SYNTHESIS OF N-ALKYL-1,2,4-OXADIAZINONES AS ANGIOTENSIN-II (AT_1) RECEPTOR ANTAGONISTS

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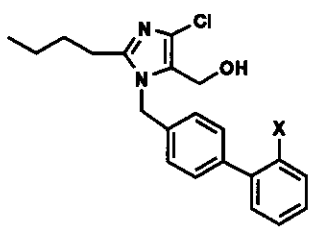
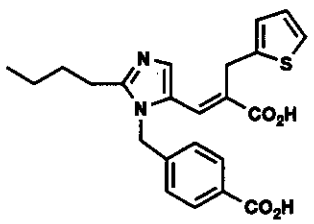
Abstract- 4-Alkyl-1,2,4-oxadiazinones were prepared by regiospecific alkylation of the corresponding 4H-oxadiazinones, which were synthesized by a trimethylaluminum mediated cyclization reaction. Alkylation was regiospecific and generally facile; in one example, however, an unusual fragmentation reaction occurred. A homochiral oxadiazineone was also prepared and alkylated under the described conditions. 4-Biphenylmethyl-1,2,4-oxadi-azinones were potent angiotensin-II receptor antagonists.

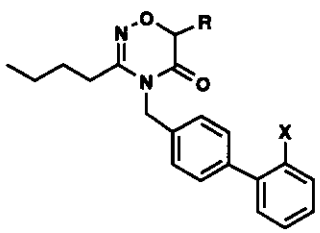
In the course of our research into preparation of novel angiotensin-II receptor antagonists, we sought to identify bioisosteric heterocycles to replace the imidazole ring in prototype antagonists such as Exp-7711,[1] DuP-753,[1] and SKF 108,566.[2] Alkyl-(4H)-1,2,4-oxadiazin-5-ones, exemplified by **1**, appeared to be attractive targets and have not been previously reported in the literature. An obvious synthetic approach to such targets would be N-alkylation of the parent heterocycles. The literature states, however, that the 1,2,4-oxadiazinone ring "appears to have acidic properties but is resistant to alkylation or acylation",[3] and even if alkylation were to be achieved questions of regiochemistry would remain to be addressed. We have overcome these difficulties and now report an improved synthesis of 4H-1,2,4-oxadiazinones and their regiospecific 4-alkylation, resulting in a series of novel and potent angiotensin-II receptor antagonists. In addition, we report synthesis of a homochiral 1,2,4-oxadiazinone.



EXP-7711 (X = CO_2H)
DuP-753 (X = tetrazole)



SKF-108,566



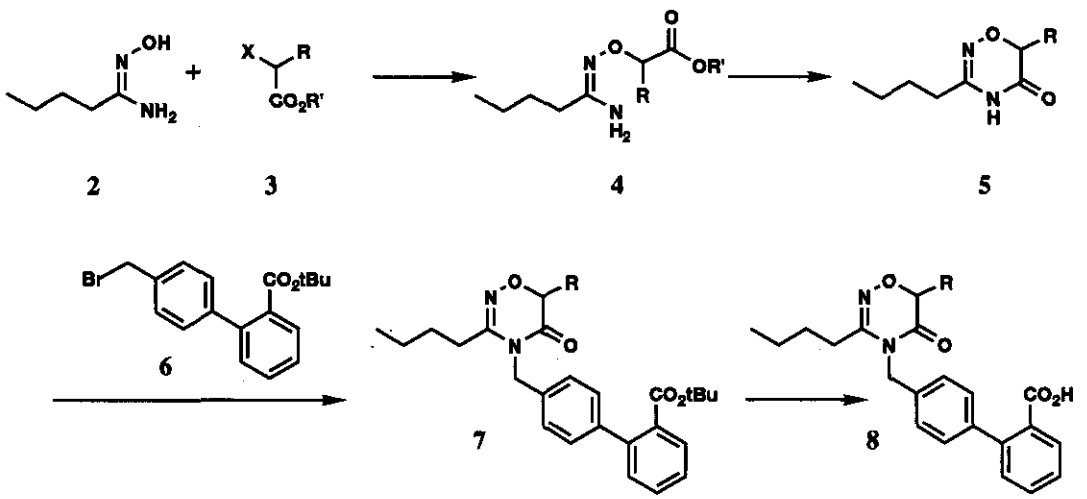
1

Oxadiazinones have been prepared by reaction of amidoximes with α-halo acid chlorides[4] or α-halo esters.[5] In our hands, reaction of amidoxime (**2**)[7]with α-bromoesters (**3**) led smoothly to the O-alkyl ester intermediates (**4**),

but subsequent ring closure was often sluggish even at elevated temperatures. Addition of trimethylaluminum to the crude ester intermediate, however, led to rapid ring closure at room temperature.[6] Thus, reaction of amidoxime (**2**) with α-bromo esters (**3**) in dimethylformamide containing excess potassium or cesium carbonate, followed by treatment of the crude product mixture with trimethylaluminum in dichloromethane led to oxadiazinones (**5a-e**) in generally good yield (Table 1 and Scheme 1). Example (**5d**) gave a low yield due to competing elimination reactions leading to cinnamates. The homochiral example (**5f**) was prepared by reaction of **2** with ethyl 2-(R)-trifluoromethanesulfonyloxy-4-phenyl butyrate[8] with presumed inversion.[9] The enantiomer ratio of **5f** was determined by chiral hplc to be greater than 96 to 4.

Reaction of oxadiazinones (**5a-f**) with biphenyl bromide (**6**)[10] in the presence of potassium or cesium carbonate in dimethylformamide gave smooth alkylation, leading to products (**7**). Esters (**7a, 7b, and 7d-f**) were isolated as viscous oils, characterized spectroscopically, then converted directly to the desired carboxylic acids (**8**) by treatment with trifluoroacetic acid (Scheme 1). The acids were purified by preparative hplc, lyophilized, and obtained as hygroscopic solids. The enantiomer ratio determined by chiral phase hplc for **8f** was the same as for **5f**, thus epimerization of the chiral center does not occur during alkylation.

