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Synthesis and activity of a new class of pathway-selective estrogen receptor ligands: Hydroxybenzoyl-3,4-dihydroquinoxalin-2(1*H*)-ones

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Abstract—The anti-inflammatory activity of non-selective estrogens has been attributed to their ability to antagonize the activity of nuclear factor κB (NF-κB), a known mediator of inflammatory responses. Here we report the identification of a potent new class of pathway-selective ER ligands that selectively antagonize NF-κB functional activity, while exhibiting a lack of classical estrogenic effect.

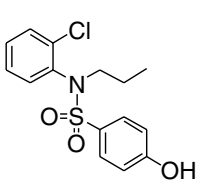
1. Introduction

Many diseases, including arthritis, asthma, atherosclerosis, inflammatory bowel disease, and sepsis, are now considered to be primarily caused by inflammatory pathways.[1] Although non-selective estrogens are known to have classical effects on the reproductive system, compounds within this class such as 17β-estradiol (E2) also have antiinflammatory activity[2–5] and have been shown to be active in several disease models of inflammation.[6–8] Estrogens bind to two estrogen receptors (ERα and ERβ), both of which can antagonize the functional activity of nuclear factor κB (NF-κB),[9,10] a known promoter of pro-inflammatory genes such as TNFα and IL-6.[11] A study in endothelial cells revealed that IL-1β-induced NF-κB reporter activity and IL-6 expression were inhibited by 17β-estradiol in an estrogen receptor (ER)-dependent fashion,[11,12] which correlates to the antiinflammatory activity of E2 in vivo.[13]

Thus, a drug discovery project was initiated to identify selective non-steroidal ligands for ER that could block the transcription of NF-κB, but would be devoid of conventional estrogenic activities. Compounds were screened in vitro in HAECT-1 cells[11] that were transfected with human ERα[12] and the reporter gene, NF-κB-luciferase. These cells were then treated with IL-1β and the test compound. The amount of luciferace present in the assay correlates directly to the degree of NF-κB transcriptional activity. Efficacy as classical estrogenic agents, characterized by stimulation of uterine proliferation, was measured by in vitro creatine kinase (CK) expression. Target in vitro profiles for drug candidate selection included an $IC_{50} < 100$ nM in the ER/NF-κB luciferase assay with an efficacy compared to that of E2 near 100% and minimal efficacy in the CK assay.

Previously, two novel structural scaffolds have been reported as pathway-selective ER ligands that selectively antagonize NF-κB functional activity.[14,15] Herein, we describe the hydroxybenzoyl-3,4-dihydroquinoxalin-2(1*H*)-ones as a new, novel scaffold identified within this program.

2. Chemistry and results



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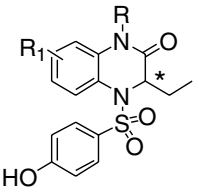

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Keywords: Hydroxybenzoyl-3,4-dihydroquinoxalin-2(1*H*)-ones; Estrogen receptor ligands; NF-κB; Anti-inflammatory activity.
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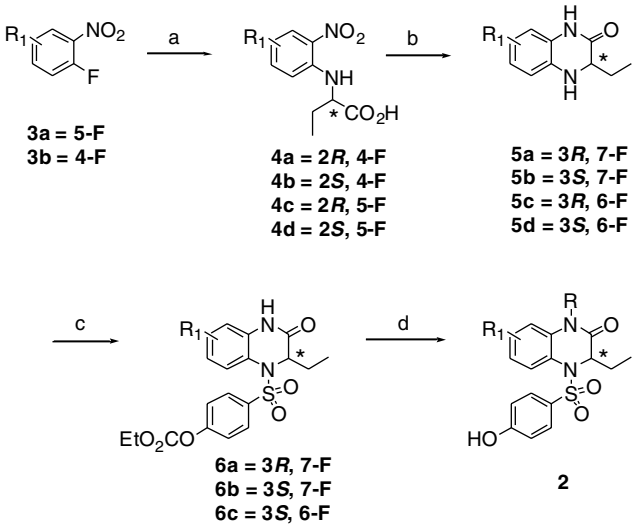
An HTS screen identified a class of 4-hydroxyphenyl sulfonamides, that is, compound **1** (ER/NF-κB-luc IC_{50} = 43 nM [% E2 = 108]) CK EC_{50} = 166 nM [% E2 = 53]), which was the focus of a medicinal chemistry program, the SAR of which has been previously described.[16] An effort to design constrained analogs of the 4-hydroxyphenyl sulfonamides first led to the identification of a series of pyrrolo[1,2-*a*]quinoxalin-5(4*H*)-yl)sulfonyl]phenols, which will be the subject of a future publication. Additional efforts to design constrained analogs that (1) were readily synthesized via chiral methods, (2) had improved aqueous solubility, and (3) possessed improved metabolic stability led to the identification of (4-hydroxyphenyl)sulfonyl-3,4-dihydroquinoxalin-2(1*H*)-ones, for example, compound **2**, the synthesis of which is depicted in Scheme 1.

The 3,4-dihydroquinoxalin-2(1*H*)-one core, compound **5**, can be synthesized as a pure enantiomer in two steps starting with an appropriately substituted *ortho*-fluoronitrobenzene, compound **3**, and either (*R*)- or (*S*)-2-aminobutyric acid. Nucleophilic aromatic substitution under basic conditions afforded the 2-[(2-nitrophenyl)amnio]-butanoic acid **4**, reduction of which via hydrogenation facilitated spontaneous ring cyclization to form the optically pure 3,4-dihydroquinoxalin-2(1*H*)-one **5**. Selective sulfonylation at the N-4 position with ethyl (4-chlorosulfonyl)phenyl carbonate[17] and pyridine afforded sulfonamide **6**, which was alkylated at the N-1 position with an alkyl halide in refluxing acetone using cesium carbonate as base. The carbonate protecting group was selected, because deprotection could occur in situ to afford the desired (4-hydroxyphenyl)sulfonyl-3,4-dihydroquinoxalin-2(1*H*)-one **2** with minimal side products.



Scheme 1. Synthesis of (4-hydroxyphenyl)sulfonyl-3,4-dihydroquinoxalin-2(1*H*)-ones. Reagents and conditions: (a) (*R*)- or (*S*)-2-aminobutyric acid, K_2CO_3, DMF, 100 °C; (b) 10% Pd/C, H_2 (50 psi), EtOH; 49–53% yield for two steps; (c) ethyl (4-chlorosulfonyl)phenyl carbonate, pyridine, CH_2Cl_2, 74–81% yield; (d) RI, Cs_2CO_3, acetone, reflux; then 2 N NaOH; 15–81% yield depending on alkyl group.

A series of N-1-substituted (4-hydroxyphenyl)sulfonyl-3,4-dihydroquinoxalin-2(1*H*)-ones are depicted in Table 1. When the effect of stereochemistry was evaluated, it was found that the 3-*S* enantiomer was more potent and efficacious in the ER/NF-κB-luciferase assay compared to the 3-*R* enantiomer (**2a** vs **2b**). When aromatic substitution on the quinoxalinone ring was examined, the 6-fluoro analogs were more potent and efficacious compared to the 7-fluoro analogs (**2b** vs **2c** and **2d** vs **2e**). Substitution at the N-1 position significantly affected potency and efficacy. Increasing the length of the non-branching carbon chain at this position resulted in an increase in potency and efficacy in the ER/NF-κB-luciferase assay (**2c**, **2e**–**2h**); however, incorporating branching into the substituent (**2i** and **2j**) resulted in a complete loss of activity. Fortunately, all compounds within this series were selective, having minimal efficacy in the CK assay.

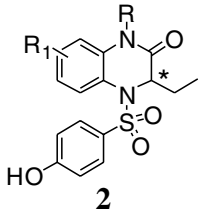
Although the (4-hydroxyphenyl)sulfonyl-3,4-dihydroquinoxalin-2(1*H*)-one series afforded active compounds in the luciferase assay with good efficacy, the in vitro target for potency (<100 nM) for the program was not achieved. Therefore, in an effort to improve potency, an amide linker (compound **9**, Scheme 2) was explored as a replacement for the sulfonamide in compound **2**.

The synthesis of the hydroxybenzoyl-3,4-dihydroquinoxalin-2(1*H*)-ones **9** starting from the common 3,4-dihydroquinoxalin-2(1*H*)-one intermediate is depicted in Scheme 2. Again, the N-4 position can be selectively acylated with an appropriately substituted methoxybenzoylchloride in the presence of a base, followed by alkylation of the N-1 position with an alkyl halide under basic conditions. Alternatively, the N-1 position can be alkylated with an activated alcohol using Mitsunobu conditions. Deprotection of the phenol was best performed with boron trichloride and tetrabutylammonium iodide[18] to avoid the formation of brominated side-products that were observed when boron tribromide was used.

An examination of the preferred stereochemistry for the hydroxybenzoyl-3,4-dihydroquinoxalin-2(1*H*)-ones yielded a surprising result. While the 3-*S* stereochemistry was optimal for potency and efficacy in the sulfonamide series (Table 1), the 3-*R* stereochemistry was found to be preferred in the amide series (Table 2). Additionally, these preliminary compounds showed that replacing the sulfonamide with an amide afforded an increase in potency and efficacy in the ER/NF-κB-luciferase assay (compound **2e** vs compound **9c**) while maintaining selectivity over CK expression.

