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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design, synthesis of new chiral fluorine-containing β-hydroxysulfonamides from natural amino acids and study of their anti-inflammatory and analgesic activities

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Abstract A series of new chiral fluorine-containing β-hydroxysulfonamides were conveniently synthesized in three steps, starting from natural L-amino acids, and evaluated for their anti-inflammatory and analgesic activities. The structures of these compounds were supported by FT-IR, ^{1}H, ^{13}C and ^{19}F NMR, elemental analysis and HRMS. Among the tested compounds, **4c**, **4g** and **4h** exhibited promising anti-inflammatory activity. Moreover, compound **4h** showed a significant analgesic activity. The structure–activity relationships of selected compounds were discussed.

Keywords (L)-amino acids · β-Hydroxysulfonamides · Arylmagnesium bromide · Anti-inflammatory · Analgesic

Introduction

The sulfonamides constitute an important class of drugs, with several types of pharmacological agents possessing antibacterial (Drews, 2000), antitumor (Supuran, 2002), anti-carbonic anhydrase (Supuran *et al.,* 2003) diuretic (Supuran *et al.,* 1996), hypoglycemic (Boyd, 1988), antithyroid (Thornber, 1979) or protease inhibitory activity among others (Supuran *et al.,* 2002). Their use as anti-inflammatory and analgesic agents is also reported in the literature (Tozkoparan *et al.*, 2007). The pharmaceutical industry continues to explore new scaffolds that incorporate the sulfonamide moiety.

Interest in new sulfonamide scaffolds has also extended to compounds such as chiral β-hydroxysulfonamides. Access to these chiral structures was established by addition of Grignard reagents to chiral amino acid esters (Kreft *et al.*, 2003; Yi-Feng *et al.*, 2009). Some of these compounds are reported as inhibitors of β-amyloid production (Kreft *et al.,* 2003).

Preparing of new fluorinated β-hydroxysulfonamides is presumed to be an attractive approach since it could improve and enlarge these structures application field. In fact, the strategic placement of fluorine in a molecule has become a rational and popular approach during design of medicinal leads. The potential of fluorine-containing biologically relevant molecules was recognized by researchers, and thus the new wave of fluorine chemistry has been rapidly expanding its biomedical frontiers. This small size atom improves metabolic stability, modulate physicochemical properties, such as lipophilicity or basicity, and enhance the binding affinity to the target protein (Biffinger *et al.,* 2004; Böhm *et al.,* 2004).

In this paper, we report a simple and efficient method for the synthesis of new chiral fluorinated β-hydroxysulfonamides in a three steps reaction, using commercially available (L)-amino acids as starting material. Their pharmacological potential was then investigated, specifically their anti-inflammatory and analgesic activities. The rational for the design of these compounds was based on the fact that such a scaffold was reported in previous series as a part of anti-inflammatory compounds and structure–activity relationship (SAR) studies demonstrated its crucial

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role (Tsai *et al.,* 2006; Carter *et al.,* 1999; Zarghi *et al.,* 2006).

Materials and methods

Chemistry

Chemicals were purchased from Sigma-Aldrich Chemical Company. Melting points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. The IR spectra (In KBr pellets) were recorded on Perkin-Elmer FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Bruker DRX-300 MHz NMR spectrometer, and ^{13}C NMR spectra were recorded on a Bruker DRX-75 MHz NMR in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard and chemical shifts are in δ (ppm). High-resolution mass spectra (HRMS) were recorded on a MicroTOF spectrometer. Elemental analysis was carried out with a Perkin-Elmer apparatus. All dry reactions were carried out under nitrogen in oven-dried glassware. All reagents and solvents were dried prior to use according to standard methods. Dichloromethane was dried over calcium hydride and distillated before use. Tetrahydrofuran was dried by heating over sodium-benzophenone and distilled before use. *N*-sulfonylated amino esters **3a–j** were prepared according to the literature (Anadi *et al.,* 2014) and were characterized by comparing their NMR spectra with the literature data (see supplementary information).

General procedure for the synthesis of N-[(1S)-1,1-diaryl-1-hydroxyalkan-2-yl]sulphonamides ***4a–l***

In a dry three-necked flask fitted with a dropping funnel and equipped with a magnetic stirrer, 29.38 mmol of Magnesium turnings, 14.69 mmol of LiCl and 0.03 mmol of $LiAlH_4$ were introduced under nitrogen atmosphere. Then, 6 ml of dry THF were added. After 5 min of stirring, 11.8 mmol of *p*-fluorobromobenzene dissolved in 30 ml of dry THF were added dropwise. The reaction mixture was stirred at room temperature for 1 h. After that, 3 mmol of *N*-sulfonyl ester **3**, dissolved in 10 mL of dry THF, were added dropwise with stirring at 0 °C. The ice bath was maintained 15 min after the addition. The reaction mixture was then stirred at room temperature for 24 h and is controlled with thin layer chromatography. A solution of H_2SO_4 (10 %) is then added dropwise at 0 °C until total disappearance of the Mg. The reaction mixture was stirred for 1 h. After that, the mixture was diluted with ethyl acetate (20 mL), washed with saturated aqueous $NaHCO_3$ solution and extracted with 3 × 20 mL of ethyl acetate. The organic layers were collected, dried over anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (cyclohexane- ethyl acetate: 80/20).

(S)-N-(1,1-bis(4-fluorophenyl)-1-hydroxypropan-2-yl)benzenesulfonamide ***(4a)*** White solid; mp 125–126 °C; $[\alpha]_D^{22} = +3.5$ (c 0.7, CH_3OH); IR (KBr, cm^{-1}) $\sqrt{}_{N-H} = 3245$; $\sqrt{}_{O-H} = 3515$; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.01$ (d, 3H, $J = 6.6$ Hz, $\underline{CH_3}$), 2.85 (brs, 1H, $\underline{OH}$), 4.36 (m, 1 H, $\underline{CH}$–NH), 4.98 (d, 1 H, $J = 8.7$ Hz, –$\underline{NH}$), 6.76–6.82 (m, 2H, Ar), 6.96–7.01 (m, 2H, Ar), 7.24–7.45 (m, 6H, Ar), 7.53–7.64 (m, 3H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 17.3$ ($\underline{CH}3$), 55.9 ($\underline{CH}$–NH), 79.9 ($\underline{C}$–OH), 115.0 (d, 2C, $J_{C-F} = 21$ Hz Ar, $\underline{CH}$–C–F), 115.2 (d, 2C, $J_{C-F} = 21$ Hz, Ar, $\underline{CH}$–C–F), 126.7 (2C, Ph, $\underline{CH}$), 127.4 (d, 2C, $J_{C-F} = 8$ Hz Ar, $\underline{CH}$–CH–C–F), 127.5 (d, 2C, $J_{C-F} = 8$ Hz, Ar, $\underline{CH}$–CH–C–F), 128.9 (2C, Ph, $\underline{CH}$), 132.4 (1C, Ph, $\underline{CH}$), 139.7 (m, 2C, Ar, $\underline{C}$–CH–CH–C–F), 140.8 (1C, Ph), 161.6 (d, 1C, $J_{C-F} = 245$ Hz, Ar, $\underline{C}$–F), 161.8 (d, 1C, $J_{C-F} = 245$ Hz, Ar, C–F); ^{19}F NMR (282,4 MHz, $CDCl_3$): $\delta = -115.3$ (m, 1 F); −114.9 (m, 1F). HRMS $[M + Na]^+$ Calcd for $C_{21}H_{19}F_2NO_3S$: 426.0951; Found: 426.0956; Elemental analysis for $C_{21}H_{19}F_2NO_3S$. Calcd: C 62.52 %, H 4.75 %, N 3.47 %; Found: C 62.59 %, H 4.70 %, N 3.53 %.

