One-pot Cascade Synthesis of Pyrazole-based Isosteres of Valdecoxib by a [3+2] Cycloaddition/[1,5] Sigmatropic Rearrangement Sequence and Evaluation of their COX Inhibitory Activity

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One-pot Cascade Synthesis of Pyrazole-based Isosteres of Valdecoxib by a [3+2] Cycloaddition/[1,5] Sigmatropic Rearrangement Sequence and Evaluation of their COX Inhibitory Activity

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Dedication ((optional))

Abstract: A series of 5-methyl-3,4-diaryl-substituted 1*H*-pyrazoles, *N*-isosteres of valdecoxib, was synthesized by a [3+2] cycloaddition/[1,5] sigmatropic rearrangement sequence starting from tosylhydrazine, aryl methyl ketones and terminal aryl alkynes bearing various substituents (H, Me, OMe, F, SO_2Me, SO_2NH_2). New pyrazoles were prepared regioselectively in a one-pot process with moderate-good yields. All compounds were used in *in vitro* cyclooxygenase (COX) assays to determine inhibitory potency and selectivity to COX-1 and COX-2. In general, these new pyrazoles are characterized by selective COX-2 inhibition activity in a micromolar range. Structure-activity relationship studies showed that compounds possessing an electron-withdrawing group (F) in one of the aryl rings displayed higher COX-2 inhibition selectivity and activity than was determined for compounds containing electron-donating groups (Me, OMe).

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of inflammation, fever and pain. The general pharmacological effects of NSAIDs arise from their inhibition of cyclooxygenase (COX) enzymes which catalyze the formation of prostanoids from arachidonic acid. COXs exist as two distinct isoforms, a constitutive form (COX-1) and an inducible form (COX-2), both of which are responsible for the synthesis of prostanoids involved in acute and chronic inflammatory states.[1] Elevated expression of COX-2 has been implicated in manifold pathological events, including chronic inflammatory diseases, coronary heart disease, stroke, and neurodegenerative disorders.[2] It has been also documented recently that COX-2 is overexpressed in many human cancer entities.[3] In consequence, expression of COX-2 has attracted growing attention as a diagnostic marker and therapeutic target in oncology.[4]

The therapeutic actions of nonselective NSAIDs rest upon their inhibition of COX-1 and COX-2; however, the inhibition of COX-1 is accompanied by adverse side effects.[5] In fact, selective COX-2 inhibitors (called coxibs) are more effective and show the advantage of reducing toxicity. In this context, a huge number of compounds based on varying structure classes have been evaluated for selective COX-2 inhibition.[6] Among the structural features, the 5-membered heterocyclic or carbocyclic motif with two vicinal aryl rings attached has evolved as a promising lead structure (Figure 1).[7] It was shown that the sulfonamide or methylsulfonyl group located in *para*-position at one of the phenyl substituents effectively interacts with the COX-2 side pocket through slow tight-binding kinetics.[8] Celecoxib,[9] rofecoxib,[10] and valdecoxib[11] are the most common coxibs, being used, for example, for the treatment of rheumatoid arthritis and osteoarthritis and for the relief of acute pain. However, owing to their adverse cardiovascular side effects and skin reactions, rofecoxib and valdecoxib were later withdrawn from the market.[12] On the other hand parecoxib,[13] a parenterally safe prodrug form of valdecoxib, is still in use for the management and treatment of acute pain. The two pyrazole-containing drugs celecoxib and deracoxib are prominent examples of marketed selective COX-2 inhibitors.[14]

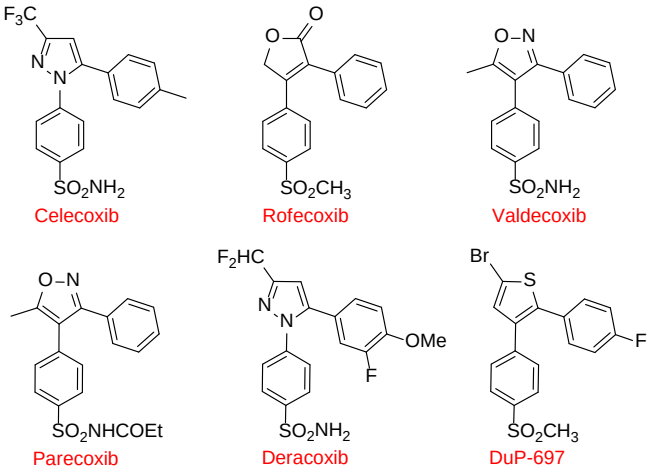

Figure 1. Selection of selective COX-2 inhibitors with a diaryl-substituted 5-membered heterocycle scaffold

