Synthesis and Evaluation of 2-Tosylamino and 2-Tosyliminopyrimidine Derivatives as Inhibitors of Some Leukocyte Functions

ARTICLE *in* EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY · MARCH 2003

Impact Factor: 3.45 · DOI: 10.1002/chin.200331172 · Source: PubMed

Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Medicinal Chemistry 38 (2003) 289–296
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
www.elsevier.com/locate/ejmech

Short communication

Synthesis and evaluation of 2-tosylamino and 2-tosyliminopyrimidine derivatives as inhibitors of some leukocyte functions

Patricia Fernandez-Ferri [a], Amalia Ubeda [a,*], Isabel Guillén [a], Jamal Lasri [b], M. Eugenia González-Rosende [c], Mohamed Akssira [b,1], José Sepúlveda-Arques [b,*]

[a] *Departamento de Farmacología, Universitat de Valencia, 46100 Burjassot, Spain*
[b] *Departamento de Química Orgánica, Universitat de Valencia, 46100 Burjassot, Spain*
[c] *Departamento de Química, Bioquímica y Biología Molecular, Facultad de Ciencias Experimentales y de la Salud, Universidad Cardenal Herrera-CEU, 46113 Moncada, Valencia, Spain*

Received 21 August 2002; received in revised form 8 December 2002; accepted 16 December 2002

Abstract

We have studied the potential anti-inflammatory effects of 20 2-tosylamino and 2-tosyliminopyrimidine new derivatives in human neutrophils. We have evaluated their interference with some leukocyte functions and 5-lipoxygenase activity. All the compounds reduced neutrophil degranulation process at concentrations in the μM range. Besides, compounds with a phenolic substitution inhibited leukotriene B_4 biosynthesis in neutrophils and decreased the cell-free 5-lipoxygenase activity. This study demonstrates that 2-tosylamino and 2-tosyliminopyrimidine derivatives can reduce the activation of neutrophil cells which may have relevance for the modulation of the inflammatory response.

Keywords: Leukocytes; Elastase; Lipoxygenase; 2-Tosyliminopyrimidines; 2-Tosylaminopyrimidines

1. Introduction

Neutrophils play a crucial role in the inflammatory response. Activated neutrophils migrate to ingest and kill invading pathogens at the inflamed area. They generate reactive oxygen species and secrete lytic proteins during the oxidative burst which can mediate tissue injury [1].

5-Lipoxygenase (5-LO) is the enzyme responsible for the production of leukotrienes, such as LTB_4 and cysteinyl-leukotrienes. Leukotrienes are potent lipid mediators of inflammation and immune response. They can regulate leukocyte functions, smooth muscle tone and vascular permeability [2].

During a project directed toward the synthesis of new anti-inflammatory compounds we reported in a previous work that a serie of 2-tosyliminohexahydroimidazopyrimidines **A** exerted inhibition of leukocytes responses [3]. As an extension of this study we planned the preparation of 2-tosylamino and 2-tosyliminodihydropyrimidines (**B**), that contain a similar functionality of compounds **A**, but with a structure where the carboxamide group was moved to the *para* position of the phenyl ring (Fig. 1).

The synthesis of the compounds **B** was attempted by alkylation of 2-tosylaminopyrimidine, however in this reaction in addition to derivatives from alkylation of the pyrimidinic nitrogen, compounds **3**, we also obtained the derivatives **4**, as a result of the exocyclic nitrogen alkylation (Fig. 2). In this paper we describe the synthesis of compounds **3** and **4** and the biological evaluation on neutrophil degranulation and LTB_4 biosynthesis.

Abbreviations: LTB_4, leukotriene B_4; 5-LO, 5-lipoxygenase; DMF, dimethylformamide; DIPEA, diisopropylethylamine; Ts, tosyl; IC_{50}, inhibitory concentration 50%.

* Corresponding authors.
E-mail addresses: ubedap@uv.es (A. Ubeda), jose.sepulveda@uv.es (J. Sepúlveda-Arques).
[1] On leave from Université Hassan II, Mohammedia, Maroc.

0223-5234/03/$ - see front matter
doi:10.1016/S0223-5234(03)00013-8

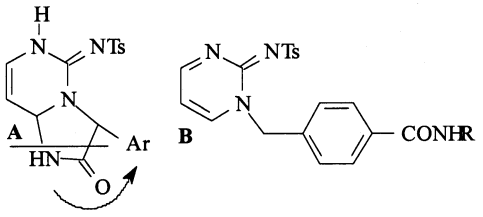


Fig. 1. Comparison of functionality between tosyliminoihexahydropyrimidines (**A**) and 2-tosylaminodihydropyrimidines (**B**).

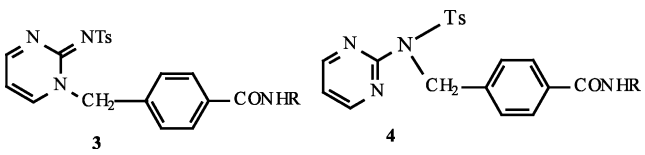
2. Chemistry

Reaction of the 2-*p*-tosylaminopyrimidine **1** with the appropriate *p*-bromomethylbenzamide (**2a**–**j**) in the presence of Hünig's base in DMF [4,5] provided the corresponding 2-tosylimino-1-substituted dihydropyrimidines (**3a**–**j**) and 2-tosylaminopyrimidines (**4a**–**j**). The relative yields (3:4) in the alkylation reaction [6–9] could be explained by steric factors due to the bulky electrophiles as it has been reported in literature [10–12]. Compound **1** was obtained from the 2-aminopyrimidine by treatment with *p*-toluenesulfonyl chloride in pyridine [4]. The required *p*-bromomethylbenzamides (**2a**–**j**) were prepared by amination of their corresponding *p*-bromomethylbenzoic acids [5].

3. Results and discussion

Inhibitory activity of pyrimidine derivatives was evaluated in human neutrophils. As can be seen from the data in Table 1, all the compounds at 10 μM inhibited degranulation process assessed as elastase release. None of the compounds, at 10 μM showed cytotoxic effects on neutrophils as assayed by the mitochondrial reduction of MTT (data not shown). Comparing the pair of amino or imino derivatives, there were not significant differences, which suggest the lack of influence of this conversion. The unsubstituted compounds (**3a** and **4a**) showed moderate inhibition, the addition of a phenyl or halogenated phenyl group (**3g**, **4g**, **3i**, **4i**, **3j** and **4j**) decreased the activity. However, the presence of a phenolic substituent increased the potency in phenyl and phenylethyl series of compounds,

Table 1
Inhibition of human neutrophil elastase release for compounds **3a**–**j** and **4a**–**j**



