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Aryltriflates as a Neglected Moiety in Medicinal Chemistry: A Case Study from a Lead Optimization of CXCL8 Inhibitors

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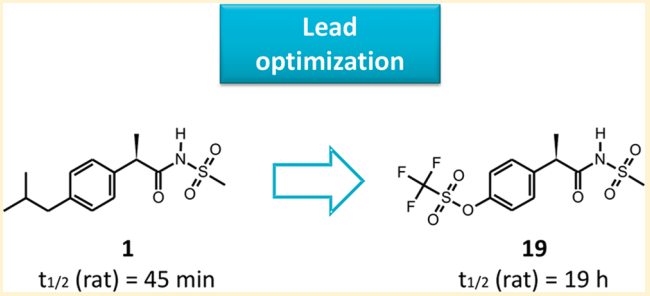
Supporting Information

ABSTRACT: Interleukin-8 and growth related oncogene−α-chemokines (formerly CXCL8 and CXCL1, respectively) mediate chemotaxis of neutrophils to inflammatory sites via interactions with two transmembrane receptors, the type A CXCL8 receptor (CXCR1) and the type B CXCL8 receptor (CXCR2). In a previous work, we published the molecular modeling-driven structure activity relationship (SAR) results culminated in the discovery of *R*-(−)-2-[(4′-trifluoromethanesulphonyloxy) phenyl]-*N*-methanesulfonyl propionamide (**19**), in which an unusual aryltriflate moiety was embedded. Although triflates are broadly used in organic synthesis, this group is scarcely used in medicinal chemistry programs. Here we detail the drug profiling-driven approach used for the selection and characterization of **19**, the most potent dual CXCR1 and CXCR2 noncompetitive inhibitor described to date. Reported data suggest that the aryltriflate moiety might represent a valid choice for the selection of clinical candidates with suitable druglike properties.



KEYWORDS: Aryltriflate, CXCR1, CXCR2, chemokine, dual noncompetitive inhibitor, drug profiling

CXCL8 and CXCL1 belong to the class of chemokines or "chemotactic cytokines", a group of low molecular weight 8−14 kDa proteins that regulate the trafficking of leukocytes in the inflamed tissues and other biological processes, including cell growth, angiogenesis, and hematopoiesis.[1−3] CXCL8 binds CXCR1 and CXCR2, whereas CXCL1 is a selective agonist for CXCR2. Both receptors belong to the seven transmembrane G-protein-coupled receptors (GPCRs) superfamily, sharing 78% amino acid identity.[4]

The CXCL8 receptor activation has been implicated as a key event in severe chronic diseases, including rheumatoid arthritis, chronic obstructive pulmonary disease, Alzheimer's disease, melanoma, and psoriasis.[5−9] To date, a limited number of small molecular weight CXCL8 inhibitors have been disclosed in the literature.[10,11] Reparixin (**1**), a potent inhibitor of CXCR1, stemmed from our internal medicinal chemistry programs, was selected as candidate drug after demonstration of its efficacy in several ischemia/reperfusion experimental models.[12] However, its short half-life in humans and the weak activity to CXCR2 limited the exploitation of its potential use for the treatment of chronic conditions. In an earlier paper, SAR results of potent CXCR1/CXCR2 noncompetitive inhibitors were disclosed.[13] As the main outcome of the work, aryltriflates showed a long plasma half-life in the tested species and dual activity to CXCR1 and CXCR2. Aryltriflates are excellent substrates for Stille and Suzuki cross-coupling reactions, Heck reactions, and Buchwald−Hartwig reactions and are used as intermediates in medicinal chemistry programs due to the wide availability of structurally diverse phenols.[14−16] Nevertheless, very few examples of lead compounds or clinical candidates embedding an aryltriflate moiety are reported in the literature and, at the time of this study, focused research performed on the Thomson Reuter Integrity portal by using the triflate as entry query highlighted that six out of the thirteen molecules reported in the preclinical or clinical phase derived from Dompé proprietary programs.[17]

Here, we describe the approach followed for the discovery and characterization of novel CXCR1/CXCR2 inhibitors, typified by *R*-(−)-2-[(4′-trifluoromethanesulphonyloxy)phenyl]-*N*-methanesulfonyl propionamide (**19**), selected as clinical candidate.

