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RESEARCH ARTICLE

Synthesis and cycloxygenase inhibitory properties of new naphthalene-methylsulfonamido, naphthalene-methylsulfonyl and tetrahydronaphthalen-methylsulfonamido compounds

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Abstract

We synthesized a series of new naphthalene derivatives: naproxen- and 6-methoxy naphthalene acetic acid-like **1**–**5**. In these compounds the carboxylic function, typical of the classical NSAIDs, was replaced by a methylsulfonamido (**1**, **2** and **6a**–**c**) or methylsulfonyl (**3**–**5**) group present in some selective COX-2 inhibitors. We also synthesized compounds **7** and **8** in which the naphthalene portion was substituted by tetrahydronaphthalene ring. Some of the new compounds were assayed for their enzymatic inhibitory activity towards cycloxygenase enzymes. Compounds **4** and **6b**, at a concentration of 10 μM exhibit percentage inhibition values of 65%, 50% and 29%, 87% towards COX-2 and COX-1, respectively. The substitution of carboxylic group with a mehylsulfonamido or a methylsulfonyl groups does not allow to direct the selectivity versus to cycloxygenase enzymes.

Keywords

Cycloxygenase inhibitors, naphthalene derivatives, naphthalene-methylsulfonamido compounds, naphthalene-methylsulfonyl compounds, tetrahydronaphthalenmethylsulfonamido compounds

History

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are competitive inhibitors of the cycloxygenase (COX) enzymes. These enzymes exist in two isoforms: COX-1, which is constitutive, and COX-2 which is inducible. COX-1 is expressed in the most of tissues and is involved in physiological production of PGs responsible of gastric cytoprotection, COX-2 in normal conditions has lower expression levels in tissues, but its expression is increased during inflammatory responses. The up-regulation of COX-2 was also observed in premalignant and malignant conditions of various cancers such as breast, prostate and lung ones which metastasize in the bones[1]. Particular attention has been recently focused on the role that COX-2 enzyme could play in Alzheimer's diseases (AD)[2,3].

After the removal from the market of some selective COX-2 inhibitors (COXIBs), due to their cardiovascular side effects, the research has focused towards the evaluation of alternative chemical structures able to maintain the COX inhibitory activity with reduced side effects[4].

With this aim, we synthesized a series of new naphthalene derivatives naproxene and 6-methoxy naphthalene acetic acid-like (6-MNA; **1**–**6**; Figure 1). In these compounds, the carboxylic function, typical of the classical NSAIDs, was replaced by a methylsulfonamido (**1**, **2**, **6a**–**c**) or methylsulfonyl (**3**–**5**) group present in some selective COX-2 inhibitors as for example NS398 or SC-57666, respectively. We also synthesized the methylsulfonamido compounds **7** and **8** in which the naphthalene portion was substituted by tetrahydronaphthalene ring.

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Methods

Chemistry

The synthesis of compounds **1** and **2** were carried out as depicted in Schemes 1 and 2.

The isocyanate **8**, obtained according to the synthetic method reported in literature[5], treated with trifluoroacetic acid in methylene chloride gave the 2,2,2-trifluoro-N-[1-(6-methoxy-naphthalen-2-yl)-ethyl]-acetamide **9**. Compound **9** by hydrolysis with potassium carbonate in aqueous methanol afforded the amine **10**. By reaction of the derivative **10**, with mesyl chloride and triethylamine, we obtained the desired compound **1**.

The N-(6-Methoxy-naphthalen-2-ylmethyl)-methanesulfonamide **2** was prepared as shown in Scheme 2. The catalytic hydrogenation with Pd/C in acid medium of the commercial available 6-methoxy-naphthalene-2-carbonitrile **11** afforded the amine **12**, which by subsequent treatment with mesyl chloride and triethylamine furnished the compound **2**.

The synthesis of the compounds **3** and **4** are shown in Schemes 3 and 4.

The reduction of the commercial available 1-(6-methoxy-naphthalen-2-yl) ethanone **13** with $NaBH_4$ afforded the alcohol[6]