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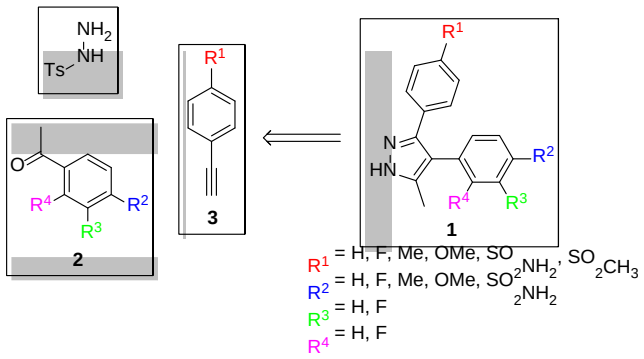
In accordance with our aim of developing new COX-2 inhibitors which are to be generated in a one-pot process, we have recently described the synthesis of a number of novel valdecoxib derivatives by Ru-catalyzed 1,3-dipolar cycloaddition of nitrile oxides with alkynes.[15] Some of the resulting 3,4-diaryl-substituted isoxazoles displayed an affinity in nanomolar range and excellent selectivity towards COX-2. In this line, the replacement of the central isoxazole moiety by a pyrazole ring should lead to new selective COX-2 inhibitors. With this in mind, and in continuation of our 1,3-dipolar cycloaddition approach, we aimed to synthesise novel 3,4-diaryl-substituted pyrazoles **1**, *N*-isosteres of valdecoxib, as potent and selective cyclooxygenase-2 inhibitors (Scheme 1). Accordingly, in this paper we describe the one step synthesis of a series of 5-methyl-3,4-diaryl-1*H*-pyrazoles **1**, by a [3+2] cycloaddition/[1,5] sigmatropic rearrangement sequence. Key steps in this one-pot reaction sequence are i) the reaction of tosylhydrazine with an acetophenone **2** to synthesize a tosylhydrazone followed by ii) [3+2] dipolar cycloaddition with an alkyne **3** and iii) subsequent [1,5] sigmatropic rearrangement to form 3,4-diarylsubstituted pyrazoles **1** (Scheme 1). To determine their potential suitability, the COX-1 and COX-2 inhibitory activity of the new compounds was evaluated *in vitro*.



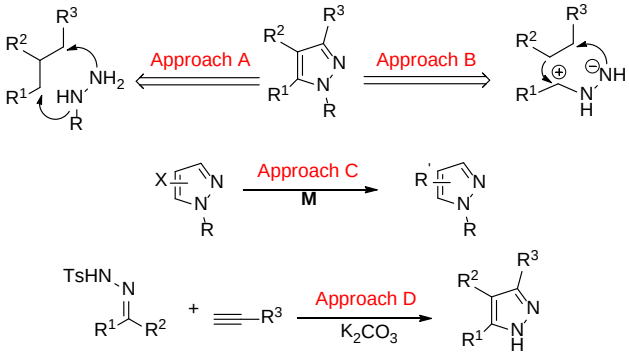
Scheme 1. Design concept of novel pyrazoles by [3+2]cycloaddition/[1,5]sigmatropic rearrangement

Results and Discussion

Chemistry

Pyrazole is an important lead structure in pharmaceutical research, reflected by a great number of pyrazole derivatives present in drugs. The most popular approaches to the synthesis of 3,4,5-trisubstituted pyrazoles are displayed in Scheme 2.[16] They consist of: A) construction of two C-N bonds by condensation of hydrazines with 1,3-dicarbonyl compounds or their 1,3-dielectrophilic synthetic equivalents; B) the generation of one C-N bond and one C-C bond by [3+2] cycloadditions of diazo compounds or other N=N containing dipoles with alkynes and alkenes, respectively. The creation of C-N or C-C bonds by transition-metal-catalyzed cross-coupling reactions of aryl electrophiles with substituted pyrazoles C) is a further general approach. Each method has its own scope and efficiency limitations. Routes based on dipolar cycloaddition reactions usually face regioselectivity problems and are limited by the availability of the diazo compounds, while condensation reaction-based methodologies require multistep routes to yield the pyrazole precursors. In fact, the pyrazole isostere of valdecoxib was synthesized by a six-step procedure starting from commercially available deoxybenzoin,[17] and showed slight anti-inflammatory and analgesic activity.

