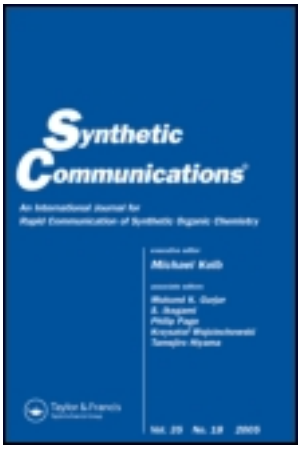

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Synthesis of New 1,2,4- and 1,3,4-Oxadiazole Derivatives as Potential Nonpeptide Angiotensin II Receptor Antagonists

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Synthesis of New 1,2,4- and 1,3,4-Oxadiazole Derivatives as Potential Nonpeptide Angiotensin II Receptor Antagonists

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Abstract: The synthesis of new 1,2,4- and 1,3,4-oxadiazole derivatives as potential nonpeptide angiotensin II receptor antagonists is described. The quinoxalinone systems used as the "northern moiety" in these compounds were alkylated through a liquid/liquid phase-transfer catalysis protocol, with good yields and high nitrogen- to oxygen-alkylated product (N/O) ratios.

Keywords: Alkylation, oxadiazoles, PTC, tetrazoles

INTRODUCTION

The renin–angiotensin system (RAS) is known to play a crucial role in cardiovascular regulation and the maintenance of blood pressure. Angiotensin II (AII) is the active hormone of the RAS, mediating a variety of physiological functions through stimulation of specific receptors on the cell surface, which can be blocked by selective receptor antagonists.[1,2]

The discovery by Du Pont of the first orally active, nonpeptide, AII receptor antagonist DuP 753 (Losartan) opened an exciting new phase of

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research to investigate AT_1-selective agents for the treatment of hypertension. Since then, a plethora of other AII antagonists have been reported.[3–5]

Recently we have described the synthesis of new potential nonpeptide angiotensin II receptor antagonists containing heterocyclic spacers, particularly 1,2,4- and 1,3,4-oxadiazole derivatives.[6,7] In the present study, we have undertaken the synthesis of a number of new AII receptor antagonist analogues in which the disubstituted oxadiazole moiety has been retained while modifications have been made to the so-called "northern moiety" (**1**–**3**) and in the acidic group (**4**) attached to the heterocyclic spacer (Figure 1).

RESULTS AND DISCUSSION

In the synthesis of the target molecules **1a**, **1b**, **2a**, and **2b** the key step consists of the alkylation of the 3-alkylquinoxalinones **5** and **10** with the benzylic bromides **8** and **9** (Scheme 1). However, it is well known that alkylation of quinoxalinones[8–10] and related heterocycles[11] commonly affords a mixture of the *N*- and *O*-alkylated products as a result of their ambident anionic character.

Most of the conventionally used methods for the alkylation of quinoxalinones involve strong bases, and consequently dry solvents and an inert atmosphere. Even so, unacceptable lack of regioselectivity is usually found. With this in mind, we started a search for more convenient and efficient methodologies, focusing enhancement of *N*-regioselectivity, for the alkylation of quinoxalinones. Our first attempt was based on Rutar and Kikelj's report describing the regioselective *N*-alkylation of benzoxazines, under solid/liquid phase-transfer catalysis.[12] As a model reaction, we performed the alkylation of the 3-methyl-1*H*-quinoxalin-2-one (**5**) with benzyl bromide (Scheme 2).

In the presence of K_2CO_3 and a catalytic amount of TEBAB (benzyltriethylammonium bromide) (20 mol%) in hot CH_3CN we obtained, after 6 h, 79% of the alkylated derivatives (**6** and **7**) in a ratio of 73 : 27, favoring the desired *N*-alkylated product (**6**) (Table 1, entry 1). In fact, this ratio is somewhat poorer than that obtained using NaH or K_2CO_3 in DMF, although the overall yield is similar.[9,10] To further develop this methodology, we

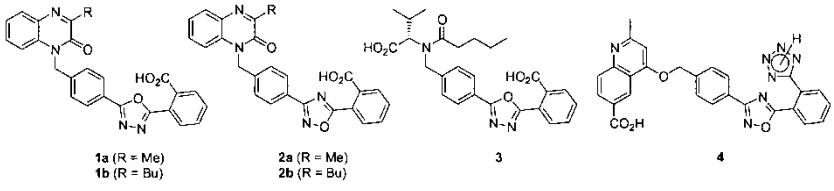
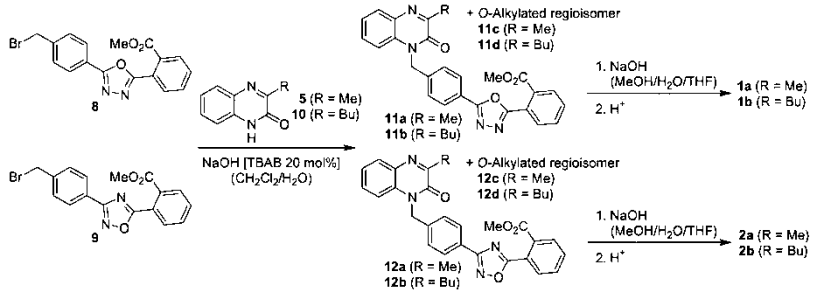


Figure 1. New AII receptor antagonist analogues.

