:15)) as a yellow powder (95 mg, 83%); mp 72–73 °C; IR (neat) ν (cm^{-1}) 3055, 2246 (CN), 1615, 1496, 1458, 1429, 1388, 1217, 1170, 1102; ^1H NMR (300 MHz, $CDCl_3$) δ 8.88 (d, J=2.4 Hz, 1H), 8.70 (d, J=2.4 Hz, 1H), 7.63 (ddd, J =7.5, 7.5 Hz and J=1.6 Hz, 1H) 7.59–7.52 (m, 1H), 7.35 (ddd, J =7.5, 7.5 Hz and J=1.6 Hz, 1H), 7.30–7.25 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8 (d, ^1J=251.8 Hz), 153.5 (d, ^3J=1.1 Hz), 146.5, 143.5, 132.9 (d, J=8.5 Hz), 131.4 (d, J=2.1 Hz), 130.6 (d, ^4J=1.2 Hz), 124.8 (d, J=3.7 Hz), 122.9 (d, ^2J=13.8 Hz), 116.4 (d, ^2J=21.4 Hz), 115.2 (d, ^5J=1.2 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): δ −114.2 (ddd, J=10.2, 7.2, 5.2 Hz); HRMS (ESI^+): calcd for $C_{11}H_7FN_3$ m/z 200.0624 [M+H], found 200.0625.

*4.9.2. 3-(2′,3′-Difluorophenyl)pyrazine-2-carbonitrile (**6b**).* Starting from 2-chloro-3-cyanopyrazine (101 mg, 0.72 mmol) and boronic acid **1e**, following general procedure, **6b** was obtained after purification by column chromatography (eluent: PE/EtOAc (8:2)) as a brown oil (96 mg, 61%); IR (neat) ν (cm^{-1}) 3097, 3056, 2245 (CN), 1490, 1477, 1393, 1269, 1057; ^1H NMR (300 MHz, $CDCl_3$) δ 8.83 (d, J=2.3 Hz, 1H), 8.68 (d, J=2.3 Hz, 1H), 7.39–7.27 (m, 2H), 7.27–7.17 (m, 1H); Selected ^{13}C NMR data (75 MHz, $CDCl_3$) δ 152.4, 150.7 (dd, ^1J=249.0, ^2J=11.0 Hz), 148.3 (dd, ^1J=254.4, ^2J=14.1 Hz), 146.6, 144.0, 130.4, 126.0 (d, J=3.8 Hz), 124.9 (d, J=4.8 Hz), 119.9 (d, ^2J=17.1 Hz), 114.9; ^{19}F NMR (282 MHz, $CDCl_3$): δ −136.5 (dm, J=20.5 Hz), −139.1 (ddd, J=20.5, 9.9, 3.6 Hz); HRMS (ESI^+): calcd for $C_{11}H_6F_2N_3$ m/z 218.0530 [M+H], found 218.0542.

*4.9.3. 3-(3′-Chloro-2′-fluorophenyl)pyrazine-2-carbonitrile (**6c**).* Starting from 2-chloro-3-cyanopyrazine (80 mg, 0.58 mmol) and boronic acid **1f**, following general procedure, **6c** was obtained after purification by column chromatography (eluent: PE/EtOAc (85:15)) as yellow crystals (92 mg, 69%); mp 131–132 °C; IR (neat) ν (cm^{-1}) 3079, 2926, 2242 (CN), 1457, 1429, 1391, 1237, 1140, 1041; ^1H NMR (300 MHz, $CDCl_3$) δ 8.89 (d, J=2.3 Hz, 1H), 8.75 (d, J=2.3 Hz, 1H), 7.66–7.60 (m, 1H), 7.52 (ddd, J =6.5, 6.5 Hz and J=1.7 Hz, 1H), 7.30 (ddd, J =8.0, 8.0 Hz and J=0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5 (d, ^1J=254.1 Hz), 152.8 (d, ^3J=1.4 Hz), 146.5, 144.0, 133.4, 130.5, 129.6 (d, J=1.5 Hz), 125.2 (d, J=4.9 Hz), 124.4 (d, ^2J=13.9 Hz), 122.4 (d, ^2J=17.8 Hz), 114.9; ^{19}F NMR (282 MHz, $CDCl_3$): δ −116.2 (dd, J=6.7, 6.5 Hz); HRMS (ESI^+): calcd for $C_{11}H_6ClFN_3$ m/z 234.0234 [M+H], found 234.0231.