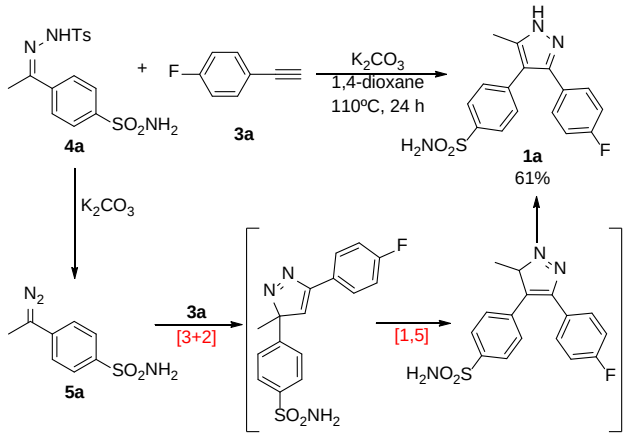
In recent years it has been shown that tosylhydrazones can be generally employed as educts in the synthesis of diazo compounds from carbonyl compounds.[18] Recently, acetophenone hydrazones[19] and tosylhydrazones[20] were used for the regioselective synthesis of 3,4,5-trisubstituted 1*H*-pyrazoles. In this context, Pérez-Aguilar and Valdés reported a new method for the regioselective preparation of 3,4,5-trisubstituted pyrazoles from readily available *N*-tosylhydrazones and terminal acetylenes through a [3+2] cycloaddition/[1,5] sigmatropic rearrangement sequence (Scheme 2, D).[21] Later, the intramolecular cyclization reaction of *N*-tosylhydrazones/[1,5] with subsequent sigmatropic rearrangement was used for the regioselective synthesis of 5-trifluoromethyl-1*H*-pyrazoles.[22] These results prompted us to evaluate the potential of this reaction sequence as a suitable method for the one-pot generation of 5-methyl-3,4-diaryl-1*H*-pyrazoles, which are not easily available using other methodologies.



Scheme 2. General approaches for synthesis of 3,4,5-trisubstituted pyrazoles.

In an initial experiment, we conducted the reaction between tosyl hydrazone **4a** and phenylacetylene **3a** in 1,4-dioxane in the presence of K_2CO_3 at 110ºC (Scheme 3). The reaction afforded the pyrazole **1a** as a single regioisomer in noticeable 61% yield. Formation of **1a** can be explained by a mechanism that involves the intermediate formation of the diazo compound **5a** from the hydrazine **4a**, followed by [3+2] dipolar cycloaddition with the terminal alkyne **3a** to give a 3*H*-pyrazole and subsequent [1,5] sigmatropic rearrangement and aromatization (Scheme 3, lower part). This initial result prompted us to investigate the scope of this transformation further; after some optimization work, we found that methyl ketones **2** can be easily transformed *in situ* to the corresponding tosyl hydrazones **4** by treatment with *p*-toluenesulfonyl hydrazide. After the addition of alkyne **3** and K_2CO_3, 3,4,5-trisubstituted pyrazoles were isolated in good

yields in one regioisomeric form. These one-pot cascade reaction conditions were applied to a set of methyl ketones **2a-i** and terminal alkynes **3a-f**, to form 3,4,5-trisubstituted pyrazoles **1a-k**. The results are summarized in Table 1.



Scheme 3. Formation of the pyrazole **1a** from the tosyl hydrazone **4a** and phenylacetylene **3a** through the [3+2] cycloaddition/[1,5] rearrangement sequence.

