Synthesis of New 1,2,4-Oxadiazoles Carrying (1'*S*,2'*S*)-*t*-Butyloxycarbonyl-1-amino-2-methyl-1-butyl and (1'*S*)-*t*-Butyloxycarbonyl-1'-amino-1'-ethyl Groups at C-5

Vanildo Martins L. Braga[a], Sebastião J. de Melo*,[a] Rajendra M. Srivastava*,[b] and
Emerson Peter da S. Falcão[a]

[a]*Departamento de Antibióticos, Universidade Federal de Pernambuco, Av. Prof. Moraes Rego s/n,*
Cidade Universitária, 50670-901 Recife-PE, Brazil

[b]*Departamento de Química Fundamental, Universidade Federal de Pernambuco, Av. Prof. Luiz Freire,*
Cidade Universitária, 50740-540 Recife-PE, Brazil

Uma síntese fácil e eficiente de 3-aril-5[(*1S*)-t-butiloxicarbonil-1-amino-(*2S*)-metil-1-butil)]-1,2,4-oxadiazóis **4a-f** e 3-fenil-5-[(*1S*)-*t*-butiloxicarbonil-1-amino-1-etil]-1,2,4-oxadiazol **6** partindo de arilamidoximas, *N-t-Boc*-L-isoleucina e *N-t-Boc*-L-alanina é descrita. As estruturasedos intermediários e compostos finais foram determinadas a partir dos dados espectroscópicos.

A facile and efficient synthesis of 3-aryl-5-[(*1S*)-*t*-butyloxycarbonyl-1-amino-(*2S*)-methyl-1-butyl)]-1,2,4-oxadiazoles **4a-f** and 3-phenyl-5-[(*1S*)-*t*-butyloxycarbonyl-1-amino-1-ethyl]-1,2,4-oxadiazole **6** starting from arylamidoximes, *N-t-Boc*-L-isoleucine and *N-t-Boc*-L-alanine is decribed. The structures of the intermediates and final compounds have been deduced from spectroscopic data.

Keywords: chiral drugs, 1,2,4-oxadiazoles, arylamidoximes, isoleucine, alanine, antiinflammatory, antipyretic

Introduction

It is known that stereoisomers of chiral drugs often exhibit pronounced differences in their pharmacokinetic and pharmacodynamic properties both in quantitative and qualitative terms.[1] So, it is extremely necessary to study each stereoisomer separately. With the correct therapeutic information it is possible to maximize the properties of the drug by taking the most potent enantiomer, the eutomer,[2] or eliminating the enantiomer that may cause side effects, the distomer. The latter can be linked to a secondary molecular target.[3] The pharmaceutical market has converged strongly to this idea of single enantiomers as substitutes for their racemates. The change to chiral technologies offers many advantages to the pharmaceutical industry, including fewer toxicological tests, lower costs for liberation and less metabolites. These advantages are also beneficial for the patient's health.[4] In the not too distant future, chiral drugs in single enantiomeric forms will probably substitute most of the existing racemates and will eventually touch every area of clinical medicine.[7]

Only in a few situations that are not common at all, it is more appropriate to use the racemate instead of the eutomer, for example with ibuprofen, a nonsteroidal antiinflammatory drug (NSAID) commercially available in the market. In this particular case, there is an enzymatic inversion of the *R*(-) distomer to the eutomer (*S*) responsible for the activity.[5] In any event, it is a single enantiomer (*S*) which is important. However, in other NSAIDs such as flurbiprofen[6] and ketoprofen,[7] this inversion is insignificant in humans, and so the application of the chiral technology for the use of the eutomer is more appropriate.

In view of the great importance of single enantiomers, our current research is focused on synthesizing new 1,2,4-oxadiazoles containing asymmetric centers in their C-5 side chain. Our main goal was to synthesize compounds possessing an amino group in the C-5 side chain. It is well known that a tertiary amine function attached to the C-5 alkyl chain of 1,2,4-oxadiazoles possess antiinflammatory as well as other interesting pharmacological activities.[8,9] With this idea in mind, we synthesized seven *Boc* protected amines. In fact, two of these new compounds **4d** and **4e** showed antiinflammatory activity. These are very significant in the sense that they can be deprotected easily to remove the Boc group followed by their transformation

* e-mail: melosj@ibest.com.br

into *N,N*-dialkyl amino compounds. These compounds will be potential candidates for analgesic, antiinflammatory and antipyretic activity. Therefore, this communication describes some biologically active 1,2,4-oxadiazoles with one or two asymmetric centers in their side chain. Such compounds have not been cited in the literature before.

