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Synthesis and Structural Studies of *N*-(*p*-Toluenesulfonyl)-amino acid 3,5-Di-*tert*-butyl-2-phenolamides

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ABSTRACT: *This paper describes the synthesis and structural studies of* N-*(*p*-toluenesulfonyl)-amino acid 3,5-di-*tert*-butyl-2-phenolamides by ^{1}H, ^{13}C, and ^{15}N. The presence of intra- and intermolecular hydrogen bonds were studied by variable temperature NMR spectroscopy. The molecular structure of two amides in the solid state was determined by X-ray diffraction experiments. The results show that* tert*-butyl substituents in the phenolic ring have important effects in the nature of hydrogen bonds and conformation of these amides.* © 2004 Wiley Periodicals, Inc. Heteroatom Chem 15:114–120, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10223

INTRODUCTION

We are interested in the synthesis and structural study of *N*-(*p*-toluenesulfonyl)-amino-acid-2-phenolamides **1–5** because they are useful intermediates for obtaining new heterocyclic compounds with important biological activity [1–4]. These compounds have constrained molecular structures where the arrangement of the intramolecular O···H···N interactions form a fused pseudobicyclic system with the amide group in the *E*,*Z* conformation (Scheme 1) [4]. However, it is the *Z*,*Z* conformer that is required to obtain benzoxazoles. Ab initio HF/6-31G* calculations of *N*-acylated-2-aminophenols predict that the *E*,*Z* conformation is more stable than the *Z*,*Z* by 1.38 kcal/mol. This energetic difference makes us think that it is possible to change the conformation of *N*-(*p*-toluenesulfonyl)-amino-acid-2-phenolamides if the intramolecular O···H···N interactions are weakened or eliminated. It is known that electron donor groups in anilines significantly diminish the interaction between the p_z orbital of nitrogen and the π system of the benzenoid ring, increasing the basicity of the nitrogen atom [5]. Thus, the presence of electron donor groups in the benzenoid ring restricts the participation of N—H in hydrogen bonding interactions. In this paper, we present the synthesis and structural studies of *N*-(*p*-toluenesulfonyl)-aminoacid 3,5-di-*tert*-butyl-2-

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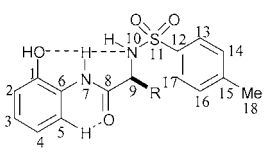
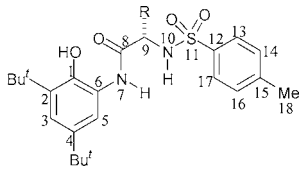


1-6



7-12

1 and **7** R = H
2 and **8** R = Me
3 and **9** R = Pr^i
4 and **10** R = Bu^t
5 and **11** R = Bz
6 and **12** R = Bu^s

SCHEME 1 *N*-(*p*-Toluenesulfonyl)-amino-acid-2-phenolamides **1–12**.

phenolamides **7–12** (Scheme 1). NMR has been used to compare the conformational behaviour in solution of compounds **7–12** with respect to that of amides **1–6**.

RESULTS AND DISCUSSION

The *N*-(*p*-toluenesulfonyl)-L-isoleucine 2-phenolamide **6** and *N*-(*p*-toluenesulfonyl), amino acid 3,5-di-*tert*-butyl-2-phenolamides **7–12** were obtained in yields above 65% by the procedure described for preparation of **1–5** [4]. The molecular structure of amides **6–12** was unequivocally established by NMR. With the purpose of assigning the protons, OH and NH heteronuclear correlation experiments were carried out. The conformational study in solution of **1–12** was performed by multinuclear magnetic resonance and variable temperature experiments. The reported structural study of **1–5** showed that they exist as *E,Z* conformers whereas amides **7–12** proved to exist in the *Z,Z* conformer as we will show below.

In the ^{13}C NMR spectra of amides **7–12** the chemical shifts of C3 and C5 appeared at lower frequencies [$\Delta\delta$ = 5.5–3.6 ppm for C3 and 3.4–0.9 ppm for C5] with respect to amides **1–6** (Table 1). This phenomenon is due to the electron donor effect of the *tert*-butyl group in the aromatic ring which increases the electronic density at C3 and C5. On the other hand, the C8 carbon atom in **7–12** appeared at higher frequencies compared to compounds **1–6**. This demonstrates that the electronic conjugation between the aromatic ring and the carbonyl group in **7–12** is inhibited and the double bond character of the C=O bond is bigger in **7–12** than in **1–6**.