Scheme 1



In the case of the phenyl substituted example (**5c**), fragmentation took place under alkylation conditions to give keto amide (**9**) as the only isolated product (75%). We initially assumed that fragmentation was due to the enhanced acidity of the α-hydrogen atom in **7c** resulting from stabilization of the corresponding anion by the adjacent phenyl ring. If this were so, then treatment of **7a**, **7b**, or **7d-f** with stronger base should result in similar fragmentation. Treatment of **7e** with lithium diisopropylamide at 25°C led to a highly colored species, but **7e** was recovered intact after aqueous workup. Attempted alkylation (MeI) or deuteration (DCl/D_2O) of the presumed

anion failed. Treatment of **5c** with cesium carbonate in dimethylformamide (e.g., in the absence of alkylating agent (**6**)) failed to give fragmentation, and the starting material was recovered intact. Further studies will be required to elucidate the scope and mechanism of this unusual fragmentation reaction.

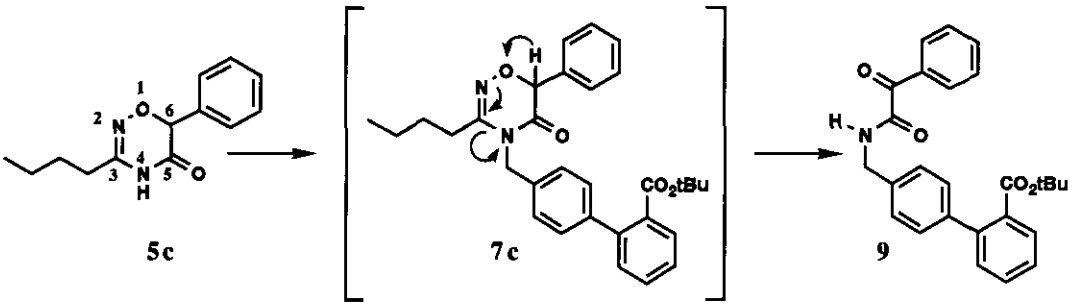
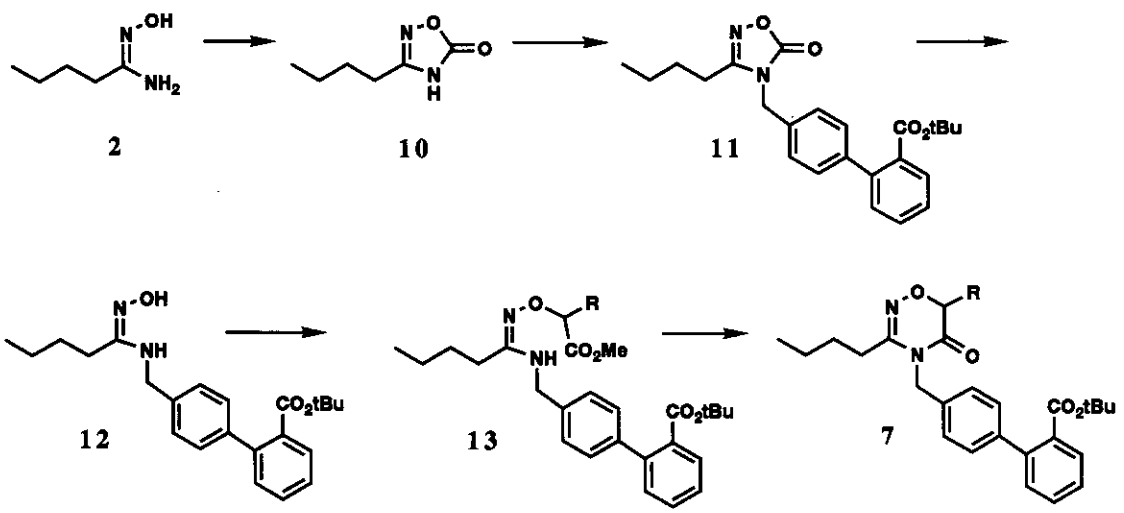


Table 1: Preparation and Alkylation of Oxadiazinones

Entry	X	R	R'	Yield of 5	Yield of 7	Yield of 8
a	**Br**	**H**	**Methyl**	**71%**	**55%**	**60%**
b	**Br**	**Methyl**	**Ethyl**	**48%**	**78%**	**54%**
c	**Br**	**Phenyl**	**Methyl**	**64%**	**--**	**--**
d	**Br**	**Benzyl**	**Ethyl**	**20%**	**58%**	**86%**
e	**Br**	**(+/-)-Phenylethyl**	**Ethyl**	**57%**	**81%**	**81%**
f	**(R)-OSO_2CF_3**	**(S)-Phenylethyl**	**Ethyl**	**56%**	**68%**	**82%**

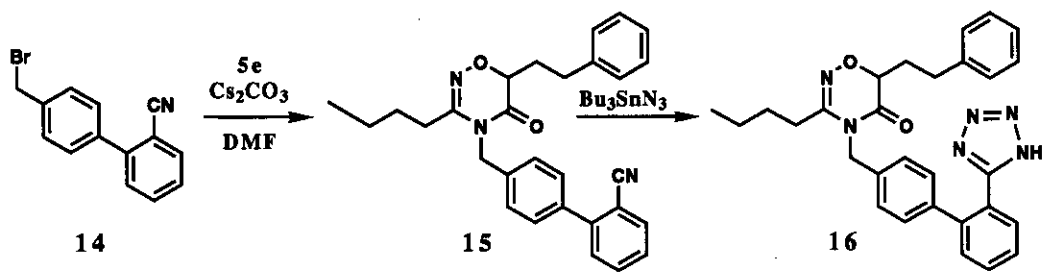
The high yield obtained for **9** suggests that alkylation of **5c** is predominantly at N_4 (rather than N_2) of the oxadiazinone. For the other examples (**a**, **b**, and **d-f**) a single N-alkyl regioisomer was obtained. Regiochemistry was proven for the series by unambiguous synthesis of **7a** and **7e** from the corresponding N-alkylamidoxime (**12**), prepared using known methodology[11] (Scheme 2). The final cyclization step (**13** -->**7**) proceeds in poor yield for the N-alkyl derivatives (**13**), possibly due to a poor equilibrium population of N-alkylamidoxime regioisomers.

