Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 5608–5616
Tetrahedron

N-Acyltrifluoromethanesulfonamides as new chemoselective acylating agents for aliphatic and aromatic amines

Sophie Guillard, Andrea Aramini, Maria C. Cesta, Sandro Colagioia, Silvia Coniglio, Filippo Genovese, Giuseppe Nano, Emanuela Nuzzo, Valerie Orlando and Marcello Allegretti*

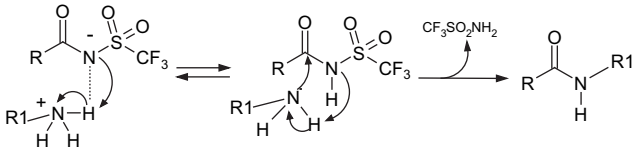
Chemistry Department, Dompé Research and Development, Dompé pha.r.ma s.p.a., Via Campo di Pile, 67100 L'Aquila, Italy

Received 13 March 2006; accepted 30 March 2006
Available online 2 May 2006

Abstract—This work describes advances in the study of the internal condensation of ammonium salts of *N*-acylsulfonamides. *N*-Acyltrifluoromethanesulfonamides show considerable advantages over the non fluorinated analogues by virtue of their higher reactivity and acidity. The reaction chemoselectivity has been investigated using a wide range of amines. The sensitivity of the reaction to steric and electronic effects confirms the potential application of these reagents in chemoselective acylation of polyamines.

1. Introduction

We have recently reported[1] that alkylammonium salts of acylmethanesulfonamides undergo internal condensation to give the corresponding amide derivatives under thermal conditions (T=120 °C, 3 h, 80 mmHg). The proposed reaction mechanism is depicted in Scheme 1.



Scheme 1.

The ionic interaction between the reagents is the crucial reaction step and, furthermore, methanesulfonamide harvesting by sublimation strongly contributes to drive the reaction equilibrium. These preliminary reactivity studies clearly demonstrate that the proximity of the reactive centres strongly influences the steric requirements of the reaction. In fact, secondary ammonium salts do not evolve to the corresponding amides and selective monoacylation of mixed primary–secondary amines has been reported to proceed in good yields.

Chemoselective acylation of mixed primary–secondary amines is a synthetic challenge and, to date, a wide range of strategies have been used to address this problem;[2–6] the observed chemoselectivity suggests promising applications of this process, but the relatively harsh conditions strongly limit the scope of the reaction. Here we report the efforts at extending the reactivity studies with the aim to select optimised conditions for the process.

2. Results and discussion

The aim of the present study is to evaluate acyltrifluoromethanesulfonamides in comparison with related acylmethanesulfonamides as novel acylating reagents for the amino group (Fig. 1).

The rationale behind this choice is based on the following considerations: (1) the marked acidity of the amide hydrogen should favour the acid–base interaction with low-basicity amines; (2) the electron-withdrawing effect of the fluorine atoms should enhance the reactivity of the electrophilic centre and (3) the higher vapour tension of trifluoromethanesulfonamide as compared to methanesulfonamide should positively influence the reaction course.

In Table 1, a comparison between the reactivity of 2-(4-isobutylphenyl)-*N*-(methylsulfonyl)acetamide **1** and its trifluoromethyl analogue **2** is described. As previously reported, **1** significantly undergoes internal condensation only when heated under vacuum in the absence of solvent (entries 1 and 2). On the contrary, comparable yields are obtained when **2** is heated either neat (entry 3) or in toluene

Keywords: Alkylammonium salts; *N*-Acyltrifluoromethanesulfonamides; Chemoselective acylation; Mixed primary–secondary amines.
* Corresponding author. Tel.: +39 0862338212; fax: +39 0862338219; e-mail: marcello.allegretti@dompe.it

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.03.097

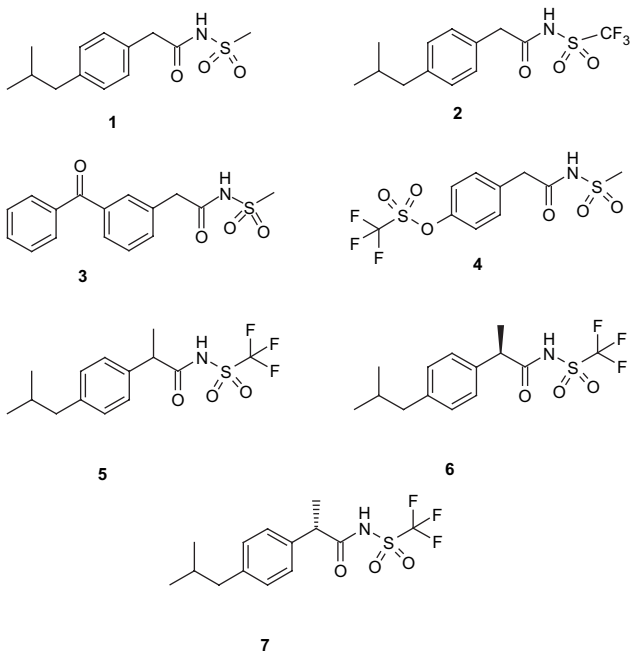


Figure 1. Substrates used as acylating agents.

Table 1. Reactivity of **1** and **2** with butylamine in various reaction conditions

Entry	Reagent	Amine	Reaction conditions	Yield (%)
1	**1**	H_2N	Neat/T=120 °C/4 h, 80 mmHg	90
2	**1**	H_2N	Toluene/reflux/8 h	0
3	**2**	H_2N	Neat/T=120 °C/4 h, 80 mmHg	90
4	**2**	H_2N	Toluene/reflux/8 h	80
5	**2**	H_2N	Toluene/rt/3 d	10
6	**2**	H_2N	Toluene/T=30 °C/1 h	Traces[a]
7	**2**	H_2N	Toluene/T=30 °C/1 h	10[a]

[a] The different yield is due to different work-up procedure (see text).

solution (entry 4). A low but significant conversion is obtained by stirring a toluene solution of the salt at room temperature for several days (entry 5). The results in entries 6 and 7 confirm the sublimation of the trifluoromethanesulfonamide as the crucial event for the reaction proceeding. In fact, after 1 h at T=30 °C (entry 6) only traces of the product are detected (GC–MS analysis) in the crude reaction mixture, whereas a subsequent analysis after simple solvent evaporation shows a consistent increase of yield (entry 7).

