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Synthesis and cyclooxygenase inhibition of various (aryl-1,2,3-triazole-1-yl)-methanesulfonylphenyl derivatives

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ABSTRACT

A series of 1,4- and 1,5-diaryl substituted 1,2,3-triazoles was synthesized by either Cu(I)-catalyzed or Ru(II)-catalyzed 1,3-dipolar cycloaddition reactions between 1-azido-4-methane-sulfonylbenzene **9** and a panel of various *para*-substituted phenyl acetylenes (4-H, 4-Me, 4-OMe, 4-NMe_2, 4-Cl, 4-F). All compounds were used in in vitro cyclooxygenase (COX) assays to determine the combined electronic and steric effects upon COX-1 and COX-2 inhibitory potency and selectivity. Structure-activity relationship studies showed that compounds having a vicinal diaryl substitution pattern showed more potent COX-2 inhibition (IC_{50} = 0.03–0.36 μM) compared to their corresponding 1,3-diaryl-substituted counterparts (IC_{50} = 0.15 to >10.0 μM). In both series, compounds possessing an electron-withdrawing group (Cl and F) at the *para*-position of one of the aryl rings displayed higher COX-2 inhibition potency and selectivity as determined for compounds containing electron-donating groups (Me, OMe, NMe_2). The obtained data show, that the central carbocyclic or heterocyclic ring system as found in many COX-2 inhibitors can be replaced by a central 1,2,3-triazole unit without losing COX-2 inhibition potency and selectivity. The high COX-2 inhibition potency of some 1,2,3-triazoles having a vicinal diaryl substitution pattern along with their ease in synthesis through versatile Ru(II)-catalyzed click chemistry make this class of compounds interesting candidates for further design and synthesis of highly selective and potent COX-2 inhibitors.

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most important class of widely used therapeutics for the treatment of inflammation and pain. The principle pharmacological effects of NSAIDs arise from their inhibition of cyclooxygenase enzymes. Cyclooxygenases (COXs) control the complex conversion of arachidonic acid to prostaglandins and thromboxanes, which trigger as autocrine and paracrine chemical messengers many physiological and pathophysiological responses.[1–3] COX is a membrane-bound heme protein which exists in two distinct isoforms, a constitutive form (COX-1) and an inducible form (COX-2). More recently, a novel COX-1 splice variant termed as COX-3 has been reported.[4] COX-1 and COX-2 share the same substrates, produce the same products and catalyze the same reaction using identical catalytic mechanisms, but differ in substrate and inhibitor selectivity. The COX-1 enzyme is responsible for maintaining homeostasis (gastric and renal integrity) whereas COX-2 induces inflammatory conditions. Besides being associated with inflammation and pain, it is also well documented that especially COX-2 is overexpressed in many human cancer entities.[5,6]

Since the discovery of the COX-2 enzyme in the early 1990s, many efforts have been made in the development of COX-2 selective inhibitors. Because of the structural similarities of the COX-1 and COX-2 enzymes, the search for selective inhibitors for COX-2 versus COX-1 represents a formidable challenge. A large number of compounds has been investigated for selective COX-2 inhibition. A common structural feature of many selective COX-2 inhibitors is the presence of two vicinal aryl rings attached to a central 5-membered heterocyclic (compounds **1**–**4**) or carbocyclic (compounds **5**–**6**) motif. A selection of different selective COX-2 inhibitors containing the diaryl 5-membered carbocycle/heterocycle scaffold is depicted in Figure 1.

Selective COX-2 inhibitors as shown in Fig. 1 demonstrate, that a broad variety of 5-membered carbocycles and heterocycles are acceptable for binding to the cyclooxygenase active site. A recent review on the current status of COX-2 inhibitors further confirms the flexibility of the carbocyclic/heterocyclic core motif for COX-2 binding.[7] However, among the multitude of known 5-membered heterocycles as selective COX-2 inhibitors, to the best of our knowledge no 1,2,3-triazoles have been reported yet. 1,2,3-Triazoles possess favorable properties for medicinal chemistry such

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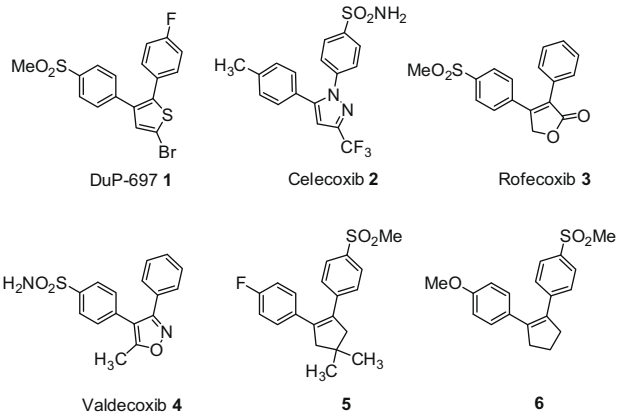


