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Synthesis and pharmacological evaluation of derivatives structurally related to nimesulide

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Summary— The present work reports the synthesis of a series of compounds structurally related to the antiinflammatory and antihistaminic agent nimesulide (**I**), in which the *p*-nitrophenyl moiety has been replaced by pyridine (**1a–c**) and pyridine *N*-oxide (**2a–c**). In addition, two compounds (**3a**, **4a**) have been synthesized in which the *p*-nitro group of **I** was substituted by a cyano and a 1*H*-tetrazol-5-yl group, respectively. Representative **1a** and **2a** were also modified by replacing the methanesulfonamido group with an acetamido group (**5a**, **6a**). The pharmacological evaluation of compounds **1–6** in comparison to **I**, indicates that such modifications are detrimental to the activity. Moreover **3a** and **4a** caused bronchoconstriction and hypotension, thus behaving as histaminic-like rather then antihistaminic agents.

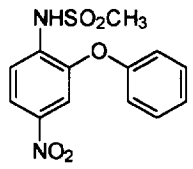
nimesulide / antiinflammatory-antihistaminic activity / *N*-pyridinyl analogue

Introduction

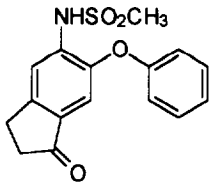
The non-steroidal antiinflammatory analgesic agent nimesulide **I** is currently employed in the treatment of inflammatory conditions, pain and fever states. This compound also displays both antianaphylactic and antihistaminic activity; in comparison, indometacin considerably potentiates histamine release, in spite of its inhibitory potency with regard to tromboxane A_2 formation [1].

Recently, compound CGP-28237 **II**, structurally related to **I**, was reported to display antiinflammatory properties with excellent gastrointestinal tolerability [2].

The positive results of the bioisosteric approach which led to **II**, prompted us to synthesize analogues



I



II

of nimesulide in which the *p*-nitrophenyl moiety was replaced by pyridine (**1a–c**) and pyridine *N*-oxide (**2a–c**), as well as by 4-cyano (**3a**) and 4-(1*H*-tetrazol-5-yl)phenyl groups (**4a**). In addition compounds **5a** and **6a** have been prepared in which the methanesulfonamido group of **1a** and respectively, **2a** is replaced by an acetamido group (see fig 1).

Chemistry

The synthesis of **1** and **2** (scheme 1) was performed through the common intermediate 3-bromo-4-nitropyridine-*N*-oxide **8** in turn obtained by conversion of 3-bromopyridine with peracetic acid into its *N*-oxide **7**, followed by nitration with HNO_3/H_2SO_4 at 90 °C.

Heating of **8** with phenol or *p*-substituted phenols in *tert*-butanol, in the presence of potassium *tert*-butoxide, gave 60–70% of the aryloxy derivatives **9a–c** besides minor amounts (30%) of 4-aryloxy-3-bromopyridine-*N*-oxides **11a–c**, easily separated by silica gel column chromatography. Reduction of **9a–c** with powdered iron in acetic acid to 4-aminopyridine derivatives **10a–c**, and subsequent condensation with mesyl chloride in 10% sodium hydroxide, afforded **1a–c** in 55–60% yield; these were then converted by peracetic acid to the *N*-oxides **2a–c** in 40–67% yields.

To obtain 4-cyano- and 4-(1-*H*-tetrazol-5-yl)-2-phenoxymethanesulfonanilide **3a**, **4a**, nimesulide **I** was reduced by catalytic hydrogenation, yielding 97% of **12a**, which was diazotized and added to a solution of CuCN and NaCN to give 72% of **3a**. The reaction of **3a** with trimethyltin azide in refluxing toluene, followed by destannylation with silica gel, afforded **4a** in 33% yield (see scheme 2). Finally the 4-acetamido derivatives **5a** and **6a** (scheme 3) were prepared from **10a** and its *N*-oxide **13a**, in turn obtained by catalytic hydrogenation of **9a**, by refluxing with acetic anhydride in acetonitrile. It is of note that **13a** failed to be converted into **2a** with mesyl chloride in 10% sodium hydroxide.

