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Original article

Synthesis, anti-inflammatory activity and molecular docking studies of 2,5-diarylfuran amino acid derivatives

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ABSTRACT

A series of 2,5-diaryl substituted furans functionalized with several amino acids were synthesized and evaluated as the cyclooxygenases COX-1 and COX-2 enzymes inhibitors. The proline-substituted compound inhibited PGE_2 secretion by LPS-stimulated neutrophils, suggesting selectivity for COX-2. Molecular docking studies in the binding site of COX-2 were performed.

1. Introduction

Cyclooxygenases (COXs) are expressed in a variety of cells and are responsible for the metabolism of membrane lipids, generating prostaglandins (PGs), which are some of the most important inflammatory mediators [1]. While COX-1 is described as a constitutive enzyme and displays relevant physiological actions, COX-2 is induced in response to pro-inflammatory stimuli, and its expression is absent or low in healthy individuals [1,2]. Although COX-2 inhibitors are widely prescribed anti-inflammatory agents, conversely several important side effects have been associated with the simultaneous inhibition of COX-1 activity [3–5]. Therefore, the development of compounds that would inhibit COX-2 almost exclusively is an important target in order to reduce adverse side effects during non-steroidal anti-inflammatory treatment, thus improving therapeutic benefits.

It is interesting to note that most of the COX-2 inhibitors bear a common structural feature, namely a central heterocycle five-member ring (pyrazole in celecoxib/Celebrex®, 3,4-dihydrofuran-2-one in rofecoxib/Vioxx® or 1,2-oxazole in valdecoxib/Bextra®), and that several developments were based on that fact using, for example, tetrahydrofuran [5] or 1H-pyrrole [6], moreover, all these described compounds are vicinal substituted. Docking studies of this class of molecules have shown that they accommodate entirely in the binding site of COX-2 in positions very close to that of SC-558 in the crystal structure of its complex with COX-2 [7]. In view of this, and as a further extension to this work we decided to synthesize a series of C2, C5 diaryl substituted furans, instead of vicinal aryl substituted, to evaluate them as cyclooxygenase enzyme (COX-1 and COX-2) inhibitors.

2,5-Diarylfuran derivatives have been synthesized via many different ways, such as Stille coupling [8], Suzuki–Miyaura coupling [9], and Paal–Knoor synthesis [10]. They have also been obtained from phenacyl bromides [11] as well as from butane or butyne diones by microwave irradiation [12], and recently from alkynes by sequential synthesis [13]. Our research group has expanded the scope of the effective use of potassium organotrifluoroborates and organotellurium compounds in cross-coupling reactions [14], and recently reported the synthesis of 2-aryl and 2,5-diarylfuran and thiophene derivatives by Suzuki-Miyaura

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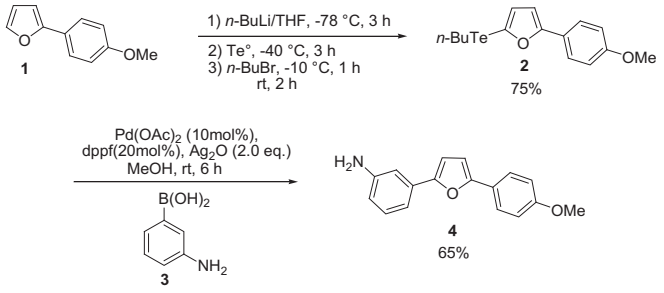


Scheme 1. Synthesis of 2,5-diarylfuran 3-AFA.

cross-coupling reactions between potassium aryltrifluoroborates and furanyl tellurides catalyzed by palladium [15]. Taking advantage of this well-established synthesis route, and that compounds functionalized with amino or carboxyl groups are commonly used for the conjugation of biomolecules [16], a series of C2, C5 diaryl substituted furans, instead of 3,4-diaryl substituted [17], and functionalized with amino acids were obtained, evaluated as cyclooxygenase enzymes (COX-1 and COX-2) inhibitors. Docking studies were also performed.