Results and Discussion

The strategy used to achieve our goals explored known protected amino acids as starting materials. We have already published one paper relating to the synthesis of 3-aryl-1,2,4-oxadiazoles carrying a protected L-alanine side chain, starting from arylamidoximes and protected aspartic acid,[10] and it has been established that the products obtained from the condensation of arylamidoximes and an appropriately protected amino acid didn't lead to isomerization. Applying a similar strategy, but using Boc-protected L-isoleucine or L-alanine and arylamidoximes, we synthesized seven 1,2,4-oxadiazoles, six containing two asymmetric centers **4a-f** and one oxadiazole having only one asymmetric center **6,** as shown below (Scheme 1). Earlier, another group has observed that even in pyridine as reaction solvent, no significant racemization occurs in the case of 1,2,4-oxadiazoles having an asymmetric carbon attached to C-5.[11]

Since the reaction conditions in the present work are mild and similar to the one reported earlier,[10] it is assumed that no racemization occurred during the synthesis of these 1,2,4-oxadiazoles. This conclusion is supported by the ^{1}H NMR spectra, which showed the presence of only one H-3 absorption for **3a-f**; had there been racemization, one would

expect two diastereomers hence more than one absorption. The 300 MHz ^{1}H NMR spectra of compounds **3a-f** showed a triplet at δ 0.95 ppm and a doublet at δ 1.02 ppm for the terminal and C-3 methyl groups. In compounds **4a-f**, the doublet due to methyl group shifted to higher field and generally overlapped with the triplet of the other methyl group. This shift is attributed to the ring current effect causing C-3 methyl group signals to move upfield.

The mass analyses agreed with the proposed structures. However the compounds **4d**, **e** and **f**, show a sequence of fragmentations which occurs during the decomposition of M[+•]. These include the loss of *t*-butyloxide radical (73 mass units), the extrusion of carbon monoxide (28 mass units), rearrangement and finally the elimination of butene-2 molecule (56 mass units) to provide the major fragments a', at *m/z* 204 (**4d**), b' *m/z* 208 (**4e**) and c', *m/z* 219 for the compound **4f**. These are depicted in Scheme 2.

The synthesis of compound **6** was carried out with the aim to shorten the side-chain containing the amino group and consequently reduce the lipophilicity.

Experimental

Melting points were determined with a Thomas Hoover apparatus and are uncorrected. Elemental analyses of compounds **4a-f** were performed in the Central Analítica do Departamento de Química Fundamental da Universidade Federal de Pernambuco. Infrared spectra were recorded on a Bruker spectrophotometer Model IFS66. 300 MHz ^{1}H-NMR and 75 MHz ^{13}C NMR spectra were recorded on a Varian Unity plus instrument, using $CDCl_3$ as solvent and TMS as internal reference. Thin-layer chromatography (tlc) was done

Scheme 1.

Ar = p-CH$_3$OPh   (**4d**)
Ar = p-Cl   (**4e**)
Ar = p-NO$_2$ (**4f**)

a', m/z = 204
b', m/z = 208
c', m/z = 219
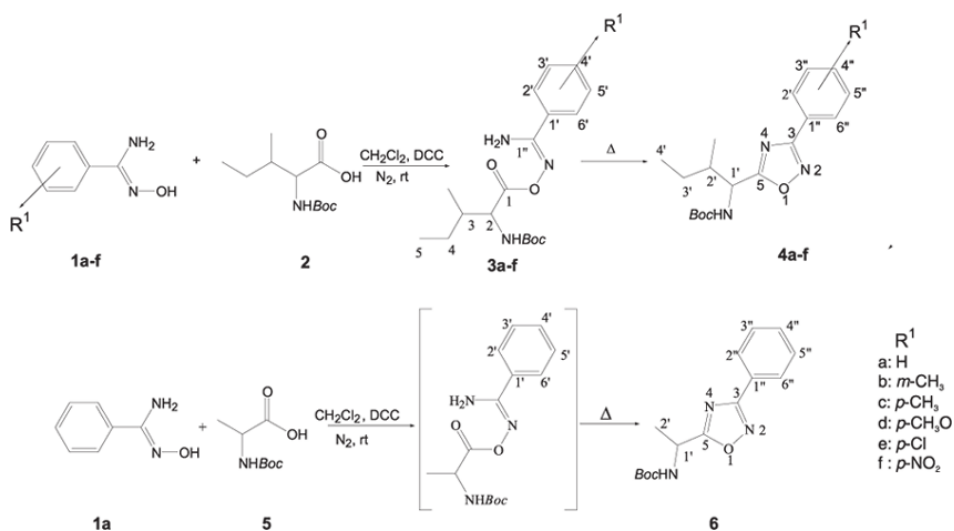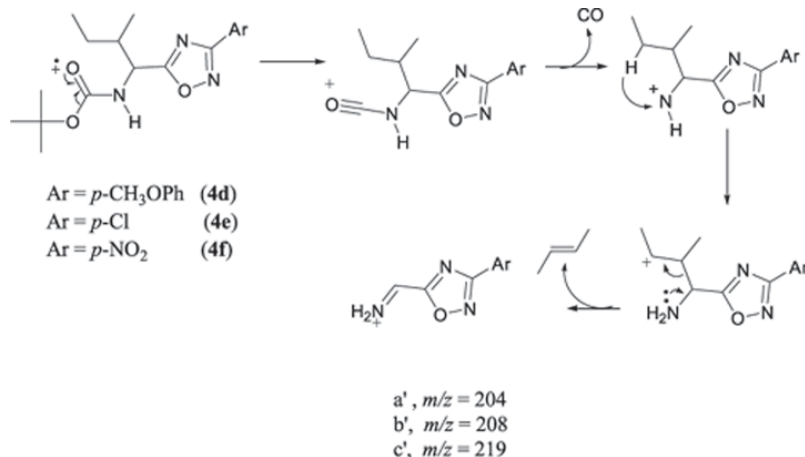
Scheme 2.

