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Revisiting the Quinoxalinedione Scaffold in the Construction of New Ligands for the Ionotropic Glutamate Receptors

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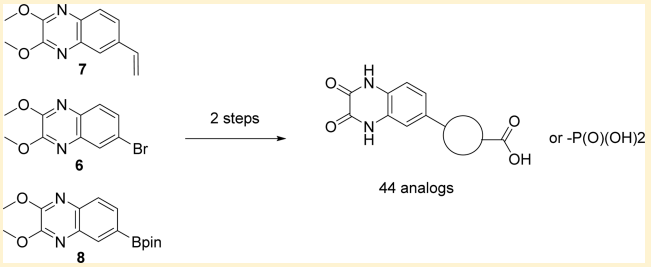
ABSTRACT: More than two decades ago, the quinoxalinedione scaffold was shown to act as an α-amino acid bioisoster. Following extensive structure−activity relationship (SAR) studies, the antagonists DNQX, CNQX, and NBQX in the ionotropic glutamate receptor field were identified. In this work, we revisit the quinoxalinedione scaffold and explore the incorporation of an acid functionality in the 6-position. The SAR studies disclose that by this strategy it was possible to tune in iGluR selectivity among the AMPA, NMDA, and KA receptors, and to some extent also obtain full receptor subtype selectivity. Highlights of the study of 44 new analogues are compound **2m** being a high affinity ligand for native AMPA receptors (IC_{50}= 0.48 μM), analogues **2e,f,h,k,v** all displayed selectivity for native NMDA receptors, and compounds **2s,t,u** are selective ligand for the GluK1 receptor. Most interestingly, compound **2w** was shown to be a GluK3-preferring ligand with full selectivity over native AMPA, KA and NMDA receptors.



KEYWORDS: *Structure−activity relationship study, Ionotropic glutamate receptor ligands, amino acids, amino acid bioisoster*

INTRODUCTION

Two decades ago the two quinoxalinediones DNQX and CNQX (Figure 1) were shown to be potent competitive antagonists of the ionotropic glutamate receptors (iGluRs).[1] By an X-ray structural study of CNQX in the ligand binding domain (LBD) of GluA2 (PDB code: 3B7D),[2] it was later shown that the quinoxalinedione acts as an α-amino acid bioisoster by forming strong ionic interactions between its dione functionality and the positively charged Arg96 residue while its 4-NH-functionality engages in hydrogen bonding with the carbonyl group of the Pro89 residue. Interestingly, the carboxylate group of Glu193, which would engage in a salt-bridge to the α-ammonium ion of an α-amino acid functionality, now engages in a charged interaction with the ammonium group of Lys218 via a water matrix network.

Numerous structure−activity-relationship (SAR) studies have been carried out by introduction and/or modification of substituents in the quinoxalinedione scaffold, which led to the discovery of the selective AMPA/KA antagonist NBQX (Figure 1).[3] However, despite extensive efforts, selectivity for one receptor subunit within one of the three iGluR groups (AMPA subunits GluA1−4, KA subunits GluK1−5 or NMDA subunits GluN2A-D) has not achieved. Reported key quinoxalinediones are non-NMDA antagonist **1a**,[3] NMDA antagonist **1b**,[4] and glycine site NMDA antagonist **1c**[5] (Figure 1).

Recently, we revisited the quinoxalinedione scaffold to explore if it could also function as a carboxylic acid bioisoster in the iGluRs (compounds **2a** and **2b**, Figure 1).[6] However, the X-ray structure of **2a** in the ligand binding domain (LBD) of GluA2 (PDB code: 4QF9) showed that the quinoxalinedione functionality remained as the amino acid bioisoster, with the carboxylate group of the α-amino acid side chain serving to stabilize the LBD in an open antagonist state.[6] From the X-ray structure it was also observed that the α-ammonium group did not engage in direct interactions with any receptor residues. We therefore decided to explore the influence on binding affinity and receptor subtype selectivity upon altering the chemical nature of the side chain. In total, 44 new analogues were prepared to explore variations in chemical functionalities, carbon chain length and flexibility (compounds **2c−x** and **2aa−2aw**; Figure 2), and how these changes influence the binding affinity profile at the iGluRs for both native and cloned homomeric iGluR receptors.

RESULTS AND DISCUSSION

As evidenced by the X-ray structure of **2a** in the LBD of GluA2 (PDB code: 4QF9), the α-ammonium group does not participate in direct interactions with the receptor protein. We therefore first decided to remove this group (**2c,d**) which would also bring simplicity to the synthesis. As a classical strategy in SAR studies, the carboxylic acid functionality was substituted with a phosphonic acid group (**2e,f**).[7,8] To possibly enhance binding affinity, the flexible side chains in **2a−f** were conformationally restricted by incorporation of a double bond (**2g−j**). Furthermore, a sulfonamide and an secondary amine (**2k,l**) were incorporated into the side chain. The four

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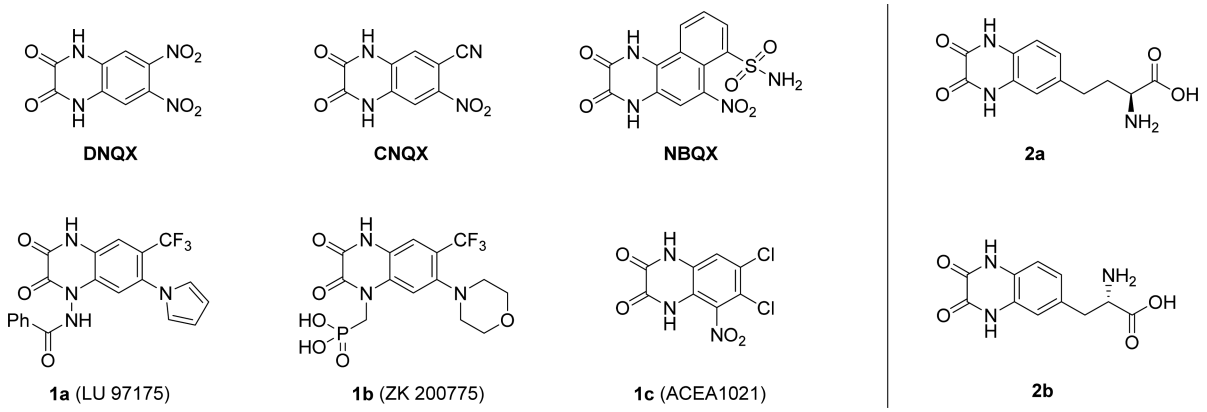

Figure 1. Chemical structure of lead compounds **2a,b** and reported key quinoxalinedione analogues DNQX, CNQX, NBQX, and **1a−c**.

analogues **2m−p** restrict the orientation of the carboxylic acid group by incorporation of an aromatic ring. Finally, analogues **2q−w** have a phenyl ring directly attached to the quinoxalinedione skeleton, tethering an acid functionality.

Chemistry. The target analogues **2c−w** were synthesized from one of the three intermediates: bromine **6**,[6] alkene **7** or boronic ester **8**, which were all prepared in a convergent manner from 4-bromo-1,2-diaminobenzene **3** (Scheme 1). First, the quinoxalinedione ring was constructed by condensation of **3** with diethyl glyoxalate to give **4** in high yield. While the dione functionality is not compatible with Pd catalyzed cross-coupling reactions, **4** was treated with thionyl chloride followed by potassium methoxide in methanol to give key intermediate bromine **6**. Subsequent Stille cross-coupling with tributyl(vinyl)stannane or a Miyaura borylation reaction led to key intermediates alkene **7** and boronic ester **8**, respectively (Scheme 1).

*Synthesis of Aryl Analogues **2q−w**.* The synthesis of target analogues **2q**, **2r**, **2v**, and **2w** commenced with a Suzuki coupling reaction of bromine **6** with the appropriately substituted arylboronic acid to give intermediates **9a−d**. Subsequent deprotection in aqueous HCl afforded analogues **2q**, **2r**, **2v**, and **2w** in good to high yield (Scheme 2).

Analogues **2s** and **2u** were also synthesized by a Suzuki cross-coupling reaction, however for these two analogues with reversed reactivity (Scheme 3). Boronic ester **8** was coupled with the appropriate aryl halides **10** and **14**, respectively, to give products **11** and **15**. Subsequent deprotection of intermediates **11** in 2 M HCl at 70 °C gave **2s**, while **15** required treatment with TMSBr in DCM followed by hydrolysis in 1 M HCl in 1,4-dioxane overnight to afford target analogue **2u** in a clean manner (Scheme 3). For the synthesis of **2t**, intermediate **13** was obtained by a Suzuki cross-coupling between bromine **6** and boronic acid **12**. Subsequent deprotection of intermediate **13** in 2 M HCl at 110 °C gave analogue **2t** in good yield (Scheme 3).

*Synthesis of **2m−p**.* Analogue **2m** was synthesized by a Heck cross-coupling reaction of bromine **6** with the vinyl arene **17** (Scheme 4), which was readily obtained from **16** by a Stille coupling reaction. Hydrolysis of **18** with 2 M HCl at 80 °C overnight gave analogue **2m** in good yield.

Following the same strategy, analogues **2n−p** were obtained by a Heck cross-coupling reaction of alkene **4** with aryl bromides **19**, **21**, and **23** to give intermediates **20**, **22**, and **24**, respectively. Global deprotection of **20** in acidic media readily gave target analogue **2o** whereas deprotection of **22** to give **2n** required first reaction with BCl_3 at rt overnight followed by hydrolysis in 2 M HCl and finally saponification conditions overnight. Saponification of intermediate **24** followed by hydrolysis with 2 M HCl afforded target analogue **2p** (Scheme 4).

*Synthesis of **2c−j**.* For the synthesis of **2c−j**, bromine **6** was coupled with either methyl 3-butenoate and ethyl acrylate to afford intermediates **26a,b**, respectively. Then, reduction of **26a−b** with palladium catalyst under hydrogen atmosphere led to compounds **27a,b**. Finally, the synthesis of analogues **2c,d**, **2g**, and **2i** were achieved by deprotection of their corresponding intermediates with 1 M HCl (Scheme 5).

Similarly (Scheme 6), Heck cross-coupling between **6** and diethyl vinylphosphonate or diethyl allylphosphonate afforded the compounds **28a,b**, respectively. Subsequent treatment with TMSBr and then 1 M HCl completed the synthesis of analogues **2h** and **2j**. Intermediates **28a,b** were reduced with palladium on carbon as catalyst to give corresponding saturated analogues **29a,b**, which were deprotected under the same conditions as stated for **2h,j**, to give **2e,f** (Scheme 6).

The synthesis of target analogue **2l** commenced by the oxidation of **7** to aldehyde **30** in a two-step procedure by first reaction with $OsO_4/NaIO_4$ to give the corresponding diol, then oxidative cleavage with $PhI(OAc)_2$. Condensation of aldehyde **30** with 3-amino propionic acid ethyl ester hydrochloride followed by subsequent reduction led to amine **31** which was deprotected under aqueous acidic conditions to afford the desired analogue **2l** in acceptable yield (Scheme 7).

Pharmacology. All analogues **2c−w** were characterized in binding assays at native iGluRs (rat synaptosomes) and cloned rat homomeric GluA2 and GluK1−3 receptors (Table 1). As anticipated, removal of the amino group (**2c,d**) did not lead to a significant loss in affinity. The two phosphonic acid analogues **2e,f** displayed selective affinity for the NMDA receptors, however, only in mid-micromolar range (K_i = 55 and 56 μM, respectively). Introduction of a double bond (**2c** vs **2g**) did not induce receptor subtype selectivity although the GluK3 affinity was increased by 10-fold, whereas for compounds **2d** vs **2i** the alkene resulted in a loss of affinity. Finally, for analogues **2e,f** vs **2h,j**, the NMDA receptor selectivity was only maintained for compound **2j** with no improved affinity (K_i = 69 μM). Selectivity for the NMDA receptors was also observed for sulfonamide **2k**. Finally, insertion of an amine (**2l**) resulted in a broad binding affinity profile at native AMPA and KA receptors but also at cloned homomeric GluK1−3 with K_i values of 45, 37, and 19 μM, respectively (Table 1).

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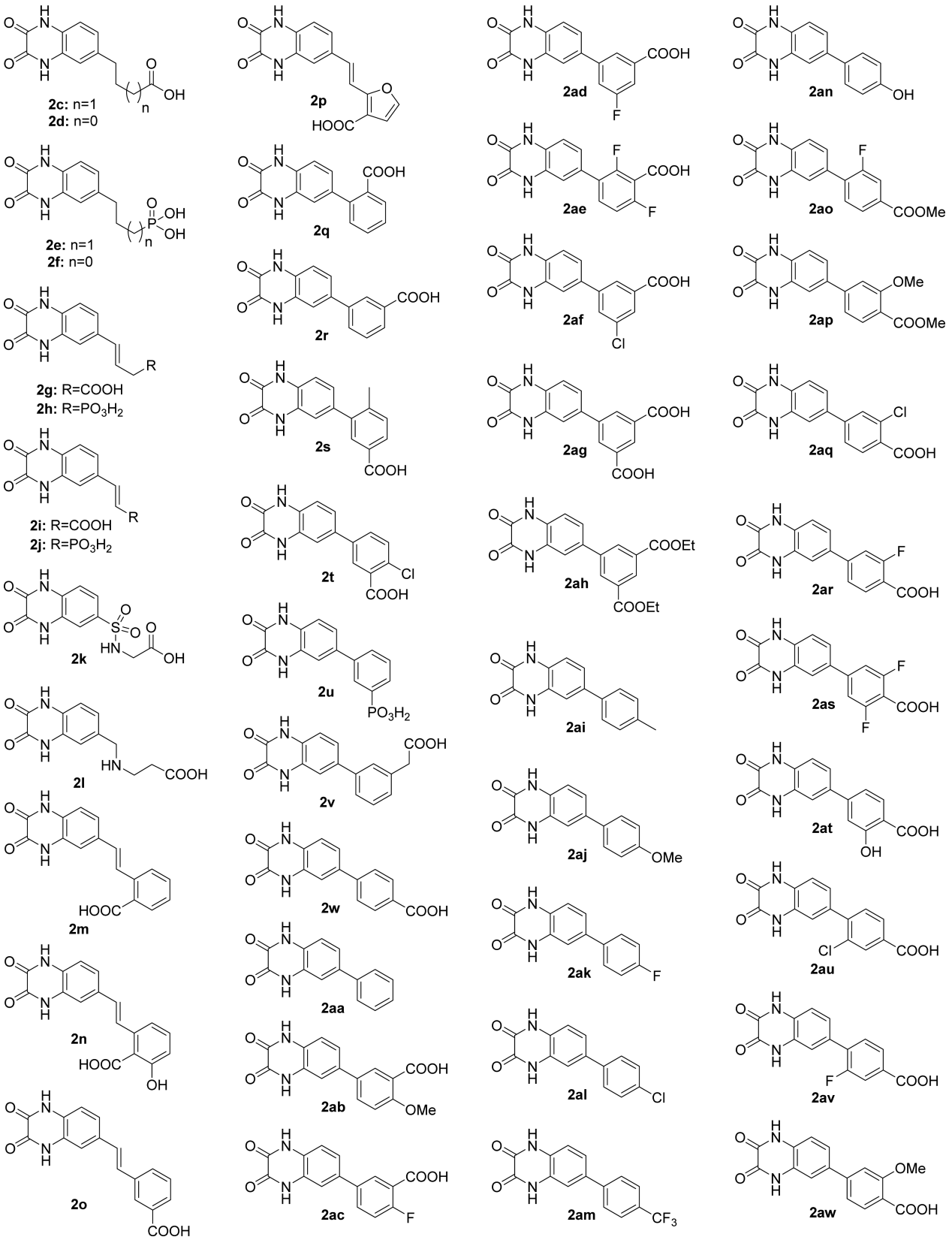

Figure 2. Chemical structure of all compounds undergoing pharmacological characterization.

In contrast, the ortho carboxy phenylvinyl analogue **2m** displayed enhanced binding affinity with sub-micromolar (IC_{50} = 0.48 μM) affinity for native AMPA receptors but also low micromolar affinity for GluK1−3 (K_i = 1.4, 2.5, 8.9 μM, respectively). Introduction of a hydroxyl group in the meta position, compound **2n**, did not lead to a significant change in the binding affinity profile compared to **2m**. Moving the carboxylic acid group to the meta position, compound **2o**, led

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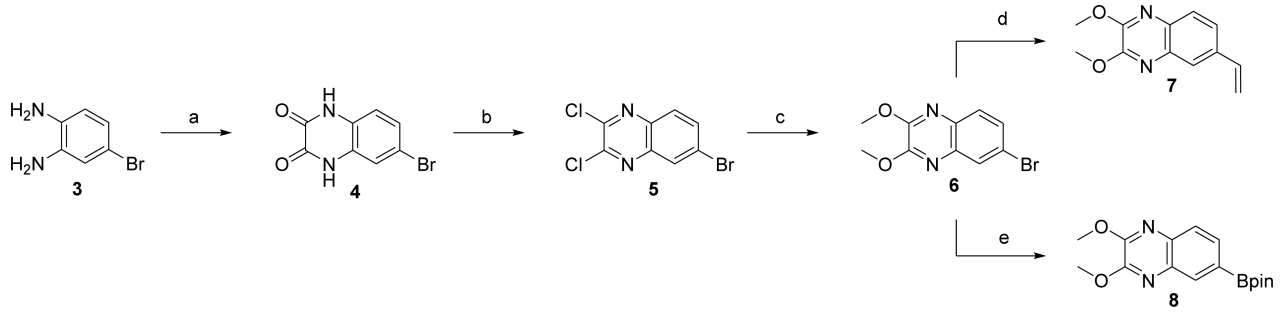
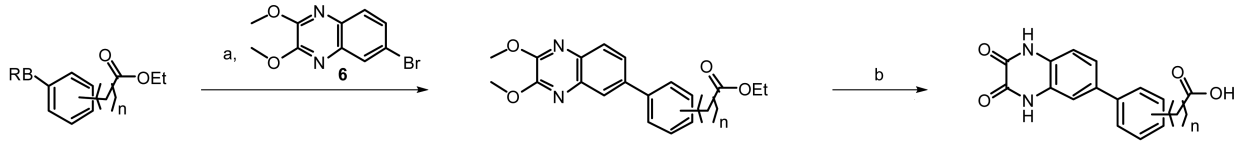
Scheme 1. Synthesis of Bromine 6, Alkene 7, and Boronic Ester 8[a]



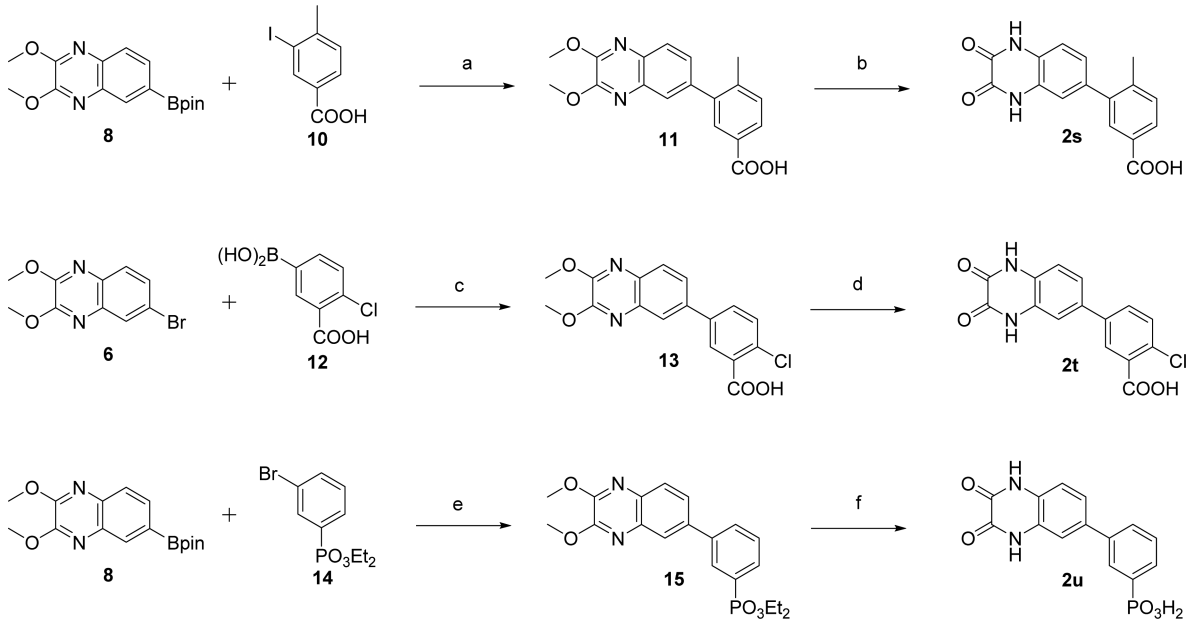
[a]Reagents and conditions: (a) diethyl oxalate, 96%; (b) thionyl chloride, DMF (cat.), 90%; (c) MeOK, MeOH, 93%; (d) $Pd(PPh_3)_4$, tributyl(vinyl)stannane, toluene, 100 °C, overnight, 93%; (e) $Pd(dppf)_2$·DCM, bis(pinacolato)diboron, AcOK, DMF, H_2O, 95 °C, 44 h, 68%.

