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Original article

Investigations concerning the COX/5-LOX inhibiting and hydroxyl radical scavenging potencies of novel 4,5-diaryl isoselenazoles

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Abstract

The aim of this study was to investigate 4,5-diaryl isoselenazoles as multiple target non-steroidal anti-inflammatory drugs (MTNSAIDs) which can intervene into the inflammatory processes via different mechanisms of action creating a new class of compounds. Here we describe the synthesis of COX/LOX inhibitors which additionally reduce the level of reactive oxygen species, such as hydroxyl radicals which are well known for supporting inflammation processes in Parkinson's disease, Alzheimer's disease and rheumatoid arthritis.

Keywords: COX-1/2; 5-LOX; Dual inhibitors; Hydroxyl radical scavenging; Isoselenazoles

1. Introduction

NSAIDs are basically used for the treatment of pain, inflammation and fever. The main mechanism of action of these drugs is the inhibition of the cyclooxygenase enzymes (COX-1 and COX-2) [1,2], which are catalyzing the biotransformation of arachidonic acid to the prostaglandins.

Gastrointestinal haemorrhage, ulceration and kidney failure are the major side effects associated with all currently available NSAIDs [3]. These unwanted side activities are caused by the interference of the physiological balance of prostaglandins. To overcome this several approaches were undertaken. One attempt haunts the strategy of selective inhibition of COX-2. Nevertheless, clinical studies have suggested that selective COX-2 inhibitors could cause typical COX-mediated side effects such as gastrointestinal injury, increased systemic blood pressure and hypersensitivity [4]. Due to safety concerns of an increased risk of cardiovascular events (including heart attack and stroke) in patients on Vioxx a voluntary withdrawal of Vioxx (rofecoxib) was announced on the worldwide market since 1999. Consequently the American Gastroenterological Association (AGA) differentiated the therapy for patients with higher gastrointestinal (GI) risks or higher cardiovascular (CV) risk in three cases [5].

Recently the target switched to a combined 5-LOX/COX inhibition, interfering both pathways, the production of prostaglandins and the biosynthesis of leukotrienes (LTs) [4,6]. This strategy led to substances like licofelone (formerly known as ML3000), which avoid side effects related to COX inhibition. Its anti-inflammatory and analgesic activities are comparable to conventional NSAIDs and selective COX-2 inhibitors but with an improved gastrointestinal safety profile. Substances like licofelone offer a new quality of curative therapy for the future [7–10].

Here we describe COX/LOX inhibitors which additionally have the potential to reduce the level of reactive oxygen species, like the hydroxyl radicals which support inflammatory processes in Parkinson's disease [11], Alzheimer's disease [12] and rheumatoid arthritis [13]. We combined the classical diaryl heterocycle with the characteristic structure of ebselen (Fig. 1), a synthetic antioxidant.

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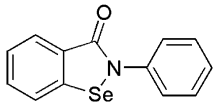


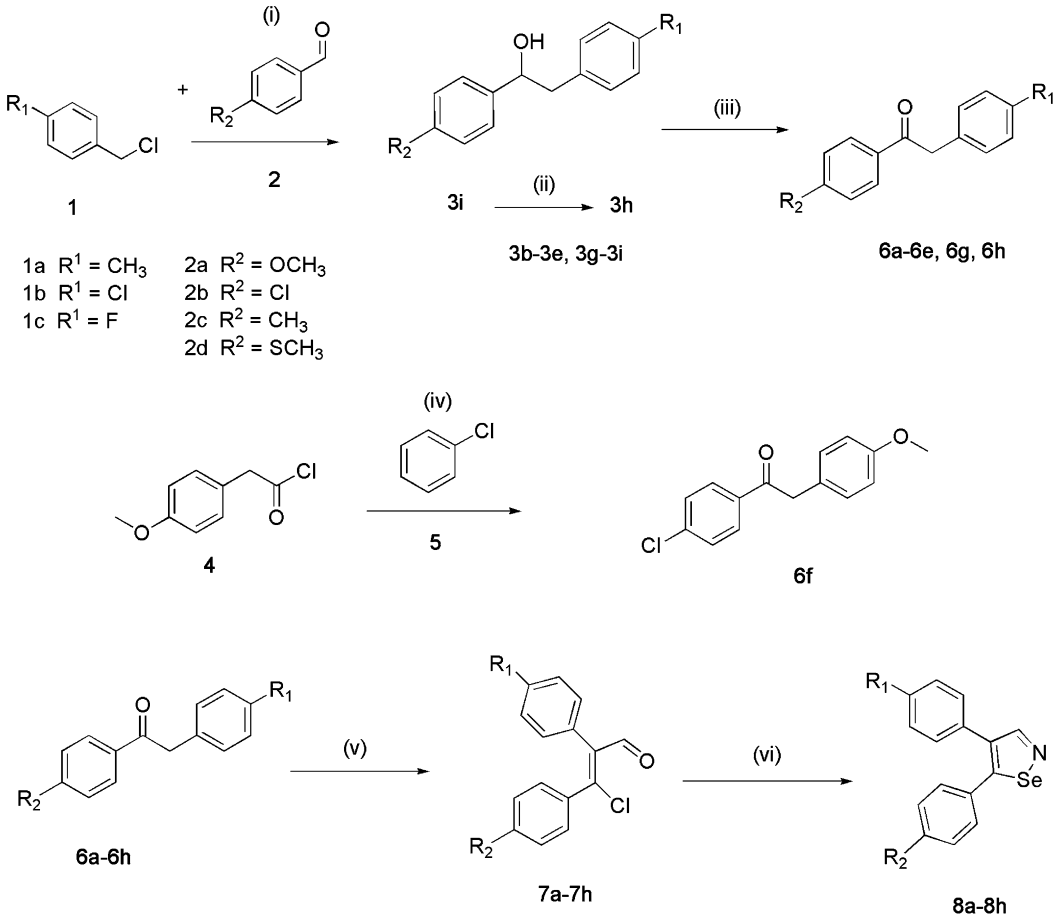
Fig. 1. Structure of ebselen.