Figure 1. Selection of selective COX-2 inhibitors with a diaryl-substituted 5-membered carbocycle/heterocycle scaffold.

as a moderate dipole character, hydrogen bonding capability, rigidity and stability under in vivo conditions.[8]

An exciting recent development in organic chemistry and medicinal chemistry is the renaissance of the well-established Huisgen [3+2] cycloaddition reaction between terminal alkynes and azides through the introduction of copper and ruthenium complexes to regioselectively catalyze 1,2,3-triazole formation. Application of copper(I)-catalyzed [3+2] cycloaddition between azides and alkynes affords 1,4-disubstituted 1,2,3-triazoles as the single regioisomers, whereas the use of ruthenium complexes leads to the formation of the corresponding 1,5-disubstituted 1,2,3-triazoles.[9,10]

We have an ongoing interest in imaging COX-2 functional expression in vivo by means of positron emission tomography (PET). For this purpose, we have synthesized various COX-2 inhibitors labeled with the short-lived positron emitters fluorine-18 (^{18}F, $t_{1/2}$ = 109.8 min)[11] and carbon-11 (^{11}C, $t_{1/2}$ = 20.4 min).[12] Recently, we have reported on the synthesis and radiopharmacological evaluation in vitro and in vivo of ^{11}C-labeled compound **6** as potential PET radiotracer for imaging COX-2. Despite the promising high affinity and selectivity of compound **6** towards COX-2, however, the corresponding ^{11}C-labeled compound **6** displayed unfavorable radiopharmacological profile in rats and tumor-bearing mice, mainly due to high metabolic instability and high nonspecific binding.[12] In this line, replacement of the central cyclopentene moiety with a 1,2,3-triazole heterocyclic ring system should lead to compounds with lower lipophilicity, which would improve radiopharmacological profile through reduction of nonspecific binding in vivo.

In this paper, we report on the synthesis and in vitro COX-1 and COX-2 inhibitory activity for a series of 1,4- and 1,5-diaryl substituted 1,2,3-triazoles possessing a SO_2Me group as COX-2 pharmacophore at the *para*-position of one of the aryl rings. 1,4- and 1,5-diaryl substituted 1,2,3-triazoles were synthesized by either Cu(I)-catalyzed or Ru(II)-catalyzed 1,3-dipolar cycloaddition reactions between 1-azido-4-methane-sulfonylbenzene **9** and a panel of various *para*-substituted phenyl acetylenes (4-H, 4-Me, 4-OMe, 4-NMe_2, 4-Cl, 4-F).

2. Chemistry

The copper(I)-catalyzed [3+2] cycloaddition between terminal alkynes and organic azides to form regiospecifically 1,4-disubstituted 1,2,3-triazoles, also referred to as click chemistry, is among the most exciting recent developments in medicinal chemistry. An extension of the [3+2] cycloaddition click chemistry reaction between organic azides and terminal alkynes was recently described by Zhang and co-workers.[10] They report on the use of ruthenium(II) complexes instead of copper(I) for the cycloaddition reaction, which led exclusively to the formation of the corresponding 1,5-disubstituted 1,2,3-triazoles. We therefore decided to exploit both metal-catalyzed [3+2] cycloaddition reactions for the construction of 1,2,3-triazoles containing either a 1,4- or 1,5-disubstitution pattern, respectively, as potential COX-2 inhibitors. For this purpose we first prepared 1-azido-4-(methanesulfonyl)benzene **9** as aromatic azide possessing the SO_2Me COX-2 pharmacophore for subsequent [3+2] cycloaddition reactions with various commercially available *para*-substituted phenyl acetylenes. The synthesis of aromatic azide **9** from commercially available 4-(methylthio)aniline **7** was accomplished under mild conditions with *tert*-butylnitrite and azidotrimethylsilane.[13] 4-(Methylthio)aniline **7** undergoes diazotation with *tert*-butylnitrite at 0 °C. The formed diazonium salt was easily converted into aromatic azide **8** in the presence of azidotrimethylsilane at room temperature. Subsequent oxidation of 4-azido-thioanisole **8** with Oxone® gave 1-azido-4-(methyl-sulfonyl)benzene **9** in excellent 95% yield for both steps. The synthesis of compound **9** is illustrated in Figure 2.