Next, a series of N-1-substituted 4-hydroxybenzoyl-3,4-dihydroquinoxalin-2(1*H*)-ones was synthesized (Table 3). A SAR trend similar to that seen in the (4-hydroxyphenyl)sulfonyl-3,4-dihydroquinoxalin-2(1*H*)-one series was observed. Again, in general, increasing the length of the non-branching carbon chain (**9a**–**9i**) resulted in an increase in potency and efficacy in the ER/NF-κB-luciferase assay. In most cases, branching of the carbon chain was again detrimental to potency in the luciferase

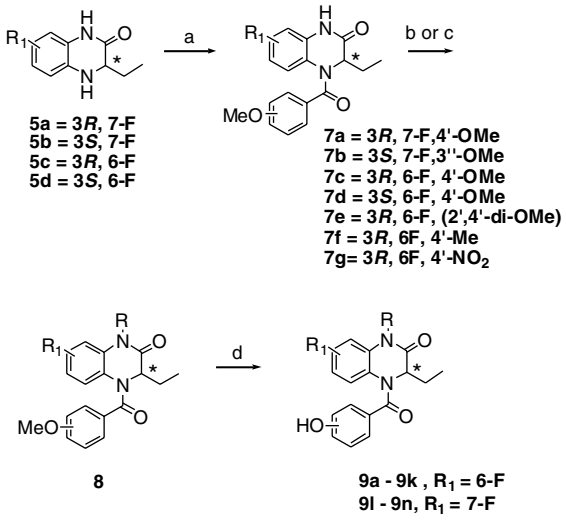
Table 1. Effect of N-1 substitution on the (4-hydroxyphenyl)sulfonyl-3,4-dihydroquinoxalin-2(1*H*)-ones versus E2 on NF-κB and CK expression in Ad5-wt-ERα-infected HAECT-1 cells[a]



2

Compound	R	R_1	Stereochemistry	ER/NFκB-luc IC_{50} (nM)	% E2—NFκB	CK EC_{50} (nM)	% E2—CK
2a	Methyl	7-F	*R*	IA[b]		1227	34
2b	Methyl	7-F	*S*	1169	85	344	20
2c	Methyl	6-F	*S*	681	108	1897	35
2d	Ethyl	7-F	*S*	738	63	43	9
2e	Ethyl	6-F	*S*	339	81	IA[b]	
2f	Allyl	6-F	*S*	5604	55	IA[b]	
2g	*n*-Propyl	6-F	*S*	157	79	4.7	17
2h	*n*-Butyl	6-F	*S*	313	106	IA[b]	
2i	*i*-Propyl	6-F	*S*	IA[b]		IA[b]	
2j	Cyclopentyl	6-F	*S*	IA[b]		IA[b]	

[a] All compounds were ER dependent (only active when ER is coexpressed with NF-κB-luciferase in HAECT cells).
[b] IA, inactive to 1 μM; % E2, efficacy (relative inhibition of test compound a 10 μM vs E2 at 0.1 nM).



Scheme 2. Synthesis of hydroxybenzoyl-3,4-dihydroquinoxalin-2(1*H*)-ones. Reagents: (a) methoxybenzoylchloride, Et_3N, CH_2Cl_2; 64–76% yield; (b) RI, K_2CO_3 or Cs_2CO_3, acetone; (c) ROH, PPh3, DIAD, CH_2Cl_2; 14% yield for two steps; (d) BCl_3, $Bu_4NH_4^+I^-$, CH_2Cl_2, 22–81% yield for two steps depending on alkyl group.

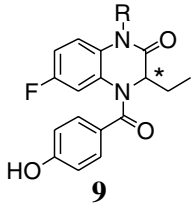
assay (**9h** vs **9j** and **9k**), with the possible exception of the *n*-propyl versus the *iso*-propyl substituent (**9f** vs **9g**). The most dramatic loss in potency was observed with the N-benzyl substitution (**9o**). One notable difference in the SAR of the sulfonamide series when compared to the amide series was observed in the N-1 allyl analogs. While this substituent afforded a highly potent and efficacious compound in the amide series (compound **9e**), the substituent was not tolerated in the sulfonamide series (compound **2f**). This difference notwithstanding, it was surprising how similar the SAR trends in the two series were considering the observed reversal of preferred stereochemistry.

The final group of compounds was synthesized to examine the importance of the presence and the position of the hydroxyl moiety in the hydroxybenzoyl-3,4-dihydroquinoxalin-2(1*H*)-one series (Table 4). These compounds were synthesized in the same manner as compound **9** (Scheme 2). The importance of the presence of the hydroxyl group was determined through the synthesis of compounds **10f-10 h**, all of which were nearly inactive in the ER/NF-κB-luciferase assay. Moving the hydroxyl group to the *meta* position on the benzoyl group (compounds **10a**–**10c**) resulted in a loss of potency and efficacy when compared to their *para*-substituted analogs; however, the introduction of an additional hydroxyl group at the *ortho* position on the benzoyl moiety in combination with one at the *para* position yielded the most potent compounds in the series (compounds **10d** and **10e**).

Having met the project's potency and efficacy goals, the solubility and microsomal stability properties of the hydroxybenzoyl-3,4-dihydroquinoxalin-2(1*H*)-ones were then examined (Table 5).

As was expected, the aqueous solubility of the compounds decreased as the lipophilicity of the substituent on the N-1 position increased. Compounds with the poorest solubility at pH 7.4 possessed the substituents allyl (**9e**), *n*-pentyl (**9i**), cyclopentyl (**9k**), and benzyl (**9o**). In general, compounds in this class were found to have poor stability in rat liver microsomes, possessing very short half-lives; however, some surprising results were observed. Unfortunately, the 3-*R* enantiomers (**9a** and **9c**), which possessed the preferred stereochemistry for potency and efficacy, were significantly less stable than the 3-*S* enantiomers (**9b** and **9d**). However, we were fortunate to find that the 2,4-dihydroxylbenzoyl-3,4-dihydroquinoxalin-2(1*H*)-ones (compounds **10d** and **10e**), the most potent compounds in the series, had very acceptable stability in rat liver microsomes with half-lives >30 min.

Table 2. Effect of stereochemistry on the 4-hydroxybenzoyl-3,4-dihydroquinoxalin-2(1*H*)-ones versus E2 on NF-κB and CK expression in Ad5-wt-ERα-infected HAECT-1 cells[a]

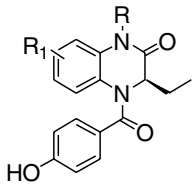


9

Compound	R	∗Stereochemistry	ER/NFκB-luc IC_{50} (nM)	% E2—NFκB	CK EC_{50} (nM)	% E2—CK
9a	Methyl	*R*	102	84	IA[b]	
9b	Methyl	*S*	303	44	IA[b]	
9c	Ethyl	*R*	139	99	107	27
9d	Ethyl	*S*	285	44	IA[b]	

[a] All compounds were ER dependent (only active when ER is coexpressed with NF-κB-luciferase in HAECT cells).
[b] IA, inactive to 1 μM; % E2 = efficacy (relative inhibition of test compound a 10 μM vs E2 at 0.1 nM).

Table 3. Effect of N-1 substitution on the 4-hydroxybenzoyl-3,4-dihydroquinoxalin-2(1*H*)-ones versus E2 on NF-κB and CK expression in Ad5-wt-ERα-infected HAECT-1 cells[a]



9- *(R)*

Compound	R	R_1	ER/NFκB-luc IC_{50} (nM)	% E2—NFκB	CK EC_{50} (nM)	% E2—CK
9a	Methyl	6-F	102	84	IA[b]	
9c	Ethyl	6-F	139	99	107	27
9e	Allyl	6-F	57	95	208	20
9f	*n*-Propyl	6-F	222	96	311	38
9g	*i*-Propyl	6-F	105	91	IA[b]	
9h	*n*-Butyl	6-F	52	95	IA[b]	
9i	*n*-Pentyl	6-F	89	102	>1000	13
9j	*i*-Butyl	6-F	262	87	IA[b]	
9k	Cyclopentyl	6-F	445	96	IA[b]	
9l	2,2,2-Trifluoroethyl	6-F	204	83	IA[b]	
9m	Methyl	7-F	74	99	89	16
9n	Ethyl	7-F	72	104	103	29
9o	Benzyl	7-F	1228	80	>10,000	24

[a] All compounds were ER dependent (only active when ER is coexpressed with NF-κB-luciferase in HAECT cells).
[b] IA, inactive to 1 μM; % E2, efficacy (relative inhibition of test compound a 10 μM vs E2 at 0.1 nM).

3. Conclusions

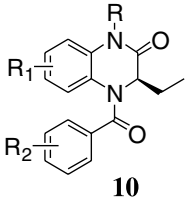
In conclusion, we have identified a new class of potent, and efficacious pathway-selective ERα ligands that antagonize ER/NF-κB functional activity. Furthermore, these compounds have weak efficacy in the creatine kinase assay relative to 17β-estradiol; therefore, they should not exhibit classical estrogenic activities. In addition to their in vitro activity, the hydroxybenzoyl-3,4-dihydroquinoxalin-2(1*H*)-ones in general have good aqueous solubility, and the 2,4-dihydroxybenzoyl analogs also have good stability in rat liver microsomes. Taken together, these data show that the hydroxybenzoyl-3,4-dihydroquinoxalin-2(1*H*)-one series yields drug-like compounds that could warrant further in vivo studies.

4. Experimental

4.1. General methods: chemistry

Solvents were purchased as anhydrous grade and were used without further purification. Melting points were measured on a Mel-Temp II (Laboratory Device, Inc.) melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian INOVA 400 instrument, and chemical shifts are reported in δ values (parts per million, ppm) relative to an internal standard tetramethylsilane in $CDCl_3$ or DMSO-d_6. Electrospray (ESI) mass spectra were recorded on a Waters Alliance-ZMD mass spectrometer. Electron impact ionization (EI, EE = 70 eV) mass spectra were recorded on a

Table 4. Effect of benzoyl aromatic substitution on the benzoyl-3,4-dihydroquinoxalin-2(1*H*)-ones versus E2 on NF-κB and CK expression in Ad5-wt-ERα-infected HAECT-1 cells[a]



10

Compound	R	R_1	R_2	ER/NFκB-luc IC_{50} (nM)	% E2—NFκB	CK EC_{50} (nM)	% E2—CK
10a	Methyl	7-F	*m*-OH	520	57	126	19
10b	Ethyl	7-F	*m*-OH	IA[b]		IA[b]	
10c	Benzyl	7-F	*m*-OH	542	65	255	17
10d	Methyl	6-F	*o*,*p*-Di-OH	20	96	169	36
10e	Ethyl	6-F	*o*,*p*-Di-OH	5.4	92	50	44
10f	Ethyl	6-F	*p*-OMe	2679	66	IA[b]	
10g	Methyl	6-F	*p*-Me	IA[b]		IA[b]	
10h	Methyl	6-F	4-NO_2	IA[b]		329	2

[a] All compounds were ER dependent (only active when ER is coexpressed with NF-κB-luciferase in HAECT cells).
[b] IA, inactive to 1 μM; % E2, efficacy (relative inhibition of test compound a 10 μM vs E2 at 0.1 nM).

Table 5. Effect of substitution on the hydroxybenzoyl-3,4-dihydroquinoxalin-2(1*H*)-ones on pharmaceutical profiling parameters[a]

Compound	R	R_1	R_2	Stereochemistry	Aqueous solubility at pH 7.4 (μg/mL)	Microsomal stability[b] (rat) $t_{1/2}$ (min)
9a	Methyl	6-F	*p*-OH	*R*	>100	6
9b	Methyl	6-F	*p*-OH	*S*	>100	>30
9c	Ethyl	6-F	*p*-OH	*R*	>100	5
9d	Ethyl	6-F	*p*-OH	*S*	>100	16
9e	Allyl	6-F	*p*-OH	*R*	10	6
9f	*n*-Propyl	6-F	*p*-OH	*R*	>100	7
9g	*i*-Propyl	6-F	*p*-OH	*R*	>100	10
9h	*n*-Butyl	6-F	*p*-OH	*R*	66	5
9i	*n*-Pentyl	6-F	*p*-OH	*R*	14	5
9j	*i*-Butyl	6-F	*p*-OH	*R*	68	5
9k	Cyclopentyl	6-F	*p*-OH	*R*	14	0
9m	Methyl	7-F	*p*-OH	*R*	>100	8
9n	Ethyl	7-F	*p*-OH	*R*	>100	9
9o	Benzyl	7-F	*p*-OH	*R*	9	9
10d	Methyl	6-F	*o*,*p*-di-OH	*R*	>100	>30
10e	Ethyl	6-F	*o*,*p*-di-OH	*R*	>100	>30

[a] Values are means of three experiments.
[b] Incubated in rat liver microsomes at a concentration of 1 μM for 15 min at 37 °C.

