Quinoxaline *N*-Oxide Containing Potent Angiotensin II Receptor Antagonists: Synthesis, Biological Properties, and Structure–Activity Relationships

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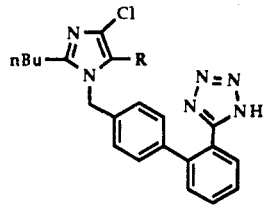
A series of novel quinoxaline heterocycle containing angiotensin II receptor antagonist analogs were prepared. This heterocycle was coupled to the biphenyl moiety via an oxygen atom linker instead of a carbon atom. Many of these analogs exhibit very potent activity and long duration of effect. Interestingly, the *N*-oxide quinoxaline analog was more potent than the nonoxidized quinoxaline as in the comparison of compounds **5** vs **30**. In order to improve oral activity, the carboxylic acid function of these compounds was converted to the double ester. This change did result in an improvement in oral activity as represented by compound **44**.

Introduction

The renin–angiotensin system plays an important role in regulating mammalian blood pressure, and agents that modulate the action of the renin–angiotensin system, especially angiotensin-converting enzyme (ACE) inhibitors, have been used for the treatment of hypertension in man.[1] Since disclosure of the first nonpeptidic angiotensin II receptor antagonist,[2] extensive research has been focused on antagonists of the angiotensin II receptor as targets for drug design, with the hope of obtaining greater pharmacological selectivity than observed with ACE inhibitors. Most notably, DuPont scientists recently reported the potent nonpeptidic angiotensin II receptor antagonist, compound 1 (losartan, DuP 753) which is now undergoing clinical trials in man.[3]

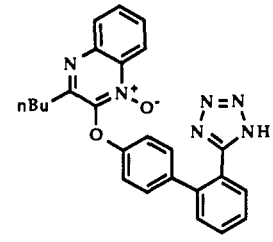


1, R=CH_2OH (losartan, DUP 753)

2, R=COOH (EXP 3174)

Substituted imidazoles or imidazole-related heterocycles such as imidazopyridine or benzimidazole have been widely reported as angiotensin II antagonists, with the imidazole group possibly acting as a mimic of the histidine residue of angiotensin II.[4] Compound **2** (EXP 3174) which contains carboxy-substituted imidazole has been shown to be more potent than the hydroxymethyl counterpart **1**.[5] Herein we report a series of quinoxaline-containing angiotensin II receptor antagonists containing an oxygen link between the heterocycle and the biphenyl acid common to compound **1**. We originally envisioned quinoxaline *N*-oxide **3** as a potential angiotensin II receptor antagonist, with the idea that an oxy anion of the *N*-oxide adjacent to the biphenyl ring might play a role similar to that of the carboxylate group in the substituted imidazole of **2**. The oxygen atom linker was selected to expedite chemical synthesis. Compound **3** was prepared and showed potent angiotensin II receptor antagonist activity both in functional[6] (K_B = 0.44 nM) and binding[7] (K_i = 4.5 nM) assays. Its *in vivo* activity, however, was disappointing in terms of duration. Further improvement was subsequently made, resulting in compounds **4** and **5** which possess very potent activities both *in vitro* and *in vivo*. The synthesis and structure–activity relationships of these compounds are described below.

Structures 3, 4, 5



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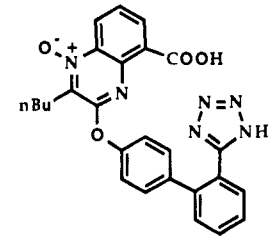

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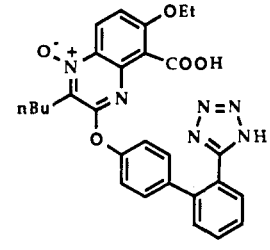

5

Chemistry

The key intermediate for the synthesis of **3–5** was hydroxy biphenyl–tetrazole **8**, which was obtained via palladium-mediated coupling of bromoanisole with bromobenzonitrile (Scheme I). Chloroquinoxaline *N*-oxide **12** was prepared starting from 1,2-phenylenediamine and ethyl 2-bromohexanoate (Scheme II).

Selective oxidation of either nitrogen atom of the quinoxaline nucleus was achieved by choosing the proper reagent.[8] Oxidation by potassium persulfate under strongly acidic conditions occurred on the less basic nitrogen atom of **11**, due to protonation of the more basic nitrogen atom, to selectively afford *N*-oxide **12** in 51% yield. Coupling of *N*-oxide **12** with biphenyl **8** was then carried out in the presence of cesium carbonate to obtain compound **3** in 62% yield (Scheme III). Regioisomeric *N*-oxide compound **15** was obtained by selective oxidation

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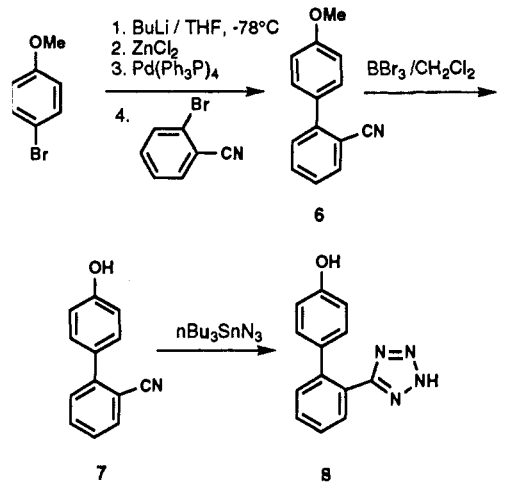
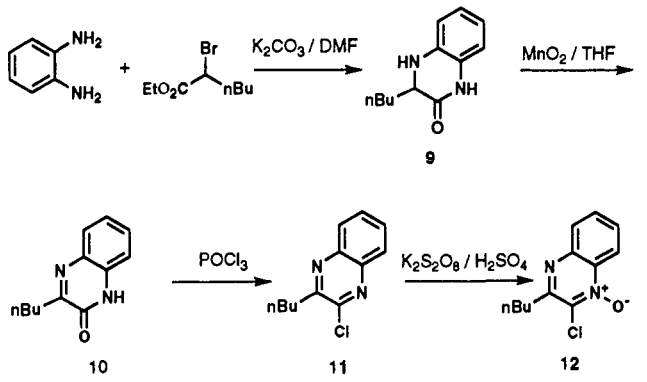
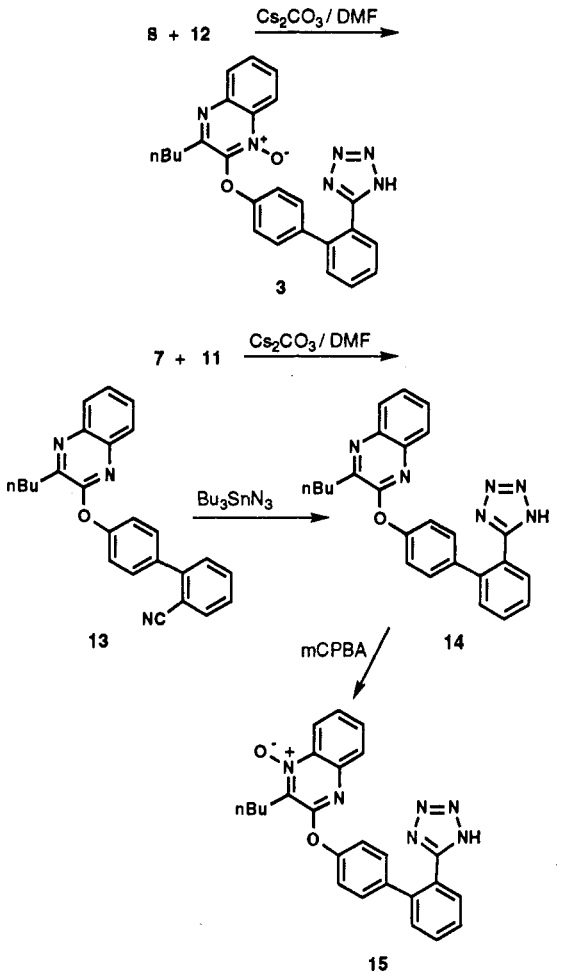
Scheme I



Scheme II



Scheme III



of the more basic nitrogen atom of **14** using *m*-chloroperoxybenzoic acid.