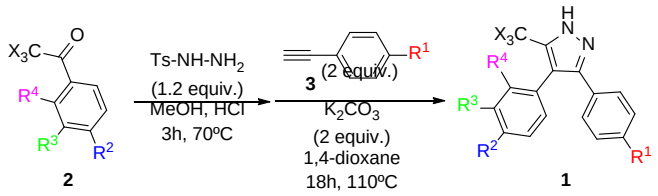


Table 1. Synthesis of diaryl-substituted pyrazoles **1** by a one-pot [3+2] cycloaddition/ [1,5] sigmatropic rearrangement sequence.

Entry	**3**, R^1	**2**, R^2, R^3, R^4, X	**1**, (yield, %)
1	**3a**, F	**2a**, SO_2NH_2, H, H, H	**1a** (33)
2	**3b**, H	**2a**, SO_2NH_2, H, H, H	**1b** (31)
3	**3c**, CH_3	**2a**, SO_2NH_2, H, H, H	**1c** (52)
4	**3d**, OCH_3	**2a**, SO_2NH_2, H, H, H	**1d** (66)
5	**3e**, SO_2NH_2	**2b**, H, H, H, H	**1e** (42)
6	**3e**, SO_2NH_2	**2c**, F, H, H, H	**1f** (51)
7	**3e**, SO_2NH_2	**2d**, CH_3, H, H, H	**1g** (82)
8	**3f**, SO_2CH_3	**2e**, OCH_3, H, H, H	**1h** (79)
9	**3f**, SO_2CH_3	**2c**, F, H, H, H	**1i** (70)
10	**3f**, SO_2CH_3	**2f**, H, F, H, H	**1j** (56)
11	**3f**, SO_2CH_3	**2g**, H, H, F, H	**1k** (66)
12	**3f**, SO_2CH_3	**2h**, H, H, H, F	**1l** (0)
13	**3e**, SO_2NH_2	**2h**, H, H, H, F	**1m** (0)
14	**3f**, SO_2CH_3	**2i**, F, H, H, F	**1n** (0)
15	**3e**, SO_2NH_2	**2i**, F, H, H, F	**1o** (0)

First, the scope of the cascade reaction was evaluated with regard to the structure of the alkyne **3** employing the methyl ketone **2a** possessing the SO_2NH_2 pharmacophore as a substrate (Table 1, entries 1-4). The reaction is general for aromatic-substituted terminal alkynes, bearing electron-donating (entries 3-4) or electron-withdrawing substituents (entry 1). However, in case of the latter a moderate drop in the yield was observed. The reaction with aromatic terminal alkynes bearing SO_2NH_2 **3e** or SO_2Me groups **3f** at *para* position of the phenyl group also led to the pyrazoles **1e-k** with good yields (entries 5-11). Regarding the structure of the ketone **2**, the process took place efficiently with acetophenone-derived hydrazones featuring all types of substituents in the aromatic ring, including the sulfonamide group. Remarkably, the reaction with electron-donating substituted acetophenones led to the straightforward synthesis of pyrazoles **1g** and **1h** in high yield. The reaction was also successful with a fluorine substituent at *ortho*, *meta* or *para* position of the aromatic ring (entries 6, 9–11). However, no reaction product was formed with a trifluoromethyl ketone as starting material (entries 12-15). Altogether, these results demonstrate that the cascade synthesis is an excellent method for the preparation of 5-methyl-3,4-diaryl-1*H*-pyrazoles in one pot with high to adequate yields.

In vitro COX-1/COX-2 inhibitory activity

Based on a [3+2] cycloaddition/[1,5] sigmatropic rearrangement sequence, we prepared a series of compounds **1a-k** possessing a central pyrazole moiety with two vicinal diaryl substituents, showing close structural correspondence to traditional selective COX-2 inhibitors e.g. valdecoxib, parecoxib and celecoxib (see Figure 1). The hitherto unknown inhibitory affinity of **1a-k** towards the COX-1 and COX-2 isoenzyme had to be evaluated. For that purpose, all isolated compounds were subjected to an *in vitro* COX fluorescent inhibitor screening assay where valdecoxib was used as a reference. The resulting *in vitro* enzyme inhibition data, along with the calculated COX-2 selectivity index (COX-2 SI = IC_{50}COX-1/IC_{50}COX-2) of the new pyrazoles **1a-k,** are summarized in Table 2, and it can be concluded that pyrazoles **1** displayed complex results with regard to COX-1/COX-2 inhibitory activity. All compounds showed no inhibitory potency against COX-1 (>100 µM). Regarding inhibition against COX-2, a more differentiated picture emerged, depending on the substituents of the aromatic rings.

