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NO-donor COX-2 inhibitors. New nitrooxy-substituted 1,5-diarylimidazoles endowed with COX-2 inhibitory and vasodilator properties

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Abstract. A series of NO-donor diarylimidazoles derived from the lead compound Cimicoxib were synthesised and evaluated for their COX-2 inhibitory activity and their stability in whole blood as well as for vasodilator properties. The products are partly transformed into the corresponding alcohols following 24-h incubation in whole blood. All of them display good COX-1/COX-2 selectivity, but are

less potent than the lead; a molecular modelling study was carried out to investigate their binding mode. The compounds are also capable of relaxing rat aorta strips precontracted with phenylephrine with a NO-dependent mechanism; this property could confer them reduced cardiotoxicity with respect to traditional COX-2 inhibitors.

Introduction

COX-2 selective inhibitors (coxibs) are an important class of drugs useful for the treatment of acute pain and chronic inflammatory diseases. They are characterised by reduced gastrotoxicity with respect to classical non-steroidal anti-inflammatory drugs (NSAIDs), due to their capacity of sparing the COX-1 isoform of the cyclooxygenase enzyme (COX).[1,2] Moreover, these products are under study for the treatment of certain forms of cancer and Alzheimer's disease.[3,4] The most important coxibs belong to the diarylheterocycle class and bear two phenyl rings on adjacent atoms of a 5- or 6-membered heterocyclic system. One of the two phenyl rings must be *p*-methylsulfonyl or *p*-aminosulfonyl substituted in order to achieve COX-2 selectivity, while different substitution patterns are allowed in the other. The R-SO_2- (R = NH_2, CH_3) moiety establishes a hydrogen bonding interaction with the Arg513 residue that is present in the active cleft of the COX-2 isoform, in place of the His513 residue present in the COX-1 isoform.[5] Examples of such drugs developed by different companies are reported in Chart 1 (Celecoxib **1**,[6] Rofecoxib **2**,[7] Valdecoxib **3**,[8] Cimicoxib **4**[9]). Rofecoxib, Valdecoxib, Celecoxib were the first products to be introduced in therapy. During the clinical use of these drugs it became more and more evident that they increase the risk of heart attack and stroke. This cardiotoxicity is due to their capacity to reduce the biosynthesis of prostacycline (PGI_2), with consequent tipping of the eicosanoid balance in favour of thrombogenic thromboxanes (e.g., TxA_2).[10] Consequently, the first two drugs have been withdrawn from the market and Celecoxib is under surveillance.[11,12] The cardiovascular implications of COX-2 inhibitors are currently object of debate and they limit the clinical application of these molecules. The concept of multi-target drug can be usefully applied to obtain safer COX-2 inhibitors. A multi-target drug is designed through the symbiotic approach by joining two drugs, or crucial parts of them, according to different schemes.[13] For example, the appropriate conjugation of a COX-2 inhibitor

with a thromboxane antagonist could give rise to a drug able to block thromboxanes and other thromboxane receptor agonists in addition to PG synthesis, thus limiting the prostacycline/thromboxane imbalance.[10] Another possibility is the design of a COX-2 selective inhibitor bearing an appropriate NO-donor moiety. In fact, nitric oxide triggers multiple actions at the level of the cardiovascular system, namely vasodilation, platelet aggregation inhibition and modulation of the platelets and leucocytes adhesion to the endothelium,[14] thus potentially alleviating the cardiovascular issues raised by common coxibs. Moreover, the increased mucosal blood flow and thickening of the mucous layer induced by NO on the stomach walls can contribute to the gastro-sparing features of COX-2 selective inhibitors.[15] Examples of NO-donor cyclooxygenase inhibitors have already been reported in literature, both non-selective (CINODs)[16] and COX-2-selective (Chart 2).[17] The latter have a therapeutic potential not only as safer drugs for the treatment of pain and inflammation, but also in a wide variety of disease states.[18] In particular, they could be useful in cancer prevention in view of their ability to inhibit cell proliferation and cancer cell progression by a dual NO/COX-2-dependent mechanism.[19] As a development of our previous works, in this paper we describe the synthesis, the COX inhibition profile and vasodilator activities of a series of analogues of the lead compound Cimicoxib[9] (**4**), which is presently undergoing Phase I clinical trials, and its methylsulfonyl analogue **5**. These analogues have been designed by substituting the 4-methoxy group present in the lead with NO-donor nitrooxy-substituted alkyloxy chains (der.s **8**, **9**, **11**, **14**, **16**). Metabolism of these products in human whole blood and their docking in the active cleft of both COX isoforms are also discussed.

Chemistry

Cimicoxib (**4)** was used as starting material for the preparation of its NO-donor derivatives (Scheme 1). This product was refluxed in 1,2-dichloroethane in the presence of BBr_3; the resulting phenol derivative **6** was reacted with *N,N*-dimethylformamide diethylacetal to give **7**. This intermediate, in which the sulfonamido group is protected in order to avoid its possible alkylation, was sequentially heated in acetonitrile in the presence of K_2CO_3 with the appropriate

(bromoalkoxy)(*t*-butyl)dimethylsilane ($Br(CH_2)_nOTBDMS$), then treated with NaOH in MeOH to regenerate the sulfonamido group and ultimately with HCl to cleave the silyl protection. The resulting alcohols **8a**, **9a** were transformed into the corresponding nitrates **8**, **9** by action of triphenylphosphine, *N*-bromosuccinimide (NBS) and $AgNO_3$ in acetonitrile solution. The *p*-methylsulfonyl-substituted compound **5** was used as starting material for the preparation of the final nitrates **11**, **14**, **16**. This product was transformed into the corresponding phenol **10** following the procedure used to prepare **6** from **4**. The reaction of **10** with (2-bromoethoxy)(*t*-butyl)dimethylsilane in acetonitrile in the presence of K_2CO_3, followed by treatment with HCl yielded the intermediate **11a** that, under the same conditions used to prepare **8** from **8a**, gave **11**. Treatment of **10** in tetrahydrofuran (THF) with the tosylate **13**, obtained by action of *p*-toluensulfonyl chloride in pyridine on **12**, and potassium *t*-butoxide afforded the expected final nitrate **14**. The alcohol **14a** was obtained from **10** following a procedure similar to that used for the preparation of **11a** from **10**. The synthesis of the final dinitrooxy compound **16** required the preparation of the allyloxy-substituted intermediate **15**. The latter was easily obtained by refluxing a THF solution of **10**, allyl bromide (AllBr) and NaH. The treatment of a mixture of $AgNO_3$ and **15** with iodine in acetonitrile at room temperature followed by reflux, according to a known procedure to prepare vicinal dinitrooxy-substituted compounds,[20] afforded the expected final compound **16**. The presence of the sulfonamido function precluded the synthesis of the corresponding dinitrooxy analogue of Cimicoxib starting from **6**, through a sequence of similar reactions.

Results and discussion

Metabolism in serum and whole human blood. Organic nitrates can undergo chemical and enzymatic metabolism.[21] All the nitrates studied in the present work were found to be stable following 24-h incubation in human serum. By contrast, they are partly transformed into the corresponding alcohols when incubated for 24 h in human whole blood (Table 1). This transformation was monitored by RP-HPLC; in the case of the mononitrooxy derivatives the metabolites could be identified with alcohols **8a**, **9a**, **11a**, **14a** by comparing their retention times with the standards at our disposal; LC/MS

confirmed this finding. The availability of internal standards allowed precise quantitative assessment of the extent of metabolism, which displays a slight dependence on the structure of the products. The less lipophilic mononitrooxyethyl-substituted compounds were metabolised just a little faster than the related mononitrooxypropyl analogues. In the case of the dinitrooxy-substituted product **16** a mixture of three metabolites was formed, which were characterised by LC/MS due to the lack of internal standards. Two of them showed the same molecular weight, identical to that of the two corresponding monohydroxy isomers **16a** and **16b**, while the third had the molecular weight of the corresponding dihydroxy analogue **16c** (Scheme 2).