(S)-N-(1,1-bis(4-fluorophenyl)-1-hydroxy-3-phenylpropan-2-yl)benzenesulfonamide ***(4b)*** White solid; mp 159–162 °C; $[\alpha]_D^{22} = +17.5$ (c 0.7, CH_3OH); IR (KBr, cm^{-1}) $\sqrt{}_{N-H} = 3281$; $\sqrt{}_{O-H} = 3484$; ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 2.53 (brs, 1H, $\underline{OH}$), 2.87 (m, 1H, $\underline{CH_2}$–Ph), 3.25 (m, 1 H, $\underline{CH_2}$–Ph), 4.66 (m, 1 H, $\underline{CH}$–NH) 4.84 (m, 1H, $\underline{NH}$), 6.73–7.48 (m, 18H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 37.9$ ($\underline{CH_2}$–Ph), 61.5 ($\underline{CH}$–NH), 80.4 ($\underline{C}$–OH), 115.0 (d, 2C, $J_{C-F} = 21$ Hz, $\underline{CH}$–C–F, Ar), 115.4 (d, 2C, $J_{C-F} = 21$ Hz, Ar, $\underline{CH}$–C–F), 126.4 (2C, Ph, $\underline{CH}$), 127.1 (d, 2C, $J_{C-F} = 7.8$ Hz, Ar, –$\underline{CH}$–CH–C–F), 127.1 (1C, Ph, $\underline{CH}$), 127.7 (d, 2C, $J_{C-F} = 7.9$ Hz, Ar, $\underline{CH}$–CH–C–F), 128.7 (2C, Ph, $\underline{CH}$), 128.8 (2C, Ph, $\underline{CH}$), 129.6 (2C, Ph, $\underline{CH}$), 132.0 (1C, Ph, $\underline{CH}$), 136.8 (1C, Ph, $\underline{C}$), 139.5 (d, 1C, $J_{C-F} = 2.5$ Hz, Ar, $\underline{C}$–CH–CH–C–F), 139.6 (d, 1C, Ar, $J_{C-F} = 2.5$ Hz, $\underline{C}$–CH–CH–C–F), 140.5 (1C, Ph, $\underline{C}$), 161.6 (d, 1C, $J_{C-F} = 245$ Hz, Ar, $\underline{C}$–F), 161.9 (d, 1C, $J_{C-F} = 245$ Hz, Ar, $\underline{C}$–F); ^{19}F NMR (282,4 MHz, $CDCl_3$): $\delta = -115.5$, −114.5; Elemental analysis for $C_{27}H_{23}F_2NO_3S$. Calcd: C 67.63 %, H 4.83 %, N 2.92 %; Found: C 67.70 %, H 4.82 %, N 2.97 %.

(S)-N-(1,1-bis(4-fluorophenyl)-1-hydroxypropan-2-yl)methanesulfonamide ***(4c)*** Yellow viscous oil; $[\alpha]_D^{22} = +30.8$ (c 0.7, CH_3OH); IR (KBr, cm^{-1}) $\sqrt{}_{N-H} = 3280$; $\sqrt{}_{O-H} = 3484$; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.26$ (d, 3H, $J = 6.6$ Hz, $\underline{CH_3}$), 2.48 (s, 3H, $\underline{CH_3}$–SO_2), 4.50 (m, 1 H, $\underline{CH}$–NH), 4.77 (d, 1 H, $J = 9$ Hz, $\underline{NH}$), 7.03 (dd, $\underline{4H}$,

$J_{H–H}$ = 8.7 Hz, $J_{H–F}$ = 15.9 Hz, Ar), 7.43 (dd, 2H, J = 5.1, 8.8 Hz, Ar), 7.49 (dd, 2H, J = 5.1, 8.8 Hz, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.3 ($\underline{C}H_3$), 41.7 ($\underline{C}H_3$–SO_2), 56.5 ($\underline{C}$H–NH), 79.9 ($\underline{C}$–OH), 115.2 (d, 2C, $J_{C–F}$ = 21 Hz, Ar, $\underline{CH}$–C–F), 115.4 (d, 2C, $J_{C–F}$ = 21 Hz, Ar, $\underline{CH}$–C–F), 127.6 (d, 2C, $J_{C–F}$ = 8.1 Hz, Ar, $\underline{CH}$–CH–C–F), 127.9 (d, 2C, $J_{C–F}$ = 8.1 Hz, Ar, $\underline{CH}$–CH–C–F), 139.5 (d, 1C, $J_{C–F}$ = 3.3 Hz, Ar, $\underline{C}$–CH–CH–C–F), 140.5 (d, 1C, $J_{C–F}$ = 3.3 Hz, Ar, $\underline{C}$–CH–CH–C–F), 161.8 (d, 1C, $J_{C–F}$ = 245 Hz, $\underline{C}$–F), 161.9 (d, 1C, $J_{C–F}$ = 245 Hz, $\underline{C}$–F); ^{19}F NMR (282,4 MHz, $CDCl_3$): δ = −114.8, −114.6; HRMS $[M + Na]^+$ Calcd for $C_{16}H_{17}F_2NO_3S$: 364.0795; Found: 364.0791; Elemental analysis for $C_{16}H_{17}F_2NO_3S$. Calcd: C 56.29 %, H 5.02 %, N 4.10 %; Found: C 56.32 %, H 4.96 %, N 4.14 %.

(S)-N-(1,1-bis(4-fluorophenyl)-1-hydroxy-3-phenylpropan-2-yl)methanesulfonamide ***(4d)*** White solid; mp 185–187 °C; $[\alpha]_D^{22}$ = + 33.6 (c 0.7, CH_3OH); IR (KBr, cm^{-1}) $\sqrt{}_{N–H}$ = 3322; $\sqrt{}_{O–H}$ = 3498; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.99 (s, 3H, $\underline{CH_3}$–SO_2), 2.66 (dd, 1H, J = 9, 14.1 Hz, $\underline{CH_2}$–Ph), 3.06 (dd, 1H, J = 2.7, 9 Hz, $\underline{CH_2}$–Ph), 4.68 (m, 2H, $\underline{CH}$–$\underline{NH}$), 7.04–7.33 (m, 9H–Ar), 7.51–7.58 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 38.3 (1C, $\underline{CH_2}$–Ph), 41.3 (1C, $\underline{CH_3}$–SO_2), 63.1 (1C, $\underline{CH}$–NH), 80.3 (1C, $\underline{C}$–OH), 115.3 (t (2d), 4C, $J_{C–F}$ = 21 Hz, Ar, $\underline{CH}$–C–F), 127.2 (1C, Ph, $\underline{C}$H), 128.1 (d, 2C, $J_{C–F}$ = 8 Hz, Ar, $\underline{CH}$–CH–C–F), 128.5 (d, 2C, $J_{C–F}$ = 8 Hz, Ar, $\underline{CH}$–CH–C–F), 128.9 (2C, Ph, $\underline{C}$H), 129.7 (2C, Ph, $\underline{C}$H), 137.6 (1C, Ph, $\underline{C}$H), 139.2 (d, 1C, $J_{C–F}$ = 3.3 Hz, Ar, $\underline{C}$–CH–CH–C–F), 140.1 (d, 1C, $J_{C–F}$ = 2.9 Hz, Ar, $\underline{C}$–CH–CH–C–F), 161.9 (d, 1C, $J_{C–F}$ = 246 Hz, Ar, $\underline{C}$–F), 162.0 (d, 1C, $J_{C–F}$ = 246 Hz, Ar, $\underline{C}$–F); ^{19}F NMR (282,4 MHz, $CDCl_3$): δ = −114.6, −114.4; HRMS $[M + Na]^+$ Calcd for $C_{22}H_{21}F_2NO_3S$: 440.1108; Found: 440.1101; Elemental analysis for $C_{22}H_{21}F_2NO_3S$. Calcd: C 63.29 %, H 5.07 %, N 3.36 %; Found: C 63.30 %, H 5.12 %, N 3.29 %.