Scheme 2



In the biphenylmethylimidazole series, replacement of the carboxylic acid group (e.g., **EXP-7711**) with a tetrazole group (e.g., **DuP-753**) leads to improved angiotensin II receptor affinity (Table 2).[1] We thus prepared biphenylmethyltetrazole (**16**) by alkylation of **5e** with biphenylmethyl nitrile (**14**), followed by conversion of the nitrile to tetrazole by reaction with tributyltin azide[12] (Scheme 3).

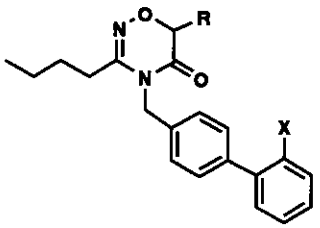
Scheme 3



Biphenylmethyloxadiazinones were evaluated for binding to angiotensin II AT_1 receptors from rat adrenal cortex (K_i) and for functional antagonism of angiotensin induced contraction of rabbit aorta (K_B). Results shown in Table 2 indicate that receptor affinity and functional antagonism increase with increased steric bulk of the 6-position substituent (**R**). Since the racemic phenylethyl analog (**8e**) and its homochiral counterpart (**8f**) do not have the same biological activity, we believe the effect of the substituent **R** to be the result of a specific receptor interaction

rather than of lipophilicity alone. The most potent carboxylic acid analog (**8e**) displays receptor binding affinity and functional antagonism equal to or better than the prototype carboxylic acid **EXP-7711**. Replacement of the carboxylic acid group with the tetrazole group (**16**) leads to improvement in receptor affinity, but not in functional antagonism.

Table 2: Biological Activity of Biphenylmethyl Oxadiazinones



Compound	R	X	K_i (nM)	K_B (nM)
8a	**H**	**CO_2H**	**6,200 ± 1,200**	**290 ± 16**
8b	**Methyl**	**CO_2H**	**720 ±120**	**220 ± 65**
8d	**Benzyl**	**CO_2H**	**790 ± 240**	**98 ±42**
8e	**(+/-)-Phenylethyl**	**CO_2H**	**50 ± 9**	**27 ± 8**
8f	**(S)-Phenylethyl**	**CO_2H**	**420 ± 33**	**170 ± 31**
16	**(+/-)-Phenylethyl**	**tetrazole**	**16 ± 2.5**	**70 ± 34**
EXP-7711	**--**	**CO_2H**	**95 ± 15**	**86 ± 4.4**
DuP 753	**--**	**tetrazole**	**5.7 ± 0.6**	**2.6 ± 0.13**

In conclusion, we have described an improved synthesis of oxadizinones and their regiospecific N-alkylation, leading to novel and potent angiotensin II (AT_1) antagonists.

EXPERIMENTAL

General. All new compounds were homogeneous by thin layer chromatography and reversed-phase hplc. Except as noted, extracts were dried over magnesium sulfate prior to concentration. Flash chromatography was carried out on E. Merck Kieselgel 60 silica gel (240-400 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 ppm downfield from an internal tetramethylsilane standard. Melting points are uncorrected.

Radioligand binding studies were performed using rat adrenal cortical membranes prepared as described by Chiu *et al.*[13] Binding experiments were performed essentially as described[13] using [^{125}I] Sar^{1}Ile^{8} angiotensin-II as the radioligand. The BSA concentration was reduced in some cases to 0.01% to attenuate drug binding to BSA.[14] Contractile responses in rabbit aorta were determined as described elsewhere.[15]

General Procedure for Preparation of Oxadiazinones. 3-Butyl-4H-1,2,4-oxadiazin-5(6H)-one (5a). Methyl bromoacetate (1.42 ml, 15.0 mmol) was added to a mixture of amidoxime **2** (1.16 g, 10 mmol)[7] and cesium carbonate (6.5 g, 20 mmol) in dimethylformamide (50 ml). The mixture was stirred at 25°C for 18 h, after which it was poured into water (300 ml), extracted with ethyl acetate (3 x 200 ml), dried, and concentrated in vacuo to provide crude (**4a**) as an amber oil. The oil was dissolved in dichloromethane (150 ml) under argon, and a solution of trimethylaluminium in hexane (25 ml of a 2.0 M solution, 50 mmol) was added. The resulting mixture was stirred for 6 h, after which it was poured into cold 0.5 N hydrochloric acid (300 ml), and extracted with dichloromethane (3 x 300 ml). The crude extract was purified using flash chromatography (200 g of silica gel eluted with 3:1 hexane : ethyl acetate); fractions containing the major product were combined and concentrated in vacuo. The residue was triturated with ether to give **5a** as white shiny flakes, 1.11 g (71 %), mp 51-52°C; nmr (δ, ppm, $CDCl_3$): 0.92 (3H, t, J = 7 Hz), 1.38 (2H, m), 1.62 (2H, m), 2.40 (2H, t, J = 7 Hz), 4.30 (2H, s); ^{13}C nmr (δ, ppm, $CDCl_3$): 13.2, 21.7, 27.4, 29.9, 66.1, 152.9, 166.6; ms: (M+H)/z = 157. Anal. Calcd for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.74; N, 17.94. Found: C, 53.93; H, 8.03; N, 18.00.

3-Butyl-6-methyl-4H-1,2,4-oxadiazin-5(6H)-one (5b). This compound was obtained as white flakes (48%), mp 80-81°C; nmr (δ, ppm, $CDCl_3$): 0.85 (3H, t, J = 7 Hz), 1.30 (2H, m), 1.40 (3H, d, J = 7 Hz), 1.55 (2H, m), 2.30 (2H, t, J = 7 Hz), 4.17 (1H, q, J = 7 Hz), 9.65 (1H, br s); ^{13}C nmr (δ, ppm, $CDCl_3$): 13.0, 13.4, 21.7, 27.8, 30.0, 71.8, 152.9, 168.9; ms: (M+H)/z = 171. Anal. Calcd for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.54; H, 8.42; N, 16.31.