on plates coated with silica gel having a fluorescent indicator P$_{254}$ (Merck) and the spots were detected under ultraviolet light. Arylamidoximes were obtained following the methodology reported in the literature.[12]

General Procedure for the Synthesis of O-[(2S, 3S)-2-t-Butyloxycarbonylamino-3-methylpentanoyl] arylamidoximes (3a-f). The appropriate arylamidoxime **1a-f** (3.7 mmol) was allowed to react with *N-t-Boc*-L-isoleucine **2** (3.7 mmol) and *N,N'*-dicyclohexylcrbodiimide (4.1 mmol) in dry CH$_2$Cl$_2$ 10 mL under N$_2$ atmosphere at room temperature for periods varying from 3 to 5 hours. The completion of the reaction was monitored by TLC. Generally, the products were purified by column chromatography on silica gel using *n*-hexane-ethyl acetate (7.0:3.0) as eluent. The same solvent system was employed for developing the TLC plates. An ultraviolet lamp was used for the detection of the spots.

Data for O-[(2S, 3S)-2-t-butyloxycarbonylamino-3-methylpentanoyl]benzamidoxime (3a). White crystals (69% yield), mp 110-111 °C. IR (KBr) ν_{max}/cm^{-1}: 3483 (νNH$_2$, asym); 3347 (νNH$_2$, sym; νNH); 2966(νC-H); 1740 (νCO$_2$); 1688 (νNHCO$_2$); 1614 and 1519 (νC=C, ar); 1586 (νC=N) ; 1519 (νC=C band); 1172 (νC-O). ^{1}H NMR (CDCl$_3$) δ: 0.95 (3H, t, *J* 7.5 Hz); 1.02 (3H, d, *J* 6.9 Hz); 1.44 (9H, s); 1.14-1.68 (2H, m); 1.84-2.00 (1H, m); 4.31 (1H, dd, *J* 8.7 Hz, *J* 6.3 Hz); 5.16 (1H, d, *J* 8.7 Hz); 5.37 (2H, bs); 7.35-7.52 (3H, m); 7.67-7.75 (2H, m). ^{13}C NMR (CDCl$_3$) 11.4 (C-5); 15.3 (CH$_3$); 25.0 (C-4); 28.3 (CH$_3$)$_3$; 37.8 (C-3); 57.3 (C-2); 80.1 (C); 130.8 (C-1'); 128.1 (C-2' and C-6'); 128.7 (C-3' and C-5'); 131.1 (C-4'); 155.9 (C1"); 157.8 (CONH); 170.1 (C-1).

Data for O-[(2S, 3S)-2-t-butyloxycarbonylamino-3-methylpentanoyl]m-tolylamidoxime (3b). White crystals (73% yield, mp 118-119 °C. IR (KBr) ν_{max}/cm^{-1}: 3494 (νNH$_2$, asym); 3343 (νNH$_2$, sym; νNH); 2967 (νC-H); 1742

(νCO$_2$); 1691 (νNHC0$_2$); 1621 and 1522 (νC=C , ar); 1587 (νC=N); 1168 (νC-O). ^{1}H NMR (CDCl$_3$) δ: 0.93 (3H, t, *J* 7.4 Hz); 1.00 (3H, d, *J* 6.9 Hz); 1.43 (9H, s); 1.10-1.70 (2H, m); 1.82-2.00 (1H, m); 2.36(3H, s); 4.30 (1H, dd, *J* 6.0 Hz, *J* 8.7 Hz); 5.19 (1H, d, *J* 8.7 Hz); 5.29 (2H, bs); 7.62 (2H, d, *J* 9.3 Hz); 8.00 (2H, m). ^{13}C NMR (CDCl$_3$): 11.4 (C-5); 15.5 (CH$_3$); 21.4 (Ar-CH$_3$); 25.0 (C-4); 28.3 (CH$_3$)$_3$; 37.6 (C-3); 57.5 (C-2); 80.0 (C); 123.8(C-6'); 127.6 (C-1'); 128.6 (C-2'); 130.2 (C-5'); 132.1 (C-4'); 138.6 (C-3'); 156.0 (C1"); 158.3 (CONH);170 (C-1).