(S)-N-(1,1-bis(4-fluorophenyl)-1-hydroxy-3-methylbutan-2-yl)methanesulfonamide ***(4e)*** White solid; mp 161–163 °C; $[\alpha]_D^{22}$ = + 25.9 (c 0.7, CH_3OH); IR (KBr, cm^{-1}) $\sqrt{}_{N–H}$ = 3352; $\sqrt{}_{O–H}$ = 3494; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.90 (d, 3H, J = 6.6 Hz, $\underline{CH_3}$–i–Pr), 1.10 (d, 3H, J = 6.6 Hz, $\underline{CH_3}$–i–Pr), 2.04 (hd, 1H, J = 1.5, 6.6 Hz, CH–i–Pr), 2.26 (s, 3H, $\underline{CH_3}$–SO_2), 2.56 (s, 1H, $\underline{OH}$), 4.41 (dd, 1H, J = 1.5, 9.4 Hz, $\underline{CH}$–NH), 4.58 (d, 1H, J = 9.4 Hz, $\underline{NH}$), 7.05 (dd, 4H, $J_{H–H}$ = 8.7 Hz, $J_{H–F}$ = 17.5 Hz, Ar), 7.47 (dd, 2H, J = 5.1, 8.7 Hz, Ar), 7.53 (dd, 2H, J = 5.1, 8.7 Hz, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.3 (1C, $\underline{CH_3}$–iPr), 22.5 (1C, $\underline{CH_3}$–iPr), 28.6 (1C, $\underline{CH}$–i–Pr), 41.9 (1C, $\underline{CH_3}$–SO_2), 64.8 (1C, $\underline{CH}$–NH), 81.6 (1C, $\underline{C}$–OH), 115.4 (t (2d), 4C, $J_{C–F}$ = 21 Hz, Ar, $\underline{CH}$–C–F), 127.1 (d, 2C, $J_{C–F}$ = 7.1 Hz, Ar, $\underline{CH}$–CH–C–F), 127.7 (d, 2C, $J_{C–F}$ = 7.9 Hz, Ar, $\underline{CH}$–CH–C–F), 140.1 (d, 1C, $J_{C–F}$ = 3.4 Hz, Ar, $\underline{C}$–CH–CH–C–F), 141.6 (d, 1C, $J_{C–F}$ = 2.9 Hz, Ar, $\underline{C}$–CH–CH–C–F), 161.8 (d, 1C, $J_{C–F}$ = 246 Hz, Ar, $\underline{C}$–F), 161.8 (d, 1C, $J_{C–F}$ = 246 Hz, Ar, $\underline{C}$–F); ^{19}F NMR (282,4 MHz, $CDCl_3$): δ = −114.8, −114.6; HRMS $[M + Na]^+$ Calcd for $C_{18}H_{21}F_2NO_3S$: 392.1108; Found: 392.1102; Elemental analysis for $C_{18}H_{21}F_2NO_3S$. Calcd: C 58.52 %, H 5.73 %, N 3.79 %; Found: C 58.60 %, H 5.69 %, N 3.80 %.

(S)-N-(1,1-bis(4-fluorophenyl)-1-hydroxy-4-methylpentan-2-yl)methanesulfonamide ***(4f)*** White solid; mp 176–178 °C; $[\alpha]_D^{22}$ = + 38.5 (c 0.7, CH_3OH); IR (KBr, cm^{-1}) $\sqrt{}_{N–H}$ = 3250; $\sqrt{}_{O–H}$ = 3505; ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 0.91 (d, 3H, J = 6.6 Hz, $\underline{CH_3}$–i–Bu), 1.08 (d, 3H, J = 6.6 Hz, $\underline{CH_3}$–i–Bu), 1.31 (m, 2H, $\underline{CH_2}$–i–Bu), 1.94 (m, 1H, $\underline{CH}$–i–Bu), 2.31 (s, 3H, $\underline{CH_3}$–SO_2), 2.54 (s, 1H, $\underline{OH}$), 4.20 (d, 1H, J = 9 Hz, $\underline{NH}$), 4.55 (m, 1H, $\underline{CH}$–NH), 7.06 (m, 4H–Ar), 7.47 (m, 4H–Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 21.0 (1C, $\underline{CH_3}$–i–Bu), 24.0 (1C, $\underline{CH}$–i–Bu), 24.2 (1C, $\underline{CH_3}$–i–Bu), 41.4 (1C, $\underline{CH_2}$–iBu), 41.8 (1C, $\underline{CH_3}$–SO2), 59.9 (1C, $\underline{CH}$–NH), 80.4(1C, $\underline{C}$–OH), 115.3 (d, 2C, $J_{C–F}$ = 21 Hz, Ar, $\underline{CH}$–C–F), 115.4 (d, 2C, $J_{C–F}$ = 21 Hz, Ar, $\underline{CH}$–C–F), 127.8 (d, 2C, $J_{C–F}$ = 7.8 Hz, Ar, $\underline{CH}$–CH–C–F), 128.0 (d, 2C, $J_{C–F}$ = 8.1 Hz, Ar, $\underline{CH}$–CH–C–F), 139.5 (d, 1C, $J_{C–F}$ = 3.4 Hz, Ar $\underline{C}$–CH–CH–C–F), 140.9 (d, 1C, $J_{C–F}$ = 3.3 Hz, Ar, $\underline{C}$–CH–CH–C–F), 161.9 (d, 1C, $J_{C–F}$ = 254 Hz, Ar, $\underline{C}$–F), 162.0 (d, 1C, $J_{C–F}$ = 261 Hz, Ar, $\underline{C}$–F); ^{19}F NMR (282,4 MHz, $CDCl_3$): δ = −114.6, −114.4; HRMS $[M + Na]^+$ Calcd for $C_{19}H_{23}F_2NO_3S$: 406.1264; Found: 406.1263; Elemental analysis for $C_{19}H_{23}F_2NO_3S$. Calcd: C 59.51 %, H 6.05 %, N 3.65 %; Found: C 59.55 %, H 6.04 %, N 3.60 %.

(S)-N-(1,1-bis(4-fluorophenyl)-1-hydroxypropan-2-yl)-2,4,6-trimethylbenzenesulfonamide ***(4g)*** White solid; mp 77–81 °C; $[\alpha]_D^{22}$ = + 4.2 (c 0.7, CH_3OH); IR (KBr, cm^{-1}) $\sqrt{}_{N–H}$ = 3396; $\sqrt{}_{O–H}$ = 3484; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.15 (d, 3H, J = 6.6 Hz, $\underline{CH_3}$–CH), 2.31 (s, 3H, $\underline{CH_3}$-mesityl), 2.48 (s, 6H, 2$\underline{CH_3}$-mesityl), 4.36 (m, 1H, $\underline{CH}$-NH), 4.98 (brs, 1H, $\underline{NH}$), 6.72 (td, 2H, J = 2.1, 8.7 Hz, Ar), 6.86 (s, 2H–Ar), 6.97 (td, 2H J = 2.1, 8.7 Hz, Ar), 7.23 (m, 2H–Ar), 7.33 (m, 2H–Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.3 (1C, $\underline{CH_3}$–CH), 20.8 (1C, $\underline{CH_3}$-mesityl), 22.9 (2C, $\underline{CH_3}$-mesityl), 55.9 (1C, $\underline{CH}$–NH), 79.8 (1C, $\underline{C}$–OH), 114.7 (d, 2C, $J_{C–F}$ = 21 Hz, Ar, $\underline{CH}$–C–F), 115.3 (d, 2C, $J_{C–F}$ = 21 Hz, Ar, $\underline{CH}$–C–F), 127.0 (d, 2C, $J_{C–F}$ = 7.9 Hz, Ar, $\underline{CH}$–CH–C–F), 127.3 (d, 2C, $J_{C–F}$ = 8 Hz, Ar, $\underline{CH}$–CH–C–F), 131.9 (2C, mesityl, $\underline{CH}$), 134.7 (1C, mesityl, $\underline{C}$), 138.4 (2C, mesityl, $\underline{C}$), 139.8 (1C, Ar, $\underline{C}$–CH–CH–C–F), 140.0 (1C, Ar, $\underline{C}$–CH–CH–C–F), 142.0 (1C, mesityl, $\underline{C}$), 161.5 (d, 1C, $J_{C–F}$ = 244 Hz, Ar, $\underline{C}$–F), 161.7 (d, 1C, $J_{C–F}$ = 244 Hz, Ar, $\underline{C}$–F); ^{19}F NMR