In accordance with literature [14] ebselen can inactivate highly reactive radicals, which was originally shown by Maiorino et al. [15] and Schöneich et al. [16]. Furthermore ebselen is a potent inhibitor of lipid peroxidase according to a Fenton-type reaction of the transition metals with hydroperoxides [17,18]. For ebselen several other modes of action were described: it very effectively reduces hydroperoxides, it is a mimic of glutathione peroxidase and acts as an inhibitor of 5- and 15-lipoxygenases, NO synthase, NADPH oxidase, protein kinase C and H^+/K^+-ATPase [14].

Due to this rationale, we synthesized diaryl isoselenazoles **8a–8h**, the combination of a diaryl heterocycle targeting the aim of dual COX/5-LOX inhibitors with a potential radical scavenging potency of the selenium moiety.

2. Chemistry

To synthesize the isoselenazole ring systems we started with a Grignard reaction (Scheme 1) to connect chloromethylbenzenes **1a–1c** with various benzaldehydes **2a–2d** gaining the secondary alcohols **3b–3i** in very good yields (up to 95%) [19]. To obtain the methylsulfonyl derivative **3h**, **3i** was oxidized with 3-chloroperbenzoic acid (Scheme 1). It was important to oxidize the thioether **3i** derivative quantitatively to **3h** before the alcohol was oxidized to the analogous ketone, because the thioether derivatives disturbed this second



6a, 7a, 8a	R^1 =	$R^2 = OCH_3$
3b, 6b, 7b, 8b	$R^1 = CH_3$	$R^2 = OCH_3$
3c, 4c, 7c, 8c	$R^1 = CH_3$	R^2 = Cl
3d, 6d,7d, 8d	R^1 = Cl	$R^2 = CH_3$
3e, 6e, 7e, 8e	R^1 = Cl	R^2 = Cl
6f, 7f, 8f	$R^1 = OCH_3$	R^2 = Cl
3g, 6g, 7g, 8g	R^1 = Cl	$R^2 = OCH_3$
3h, 6h, 7h, 8h	R^1 = F	$R^2 = SO_2CH_3$

Scheme 1. Method i: Mg in ether; method ii: 3-chloroperbenzoic acid, 0 °C, in CH_2Cl_2; method iii: $Na_2Cr_2O_7$, H_2SO_4 in CH_2Cl_2 3 h at rt; method iv: $AlCl_3$ in CH_2Cl_2, 0–20 °C; method v: DMF, 5 °C, $POCl_3$, 80 °C for 4 h; method vi: heating under reflux NH_4Cl, KSeCN, acetone, 5 h.

oxidation reaction resulting in an increase of side products. The oxidation reaction from the alcohols **3b**–**3e**, **3g** and **3h** to the ketones **6b**–**6e**, **6g** and **6h** [20] was difficult, because further oxidation products, e.g. the α-hydroxy ketones and the diketone derivatives, could also be obtained. By avoiding this problem the yield of the ketone increased up to 60% (Scheme 1). The ketone **6f** was synthesized in moderate yields with a Friedel–Crafts acylation reaction connecting 2-(4-methoxyphenyl)acetyl chloride **4** and chlorobenzene **5** [19].

The ketones **6a**–**6h** reacted in the next step with phosphoryl chloride in DMF in a modified Vilsmeier reaction [21] (Scheme 1) leading to the chloro formyl stilbene derivatives **7a**–**7h** in high yields.

The synthesis strategy for diaryl isoselenazole derivatives **8a**–**8h** was developed (Scheme 2) by modifying the conditions of the isothiazole synthesis [22] using potassium selenocyanate and ammonium chloride instead of ammonium thiocyanate. After substitution of the chloride by selenocyanate, ammonia reacted with the formyl group to an imide, which finally attacked selenocyanate releasing hydrogen cyanide (Scheme 2).

3. Results and discussion

4,5-Diaryl isoselenazoles were evaluated in vitro to determine their COX-1/2 and 5-LOX inhibitory potencies and their ROS scavenging efficacies. Table 1 summarizes the impact of the R^1 and R^2 substituents. The structure–activity relationship (SAR) data show a broad range of inhibitory activities in the COX-1 and COX-2 test systems (COX-1: IC_{50}: 0.006 μM (**8a**) to 38% inhibition at 10 μM concentration (**8h**), COX-2: 0.6 μM (**8h**) to ≫10 μM (**8b**–**8e**)). In general, different *p*-aryl substituted moieties were tolerated in maintaining COX-1 inhibiting activity but the introduction of the typical COX-2 sulfone moiety (**8h**) decreased the COX-1 activity significantly. This is in line with the previous findings [23].

By comparing the different substituents R^1 and R^2, clear decisions can be drawn with regard to the COX-1 activity. The most potent COX-1 inhibitor in this series is the dimethoxy substituted (R^1 and R^2) compound **8a** (IC_{50}: 0.006 μM) which inhibits COX-1 about 3-fold more potent compared to the monomethoxy substituted compounds **8b** (IC_{50}: 0.02 μM), **8f** (IC_{50}: 0.01 μM) and **8g** (IC_{50}: 0.02 μM).

The mean inhibitory activity of compounds **8b**, **8f** and **8g** is about 10-fold higher compared to mean inhibitory activity of the chlorine and methyl substituted compounds **8c**–**8e**. The weakest COX-1 inhibitory effect was found for **8h** (38% inhibition at 10 μM). Summarizing these data, it can be stated that the rank order for COX-1 inhibition is: dimethoxy > monomethoxy > methyl ∼ chlorine > methylsulfonyl.

