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1-Indol-2-yl-propan-2-ones as dual inhibitors of cytosolic phospholipase $A_2\alpha$ and fatty acid amide hydrolase

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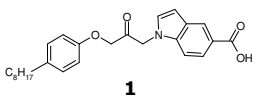
Introduction

In mammalian organism, derivatives of arachidonic acid play important roles as algesic and pro-inflammatory as well as analgesic and anti-inflammatory mediators. On the one hand, oxidation products of arachidonic acid such as prostaglandin E_2 and leukotriene B_4 formed via the arachidonic acid cascade are involved in the pathophysiology of pain and inflammation. On the other hand, the arachidonic acid amide anandamide generated via the endocannabinoid pathway has analgetic and anti-inflammatory properties. The key enzyme in the formation of oxidized derivatives of arachidonic acid is cytosolic phospholipase $A_2\alpha$ ($cPLA_2\alpha$). An important enzyme in the endocannabinoid metabolism is fatty acid amide hydrolase (FAAH), which rapidly inactivates anandamide by cleavage to arachidonic acid and ethanolamine. Therefore, inhibitors of both $cPLA_2\alpha$ and FAAH may represent new agents against pain and inflammation.

Recently we have found that the indole-5-carboxylic acid derivative **1** is a dual inhibitor of $cPLA_2\alpha$ and FAAH. In course of structure-activity relationship studies, the indole part of the molecule has been varied.[1] In further studies we replaced the octyl chain of **1** by other residues such as alkyloxy, phenoxy, benzyloxy and phenyl. The results of these structural variations of **1** on inhibitory potency against both enzymes are presented.

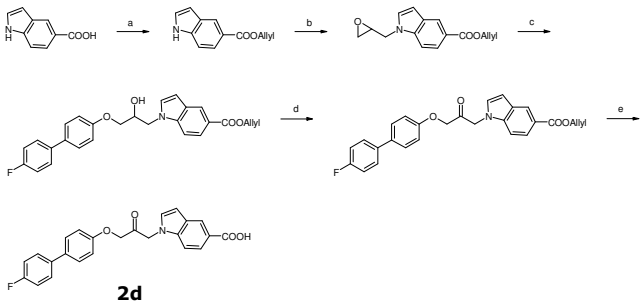


1

IC_{50} [µM] Inhib. $cPLA_2\alpha$	IC_{50} [µM] Inhib. FAAH
0.035	2.6

Synthesis

Most of the target compounds were synthesized on the route outlined below for the formation of **2d**.[2] In some cases instead of an allyl ester a benzyl ester protecting group was applied. This reaction sequence was less favourable, since cleavage of the benzyl ester in the last reaction step by catalytic hydrogenation led to the formation of indoline by-products.



2d

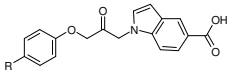
a: Allylbromide, $NaHCO_3$, DMF, room temp.; **b:** epichlorohydrin, KOH, Bu_4NBr, room temp.; **c:** 4-(4-fluorophenoxy)phenol, 4-dimethylaminopyridine, 90°C; **d:** Dess-Martin-periodinane reagent, CH_2Cl_2, room temp.; **e:** $Pd(PPh_3)_4$, CH_3COOH, THF, room temp.

Biochemical Testing

The compounds were screened in a $cPLA_2\alpha$ assay (n=2)[3] and a FAAH assay (n=2)[4] as previously described.

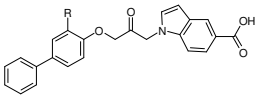
Results and Discussion

Table 1: Inhibitory activity of phenyl-, alkyloxy-, phenoxy-, benzyloxy-substituted compounds



R	Comp.	IC_{50} [µM] Inhib. $cPLA_2\alpha$	IC_{50} [µM] Inhib. FAAH	R	Comp.	IC_{50} [µM] Inhib. $cPLA_2\alpha$	IC_{50} [µM] Inhib. FAAH
	**2a**	0.064	0.46	$H_{13}C_6O$-	**3a**	0.034	3.5
	**2b**	0.027	0.53	$H_{15}C_7O$-	**3b**	0.032	3.4
	**2c**	0.019	0.23	$H_{17}C_8O$-	**3c**	0.026	2.2
	**2d**	0.037	0.24	$H_{19}C_9O$-	**3d**	0.023	1.8
	**2e**	0.041	0.25		**3e**	0.036	1.3
	**2f**	0.090	0.53		**3f**	0.019	>10
	**2g**	0.040	0.58		**3g**	0.054	1.9
	**2h**	n. a.	0.64		**3h**	0.047	2.9
	**2i**	0.035	5.9				

Table 2: Inhibitory activity of 2-substituted biaryl compounds



R	Comp.	IC_{50} [µM] Inhib. $cPLA_2\alpha$	IC_{50} [µM] Inhib. FAAH	R	Comp.	IC_{50} [µM] Inhib. $cPLA_2\alpha$	IC_{50} [µM] Inhib. FAAH
F-	**4a**	0.23	0.59	H_3C-	**4c**	3.7	> 10
Cl-	**4b**	2.8	5.0	H_3CO-	**4d**	8.1	7.4
				H_3COOC-	**4e**	n. a.	> 10

Substitution of the octyl-chain of the lead **1** by a phenyl residue led to a two-fold decrease of $cPLA_2\alpha$ inhibition, while FAAH inhibitory potency increased about six-fold. The IC_{50}-values of obtained **2a** against the two enzymes were 0.064 µM and 0.43 µM, respectively. Introduction of substituents in the phenyl residues of **2a** modified activity as shown in Tables 1 and 2. Replacement of the octyl-group of **1** by different alkoxy-, phenoxy- and benzyloxy-moieties did not improve $cPLA_2\alpha$ and FAAH inhibition substantially.

References

[1] Forster, L.; Ludwig, J.; Kaptur, M.; Bovens, S.; Schulze Elfringhoff, A.; Holtfrerich, A.; Lehr, M. *Bioorg . Med. Chem.* **2010**, *18*, 945-952
[2] Drews, A. *PhD Thesis, Univetsity of Münster,* **2008**
[3] Schmitt, M.; Lehr, M. *J. Pharm. Biomed. Anal.* **2004**, *35*, 135-142
[4] Forster, L.; Schulze Elfringhoff, A.; Lehr, M. *Anal. Bioanal. Chem* **2009**, *394*, 1679-1685