2. Methods

The COX inhibitor Screening Assay directly measures $PGF_{2\alpha}$ by $SnCl_2$ reduction of COX-derived PGH2 produced in the COX reaction. The prostanoid product is quantified via enzyme immunoassay (EIA) using a broadly specific antiserum that binds to all the major PG compounds. This assay includes COX-1 and COX-2 enzymes, allowing the screenning of isoenzyme-specific inhibitors (Cayman, catalog number 560131). In brief, amino acid-substitued compounds (10 nM; 20 μL) or celecoxib (10 nM; 20 μL) were incubated with COX-1 or COX-2 enzyme during 10 min, 37 °C. Following this period of incubation, arachidonic acid was added (10 mM; 10 μL) and incubated for 2 min at 37 °C. The reaction was stopped by adding 50 μl of HCl (1 M) and afterwards 100 μl of $SnCl_2$ saturated solution was added. The solution was incubated during 5 min, at room temperature. The PGE_2 formation was quantified in EIA procedure (420 nm). The PGE_2 formation was calculated on basis on a standard curve and percentage of inhibition was based on 100% initial activity sample.

3. Results and discussion

3.1. Synthesis of 2,5-diarylfuran amino acid derivatives

By applying the technique described by Botteselle et al. [15]. The synthesis of the desired 3-AFA **4** was accomplished starting from 2-(4-methoxyphenyl)furan **1** as depicted in Scheme 1. The resulting arylfuran **1** was converted into the butyltelluride **2** by treatment with *n*-BuLi in THF followed by the addition of elemental tellurium to generate the intermediate tellurolate, which was alkylated with *n*-BuBr. This method was previously described in the literature [18]. The 2-(butyltellanyl)-5-(4-methoxyphenyl)furan **2** was subjected to palladium(II) acetate-catalyzed Suzuki–Miyaura coupling to boronic acid **3** using 1,1′-bis-(diphenylphosphino)ferrocene (dppf) as the ligand in the presence of Ag_2O as an additive and methanol as a solvent at room temperature (Scheme 1). The 3-AFA **4** was obtained in 65% yield.

It is worth pointing out that the reaction shown above is time-dependent. Attempts to synthesize 3-AFA **4** after stirring for 2 and 3 h gave the product in low yields of 25% and 35%, respectively. When the reaction mixture was stirred for 6 h, the product was obtained in moderate yield of 65%. For the formation of the intermediates 2-(4-methoxy)furyl lithium and 2-(4-methoxy)furyl tellurolate a period of 3 h of stirring is required.

The optimal reaction conditions for promoting the coupling between the 3-AFA **4** and the Boc-glycine **5a** were examined. In the first approach diethylcianophosphonate (DEPC) was used as the catalyst, Et_3N as the base, and DMF as the solvent. The product **6a** was formed in low yield together with a few side products. This reaction condition was also used with other amino acids (Boc-alanine **5b**, Boc-leucine **5d** and Boc-phenylalanine **5f**), and in all cases with low yield and also unwanted side products were formed.

Then the peptide coupling was performed under the usual conditions [19], that is, using a two molar excess of Boc-glycine **5a**, diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole (HOB*t*) in dichloromethane (DCM) at room temperature for 20 h. The desired product Boc-Gly **6a** was obtained in an excellent yield of 81% and no side products were observed in this reaction (Scheme 2).

The reaction proved to be efficient as the conjugation with several other natural amino acids **5b**–**l**, with the appropriate side chain protection was performed and the corresponding compounds, **6a**–**l**, were obtained in moderate to excellent yields, as shown in Table 1.

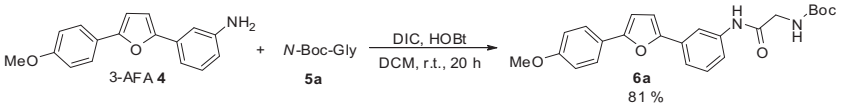
3.2. COX inhibition activity

As stated before, several COX-2 inhibitors, namely the coxibs, have as a common feature vicinal diaryl substituted heterocycles and as the compounds synthesized in our lab resemble these COX inhibitors, with the difference of being 2,5-diaryl substituted, their biological activity and the influence of different amino acids were investigated quantifying prostaglandin E2 (PGE_2) levels in neutrophil culture supernatants.