Results and discussion

The antihistaminic activity of compounds **1–6** and the antiinflammatory activity of compounds **1a–4a** were evaluated in vivo, as described in the *Experimental protocols*.

Antihistaminic activity

None of the compounds (**1a–c**, **2a–c**, **3a–6a**) displayed significant protection against histamine-induced bronchoconstriction. In comparison nimesulide reduced by 89% the effect of this autacoid on the airways, whereas indomethacin was devoid of this activity.

In contrast, when compounds **3a** and **4a** were injected intravenously at a dose of 10 mg/kg in anaesthetized guinea pig, a prompt increase in intratracheal pressure (ITP) and a fall in blood systemic pressure were recorded (fig 2). Both bronchoconstriction and hypotension, caused by two of the compounds under examination, **3a** and **4a**, were in the potency range of that of 5–10 μg/kg of histamine. The bronchoconstrictive activity of **3a** and **4a** was only partially reversible, since 5 min after their administration the ITP values were still twice the basal values. Moreover the increase in bronchial resistance caused by compounds **3a** and **4a** is abolished by pre-treatment of the animals with pyrilamine (PYR) at a dose of 2 mg/kg iv (see fig 2). This finding suggests that the action of the above compounds involves stimulation of H_1-histamine receptors in the airways.

Antiinflammatory activity

The aim of these experiments was to evaluate the antiinflammatory activity of representative compounds **1a–4a** in comparison to nimesulide. In the test used (carrageenin edema of the rat) nimesulide has been reported to have an ED_{50} of 1.25 mg/kg os [3].

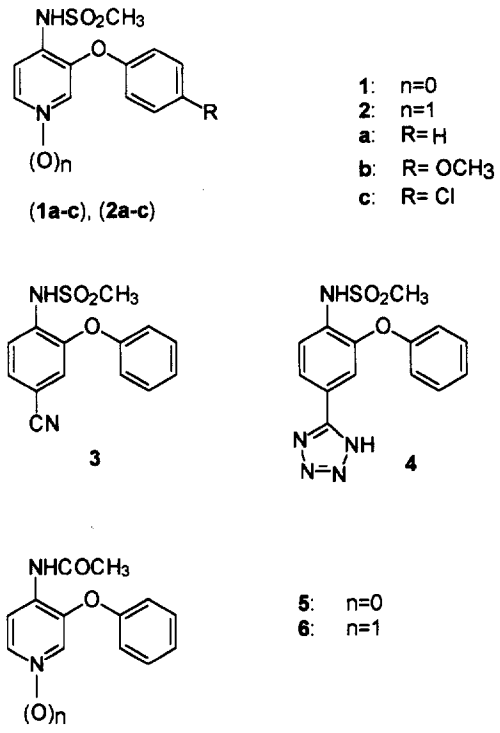


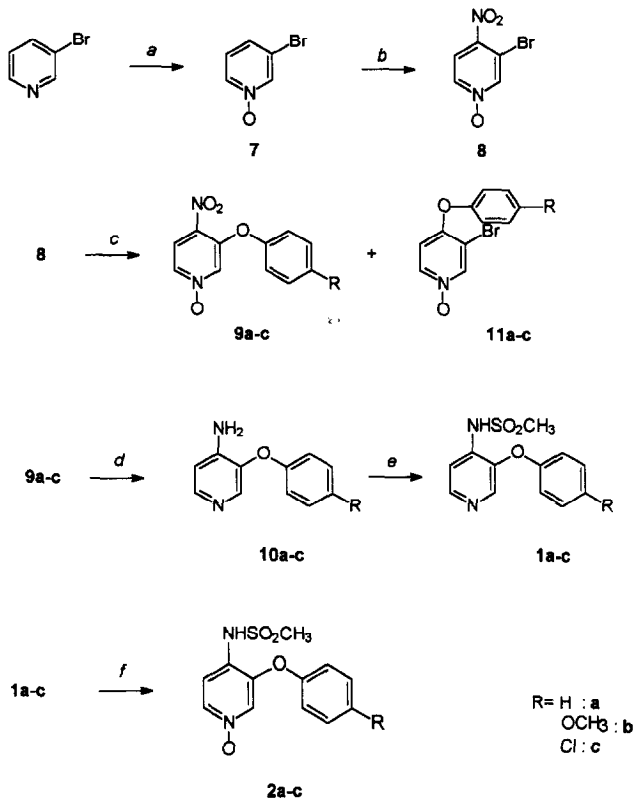
Fig 1. Compounds **1a–c**, **2a–c**, **3–6**.

