Synthesis of New 1,2,4- and 1,3,4-Oxadiazole Derivatives

Emerson Meyer, Antonio C. Joussef, Hugo Gallardo*

Departamento de Química, Universidade Federal de Santa Catarina, Florianópolis, SC - 88040-900, Brazil
Fax +55(48)3319711; E-mail: hugo@qmc.ufsc.br

Received 9 December 2002; revised 29 January 2003

Abstract: A novel series of compounds structurally related to nonpeptide angiotensin II (AII) receptor antagonists has been prepared. In these compounds, the ‘spacer’ phenyl ring commonly found in almost all AII receptor antagonists was replaced by 1,2,4- and 1,3,4-oxadiazole rings.

Key words: hypertension, heterocycles, drugs, quinolines, antagonists, oxadiazoles

The renin-angiotensin system (RAS) plays a very important role in the regulation of blood pressure and electrolyte balance via its effector hormone angiotensin II (AII). This peptide is a potent vasoconstrictor and stimulator of aldosterone secretion. The AII acts through specific receptors on the cell surface, which can be blocked by selective receptor antagonists. The discovery by DuPont of the first orally active, nonpeptide, AII receptor antagonist DuP 753 (Losartan) (1) (Figure 1), opened an exciting new phase of research to investigate AT1-selective agents for the treatment of hypertension. Since then, many other AII receptor antagonists have been prepared.1

![Figure 1](image-url)

In the course of our research to discover a structurally distinct class of AII receptor antagonists, we began to investigate a replacement for the 4-[(2'-biphenyltetrazole) group found in almost all nonpeptide AII receptor antagonists by designing new spacers based on heterocyclic rings, especially 1,3,4- and 1,2,4-oxadiazoles.

Methyl 2-[(5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl)benzoate (4) was prepared according to the general literature procedure.2 Treatment of 4-tolunitrile (2) with NaN₃–NH₄Cl in DMF at 100 °C for 18 hours led to tetrazole derivative 3, which in turn reacts with 2-carbomethoxybenzoyl chloride,³ in hot pyridine, through a two step process (the Huisgen reaction) involving acylation followed by rearrangement with elimination of N₂ to afford compound 4. Similarly, using a classical protocol, methyl 2-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]benzoate (7) was obtained by treatment of 4-tolunitrile (2) with NH₂OH in refluxing EtOH–H₂O solution to yield the corresponding amidoxime 6.³ Reaction of 6 with 2-carbomethoxybenzoyl chloride³ furnished the 1,2,4-oxadiazole derivative 7 in 42% overall yield.

Although in the preparation of 1,2,4- and 1,3,4-oxadiazole systems, the cyclization step involving o-substituted benzoyl derivatives is of a type known to be problematic,⁵ commonly requiring extended reaction times and providing low yields, the applied protocol was found to work very well, despite the presence of the sterically demanding 2-carbomethoxy moiety. Benzylcic bromination of 4 and 7 was carried out with N-bromosuccinimide in refluxing CCl₄ in the presence of a catalytic amount of benzyl peroxide as a radical initiator, leading to 5 and 8, respectively (Scheme 1).

Several different heterocyclic systems were coupled with 5 and 8, in such a way as to afford the postulated model compounds for angiotensin receptor antagonists. Reaction of 5 with 3-propylbenzimidazole (9)⁶ was performed under phase transfer catalysis (PTC) with TBAB as a phase transfer catalyst.⁷ This mild, less hazardous procedure seems to be a good alternative to the commonly applied NaH–DMF system. The esters 10 and 12 were then hydrolyzed to afford the carboxylic acids 11 and 13, respectively (Scheme 2).