Scheme 2. Synthesis of analogues 2q, 2r, 2v, and 2w[a]



[a]Reagents and conditions: (a) $Pd(PPh_3)_4$, **6**, Cs_2CO_3, DMF, H_2O, 90 °C, 2 h; (b) 2 M HCl, dioxane, 80 °C, overnight.

Scheme 3. Synthesis of Analogues 2s−u[a]



[a]Reagents and conditions: (a) $Pd(PPh_3)_4$, Cs_2CO_3, DMF, H_2O, 90 °C, 2 h, quant.; (b) 2 M HCl, 1,4-dioxane, 110 °C, 20 min, 50%; (c) $PdCl_2(dppf)$·DCM, K_2CO_3, 1,4-dioxane, H_2O, 80 °C, overnight, 62%; (d) 2 M HCl, 1,4-dioxane, 70 °C, 3h, 69%; (e) $Pd(PPh_3)_4$, Cs_2CO_3, DMF, H_2O, 90 °C, 2 h, 74%; (f) TMSBr, DCM, rt, overnight, then 1 M HCl, dioxane, 70 °C, overnight, 87%.

to a general reduction in binding affinity at all iGluRs, while substitution of the phenyl ring for a furan ring, analogue **2p**, gave a 10-fold decrease in binding affinity for AMPA receptors and a 20-fold drop in binding affinity at GluK1.

With regard to the analogues where the phenyl ring is directly attached to the quinoxalinedione, compounds **2q−w**, the point of substitution was of great influence on the binding affinities. While the ortho substituted analogue **2q** was without significant affinity for any of the iGluRs, the meta-positioned analogue (compound **2r**) displayed binding affinities for all the iGluRs in the low- to mid-micromolar range. Inducing steric clashes by the introduction of a methyl substituent in the far ortho position (compound **2s**) led to an 8-fold preference for GluK1 over GluK2−3 (Table 2), while a mid-micromolar affinity remained for the AMPA receptors (IC_{50} = 30 μM, Table 2). Interestingly, exchanging the carboxylic acid of **2r** for a

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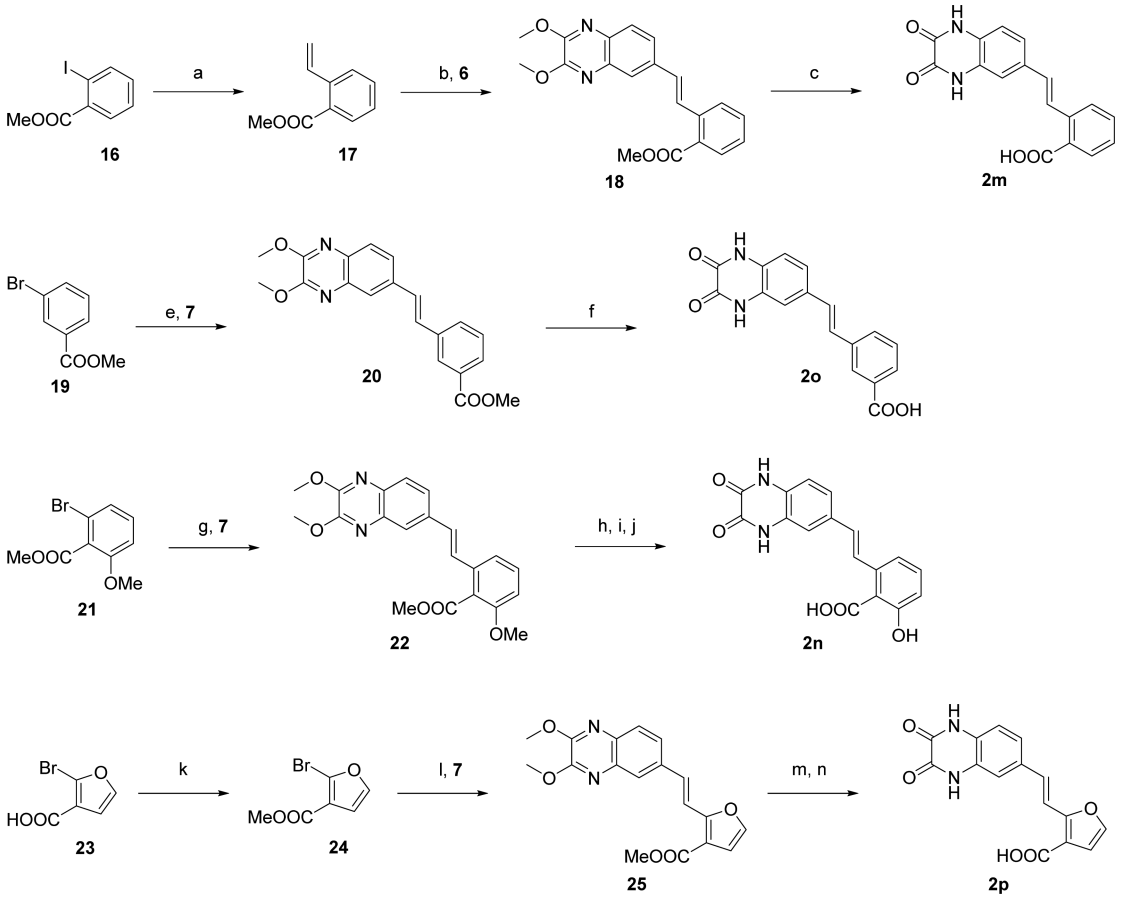
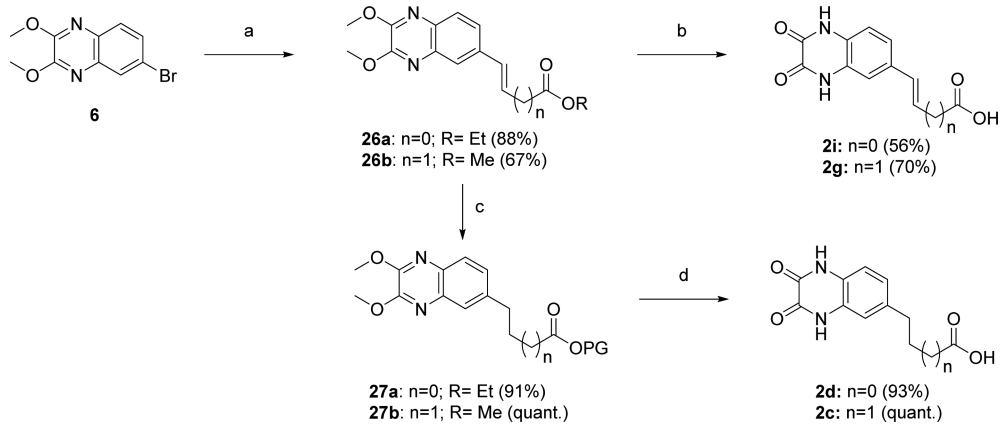
Scheme 4. Synthesis of Analogues 2m−p from Key Intermediates Bromine 6 and Alkene 7[a]



[a]Reagents and conditions: (a) $Pd(PPh_3)_4$, tributyl(vinyl)stannane, toluene, 100 °C, overnight, 44%; (b) $Pd(OAc)_2$, P(*o*-tol)$_3$, **6**, NEt_3, DMF, 100 °C, overnight, 43%; (c) 2 M HCl, dioxane, 80 °C, overnight, 75%; (e) $Pd(OAc)_2$, P(*o*-tol)$_3$, 7, NEt_3, DMF, 100 °C, overnight, 70%; (f) 2 M HCl, dioxane, 110 °C, 4 h, 48%; (g) $Pd(OAc)_2$, P(*o*-tol)$_3$, 7, NEt_3, DMF, 100 °C, overnight, 50%; (h) 1 M BCl_3 in hexane, DCM, rt, overnight; (i) 2 M HCl, dioxane, 80 °C, 3 h; (j) 2 M NaOH, DMF, 110 °C, overnight, 38% over three steps; (k) H_2SO_4, dry MeOH, 2 days, reflux, 70%; (l) $Pd(OAc)_2$, P(*o*-tol)$_3$, 7, NEt_3, DMF, 100 °C, overnight, 70%; (m) 2 M NaOH, dioxane, 50 °C, overnight, 31%; (n) 2 M HCl, dioxane, 70 °C, 3 h, 79%.

Scheme 5. Synthesis of Analogues 2c,d, 2g, and 2i[a]



[a]Reagents and conditions: (a) $Pd(OAc)_2$, P(*o*-Tol)$_3$, NEt_3, methyl 3-butenoate or ethyl acrylate, DMF, 95 °C, 3.5−6 h; (b) 1 M HCl, 1,4-dioxane, 50 °C, overnight; (c) $Pd(OH)_2$, H_2, DMF, 50 °C, 5.5−8 h; (d) 1 M HCl in 1,4-dioxane, 100 °C, 5−6 h.

phosphonic acid group gave **2u**, which was shown to be a fully selective GluK1 ligand (K_i = 12 μM). Furthermore, on introduction of a chloro substituent in the para position (compound **2t**) the affinity for the GluK1 subtype was enhanced by 12-fold, whereas tethering the carboxylic acid with a methylene group (**2v**) led to a full selectivity for the NMDA receptors. Finally, the para carboxylic acid analogue (**2w**) was without any appreciable affinity for native iGluRs, but a 4−7 fold preference was observed for the GluK3 subtype (K_i = 6.6 μM, Table 2) over GluK1 or GluK2.

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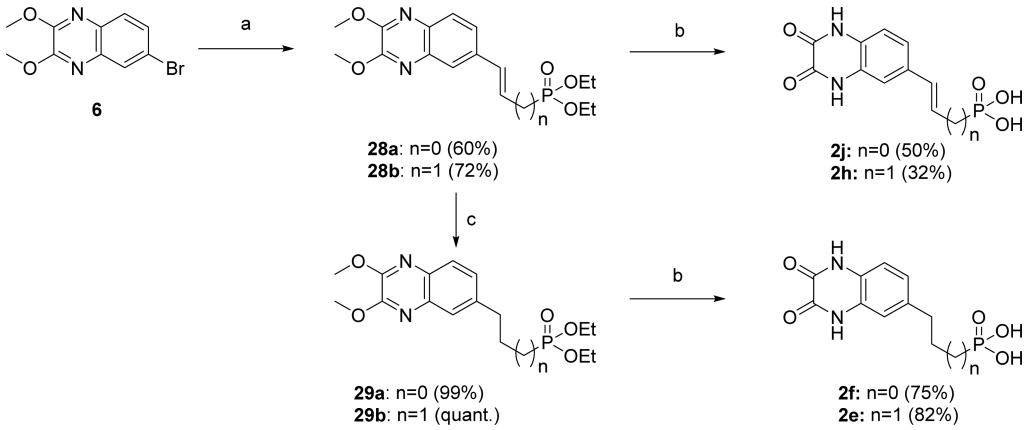
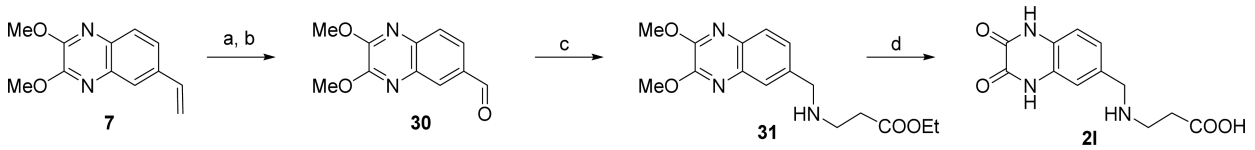
Scheme 6. Synthesis of Phosphorated Analogues 2e,f, 2h, and 2j[a]



[a]Reagents and conditions: (a) $Pd(OAc)_2$, P(*o*-tol)$_3$, NEt_3, diethyl vinylphosphonate or diethyl allylphosphonate, DMF, 95 °C, 7 h; (b) TMSBr, DCM, rt, 19 h, then 1 M HCl, 1,4-dioxane, 70 °C, overnight; (c) $Pd(OH)_2$, H_2, DMF, 50 °C, 5.5−8 h.

Scheme 7. Synthesis of Analogue 2l[a]



[a]Reagents and conditions: (a) OsO_4, $NaIO_4$, 1,4-dioxane; (b) $PhI(OAc)_2$ DCM, 60% over two steps; (c) 3-amino propionic acid ethyl ester hydrochloride, $NaBH_3CN$, AcOH, MeOH, 50%; (d) 2 M HCl, 70 °C, 3 h, 62%.

*Design and Synthesis of **2aa−aw**.* To this date, fully selective agonists or antagonists for the GluK3 subunit have not yet been reported.[9,10] However, SAR studies have previously disclosed competitive amino acid based ligands as being GluK3-preferring (5−10 fold selectivity).[11] Given the attractive GluK3-preferring binding affinity profile of **2w** with full selectivity vs native AMPA, KA and NMDA receptors (Table 2), we decided to explore this observation in a homology model of GluK3. Docking of **2w** into an antagonist state of GluK1 (PDB: 2qs4) (Figure 3) revealed that the para carboxylate group engages in hydrogen bonding interaction with the OH group of Ser173. This area of the GluK1 receptor holds residues of differentiation among the GluK subunits. For both GluK2/3, Ser173 is Asn, but also Asp174 is substituted for Glu in GluK2/3.

Inspired by these differences, we set out to design new analogues in order to explore these differences and eventually thereby enhance selectivity for GluK3 receptor. First the position of the carboxylic acid group was challenged concomitant with the incorporation of additional substituents by design of compounds **2ab−2ag** including its elimination, analogue **2aa**. These analogues were intended to be complementary to the analogues described in Table 2.

The analogues **2ai−an** (Table 4) served to explore the influence of various functional groups in the para position on binding affinity, while analogues **2ao,ap** explore the incorporation of an ester functionality together incorporation of a substituent on the phenyl ring. Finally, analogues **2aq−aw** (Table 4) explore the introduction of substituents on the phenyl ring while preserving the para carboxylic acid functionality.

The syntheses of all analogues described above (analogues **2aa−aw**) were all accomplished by Suzuki cross-coupling reactions between bromine **6** and the corresponding commercially available boronic acids to give intermediates **32aa−aw**, followed by deprotection under aqueous acidic conditions (Scheme 8).

Binding affinity profiles of **2aa−aw** were obtained for cloned homomeric GluK1−3 receptors at a 10 μM concentration and percent specific (residual) binding (% SB) recorded (Tables 3 and 4). Deleting the para carboxylic acid functionality (**2aa**) (Table 3), led to a complete loss of binding affinity across the GluK1−3 receptors. When positioning the carboxylic acid group in the meta position and concomitant introduction of one or more substituents, the most interesting observation was the 2,4-difluoro-3-carboxylic acid analogue **2ae**, which now was selective for GluK1 over GluK2,3 with an estimated IC_{50} = 10 μM. Turning to the series of para functionalized analogues **2ai−an** (Table 4), the data was disappointing as none of the analogues showed improved selectivity for GluK3 over GluK1,2 as compared with **2w**. Introduction of an additional substituent on **2w** (**2aq−aw**) was also without success in enhancing the selectivity for GluK3 over GluK1,2.

CONCLUSION

In conclusion, we designed and synthesized 44 new analogues **2c−w** and **2aa−2aw** of the broad-range iGluR quinoxalinedione antagonists **2a,b** and characterized them in binding affinity studies as ligands for the iGluRs. Highlights from the present SAR study are compound **2m** being a high affinity ligand for native AMPA receptors (IC_{50}= 0.48 μM), while analogues **2e,f,h,k,v** all displayed selectivity for native NMDA receptors. Compounds **2s,t,u** are selective ligands for the GluK1 receptor, and, most interestingly, compound **2w** was shown to be a GluK3-preferring ligand with full selectivity vs native AMPA, KA, and NMDA receptors. In all, the study demonstrates that by introduction of a tethered acid

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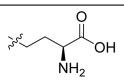
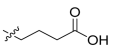
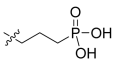
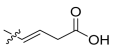
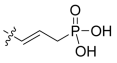
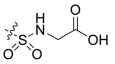
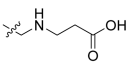
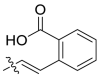
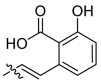
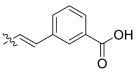
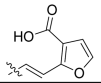
Table 1. Binding Affinities of 2a−p at Native iGluRs (AMPA, KA, and NMDA Receptors) and at Cloned Homomeric Receptors (GluA2 and GluK1-3)[b]

Cmpd		AMPA IC_{50}	KA IC_{50}	NMDA K_i	GluA2 K_i	GluK1 K_i	GluK2 K_i	GluK3 K_i
10300 2a[a]		26 [4.59 ± 0.06]	126 [3.90 ± 0.02]	78 [4.12 ± 0.08]	21 ± 2.4	16 ± 1.0	9.5 ± 1.2	59 ± 3.2
10301 2b[a]		203 [3.69 ± 0.03]	>300	>300	>100	>100	136 ± 22	>100
10302 2c		78 [4.11 ± 0.04]	≥100	>100	>100	23 ± 2.8	11 ± 0.56	~100
10303 2d		74 [4.13 ± 0.01]	67 [4.17 ± 0.02]	15 [4.84 ± 0.03]	>100	35 ± 4.1	11 ± 0.92	32 ± 3.0
10304 2e		>100	>100	55 [4.26 ± 0.02]	--	>100	>100	>100
10305 2f		>100	>100	56 [4.25 ± 0.01]	--	>100	>100	>100
10308 2g		46 [4.35 ± 0.05]	49 [4.31 ± 0.03]	>100	≈ 100	35 ± 6.0	33 ± 7.3	9.6 ± 0.95
10317 2h		> 100	>100	69 [4.17 ± 0.04]	--	>100	>100	>100
10309 2i		>100	>100	>100	>100	99 ± 37	>100	55 ± 7.2
10316 2j		>100	>100	>100	--	>100	>100	>100
10307 2k		>100	>100	53 [4.28 ± 0.03]	--	>100	>100	>100
10321 2l		26 [4.60 ± 0.07]	42 [4.37 ± 0.01]	>100	>100	45 ± 10	37 ± 0.60	19 ± 2.6
10310 2m		0.48 [6.32 ± 0.02]	24 [4.63 ± 0.03]	>100	-	1.4 ± 0.24	2.5 ± 0.89	8.9 ± 1.1
10324 2n		2.1 [5.69 ± 0.08]	39 [4.44 ± 0.10]	67 [4.17 ± 0.02]	10-100	5.4 ± 0.32	3.0 ± 1.0	3.7 ± 0.31
10311 2o		>100	>100	49 [4.31 ± 0.03]	>100	20 ± 8.6	>100	31 ± 1.5
10320 2p		4.1 [5.42 ± 0.12]	>100	16 [4.80 ± 0.03]	10-100	28 ± 2.4	14 ± 1.4	12 ± 0.84

[a]Pharmacological data taken from ref 6. [b]All values in μM. −: not tested. Data are mean values of at least three individual experiments performed in triplicate. For AMPA and KA: pIC_{50} values with SEM in brackets. For NMDA: pK_i values with SEM in brackets. [a]

functionality in the 6 position of the quinoxalinedione skeleton it is possible to tune-in a wide range of binding affinity profiles among the iGluRs.

METHODS

General Information. All reactions involving dry solvents or sensitive agents were performed under an argon atmosphere and glassware was dried prior to use. Solvents were dried according to standard procedures. Reactions were monitored by analytical thin-layer chromatography (TLC) analysis or HPLC. TLC was carried out using Merck silica gel 60 F_{254} aluminum sheets. Flash chromatography was carried out using Merck silica gel 60A (40−63 μm). HPLC was performed using a Dionex UltiMate 3000 pump and photodiode array detector (200 and 210 nm, respectively) installed with an XTerra MS C 18 3.5 μm, 4.6 mm × 150 mm column, using a 5 → 95% MeCN gradient in H_2O containing 0.1% TFA. ^1H NMR and ^{13}C NMR spectra were recorded either on a 600 MHz or a 400 Hz Bruker Avance spectrometer. MS spectra were recorded using LC-MS performed using an Agilent 1200 series solvent delivery system equipped with an autoinjector coupled to an Agilent 6400 series triple quadrupole mass spectrometer equipped with an electrospray ionization source. Gradients of 10% aqueous acetonitrile +0.05% formic acid (buffer A) and 90% aqueous acetonitrile +0.046% formic acid (buffer B) were employed. Melting points were measured with a MPA 100 Optimelt Automatic Melting Point System. All purchased chemicals were used without further purification. The purity of all

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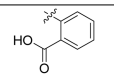
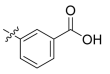
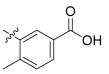
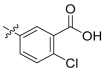
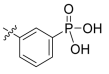
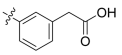
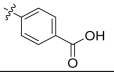
Table 2. Binding Affinities of 6-Phenyl Analogues by Variation of the Position and Distance of Carboxylic Acid Functionality[a]

Cmpd		AMPA IC_{50}	KA IC_{50}	NMDA K_i	GluA2 K_i	GluK1 K_i	GluK2 K_i	GluK3 K_i
10313 2q		>100	>100	>100	--	>100	>100	>100
10306 2r		4.4 [5.36 ± 0.06]	13 [4.88 ± 0.03]	66 [4.18 ± 0.03]	20 ± 1.5	4.8 ± 1.0	2.7 ± 0.16	4.0 ± 0.60
10318 2s		30 [4.53 ± 0.06]	>100	>100	>100	13 ± 1.1	>100	>100
10322 2t		24 [4.61 ± 0.03]	57 [4.25 ± 0.03]	>100	>100	1.2 ± 0.66	33 ± 2.5	37 ± 4.2
10319 2u		> 100	>100	>100	>100	12 ± 0.45	>100	>100
10315 2v		>100	>100	41 [4.41 ± 0.08]	--	>100	>100	>100
10314 2w		>100	>100	>100	>100	27 ± 5.1	48 ± 3.4	6.6 ± 0.69

[a]—: not tested. Data are mean values of at least three individual experiments performed in triplicate. For AMPA and KA: pIC_{50} values with SEM in brackets. For NMDA: pK_i values with SEM in brackets.