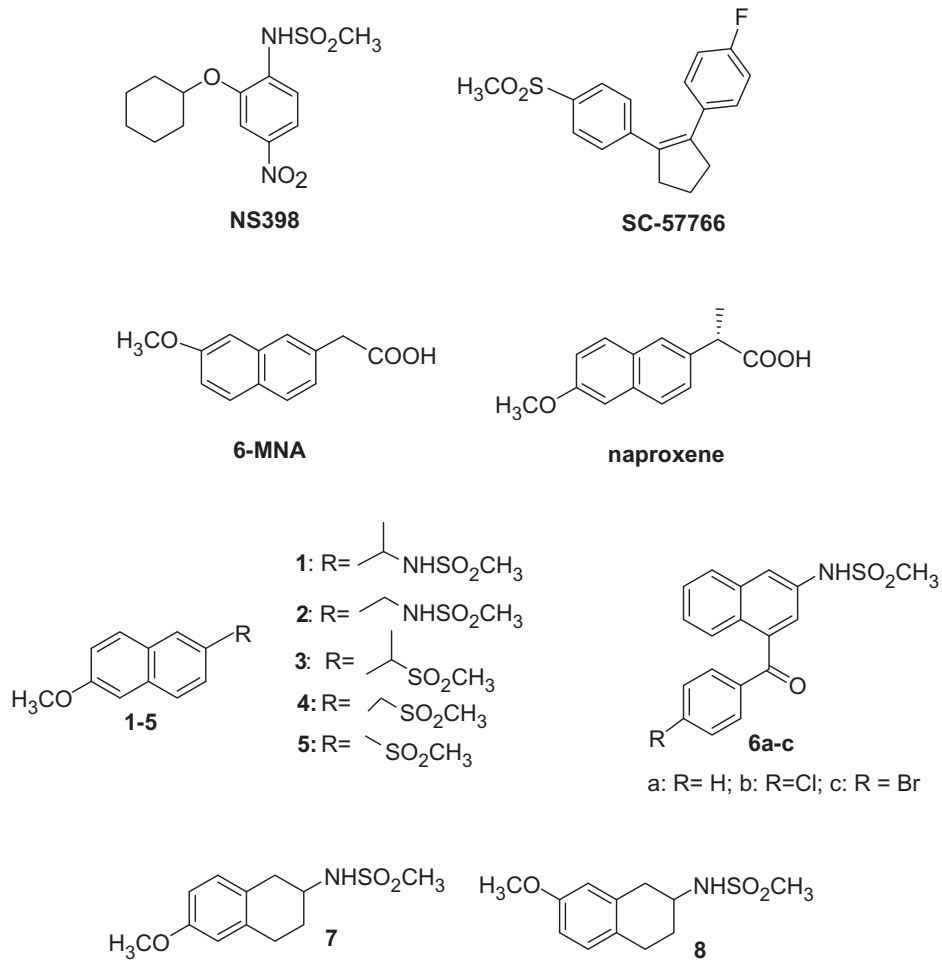
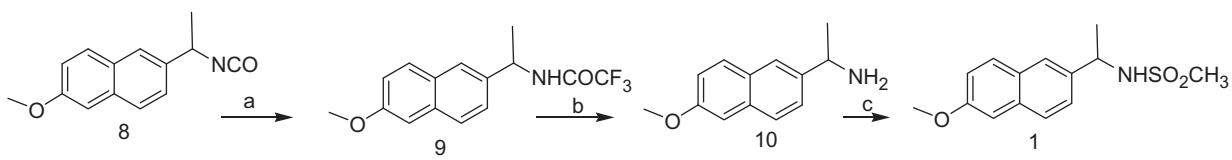
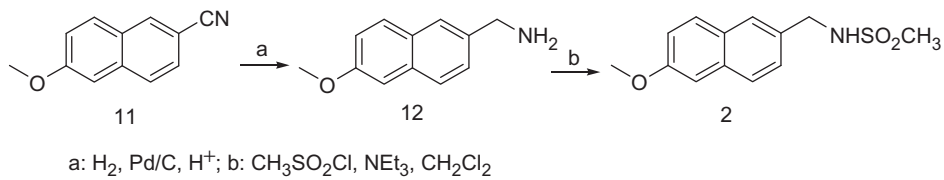


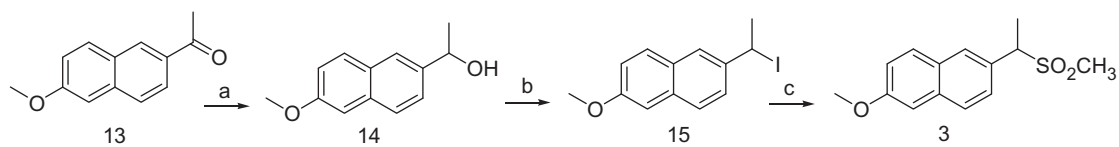
Figure 1. General structure of NS398 and SC5766, 6-MNA, naproxene and new naphthalene **1**–**6** and tetrahydronaphthalene **7** and **8** compounds.



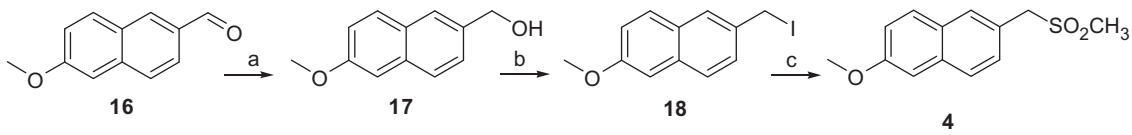
Scheme 1.



Scheme 2.

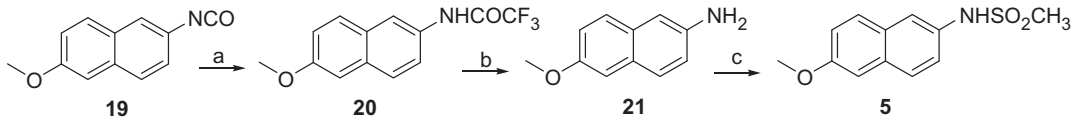


Scheme 3.



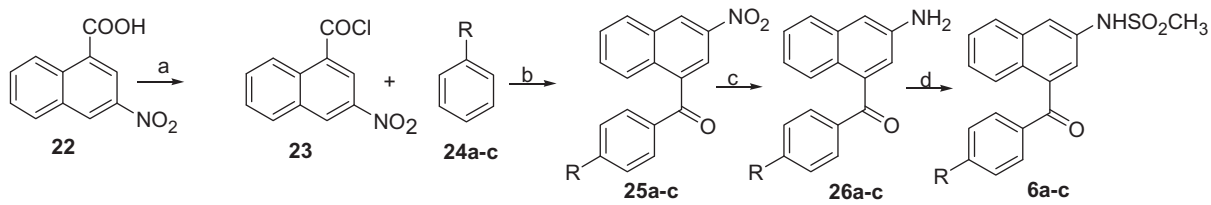
a: DIBALH, benzene, 2h, 5 °C; b: $BF_3.Et_2O$, NaI, CH_3CN; c: CH_3SO_2Na, $(C_4H_9)_4N^+Br^-$, DMF, 80 °C, 48h

Scheme 4.



a: CF_3COOH, CH_2Cl_2; b: K_2CO_3, H_2O/MeOH; c: CH_3SO_2Cl, Pyr, CH_2Cl_2

Scheme 5.



a: R= H, b:R= Cl ; c: R= Br

a: $SOCl_2$, 3h; b: $AlCl_3$; c: $NH_2NH_2.H_2O$, Ni/Raney, EtOH; d: CH_3SO_2Cl, Pyr, CH_2Cl_2

Scheme 6.