Analogs bearing a carboxylic acid group in the quinoxaline nucleus were obtained from ethyl 3-nitro-2-aminobenzoate (**20**) as shown in Scheme IV. Parent 3-nitro-2-aminobenzoate (**20**, R = H) was prepared starting from nitrophthalic anhydride as previously described.[9] Substituted (at C-6) examples were prepared starting from 2,6-difluorobenzoyl chloride. Regioselective nitration, amination, and alkoxylation proceeded very efficiently to afford **20** (R = OEt at C-6). Substitution at C-6 by replacing the fluorine atom with various alkoxy groups and sodium azide allowed preparation of many different analogs shown in Table II. Catalytic hydrogenation of the nitro group of **20** provided diamino compound **21**. Quinoxalinone nucleus **23** was then formed by condensation of diamino compound **21** with ethyl 2-bromohexanoate, followed by oxidation. Chlorination was carried out by treatment of either quinoxalinone ester **23** or the corresponding carboxylic acid **24** with phosphorus oxychloride. In the carboxylic acid case, small amounts of an anhydride derived from two molecules of **26** were sometimes formed, depending on the substituents and reaction time. The nonpolar chloroanhydride was hydrolyzed by aqueous sodium bicarbonate solution to regenerate the free acid **26**. Except for the unsubstituted example (R = H), it was necessary to carry out the hydrolysis before the chlorination because we were unable to hydrolyze the ester once it was coupled to biphenyl **8** without destroying the parent molecule.

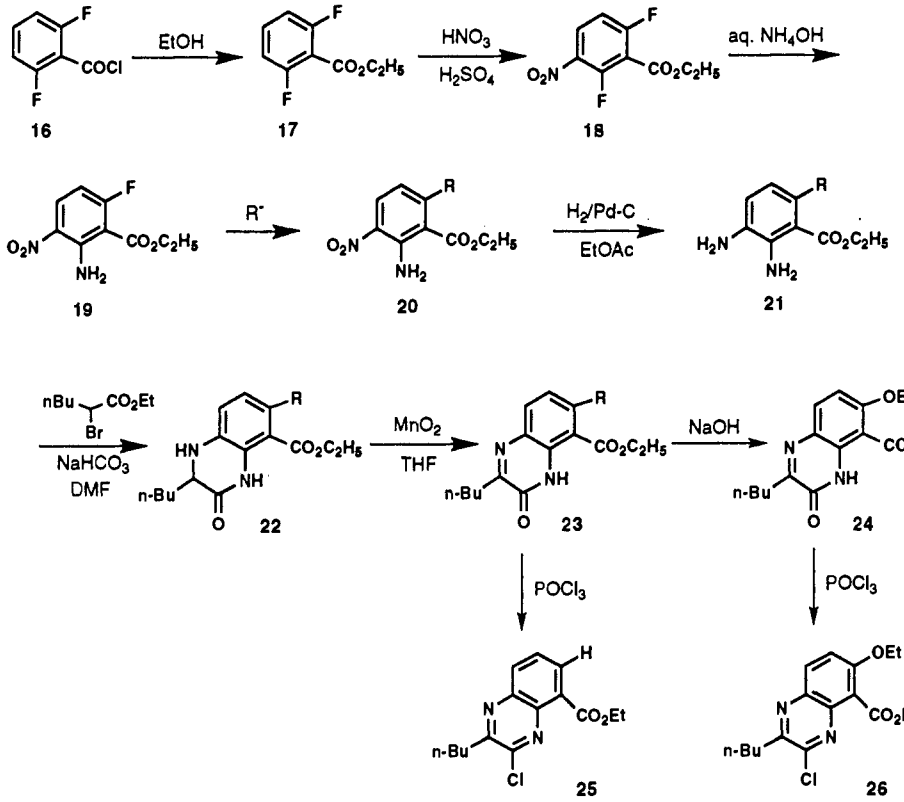
Coupling of chloro/ester **25** with biphenyl **8** in the presence of cesium carbonate followed by *m*-chloroperoxybenzoic acid oxidation afforded **28** (Scheme V), which was converted to the corresponding carboxylic acid **4**. Substituted example **5** was prepared by coupling the chloro/acid **26** with biphenyl **8**, followed by *m*-chloroperoxybenzoic acid oxidation (Scheme VI).

In order to improve the oral activity, a double ester prodrug of **5** was prepared.[10] Alkylation of **30** with 1-chloro-2-methylpropyl propionate in the presence of excess amount of silver oxide and powdered 4A molecular sieves produced prodrug ester **31** (Scheme VII). Monoalkylation at the carboxylic acid group occurred selectively in the presence of tetrazole. We believe that complex formation of silver salt with basic tetrazole diminishes its nucleophilic reactivity, thereby allowing the selective monoalkylation at the carboxylic acid group. In the presence of excess amounts of alkylating reagents and base bisalkylation does occur in high yield both at the carboxylic and tetrazole groups. The bisalkylated compound can be selectively hydrolyzed at the ester of the tetrazole group by aqueous sodium bicarbonate solution at room temperature, thus providing an alternative route for monoalkylation at the carboxyl group of various alkoxy substituted compounds of type **31**. Oxidation of **31** with *m*-chloroperoxybenzoic acid provided prodrug **32**.

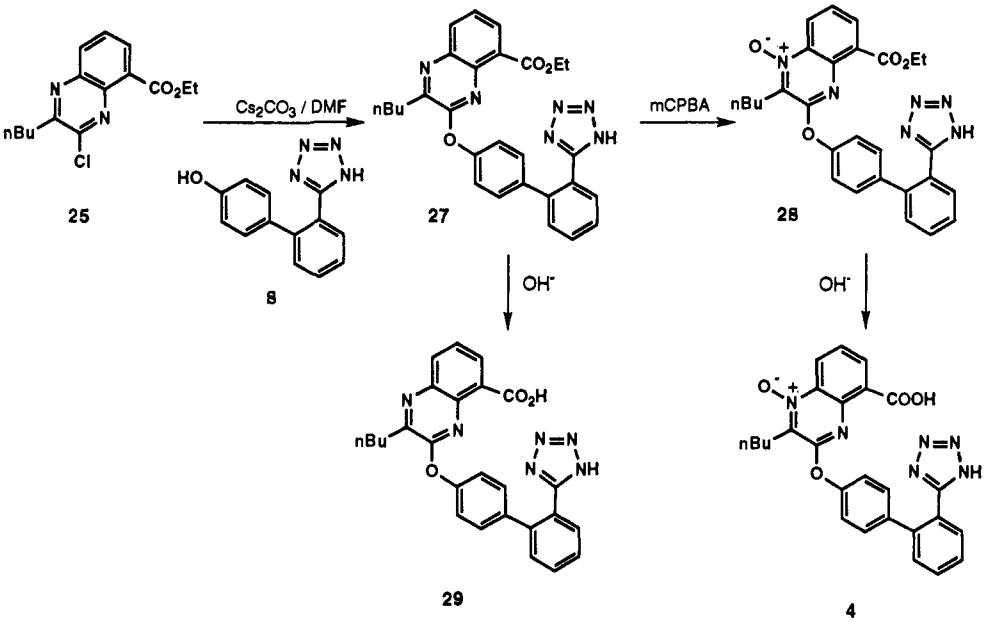
Biological Results

Compound **3**, having an *N*-oxide function adjacent to the biphenyl, was much more active than the N-1 oxide isomer **15** or nonoxidized compound **14** as shown in Table I. The N-1 oxides **15** and **34**, however, did exhibit somewhat enhanced activity compared to the nonoxidized compounds **14** and **33**. This was a surprise to us, and we

