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Syntheses and biological activities of sulfoximine-based acyclic triaryl olefins

Xiao Yun Chen [a], Seong Jun Park [a], Helmut Buschmann [b], Maria De Rosa [a,†], Carsten Bolm [a,*]

[a] Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, D-52056 Aachen, Germany
[b] Sperberweg 15, D-52076 Aachen, Germany

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ABSTRACT

Sulfoximine-based acyclic triaryl olefins **8** and **9** have been prepared and initial studies have been performed to determine their biological profiles. In contrast to their sulfonyl-substituted analog **2** sulfoximines **8** and **9** show low COX inhibitory activity. All compounds affect the estrogen receptors. While sulfone **2** interacts exclusively with ER β, sulfoximines **8** and **9** reveal almost equal blocking potencies for both estrogen receptors, ER α and ER β. In the tested series, triaryl olefin **9a** shows the highest inhibitory activities with 91% and 80%, respectively (at 10 μM).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are amongst the most widely used pharmaceutical agents for the treatment of inflammatory conditions. They exert their effect by inhibiting the biosynthesis of prostaglandins (PGs), which are formed from arachidonic acid. A key enzyme in this process is cyclooxygenase (COX), which appears in two isoforms (COX-1 and COX-2). Comprehensive studies led to the conclusion that selective COX-2 inhibitors (COXIBs) would be potent anti-inflammatory agents lacking the toxicities and negative effects associated with the inhibition of COX-1 (e.g., gastrointestinal ulceration, perforation and hemorrhage).[1] Although the reports of cardiovascular risk and the subsequent withdrawal of rofecoxib and valdecoxib have called COX-2 selective inhibitors into question,[2] recent findings revived interest in such compounds because long-term use of COXIBs led to a decrease in death rate from several cancers such as colorectal, stomach, breast, prostate, bladder, and ovarian cancer.[3] Furthermore, COX-2 over-expression was related to critical components of breast cancer including mutagenesis, angiogenesis, inhibition of apoptosis and aromatase-catalyzed estrogen biosynthesis. Based on the hypothesis that COX-2 and COX-2-derived PGE_2 play a role in breast tumor initiation and progression, COXIBs became attractive target for breast cancer prevention.[4] More recently, additional clinical applications of COX-2 inhibitors have been considered, but they have yet to be confirmed.[5]

A common structural feature of COXIBs is a *cis* orientation of two aromatic substituents fixed by a hetero- or carbocyclic core with one of the arenes having a sulfonyl or sulfonamido group in *para* position (as, for example, in VIOXX® (**1**), Fig. 1). Those polar molecular units insert into the pocket of the COX-2 active site and result in the formation of hydrogen bonds with several chain residues.[6,7] The hypothesis that such binding would be affected by the nature of the sulfur substituent stimulated our recent work on COXIBs with sulfoximidoyl substituents.[8] As shown by Knaus and co-workers the required *cis* arrangement of the two arenes can also be affected by an olefinic bridge as in triaryl alkene **2**, which revealed high COX inhibitory activity with significant COX-2 selectivity as well.[9]

The structure of alkene **2** is reminiscent of other tetrasubstituted olefins, which have the potential for broad medicinal applications. For example, Tamoxifen (**3**) is a well-established selective estrogen receptor modulator (SERM) used for the prevention and treatment of diseases such as osteoporosis and breast cancer.[10,11]

Sulfoximines **5** are monoaza analogs of sulfones **4** with several appealing features for drug development.[12] For example, their core represents a small hydrophilic functional group with a potential diversity point at the imine nitrogen, hydrogen bond acceptors at the sulfur-bound heteroatoms, and, in the case of *N*H-sulfoximines (R″ = H), a hydrogen bond donor. Consequently, sulfoximines have already found various bio-relevant applications,[13] and recent interest is best illustrated by the significant number of contributions reporting the use of this so far underrepresented molecular scaffold in medicinal and crop protection chemistry.[14,15]

In our previous study on sulfoximine-based Vioxx® analogs, we showed that the O/NH-exchange (from the sulfone to the corresponding sulfoximine) had a beneficial effect resulting in a moderately COX-inhibiting compound with reduced hERG inhibitory activity.[8,16] Encouraged by these results, we aimed to explore an extension of this concept using sulfonyl-substituted triaryl olefin

* Corresponding author.
E-mail address: Carsten.Bolm@oc.rwth-aachen.de (C. Bolm).
† Present address: Department of Medicinal Chemistry, Uppsala University, Box 574, SE-751 23 Uppsala, Sweden.