With aromatic azide **9** and a panel of various *para*-substituted phenyl acetylenes (4-H, 4-Me, 4-OMe, 4-NMe_2, 4-Cl, 4-F) in hand, we performed two different click chemistry routes to prepare the desired 1,4-diaryl-substituted triazoles **10a–f** and 1,5-diaryl-substituted triazoles **11a–f** (Fig. 3).

In a first set of reactions, we employed the Cu(I)-catalyzed [3+2] cycloaddition reaction between azide **9** and various phenyl acetylenes to prepare regioselectively triazoles **10a–f** possessing a 1,4-diaryl substitution pattern. For this purpose, equimolar amounts of aryl acetylenes and azide **9** were reacted in a mixture of EtOH/H_2O in the presence 10 mol % CuI and triethylamine (TEA) at 60 °C for 24 h to give triazoles **10a–f** in good yields (79–88%). All compounds were obtained as pure solids without the need for further purification. ^{1}H NMR analysis showed a characteristic signal between 8.13 Hz and 8.29 Hz, which is indicative of the proton in 1,2,3-triazoles containing the 1,4 substitution pattern.

Based on the intriguing finding that replacement of Cu(I) with Ru(II) complexes for click chemistry between organic azides and terminal alkynes leads to the formation of 1,5-substituted tria-

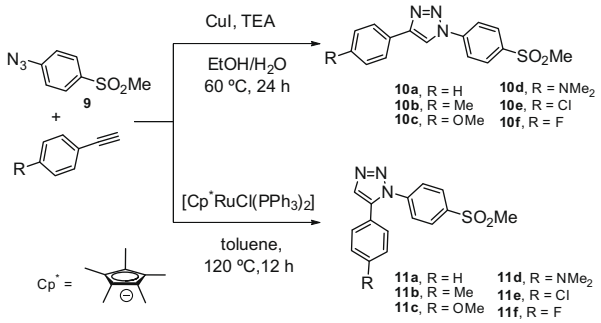


Figure 3. Copper- and ruthenium-catalyzed [3+2] cycloaddition between aromatic azide **9** and various phenyl acetylenes.

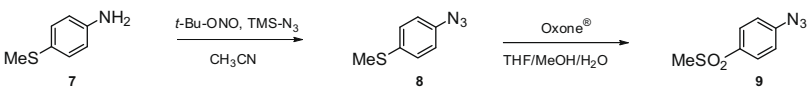


Figure 2. Synthesis of 1-azido-4-(methylsulfonyl)benzene **9**.

zoles, we set up a series of Ru-catalyzed reactions to afford 1,5-substituted 1,2,3-triazoles **11a–f**. According to literature, we choose $[Cp^*RuCl(PPh_3)_2]$ as the most suitable ruthenium complex for this reaction.[10] Unlike the Cu(I)-catalyzed reaction, Ru(II)-catalyzed click chemistry reaction between azide **9** and aryl acetylenes required more drastic reaction conditions in an aprotic solvent (toluene) at elevated temperature (120 °C). However, the desired 1,5-substituted 1,2,3-triazoles **11a–f** were obtained in much lower chemical yields (10–27%) compared to compounds **10a–f**. Moreover, 1,5-substituted 1,2,3-triazoles **11a–f** required purification by means of flash chromatography to afford sufficiently pure compounds. Consequently, the obtained low chemical yields, and the tedious isolation and purification of compounds **11a–11** via Ru(II)-catalyzed [3+2] cycloaddition reaction does not meet the criteria of click chemistry as proposed by Kolb and Sharpless.[8]

The obtained low chemical yield is somewhat surprising, since high chemical yields in the range of 80–94% were reported by Zhang and co-worker.[10] However, Zhang and co-worker were using phenyl azide as the azide component, whereas in our reaction we used more polar methylsulfone **9** as the aromatic azide component, which may have an detrimental effect on the Ru(II)-catalyzed [3+2] cycloaddition. The 1,5 substitution pattern was confirmed by the characteristic high-field-shifted ^1H NMR signals (7.78–7.88 Hz) as typically observed for the 1,2,3-triazole ring proton in compounds **11a–f**.[10]