COX inhibition. The ability of the products to inhibit COX isozymes was evaluated in human whole blood according to a well-established procedure.[22] To assess the extent of COX-2 isoform inhibition, human heparinised whole blood was incubated overnight with lipopolysaccharide (LPS) in the presence of the inhibitors, then plasma was assayed for PGE_2 production. For COX-1 inhibitory activity, whole blood samples without any anticoagulant were incubated with the inhibitors for 1 h, then serum was collected and analysed for TxB_2 production. The potencies of the products expressed as IC_{50} are collected in Table 2. Since the products proved to be partly metabolised over 24 h in whole blood into the corresponding alcohols we also measured the inhibitory potencies of the monohydroxy metabolites **8a**, **9a**, **11a**, **14a** at our disposal. Analysis of the data reported in Table 2 indicates that all the new NO-donor COX inhibitors retain a high degree of selectivity for the COX-2 isoform, but are definitely less potent than the parent compounds **4**, **5**. The metabolites display activities similar to or lower than those of the parent structures. The most active product is the nitrooxyethyloxy-substituted compound **11**, about 5 and 80 times less active than Rofecoxib (**2**) and its imidazole parent **5**, respectively.

Molecular modelling. A molecular modelling study was performed in the attempt to explain the lower COX-2 inhibitory activity found for the NO-donor hybrids and their metabolites with respect to that of the lead compounds **4** and **5**. The co-crystallized ligand coordinates were removed from the Protein Data Bank records of the two isozymes (PDB codes *1cx2* and *1q4g*) and flexible docking of all inhibitors, including their metabolites and reference compounds **4**, **5** was accomplished into the two

active sites (see Experimental Section and Supporting Information for details). None of the products showed any significant complementarity with the COX-1 active site. By contrast, all newly synthesised ligands display a binding mode to the COX-2 active site similar to that of the lead compounds. In particular, the lowest energy poses display a strong hydrogen bond between Arg513 and an oxygen atom belonging to the sulfonyl group (Fig. 1), which is known to be one of the determinants of COX-2 selectivity.[5] The amino group of aminosulfonyl-substituted compounds establishes hydrogen bonds with the carbonyl oxygen of Ser353 and Gln192, while methylsulfonyl analogues find hydrophobic contacts with Ile517 and Phe518. Due to the increased steric bulk of the substituted alkoxy chain with respect to the methoxy group, all newly synthesised ligands are forced to bind less deeply in the COX-2 active site than the reference molecules (Fig. 1). Consequently, favourable electrostatic interactions between the fluorine atom and the hydroxyl group of Ser530 are partially compromised, as well as the hydrophobic interactions between the chlorine atom and the side chains of Ala527 and Leu531. No stabilising hydrogen bonding occurs between the nitrate groups and the hydroxyl groups of Tyr348, Tyr385 or Ser530, and the hydrophobic contacts with Trp387, Met522, Val523 are not sufficient to counterbalance the strained geometry that the nitrooxyalkyl chains must adopt to avoid steric clashes with the surrounding residues. An analogous picture was found for the hydroxy metabolites. In conclusion, steric hindrance of ester or alcoholic side-chains seems to account for the lower inhibitory activity of newly synthesised compounds and metabolites with respect to reference molecules, in agreement with the structure-activity relationships reported by the authors of Cimicoxib (**4**).[9] The empirical free energy function implemented in AutoDock, which includes terms accounting for the desolvation free energy of the ligand and for its loss of conformational degrees of freedom upon binding,[23] was used to score the ligands' binding affinities. As already pointed out by other investigators,[24] the scoring function failed to rank the COX-2 inhibitors according to their relative experimental potencies. This failure can be ascribed to insufficient conformational sampling or to the scoring function itself, too coarse to discriminate between small energy differences inside a homologous series of compounds. The docking poses were then taken as a starting point for an implicit solvent MM-GBSA simulation,[25] in which the

entropic term was omitted to reduce the computational effort (see Supporting information). The resulting $\Delta G_{MM\text{-}GBSA}$ scores for the new NO-donor COX-2 selective inhibitors are shown in Table 2. As a whole, these figures are definitely higher for the new NO-donor hybrids than for the imidazole reference compounds, thus confirming the reliability of the qualitative picture given by AutoDock.

Vasodilator activity. The *in vitro* vasodilator activity of this new series of selective NO-donor COX-2 inhibitors was assessed on rat aorta strips precontracted with phenylephrine. All the products were able to relax the contracted tissues in a dose-dependent manner. Their potencies, expressed as EC_{50}, are collected in Table 2. All of them behave as potent vasodilators, definitely more active than isosorbide dinitrate (ISDN), taken as a reference.[26] The most active products **11**, **16** and the least active **9** are about 200- and 50-fold more active than ISDN. When the experiments were repeated in the presence of 1 μM ODQ (1*H*-[1,2,4]oxadiazolo[4,3-*a*]quinoxalin-1-one), a well-known inhibitor of soluble guanylate cyclase (sGC), a strong decrease in the vasodilator potencies was observed. When the experiments were performed in the presence of 10 μM oxyhemoglobin (HbO_2), a potent scavenger of nitric oxide, the same decrease occurred for both **16**, taken as example of the compounds under study, and ISDN. These findings are in keeping with the generally accepted vasodilator mechanism of nitrates which involves their entry into vascular smooth muscle cells where they are converted into NO, with the subsequent activation of soluble guanylate cyclase (sGC).[27] Interestingly, also reference compounds **4** and **5**, which are devoid of NO-releasing properties, display vasodilator activity, but in a concentration range definitely higher than that shown by the related NO-donors. As expected, this activity is not ODQ-dependent.

Conclusions. In this study the synthesis of a new class of imidazole cyclooxygenase inhibitors containing NO-donor nitrooxy groups, structurally related to Cimicoxib (**4**), has been reported. The new compounds were investigated for their metabolism and for their COX-2 and COX-1 inhibitory activity in whole blood. The nitrooxy functions undergo partial metabolism over 24 h into the corresponding alcohols. The products display a high degree of COX-2 *vs* COX-1 selectivity as well as a good COX-2 inhibitory potency, although lower than the leads; a molecular modelling study provided a sound

explanation to these findings. In addition to COX-2 inhibition, a potent, NO-dependent vasodilator activity was assessed by an in vitro functional assay. These products are worthy of additional studies in view of their therapeutic potentialities in a wide variety of disease states.

Experimental Section

Synthesis. ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker Avance 300 at 300 and 75 MHz respectively, using $SiMe_4$ as the internal standard. Low resolution mass spectra were recorded with a Finnigan-Mat TSQ-700. Melting points were determined with a capillary apparatus (Büchi 540). Flash column chromatography was performed on silica gel (Merck Kieselgel 60, 230-400 mesh ASTM); PE stands for 40-70 petroleum ether. The progress of the reactions was followed by thin layer chromatography (TLC) on 5×20 cm plates with a layer thickness of 0.2 mm. Anhydrous magnesium sulfate was used as the drying agent for the organic phases. Organic solvents were removed under vacuum at room temperature. Preparative HPLC was performed on a Lichrospher® C_{18} column (250×25 mm, 10 μm) (Merck Darmstadt, Germany) with a Varian ProStar mod-210 with Varian UV detector mod-325. Elemental analyses (C, H, N) were performed by REDOX (Monza) and the results are within ±0.4% of the theoretical values unless otherwise stated. Compounds **4**,[9] **5**,[9] **12**[28] were synthesised according to literature.