^{15}N NMR chemical shifts of nitrogen N7 in compounds **1–6** (Table 2) have the normal values for *o*-phenolamides with intramolecular hydrogen bonding [4]. Nevertheless, the signal of N7 for compounds **7–12** is shifted toward higher frequencies ($\Delta\delta$ = 7–15 ppm) with respect to amides **1–6**. These changes are caused by the absence of electronic delocalization of the amide group into the aromatic ring of **7–12** which increases the electronic density at the nitrogen nuclei [6]. The coupling constants ^1J(N—H) = 90–93 Hz for N7 in **7–12** suggest that the hydrogen atom is strongly bonded to nitrogen and also indicate a trigonal planar geometry at the N atoms [7].

It has been accepted that the ^1H NMR chemical shifts dependence on the temperature ($\Delta\delta/\Delta T$) is

TABLE 1 δ ^{13}C of **1–5** in DMSO-d_6/$CDCl_3$ and **6–12** in DMSO-d_6

	C1	*C2*	*C3*	*C4*	*C5*	*C6*	*C8*	*C9*	*C12*	*C13*	*C14*	*C15*	*C18*
1[a]	146.7	115.5	124.6	119.4	120.3	125.8	166.6	46.4	143.4	129.6	126.9	136.4	21.3
2[a]	146.5	114.8	123.9	118.8	119.8	125.9	169.8	52.8	142.8	129.3	126.6	137.2	21.0
3[a]	147.0	115.6	124.4	118.8	120.7	125.5	169.4	62.7	142.6	129.0	126.6	137.0	20.9
4[a]	146.8	115.3	124.3	119.0	120.2	125.8	170.4	56.0	142.9	129.2	126.7	136.9	21.0
5[a]	147.2	115.2	125.7	118.7	121.1	124.3	169.2	58.3	142.1	129.1	126.1	137.6	20.7
6[b]	147.4	115.2	124.4	118.6	121.4	125.6	169.1	61.1	142.4	129.2	126.6	137.7	20.8
7[c]	146.1	137.3	120.4	140.8	119.4	125.6	167.9	45.5	142.7	129.5	126.7	137.3	21.0
8[d]	145.4	138.0	120.3	141.0	118.3	126.1	171.7	52.0	142.6	129.5	126.5	137.9	20.9
9[e]	145.5	138.1	120.5	140.9	118.0	125.9	170.9	61.8	142.3	129.2	126.5	138.0	20.9
10[f]	145.9	138.0	120.4	140.9	118.2	126.0	171.7	54.7	142.4	129.3	126.5	137.9	20.9
11[g]	145.5	137.9	120.2	140.6	118.4	125.7	170.7	57.7	142.1	129.2	126.3	137.5	20.9
12[h]	145.6	138.1	120.6	140.9	118.0	125.9	171.0	60.4	142.4	129.3	126.5	138.0	20.9

[a]From reference [4].
[b]10.7 (CH_3); 14.9 (CH_3); 24.3 (CH_2); 36.9 (CH).
[c]29.6 (CH_3); 31.3 (CH_3); 33.8 (C); 34.8 (C).
[d]18.4 (CH_3); 29.6 (CH_3); 31.3 (CH_3); 33.8 (C); 34.8 (C).
[e]18.3 (CH_3); 18.9 (CH_3); 29.6 (CH_3); 30.9 (CH); 31.3 (CH_3); 33.8 (C); 34.8 (C).
[f]21.2 (CH_3); 22.7 (CH_3); 23.9 (CH_2); 29.6 (CH_3); 31.3 (CH_3); 33.8 (C); 34.8 (C); 41.4 (CH).
[g]29.5 (CH_3); 31.2 (CH_3); 33.7 (C); 34.7 (C); 38.5 (CH_2); 126.3 (*p*-Ph); 127.9 (*m*-Ph); 129.1 (*o*-Ph); 136.5 (*i*-Ph).
[h]10.2 (CH_3); 15.0 (CH_3); 24.3 (CH_2); 29.6 (CH_3); 31.3 (CH_3); 33.8 (C); 34.9 (C) 36.7 (CH).