14 which was transformed in the corresponding iodine derivative **15**. The treatment of compound **15** with the sodium salt of methane sulfinic acid in presence of tetrabutylammoniumbromide afforded the methylsulfone **3**.

Commercially available 6-Methoxy-naphthalene-2-aldehyde **16** was reduced with diisobutylaluminum hydride to afford the corresponding alcohol **17**. Compound **17** by treatment with NaI and $BF_3{\cdot}Et_2O$ afforded the corresponding iodine derivative **18**. The desidered methylsulfone **4** was obtained by treatment with the sodium salt of methane sulfinic acid of the iodine derivative **18**.

Compound **5** was obtained as reported in Scheme 5. The 6-Methoxynaphthylisocyanate **19**[7], prepared from commercially available 6-methoxy-2-naphthoic acid by Curtius rearrangement of the corresponding acyl azide, in the presence of trifluoroacetic acid and methylene chloride, gave the 2,2,2-Trifluoro-N-(6-methoxy-naphthalen-2-yl)-acetamide **20**, which by hydrolysis with potassium carbonate in aqueous methanol afforded the desidered amine **21**. Compound **21** treated with mesyl chloride and pyridine, furnished the desired compound **5**.

The general synthetic approach to compounds **6a–c** is outlined in Scheme 6. Compound **22** obtained according to the synthetic method reported in literature[8] was treated by thionyl chloride to obtain the corresponding acid chloride **23**[8]. Compound **23** treated with the appropriate benzenic derivatives **24a–c** in $AlCl_3$ afforded the 2-nitro-4-benzoyl-naphthalene derivatives **25a–c**. Compounds **25a–c** have been reduced by hydrazine hydrate and Ni/Raney to the corresponding amines **26a–c**, and then treated with mesyl chloride and pyridine to give the desired derivatives **6a–c**.

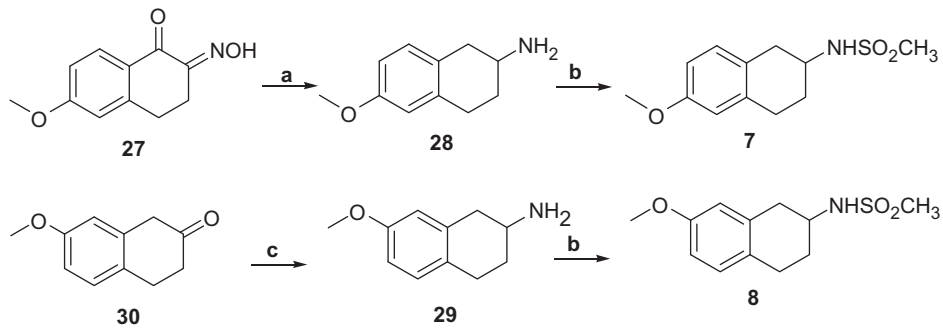
The synthesis of methylsulfonamides **7** and **8** were reported in Scheme 7. The catalytic hydrogenation of 6-methoxy-3,4-dihydro-(1,2)-naphtoquinone-2-oxime **27** with Pd/C in acid medium and the reduction of 7-methoxy-3,4-dihydro-1H-naphthalen-2-one **30** provided the amines **28**, **29**. The amines **28** and **29** treated with mesyl chloride and triethylamine furnished the desired compunds **7** and **8**.

Biological results and conclusion

For the new compounds **1–4**, **6a–b** and **7** the inhibitory activity towards COX-1 and COX-2 was evaluated *in vitro* by measuring the PGE2 production on activated J774.2 macrophages[9]. The results are reported in Table 1 together with those obtained in the same type of test with NS398 as reference drug.

Compounds **4** and **6b** at a concentration of 10 μM exhibit percentage inhibition values of 65% and 50% toward COX-2 and 29% and 87% toward COX-1, while the other compounds resulted practically inactive. However, it can be seen how similar structures have completely different activity values as shown in Table 1 for compounds naproxene-like **2** (0, 13%) and **4** (29%, 65%). These data seem to indicate that in the class of the naproxene analogues **1–4** only the methylsulfonyl group, in substitution of the carboxylic function, is suitable for the interaction towards COX-2.

Regarding the compounds **6a–b** the introduction of a chlorine substituent on the benzoyl group (**6b**) confers a good inhibitory activity even if, no COX-1 and COX-2 selectivity, with respect to the unsubstituted analogue **6a** completely devoid of any cycloxygenase inhibitory activity. In this class of compounds would seem confirmed the observation that had already been highlighted for other class of antiinflammatory drugs, namely that the presence of a halogen on the benzoyl group is able to have a positive influence on the activity.



a: H_2, Pd/C, H^+; b: CH_3SO_2Cl, NEt_3, CH_2Cl_2; c: CH_3COONH_4, $NaBH_3CN$, MeOH

Scheme 7.

Table 1. Biological data of compounds **1**–**4**, **6a**,**b** and **7**.

	% inhibition PGE2[a] (10 μM)	
Compound	COX-1	COX-2
1	0	2.5
2	0	13
3	0	0
4	29	65
6a	0	0
6b	87	50
7	18	7
NS398	59	80

[a]See Ref[9]

Experimental procedures

Chemistry

Analytical grade reagents and solvent were purchased from Sigma-Aldrich (St. Louis, MO), and were used as supplied. Solvents were dried according to standard methods. All chemical reactions were monitored by thin layer chromatography (TLC) using alumina plates coated with silica gel 60 F254 (Merck, Darmstadt, Germany) containing a fluorescent indicator; spots were detected under UV light (254 nm). Column flash chromatography separations were performed on silica gel Merck 230–400 mesh ASTM Evaporations were made *in vacuo* (rotating evaporator); Na_2SO_4 was always used as the drying agent. Melting points were determined by a Kofler apparatus (A) and are uncorrected. IR spectra for comparison of compounds were taken as paraffin oil mulls or as liquid films on a Unicam Mattson 1000 FT-IR spectrometer (Cambridge, UK). ^{1}H-NMR spectra were obtained with a Varian Gemini CTF 20 spectrometer (Mountain View, CA) operating at 80 MHz, at 25 °C in ca. 5% solution of $CDCl_3$. Chemical shifts (δ) are reported in ppm, coupling constants J are reported in Hertz. The following abbreviations are used: singlet (s), doublet (d), triplet (t), broad singlet (bs) and multiplet (m). Elemental analyses were performed in our analytic laboratory and agree with the theoretical values to within ± 0.4%. Mass spectrometry data were collected by spectrophotometer Hewelett Packard 5988A (Palo Alto, CA) by direct introduction at a nominal electron energy of 70 eV and a source temperature at 350 °C.