Neutrophils are cells that are activated, secreting microbicidal compounds, when microorganisms made their way into tissues, thus killing the injurious agent [20]. They are also the most important cells in the initial stage of sepsis [21]. In an exacerbated inflammatory response, neutrophils activities cause huge tissue damage [20], and therefore, inhibitions of neutrophils activities are a target for developing anti-inflammatory drugs.

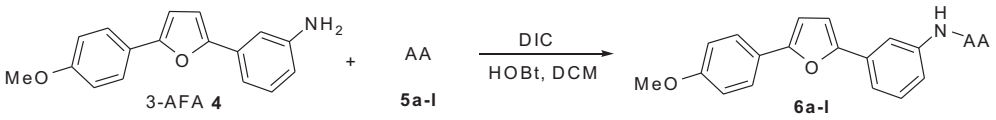
The effect on cell viability was measured on neutrophils treated with 1, 10, 100, and 1000 nM of the amino acid-substituted compounds. Concentrations greater than 100 nM reduced neutrophil viability, compared to control cells (data not shown). Incubation of neutrophils with 10 nM of the different amino acid-substituted compounds did not modify the cell viability (Fig. 1).

PGE_2 levels in the supernatant of cultured neutrophils incubated with celecoxib and compounds with proline, valine, cysteine, and phenylalanine at a final concentration of 10 nM, in absence or



Scheme 2. Peptide coupling conditions used for the conjugation of 3-AFA **4** with *N*-Boc-Gly **5a**.

Table 1
Conjugation of several natural protected amino acids **5a-l** with a free probe 3-AFA **4**.



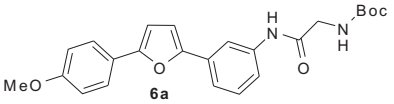
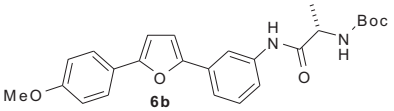
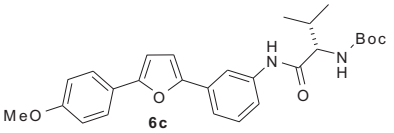
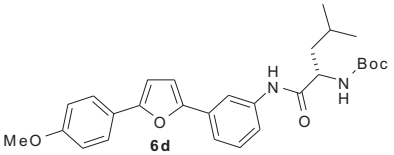
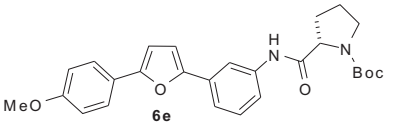
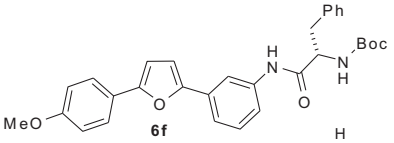
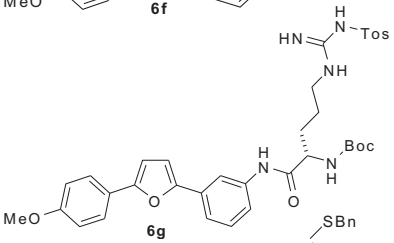
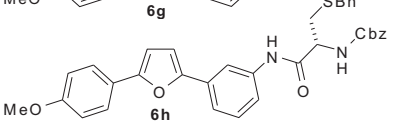
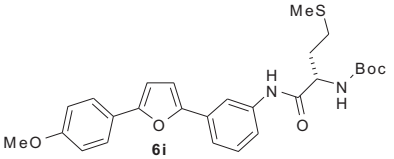
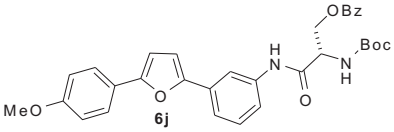
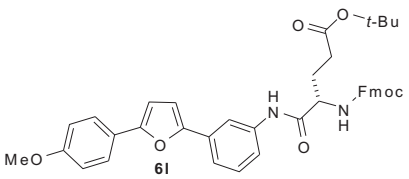
Entry	Product	Yield (%)[a]
1	 **6a**	81
2	 **6b**	63
3	 **6c**	86
4	 **6d**	79
5	 **6e**	91
6	 **6f**	73
7	 **6g**	55
8	 **6h**	50
9	 **6i**	89
10	 **6j**	85