The aim of this communication is to point out the excellent *in vitro* and *in vivo* behavior of the aryltriflate group, thus encouraging future efforts aiming to incorporate this moiety in future clinical candidates with appropriate druglike properties.

Based on molecular modeling and mutagenesis studies, the triflate group was selected as an ideal moiety due to its ability to establish hydrophobic interactions with CXCL8 receptors with minimal steric hindrance.[13] In agreement with previously published SAR and coherently with the proposed binding mode, different functionalizations of the phenylpropionyl scaffold, including aromatic/aliphatic amides, hydroxamates, and

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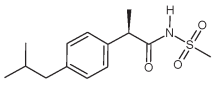
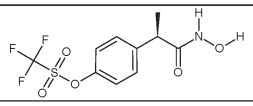
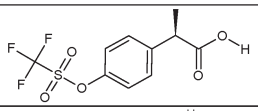
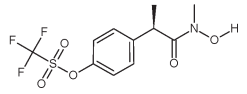
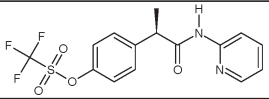
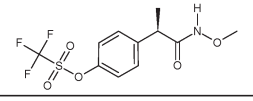
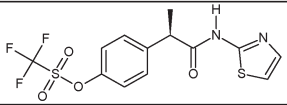
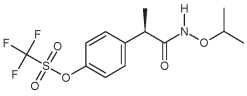
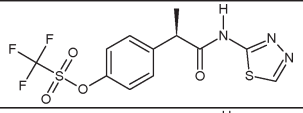
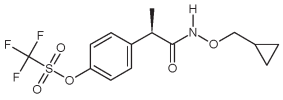
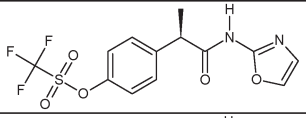
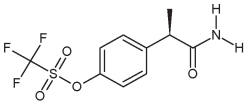
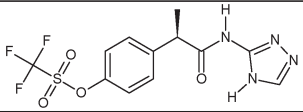
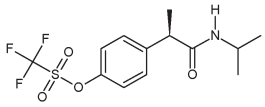
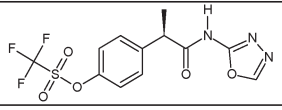
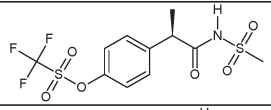
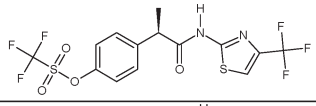
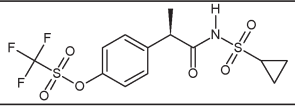
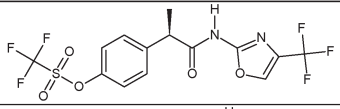
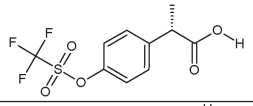
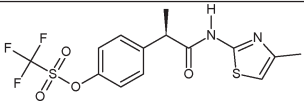
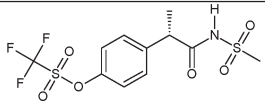
Table 1. Biological Activity of Compounds 1−22

Cmpd	Structure	CXCL8[a]	CXCL1[b]	Cmpd	Structure	CXCL8[a]	CXCL1[b]
1		68 ± 5	22 ± 1	**12**		50 ± 4	49 ± 1
2		62 ± 4	63 ± 1	**13**		47 ± 5	49 ± 3
3		43 ± 1	45 ± 3	**14**		56 ± 4	46 ± 3
4		56 ± 3	55 ± 5	**15**		49 ± 3	38 ± 5
5		54 ± 4	55 ± 3	**16**		40 ± 6	35 ± 1
6		47 ± 1	46 ± 7	**17**		58 ± 2	56 ± 5
7		44± 2	45 ± 1	**18**		58 ± 4	65 ± 1
8		44 ± 3	48 ± 5	**19**		67 ± 4	68 ± 5
9		64 ± 10	55 ± 5	**20**		44 ± 4	45 ± 2
10		60 ± 10	50 ± 1	**21**		NA[c]	NA[c]
11		58 ± 1	50 ± 1	**22**		NA[c]	NA[c]