*4.9.4. 3-(2′-Fluoro-3′-(trifluoromethyl)phenyl)pyrazine-2-carbonitrile (**6d**).* Starting from 2-chloro-3-cyanopyrazine (400 mg, 2.87 mmol) and boronic acid **1g**, following general procedure, **6d** was obtained after purification by column chromatography (eluent: PE/EtOAc (85:15)) as a yellow oil (467 mg, 56%); IR (neat) ν (cm^{-1}) 3098, 3059, 2240 (CN), 1457, 1624, 1470, 1330, 1302, 1218, 1133, 1037; ^1H NMR (300 MHz, $CDCl_3$) δ 8.91 (d, J=2.3 Hz, 1H), 8.77 (d, J=2.3 Hz, 1H), 7.84–7.82 (m, 2H), 7.48 (dd, J =7.8, 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1 (dq, ^1J=261.5, ^3J=1.9 Hz), 152.2, 146.6, 144.2, 135.2 (d, ^3J=1.4 Hz), 130.6 (d, J=1.0 Hz), 129.9 (qd, ^3J=4.5, ^3J=1.9 Hz), 124.7 (d, J=4.7 Hz), 124.5 (d, ^2J=13.4 Hz), 122.1 (q, ^1J=272.8 Hz), 119.6 (qd, ^2J=33.4, ^2J=12.4 Hz), 114.8; ^{19}F NMR (282 MHz, $CDCl_3$): δ −61.8 (d, J=13.1 Hz, 3F), −116.1 (m, 1F); HRMS (ESI^+): calcd for $C_{12}H_5F_4N_3Na$ m/z 290.0317 [M+Na], found 290.0316.

*4.9.5. 3-(2′-Fluoropyridin-3-yl)pyrazine-2-carbonitrile (**6e**).* Starting from 2-chloro-3-cyanopyrazine (80 mg, 0.58 mmol) and boronic acid **1h**, following general procedure, **6e** was obtained after purification by column chromatography (eluent: PE/EtOAc (75:25)) as a yellow powder (63 mg, 55%); mp 84–86 °C; IR (neat) ν (cm^{-1}) 2922, 2851, 2241 (CN), 1608, 1571, 1446, 1410, 1392, 1254; ^1H NMR (300 MHz, $CDCl_3$) δ 8.91 (d, J=2.3 Hz, 1H), 8.76 (d, J=2.3 Hz, 1H), 8.46–8.44 (m, 1H), 8.12 (ddd, J=9.2, 7.5, 1.9 Hz, 1H), 7.50–7.39 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0 (d, ^1J=242.1 Hz), 152.0 (d, ^3J=5.8 Hz), 150.4 (d, J=15.0 Hz), 146.6, 144.1, 142.2 (d, J=2.8 Hz), 130.3, 122.0 (d, J=4.6 Hz), 118.0 (d, ^2J=29.3 Hz), 114.8; ^{19}F NMR (282 MHz, $CDCl_3$): δ −67.5 (d, J=9.2 Hz); HRMS (ESI^+): calcd for $C_{10}H_6FN_4Na$ m/z 201.0576 [M+Na], found 201.0578.

*4.9.6. 3-(2′-Fluoro-3′-methoxyphenyl)pyrazine-2-carbonitrile (**6f**).* Starting from 2-chloro-3-cyanopyrazine (80 mg, 0.58 mmol) and boronic acid **1i**, following general procedure, **6f** was obtained after purification by column chromatography (eluent: PE/EtOAc (8:2)) as a white powder (111 mg, 84%); mp 124–125 °C; IR (neat) ν (cm^{-1}) 3094, 2949, 2243 (CN), 1587, 1486, 1430, 1398, 1275, 1065, 1026; ^1H NMR (300 MHz, $CDCl_3$) δ 8.87 (d, J=2.3 Hz, 1H), 8.71 (d, J=2.3 Hz, 1H), 7.31–7.21 (m, 1H), 7.22–7.10 (m, 2H), 3.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 149.9 (d, ^1J=252.0 Hz), 148.2 (d, ^2J=10.4 Hz), 146.5, 143.6, 130.6, 124.7 (d, J=4.8 Hz), 123.6 (d, ^2J=11.3 Hz), 122.0 (d, J=0.8 Hz), 115.9 (d, J=2.4 Hz), 115.2, 56.5; ^{19}F NMR (282 MHz, $CDCl_3$): δ −136.8 (dd, J=10.2, 3.7 Hz); HRMS (ESI^+): calcd for $C_{12}H_8FN_3ONa$ m/z 252.0549 [M+Na], found 252.0555.