TABLE 2 ^{1}H TV-NMR ($\Delta\delta/\Delta T$ in ppm K^{-1}) and δ ^{15}N of **1–12** in DMSO-d_6

	$-\Delta\delta/\Delta T$ *NH7*	$-\Delta\delta/\Delta T$ *NH10*	$-\Delta\delta/\Delta T$ *OH*	δ ^{15}*N NH7*	δ ^{15}*N NH10*
1	0.0014	0.0050		−262	−288
2	0.0021	0.0051	0.0045	−264	−276
3	0.0024	0.0053	0.0055	−259	−282
4	0.0026	0.0050	0.0054	−262	−278
5	0.0029	0.0053	0.0055	−260	−281
6	0.0024	0.0061	0.0052	−260	−281
7	0.0028	0.0044	0.0034	−255	−290
8	0.0033	0.0052	0.0047	−251	−280
9	0.0030	0.0064	0.0050	−246	−282
10	0.0032	0.0050	0.0049	−250	−280
11	0.0031	0.0059	0.0046	−249	−281
12	0.0031	0.0061	0.0049	−245	−282

a diagnostic tool to elucidate if the hydrogen atom has intra-intermolecular or solvent interactions. Accordingly, when the values ($\Delta\delta/\Delta T$) are higher than 4×10^{-3} ppm/K, solvated N—H groups are present; on the other hand, values lower than 3×10^{-3} ppm/K are attributed to N—H groups with intramolecular hydrogen bonding [8,9]. We studied the nature of hydrogen bonding by variable temperature ^{1}H NMR ($\Delta\delta/\Delta T$) in compounds **1–12**. All experiments were performed in [$^{2}H_6$]DMSO over a temperature range of 25–145°C with increments of 10°C. The ($\Delta\delta/\Delta T$) values are shown in Table 2.

The chemical shifts of H7 signals in compounds **1–6** showed a small variation with the temperature ($\Delta\delta/\Delta T$ from 1.4 to 2.9 $\times 10^{-3}$ ppm/K), therefore, we conclude that they have strong intramolecular hydrogen bondings. The low mobility of this hydrogen can be explained by the presence of a three-centre hydrogen bonding where H7 is stabilized by two five-membered chelate rings (Scheme 1) [10]. With this method it is not possible to differentiate if H7 in **7–12** has inter- or intramolecular interactions since the variation of chemical shifts with the temperature for this nuclei showed values above 3×10^{-3} ppm/K, but below 4×10^{-3} ppm/K. However, the chemical shifts for H7 in **7–12** are displaced toward minor frequencies ($\Delta\delta = 0.67$–0.95 ppm) than the corresponding signals in **1–6** (Table 3). The difference of chemical shifts reflects the force of hydrogen bonding in these compounds; it is known that the presence of strong hydrogen bonding makes significant changes in the chemical shifts of the hydrogen signals toward high frequencies [11,12]. This fact corroborates that **1–6** and **7–12** do not have the same hydrogen bonding arrangement in H7 neither the same conformation. The chemical shifts for H5 in **1–6** showed that this atom has intramolecular interactions with O2 [13]. The corresponding signals in **7–12** are displaced toward high fields and showed that the presence of the *tert*-butyl groups weakens the intramolecular H5···O=C interaction.

The X-ray molecular structure of **9** and **12** (Figs. 1–3) corroborate the different conformation of amides with *tert*-butyl groups and amides **1–6**. The amide **12** crystallizes in two conformations in the same cell unit. Conformer **12a** has the aromatic ring of the tosyl group almost eclipsing the S11—N10 bond [torsional angle N10—S11—C12—C13 is –166.2(6)° and N10—S11—C12—C17 is 14.3(9)°] (Fig. 2). However, conformer **12b** has the aromatic ring almost coplanar with the O3—S11—O4 bonds [torsional angle O3—S11—C12—C13 is –22.7(8)° and O4—S11—C12—C17 is –26.7(8)°] (Fig. 3).