Therefore in order to evidence possible antiinflammatory effects in the new compounds, even if they are lower than those of the reference drug, a dose of 10 mg/kg per os of **1a–4a** was administered to the test animal. All the tested compounds were found to be devoid of antiinflammatory activity. We note that a US patent [4] appeared while this work was in progress which claimed, for a class of substitutued phenoxypyridines including **5a**, **9a** and **10a**, a topical antiinflammatory property in mice against ear edema induced by TPA (phorbol 12-myristate acetate), at a dose of 10 μg/kg. Moreover compound **3a** was described in a Japanese Patent as an antiinflammatory agent in carrageenin edema of the rat at a dose of 50 mg/kg [5].

Experimental protocols

Chemical synthesis

Melting points were determined on a Büchi 510 capillary apparatus and are uncorrected. Analyses indicated by the chemical symbols were within ±0.4% of the theoretical values. ^{1}H-NMR spectra were recorded on a Bruker AC 200 spectro-



Scheme 1. Synthesis of compounds **1a–c**, **2a–c**.

meter; chemical shifts are reported as ppm, relative to tetramethylsilane as an internal standard. TLC on silica gel plates (Merck) was used to check product purity. Silica gel 60 (Merck; 70-230 mesh) was used for column chromatography. The structures of all compounds were consistent with their analytical and spectroscopic data.

3-Bromo-4-nitropyridine-N-oxide ***8***

The method described by Ochiai [6] was modified as follows. To a solution of 32 g (0.202 mol) of 3-bromopyridine in 120 mL CH_3COOH, 41 mL 30% H_2O_2 (0.404 mol) was added, and the solution was heated for 9 h at 70–80 °C, then kept overnight at room temperature. After concentration under reduced pressure, the residue (about 40 mL) was made alkaline with excess solid Na_2CO_3 and diluted with 100 mL $CHCl_3$ under stirring. The inorganic salts were filtered off, the organic layer was dried (Na_2SO_4) and the solvent evaporated in vacuo. The residue was distilled, collecting 31.9 g (90%) of 3-bromopyridine-*N*-oxide **7** (bp: 100 °C/0.5 mmHg). This compound was dissolved in 77 mL H_2SO_4 on cooling, and to the resulting solution, kept at 0–5 °C, a mixture of 128 mL conc HNO_3 and 77 mL conc H_2SO_4 was cautiously added. After heating at 90 °C for 1.5 h, the reaction mixture was poured onto ice and the pH adjusted to 8 with 50% NaOH. The yellow solid which separated was filtered and triturated with $CHCl_3$. Filtration and evaporation of the solvent gave 25.3 g of **8**, mp: 152 °C (lit [6] mp: 159 °C). An additional 3 g of **8** were recovered from the alkaline filtrate by extraction with $CHCl_3$, drying of the organic layer, evaporation of the solvent and crystallization of the crude residue (4 g) from benzene. Yield 72%. ^{1}H-NMR ($CDCl_3$) δ: 7.9–8.4 (m, 2H), 8.6 (s, 1H, H-2).

4-Nitro-3-phenoxypyridine-N-oxide ***9a*** *and 3-bromo-4-phenoxypyridine-N-oxide* ***11a***

To a solution of phenol (0.6 g, 6.38 mmol), *t*-BuOK (0.51 g, 4.57 mmol) and 15 mL *tert*-butanol (1 g, 4.57 mmol) of **8** was added portionwise. After refluxing for 16 h, the reaction mixture was cooled and poured into ice under stirring. The solution was made alkaline with 10% NaOH and extracted with 3 × 15 mL $CHCl_3$. The organic layers were collected and dried (Na_2SO_4), and the solvent was evaporated to give a yellow solid which was fractionated by column chromatography (silica gel, CH_2Cl_2/MeOH 95:5) collecting respectively 0.65 g (61%) of **9a** and 0.35 g (29%) of **11a**.