3-Butyl-6-phenyl-4H-1,2,4-oxadiazin-5(6H)-one (5c). This compound was obtained as a white solid (64%), mp 67-68°C; nmr (δ, ppm, $CDCl_3$): 0.86 (3H, t, J = 7 Hz), 1.22 (2H, m), 1.55 (2H, m), 2.32 (2H, t, J = 7 Hz), 5.42 (1H, s), 7.4 (5H, m), 9.45 (1H, br s); ^{13}C nmr (δ, ppm, $CDCl_3$): 13.5, 21.6, 27.7, 30.2, 77.6, 127.2, 128.5, 129.0, 132.6, 151.7, 167.1; ms: (M+H)/z = 233. Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.23; H, 6.84; N, 11.93.

3-Butyl-6-phenylmethyl-4H-1,2,4-oxadiazin-5(6H)-one (5d). This compound was obtained from petroleum ether as a white solid (20%), mp 84-85°C; nmr (δ, ppm, $CDCl_3$): 0.86 (3H, t, J = 7 Hz), 1.35 (2H, m), 1.60 (2H, m), 2.32 (2H, t, J = 7 Hz), 3.18 (2H, dd, J = 3 and 7 Hz), 4.38 (1H, dd, J = 3 and 7 Hz), 7.3 (5H, m), 9.75 (1H, br s); ^{13}C nmr (δ, ppm, $CDCl_3$): 13.4, 21.7, 27.6, 29.9, 33.8, 76.5, 126.6, 128.8, 129.1, 136.0, 152.7, 167.9; ms: (M+H)/z = 247. Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.12; H, 7.48; N, 11.28.

3-Butyl-6-(2-phenylethyl)-4H-1,2,4-oxadiazin-5(6H)-one (5e). This compound was obtained from 95 : 5 petroleum ether : ether as a white solid (57%), mp 79-80°C; nmr (δ, ppm, $CDCl_3$): 0.95 (3H, t, J = 7 Hz), 1.40 (2H, m), 1.63 (2H, m), 2.20 (2H, m), 2.42 (2H, t, J = 7 Hz), 3.18 (2H, m), 4.18 (1H, dd, J = 3 and 7 Hz), 7.3 (5H, m), 9.75 (1H, br s); ^{13}C nmr (δ, ppm, $CDCl_3$): 13.4,

21.7, 27.6, 29.3, 30.0, 30.8, 74.2, 125.9, 128.3, 140.4, 152.8, 168.8; ms: (M+H)/z = 261.1615 (calcd for $C_{15}H_{21}N_2O_2$ = 261.1603). Anal. Calcd for $C_{15}H_{20}N_2O_2$. 0.5 H_2O: C, 66.89; H, 7.86; N, 10.40. Found: C, 67.00; H, 7.66; N, 10.36.

(S)-3-Butyl-6-(2-phenylethyl)-4H-1,2,4-oxadiazin-5(6H)-one (5f). To a mixture of (R)-ethyl 2-hydroxy-4-phenyl butyrate (120 mg, 0.6 mmol)[16] and pyridine (0.048 ml, 0.6 mmol) in dichloromethane (3 ml) at 0°C under argon was added trifluoromethanesulfonic anhydride (0.115 ml, 1.7 mmol). The resulting mixture was stirred at 0°C for 1 h, after which it was filtered through a small (7 ml) pad of silica gel and washed with dichloromethane. The filtrate was concentrated in vacuo to a volume of about 3 ml and was added to a solution of **2** (35 mg, 0.3 mmol)[7] and triethylamine (0.08 ml, 0.6 mmol) in dichloromethane (2 ml). After 2 h, the mixture was poured into water (100 ml), extracted with dichloromethane (2 x 100 ml), dried, and concentrated in vacuo. The residue was dissolved in dichloromethane (5 ml); a solution of trimethylaluminum in hexanes (0.6 ml of 2 M solution, 1.2 mmol) was added, and the resulting mixture was stirred for 3 h. The mixture was then poured into 0.5 N hydrochloric acid (100 ml), extracted with dichloromethane (2 x 100 ml), dried, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (30 g), eluting with 5:1 hexane : ethyl acetate, to give **5f** as colorless plates (from ether), 44 mg (56%), mp 105-106°C; nmr (δ, ppm, $CDCl_3$): 0.95 (3H, t, J = 7 Hz), 1.40 (2H, m), 1.63 (2H, m), 2.20 (2H, m), 2.42 (2H, t, J = 7 Hz), 3.18 (2H, m), 4.18 (1H, dd, J = 3 and 7 Hz), 7.3 (5H, m), 9.75 (1H, br s); ^{13}C nmr (δ, ppm, $CDCl_3$): 13.4, 21.7, 27.6, 29.3, 30.0, 30.8, 74.2, 125.9, 128.3, 140.4, 152.8, 168.8; ms: (M+H)/z = 261.1601 (calcd for $C_{15}H_{21}N_2O_2$ = 261.1603). $[\alpha]_D$ = +12.2° (c = 0.2, $CHCl_3$). Chiral hplc analysis (Diacel OD, eluting with 0.8 ml/min of 96% hexane, 3% isopropanol, 1% ethanol) showed the enantiomer ratio to be 96.2 (R_t 21.1 min) to 3.8 (R_t 25.7 min). Anal. Calcd for $C_{15}H_{20}N_2O_2$. 0.15 H_2O: C, 68.49; H, 7.78; N, 10.65. Found: C, 68.42; H, 7.74; N, 10.66.