Data for O-[(2S, 3S)-2-t-butyloxycarbonylamino-3-methylpentanoyl]p-tolylamidoxime (3c). White crystals (65% yield), mp 105-106 °C. IR (KBr) ν_{max}/cm^{-1} : 3500 (νNH$_2$ asym) 3358 (νNH$_2$, sym); 3333 (νNH); 2965 (νC-H); 1746(νCO$_2$); 1693 (νNHCO$_2$); 1614 and 1521(νC=C, ar); 1587(νC=N); 1175 (νC-O). ^{1}H NMR (CDCl$_3$) δ: 0.94 (3H, t, *J* 7.4 Hz); 1.01 (3H, d, *J* 6.6 Hz); 1.44 (9H, s); 1.14-1.68 (2H, m); 1.82-2.00 (1H, m); 2.38 (3H, s); 4.30 (1H, dd, *J* 6.3 Hz, *J* 8.1 Hz); 5.21 (1H, d, *J* 8.4 Hz); 5.44 (2H, bs); 7.35 (2H, d, *J* 8.7 Hz); 7.61 (2H, d, *J* 8.4 Hz). ^{13}C NMR (CDCl$_3$): 11.4 (C-5); 15.5 (CH$_3$); 21.2 (Ar-CH$_3$); 25.1 (C-4); 28.3 (CH$_3$)$_3$; 37.5 (C-3); 57.4 (C-2); 80.1 (C); 123.8 (C-1'); 127.4 (C-2' and C-6'); 129.5 (C-3' and C-5'); 141.5 (C-4'); 155.9 (C-1"); 158.3 (CONH); 170.0 (C-1).

Data for O-[(2S, 3S)-2-t-butyloxycarbonylamino-3-methylpentanoyl]p-anisylamidoxime (3d). Yellow crystals (80% yield), mp = 112-113 °C. IR (KBr) ν_{max}/cm^{-1}: 3493 (ν-NH$_2$, asym); 3344 (ν-NH$_2$, sym; νNH); 2970 (νC-H); 1744 (ν-CO$_2$); 1692 (ν-NHC0$_2$);1615 and 1520 (νC=C, ar); 1565 (νC=N); 1165 (νC-O). ^{1}H NMR (CDCl$_3$) δ 0.96 (3H, t, *J* 7.4 Hz,); 1.04 (3H, d, *J* 6.9 Hz); 1.45 (9H, s); 1.16-1.70 (2H, m); 1.86-2.00 (1H, m); 3.81 (3H, s); 4.30 (1H, dd, *J* 6.3 Hz, *J* 8.1 Hz); 5.13 (1H, d, *J* 8.4 Hz); 5.49 (2H, bs); 7.91 (2H, d,

J 9.0 Hz); 8.27 (2H, d, *J* 9.0 Hz). ^{13}C NMR (CDCl$_3$): 11.4 (C-5); 15.4 (CH$_3$); 25.1 (C-4); 28.3 (CH$_3$)$_3$; 37.5 (C-3); 57.4 (C-2); 55.3 (O-CH$_3$); 80.1 (C); 113.9 (C-3' and C-5'); 122.5 (C-1'); 128.4 (C-2' and C-6'); 155.9 (C-4'); 157.8 (C-1''); 161.9 (CONH); 170.1 (C-1).