To explore the reactivity of acyltrifluoromethanesulfonamides, several ammonium salts, prepared by mixing **2** with the desired amine in toluene, have been treated under the selected conditions (Table 2).

Primary amines (entries 1–4) afford the corresponding amides in moderate to good yields. In our previous paper, we reported the lack of reactivity of secondary ammonium salts of **1**, but further experiments revealed that by prolonging the reaction time under the fusion conditions, small amount of the condensation product occurs. On the contrary, **2** shows a marked reactivity towards secondary amines; in fact, the reactions with pyrrolidine (entry 5) and *N*-butylmethylamine (entry 6) proceed in appreciable yield. The higher reactivity of **2** is in agreement with the increased electrophilic character of the carbonyl group.

On the basis of the mechanistic hypothesis, the acid–base interaction between the reagents is a crucial step for the reaction course (Table 3). Accordingly, low-basicity amines, such as anilines, fail to react with **1** since the formation of the ion-pair is highly disfavoured (entries 1 and 2). Heating a 1:1 mixture of the reagents does not lead to appreciable amounts of the amide products. The modest acidity increase caused by electron-withdrawing ring substituents, in compounds **3** and **4**, does not significantly enhance the reactivity of the substrates (entries 3 and 4).

Unlike the corresponding methanesulfonamide, **2** reacts with aniline to give the corresponding anilide (entry 5). This result is in agreement with the higher acidity and reactivity of the substrate. Substitution in the *para* position of the aniline ring with electron-withdrawing or electron-releasing groups does not markedly influence the reaction outcome (entries 6–8), whereas substituents in the *ortho* position clearly depress the aniline reactivity (entries 9–11). The observed trend highlights the importance of steric hindrance. The absolute unreactivity of 2,6-difluoroaniline (entry 12) could be explained by the low basicity and nucleophilicity of the amino group. 2,6-Difluoroaniline is, in fact, significantly less basic than the other tested anilines (pK_a=2.47). As reported for dialkyl amines, *N*-methylaniline is moderately reactive in our conditions (entry 13), while the more sterically congested 2-methyl-*N*-methylaniline fails to afford the desired condensation product (entry 14).

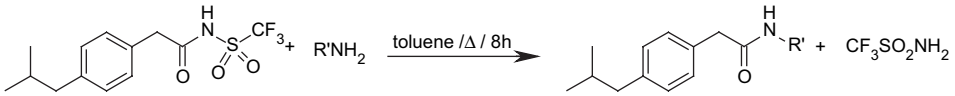
The above results confirm the hypothesis that acyltrifluoromethanesulfonamides, due to their increased reactivity, may constitute a valuable alternative to acylmethanesulfonamides as an activated intermediates for amide synthesis.

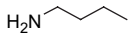
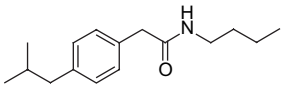
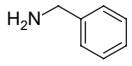
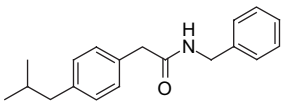
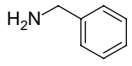
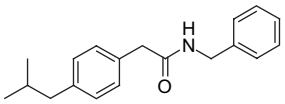
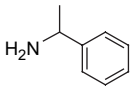
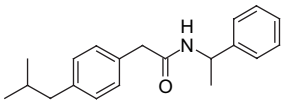
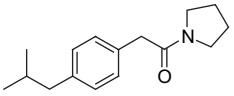
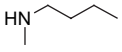
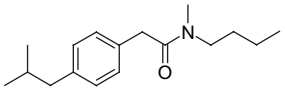
As a next step, we have verified if the enhanced reactivity of the substrate could be detrimental to the chemoselectivity of the reaction (Table 4).

When a two-fold molar excess of **2** reacts with *N*-propylaminoethylamine, the amine reagent is efficiently transformed (90% conversion yield) to give a 70:30 mixture of the amide products 2-(4-isobutylphenyl)-*N*-[2-(propylamino)ethyl]-acetamide **A** and *N*-(2-aminoethyl)-2-(4-isobutylphenyl)-*N*-propylacetamide **B**. Using a 1:1 ratio of the reagents, the reaction proceeds with high chemoselectivity (**A**/**B** ratio=97:3) although in lower yield (60%) (entries 1 and 2).

No traces of the diacylated compound are detectable. The surprising lack of reactivity of the primary amino group of **B** could be due to the engagement of a stable intramolecular interaction with the electrophilic carbonyl group. In fact, the only product detected in the reaction mixture is **C** (Fig. 2). Prolonging the reaction time to 24 h a 70:30 mixture of the

Table 2. Reactivity of **2** with alkylamines in the selected conditions



Entry	Amine	Product	Yield (%)
1			80
2			90
3			95[a]
4			35
5			40
6			45

[a] Reaction conditions: xylene/reflux/8 h.

products **A/C** is obtained. This result supports the hypothesis, confirming a marked tendency of **B** to the cyclisation.

The lower reactivity of α-branched-amines (Table 2, entry 4) suggests an additional steric effect induced by the hindrance on the α-carbon of the amine reagent. To explore this hypothesis, **2** has been reacted with a 1:1 mixture of butylamine and racemic α-methylbenzylamine. The 80:20 ratio between the products confirms the high sensitivity of the reaction to steric effects (Table 4, entry 3).

Keeping this in mind we have reasoned that the steric hindrance at the carbon next to the carbonyl group could also play a role on the substrate reactivity. With the aim to address this issue, 2-(4-isobutylphenyl)propionyltrifluoromethanesulfonamide **5** has been synthesised and reacted with several amines. Interestingly, a dramatic decrease in reactivity has been observed on moving from linear (entry 4) to branched primary amines (entry 5), whereas pyrrolidine proves unreactive under our standard conditions (entry 6). The same competition experiment described in entry 3 has been performed with **5** and higher chemoselectivity has been observed (entry 7). The results of the experiments in Table 4 confirm that steric hindrance at both the α-carbons next to the reactive centres strongly affects the reactivity of the substrate.