(282,4 MHz, $CDCl_3$): $\delta = -115.5$, -115.0; HRMS $[M + Na]^+$ Calcd for $C_{24}H_{25}F_2NO_3S$: 468.1421; Found: 468.1421; Elemental analysis for $C_{24}H_{25}F_2NO_3S$. Calcd: C 64.70 %, H 5.66 %, N 3.14 %; Found: C 64.68 %, H 5.69 %, N 3.17 %.

(S)-N-(1,1-bis(4-fluorophenyl)-1-hydroxy-3-phenylpropan-2-yl)-2,4,6-trimethylbenzenesulfonamide ***(4h)*** White solid; mp 91–93 °C; $[\alpha]_D^{22} = +7.0$ (c 0.7, CH_3OH); IR (KBr, cm^{-1}) $\surd_{N-H} = 3400$; $\surd_{O-H} = 3471$; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.28$ (s, 3H, CH_3-mesityl), 2.40 (s, 6H, 2 CH_3–mesityl), 2.57 (s, 1H, OH), 2.91 (dd, 1H, $J = 5.7$, 14.1 Hz, H–CH–Ph), 3.28 (dd, 1H, $J = 4.2$, 14.1, H–CH–Ph), 4.68 (m, 1H, CH–NH), 5.00 (d, 1H, $J = 8.7$ Hz, NH), 6.65 (t, 2H, $J = 8.7$ Hz, Ar), 6.74 (s, 2H–Ar), 6.98 (m, 2H–Ar), 7.07 (t, 2H, $J = 8.7$ Hz, Ar), 7.20 (m, 5H, Ar), 7.45 (dd, 2H, $J = 5.1$, 9 Hz, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 20.7$ (1C, CH_3–mesityl), 23.0 (2C, CH_3-mesityl), 38.0 (1C, CH_2–Ph), 61.1 (1C, CH–NH), 80.5 (1C, C–OH), 114.7 (d, 2C, $J_{C-F} = 21$ Hz, Ar, CH–C–F), 115.5 (d, 2C, $J_{C-F} = 21$ Hz, Ar, CH–C–F), 126.3 (d, 2C, $J_{C-F} = 8.1$ Hz, Ar, CH–CH–C–F), 127.0 (1C, Ph, CH), 127.5 (d, 2C, $J_{C-F} = 7.8$ Hz, Ar, CH–CH–C–F), 128.8 (2C, Ar, CH), 129.5 (2C, Ar, CH), 131.8 (2C, Ar, CH), 134.8 (1C, mesityl, C), 136.7 (1C, Ar, C), 137.9 (2C, mesityl, C), 139.7 (d, 1C, $J_{C-F} = 3.1$ Hz, Ar, C–CH–CH–C–F), 139.9 (d, 1C, $J_{C-F} = 3.1$ Hz, Ar, C–CH–CH–C–F), 141.7 (1C, Ar, C), 161.5 (d, 1C, $J_{C-F} = 244$ Hz, Ar, C–F), 161.9 (d, 1C, $J_{C-F} = 245$ Hz, Ar, C–F); ^{19}F NMR (282,4 MHz, $CDCl_3$): $\delta = -115.6$, -114.6; Elemental analysis for $C_{30}H_{29}F_2NO_3S$. Calcd: C 69.08 %, H 5.60 %, N 2.69 %; Found: C 69.13 %, H 5.58 %, N 2.65 %.

(S)-N-(1,1-bis(4-fluorophenyl)-1-hydroxy-3-methylbutan-2-yl)-2,4,6-trimethylbenzenesulfonamide ***(4i)*** White solid; mp 135–137 °C; $[\alpha]_D^{22} = +28.7$ (c 0.7, CH_3OH); IR (KBr, cm^{-1}) $\surd_{N-H} = 3335$; $\surd_{O-H} = 3481$; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 0.84$ (d, 3H, $J = 6.9$ Hz, CH_3–i–Pr), 0.0.97 (d, 3H, $J = 6.9$ Hz, CH_3–i–Pr), 1.98 (m, 1H, CH–i–Pr), 2.28 (s, 3H, CH_3-mesityl), 2.51 (s, 6H, 2 CH_3-mesityl), 2.51 (brs, 1H, OH), 4.36 (dd, 1H, $J = 1.5$, 9.6 Hz, CH–NH), 4.87 (d, 1H, $J = 9.6$ Hz, NH), 6.66 (t, 2H, $J = 8.7$ Hz, Ar), 6.80 (s, 2H, Ar), 7.02 (t, 2H, $J = 8.7$ Hz, Ar), 7.24 (dd, 2H, $J = 5.2$, 8.8 Hz, Ar), 7.39 (dd, 2H, $J = 5.1$, 9 Hz, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 17.7$ (1C, CH_3–i–Pr), 20.7 (1C, CH_3–i–Pr), 22.6 (1C, CH_3-mesityl), 22.9 (2C, CH_3-mesityl), 28.9 (1C, CH–i–Pr), 64.7 (1C, CH–NH), 81.7 (1C, C–OH), 114.6 (d, 2C, $J_{C-F} = 21$ Hz, Ar, CH–C–F), 115.4 (d, 2C, $J_{C-F} = 21$ Hz, Ar, CH–C–F), 126.6 (d, 2C, $J_{C-F} = 8.1$ Hz, Ar, CH–CH–C–F), 127.2 (d, 2C, $J_{C-F} = 7.8$ Hz, Ar, CH–CH–C–F), 131.7 (2C, mesityl, CH), 136.3 (1C, mesityl, C), 137.3 (2C, mesityl, C), 140.4 (1C, Ar, C–CH–CH–C–F), 140.5 (1C, Ar, C–CH–CH–C–F), 141.4 (1C, mesityl, C), 163.0 (1C, Ar, C–F), 163.4 (1C, Ar, C–F); ^{19}F NMR (282,4 MHz, $CDCl_3$): $\delta = -115.5$, -114.9; Elemental analysis for $C_{26}H_{29}F_2NO_3S$. Calcd: C 65.94 %, H 6.17 %, N 2.96 %; Found: C 65.89 %, H 6.09 %, N 3.02 %.