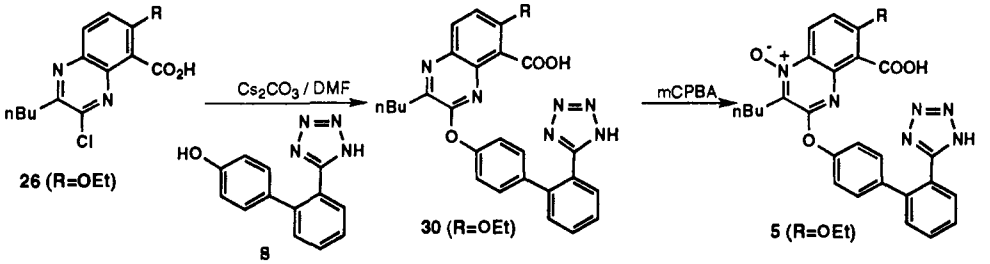
Scheme IV



Scheme V



Scheme VI



believe that the oxyanion of the N-1 oxide plays the same role as that of the nonbonding electron pair of the imidazole nitrogen atom in molecules such as compound 1.[12] Compound 3 showed potent *in vitro* activities both in binding (K_I = 4.5 nM) and functional (K_B = 0.44 nM) assays, but its *in vivo* activity was disappointing in terms of duration. In addition, the compound was chemically unstable, having a half-life of about 6 hours at pH 7.5 at 40 °C. Decom-

Scheme VII

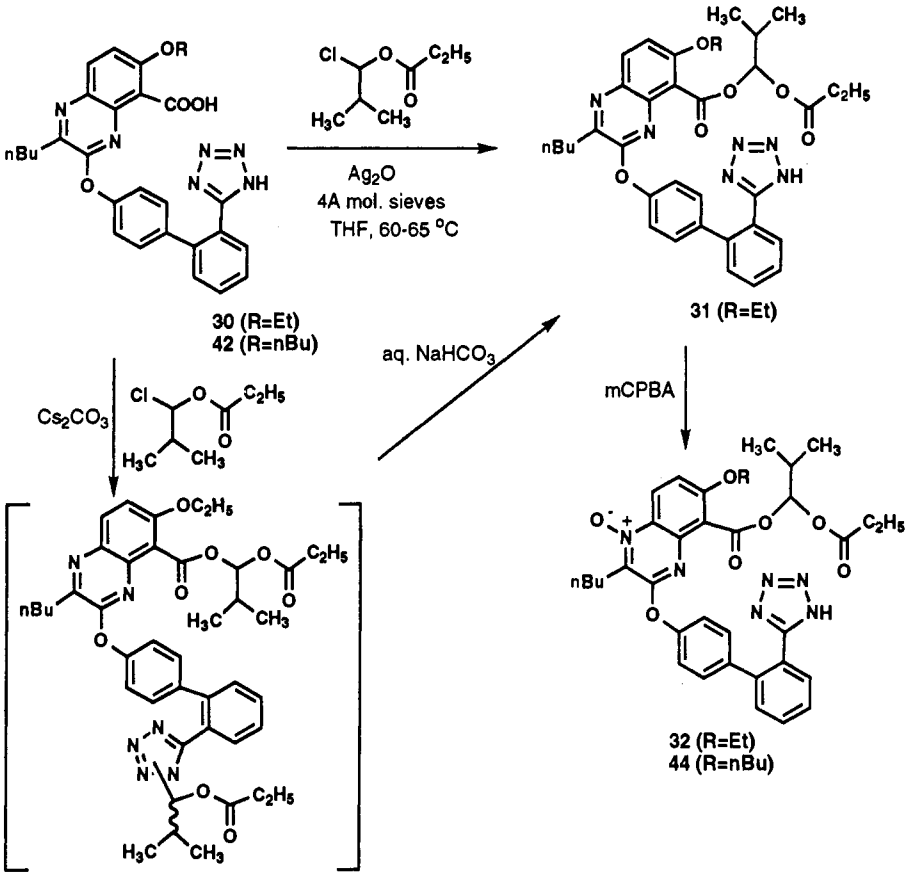
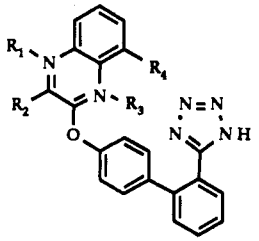


Table I. All Antagonistic *in Vitro* Activities of Quinoxaline Analogs



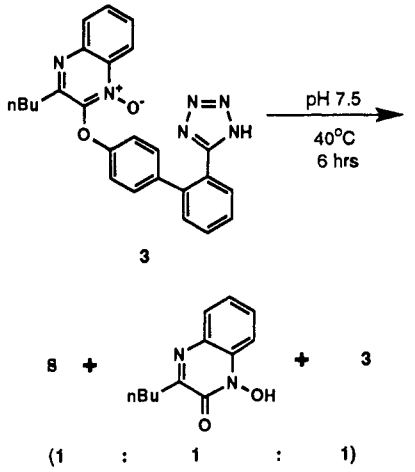
compd	R_1	R_2	R_3	R_4	mp, °C	K_i, nM (±SEM)[a]	K_B, nM (±SEM)[b]
14	none	nBu	none	none	144–145	137 ± 45	290 ± 58
3	none	nBu	O	none	100–104	4.5 ± 1.2	0.44 ± 0.076
15	O	nBu	none	none	190–191	71 ± 24	230 ± 38
33	none	Me	none	none	210–212	3450 ± 150	2300 ± 1300
34	O	Me	none	none	135–145	550 ± 74	480 ± 120
29	none	nBu	none	COOH	240–241	46 ± 10	2.1 ± 1.3
4	O	nBu	none	COOH	218–220	15 ± 6	0.5 ± 0.16
35	none	nPr	none	COOH	285–298	190 ± 43	13 ± 3.6

[a] Compounds were tested in a radioligand binding assay using rat adrenal cortical membranes with [125I]Sar1,Ile8-angiotensin II as the radioligand, n = 3–5 (see ref 7). [b] Functional potencies were determined by antagonism of angiotensin II induced contraction of isolated rabbit aorta as described elsewhere, n = 3–4 (see ref 6).

position products were hydrolyzed hydroxybiphenyl 8 and a cyclic hydroxamic acid from the quinoxaline nucleus as shown in Scheme VIII.

It has been shown that introduction of a carboxylic acid group into the heterocycle can enhance binding and functional activities.[5] The carboxylic acid analog 4 was more active than the prototype 15, and *N*-oxide 4 showed more potent activity than the nonoxidized compound 29. Replacement of the *n*-butyl substituent with *n*-propyl caused a loss of activity (29 vs 35). Compared with 3, the carboxylic acid containing compound 2 showed a longer

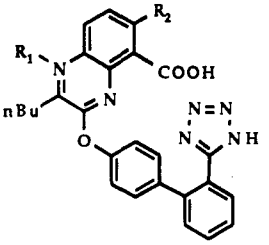
Scheme VIII



duration of action *in vivo*. The activity of this series of compounds was further improved by introducing the alkoxy group at C-6 of the quinoxaline nucleus (Table II). The *N*-oxide compounds consistently exhibited more potent activity than the parent nonoxidized compounds (36 vs 37, 30 vs 5) and ethoxyl compound 5 displayed the more potent *in vitro* activity in this series of compounds.

