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Identification of novel TACE inhibitors compatible with topical application

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ABSTRACT

Targeting the Tumor Necrosis Factor α signalling with antibodies has led to a revolution in the treatment of psoriasis. Locally inhibiting Tumor Necrosis Factor α Converting Enzyme (TACE or ADAM17) could potentially mimic those effects and help treat mild to moderate psoriasis, without the reported side effect of systemic TACE inhibitors. Efforts to identify new TACE inhibitors are presented here. Enzymatic SAR as well as ADME and physico-chemistry data are presented. This study culminated in the identification of potent enzymatic inhibitors. Suboptimal cellular activity of this series is discussed in the context of previously published results.

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The advent of antibodies targeting the Tumor Necrosis Factor α signalling has revolutionized our approach to psoriasis treatment.[1,2,3] Targeting this key pathway on a local level could potentially be a way to treat mild psoriasis with a topical compound. In this setting, the Tumor Necrosis Factor α Converting Enzyme (TACE or ADAM17) stands out as a druggable target for such an approach.[4] Recent studies have also suggested that inhibition of the TACE could also potentially benefit other acne patients,[5] highlighting this as a key target for dermatology.

TACE inhibitors have been intensely studied in the past and were thought to have great potential in treating auto-immune diseases like rheumatoid arthritis.[6] Unfortunately, these inhibitors have not been able to reach the market yet. This disappointing result has often been linked to a lack of efficacy, poor pharmacokinetics and/or toxicity issues potentially linked to a lack of selectivity *vs* other matrix metalloproteinases (MMP). The advantage of modulating TACE only locally would be to limit systemic toxicity and potentially mitigate the risks associated with previous programs.

Figure 1 highlights two of the most studied TACE inhibitors, Apratastat (**1**) and DPC333 (**2**).[7,8]

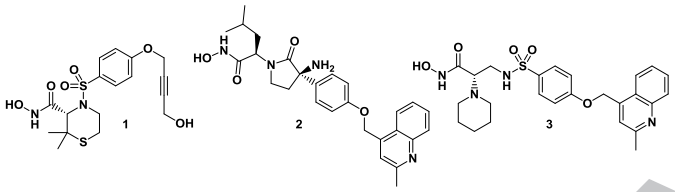
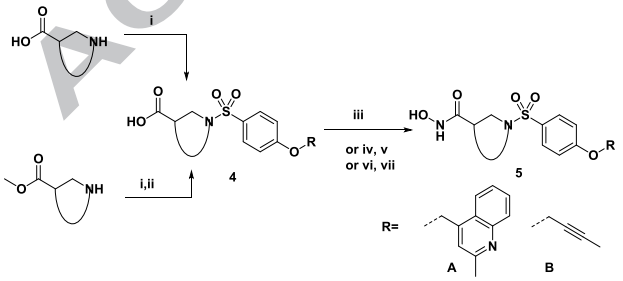


Figure 1. Apratastat (**1**), DPC-333 (**2**) and representative structure from the first generation of TACE inhibitors developed at Galderma (**3**)

Researchers at Galderma have identified a first generation of TACE inhibitors (**Figure 1**; **3** is a representative compound from this series) which has now reached the clinic.[9] In order to secure this area of interest, a back-up program was started with the aim of identifying structurally distinct inhibitors.

A quick survey of the literature highlighted the importance of either a methyl quinoline group (as in DPC-33; **2**) or an alkyne group (as in Apratastat; **1**) in the S1' pocket of the enzyme to ensure good potency and selectivity.[6] Starting from these two handles, we decided to broadly explore novel cyclic linkers to the hydroxamic Zn binding group.

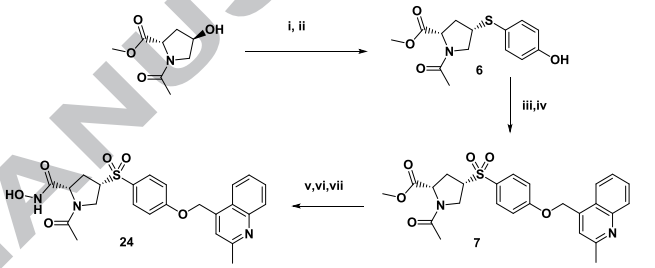
Syntheses of the compounds described in this manuscript were relatively straightforward starting from the corresponding amino acid or ester.[10,11] **Scheme 1** depicts the general strategy.