General procedure for alkylation of oxadiazinones. 4'-[[3-Butyl-5,6-dihydro-5-oxo-6-(2-phenylethyl)-4H-1,2,4-oxadiazin-4-yl]methyl][1,1'-biphenyl]-2-carboxylic acid t-butyl ester (7e). A mixture of **5e** (520 mg, 2.0 mmol), biphenyl bromide (**6**) (960 mg, 2.4 mmol),[10] and cesium carbonate (1.30 g, 4.0 mmol) in dimethylformamide (10 ml) was stirred at 25°C for 19 h, after which it was poured into brine and extracted with ethyl acetate. The extract was dried and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (300 g), eluting with 10:1 hexane : ethyl acetate, to give **7e** as a viscous oil, 850 mg (81 %); nmr (δ, ppm, $CDCl_3$): 0.90 (3H, t, J = 7 Hz), 1.25 (9H, s), 1.40 (1H, m), 1.60 (1H, m), 2.20-2.50 (4H, m), 2.90 (2H, m), 4.19 (1H, dd, J = 3 and 7 Hz), 4.78 (1H, d, J = 14 Hz), 5.20 (1H, d, J = 14 Hz), 7.10-7.90 (13H, m); ^{13}C nmr (δ, ppm, $CDCl_3$): 13.6, 22.1, 27.5, 28.2, 29.5, 30.9, 43.9, 75.0, 81.2, 126.0, 127.2, 128.4, 128.5, 129.2, 129.6, 130.4, 130.5, 130.6, 132.7, 134.8, 140.7, 141.2, 141.5, 154.7, 166.9, 167.8; ms: (M+H)/z = 527. Anal. Calcd for $C_{33}H_{38}N_2O_4$: C, 75.26; H, 7.27; N, 5.32. Found: C, 75.34; H, 7.28; N, 5.19.

4'-[(3-Butyl-5,6-dihydro-5-oxo-4H-1,2,4-oxadiazin-4-yl)methyl][1,1'-biphenyl]-2-carboxylic acid t-butyl ester (7a). This compound was obtained as a viscous oil (55%); nmr (δ, ppm, $CDCl_3$): 0.89 (3H, t, J = 7 Hz), 1.22 (9H, s), 1.37 (2H, m), 1.59 (2H, m), 2.45 (2H, t, J = 7 Hz), 4.40 (2H, s), 5.00 (2H, s), 7.20-7.90 (8H, m); ^{13}C nmr (δ, ppm, $CDCl_3$): 13.5, 21.9, 27.4, 28.1, 29.4, 43.3, 67.1, 81.0, 125.9, 127.0, 129.0, 129.5, 130.2, 130.5, 132.6, 134.5, 141.0, 141.4, 154.7, 164.8, 167.5; ms: (M+H)/z = 423. Anal. Calcd for $C_{25}H_{30}N_2O_4$. 0.59 H_2O: C, 69.33; H, 7.25; N, 6.47. Found: C, 69.41; H, 7.04; N, 6.39.

4'-[(3-Butyl-5,6-dihydro-6-methyl-5-oxo-4H-1,2,4-oxadiazin-4-yl)methyl][1,1'-biphenyl]-2-carboxylic acid t-butyl ester (7b). This compound was obtained as a viscous oil (78%); nmr (δ, ppm, $CDCl_3$): 0.90 (3H, t, J = 7 Hz), 1.22 (9H, s), 1.37 (2H, m), 1.58 (3H, d, J = 7 Hz), 1.60 (2H, m), 2.40 (2H, t, J = 7 Hz), 4.25 (1H, q, J = 7 Hz), 4.85 (1H, d, J = 14 Hz), 5.27 (1H, d, J = 14 Hz), 7.20-7.90 (8H, m); ^{13}C nmr (δ, ppm, $CDCl_3$): 13.7, 22.1, 27.6, 28.4, 29.7, 44.1, 72.6, 81.3, 126.1, 127.3, 129.2, 129.7, 130.4, 130.7, 132.8, 134.9, 141.2, 141.3, 154.0, 167.5, 167.6; ms: (M+H)/z = 437.

4'-[[3-Butyl-5,6-dihydro-5-oxo-6-(phenylmethyl)-4H-1,2,4-oxadiazin-4-yl]methyl][1,1'-biphenyl]-2-carboxylic acid t-butyl ester (7d). This compound was obtained as a viscous oil (58%); nmr (δ, ppm, $CDCl_3$): 0.79 (3H, t, J = 7 Hz), 1.10 (9H, s), 1.24 (2H, m), 1.43 (2H, m), 2.27 (2H, t, J = 7 Hz), 2.90 (1H, dd, J = 7 and 14 Hz), 3.25 (1H, dd, J = 3 and 14 Hz), 4.28 (1H, dd, J = 3 and 7 Hz), 4.60 (1H, d, J = 14 Hz), 5.10 (1H, d, J = 14 Hz), 7.00-7.72 (13H, m); ^{13}C nmr (δ, ppm, $CDCl_3$): 13.9, 22.4, 27.9, 29.9, 34.6, 44.3, 77.2, 81.4, 126.4, 127.0, 127.5, 128.6, 129.1, 129.5, 129.9, 130.6, 131.0, 133.1, 135.1, 136.7, 141.5, 141.8, 154.8, 166.6, 168.0; ms: (M+H)/z = 513.

(S)-4'-[[3-Butyl-5,6-dihydro-5-oxo-6-(2-phenylethyl)-4H-1,2,4-oxadiazin-4-yl]methyl][1,1'-biphenyl]-2-carboxylic acid (7f). This compound was obtained as a viscous oil, (68 %); nmr (δ, ppm, $CDCl_3$): 0.90 (3H, t, J = 7 Hz), 1.25 (9H, s), 1.40 (1H, m), 1.60 (1H, m), 2.20-2.50 (4H, m), 2.90 (2H, m), 4.19 (1H, m), 4.78 (1H, d, J = 14 Hz), 5.20 (1H, d, J = 14 Hz), 7.10-7.90 (13H, m); ^{13}C nmr (δ, ppm, $CDCl_3$): 13.6, 22.1, 27.5, 28.2, 29.5, 30.9, 43.9, 75.0, 81.2, 126.0, 127.2, 128.4, 128.5, 129.2, 129.6, 130.4, 130.5, 130.6, 132.7, 134.8, 140.7, 141.2, 141.5, 154.7, 166.9, 167.8; ms: (M+H)/z = 527.