3 **4**

Compound	R	Elastase	
		% Inhibition [a]	IC_{50} (μM) [b]
3a	H	60.2±2.2	ND
4a	H	61.0±2.6	ND
3b	CH_3–CH_2	53.7±2.6	ND
4b	CH_3–CH_2	45.5±3.4	ND
3c	C_6H_5–CH_2–CH_2	48.6±2.7	ND
4c	C_6H_5–CH_2–CH_2	62.0±2.3	ND
3d	4-HO–C_6H_4–CH_2–CH_2	92.0±2.1	1.5 (1.0–2.0)
4d	4-HO–C_6H_4–CH_2–CH_2	70.3±1.9	2.8 (1.6–5.0)
3e	4-F–C_6H_4–CH_2–CH_2	44.1±1.9	ND
4e	4-F–C_6H_4–CH_2–CH_2	38.2±2.5	ND
3f	2,4-Cl_2–C_6H_3–CH_2–CH_2	46.1±3.2	ND
4f	2,4-Cl_2–C_6H_3–CH_2–CH_2	37.5±3.5	ND
3g	C_6H_5	40.4±3.3	ND
4g	C_6H_5	53.9±3.2	ND
3h	4-HO–C_6H_4	81.9±2.2	1.1 (0.6–1.9)
4h	4-HO–C_6H_4	80.6±2.8	1.5 (1.0-2.2)
3i	4-F–C_6H_4	38.8±2.6	ND
4i	4-F–C_6H_4	29.9±3.5	ND
3j	2,4–Cl_2–C_6H_3	40.5±4.3	ND
4j	2,4-Cl_2–C_6H_3	23.8±2.6	ND
HIP-4		83.9±5.0	3.9 (2.0–5.5)

HIP-4: 3-(4-fluorophenyl)-8-(5,5-dimethyl-1,3-dioxan-2-yl)-5-tosylimino-2-oxo-1,2,3,5,6,8a-hexahydroimidazo[1,2-c]pyrimidine (Ref. [3]).
[a] Compounds were assayed at 10 μM.
[b] Concentration (μM) required for 50% inhibition of elastase release with confidence limits in parentheses. Only compounds that reached 70% inhibition were assayed, ND: not determined.

being **3d**, **4d**, **3h** and **4h** the most active compounds, with IC_{50} about 1 μM. The inhibition of the release of proteolytic enzymes during neutrophil infiltration and activation may limit tissue damage during the inflammatory response [1].

Data from active compounds on LTB_4 release and 5-LO activity are indicated in Table 2 (the rest of

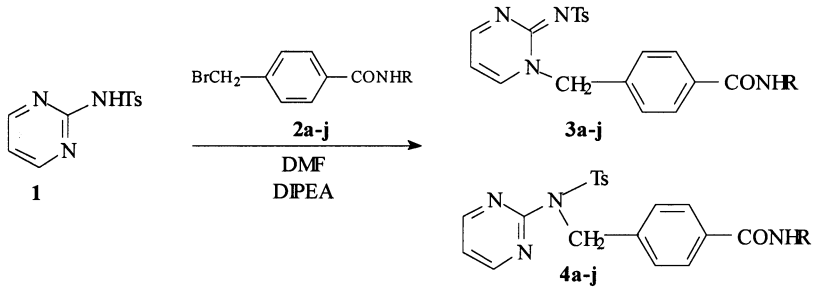


Fig. 2.

Table 2
Inhibition of human neutrophil LTB_4 release and 5-LO activity for active compounds

Compound	LTB_4 release % inhibition [a]	LTB_4 release IC_{50} (μM) [b]	5-LO activity % Inhibition [a]
3d	49.5±0.9	5.3 (3.6–8.9)	47.3±5.4
4d	51.5±3.4	3.6 (2.0–6.3)	51.0±6.6
3e	NA	ND	NA
4e	80.3±3.6	1.2 (0.9–1.6)	65.2±7.8
3f	66.4±0.9	1.4 (0.8–2.2)	61.2±1.2
4f	91.7±5.3	0.5 (0.3–0.8)	67.1±3.6
3h	44.8±2.7	5.9 (3.9–8.9)	46.9±4.6
4h	79.1±3.3	0.4 (0.3–0.6)	67.5±2.6

Reference inhibitor zileuton showed an IC_{50} of 0.23 (0.03–0.9) μM for LTB_4 release and for 5-LO activity showed an IC_{50} of 0.61 (0.5–0.8) μM.
[a] Compounds were assayed at 5 μM. NA = not active, ND: not determined.
[b] Values are means of 6–12 experiments, IC_{50} in μM is given with confidence limits in parentheses.

derivatives were not active at 10 μM). The presence of a hydroxy substituent in the aromatic ring had a general effect increasing the potency in both compounds **3** and **4**, and in both series **d** and **h** derived, respectively, from phenylethylamine and phenylamine. However, the presence of Cl as substituent had a more restricted effect and only the compounds **3f**, **4f**, containing an ethylenic chain presented activity. In the case of F as substituent only the compound **4e** behaved as a potent inhibitor. This effect can be related to a direct inhibition of the 5-LO activity, since these compounds exerted potent inhibition in the cell free assay of 5-LO activity. LTB_4 is a potent leukocyte chemotactic agent, thus the modulation of LTB_4 production contributes to reduce leukocyte infiltration at the inflammatory site.

Neutrophils play a critical role in initiating and maintaining inflammatory processes in the joint [13]. Besides, it has been reported that 5-LO inhibition may be beneficial in some inflammatory and respiratory diseases such as systemic lupus erythematous and asthma [14,15].

Present study indicates that 2-tosyliminopyrimidine derivatives exert in vitro inhibitory effects on human neutrophil functions which may confer a modulatory effect on inflammatory process.

4. Experimental

4.1. Chemistry

4.1.1. General

All reagents were purchased from Aldrich and used without purification unless stated otherwise. All experiments were made under nitrogen atmosphere. Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Flash column chromatography was performed using silica gel (Merck 60, 70–230 mesh). ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC-300 instrument in $CDCl_3$, unless otherwise indicated. Chemical shifts (δ values) and coupling constants (J values) are given in ppm and Hz, respectively. MS and HRMS were obtained using a VG Autospec TRIO 1000 instrument. The ionization mode used in mass spectra was electron impact (EI) or fast atom bombardment (FAB). ^{1}H- and ^{13}C-NMR assignments have been confirmed by homonuclear two dimensional correlations and DEPT experiments. Elemental analyses were recorded by the Servicio de Microanálisis of the University of Valencia (SCSIE).

4.1.2. 2-(p-Toluenesulfonamido)pyrimidine (*1*)

p-Toluenesulfonyl chloride (30 mmol) in pyridine (6 mL) was slowly added to 2-aminopyrimidine (20 mmol) dissolved in dry pyridine (8 mL) at 0 °C. The solution was stirred for 2 h and allowed to reach room temperature (r.t.). Water was added (100 mL) and the solid was collected and recrystallized from chloroform. Yield: 90%; m.p. 208–210 °C (lit. [4] 204–206 °C).