Table 1 (*continued*)

Entry	Product	Yield (%)[a]
11	 6l	43

[a] Isolated yields.

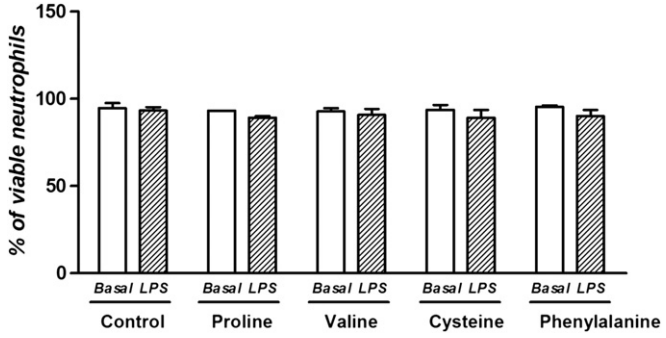


Fig. 1. Effects of substituted amino acid groups on neutrophils viability. Cells were obtained from male Wistar rats 4 h after intraperitoneal injection of oyster glycogen (1%, 10 mL). Neutrophils were incubated with 10 nM of each compound in the absence or presence of LPS (5 mg/mL) and for 18 h. Control cells were incubated with cell medium (RPMI1640 + 10% FBS). Neutrophil viability was determined by trypan blue staining.

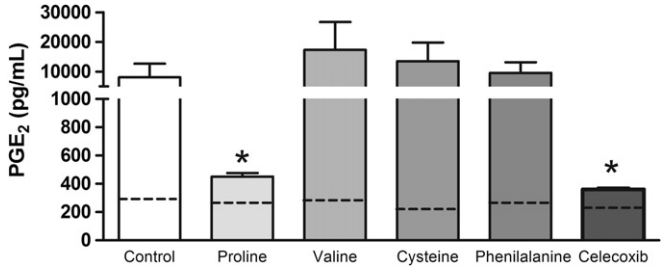


Fig. 2. PGE_2 levels were quantified in neutrophil culture supernatant by EIA. The dotted line represents the basal value. Results are expressed as the mean ± s.e.m. of cells collected from four animals. $^{*}P < 0.001$ vs. control.

presence of LPS, are shown in Fig. 2. In absence of stimulation, similar levels of PGE_2 were found in all cases as shown by the dotted line in Fig. 2. LPS induced the secretion of PGE_2, and increased levels of the mediator were detected in control cells after

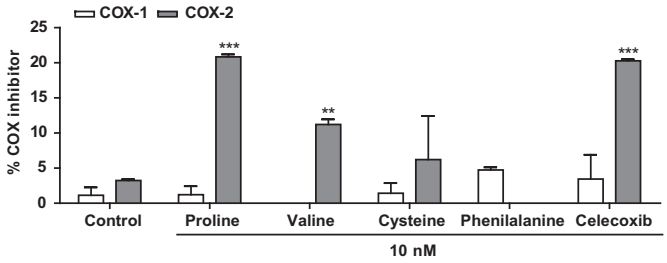


Fig. 3. Inhibition on COX-1 and COX-2 activities were measured using the EIA COX inhibitors screening assay. Results are expressed as the mean ± s.e.m. of % of inhibition. $^{***}P < 0.001$ and $^{**}P < 0.01$ vs. control.

Table 2
Binding energy for ligands in the active site of COX-2.