In contrast to compounds **1–6**, amides **9** and **12** have the *Z,Z* conformation where the hydroxyl and carbonyl groups are in the same side [torsional angles C1—C6—N7—C8 are 46.8(4)° for **9**, −43(1)° for **12a**, and 42(1)° for **12b**]. This confirms that the intramolecular interaction between H5 and O2 is not present in compounds **9** and **12** [13]. On the other side, the bond distance between O1 and O2 in **9** is 2.607(3) Å, 2.627(8) Å in **12a**, and 2.619(7) Å in **12b**, which are below the sum of the van der Waals radii of oxygen ($r_{RVD} = 1.50$ Å) and show the presence of intramolecular hydrogen bonds O1—H1—O2 [14].

The differences between amides **9** and **12** with respect to **1–6** are attributed to the presence (or absence) of intramolecular hydrogen bond C5—H5···O2 that determines their conformation. Thus, the amide group in **9** and **12** is not coplanar with the aromatic ring, and electronic conjugation between these groups is unlikely. Moreover, N7 and N10 in **9** and **12** are in anti position [with torsional angles N7—C8—C9—N10 of 148.2(3)° for **9**, 126.0(6)° for **12a** and 129.8(7)° for **12b**]. Intramolecular hydrogen bonding between H7 and N10 is not possible in these molecules.

TABLE 3 δ ^{1}H of **1–12** in DMSO-d_6

	H1	*H2*	*H3*	*H4*	*H5*	*H7*	*H9*	*H10*	*H13*	*H14*	*H18*	*CH*	*CH$_2$*	*CH$_3$*
1[a]	10.03	6.92	6.76	6.75	7.90	9.23	3.64	8.27	7.38	7.74	2.34			
2[a]	9.99	6.88	6.92	6.75	7.87	9.23	3.97	8.26	7.36	7.74	2.34			1.45
3[a]	9.76	6.84	6.91	6.71	7.56	9.23	3.78	7.93	7.27	7.70	2.30	1.95		0.77 0.82
4[a]	9.85	6.86	6.91	6.73	7.69	9.26	3.85	8.19	7.30	7.71	2.30	1.50	1.42	0.60 0.78
5[a]	9.85	6.88	6.93	6.74	7.68	9.37	4.27	8.25	7.12	7.45	2.26		3.00 2.73	
6	9.77	6.84	6.91	6.70	7.53	9.24	3.80	7.97	7.27	7.70	2.27	1.68	1.13 1.45	0.75 0.73
7[b]	9.71		7.06		7.00	8.48	3.72	7.99	7.39	7.74	2.37			
8[c]	9.92		7.06		7.00	8.51	4.05	8.16	7.34	7.72	2.33			1.20
9[d]	10.09		7.06		6.82	8.52	3.78	8.07	7.28	7.70	2.26	1.92		0.86
10[e]	10.07		7.06		6.89	8.52	4.02	8.13	7.30	7.70	2.28	1.59	1.44	0.85 0.75
11[f]	9.98		7.04		6.66	8.42	4.26	8.32	7.17	7.54	2.50		2.79 2.96	
12[g]	10.11		7.06		6.81	8.57	3.81	8.10	7.27	7.69	2.24	1.70	1.53 1.16	0.82 0.78

[a]From reference [4].
[b]1.23 (CH_3); 1.36 (CH_3).
[c]1.22 (CH_3); 1.35 (CH_3).
[d]1.23 (CH_3); 1.34 (CH_3).
[e]1.21 (CH_3); 1.34 (CH_3).
[f]1.21 (CH_3); 1.34 (CH_3); 7.22 (Ph).
[g]1.23 (CH_3); 1.34 (CH_3).