*Data for O-[(2S, 3S)-2-t-butyloxycarbonylamino-3-methylpentanoyl]p-chlorobenzamidoxime (**3e**)*. White crystals (80% yield), mp 114-115 °C. IR (KBr) ν_{max}/cm^{-1}: 3500 (*ν*-NH$_2$,asym); 3358 (*ν*NH$_2$,sym); 3315 (*ν*-NH); 2963 (*ν*C-H); 1751 (*ν*CO$_2$), 1692 (*ν*NHCO$_2$); 1615 and 1522 (*ν*C=C, ar); 1587 (*ν*C=N); 1172 (*ν*C-O). ^{1}H NMR (CDCl$_3$) *δ*: 0.95 (3H, t, *J* 7.5 Hz); 1.02 (3H, d, *J* 6.9 Hz); 1.45 (9H, s); 1.16-1.70 (2H, m); 1.80-2.00 (1H, m); 4.32 (1H, dd, *J* 6.0 Hz, *J* 8.9 Hz); 5.13 (1H, d, *J* 8.7 Hz); 5.19 (2H, bs); 7.25 (2H, d, *J* 9 Hz); 7.60 (2H, d, *J* 8.1 Hz). ^{13}C NMR (CDCl$_3$): 11.4 (C-5); 15.6 (CH$_3$); 25.1 (C-4); 28.4 (CH$_3$)$_3$; 37.6 (C-3); 57.5 (C-2); 80.2 (C); 128.3 (C-2' and C-6'); 128.9 (C-3' and C-5'); 129.2 (C-1'); 137.2 (C-4'); 155.1 (C-1''); 157.1 (CONH); 170.3 (C-1).

*Data for O-[(2S, 3S)-2-t-butyloxycarbonylamino-3-methylpentanoyl]p-nitrobenzamidoxime (**3f**)*. White crystals (75% yield), mp 110-112 °C. IR (KBr) ν_{max}/cm^{-1}: 3477 (*ν*NH$_2$,asym); 3341 (*ν*-NH$_2$,sym; *ν*NH); 2967 (*ν*C-H); 1755 (*ν*CO2); 1691 (*ν*NHC02); 1639 and 1522 (*ν*C=C, ar); 1585 (*ν*C=N); 1168 (*ν*C-O). ^{1}H NMR (CDCl$_3$) *δ*: 0.94 (3H, t, *J* 7.5 Hz); 1.02 (3H, d, *J* 6.9 Hz); 1.44 (9H, s); 1.10-1.76 (2H, m); 1.80-2.00 (1H, m); 4.31 (1H, dd, *J* 6.0 Hz, *J* 8.7 Hz); 5.15 (1H, d, *J* 9.0 Hz); 5.26 (2H, bs); 7.25-7.30 (2H, m); 7.40-7.50 (2H ,m). ^{13}C NMR (CDCl$_3$): 11.3 (C-5); 15.5 (CH$_3$); 25.0 (C-4); 28.2 (CH$_3$)$_3$; 37.4 (C-3); 57.4 (C-2); 80.3 (C); 123.8 (C-3' and C-5'); 127.9 (C-2' and C-6'); 136.9 (C-1'); 149.3 (C-4'); 155.9 (C-1''); 156.1 (CONH);169.9 (C-1).

*General Procedure for the Synthesis of 5-[(1'S, 2'S)-1-t-Butyloxycarbonylamino-2-methylbutyl)]-3-aryl-1,2,4-oxadiazoles **4a-f** and 5-[(2S)-1-t-Butyloxycarbonyl-1-aminoeth-1-yl]-3-phenyl-1,2,4-oxadiazole (**6**)*

The intermediates **3** were heated at temperatures that varied from 100 to 120 °C. The reactions were acompanied by TLC and discontinued when the TLC plate showed the disappearance of the starting compound, in three to five hours. In the case of the compound starting from *N*-t-Boc-L-alanine **5**, it was not possible to isolate the intermediate. The compounds obtained **4a-f** initially had a pasty appearance, but after some days in a dry atmosphere under vacum the compounds started to crystallize. Conversion of intermediates **3 a-f** to **4 a-f** were quantitative; however, the yields of the pure and crystalline products are given below.

*Data for 5-[(1'S, 2'S)-1'-t-Butyloxycarbonylamino-2'-methylbutyl)]-3-phenyl-1,2,4-oxadiazole (**4a**)*. Colorless

crystals (69% yield), mp 73.3-74.4 °C (ethanol-water). $[\alpha]_D^{22}$ -44° ± 6 (c = 0.005, CHCl$_3$). IR (KBr) ν_{max}/cm^{-1}: 3356 (*ν*NH); 2976 (*ν*C-H); 1716 (*ν*C=O); 1569 (*ν*C=N); 1523 (*ν*C=C, ar); 1160 (*ν*C-O). ^{1}H NMR (CDCl$_3$) *δ*: 0.95 (3H, t, *J* 7.2 Hz); 0.94 (3H, d, *J* 6.3 Hz); 1.46 (9H, s); 1.16-1.70 (2H, m); 1.94-2.12 (1H, m); 5.06 (1H, dd, *J* 5.7 Hz, *J* 8.7 Hz); 5.26 (1H, d, *J* 9.3 Hz); 7.40-7.56 (3H, m); 8.04-8.14 (2H, m). ^{13}C NMR (CDCl$_3$): 11.4 (C-4'); 15.1 (CH$_3$); 25.0 (C-3'); 28.3 (CH$_3$)$_3$; 39.2 (C-2'); 52.6 (C-1'); 80.36 (C); 126.6 (C-1''); 127.5 (C-2'' and C-6''); 128.8 (C-3'' and C-5''); 131.2 (C-4''); 155.1 (C-3); 168.1 (C-5); 178.9 (CO). MS, *m/z* (%): 332 [MH$^+$, 12%], 174 (69%), 146 (81%), 119 (100%), 104 (48%). Anal. Calc. for C$_{18}$H$_{25}$N$_3$O$_3$: C, 65.17; H, 7.54; N, 12.67. Found: C, 65.52; H, 7.53; N, 12.98.