9a: mp: 110 °C (cyclohexane/benzene, 1:1) (lit [4] mp: 110–111, EtOH), ^{1}H-NMR ($CDCl_3$) δ: 7.1–7.8 (m, $5H_{arom}$), 7.8–8.2 (m, 3H).

11a: mp: 154–155 °C (cyclohexane/benzene, 1:1), ^{1}H-NMR ($CDCl_3$) δ: 6.5–7.0 (d, 1H, J = 8 Hz, H-5), 7.0–7.8 (m, $5H_{arom}$), 7.9–8.3 (d, 1H, J = 8 Hz, H-6), 8.6 (s, 1H, H-2).

Similarly prepared were:

3-(4-Methoxyphenoxy)-4-nitropyridine-N-oxide ***9b***. Yield 68%; mp: 111–112 °C, ^{1}H-NMR ($CDCl_3$) δ: 3.8 (s, 3H, OCH_3), 6.8–7.4 (m, $4H_{arom}$), 7.6–8.3 (m, 3H).

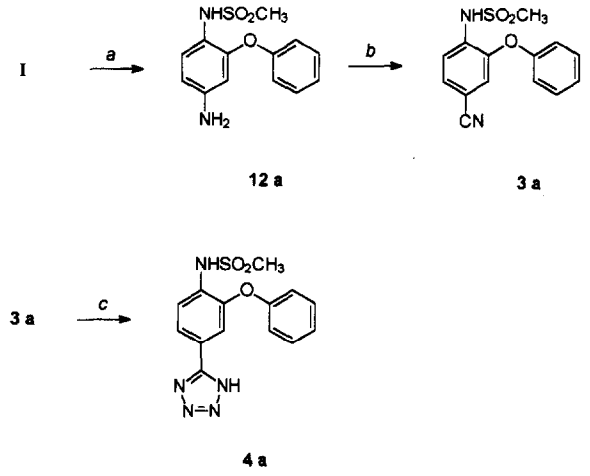
3-Bromo-4-(4-methoxyphenoxy)pyridine-N-oxide ***11b***. Yield 30%; mp: 178 °C, ^{1}H-NMR ($CDCl_3$) δ: 3.8 (s, 3H, OCH_3), 6.5–6.6 (d, 1H, J = 8 Hz, H-5), 6.8–7.1 (m, 4H), 7.8–8.1 (d, 1H, J = 8 Hz, H-6), 8.4 (s, 1H, H-2).

3-(4-Chlorophenoxy)-4-nitropyridine-N-oxide ***9c***. Yield 64%; mp: 108 °C, ^{1}H-NMR ($CDCl_3$) δ: 6.8–7.6 (m, $4H_{arom}$), 7.6–8.1 (m, 3H).

3-Bromo-4-(4-chlorophenoxy)pyridine-N-oxide ***11c***. Yield 35%; mp: 144–145 °C, ^{1}H-NMR ($CDCl_3$) δ: 6.65 (d, 1H, J = 8 Hz, H-5), 7.0–7.1 (m, 4H), 8.0–8.1 (m, 1H, H-6), 8.4 (s, 1H, H-2).