Chiu et al. reported the pronounced effect of bovine serum albumin (BSA) on the binding activity of some angiotensin II receptor antagonists which usually bore the carboxylic acid function in the imidazole heterocycle.[11] Pronounced BSA effects were also observed in this quinoxaline series of molecules, even for compounds lacking the carboxylic acid group in the quinoxaline nucleus such as 33, 34, 14, and 15 as shown in Table III. This protein binding may have effectively reduced the concentration of comopund in the binding assay and may

Table II. AII Antagonistic *in Vitro* Activities of the Analogs with Various Substituents at C-7 (R_2) of the Quinoxaline Nucleus



compd	R_1	R_2	mp, °C	K_i, nM (±SEM)[a]	K_B, nM (±SEM)[b]
36	none	F	>275	21 ± 10	0.97 ± 0.055
37	O	F	223–225	9 ± 1	0.58 ± 0.06
38	O	OMe	139–144	17 ± 1	0.13 ± 0.02
30	none	OEt	137–146	44 ± 28	0.12 ± 0.019
5	O	OEt	169–171	1.3 ± 0.5	0.026 ± 0.006
39	O	OCH_2CF_3	172–174	22 ± 3	2.0 ± 0.13
40	O	O-*n*-Pr	140–142	68 ± 7	0.19 ± 0.002
41	O	O-*i*-Pr	134–136	28 ± 8	0.49 ± 0.19
42	O	O-*n*-Bu	120–122	50 ± 3	0.27 ± 0.100
43	O	NH_2	255–258	7.4 ± 2	0.25 ± 0.031

[a,b] See Table I for an explanation of tabulated data.

therefore partially explain the higher K_i values relative to the K_B values. Another possible reason for the difference in K_i and K_B values is the finding that the functional antagonism associated with some of the compounds was not overcome by increasing concentrations of angiotensin II. That is, the antagonism was insurmountable. This would lead to an overestimation of the functional potency (K_B).

Compounds **5**, **41**, and **43**, shown in Table II, demonstrated their ability to block the pressor effects angiotensin II in conscious Sprague–Dawley rats after intravenous administration at a dose of 3 μmol/kg. The nonoxidized compounds (**36** and **30**) did not. Oral antihypertensive activity in sodium-depleted spontaneously hypertensive rats was only moderate at doses of 10 μmol/kg, except for compounds **5**, **40**, and **42**. Double esters of most of the compounds in Table II showed improvement in oral antihypertensive activity as shown by **44** in Figure 1. Several of the compounds shown in Table II exhibited a somewhat slow onset and extremely long duration of effect both after intravenous administration in the angiotensin II pressor test or after oral administration to the sodium-depleted spontaneously hypertensive rats (Figure 1). Unlike compound **1**, this series of compounds did not exhibit a biphasic time–response curve in either *in vivo* test.

Conclusion

We have prepared potent angiotensin II receptor antagonist molecules which contain a quinoxaline heterocycle. The analogs having an *N*-oxide function (e.g., **5** and **42**) exhibited more potent activity than the parent nonoxidized compounds. Double ester prodrugs such as compounds **32** and **44** displayed potent oral antihypertensive activity in rats and very long duration of action.

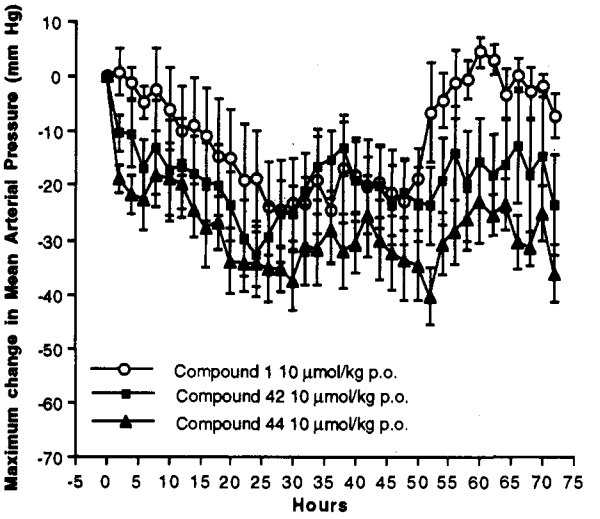


Figure 1. Maximum change in MAP in sdSHR.

Experimental Section

General. All new compounds were homogeneous by thin-layer chromatography and reversed-phase HPLC. Flash chromatography was carried out on E. Merck Kieselgel 60 silica gel (230–400 mesh). ^1H NMR and ^{13}C NMR spectra were obtained on a JEOL CPF-270 spectrometer operating at 270 or 67.5 MHz, respectively, and are reported as parts per million (ppm) downfield from an internal tetramethylsilane standard. The abbreviations of qn and sx in ^1H NMR refer to quintet and sextet, respectively. Melting points are uncorrected. Tetrahydrofuran (THF) and xylenes were dried by distillation from sodium. *N,N*-Dimethylformamide (DMF) was dried over 4A molecular sieves.

Radioligand binding studies were performed using rat adrenal cortical membranes prepared as described by Chui et al.[7] Binding experiments were performed as described[7] using [^{125}I]Sar^{1}Ile^8 angiotensin-II as the radioligand and inhibition curves were analyzed by computer-assisted iterative fitting and K_i values were calculated for the AT_1 receptor population. The bovine serum albumin (BSA) concentration was reduced to 0.01% to attenuate drug binding to BSA.[11] Compounds were also tested for functional antagonism of contractions elicited by angiotensin II in isolated rabbit thoracic aorta as described elsewhere.[6] K_B values were calculated from the shift in the angiotensin II concentration–response curve caused by a single concentration of test compound. The test compounds were administered orally as suspension in agar, and blood pressure was recorded using the method described previously.[13]

4′-Methoxybiphenyl-2-carbonitrile (6) and 4-(2-Cyanophenyl)phenol (7). To a solution of 4-bromoanisole (18.7 g, 0.1 mol) in anhydrous THF (200 mL) at −78 °C was added a solution of *n*-BuLi (2.5 M solution in hexane, 50 mL). After 0.5 h of stirring, a solution of zinc chloride (1 M solution in ether, 100 mL) was added and the mixture was stirred for 1 h at −78 °C. To this solution were added $Pd(Ph_3P)_4$ (0.85 g, 0.73 mmol) and 2-bromobenzonitrile (18.2 g, 0.1 mol). The reaction mixture was stirred at room temperature overnight and was concentrated *in vacuo*. The residue was partitioned between ethyl acetate (100 mL) and 1 N hydrochloric acid (100 mL). The organic solution was taken, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to obtain a crude product **6** which was used directly for the next reaction without further purification. (This compound can be triturated with ether to obtain a pure solid product.) To a solution of crude product **6** in CH_2Cl_2 (150 mL) at −78 °C was added boron tribromide (1 M solution in CH_2Cl_2, 200 mL). After the addition the resulting mixture was warmed to room

Table III. Effect of BSA on Inhibition Constants (K_i, nM ± SEM) for Rat Adrenal AT_1 Receptors

BSA concentration	33	34	14	15	29	5
0.22%	40 000 ± 5000	24 400 ± 2800	2 200 ± 470	580 ± 150	NT[a]	NT
0.01%	3 450 ± 150	550 ± 74	137 ± 45	71 ± 24	46 ± 10	1.3 ± 0.5
0.00%	NT	NT	NT	NT	5.5 ± 2	0.4 ± 0.1

[a] NT = not tested.

temperature and stirred overnight. The reaction was quenched by adding slowly 100 mL of methanol at −78 °C, and the resulting mixture was poured into ice–water. Ethyl acetate (300 mL) was added to this mixture, and the organic layer was taken, washed with water, and dried over $MgSO_4$. Concentration of the solution *in vacuo* afforded a solid, which was triturated with ether to obtain **7** (11.5 g, 59% overall). Compound **6**: mp 81–82 °C; ^{1}H NMR ($CDCl_3$) δ 3.97 (s, 3 H), 7.12 (d, J = 8.8 Hz, 2 H), 7.47–7.86 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 55.3, 111.0, 114.1, 119.0, 127.0, 129.8, 130.0, 130.5, 132.7, 133.7, 145.2, 160.0. Compound **7**: mp 177–178 °C; ^{1}H NMR (DMSO-d_6) δ 6.91 (d, J = 8.8 Hz, 2 H), 7.42 (d, J = 8.8 Hz, 2 H), 7.45–7.77 (m, 3 H), 7.89 (d, J = 6.5 Hz, 1 H), 9.79 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 109.8, 115.5, 118.9, 127.4, 128.4, 129.8, 130.0, 133.4, 133.8, 144.7, 158.0. Anal. ($C_{14}H_{11}NO$) C, H, N.