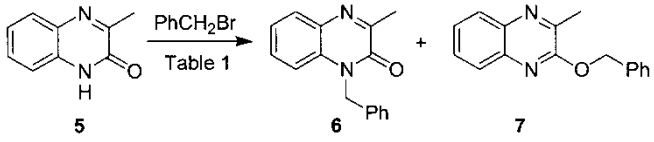


Scheme 1.

carried out the same reaction in a liquid/liquid two-phase system (CH_2Cl_2/H_2O), at room temperature with TBAB (tetrabutylammonium bromide) (20 mol%) as the phase-transfer catalyst and NaOH as the base. Although the overall yield of the alkylated derivatives was only slightly better (81% isolated yield, after 12 h), the N/O ratio obtained was significantly higher. (83 : 17 after chromatographic separation) (Table 1, entry 2). Based on this encouraging result, we examined the performance of other "quats," such as TBPB (tetrabutylphosphonium bromide), TBAHS (tetrabutylammonium hydrogensulphate), TBBC (benzyltributylammonium chloride), and TEBAB regarding their N/O regioselectivities.

Surprisingly, all "quats" showed similar N/O ratios (about 83 : 17 determined by GC), and, as expected, no reaction was observed in the absence of quaternary salt. In all cases the parent quinoxalinone was not detected in the organic phase. (Control experiments were carried out to ensure that the product distribution was not influenced by further equilibration under the reaction conditions.) On considering the solubility of the quinoxalinone **5** in aqueous alkali, we can suggest that an extraction-type mechanism is operating; that is, the deprotonation of **5** takes place in the aqueous phase and then the anion is extracted into the organic phase.[13]

By virtue of the simplicity of the PTC protocol, we elected this methodology for the synthesis of the target molecules **1a**, **1b**, **2a**, and **2b**, as shown in Scheme 1.



Scheme 2.

Table 1. Reaction conditions for the alkylation of **5**

Entry	Conditions	**6**[a]	**7**[a]
1	K_2CO_3/TEBAB (20 mol%) CH_3CN 60°C (6 h)	73	27
2	NaOH/TBAB (20 mol%) CH_2Cl_2/H_2O 25°C (12 h)	83	17

[a]Describes the relative ratio of the isolated products.

The alkylation of the quinoxalinones **5** and **10**[14] with the halides **8** and **9**[6] was performed at room temperature in a biphasic system (CH_2Cl_2/H_2O) with TBAB as the phase-transfer catalyst (20 mol%). After 12 h, TLC indicated the completion of the reaction.

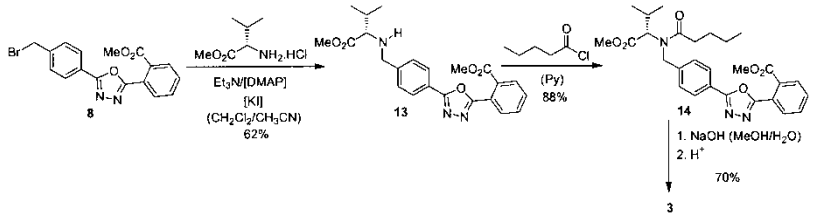
The yields and regioselectivities were in the same range as those observed in the model reaction (Table 2). The regioisomers were easily separated by flash chromatography (except in the case of the quinoxalinone **10**, entries 2 and 4, where the R_f values of the halides **8** and **9** and the *O*-alkylated products **11d** and **12d** are too close). In the ^{13}C NMR spectra of **11a**, **11b**, **12a**, and **12b** the benzylic signal at ca. δ 45 ppm was consistent with *N*- rather than *O*-alkylation (in this case the benzylic signal is observed at ca. δ 70 ppm). Furthermore, these assignments were confirmed by NOESY (Nuclear Overhauser Effect Spectroscopy) experiments, based on cross peaks connecting the *N*-benzylic methylene group protons and the proton at the C-8 position of the quinoxalinone ring. The hydrolysis of the *N*-alkylated products **11a**, **11b**, **12a**, and **12b** with NaOH in MeOH/THF/H_2O, followed by acidic workup, afforded the target compounds **1a**, **1b**, **2a**, and **2b**, respectively, in excellent yields (Table 2).