[a] % inhibition ± SD (n = 3) on the CXCL8-induced human polymorphonucleate (PMN) chemotaxis at 10^{-8} M. [b] % inhibition ± SD (n = 3) on the CXCL1-induced human PMN chemotaxis at 10^{-8} M. [c] NA not active.

acylsulfonamides matched well with the desired biological activity.[13]

The paucity of medicinal chemistry data prompted us to be careful to consider the potential usefulness of this group; thus, the identified molecules were profiled along a screening cascade to ensure suitable developability potential. We assume that presumption of the biological liability of this moiety discouraged medicinal chemists from further investigation due to the possible *in vivo* formation of potentially toxic phenol derivatives and trifluoromethanesulfonic acid; thus, metabolic stability was carefully examined. The synthesis of compounds **1**−**22** (Table 1) is reported in the Supporting Information while the biological activity was assessed as previously described.[13]

The methodology used to prioritize the choice of preclinical candidates was the assembly of a specific screening grid defined for each chemical class.

R-(−)-2-(4-Trifluoromethanesulfonyloxy)phenylpropionic acid (**2**) (Table 1) was the first compound selected with an optimal biological activity profile. However, its structural similarity to the family of nonsteroidal antiinflammatory drugs (NSAIDs) prompted us to investigate also alternative candidates, since several *in vitro* and *in vivo* studies highlighted the susceptibility of phenylpropionic acids to undergo metabolic chiral inversion by the formation of a coenzyme A thioester intermediate.[18,19]

Heteroaromatic amides (Table 1, **3**−**11**) were the first class investigated.

In fact, on the basis of reported SAR studies, the activity of heteroaryl derivatives is consistent with the formation of an intramolecular hydrogen bond involving the heteroatom in the 2-position as acceptor that plays a key role in shifting the amido/imido equilibrium.[13] The 2-aminopyridine derivative **3** was the

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Table 2. CYP Inhibition, Solubility, and log *D* of Aromatic Amides 3−11

	CYP[a] (%)						
cmpd	1A2	2D6	3A4	2C9	2C19	sol (mg/mL) @ 7.4[b]	log *D* @ 7.4[b]
3	<5	21	15	37	97	0.14	2.9
4	36	26	52	53	87	0.003	3.4
5	<5	40	66	50	70	0.013	2.2
6	15	<5	44	70	90	0.03	2.3
7	<5	<5	8	<5	21	0.06	1.4
8	ND[c]	ND	ND	ND	ND	0.05	1.6
9	14	56	52	73	94	0.0006	4.0
10	<5	38	82	87	94	0.004	2.9
11	16	<5	60	60	90	0.002	3.9

[a] % inhibition at 10 μM in the indicated CYP isoform. [b] ACDPhysChem Ver. 12. [c] ND: not determined.

Table 3. Rat Plasma Stability, Microsomal Stability, and log *D* of Hydroxamates 12−16

cmpd	rat plasma[a] (%)	rat microsomes[b] (%)	log *D* @ 7.4[c]
12	85	87	1.1
13	96	75	1.8
14	90	65	2.4
15	85	75	3.2
16	ND[d]	ND	3.3

[a] % remaining compound after 1 h in rat plasma. [b] % remaining compound after 30 min in rat microsomes. [c] ACDPhysChem Ver. 12. [d] ND: not determined.

less potent in this series, and unfortunately, substitutions around the pyridine ring were poorly tolerated (data not shown). To improve the *in silico* prediction of solubility and lipophilicity of aryltriflates **2**−**22** a trainable model (ACD/Laboratories PhysChem Ver. 12) incorporating our internal experimental data was specifically developed. Calculated log *D* and solubility values at pH 7.4 are reported (Tables 2−4).