*4.9.7. 3-(2′,4′-Difluorophenyl)pyrazine-2-carbonitrile (**6g**).* Starting from 2-chloro-3-cyanopyrazine (502 mg, 3.58 mmol) and boronic acid **1j**, following general procedure, **6g** was obtained after purification by column chromatography (eluent: PE/EtOAc (85:15)) as a yellow powder (554 mg, 71%); mp 100–102 °C; IR (neat) ν (cm^{-1}) 3050, 2927, 2243 (CN), 1596, 1430, 1387, 1270, 1154, 1101; ^1H NMR (300 MHz, $CDCl_3$) δ 8.88 (d, J=2.3 Hz, 1H), 8.72 (d, J=2.3 Hz, 1H), 7.65 (ddd, J =8.4, 8.4 Hz and J=6.2 Hz, 1H), 7.18–6.95 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7 (dd, ^1J=254.6, ^3J=12.2 Hz), 160.3 (dd, ^1J=254.6, ^3J=12.2 Hz), 152.7, 146.6, 143.6, 132.7 (dd, J=10.2, 3.7 Hz), 130.5, 119.3 (dd, J=14.0, 3.9 Hz), 115.1, 112.6 (dd, ^2J=21.9, ^4J=3.8 Hz), 105.0 (dd, ^2J=25.5, 25.5 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): δ −104.8 (m, 1F), −109.2 (m, 1F); HRMS (ESI^+): calcd for $C_{12}H_6F_2N_3$ m/z 218.0530 [M+H], found 218.0537.

*4.9.8. 3-(4′-Chloro-2′-fluorophenyl)pyrazine-2-carbonitrile (**6h**).* Starting from 2-chloro-3-cyanopyrazine (80 mg, 0.57 mmol) and boronic acid **1k**, following general procedure, **6h** was obtained after purification by column chromatography (eluent: PE/EtOAc (85:15)) as a yellow powder (97 mg, 72%); mp 144–146 °C; IR (neat) ν (cm^{-1}) 3051, 2929, 2243 (CN), 1610, 1574, 1417, 1385, 1217, 1117, 1086; ^1H NMR (300 MHz, $CDCl_3$) δ 8.88 (d, J=2.2 Hz, 1H), 8.72 (d, J=2.2 Hz, 1H), 7.59 (dd, J=8.4, 8.0 Hz, 1H), 7.39–7.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6 (d, ^1J=255.5 Hz), 152.6 (d, ^3J=1.6 Hz), 146.6, 143.8, 138.4 (d, ^3J=10.3 Hz), 132.2 (d, ^3J=3.0 Hz), 130.5, 125.5 (d, J=3.7 Hz), 121.5 (d, ^2J=14.0 Hz), 117.3 (d, ^2J=25.0 Hz), 115.0; ^{19}F NMR (282 MHz, $CDCl_3$): δ −111.3 (m); HRMS (ESI^+): calcd for $C_{11}H_6ClFN_3$ m/z 234.0234 [M+H], found 234.0229.

4.10. General procedure for KOH-mediated anionic ring closure (compounds 7a–h)

In a sealed tube were successively introduced substituted biaryl **6a–h** (1.0 equiv), KOH (5.0 equiv) and *t*-BuOH (6 mL/mmol of

substrate). The tube was sealed and the suspension was heated at 150 °C for 1.5 h. After cooling, the mixture was diluted with water and aqueous solution of HCl 2 M was added until complete precipitation. The product was then filtered and washed with water affording the desired compound.

*4.10.1. Pyrazino[2,3-c]quinolin-5(6H)-one (**7a**).* Starting from 3-(2′-fluorophenyl)pyrazine-2-carbonitrile **6a** (345 mg, 1.73 mmol), following general procedure, **7a** was isolated as a white powder (228 mg, 67%); mp>260 °C; IR (neat) ν (cm^{-1}) 3340 (NH), 3064, 2908, 1686 (C=O), 1670, 1455, 1385, 1202, 1019; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.07 (s, 1H), 9.08 (d, J=1.7 Hz, 1H), 8.96 (d, J=1.7 Hz, 1H), 8.53 (d, J=7.6 Hz, 1H), 7.62 (dd, J =7.6, 7.6 Hz, 1H), 7.40 (d, J=7.6 Hz, 1H), 7.32 (dd, J =7.6, 7.6 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.6, 148.5, 146.5, 145.3, 137.8, 137.1, 131.9, 124.2, 122.6, 117.8, 115.9; HRMS (ESI^+): calcd for $C_{11}H_8N_3O$ m/z 198.0667 [M+H], found 198.0676.