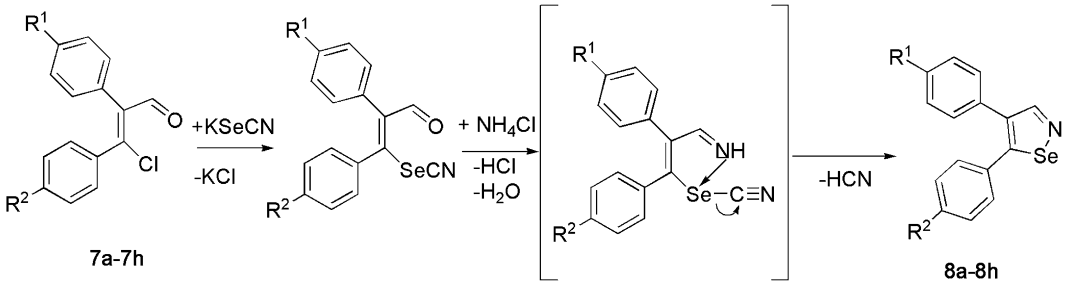
Only two compounds **8h** (IC_{50}: 0.6 μM) and **8a** (IC_{50}: 8 μM) behave as potent COX-2 inhibitors. It is worth to mention that **8h** is as potent as celecoxib (IC_{50}: 1 μM) and both share a similar COX-1/COX-2 ratio of about 10 in our assays. The quotient of the IC_{50} values of COX-2/COX-1 inhibition is an admitted and widely used parameter for the determination of enzyme selectivity using different test systems [1].

COX-2 (PDB entry: 1CX2) docking studies confirm (Fig. 2) that the substances **8a** and **8h** dock in a similar binding modus like SC-558 (Fig. 3). The different substituents in *p*-position of the phenyl groups undergo distinctive hydrogen bonds. Compound **8a** formed an H-bond from the methoxy group with the oxygen as H-bond acceptor to histidine 90. The methylsulfonyl derivative **8h** forms 2H-bonds from the sulfonyloxygens as H-bond acceptors to histidine 90 and arginine 513 (Fig. 3).

Whereas a methylsulfonyl moiety in the case of **8h** leads to an increase in COX-2 activity, all compounds possess a moderate 5-LOX inhibitory activity in a range from 67% (**8c**) to 42% (**8f**) at a concentration of 10 μM. This indicates that the impact of the substitution pattern of the phenyl moiety at 4-position is low, since all tested isoselenazoles show a moderate 5-LOX inhibition compared to the good activity of licofelone (IC_{50}: 0.18 μM) [9] or NDGA (IC_{50}: 1 μM). Noticeable is the fact that the 5-LOX inhibition of the isoselenazoles is in the same range as ebselen (IC_{50} ∼ 10 μM).

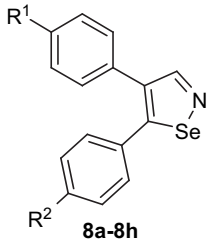
The potency of anti-inflammatory drugs often depends especially on their lipophilicity. To test this hypothesis we evaluated the log *P* values by using method 2 of the three available fragmentation methods for calculating log *P* in the ChemDraw 8.0 software. Despite the lipophilic cavity of the 5-LOX enzyme [24] the different lipophilicity of our compounds, represented by calculated log *P* values in a range from 2.46 (**8h**, 60% inhibition at 10 μM) to 4.53 (**8c**, 67% inhibition at 10 μM), did not influence the 5-LOX activity.

Ebselen was chosen as standard compound to study the ROS inhibiting activity. Despite it was published that ebselen



Scheme 2. Proposed mechanism for the formation of **8a**–**8h**.

Table 1
COX-1/2 and 5-LOX inhibiting activities and OH radical scavenging potency of the newly described 4,5-diaryl isoselenazoles



8a-8h

Compound	R^1	R^2	IC_{50}[a] (μM)			IC_{50}[b] (μM)
			COX-1	COX-2	5-LOX	OH radical scavenging
8a	OCH_3	OCH_3	0.006	8	58%[c]	14%[d]
8b	CH_3	OCH_3	0.02	0	64%[c]	0
8c	CH_3	Cl	0.2	0	67%[c]	0
8d	Cl	CH_3	0.05	0	45%[c]	0
8e	Cl	Cl	0.2	0	44%[c]	0
8f	OCH_3	Cl	0.01	16%[c]	42%[c]	0
8g	Cl	OCH_3	0.02	17%[c]	53%[c]	0
8h	F	SO_2CH_3	38%[c]	0.6	60%[c]/8	34%[d]
Celecoxib			65%[c]	1		27%[d]
Ebselen			2.1	0	54%[c]	6
NDGA			31%[c]	10%[c]	1	29
Thioctic acid			n.t.	n.t.	n.t.	11

[a] Values are means of two determinations.
[b] Values are means of three determinations.
[c] Inhibition at a concentration of 10 μM.
[d] Inhibition at a concentration of 100 μM, n.t.: not tested.

is not a very potent radical scavenger [14], we found a high potency (IC_{50}: 6 μM) in our experimental setting. In our assay we induced the production of hydroxyl radicals by a Fenton reaction. To quantify its effect the spintrap method was used.

Unfortunately most of the compounds show no significant ROS inhibiting activity. Only compound **8h** (38% inhibition at 100 μM) displayed a weak activity. In context with manifold enzyme inhibiting activities of ebselen (5- and 15-lipoxygenases, NO synthase, NADPH oxidase, protein kinase C and H^+/K^+-ATPase) shown in literature these features should be subsequently kept in mind.