4-[2-(1*H*-Tetrazol-5-yl)phenyl]phenol (8). A mixture of **7** (1.15 g, 5.9 mmol) and tri-*n*-butyltin azide (7.0 g, 21.0 mmol)[46] in xylene (20 mL) was stirred at 120 °C for 60 h and then at 130 °C for 4 h. The reaction mixture was cooled to room temperature and directly passed through a flash chromatography column on silica gel eluting with hexane/acetic acid (100:1, ca. 1 L) followed by ethyl acetate to afford **8** (0.68 g, 48%) as a solid: mp 230 °C dec; ^{1}H NMR (DMSO-d_6) δ 9.6 (br s, 2 H), 7.67–7.62 (m, 2 H), 7.53–7.48 (m, 2 H), 6.92 (d, J = 8.2 Hz, 2 H), 6.72 (d, 2 H); ^{13}C NMR (DMSO-d_6) δ 157.0, 155.2, 141.6, 131.0, 130.6, 130.4, 130.0, 129.8, 127.0, 123.2, 115.2. Anal. ($C_{13}H_{10}N_4O$) C, H, N.

3-Butyl-3,4-dihydro-2(1*H*)-quinoxalinone (9). A mixture of 1,2-phenylenediamine (10.8 g, 100 mmol), ethyl 2-bromohexanoate (22.3 g, 100 mmol), and potassium carbonate (13.8 g, 100 mmol) in DMF (50 mL) was stirred at room temperature overnight, and at 120 °C for 3 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by a flash column chromatography on silica gel eluting with hexane/ethyl acetate (3:1) to afford an oil, which was solidified upon standing at room temperature to give **9** (16.5 g, 81%): mp 90–91 °C; ^{1}H NMR ($CDCl_3$) δ 9.49 (s, 1 H), 6.89–6.64 (m, 4 H), 3.99 (s, 1 H), 3.90 (t, J = 4.7Hz, 1 H), 1.77 (m, 2 H), 1.36 (m, 2 H), 0.88 (t, J = 7.0Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.5, 132.9, 125.3, 123.7, 119.1, 115.4, 113.9, 56.3, 31.6, 27.4, 22.4, 13.9. Anal. ($C_{12}H_{16}N_2O$) C, H, N.

3-Butylquinoxalin-2(1*H*)-one (10). To a stirring solution of **9** (14.5 g, 71.0 mmol) in THF (150 mL) at 0 °C was added manganese dioxide (25 g, 270 mmol) in several portions. The resulting mixture was stirred at room temperature overnight. Dimethylformamide solvent (100 mL) was added to the reaction mixture, and it was filtered through a celite pad. Concentration *in vacuo* gave a solid, which was triturated with ether to obtain **10** (11.75 g, 82%): mp 153–154 °C; ^{1}H NMR ($CDCl_3$) δ 12.90 (s, 1 H), 7.97 (dd, J = 1.2, 7.1 Hz, 1 H), 7.66–7.41 (m, 3 H), 3.13 (t, J = 7.6 Hz, 2 H), 1.97 (qn, J = 7.6 Hz, 2 H), 1.64 (sx, J = 7.6 Hz, 2 H), 1.15 (t, J = 7.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 161.7, 156.8, 132.9, 130.9, 129.5, 128.6, 124.0, 115.7, 33.19, 29.0, 22.7, 14.0. Anal. ($C_{12}H_{14}N_2O$) C, H, N.

3-Butyl-2-chloroquinoxaline (11). A mixture of **10** (10.0 g, 49.5 mmol) and phosphorus oxychloride (50 mL) was heated at 125 °C for 2 h and was cooled to room temperature. The reaction mixture was slowly poured into a cold aqueous sodium bicarbonate solution (ca. 150 mL). The mixture was partitioned between CH_2Cl_2 (100 mL) and water. The organic layer was taken, and the aqueous layer was washed with CH_2Cl_2 (100 mL). The combined organic solution was dried over sodium sulfate and concentrated. The residue was purified by a flash chromatography column on silica gel eluting with 1% of ethyl acetate in hexane to afford **11** (9.5 g, 87%) as an oil: ^{1}H NMR ($CDCl_3$) δ 8.09–7.99 (m, 2 H), 7.79–7.73 (m, 2 H), 3.17 (t, J = 7.8 Hz, 2 H), 1.90 (qn, J = 7.8 Hz, 2 H), 1.55 (sx, J = 7.8 Hz, 2 H), 1.05 (t, J = 7.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 155.9, 147.5, 140.8, 140.6, 129.8, 129.7, 128.5, 127.9, 35.5, 29.7, 22.5, 13.8. Anal. ($C_{12}H_{13}N_2Cl$) C, H, N, Cl.

3-Butyl-2-chloroquinoxaline, 1-Oxide (12). To a solution of **11** (1.10 g, 5.0 mmol) in concentrated sulfuric acid (5 mL) at 0 °C was added potassium persulfate (1.58 g, 5.85 mmol) with stirring. The resulting mixture was stirred at room temperature for 24 h and was poured into a cold aqueous sodium acetate solution (50 mL). The product was extracted with ethyl acetate (3 × 20 mL), and the combined organic solution was dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by a flash chromatography column on silica gel eluting with hexane/ethyl acetate (10:1) to afford **12** (605 mg, 51%) as an oil: ^{1}H NMR ($CDCl_3$) δ 8.50 (dd, J = 1.2, 7.6 Hz, 1 H), 8.01 (dd, J = 1.4, 7.7 Hz, 1 H), 7.80–7.60 (m, 2 H), 3.09 (t, J = 8.2 Hz, 2 H), 1.84 (qn, J = 8.2 Hz, 2 H), 1.50 (sx, J = 8.2 Hz, 2 H), 1.00 (t, J = 8.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 157.2, 141.9, 136.1, 134.4, 131.3, 129.5, 129.3, 118.6, 36.0, 29.5, 22.3, 13.7. Anal. ($C_{12}H_{13}N_2OCl$) C, H, N, Cl.

3-Butyl-2-[[2′-1*H*-tetrazol-5-yl[1,1′-biphenyl]-4-yl]oxy]quinoxaline, 1-Oxide (3). A mixture of **12** (185 mg, 0.78 mmol), **8** (186 mg, 0.78 mmol) and cesium carbonate (500 mg, 1.53 mmol) in DMF (1.5 mL) was stirred at room temperature for 24 h under argon atmosphere. The reaction mixture was poured into water, and the aqueous solution was adjusted to pH 4 with acetic acid. The product was extracted with ethyl acetate (3 × 20 mL). The combined organic solution was dried over sodium sulfate and concentrated *in vacuo*, and the residue was purified by preparative HPLC (YMC S-10 ODS column, 30 × 500 nm, eluting with 35 mL/min of 76% aqueous methanol containing 0.1% trifluoroacetic acid). Fractions were monitored by UV absorbance at 254 nm, those containing the major product (t_R 25 min) were combined and concentrated *in vacuo* to afford **3** (212 mg, 62%) as a solid: mp 100–104 °C; ^{1}H NMR ($CDCl_3$) δ 8.31 (d, J = 8.2 Hz, 1 H), 8.10 (d, J = 8.2 Hz, 1 H), 7.87–7.34 (m, 6 H), 6.98 (d, J = 8.2 Hz, 2 H), 6.72 (d, J = 8.2 Hz, 2 H), 3.00 (t, J = 7.6 Hz, 2 H), 1.79 (qn, J = 7.6 Hz, 2 H), 1.41 (sx, J = 7.6 Hz, 2 H), 0.92 (t, J = 7.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.8, 154.4, 145.9, 141.7, 135.8, 135.1, 131.2, 130.9, 130.8, 130.7, 130.1, 129.4, 128.0, 122.9, 118.3, 115.7, 33.4, 29.9, 22.5, 13.8; MS (FAB) 439(M + H)$^+$, 423(M + H − O)$^+$. Anal. ($C_{25}H_{22}N_6O_2$·0.13H_2O) C, H, N.