4-[4-Chloro-5-(3-fluoro-4-hydroxyphenyl)-1*H*-imidazol-1-yl]benzenesulfonamide (6). To a stirred suspension of **4** (0.20 g, 0.52 mmol) in dichloroethane (20 mL) kept at 0 °C, a 1 M solution of BBr_3 in CH_2Cl_2 (5.5 mL, 5.5 mmol) was added dropwise. The reaction mixture was refluxed for 2 h, then cooled in an ice bath. A $KHCO_3$ saturated solution (10 mL) was added dropwise to the obtained suspension, then the whole mixture was poured into a $KHCO_3$ saturated solution (20 mL) and stirred for 2 h at room temperature. The precipitate was filtered off, washed with cold water (10 mL) and dried. The analytically pure sample was obtained by recrystallisation from EtOH/H_2O mixture. Yield 76%. Mp 272-273 °C (EtOH/H_2O); ^{1}H NMR (DMSO-d_6) δ: 6.81–7.05 (m, 3H, C_6H_3), 7.44 (d, 2H, C_6H_4), 7.50 (s, 2H, NH_2), 7.87 (d, 2H, C_6H_4), 8.09 (s, 1H, C*H* Im), 10.3 (br s, 1H, O*H*); ^{13}C NMR (DMSO-d_6) δ: 117.4,

117.6, 117.8, 125.6, 125.8, 126.4, 126.8, 127.5, 136.6, 138.1, 143.5, 143.6, 145.2, 145.3, 148.8, 152.0; MS (EI) 367/369 $(M)^+$. Anal. ($C_{15}H_{11}ClFN_3O_3S \cdot 0.25\ H_2O$) C, H, N.

4-[4-Chloro-5-(3-fluoro-4-hydroxyphenyl)-1*H*-imidazol-1-yl]-*N*-[(dimethylamino)methylene]benzenesulfonamide (7). To a stirred solution of **6** (0.10 g, 0.27 mmol) in acetonitrile (5 mL) *N*,*N*-dimethylformamide diethylacetal (52 μL, 0.29 mmol) was added. Stirring was continued for 1 h, then the reaction mixture was concentrated under reduced pressure. The oil thus obtained was treated with cold water (5 mL) and the resulting white solid was filtered off, washed with a small amount of cold water and dried. This product was used without any additional purification for further reaction. Yield 87%. Mp 294–295 °C (MeCN); ^{1}H NMR (DMSO-d_6) δ: 2.92 (s, 3H, CH_3), 3.15 (s, 3H, CH_3), 6.73–7.05 (m, 3H, C_6H_3), 7.38 (d, 2H, C_6H_4), 7.82 (d, 2H, C_6H_4), 8.23 (s, 1H), 8.44 (s, 1H, N=C*H*N Im), 10.2 (br s, 1H, O*H*); ^{13}C NMR (DMSO-d_6) δ: 35.0, 40.9, 117.4, 117.6, 117.8, 117.9, 125.5, 125.8, 126.4, 127.1, 127.5, 136.6, 138.1, 142.6, 145.2, 145.4, 148.8, 152.0, 159.9; MS (EI) 422/424 $(M)^+$.

4-{4-Chloro-5-[3-fluoro-4-(2-hydroxyethoxy)phenyl]-1*H*-imidazol-1-yl}benzenesulfonamide (8a). To a stirred mixture of **7** (0.34 g, 0.80 mmol) and K_2CO_3 (0.33 g, 2.40 mmol) in acetonitrile (10 mL) (2-bromoethoxy)-*t*-butyldimethylsilane (0.30 mL, 1.40 mmol) was added in one portion. The reaction mixture was heated at 70–75 °C for 8 h, then it was concentrated under reduced pressure and sequentially MeOH (5 mL) and 2 N NaOH (2 mL) were added. The resulting mixture was heated at 40 °C for 2 h, then acidified to pH 1 with 20% HCl. The solvent was removed under reduced pressure and the residue was treated with water (10 mL) to give a sticky precipitate that afforded a powder after a 2-h refrigeration. The powder was filtered off, washed with water and dried. An analytically pure sample was obtained by recrystallisation from EtOH. Yield 98%. Mp 190-191 °C (EtOH); ^{1}H NMR (CD_3OD) δ: 3.89 (t, 2H, CH_2), 4.12 (t, 2H, CH_2), 6.94–7.13 (m, 3H, C_6H_3), 7.43 (d, 2H, C_6H_4), 7.96 (d, 2H, C_6H_4), 7.98 (s, 1H, C*H* Im); ^{13}C NMR (CD_3OD) δ: 61.4, 71.9, 115.9, 118.5, 118.8, 121.0, 121.1, 127.2, 127.4, 127.5, 127.7, 128.7, 129.4, 137.7, 140.1, 145.4, 148.8, 148.9, 151.8, 155.0; MS (EI) 411/413 $(M)^+$. Anal. ($C_{17}H_{15}ClFN_3O_4S \cdot H_2O$) C, H, N.

4-{4-Chloro-5-[3-fluoro-4-(2-hydroxypropoxy)phenyl]-1*H*-imidazol-1-yl}benzenesulfonamide (9a). The product was obtained by the same procedure as for **8a**, using (3-bromopropoxy)-*t*-butyldimethylsilane. Yield 82%. Mp 194–195 °C (MeOH); ^{1}H NMR (CD_3OD) δ: 2.00 (m, 2H, C*H*$_2$CH$_2$OH), 3.74 (t, 2H, $^3J_{HH}$ = 6.2 Hz), 4.15 (t, 2H, $^3J_{HH}$ = 6.1 Hz) (C*H*$_2$CH$_2$C*H*$_2$OH), 6.94–7.11 (m, 3H, C$_6$*H*$_3$), 7.43 (d, 2H, C$_6$*H*$_4$), 7.94–7.97 (m, 3H, C$_6$*H*$_4$, C*H* Im); ^{13}C NMR (CD_3OD) δ: 32.8, 58.9, 66.7, 115.4, 118.1, 118.4, 120.4, 120.5, 126.9, 127.2, 127.3, 127.4, 127.5, 128.4, 129.0, 129.4, 137.4, 139.8, 145.1, 148.6, 151.4, 154.7; MS (EI) 425/427 $(M)^+$. Anal. ($C_{18}H_{17}ClFN_3O_4S$) C, H, N.