This class was characterized by extremely low aqueous solubility as in the case of 2-aminothiazole and 1,3,4-thiadiazole derivatives **4** and **5**. While improving water solubility, charged or polar groups in positions 3 or 4 of the heterocycles compromised affinity for CXCL8 receptors.[13] Similarly, *O*- or *N*-containing aromatic heterocycles (**6**−**8**) showed a moderate reduction of log *P* values with about 1-fold increment over the solubility but paralleled by a slight loss of potency. The trifluoromethyl substituted compounds **9** and **10**, as well as their methyl analogue **11**, retained an excellent activity but, as expected, showed reduced water solubility. The *in vitro* metabolic fate of compounds **3**−**11** was thoroughly investigated, and it was found that the triflate-substituted phenyl ring was not reactive under the conditions of the liver microsome assay (data not shown).

This series was also evaluated for cytochrome (CYP) inhibition in consideration of the known characteristic of nitrogen-containing heteroaromatic compounds to inhibit CYP enzymes by direct coordination of the heme iron. As expected, CYP2C9, CYP2C19, and CYP3A4 were inhibited by the most of the compounds at the test concentration of 10 μM. The introduction of methyl or trifluoromethyl groups in the 3 position of the heterocycle, aimed to increase the steric hindrance and to reduce the affinity for the heme iron, failed to minimize the CYP inhibition.

Table 4. Rat Microsomal Stability, Solubility, and log *D* of 2 and 17−20

cmpd	rat microsomes[a] (%)	sol (mg/mL) @ 7.4[b]	log *D* @ 7.4[b]
2	100	>10	−0.8
17	80	0.6	1.4
18	75	0.2	2.3
19	100	6.4	−0.6
20	ND[c]	1.9	−0.2

[a] % remaining compound after 30 min in liver rat microsomes. [b] ACDPhysChem Ver. 12. [c] ND: not determined.

As second step, a series of hydroxamic acid derivatives was investigated (Table 3).

Compounds **12**−**14** showed activity on both CXCR1 and CXCR2. However, hydroxamic acids may be hydrolyzed to the corresponding carboxylic acid under physiological conditions, and a recent work rationalizes the structure−plasma stability relationships for hydroxamates.[20] Compounds **12**−**14** confirmed a remarkable chemical stability (>98% at pH = 7.4; Supporting Information), a good metabolic stability in rat liver microsomes (about 75%), and an excellent rat plasma stability (average 90%) (Table 3). *O*-Alkylation of the hydroxamate group (**15** and **16**) led to an increase of log *D* but, unfortunately, to a partial loss of biological activity too (Table 3). Further enlargement of the hydrophobic substituent by either *O*- or *N*-alkylation was not tolerated, leading to the loss of biological activity (data not shown). The experimental plasma half-life of hydroxamates **12**−**14** after intravenous administration in rodents was less than 1 h. It is noteworthy that neither *in vitro* nor *in vivo* metabolites bearing a phenolic moiety were detected and that the short half-life was associated with the metabolic liability of the hydroxamate function and with the rapid clearance through phase II metabolic reactions (data not shown).

On the basis of the above results, *R*-(−)-2-(4-trifluoromethanesulfonyloxy)phenylpropionic acid (**2**), the primary amide **17**, the alkyl amide **18**, and acylsulfonamides **19** and **20** were also evaluated.

Primary amide **17** and related *N*-isopropyl derivative **18** were equipotent to both CXCR1 and CXCR2, showing also relatively low log *D* values (Table 4). Acidic compounds **2**, **19**, and **20** were found to be dual CXCR1 and CXCR2 inhibitors also with an excellent solubility (>1 mg/mL). Coherently with the observed stability of the 4-triflate-phenylpropionic moiety, a good metabolic stability was observed in rat microsomes for **17** and **18**, but the exceptional stability of the acidic compounds **2** and **19** (100% remaining compounds after 30 min of incubation) as well as their potency prompted us to further progress **2** and **19** along the screening cascade for a more detailed evaluation.