It is known that sulfonyl oxygen atoms in *p*-toluenesulfonamides can have interactions with the ortho hydrogen of the aromatic ring [15]. Compounds **9** and **12b** have the aromatic ring coplanar with the sulfonyl oxygen atoms. The interaction of the latter with the ortho hydrogen atoms is deduced from the C13···O3 short distance: 3.001(5) Å in **9**, 2.94(1) Å in **12b** and C17···O4: 2.913(4) Å in **9**, 2.905(9) Å in **12b**. On the other hand, conformer

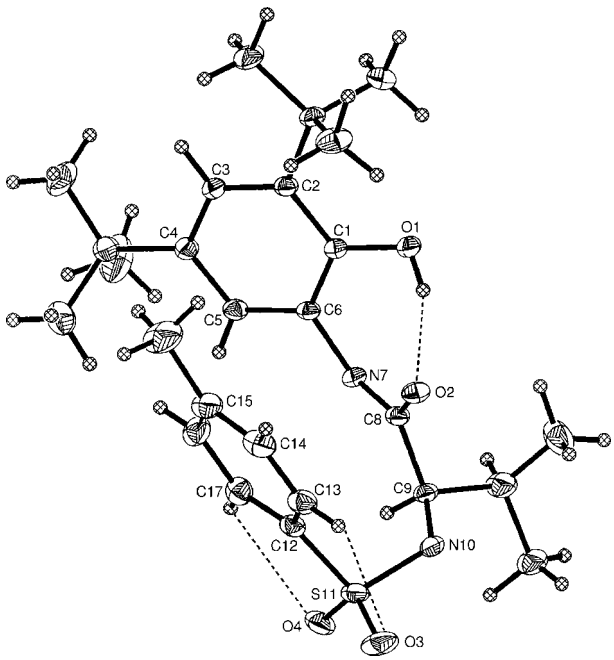


FIGURE 1 Molecular structure of **9** showing a *Z,Z* conformation.

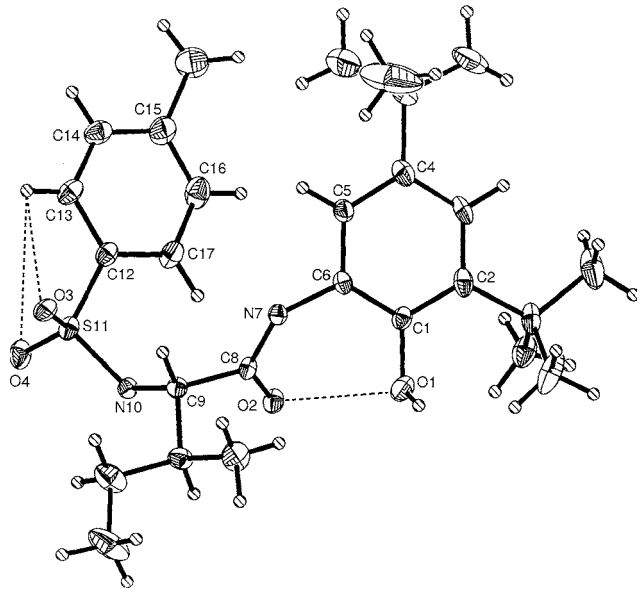


FIGURE 2 Molecular structure of **12a** showing a *Z,Z* conformation.

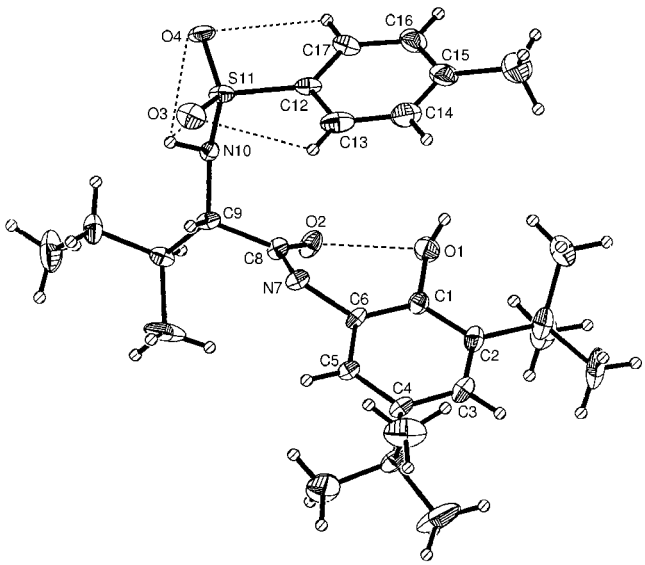


FIGURE 3 Molecular structure of **12b** showing a *Z,Z* conformation.