*Data for 5-[(1'S, 2'S)-1'-t-Butyloxycarbonylamino-2'-methylbutyl)]-3-m-tolyl-1,2,4-oxadiazole (**4b**)*. Colorless crystals (80% yield), mp 59.6-60.2 °C (ethanol-water). IR (KBr) ν_{max}/cm^{-1}: 3360 (*ν*NH); 2982 (*ν*C-H); 1685 (*ν*C=O); 1564 (*ν*C=N); 1527 (*ν*C=C,ar);1176 (*ν*C-O). ^{1}H NMR (CDCl$_3$) *δ*: 0.94 (3H, t, *J* 7.4 Hz); 0.93 (3H, d, *J* 6.3 Hz); 1.45 (9H, s); 1.14-1.82 (2H, m); 1.94-2.12 (1H, m); 2.40 (3H, s) 5.04 (1H, dd, *J* 6.0 Hz, *J* 8.9 Hz); 5.28 (1H, d, *J* 8.7 Hz); 7.27 (2H, d, *J* 8.1 Hz); 7.96 (2H, d, *J* 8.4 Hz). ^{13}C NMR (CDCl$_3$):11.4 (C-4'); 15.1 (CH$_3$); 21.3 (Ar-CH$_3$); 25.1 (C-3'); 28.3 (CH$_3$)$_3$; 39.3 (C-2'); 52.7 (C-1'); 80.3 (C); 123.8 (C-6''); 127.6 (C-1''); 128.6 (C-2''); 130.2 (C-5''); 132.0 (C-4''); 138.6 (C-3''); 155.2 (C-3); 168.2 (C-5); 178.9 (CO). MS, m/z (%): 345 [M$^+$, 8%], 289 (53%), 233 (71%), 188 (100%), 160 (52%), 133 (86%), 118 (37%). Anal. Calc. for C$_{19}$H$_{27}$N$_3$O$_3$: C, 66.00; H, 7.82; N, 12.16. Found: C, 66.52; H, 7.63; N, 12.28.

*Data for 5-[(1'S, 2'S)-1'-t-Butyloxycarbonylamino-2'-methylbutyl)]-3-p-tolyl-1,2,4-oxadiazole (**4c**)*. Colorless crystals (75% yield), mp 65.4-66.8 °C (ethanol-water). $[\zeta]_D^{22}$ -58° ± 3 (c = 0.01, CHCl$_3$). IR (KBr) ν_{max}/cm^{-1}: 3357 (*ν*-NH); 2970 (*ν*C-H); 1687 (*ν*C=O); 1569 (*ν*C=N); 1510 (*ν*C=C, ar), 1159 (*ν*C-O). . ^{1}H NMR (CDCl$_3$) *δ*: 0.93 (3H, d, *J* 6.3 Hz), 0.94 (3H, t, *J* 7.2 Hz,), 1.45 (9H, s); 1.15-1.90 (2H, m); 1.94-2.12 (1H, m); 2.41 (3H, s); 5.05 (1H, dd, *J* 5.4 Hz, *J* 8.9 Hz); 5.29 (1H, d, *J* 9.3 Hz); 7.27-7.40 (2H, m); 7.84-7.92 (2H, m). ^{13}C NMR (CDCl$_3$): 11.4 (C-4'); 15.1 (CH$_3$); 21.5 (Ar-CH$_3$; 25.0 (C-3'); 28.3(CH$_3$)$_3$; 39.2 (C-2'); 52.7 (C-1'); 80.3 (C); 123.8 (C-1''); 127.4 (C-2'' and C-6''); 129.5 (C-3'' and C-5''); 141.5 (C-4''); 155.1 (C-3); 168.1 (C-5); 178.7 (CO). MS, *m/z* (%): 345 [M$^+$, 6%], 289 (71%), 188 (98%), 160 (48%), 133 (100%), 118 (44%). Anal. Calc. for C$_{19}$H$_{27}$N$_3$O$_3$: C, 66.00; H, 7.82; N, 12.16. Found: C, 65.93; H, 8.11; N, 12.73.