3. Results and discussion

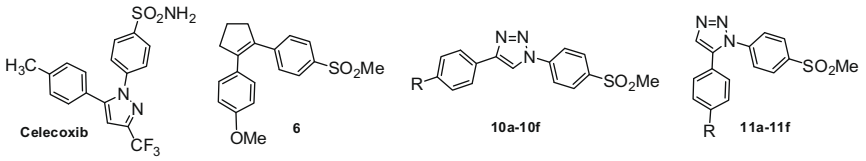
Various structure-activity relationship (SAR) studies have revealed that tricyclic compounds possessing two vicinal aryl moieties on the central heterocyclic ring system represent the major class of selective COX-2 inhibitors.[7] Moreover, the SO_2Me COX-2 pharmacophore at the *para*-position of one of the aryl rings was shown to frequently confer optimal COX-2 selectivity and potency.[14] However, various classes of compounds lacking the traditional tricyclic ring motif having a vicinal diaryl substitution pattern have also been reported as potent and selective COX-2 inhibitors. Prominent examples comprise diarylurea derivatives,[15] acyclic triaryl (*Z*)-olefins,[16] linear diaryl-substituted acetylenes,[17] and diaryl-substituted isoindole derivatives showing an uncommon 1,3-substitution pattern for the aryl rings.[18]

Based on two different metal-catalyzed [3+2] cycloaddition reactions between 1-azido-4-methane-sulfonylbenzene **9** and various phenyl acetylenes, we have prepared two classes of compounds possessing a central 1,2,3-triazole moiety. Performance of the Cu(I)-catalyzed reaction exclusively yielded 1,4-diaryl 1,2,3-triazoles **10a–f** as single regioisomers. This class of compounds exhibits a comparable molecule geometry as for various highly potent and selective COX-2 inhibitors based on 1,3-diaryl-substituted isoindoles.[18] On the other hand, 1,5-diaryl-substituted compounds **11a–f** having the preferred two vicinal aryl moieties, could be obtained through Ru(II) complex-catalyzed reaction. This class of compounds is structurally related to traditional selective COX-2 inhibitors consisting of a heterocyclic central ring scaffold with two vicinal aryl substitutents.[7] All compounds (**10a–f** and **11a–f**) possess the typical SO_2Me COX-2 pharmacophore in the *para*-position of one of the aryl rings attached to the central 1,2,3-triazole unit. To determine the resulting combined different steric and electronic effects upon COX-1 and COX-2 inhibitory potency and COX isoenzyme selectivity, all compounds were evaluated in in vitro COX inhibition assays. Celecoxib **2** and compound **6** are known highly potent and selective COX-2 inhibitors, which were used as reference compounds.[12,19] The determined enzyme inhibition data, along with calculated in vitro COX-2 selectivity index (COX-2 SI) and calculated lipophilicity values ($Log P_{o/w}$) are summarized in Table 1.

As expected, compound **6** proved to be a potent and selective COX-2 inhibitor in the performed enzyme inhibitory assay. The determined inhibitory activity with IC_{50} value of 7 nM for COX-2 is in the same range as reported in the literature, whereas the determined IC_{50} value of 5 μM against COX-1 is lower as in literature.[19] For further comparison, we also determined COX-1 and COX-2 inhibition of potent COX-2 inhibitor celecoxib **2**.

The first series of compounds (**10a–f**) containing the uncommon 1,3-disubstitution pattern of the aryl moieties showed interesting results on the inhibitory activity depending on the

Table 1
In vitro COX-1 and COX-2 enzyme inhibition data



Compound	R	COX-1 IC_{50} (μM)[a]	COX-2 IC_{50} (μM)[a]	COX-2 SI[b]	$Log P_{o/w}$[c]
Celecoxib		7.7	0.07	110	3.01
6		5.0 (9.9)[d]	0.007 (0.005)[d]	715 (1980)[d]	4.21
10a	H	20.8	0.15	139	1.84
10b	Me	45.0	2.5	18.0	2.30
10c	OMe	10.0	2.5	4.0	1.66
10d	NMe_2	>100	>10	–	1.95
10e	Cl	12.2	0.19	64	2.41
10f	F	12.5	0.21	59	1.87
11a	H	0.81	0.11	7.5	1.84
11b	Me	0.78	0.12	6.5	2.30
11c	OMe	0.83	0.17	4.9	1.66
11d	NMe_2	0.84	0.36	2.3	1.95
11e	Cl	0.70	0.04	17.5	2.41
11f	F	0.91	0.03	30.3	1.87

[a] Values are means of two determinations.
[b] In vitro COX-2 selectivity index (IC_{50} COX-1/IC_{50} COX-2).
[c] $Log P_{o/w}$ values have been calculated based on ACDLabs predictions.
[d] Literature value, Ref. 19.