Taken together we were able to prepare the novel 4,5-diaryl substituted isoselenazoles. To the best of our knowledge this is the first time that this type of compounds was synthesized. Compound **8a** is equipotent to celecoxib concerning COX-2 inhibition (IC_{50}: 1 μM vs. 0.6 μM) but more potent with regard to the COX-1 inhibition (IC_{50}: 0.006 μM vs. ~10 μM), however, the 5-LOX inhibition compared to licofelone (IC_{50}: 10 μM vs. 0.18 μM [8]) is lower. The most balanced compound in this series was compound **8h** including COX-1, COX-2 and 5-LOX inhibitory activities and weak hydroxyl radical scavenger potency.

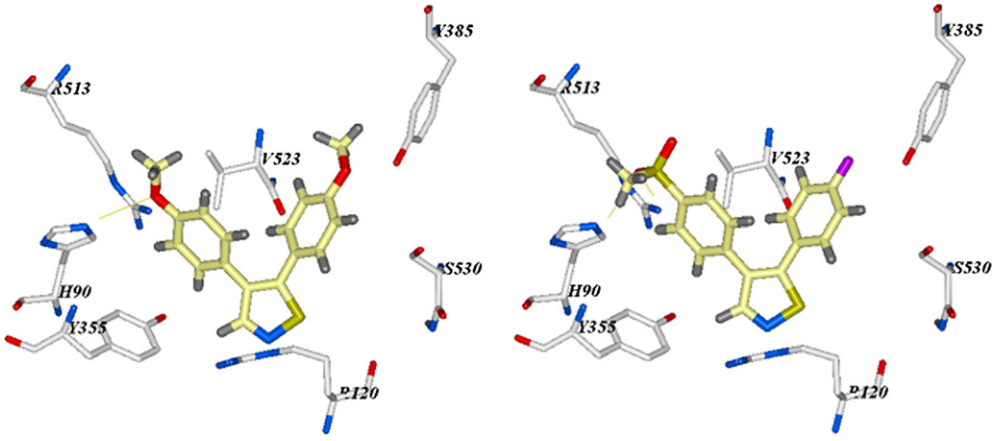


Fig. 2. Binding mode of **8a** (left) and **8h** (right) docked in COX-2 active site (COX-2 PDB file: 1CX2) using the ICM-Pro software (version 3.3-02a). Hydrogens of amino acids are not depicted for clarity.

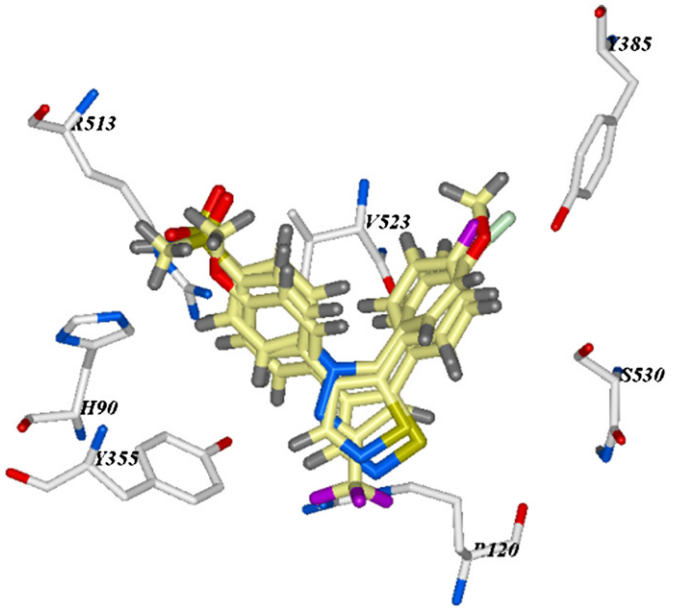


Fig. 3. Overlapping of **8a**, **8h**, and SC-558 in COX-2 (COX-2 PDB file: 1CX2) active site. Hydrogens of amino acids are not depicted for clarity.

4. Experimental section

4.1. Enzyme assays

COX-1 inhibition was determined by using platelets isolated from bovine blood, incubated with the test substance, and stimulated by the Ca ionophor A23187. The inhibition of COX-1 was assessed by quantitative HPLC determination of the formation of 12-hydroxyheptadecatrienoic acid [25].

COX-2 inhibition was determined by using aliquots of human blood samples, containing sodium heparin. The samples were incubated in the absence and presence of LPS and the test substances as described [26].

5-LOX inhibition was investigated by using bovine polymorphonuclear leucocytes, incubated with the test substance, and stimulated by the Ca ionophor A23187. The inhibition of 5-LOX was assessed by quantitative HPLC determination of the formation of leukotriene B_4 [25].

4.2. EPR spin trapping

Test assay for hydroxyl radical scavenging: DEPMPO was purchased from Calbiochem (San Diego, USA). The test solution was prepared by adding 2 μl of a solution of the test substance in acetonitrile (concentration 10, 1 or 0.1 mM/l) or pure acetonitrile, as zero value, to 192 μl demineralized water in a 1.5 ml micro-centrifuge tube. DEPMPO solution of 2 μl (20 mM/l), 2 μl $FeSO_4$ solution (5 mM/l) and 2 μl hydrogen peroxide solution (2.5 mM/l) were put on different points on the wall of the tube. The reaction was started by vortexing the tube. After 10 s a sample was gathered with a 100 μl ringcap from HIRSCHMANN® Laborgeräte and closed with wax. After exact 90 s the EPR experiment was started. Instrumental parameters were as follows: receiver gain 3.99×10^5, modulation amplitude 3.0 G, time constant 0.64 ms, conversion time 81.92 ms, attenuation 4 ms. The spectra were analyzed with the WinEPR® (Version 1.0) software. The raw data were integrated, the background noise was subtracted and the heights of the second peaks were analyzed. Each concentration was tested three times. Thioctic acid in concentrations of 10, 1 and 0.1 mM/l was used as standard substance in every test series. For an amount of 30 spectra totalling six zero values as control were analyzed.