Ligand	Goldscore	$\Delta G_{binding}$ (kcal/mol)
Redocking	78.41	−10.70
Pro-R	67.13	−9.48
Pro-S	65.39	−9.30
Cys-R	50.06	−7.65
Cys-S	83.08	−11.20
Phe-R	70.44	−9.84
Phe-S	66.71	−9.44
Val-R	74.02	−10.22
Val-S	72.41	−10.05
		−9.65

stimulation (in comparison to basal values). The valine, cysteine, and phenylalanine-substituted compounds did not modify the elevated concentration of PGE_2; on the other hand, the proline-substituted compound and celecoxib, a selective COX-2 inhibitor, decreased LPS-induced PGE_2 secretion (Fig. 2).

It has been shown that 18 h of culture rat leukocytes were found to express COX-1 and there were no detectable levels of COX-2, being the latter highly expressed after LPS stimulation [22]. Thus, by measuring the PGE_2 levels in non-stimulated and LPS-stimulated neutrophils, it is shown that all amino acid-substituted compounds did not affect COX-1 activity, as basal values of PGE_2 were not altered, but the proline-substituted

Table 3
Main interactions of Pro ligand in COX-2.

Ligand	Ligand atom	Pro	Distance (Å)
Common part of the molecule on the active site of COX-2	O1	ARG120:HH11	2.88
	O1	TYR355:HH	3.00
	O1	ALA527:HB2	3.18
	O1	ALA527:HB3	3.30
	O2	HIS90:HE2	2.02
	O2	SER353:HA	2.80
	O3	THR94:HG22	2.66
	O3	THR94:HG23	3.48
	H1	LEU352:O	2.87
	H4	TYR355:OH	2.99
	H8	LEU352:O	2.76
	H9	LEU352:O	3.17
	H10	GLN192:OE1	2.13
	H10	SER353:O	3.02
	H14	GLN192:OE1	2.68
	H14	ASP515:O	3.36
Part of the ligand exposed to the solvent	H18	PRO191:O	3.24
	H19	PRO191:O	3.39
	H19	ASP515:O	2.98
	H25	THR94:O	3.38
	H25	TYR355:O	2.50
	H26	THR94:O	3.15
	H26	GLY354:O	3.13
	H26	TYR355:O	2.50
	H27	THR94:O	2.78
	H30	GLY354:O	3.15

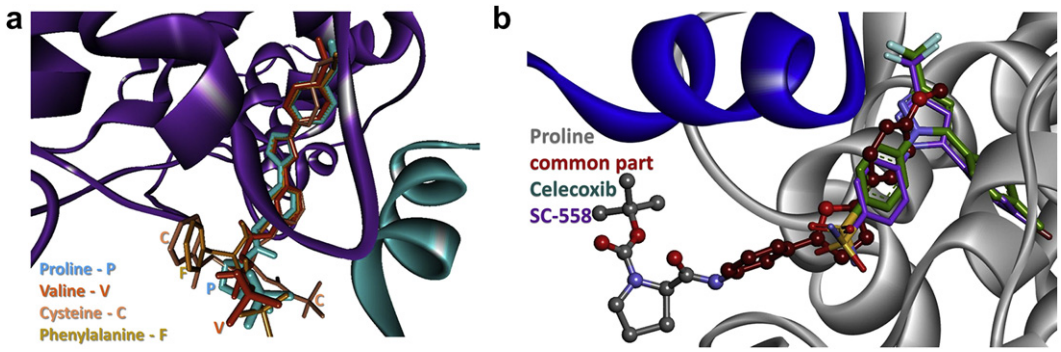


Fig. 4. (a) The ligands inside the active site. COX-2 is represented in ribbon form. In cyan is shown the part of the protein that penetrates the single leaflet of the lipid bilayer. (b) The Pro compound (the common part of the molecules is in red), docked together with celecoxib and SC-558 from the crystal structure (PDB code: 1CX2). The figure was drawn with DS-Visualizer [30].(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