(S)-N-(1-hydroxy-1,1-bis(4-(trifluoromethyl)phenyl)propan-2-yl)methanesulfonamide ***(4j)*** Yellow viscous oil; $[\alpha]_D^{22} = +16.8$ (c 0.7, CH_3OH); IR (KBr, cm^{-1}) $\surd_{N-H} = 3322$; $\surd_{O-H} = 3464$; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 1.27$ (d, 3H, $J = 6.6$ Hz, CH_3–CH), 2.50 (s, 3H, CH_3–SO2), 4.66 (m, 1H, CH–NH), 4.85 (d, 1H, $J = 9$ Hz, NH), 7.61 (m, 6H–Ar), 7.70 (d, 2H, $J = 8.4$ Hz, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 17.9$ (1C, CH_3–CH), 41.8 (1C, CH_3–SO_2), 56.0 (1C, CH–NH), 80.3 (1C, C–OH), 123.7 (q, 2C, $J_{C-F} = 270$ Hz, CF_3), 125.4 (q, 2C, $J_{C-F} = 3.8$ Hz, Ar, CH–C–CF_3), 125.7 (q, 2C, $J_{C-F} = 3.8$ Hz, Ar, CH–C–CF_3), 126.1 (2C, Ar, CH–CH–C–CF_3), 126.4 (2C, Ar, CH–CH–C–CF_3), 129.9 (q, 1C, $J_{C-F} = 33$ Hz, C–CF_3), 130.0 (q, 1C, $J_{C-F} = 33$ Hz, C–CF_3), 147.1 (1C, Ar, C–CH–CH–C–CF_3), 148.06 (1C, Ar, C–CH–CH–C–CF_3); ^{19}F NMR (282,4 MHz, $CDCl_3$): $\delta = -62.74$, -62.71; Elemental analysis for $C_{18}H_{17}F_6NO_3S$. Calcd: C 48.98 %, H 3.88 %, N 3.17 %; Found: C 49.04 %, H 3.89 %, N 3.12 %.

(S)-N-(1-hydroxy-3-phenyl-1,1-bis(4-(trifluoromethyl)phenyl) propan-2-yl)-2,4,6-trimethylbenzenesulfonamide ***(4k)*** White solid; mp 168–170 °C; $[\alpha]_D^{22} = +21.7$ (c 0.7, CH_3OH); IR (KBr, cm^{-1}) $\surd_{N-H} = 3322$; $\surd_{O-H} = 3464$; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.27$ (s, 3H, CH_3-mesityl), 2.39 (s, 6H, 2 CH_3-mesityl), 2.81 (s, 1H, OH), 3.02 (dd, 1H, $J = 4.8$, 14.4 Hz, H–CH–Ph), 3.36 (dd, 1H, $J = 4.8$, 14.4 Hz, H–CH–Ph), 4.81 (m, 1H, CH–NH), 5.14 (d, 1H, $J = 9$ Hz, NH), 6.75 (s, 2H–Ar), 6.94–7.03 (m, 2H–Ar), 7.20 (d, 2H, $J = 8.4$ Hz, Ar), 7.22-7.25 (m, 3H–Ar), 7.36 (d, 2H, $J = 8.1$ Hz, Ar), 7.61 (s, 4H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 20.6$ (1C, CH_3–mesityl), 22.8 (2C, CH_3-mesityl), 37.7 (1C, CH_2–Ph), 60.4 (1C, CH–NH), 81.0 (1C, C–OH), 124.8 (2C, Ar, CH), 125.0 (q, 2C, $J_{C-F} = 3.8$ Hz, Ar, CH–C–CF_3), 125.7 (q, 2C, $J_{C-F} = 3.8$ Hz, Ar, CH–C–CF_3), 125.8 (2C, Ar, CH), 127.2 (1C, Ph, CH), 128.7 (2C, Ar, CH), 129.0 (q, 2C, $J_{C-F} = 32$ Hz, Ar, C–CF_3), 129.0 (2C, Ar, CH), 131.8 (2C, Ar, CH), (1C, Ph, C), 136.5 (1C, mesityl, C), 138.0 (2C, mesityl, C), 142.0 (1C, mesityl, C), 147.4 (1C, Ar, C–CH–CH–C–CF_3), 147.6 (1C, Ar, C–CH–CH–C–CF_3); ^{19}F NMR (282,4 MHz, $CDCl_3$): $\delta = -62.6$, -62.6; HRMS $[M + Na]^+$ Calcd for $C_{32}H_{29}F_6NO_3S$: 644.1670; Found: 644.1681; Elemental analysis for $C_{32}H_{29}F_6NO_3S$. Calcd: C 61.83 %, H 4.70 %, N 2.25 %; Found: C 61.87 %, H 4.63 %, N 2.32 %.

(S)-N-(1-hydroxy-1,1-diphenylpropan-2-yl)benzenesulfonamide ***(4l)*** White solid; mp 113–115 °C; $[\alpha]_D^{22} = +11.5$

(c 0.7, CH_3OH); IR (KBr, cm^{-1}) $\sqrt{}_{N-H} = 3348$; $\sqrt{}_{O-H} = 3496$; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 1.14$ (3H, Me), 2.85 (brs, 1H, OH), 4.47 (m, 1H, CH–NH), 4.96 (brs, 1H, NH), 7.12–7.28 (m, 4H–Ar), 7.28–7.46 (m, 8H–Ar), 7.48–7.58 (m, 1H–Ar), 7.62–7.70 (m, 2H–Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 17.3$ (1C, CH_3–CH), 55.8 (1C, CH–NH), 80.4 (1C, C–OH), 125.6 (2C, Ph, CH), 125.7 (2C, Ph, CH), 126.8 (2C, Ph, CH), 127.0 (1C, Ph, CH), 127.2 (1C, Ph, CH), 128.3 (2C, Ph, CH), 128.4 (2C, Ph, CH), 128.9 (2C, Ph, CH), 132.2 (1C, Ph, CH), 140.9 (1C, Ph, C), 143.9 (1C, Ph, C), 144.0 (1C, Ph, C); Elemental analysis for $C_{21}H_{21}NO_3S$. Calcd: C 68.64 %, H 5.76 %, N 3.81 %; Found: C 68.72 %, H 5.70 %, N 3.84 %.

Pharmacology

Animals

Wistar rats weighing 150–170 g and swiss albinos (20–30 g) were obtained from Pasteur Institute (Tunis, Tunisia). Housing conditions and in vivo experiments were approved, according to the guidelines established by the European Union on Animal Care (CCE Council 86/609).

Anti-inflammatory activity

The anti-inflammatory activity of compounds **4a–l** on carrageenan-induced rat paw edema was evaluated by the method of Winter *et al.* (1962). Three groups of Wistar rats (n = 6) were considered. The control group received 2.5 mL/kg of vehicle solution (tween 80/absolute ethanol/saline solution (0.9 %) in the ratio 1:1:18) by the intraperitoneally (i.p.) route. The reference group received Diclofenac® which is a non-steroidal anti-inflammatory drug (10 mg/kg, i.p.) and the test groups received compounds **4c** at increasing doses (10, 25 and 50 mg/kg, i.p) and **4a, b, d–l** (50 mg/kg, i.p.). After 30 min, 0.05 ml of a 1 % carrageenan suspension was injected into the left hind paw. The paw volume up to the tibiotarsal articulation was measured using a plethysmometer (model 7150, UgoBasile, Italy) at 0 h (V0) (before carrageenan injection) and 1, 2, 3, 4 and 5 h later (VT) (after carrageenan injection). Paw swelling was determined for each rat and the difference between VT and V0 was taken as the edema value. The percent inhibition was calculated by the formula given below: % Inhibition: [(VT − V0) control–(VT − V0) treated] × 100/(VT − V0) control.