substituents at the *para*-position of one of the aryl rings. All compounds of this series displayed only very low or no inhibitory potency against the constitutive form of cyclooxygenase (COX-1) in the range of 12.2 μM to >100 μM. A more differentiated picture within compounds **10a–f** was observed with regard to their inhibition against COX-2. Compounds (**10b–d**) containing large and electron-donating substituents (Me, OMe, NMe_2) showed only very low inhibition of the COX-2 enzyme as reflected by IC_{50} values in the μM range (2.5 mM to >100 μM). On the other hand, smaller (H, F, Cl) and electron-withdrawing (F, Cl) substituents in compounds **10a**, **10e** and **10f** gave IC_{50} values in the submicromolar range (0.15–0.21 μM) and COX-2 SI values of 138 (R = H), 64 (R = Cl) and 59 (R = F), respectively, indicative of a selective and potent COX-2 inhibition. The SI value of 138 makes compound **10a** the most COX-2 selective compound within all studied triazole-containing compounds. According to these data, increasing size and electron-donating properties of the *para* substituents, as found for the Me, OMe, and NMe_2 group in compounds **10b–d**, decrease COX-2 inhibitory potency. Thus, the tolerance of the *para*-position at the aryl ring towards COX-2 inhibition potency seems to be limited mainly by the size of the substituents. This finding is in agreement with literature reports also showing a reduced inhibitory potency while increasing the size of the *para* substituent.[18] The second series of compounds (**11a–f**) contains the common vicinal substitution pattern of potent and selective COX-2 inhibitors. Compounds **11a–f** displayed submicromolar COX-2 inhibitor potency, whereas compounds **11e** and **11f** containing an electron-withdrawing Cl or F substituent, behave as particularly highly potent COX-2 inhibitors (IC_{50} = 0.04 μM and 0.03 μM). All these compounds displayed moderate inhibitor activity towards COX-1 (IC_{50} = 0.70–0.91 μM). Chlorine- and fluorine-substituted compounds **11e** and **11f** are 3- to 12-fold more potent inhibitors compared to compounds **11b**, **11c** and **11d** having an electron-donating group (Me, OMe or NMe_2). Within this series, compounds **11e** and **11f** also showed the highest COX-2 selectivity (COX-2 SI = 17.5 and 30.3). The structure-activity relationship study of these compounds indicated that the order of COX-2 inhibitory potency was F > Cl > H > Me > OMe > NMe_2. The order of COX-2 selectivity followed the same order (F > Cl > H > Me > OMe > NMe_2). This result suggests that the presence of electron-withdrawing groups like fluorine and chlorine favors selective and potent inhibition of COX-2. Several reports in the literature upon the study of tricyclic compounds possessing two vicinal aryl moieties on the central heterocyclic ring system support this observation.[7]

Direct comparison of compounds **10a–f** and compounds **11a–f** further confirm the favorable vicinal diaryl substitution pattern with regard to potent COX-2 inhibition. Compounds **11a–f**, however, showed also moderate inhibitory activity against COX-1, which was not the case for compounds **10a–f**. Highly potent compounds **11e** and **11f** are 5- to 6-fold more potent than their corresponding 1,3-diaryl-substituted counterparts **10e** and **10f**. The positive effect of the vicinal diaryl substitution on COX-2 inhibition potency was even more pronounced for compounds **10b–d** and **11b–d** having electron-donating groups (Me, OMe, NMe_2). Changing the 1,3-diaryl substitution pattern in compounds **10b–d** to the vicinal diaryl substitution pattern in compounds **11b–d** is accompanied by a 20- to 30-fold increase in COX-2 inhibition potency.

Moreover, replacement of the central cyclopentene ring in reference compound **6** with a 1,2,3-triazole moiety as in compounds **10a–f** and **11a–f** resulted in a significant reduction of lipophilicity by 2–2.5 orders of magnitude. Structurally related compounds **6** and **11c** clearly demonstrate the lipophilicity-lowering effect of the 1,2,3-triazole unit. The 1,2,3-triazole unit possesses a moderate dipole character which allows additional hydrogen bonding compared to the nonpolar cyclopentene unit in compound **6**. All novel 1,2,3-triazole-containing compounds displayed lipophilicity ($Log P_{o/w}$) values in the range of 1.66–2.41. This lipophilicity range is favorable for the further design of PET radiotracer with optimized radiopharmacological profile for imaging COX-2. In this line, the promising results on COX-2 inhibition selectivity and potency, and lipophilicity of compounds **11e** and **11f**, make 1,2,3-triazole-containing compounds interesting candidates for further development of potent and selective COX-2 inhibitors, including radiotracers for functional imaging of both COX-2 expression and activity in vivo.