The EPR spectra were acquired on a Bruker EMX EPR spectrometer. Melting points were determined with a Büchi apparatus according to Dr. Tottoli and are uncorrected. ^{1}H NMR spectra (300 MHz) were recorded on a Bruker AC 300 spectrometer. Combustion analyses were performed with a Carlo Erba Strumentiazione 1106 analyzer. Column chromatography was performed with Merck silica gel 60 (0.063–0.200 mm). The progress of the reactions was monitored by thin layer chromatography (TLC) performed with Merck silica gel 60 F-245 plates. All reagents and solvents were obtained from commercial sources and used as received. Reagents were purchased from Sigma–Aldrich Chemie Steinheim, Germany, or Acros, Nidderau, Germany.

4.3. Molecular modeling studies

Docking experiments were performed using ICM-Pro software (version 3.3-02a) by Molsoft. The coordinates for the X-ray crystal structure of the enzymes COX-2 were obtained from the RCSB Protein Data Base (COX-2 PDB file: 1CX2). The structure data were revised by adding the missing aromatic π systems and ionic attributes to the amino acids in the binding pocket and by adding hydrogen to all amino acids. The revised protein data were converted in the ICM format, the binding pockets were defined by searching the neighbours of the co-crystallized structure of COX-2 and SC-558, the receptor grid maps were calculated with a grid spacing of 0.5 Å, the grid was defined in such a way that it included the ligand and key residues in each of the *x*, *y*, *z* directions. For the ligands, 2D–3D conversion is followed by energy minimization using the MMFF option as a force field. The docking algorithm implemented in ICM-Pro (version 3.3-02a) optimized the entire ligand in the receptor field, applying a multistart Monte Carlo minimization procedure in internal coordinate space.

Many detailed information about the COX-2 active site are known [27–29]. It was possible to get structural information with high-resolution X-ray analysis from co-crystallized inhibitor enzyme complexes. In order to study the interactions we used the docking software ICM-Pro (version 3.3-02a) and the COX-2 enzyme protein data co-crystallized with SC-558 (PDB entry: 1CX2). After converting the PDB data in an ICM format, defining the receptor active site and generating the receptor grid maps we were able to calculate the interaction of the substances **8a** and **8h** with COX-2.

4.4. log P values

ChemDraw 8.0 from Cambridge Software was used to calculate log *P* values. To calculate the molecules containing selenium atoms method 2 is used. Method 2 is based on 120 atomic contributions evaluated from 893 molecules by least squares analysis. In addition to the atoms introduced for method 1, it can handle molecules that contain phosphorus and selenium atoms. This method works with a standard deviation of 0.50 log *P* units.

4.5. Chemistry

All compounds were analyzed for C, H, N. Elemental analysis were within 0.4% for elements unless indicated otherwise.

4.5.1. Method i: general procedure for the synthesis of 1,2-diaryl ethanoles (3)

To magnesium chippings (1.21 g, 50 mM) in anhydrous diethyl ether (10 ml) chloromethylbenzene **1a–1c** (50 mM) in anhydrous diethyl ether (10 ml) was added. The mixture was heated for half an hour. After cooling it down to rt, a solution of benzaldehyde **2a–2d** (45 mM) in anhydrous diethyl ether (10 ml) was added dropwise and thereafter heated for 2 h. After hydrolysis of the mixture with crushed ice, diluted hydrochloric acid was added and it was extracted with diethyl ether. The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure and after column chromatography (silica gel, ethyl acetate/petroleum ether 3:7) 24–95% of the alcohols **3b–3e**, **3g** or **3i** were obtained as colourless solid.

4.5.2. Method ii: general procedure for the synthesis of methylsulfonyl derivative (3h)

To a cooled (0 °C) solution of the thioether **3i** (10 mM) in dichloromethane (20 ml) was added 3-chloroperbenzoic acid (3.45 g, 20 mM) and stirred for 2 h (TLC control). The mixture was filtered, washed with sodium hydroxide solution (5% m/m) and water, dried over anhydrous Na_2SO_4 and concentrated to obtain 90% of methylsulfonyl **3h**.

4.5.3. Method iii: general procedure for the synthesis of 1,2-diaryl ethanones (6a–6e, 6g, 6h)

To a solution of the alcohol **3a–3e**, **3g**, **3h** (20 mM) in dichloromethane (60 ml) a solution of sodium dichromate (1.76 g, 6.7 mM) and concentrated sulfuric acid (1.5 ml) in water (10 ml) was slowly added (approximately 15 min). The mixture was stirred for 3 h at rt, extracted with dichloromethane, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. After column chromatography (silica gel, ethyl acetate/petroleum ether 1:1) between 20% and 60% of 1,2-diphenylethanone **6a–6e**, **6g**, **6h** were obtained as a colourless solid.

4.5.4. Method iv: general procedure for the synthesis of 1-(4-chlorophenyl)-2-(4-methoxyphenyl)ethanone (6f)

To a cooled (0 °C) suspension of $AlCl_3$ (8 g, 60 mM) in dichloromethane (50 ml) 2-(4-methoxyphenyl)acetyl chloride **4** (52.5 mM) was added dropwise. Subsequently chlorobenzene **5** (50 mM) was added at a temperature below 20 °C and stirred overnight. The mixture was poured cautiously into crushed ice and $Al(OH)_3$ precipitate was dissolved in concentrated hydrochloric acid. The reaction mixture was extracted with dichloromethane, the organic layers were washed with water, caustic soda solution (2% m/V) and water, dried over anhydrous $NaSO_4$ and concentrated under reduced pressure to obtain 40% of the 1,2-diphenylethanone derivative **6f**.