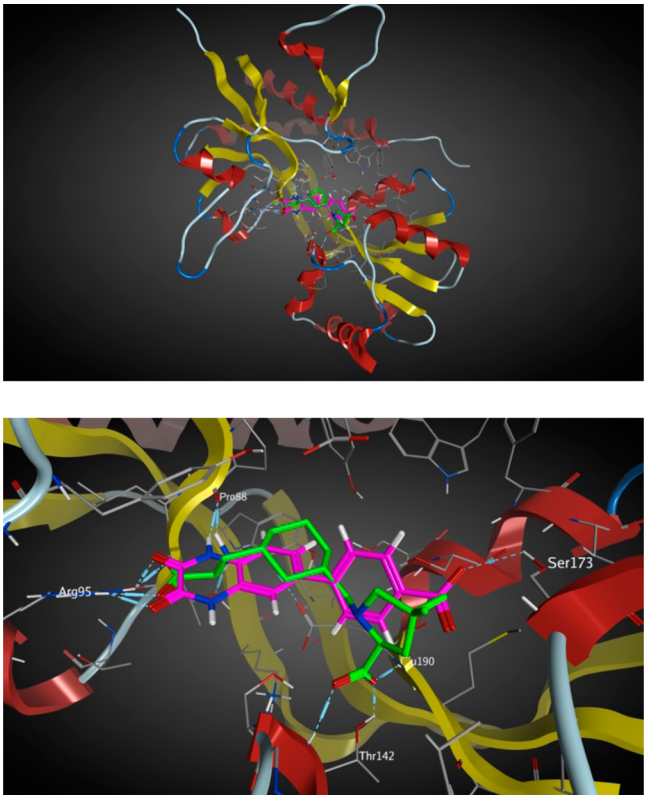


Figure 3. Docking of **2w** (green) into X-ray structure of antagonist state of GluK1 (PDB: 2qs4) crystallized with antagonist LY466195.

compounds was determined by $HPLC_{254}$ to be >95%, unless otherwise stated.

*4-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)butanoic Acid (**2c**).* In a vial, methyl-4-(2,3-dimethoxyquinoxalin-6-yl)butanoate **27b** (50 mg, 0.17 mmol, 1.0 equiv) was suspended in a mixture of 1,4-dioxane (1.0 mL) and 2 M HCl (1.0 mL). The reaction mixture was heated at 100 °C for 6 h. The mixture was cooled to room temperature and 2 M HCl (1.0 mL) was added. The white precipitate was filtered off and washed with 2 M HCl (1.0 mL) and Et_2O (1.0 mL). The solid was dried overnight at reduced pressure to afford the title compounds as a white powder (42 mg, 0.17 mmol, 99%). ^1H NMR (600 MHz, DMSO-d_6) δ 12.05 (s, 1H), 11.85 (s, 2H), 7.04 (d, J = 8.00 Hz, 1H), 6.96−6.89 (m, 2H), 2.55 (t, J = 7.65 Hz, 2H), 2.21 (t, J = 7.32 Hz, 2H), 1.81−1.71 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6, $^{13}C-^{31}P$ coupling) δ 174.7, 155.7, 155.5, 137.0, 126.0, 124.2, 123.6, 115.7, 115.0, 34.3, 33.4, 26.8; mp > 336 °C (decomposition).

*3-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)propanoic Acid (**2d**).* In a vial, ethyl-3-(2,3-dimethoxyquinoxalin-6-yl)propanoate **27a** (70 mg, 0.24 mmol, 1.0 equiv) was suspended in 1,4-dioxane (1.8 mL) and 2 M HCl (1.8 mL) was added. The mixture was stirred for 7 h at 100 °C and then cooled to room temperature. Next, 2 M HCl (1 mL) was added and the white precipitate filtered off and washed with 2 M HCl (1 mL) and Et_2O (1 mL). The solid was dried overnight at reduced pressure, to give the title compound as a white powder (52 mg, 0.22 mmol, 93%) ^1H NMR (600 MHz, DMSO-d_6) δ 12.12 (s, 1H), 11.86 (s, 1H), 11.84 (s, 1H), 7.04−7.02 (m, 1H), 6.99−6.93 (m, 2H), 2.78 (t, J = 7.49 Hz, 2H). ^1H NMR (600 MHz, MeOD-d_4) δ 7.09 (m, 3H), 2.94 (t, J = 7.54 Hz, 2H); 2.63 (t, J = 7.54 Hz, 2H). ^{13}C NMR (150 MHz, DMSO- d_6, $^{13}C-^{31}P$ coupling) δ 173.5, 155.2, 155.0, 135.8, 125.4, 123.7, 123.0, 115.0, 114.6, 35.2, 29.8; mp > 380 °C (decomposition).

*(3-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)propyl)-phosphonic Acid (**2e**).* In a vial, diethyl (3-(2,3-dimethoxyquinoxalin-6-yl)propyl)phosphonate **29b** (85 mg, 0.23 mmol, 1.0 equiv) was dissolved in DCM (0.60 mL). Then TMSBr (305 μL, 2.3 mmol, 10 equiv) was added and the reaction mixture stirred at room temperature for 24 h. After removal of solvent under reduced pressure, 1,4-dioxane and 1 M HCl (1:1) (0.4 mL) were added to the reaction mixture which was then stirred at 70 °C overnight. The solvent was removed under reduced pressure, and the solid was dried under reduced pressure overnight to give the title compound as a white solid (54 mg, 0.19 mmol, 82%). ^1H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H), 11.84 (s, 1H), 7.05 (d, J = 8.04 Hz, 1H), 6.96−6.89 (m, 2H), 2.61 (t, J = 7.46 Hz, 2H), 1.80−1.65 (m, 2H), 1.56−1.38 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, $^{13}C-^{31}P$ coupling) δ 155.2, 154.9, 136.6, 125.5, 123.6, 123.2, 115.0, 114.5, 35.3, 35.2, 27.6, 26.3, 24.8, 24.8; mp = 335 °C (decomposition).

*(2-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)ethyl)-phosphonic Acid (**2f**).* In a vial, diethyl (2-(2,3-dimethoxyquinoxalin-6-yl)ethyl)phosphonate **29a** (69.0 mg, 0.19 mmol, 1.0 equiv) was

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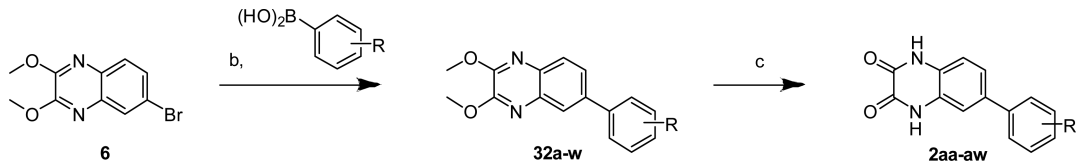
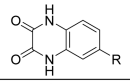
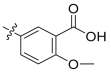
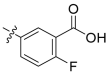
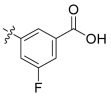
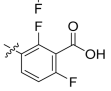
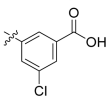
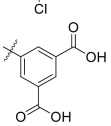
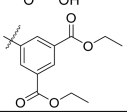
Scheme 8. Synthesis of Analogues 2aa−aw[a]



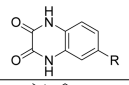
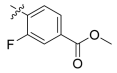
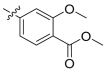
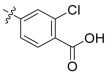
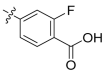
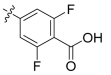
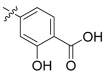
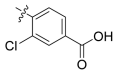
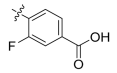
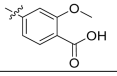
[a]Reagents and conditions: (a) $Pd(PPh_3)_4$,Cs_2CO_3, DMF/H_2O (13%−83%); (b) 2 M HCl, dioxane (34−84%).

Table 3. Binding Affinities of 2aa−ah at Cloned Homomeric GluK1-3 Subtypes[a]

		GluK1	GluK2	GluK3
Cmpd no		mean % SB at 10 μM	mean % SB at 10 μM	mean % SB at 10 μM
10328 2aa		123 ± 14	97 ± 1	84 ± 6
10336 **2ab**		84 ± 2	82 ± 6	105 ± 12
10335 **2ac**		41 ± 5	62 ± 6	79 ± 13
10338 **2ad**		64 ± 5	44 ± 4	42 ± 5
10344 **2ae**		48 ± 3	100 ± 6	102 ± 24
10339 **2af**		70 ± 11	50 ± 5	44 ± 2
10349 **2ag**		106 ± 6	106 ± 2	101 ± 6
10350 **2ah**		106 ± 5	97 ± 5	80 ± 3

[a]Compounds tested at 10 μM and results given as means ± SD of % specific binding (SB) from three experiments conducted in triplicate. Nonspecific binding was evaluated using 1 mM (*S*)-glutamic acid.

Table 4. Binding Affinity of 2ai−aw at Cloned Homomeric GluK1-3 Subtypes[a]

		GluK1	GluK2	GluK3
Cmpd no		mean % SB at 10 μM	mean % SB at 10 μM	mean % SB at 10 μM
10329 **2ai**		119 ± 14	100 ± 8	86 ± 17
10330 **2aj**		115 ± 2	96 ± 4	84 ± 6
10331 **2ak**		109 ± 6	97 ± 2	86 ± 5
10332 **2al**		127 ± 7	105 ± 4	102 ± 9
10333 **2am**		118 ± 10	105 ± 4	102 ± 11
10334 **2an**		115 ± 4	92 ± 4	76 ± 16
10337 **2ao**		113 ± 6	100 ± 5	68 ± 21
10348 **2ap**		118 ± 4	108 ± 6	105 ± 20
10340 **2aq**		104 ± 2	99 ± 9	105 ± 18
10341 **2ar**		105 ± 7	98 ± 2	93 ± 10
10342 **2as**		111 ± 8	99 ± 5	93 ± 6
10343 **2at**		103 ± 3	65 ± 7	59 ± 12
10345 **2au**		116 ± 8	86 ± 5	76 ± 3
10346 **2av**		102 ± 6	81 ± 3	84 ± 3
10347 **2aw**		101 ± 8	93 ± 4	99 ± 12

[a]Compounds tested at 10 μM and results given as means ± SD of % specific binding (SB) from three experiments conducted in triplicate. Nonspecific binding was evaluated using 1 mM (*S*)-glutamic acid.

dissolved in DCM (0.60 mL), and TMSBr (255 μL, 1.93 mmol, 10 equiv) was added. The mixture was stirred at room temperature for 24 h and then evaporated to dryness. Next, 1 M HCl (0.20 mL) was added and the mixture was stirred for 7 h at 70 °C, cooled to room temperature, and concentrated to dryness. The solid was dried under reduced pressure overnight to give the title compound as a white solid (40 mg, 0.14 mmol, 75%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H), 11.84 (s, 1H), 7.04 (d, J = 8.09 Hz, 1H), 6.96 (dd, J = 1.68 Hz, 8.26 Hz, 1H), 6.94 (s, 1H), 2.73 (m, 2H), 1.76 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6, ^{13}C−^{31}P coupling) δ 155.2, 155.0, 136.9, 136.7, 125.5, 123.7, 122.8, 115.1, 114.2, 30.1, 29.2, 28.4, 28.4; mp = 355 °C (decomposition).

*(E)-4-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)but-3-enoic Acid (**2g**).* In a vial, (*E*)-methyl-4-(2,3-dimethoxyquinoxalin-6-yl)but-2-enoate **26b** (50 mg, 0.17 mmol, 1.0 equiv) was suspended in 1,4-dioxane (1.0 mL), and 1 M HCl (1.0 mL) was added. The reaction mixture was heated overnight at 50 °C. After cooling to room temperature, 2 M HCl (2 mL) was added and the white precipitate was filtered off and washed with 1 N HCl (1.0 mL) and Et_2O (1.0 mL). The solid was dried under reduced pressure to afford the title compound as a white powder (30 mg, 0.12 mmol, 70%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.32 (s, 1H), 11.92 (s, 1H), 11.87 (s, 1H), 7.24−7.02 (m, 3H), 6.45 (d, J = 15.89 Hz, 1H), 6.26−6.06 (m, 1H), 3.19 (d, J = 7.06 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6, ^{13}C−^{31}P coupling) δ 172.6, 155.1, 154.9, 131.8, 131.3, 125.8, 124.9, 122.6, 121.0, 115.3, 112.2, 37.6; mp = 310.8−311.6 °C.

*(E)-(3-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)allyl)-phosphonic Acid (**2h**).* In a vial, (*E*)-diethyl (3-(2,3-dimethoxyquinoxalin-6-yl)allyl)phosphonate **28b** (100 mg, 0.27 mmol, 1.0 equiv) was dissolved in DCM (1.0 mL). Then TMSBr (360 μL, 2.7 mmol, 10 equiv) was added and the reaction mixture stirred at room temperature for 18 h. The solvent was removed under vacuum, and the solid redissolved in a mixture of 1,4-dioxane and 1 M HCl (1:1)

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(1.0 mL) and then stirred at 70 °C overnight. The solvent was removed under reduced pressure and the solid dried under reduced pressure overnight to give the title compound as a white solid (24 mg, 0.09 mmol, 32%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.93 (s, 1H), 11.89 (s, 1H), 7.15−7.09 (m, 2H), 7.06 (d, J = 8.20 Hz, 1H), 6.41 (dd, J = 4.37 Hz, 15.73 Hz, 1H), 6.08 (dq, J = 7.36 Hz, 14.92 Hz, 1H), 2.56 (dd, J = 7.41 Hz, 21.80 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6, ^{13}C−^{31}P coupling) δ 155.2, 155.0, 132.2, 131.7, 131.7, 131.6, 125.8, 124.7, 121.5, 121.4, 121.0, 115.3, 111.9, 33.3, 32.4; mp = 347.1−349.8 °C.

*(E)-3-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)acrylic Acid (**2i**).* In a vial, (*E*)-ethyl-3-(2,3-dimethoxyquinoxalin-6-yl)acrylate **26a** (59 mg, 0.20 mmol, 1.0 equiv) was suspended in 1,4-dioxane (0.7 mL), and 2 M HCl (0.7 mL) was added. The reaction mixture was stirred overnight at 110 °C. After cooling to room temperature, the white precipitate was filtered off and washed with 2 M HCl (1.0 mL) and Et_2O (1.0 mL). The solid was dried overnight at reduced pressure to give the title compound as a white powder (27 mg, 0.11 mmol, 56%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.38 (s, 1H), 12.05 (s, 1H), 11.96 (s, 1H), 7.52 (d, J = 15.92 Hz, 1H), 7.45 (dd, J = 1.57, 8.37 Hz, 1H), 7.31 (d, J = 1.34 Hz, 1H), 7.13 (d, J = 8.34 Hz, 1H), 6.35 (d, J = 15.93 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6, ^{13}C−^{31}P coupling) δ 167.4, 155.1, 155.0, 143.1, 128.9, 127.3, 126.0, 123.0, 118.1, 115.6, 114.5; mp > 143 °C (decomposition).

*(E)-(2-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)vinyl)-phosphonic Acid (**2j**).* In a vial, (*E*)-diethyl-(2-(2,3-dimethoxyquinoxalin-6-yl)vinyl)phosphonate **28a** (107 mg, 0.30 mmol, 1 equiv) was dissolved in DCM (1.0 mL) and TMSBr (360 μL, 2.7 mmol, 9 equiv) was added. The mixture was stirred at room temperature for 19 h and then evaporated. The solid was dissolved in a mixture of 1,4-dioxane and 1 M HCl (1:1) (1.0 mL) and stirred at 70 °C overnight. The white precipitate was filtered off, washed with 1 M HCl (0.20 mL), and dried under reduced pressure overnight to give the title compound as a white solid (41.0 mg, 0.5 mmol, 50%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.01 (s, 1H), 11.94 (s, 1H), 7.37 (dd, J = 1.57 Hz, 8.35 Hz, 1H), 7.23 (d, J = 1.40 Hz, 1H), 7.12 (d, J = 8.33 Hz, 1H), 7.10 (dd, J = 4.08 Hz, 17.49 Hz, 1H), 6.30 (dd, J = 1.06 Hz, 16.19 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6, ^{13}C−^{31}P coupling) δ 155.1, 155.1, 142.0, 142.0, 130.3, 130.1, 126.6, 125.9, 122.1, 120.3, 119.1, 115.5, 113.7; mp = 256.8−260.0 °C.

*3-(((2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)methyl)amino)-propanoic Acid (**2l**).* To a solution of ethyl 3-(((2,3-dimethoxyquinoxalin-6-yl)methyl)amino)propanoate **31** (36 mg, 0.11 mmol, 1 equiv) in dioxane (1 mL) was added 2 M HCl (1 mL), and the reaction mixture was heated at 70 °C for 3 h. The milky solution was cooled to room temperature, filtered, washed with H_2O, and dried in vacuum oven overnight, to give the title compound as a white solid (18 mg, 68 μmol, 62%). ^{1}H NMR (600 MHz, DMSO) δ 12.66 (s, 1H), 12.13 (s, 1H), 12.03 (s, 1H), 9.12 (s, 2H), 7.26 (dd, J = 8.2, 1.8 Hz, 1H), 7.23 (d, J = 1.8 Hz, 1H), 7.17 (d, J = 8.2 Hz, 1H), 4.12 (br s, 2H), 3.09 (br s, 2H), 2.70 (t, J = 7.4 Hz, 2H). ^{13}C NMR (151 MHz, DMSO) δ 171.5, 155.2, 155.1, 126.3, 126.1, 125.6, 124.8, 116.9, 115.2, 49.6, 41.9, 30.2; mp > 372 °C (decomposition).

*(E)-2-[2-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)vinyl]-benzoic Acid (**2m**).* To a solution of (*E*)-methyl 2-[2-(2,3-dimethoxyquinoxalin-6-yl)vinyl]benzoate **18** (30 mg, 86 μmol, 1.0 equiv) in dioxane (1.0 mL) was added 2 M HCl (1 mL), and the reaction mixture was heated at 80 °C overnight. A solid precipitated, and the heterogeneous mixture was evaporated under reduced pressure. H_2O (2 mL) was added and the solid isolated by filtration, then dried in a vacuum oven overnight to give the title compound as a light yellow solid (20 mg, 64 μmol, 75%). ^{1}H NMR (600 MHz, DMSO-d_6, rotamers) δ 13.03 (br s, 1H), 11.99 (s, 1H), 11.97 (s, 1H), 7.90 (d, J = 7.9 Hz, 0.3H), 7.88−7.81 (m, 2.4H), 7.76 (d, J = 16.3 Hz, 0.3H), 7.60 (td, J = 7.7, 1.4 Hz, 0.3H), 7.56 (td, J = 7.6, 1.4 Hz, 0.7H), 7.42−7.35 (m, 1H), 7.35−7.27 (m, 2H), 7.22−7.12 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6, rotamers) δ 168.6, 167.3, 155.1, 155.0, 137.7, 137.6, 132.3, 132.2, 132.0, 131.8, 130.4, 130.3, 130.2, 130.0, 129.6, 128.4, 127.4, 127.3, 126.5, 126.1, 126.1, 126.0, 125.6, 125.5, 125.4, 122.0, 121.9, 115.5, 112.6, 112.6; mp > 340 °C (decomposition).

*(E)-2-(2-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)vinyl)-6-hydroxybenzoic Acid (**2n**).* To a solution of methyl (*E*)-2-(2-(2,3-dimethoxyquinoxalin-6-yl)vinyl)-6-methoxybenzoate **22** (40 mg, 0.10 mmol, 1 equiv) in dry DCM (1 mL) was added a 1 M solution of BCl_3 in heptane (0.15 mL, 0.15 mmol, 1.5 equiv). The reaction mixture was stirred overnight at room temperature then evaporated to dryness under reduced pressure. The solid was dissolved in dioxane (0.5 mL) and 2 M HCl (0.5 mL) was added. The reaction was stirred for 3 h at 80 °C and then cooled to room temperature and filtered. The solid was dissolved in DMF (0.5 mL), 2 M NaOH (0.2 mL) was added, and then the mixture heated at 110 °C overnight. It was then cooled to room temperature followed by addition of 1 M HCl (0.5 mL). The reaction mixture was stirred for 1 h, filtered, and dried with a vacuum pump over the weekend to afford the title compound as a yellow solid (12 mg, 38 μmol, 38%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.23 (s, 1H), 11.99 (s, 1H), 11.94 (s, 1H), 10.23 (s, 1H), 7.34−7.22 (m, 4H), 7.13 (m, 3H), 6.83 (dd, J = 7.6, 1.4 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.7, 155.5, 155.1, 154.9, 135.6, 131.9, 130.6, 129.7, 126.0, 125.4, 125.2, 121.8, 120.5, 116.2, 115.5, 114.9, 112.3; mp = 295 °C (decomposition).