3-{4-[1-(4-(Aminosulfonyl)phenyl)-4-chloro-1*H*-imidazol-5-yl]-2-fluorophenoxy}ethyl Nitrate (8). To a stirred suspension of **8a** (0.80 g, 1.95 mmol) in acetonitrile (25 mL), $AgNO_3$ (0.66 g, 3.89 mmol) and Ph_3P (0.75 g, 2.86 mmol) were added. The reaction mixture was cooled at 0 °C and NBS (0.50 g, 2.80 mmol) was added in one portion. The stirring was continued at 0 °C for 1 h and then at 60 °C for 3 h. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The yellow oil thus obtained was purified by flash chromatography (eluent CH_2Cl_2/MeOH 98/2 v/v). Recrystallisation from MeOH gave the title compound as white solid. Yield 20%. Mp 191–193 °C dec. (MeOH); ^{1}H NMR (CD_3OD) δ: 4.34–4.37 (m, 2H), 4.85–4.89 (m, 2H) (C*H*$_2$C*H*$_2$OH), 6.96–7.14 (m, 3H, C$_6$*H*$_3$), 7.43 (d, 2H, C$_6$*H*$_4$), 7.94–7.98 (m, 3H, C$_6$*H*$_4$, C*H* Im); ^{13}C NMR (CD_3OD) δ: 66.9, 72.4, 116.3, 118.7, 119.0, 121.8, 121.9, 127.2, 127.4, 127.7, 127.8, 128.7, 129.5, 129.9, 135.6, 137.9, 145.4, 148.0, 148.1, 151.7, 155.0; MS (CI) 457/459 $(M+1)^+$. Anal. ($C_{17}H_{14}ClFN_4O_6S$) C, H, N.

3-{4-[1-(4-(Aminosulfonyl)phenyl)-4-chloro-1*H*-imidazol-5-yl]-2-fluorophenoxy}propyl Nitrate (9). The product was obtained by the same procedure as for **8**, using **9a** as the starting compound. The title product was recrystallised from EtOH. Yield 15%. Mp 169.5–170.5 °C dec. (EtOH); ^{1}H NMR (CD_3OD) δ: 2.23 (m, 2H, C*H*$_2$CH$_2$ONO$_2$), 4.16 (t, 2H, $^3J_{HH}$ = 5.9 Hz), 4.69 (t, 2H, $^3J_{HH}$ = 6.3 Hz) (C*H*$_2$CH$_2$C*H*$_2$ONO$_2$), 6.95–7.12 (m, 3H, C$_6$*H*$_3$), 7.43 (d, 2H, C$_6$*H*$_4$), 7.94–7.98 (m, 3H, C$_6$*H*$_4$, C*H* Im); ^{13}C NMR (CD_3OD) δ: 27.6, 70.9, 73.7, 115.6, 118.0, 118.2, 118.5, 118.7, 121.0, 121.1, 126.9, 127.1,

128.4, 129.1, 137.5, 139.8, 145.1, 148.1, 148.2, 151.4, 154.7; MS (EI) 470/472 $(M)^+$. Anal. ($C_{18}H_{16}ClFN_4O_6S$) C, H, N.

4-{4-Chloro-1-[4-(methylsulfonyl)phenyl]-1*H*-imidazol-5-yl}-2-fluorophenol (10). The product was synthesised starting from **5** following a procedure similar to the one described for the preparation of **6** from **4**. Yield 83%. Mp 243–244 °C dec.; ^{1}H NMR (DMSO-d_6) δ: 3.29 (s, 3H, C*H*$_3$), 6.82–7.09 (m, 3H, C$_6$*H*$_3$), 7.54 (d, 2H, C$_6$*H*$_4$), 8.02 (d, 2H, C$_6$*H*$_4$), 8.13 (s, 1H, C*H* Im), 10.29 (br s, 1H, O*H*); ^{13}C NMR (DMSO-d_6) δ: 43.2, 117.5, 117.7, 117.8, 117.9, 125.6, 126.1, 126.5, 127.8, 128.3, 136.7, 139.7, 140.3, 145.3, 148.9, 152.1; MS (EI) 366/368 $(M)^+$. Anal. ($C_{16}H_{12}ClFN_2O_3S$) C, H, N.

2-{4-[4-Chloro-1-(4-(methylsulfonyl)phenyl)-1*H*-imidazol-5-yl]-2-fluorophenoxy}ethanol (11a). The title product was synthesised starting from **10** following a procedure similar to that used to prepare **8a** from **7**, but without the final treatment with 20% HCl. The oil obtained after removing the solvent under reduced pressure was treated with water and extracted with EtOAc. The organic layer was washed with water, brine, dried and evaporated under reduced pressure. The oily residue was triturated with diethyl ether to give a solid that was collected by filtration. Finally, the product was recrystallised from *i*-PrOH. Yield 83%. Mp 142–143 °C (*i*-PrOH); ^{1}H NMR ($CDCl_3$) δ: 2.75 (br s, 1H, O*H*), 3.10 (s, 3H, C*H*$_3$), 4.00 (m, 2H), 4.16 (m, 2H) (C*H*$_2$C*H*$_2$), 6.87–7.00 (m, 3H, C$_6$*H*$_3$), 7.34 (d, 2H, C$_6$*H*$_4$), 7.67 (s, 1H, C*H* Im), 7.99 (d, 2H, C$_6$*H*$_4$); ^{13}C NMR ($CDCl_3$) δ: 44.4, 61.0, 70.7, 114.9, 117.4, 117.7, 119.8, 119.9, 125.7, 126.1, 129.2, 129.9, 135.6, 140.4, 147.1, 147.3, 150.5, 153.8; MS (EI) 410/412 $(M)^+$. Anal. ($C_{18}H_{16}ClFN_2O_4S$) H, N. C: calcd, 52.62; found, 53.23.

2-{4-[4-Chloro-1-(4-(methylsulfonyl)phenyl)-1*H*-imidazol-5-yl]-2-fluorophenoxy}ethyl Nitrate (11). The title product was synthesised starting from **11a** following a procedure similar to that used for the preparation of **8** from **8a**. The product was partly purified by flash chromatography (eluent PE/EtOAc 1/1 v/v) and then by preparative HPLC (Lichrospher® 250-25 C_{18}, mobile phase MeCN/H_2O 1/1 v/v, flow-rate 39 mL/min, λ = 254 nm) to give the title compound as a white powder. Yield 35%. Mp 60–65 °C; ^{1}H NMR ($CDCl_3$) δ: 3.10 (s, 3H, C*H*$_3$), 4.33–4.36 (m, 2H), 4.83–4.86 (m, 2H) (C*H*$_2$C*H*$_2$),

6.86–7.01 (m, 3H, C_6H_3), 7.33 (d, 2H, C_6H_4), 7.65 (s, 1H, C*H* Im), 7.99 (d, 2H, C_6H_4); ^{13}C NMR ($CDCl_3$) δ: 44.4, 65.7, 70.7, 115.6, 117.8, 118.0, 120.9, 121.0, 125.5, 125.7, 126.1, 129.3, 130.2, 135.7, 140.3, 140.5, 146.3, 146.4, 150.7, 154.0; MS (EI) 455/457 $(M)^+$. Anal. ($C_{18}H_{15}ClFN_3O_6S$) C, H, N.

3-(Nitrooxy)propyl 4-methylbenzenesulfonate (13). 3-Hydroxypropyl nitrate (**12**, 1.10 g, 9.10 mmol) was dissolved in dry pyridine (10 mL) at 0 °C and *p*-methylbenzenesulfonyl chloride (2.50 g, 13.1 mmol) was added in one portion. The reaction mixture was kept at 0 °C for 5 h, then it was poured into 1 N HCl solution and extracted with EtOAc. The organic layer was washed with 1 N HCl solution, brine, dried and evaporated under reduced pressure. The resulting oil was purified by flash chromatography (eluent PE/EtOAc 95/5 v/v) to give the title compound as a colourless oil which solidified upon standing. Yield 55%. ^{1}H NMR ($CDCl_3$) δ: 2.08 (m, 2H, $CH_2CH_2CH_2$), 2.45 (s, 3H, CH_3), 4.12 (t, 2H, $^3J_{HH}$ = 5.9 Hz), 4.46 (t, 2H, $^3J_{HH}$ = 6.1 Hz) ($CH_2CH_2CH_2ONO_2$), 7.36 (d, 2H, C_6H_4), 7.78 (d, 2H, C_6H_4); ^{13}C NMR ($CDCl_3$) δ: 21.7, 26.6, 65.8, 68.6, 127.9, 130.0, 132.5, 145.3; MS (EI) 275 $(M)^+$; the compound was not characterised through elemental analysis due to its instability, but it was immediately reacted in the following step.