The synthesis of the valsartan[15] analogue **3** was effected following the route outlined in Scheme 3. Alkylation of L-valine methyl ester with the halide **8**[6] was carried out using 4-(dimethylamino)pyridine (DMAP) and a catalytic amount of KI. The secondary amine **13** was acylated with valeryl chloride to furnish **14**. Finally, **14** was converted to the diacid **3** by ester hydrolysis with NaOH in MeOH/H_2O followed by acidic workup in 70% yield.

The synthetic strategy for the construction of the tetrazole derivative 4 is shown in Scheme 4. 4-Methylphenyl amidoxime (**15**)[6] was acylated with

Table 2. Yields for alkylation and hydrolysis reactions

Entry	Halide	Quinoxalinone	*N*-alkylated product/yield (%)	*O*-alkylated product/yield (%)	Acid/yield (%)
1	**8**	**5**	**11a**/76	**11c**/16	**1a**/93
2	**8**	**10**	**11b**/68	**11d**/Not isolated	**1b**/93
3	**9**	**5**	**12a**/69	**12c**/12	**2a**/93
4	**9**	**10**	**12b**/66	**12d**/Not isolated	**2b**/91

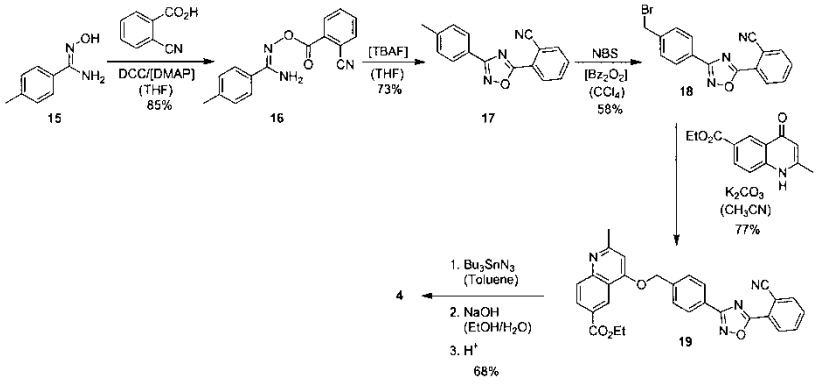


Scheme 3.

2-cyanobenzoic acid[16] in the presence of DCC/DMAP to furnish **16** in 85% yield. Upon treatment with a catalytic amount of TBAF[17] the *O*-acylamidoxime **16** underwent cyclization to the 1,2,4-oxadiazole **17** with a 73% yield. The methyl group of **17** was brominated with *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide to furnish **18**, which through the reaction with ethyl 2-methyl-4-oxo-l,4-dihydroquinoline-6-carboxylate[18] in the presence of K_2CO_3 in CH_3CN gave the *O*-alkylated product **19** as the only regioisomer. Finally, **19** was converted to the tetrazole **4** through the reaction with tributyltin azide and the subsequent ester hydrolysis, in 68% overall yield.

CONCLUSIONS

In summary, we describe a new, easy to perform, and efficient procedure, based on phas-transfer catalysis, for the alkylation of quinoxalinones. This mild, less hazardous methodology seems to be a good alternative to the commonly applied NaH/DMF system, furnishing comparable N/O ratios. Additionally, we report the synthesis of new 1,2,4- and 1,3,4-oxadiazole derivatives as potential nonpeptide angiotensin II receptor antagonists.



Scheme 4.

These compounds are currently under pharmacological evaluation, and the results will be published elsewhere.

EXPERIMENTAL

General

Melting points were measured using a Kofler hot-stage apparatus (Microquímica APF-301) and are uncorrected. Each analytical sample was homogeneous as confirmed by TLC performed on silica gel (Kieselgel 60 F 254-Merck) plates, which were visualized with UV light. Flash chromatography was performed with Merck silica gel 60 (230–400 mesh). ^{1}H NMR spectra were recorded on a Bruker AW-200 (200-MHz) instrument, with tetramethylsilane (TMS) as the internal standard, and ^{13}C NMR spectra were recorded on a Bruker (50.3-MHz) spectrometer. Elemental analyses were within $\pm 0.4\%$ of theoretical values and were determined on a Perkin-Elmer 2400 instrument. Quinoxalinones **5** and **10** were prepared according to literature procedures.[11,15]