Finnigan Trace mass spectrometer. Combustion analyses were performed by Robertson Microlit. Analytical thin-layer chromatography (TLC) was performed on precoated plates (silica gel, 60 F-254) and visualized using UV light and/or staining with a phosphomolybdic acid solution in ethanol. In general, compound purity was assessed by ^{1}H NMR and an LC/UV/MS method.[19] Biological results were obtained on compounds of >97% chemical purity as determined by the above methods.

4.2. General procedure 1: synthesis of the 3,4-dihydroquinoxalin-2(1*H*)-one cores (5a–5d)

A solution of difluoronitrobenzene (39.5 mmol), either (*S*)- or (*R*)-2-aminobutyric acid (43.0 mmol), and potassium carbonate (16.2 mmol) in dimethylformamide (40 mL), under nitrogen, was stirred at 100 °C for 14 h. The solvent was evaporated at reduced pressure, and the residue was dissolved in 11% potassium carbonate (13.9 g in 125 mL) and washed twice with ether. Concentrated hydrochloric acid (approximately 17 mL) was added dropwise with stirring. The mixture was extracted with ethyl acetate (3× 100 mL), and the extracts were washed with water (3× 100 mL). The solution was dried over magnesium sulfate and the solvent was evaporated. The resulting residue was dissolved in ethanol (200 mL) and treated in a Parr apparatus with 10% palladium on carbon (1.50 g) and 50 psi hydrogen gas for 1.5 h, after which time hydrogen uptake had ceased. The mixture was then filtered through Celite, and the solvent was evaporated at reduced pressure. The product was purified via Biotage Horizon® (40 M, silica, gradient from 15% EtOAc/hexane to 50% EtOAc/hexane).

4.2.1. (3*R*)-3-Ethyl-7-fluoro-3,4-dihydroquinoxalin-2(1*H*)-one (5a). Yield: 53% of a light brown solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.92 (t, J = 7.5 Hz,

3H), 1.55–1.68 (m, 2H), 3.62 (ddd, J = 2.1, 5.2, 6.9 Hz, 1H), 5.95 (d, J = 1.6, 1H), 6.52–6.60 (m, 2H), 6.69 (dd, J = 5.4, 8.6 Hz, 1H), 10.26 (br s, 1H); HRMS: calcd for $C_{10}H_{11}FN_2O$, 194.08558; found (ESI, $[M+H]^{1+}$), 195.09281. $[\alpha]_D^{25}$ −43.5° (c 0.01 g/mL, DMSO); Anal. Calcd for $C_{10}H_{11}FN_2O$: C, 61.85; H, 5.71; N, 14.42. Found: C, 61.85; H, 5.85; N, 14.46.

4.2.2. (3*S*)-3-Ethyl-7-fluoro-3,4-dihydroquinoxalin-2(1*H*)-one (5b). Yield: 49% of a beige solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.92 (t, J = 7.4 Hz, 3H), 1.52–1.70 (m, 2H), 3.62 (ddd, J = 2.3, 5.2, 6.8 Hz, 1H), 5.95 (d, J = 1.9, 1H), 6.51–6.60 (m, 2H), 6.69 (dd, J = 5.4, 8.5 Hz, 1H), 10.26 (br s, 1H); MS (ESI) m/z 195 ($[M+H]^+$); $[\alpha]_D^{25}$ +33.4° (c 0.01 g/mL, DMSO); Anal. Calcd for $C_{10}H_{11}FN_2O$: C, 61.85; H, 5.71; N, 14.42. Found: C, 61.84; H, 5.72; N, 14.24.

4.2.3. (3*R*)-3-Ethyl-6-fluoro-3,4-dihydroquinoxalin-2(1*H*)-one (5c). Yield: 45% of a beige solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.03 (t, J = 7.5 Hz, 3H), 1.74–1.90 (m, 2H), 3.62 (ddd, J = 2.3, 4.3, 6.3 Hz, 1H), 4.03 (br s, 1H), 6.39–6.45 (m, 2H), 5.64 (dd, J = 5.3, 8.3 Hz, 1H), 8.56 (br s, 1H); HRMS: calcd for $C_{10}H_{11}FN_2O$, 194.08558; found (ESI-FT, $[M+H]^{1+}$), 195.08807. $[\alpha]_D^{25}$ −9.2° (c 0.01 g/mL, DMSO); Anal. Calcd for $C_{10}H_{11}FN_2O$: C, 61.85; H, 5.71; N, 14.42. Found: C, 61.77; H, 5.76; N, 14.33.

4.2.4. (3*S*)-3-Ethyl-6-fluoro-3,4-dihydroquinoxalin-2(1*H*)-one (5d). Yield: 63% of an off-white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.87 (t, J = 7.4 Hz, 3H), 1.59 (m, 2H), 3.65 (ddd, J = 1.8, 1.8, 5.1 Hz, 1H), 6.24 (br s, 1H), 6.29 (ddd, J = 2.8, 8.8, 8.8 Hz, 1H), 6.45 (dd, J = 2.8, 10.5 Hz, 1H), 6.61 (dd, J = 5.6, 8.5 Hz, 1H), 10.15 (br s, 1H); MS (ESI) m/z 195 ($[M+H]^+$); $[\alpha]_D^{25}$ +18.6° (c 0.01 g/mL, DMSO); Anal. Calcd for $C_{10}H_{11}FN_2O$: C, 61.85; H, 5.71; N, 14.42. Found: C, 61.72; H, 5.80; N, 14.33.

4.3. General procedure 2: preparation of ethyl 4-{[3-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl]sulfonyl}phenyl carbonates (6a–6c)

A solution of 3,4-dihydroquinoxalin-2(1*H*)-one (11.2 mmol) in methylene chloride (30 mL) was degassed by bubbling nitrogen through the solution for 5 min. Ethyl (4-chlorosulfonyl)phenyl carbonate[17] (3.0 g, 11.3 mmol) followed by pyridine (0.92 mL, 11.4 mmol) was added. The reaction mixture was stirred at 25 °C for 14 h, after which time the solvent was removed in vacuo. The resulting residue was dissolved in ethyl acetate and filtered through a plug of silica gel (eluting with 60% EtOAc:hexane). The solution was concentrated in vacuo, and the resulting solid was recrystallized from ethyl acetate/hexane and dried in a vacuum oven.

4.3.1. Ethyl 4-{[(2*R*)-2-ethyl-6-fluoro-3-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl]sulfonyl}phenyl carbonate (6a). Yield: 74% of a white solid; mp 128–131 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.93 (t, J = 7.3 Hz, 3H), 1.23–1.33 (m, 1H), 1.29 (t, J = 7.2 Hz), 1.53–1.61 (m, 1H), 4.27 (quar, J = 7.2 Hz, 2H), 4.32 (dd, J = 5.2, 10.3 Hz, 1H), 6.58 (dd, J = 2.9, 9.5 Hz, 1H), 6.98 (ddd, J = 2.9, 8.7, 8.7 Hz, 1H), 7.40–7.46 (m, 4H), 7.60 (dd, J = 5.7, 9.0 Hz, 1H); 10.44 (br s, 1H); MS (ESI) m/z 423; MS (ESI) m/z 421. HRMS: calcd for $C_{19}H_{19}FN_2O_6S+H^+$, 423.10206; found (ESI, $[M+H]^+$), 423.1036. $[\alpha]_D^{25}$ +12.3° (c 0.0058 g/mL, DMSO).

4.3.2. Ethyl 4-{[(2*S*)-2-ethyl-6-fluoro-3-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl]sulfonyl}phenyl carbonate (6b). Yield: 81% of a white solid; mp 133–136 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.93 (t, J = 7.3 Hz, 3H), 1.20–1.31 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H), 1.51–1.62 (m, 1H), 4.27 (quar, J = 7.0 Hz, 2H), 4.32 (dd, J = 5.2, 10.4 Hz, 1H), 6.59 (dd, J = 2.9, 9.3 Hz, 1H), 6.98 (ddd, J = 2.9, 8.8, 8.8 Hz, 1H), 7.40–7.46 (m, 4H), 7.60 (dd, J = 5.7, 9.2 Hz, 1H); 10.44 (br s, 1H); MS (ESI) m/z 423; MS (ESI) m/z 421. $[\alpha]_D^{25}$ −17.4° (c 0.0058 g/mL, DMSO). Anal. Calcd for $C_{19}H_{19}FN_2O_6S$: C, 54.02; H, 4.53; N, 6.63. Found: C, 53.95; H, 4.56; N, 6.68.

4.3.3. Ethyl 4-{[(2*S*)-2-ethyl-7-fluoro-3-oxo-3,4-dihydroquinoxalin-1(2*H*)- yl]sulfonyl}phenyl carbonate (6c). Yield: 77% of a white solid; mp 140–143 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.87 (t, J = 7.4 Hz, 3H), 1.22 (m, 1H), 1.25 (t, J = 7.1 Hz, 3H), 1.52 (m, 1H), 4.22 (quar, J = 7.1 Hz, 2H), 4.29 (dd, J = 5.1, 10.3 Hz, 1H), 6.79 (dd, J = 5.4, 8.9 Hz, 1H), 7.13 (ddd, J = 2.8, 8.5, 8.5 Hz, 1H), 7.34–7.39 (m, 1H), 7.37 (dd, J = 2.2, 6.8 Hz, 2H); 7.46 (dd, J = 2.2, 6.8 Hz, 2H), 10.34 (br s, 1H); MS (ES) m/z 423.1 ($[M+H]^+$); MS (ES) m/z 440.1 ($[M+NH4]^+$); MS (ES) m/z 445.1 ($[M+NA]^+$); MS (ES) m/z 486.1 ($[M+ACN+NA]^+$); MS (ES) m/z 862.2 ($[2M+NH4]^+$); MS (ES) m/z 867.1 ($[2M+NA]^+$); $[\alpha]_D^{25}$ +10.0° (c 0.0085 g/mL, DMSO); Anal. Calcd for $C_{19}H_{19}FN_2O_6S$: C, 54.02; H, 4.53; N, 6.63. Found: C, 54.06; H, 4.68; N, 6.45.