4.5.5. Method v: general procedure for the synthesis of 3-chloro-2,3-diarylacrylaldehydes (7)

Phosphoryl chloride (4 g, 26 mM) was added dropwise to a cooled (0 °C) solution of 1,2-diphenylethanone **6a–6h** (11.7 mM) in DMF (30 ml) and the temperature was kept below 10 °C. The mixture was allowed to reach rt and stirred for an hour changing the colour to yellow. Subsequently it was heated to 80 °C for 4 h (the colour changes to orange and to dark brown at the end). Vilsmeier complex was hydrolyzed by pouring it into an aqueous solution of sodium acetate (3 mol/l, 50 ml) and crushed ice if necessary. The crude product precipitated and was recrystallized from ethanol to obtain 50–95% of 3-chloro-acrylaldehyde **7a–7h**.

4.5.6. Method vi: general procedure for the synthesis of 4,5-diaryl isoselenazoles (8)

A mixture of 3-chloro-acrylaldehydes **7a–7h** (33.34 mM), ammonium chloride (5.34 g, 100 mM), and potassium selenocyanate (14.4 g, 100 mM) in acetone (80 ml) was heated under reflux for 5 h (caution: HCN formation!). After cooling to rt the mixture was poured into a solution of saturated aqueous sodium hydrogen carbonate (100 ml) and extracted three times with ether. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. After column chromatography (silica gel, ethyl acetate/petroleum ether 3:7) 30–60% of isoselenazoles **8a–8h** were obtained as yellow oil. Some of them gave hygroscopic yellow solids after drying under reduced pressure.

4.5.7. Structural data of 1,2-diaryl ethanoles (3)

4.5.7.1. 1-(4-Methoxyphenyl)-2-p-tolylethanol (3b). Method i; reactants: **1a**, **2a**; yield: 25%; ^{1}H NMR (DMSO) 7.18 (d, 8.62 Hz, 2H), 6.99 (s, 4H), 6.82 (d, 8.57 Hz, 2H), 5.12 (d, 4.55 Hz, 1H), 4.63 (dd, 11.47 Hz, 6.38 Hz, 1H), 3.70 (s, 3H), 2.79 (dq, 13.42 Hz, 13.42 Hz, 13.39 Hz, 6.71 Hz, 2H).

4.5.7.2. 1-(4-Chlorophenyl)-2-p-tolylethanol (3c). Method i; reactants: **1a**, **2b**; yield: 55%; ^{1}H NMR (DMSO) 7.26 (d, 8.26 Hz, 2H), 7.18–7.16 (d, 7.35 Hz, 2H), 7.15 (d, 8.02 Hz, 2H), 7.08 (d, 7.73 Hz, 2H), 5.23 (d, 4.52 Hz, 1H), 4.67 (m, 1H), 2.83 (d, 6.54 Hz, 2H), 2.25 (s, 3H).

4.5.7.3. 2-(4-Chlorophenyl)-1-p-tolylethanol (3d). Method i; reactants: **1b**, **2c**; yield: 50%; ^{1}H NMR (DMSO) 7.26 (d, 8.41 Hz, 2H), 7.19–7.16 (d, 7.92 Hz, 2H), 7.15 (d, 8.34 Hz,

2H), 7.08 (d, 7.95 Hz, 2H), 5.23 (d, 4.62 Hz, 1H), 4.68 (m, 1H), 2.83 (d, 6.57 Hz, 2H), 2.25 (s, 3H).

*4.5.7.4. 1,2-Bis(4-chlorophenyl)ethanol (**3e**).* Method i; reactants: **1b**, **2b**; yield: 24%; ^{1}H NMR (DMSO) 7.32 (m, 4H), 7.26 (d, 8.30 Hz, 2H), 7.14 (d, 8.32 Hz, 2H), 5.41 (d, 4.55 Hz, 1H), 4.74 (m, 1H), 2.84 (d, 6.4 Hz, 2H).

*4.5.7.5. 2-(4-Chlorophenyl)-1-(4-methoxyphenyl)ethanol (**3g**).* Method i; reactants: **1b**, **2a**; yield: 87%; ^{1}H NMR (DMSO) 7.26 (d, 8.35 Hz, 2H), 7.19 (d, 8.6 Hz, 2H), 7.14 (d, 8.35 Hz, 2H), 6.83 (d, 8.6 Hz, 2H), 5.21 (d, 4.55 Hz, 1H), 4.66 (m, 1H), 3.7 (s, 3H), 2.84 (m, 2H).

*4.5.7.6. 2-(4-Fluorophenyl)-1-(4-(methylsulfonyl)phenyl)ethanol (**3h**).* Method ii; reactant: **3i**; yield: 90%; ^{1}H NMR (DMSO) 7.84 (d, 8.33 Hz, 2H), 7.56 (d, 8.30 Hz, 2H), 7.20 (d, 8.50 Hz, 2H), 7.02 (d, 8.83 Hz, 2H), 5.74 (s, 1H), 4.84 (dd, 7.38 Hz, 5.48 Hz, 1H), 3.17 (s, 3H), 2.85 (dd, 12.49 Hz, 5.02 Hz, 2H).

*4.5.7.7. 2-(4-Fluorophenyl)-1-(4-(methylthio)phenyl)ethanol (**3i**).* Method i; reactants: **1c**, **2d**; yield: 95%; ^{1}H NMR (DMSO) 7.22 (d, 8.36 Hz, 2H), 7.15 (m, 4H), 7.03 (t, 8.93 Hz, 2H), 5.27 (d, 4.53 Hz, 1H), 4.67 (q, 6.31 Hz, 10.89 Hz, 1H), 2.83 (d, 6.55 Hz, 2H), 2.43 (s, 3H).

*4.5.8. Structural data of 1,2-diaryl ethanones (**6**)*

*4.5.8.1. 1-(4-Methoxyphenyl)-2-p-tolylethanone (**6b**).* Method iii; reactant: **3b**; yield: 55%; ^{1}H NMR (DMSO) 8.00 (d, 8.83 Hz, 2H), 7.13 (d, 8.02 Hz, 1H), 7.08 (d, 8.11 Hz, 2H), 7.02 (d, 8.93 Hz, 2H), 4.23 (s, 2H), 3.82 (s, 3H).