Preparation of 16a and 18a was accomplished, respectively, by the reaction of 5 and 8 with ethyl 2-methyl-4-oxo-1,4-dihydroquinoline-6-carboxylate (14a)⁸ in the presence of K₂CO₃ in MeCN and the subsequent hydrolysis of the diesters (15a and 17a, respectively) with NaOH in MeOH–H₂O (Scheme 3). Synthesis of 16b,c and 18b,c was carried out by a similar sequence of reactions (Table 1). The starting quinolines 14a–c were prepared according to the Conrad–Limpach method,⁸ from the appropriate anilines and β-keto esters. It is worth noting that the alkylation methodology applied to the quinoline systems led exclusively to O-alkylated products, as confirmed by the ¹³C NMR signal of benzylic carbon at ca δ = 70, which is consistent with O- rather than N-alkylation.⁹ We tried to extend the PTC protocol to the alkylation of the quinoline systems and although the same regioselectivity was found, unfortunately the yields were considerably lower, even with extended reaction times, precluding the application of the methodology.
We performed the alkylation of 2-acetylamino-5-ethyl-1,3,4-thiadiazole (19) with halide 5 and, as expected, the reaction resulted in an equal amount of the endo N- and exo N-alkylated products. The regioselectivity was determined by \( ^1H \) NMR, after chromatographic separation, which showed the quartet signal (C5CH\(_2\)CH\(_3\)), centered at \( \delta = 2.84 \) for the product of endo N-alkylation (20) and centered at \( \delta = 3.07 \) for the product of exo N-alkylation (21), in agreement with the assignments reported by Nagao and collaborators. The hydrolysis of 20 with NaOH in MeOH–H\(_2\)O gave the acid 22. In contrast, hydrolysis of 21 resulted in complete cleavage of the acetyl group in addition to the desired saponification of the methyl ester (Scheme 4).

The compounds are undergoing pharmacological evaluation and the results will be published elsewhere.

\[ \begin{align*}
\text{Scheme 1} \\
\text{Scheme 2}
\end{align*} \]

Mps 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). IR spectra were obtained with a Perkin–Elmer Model 16 PC-FTIR spectrophotometer. \(^1H\) NMR spectra were determined on a Bruker AW-200 (200 MHz) instrument, with tetramethylsilane (TMS) as the internal standard and \(^13C\) NMR spectra were recorded on a Bruker (50.3 MHz) spectrometer. Elemental analyses were within ±0.4% of theoretical values and were determined on a Perkin–Elmer 2400 instrument. Many of the compounds were unavoidably analyzed as solvates, owing to their tendency to retain solvent under nondestructive drying conditions. Where solvation is indicated, the presence of solvent in the analytical sample was verified by NMR. Solvents were dried according to standard procedures. Tetrabutylammonium bromide is abbreviated as TBAB.

\[ \begin{align*}
\text{Scheme 1} \\
\text{Scheme 2}
\end{align*} \]

5-(4-Methylphenyl)tetrazole (3)
To a solution of 4-tolunitrile (2) (10.0 g, 84 mmol) in DMF (100 mL), sodium azide (5.98 g, 92 mmol) and NH\(_4\)Cl (4.92 g, 92 mmol) were added and the mixture was heated to 100 °C for 18 h. After being allowed to cool to r.t., the mixture was poured into ice–water and acidified with aq HCl (6 N) to pH 2–3 (CAUTION: HN\(_3\) evolution). The precipitate was filtered, washed several times with H\(_2\)O, and further purified by crystallization to afford 3.

Yield: 10.2 g (75%); colorless crystals; mp 242–243 °C (EtOH–H\(_2\)O) (lit.\(^{26}\) 242–243 °C).
A mixture of 2-carbethoxybenzoic acid (5.0 g, 27.8 mmol) in thionyl chloride (10 mL) was refluxed for exactly 1 h. The solution was cooled to r.t., the excess of thionyl chloride was evaporated under vacuum, and the residue was added dropwise to an ice-cooled solution of 3 (4.45 g, 27.8 mmol) in anhyd pyridine (30 mL). The cooling bath was removed, and the solution was heated to 100 °C until the evolution of N\textsubscript{2} ceased (about 1 h). After cooling, the reaction mixture was poured into H\textsubscript{2}O (150 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed successively with H\textsubscript{2}O (3 × 20 mL), aq HCl (5%; 3 × 20 mL), sat. aq NaHCO\textsubscript{3} (3 × 20 mL) and brine (2 × 20 mL). The organic phase was dried (MgSO\textsubscript{4}), filtered and concentrated under vacuum to give 4.
Yield: 5.47 g (67%); white solid; mp 75–76 °C (MeOH–H₂O). IR (KBr): 1736, 1242, 704 cm⁻¹.

¹H NMR (CDCl₃): δ = 2.43 (s, 3 H), 3.83 (s, 3 H), 7.30–7.99 (m, 8 H).