12a has the tosyl group eclipsing the S11—N10 bond, thus O3 and O4 have interactions only with H13 [distance C13···O3 is 3.02(1) Å and C13···O4 is 3.29(1) Å].

In conclusion, the NMR and crystallographic studies have shown that the presence of *tert*-butyl groups in the aromatic ring changes the conformation of the amide and the intramolecular interaction of the amidic N—H hydrogen is disfavoured.

EXPERIMENTAL

All solvents were freshly distilled and dried before use according to established procedures. Melting points were measured on a Mel-Temp II apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer System 200 FT-IR spectrophotometer. Elemental analyses were determined on a Perkin-Elmer Series II CHNS/O analyser 2400 instrument. HPLC were run on a Zorbax ODS C-18 semipreparative column.

The NMR spectra were obtained on a JEOL GXS-400 MHz spectrometer in [$^2H_6$]DMSO solution. Chemical shifts (ppm) are relative to electronic frequencies $(CH_3)_4Si$ for ^1H and ^{13}C and CH_3NO_2 for ^{15}N NMR. Variable temperature experiments were performed with a temperature controller to keep the temperature constant within 0.2°C. The temperature varied from 25 to 145°C in 10° increments with a delay of 5 min. Each spectrum was obtained with 16 scans. ^{15}N NMR spectra were recorded at 40.51 MHz using a multinuclear 5 mm probe. The DEPT without decoupling pulse sequence was used to detect the ^{15}N signals. The average $^1J(^{15}N—^1H)$ value was 91.5 Hz. A spectral width of 32768 Hz with a digital resolution of 0.7 Hz was used; the pulse delay was 2 s with an acquisition time of 1.35 s.

X-ray diffraction studies were performed on a Bruker Smart 6000 diffractometer. After optical alignment, the cell parameters were determined by using the reflections collected on four sets of 20 frames each [16]. Data collection was performed in the hemisphere mode and corrections were made for Lorentz and polarization effects. Computations were performed by using SAINT-NT [17]. Atomic form factors for neutral C, N, O, and H were taken from the International Tables for X-ray Crystallography [18]. The structures were solved by direct methods using the SHELXTL-NT program [19]. Hydrogen atoms with hydrogen bond were determined. However, the majority of hydrogen atoms were calculated and refined with an overall isotropic temperature factor. Anisotropic temperature factors were introduced for all non-hydrogen atoms, and least-squares refinements were carried out by minimizing $\Sigma w(|F_o| - |F_c|)^2$, where F_o and F_c are the observed and calculated structure factors. Model reached convergence with $R = \Sigma w(||F_o| - |F_c||)/|F_o|$ and $R_w = \Sigma[w(|F_o| - |F_c||)^2/\Sigma/w(F_o)2]^{1/2}$. The experimental parameters are listed in Table 4. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as CCDC 191226 (**9**) and 191227 (**12**). Copies of the data can be obtained free of charge on application to: The Director, CCDC, 12 Union Road, Cambridge, CB2 IEZ, UK (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk).

*N-(p-Toluenesulfonyl)-L-isoleucine 2-Phenolamide (**6**)*

The procedure described below is a representative of the synthesis of compounds **7–12**. A solution of *N*-(*p*-toluenesulfonyl)-L-isoleucine (100 mg, 0.35 mmol) in $SOCl_2$ (1 cm^3) was stirred at 20°C for 1 h. The excess of $SOCl_2$ was removed under vacuum and the *N*-(*p*-toluenesulfonyl)-L-isoleucine chloride obtained was immediately dissolved in a mixture of 2-aminophenol (48 mg, 0.43 mmol) and THF (25 cm^3). The mixture was stirred for 30 min and the THF removed under vacuum. HPLC on Zorbax ODS C-18 semipreparative column with acetonitrile–water (70:30) as the eluent yielded **6** (99 mg, 85%), mp 194–195°C (Found: C, 61.0; H, 6.5; N, 7.7; $C_{19}H_{24}N_2O_4S$ requires C, 60.6; H, 6.4; N, 7.4%); ν_{max} (HATR)/cm^{-1}