4.4. General procedure 3: preparation of 4-(hydroxyphenyl)sulfonyl-3,4-dihydroquinoxalin-2(1*H*)-ones (2a–2j)

To a solution of ethyl 4-{[3-oxo-3,4-dihydroquinoxalin-1(2H)-yl]sulfonyl}phenyl carbonate (0.83 mmol) in acetone (5 mL) were added cesium carbonate (0.3 g, 0.91 mmol) and the appropriate alkyl iodide (3.32 mmol). The mixture was heated at 62 °C for 2.5 h, cooled to 25 °C, and treated with a 2 N aqueous solution of sodium hydroxide (3 mL). The reaction was then stirred at 25 °C for 2 h and was acidified to pH <2 with the addition of a 2 N aqueous solution of hydrochloric acid. The resulting mixture was partitioned between ethyl acetate and a saturated aqueous solution of sodium chloride. The organic layer was separated, dried over magnesium sulfate, and concentrated. The product was purified via flash column chromatography.

4.4.1. (3*R*)-3-Ethyl-7-fluoro-4-[(4-hydroxyphenyl)sulfonyl]-1-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (2a). Yield: 73% of a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.90 (t, J = 7.3 Hz, 3H), 1.16–1.24 (m, 1H), 1.47–1.54 (m, 1H), 2.69 (s, 3H), 4.35 (dd, J = 5.2, 10.3 Hz, 1H), 6.78 (d, J = 8.8 Hz, 2H), 7.01–7.08 (m, 2H), 7.12 (d, J = 8.8 Hz, 2H), 7.56 (dd, J = 5.9, 8.3 Hz, 1H), 10.61 (br s, 1H); MS (ESI) m/z 365 ($[M+H]^+$);

MS (ESI) *m/z* 363 ([M−H]$^-$). $[\alpha]_D^{25}$ +28.4° (*c* 0.010 g/mL, DMSO).

4.4.2. (3*S*)-3-Ethyl-7-fluoro-4-[(4-hydroxyphenyl)sulfonyl]-1-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (2b). Yield: 78% of a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.90 (t, J = 7.3 Hz, 3H), 1.16–1.26 (m, 1H), 1.47–1.54 (m, 1H), 2.69 (s, 3H), 4.35 (dd, J = 5.3, 10.4 Hz, 1H), 6.78 (d, J = 8.8 Hz, 2H), 7.01–7.07 (m, 2H), 7.12 (d, J = 8.8 Hz, 2H), 7.56 (dd, J = 6.0, 8.5 Hz, 1H), 10.61 (br s, 1H); MS (ESI) *m/z* 365 ([M+H]$^+$); MS (ESI) *m/z* 363 ([M−H]$^-$). $[\alpha]_D^{25}$ −37° (*c* 0.0056 g/mL, DMSO). Anal. Calcd for $C_{17}H_{17}FN_2O_4S$: C, 56.03; H, 4.70; N, 7.69. Found: C, 56.12; H, 4.03; N, 7.45.

4.4.3. (3*S*)-3-Ethyl-6-fluoro-4-[(4-hydroxyphenyl)sulfonyl]-1-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (2c). Yield: 81% of a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.89 (t, J = 7.4 Hz, 3H), 1.13–1.26 (m, 1H), 1.45–1.56 (m, 1H), 2.73 (s, 3H), 4.35 (dd, J = 5.0, 10.0 Hz, 1H), 6.79 (d, J = 8.5 Hz, 2H), 7.10–7.19 (m, 1H), 7.18 (d, J = 8.5 Hz, 2H), 7.26 (ddd, J = 2.6, 8.6, 8.6 Hz, 1H), 7.39 (dd, J = 2.6, 9.1 Hz, 1H), 10.60 (br s, 1H); MS (ESI) *m/z* 365 ([M+H]$^+$); MS (ESI) *m/z* 363 ([M−H]$^-$). HRMS: calcd for $C_{17}H_{17}FN_2O_4S$+H$^+$, 365.09658; found (ESI+, [M+H]$^{1+}$), 365.09603; $[\alpha]_D^{25}$ −14° (*c* 0.041 g/mL, DMSO).

4.4.4. (3*S*)-1,3-Diethyl-7-fluoro-4-[(4-hydroxyphenyl)sulfonyl]-3,4-dihydroquinoxalin-2(1*H*)-one (2d). Yield: 72% of a white solid; mp 171–172 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.61 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 7.4 Hz, 3H), 1.17–1.27 (m, 1H), 1.44–1.55 (m, 1H), 3.28–3.40 (m, 1H), 3.47–3.54 (m, 1H), 4.38 (dd, J = 5.3, 10.3 Hz, 1H), 6.77 (d, J = 8.7 Hz, 2H), 7.01–7.09 (m, 2H), 7.15 (d, J = 8.8 Hz, 2H), 7.60 (dd, J = 5.9, 8.8 Hz, 1H), 10.59 (br s, 1H); MS (ESI) *m/z* 379 ([M+H]$^+$); MS (ESI) *m/z* 377 ([M−H]$^-$).

4.4.5. (3*S*)-3-Ethyl-6-fluoro-4-[(4-hydroxyphenyl)sulfonyl]-1-ethyl-3,4-dihydroquinoxalin-2(1*H*)-one (2e). Yield: 81% of a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.63 (t, J = 7.2 Hz, 3H), 1.11 (t, J = 7.3 Hz, 3H), 1.18–1.28 (m, 1H), 1.46–1.55 (m, 1H), 3.35–3.56 (m, 2H), 4.66 (dd, J = 5.2, 9.3 Hz, 1H), 6.77 (d, J = 8.8 Hz, 2H), 7.17–7.21 (m, 1H), 7.19 (d, J = 8.8 Hz, 2H), 7.27 (ddd, J = 2.8, 8.8, 8.8 Hz, 1H), 7.41 (dd, J = 2.8, 9.1 Hz, 1H), 10.60 (br s, 1H); MS (ESI) *m/z* 379 ([M+H]$^+$); MS (ESI) *m/z* 377 ([M−H]$^-$). HRMS: calcd for $C_{18}H_{19}FN_2O_4S$+H$^+$, 379.11223; found (ESI+, [M+H]1+), 379.11178 $[\alpha]_D^{25}$ −26° (*c* 0.008 g/mL, DMSO).

4.4.6. (3*S*)-1-allyl-3-ethyl-6-fluoro-4-[(4-hydroxyphenyl)sulfonyl]-3,4-dihydroquinoxalin-2(1*H*)-one (2f). Yield: 72% as a white solid; mp 181–182 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.91 (t, J = 7.3 Hz, 3H), 1.23–1.33 (m, 1H), 1.50–1.58 (m, 1H), 3.83–3.89 (m, 1H), 3.97–4.10 (m, 1H), 4.42 (dd, J = 5.4, 10.1 Hz, 1H), 4.85 (dd, J = 1.6, 17.1 Hz, 1H), 4.99 (dd, J = 1.6, 10.6 Hz, 1H), 5.27–5.37 (m, 1H), 6.79 (d, J = 9.0 Hz, 2H), 7.03 (dd, J = 5.2, 9.1 Hz, 1H), 7.19–7.26 (m, 1H), 7.22 (d, J = 8.9 Hz, 2H), 7.42 (dd, J = 2.8, 9.3 Hz, 1H), 10.63 (br s, 1H); MS (ESI) *m/z* 391 ([M+H]$^+$); MS (ESI) *m/z* 389 ([M−H]$^-$). $[\alpha]_D^{25}$ −20° (*c* 0.005 g/mL, DMSO).

4.4.7. (3*S*)-3-Ethyl-6-fluoro-4-[(4-hydroxyphenyl)sulfonyl]-1-propyl-3,4-dihydroquinoxalin-2(1*H*)-one (2g). Yield: 31% as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.68 (t, J = 7.5 Hz, 3H), 0.89 (t, J = 7.5 Hz, 3H), 1.06–1.15 (m, 1H), 1.18–1.28 (m, 1H), 1.46–1.56 (m, 1H), 3.26–3.42 (m, 2H), 4.39 (dd, J = 5.2, 10.3 Hz, 1H), 6.78 (d, J = 8.8 Hz, 2H), 7.17–7.26 (m, 4H), 7.42 (dd, J = 2.9, 9.3 Hz, 1H), 10.61 (br s, 1H); mp >250 °C. MS (ESI) *m/z* 393 ([M+H]$^+$); MS (ESI) *m/z* 391 ([M−H]$^-$). $[\alpha]_D^{25}$ −6° (*c* 0.005 g/mL, DMSO).

4.4.8. (3*S*)-1-Butyl-3-ethyl-6-fluoro-4-[(4-hydroxyphenyl)sulfonyl]-3,4-dihydroquinoxalin-2(1*H*)-one (2h). Yield: 42% as a white solid; mp 177–178 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.78 (t, J = 7.3 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H), 0.99–1.10 (m, 4H), 1.16–1.28 (m, 1H), 1.46–1.56 (m, 1H), 3.30–3.37 (m, 1H), 3.49–3.57 (m, 1H), 4.46 (dd, J = 5.2, 10.1 Hz, 1H), 6.78 (d, J = 8.8 Hz, 2H), 7.17–7.26 (m, 2H), 7.21 (d, J = 8.8 Hz, 2H), 7.43 (dd, J = 2.9, 9.4 Hz, 1H), 10.59 (br s, 1H); MS (ESI) *m/z* 407 ([M+H]$^+$); MS (ESI) *m/z* 405 ([M−H]$^-$). $[\alpha]_D^{25}$ −4° (*c* 0.0058G/ML, DMSO). Anal. Calcd for $C_{20}H_{23}FN_2O_4S$: C, 59.10; H, 5.70; N, 6.89. Found: C, 58.73; H, 5.55; N, 6.76.

4.4.9. (3*S*)-3-Ethyl-6-fluoro-4-[(4-hydroxyphenyl)sulfonyl]-1-isopropyl-3,4-dihydroquinoxalin-2(1*H*)-one (2i). Yield: 24% as a white solid; mp 122–124 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.92 (d, J = 7.5 Hz, 3H), 1.20–1.31 (m, 1H), 1.26 (d, J = 6.0 Hz, 6H), 1.50–1.60 (m, 1H), 4.28 (dd, J = 5.2, 10.3 Hz, 1H), 4.66–4.72 (m, 1H), 6.81 (dd, J = 5.4, 8.8 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 7.15 (ddd, J = 2.8, 8.6, 8.6 Hz, 1H), 7.30 (d, J = 8.8 Hz, 2H), 7.38 (dd, J = 2.8, 9.6 Hz, 1H), 10.35 (br s, 1H); MS (ESI) *m/z* 393; MS (ESI) *m/z* 391. $[\alpha]_D^{25}$ +8° (*c* 0.0054 g/mL, DMSO).