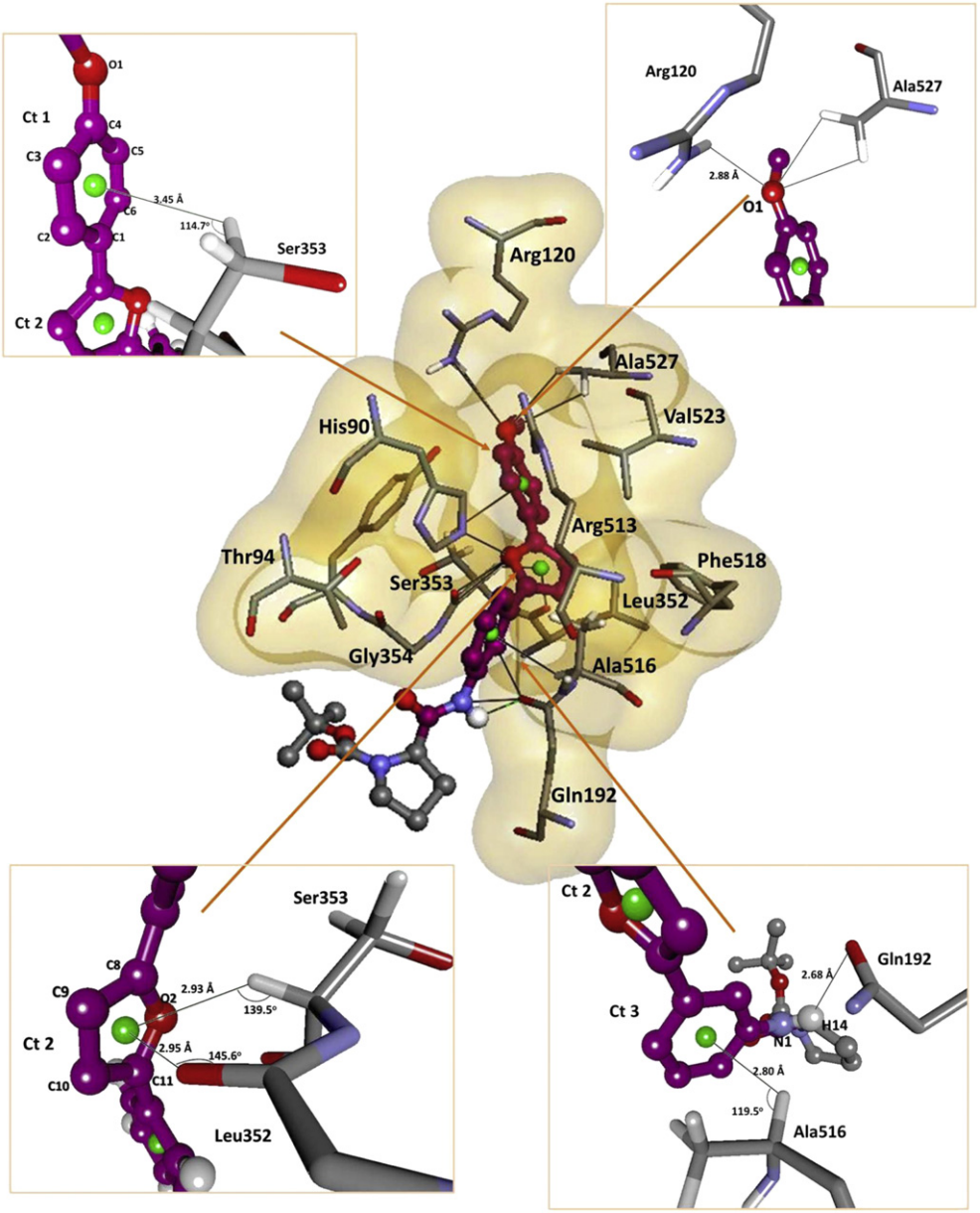


Fig. 5. The Pro-ligand···π interactions. For the sake of clarity, not all the H-atoms are shown. The figure was drawn with DS-Visualizer [30].

Table 4
Amino acid hydrophobicities.