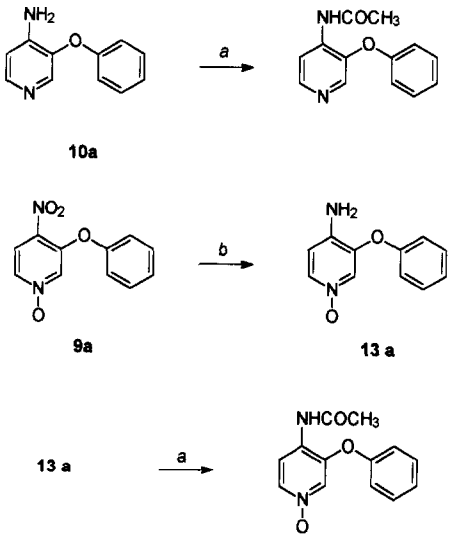
4-Amino-3-phenoxypyridine ***10a***

To a stirred solution of 2.7 g (11.6 mmol) of **9a** in 54 mL CH_3COOH, 4.2 g (75.2 mmol) powdered Fe was added in small portions, keeping the temperature at 60 °C. At the end of the addition the mixture was stirred for an additional 30 min, then the insoluble material was filtered and washed with acetic acid. The filtrate was evaporated in vacuo to give a brown oil which was treated with 10 mL H_2O, the pH adjusted to 10 with aq NaOH, and extracted with 3 × 30 mL $CHCl_3$. The organic layers were collected, dried over Na_2SO_4 and the solvent was evaporated to give 1.97 g (91%) of **10a** as a yellow solid, mp 60–62 °C. The analytical sample was purified by column chromatography (silica gel, CH_2Cl_2/MeOH, 95:5), mp: 68–70 °C. ^{1}H-NMR ($CDCl_3$) δ: 4.3 (D_2O exchangeable s, 2H, NH_2), 6.7 (d, 1H, J = 6 Hz, H-5), 6.9–7.5 (m, $5H_{arom}$), 8.0–8.2 (m, 2H).



a) H_2/10% Pd/C, EtOH
b) 1) $NaNO_2$/HCl, 5°C
2) CuCN, NaCN, H_2O, benzene, 40°C, 1h
c) 1) Me_3SnN_3, toluene, 24h
2) silica gel, MeOH, 4h

Scheme 2. Synthesis of compounds **3a** and **4a**.



a) $(CH_3CO)_2O/CH_3CN$
b) H_2/10% Pd-C/EtOH

Scheme 3. Synthesis of compounds **5a** and **6a**.
a) $(CH_3CO)_2O/CH_3CN$; b) H_2/10% Pd-C/EtOH.

Similarly prepared were:

4-Amino-3-(4-methoxyphenoxy)pyridine ***10b***. Yield 60%; mp: 101–102 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.8 (s, 3H, OCH_3), 4.4 (D_2O exchangeable s, 2H, NH_2), 6.4-7.4 (m, 5H), 7.7–8.2 (m, 2H).

4-Amino-3-(4-chlorophenoxy)pyridine ***10c***. Yield 62%; yellow oil. The hydrochloride, mp: 245–250 °C. ^{1}H-NMR (d_6-DMSO) δ: 7.0–7.8 (m, 5H), 7.8–8.8 (m, 4H), 13.9 (D_2O exchangeable s, 1H, hydrochloride)).

4-Methanesulfonamido-3-phenoxypyridine ***1a***
To a vigorously stirred mixture at 0–3 °C of 1.19 g (6.39 mmol) of **10a** in 10 mL Et_2O, and H_2O basified with a few drops of 1 M NaOH, 2.97 mL (38.3 mmol) of CH_3SO_2Cl were added dropwise, under cooling, keeping the mixture alkaline by simultaneous addition of 10% NaOH. After additional stirring at room temperature, the organic layer containing unreacted **10a** was separated and the aqueous layer was adjusted to pH 7–8 with aq HCl to separate 1 g (59%) of **1a** as a white solid, mp: 220–221 °C (CH_3COOH/H_2O, 8:2).

^{1}H-NMR (d_6-DMSO) δ: 2.8 (s, 3H, CH_3), 7.0 (d, 2H, J = 8 Hz, H-2', H-6'), 7.1 (t, 1H, J = 8 Hz, H-4'), 7.3–7.6 (m, 3H, H-5, H-3', H-5'), 8.0–8.3 (m, 2H, H-2, H-6). Anal $C_{12}H_{12}N_2O_3S$ (C, H, N, S).

Similarly prepared were:

4-Methanesulfonamido-3-(4-methoxyphenoxy)pyridine ***1b***. Yield 54%, mp: 187 °C (CH_3COOH/H_2O, 1:3), ^{1}H-NMR (d_6-DMSO) δ: 2.9 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 6.9–7.1 (m, $4H_{arom}$), 7.4 (d, 1H, J = 8 Hz, H-5), 7.9 (s, 1H, H-2), 8.0 (d, 1H, J = 8 Hz, H-6). Anal $C_{13}H_{14}N_2O_4S$ (C, H, N, S).