¹³C NMR (CDCl₃): δ = 21.61, 52.67, 120.99, 123.71, 126.84, 129.80, 129.90, 130.30, 131.31, 131.63, 142.38, 163.62, 165.18, 167.38.


Methyl 2-[5-(4-Bromomethylphenyl)-1,3,4-oxadiazol-2-yl]benzoate (8)
A solution of 7 (4.0 g, 13.6 mmol), NBS (2.42 g, 13.6 mmol) and benzoyl peroxide (0.10 g, 0.41 mmol) in CCl₄ (60 mL) was refluxed for 4 h. After cooling to r.t., the resulting suspension was filtered off and then concentrated under vacuum to provide an oil, which upon trituration with Et₂O–hexane solidified as a white powder (3.55 g, 70%; 86% purity). The crude product was used in the subsequent reactions without further purification.

Yield: 5.40 g (66%); colorless plates; mp 70–71 °C (Et₂O–hexane).

IR (KBr): 1736, 1240, 704 cm⁻¹.

¹H NMR (CDCl₃): δ = 2.49 (s, 3 H), 4.53 (s, 2 H), 7.53–8.08 (m, 8 H).

13C NMR (CDCl₃): δ = 21.80, 48.37, 123.63, 123.82, 127.34, 127.52, 127.55, 129.77, 130.11, 130.12, 131.13, 136.82, 142.42, 153.84, 154.90, 164.69, 165.14, 167.78.


Methyl 2-[5-(4-Bromomethylphenyl)-1,3,4-oxadiazol-2-yl]benzoate (9)
To a mixture of 8 (350 mg, 0.94 mmol), 2-propylbenzimidazole (9) (142 mg, 0.89 mmol) and TBAB (57 mg, 0.18 mmol) in CH₂Cl₂ (10 mL), a solution of NaOH (37 mg, 0.94 mmol) in H₂O (1 mL) was added. The mixture was stirred for 24 h at r.t. The organic phase was separated, washed with brine (3 × 10 mL) and dried (MgSO₄). After solvent removal, the crude product was chromatographed (silica gel; 1% MeOH–CH₂Cl₂). The resulting product was recrystallized from acetone–H₂O to give 10.

Yield: 301 mg (75%); white powder; mp 179–180 °C.

¹H NMR (CDCl₃): δ = 1.02 (t, J = 7.3 Hz, 3 H), 1.88 (m, 2 H), 2.83 (t, J = 7.5 Hz, 2 H), 3.82 (s, 3 H), 5.42 (s, 2 H), 7.17–8.05 (m, 12 H).

13C NMR (CDCl₃): δ = 14.67, 21.72, 30.17, 47.27, 53.40, 109.93, 120.13, 128.89, 123.15, 124.15, 124.29, 127.50, 128.22, 130.68, 131.11, 132.17, 132.37, 135.84, 140.69, 143.41, 155.84, 164.69, 165.14, 167.78.

Anal. Calcld for C₂₆H₂₂N₄O₃·0.125 H₂O: C, 71.89; H, 5.55; N, 12.15. Found: C, 72.08; H, 5.76; N, 12.46.

Methyl 2-[5-(4-Propyl-1H-benzimidazol-1-ylmethyl)phenyl]-1,3,4-oxadiazol-2-yl]benzoate (10)
The title compound was prepared from 8 by the same procedure described for the preparation of 10.

Yield: 68%; mp 121–123 °C (EtOAc–hexane).

¹H NMR (CDCl₃): δ = 1.02 (t, J = 7.3 Hz, 3 H), 1.89 (m, 2 H), 2.83 (t, J = 7.4 Hz, 2 H), 3.85 (s, 3 H), 5.41 (s, 2 H), 7.15–8.12 (m, 12 H).

¹³C NMR (CDCl₃): δ = 14.64, 21.67, 30.12, 47.29, 53.44, 110.00, 120.00, 122.76, 123.03, 124.60, 127.09, 127.25, 128.75, 130.42, 130.80, 132.20, 132.66, 132.88, 135.88, 139.99, 143.34, 155.87, 167.81, 168.74, 176.17.

Anal. Calcld for C₂₅H₂₃NO₃·0.1 C₆H₅·C, 71.89; H, 5.55; N, 12.15. Found: C, 72.08; H, 5.76; N, 12.46.