As a final step of this work, we have investigated the diastereodifferentiation of the process reacting racemic α-methylbenzylamine with the enantiopure substrates **6** and **7** (Table 5).

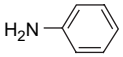
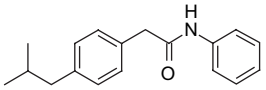
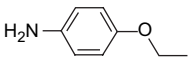
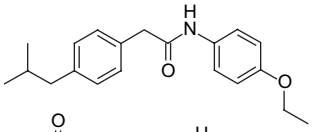
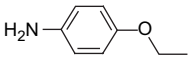
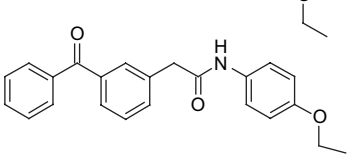
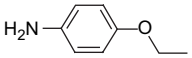
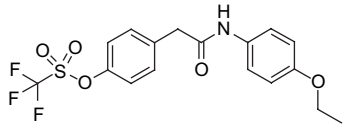
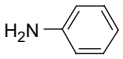
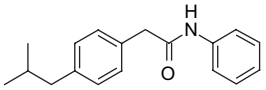
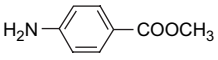
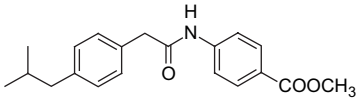
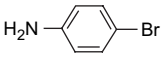
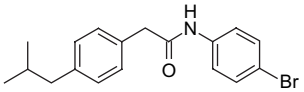
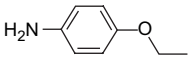
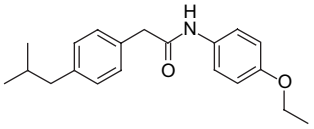
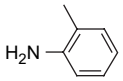
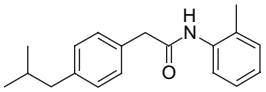
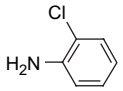
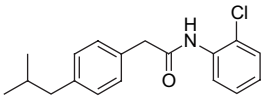
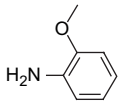
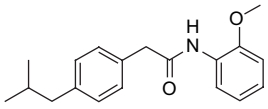
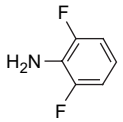
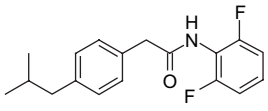
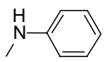
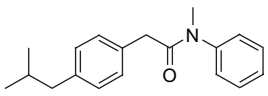
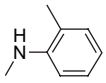
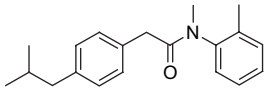
On the basis of the described steric effect, it was conceivable to expect a different reactivity of the *R* and *S* enantiomers. The four pure diastereomers have been singularly synthesised, as reference compounds for the following reaction products, by reacting **6** and **7** with the commercially available pure (*R*)(+) and (*S*)(−)-α-methylbenzylamines. Starting material **6** and the final diastereomeric product have been proved stable to epimerisation in the reaction conditions (reflux, toluene, 48 h, triethylamine as non reactive amine).

The reaction of **6** with racemic α-methylbenzylamine affords the diastereoisomers (2*R*,1*R*) with 80% diastereomeric excess but with a modest conversion yield (20%) and high recovery of the starting material (Table 5, entry 1). Prolonging the reaction time to 24 h (entry 2) the yield increases up to 82% without significant change in the enantiodiscrimination of the reaction. Analogous results have been obtained when substrates **7** and **5** have been, respectively, reacted with racemic and enantiopure α-methylbenzylamines (entries 4–6).

3. Conclusions

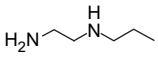
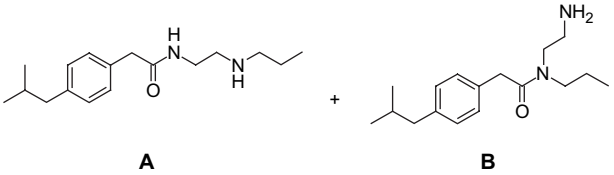
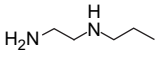
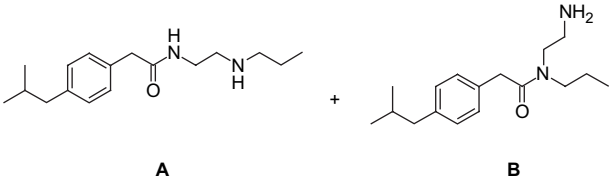
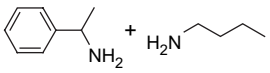
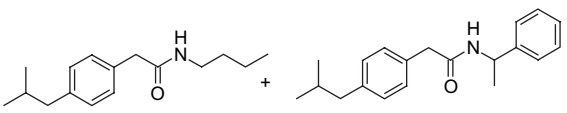
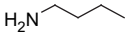
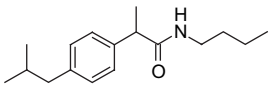
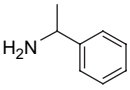
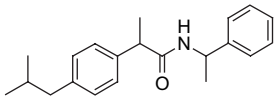
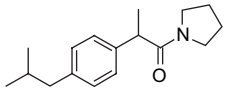
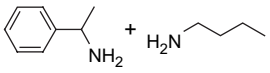
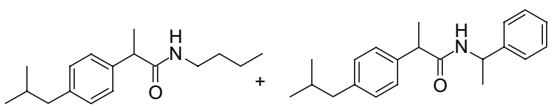
Summarizing, this work describes our advances in the study of the internal condensation of ammonium salts of

Table 3. Reaction of acylsulfonamides with aniline derivatives

Entry	Reagent	Amine	Product	Yield (%)
1	**1**			N.d.[a]
2	**1**			N.d.
3	**3**			Traces[b]
4	**4**			Traces[b]
5	**2**			70
6	**2**			80
7	**2**			75
8	**2**			71
9	**2**			59
10	**2**			37
11	**2**			Traces[b]
12	**2**			Traces[b]
13	**2**			30
14	**2**			N.d.