The first series of compounds (**1a-d**, Table 2, entries 1-4) possessing the typical sulfonamide pharmacophore in the *para*-position of the aromatic ring at position 4 of the pyrazole moiety (R^2) showed distinct results of the COX-2 inhibitory activity. With regard to the substituents at the *para*-position of the aryl ring at the position 3 of the pyrazole ring (R^1), it is clearly visible that with increasing size of the substituent the affinity towards COX-2 is reduced. While the H and F substitution pattern is connected with significant but moderate inhibition (8.3 – 11.4 µM, entries 1-2), large and electron-donating substituents resulted in only weak (CH_3, entry 3) or almost no inhibition (OCH_3, entry 4). Accordingly, increasing size and electron-donating properties of the *para* substituents decrease COX-2 inhibitory potency.

The second series of compounds (**1e-1k**, entries 5-11) possesses the typical sulfonamide or methylsulfonyl COX-2 pharmacophore in the *para*-position of the aromatic ring at position 3 of the pyrazole moiety (R^1 = SO_2NH_2, SO_2Me).

Table 2. In vitro COX-1 and COX-2 enzyme inhibition data of pyrazoles **1a-k**.

Entry	1, R^1, R^2, R^3, R^4	COX-1 IC_{50} (μM)	COX-2 IC_{50} (μM)	COX-2 SI
1	**1a**, F, SO_2NH_2, H, H	>100	8.3	>12.0
2	**1b**, H, SO_2NH_2, H, H	>100	11.4	>8.8
3	**1c**, CH_3, SO_2NH_2, H, H	>100	18.5	>5.4
4	**1d**, OCH_3, SO_2NH_2, H, H	>100	91.0	>1.1
5	**1e**, SO_2NH_2, H, H, H	>100	8.0	>12.5
6	**1f**, SO_2NH_2, F, H, H	>100	1.79	>55.9
7	**1g**, SO_2NH_2, CH_3, H, H	>100	7.1	>14.1
8	**1h**, SO_2CH_3, OCH_3, H, H	>100	33.1	>3.0
9	**1i**, SO_2CH_3, F, H, H	>100	8.22	>12.2
10	**1j**, SO_2CH_3, H, F, H	>100	2.7	>37.0
11	**1k**, SO_2CH_3, H, H, F	>100	>100	>1
12	Valdecoxib	>100	0.05	>2000

Compounds **1e-j** displayed micromolar COX-2 inhibitor activity (entries 5-10), whereas compounds **1f** and **1i** containing an electron-withdrawing fluoro substituent (R^2 = F), behave as the most potent COX-2 inhibitors (IC_{50} = 1.79 μM and 8.22 μM respectively, entries 6, 9). As shown within these results, SO_2NH_2 group as present in **1f** turned out to be a better COX-2 pharmacophore than SO_2Me as present in **1i**. Fluorine-substituted compounds **1f** and **1i** were found to be more potent in comparison with compounds having an electron-donating group **1g** or **1h** (entries 7-8). A *meta*-substituted fluorine at the aryl ring (R^3 = F) (**1j**, entry 10) results in the highest observed COX-2 inhibition potency (IC_{50} = 2.7 μM); however, if the fluorine substitution is moved to *ortho* position (R^4 =F) (**1k**, entry 11) no COX-2 inhibition was observed. The structure-activity relationship study of these compounds indicated that the order of COX-2 inhibitory potency was F > H > Me > OMe. The order of COX-2 selectivity followed the same chronology. These results suggest that the presence of small, electron-withdrawing substituents like fluorine favors selective inhibition of COX-2. This is in agreement with literature reports which also show a reduced inhibitory potency with increasing size of the *para* substituent.[23]

Direct comparison of compounds **1a-d** (entries 1-4) and compounds **1e-k** (entries 5-11) further confirms that the *para* SO_2R-penyl substituent is more favorable at position 3 than at position 4 of the pyrazole moiety regarding COX-2 affinity. Within this series of 3,4,5-trisubstituted pyrazoles, compounds **1f** and **1j** are the most potent and selective COX-2 inhibitors (IC_{50} = 1.79 μM and 2.7 μM) respectively.