2,2,2-Trifluoro-N-[1-(6-methoxynaphthalen-2-yl)-ethyl]-acetamide (9)

To a solution of 2-(1-Isocyanato-ethyl)-6-methoxynaphthalene **8** (384 mg, 1.69 mmol) in CH_2Cl_2 (15 ml) was added dropwise trifluoroacetic acid (0.175 ml, 2.28 mmol). After 10 h at reflux temperature, the mixture was cooled at room temperature and then washed with a solution of $NaHCO_3$, dried and filtered to give **9**. Yield 84%; m.p.: 175–180 °C; IR (ν, cm^{-1}): 3335 (NH), 1700 (C=O); ^{1}H-NMR δ: 7.82–7.11 (m, 6H, aromatic-H), 4.85–4.78 (m, 1H, CH), 3.9 (s, 3H, CH_3O), 1.85 (bs, 1H, NH), 1.43 (d, 3H, $J = 6.4$ Hz, CH_3); MS: 297 (M^+, 30), 185 (100); Anal. Calcd. for $C_{15}H_{14}F_3NO_2$ (297.27): C, 60.60; H, 4.75; N, 4.71%. Found: C, 61.00; H, 5.07; N, 4.32%.

1-(6-Methoxynaphthalen-2-yl)-ethylamine (10)

To a solution of 2,2,2-trifluoro-N-[1-(6-methoxynaphthalen-2-yl)-ethyl]-acetamide (**9**) (331 mg, 1.11 mmol) in MeOH (20 ml) was added a solution of K_2CO_3 (255 mg, 1.85 mmol) in H_2O/MeOH (1:1, 5 ml). The resulting mixture was stirred at room temperature for 48 h, then the solvent was evaporated and the crude residue was dissolved in CH_2Cl_2, extracted with HCl 5%, alkalized, and finally extracted with AcOEt. The organic phase was then dried, filtered and evaporated, to give an oily residue, which was purified by transformation in the corresponding hydrochloride salt, and crystallised from Et_2O/HCl. The hydrochloride salt of **10** was converted into a free base by treating an aqueous solution of the salt with solid KOH and extracting the free base with $CHCl_3$. The organic layer was washed (H_2O) filtered and evaporated to give **10** as a solid. **10**: Yield 64%; m.p.: 77–78 °C; ^{1}H-NMR δ: 7.72–7.06 (m, 6H, Ar), 4.3 (m, 1H, CH), 3.89 (s, 3H, CH_3O), 2.5 (bs, 1H, NH), 1.54 (d, 3H, $J = 6.4$ Hz, CH_3); MS: 201 (M^+, 18), 186 (100); Anal. Calcd. for $C_{13}H_{15}NO$ (201.26): C, 77.58; H, 7.51; N, 6.96%. Found: C, 77.13; H, 7.34; N, 6.98%.

(6-Methoxynaphthalen-2-yl)-methylamine (12)

A solution of 6-methoxynaphthalene-2-carbonitrile **11** (1 g, 5.46 mmol) in $CHCl_3$ (10 ml), absolute EtOH (20 ml) and 37%HCl (1 ml) was hydrogenated for 24 h in presence of Pd/C (400 mg). The catalyst was removed by filtration. The evaporation of the ethanolic solution provided **12** as hydrochloride which was crystallized from MeOH/Et_2O. **12**: Yield 81%, m.p.: 236–240 °C; IR (ν, cm^{-1}): 2654 (NH_2); ^{1}H-NMR (D_2O) δ: 7.90–7.23 (m, 6H, Ar), 4.05 (m, 2H, CH_2), 3.96 (s, 3H, CH_3O); MS: 187 (M^+, 100), 171 (38); Anal. Calcd. for $C_{12}H_{13}NO^{\bullet}HCl$ (223.63) C, 64.43; H, 6.31; N, 6.26%. Found: C, 64.05; H, 5.96; N, 6.10%.

N-[1-(6-Methoxynaphthalen-2-yl)-ethyl]-methanesulfonamide (1) and N-(6Methoxy-naphthalen-2-yl)methyl)-methanesulfonamide (2)

To a solution of appropriate hydrochloride salts of **10**, **12** (0.72 mmol) and NEt_3 (0.2 ml, 1.44 mmol) in anhydrous CH_2Cl_2 (8 ml) at 0 °C, was added dropwise CH_3SO_2Cl (0.056 ml,