4.1.3. General procedure for the synthesis of p-bromomethylbenzamides (*2a–j*)

DMF (2 drops) was added to a stirred solution of *p*-bromomethylbenzoic acid (1 g, 4.64 mmol) in dry CH_2Cl_2 (8 mL) under argon and then cooled in an ice bath at 0 °C. Oxalyl chloride (0.79 mL, 9.28 mmol) in dry CH_2Cl_2 (1.1 mL) was added dropwise and the reaction mixture was stirred at 0 °C for 3 h. The solvents were removed in vacuo and then azeotroped with toluene (3 × 1.6 mL). The remaining oil was dissolved in toluene (13.9 mL) and hexane (13.9 mL) and stirred at r.t. The corresponding amine (3.86 mmol) and pyridine (0.31 mL, 3.86 mmol) were added and the reaction mixture was stirred overnight. The resulting solid was filtered, and the solvents were removed in vacuo. The solid was dissolved in EtOAc–H_2O and the organic layer washed with HCl 1 N, saturated $NaHCO_3$ and brine, and then dried over Na_2SO_4. The solvent was removed in vacuo yielding a solid which was identified as the corresponding benzamide (**2**). Spectroscopic ^{1}H- and ^{13}C-NMR data are shown in Table 3.

Table 3
Characteristic spectral data for compounds **2a**–**j**

Product	^{13}C-NMR ($CDCl_3$–TMS) δ (ppm)	^{1}H-NMR ($CDCl_3$–TMS) δ (ppm)
2a [a]	34.4 (CH_2), 128.7 (CH), 129.9 (CH), 135.0 (C), 141.9 (C), 168.3 (C=O)	4.73 (s, 2H), 7.51 (d, J = 7.9, 2H), 7.86 (d, J = 7.9, 2H)
2b [a]	15.1 (CH_3), 33.9 (CH_2), 34.4 (CH_2), 127.8 (CH), 129.5 (CH), 134.9 (C), 141.2 (C), 165.8 (C=O)	1.16 (t, J = 7, 3H), 3.32 (qd, J = 7, J = 5, 2H), 4.77 (s, 2H), 7.55 (d, J = 8, 2H), 7.83 (d, J = 8, 2H), 8.50 (bs, 1H, NH)
2c	32.7 (CH_2), 36.0 (CH_2), 41.5 (CH_2), 127.0 (CH), 127.7 (CH), 129.4 (CH), 129.9 (CH), 135.0 (C), 139.2 (CH), 141.1 (C), 141.5 (C), 162.1 (C), 167.3 (C=O)	2.86 (t, J = 6.8, 2H), 3.64 (c, J = 6.8, 2H), 4.45 (s, 2H), 6.08 (bs, 1H, NH), 7.17 (m, 3H), 7.24 (d, J = 7, 2H), 7.35 (d, J = 8, 2H), 7.60 (d, J = 8, 2H), 8.46 (d, J = 8, 1H)
2d	33.9 (CH_2), 34.7 (CH_2), 41.2 (CH_2) 122.0 (CH),127.8 (CH), 129.1 (CH), 130.5 (CH), 132.5 (C), 134.7 (C), 135.5 (C), 146.8 (C), 154.1 (C), 166.1 (C=O)	2.89 (t, 2H, J = 7), 3.66 (c, 2H, J = 7), 4.41 (s, 2H), 6.15 (bs, 1H, NH), 7.08 (d, J = 8.4, 2H), 7.21 (d, J = 8.4, 2H), 7.36 (d, J = 8.1, 2H), 7.61 (d, J = 8, 2H)
2e	33.7 (CH_2), 35.2 (CH_2), 41.7 (CH_2), 116.0 (d, J = 20.5, CH), 127.7 (CH), 130.5 (d, J = 7.8, CH), 131.4 (CH), 134.9 (C), 141.1 (C), 144.9 (C), 162.1 (d, J = 244.7, C), 167.3 (C=O)	2.83 (t, 2H, J = 7), 3.61 (c, 2H, J = 7), 4.41 (s, 2H), 6.93 (t, J = 8.6, 2H), 7.10 (dd, J = 8.6, J = 5, 2H), 7.35 (d, J = 8, 2H), 7.61 (d, J = 8, 1H)
2f	32.7 (CH_2), 33.2 (CH_2), 40.0 (CH_2), 127.7 (CH),129.2 (CH), 129.7 (CH), 129.8 (CH), 132.2 (CH), 133.5 (C), 134.7 (C), 135.1 (C), 135.5 (C), 141.6 (C), 167.3 (C=O)	2.98 (t, J = 6.7, 2H), 3.63 (c, J = 6.7, 2H, CH_2NH), 4.42 (s, 2H), 6.17 (bs, 1H, NH), 7.12 (bs, 2H), 7.32–7.38 (m, 3H), 7.61 (d, J = 8, 2H
2g	33.8 (CH_2), 120.6 (CH),124.1(CH), 128.4 (CH), 129.0 (CH), 129.6 (CH), 135.1 (C), 139.4 (C), 141.8 (C), 165.4 (C=O)	4.75 (s, 2H), 7.20 (t, J = 7, 1H), 7.40 (t, J = 7, 2H), 7.65 (d, J = 8, 2H), 7.80 (d, J = 8, 2H), 8.00 (d, J = 7, 2H), 10.5 (bs, 1H)
2h [a]	33.9 (CH_2), 115.3 (CH), 122.5 (CH), 128.2 (CH), 129.5 (CH), 130.9 (C), 135.3 (C), 141.8 (C), 154.1 (C), 164.8 (C=O)	4.8 (s, 2H), 6.85 (d, J = 7, 2H), 7.40 (d, J = 7, 2H), 7.60 (d, J = 7, 2H), 7.90 (d, J = 8, 2H), 9.3 (bs, 1H), 10.2 (s, 1H)
2i [a,b]	33.2 (CH_2Br), 116.6 (d, J = 22, CH), 124.5 (CH), 128.3 (CH), 129.2 (CH), 135.0 (C), 135.8 (C), 141.4 (C), 157.0 (d, J = 240, C), 165.4 (C=O)	4.43 (s, 2H), 7.0 (t, J = 8, 2H), 7.45 (d, J = 7, 2H), 7.6 (dd, J = 8, J = 5, 2H), 7.9 (d, J = 8, 2H)
2j	33.4 (CH_2), 122.6 (CH),124.0 (C), 128.5 (CH), 129.5 (CH), 130.0 (C), 130.1 (CH),131.7 (CH), 134.0 (C), 142.6 (C), 145.0 (C), 165.0 (C=O)	4.46 (s, 2H), 7.19 (s, 1H), 7.47 (d, J = 7, 2H), 7.81 (d, J = 7, 2H), 8.05 (d, J = 8, 1H), 8.46 (d, J = 8, 1H)

[a] ^{1}H and ^{13}C spectra recorded in DMSO-d_6.
[b] ^{1}H spectra recorded in MeOD.

*4.1.3.1. p-Bromomethylbenzamide (**2a**).* Yield 62%; m.p. 185–187 °C.

