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Synthesis and Biological Evaluation of 1,3,4-Triaryl-3-pyrrolin-2-ones, a New Class of Selective Cyclooxygenase-2 Inhibitors

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Abstract—The synthesis and structure–activity relationships (SAR) of a series of novel selective COX-2 inhibitors are reported. The results show that some of the 1,3,4-triaryl-3-pyrrolin-2-ones **1** are more potent as COX-2 inhibitors than celecoxib, and that lactam **1d** has the same selectivity.

The recent discovery of two isoforms of cyclooxygenase, namely COX-1, expressed constitutively in all tissues, and COX-2,[1] expressed during inflammatory processes in affected tissues but not in the gastric mucosa, has prompted extensive research in developing selective COX-2 inhibitors that lack the gastrointestinal and nephrotoxic side effects[2] of currently available nonsteroidal antiinflammatory drugs,[3] all of which inhibit both COX-1 and COX-2 (e.g., diclofenac, naproxen, indomethacin). Epidemiological studies also suggest that selective COX-2 inhibitors may retard the progression of Alzheimher's disease[4] and be useful for the chemopreventive treatment of polyposis and cancer.[5] Three different structural types of highly selective COX-2 inhibitors[6] have been reported to date: methanesulfoanilides (e.g., nimesulide[7]), methylsulfonyl or sulfonamido substituted tricycles (e.g., rofecoxib,[8] celecoxib[9]), and analogues based on nonselective inhibitors (e.g., L-761,066)[10] (Fig. 1).

The spatial orientation of the aromatic rings in these structures is known to be critical for selective COX-2 inhibition. Based on this hypothesis, we report the synthesis and structure–activity relationships (SAR) studies of some 1,3,4-triaryl-3-pyrrolin-2-ones **1**, a new class of selective COX-2 inhibitors.

These lactams **1** were studied with different molecular modeling tools. Molecules were built using the module PREP of the AMBER program[10] and manually docked into the active site of COX-2. Complexes were geometrically optimized using the parm91 set of parameters with a dielectric constant of 4R and a 12 Å cutoff to disregard non-bonded interactions. Initial structures of the different complexes were generated using the information gathered from site-directed mutagenesis studies,[11] available crystal structures, and ligand molecular electrostatic potentials computed at the Hartree-Fock level with a

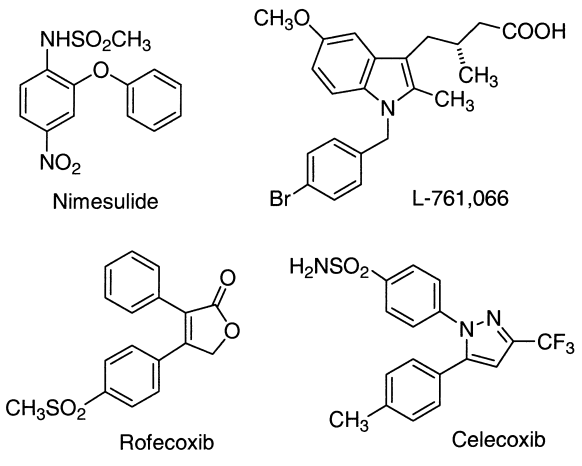

Figure 1.

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6-31G* basis set and GRID[12] calculations on the enzyme active site. All the optimized complexes evidenced good interactions between the sulfone moiety of the ligands and Arg-513. Moreover, the lactam carbonyl group acts as a hydrogen bond acceptor as counterpart of Ser-530. The 3- and *N*-phenyl rings are placed in two hydrophobic pockets composed by the residues Tyr-385, Trp-387, Phe-518, Tyr-348, Val-349, and Leu-352 for the 3-phenyl ring, and Leu-531, Ile-345, Leu-117, and Val-116 for the *N*-phenyl ring (Fig. 2).