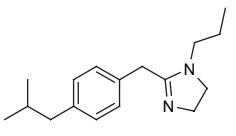
[a] N.d.: not detected.
[b] Detected by GC–MS analysis.

Table 4. Reactivity of acyltrifluoromethanesulfonamides with amines in standard conditions

Entry	Reagent	Amine	Ratio	Products[a]	Conversion yield (%)[b]
1	**2**		2:1	 **A** + **B** (70:30)	90
2	**2**		1:1	 **A** + **B** (97:3)	60
3	**2**		1:1	 (80:20)	89
4	**5**		1:1		92
5	**5**		1:1		20
6	**5**		1:1		N.d.[c]
7	**5**		1:1	 (95:5)	73

[a] Yields of isolated products are calculated after purification by flash chromatography.
[b] Conversion yields are calculated on recovered starting materials.
[c] N.d.: not detected.

N-acylmethanesulfonamides. *N*-Acyltrifluoromethanesulfonamides show considerable advantages over their non fluorinated analogues by virtue of their higher reactivity and acidity. The results in Table 5 are not optimal in terms of stereoselectivity, but they are encouraging and further studies on more hindered substrates could provide access to interesting synthetic applications.



C

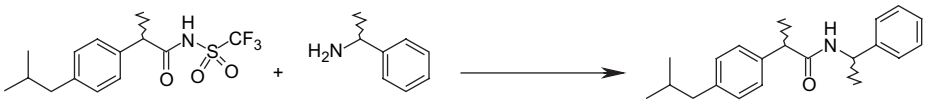
Figure 2. 2-(4-Isobutylbenzyl)1-propyl-4,5-dihydro-1*H*-imidazole (**C**).

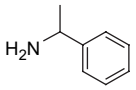
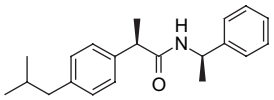
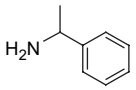
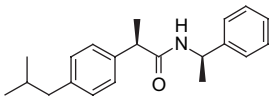
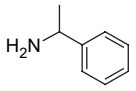
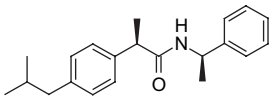
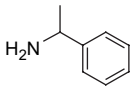
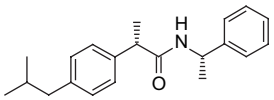
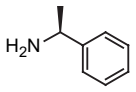
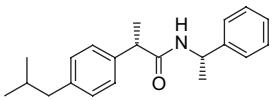
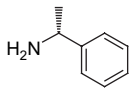
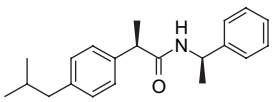
4. Experimental

4.1. General

Thin-layer chromatography was carried out with Macherey-Nagel-DURASIL-25 silica gel plates. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker ARX-300 MHz spectrometer. Column chromatography was performed on silica gel (300–400 mesh). IR spectra were recorded on Perkin–Elmer Spectrum One FTIR Spectrometer. GC–MS analysis was performed using a Thermo-Finnigan Trace 2030 UP MS chromatograph (analytical column: RTX-5MS) and a ThermoFinnigan DSQ 250 spectrometer. Uncorrected melting points were performed on a Buchi 530 apparatus. Elemental analyses were within ±0.4% of the theoretical values calculated for C, H and N

Table 5. Stereoselective reaction of *N*-acyltrifluoromethanesulfonamides with racemic and chiral α-methylbenzylamine



Entry	Reagent	Amine	Reaction conditions	Products	de (%)[a]	Yield (%)
1	**6**		Toluene/reflux/8 h	 (2*R*, 1*R*)	80	20
2	**6**		Toluene/reflux/24 h	 (2*R*, 1*R*)	40	82
3	**6**	 (2 eq.)	Toluene/reflux/24 h	 (2*R*, 1*R*)	30	85
4	**7**		Toluene/reflux/24 h	 (2*S*, 1*S*)	40	78
5	**5**		Toluene/reflux/24 h	 (2*S*, 1*S*)	40	74
6	**5**		Toluene/reflux/24 h	 (2*R*, 1*R*)	40	70

[a] Diastereoisomeric excess is calculated by chromatography purification of the products.

and is reported only with symbols. Commercially available reagents and solvents were used as received.

4.1.1. 2-(4-Isobutylphenyl)-*N*-(methylsulfonyl)acetamide (1). 1,1′-carbonyldiimidazole (CDI) (0.930 g, 5.73 mmol) was added to a solution of 4-isobutylphenyl acetic acid[7] (1.00 g, 5.21 mmol) in dry CH_2Cl_2 (25 mL) and the resulting solution was stirred for 30 min. Triethylamine (1.5 mL, 10.42 mmol) and methanesulfonamide (0.850 g, 10.42 mmol) were consecutively added and the solution stirred for 12 h at room temperature. After cooling to 0 °C, a KH_2PO_4 buffer solution (pH 2.4, 20 mL) was added and the two phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3×25 mL) and the collected organic extracts washed with brine (2×15 mL) and dried over Na_2SO_4. Solvent removal under reduced pressure afforded a crude residue, which after purification by flash chromatography (eluent mixture $CHCl_3$/MeOH 9:1), afforded the pure compound **1** (1.05 g, yield 75%) as a colourless oil. ^{1}H NMR ($CDCl_3$) δ 7.20–7.10 (m, 4H), 3.80 (s, 2H), 3.18 (s, 3H), 2.00 (d, J=7 Hz, 2H), 1.92–1.83 (m, 1H), 0.90 (d, J=7 Hz, 6H); IR (Nujol, cm^{-1}) ν 3345, 2980, 1680, 1500, 1380, 1130; EIMS m/z 269 (M+). Anal. Calcd for $C_{13}H_{19}NO_3S$: C, 57.97; H, 7.11; N, 5.20; S, 11.90. Found: C, 57.96; H, 7.09; N, 5.21; S, 11.89.