*(E)-3-(2-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)vinyl)-benzoic Acid (**2o**).* To a solution of (*E*)-methyl 3-(2-(2,3-dimethoxyquinoxalin-6-yl)vinyl)benzoate **20** (50 mg, 0.14 mmol, 1.0 equiv) in dioxane (0.5 mL) was added 2 M HCl (0.5 mL), and the reaction mixture was heated at 110 °C for 4 h. A light yellow solid precipitated, and the heterogeneous reaction mixture was cooled to room temperature. Next, 2 M HCl (1 mL) was added and the solid filtered off, then washed with 1 M HCl (1 mL) and diethyl ether (1 mL), and dried in a vacuum oven overnight, to give the title compound as a light yellow solid (21 mg, 67 μmol, 48%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.03 (s, 1H), 12.00 (s, 1H), 11.99 (s, 1H), 8.14 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.84 (d, J = 7.7 Hz, 1H), 7.51 (t, J = 7.7 Hz, 1H), 7.44 (dd, J = 8.5, 1.9 Hz, 1H), 7.33 (d, J = 16.4 Hz, 1H), 7.30 (d, J = 1.9 Hz, 1H), 7.19 (d, J = 16.4 Hz, 1H), 7.14 (d, J = 8.3 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.2, 155.2, 155.0, 137.3, 131.9, 131.3, 130.4, 129.0, 128.8, 128.2, 127.2, 126.8, 125.9, 125.4, 121.3, 115.5, 113.3; mp > 400 °C (decomposition).

*(E)-2-(2-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)vinyl)furan-3-carboxylic Acid (**2p**).* To a solution of (*E*)-methyl 2-[2-(2,3-dimethoxyquinoxalin-6-yl)vinyl]furan-3-carboxylate **25** (150 mg, 0.235 mmol, 1.0 equiv) in dioxane (0.5 mL) was added 2 M NaOH (0.5 mL). The reaction mixture was heated at 50 °C overnight and then evaporated to dryness. The crude product was purified on flash column chromatography [EtOAc/heptanes (4:6) + 0.1% AcOH] to give (*E*)-2-(2-(2,3-dimethoxyquinoxalin-6-yl)vinyl)furan-3-carboxylic acid as a yellow solid (24 mg, 73 μmol, 31%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.93 (s, 1H), 7.91 (d, J = 1.8 Hz, 1H), 7.81−7.75 (m, 3H), 7.72 (d, J = 16.5 Hz, 1H), 7.46 (d, J = 16.5 Hz, 1H), 6.80 (d, J = 1.9 Hz, 1H), 4.06 (s, 3H), 4.05 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.2, 155.4, 150.2, 150.0, 143.0, 136.9, 134.5, 130.5, 126.7, 124.7, 124.6, 115.6, 112.3, 54.1; mp = 272.3−274.8 °C; rf = 0.51 [EtOAc/heptanes (1:1) + 0.1% AcOH]. The above purified product (35 mg, 0.14 mmol, 1.0 equiv) was taken in dioxane (0.5 mL), and the solution was slightly warmed to around 50 °C until all material got dissolved. Next, 2 M HCl (0.5 mL) was dropwise added and the reaction mixture was heated at 70 °C for 3 h. A yellow solid precipitated, and the heterogeneous mixture was cooled to room temperature before being filtered and dried in vacuum oven overnight. The yellow crude solid (17 mg, 58 μmol, 79%) was pure on NMR. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.89 (s, 1H), 12.02 (s, 1H), 11.92 (s, 1H), 7.75 (d, J = 2.0 Hz, 1H), 7.52 (d, J = 16.5 Hz, 1H), 7.38 (d, J = 1.8 Hz, 1H), 7.32 (dd, J = 8.4, 1.8 Hz, 1H), 7.25 (d, J = 16.4 Hz, 1H), 7.15 (d, J = 8.3 Hz, 1H), 6.78 (d, J = 1.9 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.2, 155.5, 155.0, 155.0, 142.8, 130.8, 130.6, 126.2, 126.1, 122.7, 115.6, 114.9, 114.1, 112.3, 112.2; mp = 339 °C (decomposition).

*2-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)benzoic Acid (**2q**).* To a solution of methyl 2-(2,3-dimethoxyquinoxalin-6-yl)benzoate **9a**

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(62 mg, 0.15 mmol, 1 equiv) in dioxane (0.5 mL) was added 2 M HCl (0.5 mL) and the reaction mixture was heated at 110 °C for 4 h. A white solid precipitated, and the heterogeneous mixture was cooled to room temperature before addition of 2 M HCl (1 mL). The reaction mixture was filtered and washed with 1 M HCl (1 mL) and diethyl ether (1 mL), and then dried in vacuum oven overnight to give the title compound as a white solid (17 mg, 0.06 mmol, 40%). ^{1}H NMR (600 MHz, DMSO-d_6, two conformers) δ 12.79 (s, 1H), 12.04−11.94 (m, 2H), 7.77−7.70 (m, 1H), 7.62 (td, J = 7.6, 1.6 Hz, 0.2H), 7.58 (td, J = 7.5, 1.5 Hz, 0.8H), 7.50 (td, J = 7.6, 1.3 Hz, 0.2H), 7.47 (td, J = 7.6, 1.3 Hz, 0.8H), 7.41 (dd, J = 7.7, 1.3 Hz, 0.2H), 7.35 (dd, J = 7.5, 1.3 Hz, 0.8H), 7.19−7.14 (m, 1H), 7.09 (d, J = 1.9 Hz, 1H), 7.08−7.02 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6, two conformers) δ 169.4, 168.0, 155.2, 155.1, 140.3, 140.2, 135.8, 135.4, 132.1, 131.4, 131.2, 131.0, 130.4, 130.3, 129.3, 129.2, 127.5, 127.4, 125.4, 125.3, 124.9, 124.8, 123.3, 123.2, 115.0, 114.9, 114.8, 114.8; mp = 327.0−328.1 °C.

*3-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)benzoic Acid (**2r**).* To a solution of ethyl 3-(2,3-dimethoxyquinoxalin-6-yl)benzoate **9b** (40 mg, 0.12 mmol, 1 equiv) in dioxane (1.5 mL) was added 2 M HCl (1 mL) and the reaction mixture was heated at 80 °C overnight. A white solid precipitated and the heterogeneous mixture was evaporated under reduced pressure. H_2O (2 mL) was added and the solid was filtered, then dried in a vacuum oven overnight to give the title compound as a white solid (25 mg, 0.09 mmol, 75%). ^{1}H NMR (600 MHz, DMSO-d_6, rotamers) δ 13.12 (s, 1H), 11.94 (d, J = 8.0 Hz, 1H), 8.13 (d, J = 1.3 Hz, 1H), 7.94 (dd, J = 11.3, 7.8 Hz, 1H), 7.87 (dd, J = 16.6, 8.4 Hz, 1H), 7.62 (dt, J = 15.4, 7.7 Hz, 1H), 7.50−7.39 (m, 2H), 7.23 (dd, J = 8.3, 3.7 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.1, 165.6, 155.1, 155.1, 139.8, 139.6, 134.0, 133.8, 131.5, 131.1, 130.7, 129.6, 129.5, 128.2, 128.0, 126.9, 126.6, 126.3, 125.6, 125.5, 121.6, 121.6, 115.8, 115.8, 113.0, 113.0; mp > 400 °C (decomposition).

*3-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)-4-methylbenzoic Acid (**2s**).* To a solution of 3-(2,3-dimethoxyquinoxalin-6-yl)-4-methylbenzoic acid **11** (30 mg, 93 μmol, 1 equiv) in dioxane (0.5 mL) was added 2 M HCl (0.5 mL), and the reaction mixture was heated at 110 °C for 20 min. The solution was cooled to room temperature, filtered, and dried in a vacuum oven overnight to give the title compound as an orange solid (14 mg, 46 μmol, 50%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.92 (br s, 1H), 12.02 (s, 1H), 11.95 (s, 1H), 7.84 (dd, J = 7.9, 1.9 Hz, 1H), 7.73 (d, J = 1.9 Hz, 1H), 7.44 (d, J = 7.9 Hz, 1H), 7.22 (d, J = 8.1 Hz, 1H), 7.13 (dd, J = 8.2, 1.9 Hz, 1H), 7.10 (d, J = 1.9 Hz, 1H), 2.30 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.1, 155.2, 155.1, 140.5, 140.3, 135.0, 130.9, 130.2, 128.6, 128.2, 125.6, 124.9, 123.8, 115.3, 115.1, 20.4; mp > 400 °C (decomposition).

*2-Chloro-5-(2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)benzoic Acid (**2t**).* 2-Chloro-5-(2,3-dimethoxyquinoxalin-6-yl)benzoic acid **13** (70 mg, 0.20 mmol, 1 equiv) was dissolved in dioxane (0.5 mL) by gentle heating. Next, 2 M HCl (0.5 mL) was then added, and the reaction mixture was heated at 70 °C for 3 h. The solution was cooled to room temperature, filtered, and washed subsequently with 1 M HCl (1 mL) and Et_2O (1 mL). The crude white solid was dried in vacuum oven overnight to give the title compound as a white solid (44 mg, 0.14 mmol, 69%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.53 (s, 1H), 12.02 (s, 1H), 11.92 (s, 1H), 7.97 (d, J = 1.9 Hz, 1H), 7.74 (dd, J = 8.3, 2.0 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.45 (dd, J = 8.2, 1.3 Hz, 1H), 7.41 (s, 1H), 7.22 (d, J = 8.3 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.5, 155.1, 155.1, 138.2, 132.7, 131.9, 131.4, 130.7, 130.1, 128.3, 126.3, 125.7, 121.5, 115.8, 112.9; mp > 400 °C (decomposition).

*(3-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)phenyl)-phosphonic Acid (**2u**).* To a solution of diethyl (3-(2,3-dimethoxyquinoxalin-6-yl)phenyl)phosphonate **15** (85 mg, 0.21 mmol, 1 equiv) in DCM (0.6 mL) was added TMSBr (279 μL, 2.1 mmol, 10 equiv). The reaction mixture was stirred overnight at room temperature during which a solid was formed. The mixture was evaporated under reduced pressure until dryness. The solid was dissolved in dioxane (0.5 mL) and 1 N HCl (0.5 mL) was added, and the reaction mixture heated at 70 °C for 5h. After cooling to rt, the mixture was filtered and washed with 1 M HCl (1 mL). The solid was dried in a vacuum oven overnight to give the title compound as a white solid (58 mg, 0.18 mmol, 87%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.93 (s, 1H), 11.88 (s, 1H), 7.79 (dt, J = 13.8, 1.7 Hz, 1H), 7.66−7.62 (m, 1H), 7.57 (ddt, J = 12.6, 7.5, 1.4 Hz, 1H), 7.47 (td, J = 7.7, 3.8 Hz, 1H), 7.34−7.30 (m, 2H), 7.14 (d, J = 8.1 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6, C−P coupling) δ 155.6, 155.6, 139.6, 139.5, 136.1, 134.9, 130.0, 129.9, 129.5, 129.4, 129.3, 129.3, 128.8, 128.7, 126.7, 125.9, 122.0, 116.3, 113.4, 66.8; mp = 380 °C (decomposition).

*2-(3-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)phenyl)acetic Acid (**2v**).* To a solution of ethyl 2-(3-(2,3-dimethoxyquinoxalin-6-yl)phenyl)acetate **9d** (70 mg, 0.15 mmol, 1 equiv) in dioxane (0.5 mL) was added 2 M HCl (0.5 mL) and the reaction mixture was heated at 110 °C for 4 h. A white solid precipitated and the heterogeneous mixture was cooled to room temperature before the addition of 2 M HCl (1 mL). The reaction mixture was filtered and washed with 1 M HCl (1 mL) and diethyl ether (1 mL). The solid was dried in a vacuum oven overnight to give the title compound as a white solid (31 mg, 0.10 mmol, 70%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.37 (s, 1H), 12.00 (s, 1H), 11.96 (s, 1H), 7.49−7.44 (m, 2H), 7.42 (t, J = 7.5 Hz, 1H), 7.40−7.36 (m, 2H), 7.26 (d, J = 7.9 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 3.66 (s, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.6, 155.2, 155.1, 139.4, 135.8, 135.0, 129.0, 128.5, 127.5, 126.1, 125.2, 124.7, 121.6, 115.7, 113.0, 40.7; mp > 400 °C (decomposition).

*4-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)benzoic Acid (**2w**).* To a solution of ethyl 4-(2,3-dimethoxyquinoxalin-6-yl)benzoate **9c** (50 mg, 0.15 mmol, 1 equiv) in dioxane (0.5 mL) was added 2 M HCl (0.5 mL), and the reaction mixture was heated at 110 °C for 4 h. A light yellow solid precipitated and the heterogeneous mixture was cooled to room temperature before the addition of 2 M HCl (1 mL). The reaction mixture was filtered and washed with 1 M HCl (1 mL) and diethyl ether (1 mL). The solid was dried in a vacuum oven overnight, to give the title compound (as a light yellow solid (38 mg, 0.14 mmol, 91%). ^{1}H NMR (600 MHz, DMSO-d_6, conformers) δ 12.98 (s, 1H), 12.04 (s, 1H), 12.00 (s, 1H), 8.07−8.00 (m, 2H), 7.74 (d, J = 8.3 Hz, 0.3H), 7.71 (d, J = 8.5 Hz, 1.7H), 7.48 (dd, J = 8.3, 2.1 Hz, 1H), 7.44 (d, J = 2.2 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6, conformers) δ 167.5, 166.0, 155.6, 155.6, 144.3, 144.0, 134.3, 134.1, 130.6, 130.4, 130.0, 129.1, 127.0, 126.9, 126.7, 126.7, 126.4, 126.3, 122.3, 116.3, 113.7, 113.7; mp > 400 °C (decomposition).

General Procedure for the Synthesis of Compounds 2aa−2aw (unless Otherwise Noted). To a solution of the corresponding starting material in dioxane (0.5 mL) was added 2 M HCl (0.5 mL), and the reaction mixture was heated at 110 °C for 4 h before being cooled to rt. Next, 2 M HCl (1.0 mL) was added and the reaction mixture was filtered and washed with 1 M HCl (1.0 mL) and diethyl ether (1.0 mL). The solid was dried in a vacuum oil pump for 8 h, to give the desired product.

*6-Phenyl-1,4-dihydroquinoxaline-2,3-dione (**2aa**).* Reaction performed on a 0.218 mmol scale. The desired product was isolated as a light yellow solid (33 mg, 0.139 mmol, 64%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.97 (d, J = 6.6 Hz, 2H), 7.58 (dd, J = 8.3, 1.4 Hz, 2H), 7.47 (t, J = 8.0 Hz, 2H), 7.42−7.34 (m, 3H), 7.21 (d, J = 8.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 155.7, 155.5, 139.9, 135.6, 129.5, 127.9, 126.8, 126.6, 125.6, 122.1, 116.1, 113.4. mp = 375.7 °C (decomposed). LC-MS (m/z) calcd for $C_{14}H_{10}N_2O_2$ $[M + H]^+$, 238.25, found 239.1.

*5-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)-2-methoxybenzoic Acid (**2ab**).* Reaction performed on a 0.235 mmol scale. The desired product was isolated as a light yellow solid (40 mg, 0.129 mmol, 55%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.98 (s, 1H), 11.90 (s, 1H), 7.85 (d, J = 2.5 Hz, 1H), 7.74 (dd, J = 8.7, 2.5 Hz, 1H), 7.42−7.35 (m, 2H), 7.22 (dd, J = 16.4, 8.5 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 167.6, 158.1, 155.6, 155.5, 134.3, 131.6, 131.1, 128.8, 126.6, 125.4, 122.1, 121.6, 116.2, 113.7, 112.9, 56.4. mp = 303.8−304.4 °C. LC-MS (m/z) calcd for $C_{16}H_{12}N_2O_5$ $[M - H]^-$, 312.28, found 311.44.

*5-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)-2-fluorobenzoic Acid (**2ac**).* Reaction performed on a 0.293 mmol scale. The desired

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product was isolated as a light yellow solid (40 mg, 0.205 mmol, 70%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.41 (s, 1H), 12.01 (s, 1H), 11.92 (s, 1H), 8.03 (dd, J = 7.0, 2.6 Hz, 1H), 7.85 (ddd, J = 8.6, 4.5, 2.6 Hz, 1H), 7.47−7.38 (m, 3H), 7.22 (d, J = 8.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 165.3, 165.3, 159.8, 155.6, 155.6, 155.5, 136.1, 133.5, 132.8, 132.7, 129.8, 126.7, 125.9, 122.0, 118.4, 118.1, 116.3, 113.4. mp = 389.3 °C (decomposed). LC-MS (m/z) calcd for $C_{15}H_9FN_2O_4$ $[M + H]^+$, $[M - H]^-$, 300.25, found 301.1, 299.3.

*3-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)-5-fluorobenzoic Acid (**2ad**).* To a solution of the crude product of 3-(2,3-dimethoxyquinoxalin-6-yl)-5-fluorobenzoic Acid (**32d**) (210 mg) in dioxane (0.7 mL) was added 2 M HCl (0.7 mL), and the reaction mixture was heated at 110 °C for 4 h. A light yellow solid precipitated, and the heterogeneous mixture was cooled to rt before the addition of 2 M HCl (1 mL). The mixture was filtered, and the solid washed with 1 M HCl (1 mL), diethyl ether (1 mL), and dioxane (1 mL). The title compound was obtained as a light yellow solid (65 mg, 66% over two steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.44 (s, 1H), 12.04 (s, 1H), 11.92 (s, 1H), 7.99 (t, J = 1.5 Hz, 1H), 7.74 (dt, J = 2.1, 10.0 Hz, 1H), 7.65 (dt, J = 1.8, 9.0 Hz, 1H), 7.51 (dd, J = 2.0, 8.4 Hz, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 166.5, 166.5, 155.6, 142.6, 142.5, 134.3, 134.2, 133.0, 132.0, 131.9, 129.2, 126.7, 126.5, 123.4, 122.2, 118.0, 117.7, 116.3, 115.1, 114.8, 113.6. mp > 400 °C. LC-MS (m/z) calcd for $C_{15}H_9FN_2O_4$ $[M - H]^-$, 300.25, found 299.3.

*3-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)-2,6-difluorobenzoic Acid (**2ae**).* Reaction performed on a 0.260 mmol scale. The desired product was isolated as a dark yellow solid (41 mg, 0.130 mmol, 50%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 14.04 (s, 1H), 12.03 (s, 1H), 11.98 (s, 1H), 7.65 (td, J = 8.8, 6.3 Hz, 1H), 7.35−7.20 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 162.6, 155.6, 155.6, 133.3, 131.6, 131.6, 128.6, 126.3, 126.2, 125.2, 125.0, 124.0, 122.5, 120.6, 115.9, 115.8, 115.7, 115.7, 113.3, 113.0, 113.0. mp = 351.7−352.8 °C. LC-MS (m/z) calcd for $C_{15}H_8FN_2O_4$ $[M + H]^+$, $[M - H]^-$, 318.24, found 319.0, 317.2.

*3-Chloro-5-(2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)benzoic Acid (**2af**).* To a solution of the crude product of 3-chloro-5-(2,3-dimethoxyquinoxalin-6-yl)benzoic acid (**32f**) (150 mg) in dioxane (1 mL) was added 2 M HCl (1 mL), and the reaction mixture was heated at 110 °C for 4 h. A light yellow solid precipitated, and the heterogeneous mixture was cooled to rt before the addition of 2 M HCl (1 mL). The reaction mixture was filtered and washed with 1 M HCl (1 mL) and diethyl ether (1 mL). According to the NMR result, there are still some impurities. After washing with dioxane (1 mL), the title compound was obtained as a white solid (60 mg, 58% over two steps). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 13.49 (s, 1H), 12.04 (s, 1H), 11.91 (s, 1H), 8.07 (t, J = 1.6 Hz, 1H), 7.92 (q, J = 1.5 Hz, 1H), 7.88 (t, J = 1.7 Hz, 1H), 7.51 (dd, J = 2.0, 8.4 Hz, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.23 (d, J = 8.3 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ: 166.4, 155.6, 142.2, 134.6, 134.0, 130.5, 128.0, 126.8, 126.5, 126.0, 122.2, 116.3, 113.7. mp > 400 °C. LC-MS (m/z) calcd for $C_{15}H_9ClN_2O_4$ $[M + H]^+$, $[M - H]^-$, 316.70, found 317.1, 314.8.