3-Butyl-2-[(2′-cyanobiphenyl-4-yl)oxy]quinoxaline (13). A mixture of **11** (2.0 g, 9.1 mmol), **7** (1.77 g, 9.1 mmol), and cesium carbonate (5 g, 15.4 mmol) in DMF (10 mL) was stirred at 60 °C for 3 h, and the solid was filtered. The filtrate was concentrated *in vacuo*, and the residue was triturated with ether to afford **13** (2.35 g, 68%) as a solid: mp 136–137 °C; ^{1}H NMR ($CDCl_3$) δ 8.13 (m, 1 H), 7.92–7.50 (m, 11 H), 3.28 (t, J = 7.6 Hz, 2 H), 2.03 (qn, 2 H), 1.65 (sx, 2 H), 1.13 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ 155.5, 153.5, 151.5, 144.7, 139.2, 134.9, 133.8, 132.8, 130.7, 130.0, 129.1, 128.2, 127.6, 127.3, 127.2, 121.8, 118.7, 111.2, 33.6, 29.9, 22.7, 13.9. Anal. ($C_{25}H_{21}N_3O$) C, H, N.

3-Butyl-2-[[2′-1*H*-tetrazol-5-yl[1,1′-biphenyl]-4-yl]oxy]quinoxaline (14). A mixture of **13** (1.50 g, 3.96 mmol) and tri-*n*-butyltin azide (2.63 g, 7.92 mmol) in xylene (10 mL) was stirred at 130 °C for 48 h. The reaction mixture was cooled to room temperature, and it was directly passed through a flash chromatography column on silica gel eluting with hexane/ethyl acetate (5:1) followed by hexane/ethyl acetate/acetic acid (2:1:0.01) to afford **14** (1.22 g, 73%) as a solid: mp 144–145 °C; ^{1}H NMR ($CDCl_3$) δ 8.12 (d, J = 7.6 Hz, 1 H), 7.96 (dd, J = 2.8, 7.6 Hz, 1 H), 7.77–7.49 (m, 6 H), 7.24 (m, 4 H), 3.18 (t, J = 7.6 Hz, 2 H), 1.94 (qn, 2 H), 1.58 (sx, 2 H), 1.07 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ 155.8, 153.2, 151.7, 144.3, 140.6, 139.6, 139.0, 136.4, 131.7, 131.1, 131.0, 130.5, 129.8, 128.7, 128.1, 127.9, 127.2, 122.8, 122.5, 33.6, 30.2, 23.0, 14.2. Anal. ($C_{25}H_{22}N_6O$·0.59H_2O) C, H, N.

2-Butyl-3-[[2′-1*H*-tetrazol-5-yl[1,1′-biphenyl]-4-yl]oxy]quinoxaline, 1-Oxide (15). A mixture of **14** (406 mg, 0.96 mmol) and *m*-chloroperoxybenzoic acid (415 mg, 80–85% content) in CH_2Cl_2 (5 mL) was stirred at room temperature for 90 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by a flash chromatography column on silica gel eluting with hexane/ethyl acetate/acetic acid (1:1:0.01) to afford **15** (302 mg, 72%) as a solid: mp 190–191 °C; ^{1}H NMR (DMSO-d_6) δ 8.40 (d, J = 8.2 Hz, 1 H), 7.80–7.58 (m, 7 H), 7.30 (d, J = 8.8 Hz, 2 H), 7.21 (d, J = 8.8 Hz, 2 H), 3.15 (t, J = 7.6 Hz, 2 H), 1.72 (q, J = 7.6 Hz, 2 H), 1.43 (sx, J = 7.6 Hz, 2 H), 0.95 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (DMSO-d_6) δ 157.8, 152.2, 140.7, 139.2, 136.5, 136.3, 134.4, 131.3, 131.1, 130.6, 130.1, 127.8, 123.4, 121.4, 118.4, 26.8, 24.2, 22.3, 13.7. Anal. ($C_{25}H_{22}N_6O_2$·0.12 H_2O) C, H, N.

Ethyl 2,6-Difluorobenzoate (17). A neat liquid of 2,6-difluorobenzoyl chloride (25.0 g, 141.7 mmol, from Aldrich) was added slowly to a cold ethanol (250 mL) at ice bath temperature with stirring. The reaction mixture was stirred for 30 min at ice bath temperature and for 30 min at room temperature. It was concentrated *in vacuo* to obtain **17** (25.2 g, 96%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.49 (t, J = 7.0 Hz, 3 H), 4.55 (q, J = 7.0 Hz, 2 H), 7.05 (t, J = 8.2 Hz, 2 H), 7.45–7.55 (m, 1 H); ^{13}C NMR ($CDCl_3$)

δ 13.9, 61.9, 111.7 (d, J = 25.5 Hz), 132.3, 132.5 (d, J = 10.0 Hz), 160.4 (d, J = 256.3 Hz), 162.4.

Ethyl 2,6-Difluoro-3-nitrobenzoate (18). To cold concentrated nitric acid (1.2 g) at ice bath temperature concentrated sulfuric acid (1.6 mL) was added slowly. After the mixture stirred for 5 min, compound 17 (1.1 g, 5.9 mmol) was added, and the reaction mixture was warmed to room temperature. After 30 min, the reaction mixture was poured into an ice–water (30 mL) and the product was extracted with CH_2Cl_2 (60 mL). The organic solution was washed with aqueous sodium bicarbonate, dried voer $MgSO_4$, and concentrated *in vacuo* to obtain pure product 18 (1.28 g, 94%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.49 (t, J = 7.0 Hz, 3 H), 4.56 (q, J = 7.0 Hz, 2 H), 7.24 (t, J = 8.0 Hz, 1 H), 8.3 (m, 1 H). Anal. ($C_9H_7NO_4F$) C, H, N, F.

Ethyl 2-Amino-6-fluoro-3-nitrobenzoate (19). To a solution of compound 18 (25.0 g, 108 mmol) in ethanol (250 mL) at room temperature was added a solution of ammonium hydroxide (5 mL of 29% solution). Upon addition of ammonium hydroxide, yellow color developed instantaneously and the solid started to precipitate slowly out of the solution. After 4 h additional ammonium hydroxide solution (4 mL) was added and the reaction mixture was stirred overnight. Most of the solvent was removed *in vacuo*, and the residue was triturated with 2-propanol. The solid was filtered, washed with water (50 mL), and dried to obtain 19 (20.0 g, 81%) as a yellow solid: mp 75–77 °C; ^{1}H NMR (DMSO-d_6) δ 1.32 (t, J = 7.0 Hz, 3 H), 4.37 (q, J = 7.0 Hz, 2 H), 6.64 (t, J = 9.4 Hz, 1 H), 8.11 (br s, 2 H), 8.33 (dd, J = 9.4, 6.9 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 14.2, 62.1, 104.1 (d, J = 27.4 Hz), 105.1 (d, J = 15.7 Hz), 129.3, 132.9 (d, J = 15.7 Hz), 147.1 (d, J = 7.9 Hz), 164.3 (d, J = 23.5 Hz), 164.3. Anal. ($C_9H_9N_2O_4F$) C, H, N, F.