*4.5.8.2. 1-(4-Chlorophenyl)-2-p-tolylethanone (**6c**).* Method iii; reactant: **3c**; yield: 30%; ^{1}H NMR (DMSO) 8.03 (d, 8.55 Hz, 2H), 7.58 (d, 8.55 Hz, 2H), 7.11 (m, 4H), 4.31 (s, 2H), 2.25 (s, 3H).

*4.5.8.3. 2-(4-Chlorophenyl)-1-p-tolylethanone (**6d**).* Method iii; reactant: **3d**; yield: 27.5%; ^{1}H NMR (DMSO) 7.93 (d, 8.1 Hz, 2H), 7.42–7.3 overlapping signals (t, 7.73 Hz, 4H), 4.37 (s, 2H), 2.36 (s, 3H).

*4.5.8.4. 1,2-Bis(4-chlorophenyl)ethanone (**6e**).* Method iii; reactant: **3e**; yield: 62%; ^{1}H NMR (DMSO) 8.04 (d, 8.62 Hz, 2H), 7.61 (d, 8.61 Hz, 2H), 7.37 (d, 8.47 Hz, 2H), 7.27 (d, 8.46 Hz, 2H), 4.42 (s, 2H).

*4.5.8.5. 1-(4-Chlorophenyl)-2-(4-methoxyphenyl)ethanone (**6f**).* Method iv; reactants: **4**, **5**; yield: 50%; ^{1}H NMR (DMSO) 8.03 (d, 7.0 Hz, 2H), 7.58 (d, 6.94 Hz, 2H), 7.155 (d, 6.86 Hz, 2H), 6.86 (d, 6.9 Hz, 2H), 4.29 (s, 2H), 3.7 (s, 3H).

*4.5.8.6. 2-(4-Chlorophenyl)-1-(4-methoxyphenyl)ethanone (**6g**).* Method iii; reactant: **3g**; yield: 44%; ^{1}H NMR (DMSO) 8.01 (d, 8.59 Hz, 2H), 7.35 (d, 8.18 Hz, 2H), 7.26 (d, 7.89 Hz, 2H), 7.04 (d, 8.56 Hz, 2H), 4.33 (s, 2H), 3.83 (s, 3H).

*4.5.8.7. 2-(4-Fluorophenyl)-1-(4-(methylsulfonyl)phenyl)ethanone (**6h**).* Method iii; reactant: **3h**; yield: 60%; ^{1}H NMR (DMSO) 8.26 (d, 8.46 Hz, 2H), 8.08 (d, 8.47 Hz, 2H), 7.30 (dd, 8.43 Hz, 5.75 Hz, 2H), 7.15 (t, 8.89 Hz, 2H), 4.49 (s, 2H), 3.28 (s, 3H).

*4.5.9. Structural data of 3-chloro-2,3-diarylacrylaldehydes (**7**)*

*4.5.9.1. (Z)-3-Chloro-2,3-bis(4-methoxyphenyl)acrylaldehyde (**7a**).* Method v; reactant: **6a**; yield: 95%; ^{1}H NMR (DMSO) 9.48 (s, 1H), 7.59 (d, 8.55 Hz, 2H), 7.19 (d, 8.5 Hz, 2H), 7.09 (d, 8.55 Hz, 2H), 6.98 (d, 8.5 Hz, 2H), 3.84 (s, 3H), 3.78 (s, 3H).

*4.5.9.2. (Z)-3-Chloro-3-(4-methoxyphenyl)-2-p-tolylacrylaldehyde (**7b**).* Method v; reactant: **6b**; yield: 64%; ^{1}H NMR (DMSO) 9.49 (s, 1H), 7.60 (d, 8.77 Hz, 2H), 7.23 (d, 7.84 Hz, 2H), 7.13 (d, 8.09 Hz, 2H), 7.09 (d, 8.78 Hz, 2H), 3.83 (s, 3H).

*4.5.9.3. (Z)-3-Chloro-3-(4-chlorophenyl)-2-p-tolylacrylaldehyde (**7c**).* Method v; reactant: **6c**; yield: 68%; ^{1}H NMR (DMSO) 9.49 (s, 1H), 7.7 (d, 8.11 Hz, 2H), 7.62 (d, 6.42 Hz, 2H), 7.24 (d, 7.34 Hz, 2H), 7.18 (d, 7.09 Hz, 2H), 2.33 (s, 3H).

*4.5.9.4. (Z)-3-Chloro-2-(4-chlorophenyl)-3-p-tolylacrylaldehyde (**7d**).* Method v; reactant: **6d**; yield: 57%; ^{1}H NMR (DMSO) 9.47 (s, 1H), 7.57 (d, 7.26 Hz, 2H), 7.5 (d, 6.84 Hz, 2H), 7.36 (d, 7.9 Hz, 2H), 7.3 (d, 8.24 Hz, 2H), 2.39 (s, 3H).

*4.5.9.5. (Z)-3-Chloro-2,3-bis(4-chlorophenyl)acrylaldehyde (**7e**).* Method v; reactant: **6e**; yield: 90%; ^{1}H NMR (DMSO) 9.47 (s, 1H), 7.73 (d, 8.55 Hz, 2H), 7.63 (d, 8.42 Hz, 2H), 7.52 (d, 8.45 Hz, 2H), 7.32 (d, 8.47 Hz, 2H).

*4.5.9.6. (Z)-3-Chloro-3-(4-chlorophenyl)-2-(4-methoxyphenyl)-acrylaldehyde (**7f**).* Method v; reactant: **6f**; yield: 64%; ^{1}H NMR (DMSO) 9.49 (s, 1H), 7.69 (d, 8.56 Hz, 2H), 7.61 (d, 8.60 Hz, 2H), 7.22 (d, 8.69 Hz, 2H), 6.99 (d, 8.72 Hz, 2H), 3.78 (s, 3H).