*4.1.3.2. N-ethyl-p-bromomethylbenzamide (**2b**).* Yield 55%; m.p. 110–112 °C.

*4.1.3.3. N-phenethyl-p-bromomethylbenzamide (**2c**).* Yield 60%; m.p. 115–117 °C.

*4.1.3.4. 1-[2-(4-Bromomethylphenylcarboxamide)ethyl]-4-hydroxybenzene (**2d**).* Yield 40%; m.p. 170–173 °C.

*4.1.3.5. 1-[2-(4-Bromomethylphenylcarboxamide)ethyl]-4-fluorobenzene (**2e**).* Yield 63%; m.p. 101–114 °C.

*4.1.3.6. 1-[2-(4-Bromomethylphenylcarboxamide)ethyl]-2,4-dichlorobenzene (**2f**).* Yield 56%; m.p. 126–129 °C; MS ($C_{16}H_{14}BrCl_2NO$) *m/z* 388 (100%), 390 (47%, M+2).

*4.1.3.7. N-phenyl-4-bromomethylbenzamide (**2g**).* Yield 54%; m.p. 174–177 °C; MS ($C_{14}H_{12}BrNO$) *m/z* 289 (67%), 291 (66%, M+2).

*4.1.3.8. N-(4-hydroxyphenyl)-4-bromomethylbenzamide (**2h**).* Yield 55%; m.p. 207-210 °C; MS ($C_{14}H_{12}BrNO_2$) *m/z* 305 (88%), 307 (88%, M+2).

*4.1.3.9. N-(4-fluorophenyl)-4-bromomethylbenzamide (**2i**).* Yield 77%; m.p. 165-168 °C.

*4.1.3.10. 1-(4-Bromomethylphenylcarboxamide)-2,4-dichlorobenzene (**2j**).* Yield 37%; m.p. 132–135 °C.

*4.1.4. General procedure for preparation of compounds **3a**–**j** and **4a**–**j***

Diisopropylethylamine, DIPEA (0.65 mL, 3.6 mmol) was added dropwise to a stirred suspension of 2-(*p*-toluenesulfonamido)pyrimidine **1** (0.75 g, 3 mmol) in dry DMF (12 mL) under argon. After 40 min the corresponding bromocarboxamide **2** (3.6 mmol) was added. The reaction mixture was stirred at r.t. for 16 h and then poured onto water (100 mL). The resulting solid was collected, air dried and purified by flash column chromatography to give the exocyclic nitrogen alkylated compounds **4a**–**j** (hexane:EtOAc 1:1) and the endocyclic nitrogen alkylated compounds **3a**–**j** (EtOAc:-MeOH 9:1). Spectroscopic ^{1}H- and ^{13}C-NMR data for compounds **3a**–**j** and **4a**–**j** are shown in Tables 4 and 5, respectively.