4. Conclusion

We have prepared a series of compounds based on a central 1,2,3-triazole scaffold having two aryl substituents as novel class of COX-2 inhibitors. The geometric arrangement of the two aryl rings attached to the 1,2,3-triazole moiety can easily be steered by application of either Cu(I)-catalyzed or Ru(II)-catalyzed 1,3-dipolar cycloaddition reaction. Compounds having a vicinal diaryl substitution pattern showed more potent COX-2 inhibition compared to their corresponding 1,3-diaryl-substituted counterparts. In both series, compounds possessing an electron-withdrawing group (Cl and F) at the *para*-position of one of the aryl rings displayed higher COX-2 inhibition potency as determined for compounds containing electron-donating groups (Me, OMe, NMe_2). The obtained data show, that commonly used central carbocyclic or heterocyclic ring system in COX-2 inhibitors can be replaced by a central 1,2,3-triazole unit possessing a vicinal diaryl substitution pattern. The high COX-2 inhibition potency of some 1,2,3-triazoles having a vicinal diaryl substitution pattern along with their ease in synthesis through versatile Ru(II)-catalyzed click chemistry make this class of compounds interesting candidates for further design of highly selective and potent COX-2 inhibitors.

5. Experimental

5.1. General

All commercial reagents and solvents were used without further purification unless otherwise specified. Nuclear magnetic resonance spectra were recorded on a Varian Unity 400 MHz spectrometer. ^1H NMR and ^{13}C NMR chemical shifts were given in ppm and were referenced with the residual solvent resonances relative to tetramethylsilane (TMS). Melting points were determined on a Galen III melting point apparatus (Cambridge Instruments) and are uncorrected. All compounds were analyzed for C, H, N and S on a LECO CHNS 932 elemental analyzer. Elemental analyses were within 0.4% for elements. Flash chromatography was conducted according to Still et al.[20] using MERCK silica gel (mesh size 230–400 ASTM). Thin-layer chromatography (TLC) was performed on Merck silica gel F-254 aluminum plates with visualization under UV (254 nm). Compound **6** was prepared according to literature procedure.[12]

5.2. Chemical synthesis

5.2.1. 1-Azido-4-(methyl-sulfonyl)benzene (9)

A solution of 4-(methylthio)aniline (1.32 ml, 10.75 mmol) in CH_3CN (40 ml) was cooled to 0 °C. *tert*-Butylnitrite (384 μl, 3.24 mmol) and azidotrimethylsilane (344 μl, 2.6 mmol) were added, and the mixture was warmed up to room temperature. After stirring at room temperature for 2 h, the solvent was removed under reduced pressure and the residue was dissolved in diethyl ether. After extraction with water, the organic layer was dried (Na_2SO_4) and the solvent was evaporated. The resulting oil (1.8 g) was dissolved in a mixture of MeOH/THF (65 ml, 1:1) and water (30 ml). Oxone® (7.5 g) was added and the mixture was stir-

red at room temperature overnight. After addition of water (200 ml) and extraction with ethyl acetate, the organic layer was passed through a silica gel plug. The solvent was evaporated under reduced pressure to yield 2.04 g (96%) of compound **9** as a yellow solid. Yield: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.05 (s, 3H; SO_2CH_3), 7.18 (d, J = 8.8 Hz, 2H; Ar-H), 7.92 (d, J = 8.8 Hz, 2H; Ar-H).

5.2.2. General procedure for the Cu(I)-catalyzed synthesis of triazoles

A mixture of the respective aryl acetylene (0.575 mmol), CuI (0.0575 mmol) and triethylamine (0.0575 mmol) in 15 ml of EtOH/H_2O (1:1) was thoroughly stirred at room temperature for 15 min. Then, 1-azido-4-methanesulfonylbenzene **9** (0.575 mmol) in 5 ml of EtOH/H_2O (1:1) was added and the resulting mixture was stirred at 60 °C for 12 h. The formed precipitate was filtered off, washed with water and diethylether. The sufficiently pure products were dried in a desiccator over $CaCl_2$.

5.2.2.1. 1-(4-Methanesulfonylphenyl)-4-phenyl-1*H*-[1,2,3]triazole (10a). Yield: 88%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.13 (s, 3H; SO_2CH_3), 7.42 (m, 1H; Ar-H), 7.49 (m, 2H; Ar-H), 7.93 (d, J = 7.8 Hz, 2H; Ar-H), 8.07 (d, J = 8.6 Hz, 2H; Ar-H), 8.16 (d, J = 8.6 Hz, 2H; Ar-H), 8.29 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.33, 119.82, 120.23, 125.28, 127.46, 128.39, 128.97, 129.03, 129.76, 140.27, 147.59. Melting point: 250–253 °C.