3-{4-[4-Chloro-1-(4-(methylsulfonyl)phenyl)-1*H*-imidazol-5-yl]-2-fluorophenoxy}propyl Nitrate (14). To a stirred solution of **10** (0.25 g, 0.68 mmol) in dry THF (15 mL), kept under nitrogen, a solution of *t*-BuO^-K^+ (0.09 g, 0.75 mmol) in dry THF (10 mL) was added. The obtained mixture was stirred for 15 min at room temperature and then **13** (0.20 g, 0.72 mmol) was added in one portion. The reaction was left under stirring for 0.5 h and then was heated at 75 °C for 8 h. After this time the mixture was poured into 2 N NaOH (20 mL) and extracted with CH_2Cl_2. The organic layers were washed with water, brine, dried and evaporated under reduced pressure. The residue was purified by flash chromatography (eluent CH_2Cl_2/EtOAc 8/2 v/v) to give the pure title compound as a colourless oil which solidified upon drying. Yield 41%. Mp 80–83 °C; ^{1}H NMR ($CDCl_3$) δ: 2.26 (m, 2H, $CH_2CH_2ONO_2$), 3.10 (s, 3H, CH_3), 4.15 (t, 2H, $^3J_{HH}$ = 5.8 Hz), 4.70 (t, 2H, $^3J_{HH}$ = 6.1 Hz) ($CH_2CH_2CH_2ONO_2$), 6.86–7.00 (m, 3H, C_6H_3), 7.34 (d, 2H, C_6H_4), 7.65 (s, 1H, C*H* Im), 7.99 (d, 2H, C_6H_4); ^{13}C NMR ($CDCl_3$) δ: 26.9, 44.4, 65.0,

69.6, 114.8, 117.5, 117.8, 120.0, 120.1, 125.7, 126.1, 129.2, 130.1, 135.6, 140.4, 140.5, 146.8, 147.0, 150.5, 153.8; MS (EI) 469/471 $(M)^+$. Anal. ($C_{19}H_{17}ClFN_3O_6S$) C, H, N.

3-{4-[4-Chloro-1-(4-(methylsulfonyl)phenyl)-1*H*-imidazol-5-yl]-2-fluorophenoxy}propan-1-ol (14a). The product was synthesised starting from **10** following a procedure similar to that used to prepare **11a**. The product was purified by flash chromatography (eluent CH_2Cl_2/MeOH 98/2 v/v) to give the title compound as a colourless foam. Yield 75%. ^{1}H NMR ($CDCl_3$) δ: 2.09 (m, 2H, C*H*$_2$CH$_2$OH), 3.10 (s, 3H, C*H*$_3$), 3.89 (t, 2H, $^3J_{HH}$ = 5.7 Hz), 4.21 (t, 2H, $^3J_{HH}$ = 6.0 Hz) (CH$_2$CH$_2$C*H*$_2$OH), 6.85–6.98 (m, 3H, C$_6$*H*$_3$), 7.31-7.35 (m, 2H, C$_6$*H*$_4$), 7.65 (s, 1H, C*H* Im), 7.98-8.01 (m, 2H, C$_6$*H*$_4$); ^{13}C NMR ($CDCl_3$) δ: 31.8, 44.5, 60.0, 66.9, 114.5, 117.3, 117.6, 119.5, 119.6, 125.7, 125.8, 129.3, 130.1, 135.5, 140.5, 147.3, 147.4, 150.5, 153.8; MS (EI) 424/426 $(M)^+$. Anal. ($C_{19}H_{18}ClFN_2O_4S \cdot 0.75\ H_2O$) C, H, N.

5-[4-(Allyloxy)-3-fluorophenyl]-4-chloro-1-[4-(methylsulfonyl)phenyl]-1*H*-imidazole (15). To a stirred suspension of **10** (1.00 g, 2.73 mmol) in dry THF (25 mL), kept under nitrogen, 60% NaH (0.12 g, 2.88 mmol) was added. After 15 min allyl bromide (0.3 mL, 3.46 mmol) was added and the reaction mixture was heated at 70 °C overnight. Then, an additional amount of 60% NaH (0.03 g) and allyl bromide (0.1 mL) was added and the heating was continued for 8 more hours. After this time the reaction mixture was poured into 0.1 N NaOH (50 mL) and extracted with EtOAc. The organic layer was washed with brine, dried and evaporated under reduced pressure. The residue was recrystallised from MeOH to give the title compound as a yellow solid. Yield 88%. Mp 156–157 °C (MeOH); ^{1}H NMR (DMSO-d$_6$) δ: 3.27 (s, 3H, C*H*$_3$), 4.64–4.66 (m, 2H, OC*H*$_2$), 5.27–5.44 (m, 2H, CH=C*H*$_2$), 5.99–6.05 (m, 1H, C*H*=CH$_2$), 6.95–7.22 (m, 3H, C$_6$*H*$_3$), 7.53 (d, 2H, C$_6$*H*$_4$), 8.01 (d, 2H, C$_6$*H*$_4$), 8.14 (s, 1H, C*H* Im); ^{13}C NMR ($CDCl_3$) δ: 43.1, 69.1, 115.1, 117.2, 117.4, 118.2, 119.4, 119.5, 125.2, 126.1, 126.4, 126.5, 128.1, 128.3, 132.8, 136.7, 136.9, 139.6, 140.3, 146.1, 146.2, 149.4, 152.6; MS (EI) 406/408 $(M)^+$. Anal. ($C_{19}H_{16}ClFN_2O_3S$) C, H, N.

3-{4-[4-Chloro-1-(4-(methylsulfonyl)phenyl)-1*H*-imidazol-5-yl]-2-fluorophenoxy}propane-1,2-diyl Dinitrate (16). To an ice-cooled, stirred solution of **15** (0.44 g, 1.08 mmol) and $AgNO_3$ (0.75 g, 4.41 mmol) in acetonitrile (25 mL), iodine (0.28 g, 1.08 mmol) was added. After iodine had dissolved, the

reaction mixture was refluxed for 5 days, then filtered, poured into water and extracted with EtOAc. The organic layer was washed with brine, dried and evaporated. The oil thus obtained was purified by flash chromatography (eluent PE/EtOAc 4/6 v/v). Recrystallisation from EtOH afforded the title compound as beige plate-like crystals. Yield 52%. Mp 144.5–145.5 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 3.10 (s, 3H, CH_3), 4.34–4.36 (m, 2H, OCH_2), 4.77–4.84 (m, 1H, CH-CH_aCH_bONO$_2$), 4.93–4.98 (m, 1H, CH-CH_aCH_bONO$_2$), 5.61–6.64 (m, 1H, CHONO$_2$), 6.87–7.03 (m, 3H, C$_6H_3$), 7.33 (d, 2H, C$_6H_4$), 7.65 (s, 1H, CH Im), 7.99 (d, 2H, C$_6H_4$); ^{13}C NMR ($CDCl_3$) δ: 44.4, 66.4, 68.5, 116.0, 117.9, 118.2, 121.6, 121.7, 125.3, 125.7, 126.1, 129.3, 130.4, 135.8, 140.3, 140.6, 145.8, 145.9, 150.7, 154.0; MS (CI) 531/533 $(M+1)^+$. Anal. ($C_{19}H_{16}ClFN_4O_9S$) C, H, N.