General Procedure for the Alkylation of Quinoxalinones

A solution of NaOH (1.1 mmol) in H_2O (1 mL) was added to a solution of quinoxalinone (1.0 mmol), benzylic halide (1.1 mmol), and TBAB (0.2 mmol) in CH_2Cl_2 (10 mL). The biphasic mixture was agitated with a vibromixer at room temperature for 12 h. The organic layer was separated, and the aqueous phase was extracted twice with 10 mL portions of CH_2Cl_2. The combined organic extracts were washed with brine (2×10 mL) and dried ($MgSO_4$). The solvent was removed under vacuum, and the residue was flash chromatographed on SiO_2 using hexane/EtOAc (7 : 3 changing on a gradient to 1 : 1 for **11a**, **11c**, **12a**, and **12c** or 4 : 1 changing on a gradient to 4 : 3 for **11b** and **12b**) as eluents.

Methyl 2-{5-[4-(3-methyl-2-oxo-1*H*-quinoxalin-1-ylmethyl)phenyl]-1,3,4-oxadiazol-2-yl}benzoate (11a). White powder; yield: 76%; mp 191–192°C. ^{1}H NMR ($CDCl_3$): $\delta = 2.68$ (s, 3 H), 3.82 (s, 3 H), 5.57 (s, 2 H), 7.21–8.06 (m, 12 H). ^{13}C NMR ($CDCl_3$): $\delta = 22.17$, 46.16, 53.25, 114.69, 123.75, 124.11, 124.41, 127.98, 128.17, 130.25, 130.49, 130.91, 131.99, 132.25, 132.86, 133.43, 139.92, 155.68, 158.91, 164.45, 165.06, 167.64. Anal. calcd. for $C_{26}H_{20}N_4O_4$: C, 69.02; H, 4.46; N, 12.38. Found: C, 68.81; H, 4.47; N, 12.49.

Methyl 2-{5-[4-(3-methylquinoxalin-2-yloxymethyl)phenyl]-1,3,4-oxadiazol-2-yl}benzoate (11c). White powder; yield: 16%; mp 149–151°C. ^{1}H NMR

($CDCl_3$): $\delta = 2.72$ (s, 3 H), 3.84 (s, 3 H), 5.65 (s, 2 H), 7.58–8.15 (m, 12 H). ^{13}C NMR ($CDCl_3$): $\delta = 21.08$, 53.38, 67.89, 124.03, 124.30, 127.33, 127.43, 127.75, 128.73, 129.02, 129.66, 130.63, 131.04, 132.10, 132.35, 139.40, 140.28, 141.36, 148.54, 156.32, 164.59, 165.43, 167.89. Anal. calcd. for $C_{26}H_{20}N_4O_4$: C, 69.02; H, 4.46; N, 12.38. Found: C, 68.91; H, 4.45; N, 12.13.

Methyl 2-{3-[4-(3-methyl-2-oxo-1*H*-quinoxalin-1-ylmethyl)phenyl]-1,2,4-oxadiazol-5-yl}benzoate (12a). White powder; yield: 69%; mp 160–163°C. ^1H NMR ($CDCl_3$): $\delta = 2.68$ (s, 3 H), 3.84 (s, 3 H), 5.57 (s, 2 H), 7.19–8.13 (m, 12 H). ^{13}C NMR ($CDCl_3$); $\delta = 22.20$, 46.23, 53.32, 114.78, 124.33, 124.48, 126.77, 127.92, 128.60, 130.18, 130.29, 130.69, 132.05, 132.52, 132.83, 132.93, 133.44, 139.22, 155.72, 158.94, 167.71, 168.67, 175.98. Anal. calcd. for $C_{26}H_{20}N_4O_4$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.30; H, 4.54; N, 12.64.

Methyl 2-{3-[4-(3-methylquinoxalin-2-yloxymethyl)phenyl]-1,2,4-oxadiazol-5-yl} benzoate (12c). White powder; yield: 12%; mp 150–153°C. ^1H NMR ($CDCl_3$): $\delta = 2.72$ (s, 3 H), 3.87 (s, 3 H), 5.64 (s, 2 H), 7.55–8.22 (m, 12 H). ^{13}C NMR ($CDC1_3$): $\delta = 21.09$, 53.47, 68.11, 124.68, 127.09, 127.24, 127.46, 128.34, 128.72, 128.86, 129.60, 130.43, 130.82, 132.17, 132.62, 133.01, 139.37, 140.33, 140.64, 148.63, 156.42, 167.92, 169.03, 176.09. Anal. calcd. for $C_{26}H_{20}N_4O_4$: C, 69.02; H, 4.46; N, 12.38. Found: C, 68.72; H, 4.46; N, 12.44.