Amino Acid	Hydropathy index
	(highly hydrophilic)
Proline	−1.6
Cysteine	2.5
Phenylalanine	2.8
Valine	4.2
	(highly hydrophobic)

compound markedly reduced LPS-induced PG2 secretion, which may indicate a selective action on COX-2 activity. The effect of proline-substituted on COX-2 activity was corroborated using COX inhibitors screening assay [23,24]. As shown in Fig. 3, only proline-substituted compound exhibited the same inhibitory potency of celecoxib on COX-2 activity. Although, valine or cistein-substituted compounds did not affect PGE2 levels on LPS-stimulated neutrophils supernatant, their direct incubation with the enzymes inhibited COX-2 action. The activities were lower than those found in proline-substituted compound and celecoxib. This difference on obtained data may be due experimental conditions, involving different biological systems. While, PGE_2 levels were quantified in cultured cells, which depend on cell metabolism, COX activity was measured directly on enzyme system, without cell participation. No significant inhibition on COX-1 activity was detected in all of compounds studied. As previously reported, the adverse effects of COX inhibitors are mainly linked to inhibition of the production of COX-1 generated products, which exert physiological actions [1].

3.3. Docking studies

In order to rationalize the different biological results shown in Fig. 2, molecular docking studies of the *S* and *R*-enantiomers for compounds with Pro, Cys, Phe and Val, modeled with MarvinSketch [25], and celecoxib were performed. The GOLD program (version 4.1.1) with GOLDScore was used [26–28]. The obtained GOLDScores and corresponding binding energies are shown in Table 2.

The docking studies showed that, in all cases, the common part of the molecules, namely the 2-(4-methoxyphenyl)-5-phenylfuran moiety, fits in the long narrow hydrophobic channel of the COX-2 active site in the same fashion, whether the substituent amino acids are positioned at the entrance of the channel that opens to the active site, thus this entrance is in some instance “closed” by the amino acid moiety which is, then, exposed to the solvent (Fig. 3a). In Fig. 3b it is shown the superposition of the ligand SC-558, as it is in the X-ray crystal structure [7] (PDB code: 1CX2 [29]) to the docking results of celecoxib and the Pro compound, as representative of the poses of the compounds studied here. It can be seen that there is a good overlap between the moieties of the compounds that are located in the active site. The main interactions of the Pro-ligand are collated in Table 3. Fig. 4 shows that, along with the interactions described in Table 3, there are several C–H…π interactions, involving the phenyl ring attached to the methoxy group with Ser353, the furan ring making two different interactions with Ser353 and an O···π with Leu352, and the other phenyl ring with Ala516. Fig. 5

These results indicate that the different activities could not be attributed to the interactions of the compounds in the active site, but is more likely a consequence of the part of the ligand that is exposed to the solvent. Since these amino acids have different hydrophobicity we decided to use the Kyte & Doolittle hydrophaty index (Table 4), with values ranging from −4.5 (hydrophilic) to 4.5 (hydrophobic) [31], in order to find a correlation.

For the studied ligands the most hydrophilic moiety is proline, so it would be expected that, as this part of the ligand is exposed to the solvent, it should be the most active, moreover, the lowest activity should be expected for valine, which is the most hydrophobic. As this is precisely what was observed in the inhibition experiment, it can be rationalized that, in this case, inhibition capacity was related to the part of the ligand that was outside the active site, thus, exposed to the solvent.

4. Conclusion

We described herein the synthesis of a novel 2,5-diarylfuran scaffold and its conjugation with different amino acids (**3-AFA**). We showed that the proline-substituted compound inhibited PGE_2 secretion by LPS-stimulated neutrophils and inhibited COX-2 activity similarly to celecoxib, showing selectivity for COX-2 activity.

The analysis of docking results allowed us to postulate that the inhibition activity of the studied compounds was modulated by the hydrophilicity of the amino acid that was attached to them.

Finally, we expect that these results will contribute to the development of newer anti-inflammatory molecules with fewer adverse side effects.

Acknowledgments

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Appendix. Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.ejmech.2011.10.018.

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