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Discovery of new C3aR ligands. Part 2: Amino-piperidine derivatives

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Abstract—The synthesis and structure–activity relationships against the C3a receptor of a series of substituted aminopiperidine derivatives are reported. DMPK properties and functional activities of selected compounds are described. The compounds obtained are the first non-arginine ligands of C3aR.

The complement system is well known for its central role in the inflammation process. This wonderful machinery may sometimes turn against its host and create various inflammatory diseases, such as asthma, rheumatoid arthritis, etc. To treat such diseases, it should be possible to reduce the efficacy of the complement cascade by blocking it at strategic points with small molecules.

Our interest for C3aR ligands (see previous paper) has prompted us to screen UCB's collection of compounds against the C3a receptor. As a result, compound **1** (Fig. 1) was identified with a pIC_{50} of 5.8. We were particularly delighted as this is—to the best of our knowledge—the first C3aR ligand not to display the ubiquitous arginine.[1] A first SAR study around **1** indicated that although the regiochemistry around the pyridine seemed essential—as seen from compounds **2** and **3**, it was nonetheless possible to modify the xanthene ring and retain some activity. Compound **5** in particular was quite attractive to start a medicinal chemistry program as it had much better solubility than the starting hit (0.1 mg/ml instead of <0.0001 mg/ml).

Depending on the focus of interest, we used two main approaches to generate derivatives of **5**. 'Western' side modulations required the alkylation of commercially available arylacetic acids **A/E** with cyclohexyl tosylates. Best results were obtained by treating the arylacetic acid with two equivalents of *n*-butyllithium and treating the resulting dianion at low temperature with a cyclohexyl tosylate. The resulting acids **B/F** were finally coupled

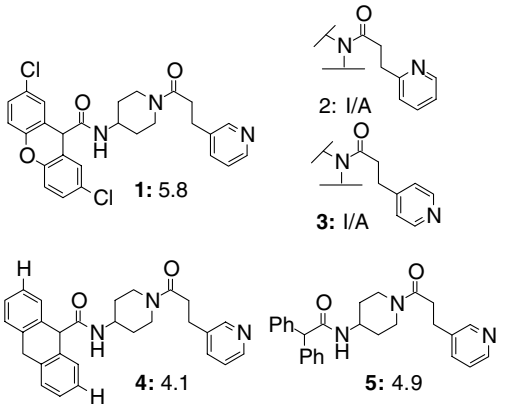

Figure 1. HTS result and preliminary SAR around **1**. Numbers refer to pIC_{50} values against C3aR. I/A, inactive.

Keywords: C3a; Inflammation; SAR; Agonist.
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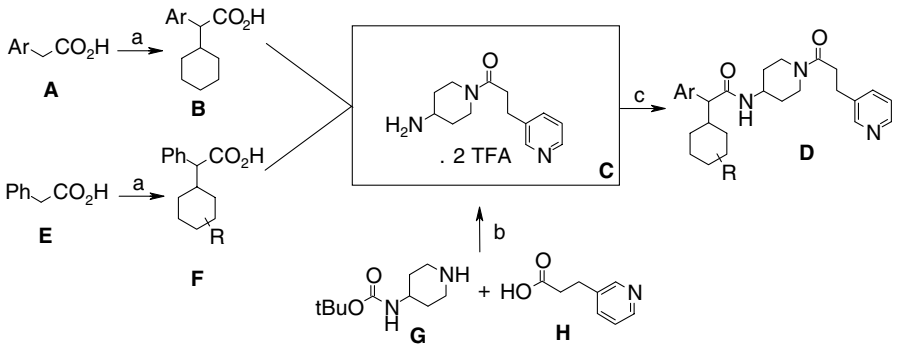


Scheme 1. 'Western' side modulations. Reagents and conditions: (a) *n*-BuLi (2 equiv), (R)CyOTs, THF, −70–20 °C (40–80%); (b) i. $(COCl)_2$, cat DMF, DCM then amine, Et_3N (60–70%). ii. TFA, DCM (100%); (c) EDCI, HOBt, DMF (40–50%).

using standard amide formation techniques with the required aminopiperidine derivative **C** (Scheme 1).