Methyl 2-{5-(4-(3-butyl-2-oxo-1*H*-quinoxalin-1-ylmetlhyl)phenyl]-1,3,4-oxadiazol-2-yl}benzoate (11b). White powder; yield: 68%; mp 125–126°C. ^1H NMR ($CDCI_3$): $\delta = 1.00$ (t, $J = 7.2$ Hz, 3 H), 1.45–1.56 (m, 2 H), 1.74–1.87 (m, 2 H), 3.02 (t, $J = 7.3$ Hz, 2 H), 3.81 (s, 3 H), 5.57 (s, 2 H), 7.16–8.06 (m, 12 H). ^{13}C NMR ($CDCl_3$): $\delta = 13.85$, 22.60, 28.78, 33.91, 45.50, 52.59, 113.95, 123.05, 123.46, 123.69, 127.35, 127.50, 129.52, 129.75, 129.85, 130.27, 131.35, 131.61, 132.03, 132.87, 139.37, 154.77, 161.26, 163.81, 164.44, 167.01. Anal calcd. for $C_{29}H_{26}N_4O_4$: C, 70.43; H, 5.30; N, 11.33. Found: C, 70.33; H, 5.23; N, 11.63.

Methyl 2-{3-[4-(3-butyl-2-oxo-1*H*-quinoxalin-1-ylmethyl)phenyl]-1,2,4-oxadiazol-5-yl}benzoate (12b). White powder; yield: 66%; mp 139–141°C. ^1H NMR ($CDCl_3$): $\delta = 1.00$ (t, $J = 7.2$ Hz, 3 H), 1.42–1.57 (m, 2 H), 1.76–1.91 (m, 2 H), 3.03 (t, $J = 7.4$ Hz, 2 H), 3.85 (s, 3 H), 5,57 (s, 2 H), 7.18–8.13 (m, 12 H). ^{13}C NMR ($CDC1_3$): $\delta = 14.64$, 23.41, 29.59, 34.74, 46.37, 53.46, 114.82, 124.38, 124.56, 124.66, 126.90, 128.02, 128.75, 130.22, 130.46, 130.82, 132.18, 132.64, 132.91, 132.97, 133.68, 139.41, 155.60, 162.11, 167.89, 168.84, 176.11. Anal. calcd. for $C_{29}H_{26}N_4O_4$: C, 70.43; H, 5.30; N, 11.33. Found: C, 70.56; H, 5.29; N, 11.64.

General Procedure for the Preparation of Carboxylic Acids 1a, 1b, 2a, and 2b

A solution of the ester (**11a**, **11b**, **12a**, **12b**) (0.50 mmol), NaOH (1.50 mmol) in MeOH (10 mL), THF (5 mL), and H_2O (2 mL) was stirred at rt for 24 h. The solvents were evaporated, and the residue was dissolved in H_2O (10 mL). The solution was acidified with aqueous HCl until pH 4, and the resulting precipitate was collected by filtration, washed with H_2O, and dried under vacuum.

2-{5-[4-(3-Methyl-2-oxo-1*H*-quinoxalin-1-ylmethyl)phenyl]-1,3,4-oxadiazol-2-yl}benzoic acid (1a). White solid; yield: 93%; mp 204–207°C (dec). ^{1}H NMR (DMSO-d_6): $\delta = 2.52$ (s, 3 H), 5.57 (s, 2 H), 7.28–7.96 (m, 12 H). ^{13}C NMR (DMSO-d_6): $\delta = 21.38$, 44.81, 114.89, 122.55, 122.74, 123.59, 126.95, 127.77, 128.96, 129.38, 129.69, 130.02, 130.21, 131.52, 132.19, 132.31, 136.63, 139.96, 154.64, 158.05, 163.84, 164.68, 168.41. Anal calcd. for $C_{25}H_{18}N_4O_4 \cdot 1.5H_2O$: C, 64.51; H, 4.55; N, 12.04. Found: C, 64.34; H, 4.35; N, 11.94.

2-{5-[4-(3-Butyl-2-oxo-1*H*-quinoxalin-1-ylmethyl)phenyl]-1,3,4-oxadiazol-2-yl}benzoic acid (1b). White solid; yield: 93%; mp 220–223°C. ^{1}H NMR (DMSO-d_6): $\delta = 0.94$ (t, $J = 7.2$ Hz, 3 H), 1.31–1.50 (m, 2 H), 1.62–1.86 (m, 2 H), 2.89 (t, $J = 7.8$ Hz, 2 H), 5.60 (s, 2 H), 7.36–7.99 (m, 12 H). ^{13}C NMR (DMSO-d_6): $\delta = 13.91$, 22.10, 28.15, 33.17, 44.81, 114.85, 122.33, 123.04, 123.61, 127.01, 127.86, 129.18, 129.73, 130.47, 131.80, 131.98, 132.31, 132.76, 140.28, 154.32, 160.65, 163.80, 164.04, 167.65. Anal. calcd. for $C_{28}H_{24}N_4O_4$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.01; H, 4.97; N, 11.80.