*5-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)isophthalic Acid (**2ag**).* Reaction performed on a 0.209 mmol scale. The desired product was isolated as a dark yellow solid (23 mg, 0. 071 mmol, 34%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.06 (s, 1H), 11.92 (s, 1H), 8.44 (t, J = 1.6 Hz, 1H), 8.35 (d, J = 1.6 Hz, 2H), 7.52 (d, J = 7.1 Hz, 2H), 7.27 (d, J = 9.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 166.9, 155.6, 140.6, 133.4, 132.6, 131.2, 126.8, 126.4, 121.8, 118.4, 116.5, 113.6, 113.6, 111.3, 111.2. mp > 400 °C. LC-MS (m/z) calcd for $C_{16}H_{10}N_2O_6$ $[M - H]^-$, 326.26, found 325.3. $HPLC_{254}$ purity > 89%.

*Diethyl 5-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)-isophthalate (**2ah**).* Reaction performed on a 0.134 mmol scale. The desired product was isolated as a white solid (38 mg, 0.100 mmol, 74%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.04 (s, 1H), 11.91 (s, 1H), 8.42 (t, J = 1.6 Hz, 1H), 8.34 (d, J = 1.6 Hz, 2H), 7.52−7.46 (m, 2H), 7.25 (d, J = 8.3 Hz, 1H), 4.40 (q, J = 7.1 Hz, 4H), 1.37 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.2, 155.6, 155.5, 140.9, 133.0, 131.8, 131.3, 128.5, 126.8, 126.5, 122.1, 116.4, 113.6, 61.9, 14.6; mp = 341.1 °C (decomposed). LC-MS (m/z) calcd for $C_{20}H_{18}N_2O_6$ $[M + H]^+$, 382.37, found 383.1. $HPLC_{254}$ purity > 91%.

*6-(p-Tolyl)-1,4-dihydroquinoxaline-2,3-dione (**2ai**).* Reaction performed on a 0.212 mmol scale. The desired product was isolated as a light yellow solid (36 mg, 0.142 mmol, 67%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.95 (s, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.40−7.33 (m, 2H), 7.27 (d, J = 7.9 Hz, 2H), 7.19 (d, J = 8.2 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 155.7, 155.5, 137.2, 137.0, 135.5, 130.1, 126.6, 126.6, 125.4, 121.8, 116.1, 113.2, 21.1. mp = 380.0 °C (decomposed). LC-MS (m/z) calcd for $C_{15}H_{12}N_2O_2$ $[M + H]^+$, $[M - H]^-$, 252.27, found 253.1, 251.1.

*6-(4-Methoxyphenyl)-1,4-dihydroquinoxaline-2,3-dione (**2aj**).* Reaction performed on a 0.233 mmol scale. The desired product was isolated as a light yellow solid (27.6 mg, 0.102 mmol, 44%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.94 (d, J = 6.1 Hz, 2H), 7.51 (d, J = 8.7 Hz, 2H), 7.37−7.29 (m, 2H), 7.17 (d, J = 8.3 Hz, 1H), 7.03 (d, J = 8.7 Hz, 2H), 3.79 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 159.3, 155.7, 155.5, 135.4, 132.2, 127.9, 126.5, 125.0, 121.6, 116.1, 114.9, 112.9, 55.7. mp = 378.4 °C (decomposed). LC-MS (m/z) calcd for $C_{15}H_{12}N_2O_3$ $[M + H]^+$, 268.27, found 269.1.

*6-(4-Fluorophenyl)-1,4-dihydroquinoxaline-2,3-dione (**2ak**).* Reaction performed on a 0.186 mmol scale. The desired product was isolated as a light yellow solid (40 mg, 84%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.98 (s, 2H), 7.67−7.56 (m, 2H), 7.38 (dd, J = 8.4, 2.0 Hz, 1H), 7.35−7.27 (m, 3H), 7.20 (d, J = 8.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 163.5, 161.0, 155.7, 155.5, 136.4, 136.4, 134.6, 128.8, 128.8, 126.6, 125.6, 122.0, 116.4, 116.2, 116.2, 113.4. mp = 381.5−383.3 °C. LC-MS (m/z) calcd for $C_{14}H_9FN_2O_2$ $[M + H]^+$, $[M - H]^-$, 256.24, found 257.1, 255.1.

*6-(4-Chlorophenyl)-1,4-dihydroquinoxaline-2,3-dione (**2al**).* Reaction performed on a 0.293 mmol scale. The desired product was isolated as a light yellow solid (65 mg, 0.237 mmol, 81%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.98 (d, J = 10.9 Hz, 2H), 7.60 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 8.6 Hz, 2H), 7.40 (dd, J = 8.4, 1.9 Hz, 1H), 7.35 (d, J = 1.9 Hz, 1H), 7.20 (d, J = 8.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 155.6, 155.5, 138.7, 134.2, 132.7, 129.5, 128.5, 126.7, 125.9, 122.0, 116.2, 113.4. mp = 383.1−384.5 °C. LC-MS (m/z) calcd for $C_{14}H_9ClN_2O_2$ $[M + H]^+$, $[M - H]^-$, 272.69, found 273.0, 271.0.

*6-(4-(Trifluoromethyl)phenyl)-1,4-dihydroquinoxaline-2,3-dione (**2am**).* Reaction performed on a 0.194 mmol scale. The desired product was isolated as a light yellow solid (41 mg, 0.134 mmol, 69%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.02 (d, J = 10.1 Hz, 2H), 7.86−7.77 (m, 4H), 7.48 (dd, J = 8.3, 2.0 Hz, 1H), 7.43 (d, J = 1.9 Hz, 1H), 7.24 (d, J = 8.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.6, 155.6, 143.9, 133.8, 127.5, 126.7, 126.5, 126.4, 126.4, 126.4, 122.4, 116.3, 113.8. mp = 383.6−385.4 °C. LC-MS (m/z) calcd for $C_{15}H_9F_3N_2O_2$ $[M + H]^+$, $[M - H]^-$, 306.24, found 307.0, 305.0.

*6-(4-Hydroxyphenyl)-1,4-dihydroquinoxaline-2,3-dione (**2an**).* Reaction performed on a 0.177 mmol scale. The desired product was isolated as a light yellow solid (26 mg, 0.118 mmol, 67%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.92 (d, J = 4.7 Hz, 2H), 9.55 (s, 1H), 7.43−7.37 (m, 2H), 7.34−7.26 (m, 2H), 7.16 (d, J = 8.2 Hz, 1H), 6.89−6.82 (m, 2H). ^{13}C NMR(101 MHz, DMSO-d_6) δ: 157.6, 155.7, 155.5, 135.8, 130.6, 127.9, 126.5, 124.7, 121.4, 116.3, 116.0, 112.7. mp > 400 °C. LC-MS (m/z) calcd for $C_{14}H_{10}N_2O_3$ $[M + H]^+$, $[M - H]^-$, 254.25, found 255.0, 253.0.

*Methyl 4-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)-3-fluorobenzoate (**2ao**).* Reaction performed on a 0.143 mmol scale. The desired product was isolated as a light yellow solid (19 mg, 0.060 mmol, 42%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.05 (s, 1H), 11.99 (s, 1H), 7.88 (dd, J = 8.1, 1.7 Hz, 1H), 7.80 (dd, J = 11.3, 1.7 Hz, 1H), 7.67 (t, J = 8.0 Hz, 1H), 7.39−7.33 (m, 2H), 7.24 (d, J = 8.3 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 155.6, 155.6, 131.4, 131.4, 131.0, 128.9, 126.6, 126.4, 126.2, 126.2, 124.1, 117.3, 117.1, 116.0, 100.0, 53.0. mp = 356.9 °C (decomposed). LC-MS (m/z) calcd for $C_{16}H_{11}FN_2O_4$ $[M + H]^+$, 314.27, found 315.38. $HPLC_{254}$ purity >88%.

*Methyl 4-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)-2-methoxybenzoate (**2ap**).* Reaction performed on a 0.124 mmol scale. The desired product was isolated as a yellow solid (33 mg, 0.100

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mmol, 81%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.02 (s, 1H), 11.95 (s, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.51 (dd, J = 8.4, 2.0 Hz, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.30 (d, J = 1.6 Hz, 1H), 7.25−7.21 (m, 2H), 3.92 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 166.3, 159.3, 155.6, 145.1, 134.4, 132.1, 126.6, 126.4, 122.5, 119.0, 118.6, 116.1, 113.9, 110.9, 56.4, 52.3. mp = 330.6 °C (decomposed). LC-MS (m/z) calcd for $C_{17}H_{14}N_2O_5$ $[M + H]^+$, 326.31, found 327.1.

*2-Chloro-4-(2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)benzoic Acid (**2aq**).* To a solution of the crude product of 2-chloro-4-(2,3-dimethoxyquinoxalin-6-yl)benzoic acid (**32q**) (300 mg) in dioxane (1.0 mL) was added 2 M HCl (1.0 mL), and the reaction mixture was heated at 110 °C for 4 h. A light yellow solid precipitated, and the heterogeneous mixture was cooled to rt before the addition of 2 M HCl (1 mL). The reaction mixture was filtered and washed with 1 M HCl (1 mL) and diethyl ether (1 mL). The solid was dried in a vacuum oil pump for 6 h, to give the mixture product of ester (50 mg). Then the reaction was repeated with the mixture of the ester. The title compound was obtained as a light yellow solid (40 mg, 45% over two steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.38 (s, 1H), 12.05 (s, 1H), 11.96 (s, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.74 (d, J = 1.8 Hz, 1H), 7.64 (dd, J = 8.1, 1.8 Hz, 1H), 7.51 (dd, J = 8.4, 2.0 Hz, 1H), 7.43 (d, J = 2.0 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 166.8, 155.6, 144.0, 133.2, 132.7, 132.3, 130.0, 128.6, 126.7, 126.7, 125.4, 122.4, 116.3, 113.8. mp = 390.6 °C (decomposed). LC-MS (m/z) calcd for $C_{15}H_9ClN_2O_4$ $[M + H]^+$, $[M - H]^-$, 316.70, found 317.15, 315.23.

*4-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)-2-fluorobenzoic Acid (**2ar**).* Reaction performed on a 0.198 mmol scale. The desired product was isolated as a white solid (30 mg, 0.099 mmol, 50%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.23 (s, 1H), 12.05 (s, 1H), 11.99 (s, 1H), 7.97 (t, J = 8.0 Hz, 1H), 7.56−7.50 (m, 3H), 7.44 (d, J = 2.0 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 165.2, 165.2, 163.4, 160.8, 155.6, 146.2, 146.1, 133.2, 132.8, 132.8, 126.8, 126.7, 122.5, 122.5, 122.4, 118.2, 118.1, 116.3, 114.9, 114.7, 113.8. mp = 396.3−397.5 °C. LC-MS (m/z) calcd for $C_{15}H_9FN_2O_4$ $[M + H]^+$, 300.25, found 301.1.

*4-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)-2,6-difluorobenzoic Acid (**2as**).* To a solution of the crude product of 4-(2,3-dimethoxyquinoxalin-6-yl)-2,6-difluorobenzoic acid (**32s**) (86 mg) in dioxane (0.8 mL) was added 2 M HCl (0.8 mL), and the reaction mixture was heated at 110 °C for 4 h. A light yellow solid precipitated and the heterogeneous mixture was cooled to rt before the addition of 2 M HCl (1 mL). The reaction mixture was filtered and washed with 1 M HCl (1 mL) and diethyl ether (1 mL). The solid was dried in a vacuum oil pump for 4 h, to give the pure product (49 mg, 41% over two steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.87 (s, 1H), 12.06 (s, 1H), 11.98 (s, 1H), 7.53 (dd, J = 8.4, 2.0 Hz, 1H), 7.46 (d, J = 2.6 Hz, 1H), 7.44−7.41 (m, 2H), 7.22 (d, J = 8.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 162.5, 162.5, 161.7, 161.6, 159.2, 159.1, 155.6, 155.5, 144.8, 132.0, 127.0, 126.7, 122.4, 116.2, 113.9, 110.5, 110.3, 110.3, 110.2. mp = 351.6−352.0 °C. LC-MS (m/z) calcd for $C_{15}H_8F_2N_2O_4$ $[M + H]^+$, $[M - H]^-$, 318.24, found 319.17, 317.25.

*4-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)-2-hydroxybenzoic Acid (**2at**).* Reaction performed on a 0.230 mmol scale. The desired product was isolated as a light yellow solid (55 mg, 0.184 mmol, 80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.91 (s, 1H), 12.03 (s, 1H), 11.96 (s, 1H), 11.36 (s, 1H), 7.87 (d, J = 8.1 Hz, 1H), 7.47 (dd, J = 8.4, 2.0 Hz, 1H), 7.42 (d, J = 1.9 Hz, 1H), 7.22 (d, J = 8.3 Hz, 1H), 7.18−7.13 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 172.1, 161.9, 155.6, 146.8, 133.8, 131.5, 126.6, 126.6, 122.3, 117.8, 116.2, 114.7, 113.7, 112.3. mp = 375.2−375.4 °C. LC-MS (m/z) calcd for $C_{15}H_{10}N_2O_5$ $[M - H]^-$, 298.25, found 297.4.

*3-Chloro-4-(2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)benzoic Acid (**2au**).* Reaction performed on a 0.453 mmol scale. The desired product was isolated as a dark yellow solid (112 mg, 0.353 mmol, 78%). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 13.36 (s, 1H), 12.04 (s, 1H), 12.00 (s, 1H), 8.03 (d, J = 1.7 Hz, 1H), 7.95 (dd, J = 8.0, 1.7 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.23 (dd, J = 5.0, 3.2 Hz, 2H), 7.20 (dd, J = 8.3, 1.8 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 166.3, 155.6, 155.6, 143.5, 132.8, 132.2, 132.0, 132.0, 130.9, 128.7, 126.2, 126.0, 124.4, 116.1, 115.6. mp = 394.1 °C (decomposed). LC-MS (m/z) calcd for $C_{15}H_9ClN_2O_4$ $[M + H]^+$, $[M - H]^-$, 316.70, found 317.15, 315.28.

*4-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)-3-fluorobenzoic Acid (**2av**).* Reaction performed on a 0.137 mmol scale. The desired product was isolated as a dark yellow solid (30 mg, 0.100 mmol,73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.30 (s, 1H), 12.05 (s, 1H), 12.00 (s, 1H), 7.86 (dd, J = 8.0, 1.6 Hz, 1H), 7.77 (dd, J = 11.3, 1.6 Hz, 1H), 7.64 (t, J = 8.0 Hz, 1H), 7.39−7.33 (m, 2H), 7.25 (d, J = 8.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 166.5, 166.4, 160.3, 157.9, 155.6, 155.6, 132.3, 132.2, 132.1, 131.2, 131.2, 129.1, 126.5, 126.4, 126.3, 126.3, 124.1, 117.4, 117.1, 115.9, 115.8, 115.8. mp > 400 °C. LC-MS (m/z) calcd for $C_{15}H_9FN_2O_4$ $[M + H]^+$, $[M - H]^-$, 300.25, found 301.06, 299.38.

*4-(2,3-Dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)-2-methoxybenzoic Acid (**2aw**).* Reaction performed on a 0.068 mmol scale. The desired product was isolated as a yellow solid (11 mg, 0.035 mmol, 52%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.59 (s, 1H), 12.02 (s, 1H), 11.95 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.50 (dd, J = 8.4, 2.0 Hz, 1H), 7.45 (d, J = 1.9 Hz, 1H), 7.27 (d, J = 1.6 Hz, 1H), 7.23 (d, J = 8.3 Hz, 1H), 7.20 (dd, J = 8.0, 1.6 Hz, 1H), 3.92 (s, 3H). mp = 306.9−308.7 °C. LC-MS (m/z) calcd for $C_{16}H_{12}N_2O_5$ $[M - H]^-$, 312.28, found 311.4.

*2,3-Dimethoxy-6-vinylquinoxaline (**7**).* To a mixture of 6-bromo-2,3-dimethoxyquinoxaline **6** (2.0 g, 7.4 mmol, 1.0 equiv) and $Pd(PPh_3)_4$ (86 mg, 0.15 mmol, 2 mol %) in dry toluene (21 mL) was added tributyl(vinyl)stannane (1.3 mL, 8.9 mmol, 1.2 equiv). The reaction mixture was heated overnight at 100 °C under argon. After filtration through Celite, the solvent was removed under reduced pressure, and the crude product purified by flash chromatography on silica gel [EtOAc/heptanes (8:92)] to afford the title compound **7** as a white solid (1.5 g, 6.9 mmol, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 1.9 Hz, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.59 (dd, J = 8.5, 1.9 Hz, 1H), 6.85 (dd, J = 17.6, 10.9 Hz, 1H), 5.87 (d, J = 17.6 Hz, 1H), 5.33 (dd, J = 10.9, 0.9 Hz, 1H), 4.15 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.8, 150.5, 137.9, 137.6, 137.0, 136.8, 127.0, 125.1, 124.8, 115.1, 54.8, 54.8; mp. = 84.9−86.1 °C (solvent: heptane); R_f = 0.45 [EtOAc/heptanes (8:92)].

*2,3-Dimethoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-quinoxaline (**8**).* A flask was charged with 6-bromo-2,3-dimethoxyquinoxaline **6** (2.0 g, 7.4 mmol), bis(pinacolato)diboron (2.8 g, 11 mmol), $Pd(dppf)_2$ ·DCM (0.6 g, 0.74 mmol, 10 mol %), and KOAc (2.5 g, 26 mmol). The flask was evacuated and filled back with argon (×3). Then, dry degassed DMF (48 mL) was added and the reaction was stirred at 95 °C for 44 h. The reaction mixture was cooled to room temperature and poured into water (500 mL). The aqueous phase was extracted with EtOAc (7 × 300 mL), and the combined organic phases dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the crude product purified by column chromatography [EtOAc/heptanes (1:3)] to give the title compound **8** as a greenish-yellow solid (1.6 g, 5.0 mmol, 68%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.03 (d, J = 1.24 Hz, 1H), 7.74 (m, 2H), 4.06 (s, 3H), 4.04 (s, 3H), 1.33 (s, 12H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 150.6, 150.0, 139.4, 136.8, 134.1, 132.2, 125.8, 84.1, 54.4, 54.3, 25.1; mp = 116.5−116.9 °C (dec.).

*Methyl 2-(2,3-Dimethoxyquinoxalin-6-yl)benzoate (**9a**).* 6-Bromo-2,3-dimethoxyquinoxaline **6** (135 mg, 0.50 mmol, 1 equiv), ethyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (165 mg, 0.60 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (46 mg, 40 μmol, 0.08 equiv), and cesium carbonate (650 mg, 2.00 mmol, 4 equiv) were added into a flame-dried two-neck round-bottom flask. The flask was evacuated and filled back with argon (×3), and then dry degassed DMF (4.5 mL) was added followed by degassed H_2O (0.22 mL). The reaction mixture was stirred at 90 °C for 2 h. The reaction mixture was cooled to room temperature and H_2O (50 mL) was added followed and extracted with EtOAc (3 × 100 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under vacuum. The crude product was purified by flash chromatography on silica gel [EtOAc/heptanes (2:8)] to afford the title compound **9a** as an amorph solid (125 mg, 0.37 mmol, 74%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88

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(d, J = 7.7 Hz, 1H), 7.80−7.72 (m, 2H), 7.55 (td, J = 7.5, 1.5 Hz, 1H), 7.49−7.40 (m, 3H), 4.17 (s, 3H), 4.15 (s, 3H), 4.09 (q, J = 7.3 Hz, 2H), 0.96 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.7, 150.3, 150.1, 141.9, 140.2, 137.0, 136.5, 131.4, 131.3, 131.0, 130.1, 127.8, 127.5, 125.9, 125.9, 61.1, 54.4, 54.4, 13.9; rf = 0.3 [EtOAc/heptanes (2:8)].

*Ethyl 3-(2,3-Dimethoxyquinoxalin-6-yl)benzoate (**9b**).* 6-Bromo-2,3-dimethoxyquinoxaline **6** (150 mg, 0.56 mmol, 1.0 equiv), 3-ethoxycarbonylphenylboronic acid (141 mg, 0.73 mmol, 1.3 equiv), $Pd(PPh_3)_4$ (51 mg, 45 μmol, 8 mol %), and Cs_2CO_3 (730 mg, 2.2 mmol, 4 equiv) were added into a flame-dried two-neck round-bottom flask. The flask was evacuated and filled back with argon (×3), and then dry degassed DMF (5 mL) was added followed by degassed H_2O (0.25 mL). The reaction mixture was stirred and heated at 90 °C for 2 h. The solution was cooled to room temperature and H_2O (50 mL) was added, and extracted with EtOAc (3 × 100 mL). The combined organic phases were dried over $MgSO_4$. The crude product was purified by flash chromatography on silica gel [EtOAc/heptanes (15:85)] to give the title compound **9b** as a white solid (89 mg, 0.26 mmol, 47%). ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 8.42−8.39 (m, 1H), 8.07 (dd, J = 1.7, 1.1 Hz, 0.5H), 8.06−8.04 (m, 1.5H), 7.91 (dd, J = 2.0, 1.2 Hz, 0.5H), 7.89 (dd, J = 2.0, 1.1 Hz, 0.5H), 7.87 (d, J = 0.5 Hz, 0.3H), 7.84 (d, J = 0.5 Hz, 0.7H), 7.79 (d, J = 2.1 Hz, 0.7H), 7.77 (d, J = 2.1 Hz, 0.3H), 7.55 (td, J = 7.8, 0.5 Hz, 1H), 4.43 (q, J = 7.1 Hz, 2H), 4.19 (s, 3H), 4.18 (s, 3H), 1.44 (t, J = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.7, 150.5, 150.3, 140.8, 138.7, 137.6, 137.0, 131.7, 131.3, 129.1, 128.7, 128.5, 127.0, 126.0, 124.7, 61.3, 54.5, 54.5, 14.5; mp = 124.1−125.0 °C; R_f: 0.25 [EtOAc/heptanes (15:85)].