Evaluation of stability in human whole blood. Compounds **8**, **9**, **11**, **14**, **16** were incubated for 24 h at 100 μM concentration both in human serum (Aldrich) and in heparinized human blood. Resulting solutions were maintained at 37 ± 0.5 °C and at appropriate time intervals aliquots were diluted 1:2 with acetonitrile containing 0.1% trifluoroacetic acid in order to deproteinize and precipitate cells, proteins and enzymes. Samples were sonicated, vortexed and then centrifuged for 15 min at 2150 × *g*. The clear supernatant was filtered by 0.45 μm PTFE filters (Alltech) and analysed by RP-HPLC, in order to accomplish separation and quantitation of unchanged compounds and metabolites. HPLC analyses were performed with a HP1100 chromatograph system (Agilent Technologies, Palo Alto, CA, USA) equipped with a quaternary pump (model G1311A), a membrane degasser (model G1379A), a diode-array detector (DAD) (model G1315B) integrated in the HP1100 system. Data analysis was accomplished using a HP ChemStation system (Agilent Technologies). The analytical column was an Agilent ZORBAX Eclipse XDB-C8 (4.6×150mm, 5 μm particle size). The mobile phase consisted of acetonitrile/water (50/50 v/v), both containing 0.1% trifluoroacetic acid, at a constant flow-rate of 1.0 mL/min. The injection volume was 20 μL (Rheodyne, Cotati, CA). The column effluent was monitored at 226 nm and 250 nm. Quantitative analysis was performed by comparison of peak areas with standards chromatographed under the same conditions. The hydrolysis of all compounds followed first-order kinetics. The observed pseudo-first-order rate constants (k_{obs}) for the hydrolysis were calculated from

the slopes of linear plots of the natural logarithm of percent remaining nitrates against time; the corresponding half-lives ($t_{1/2}$) were obtained according to the equation $t_{1/2} = 0.693/k_{obs}$. Structural information of investigated compounds and relative MS spectra were acquired by LC/MS technique, using a HP1100 chromatograph system (Agilent Technologies, Palo Alto, CA, USA) equipped with a binary pump and coupled with an API 3200 triple-quadrupole spectrometer (Applied Biosystems), operating in ESI (ElectroSpray Ionization) mode. An Agilent ZORBAX Eclipse XDB-C8 column (4.6×150 mm, 5 μm particle size) was employed; the mobile phase consisted of acetonitrile/water (70/30 v/v), both containing 0.1% trifluoroacetic acid, at a constant flow-rate of 400 μL/min. The ion source operated in positive ion mode at 300 °C with spray voltage at 5000 V and positive ions were acquired in the multiple reaction monitoring (MRM) mode. 10 μL of each solution (100 μM concentration) were injected and all separations were performed at room temperature. The substance specific voltages (DP-declustering potential, EP-entrance potential, CXP-cell exit potential and CE-collision energy) were optimized for each compound, using standard solutions at the concentration of 1 ppm.

COX inhibition. A whole blood assay[22,17b] was performed to evaluate the ability of synthesised compounds to inhibit COX-1 and COX-2 isozymes. Blood samples were obtained from healthy volunteers who had not taken any drug for at last two weeks. Volunteers, who were treated according to the Helsinki protocol for biomedical experimentation, gave their informed consent to the use of blood samples for research purposes. Blood samples were divided in two aliquots to test COX-1 and COX-2 inhibition. COX-2 aliquot was treated with sodium heparine (10 IU/mL), acetylsalicylic acid (10 μg/mL) to suppress prostanoids production from COX-1, and lipopolysaccaride from *E. coli* (LPS, 10 μg/mL). Methanolic solutions of the tested compounds at different concentrations were prepared, 10 μL aliquots were distributed in incubation tubes and the solvent was evaporated. The residues were dissolved by vortexing either in heparinized blood (1 mL) to test COX-2 inhibition, or in untreated blood (1 mL) to test COX-1 inhibition. COX-1 samples were incubated in glass tubes for 1 h at 37 °C, then were centrifuged at 2000 × *g* for 10 min and serum was tested for platelet TxB_2 production. COX-2 samples were incubated in polyethylene tubes for 24 h at 37 °C to allow COX-2 expression in

monocytes and maximal PGE_2 production. Samples were then centrifuged at 2000 × *g* for 10 min and plasma was tested for PGE_2 production; basal PGE_2 production in blood untreated with LPS was subtracted from all samples. Prostanoid production was evaluated by enzyme immunoassay (Cayman Chemical). The percent inhibition in TxB_2 (COX-1) and PGE_2 (COX-2) production in compound-treated samples were calculated by comparison with control untreated samples. The concentration of the tested compounds causing 50% inhibition (IC_{50}) was calculated from the concentration-inhibition response curve (5-6 experiments).

Vasodilator activity. Thoracic aortas were isolated from male Wistar rats weighing 180-200 g. As few animals as possible were used. The purposes and the protocols of our studies were approved by Ministero della Salute, Rome, Italy. The endothelium was removed and the vessels were helically cut: three strips were obtained from each aorta. The tissues were mounted under 1.0 g tension in organ baths containing 30 mL of Krebs-bicarbonate buffer with the following composition (mM): NaCl 111.2, KCl 5.0, $CaCl_2$ 2.5, $MgSO_4$ 1.2, KH_2PO_4 1.0, $NaHCO_3$ 12.0, glucose 11.1, maintained at 37 °C and gassed with 95% O_2-5% CO_2 (pH = 7.4). The aortic strips were allowed to equilibrate for 120 min and then contracted with 1 μM L-phenylephrine. When the response to the agonist reached a plateau, cumulative concentrations of the vasodilating agent were added. Results are expressed as EC_{50} ± SE (μM). The effects of 1 μM ODQ and 10 μM oxyhemoglobin on relaxation were evaluated in separate series of experiments. In the first case ODQ was added to the organ bath 5 minutes before the contraction, while in the second case HbO_2 was added before contraction plateaued. Responses were recorded by an isometric transducer connected to the MacLab System PowerLab. Addition of the drug vehicle (DMSO) had no appreciable effect on contraction level.

Preparation of Oxyhemoglobin. Bovine hemoglobin type 1 (H-2500 Sigma Chemical Co.) contains a mixture of oxyhemoglobin and its oxidised derivative methemoglobin. Pure oxyhemoglobin was prepared by adding a solution of commercially available hemoglobin in 50 mM phosphate saline buffer, pH 7.4, to an excess of the reducing agent sodium dithionite ($Na_2S_2O_4$) at 4 °C and was then protected from the light. Hemoglobin (64.5 mg) was gently dissolved into distilled water (1 mL); sodium

dithionite (53.6 mg) was then added to the solution which was loaded onto a chromatographic column (Sephadex G-25, Pharmacia, Uppsala, Sweden) and eluted with phosphate buffer. Two Pasteur pipets were used as columns for 1 mL of this solution. The purity of the oxyhemoglobin solution was determined spectrophotometrically (600-360 nm; $\lambda_{max} = 414$ nm, $\varepsilon = 1.25 \cdot 10^5$) by diluting the eluted solution 1:600 with buffer. The solutions were freshly prepared daily.