*4.10.2. 7-Fluoropyrazino[2,3-c]quinolin-5(6H)-one (**7b**).* Starting from 3-(2′,3′-difluorophenyl)pyrazine-2-carbonitrile **6b** (457 mg, 2.10 mmol), following general procedure, **7b** was isolated as a yellow powder (399 mg, 88%); mp>260 °C; IR (neat) ν (cm^{-1}) 3325 (NH), 3027, 2866, 1672 (C=O), 1494, 1443, 1389, 1356, 1219, 1203, 1039; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.11 (s, 1H), 9.11 (m, 1H), 9.01 (m, 1H), 8.38 (d, J=7.9 Hz), 7.64–7.48 (m, 1H), 7.36–7.29 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.5, 149.2 (d, ^1J=245.7 Hz), 148.8, 146.1 (d, ^4J=3.4 Hz), 146.0, 137.5, 126.5 (d, ^2J=14.1 Hz), 122.6 (d, ^3J=6.9 Hz), 120.2 (d, J=2.8 Hz), 120.0 (d, J=3.7 Hz), 117.3 (d, ^2J=17.5 Hz); ^{19}F NMR (282 MHz, DMSO-d_6): δ −129.6 (dd, J=10.8, 4.7 Hz); HRMS (ESI^+): calcd for $C_{11}H_7FN_3O$: m/z 216.0573 [M+H], found 216.0569.

*4.10.3. 7-Chloropyrazino[2,3-c]quinolin-5(6H)-one (**7c**).* Starting from 3-(3′-chloro-2′-fluorophenyl)pyrazine-2-carbonitrile **6c** (240 mg, 1.03 mmol), following general procedure, **7c** was isolated as a yellow powder (164 mg, 69%); mp>260 °C; IR (neat) ν (cm^{-1}) 3350 (NH), 3194, 3137, 3060, 1678 (C=O), 1610, 1488, 1390, 1348, 1236, 1178, 1030; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.32 (s, 1H), 9.13 (m, 1H), 9.02 (m, 1H), 8.57 (d, J=7.9 Hz, 1H), 7.79 (d, J=7.9 Hz, 1H), 7.35 (dd, J =7.9, 7.9 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.6, 148.9, 146.1, 146.0, 137.1, 134.3, 132.1, 123.4, 123.3, 119.8, 119.1; HRMS (ESI^+): calcd for $C_{11}H_6ClN_3ONa$ m/z 254.0097 [M+Na], found 254.0089.

*4.10.4. 7-(Trifluoromethyl)pyrazino[2,3-c]quinolin-5(6H)-one (**7d**).* Starting from 3-(2′-fluoro-3′-(trifluoromethyl)phenyl)-pyrazine-2-carbonitrile **6d** (393 mg, 1.47 mmol), following general procedure, **7d** was isolated as a yellow powder (286 mg, 73%); mp>260 °C; IR (neat) ν (cm^{-1}) 3398 (NH), 3123, 1696 (C=O), 1436, 1330, 1297, 1147, 1117, 1029; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.92 (s, 1H), 9.15 (d, J=2.0 Hz, 1H), 9.04 (d, J=2.0 Hz, 1H), 8.93 (d, J=7.8 Hz, 1H), 8.02 (d, J=7.8 Hz, 1H), 7.52 (dd, J=7.8, 7.8 Hz, 1H); Selected ^{13}C NMR data (75 MHz, DMSO-d_6) δ 159.6, 149.1, 146.5, 145.7, 136.8, 134.3, 129.5 (q, J=5.7 Hz), 129.3, 122.4, 119.8; ^{19}F NMR (282 MHz, DMSO-d_6) δ −58.7 (s); HRMS (ESI^+): calcd for $C_{12}H_7F_3N_3O$ m/z 266.0541 [M+H], found 266.0549.