*Ethyl 4-(2,3-Dimethoxyquinoxalin-6-yl)benzoate (**9c**).* 6-Bromo-2,3-dimethoxyquinoxaline **6** (150 mg, 0.56 mmol, 1 equiv), 4-ethoxycarbonylphenylboronic acid (141 mg, 0.73 mmol, 1.3 equiv), $Pd(PPh_3)_4$ (51 mg, 45 μmol, 8 mol %), and cesium carbonate (730 mg, 2.2 mmol, 4 equiv) were added into a flame-dried two-neck round-bottom flask. The flask was evacuated and filled back with argon (×3), and then dry degassed DMF (5 mL) was added followed by degassed H_2O (0.25 mL), and the reaction mixture heated at 90 °C for 2 h. The solution was cooled to room temperature and H_2O (50 mL) was added followed before to be extracted with EtOAc (3 × 100 mL). The combined organic phases were dried over $MgSO_4$. The crude product was purified by flash chromatography on silica gel [EtOAc/heptanes (2:8)] to give the title compound **9c** as a white solid (134 mg, 0.40 mmol, 71%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (d, J = 8.2 Hz, 2H), 7.97 (d, J = 2.1 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.74−7.67 (m, 3H), 4.35 (q, J = 7.2 Hz, 2H), 4.11 (s, 6H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.6, 150.6, 150.4, 144.9, 138.5, 137.6, 137.2, 130.3, 129.6, 127.3, 127.1, 126.0, 125.0, 77.4, 77.2, 76.9, 61.2, 54.5, 54.5, 14.5; mp = 185.7−186.4 °C (solvent: heptane); rf = 0.38 [EtOAc/heptanes (2:8)].

*Ethyl 2-(3-(2,3-Dimethoxyquinoxalin-6-yl)phenyl)acetate (**9d**).* 6-Bromo-2,3-dimethoxyquinoxaline **6** (143 mg, 0.54 mmol, 1 equiv), (3-(2-ethoxy-2-oxoethyl)phenyl)boronic acid (125 mg, 0.64 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (50 mg, 43 μmol, 0.08 equiv), and Cs_2CO_3 (700 mg, 2.15 mmol, 4 equiv) were added into a flame-dried two-neck round-bottom flask. The flask was evacuated and filled back with argon (×3) before dry degassed DMF (4.8 mL) was added followed by degassed H_2O (0.24 mL). The reaction mixture was heated at 90 °C for 2 h, after which the reaction mixture was cooled to room temperature. H_2O (50 mL) was added and the solution extracted with EtOAc (3 × 100 mL). The combined organic phases were dried over $MgSO_4$. Crude product was purified by flash chromatography on silica gel [EtOAc/heptane (2:8)] to give the title compound **9d** as a colorless oil (131 mg, 0.37 mmol, 69%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (d, J = 2.0 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.74 (dd, J = 8.5, 2.1 Hz, 1H), 7.67−7.59 (m, 2H), 7.43 (t, J = 7.7 Hz, 1H), 7.33−7.28 (m, 1H), 4.22−4.13 (m, 8H), 3.70 (s, 2H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6, 150.4, 150.1, 140.8, 139.4, 137.5, 136.7, 134.9, 129.2, 128.5, 128.4, 126.8, 126.1, 126.1, 124.5, 61.0, 54.4, 54.3, 41.6, 14.3; rf = 0.3 [EtOAc/heptane (2:8)].

*3-(2,3-Dimethoxyquinoxalin-6-yl)-4-methylbenzoic Acid (**11**).* 2,3-Dimethoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-quinoxaline **8** (100 mg, 0.32 mmol, 1.0 equiv), 3-iodo-4-methylbenzoic acid **10** (107 mg, 0.41 mmol, 1.3 equiv), $Pd(PPh_3)_4$ (29 mg, 25 μmol, 8 mol %), and Cs_2CO_3 (515 mg, 1.6 mmol, 5 equiv) were added into a flame-dried 8 mL vial. The vial was evacuated and filled back with argon (×3), then charged with dry degassed DMF (0.3 mL) and degassed H_2O (0.15 mL). The reaction mixture was heated at 90 °C for 4 h. After cooling to rt, H_2O (3 mL) was added and the solution extracted with Et_2O (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, and the solvent removed under vacuum. The crude product was purified by flash chromatography on silica gel [EtOAc/heptanes (2:8) + 1% of AcOH] to give the title compound as a yellow solid (104 mg, 0.32 mmol, 99%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.88 (br s, 1H), 7.87 (dd, J = 7.9, 1.9 Hz, 1H), 7.85−7.79 (m, 2H), 7.69 (d, J = 2.0 Hz, 1H), 7.54 (dd, J = 8.4, 2.1 Hz, 1H), 7.47 (d, J = 7.9 Hz, 1H), 4.07 (s, 3H), 4.05 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 167.1, 150.2, 150.1, 140.7, 140.4, 138.9, 136.4, 135.7, 130.8, 130.5, 128.7, 128.4, 127.9, 126.0, 54.0, 54.0, 20.4; mp = 235.6−237.5 °C; rf = 0.16 [EtOAc/heptanes (2:8) + 1% of AcOH].

*2-Chloro-5-(2,3-dimethoxyquinoxalin-6-yl)benzoic Acid (**13**).* To a solution of 2,3-dimethoxy-6-bromoquinoxaline **6** (100 mg, 0.37 mmol, 1 equiv) in dry degassed dioxane (5 mL) and H_2O (0.5 mL) under argon was added 5-borono-2-methoxybenzoic acid (109 mg, 0.56 mmol, 1.5 equiv), K_2CO_3 (154 mg, 1.1 mmol, 3 equiv), and $PdCl_2$(dppf)·DCM (15 mg, 18.6 μmol, 5 mol %). The reaction mixture was heated at 80 °C overnight. The mixture was cooled to room temperature, poured into 1 M HCl (10 mL), and extracted with AcOEt (3 × 20 mL). The collective organic phases were dried over $MgSO_4$ and concentrated under vacuum to give the crude product. Purification on silica gel [EtOAc/heptanes (2:8) + 0.1% AcOH] gave the title compound as a white solid (79 mg, 0.23 mmol, 62%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 (d, J = 1.9 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.82 (dd, J = 8.3, 2.4 Hz, 1H), 7.74 (dd, J = 8.9, 1.7 Hz, 1H), 7.60 (d, J = 8.3 Hz, 1H), 4.18 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.5, 150.5, 150.3, 139.3, 137.5, 137.1, 137.0, 133.8, 131.9, 131.9, 131.0, 128.6, 127.1, 125.4, 124.5, 54.4, 54.4; R_f = 0.2 [EtOAc/heptanes (2:8) + 0.1% AcOH].

*Diethyl (3-(2,3-Dimethoxyquinoxalin-6-yl)phenyl)phosphonate (**15**).* 2,3-Dimethoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-quinoxaline **8** (100 mg, 0.32 mmol, 1.0 equiv), diethyl (3-bromophenyl)phosphonate **14** (120 mg, 0.41 mmol, 1.3 equiv), $Pd(PPh_3)_4$ (29 mg, 25 μmol, 8 mol %), and Cs_2CO_3 (411 mg, 1.3 mmol, 4 equiv) were added into a flame-dried 8 mL vial. The vial was evacuated and filled back with argon (×3), then charged with dry degassed DMF (0.3 mL) and degassed H_2O (0.15 mL). The reaction mixture was heated at 90 °C for 4h. The reaction mixture was cooled to room temperature and H_2O (3 mL) was added. The solution was extracted with Et_2O (3 × 10 mL) and the combined organic phase were dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude product was purified by flash chromatography on silica [EtOAc/heptanes (1:1)] to give the title compound as an amorph solid (95 mg, 0.24 mmol, 74%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (dt, J = 13.8, 1.7 Hz, 1H), 8.03 (d, J = 2.1 Hz, 1H), 7.89 (ddt, J = 7.8, 2.1, 1.2 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.81 (ddt, J = 13.0, 7.5, 1.3 Hz, 1H), 7.76 (dd, J = 8.5, 2.1 Hz, 1H), 7.58 (td, J = 7.7, 4.4 Hz, 1H), 4.24−4.18 (m, 2H), 4.17 (s, 3H), 4.17 (s, 3H), 4.17−4.09 (m, 2H), 1.36 (t, J = 7.1 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.6, 150.3, 141.0, 140.9, 138.4, 137.6, 137.0, 131.3, 131.3, 130.8, 130.8, 130.8, 130.7, 130.0, 129.3, 129.2, 128.7, 127.0, 126.0, 124.8, 62.4, 62.4, 54.5, 54.5, 16.6, 16.5; R_f = 0.23 [EtOAc/heptanes (1:1)].

*Methyl 2-Vinylbenzoate (**17**).* To a mixture of methyl 2-iodobenzoate **16** (450 μL, 3.0 mmol, 1.0 equiv) and $Pd(PPh_3)_4$ (71 mg, 61 μmol, 2 mol %) in dry degassed toluene (8 mL) under argon was added tributyl(vinyl)stannane (1.1 mL, 3.7 mmol, 1.2 equiv). The reaction mixture was heated for 17 h at 100 °C, and then cooled to rt and filtered through Celite. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel [Et_2O/DCM (1:9)] to afford the title compound as a white solid (214 mg, 1.3 mmol, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 7.9, 0.9 Hz, 1H), 7.58 (m, 1H), 7.52−7.41 (m, 2H), 7.32

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(td, J = 7.6, 1.3 Hz, 1H), 5.65 (dd, J = 17.4, 1.3 Hz, 1H), 5.36 (dd, J = 11.0, 1.3 Hz, 1H), 3.91 (s, 3H).

*(E)-Methyl 2-(2-(2,3-Dimethoxyquinoxalin-6-yl)vinyl)benzoate (**18**).* A flame-dried 8 mL vial was charged with 2,3-dimethoxy-6-bromoquinoxaline **6** (79 mg, 0.30 mmol, 1.0 equiv), $Pd(OAc)_2$ (3.3 mg, 14.8 μmol, 5 mol %) and P(o-tol)$_3$ (9.0 mg, 29.6 μmol, 10 mol %). The vial was evacuated and filled back with argon (×3). A solution of methyl 2-vinylbenzoate **17** (48 mg, 0.30 mmol, 1 equiv) in dry degassed DMF (0.3 mL) was added followed by NEt_3 (102.6 μL, 0.74 mmol, 2.5 equiv). The reaction mixture was heated at 100 °C overnight, cooled to room temperature and quenched with water (5 mL). The solution was extracted with Et_2O (3 × 10 mL), and the combined organic phases were evaporated. The crude product was purified by flash chromatography on silica gel [EtOAc/heptanes (2:8)] to give the title compound as a white solid (45 mg, 0.13 mmol, 43%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (d, J = 16.2 Hz, 1H), 7.95 (dd, J = 7.8, 1.3 Hz, 1H), 7.88 (s, 1H), 7.78−7.72 (m, 3H), 7.53 (t, J = 7.4 Hz, 1H), 7.34 (t, J = 7.0 Hz, 1H), 7.13 (d, J = 16.2 Hz, 1H), 4.16 (s, 3H), 4.16 (s, 3H), 3.95 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.0, 150.3, 150.0, 139.3, 137.6, 137.2, 136.2, 132.4, 131.0, 130.9, 128.7, 128.2, 127.4, 127.1, 126.7, 125.3, 124.9; mp = 139.5−140.3 °C; R_f = 0.28 [EtOAc/heptanes (2:8)].

*(E)-Methyl 3-(2-(2,3-Dimethoxyquinoxalin-6-yl)vinyl)benzoate (**20**).* A flame-dried argon filled 8 mL vial was charged with 2,3-dimethoxy-6-vinylquinoxaline **7** (100 mg, 0.46 mmol, 1 equiv), methyl 3-bromobenzoate **19** (107 mg, 0.50 mmol, 1.1 equiv), $Pd(OAc)_2$ (5.2 mg, 23 μmol, 5 mol %), and P(o-tol)$_3$ (14 mg, 46 μmol, 10 mol %). The vial was evacuated and filled back with argon (×3). Dry degassed DMF (0.46 mL) was added followed by NEt_3 (160 μL, 1.1 mmol, 2.5 equiv). The reaction mixture was heated at 100 °C overnight and quenched with 1/2 saturated solution of NH_4Cl (6 mL). The solution was extracted with Et_2O (3 × 12 mL) and the combined organic phases evaporated to dryness. The crude product was purified by flash chromatography on silica gel [EtOAc/heptanes (2:8)] to give the title product as a pale yellow solid (124 mg, 0.35 mmol, 77%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.27−8.21 (m, 1H), 7.98−7.92 (m, 1H), 7.89 (d, J = 1.9 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.74−7.68 (m, 2H), 7.46 (t, J = 7.7 Hz, 1H), 7.31 (d, J = 16.3 Hz, 1H), 7.26 (d, J = 16.4 Hz, 1H), 4.17 (s, 3H), 4.16 (s, 3H), 3.96 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.1, 150.4, 150.1, 137.7, 137.6, 137.2, 135.7, 131.0, 130.8, 129.5, 128.9, 128.8, 128.4, 127.7, 126.8, 125.1, 124.6, 54.4, 54.4, 52.4; mp = 131.0−131.8 °C; rf = 0.3 [EtOAc/heptanes (2:8)].

*Methyl (E)-2-(2-(2,3-Dimethoxyquinoxalin-6-yl)vinyl)-6-methoxybenzoate (**22**).* A flame-dried argon filled 8 mL vial was charged with 2,3-dimethoxy-6-vinylquinoxaline **7** (100 mg, 0.46 mmol, 1 equiv), methyl 2-bromo-6-methoxybenzoate **21** (123 mg, 0.50 mmol, 1.1 equiv), $Pd(OAc)_2$ (5.2 mg, 23.1 μmol, 5 mol %), and P(o-tol)$_3$ (14.1 mg, 46.2 μmol, 10 mol %). The vial was evacuated and filled back with argon (×3). Dry degassed DMF (0.46 mL) was added followed by NEt_3 (160 μL, 1.15 mmol, 2.5 equiv). The septum was replaced by a pressure cap and the reaction mixture was heated at 100 °C overnight, cooled to room temperature and quenched with 1/2 saturated solution of NH_4Cl (6 mL). The solution was extracted with Et_2O (3 × 12 mL) and the combined organic phases were evaporated. The crude product was purified by flash chromatography on silica gel [EtOAc/heptanes (2:8)] to give the title product as a pale yellow solid (87 mg, 0.23 mmol, 50%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, J = 1.8 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.56 (dd, J = 8.5, 1.8 Hz, 1H), 7.31 (t, J = 8.0 Hz, 1H), 7.26 (d, J = 7.8 Hz, 1H), 7.14 (d, J = 16.1 Hz, 1H), 7.09 (d, J = 16.1 Hz, 1H), 6.80 (d, J = 8.1 Hz, 1H), 4.10 (s, 3H), 4.09 (s, 3H), 3.92 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.7, 156.8, 150.4, 150.1, 137.5, 137.3, 136.2, 135.6, 131.5, 130.7, 126.7, 125.7, 125.2, 124.8, 123.0, 117.9, 110.2, 56.2, 54.4, 52.7; rf = 0.25 [EtOAc/heptanes (2:8)].

*Methyl 2-Bromofuran-3-carboxylate (**24**).* 2-Bromofuran-3-carboxylic acid **23** (600 mg, 3.0 mmol, 1.0 equiv) was added to a flame-dried round-bottom flask. Dry MeOH (6 mL) was added followed by 5 drops of conc. H_2SO_4. The reaction mixture was heated at reflux 2 days then cooled to room temperature and carefully evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel [EtOAc/heptanes (3:7)] to give the title product as a white solid (430 mg, 2.1 mmol, 70%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, J = 2.2 Hz, 1H), 6.76 (d, J = 2.1 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.5, 144.4, 129.2, 117.4, 112.8, 51.9; rf = 0.41 [EtOAc/heptanes (3:7)].

*(E)-Methyl 2-[2-(2,3-Dimethoxyquinoxalin-6-yl)vinyl]furan-3-carboxylate (**25**).* A flame-dried vial was charged with 2,3-dimethoxy-6-vinylquinoxaline **7** (60 mg, 0.28 mmol, 1.0 equiv), methyl 2-bromofuran-3-carboxylate **24** (62 mg, 0.30 mmol, 1.1 equiv), $Pd(OAc)_2$ (3.1 mg, 13.8 μmol, 5 mol %) and P(o-tol)$_3$ (8.4 mg, 27.7 μmol, 10 mol %). The vial was evacuated and filled back with argon (×3). Dry degassed DMF (0.35 mL) was added followed by NEt_3 (96 μL, 0.69 mmol, 2.5 equiv). The reaction mixture was heated at 100 °C overnight and quenched with 1/2 saturated solution of NH_4Cl (6 mL). The solution was extracted with Et_2O (3 × 12 mL) and the combined organic phases were evaporated to dryness. The crude product was purified by flash chromatography on silica gel [EtOAc/heptanes (2:8)] to afford the title compound as a yellow solid (67 mg, 0.20 mmol, 70%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 (d, J = 1.7 Hz, 1H), 7.77 (d, J = 16.4 Hz, 1H), 7.75−7.71 (m, 2H), 7.43 (d, J = 16.4 Hz, 1H), 7.36 (d, J = 2.0 Hz, 1H), 6.76 (d, J = 1.9 Hz, 1H), 4.17 (s, 3H), 4.16 (s, 3H), 3.91 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.2, 157.1, 150.5, 150.3, 141.7, 137.7, 137.6, 135.1, 131.9, 126.9, 125.4, 125.3, 116.1, 114.4, 112.1, 54.5, 54.5, 51.8; mp = 165.4−166.7 °C; rf = 0.27 [EtOAc/heptanes (2:8)].

*(E)-Ethyl-3-(2,3-dimethoxyquinoxalin-6-yl)acrylate (**26a**).* A vial was charged with $Pd(OAc)_2$ (42 mg, 0.18 mmol, 5 mol %), P(o-Tol)$_3$ (113 mg, 0.37 mmol, 10 mol %), and 2,3-dimethoxy-6-bromoquinoxaline **6** (1.00 g, 3.7 mmol, 1.0 equiv). The vial was purged twice with argon, then dry degassed DMF (6.6 mL) was added followed by NEt_3 (1.42 mL, 10.2 mmol) and ethyl acrylate (1.22 mL, 11.4 mmol, 3.0 equiv). The septum was replaced by a pressure cap and the mixture was stirred at 100 °C for 6 h. The reaction mixture was then cooled to room temperature and H_2O (25 mL) was added. The precipitate was filtered off and washed with H_2O (3 × 5 mL). The crude product was dried, then purified by column chromatography (EtOAc/heptanes = 1:3) to afford the title compound as a white powder (940 mg, 3.26 mmol, 88%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.04 (d, J = 1.81 Hz, 1H), 7.92 (dd, J = 1.90 Hz, 8.54 Hz, 1H), 7.80 (d, J = 16.02 Hz, 1H), 7.73 (d, J = 8.51 Hz, 1H), 6.75 (d, J = 16.02 Hz, 1H), 4.21 (q, J = 7.10 Hz, 2H), 4.05 (s, 3H), 4.05 (s, 3H), 1.27 (t, J = 7.11 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6, ^{13}C−^{31}P-coupling) δ 166.2, 150.4, 150.3, 143.7, 137.9, 136.6, 132.5, 127.0, 126.5, 125.6, 118.7, 60.0, 54.1, 54.0, 14.2; rf = 0.32 [EtOAc/heptanes (1:3)].

*(E)-Methyl-4-(2,3-dimethoxyquinoxalin-6-yl)but-2-enoate (**26b**).* A vial was charged with $Pd(OAc)_2$ (21 mg, 93 μmol, 8 mol %), P(o-tol)$_3$ (57 mg, 0.18 mmol, 16 mol %), and 2,3-dimethoxy-6-bromoquinoxaline **6** (315 mg, 1.2 mmol, 1.0 equiv). The vial was purged twice with argon, followed by addition of dry degassed DMF (1.5 mL), NEt_3 (450 μL, 3.2 mmol) and methyl 3-butenoate (390 μL, 4.1 mmol, 3.4 equiv). The mixture was stirred at 100 °C for 3.5 h and cooled to room temperature. H_2O (10 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (EtOAc/heptaness = 1:5) to give the title compound as a white powder (232 mg, 0.8 mmol, 67%). ^{1}H NMR (600 MHz, DMSO- d_6) δ 7.74−7.63 (m, 3H), 6.68 (d, J = 15.88 Hz, 1H), 6.45 (m, 1H), 4.03 (s, 3H), 4.03 (s, 3H), 3.65 (s, 3H), 3.34 (d, J = 6.97 Hz, 2H). ^{13}C NMR (150 MHz, DMSO- d_6, ^{13}C−^{31}P coupling) δ 171.44, 150.08, 149.71, 136.78, 136.05, 135.27, 132.17, 126.30, 124.39, 123.70, 123.35, 53.95, 53.94, 51.63, 37.49; rf = 0.23 [EtOAc/heptanes (1:3)].