0.72 mmol). The mixture was stirred for 3 h at room temperature and after evaporated. The residue was dissolved in CH_2Cl_2, washed with 5% HCl and H_2O. The organic phase was dried over anhydrous Na_2SO_4, and the solvent evaporated to afford the methansulfonamides **1** and **2** which were crystallized by $CHCl_3$/hexane. **1**: Yield 69%; m.p.: 154–155 °C; IR (ν, cm^{-1}): 3227 (NH); ^{1}H-NMR δ: 7.77–7.09 (m, 6H, Ar), 4.73–4.65 (m, 1H, CH), 3.90 (s, 3H, CH_3SO_2), 1.57 (s, 1H, NH), 1.54 (d, 3H, $J = 6.4$ Hz, CH_3); MS: 281 (M+2, 1), 280 (M+1, 2), 279 (M^+, 20), 185 (100); Anal. Calcd. for $C_{14}H_{17}NO_3S$ (279.35) C, 60.19; H, 6.13; N, 5.01%. Found: C, 59.90; H, 6.06; N, 4.99%. **2**: yield 75%; m.p.: 174–175 °C; IR (ν, cm^{-1}): 3246 (NH); ^{1}H-NMR δ: 7.85–7.05 (m, 6H, Ar), 4.32–4.24 (d, 2H, $J = 6.4$ Hz, CH_2), 3.88 (s, 3H, CH_3O), 2.95 (s, 3H, CH_3SO_2); MS: 267 (M+2, 1), 266 (M+1, 3), 265 (M^+, 28), 185 (100); Anal. Calcd. for $C_{13}H_{15}NO_3S$ (265.33) C, 58.85; H, 5.70; N, 5.28%. Found: C, 59.11; H, 5.93; N, 5.14%.

1-(6-Methoxynaphthalen-2-yl)-ethanol (14)

To a solution of 1-(6-methoxynaphthalen-2-yl)-ethanone **13** (500 mg, 2.5 mmol) in MeOH (20 ml) was added $NaBH_4$ (277 mg, 7.5 mmol). The reaction mixture was stirred for 8 h, at r.t then evaporated at reduced pressure. The residue, dissolved in Et_2O/CH_2Cl_2 (1:1), was washed with H_2O, 10% HCl and with a saturated solution of NaCl. The organic phase was dried over anhydrous Na_2SO_4 and after evaporated. The residue obtained, crystallized from hexane afforded the pure compound **14**. **14**: Yield 55%; m.p.: 113–114 °C[6]; IR (ν, cm^{-1}): 3338 (OH); ^{1}H-NMR δ: 7.74–7.07 (m, 6H, Ar), 4.97–5.04 (m, 1H, CH), 3.90 (s, 3H, CH_3O), 1.87 (s, 1H, OH), 1.56 (d, 3H, $J = 6.4$ Hz, CH_3); MS: 202 (M^+, 54), 144 (100); Anal. Calcd. for $C_{13}H_{14}O_2$ (202.10) C, 77.20; H, 6.98%. Found: C, 77.05; H, 6.83%.

(6-Methoxynaphthalen-2-yl)-methanol (17)

A solution of 1-(6-Methoxynaphthalen-2-yl)-ethanone **16** (800 mg, 4.3 mmol) in benzene anhydrous, cooled at 0–5 °C, was added slowly dropwise under N_2 atmosphere DIBALH (6.45 mmol). The reaction mixture was stirred at 5 °C for 2 h, than was quenched with MeOH excess. Aluminum salts were removed by filtration and washed with warm MeOH; the filtrate was evaporated under reduced pressure. The crude product crystallized by CH_2Cl_2/hexane, gave pure **17**. **17**: Yield 81%; m.p.: 116–118 °C; IR (ν, cm^{-1}): 3261 (OH); ^{1}H-NMR δ: 7.74–7.04 (m, 6H, Ar), 4.78 (s, 2H, CH_2), 3.89 (s, 3H, CH_3O); MS: 188 (M^+, 100), 115 (80); Anal. Calcd. for $C_{12}H_{12}O_2$ (188.08) C, 76.57; H, 6.43%. Found: C, 76.19; H, 6.81%.

2-(1-Iodo-ethyl)-6-methoxynaphthalene (15) and 2-Iodomethyl-6-methoxynaphthalene (18)

To a solution of appropriate alcohol **14**, **17** (3.19 mmol) and NaI (957 mg, 6.38 mmol) in anhydrous CH_3CN (25 ml) was added dropwise, in 15 minutes, BF_3 Et_2O freshly distilled (9.57 mmol). The reaction mixture was stirred for 5 h (for compound **15**) and for 45 minutes (for compound **18**), then the organic phase was treated with brine (30 ml), a solution of 15% $Na_2S_2O_3$ and finally extracted with Et_2O. Ether phase washed with H_2O and with saturated solution of NaCl, dried and evaporated afforded the iodine derivatives **15** and **18** which were crystallized by hexane and AcOEt/hexane, respectively. **15**: Yield 46%; ^{1}H-NMR δ: 7.71–7.01 (m, 6H, Ar), 4.73–4.65 (m, 1H, CH), 3.91 (s, 3H, CH_3O), 1.63 (d, 3H, $J = 6.4$ Hz, CH_3); MS: 186 (M+-I); Anal. Calcd. for $C_{13}H_{13}IO$ (312.15) C, 52.02; H, 4.20%. Found: C, 52.34; H, 4.36%. **18**: Yield 32%; ^{1}H-NMR δ: 7.69–7.05 (m, 6H, Ar), 4.60 (s, 2H, CH_2), 3.89 (s, 3H, CH_3O); MS: 171 (M^+-I, 100), 128(80); Anal. Calcd. for $C_{12}H_{11}IO$ (298.12) C, 48.35; H, 3.72%. Found: C, 48.60; H, 4.01%.