General procedure for deprotection of t-butyl esters. 4'-[[3-Butyl-5,6-dihydro-5-oxo-6-(2-phenylethyl)-4H-1,2,4-oxadiazin-4-yl]methyl][1,1'-biphenyl]-2-carboxylic acid (8e). To a solution of **7e** (460 mg, 0.87 mmol) in dichloromethane (20 ml) was added trifluoroacetic acid (20 ml, 200 mmol), and the mixture was stirred at room temperature for 1.5 h. The solution was concentrated in vacuo and purified by preparative hplc on a YMC 30 x 500 mm S-10 ODS column, eluting with 50 ml/min of 78 % aqueous methanol containing 0.1 % trifluoroacetic acid. Fractions containing the major product were combined and concentrated and the residue was lyophilized from ethanol/water to provide **8e** as a hygroscopic white solid, 335 mg (81%); mp 74-80 °C; nmr (δ, ppm, CD_3OD): 0.89 (3H, t, J = 7 Hz), 1.30 (2H, m), 1.52 (2H, m), 2.00-2.60 (4H, m), 2.82 (2H, m), 4.20 (1H, dd, , J = 3 and 7 Hz), 4.84 (1H, d, J = 14 Hz), 5.20 (1H, d, J = 14 Hz), 7.10-7.90 (13H, m); ^{13}C nmr (δ, ppm, $CDCl_3$): 13.5, 22.0, 28.3, 29.5, 29.7, 30.9, 44.1, 75.1, 125.9, 126.1, 127.3, 128.4, 128.5, 128.8, 129.1, 130.7, 131.1, 132.1, 134.9, 140.6, 140.7, 142.6, 155.2, 167.0, 172.9; ms: (M+H)/z = 471.2301 (calcd for $C_{29}H_{31}N_2O_4$: 471.2284). Anal. Calcd for $C_{29}H_{30}N_2O_4$ .0.25 H_2O: C, 73.32; H, 6.47; N, 5.90. Found: C, 73.32; H, 6.44; N, 5.75.

4'-[(3-Butyl-5,6-dihydro-5-oxo-4H-1,2,4-oxadiazin-4-yl)methyl][1,1'-biphenyl]-2-carboxylic acid (8a). This compound was obtained as a white solid (60%), mp 125-130°C; nmr (δ, ppm, CD_3OD): 0.96 (3H, t, J = 7 Hz), 1.42 (2H, m), 1.61 (2H, m), 2.50 (2H, t, J = 7 Hz), 4.50 (2H, s), 5.18 (2H, s), 7.20-7.90 (8H, m); ^{13}C nmr (δ, ppm, CD_3OD): 14.2, 23.3, 29.6, 30.7, 44.9, 68.6, 127.6, 128.7, 130.5, 101.0, 132.1, 132.6, 133.2, 137.1, 142.6, 143.2, 157.3, 167.1, 172.4; ms: (M+H)/z = 367.1648 (calcd for $C_{21}H_{23}N_2O_4$: 367.1658). Anal. Calcd for $C_{21}H_{22}N_2O_4$. 1.0 H_2O: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.52; H, 6.00; N, 7.36.

4'-[(3-Butyl-5,6-dihydro-6-methyl-5-oxo-4H-1,2,4-oxadiazin-4-yl)methyl][1,1'-biphenyl]-2-carboxylic acid (8b). This compound was obtained as a white solid (54%), mp 64-66°C; nmr (δ, ppm, CD_3OD): 0.80 (3H, t, J = 7 Hz), 1.25 (2H, m), 1.40 (3H, d, J = 7 Hz), 1.45 (2H, m), 2.39 (2H, m), 4.12 (1H, q, J = 7 Hz), 4.75 (1H, d, J = 14 Hz), 5.18 (1H, d, J = 14 Hz), 7.10-7.80 (8H, m); ^{13}C nmr (δ, ppm, CD_3OD): 13.9, 14.0, 23.0, 29.2, 30.4, 45.0, 73.6, 127.1, 128.3, 130.1, 130.7, 131.8, 132.2, 132.8, 136.7, 142.1, 142.8, 156.8, 168.9, 172.0; ms: (M+H)/z = 381.1818 (calcd for $C_{22}H_{25}N_2O_4$: 381.1814). Anal. Calcd for $C_{22}H_{24}N_2O_4 \cdot 0.5\ H_2O$: C, 67.85; H, 6.47; N, 7.19. Found: C, 60.02; H, 6.31; N, 7.11.

4'-[[3-Butyl-5,6-dihydro-5-oxo-6-(phenylmethyl)-4H-1,2,4-oxadiazin-4-yl]methyl][1,1'-biphenyl]-2-carboxylic acid (8d). This compound was obtained as a white solid (86%), mp 148-150°C; nmr (δ, ppm, CD_3OD): 0.95 (3H, t, J = 7 Hz), 1.41 (2H, m), 1.60 (2H, m), 2.50 (2H, m), 3.17 (1H, dd, J = 7 and 14 Hz), 3.50 (1H, dd, J = 3 and 7 Hz), 4.56 (1H, dd, J = 3 and 7 Hz), 4.95 (1H, d, J = 14 Hz), 5.30 (1H, d, J = 14 Hz), 7.20-8.00 (13H, m); ^{13}C nmr (δ, ppm, CD_3OD): 14.0, 23.0, 29.2, 30.4, 35.2, 45.0, 78.1, 126.8, 127.7, 129.3, 130.6, 131.3, 132.2, 132.8, 133.6, 136.6, 137.8, 138.9, 143.2, 156.7, 167.8, 171.9; ms: (M+H)/z = 457.2118 (calcd for $C_{28}H_{29}N_2O_4$: 457.2127). Anal. Calcd for $C_{28}H_{28}N_2O_4 \cdot 0.5\ H_2O$: C, 72.24; H, 6.28; N, 6.02. Found: C, 71.85; H, 6.06; N, 6.02.