5.2.2.2. 1-(4-Methanesulfonyl-phenyl)-4-p-tolyl-1*H*-[1,2,3]triazole (10b). Yield: 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H; CH_3), 3.18 (s, 3H; SO_2CH_3), 7.29 (d, J = 7.8 Hz, 2H; Ar-H), 7.81 (d, J = 7.8 Hz, 2H; Ar-H), 8.06 (d, J = 8.6 Hz, 2H; Ar-H), 8.15 (d, J = 8.6 Hz, 2H; Ar-H), 8.24 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.78, 43.31, 120.17, 125.19, 125.22, 129.02, 129.52, 137.38, 139.61, 143.67, 159.15. Melting point: 298–301 °C.

5.2.2.3. 1-(4-Methanesulfonyl-phenyl)-4-(4-methoxyphenyl)-1*H*-[1,2,3]triazole (10c). Yield: 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.13 (s, 3H; SO_2CH_3), 3.87 (s, 3H; OCH_3), 7.01 (d, J = 8.6 Hz, 2H; Ar-H), 7.85 (d, J = 8.6 Hz, 2H; Ar-H), 8.05 (d, J = 8.6 Hz, 2H; Ar-H), 8.15 (d, J = 8.6 Hz, 2H; Ar-H), 8.20 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.31, 55.10, 114.38, 118.72, 120.10, 122.37, 126.67, 129.00, 140.12, 142.34, 146.01, 159.33. Melting point: 296-300 °C.

5.2.2.4. {4-[1-(4-Methanesulfonylphenyl)-1*H*-[1,2,3]triazol-4-yl]-phenyl}-dimethylamine (10d). Yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.03 (s, 6H; $N(CH_3)_2$), 3.12 (s, 3H; SO_2CH_3), 6.80 (d, J = 8.6 Hz, 2H; Ar-H), 7.79 (d, J = 8.6 Hz, 2H; Ar-H), 8.05 (d, J = 8.6 Hz, 2H; Ar-H), 8.14 (d, J = 8.6 Hz, 2H; Ar-H), 8.13 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.86, 43.35, 112.22, 117.57, 119.97, 126.34, 128.99, 131.56, 136.76, 149.06, 151.10. Melting point: 283–286 °C.

5.2.2.5. 4-(4-Chlorophenyl)-1-(4-methanesulfonylphenyl)-1*H*-[1,2,3]triazole (10e). Yield: 83%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.13 (s, 3H; SO_2CH_3), 7.46 (d, J = 8.6 Hz, 2H; Ar-H), 7.86 (d, J = 8.6 Hz, 2H; Ar-H), 8.05 (d, J = 8.6 Hz, 2H; Ar-H), 8.16 (d, J = 8.6 Hz, 2H; Ar-H), 8.28 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.32, 120.22, 120.29, 126.98, 128.69, 129.06, 129.08, 132.85, 139.74, 140.37, 146.39. Melting point: 253–255 °C.

5.2.2.6. 4-(4-Fluorophenyl)-1-(4-methanesulfonylphenyl)-1*H*-[1,2,3]triazole (10f). Yield: 79%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.13 (s, 3H; SO_2CH_3), 7.18 (m, 2H; Ar-H), 7.90 (m, 2H, Ar-H), 8.06 (d, J = 8.6 Hz, 2H; Ar-H), 8.16 (d, J = 8.6 Hz, 2H; Ar-H), 8.25 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.31, 115.93 (d, J_{C-F} = 22.9 Hz), 119.74, 120.22, 126.31 (d, J_{C-F} = 3.9 Hz), 127.35 (d, J_{C-F} = 8.4 Hz), 129.02, 132.51, 139.75, 140.29, 146.68, 162.23 (d, J_{C-F} = 244.2 Hz). Melting point: 249–253 °C.

5.2.3. General procedure for the Ru(II)-catalyzed synthesis of triazoles

A mixture of 1-azido-4-methanesulfonylbenzene **9** (113.4 mg, 0.575 mmol), the respective aryl acetylene (0.632 mmol) and [$Cp^*RuCl(PPh_3)_2$] (6.9 mg, 8.6 μmol) in toluene (5 ml) was heated in a sealed vial under argon at 120 °C for 12 h. After evaporation of the solvent, the residue was purified by flash-chromatography (50% EtOAc/petroleum ether) to give the desired product as a solid.