4.1.2. 2-(4-Isobutylphenyl)-*N*-[trifluromethylsulfonyl]-acetamide (2). Following the same procedure described for **1** and starting from 4-isobutylphenyl acetic acid (1.00 g, 5.21 mmol), compound **2** was prepared using commercial trifluoromethanesulfonamide. The pure compound **2** was obtained (0.84 g, yield 50%) as a pale yellow solid. Mp 107–109 °C; ^{1}H NMR ($CDCl_3$) δ 7.20–7.10 (m, 4H), 3.80 (s, 2H), 2.00 (d, J=7 Hz, 2H), 1.92–1.83 (m, 1H), 1.60–1.50 (br s, 1H, CON*H*), 0.90 (d, J=7 Hz, 6H); IR (Nujol, cm^{-1}) ν 3345, 2980, 1680, 1500, 1380, 1130; EIMS m/z 323 (M^+). Anal. Calcd for $C_{13}H_{19}NO_3S$: C, 57.97; H, 7.11; N, 5.20; S, 11.90. Found: C, 58.00; H, 7.08; N, 5.19; S, 11.91.

4.1.3. 2-(3-Benzoylphenyl)-*N*-(methylsulfonyl)acetamide (3). Following the same procedure as described for **1** and starting from commercial 2-(3-benzoylphenyl)acetic acid (1.00 g, 4.16 mmol), compound **3** was prepared. The pure compound **3** (1.05 g, yield 75%) was obtained as a yellow oil. ^{1}H NMR (DMSO-d_6) δ 8.28 (s, 1H), 8.20 (d, J=7 Hz, 1H), 8.02 (d, J=7 Hz, 1H), 7.80–7.67 (m, 4H+N*H*), 7.50 (m, 2H), 3.38 (m, 5H); IR (neat, cm^{-1}) ν 3150, 3000, 1650, 1450, 750; EIMS m/z 317 (M$^+$). Anal. Calcd for $C_{16}H_{15}NO_4S$: C, 60.55; H, 4.76; N, 4.41; S, 10.10. Found: C, 60.56; H, 4.73; N, 4.45; S, 10.09.

4.1.4. 4-{2-[(Methylsulfonyl)amino]-2-oxoethyl}phenyl trifluoromethanesulfonate (4). Following a synthetic procedure as already described[8] compound **4** was prepared from commercially available 4-hydroxyphenylacetic acid. The pure compound **4** (1.48 g, yield 78%) was obtained as colourless oil. ^{1}H NMR ($CDCl_3$) δ 7.38 (d, J=7 Hz, 2H), 7.18 (d, J=7 Hz, 2H), 4.95 (br s, 1H+CON*H*), 3.80 (s, 2H), 3.18 (s, 3H); IR (Nujol, cm^{-1}) ν 3345, 2980, 1685, 1500, 1380, 1130; EIMS m/z 361 (M$^+$). Anal. Calcd for $C_{10}H_{10}F_3NO_6S_2$: C, 33.24; H, 2.79; F, 15.77; N, 3.88; S, 17.75. Found: C, 33.25; H, 2.76; F, 15.79; N, 3.87; S, 17.78.

4.1.5. 2-(4-Isobutylphenyl)-*N*-[(trifluoromethyl)sulfonyl]propanamide (5). Following the same procedure as described for **1** and starting from the commercially available reagents 4-isobutylphenyl propionic acid (1.00 g, 4.85 mmol) and trifluoromethanesulfonamide (1.44 g, 9.7 mmol), compound **5** (1.26 g, yield 80%) was obtained as yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.20–7.08 (m, 4H), 3.75 (q, J=7 Hz, 1H), 2.50 (d, J=7 Hz, 2H), 1.92–1.83 (m, 1H), 1.50 (d, J=7 Hz, 3H), 0.90 (d, J=7 Hz, 6H); IR (neat, cm^{-1}) ν 3345, 2980, 1670, 1500, 1380, 1130; EIMS m/z 337 (M$^+$). Anal. Calcd for $C_{14}H_{18}F_3NO_3S$: C, 49.84; H, 5.38; F, 16.89; N, 4.15; S, 9.50. Found: C, 49.86; H, 5.36; F, 16.91; N, 4.14; S, 9.52.

4.1.6. (2*R*)-2-(4-Isobutylphenyl)-*N*-[(trifluoromethyl)sulfonyl]propanamide (6). Compound **6** was synthesised as described in Ref. 9. $[\alpha]_D^{20}$ −80.5 (c 1, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 7.20–7.08 (m, 4H), 3.75 (q, J=7 Hz, 1H), 2.50 (d, J=7 Hz, 2H), 1.92–1.83 (m, 1H), 1.50 (d, J=7 Hz, 3H), 0.90 (d, J=7 Hz, 6H); IR (neat, cm^{-1}) ν 3345, 2980, 1670, 1500, 1380, 1130; EIMS m/z 337 (M$^+$). Anal. Calcd for $C_{14}H_{18}F_3NO_3S$: C, 49.84; H, 5.38; F, 16.89; N, 4.15; S, 9.50. Found: C, 49.85; H, 5.35; F, 16.92; N, 4.16; S, 9.48.

4.1.7. (2*S*)-2-(4-Isobutylphenyl)-*N*-[(trifluoromethyl)sulfonyl]propanamide (7). Compound **7** was synthesised following the same procedure as described for **6** and starting from the commercially available reagent (2*S*)-2-(4-isobutylphenyl)propionic acid. $[\alpha]_D^{20}$ +79 (c 1, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 7.20–7.08 (m, 4H), 3.75 (q, J=7 Hz, 1H), 2.50 (d, J=7 Hz, 2H), 1.92–1.83 (m, 1H), 1.50 (d, J=7 Hz, 3H), 0.90 (d, J=7 Hz, 6H); IR (neat, cm^{-1}) ν 3345, 2980, 1670, 1500, 1380, 1130; EIMS m/z 337 (M$^+$). Anal. Calcd for $C_{14}H_{18}F_3NO_3S$: C, 49.84; H, 5.38; F, 16.89; N, 4.15; S, 9.50. Found: C, 49.87; H, 5.35; F, 16.91; N, 4.17; S, 9.48.