2-(1-Methanesulfonyl-ethyl)-6-methoxynaphthalene (3) and 2-Methanesulfonylmethyl-6-methoxynaphthalene (4)

A solution of the appropriate iodine derivatives **15**, **18** (1.04 mmol), CH_3SO_2Na (111 mg, 1.09 mmol), tetrabutylammoniumbromide (351 mg, 1.09 mmol) in anhydrous DMF (8 ml) was stirred at 80 °C for 48 h. After, the reaction mixture was treated with H_2O/ice and extracted with $CHCl_3$. The organic phase, washed with H_2O, dried, evaporated under reduced pressure, afforded the derivatives **3** and **4** which were crystallized by $CHCl_3$/hexane. **3**: Yield 42%; ^{1}H-NMR δ: 7.71–7.01 (m, 6H, Ar), 4.85–4.75 (m, 1H, CH), 3.9 (s, 3H, CH_3O), 2.74 (s, 3H, CH_3SO_2), 1.43 (d, 3H, $J = 6.4$ Hz, CH_3); MS: 265 (M+1, 0.67), 264 (M+, 3), 185 (100); Anal. Calcd. for $C_{14}H_{16}O_3S$ (264.34) C, 63.61; H, 6.10%. Found: C, 63.26; H, 6.45%. **4**: Yield 60%; m.p.: 148 °C, ^{1}H-NMR δ: 7.76-7.10 (m, 6H, Ar), 4.35 (s, 2H, CH_2), 3.91 (s, 3H, CH_3O), 2.74 (s, 3H, CH_3SO_2); MS: 251 (M+1, 1), 250 (M^+, 2), 171 (100); Anal. Calcd. for $C_{13}H_{14}O_3S$ (250.31) C, 62.38; H, 5.64%. Found: C, 61.99; H, 5.82%.

2,2,2-Trifluoro-N-(6-methoxynaphthalen-2-yl)-acetamide (20)

To a solution of 2-Isocyanato-6-methoxynaphthalene **19** (337 mg, 1.69 mmol) in CH_2Cl_2 (15 ml) was added dropwise trifluoroacetic acid (0.175 ml, 2.28 mmol). The reaction mixture was refluxed at 40 °C under stirring for 48 h. The organic solution cooled, washed with $NaHCO_3$, dried and evaporated under reduced pressure gave pure **20**. **20**: Yield 70%; m.p.: 132–140 °C, IR (ν, cm^{-1}): 3275 (NH), 1703 (C=O); ^{1}H-NMR δ: 7.96–7.45 (m, 6H, Ar), 3.90 (s, 3H, CH_3O); MS: 269 (M^+, 100); Anal. Calcd. for $C_{13}H_{10}F_3NO_2$ (269.22) C, 58.00; H, 3.74; N, 5.20%. Found: C, 58.33; H, 4.03; N, 4.85%.

6-Methoxynaphthalen-2-ylamine (21)

To a solution of 2,2,2-Trifluoro-N-(6-methoxynaphthalen-2-yl)-acetamide **20** (300 mg, 1.85 mmol) in MeOH (20 ml) was added a solution of K_2CO_3 (225 mg, 1.85 mmol) in H_2O/MeOH (1:1, 5 ml). The mixture was stirred at 40 °C for 48 h, then evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 extracted with HCl 5%, alkalized, and finally extracted with AcOEt. The organic phase, dried and evaporated under reduced pressure, gave **21** which in presence of Et_2O/HCl was transformed into the corresponding hydrochloride. The hydrochloride salt of **20** was converted into a free base by treating an aqueous solution of the salt with solid KOH and extracting the free base with $CHCl_3$ the organic layer was washed (H_2O) filtered and evaporated to give **21** as a solid. **21**:Yield 80%; m.p.: 241–245 °C, IR (ν, cm^{-1}): 3384 (NH_2), 1703 (C=O); ^{1}H-NMR δ: 7.81–7.33 (m, 6H, Ar), 3.90 (s, 3H, CH_3O), 2.45 (bs, 1H, NH_2); MS: 173 (M^+, 72), 158 (82), 130 (100); Anal. Calcd. for $C_{11}H_{11}NO$ (173.31) C, 76.28; H, 6.40; N, 8.09%. Found: C, 75.90; H, 6.70; N, 8.10%.

N-(6-Methoxynaphthalen-2-yl)-methanesulfonamide (5)

To a solution of 6-methoxynaphthalen-2-ylamine **21** (123 mg, 0.71 mmol), pyridine (0.114 ml, 1.42 mmol) in anhydrous CH_2Cl_2 (8 ml), cooled at 0 °C, CH_3SO_2Cl (0.055 ml, 0.71 mmol) was added dropwise. The mixture was stirred for 2 h at room temperature, evaporated under reduced pressure. The residue obtained was dissolved in $CHCl_3$, washed with H_2O and 5% HCl. Organic phase, dried and evaporated under reduced pressure,

afforded **5** as a crude oil that was purified by flash chromatography on silica gel (EtOAc/*n*-hexane 1:1). **5**: Yield 48%; m.p.: 177–178 °C, IR (ν, cm^{-1}): 3324 (NH); ^{1}H-NMR δ: 7.75–7.08 (m, 6H, Ar), 6.7 (s, 1H, NH), 3.9 (s, 3H, CH_3O), 2.77 (s, 3H, CH_3SO_2); MS: 253 (M+2,1), 252 (M+1, 2), 251 (M^+, 18), 172 (100); Anal. Calcd. for $C_{12}H_{13}NO_3S$ (251.30) C, 57.35; H, 5.21; N, 5.57%. Found: C, 57.00; H, 5.43; N, 5.28%.

3-Nitro-naphthalene-1-carbonyl chloride (23)

A solution of 3-Nitro-naphthalene-1-carboxylic acid **22**[8] (3 g, 0.014 mol) in $SOCl_2$ (18 ml) was refluxed for 3 h. The thionyl chloride was evaporated under reduced pressure, and the solid obtained, triturated with hexane, gave **23** that was purified by crystallization from CCl_4. **23**[8]: Yield 76%; m.p.: 139–140 °C, IR (ν, cm^{-1}): 1751 (C=O); ^{1}H-NMR δ: 8.88–7.69 (m, 6H, Ar); MS: 235 (M^+, 0.65), 126 (100).