4.4.10. (3*S*)-1-Cyclopentyl-3-ethyl-6-fluoro-4-[(4-hydroxyphenyl)sulfonyl]-3,4-dihydroquinoxalin-2(1*H*)-one (2j). Yield: 15% as a white solid; mp 137–140 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.92 (t, J = 7.3 Hz, 3H), 1.21–1.29 (m, 1H), 1.50–1.71 (m, 7H), 1.89–1.97 (m, 2H), 4.27 (dd, J = 5.2, 10.1 Hz, 1H), 4.84–4.88 (m, 1H), 6.81 (dd, J = 5.4, 8.8 Hz, 1H), 6.96 (d, J = 9.0 Hz, 2H), 7.16 (ddd, J = 2.8, 8.6, 8.6 Hz, 1H), 7.30 (d, J = 9.0 Hz, 2H), 7.38 (dd, J = 2.8, 9.6 Hz, 1H), 10.34 (br s, 1H); MS (ESI) *m/z* 419; MS (ESI) *m/z* 417. $[\alpha]_D^{25}$ +15° (*c* 0.005 g/mL, DMSO). Anal. Calcd for $C_{21}H_{23}FN_2O_4S$: C, 60.27; H, 5.54; N, 6.69. Found: C, 60.48; H, 5.51; N, 6.36.

4.5. General procedure 4: preparation of methoxybenzoyl-3,4-dihydroquinoxalin-2(1*H*)-ones (7a–7g)

To a solution of the appropriate 3,4-dihydroquinoxalin-2(1*H*)-one (6.7 mmol) in methylene chloride (50 mL) under nitrogen were added triethylamine (1.1 mL, 0.80 g, 7.9 mmol) and the appropriate methoxybenzoyl chloride (6.9 mmol). The solution was stirred for 16 h and was

then washed successively with a 1 N aqueous solution of hydrochloric acid, a 1 N aqueous solution of sodium hydroxide, water, and brine successively. The combined organic extracts were dried over magnesium sulfate and evaporated under reduced pressure. The product was purified via flash column chromatography.

4.5.1. (3*R*)-3-Ethyl-7-fluoro-4-(4-methoxybenzoyl)-3,4-dihydroquinoxalin-2(1*H*)-one (7a). Yield: 64%; δ 0.88 (t, J = 7.5 Hz, 3H), 1.33–1.44 (m, 1H), 1.55–1.66 (m, 1H), 3.77 (s, 3H), 4.83 (dd, J = 6.2, 9.0 Hz, 1H), 6.63 (ddd, J = 2.6, 8.7, 8.7 Hz, 1H), 6.68 (br s, 1H), 6.90 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 10.89 (br s, 1H); HRMS: calcd for $C_{18}H_{17}FN_2O_3$, 328.12238; found (ESI+, $[M+H]^{1+}$), 329.12930. $[\alpha]_D^{25}$ −287° (c 0.010 g/mL, DMSO).

4.5.2. (3*R*)-3-Ethyl-6-fluoro-4-(4-methoxybenzoyl)-3,4-dihydroquinoxalin-2(1*H*)-one (7c). Yield: 76% as a white solid; δ 1.18 (t, J = 7.2 Hz, 3H), 1.34–1.45 (m, 1H), 1.54–1.65 (m, 1H), 3.78 (s, 3H), 4.77 (dd, J = 6.2, 9.0 Hz, 1H), 6.57 (d, J = 9.5 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 6.94–7.04 (m, 2H), 7.28 (d, J = 8.8 Hz, 2H), 10.80 (br s, 1H); HRMS: calcd for $C_{18}H_{17}FN_2O_3$, 328.12238; found (ESI-FT, $[M+H]^{1+}$), 329.12878. $[\alpha]_D^{25}$ −336° (c 0.0098 g/mL, $CHCl_3$). Anal. Calcd for $C_{18}H_{17}FN_2O_3$: C, 65.85; H, 5.22; N, 8.53. Found: C, 65.48; H, 5.16; N, 8.15.

4.6. General procedure 4: preparation of 1-alkyl-4-(4-hydroxybenzoyl)-3,4-dihydroquinoxalin-2(1*H*)-ones (9a–9j, 9l–9o, 10a–10g)

To a stirred solution of the appropriate methoxybenzoyl-3,4-dihydroquinoxalin-2(1*H*)-one (0.61 mmol) in acetone (10 mL) under nitrogen were added either potassium carbonate or cesium carbonate (17 mmol), the appropriate alkyl iodide or alkyl bromide (3.0 mmol), and potassium iodide (3.1 mmol) in cases where the alkyl bromide was employed. The mixture was heated at reflux for 2 days, after which time the acetone was evaporated. The residue was partitioned between ethyl acetate and water, and the layers were separated and washed with water. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The product was purified via flash column chromatography. The resulting product was then dissolved in methylene chloride (6 mL) and treated with tetrabutylammonium iodide (1.13 mmol) at −78 °C followed by a 1.0 M solution of boron trichloride in methylene chloride (4.2 mL, 4.2 mmol). Stirring was continued at −78 °C for 5 min, and the reaction mixture was warmed to 0 °C, where it was stirred for 10 h. Ice water was then added and the mixture was stirred thoroughly. The layers were separated. The organic layer was washed with water and brine, and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure gave an oil, which was purified via Biotage Horizon® (SiO_2, gradient from 5% EtOAc/hexane to 35% EtOAc/hexane).

4.6.1. (3*R*)-3-Ethyl-6-fluoro-4-(4-hydroxybenzoyl)-1-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (9a). Yield: 71% as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.87 (t, J = 7.4 Hz, 3H), 1.30–1.42 (m, 1H), 1.50–1.59 (m, 1H), 3.36 (s, 3H), 4.89 (dd, J = 6.3, 9.3 Hz, 1H), 6.59 (dd, J = 2.5, 9.8 Hz, 1H), 6.71 (d, J = 8.8 Hz, 2H), 7.07 (ddd, J = 2.8, 9.1, 9.1 Hz, 1H), 7.19 (d, J = 8.8 Hz, 2H), 7.30 (dd, J = 5.4, 9.1 Hz, 1H), 10.07 (br s, 1H); MS (ESI) m/z 329 ($[M+H]^+$); MS (ESI) m/z 327 ($[M-H]^-$); HRMS: calcd for $C_{18}H_{17}FN_2O_3$, 328.1223; found (ESI-FT, $[M+H]^{1+}$), 329.12887. $[\alpha]_D^{25}$ −290° (c 0.0095 g/mL, $CHCl_3$).

4.6.2. (3*S*)-3-Ethyl-6-fluoro-4-(4-hydroxybenzoyl)-1-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (9b). Yield: 72% as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.87 (t, J = 7.2 Hz, 3H), 1.30–1.42 (m, 1H), 1.50–1.61 (m, 1H), 3.36 (s, 3H), 4.89 (dd, J = 6.1, 9.3 Hz, 1H), 6.60 (dd, J = 2.6, 9.5 Hz, 1H), 6.70 (d, J = 8.8 Hz, 2H), 7.07 (ddd, J = 2.8, 9.5, 9.5 Hz, 1H), 7.19 (d, J = 8.8 Hz, 2H), 7.30 (dd, J = 5.3, 9.1 Hz, 1H), 10.07 (br s, 1H); MS (ESI) m/z 329 ($[M+H]^+$); MS (ESI) m/z 327 ($[M-H]^-$). HRMS: calcd for $C_{18}H_{17}FN_2O_3$, 328.1223; found (ESI-FT, $[M+H]^{1+}$), 329.12904. $[\alpha]_D^{25}$ +301° (c 0.0107 g/mL, $CHCl_3$).

4.6.3. (3*R*)-1,3-diethyl-6-fluoro-4-(4-hydroxybenzoyl)-3,4-dihydroquinoxalin-2(1*H*)-one (9c). Yield: 80% as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.87 (t, J = 7.5 Hz, 3H), 1.19 (t, J = 7.0 Hz, 3H), 1.30–1.41 (m, 1H), 1.49–1.60 (m, 1H), 3.95–4.05 (m, 2H), 4.87 (dd, J = 6.4, 9.1 Hz, 1H), 6.61 (dd, J = 2.7, 9.3 Hz, 1H), 6.72 (d, J = 9.0 Hz, 2H), 7.06 (ddd, J = 2.9, 9.1, 9.1 Hz, 1H), 7.16 (d, J = 8.8 Hz, 2H), 7.35 (dd, J = 5.3, 9.1 Hz, 1H), 10.08 (br s, 1H); MS (ESI) m/z 343 ($[M+H]^+$); MS (ESI) m/z 341 ($[M-H]^-$). HRMS: calcd for $C_{19}H_{19}FN_2O_3$, 342.1380; found (ESI-FT, $[M+H]^{1+}$), 343.14482. $[\alpha]_D^{25}$ −300° (c 0.010 g/mL, $CHCl_3$). Anal. Calcd for $C_{19}H_{19}FN_2O_3$: C, 66.66; H, 5.59; N, 8.18. Found: C, 66.60; H, 5.49; N, 8.11.

4.6.4. (3*S*)-1,3-Diethyl-6-fluoro-4-(4-hydroxybenzoyl)-3,4-dihydroquinoxalin-2(1*H*)-one (9d). Yield: 70% as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.87 (t, J = 7.5 Hz, 3H), 1.18 (t, J = 7.0 Hz, 3H), 1.30–1.41 (m, 1H), 1.49–1.60 (m, 1H), 3.95–4.05 (m, 2H), 4.87 (dd, J = 6.3, 9.1 Hz, 1H), 6.61 (dd, J = 2.9, 9.6 Hz, 1H), 6.71 (d, J = 8.8 Hz, 2H), 7.06 (ddd, J = 2.8, 9.0, 9.0 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H), 7.35 (dd, J = 5.4, 9.2 Hz, 1H), 10.09 (br s, 1H); MS (ESI) m/z 343 ($[M+H]^+$); MS (ESI) m/z 341 ($[M-H]^-$); HRMS: calcd for $C_{19}H_{19}FN_2O_3$, 342.1380; found (ESI-FT, $[M+H]^{1+}$), 343.14475. $[\alpha]_D^{25}$ +295° (c 0.0098 g/mL, $CHCl_3$).