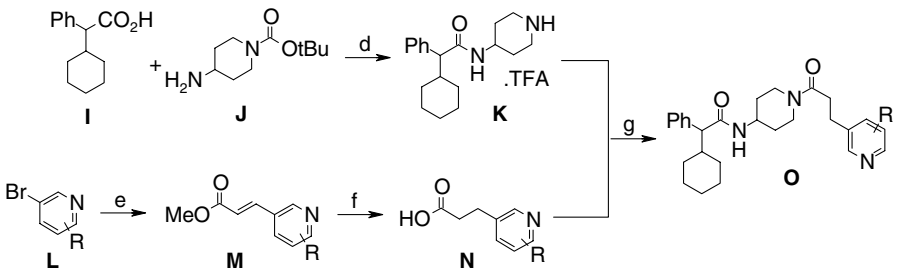
'Eastern' side modulations of the aminopiperidine scaffold required the coupling of cyclohexyl phenylacetic acid **I** with commercially available 1-Boc-4-aminopiperidine **J**. The resulting amide was deprotected **K** and coupled with the required aryl propanoic acid derivative **N**. It could be obtained by Heck coupling of methyl acrylate with the corresponding bromopyridine **L** (Scheme 2).

While the initial modifications of the diphenylmethyl based on the original xanthene substitution gave only poor results (Table 1), it was quickly discovered that the transformation of one phenyl group into a cyclohexyl **7** led to a very interesting increase of the affinity. Further modifications on the cyclohexyl group (**8**–**14**) did not bring about any other improvement in affinity. However, the two enantiomers of **7** were separated and the best enantiomer **7B** (chirality not determined) was found to be ca. 10-fold more active against C3aR than the less active enantiomer **7A**.

Substituents of the phenyl ring were then investigated and were found to have more influence on the affinity compared to cyclohexyl substitution. Meta substituted compounds with small lipophilic groups such as Me **17** and Cl **22** were found especially active with a tenfold boost over their unsubstituted counterparts. 3,5-Disubstitution gave equiactive compound **18** but its lower solubility made it a less interesting candidate.

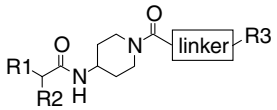
Finally, modifications of the arylpropanoyl group were investigated. We already knew from the preliminary SAR on **2** and **3** (Fig. 1) that the regiochemistry of the pyridine attachment was of prime importance. The replacement of the pyridyl ring by a phenyl in **34**–**36** led to a sharp drop in affinity, pointing to the key role of the pyridine. It was also discovered that substitution of the pyridine was very delicate. While a methoxy **29** or a methyl **33** gave poor binders, the 6-fluoro **31** kept a good affinity and the 2-fluoro **30** finally gave us a much better binder. The most promising compounds were screened internally against a panel of 20 GPCR's and did not reveal any other significant affinity.

DMPK profiling of our best compounds was uniformly disappointing (Table 2). All compounds were found to suffer from high metabolic instability in vitro as well as low oral bioavailability and rapid elimination in vivo (rat data). Compound **7** was selected as a representative candidate for further investigations. It showed a high microsomal clearance whatever the species (rat, guinea-pig, dog, and human). Portal vein experiment in rat (1 mg/kg) demonstrated a high hepatic extraction ratio. Finally, its in vivo profile in male dog (1 mg/kg) was similar to the one observed in rat with low oral bioavailability (4%) and rapid elimination half-life (0.3 h).



Scheme 2. 'Eastern' side modulations. Reagents and conditions: (d) i. $(COCl)_2$, DMF cat, DCM then amine, Et_3N; ii. TFA, DCM (75%); (e) methyl acrylate, $Pd(OAc)_2$, P(*o*-Tol)$_3$, DMF, 80 °C (50%); (f) i. H_2, Pd/C, MeOH; ii. NaOH, MeOH (90%); (g) EDCI, HOBt, DCM, Et_3N (40–50%).