Scheme 1. General synthetic approach to compounds described in this manuscript: (i) Phenoxychlorosulfonyl derivative, triethylamine, dioxane/water (2/1); (ii) NaOH, THF/water (5/1) 50° C; (iii) *N*-methylmorpholine, isobutyl chloroformate, NH2OH.HCl, DMF; (iv) EDCI.HCl, Et_3N, pentafluorophenol, *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine, DCM; (v) TFA, DCM, 50° C; (vi) *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride, Et_3N, pentafluorophenol, DCM; (vii) NH_2OH in H_2O, acetonitrile

Coupling of the amine to the known chlorosulfonyl groups followed by a saponification, when the starting material was an ester, yielded the fully functionalized acid. Conversion of the acid to the hydroxamate was done using different conditions: (1) A one step procedure using *in* situ activation of the acid with isobutylchloroformate and hydroxylamine; (2) synthesis of the THP-protected hydroxamate using an *in situ* pentafluoroester activation, followed by cleavage of the protecting group; (3) synthesis and isolation of the pentafluoroester, followed by synthesis of the hydroxamate.[12] Amide linked compounds (**10, 11** and **18**) were synthesized using a similar approach.

Synthesis of compounds **20**-**27** started form the corresponding hydroxyproline. [10,11] **Scheme 2** depicts the synthesis of analog **24**. The thioether bond was synthesized using the tosylate of the hydroxyproline. Oxidation using mCPBA followed by phenol alkylation with the available quinoline chloride derivative afforded ester **7**. Saponification, followed by pentafluoroester synthesis yielded the activated ester as the penultimate intermediate. Reaction with hydroxylamine afforded the desired compound.



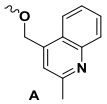
Scheme 2. Synthesis of proline-based inhibitor **24**: (i) TsCl, pyridine (52%); (ii) *p*-hydroxythiophenol, Zn, K_2CO_3, acetone (70%); (iii) mCPBA, DCM (94%); (iv) 4-(chloromethyl)-2-methyl-quinoline, K_2CO_3, KI, acetone (43%); (v) $LiOH.H_2O$, methanol (84%); (vi) *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride, Et_3N, pentafluorophenol, DCM (33%); (vii) NH_2OH in H_2O, acetonitrile (15%)

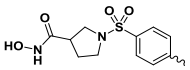
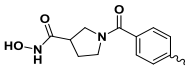
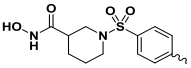
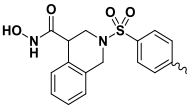
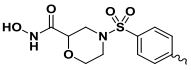
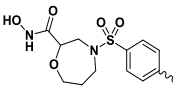
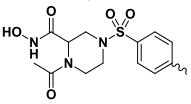
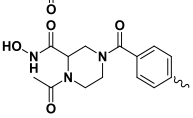
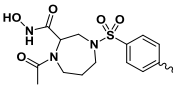
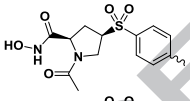
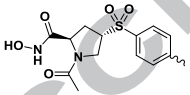
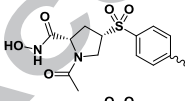
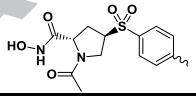
Compounds were evaluated in a standard TACE enzymatic assay.[13] Activities of the different analogs are displayed in **Table 1**. The first striking observation is that the quinoline group routinely shows activity whereas the alkyne does not (**8** *vs* **9**; **16** *vs* **17**; **24** *vs* **25**). At this stage, we decided to focus on the quinoline group even though the impact of such group on solubility and skin penetration would have to be carefully assessed.

Comparing compounds **8**/**10** and **16**/**18** showed a preference for the sulfonamide linker. 5, 6 and 7-membered rings were tolerated (apart for acetyldiazepane **19**) and so was incorporation of heteroatoms (**14** and **16**).