TABLE 4 Crystal Data of **9** and **12**

	9	**12**
Formula	$C_{26}H_{35}N_2O_4S$	$C_{27}H_{40}N_2O_4S$
fw	471.62	334.10
Space group	*P* 2(1)	*P* 1
a (Å)	10.7856 (6)	9.7934 (7)
b (Å)	8.1996 (5)	13.3358 (8)
c (Å)	15.1737 (8)	23.6592 (15)
V (Å^3)	1333.66 (13)	3074.9 (3)
Z	2	6
Absorption coefficient	0.153 mm^{-1}	1.330 mm^{-1}
F(000)	506	6042
θ Range for data collection	1.90–25.00°	0.86–29.02°
Reflections collected	8198	20569
Independent reflections	4534 [*R* (int) = 0.0303]	16877 [*R* (int) = 0.0877]
Completeness to $\theta = 25.00$	99.8%	88.1%
Absorption correction	None	None
Data/restraints/parameters	4534/1/430	16877/3/1295
Goodness-of-fit on F^2	0.961	0.836
Final *R* indices [$I > 2\sigma(I)$]	$R1 = 0.0454$, $wR2 = 0.0990$	$R1 = 0.0786$, $wR2 = 0.1812$
R indices (all data)	$R1 = 0.0688$, $wR2 = 0.1084$	$R1 = 0.1928$, $wR2 = 0.2271$
Largest diff. peak and hole	0.219 and −0.174 e Å^{-3}	0.330 and −0.302 e Å^{-3}

3446 (OH), 1654 (C═O), 1533 and 1513 (amide), 1162 (SO_2); *m*/*z*(EI, 10 eV) no M^+, 240 (100), 184 (30), 155 (72), 91 (79).

*N-(p-Toluenesulfonyl)-glycine-3,5-di-tert-butyl-2-phenolamide (**7**)*

N-(*p*-Toluenesulfonyl)-glycine (100 mg, 0.44 mmol) was treated with $SOCl_2$ (1 cm^3), 4,6-di-*tert*-butyl-2-aminophenol (96.4 mg, 0.44 mmol), and THF (25 cm^3). The amide was purified by HPLC (70:30 ratio of acetonitrile–water) to yield **7** (158 mg, 80%), mp 167–168°C (Found: C, 62.8; H, 7.6; N, 6.4; $C_{23}H_{32}N_2O_4S$ requires C, 63.9; H, 7.4; N, 6.5%); ν_{max} (HATR)/cm^{-1} 3486 (OH), 1668 (C═O), ν 1597 (amide), 1164 (SO_2); *m*/*z* (EI, 10 eV) no M^+, 414 (2), 399 (21), 350 (85), 259 (96), 243 (51), 155 (27), 91 (100).

*N-(p-Toluenesulfonyl)-dl-alanine-3,5-di-tert-butyl-2-phenolamide (**8**)*

N-(*p*-Toluenesulfonyl)-*dl*-alanine (100 mg, 0.41 mmol) was treated with $SOCl_2$ (1 cm^3), 4,6-di-*tert*-butyl-2-aminophenol (90.8 mg, 0.41 mmol), and THF (25 cm^3). The amide was purified by HPLC (70:30 ratio of acetonitrile–water) to yield **8** (119.0 mg, 65%), mp 180–182°C (Found: C, 63.7; H, 7.9; N, 6.2; $C_{24}H_{34}N_2O_4S$ requires C, 64.5; H, 7.7; N, 6.3%); ν_{max}(HATR)/cm^{-1} 3488 (OH), 3353 (NH─CO), 1663 (C═O), 1597, 1170 (SO_2); *m*/*z* (EI, 10 eV) no M^+, 429 (1), 413 (8), 364 (36), 273 (77), 243 (100), 231 (34), 155 (45), 91 (90).