Analgesic activity

The analgesic activity of the compounds of the series was performed according to the method of Koster *et al.* (1959). Swiss mice (20–30 g) were selected one day prior to each test and were divided into three groups ($n = 6$). The control group was pretreated with saline at 10 ml/kg by subcutaneous (s.c) administration. The second group was pretreated with the reference drug, Acetylsalicylate of lysine (ASL) at the dose of 200 mg/kg (s.c). The test groups received an injection of 50 mg/kg of compounds **4a–i** by the same route (s.c). Thirty minutes later, animals of all groups received, by the intraperitoneally (i.p.) route, 10 ml/kg of 1 % acetic acid. The number of writhing was recorded during 30 min after the acetic acid injection. A writhe is indicated by abdominal constriction and stretching of at least one hind limb. Analgesic activity was expressed as inhibition percent of the usual number of writhes observed in control animals. The percentages of inhibition were calculated according to the following formula:

$$\%\ \text{inhibition} = (\text{Number of writhes})_{\text{control}} - (\text{Number of writhes})_{\text{treated group}}) / (\text{Number of writhes})_{\text{control}} \times 100$$

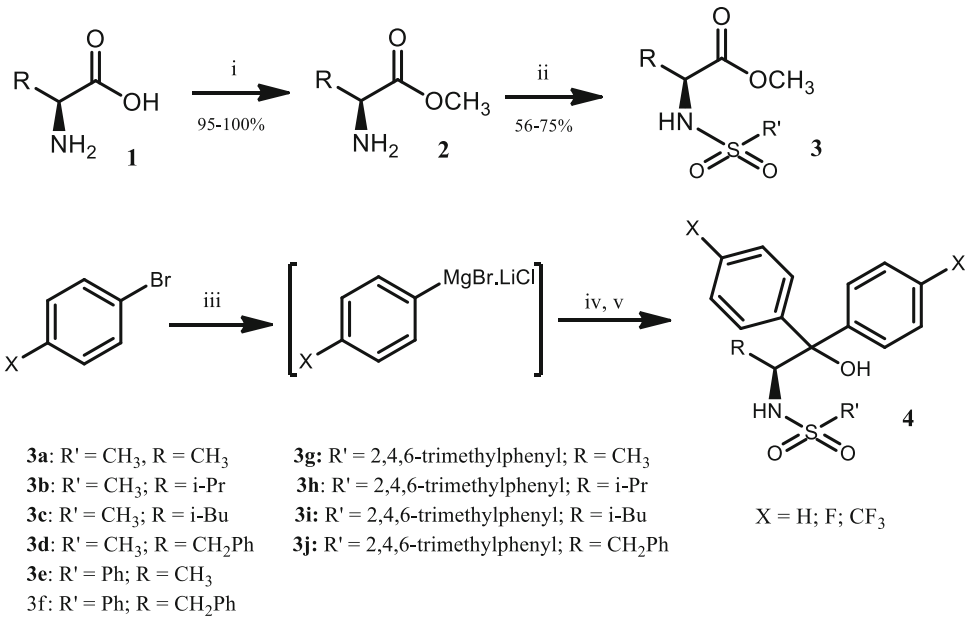
Statistics

Data are expressed as the mean ± standard error of the mean (SEM) of six animals per group. Statistical analysis was performed using paired-sample *T* Test (IBM SPSS Statistics Version 20 software). The significance of difference was considered to include values of $*p < 0.05$; $**p < 0.01$; $***p < 0.001$.

Results and discussion

Chemistry

Our synthetic route to target compounds **4a–l** are outlined in scheme 1. The commercially available (L)- amino acids **1**, were converted quantitatively to amino acid esters **2** by use of the $SiMe_3Cl$/MeOH system as described previously (Jiabo and Yaowu 2008). The *N*-sulfonylation of amino acid esters **2** with CH_3–SO_2–Cl or Ar–SO_2–Cl in CH_2Cl_2 and in the presence of Et_3N, afforded the *N*-sulfonylated amino acid esters **3a–j** in good yields (Anadi *et al.*, 2014). Compounds **3a–j** were subjected to react with Ar–Mg–Br, in the presence of LiCl, to afford products **4a–l** in good to excellent yields (Table 1). This approach, developed and used by Knochel and co-workers (Piller *et al.*, 2008) for the preparation of diaryl compounds from aryl iodide and aryl magnesium halides, was applied in this work to convert the ester group of compounds **3a–j** to the corresponding fluorine-containing diaryl alcohols **4a–l**. This method appears to be more efficient than the classic use of aryl Grignard



Scheme 1 Synthesis of compounds **4a–l** from natural amino acids. Reagents and reaction conditions: (*i*) $SiMe_3Cl$, MeOH, rt, 12 h; (*ii*) R'SO_2Cl, Et_3N, CH_2Cl_2, 0 °C-rt, 24 h; (*iii*) Mg, LiCl, $LiAlH_4$ (1 %), THF, rt, 1–2 h; (*iv*) **3**, 24 h, rt; (*v*) H_2SO_4 (10 %), 0 °C, 1 h

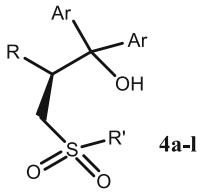
reagents (without LiCl), especially, when the aryl is substituted with electron-withdrawing groups such as fluorine and trifluoromethyl groups. As shown in Table 1, compounds **4a** and **4j** were obtained in good isolated yields in the presence of LiCl (**4a:** 95 % and **4j:** 81 %), whereas, without use of LiCl, lower yields were obtained for these compounds (**4a:** 57 % and **4j:** 16 %). On the other hand, we have found that the use of $LiAlH_4$ (1 %) is convenient and sufficient for activation of magnesium and then avoid heating for the in situ preparation of the Grignard reagent. Compounds **4a–l** were characterized by physical, chemical and spectral studies. For example, the IR of **4a** showed two absorption peaks at 3245 and 3515 cm^{-1} which correspond to the N–H and the O–H groups, respectively. The ^1H NMR spectrum of **4a** displays a broad signal at 2.85 ppm attributable to the proton of the OH group, and a doublet at 4.98 ppm attributable to the proton of the N–H group (CH–NH). The signal of the C–OH carbon is observed at 79.9 ppm. These results are in agreement with spectral data of structural analogues of **4a** such as compound **5** (Fig. 1) (Zhang *et al.,* 2014). The ^{13}C NMR spectrum of **4a** displays two different characteristic signals which correspond to the diastereotopic C-F groups at 161.6 ppm (d, $J_{C-F} = 245$ Hz) and at 161.8 ppm (d, $J_{C-F} = 245$ Hz). This non-equivalence was also observed in the ^{19}F NMR spectrum of **4a** which displays two signals of the diastereotopic fluorine atoms at −115.3 and −144.9 ppm (Fig. 1).

Pharmacology

The anti-inflammatory potential of compounds **4a–l** on carrageenan-induced rat paw edema determined by the method of Winter *et al.* is shown in Table 2. These results indicate that the compound **4c** tested at 10, 25, and 50 mg/kg i.p. exhibited potency comparable to Diclofenac® since a significant reduction of the edema was noted even at the lower dose (Fig. 2). The anti-inflammatory activity of **4c,** at 50 mg/kg appears to be similar to the reference drug after 2 and 4 h and slightly inferior after 5 h (Table 3; Fig. 3). Also, the inhibition of edema along the whole observation period was noted for the rest of the compounds. At 50 mg/kg, the highest reduction of the edema was observed 5 h after carrageen injection for three compounds of the series: 43.73 % of inhibition for compound **4a**, 50 % for compound **4g** and 50.19 % for compound **4h**, whereas the reference drug (Diclofenac®, 10 mg/kg,) produced a reduction of 60 % in paw volume. For compounds **4d**, **4e** and **4f**, the greatest reduction of edema was observed 3 h after carrageen injection with an inhibition percentage equal to 42.28, 41.97 and 40.32 %, respectively. The rest of the compounds of the series showed a moderate activity (Table 2).