4.6.5. (3*R*)-1-allyl-3-ethyl-6-fluoro-4-(4-hydroxybenzoyl)-3,4-dihydroquinoxalin-2(1*H*)-one (9e). Yield: 74% as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.89 (t, J = 7.5 Hz, 3H), 1.36–1.47 (m, 1H), 1.54–1.64 (m, 1H), 4.43–4.50 (m, 1H), 4.68–4.74 (m, 1H), 4.92 (dd, J = 6.2, 9.3 Hz, 1H), 5.08 (ddd, J = 1.7, 3.2, 17.4 Hz, 1H), 5.20 (ddd, J = 1.6, 2.9, 10.6 Hz, 1H), 5.87–5.96 (m, 1H), 6.61 (dd, J = 2.7, 9.6 Hz, 1H), 6.71 (d, J = 8.8 Hz, 2H), 7.03 (ddd, J = 2.8, 8.7, 8.7 Hz, 1H), 7.16–7.21 (m, 3H), 10.10 (br s, 1H); MS (ESI) m/z 355 ($[M+H]^+$); MS (ESI) m/z 353 ($[M-H]^-$); HRMS: calcd

for $C_{20}H_{19}FN_2O_3$, 354.1380; found (ESI-FT, $[M+H]^{1+}$), 355.1449. $[\alpha]_D^{25}$ −285° (*c* 0.0102 g/mL, $CHCl_3$).

4.6.6. (3*R*)-3-Ethyl-6-fluoro-4-(4-hydroxybenzoyl)-1-propyl-3,4-dihydroquinoxalin-2(1*H*)-one (9f). Yield: 81% as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.87 (t, J = 7.3 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H), 1.30–1.41 (m, 1H), 1.49–1.66 (m, 3H), 3.86–4.03 (m, 2H), 4.88 (dd, J = 6.1, 9.3 Hz, 1H), 6.62 (dd, J = 2.9, 9.8 Hz, 1H), 6.72 (d, J = 8.6 Hz, 2H), 7.05 (ddd, J = 2.9, 8.8, 8.8 Hz, 1H), 7.15 (d, J = 8.6 Hz, 2H), 7.36 (dd, J = 5.3, 9.1 Hz, 1H), 10.10 (br s, 1H); MS (ESI) *m*/*z* 357 ($[M+H]^+$); MS (ESI) *m*/*z* 355 ($[M-H]^-$); HRMS: calcd for $C_{20}H_{21}FN_2O_3$, 356.1536; found (ESI-FT, $[M+H]^{1+}$), 357.16057. $[\alpha]_D^{25}$ −298° (*c* 0.0102 g/mL, $CHCl_3$).

4.6.7. (3*R*)-3-Ethyl-6-fluoro-4-(4-hydroxybenzoyl)-1-isopropyl-3,4-dihydroquinoxalin-2(1*H*)-one (9g). Yield: 50% as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.84 (t, J = 7.3 Hz, 3H), 1.22–1.34 (m, 1H), 1.45–1.58 (m, 1H), 1.46 (d, J = 7.1 Hz, 3H), 1.52 (d, J = 7.0 Hz, 3H), 4.64–4.71 (m, 1H), 4.83 (dd, J = 6.1, 9.3 Hz, 1H), 6.58 (dd, J = 2.4, 9.4 Hz, 1H), 6.72 (d, J = 8.8 Hz, 2H), 7.03 (ddd, J = 2.9, 9.1, 9.1 Hz, 1H), 7.18 (d, J = 8.8 Hz, 2H), 7.42 (dd, J = 5.3, 9.1 Hz, 1H), 10.09 (br s, 1H); MS (ESI) *m*/*z* 357 ($[M+H]^+$); MS (ESI) *m*/*z* 355 ($[M-H]^-$); HRMS: calcd for $C_{20}H_{21}FN_2O_3$, 356.1536; found (ESI-FT, $[M+H]^{1+}$), 357.16064. $[\alpha]_D^{25}$ −309° (*c* 0.0099 g/mL, $CHCl_3$).

4.6.8. (3*R*)-1-Butyl-3-ethyl-6-fluoro-4-(4-hydroxybenzoyl)-3,4-dihydroquinoxalin-2(1*H*)-one (9h). Yield: 71% as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.87 (t, J = 7.5 Hz, 3H), 0.91 (t, J = 7.3 Hz, 3H), 1.28–1.41 (m, 3H), 1.49–1.61 (m, 3H), 3.87–4.08 (m, 2H), 4.88 (dd, J = 6.2, 9.3 Hz, 1H), 6.63 (dd, J = 2.5, 9.5 Hz, 1H), 6.71 (d, J = 8.8 Hz, 2H), 7.06 (ddd, J = 2.8, 8.8, 8.8 Hz, 1H), 7.14 (d, J = 8.8 Hz, 2H), 7.36 (dd, J = 5.2, 9.0 Hz, 1H), 10.10 (br s, 1H); MS (ESI) *m*/*z* 371 ($[M+H]^+$); MS (ESI) *m*/*z* 369 ($[M-H]^-$); HRMS: calcd for $C_{21}H_{23}FN_2O_3$, 370.1693; found (ESI-FT, $[M+H]^{1+}$), 371.17594. $[\alpha]_D^{25}$ −268° (*c* 0.0103 g/mL, $CHCl_3$. Anal. Calcd for $C_{21}H_{23}FN_2O_3$: C, 68.09; H, 6.26; N, 7.56. Found: C, 67.96; H, 6.60; N, 7.67.

4.6.9. (3*R*)-3-Ethyl-6-fluoro-4-(4-hydroxybenzoyl)-1-pentyl-3,4-dihydroquinoxalin-2(1*H*)-one (9i). Yield: 53% as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.85 (t, J = 7.3 Hz, 3H), 0.87 (t, J = 7.5 Hz, 3H), 1.23–1.41 (m, 5H), 1.49–1.63 (m, 3H), 3.87–4.08 (m, 2H), 4.89 (dd, J = 6.2, 9.2 Hz, 1H), 6.63 (dd, J = 2.6, 9.6 Hz, 1H), 6.71 (d, J = 8.8 Hz, 2H), 7.06 (ddd, J = 3.0, 8.6, 8.6 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H), 7.36 (dd, J = 5.3, 9.1 Hz, 1H), 10.10 (br s, 1H); MS (ESI) *m*/*z* 385 ($[M+H]^+$); MS (ESI) *m*/*z* 383 ($[M-H]^-$); HRMS: calcd for $C_{22}H_{25}FN_2O_3$ $+H^+$, 385.19220; found (ESI-FT, $[M+H]^{1+}$), 385.19204. $[\alpha]_D^{25}$ −294° (*c* 0.0095 g/mL, $CHCl_3$).

4.6.10. (3*R*)-3-Ethyl-6-fluoro-4-(4-hydroxybenzoyl)-1-isobutyl-3,4-dihydroquinoxalin-2(1*H*)-one (9j). Yield: 33% as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.83 (d, J = 6.7 Hz, 3H), 0.88 (t, J = 7.3 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H), 1.29–1.41 (m, 1H), 1.50–1.61 (m, 1H), 1.97–2.06 (m, 1H), 3.74 (dd, J = 5.7, 14.1 Hz, 1H), 3.99 (dd, J = 9.3, 14.1 Hz, 1H), 4.91 (dd, J = 6.2, 9.6 Hz, 1H), 6.64 (dd, J = 2.6, 9.6 Hz, 1H), 6.72 (d, J = 8.8 Hz, 2H), 7.06 (ddd, J = 2.8, 9.1, 9.1 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H), 7.41 (dd, J = 5.2, 9.1 Hz, 1H), 10.12 (br s, 1H); MS (ESI) *m*/*z* 371 ($[M+H]^+$); MS (ESI) *m*/*z* 369 ($[M-H]^-$); HRMS: calcd for $C_{21}H_{23}FN_2O_3$, 370.1693; found (ESI-FT, $[M+H]^{1+}$), 371.17594. $[\alpha]_D^{25}$ −272° (*c* 0.010 g/mL, $CHCl_3$). Anal. Calcd for $C_{21}H_{23}FN_2O_3$: C, 68.09; H, 6.26; N, 7.56. Found: C, 67.85; H, 6.24; N, 7.65.

4.6.11. (3*R*)-3-Ethyl-6-fluoro-4-(4-hydroxybenzoyl)-1-(2,2,2-trifluoroethyl)-3,4-dihydroquinoxalin-2(1*H*)-one (9l). Yield: 44% as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.89 (t, J = 7.4 Hz, 3H), 1.31–1.41 (m, 1H), 1.52–1.62 (m, 1H), 4.96–5.04 (m, 3H), 6.67 (dd, J = 2.8, 9.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 2H), 7.14–7.09 (m, 1H), 7.14 (d, J = 8.8 Hz, 2H), 7.58 (dd, J = 5.2, 9.1 Hz, 1H), 10.13 (br s, 1H); MS (ESI) *m*/*z* 397 ($[M+H]^+$); MS (ESI) *m*/*z* 395 ($[M-H]^-$); HRMS: calcd for $C_{19}H_{16}F_4N_2O_3$, 396.1097; found (ESI-FT, $[M+H]^{1+}$), 397.11588. $[\alpha]_D^{25}$ −137° (*c* 0.010 g/mL, $CHCl_3$).

4.6.12. (3*R*)-3-Ethyl-7-fluoro-4-(4-hydroxybenzoyl)-1-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (9m). Yield: 88% as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.86 (t, J = 7.5 Hz, 3H), 1.28–1.37 (m, 1H), 1.50–1.61 (m, 1H), 3.35 (s, 3H), 4.94 (dd, J = 6.0, 9.6 Hz, 1H), 6.67–6.73 (m, 4H), 7.15 (d, J = 8.7 Hz, 2H), 7.21 (ddd, J = 1.7, 1.7, 10.4 Hz, 1 H), 10.01 (br s, 1H); MS (ESI) *m*/*z* 327 ($[M-H]^-$); HRMS: calcd for $C_{18}H_{17}FN_2O_3$, 328.1223; found (ESI+, $[M+H]^{1+}$), 329.13036. $[\alpha]_D^{25}$ −300° (*c* 0.009 g/mL, DMSO). Anal. Calcd for $C_{18}H_{17}FN_2O_3$: C, 65.85; H, 5.22; N, 8.53. Found: C, 65.73; H, 5.46; N, 8.28.