Table 1. Structure–activity relationship of aminopiperidine derivatives



Compound	R^1	R^2	Linker	R^3	C3a pIC_{50}[a]
1	Dichloroxanthene		C_2H_4	3-Pyridyl	5.8
2	Dichloroxanthene		C_2H_4	2-Pyridyl	I/A
3	Dichloroxanthene		C_2H_4	4-Pyridyl	I/A
4	Dihydroantracene		C_2H_4	3-Pyridyl	4.1
5	Phenyl	Phenyl	C_2H_4	3-Pyridyl	4.9
6	4-Chlorophenyl	4-chlorophenyl	C_2H_4	3-Pyridyl	4.7
7	Phenyl	Cyclohexyl	C_2H_4	3-Pyridyl	6.1
7A	Phenyl	Cyclohexyl (epimer A)	C_2H_4	3-Pyridyl	5.3
7B	Phenyl	Cyclohexyl (epimer B)	C_2H_4	3-Pyridyl	6.5
8	Phenyl	4,4-Dimethylcyclohexyl	C_2H_4	3-Pyridyl	6.0
9	Phenyl	4,4-Difluorocyclohexyl	C_2H_4	3-Pyridyl	6.2
10	Phenyl	3,3,5,5-Tetramethylcyclohexyl	C_2H_4	3-Pyridyl	4.2
11	Phenyl	Cyclohexylmethylene	C_2H_4	3-Pyridyl	4.6
12	Phenyl	Methylcyclohexyl	C_2H_4	3-Pyridyl	6.1
13	Phenyl	Cyclopentyl	C_2H_4	3-Pyridyl	6.1
14	Phenyl	3-Cyclopentenyl	C_2H_4	3-Pyridyl	5.5
15	4-Methylphenyl	Cyclohexyl	C_2H_4	3-Pyridyl	6.1
16	2-Methylphenyl	Cyclohexyl	C_2H_4	3-Pyridyl	5.6
17	3-Methylphenyl	Cyclohexyl	C_2H_4	3-Pyridyl	7.1
18	3,5-Dimethylphenyl	Cyclohexyl	C_2H_4	3-Pyridyl	6.9
19	4-Methoxyphenyl	Cyclohexyl	C_2H_4	3-Pyridyl	6.2
20	4-Chlorophenyl	Cyclohexyl	C_2H_4	3-Pyridyl	6.7
21	2-Chlorophenyl	Cyclohexyl	C_2H_4	3-Pyridyl	5.7
22	3-Chlorophenyl	Cyclohexyl	C_2H_4	3-Pyridyl	7.3
23	3-Thienyl	Cyclohexyl	C_2H_4	3-Pyridyl	6.7
24	4-Fluorophenyl	Cyclohexyl	C_2H_4	3-Pyridyl	6.8
25	3,4,5-Trifluorophenyl	Cyclohexyl	C_2H_4	3-Pyridyl	7.0
26	4-Nitrophenyl	Cyclohexyl	C_2H_4	3-Pyridyl	6.5
27	2-Naphthyl	Cyclohexyl	C_2H_4	3-Pyridyl	6.1
28	Cyclohexyl	Cyclohexyl	C_2H_4	3-Pyridyl	6.0
29	Phenyl	Cyclohexyl	C_2H_4	2-Methoxy-3-pyridyl	4.8
30	Phenyl	Cyclohexyl	C_2H_4	2-Fluoro-3-pyridyl	7.5
31	Phenyl	Cyclohexyl	C_2H_4	6-Fluoro-3-pyridyl	5.9
32	Phenyl	Cyclohexyl	C_2H_2	3-Pyridyl	6.0
33	Phenyl	Cyclohexyl	C_2H_2	5-Methyl-3-pyridyl	4.3
34	Phenyl	Cyclohexyl	C_2H_4	2-Fluorophenyl	5.7
35	Phenyl	Cyclohexyl	CH_2	2,3-Difluorophenyl	5.0
36	Phenyl	Cyclohexyl	C_2H_2	2-Fluorophenyl	4.9