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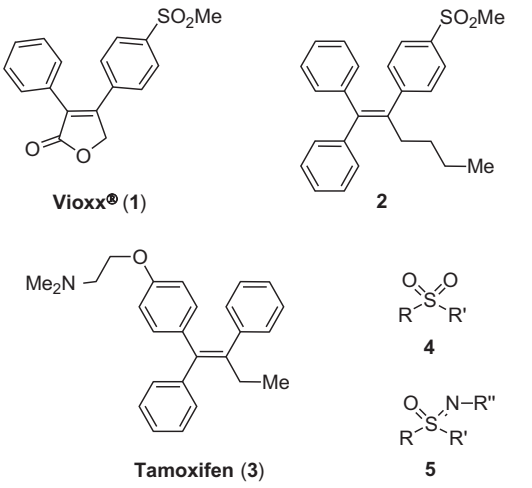
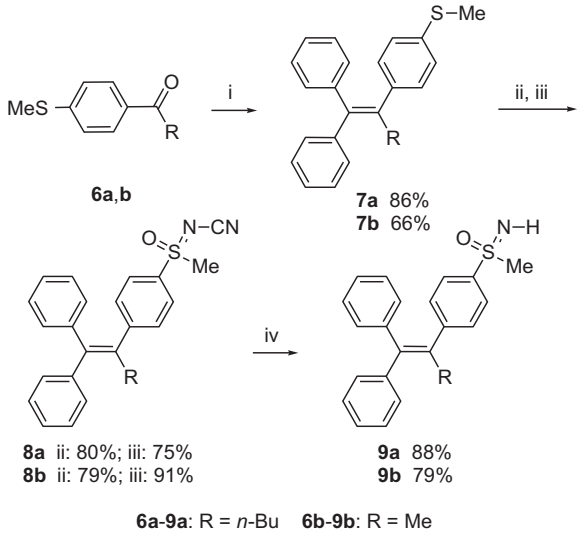


Figure 1. Bioactive compounds containing tetrasubstituted double bonds; sulfone and sulfoximine core structures.



Scheme 1. Reagents and conditions: (i) Benzophenone, $TiCl_4$ (1 M solution in DCM), Zn, dry THF, reflux 4.5 h; (ii) $PhI(OAc)_2$, NH_2CN, CH_3CN, 0 °C, 1.5 h; (iii) K_2CO_3, *m*-CPBA, MeOH, 0 °C to rt, 1.5 h; (iv) aqueous H_2SO_4 (50%), 110 °C, 4 h.

2 as starting point. Here, we report on the syntheses of sulfoximine-based analogs **8** and **9**, their COX-1/2 inhibitory activities and blocking potencies of both estrogen receptors, ER α and ER β.

Sulfoximines **8** and **9** were prepared by a combination of published procedure[9] and methods developed in our laboratories (Scheme 1).[17,18] Accordingly, compounds **7** were prepared by McMurry olefinations starting from ketones **6** and benzophenone. Metal-free oxidative imination with NH_2CN and $PhI(OAc)_2$ followed by oxidation of the intermediately formed *N*-cyano sulfilimines (not shown) with *m*-CPBA combined with K_2CO_3 in methanol afforded *N*-cyano sulfoximines **8** in high yields. The corresponding *N*H-sulfoximines **9** were then generated using 50% aqueous H_2SO_4 for the removal of the cyano group.[19]