The different proline-based isomers displayed disappointing potency and were not explored any further. Instead pyrrolidine, piperidine and piperazine were chosen as starting point for further optimization.

Table 1. Cyclic linker exploration

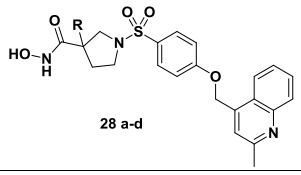


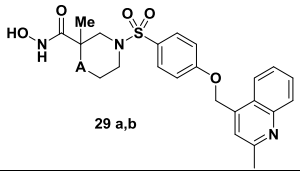
Compound	Core	Phenyl substituent	TACE enz (nM)[a]	clogD$_{7.4}$[b] /LipE[c]
1	-	-	4	0.8/7.6
3	-	-	6	2.3/5.9
8		A	210	2.2/4.5
9		B	>10000	0.9/-
10		A	6500	2.3/2.9
11		B	>10000	1.2/-
12		A	60	2.3/4.9
13		A	84	3.0/4.1
14		A	180	1.8/4.9
15		A	71	1.9/5.3
16		A	14	1.4/6.4
17		B	1500	0.3/5.5
18		A	760	1.5/4.6
19		A	200	1.5/5.2
20		A	>10000	1.7/-
21		B	>10000	0.4/-
22		A	>10000	1.7/-
23		B	>10000	0.4/-
24		A	350	1.7/4.8
25		B	>10000	0.4/-
26		A	3600	1.7/3.7
27		B	>10000	0.4/-

[a] See supplementary material for assay description. Geomean of at least 2 determinations[13]
[b] Calculated using ADMET predictor
[c] LipE: Lipophilic efficiency is determined by pIC$_{50}$-clogD$_{7.4}$

A first exploration was made around the alpha position of the hydroxamate (**Table 2**). Compounds were synthesized using the general approach outlined in **Scheme 1**.[10,11] Simple methylation of the pyrrolidine scaffold provided a nice boost in potency (**28a**). Moving to the ethyl was also overall beneficial (**28b**). However, bulkier groups did not bring any notable advantage (**28c** and **28d**).

Table 2. α-alkylation exploration





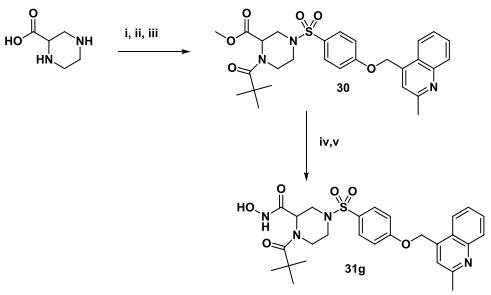
Cmpd	R	A	TACE enz (nM)[a]	clogD$_{7.4}$[b] /LipE[c]
8	H	-	210	2.2/4.5
28a	Methyl	-	35	2.5/5
28b	Ethyl	-	16	2.6/5.2
28c	Isobutyl	-	35	3.3/4.2
28d	CH2Phenyl	-	42	3.6/3.8
12	-	-	60	2.3/4.9
29a	-	CH2	40	2.6/4.8
16	-	-	14	1.4/6.4
29b	-	NAc	30	1.7/5.8

[a] See supplementary material for assay description. Geomean of at least 2 determinations[13]
[b] Calculated using ADMET predictor
[c] LipE: Lipophilic efficiency is determined by pIC$_{50}$-clogD$_{7.4}$

Surprisingly, the effect of the added methyl group in the pyrrolidine scaffold did not transfer to the piperidine scaffold (**29a** vs **12**) and was even slightly detrimental on the piperazine scaffold.

At this stage, we had reached similarly high potencies on the enzymatic assay with **28b** and **16** (respectively 16 and 14 nM). However, these compounds display significantly different logD (2.5 vs 1.4) and LipE values (5.2 vs 6.4). Considering its high LipE value, in addition to synthetic aspects, we found judicious to explore the chemical space around piperazine **16**.