The SAR study allows us to conclude that the nature of substituents R and R' play a major role in the anti-inflammatory activity of the structures of the series. In fact, replacement of the phenyl ring group on R' by CH_3 or a mesityl group (2,4,6-trimethylphenyl) is accompanied by an increase in the anti-inflammatory activity. This fact correlated with literature since the methanesulfonyl moiety was reported to be present in common anti-inflammatory structures belonging to the coxibs class (Zarghi and Arfaei 2011). On the other hand, we have found that introducing a fluorine atom in the *para*-positions of the two phenyl rings enhances obviously the anti-inflammatory activity. Indeed,

Table 1 Synthesis of products **4a–l** by reaction of Ar–Mg–Br



4a-l

Compounds	R	R'	Ar	Yields (%)
4a	$–CH_3$	–ph	4-F–Ph	95[a] (57)[b]
4b	$–Ph–CH_2$	–Ph	4-F–Ph	89[a]
4c	$–CH_3$	$–CH_3$	4-F–Ph	94[a]
4d	$–PhCH_2$	$–CH_3$	4-F–Ph	85[a]
4e	$–CH(CH_3)_2$	$–CH_3$	4-F–Ph	92[a]
4f	$–CH_2CH(CH)_2$	$–CH_3$	4-F–Ph	93[a]
4g	$–CH_3$	2, 4,6-trimethylphenyl	4-F–Ph	90[a]
4h	$–Ph–CH_2$	2, 4,6-trimethylphenyl	4-F–Ph	87[a]
4i	$–CH(CH_3)_2$	2, 4,6-trimethylphenyl	4-F–Ph	90[a]
4j	$–CH_3$	$–CH_3$	4-CF_3–Ph	81[c] (16)[b]
4k	$–PhCH_2$	2, 4,6-trimethylphenyl	4-CF_3–Ph	78[c]
4l	–CH3	Ph	Ph	92[a] (75)[b]

LiCl complexes with sulfonyl esters **3a–j**

[a] 4-F–Ph–MgBr. LiCl was prepared in 1 h before the addition of **3**

[b] Isolated yield without LiCl

[c] CF3–Ph–MgBr. LiCl was prepared in 2 h before the addition of **3**

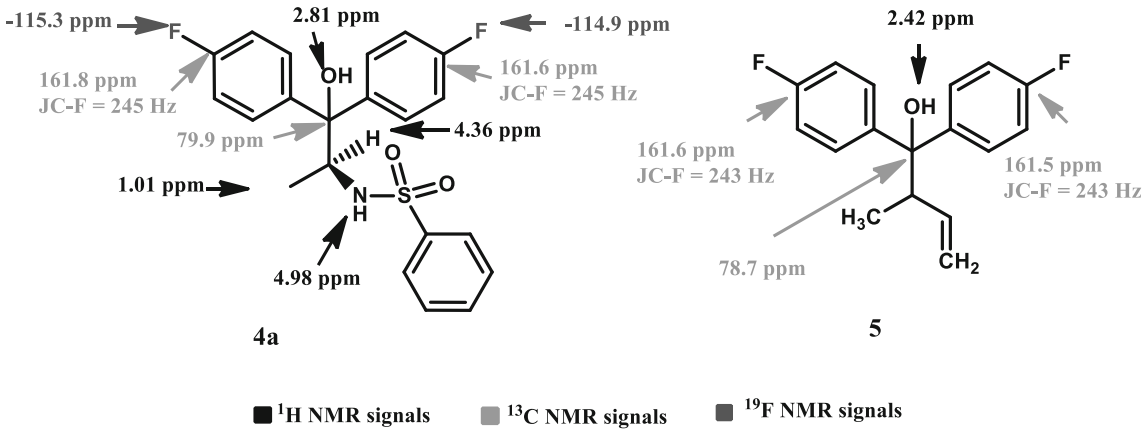


Fig. 1 Characteristic NMR chemical shifts of compounds **4a** and **5**

compound **4a** produced 43.73 % of edema inhibition better than its structural analogue without fluorine **4l** (16.55 %). This fact is not surprising since fluorine is well known nowadays in medicinal chemistry, and it has become a common practice to examine the effects of substitution of fluorine or a trifluoromethyl group on a lead compound

Table 2 Anti-inflammatory activity evaluation of compounds **4a–l** on carrageenan-induced rat paw edema, in comparison to the reference drug, Diclofenac

Sample	Dose (mg/kg)	Edema volume (10^{-2}mL) (m ± SEM)			% of edema inhibition		
		1h	**3h**	**5h**	**1h**	**3h**	**5h**
Vehicle (2,5 mL/kg)	–	27.00 ± 0.81	60.75 ± 0.50	72.50 ± 2.64	–	–	–
Diclofenac (reference)	10	16.00 ± 3.65**	25.25 ± 3.30***	29.00 ± 2.51***	41.00	58.43	60.00
4a	50	22.75 ± 1.12	39.75 ± 3.10**	44.10 ± 1.18**	12.50	34.56	43.73
4b	50	25.50 ± 2.08	49.75 ± 3.72	54.25 ± 2.00	1.92	18.10	30.62
4c	10	18.75 ± 1.70*	39.50 ± 1.29**	42.00 ± 3.16**	30.75	34.97	42.00
4c	25	17.00 ± 2.94**	35.50 ± 1.50**	39.50 ± 3.00***	40.70	41.97	45.51
4c	50	15.00 ± 0.81***	29.50 ± 4.20***	33.00 ± 3.26***	44.00	51.44	**54.48**
4c (racemic)[a]	50	19.50 ± 1.29*	38.00 ± 1.63**	41.00 ± 3.16**	27.77	37.44	43.44
4d	50	20.00 ± 3.26	35.00 ± 4.08**	46.75 ± 2.42*	25.92	42.38	35.51
4e	50	11.25 ± 2.50***	35.25 ± 2.62**	55.00 ± 3.74	58.33	41.97	24.13
4f	50	16.25 ± 1.25**	36.25 ± 2.75**	51.75 ± 0.95	39.81	40.32	28.62
4g	50	17.00 ± 0.81**	31.5 ± 4.20***	36.25 ± 2.62***	37.00	48.14	50.00
4h	50	17.25 ± 1.70**	33.5 ± 2.64***	36.00 ± 1.25***	36.11	44.85	50.19
4i	50	15.00 ± 4.61***	39.75 ± 2.06*	55.75 ± 3.30	44.44	34.56	23.10
4j	50	16.50 ± 0.57**	39.5 ± 2.38*	45.5 ± 1.29*	38.88	34.97	37.24
4k	50	23.75 ± 2.62	51.25 ± 2.21*	59.00 ± 2.94	12.00	16.00	18.62
4l	50	24.75 ± 2.21	51.00 ± 2.70	60.5 ± 1.00	8.33	16.00	16.55

The most active compound is given in bold. Reference drug is underlined

The values represent the mean difference of volume of paw ± SEM ($n = 6$)

* $p < 0.05$; ** $p < 0.01$; ***$p < 0.001$ significantly different from control group

[a] Prepared from (D, L)-alanine

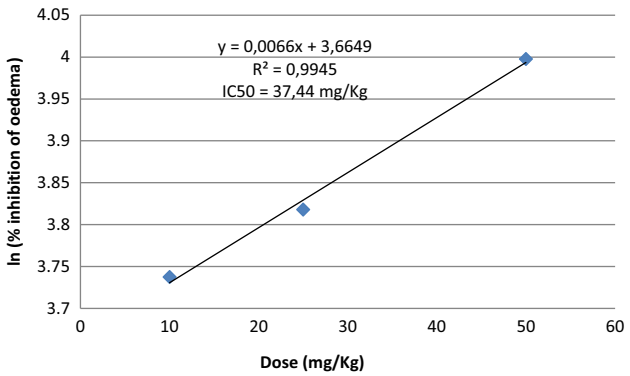


Fig. 2 Dose–effect curve 5 h after intraperitoneal administration of **4c** (50 mg/kg)

under development. There are patterns to explain how this atom contributes to the efficiency of a drug: increasing bio-absorption by lipophilic effects, polar hydrophobicity enhances binding of fluorinated molecules to protein recognition sites and selective interactions with amino acid residues in a binding site (Hagmann, 2008; Kirk, 2006; Purser *et al.,* 2008).