The inhibition studies involved *N*-cyano sulfoximine **8a** and *N*H-sulfoximines **9a** and **9b**. Those compounds were evaluated in vitro on their inhibitory activities against the two COX isoenzymes (from human platelets and human recombinant insect Sf21 cells for COX-1 and COX-2, respectively, with arachidonic acid as substrate) and their binding affinities for the two estrogen receptors,

Table 1
COX-1, COX-2, ER α and ER β inhibitory data

Entry	Compd	N subst.	R	% Inhibition (at 10 μM)			
				COX-1	COX-2	estrogen ER α	estrogen ER β
1	**2**		*n*-Bu	–[a]	–[a]	−6	77
2	**8a**	CN	*n*-Bu	5	10	54	60
3	**9a**	H	*n*-Bu	12	17	91	80
4	**9b**	H	Me	23	−13	77	53

[a] In vitro IC_{50} values reported in Ref. 9: COX-1 = >100 μM, COX-2 = 0.014 μM.

ER α and ER β. Indomethacin (for COX-1), Vioxx® (for COX-2) and diethylstilbestrol (for ER α and ER β) were used as reference compounds in those biological tests.[20]

Based on the excellent results by Knaus and co-workers, who found a remarkable COX-2 inhibitory potency in combination with an extraordinary COX-2 selectivity for sulfonyl-substituted triaryl olefin **2** (COX-1: IC_{50} >100 μM; COX-2: IC_{50} 0.014 μM), we presumed sulfoximines **8** and **9** to provide results in a comparable range. However, to our disappointment all three compounds were essentially inactive. Neither *N*-cyano sulfoximine **8a** nor *N*H-sulfoximines **9a** and **9b** showed a significant COX inhibition (5–23%; Table 1). Although this outcome was dissatisfying, the comparison of the binding behavior of the two direct analogs sulfone **2** and sulfoximine **9a** led to an interesting conclusion. Apparently, the substitution of a single oxygen atom (as in sulfone **2**) by a *N*H unit (as in the corresponding sulfoximines **9a**) led to a significant activity change. On the molecular level this was surprising because the docking studies by Knaus and co-workers had suggested the sulfonyl unit to be doubly hydrogen-bonded in the COX-2 active site (through the N*H* of Phe^{518} and a NH_2 of Arg^{513}),[9] and we expected the sulfoximine nitrogen to be a better H-bond acceptor than the two oxygens of the sulfone. In this particular case, however, the data appear to indicate that the binding mode of the two analogs (**2** and **9a**) was very different and that, perhaps, the sulfoximine *N*H was even a H-donor.

The estrogen binding affinities of sulfoximines **8** and **9** were evaluated using human recombinant enzymes.[20] In this case, sulfone **2** was employed as reference compound. The data are summarized in Table 1. While compound **2** was a good ER β selective agent with no affinity to ER α (entry 1)[21] the three sulfoximines showed a different behavior (entries 2–4). For all of them moderate to high blocking potencies for both estrogen receptors with essentially no ER αβ selectivity were found. *N*H-Sulfoximine **9a** was the most active compound with 91% and 80% inhibition for ER α and ER β, respectively, at 10 μM. In line with the observations made in the COX inhibition studies described above, the replacement of a single oxygen atom by a *N*H unit had a major impact. This can best be seen when comparing the results of sulfone **2** with those of *N*H-sulfoximine **9a** (Table 1, entry 1 vs entry 3). While the former is a good, highly selective ER β binder, the latter shows significantly better receptor inhibition but lacks the ER αβ selectivity. To draw conclusions on molecular level and to speculate on potential arrangements of the molecules in the binding sites of ER α and ER β is difficult, because, to the best of our knowledge, docking studies with neither sulfone **2** nor any sulfoximines on estrogen receptors have yet been performed. If the hydrogen bonding scheme is relevant in this case as well, as suggested above for the alternation of the COX binding behavior of sulfone **2** and the sulfoximines, remains to be established.