The general method employed for the preparation of triaryl-3-pyrrolin-2-ones **1** is outlined in Scheme 1. The synthesis starts from 4-(methylsulfonyl)acetophenone **2**,[13] which was brominated at the α carbonyl position. Alkylation of appropriate anilines with the resulting α-bromo ketone **3** in ethanol gave amino ketones **4**, which in turn were acylated with a variety of substituted phenylacetyl chloride derivatives. The closure of the lactam ring was satisfactorily accomplished in high yield by an aldol-type cyclization by treatment of amides **5** with DBU. A subsequent dehydration of the resulting lactam alcohols **6** with a *p*-toluensulfonic acid in refluxing benzene led to the target unsaturated triaryl lactams **1**.

Numerous sites of modification of the lactam ring substituents were explored. A variety of substituents at the *para* position of the *N*- and 3-phenyl rings were investigated in order to provide compounds with good COX-2 activity (<1 μM) and acceptable selectivity (ratio IC_{50} COX-1/IC_{50} COX-2 >10). In only a few cases we also evaluated the effect of F or Cl atoms at the *ortho* and *meta* positions. No changes were made in the methylsulfone moiety. The IC_{50} values of COX-2 and COX-1, and the selectivity ratios are shown in Table 1. A representative COX-2 inhibitor such as celecoxib and the nonselective

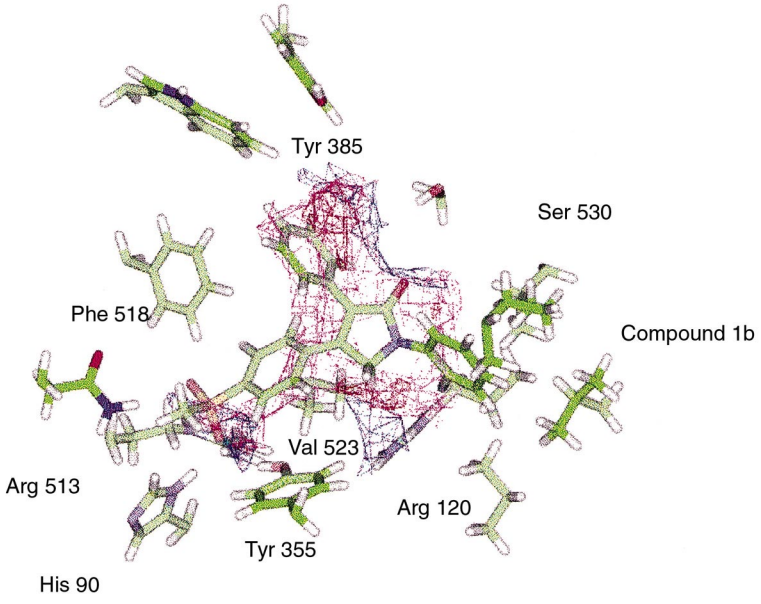
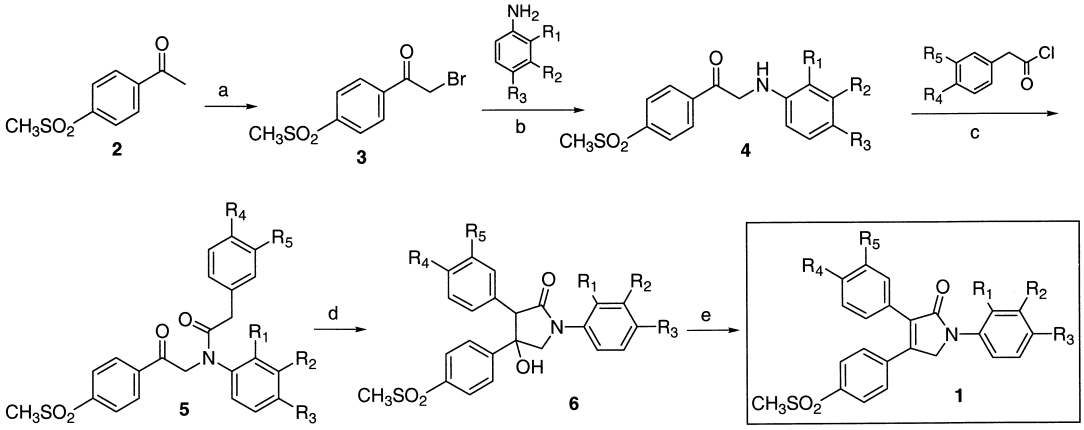


Figure 2. Compound **1b** docked at the COX-2 active site. Color surfaces indicate important regions of interaction at the active site for different probes computed with the GRID program: aromatic (magenta), sulfone (blue), and carbonyl (red).