4.1.4.1. 4-{[2-{[(4-Methylphenyl)sulfonyl]imino}-

Table 4
Characteristic Spectral Data for Compounds **3a**–**j**

Product	^{13}C-NMR ($CDCl_3$–TMS) δ (ppm)	^{1}H-NMR ($CDCl_3$–TMS) δ (ppm)
3a [a]	21.2 (CH_3), 55.8 (CH_2), 108.8 (CH), 127.0 (CH), 128.0 (CH), 128.4 (CH), 128.9 (CH), 134.3 (C), 138.2 (C), 141.1 (C), 141.4 (C), 150.9 (CH), 154.2 (C), 164.7 (CH), 167.7 (C=O)	2.37 (s,3H), 5.35 (s,2H), 6.92(dd, J = 6.4, J = 4.3,1H), 7.27(d, J = 8.1, 2H), 7.45 (d, J = 8.3, 2H), 7.50 (bs,1H,NH), 7.62 (d, J = 8.1,2H), 7.92 (d, J = 8.3,2H), 8.01 (s, 1H, NH), 8.68 (dd, J = 6.4, J = 2.3,1H), 8.74 (dd, J = 4.3, J = 2.3,1H)
3b	15.1 (CH_3); 21.8 (CH_3); 35.3 (CH_2); 53.9 (CH_2); 108.6 (CH); 127.8 (CH); 128.1 (CH); 129.1 (CH); 129.2 (CH); 135.5 (C); 136.9 (C); 140.1 (C); 142.5 (C); 149.2 (CH); 154.9(C) 164.4 (CH); 167.2 (C=O)	1.1 (t, J = 7.1, 3H), 2.3 (s, 3H), 3.4 (qd, J = 7.1, J = 5.7, 2H); 5.1 (s, 2H), 6.45 (dd, J = 6.4, J = 4.3,1H); 7.05 (d, J = 8.1, 2H); 7.2 (d, J = 8.3, 2H); 7.6 (d, J = 8.1, 2H); 7.7(d, J = 8.3, 2H); 8.03(dd, J = 6.4, J = 2.3,1H); 8.35 (dd, J = 4.3, J = 2.3,1H)
3c	21.2 (CH_3), 35.2 (CH_2), 41.7(CH_2), 55.8(CH_2), 108.8 (CH), 120.6 (CH), 124.1(CH), 127.1(CH), 128.2 (CH), 128.7 (CH), 129.0 (CH), 129.1(CH), 135.1(C), 138.6(C), 139.4(C), 141.1(C), 141.4 (C), 150.9 (CH), 154.2 (C), 164.8 (CH), 165.5 (C=O)	2.32 (s, 3H), 2.83 (t, J = 7, 2H), 3.62 (c, J = 7, 2H), 5.33(s,2H), 6.87 (dd, J = 6.6, J = 4.3,1H), 7.10 (t, J = 7.5, 1H), 7.24 (d, J = 8.2, 2H), 7.34 (t, J = 7.5, 2H), 7.45 (d, J = 8.1, 2H), 7.62 (d, J = 8.2, 2H), 7.80 (d, J = 7.5, 2H), 7.95(d, J = 8.1, 2H), 8.66 (dd, J = 6.6, J = 2.4, 1H), 8.71 (dd, J = 4.3, J = 2.4,1H), 10.26 (s, 1H)
3d [a]	21.2 (CH_3), 34.7 (CH_2), 41.1 (CH_2), 55.9 (CH_2), 108.8 (CH), 122.0 (CH), 127.0 (CH), 127.7 (CH), 128.8 (CH), 128.9 (CH), 130.0 (CH), 130.7 (C), 135.4 (C), 141.1 (C), 148.8 (C), 149.2 (CH), 154.2 (C), 164.7 (CH), 166.0 (C=O)	δ 2.32 (s, 3H), 2.83 (t, J = 7, 2H), 3.62 (c, J = 7, 2H), 5.30 (s, 2H), 6.80 (dd, J = 6.6, J = 4.1, 1H), 7.30 (d, J = 8.3, 2H), 7.40–7.62 (m, 6H), 7.80–7.89 (m, 4H), 8.64 (dd, J = 6.6, J = 2.4, 1H), 8.66 (dd, J = 4.1, J = 2.4,1H)
3e	21.3 (CH_3), 34.6 (CH_2), 41.3 (CH_2), 55.8 (CH_2), 108.1 (CH), 115.1 (d, J = 21, CH), 127.0 (CH), 127.6 (CH), 128.5 (CH), 128.7 (CH), 130.0 (d, J = 7.9, CH), 134.6 (C), 134.7 (C), 136.6 (C), 139.6 (C), 142.1 (C), 148.7 (CH), 154.4 (C), 161.3 (d, J = 244, C), 163.9 (CH), 166.8 (C=O)	2.25 (s, 3H), 2.77 (t, J = 7, 2H), 3.50 (c, J = 7, 2H), 5.09 (s, 2H), 6.42 (dd, J = 6.4, J = 4.3, 1H), 6.82 (t, J = 8.6, 2H), 7.08 (d, J = 8.1, 2H), 7.10 (m, 4H), 7.25 (bs, 1H, NH), 7.56 (d, J = 8.1, 2H), 7.67 (d, J = 8.2, 2H), 7.98 (dd, J = 6.4, J = 2.2, 1H), 8.33 (dd, J = 4.3, J = 2.2, 1H)
3f	22.0 (CH_3), 33.1 (CH_2), 39.9 (CH_2), 56.3 (CH_2), 108.6 (CH), 127.5 (CH), 128.1 (CH), 129.0 (CH), 129.2 (CH), 129.4 (CH), 129.6 (CH), 132.2 (CH), 133.1 (C), 135.1 (C), 135.8 (C), 137.1 (C), 140.1 (C), 142.5 (C), 149.1 (CH), 154.9 (C), 164.4 (CH), 167.4 (C=O)	2.28 (s, 3H), 2.95 (t, J = 6.8, 2H), 3.58 (c, J = 6.8, 2H), 5.12 (s, 2H), 6.46 (dd, J = 6.6, J = 4.1, 1H), 7.06–7.25 (m, 8H), 7.59–7.73 (m, 3H), 7.90 (dd, J = 6.6, J = 2.2, 1H), 8.40 (dd, J = 4.1, J = 2.2, 1H)
3g [a]	21.2 (CH_3), 55.8 (CH_2), 108.8 (CH), 120.7 (CH), 124.1 (CH), 127.0 (CH), 128.2 (CH), 128.6 (CH), 128.9 (CH), 135.1 (C), 138.5 (C), 139.4 (C), 141.1 (C), 141.4 (C); 150.9 (C), 154.2 (CH), 164.8 (CH), 165.5 (C=O)	2.32 (s, 3H), 5.34 (s, 2H,), 6.88 (dd, J = 6.6, J = 4.3, 1H), 7.10 (t, J = 7.5, 1H), 7.24 (d, J = 8.2, 2H), 7.36 (t, J = 7.5, 2H), 7.48 (d, J = 8.1, 2H), 7.63 (d, J = 8.2, 2H), 7.78 (d, J = 7.5, 2H), 7.94 (d, J = 8.1, 2H), 8.65 (dd, J = 6.6, J = 2.4, 1H), 8.7 (dd, J = 4.3, J = 2.4, 1H), 10.25 (s, 1H)
3h [a]	20.9 (CH_3), 55.5 (CH_2), 108.5 (CH), 115.0 (CH), 122.2 (CH), 126.7(CH), 127.7 (CH), 128.2 (CH), 128.6 (CH), 130.6 (C), 135.2 (C), 140.8 (C), 141.0 (C), 150.5 (CH), 153.8 (C), 164.4 (CH), 165.3 (C=O)	2.32 (s, 3H), 5.32 (s, 2H), 6.89 (dd, J = 6.6,J = 4.1, 1H), 7.24 (d, J = 8, 2H), 7.44–7.63 (m, 6H), 7.84–7.99 (m, 4H), 8.64 (dd, J = 6.6, J = 2.4, 1H), 8.66 (dd, J = 4.1, J = 2.4, 1H), 9.3 (s, 1H), 10.0 (s, 1H)
3i [a]	20.9 (CH_3), 55.5 (CH_2), 108.5 (CH), 115.2 (d, J = 22, CH), 122.2 (CH), 126.7 (CH), 127.9 (CH), 128.3 (CH), 128.6 (CH), 134.6 (C), 135.4 (C), 138.3 (C), 140.8 (C), 141.1 (C), 150.6 (CH), 153.9 (C), 160.5 (d, J = 240, C), 164.5 (CH), 165.1 (C=O)	2.32 (s, 3H), 5.34 (s, 2H), 6.88 (dd, J = 6.4, J = 4.3, 1H), 7.20 (t, J = 9.1, 2H), 7.23 (d, J = 8.2, 2H), 7.47 (d, J = 8.3, 2H), 7.60 (d, J = 8.2, 2H), 7.79 (dd, J = 9.1, J = 5, 2H), 7.93 (d, J = 8.3, 2H), 8.64 (dd, J = 6.4, J = 2.2, 1H), 8.71 (dd, J = 4.3, J = 2.2, 1H), 10.35 (s, 1H, NH)
3j	21.8 (CH_3), 56.4 (CH_2), 108.5 (CH), 123.4 (CH), 124.9 (C), 127.6 (CH), 127.9 (CH), 128.3 (CH), 129.2 (CH), 129.8 (CH), 130.1 (C), 130.6 (CH), 133.6 (C), 134.7 (C), 138.3 (C), 140.3 (C), 142.5 (C), 149.2 (CH), 154.8 (C), 164.5 (CH), 165.0 (C=O)	2.31 (s, 3H); 5.20 (s, 2H); 6.48 (dd, J = 6.6, J = 4.1, 1H), 7.15 (d, J = 8, 2H), 7.23 (dd, J = 9, J = 2.46, 1H), 7.36 (d, J = 2.46, 1H), 7.38 (d, J = 8.46, 2H), 7.78 (m, 4H), 7.94 (dd, J = 6.6, J = 2, 1H), 8.30 (bs, 1H, NH), 8.40 (d, J = 9, 1H), 8.52 (dd, J = 4.1, J = 2, 1H)

[a] ^{1}H and ^{13}C spectra recorded in DMSO-d_6.