(S)-4'-[[3-Butyl-5,6-dihydro-5-oxo-6-(2-phenylethyl)-4H-1,2,4-oxadiazin-4-yl]methyl][1,1'-biphenyl]-2-carboxylic acid (8f). This compound was obtained as a hygroscopic white solid (82%); mp 65-70 °C; nmr (δ, ppm, CD_3OD): 0.89 (3H, t, J = 7 Hz), 1.30 (2H, m), 1.52 (2H, m), 2.00-2.60 (4H, m), 2.82 (2H, m), 4.20 (1H, dd, J = 3 and 7 Hz), 4.84 (1H, d, J = 14 Hz), 5.20 (1H, d, J = 14 Hz), 7.10-7.90 (13H, m); ^{13}C nmr (δ, ppm, $CDCl_3$): 13.5, 22.0, 28.3, 29.5, 29.7, 30.9, 44.1, 75.1, 125.9, 126.1, 127.3, 128.4, 128.5, 128.8, 129.1, 130.7, 131.1, 132.1, 134.9, 140.6, 140.7, 142.6, 155.2, 167.0, 172.9; ms: (M+H)/z = 471.2289 (calcd for $C_{29}H_{31}N_2O_4$: 471.2284). $[\alpha]_D$ +47° (c = 0.1, chloroform). Chiral hplc analysis (Diacel OD, eluting with 1.0 ml/min of 92:7:1:0.5 hexane : ethanol : methanol : formic acid) showed the enantiomer ratio to be 96:4 (R_t 20.6 min) to 3.6 (R_t 17.5 min). Anal. Calcd for $C_{29}H_{30}N_2O_4 \cdot 1.0\ H_2O \cdot 0.15\ C_2HF_3O_2$: C, 69.59; H, 6.41; N, 5.54; F, 1.69. Found: C, 69.94; H, 6.10; N, 5.29; F, 1.90.

4'-[[Oxophenylacetyl)amino]methyl]-[1,1'-biphenyl]-2-carboxylic acid, t-butyl ester (9). A mixture of **5c** (380 mg, 1.6 mmol), biphenyl bromide (**6**) (600 mg, 2.0 mmol),[10] and cesium carbonate (975 mg, 3.0 mmol) in dimethylformamide (5 ml) was stirred at 25°C for 1 h, after which it was poured into brine and extracted with ether. The extract was washed with brine, dried and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (65 g), eluting with 4:1 hexane : ethyl acetate, to give **9** as an off white solid, 500 mg (75 %); mp 63-64°C; nmr (δ, ppm, $CDCl_3$): 1.42 (9H, s), 4.78 (2H, d, J = 7 Hz), 7.38-8.55 (14H, m); ^{13}C nmr (δ, ppm, $CDCl_3$): 27.5, 43.1, 81.2, 127.1, 127.4, 127.6, 128.4, 129.0, 129.6, 130.4, 130.6, 131.1, 132.7, 133.2, 134.3, 136.0, 141.3, 161.6, 167.7, 187.5; ms: (M-H)/z = 414. Anal. Calcd for $C_{26}H_{25}NO_4$: C, 75.16; H, 6.06; N, 3.37. Found: C, 74.97; H, 5.94; N, 3.07.

3-Butyl-1,2,4-oxadiazol-5(4H)-one (10). To a solution of amidoxime (**2**) (1.0 g, 8.6 mmol)[7] and triethylamine (2.8 ml, 20 mmol) in dichloromethane (80 ml) at -50°C under argon was added a solution of bis(trichloromethyl)carbonate (3.0 g, 10 mmol) in dichloromethane (20 ml). The resulting mixture was stirred for 2 h as it warmed to 25°C, after which it was poured into water. The pH

of the solution was adjusted to about 7.0 by addition of solid sodium bicarbonate, then the mixture was extracted sequentially with dichloromethane and ethyl acetate. The organic extracts were combined, dried, and concentrated to a red oil. The oil was purified by flash chromatography on silica gel (65 g), eluting with 1:1 hexane : ethyl acetate, to give **10** as a clear oil, 780 mg (64%); nmr (δ, ppm, $CDCl_3$): 0.97 (3H, t, J = 7 Hz), 1.41 (2H, m), 1.70 (2H, m), 2.65 (2H, t, J = 7 Hz); ^{13}C nmr (δ, ppm, $CDCl_3$): 12.8, 21.8, 24.5, 27.2, 159.6, 161.4; ms: $(M+NH_4)/z$ = 160. Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71 Found: C, 50.66; H, 7.21; N, 19.84.

4'-[[3-Butyl-5-oxo-1,2,4-oxadiazol-4(5H)-yl]methyl][1,1'-biphenyl]-2-carboxylic acid t-butyl ester (11). A mixture of **10** (750 mg, 5.3 mmol), **6** (2.4 g, 7 mmol), and cesium carbonate (3.25 g, 10 mmol) in dimethylformamide (15 ml) was stirred at 25°C for 17 h, after which it was poured into brine and extracted with ethyl acetate. The extract was dried and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (300 g), eluting with 3:1 hexane : ethyl acetate, to give **11** as a colorless oil, 1.87 g (87%); nmr (δ, ppm, $CDCl_3$): 0.95 (3H, t, J = 7 Hz), 1.30 (9H, s), 1.45 (2H, m), 1.70 (2H, m), 2.55 (2H, t, J = 7 Hz), 4.87 (2H, s), 7.30- 7.90 (8H, m); ^{13}C nmr (δ, ppm, $CDCl_3$): 13.3, 21.8, 24.4, 26.2, 27.3, 45.1, 81.0, 126.7, 127.2, 129.1, 130.2, 130.6, 132.5, 132.9, 140.8, 142.1, 159.0, 159.5, 167.3; ms: (M+H)/z = 409. Anal. Calcd for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86 Found: C, 70.73; H, 6.91; N, 6.86.