First, we estimate the chemical stability of **2** and **19** at different pH values (3.5, 7.4, and 9) to mimic the physiological environments of stomach, blood, and intestine, respectively. As expected, **2** and **19** were found stable when subjected to treatment in aqueous solutions, buffered at pH 3.5 and 7.4 (>99% of remaining compounds after 2 h at 37 °C), whereas they showed an extremely poor stability at basic pH (average of 30% of remaining compounds buffered at pH = 9, Supporting Information). Due to the strong electron withdrawing group (EWG) characteristics, the introduction of the triflate makes **2** and **19** very acidic, with

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Table 5. Stability of 2 and 19 in Human and Rat Hepatocytes[a]

	cmpd **2**			
	human hepatocytes		rat hepatocytes	
time (min)	cmpd **2**	cmpd **21**	cmpd **2**	cmpd **21**
0	2990 ± 8	<LLOQ[b]	2996 ± 10	<LLOQ
15	2932 ± 12	21 ± 4	2839 ± 12	117 ± 12
30	2844 ± 14	84 ± 8	2541 ± 15	210 ± 7
60	2696 ± 16	240 ± 16	2287 ± 17	449 ± 12
90	2620 ± 21	260 ± 10	2167 ± 22	664 ± 14
120	2541 ± 16	330 ± 17	1946 ± 21	870 ± 17

	cmpd **19**			
	human hepatocytes		rat hepatocytes	
time (min)	cmpd **2**	cmpd **21**	cmpd **2**	cmpd **21**
0	<LLOQ	<LLOQ	<LLOQ	<LLOQ
15	<LLOQ	<LLOQ	22 ± 4	7 ± 2
30	3 ± 2	<LLOQ	5 ± 1	31 ± 2
60	15 ± 3	2 ± 1	3 ± 2	50 ± 2
90	20 ± 2	3 ± 1	5 ± 2	54 ± 4
120	30 ± 3	6 ± 2	4 ± 1	56 ± 4

[a] Indicated values (±SD, n = 3) represent the levels (expressed in ng/mL) of acids **2** and **21** after the incubation of **2** and **19** in human and rat hepatocytes. LOQ for compounds **2** and **21** was 1 ng/mL in human and rat hepatocytes. [b] LLOQ = lower limit of quantification.

pK_a values of 4.0 and 4.4, respectively. Additionally, both compounds showed exceptional rat plasma stability (100% remaining compounds after 1 h of incubation) as well as high rat plasma protein binding (Supporting Information). To obtain an evaluation of their safety potential, the off-target activity was assessed. The compounds **2** and **19** did not inhibit [^{3}H]-astemizole binding (100% radioligand binding at 10 μM) in a whole-cell hERG binding assay and were devoid of inhibition activity in the five CYP marker enzymes assayed (inhibition <5% at 10 μM). In a panel of 40 GPCR and ion channel binding assays, **2** and **19** did not inhibit the reference compound binding when tested at 10 μM (Ricerca Biosciences LLC). To assess the sensitivity to the enzymatic chiral inversion, **2** and **19** were incubated at 10 μM in rat and human hepatocytes. The possible *in vivo* interconversion would greatly impair the pharmacological use of these compounds as CXCL8 inhibitors due to the lack of activity of the corresponding *S*-enantiomers.[13] We expected that the introduction of acylsulfonamido in **19** would greatly limit its potential chiral inversion. In light of these findings, the putative *S*-isomers of **2** and **19** were synthesized (**21** and **22**, respectively).

The parent compounds and their metabolites were analyzed under chiral conditions, and their corresponding levels (Table 5) clearly indicate an excellent stability of **19** in both rat and human hepatocytes.

Interestingly, as illustrated in Table 5, the clearance of **19** was proximal to zero and metabolite concentrations were lower than 40 ng/mL in human hepatocytes after 120 min of incubation. On the contrary, **2** showed higher levels of the corresponding metabolite **21** in both species. Nonetheless, a net conversion of **2** to **21** was observed in different proportion 2 h after the