[a] Values are means of three experiments. Assays were performed in 96-well format using Wheat germ agglutinin SPA beads (GE). Various concentrations of compounds were added, followed by ^{125}I-C3a (2200 Ci/mmol, PE) at 0.02 nM in 120 μl of 50 mM Tris/2 mM $MgCl_2$ gC/0.5% BSA. Non-specific binding was determined using C3a at 1 nM. Pre-coupled beads and membrane prepared from HMC-1 cells (stably expressing both Aequorin and the human C3a receptor) diluted in 80 μl buffer were then added. Plates were sealed and incubated at rt for 3 h. Bound C3a was determined by scintillation counting on a Wallac Beta Trilux scintillation counter.

None of the modifications of the 'eastern' or 'western' parts of the molecules did alleviate the metabolic instability issue. In particular, halogen substitution on the phenyl ring (**6**, **20**, and **25**) to block potential oxidation sites did not translate into any benefit. It was thus tentatively assumed that the amino-piperidine central core was responsible for the observed DMPK liabilities. New compounds will be prepared to validate this hypothesis.

In a functional activity test (Table 3), the same subtle influence of substituents was found as in our arginine derivatives.[1] It was found that although the starting hit was an antagonist, most of our cyclohexyl-bearing compounds were in fact full agonists at the C3a receptor.

In conclusion, we have identified the first C3aR binders not displaying a guanidine function in their structures. Rather surprisingly, most of these compounds were found to be agonists. They would thus constitute the first small molecules with an agonistic profile on C3aR.[2] These agonists could be useful starting points for the treatment of memory altering diseases.[3–6] Nonetheless, we still aim to turn them into antagonists for the treatment of inflammatory diseases. Preliminary data indicate that substitution of the cyclohexyl group might lead to antagonists. Furthermore, the amino-piperidine

Table 2. DMPK properties of selected compounds

Compound	Cl micros[a]	Cl hepat.[b]	Caco-2[c]	F[d] (%)	$T_{1/2}$[d] (h)
5	500	21	8.5	5	0.1
6	175		6.3	0	0.4
7	500	33	12	5	0.2
9	170		16	2	0.3
12	500	44		1	0.7
20	500	28	10	0	0.3
25	609	17		0	0.3
27	585			9	0.5
28	675			6	0.2
31	782		19	0	0.3
32	238	26	8.5	7	0.3
33	175	21	7.9	3	0.3

[a] Clearance on rat microsomes (μl/min/mg prot.).
[b] Clearance on rat hepatocytes (μl/min/10^{-6} cells).
[c] Permeability through Caco-2 cells ($\times 10^6$ cm/s).
[d] Data after single oral and iv dosing to male rat at 1 mg/kg.

Table 3. Functional activities of selected compounds

Compound	SPA binding pIC_{50}	Ant. activity[b] pEC_{50}	Ago activity[a] pEC_{50}
1	5.9	6.2	—
5	4.9	5.5	
7	6.1		5.7
22	7.3	—	6.7
25	7.0		6.1
27	6.1		5.8
30	7.5		6.7

[a] HMC-1 cells stably expressing both Aequorin and the human C3a receptor were loaded with 10 μM Coelenterazine in HBSS/Hepes 20 mM/BSA 0.2%, pH 7.4, for 2 h at 37 °C. They were then diluted four times, placed in 96-well plates (200 μl final volume, 1% DMSO), and incubated for 1 h at 37 °C. Fifty microliters of compound dilutions was then injected to get a final volume of 250 μl at 1% DMSO final concentration. Emitted light was immediately recorded for 30 s using Novostar (BMG). The maximal signal was determined in the presence of C3a agonist (Advanced Research Technologies, 50 nM).
[b] Following the 2-h incubations with Coelenterazine, the cells were plated and treated with compounds dilutions (200 μl final volume, 1% DMSO) for 1 h at 37 °C. Fifty microliters of C3a agonist (final concentration of 5 nM) was then injected. Emitted light was immediately recorded for 30 s using Novostar (BMG).

core will be modified to improve the poor DMPK profile of the family. Our efforts in that direction will be reported in due course.

References and notes

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