Table 5
Characteristic spectral data for compounds **4a**–**j**

Product	^{13}C-NMR ($CDCl_3$–TMS) δ (ppm)	^{1}H-NMR ($CDCl_3$–TMS) δ (ppm)
4a [a]	21.9 (CH_3), 50.0 (CH_2), 117.2 (CH), 127.3 (CH), 128.4 (CH), 129.1 (CH), 130.1 (CH), 133.9 (C), 138.0 (C), 142.4 (C), 144.7 (C), 157.7 (C), 158.4 (CH), 168.5 (C=O)	δ 2.36 (s, 3H), 5.46(s, 2H), 7.1(t, J = 4.8,1H), 7.36 (d, J = 8.2, 2H), 7.40 (d, J = 7.9, 2H), 7.83 (d, J = 8.2, 2H), 7.89 (d, J = 7.9, 2H), 8.54 (d, J = 4.8, 2H)
4b	15.2 (CH_3), 21.9 (CH_3), 35.2 (CH_2), 49.9 (CH_2), 116.0 (CH), 127.4 (CH), 128.2 (CH),129.2 (CH), 129.3 (CH), 134.1 (C), 137.6 (C), 141.7 (C), 144.4(C), 157.9 (C), 158.5 (CH), 167.6 (C=O)	1.13 (t, J = 7.2, 3H), 2.28 (s, 3H), 3.34 (qd, J = 7.2, J = 5.8, 2H), 5.45 (s, 2H), 6.40 (bs, 1H), 6.75 (t, J = 4.8, 1H), 7.12 (d, J = 8, 2H), 7.34 (d, J = 8.4, 2H), 7.61 (d, J = 8, 2H), 7.74 (d, J = 8.4, 2H), 8.30 (d, J = 4.8, 2H)
4c	22.0 (CH_3), 36.0 (CH_2), 41.3 (CH_2), 50.0 (CH_2), 116.1 (CH), 126.5 (CH), 127.4 (CH), 127.6 (CH), 128.3 (CH), 129.3 (CH), 129.4 (CH), 129.5 (CH), 134.0 (C), 137.6 (C), 139.4 (C), 142.0 (C), 144.4 (C), 157.9 (CH), 158.5 (C), 167.9 (C=O)	2.32 (s, 3H), 2.86 (t, J = 7, 2H), 3.61 (c, J = 7, 2H), 5.48 (s, 2H), 6.81 (t, J = 4.71, 1H), 7.1 (t, J = 7.5, 1H), 7.16 (d, J = 8.1, 2H), 7.3 (t, J = 7.5, 2H), 7.46 (d, J = 8.1, 2H), 7.58 (d, J = 7.5, 2H), 7.72 (d, J = 8.4, 2H), 7.80 (d, J = 8.4, 2H), 8.35 (d, J = 4.71, 2H)
4d	21.2 (CH_3), 34.7 (CH_2), 41.1 (CH_2), 55.9 (CH_2), 108.8 (CH), 122.0 (CH), 127.0 (CH), 127.7 (CH), 128.8 (CH), 128.9 (CH), 130.0 (CH), 130.7 (C), 135.4 (C), 141.1 (C_{ar}), 141.4 (C), 148.8 (C), 148.8 (C), 149.2 (CH), 154.2 (C), 164.7 (CH), 166.0 (C=O)	2.32 (s, 3H), 2.88 (t, J = 7, 2H), 3.64 (c, J = 7, 2H), 5.45 (s, 2H), 6.16 (bs, 1H), 6.80 (t, J = 4.8, 1H), 7.09–7.16 (m, 4H), 7.40 (d, J = 8.1, 2H), 7.58 (d, J = 8.1, 2H), 7.81 (d, J = 8.3, 2H), 8.1 (d, J = 8.3, 2H), 8.35 (d, J = 4.8, 2H)
4e	21.9 (CH_3), 35.3 (CH_2), 41.6 (CH_2), 49.9 (CH_2), 115.9 (d, J = 21, CH), 116.0 (CH), 127.3 (CH), 128.2 (CH), 129.2 (CH), 129.3 (CH), 130.6 (d, J = 7.9, CH), 133.8 (C), 134.9 (C), 137.6 (C), 142.0 (C), 144.3 (C), 157.9 (CH), 158.5 (C), 161.0 (d, J = 240, C), 167.6 (C=O)	2.30 (s, 3H), 2.80 (t, J = 7, 2H), 3.56 (c, J = 7, 2H), 5.43 (s, 2H), 6.23 (bs, 1H), 6.77 (t, J = 4.7, 1H), 6.90 (t, J = 8.6, 2H), 7.08 (dd, J = 8.6, J = 5.4, 2H), 7.14 (d, J = 8.1, 2H), 7.37 (d, J = 8.1, 2H), 7.55 (d, J = 8.3, 2H), 7.76 (d, J = 8.3, 2H), 8.32 (d, J = 4.7, 2H)
4f	22.0 (CH_3), 33.2 (CH_2), 39.9 (CH_2), 49.9 (CH_2), 116.1 (CH), 127.4 (CH), 127.6 (CH), 128.1 (CH), 129.2 (CH), 129.4 (CH), 129.7 (CH), 132.2 (CH), 133.3 (C), 133.7 (C), 135.1 (C), 135.7 (C), 137.5 (C), 142.0 (C), 144.4 (C), 157.9 (CH), 158.4 (C), 167.8 (C=O)	2.29 (s, 3H), 2.92 (t, J = 6.7, 2H), 3.56 (c, J = 6.7, 2H), 5.42 (s, 2H), 6.47 (t, J = 5.6, 1H, NH), 6.75 (t, J = 4.8, 1H), 7.06 (m, 2H), 7.13 (d, J = 8.3, 2H), 7.25 (s, 1H), 7.35 (d, J = 8.4, 2H), 7.56 (d, J = 8.3, 2H), 7.76 (d, J = 8.4, 2H), 8.30 (d, J = 4.8, 2H)
4g	22.0 (CH_3), 50.0 (CH_2), 116.0 (CH), 120.5 (CH), 124.8 (CH), 127.5 (CH), 128.3 (CH), 129.2 (CH), 129.3 (CH), 129.4 (CH), 134.2 (C), 137.6 (C), 138.4 (C), 142.5 (C), 144.4 (C), 157.9 (CH), 158.5 (C), 165.9 (C=O)	2.32 (s, 3H), 5.48 (s, 2H), 6.80 (t, J = 4.71, 1H), 7.09 (t, J = 7.5, 1H), 7.16 (d, J = 8.1, 2H), 7.29 (t, J = 7.5, 2H), 7.45 (d, J = 8.1, 2H), 7.58 (d, J = 7.5, 2H), 7.72 (d, J = 8.4, 2H), 7.79 (d, J = 8.4, 2H), 8.35 (d, J = 4.71, 2H)
4h [a]	21.1 (CH_3), 50.0 (CH_2), 115.1 (CH), 116.5 (CH), 122.4 (CH), 126.7 (CH), 127.7 (CH), 128.3 (CH), 129.4 (CH), 130.8 (C), 134.0 (C), 137.3 (C), 141.8 (C), 144.0 (C), 153.8 (C), 157.6 (C), 158.2 (CH), 164.9 (C=O)	2.36 (s, 3H), 5.48 (s, 2H), 6.74 (d, J = 9, 2H), 7.10 (t, J = 4.8, 1H), 7.38 (d, J = 8.3, 2H), 7.44 (d, J = 8.3, 2H), 7.51 (d, J = 9, 2H), 7.87 (d, J = 8.1, 2H), 7.91 (d, J = 8.1, 2H), 8.53 (d, J = 4.8, 2H), 10.0 (s, 1H)
4i	22.0 (CH_3), 50.0 (CH_2), 116.0 (CH), 116.1 (d, J = 22, CH), 122.5 (CH), 127.5 (CH), 128.3 (CH), 129.2 (CH), 129.4 (CH), 133.9 (C), 134.3 (C), 137.6 (C), 142.6 (C), 144.4 (C), 157.9 (CH), 158.4 (C), 161.0 (d, J = 240, C), 165.9 (C=O)	2.32 (s, 3H), 5.47 (s, 2H), 6.80 (t, J = 4.9, 1H), 6.97 (t, J = 9, 2H), 7.17 (d, J = 8.2, 2H), 7.45 (d, J = 8.4, 2H), 7.52 (dd, J = 9, J = 4.7, 2H), 7.71 (d, J = 8.2, 2H), 7.80 (d, J = 8.4, 2H), 8.35 (d, J = 4.9, 2H)
4j	22.0 (CH_3), 50.0 (CH_2), 116.1 (CH), 122.6 (CH), 124.0 (C), 127.6 (CH), 128.4 (CH), 128.5 (CH), 129.1 (CH), 129.3 (CH), 129.4 (CH), 129.5 (C), 133.4 (C), 133.9 (C), 137.6 (C), 143.2 (C), 144.4 (C), 158.0 (CH), 158.5 (C), 165.4 (C=O)	2.32 (s, 3H), 5.50 (s, 2H), 6.81 (t, J = 4.7, 1H), 7.19 (d, J = 9, 2H), 7.24 (dd, J = 8.8, J = 2.43, 1H), 7.35 (d, J = 2.4, 1H), 7.51 (d, J = 8.2, 2H), 7.79 (m, 4H), 8.29 (bs, 1H, NH), 8.36 (d, J = 4.7, 2H), 8.46 (d, J = 8.8, 1H)