2-[5-(4-Propyl-1H-benzimidazol-1-ylmethyl)phenyl]-1,3,4-oxadiazol-2-yl]benzoic Acid (11)
To a solution of methyl ester 10 (150 mg, 0.33 mmol) in MeOH (10 mL), a solution of NaOH (40 mg, 0.99 mmol) in H₂O (1 mL) was added, and the resulting mixture was stirred at r.t. overnight. The solvent was evaporated under vacuum, and the residue was taken up with H₂O and acidified with aq HCl to pH 4. The resulting precipitate was filtered off and washed with H₂O affording compound 11.

Yield: 132 mg (91%); white powder; mp >200 °C (gradual).

¹H NMR (DMSO-d₆): δ = 0.94 (t, J = 7.3 Hz, 3 H), 1.76 (m, 2 H), 2.83 (t, J = 7.4 Hz, 2 H), 5.62 (s, 2 H), 7.15–8.01 (m, 12 H).

¹³C NMR (DMSO-d₆): δ = 13.81, 20.38, 28.48, 45.80, 110.17, 118.52, 121.61, 121.94, 122.43, 123.08, 127.09, 127.52, 129.77, 130.53, 131.88, 131.99, 132.66, 135.21, 141.43, 142.21, 155.12, 163.80, 164.02, 167.62.

Anal. Calcld for C₂₆H₂₃NO₃·0.125 H₂O·0.5 HCl: C, 68.04; H, 4.99; N, 12.20. Found: C, 67.99; H, 4.96; N, 12.19.
2-[3-[4-(2-Propyl-1H-benimidazol-1-ylmethyl)phenyl]-1,2,4-oxadiazol-5-yl]benzoic Acid (13)

The title compound was obtained from 12 according to the procedure described for the preparation of 11.

Yield: 96%; white powder; mp 143–145 °C.

1H NMR (DMSO-d6): δ = 0.94 (t, J = 7.3 Hz, 3 H), 2.71 (s, 3 H), 3.88 (s, 3 H), 4.44 (q, J = 7.1 Hz, 2 H), 5.40 (s, 2 H), 6.73 (s, 1 H), 6.76–8.19 (m, 9 H), 8.29 (dd, J = 1.7 Hz, 1 H).

13C NMR (DMSO-d6): δ = 14.18, 21.47, 27.05, 53.55, 70.07, 101.15, 118.61, 123.04, 124.78, 127.32, 128.27, 128.57, 130.53, 130.91, 132.32, 132.72, 133.04, 134.12, 134.20, 134.28, 140.07, 151.50, 161.79, 162.44, 164.11, 166.94, 167.74, 168.26.

Anal. Calcd for C31H27N3O6: C, 68.80; H, 5.10; N, 7.76. Found: C, 68.85; H, 5.29; N, 7.84.

Ethyl 4-[4-[[2-(Carboxymethoxy)phenyl]-1,2,4-oxadiazol-2-yl]-benzyloxy]-2-methyl-quinoline-6-carboxylate (15a); General Procedure

A suspension of 5 (330 mg, 0.88 mmol), ethyl 2-methyl-4-oxo-1,4-dihydroquinoline-6-carboxylate (14a) (200 mg, 0.86 mmol) and powdered K2CO3 (297 mg, 2.15 mmol) in anhyd MeCN (10 mL) was heated under reflux for 4 h under nitrogen. After being allowed to cool to r.t., the reaction mixture was poured into H2O, and the resulting precipitate was filtered off, washed with H2O and recrystallized from acetone–H2O to give 15a.

Yield: 317 mg (70%); white powder; mp 194–196 °C.

1H NMR (CDCl3): δ = 1.38 (t, J = 7.6 Hz, 3 H), 2.96 (q, J = 7.6 Hz, 2 H), 3.86 (s, 3 H), 4.44 (q, J = 7.1 Hz, 2 H), 5.42 (s, 2 H), 6.75 (s, 1 H), 7.66–8.27 (m, 10 H), 8.97 (d, J = 1.7 Hz, 1 H).