In conclusion, we prepared sulfoximine-based acyclic triaryl olefins and investigated their inhibitory effects against COX-1 and COX-2 as well as their binding affinities to both estrogen receptors, ER α and ER β. Those results were compared with the ones obtained in studies of a sulfonyl-substituted analog. Interestingly, the sulfonimidoyl group had a major impact on the enzyme

inhibition and receptor binding. In contrast to the sulfone-based analog, all sulfoximines showed low COX inhibitory potency. Also their binding to the estrogen receptors differed. While the sulfone was selective and moderately active for ER β, the sulfoximines were essentially ER αβ unselective with remarkable inhibitions of up to 91% and 80% for ER α and ER β, respectively. Subsequent studies shall focus on testing these and other sulfoximine-based molecules in additional enzyme inhibitory assays and confirm the opportunities on modifying biological profiles by replacing single atoms by other molecular units in core fragments of drug-like molecules.[22]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.05.018.

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18. *Selected data for product characterization*: Compound **8a** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72–7.65 (m, 2H), 7.37–7.13 (m, 7H), 7.04–6.89 (m, 3H), 6.82–6.74 (m, 2H), 3.23 (s, 3H), 2.42 (t, 2H, J = 7.8 Hz), 1.44–1.08 (m, 4H), 0.73 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 142.44, 142.39, 141.9, 138.8, 133.2, 131.5, 130.7, 129.3, 128.4, 128.0, 127.5, 127.4, 126.9, 111.9, 45.0, 35.42, 31.2, 22.8, 13.9; IR (KBr): υ = 2195, 1249, 1090, 967 cm^{-1}; MS (EI), m/z (relative intensity) 414 [M$^+$, 100], 373 [31], 315 [58], 267 [14], 167 [15], 91 [17]; **8b** ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, 2H, J = 8.6 Hz), 7.44 (d, 2H, J = 8.6 Hz), 7.38–7.22 (m, 7 H), 7.10–7.04 (m, 2H), 6.90–6.84 (m, H), 3.29 (s, 3 H), 2.18 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.2, 142.7, 142.3, 141.8, 133.1, 133.0, 131.1, 130.7, 129.7, 128.7, 128.3, 127.9, 127.5, 127.3, 125.9, 44.8, 22.8; IR (KBr): υ = 2195, 1097, 965 cm^{-1}; **9a** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75–7.65 (m, 2H), 7.34–7.13 (m, 7H), 7.01–6.88 (m, 3H), 6.84–6.75 (m, 2H), 3.01 (s, 3H), 2.40 (t, 2H, J = 7.8 Hz), 1.45–1.09 (m, 4H), 0.72 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 142.8, 142.3, 141.3, 140.9, 139.5, 130.74, 130.6, 129.4, 128.4, 127. 8, 127.4, 127.1, 126.5, 46.4, 35.6, 31.2 22.9, 14.0; IR (KBr): υ = 3180, 1261, 1214, 1090, 1006 cm^{-1}; Anal. Calcd for $C_{25}H_{27}NOS$: C 77.08, H 6.99, N 3.60, found: C 76.89, H 7.158, N 3.52; HRMS (ESI), m/z: [M+H] Calcd for $C_{25}H_{27}NOS$ 390.1886, found 390.1891; **9b** ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, 2H, J = 8.4 Hz), 7.40–7.23 (m, 9H), 7.06–7.02 (m, 2H), 6.93–6.80 (m, 1H), 3.06 (s, 3H), 2.31 (bs, 1H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.6, 142.7, 142.2, 141.5, 140.7, 133.8, 130.7, 130.2, 129.8, 128.2, 127.7, 127.3, 127.0, 126.5, 46.2, 23.0; IR (KBr): υ = 3274, 1220, 1069, 969 cm^{-1}; Anal. Calcd for $C_{22}H_{21}NOS$: C 76.04, H 6.09, N 4.03, found: C 75.17, H 5.67, N 3.86; HRMS (ESI), m/z: [M+H] Calcd for $C_{22}H_{21}NOS$ 348.1415, found 348.1417.
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