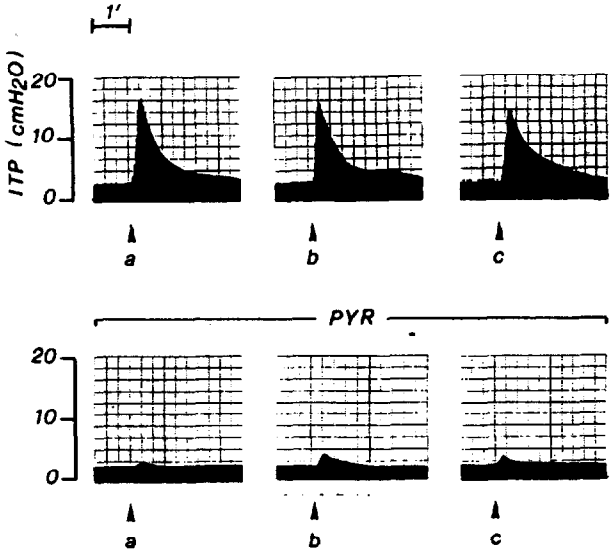


Fig 4. Original tracing showing the bronchoconstrictive effects of histamine (a; 10 µg/kg) iv), compound **3a** (b; 10 mg/kg iv) and compound **4a** (c; 10 mg/kg iv), before and after treatment with pyrilamine (PYR; 2 mg/kg iv) in anaesthesized guinea pigs. Pyrilamine was administered 5 min before the agonists.

4-Methanesulfonamido-3-(4-chlorophenoxy)pyridine ***1c***. Yield 57%, mp: 217 °C (CH_3COOH/H_2O, 1:1). ^{1}H-NMR (d_6-DMSO) δ: 2.8 (s, 3H, OCH_3), 6.9–7.1 (m, 2H), 7.3–7.6 (m, 3H), 8.0–8.1 (d, 1H, J = 9 Hz, H-6), 8.2 (s, 1H, H-2). Anal $C_{12}H_{11}ClN_2O_3S$ (C, H, Cl, N, S).

4-Methanesulfonamido-3-phenoxypyridine-N-oxide ***2a***
A solution of 0.5 g (1.89 mmol) of **1a** in 7.5 mL CH_3COOH and 0.38 mL (3.74 mmol) of 30% H_2O_2 was heated at 70–80 °C for 8 h. After concentration in vacuo, the oily residue was diluted with EtOH and unreacted **1a** was removed by filtration. The filtrate was evaporated and the residue was treated with H_2O to separate 0.25 g (47%) of **2a** as a pink solid, mp: 150–151 °C. The hydrochloride melted at 145 °C (EtOH). ^{1}H-NMR (hydrochloride) (d_6-DMSO) δ: 3.2 (s, 3H, CH_3), 4.4 (D_2O exchangeable broad s, 1H, NH), 7.1–7.4 (m, 3H), 7.4–7.6 (m, 2H), 7.7 (d, 1H, J = 7 Hz, H-5), 8.3 (s, 1H, H-2), 8.5 (d, 1H, J = 7 Hz, H-6). Anal (hydrochloride) $C_{12}H_{13}ClN_2O_4S$ (C, H, Cl, N, S).

4-Methanesulfonamido-3-(4-methoxyphenoxy)pyridine-N-oxide ***2b***
This was prepared as reported for **2a**. The oily reaction product was treated with EtOH (1:4), and the solid which slowly separated was purified by column chromatography (silica gel, CH_2Cl_2/MeOH, 95:5) to give 0.55 g (40%) of **2b**, mp: 104 °C (EtOH). ^{1}H-NMR (d_6-DMSO) δ: 3.2 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 7.0 (d, 2H, J = 8 Hz), 7.1 (d, 2H, J = 8 Hz), 7.4 (d, 1H, J = 7 Hz, H-5), 7.6 (s, 1H, H-2), 8.0 (d, 1H, J = 7 Hz, H-6), 10.4 (D_2O exchangeable broad s, 1H, NH). Anal $C_{13}H_{14}N_2O_5S$ (C, H, N, S).