*N-(p-Toluenesulfonyl)-L-valine-3,5-di-tert-butyl-2-phenolamide (**9**)*

N-(*p*-Toluenesulfonyl)-L-valine (100 mg, 0.37 mmol) was treated with $SOCl_2$ (1 cm^3), 4,6-di-*tert*-butyl-2-aminophenol (81.5 mg, 0.37 mmol), and THF (25 cm^3). The amide was purified by HPLC (70:30 ratio of acetonitrile–water). On drying, compound **9** appears as white crystals (113.8 mg, 65%), mp 188–189°C (Found: C, 65.1; H, 8.1; N, 6.7; $C_{26}H_{38}N_2O_4S$ requires C, 65.1; H, 8.3; N, 7.0%); ν_{max}(HATR)/cm^{-1} 3488 (OH), 3317 (NH─CO), 1658 (C═O), 1558, 1164 (SO_2); *m*/*z* (EI, 10 eV): no M^+ 457 (4), 413 (100), 349 (23), 301 (11), 243 (17).

*N-(p-Toluenesulfonyl)-L-leucine-3,5-di-tert-butyl-2-phenolamide (**10**)*

N-(*p*-Toluenesulfonyl)-L-leucine (100 mg, 0.35 mmol) was treated with $SOCl_2$ (1 cm^3) and 4,6-di-*tert*-butyl-2-aminophenol (77.4 mg, 0.35 mmol), and THF (25 cm^3). The amide was purified by HPLC (70:30 ratio of acetonitrile–water) to yield **10** (111.4 mg, 65%), mp 184–186°C (Found: C, 66.4; H, 8.2; N, 6.6; $C_{27}H_{40}N_2O_4S$ requires: C, 65.0; H, 8.0; N, 7.0%); ν_{max} (HATR)/cm^{-1} 3332 (OH), 3269 (NH─CO), 1664 (C═O), 1562, 1157 (SO_2); *m*/*z* (EI, 10 eV): no M^+, 455 (1), 413 (19), 363 (20), 259 (23), 243 (27), 155 (6), 91 (100).

*N-(p-Toluenesulfonyl)-L-phenylalanine-3,5-di-tert-butyl-2-phenolamide (**11**)*

N-(*p*-Toluenesulfonyl)-L-phenylalanine (100 mg, 0.3134 mmol) was treated with $SOCl_2$ (1 cm^3), 4,6 -di-*tert*-butyl-2-aminophenol (69.2 mg, 0.31 mmol), and THF (25 cm^3). The amide was purified by HPLC (70:30 ratio of acetonitrile–water) to yield **11** (106.5.0 mg, 65%), mp 147–148°C, (Found: C, 67.8; H, 7.2; N, 6.1; $C_{30}H_{38}N_2O_4S$ requires: C, 68.8; H, 7.3; N, 6.1%); ν_{max} (HATR)/cm^{-1} 3286 (OH), 3286 (NH—CO), 1639 (C=O), 1544, 1163 (SO_2); *m/z* (EI, 10 eV) no M^+ 413 (29), 281 (15), 261 (13), 219 (46), 207 (37), 155 (28), 131 (45), 100 (11), 91 (44), 69 (100), 44 (65), 32 (98).

*N-(p-Toluenesulfonyl)-L-isoleucine-3,5-di-tert-butyl-2-phenolamide (**12**)*

N-(*p*-toluenesulfonyl)-L-isoleucine (100 mg, 0.35 mmol) was treated with $SOCl_2$ (1 cm^3), 4,6-di-*tert*-butyl-2-aminophenol (77.4 mg, 0.35 mmol), and THF (25 cm^3). The amide was purified by HPLC (70:30 ratio of acetonitrile–water). On drying, compound **12** appears as white crystals (111.4 mg, 65%), mp 149–150°C (Found: C, 66.4; H, 8.2; N, 6.6; $C_{27}H_{40}N_2O_4S$ requires: C, 65.8; H, 8.2; N, 7.0%); ν_{max} (HATR)/cm^{-1} 3319 (OH), 3229 (NH—CO), 1650 (C=O), 1564, 1156 (NH—SO_2); *m/z* (EI, 10 eV) no M^+ 455 (2), 413 (100), 349 (17), 315 (13), 155 (62), 91 (75).

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