2-{3-[4-(3-Methyl-2-oxo-1*H*-quinoxalin-1-ylmethyl)phenyl]-1,2,4-oxadiazol-5-yl}benzoic acid (2a). White solid; yield: 93%; mp $>$ 181°C (gradual). ^{1}H NMR (DMSO-d_6): $\delta = 2.52$ (s, 3 H), 5.59 (s, 2 H), 7.29–8.04 (m, 12 H). ^{13}C NMR (DMSO-d_6): $\delta = 21.39$, 44.88, 114.88, 123.58, 123.82, 125.27, 127.55, 127.76, 129.00, 129.67, 129.89, 130.46, 131.89, 132.24, 132.35, 132.46, 133.06, 139.72, 154.65, 158.06 167.42, 167.61, 176.15. Anal. calcd. for $C_{25}H_{18}N_4O_4$: C, 68.49; H, 4.14; N, 12.78. Found: C, 68.50; H, 4.14; N, 13.01.

2-{3-[4-(3-Butyl-2-oxo-1*H*-quinoxalin-1-ylmethyl)phenyl]-1,2,4-oxadiazol-5-yl}benzoic acid (2b). White solid; yield: 91%; mp $>$ 156°C (gradual). ^{1}H NMR (DMSO-d_6): $\delta = 0.95$ (t, $J = 7.2$ Hz, 3 H), 1.38–1.49 (m, 2 H), 1.68–1.83 (m, 2 H), 2.91 (t, $J = 7.3$ Hz, 2 H), 5.60 (s, 2 H), 7.30–8.04 (m, 12 H). ^{13}C NMR (DMSO-d_6): $\delta = 13.90$, 22.10, 28.17, 33.17, 44.85, 114.90, 123.58, 123.77, 125.64, 127.47, 127.64, 129.15, 129.50, 129.72, 131.69, 132.02, 132.31, 138.33, 139.43, 154.33, 160.63, 167.23, 168.33, 177.54.

Anal. calcd. for $C_{28}H_{24}N_4O_4$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.79; H, 4.95; N, 11.86.

Methyl (*S*)-2-{[4-[5-(2-carbomethoxyphenyl)-1,3,4-oxadiazol-2-yl]phenyl] methyl} amino-3-methylbutanoate (13). Triethylamine (0.49 mL, 3.54 mmol) was added to a suspension of L-valine methyl ester hydrochloride (593 mg, 3.54 mmol) in dry CH_3CN (10 mL) under Ar at 25°C. A solution of methyl 2-[5-(4-bromomethylphenyl)-1,3,4-oxadiazol-2-yl]benzoate (**8**) (455 mg, 1.22 mmol) in CH_2Cl_2 (10 mL) was added to the resulting milky suspension, followed by 4-(dimethylamino)pyridine (50 mg, 0.41 mmol) and some crystals of KI. After being stirred at rt for 36 h, the mixture was concentrated under vacuum. The residue was partitioned between CH_2Cl_2 (20 mL) and water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL); the combined organic layers were washed with brine (3 × 10 mL) and dried ($MgSO_4$). After solvent removal, the crude product was purified by column chromatography on silica gel, eluting with hexane–EtOAc (4 : 1) to give **13** (320 mg, 62%) as a viscous colorless oil.

^{1}H NMR ($CDCl_3/CC1_4$): 0.96 (d, $J = 6.7$ Hz, 6 H), 1.88 (s, 1 H), 1.92 (septet, $J = 6.7$ Hz, 1 H), 2.99 (d, $J = 6.0$ Hz, 1 H), 3.63 (d, $J = 13.8$ Hz, 1 H), 3.74 (s, 3 H), 3.84 (s, 3 H), 3.93 (d, $J = 13.8$ Hz, 1 H), 7.48–8.04 (m, 8 H). ^{13}C NMR ($CDCl_3/CCl_4$): $\delta = 19.22$, 20.03, 32.38, 52.19, 52.79, 53.41, 67.24, 123.08, 124.38, 127.57, 128.13, 129.51, 130.63, 131.03, 132.06, 132.35, 145.12, 164.44, 165.72, 168.03, 176.31. Anal. calcd. for $C_{23}H_{25}N_3O_5$: C, 65.24; H, 5.95; N, 9.92. Found: C, 65.09; H, 5.95; N, 9.76.