4'-[[[1-(Hydroxyimino)pentyl]amino]methyl]-[1,1'-biphenyl]-2-carboxylic acid t-butyl ester (12). A mixture of **11** (1.25 g, 3.06 mmol), 1N sodium hydroxide solution (6 ml, 6 mmol) and methanol (15 ml) was stirred at 25°C for 16 h, after which additional 1N sodium hydroxide solution (6 ml, 6 mmol) and methanol (15 ml) were added and the mixture was stirred at 50°C for 24 h. The mixture was then poured into brine, the pH was adjusted to about 7 by addition of 1N hydrochloric acid, and the mixture was extracted with ethyl acetate. The extract was dried and concentrated, and the residue was purified by flash chromatography on silica gel (300 g), eluting with ethyl acetate, to give **12** as a viscous oil, 600 mg (51%); nmr (δ, ppm, $CDCl_3$): 0.82 (3H, t, J = 7 Hz), 1.20 (9H, s), 1.27 (2H, m), 1.50 (2H, m), 2.15 (2H, t, J = 7 Hz), 4.33 (2H, d, J = 7 Hz), 5.60 (1H, t, J = 7 Hz), 7.20-7.80 (8H, m); ^{13}C nmr (δ, ppm, $CDCl_3$): 13.7, 22.4, 27.6, 28.3, 28.5, 45.7, 81.2, 126.3, 127.1, 128.8, 128.9, 130.3, 130.4, 132.6, 138.1, 140.9, 141.5, 167.9; ms: (M+H)/z = 383.2349 (calcd for $C_{23}H_{31}N_2O_3$: 383.2334). Attempted drying in vacuo at elevated temperatures to remove residual solvents led to sample decomposition.

4'-[(3-Butyl-5,6-dihydro-5-oxo-4H-1,2,4-oxadiazin-4-yl)methyl][1,1'-biphenyl]-2-carboxylic acid t-butyl ester (7a from 12). A mixture of **12** (77 mg, 0.20 mmol), methylbromoacetate (0.03 ml, 0.32 mmol), and cesium carbonate (162 mg, 0.5 mmol) in dimethylformamide (1 ml) was stirred at 25°C for 3 h, after which it was poured into brine and extracted with ethyl acetate. The extract was dried and concentrated. The residue was filtered through a short pad of silica gel, washing with 2:1 hexane : ethyl acetate, and the filtrate was reconcentrated to give crude **13** as an oil. The oil was dissolved in dichloromethane (2 ml) and a solution of trimethylaluminum in hexane was added (0.5 ml of 2M solution, 1 mmol). The mixture was stirred at 25°C under argon for 1 h, poured into 1N hydrochloric acid, and extracted with ethyl acetate. The extract was dried and concentrated, the the residue was purified by flash chromatography on silica gel (30 g), eluting with 4:1 hexane : ethyl acetate, to give **7a** which was identical with material prepared by alkylation of **5a**, 12 mg (14%).

4'-[[3-Butyl-5,6-dihydro-5-oxo-6-(2-phenylethyl)-4H-1,2,4-oxadiazin-4-yl]methyl][1,1'-biphenyl]-2-carbonitrile (15). A mixture of **5e** (390 mg, 1.5 mmol), biphenyl bromide (**16**) (408 mg, 1.5 mmol),[10] and cesium carbonate (975 mg, 3.0 mmol) in dimethylformamide (5 ml) was stirred at 25°C for 18 h, after which the mixture was poured into water and extracted into ethyl acetate. The extract was dried and concentrated, and the residue was purified by flash chromatography on silica gel (65 g), eluting with 3:1 hexane : ethyl acetate, to give **15** as a viscous oil, 400 mg (60%); nmr (δ, ppm, $CDCl_3$): 0.80 (3H, t, J = 7 Hz), 1.25 (2H, m), 1.45 (2H, m), 2.00-2.40 (4H, m), 2.80 (2H, m), 4.08 (1H, dd, J = 3 and 7 Hz), 4.70 (1H, d, J = 14 Hz), 5.08 (1H, d, J = 14 Hz), 7.00-7.80 (13H, m); ^{13}C nmr (δ, ppm, $CDCl_3$): 13.5, 22.0, 28.2, 29.4, 29.8, 30.8, 43.8, 74.9, 110.9, 118.4, 127.4, 127.6, 128.3, 128.7, 129.2, 132.8, 134.0, 136.5, 137.5, 140.6, 144.4, 145.4, 154.7, 166.9; ms: (M+H)/z = 452.

3-Butyl-6-(2-phenylethyl)-4-[[(2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-4H-1,2,4-oxadizin-5(6H)-one (16). A solution of **15** (400 mg, 0.89 mmol) and tributyltin azide (886 mg, 2.7 mmol)[17] in *o*-xylene (0.5 ml) was stirred at 100°C for 18 h. The mixture was then transferred directly to a flash chromatography column containing silica gel (65 g), and was eluted with 60:40:1 hexane : ethyl acetate : acetic acid. Fractions containing the major ultraviolet absorbing product (λ = 254 nm) were combined and concentrated. The residue was repurified by flash chromatography on silica gel (65 g), eluting with a mixture containing 95.2% ethyl acetate, 2.6% pyridine, 0.8% acetic acid, and 1.4% water. Fractions containing the major product were combined, concentrated, and converted to the corresponding potassium salt by dissolving the residue in methanol and adjusting to pH 10.5 by addition of 0.1% potassium carbonate solution. The solution was immediately transferred to a preparative hplc column containing macroreticullar polystyrene (Jordi Gel, 30 x 250). The column was eluted first with one liter of water, then with a linear gradient from water to methanol. Fractions containing the major ultraviolet absorbing product (λ = 254 nm) were combined and concentrated in vacuo, and the residue was lyophilized to give **16** as a white powder, 224 mg (45%); nmr (δ, ppm, $CDCl_3$): 0.95 (3H, t, J = 7 Hz), 1.40 (2H, m), 1.58 (2H, m), 2.10-2.60 (4H, m), 2.95 (2H, m), 4.25 (1H, dd, J = 3 and 7 Hz), 4.85 (1H, d, J = 14 Hz)), 5.20 (1H, d, J = 14 Hz)), 7.00-7.80 (13H, m); ^{13}C nmr (δ, ppm, $CDCl_3$): 13.9, 23.0, 29.3, 30.4, 31.0, 44.9, 76.2, 127.1, 128.1, 129.5, 130.0, 130.8, 131.1, 131.8, 136.1, 142.1, 142.5, 156.8, 162.7, 168.4; ms: (M+K)/z = 533. Anal. Calcd for $C_{29}H_{29}N_6O_2K$. 1.7 H_2O: C, 61.83; H, 5.80; N, 14.92 Found: C, 61.83; H, 5.45; N, 14.64.

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