Scheme 3 depicts the synthesis of piperazine analog **31g** as a representative procedure for the synthesis of all the other N_1-modified piperazine analogs.[10,11] Sulfonamide formation occurred smoothly on the distal nitrogen using the general conditions described earlier. Esterification followed by *tert*-butyl amide synthesis afforded fully functionalized intermediate **30**. Saponification followed by a one-step hydroxylamine formation gave the desired compound **31g**.



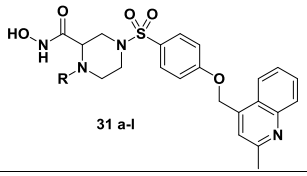
Scheme 3. Synthesis of piperidine-based inhibitor **31g**: (i) 4-((2-methylquinolin-4-yl)methoxy)benzenesulfonyl chloride, triethylamine, dioxane/water (2/1) (84%); (ii) $SOCl_2$, methanol (98%); (iii) 2,2-dimethylpropanoyl chloride, Et_3N, DCM (98%); (iv) $LiOH.H_2O$, THF/H_2O (4/1) (87%); (v) *N*-methylmorpholine, isobutyl chloroformate, $NH_2OH.HCl$, DMF (17%)

Table 3 highlights some of the substituents that were explored on the N_1-nitrogen, alpha to the hydroxamate.

Amide exploration highlighted that short aliphatic groups (**31a**, **31b**, **31e**), small cycloalkyl (**31c**, **31d**), and even phenyl (**31f**) all maintained good levels of potency. Sulfonamides (**31i**) and carbamates (**31h**) were both surveyed and also displayed good

potency. Finally, alkyl groups were rapidly scanned but showed disappointing activity (**31j**, **31k**, **31l**).

Table 3. Piperazine exploration



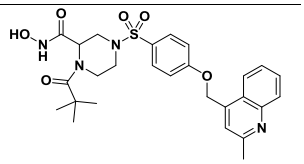
Cmpd	R	TACE enz (nM)[a]	Human Microsomes[b]	clogD$_{7.4}$[c] /LipE[d]
16		14	92	1.4/6.4
31a		23	100	1.6/6.0
31b		26	91	1.9/5.7
31c		13	88	1.9/6.0
31d		19	83	2.1/5.6
31e		23	64	2.3/4.3
31f		16	85	2.5/5.3
31g		12	47	2.3/5.6
31h		40	100	1.9/5.5
31i		29	88	1.8/5.7
31j	H	110	-[e]	1.5/5.5
31k	Me	160	80	1.8/5.0
31l		150	54	2.4/4.4

[a] See supplementary material for assay description. Geomean of at least 2 determinations[13]
[b] Stability in Human microsomes: % parent compound remaining after 15min of incubation. See supplementary material for assay description.[13]
[c] Calculated using ADMET predictor
[d] LipE: Lipophilic efficiency is determined by pIC$_{50}$-clogD$_{7.4}$
[e] Not tested

Out of all these, only compounds **31e**, **31g** and **31l** showed reasonable microsomal *instability*. This was sought after by the project team as it would favour a locally acting compound with limited systemic exposure after topical application. With the highest LipE of the three, **31g** was selected for further profiling (**Table 4**).[13]

Compound **31g** was potent in the enzymatic assay and selective *vs* an in-house panel of MMPs and ADAMs. The compound displayed properties compatible with topical administration: the metabolic instability detected in microsomes was confirmed in human hepatocytes; the compound was stable in human keratinocytes with a half-life of more than 24 hours (this ensured that the compound would not be metabolized in the skin); reasonable aqueous solubility and good Propylene Glycol/Ethanol (PG/EtOH) solubility highlighted the potential for this series in different formulations; the compound was also found to be negative in our phototoxicity assay.[14] Overall, compound **31g** presented most of the characteristics we were looking to find for a topical lead compound. Unfortunately, cellular activity measured in keratinocytes was suboptimal.