Ethyl 2-Amino-6-ethoxy-3-nitrobenzoate (20, R = OEt). Sodium hydride (1.48 g, 37.0 mmol, 60% dispersion) was added in small portions to a cold ethanol (50 mL) at ice bath temperature. When the gas evolution ceased, fluoro compound 19 (6.84 g, 30.0 mmol) was added to the cold ethoxide solution. After 40 min, additional ethanol (30 mL) was added because the mixture became too thick to stir. The mixture was warmed to room temperature and stirred for 1 h. To the reaction mixture was added 1 N HCl (45 mL), and it was stirred for 5 min. The precipitated solid was filtered, washed with water, and dried to obtain compound 20 (6.40 g, 84%) as a yellow solid: mp 68–70 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (t, J = 7.0 Hz, 3 H), 1.45 (t, J = 7.0 Hz, 3 H), 4.15 (q, J = 7.0 Hz, 2 H), 4.40 (q, J = 7.0 Hz, 2 H), 6.28 (d, J = 10.0 Hz, 1 H), 7.74 (br s, 1 H), 8.27 (d, J = 10.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.5, 61.2, 65.1, 101.2, 105.4, 127.2, 131.8, 147.4, 164.8, 167.3. Anal. ($C_{11}H_{14}N_2O_5$) C, H, N.

Ethyl 2,3-Diamino-6-ethoxybenzoate (21, R = OEt). The reduction of nitro compound 20 (7.80 g, 30.7 mmol) in ethyl acetate (150 mL) was carried out under 50 psi of hydrogen gas in the presence of 5% Pd–C (1.2 g) for 3 h. The catalyst was filtered through a Celite pad and washed with chloroform, and the filtrate solution was concentrated *in vacuo* to obtain diamino compound 21 (6.72 g, 100%) as a viscous material. This product was used directly for the next step: ^{1}H NMR ($CDCl_3$) δ 1.37 (t, J = 7.0 Hz, 3 H), 1.38 (t, J = 7.0 Hz, 3 H), 3.95 (q, J = 7.0 Hz, 2 H), 3.95 (br s, 4 H), 4.38 (q, J = 7.0 Hz, 2 H), 6.18 (d, J = 8.8 Hz, 1 H), 6.71 (d, J = 8.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.9, 60.6, 65.1, 102.4, 106.7, 120.7, 126.9, 140.2, 153.6, 168.5.

2-Butyl-6-ethoxy-5-(ethoxycarbonyl)-1,2-dihydroquinoxalin-3(4*H*)-one (22, R = OEt). A mixture of 21 (6.70 g, 29.9 mmol), ethyl 2-bromohexanoate (6.70 g, 30.0 mmol), and sodium bicarbonate (2.6 g) in DMF (100 mL) was purged with argon gas for a few minutes, and it was heated at 90 °C for 6 h, at 130 °C overnight, and at 145 °C for 4.5 h. Most of the solvent was removed *in vacuo*, and the residue was passed through a flash column on silica gel eluting with hexane/ethyl acetate (3:1) to obtain product 22 (7.20 g, 75%) as a yellow solid: mp 68–70 °C; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.6 Hz, 3 H), 1.36–1.80 (m, 12 H), 3.78 (dd, J = 8.2, 4.7 Hz, 1 H), 3.98 (q, J = 7.0 Hz, 2 H), 4.38 (J = 7.0 Hz, 2 H), 6.50 (d, J = 8.8 Hz, 1 H), 6.76 (d, J = 8.8 Hz, 1 H), 9.50 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.1, 14.8, 56.0, 61.3, 65.7, 107.4, 108.5, 117.8, 127.2, 127.6, 152.2, 167.0, 168.6. Anal. ($C_{17}H_{24}N_2O_4$) C, H, N.

2-Butyl-6-ethoxy-(5-ethoxycarbonyl)quinoxalin-3(4*H*)-one (23, R = OEt). A mixture of compound 22 (6.50 g, 20.3 mmol) and manganese dioxide (12.0 g) in THF (60 mL) was heated at reflux temperature overnight. The solid was filtered through a Celite pad and washed with ethyl acetate, and the filtrate solution was concentrated *in vacuo*. The residue was triturated with ether to obtain compound 23 (5.20 g, 80%) as a beige-colored solid: mp 123–125 °C; ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.6 Hz, 3 H), 1.50 (m, 8 H), 1.75 (qn, J = 7.6 Hz, 2 H), 2.85 (d, J = 7.6 Hz, 1 H), 2.88 (d, J = 7.6 Hz, 1 H), 4.21 (q, J = 7.0 Hz, 2 H), 4.43 (q, J = 7.0 Hz, 2 H), 6.90 (d, J = 9.4 Hz, 1 H), 7.85 (d, J = 9.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.2, 14.7, 22.7, 28.9, 33.0, 61.7, 65.4, 103.1, 108.6, 127.0, 134.1, 159.7, 160.6, 167.1. Anal. ($C_{17}H_{22}N_2O_4$) C, H, N.

2-Butyl-6-ethoxy-5-(hydrocarbonyl)quinoxalin-3(4*H*)-one (24, R = OEt). A mixture of 23 (2.11 g, 6.9 mmol), powdered NaOH solid (1.7 g, 42.5 mmol), and 18-crown-6-ether (200 mg, 0.75 mmol) in toluene (40 mL) was heated at reflux temperature for 4 h. The reaction mixture was cooled, and the product was extracted with H_2O (2 × 50 mL). The extracted aqueous solution was acidified with 4 N aqueous HCl to pH 2. The precipitated solid was collected, washed with H_2O and dried to obtain 24 (1.76 g, 92%) as a white solid, which was used directly for next reaction. The product can be recrystallized from ethanol: mp 168–169 °C; ^{1}H NMR (DMSO-d_6) δ 13.44 (br s, 1 H), 11.68 (s, 1 H), 7.79 (d, J = 8.8 Hz, 1 H), 7.07 (d, J = 8.8 Hz, 1 H), 4.20 (q, J = 6.5 Hz, 2 H), 2.74 (t, J = 7.6 Hz, 2 H), 1.66 (qn, J = 7.6 Hz, 2 H), 1.38 (m, 5 H), 0.93 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (DMSO-d_6) δ 167.3, 158.7, 158.3, 154.1, 132.6, 126.3, 108.8, 64.9, 32.7, 28.1, 22.0, 14.5, 13.8. Anal. ($C_{15}H_{18}N_2O_4$) C, H, N.

2-Butyl-3-chloro-6-ethoxyquinoxaline-5-carboxylic Acid (26, R = OEt). A solution of 24 (1.4 g, 4.8 mmol) in phosphorous oxychloride (10 mL) was heated at reflux temperature for 1 h. Most of the excess phosphorous oxychloride was removed under reduced pressure. The residue was poured into ice–water (100 mL). The product was extracted with ethyl acetate (3 × 20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with $CHCl_3$ containing 1% acetic acid to afford 26 (980 mg, 66%) as a solid: mp 147–148 °C; ^{1}H NMR ($CDCl_3$) δ 8.18 (d, J = 9.4 Hz, .1 H), 7.62 (d, J = 9.4 Hz, 1 H), 4.41 (q, J = 6.4 Hz, 2 H), 3.13 (t, J = 7.6 Hz, 2 H), 1.84 (qn, J = 7.6 Hz, 2 H), 1.58 (t, J = 6.4, Hz, 3 H), 1.50 (sx, J = 7.6 Hz, 2 H), 1.00 (t, J = 7.6 Hz, 3 H). Anal. ($C_{15}H_{17}N_2O_3Cl$) C, H, N, Cl.