4-Methanesulfonamido-3-(4-chlorophenoxy)pyridine-N-oxide ***2c***
A solution of 1.85 g (6.19 mmol) of **1c** in 28 mL CH_3COOH and 1.26 mL (12.38 mmol) 30% H_2O_2 was heated at 80 °C for 7 h, then kept overnight at room temperature. The precipitate was filtered and washed with Et_2O to give 0.6 g of **2c**. The filtrate was evaporated and the residue, treated with EtOH, separated a solid which after purification by column chromatography (silica gel, CH_2Cl_2/MeOH, 95:5), gave an additional 0.7 g of **2c** (yield 67%). The analytical sample melted at 186–187 °C (EtOH). ^{1}H-NMR (d_6-DMSO) δ: 3.05 (s, 3H, CH_3), 7.1 (d, 2H, J = 8 Hz), 7.3–7.7 (m, 3H), 7.8–8.2 (m, 2H), 10.8 (D_2O exchangeable broad s, 1H, NH). Anal $C_{12}H_{11}N_2O_4S$ (C, H, N, S).

4-Methanesulfonamido-3-phenoxyaniline ***12a***
A solution of 4 g (0.013 mol) of nimesulide (**I**) in 40 mL EtOH was hydrogenated at room temperature in the presence of 0.4 g 10% Pd/C. When hydrogen absorption ceased, the catalyst was filtered off and the filtrate was evaporated in vacuo to give 3.53 g of **12a**. Yield 97%; mp: 164–165 °C. ^{1}H-NMR (d_6-DMSO) δ: 2.9 (s, 3H, CH_3), 5.3 (D_2O exchangeable s, 2H, NH_2), 6.1 (d, 1H, J = 3 Hz), 6.2–6.4 (dd, 1H, J = 3 Hz, J = 6 Hz), 6.9–7.3 (m, 4H), 7.3–7.6 (m, 2H), 8.8 (D_2O exchangeable s, 1H, NH).

4-Methanesulfonamido-3-phenoxybenzonitrile ***3a***
To a cooled solution of **12a** (2.0 g, 7.2 mmol) in 1.8 mL conc HCl and 10 mL H_2O, 0.5 g $NaNO_2$ (0.5 g, 7.2 mmol) in 1.5 mL H_2O were added dropwise, keeping the temperature under 5 °C. The resulting dense suspension was adjusted to pH 5 with Na_2CO_3 and the mixture was added portionwise to a solution of CuCN (0.8 g, 8.9 mmol) and NaCN (0.7 g, 14.2 mmol) in 8 mL H_2O and 15 mL benzene kept under vigorous stirring at 0–5 °C. After 30 min the mixture was heated at 40 °C for an additional 1 h, then cooled and extracted with 3 × 15 mL benzene. The organic layers were collected and dried (Na_2SO_4), and the solvent was evaporated to give a brown oil, which was purified by column chromatography (silica gel, cyclohexane/ethyl acetate, 7:3) yielding 1.5 g (72%) of **3a**, mp: 135–136 °C (*i*-PrOH). ^{1}H-NMR ($CDCl_3$) δ: 1.6 (D_2O exchangeable s, 1H, NH), 3.2 (s, 3H, CH_3), 6.9–7.2 (m, 3H), 7.2–7.6 (m, 4H), 7.7 (d, 1H, J = 7 Hz). Anal $C_{14}H_{12}N_2O_3S$ (C, H, N, S).

5-(4-Methanesulfonamido-3-phenoxyphenyl)-1H-tetrazole ***4a***
Following a reported procedure [7] a mixture of **3a** (0.4 g, 1.4 mmol) and trimethyltinazide [8] (1.0 g, 5.0 mmol) in 4 mL toluene, was refluxed for 24 h. After evaporation of the solvent the oily residue was dissolved in 12 mL MeOH, and treated with 4 g silica gel. After stirring at room temperature for 4h the solvent was evaporated and the residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH, 95:5), yielding 0.15 g (33%) of **4a** as white solid, mp: 176–177 °C. ^{1}H-NMR (d_6-DMSO) δ: 3.1 (s, 3H), 7.0–7.3 (m, 3H), 7.3–7.7 (m, 3H), 7.7–7.8 (d, 1H, 8 Hz), 7.8–8.0 (d, 1H, 8 Hz), 9.8 (D_2O exchangeable s, 1H), 16.6–17.0 (D_2O exchangeable broad s, 1H). Anal $C_{14}H_{13}N_5O_3S$ (C, H, N, S).