*Ethyl-3-(2,3-dimethoxyquinoxalin-6-yl)propanoate (**27a**).* In a vial, (*E*)-ethyl-3-(2,3-dimethoxyquinoxalin-6-yl)acrylate **26a** (140 mg, 0.49 mmol, 1.0 equiv) was dissolved in DMF (2.1 mL) and purged with argon. Then $Pd(OH)_2$ (20 wt % on charcoal) (34.0 mg, 48 μmol, 10 mol %) was added and the vial was purged again with argon. The atmosphere was exchanged with H_2 and the mixture was stirred at 50 °C for 8 h. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases

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were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the title compound as colorless oil. (127 mg, 0.44 mmol, 91%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.66 (d, J = 8.34 Hz, 1H), 7.59 (d, J = 1.69 Hz, 1H), 7.41 (dd, J = 8.36, 1.94 Hz, 1H), 4.04 (q, J = 7.12 Hz, 2H), 4.03 (s, 3H), 4.02 (s, 3H), 3.00 (t, J = 7.53 Hz, 2H), 2.71 (t, J = 7.55 Hz, 2H), 1.14 (t, J = 7.11 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6, ^{13}C−^{31}P coupling) δ 172.1, 149.8, 149.5, 139.4, 136.4, 135.0, 127.6, 125.8, 125.1, 59.8, 53.8, 53.8, 34.9, 30.0, 14.0.

*Methyl-4-(2,3-dimethoxyquinoxalin-6-yl)butanoate (**27b**).* In a vial (*E*)-methyl-4-(2,3-dimethoxyquinoxalin-6-yl)but-2-enoate **26b** (100 mg, 0.34 mmol, 1.0 equiv) was dissolved in DMF (1.4 mL) and then purged with argon. Then $Pd(OH)_2$ (20 wt % on charcoal) (24.2 mg, 34 μmol, 10 mol %) were added. The flask was evacuated and recharged with H_2 gas and the mixture was stirred at 50 °C for 5.5 h. The mixture was poured into H_2O (15 mL) and extracted with EtOAc (4 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure, to give the title compound as colorless oil (99 mg, 0.34 mmol, 99%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.67 (d, J = 8.31 Hz, 1H), 7.55 (d, J = 1.53 Hz, 1H), 7.38 (dd, J = 1.86 Hz, 8.33 Hz, 1H), 4.03 (s, 3H), 4.02 (s, 3H), 3.58 (s, 3H), 2.75 (t, J = 7.56 Hz, 2H), 2.33 (t, J = 7.40 Hz, 2H), 1.95−1.88 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6, ^{13}C−^{31}P coupling) δ 173.1, 149.8, 149.4, 140.2, 136.5, 134.9, 127.3, 125.9, 125.1, 53.8, 53.8, 51.2, 34.0, 32.6, 26.1.

*(E)-Diethyl (2-(2,3-Dimethoxyquinoxalin-6-yl)vinyl)phosphonate (**28a**).* $Pd(OAc)_2$ (42 mg, 0.18 mmol, 5 mol %), P(*o*-tol)$_3$ (113 mg, 0.37 mmol, 10 mol %) and 6-bromo-2,3-dimethoxyquinoxaline **6** (1.00 g, 3.7 mmol, 1.0 equiv) were dissolved in DMF (10 mL), and the vial purged with argon. Then NEt_3 (1.41 mL, 10.2 mmol) and diethyl vinylphosphonate (1.05 mL, 6.83 mmol, 1.8 equiv) were added under argon. The reaction mixture was stirred at 95 °C for 7 h, then cooled to room temperature. H_2O (20 mL) was added, and the solution extracted with EtOAc (6 × 20 mL). The combined organic phases were washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered, and then concentrated under reduced pressure. The crude was distilled on a bulb-to-bulb distillation apparatus (80 °C, 0.2 mbar) to remove excess of diethyl vinylphosphonate and then purified by column chromatography (EtOAc, 100%) to afford the title compound as a white powder (910 mg, 2.7 mmol, 72%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.04 (s, 1H), 7.90 (dd, J = 1.72 Hz, 8.53 Hz, 1H), 7.75 (d, J = 8.48 Hz, 1H), 7.53 (dd, J = 17.56 Hz, 22.61 Hz, 1H), 6.75 (t, J = 17.57 Hz, 1H), 4.06 (s, 3H), 4.05 (s, 3H), 4.04 (q, J = 7.47 Hz, 4H), 1.27 (t, J = 7.04 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6, ^{13}C−^{31}P coupling) δ 150.4, 150.3, 146.8, 146.8, 137.8, 136.6, 133.3, 133.2, 126.5, 126.3, 125.5, 116.3, 115.0, 61.3, 61.2, 54.1, 54.0, 16.2, 16.2; mp =119.4−120.2 °C; rf = 0.37 (EtOAc).

*(E)-Diethyl (3-(2,3-Dimethoxyquinoxalin-6-yl)allyl)phosphonate (**28b**).* $Pd(OAc)_2$ (42 mg, 0.18 mmol, 5 mol %), P(*o*-tol)$_3$ (113 mg, 0.37 mmol, 10 mol %), and 6-bromo-2,3-dimethoxyquinoxaline **6** (1.00 g, 3.7 mmol, 1.0 equiv) were dissolved in DMF (4.6 mL) and the vial was purged with argon. Then NEt_3 (774 μL, 5.6 mmol) and diethyl allylphosphonate (704 μL, 4.09 mmol, 1.1 equiv) were added and the vessel was purged with argon again. The reaction mixture was stirred at 95 °C for 24 h and then cooled to room temperature. H_2O (20 mL) was added, and the solution mixture extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was distilled on a bulb-to-bulb distillation apparatus (0.2 mbar, 80 °C, 20 min) to remove the excess of the diethyl allylphosphonate. Purification by column chromatography (EtOAc 100%) afforded the title compound as yellow oil (817 mg, 2.2 mmol, 60%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74−7.63 (m, 3H), 6.73 (dd, J = 5.02 Hz, 1H), 6.30 (td, J = 7.42, 15.08 Hz, 1H), 4.11−4.00 (m, 10H), 2.87 (dd, J = 7.58 Hz, 22.12 Hz, 2H), 1.25 (t, J = 7.01 Hz, 6H). ^{13}C NMR (150 MHz, DMSO-d_6, ^{13}C−^{31}P coupling) δ 150.0, 149.6, 136.7, 136.0, 135.3, 135.3, 133.2, 133.1, 126.3, 124.3, 123.5, 123.4, 120.7, 120.6, 61.3, 61.3, 53.9, 53.9, 30.4, 29.5, 16.3, 16.2; rf = 0.49 [EtOAc/EtOH (3:1)].

*Diethyl (2-(2,3-Dimethoxyquinoxalin-6-yl)ethyl)phosphonate (**29a**).* In a vial, (*E*)-diethyl(2-(2,3-dimethoxyquinoxalin-6-yl)vinyl)-phosphonate **28a** (100 mg, 0.28 mmol, 1.0 equiv) was dissolved in DMF (1.3 mL) and the system purged with argon. Then $Pd(OH)_2$ (20 wt % on charcoal) (19.0 mg, 27 μmol, 10 mol %) was added, the vial was purged again with argon and then filled with H_2 gas, and the reaction mixture was stirred at 50 °C for 8 h. The mixture was poured into water (20 mL) and extracted with EtOAc (4 × 30 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the title compound as colorless liquid (99 mg, 0.28 mmol, 99%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71−7.62 (m, 2H), 7.46 (dd, J = 1.42 Hz, 8.35 Hz, 1H), 4.00 (q, J = 7.65 Hz, 4H), 4.04 (s, 3H), 4.04 (s, 3H), 3.01−2.90 (m, 2H), 2.23−2.10 (m, 2H), 1.23 (t, J = 7.04 Hz, 6H). ^{13}C NMR (150 MHz, DMSO-d_6, ^{13}C−^{31}P coupling) δ 149.8, 149.4, 139.8, 139.7, 136.4, 135.0, 127.4, 125.8, 124.9, 60.9, 60.9, 53.8, 53.8, 27.8, 27.8, 26.6, 25.2, 16.2, 16.2.

*Diethyl (3-(2,3-Dimethoxyquinoxalin-6-yl)propyl)phosphonate (**29b**).* In a vial (*E*)-diethyl (3-(2,3-dimethoxyquinoxalin-6-yl)allyl)-phosphonate **28b** (100 mg, 0.27 mmol, 1.0 equiv) was dissolved in DMF (1.3 mL) and the system purged with argon. $Pd(OH)_2$ (20 wt % on charcoal) (19.0 mg, 27 μmol, 10 mol %) was added, and argon atmosphere was exchanged for H_2 gas. The reaction mixture was stirred at 50 °C for 5.5 h then poured into water (20 mL) and extracted with EtOAc (4 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated, to give the title compound as a colorless liquid (99 mg, 0.27 mmol, 99%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68 (d, J = 8.33 Hz, 1H), 7.57 (s, 1H), 7.39 (dd, J = 1.73 Hz, 8,37 Hz, 1H), 4.11−3.89 (m, 10H), 2.82 (t, J = 7.30 Hz, 2H), 1.85 (dt, J = 8.51 Hz, 15.68 Hz, 2H), 1.78−1.63 (m, 2H), 1.21 (t, J = 7.04 Hz, 6H). ^{13}C NMR (150 MHz, DMSO-d_6, ^{13}C−^{31}P coupling) δ 149.8, 149.4, 140.1, 136.5, 134.9, 127.6, 125.9, 125.2, 60.8, 60.8, 53.8, 53.8, 35.1, 35.0, 24.4, 23.9, 23.5, 16.3, 16.2.

*2,3-Dimethoxyquinoxaline-6-carbaldehyde (**30**).* To a solution of 2,3-dimethoxy-6-vinylquinoxaline **7** (500 mg, 2.6 mmol, 1 equiv) in 1,4-dioxane (100 mL) was added H_2O (37,5 mL) followed by OsO_4 (440 μL, 69.1 μmol, 0.03 equiv, 4 wt % in water). The reaction mixture was stirred for 0.5 h at room temperature (black solution). $NaIO_4$ (147 mg, 0.69 mmol, 0.3 equiv) was added, and the reaction mixture was stirred for 24 h at rt. EtOAc (200 mL) was added into the reaction followed by H_2O (100 mL). The organic phase was washed with sat. $Na_2S_2O_3$ (100 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude was dissolved in DCM (22 mL), and $PhI(OAc)_2$ (764 mg, 1.1 equiv) was portion wise added to the reaction mixture which was stirred at room temperature for 4 h and then evaporated until dryness. The crude product was purified by flash chromatography on silica gel [EtOAc/heptanes (1:1)] to give the title compound as a white solid (263 mg, 1.39 mmol, 60%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.13 (s, 1H), 8.24 (s, 1H), 8.01−7.94 (m, 1H), 7.84 (d, J = 8.53 Hz, 1H), 4.18 (s, 3H), 4.17 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6, C−P coupling) δ 155.6, 155.6, 139.6, 139.5, 136.1, 134.9, 130.0, 129.9, 129.5, 129.4, 129.3, 129.3, 128.8, 128.7, 126.7, 125.9, 122.0, 116.3, 113.4, 66.8; mp =380 °C (dec.); rf = 0.21 [EtOAc/heptanes (1:1)].

*Ethyl 3-(((2,3-dimethoxyquinoxalin-6-yl)methyl)amino)-propanoate (**31**).* To a solution of 2,3-dimethoxyquinoxaline-6-carbaldehyde 30 (50 mg, 0.23 mmol, 1 equiv) in MeOH (1 mL) was added 3-amino propionic acid ethyl ester hydrochloride (53 mg, 0.35 mmol, 1.5 equiv) followed by portion wise addition of $NaBH_3CN$ (22 mg, 0.35 mmol, 1.5 equiv) and then dropwise addition AcOH (23, 6 μL, 0.41 mmol, 1.8 equiv). The reaction mixture was stirred at room temperature overnight, and then evaporated until dryness. DCM (3 mL) was added followed by a freshly prepared solution of $NaHCO_3$ (3 mL). The phases were separated, and the water phase was extracted with DCM (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Crude product was purified by flash chromatography on silica gel using pure ethyl acetate with 1% of NEt_3 as eluent to afford the title product as a colorless oil (37 mg, 0.11 mmol, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (m, 2H), 7.45 (dd, J = 8.3, 1.8 Hz, 1H), 4.21−4.08 (m, 8H), 3.94 (s, 2H), 2.92 (t, J = 6.4 Hz, 2H), 2.53 (t, J = 6.4 Hz, 2H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 150.1, 149.9,

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139.1, 137.2, 136.3, 127.0, 126.4, 125.4, 60.5, 54.2, 53.6, 44.1, 34.9, 14.3.

General Procedure for the Synthesis of Compounds 32a−w (unless otherwise noted). 6-Bromo-2,3-dimethoxyquinoxaline **6** (1.0 equiv), the corresponding boronic acid (1.3 equiv), $Pd(PPh_3)_4$ (8 mol %), and cesium carbonate (4.0 equiv) were added into a flame-dried two-neck round-bottom flask. The flask was evacuated and filled back with argon thrice, then dry degassed DMF (5 mL) was added followed by degassed H_2O (0.25 mL), and the reaction mixture heated at 90 °C for 2 h. The solution was cooled to rt and H_2O (25 mL) was added and the aqueous layer extracted with EtOAc (25 mL).The organic layer was washed with H_2O (3 × 25 mL), brine (25 mL) and dried over $MgSO_4$. The crude product was purified by flash chromatograph on silica gel (EtOAc/heptane) to afford the title compound.

*2,3-Dimethoxy-6-phenylquinoxaline (**32a**).* Reaction performed on a 0.372 mmol scale. The purified product was isolated as a white solid (58 mg, 0.219 mmol, 59%); R_f 0.42 (EtOAc/heptane, 1:4). ^1H NMR (400 MHz, DMSO-d_6) δ: 8.00 (d, J = 1.9 Hz, 1H), 7.88−7.80 (m, 4H), 7.50 (t, J = 7.6 Hz, 2H), 7.41 (d, J = 7.3 Hz, 1H), 4.07 (d, J = 3.2 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 150.7, 150.4, 139.8, 139.1, 137.39, 136.5, 129.5, 128.2, 127.4, 127.1, 126.1, 124.0, 54.5. LC-MS (m/z) calcd for $C_{16}H_{14}N_2O_2$ $[M + H]^+$, 266.30, found 267.1.

*5-(2,3-Dimethoxyquinoxalin-6-yl)-2-methoxybenzoic Acid (**32b**).* Reaction performed on a 0.557 mmol scale. The title compound was isolated as a white solid (136 mg, 0.401 mmol, 72%); R_f 0.23 (EtOAc/heptane/AcOH 1:1:0.05). ^1H NMR (400 MHz, DMSO-d_6) δ: 12.75 (s, 1H), 8.03 (d, J = 2.5 Hz, 1H), 8.00−7.96 (m, 2H), 7.87−7.80 (m, 2H), 7.26 (d, J = 8.7 Hz, 1H), 4.07 (d, J = 3.9 Hz, 6H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 170.9, 167.6, 158.2, 150.7, 150.3, 137.9, 137.4, 136.2, 131.6, 129.3, 127.1, 125.7, 123.4, 113.7, 56.4, 54.5. LC-MS (m/z) calcd for $C_{18}H_{16}N_2O_5$ $[M + H]^+$, $[M - H]^-$, 340.34, found 341.0, 339.2.

*5-(2,3-Dimethoxyquinoxalin-6-yl)-2-fluorobenzoic Acid (**32c**).* Reaction performed on a 0.557 mmol scale. The crude product was purified by flash chromatograph on silica gel (EtOAc/heptane/AcOH 1:1:0.05) to give the title compound as a white solid (152 mg, 0.401 mmol, 72%); R_f 0.49 (EtOAc/heptane/AcOH 1:1:0.05). ^1H NMR (400 MHz, DMSO-d_6) δ: 8.19 (dd, J = 6.9, 2.6 Hz, 1H), 8.06 (ddd, J = 8.6, 4.5, 2.6 Hz, 1H), 8.00 (d, J = 1.9 Hz, 1H), 7.88−7.81 (m, 2H), 7.43 (dd, J = 10.6, 8.6 Hz, 1H), 4.07 (d, J = 2.5 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 165.4, 165.4, 162.5, 159.9, 150.7, 150.5, 137.4, 137.1, 136.6, 136.0, 136.0, 133.2, 133.1, 130.4, 127.2, 125.9, 124.1, 118.2, 118.0, 54.5, 54.5.

*3-(2,3-Dimethoxyquinoxalin-6-yl)-5-fluorobenzoic Acid (**32d**).* Reaction performed on a 0.372 mmol scale. 6-Bromo-2,3-dimethoxyquinoxaline (**6**) (100 mg, 0.372 mmol, 1.0 equiv), 3-borono-5-fluorobenzoic acid (89 mg, 0.484 mmol, 1.3 equiv), $Pd(PPh_3)_4$ (35 mg, 0.030 mmol, 0.08 equiv), and cesium carbonate (485 mg, 1.488 mmol, 4.0 equiv) were added into a flame-dried two-neck round-bottom flask. The flask was evacuated and filled back with argon (×3), then dry degassed DMF (3.4 mL) was added followed by degassed H_2O (0.16 mL), and the reaction mixture heated at 90 °C for 4 h. The solution was cooled to rt and filtered with Celite. The crude product was purified by flash chromatograph on silica gel (EtOAc/heptane/AcOH 1:1:0.01) to give the title compound as a white solid, which was used in the next step without further purifications. R_f 0.26 (EtOAc/heptane/AcOH 1:4:0.05). ^1H NMR (400 MHz, DMSO-d_6) δ: 8.15 (s, 1H), 8.10 (s, 1H), 8.00 (dd, J = 10.1, 2.2 Hz, 1H), 7.96 (s, 1H), 7.95−7.91 (m, 1H), 7.86 (d, J = 8.5 Hz, 1H), 4.09 (d, J = 2.4 Hz, 6H).

*3-(2,3-Dimethoxyquinoxalin-6-yl)-2,6-difluorobenzoic Acid (**32e**).* Reaction performed on a 0.372 mmol scale. After acidification of the aqueous layer with 2 M HCl (pH = 4), the title compound precipitated out as a brown solid which was collected by filtration (98 mg, 0.283 mmol, 76%). ^1H NMR (400 MHz, DMSO-d_6) δ: 14.08 (s, 1H), 7.90−7.86 (m, 1H), 7.86−7.79 (m, 2H), 7.69 (dt, J = 8.6, 1.8 Hz, 1H), 7.34 (t, J = 8.9 Hz, 1H), 4.07 (d, J = 2.6 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 162.6, 150.8, 137.0, 136.7, 133.7, 133.6, 132.5, 129.2, 127.9, 127.8, 126.8, 126.7, 125.2, 125.1, 125.1, 125.0, 113.2, 113.2, 113.0, 112.9, 54.6, 54.5.

*3-Chloro-5-(2,3-dimethoxyquinoxalin-6-yl)benzoic Acid (**32f**).* Reaction performed on a 0.372 mmol scale. 6-Bromo-2,3-dimethoxyquinoxaline (**6**) (100 mg, 0.372 mmol, 1.0 equiv), 3-borono-5-chlorobenzoic acid (97 mg, 0.484 mmol, 1.3 equiv), $Pd(PPh_3)_4$ (35 mg, 0.030 mmol, 0.08 equiv), and cesium carbonate (485 mg, 1.488 mmol, 4.0 equiv) were added into a flame-dried two-neck round-bottom flask. The flask was evacuated and filled back with argon (× 3), then dry degassed DMF (3.4 mL) was added followed by degassed H_2O (0.16 mL), and the reaction mixture heated at 90 °C for 3h. The solution was cooled to rt and filtered with Celite. The crude product was purified by flash chromatograph on silica gel (EtOAc/heptane/AcOH 1:1:0.01) to give the title compound as a white solid, which was used in the next step without further purification. R_f 0.29 (EtOAc/heptane/AcOH 1:4:0.05). ^1H NMR (400 MHz, DMSO-d_6) δ: 8.23 (t, J = 1.6 Hz, 1H), 8.17 (t, J = 1.9 Hz, 1H), 8.09 (d, J = 2.1 Hz, 1H), 7.95−7.90 (m, 2H), 7.85 (d, J = 8.5 Hz, 1H), 4.08 (d, J = 2.1 Hz, 6H).