[a] ^{1}H and ^{13}C spectra recorded in DMSO-d_6.

*pyrimidin-1-(2H)-yl]methyl]benzamide (**3a**).* Yield 53%; m.p. 232–234 °C.

*4.1.4.2. 4-{[[4-Methylphenylsufonyl)](pyrimidin-2-yl)amino]methyl}benzamide (**4a**).* Yield 35%; m.p. 194–196 °C.

*4.1.4.3. N-ethyl-4-{[2-{[(4-methylphenyl)sulfonyl]imino}pyrimidin-1-(2H)-yl]methyl]benzamide (**3b**).* Yield 54%; m.p. 230–233 °C.

*4.1.4.4. N-ethyl-4-{[[4-methylphenylsufonyl)](pyrimidin-2-yl)amino]methyl}benzamide (**4b**).* Yield 32%; m.p. 195–197 °C.

*4.1.4.5. 4-{[2-{[(4-Methylphenyl)sulfonyl]imino}pyrimidin-1-(2H)-yl]methyl]-N-(2-phenylethyl)benzamide (**3c**).* Yield 47%; oil.

*4.1.4.6. 4-{[[4-Methylphenylsufonyl)](pyrimidin-2-yl)amino]methyl}-N-(2-phenylethyl)benzamide (**4c**).* Yield 30%; m.p. 156–158 °C.

*4.1.4.7. N-[2-(4-hydroxyphenyl)ethyl)-4-{[2-{[(4-methylphenyl)sulfonyl]imino}pyrimidin-1-(2H)-yl]methyl]benzamide (**3d**).* Yield 56%; m.p. 205–208 °C; HRMS (FAB) Calc. for $C_{27}H_{27}N_4O_4S$ (M+1) 503.1102, Found 503.1103.

4.1.4.8. N-[2-(4-hydroxyphenyl)ethyl]-4-{[[4-

*methylphenylsufonyl)](pyrimidin-2-yl)amino]methyl}benzamide (**4d**).* Yield 18%; m.p. 155–158 °C.

*4.1.4.9. N-[2-(4-fluorophenyl)ethyl]-4-{[2-{[(4-methylphenyl)sulfonyl]imino}pyrimidin-1(2H)-yl]methyl}benzamide (**3e**).* Yield 46%; oil.

*4.1.4.10. N-[2-(4-fluorophenyl)ethyl]-4-{[[(4-methylphenyl)sulfonyl](pyrimidin-2-yl]amino]methyl}benzamide (**4e**).* Yield 31%; m.p. 158–160 °C; HRMS (EI) Calc. for $C_{27}H_{25}FN_4O_3S$ 504.1631, Found 504.1637.

*4.1.4.11. N-[2-(2,4-dichlorophenyl)ethyl]-4-{[2-{[(4-methylphenyl)sulfonyl]imino} pyrimidin-1(2H)-yl]-methyl}benzamide (**3f**).* Yield 53%; oil; HRMS (FAB) Calc. for $C_{27}H_{25}Cl_2N_4O_3S$ $[M^+ + 1]$ 555.1024, Found 555.0999.

*4.1.4.12. N-[2-(2,4-dichlorophenyl)ethyl]-4-{[[(4-methylphenyl)sulfonyl](pyrimidin-2-yl) amino]methyl]}benzamide (**4f**).* Yield 33%, m.p. 137–139 °C. HRMS (EI) Calc. for $C_{27}H_{24}Cl_2N_4O_3S$554.0946, Found 554.0961.

*4.1.4.13. 4-{[2-{[(4-Methylphenyl)sulfonyl]imino}pyrimidin-1-(2H)-yl]methyl]-N-phenylbenzamide (**3g**).* Yield 54%; m.p. 234–237 °C; HRMS (FAB) Calc. for $C_{25}H_{23}N_4O_3S$ (M+1) 459.1491, Found 459.1506.

*4.1.4.14. 4-{[[4-Methylphenylsufonyl)](pyrimidin-2-yl)amino]methyl}-N-phenylbenzamide (**4g**).* Yield 33%; m.p. 195–197 °C.

*4.1.4.15. N-(4-Hydroxyphenyl)-4-{[2-{[(4-methylphenyl)sulfonyl]imino}pyrimidin-1-(2H)-yl]-methyl]benzamide (**3h**).* Yield 35%; m.p. 150–152 °C.

*4.1.4.16. N-(4-hydroxyphenyl)-4-{[[4-methylphenylsufonyl)](pyrimidin-2-yl)amino] methyl}benzamide (**4h**).* Yield 26%; m.p. 135–137 °C.

*4.1.4.17. N-(4-fluorophenyl)-4-{[2-{[(4-methylphenyl)sulfonyl]imino}pyrimidin-1(2H)-yl]methyl}benzamide (**3i**).* Yield 44%; m.p. 160–162 °C; HRMS (EI) Calc. for $C_{25}H_{23}FN_4O_3S$ $[M^+ + 2]$ 478.1475, Found 478.1473.