*4.10.5. Pyrazino[2,3-c]-1,8-naphthyridin-5(6H)-one (**7e**).* Starting from 3-(2′-fluoropyridin-3-yl)pyrazine-2-carbonitrile **6e** (165 mg, 0.82 mmol), following general procedure, **7e** was isolated as a yellow powder (84 mg, 52%); mp>260 °C; IR (neat) ν (cm^{-1}) 3365 (NH), 2970, 2842, 1679 (C=O), 1600, 1431, 1384, 1320, 1206, 1192; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.50 (s, 1H), 9.13 (d, J=2.1 Hz, 1H), 9.02 (d, J=2.1 Hz, 1H), 8.89 (dd, J=7.8, 1.7 Hz, 1H), 8.64 (dd, J=4.8, 1.7 Hz, 1H), 7.42 (dd, J=7.8, 4.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.4, 151.8, 149.3, 148.7, 146.0, 145.6, 137.4, 133.2, 119.1, 113.5; HRMS (ESI^+): calcd for $C_{10}H_7N_4O$ m/z 199.0620 [M+H], found 199.0622.

*4.10.6. 7-Methoxypyrazino[2,3-c]quinolin-5(6H)-one (**7f**).* Starting from 3-(2′-fluoro-3′-methoxyphenyl)pyrazine-2-carbonitrile **6f** (548 mg, 2.39 mmol), following general procedure except that the reaction mixture was evaporated to dryness and washed with water (17 mL), **7f** was isolated as a yellow powder (346 mg, 64%); mp 240 °C; IR (neat) ν (cm^{-1}) 3393 (NH), 3073, 1679 (C=O), 1495, 1390, 1266, 1246, 1052, 1022; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.18 (s, 1H), 9.10 (d, J=2.1 Hz, 1H), 8.97 (d, J=2.1 Hz, 1H), 8.15 (dd, J=5.4, 4.0 Hz, 1H), 7.41–7.02 (m, 2H), 3.95 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.2, 148.7, 146.6, 146.2, 145.5, 137.3, 127.6, 122.7, 118.4, 115.7, 112.7, 56.2; HRMS (ESI^+): calcd for $C_{12}H_{10}N_3O_2$ m/z 228.0773 [M+H], found 228.0764.

*4.10.7. 8-Fluoropyrazino[2,3-c]quinolin-5(6H)-one (**7g**).* Starting from 3-(2′,4′-difluorophenyl)-pyrazine-2-carbonitrile **6g** (36 mg, 0.17 mmol), following general procedure, **7g** was isolated as a yellow powder (35 mg, 97%); mp>260 °C; IR (neat) ν (cm^{-1}) 3358 (NH), 3073, 1709 (C=O), 1675, 1626, 1450, 1379, 1269, 1210; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.19 (s, 1H), 9.09 (m, 1H), 8.96 (m, 1H), 8.59 (dd, J=8.5, 6.5 Hz, 1H), 7.24–7.15 (m, 2H); Selected ^{13}C NMR data (75 MHz, DMSO-d_6) δ 159.8, 148.7, 146.1, 145.3, 139.5 (d, ^3J=12.2 Hz), 136.7, 127.1 (d, ^3J=10.5 Hz), 114.8, 110.7 (d, ^2J=23.0 Hz), 102.1 (d, ^2J=25.8 Hz); ^{19}F NMR (282 MHz, DMSO-d_6): δ −107.0 (m); HRMS (ESI^+): calcd for $C_{11}H_7FN_3O$ m/z 216.0573 [M+H], found 216.0573.

*4.10.8. 8-Chloropyrazino[2,3-c]quinolin-5(6H)-one (**7h**).* Starting from 3-(4′-chloro-2′-fluorophenyl)pyrazine-2-carbonitrile **6h** (92 mg, 0.39 mmol), following general procedure, **7h** was isolated as a yellow powder (80 mg, 88%); mp>260 °C; IR (neat) ν (cm^{-1}) 3346 (NH), 3039, 2890, 1674 (C=O), 1611, 1447, 1371, 1204, 1089; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.17 (s, 1H), 9.09 (d, J=2.1 Hz, 1H), 8.98 (d, J=2.1 Hz, 1H), 8.53 (d, J=8.6 Hz, 1H), 7.43 (d, J=1.9 Hz, 1H), 7.38 (dd, J=8.6, 1.9 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.7, 148.7, 146.0, 145.7, 138.8, 137.2, 136.2, 126.2, 122.8, 116.8, 115.2; HRMS (ESI^+): calcd for $C_{11}H_7ClN_3O$ m/z 232.0278 [M+H], found 232.0284.

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13. See Table 1 and Scheme 2 for details.
14. See Table 2 for details.