*Data for 5-[(1'S, 2'S)-1'-t-Butyloxycarbonylamino-2'-methylbutyl)]-3-p-anisyl-1,2,4-oxadiazole (**4d**)*. Colorless crystals (73% yield), mp 70.3-71.2 °C (ethanol-water). IR (KBr) ν_{max}/cm^{-1}: 3349 (*ν*-NH); 2968 (*ν*C-H); 1689 (*ν*C=O);

1568 (νC=N); 1529 (νC=C, ar); 1173 (νC-O). ^{1}H NMR (CDCl$_3$) δ: 0.93 (3H, d, J 6.3 Hz); 0.94 (3H, t, J 6.6 Hz); 1.16-1.70 (2H, m); 1.45 (9H, s); 1.90-2.10 (1H, m); 3.85 (3H, s); 5.03 (1H, dd, J 5.7 Hz, J 9.0 Hz); 5.28 (1H, d, J 9.3 Hz); 6.97 (2H, d, J 9.0 Hz); 8.01 (2H, d, J 9.0 Hz). ^{13}C NMR (CDCl$_3$): 11.4 (C-4'); 15.1 (CH$_3$); 25.1 (C-3'); 28.3 (CH$_3$)$_3$; 34.9 (O-CH$_3$); 39.3 (C-2'); 52.7 (C-1'); 80.4 (C); 114.2 (C-3" and C-5");119.1 (C-1"); 129.1 (C-2" and C-6"); 155.1 (C-3);161.9 (C-4"); 167.8 (C-5); 178.7 (CO). MS, m/z (%): 204 (100%), 176 (47%), 149 (70%), 133 (11%). Anal. Calc. for C$_{19}$H$_{27}$N$_3$O$_4$: C, 63.15; H, 7.47; N, 11.63. Found: C, 63.35; H, 7.27; N, 12.22.

Data for 5-[(1'S, 2'S)-1'-t-Butyloxycarbonylamino-2'-methylbutyl)]-3-p-chlorophenyl-1,2,4-oxadiazole (*4e*). Colorless crystals (65% yield), mp 68.2-68.8 °C (ethanol-water). [α]$_D^{22}$ = -60^0 ± 4 (c = 0.01, CHCl$_3$). IR (KBr) ν_{max}/cm^{-1}: 3364 (ν-NH); 2968 (νC-H); 1685 (νC=O); 1562 (νC=N); 1518 (νC=C, ar); 1174 (νC-O). ^{1}H NMR (CDCl$_3$) δ: 0.93 (3H, d, J 6.0 Hz); 0.95 (3H, t, J 7.5 Hz); 1.14-1.80 (2H, m); 1.45 (9H, s); 1.92-2.12 (1H, m); 5.05 (1H, dd, J 5.7 Hz, J 8.7 Hz) 5.25 (1H, d, J 8.7 Hz); 7.45 (2H, d, J 9.0 Hz); 8.02 (2H, d, J 9.0 Hz).). ^{13}C NMR (CDCl$_3$): 11.4 (C-4'); 15.1 (CH$_3$); 25.0 (C-3'); 28.2 (CH$_3$)$_3$; 39.1 (C-2'); 52.6 (C-1'); 80.4 (C); 125.1 (C-1"); 126.8 (C-2" and C-6"); 129.1 (C-3" and C-5"); 137.4 (C-4"); 155.1 (C-3); 167.3 (C-5); 179.0 (CO). MS, m/z (%): 208 (100%), 180 (47%), 153 (89%), 138, 20%). Anal. Calc. for C$_{18}$H$_{24}$N$_3$O$_3$Cl: C, 59.10; H, 6.57; N, 11.49. Found: C, 59.39; H, 6.77; N, 11.14.

Data for 5-[(1'S, 2'S)-1'-t-Butyloxycarbonylamino-2'-methylbutyl)]-3-p-nitrophenyl-1,2,4-oxadiazole (*4f*). Yellow crystals (80% yield), mp 76.1-77.2 °C (ethanol-water). IR (KBr) ν_{max}/cm^{-1}: 3337 (νNH); 2969 (νC-H); 1690 (νC=O); 1575 (νC=N); 1528 (νC=C, ar);1172 (νC-O). ^{1}H NMR (CDCl$_3$) δ: 0.97 (3H, t, J 7.4 Hz); 0.97 (3H, d, J 6.6 Hz); 1.47 (9H, s); 1.16-1.80 (2H, m); 1.96-2.12 (1H, m); 5.08 (1H, dd, J 6.0 Hz, J 9.0 Hz); 5.25 (1H, d, J 9.0 Hz), 8.29 (2H, d, J 9.0 Hz); 8.35 (2H, d, J 9.3 Hz).). ^{13}C NMR (CDCl$_3$): 11.22 (C-4'); 15.18 (CH$_3$); 25.08 (C-3'); 28.25 (CH$_3$)$_3$; 39.07 (C-2'); 52.81 (C-1'); 80.63 (C); 124.0 (C-3" and C-5"); 126.5 (C-2" and C-6"); 132.5 (C-1"); 149.6 (C-4"); 155.1 (C-3); 166.6 (C-5); 179.9 (CO). MS, m/z (%): 219 (100%), 191 (35%), 164 (52%). Anal. Calc. for C$_{18}$H$_{24}$N$_4$O$_5$: C, 57.44; H, 6.43. Found: C, 57.51; H, 6.72.