5.2.3.1. 1-(4-Methanesulfonylphenyl)-5-phenyl-1*H*-[1,2,3]triazole (11a). Yield: 22%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.09 (s, 3H; SO_2CH_3), 7.22 (m, 2H; Ar-H), 7.40 (m, 3H; Ar-H), 7.58 (d, J = 8.6 Hz, 2H; Ar-H), 7.87 (s, 1H), 8.00 (d, J = 8.6 Hz, 2H; Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.30, 121.74, 125.38, 125.90, 127.76, 128.09, 128.31, 131.08, 132.16, 145.27, 147.14. Melting point: 168–171 °C.

5.2.3.2. 1-(4-Methanesulfonyl-phenyl)-5-p-tolyl-1*H*-[1,2,3]triazole (11b). Yield: 11%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H; CH_3), 3.10 (s, 3H; SO_2CH_3), 7.00 (d, J = 7.8 Hz, 2H; Ar-H), 7.20 (d, J = 7.8 Hz, 2H; Ar-H), 7.60 (d, J = 8.6 Hz, 2H; Ar-H), 7.84 (s, 1H), 8.01 (d, J = 8.6 Hz, 2H; Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.89, 44.30, 121.71, 125.33, 127.78, 129.19, 129.41, 130.09, 132.06, 145.47, 147.11. Melting point: 136–138 °C.

5.2.3.3. 5-(4-Methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-1*H*-1,2,3-triazole (11c). Yield: 16%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.10 (s, 3H; SO_2CH_3), 3.83 (s, 3H; OCH_3), 6.91 (d, J = 8.6 Hz, 2H; Ar-H), 7.14 (d, J = 8.6 Hz, 2H; Ar-H), 7.60 (d, J = 8.6 Hz, 2H; Ar-H), 7.81 (s, 1H), 8.01 (d, J = 8.6 Hz, 2H; Ar-H)). ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.38, 55.40, 114.78, 121.72, 124.19, 125.27, 127.87, 128.12, 132.09, 145.32, 147.11, 157.33. Melting point: 154–156 °C.

5.2.3.4. *N*,*N*-dimethyl-4-(1-(4-(methylsulfonyl)phenyl)-1*H*-[1,2,3]triazol-5-yl)aniline (11d). Yield: 27%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.00 (s, 6H; $N(CH_3)_2$), 3.10 (s, 3H; SO_2CH_3), 6.65 (d, J = 8.6 Hz, 2H; Ar-H), 7.06 (d, J = 8.6 Hz, 2H; Ar-H), 7.64 (d, J = 8.6 Hz, 2H; Ar-H), 7.78 (s, 1H), 8.01 (d, J = 8.6 Hz, 2H; Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.99, 44.32, 112.42, 118.17, 121.57, 124.14, 125.29, 127.56, 132.01, 145.16, 147.09, 147.66. Melting point: 193–195 °C.

5.2.3.5. 5-(4-Chlorophenyl)-1-(4-methanesulfonylphenyl)-1*H*-[1,2,3]triazole (11e). Yield: 10%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.11 (s, 3H; SO_2CH_3), 7.17 (d, J = 8.6 Hz, 2H; Ar-H), 7.39 (d, J = 8.6 Hz, 2H; Ar-H), 8.59 (d, J = 8.6 Hz, 2H; Ar-H), 7.88 (s, 1H), 8.04 (d, J = 8.6 Hz, 2H; Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.32, 121.29, 125.18, 126.69, 127.82, 127.92, 130.18, 131.25, 132.04, 145.29, 147.11. Melting point: 171–172 °C.

5.2.3.6. 5-(4-Fluorophenyl)-1-(4-methanesulfonylphenyl)-1*H*-[1,2,3]triazole (11f). Yield: 15%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.10 (s, 3H; SO_2CH_3), 7.11 (m, 2H; Ar-H), 7.22 (m, 2H, Ar-H), 7.58 (d, J = 8.6 Hz, 2H; Ar-H), 7.86 (s, 1H), 8.02 (d, J = 8.6 Hz, 2H; Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.91, 115.83 (d, J_{C-F} = 23.2 Hz), 121.52, 126.22 (d, J_{C-F} = 3.8 Hz), 127.25 (d, J_{C-F} = 8.6 Hz), 127.62, 132.11, 144.99, 147.21, 159.73 (d, J_{C-F} = 254.2 Hz). Melting point: 180–182 °C.

5.3. In vitro cyclooxygenase inhibition assays

The ability of compound **6** and 1,2,3,-triazoles **10a–f** and **11a–f** to inhibit COX-1 and COX-2 isoenzymes (IC_{50} values, μM) was

determined using an enzyme immunoassay (EIA) kit (Catalog No. 560101, Cayman Chemical, Ann Arbor, MI USA) according to a previously published method.[16]

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