Anal. Calcd for C13H23N2O2⋅0.2 H2O: C, 68.80; H, 5.10; N, 7.76. Found: C, 68.85; H, 5.29; N, 7.84.
4-{4-[2-Carboxyphenyl]-1,2,4-oxadiazol-3-yl]benzoyl}oxy]-2-methylquinoline-6-carboxylic Acid (18a)
Yield: 77%; mp >177 °C (gradual).
1H NMR (DMSO-d6): δ = 2.73 (s, 3 H), 5.60 (s, 2 H), 7.33 (s, 1 H), 7.80–8.29 (m, 10 H), 8.77 (d, J = 1.0 Hz, 1 H).
13C NMR (DMSO-d6): δ = 24.32, 70.29, 103.64, 118.57, 123.71, 124.29, 126.20, 127.57, 128.78, 128.89, 130.48, 131.98, 132.87, 139.14, 147.46, 162.29, 162.73, 166.73, 167.44, 167.66, 176.15.

4-[4-{4-[2-Carboxyphenyl]-1,2,4-oxadiazol-3-yl]benzoyl}oxy]-2-ethylquinoline-6-carboxylic Acid (16b)
Yield: 66%; mp >242 °C (gradual).
1H NMR (DMSO-d6): δ = 1.32 (t, J = 7.5 Hz, 3 H), 2.91 (q, J = 7.5 Hz, 2 H), 5.54 (s, 2 H), 7.18 (s, 1 H), 7.76–8.18 (m, 10 H), 8.75 (s, 1 H).
13C NMR (DMSO-d6): δ = 13.42, 32.08, 69.50, 102.25, 118.82, 123.03, 123.15, 124.15, 126.99, 128.55, 128.85, 129.24, 129.76, 130.51, 131.86, 132.01, 132.72, 140.14, 150.16, 161.23, 163.88, 164.11, 167.04, 167.48, 167.72.

Yield: 63%; mp 212–214 °C.
1H NMR (DMSO-d6): δ = 2.43 (s, 3 H), 2.62 (s, 3 H), 2.63 (s, 3 H), 5.47 (s, 2 H), 6.99 (s, 1 H), 7.3–8.12 (m, 10 H).
13C NMR (DMSO-d6): δ = 136.20, 23.50, 25.89, 68.87, 101.24, 117.29, 118.12, 122.85, 123.03, 126.86, 127.41, 128.31, 129.73, 130.49, 131.76, 131.96, 132.86, 137.08, 140.61, 147.18, 158.36, 160.53, 163.88, 164.09, 167.66.

Yield: 76%; mp 148–152 °C (EtOH).
1H NMR (DMSO-d6): δ = 2.44 (s, 3 H), 2.63 (s, 6 H), 5.47 (s, 2 H), 7.01 (s, 1 H), 7.31–8.18 (m, 10 H).
13C NMR (DMSO-d6): δ = 13.26, 20.32, 25.80, 68.97, 101.18, 117.33, 118.16, 123.77, 125.75, 127.38, 128.11, 129.87, 130.46, 131.90, 132.48, 132.75, 132.96, 137.12, 140.06, 147.07, 158.35, 160.65, 167.40, 167.67, 176.11.

Yield: 63%; mp >179 °C (gradual).
1H NMR (DMSO-d6): δ = 1.20 (t, J = 7.4 Hz, 3 H), 2.81 (q, J = 7.4 Hz, 2 H), 4.55 (d, J = 4.8 Hz, 2 H), 7.55–8.02 (m, 8 H), 8.21 (b, J = 4.8 Hz, 1 H).
13C NMR (DMSO-d6): δ = 13.78, 23.11, 47.49, 121.94, 123.04, 126.65, 128.33, 129.70, 130.46, 131.76, 131.93, 132.81, 143.45, 159.85, 163.73, 164.20, 167.65, 168.07.
Synthesis of New 1,2,4- and 1,3,4-Oxadiazole Derivatives

Anal. Calcd for C_{20}H_{17}N_{5}O_{3}S \cdot 0.1 H_{2}O \cdot 0.2 HCl: C, 57.67; H, 4.21; N, 16.81. Found: C, 57.65; H, 4.14; N, 16.62.

Acknowledgments
We gratefully acknowledge support of this work by CNPq and PRONEX (Brazil). We thank Dr. Miguel S. B. Caro and co-workers by recording NMR spectra and for helpful discussions.

References