Table 4. Property Scoring Card for **31g**



	31g
TACE enz IC$_{50}$ (nM)[a]	12
MMP1/MMP3/MMP9/MMP12 IC$_{50}$ (µM)[b]	>10/>10/>10/0.93
ADAM9/ADAM10 IC$_{50}$ (µM)[b]	>10/>10
Cell assay (KHN) IC$_{50}$ (µM)[a]	1.3
Fu (Hu)[b]	3%
Human hepatocytes Clint (µL/min/1e^6 cells)[b]	14
Human keratinocytes T1/2 (hrs)[b]	>24
Aqueous Solubility (µM)[c]	20
Solubility in PG/EtOH96 (3/7) (mM)	>55
Photo-irritancy factor[b]	1

[a] See supplementary material for assay description. Geomean of at least 2 determinations[13]
[b] See supplementary material for assay description.[13]
[c] Contains 1% DMSO

In order to understand this micromolar cellular activity, a series of compounds from this manuscript were tested in the cell assay. It turned out that apart from Apratastat (**1**) and compound **3**, representing Galderma's first generation of inhibitors, none of the compounds showed submicromolar potency in keratinocytes, all the while showing good potency on the isolated enzyme assay (**Table 5**).

Table 5. Keratinocyte cellular assay

Compound	TACE enz (nM)[a]	KHN (µM)[a]	Aqueous solubility (µM)[b,c]
1	4	0.12	90
3	6	0.06	-[d]
8	210	>10	-[d]
12	60	>10	<1
13	84	>10	-[d]
16	14	9.1	61
24	350	>10	-[d]
28a	35	>10	41
31c	13	3.1	58
31g	12	1.3	20
31l	150	>10	-[d]

[a] See supplementary material for assay description. Geomean of at least 2 determinations[13]
[b] See supplementary material for assay description.[13]
[c] Contains 1% DMSO
[d] Not tested

TACE activity has been shown to be different depending on the cell type.[15] **Figure 2** displays the potency of compounds from different internal series optimized at Galderma in human keratinocytes (KHN) and in human peripheral blood mononuclear cells (hPBMC). The good correlation between the 2 assays over a good spread of IC$_{50}$ suggested that the KHN model was well suited to assess cellular potency of compounds.

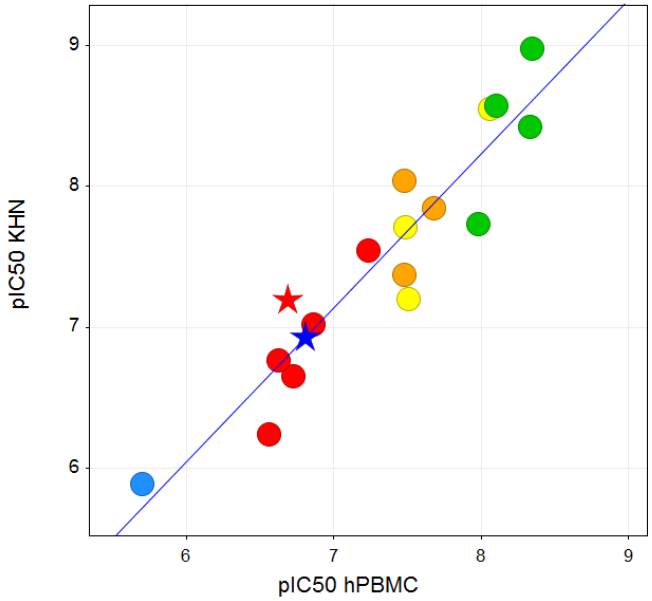


Figure 2. Cellular TNFα inhibition in human keratinocytes and in human peripheral blood mononuclear cells. Colours correspond to distinct chemical series studied at Galderma. The blue star symbol corresponds to reference compound Apratastat (**1**), the red star to compound **3**; The correlation line displays an R^2 of 0.88

To help us understand what the cause of this low cellular activity, we undertook a non-exhaustive study of enzyme to cell drop-off from different TACE inhibitor programs in the literature. We limited our study to compounds being tested in both an enzymatic and cellular assays and purposefully discarded data from whole blood assays as the impact of plasma protein binding could skew the interpretation.[8(a)] **Figure 3** displays data from 5 different literature references along with compounds from **Table 5**.[16] The distribution of compounds in the plot coming from both the literature and our own assays, suggests that other factors than potency on the enzymatic assay actually govern the potency on the more complex cell-based model for TACE inhibition.