4.6.13. (3*R*)-1,3-Diethyl-7-fluoro-4-(4-hydroxybenzoyl)-3,4-dihydroquinoxalin-2(1*H*)-one (9n). Yield: 77% as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.86 (t, J = 7.3 Hz, 3H), 1.18 (t, J = 7.3 Hz, 3H), 1.29–1.37 (m, 1H), 1.49–1.58 (m, 1H), 3.99 (quar, J = 7.3 Hz, 2H), 4.91 (dd, J = 6.2, 9.4 Hz, 1H), 6.68 (d, J = 8.7 Hz, 2H), 6.67–6.73 (m, 2H), 7.12 (d, J = 8.7 Hz, 2H), 7.27 (ddd, J = 1.5, 1.5, 10.6 Hz, 1H), 10.03 (br s, 1H); MS (ESI) *m*/*z* 341 ($[M-H]^-$); HRMS: calcd for $C_{19}H_{19}FN_2O_3+H^+$, 343.14525; found (ESI-FT, $[M+H]^{1+}$), 343.14456. $[\alpha]_D^{25}$ −248° (*c* 0.0096 g/mL, $CHCl_3$). Anal. Calcd for $C_{19}H_{19}FN_2O_3 \cdot 0.10H_2O$: C, 66.31; H, 5.62; N, 8.14. Found: C, 66.05; H, 5.36; N, 8.02.

4.6.14. (3*R*)-1-Benzyl-3-ethyl-7-fluoro-4-(4-hydroxybenzoyl)-3,4-dihydroquinoxalin-2(1*H*)-one (9o). Yield: 74% as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.92 (t, J = 7.5 Hz, 3H), 1.37–1.48 (m, 1H), 1.62–1.72 (m, 1H), 5.06 (dd, J = 5.9, 9.6 Hz, 1H), 5.18 (d, J = 16.0 Hz, 1H), 5.30 (d, J = 16.0 Hz, 1H), 6.62 (d, J = 8.8 Hz, 2H), 6.67–6.74 (m, 2H), 7.05 (d, J = 8.8 Hz, 2H), 7.11 (dd, J = 2.4, 10.2 Hz, 1H), 7.26–7.30 (m, 3H), 7.35–7.39 (m, 2 H), 10. 03 (br s, 1H); MS (ESI) *m*/*z* 405 ($[M+H]^+$); MS (ESI) *m*/*z* 403 ($[M-H]^-$); HRMS: calcd for $C_{24}H_{21}FN_2O_3+H^+$,

405.16090; found (ESI-FT, $[M+H]^{1+}$), 405.16006. $[\alpha]_D^{25}$ +250° (*c* 0.0097 g/mL, $CHCl_3$).

4.6.15. (3*R*)-3-Ethyl-7-fluoro-4-(3-hydroxybenzoyl)-1-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (10a). Yield: 72% as a white solid; ^1H NMR (DMSO-d_6, 400 MHz) δ 0.86 (t, J = 7.5 Hz, 3H), 1.30–1.39 (m, 1H), 1.51–1.60 (m, 1H), 3.34 (s, 3H), 4.91 (br s, 1H), 6.68 (d, J = 7.4 Hz, 1H), 6.70–6.75 (m, 3H), 6.82 (ddd, J = 1.8, 2.3, 8.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.21 (dd, J = 2.8, 10.4 Hz, 1H), 9.68 (br s, 1H); MS (ESI) *m*/*z* 329 ($[M+H]^+$); MS (ESI) *m*/*z* 327 ($[M-H]^-$) HRMS: calcd for $C_{18}H_{17}FN_2O_3+H^+$, 329.12960; found (ESI-FT, $[M+H]^{1+}$), 329.12884. $[\alpha]_D^{25}$ −281° (*c* 0.0098 g/mL, $CHCl_3$). Anal. Calcd for $C_{18}H_{17}FN_2O_3 \cdot 0.10H_2O$: C, 65.49; H, 5.25; N, 8.49. Found: C, 65.29; H, 4.93; N, 8.33.

4.6.16. (3*R*)-1,3-Diethyl-7-fluoro-4-(3-hydroxybenzoyl)-3,4-dihydroquinoxalin-2(1*H*)-one (10b). Yield: 74% as a white solid; δ 0.86 (t, J = 7.5 Hz, 3H), 1.18 (t, J = 6.9 Hz, 3H), 1.27–1.39 (m, 1H), 1.50–1.61 (m, 1H), 4.00 (quar, J = 6.9 Hz, 2H), 4.90 (br s, 1H), 6.64 (d, J = 7.4 Hz, 1H), 6.69–6.76 (m, 3H), 6.83 (ddd, J = 1.8, 2.5, 8.2 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.27 (dd, J = 2.6, 10.4 Hz, 1H), 9.69 (br s, 1H); MS (ESI) *m*/*z* 343; MS (ESI) *m*/*z* 341. HRMS: calcd for $C_{19}H_{19}FN_2O_3+H^+$, 343.14525; found (ESI+, $[M+H]^{1+}$), 343.14462. $[\alpha]_D^{25}$ −275° (*c* 0.0083 g/mL, $CHCl_3$). Anal. Calcd for $C_{19}H_{19}FN_2O_3 \cdot 0.10H_2O$: C, 66.31; H, 5.62; N, 8.14. Found: C, 66.14; H, 5.46; N, 7.92.

4.6.17. (3*R*)-1-Benzyl-3-ethyl-7-fluoro-4-(3-hydroxybenzoyl)-3,4-dihydroquinoxalin-2(1*H*)-one (10c). Yield: 63% as a white solid; δ 0.91 (t, J = 7.5 Hz, 3H), 1.38–1.49 (m, 1H), 1.62–1.73 (m, 1H), 5.04 (br s, 1H), 5.20 (d, J = 16.3 Hz, 1H), 5.26 (d, J = 16.3 Hz, 1H), 6.52 (d, J = 6.1 Hz, 1H), 6.70–6.83 (m, 4H), 7.04–7.10 (m, 2H), 7.26–7.30 (m, 3H), 7.34–7.39 (m, 2H), 9.71 (br s, 1H); MS (ESI) *m*/*z* 405 ($[M+H]^+$); MS (ESI) *m*/*z* 403 ($[M-H]^-$); HRMS: calcd for $C_{24}H_{21}FN_2O_3+H^+$, 405.16090; found (ESI-FT, $[M+H]^{+1}$), 405.16003. $[\alpha]_D^{25}$ −279° (*c* 0.0095 g/mL, $CHCl_3$). Anal. Calcd for $C_{24}H_{21}FN_2O_3 \cdot 0.25H_2O$: C, 70.49; H, 5.30; N, 6.85. Found: C, 70.42; H, 5.19; N, 6.75.

4.6.18. (3*R*)-4-(2,4-dihydroxybenzoyl)-3-ethyl-6-fluoro-1-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (10d). Yield: 38% as a white solid; ^1H NMR (DMSO-d_6, 400 MHz) δ 0.81 (t, J = 7.3 Hz, 3H), 1.23–1.35 (m, 1H), 1.46–1.55 (m, 1H), 3.32 (s, 3H), 4.80 (br s, 1H), 6.15 (d, J = 2.2 Hz, 1H), 6.27 (dd, J = 2.2, 8.3 Hz, 1H), 6.85 (br s, 1H), 7.05 (ddd, J = 2.9, 8.7, 8.7 Hz, 1H), 7.10 (d, J = 8.5 Hz, 1H), 7.24 (dd, J = 5.4, 9.1 Hz, 1H), 9.68 (s, 1H), 9.71 (s, 1H); MS (ESI) *m*/*z* 345 ($[M+H]^+$); MS (ESI) *m*/*z* 343 ($[M-H]^-$); HRMS: calcd for $C_{18}H_{17}FN_2O_4$, 344.1172; found (ESI-FT, $[M+H]^{1+}$), 345.12407. $[\alpha]_D^{25}$ −289° (*c* 0.0099 g/mL, $CHCl_3$).

4.6.19. (3*R*)-4-(2,4-Dihydroxybenzoyl)-1,3-diethyl-6-fluoro-3,4-dihydroquinoxalin-2(1*H*)-one (10e). Yield: 22% as a white solid; ^1H NMR (DMSO-d_6, 400 MHz) δ 0.82 (t, J = 7.4 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H), 1.22–1.34 (m, 1H), 1.45–1.56 (m, 1H), 3.87–4.06 (m, 2H), 4.81 (br s, 1H), 6.14 (d, J = 2.2 Hz, 1H), 6.28 (dd, J = 2.2, 8.3 Hz, 1H), 6.77 (br s, 1H), 7.02 (ddd, J = 2.8, 8.7, 8.7 Hz, 1H), 7.11 (d, J = 8.3 Hz, 1H), 7.29 (dd, J = 5.3, 9.1 Hz, 1H), 9.58 (s, 1H), 9.71 (s, 1H); MS (ESI) *m*/*z* 345 ($[M+H]^+$); MS (ESI) *m*/*z* 359 ($[M+H]^+$); MS (ESI) *m*/*z* 357 ($[M-H]^-$); HRMS: calcd for $C_{19}H_{19}FN_2O_4$, 358.1329; found (ESI-FT, $[M+H]^{1+}$), 359.13972. $[\alpha]_D^{25}$ −293° (*c* 0.0102 g/mL, $CHCl_3$).

4.7. (3*R*)-1-Cyclopentyl-3-ethyl-6-fluoro-4-(4-hydroxybenzoyl)-3,4-dihydroquinoxalin-2(1*H*)-one (9k)

To a stirred solution of (3*R*)-3-ethyl-6-fluoro-4-(4-methoxybenzoyl)-3,4-dihydroquinoxalin-2(1*H*)-one (**7c**) (0.47 g, 1.4 mmol) in tetrahydrofuran (4 mL) under nitrogen at 0 °C were added cyclopentanol (0.20 mL, 0.19 g, 2.2 mmol), triphenylphosphine (0.58 g, 2.2 mmol), and diethyl azodicaboxylate (0.44 mL, 0.46 g, 0.22 mmol). The reaction mixture was warmed to 25 °C and was stirred for 12 h. The solvent was evaporated in vacuo, and the product was purified via Biotage Horizon® (SiO_2, gradient from 5% EtOAc/hexane to 40% EtOAc/hexane) to yield 0.20 g (36%) of (3*R*)-1-cyclopentyl-3-ethyl-6-fluoro-4-(4-methoxybenzoyl)-3,4- dihydroquinoxalin-2(1*H*)-one. MS (ESI) *m*/*z* 397 ($[M+H]^+$).