Scheme 1. (a) Br_2, CH_2Cl_2, AcOH, rt, 73%; (b) $NaHCO_3$, EtOH, rt, 86–95%; (c) THF, rt, 67–84%; (d) DBU, CH_3CN, 0 °C; (e) *p*-TsOH, C_6H_6, reflux, 79–92% from **5**.

Table 1. In vitro COX-1 and COX-2 enzyme data for substituted 1,3,4-triaryl-3-pyrrolin-2-ones **1**

Compound	R_1	R_2	R_3	R_4	R_5	COX-2[a]	COX-1[a]	Selectivity
1a	H	H	H	H	H	0.28±0.09	2.40±0.60	8.6
1b	F	H	H	H	H	0.90±0.14	10.80±1.96	12.0
1c	H	Cl	H	H	H	1.00±0.12	9.80±0.90	9.8
1d	H	H	F	H	H	0.35±0.14	5.86±0.08	16.7
1e	H	H	CH_3	H	H	1.00±0.09	6.90±1.10	6.9
1f	H	H	CF_3	H	H	0.98±0.21	5.10±1.20	5.2
1g	H	H	H	CH_3O	H	0.34±0.09	2.68±0.85	7.9
1h	H	H	H	F	H	0.31±0.12	2.70±0.61	8.7
1i	F	H	H	F	H	0.32±0.14	2.50±0.48	7.8
1j	Cl	H	H	CH_3O	H	0.22±0.05	2.30±0.90	10.5
1k	CH_3O	H	H	F	H	1.05±0.25	4.00±1.05	3.8
1l	H	F	H	CH_3O	H	0.28±0.10	2.50±0.65	8.9
1m	H	H	CH_3	F	H	1.05±0.12	3.70±0.59	3.5
1n	H	H	CH_3O	F	H	1.20±0.41	5.28±0.94	4.4
1o	H	H	CF_3	F	H	0.95±0.63	7.20±1.10	7.6
1p	H	H	F	CH_3O	H	0.30±0.14	2.50±0.39	8.3
1q	H	H	H	F	F	1.00±0.21	8.20±1.60	8.2
Celecoxib						0.53±0.18	9.73±2.02	18.4
Indomethacin						0.41±0.07	0.19±0.06	0.5

[a]IC_{50} (μM). Average of 2–4 determinations. PGE2 levels in lipopolysaccharide (LPS)-challenged human whole blood and tromboxane 2 (TxB2) levels following blood coagulation were measured as biochemical index for COX-2 and COX-1, respectively (see ref 14).

COX inhibitor indomethacin are included for the purpose of a clear SAR summary. As can be seen in the Table, the in vitro COX-2 potency of both the parent lactam **1a** and other substituted lactams bearing a F atom at the *para* position of either the *N*- or 3-phenyl ring (**1d** and **1h**, respectively) or a *para* methoxy 3-phenyl substituent (**1g**) is higher than that of celecoxib. This good COX-2 potency is maintained when there are additional halogen (F or Cl) substituents in the *N*-phenyl ring (**1i**, **1j**, **1l** or **1p**), but strongly decreases with the introduction of bulkier *ortho* or *para* substituents (CH_3, CF_3 or CH_3O). As far as the selectivity ratio COX-1/COX-2 is concerned, most of the lactams **1** proved to be selective COX-2 inhibitors. The best ratios were obtained with lactams **1b** and, especially, **1d**, which bear a fluorine atom at the 2- or 4-position, respectively, of the *N*-phenyl ring. An additional substitution on this ring or at the 3- or 4-position of the 3-phenyl ring does not improve the selectivity.

In summary, we have designed and synthesized a variety of novel 1,3,4-triaryl-3-pyrrolin-2-ones **1** as selective COX-2 inhibitors. These compounds, in particular **1b** and **1d**,[15] may represent a new generation of NSAIDs, useful for symptomatic treatment of inflammatory diseases such as rheumatoid arthritis or osteoarthritis.

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