Methyl (*S*)-2-{[4-[5-(2-carbomethoxyphenyl)-1,3,4-oxadiazol-2-yl]phenyl] methyl} pentanoylamino-3-methylbutanoate (14). Valeryl chloride (0.19 mL, 1.63 mmol) was added dropwise to a solution of the amine **13** (300 mg, 0.71 mmol) in dry pyridine (5 mL) under N_2 at 0°C. The reaction mixture was then allowed to warm to room temperature and stirred overnight. The reaction was quenched by pouring into H_2O (15 mL) and then extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed successively with H_2O (3 × 10 mL), aqueous HCl (5%, 3 × 5 mL), saturated aqueous $NaHCO_3$ (3 × 10 mL), and brine (3 × 10 mL). The organic phase was dried ($MgSO_4$), and the solvent was removed under vacuum. Chromatography of the residue on silica gel using hexane/EtOAc (4 : 1 → 7 : 3) as the eluent gave the title compound **14** (316 mg, 88%) as a colorless oil. ^{1}H NMR analysis of **14** revealed a complex mixture of conformers and/or topomers at room temperature.

^{1}H NMR (DMSO-d_6, 100°C): $\delta = 0.92$–0.98 (m, 6 H), 1.07 (d, $J = 6.5$ Hz, 3 H), 1.37–1.47 (m, 2 H), 1.64–1.71 (m, 2 H), 2.37–2.54 (m, 3 H), 3.58 (s, 3 H), 3.91 (s, 3 H), 4.52–4.95 (m, 3 H), 7.52–8.11 (m, 8 H). Anal. calcd. for $C_{28}H_{33}N_3O_6$: C, 66.26; H, 6.55; N, 8.28. Found: C, 66.11; H, 6.32; N, 8.26.

(*S*)-2-{[4-[5-(2-Carboxyphenyl)-1,3,4-oxadiazol-2-yl]phenyl]methyl}pentanoyl amino-3-methylbutanoic acid (3). A solution of NaOH (47 mg, 1.17 mmol) in H_2O (2 mL) was added to a solution of the diester **14** (200 mg, 0.39 mmol) in MeOH (10 mL), and the resulting mixture was heated at 50°C for 18 h. After cooling, the solvent was evaporated under vacuum, and the residue was taken up with H_2O (10 mL) and acidified with aqueous HCl to pH 4. The resulting precipitate was collected by filtration, washed with H_2O, and dried under vacuum to afford **3** (132 mg, 70%) as a colorless crystalline solid.

Mp 99–102°C. IR (KBr): 2962, 2872, 1724, 1612, 1266 cm^{-1}. ^1H NMR analysis of **3** revealed a complex mixture of conformers and/or topomers at room temperature.

^1H NMR (DMSO-d_6, 100°C): $\delta = 0.89–1.08$ (m, 9 H), 1.28–1.47 (m, 2 H), 1.53–1.59 (m, 2 H), 2.29–2.53 (m, 3 H), 4.47 (brs, 1 H), 4.77 (s, 2 H), 7.53–8.06 (m, 8 H). Anal. calcd. for $C_{26}H_{29}N_3O_6 \cdot H_2O$: C, 62.76; H, 6.28; N, 8.44. Found: C, 62.63; H, 5.97; N, 8.33.

(*O*-2-Cyanobenzoyl)-4-methylphenyl amidoxime (16). A mixture of 4-methylphenyl amidoxime (**15**) (1.50 g, 10.0 mmol), 2-cyanobenzoic acid (1.40 g, 9.52 mmol), DCC (2.06 g, 10.0 mmol), and DMAP (116 mg, 0.95 mmol) in dry THF (60 mL) was stirred at room temperature for 12 h under N_2. The DCU was filtered off and washed with THF. The filtrate was evaporated and the residue was recrystallized twice from acetone/H_2O to furnish the title compound **16** (2.26 g, 85%) as a white solid. Mp 135–137°C. IR (KBr): 3322, 2932, 2854, 2228, 1742, 1614, 1262 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 2.40$ (s, 3 H), 5.71 (brs, 2 H), 7.23–8.41 (m, 8 H).

2-[3-(4-Methylphenyl)-1,2,4-oxadiazol-5-yl]benzonitrile (17). TBAF (1 M in THF, 0.72 mL, 0.72 mmol) was added dropwise to a solution of **16** (2.00 g, 7.16 mmol) in THF (50 mL), under N_2. The reaction mixture was stirred at room temperature for 48 h and then poured into EtOAc (60 mL). The organic phase was washed with H_2O (3 × 20 mL) and brine (3 × 20 mL) and then dried ($MgSO_4$). The solvent was evaporated under vacuum, and the residue was crystallized from acetone/H_2O to afford the product **17** (1.37 g, 73%) as a white solid.