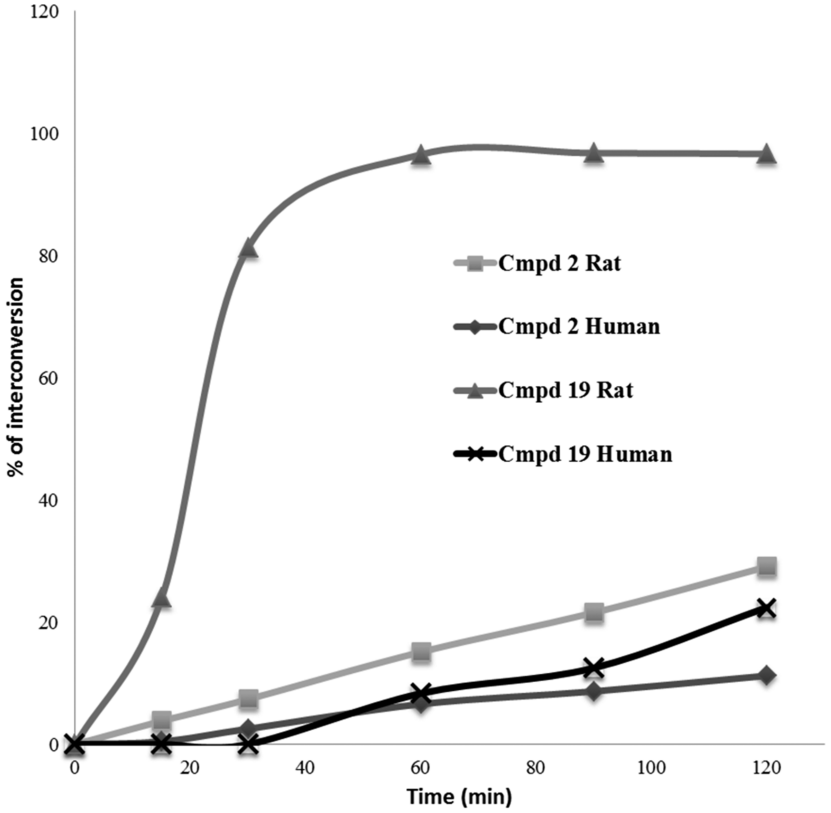

Figure 1. Percent of interconversion of **2** into **21** after the incubation of **2** and **19** in rat and human hepatocytes.

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incubation of **2** and **19**; the conversion was about 30% and 11% for **2** and 95% and 20% for **19**, in rat and human hepatocytes, respectively (Figure 1).

These observations clearly confirmed the interconversion of **2** into **21** and that the hydrolysis of acylsulfonamido embedded in **19** occurring in hepatocytes is followed by a fast acylation with inversion of the stereogenic center, leading to **21**. In contrast to the reactive character of aliphatic triflates, no traces of phenol derivatives were found. Moreover, no traces of **22** were observed, thus confirming the hypothesis that a reactive ester is a key intermediate of the enzymatic chiral inversion process. Finally, the formation of glucuronide metabolites of **2**, **19**, **21**, and **22** was not observed (Supporting Information).

Overall, in the investigated system, **19** demonstrated a remarkable *in vitro* metabolic stability because the formation of its corresponding carboxylic acids **2** and **21** occurred only in traces. Similar results were obtained using mouse and dog hepatocytes (Supporting Information). Then, in virtue of its peculiar *in vitro* metabolic profile, **19** was selected for further *in vivo* investigation.

Pharmacokinetic studies in rat showed a high elimination half-life (approximately 19 hours) and a clearance of 0.1 mL/(min kg) after intravenous administration, coherent with the marked metabolic stability and the strong protein binding.[21]

Additionally, **19** had excellent oral bioavailability in rats (F = 100%, Supporting Information), and it was mostly excreted unchanged (data not shown).

In summary, this paper reports the drug profiling approach that guided the characterization of the aryltriflate moiety incorporated in the potent CXCR1/CXCR2 clinical candidate **19**.

Interestingly, the results herein reported demonstrate for the first time that, in clear contrast with the strong reactivity of aliphatic triflates, the aryltriflate group, even if rarely used in medicinal chemistry, is chemically and biologically stable and represents a valid choice as EWG substituent of the phenyl ring in lead optimization studies.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details for the synthesis and characterization of reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS

CXCR1, type A CXCL8 receptor; CXCR2, type B CXCL8 receptor; CYP, cytochrome; EWG, electron withdrawing group; GPCRs, G-protein coupled receptors; NSAIDs, nonsteroidal antiinflammatory drugs; PMN, neutrophil polymorphonucleate leukocytes; SAR, structure−activity relationship.

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