2-Butyl-6-ethoxy-3-[[2′-1*H*-tetrazol-5-yl[1,1-biphenyl]-4-yl]oxy]-5-quinoxalinecarboxylic Acid (30, R = Et). A mixture of 26 (0.86 g, 2.79 mmol), 8 (0.70 g, 2.94 mmol) and cesium carbonate (3.25 g, 10.0 mmol) in DMF (15 mL) was stirred at 70 °C overnight. The reaction mixture was cooled, diluted with H_2O (100 mL), and acidified with 1 N aqueous HCl. The product was extracted with ethyl acetate (3 × 50 mL), dried over Na_2SO_4, and concentrated. The residue was purified by a flash chromatography column on silica gel eluting with 0.4% acetic acid in ethyl acetate to afford 30 (1.20 g, 84%) as a solid: mp 137–146 °C; ^{1}H NMR (DMSO-d_6) δ 8.01 (dd, J = 8.2, 1.2 Hz, 1 H), 7.77–7.53 (m, 5 H), 7.40 (d, J = 7.6 Hz, 2 H), 7.20 (d, J = 7.6 Hz, 2 H), 4.25 (q, J = 7.0 Hz, 2 H), 3.04 (t, J = 7.6 Hz, 2 H), 1.83 (qn, J = 7.6 Hz, 2 H), 1.44 (sx, J = 7.6 Hz, 2 H), 1.34 (t, J = 7.0 Hz, 3 H), 0.97 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (DMSO-d_6) δ 166.6, 154.7, 152.1, 148.9, 140.7, 136.2, 135.8, 133.6, 131.2, 130.7, 129.8, 129.5, 127.8, 120.6, 119.6, 115.1, 74.8, 32.3, 28.9, 22.0, 14.7, 13.8; MS (FAB) 511 (M + H)$^+$. Anal. ($C_{28}H_{26}N_6O_4 \cdot 0.40H_2O$) C, H, N.

2-Butyl-6-ethoxy-3-[[2′-1*H*-tetrazol-5-yl[1,1′-biphenyl]-4-yl]oxy]-5-quinoxalinecarboxylic Acid, 1-oxide (5, R = OEt). A mixture of 30 (0.9 g, 1.76 mmol) and *m*-chloroperoxybenzoic acid (0.6 g, 80–85% content) in CH_2Cl_2 (10 mL) was stirred at room temperature for 16 h. It was concentrated, and the residue was chromatographed on silica gel eluting with ethyl acetate containing 1% acetic acid to afford a solid, which was triturated with diisopropyl ether to obtain 5 (510 mg, 55%) as a solid: mp 169–171 °C; ^{1}H NMR ($CDCl_3$) δ 8.50 (d, J = 10 Hz, 1 H), 8.00 (d, J = 7.2 Hz, 1 H), 7.64–7.49 (m, 3 H), 7.29 (m, 3 H), 7.18 (d, J = 8.2 Hz, 2 H), 4.28 (q, J = 7.6 Hz, 2 H), 3.26 (t, J = 7.6 Hz, 2 H), 1.80 (qn, J = 7.6 Hz, 2 H), 1.48 (m, 5 H), 1.02 (t, J = 7.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.5, 161.1, 159.5, 155.0, 152.3, 140.2, 138.5, 137.6, 135.2, 131.3, 131.1, 130.9, 130.6, 129.4, 123.1,

122.8, 115.0, 65.9, 27.3, 24.3, 22.9, 14.6, 13.8; MS(FAB) 527 (M + H)$^+$. Anal. ($C_{28}H_{26}N_6O_5 \cdot 0.09H_2O$) C, H, N.

2-Methyl-1-(1-oxopropoxy)propyl 2-Butyl-6-ethoxy-3-[[2'-1*H*-tetrazol-5-yl[1,1'-biphenyl]-4-yl]oxy]-5-quinoxalinecarboxylate (31, R = Et). A mixture of acid **30** (650 mg, 1.27 mmol), silver oxide (1.50 g, 6.47 mmol), and activated 4A molecular sieves powder (1.0 g) in THF (10 mL) was stirred for 5 min at room temperature. To this mixture was added 1-chloro-2-methylpropyl propionate (0.25 g, 1.52 mmol) and the reaction mixture was heated at 65 °C for a total of 18 h, during which additional 1-chloro-2-methylpropyl propionate (2 × 0.30 g, 3.65 mmol) was added after 1.5 and 6.0 h, respectively. Ethyl acetate (150 mL) and aqueous HCl (30 mL of 1 N solution) were then added to the reaction mixture, and the mixture was stirred for 5 min, filtered through a Celite pad, and washed with ethyl acetate. The organic layer was taken from the filtrate, the aqueous layer was extracted again with ethyl acetate (30 mL), and the combined organic solution was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative TLC (EM Kiesegel 60, 20-cm × 20-cm × 2-mm TLC plates), eluting with hexane/ethyl acetate/ethanol (300:100:50) to obtain **31** (380 mg, 47%) as a glassy material: ^{1}H NMR ($CDCl_3$) δ 0.85–1.55 (m, 16 H), 1.84 (qn, J = 7.6 Hz, 2 H), 2.05 (sx, J = 7.6 Hz, 2 H), 2.30 (q, J = 7.6 Hz, 2 H), 3.05 (t, J = 7.6 Hz, 2 H looks like 2 doublets), 4.20 (m, 2 H, looks like two quartets), 6.94 (d, J = 5.3 Hz, 1 H), 7.15–8.00 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 8.8, 13.9, 14.7, 16.0, 16.5, 22.6, 27.4, 29.8, 31.5, 33.1, 65.1, 93.3, 114.0, 117.0, 121.7, 123.0, 127.9, 130.0, 130.7, 131.0, 134.0, 135.9, 137.5, 140.5, 149.5, 152.4, 155.8, 156.1, 164.3, 173.1.

2-Methyl-1-(1-oxopropoxy)propyl 2-butyl-6-ethoxy-3-[[2'-1*H*-tetrazol-5-yl[1,1'-biphenyl]-4-yl]oxy]-5-quinoxalinecarboxylate 1-Oxide (32, R = Et). A mixture of double ester **31** (385 mg, 0.60 mmol) and *m*-chloroperoxybenzoic acid (165 mg, 80–85% content) in CH_2Cl_2 (5 mL) was stirred at room temperature overnight. The solid was filtered, and the filtrate solution was directly passed through a preparative HPLC (YMC S-10 ODS column, 30 × 500 mm, eluting with 35 mL/min of 80% aqueous methanol containing 0.1% trifluoroacetic acid). Fractions were monitored by UV absorbance at 254 nm, those containing the major product (retention time 35 min) were combined and concentrated to give **32** (179 mg, 45%) as a white hydrated solid: mp 80–85 °C; ^{1}H NMR (CD_3OD) δ 0.83 (t, J = 7.6 Hz, 6 H, looks like two doublets), 1.09 (t, J = 7.6 Hz, 3 H), 1.16 (t, J = 7.6 Hz, 3 H), 1.48 (t, J = 6.4 Hz, 3 H), 1.58 (sx, J = 8.0 Hz, 2 H), 1.85 (m, 3 H, qn for 2 H + hep for 1 H), 2.40 (q, J = 7.6 Hz, 2 H, looks like two quartets), 3.30 (t, J = 7.6 Hz, 2 H), 4.34 (q, J = 7.0 Hz, 2 H), 6.79 (d, J = 4.7 Hz, 1 H), 7.32 (q, J = 6.5 Hz, 4 H), 7.55 (d, J = 9.4 Hz, 1 H), 7.68–7.84 (m, 4 H), 8.53 (d, J = 9.4 Hz, 1 H); ^{13}C NMR (CD_3OD) δ 9.2, 15.1, 16.5, 17.0, 23.9, 24.2, 25.5, 28.2, 28.4, 32.7, 66.6, 94.6, 115.6, 119.5, 122.4, 122.5, 124.3, 129.1, 130.3, 131.3, 131.8, 132.1, 132.6, 137.6, 137.8, 139.3, 142.6, 153.7, 158.8, 159.6, 165.3, 173.8; MS 655 (M + H)$^+$, 639 (M + H − O)$^+$. Anal. ($C_{35}H_{38}N_6O_7 \cdot 0.69H_2O$) C, H, N.

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