Contrary to our expectation, the inclusion of a trifluoromethyl group in compound **4j** decreased the anti-inflammatory activity compared to the mono-fluorinated parent **4c** (37.24 vs. 54.48 %). This may be related to the steric bulk of the trifluoromethyl group at this position, constraining the phenyl ring to adopt a conformation which disfavors binding to the appropriate site on the target.

Similarly, the racemic analogue of **4c** prepared from (D,L)-alanine displayed a reduced activity. Thus, 43.44 % of edema inhibition was observed for 50 mg of the racemic compound which is equivalent to 25 mg of the (*S*)-enantiomer and 25 mg of the (*R*)-enantiomer. In the opposite, 54.48 and 45.51 % of o edema inhibition were described, respectively, for 50 and 25 mg of the (*S*)-enantiomer (Table 2). This let us conclude that the anti-inflammatory activity of the compounds of our series is depending on the absolute configuration of the stereogenic center, and it is more pronounced when the asymmetric carbon has the (*S*) configuration.

The evaluation of analgesic potential of the compounds of the series according to the method of Koster *et al.* indicate that some compounds have a significant analgesic activity; however, the compounds **4c**, **4e**, **4h** and **4i** provide better protection (Table 4) and the compound **4h** revealed to be quite similar to the reference drug (60.43 vs. 60.92 %) (Figs. 4, 5).

Table 3 Comparison of the anti-inflammatory activities of compound **4c** and the reference drug, Diclofenac

	Diclofenac (Reference drug)	**4c**
Dose (m/kg)	10	50
Edema volume (10^{-2} mL) (m ± SEM)		
1 h	16.00 ± 3.65**	15.00 ± 0.81***
2 h	21.50 ± 1.29***	21.00 ± 2.16***
3 h	25.25 ± 3.30***	29.50 ± 4.20***
4 h	30.00 ± 4.69***	31.00 ± 4.16***
5 h	29.00 ± 2.51***	33.00 ± 3.26***
% of edema inhibition		
1 h	41.00	44.00
2 h	49.00	50.29
3 h	58.43	51.44
4 h	54.54	53.00
5 h	60.00	54.48

Reference drug is underlined

Data expressed as mean ± SEM ($n = 6$)

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ significantly different from the control group

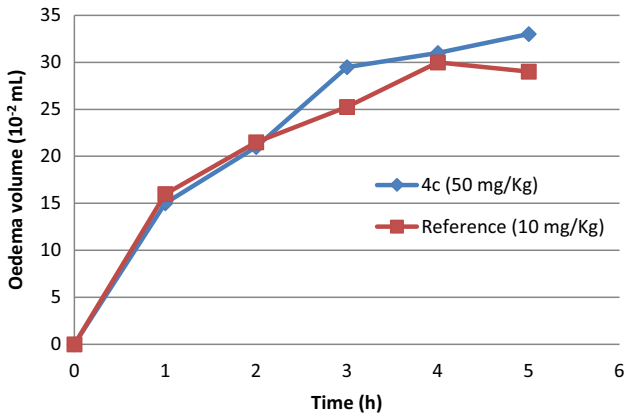


Fig. 3 Anti-inflammatory effect of the intraperitoneal administration of **4c** (50 mg/kg, i.p) and of the reference drug (Diclofenac, 10 mg/kg, i.p) in carrageenan-induced rat paw edema

Conclusion

We have prepared a series of new chiral fluorine-containing β-hydroxysulfonamides in three steps from natural (L)-amino acids. The diarylation of amino acid esters with fluorine-containing ArMgBr-LiCl complexes, in the presence of $LiAlH_4$ (1 %), have led to the desired products in good to excellent yields, and appears to be better than the classic method of the Grignard reagents preparation. This work showed significant anti-inflammatory and analgesic activities for some compounds of our prepared series. A structure–activity relationship study showed that the (*S*) configuration on the asymmetric carbon and the presence of the *para*-fluorinated di-phenyl groups seem to be necessary for the anti-inflammatory activity. The chiral fluorine-containing β-hydroxysulfonamides, prepared in this work, represent, in our acknowledgment, a new class of anti-inflammatory and analgesic compounds. However, further studies are needed to explore the molecular target and the mechanism of action of this class of compounds.

Table 4 Analgesic effect of compounds **4a–i** and of the reference drug (acetylsalicylate of lysine: ASL) in the acetic acid 1 % writhing test in mice

Sample	Dose (mg/kg)	Number of writhes ± SEM	Inhibition of writhing (%)
Vehicle (2.5 ml/kg)		68.25 ± 3.61	
Acetylsalicylate of lysine (reference drug)	**200**	**26.66 ± 3.30****	**60.92**
4a	50	66.75 ± 4.32	2.19
4b	50	50.75 ± 3.21	25.64
4c	50	37.83 ± 3.97*	44.57
4d	50	62.20 ± 3.56	8.86
4e	50	35.20 ± 4.43**	48.42
4f	50	48.00 ± 4.38	29.60
4g	50	45.00 ± 3.31	34.00
4h	**50**	**27.00 ± 1.26****	**60.43**
4i	50	36.80 ± 3.27*	46.00

The most active compounds are given in bold

Data expressed as mean ± SEM ($n = 6$)

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ significantly different from the control group

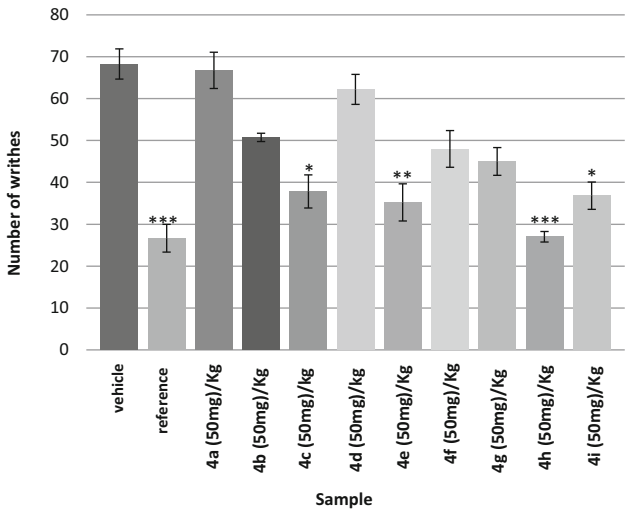


Fig. 4 Analgesic effect of compounds **4a–i** and of the reference drug (acetylsalicylate of lysine: ASL) in the acetic acid 1 % writhing test in mice. The values represent number of writhes ±SEM.*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ significantly different from the control group

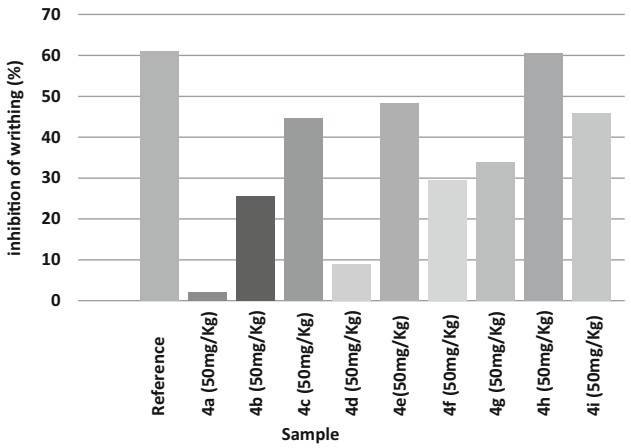


Fig. 5 Percentage inhibition of writhing for compounds **4a–i** and the reference drug (acetylsalicylate of lysine: ASL) in the acetic acid 1 % writhing test in mice

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