Data for 5-[(1'S)-t-Butyloxycarbonylaminoeth-1'-yl]-3-phenyl-1,2,4-oxadiazole (*6*) White crystals (70% yield), mp 89.3-90.3 °C (ethanol-water). [α]$_D^{22}$ -70^0 ± 2 (c = 0.02, CHCl$_3$). IR (KBr) ν_{max}/cm^{-1}: 3370 (νNH); 2983 (νC-H); 1687 (νC=O); 1571 (νC=N); 1518 (νC=C, ar); 1164 (νC-O). ^{1}H NMR (CDCl$_3$) δ: 1.43 (9H, s); 1.60 (3H, d, J 6.9 Hz); 5.06-5.24 (1H, m); 5.44 (1H, d, J 7.8 Hz); 7.38-7.52 (3H, m); 8.00-8.10 (2H, m).). ^{13}C NMR (CDCl$_3$): 20.1 (C-2'); 28.3

(CH$_3$)$_3$; 44.8 (C-1'); 80.0 (C); 126.5 (C-1"); 127.5 (C-2" and C-6"); 128.8 (C-3" and C-5"); 131.2 (C-4"); 168.3 (C-3); 173.7 (C-5); 180.1 (CO). MS, m/z (%): 289 [M$^+$, 8%], 234 (51%), 174 (72%), 160 (100%), 119 (98%), 104 (80%). Anal. Calc. for C$_{15}$H$_{18}$N$_3$O$_3$: C, 62.49; H, 6.30; N, 14.57. Found: C, 62.58; H, 6.27; N, 14.87.

Conclusion

In conclusion, we have been able to synthesize and prove the structures of seven new 1,2,4-oxadiazoles as well as six of their intermediates **3a-f** derived from L-(+)-isoleucine.

Acknowledgments

References

1. Lin, J. H.; Lu, A.Y.H.; *Pharmacol. Rev.* **1997**, *49*, 403.

2. Lehmann, P. A.; Rodrigues de Miranda, J.F.; Ariëns, E.; *J. Prog. Drug. Res.* **1976**, *20*, 101.

3. Eliel, E. L.; Wilen, S. H.; Mander, L. N.; *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994, p. 207.

4. Barreiro, E. J.; Ferreira, V. F.; Costa, P. R. R.; *Quim. Nova*, **1997**, *20*, 6.

5. Caldwell, J.; *Hum. Psychopharm. Clin.,* **2001**, *16-Suppl. 2,* S67-S71.

6. Scheuerer, S.; Williams, K.M.; Brugger, R.; McLachlan, A. J.; Brune, K.; Day, O. R.; Geisslinger, G.; *J. Pharmacol. Exptl. Ther. J.P.E.T.* **1998**, *284*, 1132.

7. Jamali, F.; Berry, B.W.; Tehrani, M. R.; Russel, S. A.; *J. Pharm. Sci.* **1988**, *77*, 666.

8. Silvestrini, B.; Pozzatti, C.; *Brit. J. Pharmacol.* **1961**, *16*, 200.

9. Silvestrini, B.; Pozzatti; C. *Arch. Intern. Pharmacodynamie* **1960**, *129*, 240.

10. Melo, S.J.; Sobral, A. D.; Lopes, H. L.; Srivastava, R. M.; *J. Braz. Chem. Soc.* **1998**, *9*, 465.

11. Borg, S.; Estenne-Bouhtou, G.; Luthmau, K.; Csöregh, I.; Hesselink, W.; Hacksell, U.; *J. Org. Chem.* **1995**, *60*, 3112.

12. Srivastava, R.M.; Brinn, I.M.; Machuca-Herrera, J.O.; Faria, H.B.; Carpenter, G.B.; Andrade, D.; Venkatesh, C.G.; de Morais, L.P.F.; *J. Mol. Struct.* **1997**, *206*, 159.