4.2. General procedure for the preparation of amides

The selected amine (1.0 mmol) was added to a solution of *N*-acylmethanesulfonamide (compounds **1–4**, 1.0 mmol) or *N*-acyltrifluoromethanesulfonamide (compounds **5–7**, 1.0 mmol) in toluene (5 mL). The resulting solution was refluxed for 8 h. After cooling to room temperature, toluene was removed under reduced pressure and the residue diluted with CH_2Cl_2 (10 mL) and washed with a KH_2PO_4 buffer solution (pH 2.4, 3×10 mL). After drying over Na_2SO_4 the organic phase was evaporated under reduced pressure and pure arylamides were obtained by flash chromatography of the crude residue.

4.2.1. *N*-Butyl-2-(4-isobutylphenyl)-*N*-acetamide (Table 1, entry 4). White solid (eluent mixture *n*-hexane/EtOAc 9:1); yield 80%; mp 57–58 °C; ^{1}H NMR ($CDCl_3$) δ 7.20–7.05 (m, 4H), 5.30 (br s, 1H, CON*H*), 3.55 (s, 2H), 3.21–3.14 (m, 2H), 2.50 (d, J=7 Hz, 2H), 1.92–1.83 (m, 1H), 1.44–1.35 (m, 2H), 1.25 (m, 2H), 0.97–0.85 (m, 9H); IR (Nujol, cm^{-1}) ν 3368, 2950, 1670, 1460; EIMS m/z 247 (M$^+$). Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.70; H, 10.15; N, 5.68.

4.2.2. *N*-Benzyl-2-(4-isobutylphenyl)acetamide (Table 2, entry 2). White solid (eluent mixture *n*-hexane/EtOAc 9:1); yield 90%; mp 100–103 °C; ^{1}H NMR ($CDCl_3$) δ 7.30–7.20 (m, 4H), 7.15–7.05 (m, 5H), 5.60 (br s, 1H, CON*H*), 4.40 (d, J=5 Hz, 2H), 3.55 (s, 2H), 2.55 (d, J=7 Hz, 2H), 1.90–1.82 (m, 1H), 0.85 (d, J=7 Hz, 6H); IR (Nujol, cm^{-1}) ν 3368, 2950, 1670, 1460; EIMS m/z 281 (M$^+$). Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.11; H, 8.19; N, 5.01.

4.2.3. 2-(4-Isobutylphenyl)-*N*-(1-phenylethyl)acetamide (Table 2, entry 4). White solid (eluent mixture $CHCl_3$/CH_3OH 98:2); yield 35%; mp 89–92 °C; ^{1}H NMR ($CDCl_3$) δ 7.32–7.20 (m, 4H), 7.18–7.05 (m, 5H), 5.55 (br s, 1H, CON*H*), 5.15–5.04 (m, 1H), 3.50 (s, 2H), 2.50 (d, J=7 Hz, 2H), 1.92–1.83 (m, 1H), 1.35 (d, J=7 Hz, 3H), 0.90 (d, J=7 Hz, 6H); IR (Nujol, cm^{-1}) ν 3368, 2950, 1670, 1460; EIMS m/z 295 (M$^+$). Anal. Calcd for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.34; H, 8.49; N, 4.70.

4.2.4. 1-[(4-Isobutylphenyl)acetyl]pyrrolidine (Table 2, entry 5). Colourless oil (eluent mixture *n*-hexane/EtOAc 9:1); yield 40%; ^{1}H NMR ($CDCl_3$) δ 7.20 (d, J=7 Hz, 2H), 7.05 (d, J=7 Hz, 2H), 3.63 (s, 2H), 3.49 (t, J=7 Hz, 2H), 3.43 (t, J=7 Hz, 2H), 2.45 (d, J=7 Hz, 2H), 1.70–1.76 (m, 5H), 0.90 (d, J=7 Hz, 6H); IR (neat, cm^{-1}) ν 2950, 1670, 1460; EIMS m/z 245 (M$^+$). Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.33; H, 9.48; N, 5.73.

4.2.5. *N*-Butyl-2-(4-isobutylphenyl)-*N*-methylacetamide (Table 2, entry 6). Colourless oil (eluent mixture *n*-hexane/EtOAc 9:1); yield 80%; ^{1}H NMR ($CDCl_3$) δ 7.20–7.05 (m, 4H), 3.55 (s, 2H), 3.15–3.10 (m, 5H), 2.50 (d, J=7 Hz, 2H), 1.92–1.83 (m, 1H), 1.44–1.35 (m, 2H), 1.30–1.20 (m, 2H), 0.97–0.85 (m, 9H); IR (neat, cm^{-1}) ν 3368, 2950, 1670, 1460; EIMS m/z 261 (M$^+$). Anal. Calcd for $C_{17}H_{27}NO$: C, 78.11; H, 10.41; N, 5.36. Found: C, 78.13; H, 10.39; N, 5.38.

4.2.6. 2-(4-Isobutylphenyl)-*N*-phenylacetamide (Table 3, entry 5). White solid (eluent mixture *n*-hexane/EtOAc 9:1); yield 70%; mp 110–112 °C; ^{1}H NMR ($CDCl_3$) δ 7.30–7.20 (m, 4H), 7.15–7.05 (m, 5H), 6.90 (br s, 1H, CON*H*), 3.36 (s, 2H), 2.51 (d, *J*=7 Hz, 2H), 1.90 (m, 1H), 0.93 (d, *J*=7 Hz, 6H); IR (Nujol, cm^{-1}) ν 3368, 2950, 1670, 1460; EIMS *m*/*z* 267 (M^+). Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.89; H, 7.88; N, 5.27.

4.2.7. Methyl 4-{[(4-isobutylphenyl)acetyl]amino}benzoate (Table 3, entry 6). Pale yellow oil (eluent mixture *n*-hexane/EtOAc 8:2); yield 80%; ^{1}H NMR ($CDCl_3$) δ 8.00 (d, *J*=7 Hz, 2H), 7.50 (d, *J*=7 Hz, 2H), 7.28–7.15 (m, 4H), 3.90 (s, 3H), 3.80 (br s, 1H, CON*H*), 3.65 (s, 2H), 2.55 (d, *J*=7 Hz, 2H), 1.85–1.78 (m, 1H), 0.90 (d, *J*=7 Hz, 6H); IR (neat, cm^{-1}) ν 3300, 2950, 1680, 1460; EIMS *m*/*z* 325 (M^+). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.83; H, 7.10; N, 4.31.