General procedure for the synthesis of 2 nitro-4-benzoyl-naphthalenes (25a–c)

To a suspension of 3-nitro-naphthalene-1-carbonyl chloride **23** (1 g, 4.25 mmol) with appropriate benzene derivative **24a–c** was added, at 0 °C, in 15 minutes, $AlCl_3$ (851 mg, 6.38 mmol). The reaction mixture was stirred at room temperature for 15 h, then triturated in ice, acidified with 37% HCl to pH = 2 and extracted with Et_2O. The ether phase, washed with 1 N NaOH, H_2O, dried and evaporated under reduced pressure, gave the respective 2 nitro-4-benzoyl-naphthalenes **25a–c**, which was purified by crystallization from CH_3COCH_3 for compounds **25a** and **25b** and isopropanol for compound **25c**. **25a**: Yield 46%; m.p.: 140-143 °C, IR (ν, cm^{-1}): 1665 (C=O); ^{1}H-NMR δ: 9.10–7.46 (m, 11H, Ar); MS: 277 (M^+, 20), 105 (100), 77 (70); Anal. Calcd. for $C_{17}H_{11}NO_3$ (277.27) C, 73.64; H, 4.00; N, 5.05%. Found: C, 73.39; H, 3.81; N, 5.05%. **25b**: Yield 54%; m.p.: 146-148 °C, IR (ν, cm^{-1}): 1672 (C=O); ^{1}H-NMR δ: 8.89–7.37 (m, 10H, Ar); MS: 311 (M^+, 20), 139 (100); Anal. Calcd. for $C_{17}H_{10}ClNO_3$ (311.72) C, 65.50; H, 3.23; N, 4.49%. Found: C, 65.55; H, 3.61; N, 4.75%. **25c**: Yield 30%; m.p.: 155–156 °C, IR (ν, cm^{-1}): 1672 (C=O); ^{1}H-NMR δ: 8.90–7.22 (m, 10H, Ar); MS: 356 (M^+, 34), 185 (98), 126 (100); Anal. Calcd. for $C_{17}H_{10}BrNO_3$ (356.17) C, 57.33; H, 2.83; N, 3.93%. Found: C, 57.65; H, 2.73; N, 3.66%.

General procedure for the synthesis of 4-benzoyl-2-naphthylamines (26a–c)

To a solution of the opportune 2 nitro-4-benzoyl-naphthalenes **25a–c** (1.80 mmol) in absolute EtOH (15 ml) was added a catalytic portion of Ni-Raney. The suspension was refluxed and NH_2NH_2 H_2O (0.393 ml, 8.10 mmol) in absolute EtOH (2 ml) was added dropwise. The mixture was refluxed for 1 h compound **26a**, 12 h compound **26b**, 8–10 h compound **26c**. The suspension was filtered through celite and evaporated under reduced pressure. The residue obtained was dissolved in H_2O, washed with Et_2O and treated with saturated solution of Et_2O/HCl to obtained the opportune amines **26a–c** as hydrochloride, which were purified by crystallization from MeOH/Et_2O. **26a**: Yield 57%; m.p.: 117 °C, IR (ν, cm^{-1}): 2613 (NH_2), 1665 (C=O); ^{1}H-NMR δ: 7.69–7.13 (m, 11H, Ar); MS: 247 (M^+-HCl, 92), 115 (100), 105 (58), 77 (78); Anal. Calcd. for $C_{17}H_{13}NO^{\bullet}HCl$ (283.75) C, 71.96; H, 4.97; N, 4.94%. Found: C, 71.80; H, 5.25; N, 4.57%. **26b**: Yield 45%; m.p.: 144–149 °C, IR (ν, cm^{-1}): 2620 (NH_2), 1672 (C=O); ^{1}H-NMR δ: 7.95–7.15 (m, 10H, Ar); MS: 281 (M^+-HCl, 60), 115 (100); Anal. Calcd. for $C_{17}H_{12}ClNO^{\bullet}HCl$ (318.20) C, 64.17; H, 4.12; N, 4.40%. Found: C, 54.55; H, 4.46; N, 4.10%. **26c**: Yield 40%; m.p.: 119-125 °C, IR (ν, cm^{-1}): 2590 (NH_2), 1675 (C=O); ^{1}H-NMR δ: 8.10–7.35 (m, 10H, Ar); MS: 325 (M^+-HCl, 38), 115 (100); Anal. Calcd. for $C_{17}H_{12}BrNO^{\bullet}HCl$ (362.65) C, 56.30; H, 3.61; N, 3.86%. Found: C, 56.58; H, 3.75; N, 3.51%.

N-(4-benzoyl-2-naphthyl)-methanesulfonamides (6a–c)

The sulfonamides **6a–c** were synthesized from 4-benzoyl-2-naphthylamines **26a–c** as previously reported for compound **5** and were purified by crystallization from Et_2O/hexane, $CHCl_3$/Et_2O and AcOEt/hexane respectively. **6a**: Yield 51%; m.p.: 48 °C, IR (ν, cm^{-1}): 3270 (NH), 1657 (C=O); ^{1}H-NMR δ: 7.86–7.34 (m, 11H, Ar), 7.11 (s, 1H, NH), 3.04 (s, 3H, CH_3SO_2); MS: 327 (M+2, 8), 326 (M+1, 15), 325 (M^+, 50), 77 (100); Anal. Calcd. for $C_{18}H_{15}NO_3S$ (325.38) C, 66.44; H, 4.65; N, 4.30%. Found: C, 66.54; H, 4.87; N, 4.21%. **6b**: Yield 40%; m.p.: 135–136 °C, IR (ν, cm^{-1}): 3269 (NH), 1657 (C=O); ^{1}H-NMR δ ppm 7.81–7.23 (m, 10H, Ar), 7.11 (s, 1H, NH), 3.06 (s, 3H, CH_3SO_2); MS: 361 (M+2, 22), 360 (M+1, 10), 359 (M^+, 58), 111 (100), 75 (65); Anal. Calcd. for $C_{18}H_{14}ClNO_3S$ (359.04) C, 60.08; H, 3.92; N, 3.89%. Found: C, 59.78; H, 3.49; N, 3.47%. **6c**: Yield 35%; m.p.: 105–115 °C, IR (ν, cm^{-1}): 3278 (NH), 1659 (C=O); ^{1}H-NMR δ: 7.84–7.22 (m, 10H, Ar), 3.03 (s, 3H, CH_3SO_2); MS: 406 (M+2, 5), 405 (M+1, 25), 404 (M^+, 40), 183 (100); Anal. Calcd. for $C_{18}H_{14}BrNO_3S$ (404.28) C, 53.48; H, 3.49; N, 3.46%. Found: C, 53.37; H, 3.36; N, 3.22%.