Mp 165–167°C. IR (KBr): 2922, 2226, 1594, 1362, 780 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 2.44$ (s, 3 H), 7.30–8.36 (m, 8 H). ^{13}C NMR ($CDCl_3$): $\delta = 22.32$, 112.44, 117.47, 124.20, 126.79, 128.33, 130.35, 130.77, 133.12, 133.73, 135.91, 142.63, 169.95, 173.08. Anal. calcd. for $C_{16}H_{11}N_3O$: C, 73.55; H, 4.24; N, 16.08. Found: C, 73.28; H, 4.13; N, 16.02.

2-[3-(4-Bromomethylphenyl)-1,2,4-oxadiazol-5-yl]benzonitrile (18). A mixture of **17** (1.00 g, 3.83 mmol), NBS (681 mg, 3.83 mmol), and benzoyl peroxide (92 mg, 0.38 mmol) in CCl_4 (25 mL) was refluxed for 4 h. After cooling to room temperature, the solvent was removed under vacuum, and

the residue was taken up with CH_2Cl_2 (30 mL). The organic phase was washed with 0.5 N aqueous NaOH (3 × 20 mL) and brine (3 × 20 mL) and then dried ($MgSO_4$). The solvent was evaporated to give 755 mg (58%, 89% purity) of crude **18** as a white powder, suitable for use without further purification. ^{1}H NMR ($CDCl_3$): $\delta = 4.55$ (s, 2 H), 7.53–8.36 (m, 8 H).

Ethyl 4-{4-[5-(2-cyanophenyl)-1,2,4-oxadiazol-3-yl]benzyloxy}-2-methylquinoline carboxylate (19). A mixture of **18** (306 mg, 0.90 mmol), ethyl 2-methyl-4-oxo-1,4-dihydroquinoline-6-carboxylate (200 mg, 0.86 mmol), and powdered K_2CO_3 (297 mg, 2.15 mmol) in anhydrous CH_3CN (10 mL) was heated under reflux for 5 h under Ar. After being allowed to cool to room temperature, the reaction mixture was poured into H_2O, and the resulting precipitate was filtered off, washed with H_2O, and recrystallized from EtOH to afford **19** (327 mg, 77%) as a white powder.

Mp 210–213°C. ^{1}H NMR ($CDCl_3$): $\delta = 1.44$ (t, $J = 7.1$ Hz, 3 H), 2.71 (s, 3 H), 4.45 (q, $J = 7.1$ Hz, 2 H), 5.42 (s, 2 H), 6.74 (s, 1 H), 7.65–8.37 (m, 10 H), 8.98 (s, 1 H). ^{13}C NMR ($CDCl_3$): $\delta = 15.06$, 26.83, 61.87, 70.47, 103.06, 112.40, 117.42, 119.85, 125.62, 126.50, 127.10, 127.54, 128.34, 128.86, 129.01, 130.31, 130.74, 133.27, 133.75, 135.91, 139.67, 151.53, 162.49, 163.30, 167.04, 169.48. Anal. calcd. for $C_{29}H_{22}N_4O_4$: C, 71.01; H, 4.52; N, 11.42. Found: C, 71.27; H, 4.48; N, 11.78.

2-Methyl-4-{4-(5-(2*H*(1*H*)-tetrazol-5-yl)phenyl]-1,2,4-oxadiazol-3-yl] benzyloxy] quinoline-6-carboxylic acid (4). Compound **19** (250 mg, 0.51 mmol) was added to a solution of Bu_3SnN_3 (0.49 mL, 1.78 mmol) in anhydrous toluene (10 mL), under Ar. After stirring at reflux for 72 h, the solvent was removed under vacuum, and the residue was taken up in EtOH (10 mL). To the resulting suspension a solution of NaOH (300 mg, 7.50 mmol) in H_2O (5 mL) was added, and the mixture was kept at 60°C for 24 h. The solvents were removed under vacuum, the residue was taken up in H_2O (10 mL) and heptane (10 mL), and the resultant biphasic mixture was stirred overnight. The aqueous phase was separated and acidified to pH 3 with aqueous HCl. The resulting precipitate was filtered off, washed with H_2O and heptane, and then dried under vacuum to furnish **4** (174 mg, 68%) as an off-white solid.

Mp > 250°C. IR (KBr): 3385, 1651, 1603, 1354 cm^{-1}. ^{1}H NMR (DMSO-d_6): $\delta = 2.63$ (s, 3 H), 5.51 (s, 2 H), 7.16 (s, 1 H), 7.74–8.18 (m, 10 H), 8.74 (s, 1 H). Anal. calcd. for $C_{27}H_{19}N_7O_4$: C, 64.15; H, 3.79; N, 19.40. Found: C, 63.81; H, 3.97; N, 19.08.

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