4.2.8. *N*-(4-Bromophenyl)-2-(4-isobutylphenyl)acetamide (Table 3, entry 7). White solid (eluent mixture *n*-hexane/EtOAc 9:1); yield 75%; mp 135–137 °C; ^{1}H NMR ($CDCl_3$) δ 7.40–7.30 (m, 4H), 7.27–7.12 (m, 4H), 7.00 (br s, 1H, CON*H*), 3.65 (s, 2H), 2.50 (d, *J*=7 Hz, 2H), 1.92–1.83 (m, 1H), 0.90 (d, *J*=7 Hz, 6H); IR (Nujol, cm^{-1}) ν 3300, 2950, 1680, 1460; EIMS *m*/*z* 345/347 ([$^{79/81}$Br] M^+). Anal. Calcd for $C_{18}H_{20}BrNO$: C, 62.44; H, 5.82; Br, 23.08; N, 4.05. Found: C, 62.46; H, 5.79; Br, 23.10; N, 4.04.

4.2.9. *N*-(4-Ethoxyphenyl)-2-(4-isobutylphenyl)acetamide (Table 3, entry 8). Yellow oil (eluent mixture *n*-hexane/EtOAc 85:15); yield 71%; ^{1}H NMR ($CDCl_3$) δ 8.00 (br s, 1H, CON*H*), 7.55 (d, *J*=7 Hz, 2H), 7.10–7.01 (m, 4H), 6.95 (d, *J*=7 Hz, 2H), 3.75 (q, *J*=7 Hz, 2H), 3.65 (s, 2H), 2.50 (d, *J*=7 Hz, 2H), 1.92–1.83 (m, 1H), 1.45 (t, *J*=7 Hz, 3H), 0.90 (d, *J*=7 Hz, 6H); IR (neat, cm^{-1}) ν 3368, 2950, 1670, 1460; EIMS *m*/*z* 311 (M^+). Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.15; H, 8.13; N, 4.48.

4.2.10. 2-(4-Isobutylphenyl)-*N*-(2-methylphenyl)acetamide (Table 3, entry 9). White solid, (eluent mixture *n*-hexane/EtOAc 9:1); yield 59%; mp 110–111 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (d, *J*=7 Hz, 1H), 7.23–7.00 (m, 7H), 6.85 (br s, 1H, CON*H*), 3.70 (s, 2H), 2.50 (d, *J*=7 Hz, 2H), 1.85–1.80 (m, 4H), 0.85 (d, *J*=7 Hz, 6H); IR (Nujol, cm^{-1}) ν 3368, 2950, 1670, 1460; EIMS *m*/*z* 281 (M^+). Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.12; H, 8.21; N, 4.95.

4.2.11. *N*-(2-Chlorophenyl)-2-(4-isobutylphenyl)acetamide (Table 3, entry 10). Yellow oil (eluent mixture *n*-hexane/EtOAc 9:1); yield 37%; ^{1}H NMR ($CDCl_3$) δ 8.05 (br s, 1H, CON*H*), 7.58 (d, *J*=7 Hz, 1H), 7.35 (d, *J*=7 Hz, 1H), 7.25–7.00 (m, 6H), 3.68 (s, 2H), 2.50 (d, *J*=7 Hz, 2H), 1.92–1.83 (m, 1H), 0.90 (d, *J*=7 Hz, 6H); IR (neat, cm^{-1}) ν 3368, 2950, 1670, 1460; EIMS *m*/*z* 300/302 ([$^{35/37}$Cl] M^+). Anal. Calcd for $C_{18}H_{20}ClNO$: C, 71.63; H, 6.68; Cl, 11.75; N, 4.64. Found: C, 71.63; H, 6.68; Cl, 11.75; N, 4.64.

4.2.12. 2-(4-Isobutylphenyl)-*N*-methyl-*N*-phenylacetamide (Table 3, entry 13). Light brown oil (eluent mixture *n*-hexane/EtOAc 9:1); yield 30%; ^{1}H NMR ($CDCl_3$) δ 7.40–7.30 (m, 3H), 7.15 (d, *J*=7 Hz, 2H), 7.05–6.90 (m, 4H), 3.45 (s, 2H), 3.30 (s, 3H), 2.42 (d, *J*=7 Hz, 2H), 1.92–1.83 (m, 1H), 0.85 (d, *J*=7 Hz, 6H); IR (neat, cm^{-1}) ν 3368, 2950, 1670, 1460; EIMS *m*/*z* 281 (M^+). Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.08; H, 8.20; N, 5.01.

4.2.13. 2-(4-Isobutylphenyl)-*N*-[2-(propylamino)ethyl]-acetamide (Table 4, compound A). Pale yellow oil (eluent mixture *n*-hexane/EtOAc 8:2); ^{1}H NMR ($CDCl_3$) δ 7.18–7.12 (m, 4H), 6.05 (br s, 1H, CON*H*), 3.50 (s, 2H), 3.30–3.25 (m, 2H), 2.74–2.66 (m, 2H), 2.45–2.52 (m, 4H), 1.92–1.83 (m, 1H), 1.62 (br s, 1H, N*H*), 1.48–1.30 (m, 2H), 0.95–0.80 (m, 9H); IR (neat, cm^{-1}) ν 3360, 3060, 1914, 1643, 1456, 1233, 650; ESIMS *m*/*z* 276 (M^+). Anal. Calcd for $C_{17}H_{28}N_2O$: C, 73.87; H, 10.21; N, 10.13. Found: C, 73.88; H, 10.23; N, 10.15.