6-Methoxy-1,2,3,4-tetrahydro-naphthalen-2-ylamine (28)

A solution of 6-Methoxy-3,4-dihydro-[1,2]-naphthoquinone-2-oxime **27** (1 g, 4.9 mmol) in MeOH (50 ml) and HCl 10% (9 ml) was hydrogenated at 50 °C at 1 atm in the presence of Pd/C (500 mg). After 20 h the catalyst was reactivated and the hydrogenation continued for another 20 h. The reaction mixture was filtrated and evaporated under reduced pressure. The crude residue crystallized from EtOH furnished the desired hydrochloride derivative **28**. The hydrochloride salt of **28** was converted into the free base by treating an aqueous solution of the salt with solid KOH, then extracting the free bases with $CHCl_3$. The organic layer washed (H_2O) filtered and evaporated gave **28** as a solid. **28**: Yield 60%; m.p.: 230–240 °C, IR (ν, cm^{-1}): 3146, 2621 (NH_2); ^{1}H-NMR δ: 7.22–6.59 (m, 3H, Ar), 3.75 (s, 3H, CH_3O), 2.91–2.76 (m, 3H, aliphatic), 1.56–1.26 (m, 4H, aliphatic); MS: 177 (M^+, 0.89), 174 (82); Anal. Calcd. for $C_{11}H_{15}NO$ (177.24) C, 74.54; H, 8.53; N, 7.90%. Found: C, 74.25; H, 8.86; N, 7.61%.

7-Methoxy-1,2,3,4-tetrahydro-naphthalen-2-ylamine (29)

To a solution of 7-Methoxy-3,4-dihydro-1H-naphthalen-2-one **30** (500 mg, 2.84 mmol) in anhydrous MeOH (15 ml) was added CH_3COONH_4 (2.19 g, 28.4 mmol) and $NaBH_3CN$ (125 mg, 199 mmol). The mixture was stirred for 48 h, then acidified with HCl (37%) to pH < 2, evaporated under reduced pressure. The residue was dissolved in H_2O, washed with Et_2O, alkalized and extracted with Et_2O. The ether phase, dried and evaporated under reduce pressure, gave 7-Methoxy-1,2,3,4-tetrahydro-naphthalen-2-ylamine **29** which, in the presence of Et_2O/HCl was transformed into the corresponding hydrochloride. The hydrochloride salt of **29** was converted into the free base by treating an aqueous solution of the salt with solid KOH then extracting the free base with $CHCl_3$. The organic layer was washed (H_2O) filtered and evaporated to give **29** as a solid. **29**: Yield 52%; m.p.: 220-225 °C, IR (ν, cm^{-1}): 3490, 2930 (NH_2); ^{1}H-NMR (δ ppm): 7.22–6.58 (m, 3H, Ar), 3.75 (s, 3H, CH_3O), 2.91–2.76 (m, 3H, aliphatic), 1.57–1.25 (m, 4H, aliphatic); MS: 177 (M^+, 0.79), 174 (82); Anal. Calcd. for $C_{11}H_{15}NO$ (177.24) C, 74.54; H, 8.53; N, 7.90%. Found: C, 74.98; H, 8.90; N, 7.55%.

N-(6-Methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-methanesulfonamide (7) N-(7-Methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-methanesulfonamide (8)

Sulfonamides compounds **7** and **8** were synthesized from compounds **28** and **29** as previously reported for **1** and **2**. Compounds **7**, **8** were purified by crystallization from CH_2Cl_2/hexane and CH_3COCH_3/hexane, respectively. **7**: Yield 20%; m.p.: 132–134 °C, IR (ν, cm^{-1}): 3268 (NH); ^{1}H-NMR δ: 6.36–6.71 (m, 3H, Ar), 4.43 (bs, 1H, NH), 3.71 (s, 3H, CH_3O), 2.97 (s, 3H, CH_3SO_2), 3.04–2.55 (m, 4H, aliphatic), 2.56–2.12 (m, 3H, aliphatic); MS: 257 (M+2, 0.87), 256 (M+1, 1.76), 255 (M^+, 12), 160 (100); Anal. Calcd. $C_{12}H_{17}NO_3S$ (255.33) C, 56.45; H, 6.71; N, 5.49%. Found: C, 56.76; H, 6.78; N, 5.21%. **8**: Yield 51%; m.p.: 101–108 °C, IR (ν, cm^{-1}): 3261 (NH); ^{1}H-NMR δ: 6.91–6.56 (m, 3H, Ar), 4.5 (bs, 1H, NH), 3.74 (s, 3H, CH_3O), 2.98 (s, 3H, CH_3SO_2), 3.06–2.75 (m, 4H, aliphatic), 2.02 (m, 3H, aliphatic); MS: 257 (M+2, 1), 256 (M+1, 2), 255 (M^+, 10), 160 (100); Anal. Calcd. $C_{12}H_{17}NO_3S$ (255.33) C, 56.45; H, 6.71; N, 5.49%. Found: C, 56.13; H, 6.92; N, 5.28%

Enzyme assays

Compounds **1**–**4**, **6a**,**b** and **7** were tested following the procedure previously described[9] in intact cell assays to verify their capacity to inhibit PGE2 production, considered as an index of activity on COX-1 and COX-2.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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