Molecular modelling. All COX-2 inhibitors used in the simulations were constructed using standard bond lengths and angles with the MOE modelling suite.[29] All quantum mechanical calculations were performed with the GAMESS-US software package.[30] The crystal structures of COX-2 and COX-1 EI complexes were downloaded from the Brookhaven Protein Data Bank[31] (entry codes *1cx2* and *1q4g*). Docking was performed with the Lamarckian Genetic Algorithm (LGA) implemented in AutoDock 3.0.5.[23] EI complexes setup and refinement as well as MM-GBSA simulations were performed with the AMBER 8 software package.[32] All calculations were performed on a Beowulf-type 8-CPU Linux cluster (4 Intel Pentium IV 2.4-3.0 GHz – 4 AMD Athlon XP 1.8-2.4 GHz).

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Supporting information available. Elemental analyses; detailed computational procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

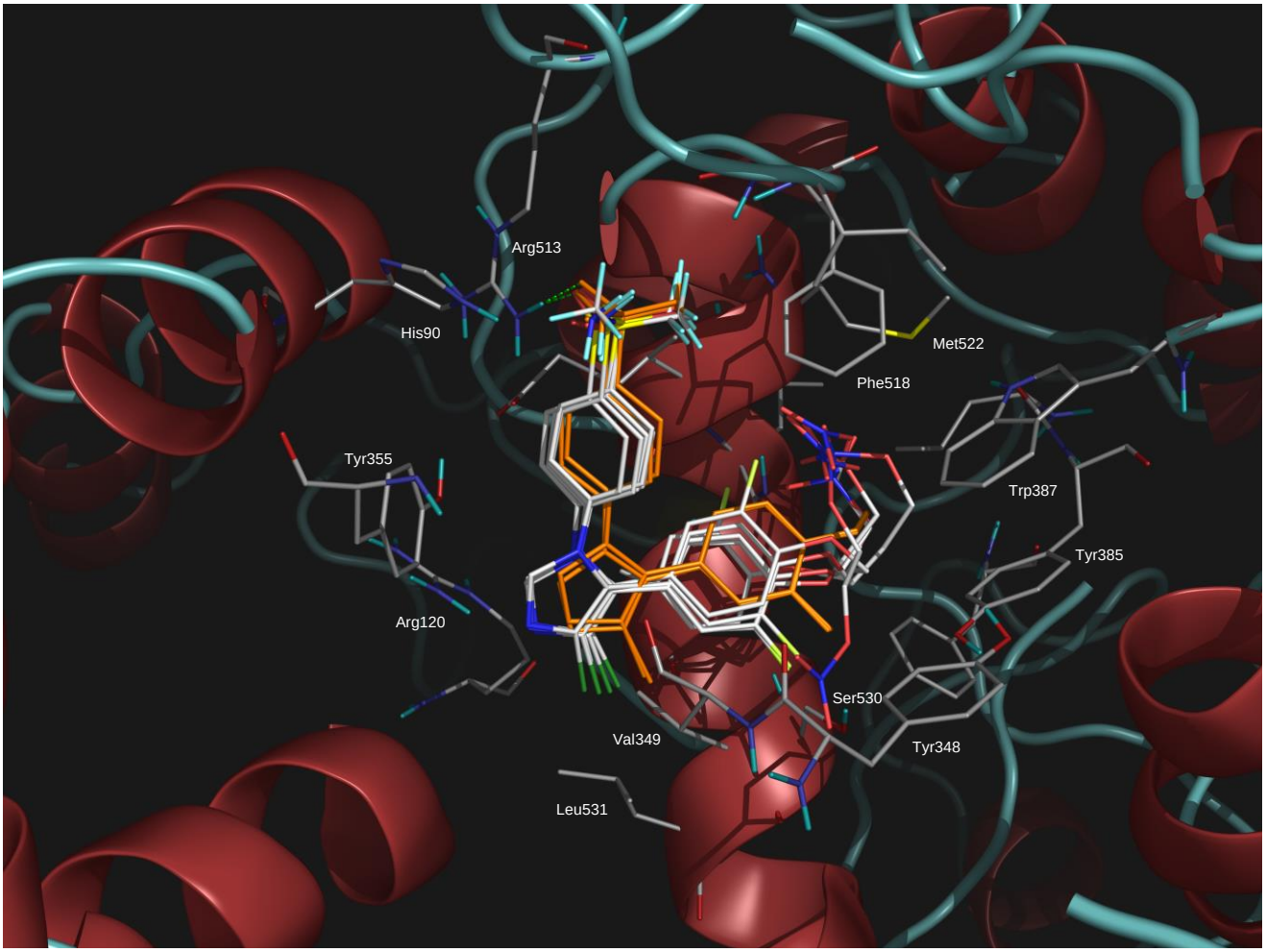
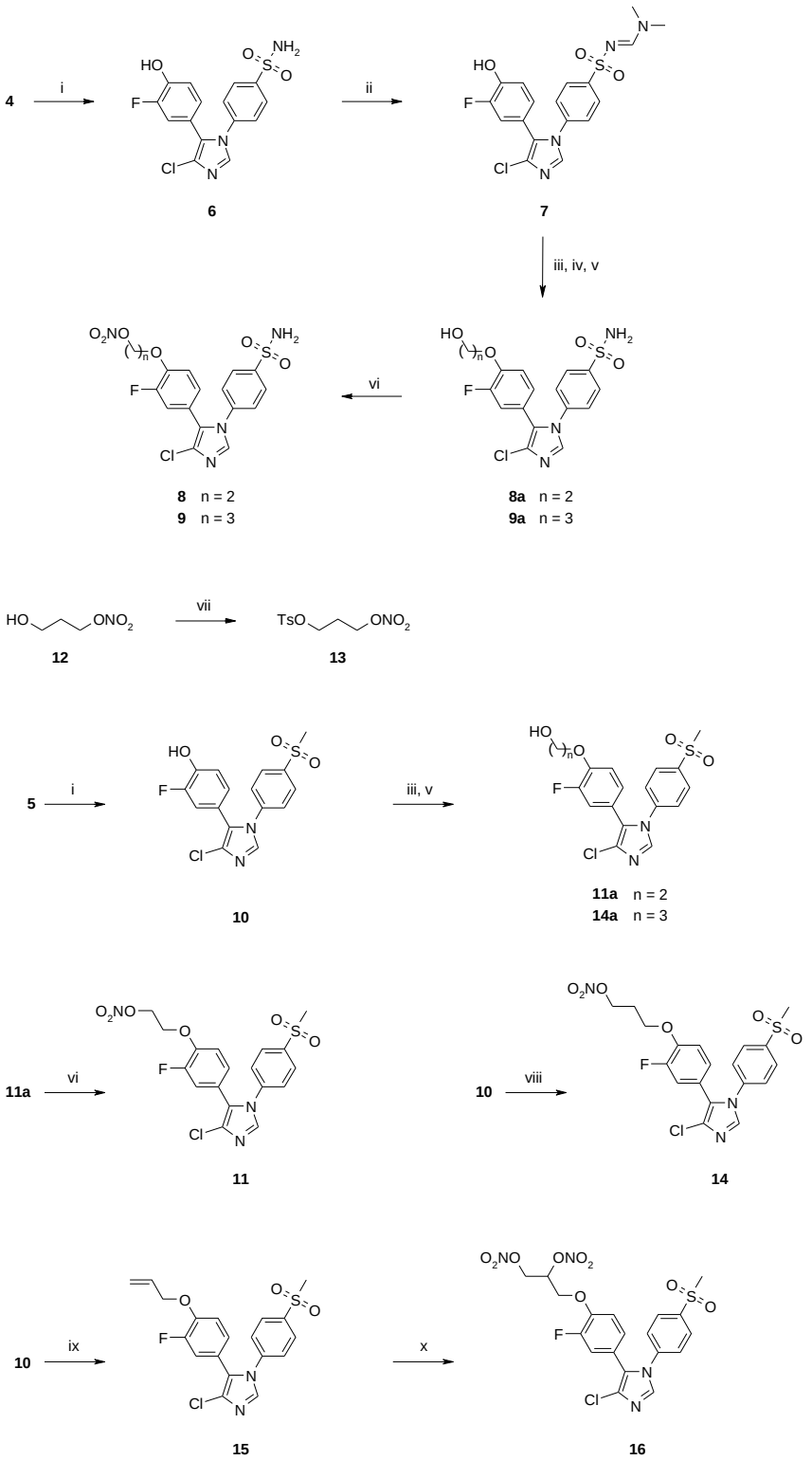