*4.1.4.18. N-(4-fluorophenyl)-4-{[[(4-methylphenyl)sulfonyl](pyrimidin-2-yl)amino] methyl}benzamide (**4i**).* Yield 39%; m.p. 208–210 °C; HRMS (EI) Calcd for $C_{25}H_{21}FN_4O_3S$ 476.1318, Found 476.1321.

*4.1.4.19. N-(2,4-dichlorophenyl)-4-{[2-{[(4-methylphenyl)sulfonyl]imino}pyrimidin-1-(2H)-yl]methyl]benzamide (**3j**).* Yield 46%; m.p. 185–187 °C; HRMS (FAB) Calcd for $C_{25}H_{21}Cl_2N_4O_3S$ $[M^+ + 1]$ 527.0711, Found 527.0703.

*4.1.4.20. N-(2,4-dichlorophenyl)-4-{[[4-methylphenylsufonyl)](pyrimidin-2-yl)amino] methyl}benzamide (**4j**).* Yield 31%; m.p. 190-192 °C; HRMS (FAB) calcd for $C_{25}Cl_2H_{21}N_4O_3S$ $[M^+ + 1]$ 527.0711, Found 527.0718.

4.2. Biopharmacological methods

4.2.1. Materials

[5,6,8,9,11,12,14,15(n)-^{3}H]leukotriene B_4 was purchased from Amersham Iberica, (Madrid, Spain). The rest of reagents were from Sigma Chemical Co. (St. Louis, MO).

4.2.2. Isolation of human neutrophils

Venous blood was obtained, with informed consent, from healthy volunteers. Leukocytes were obtained and purified as described previously [16]. Viability was greater than 95% by the trypan blue exclusion test. The mitochondrial dependent reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) to formazan [17], was used to assess the possible cytotoxic effect of test compounds on human neutrophils

4.2.3. Elastase release by human neutrophils

A suspension of neutrophils (2.5×10^6 cells ml^{-1}) in phosphate buffer saline containing 1.26 mM Ca^{2+} and 0.9 mM Mg^{2+} (pH 7.4) were preincubated with test compounds or vehicle for 5 min and then stimulated with cytochalasin B (10 μM) and *N*-formyl-L-methionyl-L-leucyl-L-phenylalanine (fMLP, 10 nM) for 10 min at 37 °C. Elastase activity was determined in supernatants, using *N-ter*-butoxy-carbonyl-L-alanine *p*-nitrophenyl ester (200 μM) as substrate and *p*-nitrophenol release was measured. Possible direct inhibitory effects on elastase activity were also assessed [18].

4.2.4. Synthesis and release of LTB_4 by human neutrophils

A suspension of human neutrophils (5×10^6 cells ml^{-1}) was preincubated with test compounds or vehicle for 5 min and then stimulated with calcium ionophore A23187 (1 μM) for 10 min at 37 °C. Leukotriene B_4 levels in supernatants were measured by radioimmunoassay [19]. High-speed ($100{,}000 \times g$) supernatants from sonicated human neutrophils were obtained and incubated under appropiate conditions with 10 μM arachidonic acid to assess 5-lipoxygenase activity [20].

4.2.5. Statistical analysis

The results are presented as mean ± S.E.M.; n represents the number of experiments. Inhibitory concentration 50% (IC_{50}) and 95% confidence limits were calculated from four significant concentrations ($n = 6$) using Graph Pad Prism 2. The level of statistical significance was determined by analysis of variance (ANOVA) followed by Dunnett's t-test for multiple comparisons.

Acknowledgements

This work was supported by grant 1FD97-0373-C02-01; CICYT-FEDER. P. Fernandez-Ferri thanks Generalitat Valenciana for a scholarship.

References

[1] J.J. Smith, R.P.J. Roe, Am. Chem. Soc. 90 (1994) 8234–8238.
[2] W.R. Henderson, Ann. Intern. Med. 121 (1993) 684–687.
[3] A. Vidal, M.L. Ferrándiz, A. Ubeda, A. Acero-Alarcón, J. Sepúlveda-Arques, M.J. Alcaraz, J. Pharm. Pharmacol. 53 (2001) 1379–1385.
[4] A. Acero-Alarcón, T. Armero-Alarte, J.M. Jordá-Gregori, C. Rojas-Argudo, E. Zaballos-García, J. Server-Carrió, F.Z. Ahjyaje, J. Sepulveda-Arques, Synthesis 12 (1999) 2124–2130.
[5] C. Hamdouchi, J. Blas, M. Prado, J. Gruber, B.A. Heinz, A. Vance, L. Bochis, J. Med. Chem. 42 (1999) 50–59.
[6] R.B. Angier, W.V. Curran, J. Org. Chem. 26 (1961) 1891–1895.
[7] C.G. Overberger, I.C. Kogon, J. Am. Chem. Soc. 76 (1954) 1065–1066.
[8] N.W. Bristow, P.T. Charlton, D.A. Peak, W.F. Short, J. Chem. Soc. (1954) 616–21.
[9] P. Guerret, R. Jacquier, G. Maury, Bull. Soc. Chim. Fr. 9 (1972) 3503–21.
[10] R.J. Bochis, L.E. Olen, M.H. Fischer, R.A. Reamer, J. Med. Chem. 24 (1981) 1483–1487.
[11] A.P. Gray, D.E. Heitmeier, J. Am. Chem. Soc. 81 (1959) 4347–4350and references therein.
[12] K. Undheim, T. Benneche, in: A.R. Katrizky, C.W. Rees (Eds.), Comprehensive Heterocyclic Chemistry, Ch. 6.02, Pergamon Press, Oxford, 1996, p. 114.
[13] B.T. Wipke, P.M. Allen, J. Immunol. 167 (2001) 1601–1608.
[14] K.V. Hackshaw, Y. Shi, S.R. Brandwein, K. Jones, J.Y. Westcott, J. Rheumatol. 22 (1995) 462–468.
[15] J.M. Drazen, E. Israel, P.M. O′Byrne, N. Engl. J. Med. 340 (1999) 197–206.
[16] G. Bustos, M.L. Ferrándiz, M.J. Sanz, M. Payá, M.J. Alcaraz, Naunyn-Schmiedeberg's Arch. Pharmacol. 351 (1995) 298–304.
[17] S.S. Gross, R. Levi, J. Biol. Chem. 267 (1992) 25722–25729.
[18] V. Escrig, A. Ubeda, M.L. Ferrándiz, J. Darias, J.M. Sanchez, M.J. Alcaraz, M. Paya, J. Pharmacol. Exp. Ther. 282 (1997) 123–131.
[19] M.A. Moroney, M.J. Alcaraz, R.A. Forder, F. Carey, J.R.S. Hoult, J. Pharm. Pharmacol. 40 (1988) 787–792.
[20] J.E. Tateson, R.W. Randall, C.H. Reynolds, W.P. Jackson, P. Bhattacherjee, J.A. Salmon, L.G. Garland, Br. J. Pharmacol. 94 (1988) 528–539.