The resulting product was then dissolved in methylene chloride (5 mL) and treated with tetrabutylammonium iodide (0.34 g, 0.93 mmol) at −78 °C followed by a 1.0 M solution of boron trichloride in methylene chloride (3.4 mL, 3.4 mmol). Stirring was continued at −78 °C for 5 min, and the reaction mixture was warmed to 0 °C, where it was stirred for 10 h. Ice water was then added and the mixture was stirred thoroughly. The layers were separated. The organic layer was washed with water and brine, and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure gave an oil, which was purified via Biotage Horizon® (SiO_2, gradient from 5% EtOAc/hexane to 35% EtOAc/hexane) to yield 76 mg (40%) of **11g** as a white solid. ^1H NMR (DMSO-d_6, 400 MHz) δ 0.84 (t, J = 7.4 Hz, 3H), 1.23–1.34 (m, 1H), 1.46–1.55 (m, 1H), 1.57–1.65 (m, 2H), 1.86–2.08 (m, 5H), 2.16–2.24 (m, 1H), 4.64–4.73 (m, 1H), 4.83 (dd, J = 6.2, 9.6 Hz, 1H), 6.61 (d, J = 9.1 Hz, 1H), 6.72 (d, J = 8.9 Hz, 2H), 7.05 (ddd, J = 2.9, 9.1, 9.1 Hz, 1H), 7.17 (d, J = 8.9 Hz, 2H), 7.38 (dd, J = 5.5, 9.1 Hz, 1H), 10.09 (br s, 1H); MS (ESI) *m*/*z* 383 ($[M+H]^+$); MS (ESI) *m*/*z* 381 ($[M-H]^-$); HRMS: calcd for $C_{22}H_{23}FN_2O_3$, 382.1693; found (ESI-FT, $[M+H]^{1+}$), 383.17555. $[\alpha]_D^{25}$ −309° (*c* 0.0095 g/mL, $CHCl_3$).

4.8. General procedure 5: preparation of 1-alkyl-4-benzoyl-3,4-dihydroquinoxalin-2(1*H*)-ones (10f–10h)

To a solution of the appropriate 3,4-dihydroquinoxalin-2(1*H*)-one (0.67 mmol) in methylene chloride (5 mL) under nitrogen were added triethylamine (0.11 mL, 0.79 mmol) and the appropriate benzoyl chloride (0.69 mmol). The solution was stirred for 16 h and was then washed successively with a 1 N aqueous solution of hydrochloric acid, a 1 N aqueous solution of sodium hydroxide, water, and brine successively. The combined organic extracts were dried over magnesium sulfate and

evaporated under reduced pressure. The resulting residue was dissolved in acetone (11 mL) under nitrogen to which were added cesium carbonate (18.7 mmol) and the appropriate alkyl iodide (3.3 mmol). The mixture was heated at reflux for 2 days, after which time the acetone was evaporated. The residue was partitioned between ethyl acetate and water, and the layers were separated and washed with water. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The product was purified via flash column chromatography.

4.8.1. (3*R*)-1,3-Diethyl-6-fluoro-4-(4-methoxybenzoyl)-3,4-dihydroquinoxalin-2(1*H*)-one (10f). Yield: 84%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.88 (t, J = 7.3 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H), 1.31–1.42 (m, 1H), 1.51–1.61 (m, 1H), 3.79 (s, 3H), 4.01 (quar., J = 7.3 Hz, 2H), 4.89 (dd, J = 6.3, 9.3 Hz, 1H), 6.65 (d, J = 7.6 Hz, 1H), 6.92 (d, J = 8.7 Hz, 2H), 7.07 (ddd, J = 3.3, 9.1, 9.1 Hz, 1H), 7.27 (d, J = 8.7 Hz, 2H), 7.36 (dd, J = 5.2, 9.1 Hz, 1H); MS (ESI) m/z 357. HRMS: calcd for $C_{20}H_{21}FN_2O_3$+H^+, 357.16090; found (ESI-FT, $[M+H]^{1+}$), 357.16057. $[\alpha]_D^{25}$ −290° (c 0.0102 g/mL, $CHCl_3$). Anal. Calcd for $C_{20}H_{21}FN_2O_3 \cdot 0.30H_2O$: C, 66.40; H, 6.02; N, 7.74. Found: C, 66.42; H, 5.92; N, 7.74.

4.8.2. (3*R*)-3-Ethyl-6-fluoro-1-methyl-4-(4-methylbenzoyl)-3,4-dihydroquinoxalin-2(1*H*)-one (10g). Yield: 88% as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.83 (t, J = 7.4 Hz, 3H), 1.27–1.38 (m, 1H), 1.48–1.57 (m, 1H), 2.28 (s, 3H), 3.32 (s, 3H), 4.86 (br s, 1H), 6.61 (br s, 1H), 7.04 (ddd, J = 2.8, 8.8, 8.8 Hz, 1H), 7.14 (d, J = 7.9 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 7.27 (dd, J = 8.3, 9.1 Hz, 2H); MS (ESI) m/z 327. HRMS: calcd for $C_{19}H_{19}FN_2O_2$+H^+, 327.15033; found (ESI-FT, $[M+H]^{1+}$), 327.14989. $[\alpha]_D^{25}$ −258° (c 0.010 g/mL, $CHCl_3$).

4.8.3. (3*R*)-3-Ethyl-6-fluoro-1-methyl-4-(4-nitrobenzoyl)-3,4-dihydroquinoxalin-2(1*H*)-one (10h). Yield: 74% as a white solid; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.86 (t, J = 7.2 Hz, 3H), 1.29–1.41 (m, 1H), 1.50–1.60 (m, 1H), 3.28 (s, 3H), 4.93 (br s, 1H), 6.65 (br s, 1H), 7.07 (t, J = 7.4 Hz, 1H), 7.29 (dd, J = 5.3, 9.1 Hz, 1H), 7.63 (d, J = 8.0 Hz, 2H), 8.18 (d, J = 8.0 Hz, 2H); MS (ESI) m/z 358. HRMS: calcd for $C_{18}H_{16}FN_3O_4$+H^+, 358.11976; found (ESI-FT, $[M+H]^{1+}$), 358.1193. $[\alpha]_D^{25}$ −315° (c 0.0098 g/mL, $CHCl_3$).

4.9. General procedure 6: Optical purity assessment

The enantiomeric purity of each compound was determined using a Chiralpak AD-H 5u, 250 mm × 4.6 mm ID column at 2.0 mL/min flow rate via Analytical Supercritical Fluid Chromatography (Berger Instruments, Inc. Newark, DE, USA) at 35 °C with a detection wavelength of 220 nm. The SFC modifier utilized was 20% MeOH. The chiral method was developed by mixing enantiomeric pairs and achieving baseline separation. Retention times for each enantiomer are reported.

4.9.1. (3*R*)-3-Ethyl-6-fluoro-4-(4-hydroxybenzoyl)-1-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (9a). The enantiomeric purity was determined to be 97.3% (with 2.7% of the undesired enantiomer). Retention time: 3.59 min.

4.9.2. (3*S*)-3-Ethyl-6-fluoro-4-(4-hydroxybenzoyl)-1-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (9b). The enantiomeric purity was determined to be 95.7% (with 4.3% of the undesired enantiomer). Retention time: 4.91 min.

4.9.3. (3*R*)-1,3-diethyl-6-fluoro-4-(4-hydroxybenzoyl)-3,4-dihydroquinoxalin-2(1*H*)-one (9c). The enantiomeric purity was determined to be 97.6% (with 2.4% of the undesired enantiomer). Retention time: 3.42 min.

4.9.4. (3*S*)-1,3-diethyl-6-fluoro-4-(4-hydroxybenzoyl)-3,4-dihydroquinoxalin-2(1*H*)-one (9d). The enantiomeric purity was determined to be 95.8% (with 4.2% of the undesired enantiomer). Retention time: 5.02 min.

4.9.5. ((3*R*)-3-Ethyl-7-fluoro-4-[(4-hydroxyphenyl)sulfonyl]-1-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (2a). The enantiomeric purity was determined to be 95.8% (with 4.2% of the undesired enantiomer). Retention time: 3.82 min.

4.9.6. ((3*S*)-3-Ethyl-7-fluoro-4-[(4-hydroxyphenyl)sulfonyl]-1-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (2b). The enantiomeric purity was determined to be 97.3% (with 2.7% of the undesired enantiomer). Retention time: 4.87 min.

4.10. General procedure 7: solubility assay conditions

Solid compound was dissolved in DMSO at 8 mg/mL to make a stock solution from which 13 μL was added to 1.0 mL of aqueous buffer (part number 110090, pION Inc., Woburn, MA, USA) at pH 7.4 in a 96-deep well plate (2 mL polypropylene). The solution was incubated for 18 h at ambient temperature and then filtered using a 96-well filter plate (0.2 μm, Corning, Acton, MA, USA). The supernatant was quantitated in a UV plate (part number 110614, pION Inc.) using a UV plate reader (Molecular Devices, Spectra Max 190, Sunnyvale, CA, USA). Liquid handling was carried out on a Tecan Genesis robot under the control of pION PSR4S software version 1.3.

4.11. General procedure 8: ER/NF-κB luciferase and CK assay conditions

4.11.1. Cell preparation. T-175 flasks of 100% confluent HAECT-1 cells (immortalized human aortic endothelial cells) were washed with 8 mL HBSS (HEPES-buffered saline solution) and infected for 4 h with 6 mL of a 1:10 dilution of Ad5-wt-hERα virus (an adenovirus transfection vector that mediates CMV promoter-driven expression of human ERα) in phenol red free Endothelial Cell Basal medium (Clonetics, San Diego, CA, Catalog # CC-3129) containing 0.25% bovine serum albumin (EBM-BSA). After 4 h, cells were washed with EBM-BSA and incubated overnight in the same medium. Following overnight incubation, cells were washed with EBM-BSA and infected for 2 h with 6 mL of a 1:10 dilution of Ad5-3x(NF-κB). Luc virus (Adenovirus luciferase expression vector driven by 3 repeats of the MHC NFκb site 5′ to the thymidine kinase promoter) in EBM-BSA. After 2 h, cells were washed and

incubated at 34 °C for 1 h. Cells were then washed, trypsinized, counted, and resuspended in 95%FBS/5% dimethylsulfoxide at a concentration of 4×10^6 cells/mL, frozen as 1 or 5 mL aliquots in cryo-vials, and stored at −150 °C. Control (no ER infection) cells were processed as above without Ad5-wt-hERα virus infection.

4.11.2. IL-6 and creatine kinase assays. ERα infected HAECT-1 cells or control cells were thawed, diluted 42× in warm EBM-BSA, plated into 96-well plates at 0.1 mL/well, and incubated for 4 h at 34 °C. Test compounds were added to the cells as 2× stocks in EBM-BSA containing 2 ng/mL IL-1β (R&D Systems) and plates were returned to the incubator (34 °C). After 15-20 h, 100 μL aliquots of media were removed from the cells and assayed for IL-6 content using a BioSource human IL-6 ELISA Kit. Cells were subsequently washed with 300 μL of Dulbecco's phosphate-buffered saline and lysed in 50 μL of Cell Culture Lysis Reagent (Promega). The amount of luciferase was quantified on a Wallac Victor^2 Luminometer (Gaithersburg, MD) using 10 μL of lysate and mixing with 100 μL of Promega Luciferase Assay reagent. Creatine kinase was determined from the rate of increase in A_{340} following addition of 100 μL of CK assay reagent (Sigma, cat. No 47-10) to the remainder of the cell lysate.

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