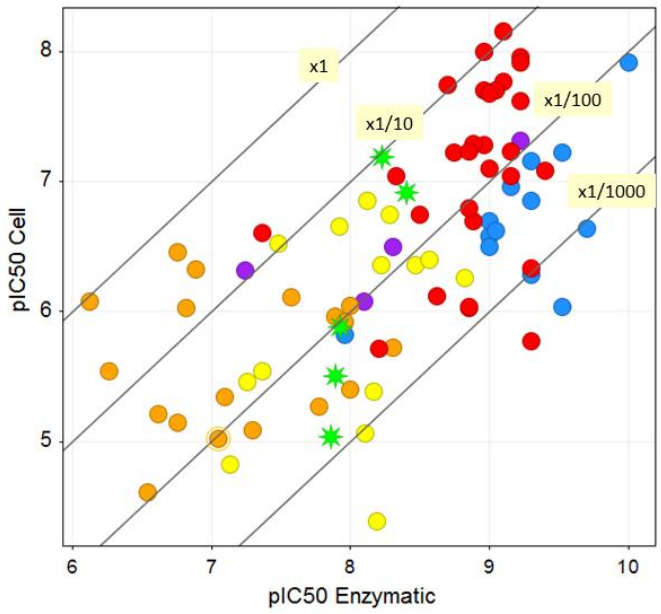


Figure 3. Enzymatic and cellular TACE inhibition data taken from 5 references. Colours correspond to the different literature references: blue (16a), red (16b), purple (16c), orange (16d) and yellow (16e). Compounds from **Table 5** are depicted as green stars.

Although not explicitly stated in the publications mentioned above, the reasons for the non-correlation between isolated TACE enzyme assays and cell-based assays could be multiple:

- Cell permeability has often been a culprit for lack of cellular activity,[17] however it is not clear whether TACE is an intracellular or extracellular target.[18]
- Poor solubility in the assay medium could impact results. Aqueous solubility of some of the compounds is shown in **Table 5** and although the solubilities are higher than the highest concentration tested in the assay for the most part, we cannot rule out the possibility of precipitation in some cases.
- Barlaam *et al* mentioned the possible impact of an entropic effect due to the colocalization of TACE and its substrate.[19] Residence time and tight binding could thus be a key factor for these inhibitors.[20]

Faced with these hypotheses and the associated work to further understand the behaviour of the molecules presented herein, the project team pragmatically decided to stop work on these series. The project strategy shifted towards the use of a cell-based assay as the primary pharmacological assay to bypass this issue. Results from novel cell-potent series will be communicated shortly.

In conclusion, we have identified novel potent TACE inhibitors. If compound **31g** displayed properties fully compatible with topical administration and limited systemic exposure, its relatively weak cellular potency precluded any further development of this molecule.

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10. Representative syntheses of the following compounds are described in the supplementary material: **31g**, **31k**, **31f**, **29a**, **28b**, **24**.
11. Full characterization of all new compounds are described in the supplementary material
12. See references cited in: Beillard, A ; Bhurruth-Alcor, Y. ; Bouix-Peter, C. ; Bouquet, K. ; Chambon, S. ; Clary, L. ; Harris, C.S.; Millois, C.; Mouis, G.; Ouvry, G.; Pierre, R.; Reitz, A. ; Tomas, L. *Tetrahedron Lett.* **2016**, *57*, 2165
13. Assays are described in the supplementary material
14. Based on https://ntp.niehs.nih.gov/iccvam/suppdocs/feddocs/oecd/oecdtg432-508.pdf , a test substance with a PIF < 2 predicts: "no phototoxicity". A PIF >2 and< 5 predicts: "probable phototoxicity" and a PIF > 5: "phototoxicity". See Supplementary Material for more details.
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Supplementary Material

Graphical Abstract

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Identification of novel TACE inhibitors compatible with topical application.

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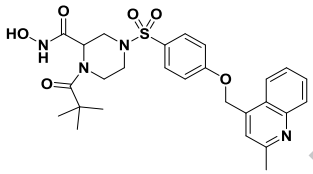

Cmpd 31g