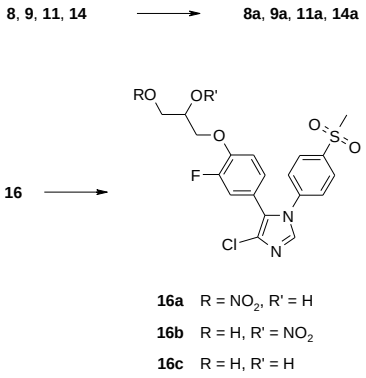
Figure 1. Superposition of docked ligands inside the COX-2 active site. Since their alcoholic metabolites display binding poses very similar to those of the parent compounds, they have not been included for clarity. Reference compounds **4**, **5** are coloured in orange. Protein carbon atoms are coloured in gray to distinguish them from ligand carbons. Non-polar hydrogens have been omitted for clarity, except for the ligand methylsulfonyl group. A green dotted line evidences the hydrogen bond between the ligand sulfonyl group and Arg513. This figure was generated with PyMOL.[33]

Scheme 1[a]



[a] Reagents and conditions: (i) BBr_3, $ClCH_2CH_2Cl$, reflux; (ii) $(EtO)_2CHNMe_2$, RT; (iii) $Br(CH_2)_nOTBDMS$, K_2CO_3, MeCN, reflux; (iv) 2 N NaOH, MeOH, 40 °C; (v) 1 N HCl, MeOH; (vi) Ph_3P, NBS, $AgNO_3$, MeCN, 0 °C, then 60 °C; (vii) TsCl, Py, 0 °C; (viii) **13**, *t*-BuOK, THF, 60 °C; (ix) AllBr, NaH, THF, reflux; (x) I_2, $AgNO_3$, MeCN, RT, then reflux.

Scheme 2. Metabolic fate in human whole blood.

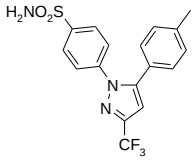


16a R = NO_2, R' = H

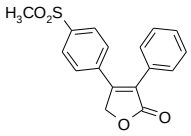
16b R = H, R' = NO_2

16c R = H, R' = H

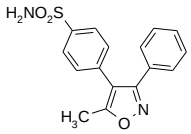
Chart 1. Examples of diarylheterocyclic COX-2 inhibitors.



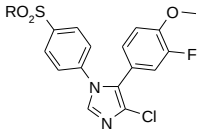
1
Celecoxib



2
Rofecoxib

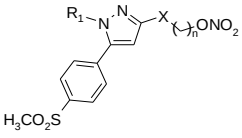


3
Valdecoxib



4 R = NH_2 Cimicoxib
5 R = CH_3

Chart 2. General structure of nitrooxyalkyl COX-2 selective inhibitors.



R_1 = cycloalkyl, aryl, benzyl
X = CH_2, CH=CH, C=O, C=NOR_2
R_2 = H, CH_3
n = 0 - 5

Table 1. Stability following 24-h incubation in human serum and in human whole blood.

	Human serum	Human whole blood		
Compound	% unchanged	% unchanged (± SE)	% metabolites (± SE)	$t_{1/2}$ (h)
8	> 98%	58.8 (± 3.4)	**8a**: 43.4 (± 2.2)	28.1
9	> 98%	64.1 (± 2.4)	**9a**: 37.2 (± 2.0)	39.2
11	> 98%	53.3 (± 2.9)	**11a**: 45.9 (± 1.0)	27.1
14	> 98%	60.6 (± 1.5)	**14a**: 44.8 (± 1.5)	37.5
16	> 97%	43.6 (± 3.9)	**16a** + **16b**: 47[a]	21.0
			16c: 14[a]	

[a] Quantitative assessment was performed using the calibration curve of compound **16** since no standards were available.

Table 2. Experimental inhibitory potencies, vasodilator activities and calculated Δ*G* values.

Compound	IC_{50}^{COX-2} [a]	IC_{50}^{COX-1} [a]	Vasodilation EC_{50} [b]	$\Delta G_{MM\text{-}GBSA}^{COX-2}$ [c]
ISDN	-	-	4.7 ± 0.6	-
			>100[d]	
			55 ± 10[e]	
1	1.3 ± 0.4	14 ± 2	-	-
2	1.5 ± 0.8	64 ± 13	-	-
4	0.10 ± 0.03	1.9 ± 0.2	25 ± 3[d]	-37.44
5	0.090 ± 0.019	5.8 ± 0.9	24 ± 2[d]	-35.89
8	29 ± 4	>100	0.051 ± 0.006	-30.81
			12 ± 2[d]	
8a	20 ± 8	>100	-	-
9	16 ± 7	>100	0.10 ± 0.02	-30.17
			18 ± 2[d]	
9a	>100	>100	-	-
11	6.9 ± 2.0	>100	0.021 ± 0.004	-30.85
			6.5 ± 1.1[d]	
11a	56 ± 10	>100	-	-
14	14 ± 3	>100	0.078 ± 0.014	-30.87
			6.3 ± 0.6[d]	
14a	>100	>100	-	-
16	76 ± 18	>100	0.021 ± 0.003	-28.88[f]
			>100 [d]	
			0.061 ± 0.006[e]	

[a] Values reported as IC_{50} (μM) ± SEM. [b] Values reported as EC_{50} (μM) ± SEM. [c] kcal/mol, evaluated through a simplified MM-GBSA approach which neglects the entropic term in the $\Delta G_{binding}$ calculation. [d] In the presence of 1 μM ODQ. [e] In the presence of 10 μM HbO_2. [f] Since the compound exists as a couple of enantiomers, whose ratio is unknown, the calculated Δ*G* is reported as the average Δ*G* of the two docked enantiomers, which indeed showed very close values.

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SYNOPSIS TOC

NO-donor COX-2 inhibitors. New nitrooxy-substituted 1,5-diarylimidazoles endowed with COX-2 inhibitory and vasodilator properties.

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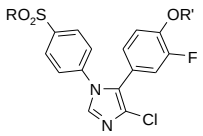

R = NH_2, CH_3

R' = $(CH_2)_2ONO_2$, $(CH_2)_3ONO_2$, $CH_2(CHONO_2)CH_2ONO_2$