4-Acetamido-3-phenoxypyridine ***5a***
A solution of 1.34 g (7.3 mmol) of **10a**, 0.74 mL (7.3 mmol) of $(CH_3CO)_2O$ and 15 mL CH_3CN was stirred at room temperature for 15 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 and washed with 10% Na_2CO_3. The organic layer, dried (Na_2SO_4) and evaporated, gave an oily residue which was purified by column chromatography (silica gel, CH_2Cl_2/MeOH, 95:5) yielding 1.25 g (75%) of **5a**, mp: 132 °C (*i*-PrOH) (lit [4], mp: 128–130 °C). ^{1}H-NMR ($CDCl_3$) δ: 2.2 (s, 3H, CH_3), 7.0–7.5 (m, $5H_{arom}$), 7.9 (D_2O exchangeable s, 1H, NH), 8.1 (s, 1H, H-2), 8.25 (d, 1H, J = 6 Hz), 8.35 (d, 1H, J = 6 Hz). Anal $C_{13}H_{12}N_2O_2$ (C, H, N).

4-Acetamido-3-phenoxypyridine-N-oxide ***6a***
A solution of 2.5 g (0.011 mol) of **9a** in 70 mL EtOH was hydrogenated at room temperature in the presence of 0.25 g 10% Pd/C. After hydrogen absorption ceased, the catalyst was filtered off and the filtrate was evaporated in vacuo. The solid residue was taken up with Et_2O (15 mL) and filtered to give 1.93 g (yield 88%) of 4-amino-3-phenoxy-pyridine-*N*-oxide (**13a**), mp: 166–168 °C (benzene/EtOH 8:12). ^{1}H-NMR (d_6-DMSO) δ: 6.1 (D_2O exchangeable s, 1H, NH), 6.7 (d, 1H, J = 8 Hz, H-5), 7.0–7.3 (m, 3H), 7.3–7.6 (m, 2H), 7.6 (s, 1H, H-2), 7.8 (d, 1H, J = 8 Hz, H-6).

Conversion of **13a** into **6a** was accomplished following the procedure reported for **5a**. Yield 70%; mp: 199–200 °C (EtOH). ^{1}H-NMR ($CDCl_3$) δ: 2.2 (s, 3H, CH_3), 6.8–7.2 (d, 2H, J = 10 Hz), 7.2–7.5 (m, 3H), 7.6–8.0 (m, 2H, H-2, H-5), 8.2 (D_2O exchangeable s, 1H, NH), 8.4 (d, 1H, J = 8 Hz, H-6). Anal $C_{13}H_{12}N_2O_3$ (C, H, N).

Pharmacological methods

Antihistaminic activity
Experiments were performed using male Hartley guinea pigs (400 ± 45 g body weight) obtained from BMG-Allevamento (Cividate al Piano, BG, Italy). The animals were housed under conditions of constant temperature and humidity with a standard diet (8-GP-17, Charles River, Italy) and water ad libitum. Fasted guinea pigs were anaesthetized (ethylurethane, 1.3–1.5 g/kg ip) and respiration was fully arrested with pancuronium bromide (2 mg/kg iv). Airway insufflation pressure (intratracheal pressure, ITP) and systemic blood pressure (BP), via femoral artery, were recorded following the method of

Konzett-Rössler using Hewlett-Packard instruments (Hewlett-Packard, Waltham, MA, USA) [1]. Bronchoconstriction was induced with histamine (10 μg/kg iv). Test compounds were administered intravenously in a single dose of 10 mg/kg iv). Nimesulide (1 mg/kg iv), indomethacin (1mg/kg iv) and pyrilamine (2 mg/kg iv) were employed as reference standards.

Antiinflammatory activity

Edema, induced by the subplantar injection of carrageenin in the hind paw of rats, was measured by the mercury displacement method [9]. Groups of five rats were used and the increase in paw volume was estimated over 6 h by subtracting the volume of the controlateral paw which received an equal volume of saline. Representative compounds **1a–4a** were administered orally, 30 min before carrageenin injection, at a dose of 10 mg/kg. Nimesulide was administered at a dose of 4 mg/kg.

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