*Diethyl 5-(2,3-Dimethoxyquinoxalin-6-yl)isophthalate (**32h**) and 3-(2,3-Dimethoxyquinoxalin-6-yl)-5-(ethoxycarbonyl)benzoic Acid (**32g**).* 6-Bromo-2,3-dimethoxyquinoxaline (**6**) (150 mg, 0.557 mmol, 1.0 equiv), (3,5-bis(ethoxycarbonyl)phenyl) boronic acid (164 mg, 0.724 mmol, 1.3 equiv), $Pd(PPh_3)_4$ (52 mg, 0.045 mmol, 0.08 equiv), and cesium carbonate (726 mg, 1.23 mmol, 4.0 equiv) were added into a flame-dried two-neck round-bottom flask. The flask was evacuated and filled back with argon (×3), then dry degassed DMF (5.0 mL) was added followed by degassed H_2O (0.25 mL), and the reaction mixture heated at 90 °C for 24 h, and 48h at rt. The solution was cooled to rt and H_2O (25 mL) was added and the aqueous layer extracted with EtOAc (25 mL).The aqueous layer was adjusted the pH to 4−5 with 2 M HCl to give the product **32ag** as a brown precipitate, which was collected by filtration and used in the next step without further purification. The EtOAc layer concentration on rotorvap and purified by flash chromatograph on silica gel (EtOAc/heptane 1:10 to 1:4) to give **32h** as a white solid (55 mg, 0.134 mmol, 24%); R_f 0.42 (EtOAc: heptane 1:4). ^1H NMR (400 MHz, DMSO-d_6) δ: 8.52 (d, J = 1.6 Hz, 2H), 8.49 (d, J = 1.6 Hz, 1H), 8.07 (d, J = 2.0 Hz, 1H), 7.93 (dd, J = 8.5, 2.1 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 4.42 (q, J = 7.1 Hz, 4H), 4.09 (d, J = 3.0 Hz, 6H), 1.39 (t, J = 7.1 Hz, 6H). ^1H NMR (400 MHz, DMSO-d_6) δ: 8.49−8.44 (m, 3H), 8.01 (d, J = 2.0 Hz, 1H), 7.89 (dd, J = 8.5, 2.1 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 4.07 (d, J = 2.5 Hz, 6H), 1.38 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 166.7, 165.4, 150.8, 150.7, 140.8, 137.4, 137.0, 136.9, 132.7, 132.2, 131.7, 131.6, 129.1, 127.4, 126.0, 124.5, 61.8, 54.5, 54.5, 14.6.

*2,3-Dimethoxy-6-(p-tolyl)quinoxaline (**32i**).* Reaction performed on a 0.557 mmol scale. The title compound was isolated as a white solid (73 mg, 0.262 mmol, 47%); R_f 0.42 (EtOAc/heptane, 1:4). ^1H NMR (400 MHz, DMSO-d_6) δ: 7.97 (d, J = 1.9 Hz, 1H), 7.86−7.79 (m, 2H), 7.70 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 4.06 (d, J = 3.3 Hz, 6H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 150.6, 150.3, 139.0, 137.5, 137.4, 136.9, 136.3, 130.1, 127.2, 127.0, 125.9, 123.6, 54.5, 21.1.

*2,3-Dimethoxy-6-(4-methoxyphenyl)quinoxaline (**32j**).* Reaction performed on a 0.557 mmol scale. The title compound was isolated as a white solid (86 mg, 0.289 mmol, 52%); R_f 0.33 (EtOAc/heptane, 1:4). ^1H NMR (600 MHz, DMSO-d_6) δ: 7.94 (d, J = 2.0 Hz, 1H), 7.83−7.81 (m, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.77−7.74 (m, 2H), 7.06 (d, J = 8.7 Hz, 2H), 4.06 (d, J = 6.2 Hz, 6H), 3.82 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 159.6, 150.6, 150.1, 138.8, 137.4, 136.0, 132.1, 128.5, 126.9, 125.7, 123.2, 115.0, 55.7, 54.4, 54.4. LC-MS (m/z) calcd for $C_{17}H_{16}N_2O_3$ $[M + H]^+$, 296.33, found 297.1.

*6-(4-Fluorophenyl)-2,3-dimethoxyquinoxaline (**32k**).* Reaction performed on a 0.557 mmol scale. The title compound was isolated as a white solid (64 mg, 0.223 mmol, 40%); R_f 0.42 (EtOAc/heptane, 1:4). ^1H NMR (400 MHz, DMSO-d_6) δ: 7.99 (d, J = 1.2 Hz, 1H), 7.89−7.80 (m, 4H), 7.32 (t, J = 8.8 Hz, 2H), 4.07 (d, J = 2.7 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 161.3, 150.7, 150.4, 138.0, 137.4, 136.4, 136.2, 136.2, 129.5, 129.4, 127.1, 126.0, 123.9, 116.4, 116.2, 54.5. LC-MS (m/z) calcd for $C_{16}H_{13}FN_2O_2$ $[M + H]^+$, 284.29, found 285.1.

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*6-(4-Chlorophenyl)-2,3-dimethoxyquinoxaline (**32l**).* Reaction performed on a 0.372 mmol scale. The title compound was isolated as a white solid (73 mg, 0.242 mmol, 65%); R_f 0.41 (EtOAc/heptane, 1:4). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.00 (d, J = 2.2 Hz, 1H), 7.89−7.78 (m, 4H), 7.54 (d, J = 8.5 Hz, 2H), 4.06 (d, J = 2.3 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 150.7, 150.5, 138.6, 137.7, 137.4, 136.7, 133.0, 129.4, 129.2, 127.1, 125.9, 124.1, 54.5.

*2,3-Dimethoxy-6-(4-(trifluoromethyl)phenyl)quinoxaline (**32m**).* Reaction performed on a 0.557 mmol scale. The title compound was isolated as a white solid (124 mg, 0.373 mmol, 67%); R_f 0.37 (EtOAc/heptane, 1:4). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.11 (d, J = 2.1 Hz, 1H), 8.06 (d, J = 8.1 Hz, 2H), 7.93 (dd, J = 8.5, 2.1 Hz, 1H), 7.86 (dd, J = 9.5, 8.2 Hz, 3H), 4.08 (d, J = 1.8 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 150.8, 150.7, 137.4, 137.3, 137.1, 128.2, 127.3, 126.3, 126.3, 126.2, 126.1, 124.7, 54.6, 54.6.

*4-(2,3-Dimethoxyquinoxalin-6-yl)phenol (**32n**).* Reaction performed on a 0.557 mmol scale. The title compound was isolated as a white solid (106 mg, 0.379 mmol, 68%); R_f 0.16 (EtOAc/heptane, 1:4). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.60 (s, 1H), 7.90 (d, J = 1.8 Hz, 1H), 7.78 (d, J = 2.9 Hz, 2H), 7.64 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 4.06 (d, J = 4.4 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 157.8, 150.5, 150.0, 139.2, 137.4, 135.8, 130.4, 128.5, 126.9, 125.6, 122.8, 116.3, 54.4. LC-MS (m/z) calcd for $C_{16}H_{14}N_2O_3$ [M + H]$^+$, 282.30, found 283.0.

*Methyl 4-(2,3-Dimethoxyquinoxalin-6-yl)-3-fluorobenzoate (**32o**) and 4-(2,3-Dimethoxyquinoxalin-6-yl)-3-fluorobenzoic Acid (**32v**).* 6-Bromo-2,3-dimethoxyquinoxaline **6** (150 mg, 0.557 mmol, 1.0 equiv), (2-fluoro-4-(methoxycarbonyl) phenyl) boronic acid (143 mg, 0.724 mmol, 1.3 equiv), Pd(PPh$_3$)$_4$ (52 mg, 0.045 mmol, 0.08 equiv), and cesium carbonate (726 mg, 2.23 mmol, 4.0 equiv) were added into a flame-dried two-neck round-bottom flask. The flask was evacuated and filled back with argon (× 3), then dry degassed DMF (5 mL) was added followed by degassed H_2O (0.25 mL), and the reaction mixture heated at 90 °C. After 24 h, there are still lots of starting material. The solution was cooled to rt, and H_2O (25 mL) was added and the aqueous layer extracted with EtOAc (25 mL). The aqueous layer was adjusted the pH to 4−5 with 2 M HCl to give the product **32v** as a brown precipitate (25 mg, 0.076 mmol, 22%), which was collected by filtration and used in the next step without further purification. The EtOAc layer was purified by flash chromatograph on silica gel (EtOAc/heptane 1:8 to 1:4) to give the title compound **32o** as a white solid (16 mg, 0.047 mmol, 13%); R_f 0.26 (EtOAc/heptane, 1:4). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.99 (t, J = 1.8 Hz, 1H), 7.93−7.88 (m, 2H), 7.85 (dd, J = 13.4, 1.9 Hz, 2H), 7.78 (dt, J = 8.5, 1.9 Hz, 1H), 4.08 (d, J = 3.2 Hz, 6H), 3.91 (s, 3H). LC-MS (m/z) calcd for $C_{18}H_{15}FN_2O_2$ [M + H]$^+$, 342.33, found 343.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.32 (s, 1H), 7.97 (t, J = 1.8 Hz, 1H), 7.88 (d, J = 1.6 Hz, 1H), 7.85 (d, J = 7.4 Hz, 1H), 7.82 (d, J = 2.0 Hz, 1H), 7.81−7.75 (m, 2H), 4.08 (d, J = 2.8 Hz, 6H).

*Methyl 4-(2,3-Dimethoxyquinoxalin-6-yl)-2-methoxybenzoate (**32p**).* Reaction performed on a 0.372 mmol scale. The title compound was isolated as a white solid (83 mg, 0.234 mmol, 63%); R_f 0.11 (EtOAc/heptane 1:4). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.13 (d, J = 2.1 Hz, 1H), 7.95 (dd, J = 8.6, 2.1 Hz, 1H), 7.85 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 1.6 Hz, 1H), 7.45 (dd, J = 8.1, 1.6 Hz, 1H), 4.08 (d, J = 2.6 Hz, 6H), 3.98 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 166.4, 159.3, 150.7, 150.6, 144.9, 137.9, 137.3, 137.1, 132.0, 127.1, 126.3, 124.6, 119.3, 119.1, 111.5, 56.5, 54.5, 52.3.

*2-Chloro-4-(2,3-dimethoxyquinoxalin-6-yl)benzoic Acid (**32q**).* Reaction performed on a 0.372 mmol scale. The crude product was purified by flash chromatograph on silica gel (EtOAc/heptane: AcOH 1:1:0.01) to give the title compound as a white solid, which was used without further purification in the next step. R_f 0.41 (EtOAc/heptane/AcOH 1:1:0.01).

*4-(2,3-Dimethoxyquinoxalin-6-yl)-2-fluorobenzoic Acid (**32r**).* Reaction performed on a 0.372 mmol scale. The crude product was purified by flash chromatograph on silica gel (EtOAc/heptane/AcOH 1:5:0.005 to 1:2:0.005) to give the title compound as a white solid (65 mg, 0.197 mmol, 53%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.23 (s, 1H), 8.14 (d, J = 2.1 Hz, 1H), 7.99−7.93 (m, 2H), 7.86−7.76 (m, 3H), 4.08 (d, J = 1.7 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 163.4, 150.8, 150.8, 145.9, 137.4, 137.3, 136.4, 136.4, 133.0, 133.0, 127.2, 126.0, 124.8, 123.2, 123.1, 115.7, 115.4, 54.6, 54.6.

*4-(2,3-Dimethoxyquinoxalin-6-yl)-2,6-difluorobenzoic Acid (**32s**).* Reaction performed on a 0.372 mmol scale. The crude product was purified by flash chromatograph on silica gel (EtOAc/heptane/AcOH 1:5:0.005 to 1:2:0.005) to give the title compound as a white solid, which was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.88 (s, 1H), 8.18 (d, J = 2.1 Hz, 1H), 7.97 (dd, J = 8.6, 2.2 Hz, 1H), 7.84 (d, J = 8.6 Hz, 1H), 7.74 (d, J = 9.6 Hz, 2H), 4.08 (d, J = 1.2 Hz, 6H). LC-MS (m/z) calcd for $C_{17}H_{12}F_2N_2O_4$ [M + H]$^+$, [M − H]$^-$, 346.29, found 347.0, 345.0.

*4-(2,3-Dimethoxyquinoxalin-6-yl)-2-hydroxybenzoic Acid (**32at**).* Reaction performed on a 0.372 mmol scale. The crude product was purified by flash chromatograph on silica gel (EtOAc/heptane/AcOH 1:1:0.05) to give the title compound as a white solid (49.5 mg, 0.152 mmol, 41%); R_f 0.12 (EtOAc/heptane/AcOH 1:4:0.05). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 8.01 (d, J = 2.1 Hz, 1H), 7.90−7.84 (m, 2H), 7.80 (d, J = 8.5 Hz, 1H), 7.38−7.32 (m, 2H), 4.06 (d, J = 3.8 Hz, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ: 171.9, 163.7, 150.6, 150.3, 142.8, 139.3, 137.3, 136.5, 131.1, 126.9, 126.1, 123.9, 120.2, 115.2, 114.5, 54.4.

*3-Chloro-4-(2,3-dimethoxyquinoxalin-6-yl)benzoic Acid (**32au**).* Reaction performed on a 0.734 mmol scale. After acidification of the aqueous layer with 2 M HCl (pH = 4), the title compound precipitated out as a brown solid which was collected by filtration (156 mg, 0.447 mmol, 61%); R_f 0.26 (EtOAc/heptane/AcOH 1:1:0.005). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.06 (d, J = 1.6 Hz, 1H), 7.98 (dd, J = 8.0, 1.7 Hz, 1H), 7.87−7.81 (m, 2H), 7.69−7.61 (m, 2H), 4.07 (d, J = 6.2 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 166.4, 150.9, 150.8, 143.6, 136.8, 136.7, 136.7, 132.6, 132.2, 132.1, 130.9, 128.7, 128.2, 127.0, 126.5, 54.6, 54.5.

*4-(2,3-Dimethoxyquinoxalin-6-yl)-2-methoxybenzoic Acid (**32w**).* 6-Bromo-2,3-dimethoxyquinoxaline (**6**) (100 mg, 0.372 mmol, 1.0 equiv), (3-methoxy-4-(methoxycarbonyl)phenyl)boronic acid (102 mg, 0.484 mmol, 1.3 equiv), Pd(PPh$_3$)$_4$ (35 mg, 0.030 mmol, 0.08 equiv), and cesium carbonate (485 mg, 1.488 mmol, 4.0 equiv) were added into a flame-dried two-neck round-bottom flask. The flask was evacuated and filled back with argon (× 3), then dry degassed DMF (3.4 mL) was added followed by degassed H_2O (0.16 mL), and the reaction mixture heated at 90 °C for 24 h. The solution was cooled to rt and H_2O (25 mL) was added and the aqueous layer extracted with EtOAc (25 mL). The aqueous layer was adjusted to pH 4−5 with 2 M HCl to give the product **32w** as a brown precipitate, which was collected by filtration (16 mg, 13%).The EtOAc layer was concentrated and purified on flash chromatography on silica gel (EtOAc/heptane 1:8 to 1:4) to give the compound **32p** as a white solid (63 mg, 46%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.10 (d, J = 2.1 Hz, 1H), 7.93 (dd, J = 8.6, 2.1 Hz, 1H), 7.83 (d, J = 8.5 Hz, 1H), 7.76 (d, J = 7.9 Hz, 1H), 7.47 (d, J = 1.6 Hz, 1H), 7.42 (dd, J = 8.0, 1.6 Hz, 1H), 4.07 (d, J = 3.1 Hz, 6H), 3.97 (s, 3H).

Modeling. All in silico work was carried out using MOE version 2016.08.02 (Chemical Computing Group). The receptor protein was prepared using the function "Protonate 3D". Docking was performed using standard setup with flexible side chains and exclusive solvent molecules.

Radioligand Binding. Ligand affinities at native AMPA, KA, and NMDA receptors (rat brain synaptosomes) were determined using the radioligands [^{3}H]AMPA, [^{3}H]KA, and [^{3}H]CGP-39653, respectively, as previously described.[12] Ligand affinities at recombinant homomeric rat GluA2 were determined using [^{3}H]AMPA. Ligand affinities at recombinant homomeric rat GluK2 and GluK3 were determined using [^{3}H]KA as the radioligand as previously detailed.[13] Ligand affinities at recombinant homomeric rat GluK1 were determined using the new radioligand [^{3}H]-NF608 as previously described.[14] Data were analyzed using GraphPad Prism 7 (GraphPad Software, San Diego, CA) to determine ligand IC_{50} and K_i values.

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C.S.D., design and synthesis of analogues. D.R., design and synthesis of analogues. N.L., design and synthesis of analogues. B.N., pharmacological evaluation of analogues. D.S.P., pharmacological evaluation of analogues. L.B., design and synthesis of analogues, in silico modeling

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Notes

The authors declare no competing financial interest.

REFERENCES

(1) Honoré, T., Davies, S. N., Drejer, J., Fletcher, E. J., Jacobsen, P., Lodge, D., and Nielsen, F. E. (1988) Quinoxalinediones: potent competitive non-NMDA glutamate receptor antagonists. *Science 241*, 701−3.

(2) Menuz, K., Stroud, R. M., Nicoll, R. A., and Hays, F. A. (2007) TARP auxiliary subunits switch AMPA receptor antagonists into partial agonists. *Science 318*, 815−817.

(3) Löscher, W. (1999) A new pyrrolyl-quinoxalinedione series of non-NMDA glutamate receptor antagonists: Pharmacological characterization and comparison with NBQX and valproate in the kindling model of epilepsy. *Eur. J. Neurosci. 11*, 250−262.

(4) Turski, L., Huth, a, Sheardown, M., McDonald, F., Neuhaus, R., Schneider, H. H., Dirnagl, U., Wiegand, F., Jacobsen, P., and Ottow, E. (1998) ZK200775: a phosphonate quinoxalinedione AMPA antagonist for neuroprotection in stroke and trauma. *Proc. Natl. Acad. Sci. U. S. A. 95*, 10960−10965.

(5) Tsuchida, E., and Bullock, R. (1995) The effect of the glycine site-specific N-methyl-D-aspartate antagonist ACEA1021 on ischemic brain damage caused by acute subdural hematoma in the rat. *J. Neurotrauma 12*, 279−288.

(6) Demmer, C. S., Møller, C., Brown, P. M. G. E., Han, L., Pickering, D. S., Nielsen, B., Bowie, D., Frydenvang, K., Kastrup, J. S., and Bunch, L. (2015) Binding Mode of an α-Amino Acid-Linked Quinoxaline-2,3-dione Analogue at Glutamate Receptor Subtype GluK1. *ACS Chem. Neurosci. 6*, 845−854.

(7) Lassalas, P., Gay, B., Lasfargeas, C., James, M. J., Tran, V., Vijayendran, K. G., Brunden, K. R., Kozlowski, M. C., Thomas, C. J., Smith, A. B., Huryn, D. M., and Ballatore, C. (2016) Structure Property Relationships of Carboxylic Acid Isosteres. *J. Med. Chem. 59*, 3183−3203.

(8) Ballatore, C., Huryn, D. M., and Smith, A. B. (2013) Carboxylic Acid (Bio)Isosteres in Drug Design. *ChemMedChem 8*, 385−395.

(9) Bunch, L., and Krogsgaard-Larsen, P. (2009) Subtype selective kainic acid receptor agonists: discovery and approaches to rational design. *Med. Res. Rev. 29*, 3−28.

(10) Larsen, A. M., and Bunch, L. (2011) Medicinal chemistry of competitive kainate receptor antagonists. *ACS Chem. Neurosci. 2*, 60−74.

(11) Krogsgaard-Larsen, N., Storgaard, M., Møller, C., Demmer, C. S., Hansen, J., Han, L., Monrad, R. N., Nielsen, B., Tapken, D., Pickering, D. S., Kastrup, J. S., Frydenvang, K., and Bunch, L. (2015) Structure−Activity Relationship Study of Ionotropic Glutamate Receptor Antagonist (2 *S*, 3 *R*)-3-(3-Carboxyphenyl)pyrrolidine-2-carboxylic Acid. *J. Med. Chem. 58*, 6131−6150.

(12) Assaf, Z., Larsen, A. P., Venskutonytė, R., Han, L., Abrahamsen, B., Nielsen, B., Gajhede, M., Kastrup, J. S., Jensen, A. a, Pickering, D. S., Frydenvang, K., Gefflaut, T., and Bunch, L. (2013) Chemo-enzymatic synthesis of new 2,4-syn-functionalized (S)-glutamate analogues and structure-activity relationship studies at ionotropic glutamate receptors and excitatory amino acid transporters. *J. Med. Chem. 56*, 1614−28.

(13) Sagot, E., Pickering, D. S., Pu, X., Umberti, M., Stensbøl, T. B., Nielsen, B., Chapelet, M., Bolte, J., Gefflaut, T., and Bunch, L. (2008) Chemo-enzymatic synthesis of a series of 2,4-syn-functionalized (S)-glutamate analogues: new insight into the structure-activity relation of ionotropic glutamate receptor subtypes 5, 6, and 7. *J. Med. Chem. 51*, 4093−103.

(14) Alcaide, A., Marconi, L., Marek, A., Haym, I., Nielsen, B., Møllerud, S., Jensen, M., Conti, P., Pickering, D. S., and Bunch, L. (2016) Synthesis and pharmacological characterization of the selective GluK1 radioligand (S)-2-amino-3-(6-[3 H]-2,4-dioxo-3,4-dihydrothieno[3,2-d]pyrimidin-1(2H)-yl)propanoic acid ([3 H]-NF608). *MedChemComm 7*, 2136−2144.

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