A major point of interest and motivation of this study was the question as to whether the substitution of the oxygen by nitrogen (O versus NH) in the five-membered heterocycle in the valdecoxib lead structure would affect the inhibition potency towards COX-2. In Figure 2, valdecoxib, fluoro-substituted valdecoxib and the corresponding pyrazole derivatives **1b** and **1a**, i.e. valdecoxib *NH*-isosteres are displayed. It is clearly visible from the IC_{50} values that the COX-2 affinity has significantly dropped by two decimal powers through exchanging the oxazole for a pyrazole moiety.

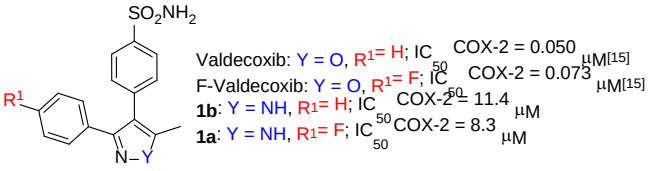


Figure 2. Relation of COX-2 affinity for valdecoxib and its *NH*-isosteric analog with and without fluoro substitution.

It can be assumed that the free hydrogen on the pyrazole nitrogen interacts with the COX-2 enzyme e.g. via hydrogen bonds and thus prevents a binding with high affinity.[24] Notably, the COX-2 affinity of valdecoxib and its isosteric NH anolog is only slightly altered by introduction of a fluorine substituent.

Conclusions

By means of a [3+2] cycloaddition/[1,5] sigmatropic rearrangement sequence, we have prepared a series of new compounds, isosteres of the valdecoxib lead structure displaying a central pyrazole scaffold, with two vicinal aryl substituents. The whole process can be performed as a two-step cascade reaction, which makes the access to 3,4,5-trisubstituted 1*H*-pyrazoles very simple. An outstanding feature of this approach is the one-pot process yielding the 5-methyl-3,4-diaryl-substituted 1*H*-pyrazoles in good yields. In general, these new pyrazoles are characterized by COX-2 inhibition in the micromolar range. However, those compounds bearing bulky or electron-donating groups showed a significantly lower affinity towards COX-2. Interestingly, compounds possessing a fluorine substituent at the aromatic rings displayed the highest COX-2 inhibition activity, and it was demonstrated that the position of the fluorine substituent (*ortho vs. meta vs. para*) has a major impact on COX-2 affinity. By direct comparison of valdecoxib and its isosteric NH-analog with regard to COX-2 activity, it was found that the isosteric exchange of nitrogen for oxygen did not result in improved but rather in significantly reduced affinity.

Experimental Section

Details of experimental procedure, compound characterization data, COX inhibition assay and copies of ^1H and ^{13}C NMR spectra are available in supporting information.

Acknowledgements

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Keywords: pyrazole • COX inhibition • cycloaddition • sigmatropic rearrangement • tosylhydrazone

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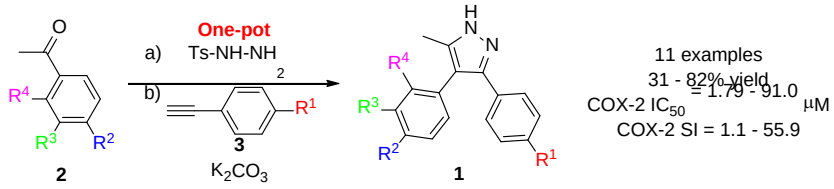

5-methyl-3,4-diaryl-substituted 1*H*-pyrazoles ***1***, *N*-isosteres of the COX-2 inhibitor valdecoxib, were synthesized regioselectively by a [3+2] cycloaddition/[1,5] sigmatropic rearrangement sequence. Different substituents on the aromatic rings (H, Me, OMe, F, SO_2NH_2, SO_2Me) are well tolerated. Structure-activity relationship studies showed that compounds possessing a fluorine atom displayed the highest COX-2 inhibition selectivity and activity.