4.2.14. *N*-(2-Aminoethyl)-2-(4-isobutylphenyl)-*N*-propylacetamide (Table 4, compound B). Pale yellow oil (eluent mixture *n*-hexane/EtOAc 8:2); ^{1}H NMR ($CDCl_3$) δ 7.02 (m, 4H), 3.50 (t, *J*=7 Hz, 2H), 3.45 (s, 2H), 3.35 (m, 2H), 3.20 (t, *J*=7 Hz, 2H), 2.50 (d, *J*=7 Hz, 2H), 2.05 (br s, 2H, NH_2), 1.85 (m, 1H), 1.50 (m, 2H), 1.02–0.92 (m, 9H); IR (neat, cm^{-1}) ν 3345, 2950, 1670, 1460; ESIMS *m*/*z* 276 (M^+). Anal. Calcd for $C_{17}H_{28}N_2O$: C, 73.87; H, 10.21; N, 10.13. Found: C, 73.89; H, 10.24; N, 10.09.

4.2.15. 2-(4-Isobutylbenzyl)-1-propyl-4,5-dihydro-1*H*-imidazole (compound C). Colourless oil (eluent mixture *n*-hexane/EtOAc 8:2); ^{1}H NMR ($CDCl_3$) δ 7.19 (d, *J*=7 Hz, 2H), 7.09 (d, *J*=7 Hz, 2H), 3.78 (t, *J*=10 Hz, 2H), 3.62 (s, 2H), 3.35 (t, *J*=10 Hz, 2H), 2.97 (t, *J*=7 Hz, 2H), 2.48 (d, *J*=7 Hz, 2H), 1.92–1.83 (m, *J*=7 Hz, 1H), 1.35–1.28 (m, *J*=7 Hz, 2H), 0.90 (d, *J*=7 Hz, 6H), 0.75 (t, *J*=7 Hz, 3H); IR (neat, cm^{-1}) ν 2957, 1605, 1460, 1125; ESIMS *m*/*z* 258 (M^+). Anal. Calcd for $C_{17}H_{26}N_2$: C, 79.02; H, 10.14; N, 10.84. Found: C, 79.05; H, 10.12; N, 10.83.

4.2.16. (2*R*)-2-(4-Isobutylphenyl)-*N*-[(1*R*)-1-phenylethyl]propanamide (Table 5, entry 1). White solid (eluent mixture *n*-hexane/EtOAc 7:3); mp 107–109 °C; $[\alpha]_D^{20}$ +22.6 (*c* 1, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 7.30–7.05 (m, 9H), 5.50 (br s, *J*=7 Hz, 1H, CON*H*), 5.14–5.07 (m, 1H), 3.55 (q, *J*=7 Hz, 1H), 2.47 (d, *J*=7 Hz, 2H), 1.92–1.83 (m, *J*=7 Hz, 1H), 1.51 (d, *J*=7 Hz, 3H), 1.39 (d, *J*=7 Hz, 3H), 0.91 (d, *J*=7 Hz, 6H); IR (neat, cm^{-1}) ν 3286, 2950, 2864, 1642, 1540, 1447; EIMS *m*/*z* 309 (M^+). Anal. Calcd for $C_{21}H_{27}NO$: C, 81.51; H, 8.79; N, 4.53. Found: C, 81.55; H, 8.77; N, 4.51.

4.2.17. (2*S*)-2-(4-Isobutylphenyl)-*N*-[(1*S*)-1-phenylethyl]-propanamide (Table 5, entry 4). White solid (eluent mixture *n*-hexane/EtOAc 7:3); mp 108–110 °C; $[\alpha]_D^{20}$ −23.2 (*c* 1, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 7.30–7.05 (m, 9H), 5.50 (br s, *J*=7 Hz, 1H, CON*H*), 5.14–5.07 (m, 1H), 3.55 (q, *J*=7 Hz, 1H), 2.47 (d, *J*=7 Hz, 2H), 1.92–1.83 (m, *J*=7 Hz, 1H), 1.51 (d, *J*=7 Hz, 3H), 1.39 (d, *J*=7 Hz, 3H), 0.91 (d, *J*=7 Hz, 6H); IR (neat, cm^{-1}) ν 3286, 2950, 2864, 1642, 1540, 1447; EIMS *m*/*z* 309 (M^+). Anal. Calcd for $C_{21}H_{27}NO$: C, 81.51; H, 8.79; N, 4.53. Found: C, 81.52; H, 8.81; N, 4.50.

References and notes

1. Coniglio, S.; Aramini, A.; Cesta, M. C.; Colagioia, S.; Curti, R.; D'Alessandro, F.; D'Anniballe, G.; D'Elia, V.; Nano, G.; Orlando, V.; Allegretti, M. *Tetrahedron Lett.* **2004**, *45*, 5375–5378.
2. Koščovà, S.; Buděšinský, M.; Hodačovà, J. *Collect. Czech. Chem. Commun.* **2003**, *68*, 744–750.
3. Pittelkow, M.; Lewinsky, R.; Christensen, J. B. *Synthesis* **2002**, *15*, 2195–2202.
4. Xu, D.; Prasad, K.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **1995**, *36*, 7357–7360.
5. (a) Kondo, K.; Sekimoto, E.; Miki, K.; Murakami, Y. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2973–2974; (b) Kondo, K.; Sekimoto, E.; Nakao, J.; Murakami, Y. *Tetrahedron* **2000**, *56*, 5843–5856.
6. Laduron, F.; Tamborowski, V.; Moens, L.; Horváth, A.; De Smaele, D.; Leurs, S. *Org. Process Res. Dev.* **2005**, *9*, 102–104.
7. Nicholson, J. S.; Adams, S. S. U.S. 3385887, May 28, 1968.
8. Aureli, L.; Cruciani, G.; Cesta, M. C.; Anacardio, R.; De Simone, L.; Moriconi, A. *J. Med. Chem.* **2005**, *48*, 2469–2479.
9. Allegretti, M.; Bertini, R.; Cesta, M. C.; Bizzarri, C.; Di Bitondo, R.; Di Cioccio, V.; Galliera, E.; Berdini, V.; Topai, A.; Zampella, G.; Russo, V.; Di Bello, N.; Nano, G.; Nicolini, L.; Locati, M.; Fantucci, P.; Florio, S.; Colotta, F. *J. Med. Chem.* **2005**, *48*, 4312–4331.