*4.5.9.7. (Z)-3-Chloro-2-(4-chlorophenyl)-3-(4-methoxyphenyl)-acrylaldehyde (**7g**).* Method v; reactant: **6g**; yield: 64%; ^{1}H NMR (DMSO) 9.48 (s, 1H), 7.63 (d, 8.69 Hz, 2H), 7.5 (d, 8.41 Hz, 2H), 7.3 (d, 8.41 Hz, 2H), 7.1 (d, 8.73 Hz, 2H), 3.85 (s, 3H).

*4.5.9.8. (Z)-3-Chloro-2-(4-fluorophenyl)-3-(4-(methylsulfonyl) phenyl)acrylaldehyde (**7h**).* Method v; reactant: **6h**; yield: 20%; ^{1}H NMR (DMSO) 9.46 (s, 1H), 8.08 (d, 8.06 Hz, 2H), 7.96 (d, 8.13 Hz, 2H), 7.42–7.20 (m, 4H), 3.29 (s, 3H).

*4.5.10. Structural data of 4,5-diaryl isoselenazoles (**8**)*

*4.5.10.1. 4,5-Bis(4-methoxyphenyl)-1,2-selenazole (**8a**).* Method vi; reactant: **7a**; yield: 56%; mp: 79 °C; ^{1}H NMR (DMSO) 9.48 (s, 1H), 7.59 (d, 8.69 Hz, 2H), 7.19 (d, 8.69 Hz,

2H), 7.09 (d, 8.72 Hz, 2H), 6.98 (d, 8.72 Hz, 2H), 3.84 (s, 3H), 3.78 (s, 3H). Anal ($C_{17}H_{15}NO_2Se \times 2/5\ C_3H_6O$) C, H, N, S.

*4.5.10.2. 5-(4-Methoxyphenyl)-4-p-tolyl-1,2-selenazole (**8b**).* Method vi; reactant: **7b**; yield: 21%; mp: 85 °C; ^{1}H NMR (DMSO) 9.18 (s, 1H), 7.22–7.14 (m, 6H), 6.91 (d, 8.77 Hz, 2H), 3.74 (s, 3H), 2.29 (s, 3H). Anal ($C_{17}H_{15}NOSe \times 4/9\ C_6H_{14}$) C, H, N.

*4.5.10.3. 5-(4-Chlorophenyl)-4-p-tolyl-1,2-selenazole (**8c**).* Method vi; reactant: **7c**; yield: 61%; mp: 91 °C; ^{1}H NMR (DMSO) 9.25 (s, 1H), 7.44 (d, 8.51 Hz, 2H), 7.28 (d, 8.52 Hz, 2H), 7.18 (s, 4H), 2.29 (s, 3H). Anal ($C_{16}H_{12}ClNSe$) C, H, N, S.

*4.5.10.4. 4-(4-Chlorophenyl)-5-p-tolyl-1,2-selenazole (**8d**).* Method vi; reactant: **7d**; yield: 48%; mp: 108 °C; ^{1}H NMR (DMSO) 9.25 (s, 1H), 7.43 (d, 8.55 Hz, 2H), 7.31 (d, 8.54 Hz, 2H), 7.19 (d, 8.29 Hz, 2H), 7.16 (d, 8.07 Hz, 2H), 2.29 (s, 3H). Anal ($C_{16}H_{12}Cl_2NSe \times 1/5\ C_6H_{14}$) C, H, N, S.

*4.5.10.5. 4,5-Bis(4-chlorophenyl)-1,2-selenazole (**8e**).* Method vi; reactant: **7e**; yield: 58%; mp: 89 °C; ^{1}H NMR (DMSO) 9.29 (s, 1H), 7.46 (d, 8.3 Hz, 2H), 7.44 (d, 8.02 Hz, 2H), 7.31 (d, 8.46 Hz, 2H), 7.28 (d, 8.47 Hz, 2H). Anal ($C_{15}H_9Cl_2NSe \times 1/3\ C_3H_6O$) C, H, N, S.

*4.5.10.6. 5-(4-Chlorophenyl)-4-(4-methoxyphenyl)-1,2-selenazole (**8f**).* Method vi; reactant: **7f**; yield: 40%; mp: 78 °C; ^{1}H NMR (DMSO) 9.25 (s, 1H), 7.45 (d, 8.44 Hz, 2H), 7.29 (d, 8.51 Hz, 2H), 7.22 (d, 8.67 Hz, 2H), 6.93 (d, 8.44 Hz, 2H), 3.75 (s, 3H). Anal ($C_{16}H_{12}ClNOSe \times 1/2\ C_3H_6O$) C, H, N, S.

*4.5.10.7. 4-(4-Chlorophenyl)-5-(4-methoxyphenyl)-1,2-selenazole (**8g**).* Method vi; reactant: **7g**; yield: 67%; ^{1}H NMR (DMSO) 9.22 (s, 1H), 7.43 (d, 8.33 Hz, 2H), 7.32 (d, 8.37 Hz, 2H), 7.2 (d, 8.55 Hz, 2H), 6.94 (d, 8.54 Hz, 2H), 3.75 (s, 3H). Anal ($C_{16}H_{12}ClNOSe$) C, H, N, S.

*4.5.10.8. 4-(4-Fluorophenyl)-5-(4-(methylsulfonyl)phenyl)-1,2-selenazole (**8h**).* Method vi; reactant: **7h**; yield: 58%; mp: 150 °C; ^{1}H NMR (DMSO) 9.33 (s, 1H), 7.91 (d, 8.52 Hz, 2H), 7.52 (d, 8.53 Hz, 2H), 7.35 (dd, 8.86 Hz, 5.49 Hz, 2H), 7.23 (t, 8.92 Hz, 2H), 3.24 (s, 3H).

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